Relation Between Change in Blood Pressure in Acute Stroke and Risk of Early Adverse Events and Poor Outcome

Else C. Sandset, MD; Gordon D. Murray, PhD; Philip M.W. Bath, FRCP, FESO; Sverre E. Kjeldsen, MD, PhD; Eivind Berge, MD, PhD; on behalf of the Scandinavian Candesartan Acute Stroke Trial (SCAST) Study Group

Background and Purpose—The Scandinavian Candesartan Acute Stroke Trial (SCAST) found no benefits of candesartan in acute stroke. In the present analysis we aim to investigate the effect of change in blood pressure during the first 2 days of stroke on the risk of early adverse events and poor outcome.

Methods—SCAST was a multicenter, randomized controlled, double-blind trial of candesartan in acute stroke. The trial recruited 2029 patients presenting within 30 hours of acute stroke and with systolic blood pressure (SBP) ≥140 mm Hg. Treatment was given for 7 days. Change in blood pressure was defined as the difference in SBP between baseline and Day 2 and was used to divide patients into groups with increase/no change, a small decrease, moderate decrease, or large decrease in SBP. The primary effect parameter was early adverse events (recurrent stroke, stroke progression, and symptomatic hypotension) during the first 7 days, analyzed using logistic regression, with the group with a small decrease in SBP as the reference group. Secondary effect parameters were neurological status at 7 days and functional outcome at 6 months.

Results—Patients with a large decrease or increase/no change in SBP had a significantly increased risk of early adverse events relative to patients with a small decrease (OR, 2.08; 95% CI, 1.19–3.65 and OR, 1.96; 95% CI, 1.13–3.38, respectively). Patients with an increase/no change in SBP had a significantly increased risk of poor neurological outcome as compared with the other groups (P=0.001). No differences were observed in functional outcome at 6 months.

Conclusions—Our findings support the suggestion from SCAST that blood pressure reduction may be harmful and that routine blood pressure-lowering treatment should probably be avoided in the acute phase.

Clinical Trial Information—Clinical Trial Registration: www.clinicaltrials.gov. Unique identifier: NCT00120003. (Stroke. 2012;43:2108-2114.)

Key Words: acute stroke ■ blood pressure ■ candesartan ■ cerebral autoregulation

The initial rise in blood pressure commonly observed in acute stroke is a pathophysiological response, and a spontaneous fall is typically seen within 10 to 14 days.1,2 Autoregulatory mechanisms ensure a near constant cerebral blood flow across a wide range of blood pressure under normal circumstances. Due to disruption of autoregulation in acute stroke, cerebral perfusion relies on the systemic arterial pressure.3 Hypotension may further escalate ischemic damage by decreasing blood flow to the infarcted zone and surrounding penumbra. On the other hand, high blood pressure may increase the risk of cerebral edema and hemorrhagic transformation of ischemic stroke.4

Blood pressure-lowering in the acute phase of stroke has long been a matter of debate.5–7 Several observational studies have reported a relationship between baseline systolic blood pressure (SBP) and short- and long-term outcome,8–10 and studies of blood pressure-lowering treatment with the angiotensin receptor blocker candesartan have shown promising effects in several experimental studies11,12 and one clinical study.13 Other clinical studies have indicated that a large decline in SBP within 24 hours of stroke is associated with poor outcome,14 including a randomized and placebo-controlled trial of intravenous nimodipine.15

On this background, the Scandinavian Candesartan Acute Stroke Trial (SCAST) was undertaken to investigate the effect of blood pressure-lowering with the angiotensin receptor blocker candesartan in acute stroke.16 Treatment with candesartan caused a modest reduction of blood pressure
compared with placebo, but candesartan did not reduce vascular events or improve functional outcome during the 6-month follow-up period. Instead, candesartan was associated with an increase in stroke progression and other early adverse events, a finding that is compatible with the hypothesis that lowering blood pressure may decrease regional cerebral perfusion.

As a secondary analysis we aim to investigate the effect of a decline in SBP over the first 2 days after stroke on the risk of adverse events and poor short- and long-term outcome irrespective of treatment assignment. We also aim to assess, using a prediction model, whether the effect of candesartan was dependent on the level of blood pressure reduction.

Materials and Methods

Patients and Procedures

Study design and participants have been described in detail elsewhere. The study recruited in total 2029 patients presenting within 30 hours of acute ischemic or hemorrhagic stroke and with MAP ≤ 140 mm Hg. Written informed consent was sought from all patients. Nonwritten or waiver of consent was accepted only after approval from the local ethics committees. Patients were allocated in a 1:1 ratio to treatment with candesartan or placebo, and both patients and investigators were masked to treatment. Trial treatment was administered for 7 days with a fixed-dose escalation scheme, doses increasing from 4 to 16 mg once daily during the first 3 days. All patients received standard stroke care, and therapeutic agents other than angiotensin receptor blockers were administered at the discretion of the investigators, including antihypertensive agents. Clinical visits took place on Day 7 and at 1 and 6 months.

Blood pressure before randomization was measured twice with an interval of 10 minutes with a validated automated monitor (UA-767 Plus 30; A&D Medical, San Jose, CA). The mean value of the 2 was used for the analyses. During the treatment period, SBP and diastolic blood pressure (DBP) were measured daily during the morning round with the patient in the supine position using the automated monitor provided. Mean arterial pressure (MAP) was calculated as two thirds of the DBP plus one third of the SBP. The greatest drop in blood pressure occurred between admission (Day 1) and Day 2, and this was used as the measure of change in SBP (ΔSBP) and MAP (ΔMAP) in the acute phase.

Effect Parameters

The primary effect parameter for the present study was adverse events during the first 7 days, defined as the combined end point of recurrent stroke, stroke progression, and symptomatic hypotension. Recurrent stroke was defined as a sudden, persistent, and clinically significant neurological deterioration occurring after the first 72 hours and was classified as ischemic, hemorrhagic, or of unknown type. Within the first 72 hours after stroke onset it is more difficult to differentiate true recurrence from progression of the index stroke, and recurrence was diagnosed only if symptoms originated from a new arterial territory. Stroke progression was defined as a reduction of ≥ 2 points in one or more of the Scandinavian Stroke Scale (SSS) subscores during the first 72 hours after exclusion of systemic reasons for deterioration. Symptomatic hypotension was defined as a sudden, clinical deterioration (transient or persistent) in combination with an abrupt reduction in blood pressure (> 30%, relative to the previous measurement) as judged by the clinician. All events were adjudicated by an independent end point committee. The committee was blinded to treatment assignment, but had access to clinical information provided by the clinicians.

Secondary effect parameters were neurological status at 7 days, difference in neurological status from baseline to Day 7, and functional outcome at 6 months. Neurological status was measured using the SSS (range from 0–58 with 0 representing maximum neurological deficit and 58 normal neurological function). Differ-

ence in SSS from baseline to Day 7 (ΔSSS) was defined as the change in SSS from baseline to Day 7 relative to the maximal possible improvement: ([SSS Day 7 – SSS Day 1]/[SSS maximum – SSS Day 1]) × 100. Functional outcome was measured using the modified Rankin Scale.

Statistical Methods

The present analysis was prespecified in the original Statistical Analysis Plan and includes the full intention-to-treat population of SCAST. We first wanted to assess a possible association between ΔSBP and risk of early adverse events. Based on findings suggesting that both a significant increase in SBP or a significant decrease in SBP is associated with poor outcome, we chose to classify ΔSBP into the following 4 groups of near equal size. Group 1 consisted of patients with no change or an increase in SBP, whereas patients with a decrease in SBP were divided into tertiles; Group 2, patients with a small decrease (0–14 mm Hg); Group 3, moderate decrease (14–28 mm Hg); and Group 4, large decrease (≥ 28 mm Hg) in SBP. Group 2 was used as the reference group for all analyses. Baseline differences among the 4 groups were compared using the χ² method for categorical variables and one-way analysis of variance with probability values for linear trend for continuous variables.

The risk of early adverse events in the 4 groups was analyzed using logistic regression and is reported as ORs with 95% CIs. To control for the effect of treatment we first performed stratified analyses analyzing separately patients receiving candesartan and patients receiving placebo. We adjusted for the following known baseline predictors: age, SSS, SBP, stroke diagnosis (ischemic versus all other), and duration of symptoms. In the analysis of both groups combined, we also adjusted for study treatment. Neurological outcome (SSS score) at 7 days and the change in SSS score from baseline to Day 7 were analyzed using the Kruskal-Wallis test. For functional outcome (modified Rankin Scale), we used ordinal logistic regression analysis.

Baseline hemodynamic parameters (SBP, DBP, and MAP) were divided into tertiles using the lowest tertile as the reference group. The risk of early adverse events within each tertile was studied using logistic regression. To assess the impact of a fixed change in blood pressure at any given level of SBP at trial entry, we tested the relation between ΔSBP (grouped as defined previously) and the risk of early adverse event within each tertile of baseline SBP.

Finally, we wanted to assess whether the risk of early adverse events was associated with predicted expected blood pressure reduction and whether the effect of candesartan was dependent on the predicted expected blood pressure reduction. We identified baseline predictors of ΔSBP (apart from allocated treatment) in the entire patient population using univariate, backward stepwise and multivariable linear regression analysis. Based on the predictors identified in the multivariate model, we constructed a model to predict ΔSBP in all patients. The predicted ΔSBP was then divided into tertiles (identifying patients at low, moderate, or high risk of a large blood pressure decline). Within each tertile we tested whether there was an association between candesartan and the risk of early adverse events using logistic regression analysis. The analyses were performed using SPSS Version 18 (Chicago, IL).

Results

In total, 2029 patients were randomized. SBP values on admission and on Day 2 were available in 1997 patients (98%). The mean age was 71 years and 843 (44%) were female. A reduction in SBP from baseline was observed in 1421 patients (71%), whereas 576 patients (29%) had unchanged or increased SBP. The mean blood pressure at baseline was 171/90 mm Hg and mean difference in SBP from baseline to Day 2 was −12.7 ± 21.9 mm Hg. The group with the largest decline in SBP had significantly higher baseline SBP and DBP, shorter duration of stroke symptoms.
before randomization, and less severe strokes compared with the other groups (Table 1). As expected, a larger proportion of patients received candesartan in this group (257 [54%]; $P = 0.03$). A significantly higher proportion of patients with an increase/no change in SBP were treated with angiotensin-converting enzyme inhibitors at baseline and had received thrombolytic treatment before randomization.

Table 2 shows, for both treatment groups combined, the crude and adjusted OR for early adverse events for the different hemodynamic parameters. Patients with a large decrease in SBP or an increase or no change in SBP had a significantly increased risk of early adverse events both in the crude and in the adjusted analysis. The same was seen in the analysis stratified according to treatment (although the differences were statistically not significant in the stratified analysis), and the impact of adjustment was minimal (Figure 1). In an adjusted sensitivity analysis excluding symptomatic hypotension from the combined end point, the results were comparable (large decrease versus small decrease: OR, 1.30; 95% CI, 0.72–2.35; increase/no change: OR, 1.82; 95% CI, 1.05–3.17; $P = 0.12$). A large decrease in MAP from baseline to Day 2 was associated with an increased risk of early adverse events in the crude analysis but not in the adjusted analysis.

Table 3 shows neurological status at 7 days and functional status at 6 months. The patients with an increase/no change in SBP had significantly worse neurological outcome compared with the other groups, but there was no increased risk in patients with a large decrease in SBP. Patients with an increase/no change in SBP also had smaller improvements in SSS, but the difference did not reach statistical significance ($P = 0.08$). No differences were observed in modified Rankin Scale at 6 months.

We identified a significant association between the highest baseline SBP tertile and early adverse events (Table 2). The probability value, based on an assumption of a linear trend for the effect of baseline SBP tertiles on early adverse events, was 0.03. No differences were observed with regards to DBP or MAP at baseline on the risk of early adverse events.
Figure 2 represents the relation between \( /H_9004\) SBP and early adverse events within each tertile of baseline SBP. In patients with the lowest SBP at baseline, a large drop in SBP was associated with an increased risk of early adverse events (OR, 3.63; 95% CI, 1.09–12.11), but, overall, there was no significant difference between the groups (\( P = 0.20 \)). The same trend was observed in the patients with the highest baseline SBP (OR, 2.25; 95% CI, 0.94–5.38). No differences were seen in the group with moderately elevated SBP at baseline.

Finally, we identified significant predictors of \( /H_9004\) SBP and assessed whether the risk of early adverse events was associated with predicted/expected SBP reduction. The final predictive model is shown in online-only Data Supplement Table 2.

### Table 2. Risk of Early Adverse Events According to Hemodynamic Parameters for Both Treatment Groups Combined

<table>
<thead>
<tr>
<th>Events</th>
<th>All Events</th>
<th>Stroke Recurrence</th>
<th>Stroke Progression</th>
<th>Symptomatic Hypotension</th>
<th>Crude OR</th>
<th>95% CI</th>
<th>( P ) Value</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP difference, baseline to Day 2*</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large decrease</td>
<td>49/477</td>
<td>6</td>
<td>36</td>
<td>7</td>
<td>2.58</td>
<td>1.51–4.41</td>
<td>0.01</td>
<td>2.08</td>
<td>1.19–3.65</td>
<td>0.04</td>
</tr>
<tr>
<td>Moderate decrease</td>
<td>32/474</td>
<td>9</td>
<td>20</td>
<td>3</td>
<td>1.63</td>
<td>0.92–2.89</td>
<td>0.14</td>
<td>1.47</td>
<td>0.82–2.62</td>
<td></td>
</tr>
<tr>
<td>Small decrease (reference)</td>
<td>20/470</td>
<td>3</td>
<td>17</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase/no change</td>
<td>46/576</td>
<td>11</td>
<td>32</td>
<td>3</td>
<td>1.95</td>
<td>1.14–3.35</td>
<td>0.01</td>
<td>1.96</td>
<td>1.13–3.38</td>
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<tr>
<td>MAP difference, baseline to Day 2*</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large decrease</td>
<td>47/467</td>
<td>8</td>
<td>33</td>
<td>6</td>
<td>1.96</td>
<td>1.19–3.24</td>
<td>0.04</td>
<td>1.71</td>
<td>1.02–2.88</td>
<td>0.12</td>
</tr>
<tr>
<td>Moderate decrease</td>
<td>29/458</td>
<td>6</td>
<td>21</td>
<td>2</td>
<td>1.18</td>
<td>0.68–2.06</td>
<td>1.47</td>
<td>1.13</td>
<td>0.64–1.97</td>
<td></td>
</tr>
<tr>
<td>Small decrease (reference)</td>
<td>25/463</td>
<td>5</td>
<td>18</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase/no change</td>
<td>46/609</td>
<td>10</td>
<td>33</td>
<td>3</td>
<td>1.43</td>
<td>0.87–2.37</td>
<td>1.55</td>
<td>0.93</td>
<td>0.93–2.58</td>
<td></td>
</tr>
<tr>
<td>Baseline systolic blood pressure†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertile 1 (140–160.5 mm Hg)</td>
<td>42/681</td>
<td>11</td>
<td>26</td>
<td>5</td>
<td>1</td>
<td></td>
<td></td>
<td>0.04</td>
<td>1</td>
<td>0.05</td>
</tr>
<tr>
<td>Tertile 2 (160.5–177.5 mm Hg)</td>
<td>45/678</td>
<td>7</td>
<td>32</td>
<td>6</td>
<td>1.08</td>
<td>0.70–1.67</td>
<td>1.47</td>
<td>0.82</td>
<td>0.67–1.62</td>
<td></td>
</tr>
<tr>
<td>Tertile 3 (&gt; 177.5 mm Hg)</td>
<td>64/670</td>
<td>11</td>
<td>51</td>
<td>2</td>
<td>1.61</td>
<td>1.07–2.41</td>
<td>1.57</td>
<td>1.04</td>
<td>1.04–2.38</td>
<td></td>
</tr>
<tr>
<td>Baseline diastolic blood pressure†</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Tertile 1 (&lt; 84.5 mm Hg)</td>
<td>47/645</td>
<td>10</td>
<td>33</td>
<td>4</td>
<td>1</td>
<td></td>
<td></td>
<td>0.41</td>
<td>1</td>
<td>0.15</td>
</tr>
<tr>
<td>Tertile 2 (84.5–95.5 mm Hg)</td>
<td>57/666</td>
<td>8</td>
<td>44</td>
<td>5</td>
<td>1.28</td>
<td>0.86–1.92</td>
<td>1.51</td>
<td>1.00</td>
<td>1.00–2.29</td>
<td></td>
</tr>
<tr>
<td>Tertile 3 (&gt; 95.5 mm Hg)</td>
<td>47/671</td>
<td>11</td>
<td>32</td>
<td>4</td>
<td>1.03</td>
<td>0.68–1.57</td>
<td>1.29</td>
<td>0.83</td>
<td>0.83–2.00</td>
<td></td>
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<tr>
<td>Baseline MAP†</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Tertile 1 (&lt; 110.8 mm Hg)</td>
<td>47/675</td>
<td>10</td>
<td>32</td>
<td>5</td>
<td>1</td>
<td></td>
<td></td>
<td>0.57</td>
<td>1</td>
<td>0.34</td>
</tr>
<tr>
<td>Tertile 2 (110.8–122.0 mm Hg)</td>
<td>48/681</td>
<td>9</td>
<td>34</td>
<td>5</td>
<td>1.01</td>
<td>0.67–1.54</td>
<td>1.11</td>
<td>0.73</td>
<td>0.73–1.70</td>
<td></td>
</tr>
<tr>
<td>Tertile 3 (&gt; 122.0 mm Hg)</td>
<td>56/673</td>
<td>10</td>
<td>43</td>
<td>3</td>
<td>1.21</td>
<td>0.81–1.82</td>
<td>1.35</td>
<td>0.89</td>
<td>0.89–2.05</td>
<td></td>
</tr>
</tbody>
</table>

Data represent numbers of patients.

SBP indicates systolic blood pressure; MAP, mean arterial pressure.

*Adjusted for trial treatment, age, diagnosis, stroke severity, time to treatment, and baseline SBP.
†Adjusted for trial treatment, age, diagnosis, stroke severity, and time to treatment.

Figure 1. Adjusted risk of early adverse events according to \( \Delta/\text{SBP} \) in the treatment groups separately and in both groups combined. Risk estimates are ORs with 95% CIs relative to patients with a small decrease in SBP. Adjusted for trial treatment, age, diagnosis, stroke severity, time to treatment, and baseline systolic blood pressure. §Reference group. *\( P = 0.25 \), **\( P = 0.04 \), and ***\( P = 0.40 \). SBP indicates systolic blood pressure.
Table I. Of the 2029 patients included in SCAST, 1947 (96%) had complete data and could be included in the model. A short time to randomization and previous hypertension were both significant predictors of a smaller SBP decline. High SBP and DBP, ischemic stroke, and high SSS score at baseline were significant predictors of a larger SBP decline. Patients predicted to have a large fall in SBP were at highest risk of early adverse events (Table 4). Treatment with candesartan was associated with a nonsignificant increased risk of early adverse events in all subgroups, and in patients predicted to have the largest drop in SBP, the risk increase was nearly significant ($P=0.06$). There was no significant heterogeneity among the 3 groups ($P=0.96$).

Discussion

Although the overall result of SCAST was neutral, there were nonsignificant differences against blood pressure-lowering treatment for both coprimary and all the secondary effect variables. The results of the present analyses support the assumption that these trends were caused by blood pressure-lowering. A large drop in SBP was associated with an increased risk of early adverse events irrespective of whether patients received candesartan or placebo. This association was strongest in the group with the lowest SBP at baseline. When identifying patients at high, moderate, and low risk of a large SBP, we observed that the patients with a high predicted risk of a large SBP also had the highest risk of early adverse events during treatment with candesartan. We found no association between a large drop in SBP and short-term neurological outcome or long-term functional outcome as seen in another study.21

The patients with the highest SBP at baseline in this study had the highest risk of early adverse events. This is consistent with the results of previous studies, which have demonstrated a relationship between SBP in the acute phase of stroke and SSS indicates Scandinavian Stroke Scale; mRS, modified Rankin Scale; IQR, interquartile range.

*Analysis by Kruskal-Wallis test.
†$\Delta$SSS = $[\text{SSS Day 7} - \text{SSS Day 1}] / [\text{SSS maximum} - \text{SSS Day 7}] \times 100$.
‡Analysis by ordinal regression adjusted for trial treatment, age, SSS, systolic blood pressure, and diagnosis at baseline.

![Figure 2](http://stroke.ahajournals.org/DownloadedFromStroke.org)
early adverse events and poor long-term outcome. These results are supported by a recent population-based study, which suggested that optimal outcome in acute stroke is determined both by initial blood pressure levels and also the magnitude of blood pressure change over the first 24 to 48 hours.

In the patients with an increase in SBP, we observed an increased risk of early adverse events. The reason for this association cannot be given from our study, but it is possible that this effect is not caused by the increase in blood pressure per se, but rather that the increase in blood pressure is a marker for other disease, pain, or infection. Patients in this group had lower SSS score at the time of inclusion and received thrombolysis more often than those in the other groups, which might signify that patients in this group had a poorer prognosis at baseline. Alternatively, the persistence of high SBP in this group can be taken as a sign of failure of spontaneous or therapeutic recanalization or complications such as intracranial edema or hemorrhage.

The strength of this study is that we have nearly complete data on a large group of patients with acute stroke and high blood pressure and that we have serial, standardized blood pressure measurements with a validated automated blood pressure monitor. The analyses were planned in advance of the trial, and adjustments were made for a limited number of prespecified variables. The main limitations are that the statistical power is limited for subgroup analyses and that the comparisons are nonrandomized. There is therefore a possibility of confounding effects from variables that were not included in the analyses, and the results must therefore be interpreted with caution. In particular, there is a risk of confounding when combining the patients in the 2 treatment groups. However, the results of the stratified analyses of the individual treatment groups were nearly identical to the result of the analysis of both treatment groups combined, although the differences did not reach statistical significance, probably due to lower numbers.

In conclusion, the present analysis supports the suggestion from SCAST that blood pressure-lowering may be harmful. Large reductions in blood pressure should probably be avoided, and blood pressure-lowering should not be given routinely in the acute phase of stroke. Ongoing randomized controlled trials will show whether benefits can be obtained from other modes of blood pressure reduction or whether there are subgroups of patients that may benefit from such treatment in the acute phase of stroke.

Sources of Funding
The sponsor of the trial was Oslo University Hospital Ullevål. Funding was by grants from the South-Eastern Norway Regional Health Authority and Oslo University Hospital Ullevål. AstraZeneca supplied the study drugs, and AstraZeneca and Takeda supported the trial with limited, unrestricted grants.

Disclosures
P.M.W.B., S.E.K., E.B., and E.C.S. have received payment for lectures; P.M.W.B., S.E.K., and E.B. have received payment for board membership and expenses related to meetings; P.M.W.B. and S.E.K. have accepted support to their institutions for academic trials. All of these activities were unrelated to the submitted work.

References

### Table 4. Association Between Trial Treatment and Early Adverse Events in Subgroups at Predicted Low, Moderate, and High Risk of a Large Decline in Blood Pressure

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Both Groups Combined</th>
<th>Candesartan Group</th>
<th>Placebo Group</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>42/650 (7)</td>
<td>25/323 (8)</td>
<td>17/327 (5)</td>
<td>1.53</td>
<td>0.81–2.89</td>
<td>0.20</td>
<td>0.96</td>
</tr>
<tr>
<td>Moderate</td>
<td>42/648 (7)</td>
<td>25/334 (7)</td>
<td>17/314 (5)</td>
<td>1.43</td>
<td>0.75–2.67</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>61/649 (10)</td>
<td>37/290 (13)</td>
<td>23/289 (8)</td>
<td>1.72</td>
<td>1.00–2.96</td>
<td>0.06</td>
<td></td>
</tr>
</tbody>
</table>

Data represent no. (%).
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Supplemental table 1 Multivariate predictive model of ΔSBP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta</th>
<th>95 % CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to randomization</td>
<td>0.32</td>
<td>0.22 to 0.43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP</td>
<td>-0.40</td>
<td>-0.46 to -0.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP</td>
<td>-0.07</td>
<td>-0.14 to -0.001</td>
<td>0.05</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>-4.53</td>
<td>-7.13 to -1.93</td>
<td>0.001</td>
</tr>
<tr>
<td>SSS score on day 1</td>
<td>-0.18</td>
<td>-0.25 to -0.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.35</td>
<td>0.40 to 4.30</td>
<td>0.02</td>
</tr>
</tbody>
</table>

R square 0.17, Standard error of the Estimate 20.2