Response of Blood Pressure and Blood Glucose to Treatment With Recombinant Tissue-Type Plasminogen Activator in Acute Ischemic Stroke

Evidence From the Virtual International Stroke Trials Archive

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Background and Purpose—Elevations in blood pressure (BP) and blood glucose are common during stroke and may represent a stress response secondary to the acute neurological deficit. If so, they should settle more completely in recombinant tissue-type plasminogen activator (rtPA)-treated patients in association with improved neurological status.

Methods—We performed a controlled comparison of 24-hour declines in BP and glucose in rtPA-treated and control patients from the Virtual Stroke International Stroke Trial Archive (VISTA) database. Twenty-four-hour falls in BP and glucose were compared using multiple regression to account for baseline imbalances. The logarithmic transformation of glucose was used and 24-hour differences expressed as ratios of 24 hours to admission geometric means. Two-way analysis of variance was used to test for interaction between rtPA and early improvement for 24-hour falls in BP and blood glucose.

Results—BP analysis included 5406 patients (rtPA=41%) and glucose analysis 4288 (rtPA=37%). rtPA-treated patients were younger, less likely to have a history of hypertension or diabetes, and had more severe strokes on admission. BP and glucose were lower at baseline in rtPA-treated patients than control subjects. On regression, rtPA predicted significantly greater 24-hour falls in systolic BP (β=3.9; 95% CI, 2.8–5.0), diastolic BP (β=3.1; 95% CI, 2.4–3.9), and glucose (β=0.97; 95% CI, 0.95–0.99). rtPA did not interact with early neurological improvement for 24-hour falls in systolic BP (P=0.72), diastolic BP (P=0.79), or blood glucose (P=0.51).

Conclusions—A stress response does not appear to be the principal cause of elevations in BP and glucose during stroke. (Stroke. 2012;43:00-00.)

Key Words: cerebral infarct ■ hyperglycemia ■ hypertension ■ stroke care ■ thrombolysis

Elevations in blood pressure (BP) and blood glucose are commonly seen in the acute phase of stroke.1–4 Both are transient phenomena, which spontaneously return to premorbid levels over the course of several days.5,6 Such elevations are associated with greater risks of stroke morbidity and mortality1,4,7; however, the benefits of modulating these parameters acutely remain controversial with randomized trial data not demonstrating a clear benefit.2,8 It remains unclear whether these elevations are causally related to poorer outcomes.1,2,8,9

It has been suggested that these elevations may represent a stress response secondary to the acute neurological deficit.3,8,9 Were this to be the case, elevations in BP and blood glucose would settle with reperfusion and improving neurological status. Patients treated with recombinant tissue-type plasminogen activator (rtPA) within 4.5 hours of the onset of symptoms have better functional outcomes than controls10–12 due to clot lysis and reperfusion of the ischemic penumbra. Should elevations in BP and blood glucose settle more completely in rtPA-treated patients than control subjects, in association with improved neurological status, it would lend support to the concept of these elevations being a stress response secondary to the acute neurological deficit. Were elevations in BP and glucose to arise as part of the same underlying stress response, some correlation between the 2 would be expected over the first 24 hours.

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Published work has shown that in rtPA-treated patients, elevations in BP settle more rapidly and completely among those who achieve vessel recanalization as determined by Doppler ultrasound in comparison with those who do not. An analysis of the National Institute of Neurological Disorders and Stroke rtPA stroke study found 24-hour declines in systolic blood pressure (SBP) to be greater in rtPA-treated patients than control subjects. However, analyses of the European Cooperative Acute Stroke Study (ECASS) and ECASS II trials did not show clear differences in BP between rtPA-treated patients and control subjects, and an analysis of the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) did not find any BP difference with reperfusion of the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET).

An analysis of the National Institute of Neurological Disorders and Stroke rtPA stroke study found 24-hour declines in systolic blood pressure (SBP) to be greater in rtPA-treated patients than control subjects. However, analyses of the European Cooperative Acute Stroke Study (ECASS) and ECASS II trials did not show clear differences in BP between rtPA-treated patients and control subjects, and an analysis of the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) did not find any BP difference with reperfusion or recanalization. To our knowledge, no prior studies have investigated the response of blood glucose to treatment with rtPA nor how the response of BP and glucose to rtPA interacts with early neurological status.

**Methods**

We undertook a controlled comparison of 24-hour changes in BP and blood glucose in rtPA-treated patients and untreated control subjects from the Virtual Stroke International Stroke Trial Archive (VISTA) database. The characteristics of this database have been described previously. We recruited patients from trials of putative neuroprotective agents, in many of which approximately 50% of participants concurrently received rtPA as part of normal practice. All included trials received research ethics committee approval and participants gave informed consent. All VISTA data are anonymous.

We included VISTA patients who had admission and 24-hour recordings of BP or blood glucose for whom the use or avoidance of rtPA was documented and for whom information was available on baseline prognostic variables and early neurological status (National Institutes of Health Stroke Scale score at admission and 24 hours). For these patients we also collected data on concomitant antihypertensive and antihyperglycemic therapies. To maximize patient numbers, we created 2 samples, 1 with the required BP measurements and 1 with the required glucose measurements.

Baseline characteristics in rtPA and control groups were compared using the Mann-Whitney U test for continuous variables and Fisher exact test for categorical variables.

Changes in systolic and diastolic blood pressure (DBP) and blood glucose between admission and 24 hours were described by paired t tests. Changes over 24 hours in rtPA and control groups were compared using Student t test. Glucose was not Normally distributed so the logarithmic transformation was used. The comparison between the rtPA and control groups for 24-hour glucose changes was confirmed by a nonparametric Mann-Whitney U test of the untransformed differences in glucose between admission and 24 hours.

Early neurological improvement was defined as an improvement in National Institutes of Health Stroke Scale score of ≥4 points from admission to 24 hours. Twenty-four-hour changes in SBP, DBP, and glucose were grouped by receipt of rtPA and early neurological improvement. Two-way analysis of variance was used to test for interaction between the 2.

Multiple linear regression was used to adjust for baseline imbalances. Variables were retained in the final model if they were statistically significant (P<0.05). The blood glucose analysis was performed after logarithmic transformation. The resulting coefficients were exponentiated to give the proportional changes in the ratio of the geometric mean of glucose at 24 hours to baseline. Standard regression diagnostics were performed to assess assumptions. No significant collinearity was detected between any of the predictor variables.

Spearman rank correlation coefficient was used to investigate correlations between admission National Institutes of Health Stroke Scale score and values of SBP, DBP, and glucose and between 24-hour changes in BP and blood glucose.

Two-way analysis of variance was performed using Minitab 15; all other analyses used PASW 18. A probability value <0.05 was considered significant.

**Results**

**Population**

Our BP analysis included 5406 patients, of whom 2229 (41.2%) received rtPA. Our blood glucose analysis included 4288 patients, of whom 1602 (37.4%) received rtPA. The baseline characteristics of the groups are shown in the Table. In both analyses the groups were imbalanced at baseline with the rtPA group being younger, less likely to have a history of hypertension or diabetes, and having more severe strokes. A detailed breakdown of concomitant antihypertensive medications is available as an online supplement (http://stroke.ahajournals.org).

**Table. Baseline Characteristics of Patients**

<table>
<thead>
<tr>
<th>BP Analysis</th>
<th>Glucose Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=2229</td>
<td>n=1602</td>
</tr>
<tr>
<td>n=3177</td>
<td>n=2686</td>
</tr>
<tr>
<td>Age, y</td>
<td>70 (19) 72 (18)</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>952 (42.7) 1479 (46.6)</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>1566 (70.3) 2416 (76.0)</td>
</tr>
<tr>
<td>History of diabetes (%)</td>
<td>438 (19.7) 794 (25.0)</td>
</tr>
<tr>
<td>History of atrial fibrillation (%)</td>
<td>532 (23.9) 854 (26.9)</td>
</tr>
<tr>
<td>Prior stroke (%)</td>
<td>302 (13.5) 708 (22.3)</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>888 (39.8) 887 (27.9)</td>
</tr>
<tr>
<td>Baseline NIHSS score*</td>
<td>13 (8) 11 (8)</td>
</tr>
<tr>
<td>Concomitant antihypertensive therapies (%)</td>
<td>722 (32.4) 962 (30.3)</td>
</tr>
</tbody>
</table>

*Median (interquartile range).

BP indicates blood pressure; rtPA, recombinant tissue-type plasminogen activator; NIHSS, National Institutes of Health Stroke Scale.

[Image: Table. Baseline Characteristics of Patients]
A total of 4253 patients had complete data on both BP and blood glucose and were used to investigate the correlation between the 2.

**Blood Pressure**

Mean SBP at admission and 24 hours in rtPA and control patients are displayed in Figure 1. Mean SBP was significantly lower in rtPA-treated patients than control subjects on admission, but despite this, mean 24-hour falls in SBP were significantly greater in rtPA-treated patients than control subjects: 11 mm Hg (95% CI, 10–12) and 8.3 mm Hg (95% CI, 7.5–9.2), respectively ($P<0.001$).

Mean DBP at admission and 24 hours in rtPA and control patients is displayed in Figure 2. Mean DBP was significantly lower in rtPA-treated patients than control subjects on admission, but mean 24-hour falls in DBP were significantly greater in rtPA-treated patients than control subjects: 7.3 mm Hg (95% CI, 6.6–8.0) and 5.8 mm Hg (95% CI, 5.2–6.4), respectively ($P<0.001$).

After adjustment for baseline imbalances, rtPA remained a significant predictor of greater 24-hour falls in SBP ($\beta=3.9$; 95% CI, 2.8–5.0; $P<0.001$) and DBP ($\beta=3.1$; 95% CI, 2.4–3.9; $P<0.001$).

Figure 3 shows 24-hour changes in SBP and DBP grouped by receipt of rtPA and achievement of early neurological improvement. Early neurological improvement and receipt of rtPA did not interact for 24-hour changes in SBP ($P=0.716$) or DBP ($P=0.790$).

**Glucose**

The geometric mean of glucose at admission and 24 hours in rtPA and control patients are displayed in Figure 4. The geometric mean of glucose was lower in rtPA-treated patients than control subjects at admission. Despite this, the ratio of the geometric mean at 24 hours to the geometric mean at admission was significantly lower in rtPA-treated patients than control subjects: 0.94 (95% CI, 0.92–0.95) and 0.96 (95% CI, 0.95–0.97), respectively ($P=0.01$). Greater 24-hour glucose falls in the rtPA group was confirmed by a nonparametric Mann-Whitney $U$ test ($P=0.006$).

After adjustment for baseline imbalances, rtPA remained a significant predictor of smaller ratios of the geometric mean at 24 hours to the geometric mean at admission: $\beta=0.97$ (0.95–0.99; $P<0.001$).

Among patients without a history of diabetes, the geometric means of glucose were similar in rtPA-treated patients and control subjects at baseline: 6.5 mmol/L (95% CI, 6.4–6.6) and 6.6 mmol/L (95% CI, 6.5–6.6), respectively ($P=0.173$). Glucose did not change significantly from baseline to 24 hours in control subjects; the geometric mean at 24 hours was
Among rtPA-treated patients, glucose fell to 6.2 mmol/L (95% CI, 6.1–6.3) at 24 hours. The ratio of the geometric mean at 24 hours to the geometric mean at baseline was 0.95 (95% CI, 0.94–0.97), a significantly greater fall than the control group ($P < 0.001$). A Mann-Whitney $U$ test confirmed significant differences in 24-hour changes in glucose between the groups ($P < 0.001$).

Among patients with diabetes, the geometric means of glucose were similar at baseline in the rtPA and control groups: 9.7 mmol/L (95% CI, 9.3–10.2) and 9.9 mmol/L (95% CI, 9.6–10.2), respectively ($P = 0.560$). Twenty-four-hour glucose also did not differ significantly between the rtPA and control groups: 8.5 mmol/L (95% CI, 8.2–8.9) and 8.8 mmol/L (95% CI, 8.6–9.1), respectively ($P = 0.123$). The ratios of the geometric mean at 24 hours to the geometric mean at baseline in the rtPA and control groups were 0.88 (95% CI, 0.84–0.92) and 0.90 (95% CI, 0.87–0.92), respectively, and did not significantly differ ($P = 0.381$).

Figure 3 shows the ratios of the geometric mean of glucose at 24 hours to admission grouped by receipt of rtPA and achievement of early neurological improvement. There was no interaction between the 2 ($P = 0.511$).

**Correlation**

Baseline National Institutes of Health Stroke Scale score showed a statistically significant but minor correlation with baseline SBP ($\rho = -0.049$; $P < 0.001$), DBP ($\rho = -0.114$; $P < 0.001$), and glucose ($\rho = 0.148$; $P < 0.001$). There was no correlation of 24-hour changes in blood glucose with 24-hour changes in SBP ($\rho = 0.009$ $P = 0.563$) or DBP ($\rho = -0.010$ $P = 0.535$).

**Discussion**

**Response to Reperfusion**

In a large and diverse sample, we found acute elevations in BP and blood glucose to settle more completely in rtPA-treated patients than control subjects, confirming an earlier report regarding BP and presenting a new finding for glucose. The differences were small but remained significant after adjusting for baseline imbalances.
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leads to penumbral salvage and improved neurological status. However, 1 study of consecutive rtPA-treated patients found only 56.3%,20 to achieve complete recanalization as recorded by Doppler ultrasound. Consistent with this, in our sample, fewer than half of rtPA-treated patients had early neurological improvement. This may contribute toward the small differences in BP and glucose observed between the groups.

The response of blood glucose to reperfusion is likely to be most evident in patients with “stress” hyperglycemia, which has been defined as acute hyperglycemia with normal HbA1c.21 Prior work has found the course of acute hyperglycemia6 and its relationship with outcomes7 to differ between diabetic and nondiabetic patients. The presence of patients with diabetes will likely have diluted any response to reperfusion observed in nondiabetic patients with acute-onset hyperglycemia. Consistent with this, we found differences in 24-hour glucose changes between rtPA-treated patients and control subjects to be absent in patients with diabetes; however, the differences in power between the analyses of diabetic and nondiabetic patients must be borne in mind. Even among the patients without a recorded history of diabetes, it is likely that many will have had undiagnosed diabetes or prediabetes. One study found 40% of all patients with stroke to have previously undiagnosed diabetes or impaired glucose tolerance.22

The decision to administer rtPA was not randomized and so the groups were highly imbalanced at baseline, reflecting the criteria for receipt of rtPA. The differences in 24-hour falls in BP and glucose remained significant on adjustment for baseline demographic factors and concomitant medications; however, residual confounding factors may remain.

Stress Response

Were treatment with rtPA to cause the greater reductions in BP and glucose observed by resolution of the acute neurological deficit, an interaction between rtPA and early neurological improvement would be expected with the greatest falls in BP and glucose arising in rtPA-treated patients with early neurological improvement; and among control subjects, greater falls being observed in patients with neurological improvement (who may have spontaneously reperfused). This was not found to be the case. BP and glucose were lower in the rtPA than control group at admission despite baseline stroke severity being greater in the rtPA group; as expected from this, there was negligible correlation between admission National Institutes of Health Stroke Scale score and admission BP and glucose. In this light, it is unlikely that acute elevations in BP and glucose after stroke arise secondary to the neurological deficit nor that the greater 24-hour declines in BP and glucose seen in rtPA-treated patients were due to rtPA leading to resolution of the acute neurological deficit. Moreover, were both elevations in BP and blood glucose to arise from the same underlying stress response, some correlation between the 2 would be expected, which was not found to be the case.

We hypothesized that if the elevations in BP and glucose observed in the acute phase of stroke to arise as a stress response secondary to the acute neurological deficit, they should settle more completely in patients treated with rtPA in

Our BP results are consistent with earlier work in this area, which has shown acute BP elevations to settle more rapidly and completely among rtPA-treated patients who achieve recanalization.13,14 They also confirm an earlier finding that rtPA-treated patients see greater falls in SBP than control subjects.15

We reported smaller differences than those reported in early work, likely reflecting methodological differences. Work by Delgado-Mederos et al14 suggests that the difference in SBP between recanalized and nonrecanalized patients peaks at approximately 12 hours after treatment with rtPA and subsequently narrows. Our study was limited to 2 measurements of BP and so possibly missed the period of greatest differences. Silver et al’s analysis of the National Institute of Neurological Disorders and Stroke rtPA stroke study15 reported the median largest reduction in SBP from baseline at any point during the first 24 hours to be 35 mm Hg in rtPA-treated patients and 30 mm Hg in control subjects. In our study, it is likely that larger differences in blood pressure were present before 24 hours and so the magnitude of the effect is underestimated by our study. It is not known how the temporal profile of blood glucose varies with reperfusion, but this weakness may also have masked larger glucose differences.

We were interested in the relationship of rtPA to elevations in BP and glucose because rtPA promotes reperfusion and so

Figure 4. Geometric means of glucose at admission and 24 hours in rtPA and control patients are shown on a zeroed (A) and enlarged scale (B). B shows 95% CIs and probability values from independent sample t test. rtPA indicates recombinant tissue-type plasminogen activator.
association with improved neurological status. Although a response to treatment with rtPA was observed, the lack of association with improved neurological status does not support our hypothesis. The response to treatment with rtPA need not be due to resolution of the acute neurological deficit; treatment may affect BP and glucose by the reperfusion of specific autonomic centers involved in their control,\textsuperscript{21} the prevention of the Cushing reflex, or reduction of cerebral inflammation.

**Conclusions**

Elevations in BP and blood glucose settled more completely in rtPA-treated patients in comparison to untreated control subjects but the differences were small. The response of elevations in BP and glucose to rtPA exposure does not appear to be explained by the resolution of the neurological deficit. Although the contribution of a stress response secondary to the acute neurological deficit cannot be excluded, our data do not support this as being the principal mechanism by which acute cerebral ischemia leads to elevations in BP and glucose.

**Appendix**


**Disclosures**

R.L.F. is supported by studentships from Wyeth/Pfizer and Johnson and Johnson. P.M.W.B. is Stroke Association Professor of Stroke Medicine and a member of the VISTA Executive Committee. K.R.L. is Associate Director of the National Institute of Health Research Stroke Research Network and chaired the independent data monitoring committee for the ECASS III trial, chairs the VISTA collaboration, and serves of the Steering Committee for the Safe Implementation of Thrombolysis (SITS) collaboration. He has received fees and expenses from Boehringer Ingelheim for committee work and lectures.

**References**

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Supplemental Material

Additional Information on Concomitant Anti-Hypertensive Medications
S1

Supplementary Table 1 shows a breakdown of the classes of anti-hypertensive drugs received by patients in each group. p-values are derived from Fisher’s Exact Test.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>r-tPA (n=2229)</th>
<th>Control (n= 3177)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-Inhibitors/ Angiotensin Receptor Blockers (%)</td>
<td>225 (10.1)</td>
<td>411 (13.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Alpha Blockers (%)</td>
<td>2 (0.09)</td>
<td>4 (0.13)</td>
<td>0.518</td>
</tr>
<tr>
<td>Beta Blockers (%)</td>
<td>346 (15.6)</td>
<td>219 (6.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dihydropyridine Calcium Channel Blockers (%)</td>
<td>48 (2.2)</td>
<td>77 (2.4)</td>
<td>0.522</td>
</tr>
<tr>
<td>Verapamil (%)</td>
<td>12 (0.54)</td>
<td>20 (0.63)</td>
<td>0.722</td>
</tr>
<tr>
<td>Diltiazem (%)</td>
<td>21 (0.94)</td>
<td>38 (1.2)</td>
<td>0.426</td>
</tr>
<tr>
<td>Furosemide (%)</td>
<td>100 (4.5)</td>
<td>242 (7.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thiazides (%)</td>
<td>33 (1.5)</td>
<td>69 (2.2)</td>
<td>0.068</td>
</tr>
<tr>
<td>Potassium Sparing Diuretics (%)</td>
<td>3 (0.13)</td>
<td>25 (0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vasodilators (%)</td>
<td>144 (6.5)</td>
<td>129 (4.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sympatholytics (%)</td>
<td>20 (0.89)</td>
<td>58 (1.8)</td>
<td>0.005</td>
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S2

Supplementary table 2 shows the r-tPA regression coefficient for 24 hour changes in systolic and diastolic blood pressure adjusted for all drug classes, and only for those imbalanced at baseline.

<table>
<thead>
<tr>
<th></th>
<th>Regression Coefficient</th>
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<tr>
<td>Systolic Blood Pressure</td>
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<td></td>
</tr>
<tr>
<td>Adjusted for all drug classes</td>
<td>3.8 (2.7- 4.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for drug classes imbalanced at baseline</td>
<td>3.8 (2.6- 4.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for all drug classes</td>
<td>2.8 (2.1- 3.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for drug classes imbalanced at baseline</td>
<td>2.9 (2.2- 3.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Supplementary table 3 shows a breakdown of the number of anti-hypertensive drugs received by patients in each group. Using a $X^2$ test there was no significant association between the number of drugs received and receipt of r-tPA ($p=0.137$)

<table>
<thead>
<tr>
<th>Number of Anti-Hypertensive Drugs</th>
<th>r-tPA (n= 2229)</th>
<th>Control (n= 3177)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1507</td>
<td>2215</td>
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<tr>
<td>1</td>
<td>497</td>
<td>639</td>
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<td>2</td>
<td>166</td>
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<tr>
<td>3</td>
<td>40</td>
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<tr>
<td>4</td>
<td>16</td>
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<tr>
<td>5</td>
<td>3</td>
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<td>6</td>
<td>0</td>
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</tr>
<tr>
<td>7</td>
<td>0</td>
<td>1</td>
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</tbody>
</table>

Supplementary table 4 shows the r-tPA regression coefficients for 24 hour changes in systolic and diastolic blood pressure adjusted for the number of anti-hypertensive drugs received.

<table>
<thead>
<tr>
<th></th>
<th>Regression Coefficient</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic Blood Pressure</td>
<td>3.8 (2.7 - 5.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>3.0 (2.3 - 3.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>