Effect of Blood Pressure Lowering in Early Ischemic Stroke
Meta-Analysis

Meng Lee, MD; Bruce Ovbiagele, MD, MS; Keun-Sik Hong, MD; Yi-Ling Wu, MS; Jing-Er Lee, MD, PhD; Neal M. Rao, MD; Wayne Feng, MD; Jeffrey L. Saver, MD

Background and Purpose—Elevated blood pressure is common in acute stage of ischemic stroke and the strategy to manage this situation is not well established. We therefore conducted a meta-analysis of randomized controlled trials comparing active blood pressure lowering and control groups in early ischemic stroke.

Methods—Pubmed, EMBASE, and Clinicaltrials.gov from January 1966 to March 2015 were searched to identify relevant studies. We included randomized controlled trials with blood pressure lowering started versus control within 3 days of ischemic stroke onset. The primary outcome was unfavorable outcome at 3 months or at trial end point, defined as dependency or death, and the key secondary outcome was recurrent vascular events. Pooled relative risks and 95% confidence intervals were calculated using random-effects model.

Results—The systematic search identified 13 randomized controlled trials with 12,703 participants comparing early blood pressure lowering and control. Pooling the results with the random-effects model showed that blood pressure lowering in early ischemic stroke did not affect the risk of death or dependency at 3 months or at trial end point (relative risk, 1.04; 95% confidence interval, 0.96–1.13; P=0.35). Also, blood pressure lowering also had neutral effect on recurrent vascular events, as well as on disability or death, all-cause mortality, recurrent stroke, and serious adverse events.

Conclusions—This meta-analysis suggested blood pressure lowering in early ischemic stroke had a neutral effect on the prevention of death or dependency. (Stroke. 2015;46:1883-1889. DOI: 10.1161/STROKEAHA.115.009552.)

Key Words: blood pressure ■ infarction ■ meta-analysis ■ stroke

Elevated blood pressure is common in acute stage of ischemic stroke, occurring in two thirds to three quarters of patients.1,2 The early hypertension that follows ischemic stroke often reflects undiagnosed or undertreated hypertension as well as neuroendocrine response to physiological stress.3 Many patients have spontaneous declines in blood pressure during the first 24 hours after onset of stroke.4 The best strategy to manage this early elevation of blood pressure in patients with ischemic stroke is not well established.4 On one hand, blood pressure lowering may reduce cerebral edema, deter hemorrhagic transformation of the cerebral infarction, and accelerate the transition to long-term antihypertensive therapy. However, early blood pressure lowering may reduce collateral flow through arteries that have lost autoregulatory function because of ischemia and increase the size of the cerebral infarction.3

Accordingly, randomized controlled trials (RCTs) are needed to clarify optimum blood pressure management regimens in early ischemic stroke. A systematic review and meta-analysis through 2008 identified 12 small RCTs, which included a total of only 1153 patients with stroke, and concluded there was insufficient evidence to assess the effect of blood pressure lowering on functional outcome or death.5 However, this meta-analysis included both ischemic and hemorrhagic stroke trials and several trials enrolled patients after 3 days of stroke onset. Several large trials have been published in the interval since the most recent meta-analysis6 and offer more evidence on this issue. We therefore conducted a systematic review and meta-analysis of RCTs comparing active blood pressure lowering and control groups in early ischemic stroke to date.

Methods

This study was performed in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis: The PRISMA Statement.6

Data Sources and Searches

We systematically searched PubMed, EMBASE, and the clinical trial registry maintained at Clinicaltrials.gov from 1966 to March 10, 2015.
using the following search terms: stroke or cerebrovascular disease or cerebrovascular attack or cerebral ischemia or brain infarct or transient ischemic attack AND antihypertensive therapy or blood pressure lowering or blood pressure reduction or thiazide or β-antagonists or α-antagonist or angiotensin-converting enzyme inhibitors or angiotensin antagonists or angiotensin inhibitors or calcium channel blockers AND acute or early or immediate or rapid. We restricted our search to human beings and clinical trials. There were no language restrictions. We also reviewed the introduction and discussion sections of retrieved trials and prior meta-analysis to identify additional trials. Some data not provided by original articles but published in the latest Cochrane Review were also used.

Study Selection
The cutoff of 3 days for blood pressure lowering intervention to be considered started in the early time period was chosen pragmatically. In the absence of a universally accepted threshold, this threshold was considered physiologically reasonable and had been previously used in an analysis of a subgroup of a large clinical trial, The Prevention Regimen for Effectively Avoiding Second Stroke (PRoFESS). Also, studies were selected when they met the following entry criteria: (1) studies were RCTs; (2) all participants in the study or in a separately reported subgroup were patients with ischemic stroke confirmed by brain computed tomography or magnetic resonance imaging; (3) the active treatment consisted of blood pressure lowering intervention. We included trials in which baseline antihypertensive were stopped in the control arm, whereas the intervention arm consisted of a trial-specific regimen (eg, The Scandinavian Candesartan Acute Stroke Trial [SCAST], China Antihypertensive Trial in Acute Ischemic Stroke [CATIS]) or continuing the patients baseline blood pressure lowering therapy (Continue Or Stop post-Stroke Antihypertensive Collaborative Study [COSSACS]). We also included trials in which baseline antihypertensive were continued as background therapy in both arms and an additional blood pressure regimen added to the intervention arm. (4) Reported outcome included dependency or death (modified Rankin Scale, 3–6 or nearest equivalent) if measured. The key secondary outcome was recurrent vascular events at 3 months or at trial end point. Additional outcomes of interest were disability or death (modified Rankin Scale, 2–6), death from any cause, and recurrent stroke at 3 or 6 months. We also looked at death or dependency, death or disability, all-cause mortality, and serious adverse events at 2 weeks or 1 month.

Data were analyzed according to the intention-to-treat principle. A random-effect estimate based on the Mantel–Haenszel method was computed when ≥2 studies provided sufficient data for a given outcome. Statistical heterogeneity was assessed using a χ² and the I² statistics. Study-level estimates were considered heterogeneous if either the χ² test was significant at the P=0.10 level or the I² statistic was >50%. Publication bias was assessed by visual examination of funnel plots. The Cochrane Collaboration’s Review Manager Software Package (RevMen 5.2) was used for this meta-analysis.

Results
Of the 51 RCTs retrieved for detailed assessment, 38 were excluded for the following reasons: trials of intracranial hemorrhage—2; trials of neuroprotective drugs—2; end point different than specified in meta-analysis plan—25; and patients not enrolled within 3 days of stroke onset—8. One trial, Paramedic Initiated Lisinopril For Acute Stroke Treatment (PIL-FAST; 64% were ischemic stroke patients), was further excluded because a results in patients with ischemic stroke were not reported separately from those with intracranial hemorrhage or stroke-mimicking conditions (Figure 1). Our final analysis included 13 RCTs comprising 12 703 individuals, with 6392 (50%) participants randomly assigned.

Study Quality Assessment
Jadad score was used to assess study quality because all included studies were RCTs. This 5-point scoring system evaluates the randomization process (2 questions), blinding (2 questions), and the description of withdrawals and dropouts (1 question).

Statistical Analysis
The primary outcome was unfavorable outcome at 3 months or at trial end point, defined as dependency or death (modified Rankin Scale, 3–6 or nearest equivalent) if measured. The key secondary outcome was recurrent vascular events at 3 months or at trial end point. Additional outcomes of interest were disability or death (modified Rankin Scale, 2–6), death from any cause, and recurrent stroke at 3 or 6 months. We also looked at death or dependency, death or disability, all-cause mortality, and serious adverse events at 2 weeks or 1 month.

Data were analyzed according to the intention-to-treat principle. A random-effect estimate based on the Mantel–Haenszel method was computed when ≥2 studies provided sufficient data for a given outcome. Statistical heterogeneity was assessed using a χ² and the I² statistics. Study-level estimates were considered heterogeneous if either the χ² test was significant at the P=0.10 level or the I² statistic was >50%. Publication bias was assessed by visual examination of funnel plots. The Cochrane Collaboration’s Review Manager Software Package (RevMen 5.2) was used for this meta-analysis.

Results
Of the 51 RCTs retrieved for detailed assessment, 38 were excluded for the following reasons: trials of intracranial hemorrhage—2; trials of neuroprotective drugs—2; end point different than specified in meta-analysis plan—25; and patients not enrolled within 3 days of stroke onset—8. One trial, Paramedic Initiated Lisinopril For Acute Stroke Treatment (PIL-FAST; 64% were ischemic stroke patients), was further excluded because a results in patients with ischemic stroke were not reported separately from those with intracranial hemorrhage or stroke-mimicking conditions (Figure 1). Our final analysis included 13 RCTs comprising 12 703 individuals, with 6392 (50%) participants randomly assigned.
<table>
<thead>
<tr>
<th>Trial, Publication Year, Country</th>
<th>Population</th>
<th>Characteristics of Included Trials</th>
<th>Median or Mean Time From Stroke Onset to Randomization, h</th>
<th>Sample Size (% men)</th>
<th>Percentage of Patients Receiving Thrombolytic Therapy</th>
<th>Mean Age, y</th>
<th>Percentage Taking Antihypertensive Medication at Baseline</th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCESS, 2003, Germany</td>
<td>Ischemic stroke with a motor deficit, SBP ≥200 mm Hg and DBP ≥110 mm Hg, within 36 h of admission</td>
<td>All patients</td>
<td>30</td>
<td>339 (51)</td>
<td>NA</td>
<td>68</td>
<td>NA</td>
<td>Candesartan for 7 d</td>
<td>Placebo for 7 d</td>
</tr>
<tr>
<td>CATIS, 2014, China</td>
<td>Ischemic stroke within 48 h of symptom onset, SBP between 140 and 220 mm Hg</td>
<td>All patients</td>
<td>15</td>
<td>4071 (64)</td>
<td>0</td>
<td>62</td>
<td>49</td>
<td>Antihypertensive treatment during hospitalization</td>
<td>No antihypertensive treatment during hospitalization; placebo not used</td>
</tr>
<tr>
<td>CHHIPS, 2009, United Kingdom</td>
<td>Ischemic stroke within 36 h of symptom onset, SBP &gt;160 mm Hg</td>
<td>NA</td>
<td>99</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>Labetalol or lisinopril for 14 d</td>
<td>Placebo for 14 d</td>
<td></td>
</tr>
<tr>
<td>COSSACS, 2010, United Kingdom</td>
<td>Cerebral infarction with within 48 h</td>
<td>Subgroup of patients in whom ischemic stroke was confirmed on CT scan</td>
<td>NA</td>
<td>444</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>Continue pre-existing antihypertensive drugs for 2 wk</td>
<td>Stop pre-existing antihypertensive drugs for 2 wk</td>
</tr>
<tr>
<td>ENOS, 2015, multiple countries</td>
<td>Ischemic stroke within 48 h of onset, SBP between 140 and 220 mm Hg</td>
<td>Ischemic stroke subgroup</td>
<td>NA</td>
<td>3348</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Transdermal GTN for 7 d</td>
<td>No transdermal GTN</td>
</tr>
<tr>
<td>Eveson et al, 2007, United Kingdom</td>
<td>Ischemic stroke within the previous 24 h with SBP &gt;140 or DBP &gt;90</td>
<td>All patients</td>
<td>19</td>
<td>40 (63)</td>
<td>NA</td>
<td>74</td>
<td>60</td>
<td>Lisinopril for 14 d</td>
<td>Placebo for 14 d</td>
</tr>
<tr>
<td>INWEST, 2000, West European countries</td>
<td>Ischemic stroke within 24 h in the carotid artery territory</td>
<td>All patients</td>
<td>11</td>
<td>265 (47)</td>
<td>NA</td>
<td>72</td>
<td>NA</td>
<td>Nimodipine for 21 d</td>
<td>Placebo for 21 d</td>
</tr>
<tr>
<td>Kaste et al, 1994, Finland</td>
<td>Ischemic hemispheric stroke and admitted within 48 h of stroke onset</td>
<td>All patients</td>
<td>20</td>
<td>350(67)</td>
<td>NA</td>
<td>57</td>
<td>NA</td>
<td>Nimodipine for 21 d</td>
<td>Placebo for 21 d</td>
</tr>
<tr>
<td>PROFESS, 2009, Multiple countries</td>
<td>Ischemic stroke within 72 h of stroke onset, SBP 121 to 180 mm Hg</td>
<td>Acute subgroup (within 72 h of onset)</td>
<td>58</td>
<td>1360(65)</td>
<td>NA</td>
<td>67</td>
<td>96</td>
<td>Telmisartan for 90 d</td>
<td>Placebo for 90 d</td>
</tr>
<tr>
<td>RIGHT, 2013, United Kingdom</td>
<td>Acute stroke within 4 h with SBP ≥140 mm Hg</td>
<td>Ischemic stroke subgroup</td>
<td>NA</td>
<td>27</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Transdermal GTN patch for 7 d</td>
<td>No transdermal GTN patch</td>
</tr>
<tr>
<td>SCAST, 2011, North European countries</td>
<td>Ischemic stroke within 30 h of symptom onset with SBP ≥140 mm Hg</td>
<td>Ischemic stroke subgroup</td>
<td>NA</td>
<td>1733</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Candesartan for 7 d</td>
<td>Placebo for 7 d</td>
</tr>
<tr>
<td>VENTURE, 2015, South Korea</td>
<td>Ischemic stroke within 24 h from onset with SBP 150–185 mm Hg</td>
<td>All patients</td>
<td>NA</td>
<td>372</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>Valsartan for 7 d</td>
<td>No antihypertensive treatment during the treatment period</td>
</tr>
<tr>
<td>VENUS, 2001, The Netherlands</td>
<td>Ischemic stroke within 6 h and hemiparesis, SBP between 130 and 220 mm Hg</td>
<td>Ischemic stroke subgroup</td>
<td>NA</td>
<td>261</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Nimodipine for 10 d</td>
<td>Placebo for 10 d</td>
</tr>
</tbody>
</table>

ACCESS indicates Acute Candesartan Cilexetil Therapy in Stroke Survivors; CATIS, China Antihypertensive Trial in Acute Ischemic Stroke; CHHIPS, Controlling Hypertension and Hypotension Immediately Post Stroke; COSSACS, Continue or Stop Post-Stroke Antihypertensives Collaborative Study; CT, computed tomography; DBP, diastolic blood pressure; ENOS, Efficacy of Nitric Oxide in Stroke; GTN, glyceryl trinitrate; INWEST, Intravenous Nimodipine West European Stroke Trial; NA, not available; PROFESS, The Prevention Regimen for Effectively Avoiding Second Stroke; RIGHT, Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial; SBP, systolic blood pressure; SCAST, The Scandinavian Candesartan Acute Stroke Trial; VENTURE, Valsartan Efficacy on Modest Blood Pressure Reduction in Acute Ischemic Stroke; and VENUS, The Very Early Nimodipine Use in Stroke.
to the active treatment group and 6311 (50%) to the control group. The study design, quality, and baseline characteristics of these RCTs are shown in Tables 1 and 2. Most trials were conducted in Europe, whereas 1 large trial was from China. Analyzed data were abstracted from whole trials that enrolled only patients with ischemic stroke (6 trials),10,14–17,19 separately reported subgroups of patients with ischemic stroke (6 trials),9,11,18,20–22 and a separately reported subgroup of patients with ischemic stroke enrolled within 72 hours (1 trial).8 The median time from stroke onset to randomization ranged from 11 to 58 hours. The magnitude of lowering of blood pressure in active treatment groups, when compared with control groups, was reported in 7 trials at day 7 or day 14, ranged from −3.5 to 20 mm Hg for systolic blood pressure and 0 to 9 mm Hg for diastolic blood pressure. Among 13 trials, 12 reported outcome for the primary end point analysis (ie, death or dependency) and 6 reported outcome for the key secondary end point (ie, recurrent vascular events) analysis. The overall quality of trials was good (Jadad score, median 4 points, ranged from 3–5).

Pooling the results from 12 trials with the random-effects model showed that blood pressure lowering in early ischemic stroke did not affect the risk of death or dependency at 3 months or at trial end point (relative risk, 1.04; 95% confidence interval, 0.96–1.13; P=0.35). There was significant heterogeneity among studies (I²=51%; P for heterogeneity=0.02; Figure 2). The funnel plots showed no major asymmetry (Figure 3).

### Table 2. Characteristics of Included Trials

<table>
<thead>
<tr>
<th>Trial, Publication Year, Country</th>
<th>Baseline NIHSS Score</th>
<th>Baseline SBP/DBP, mm Hg</th>
<th>SBP/DBP Difference at Randomization, mm Hg (Control–Active)</th>
<th>SBP/DBP Difference at 24 h After Randomization, mm Hg (Control–Active)</th>
<th>SBP/DBP Difference at 14 d After Randomization, mm Hg (Control–Active)</th>
<th>Outcome Assessment</th>
<th>Jadad Score, 5-Point Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCESS,14 2003, Germany</td>
<td>NA</td>
<td>Active: 188/99 Control: 190/99</td>
<td>2.7/1.8 Day 7: 4.5/2.7</td>
<td>Vascular events and mortality at 12 mo; BI comparison at 3 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CATIS,16 2014, China</td>
<td>Active: 4 Control: 4</td>
<td>Active: 166/96 Control: 165/96</td>
<td>8.1/3.8 8.6/3.9</td>
<td>mRS at 14 d (or discharge if earlier than 14 d) and 3 mo; vascular events, recurrent stroke, and death at 3 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHHIPS,20 2009, United Kingdom</td>
<td>NA</td>
<td>NA NA NA NA</td>
<td>mRS&gt;3 at 2 wk</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COSSACS,11 2010, United Kingdom</td>
<td>NA</td>
<td>NA NA NA NA</td>
<td>Dead or dependent (mRS&gt;3) at 2 wk</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENOS,22 2015, Multiple countries</td>
<td>NA</td>
<td>Active: 158/83 Control: 162/86</td>
<td>NA NA</td>
<td>mRS &gt; 2 at 90 d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eveson et al,15, 2007, United Kingdom</td>
<td>Active: 13 Control: 10</td>
<td>Active: 174/91 Control: 170/94</td>
<td>NA 20/9</td>
<td>mRS at 3 mo, death, cardiovascular events, SAE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INWEST,18 2000, West European countries</td>
<td>NA</td>
<td>Active: 160/89 Control: 160/89</td>
<td>4.4/9.4 -3.5/0</td>
<td>Death or dependency (BI &lt; 60) at day 21, death on day 21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaste et al,17 1994, Finland</td>
<td>NA</td>
<td>Active: 156/92 Control: 155/93</td>
<td>1.9/4.9 Day 7: 6.3/2.9</td>
<td>mRS at 3 and 12 mo, death at 12 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROFESS,82009, Multiple countries</td>
<td>Active: 3 Control: 3</td>
<td>Active: 146/84 Control: 147/84</td>
<td>NA Day 7: 6.1/3.2</td>
<td>mRS at 30 d, death at 90 d; stroke recurrence, combined vascular, SAE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIGHT,21 2013, United Kingdom</td>
<td>NA</td>
<td>NA NA NA NA</td>
<td>mRS at 90 d, death and early neurological deterioration at 7 d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCAST,7 2011, North European countries</td>
<td>NA</td>
<td>NA NA NA NA</td>
<td>mRS&gt;2 at 6 mo, vascular events at 6 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VENTURE,19 2015, South Korea</td>
<td>NA</td>
<td>Active: 162/ 90 Control: 163/ 91</td>
<td>0.3/1.8 7: 1.9/1.7</td>
<td>mRS&gt;3 at 90 d, early neurological deterioration at 7 d, vascular events, death, and BI comparison at 90 d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VENUS,5, 2001, The Netherlands</td>
<td>NA</td>
<td>No significant difference</td>
<td>NA mRS&gt;3 at 3 mo, death at 10 d</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
For additional outcomes, blood pressure lowering also had neutral effect on recurrent vascular events, as well as on disability or death, all-cause mortality, recurrent stroke, and serious adverse events (Table 3).

Discussion

The current meta-analysis, which pooled data from all relevant trials with amalgamable outcome assessment, suggested that blood pressure lowering in early ischemic stroke did not affect the risk of death or dependency at 3 months. Also, the risks of recurrent vascular events, recurrent stroke, death, and serious adverse events were not different between active treatment and control groups. Hypertension is an important modifiable factor in the prevention of recurrent stroke, and these results suggest that the introduction of therapy in the subacute phase is not associated with harm.

The median time to initiation of blood pressure lowering was not earlier than 15 hours of stroke onset, and the duration of active treatment was within 2 weeks among most included trials. When blood pressure remained untreated during the first 2 weeks, the frequency of recurrent stroke was low at 3 to 6 months, affording little opportunity for active blood pressure reduction to improve outcome. Conversely, when blood pressure was actively treated in the subacute time period, there apparently was little risk of infarct extension and neurological deterioration because of failure of collateral circulation. It is likely that the fate of the threatened penumbra has mostly been determined by 10 hours after onset.

These findings in patients with ischemic stroke contrast with those in intracerebral hemorrhage. A recent large trial, the second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2), found a trend of benefit in reducing death or disability with early blood pressure lowering in intracranial hemorrhage. Several pathophysiologic differences between ischemic and hemorrhagic brain injury may contribute to this distinction. Early after intracerebral hemorrhage onset, systolic blood pressure is substantially elevated compared with usual premorbid levels, whereas systolic blood pressure after major ischemic stroke is much closer to the long-term premorbid level, and treating the lesser deviation from baseline levels may have reduced physiological effects. In intracerebral hemorrhage, early hematoma expansion may be a physiological target more susceptible to alteration by blood pressure moderation than any of the mechanisms of early worsening in ischemic stroke.

Because most patients were not enrolled earlier than 15 hours of stroke onset, an important remaining unanswered question in blood pressure management in ischemic stroke involves the hyperacute period, within the first few hours after onset, when there is still substantial penumbral, at-risk tissue. Although The Field Administration of Stroke Therapy–Magnesium (FAST-MAG) trial enrolled stroke patients within 2 hours of stroke onset and blood pressure lowering effect of magnesium may exist, yet this was a neuroprotective trial, so we chose to exclude this trial.

Full data sets from forthcoming trials, such as Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED), may help to resolve this remaining issue.

Some limitations of our study need to be mentioned. First, meta-analyses may be biased when the literature search fails to identify all relevant trials or the selection criteria for including a trial are applied in a subjective manner. To minimize these risks, we performed thorough searches across multiple literature databases and used explicit criteria for study selection, data abstraction, and data analysis. Second, because this is a study-level
Secondary outcomes

None.

Discussion

We are grateful to Professor Philip Bath for providing data of ischemic stroke subset in Efficacy of Nitric Oxide in Stroke trial.

Acknowledgments

We are grateful to Professor Philip Bath for providing data of ischemic stroke subset in Efficacy of Nitric Oxide in Stroke trial.

Sources of Funding

This work was supported by grants from Ministry of Science and Technology Taiwan (NSC 102-2628-B-182-012 and MOST103-2314-B-182-056). The sponsors played no role in the study design, data collection, and analysis, or decision to submit the article for publication.

Disclosures

None.

References


Effect of Blood Pressure Lowering in Early Ischemic Stroke: Meta-Analysis
Meng Lee, Bruce Ovbiagele, Keun-Sik Hong, Yi-Ling Wu, Jing-Er Lee, Neal M. Rao, Wayne Feng and Jeffrey L. Saver

Stroke. 2015;46:1883-1889; originally published online May 28, 2015;
doi: 10.1161/STROKEAHA.115.009552
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/46/7/1883

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/04/07/STROKEAHA.115.009552.DC1
http://stroke.ahajournals.org/content/suppl/2016/04/07/STROKEAHA.115.009552.DC2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
虚血性脳卒中早期における血圧低下的効果

メタ解析

Effect of Blood Pressure Lowering in Early Ischemic Stroke

Meta-Analysis

Meng Lee, MD; Bruce Ovbiagele, MD, MS; Keun-Sik Hong, MD, et al.

1Department of Neurology, Chang Gung University College of Medicine, Chang Gung Memorial Hospital, Chiayi, Taiwan; 2Department of Neurosciences, Medical University of South Carolina, Charleston; and 3Department of Neurology, Ilan Paik Hospital, Inje University, Goyang, South Korea.

背景および目的：虚血性脳卒中の急性期では血圧が上昇することが多いが、この血圧上昇を管理する戦略は十分に確立されていない。したがって、我々は虚血性脳卒中に早期に経験的に降圧療法を行った群と行わなかった対照群を比較した無作為化比較試験のメタ解析を行った。

方法：1966年1月～2015年3月までのPubMed、EMBASE、およびClinicaltrials.govを検索して該当する研究を同定し、虚血性脳卒中発症後3日以内に降圧療法を開始した群と対照群を比較した無作為化比較試験を選択した。主要評価項目は3カ月目もしくは試験終了時に要介護もしくは死亡で定義された転帰不良とし、副次評価項目は血管イベントの再発とした。無作為効果モデルを用いて統合相対リスクおよび95%信頼区間（CI）を算出した。

結果：系統的調査により、早期降圧治療群と対照群を比較した13件の無作為化比較試験（被験者12,703例）を特定した。無作為効果モデルの結果を統合したところ、早期に虚血性脳卒中患者の血圧を低下させても、3カ月目または試験終了時の死亡もしくは要介護のリスクに影響がないことが明らかになった（相対リスク = 1.04, 95% CI: 0.96～1.13, P = 0.35）。また、降圧療法は血管イベントの再発に対してだけではなく、障害または死亡、総死亡率、脳卒中再発、重篤な有害事象に関しても中立的な効果を示した。

結論：本メタ解析によって、虚血性脳卒中患者の早期降圧治療は死亡もしくは要介護の予防に関して中立的な効果を示すことが示唆された。

Stroke 2015; 46: 1883-1889. DOI: 10.1161/STROKEAHA.115.009552.

<table>
<thead>
<tr>
<th>試験群もしくはサブグループ</th>
<th>降圧治療群</th>
<th>対照群</th>
<th>集計</th>
<th>集計</th>
<th>リスク比</th>
<th>集計</th>
<th>リスク比</th>
</tr>
</thead>
<tbody>
<tr>
<td>イベント</td>
<td>合計</td>
<td>イベント</td>
<td>合計</td>
<td>重み付け</td>
<td>M→H</td>
<td>無作為</td>
<td>95% CI</td>
</tr>
<tr>
<td>CATIS19</td>
<td>500</td>
<td>1,988</td>
<td>502</td>
<td>1,987</td>
<td>16.5%</td>
<td>1.00 [0.89, 1.11]</td>
<td>1.27 [0.90, 1.79]</td>
</tr>
<tr>
<td>CHIPS20</td>
<td>44</td>
<td>64</td>
<td>19</td>
<td>35</td>
<td>4.6%</td>
<td>0.70 [0.50, 0.99]</td>
<td>0.98 [0.93, 1.03]</td>
</tr>
<tr>
<td>COSSAC11</td>
<td>46</td>
<td>241</td>
<td>55</td>
<td>203</td>
<td>4.7%</td>
<td>1.07 [0.48, 2.38]</td>
<td>1.23 [1.05, 1.44]</td>
</tr>
<tr>
<td>ENOS22</td>
<td>985</td>
<td>1,664</td>
<td>1,015</td>
<td>1,678</td>
<td>20.6%</td>
<td>1.07 [0.88, 1.31]</td>
<td>1.13 [0.88, 1.46]</td>
</tr>
<tr>
<td>Eveson515</td>
<td>7</td>
<td>18</td>
<td>8</td>
<td>22</td>
<td>1.0%</td>
<td>0.55 [0.33, 0.93]</td>
<td>0.91 [0.54, 1.54]</td>
</tr>
<tr>
<td>INWEST315</td>
<td>143</td>
<td>173</td>
<td>62</td>
<td>92</td>
<td>12.5%</td>
<td>1.07 [0.55, 2.12]</td>
<td>1.13 [0.68, 1.91]</td>
</tr>
<tr>
<td>Kaste517</td>
<td>83</td>
<td>173</td>
<td>77</td>
<td>172</td>
<td>8.5%</td>
<td>1.07 [0.48, 2.38]</td>
<td>1.23 [1.05, 1.44]</td>
</tr>
<tr>
<td>PROFESS8</td>
<td>106</td>
<td>647</td>
<td>103</td>
<td>713</td>
<td>7.5%</td>
<td>1.07 [0.88, 1.31]</td>
<td>1.13 [0.88, 1.46]</td>
</tr>
<tr>
<td>RIGHT23</td>
<td>8</td>
<td>16</td>
<td>10</td>
<td>11</td>
<td>2.3%</td>
<td>0.55 [0.33, 0.93]</td>
<td>0.91 [0.54, 1.54]</td>
</tr>
<tr>
<td>SCAT19</td>
<td>276</td>
<td>862</td>
<td>267</td>
<td>871</td>
<td>13.9%</td>
<td>1.04 [0.91, 1.20]</td>
<td>1.13 [0.98, 1.31]</td>
</tr>
<tr>
<td>VENTURE7</td>
<td>46</td>
<td>187</td>
<td>42</td>
<td>185</td>
<td>4.2%</td>
<td>1.08 [0.75, 1.56]</td>
<td>1.13 [0.98, 1.31]</td>
</tr>
<tr>
<td>VENUS18</td>
<td>44</td>
<td>133</td>
<td>30</td>
<td>128</td>
<td>3.7%</td>
<td>1.41 [0.95, 2.10]</td>
<td>1.13 [0.98, 1.31]</td>
</tr>
</tbody>
</table>

合計（95% CI）: 6,186 / 6,097 100.0% 1.04 [0.98, 1.13]

イベント数の合計: 2,288 / 2,190

異質性: Tau² = 0.01, Q² = 22.38, df = 11 (P = 0.02); I² = 51%

全体の効果に関する検定: Z = 0.93 (P = 0.35)

図2 3カ月目または試験終了時の虚血性脳卒中患者の死亡もしくは要介護（早期降圧治療群 対 対照群）に関する95%信頼区間（CI）による相対リスクの推定値。
배경과 목적
허혈뇌졸중의 급성기에는 혈압이 높은 경우가 흔하며, 이때의 치료 전략에 대해서는 잘 알려져 있지 않다. 따라서 허혈뇌졸중 초기에 적극적인 혈압강하를 대조군과 비교한 무작위 시험연구들의 메타분석을 시행하였다.

방법
적절한 연구를 선정하기 위해 1966년 1월부터 2015년 3월의 기간 중의 Pubmed, EMBASE, Clinicaltrials.gov를 검색하였다. 허혈뇌졸중 발병 3일 이내에 혈압강하 치료를 시작한 군과 대조군을 비교한 무작위 시험을 분석에 포함시켰다. 일차 결과지표는 3개월째 또는 연구 종료 시점에 나쁜 예후를 보이는 경우로 의존성(dependency) 또는 사망으로 정의하였다. 핵심 이차 결과지표는 혈관질환의 재발로 정하였다. 통합 상대위험도와 95% 신뢰구간을 이용해 계산하였다.

결과
체계적 검색을 통해 총 12703명이 조기 혈압강하군과 대조군으로 참여한 13개의 무작위 시험을 선정하였다. 확률효과모형으로 각 결과를 취합한 결과 허혈뇌졸중 초기의 혈압강하는 뇌졸중 후 3개월째 또는 연구 종료 시점의 사망이나 dependency의 위험에 영향을 미치지 않았다(relative risk, 1.04; 95% confidence interval, 0.96 - 1.13; P=0.35). 또한, 혈압강하 치료는 혈관질환의 재발, 장애 또는 사망, 모든 원인의 사망, 뇌졸중 재발, 심각한 유해 경험 등에도 중립적인(neutral) 효과를 보였다.

결론
이번 메타분석 결과 허혈뇌졸중 초기의 혈압강하는 사망이나 의존성의 예방 측면에서 중립적인(neutral) 효과를 나타냈다.
천막하 미세출혈
편두통 미세혈관병증의 또 다른 징후

Infratentorial Microbleeds
Another Sign of Microangiopathy in Migraine

Enrico B. Arkink, MD; Gisela M. Terwindt, MD, PhD; Anton J.M. de Craen, PhD; Junya Konishi, MD, PhD; Jeroen van der Grond, PhD; Mark A. van Buchem, MD, PhD; Michel D. Ferrari, MD, PhD; Mark C. Kruit, MD, PhD; on behalf of the PROSPER Study Group*

(Stroke. 2015;46:1987-1989.)

Key Words: cerebral small vessel disease ■ magnetic resonance imaging ■ migraine disorders

배경과 목적
편두통은 증상성 뇌졸중과 무증상성 백색질고음영 및 천막하 혈색의 위험인자이다. 이러한 무증상 병변은 소혈관 병리와 연결되어 있다. 천막혈관 경색의 신경병리적 소견은 혈관경색의 다른 생물표지자(biomarker)이지만 아직 편두통에서 연구되지 않았다.

방법
PROSPER (the Prospective Study of Pravastatin in the Elderly at Risk) MRI 연구에서 63명의 편두통 환자(전조가 있는 25명, 전조가 없는 35명, 전조 여부를 모르는 3명)와 대조군(73–85세)에서 CMBs가 확인되었다. CMBs, 경색, 백색질고음영 부담의 동시 발생에 편두통의 변형 역할(modifying role)을 평가하였다.

결과
천막하 미세출혈은 대조군보다 전조가 없는 편두통 환자에서 더 흔했다(14% 대 4%). 다른 위치의 CMBs, 경색, 백색질고음영은 군 간에 차이가 없었다. CMBs가 있는 편두통 환자들은 CMBs가 있는 대조군보다 경색이 흔했다(65% 대 43%), 경색이 있는 대조군과 비교하여, 경색이 있는 편두통 환자들은 CMBs가 더 흔했다(55% 대 30%).

결론
편두통은, 특히 전조가 없는, 고령에서 천막하 CMBs와 관련이 있다. CMBs와 경색은 편두통 환자에서 대조군보다 더 자주 동시 발생한다. 이는 편두통 병태생리에서 소혈관침범의 가설을 지지한다.