Original Contribution

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

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***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;46:00-00. 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-analysis[5] 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

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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[5] to identify additional trials. Some data not provided by original articles but published in the latest Cochrane Review were also used.[7]

## 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).[8] 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],[9] China Antihypertensive Trial in Acute Ischemic Stroke [CATIS][10]) or continuing the patients baseline blood pressure lowering therapy (Continue Or Stop post-Stroke Antihypertensives Collaborative Study [COSSACS][11]). 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) or recurrent vascular events at 3 months or at the trial end point. All data from eligible trials were independently abstracted by 2 investigators (M.L. and K.-S.H.) according to standard protocol. Discrepancies were resolved by discussion with a third investigator (Y.-L.W.) and by referencing the original report.

## Study Quality Assessment

Jadad score was used to assess study quality because all included studies were RCTs.[12] This 5-point scoring system evaluates the randomization process (2 questions), blinding (2 questions), and the description of withdrawals and dropouts (1 questions).

## 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 $\chi^2$ and the $I^2$ statistics. Study-level estimates were considered heterogeneous if either the $\chi^2$ test was significant at the $P$=0.10 level or the $I^2$ 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).[13] Our final analysis included 13 RCTs,[8–11,14–21] comprising 12 703 individuals, with 6392 (50%) participants randomly assigned

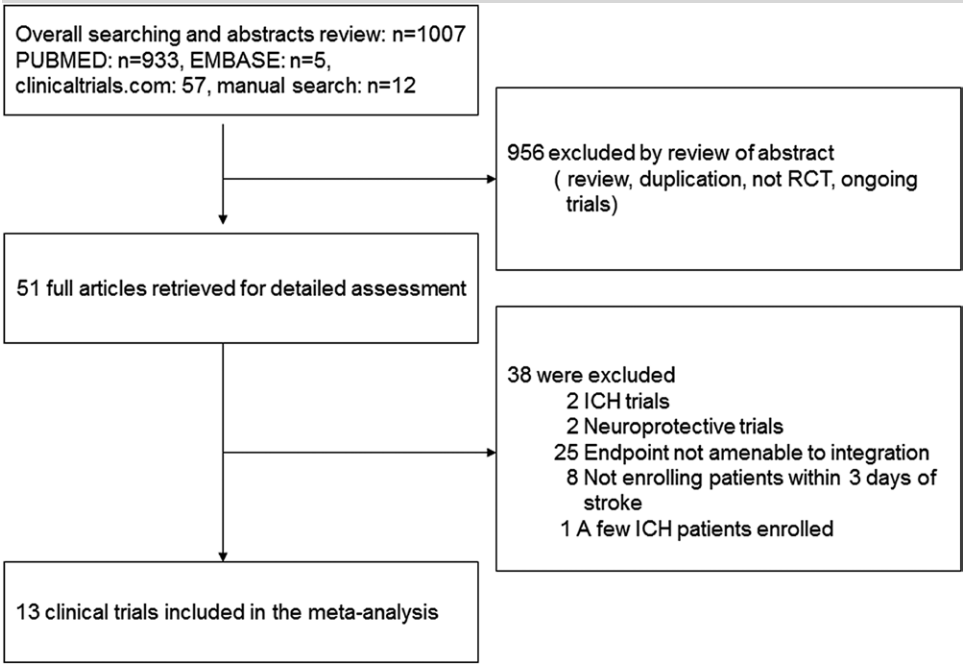


**Figure 1.** Flow chart of study selection process. RCT indicates randomized controlled trial; and ICH, intracerebral hemorrhage.

**Table 1. Characteristics of Included Trials**

| Trial, Publication Year, Country | Population | Patients Enrolled for This Meta-Analysis | Median or Mean Time From Stroke Onset to Randomization, h | Sample Size (% men) | Percentage of Patients Receiving Thrombolytic Therapy | Mean Age, y | Percentage Taking Antihypertensive Medication at Baseline | Intervention | Control |
|---|---|---|---|---|---|---|---|---|---|
| ACCESS,[14] 2003, Germany | Ischemic stroke with a motor deficit, SBP≥200 mm Hg and DBP ≥110 mm Hg, within 36 h of admission | All trial patients | 30 | 339 (51) | NA | 68 | NA | Candesartan for 7 d | Placebo for 7 d |
| CATIS,[10] 2014, China | Ischemic stroke within 48 h of symptom onset, SBP between 140 and 220 mm Hg | All trial patients | 15 | 4071 (64) | 0 | 62 | 49 | Antihypertensive treatment during hospitalization | No antihypertensive treatment during hospitalization; placebo not used |
| CHHIPS,[20] 2009, United Kingdom | Ischemic stroke within 36 h of symptom onset, SBP>160 mm Hg | Ischemic stroke subgroup | NA | 99 | 0 | NA | NA | Labetalol or lisinopril for 14 d | Placebo for 14 d |
| COSSACS,[11] 2010, United Kingdom | Cerebral infarction with within 48 h | Subgroup of patients in whom ischemic stroke was confirmed on CT scan | NA | 444 | 0 | NA | NA | Continue pre-existing antihypertensive drugs for 2 wk | Stop pre-existing antihypertensive drugs for 2 wk |
| ENOS,[22] 2015, multiple countries | Ischemic stroke within 48 h of onset, SBP between 140 and 220 mm Hg | Ischemic stroke subgroup | NA | 3348 | NA | NA | NA | Transdermal GTN for 7 d | No transdermal GTN |
| Eveson et al,[15] 2007, United Kingdom | Ischemic stroke within the previous 24 h with SBP≥140 or DBP≥90 | All trial patients | 19 | 40 (63) | NA | 74 | 60 | Lisinopril for 14 d | Placebo for 14 d |
| INWEST,[16] 2000, West European countries | Ischemic stroke within 24 h in the carotid artery territory | All trial patients | 11 | 265 (47) | NA | 72 | NA | Nimodipine for 21 d | Placebo for 21 d |
| Kaste et al,[17] 1994, Finland | Ischemic hemispheric stroke and admitted within 48 h of stroke onset | All trial patients | 20 | 350(67) | NA | 57 | NA | Nimodipine for 21 d | Placebo for 21 d |
| PRoFESS,[8] 2009, Multiple countries | Ischemic stroke within 72 h of stroke onset, SBP 121 to 180 mm Hg | Acute subgroup (within 72 h of onset) | 58 | 1360(65) | NA | 67 | 96 | Telmisartan for 90 d | Placebo for 90 d |
| RIGHT,[21] 2013, United Kingdom | Acute stroke within 4 h with SBP≥140 mm Hg | Ischemic stroke subgroup | NA | 27 | NA | NA | NA | Transdermal GTN patch for 7 d | No transdermal GTN patch |
| SCAST,[9] 2011, North European countries | Ischemic stroke within 30 h of symptom onset with SBP≥140 mm Hg | Ischemic stroke subgroup | NA | 1733 | NA | NA | NA | Candesartan for 7 d | Placebo for 7 d |
| VENTURE,[19] 2015, South Korea | Ischemic stroke within 24 h from onset with SBP 150–185 mm Hg | All trial patients | NA | 372 | 0 | NA | NA | Valsartan for 7 d | No antihypertensive treatment during the treatment period |
| VENUS,[18] 2001, The Netherlands | Ischemic stroke within 6 h and hemiparesis, SBP between 130 and 220 mm Hg | Ischemic stroke subgroup | NA | 261 | NA | NA | NA | Nimodipine for 10 d | Placebo for 10 d |

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.

**Table 2. Characteristics of Included Trials**

| Trial, Publication Year, Country | Baseline NIHSS Score | Baseline SBP/DBP, mm Hg | SBP/DBP Difference at 24 h After Randomization, mm Hg (Control–Active) | SBP/DBP Difference at 14 d After Randomization, mm Hg (Control–Active) | Outcome Assessment | Jadad Score, 5-Point Maximum |
|---|---|---|---|---|---|---|
| ACCESS,[14] 2003, Germany | NA | Active: 188/99 Control: 190/99 | 2.7/1.8 | Day 7: 4.5/2.7 | Vascular events and mortality at 12 mo; BI comparison at 3 mo | 3 |
| CATIS,[10] 2014, China | Active: 4 Control: 4 | Active: 166/96 Control: 165/96 | 8.1/3.8 | 8.6/3.9 | mRS at 14 d (or discharge if earlier than 14 d) and 3 mo; vascular events, recurrent stroke, and death at 3 mo | 3 |
| CHHIPS,[20] 2009, United Kingdom | NA | NA | NA | NA | mRS>3 at 2 wk | 5 |
| COSSACS,[11] 2010, United Kingdom | NA | NA | NA | NA | Dead or dependent (mRS>3) at 2 wk | 3 |
| ENOS,[22] 2015, Multiple countries | NA | Active: 158/83 Control: 162/86 | NA | NA | mRS > 2 at 90 d | 4 |
| Eveson et al,[15] 2007, United Kingdom | Active: 13 Control: 10 | Active: 174/91 Control: 170/94 | NA | 20/9 | mRS at 3 mo, death, cardiovascular events, SAE | 4 |
| INWEST,[16] 2000, West European countries | NA | Active: 160/89 Control:160/31 | 4.4/9.4 | -3.5/0 | Death or dependency (BI < 60) at day 21, death on day 21 | 4 |
| Kaste et al,[17] 1994, Finland | NA | Active: 156/92 Control: 155/93 | 1.9/4.9 | Day 7: 6.3/2.9 | mRS at 3 and 12 mo, death at 12 mo | 3 |
| PRoFESS,[8]2009, Multiple countries | Active: 3 Control: 3 | Active: 146/84 Control: 147/84 | NA | Day 7: 6.1/3.2 | mRS at 30 d, death at 90 d; stroke recurrence, combined vascular, SAE | 4 |
| RIGHT,[21] 2013, United Kingdom | NA | NA | NA | NA | mRS at 90 d, death and early neurological deterioration at 7 d | 2 |
| SCAST,[9] 2011, North European countries | NA | NA | NA | NA | mRS>2 at 6 mo, vascular events at 6 mo | 5 |
| VENTURE,[19] 2015, South Korea | NA | Active: 162/ 90 Control: 163/ 91 | 0.3/1.8 | Day 7: 1.9/1.7 | mRS>3 at 90 d, early neurological deterioration at 7 d, vascular events, death, and BI comparison at 90 d | 3 |
| VENUS,[18] 2001, The Netherlands | NA | NA | No significant difference | NA | mRS>3 at 3 mo, death at 10 d | 4 |

ACCESS indicates Acute Candesartan Cilexetil Therapy in Stroke Survivors; BI, Barthel index; 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; INWEST, Intravenous Nimodipine West European Stroke Trial; mRS, modified Rankin Scale; NA, not available; NIHSS, National Institutes of Health Stroke Scale; PRoFESS, The Prevention Regimen for Effectively Avoiding Second Stroke; RIGHT, Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial; SAE, serious adverse events; 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 5 trials at 24 hour, ranged from 0.3 to 8.1 mm Hg for systolic blood pressure and 1.8 to 9.4 mm Hg for diastolic blood pressure. The magnitude of lowering of systolic 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 ($I^2$=51%; $P$ for heterogeneity=0.02; Figure 2). The funnel plots showed no major asymmetry (Figure 3).

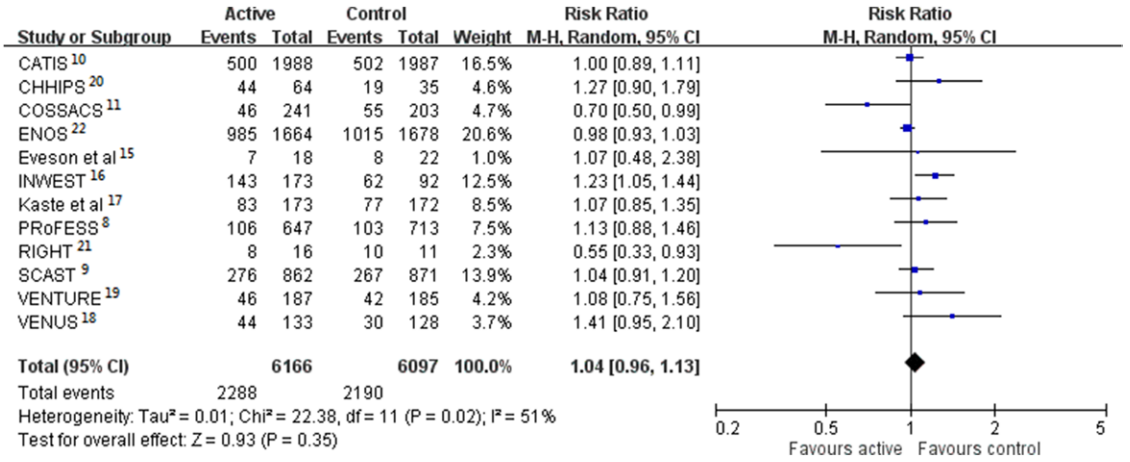


**Figure 2.** Relative risk with 95% confidence interval (CI) estimates for death or dependency (early blood pressure lowering vs control) at 3 months or at trial end point among patients with ischemic stroke.

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.[3] It is likely that the fate of the threatened penumbra has mostly been determined by 10 hours after onset.[23]

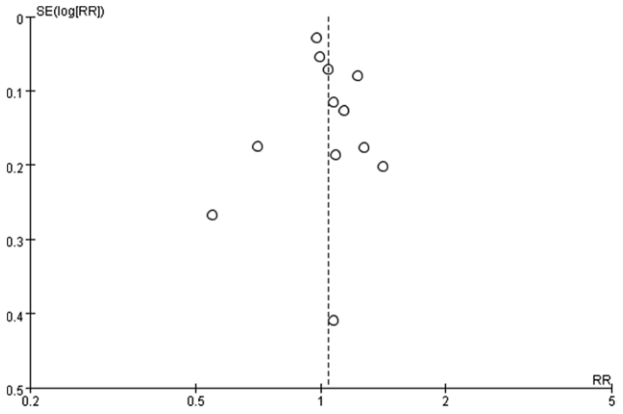


**Figure 3.** The funnel plot of included trials. RR indicates relative risk.

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.[24] 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.[25,26] 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.[27]

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.[28] Full data sets from forthcoming trials, such as Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED), may help to resolve this remaining issue.[29]

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

**Table 3. Effect of Early Blood Pressure Lowering on Clinical Outcomes**

| | No. of Trials | Risk Ratio (95% CI) | *P* Value |
|---|---|---|---|
| Primary outcome | | | |
| Unfavorable outcome at 3 mo or at trial end point[8–11,15–19] | 12 | 1.04 (0.96–1.13) | 0.19 |
| Secondary outcomes | | | |
| 3 or 6 mo outcomes | | | |
| Recurrent vascular events[8–10,14,15,19] | 6 | 0.90 (0.65–1.25) | 0.54 |
| Recurrent stroke[8,10,15,19] | 4 | 1.00 (0.54–1.84) | 0.74 |
| mRS 2–6[8,10,15,19,22] | 5 | 1.01 (0.98–1.04) | 0.43 |
| All-cause mortality[8–10,14,15,17,19,21,22] | 9 | 0.99 (0.83–1.17) | 0.87 |
| 2 wk or 1 mo outcomes | | | |
| mRS 3–6[8,10] | 2 | 1.01 (0.93–1.10) | 0.79 |
| mRS 2–6[8,10] | 2 | 1.00 (0.95–1.05) | 0.91 |
| All-cause mortality[8,10,15,17,18] | 5 | 1.25 (0.71–2.21) | 0.43 |
| Serious adverse events[8,15] | 2 | 1.32 (0.80–2.18) | 0.28 |

CI indicates confidence interval; and mRS, modified Rankin Scale.

meta-analysis, we could not perform multivariate adjustment for differences in individual patient; an individual patient data meta-analysis, such as the ongoing plans of the Blood Pressure in Acute Stroke Collaboration, would be needed to mitigate this concern. Third, different types of stroke (large vessel, lacunar, embolic, etc) may have different response to blood pressure lowering but that was not captured in the analysis. Blood pressure lowering in acute stroke may impair the penumbra and worsen the neurological deficit differentially in large vessel stroke compared with lacunar stroke. Further studies for blood pressure lowering in acute stroke would benefit from careful subtyping of stroke mechanism and potentially from penumbral imaging to identify subpopulations with distinct responses to therapy.

In conclusion, this meta-analysis of completed clinical trials suggested blood pressure lowering in early ischemic stroke had a neutral effect on the prevention of death or dependency. Further studies with an appropriately phenotyped population that is recruited in the hyperacute phase of ischemic stroke are warranted.

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## Disclosures

None.

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