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Ultra-Early Blood Pressure Reduction Attenuates Hematoma Growth and Improves Outcome in Intracerebral Hemorrhage

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Abstract

Objective: The aim was to investigate whether intensive blood pressure treatment is associated with less hematoma growth and better outcome in intracerebral hemorrhage (ICH) patients who received intravenous nicardipine treatment ≤2 hours after onset of symptoms.

Methods: A post-hoc exploratory analysis of the Antihypertensive Treatment of Acute Cerebral Hemorrhage 2 (ATACH-2) trial was performed. This was a multicenter, international, open-label, randomized clinical trial, in which patients with primary ICH were allocated to intensive versus standard blood pressure treatment with nicardipine ≤4.5 hours after onset of symptoms. We have included 913 patients with complete imaging and follow-up data in the present analysis.

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Author Contributions

Q.L. and J.G. contributed to the conception and design of the study. Q.L., A.W., A.Q., A.M., G.F., K.S., A.S., D.D., A.V., and J.G. contributed to the acquisition and analysis of data. Q.L. and J.G. contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest

Nothing to report.

Additional supporting information can be found in the online version of this article.

Results: Among the 913 included patients, 354 (38.7%) had intravenous nicardipine treatment initiated within 2 hours. In this subgroup of patients treated within 2 hours, the frequency of ICH expansion was significantly lower in the intensive blood pressure reduction group compared with the standard treatment group ($p = 0.02$). Multivariable analysis showed that ultra-early intensive blood pressure treatment was associated with a decreased risk of hematoma growth (odds ratio, 0.56; 95% confidence interval [CI], 0.34–0.92; $p = 0.02$), higher rate of functional independence (odds ratio, 2.17; 95% CI, 1.28–3.68; $p = 0.004$), and good outcome (odds ratio, 1.68; 95% CI, 1.01–2.83; $p = 0.048$) at 90 days. Ultra-early intensive blood pressure reduction was associated with a favorable shift in modified Rankin Scale score distribution at 3 months ($p = 0.04$).

Interpretation: In a subgroup of ICH patients with elevated blood pressure given intravenous nicardipine ≤2 hours after onset of symptoms, intensive blood pressure reduction was associated with reduced hematoma growth and improved functional outcome.

Introduction

Intracerebral hemorrhage (ICH) is the stroke subtype with the highest morbidity and mortality.[1,2] It is estimated that ~60% of patients survive the first month and most of the survivors suffer long-term disability.[3,4] An acute hypertensive response is commonly observed early after the onset of symptoms and is associated with higher risk of hematoma growth and poor outcome.[5-7] Acute reduction of elevated blood pressure (BP) is an appealing treatment strategy that might limit hematoma growth and improve outcome.

The two largest randomized controlled trials of intensive BP lowering were the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2) and the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH-2) trial.[8,9] The largest was the INTERACT2, which found that intensive lowering of BP was associated with lower likelihood of poor outcome on a range of secondary measures, but did not meet statistical significance on the primary outcome of reduced rate of death and disability.[8] In addition, intensive BP lowering did not result in a statistically significant reduction of hematoma growth. Some authors interpreted these data as showing that intensive BP lowering probably does improve outcome, and many secondary analyses support this.[2,10,11] The second largest trial was the ATACH-2 trial, which included 1,000 patients randomized to intensive BP reduction and standard guideline-based treatment. This trial found no effect of intensive BP lowering on hematoma growth or functional outcome in primary or secondary analyses.[9]

One potential explanation for the difficulty in clarifying a benefit of BP lowering is that there might be a therapeutic time window much earlier than the enrollment window in these trials. The ATACH-2 trial enrolled patients ≤4.5 hours after onset of symptoms, and INTERACT enrolled patients ≤6 hours after onset. The frequency of hematoma growth decreases nonlinearly with increasing time from symptom onset to diagnosis, and there might be more opportunity to limit hematoma growth if treatment is initiated earlier.[12,13] Given that the underlying mechanism of anti-expansion treatment is based on limitation of hematoma growth, the time to BP reduction should be considered a key factor in interpretation and analysis of these results. Although both trials analyzed the time to randomization, patients were randomized to a treatment strategy rather than to a specific

therapy. In these studies, when secondary analyses of a time effect were performed, this approach might have been inadequate because the time to randomization was used, rather than the time to treatment. It might be that those who received an antihypertensive agent in the first 2 hours, rather than being randomized within the first 2 hours, might be those with the most opportunity to benefit from intensive BP lowering. We therefore performed a post-hoc subgroup analysis of the ATACH-2 trial, focusing on those who received intravenous nicardipine within 2 hours of symptom onset, to evaluate whether intensive BP lowering is associated with reduced hematoma expansion and improved outcome.

Patients and Methods

Study Design and Participants

The ATACH-2 trial was an international, randomized, open-label trial designed to determine the effectiveness of intensive versus guideline-recommended standard BP reduction in patients with supratentorial ICH.[9] Briefly, patients aged ≥18 years with a Glasgow Coma Scale (GCS) score of ≥5 on arrival and ICH volumes <60ml were randomized to intensive or standard BP treatment in a 1:1 ratio. The goal of treatment was to reduce and maintain a systolic BP target of 140–179mmHg in the standard treatment group and 110–139mmHg in the intensive treatment group using intravenous nicardipine started ≤4.5 hours after onset of symptoms. Intravenous nicardipine was the preferred primary agent to be used, as necessary, for lowering BP. Intravenous antihypertensive medication could be used before randomization to lower the systolic BP to <180 but not <140mmHg at the time of randomization. If the systolic BP was higher than the target, despite use of nicardipine, intravenous labetalol was also permitted. Intravenous diltiazem or urapidil could be used in countries without labetalol. The ATACH-2 protocol was approved by the institutional review board at each participating site (ClinicalTrials.gov no. NCT01176565). Written informed consent was obtained from each participant or their legal representatives.

Subgroup Analysis

For this analysis, we focused on those patients receiving nicardipine (irrespective of whether randomized) within 2 hours of symptom onset. This time point was chosen as the shortest clinically feasible time frame for providers to see the patient, make a diagnosis, and initiate treatment.

Imaging and Outcome

The neurological severity was assessed using the GCS by trained medical staff. Baseline and follow-up computed tomography (CT) scans were analyzed centrally. The time interval between symptom onset and first intravenous infusion of nicardipine was recorded. Times of use of secondary antihypertensives, including labetalol, urapidil, and diltiazem, were not available. The goal of treatment was to reach the target level ≤2 hours after randomization using intravenous nicardipine infusion and to maintain the BP within the target range during the first 24 hours. Post-discharge follow-up included telephone interview at 1 month and in-person clinical evaluation at 3 months. For the present analysis, the primary outcome was hematoma growth defined as an increase of hematoma volume >33% between baseline and follow-up CT scans, as in the original trial.[9] According to the dataset available for public

use, hematoma growth was originally evaluated based on follow-up CT scans performed between 1,080 and 1,800 min after randomization. For this analysis, we included hematoma growth on any follow-up scan irrespective of time after baseline CT. We analyzed the effect of intensive BP reduction on the rate of delayed intraventricular hemorrhage (IVH), operationally defined as newly occurring IVH on follow-up CT imaging when the baseline CT was free of IVH.[14] Secondary outcomes were good outcome (defined as 3 month mRS score of 0–3) and functional independence (defined as 3 month mRS score of 0–2). We also performed a shift analysis of mRS scores at 3 months. The magnitude of systolic BP reduction was defined as the difference between systolic BP measured immediately before use of intravenous nicardipine and the minimum systolic BP achieved at 2 hours after randomization. The attained BP was defined as the minimum systolic BP achieved at 2 hours after randomization.

Statistical Analysis

Categorical variables were expressed as counts with percentages and continuous variables as means (SD) or medians (interquartile range). Baseline clinical, imaging, and outcome variables were compared for categorical variables using Pearson χ^2 or Fisher's exact test, as appropriate. Continuous data were compared using Student independent *t* tests or Mann–Whitney *U* tests, as appropriate. The effect of intensive BP reduction on hematoma growth and functional outcome at 3 months was assessed using a logistic regression, adjusting for age, ethnicity, nicardipine pretreatment before randomization, time from onset to nicardipine, systolic BP before nicardipine, GCS score, baseline hematoma volume, and presence of IVH. A p value <0.05 was considered statistically significant. Statistical analyses were performed using R v.3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Population

A total of 1,000 patients (620 men and 380 women) were enrolled in the ATACH-2 trial between May 2011 and September 2015. Of these, 913 participants were included in our final analysis. The flowchart of patient selection is illustrated in Figure 1. A total of 87 patients were excluded from our present analyses owing to missing data on the time from onset to nicardipine treatment (n = 24), systolic BP (n = 8), 3 month mRs score (n = 36), and lack of CT scans (n = 19).

Among the included patients, 354 (38.7%) received intravenous nicardipine within 2 hours of symptom onset. The characteristics of patients who received intravenous nicardipine ≤2 hours after onset of symptoms versus those treated after 2 hours are illustrated in Table 1 and Supplementary Table 1. A total of 479 (52.4%) patients received intravenous nicardipine before randomization. The number of patients receiving nicardipine before randomization did not differ significantly between intensive and standard treatment groups ($p = 0.143$). The mean time from nicardipine injection to randomization was 71.3 minutes. The attained BP was similar between patients with nicardipine infusion ≤2 hours and those who had nicardipine infusion >2 hours in both the intensive treatment group and the standard

treatment group. The attained BP was 120.5 ± 13.9mmHg in the intensive treatment group and 140.6 ± 16.7mmHg in the standard treatment group ($p < 0.001$) in patients who received intravenous nicardipine ≤2 hours after onset of symptoms.

BP Reduction and Hematoma Growth

Table 2 shows the clinical characteristics of the subgroup of patients who received nicardipine within 2 hours, stratified by treatment arm. The frequency of hematoma growth was significantly lower in the intensive BP reduction group compared with the standard treatment group (35 of 192 [18.2%] versus 46 of 162 [28.4%]; $p = 0.02$). Delayed IVH was less frequent in patients receiving intensive BP reduction versus standard treatment (7 of 192 [3.6%] versus 14 of 162 [8.6%]; $p = 0.047$) in patients who received nicardipine ≤2 hours after onset of symptoms (Table 2). In multivariable analysis adjusting for age, baseline hematoma volume, ethnicity, nicardipine pretreatment before randomization, time from onset to nicardipine, systolic BP before nicardipine, baseline GCS score, and presence of IVH, intensive BP reduction was associated with reduced risk of hematoma growth in this subgroup (odds ratio [OR], 0.56; 95% confidence interval [CI], 0.34–0.92, $p = 0.02$; Table 3).

Effect of Intensive BP Reduction on Outcome

Among those treated within 2 hours, patients in the intensive BP reduction group were more likely to be functionally independent (mRS 0–2) than those with standard treatment (80 of 192 [41.7%] versus 45 of 162 [27.8%]; $p = 0.006$). There was no statistically significant difference in the rate of death at 3 months in the intensive treatment group compared with the standard treatment group (11 of 192 [5.7%] versus 14 of 162 [8.6%], $p = 0.29$). In multivariable analysis, intensive BP reduction was associated with functional independence (OR, 2.17; 95% CI, 1.28–3.68; $p = 0.004$) and good outcome (OR, 1.68; 95% CI, 1.01–2.83; $p = 0.048$) after adjusting for age, ethnicity, nicardipine pretreatment before randomization, time from onset to nicardipine, systolic BP before nicardipine, baseline GCS, baseline hematoma volume, and presence or absence of IVH (Table 3). In addition, we found no evidence for an interaction between pre- and post-randomization treatment and study arm.

A shift analysis of 3 month mRS scores is illustrated in Figure 2. In patients treated after 2 hours, there was no significant difference between intensive BP reduction and standard treatment in the ordinal distribution of mRS scores at 3 months (OR, 0.80; 95% CI, 0.59–1.07; $p = 0.13$). However, intensive BP reduction was associated with a significant shift towards good outcome in patients who received intravenous nicardipine within 2 hours (OR, 1.48; 95% CI, 1.02–2.15; $p = 0.04$).

For patients who received nicardipine after 2 hours, there were no significant differences in the rate of functional independence, good outcome, and mortality in the intensive treatment group compared with the standard treatment group (all p values >0.05). Supplementary Table 2 shows an analysis examining those who received intravenous nicardipine ≤3 and ≤4 hours after onset of symptoms.

Discussion

In our exploratory analysis of data from the ATACH-2 trial, we evaluated whether those patients treated rather than randomized within 2 hours of symptom onset specifically benefitted from intensive BP reduction. We found that within this subgroup, intensive BP reduction reduced the risk of hematoma growth and was associated with improved outcome compared with standard BP control. These effects were not found in those treated after 2 hours or in the whole trial. Our findings suggest that any benefit of intensive BP reduction is time dependent and that time to antihypertensive therapy might be crucial.

Observational studies suggest that acute elevation of BP occurs in 75–80% of patients with ICH.[6,15–17] Elevated systolic BP has been associated with hematoma growth and poor outcome.[7,18] However, whether intensive BP reduction attenuates hematoma growth remains unproved. Multiple trials have evaluated this and found trends towards reduced ICH expansion, without definitively establishing this effect.[8,9,19,20] If there is an effect on expansion, it is likely that patients at highest risk will need to be selected. Some studies have selected high-risk patients using the computed tomography angiography (CTA) spot sign, a radiologic predictor of expansion.[21,22] However, trials of hemostatic therapy in spot-sign-positive patients failed to demonstrate a benefit.[23] Likewise, post-hoc analyses of ATACH-2 examining the CTA spot sign[24] and noncontrast CT markers of high risk of expansion[25] also failed to find a benefit of intervention.

One possibility is that even these radiographic markers cannot overcome the powerful effect of time to intervention. Multiple studies have found that hematoma growth is most frequent in the first hours after onset.[21,22,26,27] Secondary analyses of INTERACT2 demonstrated that greater systolic BP reduction is associated with reduced hematoma growth when the target BP is achieved early and maintained constantly.[13] Clinical trials of Factor VIIa found that the ability of this hemostatic agent to reduce hematoma growth was most powerful in the first 2.5 hours.[28,29] A large study of reversal of anticoagulation suggested a benefit of intensive BP reduction, plus rapid anticoagulant reversal, only within the first few hours.[30]

It is of note that subgroup analyses of the ATACH-2 trial and INTERACT2 did not find a clear benefit in those patients randomized early versus late.[8-10,13] In the ATACH-2 study, a significant proportion of patients received BP-lowering treatment before randomization.[11] It might be that in many patients, the time to use of the antihypertensive agent was different from the time to randomization and that the time to antihypertensive therapy is the crucial variable. It is noteworthy that those treated with nicardipine within 2 hours disproportionately received benefit from intensive BP reduction. However, the BP trends were similar in patients receiving early versus late treatment. It is not clear whether earlier initiation of treatment is a marker of earlier and more aggressive care overall. Perhaps earlier initiation of treatment is a marker of a more severe hypertensive response or other unmeasured confounders. In addition, some have suggested that antihypertensive therapy reduces BP variability,[31] not only BP magnitude, and it might be that early treatment provided a benefit in addition to BP reduction, by reducing variability in the early phase. We are also interested to observe that intensive BP reduction is associated with a lower frequency of delayed IVH in patients treated within 2 hours. Given that delayed IVH is

a well-established predictor of poor outcome, the better functional outcome with early intensive BP reduction might be attributed to attenuation of both hematoma growth and delayed IVH.

Our study has several clinical implications. First, intensive BP reduction might be effective only within a much more narrow therapeutic time window than previously believed. Future trials should focus on the initiation of therapy rather than simply on randomization within the first 2 hours. Second, it suggests that any therapy aimed at limiting hematoma growth, such as hemostatic therapy or reversal of anticoagulation, might also need to be focused on this early time window. Last, it highlights the value of early recognition, rapid transport, and prompt initiation of treatment. As with ischemic stroke, if ICH has a narrow therapeutic time window, early initiation of antihypertensive therapy might be warranted in hyperacute stroke patients with systolic BP >180mmHg. Mobile stroke units might be helpful in implementing ultra-early diagnosis and treatment.[32]

Several limitations should be noted when interpreting our results. First, this was not a preplanned analysis and should therefore be considered exploratory and validated in future prospective trials. Second, given that initiation of nicardipine was based upon local providers and BP at the time, those treated within 2 hours might represent a specific population (those with the most severely elevated BP, leading providers to initiate treatment even before randomization). We attempted to control for this in our analyses, but unmeasured confounders might have remained that led to early treatment. Likewise, those patients with BP well-controlled initially that then elevated later and who received nicardipine later would be in the “delayed” treatment group even though treatment was appropriately on protocol. Third, the population included in the ATACH-2 trial was less severely injured, with smaller baseline hematomas, than the real-world ICH population. Fourth, data were available only for the time to initiation of nicardipine, and we do not have data on timing of other antihypertensive agents. Fifth, given that ATACH-2 included only patients with at least one reading of systolic BP of ≥180mmHg, it is not clear whether our findings are generalizable to ICH patients with lower presenting BPs.

Conclusions

In our secondary analysis of the ATACH-2 trial, we found that of those receiving nicardipine within 2 hours of symptom onset, intensive BP treatment was associated with lower risk of ICH expansion and improved outcomes in comparison to those who received it later. Intervention within this ultra-early time frame might be necessary to establish a benefit of intensive BP reduction definitively.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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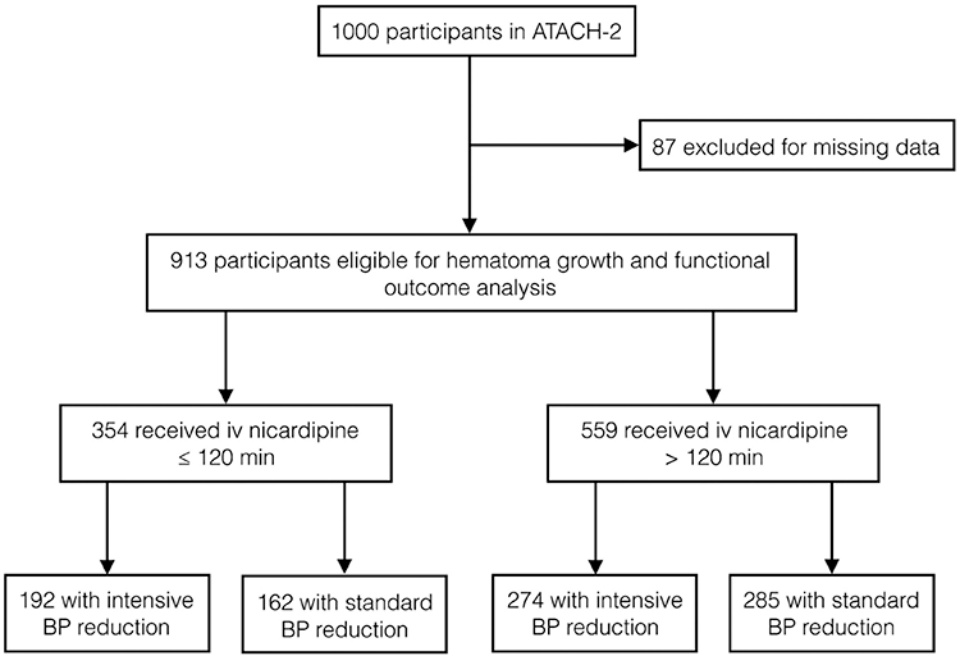

FIGURE 1:

Flowchart of patient selection. ATACH-2 = Antihypertensive Treatment of Acute Cerebral Hemorrhage; BP = blood pressure; iv = intravenous.

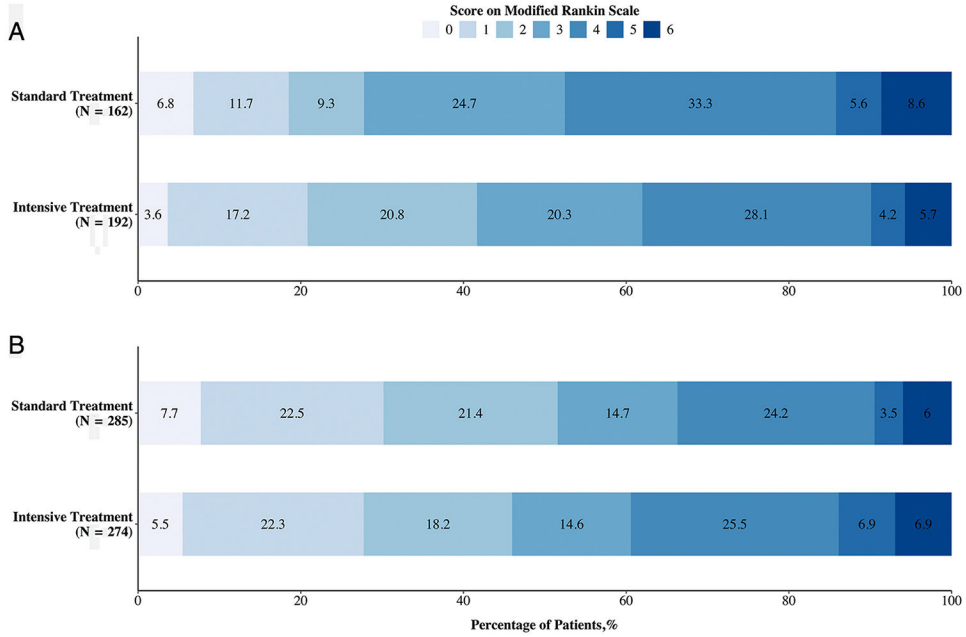

FIGURE 2:

Distribution of 3 month modified Rankin Scale (mRS) scores according to treatment group. (A) Intensive treatment was associated with good functional outcome in shift analysis of mRS scores in patients treated ≤2 hours after onset of symptoms ($p = 0.04$). (B) There was no significant difference in ordinal analysis of mRS between treatment groups in patients treated >2 hours after onset of symptoms ($p = 0.13$).

TABLE 1.

Baseline Demographic and Clinical Characteristics

Characteristics	Time to Nicardipine ≤2 h (n = 354)	Time to Nicardipine >2 h (n = 559)
Age, mean (SD)	60.7 (13.4)	62.9 (12.9)
Male sex, n (%)	215 (60.7)	344 (61.5)
History of hypertension, n (%)	278 (78.5)	447 (80.0)
Hyperlipidemia, n (%)	87 (24.6)	129 (23.1)
Prior ischemic stroke, n (%)	54 (15.3)	95 (17.0)
Smoker, n (%)	170 (48.0)	230 (41.1)
Time to randomization, min, mean (SD)	116.2 (53.6)	229.0 (32.9)
Received nicardipine before randomization, n (%)	290 (81.9)	189 (33.8)
GCS score, median (IQR)	15 (13–15)	15 (13–15)
Baseline hematoma volume, ml	14.6 (13.0)	13.3 (11.6)
Hematoma growth, n (%)	81 (22.9)	126 (22.5)
Intraventricular hemorrhage, n (%)	95 (26.8)	140 (25.0)
Surgical evacuation, n (%)	17 (4.8)	22 (3.9)
3 month mRS, median (IQR)	3 (2–4)	3 (1–4)
Functional independence (mRS 0–2), n (%)	125 (35.3)	273 (48.8)
Good outcome (mRS 0–3), n (%)	204 (57.6)	355 (63.5)
Death, n (%)	25 (7.1)	36 (6.4)

GCS = Glasgow Coma Scale; IQR = interquartile range; mRS = modified Rankin Scale.

TABLE 2.

Comparison of Demographic, Imaging, and Clinical Characteristics in Patients Who Received Nicardipine Within 2 hours of Symptom Onset

Characteristics	Intensive Treatment (n = 192)	Standard Treatment (n = 162)	*p*
Age, yr	61.2 (13.5)	60.2 (13.3)	0.441
Male sex, n (%)	120 (62.5)	95 (58.6)	0.459
History of hypertension, n (%)	154 (80.2)	124 (76.5)	0.403
Hyperlipidemia, n (%)	50 (26.0)	37 (22.8)	0.486
Prior ischemic stroke, n (%)	32 (16.7)	22 (13.6)	0.421
Received nicardipine before randomization, n (%)	152 (79.2)	138 (85.2)	0.143
GCS score, median (IQR)	15 (13–15)	15 (13–15)	0.823
Baseline hematoma volume, ml	14.5 (12.6)	14.8 (13.6)	0.848
Intraventricular hemorrhage, n (%)	49 (25.5)	46 (28.4)	0.543
Hematoma growth, n (%)	35 (18.2)	46 (28.4)	0.023
Delayed IVH, n (%)	7 (3.6)	14 (8.6)	0.047
Surgical evacuation, n (%)	6 (3.1)	11 (6.9)	0.099
SBP before nicardipine, mmHg	211.5 (22.2)	211.1 (24.2)	0.869
DBP before nicardipine, mmHg	118.1 (21.9)	113.5 (20.9)	0.045
Magnitude of SBP reduction, mmHg	91.1 (25.1)	70.5 (27.6)	<0.001
3 month mRS, median (IQR)	3 (2–4)	3 (2–4)	0.042
Functional independence (mRS 0–2), n (%)	80 (41.7)	45 (27.8)	0.006
Good outcome (mRS 0–3), n (%)	119 (62)	85 (52.5)	0.071
Death, n (%)	11 (5.7)	14 (8.6)	0.287

DBP = diastolic blood pressure; GCS = Glasgow Coma Scale; IQR = interquartile range; IVH = intraventricular hemorrhage; mRS = modified Rankin Scale; SBP = systolic blood pressure.

TABLE 3.

Association of Ultra-Early (≤2 hour) Intensive Blood Pressure Treatment and Outcomes

	Unadjusted analysis		Adjusted analysis[a]	
Outcome	**Relative risk (95% CI)**	***p***	**Relative risk (95% CI)**	***p***
Hematoma growth	0.56 (0.34–0.93)	0.024	0.56 (0.34–0.92)	0.022
Functional independence	1.86 (1.19–2.91)	0.007	2.17 (1.28–3.68)	0.004
Good outcome	1.48 (0.97–2.26)	0.072	1.68 (1.01–2.83)	0.048
Death	0.64 (0.28–1.46)	0.29	0.62 (0.27–2.12)	0.600

[a]Adjusted for age, baseline hematoma volume, ethnicity, nicardipine pretreatment before randomization, time from onset to nicardipine, systolic blood pressure before nicardipine, baseline Glasgow Coma Scale score, and intraventricular hemorrhage. CI = confidence interval.