




Association between blood pressure and outcome in patients with acute ischemic stroke treated with alteplase

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ABSTRACT

Background: The role of blood pressure (BP) in acute stroke remains unclear. We investigated the impact of BP trajectories during the first 24 hours (h) after hospital admission on outcomes in acute ischemic stroke patients treated with intravenous alteplase.

Methods: In 424 ischemic stroke patients from the NOR-TEST I trial treated with alteplase, we assessed systolic BP (sBP) at baseline, change in sBP between 0 h and 24 h, and increase in sBP over the same period. Outcomes included modified Rankin Scale (mRS) at 3 months, NIHSS at 24 h, and symptomatic intracerebral haemorrhage (sICH) within 48 h.

Logistic and linear regression analyses were used to explore the association of blood pressure trajectories and outcome adjusted for age, sex, time from onset of symptoms to intravenous thrombolysis (IVT) and NIHSS at admittance (NIHSSadm).

Results: Mean sBP at baseline (admittance), 2 h and 24 h were 155, 147 and 142 mmHg, respectively. An increase in sBP from baseline to 24 h was seen in 115 patients (27 %), while 409 showed an overall change. In unadjusted analyses, sBP increase (but not baseline sBP or change in sBP) was associated with worse mRS at 3 months. This remained significant after adjustment (OR 0.933, 95 %CI 0.876 – 0.993). Higher baseline sBP and sBP increase predicted worse NIHSS at 24 h. sBP increase and baseline sBP were also associated with sICH within 48 h, but only baseline sBP remained significant after adjustment (OR 1.022, 95 % CI 1.003–1.042).

Conclusions: An increase in sBP within the first 24 h was associated with worse neurological and functional outcomes at 3 months, while higher baseline sBP was linked to worse neurological outcomes and sICH in acute ischemic stroke patients treated with alteplase.

Clinical trial registration: NCT01949948.

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Introduction

High blood pressure (BP) in acute ischemic stroke is common and may result from previous hypertension or a pathophysiological response following the ischemic event. Elevated systolic BP defined as ≥ 140 mm Hg is observed in >60 % of patients presenting to the emergency department with acute stroke [1]. BP is usually highest on admission and decreases spontaneously during the natural course of stroke, typically within the first one or two weeks. Two-thirds of patients are normotensive during the first week [1,2]. The impact of systolic blood pressure (sBP) and BP trajectories on outcome after stroke is still unclear and management of BP in acute stroke is continuously under debate. In a systematic review it was showed that high admission BP increased the risk of death and long-term dependence [3]. Several other studies have shown that higher BP variability is associated with worse functional outcome after stroke [4,5]. There is no evidence for a benefit of actively reducing high BP in acute ischemic stroke [6].

Neurological deterioration occurs in 10-20 % patients with acute stroke, mostly within the first 24 h from stroke onset and it has been associated with worse outcome [7]. Many predictors of neurological deterioration in addition to blood pressure have been identified in previous studies, including e.g. higher age, cardiovascular diseases, increased stroke severity (higher NIHSS at admission), unstable carotid plaque, pro-inflammatory cytokines and reocclusion after initial recanalization in thrombectomy among others [8,9].

In patients treated with intravenous thrombolysis (IVT) severe hypertension and BP variability have been associated with poor functional outcome, symptomatic intracerebral hemorrhage (sICH) and death [10]. Nevertheless, the optimal approach for blood pressure management, both during and after reperfusion therapy, remains controversial. The ENCHANTED trial compared intensive versus guideline-recommended BP control in patients with acute ischemic stroke receiving IVT [11]. The trial showed that early intensive BP lowering within six hours of stroke onset did not improve functional outcome at 90 days in patients with stroke of mild to moderate severity, even though the incidence of sICH was decreased [11]. In another recent study among patients with stroke receiving IVT, an elevated mean sBP and high sBP variability predicted poor functional outcome and sICH [4].

The uncertainties regarding the effect of BP levels and change in sBP within the first 24 h of ischemic stroke have consequently been highlighted in a recently published update on BP management for acute ischemic stroke [12]. In patients treated with IVT, the upper limits of blood pressure are emphasized. However, the potential significant effects of blood pressure change, and variability have not yet been determined. [13].

The aims of the present study were to investigate the impact of sBP at baseline, change and increase within the first 24 h on outcome in patients with acute ischemic stroke treated with i.v. alteplase.

Methods

The Norwegian Tenecteplase Stroke Trial (NOR-TEST) was a multicentre, prospective, randomised, open-label, blinded endpoint, phase III trial designed to investigate the safety and efficacy of tenecteplase 0.4 mg/kg versus alteplase 0.9 mg/kg in ischemic stroke conducted in 13 stroke units in Norway from 2012 to 2016 [11]. Patients ≥ 18 years with suspected acute ischemic stroke who were eligible for IVT and admitted within 4.5 hours (h) of symptom onset were included. Patients with unknown symptom onset or awakening with symptoms but admitted within 4.5 h, were also included if MRI mismatch was observed [14,15]. In all, 1100 patients were included. Study design, randomisation and data collection are described in detail previously [14,15]. The present study is a sub study of NOR-TEST where patients with transient ischemic attacks (TIA), stroke mimics, and patients randomized to treatment with tenecteplase 0.4 mg/kg. were excluded as current guidelines recommend against using tenecteplase at a dose of 0.40 mg/kg. [16]. In all, 424

patients with acute ischemic stroke and receiving thrombolysis with alteplase were included in this study.

The primary outcome was functional outcome defined according to the modified Rankin Scale (mRS) at 3 months after stroke. Good clinical outcome was defined as mRS 0-2.

Secondary outcomes were neurological function assessed by the National Institute of Health Stroke Scale (NIHSS) at 24 h after IVT and symptomatic ICH (sICH) occurring within 48 h.

All patients were treated in stroke units. Blood pressure was measured by trained nurses at admission, at 2 h and 24 h after IVT using semi-automatic blood pressure monitoring according to the study protocol. For the analyses, sBP were used. The change in sBP was expressed by the highest differences in sBP between baseline and 24 h using absolute values in mmHg and included highest absolute values for either increase or decrease. Increase in sBP was expressed in absolute values within 24 h. Blood pressure trajectory was defined as the change in systolic blood pressure (sBP), expressed as the largest absolute difference in sBP between baseline and 24 h (in mmHg), representing the highest absolute value for either an increase or a decrease.

Cerebral computed tomography (CT), and CT angiography were done at admission prior to IVT and study inclusion. Follow-up imaging consisted of either cerebral magnetic resonance imaging (MRI) or cerebral CT at 24-48 h after treatment. sICH was defined according to the European Cooperative Acute Stroke Study (ECASS) III criteria [17].

Statistics

Continuous variables are given in mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. Categorical variables are presented as number and percentages (%). To assess the impact of sBP on the outcome variables, linear regression was performed with NIHSS 24 h as dependent variable, and logistic regression analyses were conducted with dichotomized mRS at 3 months, and sICH within 48 h as outcomes. The main covariates were sBP at baseline, change and increase in sBP between 0 h and 24 h. The analyses were performed unadjusted and adjusted for age, sex, time from symptom onset to thrombolysis, and stroke severity at admittance to hospital (NIHSSadm). The results are given in odds ratio (OR) with 95 % confidence interval (95 %CI) in the logistic regression analyses and beta coefficient (B) with 95 % CI in the linear regression analysis. The significance level was set at $p < 0.05$. All analyses were performed using IBM SPSS r27.00 (SPSS Inc., Chicago, IL, USA).

Ethics

NOR-TEST was performed in accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from every patient or from close relatives when the patient was not able to sign. The trial was reviewed and approved by the Regional Committee for Medical and Health Research Ethics and the Norwegian Medicines Agency.

Results

Of the 1100 patients admitted with suspected stroke and treated with IVT, 676 patients were excluded due to TIA (77 patients), stroke mimics (190 patients), and due to treatment with tenecteplase (409 patients), leaving 424 patients to be included in this sub study. Mean age was 70.8 years (SD 13.9), and 35.4 % were female. In all, 18 patients had a sICH within 48 h. The population characteristics and outcome are shown in Table 1 and table 2.

Change in sBP within 24 hours

The mean sBP was 155 mmHg (SD 23.5) at baseline (before thrombolysis), 147 mmHg (SD 22.8) at 2 h and 142 mmHg (SD 21.4) at 24 h. In

Table 1

Characteristics of 424 patients with ischemic stroke treated with thrombolysis.

	N 424
Age, years	70.8 (13.9)
Mean age (SD)	72.0 (62 – 81)
Median age (IQR)	
Sex, n (%)	150 (35.4)
Women	
Stroke risk factors, n (%)	193 (45.5)
Hypertension	55 (13.0)
Hypercholesterolemia	64 (15.1)
Diabetes mellitus	60 (14.2)
Atrial fibrillation	96 (22.6)
Current smoker	132 (31.1)
Previous smoker	72 (17.0)
Ischaemic heart disease	97 (22.9)
Previous stroke or TIA	
Pre-mRS, n (%)	398 (93.7)
0 – 2	26 (6.1)
≥ 3	
TOAST classification, n (%)	89 (21.0)
Large vessel disease	122 (28.8)
Cardioembolism	54 (12.7)
Small vessel disease	20 (4.7)
Other causes	134 (31.6)
Unknown or several causes	

SD, Standard deviation; IQR, interquartile range; mRS, modified Rankin Scale; TOAST, Trial of ORG. 10172 in Acute Stroke Treatment.

versus 69.0 %, $p < 0.001$).

Association between change in sBP and functional outcome

In the unadjusted analyses, increase in sBP between baseline and 24 h, higher age, being female and more severe stroke symptoms at admittance (NIHSSadm) were associated with worse functional outcome at 3 months post-stroke (mRS). When adjusting for age, sex and NIHSSadm, increase in sBP between baseline and 24 h remained significant (OR 0.933, 95 %CI 0.876 – 0.993, p 0.03), together with age and NIHSSadm. (Table 3 and 4).

In the unadjusted analyses, increase and decrease in sBP, sBP change, higher age and more severe stroke symptoms at admittance (NIHSSadm) were associated with worse neurological function (higher NIHSS score) at 24 h, while increase in sBP the first 24 h (B 0.167, 95 % 0.045 – 0.289, p 0.008) and higher sBP at baseline (B 0.072, 95 % 0.016 – 0.127 p 0.012) together with NIHSS at admittance remained significantly associated with worse neurological function after 24 h in the adjusted analysis. Higher sBP at baseline, increase in sBP and change in sBP the first 24 h after admission in addition to age, significantly increased the odds of sICH in the unadjusted analyses. Higher sBP at baseline remained significantly related to sICH when adjusting for age, sex and NIHSS adm (OR 1.022, 95 % CI 1.003– 1.042 p 0.022), (Table 3 and Table 4).

None of the analyses examining the association between large vessel occlusion (LVO) and outcome, or between thrombectomy and outcome,

Table 2

Outcome of 424 patients with stroke treated with alteplase.

NIHSS _{adm} , mean (SD)	6.4 (5.6)
NIHSS _{adm} , median (IQR)	4.0 [2–9]
NIHSS _{24 h} , mean (SD)	4.4 (6.3)
NIHSS _{24 h} , median (IQR)	2.0 (0–6)
mRS 0–2 at 3 months post-stroke, n (%)	309 (75.1)
sICH _{48 h} , n (%)	18 [4,3]
sBP _{baseline} mean mmHg (SD)	155 (23.5)
sBP _{2h} mean mmHg (SD)	147 (22.8)
sBP _{24h} mean mmHg (SD)	142 (21.4)

SD, Standard deviation; IQR, interquartile range; mRS, modified Rankin Scale; sICH, symptomatic intracerebral hemorrhage, sBP systolic Blood pressure.

all, 409 had a change in sBP between 0 and 24 h (mean 28.35 mmHg). There were 115 patients (27.1 %) with an increase in sBP from baseline until 24 h (mean 15.01 mmHg) and 294 patients (69.3 %) with a decrease in sBP (mean 24 mmHg).

Of the 421 patients with mRS registered at 3 months, a good functional outcome (mRS 0–2) was reached in 309 (75.1 %), and good functional outcome was more common in patients with a decrease in sBP compared to those with an increase in sBP during the first 24 h (77.9 %

Table 4

Adjusted regression analyses: The effect of blood pressure adjusted for age, sex, time from symptom onset to IVT and NIHSS at admission on outcome in patients with ischemic stroke treated with alteplase.

	NIHSS _{24h}		Good functional outcome (mRS 0-2) 3months		sICH	
	B 95 % CI	p	OR 95 % CI	p	OR 95 % CI	p
BP _{adm}	0.072 (0.016 – 0.127)	0.012	ns	-	1.022 (1.003– 1.042)	0.022
BP _{change}	Ns		ns		1.023 (0.997 – 1.049)	0.079
BP _{increase}	0.167 (0.045 – 0.289)	0.008	0.933 (0.876 – 0.993)	0.030	ns	-
Age, years	ns		0.883 (0.833 – 0.937)	<0.001	ns	-
Sex, men	ns		ns	-	ns	-
NIHSS _{adm}	0.517 (0.353 – 0.681)	<0.001	0.891 (0.810 – 0.980)	0.017	ns	-

Table 3

Unadjusted linear and logistic regression analyses of associations between sBP measures and outcome.

	NIHSS _{24h}		Good functional outcome (mRS 0–2) 3months		sICH	
	B	95 % CI	OR	95 % CI	OR	95 % CI
sBP _{baseline}	0.021	(–0.005 – 0.47)	0.121	0.999 (0.989 – 1.005)	0.705	1.023 (1.004 – 1.041)
sBP _{change}	0.069 (0.033 – 0.105)		<0.001	0.988 (0.975 – 1.001)	0.067	1.025 (1.000 – 1.051)
sBP _{increase}	0.189 (0.096 – 0.282)		<0.001	0.954 (0.927 – 0.986)	0.005	1.067 (1.010 – 1.127)
sBP _{decrease}	0.046 (0.004 – 0.088)		0.033	0.993 (0.977 – 1.010)	0.418	1.031 (1.000 – 1.063)
Age, years	0.092 (0.047 – 0.138)		<0.001	0.910 (0.888 – 0.934)	<0.001	1.047 (1.004 – 1.092)
Sex, men	1.007 (–0.265 – 2.278)		0.120	0.548 (0.348 – 0.865)	0.010	2.375 (0.917 – 6.153)
NIHSS _{adm}	0.639 (0.549 – 0.730)		<0.001	0.856 (0.821 – 0.894)	<0.001	1.068 (0.997 – 1.145)
Time from symptom onset to IVT	0.000 (–0.007 – 0.006)		0.919	1.000 (0.998 – 1.002)	0.945	1.001 (0.994 – 1.008)
Large vessel occlusion (LVO)				1.366 (0.786 – 2.375)	0.268	0.530 (0.193 – 1.452)
Thrombectomy				1.938 (0.764 – 4.910)	0.163	0.927 (0.118 – 7.30)

showed significant associations (Table 3)

Discussion

In this study we found a significant association between increasing sBP the first 24 h after intravenous thrombolysis by alteplase, and worse functional outcome (mRS) at 3 months after acute ischemic stroke.

Further, we found that higher sBP at baseline and increasing sBP between 0 h and 24 h were associated with worse neurological function at 24 h. In addition, higher sBP at baseline increased the risk of intracerebral hemorrhage within 48 h from stroke onset.

Finally, worse stroke severity at hospital admission and higher age were associated with worse functional outcome at 3 months post-stroke, and stroke severity was significantly associated with worse neurological function at 24 h.

Our results align with previous studies on the impact of acute BP levels before and after systemic thrombolysis on functional outcomes in patients with acute ischemic stroke [18,19]. However, few studies have explored the associations between BP trajectories and 3 months outcome in thrombolysed patients. In our study, a good functional outcome (mRS 0–2) was more common in patients with a decrease in sBP within the first 24 h compared to those with an increase in sBP, consistent with previous studies [20,21].

The results suggest that high sBP prior to IVT is associated with worse neurological outcome. In the ECASS II study comparing the effect of IVT against placebo, favourable outcome was associated with lower baseline sBP in the thrombolysis group [22].

Results from the Third International Stroke Trial (IST-3) did also show that high baseline BP and a large BP variability during the first 24 h might be associated with a poor prognosis [23]. Another recent study found that BP higher than 185/110 was associated with poor 3 months mRS outcome [21]. This is in line with a systematic review and meta-analysis by Malhotra et al. showing that elevated BP at baseline had an adverse impact on outcomes in patients with acute ischemic stroke receiving IVT [19]. Although observational studies suggest favorable outcomes in patients with lower sBP before IVT and a natural decrease in sBP within the first 24 hours post-IVT, trials testing anti-hypertensive drug therapy in patients with sBP <185 mmHg have not demonstrated clinical benefits [11,24]. Guidelines recommend a careful approach to acute treatment of BP in acute ischemic stroke due to a possible unstable cerebral perfusion [25].

Hence, aggressive BP lowering before and after reperfusion therapy may exacerbate cerebral hypoperfusion and cause further ischemic core growth [11].

Most of the patients included in the present study, had minor to moderate stroke with mean NIHSS at baseline 6.37, which might account for fairly low rates of symptomatic intracerebral hemorrhages (4.27 %). Even though, we found an association between higher sBP on admittance and increased risk of sICH, also showed by others [26,27].

Underlying mechanisms of high BP in acute stroke are still poorly understood. Possible contributing mechanisms are early activation of sympathetic pathways and altered cerebral autoregulation within the ischemic penumbra [28]. Impaired autoregulation in acute cerebral ischemia, elevated BP and BP variability are associated with decreased cerebral perfusion [29], which may reduce the chance of reperfusion of potentially viable penumbra around the ischemic core and thereby increasing the risk of infarct expansion with reduced neurological function, consequently. Compromised cerebral perfusion may therefore explain some of the effect on functional outcomes in patients treated with thrombolysis.

Further, elevation in systemic BP levels can increase the risk of sICH, which again might result in early neurological deterioration and poorer outcome. Moreover, in patients with large vessel occlusion treated with reperfusion therapies an association between increasing baseline sBP levels and lower odds of recanalization have been shown, which might explain the worse outcome among some of the patients [30].

In addition to the impact of BP and other established clinical risk factor for outcome after stroke, the importance of serum biomarkers in treatment and prognosis of patients with acute stroke treated with thrombolysis has also been recognized. Factors such as Sirtuin 6 and peripheral blood systemic inflammation markers have been identified as significant risk factors for poor short-term prognosis [31]. In the present study, data on serum biomarkers were not available. Although the aim of this study was to investigate the impact of blood pressure on functional outcome after stroke, it would have been a strength if we had been able to adjust for various biomarkers.

The present study has several strengths and limitations. Firstly, the study represents a post-hoc analysis of data from a randomized controlled trial primarily comparing two intravenous thrombolytic agents. Since the dosage of tenecteplase 0.4 mg/kg used in the NOR-TEST study has been shown to be unsafe in moderate and severe stroke, and therefore not recommended used, we included only patients treated with alteplase in our analyses ([16], [32]).

Secondly, when investigating the impact of BP changes on outcome during the acute phase of stroke, continuous blood pressure monitoring would have been preferable, as it could have minimized the loss of extreme values. We only had three BP measurements within the first 24 h, which implies that there might have been more variability in BP values not identified. In the analyses, actual blood pressure values were used without adjustment for, or consideration of, antihypertensive medication use prior to thrombolysis, which cannot be excluded as a potential source of bias. Had a larger proportion of the included patients not received antihypertensive therapy, this could have resulted in higher blood pressure levels in more patients and, consequently, may have influenced the outcomes of the analyses. However, previous trials evaluating antihypertensive treatment in patients with sBP <185 mmHg have not demonstrated any clinical benefit [11,24], and the resulting data should be interpreted with appropriate caution.

Some previous studies use both systolic and diastolic BP measurements, however, we used only sBP, as there seems to be a stronger predictive value for sBP than for diastolic BP in patients with ischemic stroke (33,34). In 2016, the median age in the Norwegian stroke population was 76 years. In contrast, the median age of patients treated with alteplase in the present study was 72 (62–81). One possible explanation for this younger age distribution compared to the general Norwegian stroke population might be that in our study all patients received thrombolytic treatment. However, the younger age of the included patients may have influenced the outcomes in a favorable direction, as increasing age is a well-known risk factor for both neurological deterioration and poorer functional outcomes. Consequently, the fact that the included patients were significantly younger than the general stroke population in Norway may limit the generalizability of the findings. Nevertheless, the NIHSS score was comparable to the stroke severity reported by the nationwide Norwegian stroke registry (35). Strength of the study is that patients were included prospectively, they all received intravenous alteplase, and data were strictly registered in a protocol including BP measures on fixed intervals. Further, in contrast to many observational studies, a large proportion had outcome data at scheduled follow-up.

Conclusion

The present study suggests that in patients with acute ischemic stroke receiving intravenous alteplase, an increase in sBP the first 24 h was associated with worse functional outcome 3 months post-stroke. Further, higher sBP at admittance and an increase in sBP from 0 h to 24 h after treatment were predictors of worse neurological function at 24 h. Higher sBP at admittance did also increase the risk of sICH. The results indicate that high blood pressure at baseline is detrimental and associated with severe outcomes. Large fluctuations in systolic blood pressure, especially increase in sBP the first 24 h after thrombolysis should be avoided.

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Trial registration

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Blood pressure and outcome after thrombolysis in ischemic stroke.

CRediT authorship contribution statement

Ole Morten Rønning: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Linn Nordby:** Writing – review & editing. **Nicola Logallo:** Writing – review & editing, Resources, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization. **Christopher E Kvistad:** Writing – review & editing, Resources, Methodology, Investigation. **Espen Saxhaug Kristoffersen:** Writing – review & editing. **Håkon Ihle-Hansen:** Writing – review & editing. **Hege Ihle-Hansen:** Writing – review & editing. **Vojtech Novotny:** Writing – review & editing, Resources, Project administration, Investigation. **Ulrike Waje-Andreassen:** Writing – review & editing. **Halvor Naess:** Writing – review & editing. **Lars Thomassen:** Writing – review & editing, Resources, Project administration, Investigation, Funding acquisition. **Bente Thommesen:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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