**Reciprocal interaction of 24h blood pressure variability and systolic blood pressure on outcome in stroke thrombolysis**

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**Abstract**

**Background and purpose:**

Significance and management of blood pressure (BP) changes in acute stroke care are unclear. Here we aimed to investigate the impact of 24h-BP-variability (BPV) on outcome in patients with acute ischemic stroke treated with intravenous thrombolysis.

**Methods:**

From the SITS International Stroke Thrombolysis registry 28976 patients with documented pretreatment systolic BP (BPsys), at 2 hours and 24 hours were analyzed. The primary measure of BP variability was successive variability (BPVSV). Data were pre-processed using coarsened exact matching. We assessed early neurological improvement (ENI), symptomatic intracerebral hemorrhage (SICH) and long-term functional outcome [modified Rankin Scale (mRS) at 90 days] by binary and ordinal regression analysis.

**Results:**

Attempts to explain BPVSV with patients’ characteristics at admission found BPsys (5.5% variance) to be most influential, yet 92% of BPV variance remained unexplained. Independently from BPsys, BPVSV was associated with poor functional outcome mRS 0—2 (OR 0.94, 95% CI 0.90-0.98), disadvantage across the shift of mRS (OR 1.04, 95% CI 1.01-1.08), mortality (OR 1.10, 95% CI 1.01-1.08), SICHSITS (OR 1.14, 95% CI 1.06-1.23), and SICHECASS (OR 1.24, 95% CI 1.10-1.40). Analyzing BPVSV as a function of pretreatment BPsys significantly improved the prediction of functional outcome (mRS 0—1, mRS 0–2, ENI, mRS-shift: all PInteraction<0.01). Excluding patients with atrial fibrillation in a sensitivity analysis gave consistent results overall.

**Conclusion:**
This study suggests the need for a more individual blood pressure management accounting for pretreatment BP and the acute BP course (i.e. BPV) to achieve best possible outcome for the patient.

**Introduction:**

In the acute phase of stroke, up to three-quarters of patients experience high blood pressure (BP); a phenomenon yet understood incompletely[1-3](#_ENREF_1). Guidelines recommend tolerating a BP up to 220/120 mmHg, 185/110 mmHg, and 180/105 mmHg in patients in general, before, and after administering intravenous thrombolysis (IVT) because of the most feared complication symptomatic intracerebral hemorrhage (SICH)[4](#_ENREF_4), [5](#_ENREF_5). Most observational studies found an association between higher admission systolic BPsys and worse outcome describing a distinct u-shaped admission BPsys relation. Thereby, a range of 141-150mmHg systolic blood pressure yielded best functional outcome at 90 days after stroke[6-11](#_ENREF_6).

Even so, clinical trials investigating active blood pressure lowering in acute ischemic stroke have not shown an advantage from BP intervention neither for safety nor functional outcome[12-16](#_ENREF_12). One recent post hoc analysis from a clinical trial showed a positive association of BP lowering and functional stroke outcome irrespective of whether the patient received recombinant tissue-type plasminogen activator or not[17](#_ENREF_17). Regarding bleeding complications following IVT, reports are conflicting where some reported an association between post-thrombolysis BP elevation and hemorrhagic transformation, but others did not[18-20](#_ENREF_18). The randomized ENhanced Control of Hypertension and Thrombolysis strokE stuDy (ENCHANTED, blood pressure arm) investigating superior efficacy and lower risk of any intracerebral hemorrhage of early intensive lowering of BP (systolic target 130-140 mmHg) versus BP control as recommended in guidelines (systolic target <180 mmHg) is ongoing and results are highly anticipated[21](#_ENREF_21" \o "Anderson, 2016 #410).

For several years, stroke neurologists have focused not just on standard BP parameters, but also on BP variability (BPV, for review Manning et al. [22](#_ENREF_22" \o "Manning, 2015 #308)). For the short term BPV, higher BPV was shown to increase the rates of SICH, death and poor outcome after stroke[23-27](#_ENREF_23" \o "Fukuda, 2015 #218). Recently, a post hoc analysis of two clinical trials investigating BPV (assessed as standard deviation) showed no significant association with two-week functional dependency after stroke and in-hospital mortality [28](#_ENREF_28" \o "Tziomalos, 2016 #304). More recently, higher BPV within 24h after stroke was demonstrated to be associated with poor prognosis after IVT [17](#_ENREF_17" \o "Berge, 2015 #227), [29](#_ENREF_29" \o "Manning, 2015 #219).

BP management in acute ischemic stroke is relevant for clinical practice, but individual strategies are not yet established. Here we determined the influence of BP and BPV during the first 24h on short- and long-term outcome in a large international cohort of patients who received IVT, reflecting the status quo of BP management.

**Methods:**

*Study setting*

Acute ischemic stroke patients treated with IVT (Actilyse®, Boehringer-Ingelheim, Germany) and recorded in the Safe Implementation of Treatment in Stroke (SITS) international registry between 2002 and 2013 (https://sitsinternational.org) were considered for analysis (N = 58294). Only patients with complete baseline, imaging, outcome, and BP-measurements (n=28.976, 49.7%) comprised the current study sample[30](#_ENREF_30" \o "Wahlgren, 2007 #43).

The SITS registry is an ongoing large international registry prospectively enrolling at 1422 centers in 70 countries. Stroke centers contributing to SITS assessed stroke severity with the National Institutes of Health Stroke Scale (NIHSS) score. For full details of methodology including issues of management regarding patients’ data including source data and identification, the reader is kindly referred to previous published work[30](#_ENREF_30" \o "Wahlgren, 2007 #43), [31](#_ENREF_31" \o "Wahlgren, 2008 #216).

*Definition of blood pressure variability*

BP values in SITS were documented at least at three time points – pretreatment, at 2 hours, and at 24 hours after IVT. At each time-point there was only one BP reading documented. Of these three systolic BP values BPV was calculated. As primary measure of variability, we choose successive variation (SV) for analysis of BPV (BPVSV), because it addresses the time sequence in measurements more appropriately than other measures[32](#_ENREF_32" \o "Schachinger, 1989 #213). SV was calculated as square root of average squared difference between two successive BP measurements according to following equation: 

*Outcome definitions*

Functional outcome at 3-month was measured by the modified Rankin scale (mRS) – it ranges from 0 to 6. If raters judged 0 or 1, excellent functional outcome, if 0 to 2, good or functional independent outcome was concluded.

The primary aim of this study was to investigate the relationship of the influence of BPVSV and pretreatment systolic BP (BPsys) on excellent and good outcome after 3-months. In addition, an ordinal analysis of the 3-months mRS was performed. Recanalization leads to an improvement in neurological outcome as measured early and may likely be associated with a drop in blood pressure *[33-35](#_ENREF_33" \o "Mazighi, 2009 #412)*. Because the overall number with documented cases of recanalization was low (<20%) and this was not the primary aim of the study, we chose two outcome definitions of early neurological improvement (ENI) within 24 hours as a proxy for presumed vessel patency: i) ENI20% defined as improvement of ≥20% on the NIHSS, because this definition was previously demonstrated to be the best predictor of functional 3-month outcome and ii) ENI8 defined as an improvement of ≥8 points on the NIHSS [36-38](#_ENREF_36" \o "Nam, 2009 #211).

Safety measures included the occurrence of symptomatic intracerebral hemorrhage (SICH) after IVT according to SITS and ECASS-2 definition (for details see online supplement).

*Ethics*

Patients within SITS received thrombolysis as standard of care. This was a retrospective analysis. Therefore, new ethics review was not necessary for data analysis because ethical approvals had been obtained in countries where they are required. In other countries SITS was approved as an anonymized register without need for ethical approval.

*Statistical Analysis*

*For information how the sample was preprocessed – that is imputation strategies, listwise deletion and coarsened exact matching — we kindly refer the reader to the methods part of the online supplement.*

Normally distributed data are presented as mean and standard deviation (SD), non-normally distributed data as median and interquartile range [IQR]. For categorical variables counts and percentages are given. Univariate statistics used Student’s T-test, Mann-Whitney test, or Chi-Square-Test where appropriate.

*Analysis of blood pressure variability*

BPVSV was primarily used as a continuous variable in all analyses. Importantly, BPVSV was categorized for presentation purposes of the matched cohort only, representing cohorts of low (BPVSV <15), medium (BPVSV 15—29.9), high (BPVSV 30—45), highest (BPVSV >45). Associations of covariates and factors on BPVSV were tested by Spearmans Rank, a linear multivariable regression analysis further estimated the relevance of each variable in the presence of others. Association between BPVSV and 3-months outcome were estimated by binomial and ordinal logistic regression. In multivariable regression analysis adjustments were made for age, sex, NIHSS, BPsys, history of arterial hypertension, history of diabetes mellitus, history of hypercholesterolemia, current smoking, prior stroke, history of atrial fibrillation (AF), history of coronary heart failure.

We allowed for interactions of BPsys and BPVSV on a multiplicative scale and compared the model including the interaction with the main model by a likelihood ratio test [39](#_ENREF_39" \o "David W. Hosmer, 2013 #123). For main predictors a two-sided p-value of <0.01, and for interactions terms a p-value of <0.05 was considered as statistically significant. For odds ratios and 95% confidence intervals to reflect meaningful values (because of the high number of patients), reported odds ratios for continuous variables BPVSV and BPsys reflect a change from the 25th to the 75th percentile. Graphical presentation of the interaction, BPsys\* BPVSV, is on the scale of predicted probabilities using example values of BPVSV (0, 15, 30, 45, 60) varying across all values of BPsys.

Statistical analysis was performed with Statistical Package for the Social Sciences, SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and R (R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. [http://www.R-project.org/)](http://www.R-project.org/%29).

Sensitivity analysis

Patients who suffer from AF usually present with higher variability in BP readings[40](#_ENREF_40" \o "Shuler, 1998 #305), [41](#_ENREF_41" \o "Pagonas, 2013 #306). Therefore, we excluded patients who had known history of atrial fibrillation at presentation, testing only non-AF-patients for sensitivity analysis. This sensitivity analysis should exclude that results of BPV are driven exclusively from AF population. We had no information in this dataset on patients with newly diagnosed AF.

**Results:**

*Patients’ characteristics according to successive variation of blood pressure (*BPVSV*)*

Of 28,976 patients in the entire cohort 16,434 patients remained after preprocessing. **Table 1** shows patients baseline characteristics in the entire cohort and the matched cohort. BPVSV was categorized into groups (<15, 15—29.9, 30—45, and >45) for presentation purposes only reflecting 60.2%, 32.4%, 6.0%, and 1.4% of the matched cohort, respectively.

*Successive Blood Pressure Variability*

Associations between BPVSV and other covariates were found. Best associative strength was found in a positive, moderate correlation of pretreatment systolic BP (*r* = 0.267, p < 0.000001) and BPVSV. Furthermore, longer stroke onset to treatment times (*r*= 0.029, p = 0.000001) and higher age (*r*= 0.101, p < 0.000001) were weakly correlated to higher BPVSV, whereas correlation between BPVSV and NIHSS (*r* = -0.013, p = 0.024) was hardly evident. Patients experiencing higher BPVSV were female, had history of hypertension, diabetes, hypercholesterolemia, AF, smoking, and had prior stroke (all p < 0.01). No association was found for patients with history of heart failure (p = 0.787).

To further determine which baseline factor would explain most of the variance of BPVSV, linear multivariable regression analysis demonstrated pretreatment systolic BP to be most influential (5.55% explained variance), followed by age (1.18% explained variance). Interestingly, patients with history of hypertension were only marginally predictive for higher BPVSV (0.2% explained variance). All other variables also explained less than 1% variance leaving 92% of the variance in BPV unexplained (**Figure 1**).

*Outcome analysis according to successive variation of blood pressure (*BPVSV*)*

*Early neurological improvement*

Regarding short-term outcome, univariate analysis of BPVSV was not significantly associated with ENI20% (p = 0.428) and ENI8 (p = 0.394). Adjustment with relevant confounders in multivariable analysis did not change this result (**Table 2**).

*3-months outcome*

Excellent outcome was not significantly associated with BPVSV by means of univariate (p = 0.346) and multivariable adjustment (**Table 2**).

Functional independency was less likely in patients with higher BPVSV by means of univariate (p = 0.021) and multivariable regression analysis (**Table 2**).

A shift to the next higher (worse) mRS category (categorical shift) was more likely in patients with higher BPVSV in multivariable regression analysis (**Table 2**).

Mortality within 90 days after stroke was more likely in patients who experienced higher BPVSV (univariable: p = 0.004, multivariable: **Table 2**).

*Symptomatic intracerebral hemorrhage*

In terms of safety, BPVSV associated with the presence of SICHSITS (p = 0.0001) and SICHECASS (p = 0.0017). Adjustment in multivariable analysis reinforced these results irrespective of the bleeding definition used (**Table 2**)

*Outcome analysis according to* pretreatment *systolic Blood Pressure (*BPVsys*)*

Higher BPVsys was significantly associated with lower odds ratios for early neurological improvement, lower rates of favorable outcome at 3 month and higher risk of SICH in multivariable analysis. No association with mortality was found (for details see **Table 2**).

*Successive Variation Blood Pressure Variability (*BPVSV*) and* pretreatment *systolic Blood Pressure (*BPsys*) Interaction (*BPVSV-by-BPsys *Interaction)*

Determining outcome across the mRS at different levels of BPVSV and across the range of BPsys revealed an X-shaped relationship (**Figure 2**): BPVSV—by—BPsys interaction was found for outcomes of ENI20% but not ENI8 for excellent and good functional outcome as well as for the shift analysis of the mRS. This relationship was not obvious for mortality and safety (**Table 3**).

*Sensitivity analysis of* BPVSV-by-BPsys *Interaction in patients presenting with no history of atrial fibrillation*

Outcome analysis in no-AF-patients regarding BPsys and BPVsv and their interaction was largely unchanged and is shown in supplemental Table I and Table II.

**Discussion:**

In this study with a large cohort of ischemic stroke patients treated with IVT, we highlight the prognostic significance of successive BPVSV for functional outcome after stroke and especially for safety. A novel finding in our study is the better prediction of short- and long-term functional outcomes when considering the reciprocal interactionof pretreatment BP (BPsys high, medium, or low) and the course of BP 24-hours post-thrombolysis (accounted by BPVSV).

BPV in our study was associated with several definitions of functional outcome and safety. Importantly, these results were independent of BPsys (a well-known predictor of safety [19](#_ENREF_19" \o "Butcher, 2010 #302), [20](#_ENREF_20" \o "Perini, 2010 #301) and functional outcome after stroke [6](#_ENREF_6" \o "Leonardi-Bee, 2002 #220), [8](#_ENREF_8" \o "Ahmed, 2009 #41), [11](#_ENREF_11" \o "Geeganage, 2010 #237), [17](#_ENREF_17" \o "Berge, 2015 #227), [42](#_ENREF_42" \o "Schrader, 2003 #225), [43](#_ENREF_43" \o "Potter, 2009 #224)). A post hoc analysis from The Third International Stroke Trial (IST-3) reported an association of higher BPV with adverse events, the occurrence of SICH and poor 6-months outcome[17](#_ENREF_17" \o "Berge, 2015 #227). Our results may complement those in so far that we found short-term BPV to be of significance for safety (SICH) and several long-term outcome definitions. Concerning short-term outcome (2 week outcome and in-hospital outcome), two most recent studies did not find any importance of BPV in outcome prediction[28](#_ENREF_28" \o "Tziomalos, 2016 #304), [29](#_ENREF_29" \o "Manning, 2015 #219). Our results support these studies for the most part as we found no clear association of BPV with early neurological improvement too (ENI20 and ENI8).

The overall comparability of those studies with ours is narrow due to smaller sample sizes, different acquisition of BP intervals, and various definitions of BPV and outcomes.

Pursuing the notion of both BP characteristics (BPsys and BPVsv) being relevant to several issues, we put both in context by analyzing if patients with a particular pretreatment BP would yield different functional outcomes with various degrees of BPV (see Figure 2A and 2B). For patients who presented with normal BPsys, neither high nor low, BPVsv seemed to influence the outcome in some way or other. However, patients presenting with low BPsys appeared to benefit from low BPVsv. Equally did patients with high pretreatment BPsys and high BPVsv. This combination (high BPsys + high BPVsv) appear for example when physicians actively intervene on high BPsys, but may also be attributed to the “natural” BP course after stroke – the trend of BP to decline over time. In this regard, the posthoc analysis of IST-3 suggested similarly a good outcome at six months after stroke when BP-lowering was more intense during the first 24h[17](#_ENREF_17" \o "Berge, 2015 #227) , whereas other studies did not [12-16](#_ENREF_12" \o "Muir, 2004 #236). In patients in whom pretreatment BPsys is within the normal range, physicians usually restrain active elevation of BP (resulting in low BPVSV). The combination of high BPsys and low BPVsv seems unfavorable, most probably because BPsys remains too high due to lack of extrinsic or intrinsic modulation or due to insufficient response to possible interventions. An equally unfavorable combination seems to be low BPsys and high BPVsv that might be explainable by exceedingly BP-lowering leading to cerebral hypoperfusion or vice versa unstable conditions and the need for interventional elevation of BP.

Overall, these results indirectly indicate that patients may benefit from BP management that is personalized. This hypothesis could (at least partially) explain inconsistencies in several observational studies concerning BP lowering, where some suggested much lower absolute BPsys values to be favorable (range between 140-150mmHg)[6](#_ENREF_6" \o "Leonardi-Bee, 2002 #220), [8](#_ENREF_8" \o "Ahmed, 2009 #41), [11](#_ENREF_11" \o "Geeganage, 2010 #237). In contrast, several posthoc analyses of randomized clinical trials reported no advantage[12-16](#_ENREF_12" \o "Muir, 2004 #236). The blood pressure arm of the ENCHANTED trial is still ongoing; possibly the results will reveal new insights regarding the importance of BP lowering in thrombolyzed patients[21](#_ENREF_21" \o "Anderson, 2016 #410).

Certainly, BP management in the acute phase of stroke should include aspects of the presence of penumbra, presence of vessel occlusion, collateral flow, revascularization status, and stroke etiology[44](#_ENREF_44" \o "Ntaios, 2012 #307). Although our analysis falls short to address these individual aspects due to its retrospective design, we interpret our findings a step towards a better understanding of BP and BPV in acute stroke.

The authors may also point towards a better understanding of variability as BP characteristic (see Manning Stroke 2015 for review[22](#_ENREF_22" \o "Manning, 2015 #308)). In observational studies, where BP management is not actively monitored, it is unclear what we exactly measure when we measure BPV. BPV is under the influence of numerous extrinsic (administered and pre-existing medication, arrhythmia requiring betablockade, vegetative and emotional stressor, positioning (e.g. lying vs. upright) and continuous recording vs manual measurement) and intrinsic factors (arterial hypertension, fluid balance, stroke subtype, recanalization, autonomic regulation or dysregulation)[45-47](#_ENREF_45" \o "Qureshi, 2004 #146). Even so, attempts to explain BPV in the multivariable analysis by all available patients’ baseline characteristics left 92% variance unexplained in our study.

Interestingly, BPsys was the strongest predictor for BPV. As for some definitions of BPV, this could easily be explainable because pretreatment systolic BP influences e.g. standard deviation to a certain extent (depending on the number of available BP readings). Therefore, we considered a similar type of influence for the variability measure chosen in this study (successive blood pressure variability). In the SITS-protocol BP is documented at only three time points, the individual centers were not required to standardize their protocol when measuring BP — both facts that might lead to bias in interpretation of BP and BPV.. In clinical routine BP is measured at least hourly after IVT up to follow-up imaging, unfortunately these data are not available in the SITS registry. However, as shown in the supplement we demonstrate that the variability formula of BPVSV is less prone to single values [32](#_ENREF_32" \o "Schachinger, 1989 #213). This also improves plausibility that our finding of BPsys-by-BPVSV interaction is not explainable as a by-product of the chosen BPV definition.

Besides the main limitation of uncontrolled data and retrospective analysis, our study has additional limitations. Although we demonstrated non-influence of NIHSS and other baseline factors on BPV in linear regression, BPV may still be an epiphenomenon of clinical parameters, e.g. severity of stroke, lesion growth (as demonstrated by Delgado-Mederos et al.[48](#_ENREF_48" \o "Delgado-Mederos, 2008 #186)), or BP-lowering interventions. We present an effect of the interaction between BP and BPV for the whole cohort and for those patients without AF, but most likely, there were subgroups of patients (different stroke etiologies, presence of penumbra, vessel occlusion, recanalization status, collateral flow) for whom this interaction might be more or less relevant. None of these factors was investigated in a well-structured way with respect to BPV.

Due to the retrospective design of this study we were not able to control neither for a single nor much less for all of those variables. Only about a half of all patients registered in SITS were further analyzed and after pre-processing only 16,434 patients (28%), this may have caused bias. Matching may reduce overall degree of bias [49-51](#_ENREF_49" \o "Ho D,  #125), however it has to be stressed that control of unobserved variables – as in randomized trials – is not possible.

Despite these limitations we interpret our findings as novel and significant with implications for patient care and future studies. The main strength of our study is that it comprises by far the largest cohort of IVT treated patients in whom this analysis has been completed.

**Conclusion:**

Blood pressure variability during 24h after thrombolysisis of significant but currently under investigated relevance for stroke outcome. Putting the course of blood pressure 24h post-thrombolysis in relation to its pretreatment value significantly improved the prediction of specific short- and long-term outcomes of stroke in this study. Thus, future clinical trials should carefully consider both – pretreatment blood pressure and its variability over time.

**Authors’ contributions:**

L.K. and C.H. developed the idea for this study by interaction of intellectual content, collected and analyzed clinical data, performed the statistical analysis, and contributed equally to writing the manuscript. N.A. collected and analyzed clinical data and contributed by editing the manuscript for important intellectual content. G.R. gave advice in statistical and mathematical methods and analysed clinical data. M.M., P.F. and KRL edited the manuscript for important intellectual content. P.R. collected and analyzed clinical data, supervised data acquisition, and edited the manuscript for important intellectual content. All authors revised the final version of the manuscript.

**Disclosures:**

L.K. and C.H. have nothing to declare.

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All other authors declare no conflicts of interest.

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**Table 1.** Patients characteristics and univariate outcome in the entire cohort, matched cohort including successive blood pressure variability

|  |  |  |  |
| --- | --- | --- | --- |
|  | Entire cohort | Matched cohort | *Successive blood pressure variability categories* |
|  | All(N = 28976) | All(N = 16434) | **<15**(N = 9893) |  | **15—29.9**(N = 5322) |  | **30—45**(N=988) |  | **>45**(N=231) |
| *Patients characteristics* |  |  |  |  |  |  |  |  |  |
| Age — y, median (IQR 25-75) | 70 (60—77) | 71 (63—77) | 71 (63—77) |  | 71 (63—77) |  | 73 (65—77) |  | 73 (66—78) |
| Baseline NIHSS, median (IQR 25-75) | 11 (7—17) | 11 (7—16) | 11 (7—16) |  | 11 (7—16) |  | 12 (7—17) |  | 12 (7—16) |
| Onset to treatment time — min | 147 (119—175) | 145 (120—170) | 145 (120—170) |  | 146 (120—170) |  | 145 (120—170) |  | 150 (120—174) |
| Pretreatment Systolic Blood Pressure | 150 (136—167) | 155 (140—168) | 155 (140—168) |  | 156 (141—169) |  | 157 (141—170) |  | 160 (140—173) |
| Sex — female, N (%) | 12373 (42.7) | 6625 (40.3) | 3950 (39.9) |  | 2150 (40.4) |  | 427 (43.2) |  | 98 (42.4) |
| History of arterial hypertension, N (%) | 18309 (63.2) | 11455 (69.7) | 6880 (69.5) |  | 3651 (68.6) |  | 738 (74.7) |  | 186 (80.5) |
| History of diabetes mellitus, N (%) | 4899 (16.9) | 1809 (11) | 1080 (10.9) |  | 566 (10.6) |  | 128 (13) |  | 35 (15.2) |
| History of hypercholesterolemia, N (%) | 9825 (33.9) | 5706 (34.7) | 3356 (33.9) |  | 1919 (36.1) |  | 362 (36.6) |  | 69 (29.9) |
| History of active smoking, N (%) | 6197 (21.4) | 3364 (20.5) | 1998 (20.2) |  | 1135 (21.3) |  | 184 (18.6) |  | 47 (20.3) |
| Prior stroke, N (%) | 3617 (12.5) | 2157 (13.1) | 1287 (13) |  | 655 (12.3) |  | 178 (18) |  | 37 (16) |
| History of atrial fibrillation, N (%) | 6641 (22.9) | 3975 (24.2) | 2338 (23.6) |  | 1316 (24.7) |  | 247 (25) |  | 74 (32) |
| History of coronary heart failure, N (%) | 2422 (8.4) | 1304 (7.9) | 747 (7.6) |  | 444 (8.3) |  | 89 (9) |  | 24 (10.4) |
| *Outcome definitions* |  |  |  |  |  |  |  |  |  |
| Symptomatic Intracerebral hemorrhage |  |  |  |  |  |  |  |  |  |
| SITS definition, N (%) | 412 (1.4) | 272 (1.7) | 144 (1.5) |  | 96 (1.8) |  | 23 (2.3) |  | 9 (3.9) |
| ECASS defintion, N (%) | 1322 (4.6) | 755 (4.6) | 426 (4.3) |  | 244 (4.6) |  | 64 (6.5) |  | 21 (9.1) |
| Modified Rankin Score d90, N (%) |  |  |  |  |  |  |  |  |  |
| 0 | 6602 (22.8) | 3732 (22.7) | 2264 (22.9) |  | 1209 (22.7) |  | 214 (21.7) |  | 45 (19.5) |
| 1 | 6088 (21) | 3570 (21.7) | 2151 (21.7) |  | 1200 (22.5) |  | 181 (18.3) |  | 38 (16.5) |
| 2 | 4567 (15.8) | 2660 (16.2) | 1631 (16.5) |  | 853 (16) |  | 146 (14.8) |  | 30 (13) |
| 3 | 3729 (12.9) | 2106 (12.8) | 1264 (12.8) |  | 682 (12.8) |  | 124 (12.6) |  | 36 (15.6) |
| 4 | 3239 (11.2) | 1879 (11.4) | 1131 (11.4) |  | 589 (11.1) |  | 123 (12.4) |  | 36 (15.6) |
| 5 | 1418 (4.9) | 763 (4.6) | 439 (4.4) |  | 252 (4.7) |  | 59 (6) |  | 13 (5.6) |
| 6 | 3333 (11.5) | 1724 (10.5) | 1013 (10.2) |  | 537 (10.1) |  | 141 (14.3) |  | 33 (14.3) |
| Early Neurological Improvement <24h |  |  |  |  |  |  |  |  |  |
| 8 points less on NIHSS | 6411 (22.1) | 3533 (21.5) | 2078 (21) |  | 1193 (22.4) |  | 220 (22.3) |  | 42 (18.2) |
| 20 % less on NIHSS | 18786 (64.8) | 10805 (65.7) | 6490 (65.6) |  | 3577 (67.2) |  | 607 (61.4) |  | 131 (56.7) |

**Table 2.** Adjusted influence of pretreatment systolic blood pressure and successive blood pressure variability on outcomes of short-term, safety, and long-term outcome

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Successive blood pressure variability (BPVSV)**odds ratio (95% confidence interval)† | P-Value | **Pretreatment systolic blood pressure (BPsys)**odds ratio (95% confidence interval) \* | P-Value |  |  |
| *Short term outcome* |  |  |  |  |  |  |
| Early neurological improvement (NIHSS improvement 20%) | 0.96 (0.93— 1.00) | 0.069 | **0.86 (0.82—0.90)** | **<0.0001** |  |  |
| Early neurological improvement (NIHSS 8-point) | 1.01 (0.96— 1.06) | 0.737 | **0.87 (0.82—0.92)** | **<0.0001** |  |  |
| *Outcome 90 days after stroke* |  |  |  |  |  |  |
| Excellent (mRS 0–1) | 0.98 (0.94—1.02) | 0.239 | **0.84 (0.80—0.89)** | **<0.0001** |  |  |
| Functional independent (mRS 0–2) | **0.94 (0.90—0.98)**  | **0.002** | **0.89 (0.84—0.93)** | **<0.0001** |  |  |
| Ordinal shift mRS (shift to next higher (worse) category) | **1.04 (1.01—1.08)**  | **0.014** | **1.14 (1.10—1.19)** | **0.014** |  |  |
| Death (mRS 6) | **1.10 (1.03—1.16)**  | **0.002** | 1.06 (0.98—1.15) | 0.135 |  |  |
|  |  |  |  |  |  |  |
| *Symptomatic intracerebral hemorrhage* |  |  |  |  |  |  |
| SITS definition | **1.24 (1.10—1.40)** | **0.0003** | **1.24 (1.03—1.48)** | **0.02** |  |  |
| ECASS definition | **1.14 (1.06—1.23)** | **0.0009** | **1.20 (1.08—1.34)** | **0.001** |  |  |

Adjusted for age, sex, baseline National Institutes of Health Stroke Scale (NIHSS), history of arterial hypertension, history of diabetes mellitus, history of hypercholesterolemia, history of smoking, history of atrial fibrillation, history of coronary heart failure, and prior stroke.

\*Indicating a 25 point change in systolic blood pressure (= change from 25th percentile to 75th percentile)
† Indicating a 12 point change in blood pressure variability (= change from 25th percentile to 75th percentile)

**Table 3.** Relationship of pretreatment systolic blood pressure and successive blood pressure variability \* across different outcomes in all patients

|  |  |
| --- | --- |
| **Interaction BPsys-by-BPVSV**P Interaction | ALL(n=16434) |
| *Short term outcome* |  |
| Early neurological improvement (NIHSS improvement 20%) | **0.001** |
| Early neurological improvement (NIHSS 8-point) | 0.09 |
| *Outcome 90 days after stroke* |  |
| Excellent (mRS 0–1) | **<0.0001** |
| Functional independent (mRS 0–2) | **0.002** |
| Ordinal shift mRS (shift to next higher (worse) category) | **<0.0001** |
| Death (mRS 6) | 0.11 |
|  |  |
| *Symptomatic intracerebral hemorrhage* |  |
| SITS definition | 0.343 |
| ECASS definition | 0.352 |

\*Multivariable regression analysis including multiplicative interaction of pretreatment systolic BP and successive BP-variability; adjusted for confounders of age, sex, baseline National Institutes of Health Stroke Scale (NIHSS), history of arterial hypertension, history of diabetes mellitus, history of hypercholesterolemia, history of smoking, history of atrial fibrillation, history of coronary heart failure, and prior stroke.

**Figure 1. Baseline factors explaining Successive Blood Pressure variability**



**Figure 2.** Relationship of pretreatment systolic BP and successive BPV influencing functional outcome: (A) Probability of reaching modified Rankin scale category by range of pretreatment systolic blood pressures; given are example categories of successive blood pressure variability (no=0, low=15, med=30, high=45, highest=60), (B) Probability of good functional outcome (mRS 0-2) for conditioned values of successive blood pressure variability (0, 15, 30, 45, 60).

A B

 