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Pulse Pressure Variability is Associated with Unfavorable Outcomes in Acute Ischemic Stroke Patients Treated with Intravenous Thrombolysis

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Abstract

Background and purpose: Blood pressure (BP) variability has been associated with worse neurologic outcomes in acute ischemic stroke (AIS) patients receiving treatment with intravenous thrombolysis (IVT). However, no study to date has investigated whether pulse pressure (PP) variability may be a superior indicator of the total cardiovascular risk, as measured by clinical outcomes.

Methods: We calculated PP variability from 24 hours PP measurements following tPA-bolus in AIS patients enrolled in the Combined Lysis of Thrombus using Ultrasound and Systemic tPA for Emergent Revascularization (CLOTBUST-ER) trial. The outcomes of interest were the pre-specified efficacy and safety endpoints of CLOTBUST-ER. All associations were adjusted for potential confounders in multivariable regression models.

Results: We analyzed data from 674 participants. PP variability was identified as the BP parameter with the most parsimonious fit in multivariable models of all outcomes, and was independently associated ($p<0.001$) with lower likelihood of both 24-hour neurological improvement and 90-day independent functional outcome. PP variability was also independently related to increased odds of any intracranial bleeding ($p=0.011$) and 90-day mortality ($p<0.001$). Every 5mmHg-increase in the 24-hour PP variability was independently associated with a 36% decrease in the likelihood of 90-day independent functional outcome ($OR_{adjusted}= 0.64$, 95%CI:0.52-0.80) and a 60% increase in the odds of 90-day mortality ($OR_{adjusted}= 1.60$, 95%CI:1.23-2.07). PP variability was not associated with symptomatic intracranial bleeding at either 24 or 36 hours after IVT administration.

Conclusions: Increased PP variability appears to be independently associated with adverse short-term and long-term functional outcomes of AIS patients treated with IVT.

Introduction

Elevated blood pressure (BP) levels, both prior to and after the administration of intravenous thrombolysis (IVT), are known to have an adverse impact on the outcomes of patients with acute ischemic stroke (AIS) receiving tissue plasminogen activator (tPA). Increasing BP values have been independently associated with increased likelihood of symptomatic intracranial hemorrhage (sICH) and lower probability of functional independence at 3 months.[1] Blood pressure (BP) variability has increasingly been recognized as a novel risk factor that can provide complementary information on clinical outcomes of AIS patients treated with systemic thrombolysis.[2] Increased systolic BP (SBP) and diastolic BP (DBP) variability has previously been independently associated with worse functional outcomes in AIS receiving treatment with IVT.[3-5]

However, no study to date has evaluated the potential impact of pulse pressure (PP) variability, which is considered to be a superior indicator of the total cardiovascular risk, on the outcomes of AIS patients treated with IVT.[6] Moreover, elevated PP levels in the acute phase of stroke have emerged as an independent adverse

predictor of short-term and long-term outcomes in patients with acute or hemorrhagic stroke.[7-9] In view of these considerations, we sought to evaluate the association of PP variability during the first 24 hours following tPA bolus on the outcomes of AIS patients enrolled in the Combined Lysis of Thrombus using Ultrasound and Systemic tPA for Emergent Revascularization (CLOTBUST-ER) trial.[10]

Methods

We analyzed hourly BP measurement data during the first 24 hours following the tissue plasminogen activator (tPA) bolus in patients with AIS symptom onset less than 4.5 hours who were randomized in the CLOTBUST-ER trial.[11] Detailed inclusion and exclusion criteria, comprehensive trial protocol and statistical analysis plan of CLOTBUST-ER have been published elsewhere.[8] BP measurements prior to the tPA bolus were also recorded for all participants.[10,11] All patients in the active (ultrasound+tPA treatment) and control (tPA treatment only) groups underwent serial BP measurements with automated BP monitors used at each individual center every 15 minutes for the first 2 hours, every 30 minutes from two to eight hours and then hourly from eight to twenty four hours after the tPA bolus. [10,11] BP goals were prespecified in the study protocol as SBP ≤185mmHg and DBP ≤110mmHg prior to the tPA infusion; the BP goals were set at SBP ≤180mmHg and DBP ≤105 mmHg during and for the first 24 hours after the tPA infusion initiation,[10,11] according to the recommendations from the American Heart Association (AHA) / American Stroke Association (ASA).[12] BP measurement frequency and pre-specified goals described above were univocally followed by all participating centers. CLOTBUST-ER investigators were instructed to implement their site-specific blood pressure lowering algorithms, with no particular recommendations on the antihypertensive agent to be used.[11]

Pulse pressure (PP) was calculated by subtracting the diastolic BP from the corresponding SBP reading of each patient at a given time point. We estimated the SBP, DBP and PP values for each subject during the 24-hour monitoring period.[13] We additionally calculated the corresponding variability of each of the aforementioned BP parameters during the 24-hour measurement period as the within-subject standard deviation of mean,[14,15] and also the association with baseline National Institutes of Health Stroke Scale score.

We evaluated the associations of SBP, DBP and PP variability within the first 24 hours with the following pre-specified efficacy endpoints of CLOTBUST-ER[10,11]: i) the distribution of modified Rankin Scale (mRS) scores (ranging between 0 and 6) at day 90 after tPA administration ii) rate of independent functional outcome at 90 days following tPA treatment, defined as a mRS score of 0 or 1 for subjects with pretreatment National Institutes of Health Stroke scale (NIHSS) scores of 10–14 and mRS scores less or equal to 2 for subjects with pretreatment NIHSS scores more than 14 at the 90 day follow-up; iii) rate of clinical recovery assessed at 24 hours after tPA administration, defined as a reduction of 10 or more points on the 24 hour

NIHSS score compared with pretreatment NIHSS, or a total 24 hour NIHSS score of 3 or less; iv) rate of neurological improvement at 24 hours after tPA administration, defined as a reduction of 5 or more points on the 24 hour NIHSS score compared with the pretreatment NIHSS score; v) the distribution of mRS scores at day 7 after tPA administration or at hospital discharge.

We also assessed the relationships of SBP, DBP and PP variability within the first 24 hours with the following prespecified safety endpoints of CLOTBUST-ER[10,11,16] i) rates of sICH at 24 hours, defined as any parenchymal hemorrhage type 2 associated with 4 or more points worsening on the NIHSS scale compared with the best prior examination within 24h after tPA bolus; ii) rates of sICH at 36 hours, defined per the SITS MOST definition as local or remote parenchymal hemorrhage type 2 on the 22–36 h post-treatment imaging scan, combined with a neurological deterioration of 4 points or more on the NIHSS score from baseline, or from the lowest NIHSS value between baseline and 24 h, or leading to death; iii) presence of any ICH within 24 hours following tPA administration; iv) asymptomatic ICH within 24 hours after tPA bolus, defined as any ICH on neuroimaging not conforming to the definition of neurological deterioration; v) rates of all-cause mortality within the first 90 days following tPA administration.

The ascertainment of both NIHSS and mRS-scores was performed by trained and certified investigators of the CLOTBUST-ER trial. All intracranial bleeds that were associated with neurological deterioration, as defined above, were sent to a central imaging core lab for independent adjudication.[10,11]

Statistical analysis

Patients with missing follow-up data at three months were censored from analyses of efficacy endpoints that were assessed at 90 days after symptom onset. The association of each BP parameter with the safety and efficacy endpoints of interest was investigated in multivariable logistic and ordinal regression models adjusting for all baseline characteristics. All baseline characteristics, including pre-treatment BP, which were associated with the corresponding endpoints under evaluation in initial univariable analyses at p values less than 0.1 (Supplemental Tables I & II). The final variables that were independently associated in the multivariable regression analyses with the outcomes of interest were selected using an alpha value of 0.05. Adjusted associations were provided as odds ratios (ORs) or common odds ratios (cORs), with their corresponding 95% confidence intervals (95%CI). In cases of more than one BP parameter independently associated with the same outcome of interest we compared the fit of the different multivariable models with the use of the Akaike Information Criterion (AIC), where a smaller AIC value indicated a better fit with the data and hence a superior multivariate logistic regression model.[17,18] For the multivariable models with the lowest AIC, we provided additional analyses and graphical representations of the probability of each outcome of

interest by 5 mmHg sequential increases of the corresponding blood pressure parameter. Finally, we used the Kruskal-Wallis test to investigate for potential differences in the PP variability in the first 24 hours following tPA bolus according to the category of the antihypertensive agent that was used.

All statistical analyses were conducted with the Stata Statistical Software Release 13 (College Station, TX, StataCorp LP).

The study was approved by the institutional review board at every site or national ethics committee, as required.[11] Written informed consent was obtained from the patient or a legal representative before enrolment.[11]

Data Availability Statement

Data will be available from corresponding author upon reasonable request.

Results

From the total 676 patients randomized in the CLOTBUSTER trial we excluded 2 patients due missing all serial BP measurements during the first 24 hours following tPA bolus administration. The mean number of serial 24 hour BP recordings per the remaining 674 patients (mean age: 66.8±10.6 years, median baseline NIHSS score: 14 points) was 22 (median 24, interquartile range 22-24). Patient baseline characteristics and outcomes are presented in Table 1.

Multivariable analyses are presented in Supplemental Table III. The likelihood of an independent functional outcome at 90 days was independently associated with the PP variability per 1mmHg increase. Clinical recovery at 24 hours was also independently associated with the SBP variability, DBP variability and PP variability per 1mmHg increase. The probability of 24-hour neurological improvement was independently associated with the SBP variability, DBP variability and PP variability per 1mmHg increase. Neurological deterioration in the first 24 hours after tPA bolus was independently associated with the SBP variability, DBP variability and PP variability per 1mmHg increase. Functional improvement at 7 days after hospital admission or at hospital discharge was independently associated with the 24-hour SBP variability, DBP variability and PP variability per 1mmHg increase. Likewise, 90-day functional improvement was independently related to the 24-hour SBP variability, DBP variability and PP variability per 1mmHg increase.

PP variability was identified as the BP parameter with the most parsimonious fit, associated with the smallest AIC values from all BP parameters in the aforementioned multivariate models (Supplemental Table III). PP variability was also the only blood pressure parameter that was independently associated with a higher risk for any ICH at 24 hours ($OR_{adjusted}$=1.05, 95%CI: 1.01-1.09) and all-cause mortality ($OR_{adjusted}$=1.09, 95%CI: 1.04-1.13) per 1mmHg increase. The probability of symptomatic ICH at either 24 or 36 hours after

IVT administration was not found to be related to SBP, DBP or PP variability (Supplemental Table III). Figure 1 provides a graphical representation of the sequential mean PP measurements for the first 24 hours after tPA bolus in patients with and without neurological deterioration at 24 hours.

Every 5mmHg increase in the 24-hour PP variability (Table 2) was independently associated with a lower likelihood of 24-hour neurological improvement ($OR_{adjusted}$=0.66, 95%CI: 0.54-0.80), lower likelihood of 24-hour clinical recovery ($OR_{adjusted}$=0.71, 95%CI: 0.57-0.88; Figure 2A), decreased odds of independent functional outcome at 90 days ($OR_{adjusted}$=0.64, 95%CI:0.52-0.80; Figure 2B), functional improvement (shift analysis of 1 point decrease in mRS-scores across all subgroups) at day 7 or discharge ($cOR_{adjusted}$=0.68, 95%CI:0.57-0.82), and at 90 days ($cOR_{adjusted}$=0.66, 95%CI: 0.55-0.78) in multivariable binary or ordinal logistic regression models. Finally, a 5mmHg increase in 24-hour PP variability was independently related to increased odds of all-cause mortality at 90 days ($OR_{adjusted}$=1.60, 95%CI: 1.23-2.07; Figure 3A) in multivariable analyses adjusting for potential confounders. The corresponding association of 5mmHg increase in PP variability with the likelihood of any ICH at 24-hours did not retain its statistical significance in multivariable logistic regression models ($OR_{adjusted}$ =1.21, 95%CI: 0.94-1.56; Figure 3B).

Patients with history of antihypertensive treatment during the first 24 hours after tPA administration were found to have significantly higher levels of 24-hour PP variability compared to patient receiving no antihypertensive treatment (13.8±5.5 vs. 12.5±5.5, p=0.006). No difference in the levels of 24 hour PP variability according to the category of the antihypertensive agent used was uncovered (p=0.498; Figure 4).

Discussion

The present analyses of CLOTBUSTER data indicate that PP variability during the first 24 hours following the tPA bolus has a significant predictive value for both short-term and long-term clinical outcomes in AIS patients. Every 5mmHg increase in the 24-hour PP variability was independently associated with a 34% lower chance of 24-hour neurological improvement, 29% lower likelihood of clinical recovery at 24 hours, 36% decrease in the likelihood of 90-day independent functional outcome and a 60% increase in the odds of 90-day mortality.

Our findings are in accordance to previous observational studies in consecutive AIS patients with and without treatment with IVT, which reported an independent association of PP with increased risk of mortality both at hospital discharge and at 1 year following stroke onset, higher likelihood of neurological deterioration during hospitalization and functional dependence at three months, and increased odds of 1 year stroke recurrence .[8,9,19,20] PP variability during endovascular thrombectomy (EVT) has also been identified as an independent predictor of worse clinical outcomes in AIS patients receiving treatment with EVT.[21] Interestingly,

widened PP has also been highlighted as an independent predictor for higher mortality in ICH patients.[22] PP in the acute stage of ischemic stroke has been reported to have a nonlinear J-shaped relationship with major vascular events and stroke recurrence during the first year after stroke onset, displaying a stronger predictive power than other commonly used BP parameters.[23] In addition, primary prevention studies have provided robust evidence that increased PP is strongly associated with adverse long-term outcomes, including vascular events, first-ever stroke and all-cause mortality.[24]

The superiority of PP as a cardiovascular risk marker in hypertension is well established, while it is known that with advancing age, the optimal predictor of cardiovascular risk shifts from diastolic BP to systolic BP and then to PP.[25] It is also known that at optimal achieved systolic BP, cardiovascular risk is still defined by low or high diastolic BP, highlighting that PP is potentially more informative than individual information on systolic or diastolic BP measurements.[26] Elevated PP, as a marker of arterial stiffness, has been correlated with a higher affinity to mortality and dependency risk following ischemic stroke compared to other BP indices.[27] Apart from elevated PP being a known surrogate marker of arterial stiffness, it has been associated with impairment of collateral circulation in patients with AIS due to large artery atherosclerosis.[28] Increased PP results in a cerebral blood flow pulsatility increment, which could be harmful to cerebral microcirculation at the acute phase of cerebral ischemia.[29] On the other hand, a low PP may reduce cerebral perfusion by disrupting the autoregulation of cerebral blood flow during the acute stage of an ischemic stroke.[30]

To the best of our knowledge, the present study is the first to highlight the impact of PP variability on the short-term and long-term outcomes of AIS patients treated with IVT using data from a phase III RCT with an adequate sample of patients and consecutive BP recordings in the acute stroke stage. Compared to previous reports investigating the association of SBP or DBP variability with the outcomes following IVT treatment for AIS, we hypothesized that PP variability as a potentially superior marker of arterial stiffness and cerebrovascular hemodynamics would provide additional insight. Nevertheless, some limitations of the present report also need to be acknowledged. First, per study protocol there are no data on the recanalization status during the first 24 hours after tPA bolus. Therefore, potential differences on the reported associations according to the recanalization status, or the impact of recanalization status on PP variability, cannot be further investigated. However, observational studies of AIS patients treated with EVT suggest that the association of increased BP variability with worse clinical outcomes is present in both successfully recanalized and non-recanalized patient groups.[31,32] Additionally, we have no information on the timing of intracranial bleeding, therefore increased PP variability could be the result rather than the cause of intracranial bleeding. Moreover, as no follow-up imaging data on the extent of cerebral ischemia were available within CLOTBUST-ER we were unable to evaluate the association of PP variability with infarct expansion. Second, no independent

association of PP –or any other BP parameter– with the sICH risk was identified in our multivariable analyses. Even though previous studies have reported a significant association of poor outcome with increased BP variability despite the lack of any association with ICH occurrence,[33] we consider that the lack of any association between PP variability and sICH may be related to the limited number of sICH events at both 24 (n=13) and 36 hours (n=15) within the CLOTBUSTER trial, and therefore the limited statistical power to uncover a significant association. Third, as BP variation is known to differ significantly between stroke subtypes[34] we cannot exclude the confounding role of different stroke etiology and underlying pathophysiologic mechanisms (embolism vs. in-situ atherothrombosis) in the reported outcomes. However, taking into account that patients were included in the CLOTBUST-ER trial if they had an NIHSS score of at least 10, with the vast majority (72%) of enrolled patients finally having NIHSS scores of 12 or more,[35] we postulate that the percentage of patients with non-embolic stroke (lacunar infarcts) is negligible. In the presence of a proximal vessel occlusion, the association of increased BP variability with worse neurological outcome has been reported to be more pronounced in patients with large lesion core volume, concurrent viable ischaemic penumbra and good collaterals.[36] Finally, although differences on the effect of classes of anti-hypertensives in the SBP variability has previously been suggested,[37,38] in our analyses we failed to uncover any differences in PP variability according to classes of anti-hypertensive medications used in CLOTBUST-ER. The disparity of our findings with previous reports could be attributed to the different patient population with AIS in our study and the preference of certain drug classes over another (Supplemental Figure I), suggesting the possibility of selection bias.

In conclusion, increased PP variability appears to be independently associated with adverse short-term and long-term clinical outcomes in AIS patients treated with IVT. Our report adds to the evidence that variability of BP is detrimental in the setting of IVT treatment for AIS, suggesting that tight BP monitoring and control need to be implemented during the first hours following IVT administration. Additionally, the use of antihypertensive agents known to be associated with less blood pressure fluctuations (e.g. calcium channel blockers, non-loop diuretics) might be favored over antihypertensive medications that have been related with increased blood pressure variability (e.g. b-blockers). [37,38] The potential effect of pharmacological interventions aiming at reducing PP variability and improving functional outcome of AIS patients treated with IVT needs to be tested within the setting of a properly designed and adequately powered RCT.

Disclosures

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References

1. Malhotra K, Ahmed N, Filippatou A, Katsanos AH, Goyal N, Tsioufis K, et al. Association of Elevated Blood Pressure Levels with Outcomes in Acute Ischemic Stroke Patients Treated with Intravenous Thrombolysis: A Systematic Review and Meta-Analysis. J Stroke. 2019;21:78-90.

2. Tsivgoulis G, Ntaios G. Blood pressure variability in subacute ischemic stroke: a neglected potential therapeutic target. Neurology. 2012;79:2014-5.

3. Endo K, Kario K, Koga M, Nakagawara J, Shiokawa Y, Yamagami H, et al. Impact of early blood pressure variability on stroke outcomes after thrombolysis: the SAMURAI rt-PA Registry. Stroke. 2013 Mar;44:816-8.

4. Kellert L, Hametner C, Ahmed N, Rauch G, MacLeod MJ, Perini F, et al. Reciprocal Interaction of 24-Hour Blood Pressure Variability and Systolic Blood Pressure on Outcome in Stroke Thrombolysis. Stroke. 2017;48:1827-1834.

5. Delgado-Mederos R, Ribo M, Rovira A, Rubiera M, Munuera J, Santamarina E, et al. Prognostic significance of blood pressure variability after thrombolysis in acute stroke. Neurology. 2008;71:552-8.

6. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart Disease? The Framingham heart study. Circulation. 1999;100:354-60.

7. Aslanyan S, Weir CJ, Lees KR; GAIN International Steering Committee and Investigators. Elevated pulse pressure during the acute period of ischemic stroke is associated with poor stroke outcome. Stroke. 2004;35:e153-5.

8. Chang JJ, Khorchid Y, Dillard K, Kerro A, Burgess LG, Cherkassky G, et al. Elevated Pulse Pressure Levels Are Associated With Increased In-Hospital Mortality in Acute Spontaneous Intracerebral Hemorrhage. Am J Hypertens. 2017;30:719-727.

9.Tsivgoulis G, Spengos K, Zakopoulos N, Manios E, Xinos K, Vassilopoulos D, Vemmos KN. Twenty four hour pulse pressure predicts long term recurrence in acute stroke patients. J Neurol Neurosurg Psychiatry. 2005;76:1360-5.

10. Alexandrov AV, Köhrmann M, Soinne L, Tsivgoulis G, Barreto AD, Demchuk AM, et al. Safety and efficacy of sonothrombolysis for acute ischaemic stroke: a multicentre, double-blind, phase 3, randomised controlled trial. Lancet Neurol. 2019;18:338-347.

11. Schellinger PD, Alexandrov AV, Barreto AD, Demchuk AM, Tsivgoulis G, Kohrmann M, et al. Combined lysis of thrombus with ultrasound and systemic tissue plasminogen activator for emergent revascularization in acute ischemic stroke (CLOTBUST-ER): design and methodology of a multinational phase 3 trial. Int J Stroke. 2015;10:1141-8.

12. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44:870-947.

13. Vemmos KN, Tsivgoulis G, Spengos K, Zakopoulos N, Synetos A, Kotsis V, et al. Association between 24-h blood pressure monitoring variables and brain oedema in patients with hyperacute stroke. J Hypertens. 2003;21:2167-73.

14. Zakopoulos NA, Tsivgoulis G, Barlas G, Papamichael C, Spengos K, Manios E, et al. Time rate of blood pressure variation is associated with increased common carotid artery intima-media thickness. Hypertension. 2005;45:505-12.

15. Zakopoulos NA, Tsivgoulis G, Barlas G, Spengos K, Manios E, Ikonomidis I, et al. Impact of the time rate of blood pressure variation on left ventricular mass. J Hypertens. 2006;24:2071-7.

16. Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet 2007;369:275-82.

17. Akaike, H. Likelihood of a model and information criteria. Journal of Econometrics 1981; 16: 3-14.

18. Matusevicius M, Cooray C, Bottai M, Mazya M, Tsivgoulis G, Nunes AP, et al. Blood Pressure After Endovascular Thrombectomy: Modeling for Outcomes Based on Recanalization Status. Stroke. 2019 Dec 11:STROKEAHA119026914. doi: 10.1161/STROKEAHA.119.026914. [Epub ahead of print]

19. Vemmos KN, Tsivgoulis G, Spengos K, Manios E, Daffertshofer M, Kotsis V, et al. Pulse pressure in acute stroke is an independent predictor of long-term mortality. Cerebrovasc Dis. 2004;18:30-6.

20. Grabska K, Niewada M, Sarzyńska-Długosz I, Kamiński B, Członkowska A. Pulse pressure--independent predictor of poor early outcome and mortality following ischemic stroke. Cerebrovasc Dis. 2009;27:187-92.

21. Maïer B, Turc G, Taylor G, Blanc R, Obadia M, Smajda S, et al. Prognostic Significance of Pulse Pressure Variability During Mechanical Thrombectomy in Acute Ischemic Stroke Patients. J Am Heart Assoc. 2018;7:e009378.

22. Chang JJ, Khorchid Y, Dillard K, Kerro A, Burgess LG, Cherkassky G, et al. Elevated Pulse Pressure Levels Are Associated With Increased In-Hospital Mortality in Acute Spontaneous Intracerebral Hemorrhage. Am J Hypertens. 2017;30:719-727.

23. Lee KJ, Kim BJ, Han MK, Kim JT, Cho KH, Shin DI, et al. Predictive Value of Pulse Pressure in Acute Ischemic Stroke for Future Major Vascular Events. Stroke. 2018 Jan;49:46-53.

24. Mancusi C, Losi MA, Izzo R, Canciello G, Carlino MV, Albano G, et al. Higher pulse pressure and risk for cardiovascular events in patients with essential hypertension: The Campania Salute Network. Eur J Prev Cardiol. 2018;25:235-243.

25. Franklin SS, Larson MG, Khan SA, Wong ND, Leip EP, Kannel WB, Levy D. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. Circulation 2001; 103:1245–1249.

26. Böhm M, Schumacher H, Teo KK, Lonn E, Mahfoud F, Mann JFE, et al. Achieved diastolic blood pressure and pulse pressure at target systolic blood pressure (120-140 mmHg) and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials. Eur Heart J. 2018;39:3105-3114.

27. Dawson SL, Manktelow BN, Robinson TG, Panerai RB, Potter JF. Which parameters of beat-to-beat blood pressure and variability best predict early outcome after acute ischemic stroke? Stroke 2000;31:463–468.

28. Acampa M, Romano DG, Lazzerini PE, Leonini S, Guideri F, Tassi R, et al. Increased Arterial Stiffness is Associated with Poor Collaterals in Acute Ischemic Stroke from Large Vessel Occlusion. Curr Neurovasc Res. 2018;15:34-38.

29. Ogoh S, Fadel PJ, Zhang R, Selmer C, Jans Ø, Secher NH, Raven PB. Middle cerebral artery flow velocity and pulse pressure during dynamic exercise in humans. Am J Physiol Heart Circ Physiol 2005; 288:H1526-H1531.

30. Tang SC, Yin JH, Liu CH, Sun MH, Lee JT, Sun Y, et al. Low Pulse Pressure After Acute Ischemic Stroke is Associated With Unfavorable Outcomes: The Taiwan Stroke Registry. J Am Heart Assoc. 2017;6. pii: e005113. doi: 10.1161/JAHA.116.005113.

31. Anadani M, Orabi MY, Alawieh A, Goyal N, Alexandrov AV, Petersen N, et al. Blood Pressure and Outcome After Mechanical Thrombectomy With Successful Revascularization. Stroke. 2019;50:2448-2454.

32. Goyal N, Tsivgoulis G, Pandhi A, Dillard K, Alsbrook D, Chang JJ, et al. Blood pressure levels post mechanical thrombectomy and outcomes in non-recanalized large vessel occlusion patients. J Neurointerv Surg. 2018;10:925-931.

33. Kellert L, Sykora M, Gumbinger C, Herrmann O, Ringleb PA. Blood pressure variability after intravenous thrombolysis in acute stroke does not predict intracerebral hemorrhage but poor outcome. Cerebrovasc Dis. 2012;33:135-40.

34. Tsivgoulis G, Zakopoulos N, Spengos K. Impact of stroke subtype on blood pressure course during the acute stage of cerebral ischemia. Stroke. 2007;38:860.

35. Alexandrov AV, Tsivgoulis G, Köhrmann M, Katsanos AH, Soinne L, Barreto AD, et al. Endovascular equipoise shift in a phase III randomized clinical trial of sonothrombolysis for acute ischemic stroke. Ther Adv Neurol Disord. 2019;12:1756286419860652.

36. de Havenon A, Bennett A, Stoddard GJ, Smith G, Chung L, O'Donnell S, et al. Determinants of the impact of blood pressure variability on neurological outcome after acute ischaemic stroke. Stroke Vasc Neurol. 2017;2:1-6.

37. Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. Lancet 2010;375:906–915.

38. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, et al. Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. Lancet Neurol. 2010;9:469-80.

TABLES

Table 1. Baseline characteristics and outcomes of the study population

Variables	
Baseline characteristics	
Sonothrombolysis treatment (%)	334 (49.5%)
Age (years, mean±SD)	66.8±10.6
Male sex (%)	392 (58.2%)
Baseline NIHSS score (median, IQR)	14 (11-18)
Hypertension (%)	409 (60.9%)
Diabetes mellitus (%)	155 (23.0%)
Atrial fibrillation (%)	116 (17.2%)
Systolic BP before alteplase bolus (mmHg, mean±SD)	150.0±20.3
Diastolic BP before alteplase bolus (mmHg, mean±SD)	81.7±13.2
Serum glucose before alteplase bolus (mg/dl, mean±SD)	138.5±53.2
Time from symptom onset to alteplase bolus (min, median, IQR)	121 (95-165)
Alteplase bolus within 3h from symptom onset (%)	562 (83.5%)
USA centers (%)	91 (13.5%)
Any antihypertensive treatment during the first 24 hours after alteplase bolus	190 (28.7%)
Efficacy outcomes	
Independent functional outcome at 90 days (%)	227 (37.1%)*
Days to discharge (median, IQR)	7 (5-12)**
NIHSS score at 24 hours (median, IQR)	8 (3-15)***
Clinical recovery at 24 h (%)	216 (34.1%)***
Neurological improvement at 24 h (%)	356 (56.2%)***
mRS at 7-days/ hospital discharge (median, IQR)	3 (1-5)****
mRS at 90 days	3 (1-4)*
Safety outcomes	
Symptomatic ICH at 36 hours (%)	15 (2.2%)

Symptomatic ICH at 24 hours (%)	13 (1.9%)
Asymptomatic ICH at 24 hours (%)	60 (8.9%)
Any ICH at 24 hours (%)	73 (10.8%)
All-cause mortality at 90 days (%)	99 (16.2)*

* missing data in 62 patients

** missing data in 89 patients

*** missing data in 41 patients

**** missing data in 59 patients

BP: blood pressure, SD: standard deviation, NIHSS: National Institutes of Health Stroke Scale, IQR: interquartile range, NIHSS: National Institutes of Health Stroke Scale, mRS: modified Rankin Scale, ICH: intracranial hemorrhage

Table 2. Overview of the independent associations of efficacy and safety endpoints in the study population with 24-hour pulse pressure variability increase per 1 mmHg and 5 mmHg on multivariable binary logistic and ordinal logistic regression models adjusting for potential confounders.

Outcome	per 1mmHg increase in PPV		per 5mmHg increase in PPV	
	$OR_{adjusted}$ (95%CI)	p-value	$OR_{adjusted}$ (95%CI)	p-value
Independent functional outcome at 90 days	0.91 (0.87, 0.96)	<0.001	0.64 (0.52, 0.80)	<0.001
Clinical recovery at 24 h	0.91 (0.87, 0.96)	<0.001	0.71 (0.57, 0.88)	0.002
Neurological improvement at 24 hours	0.91 (0.87, 0.94)	<0.001	0.66 (0.54, 0.80)	<0.001
Neurological deterioration at 24	1.06 (1.01, 1.11)	0.013	1.32 (0.99, 1.78)	0.062

hours				
mRS at 7 days/ discharge*	0.98 (0.97, 0.99)	<0.001	0.68 (0.57, 0.82)	<0.001
mRS at 90 days*	0.98 (0.97, 0.99)	<0.001	0.66 (0.55, 0.78)	<0.001
Symptomatic ICH at 24 hours	1.01 (0.98, 1.04)	0.592	1.32 (0.75, 2.34)	0.333
Symptomatic ICH at 36 hours	1.01 (0.98, 1.03)	0.680	1.49 (0.88, 2.51)	0.137
Asymptomatic ICH at 24 hours	1.00 (0.98, 1.02)	0.922	1.09 (0.80, 1.47)	0.591
Any ICH at 24 hours	1.05 (1.01, 1.09)	0.011	1.21 (0.94-1.56)	0.142
Mortality at 30 months	1.09 (1.04, 1.13)	<0.001	1.60 (1.23-2.07)	<0.001

*reported as common odds ratios

All associations are adjusted for the baseline characteristic associated with the corresponding outcome of interest with a p value of less than 0.1 in univariable analyses provided in Supplemental Tables III&IV

PPV: pulse pressure variability, OR: odds ratio, mRS: modified Rankin Scale, ICH: intracranial hemorrhage

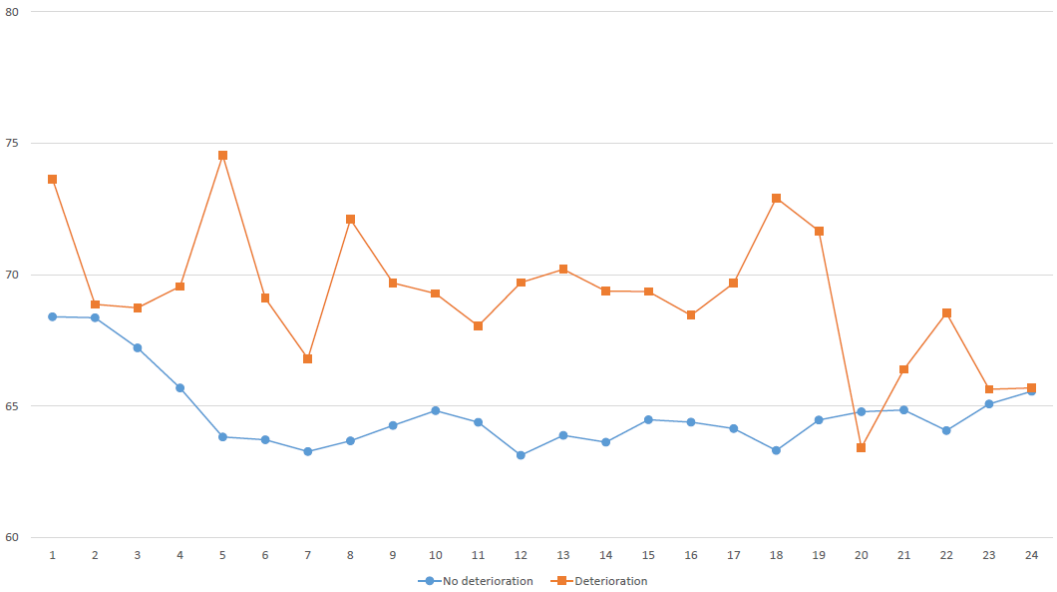
FIGURES

Figure 1. Graphical representation of sequential hourly measurements of mean pulse pressure for the first 24 hours after tPA bolus in patients with and without neurological deterioration at the first 24 hours following tPA bolus.

Figure 2. Graphical representation of the probability of (A) 24-hour clinical recovery and (B) 90-day independent functional outcome by 5mmHg increase in the 24-hour pulse pressure variability at 24-hours following tPA bolus.

Figure 3. Graphical representation of the probability of (A) 90-day all-cause mortality and (B) any intracranial hemorrhage by 5mmHg increase in the 24-hour pulse pressure variability at 24-hours following tPA bolus.

Figure 4. Box plots on the pulse pressure variability at 24-hours following tPA bolus stratified by the classes of the antihypertensive agents used.



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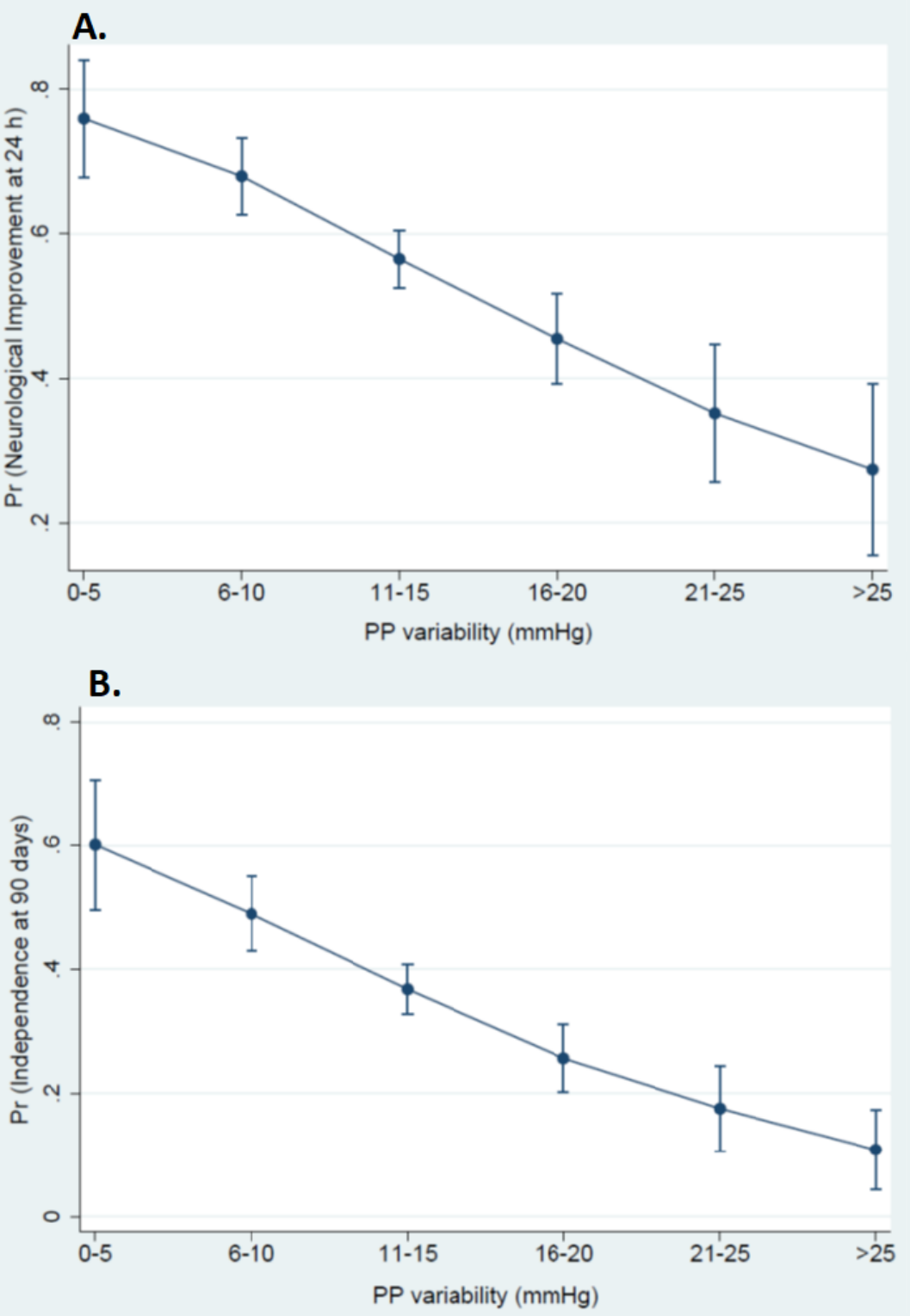

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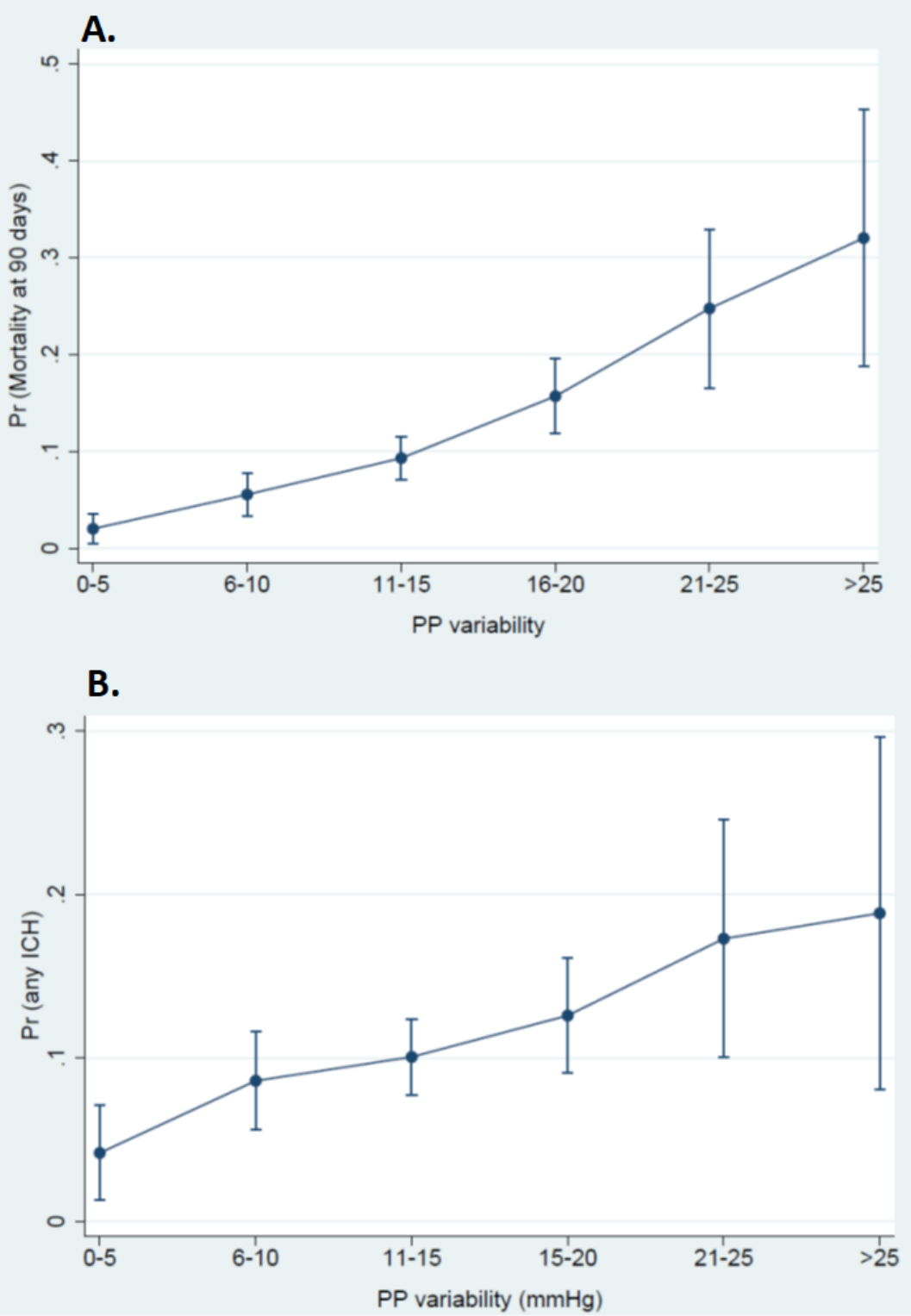

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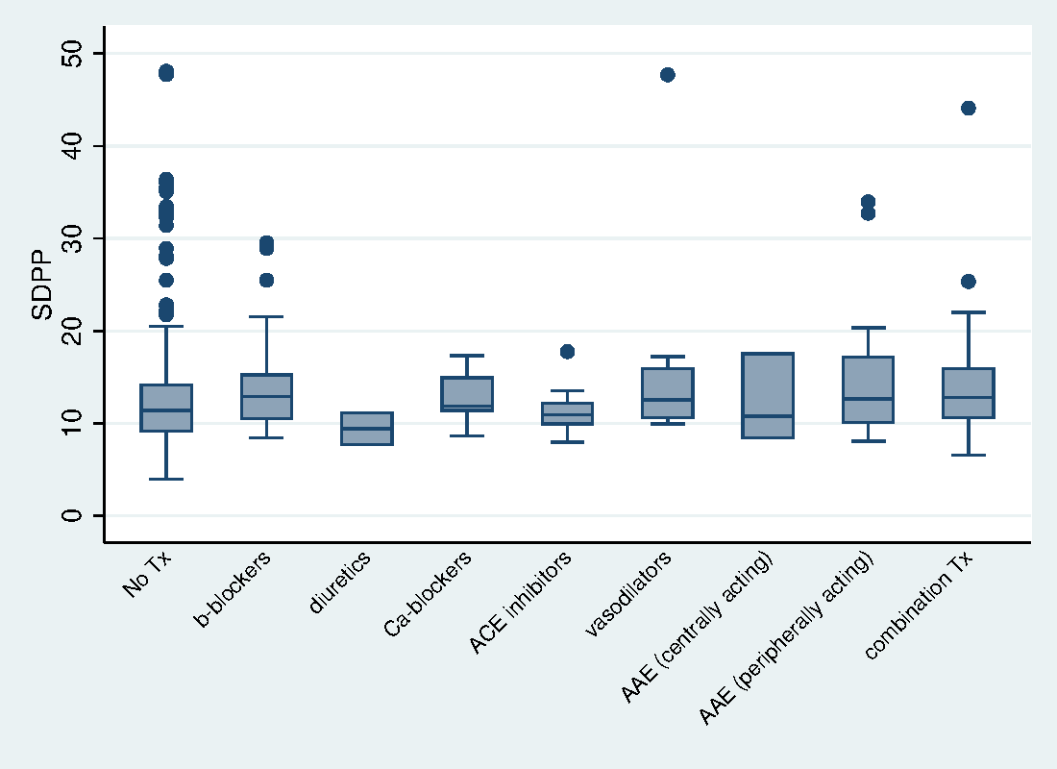

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