Disputes & Debates: Editors' Choice

Editors' Note: Cerebral Microbleeds and Treatment Effect of Intravenous Thrombolysis in Acute Stroke: An Analysis of the WAKE-UP Randomized Clinical Trial

Dr. Schlemm et al. performed a prespecified analysis of the association of cerebral microbleeds (CMBs) with the treatment effect of IV alteplase vs placebo in the randomized controlled WAKE-UP (Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke) trial of patients with acute ischemic stroke with unknown time of symptom onset and diffusion-weighted imaging–fluid-attenuated inversion recovery mismatch on MRI. Among 459 patients available for analysis, there was no evidence of reduced treatment effect of alteplase in the 98 (21.4%) patients who had at least 1 CMB on baseline imaging. However, CMBs were associated with a nonsignificant increased risk of symptomatic intracranial hemorrhage (ICH; 11.2% vs 4.2%; adjusted odds ratio 2.32, 95% CI 0.99–5.43). In response, Drs. Meinel and Seiffge highlight the importance of distinguishing patients with CMBs from cerebral amyloid angiopathy or other cerebral small vessel disease—who have an increased risk of postthrombolysis ICH—from those with other causes of CMBs and other such lesions on susceptibility-weighted imaging, like those seen after valve implantation, extracorporeal membrane oxygenation, or prolonged intensive care unit stay. They also recommend examining the interaction of CMBs and white matter hyperintensities to better elucidate the risk of postthrombolysis hemorrhage. Responding to these comments, the authors note that new CMBs in acute ischemic stroke patients after IV thrombolysis were associated with an increased risk of hemorrhagic complications in prior literature, whereas new CMBs after cardiac surgery were not associated with bleeding risk, suggesting different risk profiles for patients with different causes of acute CMBs—a topic meriting further investigation in histopathology and observational studies. This exchange highlights the challenges of disentangling cause-specific bleeding risks associated with CMBs when examining ICH outcomes in patients undergoing thrombolysis.

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Neurology® 2022;98:816. doi:10.1212/WNL.0000000000200610

Reader Response: Cerebral Microbleeds and Treatment Effect of Intravenous Thrombolysis in Acute Stroke: An Analysis of the WAKE-UP Randomized Clinical Trial

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Neurology® 2022;98:816–817. doi:10.1212/WNL.0000000000200611

We congratulate Schlemm et al.[1] for this important and helpful analysis of the WAKE-UP trial.

In a recent cohort of patients with artificial heart valves, susceptibility-weighted imaging (SWI) lesions fulfilling the criteria of cerebral microbleeds (CMBs) frequently evolved around the timepoint of valve implantations but remained stable in the long term.[2] Postinterventional distribution of SWI lesions was suggestive of cerebral amyloid angiopathy, and 24% fulfilled the

Author disclosures are available upon request (journal@neurology.org).

criteria of possible or probable cerebral amyloid angiopathy (CAA) according to the modified Boston criteria.[2] In addition to cardiopulmonary bypass, the differential diagnosis of SWI lesions includes prior use of extracorporeal membrane oxygenation or prolonged intensive care unit stay, as well as foreign materials.[3] We think that recognizing such transient or nonvascular causes of SWI lesions and CMBs as compared to true CAA or hemorrhagic small vessel disease could be crucial to differentiate patients who have an increased risk of intracranial hemorrhage after IV thrombolysis[4] or with anticoagulation.[5]

Also, we noticed that patients with SWI lesions seen with cardiopulmonary bypass seldom had white matter lesions. We suggest future analysis on the interaction of CMBs and white matter hyperintensities regarding bleeding risk after IV thrombolysis.

1. Schlemm L, Braemswig TB, Boutitie F, et al. Cerebral microbleeds and treatment effect of intravenous thrombolysis in acute stroke: an analysis of the WAKE-UP randomized clinical trial. *Neurology*. 2022;98(3):e302-e314.
2. Breiding PS, Duerrenmatt JT, Meinel FG, et al. Prevalence and evolution of susceptibility-weighted imaging lesions in patients with artificial heart valves. *J Am Heart Assoc*. 2019;8(15):e012814.
3. Auriel E, Charidimou A, Gurol ME, et al. Validation of clinicoradiological criteria for the diagnosis of cerebral amyloid angiopathy-related inflammation. *JAMA Neurol*. 2016;73(2):197-202. doi: 10.1001/jamaneurol.2015.4078
4. Charidimou A, Turc G, Oppenheim C, et al. Microbleeds, cerebral hemorrhage, and functional outcome after stroke thrombolysis. *Stroke*. 2017;48(8):2084-2090.
5. Charidimou A, Karayiannis C, Song TJ, et al. Brain microbleeds, anticoagulation, and hemorrhage risk: meta-analysis in stroke patients with AF. *Neurology*. 2017;89(23):2317-2326.

Author Response: Cerebral Microbleeds and Treatment Effect of Intravenous Thrombolysis in Acute Stroke: An Analysis of the WAKE-UP Randomized Clinical Trial

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Neurology® 2022;98:817. doi:10.1212/WNL.0000000000200612

We are grateful for the interest in our article on the treatment effect of alteplase in acute ischemic stroke patients with preexisting cerebral microbleeds (CMBs).[1] The readers point out that new lesions are observed on susceptibility-weighted imaging (SWI) in patients with artificial heart valves that meet the imaging criteria of CMBs and suggest that these lesions should be differentiated from CMBs associated with small vessel disease to better identify patients with an increased bleeding risk.[2] Of interest, a previous study showed that new CMBs occurring in acute ischemic stroke patients after receiving IV thrombolysis (IVT) were indeed associated with an increased risk of IVT-related hemorrhagic complications.[3] On the other hand, new CMBs were not associated with an increased risk of bleeding in patients undergoing cardiac surgery.[2,4] However, IVT may constitute a different bleeding risk than cardiopulmonary bypass and extracorporeal membrane oxygenation, or a prolonged intensive care unit stay. The question of whether CMBs in patients with artificial heart valves represent a different pathophysiologic entity with a different bleeding risk merits further research and would profit from histopathology studies and observational studies in stroke and nonstroke cohorts with long-term follow-up.

1. Schlemm L, Braemswig TB, Boutitie F, et al. Cerebral microbleeds and treatment effect of intravenous thrombolysis in acute stroke: an analysis of the WAKE-UP randomized clinical trial. *Neurology*. 2022;98(3):e302-e314.
2. Breiding PS, Duerrenmatt JT, Meinel FG, et al. Prevalence and evolution of susceptibility-weighted imaging lesions in patients with artificial heart valves. *J Am Heart Assoc*. 2019;8(15):e012814.
3. Braemswig TB, Villringer K, Turc G, et al. Predictors of new remote cerebral microbleeds after IV thrombolysis for ischemic stroke. *Neurology*. 2019;92(7):e630-e638.
4. Patel N, Banahan C, Janus J, et al. Perioperative cerebral microbleeds after adult cardiac surgery. *Stroke*. 2019;50(2):336-343.

Author disclosures are available upon request (journal@neurology.org).

CORRECTION

Characterization of the Biomechanical and Situational Aspects of High Magnitude Subconcussive Impacts in Collegiate Football

Neurology® 2022;98:818. doi:10.1212/WNL.0000000000200102

In the Sports Concussion abstract "Characterization of the Biomechanical and Situational Aspects of High Magnitude Subconcussive Impacts in Collegiate Football" by Lacelle et al.,[1] the second author's name should have been listed as "Mario D. Bassi." The AAN scientific programming staff regret the error.

Reference

1. Lacelle KL, Bassi M, Champagne AA, et al. Characterization of the biomechanical and situational aspects of high magnitude subconcussive impacts in collegiate football. *Neurology*. 2020;95(20 suppl 1):S1.

CORRECTION & REPLACEMENT

Clinical Outcomes in Multifocal Motor Neuropathy

A Combined Cross-Sectional and Follow-up Study

Neurology® 2022;98:818. doi:10.1212/WNL.0000000000012098

In the article "Clinical Outcomes in Multifocal Motor Neuropathy: A Combined Cross-Sectional and Follow-up Study" by Herraets et al.,[1] several previous instances of the term "median age" within the text now appear as "mean age." In addition, the following references were mistakenly omitted: "Nobile-Orazio E. Multifocal motor neuropathy. *J Neuroimmunol*. 2001;115: 4-18" and "Terenghi F, Cappellari A, Bersano A, Carpo M, Barbieri S, Nobile-Orazio E. How long is IVIg effective in multifocal motor neuropathy? *Neurology*. 2004;62:666-668." They now appear within the list of references as numbers 8 and 14, respectively. These references are also cited accordingly at corresponding locations within the article's text and the other references and in-text citations have been renumbered as needed. All changes are identified in the Highlighted Changes supplement linked from the updated version. The authors and publisher regret these errors.

Reference

1. Herraets I, van Rosmalen M, Bos J, et al. Clinical outcomes in multifocal motor neuropathy: a combined cross-sectional and follow-up study. *Neurology*. 2020;95(14):e1979-e1987.