Editors' Note: WriteClick submissions this week reference the article by Dr. Park et al., "Is asymptomatic hemorrhagic transformation really innocuous?" and bring up the possibility of confounding factors in the analysis. Drs. Libman and Kwiatkowski ask that the authors reanalyze their data to adjust for lesion volume. The authors regret that they were not able to measure lesion volume in their study but point out that reports suggest clinical variables are better prognosticators of stroke outcome than radiologic variables. Drs. El-Zammar and Levine suggest the possibility of bias due to stroke etiology, thrombolysis administration, and the statistical handling of disability scores. The authors respond by explaining their statistical methodology but admit the possibility of residual bias despite their adjustments. All agree that analyzing prognostic factors in stroke outcome remains a challenging endeavor.

Megan Alcauskas, MD, and Robert C. Griggs, MD

IS ASYMPTOMATIC HEMORRHAGIC TRANSFORMATION REALLY INNOCUOUS?

Richard B. Libman, New Hyde Park, NY; Thomas Kwiatkowski, Lake Success, NY; Park et al.¹ found

that patients with asymptomatic hemorrhagic transformation of an infarct had worse functional outcome in 3 months compared to patients without hemorrhagic transformation. The concept of whether asymptomatic hemorrhagic transformation may exert subtle adverse effects that may ultimately lead to a worse outcome has been difficult to approach. Sample size has been an issue with the possibility of inadequate power to detect an adverse effect of asymptomatic hemorrhagic transformation.² In our study of asymptomatic hemorrhagic transformation and outcome, initial analysis suggested that asymptomatic hemorrhagic transformation decreased the odds of a favorable outcome.³ However, lesion volume is associated with both hemorrhagic transformation and outcome. When controlling for lesion volume, asymptomatic hemorrhagic transformation was no longer associated with a worse long-term outcome.³ Park et al. controlled for several variables potentially associated with both functional outcome and hemorrhagic transformation, including

stroke subtype, initial NIH Stroke Scale (NIHSS) score, initial fasting blood glucose, total cholesterol, thrombolytic administration, and use of heparin. They did not, however, control for lesion volume. Could the authors reanalyze their data adjusting for lesion volume to see whether the relationship between asymptomatic hemorrhagic transformation and poor outcome persists? Until this is done, the possibility of confounding remains, and the evidence that asymptomatic hemorrhagic transformation worsens long-term outcome remains tentative.

Author Response: Hee-Joon Bae, Gyeonggi-Dong, Korea; Jung Hyun Park, Gyeongju, Korea; Juneyoung Lee, Seoul, Korea; Philip B. Gorelick, Chicago: We agree with Libman et al. that initial

infarction volume may be an important prognostic determinant after acute ischemic stroke and that adjustment using lesion volume could attenuate the impact of hemorrhagic transformation on functional outcome. As we mentioned in the article, we were not able to measure infarct volume.¹ It has been reported that the prognosis of acute ischemic stroke may be predicted by clinical variables only^{1,4,5} and that outcome prediction may not be significantly improved with CT-derived radiologic variables compared to using simple clinical variables.⁵ We calculated the odds of a worse outcome at 90 days with the NIHSS, which was put into the models as a continuous variable, and the results were similar to those described in our study: asymptomatic HT was significantly associated with a worse outcome.

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1. Park JH, Ko Y, Kim W-J, et al. Is asymptomatic hemorrhagic transformation really innocuous? *Neurology* 2012;78:421–426.
2. Kent DM, Hinchey J, Price LL, Levine SR, Selker HP. In acute ischemic stroke, are asymptomatic intracranial hemorrhages clinically innocuous? *Stroke* 2004;35:1141–1146.
3. Libman RB, Kwiatkowski T, Lyden P, et al. Asymptomatic hemorrhagic transformation of cerebral infarction does not worsen long-term outcome. *J Stroke Cerebrovasc Dis* 2005;14:50–54.
4. Counsell C, Dennis M, McDowall M, Warlow C. Predicting outcome after acute and subacute stroke: development

and validation of new prognostic models. *Stroke* 2002;33:1041–1047.

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Ziad M.K. El-Zammar, Syracuse, NY; Steven R. Levine, Brooklyn, NY: Park et al.¹ suggest asymptomatic hemorrhagic transformation (AsxHT) may worsen outcome, as did Kimura et al.² Libman et al.³ did not find this relationship. There may be several explanations.

The definition of AsxHT by Park et al. used different radiologic and clinical criteria.⁴ Gradient echo MRI is more sensitive for deoxyhemoglobin than conventional MRI or CT. Cardiac embolism causes more severe stroke and frequent hemorrhagic transformation (HT) and is more commonly associated with worse outcomes. Perhaps adjusted analyses could not account for this. The adjusted odds ratio (OR) was 1.9 in all 6 cases of comparing modified Rankin Scale (mRS) scores, suggesting an identical contribution of AsxHT to each notch of worsening mRS across the full spectrum of mRS.

This is difficult to understand, especially since clinical judgment decided the contribution of HT to symptoms. The rate of thrombolysis based on the 3-month mRS—26% with mRS = 5 were thrombolized, vs 8% for each of mRS 0, 1, and 2, and 11%, 13%, and 15% for mRS = 3, 4, and 6—is notable. There may also be bias in who received thrombolysis based on baseline NIHSS. Controlling these prognostic factors is challenging, leaving this important issue open to further investigation.

Author Response: Hee-Joon Bae, Gyeonggi-Dong, Korea; Jung Hyun Park, Gyeongju, Korea; Juneyoung Lee, Seoul, Korea; Philip B. Gorelick, Chicago: We thank El-Zammar et al. for their com-

ments. A key point for the interpretation of table 3 is to focus on change of the adjusted ORs for explanatory variables with different cutoff values of the mRS score.¹ We used an ordinal logistic regression model to reflect the ordinal nature of the mRS in our analysis. The ordinal logistic regression model assumes that the odds of having higher mRS scores with AsxHT to those without AsxHT are constant across all cutoff values of the mRS.^{5–6} In our dataset, the proportional odds assumption was not satisfied for all variables. Therefore, the partial proportional odds model was employed and, as a result, the estimated ORs for variables not satisfying the assumption were varied according to a cutoff value of the mRS. The adjusted OR of 1.9 for AsxHT means that AsxHT was associated with a 1.9 times higher odds of resultant higher mRS scores than without AsxHT regardless of cutoff values of the mRS. Finally, in our study the rate of thrombolysis increased as the 3-month mRS score worsened. As mentioned in the article, we admit the possibility of residual confounding although we adjusted both variables in the model.

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1. Park JH, Ko Y, Kim W-J, et al. Is asymptomatic hemorrhagic transformation really innocuous? *Neurology* 2012;78:421–426.
2. Kimura K, Iguchi Y, Shibasaki K, Aoki J, Terasawa Y. Hemorrhagic transformation of ischemic brain tissue after t-PA thrombolysis as detected by MRI may be asymptomatic, but impair neurological recovery. *J Neurol Sci* 2008;15:136–142.
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CORRECTION

Nemaline myopathy with stiffness and hypertonia associated with an *ACTA1* mutation

In the Clinical/Scientific Note “Nemaline myopathy with stiffness and hypertonia associated with an *ACTA1* mutation” by R.K. Jain et al. (*Neurology*® 2012;78:1100–1103), there are 2 errors on page 1100. In the right-hand column, paragraph 3 should read “(Lys326Asn in the mature protein)” and paragraph 7 should read “. . . increased sensitivity to Ca²⁺ (figure, F).” The authors regret the errors.

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

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Is asymptomatic hemorrhagic transformation really innocuous?

Richard B. Libman, Hee-Joon Bae, Ziad M.K. El-Zammar, et al.

Neurology 2012;78;1703-1704

DOI 10.1212/WNL.0b013e3182598e5b

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