Clinical and Imaging Data at 5 Days as a Surrogate for 90-Day Outcome in Ischemic Stroke

Karen C. Johnston, MD, MSc; Kevin M. Barrett, MD; Yong Hong Ding, MD; Douglas P. Wagner, PhD†; for the ASAP Investigators

Background and Purpose—A simple, easily measured surrogate outcome measure for use in early treatment trials for acute ischemic stroke therapies would be highly valued. We hypothesized that day-5 NIH stroke scale score (NIHSS) and day-5 diffusion weighted imaging (DWI) volume would predict clinical outcome better than either alone and could be considered as a possible surrogate outcome in early phase acute stroke trials.

Methods—The prospective Acute Stroke Accurate Prediction (ASAP) trial included a prespecified subgroup evaluated for early outcome. Logistic regression analysis was used to assess the prediction of modified Rankin (mRankin) of 0 or 1.

Results—A total of 204 subjects completed the substudy, and 116 (57%) had excellent outcome at 3 months. The area under the ROC curve (AUC) for day-5 NIHSS predicting 3-month excellent outcome was 0.84; for DWI volume predicting outcome was 0.76, and for the multivariable model combining both was 0.84.

Conclusions—The results of the early outcome substudy of the ASAP trial suggest that early stroke severity and infarct volume measures are predictive of 3-month excellent outcome. In our data set the DWI volume does not add clinically relevant information in predicting 3-month outcome. Validation of these results is required. (Stroke. 2009;40:1332-1333.)

Key Words: cerebral ischemia ■ prognosis ■ stroke outcome ■ models ■ statistical ■ surrogate
Early clinical status is a strong predictor of 3-month outcome and may be useful in clinical and research settings. For proof of concept studies, use of a day-5 outcome may substantially reduce the time, cost, and frequency of subjects lost to follow-up while allowing an accurate determination of the appropriateness of proceeding to phase III trials. Additionally, this information may provide an imputation method for trials with early outcome information and a small number of patients missing final outcome data. The strong prediction supports a potential role for day-5 outcome. Once validated, our simple nomogram (supplemental Figure I) may be valuable in similar populations and may be useful in trials with adaptive designs and rapid accrual, as they may facilitate early adjustment of pretrial estimates of event rates. These potential benefits may, in some trials, outweigh the disadvantages of an imperfect but highly predictive estimate of 3-month outcome.

Acknowledgments
The authors gratefully acknowledge the contribution of the ASAP trial investigators and patients, without whose efforts this work would not have been possible. Special gratitude is expressed to Dr David Kallmes at the Mayo Clinic Rochester, Minnesota for his contributions in leading the imaging evaluation team. The authors dedicate this manuscript to the memory of Doug Wagner who died just days before it was submitted.

Sources of Funding
This research was funded by the National Institutes of Health- National Institute of Neurological Disorders and Stroke (NIH-NINDS) (K23NS02168); The ASAP study was funded by the NIH-NINDS (K23NS02168); and Drs Johnston and Wagner received support from this grant.

Disclosures
None.

References

Discussion
Our data from the early outcome substudy of the ASAP trial demonstrate that day-5 imaging and clinical information are highly predictive of 3-month outcome in AIS patients. The AUC of the univariate model using early outcome NIHSS score was 0.84 which exceeded our prespecified definition of success (0.80); however, the addition of the early imaging data did not improve the accuracy of the prediction. A previous study using CT infarct volumes measured between days 6 and 11 demonstrated only modest correlation between infarct volume and 3-month clinical outcomes. MRI adds information in the acute stroke setting but offers no clinically relevant improvement on 3-month outcome prediction.

Based on our data, a scoring system using age-adjusted day-5 NIHSS score to predict functional outcomes is most likely to have the greatest clinical utility. Age-adjustment of the day-5 NIHSS score maximizes predictive accuracy because of the strong independent association of age and mRS. A simple nomogram can provide the adjustment for younger patients with mild to moderate strokes, but should be used cautiously before external validation (supplemental Figure I).

Our study is limited by small sample size, single site of enrollment, and young population with mild strokes. A larger sample may have demonstrated a significant contribution by DWI. The additional predictive power added by imaging was much smaller than estimated and may have resulted from the use of a single volume measure that did not capture information on infarct location or evolution. Incorporation of perfusion MR sequences, or clinical covariates such as diabetes or prestroke disability may have improved predictive power.

The relationships identified in this study have not been externally validated. As the sample size is small and our cohort was young with mild to moderately severe strokes, these data are only hypothesis generating requiring validation in a more robust data set.
Clinical and Imaging Data at 5 Days as a Surrogate for 90-Day Outcome in Ischemic Stroke
Karen C. Johnston, Kevin M. Barrett, Yong Hong Ding and Douglas P. Wagner
for the ASAP Investigators

Stroke. 2009;40:1332-1333; originally published online February 19, 2009;
doi: 10.1161/STROKEAHA.108.528976
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/40/4/1332

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/