Journal of the American College of Cardiology
© 2010 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 56, No. 13, 2010
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.05.033

EDITORIAL COMMENT

Biomarkers in Stroke

When Will They Impact Care?*

Christopher B. Granger, MD,
Daniel T. Laskowitz, MD, MHS
Durham, North Carolina

Large, well-defined patient datasets, improved statistical techniques, and interest by the clinical and research communities have enabled the development of models to predict outcome in patients with cardiovascular disease. A number of biomarkers, including troponin and B-type natriuretic peptide (BNP), provide important independent prognostic and diagnostic information and are important variables in risk models. Both the American (1) and European (2) guidelines for management of non–ST-segment elevation acute coronary syndromes have made quantitative risk stratification a Class I recommendation. This recommendation is based on studies showing that risk stratification can identify which patients derive optimal benefit from various treatments, such as an early invasive strategy (3), or use of more potent antithrombotic therapy (4). In contrast to cardiac disease, there is a paucity of validated markers in ischemic stroke, and the American Heart Association makes no recommendations regarding their use in risk stratification (5). Nevertheless, risk models that enable clinicians to determine prognosis of stroke patients could be useful for decisions about intensity of monitoring and treatment, as well as for risk adjustment for observational research or quality improvement studies.

See page 1045

Evaluation of biomarkers for the prediction, diagnosis, classification, and prognosis of stroke has been a fertile ground for investigation (6,7). Because diagnostic uncertainty may contribute to the underuse of fibrinolytic therapy and other targeted therapies, a biomarker-based test that could aid in establishing the diagnosis and etiology of stroke would have potential for significant clinical impact. The identification of biochemical markers of cerebral ischemia has proven challenging for a variety of reasons, including the complexity of the ischemic cascade and presence of the blood-brain barrier. Thus, although statistical associations with stroke have been demonstrated with individual markers of inflammation, glial activation, and neuronal injury (7), no single biomarker has ever been demonstrated to be clinically useful as a standalone diagnostic test. One way to address this difficulty is by simultaneously evaluating multiple biomarkers that contribute complementary information. Preliminary studies suggest that such a biomarker panel may add time-sensitive diagnostic information in the early evaluation of stroke (6).

A biomarker that predicts functional outcome after stroke could also play an important role in clinical decision making. Prognosis in stroke has been shown to be related to patient factors such as age and initial neurological deficit as assessed by the National Institutes of Health Stroke Scale (NIHSS) (8,9). Although several studies have demonstrated associations between biomarkers of inflammation and outcome, none of these studies has demonstrated significant incremental predictive capacity over traditional historical and clinical factors, thus limiting their clinical significance.

In this issue of the *Journal*, Katan et al. (10) demonstrate that a novel biomarker, midregional pro-atrial natriuretic peptide (MR-proANP), is a powerful and independent marker of outcome following ischemic stroke. Using a single-center cohort of 362 patients with ischemic stroke, they found that MR-proANP levels were associated with severity of stroke, history of heart failure, and atrial fibrillation. Elevation of MR-proANP was strongly associated with mortality and functional outcome at 90 days. The authors observed a 4-fold increased risk of poor outcome associated with increasing quartiles of midregional pro-BNP levels. A model incorporating pro-ANP and the NIH stroke scale provided excellent discrimination of risk, with a *c*-index of 0.92. Moreover, MR-proANP elevation was related to etiology of stroke, as higher levels were found in patients with cardioembolic stroke, even after adjusting for heart failure and atrial fibrillation. The same investigators, using the same dataset and methodology, have previously demonstrated that another biomarker, copeptin, a fragment of pro-vasopression, was also independently related to death and especially to functional recovery (11). MR-proANP provided prognostic information that was independent from copeptin and appeared to be more strongly predictive of death.

Brain natriuretic peptide (BNP) has been shown to be a powerful prognostic biomarker in patients with heart failure (12) and even in a general population (13). Studies have also demonstrated elevations of BNP in the setting of acute stroke (6) and prognostic importance of BNP in patients suffering ischemic stroke (7). It remains unclear whether the

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Duke Clinical Research Institute, Duke University, Durham, North Carolina. Dr. Granger has received research grants from Astellas Pharma US, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Lilly, Medtronic Vascular Inc., Merck & Co., Sanofi-Aventis, and The Medicines Co.; and consulting fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Hoffmann-LaRoche, Novartis Pharmaceutical Co., Otsuka Pharmeceutical, Sanofi-Aventis, and The Medicines Co. Dr. Laskowitz is a consultant for Astute Medical, Inc.

Table 1 Phases of Evaluation of MR-proANP

1. Proof of concept: MR-proANP levels differ between subjects with and without death
2. Prospective validation: MR-proANP predicts death in a (single, small) prospective cohor
3. Incremental value: MR-proANP appears to add predictive information to established, standard risk markers such as age and NIHSS
4. Clinical utility: It is unknown whether MR-proANP changes risk assessement sufficiently to change recommended therapy
5. Clinical outcomes: It is unknown whether use of MR-proANP to guide therapy improves clinical outcomes, especially when tested in a randomized clinical trial
6. Cost-effectiveness: It is unknown whether impact of use of MR-proANP justifies the additional costs of testing and treatment

Adapted with permission from Hlatky et al. (14).

MR-proANP = midregional pro-atrial natriuretic peptide; NIHSS = National Institutes of Health Stroke Scale.

widely available BNP assays would have performed as well as MR-proANP in this dataset.

This study addresses the early phases of evaluation (14) of MR-pro-ANP as a potential risk marker following stroke: proof of concept that the marker is higher in patients with the event, prospective validation that the marker is predictive in a prospective cohort, and incremental value over clinical variables (Table 1). Although an important advance, the current study was performed at a single center with only 44 deaths, and the results need to be validated in an independent study. A number of important questions remain. Does this biomarker change predicted risk enough to alter recommended therapy? Does use of the biomarker result in improved care and clinical outcomes? And is it cost effective? Although challenging, these questions must be answered before biomarkers will inform and improve stroke care.

Reprint requests and correspondence: Dr. Christopher B. Granger, Duke Clinical Research Institute, 2400 Pratt Street, Room 0311 Terrace Level, Durham, North Carolina. E-mail: grang001@mc.duke.edu.

REFERENCES

1. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2007;50:e1–157.
2. Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J 2007;28:1598–660.
3. Mehta SR, Granger CB, Boden WE, et al., TIMACS Investigators. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med 2009;360:2165–75.
4. Morrow DA, Antman EM, Snapinn SM, et al. An integrated clinical approach to predicting the benefit of tirofiban in non-st elevation acute coronary syndromes: application of the TIMI risk score for UA/NSTEMI in PRISM-PLUS. Eur Heart J 2002;23:223–9.
5. Adams HP Jr., del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Circulation 2007;115:e478–534.
6. Laskowitz DT, Kasner SE, Saver J, Remmel KS, Jauch EC, BRAIN Study Group. Clinical usefulness of a biomarker-based diagnostic test for acute stroke: the Biomarker Rapid Assessment in Ischemic Injury (BRAIN) study Stroke 2009;40:77–85.
7. Whiteley W, Chong WL, Sengupta A, Sandercock P. Blood markers for the prognosis of ischemic stroke: a systematic review. Stroke 2009;40:e380–9.
8. Counsell C, Dennis M, McDowall M, Warlow C. Predicting outcome after acute stroke: development and validation of new models. Stroke 2002;33:1041–7.
9. Konig IR, Ziegler A, Bluhmki E, et al. Virtual International Stroke Trials Archive (VISTA) Investigators. Predicting long-term outcome after acute ischemic stroke: a simple index works in patients from controlled clinical trials. Stroke 2008;39:1821–6.
10. Katan M, Fluri F, Schuetz P. Midregional pro-atrial natriuretic peptide and outcome in patients with acute ischemic stroke. J Am Coll Cardiol 2010;56:1045–53.
11. Katan M, Fluri F, Morgenthaler NG, et al. Copeptin: a novel, independent prognostic marker in patients with ischemic stroke. Ann Neurol 2009;66:799–808.
12. Doust JA, Pietrzak E, Dobson A, Glasziou P. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. BMJ 2005;330:625.
13. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 2004;350:655–63.
14. Hlatky MA, Greenland P, Arnett DK, et al., American Heart Association Expert Panel on Subclinical Atherosclerotic Diseases and Emerging Risk Factors and the Stroke Council. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. Circulation 2009;119:2408–16.

Key Words: biomarker ■ MR-proANP ■ outcome ■ stroke.