Prognostic Value of Copeptin
One-Year Outcome in Patients With Acute Stroke

Sandrine A. Urwyler, BMed; Philipp Schuetz, MD; Felix Fluri, MD; Nils G. Morgenthaler, MD, PhD; Christian Zweifel, MD; Andreas Bergmann, PhD; Roland Bingisser, MD; Ludwig Kappos, MD; Andreas Steck, MD; Stefan Engelter, MD; Beat Müller, MD; Mirjam Christ-Crain, MD; Mira Katan, MD

Background and Purpose—An accurate long-term outcome prediction may improve management of stroke patients. We investigated the ability of copeptin to predict 1-year outcome in stroke patients.

Methods—In this preplanned post hoc analysis, the National Institutes of Health Stroke Scale score and copeptin levels were measured on admission in a cohort of patients with ischemic stroke. The primary end point was functional outcome (modified Rankin Scale score <3 or 3–6) after 1 year. The secondary end point was all-cause mortality.

Results—Of 362 patients, 341 (94.2%) completed the 1-year follow-up, 146 (43%) patients had an unfavorable functional outcome, and 66 (20%) died. Multivariate logistic-regression analysis adjusted for age and National Institutes of Health Stroke Scale score showed that copeptin was an independent predictor of functional outcome (odds ratio = 4.00; 95% CI, 1.94–8.19) and death (odds ratio = 2.68; 95% CI, 1.24–5.82). The area under the receiver operating characteristic curve of copeptin was 0.72 (95% CI, 0.67–0.77) for functional outcome and 0.74 (95% CI, 0.69–0.78) for mortality. Copeptin improved the area under the receiver operating characteristic curve of the National Institutes of Health Stroke Scale score for functional outcome from 0.70 (95% CI, 0.64–0.74) to 0.76 (95% CI, 0.71–0.82; P=0.002) and for mortality from 0.74 (95% CI, 0.69–0.78) to 0.78 (95% CI, 0.71–0.85; P=0.04).

Conclusions—Copeptin levels are a useful, complementary tool to predict functional outcome and mortality 1 year after stroke.

Clinical Trial Registration—ISCTRN 00390962; clinicaltrials.gov No. NCT00390962.

Key Words: biomarkers ▪ copeptin ▪ 1-year outcome ▪ stroke

Stroke ranks second to ischemic heart disease as a cause of death worldwide and is the leading cause of serious disability.1 Mortality after 1 year ranges between 21% and 27%; 15% to 30% of survivors are permanently disabled.1 Costs of long-term care account for ≈50% of total costs.2 Early treatment and adequate rehabilitation are known to reduce dependency at 6 months and may improve long-term outcome.2 Prediction of long-term outcome at stroke onset based on clinical deficits only is difficult;1 therefore, rapid measurement of blood biomarkers predicting long-term functional outcome and mortality could prove useful. We recently demonstrated in a prospective cohort study that the biomarker copeptin predicted outcome 90 days after stroke onset and improved the prognostic accuracy of the National Institutes of Health Stroke Scale (NIHSS) score.4 This follow-up study evaluated copeptin as a marker to predict functional outcome and mortality in acute stroke patients 1 year after admission.

Patients and Methods

Setting
This study was based on a prospective cohort study (ClinicalTrials.gov number, NCT00390962).4 A complete description has been reported previously.4 In brief, vital signs, relevant comorbidities, risk factors, and stroke severity on admission as assessed by the NIHSS were recorded. Copeptin was measured with a sandwich immunoluminometric assay.5 For follow-up, we used structured telephone interviews performed by 1 trained medical student, blinded to copeptin levels.6 The primary end point of this study was functional outcome in patients 1 year after stroke, defined by a modified Rankin Scale score (unfavorable outcome = modified Rankin Scale score ≥2). The secondary end point was death from any cause within the 1-year follow-up.

Statistical Analysis
Discrete variables are expressed as counts (percentages) and continuous variables as medians and interquartile ranges (IQRs). Two-group and multigroup comparisons were performed with the

Received March 22, 2010; accepted March 30, 2010.

From the Departments of Endocrinology (S.U., P.S., M.C.-C., M.K.) and Neurology (F.F., L.K., A.S., S.E., M.K.), University Hospital, University of Basel, Switzerland; Research Department (N.G.M., A.B.), Brahms AG, Hennigsdorf/Berlin, Germany; Departments of Neurosurgery (C.Z.) and Emergency Medicine (R.B.), University Hospital, Basel, Switzerland; and Department of Internal Medicine (B.M.), Kantonsspital Aarau, Switzerland.

The last 2 authors contributed equally to this work.

Correspondence to Mira Katan, MD, University Hospital, Petersgraben 4, CH-4031 Basel, Switzerland. E-mail katanm@uhbs.ch

© 2010 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.110.584649

1564
Mann–Whitney U test and Kruskal-Wallis 1-way ANOVA, respectively. The relation of copeptin to outcomes was assessed in logistic-regression models. For multivariate analysis, we included confounders, known risk factors, and other outcome predictors as assessed in univariate analysis. Receiver-operating-characteristic curves were calculated to assess discrimination. To estimate the additive benefit of copeptin to the NIHSS score, we used likelihood ratio tests. Kaplan–Meier survival curves were constructed for mortality prediction. All testing was 2 tailed, and probability values <0.05 were considered statistically significant. Calculations were performed with STATA 9.2 (Stata Corp, College Station, Tex) and Graphpad Prism 5 (Graphpad Software).

**Results**

**Patients**

Of the original 362 ischemic stroke patients, 4 341 (94.2%) completed the 1-year follow-up. In 5 patients, copeptin values were missing, leaving 336 patients for the final analysis. Baseline characteristics have been reported previously. The median age of the patients was 75 (IQR, 65 to 83) years, 40% were women, and the median NIHSS score on admission was 5 points (IQR, 2 to 10).

**Primary End Point**

In the 146 patients (43%) with an unfavorable functional outcome, copeptin levels were higher compared with those in patients with a favorable outcome (19.30; IQR, 9.60 to 36.98 pmol/L vs 8.12; IQR, 4.58 to 14.65 pmol/L; P<0.0001). Univariate and multivariate logistic-regression analyses showed that copeptin was associated with functional outcome (Table). The area under the curve (AUC) of copeptin was 0.72 (95% CI, 0.67 to 0.77) and significantly higher than for white blood cell count (WBC), C-reactive protein (CRP), and glucose but similar to the AUC for NIHSS score (0.70; 95% CI, 0.64 to 0.76).

We stratified patients into copeptin tertiles and compared outcome within 6 predefined NIHSS risk categories. Increasing copeptin tertiles were associated with
higher risk for adverse outcome (Figure 1a). Similarly, the combination of copeptin and NIHSS score in a combined logistic-regression model improved the NIHSS score (AUC of the combined model: 0.78; 95% CI, 0.72 to 0.84; \( P < 0.01 \)). This was not true for glucose, CRP, or WBC.

Secondary End Point
Sixty-six patients (20%) died. Copeptin levels in nonsurvivors (28.10 pmol/L; IQR, 13.20 to 60.88) were higher compared with those in survivors (9.34 pmol/L, IQR, 5.37 to 19.00; \( P < 0.0001 \)). In univariate and multivariate analyses, copeptin was an independent predictor for mortality. Receiver-operating-characteristic analysis showed similar results for the NIHSS score (AUC=0.74; 95% CI, 0.66 to 0.81) and copeptin (AUC=0.74; 95% CI, 0.69 to 0.78) but inferior results for WBC, CRP, and glucose. Stratification of patients into copeptin tertiles confirmed increased mortality risk in 6 predefined NIHSS risk groups (Figure 1b). The combination of NIHSS score and copeptin improved the AUC to 0.79 (95% CI, 0.71 to 0.87; \( P < 0.05 \)). We found an increased risk for mortality with increasing copeptin tertiles, particularly from the second to the third tertile (Figure 2).

Discussion
The ability to use biochemical markers to improve the prognostic accuracy after acute ischemic stroke is attractive.\(^8\) Several biomarkers were evaluated previously: brain natriuretic peptide, CRP, WBC, and glucose have a significant association with outcome in stroke patients.\(^8\) However, most studies were small and did not adjust the blood markers for age and stroke severity in multiple logistic-regression models.\(^8\) None of these markers increased the predictive power of the NIHSS score nor accuracy for long-term outcome.\(^8\)

This study shows that copeptin is a reliable and independent marker to predict long-term outcome in patients with ischemic stroke. Importantly, copeptin improved the prognostic value of the NIHSS score for long-term mortality and functional outcome at 1 year and was a better prognostic marker compared with other markers. Copeptin remained a significant predictor even after adjusting for age and stroke severity and added information for risk stratification beyond the NIHSS score.

Copeptin, though not a specific biomarker, is an attractive tool for routine clinical use because it is easy and quick to measure. In contrast to other brain markers, it directly mirrors intracerebral processes and is released into the systemic circulation, thus bypassing the blood-brain barrier. The strengths of this study are the prospective, consecutive inclusion of well-characterized stroke patients, blinded outcome assessment, and thorough follow-up interviews. As a limitation, our results need validation in an independent cohort of patients.
In conclusion, we believe that copeptin levels may reliably predict long-term stroke prognosis at its onset. This will allow identification of high-risk patients for whom secondary prevention and intensive rehabilitation can be directed to improve their outcome.

Acknowledgments
We are grateful to the Department of Neurology; the nurses, physicians, and patients who participated in the study; and the staff of the central laboratory of the University Hospital Basel, notably Melanie Wieland and Heike Freidank, for their assistance and technical support. We thank Dr. Albert Shun for the helpful and critical review of the manuscript.

Sources of Funding
This study was supported by in-house grants from the Departments of Endocrinology, Diabetes, Clinical Nutrition, and Neurology of the University Hospital of Basel, Switzerland, as well as by a grant for young research scientists of the University of Basel, Switzerland to M.K. and by research grants of the Swiss National Foundation, PP00P3-12346, to M.C.-C.

Disclosures
N.G.M. and A.B. are employees of B.R.A.H.M.S., the manufacturer of the copeptin assay (B.R.A.H.M.S. CT-proAVP LIA, B.R.A.H.M.S. AG, Hennigsdorf/Berlin, Germany). B.M., M.C.-C., and P.S. have served as consultants and received payments from B.R.A.H.M.S. to attend meetings, speaking engagements, or research unrelated to this trial. M.K. received speaking honoraria from B.R.A.H.M.S. unrelated to this trial. L.K. has received payments from several companies regarding his research within the field of multiple sclerosis research unrelated to this trial.

References
Prognostic Value of Copeptin: One-Year Outcome in Patients With Acute Stroke

Sandrine A. Urwyler, Philipp Schuetz, Felix Fluri, Nils G. Morgenthaler, Christian Zweifel, Andreas Bergmann, Roland Bingisser, Ludwig Kappos, Andreas Steck, Stefan Engelter, Beat Müller, Mirjam Christ-Crain and Mira Katan

Stroke. 2010;41:1564-1567; originally published online May 27, 2010;
doi: 10.1161/STROKEAHA.110.584649

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 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/41/7/1564

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/