Copeptin and Long-Term Risk of Recurrent Vascular Events After Transient Ischemic Attack and Ischemic Stroke

Population-Based Study

Stefan Greisenegger, MD; Helen C. Segal, PhD; Annette I. Burgess, DPhil; Debbie L. Poole, HNC; Ziyah Mehta, DPhil; Peter M. Rothwell, MD, PhD, FMedSci

Background and Purpose—Copeptin, the C-terminal portion of provasopressin, is a useful prognostic marker in patients after myocardial infarction and heart failure. More recently, high levels of copeptin have also been associated with worse functional outcome and increased mortality within the first year after ischemic stroke and transient ischemic attack (TIA). However, to date, there are no published data on whether copeptin predicts long-term risk of vascular events after TIA and stroke.

Methods—We measured copeptin levels in consecutive patients with TIA or ischemic stroke in a population-based study (Oxford Vascular Study) recruited from 2002 to 2007 and followed up to 2014. Associations with risk of recurrent vascular events were determined by Cox-regression.

Results—During 6000 patient-years in 1076 patients, there were 357 recurrent vascular events, including 174 ischemic strokes. After adjustment for age, sex, and risk factors, copeptin was predictive of recurrent vascular events (adjusted hazard ratio per SD, 1.47; 95% confidence interval, 1.47–1.64; P<0.0001), vascular death (1.85; 1.60–2.14; P<0.0001), all-cause death (1.75; 1.58–1.93; P<0.0001), and recurrent ischemic stroke (1.22; 1.04–1.44; P=0.017); and improved model-discrimination significantly: net reclassification improvement for recurrent vascular events (32%; P<0.0001), vascular death (55%; P<0.0001), death (66%; P<0.0001), and recurrent stroke (16%; P=0.044). The predictive value of copeptin was largest in patients with cardioembolic index events (adjusted hazard ratio, 1.84; 95% confidence interval, 1.53–2.20 versus 1.31, 1.14–1.50 in noncardioembolic stroke; P=0.0025). In patients with cardioembolic stroke, high copeptin levels were associated with a 4-fold increased risk of vascular events within the first year of follow-up (adjusted hazard ratio, 4.02; 95% confidence interval, 2.13–7.70).

Conclusions—In patients with TIA and ischemic stroke, copeptin predicted recurrent vascular events and death, particularly after cardioembolic TIA/stroke. Further validation is required, in particular, in studies using more extensive cardiac evaluation. (Stroke. 2015;46:3117-3123. DOI: 10.1161/STROKEAHA.115.011021.)

Key Words: biomarkers • risk • stroke

A ccurate prediction of recurrent vascular events after transient ischemic attack (TIA) and ischemic stroke is important for patients and researchers. Patients at high risk might profit from more aggressive secondary preventive strategies and should be included in trials of new treatments. Assessment of long-term risk should be as easy as possible for clinicians, ideally drawing on clinical variables taken from patient history and physical examination. However, in contrast to primary prevention of cardiovascular disease and after myocardial infarction (MI), there is no overall accepted prediction model for long-term risk of recurrent vascular events or death after ischemic stroke or TIA. Comparable with chronic heart failure (CHF) and coronary heart disease, blood biomarkers might enable better risk stratification after ischemic stroke or TIA.

Copeptin, the C-terminal portion of provasopressin, is a useful prognostic marker after MI and in patients with CHF. High levels of copeptin might improve risk stratification after stroke and TIA and have also been associated with worse functional outcome and increased mortality after ischemic stroke and TIA at 3 months and after 1 year. However, there are no published data on the long-term prognostic value of copeptin.

The aims of our study were, therefore, multiple. First, to determine whether copeptin predicts the long-term risk of...
vascular events after TIA and stroke. Second, to determine an abnormal threshold of copeptin levels in healthy control subjects without vascular disease that might facilitate better stratification of risk in patients with TIA or ischemic stroke. Third, to determine any heterogeneity in predictive value of copeptin across different causal subtypes of TIA and stroke to refine predictive utility and aid understanding of mechanisms. Fourth, to determine whether the predictive value of copeptin is consistent over time on repeated measurement during follow-up. Finally, to set the predictive value of copeptin into context by comparison with other commonly studied blood biomarkers.

Methods

Patients

The methods of Oxford Vascular Study (OXVASC) have been reported previously. Briefly, OXVASC is an ongoing population-based study of the incidence and outcome of cerebrovascular, cardiovascular, and peripheral vascular events. The study population comprises all 92 728 individuals, irrespective of age, registered with 100 family physicians in 9 general practices in Oxfordshire, United Kingdom. Standard definitions of TIA and stroke were used, which have been reported previously. Minor stroke was defined as National Institutes of Health Stroke Scale score of ≤3 points. A detailed description of patient ascertainment and follow-up is given in the Methods in the online-only Data Supplement. The methodology of the OXVASC was approved by the Oxfordshire Research Ethics Committee. Informed consent was sought, where possible, or assent was obtained from a relative.

Controls

Recruitment of controls to OXVASC started in 2006. Controls were recruited through the cases, by encouraging patients to invite their spouses, and friends to take part. Clinical fellows interview all controls that were able to attend our clinic, and research nurses interviewed those who preferred to be seen at home. To be eligible as a control, volunteers had to be free of any history of stroke, TIA, or MI. In addition, they had to be registered with one of the study general practices. To maintain a reasonable parity of age of patients versus controls, control subjects aged <50 years were only included if they had been invited by a patient whose vascular event occurred under the age of 50 years.

Blood Sampling, Processing, and Copeptin Measurement

Nonfasting blood samples were taken at the time of first assessment (as soon as possible after the event either while the patient was an inpatient or attending the OXVASC outpatient emergency TIA and stroke clinic), and sampling was repeated in a consecutive subgroup of patients after 1 year. In addition, copeptin levels were determined in 401 control subjects (spouses or friends of cases). Lithium heparin was used as anticoagulant (Vacutainer tubes; Becton Dickinson, Chicago, IL). Samples were centrifuged at 3000 g for 10 minutes, and aliquots of plasma were stored at –80°C before analysis when required to freezing were documented, typically within 4 hours of taking. For measurement of copeptin levels, previously unthawed blood samples were used. Plasma levels were assessed in a blinded batch analysis by a chemiluminescence sandwich immunoassay (Thermo Fisher Scientific, copeptin ultrasensitive Kryptor assay; BRAHMS GmbH, Henningsdorf, Germany). The lower detection limit was 0.9 pmol/L, and the intra-assay and inter assay coefficients of variation were 5.7% and 3.1%, respectively.

Statistics

Discrete variables are summarized as counts (percentage), and continuous variables as medians and interquartile ranges (IQRs). Two-group comparisons of baseline copeptin levels were performed using the Mann–Whitney U test and by the Kruskal–Wallis test for multigroup comparisons. Correlations of baseline copeptin levels with time to sampling and with copeptin levels at 1 year were calculated by linear regression. Copeptin levels were log-transformed as they were markedly skewed to decrease impact of extreme observations. Kaplan–Meier analysis was used for survival curves, and log-rank tests were used to assess significance. Cox-regression was used to establish hazard ratios (HRs). Copeptin levels were entered into the model per SD increase in log-transformed Copeptin. For sensitivity analysis, copeptin levels were also analyzed by tertiles and by using the 90th and 95th percentile of levels measured in control subjects as a cutoff in patients. Associations of copeptin levels with the outcome parameters were calculated unadjusted, adjusted for age and sex (model 1), and adjusted for variables included in model 1 plus hypertension, diabetes mellitus, previous MI, previous stroke, previous peripheral vascular disease, smoking, CHF, atrial fibrillation, previous therapy with antiplatelet agents, previous antihypertensive therapy, and previous therapy with statins (model 2). For sensitivity analysis, copeptin levels were also entered categorized into tertiles and by using a cutoff (the 90th percentile of levels measured in control subjects and alternatively the 95th percentile). Differential associations in subgroups were analyzed by inclusion of appropriate interaction terms. Group differences were tested adding the appropriate interaction term in the model.

Model discrimination was assessed by c-statistics, the relative integrated discrimination improvement (IDI) and the net reclassification improvement (NRI). C-statistics were determined by calculating the area under receiver operating characteristic curve (area under the curve [AUC]). The relative IDI was calculated to facilitate interpretation of IDI. For NRI, the continuous (category free) NRI was analyzed. All calculations were done using SPSS 22.0 (SPSS Inc., Chicago, IL).

Results

A total of 1076 consecutive eligible patients with TIA (n=388), minor ischemic stroke (n=451), or major ischemic stroke (n=237) were recruited from 2002 to 2007 and followed up until 2014. The median age at entry was 75 (IQR, 66–83) years, and 48.4% were women (Table 1). Copeptin levels were determined at baseline (median time to sampling 5 days, IQR, 2–10), and sampling was repeated in a consecutive subgroup of 384 patients after 1 year. Copeptin levels at baseline were strongly correlated with 1-year levels (r=0.48), but only weakly with time from event to sampling (r=0.01). The median copeptin level in control subjects was 3.34 (IQR, 2.38–5.28) pmol/L.

During 6000 patient-years of follow-up with a median of 5.7 years, the composite end point of all subsequent vascular events (consisting of any stroke, MI, peripheral vascular disease, and vascular death) occurred in 357 cases, and 461 patients died of any cause. After adjustment for age, sex, hypertension, diabetes mellitus, previous MI, previous stroke, previous peripheral vascular disease, smoking, CHF, atrial fibrillation and therapy with antiplatelet agents, statins or antihypertensive agents, copeptin was predictive of subsequent vascular events (adjusted HR, 1.47; 95% confidence interval [CI], 1.31–1.64; P<0.0001; Table 2); results were consistent for recurrent ischemic stroke (1.22; 1.04–1.44; P=0.017), vascular death (1.85; 1.60–2.14; P<0.0001), and all-cause death (1.75; 1.58–1.93; P<0.0001). In addition, there was also a trend for recurrent MI (HR, 1.32; 0.96–1.80; P=0.087), but statistical power was limited because of a smaller number of patients with recurrent MI (n=46).
Table 2. Associations of Copeptin and Recurrent Vascular Events and Death*

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Vascular Events (357 Events)</th>
<th>Recurrent Ischemic Stroke (174 events)</th>
<th>Vascular Death (200 Events)</th>
<th>All-Cause Death (461 Events)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>P Value</td>
<td>P Value</td>
<td>P Value</td>
<td>P Value</td>
</tr>
<tr>
<td>TIA/minor stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.71 (1.54–1.89)</td>
<td>1.37 (1.17–1.59)</td>
<td>2.24 (1.97–2.56)</td>
<td>2.01 (1.84–2.20)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.56 (1.41–1.74)</td>
<td>1.31 (1.12–1.53)</td>
<td>1.97 (1.72–2.25)</td>
<td>1.79 (1.63–1.96)</td>
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<tr>
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<td>&lt;0.0001</td>
<td>0.0009</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.47 (1.31–1.64)</td>
<td>1.22 (1.04–1.44)</td>
<td>1.85 (1.60–2.14)</td>
<td>1.75 (1.58–1.93)</td>
</tr>
<tr>
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<td>&lt;0.0001</td>
<td>0.017</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<tr>
<td>TIA/minor stroke</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.51 (1.34–1.70)</td>
<td>1.42 (1.21–1.68)</td>
<td>1.97 (1.68–2.31)</td>
<td>1.75 (1.58–1.95)</td>
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<tr>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.38 (1.21–1.56)</td>
<td>1.37 (1.15–1.62)</td>
<td>1.76 (1.49–2.08)</td>
<td>1.56 (1.39–1.74)</td>
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<tr>
<td></td>
<td>&lt;0.0001</td>
<td>0.0004</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.27 (1.11–1.45)</td>
<td>1.30 (1.09–1.57)</td>
<td>1.59 (1.33–1.91)</td>
<td>1.51 (1.34–1.71)</td>
</tr>
<tr>
<td></td>
<td>0.0006</td>
<td>0.0045</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Cl indicates confidence interval; HR, hazard ratio; and TIA, transient ischemic attack.

*Given per 1 SD (log) unit increase.

†Model 1: adjusted for age and sex; model 2: model 1 plus adjustment for hypertension, diabetes mellitus, previous myocardial infarction, previous stroke, previous peripheral vascular disease, current smoker, previous chronic heart failure, atrial fibrillation, previous antiplatelet agents, previous antihypertensive therapy, and previous statins.
for recurrent ischemic stroke: model with AUC without copeptin: 0.65 (0.60–0.69); model with AUC with copeptin: 0.64 (0.61–0.69); $P_{\text{ns}}$; relative IDI of 8.1% ($P_{\text{ns}}$); continuous NRI of 16% ($P=0.044$).

We detected a significant interaction between copeptin levels and cause of the index event and a borderline significant interaction with sex (Table 3). The predictive value of copeptin was pronounced in male patients (men: HR, 1.60; 95% CI, 1.40–1.83; women: HR, 1.25; 1.05–1.50; $P=0.024$) and in patients with cardioembolic stroke (cardioembolic stroke: HR, 1.84; 95% CI, 1.53–2.20 and noncardioembolic stroke: HR, 1.31; 1.14–1.50; $P=0.0025$). Among patients with cardioembolic stroke, those with high levels of copeptin (defined as levels above the 90th percentile of levels measured in controls) had a 4-fold increased risk of vascular events within the first year after stroke or TIA when compared with patients with normal levels (Figure 1B; adjusted HR, 4.02; 95% CI, 2.13–7.70). This difference was smaller among patients with noncardioembolic stroke (Figure 1C; adjusted HR, 1.59; 1.04–2.43). Otherwise subgroup analysis revealed consistent findings across sex, age, vascular risk factors, and stroke severity.

In addition, we did not detect an interaction between time from index event to blood sampling, ie, we were unable to demonstrate a difference in the association between copeptin and recurrent vascular events in those where blood was taken early (within the first 2 days) or later (data not shown).

### Discussion

In this population-based study of >1000 patients with ischemic stroke or TIA with a median follow-up time of >6 years, copeptin was predictive of recurrent vascular events, ischemic stroke, vascular death, and death of any cause and provided additional prognostic information beyond established clinical risk factors.

Copeptin is the c-terminal portion of provasopressin, and it is produced in an equimolar ratio to arginine-vasopressin. Compared with arginine-vasopressin, it is more stable in the circulation and therefore serves as a useful surrogate marker for the arginine-vasopressin axis. Release of arginine-vasopressin and copeptin is triggered in response to stimuli such as low cardiac output and hyponatremia in patients with CHF. In addition, copeptin has been associated with left ventricular remodeling in patients after MI with clinical signs of cardiac failure, and it also may be associated with occurrence of malign arrhythmias. In our study, the predictive value of copeptin for recurrent vascular events was significantly higher in the group of patients with cardioembolic stroke, and this association was particularly pronounced within the first year after the index event. However, even if the predictive value of copeptin was lower in patients with noncardioembolic stroke, levels were still significantly associated with recurrent vascular events; therefore, the value of copeptin as a biomarker in stroke or TIA should not be restricted to patients with cardioembolic stroke. Copeptin is a useful marker of the endogenous stress–response in healthy subjects and in acute disease. Given the strong relation of the stress response to blood pressure variables, the predictive value of copeptin might also be explained by association with blood pressure. In fact, recent studies reported an association of copeptin levels with hypertension in middle-aged men and women and with increased systolic and diastolic blood pressure on 24-hour–ambulatory blood pressure monitoring in adolescents with essential hypertension. In our study, we detected higher copeptin levels in hypertensives, but the predictive value of copeptin was independent of hypertension status. However, currently, there are no data on copeptin in relation to specific
Losartan (OPTIMAAL) study, a second measurement of Trial in Myocardial Infarction with Angiotensin II Antagonist work in patients after MI and signs of CHF in the Optimal of individual variation unlikely. Moreover, similar to previous strongly correlated with 1-year levels making effects because we previously assayed and analyzed in the OXVASC study. Copeptin had the highest predictive value in the prognosis of recurrent vascular events (Figure 2), and the statistical significance exceeded all other biomarkers.

One particular strength of our study is the high rate of statin use (84%), antiplatelet therapy or oral anticoagulation (97%), and strict blood pressure control (83%), such that potential for confounding by variation in risk factor control was limited. Therefore, given the fact that our study comprises a population of optimized secondary prevention, the detected predictive value of copeptin relied on treatment failures. Hence, copeptin might be a promising biomarker for risk stratification in future studies of secondary prevention in patients with stroke/TIA.

Our study also has limitations: first, previous studies analyzed associations of copeptin levels and outcome after ischemic stroke/TIA. However, the main focus of these studies was predominately the evaluation of associations of copeptin levels and functional outcome (assessed by the modified Rankin Scale score at 3 months and after 1 year; Table III in the online-only Data Supplement), whereas evidence of usefulness of copeptin in the context of recurrent stroke and death is limited, and data are missing entirely for recurrent vascular events/vascular death after ischemic stroke/TIA (Table III in the online-only Data Supplement). For risk stratification after cerebrovascular events, evaluation of recurrent stroke is central. In addition, evaluation of other recurrent vascular events (such as recurrent MI) is also crucial because death after TIA or stroke is more likely to occur as a consequence of heart disease than of stroke. Biomarkers of proven predictive value in heart disease such as copeptin might be important tools to improve risk prediction after stroke/TIA. Second, even though our sample size and number of deaths were substantial, we could adjust only for a limited number of confounding factors and it is possible that some other factors were unmeasured. However, our primary interest is in the predictive utility of copeptin rather than define any causal associations. Third, risk association of biomarkers might have nonlinear effects, and it would have been of particular interest to investigate the shape of the association by using spline regression analysis. However, our study did not have enough power to analyze the exact shape of association of levels. Fourth, additional adjustment for measures of cardiac function (such as the left ventricular ejection fraction or left ventricular volumes) in the Cox-regression models would have increased validity of the article. Unfortunately, indices of cardiac function were not assessed systematically in the OXVASC study. However, previous studies found a good correlation of copeptin with markers of cardiac function, and the predictive value of copeptin for prediction of death in patients with CHF was independent...
of markers of cardiac function. Therefore, we think that our results are robust even despite the evident lack of adjustment for additional cardiac indices.

Conclusions
In our study, copeptin was a promising biomarker in the long-term prognosis of patients with ischemic stroke or TIA, particularly in patients with events of cardioembolic stroke. Copeptin might enable better risk stratification for future therapeutic studies, but further validation is required, in particular, in studies using more extensive cardiac evaluation.

Acknowledgments
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Disclosures
None.

References


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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/46/11/3117

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2015/10/08/STROKEAHA.115.011021.DC1
http://stroke.ahajournals.org/content/suppl/2016/05/30/STROKEAHA.115.011021.DC2
Supplemental Data

Copeptin and long-term risk of recurrent vascular events after TIA and ischemic stroke: population-based study

Stefan Greisenegger Helen C Segal, Annette I Burgess, Debbie L Poole, Ziyah Mehta, Peter M Rothwell

- Supplementary Methods
- Supplementary Table I-III
- Supplementary References
Supplementary Methods

In the UK, the vast majority of individuals register with a general practice, which provides their primary health care and holds a lifelong record of all medical consultations, and details of medications, blood pressure measurements, and investigations. Patients who had an event whilst temporarily away from Oxfordshire were included, but visitors to Oxfordshire who were not registered with one of the study practices were excluded. The population structure derived from the general practice age/sex registers was stable over the study period.

Multiple overlapping methods of “hot” and “cold” pursuit were used to achieve near complete ascertainment of all individuals with TIA or stroke. All participating practices held accurate age-sex patient registers, and allowed regular searches of their computerized diagnostic coding systems. All practices refer patients to only one secondary care center. Case ascertainment was by prospective daily searches for acute events (“hot pursuit”) and retrospective searches of hospital and primary care administrative and diagnostic coding data (“cold pursuit”). Hot pursuit was based on the daily assessment of all patients with a possible vascular event identified by: 1) Daily searches of Emergency Department admission and symptom/diagnosis registers; 2) Daily listing from the central admissions department of all patients from our general practices admitted to hospital, and assessment of these patients in hospital; 3) Daily visits to the cardiac surgery and vascular surgery wards and review of daily lists of all patients referred to vascular surgery; 4) Daily
identification via Bereavement Officers of patients dead on arrival at hospital or who died soon after; 5) Daily assessment of all patients undergoing diagnostic angiographic, angioplasty/stenting or arterial surgical procedures in any territory.

The methods of cold pursuit were: 1) Weekly review of all listed surgical procedures undertaken by vascular and cardiovascular surgery; 2) Frequent contact with general practices and monthly searches of computerized practice diagnostic codes; 3) Monthly practice-specific list of all patients with relevant diagnostic codes from the coding departments covering all acute and community hospitals; 4) Monthly visits to the Coroner’s Office to review out-of-hospital deaths; 5) Review of all death certificates and relevant clinical details in the study general practices; 6) Practice-specific listings of all ICD-10 death codes from the local Department of Public Health; 7) Review of vascular surgery outpatient clinic letters to identify all patients attending vascular clinics who were not admitted to hospital.

A study clinician assessed patients as soon as possible after the event. Informed consent was sought, where possible, or assent was obtained from a relative. Standardized clinical history and cardiovascular examination were recorded. We also recorded from the patient, their hospital records and their general practice records, details of the clinical event, medication, past medical history, all investigations relevant to their admission and all interventions occurring subsequent to the event. If a patient died prior to assessment, we obtained eyewitness accounts and reviewed any relevant records. If death occurred outside hospital or prior to investigation, the autopsy result was reviewed. Clinical details were sought
from primary care physicians or other clinicians on all deaths of possible vascular etiology. Clinical assessments and initial diagnoses were made by clinical research fellows. All cases were also reviewed by a senior neurologist (PMR).

All patients were followed-up face-to-face at 1 month, 6 months, 1, 5 and 10 years by a research nurse or physician to determine recurrent strokes and acute coronary events. We defined non-fatal and fatal acute coronary events according to published criteria\textsuperscript{1} based on the availability of history, ECG findings, cardiac biomarkers, autopsies, or death certificates. ST-elevation MI and non-ST elevation MI were defined by using standard criteria.\textsuperscript{2} For patients who had moved out of the study area, telephone follow-up was performed. All recurrent strokes or cardiac events that presented to medical attention would also have been identified acutely by the ongoing daily case-ascertainment. If a recurrent vascular event was suspected at a follow-up visit or referred by the family physicians to clinic or admitted, the patient was reassessed and investigated by a study clinician.

Classification of deaths was blind to biomarker results and was done by review of clinical records and death certificates in the study practices. Practice-specific listings of all ICD-10 (International Classification of Diseases) death codes were also obtained from central registers. All deaths with the underlying cause coded for the purposes of national statistics as being due to ischemic heart disease (ICD I219, I251, I259), aortic valve stenosis (I350), heart failure (I500, I501), cerebrovascular disease (ICD I606, I619, I633, I634, I639, I64X, I678, I679, I694, I698), peripheral vascular disease (ICD
I710, I711, I713, I714, I739), hypertensive renal failure (I12.0); in addition one case of visceral ischemia was added (K559).
**Supplementary Table I** Associations of Copeptin and recurrent vascular events and death by tertiles of Copeptin and by applying the 90th percentile of Copeptin-levels in controls as cut-off

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Tertiles of Copeptin</th>
<th>90th perc of Copeptin in controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I (ref)</td>
<td>II</td>
</tr>
<tr>
<td>All vascular events</td>
<td>1</td>
<td>1.18 (0.88-1.57)</td>
</tr>
<tr>
<td>Recurrent ischemic stroke</td>
<td>1</td>
<td>1.32 (0.89-1.95)</td>
</tr>
<tr>
<td>Vascular death</td>
<td>1</td>
<td>1.39 (0.90-2.14)</td>
</tr>
<tr>
<td>All cause death</td>
<td>1</td>
<td>1.47 (1.12-1.93)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, hypertension, diabetes, previous MI, previous stroke, previous peripheral vascular disease, current smoker, previous chronic heart failure, atrial fibrillation, previous antiplatelet agents, previous antihypertensive therapy, previous statins (Model 2)*
**Supplementary Table II** Absolute risk at 5 years for recurrent vascular events and death in patients with high versus normal Copeptin-levels*

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>absolute risk (95%CI)</th>
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<tbody>
<tr>
<td></td>
<td>High Copeptin-levels</td>
</tr>
<tr>
<td>All vascular events</td>
<td>0.38 (0.33-0.42)</td>
</tr>
<tr>
<td>Recurrent ischemic stroke</td>
<td>0.17 (0.13-0.21)</td>
</tr>
<tr>
<td>Vascular death</td>
<td>0.26 (0.22-0.30)</td>
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<tr>
<td>All cause death</td>
<td>0.29 (0.25-0.33)</td>
</tr>
</tbody>
</table>

*using the 90th percentile in controls as cut-off
**Supplementary Table III** Previous studies analyzing associations of Copeptin with outcome after Stroke or TIA

<table>
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<tr>
<th>Study</th>
<th>reference n</th>
<th>duration of FU</th>
<th>mRS 3-6 at FU</th>
<th>recurrent stroke</th>
<th>vascular death</th>
<th>all-cause death</th>
<th>vascular events</th>
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</thead>
<tbody>
<tr>
<td>This study</td>
<td>x 1076 (stroke/TIA)</td>
<td>5.7 years</td>
<td>not evaluated</td>
<td>174</td>
<td>200</td>
<td>461</td>
<td>357</td>
</tr>
<tr>
<td>De Marchis et al (2014)</td>
<td>10 302 (TIA)</td>
<td>90 days</td>
<td>not evaluated</td>
<td>11</td>
<td>not evaluated</td>
<td>3</td>
<td>not evaluated</td>
</tr>
<tr>
<td>De Marchis et al (2013)</td>
<td>12 783 (stroke)</td>
<td>90 days</td>
<td>300</td>
<td>not evaluated</td>
<td>not evaluated</td>
<td>118</td>
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<td>Zhang et al (2013)</td>
<td>14 245 (stroke)</td>
<td>1 year</td>
<td>99</td>
<td>not evaluated</td>
<td>not evaluated</td>
<td>41</td>
<td>not evaluated</td>
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<tr>
<td>Katan et al (2011)</td>
<td>9 107 (TIA)</td>
<td>90 days</td>
<td>not evaluated</td>
<td>2</td>
<td>not evaluated</td>
<td>1</td>
<td>not evaluated</td>
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<tr>
<td>Urwyler et al (2010)*</td>
<td>13 362 (stroke)</td>
<td>1 year</td>
<td>not evaluated</td>
<td>not evaluated</td>
<td>not evaluated</td>
<td>66</td>
<td>not evaluated</td>
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<tr>
<td>Katan et al (2009)*</td>
<td>11 362 (stroke)</td>
<td>90 days</td>
<td>151</td>
<td>not evaluated</td>
<td>not evaluated</td>
<td>44</td>
<td>not evaluated</td>
</tr>
</tbody>
</table>

mRS=modified Rankin Scale; FU=follow up
*identical population
Supplemental References

1. Luepker RV. Case Definitions for Acute Coronary Heart Disease in Epidemiology and Clinical Research Studies: A Statement From the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. Circulation 2003;108:2543–2549.

Copeptin and Long-Term Risk of Recurrent Vascular Events After Transient Ischemic Attack and Ischemic Stroke
Population-Based Study
Stefan Greisenegger, MD 1,2; Helen C. Segal, PhD 1; Annette I. Burgess, DPhil 1, et al.
1 Centre for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neuroscience, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom; and 2 Department of Neurology, Medical University of Vienna, Vienna, Vienna Austria

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