Low Serum Homoarginine Is a Novel Risk Factor for Fatal Strokes in Patients Undergoing Coronary Angiography

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Background and Purpose—Low serum concentrations of the amino acid homoarginine have been associated with endothelial dysfunction and an increased risk of all-cause and cardiovascular mortality. We aimed to investigate whether homoarginine levels are also associated with fatal strokes and a history of nonfatal cerebrovascular disease.

Methods—Serum homoarginine was measured in 3305 participants of the Ludwigshafen Risk and Cardiovascular Health (LURIC) study who were referred to coronary angiography at baseline (1997 to 2000) and were followed up with respect to mortality.

Results—During a median follow-up time of 9.9 years, 991 patients died including 61 fatal (ischemic and hemorrhagic) strokes. In a binary logistic regression analysis, the odds ratio (with 95% CI) for fatal stroke per SD of homoarginine was 0.52 (0.37 to 0.73; \(P<0.001\)) and remained significant after multivariable adjustments (0.62 [0.42 to 0.91]; \(P=0.014\)). For previous cerebrovascular disease events, the multivariable adjusted OR per SD of homoarginine was 0.82 (0.70 to 0.96; \(P=0.014\)).

Conclusions—Low homoarginine levels are a novel risk factor for fatal strokes and are reduced in patients with a history of cerebrovascular disease. Further studies are needed to explore the significance of homoarginine to risk stratification and therapeutic approaches in the prevention of strokes. (Stroke. 2011;42:00-00.)

Key Words: amino acids ■ cerebrovascular ■ homoarginine ■ mortality ■ prospective

Homoarginine is an amino acid that seems to be mainly synthesized from lysine in the kidney.1 Previous studies suggest a role of homoarginine in the metabolism of the vasodilator nitric oxide.2–5 Homoarginine has been shown to serve as a substrate for nitric oxide synthase and has been associated with endothelial function.2 Homoarginine may also play a role in insulin secretion, inhibition of platelet aggregation, and blood pressure regulation.4–5 In the Ludwigshafen Risk and Cardiovascular Health (LURIC) study, we have shown that low homoarginine concentrations are associated with an increased risk of all-cause and cardiovascular mortality.6 These data among patients referred to coronary angiography were confirmed by similar results in hemodialysis patients.6 Whether homoarginine levels are also associated with risk of strokes has not been examined so far. Hence, we investigated in the LURIC study whether serum homoarginine levels are associated with risk of strokes.

Methods

Baseline examinations of the LURIC cohort (1997 to 2000) and follow-up procedures have been published previously with some disease classifications being updated meanwhile.6,7 In brief, the LURIC study consists of 3316 white patients who were referred to coronary angiography at a tertiary care center in southwest Germany. Written informed consent was obtained from all study participants and the “Ärztekammer Rheinland-Pfalz” gave ethical approval for the study. Previous cerebrovascular disease events were defined as a documented history of a foregoing transient ischemic attack, prolonged ischemic deficit, or cerebral infarction. Serum homoarginine was determined in 3305 study participants by means of a high-performance liquid chromatography method, as previously described.6 Binary logistic regression analyses of patients with fatal stroke versus the remaining study cohort were performed with the SD of homoarginine (derived from the entire cohort) as an explanatory (independent) variable. Several possible confounders including established risk factors of stroke were stepwise included as indicated.8 Similarly, we calculated logistic regression analyses with a dichotomous outcome variable for the presence or absence of a history of cerebrovascular disease events at baseline. Statis-
### Results

The homoarginine concentration (mean±SD) in the entire LURIC cohort was 2.42±1.05 μmol/L. Baseline characteristics are shown in Table 1. During a median follow-up period of 9.9 years, 991 patients died including 61 fatal strokes. In a binary logistic regression analysis, the OR (with 95% CIs) for fatal stroke per SD of homoarginine was 0.52 (0.37 to 0.73; \( P<0.001 \)). This association remained statistically significant after adjustments for various possible confounders (Table 2). Unadjusted OR for a previous (nonfatal) cerebrovascular disease event at baseline (n=302) per SD of homoarginine was 0.67 (0.58 to 0.78; \( P<0.001 \)). After multivariable adjustments (according to Model 4 in Table 2), this association remained significant with 0.82 (0.70 to 0.96; \( P=0.014 \)).

### Discussion

In patients referred to coronary angiography, we show that low serum homoarginine levels are an independent risk factor for fatal strokes and a history of cerebrovascular disease events.

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### Disclosures

None.

### References


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