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Low Glomerular Filtration Rate, Recurrent Stroke Risk and Effect of Renin Angiotensin System Modulation

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Abstract

Background and Purpose—To investigate the association of low glomerular filtration rate {eGFR} < 60 mL/min with recurrent stroke risk, and evaluate whether add-on renin-angiotensin system (RAS) modulator therapy is associated with lower recurrent stroke risk in patients with low eGFR.

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- *Acquisition of data*: Ovbiagele, Bath, and Diener.
- *Analysis and interpretation of data*: Ovbiagele, Bath, Cotton, Sha, Diener
- *Drafting of the manuscript*: Ovbiagele
- *Critical revision of the manuscript for important intellectual content*: Ovbiagele, Bath, Cotton, Sha, Diener
- *Statistical analysis*: Cotton, Sha

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Methods—We analyzed the database of a multicenter trial involving 18,666 patients with recent ischemic stroke followed for 2.5 years. Primary outcome was time to first recurrent stroke. Independent associations of low eGFR with outcome in the entire cohort; and add-on telmisartan treatment with outcome among those with low eGFR were evaluated.

Results—Low eGFR was observed in 3630 (20.1 %) patients. Low eGFR patients were older, more likely female, with a known history of hypertension. In unadjusted analyses, low eGFR patients were more likely to experience a recurrent stroke (HR 1.34, 95% CI: 1.20 – 1.49). After adjusting for confounders, low eGFR was still associated with recurrent stroke, but to a lesser extent (HR 1.16, 95% CI: 1.04 – 1.31). Telmisartan treatment among low eGFR patients was not independently associated with recurrent stroke (HR 1.08, 95% CI: 0.89 – 1.31).

Conclusions—Low eGFR is independently associated with a higher risk of recurrent stroke, but short-term add-on telmisartan therapy does not seem to mitigate this risk.

Clinical Trial Registration-URL—http://www.clinicaltrials.gov. **Unique identifier**: NCT00153062

Keywords

Chronic kidney disease; Outcomes; Stroke; Ischemic; renal; recurrent; Prognosis; renin-angiotensin; Antihypertensive therapy; Telmisartan; vascular risk; myocardial infarction; glomerular filtration rate

Background

The relationship of low eGFR with recurrent stroke risk after a recent ischemic stroke has rarely been investigated.[1] Furthermore, renin angiotensin system (RAS) modulators that limit CKD progression,[2] and reduce vascular risk in cardiac disease patients, independent of their blood pressure lowering,[3] have not been assessed for potential benefit in recent stroke patients with CKD. In this study we evaluated the association of low estimated glomerular filtration rate (eGFR) with recurrent stroke risk, and assessed whether add-on RAS modulator therapy is related to lower recurrent stroke risk among stroke patients with low eGFR.

Methods

We reviewed data from the Prevention Regimen for Effectively Avoiding Second Strokes Trial (PRoFESS). The methods and main results of this trial have previously been reported.[4] Briefly, from September 2003 to July 2006, PRoFESS enrolled 20, 332 patients from 695 centers in 35 countries who recently had an ischemic stroke. Patients with cardioembolic strokes requiring anticoagulation, known severe renal insufficiency defined as renal artery stenosis or serum creatinine > 265 micromol/L (>3.0 mg/dL) were excluded.[4] Average patient follow-up was 2.5 years. The primary outcome was first recurrence of stroke of any type. The trial was approved by the ethics committee or institutional review board at each national or local site, and all participants provided written informed consent.[4]

Since no difference in efficacy was discerned between any of the treatment arms in PRoFESS, all patients were included in this analysis.[4] Estimated glomerular filtration rate

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per the Modification of Diet in Renal Disease Study Group equation was calculated for each eligible patient.[5] CKD was defined as eGFR < 60 mL/min per 1.73m^2. Patients with implausibly low serum creatinine levels (<18 micromol/L {<0.2 mg/dL}) were excluded (n=1629). CKD was categorized by stage using a slightly modified version of the National Kidney Foundation (NKF) guidelines.[6] Stepwise Cox proportional hazard models were used to estimate the risk of the primary outcome, which was time to first recurrent stroke. We forced these baseline covariates into the stepwise model: age, sex, history of prior stroke, known diabetes, previous myocardial infarction, average trial blood pressure, known hypertension, and selecting other covariates with a p-value ≤ 0.10. Tests for two-way interactions involving telmisartan treatment were performed for pre-specified baseline features including age, history of diabetes, and small vessel stroke subtype.

Results

Of the 20332 subjects enrolled in PRoFESS, eGFR was determined in 18,666 (91.8%) patients with serum creatinine within the range of 18 to 265 micromol/L (0.2 to 3.0 mg/dL). Overall, mean age was 66.0+/−8.5 years, 6612 (35.9%) were women and 3630 (20.1%) had CKD. Among those with baseline CKD, mean age was 69.2 ± 8.6 years and 1944 (50.0 %) were women. Baseline characteristics are shown in Supplementary Table I. Patients with CKD were more likely to be older, female, with a baseline history of hypertension, coronary artery disease, symptomatic cerebrovascular disease, and antihypertensive drug use; and less likely to be smokers.

Absolute risks of recurrent vascular events by baseline eGFR were consistently worse among PRoFESS patients with low eGFR (Supplementary Table II), and CKD severity by modified NKF staging showed an association of eGFR with vascular events in a dose dependent manner (Supplementary Table III). In unadjusted analyses, low eGFR patients were more likely to experience a recurrent stroke (HR 1.34, 95% CI: 1.20 – 1.49). After adjusting for confounders, low eGFR was still associated with recurrent stroke, but to a lesser extent (HR 1.16, 95% CI: 1.04 – 1.31). Telmisartan treatment among low eGFR patients was not independently associated with recurrent stroke (HR 1.08, 95% CI: 0.89 – 1.31).

For the outcome of recurrent stroke, there were no significant two-way interactions involving telmisartan treatment between eGFR category vs. pre-specified variables of age, small vessel disease stroke type, and diabetes.

Discussion

We observed that among patients with a recent ischemic stroke, recurrent stroke risk was significantly higher for those patients with eGFR below 60 mL/min than for those patients with higher eGFR values, even after adjusting for potential major confounders. These results suggest that there may be clinical relevance in the utilization of eGFR in recurrent stroke risk prognostication among recent ischemic stroke patients. On the other hand, unlike results of analyses of cardiac disease patients,[3] we did not find that add-on treatment with a renin-angiotensin modulator was independently related to better clinical outcomes.

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The strength of the association between CKD and recurrent stroke risk appears to be less than that reported with primary stroke.[7] This difference may be due to insufficient follow-up period in the current study or implementation of vascular risk reduction therapies after a primary stroke likely mitigates some of the avenues through which CKD may promote deleterious vascular effects. Multiple explanations have been proposed for the link between CKD and vascular demise including an enhancement of less conventional vascular risk factors, and activation of the renin-angiotensin system by the initial renal endothelial damage with resultant upregulation of inflammatory mediators (cytokines, chemokines, adhesion molecules) and superoxide scavenging of nitric oxide.[8] Meanwhile, the null effect of add-on RAS modulation in the ischemic stroke patients with CKD in this study might be due to the heterogeneous nature of ischemic stroke, the dose of the agent used, differences among individual RAS modulators. Only a dedicated randomized clinical trial using a RAS modulator in stroke patients with CKD can clarify this issue properly.

Our study is limited because it is a post-hoc analysis of a completed randomized trial, these results may not apply to patients whose index stroke is due to a presumed cardioembolic mechanism, and the follow-up time may have been too brief to see any potentially protective benefits of the RAS modulator. The study was strengthened by the rigorous procedures of the PRoFESS trial design, inclusion of subjects enrolled from around the world and large sample size.[8]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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