Decreased Glomerular Filtration Rate Is a Risk Factor for Hemorrhagic But Not for Ischemic Stroke

The Rotterdam Study

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Background and Purpose—Persons with early stages of chronic kidney disease, defined by a decreased glomerular filtration rate (GFR), have an increased risk of cardiovascular disease. It is unclear whether decreased GFR is a risk factor for stroke. We assessed the association between GFR and stroke in a prospective population-based cohort study.

Methods—The study was based on 4937 participants of the Rotterdam Study who at baseline (1990 to 1993) were aged 55 years or over, free from stroke, and had serum creatinine assessment. GFR was estimated with the Cockcroft-Gault equation. Follow-up for incident cerebrovascular disease was complete until January 1, 2005. Data were analyzed with Cox proportional hazards models with adjustment for relevant confounders and results were expressed as hazard ratios with 95% CIs.

Results—During an average follow-up of 10.2 years, 586 strokes (338 ischemic, 44 hemorrhagic, and 204 unspecified strokes) occurred. We found no association between GFR and risk of overall stroke or risk of ischemic stroke. In contrast, with decreasing GFR, the risk of hemorrhagic stroke strongly increased; the age- and sex-adjusted hazard ratio for hemorrhagic stroke was 4.10 (95% CI, 1.25 to 13.42) for lowest versus highest quartile of GFR, and there was a clear and highly significant dose–effect relationship. Adjustment for other vascular risk factors only slightly attenuated this association.

Conclusions—Decreased GFR is a strong risk factor for hemorrhagic, but not ischemic stroke. (Stroke. 2007;38:3127-3132.)

Key Words: cerebrovascular disease ■ epidemiology ■ intracerebral hemorrhage ■ risk factors ■ stroke

The clinical spectrum of chronic kidney disease ranges from an unnoticed decrease in glomerular filtration rate (GFR) to end-stage renal failure. The prevalence of chronic kidney disease, especially subclinical stages, is very high among elderly subjects.1 It has been shown that chronic kidney disease is closely related to ischemic heart disease. On the one hand, risk factors for ischemic heart disease like hypertension, smoking, and diabetes mellitus are more prevalent among patients with chronic kidney disease.2,3 On the other hand, chronic kidney disease itself has numerous effects that potentially may harm the cardiovascular system, including inhibition of erythropoiesis and platelet function4,5 and induction of volume overload, dyslipidemia, hypertension, and vascular calcification.6 As a result, patients with chronic kidney disease are at increased risk of ischemic heart disease; the ischemic heart disease death rate among patients with end-stage kidney disease is 10 to 30 times higher than in the general population.9 Also, persons with early stages of chronic kidney disease, usually diagnosed by means of a decreased glomerular creatinine filtration rate or increased serum cystatin C level, have an increased risk of coronary heart disease and ischemic cardiac death, which is independent of other conventional cardiovascular risk factors.10–14 Therefore, it is commonly thought that chronic kidney disease is not only a marker of the presence of cardiovascular risk factors, but in addition plays a causal role in the pathophysiology or propagation of ischemic heart disease.

Despite the evidence for chronic kidney disease being a risk factor for ischemic heart disease and the overlap between ischemic heart disease and stroke risk factors, it remains uncertain whether GFR is also associated with risk of stroke; the few studies that reported on this association showed a small and nonsignificant increase in stroke risk with decreasing GFR.13,14 No studies reported on the association between GFR and subtypes of stroke.

The aim of our present study was to assess whether decreased GFR is a risk factor for ischemic and hemorrhagic stroke in the general population.
Materials and Methods

Population

The Rotterdam Study is a population-based cohort study on chronic and disabling diseases.14 All inhabitants of Ommoord, a district of the city of Rotterdam in The Netherlands, aged 55 years and over, were invited to participate. Participation rate of those invited for the study was 78%; in total, 7983 subjects participated in the first study survey (1990 to 1993). The Medical Ethics Committee of Erasmus University Rotterdam approved the study. Written informed consent to retrieve information from treating physicians was obtained from all participants.

Assessment of Stroke

History of stroke at baseline was positive if a stroke was reported during the baseline interview and confirmed by medical records (n=261). After enrollment into the Rotterdam Study, participants were continuously monitored for strokes through automated linkage of the study database with files from general practitioners and the municipality. Also, nursing home physicians’ files and files from general practitioners of participants who moved out of the district were scrutinized. For reported events, additional information (including brain imaging) was obtained from hospital records. Research physicians discussed information on all potential strokes with an experienced stroke neurologist (P.J.K.) to verify all diagnoses.16,17 Subarachnoid hemorrhages were excluded. A stroke was subclassified as ischemic if a CT or MRI scan, made within 4 weeks after the stroke occurred, confirmed the diagnosis or if indirect evidence (deficit limited to one limb or completely resolved within 72 hours, atrial fibrillation in absence of anticoagulants) pointed at an ischemic nature of the stroke. A stroke was subclassified as hemorrhagic if a relevant hemorrhage was shown on CT or MRI scan. Supratentorial hemorrhagic strokes were subclassified as deep or lobar based on neuroimaging. If we could not retrieve enough information to subclassify a stroke as ischemic or hemorrhagic, it was called unspecified. Follow-up was complete until January 1, 2005, for 98.7% of potential person-years.18

Glomerular Filtration Rate Assessment

During the baseline center visit, nonfasting blood was collected and centrifuged within 30 minutes at 3000 rotations per minute for 10 minutes. Subsequently, the serum was stored at −20°C for 1 week until serum creatinine level was assessed by a nonkinetic alkaline picrate (Jaffé) method19 (Kone Autoanalyser; Kone Corp., Espoo, Finland, and Elan; Merck, Darmstadt, Germany). The method was standardized against high-performance liquid chromatography. The within-run precision was >98.5% and the day-by-day precision was >95.0%. Creatinine clearance was computed with the Cockcroft-Gault equation20 corrected with a factor 0.9 and standardized for 1.73 m² body surface area using the Dubois formula:21 GFR=(140-age [years]) (weight [kg]×1.23) (0.85 if female) (serum creatinine [µmol/L])¹/₂ (1.73) (weight [kg])⁻¹/₂ (height [cm])⁻⁰.⁷²⁵ (0.007184)⁻¹. Creatinine clearance generally exceeds GFR by 10% to 15% due to urinary creatinine derived from tubular secretion.22 The Cockcroft-Gault estimate of GFR was therefore additionally corrected with a factor of 0.9. Because 98.5% of our participants were white and 99.2% had at least one white parent, adjustment for ethnicity was not required.

Other Measurements

Blood pressure was measured twice in a sitting position on the right arm with a random-zero sphygmomanometer. We used the average of these 2 measurements in the analyses. Left ventricular hypertrophy was assessed with a 12-lead resting electrocardiogram and the Modular ECG Analysis System (MEANS)23 implemented on an ACTA ECG (ESAOTE, Florence, Italy). We considered diabetes mellitus to be present if a random or postload glucose level was 11.1 mmol/L or higher or if a person used antidiabetic medication. Total cholesterol, high-density lipoprotein, uric acid, and C-reactive protein were measured in nonfasting baseline serum with an automated enzymatic procedure. Carotid intima media thickness was measured by longitudinal 2-dimensional ultrasound of the carotid artery. We calculated the mean common carotid artery intima media thickness as the mean of 4 locations: the near and far wall of both the right and left common carotid artery. History of myocardial infarction was positive if a participant had reported a myocardial infarction that was confirmed by electrocardiogram or medical records. Use of medication and smoking history were assessed during a home interview. The number of pack-years of smoking was calculated by multiplying the number of cigarette packs smoked per day by the number of years smoked. The proportion of missing values was ≤1% for all variables with the exception of intima media thickness (17% missing), serum C-reactive protein (7% missing), and serum uric acid (3% missing).

Population for Analysis

Of all 7983 participants who were enrolled into the Rotterdam study, 7722 were free from stroke at study baseline. Of these, 1723 participants visited the research center after December 31, 1992, when creatinine assays had been stopped due to financial constraints. For the present study, 1062 participants could not be included due to missing data; 844 did not visit the research center, 69 had unsuccessful blood sampling, 131 did not have weight or height measured, and 18 refused informed consent for retrieval of stroke follow-up data. Consequently, 4937 participants were included in the analyses.

Statistical Analysis

We used Cox proportional hazards models to calculate hazard ratios (HRs) with 95% CIs for the associations between GFR and stroke after inspection of log(-log) survival curves. Hazard ratios were calculated for GFR quartiles (relative to the lowest quartile). Subsequently, we compared the risk of stroke among participants with chronic kidney disease as defined by the internationally accepted accepted criterion of a GFR below 60 mL/min/1.73 m²24 with the risk of participants without chronic kidney disease. We constructed 3 models: in model 1, we adjusted for age and sex; and in model 2, we adjusted for age, sex, systolic blood pressure, diastolic blood pressure, antihypertensive drug use, and left ventricular hypertrophy. In model 3, we adjusted for age, sex, and a propensity score; for the analyses concerning quartiles of GFR, we calculated the propensity score with a linear regression model entering GFR as the dependent variable. For the analyses concerning chronic kidney disease, we calculated a linear propensity score with a logistic regression model entering diagnosis of chronic kidney disease as the dependent variable.25 The propensity scores were based on systolic blood pressure, diastolic blood pressure, antihypertensive drug use, diuretic use, left ventricular hypertrophy, pack-years of smoking, diabetes mellitus, serum cholesterol, serum high-density lipoprotein, carotid intima media thickness, serum uric acid, serum C-reactive protein, previous myocardial infarction, previous atrial fibrillation, waist-to-hip ratio, antithrombotic drug use, and lipid-lowering drug use. For missing values in confounders and effect modifiers, the mean value was imputed. All analyses were performed with SPSS for Windows, release 11.0.1 (SPSS Inc).

Results

The median age of the participants of the present study was 69 years and 61% were women. Other baseline characteristics are described in Table 1. The 1062 participants who were not included in the present study due to missing data were older than the included participants (median age, 80.3 versus 68.9 years; Mann–Whitney P<0.001) and also more likely to be female (72% versus 61%, Mann–Whitney P<0.001).
Baseline Characteristic | Median* or Percentage | P Value for Association With GFR†
--- | --- | ---
Serum creatinine, μmol/L | 81 (72–91) | ...
Body surface area, m² | 1.8 (1.7–1.9) | ...
GFR, mL/min/1.73 m² | 68.0 (57.3–78.8) | ...
Both parents white, % | 98... | ...
Age, years | 68.9 (62.3–76.7) | <0.001
Female sex, % | 61.3 | 0.78
Systolic blood pressure, mm Hg | 138 (123–153) | 0.002
Diastolic blood pressure, mm Hg | 73 (66–81) | 0.07
Carotid intima media thickness, mm | 0.78 (0.69–0.88) | 0.68
Serum C-reactive protein, mg/L | 1.87 (0.90–3.63) | 0.64
Cholesterol, mmol/L | 6.6 (5.8–7.4) | 0.42
High-density lipoprotein, mmol/L | 1.3 (1.1–1.6) | <0.001
Serum uric acid, μmol/L | 310 (267–370) | <0.001
Diabetes mellitus, % | 10.3 | 0.01
Left ventricular hypertrophy, % | 5 | 0.01
Previous myocardial infarction, % | 12.0 | 0.09
Atrial fibrillation, % | 5 | 0.004
Waist-to-hip ratio, cm/cm | 0.90 (0.83–0.97) | <0.001
Smoking, pack-years | 2.5 (0–26) | 0.04
Antihypertensive medication, % | 13 | 0.81
Diuretic use, % | 16 | 0.17
Antithrombotic drug use | 4 | <0.001
Lipid-lowering drug use, % | 2 | 0.28

*With 25th and 75th percentiles.
†P values estimated with linear regression model adjusted for all other characteristics.

During on average 10.2 years of follow-up, 586 first-ever strokes occurred. Of these, 338 could be subclassified as ischemic and 44 as hemorrhagic; 204 were unspecified. The diagnosis was made without the use of neuroimaging in 9% of all ischemic stroke cases, in 0% of all hemorrhagic stroke cases, and in 96% of all unspecified stroke cases. The participants who did not have neuroimaging were older than those who did have neuroimaging (median age, 78.3 versus 70.7 years; Mann–Whitney P<0.001) and also more likely to be female (69% versus 56%; Mann–Whitney P<0.01).

Inspection of log(-log) survival curves showed that the proportional hazards assumption was not violated. In an age- and sex-adjusted Cox model, we found a slightly but nonsignificantly increased risk of stroke (HR, 1.14; 95% CI, 0.84 to 1.54) for the lower compared with the upper quartile of GFR (Table 2). We found no association between GFR and the risk of ischemic stroke. In contrast, the hazard of hemorrhagic stroke was 4.10 (95% CI, 1.25 to 13.42) times higher in the lowest compared with the highest quartile of GFR and showed a clear trend toward increasing hemorrhagic stroke risk with decreasing GFR (age- and sex-adjusted HR, 2.03; 95% CI, 1.31 to 3.15 per standard deviation decrease in GFR). None of the putative confounders that were tested changed the estimates of the HRs more than 4%. Adjustment for all measures of hypertension (model 2) increased all HRs slightly. Adjustment for the propensity score of all potential confounders hardly attenuated the HRs.

When we looked separately at subtypes of hemorrhages, the HR was 2.76 (95% CI, 1.34 to 5.67) per SD for deep hemorrhages (n=16) and 2.77 (95% CI, 1.02 to 7.53) per SD for lobar hemorrhages (n=8).

When we compared the risk of stroke between participants with and without chronic kidney disease,24 we found that participants with chronic kidney disease had a slightly and nonsignificantly increased risk of ischemic stroke (HR, 1.25; 95% CI, 0.97 to 1.61; Table 3) and a strongly increased risk of hemorrhagic stroke (HR, 3.02; 95% CI, 1.45 to 6.27).

**Discussion**

In this population-based study, we found a strong and graded inverse association between GFR and risk of hemorrhagic stroke that was independent from other vascular risk factors. We found no association between GFR and risk of ischemic stroke.

Strengths of our study are the meticulous stroke case finding and the nearly complete follow-up (loss of potential person-years, 1.3%). To our knowledge, our study is the first that assessed the association between GFR and the risk of subtypes of stroke in the general population. Our stringent stroke-monitoring procedures allowed us to include also patients with stroke who had not been referred to a neurologist (31% of all stroke cases). Like in these cases, neuroimaging had not been performed; we could subclassify only 16% of them into ischemic or hemorrhagic. In contrast, 92% of strokes that had been referred to a neurologist could be subclassified. As a result, we could not determine the subtype of stroke in 204 participants. It is expected that approximately 80% of these are ischemic and 20% hemorrhagic. Because participants with unspecified stroke were censored at the time of stroke in the subtype analyses, they did not influence the hazard ratios for subtypes of stroke.

Not all participants of the Rotterdam Study who were stroke-free at baseline were included in the analyses. The 1723 participants who were not included in the present study because they visited the research center after the creatinine assays were stopped did not introduce bias because participants were invited to visit the research center in random order. However, 1062 participants were not included in the present study as a result of missing data. These participants were on average a little older, more often female, and possibly less healthy than those in the study population. Because this makes the study population more homogeneous than the source population, some associations may have been slightly underestimated.

The Cockcroft-Gault equation20 and the abbreviated Modification of Diet in Renal Disease equation26 are the most widely used equations to estimate GFR. Because the latter equation has been developed in a population for which 99.6% of our participants would not meet inclusion criteria, we chose to use the Cockcroft-Gault equation in our present study. We measured blood pressure twice on a single day. Because we thereby ignored day-by-day variations in blood...
pressure, some residual confounding of the relation between GFR and risk of stroke by blood pressure may remain. However, adjustment for blood pressure did not attenuate the associations we found at all. We measured serum creatinine only once, ignoring possible intraindividual fluctuations in serum creatinine levels. This may have caused our estimates to be slightly underestimated. Furthermore, serum creatinine is influenced by nonrenal factors and additional measurement of urinary albumin might have improved the sensitivity and specificity of our assessment of kidney function. However, urinary albumin was not measured in our study. Relatively few participants developed a hemorrhagic stroke due to the low incidence rate of this disease; therefore, the 95% CIs are fairly wide. However, the high level of statistical significance and the strong dose–response relationship show that our study had enough precision to claim that the risk of hemorrhagic stroke increases with decreasing GFR.

Few studies reported on the association between GFR and stroke in the general population and none of these studies divided stroke into ischemic and hemorrhagic. A pooled analysis of 4 population-based studies showed that the risk of stroke seemed increased by 17% among participants with chronic kidney disease (stage 3 or 4) compared with participants without chronic kidney disease, although this finding was not statistically significant.14 This is of the same magnitude as our finding of a 25% nonsignificant increased risk of ischemic stroke in participants with GFR <60 mL/min/1.73 m².

### Table 2. Hazard Ratios for the Association Between GFR and Risk of Stroke (N=4937)

<table>
<thead>
<tr>
<th>Event</th>
<th>GFR*</th>
<th>Model 1†</th>
<th>Model 2†</th>
<th>Model 3†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stroke (n=586)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 4</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>Quartile 3</td>
<td>0.86 (0.65–1.14)</td>
<td>0.88 (0.66–1.16)</td>
<td>0.85 (0.64–1.13)</td>
<td></td>
</tr>
<tr>
<td>Quartile 2</td>
<td>1.15 (0.88–1.51)</td>
<td>1.16 (0.89–1.52)</td>
<td>1.10 (0.84–1.44)</td>
<td></td>
</tr>
<tr>
<td>Quartile 1</td>
<td>1.14 (0.84–1.54)</td>
<td>1.15 (0.85–1.55)</td>
<td>1.04 (0.77–1.41)</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke (n=338)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 4</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>Quartile 3</td>
<td>0.88 (0.63–1.22)</td>
<td>0.89 (0.64–1.24)</td>
<td>0.87 (0.62–1.20)</td>
<td></td>
</tr>
<tr>
<td>Quartile 2</td>
<td>1.13 (0.82–1.56)</td>
<td>1.16 (0.84–1.60)</td>
<td>1.09 (0.79–1.51)</td>
<td></td>
</tr>
<tr>
<td>Quartile 1</td>
<td>0.87 (0.59–1.29)</td>
<td>0.90 (0.61–1.32)</td>
<td>0.81 (0.54–1.20)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke (n=44)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 4</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>Quartile 3</td>
<td>1.76 (0.58–5.29)</td>
<td>1.79 (0.59–5.38)</td>
<td>1.73 (0.58–5.22)</td>
<td></td>
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<tr>
<td>Quartile 2</td>
<td>3.06 (1.06–8.86)</td>
<td>3.12 (1.08–9.03)</td>
<td>2.92 (1.00–8.48)</td>
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<tr>
<td>Quartile 1</td>
<td>4.10 (1.25–13.42)</td>
<td>4.14 (1.27–13.54)</td>
<td>3.68 (1.12–12.09)</td>
<td></td>
</tr>
</tbody>
</table>

†Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, systolic blood pressure, diastolic blood pressure, antihypertensive drug use, and left ventricular hypertrophy. Model 3: adjusted for age, sex, and propensity score (systolic blood pressure, diastolic blood pressure, antihypertensive drug use, left ventricular hypertrophy, diuretic use, pack-years of smoking, diabetes mellitus, serum cholesterol, serum high-density lipoprotein, carotid intima media thickness, serum uric acid, serum C-reactive protein, previous myocardial infarction, previous atrial fibrillation, waist-to-hip ratio, antithrombotic drug use, lipid-lowering drug use).

### Table 3. Hazard Ratios for the Association Between Chronic Kidney Disease and Risk of Stroke (N=4937)

<table>
<thead>
<tr>
<th>Event</th>
<th>GFR (ml/min/1.73 m²)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stroke (n=586)</td>
<td>≥60 (N=2652)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td></td>
<td>&lt;60 (N=2285)</td>
<td>1.29 (1.06–1.57)</td>
</tr>
<tr>
<td>Ischemic stroke (n=338)</td>
<td>≥60 (N=2652)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td></td>
<td>&lt;60 (N=2285)</td>
<td>1.25 (0.97–1.61)</td>
</tr>
<tr>
<td>Hemorrhagic stroke (n=44)</td>
<td>≥60 (N=2652)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td></td>
<td>&lt;60 (N=2285)</td>
<td>3.02 (1.45–6.27)</td>
</tr>
</tbody>
</table>

*Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, systolic blood pressure, diastolic blood pressure, antihypertensive drug use, and left ventricular hypertrophy. Model 3: adjusted for age, sex, and propensity score (systolic blood pressure, diastolic blood pressure, antihypertensive drug use, left ventricular hypertrophy, diuretic use, pack-years of smoking, diabetes mellitus, serum cholesterol, serum high-density lipoprotein, carotid intima media thickness, serum uric acid, serum C-reactive protein, previous myocardial infarction, previous atrial fibrillation, waist-to-hip ratio, antithrombotic drug use, lipid-lowering drug use).*
compared with participants with GFR ≥60 mL/min/1.73 m². In another study, the risk of stroke was moderately increased in the lowest GFR quintile compared with the highest GFR quintile with a 92% increased risk among participants with GFR below the 7th percentile. This effect largely disappeared after adjustment for confounding.13

In most studies, including ours, adjustment for cardiovascular risk factors did not markedly change the associations between GFR and the risk of cardiovascular disease,10–1427 which means either that GFR is a better marker for vascular pathology than other vascular risk factors or that chronic kidney disease is a causal factor in the pathogenesis of coronary heart disease and hemorrhagic stroke. On the other hand, the adjusted estimates may be underestimations of the true associations because at least part of the presumed effect of chronic kidney disease on cardiovascular disease is through the risk factors that were adjusted for.

There are at least two hypotheses that may explain how GFR can be associated with hemorrhagic stroke and not with ischemic stroke. A first explanation assumes a noncausal association between GFR and hemorrhagic stroke. Decreased GFR is often attributable to renal small vessel disease, which is presumably correlated with small vessel disease in the brain.28 Therefore, decreased GFR may be a marker of cerebral small vessel disease, which is presumed to be the main pathophysiological mechanism in the majority of brain hemorrhages, whereas it plays a much smaller role in brain infarctions. An alternative explanation assumes that chronic kidney disease has a causal role in hemorrhagic stroke pathophysiology. An important sequel of chronic kidney disease is platelet dysfunction. This becomes apparent by prolonged bleeding time, mucocutaneous ecchymoses, and mucosal oozing in patients with severe chronic kidney disease.5 It is possible that a slightly decreased GFR also influences platelet function, which might explain the increased risk of hemorrhagic stroke in persons with decreased GFR.

In conclusion, we found that GFR is a risk factor for hemorrhagic stroke and not for ischemic stroke. We think this is an important finding because our knowledge of causes of hemorrhagic stroke is very limited and we might have identified an important risk factor. This finding may provide insight into hemorrhagic stroke pathophysiology. In addition, it identifies a potentially treatable cause of this devastating disease.

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Disclosures
None.

References
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