Impact of Proteinuria and Glomerular Filtration Rate on Risk of Thromboembolism in Atrial Fibrillation: The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study

Alan S. Go, Margaret C. Fang, Natalia Udaltsova, Yuchiao Chang, Niela K. Pomernacki, Leila Borowsky, Daniel E. Singer and for the ATRIA Study Investigators

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Impact of Proteinuria and Glomerular Filtration Rate on Risk of Thromboembolism in Atrial Fibrillation

The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study

Alan S. Go, MD; Margaret C. Fang, MD, MPH; Natalia Udaltsova, PhD; Yuchiao Chang, PhD; Niela K. Pomernacki, RD; Leila Borowsky, MPH; Daniel E. Singer, MD; for the ATRIA Study Investigators

**Background**—Atrial fibrillation (AF) substantially increases the risk of ischemic stroke, but this risk varies among individual patients with AF. Existing risk stratification schemes have limited predictive ability. Chronic kidney disease is a major cardiovascular risk factor, but whether it independently increases the risk for ischemic stroke in persons with AF is unknown.

**Methods and Results**—We examined how chronic kidney disease (reduced glomerular filtration rate or proteinuria) affects the risk of thromboembolism off anticoagulation in patients with AF. We estimated glomerular filtration rate using the Modification of Diet in Renal Disease equation and proteinuria from urine dipstick results found in laboratory databases. Patient characteristics, warfarin use, and thromboembolic events were ascertained from clinical databases, with validation of thromboembolism by chart review. During 33 165 person-years off anticoagulation among 10 908 patients with AF, we observed 676 incident thromboembolic events. After adjustment for known risk factors for stroke and other confounders, proteinuria increased the risk of thromboembolism by 54% (relative risk, 1.54; 95% CI, 1.29 to 1.85), and there was a graded, increased risk of stroke associated with a progressively lower level of estimated glomerular filtration rate compared with a rate ≥60 mL · min⁻¹ · 1.73 m⁻²; relative risk of 1.16 (95% CI, 0.95 to 1.40) for estimated glomerular filtration rate of 45 to 59 mL · min⁻¹ · 1.73 m⁻² and 1.39 (95% CI, 1.13 to 1.71) for estimated glomerular filtration rate <45 mL · min⁻¹ · 1.73 m⁻² (P=0.0082 for trend).

**Conclusions**—Chronic kidney disease increases the risk of thromboembolism in AF independently of other risk factors. Knowing the level of kidney function and the presence of proteinuria may improve risk stratification for decision making about the use of antithrombotic therapy for stroke prevention in AF. (Circulation. 2009;119:1363-1369.)

**Key Words:** atrial fibrillation ■ kidney failure, chronic ■ proteinuria ■ risk factors ■ stroke

**Clinical Perspective p 1369**

End-stage renal disease (ESRD) requiring renal replacement therapy is associated with progressive vascular atherosclerosis, metabolic abnormalities, and prothrombotic tendencies, and it is considered a potent risk factor for ischemic stroke in the general population on the basis of limited data. Previous studies have yielded conflicting data on the impact of AF on outcomes in patients with ESRD. Chronic kidney disease (CKD), defined as reduced glomerular filtration rate and/or proteinuria, markedly increases the risk for cardiovascular events in the general population, although conflicting data exist for its association specifically with ischemic stroke in the absence of AF. Even less is known about the incremental effect of CKD and its severity on the risk of ischemic stroke in the setting of AF.

To address these issues, we examined the independent effect of 2 measures of CKD, reduced glomerular filtration rate and proteinuria, on the risk of thromboembolism off antithrombotic therapy.
anticoagulation therapy in a large cohort of adults with nonvalvular AF.

Methods

Study Population
Assembly of the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) cohort has been described in detail previously. Briefly, we identified all patients ≥18 years of age with diagnosed AF within Kaiser Permanente of Northern California, a large integrated healthcare delivery system, using physician-assigned diagnoses of AF found in an ambulatory visit (International Classification of Diseases, ninth edition [ICD-9] code 427.31) and ECG databases between July 1, 1996, and December 31, 1997. We focused on patients with presumed chronic nonvalvular AF by excluding patients with diagnosed mitral stenosis or valvular repair or replacement, transient perioperative AF, or concomitant hyperthyroidism.

This study was approved by institutional review boards of the collaborating institutions. Waiver of informed consent was obtained given the nature of the study.

Measurement of Kidney Function
Kidney function was assessed 2 ways: level of estimated glomerular filtration rate (eGFR) and presence of proteinuria. To assess the level of eGFR, we identified all outpatient serum creatinine tests (range, 0.1 to 20.0 mg/dL) performed among cohort members found in health plan laboratory databases between January 1, 1995, and September 30, 2003. The baseline level of eGFR was defined on the basis of the nearest measurement up to 12 months before the index date or up to 90 days after the index date if no prior measurement within 12 months was available. All Kaiser Permanente of Northern California laboratories used the same serum creatinine assay during the study period, with 85% of tests performed by a single regional laboratory. Because we were interested in the absolute level of kidney function associated with the risk of thromboembolism, we calibrated serum creatinine test results with the Cleveland Clinic Laboratory used to develop the Modification of Diet in Renal Disease glomerular filtration rate–estimating equation.20,21 We next calculated at baseline and throughout follow-up each patient’s eGFR using the abbreviated 4-variable Modification of Diet in Renal Disease equation: eGFR (mL · min−1 · 1.73 m−2) = 186 × [serum creatinine (mg/dL)]−1.154 × (age)−0.203 × (0.742 if female) × (1.212 if black).20,21 Using a modification of the National Kidney Foundation classification for CKD,12,13 we categorized level of eGFR as follows: ≥60, 45 to 59, and <45 mL · min−1 · 1.73 m−2. Proteinuria was defined as a urine dipstick protein result of ≥1+ (~30 mg/dL or higher) in the absence of potential urinary tract infection (ie, concomitant positive urine nitrite or esterase) found in laboratory databases.13 Receipt of renal replacement therapy (peritoneal dialysis, hemodialysis, or kidney transplant) was identified from a health plan ESRD treatment registry.13 We excluded patients with prior kidney transplant because we were interested in the effect of de novo CKD.

Patient Characteristics
We used administrative databases for information on patient age, sex, and self-reported race/ethnicity updated through August 2008. US Census block data from the 2000 survey were used to classify cohort members’ educational attainment and annual household income status.13 As previously described,1,19 we searched automated inpatient, outpatient, laboratory, and pharmacy databases for the 5 years before the index date to identify the following known or putative risk factors for ischemic stroke in AF: previous ischemic stroke, diagnosed heart failure, known coronary heart disease, and hypertension. We also used a validated longitudinal health plan diabetes registry to identify patients with diabetes mellitus.19 We have previously validated the use of these approaches to ascertain these selected diagnoses in this cohort.19 Each of these characteristics also was updated during follow-up through September 30, 2003, with the same methods.

Identification of Periods Off Anticoagulation
To examine the role of kidney function measures on risk of thromboembolism, we focused on periods of follow-up off anticoagulation. To identify periods off warfarin therapy, we assigned use of warfarin based on a combination of data from prescriptions and outpatient international normalized ratio measurements found in pharmacy and laboratory databases, respectively. Longitudinal warfarin exposure was based on number of days of supply per prescription and intervening international normalized ratios. For any 2 consecutive prescriptions with a gap of up to 60 days, a patient was considered to be continually on warfarin. For gaps >60 days, we considered the patient to be continually on warfarin if there were intervening international normalized ratio measurements at least every 42 days. Otherwise, the patient was considered off warfarin from day 31 after the end date of the first prescription until the start date of the next prescription. This grace period of 30 days at the end of each warfarin period was given because changes in warfarin dose are common. We previously demonstrated the validity of this approach based on chart review.22

Identification of Thromboembolic Events
From the index date through September 30, 2003, we prospectively searched hospitalization and billing claims databases for potential thromboembolic events based on relevant ICD-9 codes for stroke and peripheral embolism found in the primary discharge diagnosis position as previously described.22 Potential events were adjudicated by a Clinical Outcomes Committee composed of physicians using medical records review, with a final decision made by a consulting neurologist if consensus was not reached by the committee. A valid ischemic stroke was defined as a documented acute neurological deficit lasting >24 hours that was not explained by other causes (ie, primary hemorrhage, trauma, infection, or vasculitis). A peripheral thromboembolic event was considered valid if an embolus was demonstrated by radiographic imaging, intraoperative examination, or pathological findings in the absence of underlying atherosclerotic disease.

Follow-Up and Disenrollment
Follow-up occurred through September 30, 2003, disenrollment, or death. Membership gaps lasting >90 days without evidence of interim medical care were considered disenrollment from the health plan, and patients were censored at the last known membership date. Disenrollment as a result of death through September 30, 2003, was ascertained from hospital databases, health plan member reporting, Social Security Administration vital status files, and the California State death certificate registry.23

Statistical Analyses
All analyses were conducted with SAS, version 9.1 (SAS Institute, Inc, Cary, NC). Continuous variables were compared across levels of eGFR by use of the Spearman correlation coefficient, and categorical variables were compared by use of the Cochran-Armitage test for trend. Event rates were initially calculated with log-linear (Poisson regression) models with a generalized estimating equations approach to account for the same subjects contributing person-years off warfarin and at different levels of eGFR and/or the presence or absence of documented proteinuria over time.

To evaluate the independent association of level of eGFR and proteinuria with risk of thromboembolism, we performed multivariable Poisson regression models with generalized estimating equations that adjusted for sociodemographic characteristics and known or putative risk factors for stroke in AF (ie, previous ischemic stroke, heart failure, hypertension, diabetes mellitus, and coronary heart disease).24 We included eGFR in the model as a time-varying categorical variable (≥60 [reference], 45 to 59, and <45 mL · min−1 · 1.73 m−2) and documented proteinuria as a time-dependent dichotomous variable. We also examined for a possible interaction between
Table 1. Distribution of Baseline eGFR Among 13 535 Adults With Nonvalvular AF and No Prior Kidney Transplant

<table>
<thead>
<tr>
<th>eGFR, mL · min⁻¹ · 1.73 m⁻²</th>
<th>Overall (n=13 535), n (%)</th>
<th>Men (n=7746), n (%)</th>
<th>Women (n=5789), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>7690 (56.8)</td>
<td>4633 (59.9)</td>
<td>3051 (52.7)</td>
</tr>
<tr>
<td>45–59</td>
<td>2499 (18.5)</td>
<td>1208 (15.6)</td>
<td>1291 (22.3)</td>
</tr>
<tr>
<td>&lt;45</td>
<td>1338 (9.9)</td>
<td>693 (8.9)</td>
<td>645 (11.1)</td>
</tr>
<tr>
<td>Missing</td>
<td>2008 (14.8)</td>
<td>1206 (15.6)</td>
<td>802 (13.9)</td>
</tr>
</tbody>
</table>

Results are given for the overall cohort and stratified by gender.

*Calculated from abbreviated Modification of Diet in Renal Disease estimating equation: eGFR (mL · min⁻¹ · 1.73 m⁻²) = 186 × [serum creatinine (mg/dL)]⁻¹.154 × (age)⁻0.203 × (0.742 if female)/(1.212 if black).²⁰,²¹

eGFR and proteinuria on risk of thromboembolism in a separate multivariable model. Analyses using only baseline kidney function showed a similar trend for eGFR and proteinuria, so only results from models using time-varying kidney function status are reported.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline Kidney Function

Among 13 535 adults with nonvalvular AF and no prior kidney transplant, mean age was 71.6 years at entry, and 42.8% were women. A total of 85.2% of the cohort had available information on baseline eGFR (Table 1). At baseline, 18.5% of men and 25.9% of women of the subset with known kidney function at entry had a reduced eGFR of 45 to 59 mL · min⁻¹ · 1.73 m⁻², and 10.6% men and 12.9% women had an eGFR < 45 mL · min⁻¹ · 1.73 m⁻². Only 0.9% of men and 0.7% of women of the subset with known baseline kidney function met the criteria for ESRD at study entry, defined as an eGFR < 15 mL · min⁻¹ · 1.73 m⁻² or receiving maintenance dialysis. A total of 6444 subjects had available data on urine dipstick protein assessments on or before the index date.

Baseline Patient Characteristics by Level of Kidney Function

Patients with lower levels of eGFR at baseline were older than those with higher eGFR, and the distribution of race and gender across levels of eGFR varied significantly (Table 2). At progressively lower baseline levels of eGFR, the prevalence was higher for prior ischemic stroke, diagnosed heart failure, diagnosed hypertension, diabetes, and known coronary disease. Proteinuria was documented in a higher proportion of patients with lower eGFR levels. Of note, baseline warfarin use was slightly lower with lower levels of eGFR (Table 2).

Follow-Up

The median number of outpatient serum creatinine results per patient from baseline through the end of follow-up was 8 (interquartile range, 4 to 14), and 98.7% of the patients had at least 1 known eGFR during follow-up. Overall, 9200 members (68.0% of the cohort) had ≥1 urine dipstick protein assessments during follow-up. There were a total of 33 165 person-years of follow-up off warfarin therapy contributed by 10 908 patients (80.6% of the cohort). Among the 10 908 patients who contributed time off warfarin therapy, 10 614 (97.3%) had at least 1 eGFR result and 8746 (80.2%) had at least 1 available urine dipstick proteinuria result at baseline or during follow-up. A total of 1604 subjects were censored because of disenrollment from the health plan; 6 patients

Table 2. Characteristics by Level of Baseline eGFR in 13 35 Adults With Nonvalvular AF and No Prior Kidney Transplant

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>eGFR, mL · min⁻¹ · 1.73 m⁻²</th>
<th>≥60 (n=7690), n (%)</th>
<th>45–59 (n=2499), n (%)</th>
<th>&lt;45 (n=1338), n (%)</th>
<th>Missing (n=2008), n (%)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (interquartile range) serum creatinine, mg/dL</td>
<td>0.9 (0.8–1.1)</td>
<td>1.2 (1.1–1.4)</td>
<td>1.7 (1.5–2.1)</td>
<td>n/a</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Median (interquartile range) age, y</td>
<td>72 (64–78)</td>
<td>76 (70–82)</td>
<td>78 (73–83)</td>
<td>71 (62–78)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>3051 (39.7)</td>
<td>1291 (51.7)</td>
<td>645 (48.2)</td>
<td>802 (39.9)</td>
<td>0.0054</td>
<td></td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>White</td>
<td>6576 (85.5)</td>
<td>2211 (88.5)</td>
<td>1175 (87.8)</td>
<td>1705 (84.9)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>347 (4.5)</td>
<td>82 (3.3)</td>
<td>47 (3.5)</td>
<td>52 (2.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Asian/Pacific Islander</td>
<td>388 (5.0)</td>
<td>123 (4.9)</td>
<td>76 (5.7)</td>
<td>134 (6.7)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Native American</td>
<td>195 (2.5)</td>
<td>63 (2.5)</td>
<td>34 (2.5)</td>
<td>48 (2.4)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>184 (2.4)</td>
<td>20 (0.8)</td>
<td>6 (0.4)</td>
<td>69 (3.4)</td>
<td>0.0054</td>
</tr>
<tr>
<td></td>
<td>Hispanic ethnicity</td>
<td>253 (3.3)</td>
<td>78 (3.1)</td>
<td>62 (4.6)</td>
<td>57 (2.8)</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>Prior ischemic stroke, n (%)</td>
<td>647 (8.4)</td>
<td>282 (11.3)</td>
<td>182 (13.6)</td>
<td>137 (6.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Diagnosed heart failure, n (%)</td>
<td>2072 (26.9)</td>
<td>1023 (40.9)</td>
<td>759 (56.7)</td>
<td>290 (14.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Diagnosed hypertension, n (%)</td>
<td>3669 (47.7)</td>
<td>1493 (59.7)</td>
<td>931 (69.6)</td>
<td>798 (39.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus, n (%)</td>
<td>1301 (16.9)</td>
<td>502 (20.1)</td>
<td>361 (27.0)</td>
<td>168 (8.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Known coronary disease, n (%)</td>
<td>2064 (26.8)</td>
<td>879 (35.2)</td>
<td>587 (43.9)</td>
<td>387 (19.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Documented proteinuria, n (%)</td>
<td>697 (9.1)</td>
<td>382 (15.3)</td>
<td>333 (24.9)</td>
<td>73 (3.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Baseline warfarin use, n (%)</td>
<td>4189 (54.5)</td>
<td>1335 (53.4)</td>
<td>681 (50.9)</td>
<td>992 (49.4)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

*Probability value represents comparisons across categories of kidney function (not including missing) using the Spearman correlation coefficient for continuous variables (mean and median values) and the Cochran-Armitage test for categorical variables.
Kidney Function and Thromboembolism Off Anticoagulation

During follow-up, there were a total of 676 validated thromboembolic events (637 ischemic strokes, 39 other thromboembolism) during periods off warfarin therapy. This included 344 events among individuals with an eGFR ≥60 mL · min⁻¹ · 1.73 m⁻², 168 events among those with an eGFR of 45 to 59 mL · min⁻¹ · 1.73 m⁻², 149 events in patients with an eGFR <45 mL · min⁻¹ · 1.73 m⁻² and 15 events with unknown kidney function. The rate of thromboembolism off warfarin increased significantly with lower eGFR, ranging from a 16% increased rate for eGFR of 45 to 59 mL · min⁻¹ · 1.73 m⁻², 39% for eGFR <45 mL · min⁻¹ · 1.73 m⁻² and 54% with unknown kidney function (the Figure). Rates of thromboembolism were higher with documented proteinuria at every level of eGFR (Table 3). Of note, for the 676 observed thromboembolic events that occurred off warfarin, the median time between measurement of eGFR and event was 61 days (interquartile range, 10 to 173 days); the median time between measurement of dipstick proteinuria and the event was 298 days (interquartile range, 93 to 646 days).

In multivariable analysis, compared with eGFR ≥60 mL · min⁻¹ · 1.73 m⁻², there was a higher adjusted rate of thromboembolism associated with declining kidney function ranging from a 16% increased rate for eGFR of 45 to 59 mL · min⁻¹ · 1.73 m⁻² up to 39% for eGFR <45 mL · min⁻¹ · 1.73 m⁻² (P=0.0082 for trend across eGFR categories) (Table 4). Results were not significantly different when patients with ESRD were excluded from the subgroup of patients with eGFR <45 mL · min⁻¹ · 1.73 m⁻². In addition, documented proteinuria was associated with a 54% increased adjusted rate of thromboembolism, even after controlling for level of eGFR, sociodemographic characteristics, and known risk factors for stroke in AF (Table 4). There was no significant interaction between level of eGFR and proteinuria (P=0.082).

Discussion

Within a large, ambulatory cohort of adults with AF, we found that a lower level of eGFR was associated with a graded, increased risk of ischemic stroke and other systemic embolism independently of known risk factors in AF. Documented proteinuria also significantly increased the risk of thromboembolism even after accounting for level of eGFR and other confounders. The magnitude of association for having dipstick proteinuria and for levels of eGFR <45 mL · min⁻¹ · 1.73 m⁻² was in the range seen for other known thromboembolic risk factors in AF such as older age (per decade), heart failure, hypertension, diabetes, and female gender.²⁵

Previous studies involving CKD and AF have focused primarily on the epidemiology and impact of AF on outcomes in patients with ESRD treated with chronic dialysis rather than the role of kidney dysfunction on thromboembolism in the setting of AF. In patients with ESRD, the rate of ischemic stroke is high overall,⁹ and risk factors for stroke such as hypertension, diabetes mellitus, coronary disease, and heart failure are common.²⁶ Furthermore, a study of 215 ESRD patients on chronic dialysis with no history of AF or cardiovascular disease observed that 33% of subjects had left atrial appendage thrombi identified by transesophageal echocardiography.²⁷ In patients receiving chronic dialysis, AF appears to be a common acute and chronic complication,¹¹,²⁸ and some but not all studies suggest that AF further increases the risk of ischemic stroke significantly after accounting for other known risk factors.¹⁰,²⁹ Even less is known about the epidemiology and outcomes of AF in patients with CKD not yet requiring renal replacement therapy. Thus, our study provides novel insights in demonstrating that the presence and severity of CKD (as reflected by reduced eGFR and proteinuria) are associated with a higher risk of ischemic stroke and other
thromboembolism in patients with AF independently of known risk factors for stroke in AF.

Why would kidney dysfunction increase the risk of stroke in AF? AF itself leads to disorganized contraction of the atria, with a decrease in atrial blood flow and a resultant increase in blood pooling and stasis, especially in the left atrial appendage. AF also may lead to a hypercoagulable state through various metabolic pathways, although delineation of these specific factors and their contributions to thromboembolism are less clear. Collectively, these effects predispose to thrombus formation and subsequent systemic emboli. ESRD treated with chronic dialysis is associated with a prothrombotic state, including increased levels of various endothelium-related factors such as plasminogen activator inhibitor-1 and von Willebrand factor, as well as abnormalities in various coagulation factor levels and activity (eg, fibrinogen, fibrinopeptide A, thromboplastin, and factors VII, VIII, and IX through XII) and inflammation (eg, C-reactive protein and interleukin-6). ESRD is further associated with greater arterial media calcification and arterial stiffness, which are associated with higher cardiovascular event rates. Procoagulant and inflammatory pathways also are abnormally affected in mild to moderate CKD independently of other coexisting illnesses and vascular risk factors along with alterations in arterial compliance. Of interest, AF-associated thrombus is composed predominantly of fibrin rather than platelets and therefore tends to resemble that found in venous thromboembolic disease rather than typical arterial thromboses. Among 19,073 middle-aged and elderly subjects followed up for a mean of 11.8 years, baseline eGFR of 15 to 59 mL · min⁻¹ · 1.73 m⁻² was associated with a significantly increased risk of venous thromboembolism (adjusted hazard ratio, 1.71; 95% CI, 1.18 to 2.49) after adjustment for age, gender, race, diabetes, hypertension, body mass index, and factor VIIIc, although there was no association with serum cystatin C. With regard to proteinuria, among 298 consecutive patients with nephrotic syndrome (proteinuria ≥3.5 g/dl), compared with proteinuria of 3.5 to 4.8 g/dl, urinary protein excretion of ≥8.2 g/dl was associated with a significantly increased risk of venous thromboembolism (hazard ratio, 5.2; 95% CI, 1.1 to 23.0), although other potential confounders were not accounted for in the analysis. Thus, CKD may contribute to an increased risk of ischemic stroke and other thromboembolic events in patients with AF by augmenting the underlying prothrombotic state through several different pathophysiologic pathways.

In addition to the large, diverse cohort of patients with AF, our study was strengthened by long-term, longitudinal information on kidney function, the ability to characterize periods off anticoagulants, and the accounting for the presence of other known risk factors for stroke during follow-up. These factors allowed a more careful evaluation of the independent contribution of eGFR and proteinuria to thromboembolic risk off anticoagulation. Furthermore, all thromboembolic events were validated by medical records review using standardized criteria by researchers blinded to kidney function status. Our study also had several limitations. A small proportion of subjects did not have known kidney function, and information on use of aspirin therapy over time was not available. We also did not characterize the subtype of ischemic stroke, although the majority of strokes in the setting of AF are cardioembolic. The use of the Modification of Diet in Renal Disease equation for estimating GFR has not been validated in nonblack ethnic minorities, so misclassification may be present in such patients in our study sample. Even though we controlled for the presence or absence of hypertension and diabetes, systematic data were unavailable on the severity of these conditions, which may be associated with level of kidney function and can increase the risk of ischemic stroke. Finally, although our study was conducted within an insured sample of patients in Northern California that is very representative of the local and statewide population, our results may not be fully generalizable to all other healthcare settings and populations in the United States.

Conclusions

We found that proteinuria and reduced eGFR were associated with a higher rate of thromboembolism in patients with nonvalvular AF independently of other stroke risk factors in this setting. Our study suggests that patients with AF should be evaluated for both level of eGFR and the presence of proteinuria because this information may help to improve risk stratification and decision making about the use of antithrombotic therapy to prevent stroke in patients with AF.

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Disclosures

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References


Go et al Kidney Disease and Stroke in Atrial Fibrillation 1367

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CLINICAL PERSPECTIVE

Atrial fibrillation is a potent risk factor for ischemic stroke, but accurately determining a patient’s individual risk is challenging because current stroke risk classification methods have only modest prognostic ability. Chronic kidney disease (reduced glomerular filtration rate and/or proteinuria) is a major cardiovascular risk factor that is especially common among older persons, but whether it independently increases the risk for ischemic stroke in atrial fibrillation is poorly understood. Among 13,535 adults with atrial fibrillation, we examined the risk of thromboembolic events (ischemic stroke and other arterial embolism) associated with the level of estimated glomerular filtration rate and the presence of proteinuria. During 33,165 person-years off warfarin, we confirmed 676 thromboembolic events. After adjustment for known stroke risk factors (prior stroke, age, hypertension, diabetes, and heart failure) and other confounders, proteinuria increased the risk of thromboembolism by 54% (adjusted relative risk, 1.54; 95% CI, 1.29 to 1.85), and there was a graded, increased risk of thromboembolism associated with lower level of estimated glomerular filtration rate. Compared with glomerular filtration rate ≥60 mL·min⁻¹·1.73 m⁻², the adjusted relative risk for thromboembolism was 1.16 (95% CI, 0.95 to 1.40) for 45 to 59 mL·min⁻¹·1.73 m⁻² and 1.39 (95% CI, 1.13 to 1.71) for <45 mL·min⁻¹·1.73 m⁻² (P=0.0082 for trend). Chronic kidney disease increases the risk of thromboembolism in atrial fibrillation independently of other known risk factors. Clinicians should consider ascertaining information about the level of estimated glomerular filtration rate and the presence of proteinuria in patients with atrial fibrillation, which may improve risk stratification for decision making about the use of antithrombotic therapy for stroke prevention.

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