Risk of Thromboembolic Events in Atrial Fibrillation With Chronic Kidney Disease

Wu-Tao Zeng, MD, PhD*; Xiu-Ting Sun, MD*; Kai Tang, MD, PhD*; Wei-Yi Mei, MD, PhD; Li-Juan Liu, MD, PhD; Qing Xu, MD; Yun-Jiu Cheng, MD

**Background and Purpose**—Chronic kidney disease may increase the risk for ischemic stroke or systemic embolism in patients with nonvalvar atrial fibrillation (AF). We conducted a meta-analysis to summarize all published studies to investigate the link between chronic kidney disease and risk of thromboembolic events in AF.

**Methods**—We performed a literature search using MEDLINE (source PubMed, 1966 to July, 2014) and EMBASE (1980 to July 2014) with no restrictions. Pooled effect estimates were obtained by using random-effects meta-analysis.

**Results**—Eighteen studies involving 538479 patients and 41 719 incident thromboembolic events were identified. From the pooled analysis, AF patients with estimated glomerular filtration rate <60 mL/min compared with those with estimated glomerular filtration rate 260 mL/min experienced a significantly increased risk for developing thromboembolic events (relative risk, 1.62 [95% confidence interval, 1.40–1.87; P<0.001]). The annual rate of thromboembolic events increased by 0.41% (95% confidence interval, 0.17%–0.65%) for a 10 mL/min decrease in renal function. Addition of renal impairment to CHADS2 slightly improved the stroke risk stratification.

**Conclusions**—Impaired renal function is an independent predictor of stroke or systemic embolism in patients with nonvalvar AF. Consideration of renal function may improve stroke risk stratification in patients with AF. (Stroke. 2015;46:157-163. DOI: 10.1161/STROKEAHA.114.006881.)

Key Words: atrial fibrillation • chronic kidney disease • ischemic stroke

Atrial fibrillation (AF) has gained much attention as an independent risk factor for ischemic stroke and its association with increased mortality and morbidity.1 Chronic kidney disease (CKD), defined as reduced glomerular filtration rate or proteinuria, markedly increases the risk of stroke by 2.1-folds,2 risk of myocardial infarction by 2.0-folds,3 and risk of combined cardiovascular events by 2.3-folds in the general population.4 AF frequently coexists with CKD: about one-third of outpatients with AF have CKD, and 15% of patients with CKD have AF. There was an almost 4-fold increase in risk of AF in patients with stage 4 CKD compared with age-matched and sex-matched patients without CKD.5–7 CKD is a well-established risk factor for atherosclerotic disease,8 but conflicting data exist about the incremental effect of CKD and its severity on the risk of ischemic stroke in the setting of AF. Although several latest studies have reported that CKD is associated with increased risk of stroke among patients with AF,5,9,10 patients with renal disease were under-represented in most trials that validated stroke risk stratification schemes, and current risk scores, such as CHADS2 and CHA2DS2-VASc, do not include CKD as a potential risk factor for thromboembolic events.11,12 Therefore, there is limited information on whether moderate–severe CKD improves the predictive value of stroke risk stratification. To help resolve this uncertainty of CKD as a prognostic tool, we conducted a meta-analysis to evaluate the effect of renal function on the risk of thromboembolic events in nonvalvar AF patients and, second, to assess the additive prognostic value of moderate–severe CKD on CHADS2 scores.

**Methods**

**Search Strategy and Selection Criteria**

We did a computerized search of English-language publications listed in the electronic databases MEDLINE (source PUBMED, 1966 to July 2014) and EMBASE (1980 to July 2014) using the following text and key words in combination both as MeSH terms and text words: renal, kidney, atrial fibrillation, ischemic stroke, thromboembolic events, randomized controlled trial, cohort studies, and prospective studies.

To minimize differences between studies, we imposed the following methodological restrictions for the inclusion criteria: (1) Studies that contained the minimum information necessary to estimate the relative risk (RR) associated with CKD, including case–control, cohort studies and randomized controlled trials published as original articles; (2) Studies in which populations were representative of patients with CKD and not those limited exclusively to patients with end-stage renal disease. In instances of multiple publications, the most up-to-date or comprehensive information was used. Citations initially selected by systematic search were first retrieved as a title
or abstract and preliminarily screened. Potentially suitable citations were then retrieved as complete manuscripts and assessed for compliance to inclusion criteria.

Data Abstraction
Articles were reviewed and cross-checked independently by 2 authors (W.T. Zeng, X.T. Sun). Data on the following characteristics were independently extracted: author identification, year of publication, type of study design, study population, study location, numbers of disease outcomes of interest; mean duration of follow-up; type of thromboembolic event; RR with 95% confidence interval (CI), and reported adjustment for potential confounders. Corresponding author was contacted to verify the extracted data and to request data where it was unavailable from the published article. Any disagreements were resolved by consensus.

Data Analysis
Summary RRs (95% CI) and area under the curve (AUC or C-statistic) were calculated by pooling the study-specific estimates using a random-effects model that included between-study heterogeneity because significant heterogeneity was anticipated among studies. Pooled RRs were expressed with 95% CIs. We calculated the I² (95% CI) statistic to assess heterogeneity across studies, applying the following interpretation for I²: <50%, low heterogeneity; 50% to 75%, moderate heterogeneity; and >75%, high heterogeneity. Sensitivity analyses were performed to evaluate whether the results could have been affected markedly by using fixed-effect model, trim and fill method, and different inclusion and exclusion criteria. Subgroup analyses and meta-regression models were performed to investigate potential sources of between-study heterogeneity. Small study bias, consistent with publication bias, was assessed with funnel plot by Begg’s adjusted rank correlation test and by Egger’s regression asymmetry test. Restricted cubic spline regression model was used to test the linearity in the relationship between renal function and the outcomes. Interactions with estimated glomerular filtration rate (eGFR) were illustrated by plotting the estimated probability of 1-year events. We used STATA, version 11.0 (Stata Corp), for all analyses. Statistical tests were 2-sided and used a significance level of P<0.05.

Results

Study Selection
With the search strategy, 1021 unique citations were initially retrieved. Of these, 261 articles were considered of interest, and full text was retrieved for detailed evaluation. Two hundred forty-three of these 261 articles were subsequently excluded because they included only patients with end-stage renal disease or did not provide enough data to estimate relative risk. Finally, 18 articles were eligible for inclusion (Figure I in the online-only Data Supplement).

Study Characteristics
Eighteen independent eligible studies reporting 538,479 patients and 41,719 incident thromboembolic events were identified. Six studies were based in Europe, 6 in Asia, 1 in North America, and 5 were multinational. Studies were published between March 2009 and April 2014. There were 10 prospective cohort studies, 2 retrospective studies, and 6 randomized controlled trials. Of the primary studies, 100% had described independent, consecutive sampling of their cohort. Average follow-up duration ranged from 11 to 144 months. Patients were followed up for an average of over 2 years in 50% of the studies. The sizes of the cohorts ranged from 387 to 283,969, with 7 largest studies recruiting over 10,000 participants.

Of all the studies, 6 included only patients off anticoagulation and 6 investigated only patients taking oral anticoagulants (OACs). Fourteen studies reported the incidence of a composite outcome (ischemic stroke or systematic embolism) as an outcome of interest and 4 studies only reported the incidence of ischemic stroke. Fourteen studies (77.8%) provided ≥1 adjusted risk estimate, and 11 (75.8%) of them reported an adjusted estimate for CHADS₂; congestive heart failure, hypertension, age, diabetes mellitus, stroke/transient ischemic attack. Detailed information on adjustments is reported in Table 1.

CKD and Risk of Thromboembolic Events in Atrial Fibrillation
Figure 1 showed the results from the random effects model combining the RRs for thromboembolic events. Overall, patients with eGFR <60 mL/min compared with those with eGFR ≥60 mL/min experienced a significantly increased risk for developing thromboembolic events (RR, 1.69 [95% CI, 1.36–2.12; P<0.001]). These measurements of heterogeneity were likely driven by the extremely large overall number of participants in our analysis (>500,000). The point estimates of the RRs were consistently >1 in all studies, and study subgroups were more homogeneous.

The findings from the sensitivity analyses based on different inclusion and exclusion criteria are presented in Table 2. Risk estimates changed little after analyses with fixed-effects models, trim and fill method, or exclusion of the 2 largest and the outlier studies. Even the analysis was confined to those studies adjusted for CHADS₂, and the overall combined RR did not materially change (RR, 1.69 [95% CI, 1.36–2.12; P<0.001]).

Visual inspection of the Begg funnel plot did not identify substantial asymmetry. The Begg rank correlation test and Egger linear regression test also indicated no evidence of publication bias (Begg, P=0.20; Egger, P=0.09; Figure II in the online-only Data Supplement).

Stratified Analyses
To explore the study heterogeneity, we performed stratified analyses across several key study characteristics and clinical factors (Figure 2). We observed no significant differences across subgroups according to study type (RR, 1.75; 1.47–2.08 for randomized controlled trials and 1.55, 1.30–1.85 for cohort studies; P=0.67), sample size (RR 1.48, 1.28–1.71 for studies with patients >10000 and 1.98, 1.40–2.79 for studies with patients <10000; P=0.21), duration of follow-up (RR 1.56, 1.25–1.94 for studies with average follow-up ≥2 years and 1.71, 1.42–2.07 for studies with average follow-up <2 years; P=0.66), level of adjustment (RR 1.69, 1.36–2.11 for studies adjusted for risk profiles and 1.56, 1.27–1.98 for studies unadjusted for risk profiles; P=0.75) or OACs treatment (RR 1.51, 1.29–1.77 for patients taking OACs and 1.54, 1.35–1.75 for patients not taking OACs; P=0.56).

Significant heterogeneity between pooled analyses were noted for studies with ≥400 thromboembolic events compared with those with <400 events (RR 1.44, 1.26–1.64 versus 2.31, 1.49–3.59; P=0.03) and stroke compared with stroke plus systemic thromboembolism (RR 1.23, 1.09–1.38 versus 1.73, 1.46–2.06; P=0.03).
### Table 1. Summary of Available Studies Included in the Present Meta-Analysis

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Country</th>
<th>Type of Study</th>
<th>Average Follow-Up (months)</th>
<th>No. of Patients, n</th>
<th>No. of Events, n</th>
<th>End Points</th>
<th>Variables Adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swedish Atrial Fibrillation Cohort, 2014⁴</td>
<td>Sweden</td>
<td>Retrospective cohort study</td>
<td>25</td>
<td>283969</td>
<td>19493</td>
<td>Ischemic stroke or systemic embolism</td>
<td>Age and sex</td>
</tr>
<tr>
<td>Nakagawa K, 2011¹¹</td>
<td>Japan</td>
<td>Prospective cohort study</td>
<td>67</td>
<td>387</td>
<td>7</td>
<td>Ischemic stroke</td>
<td>Age and sex</td>
</tr>
<tr>
<td>Roldán V, 2013³⁹</td>
<td>Spain</td>
<td>Prospective cohort study</td>
<td>29</td>
<td>978</td>
<td>39</td>
<td>Ischemic stroke or systemic embolism</td>
<td>Age, sex, hypertension, DM, CHF, CHD, stroke</td>
</tr>
<tr>
<td>RE-LY Trial, 2013²⁷</td>
<td>Multinational</td>
<td>Randomized controlled trial</td>
<td>24</td>
<td>17951</td>
<td>516</td>
<td>Ischemic stroke or systemic embolism</td>
<td>None</td>
</tr>
<tr>
<td>ARISTOTLE trial, 2012²⁸</td>
<td>Multinational</td>
<td>Randomized controlled trial</td>
<td>22</td>
<td>18122</td>
<td>475</td>
<td>Ischemic stroke or systemic embolism</td>
<td>None</td>
</tr>
<tr>
<td>ATRIA Study, 2009¹</td>
<td>USA</td>
<td>Prospective cohort study</td>
<td>29</td>
<td>13535</td>
<td>676</td>
<td>Ischemic stroke or systemic embolism</td>
<td>Age, sex, race, hypertension, DM, CHF, CHD, stroke</td>
</tr>
<tr>
<td>Lin WY, 2014²⁰</td>
<td>China</td>
<td>Prospective cohort study</td>
<td>53</td>
<td>617</td>
<td>10</td>
<td>Ischemic stroke or systemic embolism</td>
<td>Age, hypertension</td>
</tr>
<tr>
<td>J-ROCKET AF, 2013³⁹</td>
<td>Japan</td>
<td>Randomized controlled trial</td>
<td>15</td>
<td>1278</td>
<td>33</td>
<td>Ischemic stroke or systemic embolism</td>
<td>None</td>
</tr>
<tr>
<td>SWEDEHEART registry, 2014²¹</td>
<td>Sweden</td>
<td>Prospective cohort study</td>
<td>12</td>
<td>24314</td>
<td>1145</td>
<td>Ischemic stroke</td>
<td>None</td>
</tr>
<tr>
<td>Loire Valley Atrial Fibrillation Project, 2011²⁷</td>
<td>France</td>
<td>Prospective cohort study</td>
<td>12</td>
<td>8962</td>
<td>434</td>
<td>Ischemic stroke or systemic embolism</td>
<td>Age, sex, hypertension, DM, CHF, CHD, stroke</td>
</tr>
<tr>
<td>Guo Y, 2013³⁵</td>
<td>China</td>
<td>Prospective cohort study</td>
<td>23</td>
<td>1034</td>
<td>78</td>
<td>Ischemic stroke</td>
<td>Age, hypertension, DM, CHF, CHD, stroke</td>
</tr>
<tr>
<td>Chao TF, 2014³⁴</td>
<td>China</td>
<td>Prospective cohort study</td>
<td>38</td>
<td>536</td>
<td>14</td>
<td>Ischemic stroke or systemic embolism</td>
<td>Age, sex, hypertension, DM, CHF, CHD, stroke</td>
</tr>
<tr>
<td>ROCKET AF, 2013³⁰</td>
<td>Multinational</td>
<td>Randomized controlled trial</td>
<td>23</td>
<td>14264</td>
<td>575</td>
<td>Ischemic stroke or systemic embolism</td>
<td>Age, sex, hypertension, DM, CHF, CHD, stroke</td>
</tr>
<tr>
<td>Leipzig Heart Center AF Ablation Registry, 2013³⁰</td>
<td>Germany</td>
<td>Prospective cohort study</td>
<td>18</td>
<td>2069</td>
<td>31</td>
<td>Ischemic stroke</td>
<td>Age, sex, hypertension, DM, CHF, CHD, stroke</td>
</tr>
<tr>
<td>AMADEUS trial, 2013³¹</td>
<td>Multinational</td>
<td>Randomized controlled trial</td>
<td>11</td>
<td>4576</td>
<td>45</td>
<td>Ischemic stroke or systemic embolism</td>
<td>Age, sex, hypertension, DM, CHF, CHD, stroke</td>
</tr>
<tr>
<td>Taiwan NHI program, 2011²⁷</td>
<td>China</td>
<td>Retrospective cohort study</td>
<td>55</td>
<td>7920</td>
<td>472</td>
<td>Ischemic stroke</td>
<td>Age, sex, hypertension, DM, CHF, CHD, stroke</td>
</tr>
<tr>
<td>Danish national registries, 2012³⁶</td>
<td>Denmark</td>
<td>Prospective cohort study</td>
<td>144</td>
<td>132372</td>
<td>17654</td>
<td>Ischemic stroke or systemic embolism</td>
<td>Age, sex, hypertension, DM, CHF, CHD, stroke, sex, vascular disease</td>
</tr>
<tr>
<td>Eikelboom JW, 2012²²</td>
<td>Multinational</td>
<td>Randomized controlled trial</td>
<td>13</td>
<td>5595</td>
<td>222</td>
<td>Ischemic stroke or systemic embolism</td>
<td>Age, sex, hypertension, DM, CHF, CHD, stroke</td>
</tr>
</tbody>
</table>

AMADEUS indicates Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation; CHD, coronary heart disease; CHF, congestive heart failure; DM, diabetes mellitus; J-ROCKET, Japanese Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; NHI, national health insurance; ROCKET, Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; and SWEDEHEART, Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies.

#### Renal Function and Rate of Thromboembolic Events

In the cubic spline model that included 8 studies reporting information on event rates in varying levels of renal function, we did not find evidence suggesting any nonlinear relation between eGFR and thromboembolic risk (P for nonlinearity =0.31). A linear increase was observed in annual rate of thromboembolic events with decreasing renal function (Figure 3). The rate increased by 0.41% (95% CI, 0.17–0.65) for a 10 mL/min decrease in renal function. According to the Cockcroft–Gault equation, patients with eGFR ≥80 mL/min had annual stroke or systemic embolism rates of 2.11% compared with 2.94% in patients with eGFR 50 to <80 mL/min and 4.54% in patients with eGFR <50 mL/min.

#### Risk Discrimination Models

Eight studies reported on changes in measures of risk discrimination on the addition of CKD to CHADS² prediction model.⁵,⁹,¹⁹,₂²,₂₄,₂₅,₃⁸,₃¹ These studies comprised a total of...
328,889 patients and 21,307 incident outcomes recorded during a weighted mean follow-up duration of ≈2 years. Studies reported findings in relation to thromboembolic risk discrimination as AUC or C-statistic. The pooled AUCs of the CHADS2, CHA2DS2-VASc, and CHADS2-CKD scores in predicting thromboembolic events were 0.66 (95% CI, 0.62–0.70), 0.68 (95% CI, 0.64–0.71), and 0.69 (95% CI, 0.65–0.73), respectively. There was a slightly significant improvement of CHADS2 score by the addition of CKD (pooled AUC difference, 0.03 [95% CI, 0.01–0.05]), but the AUC for CHADS2-CKD and CHA2DS2-VASc scores were not statistically different (Table 3).

**Discussion**

The present meta-analysis, involving >500,000 patients and >400,000 patients with thromboembolic events from 18 studies, found a significantly increased risk of thromboembolic events associated with renal impairment in patients with AF, even after reported adjustment for CHADS2, risk factors. The association seemed to be similar in patients taking or not taking OACs. Incidence of thromboembolic events was inversely associated with renal function, and the addition of renal impairment to CHADS2 scores yielded a slight improvement in risk discrimination (0.03 point estimate).

Recent studies have suggested that nonvalvular AF patients with heart failure (RR=1.4), hypertension (RR=1.6), older age (RR=1.4), diabetes mellitus (RR=1.7), and previous ischemic stroke (RR=2.5) were at risk of developing thromboembolic events, whereas conflicting results were reported for renal impairment.35 This meta-analysis is the first to our knowledge to confirm CKD to be an independent risk factor for thromboembolism in patients with nonvalvular AF. Although the risk magnitude seems to be less robust than previous ischemic stroke, it is at least as strong as other well-established major risk factors, such as heart failure, hypertension, older age, diabetes mellitus.35 However, CKD is common in AF patients, and the combination of end-stage renal disease and AF in patients treated with chronic hemodialysis may confer significantly greater thromboembolic risk. For example, Vazquez et al demonstrated that approximately

![Figure 1. Forrest plot showing relative risk of thromboembolic events associated with renal impairment in atrial fibrillation (AF) patients. The size of each square is proportional to the study’s weight (inverse of variance), AMADEUS indicates Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation; CI, confidence interval; J-ROCKET, Japanese Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; NH1, national health insurance; ROCKOT, Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; RR, relative risk; and SWEDEHEART, Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies.](http://stroke.ahajournals.org/content/36/1/160)
one third of hemodialysis patients with AF have thromboembolic complications within 1 year of follow-up. Thus, given the multifactorial nature of thromboembolism, it is highly likely that the concomitant action of CKD may be responsible for a proportion of thromboembolic events in the AF patients.

Understanding the mechanisms that underlie the association between kidney dysfunction and the risk of stroke in AF is of particular importance to help frame appropriate therapeutic decisions. First, AF per se confers a hypercoagulable state through various pathways. Disorganized contraction of the atria with a decrease in atrial blood flow, endothelial and endocardial damage and dysfunction, and increased expression of tissue factor and von Willebrand factor, increased platelet activation and fibrinolysis may predispose to thrombus formation and subsequent systemic emboli. Second, patients with CKD without AF is associated with a prothrombotic state, including endothelial damage, alteration in protein C metabolism, defects in the expression of glycoprotein Ib, elevated levels of various plasminogen activator inhibitor-1 and von Willebrand factor, abnormalities in various coagulation factor levels and activity, as well as inflammation.

Third, CKD is further associated with abnormality of neurohormonal (eg, renin–angiotensin–aldosterone system), inflammatory, and oxidative pathways or mineral metabolism (eg, hyperparathyroidism), which may result in atherosclerosis and thus greater risk of thromboembolic events. Therefore, CKD may contribute to an increased risk of ischemic stroke and other thromboembolism in AF patients by augmenting the underlying prothrombotic state through several different pathophysiological pathways.

In spite of the clear association between kidney dysfunction and thromboembolism in AF population, CKD has not been formally included in any of the current stroke stratification schemes, although it was previously proposed that the small c in CHA2DS2-VASc score could represent informally chronic renal impairment. There is 1 factor that may confound the interpretation of renal impairment in AF patients. It has been proposed that renal impairment does not add much predictive value to current schemes, especially because the components of clinical scores are themselves related to renal dysfunction. For example, increasing age and heart failure are independently associated with low eGFR. However, our result found that

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**Table 2**. Sensitivity and Heterogeneity Analysis of Pooled Relative Risks of Thromboembolic Events in Atrial Fibrillation Patients With CKD

<table>
<thead>
<tr>
<th>Statistical model</th>
<th>n, Studies (RR (95% CI))</th>
<th>I² (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random effects</td>
<td>18 (1.62 (1.40–1.87)) 70.85 (67.19–86.37)</td>
<td></td>
</tr>
<tr>
<td>Fixed effect</td>
<td>18 (1.43 (1.35–1.51)) 70.85 (67.19–86.37)</td>
<td></td>
</tr>
<tr>
<td>Trim and fill method</td>
<td>Random effects 26 (1.35 (1.15–1.18)) 84.20 (77.91–88.70)</td>
<td></td>
</tr>
<tr>
<td>Fixed effect</td>
<td>26 (1.33 (1.26–1.40)) 84.20 (77.91–88.70)</td>
<td></td>
</tr>
</tbody>
</table>

**Analysis of all studies with**
- Adjustment for CHADS2 | 11 (1.69 (1.36–2.12)) 79.15 (63.30–88.15)
- Analysis of all studies except Two largest studies* | 16 (1.69 (1.42–2.00)) 78.13 (64.98–86.34)
- Two outlier studies† | 16 (1.49 (1.33–1.66)) 66.25 (42.85–80.06)

CI indicates confidence interval; CHADS2, congestive heart failure, hypertension, age, diabetes mellitus, stroke/transient ischemic attack; CKD, chronic kidney disease; and RR, relative risk.

*Studies with patients over 100,000: Danish national registries and Swedish Atrial Fibrillation Cohort.
†Studies with largest relative risk by Chao and Lin.

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**Figure 2**. Stratified analysis of relative risk of thromboembolic events associated with renal impairment in atrial fibrillation (AF) patients and heterogeneity analysis. CI indicates confidence interval; OAC, oral anticoagulant drug; RCT, randomized controlled trial; RR, relative risk; and TE, thromboembolic events.
renal dysfunction further increases the risk of ischemic stroke significantly after accounting for other known thromboembolic risk factors. In addition, our study demonstrated that adding renal dysfunction to the CHADS$_2$ score yields a small but statistically significant improvement in c-statistic. Given these findings, further studies are warranted to elucidate the additive predictive value of renal dysfunction to the CHA$_2$DS$_2$-VASc score.

Strengths of this meta-analysis include the strict inclusion criteria, the large number of patients analyzed, the robustness of the findings in sensitivity analyses, and the fact that all subgroup analyses were prespecified a priori. The absence of important publication bias supports the robustness of the study findings. A possible limitation of our study is the heterogeneity of the studies with regard to adjustment of the estimates for potential confounders. Although differences in number of events and the outcomes of interest, at least in part, explain this finding, the specific mechanism remains unclear. Inclusion of different types of studies into one meta-analysis may also introduce heterogeneity into the results. Despite this, the consistency of the finding of an increased thromboembolic risk among cohort studies and randomized controlled trials suggests that the association is valid. Another limitation was the lack of individual participant data, which precluded determining the independent associations of individual variables with study outcomes. Instead, we used between-study meta-regressions, when possible.

In conclusion, impaired renal function is a predictor of incident stroke and systemic embolism in patients with non-valvular AF taking and not taking OACs, independent of conventional thromboembolic risk factors. Adding CKD to the CHADS$_2$ stroke risk scores slightly improved the risk discrimination, and consideration of renal function may improve stroke risk stratification in patients with AF.

Disclosures

None.

References


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Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/04/07/STROKEAHA.114.006881.DC1
배경과 목적
만성신장질환은 비판막성 심방세동(atrial fibrillation, AF) 환자에서 혈관뇌졸중이나 전신색전증의 위험을 증가시킬 수 있다. 본 연구에서는 AF에서 만성신장질환과 혈관색전 사건 위험도 간의 관계를 알바한 연구들을 요약하기 위해 메타분석을 시행하였다.

방법

결과
538479명의 환자를 대상으로 한 18개의 연구에서 41719례의 혈전 사건이 확인되었다. 통합분석에서, 추정 시기체여과율 <60 mL/min인 AF 환자가 ≥60 mL/min인 AF 환자에 비해 혈전색전 사건이 발생할 위험이 유의하게 증가하였다(relative risk, 1.62 [95% CI, 1.40–1.87; P<0.001]). 혈관색전 사건의 연간 발생률은 신장기능이 10 mL/min 감소할 때 0.41% (95% CI, 0.17%–0.65%) 증가하였다. CHADS3에 신장 장애를 추가했을 때 뇌졸중 위험도 계층화가 약간 개선되었다.

결론
신장기능의 장애는 비판막성 AF 환자에서 뇌졸중이나 전신색전증의 독립적인 예측 인자이다. 신장기능을 고려하는 것이 AF 환자의 뇌졸중 위험도 계층화를 개선하는데 도움이 될 것이다.
Abstract 7

중상성 주요 대뇌동맥질환 환자에서의 극단적 관류 저하, 혈압 조절 및 5년 뇌졸중 위험성

Misery Perfusion, Blood Pressure Control, and 5-Year Stroke Risk in Symptomatic Major Cerebral Artery Disease

Hiroshi Yamauchi, MD, PhD; Shinya Kagawa, MS; Yoshihiko Kishibe, RT; Masaaki Takahashi, RT; Tatsuya Higashi, MD, PhD

Key Words: blood pressure ■ cerebrovascular disease ■ positron emission tomography ■ prognosis

배경과 목적
중상성대뇌동맥질환 및 극단적 관류저하(misery perfusion, MP)가 있는 고위험 환자에서, 엄격한 혈압(blood pressure, BP) 조절의 유용성은 아직 논란의 여지가 있다. 연구자들은 (1) MP가 5년 뇌졸중 위험도의 예측 인자인지, (2) 추적 관찰 기간의 BP, MP 및 뇌졸중 위험도 사이의 상호 관계를 분석하고자 하는 목적을 갖고 본 연구를 진행하였다.

방법
중상성 주요 대뇌동맥 질환을 갖고 어느 정도 일상 생활이 가능한 130명의 환자를 수집하였다. 초기 혈액학적 측정은 150g/100mL의 양적 자방산단층영상(positron emission tomography)을 이용하여 측정하였으며, 대상 환자들을 의학적 치료를 받으며 5년 간 혹은 뇌졸중 재발 또는 사망이 발생할 시점까지 추적 관찰하였다.

결과
5년의 추적 관찰 기간 동안, 뇌졸중은 MP가 있는 환자 16명 중 6명 그리고 MP가 없는 환자 114명 중 15명에서 발생하였다(로그-순위 검정: P<0.01). MP가 있는 환자에서 4건(25%)의 동측 허혈 뇌졸중이 발생하였고, MP가 없는 환자에서는 4건이 발생하였다 (P<0.001). 동측의 허혈뇌졸중 발생 위험은 2년이 지나면서 급격히 감소하였고, MP가 없는 환자에서는 단 한 건의 동측 허혈뇌졸중만 발생하였다. 관류가 저하된 환자(MP 포함)에서 정상적인 수축기 BP(130 mmHg)을 유지할 때 동측 허혈뇌졸중의 위험이 증가하였으나, MP가 없는 환자에서 수축기 BP가 130~149 mmHg 범위 밖으로 유지되면 모든 종류의 뇌졸중 위험도가 증가하였다.

결론
MP가 있는 환자는 5년 뇌졸중 재발 위험도가 증가하는데, 그러한 추가 위험의 상당수는 2년이 지나면서 감소한다. MP를 바탕하여 관류가 저하된 환자에서 적극적인 BP 조절은 위험을 임원 가능성이 있다.