Meta-Analysis of the Influence of Chronic Kidney Disease on the Risk of Thromboembolism Among Patients With Nonvalvular Atrial Fibrillation

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Chronic kidney disease (CKD) and atrial fibrillation (AF) frequently coexist. However, the extent to which CKD increases the risk of thromboembolism in patients with nonvalvular AF and the benefits of anticoagulation in this group remain unclear. We addressed the role of CKD in the prediction of thromboembolic events and the impact of anticoagulation using a meta-analysis method. Data sources included MEDLINE, EMBASE, and Cochrane (from inception to January 2014). Three independent reviewers selected studies. Descriptive and quantitative information was extracted from each selected study and a random-effects meta-analysis was performed. After screening 962 search results, 19 studies were considered eligible. Among patients with AF, the presence of CKD resulted in an increased risk of thromboembolism (hazard ratio [HR] 1.46, 95% confidence interval [CI] 1.20 to 1.76, p = 0.0001), particularly in case of end-stage CKD (HR 1.83, 95% CI 1.56 to 2.14, p <0.00001). Warfarin decreased the incidence of thromboembolic events in patients with non—end-stage CKD (HR 0.39, 95% CI 0.18 to 0.86, p <0.00001). Recent data on novel oral anticoagulants suggested a higher efficacy of these agents compared with warfarin (HR 0.80, 95% CI 0.66 to 0.96, p = 0.02) and aspirin (HR 0.32, 95% CI 0.19 to 0.55, p <0.0001) in treating non—end-stage CKD. In conclusion, the presence of CKD in patients with AF is associated with an almost 50% increased thromboembolic risk, which can be effectively decreased with appropriate antithrombotic therapy. Further prospective studies are needed to better evaluate the interest of anticoagulation in patients with severe CKD. © 2014 Elsevier Inc. All rights reserved. (Am J Cardiol 2014;114:646–653)

Thromboembolic events are one of the most feared complications of atrial fibrillation (AF).1 Chronic kidney disease (CKD) is relatively prevalent in patients with AF.2 The extent to which the presence of CKD may increase the risk of thromboembolism in patients with AF has not yet been fully elucidated. Oral anticoagulation is the mainstay of thromboembolic prevention in patients with AF,3 but data on efficacy and safety in the CKD and dialysis population have been scarce and contradictory.4,5 Our aim was to systematically evaluate, through a meta-analysis method, the impact of the presence of CKD in patients with AF as regards risk of thromboembolism and the potential benefit of anticoagulation in that setting.

Methods

We performed a search in MEDLINE (by way of Ovid and PubMed), EMBASE, and Cochrane (from inception to January 3, 2014) databases using the following search string: “atrial fibrillation” AND (“renal failure” OR “chronic renal disease” OR “dialysis”) AND (“stroke” OR “thromboembolism”). The reference lists of the accessed full-text reports were further researched for sources of potential information relevant to this analysis. The authors of full-text reports and abstracts were contacted by e-mail to retrieve additional information.

Only longitudinal studies assessing the occurrence of a composite end point of stroke or systemic embolism (and including transient ischemic attack) during follow-up in patients with AF were considered for inclusion. Both registries and randomized trials were considered eligible for analysis. The methods sections of evaluated studies were reviewed to confirm the suitability and composition of the reported end point. Studies assessing only stroke (either ischemic, hemorrhagic, or a composite of both) and providing no data on systemic embolism were not considered representative of the full spectrum of thromboembolism in AF and were excluded from analysis. Similarly, studies only reporting stroke or systemic embolism in association with myocardial infarction, hospitalization, or death not due to stroke or systemic embolism were not included.
To be included in the systematic review, the studies needed to have a design allowing extraction of information concerning at least 1 of the 2 main aims of this study: (1) assessment of the incidence of stroke and systemic embolism in patients with AF according to the presence of CKD (including dialysis treatment) and (2) estimating the impact of anticoagulation in patients with CKD and AF. The population, intervention, comparison, and outcome approach was used for this aim. The population of interest included patients with nonvalvular AF with CKD or treated with dialysis. The term end-stage CKD was used for patients with disease requiring renal replacement therapy, either dialysis or transplantation. Non—end-stage CKD was used for the remaining patients with renal disease. The intervention was anticoagulation. Comparisons were performed among the following groups: adjusted-dose warfarin (target international normalized ratio of 2 to 3) versus no treatment, aspirin or low dosage non—adjusted-dose warfarin (target international normalized ratio <1.5); warfarin versus novel oral anticoagulants; and novel oral anticoagulants versus aspirin. The outcome has been defined previously.

Two independent reviewers (RP and SCB) screened all abstracts and titles to identify potentially eligible studies. The full text of these potentially eligible studies was then evaluated to determine the eligibility of the study for the review and meta-analysis. Disagreements regarding eligibility were resolved by consensus with the help of a third reviewer (SB).

Data extraction and presentation for the preparation of this report followed the recommendations of the Preferred
Table 1
Selected studies for the systematic review: baseline information and main findings

<table>
<thead>
<tr>
<th>Author, Ref</th>
<th>Study Design, Acronym</th>
<th>Sample Size (pts)</th>
<th>Intervention or Baseline Anti-thrombotics</th>
<th>Dialysis pts (%) HD/PD</th>
<th>CKD pts (%) eGFR Cutoff (ml/min)</th>
<th>Length of FUP (yrs)</th>
<th>Association of CKD With Stroke and/or SE</th>
<th>Anticoagulation in pts With CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roldan10,11</td>
<td>Prospective Single-center Observational</td>
<td>978</td>
<td>Acenocoumarol 100%</td>
<td>NA</td>
<td>eGFR 30–59, 28%</td>
<td>Median 2.4</td>
<td>eGFR 1.06</td>
<td>Stroke or SE</td>
</tr>
<tr>
<td>Banerjee12</td>
<td>Retrospective Regional Observational (4 hospitals)</td>
<td>5,912</td>
<td>VKA 52.5% Antiplatelet 30.8%</td>
<td>Baseline or FUP 2.2%</td>
<td>eGFR &lt;30, 3%</td>
<td>Mean 2.5</td>
<td>Renal impairment 1.06</td>
<td>Stroke or SE</td>
</tr>
<tr>
<td>Olesen6</td>
<td>Retrospective Nationwide Observational</td>
<td>132,372</td>
<td>W 28.3% A 18.9% Baseline RRT 0.7%</td>
<td>NA</td>
<td>Maximum 12</td>
<td></td>
<td>Stroke or SE</td>
<td></td>
</tr>
<tr>
<td>Friberg13,14</td>
<td>Retrospective Nationwide Observational</td>
<td>170,291</td>
<td>W baseline 40% W baseline/FUP 47%</td>
<td>NA</td>
<td>Renal disease &lt;6.0%</td>
<td>Mean 1.5</td>
<td>Renal failure 1.16</td>
<td>Ischemic stroke/ US/TIA/SE</td>
</tr>
<tr>
<td>Eikelboom15</td>
<td>RCT AVERROES</td>
<td>5,599</td>
<td>Apixra vs A (1:1) 5mg bid vs 81–324 mg od</td>
<td>Exclusion criteria eGFR 30–60, 30.3%</td>
<td>eGFR &lt;30, 0.4%</td>
<td>1.1</td>
<td>Stage III CKD 1.6</td>
<td>Stroke or SE</td>
</tr>
<tr>
<td>Connolly16</td>
<td>RCT</td>
<td>695</td>
<td>W 26.0% A 61.4%</td>
<td>NA</td>
<td>eGFR &lt;60, 20.8%</td>
<td>Median 5.5</td>
<td>eGFR &lt;60 3.63</td>
<td>Ischemic stroke/ TIA/SE</td>
</tr>
<tr>
<td>Cha17</td>
<td>Retrospective Single-center Observational</td>
<td>14,264</td>
<td>Riva vs W (1:1) 20 mg od</td>
<td>Exclusion criteria eGFR &lt;50, 20.7%</td>
<td>eGFR &lt;30, 41.6%</td>
<td>Median 1.9</td>
<td>eGFR 1.12</td>
<td>Stroke or SE</td>
</tr>
<tr>
<td>Patel18</td>
<td>RCT</td>
<td>1,936</td>
<td>Low risk A 46.1% High risk 1:1 W vs low W +A 53.9%</td>
<td>NA</td>
<td>eGFR 30–59, 41.6%</td>
<td></td>
<td>Stage III CKD (pts treated with A) 2.0</td>
<td></td>
</tr>
<tr>
<td>Piccini19</td>
<td>RCT ROCKET-AF</td>
<td>1,201</td>
<td>Apixra vs W (1:1) 20 mg od</td>
<td>Exclusion criteria eGFR &lt;50, 16.6%</td>
<td>eGFR &lt;30, 1.5%</td>
<td>Median 1.8</td>
<td></td>
<td>Stroke or SE</td>
</tr>
<tr>
<td>Hart20</td>
<td>RCT SPAF-III</td>
<td>18,201</td>
<td>Apixra vs W (1:1) 20 mg od</td>
<td>Exclusion criteria eGFR &lt;50, 16.6%</td>
<td>eGFR &lt;30, 1.5%</td>
<td>Median 1.8</td>
<td></td>
<td>Ischemic stroke or SE</td>
</tr>
<tr>
<td>Granger21</td>
<td>RCT ARISTOTLE</td>
<td>399</td>
<td>W 58.1% A 41.4% 23% HD</td>
<td>NA</td>
<td>eGFR &lt;60, 100% eGFR &lt;15, 33.1%</td>
<td>Mean W 2.6</td>
<td></td>
<td>W 0.28</td>
</tr>
<tr>
<td>Hohnloser22</td>
<td>RCT</td>
<td></td>
<td></td>
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The American Journal of Cardiology (www.ajconline.org)
Reporting Items for Systematic Reviews and Meta-Analyses group. The following data were extracted for characterizing each patient sample in the selected studies, whenever available: criteria for defining CKD, number of patients with CKD (and when available, number in each estimated glomerular filtration rate [eGFR] category of the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative classification) or on dialysis in each study, and type and frequency of antithrombotic treatment (warfarin or other vitamin K antagonists, novel oral anticoagulants, aspirin, or other antiplatelet agents).

Data were pooled using random effects, according to the Mantel-Haenszel model, through Review Manager (RevMan), version 5.1 (The Nordic Cochrane Center, The Cochrane Collaboration, 2011, Copenhagen, Denmark). The measurement of treatment effect and AF, CKD, or dialysis exposure was performed using dichotomous adjusted hazard ratios (HR) and 95% confidence intervals (CI). Pairwise comparisons were performed for the primary end point in the settings defined in the third paragraph of the Methods section. Comparison of the treatment effect of adjusted-dose warfarin versus the novel oral anticoagulants was performed through the use of risk ratios (number of events or the incidence in each treatment group) from randomized controlled trials. Additional sensitivity analyses were performed, whenever data were available, regarding end-stage CKD on dialysis treatment. Statistical heterogeneity on each outcome of interest was assessed and quantified using the Cochran Q test and the I² statistic, respectively. The I² statistic describes the percentage of total variation across studies due to heterogeneity rather than chance. Values of <25%, 25% to 50%, and >50% are by convention classified low, moderate, and high degrees of heterogeneity, respectively. The presence of publication bias was evaluated through the use of funnel plots if the appropriate requisites concerning the minimum number of included studies in a forest plot were met (at least 10 studies).

**Results**

Overall, 962 entries were retrieved for title and abstract analysis. Of these, 783 were excluded as they did not meet inclusion criteria for the meta-analysis and 106 were duplicate entries. The remaining 73 studies were carefully evaluated, and after full-text review, only 19 studies (all full-text reports) were finally considered eligible. The stepwise selection process is illustrated in Figure 1. There was complete agreement between investigators on the inclusion of all the selected trials. Information on risk stratification, study design, number of participants, and the main findings in each study are provided in Table 1. Following the predefined inclusion and exclusion criteria, ≤5 studies were included in each of the traced forest plots. Accordingly, no funnel plots were drawn.

Of the selected studies, 10 provided information concerning the impact of CKD on the incidence of stroke or systemic embolism in patients with AF, different equations were used for estimating the eGFR and classifying patients as having CKD: Cockcroft-Gault formula was used in 5 studies and the Modification of Diet in Renal Disease was used in 5. Also, in 2 investigations, the chronic kidney disease epidemiology

**Table 1**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>RCT</th>
<th>RE-LY</th>
<th>Multicentric Observational Study</th>
<th>Prospective Multicentric Observational Study</th>
<th>Go²</th>
<th>Singer²⁴</th>
<th>Connolly²⁵</th>
<th>Hijazi²⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ischemic stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.34</td>
<td>1.29–1.65</td>
<td>1.23–1.71</td>
<td>eGFR &lt; 45</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.16</td>
<td>0.85–1.24</td>
<td>1.06–1.24</td>
<td>eGFR &lt; 45</td>
</tr>
<tr>
<td><strong>eGFR 45, 10,908 W None NA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
collaboration and cystatin C clearance were also used for assessing the safety and efficacy of apixaban and dabigatran at different levels of eGFR. The remaining selected studies for the systematic review did not use any of these, because the diagnosis of CKD was retrieved from codification. A cutoff of 50 to 60 ml/min was used in most studies for defining the presence of CKD.

According to data on Figure 2, in patients with AF the presence of CKD was associated with a higher rate of thromboembolic events (HR 1.46, 95% CI 1.20 to 1.76, p = 0.0001). All included studies were in favor of the association of CKD with an increase in thromboembolism in patients with AF. However, their high heterogeneity is shown by the I² statistic of ≥80%. Information concerning the risk of stroke or systemic embolism in patients with AF who were also on dialysis was provided by only 1 study: in the national Danish registry thromboembolism was found to be increased in this specific population (HR 1.83, 95% CI 1.56 to 2.14, p <0.00001).5

Baseline data, design, and the main findings of trials providing information regarding warfarin in this setting5,15,17,18,20,21,23,25 are listed in Table 1. Information concerning time in therapeutic range is only known for the 3 included randomized controlled trials of the novel oral
anticoagulants controlled with warfarin (64% in Randomized Evaluation of Long-Term Anticoagulation Therapy [RE-LY], 55% in Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation [ROCKET-AF], and 62% in Apixaban for Reduction In Stroke and Other Thromboembolic Events in atrial fibrillation [ARISTOTLE] trials). As regards the presence of heparin treatment in patients on dialysis, this information was absent or lacked details concerning the protocol used in the included studies.

The use of warfarin was associated with a major decrease in thromboembolic events (HR 0.39, 95% CI 0.18 to 0.86, p <0.0001) in patients with CKD. The effect was present in all studies but one (which revealed a strong trend for benefit of warfarin; Figure 3). Despite the overall favorable trend, a high heterogeneity, I² statistic of 91%, was observed driven by the differences in treatment effect. Only 1 study assessing the role of warfarin in the prevention of thromboembolism in patients on dialysis mis the inclusion criteria for this meta-analysis. There, warfarin displayed a protective effect (HR 0.44, 95% CI 0.26 to 0.74, p = 0.002). Also, the use of warfarin did not lead to an increased risk of bleeding (HR 1.27, 95% CI 0.91 to 1.77, p = 0.15).

In Table 1, data concerning renal function subanalysis of 4 randomized controlled trials involving the use of the novel oral anticoagulants in patients with AF are listed. In the Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial, aspirin was the treatment of the control arm, and in the others, the RE-LY, ROCKET-AF, and ARISTOTLE trials, warfarin was used. Data concerning the effectiveness of the novel oral anticoagulants versus warfarin and also versus aspirin in patients with CKD (moderate or preterminal CKD) and AF are shown in Figure 4. A very low level of heterogeneity was found among the 3 selected trials (I² = 0%) showing an overall benefit of the novel oral anticoagulants compared with warfarin (HR 0.80, 95% CI 0.66 to 0.96, p = 0.02). Apixaban was more effective than aspirin in preventing stroke or systemic embolism in the non–end-stage CKD population (HR 0.32, 95% CI 0.19 to 0.55, p <0.0001). In these novel oral anticoagulants trials, only a small minority of patients had eGFR <30 ml/min and no patients on dialysis were included.

Discussion
The observed findings in this meta-analysis suggest an increased risk of thromboembolism when CKD is present in patients with AF, with an incremental relation between the severity of renal dysfunction and the risk of thromboembolism. Anticoagulation seems to be effective in decreasing thromboembolic events in non–end-stage CKD, with a particular benefit of novel oral anticoagulants in the moderate CKD population (eGFR 30 to 60 ml/min) with AF. Regarding end-stage CKD, data result from a single large national registry and seem in favor of benefit from warfarin. However, data on the novel oral anticoagulants in patients with end-stage or severe CKD with eGFR <25 to 30 ml/min are currently lacking.

Preliminary evidence has suggested that adding CKD to the currently available risk stratification schemes for thromboembolism in patients with AF may be worth further evaluation. In a subanalysis of the AVERROES trial, when adjusting for the CHADS2 score in multivariate analysis, stage III CKD remained an independent predictor of stroke or systemic embolism (HR 1.6, p <0.01). Piccini et al have tested the impact of adding CKD to the CHADS2 score and developed the R2CHADS2 score (CHADS2 plus 2 points if creatinine clearance <60 ml/min). This was derived from the ROCKET-AF cohort and validated in the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study population. They found that, when using the R2CHADS2 score, almost 20% of patients were successfully reclassified into a more appropriate risk category (i.e., it improved the net reclassification index by 17.4% relative to CHADS2; 95% CI 12.1% to 22.5%), even if C statistics displayed similar values (CHADS2 = 0.673 vs R2CHADS2 = 0.672).

A score comprising 8 variables (age, previous stroke, female gender, diabetes mellitus, heart failure, hypertension, proteinuria, and eGFR <45 ml/min or end-stage renal disease) has been recently derived using data from the ATRIA cohort. Its external validation has shown promising results with higher C statistics (0.70; 95% CI 0.67 to 0.72) than the CHADS2 (0.66; 95% CI 0.64 to 0.69) or CHA2DS2-VASc (0.68; 95% CI 0.66 to 0.70) score for the discrimination of all thromboembolic events. The discriminative performance of this score was even better if only severe thromboembolic events were considered (C statistic = 0.75; 95% CI 0.73 to 0.78), remaining better than CHADS2 (C statistic = 0.71; 95% CI 0.68 to 0.73) and CHA2DS2-VASc (C statistic = 0.72; 95% CI 0.69 to 0.74) scores. When assessing the net reclassification improvement obtained by the use of the new score, it was verified that 24% to 25% of patients were correctly reclassified into an adequate risk category, compared with CHADS2 and CHA2DS2-VASc scores, respectively (the percentage increased to 33% if only severe events were measured).

In contrast, different findings were observed by Roldan et al in a smaller population of patients with nonvalvular AF stable on oral anticoagulation for >6 months, where adding eGFR (1 point to eGFR 30 to 59 ml/min and 2 points to <30 ml/min) to the CHADS2 and CHA2DS2-VASc scores resulted in no significant improvement in C statistics or integrated discrimination improvement. In addition, Banerjee et al found that renal impairment and/or eGFR (categorized as 3 different categories: <30, 30 to 59, and >60 ml/min) did not increase the risk of ischemic stroke or systemic thromboembolism after adjustment for the CHADS2 risk factors. Thus, if added to CHADS2 or CHA2DS2-VASc scores, eGFR did not independently add to the predictive value of any of these.

The increased risk of thromboembolism when CKD is present may be explained by the coexistent platelet dysfunction, a prothrombotic and inflammatory state, and more severe vascular disease, frequently found in these patients. It has also been proposed that the presence of CKD may be a marker of target organ lesion. Furthermore, an association of low eGFR with an increased prevalence of markers of left atrial stasis (dense spontaneous echocardiographic contrast and low flow velocities in the left atrial appendage) in patients with AF.
on transesophageal echocardiogram may also account for this thromboembolic trend.28
Oral anticoagulants were advantageous in the prevention of stroke or systemic embolism in patients with non—end-stage CKD. Among patients on dialysis, the only study assessing the efficacy of warfarin in the prevention of thromboembolism demonstrated a benefit of this drug.5 Besides scarcity of data, the increased risk of hemorrhagic stroke in this population when treated with warfarin26 may deter the practicing physician from starting anticoagulation.

The observed advantage of the novel oral anticoagulants in the eGFR 30 to 60 ml/min strata mimics the results observed in meta-analysis of the recent trials involving these agents,30 suggesting that their advantage concerning efficacy is maintained despite the presence of moderate CKD. Also, according to data from the subanalysis of the AVERROES trial in the stage III CKD population, apixaban displays a higher efficacy compared with aspirin, with a similar bleeding risk.31 However, only a minority of patients with eGFR 25 to 30 ml/min and none with lower eGFR values have been included in these trials, which does not allow any firm conclusions concerning the use of these agents in those specific types of patients.

There are several limitations to this investigation, which are in part inherent to the meta-analysis method: some of the selected studies were small and the majority was retrospective. Different methods for stroke definition have been used (e.g., with variable usage of imaging), and some uncertainties also remain concerning the chosen AF classification in some studies or even the reliability of its identification. Furthermore, a high heterogeneity of the assessed populations was illustrated by the relatively elevated I² score in most forest plots.

Disclosures

The authors have no conflicts of interest to disclose.


