Systematic review and meta-analysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis

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Abstract

Background. The reported incidence, prevalence and outcomes of atrial fibrillation (AF) in patients with end-stage renal disease (ESRD) are variable. The risks and benefits of warfarin anticoagulation need to be defined as the risk of bleeding in ESRD patients may overwhelm the benefits of embolic stroke prevention. We undertook a systematic literature review to clarify these issues.

Methods. A literature search was undertaken using Medline and EMBASE from 1990 to September 2011. Studies that reported incidence, prevalence or selected outcomes in ESRD patients with AF were included. Cross-sectional, cohort and randomized controlled trials with >25 participants were included. The lists of authors and abstracts from the search were reviewed by two investigators to determine the manuscripts for full text review. Data were abstracted to a form designed specifically for this study. The quality of the studies was assessed using the Newcastle–Ottawa scale. Event rates were calculated using a random-effects model.

Results. Twenty-five studies met our inclusion criteria. The prevalence of AF was 11.6% and the overall incidence was 2.7/100 patient-years. The risk of mortality and stroke was increased in ESRD patients with AF at 26.9 and 5.2/100 patient-years versus 13.4 and 1.9/100 patient-years compared with ESRD patients without AF. The majority of studies do not support a protective effect for warfarin in ESRD patients with AF.

Conclusions. The incidence and prevalence of AF in ESRD patients are higher than in the general population and are associated with an increased risk of stroke and mortality. An appropriately designed randomized controlled trial is required to determine whether anticoagulation is an appropriate therapeutic strategy in patients with end-stage renal disease and atrial fibrillation.

Keywords: atrial fibrillation; hemodialysis; mortality; prevalence; stroke

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the general population and is associated with an increased risk of stroke that can be estimated using the CHADS² score [1]. One point is assigned for a history of congestive heart failure, age >75 years, diabetes mellitus and two points for stroke or transient ischemic attack (TIA). Anticoagulation with warfarin is recommended for patients with a CHADS² score of ≥2. The greatest accepted risk with warfarin is bleeding, but there is also emerging evidence that warfarin may contribute to vascular calcification and precipitate calcific uremic arteriolopathy in patients with end-stage renal disease (ESRD) [2, 3].

The incidence and prevalence of AF in patients with ESRD appears to be increasing due to the effects of increasing age in the ESRD population in addition to the higher burden of comorbid illness [4]. Hypertension, diabetes mellitus and congestive heart failure are also highly prevalent in people with ESRD, so that the majority of patients would require warfarin anticoagulation for their AF based on their CHADS² score. However, we have shown previously that patients with ESRD are at an ~10-fold increased risk of bleeding compared with the general population when treated with warfarin [5]. We have also shown an increased risk of valvular calcification for patients with ESRD on a long-term warfarin therapy [3]. Thus, the risk-benefit ratio of warfarin therapy is uncertain in patients with ESRD despite the high CHADS² score in this population.

Given the potential equipoise experienced by clinicians managing patients with ESRD and AF, we performed a systematic review to summarize what is known of the incidence and prevalence of AF, and the risks of mortality and stroke, treated or untreated with warfarin or antiplatelet agents.
Materials and methods

With the assistance of a trained librarian, a literature search was undertaken using Medline and EMBASE from 1990 to September 2011. The search strategy included patients with chronic kidney disease (chronic renal, ckd or ckr), renal transplant [kidney, dialysis (end-stage renal, end-stage kidney, esrd or esrf, dialysis, hemodialysis, hemodiagnosis], AF (heart atrium fibrillation, auricular) and atrial flutter (full search details available on request).

Studies were included if they described incidence, prevalence or outcomes of AF with or without anticoagulation in patients with ESRD treated with hemodialysis or peritoneal dialysis. We included cross-sectional and cohort studies or randomized controlled trials with at least 25 participants. The lists of authors and abstracts generated from the search were reviewed by two independent investigators to determine the manuscripts that should be viewed in full text. Any disagreements were resolved by a third investigator. Data were abstracted to a form generated specifically for this purpose by two of the investigators with disagreements resolved by consensus. The study quality was judged using the Newcastle-Ottawa scale for observational studies [6]. Pooled estimates were calculated for (i) incidence and (ii) prevalence of AF in hemodialysis patients as well as for the event rates of (iii) stroke and (iv) all-cause mortality with and without AF in the hemodialysis population. A summary of pooled-effect estimates and corresponding 95% CI were derived by using the DerSimonian-Laird random-effects model, which incorporates between-study variance. To assess heterogeneity of the event rates across studies, we used the Cochrane Q-statistic test and the I² statistic [8]. A funnel plot was used to assess for the presence of publication bias [9]. All analysis was conducted using Comprehensive Metaanalysis V2 software (Version 2.2, Biostat, Englewood NJ).

Additional information was provided for the following studies by correspondence with the authors: Wizemann et al.––the numbers required to calculate crude mortality rates, Sanchez Perales et al. –– follow-up data to calculate stroke rates, Lai et al. –– follow-up for patients on hemodialysis treated with and without warfarin to facilitate calculation of thromboembolic stroke rates and Genovesi et al. –– follow-up data to calculate the incidence of AF [7–10]. However, this author was not able to provide an accurate denominator (patient-years) to allow for the calculation of CVA, which was therefore estimated from the 3-year follow-up data stated in the manuscript [10].

Prevalence data for the Winkelmayer et al. manuscript were based on the 2006 cohort but the reported 1-year mortality included data from the 1992–2005 population.

Results

The study selection process is outlined in Figure 1. A total of 25 studies met our eligibility criteria [10–34]. Baseline characteristics of the studies are presented in Table 1. All of the studies were either cross-sectional or cohort studies, with an average Ottawa–NewCastle Score of 7.3 (range 3–9). The funnel plots did not suggest a publication bias. The majority of patients were male (54%) with an average age of 62 years. The prevalence of AF was 11.6%, with a range of 4.5–27% in the studies (Figure 2) [4, 10, 11, 13, 16–27, 29, 30, 33]. The overall incidence was 2.7/100 patient-years with a reported range of 0.97–5.9 events/100 patient-years [10, 11, 13, 15, 17, 22, 28, 29] (Figure 3). Mortality was increased in patients with ESRD and AF compared with patients with ESRD without AF: 26.9/100 patient-years compared with 13.4/100 patient-years [4, 10, 13, 15, 21, 22, 27–30, 32, 33] (Figure 4). Additionally, the stroke rate was increased in patients with AF at 5.2/100 patient-years compared with 1.9/100 patient-years [10–13, 20–22, 27–30, 32, 33] (Figure 5). There was evidence of significant heterogeneity in the estimates. In the five studies in which the use versus non-use of warfarin for ESRD patients with AF was examined, warfarin was protective against ischemic stroke in one study [12], had no effect on the overall risk of stroke in one and increased the risk 2-fold in two studies [10, 20] and 3-fold [30] in one study. In the Chan et al. study, which reported an increased risk of stroke in association with warfarin use, the greatest risk of stroke was in patients without in-facility monitoring of INR [20].

Discussion

A paucity of literature exists regarding the risk of AF and the effects of warfarin anticoagulation in patients with ESRD. In this systematic review, we found highly variable incidence and prevalence of AF and stroke rates due to AF in patients with ESRD. The use of warfarin for stroke prevention is not supported by the studies with the largest patient numbers and in which both hemorrhagic and ischemic stroke are included in the analysis.

The pooled estimate of incidence of AF in patients with ESRD in these studies was 2.7/100 patient-years with a high degree of variability (range 0.97–5.9/100 patient-years) [10, 11, 13, 15, 17, 22, 28, 29]. The variability in incidence is likely a reflection of study design, patient population characteristics and type of AF that was documented. Ansari et al. reported only symptomatic arrhythmias in the hemodialysis unit over a 3-year period; 0.97/100 patient-years [17]. The study by Abbott et al. and Wizemann et al. only included hospitalized AF with an overall incidence of 1.25/100 patient-years and 1.0/100 patient-years, respectively [10, 15]. All three of these studies likely underestimate the true incidence of AF as patients may be asymptomatic. The highest reported incidence of AF is from the prospective studies at 4.1 and 5.9/100 patient-years, suggesting the possibility that episodes of AF may have been missed in the retrospective studies [11, 13]. Any episodes of AF, including self-terminating episodes occurring post hemodialysis, were included in some studies, whereas only persistent AF was documented in other studies. In the cross-sectional study by Atar et al. 67% of the documented AF
was paroxysmal [18]. The importance of paroxysmal AF should not be underestimated, as demonstrated in the study by Chou et al. in which this form of the arrhythmia was associated with the greatest risk of stroke [21]. In anticoagulation guidelines for the general population, no distinction is made between paroxysmal and persistent AF.

There is also a tremendous variability in the reported prevalence of AF (11.6%, range 5.4–27%) [4, 10, 11, 13, 16–27, 29, 30, 33]. In addition to the differences in study
table 1. Included studies with study type, basic demographic information and study quality

<table>
<thead>
<tr>
<th>First author</th>
<th>Publication year</th>
<th>Study type</th>
<th>n</th>
<th>Men (%)</th>
<th>Age</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abe</td>
<td>1996</td>
<td>Cross-sectional, prospective</td>
<td>221</td>
<td>142 (64.3)</td>
<td>55</td>
<td>N/A</td>
</tr>
<tr>
<td>Abbott</td>
<td>2003</td>
<td>R. cohort</td>
<td>3374</td>
<td>1802 (53.4)</td>
<td>58.9</td>
<td>7</td>
</tr>
<tr>
<td>Acar</td>
<td>2010</td>
<td>Cross-sectional</td>
<td>183</td>
<td>93 (50.8)</td>
<td>52</td>
<td>N/A</td>
</tr>
<tr>
<td>Ansari</td>
<td>2001</td>
<td>R. cohort</td>
<td>106</td>
<td>a</td>
<td>a</td>
<td>3</td>
</tr>
<tr>
<td>Atar</td>
<td>2006</td>
<td>Cross-sectional</td>
<td>275</td>
<td>164 (59.6)</td>
<td>49.0</td>
<td>N/A</td>
</tr>
<tr>
<td>Bozbas</td>
<td>2007</td>
<td>Cross-sectional</td>
<td>94</td>
<td>50 (53.2)</td>
<td>52.5</td>
<td>N/A</td>
</tr>
<tr>
<td>Chan</td>
<td>2009</td>
<td>R. cohort</td>
<td>1671</td>
<td>952 (60.0)</td>
<td>72.6</td>
<td>9</td>
</tr>
<tr>
<td>Chou</td>
<td>2010</td>
<td>R. cohort</td>
<td>219</td>
<td>89 (40.6)</td>
<td>69.5</td>
<td>7</td>
</tr>
<tr>
<td>To</td>
<td>2007</td>
<td>R. cohort</td>
<td>155</td>
<td>97 (62.3)</td>
<td>56.9</td>
<td>6</td>
</tr>
<tr>
<td>Fabbian</td>
<td>2000</td>
<td>Cross-sectional</td>
<td>316</td>
<td>205 (64.9)</td>
<td>63</td>
<td>N/A</td>
</tr>
<tr>
<td>Fujii</td>
<td>2011</td>
<td>P. matched cohort</td>
<td>60</td>
<td>21 (35)</td>
<td>66</td>
<td>8</td>
</tr>
<tr>
<td>Genovesi</td>
<td>2008</td>
<td>P. cohort</td>
<td>476</td>
<td>277 (58.2)</td>
<td>66.6</td>
<td>7</td>
</tr>
<tr>
<td>Jassal</td>
<td>1997</td>
<td>Cross-sectional</td>
<td>62</td>
<td>a</td>
<td>71.3</td>
<td>N/A</td>
</tr>
<tr>
<td>Krane</td>
<td>2009</td>
<td>P. cohort</td>
<td>1253</td>
<td>676 (54)</td>
<td>65.7</td>
<td>4</td>
</tr>
<tr>
<td>Lai</td>
<td>2010</td>
<td>R. cohort</td>
<td>93</td>
<td>a</td>
<td>a</td>
<td>4</td>
</tr>
<tr>
<td>Phelan</td>
<td>2011</td>
<td>R. cohort</td>
<td>845</td>
<td>523 (61.9)</td>
<td>66.7</td>
<td>5</td>
</tr>
<tr>
<td>Sanchez-Perales</td>
<td>2010</td>
<td>Uncertain</td>
<td>449</td>
<td>245 (54.6)</td>
<td>64.4</td>
<td>7</td>
</tr>
<tr>
<td>Schonburg</td>
<td>2008</td>
<td>R. cohort</td>
<td>522</td>
<td>363 (70.0)</td>
<td>61</td>
<td>6</td>
</tr>
<tr>
<td>Vazquez</td>
<td>2006</td>
<td>P. cohort</td>
<td>164</td>
<td>92 (56.1)</td>
<td>56.9</td>
<td>5</td>
</tr>
<tr>
<td>Vazquez</td>
<td>2009</td>
<td>P. cohort</td>
<td>256</td>
<td>146 (57)</td>
<td>65.0</td>
<td>7</td>
</tr>
<tr>
<td>Wizemann</td>
<td>2010</td>
<td>P. cohort</td>
<td>17,513</td>
<td>a</td>
<td>a</td>
<td>8</td>
</tr>
<tr>
<td>Wiesholzer</td>
<td>2001</td>
<td>R. cohort</td>
<td>430</td>
<td>252 (58.6)</td>
<td>a</td>
<td>5</td>
</tr>
<tr>
<td>Winkelmayer (JASN)</td>
<td>2011</td>
<td>R. cohort</td>
<td>223,477</td>
<td>121697 (54.5)</td>
<td>62.3</td>
<td>7</td>
</tr>
<tr>
<td>Winkelmayer (cJASN)</td>
<td>2011</td>
<td>P. cohort</td>
<td>1185</td>
<td>508 (42.9)</td>
<td>68.9</td>
<td>8</td>
</tr>
</tbody>
</table>

R, retrospective; P, prospective.
aNot reported.
bData extracted from the 2006 prevalent cohort.
cData extracted from the propensity-score cohorts with and without AF.

Study name | Year | Events/Total N | Rate and 95% CI
---|------|---------------|-------------------
Abe | 1996 | 12 / 221 | 11.6
Jacobs | 1997 | 6 / 62 | 11.6
Fabbian | 2000 | 74 / 316 | 11.6
Anasari | 2001 | 3 / 106 | 11.6
Wiesholzer | 2001 | 61 / 430 | 11.6
Vazquez | 2003 | 26 / 190 | 11.6
Atar | 2006 | 30 / 275 | 11.6
Bozbas | 2007 | 15 / 945 | 11.6
To | 2007 | 27 / 155 | 11.6
Genovesi | 2008 | 127 / 476 | 11.6
Schonburg | 2008 | 73 / 522 | 11.6
Chan | 2009 | 2193 / 48825 | 11.6
Krane | 2009 | 117 / 1239 | 11.6
Vazquez | 2009 | 31 / 256 | 11.6
Acar | 2010 | 24 / 183 | 11.6
Chou | 2010 | 219 / 2380 | 11.6
Sanchez-Perales | 2010 | 33 / 443 | 11.6
Wizemann | 2010 | 2188 / 17513 | 11.6
Fujii | 2011 | 30 / 328 | 11.6
Winkelmayer (JASN) | 2011 | 23893 / 223477 | 11.6

Summary %
(events per 100 patient years)

Fig. 2. Prevalence of atrial fibrillation in patients with ESRD.
design mentioned above, the technique used to diagnose the arrhythmia was different across the studies. In some cases, there is no mention of how patients were monitored, whereas in other studies monthly electrocardiograms or 24-h Holter monitoring were used which would potentially identify asymptomatic individuals [24]. Some of the prevalence studies were performed in incident dialysis patients, while others were a cross-section of patients already well established on dialysis. Given the abundance of risk factors for AF, which may develop or worsen on dialysis, such as hypertension, left ventricular hypertrophy and valvular heart disease, the prevalence of
AF may increase if competing risks do not ultimately lead to mortality for the same patients. For the same reason, cross-sectional studies reporting prevalence may have different estimates than retrospective or prospective cohort studies in which prevalence incorporates incidence.

The estimated risks and benefits of anticoagulation for patients with ESRD and AF remain unclear. Overall, patients with ESRD experience a 5–10-fold higher rate of ischemic and hemorrhagic stroke compared with the general population: the risks and benefits of intervention are likely to be very different [34]. In our review, the highest risk of thromboembolism is reported in the studies by Vazquez et al. in which they have quoted a 4.6, 5.2 and 9.8-fold increased risk associated with AF [27–29]. However, this group of investigators included systemic embolism and transient ischemic attacks, which were not included in the other studies. Furthermore, the diagnosis of TIA is often clinical and may be prone to subjective clinical interpretation. The 9.8-fold increased risk was based on a total of seven ischemic strokes over 4 years of which 2 occurred in patients who did not have AF. The small number of events affects the stability of the estimates. The use of anticoagulants and the incidence of hemorrhagic stroke were not discussed. In the study by Chan et al., in which all patients had AF, 44.7% of patients were on warfarin, 11.4% on clopidogrel and 37.3% were on aspirin [20]. The use of aspirin or clopidogrel was not associated with an increased risk of stroke. However, the use of warfarin was associated with an ~2-fold greater risk of stroke compared with warfarin nonuse (hazard ratio for ischemic stroke was 1.8 and hazard ratio for hemorrhagic stroke was 2.2). In a similar type of study, Winkelmayer et al. did not show an increased rate of overall stroke in patients treated with warfarin versus those patients not treated with warfarin. However, warfarin did not decrease the risk of ischemic stroke (7.4 versus 7.8/100 patient-years) but doubled the risk of hemorrhagic stroke (2.6 versus 1.1/100 patient-years) [32]. Wizeman et al. reported a 2-fold greater risk of stroke in patients with AF over the age of 75 treated with warfarin compared with elderly patients not treated with warfarin [10]. In the study by Wiesholzer et al. AF did not increase the risk of stroke (combined ischemia and hemorrhagic), but there was a 3-fold greater risk of stroke for patients treated with either salicylates or warfarin [30]. Contrary to these results, the use of warfarin was associated with a decreased thromboembolic stroke risk in the study by Lai et al. in patients on hemodialysis [12]. However, in that study, intracerebral bleeding was not included in the stroke outcome (14 intracerebral bleeds, entire population).

Although the investigators from each of the studies attempted to control for other variables that might also
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affect morbidity and mortality, residual confounding by indication is possible, even probable, with patients who are most likely to have strokes being preferentially treated with warfarin. As in the general population, an increase in the CHADS<sub>2</sub> score for patients on hemodialysis was associated with an increased risk of stroke [10, 20, 21]. However in the study by Chan et al., the increased risk of stroke associated with warfarin persisted even in the highest CHADS<sub>2</sub> group [20]. In the study by Winkel- mayer et al., the use of warfarin did not decrease the risk of ischemic stroke and increased the risk of hemorrhagic stroke even in the patients with a CHADS<sub>2</sub> score of >2.0. It is plausible that the pre-existing platelet dysfunction and routine use of heparin during hemodialysis reduce the risk of ischemic stroke in patients with ESRD and AF, thereby reducing the potential benefit and increasing the potential risk of warfarin anticoagulation. In the study by To et al., the risk of major hemorrhage outnumbered that of cerebrovascular events by 3.5:1 [22]. A study of patients’ preferences in the general population suggests that many patients would be prepared to endure two to three or more episodes of major hemorrhage caused by anticoagulation if a single stroke was prevented by therapy [35]. Therefore, the high frequency of hemorrhage in patients with ESRD does not necessarily preclude warfarin therapy if such therapy was actually demonstrated to reduce the risk of stroke.

In almost all studies, the risk of mortality is increased in patients with a history of AF compared with those patients who remain in sinus rhythm [10, 13, 15, 21, 22, 27–30, 32, 33]. It is unclear whether the increased risk of death is secondary to thromboembolic events related to AF or secondary to co-existent cardiovascular disease or other comorbidity. In the majority of studies, patients with AF are older and more likely to have hypertension and coronary artery disease. Left ventricular systolic dysfunction and valvular heart disease are also more common in patients with AF. In the study by Abbott et al., coexisting cardiovascular disease appeared to be the predominant cause of death but thromboembolic complications may have been undiagnosed [15].

There are a number of limitations to our study. Many of the studies involved the same investigators, and it is not possible to completely exclude some overlap in the patient populations. Definitions, methods of detection and outcomes were highly variable between investigators limiting the accuracy of our estimates. Some investigators did not differentiate hemorrhagic versus ischemic stroke and more detailed information on stroke type (large vessel, small vessels, cardio-embolism) was not available. The differences in the study design and patient populations likely contributed to the tremendous heterogeneity which affects the confidence that clinicians can apply to our point estimates. However, we believe that the presentation of the data in this way may still be helpful given the heterogeneity of the ESRD population and the large international study that would be required to definitively determine the role of anticoagulation in this vulnerable population. Lastly, the included studies depend on the date of search and new information continues to be published. For example, Wetmore et al. published a cohort study of the prevalence of AF in ESRD patients in the USA in Kidney International in 2012 [36]. The overall prevalence was similar to that reported in the Winkelmayer publication using the United States Renal Data System database. Since this study was published outside of our search strategy and is unlikely to affect our estimates, it has not been included. Strengths of this work include importance of the topic, the comprehensive search strategy, duplicate assessment of references and duplicate data abstraction.

In conclusion, the incidence and prevalence of ESRD patients with AF is higher than that found in the general population and appears to be associated with about a 2-fold increased risk of stroke and mortality. Overall, warfarin does not appear to decrease the risk of the combined outcome of hemorrhagic and ischemic stroke. However, the monitoring of INR with target values of 2 to 3 was problematic in at least two studies. It is unclear whether using a combination of the newer CHA<sub>2</sub>DS<sub>2</sub>-VASc score to predict stroke risk and the HAS-BLED or ATRIA hemorrhage risk prediction scores would be more helpful in determining which patients are most likely to benefit from anticoagulation [37–39]. Similarly, it is unclear whether any of the newer anticoagulation medications (such as betrixaban, which has minimal renal excretion) would be effective and safer than warfarin for patients with ESRD. Given the limitations of the observational study designs used to date to address these issues in the ESRD population, a randomized controlled trial is required to clarify the optimal anticoagulation strategy in this patient population.

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References


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