Severe Renal Impairment and Stroke Prevention in Atrial Fibrillation

Implications for Thromboprophylaxis and Bleeding Risk

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The prevalence of atrial fibrillation (AF) in end-stage renal failure is high, with an increased risk of stroke among these patients with AF compared with the AF population without severe renal impairment. Many trials have shown the net clinical benefit of oral anticoagulation therapy for primary and secondary prevention of stroke in patient populations with AF. However, current stroke risk stratification schemes are based on studies that have deliberately excluded patients with severe renal impairment. Indeed, there are no large randomized controlled trials that assess the real risk/benefit of full intensity anticoagulation in patients with severe renal impairment. Also, rates of major bleeding episodes in anticoagulated hemodialysis patients with AF are high. These data are influenced by the lack of appropriate monitoring, the difficulties in maintaining the international normalized ratio target (variable between the studies), and an inaccurate bleeding classification. Thus, the limited available data may be difficult to apply to such a heterogeneous patient population, characterized by both an increased risk of bleeding and a hypercoagulability state, as seen in the patient population with severe renal impairment.

The frequency of atrial fibrillation (AF) in patients with end-stage renal failure is 10- to 20-fold higher than in the general population (1–3), although significant variability in the prevalence exists between the studies, ranging from 7% to 27% (1–4), and is largely dependent on demographic characteristics, duration of renal replacement therapy, and method of AF detection. In the CRIC (Chronic Renal Insufficiency Cohort) study, for example, nearly 1 in 5 participants had evidence of AF at study entry, a prevalence similar to that reported among patients with end-stage renal failure (3). Also, the large U.S.-based Renal Data System reported an AF prevalence of 13% in patients on hemodialysis and 7% in patients undergoing peritoneal dialysis (4). Both AF and severe renal impairment are age-dependent (3–6), but studies also report an increased prevalence of AF in patients with chronic kidney disease (defined as reduced glomerular filtration rate and/or proteinuria) (7), compared to age- and sex-matched people with normal renal function (8). As the long-term dialysis patient population grows older, the prevalence of AF is also likely to increase in this population (9–12).

In the population with severe renal impairment, AF detection is related to the diagnosis of ischemic heart disease and degenerative valvular heart disease (13), as well as accelerated vascular calcification and the presence of left ventricular hypertrophy (14,15). There is also an intimate relationship to hypertension, given the strong interrelationships of the latter to AF and renal dysfunction, as reflected by the high incidence of microalbuminuria (an early indicator of renal “dysfunction”) in hypertensive patients with AF (16). Other reported risk factors for the development of AF in patients with severe renal impairment are the fluctuating electrolytes levels during hemodialysis, sympathetic nervous system activation, and modulation of the renin angiotensin system (1). In patients with severe renal impairment who are on dialysis (i.e., end-stage renal failure), cardiovascular disease annual mortality rates are 9% (17), 5 to 30 times higher than in subjects from the general population of same age, sex, and ethnicity (17,18).

Search Strategy

We performed a comprehensive literature search by using electronic bibliographic databases (i.e., MEDLINE, EMBASE, the Database of Abstracts of Reviews of Effects [DARE], and the Cochrane Database of Systematic Reviews), scanning reference lists from included articles and hand searching abstracts from national and international cardiovascular meetings. For the
search, we had used the search term atrial fibrillation plus 1 or more of the following: renal failure, renal dysfunction, end-stage renal failure, dialysis, hemodialysis, stroke, bleeding/hemorrhage, stroke prevention, and thromboprophylaxis. Where necessary, study authors were contacted to obtain further data. Only studies with clearly defined populations with “severe renal impairment” were included.

Chronic kidney disease is a broad term, and so we have tried to avoid its use as far as possible. Instead we have used the term severe renal impairment as defined in recent clinical trials as a creatinine clearance of <30 ml/min and end-stage renal failure to mean severe renal impairment with the necessity for renal dialysis. Clearly, severe renal impairment with dialysis (= end-stage renal failure) may have many differences in comorbidities, drugs, and nondrug interventions compared with patients with severe renal impairment without dialysis. Given that there is a vast amount of literature of relatively poor general quality, we have essentially done a semi-systematic review of the published reports, rather than conduct a formal Cochrane-style systematic review and critical appraisal.

Risk of Stroke in Severe Renal Impairment

The major complication of AF is ischemic stroke and thromboembolism, and some studies (11,15,19,20) have demonstrated that the presence of AF increases the risk of stroke in dialysis patients, although other studies have not reported this association (21–24) (Table 1).

In a recent large prospective cohort study of AF patients, Go et al. (25) found that a lower level of estimated glomerular filtration rate (eGFR) was associated with a graded, increased risk of ischemic stroke and other systemic embolism, independently of known risk factors in AF. The adjusted hazard ratio (HR) for thromboembolism was 1.39 (95% confidence interval [CI]: 1.13 to 1.71) and 1.16 (95% CI: 0.95 to 1.40) for an eGFR <45 ml/min and eGFR of 45 to 59 ml/min, respectively, compared with an eGFR ≥60 ml/min (25). Another study by Vazquez et al. (15) demonstrated that the risk of ischemic stroke was 4.75 per 100 patient-years among patients undergoing dialysis who had AF compared with 0.48 per 100 patient-years in those who maintained sinus rhythm during dialysis. Therefore, AF was associated with a 9.8-fold increased risk of stroke among dialysis patients (15). However, a previous study performed in the same center reported a 4.6-fold (95% CI: 2.4 to 8.6) increased relative risk of developing a thromboembolic event (19). The elevated risk of stroke in the more recent study by Vazquez et al. (15) may be explained by the inclusion of older patients (65 years vs. 57 years) with the presence of more comorbidities (elevated body mass index, hypertension, 30% with diabetes, 10% with bundle branch block, half with echocardiographic parameters of dilated left atrium and heart calcification), compared with their earlier study (19).

These variables have been shown to be closely associated with AF in the general population, and complicate the evaluation of the influence of renal insufficiency per se on stroke risk, in the presence of AF (19). In the U.S. Renal Data System study, patients with end-stage renal failure and AF had a 1.8-fold higher rate of ischemic strokes, whereas hemorrhagic stroke rates were comparable to end-stage renal failure patients in sinus rhythm (20). Conversely, in the Rotterdam study, decreased GFR did not significantly increase the risk of ischemic stroke (HR: 1.25; 95% CI: 0.97 to 1.61), but was a strong predictor of hemorrhagic stroke (HR: 3.02; 95% CI: 1.45 to 6.27) (22).

The discrepancy between studies that report an association between AF and ischemic stroke in hemodialysis patients (19) and studies that do not report such an association (21,22), may be partly explained by the follow-up period studied. For example, Genovesi et al. (21) considered presentation of a stroke within the overall 3-year follow-up period, and did not consider that the high mortality rate of patients on hemodialysis would reduce the time of exposure risk, whereas Vazquez et al. (19) considered only the period in which the patients were followed up. Furthermore, there may be underdiagnosis of (asymptomatic) AF in hemodialysis patients, perhaps due to a lack of accurate continuous rhythm monitoring.

Thromboembolism in AF and Severe Renal Impairment: Pathophysiological and Clinical Observations

The presence of AF per se confers a hypercoagulable state (26) through various pathways. Virchow’s triad of abnormalities that predispose to thrombus formation, flow abnormalities (secondary to blood stasis in the left atrium) (26), abnormalities of the vessel wall (endothelial and endocardial damage and dysfunction, and increased expression of tissue factor and von Willebrand factor) (26) and abnormal blood constituents (increased platelet activation and fibrinolysis) (26) are fulfilled in AF, resulting in this arrhythmia conferring a prothrombotic or hypercoagulable state.

Patients with end-stage renal failure treated with chronic dialysis without AF are also at increased risk of thromboembolic events due to the alteration of many physiological mechanisms that lead to substantial changes in hemostasis. These are represented by increased atherosclerosis and endothelial damage, alteration in protein C metabolism, defects in the expression of glycoprotein (GP) I, elevated plasminogen activator inhibitor-1 to tissue-type plasminogen activator ratios, and inhibition of plasmin by increased levels of lipoprotein(a) (1,27). For example, Tanaka et al.
(28) noted an inverse relationship of eGFR to thrombin-antithrombin (TAT) and fibrin D-dimer levels (both indexes of thrombogenesis). In another study, renal insufficiency was independently associated with elevations in inflammatory and procoagulant biomarkers (29). These findings lend support to the notion that enhanced coagulation activation appears to be related to a reduction in residual renal function in patients with AF (27).

Clinically, the combination of end-stage renal failure and AF in patients treated with chronic hemodialysis may confer significantly greater thromboembolic risk. For example, Vazquez et al. (12) demonstrated that approximately one-third of hemodialysis patients with AF have thromboembolic complications within 1 year of follow-up. Given the high risk for thromboembolic complications, we would perhaps assume that hemodialysis patients with AF may benefit from warfarin therapy.

A study by Chan et al. (30) investigated the association between the use of warfarin, clopidogrel or aspirin and new stroke, mortality, and hospitalization in a retrospective cohort analysis of 1,671 incident hemodialysis patients with pre-existing AF (mean follow-up of 1.6 years). Compared with non-warfarin users, warfarin use was associated with a significantly increased risk for new stroke (HR: 1.93; 95% CI: 1.29 to 2.90) without an increase in all-cause mortality or hospitalization, whereas clopidogrel or aspirin use was not associated with increased risk for new stroke. However, this study has some limitations, as follows: 1) the highest risk for stroke in warfarin users compared with nonusers was more evident in those who received no international normalized ratio (INR) monitoring in the first 90 days of dialysis (HR: 2.79; 95% CI: 1.65 to 4.70); 2) a higher percentage (29%) of patients who were on warfarin and survived their stroke stopped the drug on discharge from hospital, which suggests a reasonable number of strokes were likely to be hemorrhagic in nature, or intracranial hemorrhages; 3) the increase in strokes among warfarin users may have been due to anticoagulation, with higher INR levels that may have led to an inherently higher baseline stroke risk that was not fully adjusted for by covariates, such as the CHADS2 score; and 4) INR recordings were not accurately reported (30). Hence, these data need to be interpreted with a little caution, but would still illustrate the “fragile” nature of this high-risk patient population. Indeed, Wizemann et al. (31) also reported that warfarin use in patients with AF was associated with a significantly higher stroke risk, particularly in those over 75 years of age.

In summary, the presence of end-stage renal failure is associated with increased thromboembolism, partly in relation to greater coagulation and platelet abnormalities, but the various comorbidities associated with end-stage renal disease (e.g., hypertension, diabetes, and so on) may well be contributory.

**Bleeding Risk in Severe Renal Impairment: Pathophysiological and Clinical Observations**

Observational data has underlined the increased risk of bleeding complications (especially gastrointestinal bleeding) exacerbated further by heparin anticoagulation with each dialysis treatment (32). Gastrointestinal bleeding, with recurrent episodes and multiple bleeding sites, occurs with greater frequency and is associated with higher mortality in uremic than in nonuremic patients, with upper gastrointestinal bleeding accounting for 3% to 7% of all deaths in patients with end-stage renal failure (32,33).

Clinically and pathophysiological, patients with severe renal impairment at all stages of the disease have increased risk factors for bleeding (1). Pathophysiological reasons include platelet abnormalities, reduction in intracellular ADP and serotonin, impaired release of the platelet alpha-granule protein and beta-thromboglobulin, enhanced intracellular cAMP and abnormal mobilization of platelet Ca2+, abnormal platelet arachidonic acid metabolism, defective cyclo-oxygenase activity, abnormality of the activation-dependent binding activity of GP III/IIia, increased formation of vascular PGI2, and altered von Willebrand factor (1). An increased risk of hemorrhage in uremic patients is also related to uremic toxins, especially parathyroid hormone, altered blood rheology (anemia), erythropoietin deficiency, and the use of specific treatments (e.g., nonsteroidal anti-inflammatory drugs). Furthermore, this population frequently needs to undergo invasive procedures (i.e., biopsies) that increase the bleeding risk. In a retrospective cohort of patients discharged from hospital on warfarin therapy, for example, severe renal impairment was independently identified as a risk factor for subsequent major hemorrhage (34).

In summary, end-stage renal disease can also be related to more bleeding related to functional abnormalities within platelets and other pathways, as well as to other factors, for example, toxins, uncontrolled hypertension, repeated cannulations for dialysis, and so on.

**Oral Anticoagulants in Severe Renal Impairment**

The management of chronic dialysis patients with AF with warfarin is controversial as there is no evidence base for this therapy, given that the proposed stroke risk stratification schemes are based on studies that actively excluded end-stage renal failure patients (35–41). The majority of trials employed renal function exclusion criteria, most typically serum creatinine 3 mg/dl or a creatinine clearance of <30 ml/min (i.e., RE-LY [Randomized Evaluation of Long Term Anticoagulant Therapy] [42]). However, some novel anticoagulant trials (ROCKET-AF [Rivaroxaban with adjusted-dose Oral warfarin for the prevention of stroKE in paTients with atrial Fibrillation] [43], ARISTOTLE [Apixaban for Reduction In STroke and Other Thromboembolic Events in atrial fibrillation] [44]) have a lower dose of the study drug available to randomize patients with serum creatinine >1.5 g/l (plus either age ≥80 years or weight ≤60 kg), in the
<table>
<thead>
<tr>
<th>First Author Year (Ref. #)</th>
<th>Study</th>
<th>n</th>
<th>Population</th>
<th>Indication</th>
<th>Follow-Up, months</th>
<th>INR</th>
<th>Warfarin/Control</th>
<th>Bleeding Events/Pt-Yrs</th>
<th>Warfarin/Control</th>
<th>Thromboembolic Events</th>
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<tbody>
<tr>
<td>Mokrzycki et al. 2001 (56)</td>
<td>RCT</td>
<td>85</td>
<td>HD</td>
<td>Newly placed TCC</td>
<td>12</td>
<td>1 mg</td>
<td>41 warfarin/44 control</td>
<td>1 event/165 (0.06) 1 event 18.4 (0.05)</td>
<td>No benefit of warfarin on thrombosis-free catheter survival</td>
<td></td>
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<tr>
<td>Coli et al. 2006 (57)</td>
<td>RCT</td>
<td>144</td>
<td>HD</td>
<td>Prevention of TCC thrombosis (early vs. delayed initiation of warfarin)</td>
<td>12</td>
<td></td>
<td>63 warfarin/81 ticlopidine</td>
<td>† 10/81 (12) 33/63 (52)</td>
<td></td>
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<tr>
<td>Biggers et al. 1977 (47)</td>
<td>Retrospective cohort study</td>
<td>125</td>
<td>HD</td>
<td>Prevention recurrent Scribner external A-V shunt thrombosis</td>
<td>84</td>
<td></td>
<td>48 warfarin/77 control</td>
<td>50 major events/94 (0.5) 9 events/360 (0.025)</td>
<td>†</td>
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<tr>
<td>LeSar et al. 1999 (51)</td>
<td>Case series</td>
<td>12</td>
<td>HD</td>
<td>Prevention of recurrent PTFE graft thrombosis</td>
<td>24</td>
<td></td>
<td>10 warfarin/2 control</td>
<td>4 events/40 (0.1) †</td>
<td>Stroke 3.78 (total) 4.46 (AF – OAC) 1.0 AF (AF – OAC) 2.8 (– AF)</td>
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<tr>
<td>Vazquez et al. 2000 (12)</td>
<td>Prospective</td>
<td>190</td>
<td>HD</td>
<td>AF 13.6 pt-yrs</td>
<td>12</td>
<td></td>
<td>Warfarin in AF Not reported</td>
<td>† Stroke (pt-yrs): 3.78 (total) 4.46 (AF – OAC) 1.0 AF (AF – OAC) 2.8 (– AF)</td>
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<tr>
<td>Wiesholzer et al. 2001 (23)</td>
<td>Retrospective</td>
<td>125</td>
<td>HD</td>
<td>AF 14.2 pt-yrs</td>
<td>1.11–1.16 pt-yrs</td>
<td></td>
<td>AF 14.2 pt-yrs warfarin</td>
<td>13 major events/49 (0.26) 39 events/369 (0.11) RR: 2.36 95% CI: (1.19–4.27)</td>
<td>†</td>
<td></td>
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<tr>
<td>Vazquez et al. 2003 (50)</td>
<td>Observational cohort study</td>
<td>240</td>
<td>214 HD</td>
<td>Prevention of thrombosis or embolism in AF, valve prosthesis, or rheumatic</td>
<td>20</td>
<td></td>
<td>29 warfarin/211 control</td>
<td>5 events/9.3 (0.54) 3 events/8.6 (0.35) 2 events/7.9 (0.25)</td>
<td>2 graft failure 3 graft failure 5 graft failure</td>
<td></td>
</tr>
<tr>
<td>O'Shea et al. 2003 (52)</td>
<td>Case series</td>
<td>29</td>
<td>HD</td>
<td>Prevention of recurrent PTFE graft thrombosis</td>
<td>8.6</td>
<td></td>
<td>13 warfarin/12 UHF (6,000 twice daily) 11 LMWH (enoxaparin 30–40 mg/day)</td>
<td>2 graft failure 3 graft failure 5 graft failure</td>
<td></td>
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<tr>
<td>Obialo et al. 2003 (58)</td>
<td>Nonrandomized, nonblinded, prospective trial</td>
<td>63</td>
<td>HD</td>
<td>Prevention of TCC thrombosis</td>
<td>36</td>
<td></td>
<td>11 warfarin/21 aspirin 325 mg</td>
<td>2 graft failure 3 graft failure 5 graft failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbott et al. 2003 (14)</td>
<td>USRDS administrative database</td>
<td>3,374</td>
<td>HD</td>
<td>AF 12.5/1,000 person years* 1.25*</td>
<td>48</td>
<td></td>
<td>AF 8.1 pt-yrs warfarin</td>
<td>† Stroke 3.0 (AF)</td>
<td>continued on next page</td>
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ARISTOTLE (44) or a creatinine clearance 30 to 49 ml/min in the ROCKET-AF trial (43). Given that patients with end-stage renal disease have a much higher risk of stroke than the general population, it would be reasonable to assume that AF patients with end-stage renal disease have an even higher risk of stroke than those without end-stage renal disease.

The current consensus of opinion is that there is an elevated hemorrhagic risk with anticoagulant therapy in end-stage renal failure patients on chronic dialysis (33,45–47), with some studies considering hemodialysis as a contraindication to warfarin (23). Warfarin has a further additional adverse effect on hemodialysis patients. Acting as a vitamin K antagonist, warfarin reduces the function of endogenous vitamin K–dependent inhibitors of calcification, such as the matrix Gla protein, therefore facilitating vascular calcification, at least in experimental studies (48). Some case reports have also demonstrated an association between warfarin use and the development of calcific uremic arteriopathy (49).

The bleeding risk associated with anticoagulation use in hemodialysis patients has been demonstrated by some observational studies (14,46,50–55), but few have addressed the risk-benefit of warfarin for stroke thromboprophylaxis in the hemodialysis population with AF. Most studies (47,51–53,56–59) evaluated warfarin use to prevent access thrombosis, the most frequently identified thrombotic event in the maintenance of hemodialysis patients. Therefore, the potential benefit of warfarin for stroke prevention in the hemodialysis population with AF may be underestimated. One observational study, based on U.S.-based Renal Data Service DMMS Wave 2 (Dialysis Morbidity and Mortality Wave 2 Study) data of 123 hemodialysis patients hospitalized for AF, demonstrated that only the use of warfarin and a systolic blood pressure >130 mm Hg were associated with increased survival (14).

A recent systematic review of warfarin use in hemodialysis patients noted that major bleeding rates ranged from 0.10 to 0.54 events per patient-year of warfarin exposure, twice as high as those of hemodialysis patients receiving either no warfarin or subcutaneous heparin (55). However, the 4 studies evaluating full-intensity anticoagulation were either observational cohort studies or case series involving hypercoagulable hemodialysis patients, and these results have not been confirmed in a randomized controlled trial evaluating dose-adjusted warfarin for any indication in patients with severe renal impairment.

In the cohort studies, where the incidence of major bleeding episodes was at least double that of patients exposed to intradialysis heparin only, a lack of INR control and appropriate monitoring may have contributed to the excess bleeding risk in patients on warfarin (55). Overall, the type and severity of comorbid illnesses were the most important risk factors for anticoagulant-related bleeding. Cardiovascular disease, liver dysfunction, and severe renal impairment were associated with increased risk of bleeding (55). Concurrent intake of antiplatelet agents, especially aspirin, also increased the risk of anticoagulant-
related bleeding (55). In a small retrospective study on hemodialysis patients by Vazquez et al. (50), the risk of hemorrhage without anticoagulation was high (11 episodes/100 patient-years), but this risk of bleeding was more than doubled on warfarin therapy (26 episodes per 100 patient-years; relative risk: 2.36, 95% CI: 1.19 to 4.27). However, this risk of hemorrhage was usually confined to the digestive tract, which was nonfatal, rather than the debilitating intracranial hemorrhage, and there were no serious clinical sequelae (50). Recently, Holden et al. (54) completed a retrospective review of 255 patients who were undergoing hemodialysis and found major bleeding rates of 3.1% and 0.8% for patients receiving warfarin and those not receiving therapy, respectively.

Therefore, the true bleeding risk associated with the use of warfarin in hemodialysis patients remains unknown, given the reliance on small observational studies with potential confounding by comorbid conditions (54). Furthermore, many of the studies assessing hemorrhagic risk were performed many years ago (47), and changes in management of patients with severe renal impairment over the last 20 years may affect the interpretation of these studies.

In a recent analysis, Limdi et al. (59) studied 578 patients, evaluating the influence of kidney function on warfarin dosage, anticoagulation control, and risk of hemorrhagic complications. AF was an indication for warfarin (patients could have ≥1 indication) in 134 (40%), 99 (56.2%), and 23 (43.4%) patients with an eGFR ≥60 ml/min, 30 to 50 ml/min, and <30 ml/min, respectively. This study demonstrated that patients with severe renal impairment (eGFR <30 ml/min/1.73 kg/m²) required significantly lower warfarin doses (warfarin dosage requirements stratified by GFR were 4.8 mg/day [4.6 to 5.0 mg/day], 4.3 mg/day [4.0 to 4.6 mg/day], and 3.9 mg/day [3.5 to 4.4 mg/day] with an eGFR ≥60 ml/min, 30 to 50 ml/min, and <30 ml/min, respectively, p = 0.0002) compared with patients with no, mild, or moderate renal impairment, independent of CYP2C9 and VKORC1 genotype (59). Furthermore, this study showed that patients with severe renal impairment spent less time within the therapeutic INR target range (INR: 2.0 to 3.0) and were at a higher risk for over-anticoagulation (INR >4.0; p = 0.052) (60). Indeed, the proportion of INR in target range as stratified by eGFR ≥60, 30 to 50, and <30 ml/min, was 49.7%, 45.7%, and 45.6%, respectively (p = 0.049) (59). Further, patients with severe renal impairment had a 2.4-fold (95% CI: 1.1 to 5.3) increased risk of major hemorrhage compared with patients with lesser degrees of renal dysfunction (59). According to these results, diminished renal function may have implications for a larger proportion of warfarin users than previously estimated. Therefore, the relative contraindication for oral anticoagulation in patients on dialysis programs should be carefully assessed on an individual patient basis, in view of the potential benefits of anticoagulant therapy.

Risk Stratification Schema for Stroke and Bleeding in Patients With AF and CKD

For the majority of patients with nonvalvular AF, stroke risk stratification is commonly used, and the most popular schema is the CHADS2 score (60). The CHADS2 score, which is an amalgamation of the risk factors used in the Atrial Fibrillation Investigators and the Stroke Prevention in Atrial Fibrillation Investigators stroke risk schema, assigns 1 point for congestive heart failure, hypertension, age ≥75 years, and diabetes, and 2 points for stroke/transient ischemic attack (TIA) (60). The CHADS2 score is the basis of other contemporary stroke risk stratification schema, including those in international guidelines (61,62). However, all the published stroke schema do not incorporate severe renal impairment as 1 of the established stroke risk factors, given that such patients—although recognized as being at high stroke risk—have not been studied in clinical trials, and are also at substantial risk of bleeding, death, and cardiovascular events.

Severe renal impairment is also not included in the most recently published stroke risk schema within the new European Society of Cardiology guidelines, the CHA2DS2-VASc score (63,64). The latter is an acronym that denotes Cardiac failure or dysfunction, Hypertension, Age ≥75 years [doubled], Diabetes, Stroke [doubled]–Vascular disease, Age 65 to 74 and Sex category [female], whereby 2 points are assigned for a history of stroke or TIA or age ≥75 years, and 1 point each for age 65 to 74 years, a history of hypertension, diabetes, recent cardiac failure, and vascular disease (63). Pending validation in appropriate large prospective cohorts, the final letter c in the CHA2DS2-VASc acronym could possibly be used to informally denote “chronic severe renal impairment” in future refinements of stroke risk stratification, with the caveat that renal function may not remain static (and deteriorate over time), especially in elderly AF patients with multiple comorbidities and concomitant drug therapies.

Also, many stroke risk factors are also risk factors for bleeding, and the 3 published bleeding risk schema used in AF cohorts have included renal impairment as a risk factor (65–67). It is important to stress that these bleeding risk schema have not been formally validated in AF populations with severe renal impairment, and much caution is necessary before routine application of these bleeding risk scores—which were initially proposed for use in the majority of general AF populations seen in everyday clinical practice (64,66,67)—to patients with severe renal impairment and those with end-stage renal failure.

Recently, Reinecke et al. (1) presented an individualized risk stratification algorithm for oral anticoagulation in AF and severe renal impairment. A CHADS2 score of 6 represents an annual average stroke rate of 18.2% (60), but
it has been demonstrated that in unselected patients with end-stage renal failure and AF, the annual stroke rate ranges from 17.4% to 24% (19,22), even in the absence of all the CHADS2 risk factors. This again suggests that CHADS2 risk score may underestimate the stroke risk in renal patients (1). Therefore, the authors added prosthetic valve disease, mitral stenosis, and left ventricular impairment to the CHADS2 classification, and divided stroke risk factors into “major” (previous stroke or TIA, prosthetic heart valve, mitral stenosis >2) and “minor” (age, hypertension, diabetes, left ventricular ejection fraction <35%), to decide upon the indication for warfarin (1 major or ≥1 minor). In addition, they added bleeding risk stratification (previous hemorrhages, liver disease, active malignancies, eGFR <30 ml/min, age ≥75 years, active alcohol abuse, dementia, falls) to evaluate contraindications to anticoagulation therapy. According to this classification system, patients who have already been taking oral anticoagulation for >3 months without hemorrhage are classified as a “positive selection” group, with a lower risk of bleeding (1). However, this algorithm has limited application in aiding decision-making because the severity of the bleeding risk factors leading to the contraindication must be evaluated on an individual patient basis.

Thus, one possible management approach is shown in Figure 1, partly adapted from the algorithm proposed by Reinecke et al. (1) (and Lip [68]), and incorporating approaches to stroke and bleeding risk assessments from

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**Figure 1** Algorithm for Oral Anticoagulation in AF and Chronic Renal Disease

OAC indicates oral anticoagulation, for example, with vitamin K antagonists (VKAs) (target international normalized ratio [INR]: 2.0 to 2.5), but new drugs that may be viable alternatives to the VKAs that are suitable for use in severe renal impairment could ultimately be considered. *Risk factors for stroke and thromboembolism could be assessed using the CHA2DS2-VASc score (63,64), although the real stroke risk is likely to be higher than reported in cohorts with no renal failure. Oral anticoagulation (essentially warfarin) should be given for those at high stroke risk (e.g., a CHA2DS2-VASc score of ≥2). If patients have already been taking OAC (e.g., for >3 months) with no bleeding complications, these patients probably represent a “positive selection” group with a lower bleeding risk. +Bleeding risk could be assessed using a validated scoring system used in the atrial fibrillation (AF) population (e.g., the HAS-BLED score [67]), although the real bleeding risk in severe renal impairment is likely to be higher than that reported in cohorts with no renal failure, and all published bleeding risk scores have not been specifically validated in an AF population with severe renal impairment. A HAS-BLED score of ≥3 would indicate a high enough bleeding risk to be concerned, whereby regular review and follow-up is necessary. eGFR = estimated glomerular filtration rate. Adapted from the algorithm proposed by Reinecke et al. (1) and Lip (68), adapted with permission from the latter.
recent guidelines (64). Oral anticoagulation is far superior to antiplatelet therapy for stroke prevention, and the major bleeding rate (particularly, fatal bleeding) with aspirin may be similar to that seen with warfarin (especially in the elderly [39,64,69]), and aspirin–clopidogrel combination therapy also confers a major bleeding risk comparable to that seen with warfarin (70).

Given that AF patients with severe renal impairment are at high stroke and bleeding risk (71), well-controlled oral anticoagulation would still be the best option—in the absence of high-quality evidence and large prospective randomized clinical trials that have specifically investigated this population—but regular review and reassessment of risk profile is definitely needed. If the patient is taking warfarin, stroke and bleeding rates can be closely related to quality of anticoagulation control, so extra efforts to ensure excellent time in therapeutic range rates can be closely related to quality of anticoagulation control, so extra efforts to ensure excellent time in therapeutic range (perhaps aiming for a target INR of 2.0 to 2.5) would help offer the best balance between stroke prevention and bleeding risk (72). New oral anticoagulant drugs that can be used in severe renal impairment, such as betrixaban (73), may alter our approach to managing this complex and high-risk group of patients, but the benefit and safety of these agents would need to be confirmed in large prospective clinical trials.

Conclusions

The frequency of AF is increased in patients receiving hemodialysis, with a reported prevalence between 7% and 27%, and the presence of AF in patients with severe renal impairment is associated with a significantly increased risk of ischemic stroke (reaching a 9.8-fold increase). However, there are no large randomized trials that have assessed the real risk/benefit of full-intensity anticoagulation in such patients. Of note, rates of major bleeding episodes in anticoagulated hemodialysis patients with AF are high. Also, these data are influenced by the lack of appropriate monitoring, the difficulties in maintaining the INR target (variable between the studies), and an inaccurate bleeding classification. The limited available data may be difficult to apply to such a heterogeneous patient population characterized by both an increased risk of bleeding and thromboembolism, as seen in the population with severe renal impairment.

In the future, new oral anticoagulant agents that are not affected by renal impairment will hopefully improve the balance between stroke risk reduction and bleeding risk in patients with renal impairment, although a specific clinical trial in AF patients with impaired renal function is warranted (72). For now, oral anticoagulants should not be contraindicated in this patient population, but rather be considered on a patient-by-patient basis (67) (Fig. 1). Warfarin may need to be initiated at a lower dosage and monitored more closely in patients with severe renal impairment compared with AF patients with normal kidney function (24). The regular attendance of hemodialysis patients for each dialysis treatment session provides the opportunity for careful monitoring of prothrombin time ratios, thereby decreasing the risk of major hemorrhage.

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