

Dilemmas in the Management of Atrial Fibrillation in Chronic Kidney Disease

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ABSTRACT

Patients with chronic kidney disease (CKD) have an increased risk for cardiovascular morbidity and mortality. Little attention has been paid to the problem of atrial fibrillation, although this arrhythmia is very frequent with a prevalence of 13 to 27% in patients on long-term hemodialysis. Because of the large number of pathophysiologic mechanisms involved, these patients have a high risk for both thromboembolic events and hemorrhagic complications. Stroke is a frequent complication in CKD: The US Renal Data System reports an incidence of 15.1% in hemodialysis patients compared with 9.6% in patients with other stages of CKD and 2.6% in a control cohort without CKD. The 2-yr mortality rates after stroke in these subgroups were 74, 55, and 28%, respectively. Although oral coumadin is the treatment of choice for atrial fibrillation, its use in patients with CKD is reported only in limited studies, all in hemodialysis patients, and is associated with a markedly increased rate of bleeding compared with patients without CKD. With regard to the high risk for stroke and the conflicting data about oral anticoagulation, an individualized stratification algorithm is presented based on relevant studies.

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With the rise in obesity, diabetes, and hypertension, the prevalence of chronic kidney disease (CKD) has doubled in the past 10 yr worldwide.^{1–5} Its incidence and prevalence⁶ have become a global challenge.⁷ Because the terms for and definitions of renal failure were previously used inconsistently, the Kidney Dialysis Outcomes Quality Initiative (KDOQI) introduced in 2002 a systematic classification for different stages of CKD on the basis of estimated GFR (eGFR; Table 1) to clarify diagnosis and guide therapy.⁸ Thus, CKD is recognized as a silent epidemic affecting more than 20 million Americans⁸ and accordingly also a substantial pro-

portion of the population in other countries.^{3,9}

Apart from the direct concern of treating patients with all stages of CKD (prevention, specific drugs, and renal replacement therapy), the high risk for cardiovascular events represents the major cause for morbidity and mortality in this population.^{10–14} With regard to the large number of patients affected, one special aspect of cardiovascular disease in CKD has received surprisingly little attention. Atrial fibrillation is very frequent in patients with CKD, and although related morbidity and mortality seem to be remarkably high, information about its management are limited.

EPIDEMIOLOGY OF ATRIAL FIBRILLATION

In the general population, the prevalence of atrial fibrillation is estimated to range between 0.4 and 1.0% depending on age, with a prevalence of approximately 8% in patients ≥ 80 yr of age.¹⁵ Currently, only the prevalence of atrial fibrillation in patients who have ESRD (see Appendix) and require dialysis but not in other stages of CKD is available. On the basis of the diagnostic categories of atrial fibrillation reported in the large US Renal Data System (USRDS), a prevalence of 13% in patients on hemodialysis and 7% in patients undergoing peritoneal dialysis was observed.¹⁶ Smaller but more detailed longitudinal studies of patients on maintenance hemodialysis detected episodes of atrial fibrillation by repetitive 24-h electrocardiogram Holter monitoring in 13 to 27% of the patients.^{17–19} Thus, the prevalence of atrial fibrillation in patients with ESRD seems to be 10- to 20-fold higher, depending on age, than in the general

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Table 1. Classification of various stages of CKD^a

CKD Stage	eGFR	Prevalence (%)	Affected Patients	Definition
1	≥90 ml/min	3.3	Approximately 5,900,000	Renal injury (e.g., proteinuria) without reduced eGFR
2	89 to 60 ml/min	3.0	Approximately 5,300,000	Mildly decreased eGFR
3	59 to 30 ml/min	4.3	Approximately 7,600,000	Moderately decreased eGFR
4	29 to 15 ml/min	0.2	Approximately 400,000	Severely decreased eGFR
5 (almost identical to ESRD, see Appendix)	<15 ml/min	0.3	Approximately 500,000	Kidney failure, mostly indication for renal replacement therapy

^aThe estimation of affected patients refers to the US population. Adapted from references.^{1,8}

population (Figure 1A). Fibrillation is highly correlated with the diagnosis of structural heart disease in these patients, particularly coronary artery disease, degenerative valvular disease as a result of accelerated calcifications, and left ventricular hypertrophy.^{19–22}

Fluctuating levels of electrolytes during hemodialysis as well as sympathetic nervous system activation and modulation of the renin-angiotensin system represent additional predisposing factors for atrial fibrillation in CKD.^{18,22–24}

CKD, ATRIAL FIBRILLATION, AND RELATED MORBIDITY AND MORTALITY

Because of the strong relationship of atrial fibrillation to structural heart disease, the direct impact of atrial fibrillation on morbidity and mortality is problematic to assess. It is difficult to determine whether patients have complications related to atrial fibrillation or to advanced structural heart disease accompanied by atrial fibrillation.

Compared with patients with eGFR >59 ml/min, those with eGFR between 45 and 59 ml/min have a 1.2-fold higher adjusted hazard ratio for death that increases to a 5.9-fold increase in those with eGFR <15 ml/min. Furthermore, the hazard ratios for hospitalization are 1.1-fold higher in patients with eGFR between 45 and 59 ml/min and rise to 3.1-fold in those with ESRD.¹¹

Regarding atrial fibrillation, cross-sectional data from the USRDS showed that patients who have ESRD and have known atrial fibrillation have an annual mortality rate of 5% compared with only 2% in those without it.¹⁶ The 3-yr mortality rates for patients who had ESRD and had been hospitalized for atrial fibrillation were also significantly higher (53%; *n* = 123) than in control subjects (45%; *n* = 3245).²¹ Moreover, one longitudinal, single-center study (*n* = 190) reported 4-yr mortality rates of 81% in patients with ESRD and atrial fibrillation compared with only 29% in those without.²⁵ There are no data about the impact of atrial fibrillation on the mortality of patients in other stages of CKD besides ESRD; therefore, regardless of whether atrial fibrillation is an independent risk factor for mortality or represents only a

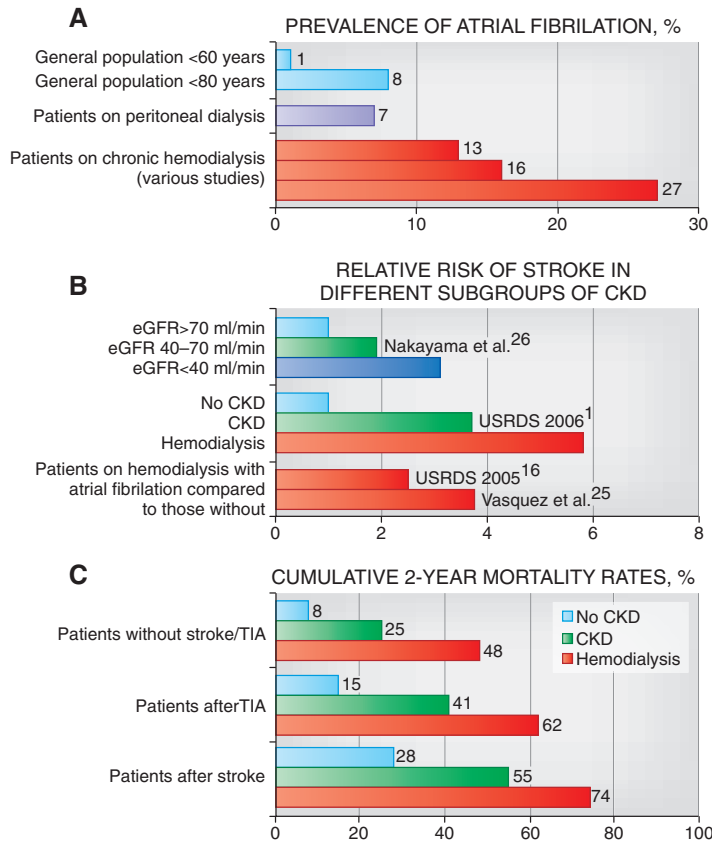


Figure 1. Synopsis of atrial fibrillation in CKD. Various stages of CKD are displayed by the same colors in all panels (blue, no CKD; green, CKD without hemodialysis; red, hemodialysis; purple, peritoneal dialysis). (A) The prevalence of atrial fibrillation in patients on hemodialysis is 10- to 20-fold higher than in the general population, whereas patients with peritoneal dialysis were less frequently affected.^{15–19} (B) Risk for stroke is increased by each stage of CKD, with the highest risk in the patients who are on hemodialysis and have atrial fibrillation.^{1,16,25,26} (C) Cumulative 2-yr mortality rates after stroke or transient ischemic attacks (TIA) demonstrate the dramatic death rates in patients who have CKD or are on hemodialysis.¹

risk predictor, physicians should carefully consider the consequences of atrial fibrillation in their patients with CKD, because it indicates a markedly increased risk for medical comorbidities and death.

STROKE IN CKD

The major complication of atrial fibrillation is ischemic stroke.¹⁵ In CKD, the rate of stroke is markedly higher in all stages. In a Japanese community-based observational study of 1977 healthy individuals without ESRD,²⁶ the hazard rate ratios for stroke in the subgroup with eGFR between 40 and 70 ml/min was 1.9, and with a GFR <40 ml/min was 3.1 compared with those with an eGFR >70 ml/min (Figure 1B). In the VALIANT trial that included patients with acute myocardial infarction and signs of heart failure but without ESRD, there was a significant stepwise increase in stroke rates from 2 to 6% after 3 yr with decreasing eGFR from ≥ 75 to <45 ml/min.¹⁴ The stroke incidence in the USRDS was 15.1% in hemodialysis patients compared with 9.6% in patients who had CKD and were not on hemodialysis and 2.6% in matched patients without CKD.¹ After occurrence of a stroke or transient ischemic attack, the 2-yr mortality rates are dramatically increased in patients with CKD compared with those without (Figure 1C).

With regard to atrial fibrillation, one single-center analysis of hemodialysis patients observed thromboembolic event rates of 24% per year in those with atrial fibrillation compared with 5% in those with sinus rhythm, a 4.6-fold increased relative risk.²⁵ In the USRDS, patients with ESRD and atrial fibrillation had a 1.6-fold higher rate of stroke than those without atrial fibrillation. This was based exclusively on a 1.8-fold higher rate of ischemic strokes, whereas hemorrhagic stroke rates were similar. There was no difference in the rates of stroke between patients on hemodialysis or peritoneal dialysis.¹

ORAL ANTICOAGULATION

Oral anticoagulation with coumadin is an effective therapy to reduce the risk for

stroke related to atrial fibrillation in a majority of patients; however, only a few studies evaluated the use of oral anticoagulation in patients with CKD. A Spanish registry observed the outcome of patients who were in various stages of CKD and took oral anticoagulation for deep vein thrombosis. Bleeding side effects were defined as major when they occurred in retroperitoneal, intraspinal, or intracranial regions or when they required transfusions or surgery. In the subgroup with an eGFR <30 ml/min ($n = 1037$), the rates of major and fatal bleeding after 3 mo were 7.3 and 2.2%, respectively, which were significantly higher than the respective 2.1 and 0.5% in the group with an eGFR >30 ml/min ($n = 17,214$); however, the rates of embolic events, especially fatal pulmonary embolism, were also markedly higher in those with an eGFR <30 ml/min (6.4 *versus* 1.3%).²⁷

With regard to atrial fibrillation, one single-center report of patients with ESRD observed an annual rate of 11% for hemorrhages in patients who were not on anticoagulation, 16% in those treated with antiplatelet therapy, and 26% in those on oral anticoagulation. Of note, in 10 of the 13 patients who were on coumadin and had bleeding, the international normalized ratio (INR) was higher than intended (no values specified in the article), but none of the bleeding complications with oral anticoagulation was fatal.²⁸ Another study of 430 hemodialysis patients found a 8.3-fold higher rate of stroke in patients on oral anticoagulation or on salicylates compared with those without regardless of whether they had atrial fibrillation.²⁹ In contrast, retrospective analyses from the USRDS of patients who started their hemodialysis in 1996 and were subsequently hospitalized for atrial fibrillation found a significantly lower cumulative 3-yr all-cause mortality of 33% in patients taking coumadin compared with 56% in those without oral anticoagulation ($n = 123$).²¹

ALTERNATIVES FOR LONG-TERM ANTICOAGULATION

Numerous alternatives to long-term anticoagulation are available; however,

low-molecular-weight heparins, such as enoxaparin, dalteparin, nadroparin, tinzaparin, heparoids (danaparoid), and other therapies (argatroban), have a strong tendency for accumulation in all but especially advanced stages of CKD.^{30–32} In nearly all safety studies and larger clinical trials evaluating these drugs, patients with CKD were excluded. Regarding the use of these drugs, only case reports or small series have been published, and they included patients who were treated for a short period. Some of these studies demonstrated no or low complication rates, whereas others reported high rates of often fatal bleeding complications.^{30–34} There is ongoing discussion about whether dalteparin may provide some advantages in CKD as a result of its pharmacokinetic profile; however, the evidence is also derived from small, short-term observations.^{35,36} In accordance with the American College of Chest Physicians conference on antithrombotic and thrombolytic therapy,³² the benefit of alternative drugs for long-term anticoagulation in CKD seems uncertain.

BALANCE BETWEEN THROMBOEMBOLISM AND HEMORRHAGE

Although the available data are limited and in part conflicting, they do suggest the situation in patients with atrial fibrillation and CKD is a special one. Many physiologic mechanisms are altered in CKD,^{37,38} which lead to substantial changes in hemostasis (Table 2) with the paradox that patients in all stages of CKD but especially with ESRD have both a prothrombotic state predisposing to high risk for thromboembolism and a coagulopathy with an increased tendency for bleeding.^{1,25,27,28,38–41} This explains the high rate of ischemic strokes and also the high rate of bleeding. It is plausible that possible benefits of oral anticoagulation for stroke prevention may be outweighed by hemorrhagic risk. Even in patients on oral anticoagulation due to atrial fibrillation in the general population, there is a small range in a

Table 2. Factors influencing hemostasis in CKD

Factors Predisposing for Bleeding	Procoagulant Factors
Platelet abnormalities including subnormal dense granule content	Atherosclerosis and diffuse endothelial damage
Reduction in intracellular ADP and serotonin	Dysfunctional activated protein C metabolism
Impaired release of the platelet α -granule protein and β -thromboglobulin	Both elevated plasminogen activator inhibitor-1 to tissue-type plasminogen activator ratios and inhibition of plasmin by increased levels of lipoprotein(a)
Enhanced intracellular cAMP and abnormal mobilization of platelet Ca^{2+}	Defects in the expression of glycoprotein GPIIb (the receptor for von Willebrand factor)
Abnormal platelet arachidonic acid metabolism	
Defective cyclo-oxygenase activity	
Abnormality of the activation-dependent binding activity of GPIIb/IIIa	
Increased formation of vascular PGI ₂	
Altered von Willebrand factor	

Indirectly:

Presence of uremic toxins, especially parathyroid hormone
 Anemia/altered blood rheology
 Erythropoietin deficiency
 Specific drug treatment (e.g., nonsteroidal anti-inflammatory drugs)

ADP, adenosine diphosphate; GP, glycoprotein; PG, prostaglandin. Adapted from references.^{37,38,41}

U-shaped distribution for preventing ischemic stroke and avoiding hemorrhagic complications at an INR of 2.0 to 3.0.⁴² It is not clear what the optimum INR range is for patients with CKD.

INDIVIDUAL RISK STRATIFICATION AS A WAY OUT OF THE DILEMMA

In this complex situation with few, small, and diverging studies, carefully performed individual risk stratification may represent the best approach. Such an individualized approach was suggested by Lo *et al.*,³⁰ who compared the risk for ischemic stroke from the Cardiac Failure, Hypertension, Age, Diabetes, and Stroke (CHADS₂) score⁴³ to the risk for hemorrhages as estimated from the Outpatient Bleeding Risk Index.⁴⁵ If the presumed stroke risk outweighs the expected rate of bleeding, then, the authors suggested, the patient should be placed on oral anticoagulation. Although this approach has some appeal, there are major limitations: During validation of the CHADS₂ score, CKD was not consid-

ered. Moreover, a CHADS₂ score of 6 points represents the highest achievable value and means that the patient had cardiac failure, hypertension, age >75 yr, diabetes, and previous stroke. Such patients had average annual stroke rates of 18.2%.^{15,43} In contrast, in unselected patients who had ESRD with atrial fibrillation, the majority did not have all of these CHADS₂ risk factors but suffer from average annual stroke rates ranging from 17.4 up to 24%.^{1,25} This suggests the CHADS₂ score might underestimate the stroke risk in renal patients. The Outpatient Bleeding Risk Index as well as other clinical prediction rules for hemorrhage also show insufficient accuracy in the general population.^{44,45} Moreover, these prediction rules for bleeding risk are derived from small cohorts with ≤ 600 patients, again with no or a low (<20%) proportion of patients with CKD⁴⁵; therefore, just calculating and comparing these distinct risk scores for stroke and hemorrhage seems oversimplified and probably not suitable for clinical practice.

Nevertheless, some evidence-based data provide helpful information. First,

the CHADS₂ score is a feasible and useful tool to estimate the risk for ischemic stroke,^{15,43} but one has to be aware that, in CKD, the patient's real risk is likely higher.¹ Second, bleeding complications on oral anticoagulation in CKD are frequent with an increased proportion of fatal bleeding, but the rate is not unacceptably higher.^{27–29} In the largest cohort of 123 patients who had ESRD with atrial fibrillation and were on oral anticoagulation, patients had significantly better overall long-term survival compared with those not treated,²¹ whereas patients who had ESRD and sustained ischemic stroke had a dramatic 2-yr mortality rate of 75% (Figure 1C).¹ Third, the risk for hemorrhages seems to be especially increased during the first 30 to 90 d after initiation of oral anticoagulation,^{27,44,46,47} because initial therapy often results in INR values >3.0.^{28,44} Moreover, these hemorrhages in the early phase may be caused by some patient-inherent factors, such as cerebral microangiopathy. Patients on oral anticoagulation for >90 d without a major bleeding event represent a selected group with a smaller risk for future hemorrhages.^{44,46,47} Fourth, the most relevant clinical factors associated with a markedly increased bleeding risk have been identified (Figure 2).^{44,45} Although they are not easily condensed to a simple points score,⁴⁵ they can reliably raise awareness of increased bleeding risk.

Considering the available evidence and current guidelines for management of atrial fibrillation,¹⁵ we propose a risk stratification algorithm presented in Figure 2. In its current form, it is partially evidence based but feasible for deciding whether a patient should be placed on oral anticoagulation. One potential weakness of the proposed algorithm is that the consideration of bleeding risk cannot simply be calculated by a scoring system but rather needs the input of the treating physician, who is competent in evaluating the complex medical conditions typical of CKD. For example, dementia and recurrent falls may be important factors for serious hemorrhages on oral anticoagulation not only because of mistakes during drug taking or injuries but also as strong predictors of cerebral mi-

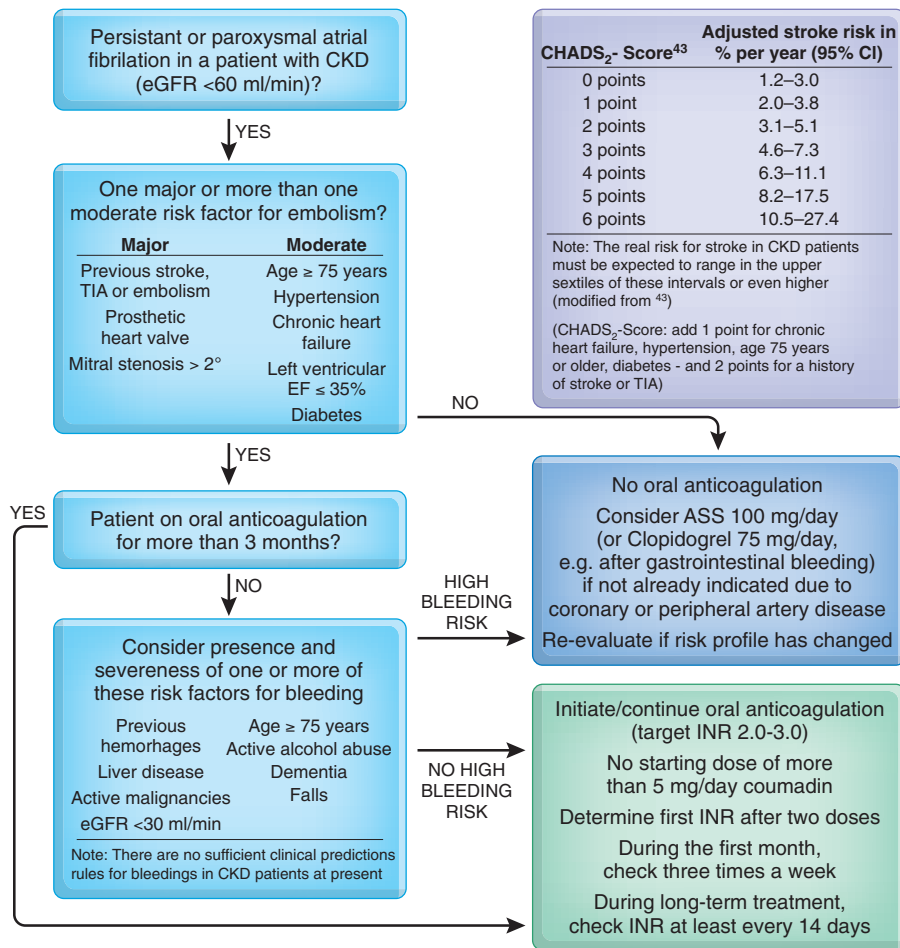


Figure 2. Algorithm for oral anticoagulation in atrial fibrillation and CKD. All patients with permanent, persistent, and especially paroxysmal atrial fibrillation are at high risk for ischemic stroke. For these individuals, the listed risk factors should be assessed.^{15,43} Because they all have CKD, their real stroke risk is likely higher than reported CHADS₂ rates (top right; also see text). If a patient has no or only one moderate risk factor, then proceed to the blue “no oral anticoagulation” box on the right. If patients have already been taking oral anticoagulation for >3 mo without hemorrhage, then they probably represent a “positive selection” group with a lower risk for bleeding. Nevertheless, the INR should be evaluated every 14 d during long-term treatment and be adjusted within a precise target range of 2.0 to 3.0.

croangiopathy with a high risk for spontaneous bleeding. Conversely, a patient who had experienced a previous gastrointestinal bleed while taking nonsteroidal anti-inflammatory drugs but does not use them anymore may not have a real contraindication. The design of this algorithm might increase the use of oral anticoagulation in patients with CKD, which is justified because of the high rate of disabling and fatal stroke in CKD¹ that outweighs the risk for nonfatal or fatal hemorrhages.^{27–29} In general, there has been a trend to withhold otherwise established beneficial treatment

strategies such as oral anticoagulation in patients with CKD.^{22,48} No doubt, more prospective data and appropriate guidelines are needed to define more precisely how to treat patients with atrial fibrillation and CKD.

APPENDIX

Statement from the National Kidney Foundation’s Practice Guidelines for Chronic Kidney Disease⁷ regarding the use of the term “end-stage renal disease”:

“Kidney failure is not synonymous with end-stage renal disease (ESRD). ‘End-stage renal disease’ is an administrative term in the United States. It indicates that a patient is treated with dialysis or transplantation, which is the condition for payment for health care by the Medicare ESRD Program. The classification of ESRD does not include patients with kidney failure who are not treated with dialysis and transplantation. Thus, although the term ESRD provides a simple operational classification of patients according to treatment, it does not precisely define a specific level of kidney function.”

DISCLOSURES

None.

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