

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Atrial Fibrillation and Thromboembolism in Patients With Chronic Kidney Disease



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ABSTRACT

A bidirectional relationship exists between atrial fibrillation (AF) and chronic renal disease. Patients with AF have a higher incidence of renal dysfunction, and the latter predisposes to incident AF. The coexistence of both conditions results in a higher risk for thromboembolic-related adverse events but a paradoxical increased hemorrhagic risk. Oral anticoagulants (both vitamin K antagonists [VKAs] and non-VKA oral anticoagulants [NOACs]) have been demonstrated to be effective in mild to moderate renal dysfunction. Patients with severe renal impairment were excluded from the non-VKA oral anticoagulant trials, so limited data are available. In end-stage renal failure, the net clinical benefit of VKAs in dialysis-dependent patients remains uncertain, although some evidence suggests that such patients may do well with high-quality anticoagulation control. Risk stratification and careful follow-up of such patients are necessary to ensure a net clinical benefit from thromboprophylaxis. (J Am Coll Cardiol 2016;68:1452-64) © 2016 by the American College of Cardiology Foundation.

Chronic kidney disease (CKD) is defined by Kidney Disease Improving Global Outcomes as a reduction in renal function with a reduction in glomerular filtration rate (GFR) <60 ml/min/1.73 m² for 3 months or longer or with the presence of albuminuria (1,2). The scheme of CKD stages 1 to 5 is conventionally classified on the basis of GFR, ranging from CKD stage 1, which has preserved renal function (GFR >90 ml/min) to CKD stage 5, which has the worst renal function (GFR <15 ml/min). CKD has potential for gradual progression to end-stage renal disease (ESRD), which requires dialysis to correct the accompanying fluid and electrolyte imbalance.

The increasing incidence and prevalence of CKD are also associated with a parallel rise in incident atrial fibrillation (AF) (3-6). The main reason for this epidemiological coupling is the improving longevity in

Western countries, resulting in a rapidly increasing elderly population, as well as a contemporary increase in the collective risk factors shared by both conditions, such as diabetes mellitus and hypertension.

Unsurprisingly, CKD and AF are not independent conditions, as several studies and national registries have highlighted the increased incidence of AF among those with worsening renal function (7-14). Indeed, the incidence of AF development can be as high as 12.1/1,000 patient-years in ESRD compared with 5.0/1,000 patient-years in controls (15). Likewise, a new diagnosis of AF not only heralds the progression of CKD but also hastens the development of ESRD (16-18). AF also leads to the progression of CKD, even among those with relatively “normal” renal function, with no detectable proteinuria on dipstick test at baseline (19). Thus, a bidirectional relationship exists between these 2 conditions.



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AF per se can result in increased risk of ischemic stroke and systemic thromboembolism and independently increased risk of cardiovascular death. However, the concurrent presence of both AF and CKD further exacerbates the stroke and mortality risks, with a 66% increase in relative risk of death (20-23). Hence, the presence of both of these conditions results in an increase in the propensity for thromboembolism-related adverse events (including stroke, systemic thromboembolism, myocardial infarction, and death) but a paradoxical increase in hemorrhagic risk.

Stroke/thromboembolism and bleeding risks can be assessed using clinical risk scores, such as the CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke, transient ischemic attack [TIA], or thromboembolism, vascular disease [prior myocardial infarction, peripheral arterial disease or aortic plaque], age 65-74 years, sex category [female]) and HAS-BLED (hypertension, abnormal renal/liver function, prior stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol) scores, to enable risk stratification of patients requiring thromboprophylaxis (24,25). Oral anticoagulants (both vitamin K antagonists [VKAs] and non-VKA oral anticoagulants [NOACs]) provide effective thromboprophylaxis in patients with mild to moderate renal dysfunction (creatinine clearance [CrCl] of 30 to 79 ml/min), in both clinical trials and observational studies (26,27). Patients with severe renal impairment (CrCl < 25 to 30 ml/min) were excluded from the phase 3 randomized trials of NOACs, so limited trial data are available.

Initially, this review discusses the pathophysiological and clinical bases underlying the increased risk of thromboembolism and hemorrhage among AF patients with CKD. Second, we review the data for the use of oral anticoagulants for stroke prevention in AF across the spectrum of renal dysfunction.

SEARCH STRATEGY

A comprehensive search of published studies was performed using electronic bibliographic databases (i.e., PubMed, Medline, EMBASE, DARE, Cochrane database), scanning reference lists from included papers, and manual searching abstracts from national and international cardiovascular meetings. Search terms included: atrial fibrillation; chronic kidney disease; renal failure; antithrombotic treatment; vitamin K antagonist; dabigatran; rivaroxaban; apixaban; and edoxaban. Bibliographies of all selected papers and reviews were reviewed for other relevant

papers. Finally, the supplements of major journals were searched manually to identify relevant abstracts that had not been published as peer-reviewed papers.

PATHOPHYSIOLOGY AND EPIDEMIOLOGY OF THROMBOEMBOLISM IN CKD: A BRIEF OVERVIEW

PATHOPHYSIOLOGICAL INSIGHTS. AF confers a prothrombotic or hypercoagulable state through numerous pathophysiological pathways, fulfilling Virchow's triad for thrombogenesis, as shown by abnormalities in blood flow, in the vessel wall, and in blood constituents (28). The propensity of thrombus formation is further enhanced by the relationship between CKD and additional changes (29) in blood flow within the left atrium (and left atrial appendage), endothelial damage/dysfunction, or up-regulation of platelet and coagulation factors (Table 1).

In relation to changes in blood flow, worsening GFR in AF is associated with reduced left atrial appendage emptying velocity and formation of dense spontaneous echocardiographic contrast, indicative of significant blood stasis and increased thrombogenic risk (30,31). Second, CKD-related endothelial damage/dysfunction to the vessel wall may manifest directly as abnormal endothelial function (e.g., as assessed by flow-mediated dilation) or increased pulse-wave velocity (32-36), or indirectly, as elevated levels of endothelin and von Willebrand factor (33,37). Endothelial damage/dysfunction can also be reflected in intima-media thickening (38), which is predictive of a 10-fold increase in cardiovascular mortality in patients with ESRD (odds ratio: 10.20; 95% confidence interval [CI]: 3.67 to 28.3; $p < 0.0001$) (39,40).

Third, increased thrombogenesis in CKD is also related to an increase in platelet and coagulation abnormalities ("abnormal blood constituents") through several pathways, for example, increased procoagulant and inflammatory complexes (41-45), up-regulation of the tissue factor pathway and its interactions with platelets (46,47), reduction of antithrombin III and plasminogen-activator inhibitor (PAI)-1 levels (47,48), reduced von Willebrand factor degradation (49), and increased platelet aggregability (50).

CKD per se is also associated with various other factors contributing to an increased thromboembolic risk, for example, activation of the renin-angiotensin-aldosterone system (51), chronic inflammation (43), aortic or vascular calcification, and dysfunction of

ABBREVIATIONS AND ACRONYMS

AF	= atrial fibrillation
b.i.d.	= twice daily
CKD	= chronic kidney disease
ESRD	= end-stage renal disease
FDA	= Food and Drug Administration
NOAC	= non-vitamin K antagonist oral anticoagulant
TTR	= time in therapeutic range
VKA	= vitamin K antagonist

TABLE 1 Pathophysiology of Thromboembolism in CKD

First Author (Year) (Ref. #)	Study Type	N	Population	Findings
Blood stasis in left atrium and atrial appendage				
Yagishita et al. (2010) (30)	Observational	321	Patients with persistent atrial fibrillation	GFR is an independent predictor of reduced left atrial appendage emptying velocity and presence of left atrium spontaneous echocardiographic contrast
Providência et al. (2013) (31)	Observational	372	Patients with nonvalvular atrial fibrillation	eGFR is positively associated with dense, spontaneous echocardiographic contrast, and low flow velocities in the left atrium
Damage to vessel wall and endothelial damage/dysfunction				
Heintz et al. (1994) (37)	Comparative	40	CKD and healthy controls	CKD patients have higher endogenous levels of ET-1, plasma cAMP, and enhanced ET-1-stimulated ADP-induced platelet aggregation than healthy controls
Blacher et al. (1999) (32)	Observational	241	ESRD patients	Increased aortic PWV in ESRD predicts all-cause cardiovascular mortality
Bolton et al. (2000) (33)	Cross-sectional	67	23 HD patients, 16 NDD patients, and 28 healthy controls	Reduced flow-mediated EDD in HD and NDD patients compared to controls; increased vWF and adhesion molecules in renal dysfunction
Yildiz et al. (2003) (34)	Comparative	104	104 HD patients vs. 49 healthy controls	Reduced flow-mediated EDD and EID in hemodialysis patients compared to controls
Hrafnkelsdóttir et al. (2004) (137)	Comparative	18	Nondiabetic, nonsmoking CKD patients and age-matched controls	Maximal release of active t-PA and capacity for active t-PA release markedly impaired in CKD patients versus controls
Wang et al. (2005) (35)	Observational	102	NDD CKD patients with various GFR	Decreased GFR was independently associated with an increased PWV
Carrero et al. (2012) (36)	Observational	630	NDD CKD versus ESRD	Prolactin levels increased along with reduced kidney function, related to FMD, PWV, and increased risk of cardiovascular events and mortality
Recio-Mayoral et al. (2011) (38)	Comparative	141	76 CKD vs. 65 age- and sex-matched controls	CKD patients had increased CRP levels, reduced FMD, and increased IMT values compared to controls
Platelet and coagulation abnormalities				
Shlipak et al. (2003) (41)	Cross-sectional	5,888	Population-based cohort of age >65 yrs	CRP, fibrinogen, IL-6, factor VII, factor VIII, plasmin-antiplasmin complex, and D-dimer levels significantly higher in CKD
Pecoits-Filho et al. (2003) (42)	Observational	176	176 NDD patients	Lower GFR associated with increased CRP, IL-6, hyaluronan, and neopterin levels
Keller et al. (2008) (43)	Cross-sectional	6,814	Population-based cohort 45-84	CRP, IL-6, TNF, TNF- α R1, intercellular adhesion molecule-1, fibrinogen, and factor VIII levels are significantly higher in CKD
Landray et al. (2004) (44)	Comparative	522	334 CKD patients, 92 CAD patients, 96 healthy controls with no prior CV or renal disease	CKD is associated with higher fibrinogen, plasma vWF, and soluble P-selectin, but not CRP
Tanaka et al. (2009) (45)	Observational	190	Patients not receiving oral anticoagulant stratified by CrCl	Decreased GFR predicts for elevation of TAT and D-dimer in patients with AF
Mercier et al. (2001) (46)	Cross-sectional	150	50 ESRD patients, 50 NDD CKD patients, and 50 healthy controls	Reduced renal function associated with enhanced tissue factor coagulation due to platelet, monocyte, and endothelial injury
Costa et al. (2008) (48)	Observational	50	50 ESRD patients vs. 25 healthy controls	Higher levels of CRP, s-IL2R, IL-6, and D-dimer, and significantly lower levels of PAI-1 in ESRD patients; the t-PA/PAI-1 ratio was also significantly higher in ESRD patients
Adams et al. (2008) (47)	Comparative	102	66 CKD stage 4 and 5 patients versus 36 healthy controls	Up-regulation of the tissue factor pathway, increased prothrombin fragments 1 + 2, and reduction in antithrombin III in CKD compared with healthy controls
Shen et al. (2012) (49)	Observational	104	104 NDD patients versus 32 healthy controls	Increased vWF-antigen level and decreased ADAMTS13 activity in CKD
Yagmur et al. (2015) (50)	Comparative	84	30 HD patients, 34 renal transplant recipients, 20 healthy controls	Increased platelet hyperaggregability in CKD

ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; ADP = adenosine diphosphate; AF = atrial fibrillation; CAD = coronary artery disease; cAMP = cyclic adenosine monophosphate; CKD = chronic kidney disease; CrCl = creatinine clearance; CRP = C-reactive protein; CV = cardiovascular; EDD = endothelium-dependent dilation; eGFR = estimated glomerular filtration rate; EID = endothelium-independent dilation; ESRD = end-stage renal disease; ET = endothelin; FMD = flow-mediated dilation; GFR = glomerular filtration rate; HD = hemodialysis; IL = interleukin; IMT = intima-media thickness; MDRD = Modification of Diet in Renal Disease; NDD = nondialysis dependent; PAI = plasminogen activator inhibitor; PWV = pulse wave velocity; s-IL2R = serum interleukin-2 receptor; TAT = thrombin-antithrombin complex; TNF = tumor necrosis factor; TNF- α R1 = tumor necrosis factor- α soluble receptor 1; t-PA, tissue-type plasminogen activator; vWF = von Willebrand factor.

TABLE 2 Epidemiological Insight Into Stroke Risk in Patients With AF and CKD

First Author (Year) (Ref. #)	Study Type	N	Findings
Go et al. (2009) (55)	Retrospective	10,908 AF with CKD	Compared with GFR ≥ 60 ml/min/1.73 m ² : eGFR: 45–59 ml/min; RR: 1.16 (95% CI: 0.95–1.40) eGFR <45 ml/min; RR: 1.39 (95% CI: 1.13–1.71) (p = 0.0082 for trend).
Friberg et al. (2012) (138)	Retrospective	182,678 AF patients (8,113 with CKD)	CKD stage 1 and below: multivariate HR: 1.11 (95% CI: 0.99–1.25)
Olesen et al. (2012) (56)	Retrospective	132,372 AF patients (3,587 with NDD CKD; 901 with ESRD)	Compared with GFR ≥ 90 ml/min/1.73 m ² : NDD CKD HR: 1.49 (95% CI: 1.38–1.59) ESRD, HR: 1.83 (95% CI: 1.57–2.14)
Guo et al. (2013) (18)	Prospective	617 AF patients	Risk of stroke or death: HR: 2.90 (95% CI: 1.88–4.48) Risk of stroke in 6 months: Absolute decrease in eGFR ≥ 25 ml/min/1.73 m ² : HR: 2.77 (95% CI: 1.26–6.09) Relative decrease in eGFR $\geq 25\%$: HR: 2.57 (95% CI: 1.14–5.80)
Roldán et al. (2013) (61)	Prospective	978 AF patients on VKA	Every decrease in eGFR of 30 ml/min/1.73 m ² : HR: 1.42 (95% CI: 1.11–1.83)
Bonde et al. (2014) (57)	Retrospective	154,254 nonvalvular AF patients (148,598 with NRD; 4,519 with NDD; 1,142 receiving RRT)	Compared with GFR ≥ 60 ml/min/1.73 m ² : NDD CKD, HR: 1.32 (95% CI: 1.23–1.42) RRT, HR: 2.01 (95% CI: 1.74–2.33)
Chao et al. (2014) (139)	Retrospective	10,999 AF patients with ESRD in Taiwan	11.7% of patients experienced ischemic stroke Absolute stroke and thromboembolism event rate: 6.9/100 patient-years
Banerjee et al. (2014) (140)	Prospective	8,962 AF patients (2,982 with CKD)	Compared with GFR ≥ 60 ml/min/1.73 m ² : eGFR 30–59 ml/min HR: 1.53 (95% CI: 1.10–2.12) eGFR <30 ml/min HR: 1.78 (95% CI: 0.99–3.19)

CI = confidence interval; HR = hazard ratio; NDD = nondialysis-dependent; RR = relative risk; RRT = renal replacement therapy; other abbreviations as in Table 1.

calcium-phosphate mineral metabolism, which has been related to renal dysfunction (52–54).

EPIDEMIOLOGICAL INSIGHTS. An increase in stroke risk with progressive severe CKD among AF patients is evident from several large observational studies (Table 2).

The ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study (55) found that the presence of proteinuria increased risk of thromboembolism in AF by 54%. Progressive worsening of GFR was also associated with increased risk of stroke, where a GFR <45 ml/min/1.73 m² conferred an increased risk of 39% compared with a GFR >60 ml/min/1.73 m².

In separate analyses from the Danish nationwide cohort study, Olesen et al. (56) and Bonde et al. (57) reported that patients with concurrent AF and CKD experienced significantly higher rates of stroke, thromboembolism, hemorrhage, and death than those without renal disease. Those with ESRD requiring renal replacement therapy fared the worst: such patients were twice as likely to experience stroke and thromboembolism (57) than those without renal dysfunction (15). Similar relationships, for example, between an increased incidence of AF with progressive renal failure and a resultant increase in adverse events, have been shown in the Swedish national cohort study, as well as in various studies from Asian countries (15,58–60).

Among those with CKD (GFR <60 ml/min/1.73 m²), the sequential deterioration of renal function over time is equally pertinent, as an absolute reduction in estimated GFR (eGFR) ≥ 25 ml/min/1.73 m² or a relative reduction of eGFR $\geq 25\%$ effectively more than doubles the risk of ischemic stroke compared to those with relatively “stable” renal function over a 6-month period (18). Even among AF patients treated with effective anticoagulation, every 30 ml/min/1.73 m² reduction in eGFR confers a markedly increased risk of thrombotic or vascular event (hazard ratio [HR]: 1.42; 95% confidence interval [CI]: 1.11 to 1.83; p = 0.006) (61). Worsening renal clearance is not only an independent predictor of stroke mortality but is associated with a worse adverse outcome after stroke (62,63).

HEMORRHAGIC TENDENCY IN CKD

Although it significantly increases the risk of thromboembolism and ischemic stroke in AF, CKD also paradoxically results in an increased risk of hemorrhagic events.

Evidence from both the Rotterdam study and the Japanese CIRCS (Circulatory Risk in Communities Study) trial shows that the presence of reduced renal function (GFR <60 ml/min/1.73 m²) results in a more than 4-fold increased risk of hemorrhagic stroke in men and a 7-fold increased risk in women (64,65). CKD patients undergoing chronic dialysis had a

relative risk of intracerebral hemorrhage that could be >10-fold higher (66). Worsening renal function and associated vascular dysfunction may result in an increased tendency for formation of magnetic resonance imaging-defined cerebral microbleeds, which have the potential of contributing to subsequent intracerebral hemorrhage (67).

The risk of gastrointestinal bleeding is also increased, whether peptic ulcer-related, nonpeptic ulcer-related, or nonvariceal gastrointestinal bleeds; of note, the recurrence, frequency, and severity of such episodes are all closely linked to impairment of renal function (68–70). Similar to intracranial hemorrhage, both forms of renal replacement therapy (peritoneal dialysis and hemodialysis) are associated with an increased risk of gastrointestinal hemorrhage, conferring hazard ratios of 3.71 (95% CI: 2.00 to 6.87; $p < 0.001$) and 11.96 (95% CI: 7.04 to 20.31; $p < 0.001$), respectively (71).

The pathophysiological causes of the increased risk of hemorrhagic events are clearly multifactorial. They can be a direct result of uremia-related platelet dysfunction or impaired platelet adhesion and aggregation; impaired platelet glycoprotein IIb or IIIa receptor activation and subsequent binding to glycoprotein; altered von Willebrand factor; and nitric oxide metabolism (72–74). Extrinsically, the propensity to bleed can be the result of concurrent use of antiplatelet agents or nonsteroidal anti-inflammatory drugs. Moreover, patients with ESRD would be subject to frequent invasive diagnostic and invasive strategies, such as central venous access and hemodialysis (plus subsequent frequent heparin exposure), which could also increase their bleeding risk.

STROKE AND BLEEDING RISK STRATIFICATION IN AF WITH CKD

In the general AF population, the risk of stroke is 5-fold increased overall, according to the presence or absence of various stroke risk factors. The more common risk factors have been used to formulate stroke risk stratification schemes to help decision making about whether an oral anticoagulant (OAC) should be recommended or not for stroke prevention.

However, all risks that are scored on the basis of clinical factors have modest predictive value for identifying “high-risk” patients who sustain events. Current AF guidelines have adopted the use of the CHA₂DS₂-VASc score, given that it can reliably identify truly “low-risk” patients (i.e., CHA₂DS₂-VASc score of 0 in men, 1 in women) who do not need antithrombotic therapy (75,76). Subsequent to this step, effective stroke prevention can be offered to

those AF patients with ≥ 1 stroke risk factors. Effective stroke prevention means OACs, whether as well-controlled VKA therapy or one of the NOACs.

Despite being a contributor to an increased thromboembolic risk, moderate-severe renal impairment is not included in the CHA₂DS₂-VASc score, as attempts to incorporate renal impairment into the stroke risk stratification scheme have not shown an independent additive predictive value for renal impairment over the CHA₂DS₂-VASc score components, probably because CKD is strongly associated with the various single-risk factor components of the CHA₂DS₂-VASc score (i.e., heart failure, hypertension, and diabetes mellitus, among others).

One study advocating the addition of renal impairment for stroke risk stratification proposed the R₂CHADS₂ score (the additional R was for impaired renal function and given 2 points). In its initial derivation study from a highly selected anticoagulated clinical trial population with exclusion of those with severe CKD, the R₂CHADS₂ score modestly improved the c-index (a statistical measure of the score’s predictive value for high-risk patients who sustain events) of the CHADS₂ and CHA₂DS₂-VASc scores (77). However, the statistically significant modest improvement in predictive value of R₂CHADS₂ for thromboembolism has not been replicated in a small-sized ESRD cohort (78) and other similar studies (79,80) or in an AF cohort undergoing invasive catheter ablation of AF (81). In other large “real-world” non-anticoagulated AF cohorts, renal dysfunction (whether with 1 or 2 points, as with R₂CHADS₂) did not independently improve the predictive value of the CHADS₂ and CHA₂DS₂-VASc scores (82,83).

For hemorrhagic risk stratification in AF, guidelines currently recommend the use of the HAS-BLED score for assessing bleeding risk. A high HAS-BLED score should not lead to withholding of oral anticoagulation therapy, but a high HAS-BLED score among those with CKD should flag the patients potentially at risk of bleeding for more careful review or follow-up and the correction of modifiable risk factors, such as uncontrolled hypertension (the H of the HAS-BLED), labile international normalized ratios, alcohol excess, or concomitant use of nonsteroidal anti-inflammatory drugs and aspirin.

For those patients with previous gastrointestinal hemorrhage, the resumption of oral anticoagulant treatment has been associated with a significant reduction of mortality and thromboembolic events (84,85). Similar findings have also been seen in an ESRD cohort of patients with an increased risk of recurrence of gastrointestinal bleed upon restarting warfarin (86).

CLINICAL MANAGEMENT OF AF AND CKD

The approach to clinical management of AF patients with CKD has recently been comprehensively addressed by a position paper from the European Heart Rhythm Association, endorsed by the Heart Rhythm Society and the Asia Pacific Heart Rhythm Society (87). In general, the management of AF is patient-centered and symptom-directed when it comes to deciding on rate or rhythm control strategies (88,89); however, limited data are available on the differential management of AF in patients with CKD. Drug pharmacokinetics of antiarrhythmic agents and some anticoagulants may be influenced by CKD, and dosages may need adjustment due to the prolonged half-lives of various drugs and reduced clearance (87). Some drugs can even be removed by dialysis.

One recent study in European countries reported that patients with mild to moderate CKD were more likely treated with a rhythm control approach, whereas patients with severe CKD were more likely treated with a rate control approach (90). Also, AF ablation procedures were infrequently performed in patients with advanced CKD (90).

This approach seems justified, given the lack of proven long-term efficacy of ablation procedures in patients with CKD. In fact, one meta-analysis of observational studies in this clinical setting found CKD to be associated with a higher AF recurrence risk (91). Similar data have been reported for AF patients undergoing chronic dialysis (92). Indeed, worsening renal function during follow-up after catheter ablation seems to be associated with the highest risk of AF recurrence (93). In patients with new-onset AF after myocardial infarction, there were no significant differences in short- and long-term mortality rates between rate and rhythm control strategies in patients with CKD (94).

ORAL ANTICOAGULATION IN CKD: USING VITAMIN K ANTAGONISTS

Although oral anticoagulation is the mainstay of treatment for the prevention of ischemic stroke and thromboembolism in patients with AF, less evidence exists for those with significant renal impairment, given that such patients were excluded from the randomized trials. Hence, the prescription of oral anticoagulants (essentially VKAs, e.g., warfarin) among those with significant renal impairment varies from as low as 2% in Germany to as high as 37% in Canada (58). This heterogeneity in clinical practice reflects the uncertainty about the risks and benefits of anticoagulation use within this patient group.

For AF patients with concomitant ESRD requiring renal replacement therapy, conflicting findings exist from observational studies relating to the efficacy and safety associated with use of VKAs (Table 3).

Of the 17 studies reviewed, only the study by Abbott et al. (95) showed a clear mortality benefit, and Olesen et al. (96), Bonde et al. (57), Genovesi et al. (97), Chan et al. (98), and Findlay et al. (99) found a reduction in stroke or thromboembolism event rates. Other studies involving ESRD patients and use of VKA have demonstrated either equivocal results (100-102) or even potential harm from VKA use (100,103-110).

Several large studies (104,105,108) have demonstrated that AF patients who are receiving hemodialysis and taking warfarin experienced a more than 2-fold increase in the risk of ischemic stroke compared to non-VKA users. Elderly patients (>75 years of age) appear to be particularly at risk compared with those below 65 years of age (105). At the same time, those taking VKA while receiving hemodialysis may have a higher risk of hemorrhagic stroke than of thromboembolic events (107).

Possible explanations for the lack of efficacy of VKA in protection against stroke and thromboembolism and potential increase in stroke risk may be the poor quality of anticoagulation control, as reflected by a low time in therapeutic range (TTR) for patients receiving renal replacement therapy. Indeed, the Swedish AF cohort study suggests that the improved TTR is associated with lower risk of thromboembolism and hemorrhage (58).

Another possible explanation may potentially be dependent on the modality used in renal replacement therapy. A recent Hong Kong AF cohort suggested that ESRD patients receiving peritoneal dialysis had a thrombotic risk similar to that of their nonperitoneal dialysis counterparts. Importantly, warfarin use in this particular patient group not only provided protection against ischemic stroke (HR: 0.16; 95% CI: 0.04 to 0.66; $p < 0.01$ compared with aspirin; and HR: 0.19; 95% CI: 0.06 to 0.65; $p < 0.01$ compared with no antithrombotic therapy) but there was no increased risk of intracranial hemorrhage (with only 2 events occurring, 1 in the aspirin group and 1 in the no-antithrombotic therapy group) (98).

Among non-dialysis-dependent CKD patients with AF, there are more robust data favoring the use of dose-adjusted VKA in AF (Table 4). In all 5 studies and 1 meta-analysis reviewed, dose-adjusted warfarin provided better protection against ischemic stroke and systemic embolism than nonuse (56,57,109,111-113). The efficacy of warfarin in reducing thromboembolism must be balanced against a small but significant

TABLE 3 VKA Use and Stroke Rates in ESRD			
First Author (Year) (Ref. #)	Study Type	Number (% With AF)	Findings
Wiesholzer et al. (2001) (103)	Retrospective observational	430 (14.3%)	Stroke rate/100 patient-years: AF with VKA: 4.46 AF without VKA: 1.0
Abbott et al. (2003) (95)	Retrospective observational	3,374 (1.25%)	3-year survival rate: AF with VKA: 70% AF without VKA: 55%
Chan et al. (2009) (104)	Retrospective observational	48,825 (3.42%)	90-day HR: AF with VKA: 1.93 (95% CI: 1.29-2.90)*
Wizemann et al. (2010) (105)	Observational (DOPPS)	17,513 (12.5%)	Stroke rate in subjects >75 yrs of age: Warfarin user: 2.17 (95% CI: 1.04-4.53)
Phelan et al. (2011) (106)	Retrospective	845 requiring dialysis (141 on warfarin)	Stroke rate/100 patient-years: VKA user: 1.7 vs. non-VKA user: 0.7 (p = 0.636) Major hemorrhage rate/100 patient-years: VKA user: 10.8 vs. non-VKA user: 8.0 (p = 0.593)
Winkelmayer et al. (2011) (107)	Retrospective observational	2,313 ESRD patients with new AF	HR for ischemic stroke: VKA user 0.92 (95% CI: 0.61-1.37) HR for hemorrhagic stroke: VKA user 2.38 (95% CI: 1.15-4.96)
Olesen et al. (2012) (56)	Subgroup analysis	901 patients with AF requiring dialysis	HR compared with no antithrombotic agent, dialysis-dependent patients: VKA: 0.44 (95% CI: 0.69-1.01)
Knoll et al. (2012) (100)	Prospective	235 patients on dialysis (19.6% on VKA)	No stroke or bleed experienced HR for mortality in VKA user: 0.80 (95% CI: 0.28-2.29)
Sood et al. (2013) (108)	Observational (DOPPS)	41,844 (9.71%)	Stroke rate/100 patient-years: VKA: 3.3 No VKA or antiplatelet: 2.1†
Bonde et al. (2014) (57)	Retrospective	154,254 nonvalvular AF patients (1,142 on RRT and 260 receiving VKA)	Stroke and thromboembolic risk in non-VKA users: HR: 1.82 (95% CI: 1.58-2.12)‡
Shah et al. (2014) (109)	Retrospective	1,626 patients with AF on RRT (756 VKA users)	HR for ischemic stroke comparing VKA vs. non-VKA users: 1.14 (95% CI: 0.78-1.67) HR for bleeding: 1.44 (95% CI: 1.13-1.85)
Chen et al. (2014) (102)	Retrospective	500 with AF and ESRD (250 receiving VKA)	Compared with control group (no VKA or antiplatelet agent): HR for ischemic stroke: 1.017 (95% CI: 0.673-1.537)
Wakasugi et al. (2014) (110)	Prospective	60 Japanese patients with AF requiring dialysis (28 VKA users)	Comparing VKA vs. non-VKA users HR for ischemic stroke: 3.36 (95% CI: 0.67-16.66)
Chan et al. (2015) (98)	Retrospective	271 patients with AF on peritoneal dialysis (70 on VKA)	Comparing VKA vs. aspirin users: HR for ischemic stroke: 0.16 (95% CI: 0.04-0.66) Comparing VKA vs. nonusers of antithrombotic agents: HR for ischemic stroke: 0.19 (95% CI: 0.06-0.65)
Findlay et al. (2015) (99)	Retrospective	1,382 patients with ESRD, of whom 293 with AF (118 on VKA; 175 without VKA)	Stroke rate: AF with VKA: 11.4% AF without VKA: 14.4%
Genovesi et al. (2015) (97)	Prospective	290 patients with AF requiring dialysis (134 on VKA at recruitment)	Comparing VKA vs. non-VKA users: HR for stroke/thromboembolic events: 0.12 (95% CI: 0.00-3.59)
Shen et al. (2015) (101)	Retrospective	12,284 patients on RRT (1,383 started on VKA)	Comparing VKA vs. non-VKA users: HR for ischemic stroke: 0.68 (95% CI: 0.47-0.99) HR for mortality: 0.84 (95% CI: 0.73-0.97)

*AF with VKA covariate adjusted model: adjusted for CHADS₂ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack [TIA], or thromboembolism) score, sex, race, Charlson comorbidity index, entry date, body mass index, facility standardized mortality ratio, cardiovascular drugs, dialysis adequacy, baseline laboratory values, heparin dosage, and heparin regimens. †VKA users include patients with AF, thromboembolic disease, or central vascular catheter. ‡Adjusted for aspirin treatment and all risk factors included in CHA₂DS₂-VASC (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack [TIA], or thromboembolism, vascular disease [prior myocardial infarction, peripheral arterial disease or aortic plaque], age 65-74 years, sex category [female]) score.

DOPPS = Dialysis Outcomes and Practice Pattern Study; VKA = vitamin K antagonist; other abbreviations as in Tables 1 and 2.

increase in hemorrhage tendency (19% to 36%), with an even higher event rate if there is concurrent antiplatelet use (56,109). Therefore, VKAs can be beneficial in non-dialysis-dependent CKD patients with AF, but the propensity for harm due to VKAs in ESRD has yet to be fully defined, especially in a patient taking hemodialysis therapy. Some evidence suggests that such ESRD patients may do well with

high-quality anticoagulation control. One recent ancillary analysis from a clinical trial cohort found that good-quality anticoagulation control (TTR >70%) was an independent predictor of lower risks of stroke, death, and major bleeding (114). Risk stratification and careful follow-up of such patients are necessary to ensure a positive net clinical benefit from thromboprophylaxis.

TABLE 4 VKA Use and Stroke/Thromboembolic Event Rate in Nondialysis-Dependent CKD Patients

First Author (Year) (Ref. #)	Study Type	Number	Findings
Lai et al. (2009) (111)	Observational	307	% Stroke event rate/yr: Dose-adjusted warfarin (INR target: 2-3): 3.48 No VKA: 13.57
Hart et al. (2011) (112)	Post hoc analysis	516	% Stroke/embolic event rate/yr: Dose-adjusted warfarin: 1.45 Dose-adjusted warfarin plus aspirin: 7.05
Olesen et al. (2012) (96)	Subgroup analysis	3,587	HR of stroke compared with no antithrombotic NDD CKD: Warfarin only: 0.84 (95% CI: 0.69-1.01) Warfarin + aspirin: 0.76 (95% CI: 0.56-1.03) Aspirin only: 1.25 (95% CI: 1.07-1.47)
Bonde et al. (2014) (57)	Retrospective	154,254 nonvalvular AF patients (4,519 on NES CKD, 1,130 on VKA)	Stroke and thromboembolic risk in non-VKA users: HR: 1.31 (95% CI: 1.22-1.41)*
Shah et al. (2014) (109)	Retrospective	204,210 NES patients with AF (103,652 on VKA)	Stroke risk with warfarin use in nondialysis patients: HR: 0.87 (95% CI: 0.85-0.90) Bleeding risk in nondialysis patients: HR: 1.19 (95% CI: 1.13-1.85)
Providência et al. (2014) (113)	Meta-analysis	19 studies, 379,506 patients with CKD and AF	Stroke and thromboembolic risk in non-NES VKA users: HR: 0.39 (95% CI: 0.18-0.86)

*Adjusted for aspirin treatment and all risk factors included in the CHA₂DS₂-VASc score.

INR = international normalized ratio; NES = non-end-stage; other abbreviations as in Tables 1 and 3.

WHAT ARE THE POSSIBLE PATHOPHYSIOLOGICAL MECHANISMS?

Apart from the abnormalities of Virchow's triad discussed previously, murine and human studies have demonstrated that VKA contributes to vascular calcification through inactivation of the matrix protein Gla (115,116). Increased vascular calcification, either as a direct result of development of ESRD or due to concurrent VKA usage, may potentially increase the likelihood of development of noncardioembolic stroke, which will not be remedied by VKA use. Moreover, VKA administration has been implicated in development of calciphylaxis, a painful and lethal complication among patients with ESRD, as cutaneous arteries and arterioles undergo calcification and occlusion (117,118).

ORAL ANTICOAGULATION IN CKD: USING NON-VKA ORAL ANTICOAGULANTS

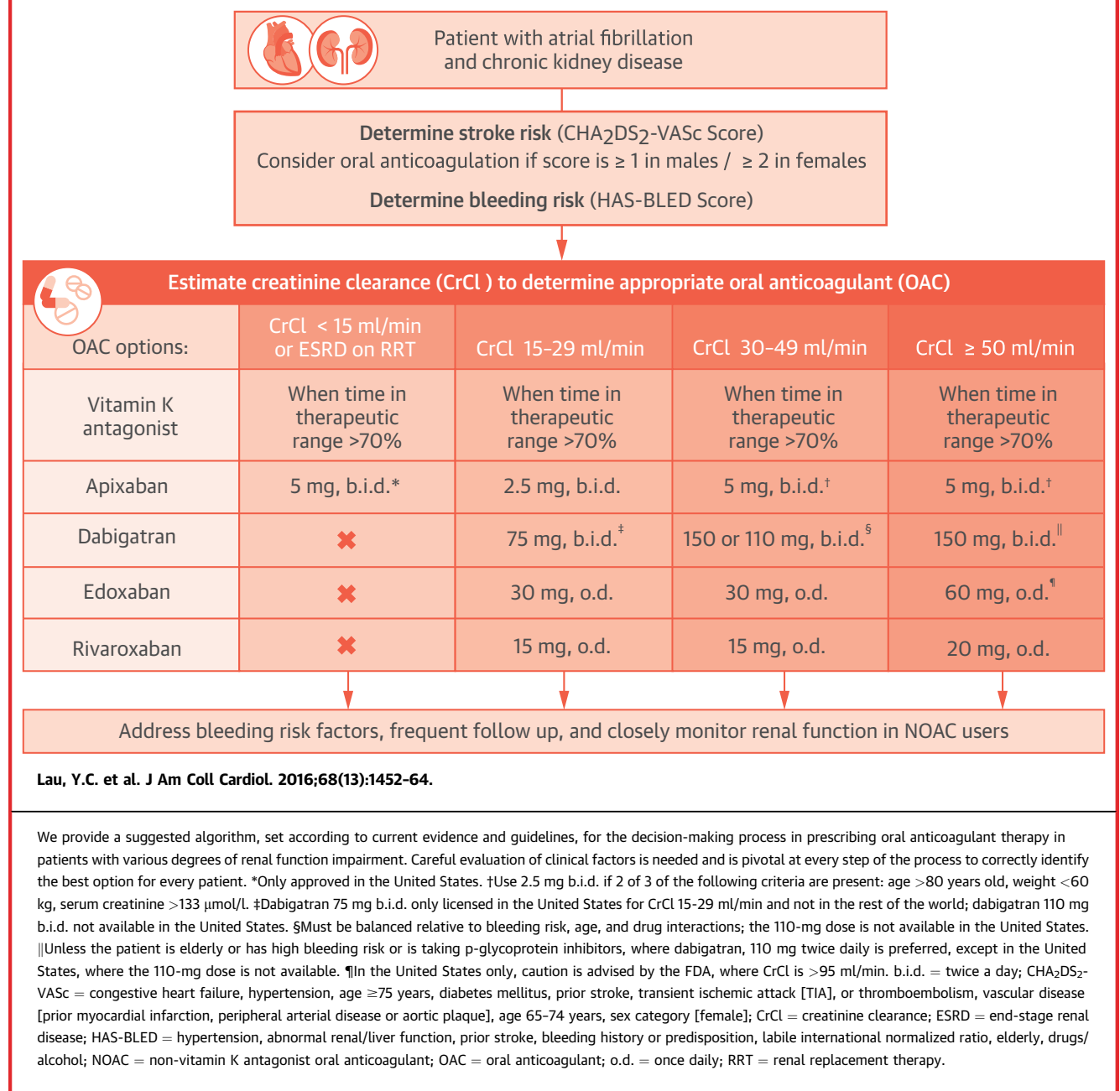
When NOACs were introduced, namely the direct thrombin inhibitor (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban), they were considered viable alternatives for patients with mild to moderate CKD requiring an oral anticoagulant for thromboprophylaxis.

All 4 NOACs demonstrated noninferiority or even superiority in stroke prevention and noninferiority (or, in some cases, superiority) in bleeding profile compared with warfarin (119-123). Subgroup analyses of patients with renal dysfunction showed that both of the dabigatran dosages are effective and safe, regardless of renal function (124), whereas a reduction in rivaroxaban dosage to 15 mg once per

day in patients with moderate CKD provides efficacy and safety comparable to that of warfarin (125). Among patients with moderately reduced renal function (GFR as low as 30 ml/min), the apixaban and edoxaban subgroups of the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) and ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) trials showed a reduced bleeding risk compared with that of warfarin (126,127). Additional benefits include medication delivery in fixed doses that do not require monitoring and that have a lower propensity for interaction with food or other medications (128,129).

Nonetheless, as all NOACs have a degree of renal excretion (varying from 25% in apixaban to 80% in dabigatran), in their respective trials, participants with severe renal dysfunction or ESRD were excluded. Therefore, the European guidelines recommend that the NOACs are best not used where severe renal impairment (GFR <25 to 30 ml/min) is present (75,130). Among patients with moderately impaired renal function (GFR 30 to 49 ml/min), dose alteration according to manufacturer's recommendations is advised. The Cockcroft-Gault method should be used (rather than the Modification of Diet in Renal Disease [MDRD] or Chronic Kidney Disease Epidemiology equations) for the assessment of renal function, as this formula was used during various randomized trials of NOACs and does not result in overestimation of renal function in elderly patients or those with

CENTRAL ILLUSTRATION Proposed Algorithm for Oral Anticoagulant Choices in Patients With Atrial Fibrillation and Chronic Kidney Disease



lower GFR, hence, providing better dose adjustment in this patient group (29,131).

For patients in the United States, the Food and Drug Administration (FDA) has approved dabigatran, 75 mg twice a day (b.i.d.); rivaroxaban, 15 mg once daily; and apixaban, 2.5 mg b.i.d., for patients with a CrCl of 15 to 29 ml/min. These dosages are not approved on the basis of clinical trial outcome data

but on pharmacological modeling data. Using pharmacokinetic findings in patients who received hemodialysis, the FDA has also approved the use of apixaban, 5 mg b.i.d. (i.e., no dose adjustment), in AF patients receiving chronic, stable hemodialysis treatment (132). The FDA also raised concerns about the use of edoxaban in AF patients with CrCl >95 ml/min, but differences in stroke/thromboembolism, all-cause

mortality, and cardiovascular mortality in relation to CrCl renal subgroups were not statistically significant in a comparison between edoxaban-treated and warfarin-treated subgroups (133). The prescribing label for edoxaban in Europe and elsewhere does not have the FDA caution/restriction for use in AF patients with CrCl >95 ml/min.

A recent meta-analysis has demonstrated the relative safety and efficacy of all 4 NOAC agents over that of warfarin across various degrees of renal impairment (26). Although there is currently no head-to-head clinical trial comparing one NOAC with another, the same analysis also revealed that in “moderate renal dysfunction” (CrCl 25 to 49 ml/min), apixaban possessed a relatively better safety profile while retaining similar power of efficacy in protection against thromboembolic events (26). In those with “mild renal dysfunction” (CrCl 50 to 79 ml/min), dabigatran, 110 mg, and apixaban, rivaroxaban, and edoxaban, 30 mg, appear broadly comparable (26).

CONCLUSIONS AND FUTURE PERSPECTIVES

Renal dysfunction and AF commonly coexist, and the concurrent existence of both conditions results in a paradoxical increase in both thromboembolic and hemorrhagic risks. Several pathophysiological factors have been demonstrated to induce a prothrombotic state while increasing bleeding risk in such patients. The thromboembolic and hemorrhagic risks are particularly high among dialysis-dependent patients with ESRD. However, at this juncture, data supporting the long-term use of VKA for thromboprophylaxis in AF remain limited. Any potential benefit conferred by VKA appears to be outweighed by a disproportionate increase in bleeding risk (and thrombotic events). One specific NOAC (apixaban) has recently

been licensed for use in individuals undergoing hemodialysis on the basis of limited pharmacokinetic studies only. To the best of our knowledge, no specific outcome studies have been designed to explore the comparative efficacy and safety of the different OAC treatments in patients with severe CKD. Large observational cohort studies with various NOACs and well-managed VKA therapy (with TTR >70%) may offer some comparative efficacy and safety data.

Conversely, the use of various oral anticoagulants (whether VKAs or NOACs) among AF patients with mild CKD has been shown to reduce morbidity and mortality from stroke and systemic thromboembolism. Even in moderately impaired renal function (CrCl 30 to 49 ml/min) apixaban and edoxaban appear to have a good safety profile (Central Illustration).

The key would be careful patient selection through the use of risk stratification scores (e.g., using CHA₂DS₂-VASC and HAS-BLED scores). Upon initiation of oral anticoagulation, we should ensure that steps are taken to reduce bleeding risk (e.g., aiming for a high TTR, namely >70%) (134), plus regular monitoring of renal function if a NOAC is chosen, to allow for dose alteration as needed. Patients with CKD and AF are prone to experience fluctuations of renal function due to acute illness (135); thus, making timely dose alterations is vital to preventing adverse events (136). As a result of an increasingly elderly population, the necessity of managing AF with concurrent CKD will increase rather than decrease in the near future.

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