Kidney Medicine

Atrial Fibrillation in Kidney Failure: Challenges in Risk Assessment and Anticoagulation Management

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Management of atrial fibrillation (AF) is a clinical conundrum in people with kidney failure. Stroke risk is disproportionately high, but clinicians have a limited armamentarium to improve outcomes in this population in whom there is a concurrently high bleeding risk. Direct oral anticoagulants may have a superior benefit–risk profile compared with vitamin K antagonists in people on hemodialysis. Although research has predominantly focused on identifying a safe and effective oral anticoagulation option to reduce stroke risk in people with kidney failure (and predominantly those on hemodialysis), it remains uncertain how clinicians discriminate between people who would derive net clinical benefit as opposed to net harm. The recommended CHA_2DS_2-VASc score cutoffs provide poor discriminatory value, and there is an urgent need to identify robust markers of thromboembolic risk in kidney failure.

There is increasing data to challenge the prior dogma of risk equivalence across AF type, and the American Heart Association highlights moving beyond AF as a binary entity to consider the prognostic significance of AF burden. Implantable cardiac monitor studies reveal high rates and varied burden of subclinical and paroxysmal AF in people on hemodialysis. The association between AF burden and the proarrhythmic environment of hemodialysis with cyclical volume loading, offloading, and electrolyte changes is not well studied. We review the significance of AF burden as a contributor to thromboembolic risk, its potential as the missing link in risk assessment, and updated evidence for anticoagulation in people with kidney failure.

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INTRODUCTION

Atrial fibrillation (AF) is a challenging cardiovascular problem in people with kidney failure. Significant practice variation and clinician uncertainty exists as a result of a paucity of evidence to guide decision making in mitigating thromboembolic risk.[1] The compelling benefits of vitamin K antagonists (VKAs) for stroke risk reduction in the general population have not been replicated in people with kidney failure,[2] and use of VKAs has fallen out of favor. Recent studies report the superior benefit–risk profile of direct oral anticoagulants (DOACs) compared with VKAs in people treated by hemodialysis,[3,4] although data for efficacy remain outstanding. Although the availability of safe oral anticoagulation (OAC) options in kidney failure is important, appropriate patient selection for treatment is also imperative—identifying the highest risk patients who may derive net clinical benefit without exposing others to unnecessary bleeding risk.

The prognostic significance of AF burden to thromboembolic risk is an emerging area of research, with new data challenging prior dogma of risk equivalence across AF type. This review examines the current evidence for stroke risk stratification in kidney failure and explores the relevance of AF type and burden to stroke risk. We also provide an update on evidence for OAC and address limitations and future directions in this important area.

STROKE RISK ASSESSMENT IN KIDNEY FAILURE

People with kidney failure experience 5- to 10-fold higher rates of ischemic stroke compared with the general population,[5] and those with AF have a 2-fold higher rate than those without AF.[6] This risk is traditionally associated with clinical risk factors derived from non-anticoagulated general AF cohorts and randomized controlled trials (RCTs) conducted more than 20 years ago[7]; this information has resulted in development of stroke risk prediction scores to inform clinical decision making and standardize OAC use. Guidelines recommend the use of CHA_2DS_2-VASc scores to assess risk of thromboembolic stroke,[8-10] recommending OAC when CHA_2DS_2-VASc ≥ 2 in men and ≥ 3 in women.[8] There is little data on the predictive performance of the CHA_2DS_2-VASc score in the kidney failure population.

Given concurrent increased stroke and bleeding risk, risk assessment and careful patient selection is essential in kidney failure.[5] Original development cohorts excluded people with chronic kidney disease (CKD), and external validation studies in kidney failure cohorts only report modest discrimination.[9-12] Yet for risk prediction and clinician decision making, calibration (the accuracy of predicted absolute risks) may be more important in weighing the relevant stroke and bleeding risks. The only CHA_2DS_2-VASc validation study to report calibration found modest discrimination with poor calibration in a prospective Dutch cohort of 2051 people receiving dialysis,[11] under-predicting stroke risk with respect to the actual agreement between observed and predicted probabilities. It also highlighted poor predictive performance of another 14 stroke risk models, with only the Framingham Heart Score showing good calibration but poor discrimination.[11]

De Vriese and Heine[13] have proposed an alternative algorithm to estimate net clinical benefit from OAC. The

"Dialysis Risk Score" includes stroke history (3 points), diabetes, and age greater than 75 (1 point each) from the CHA_2DS_2-VASc score (because they were significantly associated with subsequent stroke) while omitting hypertension and heart failure (Box 1).[8,13-15] A history of gastrointestinal bleeding has been shown to predict future events and has been included in the risk score (subtract 1 point).[16] It is proposed to consider OAC when the Dialysis Risk Score is ≥2. The authors reported only 44% of Valkyrie trial participants had an indication for OAC based on this alternative method.[13]

With the potential advent of DOACs, there is an urgent need to better understand the pathophysiologic relationship and establish robust predictors of thromboembolic risk beyond the CHA_2DS_2-VASc score in people with AF and kidney failure.

AF Type and Burden: A Dose–Response Relationship for Stroke Risk?

Conventionally, AF is regarded as a binary entity (present or absent) and is a risk factor for stroke irrespective of AF type and burden. This is based on the understanding that atrial stasis promotes thrombogenesis and embolism. Recent data have challenged this paradigm of risk equivalence, and it is biologically plausible that spending more time in AF leads to increased thromboembolic risk.

Current guidelines classify AF by pattern—first-diagnosed AF, paroxysmal AF (<7 days duration), persistent AF (≥7 days duration), long-standing persistent AF (>12 months duration where rhythm control strategy is adopted), and permanent AF (AF that is accepted for rate control strategy).[8] However, there is significant heterogeneity within these groups. Asymptomatic episodes can go undetected, and paroxysmal AF may include a range of frequency, duration, and overall AF burden. Prognostic significance of AF burden (whether paroxysmal or subclinical) remains unclear[17] but may be relevant to stroke risk in the kidney failure population where CHA_2DS_2-VASc scores are high.

Data from cardiac implantable electronic devices (pacemakers, implantable defibrillators, and cardiac resynchronization devices) provide insight into the association between paroxysmal AF burden and stroke events. A linear increase in thromboembolic events has been reported in a retrospective study of 568 people with an implanted pacemaker and paroxysmal AF. This risk exponentially increased when combining AF duration and $CHADS_2$ score (0.8% vs 5%).[18] A similar association was identified with CHA_2DS_2-VASc for clinical risk scoring.[19]

Subclinical AF: The Unknown Risk

Subclinical AF is defined as asymptomatic AF detected on monitoring or on interrogation of a cardiac device, detecting even low levels of AF.[8] Given the high prevalence of structural heart disease and the proarrhythmic environment of kidney failure and kidney replacement therapy, it is plausible that subclinical AF contributes to disproportionately high rates of stroke in this population. Using implantable cardiac monitors in a cryptogenic stroke cohort, the CRYSTAL-AF study first reported an association between subclinical AF and ischemic stroke risk.[20] Meta-analyses of cardiac implantable electronic device cohort studies support this association, although stroke risk was lower than that of clinical AF despite adjustment for CHA_2DS_2-VASc score.[21] However, temporal dissociation has also been reported with <30% of people having an episode of subclinical AF in the 30 days preceding a stroke event, suggesting a more complex relationship.[21]

Recent data suggest that subclinical AF is prevalent in kidney failure. In a study of 50 people treated by hemodialysis who had implantable cardiac monitors, Wong

Box 1. The Dialysis Risk Score Compared With the CHA_2DS_2-VASc Scoring System

The Dialysis Risk Score – An Alternative Anticoagulant Strategy in Hemodialysis[a]		The CHA_2DS_2-VASc Scoring System[b]	
Clinical Characteristic	**Score**	**Clinical Characteristic**	**Score**
Prior TIA/ischemic stroke	3	Congestive heart failure/LV dysfunction	1
Diabetes	1	Hypertension	1
Age >75 y	1	Age ≥75 y	2
Gastrointestinal bleeding <1 y	-1	Diabetes	1
		Stroke/TIA/thromboembolism	2
		Vascular disease	1
		Age 65-74 y	1
		Sex category (female gender)	1

Abbreviations: AF, atrial fibrillation; LV, left ventricular; OAC, oral anticoagulant; TIA, transient ischemic attack.
[a]De Vriese and Heine[13] propose to initiate anticoagulation in AF and hemodialysis when the Dialysis Risk Score is ≥ 2.
[b]Guidelines recommend considering OAC when CHA_2DS_2-VASc score 1 (males) or 2 (females; class IIA) and recommend commencing OAC when CHA_2DS_2-VASc ≥ 2 (males) or 3 (females; class IA).[8,14]

et al[22] first reported AF in 42% of participants monitored over a 12-month period. New AF was identified in 28% with the majority (86%) subclinical or asymptomatic. The Monitoring in Dialysis study[23] supported these findings and further reported a median of 7 days with AF but ranging from 1-161 days.[24] Subclinical AF has not been characterized in peritoneal dialysis cohorts, although there is no difference in AF incidence between hemodialysis and peritoneal dialysis cohorts beyond 90 days after dialysis commencement.[25] In a population where CHA_2DS_2-VASc scores are high, the interaction between clinical risk factors and AF type or burden may inform stroke risk.[26]

Relevance of AF Burden to Kidney Failure

The relationship between established structural heart disease and atrial remodeling, vascular risk factors, thrombogenesis, and the proarrhythmic milieu of kidney failure is complex. Chronic volume overload in kidney failure may activate the sympathetic and renin-angiotensin-aldosterone system or induce atrial and ventricular stretch with atrial electrical remodeling. The cyclical volume and electrolyte changes of hemodialysis may precipitate intradialytic or peridialytic AF. Some episodes will self-terminate, but subclinical AF may go unrecognized for extended periods of time.[24] The prognostic significance of these episodes is unclear, and there is likely to be significant clinician variability in OAC practice in this population.

Current guidelines do not recommend the use of AF burden in anticoagulation decision making.[8,14] Yet this practice would consider a 60-year-old man with kidney failure on hemodialysis with hypertension and diabetes with CHA_2DS_2-VASC score of 2 to have a modest stroke risk of 2.2% per year, regardless of whether he had permanent AF, 10 paroxysmal episodes a year, or 2 short-lived self-terminating episodes. There is increasing evidence that risk is not equivalent across paroxysmal and nonparoxysmal AF,[27] and the American Heart Association concluded that patients with nonparoxysmal AF have a higher risk of stroke than those with paroxysmal AF.[17] It is likely there is a significant difference in stroke risk across the 3 scenarios presented with relevance to the kidney failure (and particularly hemodialysis) population who are frequently exposed to arrhythmic precipitants. A study of 40 patients treated by kidney replacement therapy who received a dual-chamber implantable cardioverter defibrillator in the Implantable Cardioverter-Defibrillator in Dialysis Patients (ICD-2) trial demonstrated an association between volume removal and dialysate potassium concentration,[28] although this was not replicated in the Monitoring in Dialysis study using implantable cardiac monitors.[24] This also raises the potential for stroke risk to be dynamic according to volume status, electrolyte changes, and dialysis prescription. The concept of cardioprotective hemodialysis to minimize cardiovascular harm is not new, but attention to dialysis prescription to modulate AF burden and stroke risk warrants consideration.

Appropriate risk stratification in kidney failure is the missing link in the management of AF and cardiovascular risk. In the general population, Kaplan et al[29] demonstrated that AF burden further stratified stroke risk in the intermediate-risk population. In people with CHA_2DS_2-VASc score 2, stroke risk crossed an actionable threshold of >1% annualized stroke risk with >23.5 hours of maximum daily AF duration.[29] People with low CHA_2DS_2-VASc scores and long duration of AF remained low risk.[29] An actionable stroke risk has not been identified in people with kidney failure but would be useful in anticoagulation decision making.

BLEEDING RISK IN KIDNEY FAILURE

Uremic platelet dysfunction, endothelial dysfunction, and anemia may all contribute to the increased bleeding risk in people with kidney failure.[30] Bleeding rates are higher in the hemodialysis population at 60.8/1000 person-years compared with people on peritoneal dialysis at 34.6/1000 person-years.[31] Bleeding rates are 0.9/1000 person-years in the general population.[32] Bleeding risk scores (HAS-BLED, ORBIT, $HEMORR_2HAGES$, and ATRIA) all include CKD as a risk factor and do not provide discriminative value in kidney failure.[8,14,33] The strongest predictors of bleeding are a history of prior bleeding or gastrointestinal bleeding in the past 12 months,[16,31] and their inclusion in the design of future risk scores will be important.[13] Frequent pragmatic assessments are essential in this population.

ORAL ANTICOAGULATION IN KIDNEY FAILURE

Anticoagulation use for AF in people with kidney failure has long been controversial. Yet clinicians continue to endeavor to mitigate the risks of AF-related harm. The US Renal Data System reported 52.1% of people receiving dialysis were receiving OAC in the setting of AF despite uncertainty in the evidence.[34]

Evidence for VKAs

Observational studies and meta-analyses over the last decade have reported mixed outcomes of VKA use in kidney failure. The SWEDEHEART registry of people with acute myocardial infarction and associated AF reported VKAs were associated with a reduced risk of a composite cardiovascular end point, including ischemic stroke.[35] These findings were consistent across CKD strata, including a small kidney failure cohort (n=478) with an estimated glomerular filtration rate <15 mL/min/1.73 m^2.[35] There was no increased risk of bleeding in this study, but this may reflect the >75% time spent in prothrombin therapeutic range,[35,36] which is difficult to reproduce in people treated by hemodialysis.[37] Recent

kidney failure DOAC trials reported the time in therapeutic range to only be 44%-50.7%.[3,4,38]

A pooled meta-analysis of 15 studies in kidney failure and with AF did not report a reduction in ischemic stroke or all-cause mortality with VKA therapy but a significantly increased risk of hemorrhagic stroke (without an increase in the overall risk of bleeding).[2] Another meta-analysis of 12 studies, including people on peritoneal dialysis, kidney transplant recipients, and people with stage 5 CKD only, reported a nonsignificant trend toward reduction in ischemic stroke with a significant increase in total bleeding risk and no effect on mortality.[39]

The association between VKAs and accelerated vascular calcification also warrants careful consideration.[40] Aside from inhibiting VKA-dependent coagulation factors, off-target effects include interfering with vitamin K-dependent inhibitors of vascular arterial media calcification. Retrospective and cross-sectional studies report an association between VKA therapy and measures of vascular calcification,[40] including reduced aortic compliance in hemodialysis cohorts.[41] Arterial stiffness may be associated with left ventricular hypertrophy, diastolic dysfunction, and heart failure, further contributing to cardiovascular burden in kidney failure. Another major deterrent is calciphylaxis, which is frequently associated with VKA use,[42] characterized by aggressive cutaneous calcification, necrotic ulceration, and infection, and has an annual mortality rate of up to 67%.[43]

Observational data in this area should be interpreted with caution. Two RCTs comparing VKAs with no OAC and assessing stroke and bleeding risk are ongoing (AKDIAL [Oral Anticoagulation in Haemodialysis Patients], NCT02886962; and DANWARD [The Danish Warfarin-Dialysis Study], NCT03862859) and will provide valuable data.

DOACs: Emerging Evidence for Safety

With minimal renal clearance, rivaroxaban and apixaban are the 2 DOACs potentially suitable for use in people with kidney failure and have been studied in hemodialysis cohorts. Based on pharmacokinetic studies alone, apixaban (5 mg or 2.5 mg twice daily)[44] and rivaroxaban (15 mg daily)[45] were both approved for use by the US Food and Drug Administration in people with creatinine clearance (CrCl) <25 mL/min, including dialysis-dependence, unless adjustments are indicated by age greater than or equal to 80 years or weight ≤60 kg. The European Medicines Agency and Therapeutic Goods Association in Australia have not, to date, approved them for use in people with CrCl <15 mL/min.

Real world data supports the pharmacokinetic evidence for safety in kidney failure. A retrospective study of people with stage 4 and 5 CKD (88% stage 5 CKD or dialysis-dependent) found that rivaroxaban use <20 mg was associated with a 32% reduction in major bleeding compared with VKA, with no significant difference in stroke incidence.[46] A US Renal Data System propensity score-matched cohort study reported apixaban use was associated with a 28% reduction in major bleeding compared with warfarin use with no difference in stroke rates between the 2 cohorts.[47] Another study reported apixaban use was associated with at least 32% lower risk of bleeding compared with warfarin.[48] Label-concordant dosing may provide a mortality benefit compared with reduced-label dosing.[48]

Randomized trials of DOACs in the hemodialysis population have recently been completed and provide supportive safety data (Table 1).[3,4,38] In 132 people on hemodialysis, the Valkyrie extension study with median 1.88 years of follow-up reported a 63% reduction in fatal and nonfatal cardiovascular events in the pooled rivaroxaban group compared with VKAs. In a high thrombotic risk group (median age 80, median CHA_2DS_2-VASc score 5, and history of stroke 30%), the event rate was high in both the VKA group (63.8/100 person-years) and pooled rivaroxaban groups (23.8/100 person-years). There were no differences in secondary outcomes of all-cause and cardiovascular mortality or risk of stroke. The risk of major bleeding was reduced by 56% in the pooled rivaroxaban group compared with VKAs.[3]

The investigator-initiated AXADIA-AFNET 8 (A Randomised Controlled Trial Comparing Apixaban to the Vitamin K antagonist Phenprocoumon in Patients on Chronic Hemodialysis) and prematurely terminated RENAL-AF (Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation) trials compared apixaban with a VKAs in a hemodialysis cohort with AF and CHA_2DS_2-VASc ≥2.[4,38] The AXADIA-AFNET 8 trial randomized 97 participants to either apixaban 2.5 mg twice daily or the VKA phenprocoumon.[4] There were no apparent differences in safety and efficacy between the apixaban and VKA arms over a mean of 1.27 years. Noninferiority could not be shown according to prespecified hierarchical testing procedures for the primary safety outcome (all-cause death and major bleeding events or clinically relevant nonmajor bleeding) but there were no differences in observed event rates (apixaban 22 [45.8%] vs VKA 25 [51.0%] p[NI]=0.16]. Overall safety event rate was high at 36.4/100 person-years with 48.5% of participants experiencing an event during the trial period. There were no differences in the composite outcome of cardiovascular and thrombotic events hazard ratio 0.76 (95% confidence interval, 0.34-1.70)—the majority of events were cardiovascular deaths, and only 1 ischemic stroke/transient ischemic attack was reported.[4]

The RENAL-AF trial aimed to recruit 760 participants but was prematurely terminated due to enrollment challenges.[38] A total of 154 participants were randomized to either apixaban 5 mg twice daily or 2.5 mg twice daily (as per label recommendations) or the VKA warfarin. After a median follow-up of just under 1 year, there were no significant differences in the primary safety or secondary efficacy outcomes between the apixaban and VKA group, with inadequate power to draw any conclusions. Gastrointestinal bleeding was the main contributor to major

Table 1. Completed Randomized Controlled Trials of DOACs in People Receiving Hemodialysis

Study	Recruited Cohort	Intervention	Follow-up	Primary Outcome	Secondary Outcomes
Valkyrie study[3]	132 prevalent HD with AF and $CHA_2DS_2VASc \geq 2$; Median age 80, median CHA_2DS_2VASc 5, stroke history 30%	Rivaroxaban 10 mg or rivaroxaban 10 mg with vitamin K2 compared with VKA	1.88 y (IQR 1.01-3.38)	Composite fatal and nonfatal cardiovascular events; rivaroxaban: HR, 0.41 (95% CI, 0.25-0.68); rivaroxaban with vitamin K2: HR, 0.34 (95% CI, 0.19-0.61)	Efficacy end points: symptomatic limb ischemia: 19 in pooled rivaroxaban group compared with 20 in VKA ($P = 0.008$); no differences in other individual components of the fatal and nonfatal cardiovascular events Safety end point (life-threatening, major, and minor bleeding): pooled rivaroxaban group: HR, 0.44 (95% CI, 0.23-0.85)
RENAL-AF[38]	154 prevalent HD[a] with AF and $CHA_2DS_2VASc \geq 2$; Median age 68 y, median CHA_2DS_2VASc 4, stroke history 19%	Apixaban 5 mg or 2.5 mg twice daily (per label recommendations) vs VKA	0.9 y (IQR not available)	Composite of all-cause death, major bleeding, and clinically relevant nonmajor bleeding (HR, 1.20; 95% CI, 0.63-2.30)	Stroke: apixaban: 3.0% (95% CI, 0.5-9.7); VKA: 3.3% (95% C,I 0.6-10.5) Death: apixaban: 21 events (26%); VKA: 13 events (18%)
AXADIA-AFNET 8[4]	97 prevalent HD[b] with AF and $CHA_2DS_2VASc \geq 2$; Median age 77, median CHA_2DS_2VASc, stroke history not available	Apixaban 2.5 mg twice daily vs VKA	1.27 y (IQR 0.48-1.92)	Composite of all-cause death, major bleeding and clinically relevant nonmajor bleeding; HR, 0.93 (95% CI 0.53-1.65)	Composite of myocardial infarction, ischemic stroke, all-cause death and DVT/PE: HR, 0.76 (95% CI 0.34-1.70)

Abbreviations: AF, atrial fibrillation; CI, confidence interval; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; HD, hemodialysis; HR, hazard ratio; IQR, interquartile range; PE, pulmonary embolism; VKA, vitamin K antagonist.
[a]Trial stopped prematurely due to enrollment challenges. Initial targeted sample size 762 participants to test a noninferiority hypothesis.
[b]Initial recruitment target of 222 participants, but this was amended to test a noninferiority null hypothesis.

bleeding with hemodialysis access site bleeding responsible for the majority of clinically relevant nonmajor bleeding. Similar to the AXADIA-AFNET 8 trial, ischemic stroke was infrequent with only 3 events reported overall, and death was the most common key secondary outcome.[38]

Importantly, RENAL-AF reported pharmacokinetics data at steady state in 49 participants.[38] The observed exposures (12-hour area under the curve) of apixaban 5 mg and 2.5 mg twice daily doses were similar to exposures in participants from the original ARISTOTLE trial[49] with mild to advanced CKD (CrCl 15-90 mL/min). The 12-hour area under the curve in the apixaban 5 mg twice daily dose in RENAL-AF was significantly higher than those with normal kidney function (CrCl ≥90 mL/min). However, the one-year incidence of major or clinically relevant nonmajor bleeding in the apixaban arm was not significantly different to the VKA arm (31.5% vs 25.5%; hazard ratio, 1.25; 95% confidence interval, 0.63-2.30).[38]

Randomized trial data now clearly demonstrate the disproportionately high mortality and bleeding risk on anticoagulation (Fig 1); 22%-26% of RENAL-AF participants had a bleeding event in under 1 year of follow-up[38] even in excess of observational data.[47] This needs to be carefully weighed against reported ischemic stroke (5.2/100 person-years) and mortality rates (26.9/100 person-years).[6] In the absence of an RCT with a non-anticoagulated control arm, it is uncertain what proportion of bleeding is attributable to anticoagulation. The Strategies for the Management of Atrial Fibrillation in patiEnts receiving Dialysis (SAFE-D; NCT03987711) trial comparing VKA with apixaban and no anticoagulation is ongoing. The upcoming Stroke Prophylaxis With Apixaban in Chronic Kidney Disease Stage 5 Patients with Atrial Fibrillation (SACK; NCT05679024) trial comparing apixaban 2.5 mg twice daily with no oral anticoagulation will include people on kidney replacement therapy and those with estimated glomerular filtration rate <15 mL/min/1.73 m^2 not on kidney replacement therapy.

Clinical Challenges and Implications for Management

Limited data in advanced CKD allow shared decision making between the clinician and patient, particularly in cases of declining kidney function where treatment decisions may be difficult (Table 2).[2-4,8,10,13,50,51] However, guideline recommendations in kidney failure are inconsistent given clinical equipoise (Table 3)[8,26,33] and have typically been directed by studies in the hemodialysis population. It is important to note the absence of data to guide management of people on peritoneal dialysis. The anticoagulation threshold for net clinical benefit in people with kidney failure and AF has not been established and may be different for people treated by hemodialysis or peritoneal dialysis. Some clinicians may

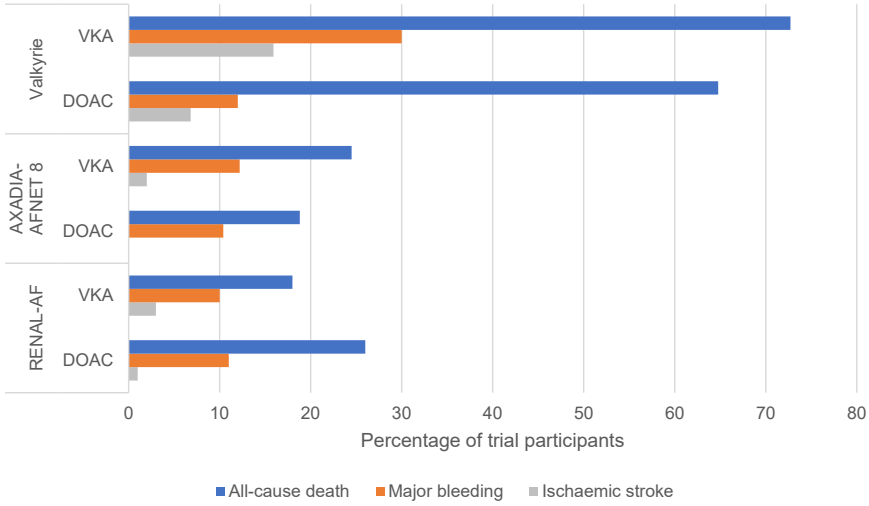

Figure 1. Comparison of stroke, major bleeding, and all-cause death rates[a] in randomized controlled trials of DOACs in people receiving hemodialysis. Abbreviations: DOAC, direct oral anticoagulant; VKA, vitamin K antagonist. [a]Event rates have been reported to allow for available data. The event rates may reflect the median follow-up across the Valkyrie (1.88 years), AXADIA-AFNET 8 (1.27 years), and RENAL-AF (0.9 years) trials.

consider overall bleeding risks to be prohibitively high, considering competing risks of mortality in the elderly and comorbid. Identifying robust markers of thromboembolic risk will be imperative to establish if there is any role for anticoagulation in people with kidney failure with AF.

Perioperative anticoagulation management will be an important consideration to transplant nephrologists and

Table 2. Summary Practice Points Across the Spectrum of Chronic Kidney Disease

	Practice Points
General population[8]	• A risk factor approach to stroke risk assessment recommended, using the CHA_2DS_2VASc score to initially identify people at "low stroke risk" (score = 0 in men or 1 in women) who should not be offered OAC • OAC is recommended for stroke prevention in people with AF with CHA_2DS_2VASc ≥2 in men or ≥3 in women • In people who are eligible for OAC, DOACs are recommended in preference to VKAs (excluding people with mechanical heart valves or mitral stenosis) • A structured risk-score-based bleeding risk assessment (such as the HAS-BLED) is recommended to identify nonmodifiable and address modifiable bleeding risk factors • Stroke and bleeding risk reassessment is recommended at periodic intervals to inform treatment decisions and address potentially modifiable bleeding risk factors • Clinical pattern of AF (ie, first detected, paroxysmal, persistent, or permanent) should not condition the indication to OAC use
Advanced CKD (15-29 mL/min/1.73 m^2)	• Commonly used stroke and bleeding risk assessment scores did not include people with advanced CKD in validation cohorts, and predictive performance is poor[10] • There is little randomized data on DOAC use in advanced CKD, and treatment decisions in people with declining kidney function is challenging • Apixaban may be used down to a CrCl of 25 mL/min based on the inclusion criteria of the ARISTOTLE trial and subgroup analysis[50] • Observational cohort data suggests rivaroxaban may efficacious and safe when used in CrCl <30 mL/min compared with VKA use[51]
Kidney failure (eGFR <15 mL/min/1.73 m^2)	• Stroke and bleeding risk are both disproportionately high in kidney failure • The Dialysis Risk Score[13] may be used to identify people with kidney failure who may derive net clinical benefit from OAC • VKAs should only be used in select people who may derive substantial benefit without significant bleeding risk. Meta-analyses of observational data report increased major bleeding risk without significant reduction in ischemic stroke or mortality risk.[2] • Apixaban and rivaroxaban may be used in kidney failure based on limited data suggesting equivocal or reduced bleeding risk compared with VKAs.[3,4] Due to underpowered trial data, efficacy data for stroke risk reduction remains outstanding.

Abbreviations: AF, atrial fibrillation; CKD, chronic kidney disease; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; OAC, oral anticoagulation; VKA, vitamin K antagonist.

Table 3. Clinical Guideline Recommendations on the Utility of Anticoagulation in Chronic Kidney Disease Categories

	AHA[14]	ESC[8]	KDIGO[33]
CrCl 30-49mL/min	DOACs are recommended over warfarin in DOAC-eligible patients. Use apixaban, dabigatran, or rivaroxaban according to dose reduction recommendation.	DOACs are recommended over warfarin in DOAC-eligible patients. Use apixaban, dabigatran, or rivaroxaban according to dose reduction recommendation.	DOACs are recommended over warfarin in DOAC-eligible patients. Use apixaban, dabigatran, or rivaroxaban according to dose reduction recommendation.
CrCl 15-29mL/min	DOACs are recommended over warfarin in DOAC-eligible patients. Use apixaban, dabigatran, or rivaroxaban according to dose reduction recommendation.	Consider warfarin based on limited clinical data. Use apixaban 2.5 mg twice daily or rivaroxaban 15 mg daily with caution. Do not use dabigatran.	Consider warfarin, apixaban 2.5 mg twice daily or rivaroxaban 15 mg daily. No dabigatran recommendation.
CrCl<15mL/min including on kidney replacement therapy	Consider warfarin based on limited clinical data; consider apixaban 2.5 mg twice daily or rivaroxaban 15 mg daily with limited clinical safety data.	No specific recommendation regarding warfarin. Do not use DOAC.	Equipoise for warfarin use based on observational and meta-analysis data; consider apixaban 2.5 mg twice daily or rivaroxaban 15 mg daily with limited clinical safety data.

Abbreviations: AHA, American Heart Association; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; ESC, European Society of Cardiology; KDIGO, Kidney Disease: Improving Global Outcomes.

surgeons. Reversal of VKAs is relatively simple and has been managed safely for decades, but evidence for DOAC reversal is predominantly in elective surgery or in major bleeding and emergent invasive procedures. Anti-Xa assays can be used to exclude clinically relevant concentrations of factor Xa, but DOAC assays are not readily available. Prothrombin complex concentrate (plasma-derived concentrate of the vitamin K-dependent clotting factors in their inactive form) and andexanet alfa (recombinant factor Xa) have both been evaluated in rivaroxaban and apixaban-associated major bleeding cohorts,[52-54] but not in emergency surgery.[55]

LEFT ATRIAL APPENDAGE OCCLUSION

Left atrial appendage occlusion is a device-based, nonpharmacologic option that may be an attractive option in kidney failure. The left atrial appendage is believed to be the source of thrombi in >90% of patients with AF-related strokes, and left atrial appendage occlusion is a reasonable alternative in people with contraindications to systemic anticoagulation.[56,57] Data on safety and efficacy remain outstanding, but early reports are promising. A prospective study of 92 people receiving dialysis comparing left atrial appendage occlusion with OAC and no anticoagulation did not report any stroke events in the left atrial appendage occlusion cohort after 2 years of follow-up, with reduced bleeding rates noted when compared with OAC.[58] The WatchAFIB (NCT02039167) and STOPHARM (NCT02885545) trials of left atrial appendage occlusion involving people with stage 4/5 CKD and those on hemodialysis were both terminated because of slow recruitment. A prospective observational study of the Watchman left atrial appendage occlusion device (WATCH-HD; NCT03446794) and an RCT comparing standard care with the Amplatzer Cardiac Plug (LAA-KIDNEY; NCT05204212) in people with kidney failure is ongoing.

FACTOR XI INHIBITORS

There is increasing evidence that factor XI is essential for thrombosis but may be less relevant to hemostasis. Factor XI inhibitors may be appealing anticoagulants in populations who are at high risk of bleeding, including those with kidney failure.[59] Thrombosis is an intravascular process where factor XI is essential for thrombus expansion and stabilization via the intrinsic coagulation pathway. In contrast, hemostasis is believed to be predominately mediated by the extrinsic pathway where vessel injury triggers rapid thrombin generation without need for feedback to factor XI.[59] People with congenital factor XI deficiency rarely experience spontaneous bleeding and have a lower risk of thrombosis, which is correlated with factor XI levels without an associated increase in bleeding events.[60]

Phase 2 factor XI inhibitors studies have shown proof-of-concept, with a 40%-50% reduction in venous thromboembolism and 59% reduction in bleeding compared with enoxaparin as standard of care in the elective hip and knee replacement population.[61] In hemodialysis, phase 2 RCTs of factor XI antisense inhibitors fesomersen (BAY 2976217; NCT04534114) and IONIS-FXI RX (ISIS 416858; NCT03358030) are recently completed and reportedly are well tolerated and safe, although the results are yet to be published. Phase 1 (NCT03787368) and phase 2 (NCT04523220) studies of intravenous and subcutaneous osocimab (human monoclonal antibody) are ongoing in the hemodialysis population.

CONCLUSION

Management of AF-related complications in people with kidney failure is a common clinical conundrum. Thromboembolic risk is high, but the extent to which AF influences stroke risk is uncertain, and clinicians have a limited armamentarium to improve outcomes for this population. Recent randomized trial data report an improved safety profile for DOACs compared with VKA anticoagulation in people on hemodialysis, although overall bleeding risk is high. It follows that dedicated risk prediction to identify people at high thromboembolic risk in kidney failure is vitally important. AF burden has been shown to refine stroke risk in general AF cohorts. Variability in AF burden may translate to a dynamic stroke risk in people receiving dialysis, further challenging clinical decision making, and is a promising avenue of investigation in kidney failure.

ARTICLE INFORMATION

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