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CURRENT OPINION

Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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Introduction

Patients with chronic kidney disease (CKD) are predisposed to heart rhythm disorders, including atrial fibrillation (AF)/atrial flutter, supraventricular tachycardias, ventricular arrhythmias, and sudden cardiac death (SCD). While treatment options, including drug, device, and procedural therapies, are available, their use in the setting of CKD is complex and limited. Patients with CKD and end-stage kidney disease (ESKD) have historically been under-represented or excluded from randomized trials of arrhythmia treatment strategies,[1] although this situation is changing.[2] Cardiovascular society consensus documents have recently identified evidence gaps for treating patients with CKD and heart rhythm disorders.[3–7]

To identify key issues relevant to the optimal prevention, management, and treatment of arrhythmias and their complications in patients with kidney disease, Kidney Disease: Improving Global Outcomes (KDIGO) convened an international, multidisciplinary Controversies Conference in Berlin, Germany, titled *CKD and Arrhythmias* in October 2016. The conference agenda and discussion questions are available on the KDIGO website (http://kdigo.org/conferences/ckd-arrhythmias/; 13 February 2018).

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Atrial fibrillation and stroke in kidney disease

Epidemiology

Atrial fibrillation is the most common sustained arrhythmia.[8] Chronic kidney disease affects 10% of adults worldwide,[9] and patients with CKD have an increased burden of AF compared with those without CKD (Supplementary material online, *Table S1*). The prevalence of AF is high: estimates range from 16% to 21% in CKD patients not dependent on dialysis[10–12] and 15% to 40% in patients on dialysis (Supplementary material online, *Table S1*).[13–18] Chronic kidney disease and AF share many risk factors, making it difficult to discern the contributions of individual factors to either condition or associated outcomes (*Figure 1*). For non-dialysis CKD, there seems to be an independent relationship between CKD and the risk of AF,[19–25] although this association has not been well characterized across the spectrum of estimated glomerular filtration rate (eGFR) or proteinuria.[13,14,26,27] In the USA, both incidence and prevalence of AF are increasing among haemodialysis patients,[27,28] which could be because of older age of patients, better ascertainment of AF, and improved survival after vascular events.

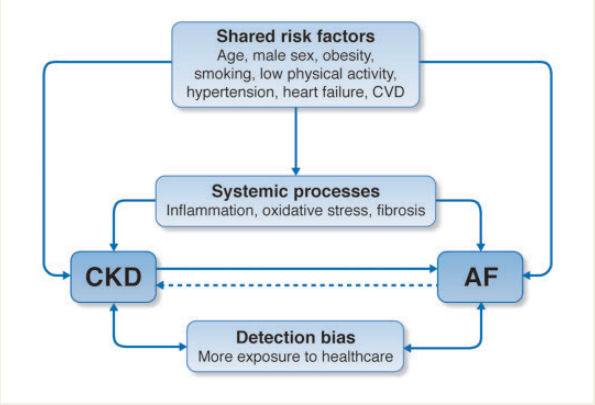

Figure 1 Relationship between chronic kidney disease and atrial fibrillation: shared risk factors and outcomes. Chronic kidney disease and atrial fibrillation share a number of risk factors and conditions that promote their incidence, possibly via systemic processes such as inflammation, oxidative stress, or fibrosis. It is established that chronic kidney disease increases the incidence of atrial fibrillation and there is some evidence to suggest that atrial fibrillation also increases chronic kidney disease progression. When examining the strength of these associations, we acknowledge the potential impact of detection bias in observational studies where more frequent exposure to healthcare likely prompts more clinical findings in this comorbid population. AF, atrial fibrillation; CKD, chronic kidney disease; CVD, cardiovascular disease.

Consequences of atrial fibrillation in chronic kidney disease

The risk of stroke is elevated in non-dialysis[29–32] and dialysis[29,31,33] CKD (Supplementary material online, *Table S2*). Separately, both CKD and AF are risk factors for stroke, but it is currently unknown whether the prognostic significance of CKD markers and AF is independent or interdependent. The association between AF and CKD may be bidirectional; AF may predict new-onset low GFR and proteinuria.[21] In CKD, the adjusted risk ratios of stroke with AF have varied considerably across CKD subpopulations, ranging from 4.2 in women in the general population,[34] 1.3 in dialysis patients,[33,35] and with modestly significant (1.4)[36] and non-significant[37] associations after kidney transplantation. These differences may be due to greater competing risk of death in more advanced CKD,[35] a higher baseline risk of stroke in CKD without AF, or a higher prevalence of unrecognized AF.

AF increases the risk of incident CKD and progression to ESKD[21,38–40] (Supplementary material online, *Table S3*), and increases risk of death in patients with non-dialysis CKD and those on dialysis.[13,35,41,42] Other outcomes related to AF, including heart failure, SCD, and myocardial infarction (MI), require further research. The contribution of AF as a mediator of stroke in CKD, as well as the stroke subtypes observed, requires further study. The competing risk of death in CKD may reduce the importance of the contribution of AF to stroke, which could mitigate the effectiveness of some stroke prevention strategies.[35]

Stroke risk scores

The predictive value and calibration of the $CHADS_2$ and CHA_2DS_2-VASc stroke prediction scores have only been evaluated in dialysis patients, in which performance appears to be similar to their performance in the general population.[16,33,43,44]

Inclusion of CKD in risk scores to improve stroke prediction has demonstrated variable results. Adding two points for creatinine clearance < 60 mL/min to $CHADS_2$ (called R_2CHADS_2) improved net reclassification index (NRI) but not C-statistic in one large study using external validation[30] but did not improve NRI or C-statistic in other studies.[45,46] The ATRIA score, which includes terms for GFR < 45 mL/min/1.73 m^2 and proteinuria, demonstrated improved NRI and borderline improvement in C-statistic compared with $CHADS_2$ and CHA_2DS_2-VASc in external validation,[47] although NRI may not be clinically meaningful.[48] For these reasons and for the potential for categorically recommending oral anticoagulant (OAC) to most patients with CKD without regard to competing risks, CHA_2DS_2-VASc remains the most commonly recommended score for risk stratification,[5,49] and observational data have shown that a treatment threshold of CHA_2DS_2-VASc ≥ 2 is associated with OAC benefit, even in CKD.[50]

Bleeding risk scores

The HAS-BLED, ORBIT, $HEMORR_2HAGES$, and ATRIA bleeding risk scores all include CKD measures. Although the formal use of these bleeding risk scores has not been recommended by the majority of professional society guidelines,[49,51] the increased risk of bleeding with and without OAC in CKD is well described and should be considered in clinical decision making.

Stroke prevention and oral anticoagulation

The pathophysiologic mechanisms responsible for stroke/thromboembolism in patients with CKD and AF are multifactorial and poorly

Table 1 Evidence from randomized trial data regarding therapeutic anticoagulation on the basis of kidney function[4,63,64]

eCrCl (mL/min)[a]	Warfarin	Apixaban[b]	Dabigatran	Edoxaban[c]	Rivaroxaban
>95	Adjusted dose (INR 2–3)	5 mg b.i.d.	150 mg b.i.d.	60 mg QD[d]	20 mg QD
51–95	Adjusted dose (INR 2–3)	5 mg b.i.d.	150 mg b.i.d.	60 mg QD	20 mg QD
31–50	Adjusted dose (INR 2–3)	5 mg b.i.d.(eCrCl cut-off25 mL/min)	150 mg b.i.d. or 110 mg b.i.d.[e]	30 mg QD	15 mg QD

INR, international normalized ratio.
[a]Cockcroft-Gault estimated creatinine clearance (eCrCl).
[b]Apixaban dose modification from 5 mg b.i.d. to 2.5 mg b.i.d. if patient has any two of the following: serum creatinine ≥1.5 mg/dL, age ≥80 years, or body weight ≤60 kg.
[c]In the ENGAGE-AF TIMI 48 study, the dose was halved if any of the following: eCrCl of 30–50 mL/min, body weight ≤60 kg, or concomitant use of verapamil or quinidine (potent P-glycoprotein inhibitors).
[d]This dose has not been approved for use by the US Food and Drug Administration in this category of kidney function.
[e]In countries where 110 mg b.i.d. is approved, clinicians may prefer this dose after clinical assessment of thromboembolic vs bleeding risk. This dose has not been approved for use by the US Food and Drug Administration.

understood; the precise contribution of cardio-embolic vs. non-cardioembolic factors is unclear. Atrial fibrillation may be a direct cause of cardio-embolic stroke, a risk marker of ischaemic stroke including atherothrombotic subtypes, and in rare cases, a consequence of stroke.[52]

Chronic kidney disease patients with estimated creatinine clearance of 30–50 mL/min

Pivotal randomized controlled trials (RCTs) have established that direct oral anticoagulants (DOACs) are non-inferior to warfarin among patients with Cockroft–Gault estimated creatinine clearance (eCrCl) of 30–50 mL/min (for apixaban, 25–50 mL/min).[53–56] However, there is insufficient evidence to recommend any one DOAC over any other in this population because no head-to-head trials have directly compared individual DOACs[57–62] (*Table 1*). Indirect comparisons are challenging because these trials differed in inclusion criteria and outcome definitions.

Although efficacy (prevention of stroke and systemic embolism) may merely be non-inferior to warfarin, the safety profile of DOACs compared to warfarin does appear to be superior. In all pivotal RCTs, DOACs have been associated with a significant reduction (about 50%) in risk of intracranial haemorrhage compared to warfarin. Among patients with eCrCl between 25 and 50 mL/min, treatment with apixaban and edoxaban resulted in significantly fewer major bleeding events compared with warfarin (*Figure 2*).[63] Although these observations do not necessarily indicate the superiority of apixaban and edoxaban relative to other DOACs, it may be helpful to clinicians when treating patients at particularly high-bleeding risk or low time in therapeutic range (TTR) values while receiving warfarin or other vitamin K antagonists (VKAs).

Chronic kidney disease G4, G5, and G5D

In the absence of trial data, the results from observational studies on the efficacy and safety of anticoagulation for stroke prevention in CKD patients with eCrCl < 30 mL/min not on dialysis are conflicting as they are for CKD G5D (*Table 2*).[65] There is insufficient high-quality evidence to recommend warfarin or other VKAs for prevention of stroke in CKD G5D patients with AF, especially when balancing the significant risks of bleeding, accelerated vascular calcification, and calcific uraemic arteriopathy associated with VKA therapy.[66] A pooled meta-analysis of 56 146 CKD G5D patients with AF from 20 observational cohort studies demonstrated an increase in all-cause bleeding associated with VKA therapy without benefit in reduction of all-cause stroke or ischaemic stroke.[65] Yet, a well-conducted observational analysis of acute MI patients with AF from the SWEDEHEART registry (2003–2010) found that VKA therapy was associated with a reduced risk of a composite of death, MI, and ischaemic stroke with no increase in bleeding risk across the spectrum of CKD.[67] The high time in international normalized ratio (INR) TTR in Sweden (>75%) likely contributed to these findings and has been difficult to replicate in other health systems.[68] A large US health care system analysis found that CKD severity is associated with decreased TTR despite similar INR monitoring intensity.[69] These findings suggest that TTR is more likely to be poor in CKD and can mediate the increased stroke and bleeding risk in CKD.[70] VKAs may lead to CKD via repeated subclinical glomerular haemorrhages[71] or through accelerated tissue or vascular calcification.[72]

The US Food and Drug Administration recently approved mention of the doses of apixaban 5 mg twice daily (with contingent dose modifications) and rivaroxaban 15 mg daily in CKD G5 and G5D (and dabigatran 75 mg orally twice daily for eCrCl 15–30 mL/min) on the respective labels based on single/limited dose pharmacokinetic and pharmacodynamic data with no clinical safety data.[73–76] The conference attendees suggest consideration of the lower dose of apixaban 2.5 mg orally twice daily in CKD G5/G5D to reduce bleeding risk until clinical safety data are available, an approach supported by a recent pharmacokinetic study comparing the two doses.[77] Recognizing that many CKD patients would likely qualify for a dose reduction to apixaban 2.5 mg orally twice daily anyway (if age ≥80 years or body weight ≤ 60 kg), this suggestion honours the 'first do no harm' principle, while acknowledging the lack of clinical efficacy or safety data in this regard (*Table 2*).

Randomized clinical trials are particularly needed to evaluate VKA use in patients with CKD G5D. A clinical trial evaluating VKAs vs. no oral anticoagulation (AVKDIAL, NCT02886962) is planned. It is not known whether DOACs have an advantage over VKAs in CKD G5D patients with AF. The AXADIA (NCT02933697) and RENAL-AF (NCT02942407) trials of apixaban vs. VKAs in ESKD are enrolling in Germany and USA.

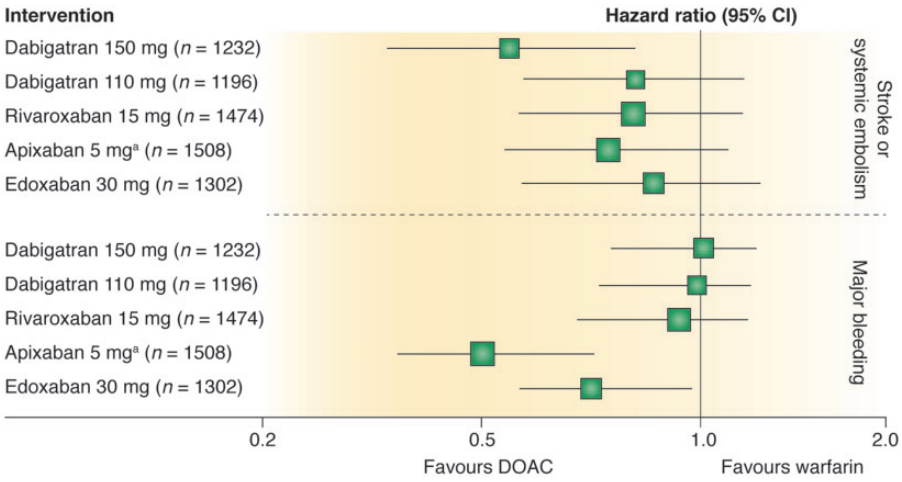

Figure 2 Efficacy and safety of direct oral anticoagulants (DOACs) vs. warfarin in the subgroup of patients with moderate chronic kidney disease from randomized controlled trials in atrial fibrillation. Comparison of hazard ratios and 95% confidence intervals for primary efficacy and safety outcomes for 150 and 110 mg dabigatran twice daily, 15 mg rivaroxaban once daily, 5 mg apixaban twice daily, and 30 mg edoxaban once daily. Chronic kidney disease was defined as estimated creatinine clearance of 30 to 49 mL/min or as 25 to 49 mL/min for apixaban. [a]Apixaban 2.5 mg twice daily if patient had any two of the following: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥1.5 mg/dL. Reproduced from Qamar and Bhatt[63] with permission from the publisher.

Table 2 Chronic kidney disease categories lacking randomized clinical trial data on the utility of anticoagulation[4,63,64]

eCrCl (mL/min)[a]	Warfarin	Apixaban[b]	Dabigatran	Edoxaban	Rivaroxaban
15–30	Adjusted dose for INR 2–3 could be considered	2.5 mg PO b.i.d. could be considered	Unknown (75 mg PO b.i.d.)[c,d]	30 mg QD[e] could be considered	15 mg QD could be considered
<15 not on dialysis	Equipoise based on observational data and meta-analysis	Unknown (2.5 mg PO b.i.d.)[c]	Not recommended	Not recommended	Unknown (15 mg QD)[c]
<15 on dialysis	Equipoise based on observational data and meta-analysis	Unknown (2.5 mg PO b.i.d.)[c]	Not recommended	Not recommended	Unknown (15 mg QD)[c]

INR, international normalized ratio.
Dosing of direct oral anticoagulants (DOACs) based solely on limited pharmacokinetic and pharmacodynamic data (no randomized efficacy or safety data exist).
[a]Cockcroft-Gault estimated creatinine clearance.
[b]Apixaban dose needs modification to 2.5 mg b.i.d. if patient has any two of the following: serum creatinine ≥1.5 mg/dL, age ≥80 years, or body weight ≤60 kg.
[c]DOAC doses listed in parenthesis are doses that do not currently have any clinical safety or efficacy data. The doses of DOACs apixaban 5 mg b.i.d.[b], rivaroxaban 15 mg QD and dabigatran 75 mg b.i.d. are included in the United States Food and Drug Administration approved labelling based on limited dose pharmacokinetic and pharmacodynamics data with no clinical safety data. We suggest consideration of the lower dose of apixaban 2.5 mg PO b.i.d. in CKD G5/G5D to reduce bleeding risk until clinical safety data are available.
[d]Dabigatran 75 mg available only in the USA.
[e]The dose was halved if any of the following: estimated CrCl of 30–50 mL/min, body weight of ≤60 kg, or concomitant use of verapamil or quinidine (potent P-glycoprotein inhibitors).

Pragmatic considerations while managing anticoagulation in chronic kidney disease

In pivotal RCTs, study eligibility and DOAC dose assignments were based on kidney function as assessed using eCrCl (Cockcroft-Gault). However, in clinical practice, other measures such as eGFR are routinely used. Given the imprecision in measures for estimating kidney function, individualization of DOAC dosing based on either method is reasonable.[78–80] Important safety concerns, mainly increased fatal or non-fatal bleeding, emerged after the early 'off-label' prescriptions of dabigatran and rivaroxaban in patients with CKD G5D.[81–83] A recent study of 1473 AF patients with renal indication for dose reduction found that 43% were potentially overdosed with DOACs, resulting in higher bleeding risk.[84] These adverse signals suggest the

Table 3 Recommendations for discontinuation of direct oral anticoagulant prior to elective procedures, according to the risk of bleeding of any specific procedure intervention (low vs. high risk procedures)

	Dabigatran		Apixaban–Edoxaban–Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 or 24 h after last intake)			
	Low risk	High risk	Low risk	High risk
CrCl ≥ 80 mL/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–80 mL/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h
CrCl 30–50 mL/min[a]	**≥48 h**	**≥96 h**	≥24 h	≥48 h
CrCl 15–30 mL/min[a]	No official indication	No official indication	**≥36 h**	**≥48 h**
CrCl < 15 mL/min	No official indication for use There is no need for bridging with LMWH/UFH			

Bold values deviate from the common stopping rule of ≥24 h low risk, ≥48 h high risk. Low risk is defined as a low frequency of bleeding and/or minor impact of a bleeding. High risk is defined as a high frequency of bleeding and/or important clinical impact. Adapted from Heidbuchel *et al.*[4]
CrCl, creatinine clearance; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; UFH, unfractionated heparin.
[a]Many of these patients may be on the lower dose of dabigatran (110 mg b.i.d.) or apixaban (2.5 mg b.i.d.), or have to be on the lower dose of rivaroxaban (15 mg OD) or edoxaban (30 mg OD). Dabigatran 110 mg b.i.d. has not been approved for use by the US Food and Drug Administration.

need for systemic measures focused on patient safety to guide clinicians regarding the use of DOACs.[85]

Team-based, multidisciplinary active communication, particularly involving the nephrologist, cardiologist (or cardiac electrophysiologist), primary care physician, and when possible, clinical pharmacist, may be useful to evaluate the risk–benefit of any decision regarding choice of VKA or a DOAC.[5,85]

For CKD patients receiving DOAC therapy, we recommend periodic monitoring of kidney function because decline over time may necessitate dose modification.[86] There are no data to indicate the optimal frequency of monitoring, but it may be clinically reasonable to assess kidney function every 6 to 12 months, (or at least yearly, consistent with professional society guidelines),[5] with more or less frequent monitoring as appropriate based on recency of DOAC initiation, CKD severity, and CKD trajectory. For all CKD patients on anticoagulant therapy, annual re-evaluation of treatment goals and discussion of pros and cons of anticoagulant therapy should be considered.

Periprocedural/perioperative management of DOACs is contingent upon individual agents and eCrCl, for which recommended parameters exist (*Table 3*).[4,87] For patients with CKD G5D on anticoagulants, strategies to reduce bleeding warrant systematic research but may include minimizing heparin with dialysis, use of citrate locks for catheters,[88] consideration of prophylaxis for gastrointestinal bleeding when clinically indicated, tight blood pressure control, and discontinuation of concurrent antiplatelet agents if clinically reasonable.

Anticoagulation reversal protocols are well established for warfarin and VKAs. Idarucizumab has been approved for reversing dabigatran, and andexanet alfa has been developed for reversal of anti-Xa agents. Data specific to reversal in CKD patients are limited.[89]

Antiplatelet therapy for stroke prevention for atrial fibrillation in chronic kidney disease

In a general, mostly non-CKD population, the AVERROES trial of aspirin vs. apixaban was stopped early due to a higher risk of stroke with aspirin but with similar bleeding risk in both groups.[90] However, there is insufficient evidence to recommend single or dual antiplatelet therapy for prevention of stroke/thromboembolism in AF among patients with CKD G4, G5, or G5D, even when OAC is considered undesirable. Similarly, these patients should not receive concomitant antiplatelet therapy while taking anticoagulants, unless there is a specific secondary indication (e.g. recent coronary stent). The duration of concomitant single or dual antiplatelet therapy in those receiving anticoagulants needs to be minimized and individualized based on clinical factors and type of stent.[91]

Left atrial appendage occlusion in chronic kidney disease

The left atrial appendage (LAA) is believed to be the site of thrombus formation for most AF-related cardio-embolic strokes. Circulatory exclusion of the LAA represents a non-pharmacological, device-based therapy for stroke prevention that could conceivably be an option in moderate to high stroke risk in CKD, particularly with contraindications to long-term OAC. Five-year data from two randomized trials of the Watchman® LAA occlusion device demonstrated a reduction in stroke risk comparable to warfarin but with additional reduction in major bleeding.[92] However, CKD prevalence or severity was not reported and could have been under-represented. The majority of patients receiving the device in trials and in practice are continued on dual- or single-antiplatelet drug therapy, which may be associated with higher bleeding risk in CKD. Moreover, enrolled subjects were without contraindications and hence randomized. Registry data of the Amplatzer Cardiac Plug, a similar device, has shown comparable procedural safety in CKD vs. normal kidney function.[93] A randomized trial of LAA occlusion vs. VKAs in CKD Stages 4 and 5 (CKD G4 and G5) is ongoing (https://clinicaltrials.gov/ct2/show/NCT02039167; 13 February 2018).

Rate vs. rhythm control of atrial fibrillation

Indications for a rhythm control strategy in CKD patients mirror those in the general population. The major evidence-based indication

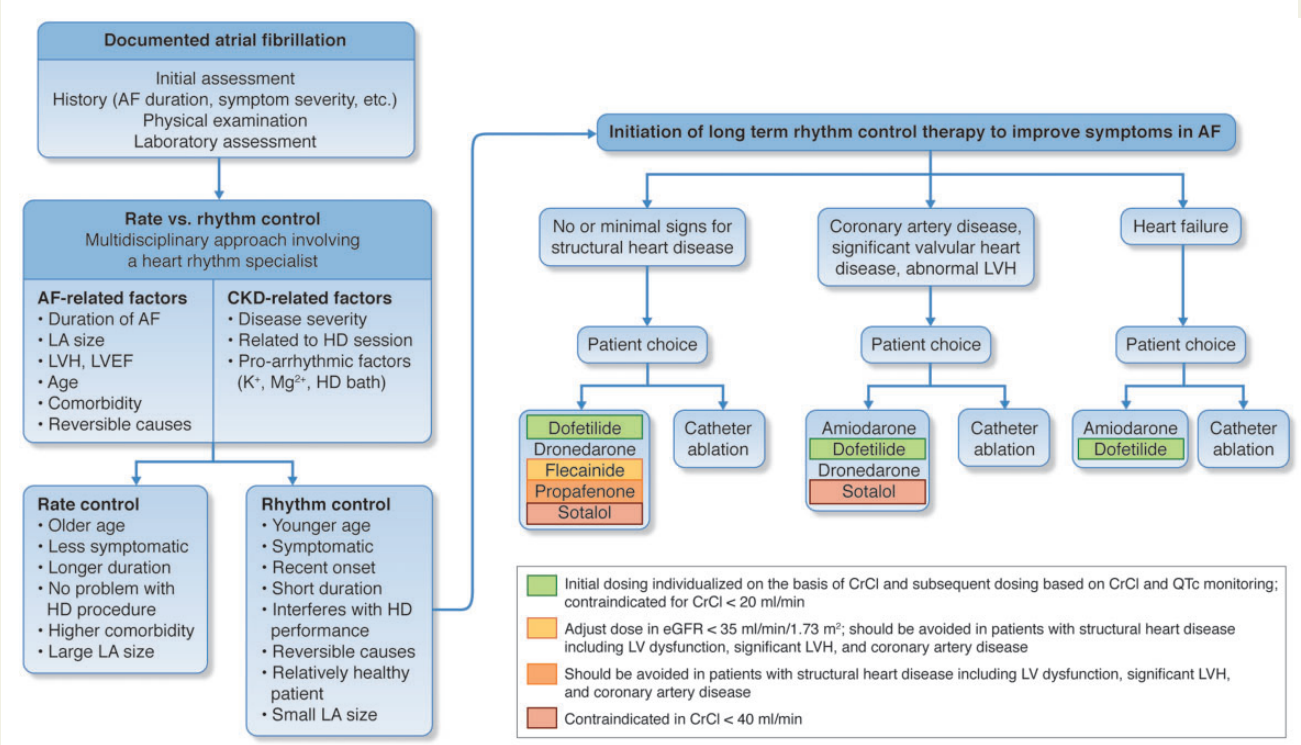

Figure 3 Algorithm for decision-making about rate vs. rhythm control in chronic kidney disease. Especially since chronic kidney disease patients show a lot of specific characteristics regarding history, comorbidities and personal preferences, in each patient an individualized decision should be made. Many aspects should be taken into account: the duration of atrial fibrillation, the symptom severity, renal clearance (risk of toxicity, dialyzability), and potential contraindications for antiarrhythmic drugs due to structural heart disease, which is very frequent in these patients (such as left ventricular hypertrophy, reduced ejection fraction, obstructive coronary artery disease). Moreover, proarrhythmic effects (such as QT prolongation) may be pronounced because of electrolyte imbalances in chronic kidney disease. The figure suggests an algorithm presenting the most relevant criteria that should be incorporated into a multidisciplinary decision-making process, including the treating nephrologist, a heart rhythm specialist, and eventually also physicians of other disciplines. Of note, regardless of which strategy is chosen, oral anticoagulation should always be administered in early stages of chronic kidney disease and at least be considered in advanced stages of chronic kidney disease (see section on Stroke prevention and oral anticoagulation). AF, atrial fibrillation; CKD, chronic kidney disease; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HD, haemodialysis; LA, left atrial; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy. Adapted in part from Kirchhof *et al.*[5]

for a rhythm-control strategy for AF is symptom reduction, although many patients are asymptomatic.[5,49] Older randomized trials have demonstrated that rhythm and rate control strategies are equivalent in terms of their effects on risks of heart failure, stroke, and survival.[94–97] Retrospective analyses have suggested rhythm control with ablation provides superior outcomes, but the evidence is limited. Regardless of which strategy is pursued, anticoagulation should also be continued based on stroke risk (as indicated by the $CHADS_2$ or CHA_2DS_2-VASc score), unless otherwise contraindicated. Additional factors that may favour attempts at rhythm control include difficulty in achieving adequate rate control, younger patient age, tachycardia-mediated cardiomyopathy, first episode of AF, AF that is precipitated by an acute illness or surgery, and patient preference (*Figure 3*).[5,49] Haemodialysis patients with haemodynamic instability due to AF during dialysis sessions may benefit from rhythm control. The impact of its treatment on outcome is unknown.[98] Patients without clear indications for a rhythm control strategy should default to rate control. In the general population of patients with permanent AF and preserved ejection fraction, lenient rate control (i.e. resting heart rate < 110 beats per minute) has been shown to be equivalent to a strict rate control for a combined endpoint including stroke, heart failure, death, and need for pacemaker or implantable cardioverter-defibrillator (ICD).[99]

No RCTs have specifically compared rate vs. rhythm control or strict vs. lenient rate control in patients with CKD or ESKD. In a *post hoc* analysis of the GUSTO III trial, treatment with a rhythm or rate control strategy did not significantly impact short- or long-term mortality regardless of kidney disease status.[100]

Considerations about rate control

Special considerations in CKD include alterations in symptomatology and a potentially increased propensity to develop tachycardia-mediated cardiomyopathy, given the prevalence of structural heart disease. Moreover, the pharmacokinetic and dialyzability of rate control agents in CKD need to be considered (*Table 4*). When the ventricular rate cannot be controlled with medical therapies alone, atrioventricular nodal ablation and pacemaker implantation can be considered. However, the high rates of complications from transvenous devices in haemodialysis patients should enter into the decision-

Table 4 Characteristics of antiarrhythmic drugs for rate control in chronic kidney disease

Drug	Protein binding	Elimination	Dialyzable	Dosing in CKD
Atenolol	5%	Excreted unchanged in urine	Yes	Dose may need to be reduced
Propranolol	>90%	Hepatic metabolism	No	Serum creatinine may increase, but no dose adjustment is needed
Bisoprolol	30%	50% excreted unchanged in urine	No	Dose may need to be reduced in advanced CKD
Metoprolol	12%	Hepatic metabolism	Yes	No dosage reduction needed
Carvedilol	99%	Mainly biliary and 16% urinary	No	Specific guidelines for dosage adjustments in renal impairment are not available; it appears no dosage adjustments are needed
Labetalol	50%	Inactive metabolites excreted in urine (5% unchanged) and bile	No	Dose reduction recommended in the elderly
Verapamil	90%	70% is excreted in the urine and 16% in faeces	No	Dose reduction by 20–25% if CrCl < 10 mL/min, not cleared by haemodialysis
Diltiazem	70–80%	2–4% unchanged drug excreted in the urine	No	Use with caution
Digoxin	20–30%	Main route of elimination is renal (closely correlated with the GFR) with 25–28% of elimination by non-renal routes	No	Dosage adaptation is required, monitoring of serum digoxin levels

Modified from Potpara *et al.*[101] and Weir *et al.*[102]
Metoprolol elimination data from Hoffman *et al.*[103]
Labetalol protein binding data from Drugbank.ca[104] and dialyzability data from in vitro data by Daheb *et al.*[105]
All other dialyzability data from Frishman.[106]
CKD, chronic kidney disease; CrCl, creatinine clearance; GFR, glomerular filtration rate.

making process.[107] Whether leadless pacemakers have a role in this situation remains to be determined.

Considerations about rhythm control

Direct current cardioversion (DCCV) is the most commonly used method of rhythm restoration in patients with persistent AF. The success rate of DCCV been reported to be similar regardless of kidney function.[108] However, the risk of recurrence of AF increases as eGFR decreases, although patients with mild-to-moderate CKD in whom sinus rhythm is maintained may experience an improvement in kidney function.[109] Direct current cardioversion alone is generally insufficient to maintain normal sinus rhythm, and long-term antiarrhythmic drugs or ablation are necessary for rhythm control.

The use of antiarrhythmic drugs for rhythm control is limited in patients with CKD because of issues with renal clearance and proarrhythmic risks in individuals with structural heart disease (*Table 5*). Amiodarone, the antiarrhythmic drug most commonly used to treat AF, does not appear to negatively affect survival, regardless of eGFR function, even in ESKD.[111] Whether CKD patients treated with amiodarone are at higher risk for organ toxicity is unknown.

Catheter ablation is more effective than antiarrhythmic drugs alone for maintenance of sinus rhythm. The safety and efficacy of AF ablation in CKD was evaluated in 21 091 ablations, in which 1593 cases (7.6%) had CKD and 60 were on dialysis.[112] Among patients selected for AF ablation, those with and without CKD had similar rates of post-procedural complications and subsequent AF hospitalization, DCCV, and repeat ablation, although the patients with CKD were more likely to be re-admitted for heart failure. A meta-analysis of four studies of pulmonary vein isolation using radiofrequency ablation in patients with CKD showed a nearly two-fold increased risk of AF recurrence, possibly as a result of larger pre-ablation left atrial volumes, which may serve as a marker for non-pulmonary vein triggers of AF.[113] In a study of CKD patients undergoing cryoballoon ablation, patients with CKD G3 had significantly higher rates of AF recurrence compared with those with CKD G1 and G2.[114] No cases of contrast-induced nephropathy were reported. In general, sinus rhythm maintenance via ablation is associated with improved eGFR, while ablation failure is associated with eGFR decline.[115]

Atrial fibrillation ablation may potentially provide survival benefit in the setting of reduced left ventricular ejection fraction (LVEF) and heart failure. A randomized trial of catheter ablation compared to usual care in AF and LVEF < 35% recently reported an improvement in survival associated with ablation[116,117] (https://clinicaltrials.gov/ct2/show/NCT00643188; 13 February 2018).

In contrast to atrial fibrillation, radiofrequency ablation for rhythm control of atrial flutter should be considered as first-line therapy in CKD patients given the high success and low complication rates of ablation. Patients with CKD are at higher risk of long-term AF following ablation of atrial flutter and may require long-term monitoring to survey for AF recurrences if a withdrawal of anticoagulation is being considered.[118]

Lifestyle modifications

Weight loss and exercise, can reduce the burden of AF in the general population,[119,120] as does treatment for obstructive sleep apnoea.[121,122] Patients on haemodialysis have a four-fold higher risk of sleep-disordered breathing compared with control patients matched for age, gender, race, and body mass index.[123,124] However, in a claims-based study of older patients in the USA,

Table 5 Characteristics of antiarrhythmic drugs for maintaining sinus rhythm in chronic kidney disease

Drug	Protein binding	Elimination	Dialyzable	Dosing in CKD	Special considerations in CKD
Flecainide	40%	35% excreted unchanged in urine	No	Dose reduction if eGFR <35 mL/min/1.73 m^2	Do not use if significant structural heart disease present
Propafenone	95%	38-50% excreted in urine as active metabolites (1% unchanged)	No	Careful monitoring recommended (in hospital initiation if advanced CKD)	Do not use if significant structural heart disease present
Amiodarone	99%	No renal elimination	No	No dosage requirements; not dialyzable; many drug-to-drug interactions	
Dronedarone	98%	6% excreted in urine	Unlikely to be dialyzed	No dosage adaptation required in kidney failure	Do not use if EF <35% or recent CHF
Dofetilide	60–70%	80% renally excreted, as unchanged (80%) or inactive/minimally active metabolites	Unknown	Initial dose individualized on the basis of CrCl and subsequent dosing based on CrCl and QTc monitoring	Contraindicated for CrCl <20 mL/min
Sotalol	Not protein bound	70% excreted unchanged in urine	Yes—give maintenance dose after dialysis or supplement with 80 mg after HD	A relative contraindication in view of the risk of proarrhythmic effects; in rare and selected cases—dose to be halved or reduced to one quarter in CKD	A relative contraindication in view of the risk of proarrhythmic effects

CHF, congestive heart failure; CKD, chronic kidney disease; CrCl, creatinine clearance; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HD, haemodialysis.
Modified from Potpara *et al.*[101]
Propafenone elimination data from Drugbank.ca.[110]
Dialyzability data from Frishman.[106]

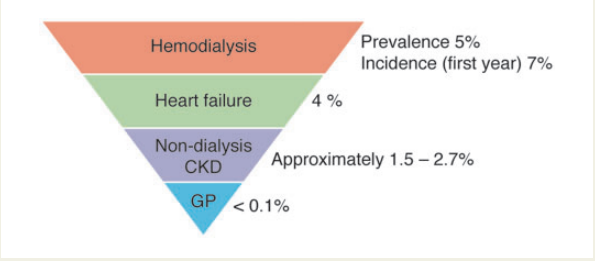

Figure 4 Annual rates of sudden cardiac death. CKD, chronic kidney disease; GP, general population.

sleep-disordered breathing in haemodialysis patients was not associated with AF.[125]

Prevention of sudden cardiac death

Incidence and aetiology of sudden cardiac death in chronic kidney disease and end-stage kidney disease populations

There is an increased risk of SCD in CKD (Supplementary material online, *Table S4*).[126–132] SCD accounts for 25–29% of all-cause mortality in haemodialysis patients and around 30–35% of all-cause mortality in patients initiating dialysis.[133–139] Recent data indicate that although all-cause mortality rates in haemodialysis patients have been decreasing, the rates of SCD remain the same, indicative of an increased proportion of patients dying from SCD.[140] Risk of all-cause mortality is substantially higher in dialysis (15–20% at 1 year) than in heart failure or post-infarction patients (3–8% at 1 year).[140–143] Annual risk of SCD is higher in haemodialysis patients in comparison to other patient populations (*Figure 4*): 5–7% in haemodialysis patients, 4% in heart failure patients, and 1.5–2.7% in non-dialysis patients. The annual rates in non-dialysis patients are comparable to that of post-infarction patients.[126,132,136,140,142–144] Nephrologists should be encouraged and educated to discuss risks and potential treatment options with patients, and enhance participation in clinical trials.

There is a significant gap of knowledge in the understanding of electrical and haemodynamic mechanisms underlying SCD (*Figure 5*). In a retrospective study of haemodialysis patients who were prescribed a wearable cardioverter defibrillator, 80% of cardiac arrests were recorded as ventricular tachyarrhythmias (ventricular tachycardia or ventricular fibrillation) compared to 20% bradyarrhythmias.[145] In a recent study with continuous electrocardiogram (ECG) monitoring, bradyarrhythmias and asystole, rather than ventricular tachyarrhythmias, were important determinants of SCD in ESKD patients.[146]

The definitions of sudden death and SCD in ESKD patients need to be refined. The unexpected nature of sudden death needs to be

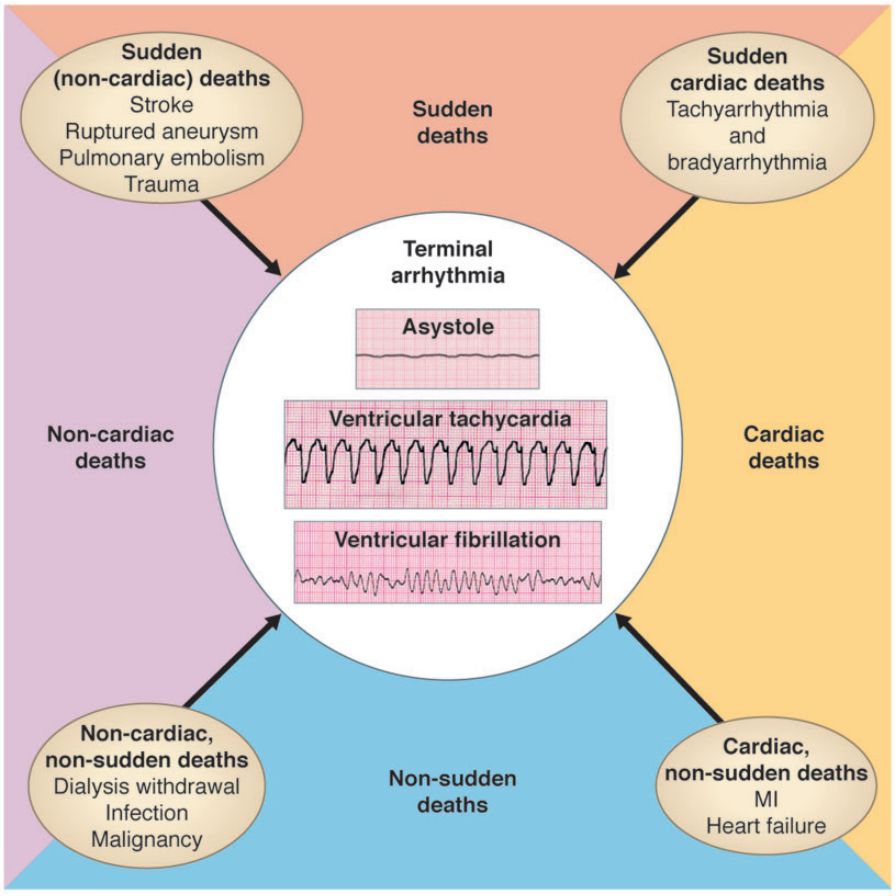

Figure 5 Mechanisms of death in chronic kidney disease patients.

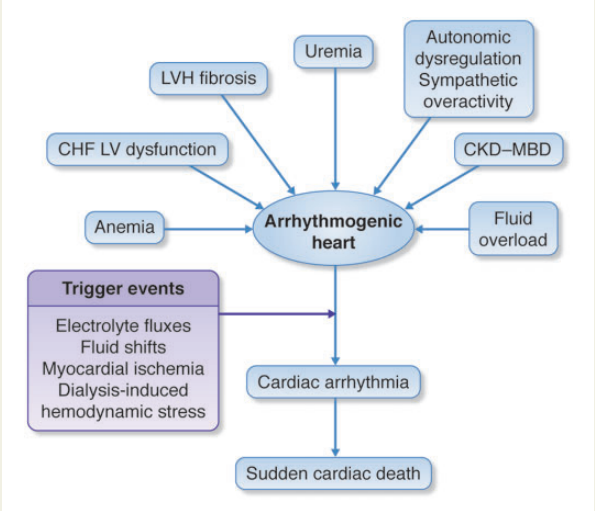

Figure 6 Potential predisposing factors of sudden cardiac death. CHF, congestive heart failure; CKD-MBD, chronic kidney disease-mineral and bone disorders; LV, left ventricular; LVH, left ventricular hypertrophy.

emphasized to avoid misclassifications. Supplementary material online, *Table S5* proposes definitions of sudden death, SCD, and aborted cardiac arrest pertinent for ESKD patients.

Risk factors for sudden cardiac death in chronic kidney disease and end-stage kidney disease patients

The mechanisms of SCD in CKD and ESKD incorporate the long-standing, pathophysiologic abnormalities that predispose to the arrhythmogenic conditions and the triggering mechanisms which precipitate sudden cardiac arrhythmia (*Figure 6*).

The roles of myocardial ischaemia, electrolyte, and volume shifts with haemodynamic instability, left ventricular hypertrophy, fibrosis and dysfunction, as well as autonomic dysregulation and sympathetic overactivity in the pathway leading to SCD, will all need to be further evaluated.

Risk factors predisposing to SCD have been identified in ESKD patients (Supplementary material online, *Table S6*) and usually their combinations contribute to SCD.[136,147] Future studies need to determine whether SCD-specific risk factors could be recognized.[7] Since it is difficult to identify SCD-specific risk factors in patients without ESKD, it might be that just cardiac death-specific risk factors will

suffice to evaluate life-saving interventions in ESKD patients.[148] The primary focus should be on modifiable risk factors which could be targets for intervention (Supplementary material online, *Table S6*).[147]

The role of modifiable biomarkers (defined as laboratory tests that are measurable in blood, urine, or saliva) has been investigated in risk stratification of CKD and ESKD but requires further studies.[149] Troponins and brain natriuretic peptides could have an additive value and should be further explored to assess their role in a comprehensive risk assessment for SCD.[150–153]

There are very limited data regarding the prognostic significance of incidentally detected arrhythmias in CKD and ESKD. Identification of episodes of non-sustained ventricular tachycardia, frequent premature ventricular complexes, bradyarrhythmias and pauses may be useful in identifying patients at risk of SCD.[154] Ongoing and upcoming studies with long-term ECG monitoring devices (implantable loop recorders or external ECG monitoring patches worn over a few days to weeks) will provide data regarding incidence and prognostic significance of these arrhythmias.

Syncope is yet another important and not infrequent event observed in CKD and ESKD patients, but its prognostic significance is uncertain.[155] Transient loss of consciousness due to hypovolaemia or hypotension should be classified as syncope and considered as such for prognostication and treatment.

The role of defibrillator therapies for primary and secondary prevention of sudden cardiac death in end-stage kidney disease

Data regarding secondary prevention ICD therapy indicate some benefits but further studies are needed to assess longer-term risk vs. benefit that account for competing risks of death.[7,156,157] Primary prevention ICD therapy is indicated in patients with LVEF ≤ 35% although data on benefits of primary prevention ICD therapy in patients with LVEF ≤ 35% and advanced CKD are not encouraging,[158] as compromised by competing morbidity and mortality and high risk of complications. Patients with LVEF ≤ 35% account for 10–15% of dialysis patients,[159,160] but no data exist for the majority of dialysis patients with LVEF > 35%. Available data seem to suggest that the benefit of ICDs decreases with declining GFRs, in relationship to competing risks of comorbidity and mortality and high risk of complications.[129,161] Studies with subcutaneous defibrillators, which do not have transvenous hardware, are needed since this approach might be associated with fewer and less severe complications, such as infection.[162] Wearable cardioverter defibrillators may provide protection for a limited high-risk period.[145] Further assessment of pacing devices for bradyarrhythmias (including leadless pacemakers) is needed.[146]

Potassium homeostasis and handling in chronic kidney disease and dialysis

Electrolyte abnormalities and risk for cardiovascular or arrhythmic events

Although definitive evidence for causality is lacking, both hyperkalaemia and hypokalaemia have been associated with higher risk of all-cause and cardiovascular mortality in patients with ESKD. In patients on haemodialysis, when pre-dialysis serum potassium values (i.e. potassium values on blood drawn at the start of the haemodialysis procedure, in keeping with clinical practice) rise or fall away from 5 mEq/L, the risk for sudden cardiac arrest increases.[147] Among incident haemodialysis patients, higher mortality and hospitalization rates have been documented to occur immediately after the 2-day interdialytic interval.[163,164] A contributing factor may be larger fluid accumulation followed by excessive ultrafiltration and abrupt fluctuations in serum potassium concentrations (Supplementary material online, *Figure S1*).[165] In contrast, hypokalaemia is more common in patients on peritoneal dialysis, and hypokalaemia has been associated with increased risk of all-cause, cardiovascular, and infectious mortality in this subgroup of patients.[166]

Treatment options for improving potassium homeostasis

Treatments for hyperkalaemia include dietary restriction, correction of acidosis, increasing distal sodium load, and loop diuretics, and in the case of hypokalaemia, potassium-sparing diuretics and potassium supplements could be used.[167] It may be possible to reduce the dose or stop drugs that interfere with potassium homeostasis, such as nonsteroidal anti-inflammatory drugs, sulfamethoxazole-trimethoprim, calcineurin inhibitors, and non-selective beta blockers. Pharmacologic treatments for managing hyperkalaemia include the cation-exchange resin kayaexalate,[168] calcium-resin resonium,[169] the potassium-binding polymer patiromer,[170] and the potassium trap ZS-9.[167] Beyond the treatment of hyperkalaemia, these agents might also enable more patients with concomitant CKD to be started on or maintained on guideline-recommended renin–angiotensin–aldosterone system (RAAS) inhibitors, and this possibility is currently being investigated.[167] In addition to reducing serum potassium, patiromer has been shown to reduce serum aldosterone levels in patients with CKD and hyperkalaemia taking RAAS inhibitors.[171] Other important questions regarding potassium binders relate to their safety and efficacy in post-kidney transplant patients, patients with Type IV renal tubular acidosis, or patients taking calcineurin inhibitors.

Data from three clinical trials have indicated that dual RAAS blockade therapy increases the risk of hyperkalaemia in patients with CKD.[172–174] Meta-analysis data have indicated that mineralocorticoids can mediate hyperkalaemia in patients undergoing dialysis, but large trials are needed to better evaluate this process and its clinical significance.[175] In patients with Type 2 diabetes, a sodium-glucose cotransporter 2 (SGLT2) inhibitor has been associated with small mean changes in serum electrolytes and less hyperkalaemia compared to placebo, especially in patients taking anti-hypertensives that interfere with potassium excretion.[176]

Dialysate and dialysis parameters

For patients undergoing haemodialysis, both the potassium concentration in the dialysate and the schedule of haemodialysis treatments affect the risk of sudden death (*Figure 6*). Potential confounding factors, such as nutrition, treatment compliance, and comorbidities, have not been thoroughly evaluated. It is also not clear whether or how much central venous pressure, hypervolemia, and pulmonary hypertension predispose patients to arrhythmic events. Three studies have indicated that a low potassium dialysate concentration (<2 mEq/L) is associated

Table 6 Arrhythmias and chronic kidney disease: current knowledge gaps and future research recommendations

- Should AF be a required secondary endpoint in future cardiovascular clinical trials among CKD patients? This will enable future studies to examine the contribution of AF to various outcomes (e.g. cognitive impairment).
- Can we improve upon risk assessment in patients with CKD/CKD G5D by examining unique risk factors for stroke (e.g. proteinuria) and bleeding (e.g. proteinuria, platelet dysfunction, vascular access, dialysis anticoagulation)?
- Based on a review of large observational studies, can we ascertain the combinations of risk factors that predict competing SCD vs. non-SCD and cardiac vs. non-cardiac death endpoints in patients with CKD/CKD G5D?
- Are there modifiable risk factors (e.g. long chain omega-3 fatty acids) or pharmacological therapies for SCD worth investigating?
- What is the incidence and prognostic significance of syncope in dialysis patients (on conventional or novel modalities) and transient hypotension, hypovolemia, and bradycardia during and outside dialysis sessions?
- Is there a role for biomarkers (e.g. troponins, BNP) and markers of autonomic dysregulation and sympathetic overactivity in predicting cardiac death and SCD? Is there prognostic significance in incidentally detected arrhythmias?
- Among patients on dialysis, can we use modern imaging techniques (e.g. cardiac magnetic resonance imaging with T1 mapping and speckle tracking imaging echocardiography both during haemodialysis and on a non-dialysis day), long-term ECG monitoring, and emerging biomarkers to ascertain predisposing factors to SCD?
- Since patients with CKD G5D have consistently lower time in TTR values (despite comparable intensity of monitoring) that may contribute to higher risk of bleeding, what is the evidence regarding the role of TTR in decision-making and transitioning to DOAC therapy with suboptimal TTR?
- Estimates of kidney function using eGFR and eCrCl are not equivalent and can lead to important dose discrepancies with DOACs. Both the conference participants and ESC advocate the use of eGFR (over eCrCl) in future trials because of established superiority in estimating kidney function and to reconcile the measure used in pragmatic clinical practice. For adoption of this measure in future trials however, we recognize that there would be need for upfront endorsement of eGFR as the preferred measure for estimating kidney function by regulatory agencies.
- Should serial measurements of kidney function be considered to determine if anticoagulation (e.g. DOACs) is associated with changes in kidney function?
- Does heparin use during haemodialysis alter the risk–benefit ratio when used with concomitant oral anticoagulation? Are there clinical efficacy or safety data evaluating whether the use of erythropoietin therapy influences stroke reduction with anticoagulant therapy?
- Is there utility in employing left atrial appendage occluder devices in patients with CKD G5D who are already at high risk of bleeding and endovascular infections?
- What is the role of DOACs among kidney transplant patients? Do specific drug–drug interactions favour certain agents over others?
- Is ICD therapy efficacious in the primary and secondary prevention of SCD in ESKD? If so, what are the risk–benefit ratios? Utility of leadless pacemakers? Additional studies examining transvenous, subcutaneous, and wearable defibrillators are needed in CKD patients with EF >35% since they account for 90% of ESKD patients.
- What are the long-term outcomes of rate vs. rhythm control in CKD or dialysis patients? What should guide the selection of rate vs. rhythm control in this patient population? For the former, what is the optimal rate control and what are the preferred rate-controlling agents? Utility of transvenous vs. leadless permanent pacemaker following AV node ablation? For rhythm control, what is benefit–risk ratio for ablation vs. antiarrhythmic drugs?
- What is the ideal ablation approach? For antiarrhythmic drugs, are there comparative trials to provide information on safety, pharmacokinetics and efficacy on various agents (especially amiodarone)? Is there a long-term need for oral anticoagulation in patients with successful rhythm control?
- Does personalizing dialysis prescription (e.g. electrolyte dialysate, close monitoring of potassium levels or volume management) reduce the risk for SCD? Do changes in other electrolytes associated with arrhythmic predisposition in haemodialysis patients (such as magnesium) affect clinical outcomes?

AF, atrial fibrillation; AV, atrioventricular; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; DOAC, direct oral anticoagulant; ECG, electrocardiogram; eCrCl, estimated creatinine clearance; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; ESKD, end-stage kidney disease; G5D, CKD stage G5 patients on dialysis therapy; ICD, implantable cardioverter-defibrillator; SCD, sudden cardiac death; TTR, time in therapeutic range.

with a higher incidence of sudden death, especially when pre-dialysis patient serum levels are <5 mEq/L.[147,177,178] For patients with a pre-dialysis serum potassium concentration of >5 mEq/L, the risks associated with low potassium dialysates have not been statistically significant. In Dialysis Outcomes and Practice Patterns Study (DOPPS), mortality rates were similar in patients prescribed 2 and 3 mEq/L dialysate.[179] Rapid correction of acidaemia, low serum or dialysate calcium, and high ultrafiltration rates may contribute to the arrhythmogenic potential of low potassium dialysate.[147,180] In a study of 50 patients undergoing thrice-weekly dialysis, risk of SCD and significant arrhythmias was greater during the 72-h vs. 48-h breaks. There were no analyses specifically related to potassium levels in these studies.[146] Whether shortening the interval between haemodialysis sessions could result in clinically significant reductions in sudden cardiac arrest and its relationship to potassium levels is not clear and warrants further study. Dialysate concentrations of bicarbonate, calcium, magnesium, and glutamic acid also are likely to be relevant to risk for arrhythmic events. It is possible that personalizing dialysis parameters

for individual patients could reduce risk of SCD, but this is untested and would be logistically complicated to implement.

Fluid control during dialysis

Ultrafiltration rates higher than 10 mL/h/kg have been associated with a higher likelihood of intradialytic hypotension and risk of mortality.[181] Haemodynamic stress during dialysis induces cardiac stunning, which over time may progress to the development of regional fixed systolic dysfunction, consistent with underlying myocardial hibernation and fibrosis.[182] A retrospective analysis has indicated that greater interdialytic weight gain is associated with an increased risk of cardiovascular morbid events[183]; therefore, strategies that mitigate interdialytic weight gain warrant investigation.

Conclusion

People with CKD have an increased burden from AF relative to those without CKD, and an elevated risk of stroke. For preventing stroke in patients with eCrCl 30–50 mL/min, DOACs are non-inferior to warfarin and have a more favourable safety profile. For CKD G5D patients with AF, there are insufficient clinical efficacy and safety data to routinely recommend VKA treatment for preventing stroke.

Evidence from older randomized trials indicates that pharmacological rhythm and rate control strategies are equivalent in terms of their efficacy on risks of heart failure, stroke, and survival. However, catheter ablation, which is superior to antiarrhythmic drug therapy for freedom from AF recurrence, has comparable safety in CKD and non-CKD. The role of AF ablation may continue to evolve, particularly among other co-morbid conditions such as heart failure. Regardless of whether a rhythm or rate strategy is pursued, anticoagulation should also be prescribed unless otherwise contraindicated based on stroke risk.

The risk for SCD is increased in patients with CKD, and for those with ESKD on dialysis, several factors that increase risk have been identified. Studies are needed to identify risk factors for SCD in CKD non-dialysis patients. For preventing SCD in ESKD, primary prevention ICD therapy is indicated in patients with LVEF $\leq$ 35%, although data on its benefits in these patients are not encouraging. Data regarding secondary prevention ICD therapy indicate some benefits, but further studies are needed to assess long-term risk–benefit ratios in these patients. Available data seem to suggest that the benefit of ICDs decreases with declining GFR.

For patients undergoing haemodialysis, both the potassium concentration in the dialysate and the schedule of haemodialysis treatments affect the risk of sudden death. Whether shortening the interval between haemodialysis sessions could result in clinically significant reductions in sudden cardiac arrest is not yet clear and warrants further study. It is possible that personalizing dialysis parameters for individual patients could reduce risk of SCD, but this is untested and would be logistically complicated to implement.

Recent guidelines include considerable practical and scientific detail on management of these arrhythmias in CKD.[3–7,85,184] However, there remain substantial evidence gaps, which will require clinical trials, and when not possible, robust observational data. We have outlined research recommendations in the hopes that future investigations can better advance the evidence base in this area (*Table 6*). A multidisciplinary approach is vital for understanding the mechanisms of arrhythmias in CKD as well as for evaluating therapies and improving clinical care. Nephrologists and cardiologists should initiate and continue partnerships in designing and conducting clinical trials as well as treating individual patients with CKD and AF.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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