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

Mintu P. Turakhia1*, Peter J. Blankestijn2, Juan-Jesus Carrero3, Catherine M. Clase4, Rajat Deo5, Charles A. Herzog6, Scott E. Kasner7, Rod S. Passman8, Roberto Pecoits-Filho9, Holger Reinecke10, Gautam R. Shroff11, Wojciech Zareba12, Michael Cheung13, David C. Wheeler14, Wolfgang C. Winkelmayer15, and Christoph Wanner16*, for Conference Participants†

1Stanford University School of Medicine, Veterans Affairs Palo Alto Health Care System, 3801 Miranda Ave, 111C, Palo Alto, CA 94304, USA; 2Department of Nephrology, room F03220, University Medical Center, P.O. Box 85500, 3508GA Utrecht, The Netherlands; 3Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Nobels väg 12A, Box 281, 171 77 Stockholm, Sweden; 4Department of Medicine and Department of Health Research Methods, Evidence, and Impact, McMaster University, St. Joseph’s Healthcare, Marion Wing, 3rd Floor, M333, 50 Charlton Ave. E. Hamilton, Ontario L8N 4A6, Canada; 4Section of Electrophysiology, Division of Cardiovascular Medicine, Perelman School of Medicine at the University of Pennsylvania, 3400 Spruce Street, 9 Founders Cardiology, Philadelphia, 19104 PA, USA; 5Division of Cardiology, Department of Medicine, Hennepin County Medical Center and University of Minnesota, Minneapolis, Minnesota and Chronic Disease Research Group, Minneapolis Medical Research Foundation, 914 S. 8th Street, S4.100, Minneapolis, 55404 MN, USA; 6Department of Neurology, JW Gates Bldg. Hospital of the University of Pennsylvania, 3400 Spruce St., Philadelphia, 19104-4283 PA, USA; 7Northwestern University Feinberg School of Medicine and the Bluhm Cardiovascular Institute, 201 E. Huron St. Chicago, 60611 IL, USA; 8Division of Medicine, Pontificia Universidade Catolica do Parana, Rua Imaculada Conceicao 1155, 80220-901 Curitiba PR, Brazil; 9Department für Kardiologie und Angiologie Universitätsklinikum Münster, Albert-Schweitzer-Campus 1, Gebäude A1, 48149 Münster, Germany; 10Division of Cardiology, Hennepin County Medical Center, 701 Park Avenue, Minneapolis, 55415 MN, USA; 11Heart Research Follow-up Program, Cardiology Division, University of Rochester Medical Center, Saunders Research Building, 265 Crittenden Blvd. CU 420653, Rochester, 14642 NY, USA; 12KDIGO, Avenue Louise 65, Suite 11, 1050 Brussels, Belgium; 13Centre for Nephrology, University College London, Rowland Hill Street, London NW3 2PF, UK; 14Selzman Institute for Kidney Health, Section of Nephrology, Department of Medicine, Baylor College of Medicine, One Baylor Plaza, ABBR R705, MS: 395, Houston, 77030-3411 TX, USA; and 15Division of Nephrology, Department of Medicine, University Hospital of Würzburg, Oberdunnerbachstr. 6 Würzburg D-97080, Germany

Received 13 October 2017; revised 18 December 2017; editorial decision 25 January 2018; accepted 27 January 2018

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, although this situation is changing.1,2 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).

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

* Corresponding author. M.P.T. Tel: (650) 858-3932, Fax (650) 852-3473, Email: mintu@stanford.edu; C.W. Tel: +49-931-201 39030, Fax: +49-931-201 639300, Email: Wanner_C@ukw.de
† Other conference participants: Kerstin Aman, Germany; Debashis Banerjee, UK; Nisha Bansal, USA; Giuseppe Boriani, Italy; Jared Bunch, USA; Christopher T. Chan, Canada; David M. Charytan, USA; David Conen, Canada; Allon N. Friedman, USA; Simonetta Genovesi, Italy; Rachel M. Holden, Canada; Andrew A. House, Canada; Michel Jadoul, Belgium; Alan G. Jardine, UK; David W. Johnson, Australia; Min Jun, Australia; Laura Labriola, Belgium; Patrick B. Mark, UK; Peter A. McCullough, USA; Thomas D. Nolin, USA; Tijana S. Potpara, Serbia; Patrick H. Pun, USA; Antonio L. P. Ribeiro, Brazil; Patrick Rossignol, France; Jenny I. Shen, USA; Manish M. Sood, Canada; Yusuke Tsukamoto, Japan; Angela Yee-Moon Wang, Hong Kong; Matthew R. Weir, USA; James B. Wetmore, USA; Jerzy K. Wrancz, Poland; Hiro Yamasaki, Japan.
© The Author(s) 2018. Published by Oxford University Press on behalf of the European Society of Cardiology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Atrial fibrillation and stroke in kidney disease

Epidemiology

Atrial fibrillation is the most common sustained arrhythmia. Chronic kidney disease affects 10% of adults worldwide, 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). 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, although this association has not been well characterized across the spectrum of estimated glomerular filtration rate (eGFR) or proteinuria. In the USA, both incidence and prevalence of AF are increasing among haemodialysis patients, which could be because of older age of patients, better ascertainment of AF, and improved survival after vascular events.

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. 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) and non-significant associations after kidney transplantation. These differences may be due to greater competing risk of death in more advanced CKD, 15 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 31,38–40 (Supplementary material online, Table S2), and increases risk of death in patients with non-dialysis CKD and those on dialysis. 13,35,41 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.

Stroke risk scores

The predictive value and calibration of the CHADS2 and CHA2DS2-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. 16,33,42

Inclusion of CKD in risk scores to improve stroke prediction has demonstrated variable results. Adding two points for creatinine clearance < 60 mL/min to CHADS2 (called R2CHADS2) 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. The ATRIA score, which includes terms for GFR < 45 mL/min/1.73 m2 and proteinuria, demonstrated improved NRI and borderline improvement in C-statistic compared with CHADS2 and CHA2DS2-VASc in external validation, although NRI may not be clinically meaningful. For these reasons and for the potential for categorically recommending oral anticoagulant (OAC) to most patients with CKD without regard to competing risks, CHA2DS2-VASc remains the most commonly recommended score for risk stratification, and observational data have shown that a treatment threshold of CHA2DS2-VASc ≥ 2 is associated with OAC benefit, even in CKD.

Bleeding risk scores

The HAS-BLED, ORBIT, HEMORR2HAGES, 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, 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
bleeding events compared with warfarin (with apixaban and edoxaban resulted in significantly fewer major

Among patients with eCrCl between 25 and 50 mL/min, treatment DOACs have been associated with a significant reduction (about 50%) in risk of intracranial haemorrhage compared to warfarin.

Table 2 Evidence from randomized trial data regarding therapeutic anticoagulation on the basis of kidney function4,63,64

<table>
<thead>
<tr>
<th>eCrCl (mL/min)</th>
<th>Warfarin</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;95</td>
<td>Adjusted dose (INR 2–3) 5 mg b.i.d.</td>
<td>150 mg b.i.d.</td>
<td>60 mg QD</td>
<td>20 mg QD</td>
<td></td>
</tr>
<tr>
<td>51–95</td>
<td>Adjusted dose (INR 2–3) 5 mg b.i.d.</td>
<td>150 mg b.i.d.</td>
<td>60 mg QD</td>
<td>20 mg QD</td>
<td></td>
</tr>
<tr>
<td>31–50</td>
<td>Adjusted dose (INR 2–3) 5 mg b.i.d. (eCrCl cut-off 25 mL/min)</td>
<td>150 mg b.i.d. or 110 mg b.i.d.a</td>
<td>30 mg QD</td>
<td>15 mg QD</td>
<td></td>
</tr>
</tbody>
</table>

INR, international normalized ratio.

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.

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).

This dose has not been approved for use by the US Food and Drug Administration in this category of kidney function.

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 Cockcroft–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 DOACs57–62 (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 uremic 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 SWEDHEART 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.65 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 haemorrhages71 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.
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.\(^7\)–\(^8\) 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.\(^8\)–\(^1\)

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.\(^6\)\(^4\) These adverse signals suggest the need for caution in the use of DOACs in patients with chronic kidney disease.
need for systemic measures focused on patient safety to guide clinicians regarding the use of DOACs. 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.

For CKD patients receiving DOAC therapy, we recommend periodic monitoring of kidney function because decline over time may necessitate dose modification. 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.

For CKD patients on anticoagulants, 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). For patients with CKD G4 and G5 on anticoagulants, strategies to reduce bleeding warrant systematic research but may in-clude minimizing heparin with dialysis, use of citrate locks for catheters, 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, andandexanet alfa has been developed for reversal of anti-Xa agents. Data specific to reversal in CKD patients are limited.

**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. However, there is insufficient evidence to recommend single or dual antiplatelet therapy for prevention of stroke/thromboembolism in CKD. Moreover, 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.

**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 concomitant single or dual antiplatelet therapy. 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 concomitant single or dual antiplatelet therapy. 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 concomitant single or dual antiplatelet therapy.

**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...
for a rhythm-control strategy for AF is symptom reduction, although many patients are asymptomatic. 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. 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 CHADS2 or CHA2DS2-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). 

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. 

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-
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 has been reported to be similar regardless of kidney function. 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.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 for maintenance of sinus rhythm 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 ablation116,117 (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, as does treatment for obstructive sleep apnoea.119,120 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,
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 investigated.

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Protein binding</th>
<th>Elimination</th>
<th>Dialyzable</th>
<th>Dosing in CKD</th>
<th>Special considerations in CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecainide</td>
<td>40%</td>
<td>35% excreted unchanged in urine</td>
<td>No</td>
<td>Dose reduction if eGFR &lt;35 mL/min/1.73 m²</td>
<td>Do not use if significant structural heart disease present</td>
</tr>
<tr>
<td>Propafenone</td>
<td>95%</td>
<td>38-50% excreted in urine as active metabolites (1% unchanged)</td>
<td>No</td>
<td>Careful monitoring recommended (in hospital initiation if advanced CKD)</td>
<td>Do not use if significant structural heart disease present</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>99%</td>
<td>No renal elimination</td>
<td>No</td>
<td>No dosage requirements; not dialyzable; many drug-to-drug interactions</td>
<td></td>
</tr>
<tr>
<td>Dronedarone</td>
<td>98%</td>
<td>6% excreted in urine</td>
<td>Unlikely to be dialyzed</td>
<td>Do not use if eGFR &lt;35% or recent CHF</td>
<td>Contraindicated for CrCl &lt;20 mL/min</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>60–70%</td>
<td>80% renally excreted, as unchanged (80%) or inactive/ minimally active metabolites</td>
<td>Unknown</td>
<td>Initial dose individualized on the basis of CrCl and subsequent dosing based on CrCl and QTc monitoring</td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td>Not protein bound</td>
<td>70% excreted unchanged in urine</td>
<td>Yes—give maintenance dose after dialysis or supplement with 80 mg after HD</td>
<td>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</td>
<td>A relative contraindication in view of the risk of proarrhythmic effects</td>
</tr>
</tbody>
</table>

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.

Figure 5 Annual rates of sudden cardiac death.
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 be emphasized to avoid misclassifications. Supplementary material online, Table S5 proposes definitions of sudden death, SCD, and aborted cardiac arrest pertinent for ESKD patients.

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

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. 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. 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. 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. 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, as compromised by competing morbidity and mortality and high risk of complications. Patients with LVEF < 35% account for 10–15% of dialysis patients, 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. 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. Wearable cardioverter defibrillators may provide protection for a limited high-risk period. Further assessment of pacing devices for bradyarrhythmias (including leadless pacemakers) is needed.

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. Among incident haemodialysis patients, higher mortality and hospitalization rates have been documented to occur immediately after the 2-day interdialytic interval. A contributing factor may be larger fluid accumulation followed by excessive ultrafiltration and abrupt fluctuations in serum potassium concentrations (Supplementary material online, Figure S1). 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.

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. 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 kayexalate, calcium-resin resol, the potassium-binding polymer patiromer, and the potassium trap ZS-9. 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.

In addition to reducing serum potassium, patiromer has been shown to reduce serum aldosterone levels in patients with CKD and hyperkalaemia taking RAAS inhibitors. 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. 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. 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.

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, hypervolaemia, 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, atioventricular; 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. 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. Rapid correction of acidemia, low serum or dialysate calcium, and high ultrafiltration rates may contribute to the arrhythmogenic potential of low potassium dialysate. 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. 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. 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. A retrospective analysis has indicated that greater interdialytic weight gain is associated with an increased risk of cardiovascular morbidity events: 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 eGFR 30–50 mL/min, DOACs are non-inferior to warfarin and have a more favourable safety profile. For CKD GSD 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 ≤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. 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.

**Acknowledgements**

We thank Jennifer King, PhD, for assistance with the manuscript preparation.

**Funding**

The conference was sponsored by KDIGO (Kidney Disease: Improving Global Outcomes) and supported in part by unrestricted educational grants from AstraZeneca, Bayer HealthCare, Boston Scientific, Daiichi-Sankyo, Fresenius Medical Care, Sanofi-Genzyme, Medtronic, Relypsa, and Vifor Fresenius Medical Care Renal Pharma. All conference attendees received travel support for meeting participation.

**Conflict of interest:** M.P.T. has received research support from AstraZeneca, Boehringer Ingelheim, Cardiva Medical, Janssen, Medtronic, and Veterans Health Administration; has served as a consultant to Akebia, AliveCor, Boehringer Ingelheim, Cardiva Medical, iBeat, iRhythm, Medtronic, Precision Health Economics, and St Jude Medical; has received speaker honoraria from Medscape/theheart.org; has reported equity in AliveCor, iBeat, Zipline Medical; and is an editor for JAMA Cardiology. P.J.B. has received research support from the Dutch Kidney Foundation, the European Commission, Medtronic, The Netherlands Organisation for Health Research and Development, and St. Jude Medical. All monies were paid to institution. J.J.C. has received institutional research grants from AstraZeneca, Vifor Fresenius Medical Care Renal Pharma and Swedish Heart and Lung Foundation and speaker honorarium from Vifor Fresenius Medical Care Renal Pharma.

C.A.H. has served as a consultant to Abbvie, Bristol-Myers Squibb, Fibrogen, Relypsa, Sanofi, ZS Pharma; received research support from Amgen and Zoll; owns stock in Boston Scientific, GE, Johnson & Johnson and Merck. S.E.K. has received research support from WL Gore and Associates, Bayer and Bristol-Myers Squibb; and has served as a consultant to Abbvie, Boehringer Ingelheim and Johnson & Johnson. R.S.P. has received personal fees from Biotronik and Medtronic; non-financial support from Kardic; and research support from Pfizer. R.P.-F. has served on advisory boards and/or received speaker honoraria from Akebia, AstraZeneca, Baxter, Fresenius Medical Care, Janssen, and Novartis. He has also received research support from Baxter and Fresenius Medical Care. H.R. has received personal fees and non-financial support from Bristol-Myers Squibb and Pfizer.

W.Z. has received research support from Boston Scientific and Zoll. D.C.W. has served as a consultant to Amgen, AstraZeneca, Boehringer Ingelheim, GSK, Janssen, and Vifor Fresenius Medical Care Renal Pharma; and has received speaker honoraria from Amgen and Kyowa Kirin. W.C.W. has served as a scientific advisor to AMAG, Amgen, AstraZeneca, Bayer, Daiichi Sankyo, Vifor Fresenius Medical Care Renal Pharma, and ZS Pharma; has served on clinical trial executive committee for Akebia and endpoint adjudication committee for Medtronic; he has also served as a consultant to Relypsa and received speaker honorarium from Fibrogen. C.W. has served as a consultant to Boehringer-Ingelheim and Sanofi Genzyme. All other authors have nothing to disclose.
Chronic kidney disease and arrhythmias: a KDIGO conference report

References

43. Chan PH, Huang D, Yip PS, Hai J, Tse HF, Chan TM, Lip GY, Lo WK, Siu CW.
42. Nelson SE, Shroff GR, Li S, Herzog CA. Impact of chronic kidney disease on
40. Bansal N, Fan D, Hsu CY, Ordonez JD, Marcus GM, Go AS. Incident atrial fibrillation
Chronic kidney disease and arrhythmias: a KDIGO conference report


