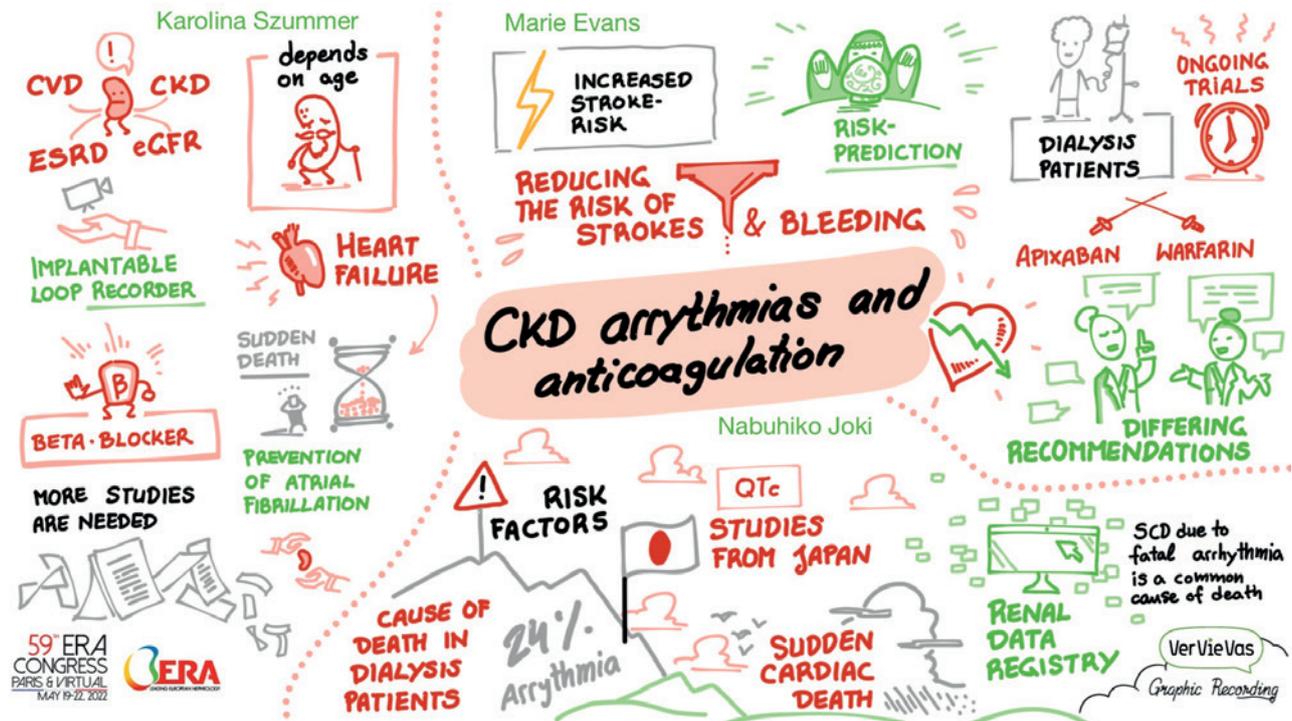


## Symposium 5.1

# CKD Arrhythmias and Anticoagulation



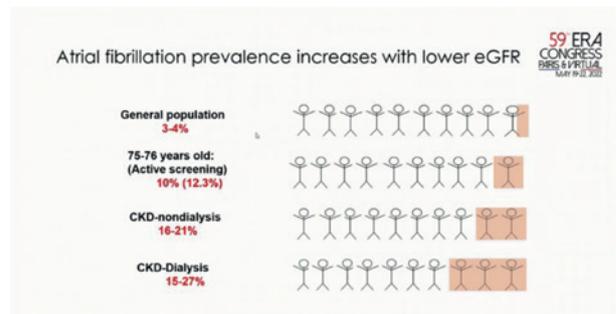
### Arrhythmias and heart failure in CKD and ESKD

Karolina Szummer, Sweden

Chronic kidney disease (CKD) progression is often associated with structural and functional alterations of the heart. Renal patients commonly exhibit an elevated cardiovascular risk manifesting as ischemic heart disease, heart failure, arrhythmias, and sudden cardiac death. Arrhythmias are notably more common in CKD patients compared to the general population, even the elderly. Numerous mechanisms are involved in the occurrence of CKD-associated arrhythmias, including uremia, electrolyte imbalance, diabetes, inflammation, myocardial structural alterations, coronary artery disease, disturbed left ventricular function, left ventricular hypertrophy, and repolarization.

Atrial fibrillation (AF) is generally considered the most common type of arrhythmia in this population, but ventricular tachycardia, bradyarrhythmias, and AV blocks can also be present. A recent study by Kim et al. showed that lower eGFR, and particularly albuminuria, were consistently associated with a higher prevalence of AF and nonsustained ventricular tachycardia. Another study by Sacher et al. identified potassium >5.0 mmol/l to be associated with a higher risk for conduction disorder, and potassium <4.0 mmol/l with a higher risk for ventricular arrhythmias in hemodialyzed patients.

CKD patients also exhibit structural and functional left- and right ventricular abnormalities, with or without changes in left ventricular (LV) ejection



**Figure 1.** The prevalence of atrial fibrillation in the general and the CKD population

fraction. eGFR is directly associated with LV ejection fraction, right ventricular systolic function, and death due to heart failure in this population. The beta-blockers reduce mortality from sudden cardiac death in both predialysis and dialysis CKD patients with reduced LV ejection fraction and dilated cardiomyopathy. The recently introduced SGLT2-inhibitors also showed very promising results in reducing the risk of cardiovascular death or hospitalization for heart failure with or without preserved ejection fraction regardless of the presence of diabetes. Furthermore, it appears that treatment with SGLT2-inhibitors is also associated with a significantly lower risk of incident AF compared to placebo, but more research is needed to evaluate the clinical significance of this effect. The novel mineralocorticoid receptor antagonist, finerenone, also reduces the risk of new-onset AF and flutter and cardiovascular events with a favorable safety profile. Thus, heart failure treatment has an important role in preventing and reducing the frequency of arrhythmias in CKD and end-stage kidney disease (ESKD) patients, but more studies are needed to further explore clinical outcomes in these cohorts.

## Anticoagulation in patients with CKD and ESKD

Marie Evans, Sweden

Atrial fibrillation (AF) is the most common arrhythmia worldwide. The risk of developing it is higher in males and increases with age. As many as one-third of dialyzed patients may develop AF and the condition is associated with a three-fold higher risk of cerebrovascular events, predominantly ischemic stroke. A similar risk level for cerebrovascular events is observed in CKD patients with AF. Therefore, the European Society of Cardiology (ESC) 2020 Guidelines strongly recommend introducing oral anticoagulant therapy (OAC) for stroke prevention in AF patients with CHA2-DS2-VAS scores  $\geq 2$  in men and  $\geq 3$  in women. This guidance is supported by the results of several randomized controlled trials which showed a consistent and significant stroke risk reduction with OAC. Nevertheless, the decision to introduce OAC should be evaluated cautiously and include several risk assessments, especially in the populations with a known high risk for bleeding. The risks for the thromboembolic event and bleeding should be assessed simultaneously with CHA2-DS2-VASc and rHAS-BLED scores before introducing OAC. The latest ESC guidelines also strongly favor the use of the novel direct OACs (DOACs) for stroke prevention in AF instead of the traditional vitamin K antagonists (VKA), except for patients with mechanical heart valves or moderate-to-severe mitral stenosis. This recommendation is based on the DOACs' higher efficacy and superior safety profile compared to VKA.

Still, the CKD population is highly specific and requires distinct evaluation. Firstly, in the most clinically relevant stages of CKD, the predictive performance of the majority of risk scores is poor. Therefore, the Modified CHADS2 score should be preferred for risk estimation in this population. Secondly, more than half of patients with CKD stages 4 to 5 exhibit an INR result within the therapeutic range <75% of the time, which is potentially associated with a higher risk of adverse events, including bleeding. Finally, warfarin treatment is associated with a higher risk of developing calciphylaxis, while its efficacy in CKD patients is ambiguous.

Among the currently available DOACs, dabigatran has the highest, and apixaban exhibits the lowest renal elimination. Their dependence on renal clearance and several troubling safety signals still impedes DOACs' use in Europe, while the FDA has allowed the use of apixaban in CKD, ESKD, and even dialyzed patients in the USA.

In the currently available studies, certain DOACs appear to be associated with a higher incidence of fatal or intracranial bleeding while exhibiting no substantial benefit in lowering the incidence of a new stroke, transient ischemic attack, or systemic thromboembolism compared to no anticoagulation. On the other hand, meta-analyses show that the DOACs exhibit similar benefits as warfarin in preventing all strokes and systemic embolic events without increasing the risk of major bleeding events among patients with CKD and AF. The several compelling ongoing trials (AXADIA, SAFE-D, DANWARD, ApiDP, AVKDIAL, SACK) are expected to provide a more specific answer to the remaining question of whether DOACs are efficient and safe in CKD patients.

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
<b>eCL<sub>r</sub> &lt; 15 mL/min</b>				
FDA	Dosing recommendations cannot be provided	Not specifically addressed	Standard dosing <sup>1</sup>	Not recommended
EMA	Contraindicated	Not recommended	Not recommended (no clinical experience)	Not recommended
Health Canada	Contraindicated	Not recommended	Not recommended	Not recommended
<b>CKD-SD</b>				
FDA	Dosing recommendations cannot be provided	No specific clinical guidance provided <sup>2</sup>	Standard dosing <sup>1</sup>	Not recommended if eCL <sub>r</sub> < 15 mL/min
EMA	Not specifically addressed	Not recommended if eCL <sub>r</sub> < 15 mL/min	Not recommended (no clinical experience)	Not recommended
Health Canada	Contraindicated if eCL <sub>r</sub> < 30 mL/min	Not specifically addressed	Not recommended	Not recommended

**Figure 2.** Regional differences in recommendations for DOAC use in patients with CKD (from ref. 9)

## Sudden death in patients with ESKD

Nabuhiko Joki, Japan

Sudden cardiac death (SCD) is the leading cause of cardiovascular mortality among ESKD patients in most parts of the world. It is attributed to sudden fatal arrhythmias, such as ventricular tachycardia or fibrillation. Nevertheless, in Japan, the major cause of cardiac death is heart failure. One possible reason for this discrepancy might be the lack of a universally established and accepted definition of SCD in the clinical setting. However, recent lines of evidence suggest that similar to other countries, SCD might be more common in the Japanese dialysis clinical setting than previously thought.

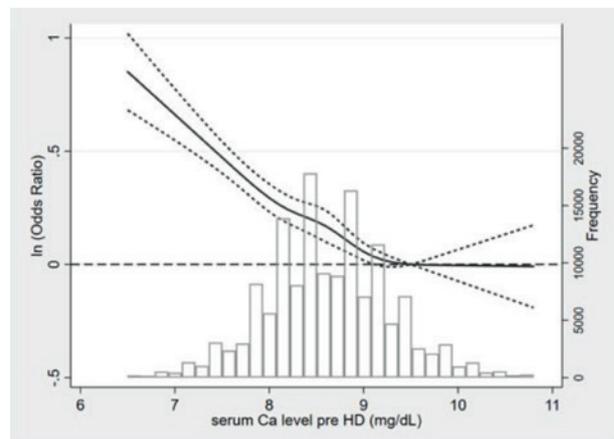
Prolongation of the QT interval has been directly associated with ventricular arrhythmias and SCD. The risk factors for QT prolongation include age, female gender, existing cardiac condition or electrolyte disturbances, and certain medications. Among dialyzed patients, additional risk factors also involve hypokalemia, hypocalcemia, and cardiovascular disease, rendering this population especially vulnerable and disposed to SCD associated with QT prolongation. These patients already have a longer median corrected QT (estimated at a standard heart rate of 60 bpm) at the initiation of dialysis and it continues to prolong further during the time on dialysis.

The prolonged corrected QT (QTc) has been linked with incident cardiovascular events in middle-aged and older adults without prior cardiovascular disease. Each 10 ms increase in the QTc baseline is associated with growing incident cardiovascular events. Similar findings have been reported for hemodialyzed patients inspiring a national cross-sectional study among Japanese dialysis patients based on the Renal Data Registry from the Japanese Society for Dialysis Therapy. The authors tried to identify the factors associated with QT and its relationship with SCD in this population.

Nearly 230,000 hemodialyzed patients were enrolled. The selection included only patients with ECG data and no AF. All automatically measured QT intervals and heart rates were analyzed and QTcs were calculated with the Bazett correction formula ( $QTc = QT / \sqrt{RR}$ ).  $QTc > 500ms$  was considered prolonged. The results showed a nearly normal distribution of QTc and virtually no difference in mean QTc between males and females. Patients with prolonged QTc more often had diabetes, cardiovascular and/or cerebrovascular disease, lower serum albumin, calcium, transferrin saturation, and higher CRP.

The odds for prolonged QTc increased linearly at predialysis serum calcium levels below 2.25mmol/L. A U-shaped association was observed between serum phosphorus and prolonged QTc, with the lowest odds at a serum phosphorus level of 1.45mmol/L. At serum phosphorus of 0.65mmol/L and 2.4mmol/L, the odds ratio was 1.5. Transferrin saturation (TSAT) was strongly and almost linearly associated with odds for QTc prolongation, whereas serum magnesium, PTH, and ferritin levels were only weakly associated with prolonged QTc.

The cross-sectional design of this study precludes the decision on the causal effects of investigated variables on prolonged QTc. However, further investigation is on the way to examine the association between QTc prolongation and cardiovascular disease in hemodialyzed Japanese patients.



**Figure 3.**  
Association between  $QTc > 500ms$  and predialysis serum calcium levels

## Further readings

1. Kim ED, Soliman EZ, Coresh J, Matsushita K, Chen LY. Two-Week Burden of Arrhythmias across CKD Severity in a Large Community-Based Cohort: The ARIC Study. *J Am Soc Nephrol*. 2021;32(3):629-638. doi:10.1681/ASN.2020030301
2. Sacher F, Jesel L, Borni-Duval C, et al. Cardiac Rhythm Disturbances in Hemodialysis Patients: Early Detection Using an Implantable Loop Recorder and Correlation With Biological and Dialysis Parameters. *JACC Clin Electrophysiol*. 2018;4(3):397-408. doi:10.1016/j.jacep.2017.08.002
3. Mavrakanas TA, Khattak A, Singh K, Charytan DM. Echocardiographic parameters and renal outcomes in patients with preserved renal function, and mild-moderate CKD. *BMC Nephrol*. 2018;19(1):176. Published 2018 Jul 11. doi:10.1186/s12882-018-0975-5
4. Kotecha D, Gill SK, Flather MD, et al. Impact of Renal Impairment on Beta-Blocker Efficacy in Patients With Heart Failure [published correction appears in *J Am Coll Cardiol*. 2020 Apr 7;75(13):1615]. *J Am Coll Cardiol*. 2019;74(23):2893-2904. doi:10.1016/j.jacc.2019.09.059
5. Okunrintemi V, Mishriky BM, Powell JR, Cummings DM. Sodium-glucose co-transporter-2 inhibitors and atrial fibrillation in the cardiovascular and renal outcome trials. *Diabetes Obes Metab*. 2021;23(1):276-280. doi:10.1111/dom.14211
6. Filippatos G, Bakris GL, Pitt B, et al. Finerenone Reduces New-Onset Atrial Fibrillation in Patients With Chronic Kidney Disease and Type 2 Diabetes. *J Am Coll Cardiol*. 2021;78(2):142-152. doi:10.1016/j.jacc.2021.04.079
7. de Jong Y, Fu EL, van Diepen M, et al. Validation of risk scores for ischaemic stroke in atrial fibrillation across the spectrum of kidney function. *Eur Heart J*. 2021;42(15):1476-1485. doi:10.1093/eurheartj/ehab059
8. Szummer K, Gasparini A, Eliasson S, et al. Time in Therapeutic Range and Outcomes After Warfarin Initiation in Newly Diagnosed Atrial Fibrillation Patients With Renal Dysfunction. *J Am Heart Assoc*. 2017;6(3):e004925. Published 2017 Mar 1. doi:10.1161/JAHA.116.004925
9. Shroff GR, Stoecker R, Hart A. Non-Vitamin K-Dependent Oral Anticoagulants for Nonvalvular Atrial Fibrillation in Patients With CKD: Pragmatic Considerations for the Clinician. *Am J Kidney Dis*. 2018;72(5):717-727. doi:10.1053/j.ajkd.2018.02.360
10. Kimachi M, Furukawa TA, Kimachi K, Goto Y, Fukuma S, Fukuhara S. Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease. *Cochrane Database Syst Rev*. 2017;11(11):CD011373. Published 2017 Nov 6. doi:10.1002/14651858.CD011373.pub2
11. Chen C, Cao Y, Zheng Y, et al. Effect of Rivaroxaban or Apixaban in Atrial Fibrillation Patients with Stage 4-5 Chronic Kidney Disease or on Dialysis. *Cardiovasc Drugs Ther*. 2021;35(2):273-281. doi:10.1007/s10557-021-07144-8
12. Mavrakanas TA, Garlo K, Charytan DM. Apixaban versus No Anticoagulation in Patients Undergoing Long-Term Dialysis with Incident Atrial Fibrillation. *Clin J Am Soc Nephrol*. 2020;15(8):1146-1154. doi:10.2215/CJN.11650919
13. Beinart R, Zhang Y, Lima JA, et al. The QT interval is associated with incident cardiovascular events: the MESA study. *J Am Coll Cardiol*. 2014;64(20):2111-2119. doi:10.1016/j.jacc.2014.08.039
14. Joki N, Tanaka Y, Hayashi T. Sudden Death, A Common Cause of Death in Japanese Hemodialysis Patients. *J Atheroscler Thromb*. 2020;27(4):303-305. doi:10.5551/jat.ED122
15. Genovesi S, Rossi E, Nava M, et al. A case series of chronic haemodialysis patients: mortality, sudden death, and QT interval. *Europace*. 2013;15(7):1025-1033. doi:10.1093/europace/eus412

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All the speakers reviewed and approved the content.