EHRA POSITION PAPER

Chronic kidney disease in patients with cardiac rhythm disturbances or implantable electrical devices: clinical significance and implications for decision making-a position paper of the European Heart Rhythm Association endorsed by the Heart Rhythm Society and the Asia Pacific Heart Rhythm Society

Giuseppe Boriani (Chair, Italy)*, Irina Savelieva (Co-chair, UK), Gheorghe-Andrei Dan (Romania), Jean Claude Deharo (France), Charles Ferro (UK), Carsten W. Israel (Germany), Deirdre A. Lane (UK), Gaetano La Manna (Italy), Joseph Morton (Australia), Angel Moya Mitjans (Spain), Marc A. Vos (The Netherlands), Mintu P. Turakhia (USA), and Gregory Y.H. Lip (UK)

Document reviewers: Bulent Gorenek (Review Coordinator, Turkey), Yoshihide Takahashi (Japan), Dennis Lau (Australia), Mina Chung (USA), Jens Cosedis Nielsen (Denmark), Laurent Fauchier (France), Tatjana Potpara (Serbia), Francisco Marin (Spain), Gulmira Kudaiberdieva (Turkey), Gerhard Hindricks (Germany), Cecilia Linde (Sweden), and Michele Brignole (Italy)

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* Corresponding author. Giuseppe Boriani, Institute of Cardiology, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, S.Orsola-Malpighi University Hospital, Via Massarenti 9, 40138 Bologna, Italy. Tel: +39 051 349858; fax: +39 051 344859. *E-mail address:* giuseppe.boriani@unibo.it

Introduction

The kidney exerts multiple functions, and pathophysiological interactions between the kidney and the heart have important clinical implications, but it has only recently become clear that these interactions should be studied across the whole spectrum of reduced kidney function and not only in cases with severe, end-stage renal disease (ESRD), as has been done for many years.[1] The prevalence of chronic kidney disease (CKD), defined as a glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2 for >3 months, exceeds 10% in the adult population and reaches 47% in subjects older than 70 years, according to data from the USA, with a trend towards a recent increasing prevalence.[1,2]

Many interactions between kidney and cardiovascular functions have important implications for clinical management and health policy (*Figure 1*), since even mild forms of kidney disease are associated with an increased risk of cardiovascular morbidity and overall mortality, and renal function may worsen over time.[1,3]

Although cardiovascular disease (CVD) and cardiac disorders are more frequent and severe in CKD, they are often not recognized, or undertreated, in view of the complexity of patient management in this setting.[4] On the other hand, the presence and evolution of CKD is often not evaluated and monitored in patients with various forms of heart diseases, including patients with cardiac rhythm disturbances, a setting where CKD is associated with challenging decision-making on the management of specific treatments and interventions. In patients with cardiac diseases, CKD predisposes to acute kidney injury and *vice versa*, and
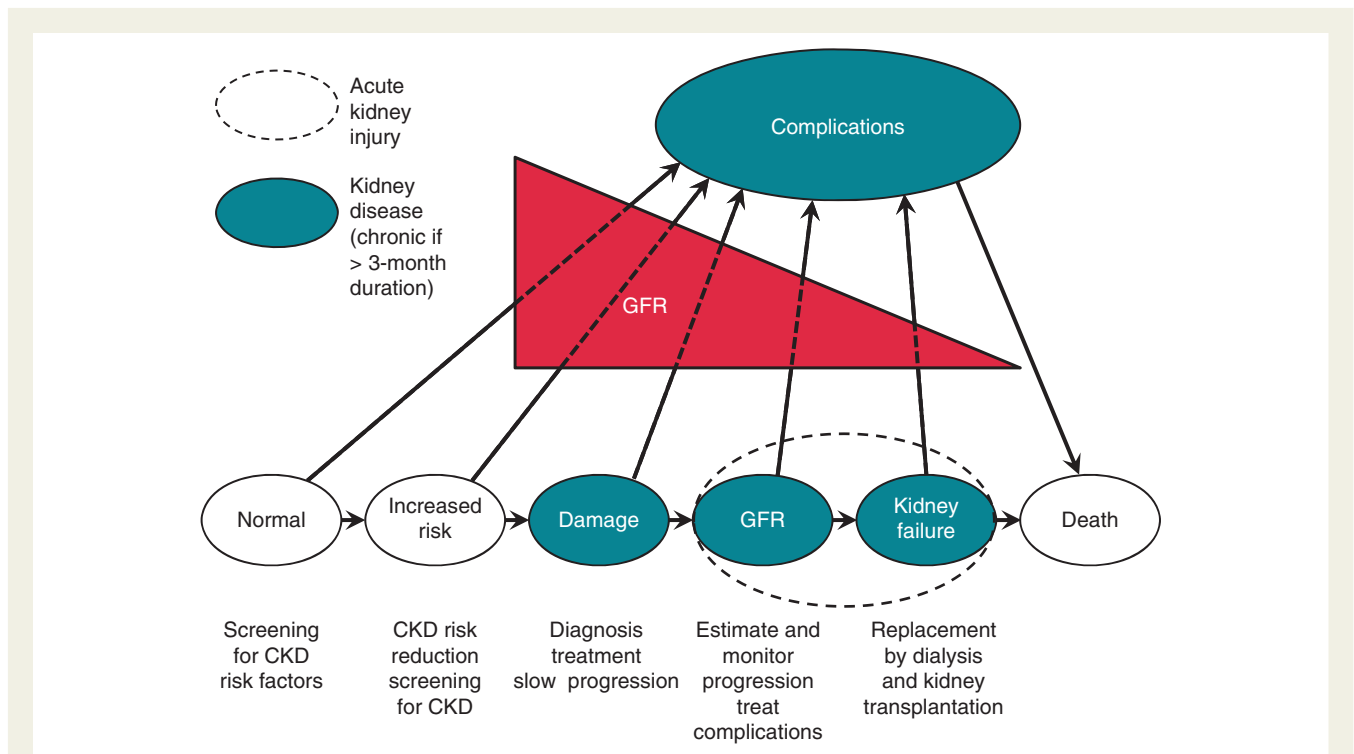
Figure 1 Stages of the development and progression of chronic kidney disease (CKD), including complications and strategies to improve outcomes. Modified from Eckardt *et al.*[1] GFR, glomerular filtration rate.

both may strongly influence clinical management of cardiac conditions.

Considering the need for increasing the awareness of CKD among the cardiologists, with specific focus on those dedicated to management of arrhythmic disorders, as well as the need to create the basis for collaborative, personalized, patient-centred care, with integration of different healthcare specialists, the European Heart Rhythm Association (EHRA), in collaboration with Heart Rhythm Society (HRS) and Asian Pacific Heart Rhythm Society (APHRS), has promoted the present document, resulting from an interaction between cardiologists and nephrologists.

How to stage chronic kidney disease and how to monitor the impairment in renal function?

Chronic kidney disease is defined as the presence of kidney abnormalities, which can involve its structure and/or its function, for a period of longer than 3 months, with implications for health.[5] This definition incorporates both a measure of chronicity as well as the concept that a variety of abnormalities of kidney structure or function may exist; not all may have implications for the health of the individual and therefore need to be taken in context.

The kidney has many functions, including excretory, metabolic, and endocrine. The GFR is the only one component of excretory function, but is widely accepted as the best overall index of kidney function, because it is generally reduced after widespread structural damage and most other kidney function declines in parallel with GFR.[5]

The GFR can be estimated from the serum creatinine using a number of equations to give an estimated GFR (eGFR).[5] Supplementary material online, *Table S1* summarizes the equations proposed for eGFR.

The Cockcroft–Gault equation was proposed around 40 years ago,[6] but has a series of bias in patients with a higher body weight or BMI, and its overall accuracy is lower than that of the two other formulas for eGFR described below.[7]

The Modification of Diet in Renal Disease (MDRD)[8] equation uses four variables (age, gender, serum creatinine, and ethnicity) to calculate eGFR and is one of the most widely used and routinely reported by laboratories globally.

The chronic kidney disease epidemiology collaboration equation (CKD-EPI) equation[9] uses the same four variables as the MDRD equation and is becoming more widely adopted.[5] The CKD-EPI equation has a less bias than the MDRD study equation, especially at GFR >60 mL/min/1.73 m^2, a small improvement in precision and greater accuracy.[10] The clinician should remain aware of caveats for any estimating equation, which may influence the accuracy in a given individual patient and consider using additional tests (such as cystatin C or a clearance measurement) for confirmatory testing in specific circumstances when eGFR based on serum creatinine is less accurate.[5,9] For example, in chronic heart failure, cystatin C may be a more sensitive marker of impaired GFR compared with creatinine partly due to the loss of muscle mass associated with this condition.[11]

The current recommended staging of CKD is based on a classification encompassing cause and severity, as expressed by the level of GFR and the level of albuminuria (Cause, GFR, and Albuminuria referred to as CGA staging: *Table 1*; 5 KDIGO). A threshold GFR of <60 mL/min/1.73 m^2 (GFR categories G3a–G5) for >3 months is used to indicate CKD as this is less than half of the normal value in young adults of 125 mL/min/1.73 m^2.[5] Albuminuria is included as an additional marker of severity of injury, because albuminuria itself is strongly associated not only with progression of CKD but also with adverse, mainly cardiovascular, prognosis.[12–14] Albuminuria detection is recommended in patients with cardiac disease and the appropriate tests, in order of preference, are urinary albumin, reported as a ratio of urinary creatinine (albumin-to-creatinine ratio), a timed urine collection for urinary albumin, urine protein-to-creatinine ratio, and reagent strip point-of-care urinalysis.[5]

The presence of CKD should be monitored over time: renal function and albuminuria should be repeated at least once a year but more frequently if the patient has a high risk of progression and/or where measurement will impact therapeutic decisions.[5] Progression

Table 1 Staging of chronic kidney disease according to the CGA approach (Cause, Glomerular Filtration, and Albuminuria)

Cause of CKD	GFR categories (ml/min/1.73 m^2)	Albuminuria categories
Presence or absence of systemic disease	G1: $\geq$90 (normal or high)	ACR (mg/g): A1 $<$30 (normal or mildly increased) A2 30–300 (moderately increased) A3 $>$300 (severely increased)
Location within the kidney of pathological–anatomical findings (glomerular, tubulointerstitial, vascular, cystic, and congenital diseases)	G2: 60–89 (mildly decreased)	ACR (mg/mmol): A1: $<$3 (normal or mildly increased) A2: 3–30 (moderately increased) A3: $>$300 (severely increased)
	G3a: 45–59 (mildly to moderately decreased) G3b: 30–44 (moderately to severely decreased) G4: 15–29 (severely decreased) G5: $<$15 [kidney failure (includes ESRD)]	AER (mg/24 h): A1: $<$30 (normal or mildly increased) A2: 30–300 (moderately increased) A3: $>$300 (severely increased)

CKD, chronic kidney disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate; ACR, albumin-to-creatinine ratio; AER, albumin excretion rate.

of CKD is based on a decline in GFR category, recognizing that small fluctuations in GFR are common and are not necessarily indicative of progression.[5] Rapid progression is currently defined as a sustained decline in eGFR of >5 mL/min/1.73 m^2/year. In patients with CKD progression, current management should be reviewed and potentially reversible causes of progression assessed. Consideration should also be given to a specialist referral.

Epidemiology of chronic kidney disease and its relationships to hypertension, heart failure, and atrial fibrillation

There is growing global awareness and recognition of early CKD as a public health problem since the introduction of a clearer, multi-layered definition of the condition based on GFR initially proposed by the National Kidney Foundation Kidney Disease Outcome Quality Initiative in 2002[15] and subsequently updated in the KDIGO clinical practice guidelines.[5,16]

Data from the National Health and Nutrition Examination Surveys in the USA suggest that the prevalence of moderately reduced GFR (30–59 mL/min/1.73 m^2) significantly increased in 1999–2004, as compared to 1988–1994, from 5.4 to 7.7%, and also the prevalence of severely reduced GFR (15–29 mL/min/1.73 m^2) significantly increased from 0.21 to 0.35%.[17] Most of the increase can be explained by the increasing prevalence of hypertension and diabetes.[17] Other countries suggest a similar prevalence with marked increases in older age groups.[17–24]

Chronic kidney disease and CVDs share many common risk factors such as hypertension, diabetes, and age. Epidemiological studies and surveys show an age-associated GFR decline, observed in both longitudinal and cross-sectional studies, although with substantial variability among individuals within the population.[5] Chronic kidney disease is an independent risk factor for cardiovascular morbidity and mortality, with an inverse graded relationship with GFRs <60 mL/min/1.73 m^2,[12,25] and perhaps <90 mL/min/1.73 m^2,[26] independent of other risk factors. Although cardiovascular risk in ESRD is extreme,[27,28] the public health burden of CVD caused by early-stage CKD is much greater.[29] In a recent meta-analysis of the relationship between eGFR and cardiovascular risk, a 30% lower GFR was consistently associated with a 20–30% higher risk of major vascular events and all-cause mortality.[30] If causal, this would imply that up to 10% of vascular events in middle age and 20% in old age might be attributable to reduced renal function. The phenotype of CVD associated with CKD is multifactorial with arterial stiffening causing heart failure, stroke, arrhythmic sudden death, and premature atherosclerosis causing vascular occlusive events.[31,32]

A strong, independent and graded relationship also exists between the degree of albuminuria and cardiovascular risk.[12] Cardiovascular risk is increased even within currently defined normal levels of albuminuria and below those that can be detected by a standard urinary dipstick.[12] Albuminuria, together with eGFR, exerted a multiplicative effect on the risks of all-cause and cardiovascular mortality.

There is a close relationship between the heart and kidney with accumulating evidence that dysfunction of one organ negatively affects the other, the so-called Cardio-Renal Syndrome (CRS).[33–35] Acute heart failure leading to CKD is defined as type 1 CRS, chronic heart failure leading to CKD as type 2 CRS, acute kidney disease leading to an acute cardiac disorder (e.g. arrhythmia, heart failure, cardiac ischaemic event, etc.) as type 3 CRS, and CKD leading to cardiac problems and adverse cardiac events as type 4 CRS, whereas type 5 CRS refers to a systemic condition (e.g. sepsis) causing both cardiac and renal dysfunction.

Observational data show that heart failure and CKD commonly coexist with CKD documented in 26–63% of heart failure patients,[36–38] but cannot determine which of the two disease processes was primary vs. secondary.[34] The close relationship between CKD and heart failure is also demonstrated in other cardiovascular conditions. Approximately 30% of patients with hypertension will have CKD, whereas nearly 90% of patients with CKD will also be hypertensive.[39] Similarly, the prevalence of atrial fibrillation (AF) in the general population is ~1–2% and increases markedly with age,[40–44] and ~11–23% of patients with AF will have CKD.[40,44–47]

Having CKD is associated with an increased risk of subsequently developing AF and *vice versa*.[48] The prevalence of AF in patients on dialysis is high with estimates ranging from 7 to 27% and also increases with age.[49] However, the relative risk is much higher in the young.[49] Among dialysis patients aged >65, the incidence of AF is quite high (15%) and incidence and prevalence have both steadily increased since 1995.[50,51] Fortunately, mortality and stroke incidence after the development of AF in this population has continued to decline.[50] The prevalence of AF in the pre-dialysis CKD population appears to be similar to that of the dialysis population at 4–21%.[52–55] Chronic kidney disease is also present in a substantial proportion of patients with acute coronary syndromes; indeed, large registries report that almost 40% of patients with non-ST-elevation myocardial infarction and 30% of those with ST-elevation myocardial infarction have significant renal impairment, with GFR <60 mL/min/1.73 m^2.[56,57]

Progression of chronic kidney disease and impact on patients' outcomes

Reduced glomerular filtration and proteinuria have repeatedly been shown to increase risk of cardiovascular events across a spectrum of cardiovascular risk profiles.[12,58–60] Death from CVD is a common cause of death patients with progression of CKD. The increase in cardiovascular risk is generally proportional due to the severity of CKD, which is due to a combination of the independent risk attributable to CKD as well as the increased prevalence of other cardiovascular risk factors, such as diabetes and hypertension, in advanced CKD.

Patients with less severe CKD are more likely to die of CVD than to develop kidney failure.[58,61] The cause of death is most commonly linked to CVD, as incident coronary heart disease is quite common.[62] In a study of 28 000 patients with GFR ≤90 mL/min from a single healthcare system in the USA, the 5-year rate of renal replacement therapy for CKD stages 2, 3, and 4 was 1.1, 1.3, and

19.9%, respectively, whereas the mortality rate was 19.5, 24.3, and 45.7%.[27] Congestive heart failure, coronary disease, and diabetes were more prevalent in patients who died. However, younger patients with significant proteinuria, more localized kidney disease, and an absence of other cardiovascular risk factors are more likely to progress to renal replacement therapy prior due to a lower competing risk of cardiovascular death.[63]

Clinical predictors of accelerated progression may therefore also predict the development of cardiovascular sequelae. Multivariate analyses from a number of observational studies have defined clinical predictors of accelerated GFR decline, including more severe proteinuria, higher blood pressure, lower serum high-density lipoprotein, black ethnicity, smoking, physical inactivity, and obesity.[64–66] More recently, a model including age, sex, eGFR, and laboratory tests commonly performed in CKD patients (albuminuria, serum calcium, serum phosphate, serum bicarbonate, and serum albumin) predicted CKD progression with high discrimination (C-statistic 0.917 in derivation and 0.841 in validation).[67]

Atrial fibrillation has been shown to accelerate CKD progression. In a regional US healthcare system study of 206 229 patients with GFR <60 mL/min, incident AF increased the risk of progression to ESRD (HR 1.67).[68] Such modification of progression by AF has been demonstrated even in relatively preserved function with no dipstick-detectable proteinuria.[48] More recent observational data suggest that anticoagulation in AF could be associated with a slowing of CKD progression.[69,70] Therefore, treatment of secondary factors associated with CKD progression, which may include CVD s themselves, could favourably reduce the cumulative risk of cardiovascular morbidity and mortality.

Implications of chronic kidney disease in the management of a patient with arrhythmias

Arrhythmogenesis in chronic kidney disease: electrolyte disturbances, modulation of arrhythmia mechanisms, and fibrosis

The cardio-renal axis is regulated in such a way that a disturbed balance will both result in cardiac and renal remodelling, a process which is highlighted when considering arrhythmias in patients with impaired renal function.

Patients with the various stages of CKD may present a wide spectrum of arrhythmias, including supraventricular tachycardias, and particularly AF, ventricular ectopic beats, sustained 'malignant' ventricular tachyarrrhythmias, and sudden cardiac death (SCD).[71] In more advanced stages, bradyarrhythmias and asystole may also occur, usually associated with hyperkalaemia or other electrolyte derangements.[71]

Ventricular tachyarrhythmias may lead to SCD, but the nature and risk of SCD in dialysis patients remain obscure, although a link with progressive coronary artery disease and myocardial ischaemia has been established. Cardiac arrest after acute myocardial infarction is twice as common in patients on dialysis compared with those with normal renal function.[72] The pathological processes that cause

coronary artery disease are also likely involved in CKD: hyperlipidaemia, hypertension, diabetes, acid–base balance, calcium phosphate metabolism, and inflammatory factors. Still, it appears that arrhythmogenesis in CKD patients also has additional contributing factors other than atherosclerosis. In studies on statins, a dissociation was found between the positive effect on major cardiovascular events and the lack of benefit on cardiovascular mortality and SCD.[72,73]

Arrhythmogenesis in patients with CKD is related to many potentially concurring factors, as presented in *Table 2*. Among these additional factors favouring arrhythmogenesis, some deserve special consideration:

1. *Left ventricular (LV) hypertrophy and fibrosis*: LV hypertrophy and QT-prolongation (acquired long QT) are common among CKD patients. Left ventricular hypertrophy may, in some cases, evolve to heart failure, an important extra contributor to arrhythmias and SCD.[74] Increased amounts of certain uraemic toxins and an imbalance in the activity of parathyroid hormone promote different forms of cardiac fibrosis. Fibrosis not only compromises the contractile performance, but also hampers intercellular coupling, slows conduction, and thereby increases the propensity to develop ventricular arrhythmias.

2. *Autonomic imbalance*: Sympathetic overactivity is present in all stages of CKD and has long-term pro-arrhythmic effects: it increases repolarization heterogeneity and induces hypertrophy and fibrosis.

3. *Rapid fluid and electrolyte shifts*: Fluid and electrolyte shifts during conventional dialysis treatment may trigger AF or ventricular arrhythmias by favouring electrical instability.[71,75] A number of electrolyte disturbances are known for their increased risk for pro-arrhythmia:

   - *Acute or chronic hypokalaemia*: Hypokalaemia evokes both supraventricular and ventricular tachyarrhythmias. In the ventricles, it delays repolarization (an increase in QT interval) in ventricular myocytes, while increasing the automaticity in

Table 2 Factors involved in arrhythmogenesis in CKD

Electrolyte alterations (chronic and acute)
Autonomic imbalance
Haemodynamic instability during haemodialysis
Prolongation and increased dispersion of ventricular repolarization
Left ventricular hypertrophy
Left ventricular dysfunction
Myocardial fibrosis
Scars due to myocardial infarction
Macro and microvessels angiopathy (atherosclerosis, diabetic microangiopathy, vascular calcification, etc.)
Endothelial dysfunction
Inflammatory processes
Oxidative stress
Acidosis and acidaemia
Anaemia
Uraemic state

Purkinje fibres (an increase in ventricular ectopy). The appearance of U-waves in the ECG is one of the typical characteristics.

- *Acute or chronic hyperkalaemia*: Hyperkalaemia is associated with changes at the ECG which, in progression, include tall, peaked T waves with a shortened QT interval (initial findings), followed, with progression of the disorder by lengthening of the PR interval and QRS duration, disappearance of the P wave, idioventricular rhythms, and ultimately marked widening of the QRS up to a sine-wave pattern. Pronounced shortening of the action potential duration may favour re-entrant arrhythmias in conditions of slowed conduction.[76] Ventricular standstill with asystolic cardiac arrest can be a terminal event. The progression and severity of ECG changes have no strict correlation with serum potassium concentrations, and changes are more evident if hyperkalaemia has a rapid onset. Hyperkalaemia can also cause a type I Brugada pattern.
- *Hypocalcaemia*: This condition, frequently seen in chronic renal insufficiency, is able to decrease contractility and to increase excitability. It appears most frequently in combination with other electrolyte abnormalities.
- *Hyperphosphataemia*: It is characteristic of ESRD, and may facilitate ventricular tachyarrhythmias and SCD.
- *Hypo- or hypermagnesaemia*: These electrolyte alterations usually develop in combination with derangements of the other electrolytes and their independent contribution to arrhythmogenesis is uncertain.

Changes in drug pharmacokinetics in chronic kidney disease with specific focus on antiarrhythmic agents, beta-blockers, and antithrombotic drugs

Pharmacokinetic (PK) studies are not performed routinely in patients with CKD; however, physicians should be aware of the data published in guidelines or provided as summary of product characteristics (SmPC). Potential problems associated with modified PK in CKD patients are:[5]

1. reduced ability to excrete drugs and/or their metabolites,

2. increased sensitivity to medications (e.g. those bound to albumin in hypoalbuminaemic states such as nephritic syndrome),
3. diminished tolerance of side effects, particularly in the elderly, and
4. loss of efficacy

A detailed list of the main alterations of drug PK in CKD patients is summarized in *Table 3*.

Despite several guidelines, there are still controversies regarding the best modality to guide therapeutic decisions of common drugs in patients with CKD.[77] The current guidelines recommend evaluation of GFR when deciding the dose of the drug.[5] Cockcroft−Gault formula, MDRD, or CKD-EPI equations could be used for this purpose each demonstrating virtues and limitations. In the case of drugs with narrow therapeutic ranges (the case of many antiarrhythmic drugs), when precision is desired or in special cases when formula estimate is inaccurate (low muscle mass), direct determination of GFR is required. As recommended by the guidelines,[5] people with CKD should receive, when possible, the same treatment as those with normal renal function. However, the dosages may need adjustment according to GFR, given the implications on prolonged half-life and reduced clearance of the drug, especially for drugs with narrow therapeutic ranges.[77]

The loading dose of a drug is a function of peak concentration desired, volume of distribution, bioavailability (which is 1 for intravenous-administered drugs), and weight. There are no guideline recommended loading doses for antiarrhythmics, beta-blockers, and most antithrombotic drugs. Without a loading dose, maintenance doses will achieve 90% of their steady-state level in 3−4 half lives. The dosage could be adapted in CKD patients through reduction in dose and/or lengthening the dosage interval (more useful with drugs with a longer half-life and a wider therapeutic range).

The main PK characteristics and suggestions for appropriate prescription in CKD patients for most used beta-blockers and antiarrhythmic drugs are described in *Table 4*.[78]

The main PK characteristics for oral anticoagulants and dosing recommendations, in relation with renal function (usually evaluated with the Cockcroft−Gault formula in trials) and according to regulatory approvals, are provided in *Table 5*.[79,80]

Table 3 Main alterations in drug PK in patients with CKD

PK characteristics	Alterations in CKD
Bioavailability	Decreased absorption (alkaline media, reduced peristalsis, bowel oedema, and phosphate chelation)
	Altered first pass (decreased biotransformation of parent drug and impaired protein binding resulting in more free drug available for liver)
Volume of distribution	Increased volume of distribution or extracellular volume overload
	Decreased volume of distribution in muscle wasted patients
Protein binding	Increased or decreased protein binding with a correspondent decrease or increase in free (active) drug concentration
	Low albumin increases active drug
	Organic acids accumulate in renal failure and compete with acid drugs for protein binding
Drug metabolism/renal elimination	Drug metabolism could be modified and unpredictable (increased or decreased)
	Non-renal elimination could be compensatory increased resulting in higher concentrations of potential toxic metabolites
	Parent compound could accumulate in CKD

Table 4 Main PK characteristics and suggestions for appropriate prescription in CKD patients for most used beta-blockers and antiarrhythmic drugs (modified from ref.[78])

Drug	PK and elimination	Indications for CKD
Atenolol	About 5% bound to plasma protein; $T_{1/2}$ ~6 h but action duration is 24 h; excreted unchanged in urine	Dose may need to be reduced
Bisoprolol	Approximately 30% bound to protein; peak plasma concentration in 2−4 h; metabolized by the liver but ~50% excreted unchanged in urine	Monitoring; dose may need to be reduced in advanced CKD
Carvedilol	99% protein bound; $T_{1/2}$ ~6−10 h; elimination mainly biliary and 16% urinary	Dosage adjustment usually not required excepting advanced renal failure and elderly
Labetalol	90% protein bound; $T_{1/2}$ ~6−8 h metabolized by liver with inactive metabolites excreted in urine and bile; <5% excreted unchanged in urine	Dose reduction recommended in the elderly
Metoprolol	Approximately 12% protein bound; $T_{1/2}$ ~3−5 h but the effect persists for 12 h; <5% excreted unchanged in urine	No dosage reduction needed
Sotalol	Not protein bound; $T_{1/2}$ ~7−18 h; not metabolized; excreted unchanged in urine (~70%)	Dose to be reduced to one half in CKD and one quarter in severe renal failure where there is relative contraindication in view of the risk of pro-arrhythmic effects
Procainamide	15% protein bound; bounds to different tissues; active hepatic metabolite; variable hepatic and renal elimination (60% unchanged); longer elimination in renal failure	Reduction of dose recommended
Quinidine	85% protein bound; 50−90% metabolized by the liver to active metabolites; $T_{1/2}$ ~6 h; 20% excreted in urine	Pro-arrhythmia; could interfere with renal clearance of other drugs
Lidocaine	65% protein bound; 80% rapidly metabolized by the liver to active metabolites; $T_{1/2}$ <2 h; <10% excreted unchanged in urine	No special requirements
Mexiletine	50−70% protein bound; $T_{1/2}$ ~5−17 h; ~15% excreted unchanged in urine	No special requirements
Flecainide	$T_{1/2}$ ~20 h; metabolized by the liver and excreted unchanged in urine (35%)	Dose reduction if GFR <35 mL/min/1.73 m^2
Propafenone	95% protein bound; metabolized by the liver to active metabolites, excreted in urine (38%); two genetically determined pathways of metabolism (>90% people are rapid metabolizers with $T_{1/2}$ ~2−10 h); <1% excreted unchanged in urine	Careful monitoring recommended (in hospital initiation if advanced CKD)
Vernakalant	25−50% protein bound, extensively and rapidly distributed in the body after intravenous administration, not extensively bound to plasma proteins. Mainly eliminated by the liver with $T_{1/2}$ ~3−5.5 h	Available for intravenous administration at the dose of 3.0 mg/kg followed by 2.0 mg/kg if required
Amiodarone	99% protein bound; widely distributed to different tissues; metabolized by the liver to two active metabolites; no renal elimination	No dosage requirements; not dialyzable; many drug-to-drug interactions
Dronedarone	~98% protein bound; metabolized by the liver to active and inactive metabolites; $T_{1/2}$ ~13−19 h; 6% excreted in urine	No dosage adaptation required in mild and severe renal failure
Dofetilide	High (>90%) bioavailability; protein binding of 60−70%; 80% excreted by the kidney, as unchanged dofetilide (80%) or as inactive or minimally active metabolites (20%); $T_{1/2}$ ~10 h	Dose individualized on the basis of GFR; contraindicated if GFR <20 mL/min
Diltiazem	70−80% protein bound; extensive first-pass effect, metabolization in the liver to active metabolites; bioavailability of ~40%; $T_{1/2}$ ~3.5−9 h; only 2−4% unchanged drug excreted in the urine	Use with caution
Verapamil	About 90% protein bound. High first-pass metabolism, Metabolized in the liver to at least 12 inactive metabolites. Bioavailability 10−35%. 70% is excreted in the urine and 16% in faeces. $T_{1/2}$ ~5−12 h	Dose reduction by 25−50% if CrCl <10 mL/min. Not cleared by haemodialysis
Adenosine	Rapid cell uptake and clearance; PK difficult to be studied; not dependent on renal function	No dosage adaptation required
Digoxin	20−30% protein bound; $T_{1/2}$ ~26−45 h; main route of elimination is renal (closely correlated with the GFR) with 25−28% of elimination by non-renal routes	Dosage adaptation is required, with monitoring of serum digoxin levels

CKD, chronic kidney disease; CrCl, creatinine clearance; GFR, glomerular filtration rate; PK, pharmacokinetics.

Table 5 Main PK characteristics for oral anticoagulants and dosing recommendations, according to regulatory approvals (modified from refs[79,80])

	Warfarin	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fraction renally excreted of absorbed dose		80%	27%	50%	35%
Bioavailability	95–100%	3–7%	50%	62%	66% without food. Almost 100% with food
Fraction renally excreted of administered dose		4%	14%	37%	33%
Approved for CrCl		≥30 mL/min	≥15 mL/min	≥15 mL/min	≥15 mL/min
Dosing recommendation	CrCl ≥30 mL/min: no adjustment	CrCl ≥50 mL/min: no adjustment (i.e. 150 mg b.i.d.)	Serum creatinine ≥1.5 mg/dL: no adjustment (i.e. 5 mg b.i.d.)	60 mg daily for CrCl 50–95 mL/min, 30 mg daily for CrCl 15–50 mL/min, weight ≤60 kg; not recommended for CrCl >95 mL/min	CrCl ≥50 mL/min: no adjustment (i.e. 20 mg qd)
Dosing if CKD	When CrCl <30 mL/min: use lower doses and monitor closely	When CrCl 30–49 mL/min, 150 mg b.i.d. is possible (SmPC) but 110 mg b.i.d. is recommended if high risk of bleeding[79]	CrCl 15–29 mL/min: 2.5 mg b.i.d. Serum creatinine ≥1.5 mg/dL in combination with age of ≥80 years or weight ≤60 kg (SmPC) or with other factors that increase bleeding risk (e.g. diltiazem): 2.5 mg b.i.d.	60 mg daily for CrCl 50–95 mL/min, 30 mg daily for CrCl 15–50 mL/min, weight ≤60 kg; not recommended for CrCl >95 mL/min	15 q.d. when CrCl 15–49 mL/min
Not recommended if		CrCl <30 mL/min	CrCl <15 mL/min	If CrCl >95 mL/min or <15 mL/min	CrCl <15 mL/min

Risk of thromboembolic events and risk of bleeding in atrial fibrillation

Patients with CKD are at a high risk of developing incident arrhythmias, such as AF. The presence of AF is also associated with a higher risk of ESRD among patients with CKD.[50,68] When AF is present, patients with associated CKD are at a high risk of stroke and thromboembolism, as well as major bleeding, as included in Tables 6–8.[55,81–94] Patients with renal replacement therapy, whether dialysis or renal transplantation, are at particularly a high risk of thromboembolism and bleeding.[55,82,89]

With regard to stroke risk per se, AF patients with CKD are clearly at higher risk. Also, the addition of renal impairment (with two points), or the presence of proteinuria or reduced creatinine clearance, was proposed to improve a prediction value of the $CHADS_2$ score for stroke, leading to the R_2CHADS_2 (Renal dysfunction [doubled], Congestive heart failure, Hypertension, Age >75, Diabetes, previous Stroke [doubled]) in a substudy from the ROCKET-AF (Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) trial and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) stroke risk scores.[95,96]

Nonetheless, the limitations of the R_2CHADS_2 score include its derivation in a selected anticoagulated trial cohort that excluded patients with severe renal impairment (creatinine clearance <30 mL/min), as well as the evidence that some patients at risk of stroke ($CHADS_2$ score 0–1) were excluded from the ROCKET-AF trial. The R_2CHADS_2 score is also inferior to the CHA_2DS_2-VASc score in predicting stroke and thromboembolism.[97] Also, those classed as a 'low risk' using the ATRIA score are not a 'low risk' with stroke rates >4%/year if assessed by the CHA_2DS_2-VASc score and left untreated.[98,99] In multiple 'real-world' non-anticoagulated cohorts including a broad range of renal (dys)function and stroke risk, CKD does not independently add to the risk of stroke, beyond established stroke risk prediction rules, such as the CHA_2DS_2-VASc score.[84,87,100] Furthermore, in one trial cohort with a wider range of renal (dys)function and stroke risk, CKD did not significantly add to the stroke prediction value of the CHA_2DS_2-VASc score.[88]

However, renal dysfunction may be co-morbidity determining the higher stroke risk among females,[101] and may have implications for optimizing good quality anticoagulation control among patients on vitamin K antagonists (VKA, e.g. warfarin). Thus, renal disease is one component of 'Medical co-morbidities' within the $SAMe-TT_2R_2$ score (Sex female, Age <60 years, Medical history [more than two co-morbidities], Treatment [interacting drugs, e.g. amiodarone for rhythm control], Tobacco use [doubled], Race [doubled]) that helps prediction of those patients likely to achieve good anticoagulation control, with a high time in therapeutic range (TTR).[102] Indeed, a high TTR is associated with a low risk of thromboembolism and bleeding.[103,104]

Renal impairment also increases the risk of bleeding, and scores one point in the HAS-BLED score[105] for predicting major haemorrhage in patients with AF.

Optimal thromboprophylaxis in patients with AF and end-stage CKD is a controversial area. Patients with haemodialysis on warfarin seem to be at particularly a high risk of serious bleeding, which may

Table 6 Risk of thromboembolic and bleeding events in AF patients with renal impairment

Author, year, country	Study population	Definition of renal impairment	ATT therapy	Thromboembolic events	Bleeding events
Providência, 2014[81]	Meta-analysis 19 studies 379 506 patients AF patients with CKD	Cockroft−Gault ($n = 5$) MDRD ($n = 5$) CKD-EPI ($n = 2$) Coding	Warfarin, NOACs, aspirin, or none	CKD ↑ TE risk [HR (95% CI) 1.46 (1.20−1.76); $P = 0.0001$] End-stage CKD ↑ TE risk [HR (95% CI) 1.83 (1.56−2.14); $P < 0.00001$] Warfarin ↓TE in non-end-stage CKD patients [HR (95% CI) 0.39 (0.18−0.86); $P < 0.00001$] NOACs ↓TE compared with warfarin [HR (95% CI) 0.80 (0.66−0.96); $P = 0.02$] and aspirin [HR (95% CI) 0.32 (0.19−0.55); $P < 0.0001$] in non-end-stage CKD patients	
Shah, 2014, Canada[82]	Retrospective population-based cohort study Patients aged ≥65 years admitted to the hospital with primary/secondary diagnosis of AF from 1998 to 2007	Dialysis: $n = 1626$ Mean (SD) age: 75 (8) years; 634 (39.0%) women Non-dialysis: $n = 204\,210$ Mean (SD) age: 78 (10); 104 652 (51.2%) women	Warfarin vs. no warfarin OAC: 756 (46.4%) dialysis vs. 103 473 (50.7%) non-dialysis	No. of events (incidence rate per 100 patient-years) Dialysis patients: 107 (3.12) On warfarin vs. off-warfarin: 52 (3.37) vs. 55 (2.91) Non-dialysis patients: 19 489 (2.35) On warfarin vs. off-warfarin: 9241 (2.19) vs. 10 248 (2.51) Warfarin use not associated with ↓stroke risk in dialysis patients [adjusted HR (95% CI) 1.14 (0.78−1.67)] ↓Stroke risk with warfarin use in non-dialysis patients [adjusted HR (95% CI) 0.87 (0.85−0.90)]	No. of events (incidence rate per 100 patient-years) Dialysis patients: 275 (8.89) On warfarin vs. off-warfarin: 149 (10.88) vs. 126 (7.31) Non-dialysis patients: 34 035 (4.32) On warfarin vs. off-warfarin: 18 340 (4.64) vs. 15 695 (4.00) Warfarin use ↑bleeding risk in dialysis [adjusted HR (95% CI) 1.44 (1.13−1.85)] and non-dialysis [HR (95% CI) 1.19 (1.13−1.85)] patients
Kooiman, 2014, The Netherlands[83]	724 AF patients without CKD or non-dialysis-dependent CKD on OAC attending the Leiden clinic between 1997 and 2005 Follow-up: 31 December 2010 Median follow-up 2.1 years for stroke/TIA and 2.3 years for major bleeding events Mean (SD) age 75 (10); 43.5% women	Abbreviated MDRD formula No CKD (eGFR >60 mL/min): $n = 300$ Moderate CKD (30−60 mL/min): $n = 294$ Severe CKD (eGFR <30 mL/min) = 130	All OACs	45/724 (6.2%) (1.67/100 patient-years) stroke/TIA ↑Stroke/TIA risk in patients with severe CKD vs. those without CKD [HR (95% CI) 2.75 (1.25−6.05)] vs. those with moderate CKD [HR (95% CI) 3.93 (1.71−9.00)] Similar stroke/TIA risk for patients with moderate CKD vs. without CKD (data not reported)	ISTH criteria for major bleeding 113/724 (15.6%) (4.8/100 patient-years) Non-significant ↑ in major bleeding risk with severe CKD vs. no CKD [HR (95% CI) 1.66 (0.97−2.86)] and those with moderate CKD [HR (95% CI) 1.86 (1.08−3.21)] Similar risk of major bleeding for patients with moderate CKD vs. no CKD (data not reported)
Friberg, 2014, Sweden*[84]	Retrospective analysis of Swedish AF national registry 307 351 patients with hospital diagnosis of AF between 1 July 2005 and 31 December 2010 13 435 (4.4%) with previous diagnosis of renal failure	ICD-10 codes (N17-19) or local codes for dialysis or renal transplantation Mean (SD) age; % women Renal failure: 78.4 (10.3); 4802 (35.7%) No renal failure: 74.8 (12.5); 123 333 (45.6%)	Warfarin at baseline Renal failure: 3766 (28.0%) No renal failure: 10 794 (39.9%)	↑ Annual rate of ischaemic stroke [3.9 vs. 2.9%; HR (95% CI) 1.25 (1.16−1.34)] and TE [8.2 vs. 5.2%; HR (95% CI) 1.42 (1.35−1.49)] with renal failure; however, no significant difference after full adjustment for confounders [adjusted HR (95% CI) 1.02 (0.95−1.10) and 1.12 (1.07−1.18) for ischaemic stroke and TE, respectively] Irrespective of renal function, patients on warfarin at baseline had ↓ stroke and TE than those not on warfarin at baseline [HR 0.69 vs. 0.70 in patients with and without renal failure; P-value for interaction $P = 0.865$]	↑ Annual rate of any bleeding [9.8 vs. 4.1%; HR (95% CI) 2.24 (2.14−2.35); and ICH [0.8 vs. 0.5%; HR (95% CI) 1.50 (1.28−1.74)] with renal failure Renal failure-independent risk factor for any bleeding [adjusted HR (95% CI) 1.56 (1.48−1.63)] and ICH [adjusted HR 1.27 (1.09−1.49)]

Continued

Table 6 *Continued*

Author, year, country	Study population	Definition of renal impairment	ATT therapy	Thromboembolic events	Bleeding events
Chao, 2014, Taiwan[85]	Retrospective analysis of Taiwan's National Health Insurance Research Database between 1 January 1996 and 31 December 2011 10 999 AF patients with ESRD undergoing renal replacement therapy, not on OAC or APT Mean (SD) age 71.0 (11.1) years; 5913 (53.8%) women	ESRD defined by ICD-9-CM codes	None	Ischaemic stroke 1217 pts. (11.7%); incidence rate of 6.9 per 100 patient-years	† 9.7% severe bleeding (bleeding not defined)
Roldán, 2013, Spain*[86]	978 consecutive stable anticoagulated (INR 2.0–3.0 within previous 6 months) AF patients from outpatient clinic Median (IQR) age 76 (70–81); 482 (49.3%) women Median (IQR) follow-up: 875 (706–1059) days	MDRD Renal impairment: eGFR <60 mL/min/1.73 m^2	OAC	CV events (stroke, TIA, peripheral embolism, ACS, acute HF, and cardiac death) 113 patients (4.82%/year) adverse CV events; 39 (1.66%/year) strokes eGFR (categorical variable per 30 mL/min/1.73 m^2 decrease) was significantly associated with thrombotic/vascular events [unadjusted HR (95% CI) 1.42 (1.11–1.83); $P = 0.006$] Adjusted for 'high-risk' (CHA$_2$DS$_2$-VASc score ≥2) eGFR (per 30 mL/min/1.73 m^2 decrease) was significantly associated with thrombotic/vascular events [adjusted HR (95% CI) 1.37; 1.07–1.76; $P = 0.012$]	ISTH criteria for major bleeding 81 patients (3.46%/year) haemorrhagic events 16 ICH (0.68%/year) eGFR (categorical variable per 30 mL/min/1.73m^2 decrease) ↑ risk of bleeding (HR 1.44; 1.08–1.94; $P = 0.015$) Adjusted for 'high-risk' (HAS-BLED ≥3) eGFR (per 30 mL/min/1.73 m^2 decrease) was significantly ↑ risk of bleeding [adjusted HR (95% CI) 1.34 (1.00–1.80); $P = 0.046$]
Banerjee, 2013, France*[87]	Loire Valley cohort 5912 patients with first recorded AF diagnosis in hospital between 1 January 2000 and December 2010 with baseline serum creatinine data Mean follow-up: 2.45 (3.56) years	History of renal failure or baseline serum creatinine level >133 μmol/L (men) or >115 μmol/L (women) eGFR (mL/min/1.73m^2) three groups: ≥60 ($n = 4375$) 30–59 ($n = 1196$) <30 ($n = 341$)		TE (ischaemic stroke, TIA, and peripheral artery embolism) No. TE events and rate (95% CI) at 1 year eGFR ≥60: 64; 3.4 (2.4–4.8) eGFR 30–59: 92; 5.7 (4.2–7.8) eGFR <30: 15; 7.7 (4.3–13.6) Normal: 119; 4.4 (3.2–5.9) As a categorical variable only, eGFR was an independent predictor of TE after adjustment for age, sex, and CHADS$_2$ risk factors but not for baseline characteristics	†
Apostolakis, 2013, multicentre[88]	AMADEUS cohort 4576 AF patients. receiving OAC Mean (SD) age 70 (9) years; 1526 (33.4%) women Mean (SD) follow-up: 325 (164) days	Baseline serum creatinine available in 4554 (99.5%) Three most widely used equations to calculate renal function CrCl (Cockroft–Gault formula), MDRD and CKD-EPI Based on CrCl: 1470 (32.35) <60 mL/min 68 (1.5%) <30 mL/min	Warfarin or idraparinux	Composite of all stroke/non-CNS SE 45 strokes/non-CNS SE (1.1 events per 100 patient-years) Only data for CrCl and MDRD reported here (number of events (n/100 patient-years) CrCl ≥90: 6 (0.6) 60–89: 13 (0.8) 30–59: 26 (2.2) <30: 0 MDRD ≥90: 2 (0.4) 60–89: 17 (0.8) 30–59: 25 (1.9) <30: 1 (1.9) Adjustment for demographic characteristics and co-morbidities, patients with CrCl <60 mL/min had double the risk of risk/SE compared with those with CrCl ≥60 mL/min [adjusted HR (95% CI) 2.27 (1.14–4.52)]	ISTH criteria for major bleeding 103 major bleeds (2.5 events per 100 patient-years) CrCl ≥90: 15 (1.3) 60–89: 38 (2.4) 30–59: 48 (3.8) <30: 2 (3.2) MDRD ≥90: 7 (1.6) 60–89: 53 (2.4) 30–59: 42 (3.2) <30: 1 (1.9) Patients with CrCl <60 mL/min had ↑ risk of major bleeding compared with patients with CrCl ≥60 mL/min [adjusted HR (95% CI) 1.58 (1.05–2.39); $P = 0.027$]

Olesen, 2012, Denmark*[55]	Retrospective analysis of Danish national registries 132 372 patients with hospital discharge diagnosis of AF between 1997 and 2008 No renal disease at baseline: 127 884 (96.6%) Mean (SD) age 73.2 (12.9); 46.9% women Non-end-stage CKD 3587 (2.7%) Mean (SD) age 76.5 (11.0); 41.0% women end-stage CKD (dialysis or previous kidney transplant): 901 (0.7%) Mean (SD) age 66.8 (11.7); 33.6% women	ICD codes	OAC ± ASA, ASA, or none	No. of stroke/TE events; event rate per 100 patient-years (95% CI) No renal disease: 16 648; 3.61 (3.55−3.66) Non-end-stage CKD: 842; 6.44 (6.02−6.89) End-stage CKD: 164; 5.61 (4.82−6.54) Compared with patients with no renal disease, non-end-stage CKD patients [HR (95% CI) 1.49 (1.38−1.59; $P < 0.001$)] and those on renal replacement [HR (95% CI) 1.83 (1.57−2.14; $P < 0.001$] had ↑ risk of stroke/TE Warfarin ↓ stroke/TE risk in both groups [adjusted HR (95% CI)] No renal disease: ASA: 0.59 (0.56−0.61) OAC: 1.10 (1.06−1.14) OAC + ASA: 0.69 (0.64−0.74) Non-end-stage CKD: ASA: 0.84 (0.69−1.01) OAC: 1.25 (1.07−1.47) OAC + ASA: 0.76 (0.56−1.03) Renal replacement: ASA: 0.44 (0.26−0.74) OAC: 0.88 (0.59−1.32) OAC + ASA: 0.82 (0.37−1.80)	No. of major bleeding events; event rate per 100 patient-years (95% CI) No renal disease: 16 195; 3.54 (3.48−3.59) Non-end-stage CKD: 1097; 8.77 (8.26−9.30) Renal replacement: 243 8.89 (7.84−10.08) Adjusted HR (95% CI) No renal disease: ASA: 1.28 (1.23−1.33) OAC: 1.21 (1.16−1.26) OAC + ASA: 2.18 (2.07−2.30) Non-end-stage CKD: ASA: 1.36 (1.17−1.59) OAC: 1.12 (0.96−1.30) OAC + ASA: 1.63 (1.32−2.02) Renal replacement: ASA: 1.27 (0.91−1.77) OAC: 1.63 (1.18−2.26) OAC + ASA: 1.71 (0.98−2.99)
Go, 2009, USA*[90]	ATRIA cohort 13 535 AF patients diagnosed between 1 July 1996 and 31 December 1997 Mean age of ATRIA cohort 71.6 years; 42.8% women Follow-up until 30 September 2003	MDRD Baseline serum creatinine not available in 2627 (19.4%) patients eGFR ≥60 mL/min/1.73 m²: $n = 7690$ 45−59 mL/min/1.73m²: $n = 2499$ <45 mL/min/1.73m²: $n = 1338$	None 33 165 patient-years off-OAC among 10 908 AF patients	676 TE events (637 ischaemic strokes) during periods off-warfarin eGFR ≥60 mL/min/1.73 m²: 344 events 45−59 mL/min/1.73 m²: 168 events <45 mL/min/1.73 m²: 149 events 15 events in patients with unknown kidney function Crude rates of TE off-warfarin by eGFR eGFR ≥60: 1.63 45−59 : 2.76 <45: 4.22 Rate of TE off-warfarin ↑ significantly with lower eGFR Adjusted (for age, sex, ethnicity, education, income, previous stroke, HF, DM, hypertension, and CHD) HR (95% CI) for TE compared with eGFR ≥60 eGFR 45−59: 1.16 (0.95−1.40) eGFR <45: 1.39 (1.13−1.71) Graded increased independent risk of TE with eGFR <45 mL/min/1.73 m²	†

AMADEUS, Atrial fibrillation trial of Monitored, Adjusted Dose vitamin K antagonist, comparing Efficacy and safety with Unadjusted SanOrg 34006/idraparinux study; ACS, acute coronary syndrome; AF, atrial fibrillation; ASA, aspirin; ATRIA, AnTicoagulation and RIsk factors in Atrial fibrillation; ATT, antithrombotic therapy; CI, confidence interval; CKD, chronic kidney disease; CKD-EPI, chronic kidney disease epidemiology collaboration equation; CNS, central nervous system; CrCl, creatinine clearance; CV, cardiovascular; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; ESRD, end-stage renal disease; HF, heart failure; HR, hazard ratio; ICD, International Classification of Disease; ICH, intracranial haemorrhage; IQR, interquartile range; ISTH, International Society of Thrombosis and Haemostasis; MDRD, Modification of Diet in Renal Diet; min, minute; mL, millilitres; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulation; SD, standard deviation; TE, thromboembolism; TIA, transient ischaemic attack; vs., versus.

†, not reported; *, included in meta-analysis[81]; ↑, increase; ↓, decrease.

Table 7 Annual rates of stroke/systemic embolism in patients with normal and impaired renal function enrolled in NOAC phase III trials

Trial	Stroke/SE in patients with eGFR ≥50 mL/min (%/year)		HR (95% CI)	Stroke/SE in patients with eGFR 30–49 mL/min (%/year)		HR (95% CI)	P-value for interaction
	Intervention	Control		Intervention	Control		
RE-LY[a91]	≥80 mL/min Dabigatran 110 mg 0.88	Warfarin 1.05	0.84 (0.54–1.32)	Dabigatran 110 mg 2.32	Warfarin 2.70	0.85 (0.59–1.24)	0.91
	Dabigatran 150 mg 0.71	Warfarin 1.05	0.67 (0.42–1.09)	Dabigatran 150 mg 1.53	Warfarin 2.70	0.56 (0.37–0.85)	0.75
	50–79 mL/min Dabigatran 110 mg 1.69	Warfarin 1.83	0.93 (0.70–1.23)				
	Dabigatran 150 mg 1.25	Warfarin 1.83	0.68 (0.50–0.92)				
AVERROES[c92]	≥60 mL/min Apixaban 5 mg[b] 1.7	Aspirin 81–324 2.8	0.57 (0.37–0.87)	<60 mL/min Apixaban 2.5–5 mg[b] 1.8	Aspirin 81–324 5.6	0.32 (0.18–0.55)	0.10
ARISTOTLE[d93]	>80 mL/min Apixaban 5 mg[b] 0.99	Warfarin 1.12	0.88 (0.64–1.22)	Apixaban 2.5–5 mg[b] 2.11	Warfarin 2.67	0.79 (0.55–1.14)	0.71
	>50–80 mL/min Apixaban 5 mg[b] 1.24	Warfarin 1.69	0.74 (0.56–0.97)				
ROCKET-AF[e94]	Rivaroxaban 20 mg 1.57	Warfarin 2.00	0.78 (0.63–0.98)	Rivaroxaban 15 mg 2.32	Warfarin 2.77	0.84 (0.57–1.23)	0.76

ARISTOTLE, Apixaban for Reduction In STroke and Other ThromboemboLic Events in atrial fibrillation; AVERROES, Apixaban VErsus acetylsalicylic acid to Reduce the Risk Of Embolic Stroke; RE-LY, Randomized Evaluation of Long-term anticoagulation therapy; ROCKET-AF, Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation.

[a]RE-LY compared creatinine clearance ≥80 vs. 50–79 vs. <50 mL/min.
[b]Serum creatinine >133 mmol/L plus aged ≥80 years or body weight ≤60 kg.
[c]AVERROES compared eGF ≥60 vs. <60 mL/min.
[d]ARISTOTLE compared eGFR ≤50 vs. >50–80 vs. >80 mL/min.
[e]On treatment analyses reported.

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Table 8 Annual rates of major bleeding in patients with normal and impaired renal function enrolled in NOAC phase III trials

Trial	Major bleeding in patients with eGFR ≥50 mL/min (%/year)		HR (95% CI)	Major bleeding in patients with eGFR 30–49 mL/min (%/year)		HR (95% CI)	*P*-value for interaction
	Intervention	Control		Intervention	Control		
RE-LY[a90]	≥80 mL/min Dabigatran 110 mg 1.48	Warfarin 2.43	0.61 (0.44−0.84)	Dabigatran 110 mg 5.45	Warfarin 5.49	0.99 (0.77−1.28)	0.06
	Dabigatran 150 mg 2.04 50−79 mL/min Dabigatran 110 mg 2.84 Dabigatran 150 mg 3.35	Warfarin 2.43 Warfarin 3.70 Warfarin 3.70	0.84 (0.62−1.13) 0.76 (0.62−0.94) 0.91 (0.75−1.11)	Dabigatran 150 mg 5.50	Warfarin 5.49	1.01 (0.79−1.30)	0.64
AVERROES[c91]	≥60 mL/min Apixaban 5 mg[b] 0.9	Aspirin 81−324 0.8	1.1 (0.56−2.0)	<60 mL/min Apixaban 2.5−5 mg[b] 2.5	Aspirin 81−324 2.2	1.2 (0.65−2.1)	0.82
ARISTOTLE[d92]	>80 mL/min Apixaban 5 mg[b] 1.46	Warfarin 1.84	0.80 (0.61−1.04)	Apixaban 2.5−5 mg[b] 3.221	Warfarin 6.44	0.79 (0.55−1.14)	0.03
	>50−80 mL/min Apixaban 5 mg[b] 2.45	Warfarin 3.21	0.77 (0.62−0.94)				
ROCKET-AF[e93]	Rivaroxaban 20 mg 3.39	Warfarin 3.17	1.07 (0.91−1.26)	Rivaroxaban 15 mg 4.49	Warfarin 4.70	0.95 (0.72−1.26)	0.48

ARISTOTLE, Apixaban for Reduction In STroke and Other ThromboemboLic Events in atrial fibrillation; AVERROES, Apixaban VErsus acetylsalicylic acid to Reduce the Risk Of Embolic Stroke; RE-LY, Randomized Evaluation of Long-term anticoagulation therapy; ROCKET-AF, Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation.

[a]RE-LY compared creatinine clearance ≥80 vs. 50−79 vs. <50 mL/min.
[b]Serum creatinine >133 mmol/L plus aged ≥80 years or body weight ≤60 kg.
[c]AVERROES compared eGF ≥60 vs. <60.
[d]ARISTOTLE compared eGFR ≤50 vs. >50−80 vs. >80 mL/min.
[e]On treatment analyses reported.

outweigh the reduction in stroke by warfarin.[82] Nonetheless, the Swedish AF cohort study suggests that the quality of anticoagulation control, as reflected by the average TTR matters more, since high TTR is associated with a lower risk of thromboembolism and bleeding.[84] All the non-VKA oral anticoagulants (NOACs) have a degree of renal excretion, and in their respective trials, those with severe renal failure were excluded. Thus, guidelines recommend that the NOACs are best used as they were studied in their respective trials, and should not be used where severe renal impairment (eGFR $<25-30$ mL/min) is evident, while dose reduction is needed if eGFR is between 30 and 49 mL (min).[80]

Association with other co-morbidities (hypertension, chronic obstructive pulmonary disease, etc.)

Chronic kidney disease often does not occur in isolation, and is often present in AF patients given their increased age, associated co-morbidities, and concomitant drug therapies. Normal or mild renal function at baseline does not preclude some AF patients developing severe renal impairment at follow-up. Therefore, appropriate monitoring of renal function is indicated in patients with co-morbidities, as well as in frail patients. Indeed, ~20% of AF patients show a significant reduction in eGFR over a 2-year follow-up period.[86] Given the close relationship between AF and other arrhythmias with heart failure, a presentation with decompensated heart failure and the concomitant use of diuretics, ACE inhibitors, etc. may significantly compromise renal function, especially in patients with reduced renal reserve.

Various additional co-morbidities present among patients with AF and CKD may predispose to cardiac arrhythmias, especially AF. Hypertension is closely related to CKD, in a bidirectional relationship. Poorly controlled hypertension increases adverse cardiovascular events in patients with AF.[106] Treatment of hypertension with an ACE inhibitor or angiotensin receptor blocker may reduce new onset AF and cardiovascular events, particularly among the elderly.[107] The presence of hypertensive LV hypertrophy increases the risk of incident AF, and associated cardiovascular events.[108,109]

Respiratory conditions such as obstructive sleep apnoea and chronic obstructive pulmonary disease (especially if both are present) have been associated with incident arrhythmias.[110] Sleep apnoea may contribute to cardiovascular events in this population;[111,112] indeed, sleep apnoea does improve the predictive value of the CHADS$_2$ score for stroke risk.[113] Severity of sleep apnoea may influence the degree of responsiveness to antiarrhythmic drugs.[114]

Excessive alcohol consumption predisposes to AF,[115,116] and importantly, increases the risk of stroke and death among AF patients,[117] as does high body mass index, as an index of obesity.[118] Conversely, lifestyle changes, including weight reduction, have a positive impact on AF progression. In a recent randomized trial, weight reduction with intensive risk factor management resulted in a reduction in AF symptom burden and severity as well as in beneficial cardiac remodelling.[119]

Contrast-induced acute kidney injury

This section is described in Supplementary material online.

Implications of arrhythmias in the management of a patient with chronic kidney disease

Ventricular tachyarrhythmias and sudden death in advanced chronic kidney disease and in patients treated with haemodialysis

Sudden cardiac death is the most common cause of death in dialysis patients, even in the paediatric population,[120] accounting for over 50% of all cardiac deaths and 25% of all deaths.[29,121–125] The risk of SCD is also increased in patients with non-dialysis-dependent CKD, with the risk of SCD increasing linearly with declining renal function.[126–129] The risk for SCD has been reported as being 17% higher for every 10 mL/min/1.73 m^2 decrease in eGFR.[126] The prognosis of cardiac arrests is worse in both dialysis patients and patients with stages of CKD corresponding to moderate-to-severe impairment of renal function.[29,130,131]

The mechanisms that underlie SCD in renal patients are complex and many factors, both general and specific to kidney failure, have been associated with the increased risk for SCD.[131,132] Ischaemic heart disease is present in 80% of patients with SCD in the general population and is highly prevalent in patients with CKD.[32,133] In patients starting dialysis, the prevalence of ischaemic heart disease is estimated at 40–60%[29,134] and its presence is associated with an increased risk of SCD.[135]

Left ventricular hypertrophy and its associated decreased myocardial capillary density and disturbances in intraventricular conduction, as well as LV diastolic and systolic failure/dysfunction, predispose to ventricular arrhythmias and SCD.[31,136] The prevalence of all of these features increases with a decreasing GFR and all of them are very common in dialysis patients.[137–139] Vascular disease in CKD is not only characterized by intimal atheroma but also by arteriosclerosis, a disease of the medial arterial layer associated with increased collagen content and calcification.[31,32] Increased arterial stiffness is associated with LV hypertrophy, myocardial fibrosis and LV dysfunction, as well as increased mortality.[31,32] Coronary artery calcification is associated with an increased spatial QRS-T angle, an important marker for SCD in various patient groups.[140,141] Sympathetic overactivity is highly prevalent in dialysis patients and starts early in the course of CKD, probably driven by kidneys themselves as it is reduced by nephrectomy.[142,143] In dialysis patients, plasma norepinephrine is independently associated with survival and cardiovascular events.[144]

Cardiac arrhythmias and SCD are more common on Mondays and Tuesdays after haemodialysis-free weekends, and during the 12 h after initiation of a haemodialysis session.[145–148] These findings suggest that major shifts in blood pressure, electrolytes, and fluid may induce triggers that result in arrhythmias.[131,149] The use of haemodialysis catheters, rather than an arteriovenous fistula, is also associated with an increased risk of SCD.[149,150] The risk of SCD in dialysis patients falls after successful transplantation.[29]

Most of the evidence available regarding approaches to reducing the risk of SCD in patients with CKD comes from subanalyses of population studies and clinical trials.[131] Beta-blockers reduce the risk of SCD in a number of high-risk populations.[151–153]

Randomized controlled trials providing this evidence have generally excluded individuals with CKD.[154,155] In dialysis patients, the use of beta-blockers may be limited by hypotensive episodes associated with fluid removal. A *post hoc* analysis suggests that the use of beta-blockers in patients with CKD is associated with a reduction in SCD risk.[156] Statin therapy is generally safe and is associated with significant reductions in cardiovascular mortality in patients with CKD receiving dialysis.[157–159]

Limited data exist on the reduction of SCD as a specific outcome. Dysregulation of the renin–angiotensin–aldosterone system is a fundamental abnormality in CKD with studies, demonstrating that elevated aldosterone concentrations are an independent risk factor for SCD in patients with CKD.[160] Whether ACE inhibitors and ARBs reduce SCD in patients with CKD is not clear.[132] However, use of an ACE inhibitor and/or ARB are associated with a significant reduction in the risk of SCD in dialysis patients with a positive correlation between drug dose and survival.[161] Mineralocorticoid receptor blockers are also known to reduce SCD by ∼30% in clinical trials enrolling patients with heart failure,[162] and these benefits extend to the CKD subgroup. Nonetheless, use of these agents may be limited in patients with CKD, especially those on dialysis because of the associated potential for hyperkalaemia and hypotension.

Recently, several dialysis-related factors have been identified, which are associated with an increased risk for SCD, including increased fluid removal and exposure to low potassium dialysate, thereby providing potentially useful methods for altering dialysis treatment.[163] Various modifications have been prospectively investigated including increased frequency and dose of dialysis. Encouraging effects on surrogate endpoints (such as LV mass) have been reported with long-hours nocturnal haemodialysis.[164,165] No beneficial effects have been reported with regard to reducing (cardiovascular) mortality thus far.[149]

Atrial fibrillation and supraventricular tachyarrhythmias in advanced chronic kidney disease and in the chronic kidney disease patient treated with haemodialysis: haemodynamic effects and acute and long-term treatments

Despite the existence of well-established, evidence-based approaches to symptomatic control (rhythm and rate) of AF,[80,166] most studies have excluded patients with functionally significant CKD.[167] There are multiple clinically relevant and important differences in this group of complex patients, suggesting that accepted treatment strategies may not be as effective or indeed may cause significant adverse effects and harm.[167]

Perhaps, the most important relates to the occurrence of intradialytic hypotension in ∼20–30% of dialysis sessions, as the direct result of an inadequate cardiovascular response to the reduction in blood volume that occurs when a large volume of water is removed during a short period of time.[168–173] This needs urgent treatment by stopping ultrafiltration, placing the patient in the Trendelenburg position and saline administration. Such episodes often result in volume overload leading to LV remodelling, diastolic and systolic dysfunction, and arrhythmogenic myocardial fibrosis.[170] Indeed,

intradialytic hypotension is associated with a significant increase in cardiovascular morbidity and mortality.[168–171]

As in the general population, for patients with CKD presenting with newly diagnosed AF, the short-term treatment goal should be control of their symptoms with rate or rhythm control therapies.[174,175] Except for the need of emergency cardioversion to restore sinus rhythm in patients with haemodynamic instability, the initial therapeutic approach should include assessment for the underlying causes of AF and ventricular rate control to improve haemodynamic status and relieve symptoms.[80,168,174–176]

Recent studies in the AF population have suggested that lenient control (<110 b.p.m.) of resting heart rate was associated with better outcomes than strict control (80 b.p.m.),[177] and that rhythm control through DC cardioversion does not improve outcomes compared with rate control using beta-blockers and digoxin.[178] Whether these results are applicable to patients with CKD, especially those on dialysis, is uncertain. The differences in cardiovascular function and structure, especially in blood vessel compliance, as well as the compensatory haemodynamic changes required during routine fluid removal in a haemodialysis session might well modify the relationships between rhythm control, rate control, and outcomes.[179] An estimated 20% of ventricular filling is a consequence of atrial contraction and its importance may well be exaggerated during episodes of cardiovascular stress during a haemodialysis session.[179]

In CKD, there are limited data on safety for any of the agents recommended for rate and rhythm control (amiodarone, dronedarone, propafenone, and flecainide), not to mention the risks associated with anticoagulation.[180] Therefore, catheter-based ablation is increasingly used for rhythm control also in this complex clinical context. In patients with CKD with an eGFR of ≥ 30 mL/min/1.73 m^2, maintenance of sinus rhythm following AF ablation (achieved in ∼74% of patients at 1 year) was associated with a significant improvement in renal function.[181] Even in the specific setting of CKD patients, persistent AF and underlying atrial fibrosis resulted the main determining factor of success.[181] In general, catheter ablation is associated with reduced rates of symptomatic AF recurrence compared with drug treatment for rhythm and rate control.[182,183] In patients under haemodialysis radiofrequency, catheter ablation is increasingly performed for rhythm control of AF, since the use of antiarrhythmic agents is largely restricted in this context. Small studies suggest that the technique might not be as effective as in the general population.[184,185] In a single-centre study with a 5-year follow-up, multiple ablation procedures for AF achieved an efficacy of ∼80% in terms of sinus rhythm maintenance, similar to the efficacy of non-haemodialysis patients, whereas the efficacy of a single procedure was scarce.[186] Other reports confirm the high recurrence rate of AF in haemodialysis patients and the need for repeated procedures.[187] In CKD patients treated with AF ablation, the risk of procedure-related vascular complications is increased in comparison with patients with normal kidney function.[71] His bundle ablation is another option, targeted at rate control, but requires a pacemaker implant.

Antiarrhythmics, beta-blockers, antithrombotics, and dialysis

This section is presented in Supplementary material online.

Implications of arrhythmias in the perioperative management of a patient with chronic kidney disease

Patients with CKD not only have an increased risk of CVD, but also a worse associated prognosis.[12] Cardiac mortality is 10- to 20-fold greater in dialysed patients than in matched controls.[188] Chronic kidney disease patients frequently have structural cardiac disease and abnormal ventricular function, and are therefore at higher risk of developing ventricular arrhythmias in the perioperative period.[189] Arrhythmias are already present in 32% of dialysis patients.[190]

Preoperative medical optimization prior to elective surgery includes appropriate dialysis prescription, correction of anaemia and electrolyte imbalance (with special focus on hyperkalaemia), tailoring blood pressure, and heart failure treatment and strategies to reduce perioperative bleeding. Assessment of the cardiac risk is mandatory preoperatively in order to avoid ischaemic and arrhythmic complications.[191] The Revised Cardiac Risk Index is a simple and valuable tool in this regard; a score of ≥ 3 defines a high-risk patient.[192] Furthermore, renal function may deteriorate postoperatively and strategies to protect against this may include adequate hydration, avoidance of nephrotoxins, and specific therapies to prevent contrast-induced nephrotoxicity. Patients with type 2 diabetes are often treated with the biguanide metformin, which is excreted by the kidney. Metformin needs to be withheld for 48 h from the time of an angiographic study if intravenous iodinated contrast media are to be given, in order to prevent high serum metformin concentrations, that in case of contrast-induced nephropathy could lead to lactic acidosis.

Beta-blockers should be continued during the perioperative period in patients receiving this therapy as outlined in contemporary guidelines.[189] Initiation of beta-blockers for high-risk non-cardiac surgery may also be considered. However, the effect of beta-blockers in this setting is still debated.

Patients with CKD may present unique challenges in the perioperative management of arrhythmias. Generally, the above mentioned principles apply in the prevention of supraventricular and ventricular arrhythmias. Patients should be appropriately monitored. Particular attention should be given to the daily assessment of the corrected QT interval and heart rate. Patients with dysrhythmias should be approached in the same manner as the general population, but the choice of antiarrhythmic agents (including beta-blockers) and pacing devices, including implantable defibrillators, has to consider some specific recommendations, dictated by the potentially less favourable risk−benefit ratio of therapeutic options in this particular setting.[193]

A more detailed discussion about antiarrhythmic drug recommendations for CKD patients is presented elsewhere in this document. It is important to emphasize that even non-renally cleared drugs need to be used with caution in the CKD patient because of associated electrolyte abnormalities and the frequent co-existence of LV hypertrophy and heart failure.

Haemodynamically unstable ventricular arrhythmias should be treated by immediate cardioversion. Prevention of recurrent monomorphic ventricular arrhythmias in the perioperative phase may require therapy with amiodarone or the use of infusions of other antiarrhythmic drugs depending on their particular pharmakokinetics and pharmacodynamic properties in renal patients. Catheter ablation strategies can be used in appropriate cases. Prevention of recurrent polymorphic ventricular tachycardia may require multiple strategies including cardiac pacing and/or isoprenaline infusion to prevent bradycardia, correction of hypokalaemia and hypomagnesaemia, and removal of QTc prolonging drugs.

Implications of chronic kidney disease in the management of a patient with an implantable electrical device

Impact of chronic kidney disease on indication to treatment and patients' outcomes in patients with cardiac implantable devices

Pacing for bradycardia

Pacemakers are implantable devices indicated mainly in patients with symptomatic, persistent, or intermittent bradycardia.[194] Although the current implantation technique has led to consider pacemaker implantation as similar to minor surgery, the implant and the subsequent follow-up are not free of risks or complications, either at short or long term, such as haematoma, pneumothorax, infection, or lead-related problems.[194]

Patient clinical status and co-morbidities increase the risk of complications.[195] There are limited data in the literature on the implications of permanent pacing on patients' outcome and pacemaker complications in patients with CKD. In a retrospective study of patients with CKD on haemodialysis, patients with an implanted pacemaker had greater long-term mortality, but propensity score analysis revealed that the presence of a pacemaker was not an independent predictor of mortality in this setting.[196]

In patients with pacemakers, capture threshold is affected by many factors, including potassium level, and loss of capture may occur in cases of severe hyperkalaemia, with the atrial myocardium usually being more sensitive than the ventricular myocardium to acute rise in potassium levels.[197,198] In view of frequent fluctuations of potassium levels, patients with CKD could benefit, in terms of increased safety and extended device longevity, from devices with beat-to-beat automatic ventricular threshold adjustment on the basis of automatic capture verification,[199] but no specific data on CKD patients are available in the literature.

The practical issue of limitations in vascular access in the presence of a cardiac implantable electronic device (CIED) in a patient with or approaching ESRD should be considered. Arteriovenous access created ipsilateral to CIED placement should be avoided as much as possible, since they have a higher primary failure rate compared with the contralateral arm.[200] In case of pacemaker implant in a patient with previous arteriovenous fistula, the pacemaker should be implanted on the contralateral side.

In case of device replacement in patients with CKD, the possible interaction between anticoagulants, especially the NOACs, and renal function must be strictly monitored to minimize the risk of bleeding complications.[79]

Cardiac resynchronization therapy for heart failure

About half of dialysis patients will develop heart failure either at presentation or during follow-up,[201] and CKD has a prevalence ranging up to 55% in patients with heart failure, with poor prognostic implications. In patients with ESRD, cardiac resynchronization therapy (CRT) is sometimes perceived as being at a potentially greater risk with fewer benefits. However, an analysis of the IMPROVE HF registry[202] showed that implants of CRT device did not decline in the subgroups of patients with more advanced stages of CKD, according to eGFR.

Patients with ESRD have not been studied in the major randomized trials on CRT since they were excluded from enrolment. *Table 9* summarizes studies evaluating CRT in heart failure patients with mild-to-moderate CKD and in heart failure patients with ESRD also treated with haemodialysis.[203–211] In general, these data from several studies and a meta-analysis suggest[203–211] that mild-to-moderate CKD is associated with benefits from CRT similar to those observed in heart failure patients without CKD, but with a higher risk of adverse outcomes.[203,211] More advanced CKD is an independent predictor of cardiac mortality and heart failure hospitalization.[210] Furthermore, although CRT can be safely performed in most patients with CKD, it has usually a limited impact on delaying or preventing deterioration of renal function, up to the stage requiring haemodialysis.[207] In patients with mild heart failure (NYHA Class I and II), enrolled in the REVERSE study, CRT in patients with CKD improved LV function and induced a reverse LV remodelling, although to a lesser extent than in those with normal kidney function.[208]

Implantable cardioverter-defibrillator for sudden death

Patients with CKD are at a markedly increased risk of death from cardiovascular causes, including SCD. In patients with CKD, SCD accounts for over 50% of all cardiac deaths and 25% of all deaths, and its estimated annual rate is ∼7%.[29,121–124]

The role of implantable cardioverter-defibrillators (ICDs) in this subgroup of patients is difficult to assess. First, randomized clinical trials of ICD therapy provide limited data regarding patients with CKD and ESRD because, in most trials, these patients were either excluded or the renal function was not reported. In addition, data on the ICD effect in CKD are somewhat divergent. *Table 10* summarizes the most relevant studies which have evaluated the role of ICD therapy in CKD patients.[121,212–217]

In general, it is expected that given the substantial co-morbidities in patients with CKD, the benefit of ICD therapy may be attenuated. Chronic kidney disease patients have an increased mortality due to other cardiac and non-cardiac causes; elevated defibrillation thresholds may render the myocardium refractory to ICD therapy and the higher complication rate may negate the benefit of ICD implantation in CKD patients. A recent study assessed the association between kidney function and ICD-related complications.[218] In a cohort of 3147 patients, implanted at a single centre from 1996 to 2012, comparisons were made between patients with normal, moderately, and severely impaired kidney function. Patients with eGFR <30 mL/min/1.73 m^2 had a higher rate of haematoma, pneumothorax, and infection. In a retrospective analysis, CKD was associated with adverse prognosis after ICD implantation, but not after CRT with a defibrillator (CRTD) implantation and GFR decreased in patients with ICD, but not in CRTD patients.[219]

There is still uncertainty about the benefit of the ICD for primary prevention of SCD in CKD patients.[220,221] A thorough assessment of individual risk/benefit of the therapy should guide decisions in this situation. The survival benefit observed in CKD patients who receive the ICD for secondary prevention of SCD favours use of ICD therapy in this population[121,201] (*Table 10*). In view of these data, withholding device therapy based only on the presence of CKD would be inappropriate in that specific setting. On the other hand, data indicate that primary prevention of SCD by an ICD does not convey a prognostic benefit in patients on haemodialysis, with a creatinine clearance of <35 mL/min[126] or BUN >26 mg/dL in conjunction with at least two other factors (age >70 years, NYHA >II, AF, and bundle branch block).[222] In another study based on a decision-analysis model for patients with CKD,[223] the benefit from primary prevention ICD implantation was strictly linked to patient's age, in combination with the stage of CKD. The result suggests careful consideration of ICD implantation for older patients with more advanced stages of CKD.

Recently, there has been a growing interest in subcutaneous ICD, a device with an electrode system that is placed entirely outside the thoracic cavity.[224] Interest was fuelled by the possibility of resolving problems related to access to the heart via the vascular system and problems linked to transvenous leads. According to early reports from the EFFORTLESS S-ICD Registry, CKD was present in 9% of the patients implanted with a subcutaneous ICD, but no specific data on patients' outcomes and device performance in this specific population are currently available.[224]

Another option that can be considered for protecting against the risk of SCD is the wearable cardioverter-defibrillator.[225] This device can be a valid solution in situations with a high, but transient increase in arrhythmic risk, such as the early phase after a large myocardial infarction with marked depression of LV function, or the acute phase of a myocarditis.

Risk of infections and management

Cardiac implantable electronic devices are increasingly used in patients with CKD and ESRD,[226] with a reported prevalence of ∼4% for pacemakers and 6% for ICDs.[227,228] In North America, the rate of utilization of ICDs dramatically increased after 2000.[229] Unfortunately, CIED infection rates increase faster than implantation rates.[230,231] Analysis of hospital discharge records including 4.2 million CIED implantations performed in the USA from 1993 to 2008 showed that 69 000 patients required treatment for CIED infection.[232] The average annual increase in CIED implantation was 4.7%, while the incidence rate of infection increased by 210% from 2660 cases in 1993 to 8230 cases in 2008. The annual rate of infection rose at a steady pace until 2004 when it jumped from 1.53% during that year to 2.41% in 2008 ($P < 0.001$).[232] Renal failure was one of the most significant co-morbidities associated with infection, along with respiratory failure, heart failure, and diabetes.[233] Consistently, GFR <60 mL/min has been shown to be part of a six factor score predicting the risk of CIED infection.[234] A retrospective analysis of 1651 patients showed that scores ranged from 0 to 25 and identified three risk groups, i.e. low: score 0–7 with 1% infection,

Table 9 Summary of studies evaluating the role of CRT therapy in heart failure patients with CKD

Author	Type of study	Number of patients	Follow-up duration	Definition of CKD	Main conclusion
Cleland et al.[203] (2005)	Randomized controlled trial	813 heart failure patients randomized to medical therapy alone or with CRT	29.4 months	GFR <60.3 mL/min/1.73 m^2 (median of the population)	If reduced GFR same benefit of CRT vs. medical therapy alone with regard to death from any cause or unplanned hospitalization for a major cardiovascular event
Shalabi et al.[204] (2008)	Single-centre retrospective cohort study	330 patients with severe heart failure treated with CRT	19.7 ± 9.0 months	Elevated serum creatinine	Worse survival free of death or heart failure hospitalization in the highest tertile of serum creatinine compared with all others. For each 0.1 mg/dL increase in creatinine level, there was an 11% increase in mortality
Van Bommel et al.[205] (2010)	Registry	716 heart failure patients treated with CRT	25 ± 19 months		Lower GFR at baseline was strongly predictive of death [HR of 1.18 per decrease of 10 mL/min/1.73 m^2 (95% CI 1.09−1.27, $P < 0.001$)]
Goldenberg et al.[206] (2010)	*Post hoc* analysis of patients enrolled in the MADIT CRT trial	1803 patients with mild heart failure randomized to CRTD or ICD treatment	12 months	Ratio of blood urea nitrogen to serum creatinine (an index of prerenal function)	An elevated ratio of blood urea nitrogen to serum creatinine experienced a significantly greater reduction in the risk of heart failure or death with CRTD therapy when compared with patients with a low ratio
Lin et al.[207] (2011)	Single-centre retrospective cohort study	CRT in 482 heart failure patients, of whom 71% had CKD	36.45 + 26.55 months	GFR ≤60 mL/min/1.73 m^2	Survival was superior in patients with normal or mild renal dysfunction compared with patients with CKD
Mathew et al.[208] (2012)	*Post hoc* analysis of patients enrolled in the REVERSE trial	561 patients with mild heart failure randomized to CRT or control therapy	12 months	GFR <60 mL/min/1.73 m^2	CRT improves LV function and reduces LV volumes to a lesser extent in patients with CKD than in those with normal kidney function
Friedman et al.[209] (2013)	Case−control study	15 dialysis-dependent heart failure patients and a control group of CRT patients	Up to 3 years	Dialysis	In dialysis patients, CRT implantation has no serious complications and certain patients have important improvement. Compared with matched controls, dialysis patients are at an increased risk for adverse events
Hosoda et al.[210] (2014)	Single-centre retrospective cohort study	CRT in 15 dialysis-dependent heart failure patients	30.3 ± 22.0 months	eGFR <50 mL/min	Patients with a e-GFR of <50 mL/min had significant higher all-cause mortality (log-rank $P = 0.033$) and higher cardiac mortality combined with HF hospitalization (log-rank $P = 0.017$) than those with eGFR ≥50 mL/min
Garg et al.[211] (2013)	Meta-analysis of 14 observational studies and 4 randomized trials 9419 patients	Heart failure patients treated with CRT	1−4.25 years	eGFR <45 or 60 mL/mm/1.73 m^2; creatinine level >1.5 or 1.8 or 2 mg/dL; haemodialysis	Modest improvement in eGFR with CRT among CKD patients (mean difference 2.30 mL/min/1.73 m^2; 95% CI 0.33−4.27). Similarly, a significant improvement in LV ejection with CRT in CKD patients (mean difference 6.24%; 95% CI 3.46−9.07)

CKD, chronic kidney disease; CRT, cardiac resynchronizzation therapy; CRTD, cardiac resynchronization therapy plus defibrillation; eGRF, estimated glomerular filtration rate; HR, hazard ratio.

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Table 10 Summary of studies evaluating the role of ICD therapy in CKD patients

Author	Type of study	ICD indication	Number of patients	Follow-up duration	Definition of CKD	Main conclusion
Herzog et al.[121] (2005)	Registry	Secondary prevention	460 ICD group and 5582 no-ICD group	17.9 ± 15.5 months (ICD) 14.0 ± 14.9 months (no-ICD)	Haemodialysis patients	ICD implantation reduces the risk of death by 42%
Korantzopoulos et al.[212] (2009)	Meta-analysis of 11 observational studies	Primary and secondary prevention	735 CKD patients out of 3010	1−4.25 years	eGFR <45 or 60 mL/mm/1.73 m^2; creatinine level >1.5 or 1.8 or 2 mg/dL; haemodialysis	Mortality is 3.44-fold higher in CKD patients
Sakhuja et al.[213] (2009)	Meta-analysis of six retrospective cohort studies and one case−control study	Primary and secondary prevention	89 haemodialysis patients out of 2516	12−48 months	Haemodialysis; an eGRF value of 60 mL/mm/1.73 m^2	Mortality is 2.67-fold higher in haemodialysis patients No difference in mortality between haemodialysis and CKD patients
Hage et al.[214] (2013)	Single-centre retrospective cohort study	Primary vs. secondary prevention	409 primary prevention (141 CKD) 287 secondary prevention (115 CKD)	50 ± 24 months	eGFR <60 mL/mm/1.73 m^2	In CKD, higher mortality risk for primary but not secondary prevention patients; Higher risk of appropriate therapy for primary but not secondary prevention patients
Pun et al.[215] (2014)	Meta-analysis of randomized control trials	Primary prevention	1040 CKD 1827 no-CKD	2.7 ± 1.5 years	eGFR <60 mL/mm/1.73 m^2	Survival benefit with ICD in patients with eGFR ≥60 mL/mm/1.73 m^2 only
Hess et al.[216] (2014)	Registry	Primary prevention	21 226 CKD 26 056 no-CKD	2.9 years [2.4−3.3]	eGFR ≤60 mL/mm/1.73 m^2	Graded higher risk of death [2.08−4.8 HR] depending on the severity of renal failure
Makki et al.[217] (2014)	Meta-analysis of: observational retrospective studies Observational studies (retrospective prospective)	Primary and secondary prevention	Role of ICD in CKD patients: 17 160 CKD Effect of CKD in ICD recipients: 5233 (1843 CKD)	17−48 months 12−51 months	eGFR <60 mL/mm/1.73 m^2; creatinine level >1.5 or 1.8 or 2 mg/dL; haemodialysis	The ICD provides survival benefit in CKD patients at a high risk of SCD [HR = 0.65] CKD is associated with an increase in all-cause mortality in ICD recipients [HR = 2.86]

ICD, implantable cardiac defibrillator; CKD, chronic kidney disease; eGRF, estimated glomerular filtration rate; HR, hazard ratio.

medium: score 8–14 with 3.4% infection, and high: score ≥15 with 11.1% infection.

Chronic kidney disease is one of the main risk factors for mortality (OR: 4.28; 95% CI 4.04–4.53) in CIED-infected patients.[232,235,236] The clinical presentation of CIED infection in haemodialysis patients differs from non-haemodialysis patients, being more frequently bloodstream and complicated by lead-related endocarditis; however, pocket infection is less frequently observed.[236] Uraemia is associated with a state of immune dysfunction characterized by immunodepression that contributes to the high prevalence of infections among these patients, as well as by immunoactivation resulting in inflammation.[237] A progressive increase in the risk of bleeding complications following CIED implantation as the degree of renal insufficiency worsens has been shown.[238] Impaired platelet function and coagulation abnormalities may also play a role in this excessive risk of bleeding. Moreover, a significant number of patients receive haemodialysis through central venous catheters, which are known to be associated with very high rates of catheter-related bacteraemia and subsequent risk of transvenous CIED infection.[239] To minimize the risk of infections, in candidates to implant of a CIED, the type of device (single- or multichamber), the access and routes for leads implantation should be decided on an individual basis, taking into account the increased risk for infection and vascular complications associated with more complex implant (such as CRT). Antibiotic prophylaxis should always be prescribed at the time of CIED implant. In patients already implanted with a transvenous CIED, dialysis catheter should be avoided and contralateral access for arteriovenous fistula should be preferred.

The general principles of CIED infection treatment involve effective antibiotic treatment, complete removal of the generator and leads, and implantation of a new system on an 'as-needed' basis.[240,241] These principles apply to ESRD patients. Small series show that device removal in haemodialysis patients is not associated with a higher rate of complication when compared with non-haemodialysis patients. However, device removal is less frequently performed in haemodialysis patients (82 vs. 95% of the cases), probably reflecting the perception of increased risk and poor prognosis in this population.[236] In a recent study, 29.4% of 503 patients undergoing CIED removal from 2001 to 2011 had advanced renal failure.[242]

Based on the high rate of infectious complications in haemodialysis and ESRD patients, non-endovascular routes (i.e. epicardial or subcutaneous) for implantation of CIEDs should be considered.[239,242] The rationale behind this proposal is that epicardial or subcutaneous leads traverse the subcutaneous tissue and do not use the central venous system. In these cases, experienced operators may reduce the time of the procedure and procedure-related complications.

Risk of syncope

This section is included in Supplementary material online.

Pregnancy

This section is given in Supplementary material online.

Life expectancy

This section is provided in Supplementary material online.

Implications of an implantable electrical device on the management of a patient with chronic kidney disease

Perioperative management for electromagnetic interferences

Chronic kidney disease does not represent a unique problem for the management of CIEDs in the perioperative setting. However, CKD patients frequently require surgical or endoscopic interventions and therapies that may expose the CIED to electromagnetic interference (EMI). Guidelines on the management of CIEDs in the perioperative setting[243] should be applied, focusing particularly on conditions where CIED function could be affected by the use of electrocautery.

The risk of such interference or damage to the pulse generator or pacemaker resetting is generally low in the modern era. Bipolar electrocautery is preferred to reduce the risk of device over-sensing and pacemaker inhibition or inappropriate ICD therapy. Bipolar electrocautery rarely causes significant EMI unless applied near to the CIED (<5 cm). Monopolar electrocautery is more likely to create EMI and pulses should be <5 s duration. Device reset is uncommon with electrocautery and electrocautery delivered below the umbilicus is considerably less likely to cause CIED interference. Device reset occurs infrequently with electrosurgery, and pacing threshold increase or undersensing due to damage to the electrode/myocardial tissue interface can occur. Therefore, all devices need to be checked after electrocautery. Patients with CKD and CIED are particularly prone to perioperative complications and thus require close perioperative monitoring. Reprogramming all pacemaker CIEDs to a non-sensing mode at the time of a procedure using electrocautery is not recommended. Likewise, routinely deactivating all ICD tachycardia therapies is also not recommended. Advice should be individualized, based on an individual patient profile, including evaluation of records from the CIED follow-up clinic.

The physician needs to know a series of device factors, such as type of device, type of leads (unipolar vs. bipolar), programming, battery longevity, as well as patient factors (pacemaker dependency and risk of intraoperative ventricular arrhythmias) and understand the details of the surgical procedure to be performed (including anatomical site, patient position during surgery [i.e. prone vs. supine], the type of electrocautery to be used, and the location of applications relative to the implanted device location).

When planning the strategy for device management in the perioperative period, key questions are:

1. Does the device need to be interrogated and checked preoperatively?
2. Does the device require intraoperative reprogramming?
3. Can a magnet be applied to the device?

All devices should be interrogated postoperatively. There is a considerable institutional variation in practice and physician preference. In general, the device should be checked prior to surgery if not checked electively in the preceding months or if battery longevity is unknown.

Pacemaker-dependent patients need either application of a magnet during delivery of diathermy pulses or reprogramming to a non-sensing mode (VOO/DOO) if diathermy above the umbilicus is planned or monopolar diathermy is used.

Implantable cardioverter-defibrillator therapies need to be turned off, preferably temporarily by a magnet taped over the device that can be taken away if ventricular tachyarrhythmia needs to be treated.[244] Unlike pacemakers, ICDs do not pace asynchronously during magnet application. In all these cases, it is important to assess that the magnet function of the ICD had not been previously disabled with the programmer, as possible with some devices. The patient needs to be monitored intraoperatively with external defibrillation equipment available in the room. Postoperative device reprogramming must ensure that tachycardia therapies are activated.

Procedures involving therapeutic radiation present particular risks to the CIED, are a common source of EMI, and may cause device reset. The device should be checked pre- and post-irradiation and careful attention paid to battery life and programmed parameters. The device may require shielding from the radiation beam and occasionally repositioning pretreatment. Elective external cardioversion can cause power-on-reset with only back-up function of the device or lead damage. It should always be applied in the anterior−posterior mode[245] since all cases of exit block have been reported in sternal−apical application of shock paddles. Radiofrequency ablation procedures may create EMI with effects similar to monopolar electrocautery.

Management for magnetic resonance imaging scanning

Issues regarding the safety of magnetic resonance imaging (MRI) scanning for implanted electrical devices are complex and under discussion as device technology evolves in this field. There are MRI-conditional pacemaker and ICD systems. However, the type of MRI scanner (1.5 vs. 3.0 Tesla), body site to be scanned, type of CIED, the type of implanted leads, pacemaker dependency, and the presence of abandoned leads are only some of the issues to be considered. Recommendations on the use of MRI in CIED patients with specific algorithms and check lists should be considered.[194,246] Independently of the CIED labelled as 'MRI conditional', the physician is responsible for adequate monitoring of the patient (voice, ECG, and oxygen saturation) and the availability of a device programmer, external defibrillator, emergency equipment, and the presence of a trained staff for resuscitation. Patients with CKD are generally not considered appropriate for gadolinium-enhanced scanning because of the risk of gadolinium-induced systemic sclerosis.

End-of-life issues

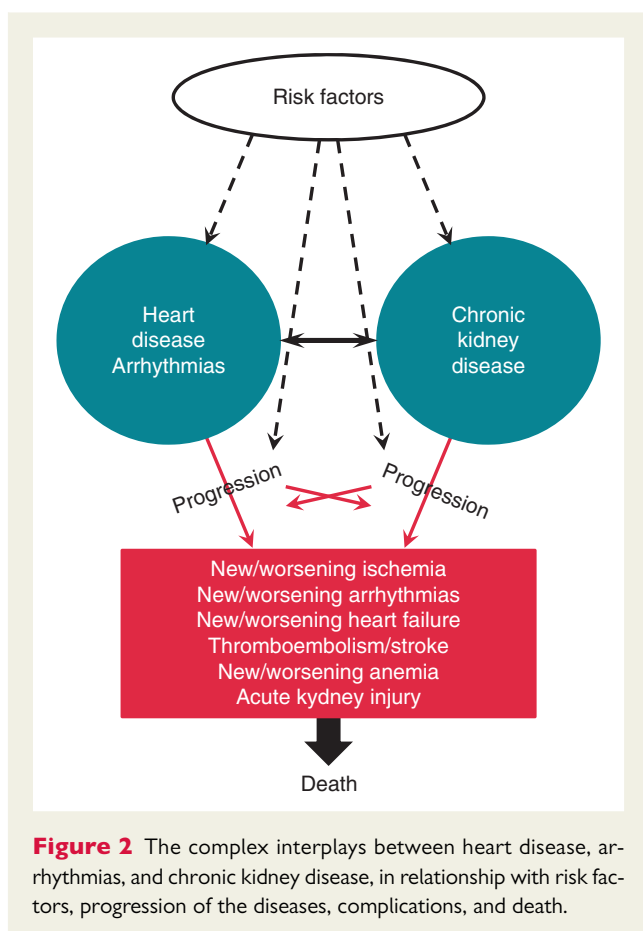This section is summarized in Supplementary material online.

The costs of chronic kidney disease and related organizational issues

Prevalence and incidence of both CKD and CVD increase with age; in western countries, progressive ageing of the population emphasizes the need to consider the problem of costs related to these diseases, which appear to assume the dimensions of public health threats.

Chronic kidney disease may remain silent for a long time, before reaching the most advanced stages, and at that point few opportunities exist to prevent adverse outcomes, cardiovascular complications, and need for dialysis, thus with an adverse impact on patients' quality of life and significant costs for the healthcare system. In this regard, screening of patients at higher risk for CKD, those with heart failure, diabetes, hypertension, or a family history of hypertension, diabetes, or CKD, should be considered as attractive and potentially cost-saving. Management of the terminal stage of ESRD with dialysis is very expensive for healthcare systems. For dialysis, the reported costs are ∼$70 000 per year in the USA;[247] this huge financial impact is confirmed by the high tariffs for hospital reimbursement, in the range of $700−1600 per week for dialysis, in a survey published in 2012 considering five European countries, Canada and the USA.[248] It is noteworthy that, in the USA, the cost of hospital dialysis has been assumed as the benchmark to define societal willingness to pay for a QALY (quality-adjusted life years), thus indicating that this expensive but effective treatment represents the upper boundary of what to consider affordable in cost-effectiveness and cost-utility analysis.[249−251]

In the cardiovascular field, and specifically in the management of rhythm disturbances, many devices, intervention, or treatments have a high, usually up-front, cost.[249] These treatments are targeted to reduce symptoms, morbidity, and mortality related to arrhythmic conditions, which, *per se*, induce substantial costs, usually in terms of disease-related hospitalizations.[252] For these treatments, Health Technology Assessments, corresponding to systematic, multidisciplinary assessments of clinical effectiveness and safety as well as cost-effectiveness of medical interventions, are increasingly used, for evaluating the clinical, economic, social, and organizational impacts of new technologies.[249] Chronic kidney disease has a substantial impact on many responses to treatments, complications, costs, and outcomes; therefore, it is an important determinant not only of clinical but also of economic evaluations. In this complex scenario, there is a need to collect additional data on the impact of CKD on patients' outcomes in the 'real world', through prospective registries, since more advanced stages of renal impairment usually constitute a criterion of exclusion from randomized clinical trials.[45−47] Moreover, management of CKD in cardiac patients, and particularly in patients with heart failure and rhythm disturbances, may significantly benefit from a holistic approach based on collaborative, personalized, patient-centred care, with integration of different healthcare specialists, such as cardiologists and nephrologists. In this regard, the bidirectional interaction between the heart and the kidney (*Figure 2*) has been object of increasing interest in recent years, mainly focused on haemodynamic cardiac function and its acute or chronic deterioration,[33] but also issues related to rhythm disturbances and implantable electrical devices, as detailed in this review, which should be considered when planning new closer interactions between cardiologists and nephrologists.

Finally, even if the different organizations of care across western countries, as well as their different financial profiles, strongly influence the access to more advanced technologies,[253] increased efforts should be dedicated to assess the risk−benefit and cost−benefit of more advanced treatments, as well as preventive strategies in complex patients such as those with CKD or at risk of developing CKD.[254]

Figure 2 The complex interplays between heart disease, arrhythmias, and chronic kidney disease, in relationship with risk factors, progression of the diseases, complications, and death.

Areas for further research

1. Heart disease, arrhythmias, and CKD have complex interactions, as shown in *Figure 2*. Therefore, the clinical and epidemiological impact of CKD in cardiac patients requires improved knowledge of the risk–benefit ratio of pharmacological therapies for cardiac disease and arrhythmias, as well as for device therapy, in the specific setting of the different stages of CKD. This can be accomplished by observational studies and registries, with extended follow-up (3–5 years) in order to assess the evolution of cardiac and renal functional status and the consequent impact on response to therapies and the occurrence of adverse outcomes (death, SCD, stroke and thromboembolism, acute coronary events, heart failure, syncope and ventricular tachyarrhythmias, acute kidney injury, CIED infections, etc.).

2. Prevention of thromboembolic events and stroke in patients with AF and more advanced CKD, with eGFR <25–30 mL/min, remains challenging since currently available NOACs, which all have a degree of renal excretion, have not been tested and validated in this setting. Testing and validation of alternatives to warfarin are needed, in view of the combined increased risk of stroke and thromboembolism, as well as major bleeding, associated with more advanced CKD. Moreover, the role of percutaneous left atrial appendage occlusion should also be carefully evaluated, in terms of risk–benefit ratio vs. usual care.

3. Well-controlled VKA therapy, with a high TTR (>70%), confers the best efficacy and safety in CKD patients[84] and strategies to

improve a TTR by education[255] or 'flagging up' patients less likely to achieve good TTRs with the SAMe-TT$_2$R$_2$ score[102] may help. This approach would need testing in large prospective observational cohorts or trial settings.

4. The traditional model of care delivery may be not adequate for clinical settings with a high degree of complexity, such as patients with cardiac diseases, rhythm disturbances, and advanced CKD. Therefore alternative, interdisciplinary methods for home care, with appropriate patient should surveillance and monitoring,[256,257] should be validated (in terms of safety, effectiveness, and cost-effectiveness) also including the use of technology for remote monitoring, defining the appropriate role of all the stakeholders (family caregivers, nurses, physicians of the various disciplines involved, etc.).[256,258]

Consensus statements

1. Since CKD, defined as a GFR <60 mL/min/1.73 m^2 for >3 months, is common (it exceeds 10% in the adult population with a substantial increase in the elderly) and increases the risk of cardiovascular morbidity and overall mortality, with profound influences on the risk–benefit profile of many treatments and interventions, it is appropriate to measure and monitor kidney function in any patient with a cardiac disease or rhythm disturbances, such as AF or sustained ventricular tachyarrhythmias.

- The GFR can be estimated from the serum creatinine using a number of equations to give an eGFR, but clinician should remain aware of caveats for any estimating equation, which may influence the accuracy in a given individual patient and consider using additional tests (such as cystatin C or a clearance measurement) for confirmatory testing in specific circumstances when eGFR based on serum creatinine is less accurate.

2. In patients with CKD, arrhythmogenesis and the risk of SCD are related to many potentially concurring factors (rapid fluid and electrolyte shifts and particular acute or chronic hyperkalaemia or hypokalaemia, autonomic imbalance, prolongation and increased dispersion of ventricular repolarization, anaemia, acidosis, etc.) that need to be clinically evaluated, prevented, and corrected. Beta-blockers may be beneficial, although there is no direct evidence to support this.

3. Drug PK may be profoundly altered in CKD; therefore, drug dosages may need adjustment according to GFR, given the implications on prolonged half-life and reduced clearance of the drug, especially for drugs with a narrow therapeutic range, such as antiarrhythmic agents and anticoagulants. Specific considerations on removal of drugs by dialysis are required in patients treated by haemodialysis. In patients with AF, catheter-based ablation is increasingly used for rhythm control, and atrial fibrosis and persistent AF result to be the main determining factor of success, which overall, especially in haemodialysis patients, may require repeated procedures, as a consequence of the high recurrence rate of AF.

4. Patients with AF and associated CKD have a high risk of stroke and thromboembolism, as well as major bleeding, and these risks are particularly high in patients with renal replacement therapy, whether dialysis or renal transplantation. In patients with CKD, choice and monitoring of thromboprophylaxis deserves special clinical surveillance.

- All the NOACs have a degree of renal excretion, and should not be used where severe renal impairment (creatinine clearance <25–30 mL/min) is evident. In this setting, warfarin is at present time the anticoagulant of choice.

- The SAMe-TT$_2$R$_2$ score can be considered to identify patients less likely to achieve good TTRs while on VKAs, who should be targeted for more regular review and follow-up, with additional efforts (e.g. education) to improve the TTR.

5. In patients who need treatment with a CIED (a pacemaker, an ICD, or a device for CRT), clinical evaluation should consider that more advanced stages of CKD might be associated with effects similar to those observed in patients without CKD, but with a higher risk of adverse outcomes, including all-cause and cardiac mortality, all-cause and cardiovascular hospitalizations, and CIED infection. Therefore, individual assessment of the risk–benefit ratio of device therapy is needed. To minimize the risk of infections, in candidates to implant of a CIED, the access and routes for leads implantation should be decided on an individual basis, taking into account the increased risk for infection and vascular complications. In patients already implanted with a transvenous CIED, dialysis catheter should be avoided and contralateral access for arteriovenous fistula should be preferred.

6. Management of rhythm disturbances and CIEDs in patients with cardiac disease and CKD is complex and may require urgent and challenging decision-making (acute worsening of heart failure or renal function, electrical storms, surgical emergencies, etc.), thus requiring close collaboration between cardiologists, nephrologists, and other specialists.

Supplementary material

Supplementary material is available at *Europace* online.

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