Ventricular arrhythmia in chronic kidney disease patients

Arritmia ventricular em pacientes com doença renal crônica

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Abstract

Patients with chronic kidney disease (CKD) are susceptible to the occurrence of ventricular arrhythmias. The leading cause of death in dialysis patients is cardiac arrhythmias. The pathophysiology of arrhythmias in this population is complex and seems to be related to structural cardiac abnormalities caused by CKD, associated with several triggers, such as water and electrolyte disorders, hormonal conditions, arrhythmogenic drugs, and the dialysis procedure itself. Little is known about the clinical outcomes in CKD patients with asymptomatic ventricular arrhythmias. The results of treatments with anti-arrhythmic drugs and invasive devices are controversial in these patients, according to the available literature. The aim of this study was to review this often-neglected topic, which is of special importance in the CKD population.

Keywords: arrhythmias, cardiac; epidemiology; renal insufficiency, chronic.

Resumo

A população com doença renal crônica (DRC) está vulnerável à ocorrência de arritmias ventriculares. Os distúrbios do rítmo cardíaco constituem a principal causa de morte em pacientes dialíticos. A fisiopatologia das arritmias nesta população é complexa e parece relacionar-se às alterações da estrutura cardíaca causadas pela DRC, associadas a diversos gatilhos, tais como: distúrbios hidro-eletrolíticos e hormonais, uso de drogas arritmogênicas e aqueles relacionados ao próprio procedimento dialítico. Pouco se sabe sobre os desfechos clínicos dos pacientes com DRC portadores de arritmias ventriculares assintomáticas. O tratamento desta população com anti-arrítmicos e dispositivos invasivos tem resultados controversos na literatura. O objetivo desse trabalho foi revisar este tema muitas vezes negligenciado, mas de especial importância na população com DRC.

Palavras-chave: arritmias cardíacas; epidemiologia; insuficiência renal crônica.

Introduction

The association between chronic kidney disease (CKD) and high cardiovascular morbidity and mortality is well known.[1,2] Uremic cardiac disease progresses rapidly and is usually severe, following a different pattern from that of cardiac disease in the general population. According to the United States Renal Data System (USRDS), the leading cause of death among CKD patients undergoing dialysis is related to cardiac arrhythmias (Figure 1).[3] Although this is a topic of particular relevance, little is known about the impact and management of ventricular arrhythmias in the CKD population. The aim of this study was to review the literature related to ventricular arrhythmias in CKD patients.

Definitions

Ventricular extrasystole is a premature ectopic heartbeat originating in the ventricles. An episode of three or more consecutive ventricular complexes, associated with a heart rate higher than 100 bpm and lasting less than 30 seconds, is referred to as nonsustained ventricular tachycardia (VT). Sustained VT is defined as VT that lasts more than 30 seconds, leads to syncope or cardiac arrest, or requires electric cardioversion or shock delivery by an implantable cardioverter-defibrillator (ICD).[4]

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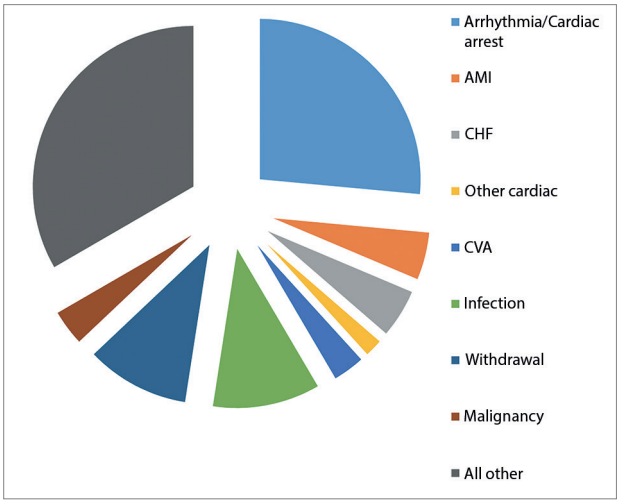
Figure 1. Causes of death in CKD patients undergoing dialysis. Sudden cardiac arrest secondary to arrhythmic disorders is the leading cause of death in these patients. AMI: acute myocardial infarction; CHF: Congestive Heart Failure; CVA: cerebrovascular accident. Data from United States Renal Data System.[3]



When the VT is polymorphic, there are different QRS patterns, suggesting several focal ventricular activations. In this case, myocardial ischemia is an important cause. Monomorphic VT has the same QRS configuration in each beat. In general, it is caused by reentry and originates from a single focus or an anatomical substrate (infarct scar, cardiomyopathy, heart surgery, etc.).[4]

Ventricular fibrillation is identified by the absence of a P wave with abnormal QRS complexes, with markedly different morphologies, varying its amplitudes and axes. The rhythm is irregular, usually greater than 300 beats per minute, leading to cardiac arrest.[5]

Sudden death is defined as "unexpected death that occurs suddenly, in less than an hour from the beginning of the symptoms";[6] or "unwitnessed and unexpected death, in the absence of a known non-cardiac cause, which occurs in patients who were well the last 24 hours".[6] In the general population, about 50% of cases of sudden death are due to sustained VT and ventricular fibrillation.[7] In CKD patients, the electrocardiographic rhythm that causes cardiac arrest is unknown. However, it seems that tachyarrhythmia plays an important role.[8]

Epidemiology

Few studies have investigated the occurrence of ventricular arrhythmia in CKD patients in different stages of disease. Studies using 24h electrocardiographic monitoring (Holter monitor) in dialysis patients confirm the high prevalence of ventricular arrhythmias in this population, ranging from 19-72%.[9-12] Data from our group have shown that ventricular arrhythmia was present in 35% of non-dialyzed patients,[13] 45% of patients underwent peritoneal dialysis,[14] 48% of patients underwent hemodialysis[15] and 30% of patients underwent renal transplantation.[16]

Little is known about the impact of the presence of asymptomatic ventricular arrhythmia on clinical outcomes in the CKD population, especially in relation to the risk of sudden death. Our group recently showed that the presence of complex ventricular arrhythmia was associated with an increased risk of cardiovascular events, hospitalization, and death in this population.[17]

In a retrospective study including 75 hemodialysis patients with ICDs, ventricular tachyarrhythmias were responsible for 79% of cardiac arrests, suggesting that ventricular arrhythmias are the most important final event in this population.[8] On the other hand, an Australian study of predominantly elderly CKD patients pointed out that bradycardia or asystolia were the major contributors to sudden death in hemodialysis patients.[18] These conflicting results suggest that the type of arrhythmia and terminal event may differ according to patient age, severity of cardiac disease, and length of time on dialysis.

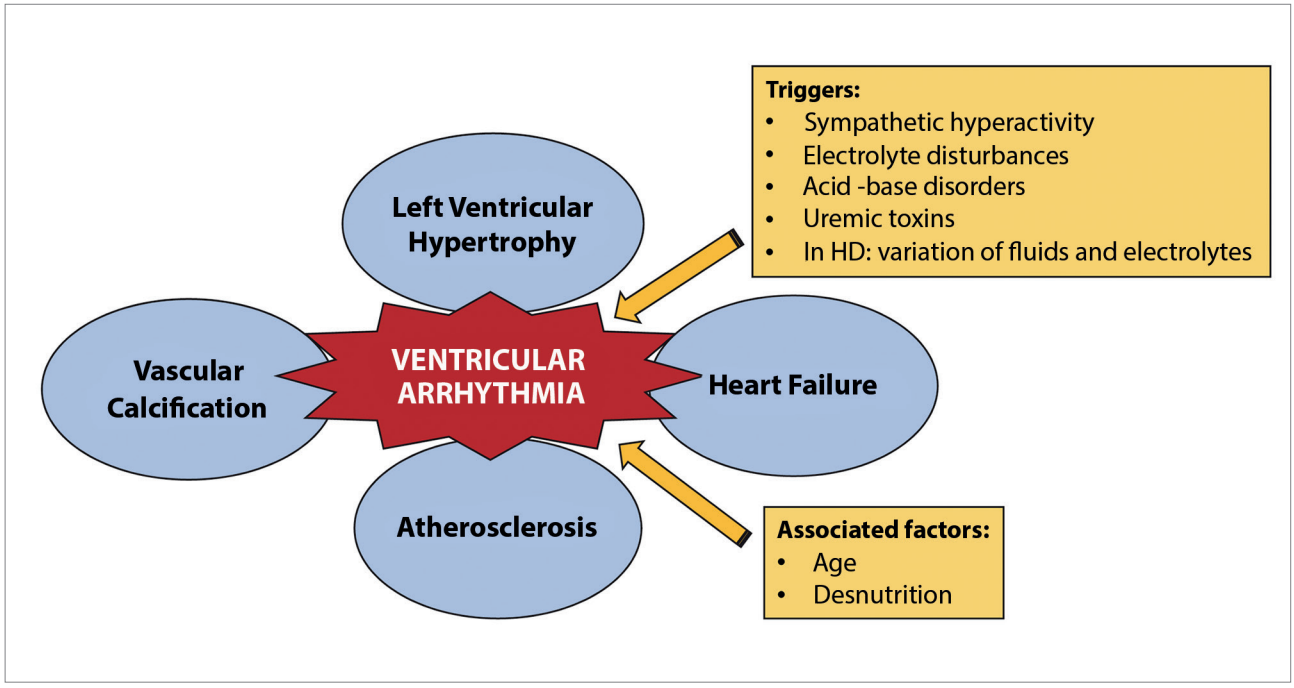
Pathophysiology

A vulnerable diseased myocardium and a transient trigger are required for the occurrence of ventricular arrhythmias. In patients with normal renal function, ischemia due to atheromatous plaque rupture, focal myocardial scars, or systolic dysfunction are the most common substrates for the occurrence of fatal arrhythmias.[7]

In CKD patients, this process is more complex,[19] and the increased susceptibility to ventricular arrhythmias in this population seems to be related to metabolic disturbances and cardiac structural disorders caused directly by renal disfunction[20,21] (Figure 2).

Experimental electrophysiological studies have shown that mice with CKD have peculiarities predisposing to arrhythmogenic cardiac events, such as action potential prolongation, increased electrical instability, frequent early depolarization, and greater sensitivity to induction of ventricular fibrillation. There are also changes in intracellular calcium homeostasis, with reduction of calcium content in the sarcoplasmic reticulum.[22]

Figure 2. Pathophysiology of ventricular arrhythmias in chronic kidney disease (CKD) patients. Muscle and vascular cardiac abnormalities secondary to CKD lead to myocardial electrical instability and make these patients susceptible to trigger arrhythmias after internal or external stimuli. HD: hemodialysis.



A recent study showed that indoxyl sulfate has an arrhythmogenic effect in cardiomyocytes *in vitro* and indicated an independent association between levels of this uremic toxin and QT interval prolongation in CKD patients not on dialysis.[23]

Another uremic toxin that has been the subject of many recent studies is FGF23, which is a cause of left ventricular hypertrophy and an independent predictor of cardiovascular events, CKD progression, and death from all causes in CKD patients.[24] Deo *et al.*[25] showed that this phosphatonin is not independently associated with fatal arrhythmias in the CKD population.[5]

On the other hand, a recent post hoc analysis of the EVOLVE (Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events) study showed that reduction of FGF23 with cinacalcet can decrease the risk of sudden death.[24] In this study, it was not possible to discriminate whether the beneficial effect was directly related to the reduction of FGF23 or was an indirect effect of the actions of other drugs.

In the context of mineral and bone disorders, parathormone (PTH) also plays an important role. Its elevation is independently associated with the occurrence of sudden death in CKD population, especially when the level is above 495 pg/mL.[26] The risk may increase in the case of association with vitamin D deficiency.[27] Vitamin D deficiency is also an independent risk factor for sudden cardiac death in diabetic hemodialysis patients.[28] The physiopathology of this association may be related to left ventricular hypertrophy and coronary artery calcification, which make the myocardium vulnerable to the occurrence of arrhythmias.

In the general population, patients with electrocardiographic evidence of left ventricular hypertrophy (LVH) have higher prevalence, complexity, and severity of ventricular arrhythmias.[29] LVH is the most common cardiovascular complication in CKD patients.[30] Its physiopathology encompasses hemodynamic factors, such as hypertension, hypervolemia, sympathetic hyperactivity and inappropriate activation of endothelin and renin-angiotensin systems. In addition, non-hemodynamic factors are involved, such as anemia, inflammation, and mineral and bone disorders.[30]

Elevated levels of phosphorus, PTH and FGF23 contribute not only to hypertrophy but also to myocardial fibrosis. The fibrosis is aggravated by non-atherosclerotic ischemia caused by the disproportion between the number of cardiac muscle fibers and the capillary density.[31] The consequence of fibrosis is left ventricular diastolic dysfunction. The increase in the number of cardiomyocytes, the appearance of fibrotic bands and the disorganization of muscle fibers

increase the electrical instability of the myocardium and predispose to the occurence of arrhythmias.[15,16,32]

An association between low ejection fraction and sudden death has also been demonstrated in CKD patients.[11,32] A Chinese cohort of peritoneal dialysis patients has shown that systolic dysfunction is the most important predictor of sudden death in this population. The prolonged increase in preload and afterload, excessive oxygen demand and the consequent death of cardiomyocytes lead to the adaptive process known as cardiac remodeling, with dilatation of the chambers and reduction of their contractility.[33] Systolic dysfunction seems to predispose to electrical instability and ventricular arrhythmia, because of sympathetic neurohumoral activation, which would explain the pathophysiological mechanism of the association between systolic dysfunction and ventricular arrhythmias.[32]

Macrovascular disease has a more rapid progression in CKD patients and works as a substrate and a trigger for arrhythmias in this population.[34] The inflammatory environment in CKD patients accelerates endothelial dysfunction and the atherosclerotic process,[35,36] particularly in dialysis patients.[37] High phosphorus contributes to intima calcification and media calcification, promoting an accelerated vascular aging. Patients with PO4 greater than 6.5 mg/dl present a 20% higher risk of sudden death when compared to those with PO4 between 2.4-6.5mg/dl, which may be related to calcification of the cardiac conduction system and to vascular calcification.[26]

Our group and other researchers[38-40] have documented the relationship between coronary artery calcification and increased cardiovascular mortality in CKD patients. Vascular calcification may also play a role in the pathophysiology of ventricular arrhythmias in this population. Di Iorio *et al.*[41] demonstrated that in CKD stage 4 and 5D patients, coronary artery calcification progression was a predictor of QT interval prolongation, which is a known risk factor for fatal ventricular arrhythmias. Other mechanisms that could be involved include the loss of coronary artery dilation and the increased afterload due to aortic calcification,[40,42,43] which is a cause of spontaneous ventricular depolarization (mechano-electrical feedback).[44]

In the presence of such a number of anatomical substrates in CKD patients, electrolyte disturbances become important triggers for the occurrence of arrhythmias. In experimental and clinical models, imbalances between intracellular and extracellular ionic concentrations of potassium, calcium, and magnesium were able to trigger arrhythmias.[45]

In CKD patients, potassium disorders are frequent and have particular importance. Hyperkalemia has been associated with successive electrocardiographic changes, such as high and peaked T waves, short QT interval, prolonged PR interval, QRS widening, P wave disappearance, and, finally, idioventricular rhythm with sinusoidal pattern.

Excessive reduction in the duration of action potentials may promote reentrant arrhythmias in conditions of slow electric conduction. Hyperkalemia in combination with hypocalcemia, hyperphosphatemia, and hypomagnesemia or hypermagnesemia may have adjuvant effects in triggering arrhythmias in this population.[46]

It has been observed that, in dialysis patients, ventricular arrhythmias often occur after the longer interdialytic period (Mondays and Tuesdays). Dialysis sessions may trigger the arrhythmic process due to blood pressure instability, fluid and electrolyte imbalances, and acid-basic disequilibrium.[47]

Adrenergic hyperactivity may also be important in the pathophysiology of arrhythmias in dialysis patients. Studies in humans show that CKD increases the adrenergic discharge of the sympathetic nervous system, mediated by renal afferent nerve pathways.[47] The increase in autonomic tone results in a predisposition to a higher frequency of extrasystoles and is associated with increases in mortality, risk of cardiovascular events, and sudden death in CKD patients.[11,48]

Diagnosis and risk assessment

Ventricular arrhythmias may manifest clinically as palpitations, presyncope, syncope, or chest pain.[4] The majority of individuals with cardiac arrhythmias have structural heart disease. Frequently, the underlying disease is not recognized, and sudden cardiac death is the first manifestation. For this reason, assessment of the risk of ventricular arrhythmia should be performed on the basis of clinical data and complementary tests.

Electrocardiogram (EKG) and 24h EKG monitoring (Holter monitor)

The electrocardiogram (EKG) is an important cardiac screening method and is more valuable during active symptom manifestation. In asymptomatic patients, this exam may indicate underlying structural cardiac disease that can act as a substrate for the occurrence of ventricular arrhythmia.

EKG monitoring performed over the course of a 24h period (Holter monitor) increases the chance of detection of an arrhythmic episode by more than 10 times.[49] This test may also detect other noninvasive risk markers, such as nonsustained monomorphic VT, decreased heart rate variability, the presence of delayed action potentials, and T wave alternation.[4]

Heart rate variability is a method to assess autonomic nervous system function. Decrease in heart rate variability is a predictor of adrenergic activation and increases the risk of sudden death in both the general and hemodialysis populations.[50]

Detection of repolarization defects and QT interval abnormalities are also important. In dialysis patients, the acquired long QT interval syndrome is highly prevalent and may contribute to the occurrence of sudden death.[51,52] On the other hand, hypercalcemia, hyperkalemia, and digitalis intoxication, common conditions in CKD patients, can shorten the QT interval.[53] This alteration also increases the risk of polymorphic VT and sudden death.[4]

The QT interval dispersion, characterized by heterogeneous QT duration among EKG leads, reflects regional differences in ventricular recovery time. This finding has been linked to the occurrence of malignant ventricular arrhythmias in different kinds of heart disease. Lorincz *et al.*[52] showed that hemodialysis increases QT interval dispersion in CKD patients.[2] It is possible that this phenomenon reflects a heterogeneous repolarization of different ventricular regions during hemodialysis, resulting in a predisposition to the occurrence of arrhythmias.

Echocardiogram and cardiac magnetic resonance imaging (MRI)

Echocardiography helps to detect structural heart disease, mainly systolic dysfunction, which is considered the most important risk factor for arrhythmia in the general population.[4] In dialysis patients, the test should preferably be performed preferably on a day without a hemodialysis session and with the patient at dry weight, since hemodynamic fluctuations may affect the echocardiographic findings.[54]

Cardiac MRI is a good option to assess myocardial fibrosis and LVH. MR angiography may help to detect cardiac scars, which are the most common substrate for the occurrence of sustained monomorphic VT.[4] In CKD patients, the MR angiography must be performed without gadolinium, due to the risk of nephrogenic systemic fibrosis.[55] High costs restrict the routine use of this modality.[56]

Dobutamine stress echocardiography, myocardial scintigraphy, and coronary angiography

Detection of coronary artery disease is also relevant, as it is highly prevalent in CKD patients. Both dobutamine stress echocardiography and myocardial scintigraphy have moderate sensitivity and specificity (75-90%) for the detection of obstructive coronary artery disease in CKD patients. Coronary angiography is the gold standard, but carries the risk of contrast-induced nephropathy in non-dialysis CKD patients. This modality should be reserved for patients at high risk of acute coronary syndrome and those who may benefit from revascularization therapy.[57]

Prevention and treatment

Treatment of arrhythmias initially involves correction of modifiable factors, such as withdrawal of drugs causing QT prolongation (clarithromycin, chlorpromazine, haloperidol, amiodarone, procainamide, etc.), adjustment of metabolic and electrolyte imbalances, and interruption of drugs that stimulate the sympathetic nervous system (such as caffeine and amphetamine analogs).[4]

In hemodialysis patients, one therapeutic option is modification of the dialysate composition. When serum potassium is less than 4.0 mg/dl, potassium replacement in the dialysate should be performed. Increasing potassium in the dialysate reduces ventricular ectopic beats and raises serum potassium levels in these patients, contributing to reductions in the QT interval and in QT dispersion during dialysis.[11]

The use of dialysate with potassium < 2 mEq/l is associated with an increased risk of sudden death and should be avoided.[58] Avoiding dialysate with calcium

< 2,5 mEq/l also seems to reduce the risk of fatal arrhythmias.[59] Other possible procedures include better control of interdialytic weight gain, reduction of the dialysate temperature, and, potentially, the use of intensive hemodialysis modalities.[60]

Multiple trials have shown that frequent or prolonged (nocturnal) dialysis reduces left ventricular mass and improves heart rhythm. Observational studies also indicate that daily hemodialysis is associated with a lower risk of cardiovascular death and hospitalization. The explanation for these findings may be lower neurohumoral activation and lower electrolyte translocation, with greater myocardial stability.[61]

Coronary reperfusion, angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), aldosterone antagonists, and beta-blockers reduce the risk of sudden death after acute myocardial infarction in the general population.[4] The cardiovascular benefits of these drugs and procedures have also been studied in CKD patients with conflicting results, especially due to the high risk of hyperkalemia in this population.[62-64] Of note, none of the studies specifically analyzed the impact of these drugs on the reduction of ventricular arrhythmias in CKD patients.

Many arrhythmias are caused or aggravated by sympathetic stimulation and respond favorably to beta-blockers. These drugs are considered first-line therapy for symptomatic ventricular arrhythmias, although they are less effective in treatment of arrhythmias associated with structural heart disease.[4] In the CKD population, a randomized trial showed a survival benefit with carvedilol in hemodialysis patients with heart disease.[11] There are also data showing increased survival after cardiac arrest in hemodialysis patients taking beta-blockers.[65] However, a secondary analysis of the Hemodialysis (HEMO) study did not demonstrate that these drugs could reduce the risk of fatal arrhythmias.[66]

The use of statins has been associated with a lower risk of cardiovascular events and death in non-dialyzed CKD patients.[67] However, the benefits of these drugs are still controversial in the dialysis population[68] and in transplant recipients.[69]

Anti-arrhythmic drugs have an important role in reducing symptomatic arrhythmias and ICD shocks in the general population.[4] Drugs that block membrane activation through cardiac ion channels (propafenone, sotalol, quinidine, etc.) have high toxicity and can aggravate arrhythmias, especially in CKD patients. In patients using propafenone, a reduction in renal function contributes to accumulation of N-acetyl-procainamide, a potentially arrhythmogenic toxic metabolite.[70]

Doses of the following drugs should be adjusted according to renal function (Table 1): digoxin, procainamide, atenolol, and sotalol. Carvedilol does not require adjustment; however, slow and cautious dose progression should be considered, especially in elderly patients. Other agents (amiodarone, flecainide, and metoprolol) can be used at normal doses in CKD patients.[46,70] Caution should be used with amiodarone in relation to thyroid, lung, liver, and nervous system toxicity. This drug is contraindicated in patients with left ventricular ejection fraction < 35% due to increased mortality, especially in patients with New York Heart Association (NYHA) heart failure functional class III or greater.[4]

Digoxin is excreted in the urine and has a narrow therapeutic window. Therefore, dose reduction is crucial in CKD patients. The accumulation and toxicity of digoxin may lead to the same arrhythmia that the drug is intended to treat or avoid. Regular EKG and digoxin concentration monitoring are highly recommended in these patients.[70]

ICDs are used for primary and secondary prevention in the general high-risk population with preserved renal function. Criteria for ICD insertion include good functional status and life expectancy of at least one year. ICDs are effective in reversing VT and ventricular fibrillation, resulting in decreased mortality in these patients.[4] In CKD patients, the role of ICDs in the prevention of sudden death is controversial.

A recent meta-analysis of CKD patients not undergoing dialysis showed that the impact of ICD implantation on primary prevention of sudden death depends on the baseline renal function, with the benefit observed to decrease to the same extent that the glomerular filtration rate declined.[71] In dialysis patients, several authors have shown high mortality and a higher risk of complications with ICD implantation. Although these patients have a higher incidence of ventricular fibrillation and a higher frequency of shocks administered by the device, survival outcomes by primary prevention are disappointing. In secondary prevention, there may be

Table 1 Dosage adjustment according to renal impairment of digoxin and anti-arrhythmic drugs

Digoxin	CrCl > 50 mL/minute: No dosage adjustment necessary. CrCl 10 to 50 mL/minute: 0.0625 mg every 24 to 36 hours CrCl < 10 mL/minute: 0.0625 mg every 48 hours Hemodialysis: Non-dialyzable. 0.0625 mg every 48 hours Peritoneal dialysis: 0.0625 mg every 48 hours
Procainamide	CrCl > 50 mL/minute: No dosage adjustment necessary. CrCl 10 to 50 mL/minute: Reduce initial daily dose by 25% to 50% CrCl < 10 mL/minute: Reduce initial daily dose by 50% to 75%. Monitor procainamide concentrations closely. Hemodialysis: Moderately hemodialyzable (20% to 50%); monitor procainamide) concentrations; supplementation may be necessary. Peritoneal dialysis: Not peritoneal dialyzable.
Atenolol	CrCl > 35 mL/minute: No dosage adjustment necessary. CrCl 15 to 35 mL/minute: Maximum dose: 50 mg daily CrCl < 15 mL/minute: Maximum dose: 25 mg daily Hemodialysis: Moderately dialyzable (20% to 50%); administer dose post-dialysis or administer 25 to 50 mg supplemental dose. Peritoneal dialysis: Elimination is not enhanced; supplemental dose is not necessary.
Sotalol	Dose escalations in renal impairment should be done after administration of at least 5 to 6 doses at appropriate intervals. CrCl > 60 mL/minute: Administer every 12 hours. CrCl 40 to 60 mL/minute: Administer every 24 hours. CrCl < 40 mL/minute: Use is contraindicated. Hemodialysis: Use is contraindicated. Peritoneal dialysis: Use is contraindicated.

CrCl = Creatinine Clearance.

some benefit,[72] but there are no guidelines indicating this therapy in CKD patients.

Of note, the annual mortality in dialysis patients with an ICD between 1994 and 2006 was as high as 44.8% in the United States, and most of the deaths were attributed to cardiovascular causes. The post-implant infection rates were high, especially in the first year (988 events/1000 patient-years), although the majority of infections were not ICD-related.[73] The insertion of transvenous cardiac devices may also lead to central vein stenosis, which adversely affects the maturation and preservation of arteriovenous fistulas for hemodialysis.[74]

Catheter ablation efficacy and risks depend on the origin of VT, associated heart disease, and operator skill. Complications include tamponade, stroke, heart block, and, frequently, vascular access complication.[4] In CKD patients, there is limited experience with ablation for treating ventricular arrhythmia. We found no studies that evaluated the success rate and complications of ablation in this population.

Perspectives and conclusion

Further studies with emphasis on the clinical management of arrhythmias in CKD patients are needed, because the currently available data regarding cardioprotective medication, anti-arrhythmic drugs, and invasive therapy are lacking. There are drugs under investigation, such as carvedilol analogs, which have shown encouraging results in hypercalcemia-induced arrhythmia, catecholaminergic tachycardia, and arrhythmia related to heart failure.[75]

Modern subcutaneous and external cardiac defibrillators, with improved efficacy and safety, are in the development phase. Such strategies could avoid vascular complications and minimize the risk of infection, which are desirable outcomes in the CKD population in particular. In the future, there will be devices capable of measuring intracardiac pressure, and these may assist in the earlier detection of cardiac function deterioration. Such advances would allow therapy based on the hemodynamic effects of arrhythmia, avoiding shocks in well-tolerated arrhythmias.

While such technologies are not available, the management of ventricular arrhythmia in CKD patients should focus initially on risk stratification and prevention. Physician should be attentive to modifiable risk factors and to the treatment of comorbidities that cause structural cardiac abnormalities, such as hypertension, fluid overload, bone mineral disorders,

and anemia. The most important aim with all these actions is to reduce the risk of arrhythmias and sudden death, the leading cause of death in this population.

References

1. Foley RN, Murray AM, Li S, Herzog CA, McBean AM, Eggers PW, et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. J Am Soc Nephrol 2005;16:489-95. DOI: http://dx.doi.org/10.1681/ASN.2004030203
2. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296-305. PMID: 15385656 DOI: http://dx.doi.org/10.1056/NEJMoa041031
3. USRDS Annual Data Report. Mortality. Betheseda: US Renal Data System; 2011 [cited 2017 Apr 12]. Available from: https://www.usrds.org/2011/view/v2_05.asp
4. John RM, Tedrow UB, Koplan BA, Albert CM, Epstein LM, Sweeney MO, et al. Ventricular arrhythmias and sudden cardiac death. Lancet 2012;380:1520-29. DOI: http://dx.doi.org/10.1016/S0140-6736(12)61413-5
5. Prutkin JM, ed. Goldberger AL, Saperia GM. ECG tutorial: Ventricular Arrhythmias [cited 2013 Nov 25]. Available from: www.uptodate.com
6. Pratt CM, Greenway PS, Schoenfeld MH, Hibben ML, Reiffel JA. Exploration of the precision of classifying sudden cardiac death. Implications for the interpretation of clinical trials. Circulation 1996;93:519-24. PMID: 8565170 DOI: http://dx.doi.org/10.1161/01.CIR.93.3.519
7. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. N Engl J Med 2001;345:1473-82. DOI: http://dx.doi.org/10.1056/NEJMra000650
8. Wan C, Herzog CA, Zareba W, Szymkiewicz SJ. Sudden cardiac arrest in hemodialysis patients with wearable cardioverter defibrillator. Ann Noninvasive Electrocardiol 2014;19:247-57. DOI: http://dx.doi.org/10.1111/anec.12119
9. Bozbas H, Atar I, Yildirir A, Ozgul A, Uyar M, Ozdemir N, et al. Prevalence and predictors of arrhythmia in end stage renal disease patients on hemodialysis. Ren Fail 2007;29:331-9. DOI: http://dx.doi.org/10.1080/08860220701191237
10. Abe S, Yoshizawa M, Nakanishi N, Yazawa T, Yokota K, Honda M, et al. Electrocardiographic abnormalities in patients receiving hemodialysis. Am Heart J 1996;131:1137-44. PMID: 8644592 DOI: http://dx.doi.org/10.1016/S0002-8703(96)90088-5
11. Bleyer AJ, Hartman J, Brannon PC Reeves-Daniel A, Satko SG, Russell G. Characteristics of sudden death in hemodialysis patients. Kidney Int 2006;69:2268-73. PMID: 16672908 DOI: http://dx.doi.org/10.1038/sj.ki.5000446
12. Davis TR, Young BA, Eisenberg MS, Rea TD, Copass MK, Cobb LA. Outcome of cardiac arrests attended by emergency medical services staff at community outpatient dialysis centers. Kidney Int 2008;73:933-9. DOI: http://dx.doi.org/10.1038/sj.ki.5002749
13. Bonato FO, Lemos MM, Cassiolato JL, Canziani ME. Prevalence of ventricular arrhythmia and its associated factors in nondialyzed chronic kidney disease patients. PLoS One 2013;8:e66036. DOI: http://dx.doi.org/10.1371/journal.pone.0066036
14. Canziani ME, Saragoça MA, Draibe SA, Barbieri A, Ajzen H. Risk factors for the occurrence of cardiac arrhythmias in patients on continuous ambulatory peritoneal dialysis. Perit Dial Int 1993;13:S409-11.
15. Saragoça MA, Canziani ME, Cassiolato JL, Gil MA, Andrade JL, Draibe SA, et al. Left ventricular hypertrophy as a risk factor for arrhythmias in hemodialysis patients. J Cardiovasc Pharmacol 1991;17:S136-8. PMID: 1715462
16. Marcassi AP, Yasbek DC, Pestana JO, Fachini FC, De Lira Filho EB, Cassiolato JL, et al. Ventricular arrhythmia in incident kidney transplant recipients: prevalence and associated factors. Transpl Int 2011;24:67-72. DOI: http://dx.doi.org/10.1111/j.1432-2277.2010.01149.x
17. Bonato FO, Watanabe R, Lemos MM, Cassiolato JL, Wolf M, Canziani ME. Asymptomatic Ventricular Arrhythmia and Clinical Outcomes in Chronic Kidney Disease: A Pilot Study. Cardiorenal Med 2016;7:66-73. DOI: http://dx.doi.org/10.1159/000449260
18. Wong MC, Kalman JM, Pedagogos E, Toussaint N, Vohra JK, Sparks PB, et al. Bradycardia and asystole is the predominant mechanism of sudden cardiac death in patients with chronic kidney disease. J Am Coll Cardiol 2015;65:1263-5. DOI: http://dx.doi.org/10.1016/j.jacc.2014.12.049
19. Pun PH, Middleton JP. Sudden cardiac death in hemodialysis patients: a comprehensive care approach to reduce risk. Blood Purif 2012;33:183-9. DOI: http://dx.doi.org/10.1159/000334154
20. Pun PH, Smarz TR, Honeycutt EF, Shaw LK, Al-Khatib SM, Middleton JP. Chronic Kidney Disease is associated with increased risk of sudden cardiac death among patients with coronary artery disease. Kidney Int 2009;76:652-8. PMID: 19536082 DOI: http://dx.doi.org/10.1038/ki.2009.219
21. Herzog CA, Mangrum JM, Passman R. Sudden cardiac death and dialysis patients. Semin Dial 2008;21:300-7. DOI: http://dx.doi.org/10.1111/j.1525-139X.2008.00455.x
22. Hsueh CH, Chen NX, Lin SF, Chen PS, Gattone VH 2nd, Allen MR, et al. Pathogenesis of Arrhythmias in a Model of CKD. Am Soc Nephrol 2014;25:2812-21. DOI: http://dx.doi.org/10.1681/ASN.2013121343
23. Tang WH, Wang CP, Chung FM, Huang LL, Yu TH, Hung WC, et al. Uremic retention solute indoxyl sulfate level is associated with prolonged QTc interval in early CKD patients. PLoS One 2015;10:e0119545. DOI: http://dx.doi.org/10.1371/journal.pone.0119545
24. Moe SM, Chertow GM, Parfrey PS, Kubo Y, Block GA, Correa-Rotter R, et al.; Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) Trial Investigators*. Cinacalcet, Fibroblast Growth Factor-23, and Cardiovascular Disease in Hemodialysis: The Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) Trial. Circulation 2015;132:27-39. PMID: 26059012 DOI: http://dx.doi.org/10.1161/CIRCULATIONAHA.114.013876
25. Deo R, Katz R, de Boer IH, Sotoodehnia N, Kestenbaum B, Mukamal KJ, et al. Fibroblast growth factor 23 and sudden versus non-sudden cardiac death: the cardiovascular health study. Am J Kidney Dis 2015;66:40-6. PMID: 25572028 DOI: http://dx.doi.org/10.1053/j.ajkd.2014.10.025
26. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO(4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol 2001;12:2131-8.
27. Deo R, Katz R, Shlipak MG, Sotoodehnia N, Psaty BM, Sarnak MJ, et al. Vitamin D, parathyroid hormone, and sudden cardiac death: results from the Cardiovascular Health Study. Hypertension 2011;58:1021-8. DOI: http://dx.doi.org/10.1161/HYPERTENSIONAHA.111.179135
28. Drechsler C, Pilz S, Obermayer-Pietsch B, Verduijn M, Tomaschitz A, Krane V, et al. Vitamin D deficiency is associated with sudden cardiac death, combined cardiovascular events, and mortality in haemodialysis patients. Eur Heart J 2010;31:2253-61. DOI: http://dx.doi.org/10.1093/eurheartj/ehq246
29. Spacek R, Gregor P. Ventricular arrhythmias in myocardial hypertrophy of various origins. Can J Cardiol 1997;13:455-8. PMID: 9179083
30. Cerasola G, Nardi E, Palermo A, Mulè G, Cottone S. Epidemiology and pathophysiology of left ventricular abnormalities in chronic kidney disease: a review. J Nephrol 2011;24:1-10. DOI: http://dx.doi.org/10.5301/JN.2010.2030

31. Amann K, Rychlík I, Miltenberger-Milteny G, Ritz E. Left ventricular hypertrophy in renal failure. Kidney Int Suppl 1998;68:S78-85. DOI: http://dx.doi.org/10.1046/j.1523-1755.1998.06818.x
32. Wang AY, Lam CW, Chan IH, Wang M, Lui SF, Sanderson JE. Sudden cardiac death in end-stage renal disease patients: a 5-year prospective analysis. Hypertension 2010;56:210-6. DOI: http://dx.doi.org/10.1161/HYPERTENSIONAHA.110.151167
33. Di Lullo L, House A, Gorini A, Santoboni A, Russo D, Ronco C. Chronic kidney disease and cardiovascular complications. Heart Fail Rev 2015;20:259-72. DOI: http://dx.doi.org/10.1007/s10741-014-9460-9
34. Lindner A, Charra B, Sherrard DJ, Scribner BH. Accelerated atherosclerosis in prolonged maintenance hemodialysis. N Engl J Med 1974;290:697-701. PMID: 4813742 DOI: http://dx.doi.org/10.1056/NEJM197403282901301
35. Mezzano D, Pais EO, Aranda E, Panes O, Downey P, Ortiz M, et al. Inflammation, not hyperhomocysteinemia, is related to oxidative stress and hemostatic and endothelial dysfunction in uremia. Kidney Int 2001;60:1844-50. DOI: http://dx.doi.org/10.1016/S0085-2538(15)48065-2
36. Zalba G, Fortuño A, Díez J. Oxidative stress and atherosclerosis in early chronic kidney disease. Nephrol Dial Transplant 2006;21:2686-90. DOI: http://dx.doi.org/10.1093/ndt/gfl398
37. Jofré R, Rodriguez-Benitez P, López-Gómez JM, Pérez-Garcia R. Inflammatory syndrome in patients on hemodialysis. J Am Soc Nephrol 2006;17:S274-80.
38. Watanabe R, Lemos MM, Manfredi SR, Draibe SA, Canziani MEF. Impact of cardiovascular calcification in nondialyzed patients after 24 months of follow-up. Clin J Am Soc Nephrol 2010;5:189-94. DOI: http://dx.doi.org/10.2215/CJN.06240909
39. Moe SM, O'Neill KD, Reslerova M, Fineberg N, Persohn S, Meyer CA. Natural history of vascular calcification in dialysis and transplant patients. Nephrol Dial Transplant 2004;19:2387-93. DOI: http://dx.doi.org/10.1093/ndt/gfh303
40. Amann K. Media Calcification and intima calcification are distinct entities in chronic Kidney disease. Clin J Am Soc Nephrol 2008;3:1599-605. DOI: http://dx.doi.org/10.2215/CJN.02120508
41. Di Iorio BR, D'Avanzo E, Piscopo C, Grimaldi P, Cucciniello E, Cillo N, et al. Progression of vascular calcification increases QT interval in haemodialysis patients. Nephrol Dial Transplant 2006;21:3609-10. DOI: http://dx.doi.org/10.1093/ndt/gfl417
42. Lau WL, Pai A, Moe SM, Giachelli CM. Direct effects of phosphate on vascular cell function. Adv Chronic Kidney Dis 2011;18:105-12. DOI: http://dx.doi.org/10.1053/j.ackd.2010.12.002
43. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al.; American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Hypertension 2003;42:1050-65. PMID: 14604997 DOI: http://dx.doi.org/10.1161/01.HYP.0000102971.85504.7c
44. Lerman BB, Burkhoff D, Yue DT, Sagawa K. Mechanoelectrical feedback: independent role of preload and contractility in modulation of canine ventricular excitability. J Clin Invest 1985;76:1843-50. PMID: 4056056 DOI: http://dx.doi.org/10.1172/JCI112177
45. Hoffman BF, Cranefield PF. Electrophysiology of the Heart. New York: McGraw-Hill; 1960. p. 4-323.
46. Boriani G, Savelieva I, Dan GA, Deharo JC, Ferro C, Israel CW, et al.; Document reviewers. 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. Europace 2015;17:1169-96. DOI: http://dx.doi.org/10.1093/europace/euv202
47. Kiuchi MG, Mion Jr D. Chronic kidney disease and risk factors responsible for sudden cardiac death: a whiff of hope? Kidney Res Clin Pract 2016;35:3-9.
48. Zoccali C, Mallamaci F, Parlongo S, Cutrupi S, Benedetto FA, Tripepi G, et al. Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. Circulation 2004;105:1354-9. PMID: 11901048 DOI: http://dx.doi.org/10.1161/hc1102.105261
49. Fleg JL, Kennedy HL. Cardiac arrhythmias in a healthy elderly population: detection by 24-hour ambulatory electrocardiography. Chest 1982;81:302-7. DOI: http://dx.doi.org/10.1378/chest.81.3.302
50. Franczyk-Skóra B, Gluba-Brzózka A, Wranicz JK, Banach M, Olszewski R, Rysz J. Sudden cardiac death in CKD patients. Int Urol Nephrol 2015;47:971-82. DOI: http://dx.doi.org/10.1007/s11255-015-0994-0
51. Bignotto LH, Kallás ME, Djouki RJ, Sassaki MM, Voss GO, Soto CL, et al. Electrocardiographic findings in chronic hemodialysis patients. J Bras Nefrol 2012;34:235-42. DOI: http://dx.doi.org/10.5935/0101-2800.20120004
52. Lorincz I, Mátyus J, Zilahi Z, Kun C, Karányi Z, Kakuk G. QT dispersion in patients with end-stage renal failure and during hemodialysis. J Am Soc Nephrol 1999;10:1297-302.
53. Friedmann AA, Grindler J, Oliveira CAR. Encurtamento do intervalo QT. Diagn Tratamento 2012;17:192-4.
54. Chiu DY, Green D, Abidin N, Sinha S, Kalra PA. Echocardiography in Hemodialysis Patients: uses and challenges. Am J Kidney Dis 2014;64:804-16. PMID: 24751169 DOI: http://dx.doi.org/10.1053/j.ajkd.2014.01.450
55. Daftari Besheli L, Aran S, Shaqdan K, Kay J, Abujudeh H. Current status of nephrogenic systemic fibrosis. Clin Radiol 2014;69:661-8. PMID: 24582176 DOI: http://dx.doi.org/10.1016/j.crad.2014.01.003
56. Di Lullo L, House A, Gorini A, Santoboni A, Russo D, Ronco C. Chronic kidney disease and cardiovascular complications. Heart Fail Rev 2015;20:259-72. DOI: http://dx.doi.org/10.1007/s10741-014-9460-9
57. Cai Q, Mukku VK, Ahmad M. Coronary artery disease in patients with chronic kidney disease: a clinical update. Curr Cardiol Rev 2013;9:331-9. DOI: http://dx.doi.org/10.2174/1573403X10666140214122234
58. Pun PH, Lehrich RW, Honeycutt EF, Herzog CA, Middleton JP. Modifiable risk factors associated with sudden cardiac arrest within hemodialysis clinics. Kidney Int 2011;79:218-27. PMID: 20811332 DOI: http://dx.doi.org/10.1038/ki.2010.315
59. Pun PH, Horton JR, Middleton JP. Dialysate calcium concentration and the risk of sudden cardiac arrest in hemodialysis patients. Clin J Am Soc Nephrol 2013;8:797-803. DOI: http://dx.doi.org/10.2215/CJN.10000912
60. Pun PH. The interplay between CKD, sudden cardiac death, and ventricular arrhythmias. Adv Chronic Kidney Dis 2014;21:480-8. DOI: http://dx.doi.org/10.1053/j.ackd.2014.06.007
61. McCullough PA, Chan CT, Weinhandl ED, Burkart JM, Bakris GL. Intensive Hemodialysis, Left Ventricular Hypertrophy, and Cardiovascular Disease. Am J Kidney Dis 2016;68:S5-14. DOI: http://dx.doi.org/10.1053/j.ajkd.2016.05.025
62. Efrati S, Zaidenstein R, Dishy V, Beberashvili I, Sharist M, Averbukh Z, et al. ACE inhibitors and survival of hemodialysis patients. Am J Kidney Dis 2002;40:1023-9. PMID: 12407648 DOI: http://dx.doi.org/10.1053/ajkd.2002.36340
63. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al.; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Eng J Med 2001;345:861-9. DOI: http://dx.doi.org/10.1056/NEJMoa011161
64. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Eng J Med 2001;345:851-60. DOI: http://dx.doi.org/10.1056/NEJMoa011303

65. Pun PH, Lehrich RW, Smith SR, Middleton JP. Predictors of survival after cardiac arrest in outpatient hemodialysis clinics. Clin J Am Soc Nephrol 2007;2:491-500. DOI: http://dx.doi.org/10.2215/CJN.02360706
66. Tangri N, Shastri S, Tighiouart H, Beck GJ, Cheung AK, Eknoyan G, et al. β-Blockers for prevention of sudden cardiac death in patients on hemodialysis: a propensity score analysis of the HEMO Study. Am J Kidney Dis 2011;58:939-45. DOI: http://dx.doi.org/10.1053/j.ajkd.2011.06.024
67. Zhang X, Xiang C, Zhou YH, Jiang A, Qin YY, He J. Effect of statins on cardiovascular events in patients with mild to moderate chronic kidney disease: a systematic review and meta-analysis of randomized clinical trials. BMC Cardiovasc Disord 2014;14:19. DOI: http://dx.doi.org/10.1186/1471-2261-14-19
68. Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 2005;353:238-48. PMID: 16034009 DOI: http://dx.doi.org/10.1056/NEJMoa043545
69. Palmer SC, Navaneethan SD, Craig JC, Perkovic V, Johnson DW, Nigwekar SU, et al. HMG CoA reductase inhibitors (statins) for kidney transplant recipients. Cochrane Database Syst Rev 2014;1:CD005019.
70. Cervelli MJ, Russ GR. Principles of Drug Therapy, Dosing, and Prescribing in Chronic Kidney Disease and Renal Replacement Therapy. In: Johnson RJ, Feehally J, Floege J. Comprehensive Clinical Nephrology. 4th ed. St. Louis: Elsevier; 2010. p. 871-893.
71. Pun PH, Al-Khatib SM, Han JY, Edwards R, Bardy GH, Bigger JT, et al. Implantable cardioverter-defibrillators for primary prevention of sudden cardiac death in CKD: a meta-analysis of patient-level data from 3 randomized trials. Am J Kidney Dis 2014;64:32-9. PMID: 24518128 DOI: http://dx.doi.org/10.1053/j.ajkd.2013.12.009
72. Herzog CA, Li S, Weinhandl ED, Strief JW, Collins AJ, Gilbertson DT. Survival of dialysis patients after cardiac arrest and the impact of implantable cardioverter defibrillators. Kidney Int 2005;68:818-25. PMID: 16014061 DOI: http://dx.doi.org/10.1016/S0085-2538(15)50904-6
73. Charytan DM, Patrick AR, Liu J, Setoguchi S, Herzog CA, Brookhart MA, et al. Trends in the use and outcomes of implantable cardioverter-defibrillators in patients undergoing dialysis in the United States. Am J Kidney Dis 2011;58:409-17. DOI: http://dx.doi.org/10.1053/j.ajkd.2011.03.026
74. Poulikakos D, Banerjee D, Malik M. Risk of sudden cardiac death in chronic kidney disease. J Cardiovasc Electrophysiol 2014;25:222-31. DOI: http://dx.doi.org/10.1111/jce.12328
75. Zhou Q, Xiao J, Jiang D, Wang R, Vembaiyan K, Wang A, et al. Carvedilol and its new analogs suppress arrhythmogenic store overload-induced Ca2+ release. Nat Med 2011;17:1003-9. DOI: http://dx.doi.org/10.1038/nm.2406