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Sudden cardiac death in patients with kidney failure on renal replacement therapy: An unsolved problem

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ABSTRACT

Sudden cardiac death is an important cause of mortality in patients with kidney failure undergoing renal replacement therapy, either hemodialysis or peritoneal dialysis. The risk factors associated with sudden cardiac death in these patients only partly overlap with those in the general population. Kidney failure per se and hemodialysis therapy expose these patients to an increased risk of sudden cardiac death compared with individuals with preserved renal function. Studies of the implantable cardioverter defibrillator for primary prevention of sudden cardiac death in patients with kidney failure have failed to demonstrate its usefulness. Moreover, the incidence of complications associated with cardiac electronic device implantation in this population is extremely high.
This review aims to provide an update on the available studies on the pathophysiology and prevention of sudden cardiac death in patients with kidney failure undergoing dialysis and to propose the adoption of clinical practices to reduce its incidence.

KEYWORDS Cardiac implantable electronic device complications; Dialysis bath; Hemodialysis; Implantable cardioverter defibrillator; Kidney failure; QT interval; Sudden cardiac death

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Sudden cardiac death (SCD) is a frequent cause of death in kidney failure patients on dialysis therapy. The U.S. Dialysis and Transplant Registry reports that, in 2019, 44.9% of patients on hemodialysis, whose cause of death was known, experienced death caused by "arrhythmia/cardiac arrest."[1] However, within this large number of patients are included subpopulations with markedly different characteristics. Patients with kidney failure, both those on hemodialysis and those on peritoneal dialysis, have a high prevalence of ischemic heart disease and heart failure,[1] placing them at risk for SCD without the complicating factor of hemodialysis. However, there are a number of risk factors for SCD that are specific to kidney failure, especially for patients on hemodialysis.

Pathophysiology of SCD in patients with kidney failure on dialysis

Intradialytic SCD

The relationship between the hemodialysis session and SCD in patients undergoing kidney replacement treatment is complex. First, sudden cardiac arrests (SCAs) occurring during the hemodialysis session should be differentiated from extradialytic SCDs. Intradialytic SCAs are infrequent events with poor prognoses. The reported rate of SCA is 4.5 to 7.0 per 100,000 hemodialysis treatments,[2,3] but only 40% to 45% of patients are successfully resuscitated and are still alive 12 to 24 hours after the event.[3,4] Davis et al[4] described 110 episodes of intradialytic SCA. The initial rhythm recorded at the time of the event was ventricular fibrillation in 65% of the cases, ventricular tachycardia in 2%, pulseless electrical activity in 23%, and asystole in 10%. In contrast, the study by Pun et al[5] reported that of a total of 398 episodes of intradialytic SCA, 66% were associated with an initial nonshockable rhythm (pulseless electrical activity in 26.4% of cases, asystole in 17.0%, and an unknown nonshockable rhythm in 23%). Of the 34% of patients who had shockable rhythm, ventricular fibrillation was present in 14%, ventricular tachycardia in 1%, and an unknown shockable rhythm in 19%. Although the rhythm that is underlying the SCA is not always a shockable arrhythmia, patients for whom cardiopulmonary resuscitation

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had been initiated directly by dialysis staff had 3 times greater survival as well as better neurologic status on discharge than patients for whom cardiopulmonary resuscitation was performed exclusively by emergency medical services.[5]

An association between SCA and hemodialysis bath composition has been described. Dialysate potassium concentrations < 2 mmol/L are associated with a 2-fold increase in the risk of intradialytic SCA.[2] The incidence of SCA is also doubled in patients on hemodialysis with low ionized calcium concentrations in the dialysis bath (ie, 1.25 mmol/L).[6] SCA seems to be more frequent during the first hemodialysis session of the week, whereas it seems not to be associated with the presence of risk factors such as the presence of coronary artery disease or heart failure with a reduced ejection fraction.[2,3]

Extradialytic SCD

It has been shown that the hemodialysis session induces major changes in myocardial cell repolarization and that these alterations have a close relationship with the concentrations of electrolytes (potassium and calcium) in the dialysate and the pre–post dialysis gradient of their serum levels (ie, the difference between the potassium and calcium serum concentrations before and after the dialysis session). Dialysis baths with low concentrations of potassium and ionized calcium are associated with higher differences in serum potassium and calcium levels between the beginning and end of the dialysis session.[7,8] Moreover, there is an inverse correlation between the delta of serum potassium and ionized calcium from the beginning to the end of the hemodialysis session and the prolongation of the QT interval.[7,8] This phenomenon may induce the occurrence of both intradialytic and extradialytic life-threatening arrhythmias. Indeed, in a population of 37,765 patients on hemodialysis, researchers from the Dialysis Outcomes and Practice Patterns Study group described an increased risk of extradialytic SCD associated with potassium concentrations < 1.5 mmol/L in the dialysis bath, compared with concentrations of 3 mmol/L (hazard ratio [HR] 1.39, 95% confidence interval [CI] 1.12–1.74). The risk increased by approximately 20% for each mmol/L of lower potassium concentration in the dialysate.[9]

Abbreviations

CIED: cardiac implantable electronic device

CKD: chronic kidney disease

ICD: implantable cardioverter defibrillator

RCT: randomized controlled trial

S-ICD: subcutaneous implantable cardioverter defibrillator

SCD: sudden cardiac death

TV-ICD: transvenous implantable cardioverter defibrillator

An additional important factor is the bicarbonate content of the dialysis bath. Too-rapid correction of acidosis promotes the shift of potassium from the extracellular to the intracellular compartment. This can lead to an abrupt reduction in serum potassium levels, with onset of hypokalemia, even though the total amount of potassium removed by the dialysis session remains unchanged.[10] It is therefore not advisable to use a dialysis bath with high bicarbonate concentrations (greater than 34 mmol/L), particularly in association with low potassium and ionized calcium concentrations and in patients with a prolonged QTc predialysis.[11]

Despite the evidence on the possible proarrhythmic effect of dialysis baths with low concentrations of potassium and ionized calcium and high concentrations of bicarbonate, these dialysates are still often used by nephrologists. The decision as to which dialysis bath concentrations to use is complex and is not only determined by the patient's arrhythmic risk. Nephrologists are concerned that using a dialysate with higher potassium concentrations may increase the risk of hyperkalemia occurring in the interdialytic interval, a condition associated with increased sudden and overall mortality in patients with kidney failure.[12] In addition, higher ionized calcium concentrations could lead to an increased risk of vascular calcifications and low bicarbonate concentrations to insufficient correction of acidosis, both conditions associated with worse prognoses in this population.[13,14] The prevalence of QT prolongation is already high under baseline conditions in patients with kidney failure.[15,16] As in the patient with normal kidney function, a prolongation of the QT interval is associated with a higher risk of SCD in hemodialysis.[16,17] Special care should therefore be given in those patients taking drugs that increase the duration of the QT interval. A recent study has shown that compared with initiation of antiemetics with lesser QT-prolonging potential, initiation of ondansetron was associated with higher short-term risk of SCD (HR 1.44; 95% CI 1.08–1.93) among people receiving hemodialysis.[18] Moreover, compared with amoxicillin-based antibiotic treatment, respiratory fluoroquinolone treatment is associated with a higher short-term risk of SCD among patients with hemodialysis-dependent kidney failure (HR 1.95; 95% CI 1.57–2.41).[19] In addition, the increased risk of SCD induced by QT-prolonging antibiotics is higher when the baseline serum-to-dialysate potassium gradient is $\geq$ 3 mEq/L (HR 2.22; 95% CI 1.46–3.40 vs HR 1.43, 95% CI 1.04–1.96).[20] Similarly, a serum-to-dialysate potassium gradient > 4 mEq/L increases the risk of SCD in patients on hemodialysis taking selective serotonin reuptake inhibitors.[21]

Although most SCDs occur outside the hemodialysis session, an association between the timing of hemodialysis sessions and that of extradialytic SCDs has been shown. Two peaks of SCDs in patients on hemodialysis have been described during the first short interdialytic interval of the week and at the end of the long interdialytic interval.[12,22] In addition, patients with higher predialytic potassium serum values are more likely to experience SCDs.[12,23] Uncertainties exist as to what kind of arrhythmia underlies the excess SCDs in the dialysis population. Although some data derived from querying implantable cardioverter defibrillators (ICDs) suggest that SCD is caused by ventricular fibrillation,[24] recent data from implanted loop recorders show a high incidence of bradyarrhythmia and asystole episodes in a number of cases associated with SCD.[25–27] Of note, many of these events occurred during the long interdialytic interval.[26] It is

possible to speculate that the arrhythmic events leading to SCDs in these patients are not always the same and may depend in part on the type of electrolyte imbalance. The long interdialytic interval is frequently associated with major increases in potassium levels, as well as low plasma pH values, a factor that contributes to increased serum potassium values caused by the shift from the intracellular to the extracellular compartment of the potassium ions, in exchange with hydrogen ions. The resulting hyperkalemia could be the determinant for fatal bradyarrhythmia in the long interdialytic interval. On the other hand, an excessively high predialytic serum potassium value may lead too rapid a change in potassium levels during the hemodialysis session, inducing myocardial electrical instability and the possible onset of life-threatening ventricular tachyarrhythmias in the hours immediately following hemodialysis sessions. These events could be aggravated by the use of dialysis baths with low potassium and ionized calcium concentrations that could lead to dangerous increases in the ventricular repolarization time.[8,28] This hypothesis is supported by the recent demonstration of a lower risk of SCD in patients with dialysate ionized calcium 1.50 mmol/L than in patients dialyzed with ionized calcium 1.25 mmol/L (HR 0.81, 95% CI 0.67–0.97).[29] Moreover, loop recorder data show a reduction of clinically significant arrhythmias (bradycardia, ventricular tachycardia, or asystole) with 3.0 mmol/L potassium vs 2.0 mmol/L potassium dialysis bath use.[30] Of note, the patients with higher dialysate potassium concentrations were taking, on nonhemodialysis days, a potassium binder, sodium zirconium cyclosilicate, which protected them from the onset of severe hyperkalemia. All this evidence suggests that eliminating the long interdialytic interval might be useful in reducing risk of SCD in patients on hemodialysis. However, although it has been described that frequent nocturnal hemodialysis associates with a shortening of ventricular repolarization time in patients with kidney failure and prolonged QTc interval,[31] no studies are currently available that have investigated the incidence of life-threatening arrhythmias in patients undergoing daily hemodialysis. A point to emphasize is that, beyond electrolyte imbalances, other factors could play an important role in determining excess sudden mortality in patients with kidney failure undergoing kidney replacement therapy. In this population, the prevalence of heart failure with reduced ejection fraction and ischemic heart disease are extremely high.[1] Atrial fibrillation is also highly prevalent and it presence is associated with a 3-fold increase in the risk of SCD (HR 2.85, CI 95% 1.28–6,37), suggesting that atrial fibrillation may be a triggering factor of fatal arrhythmia in the presence of a predisposing substrate, such as the heart of patients on renal replacement therapy.[12] This observation is in agreement with findings recently reported in 2 studies performed in general populations from UK and Korea.[32,33] Furthermore, markers of chronic inflammation and malnutrition—conditions that are very common in the presence of kidney failure—are associated with an increased rate of SCD in this population.[34]

SCD in patients undergoing peritoneal dialysis

Peritoneal dialysis provides renal replacement therapy that guarantees a greater hemodynamic and cardiac electrical stability compared to hemodialysis. However, patients undergoing peritoneal dialysis, in whom electrolyte imbalances are much less frequent and less important[35] than in patients on hemodialysis, have a prevalence of SCD that is nonetheless high.[1] A study from Korea performed in a large cohort of patients with kidney failure showed that SCD accounted for 21.7% and 19.6% of total deaths in patients on hemodialysis and peritoneal dialysis, respectively.[36] In patients undergoing peritoneal dialysis, the rate of SCD is related to the highest tertile of troponin and brain natriuretic peptide values, suggesting an important role of heart disease.[37] A study comparing hemodialysis with peritoneal dialysis patients showed that the incidence of SCD was no different in the 2 populations, although overall survival was higher in patients on peritoneal dialysis. Factors associated with an increased incidence of SCD in patients on peritoneal dialysis were reduced left ventricular ejection fraction, previous strokes, and ischemic heart disease.[27] These observations suggest that although the incidence of SCDs is also high in patients on peritoneal dialysis, the associated factors may partly differ from those highlighted in patients on hemodialysis. A recent interesting observation seems to confirm this hypothesis; a patient undergoing peritoneal dialysis experienced a sudden onset of recurrent torsade de pointes-induced syncope related to a marked QT interval prolongation after switching to hemodialysis.[38]

Uremic toxins and cardiac electrophysiology

In in vitro models, exposure of myocardial cells to uremic toxins induces alterations in a number of ion channels. Specifically, uremic toxins reduce IKr, IK, and L-type calcium currents of the myocardiocyte, impairing ventricular repolarization. In addition, several in vivo studies in animal models of advanced chronic kidney disease (CKD) demonstrate that uremic toxins exert a variety of unfavorable effects on cardiac electrophysiology. Slowed conduction velocity, prolonged action potential and ventricular repolarization time, increased occurrence of ventricular tachyarrhythmias, and SCD are all observed in animal models in which a state of uremia was induced.[39] These experimental observations suggest that uremia per se exerts a proarrhythmic effect that could make patients with kidney failure particularly prone to developing life-threatening arrhythmias.

ICDs for prevention of SCD in patients with kidney failure on dialysis

As with all other cardiac diseases, the concomitant presence of CKD is an important predictor of mortality in patients implanted with ICDs,[40] and the negative influence of kidney disease is greater with more impaired kidney function. A meta-analysis including the pooled data from the MADIT-I, MADIT-II (Multicenter Automatic Defibrillator Implantation

Trial), and SCD-HFT (Sudden Cardiac Death in Heart Failure Trial) showed that the implantation of ICDs for primary prevention was associated with improved survival for patients with estimated glomerular filtration rate (eGFR) > 60 mL/min, but not for those with eGFR < 60 mL/min.[41] There are several observational studies in patients with CKD also showing this finding.[40,42–44]

In a large population of patients with ICDs implanted for primary prevention, patients on hemodialysis had a 5-fold higher risk of death (HR 4.80, 95% CI 4.46–5.17) than those without CKD and 2.5-fold higher (HR 2.29, 95% CI 2.12–2.46) compared with patients with CKD not on kidney replacement therapy.[43] Several studies confirm these results.[45,46] This raises the question of whether or not it is correct to apply conventional cardiology guidelines when deciding whether to implant an ICD in a patient on hemodialysis. Beyond the predictable observation that in patients with kidney failure the outcomes are worse, the real issue is to understand whether or not a patient on hemodialysis can benefit from ICD placement in terms of overall survival.

To reach a conclusion on this issue, it is necessary to evaluate the evidence from trials comparing patients on hemodialysis who had an indication (for primary or secondary prevention of SCD) for ICD placement and received it with patients who, despite having the indication, were not implanted. No randomized controlled trials (RCTs) are available on this issue, as the presence of kidney failure has always been an exclusion criterion. The only RCT comparing dialysis patients with ICDs with a control group of nonimplanted patients on dialysis has very special features and will be treated separately.[43]

A retrospective study comparing hemodialysis patients receiving ICDs in primary prevention with comparable patients on hemodialysis without ICDs showed that, after adjustment with propensity matching, there was no significant differences in mortality between the 2 groups (HR 0.94, 95% CI 0.67–1.31).[47] These data are in agreement with the results of other observational studies,[48] although discordant data are present in the literature.[49]

More favorable evidence exists for patients with kidney failure undergoing ICD placement for secondary prevention of SCD. Herzog et al[50] demonstrated a benefit for HD patients who had received ICDs after having a resuscitated SCA. ICD placement was independently associated with a 42% relative reduction in mortality. However, only 460 of 6042 patients (7.6%) had received the device, demonstrating a clear underuse of the ICD in secondary prevention in patients on hemodialysis. Charytan et al[51] confirmed the presence of a better outcome in patients with kidney failure who received an ICD for secondary prevention, showing that they had an overall 14% (95% CI 9%–19%) lower mortality risk compared with propensity-matched controls. Similar results were shown by a study that evaluated the efficacy of secondary-prevention ICDs in reducing all-cause mortality in patients on dialysis using the U.S. Dialysis and Transplant Registry dataset between 2004 and 2010 for all patients who were resuscitated from SCA. The observed survival at 2 years was 53% among patients who received ICDs and 27% among those without ICDs (HR 0.54; 95% CI 0.53–0.54.[52] Unfortunately, more recent studies confirming these observations are lacking.

In a large population of patients on dialysis, the cumulative incidence of SCD was higher in those with ICD indications regardless of whether they had received ICDs or not. However, the study showed that even patients without known indications for ICDs had high rates of SCD at follow-up.[53] Thus, we can assume that the presence of kidney failure per se, particularly in patients undergoing kidney replacement therapy, may be an important risk factor for SCD.

This assumption was the basis of the only RCT designed and performed in patients on hemodialysis to evaluate whether or not ICD placement in primary prevention was able to protect this population from the occurrence of SCD.[43] The originality of the study is that the main exclusion criterion was the presence of a standard indication for ICDs. The study included 188 patients on hemodialysis with left ventricular ejection fractions $\geq$ 35% after appropriate screening and optimization of other treatments. The study was stopped for futility after a follow-up of 6.8 years, during which 19 SCDs occurred, including 11 in the ICD group and 8 in the control group. The 5-year cumulative incidence was 9.7% (95% CI 3.3%–16.2%) in the ICD group and 7.9% (95% CI 1.7–14.0%) in the control group, with a nonsignificant HR of 1.32 (95% CI 0.53–3.29; $P = .55$). The 5-year mortality was, as expected, very high (52.7%), but not different between the 2 groups (HR 1.02, 95% CI 0.69–1.52; $P = .92$). There were 25 adverse events, mostly related to the implantation procedure, lead dysfunction, inappropriate shocks, and subclavian vein stenosis. Device explantation had to be performed in 6 patients, in most cases because of the presence of bacteremia.

Transvenous vs nontransvenous ICDs in patients with kidney failure on dialysis

In patients with kidney failure undergoing hemodialysis, the incidence of cardiac implantable electronic device (CIED) complications is particularly high. First, hemodialysis patients undergoing ICD placement are at higher risk of developing postprocedural complications, including hemorrhage and hematoma, need for blood transfusion, mechanical complications requiring lead revision, and longer hospitalization than for patients without kidney failure. In-hospital mortality is 4 times higher (odds ratio [OR] 4.56; CI 3.08–6.76).[54] Patients on hemodialysis require functioning vascular access to perform renal replacement therapy. Once implantation is performed, the permanent transvenous lead can cause subclavian vein stenosis in a high proportion of patients on hemodialysis,[55] precluding the possibility of central venous access. This can be a serious problem for those patients for whom it is difficult to use the peripheral vascular bed to make the arteriovenous fistula.

The incidence of CIED-related infections is high in patients with kidney failure. Polyzos et al[56] described a more than 8-fold increase (OR 8.7, 95% CI 3.4–22.3) in the risk of infection in this population compared with patients with preserved

renal function. These data were confirmed by a recent meta-analysis.[57] CIED-related infections are also more severe in patients with kidney failure and are associated with higher mortality and double the treatment costs compared with patients without kidney failure.[58] Furthermore, in patients on hemodialysis, lead extraction for infection is associated with higher mortality at 1 and 6 months compared with patients without CKD.[59] Because of this high mortality risk, less than one-third of infected leads are removed in patients on hemodialysis with CIED-related infection.[60] However, recent evidence shows that 1-year mortality is significantly reduced in patients with kidney failure in whom the extraction procedure has been performed.[61]

Recently, the subcutaneous ICD (S-ICD) has become an alternative to transvenous ICD (TV-ICD) for patients with limited vascular access or high risk of infection, who do not require cardiac pacing.[62] The option of an ICD without leads is certainly an attractive option for patients on hemodialysis. The first studies describing the use of S-ICD in patients with kidney failure on renal replacement therapy date back approximately 10 years and show no differences in terms of periprocedural complications between patients on hemodialysis and those with normal renal function.[63–65] A more recent retrospective study showed that the rate of inappropriate shocks was similar between dialysis and patients not on dialysis implanted with S-ICDs, with no deaths caused by arrhythmia, or higher number of device-associated infections and complications during a 5-year follow-up.[66] The proportion of patients on hemodialysis with indications for ICD placement who received S-ICDs rapidly increased between 2012 and 2018, from 10% to 69%.[67] However, contrary to expectations, the clinical evidence on CIED-related infections among patients on maintenance hemodialysis is not all in agreement. A small retrospective study describes a significant increase in CIED-related infection events (HR 8.72, 95% CI 1.18–12.85), and hospitalizations (HR 2.59, 95% CI 1.12–6.41) in the TV-ICD group compared with patients with S-ICDs.[68] Nevertheless, a much larger study, using a propensity score analysis, shows that S-ICDs are not associated with reduced risk of bacteremia and sepsis (HR 1.01, 95% CI 0.80–1.26) and hospital admissions (HR 1.01, 95% CI 0.88–1.16) compared with TV-ICDs.[69] Survival data also do not all point in the same direction; a higher cardiovascular mortality (HR 9.17, 95% CI 1.12–8.33) with TV-ICD compared with S-ICD was reported by Schiedat[68] but Pun et al[69] showed no difference in the risk of death after propensity weighting (HR 1.12, 95% CI 0.96–1.30). Beyond the results of studies on infection and mortality, the use of S-ICDs for the prevention of SCD in patients with kidney failure may also be troublesome, as a non-negligible proportion of SCDs of patients on hemodialysis is caused by bradyarrhythmia and asystole events,[25–27] and the S-ICD does not readily have pacing functions. Therefore, at present, based on the available studies, there is not sufficient evidence to recommend routine use of S-ICDs instead of TV-ICDs in patients on hemodialysis with indications for ICDs. The choice should therefore be based on the clinical characteristics of the patient on a case-by-case basis.

A pacing-defibrillation system consisting of a leadless pacemaker in wireless communication with a S-ICD capable of providing antitachycardia and antibradycardia pacing was recently introduced.[58] The system was tested on 293 patients. Communication among the wireless devices was successful in 98.8% of the tests performed. The percentage of arrhythmic events successfully interrupted by anti-tachycardia pacing was 61.3%, and there were no episodes for which antitachycardia pacing was not delivered because of failure of device communication. The study demonstrates how new technologies might help the frail and complex population of hemodialysis patients at high risk for SCD. However, in patients with kidney failure, the implantation of leadless cardiac devices is not without problems. A recent registry showed that in a large

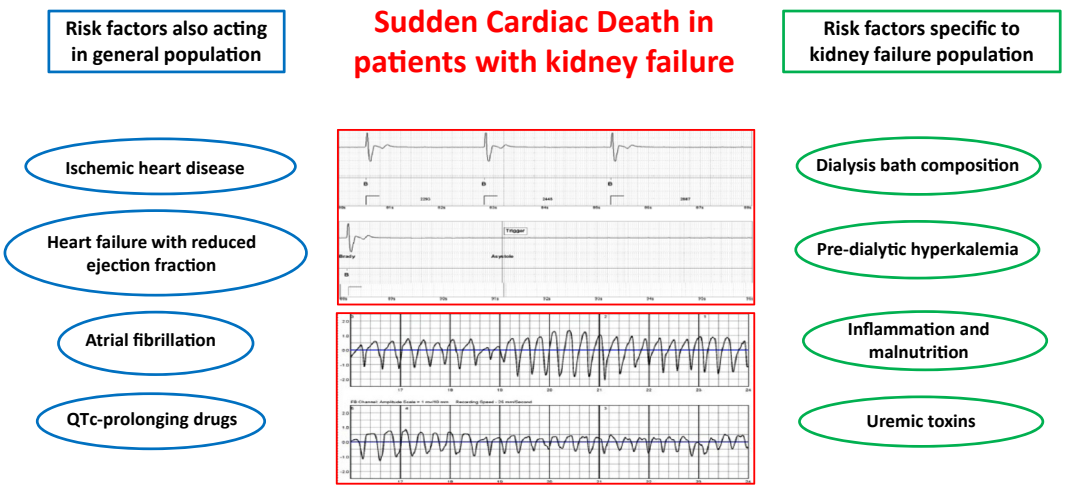

Figure 1

Main factors associated with *SCD* in patients with kidney failure on dialysis. ECG traces show an episode of asystole and one of ventricular fibrillation, occurred in 2 patients on hemodialysis who died of SCD. ECG = electrocardiogram; SCD = sudden cardiac death. The upper ECG panel is reproduced from Wong et al[25]; the bottom ECG panel is reproduced from Wan et al.[24]

Table 1 Practical suggestions for the prevention of SCD in patients with kidney failure on dialysis

Recommendation	Details
1. Train the staff of the dialysis unit.	Provide all dialysis units with an external defibrillator and educate medical and nursing staff in its use as well as in recommending basic life support to be performed in case of intradialytic SCA.[5]
2. Perform cardiac risk stratification.	Assess the presence of ischemic heart disease, severe reduction of ejection fraction, and atrial fibrillation, and implement all appropriate pharmacologic and clinical measures.
3. Manage dialysis bath composition.	Identify patients with prolonged ventricular repolarization time (QTc), and give them special attention, tailoring the dialysis bath composition. Use potassium concentrations higher than 2 mmol/L[2,9] and ionized calcium concentrations greater than 1.25 mmol/L.[6,29] Do not combine low potassium and calcium concentrations,[8] and do not combine high concentrations of bicarbonate with low concentrations of potassium and ionized calcium.[11]
4. Consider the type of dialysis.	Evaluate the possibility of using peritoneal dialysis instead of hemodialysis in patients with high arrhythmic risk.
5. Monitor drug use	Pay attention to QTc-prolonging drugs (antiemetics, antibiotics, antipsychotics).[18,20,21]
6. Prevent hyperkalemia.	Use potassium binders (sodium zirconium cyclosilicate)[30] and dietary prescription[75] to avoid hyperkalemia.
7. Consider ICD for secondary prevention of SCD.	Do not deny the opportunity to benefit from an ICD to patients who underwent a resuscitated episode of SCA, as available studies suggest better survival in patients on hemodialysis who have received ICDs in secondary prevention.[50,51]
8. Evaluate ICD for primary prevention of SCD.	In patients with cardiologic indications, individually evaluate ICD implantation jointly between electrophysiologists and nephrologists because of the unavailability of clear evidence on the usefulness of ICDs in primary prevention.[47,48]
9. Consider beta blocker prescription.	Several studies have shown an association between the use of beta blockers and a reduction of SCD, particularly in patients with ischemic heart disease.[9,72–74]

ICD = implantable cardioverter defibrillator; SCA = sudden cardiac arrest; SCD = sudden cardiac death.

population of patients undergoing leadless pacemaker implantation, periprocedural complications, and intrahospital mortality were significantly higher in patients on hemodialysis than in patients without CKD (OR 1.33, 95% CI 1.13–1.57, and OR 1.38, 95% CI 1.18–1.63, respectively). In addition, the duration of hospitalization and associated costs were also higher in patients with kidney failure.[70]

In patients for whom the risk of SCD may be transient, the wearable cardioverter defibrillator (WCD) has been proposed as a risk mitigation solution.[71] Wan et al[24] retrospectively studied 75 patients undergoing hemodialysis who had been prescribed WCDs between 2004 and 2011 and had experienced at least 1 episode of SCA. There were 84 events reported: 66 (78.6%) caused by ventricular tachycardia or ventricular fibrillation and 18 (21.4%) caused by asystole. Acute survival at 24 hours was 71%, but survival at 30 days and 1 year was 51% and 31%, respectively. Thus, the use of WCD in hemodialysis patients seems to be associated with better post-SCA survival than historical data show; however, WCD cannot be proposed for long-term use for the prevention of SCD.

Medical interventions in patients with kidney failure on dialysis

Data on pharmacologic therapy for the prevention of SCD in dialysis patients are scarce. To our knowledge, there are no studies on this subject with regard to inhibitors of the renin-angiotensin-aldosterone system (angiotensin converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], sacubitril-valsartan, and mineralcorticoid receptor antagonists). This class of drugs should, in any case, be used with caution in patients with kidney failure, as it may induce hyperkalemia, a factor associated with increased all-cause and sudden mortality in this population.[12,23]

Robust data are available about the effect of beta blockers on the incidence of SCD in patients on hemodialysis. A subanalysis of the HEMO (Hemodialysis) study showed that beta blockers use (521 of 1747 patients were taking beta blockers) was not associated with lower risk of SCD in multivariable (HR 0.87; 95% CI 0.62–1.22), or propensity-matched (HR 0.91; 95% CI 0.55–1.50) analyses; however, there was a significant interaction between beta blockers and SCD (interaction P = .03) in patients with (HR 0.65; 95% CI 0.42–1.01) and without coronary artery disease (HR 1.61; 95% CI 0.92–2.80).[72] A retrospective study, performed in 316 patients on hemodialysis followed up for 4.9 years, showed that beta blockers were significantly associated with a lower risk of SCD (HR 0.201, 95% CI 0.058–0.693; P = .011).[73] Moreover, Jadoul et al[9] observed a lower incidence of SCD in beta blockers users (HR 0.88; 95% CI 0.78–0.99) in a population of 37,765 patients on hemodialysis enrolled from 12 countries. In this study, a higher risk of SCD was evident for amiodarone prescription (HR 1.44, 95% CI 1.16–1.81), but this association likely reflected a prescription by indication bias. Finally, a study by Pun et al[74] aimed to identify modifiable factors associated with survival after cardiac arrest in hemodialysis clinics, demonstrated a significant association between beta blocker consumption and lower mortality at 24 hours and 6 months (OR 0.32, 95% CI 0.17–0.61).

Conclusion

Prevention of SCD in patients with kidney failure on hemodialysis is a complex and—in many respects—an unsolved problem. The pathogenesis of SCD in this population is

multifactorial and includes both factors also present in the general population and factors unique to kidney failure and related to the dialysis session per se (Figure 1). Although several issues remain uncertain, a number of practical behaviors can be adopted to reduce excess SCD in these patients (Table 1).

Close collaboration between nephrologists and cardiac electrophysiologists is essential to improve both the knowledge of this important phenomenon and the possibilities of intervention for its prevention in such fragile and high-risk patients.

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