Nephrol Dial Transplant (2021) 36: 396–405
doi: 10.1093/ndt/gfz182
Advance Access publication 20 September 2019

ndt
Nephrology Dialysis Transplantation

REVIEW

Sudden cardiac death in dialysis patients: different causes and management strategies

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ABSTRACT

Sudden cardiac death (SCD) represents a major cause of death in end-stage kidney disease (ESKD). The precise estimate of its incidence is difficult to establish because studies on the incidence of SCD in ESKD are often combined with those related to sudden cardiac arrest (SCA) occurring during a haemodialysis (HD) session. The aim of the European Dialysis Working Group of ERA-EDTA was to critically review the current literature examining the causes of extradialysis SCD and intradialysis SCA in ESKD patients and potential management strategies to reduce the incidence of such events. Extradialysis SCD and intradialysis SCA represent different clinical situations and should be kept distinct. Regarding the problem, numerically less relevant, of patients affected by intradialysis SCA, some modifiable risk factors have been identified, such as a low concentration of potassium and calcium in the dialysate, and some advantages linked to the presence of automated external defibrillators in dialysis units have been documented. The problem of extra-dialysis SCD is more complex. A reduced left ventricular ejection fraction associated with SCD is present only in a minority of cases occurring in HD patients. This is the proof that SCD occurring in ESKD has different characteristics compared with SCD occurring in patients with ischaemic heart disease and/or heart failure and not affected by ESKD. Recent evidence suggests that the fatal arrhythmia in this population may be due more frequently to bradyarrhythmias than to tachyarrhythmias. This fact may partly explain why several studies could not demonstrate an advantage of implantable cardioverter defibrillators in preventing SCD in ESKD patients. Electrolyte imbalances, frequently present in HD patients, could explain part of the arrhythmic phenomena, as suggested by the relationship between SCD and timing of the HD session. However, the high incidence of SCD in patients on peritoneal dialysis suggests that other risk factors due to cardiac comorbidities and uraemia per se may contribute to sudden mortality in ESKD patients.

Keywords: dialysate, end-stage kidney disease, implantable cardiac device, sudden cardiac arrest, sudden cardiac death

INTRODUCTION

Sudden cardiac death (SCD) is defined as an unexpected death due to cardiac causes in a person with known or unknown cardiac disease, within 1 h of symptom onset (witnessed SCD) or within 24 h of the last proof of life (unwitnessed SCD). Since cause of death is subject to interobserver variability, there can be misclassification of SCD [1].

SCD is a leading cause of death among the general population, accounting for up to 15% of all deaths [2]. SCD represents

an important cause of death in end-stage kidney disease (ESKD) patients [3], but the precise estimate of its incidence is difficult to establish because studies on the incidence of SCD in ESKD are often combined with those related to sudden cardiac arrest (SCA) occurring during a haemodialysis (HD) session. However, extradialysis SCD and intradialysis SCA represent different clinical situations and should be kept distinct. In fact, the dialysis session may itself favour the onset of life-threatening arrhythmias, beyond the clinical conditions of the patient. Moreover, hypotension and syncope are quite common during HD sessions and highlight a series of risk factors [4, 5]. Their occurrence requires immediate interventions of health-care professionals for a prompt diagnosis and for differentiating these events from SCA. The aim of the European Dialysis (EUDIAL) Working Group was to critically review the current literature examining the causes of extradialysis SCD and intradialysis SCA in ESKD patients and potential management strategies to reduce the incidence of such events.

EPIDEMIOLOGY OF SCD AND INTRADIALYSIS SCA IN ESKD PATIENTS

In the US Renal Data System database, arrhythmia and cardiac arrest were the single greatest cause of death, comprising 40% of known causes of death among dialysis patients, constituting nearly 78% of all cardiovascular causes of death [3]. Compared with peritoneal dialysis (PD), the rate of SCD is ∼50% higher in HD patients 3 months after dialysis initiation, although these rates reach parity by 2 years [3]. Although SCD accounts for a considerable number of deaths in ESKD patients, it is somewhat surprising that the number of such deaths during dialysis sessions is not greater, considering the increased prevalence of left ventricular hypertrophy and coronary atheromatous and arteriosclerotic disease in HD patients and the changes in cardiac perfusion and electrolyte fluxes. Karnik *et al.* [6] reported a rate of intradialysis SCA of 7.0/100 000 HD sessions, while Pun *et al.* [7] described a rate of 4.5 per 100 000 dialysis treatments. The incidence of such events is therefore relatively low, but the prognosis after an intradialysis SCA is very poor. Karnik *et al.* [6] observed that only 40% of patients were successfully resuscitated and were still alive after 2 days. Of the 60% who died within 48 h of the arrest, 13% died in the dialysis unit.

PATHOPHYSIOLOGY OF SCD AND INTRADIALYSIS SCA IN ESKD PATIENTS

When faced with sudden death, presumably of cardiac origin (SCD), it is not easy to determine what arrhythmia led to death. It may happen so that when the first electrocardiogram (ECG) is performed it is impossible to understand whether any recorded asystolic bradyarrhythmia is the cause of the event or is the consequence of an episode of ventricular fibrillation (VF). This doubt can be resolved only if a device [e.g. ECG Holter, intracardiac device or implantable loop recorder (ILR)] was recording the fatal event [8].

The rhythm most easily recorded in cardiopathic patients at the time of SCD appears to be VF [9, 10]. However, Cobb *et al.* [11] suggested that the episodes of VF represent the cause of SCD in a smaller proportion than previously thought. It is not clear what fatal arrhythmia is occurring in dialysis patients who undergo SCD. Wan *et al.* [12] showed that 78.6% of the SCAs occurring in 75 HD patients bearing a wearable cardioverter defibrillator were due to ventricular tachycardia (VT) or VF and only 21.4% were due to asystole. The average left ventricular ejection fraction (LVEF) of the study population was 27.4%, with <19% of patients having an LVEF >35%. A subsequent study performed in HD patients with an implanted cardiac monitor recorded eight unexpected SCDs due to severe bradycardia with asystole. In this population, one of the exclusion criteria was the presence of LVEF <35% [13]. The idea that SCDs may be due mainly to bradyarrhythmias has been strengthened by two recent studies in HD patients with ILRs. Sacher *et al.* [14] studied 71 HD patients (follow-up 21 months), documenting four SCDs in diabetic patients due to progressive bradycardia followed by asystole. Three of the four subjects had an LVEF >50% (for one of them, LVEF was not known). Furthermore, Roy-Chaudhury *et al.* [15] documented 14 episodes of asystole and only one of sustained VT in a population of 66 younger HD patients implanted with an ILR and followed for 6 months. None of these arrhythmias were fatal. Eighty-six percent of patients with clinically significant arrhythmia were diabetic and their mean LVEF was 55%. Several authors have suggested that there is a relationship between the timing of SCDs and the dialysis session in HD patients, showing two frequency peaks, one at the end of the longer interdialytic interval (LIDI) and the second immediately after the first dialysis session of the week [16, 17]. The study by Wong *et al.* [13] confirmed that the risk of SCD was greater during the LIDI. Furthermore, all the events recorded by Sacher *et al.* [14] occurred during the LIDI and the clinically significant arrhythmias described by Roy-Chaudhury *et al.* [15] had the highest frequency during the last 12 h of the LIDI. None of the described studies could provide evidence of an association between plasma electrolyte levels and fatal events. However, the study by Sacher *et al.* [14] showed that a higher risk for cardiac conduction disorders was related to plasma potassium (K^+) concentration >5.0 mmol/L and a higher risk for ventricular arrhythmia to a plasma K^+ concentration <4.0 mmol/L. Epidemiological studies suggested a significant association between the values of pre-dialysis hyperkalaemia and SCD [17, 18]. Combining all this evidence, we hypothesize that during the first short interdialysis period of the week HD patients suffer from a sudden decrease in plasma K^+ concentration, whereas at the end of the LIDI they may present with marked hyperkalaemia and acidosis. Both conditions can lead to cardiac electrical instability, which could potentially result in life-threatening arrhythmias (i.e. VF or bradyarrhythmia with asystole). However, it is possible that other risk factors due to cardiac comorbidities and uraemia per se may contribute to sudden mortality in ESKD patients. In fact, PD patients, who do not undergo rapid changes in electrolyte concentrations, also show a high rate of SCD [19]. PD is less intense than HD: the treatment is more or less continuous with slight variations related to different modes of PD. Therefore it is also more

difficult to identify a causal relationship between the actual treatment and treatment-induced SCD. Nevertheless, the death risk for abnormalities in plasma K^+ concentration could be even higher in PD compared with HD patients since PD patients are at a higher risk for hypokalaemia, a clinical situation that can lead to dangerous tachyarrhythmias [20]. A link between SCD in PD patients with reduced LVEF and elevated plasma levels of pro-brain natriuretic peptide (pro-BNP) and troponin T has been shown, suggesting an important role of heart failure and ischaemic heart disease as factors associated with increased sudden mortality in this population [21]. Some cardiovascular comorbidities have also been associated with SCD in patients undergoing HD. In particular, a higher risk of SCD in incident HD patients affected by obstructive sleep apnoea (OSA), after adjusting for possible confounding factors, was shown when compared with subjects without OSA [22]. Moreover, among HD patients with severe aortic stenosis, without aortic valve replacement, the risk of SCD was particularly high [23].

In conclusion, both brady- and tachyarrhythmias may underlie SCD in ESKD patients. Recent data suggest that the former may be most frequently responsible for the fatal event in HD patients and a relationship between SCD and dialysis timing has been shown. Diabetic patients seem to be particularly exposed to this type of death, even in the presence of a normal LVEF and should therefore be monitored more carefully.

More than a decade ago, Davis *et al.* [24] described 110 episodes of intradialysis SCA that occurred in dialysis clinics, including 10 before, 72 during and 20 immediately after the end of the HD session. In the majority of cases occurring during and after the HD session, the initial recorded arrhythmia was a VF or a VT episode (67% and 85%, respectively), whereas in the other cases, the first monitored ECG rhythm was a pulseless electrical activity or asystole. Only 46% of patients survived at least 24 h after SCA and 24% were discharged alive from the hospital. The prognosis was better for those patients whose event was associated with tachyarrhythmia compared with bradyarrhythmia [24]. It should be remembered that two-thirds of events occurred before the routine installation of automated external defibrillators (AEDs) in dialysis facilities. However, even when an AED was available, the device was applied prior to emergency medical services (EMS) arrival in only half of those SCA events [24].

These findings are partially in contrast to those described in a more recent study that examined 398 cases of SCA occurring at outpatient dialysis facilities [25], designed to assess the impact of dialysis practice guidelines recommending basic life support (BLS) training for outpatient dialysis staff and availability of AEDs in dialysis clinics [26]. Dialysis staff initiated cardiopulmonary resuscitation (CPR) before the arrival of EMS in 81% of events. Sixty-six percent of the SCAs presented with a non-shockable initial monitored rhythm, and dialysis staff applied an AED before EMS arrival in 52% of cases. Staff-initiated AED application was more likely within larger dialysis clinics, but there were no significant patient or cardiac arrest characteristics associated with AED use by dialysis staff. Almost half of the patients (48%) survived to hospital admission and only 26% of the total population was discharged alive from the hospital. Patients on whom CPR had been initiated directly by dialysis staff had 3 times greater survival, as well as a favourable neurologic status upon discharge, than patients on whom CPR was performed exclusively by EMS, but there was no advantage to early use of the AED, presumably because only 37% of patients demonstrated a shockable arrhythmia [25]. As about only half of patients with access to AEDs had monitoring by the dialysis staff, then it is possible that increased AED usage could have identified more shockable rhythms.

Many factors influence the ability of a victim or patient to receive effective BLS prior to the arrival of EMS [25]. Measurement of time to correct AED application and shock delivery (in shockable rhythms) may allow the standardization of response at outpatient dialysis facilities. In a report on the results of public access to defibrillation for cardiac arrests (occurring at home in 87% of cases), earlier intervention (in 4.8 min versus 6.2 min) was associated with a higher rate of shockable rhythms (close to 24%) and with a tripling of survival (from 3.3% to 10.5%) [27].

In summary, even though intradialysis SCA outcomes are poor, outcomes are greater than those for unselected out-of-hospital SCA, and early application of AEDs is a likely next step for potentially improving these outcomes. Finally, it should be noted that only ∼20% of unselected patients who suffer an in-hospital cardiac arrest have a shockable rhythm and have a survival to hospital discharge of ∼25% [28].

The incidence of intradialysis SCA is reported to be greater during the first dialysis session of the week [6, 24]. At this time, patients have the highest levels of plasma K^+ and metabolic acidosis. A potassium dialysate (K^+D) concentration <2 mmol/L is associated with a >2-fold increase in the risk of SCA in patients with pre-dialysis serum concentrations within the normal reference range [6, 7]. The risk of intradialysis SCA is also doubled in patients treated with a low calcium dialysate ($Ca^{2+}D$) concentration (1.25 mmol/L) and increases in those with a higher serum-to-$Ca^{2+}D$ gradient (40% for 1 mmol/L increment) [29]. It is interesting to note that the association between SCA and low K^+D and low $Ca^{2+}D$ persisted after adjustment for a history of coronary heart disease and congestive heart failure, while these traditional risk factors were not significantly influential on SCA incidence [7]. Several studies have shown that the HD session induces a prolongation of ventricular repolarization time (expressed by the QT interval of an ECG) inversely related to the calcium beginning-to-end plasma gradient during the HD session [30–32]. This phenomenon is particularly evident when both low $Ca^{2+}D$ (1.25 mmol/L) and low K^+D (2 mmol/L) concentrations are employed [32].

A marked prolongation of the QT interval due to sudden intradialysis changes of plasma electrolytes could potentially induce episodes of 'torsades de point' fibrillation. In contrast, predialysis hyperkalaemia could induce pulseless electrical activity or asystolic events [32]. Knowledge of the patient's electrolyte balance can predict the necessary advanced cardiac life support steps in the event of cardiac events.

DIALYSIS TREATMENT PRACTICES

Dialysate potassium

The control of plasma K^+ remains a pervasive challenge in the management of HD patients. One of the main goals of HD is the removal of K^+ that has accumulated in the body in the interval between two dialysis sessions. A correct K^+ mass balance during HD is crucial: for the vast majority of patients this should be negative and of the same order of magnitude as the positive interdialytic K^+ mass balance in order to prevent both dangerous intradialysis hypokalaemia and fatal interdialysis hyperkalaemia [33]. Indeed, some studies have shown that high pre-dialysis K^+ concentrations are associated with an increased risk of SCD [7, 34]. The magnitude of the plasma K^+ concentration is dependent upon dietary K^+ intake, urinary K^+ excretion and K^+ losses in the stool, the utilization of K^+ binders, K^+D concentration, dialysate glucose and bicarbonate concentrations, the efficiency of the dialyser and the duration and frequency of dialysis [35]. Plasma K^+ concentration rapidly decreases during the first 60 min and stabilizes during the last 60 min of dialysis. Plasma K^+ reaches a steady state during the last hour of dialysis, while K^+ continues to be lost into the dialysate. It can therefore be assumed that the K^+ removal rate is equal to the intra- to extracellular mass transfer rate at these time points [33].

The QT interval is a recognized ECG marker of the ventricular repolarization time and its prolongation has been associated with an increased risk of SCD in both pathological and healthy populations and also in HD patients [36–39]. Electrolyte disorders are one of the main HD-related factors that can cause QT interval alterations and cardiac arrhythmias, because of their involvement in the genesis, duration, morphology and propagation of the cellular action potential. The electrolytes that mostly influence the ventricular repolarization are K^+ and ionized Ca^{2+} [40]. The Nernst equation indicates that the electrical activity of the heart is related to the ratio of the intracellular and extracellular K^+ levels. Using a lower K^+D concentration, one removes K^+ mainly from the extracellular space and very little from the intracellular one. Surprisingly, most patients are able to tolerate the intradialysis hyperpolarization of the cardiac muscle membrane potential, induced by an increase in the intracellular: extracellular K^+ ratio brought about by a reduction in the extracellular K^+ value as a result of dialysis. The frequency of arrhythmias is greater during the last 2 h of dialysis and immediately post-dialysis [32]. K^+ modelling, first suggested by Redaelli *et al.* [41], involves decreasing the K^+D concentration exponentially to maintain a constant plasma–K^+D gradient of 1.5 mmol/L. Santoro *et al.* [42] observed greater arrhythmogenic activity with the use of a constant and relatively low K^+D concentration compared with decreasing K^+ profiling in dialysis-sensitive arrhythmic patients.

Given the above, there is no good evidence that intradialysis ventricular arrhythmias are associated with an increased risk of overall mortality or sudden mortality [43, 44] or that the use of dialysis modalities with a profiled K^+D improves clinical outcomes. However, higher K^+ gradients (serum K^+ concentration–K^+D concentration) are independently associated with a greater risk of all-cause hospitalizations and emergency department visits [45]. In addition, a low K^+D concentration (<2 mmol/L) is associated with an increased incidence of intradialysis SCA [7] and extradialysis SCD compared with a K^+D concentration >3 mmol/L [18].

In conclusion, the true challenge in HD patients is to avoid both life-threatening pre-dialysis hyperkalaemia (plasma K^+ level >6 mmol/L) and post-dialysis relative hypokalaemia (or at least a very rapid decrease of plasma K^+ concentration and the related risk of lethal arrhythmias). Resins (calcium or sodium polystyrene sulphonate) may be used; although K^+-binding sodium-based resins have been prescribed for 50 years, there have been no large studies of their effects among HD patients [46]. Newer K^+ binding medications are currently available that could help to reduce the incidence of pre-dialysis hyperkalaemia [47, 48]. Although possibly less acceptable to patients, alternative dialysis strategies, such as longer or more frequent HD sessions, may be required to control hyperkalaemia.

Dialysate calcium

In the last decade there has been a shift in Ca^{2+}D prescription down from 1.75 to 1.25 mmol/L [49]. A lower Ca^{2+}D concentration may induce an increase in myocardial repolarization time and QT interval [30, 32]. Lower Ca^{2+}D concentrations are also associated with a higher risk of intradialysis SCA [29]. The prescription of an individualized Ca^{2+}D concentration for HD patients requires an integrated quantitative assessment of bone mineral metabolism and of cardiovascular status. When choosing a Ca^{2+}D concentration, the impact on calcium balance and the change in serum calcium levels must be considered, with the awareness that these two aims might not necessarily be achieved at the same time [49].

In conclusion, a low Ca^{2+}D concentration should be avoided in patients presenting with prolonged basal QT interval and should not be used in combination with a lower K^+D concentration. The Ca^{2+}D concentration should be designed so as not to lower serum Ca^{2+}, especially in patients at risk of hypokalaemia at the end of the dialysis session.

Dialysate bicarbonates

The main potential adverse effects associated with a high dialysate bicarbonate (D_{BIC}) concentration are increased carbon dioxide formation, electrolyte imbalances and QT prolongation [50]. During HD, an increase in serum bicarbonate levels leads to a decrease in serum Ca^{2+} concentration. This phenomenon is primarily caused by an alkalosis-induced change in the electrical charge of proteins, which increases the amount of complexed calcium. A correction of metabolic acidosis that is too rapid can then compromise vascular and cardiac contraction due to the decrease in Ca^{2+} [51]. Furthermore, Fissell and Hakim [52] emphasized that dialysis treatment lowers plasma K^+, both by removal of K^+ into the dialysate and also by a rapid shift of K^+ from the extracellular into the intracellular space, as metabolic acidosis is corrected. Moreover, a randomized controlled trial (RCT) reported an association between higher D_{BIC} concentration and a faster decrease in intradialysis plasma K^+ concentrations [53]. When higher D_{BIC} concentrations are

employed, the combination of a sudden decrease in plasma Ca^{2+} and K^+ induced by metabolic alkalosis could lead to dangerous prolongation of ventricular repolarization time. An RCT observed a prolongation of the QT interval in association with high D_{BIC}, low K^+D and low $Ca^{2+}D$ concentrations [54]. This association was an independent predictor of prolongation of the QT interval [39].

In summary, individualizing the treatment to the patient is important to correct metabolic acidosis while avoiding symptoms of transient secondary metabolic alkalosis and potential harm. High D_{BIC} concentrations may lead to sudden reductions in plasma concentrations of both K^+ and Ca^{2+}. This phenomenon causes an increase in ventricular repolarization time and prolongation of the QT interval, potentially increasing the risk for life-threatening arrhythmias. It is therefore advisable not to combine lower $Ca^{2+}D$ and K^+D concentrations with high D_{BIC} concentrations, particularly in patients with a prolonged basal QT interval.

Dialysate magnesium

An electrolyte that has received little attention is magnesium. A large observational study from Japan using data from 142 555 HD patients reported a J-shaped curve between magnesium concentrations and all-cause mortality (both cardiovascular and non-cardiovascular) [55]. Moreover, it has been shown that serum magnesium concentrations are independently and inversely associated with all-cause mortality, cardiovascular mortality and sudden death in European HD patients [56].

Future magnesium research should address dialysate selection specific to magnesium concentrations (the standard dialysates contain ∼0.5 mmol/L and serum magnesium typically decreases during dialysis, which can be affected by citrate-containing dialysates and higher D_{BIC} concentrations) [57] and the potential role in electrophysiologic abnormalities in the HD population. These steps may allow future tailoring of the dialysate specific to cardiac arrhythmias and SCD and SCA.

Ultrafiltration

An ultrafiltration volume >5.7% of body weight has been related to a higher risk for SCD {hazard ratio [HR] 1.13 [95% confidence interval (CI) 1.00–1.27]; P = 0.04} [18]. Moreover, Pun *et al.* [7] found an association between intradialysis SCA and percent volume removed during the dialysis session [odds ratio (OR) 1.11 (95% CI 1.02–1.20); P = 0.011]. However, more data are needed to prove that an excessive ultrafiltration volume has a causal relationship with the incidence of sudden mortality in HD patients.

PREVENTION TOOLS—DRUGS

A paucity of evidence exists regarding the role of cardiovascular drugs in the prevention of SCA in HD patients. This is mainly due to commonly excluding HD patients in RCTs. Below is a summary regarding the efficacy and safety of drugs acting on the electrophysiological properties of the heart and/or on the sympatho-vagal regulation of the heart and vessels with regard to the specific setting of HD patients.

β-blockers

Conflicting results regarding the efficacy and safety of β-blockers in HD patients have been found. For example, a systematic review included three RCTs that found a significant risk reduction for β-blockers in cardiovascular mortality and cardiovascular events, but also nine observational studies that did not find any effect in these outcomes [58]. In contrast, in three other observational studies, β-blockers were associated with a lower risk for SCD in HD patients [18] or a reduction in all-cause mortality [59, 60]. In another RCT, including 114 HD patients, a significant reduction in all-cause and cardiovascular mortality, yet no statistically significant reduction in SCD, was found for the patients treated with carvedilol [61]. In a *post hoc* analysis of the Hemodialysis Study, including 1747 patients, no association between β-blocker intake and SCD was found [62].

Angiotensin-converting enzyme inhibitors (ACEis)/ angiotensin receptor blockers (ARBs)

So far, no convincing data on the benefit of ACEis or ARBs for preventing SCD in HD patients has been found. No significant reduction in the risk of cardiovascular events in the treatment group with an ACEi or ARB was found in a systematic review [63]. For example, RCTs on fosinopril and olmesartan have both failed to demonstrate a reduction in the risk of cardiovascular events or all-cause mortality in HD patients [64, 65]. Similarly, in another study, the risk of SCD was not statistically significantly reduced for the HD patients treated with spironolactone [66]. However, in two observational studies, a reduction in cardiovascular mortality or overall mortality was found for HD patients treated with an ACEi [67, 68].

Potassium binding agents

Sodium polystyrene sulphonate and calcium polystyrene sulphonate are commonly used in the general population to treat chronic hyperkalaemia [48, 69], however, contradicting effects of fludrocortisone or sodium zirconium cyclosilicate (ZS-9) on plasma K^+ levels in HD patients have been found [70–72]. In these two RCTs, outcomes associated with SCD and cardiovascular mortality were not reported [48, 69].

Calcium channel blockers (CCBs)

In an observational study, a beneficial, although not statistically significant, effect of CCBs for HD patients was found on death at 24 h after SCA [73]. Similarly, in another observational study including 4065 HD patients, the use of CCBs was associated with a 23% lower risk of cardiovascular mortality [74].

Calcimimetics

In the Cochrane review of Ballinger *et al.* [75], including 18 studies with 7446 participants, no effect on all-cause or cardiovascular mortality was found for patients treated with cinacalcet. SCD was not included as an outcome in this review and was only investigated in one study, in which no differences in SCD were found between cinacalcet and usual care [76]. Etelcalcetide, which was compared with placebo in two RCTs, significantly reduced parathyroid hormone levels; however, hypocalcaemia was more common in the etelcalcetide group

and led to prolongation of QT intervals in many patients. No mortality or cardiovascular outcomes were reported [77].

Amiodarone

Amiodarone exerts many electrophysiological effects and is widely used for both atrial and ventricular tachyarrhythmias, despite the risk of adverse effects (on the thyroid gland, lungs and liver). However, there have been no consistent findings regarding its effectiveness in preventing SCD in HD patients. In an analysis of Dialysis Outcomes and Practice Patterns Study (DOPPS) amiodarone was associated with a higher risk for SCD in HD patients [HR 1.44 (95% CI 1.16–1.81)] [18], however, as for any observational study, no conclusion on causality can be drawn. In a Cochrane systematic review [78] including 24 studies, amiodarone was associated with a significant reduction in the risk of SCD, cardiac and all-cause mortality for persons at high risk (primary prevention) or who have recovered from an SCA (secondary prevention), however, no specific subgroups of ESKD or HD patients were included in these studies.

Digoxin

In a retrospective observational cohort study including 120 864 incident HD patients, digoxin use was associated with a 28% increased risk of death and the increase in mortality risk was most pronounced in patients with lower pre-dialysis serum K^+ levels [79].

In conclusion, contradicting and limited evidence have been found on the efficacy and safety of anti-arrhythmic drugs for HD patients in terms of SCD or fatal cardiovascular events. In addition, poor long-term adherence to drug therapy is found in dialysis patients [80, 81], which might limit the validity of the findings to daily clinical practice. Therefore no strong recommendations in favour of any specific medication or type of medication can be made and large high-quality RCTs in HD patients are needed.

PREVENTION TOOLS—IMPLANTABLE CARDIOVERTER DEFIBRILLATORS (ICDs)

Guidelines for sudden death prevention published by the main cardiology associations recommend implanting an implantable cardioverter defibrillator (ICD) in primary prevention in patients with LVEF <35% and with a life expectancy of at least 1 year and, in the setting of secondary prevention, in patients with documented VF or haemodynamically not tolerated VT in the absence of reversible causes [82]. However, the presence of ESKD was an exclusion criterion in the RCTs that demonstrated that the ICD confers a survival benefit in populations with a high risk of SCD [83–85]. Several observational studies have shown that, in patients implanted with an ICD in primary prevention, the presence of ESKD constitutes a negative prognostic factor in terms of mortality [86–88]. However, when populations of dialysis patients with indication for ICD implantation are compared, data are not consistent. Hiremath *et al.* [89], in an observational study collecting data from two registries, showed that an ICD implant is associated with better survival in ESKD patients with ventricular dysfunction (LVEF <35%) when compared with patients not implanted with the device [HR 0.40 (95% CI 0.19–0.82)] [89]. The risk of bias and unmeasured confounding obviously constitutes an important limitation and propensity score matching can be employed for reducing this risk. Indeed, Pun *et al.* [90], comparing two propensity-matched cohorts of ESKD patients, one that received an ICD in primary prevention and the other without ICD, did not observe differences in mortality in the two groups (43.4% in the ICD cohort versus 39.7% in the control group). The uncertainty about evidence leads to the fact that only a minority of ESKD patients with an indication for ICD implantation actually receive the device. In an Italian population of 2072 ESKD patients (154 of them having an LVEF <35%), only 52 (33%) were implanted with an ICD. As expected, mortality was higher in patients with an ICD indication than in those without [HR 1.59 (95% CI 1.06–2.38)], but subjects with ventricular dysfunction and without an ICD implant had the worst prognosis [HR 2.67 (95% CI 2.09–3.39)]. The rate of SCD was higher not only in patients with an ICD indication, but also patients without an ICD indication had a high incidence of SCD [91]. The high incidence of SCD in dialysis patients with preserved LVEF is the rationale of the only RCT so far performed in this population, the ICD2 trial [92]. This very recent study is particularly interesting because the presence of LVEF <35% was an exclusion criterion, thus leading to an RCT exploring a new indication for ICD implantation in the specific setting of dialysis patients. The study tried to answer the question whether ESKD per se is a risk factor for SCD, independent of a low ejection fraction, and if this risk can be minimized by ICD implantation. Indeed, patients who, according to the guidelines, would have a classical indication for ICD implantation for primary prevention of SCD, on the basis of a depressed ejection fraction, were not recruited. The trial was stopped, as per the recommendation of the data and safety monitoring board, for futility reasons (i.e. inability of the RCT to achieve its original objectives) after inclusion of 188 patients of the 200 planned, 97 in the ICD group and 91 in the control group. The median duration of follow-up was 6.8 years. The 5-year mortality rate was high and similar in the two groups (50.6% in the ICD group versus 54.5% in the control group). The cumulative incidence of SCD was 9.7% in the ICD group versus 7.9% in the control group [HR 1.32 (95% CI 0.53–3.29)] [92]. The reasons for the failure of the ICD strategy to reduce total and sudden mortality may be several: first of all, we must consider the possibility of a failure of the device linked to the presence of non-shockable rhythms (asystole/pulseless electrical activity) or of an arrhythmia arising in a setting of hyperkalaemia and/or severe disorders of the acid–base balance [13, 93], leading to ineffective termination by ICD shocks or immediate reinitiation after shock delivery. Only post-mortem analysis of the intracardiac ECGs (actually planned in the design of the ICD2 trial) was able to clarify what arrhythmia was associated with SCD. It is important to underline that the rate of device-related adverse events was very high (27.5%) [92]. They were directly related to the ICD implantation procedure (haematoma or infection) or were due to lead dysfunction. ICD explantation was necessary in 7.5% of cases, mostly because of bacteraemia [92]. The outcome of patients implanted with an ICD appears more

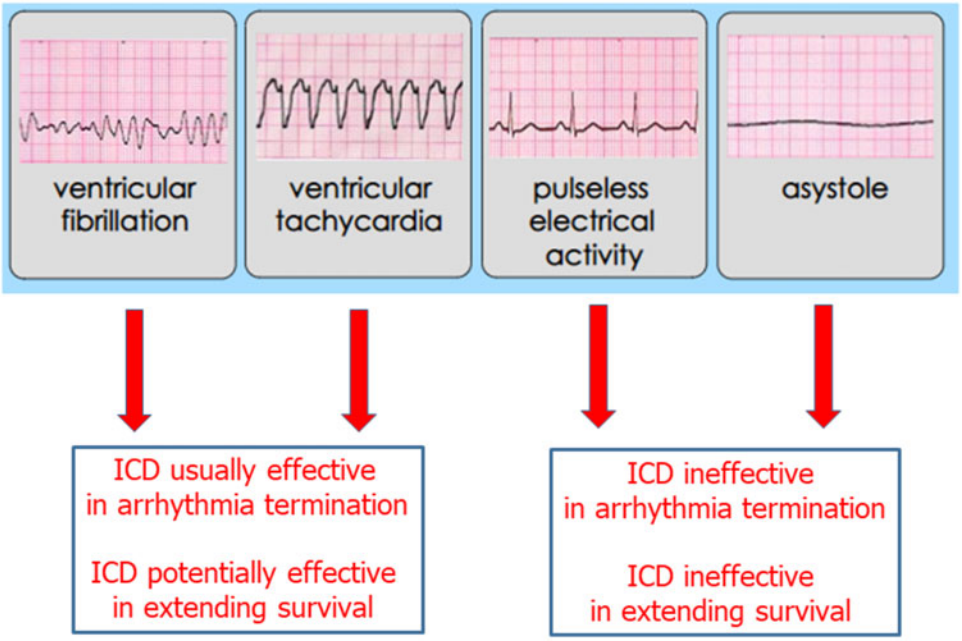

FIGURE 1: It shows the arrhythmias potentially leading to SCD and the role of ICD therapy.

convincing in the clinical setting of secondary prevention. Herzog *et al.* [94] retrospectively analysed a population of 6042 dialysis patients hospitalized for VF/cardiac arrest, discharged alive and surviving at least 30 days from admission. Only 7.6% of these patients had an ICD implantation. The latter was independently associated with a 42% reduction in death risk [HR 0.58 (95% CI 0.50–0.66)] [94]. Charytan *et al.* [95] showed in a population of 9528 dialysis patients who received an ICD for secondary prevention between 1994 and 2006 an overall 14% (95% CI 9–19) lower mortality risk compared with propensity-matched controls [95].

An important problem is the high rate of complications associated with ICD implantation in dialysis patients. A meta-analysis showed a significant increase in infectious complications associated with the presence of ESKD [HR 8.73 (95% CI 3.42–22.31)] [96]. Infections of the ICD system require complete removal of the implanted system, a procedure associated with inherent risk and complications [97]. Other frequent complications are those related to lead dislodgement requiring revision, lead dysfunction requiring extraction, bleeding and venous thrombosis [92, 98, 99]. It has been suggested that the use of subcutaneous ICDs may be an advantage for reducing the risk of central venous stenosis and infection compared with an endocardial ICD with transvenous leads, but this kind of device may not be useful in case of severe bradyarrhythmias [100].

In general, the decision to implant an ICD in the setting of ESKD and dialysis is clinically challenging and should require an interdisciplinary approach, with strict collaboration between nephrologists and cardiologists, targeted to assess in the individual case the risk–benefit of every specific treatment option [97]. Clinical decision making may be even more difficult in case of life-threatening ventricular tachyarrhythmias that appear to be facilitated by transient but not entirely correctable causes [101].

In a clinical perspective, the challenge in decision making about ICD implantation is that, given the substantial comorbidities that frequently exist in ESKD patients, the benefit of ICD therapy may be attenuated due to the competing causes for death. This important issue may also be associated with a series of factors, including electrolyte imbalances, that increase the risk of ineffective shock therapy or onset of non-shockable rhythms (asystole/pulseless electrical activity) as the pathophysiological mechanism of arrhythmic SCD (Figure 1).

CONCLUSIONS

SCD remains a major cause of death in the ESKD population, despite the efforts made in recent years to prevent it and to identify patients at greater risk. Regarding the problem, numerically less relevant, of patients affected by intradialysis SCA, some modifiable risk factors have been identified, such as low K^{+}D and Ca^{2+}D concentrations, and some advantages linked to the presence of AEDs in dialysis units have been documented. However, it must be recognized that the arrhythmia determining the fatal event is not always shockable. The problem of extradialysis SCD is more complex and its causes remain partly unknown. A reduced LVEF associated with SCD is present only in a minority of cases occurring in HD patients. This demonstrates that SCD occurs with different characteristics in ESKD compared with patients with ischaemic heart disease and/or heart failure and not affected by ESKD. Recent evidence suggests that in this population, bradyarrhythmias may represent the fatal arrhythmia more frequently than tachyarrhythmias. This fact may partly explain why several studies could not demonstrate an advantage of ICDs in preventing SCD in ESKD patients. Electrolyte imbalances, frequently present in HD patients, could explain part of the arrhythmic phenomena, as suggested by the relationship between SCD and timing of the

HD session. However, the high incidence of SCD in PD patients suggests that other factors are also involved in determining sudden mortality in the uraemic patient.

CONFLICT OF INTEREST STATEMENT

S.G. declares speaker's fees of a small amount from AstraZeneca and Pfizer. G.B. declares speaker's fees of a small amount from Medtronic, Boston Scientific and Biotronik. D.S. is consulting for American Renal Clinical Research Services and CHF Solutions. All other authors declare no conflicts of interest.

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Received: 12.7.2019; Editorial decision: 1.8.2019

Nephrol Dial Transplant (2021) 36: 405–412
doi: 10.1093/ndt/gfz196
Advance Access publication 17 October 2019

Phosphate and bone fracture risk in chronic kidney disease patients

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ABSTRACT

In chronic kidney disease (CKD), phosphate homoeostasis plays a central role in the development of mineral and bone disorder (MBD) together with decreased serum calcium and elevated serum parathyroid hormone, fibroblast growth factor 23 and sclerostin levels. Today there are only a few data exploring the direct role of abnormal phosphate homoeostasis and hyperphosphataemia in the development of CKD-MBD. On the other hand, several studies have looked at the link between hyperphosphataemia and cardiovascular morbidity and mortality in CKD, but there is a lack of evidence to indicate that lowering phosphate levels improves cardiovascular outcomes in this population. Furthermore, the impact of liberalizing phosphate targets on CKD-MBD progression and bone fracture is currently not known. In this review we discuss the central role of phosphate in the pathogenesis of CKD-MBD and how it may be associated with fracture risk, both in hyper- and hypophosphataemia.

Keywords: bone fractures, CKD, MBD, phosphate levels