Cardiac Arrest in Patients on Renal Replacement Therapy: The Prevalence, Etiologies and Outcomes

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Abstract
Cardiac arrest represents a significant cause of mortality among patients with End-Stage Renal Disease (ESRD) undergoing renal replacement therapy. This review aimed to synthesize current knowledge on the risk, mechanisms, outcomes and preventative measures for cardiac arrest in this vulnerable population. We conducted a comprehensive literature search in PubMed, identifying both prospective and retrospective studies that reported on cardiac arrest in adult ESRD patients on dialysis. The analysis included variables such as demographics, traditional and non-traditional risk factors and mechanisms of cardiac arrest and prevention strategies. Our review article revealed that cardiovascular disease is a significant burden in ESRD, with cardiac arrest accounting for a significant proportion of mortality. Traditional risk factors included hypertension, diabetes, age, male sex and smoking. Non-traditional risk factors include duration of dialysis treatment, hypotension, inflammation, oxidative stress, mineral bone disorders, electrolyte imbalances, anemia and arrhythmias. Dialysis variables, such as timing, temperature and dialysate composition, were also implicated. We identified several preventative measures, including managing traditional cardiovascular risk factors, modifying dialysis prescriptions, regular cardiac monitoring, consideration of alternative dialysis modalities and medications and optimization of electrolytes and anemia. Our findings underscore the necessity for future research to further understand the intricate relationship between cardiac arrest and hemodialysis, aiming to refine and enhance preventative strategies to improve patient outcomes.

Introduction
Cardiac arrest represents a significant and often fatal event in the lives of patients undergoing dialysis. Notably, the incidence of this abrupt cessation of cardiac pump function is much higher in the dialysis population, emphasizing the vital intersection of cardiac health and kidney disease management. End-stage renal disease (ESRD) is a prevalent health issue worldwide, with hemodialysis as the most common modality of renal replacement therapy [1]. However, despite the extensive use of this life-sustaining treatment and advancements in ESRD care, mortality rates remain high, predominantly due to cardiovascular events [2]. The risk of cardiac arrest in this patient group is exacerbated by both traditional factors such as age and hypertension and non-traditional factors unique to ESRD, including fluid and electrolyte imbalances and dialysis-related variables [2].

In the current literature, a comprehensive understanding of cardiac arrest risk in dialysis patients, including its etiology, prevalence and outcomes, is notably lacking. This review is designed to fill that gap by providing a broad overview of existing research on cardiac arrest events in patients on dialysis. Our analysis covers the underlying mechanisms, key risk factors, potential preventative strategies, outcomes and future research directions. By elucidating the intricate relationship between hemodialysis and cardiac arrest, we aim to provide insights that can inform and guide clinical practice. Our goal is to contribute to improved patient care strategies and better outcomes for this highly vulnerable patient population.

Methods
A comprehensive search of the PubMed databases was performed from inception to December 2022 to identify relevant articles. A combination of keywords and medical subject headings (MeSH) terms, including “cardiac arrest”, “cardiac death”, “chronic kidney disease”, “ESRD”, “dialysis”, “hemodialysis”, “heart arrest”, was used to generate the search strategy. In addition, the reference lists of included studies and relevant review articles were screened for potentially relevant studies.

Inclusion Criteria
Studies were included in this review if they met the following criteria
1. Conducted in patients on renal replacement therapy
2. Focused on cardiac arrest and cardiac death
3. Included information on etiology and prevalence
4. Reported outcomes related to post cardiac arrest
5. Published in English language and
6. Studied adult humans

Exclusion Criteria
1. Studies that were not conducted on human subjects, or studied in the pediatric population were excluded.

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2. Case reports and papers not published in the U.S. were also excluded.

Data Extraction and Analysis

Two reviewers screened the titles and abstracts of all identified studies to determine eligibility for inclusion. The full-text articles of potentially eligible studies were then obtained and reviewed in detail by the same reviewers. Any discrepancies between the 2 reviewers were resolved through discussion and consensus. The extracted data included study design, patient characteristics, interventions, outcomes and adverse events. Data were summarized qualitatively due to the heterogeneity of the included studies.

Prevalence

The prevalence of cardiac disease in dialysis patients is alarming, with Cardiovascular Disease (CVD) accounting for approximately 40% to 50% of all deaths in patients with Chronic Kidney Disease (CKD) and ESRD, compared to 26% in normal kidney function [3]. Pun et al. found that specifically the incidence of cardiac arrest in hemodialysis patients is approximately 20 times higher than in the general population [4]. The same study also found that timing and schedule of dialysis treatments also appear to play a role in the risk of cardiac arrest with the highest risk of cardiac arrest occurring around the 72-hour period from the last dialysis session [4]. Post arrest analysis by Yan et al. found that in out of hospital arrests, the incidence of return of spontaneous circulation (ROSC) was 29.7% and 22.0%, which are considerably lower than for the general population [5].

Etiologies

Cardiac arrest in dialysis patients is a complex issue that involves multiple factors. One of the main predisposing risk factors for cardiac arrest is pre-existing Cardiovascular Disease (CVD) patients. CVD in end-stage renal disease (ESRD) and dialysis patients is multifactorial, with traditional cardiovascular risk factors such as age, male sex, diabetes, hypertension, smoking and the duration of hemodialysis commonly present in this population [6].

a. Hypertension

The prevalence of hypertension in dialysis patients is high, reaching about 70-80%, while the prevalence of hypertension in the general population is closer to 50% (7, 8). Hypertension in renal disease patients can be challenging to control as sodium balance, the Renin-Angiotensin-Aldosterone System (RAAS) and vascular resistance homeostasis are all disrupted [9]. Hypertension induces positive feedback loops of renal damage, leading to glomerular hyperfiltration initially, which over time causes structural changes to the glomerulus, including hypertrophy, sclerosis and proteinuria, which themselves enhance the process of renal damage [9]. High blood pressure also puts additional strain leading to vascular disease and left ventricular hypertrophy (LVH), which by extension increases the risk for heart failure [10,11]. The creation of arteriovenous fistulas or grafts for hemodialysis, a routine procedure in ESRD patients, is linked with significantly higher levels of this marker compared to healthy controls and were associated with an increased risk of CVD and myocardial fibrosis [12]. Furthermore, they suggested that the uremic milieu in ESRD patients may contribute to the activation of inflammatory and oxidative stress pathways, leading to endothelial dysfunction and vascular calcification [16]. This uremic milieu also further exacerbates these cardiovascular risk factors, including hypertension, fluid overload, diabetes and dyslipidemia [17]. Parekh et al. found in a large prospective study that higher interleukin-6 (IL-6) levels and particularly CRP was associated with higher risks of Sudden Cardiac Death (SCD), likely explained by the development of atherosclerosis and ultimately plaque instability [18]. These same factors are also associated with arrhythmias, such as atrial fibrillation, which is possibly explained by a direct effect on ion channel functions [18].

Another acute phase reactant, ferritin, has been studied in its association with increased mortality [19]. A rise in serum ferritin by 400ng/mL per quarter compared to stable levels, was found to be associated with increased mortality risk in dialysis patients, independent of iron therapy (19).

On another note, the association between higher levels of albumin and decreased risk of cardiac arrest in dialysis patients has been previously described [20]. Albumin levels in this population are typically low due to reduced albumin synthesis in the setting of a chronic inflammatory state, albumin loss in the urine and protein loss from dialysis itself [20]. Albumin contributes to uremic toxin removal and has anticoagulant/antithrombotic effects so lower levels of this marker is unsurprisingly associated with higher risk of cardiac arrest [20].

e. Calcium and Phosphate

Atherosclerosis in patients with renal impairment is accelerated not only by oxidative stress but also the induced calcium and phosphorus bone mineral disorder causing vascular calcification [21]. On top of filtering impairment of calcium and phosphorus, a decrease in
active vitamin D production by the kidneys impairs intestinal calcium absorption and promotes phosphate retention [21]. This promotes increased levels of phosphate in the blood (hyperphosphatemia) leading to a secondary hyperparathyroidism that then upregulates blood calcium levels via osteoclastic activity in the bone [21]. In a prospective study by Cano-Megias et al., the authors found that a Coronal Artery Calcium (CAC) score of 400 HU and above was a possible predictor of all-cause cardiovascular mortality (from myocardial infarction or coronary heart disease related death) in dialysis patients in the long-term [22]. This study also discusses other pertinent studies showcasing the significant cardiovascular mortality differences in dialysis patients with lower CAC scores (<400HU) and higher CAC scores (400HU and above). Haydar et al. found that higher CAC scores signifies a higher coronary artery disease burden, a greater severity of disease and a higher number of vessels involved, ultimately leading to worse outcomes [23].

Calcific uremic arteriolopathy (calciphylaxis) manifests as calcification and occlusion of small blood vessels, predominantly affecting the skin and subcutaneous tissues [24]. Calciphylaxis causes painful skin ulcers and necrosis and has been associated with an increased risk of cardiac arrest [24]. The exact mechanism linking calciphylaxis and cardiac arrest is not clear, but it may be related to the overall high burden of cardiovascular disease in these patients, as well as disturbances in calcium and phosphate metabolism [24].

f. Potassium

In addition to calcium and phosphate, potassium level disorders are associated with cardiac arrest and mortality in dialysis patients. Predialysis potassium levels of less than 4mmol/L and greater than 6mmol/L were much stronger predictors of mortality [25]. In other studies, the lower limit was 3.5 and the upper limit was 5.5 [25]. Meanwhile, a predialysis potassium level of 5.1mmol/L was found to have the lowest sudden cardiac arrest risk [25]. This can be explained by the rapid correction and shifting of intracellular potassium [25,26]. In the first hour of dialysis, serum potassium decreases about 1mEq/L and in the next 2 hours after, it decreases about an additional 1mEq/L [25]. This causes an extracellular shift of potassium into the serum, but reflects an overall low total potassium level in the body [25]. Therefore, anyone with lower predialysis potassium levels can have more severe hypokalemia post dialysis [25].

g. Arrhythmias

Cardiac electrophysiology is also disrupted in these patients. ESRD patients undergoing hemodialysis have a higher prevalence of QTc prolongation then the general population [27]. This Electrocardiogram (ECG) abnormality is a known risk factor for arrhythmias and sudden cardiac death [28,29]. Kim et al. found that lower levels of ionized calcium and potassium were associated with QTc prolongation and suggested that periodic follow-up and monitoring of these electrolytes was warranted [28]. A study by Raizada et al. found that 58% of ESRD patients on chronic hemodialysis had QTc interval prolongation (>440 msec) [27]. The study also revealed a significant association between QTc prolongation and polymorphisms of Renin-Angiotensin System (RAS) genes, including angiotensin-converting enzyme-insertion/deletion (ACE-I/D) and angiotensin type 1 receptor-A1166C (AT1R-A1166C) [27]. The authors concluded that these polymorphisms contribute additively to QTc prolongation in ESRD patients, potentially increasing their risk for sudden cardiac death [27]. In addition to QTc prolongation, the risk of atrial fibrillation, a common arrhythmia in ESRD patients, is increased by the presence of left ventricular hypertrophy and myocardial fibrosis [27].

On the contrary, Roberts et al. actually found in the CRASH-ILR study that bradyarrhythmias was the more common arrhythmic event leading to mortality in their patient population [30]. They proposed that this could be due to calcific and fibrotic processes [30].

h. Dialysate

Dialysis patients, because of the factors we already listed, are at high vasculopathy risk which then leads to cardiac arrest and other poor cardiovascular outcomes such as coronary artery disease, peripheral artery disease, cerebrovascular disease, leading to Myocardial Infarction (MI), limb ischemia and strokes. Dialysate itself is an important factor to consider in terms of risk for cardiac arrest. Composition, temperature and timing of dialysis all play a role in the risk of cardiac arrest, specifically [31-33]. In terms of composition, a study by Pun et al. highlighted the association between dialysate potassium concentration and cardiac arrest, finding that lower dialysate potassium levels were associated with a higher risk of cardiac arrest in dialysis patients [31]. This finding is supported by a large-scale study by Yadav et al., which identified low dialysate potassium (K(D) <3 mEq/L) associated with a higher risk of sudden death [32].

In addition to its composition, the temperature of the dialysate can also influence cardiac outcomes in dialysis patients [33]. A study by Tsijumoto et al. demonstrated that cooler dialysate could reduce the risk of intradialytic hypotension, a known risk factor for cardiac events [33]. Furthermore, other dialysis-related factors have been identified as potential risk factors for cardiac arrest. For instance, Rhee et al. (2001) found that dialysis sessions on Monday had a higher incidence of cardiac arrest and these patients were more likely to have a systolic blood pressure drop prior to arrest [34].

i. Anemia and use of erythropoietin stimulating agents (ESA)

Anemia in Chronic Kidney Disease (CKD) is multifactorial; mechanisms involved include decreased EPO production, iron deficiency, increased hepcidin levels from chronic inflammation [35]. Anemia causes a high output cardiac state while also causing peripheral vasodilation, leading to low peripheral vascular resistance [36,37]. This ultimately worsens any pre-existing cardiac systolic or diastolic dysfunction, can even cause LVH therefore increase mortality [38]. Anemia in CKD can be treated with iron therapy and ESA. In the 2012 KDIGO clinical practice guidelines, a hemoglobin of 11.5 g/dL is recommended, but a hemoglobin concentration of 12-13.5 g/dL is the target level. This is because lower hemoglobin levels are associated with increased all-cause mortality and cardiovascular events [39].

On the contrary, Roberts et al. actually found in the CRASH-ILR study that bradyarrhythmias was the more common arrhythmic event leading to mortality in their patient population [30]. They proposed that this could be due to calcific and fibrotic processes [30].

Sakaguchi et al. found that long-acting ESA users had an increased rate of cardiovascular mortality compared to short-acting ESA users [40]. This could be explained by the pharmacologic differences, specifically the longer half-life and increased activity, enhancing a prothrombotic state with platelet aggregation and exacerbating atherosclerotic lesions [40].
Outcomes

In dialysis patients, Sudden Cardiac Death (SCD) account for 20-30% of all deaths and is the most common cause of death [2]. Wong et al. (2015) reported a high incidence of in-hospital Cardiopulmonary Resuscitation (CPR) among adults undergoing maintenance dialysis, with an annual rate of 1.4 events per 1,000 in-hospital days [41]. Approximately 21.9% of these patients survived to hospital discharge, albeit with a median post-discharge survival of only 5 months [41]. Over time, although the incidence of CPR and proportion of CPR recipients surviving to discharge increased, there was no significant improvement in post-discharge survival [41]. Moreover, compared to other populations, CPR incidence was higher among dialysis patients and their long-term survival after CPR was notably worse [41].

On a related note, Wan et al. provided a specific focus on Sudden Cardiac Arrest (SCA) events among hemodialysis patients [42]. In their cohort, 78.6% of SCA events were due to Ventricular Tachycardia Or Fibrillation (VT/VF), while the remaining 21.4% were due to asystole (42). There was a distinct temporal pattern in the occurrence of these SCA events, with a peak incidence between 09:00 and 14:59 [42]. The acute 24-hour, 30-day and 1-year survival rates post-SCA were 70.7%, 50.7%, 31.4%, respectively [42].

Prevention

Preventative measures for negative cardiac outcomes in HD patients are crucial, encompassing both the management of traditional cardiovascular risk factors and non-traditional risk factors. This includes optimal control of hypertension and diabetes, as well as regular monitoring and treatment of electrolytes, mineral bone disorders to address vascular calcification, hyperphosphatemia, anemia and inflammation. When considering HD modalities, the use of nocturnal home hemodialysis has shown promise in improving echocardiographic features associated with sudden cardiac death [43]. This suggests that this specific dialysis modality may offer cardiovascular benefits [43]. However, further research is required to validate these findings and investigate the underlying mechanisms involved [43]. Cardiac arrest can have devastating consequences in hemodialysis patients. To mitigate the risk of adverse cardiac events, the dialysate prescription should be consistently assessed and modified, particularly post-hospitalization [44].

Electrolyte monitoring and control are other ways to reduce the risk. The use of low potassium baths were found to be associated with higher risk of sudden cardiac arrest [45]. Other studies suggest that avoiding prescription of a low potassium bath may decrease this risk [45,46]. KDIGO guidelines also recommend using phosphate binders and dietary modification to maintain serum phosphate around the normal range in individuals on dialysis, as hyperphosphatemia is a risk factor for cardiovascular events [47]. While kidney transplantation is considered the gold standard for managing end-stage renal disease (ESRD), it has been demonstrated to improve cardiovascular outcomes in ESRD patients [48]. This improvement is likely attributed to the restoration of kidney function, leading to reduced uremic toxins and improved anemia [48]. Nonetheless, cardiovascular risk remains higher in kidney transplant recipients compared to the general population, necessitating ongoing cardiovascular risk management [48].

In terms of medication strategies, the use of renin-angiotensin system inhibitors has shown potential in reducing LVH and myocardial fibrosis, which can benefit HD patients. A study by Ni et al. in 2014 demonstrated the effectiveness of spironolactone, a medication that blocks the effects of aldosterone, in reducing blood pressure in patients with refractory hypertension undergoing dialysis [49]. The study revealed significant improvements with a 3-month treatment of 25 mg/day of spironolactone, including a reduction of 16.7/7.6 mm Hg in morning blood pressure and a reduction of 10.9/5.8 mm Hg in mean 24-hour ambulatory blood pressure [49].

As discussed above, elevated inflammatory markers are associated with SCD there are studies showing pharmacological and non-pharmacologic strategies to reduce these markers. Pharmacologic strategies, although largely lacking in clinical outcomes, include IL-1 inhibitors, statins, cholecalciferol, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB), sevelamer [50]. In a prospective study, Elshinnawy et al. found that intradialytic exercise not only decreased the levels of the inflammatory markers, CRP and IL-6, but also increased serum albumin levels [51]. Other non-pharmacologic strategies include dietary factors and short, daily dialysis, but data is still lacking in this area [50].

Given the associated risks of anemia and ESA use with cardiovascular events, the KDIGO 2012 guidelines recommend starting ESA therapy in dialysis patients when hemoglobin levels are between 9.0-10.0 g/dL to maintain a hemoglobin goal of 10.0-11.5 g/dL while the European Best Renal Practice guidelines recommend starting ESA therapy when hemoglobin levels are less than 11.0 g/dL with no clear evidence of target levels [52]. Mimura et al. recommends that hemoglobin target should not be greater than 13.0 g/dL for all CKD patients [52]. Similarly, these authors do not recommend higher doses of ESA to achieve target hemoglobin levels [52].

Monitoring

Monitoring dialysis patients closely is important in the prevention of cardiac arrest. Cardiac monitoring for electrocardiogram (ECG) changes, particularly QTc prolongation, is essential in identifying those at a high risk of sudden cardiac death [27,53]. Kramann et al. 2014 discovered that speckle-tracking echocardiography outperformed routine echocardiography in detecting early signs of uremic cardiomyopathy [54]. Furthermore, this method showed promise in predicting cardiovascular mortality in dialysis patients, a finding that has been cited by 92 other studies (54). On the other hand, Poulikakos et al. suggested routine ECG monitoring intradialysis to calculate the QRS-T angle, as studies have shown an association between abnormal angles with sudden cardiac death [55]. However, there needs to be a standardization of how to calculate the QRS-T angle [55].

Alongside monitoring, investigations into therapeutic interventions have also been significant. Jukema et al., for instance, explored the efficacy of implantable cardioverter-defibrillators (ICDs) in preventing sudden cardiac death in ESRD patients [56]. However, their research indicated no mortality benefit and the associated risks, such as infection and non-rhythmic causes of death, seemed to outweigh the benefits for these patients [56]. They recommended further research into whether subcutaneous ICDs may offer a more viable solution for ESRD patients requiring dialysis [56]. This was supported by Dasgupta et al.’s study which showed increased complication rates, not including death, in individuals who had prophylactic permanent pacemaker or ICD placement [57]. On the contrary, Herzog et al. supported the use of ICD implantation as means of secondary prevention in cardiac arrest survivors [58]. Roberts et al. suggests that further studies need to be done to assess if pacemaker implantation is a...
viable option to reduce SCD risk [30]. Similarly, Sacher et al. found that Implantable Loop Recorder (ILR) implantation may be useful in patients who are prone to underlying arrhythmias and therefore, can allow early detection and possible intervention of treatment to reduce the risk of SCD [59].

In parallel, innovative studies are being conducted in the realm of biomarkers, aiming to provide insights into the pathogenesis of CVD in ESRD patients and to discover potential therapeutic targets. The use of novel biomarkers, such as circulating microRNAs, is an area of growing interest [60]. A study by Zhou et al. corroborated this interest by suggesting that circulating microRNAs might serve as potential biomarkers for CVD in ESRD patients [60]. This line of research offers a promising avenue for developing targeted interventions and possibly personalized treatments.

**Conclusion**

This review article highlights the profound relationship between cardiac arrest and hemodialysis in patients with end-stage renal disease (ESRD). Cardiovascular disease remains a significant burden in ESRD, accounting for up to half of all deaths in this population. Multiple facets contribute to the elevated cardiovascular risk among dialysis patients, encompassing traditional risk factors such as hypertension, diabetes, arrhythmias and the duration of dialysis treatment, as well as non-traditional factors including inflammation, oxidative stress, mineral bone disorders, electrolyte imbalances and anemia. Dialysis itself is implicated, with data suggesting that the timing, temperature, composition of the dialysate can significantly influence cardiac outcomes, particularly cardiac arrest. Monitoring and modifying these variables offer an avenue for potential intervention. Specifically, low dialysate potassium concentration was found to be associated with an increased risk of cardiac arrest.

Preventative measures for mitigating the risk of cardiac arrest in hemodialysis patients are multifaceted, ranging from the management of traditional cardiovascular risk factors to addressing non-traditional factors specific to ESRD. Furthermore, considering different modalities of dialysis, like nocturnal home hemodialysis medications such as renin-angiotensin system inhibitors may offer additional benefits. Despite the grim outcomes associated with cardiac arrest in this population, strategies aimed at prevention, including close monitoring of dialysis prescriptions and regular cardiac monitoring for ECG changes, can play a vital role in reducing the risk. It is essential for future research to continue to elucidate the complex relationship between cardiac arrest and hemodialysis and to refine strategies for reducing cardiovascular risk in this vulnerable patient population. There should be a focus on developing personalized, patient-centric approaches that account for the individual’s complete health picture, considering both kidney disease and associated cardiovascular risks.

Through continued advancements in our understanding of the intersection between ESRD and cardiovascular disease, we anticipate that this will result in the refinement of therapeutic interventions and the development of novel treatment strategies that will substantially improve the prognosis and quality of life for patients suffering from ESRD.

**References**


