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Cardiac Device Therapy in Patients with Chronic Kidney Disease – an Update

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Review

Cardiac Device Therapy in Patients with Chronic Kidney Disease—An Update

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Abstract: Cardiovascular diseases (CVDs) and chronic kidney disease (CKD) are frequently interconnected and their association leads to an exponential increase in the risk of both fatal and non-fatal events. In addition, the burden of arrhythmias in CKD patients is increased. On the other hand, the presence of CKD is an important factor that influences the decision to pursue cardiac device therapy. Data on CKD patients with device therapy is scarce and mostly derives from observational studies and case reports. Cardiac resynchronization therapy (CRT) is associated with decreased mortality, reduced heart failure symptoms and improved renal function in early stages of CKD. Implantable cardioverter defibrillators (ICDs) are associated with a signficant reduction in the mortality of CKD patients only for the secondary prevention of sudden cardiac death. Cardiac resynchronization therapy defibrillator (CRT-D) is preffered in patients that meet the established criteria. The need for cardiac pacing is 3-fold higher in dialysis patients. CKD is an independent risk factor for infections associated with cardiac devices.

Keywords:

1. Introduction

Cardiovascular diseases (CVDs), particularly heart failure (HF), are the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD) [1]. Moreover, the relationship between these two conditions is bidirectional, as the evolution of one condition influences the development of the other and vice versa [1,2]. The progression of CKD is one of the main determinants of a worse prognosis in cardiac disorders, as decreased renal function is associated with increased hospital admissions and deaths [3]. CKD also promotes the occurence of arrhythmias, sudden cardiac death through electrolyte disorders, left ventricular hypertrophy, myocardial fibrosis, uremic status or sympathetic overactivity [4]. The presence of advanced renal impairment is an important element that affects the choice of cardiac implantable electronic device (CIED)/cardiac assist device treatment in patients with HF or in need for cardio-pulmonary support. The safety and efficacy of these therapies in CKD patients is still questionable due to lack of evidence caused by their exclusion from large clinical trials [1,2]. Also, end stage renal disease (ESRD) and dialysis are risk factors for systemic CIED infections due to the constant need for vascular access or altered immune response [7]. On the other hand, dyssynchrony caused by right-ventricular pacing can cause pacing induced HF, with reduction of left ventricular systolic function which leads to low cardiac output, inadequate renal perfusion and decreased renal function [5,6].

The decision to implant cardiac devices is often difficult, and requires a formal risk-benefit analysis even in the general population, in the absence of strong guideline recomandations The purpose of this review is to detail the particularities of cardiac device use in CKD patients.

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2. CIED in CKD Patients with HF

2.1. Cardiac Resynchronization Therapy (CRT)

Current European Society of Cardiology (ESC) guidelines recommend the use of CRT for symptomatic patients with normal sinus node function, wide QRS complex with left bundle branch block morphology, and persistent severe left ventricular systolic dysfunction despite optimal pharmacological treatment [8]. Whether renal function has an impact on the benefits of CRT has been largely debated, but we have to bear in mind that all available data comes from observational studies. The outcomes of CKD patients with CRT are mainly influenced by the responder status (defined as an increase in the left ventricular ejection fraction (LVEF) by at least 5% or a decrease of the left ventricular end-systolic volume (LVESV) by more than 10%), or the non-responder status. Whether CKD per se influences patients' response to CRT is still debated.

In a study that included 179 patients with a mean LVEF of 24%, patients with CKD stages 3-5 had a good functional response to CRT that was similar to that of patients with normal renal function and translated into an improvement in HF symptomatology. Although the overall mortality was higher in renal patients, those who qualified as CRT-responders had a long-term survival benefit [9]. Moreover, in patients with severe HF, CRT was associated with a sustained improvement in renal function defined as an increase of eGFR by at least 10 ml/min/1.73 m^2 in all CKD stages, leading to a significant reduction in the number of deaths and necessity of cardiac mechanical support [10].

A larger study that included 588 patients with ischemic HF and CKD concluded that CRT responders may experience an improvement in eGFR and a decrease in the short-term mortality rate, especially in those with stages 4 and 5 of CKD. However, the effect on the mortality rate did not reach statistical significance in the long-term [11].

In another study that included 178 patients with a median LVEF of 25% and a non-ischemic etiology, renal impairment did not significantly influence patients' response to CRT. Nevertheless, patients with CKD had a 5.5 fold increased risk of death compared with patients with normal renal function. Again, an improvement in renal function was documented only in CRT responders [12].

However, patients with ***advanced*** stages of CKD may experience a lower response to CRT [13]. In a retrospective study that included 798 patients from the entire CKD spectrum with a LVEF below 35%, patients with more advanced CKD (stages 3-5) and CRT had lower survival rates and more hospitalizations for HF compared to those with CKD stages 1-2. There was a benefit on cardiac remodeling with an improvement in the LVEF and LVESV across all stages, albeight less significant for those with moderate to severe renal dysfunction. The study showed a preservation of renal function after initiation of CRT in patients with eGFR<60 ml/min/1.73 m^2, with a small improvement of eGFR (0.8 ml/min from baseline) at 6 months in responders as compared to non-responders. [14].

There is also data reporting an increase of 66% in the mortality rate of CKD patients who received CRT, which is possibly limited to those without an improvement in renal function [15]. In another observational study that followed 1000 patients with CRT for a mean period of 3,7 years, there was also a higher mortality rate and an increase in the number of admissions for HF in CRT patients with moderate and severe CKD, but with a benefit in the survival rate and number of hospitalizations in patients with CRT defibrillator (CRT-D). Thus, one may conclude that CRT-D is a better choice than CRT-P in patients with renal disease [16]. In this study, the impact of CKD on the mortality rate was similar in patients receiving CRT and CRT-D[17] [18].

In conclusion, available data suggest that in CRT responders, there is a significant improvement in both the mortality rates and cardiac functional response. Moreover, CRT responders may experience an improvement of the renal function. However, we have to bear in mind that in advanced stages of CKD, these benefits are attenuated. Left ventricular hypertrophy, myocardial fibrosis, activation of the renin-angiotensin-aldosterone (RAA) system, increased inflammatory status and oxidative stress are several potential explanations for both the negative influence of CKD on the mortality rate and the decreased response to CRT in advanced stages of CKD. On the other hand, an improvement in the left ventricular systolic function in CRT responders enhances the renal blood flow, decreases the venous congestion and therefore leads to an increase in the eGFR [10,11,15].

2.2. CIED for Sudden Cardiac Death (SCD) Prevention in CKD Patients

Implantable cardioverter defibrillator (ICD) therapy has been traditionally indicated for both primary and secondary prevention of SCD in patients with ischemic HF who either had persistent reduced LVEF despite 3 months of optimal medical therapy or were survivors of ventricular arrhythmias causing haemodynamic instability. In both situations, ICD therapy reduces the risk of SCD and all-cause mortality [8]. In the last years, ICD therapy also gained indication for the prevention of SCD in patients with cardiomyopathies, in which case the decision is mainly driven by the extent of myocardial fibrosis [19]. However, the efficacy of ICD remains uncertain in patients with moderate to severe renal disease because of their exclusion from clinical trials and paucity of evidence [20].

The influence of ICD therapy on all-cause death was assessed in over 17,000 patients with CKD. ICD therapy led to a decrease in the overall mortality rate in patients who were at high risk for sudden cardiac death and received the device for primary prevention. However, in patients that already had ICD therapy, the development of CKD increased the risk of all-cause mortality by 2.86 times [21]. Other studies suggest that the beneficial effect on survival of ICD therapy may be limited to early stages of CKD, with the loss of this effect in stages 4 and 5 [22]. The excess of mortality in ESRD patients with ICD can be partially explained by higher defibrillation thresholds, increased number of comorbidities and a higher frequency of device associated infections. Moreover, patients with CKD frequently present with left ventricular hypertrophy, fluid overload, electrolytic imbalance and autonomic disorders, all of these leading to a higher rate of electric storms [22].

The evidence on the benefits of ICD therapy in CKD patients is still controversial. There are studies that suggest better survival rates with ICD therapy, irrespective of the type of indication [23], while others conclude a higher mortality rate and an elevated burden of antitachycardia pacing or shocks [24]. A major limitation comes from the fact that many studies combined patients with ICD in both primary and secondary prevention, with or without HF. Therefore, we believe it would be useful to have a separate view according to the indication.

2.2.1. ICD for Primary Prevention of SCD

The main concern about the efficacy of ICD therapy in CKD patients comes from a meta-analysis that included three cornerstone trials on this matter - MADIT I, MADIT II and SCD-HeFT, which concluded that the decline of glomerular filtration rate is associated with a lower benefit on survival. Moreover, ICD patients with an eGFR below 60 ml/min/1.73 m^2 had lower survival rates when compared to those without or with mild renal disease and ICD and to those without ICD therapy and normal kidney function. These results can be explained partially by the presence of non-arrhythmic events causing death, higher defibrillation thresholds or decreased ICD exposure of CKD patients secondary to a shorter life expectancy compared with non-CKD population. However, there were no concerns on the safety of the device, as the renal function had no impact on ICD related complications rate [25].

Hess et al. conducted a larger retrospective study on over 47,000 patients with CKD who underwent ICD implantation for primary prevention of SCD. The risk of mortality after ICD procedure was significantly higher in patients with renal disease. The burden of death was inversely proportional with renal function, and doubled for patients with eGFR between 30-60 ml/min, while those with severe CKD (eGFR < 30 ml/min) had a 4.2 times higher risk of mortality. ESRD patients had a 4.8 greater risk of death, displaying the worst prognosis. The authors suggest that CKD is not the only factor that increased the burden of mortality as patients with renal impairment had significantly more comorbidities. They identified several factors alongside severity of renal disease strongly connected with the chance of death: older age, degree of systolic dysfunction (lower LVEF) or HF symptoms (NYHA class), diabetes mellitus, hyponatremia, supraventricular tachycardia like atrial fibrillation/flutter [26].

In an observational study that included 5877 patients with CKD and LVEF <40%, ICD therapy did not lower the rate of all-cause mortality, and it was associated with an increased number of hospitalisations in relation to HF [27]. In another observational study that included 303 dialysis patients with LVEF <35%, patients that received ICD therapy for the primary prevention of SCD did not have a significant survival advantage [28]. These results were also consistent in dialysis patients with a LVEF >35% [29].

2.2.2. ICD for Secondary Prevention of SCD

Ventricular arrhythmias are the main cause of SCD in advanced CKD stages. Moreover, SCD has a higher prevalence in haemodialysis (HD) patients and is responsible for 1/3 of deaths in HD patients and 2/3 of deaths in patients with advanced CKD [30] [31]. In a systematic review and meta-analysis that included almost 120,000 CKD patients, ICD therapy for the secondary prevention of SCD was associated with a reduced risk of all-cause mortality [32]. The benefits of ICD therapy on survival was also evaluated in a study that included more than 41,000 dialysis patients who survived from an event like sudden cardiac arrest (SCA), ventricular tachycardia/fibrillation and were followed for 8 years. In this cohort, 3.4% (1442) of patients received an ICD for the secondary prevention of SCD. Patients with ICD had a significantly lower short- and long-term mortality rate when compared to those without ICD. The increase in the mortality rate was mainly driven by a higher comorbidity burden, and a higher number of both infectious and embolic complications. The positive results for ICD therapy could be explained through an elevated arrhythmic load in ESRD patients and from the characteristics of those selected for receiving such a device: less comorbidities (low CCI), younger age and fewer cardiac events [33].

The higher rates of infections, mainly endocarditis, or vascular access limitation in dialysis patients makes the implant of a transvenous ICD difficult. Subcutaneous implantable cardioverter defibrillator (S-ICD) is safer in terms of infectious complications, but is associated with an increased risk of death and higher rates of electrical shocks [34].

In conclusion, the benefits of ICD therapy in CKD patients are limited to the indication for secondary prevention of SCD. As previously anticipated, in CKD patients that qualify for ICD therapy and associate HF with reduced ejection fraction, CRT-D may be superior to ICD. In a retrospective study that included over 1000 patients with CKD stages 3-5, including patients on dialysis, CRT-D was associated with a significantly lower mortality rate and a reduced number of hospitalisations for HF when compared to ICD therapy alone. The authors noted a tendency for a more rapid progression rate to end-stage renal disease in the ICD group, but without reaching statistical significance [35]. A subgroup analysis of the MADIT-CRT trial concluded a better survival rate and less HF related events in patients with moderate CKD that received CRT-D compared to those with ICD only. On the other hand, CRT-D din not improve the mortality rate in those with normal renal function, but had a significant effect on reducing HF related events [17].

Finally, the benefits on survival of CRT-D therapy over ICD only were confirmed in a meta-analysis performed on 13,095 patients, including dialysis patients. CRT-D has a favorable effect on cardiac remodeling, was associated with an increase in eGFR due to an increase in the kidney perfusion and also with a decrease of the sympatetic overactivation, all of these leading to a decreased burden of ventricular arrhytmic events. [23] These results are also supported by the aforementioned meta-analysis, performed on 120,000 CKD patients [32].

Therefore, CRT-D may be the preffered CIED in CKD patients that meet the established criteria.

2.3. Left Ventricular Assist Device (LVAD) and CKD

As previously mentioned, CKD is a well-known predictor for worse outcomes in patients with advanced HF. LVADs are recommended for bridge-to-transplantation, destination therapy, bridge-to-decision or bridge-to-recovery in patients with end-stage HF, refractory to maximal tolerated medical therapy [36].

In a retrospective study that followed 213 patients in terms of post-LVAD outcomes according to preexisting moderate or severe renal dysfunction, the mortality rate was higher in those with a decline in the renal function before LVAD implant and the incidence of stroke or transient ischemic attack and hospitalisations for HF was higher too. Impaired renal function was also associated with right ventricular systolic dysfunction [37].

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In a large cohort that included over 20,000 patients with LVAD, CKD stages 4-5 was associated with an increased risk of death when compared to early stages. In addition, the duration of hospital stay was longer, with greater financial costs and an increased necessity for transitional care services at discharge [38]. Moreover, patients with CKD had a significant higher rate of renal replacement therapy post-LVAD therapy [39]. These results were also confirmed by a recently published systematic review and meta-analysis performed in over 26,000 patients with CKD [40].

Data regarding the long-term benefit of LVAD in patients with advanced CKD and HF are scarce. In a retrospective study that included 496 patients with CKD and 95 ESRD patients, dialysis patients had significantly higher mortality rates when compared to non-dialysis patients with CKD. However, dialysis did not increase the rate of complications like bleeding, pump thrombosis, ischemic or haemorrhagic stroke, sepsis, or infections [41].

These results are in line with another retrospective study conducted in over 400 patients, with LVAD used as bridge to heart transplant. In patients with ESRD, the mortality rate post-LVAD was significantly higher and most of them died before receiving a heart transplant [42]. However, there was not strong enough evidence to support a causal effect between the increased post-LVAD mortality and ESRD. Complications such as infection, stroke, bleeding, older age or comorbidities – more frequently seen in ESRD - could also increase the mortality and lead to a poor prognosis [43,44].

In an observational study performed on 131 patients, almost half of them with pre-existing CKD, LVAD implantation was associated with an improvement in kidney function at 1 month distance [45]. On the other hand, the coexistence of AKI at the moment of LVAD implantation was associated with significantly more in-hospital deaths, as well as more frequent LVAD related complications: bleeding, sepsis or discharge to a nursing facility [46]. The incidence of AKI post-LVAD implantation varies between 11% and 45% and its occurrence is explained among other factors by prolonged hypovolemia, congestion, right ventricle failure, cardio-renal syndrome, vasoplegia or haemolysis [47]. The occurence of AKI and the need for RRT after LVAD is more prevalent in patients with preexisting CKD [39] and leads to an increased mortality and a decreased renal function at 12 months distance [48].

In conclusion, in patients with advanced HF and CKD, particularly in advanced stages shared decision-making regarding LVAD treatment is advisable.

3. CIED for Bradyarrhythmias in CKD

The incidence of cardiac arrest due to bradyarrhythmias or asystole in dialysis patients varies between 10% and 30%, and occurs more frequently in long interdialytic periods[4,49–51]. Moreover, bradycardia and asystole are the main mechanism of SCD in end-stage renal disease patients [52]. In a prospective cohort study Rautavaara et al. underline the importance of continous and/or in centre electrocardiographic monitoring. In their analysis, bradyarrhythmias occured especially during in-centre HD and no bradycardia was found on ambulatory 12 lead electrocadiogram (ECG). However, the rate of bradycardia was a sigificantly higher in those with long PR or RR interval on ambulatory 12 lead ECG [51].

Data derived from observational studies concluded that the need for cardiac pacing is 3 times higher in dialysis patients. Moreover, hemodialysis is more frequently associated with the need for cardiac pacing when compared to peritoneal dialysis [53]. In a longitudinal retrospective study that included 260 ESRD patients on RRT, patients with cardiac pacemakers had a higher mortality burden, but cardiostimulation was not independently associated with an increased risk of death, factors such as infections or arrhytmic events being more common. Patients with dual chamber pacemakers had a better survival rate. Moreoveor, device implantation before the starting RRT was associated with better outcomes when compared to cardiac stimulation after the initiation of RRT, but these results were mainly driven by a higher comorbidity burden in dialysis patients [54].

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4. CIED Related Infections: Particularities in CKD Patients

CIED related infections are associated with increased rates of mortality and morbidity, as well as with an increased financial burden on the healthcare system [55]. In recent years, there was a 2- to 4-fold increase in the number of CIED infections. The risk of infections is higher in CRT recipients, especially in the first year after implantation or in patients with repeated procedures [55–57].

Many factors can contribute and promote a device related infection. These factors can be either patient related (age, male sex, comorbidities such diabetes, renal insufficiency or chronic obstructive pulmonary disease, medication like anticoagulation or immune-modulating therapy; medical history, need for vascular access), linked to the procedure (improper antibiotic prophylaxis, reintervention or device replacement, duration, temporary pacing, operator experience, haematoma, leads dislodgement) or device associated (number of leads, dual or single chamber device, epicardial leads, pocket). In a meta-analysis that included 26 172 patients, CKD including dialysis was associated with a significant higher risk for CIED infections. In addition, the risk increased with a number of comorbidities such diabetes mellitus or congestive heart failure and with CKD related conditions like central venous catheter presence or corticosteroid use [58].

In CIED related infections, current guidelines recommend the complete extraction of the system with complementary antibiotic therapy [55]. In a study that included 1420 patients (261 with CKD) that undergone transvenous lead extraction, the presence of CKD and dialysis status did not affect the success of the procedure or the complication rate. However, patients with CKD had a significant worse survival at both 1 and 6 months of follow up [59]. Device extraction was superior to medical therapy in terms of survival among over 540,000 patients with CIED infection with ESRD [60].

Leadless CIEDs could be a useful alternative in CKD patients due to their difficult vascular access and higher liability for infections [61].

5. Conclusions

To conclude, the decision of implanting a cardiac device in a CKD patient should be personalized. Similarly to the general population, the benefits and risks should be equally taken into consideration. In addition, in ESRD patients, the type of RRT may influence the risk of associated complications, especially infections. CRT is more effective in early stages of CKD, in which case is associated with a higher rate of response too. ICD has solid evidence for the secondary prevention of SCD, while in the primary prevention the mortality rate is significantly increased when compared to general population. LVADs are usually associated with an increased mortality rate in CKD patients, with limited evidence supporting an improvement in kidney function after their implant. Cardiac pacing indications are similar to those in general population.

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