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**REVIEW ARTICLE**

# Therapeutic Approach to Patients with Heart Failure with Reduced Ejection Fraction and End-stage Renal Disease

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**Abstract:** ***Background*:** Several risk factors including Ischemic heart disease, uncontrolled hypertension, high output Heart Failure (HF) from shunting through vascular hemodialysis access, and anemia, contribute to development of HF in patients with End-Stage Renal Disease (ESRD). Guideline-directed medical and device therapy for Heart Failure with Reduced Ejection Fraction (HFrEF) has not been extensively studied and may have limited safety and efficacy in patients with ESRD.

***Results*:** Maintenance of interdialytic and intradialytic euvolemia is a key component of HF management in these patients but often difficult to achieve. Beta-blockers, especially carvedilol which is poorly dialyzed is associated with cardiovascular benefit in this population. Despite paucity of data, Angiotensin-converting Enzyme Inhibitors (ACEI) or Angiotensin II Receptor Blockers (ARBs) when appropriately adjusted by dose and with close monitoring of serum potassium can also be administered to these patients who tolerate beta-blockers. Mineralocorticoid receptors in patients with HFrEF and ESRD have been shown to reduce mortality in a large randomized controlled trial without any significantly increased risk of hyperkalemia. Implantable Cardiac-defibrillators (ICDs) should be considered for primary prevention of sudden cardiac death in patients with HFrEF and ESRD who meet the implant indications. Furthermore in anemic iron-deficient patients, intravenous iron infusion may improve functional status. Finally, mechanical circulatory support with left-ventricular assist devices may be related to increased mortality risk and the presence of ESRD poses a relative contraindication to further evaluation of these devices.

**Keywords:** Therapeutic approach, heart failure, end stage renal disease, hemodialysis, beta-blockers, ESRD.

## 1. INTRODUCTION

Heart Failure with Reduced Ejection Fraction (HFrEF) and End-stage Renal Disease (ESRD) are global epidemics and are also leading causes of morbidity and mortality [1-4]. Despite current advances in medical and device-based therapies, the long-term prognosis of patients with heart failure continues to be poor [5]. Studies have shown that in addition to higher mortality from progressive pump failure and sudden cardiac death, heart failure patients suffer from multiple comorbidities that elevate their morbidity and mortality [6-8]. Among the co-morbidities, a large proportion of patients have varying degrees of renal dysfunction ranging from mild chronic kidney disease to ESRD requiring dialysis. Previous studies have shown that patients with ESRD are at heightened risk for varying cardiovascular (CV) and cerebrovascular events. CV mortality and morbidity are about 2 to 10 times that of general population with normal renal function. Among patients on hemodialysis (HD), heart disease is the leading cause of mortality [9]. It is estimated that patients on dialysis have 8% higher mortality than the general population and cardiovascular mortality is estimated to be 43% [10]. Approximately 70% of patients with ESRD on HD also have HFrEF [11]. In addition, in patients with ESRD, heart failure is a common manifestation with nearly 30-40% patients on HD shown to have prevalent heart failure [12-15]. In ARIC study [16], the presence of HF at the time of dialysis initiation, both hemodialysis (HD) and Peritoneal Dialysis (PD), is associated with higher short and long term mortality. The median survival is estimated to be 36 months. HFrEF and ESRD share common risk factors in the form of diabetes mellitus, hypertension, coronary artery disease, obesity, tobacco use etc. Furthermore these 2 highly co-morbid conditions utilize significant amount of health care resources imposing significant burden on the health care system. Available data on the use of optimal medical therapy in patients with coexistent HFrEF and ESRD on dialysis is limited to post hoc analysis with very few prospective trials. Despite lack of evidence, the National Kidney Foundation Kidney Disease Outcome Quality Initiative group recommend medical therapy involving the use of Beta Blockers (BB), Angiotensin Converting Enzyme Inhibitors (ACEI), Angiotensin Receptor Blockers (ARB) and Mineralocorti-

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coid Receptor Blockers (MRA) in all patients with ESRD on HD and coexistent heart failure with reduced ejection fraction [17]. Further, most randomized controlled trials have systematically excluded patients with ESRD with the concern that the investigational drug might lead to potential side effects. This led to underutilization of optimal heart failure as noted in several published studies [18, 19]. It is important to note that use of such heart failure therapies is needed to improve outcomes like reduction in hospitalizations and mortality [20-23].

In this current review, we sought to identify the existing literature with regards to use of current guideline directed medical therapy in patients with HFrEF and ESRD on dialysis.

## 2. BETA-BLOCKERS AND ESRD

Several RCT have clearly established the beneficial effects of the beta-blockers in patients with chronic systolic heart failure and normal or mildly reduced renal function. Earlier studies have shown that in patients on dialysis, high plasma norepinephrine levels predict adverse cardiovascular events and mortality [24] but limited evidence exists about the safety and efficacy of these agents in patients with HFrEF and ESRD.

To date, only one randomized control trial (RCT) has examined the effects of beta-blockers in such patient population. The study examined 114 patients on dialysis and with chronic systolic heart failure with LVEF < than 30% and NYHA FC II-III, for 12 months. It has been noted that the use of Carvedilol is associated with significant improvement in LVEF and NYHA class [25] and reduction in all-cause mortality [22] (51.7% mortality rate in the carvedilol group versus 73.2% in the placebo group; $P < 0.01$) that was noted on extended follow up for about 24 months. There was also a trend toward reduction in sudden cardiac death and pump failure deaths [HR] 0.76; P = 0.12) although this was not statistically significant. A statistically significantly lower rate of CV mortality (29.3% *versus* 67.9%; $P < 0.0001$) and all-cause hospital admission (34.5% *versus* 58.9%; $P < 0.005$) was also noted in the carvedilol group than in the placebo group. Further, the study also showed that in recipients of carvedilol, there was a lower rate of fatal myocardial infarctions, fatal strokes, and hospital admissions for worsening HF. There was also a significant improvement in LVEF as demonstrated by the 2-year echocardiographic data (Table **1**).

The dialyzability of beta-blockers may be associated with differential effects on outcomes. In a retrospective cohort of 6588 patients on hemodialysis, beta blockers that

**Table 1. Representative clinical trials of heart failure with reduced ejection fraction and end stage renal disease: Study design and outcome.**

| Trial | No of Patients | Dialytic Modality (HD:Hemodialysis, PD: Peritoneal Dialysis) | Presence of HF (LVEF < 45%) (% of Patients) | Design | Intervention | Control | Follow Up | Outcome |
|---|---|---|---|---|---|---|---|---|
| Cice 2001 | 114 | HD | 100 | Randomized, double-blind placebo controlled | Carvedilol (25 mg bid or maximum tolerated dose) | Placebo | 12 months | Carvedilol improved LVEF relative to placebo (26.3% to 34.8%, p < 0.05) and LV end-diastolic volume (100 ml/m$^2$ to 94 ml/m$^2$ P < 0.05) and LV end-Systolic volume (74 ml/m$^2$ to 62 ml/m$^2$ P < 0.05) |
| Cice 2003 | 114 | HD | 100 | Randomized, double-blind placebo controlled | Carvedilol (25 mg bid or maximum tolerated dose) | Placebo | 24 months | Carvedilol reduced all-cause mortality (HR, 0.51; 95% CI, 0.32 to 0.82; P < 0.01) and cardiovascular mortality (HR, 0.32; 95% CI, 0.18 to 0.57; p < 0.0001). |
| Cice 2010 | 332 | HD | 100 | Randomized, double-blind placebo controlled | Telmisartan (target dose 80 mg/day) | Placebo | 36 months | Telmisartan reduced all-cause mortality (35.1% *vs*. 54.4%; P < 0.001), CV death (30.3% *vs*. 43.7%; P < 0.001) and hospital admission for CHF (33.9% *vs*. 55.1%; P < 0.0001). |
| Taheri 2009 | 16 | HD | 100 | Randomized, double-blind placebo controlled | Spironolactone (25 mg 3x/wk post-HD) | Placebo | 6 months | Spironolactone improved LVEF relative to placebo (LVEF: 6.2 ± 1.6 *vs*. 0.83 ± 4.9%, P<0.05). |
| Taheri 2012 | 18 | PD | 100 | Randomized, double-blind placebo controlled | Spironolactone (25 mg every other day) | Placebo | 6 months | Spironolactone improved LVEF relative to placebo (25.7 ± 7.3 *vs*. 33.3 ± 7.8%, P= 0.002) |

are poorly dialyzed such as bisoprolol or carvedilol provide a survival benefit compared with easily dialyzed beta blockers such as metoprolol [26]. More recently, Tang *et al*. have shown that in patients with heart failure and receiving long term hemodialysis, beta-blockers are associated with improved survival [27]. Overall, beta blockers appear safe and efficacious in these patients if initiated at low doses and adjusted carefully to avoid hypotensive episodes.

## 3. ACEI AND ESRD

ACE inhibitors and their beneficial effects in patients with HFrEF have been examined in multiple randomized clinical trials. ACE inhibitor use is associated with improved survival in patients with HFrEF by their beneficial effects on reducing ventricular remodeling [28] and also by their effects on left ventricular ejection fraction as shown in clinical trials [29, 30]. In addition some of the survival benefit might also be due to slower progression of the underlying disease in patient subset with advanced chronic kidney disease [31-36].

Because of their significant beneficial effects, current guidelines recommend them as class I agents. However, the data supporting their role in dialysis patients is sparse. In a double blind placebo-controlled RCT in 397 HD patients with LVH [37], fosinopril failed to show any significant effect on a composite CV end-point. Furthermore, the study was underpowered to estimate survival benefit with fosinopril. Among HD patients who participated in the HEMO study, using proportional hazards regression and a propensity score analysis, Chang *et al*. evaluated the effects of ACEI use [38]. The authors found no significant associations between ACEI use and mortality, CV hospitalization, and other CV outcomes. Surprisingly, in the proportional hazards model, ACEI use was even associated with a higher risk of HF hospitalization. In a retrospective analysis of the data from the Minnesota Heart Survey [39], dialysis patients hospitalized with HF had no benefit in either short-term (30 days) or long-term (1 year) survival, from use of ACEI or ARB treatment. Retrospective analysis conducted by Berger *et al*. using Cooperative cardiovascular project showed that in a sample of 1025 patients receiving hemodialysis, ACEI use was associated with significant mortality reduction (17.3 *vs.* 33.4%, P value: < 0.001) even after adjustment for baseline demographic risk factors and clinical risk factors (RR 0.58 (0.42-.77) [40]. Studies conducted by Efrati S *et al*. [41] and McCullough PA *et al*. [42] conferred similar beneficial effects. At this time, review of the literature suggests some beneficial effect with ACE inhibitors in ESRD patients, but much of the evidence comes from observational data and registry analysis which by itself is not sufficient to assess the safety and efficacy of the ACE inhibitor use in the proposed patient population. Lack of available data highlights the critical need for a large-scale clinical trial, to determine if a statistically significant reduction in mortality can be achieved in this patient population who are at high risk of adverse primary and secondary cardiovascular outcomes.

## 4. ANGIOTENSION RECEPTOR BLOCKER (ARB) AND HD

A single RCT has been conducted so far using ARBs in ESRD patients. In a multicenter Italian trial [43] 332 HD patients with HF (NYHA II-III; LVEF ≤ 40%), who were randomized to telmisartan or placebo, in addition to ACEI therapy, telmisartan showed statistically significantly reduction in all-cause mortality (35.1% versus 54.4%; $P < 0.001$), CV death (30.3% versus 43.7%; $P < 0.001$), and hospital admission for HF (33.9% versus 55.1%; $P < 0.0001$). With regards to safety, adverse effects, mainly in the form of hypotension, occurred in 16.3% of the telmisartan group versus 10.7% in the placebo group (Table **1**).

## 5. MINERALOCORTICOID RECEPTOR ANTAGONISTS (MRA) AND ESRD

Multiple animal and human studies have shown that despite the Renin-angiotensin-aldosterone blockade, aldosterone breakthrough leads to progression of renal and cardiac disease supporting the role of MRA in this patient population [44-49]. Although in general, serum potassium levels rise after MRA administration, life-threatening or clinically meaningful hyperkalemia may be less of an issue in the ESRD patients, as potassium levels are regulated by the hemodialysis treatments and not by the renal tubule. In addition, other metabolic derangements like hypercalcemia may play a protective role because of the membrane stabilizing action of the calcium. Racial differences also play a role with ability of the African American patients to better tolerate hyperkalemia due to lower dietary intake, high rates of unprovoked hypokalemia, lower renin activity and differences in urinary potassium excretion.

In Iran, Taheri *et al*. conducted a small double-blind RCT of spironolactone 25 mg/day versus placebo, in addition to an ACEI or an ARB, in 16 HD patients with HFrEF (NYHA classes III-IV and LVEF < 45%). After 6 months of treatment, significant increase in mean LVEF with decrease in mean LV mass was noted in the spironolactone group than in the placebo group. The incidence of hyperkalemia was unchanged in both groups [50]. In another study with an identical design conducted by the same research team, a significant increase in LVEF (25.7 ± 7.3 *vs.* 33.3 ± 7.8, P = 0.002) in the spironolactone group (25 mg taking every other day) but not in the placebo group and a non-significant increase in serum potassium in both groups was noted in 18 continuous ambulatory peritoneal dialysis (CAPD) patients with HFrEF (NYHA classes III-IV and LVEF < 45%) [51]. Chua *et al*. recently reviewed 6 RCTs that evaluated the safety of low-dose spironolactone in Hemodialysis (HD) patients of which, about 50% were on background therapy with ACEI or ARB therapy. The authors found that the incidence of hyperkalemia with spironolactone treatment was similar to that in control groups; however, all these studies involved small populations of compliant subjects, who were at low risk for hyperkalemia [52]. At this time, safety and positive effect of MRN in patients on dialysis remain unclear. Currently, the ALCHEMIST trial designed to establish the effects of the spironolactone vs placebo on major cardiovascular events in chronic hemodialysis patients (NCT01848639) and HFrEF (LVEF < 40%) is recruiting subjects at this time.

## 6. DIGOXIN

Digoxin use in patients with HF and ESRD was analyzed by Chan *et al*. for survival benefit in a retrospective cohort, using covariate- and propensity-score-adjusted Cox models. They noted that Digoxin use was associated with a 28% increased risk for death in over 120,000 patients on incident HD. Increasing serum digoxin concentration was also significantly associated with mortality, most markedly in patients with lower pre-dialysis serum potassium [53].

## 7. NEW DRUGS

Ivabradine, an inhibitor of the $I_f$ ionic current, has not been studied in patients with estimated glomerular filtration rate (eGFR) below 15 ml per minute per 1.73 m2 of body-surface area [54]. Use of Ivabradine in patients with estimated glomerular filtration rate (eGFR) below 15 ml per minute per 1.73 m2 of body-surface area is limited. In CARVIVA HF trial, Ivabridine 7.5 mg bid was tested in hemodialysis patients with heart failure. Approximately 46% of patients were noted to have systolic and 54% to have diastolic HF. Patients on ivabradine alone or in combination with carvedilol demonstrated better exercise tolerance and quality of life compared with carvedilol alone [55-57]. Due to small sample size and lack of studies with hard outcomes such as HF mortality and hospitalization, the use of ivabradine is not encouraged in patients with HFrEF and ESRD until further evidence is available.

Sacubitril-Valsartan otherwise known as LCZ696, proven to be effective in reducing cardiovascular death or heart failure hospitalization in the PARADIGM-HF trial of angiotensin receptor-neprilysin inhibitor *vs.* enalapril in HFrEF, systematically excluded patients with eGFR below 30 ml per minute per 1.73 m2 of body-surface area at screening or at the time of randomization [58, 59]. Therefore, the use of the new combination should be reserved for patients without advanced chronic kidney disease.

Role and the implications of diuretic therapy with concomitant ESRD:

Diuretic use has been shown to be low upon initiation of dialysis due to the belief that dialysis patients do not have significant urine volume [60]. Previous studies have shown that diuretics affect water and sodium excretion in patients with end stage renal disease but the effects on preserving residual renal volume in such patients is limited [61-64]. Presently, data is limited on role of diuretics in patients with heart failure and end stage renal disease.

## 8. ICD IN PATIENTS WITH CHRONIC SYSTOLIC HEART FAILURE AND ESRD

### 8.1. Transvenous Type

Survival is lower in patients with HF and ESRD and approximately of 20% patients die from SCD. This is compounded by the fact that prescription rates of ICD are reported to be lower due to lack of definitive evidence supporting their use in this group of patients [65]. In addition, randomized clinical trials that have shown the benefit of ICD in patients with heart failure with reduced ejection fraction have systematically excluded the ESRD patients [66, 67]. Some studies have shown that despite ICD use, mortality was still noted to be higher [68]. In analysis by Friedman *et al*. [69], dialysis patients with CRT were associated with increased risk of mortality and all-cause hospitalization and they were less likely to demonstrate echocardiographic response. It is important to note that although the overall outcome was not good, some patients had shown substantial echocardiographic response thereby suggesting some role in this highly comorbid patients. Also, patient did not experience any procedure related complications. In a meta-analysis by Chen *et al.* [10], the use of ICD was associated with overall survival and 2 year survival rate. The studies have shown a median survival of 1.1-3.2 years in ESRD patients with ICD. It is important to note that in patients with HF and on HD, use of ICD did not impact survival. In HD patients, the transvenous placement of CRT and other cardiac rhythm devices has been associated with an increased risk of device-related infections and central vein stenosis [70]. To avoid such risks, the use of an epicardial approach has recently been suggested for CRT devices in these patients, rather than the classical transvenous route [71].

### 8.2. Subcutaneous ICD

Recent analysis by El-Chami *et al*. has shown that in about 27 patients on chronic dialysis, use of SC ICD is associated with lower risk of infections when compared to transvenous ICD. In addition, patients were also noted to have lower incidence of inappropriate shocks [72].

### 8.3. Left Ventricular Assist Devices (LVADs) and ESRD

Patients with ESRD are rarely referred for LVAD implantation with only 1.5% of patients with new implants requiring dialysis before surgery based on data from the INTERMACS database [73]. The majority of patients with cardiorenal syndrome on renal replacement therapy (RRT) before LVAD implantation, show improvement of their renal function and are weaned off RRT [74, 75]. The remaining patients who continue to require RRT are either listed for heart and kidney transplantation or remain on LVAD support as Destination Therapy (DT). Limited data exists at this time about the role of LVAD in DT patients on RRT with most of the data limited to single center studies with very dismal outcomes. In one study, 1-year survival rate was reported to be 0% in 22 LVAD recipients who were on chronic HD without subsequent heart transplantation [76]. In a recent study by Bansal *et al*., patients with ESRD (median duration was 4 years) at the time of LVAD placement were noted to have extremely poor prognosis with most surviving for less than 3 weeks [77].

### 8.4. Practical Considerations

Patients with HFrEF and ESRD represent a subgroup of patients not adequately studied in large randomized trials of medical and device therapies. The rates of mortality and rehospitalization remain higher than those in the general HFrEF population. The first step in the management of these patients should include optimization of risk factors including obstructive coronary artery disease, severe valvular disease, uncontrolled hypertension, high output HF secondary to arterio-venous fistula and anemia (Fig. **1**). Optimization of vol-

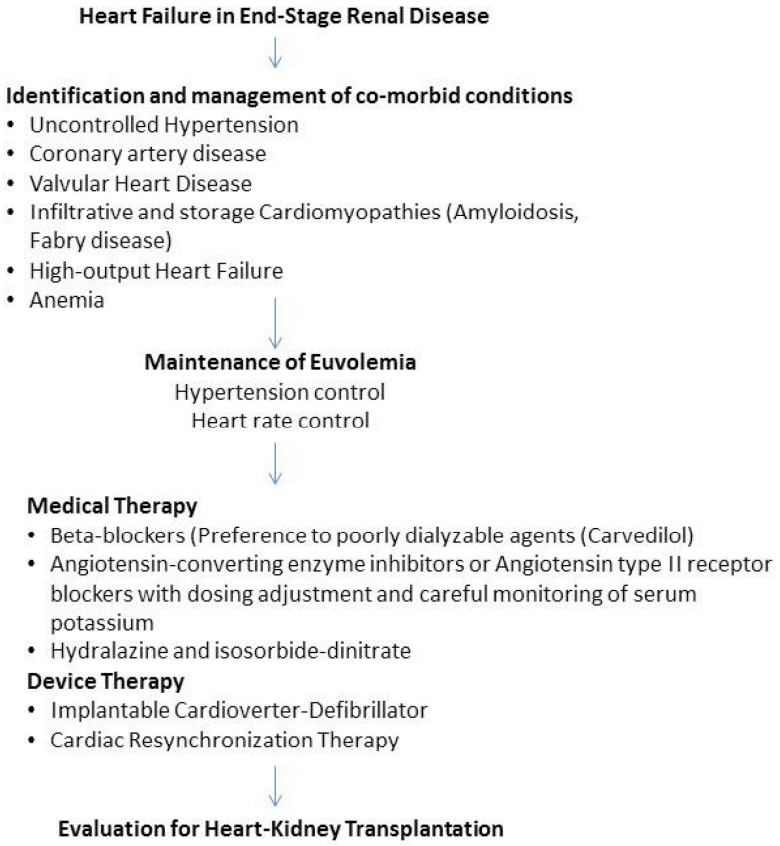


**Fig. (1).** Treatment algorithm of patients with Heart Failure and End-Stage Renal Disease.

ume status is often challenging. These patients often develop intradialytic hypotension which limits volume removal and leads to interdialytic hypervolemia. Approaches to overcome these difficulties include: Careful assessment of volume status and target dry weight, dosing of beta blockers and ACE/ARBs on non-dialysis days, low sodium intake, use of cool dialysate solution to increase vascular resistance, and if the above fail, increase of dialysis time and frequency or even nocturnal dialysis. Since anemia is associated with increased mortality in HFrEF and a previous randomized controlled (FAIR-HF) showing symptomatic benefit from intravenous iron infusion in patients with ferritin<100 mcg/l or transferrin saturation <20% [78], intravenous iron supplementation may be beneficial to iron deficient patients with HFrEF and ESRD. Beta-blockers, preferably non-dialyzable such as carvedilol or bisoprolol, should be the first line treatment in these patients. In patients tolerating b-blockers, the addition of ACEI or ARBs with careful monitoring of serum potassium should be considered. These agents should be initiated at low doses and up-titrated slowly every two to four weeks to avoid hypotension and decompensation. In patients with HFrEF with NYHA II to IV symptoms that are intolerant to ACEI/ARBs, a combination of hydralazine plus nitrate could be used. The use of mineralocorticoid receptor antagonists, angiotensin receptor-neprilysin inhibitors and ivabradine is controversial and cannot be recommended until more data are available. Among devices therapies, ICDs and CRT should be implanted according to the standardized criteria. Finally, patients with refractory stage D HF should be evaluated for heart/kidney transplant listing.

## CONCLUSION

Although, there is a growing population of patients with ESRD supported by LVADs as either bridge to transplant or DT, careful consideration of the risks is necessary before the evaluation for mechanical circulatory support. Better representation of these patients with HFrEF and ESRD in ongoing and future clinical trials will provide valuable evidence on the safety and efficacy of established and emerging medical and device therapies.

## CONSENT FOR PUBLICATION

Not applicable.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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