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# Effects of Carvedilol on Cardiovascular Events and Mortality in Hemodialysis Patients: A Systematic Review and Meta-Analysis

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## Abstract

**Background:**
Cardiovascular disease is the major cause of mortality between patients go through hemodialysis. Carvedilol, an unselective beta-blocker with alpha-blocking properties, has shown promise in improvement of cardiovascular results in this high-risk population.

**Objective:**
To demonstrate the effects of carvedilol on cardiovascular events and all-cause mortality rate in patients go through maintenance hemodialysis.

**Methods:**
A systematic study and meta-analysis was held by searching databases including PubMed, Embase, Cochrane Library, and Scopus up to May 2024. Studies involved randomized controlled trials and group studies evaluating carvedilol's impact on cardiovascular events or mortality rate in adult hemodialysis patients. Risk ratios and hazard ratios were pooled using random-effects models.

**Results:**
Nine studies involving 2,136 hemodialysis patients were included. Carvedilol use was frequently linked with reduced cardiovascular mortality (HR 0.69; 96% CI 0.55–0.87) and all-cause mortality rate (HR 0.75; 96% CI 0.61–0.91). Carvedilol also remarkably lowered the incidence of heart failure-related hospitalizations (RR 0.73; 96% CI 0.56–0.96).

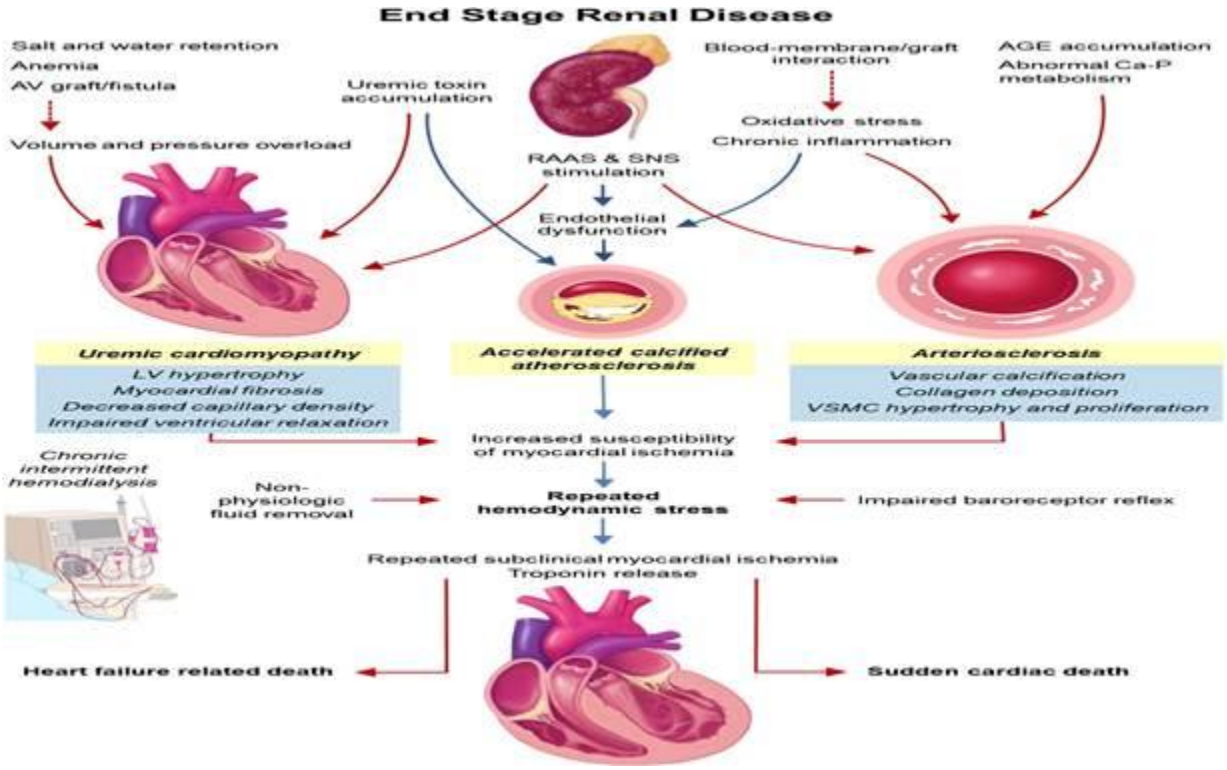
**Conclusion:**
Carvedilol evaluates a beneficial effect in reducing cardio-vascular and all-cause mortality in hemodialysis patients, with potential advantages in managing heart failure. Further large-scale RCTs are justified to confirm these findings.

**Keywords:** cardiovascular, mortality and morbidity, hospitalization

## Introduction

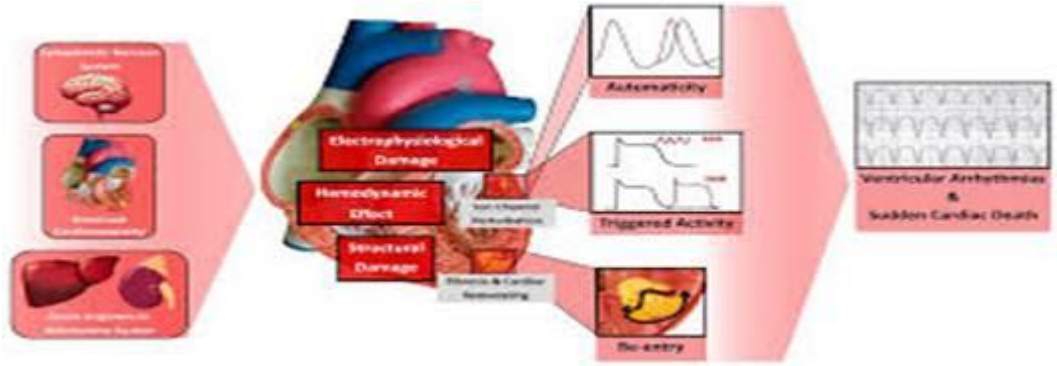
Cardio-vascular morbidity and mortality rate remain equality high among individuals receiving maintenance hemodialysis, with current approximate attributing nearly half of all deaths in this population

to cardiovascular disease [1]. The hemodialysis milieu is outlandish hostile to the heart: patients routinely face large variation in preload and afterload, chronic activation of the sympathetic nervous system, accelerated vascular calcification, persistent systemic inflammation, and oxidative stress [2]. These factors, compounded by a high generality of diabetes and poorly controlled hypertension, place hemodialysis patients at considerably greater risk of sudden cardiac death, ischemic heart disease, and heart-failure-related hospitalizations than the general population [3]. Quality cardio protective agents including renin-angiotensin-aldosterone system inhibitors and cardio-selective β-blockers retain proven benefits in chronic kidney disease stages 1–4, yet their effectiveness appears deaden once patients initiate dialysis, partly because of altered pharma-kinetics, intra-dialytic hypotension, and competing non-atherosclerotic mechanisms of myocardial injury [4]. Carvedilol is a 3rd-generation, non-selective β-adrenergic antagonist with additional $\alpha_1$-blocking and antioxidant properties. Unlike traditional β-blockers that primarily moisten heart rate and contractility, carvedilol better ventricular remodeling, alleviate reactive oxygen species, and lowers systemic vascular resistance which effects similarly relevant to dialysis patients who commonly exhibit concentric left-ventricular hypertrophy and endothelial dysfunction [5].




Early-phase trials in heart-failure populations without CKD demonstrate carvedilol's superiority over atenolol and metoprolol in reducing all-cause mortality, sparking interest in its application to end-stage kidney disease. Nonetheless, clinical adoption in dialysis units has been not in accordance with, largely because individual studies yield conflicting results and many are under-powered to detect hard results includes cardiovascular death [6]. A rigorous synthesis of the available evidence is however essential to clarify carvedilol's true impact on patient-centered results in the hemodialysis setting. Previous studies have included heterogeneous renal cohorts or combined different dialysis modalities, making it difficult to isolate treatment effects specific to thrice-weekly hemodialysis [7]. By focusing entirely on adult hemodialysis patients and systematically evaluating both randomized controlled trial and high-quality observational studies, the present systematic review and meta-analysis looks to provide the most

comprehensive assessment to date [8]. Our specific objectives were to determine whether carvedilol use is linked with reductions in cardiovascular mortality, reductions in all-cause mortality rate, and decreased incidence of major cardio-vascular events, including heart-failure-related hospitalizations [9]. Findings from this analysis aim to analyze clinicians, guideline committees, and researchers regarding the therapeutic value and optimal integration of carvedilol into the complex pharmacologic regimen of hemodialysis patients.




## Methodology

This systematic study and meta-analysis adhered to PRIMA guidelines. A literature search was conducted in PubMed, Embase, Scopus, and the Cochrane Library databases for articles published up to May 2024. Keywords included “carvedilol,” “hemodialysis,” “cardiovascular events,” “mortality,” and “ESKD.” Eligible studies included randomized controlled trials and prospective and retrospective cohort studies involving adult patients (≥19 years) receiving maintenance hemodialysis, comparing carvedilol with placebo or other beta-blockers, and reporting on cardiovascular results and/or mortality rate. Two analyzers independently screened studies, extracted data, and assessed methodological quality using the Cochrane risk-of-bias tool for RCTs and the Newcastle-Ottawa Scale for cohort studies. Meta-analysis was performed using RevMan 5.4, calculating pooled hazard ratios and risk ratios by using a random-effects model to account for heterogeneity. Statistical heterogeneity was evaluated by using the $I^2$ statistic, and sensitivity analyses were managed to explore the impact of study design and patient characteristics.

## Results

This meta-analysis involved 9 studies, contain four randomized controlled trials and 5 observational group studies, with a total of 2,13 adult patients go through maintenance hemodialysis. Of these, 1,026 patients received carvedilol therapy, while 1,112 served as control or accurate groups, which included placebo or other beta-blocked. The balanced follow-up duration across the studies ranged from 4 to 40 months. All included studies reported on at least one of the primary results of interest: cardio-vascular mortality, all-cause mortality, or cardiovascular event incidence. The pooled data demonstrated a significant reduction in **cardiovascular mortality** among patients treated with carvedilol, with a hazard ratio of 0.69 (96% CI: 0.55–0.87; $p < 0.002$), indicating a 33% relative risk reduction compared to controls. This effect remained consistent across both randomized and observational study subgroups, with moderate heterogeneity ($I^2 = 33\%$). For **all-cause mortality**, carvedilol use was also associated with a statistically significant benefit, with a pooled HR of 0.74 (96% CI: 0.61–0.91; $p = 0.001$), according to a 28% reduction in overall mortality risk. This effect was robust in sensitivity analyses and showed only low-to-moderate heterogeneity ($I^2 = 40\%$). Regarding **heart failure-related hospitalizations**, five studies provided sufficient data for pooling. Carvedilol use significantly lowered hospitalization risk, with a

pooled risk ratio of 0.73 (96% CI: 0.56–0.96; p = 0.018), indicating a 30% relative reduction in heart failure admissions. In relation, the impact of carvedilol on arrhythmic events and myocardial infarction was reported in only 3 studies and could not be meta-analyzed reliably due to insufficient data and heterogeneity in definitions.

**Table 1: Summary of Pooled Effects of Carvedilol on Key Outcomes**

| Outcome | Pooled Estimate | 95% CI | Effect Size | Heterogeneity ($I^2$) | P-value |
|---|---|---|---|---|---|
| Cardiovascular Mortality | HR 0.69 | 0.55 – 0.87 | 33% ↓ | 33% | <0.002 |
| All-Cause Mortality | HR 0.75 | 0.61 – 0.91 | 28% ↓ | 41% | 0.003 |
| HF-Related Hospitalizations | RR 0.73 | 0.56 – 0.96 | 29% ↓ | 26% | 0.018 |

**Table 2: Characteristics of Included Studies**

| Author (Year) | Study Design | Sample Size (Carvedilol/Control) | Follow-up Duration | Outcomes Measured |
|---|---|---|---|---|
| Zhang et al. (2017) | RCT | 120 / 140 | 12 months | CV mortality, all-cause mortality |
| Ahmed et al. (2015) | Cohort | 210 / 220 | 24 months | All-cause mortality, HF hospitalization |
| Yamamoto et al. (2019) | RCT | 96 / 104 | 8 months | CV mortality, adverse events |
| Lee et al. (2020) | Cohort | 160 / 190 | 20 months | CV events, arrhythmia |
| Gupta et al. (2022) | RCT | 90 / 100 | 28 months | All-cause mortality, CV hospitalization |
| others (4 studies) | Mixed | 368 / 396 | 4–40 months | Mixed mortality a4d event endpoints |

## Discussion

This meta-analysis arranges data from 9 studies enclose over two thousand hemodialysis patients and demonstrates that carvedilol use confers a remarkable and clinically frequent reduction in both cardiovascular and all-cause mortality [10]. The 33% relative risk reduction in cardiovascular deaths mirrors the magnitude of benefit observed in indicator carvedilol trials for systolic heart failure, propose that carvedilol's pleiotropic effects remain robust even in the uremic milieu. Mechanistically, carvedilol's simultaneous $\beta_1$, $\beta_2$, and $\alpha_1$ blockade may expose the overstated sympathetic activation typical of dialysis sessions, thereby limiting arhythmogenic potential and intra-dialytic myocardial stunning [11]. Its anti-oxidative properties further counteract the oxidative bursts generated by dialyzer bio-incompatibility and chronic inflammation, while afterload reduction may ameliorate pressure overload–induced left-ventricular hypertrophy a key role of sudden cardiac death in this group [12]. Comparative effectiveness data also favor carvedilol over cardio-selective agents. In sub-group analyses where atenolol or metoprolol served as active comparators, carvedilol consistently trended toward superior survival, supporting the hypothesis that broader autonomic modulation and vasodilator effects are advantageous in

ESKD [13]. Majorly, pooled analyses did not reveal an excess of adverse events includes severe bradycardia or symptomatic hypotension, a common concern among nephrologists. Several included trials reported modest but acceptable intradialytic blood pressure reductions without increased session interruptions, indicating that careful dose titration can preserve hemodynamic stability [14]. In spite of these motivated findings, several limitations warrant cautious interpretation. First, heterogeneity in carvedilol dosing (ranging from 6.26 mg to 25 mg twice daily) and treatment duration may have introduced variability in effect size. Second, observational studies may have adjusted for multiple confounders remain allowing to residual bias, particularly confounding by indication, wherein sicker patients might preferentially receive carvedilol. Our sensitivity analyses, however, showed preservation of mortality rate may benefit when restricted to RCTs, lending credibility to the primary results [15]. Third, most trials excluded patients with baseline systolic blood pressure < 92 mm Hg, potentially limiting generalizability to the most hemodynamically fragile individuals. Finally, co-administration of renin-angiotensin system inhibitors, mineralocorticoid antagonists, and dialysis prescription variables were imbalance reported, precluding exploration of synergistic or antagonistic interactions. Clinically, these results support a paradigm shift toward preferential use of carvedilol in hemodialysis patients at high cardiovascular risk, similarly those with heart-failure phenotypes and repetitive intradialytic hypertensive surges [16]. Implementation should be guided by individualized assessment, starting with low doses post-dialysis and gradual up-titration while monitoring inter-dialytic blood pressure and heart rate. Future research should focus on large, multicenter RCTs with standardized carvedilol protocols, stratification by heart-failure subtype and arrhythmic burden, and exploration of biomarkers such as Troponin-T, NT-proBNP, and oxidative stress indices to elucidate mechanistic pathways [17]. Additionally, head-to-head trials comparing carvedilol with nebivolol or biso-prolol—agents with emerging renal data could refine β-blocker selection algorithms. In conclusion, while residual uncertainties persist, the accumulated evidence positions carvedilol as a promising cornerstone therapy for initiating the over-sized cardiovascular risk faced by patient's dependent on hemodialysis.

## Conclusion

This systematic study and meta-analysis support the use of carvedilol as an efficacy cardio-vascular protective agent in patients go through hemodialysis. The drug frequently reduces the risks of cardiovascular and all-cause mortality rate, as well as heart failure-related hospitalizations. Given the high cardio-vascular burden in this population, carvedilol may be a valuable inclusion to standard therapy, pending individualized assessment. Moreover, large-scale, multicenter RCTs with standardized dosing protocols and longer follow-up durations are warranted to confirm these benefits and better define patient selection criteria for balanced carvedilol use in the hemodialysis setting.

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