Review

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

Zhouke Tan,[1] Guibao Ke,[2,3] Junlin Huang,[4] Die Yang,[5] Mingjing Pi,[6] Li Li,[6] Xiaolin Liu,[7] Shaohua Tao,[8] Lvlin Chen,[8] Guobiao Liang,[9] Shuangxin Liu[2,3]

[1]Department of Nephrology, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou, China
[2]The Second School of Clinical Medicine, Southern Medical University, Guangzhou, Guangdong, China
[3]Department of Nephrology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China
[4]Department of Cardiology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China
[5]Department of Nephrology, Zunyi First People's Hospital, Zunyi, Guizhou, China
[6]Nanfang Hospital, Southern Medical University First School of Clinical Medicine, Guangzhou, Guangdong, China
[7]Department of Internal Medicine, The People's Hospital of Jiuzhaigou County, Jiuzhaogou, Sichuan, China
[8]Department of Intensive Care Medicine, Affiliated Hospital/ Clinical Medical College of Chengdu University, Chengdu, Sichuan, China
[9]Kidney Transplantation Center, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou, China
*Zhouke Tan, Guibao Ke, and Junlin Huang contributed equally to this work as first authors.

Carvedilol, the third generation of vasodilators; serves as the blocker of non-selective beta-adrenergic receptor and alpha1 adrenergic receptor. It could protect the cardiovascular system of patients receiving dialysis treatment. However, current clinical trials discussing the therapeutic benefit of carvedilol on patients receiving dialysis treatment remain inconsistent. Consequently, we decided to perform a meta-analysis to evaluate the clinical efficacy of carvedilol on patients receiving dialysis treatment.

A search was conducted using EMBASE, Pubmed, Cochrane Central Register of Controlled Trials, Wanfang database, Chinese National Knowledge Infrastructure (CNKI), and VIP information database up to February 2020. We research publications (include English and Chinese language) that discuss the effects of carvedilol on cardiovascular events, all-cause mortality, hospitalizations or left ventricular ejection fraction (LVEF) in dialysis population.

Our analysis included 4 randomized control trials and 2 observational studies. We discussed the therapeutical effects of carvedilol on all-cause mortality, cardiovascular events, hospitalizations, and LVEF of patients receiving dialysis treatment. Totally, this analysis reported 2998 hemodialysis (HD) patients. We found a significant association between carvedilol and reduced incidence of all-cause mortality, cardiovascular events and hospitalizations in HD patients. In addition, carvedilol significantly improves LVEF (n = 241; WMD = 6.95; 95% CI, 0.54 to 13.36; I^2 = 90%) in HD population.

Our systematic review and meta-analysis demonstrates that carvedilol is associated with a reduced incidence of cardiovascular events, all-cause mortality and hospitalizations in patients on HD. Besides; carvedilol significantly improves LVEF in HD population. Nevertheless, high-quality and well-powered evidence is still needed, so as to further confirm the impacts of carvedilol on HD patients.

IJKD 2020;14:256-66
www.ijkd.org

Keywords. carvedilol, cardiovascular events, mortality, hemodialysis

INTRODUCTION

Cardiovascular events is the major killer of Hemodialysis (HD) patients because of the following reasons.[1-3] First, approximately 80% of HD patients have one or more types of cardiac diseases,[4] which increases the possibility of cardiovascular events.

The mortality rate of chronic kidney disease (CKD) patients receiving dialysis is 6.1 to 7.8 times higher than the general population. Second, intermittent HD sessions expose patients to a high variability in hemodynamics, heart rate and electrolytes, which also increase the risk of cardiovascular events and mortality. Third, over activated sympathetic nervous system in HD patients can trigger cardiovascular events.[5-7] Finally, due to the lack of evidence-based drug therapy strategies and the complex pathophysiology in dialysis patients, cardiovascular events remains a big challenge to improve the survival rate of patients receiving dialysis.[8] Carvedilol, the blocker of non-selective beta-adrenergic receptor and alpha1 adrenergic receptor; offers multiple favorable effects such as antioxidant, antiapoptotic, and antiarrhythmic actions.[9-11] Thus, it may theoretically play a unique cardiovascular protective role in the patients receiving dialysis. However, only a clinical trial demonstrated that carvedilol improved survival rate of chronic dialysis patients with severe heart failure,[12] while other studies failed to demonstrate that carvedilol could help improve the survival rate[13,14] in the dialysis population. Considering the fact that the effect of carvedilol on dialysis patients still remains controversial, we thus aimed to perform a meta-analysis to evaluate the effects of carvedilol on patients requiring dialysis.

MATERIALS AND METHODS

We perform the systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Ethical approval is not required because this meta-analysis does not directly involve any patient.

Data Sources and Search Strategy

A search was conducted using EMBASE, Pubmed, Cochrane Central Register of Controlled Trials, Wanfang database, Chinese National Knowledge Infrastructure (CNKI), and VIP information database up to February 2020. We research publications (include English and Chinese language) that discuss the effects of carvedilol on cardiovascular events, all-cause mortality, hospitalizations or left ventricular ejection fraction (LVEF) in dialysis population. The search strategy comprised a combination of free text terms and MeSH terms, primarily including: "Carvedilol", "Hemodialysis", "Hemodialyses", "Dialysis", and "Renal Replacement Therapy". We also reviewed the reference lists in order to search additional relevant studies.

Inclusion and Exclusion Criteria

Inclusion criteria was considered: a) participants: adult HD patients, b) study design: randomized controlled trial and observational studies, c) outcomes: cardiovascular events, all-cause mortality, and hospitalizations, d) intervention: the intervention group received standard care + carvedilol treatment, while the comparison group received standard care + placebo therapy or only standard care.

Exclusion criteria was considered: abstracts, reviews, duplicate publications, editorials, comments, case reports, publications without available data, and cell or animal experiments.

Data Extraction and Study Quality Assessment

Data from the included studies were extracted and recorded independently by two authors (D.Y. and J.H.) and disagreements were resolved by consensus. The following information recorded in each included study were extracted for both RCTs and observational studies: first author, year of publication, study design, dosage of carvedilol, sample size, follow-up, cardiovascular events, all-cause mortality, hospitalizations, mean and SD of LVEF (if the LVEF data was presented as mean and SE, it was converted to mean and SD). For RCTs, two reviewers (L.L. and M.P.) evaluated risk of bias of studies with the Cochrane collaboration risk of bias (ROB) tool.[15] For observational studies, the Newcastle-Ottawa Scale[16] was used to assess the quality of our included studies by the reviewers (L.L. and M.P.). Conflicts were resolved by the third reviewer (G.K.).

Statistical Analysis

We used the risk ratio (RR) and weighted mean difference (WMD) to compare dichotomous and continuous variables respectively. All results were reported with a 95% confidence intervals (CIs). Heterogeneity among studies was assessed using the I^2 statistics ($I^2 > 50\%$ suggested substantial heterogeneity). We used fixed effects or random effects model because it takes into account the heterogeneity across studies. Pre-stratified subgroup

analysis was performed to investigate possible sources of heterogeneity, including study design. The presence of publication bias was also evaluated with Egger's tests and funnel plots. If the all-causes mortality were present merely in figures, two authors (L.L. and G.K.) would use Engauge Digitizer 10.8 to collect data from the statistical graphs independently. Then, the mean values of all-cause mortality would be used to perform meta-analysis.[17] All analyses were performed using RevMan 5.3 and Stata 12.0. We considered $P < .05$ as statistically significant.

RESULTS

Search Results

In total, our comprehensive search yielded 248 articles. First, 36 duplicate articles were excluded and 212 articles were remained for screening. Then, we excluded 167 of the 212 articles after examining the title and abstract in more detail. We scrutinized the full texts of the remaining 45 studies, of which 39 were excluded, due to a lack of necessary data related to our study. Eventually, after a careful selection based on our above-mentioned inclusion criteria, 6 studies (Figure 1) with a total of 2998 participants were included in this meta-analysis (4 RCTs[7,12,14,18] and 2 observational studies[13,19]).

Study Characteristics

The main characteristics of the 6 studies included are shown in Table 1 and 2. Patients in these 6 studies had a long-term HD history. The intervention groups received standard care + carvedilol treatment, while the control groups received standard care + placebo therapy or only standard care. All LVEF measurements were estimated by echocardiogram. The author's judgments over the risk of bias for each included study were shown in Supplementary Table 1 and 2. Four RCTs and 2 observational

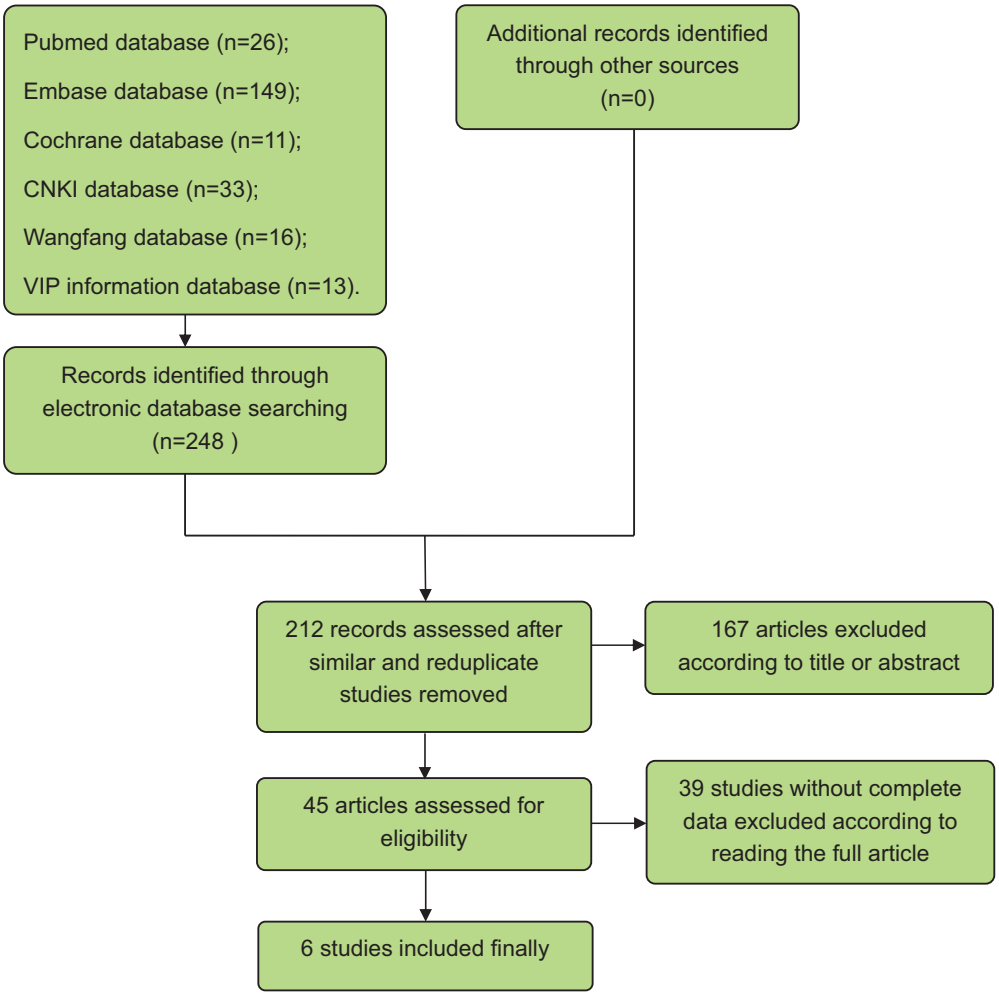


Figure 1. It shows flow diagram illustrating the selection of studies for this meta-analysis.

Table 1. Characteristics of Included Studies

Study	Center	Study Design	Age Carvedilol/Placebo	N Carvedilol/ Placebo	Interventions Carvedilol / Placebo		F/U (m)	Outcomes reported relevant to this meta-analysis
Cice et al, 2003	Italy	RCT	55.1 ± 7.6	58/56	1) Received 25mg bid Carvedilol; 2) Dialyzed four times a week; 3) Digitalis, ACEI, angiotensin II receptor antagonists, and nitrates.	1) Dialyzed four times a week; 2) Digitalis, ACEI, angiotensin II receptor antagonists, and nitrates.	24	All-cause mortality, Cardiovascular events, Hospitalizations, LVEF
Kojima et al, 2007	Japan	RCT	62.5 ± 7.16	10/10	1) Received 2.5 mg carvedilol a day. Dose was doubled every week until reaching 10 mg/d; 2) Conventional therapy; 3) Dialyzed 3 times weekly	1) Conventional therapy; 2) Dialyzed 3 times weekly .	3	All-cause mortality, Cardiovascular events, Hospitalizations, LVEF
Tang et al, 2008	China	RCT	38 ± 9	18/17	1) Received 10mg carvedilol bid; 2) Dialyzed 2-3 times weekly; 3) ACEI, angiotensin II receptor antagonists, nifedipine, iron agent, calcium agent, vitamin D3, erythropoietin.	1) Received 10 mg oryzanol bid; 2) Dialyzed 2-3 times weekly; 3) ACEI, angiotensin II receptor antagonists, nifedipine, iron agent, calcium agent, vitamin D3, erythropoietin.	2	All-cause mortality, Cardiovascular events, LVEF
Roberts et al, 2016	Australia	RCT	56.1 ± 10.3/61.4 ± 13.0	26/23	1) Receive carvedilol from 6.25mg twice daily to 25mg twice daily or to the maximum tolerated dose; 2) Standard treatment without carvedilol (detail not mentioned); 3) Dialyzed regularly.	1) Standard treatment without carvedilol (detail not mentioned); 2) Dialyzed regularly.	12	All-cause mortality, Cardiovascular events, Hospitalizations
Ma et al, 2018	China	Observational study	65.42 ± 9.83/63.66 ± 8.42	14/58	1) Received 5mg carvedilol bid. Dose reached 10 mg bid in 1-2 weeks; 2) CCB, ACEI, angiotensin II receptor antagonists, and nitrates; 3) Dialyzed regularly (more than 10h a week).	1) CCB, ACEI, angiotensin II receptor antagonists, and nitrates; 2) Dialyzed regularly (more than 10h a week).	43	All-cause mortality Cardiovascular events LVEF
Tang et al, 2016	China	Observational study	65.6 ± 11.5	1008/1700	1) Received 16.4mg carvedilol a day; 2) Standard treatment (detail not mentioned); 3) Dialyzed regularly.	1) Standard treatment (detail not mentioned); 2) Dialyzed regularly.	60	All-cause mortality

Data shown as mean [± SD]. N, number; F/U, follow-up; m, months; RCT, randomized controlled trial; LVEF, left ventricular ejection fraction; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor.

Table 2. All-cause Mortality, Cardiovascular Events, Hospitalizations, and LVEF in Studies Using Carvedilol

Study	All-cause Mortality		Cardiovascular Events		Hospitalizations		LVEF	
	Carvedilol	Placebo	Carvedilol	Placebo	Carvedilol	Placebo	Carvedilol	Placebo
Cice et al, 2003	30 (52%)	41 (73%)	17 (29%)	39 (70%)	20 (34%)	33 (59%)	37 [10]	24 [10]
Kojima et al, 2007	0	0	0	0	0	0	63.5 [5.4]	66.4 [5.1]
Tang et al, 2008	0	0	2 (11%)	1 (6%)	Unclear	Unclear	46.8 [5.4]	38.8 [5.3]
Roberts et al, 2016	1 (4%)	0	1 (4%)	3 (13%)	14 (54%)	14 (61%)	Unclear	Unclear
Ma et al, 2018	5 (36%)	19 (36%)	3 (21%)	10 (17%)	Unclear	Unclear	68.6 [8.0]	59.2 [9.7]
Tang et al, 2016	555 (55%)	1190 (70%)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Data shown as mean [± SD] or absolute (percentage). LVEF, left ventricular ejection fraction.

Supplementary Table 1. Risk of bias assessment quality of included RCTs

Study	Adequate random sequence generation	Allocation concealment	Blinding of participants and personnel	Adequate assessment of each outcome	Selective outcome reporting avoided	Free of Other Bias
Cice 2003	Yes	Unclear	Unclear	Yes	Yes	Yes
Kojima 2007	Yes	Unclear	Unclear	Yes	Yes	Yes
Roberts 2016	Yes	Unclear	Unclear	Yes	Yes	Yes
Tang 2008	Yes	Unclear	Unclear	Yes	Yes	Yes

Note: Risk of bias was assessed with use of the Cochrane risk-of-bias tool. The overall risk of bias of a study was considered "high" if more than 1 item was rated as "high risk" or if fewer than 2 items were rated as "low risk"; The overall risk of bias of a study was considered "moderate" if 2 or 3 items were rated as "low risk"; The overall risk of bias of a study was considered "low" if more than 4 items were rated as "low risk".

Supplementary Table 2. Risk of Bias in Observational Studies Using Newcastle-Ottawa Scale

Study	Selection				Comparability	Outcome			Total score
	Exposed cohort	Nonexposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequate follow-up	
MA 2018	*	*	*	-	**	*	*	*	8
Tang 2016	*	*	*	*	**	*	*	*	9

Note: A higher overall score corresponds to a lower risk of bias, a study awarded with ≥ 5 stars was defined as a high-quality study.

studies were at low risk.

Association of Carvedilol Therapy with All-cause Mortality

In the pooled analysis of 6 studies (n = 2998), compared with the patients with no carvedilol treatment, carvedilol reduced all-cause mortality in HD patients (RR = 0.79, 95% CI: 0.74 to 0.84; $P < .01$ in the fixed effects model, Figure 2a). There was no heterogeneity among studies ($P > .05$, $I^2 = 0\%$). Besides, subgroup analysis also showed that the results of 4 RCTs and 2 observational studies were consistent.

Association of Carvedilol Therapy with Cardiovascular Events

Meta-analysis of 5 studies (n = 290, 4 RCTs and 1 observational study) showed a significant decline in cardiovascular events of patients who received carvedilol treatment (RR = 0.51, 95% CI: 0.35 to 0.75; $P < .01$ in the fixed effects model, Figure 2b). Heterogeneity was detected among studies ($P > .05$, $I^2 = 34\%$). Since we only use one observational study, we did not perform subgroup-analysis.

Association of Carvedilol Therapy with Hospitalizations

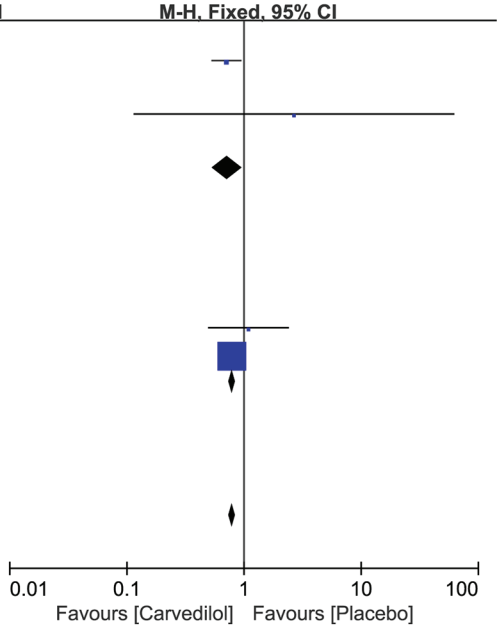
Meta-analysis of 3 RCTs (n = 183) showed a noticeable reduction in hospitalizations with carvedilol treatment (RR = 0.68, 95% CI: 0.49 to 0.93; $P < .05$ in the fixed effects model, Figure 2c). Heterogeneity was found among studies ($p = 0.2$, $I^2 = 39\%$).

Association of Carvedilol Therapy with LVEF Change

Meta-analysis of 4 studies (n = 241, 3 RCTs, 1 observational study) showed carvedilol significantly improves LVEF (WMD = 6.95, 95% CI: 0.54 to 13.36; $P < .05$ in the random effects model, Figure 2d) in HD patients. However, heterogeneity was detected among studies ($P < .01$, $I^2 = 90\%$). Similarly, since

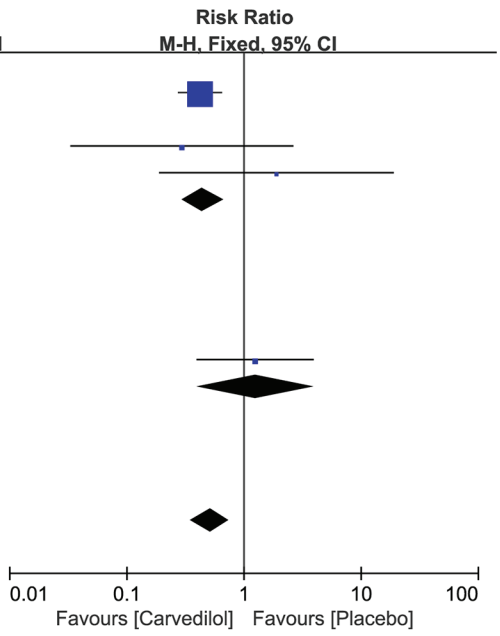
(a)

Study or Subgroup	Carvedilol Events	Carvedilol Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 RCT						
Cice 2003	30	58	41	56	4.5%	0.71 [0.53, 0.95]
Kojima 2007	0	10	0	10		Not estimable
Roberts 2016	1	26	0	23	0.1%	2.67 [0.11, 62.42]
Tang 2008	0	18	0	17		Not estimable
Subtotal (95% CI)		**112**		**106**	**4.5%**	**0.73 [0.54, 0.98]**
Total events	31		41			
Heterogeneity: Chi² = 0.70, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 2.07 (P = 0.04)						
1.1.2 Observational study						
Ma 2018	5	14	19	58	0.8%	1.09 [0.49, 2.41]
Tang 2016	555	1008	1190	1700	94.7%	0.79 [0.74, 0.84]
Subtotal (95% CI)		**1022**		**1758**	**95.5%**	**0.79 [0.74, 0.84]**
Total events	560		1209			
Heterogeneity: Chi² = 0.65, df = 1 (P = 0.42); I² = 0%						
Test for overall effect: Z = 7.29 (P < 0.00001)						
Total (95% CI)		**1134**		**1864**	**100.0%**	**0.79 [0.74, 0.84]**
Total events	591		1250			
Heterogeneity: Chi² = 1.74, df = 3 (P = 0.63); I² = 0%						
Test for overall effect: Z = 7.56 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.24, df = 1 (P = 0.62), I² = 0%						



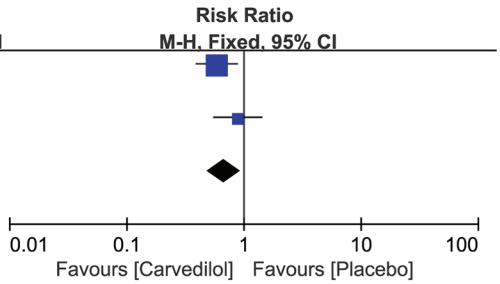
(b)

Study or Subgroup	Carvedilol Events	Carvedilol Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 RCT						
Cice 2003	17	58	39	56	83.0%	0.42 [0.27, 0.65]
Kojima 2007	0	10	0	10		Not estimable
Roberts 2016	1	26	3	23	6.7%	0.29 [0.03, 2.64]
Tang 2008	2	18	1	17	2.2%	1.89 [0.19, 18.97]
Subtotal (95% CI)		**112**		**106**	**91.9%**	**0.45 [0.29, 0.68]**
Total events	20		43			
Heterogeneity: Chi² = 1.71, df = 2 (P = 0.43); I² = 0%						
Test for overall effect: Z = 3.78 (P = 0.0002)						
1.2.2 Observational study						
Ma 2018	3	14	10	58	8.1%	1.24 [0.39, 3.93]
Subtotal (95% CI)		**14**		**58**	**8.1%**	**1.24 [0.39, 3.93]**
Total events	3		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.37 (P = 0.71)						
Total (95% CI)		**126**		**164**	**100.0%**	**0.51 [0.35, 0.75]**
Total events	23		53			
Heterogeneity: Chi² = 4.53, df = 3 (P = 0.21); I² = 34%						
Test for overall effect: Z = 3.39 (P = 0.0007)						
Test for subgroup differences: Chi² = 2.69, df = 1 (P = 0.10), I² = 62.8%						



(c)

Study or Subgroup	Carvedilol Events	Carvedilol Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cice 2003	20	58	33	56	69.3%	0.59 [0.39, 0.89]
Kojima 2007	0	10	0	10		Not estimable
Roberts 2017	14	26	14	23	30.7%	0.88 [0.55, 1.43]
Total (95% CI)		**94**		**89**	**100.0%**	**0.68 [0.49, 0.93]**
Total events	34		47			
Heterogeneity: Chi² = 1.64, df = 1 (P = 0.20); I² = 39%						
Test for overall effect: Z = 2.41 (P = 0.02)						



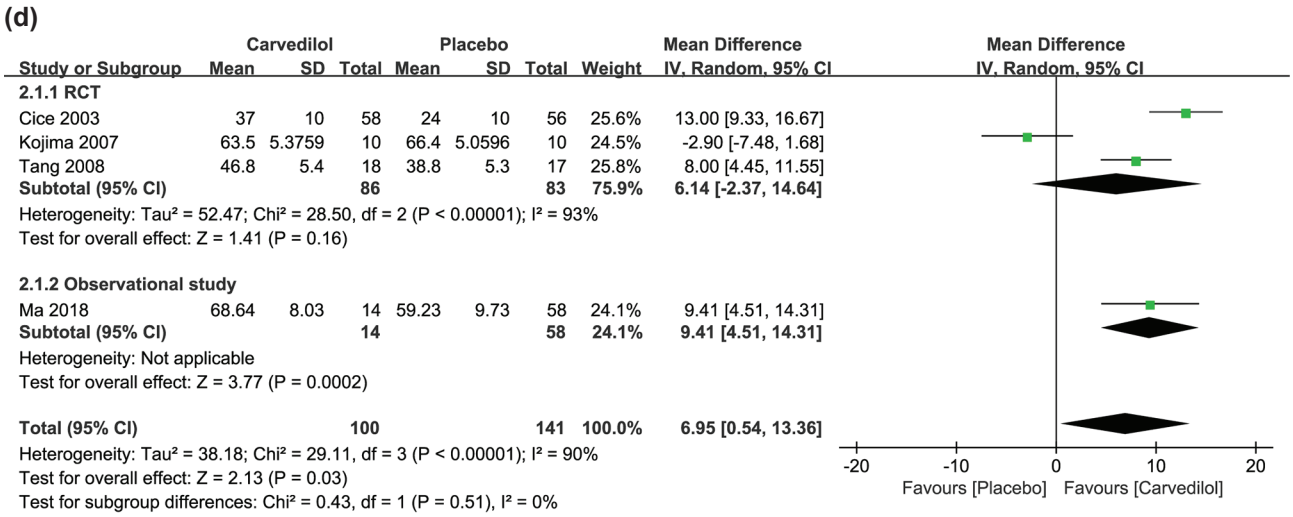


Figure 2. It demonstrates forest plots for all-cause mortality, cardiovascular events, hospitalizations, and LVEF outcomes; respectively: carvedilol associated with reduced all-cause mortality (a), cardiovascular events (b), and hospitalizations (c) in HD patients. Furthermore, carvedilol significantly improves LVEF (d) in dialysis population (LVEF, left ventricular ejection fraction; HD, hemodialysis).

we only use one observational study, we did not perform subgroup-analysis.

Publication Bias

The potential publication bias was detected by Egger's test and funnel plots (Figure 3a and 3b). We found no publication bias for carvedilol on all-cause mortality (Egger's test, $P > .05$) and cardiovascular events (Egger's test, $P > .05$). Besides, apart from all-cause mortality and cardiovascular events, we do not draw the funnel plots for other parameters in this meta-analysis, due to the small size of these parameters in our included studies.

DISCUSSION

To the best of our knowledge, the present research is the first meta-analysis that evaluated the clinical efficacy of carvedilol on HD patients. Our analysis included 4 RCTs and 2 observational studies, reporting 2998 HD patients. First, Carvedilol was associated with a 49% reduction in cardiovascular events, a 21% reduction in all-cause mortality and a 32% reduction in hospitalizations in HD patients. Besides, carvedilol significantly improves LVEF in HD population. Our research outcome could help update the information over the unique role of carvedilol in protecting patients receiving HD.

Approximately 80% of HD patients have one or more types of cardiac disease.[4] Also, intermittent HD sessions (usually three times a week) expose patients to a high variability in hemodynamics, heart rate and electrolytes. What's more, overactivated sympathetic nervous system in HD patients further triggers off cardiovascular events.[5-7] Given the high incidence of cardiovascular events, HD patients may benefit from β-blockers therapy,[20,21] especially the carvedilol, which is widely used in patients with heart failure (HF),[22,23] chemotherapy-induced cardiotoxicity,[24] arterial stiffness,[25] left ventricular function dysfunction,[26] acute coronary syndrome,[27] and hypertension[28]. However, few high-quality and well-powered studies have evaluated cardiovascular therapy's effects on HD patients. Most studies have excluded patients with advanced CKD due to the risk of side effects, such as hyperkalemia, hypotension, fluid overload, anemia and so forth.[29-32] Wali *et al.* reported a meta-analysis on RCTs addressing the efficacy and safety of carvedilol in HF treatment on CKD patients.[33] They suggested that treatment with carvedilol in CKD patients reduced the relative risks for all-cause, cardiovascular, and HF mortality in HF patients with CKD.[33] However, their finding did not determine whether carvedilol therapy could benefit advanced CKD or HD patients. Our meta-analysis filled such a gap by including data of 2998 HD patients and extracted from six studies. The pooled result suggested that carvedilol might play a unique cardiovascular protective role in the patients receiving dialysis.

First, our analysis focused on the association of carvedilol therapy with mortality rate, in that

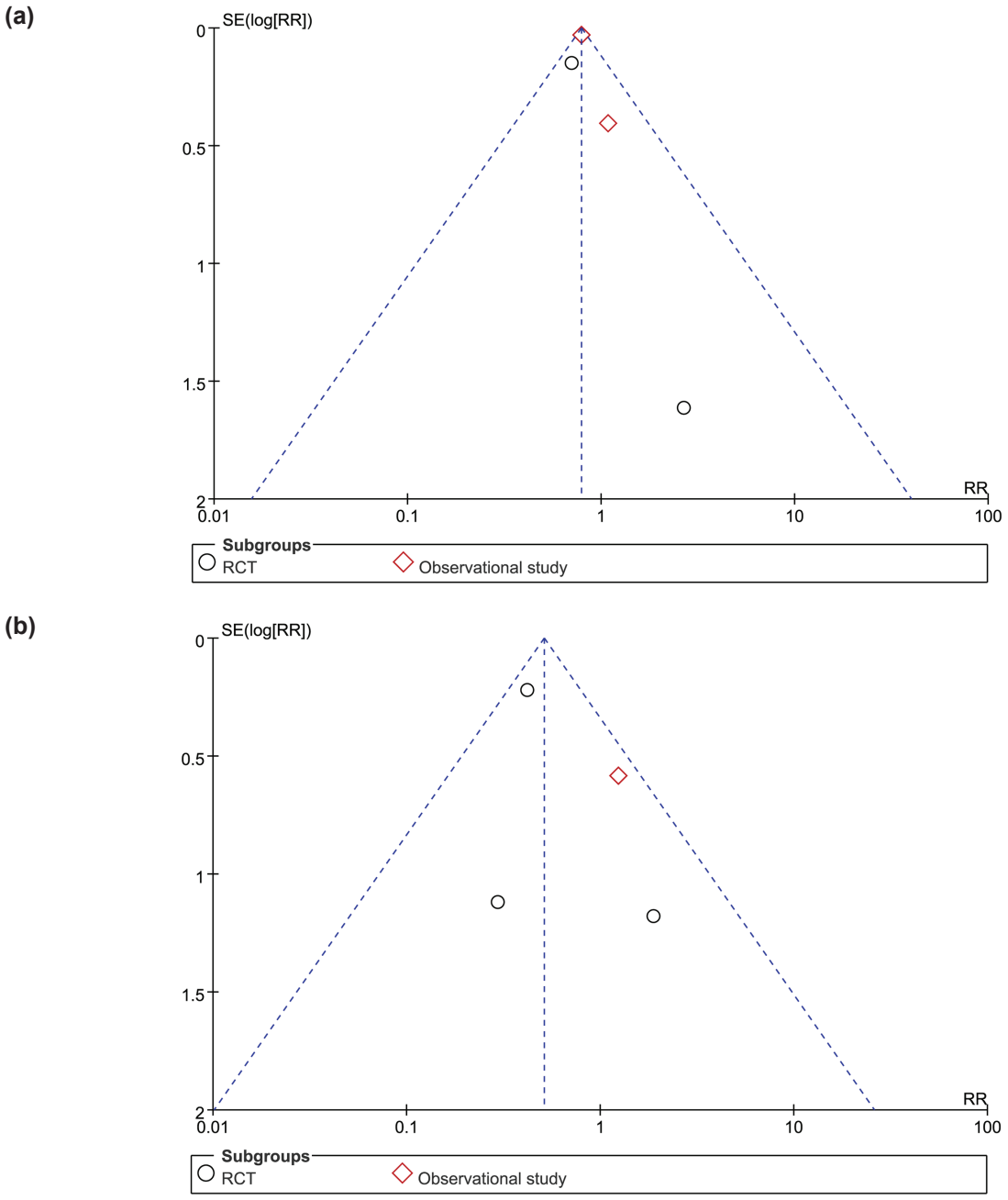


Figure 3. It shows publication bias assessment by funnel plot for all-cause mortality (a) and cardiovascular events(b).

mortality rate is one important clinical index, and mortality rates are high for HD patients. For HD patients initiating their renal replacement therapy within 3 years, the mortality rate almost reached 50%.[34] In addition, we also discussed the association of carvedilol therapy with Cardiovascular events, because Cardiovascular events is the leading killer of HD patients.[2,3,35] Moreover, we continued to analyze the association between carvedilol therapy and LVEF, as LVEF is the most frequently used parameter to define left ventricular systolic (dys-) function[36] and is strongly associated with the increased mortality rate in CKD patients.[37,38] Volume overload, chronic pressure and non-hemodynamic, such as oxidative stress and abnormal renin-angiotensin-aldosterone system (RAAS) activation, lead to the development of left ventricular systolic and diastolic dysfunction[39] of CKD patients. Our meta-analysis showed that carvedilol significantly improves LVEF in HD population, and thus was

consistent with the findings which showed that carvedilol was associated with a 49% reduction in cardiovascular events, a 21% reduction in all-cause mortality, and a 32% reduction in hospitalization of HD patients.

In sum, carvedilol is associated with a reduced possibility of cardiovascular events, all-cause mortality and hospitalizations in patients receiving HD. Besides; carvedilol significantly improves LVEF in dialysis population. Carvedilol can block sympathetic neural and RAAS activation, antioxidant, antiapoptotic, antiarrhythmic actions and so forth. Hence, it can provide a potential protective mechanism for HD patients.

Limitations of this systematic review and meta-analysis are as follows. Firstly, we were unable to minimize the heterogeneity's impacts through stratified analyses or subgroup, especially in LVEF comparisons, because of the limited number of included studies. The random effects model might reduce the effect of heterogeneity, but does not minimize it. Secondly, the included RCTs have a relatively small sample size and a short-term follow-up, which may lack strong persuasiveness. Thirdly, because of the limited number of studies (such as metoprolol, nebivolol, and bisoprolol), we could just quantitatively assess the effects of carvedilol. Hence, further clinical trials are needed to test the effects of other beta-blockers. Fourthly, different doses, different lengths of intervention time in each study might cause a potential bias. Also, different experiments had different designs, and the condition of patients also differed. Moreover, the small number of included studies could afford modest ability to detect the presence of publication bias.[40] Thus, high-quality and well-powered evidence is needed for future study.

CONCLUSION

The results of this meta-analysis support the argument that treatment with carvedilol can reduce rates of cardiovascular events, all-cause mortality and hospitalization in HD patients. Besides, carvedilol significantly improves LVEF in HD population. Nevertheless, high-quality and well-powered evidence is still needed to confirm the therapeutic impacts of carvedilol on HD patients.

ACKNOWLEDGEMENTS

This study was supported by Sichuan Provincial Health and Family Planning Commission (No. 18PJ446), Sichuan Provincial Science and Technology Foundation (No. 18ZDYF0922), the Education Department Fund Project of Guizhou Province, Grant No.KY (2017) 045, Guangzhou City Science and Technology Project (No. 201707010009), the National Natural Science Foundation (No. 81670656, No. 81870508), Guangdong Province High-level Hospital Construction Project (No. DFJH201901), and Medical Scientific Research Foundation of Guangdong Province People's Hospital.

DISCLOSURE STATEMENT

The authors declare no conflicts of interest.

REFERENCES

1. Eknoyan G, Beck GJ, Cheung AK, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med. 2002; 347:2010-9.
2. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis. 1998; 32:S112-9.
3. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2017 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis. 2018; 71:A7.
4. Cheung AK, Sarnak MJ, Yan G, et al. Cardiac diseases in maintenance hemodialysis patients: results of the HEMO Study. Kidney Int. 2004; 65:2380-9.
5. Daugirdas JT. Pathophysiology of dialysis hypotension: an update. Am J Kidney Dis. 2001; 38:S11-7.
6. Converse RL, Jacobsen TN, Toto RD, et al. Sympathetic overactivity in patients with chronic renal failure. N Engl J Med. 1992; 327:1912-8.
7. Roberts MA, Pilmore HL, Ierino FL, et al. The ¦Â-Blocker to Lower Cardiovascular Dialysis Events (BLOCADE) Feasibility Study: A Randomized Contr olled Trial. Am J Kidney Dis. 2016; 67:902-11.
8. Weir MA, Herzog CA. Beta blockers in patients with end-stage renal disease-Evidence-based recommendations. Semin Dial. 2018; 31:219-25.
9. Cheng J, Kamiya K, Kodama I. Carvedilol: molecular and cellular basis for its multifaceted therapeutic potential. Cardiovasc Drug Rev. 2001; 19:152-71.
10. Spallarossa P, Garibaldi S, Altieri P, et al. Carvedilol prevents doxorubicin-induced free radical release and apoptosis in cardiomyocytes in vitro. J Mol Cell Cardiol. 2004; 37:837-46.
11. DiNicolantonio JJ, Beavers CJ, Menezes AR, et al. Meta-analysis comparing carvedilol versus metoprolol for the prevention of postoperative atrial fibrillation following coronary artery bypass grafting. Am J Cardiol. 2014; 113:565-9.
12. Cice G, Ferrara L, D'Andrea A, et al. Carvedilol increases two-year survivalin dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. J

Am Coll Cardiol. 2003; 41:1438-44.

13. Ma JC, Du LB, Liang XL, Shi W, Liu SX. Effect of carvedilol on cardiac function of hemodialysis patients with diabetic nephropathy. J Nephrol Dialy Transplant (China). 2018; 27:147-50.
14. Kojima M, Sato K, Kimura G, Ueda R, Dohi Y. Carvedilol reduces elevated B-type natriuretic peptide in dialyzed patients without heart failure: ca rdioprotective effect of the beta-blocker. J Cardiovasc Pharmacol. 2007; 49:191-6.
15. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011; 343:d5928.
16. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010; 25:603-5.
17. Shi X, Chen Q, Wang F. Mesenchymal stem cells for the treatment of ulcerative colitis: a systematic review and meta-analysis of experimental and clinical studies. Stem Cell Res Ther. 2019; 10:266.
18. Tang YW, Wang HM, Tang GM, Hu JH, Sun SH. Effect of blocking sympathetic activities with carvedilol on cardiac structure and heart function in maintained hemodialysis patients. Chongqing Medical Journal. 2008; 37:1791-4.
19. Tang C-H, Wang C-C, Chen T-H, Hong C-Y, Sue Y-M. Prognostic Benefits of Carvedilol, Bisoprolol, and Metoprolol Controlled Release/Extended Release in Hemodialysis Patients with Heart Failure: A 10-Year Cohort. J Am Heart Assoc. 2016; 5:e002584.
20. Jin J, Guo X, Yu Q. Effects of Beta-Blockers on Cardiovascular Events and Mortality in Dialysis Patients: A Systematic Review and Meta-Analysis. Blood purif. 2019; 48:51-9.
21. Assimon MM, Brookhart MA, Fine JP, Heiss G, Layton JB, Flythe JE. A Comparative Study of Carvedilol Versus Metoprolol Initiation and 1-Year Mortality Among Individuals Receiving Maintenance Hemodialysis. Am J Kidney Dis. 2018; 72:337-48.
22. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016; 18:891-975.
23. Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2016; 68:1476-88.
24. Huang S, Zhao Q, Yang Z-G, et al. Protective role of beta-blockers in chemotherapy-induced cardiotoxicity-a systematic review and meta-analysis of carvedilol. Heart Fail Rev. 2019; 24:325-33.
25. Shah NK, Smith SM, Nichols WW, et al. Carvedilol reduces aortic wave reflection and improves left ventricular/vascular coupling: a comparison with atenolol (CENTRAL Study). J Clin Hypertens (Greenwich). 2011; 13:917-24.
26. Li T, Yuan G, Ma C, Jin P, Zhou C, Li W. Clinical efficacy of carvedilol treatment for dilated cardiomyopathy: A meta-analysis of randomized controlled trials. Medicine. 2019; 98:e15403.
27. Ilardi F, Gargiulo G, Schiattarella GG, et al. Effects of Carvedilol Versus Metoprolol on Platelet Aggregation in Patients With Acute Coronary Syndrome: The PLATE-BLOCK Study. Am J Cardiol. 2018; 122:6-11.
28. Sorriento D, De Luca N, Trimarco B, Iaccarino G. The Antioxidant Therapy: New Insights in the Treatment of Hypertension. Front Physiol. 2018; 9:258.
29. Allon M. Evidence-based cardiology in hemodialysis patients. J Am Soc Nephrol. 2013; 24:1934-43.
30. Hahn L, Hahn M. Carvedilol-induced hyperkalemia in a patient with chronic kidney disease. J Pharm Pract. 2015; 28:107-11.
31. Nowicki M, Miszczak-Kuban J. Nonselective Beta-adrenergic blockade augments fasting hyperkalemia in hemodialysis patients. Nephron. 2002; 91:222-7.
32. Bi S-H, Linke L, Wu J, Cheng L-T, Wang T, Ahmad S. Effects of beta-blocker use on volume status in hemodialysis patients. Blood Purif. 2012; 33:311-6.
33. Wali RK, Iyengar M, Beck GJ, et al. Efficacy and safety of carvedilol in treatment of heart failure with chronic kidney disease: a meta-analysis of randomized trials. Circ Heart Fail. 2011; 4:18-26.
34. Collins AJ, Foley RN, Chavers B, et al. 'United States Renal Data System 2011 Annual Data Report: Atlas of chronic kidney disease & end-stage renal disease in the United States. Am J Kidney Dis. 2012; 59:A7.
35. Hensen LCR, Goossens K, Delgado V, Abou R, Rotmans JI, Jukema JW, Bax JJ. Prevalence of left ventricular systolic dysfunction in pre-dialysis and dialysis patients with preserved left ventricular ejection fraction. Eur J Heart Fail. 2018; 20:560-8.
36. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015; 16:233-70.
37. Payne J, Sharma S, De Leon D, et al. Association of echocardiographic abnormalities with mortality in men with non-dialysis-dependent chronic kidney disease. Nephrol Dial Transplant. 2012; 27:694-700.
38. Parfrey PS, Foley RN, Harnett JD, Kent GM, Murray DC, Barre PE. Outcome and risk factors for left ventricular disorders in chronic uraemia. Nephrol Dial Transplant. 1996; 11:1277-85.
39. Herzog CA, Asinger RW, Berger AK, et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2011; 80:572-86.
40. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015; 350:g7647.

Correspondence to:
Shuangxin Liu, MD
Department of Nephrology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, 106 Zhongshan No. 2 Road, Guangzhou, China
E-mail: 13543456446@163.com

Received January 2020
Revised March 2020
Accepted May 2020