

## Carvedilol as nephroprotective agent: a meta-analysis of randomized controlled trials

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### ABSTRACT

**Background:** Carvedilol is supposed to have nephroprotective effects owing to its additional antioxidant activity. We aimed to analyse the nephroprotective efficacy of carvedilol versus other active treatments and placebo using its effect on urine albumin to creatinine ratio (UACR).

**Methods:** Electronic database search in PUBMED, EMBASE, cochrane library was conducted using search terms “carvedilol” and “proteinuria”. Randomized or cross-over studies comparing effects of carvedilol versus other active treatment or placebo were included under analysis. Inverse variance method and both random and fixed effect models were used in the analysis. RevMan 5.3 software was used for statistical analysis.

**Results:** Total four studies (n) were eligible with 1036 (N) patients included in the analysis. Carvedilol failed to show significant effect on UACR when compared with all active treatments (standardised mean difference, SMD = -0.80 mg/g, 95% CI = -2.37, 0.76, n=5, N=1036) and placebo (mean difference, MD = -0.88 mg/g, 95% CI=-5.26, 3.51, n=2, N=75). It was superior to beta-1 blockers (SMD = -0.26 mg/g, 95% CI=-0.39, -0.13, n=2, N=963) and inferior to ACEIs/ARBs (MD = 7.45, 95% CI=0.29, 14.61, n=2, N=73).

**Conclusions:** There are low quality evidences to suggesting nephroprotective efficacy of carvedilol to be superior to beta-1 blockers in patients especially with diabetes as co-morbidity. Considering the drawbacks of our study, results need to be cautiously interpreted.

**Keywords:** Carvedilol, Nephroprotective, Antioxidant, UACR

### INTRODUCTION

Proteinuria or macro albuminuria is diagnosed when daily urine albumin excretion is >300 mg/d.<sup>1,2</sup> It is an indicator of the structural damage to the kidney and severity of proteinuria correlates with the severity of renal failure.<sup>1,2</sup> Among the various causes for renal failure leading to chronic kidney failure and proteinuria, hypertension and type-2 DM are two most common causes.<sup>1,2</sup> Whatever the cause of chronic kidney disease, eventually >85% of patients of end stage chronic kidney disease develop hypertension.<sup>1,2</sup> The best parameters to assess the severity of functional failure of the kidney are urine albumin to creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR).<sup>3</sup> UACR appears to be the better than eGFR as an indicator of clinical outcomes

in these patient.<sup>3</sup> Proteinuria is considered as one of the independent predictor of cardiovascular related events.<sup>4</sup> Hence, treating a patient of hypertension with chronic kidney failure requires additional nephroprotective action through reduction of proteinuria.<sup>4</sup> Unlike treating a case of hypertension without proteinuria or with micro albuminuria, in whom lowering of blood pressure to target level is sufficient to achieve nephroprotective action, treating a case of hypertension with proteinuria or macro albuminuria requires additional proteinuria reduction effects.<sup>4</sup> The amount of reduction in proteinuria of >30% of the initial values has shown to achieve nephroprotective action.<sup>4</sup>

Two classes of antihypertensive drugs with significant nephroprotective action are angiotensin converting

enzyme-inhibitors/angiotensin receptor blockers (ACE-Is/ARBs) and non-dihydropyridine calcium channel blockers (verapamil, diltiazem).<sup>4</sup> A new generation of dihydropyridines with L/N-type and L/T-type of calcium channel blocking action have shown some promising nephroprotective actions.<sup>5,6</sup> With regard to role of diuretics, non-selective and selective beta-1 blockers, evidences suggest lack of their nephroprotective efficacy.<sup>4</sup> In fact use of diuretics as monotherapy is supposed to be associated with worsening of proteinuria.<sup>4</sup> Still, this class of drugs are essential in most of these patients from the point of achieving target level blood pressure and prevention of other cardiovascular events.<sup>7</sup> Among the beta-blockers, carvedilol a third generation beta-blocker with antioxidant action has shown nephroprotective action in few studies.<sup>8-13</sup> However, this effect is not proved consistently in all studies. Hence, present study aims at analysing the nephroprotective effects of carvedilol on UACR and eGFR, apart from its effects on hemodynamic parameters.

## METHODS

### *Literature search methodology*

Two authors independently conducted electronic database search in PUBMED, Cochrane library and EMBASE for the randomized trials or cross-over trials using search terms “carvedilol” and “proteinuria.” Limits applied for the search in PUBMED were “randomized controlled studies”, and “humans” while the limits applied for search in EMBASE were “randomized controlled trial” “conference paper” “article” “article in press” “embase” and “humans”. No limits were applied in Cochrane library search. Search was limited to studies published up to 31<sup>st</sup> December 2015 with no language restriction applied.

### *Eligibility criteria*

Either crossover studies or randomized trials with head-to-head comparison of carvedilol with placebo or any active treatment in patients of either sex aged >18 years with primary hypertension and features of nephropathy indicated by micro or macro albuminuria were eligible for inclusion. Studies conducted on patients with complication like myocardial infarction or heart failure or those with incomplete data required for statistical analysis or those published as abstracts were considered under exclusion criteria.

### *Data extraction and synthesis*

Two authors independently extracted baseline demographic, clinical data and other required data in data extraction sheet. Final data was prepared after reaching consensus between the two authors with regard to any discrepancies in data extracted. UACR, eGFR and changes in systolic and diastolic blood pressure were extracted. The ‘mean change’ values of these parameters

were used for the statistical evaluation. Two of the four eligible studies published data on the ‘mean change’ values in above parameters.<sup>8-11</sup> The ‘Mean change’ values for two studies were calculated by using the ‘baseline’ and ‘study end point’ values.<sup>9-10</sup> Study by Saul et al., published UACR values as mg/mmol, was converted to mg/g by multiplying the mg/mmol values by 8.84.<sup>8</sup> For studies publishing 95% confidence interval values instead of standard deviation values, we calculated the standard deviation values by using the standard formula. Few of the data’s in study by Java et al., were published as log-transformed values of mean with standard error of mean.<sup>9</sup> Using the standard formula, we calculated the standard deviation from standard error of mean.

### *Outcome measures*

Primary outcome measure was changes in UACR and secondary outcome measures were the changes in eGFR, SBP, DBP observed at the end of study period.

### *Statistical methods*

Effects on outcome measures between two groups were assessed by calculating the mean difference (MD) values. When study by Java et al was included in analysis, we calculated standardised mean difference (SMD) values. Inverse variance method and both fixed and random effect models were used in analysis. Sensitivity analysis was conducted by comparing results of fixed effect model and random effects model. Heterogeneity between the studies was analyzed by using Cochrane Q test for heterogeneity and  $I^2$  test. A chi square test with P value <0.10 and  $I^2$  test value of >50% was considered as indicator of significant heterogeneity. Funnel plot method was used for assessment of publication bias. Statistical analysis was conducted by using RevMan software version 5.3.

### *Quality evaluation*

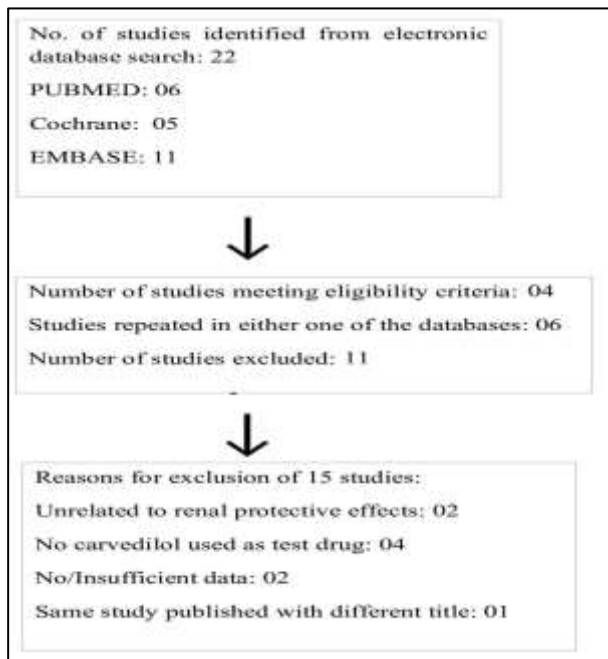
Un-blinded quality assessment of published data of eligible studies was done independently by two authors as described by Nancy et al.<sup>14</sup> Final scores for the individual studies were allotted after arriving at consensus between the authors.

## RESULTS

### *Data search results*

(Figure 1) shows the results of data search and the attrition diagram with number of studies excluded and reasons for exclusion. Excluded studies did not involve those articles published in language other than English. Four RCTs comparing carvedilol with placebo or other active treatment groups were eligible and included in the analysis. Study by Marchi et al which appeared to be eligible could not be included in the study because of our failure to get the full text of the article by any means.<sup>11</sup>

Study by Fassbinder et al., was excluded because of lack of required data.<sup>12</sup>



**Figure 1: Flow chart of literature search result and attrition diagram.**

### Characters of included studies

(Table 1 and 2) show the baseline demographic, clinical features and characteristics of individual studies included in the analysis. Differences in the baseline demographic and clinical features between the two comparator groups in all the four studies were statistically insignificant. Studies varied with regard to the etiology behind nephropathy wherein two studies were on patients with hypertension and type-2 DM, one study on hypertension and remaining one on renal transplant recipient's with hypertension as causes for nephropathy.

Two studies Saul et al., and Java et al included patients of micro albuminuria whereas remaining two studies included patients with macro albuminuria. Cross-over design of study by Tylicki et al might not have had significant intra-trial heterogeneity but perhaps would lead to significant inter-study heterogeneity considering inclusion of renal transplant recipients as subjects. Quality score achieved by two studies was than >80% and <75% in remaining two studies. Considering these significance variations in individual study characteristics, there is a possibility of significant inter-trial heterogeneity. There was evidence of significant publication bias with most of the effect size measures estimated by random effect model. The presence of significant inter-trial heterogeneity and publication bias indicate the quality of evidence of the effect size value results to be of low quality.

**Table 1: Characteristics and quality scores of individual studies.**

Study	Saul	Java	Tylicki	Bakris
No. of patients	N = 91	N =34	N =14	N=930
Study design and duration	Randomized double blind parallel group 9 months	Randomized ?open label parallel group 4 months	Randomized double blind cross-over 2 months	Randomized double blind parallel group
Centres and country	Single centre USA	Single centre USA	Single centre Poland	Multi centre USA
Disease	Hypertension	Hypertension type-2 DM	Hypertension renal transplant recipients	Hypertension type-2 DM
Intervention	C: 20-40mg/d, C: max 50mg/d, C:12.5-25mg/d, L: 10-20mg/d, M: max 100mg BD, Lo:50-100mg/d, C+L, Placebo, Placebo			C:12-50mg/d M:100-400mg/d
Other interventions	None, DHPs, N/A	ACEIs, Anti diabetics:		ACE-Is/ARBs, Thiazides, DHPs Hypolipidemics Anti-diabetics, TZD, Metformin, SUs, Insulin
Quality score	83.3%	73.3%	73.3%	88.2%

N/A : Not Available, C: Carvedilol, L: Lisinipril, M: Metoprolol, Lo:Losartan, DHPs: Dihydropyridines, ACE-Is: Angiotensine Converting Enzyme Inhibitors, TZD: Thiazolidiniones, SUs: Sulfonyl ureas,

**Table 2: Baseline demographic characteristics of included patients.**

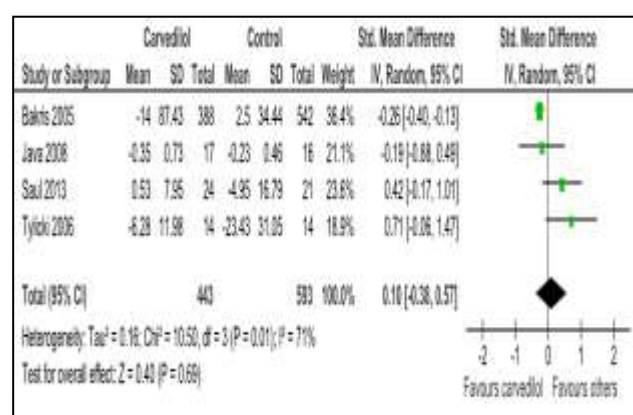
Factors	Age	M:F	BMI	UACR	SBP	DBP	TC	LDL-C	HDL-C	TGs
<b>Saul et al</b>										
C grp	53±10	17:7	28.8±4.7	0.66±0.13	138.1±1.7	89.9±1.4	193.1±46.7	122.7±37.2	47.0±13.6	116.9±42.2
L grp	53±10	16:5	29.0±4.7	1.70±0.82	140.5±2.3	90.3±1.3	195.4±37.2	121.6±33.3	49.3±11.4	121.9±38.5
C+L grp	52±13	17:6	28.8±6.0	0.52±0.12	139.5±2.2	91.2±2.3	187.8±32.9	110.3±32.5	53.4±20.1	121.0±76.8
P grp	51±13	15:8	28.8±4.2	1.10±1.16	136.0±2.2	89.9±1.5	191.2±46.7	117.7±31.0	49.3±10.7	121.0±54.5
<b>Java et al</b>										
C grp	52.5(33-70)	5:13	33.4±11.0	6.15#±1.15	N/A	N/A	179±12.8	103±11.6	40±2.6	N/A
M grp	53.5(30-70)	7:9	31.6±14.4	6.13#±1.18	N/A	N/A	189±10	116±8.0	44±4.2	N/A
<b>Tylici et al</b>										
C and Lo grps	45.36±3.06	9:5	25.38±1.06	51.05\$±25.6	N/A	N/A	N/A	N/A	N/A	N/A
<b>Bakris et al</b>										
C grp	60.8±9.2	241:147	33.6±5.9	N/A	149±11	87±8	N/A	N/A	N/A	N/A
M grp	53±10	295:247	33.7±6.0	N/A	148±11	87±8	N/A	N/A	N/A	N/A

All values are in mean±SD; N/A: Not Available; UACR:Urine Albumin-to-Creatinine Ratio, values in mg/g, \$: UACR values are in mmol/g, #: UACR values are in log-transformed 24h UACR (g/g). Values of plasma glucose are in mg/dl. Values of Total cholesterol (TC) and other lipid parameters are in mg/dl. BMI: Body Mass Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure. C: Carvedilol, L: Lisinipril, M: Metoprolol, Lo:Losartan, P:Placebo.

**Table 3: Effect of carvedilol on UACR compared various active treatment groups and placebo.**

Comparator groups (Studies included and 'N')	Random effect model	Fixed effect	$\chi^2$	I <sup>2</sup>
Carvedilol versus Active treatment (All four studies, N=1036)	0.10 (-0.38, 0.57) <sup>#</sup>	-0.21 (-0.33, -0.08) <sup>#</sup>	0.01	71
Carvedilol versus Beta-1 blockers (Bakris et al, Java et al, N=963)	-0.49 (-1.11, 0.12) <sup>#</sup>	-0.26 (-0.39, -0.13) <sup>**</sup>	0.83	00
Carvedilol versus ACEIs/ARBs (Saul et al, Tylicki et al, N=73)	8.61 (-1.52, 18.75) 30	7.45 (0.29, 14.61) <sup>*</sup>	0.23	
Carvedilol versus Placebo (Saul et al, Tylicki et al, N=75)	-1.05(-8.15, 6.05)	-0.88 (-5.26, 3.51)	0.11	62
ACEIs/ARBs versus Placebo (Saul et al, Tylicki et al, N= 72)	-11.71(-29.35, 7.20)	-7.25 (-14.99, 0.48)	0.05	75

\* Significant difference; N= Total number of patients included in analysis;  $\chi^2$ = Chi-square test P-value; I<sup>2</sup>= I<sup>2</sup> test value in %; # = these are standardized mean difference (SMD) values; Remaining are Mean Difference (MD) values.

**Figure 2: Forest plot showing mean difference in UACR between carvedilol versus all other active treatments.**

### Outcome measures

Considering the possibility of significant inter-trial heterogeneity, we present the results of random effects model as representatives of true effects and results of fixed effect model if there is no inter-trial heterogeneity. Only significant observation was superiority of carvedilol over beta-1 blockers with regard to decrease in UACR. Table 3 and Figure 2 show the effect of carvedilol on UACR when compared with various active treatment groups and placebo. Unfortunately, we did not get sufficient data to analyse the effects of carvedilol on eGFR and hemodynamic parameters.

### DISCUSSION

Results of our study indicate superiority of carvedilol over beta-1 blockers and superiority of ACE-Is/ARBs over



carvedilol. Quite interestingly, carvedilol treated group failed to show their superiority over placebo. It can be said that the carvedilol and ACE-Is/ARBs as monotherapy appear to be superior to beta-blockers however; lack of superiority of carvedilol over placebo needs to be explained. When we compared the ACE-Is/ARBs with placebo group, it was found that even ACE-Is/ARBs treated group did not showed superiority over placebo group. Same two studies by Saul et al and Tylicki et al were included in comparison of placebo with carvedilol and placebo with ACE-Is/ARBs. Considering the type of patients included in these two studies, it could be presumed that the insignificant differences between carvedilol with placebo and ACE-Is/ARBs with placebo could be attributed to the cause of chronic kidney failure. Both of these studies included non-diabetic patients with hypertension as a cause of renal failure. Even the most efficacious class of drugs like ACE-Is/ARBs have failed to show significant nephroprotective effect in non-diabetic chronic kidney disease patients.<sup>15</sup> Hence the insignificant difference between carvedilol and ACE-Is/ARBs with placebo observed in our study perhaps can be attributed to the cause of renal failure.

Role of renin-angiotensin-aldosterone system in chronic renal failure highlights the importance and benefits achieved by using ACE-Is/ARBs.<sup>15</sup> One of the outstanding features seen only with ACE-Is/ARBs as nephroprotective agent is their ability to prevent onset of nephropathy.<sup>15</sup> However these drugs need to be used at low doses in patients with chronic kidney disease with raised serum creatinine level and have risk of hyperkalemia.<sup>16</sup> Hence the need for an add-on drug with no added risk of hyperkalemia is needed under such circumstances. Though there are contradictory evidences on to the nephroprotective efficacy of diuretics, considering the importance of achieving target level blood pressure diuretics are preferred as ad-on second line drugs to ACE-Is/ARBs.<sup>17,18</sup> Unlike non-DHP CCBs, DHPs have failed to show nephroprotective effects.<sup>4</sup> The added advantage of DHPs over other antihypertensive drugs is their benefits of protection against stroke among all the cardiovascular related events.<sup>19</sup> With regard to beta-blockers, considering the role of increased activity of sympathetic nervous system behind renal failure and cardiovascular related mortality, idea of using beta-blockers is theoretically favoured.<sup>20</sup> However, this idea is hindered by the risk of reduction in GFR owing to decreased cardiac output by non-selective beta-blockers.<sup>20</sup> Carvedilol as a new generation beta-blocker has no such effects on renal blood flow and GFR.<sup>21</sup> Added to this, many studies including our meta-analysis support superiority of carvedilol over beta-1 blockers as nephroprotective agent.<sup>8-13</sup>

Achieving target level blood pressure is of high significance in patients with chronic renal failure.<sup>18</sup> But another thing which is also perhaps important in patients of chronic renal failure is the prevention of development of heart failure. This is because patients of chronic kidney

disease are at high risk of progression of renal failure in presence of heart failure and vice-versa.<sup>22</sup> Carvedilol and other beta-1 blockers were found to be non-inferior to other classes of antihypertensive drugs with regard to primary prevention of heart failure.<sup>23</sup> DHPs may not be superior with regard to primary prevention of heart failure.<sup>24</sup> Hence, carvedilol in patients with chronic renal failure may be preferred in this regard. To conclude, our study supports the nephroprotective efficacy of carvedilol to be superior to beta-1 blockers in patients especially with diabetes as co-morbidity. Perhaps the lowering of blood pressure to target level irrespective of the antihypertensive drug used, appears to be the better strategy in achieving nephroprotective efficacy in patients of chronic kidney disease with hypertension as a cause for renal failure. Considering the differences in strategies behind achieving nephroprotection in patients with micro albuminuria and macro albuminuria, impact of including studies of both types of proteinuria in our meta-analysis there is possibility of bias. This could be a significant drawback, but the major drawbacks of our study are calculation of the “mean change” values by using baseline and study end point values and inability to get the data from the study by Marchi et al. Apart from these, considering the small sample size and evidence of publication bias results of our study needs to be cautiously interpreted.

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