Clinical efficacy of carvedilol treatment for dilated cardiomyopathy
A meta-analysis of randomized controlled trials

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Abstract
Background: Clinical trials examining the therapeutic benefit of carvedilol on patients with dilated cardiomyopathy have reported inconsistent results. The aim of this study was to evaluate the clinical efficacy of carvedilol on patients with dilated cardiomyopathy.

Methods: PubMed, Embase, Cochrane Library, web of science, China National Knowledge Infrastructure (CNKI), Wanfang, and Chinese Scientific and Technological Journal (VIP) databases were searched for randomized controlled trials (RCTs) before March 2018. Weighted mean differences (WMDs) and 95% confidence intervals (CIs) were used to evaluate the effects of carvedilol on patients with dilated cardiomyopathy.

Results: Twenty one studies including 1146 participants were included. There were significant improvements on heart rate (HR) (WMD = −14.18, 95% CI: −17.72 to −10.63, P < .001), LVEF (WMD = 7.28, 95% CI: 6.53–8.03, P < .001), SBP (WMD = −10.74, 95% CI: −12.78 to −8.70, P < .001), DBP (WMD = −4.61, 95% CI: −7.32 to −1.90, P = .001), LVEDD (WMD = −2.76, 95% CI: −4.89 to −0.62, P = .011), LVEDV (WMD = −3.63, 95% CI: −6.55 to −0.71, P = .015), LVEDV (WMD = −9.30, 95% CI: −11.89 to −6.71, P < .001), LVESV (WMD = −12.28, 95% CI: −14.86 to −9.70, P < .001) under carvedilol treatment compared with control.

Conclusion: This meta-analysis demonstrates that carvedilol significantly improves cardiac function on patients with dilated cardiomyopathy. Further large scale, high-quality and multicenter RCTs are still required to confirm the impacts of carvedilol on patients with dilated cardiomyopathy.

Abbreviations: CI = confidence interval, DBP = diastolic blood pressure, DCM = dilated cardiomyopathy, HR = heart rate, LVEF = left ventricular ejection fraction, LVEDD = left ventricular end-diastolic dimension, LVEDV = left ventricular end-diasstolic volume, LVESD = left ventricular end-systolic diameter, LVESV = left ventricular end-systolic volume, NYHA = New York Heart Association, RCT = randomized controlled trial, SBP = systolic blood pressure, WMD = weighted mean difference.

Keywords: carvedilol, dilated cardiomyopathy, heart failure, meta-analysis

1. Introduction
Dilated cardiomyopathy (DCM) is classic symptom of the enlarged left or right or both ventricular chamber that is accompanied by a type of dilated or eccentric “hypertrophy” in which myocytes are particularly elongated resulting in systolic dysfunction.[1] DCM is a main and common cause of heart failure and sudden cardiac death (SCD). Clinical research suggested that long-term therapy with beta-blockers might generate hemodynamic and clinical benefits,[2] especially on patients with chronic heart failure.[3] Beta-blockers inhibit the long-term excitatory effects of sympathetic nerve on the heart.[4] Based on receptor-level activity, β-blockers can be classified into 3 generations: first generation, nonselective drugs that block both β1AR and β2AR; second generation, cardioselective agents, with higher affinity for β1AR; and third generation, β-blockers with vasodilative properties, mediated by α1AR blockade, β2AR agonism, or NO synthesis.[5] Carvedilol, as the third generation of vasodilators and non-selective beta-blocker acting on β1-, β2-, and α1-adrenoceptors, has been widely used to treat DCM patients with heart failure via blocking sympathetic neural activation, which has shown greater cardiovascular benefits than traditional β blockers.[6] Carvedilol is rapidly absorbed in the gastrointestinal tract and is extensively metabolized in the liver, resulting in a shorter half-life compared with other β-blockers.[7] Furthermore, it could penetrate across the blood–brain barrier and increase the effects of central nervous system as well as the membrane-stabilizing properties of antiarrhythmic molecules.[8] It could reverse left ventricular enlargement and improve survival in patients with various cardiac failure degrees. Some studies indicated that carvedilol could increase left ventricular ejection fraction (LVEF), reduce the heart rate and further protect heart function.[9] Rather, the beta-blockers are not beneficial for all DCM patients. Carvedilol insignificantly increase ejection fraction in early onset of LVEF reduction.[10] Due to the heterogeneity of cardiomyopathy in patients and only a few small-scale randomized controlled trials exploring the effects of

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carvedilol for DCM, the safety and clinical efficacy of carvedilol was desired to be summarized and evaluated. To investigate the improvement of general cardiac function index, a meta-analysis of all known clinical RCTs meeting the inclusion criteria was performed to critically evaluate the benefits of carvedilol in patients with DCM.

2. Materials and methods
This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement[11] and Cochrane Collaboration’s guideline.[12] Ethical approval is not required because this meta-analysis will not involve any patient directly.

2.1. Search strategy
Two authors independently searched the electronic databases, PubMed, Web of Science, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang, and Chinese Scientific and Technological Journal (VIP) databases up to March 2018, using the MESH terms and text words: dilated cardiomyopathy, carvedilol, and randomized trial. The reference lists of identified articles and original articles were also reviewed. Searches were restricted by papers published in English and Chinese language.

2.2. Selection criteria
The inclusion criteria were as follows: randomized controlled trials (RCTs); patients with a diagnosis of DCM; carvedilol alone or in combination with other treatments compared with controls; reported functional cardiac parameters (heart rate [HR], left ventricular ejection fraction [LVEF], systolic blood pressure [SBP], diastolic blood pressure [DBP], left ventricular end-diastolic dimension [LVEDD], left ventricular end systolic diameter [LVESD], left ventricular end diastolic volume [LVEDV], left ventricular end-systolic volume [LViESV], etc.); English or Chinese language publications.

The exclusion criteria were as follows: non-randomized controlled clinical trials; relevant data wasn’t reported; healthy persons enrolled in the control group; reviews, case report, abstract, or animal studies; duplicated data.

2.3. Data extraction
Two authors independently extracted eligible data according to the inclusion and exclusion criteria, and discrepancies were resolved by the third author. The following data were extracted: the first author, year of publication, country, sample size, age, sex distribution, interventions, New York Heart Association (NYHA) classification, outcome measurements.

2.4. Quality assessment
The methodological quality of the included studies was evaluated using the Cochrane Handbook for Systematic Review of Interventions.[12] The items included random sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. The risk of bias was categorized as low, unclear, or high.

2.5. Statistical analysis
Statistical analysis was performed using Stata 12.0 and Review Manager Version 5.3. A P-value <.05 was considered statistically significant. Continuous variables were expressed as the weighted mean difference (WMD) with 95% confidence intervals (95% CIs). Heterogeneity was assessed using the Cochran Q test and an I² statistic. If I² value ≥50% or chi-squared value <0.05 indicated significant heterogeneity, therefore the random effects model was used. Otherwise, the fixed effects model was used. Sensitivity analysis was performed to detect the influence of a single study on the overall estimate via omitting 1 study in turn when necessary. The Begg and Egger testing was used to quantify the publication bias across studies.

3. Results
3.1. Description of the included studies
A total of 1433 relevant studies were identified through the initial search of databases. Of which, 260 duplicates were excluded and 1041 studies were excluded on the basis of initial screening of the titles and abstracts. By reading the full text, 111 articles were excluded due to they failed to meet the inclusion criteria. Ultimately, 21 eligible studies[13–33] were included in this meta-analysis, including 587 cases in the experiment group and 559 cases in the control group (Fig. 1).

The baseline characteristics of the 21 studies are summarized in Table 1. The publication years of the articles were ranged from 1994 to 2016. The mean age of the participants ranged from 4.6 to 70.8 years, and sample sizes ranged from 6 to 78. The total duration of the intervention ranged from 3 to 12 months. Ten studies were conducted in China,[24–33] Five studies were performed in Italy,[13,15–17,21] and 2 studies were conducted in Turkey.[18,20] One study was conducted in each of Japan,[23] Brazil,[19] Iran,[22] and USA.[14]

3.2. Quality assessment of included studies
Among the 21 included studies, 2 studies[24,32] were published with a high risk with random sequence generation, while the rest described random sequence generation without specific random method. Nine studies[13–17,19,21–23] including 15 groups provided analyzable data for HR. The random effect model was performed due to significant heterogeneity (P < .05) was found in the HR analysis. The pooled estimate of effect size showed that HR was significantly decreased in carvedilol group (WMD = –1.48, 95% CI: –1.72 to –1.06, P < .001) (Fig. 3). However, considering significant heterogeneity was detected in the HR analysis, and sensitivity analysis was conducted after omitting Cice et al.[16] The heterogeneity still significant, but the results were consistent with the primary analysis. The result of the Egger and Beggs testing showed no publication bias (Egger P = .146, Begg P = .805).
3.3.2. Effects of carvedilol on the LVEF. A total of 19 studies\(^{13–20,22–33}\) including 21 groups provided analyzable data for LVEF. The fixed-effect model was performed because of low heterogeneity (\(P = .044, I^2 = 37.4\%\)). The result suggested that compared with controls, carvedilol therapy significantly increased LVEF (WMD = 7.28, 95% CI: 6.53–8.03, \(P < .001\)) (Fig. 4). The result of the Egger and Begg testing showed no publication bias (Egger \(P = .882\), Begg \(P = .205\)).

3.3.3. Effects of carvedilol on the SBP. A total of 10 studies\(^{16,18,20–23,25,26,33}\) including 11 groups evaluated the effect of carvedilol on the improvement of the SBP. This outcome variable was analyzed with the fixed-effects model, and the pooled estimate of effect size suggested that, compared with control, carvedilol therapy was associated with a significantly decreased SBP (WMD = −10.74, 95% CI: −12.78 to −8.70, \(P < .001\)), with low heterogeneity among the studies (\(P = .311, I^2 = 14.0\%\)) (Fig. 5). The result of the Egger and Begg testing showed no publication bias (Egger \(P = .225\), Begg \(P = .938\)).

3.3.4. Effects of carvedilol on the DBP. A total of 9 studies\(^{16,18,20,22,23,25,26,33}\) including 10 groups evaluated the effect of carvedilol on the improvement of the DBP. The pooled estimate of 9 studies indicated that carvedilol could notably reduce DBP when compared with those in the controls therapy for DCM (WMD = −4.61, 95% CI: −7.32 to −1.90, \(P = .001\)) (Fig. 6). There was a significant heterogeneity was found among those studies. Therefore, a sensitivity analysis was performed by removing the study by Zhao et al.\(^{28}\) The heterogeneity significantly decreased, and the results were consistent with the primary analysis. The result of the Egger test showed no publication bias (Egger \(P = .319\), Begg \(P = .531\)).

3.3.5. Effects of carvedilol on the LVEDD. There were 6 studies\(^{17,22,23,29,30,32}\) related to LVEDD. The pooled estimate of
Table 1
Characteristics of the included studies.

| Study          | Year | Country | Sample size (E/C) | Male/female (E/C) | Age(yr)(E/C) | NYHA | Interventions (T/C) | Main outcomes | Follow-up |
|----------------|------|---------|-------------------|-------------------|--------------|------|---------------------|---------------|-----------|
| Metra et al    | 1994 | Italy   | 20/20            | E:18/2            | E:50±10      | I/II | Carvediol: 6.25–25 mg bid | Placebo       | LVEF, HR, MAP, CI, RAP, PAP, PWP, PVR, SW, SVR, SWI | 3m          |
| Quai et al     | 1996 | USA     | 21/15            | E:18/3            | E:58±4       | I/II | Carvediol: 6.25–100 mg bid | Placebo       | LVEF, LVEDV, EDVI, ESVI, TPFI, PFR | 4m          |
| Cice et al     | 2000 | Italy   | 78/77            | E:58/20           | E:56.0±5     | I/II | Carvediol: 3.125–50 mg bid | Placebo       | LVEF, HR, PVC, PVR, NSVT, adverse effect | 6m          |
| Cice et al     | 2001 | Italy   | 58/56            | E:32/26           | E:54.9±8.1   | I/II | Carvediol:3.125–25 mg bid | Placebo       | LVEF, LVEDV, LVEDS, HR, SBP, DBP, NYHA, adverse effect | 12m         |
| Neglia et al   | 2007 | Italy   | 8/8              | E:7/1             | E:60±9       | I/II | Carvediol: 3.125–25 mg bid | Placebo       | LVEF, HR, SBP, RRP, CFR | 6m          |
| Kurum et al    | 2007 | Turkey  | 30/30            | E:24/6            | E:59.4±10.6  | I/II | Carvediol: 3.125 mg qd + standard treatment | Standard treatment | LVEF, HR, NM ratio | 4m          |
| Tati et al     | 2005 | Turkey  | 30/30            | E:20/10           | E:59.4±10.6  | I/II | Carvediol: 3.125–25 mg bid | Placebo       | LVEF, HR, NM ratio | 6m          |
| Chizola et al  | 2006 | Brazil  | 15/7             | E:10/5            | E:46.7±9.4   | I/II | Carvediol: 6.25–25 mg bid | Placebo       | LVEF, HR, NM ratio | 6m          |
| Huang et al    | 2013 | China   | 40/37            | E:23/17           | E:5.3±16.6   | I/II | Carvediol:0.1–0.8 mg/kg qd + standard treatment | Standard treatment | LVEDD, LVSSD, LVEF, LVEF | 6m          |
| Yeoh et al     | 2008 | Japan   | 16/16            | E:9/7             | E:56.0±10.2  | NR   | Carvediol: 6.25–25 mg bid | Placebo       | HR, LVEDD, LVSSD, SBP, DBP | 6m          |
| Ajami et al    | 2010 | Iran    | 8/6              | NR                | E:16.0±7.3   | NR   | Carvediol: 3.125–90 mg bid | Placebo       | HR, LVEDD, SBP, DBP | 6m          |
| Palazzuoli et al | 2002 | Italy   | 28/20            | NR                | E:56.2±11.0  | III  | Carvediol: 12.5–25 mg bid | Placebo       | LVEF, HR, NM ratio | 12m         |
| Wang et al     | 2001 | China   | 12/12            | E:5/7             | C:57.2±10.6  | IV/IV| Carvediol:2.5–15 mg bid + placebo | Standard treatment | LVEF, SBP, DBP, LVEDV, WS, SV, FS | 3m          |
| Wu et al       | 2002 | China   | 30/12            | E:17/13           | C:57.8±10.5  | I/II | Carvediol: 2.5–15 mg qd | Placebo       | LVEF, LVEDV, SV, HR, SBP, DBP, FS | 4m          |
| Zhao et al     | 2003 | China   | 34/40            | E:19/11           | C:56.0±10.5  | I/II | Carvediol: 2.5–20 mg bid + placebo | Standard treatment | LVEF, SV, SBP, DBP | 7.21±6.55, 3.14m |
| Zhao et al     | 2004 | China   | 15/15            | E:12/3            | C:56.0±10.5  | I/II | Carvediol: 2.5–15 mg bid + placebo | Standard treatment | LVEF, LSVD, SV, HR, SBP, DBP | 3m          |
| Luo et al      | 2004 | China   | 30/30            | NR                | C:55.7±9.8   | IV/IV| Carvediol: 2.5–15 mg bid + placebo | Standard treatment | LVEF, LVEDD, LVEF | 6m          |
| Wang et al     | 2007 | China   | 26/24            | E:18/18           | C:56.1±13.8  | IV/IV| Carvediol: 2.5–25 mg bid + placebo | Standard treatment | LVEF, LVEDD, LVEDS | 6m          |
| Bi et al       | 2008 | China   | 15/15            | E:18/12           | C:46.0±10.2  | IV/IV| Carvediol: 2.5–10 mg bid + placebo | Standard treatment | LVEF, SV, FS, HR, SBP, DBP | 6m          |
| Yang et al     | 2013 | China   | 42/40            | C:23/19           | C:70.8±5.3   | IV/IV| Carvediol:3.125–25 mg bid + placebo | Standard treatment | LVEF, LVEDD, LVEDS, LVEF | 6m          |
| Zhang et al    | 2016 | China   | 31/31            | NR                | C:47.2±10.5  | I/II | Carvediol: 3.125–25 mg bid + placebo | Standard treatment | LVEF, LVEDV, LVEDS, LVEF, DBP, LVEF | 6m          |

6MWD = 6-minute walk distance, CFR = coronary flow reserve, CL = cardiac index, DBP = diastolic blood pressure, EDVI = end-diastolic volume index, ESVI = end-systolic volume index, FS = fraction shortening, HR = heart rate, NS = non-sustained ventricular, NYHA = New York Heart Association, PAP = mean pulmonary artery pressure, PFR = peak filling rate, PVC = premature ventricular contractions (per minute), PVR = pulmonary vascular resistance, RPP = rate pressure product, SBP = systolic blood pressure, SV = stroke volume, SWI = stroke work index, TPFR = time to peak filling rate.

Effect size suggested that compared with the control group, carvedilol therapy could significantly reduce LVEDD (WMD = -2.77, 95% CI: -4.90 to -0.62, P = .011), with high heterogeneity among the studies (P < .001, I² = 81.8%) (Fig. 7). A sensitivity analysis was conducted after removing Yeoh et al. [23] and the results were consistent with the initial analysis.

3.3.6. Effects of carvedilol on the LVEDS. LVEDS was measured in 5 studies. [17,23,29,30,32] The pooled estimate of effect size suggested that carvedilol therapy was associated with significantly decreased LVEDS (WMD = -3.63, 95% CI: -6.55 to -0.71, P = .015), with significant heterogeneity among the studies (P = .001, I² = 78.8%) (Fig. 8). A sensitivity analysis was
performed after removing Yeoh et al.\textsuperscript{[23]} and the results were consistent with the initial analysis.

### 3.3.7. Effects of carvedilol on the LVEDV

Three trials\textsuperscript{[13,16,17]} assessed the LVEDV of patients with DCM. Compared with the control group (WMD = -9.30, 95\% CI: -11.89 to -6.71, \( P < .001 \)), a decrease in the LVEDV was observed in the carvedilol group, with no heterogeneity among the studies (\( P = .601 \), \( I^2 = 0\% \)) (Fig. 9).

### 3.3.8. Effects of carvedilol on the LVESV

Two studies\textsuperscript{[16,17]} reported the LVESV between the experimental and control group. The fixed-effect model was performed because of low heterogeneity (\( P = .597 \), \( I^2 = 0\% \)). Pooling results of the studies showed that carvedilol therapy could significantly decrease LVESV (WMD = -12.28, 95\% CI: -14.86 to -9.70, \( P < .001 \)) (Fig. 10).

### 4. Discussion

Our study revealed that carvedilol has a superior performance in clinical efficiency of DCM using systematic review and meta-analysis. It highlights that carvedilol decreased the HR, DBP,
SBP, LVEDD, LVEDV, LVESD, LVESV, and increased LEVF, which contributes to the protection of heart function and the maintenance of good blood supply of visceral organs.

Dilated cardiomyopathy is the response of myocardial cells to various genetic and environmental factors. A common outcome is heart failure (HF). The course of disease was progressive and the mortality was high. Mounting evidence indicates that adrenergic receptors are functionally involved in cardiovascular disorders, particularly heart failure.[34] Then how to treat HF caused by DCM?

General treatment includes low-fat food, no smoking and alcohol, and patients are encouraged to have low-intensity walking. In terms of medicinal treatment, there are currently several drugs. Diuretics prevent the progression of heart failure by promoting the drainage of Na+ and water, which further eliminate edema and reduce the cardiopulmonary load. Cardiac drugs, such as digoxin, can reduce ventricular volume, slow down heart rate, and relieve heart failure. One class of them treating HF is beta-blockers which target to adrenergic receptors, and carvedilol as a representative has outstanding performance in the treatment of heart failure.[35]

Firstly, carvedilol can make dilation of peripheral blood vessels and reduce circulation resistance by blocking α1 receptor, which improve hemodynamics. Secondly, carvedilol could reduce the neuron injury mediated by free radical which is caused by increased ventricular wall tension when heart failure happens by eliminating oxygen free radicals.[36] Thirdly, carvedilol inhibits myocardial apoptosis, inflammation, and ventricular remodeling,[37] and decreases platelet aggregation and improves ventricular function as well as clinical status. Exploration on its specific mechanism was widely carried out. For example, the anti-inflammatory effects of carvedilol are listed as follows: carvedilol inhibited T cell activation by suppressing NF-κB activity,[38] it may be associated with its reactive oxygen species (ROS)-scavenging effects[39]; carvedilol inhibited the formation of NLRP3 inflammasome through a Sirt1-dependent pathway.[6] Thus it can be seen carvedilol has the potential to be positioned as a novel protection for myocardial cells. Strikingly, all adrenergic receptors primarily transmit signal through heterotrimeric G proteins which regulate cardiac function and physiology. This implies that carvedilol target these G protein-coupled receptors to modulate cardiac function.[40]

In short, on one hand, carvedilol directly increase cardiac contractility by activating cAMP-mediated pro-contractile signaling pathway. On the other hand, carvedilol induces reverse remodeling in the failing heart, improves survival, reduces risk of arrhythmias, improves coronary blood flow, and protects the heart against the cardio-toxic overstimulation by the sympathetic...
Figure 5. Forest plot showing the effect of carvedilol on systolic blood pressure.

Figure 6. Forest plot showing the effect of carvedilol on diastolic blood pressure.
nervous system.\textsuperscript{[41]} Except for the pharmacological evidence, carvedilol is the only approved for treatment of chronic heart failure in the United States and other countries.\textsuperscript{[3]}

This meta-analysis has several limitations. The included RCTs have a relatively small sample size; we assess the effects of carvedilol on patients with DCM from 6 aspects: HR, LVEF, SBP, DBP, LVEDD, LVESD, LVEDV, LVESV. However, those outcomes are not simultaneously included in every study; lack of sufficient data to analyze the effects of carvedilol on cardiovascular events and mortality in patients...
with DCM; different lengths of intervention time, different doses in each study might cause a potential bias. Owing to the relatively small number of trials, we could not assess or conduct subgroup analysis whether carvedilol is differentially effective in ischemic and nonischemic dilated cardiomyopathy. Based on these limitations, future clinical studies should focus on employ a clear description of randomization, allocation concealment, and blinding recruit large cohorts of DCM patients to ensure adequate sample size; explore optimized treatment protocols of carvedilol; investigate to the efficacy and safety of carvedilol on patients with DCM.

5. Conclusion

This review of 21 randomized trials shows that carvedilol can improve cardiac function of patients with DCM. Further RCTs are needed to explore the optimal dose of carvedilol, and further large, rigorous trials are still warranted to confirm the effects of carvedilol on patients with DCM.
Author contributions

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