Systematic Review Article

Carvedilol in Pediatric Dilated Cardiomyopathy Patients: A Systematic Review of Clinical Outcomes

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ABSTRACT

Dilated cardiomyopathy (DCM) is a cardiac disease that affects the heart's muscles and makes it difficult for the heart to pump blood by enlarging and stiffening the heart chamber walls (usually the left ventricle). DCM is estimated to occur in 1 out of 250-2,500 adults and 0.57-1.13 out of 100,000 children. It is associated with high morbidity and mortality. Carvedilol is used off-label in children with heart failure, but its effectiveness across pediatric DCM studies remains uncertain. To synthesize reported clinical outcomes of carvedilol in patients < 18 years with DCM, a comprehensive literature was conducted in Pubmed and Embase. Eligible designs included randomized trials and cohort studies reporting carvedilol outcomes in pediatric DCM. Six studies reported improvements in left ventricular ejection fraction; two studies reported a reduction in heart rate. Across heterogeneous designs, carvedilol was generally associated with improved cardiac function in most patients, notably left ventricular ejection fraction (LVEF) and reduction in heart rate. However, dosing, co-therapies, and follow-up varied, and adverse effects were inconsistently reported. Overall, current evidence suggests carvedilol may benefit children with DCM, but larger randomized control trials are needed to confirm efficacy and safety.

Keywords: Beta blockers; Carvedilol; Dilated cardiomyopathy; Efficacy of carvedilol; Pediatric dilated cardiomyopathy; Pediatric heart failure; Pediatric treatment for dilated cardiomyopathy

INTRODUCTION

Dilated cardiomyopathy is characterized by the significant structural enlargement of one or more heart chambers—predominantly in the left ventricle due to its strenuous task of sending blood to the furthest regions of the body—that contributes to the lack of ability for the heart to contract and pump enough oxygenated blood out. The left ventricle can increase to 140% of its original size and weight along with having abnormally weak and thin walls (Figure 1). In children, body size must be considered when deciding if the patient has DCM and so the diagnosis is made based on left ventricle (LV) end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD). Lower ratios of LV mass-to-volume or wall thickness-cavity dimension are morphological features that should also be considered (1). Additionally, DCM patients may experience a loss of myocardial cells by around 10% or an increased cardiac calcium sensitivity. As the ventricle stretches and original myocardial cells are damaged, an increased

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amount of scar tissue (fibrosis) can build up within the walls, especially in the endocardium. This myocardial remodeling is an important contributor to worsening heart failure because scar tissue does not contract as well as myocardial cells do, impairing the contractile force of the heart along with disrupting the electrical signals traveling within the walls (1). Furthermore, chamber enlargement may lead to the atrioventricular valve leaflets to allow varying degrees of mitral or tricuspid regurgitation. Over time, the persistent mitral regurgitation can lead to the thickening of the mitral leaflets, reducing the amount of blood flow to the left ventricle and causing the heart to work harder to pump blood through the body. As a result, the heart chambers will continue to deteriorate, and ejection fraction will decrease. While a healthy pediatric heart may be able to pump around 20-30 millimeters of blood per beat depending on the child's age, size and activity, a child with pediatric DCM may only be able to pump around 30-40% of that blood volume (2). Due to compensatory mechanisms that the body can put in place, DCM signs may not be caught right away.

However, once symptoms show up, dilated cardiomyopathy can often be associated with issues like heart failure, myocarditis, irregular breathing, chest pain, cardiomegaly, tachycardia, poor feeding, and fatigue. Most of these symptoms are the result of the strain on the heart causing the body to work improperly or over-exert itself. A few of these conditions are common to other diseases and so tests are needed to detect the exact cause of the child's illness. Some of the noninvasive diagnoses techniques for DCM include echocardiogram, electrocardiograms, Doppler studies, chest radiographs, and blood counts. These studies can indicate the type of cardiomyopathy along with the degree of dysfunction and irregularity of heart muscle. Meanwhile, a few of the more invasive procedures for detecting DCM are cardiac catheterizations and angiographies. More invasive procedures should be reserved as a last resort as they can harm the patient.

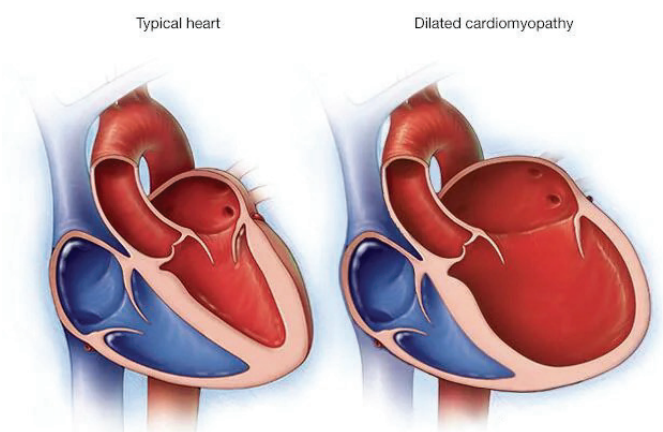

Figure 1. Diagram of a normal heart (left) compared to a heart with DCM (right) The left ventricle (right lower chamber) is significantly enlarged in the heart to the right with thinner muscle walls. This decreases the efficiency of the heart and reduces cardiac output, resulting in poor perfusion of blood to other organs. Adapted from Mayo Clinic: Dilated Cardiomyopathy (3).

Carvedilol is the most common type of beta blocker used to treat patients with heart failure and works by reducing symptoms and by making contractions easier for the heart. It can be used alone or with other medications (4, 5). Carvedilol is classified as both a beta-blocker and an alpha blocker. Carvedilol's categorization illustrates how the medication is non-selective, meaning it does can bind to beta-1, beta-2, and alpha-1 receptors as well. However, because carvedilol is nonspecific, the medication can affect other parts of the body such as the skin, iris, muscles, liver, and kidneys. Beta-2 receptors can be found within the lungs in addition to the T-tubules of cardiac muscle cells and so it is not typically suitable for children with asthma or other breathing conditions as the medication can worsen the lung condition.

Carvedilol was once restricted from being used on children but is now under new light and being recognized as an effective treatment in pediatric DCM patients (6). Although still unapproved by the FDA for children under the age of 18 years old, many doctors have decided that the benefits of Carvedilol may outweigh the risks and have started to prescribe the medication to children with heart failure (7).

Although still debated upon and under-researched, there are now numerous studies from all over the globe that point to the finding that Carvedilol can be an effective medication for treating pediatric dilated cardiomyopathy. Twenty-first-century studies on carvedilol in DCM patients have illustrated an overall trend in the reversal of heart failure symptoms in patients taking the medication. To measure the effectiveness of Carvedilol in pediatric DCM patients, scientists measured the left Ventricular ejection fraction (LVEF), heart rate, shortening fraction, brain natriuretic peptide (BNP) concentration, and the size of the heart chambers before and after the child took

the medication for a set period. The LVEF is a measure of how much blood the heart's left ventricle pumps out with each beat. It can be calculated by dividing the amount of blood pumped out of the ventricle per pump (stroke volume) by the total amount of blood in the ventricle before pumping (end-diastolic volume). LVEF is commonly measured in dilated cardiomyopathy patients because it is a key indicator of the heart's ability to pump blood.

The objective of this study is to systematically review and summarize the preexisting literature and pool their data in a meta-analysis to determine the impact of carvedilol on cardiac function in pediatric DCM. Establishing carvedilol as a potentially beneficial medication option for DCM in children may accelerate the incorporation of effective treatment into standard treatment for the condition. The researcher of the study hypothesizes that carvedilol may produce heart rate reductions and an increase in LVEF, improving the cardiac function of pediatric patients with DCM.

METHODS AND MATERIALS

We searched Pubmed and Embased from inception to April 30, 2025. Reference lists of included articles were screened for additional studies. We included human studies enrolling in the pediatric population (<18) with a diagnosis of DCM or heart failure. Eligible designs were randomized trials, cohort studies with a comparator (placebo/standard of care). Studies had to report at least one outcome of interest (e.g., LVEF, HR) and be published in English. Randomized trials were assessed with the ROB1 tool (Figure 2).

Statistical analyses were performed in R (version 4.1) using the meta package. We applied inverse-variance random-effects models (REML with Hartung-Knapp) to pool post-treatment and change-from-baseline LVEF means and to estimate the RCT mean difference; when SD of change was unavailable, it was imputed from pre/post SDs assuming r=0.5 (sensitivity r=0.3-0.8). The RCT was summarized as a post-treatment mean difference (meta count); we reported 95% Cis, I2, \tau2, showed prediction intervals for pooled means, and pre-specified a subgroup by study design.

RESULTS

The search yielded sixty-three studies (Figure 3 (PRISMA diagram)). There were six randomized control trials included, totaling four hundred ninety-two patients. These studies were published between January of 2009 to December of 2022. Descriptive data is displayed in Table 1 and a quality assessment was demonstrated in Figure 3.

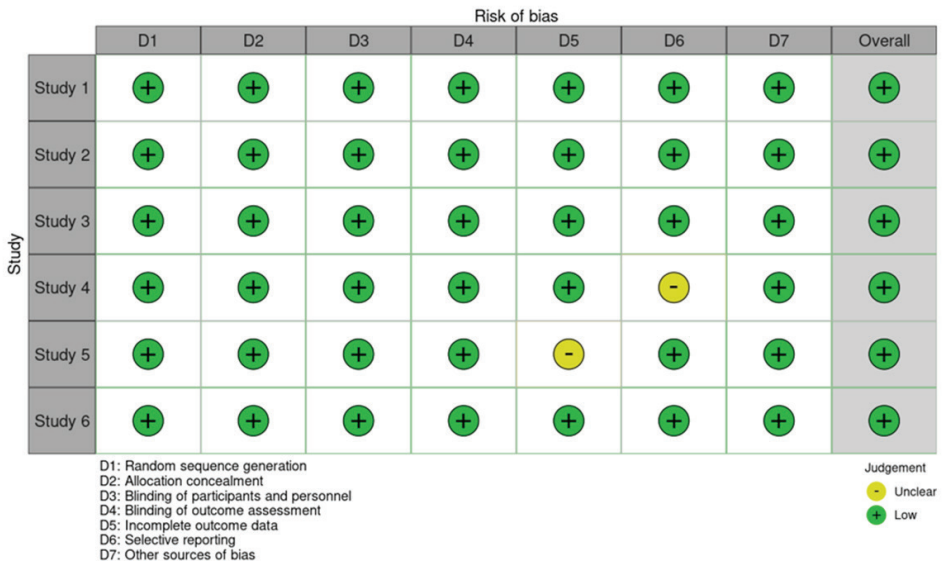

Figure 2. Quality assessment of randomized trials using a ROB1 template from robvis (8). Green circles indicate a low risk of potential bias while yellow circles indicate an unclear understanding of whether bias impacted the study. All of the studies had green circles overall, identifying the studies as trustworthy.

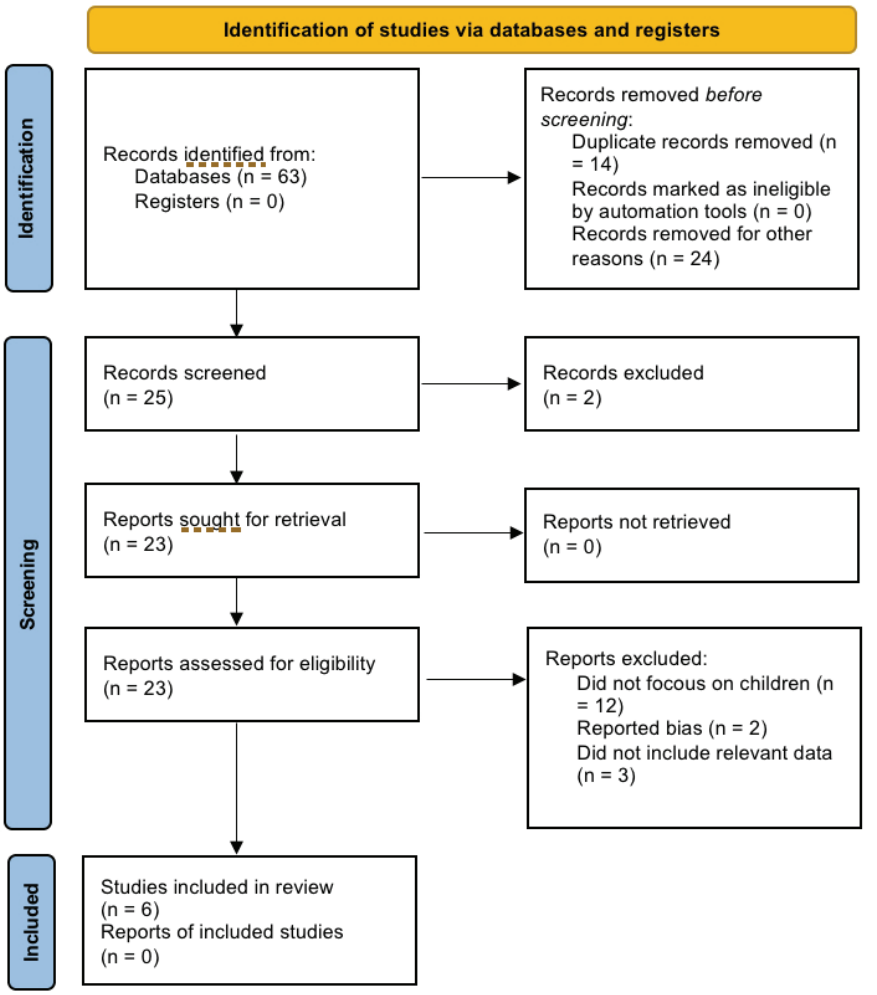

Figure 3. PRISMA flow diagram of study selection using a PRISMA chart template from PRISMA (9). The PRISMA diagram displays the study selection process for including or eliminating studies into the systematic review.

General Findings

On average, patients taking carvedilol, especially when the dosage is high, will experience a left ventricular ejection fraction increase of around 10% along with a reduction in heart rate, which may result in less stress on the heart, lessen heart failure symptoms, and reduce the chances of needing a heart transplant (Figure 6). Since first being tested over two decades ago, pediatric dilated cardiomyopathy studies have found that Carvedilol not only reproduces hemodynamic and symptomatic improvement in chronic heart failure but can also reduce mortality rates of both children and adults. Carvedilol therapy is associated with a 65% reduction in the risk of death compared to placebo treatments. Additionally, carvedilol is associated with a 27-38% reduction in risk of hospitalization. This reduction in mortality when taking carvedilol applies to all children regardless of age, sex, cause of heart failure, ejection fraction, exercise tolerance, systolic blood pressure, and heart rate. In Cantarutti's recent study involving 135 kids, children given Carvedilol had an average heart rate reduction of 30% and an ejection fraction improvement of approximately 13% (10) while another study identified that over 75% of conditions of the children in their program either improved or remained stable (11). In all the studies that provided data on the reasoning for stopping treatment, one of the most common reasons for the discontinuation of treatment was due to a worsening

Table 1. Characteristics of included studies

Authors	Year	Country	Patient size and age	Patient diagnosis	Follow-up time	Medications	LVEF increase	HRR	Other findings
Adorisio, Pontrelli, Cantarutti, Bellettini, et al.	2022	Italy	100 kids (<18)	N/a	N/a	Carvedilol	>13%	>20%	LVESD: R^2 =0.1, p = 0.003
Oflaz, Balli, Kibar, Ece, et al.	2013	Türkiye	34 participants aged 3-12 years old. Median age = 7.4	Idiopathic DCM	Average = 9.5 months	Carvedilol, standard therapy	N/a	N/a	QTc reduction
Rossano, Canter, Hsu, Pahl, et al.	2016	United States of America, Canada	118 patients Average age = 4.4 years old	Form of heart disease	1 to 3 years	Carvedilol	6%	N/a	N/a
Askari, Semizel, Bostan, Cil	2009	Türkiye	16 children 7 months to 11.5 years old	Idiopathic DCM	N/a	Carvedilol	8%	5%	N/a
Huang, Zhang, Chen, et al.	2012	China	89 Children	CHF caused by DCM	6 months	Carvedilol	Increase	N/a	BNP concentration decreases by 30%
Cantarutti, Ciabattini, Amodeo, et al.	2022	Italy	135 children	DCM or CHF	1 to 3 years after maximum dosage	High dosage carvedilol	13%	30%	N/a

The table reports the six studies which include clinical trials that test the effectiveness of carvedilol using cardiac measurements such as heart rate or LVEF.

condition of the heart seen in those who were put into the placebo group. In 2023, the American Heart Association released a scientific statement that included its recommended guidelines for treating pediatric DCM. In the scientific statement, the association acknowledged carvedilol as an adequate treatment medication for the disease, claiming "carvedilol did have an improvement in fractional shortening. [And a] post hoc analysis found that children with a systematic LV treated with carvedilol had echocardiographic evidence of reduced LV size and natriuretic peptide concentrations" (12).

LVEF Outcomes

All six studies in Table 1 included LVEF outcomes and 4 out of 6 included their specific results. Overall, they found that carvedilol causes significant increases in LVEF percentage and is therefore effective at treating pediatric DCM and CHF. The normal ventricular election fraction for children is usually around 55% to 70%. Thus, the average increase of the LVEF from 30.2 ± 10% before treatment in Adorisio's study (13) and the ejection fraction increased from 35.2 ± 6.8% to 43.1 ± 11.2% from Askari's study (14) demonstrate the improvement of cardiac muscles after receiving Carvedilol. Although the LVEF results do not reach the healthy range for LVEF in children, Carvedilol notably improves the condition and ejection fractions to a safer degree.

Across six studies, the pooled increase in LVEF was 12.8% (95% CT 11.6-14.0), with substantial heterogeneity (I^2=78.5%). Observational pre-post studies pooled 13.4% (95% CT 12.2-14.7; I^2=72.3%), whereas the RCT carvedilol arm showed 7.7% (95% CI 4.2-11.3) (Figure 4).

Across six studies, the random-effects pooled post-treatment LVEF was 45.5% (95% CT 43.3-47.7), with moderate heterogeneity ($I^2 \approx 45\%$). By subgroup, observational pre-post studies pooled 45.8% (95% CT 43.1-48.4), while the RCT carvedilol arm showed 43.5% (95% CT 39.8-47.3). Individual study means ranged from 43.1% to 53.0%, indicating broadly consistent post-therapy LVEF in the mid-40s across settings (Figure 5).

HRR Outcomes

Two out of the six studies in Table 1 indicated HRR outcomes. The researchers found the carvedilol plays a role in reducing heart rate, which is beneficial to those with DCM because an elevated heart rate and blood pressure could strain the heart. Overall, the studies illustrated a percentage increase in HRR of around 18%, which suggests Carvedilol is beneficial in improving pediatric DCM. However, the two studies indicated slightly different outcomes, where the study by Cantarutti suggested a HRR of >30% while the study by Adorisio reported a >20% HRR increase. The discrepancies between study finds could be the result of any number of findings, including baseline severity of patients, dosing, dose titration speeds, or concomitant. In

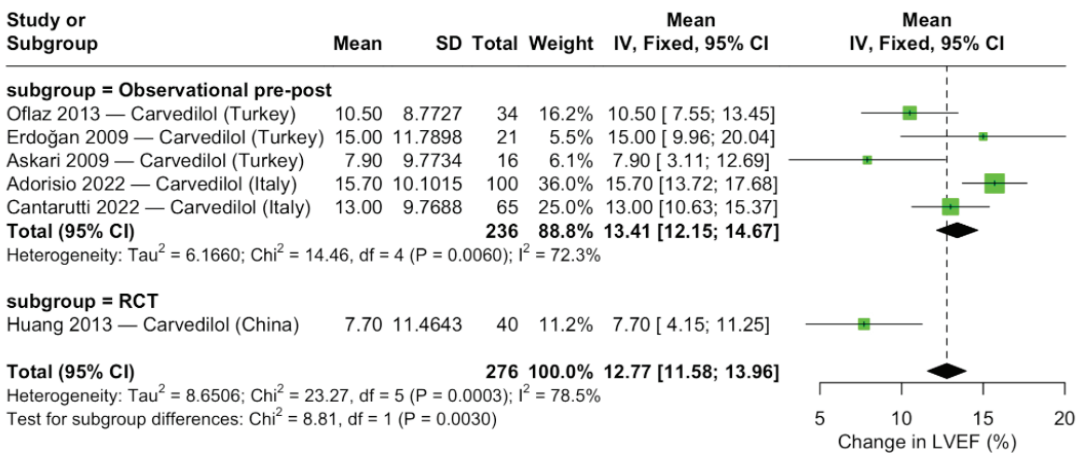

Figure 4. Forest plot for LVEF changes. A low percentage of LVEF indicates a low efficiency of the left ventricle. The pooled increase in LVEF across the six studies was 12.8%.

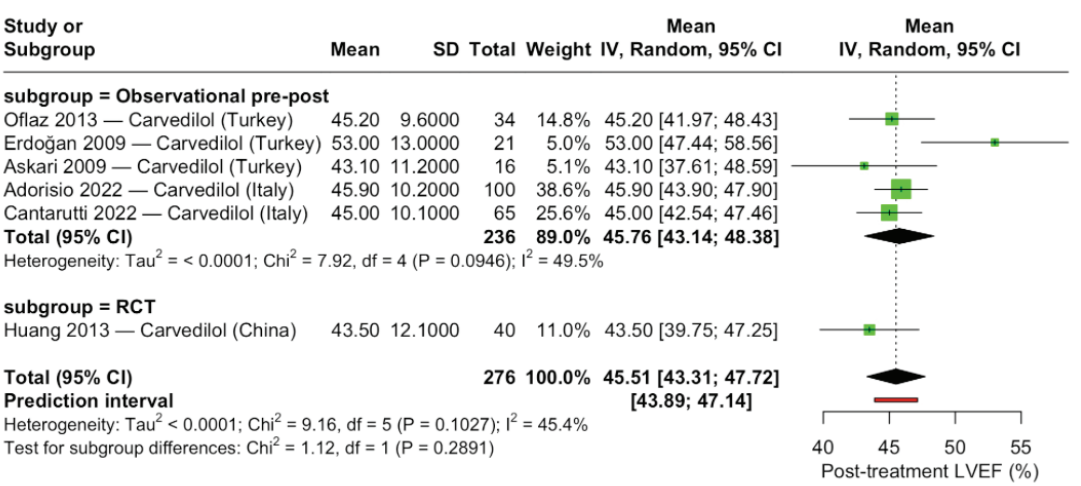

Figure 5. Forest plot for post treatment LVEF. Across the six studies, the random-effects pooled post-treatment LVEF was 45.5%. This increase from 12.8% signifies an increase contractibility and efficiency of the left ventricle.

Cantaurutti's study, the patients received a "high dosage" of carvedilol. Meanwhile, the patients in Adorisio's study received a dosage based on the maximal tolerated dose of the child, possibly resulting in the difference in heart rate reduction percentage. Furthermore, the results should be interpreted with caution as this discrepancy highlights the need for further investigation to draw definitive conclusions on the medication.

Shortening Fraction

Three out of six studies in Table 1 revealed the shortening fraction outcomes of the patients taking carvedilol. In the study by Oflaz *et al*., the results demonstrated that after six months of carvedilol therapy, LVSF increased significantly by an unspecified amount (15). In the randomized control trial by Rossano (16), the results reported an increase in shortening fraction from 16% ± 8 at carvedilol initiation to 21% ± 9 at one year and to 22% ± 8 at 3 years. The study by Askari *et al*. showed a similar trend, with the shortening fraction improving from 17.2 ± 6.1% to 22.7 ± 5.1%. Like the other findings of the studies in Table 1, the data on shortening fractions concludes that the use of carvedilol in addition to standard therapy for DCM in children can improve cardiac function because a higher shortening fraction value suggests better left ventricular systolic function.

DISCUSSION

In this systematic review, a brief explanation of dilated cardiomyopathy and causes of the disease are provided before the article explores the effectiveness of a prominent medication used to treat the condition, carvedilol, on pediatric dilated cardiomyopathy patients. Across 6 studies, carvedilol was associated with a pooled increase in LVEF at about 12.8% (95% CT 11.6-14.0) post-treatment. Although the LVEF results do not reach the healthy range for LVEF in children, Carvedilol notably improves the condition and ejection fractions to a safer degree. Additionally, the studies illustrated a percentage increase in HRR of around 18% and the studies that involved shortening fraction outcomes demonstrated an increase as well.

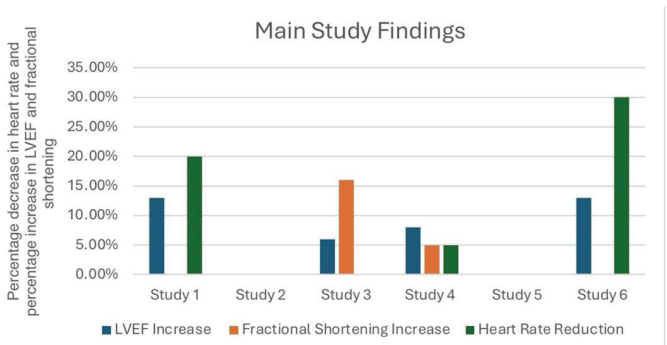

Figure 6. Bar graph of main findings from the six studies included in the systematic review, using Microsoft Excel (17). The graph displays the percentage of LVEF increase (blue), fractional shortening increase (orange), and heart rate reduction (green) found in each study. A missing bar represents that no data on the category was reported.

Study Methods and Prior Evidence

All studies included in the systematic review had to test the efficacy of carvedilol in pediatric patients with DCM. Each of the randomized control trials must have administered Carvedilol to patients and measured aspects of the child's symptoms before and after the treatment was complete. Some of the studies in Table 1 accomplished testing the effectiveness of carvedilol in Pediatric DCM patients by administering Carvedilol to all patients while others operated by comparing patients receiving Carvedilol to a control group using placebo drugs or by having groups of children receiving different dosages of the medication. Most studies involved an initial dose of around 0.1 mg/kg/day and set maximum doses of less than 0.5-1 mg/kg/day. In the studies by Adorisio *et al*., Askari *et al*., and Rossano *et al*., the researchers measured the left ventricular end-diastolic and end systolic diameter before and after carvedilol treatment using regression analysis and echocardiographic data. In the study by Oflaz *et al*., all patients had undergone carvedilol therapy in addition to standard therapy for at least 6 months. Meanwhile, In the study by Cantarutti *et al*., a group of children were given high dosages while a second group were given lower dosages and then the two groups were compared. The trials focused on the effects of carvedilol on heart rate variability analytics and the QT-interval dispersion. In the majority of these studies, children increased their dosage during the study if deemed necessary by the child's physician.

With the efforts of scientists in the twenty first century, much research has been done to understand the efficacy, safety, and best dosage for those taking Carvedilol and physicians now have substantially more options and knowledge on how to treat pediatric DCM. Previously, researchers' knowledge on using carvedilol in children was influenced by its proven benefits in adult heart failure. Scientists hypothesized that carvedilol could offer similar advantages to children with DCM.

Furthermore, data now suggests that there is evidence to support carvedilol's ability in improving cardiac function in children with DCM in trials from around 6 months to three years. However, this leads to the question of whether carvedilol is an effective long-term medication for treating pediatric DCM or if it is only a temporary solution to the dilation of the heart chambers. Given the lack of information on the long-term effects of carvedilol and if patients continued to mange symptoms using carvedilol after the research was conducted, it becomes crucial for us to learn more about the medication and its role in treating pediatric DCM.

Improvements and Mechanism

Overall, the quality of the studies included in Table 1 of the systematic review are exceedingly high based on the robvis bias checker. Each randomized trial was assessed on and selected for its high quality and relevance, but each study could incorporate small improvements. In most medical research studies, a good patient population size aims for 100 patients at a minimum. However, the number of children available for studies testing pediatric dilated cardiomyopathy is quite small, causing achieving a large population size to be difficult. Three of the studies in the chart had patient populations of less than the minimum recommended trial size and should be noted when considering the data. Additionally, two of the studies recorded the beneficial effects of carvedilol in pediatric DCM patients but did not include numerical information of the LVEF change in patients in the study. Considering that LVEF is a comprehensive and clinically relevant measure of heart muscle function in pediatric DCM patients, the researchers could have prioritized providing data for the LVEF over other factors like shortening fraction or BNP (18). Additionally, the inconsistencies between treatments and the smaller populations across the trials exacerbate the differences in outcomes between the studies. In order to gain more standardized results, it would be advisable to obtain a larger population size for the studies and standardize treatment involving carvedilol.

The medication carvedilol acts as a beta and as an alpha blocker to change the child's cardiovascular system and reduce symptoms. The medication inhibits adrenergic receptors, leading to a decreased impact of adrenaline and norepinephrine on the heart, leading to a reduced strain on the heart and an increased LVEF. In the scientific studies reviewed in this systematic review, the trials all proved this trend of carvedilol improving cardiac function and increasing LVEF. Pediatric patients taking carvedilol experienced a lower mortality rate compared to those who took placebo medications for their heart failure. Carvedilol therapy was associated with a 65% reduction in the risk of death compared to placebo treatments and carvedilol is associated with a 27-38% reduction in risk of hospitalization.

Ongoing Studies and Limitations

Since Carvedilol is still relatively new to being used to treat pediatric dilated cardiomyopathy, more studies are needed to investigate the efficacy, safety, and optimal dosing of Carvedilol in patients. Researchers hope to gain insight into the best use and long-term effects of Carvedilol in patients and so doctors and scientists are working together to gain more knowledge on the medication. In 2024, an article was released by Minjae Yoon, *et al*. from various cardiology divisions of hospitals in the Republic of Korea calling for enrollment into a study on Carvedilol in pediatric patients. The researchers noted that "the benefit of beta-blockers in heart failure with preserved ejection fraction (HFpEF) [was still] uncertain [as] recent studies have shown that beta-blockers are associated with improved survival in those with low global longitudinal strain (GLS <14%) but not in those with GLS ≥ 40%" (19). The team claimed that their goal for the study would to be to evaluate the effect and safety of carvedilol-SR in different GLS categories of patients with hypertension and HFpEF. The study will be composed of randomized double-blind multi center trials and will include 100 patients with HFpEF from three hospitals in South Korea. The study will involve individuals over the age of 19 who have evidence of a structural heart disease. Any eligible participants who enroll will be randomized 1:1 in the carvedilol-SR group or the placebo group. Patients that receive carvedilol will be given 8, 16, 32, or 64mg of Carvedilol-SR daily for 6th months and the dosage may increase according to the discretion of the treating physicians.

Dilated Cardiomyopathy is a progressive condition and in some pediatric cases it is incurable. Thus, it is important for early medical treatment to continue into adulthood to prevent worsening of symptoms if necessary. Carvedilol is a long-term medication treatment that some may be prescribed to take for the rest of their lives (4). However, the long-term effects of carvedilol in developing children are still largely unknown. In adults, although carvedilol is usually well-tolerated and tends to have fewer side effects than other beta blockers, it could worsen existing heart failure or cause fluid buildup around the body over time.

While conducting the systematic review, limited data was available and all relevant information was difficult to capture from the studies. The study relied on and collected data from other sources. There was moderate heterogeneity throughout the sources, meaning some studies conducted randomized trials on pediatric patients but left out relevant information to this meta-analysis such as the LVEF percentage increase. Additionally, there is a lack of previous research on the effects of carvedilol on pediatric DCM along with a low sample size in the existing data, allowing for possibly skewed conclusions. As a result, the review may include incomplete and potentially inaccurate information.

CONCLUSION

This systemic review and meta-analysis including 6 studies and 492 patients suggest that carvedilol reduces pediatric heart rate and increases left ventricular ejection fraction. Our findings are consistent with previous scientific conclusions and provides evidence that carvedilol is effective in treating pediatric DCM. The review highlighted the latest information on the medication and affirmed its role in reversing the harmful effects of pediatric DCM.

In this study, a brief explanation of dilated cardiomyopathy and causes of the disease are provided before the article explores the effectiveness of a prominent medication used to treat the condition, carvedilol, on pediatric dilated cardiomyopathy patients. Dilated cardiomyopathy (DCM) is a cardiac disease that affects the heart's muscles and makes it difficult for the heart to pump blood by enlarging and stiffening the heart chamber walls. The condition is characterized by the significant structural enlargement of one or more heart chambers and a loss in myocardial cells with a build up of scar tissue. DCM occurs in a small population of children worldwide, but the condition can lead to a reduced quality of life for those who are affected.

The medication carvedilol acts as a beta and as an alpha blocker to change the child's cardiovascular system and reduce symptoms. The medication inhibits adrenergic receptors, leading to a decreased impact of adrenaline and norepinephrine on the heart, leading to a reduced strain on the heart and an increased LVEF. In the scientific studies reviewed in this systematic review, the trials all proved this trend of carvedilol improving cardiac function and increasing LVEF. Pediatric patients taking carvedilol experienced a lower mortality rate compared to those who took placebo medications for their heart failure. Carvedilol therapy was associated with a 65% reduction in the risk of death compared to placebo treatments and carvedilol is associated with a 27-38% reduction in risk of hospitalization. This reduction in mortality when taking carvedilol applies to all children regardless of age, sex, and cause of heart failure.

With the efforts of scientists in the twenty first century, much research has been done to understand the efficacy, safety, and best dosage for those taking Carvedilol and physicians now have substantially more options and knowledge on how to treat pediatric DCM. We now know that there is evidence to support carvedilol's ability in improving cardiac function in children with DCM in trials from around 6 months to three years. This leads to the question of whether carvedilol is an effective long-term medication for treating pediatric DCM or if it is only a temporary solution to the dilation of the heart chambers.

CONFLICT OF INTERESTS

The author declares that there are no conflicts of interest regarding the publication of this article.

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