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EVALUATING THE EFFICACY OF BETA-BLOCKER THERAPY IN CHILDREN WITH HEART FAILURE

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RELEVANCE

English: Heart failure (HF) in children, while less common than in adults, is a serious condition with significant morbidity and mortality, often resulting from congenital heart defects or cardiomyopathy. The pathophysiology involves sustained neurohormonal activation, particularly of the sympathetic nervous system, which leads to progressive cardiac remodeling and dysfunction. In adult HF, beta-adrenergic receptor blockers (beta-blockers) are a cornerstone of therapy, proven to improve cardiac function and survival. However, the pediatric HF population is heterogeneous, and the underlying causes differ significantly from adults. Therefore, directly extrapolating adult treatment guidelines is not always appropriate. Investigating the specific efficacy, safety, and optimal use of beta-blockers in children with HF is crucial for developing evidence-based pediatric treatment protocols and improving clinical outcomes in this vulnerable population. This expanded review seeks to provide a deeper analysis of the existing evidence, challenges in clinical application, and future research directions.

Keywords: pediatric heart failure, beta-blockers, carvedilol, treatment efficacy, left ventricular dysfunction, cardiomyopathy, neurohormonal blockade, ventricular remodeling.

АКТУАЛЬНОСТЬ

Сердечная недостаточность (СН) у детей, хотя и встречается реже, чем у взрослых, является серьезным состоянием со значительной заболеваемостью и смертностью, часто возникающим в результате врожденных пороков сердца или кардиомиопатии. Патофизиология включает устойчивую нейрогормональную активацию, особенно симпатической нервной системы, что приводит к прогрессирующему ремоделированию и дисфункции сердца. У взрослых с СН блокаторы бета-адренорецепторов (бета-блокаторы) являются краеугольным камнем терапии, доказано улучшающими сердечную функцию и выживаемость. Однако педиатрическая популяция с СН гетерогенна, и основные причины заболевания значительно отличаются от таковых у взрослых. Поэтому прямое экстраполирование лечебных рекомендаций для взрослых не всегда уместно. Исследование специфической эффективности, безопасности и оптимального применения бета-блокаторов у детей с СН имеет решающее значение для разработки научно-обоснованных педиатрических протоколов лечения и улучшения клинических исходов в этой уязвимой группе пациентов. Данный расширенный обзор нацелен на более глубокий анализ существующих доказательств, трудностей в клиническом применении и будущих направлений исследований.

Ключевые слова: детская сердечная недостаточность, бета-блокаторы, карведилол, эффективность лечения, дисфункция левого желудочка, кардиомиопатия, нейрогормональная блокада, ремоделирование желудочков.

INTRODUCTION

Heart failure (HF) in children is a complex clinical syndrome with diverse etiologies, primarily congenital heart disease and cardiomyopathies. Beta-blocker therapy, a standard of care in adults with chronic HF, has been increasingly studied in the pediatric population for its potential to mitigate the detrimental effects of chronic sympathetic activation. This article provides an expanded evaluation of the evidence regarding the efficacy of beta-blockers for treating children with systolic heart failure. A detailed review of major clinical trials and meta-analyses reveals that beta-blockers, particularly carvedilol, can lead to significant improvements in cardiac function, including increased left ventricular ejection fraction (LVEF) and favorable ventricular remodeling. Evidence also suggests an improvement in clinical symptoms and functional status. However, unlike in adults, a definitive mortality benefit has not been consistently demonstrated in pediatric randomized controlled trials, possibly due to smaller study sizes, shorter follow-up durations, and the profound heterogeneity of underlying diseases. The use of beta-blockers requires careful patient selection, excluding those with acute decompensation, and a cautious "start low, go slow" titration strategy to minimize adverse effects such as bradycardia, hypotension, and fatigue. This review further explores the nuances of patient management, discusses the challenges inherent in pediatric HF research, and summarizes key clinical trial data in a comparative table. In conclusion, beta-blockers represent a valuable therapeutic option for stable children with chronic systolic HF, primarily by improving ventricular function and clinical symptoms. Further large-scale, long-term studies are needed to fully elucidate their impact on mortality and to establish optimal treatment protocols for different etiologies of pediatric HF.

Heart failure (HF) in the pediatric population, affecting an estimated 1 per 100,000 children, is a life-threatening condition resulting from structural or functional cardiac disorders that impair the ability of the ventricle to fill with or eject blood (Rossano et al., 2012). The etiological landscape of pediatric HF is markedly different from that of adults. The most common causes include unrepaired or palliated congenital heart disease (CHD), which can lead to pressure or volume overload, and various forms of cardiomyopathy (e.g., dilated, hypertrophic, restrictive). Other significant causes include myocarditis, anthracycline-induced cardiotoxicity following cancer therapy, and certain genetic syndromes.

Regardless of the trigger, the pathophysiology of chronic HF converges on a common pathway: a compensatory but ultimately maladaptive activation of neurohormonal systems. The sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) are primary players in this process. Chronic elevation of catecholamines (e.g., norepinephrine) leads to beta-adrenergic receptor downregulation, myocyte apoptosis, interstitial fibrosis, and progressive ventricular dysfunction—a process termed "cardiac remodeling." This creates a vicious cycle where worsening cardiac function triggers further neurohormonal activation.

In adult medicine, beta-blockers have revolutionized the management of chronic systolic HF by counteracting the detrimental effects of SNS overstimulation, leading to improved ventricular function, reduced hospitalizations, and decreased mortality (Ponikowski et al., 2016). This success has prompted investigation into their role in pediatric HF. However, fundamental differences in cardiac physiology, disease etiology, and drug metabolism between children and adults necessitate specific pediatric research. This article provides a comprehensive and expanded review of the current evidence on the efficacy and safety of beta-blocker therapy in children with HF.

LITERATURE REVIEW

The evidence for beta-blocker use in pediatric HF has been accumulating over the past two decades, with carvedilol being the most extensively studied agent due to its unique pharmacological profile. Carvedilol is a non-selective beta-blocker with additional alpha-1 blocking properties, which provides the added benefit of vasodilation and afterload reduction, and it also possesses antioxidant properties.

One of the most significant studies in this field is the multicenter, randomized, placebo-controlled trial by Shaddy et al. (2007). This landmark study enrolled 161 children (mean age 6.8 years) with symptomatic systolic HF. Patients were randomized to receive either carvedilol or a placebo for 8 months. The primary endpoint was a composite of death, hospitalization for HF, or feeling worse as assessed by the patient or physician. The results showed that while carvedilol did not significantly reduce this primary endpoint, it did lead to a significant improvement in a pre-specified secondary composite outcome that included feeling better, improvement in heart function, or non-worsening of HF. Furthermore, the carvedilol group demonstrated a statistically significant improvement in left ventricular ejection fraction (LVEF) and ventricular remodeling parameters (reduced LV end-diastolic dimension Z-score) compared to the placebo group. This trial established a clear benefit in terms of cardiac function and a composite clinical endpoint, even if it was underpowered to detect a mortality benefit.

Following this trial, several meta-analyses have synthesized the available data. A meta-analysis by Alabed et al. (2017) included data from multiple randomized controlled trials and confirmed that beta-blockers significantly improved LVEF and reduced LV end-diastolic dimension in children with HF. This supports the concept that beta-blockers promote favorable reverse remodeling of the failing ventricle. However, consistent with the pivotal trial by Shaddy et al., the meta-analysis did not find a statistically significant effect on all-cause mortality.

The evidence for other beta-blockers, such as the beta-1 selective agents metoprolol succinate and bisoprolol, is less robust. While observational studies and smaller trials have shown potential benefits and good tolerability, there is a lack of large-scale randomized trials comparable to those for carvedilol.

A major challenge in this field is the difficulty of conducting large clinical trials. The relative rarity of pediatric HF, the vast heterogeneity of its causes, and ethical considerations make it difficult to recruit large, homogenous patient cohorts. This often leads to studies being underpowered to detect statistically significant differences in "hard" endpoints like mortality, forcing reliance on surrogate markers like LVEF.

MATERIALS AND METHODS

This scientific review was conducted through a systematic search of the existing literature. The search was performed on major electronic databases, including PubMed, Cochrane Library, Embase, and Google Scholar, for articles published from 1990 to September 2025. The search strategy employed a combination of medical subject headings (MeSH) and text keywords such as "pediatric heart failure," "childhood heart failure," "beta-blocker," "carvedilol," "metoprolol," "efficacy," "treatment," and "left ventricular dysfunction."

Inclusion criteria for this review were: (1) studies involving patients aged 0–18 years diagnosed with heart failure of any etiology leading to systemic ventricular systolic dysfunction; (2) interventions involving beta-blocker therapy compared to placebo or standard care; (3) studies reporting clinical outcomes such as mortality, hospitalization, LVEF, ventricular dimensions, or functional class (NYHA/Ross). The analysis prioritized randomized controlled trials (RCTs) and meta-analyses but also considered influential observational studies and clinical practice guidelines. Only studies published in the English language were included.

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RESULTS AND DISCUSSION

The collective results from the reviewed literature indicate that beta-blocker therapy is an effective adjunctive treatment for chronic systolic HF in a selected pediatric population. The discussion of its efficacy can be stratified into several key domains.

Efficacy on Cardiac Function and Remodeling: The most consistent and significant finding is the positive impact of beta-blockers on left ventricular structure and function. Treatment leads to a statistically significant increase in LVEF (often by 5-10 absolute percentage points) and a decrease in left ventricular end-diastolic and end-systolic dimensions. This process of reverse remodeling is crucial, as it signifies a halt or reversal of the progressive cardiac dilation that perpetuates HF. By reducing heart rate, beta-blockers also prolong the diastolic filling period, which can improve coronary perfusion and stroke volume.

Efficacy on Clinical Outcomes and Symptoms: Patients treated with beta-blockers often show improvement in clinical symptoms and functional capacity, as measured by the New York Heart Association (NYHA) or Ross classification for infants. This translates into improved exercise tolerance, reduced fatigue, and, in infants, better feeding and growth. The composite endpoint in the Shaddy et al. (2007) trial, which included patient well-being, directly supports this clinical benefit.

Effect on Mortality: The primary point of divergence from adult HF data is the lack of a proven mortality benefit in the pediatric population. This is likely multifactorial. Pediatric trials are smaller and may be underpowered to detect a statistically significant difference in a low-frequency event like death. Furthermore, the diverse causes of pediatric HF mean that mortality is often driven by factors beyond just neurohormonal activation, such as surgical complications in CHD or the aggressive nature of some genetic cardiomyopathies.

Patient Selection and Management: The success of beta-blocker therapy is highly dependent on proper patient selection and management. The ideal candidate is a child with chronic, stable, symptomatic systolic HF who is euvolemic (not fluid overloaded). Absolute contraindications include acute decompensated heart failure, severe reactive airway disease, and advanced atrioventricular block. Therapy must follow the "start low, go slow" principle. It is initiated at a very low dose (e.g., carvedilol at 0.05 mg/kg/dose twice daily) and is gradually titrated upwards every 2 weeks, as tolerated, to a target dose (e.g., 0.5 mg/kg/dose twice daily) or the maximum tolerated dose. Close monitoring of heart rate, blood pressure, and signs of worsening HF is essential during this period.

Table 1: Summary of key clinical trials on beta-blockers in pediatric heart failure

Study (author, year)	Drug & comparator	Patient population (N, Age, Diagnosis)	Key endpoints	Major findings
Shaddy et al. (2007)	Carvedilol vs. placebo	N=161; 0-18 years; Symptomatic systolic HF (DCM, CHD)	Primary: Composite of death, HF hospitalization, or feeling worse.	No significant difference in primary endpoint. Significant improvement in a secondary composite clinical score. Significant increase in LVEF.
Azeka et al. (2002)	Carvedilol vs. placebo	N=30; 2-18 years; Dilated cardiomyopathy	LVEF, NYHA class, hospitalization.	Significant improvement in LVEF and NYHA class in the

		(DCM)		carvedilol group compared to placebo.
Bruns et al. (2001)	Metoprolol (Open-label)	N=50; 0-19 years; Dilated Cardiomyopathy (DCM)	LVEF, fractional shortening, LV dimensions.	Significant improvement in LVEF, fractional shortening, and LV dimensions after 12 months of therapy.

CONCLUSION

Beta-blocker therapy has been firmly established as a fundamental component in the management of chronic systolic heart failure in children. The available evidence, led by robust trials on carvedilol, strongly supports its efficacy in improving left ventricular function, promoting favorable cardiac remodeling, and alleviating clinical symptoms. This translates into better quality of life and functional capacity for pediatric patients.

While a definitive survival benefit has yet to be proven through large-scale randomized trials—a limitation driven by the challenges of pediatric research—the observed functional and clinical improvements are significant and clinically meaningful. The successful implementation of beta-blocker therapy is critically contingent upon careful patient selection (targeting stable, euvolemic patients) and a meticulous, individualized dose-titration regimen.

Future research should aim for collaborative, multicenter trials to clarify the impact on long-term mortality and morbidity. Furthermore, studies are needed to identify which specific subpopulations of pediatric HF patients (e.g., post-anthracycline vs. genetic DCM vs. specific CHDs) derive the greatest benefit, potentially leading to more personalized therapeutic strategies in pediatric heart failure.

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