# How effective is disopyramide in treating pediatric hypertrophic cardiomyopathy? State of the art and future directions

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## Abstract

Pediatric hypertrophic cardiomyopathy (HCM) has a wide range of clinical manifestations. Left ventricular outflow tract obstruction (LVOTO) at rest is present in up to one-third of children with HCM, with a further 50-60% of symptomatic children developing a gradient under exertion. Treatment options are limited, and there is a relative lack of data on the pediatric population. Disopyramide is a sodium channel blocker with negative inotropic properties. This therapy effectively reduces LVOTO in adults with HCM and delays surgical interventions, but it is not licensed for use in children.

We aimed to review and analyze the influence of disopyramide over the pathophysiological, clinical, electrocardiographic, and echocardiographic characteristics of patients with HCM in infancy, childhood, adolescence, and adult age. While disopyramide remains a cornerstone in the management of pediatric HCM, the advent of mavacamten and aficamten heralds a new era of potential advancements. These emerging therapies could significantly improve the quality of life and prognosis for young patients with HCM.

## Introduction

Hypertrophic cardiomyopathy (HCM) is the second most common cardiomyopathy in children and the most common cause of sudden cardiac death (SCD) in children and young adults [1,2]. It is defined as a myocardial disorder characterized by left ventricular wall hypertrophy (LVH) in the absence of secondary cardiac or systemic conditions capable of determining such thickness [3]. The estimated prevalence is reported to be 0.02% in the pediatric population [4].

Primary HCM is an autosomal dominant disease caused by a mutation in genes encoding components of the cardiac sarcomere: β-myosin heavy chain (*MYH7*) and myosin-binding protein C (*MYBPC3*). However, clinical variability is extremely high even within the same family, suggesting that external factors also contribute to the phenotypic expression of the disease [3]. Patients affected by inherited metabolic storage diseases (*e.g.*, Anderson-Fabry, Danon, and Pompe disease, disorders of fatty acid metabolism, and lysosomal storage disorders), mitochondrial diseases, syndromic diseases (*e.g.*, Noonan disease), and neuromuscular diseases (*e.g.*, Frederich ataxia) may present a secondary HCM in the absence of mutations in sarcomere proteins. The clinical manifestations and the pattern of left ventricular hypertrophy mimic that of primary HCM; nevertheless, etiopathogenesis, prognosis, and treatment are different [5,6]. In over 50% of infants, the cause of HCM remains idiopathic [1].

## Diagnosis of hypertrophic cardiomyopathy: from morphological highlights to clinical presentation

The clinical presentation of HCM is highly heterogeneous, linked to the etiology of HCM and mainly determined by the pattern and extent of LVH, which can lead to the narrowing of the left ventricle (LV) cavity with resulting diastolic dysfunction and myocardial ischemia due to an increased myocardial oxygen demand. No single pattern of LVH is typical, but generally, the hypertrophy is asymmetric and affects the basal and mid-ventricular septum; up to 50% of infants show a concentric pattern, and less frequent is the involvement of only the apical segment [7]. Depending on the hemodynamic subsets, HCM can be classified into obstructive HCM (oHCM) and non-obstructive HCM. Indeed, in patients affected by HCM, the development of a dynamic pressure gradient across the left ventricular outflow tract (LVOT) is commonly reported, resulting from dynamic subaortic obstruction produced by mitral valve anterior systolic displacement (SAM) consisting in the movement of the anterior mitral valve leaflet toward the ventricular septum and septal hypertrophy [7]. oHCM is defined by the presence of dynamic LVOT obstruction with an LVOT peak pressure gradient >30 mmHg, which is variable day-to-day and is influenced by factors acting on ventricular contractility and loading [5]. Up to one-third of children with HCM have resting LVOT obstruction, while 50-60% of symptomatic children develop a gradient in physical effort [8].

Commonly reported symptoms are dyspnea, chest pain, arrhythmia, fatigue, palpitation, and dizziness, which may be present at rest or on exertion, even though most patients with HCM are mildly symptomatic or asymptomatic [9]. In pediatric patients with HCM, congestive heart failure associated with dyspnea, poor feeding, and stunting are often the first manifestations. Syncope may be a precursor to future SCD, which, however, frequently occurs without warning signs and symptoms [5].

## Role of cardiac imaging

Screening with an electrocardiogram (ECG) of all first-degree relatives of patients with HCM can lead to early identification of those affected, as ECG abnormalities can precede the overt development of the pathology by many years. The resting 12-lead ECG is abnormal in 75% to 95% of patients with HCM and the commonest abnormalities are ventricular hypertrophy, repolarization abnormalities with ST depression and negative T waves in the left leads (D1, aVL and/or V4-V6), giant negative T waves in apical HCM, left axis deviation, pathologic Q waves/pseudoinfarction pattern and left atrial enlargement as a result of left ventricular diastolic dysfunction [7]. Even a short PR interval without preexcitation may be present, while atrioventricular (AV) conduction delay is a frequent finding in HCM caused by mitochondrial diseases [3]. Typical arrhythmias are malignant ventricular arrhythmias (ventricular tachycardia or fibrillation), secondary to the unstable electrophysiological substrate with areas of myocyte disarray and fibrosis resulting from cellular necrosis caused by microvascular ischemia and atrial fibrillation, related to left atrial enlargement [7].

Echocardiography is the gold standard to confirm the diagnosis, which is based on the presence of a maximal LV wall thickness of two standard deviations above the mean for age and body surface area; any pattern of hypertrophy (concentric, eccentric, interventricular, distal, and apical) is sufficient to make the diagnosis [10] (Figure 1). Hypertrophy generally develops during puberty in primary HCM and in infancy in secondary HCM; in this last class of patients the thickness of LV is often concentric and associated with right ventricle hypertrophy. Other typical echocardiographic findings are LV cavitary obstruction during systole, impairment of the diastolic filling in LV associated with an abnormal transmitral inflow pattern (decreased E/A ratio) and left atrial enlargement. In cases of significant LVOT obstruction (LVOT peak pressure gradient >30 mmHg) at rest or after provocation, generally occurring in mid to late systole, it is possible to identify a high-velocity stream in the subaortic region and the SAM of the mitral valve. SAM often determines posteriorly directed mitral regurgitation, while regurgitation in other directions is an index of intrinsic valve abnormalities.

Both LVOT obstruction and SAM are dynamic conditions (Figure 2). LV systolic function is generally increased; depressed LV ejection fraction is a poor prognosis factor and represents the end-stage of HCM [3]. By using advanced echocardiographic techniques, such as speckle tracking, 3D echocardiography, and stress echocardiography, it is possible to improve diagnostic effectiveness and management. By analyzing the radial, longitudinal, and circumferen-

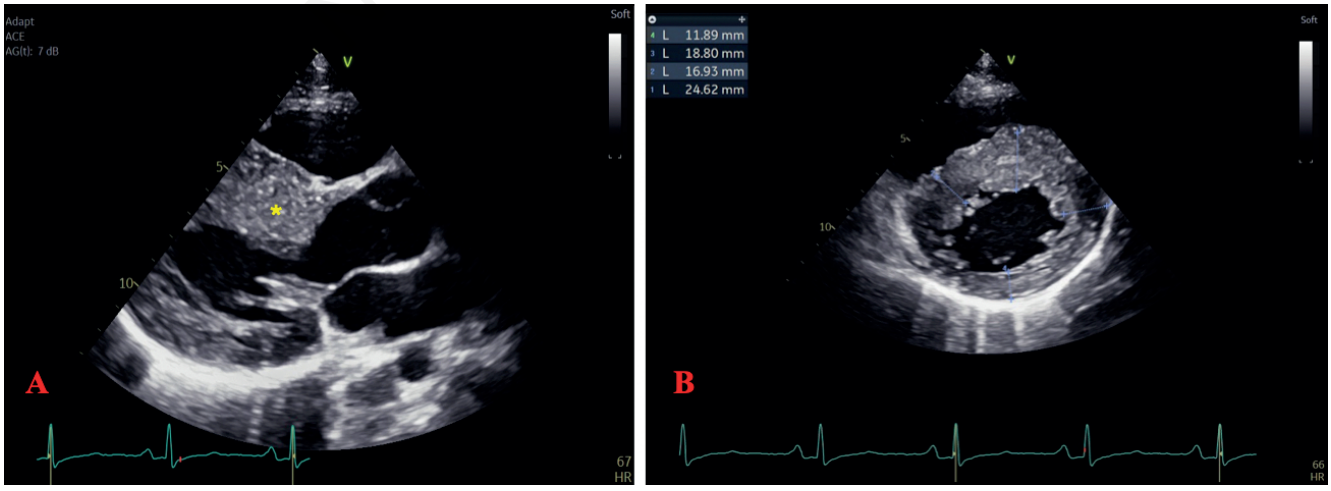


**Figure 1.** A) Parasternal long axis view of a pediatric hypertrophic cardiomyopathy patient depicting distribution of hypertrophy, especially in the interventricular septum; B) short axis view of the same patient with an interventricular wall thickness of 24.62 mm.

tial myocardial deformation, it is possible to early detect myocardial dysfunction in patients with preserved ventricular ejection fraction [11]. Indeed, it is known that up to 50% of patients with asymmetric septal HCM show a reduced systolic shortening and a paradoxical lengthening of the segments involved by hypertrophy; the reduction of myocardial strain is directly proportional to the extent of septal hypertrophy. Moreover, this technique allows for better identification of the pattern of ventricular thickness (Figure 3). Studies also showed a correlation between the reduction of longitudinal strain and the onset of ventricular tachycardia or exercise intolerance [12]. 3D echocardiography allows better assessment of biventricular dimension, LVH, and ejection fraction and a higher definition of mitral valve and LVOT anatomy, thus optimizing time for cardiac catheterizations or surgical interventions [13]. Stress echocardiography can be performed using a cycle ergometer or treadmill or with dobutamine administration. According to the 2023 European Society of Cardiology guidelines, stress echocardiography is used as a diagnostic tool in symptomatic patients with a resting LV outflow gradient of <50 mmHg to assess its increase during exercise [4].

In our experience, stress echocardiography is useful in patients (sub-symptomatic or asymptomatic) who, during echocardiography, present criteria of HCM without significant LVOT obstruction. In these cases, stress echocardiography shows inducible LVOT obstruction, allowing early identification of patients eligible for therapy. In addition, it provides insight into functional capacity and exercise tolerance, useful in correlating symptoms like chest pain or shortness of breath with the presence of obstruction or ischemia [14]. Its use in the pediatric population has been so far not well established as compared to adults. However, it is useful to identify patients with inducible LVOT obstruction >30 mmHg not detectable by rest echocardiography [15]. Moreover, it allows the differentiation of pediatric patients with HCM from athletes, in whom LVOT gradient during exercise is normally reported [16]. In adults, it is known that those with LVOT during exertion have a higher risk of cardiovascular events, while in the pediatric population, long-term prospective studies determining the outcomes of patients with exercise-induced LVOT obstruction are not yet available [15].

## Treatment of obstructive hypertrophic cardiomyopathy

### Standard management

The goal of drug therapy is to relieve symptoms, improve quality of life, and reduce mortality from SCD events related to oHCM [17]. Nowadays, there is no clear evidence in the literature to suggest that medical therapy can change the natural history of disease in addition to improving symptoms. Medical therapy is structured at different levels according to tolerance and the patient's individual response [17].

β blockers (BB) and non-dihydropyridine calcium channel blockers (NDCCB) are both considered first-line treatments. BB reliably decreases LVOT gradient due to their intrinsic negative inotropic function, thus improving the diastolic function of the LV and ventricular filling [18]. Medications need to be titrated to a dose since symptom relief is observed; the failure of BB therapy should be declared when no improvement in symptoms is observed while observing the heart's effect of BB action of the drugs (*i.e.*, lowering resting heart rate) [19].

NDCCB class medication has been demonstrated to have an active role in symptom relief in oHCM. According to Taha *et al.* specifically, in a direct comparison between metoprolol and verapamil, the calcium channel blocker demonstrated not only the effectiveness in treating symptoms but also the ability to improve the patient's New York Heart Association (NYHA) functional class [20]. A limitation in the use of this class of drugs may lie in vasodilating properties that could potentially increase the LVOT gradient [17].

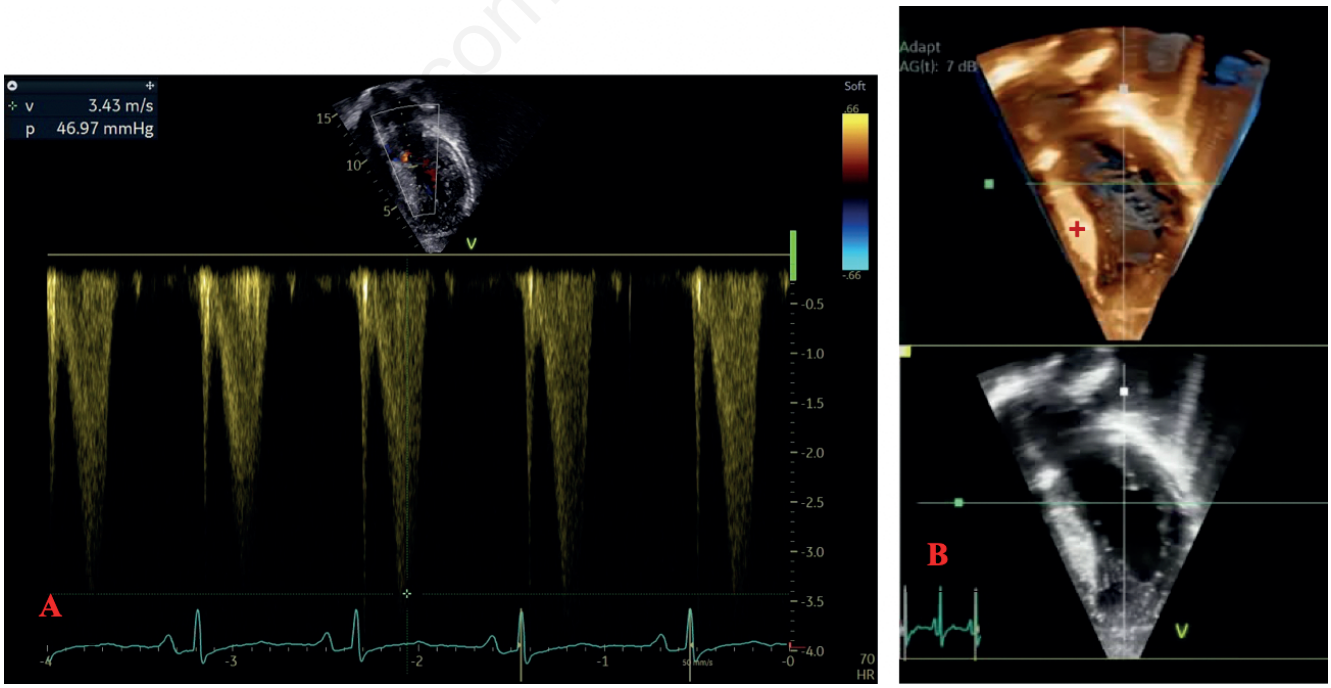


**Figure 2.** A) Patient with septal hypertrophy with a peak gradient of 46.97 mmHg at rest; B) 3D echocardiography in hypertrophic cardiomyopathy with significant interventricular septal hypertrophy (+) apical four chamber view.

## Invasive treatment

Invasive non-pharmacological treatment of the oHCM is based on the reduction of the anatomical thickness of the interventricular septum, where the gradient is located. Septal reduction therapy (SRT) is contemplated in patients who persist symptomatic despite an optimal medical therapy or in which it is not possible to optimize it due to the occurrence of not-tolerated side effects [21]. SRT can be performed by surgical or percutaneous technique. The surgical technique, which involves extensive septal myotomy (ESM) through a trans-aortic approach, is feasible for a wide range of patients, with a mortality rate of less than 1% and a success rate of 90-95% [22]. ESM, if properly performed, can reduce up to eliminate the SAM of the mitral valve that produces an abnormal coaptation of the valve leaflets and a various degree of mitral regurgitation [23,24]. The correction of functional mitral valve dysfunction improves left atrium reverse remodeling, reduces burden of pulmonary hypertension, improves exercise capacity, and reduces the risk of gastrointestinal bleeding and onset of arrhythmic burden [25-28]. The trans-aortic approach may not be feasible in the entire pediatric population because of the small size of the aortic anulus. In this population, the Konno procedure, or the trans-apical approach, has proved to be effective [29]. Percutaneous trans-catheter therapy consists of alcohol septal ablation (ASA); this is a well-established procedure for SRT in the adult population, but no consistent data are available in the pediatric population [17].

## Disopyramide in obstructive hypertrophic cardiomyopathy

Disopyramide is a class I antiarrhythmic drug with a negative inotropic effect, known since 1980, and primarily used in atrial fibrillation. Disopyramide was introduced in the 2014 European Society of Cardiology guidelines as a class I recommendation and in the 2011 American Heart Association (AHA) guidelines as a class IIa recommendation for the treatment of oHCM, in addition to BB. This recommendation is not only to reduce the risk of arrhythmias but also to reduce the LVOT gradient [30]. Due to its negative inotropic effect, disopyramide reduces the acceleration of flow during the initial phase of systole, thereby reducing SAM and ultimately lowering the LVOT gradient. The modest reduction in ejection fraction caused by the negative inotropic effect of this drug reduces the hyperkinetic contraction of these patients, leading to better ventricular emptying capacity by reducing outflow obstruction [31]. Reduction in gradient leads to clinical improvement and symptom reduction [32]. The mechanism of action of

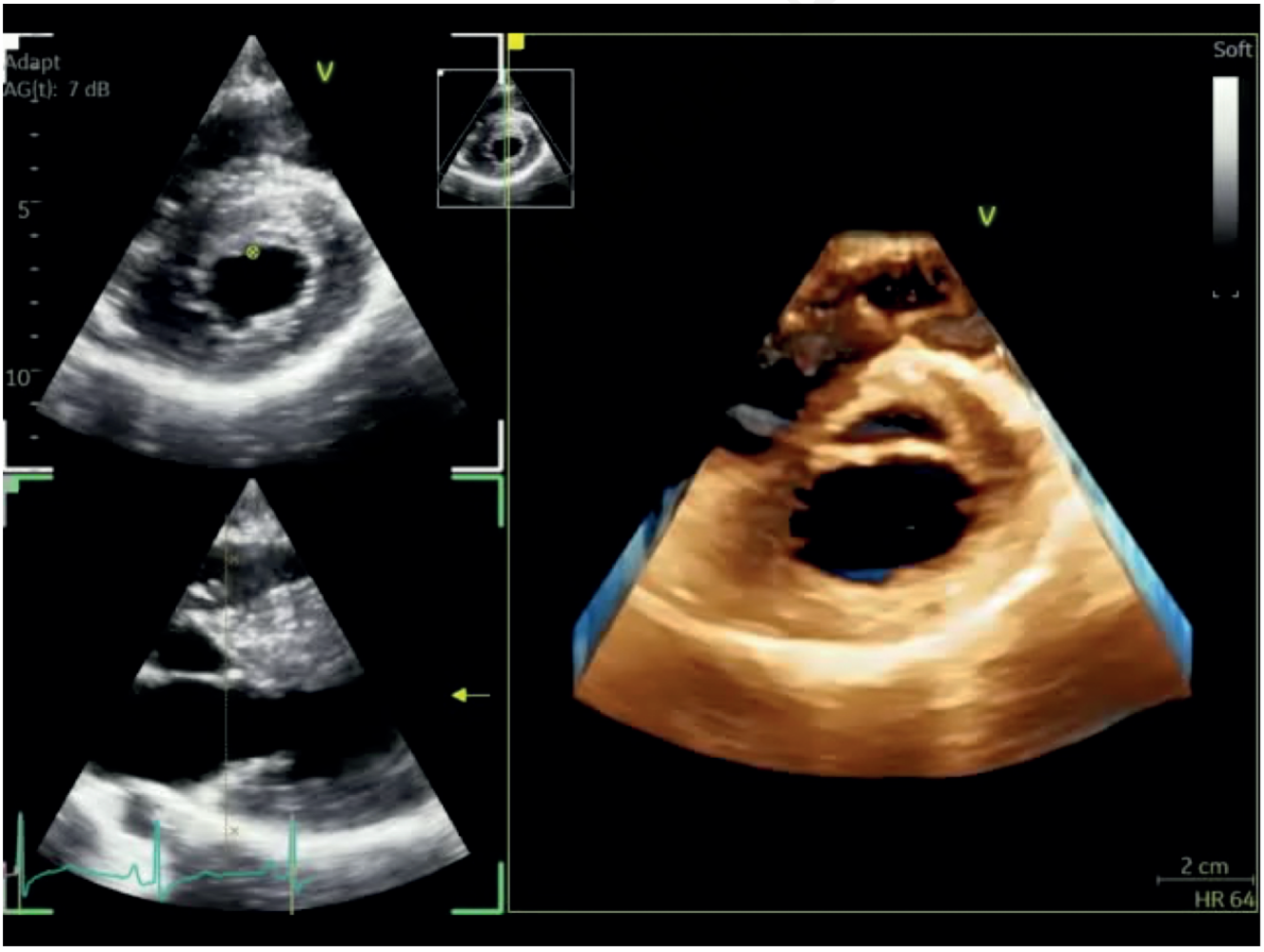


**Figure 3.** 3D echocardiography for assessment of left ventricular geometry and papillary muscle evaluation.

disopyramide was studied by Coppini *et al*., who suggested that the negative inotropic effect results from a reduction in intracellular calcium during systole mediated by the inhibition of various ion channels. This also leads to a shortening of the action potential with a consequent protective effect against arrhythmias [31].

The efficacy of disopyramide in managing LVOT obstruction by reducing the gradient, even by 50-60%, with concurrent symptom improvement has been demonstrated in multicenter studies by Sherrid *et al*. and in a study by Coppini *et al*. [31-33]. These studies also highlighted disopyramide's good safety profile; in the cohort of treated patients, there were no significant differences in survival, which was even better due to gradient reduction [33]. In the cohort of Maurizi *et al*., the efficacy of disopyramide was demonstrated in more than a quarter of treated patients [34]. Similar results were obtained in studies by Tropiceanu and O'Connor in pediatric patients, which showed the efficacy of this molecule in reducing symptoms in pediatric HCM patients [8,35].

The group of patients benefiting the most from this treatment includes those in NYHA I-II class, younger ages, and lower LVOT gradients [34]. Similar results were obtained by Sherrid, who found that patients not responding to disopyramide had very high resting gradients (>89 mmHg) [36]. Since disopyramide's effect is achieved through its negative inotropic mechanism, which lowers diastolic relaxation pressures, the greatest effect is observed in patients with greater contractility. Consequently, some authors have questioned the efficacy of disopyramide in non-obstructive HCM patients [34].

## *Indication about the use of disopyramide*

Disopyramide has been studied with good results in symptomatic HCM patients in addition to BB therapy to delay or avoid surgery [36]. Sherrid *et al*. used disopyramide in a group of oHCM patients with an LVOT gradient of at least 30 mmHg at rest who were symptomatic and unresponsive to first-line treatment with BB or verapamil [33]. In pediatric patients, the efficacy of disopyramide has been demonstrated in HCM patients under 21 years old with symptoms not controlled by first-line therapy [8,35]. These indications are supported by the 2020 AHA guidelines, which recommend disopyramide as a class Ib treatment for patients with symptoms consistent with LVOT obstruction unresponsive to first-line therapy with BB or NDCCB [37].

Various protocols have been tested in the literature regarding disopyramide dosing. In pediatric patients, due to faster metabolism, the dose used ranges from 2 mg/kg three times a day, with the possibility of increasing the dose while monitoring the corrected QT interval (QTc) up to 20 mg/kg/day. Because of this wide dosage range and rapid metabolism, plasma levels of disopyramide are very useful in dose titration in pediatric patients. The therapeutic range is about 6-16 mg/kg in three doses [30,35]. In the adult population, the maximum dose is 300 mg twice daily without the need to monitor blood levels of the drug, except for patients with impaired renal clearance [36]. Dose increases can be made every 4 days with QTc monitoring, avoiding increases if the QTc prolongs by more than 25% of the baseline value, though it is safer not to exceed an increase of more than 10-15% from the baseline [30]. The study by Maurizi *et al*. also showed that disopyramide's efficacy is the same regardless of the dose used, but adverse effects are dose-dependent. Coppini *et al*. supported this finding, highlighting disopyramide's superiority over other negative inotropic drugs but arguing that its efficacy is not dose-dependent, contrary to Sherrid's study, which shows that the gradient effect is dose-dependent [31,36].

## *Effects of disopyramide on clinical symptoms, echocardiographic and electrocardiographic findings*

Symptoms improvement represents the primary endpoint of most studies, showing the most promising results. Various studies have demonstrated that disopyramide can reduce symptoms at 6 months, particularly dyspnea and chest pain [8]. Regarding the outflow gradient, not all studies in the pediatric population have shown an echocardiographic reduction in the outflow gradient, unlike in adults. It should be noted that the gradient is dynamic and depends on heart rate, making it not always a reliable and reproducible measure. Despite this, many studies have shown a reduction in mitral SAM in a portion of subjects, indicating that this mechanism may also be implicated in the appearance and exacerbation of reported symptoms [8]. Despite that, O'Connor *et al.* demonstrated a reduction in the outflow tract gradient in 7 of the 8 patients studied, with a median reduction of about 58%, comparable to studies in the adult population [35]. Multicenter studies in the adult population by Sherrid *et al.* demonstrated a gradient reduction in two-thirds of patients, with better results in those with higher gradients [33]. Yedidya *et al*. also showed that measuring global and longitudinal strain after disopyramide administration in oHCM patients resulted in a strain reduction in all segments, greater in those with higher baseline values, correlating with the beneficial effect on LVOT obstruction in these patients, further proof that the results obtained from this molecule are due to its negative inotropic effect [38].

QT prolongation has been described on ECG after disopyramide use, partially due to QRS prolongation caused by the inhibition of the peak sodium current, slowing AV conduction [31]. The risk associated with QT prolongation is the induction of ventricular arrhythmias. However, Coppini's study debunked this concern, demonstrating that QT prolongation is proportional to the baseline QT and the reduction in differences in QT duration between different myocardial regions results in a reduced arrhythmic effect [31]. In fact, multicenter studies have shown that ventricular arrhythmias occurred in less than 1% of treated patients [36]. In the pediatric population, no significant prolongations of PR and QT were reported, and any prolongation occurred within the first 6 months of treatment [8]. QT prolongation, present in 68% of cases in Maurizi *et al*.'s study, led to therapy discontinuation in a very small group of patients [34]. QT prolongation usually happens within the first 6 months of starting the drug. Therefore, initiating disopyramide with telemetric monitoring is recommended to keep the arrhythmic risk under control. QT prolongation can exceed 500 ms, as demonstrated by O'Connor *et al*. [35]. In Sherrid *et al*.'s group, no patients treated with disopyramide showed QT prolongation [32]. In addition, disopyramide can be continued even if the QTc is 550 ms in patients with wide QRS and 525 ms with narrow QRS without developing arrhythmias. In the examined studies, one patient developed AV block, requiring cardioverter-defibrillator implantation [36]. Despite the safety profile demonstrated by various studies, it is still advisable to avoid combining disopyramide with other QT-prolonging drugs [31]. Table 1 depicts the major findings in the current literature about the effects of disopyramide and ECG modifications in pediatric cohorts.

The real side effect of disopyramide is its anticholinergic effect, which can manifest especially in the first weeks of treatment with dry mouth, constipation, and ocular redness. These symptoms tend to reduce over time [30]. Sherrid *et al.* also demonstrated the safety of combining therapy with pyridostigmine to reduce anticholinergic effects [33]. In the pediatric population, the proportion of patients who discontinued therapy was higher than in adults, but with a lower proportion of discontinuation due to anticholinergic effects [8]. Preventive measures can mitigate these symptoms [30].

Disopyramide increases AV node conduction, so it is recommended to use it in combination with drugs that block the AV node, such as BB [37].

Initially, cases of hypertension may occur, probably related to the reduction of the outflow gradient, but these tend to normalize during follow-up [39]. Sherrid *et al*. demonstrated the absence of negative effects on the renal, hepatic, hematologic, and central nervous systems, allowing its use for many years [33].

## Future directions

Several studies emphasize that the effect of disopyramide tends to diminish over time. Indeed, the reduction of the outflow gradient is less during the follow-up months. A proportion of treated patients still undergo myectomy, indicating that disopyramide cannot halt the progression of the disease [8,32,35]. Maurizi *et al*. reported that 50% of treated patients ended up needing surgery, and these were patients with more significant symptoms in NYHA class III and IV [34]. As research continues to advance, the landscape of treatment for HCM is approaching with novel strategies.

Mavacamten is a novel cardiac myosin inhibitor recently approved by the Food and Drug Administration for the treatment of oHCM in adults. It works by reducing cardiac contractility through the inhibition of cross-bridging between myosin and actin [40,41].

Several trials, including PIONEER-HCM, EXPLORER-HCM, VALOR-HCM, and MAVA-LTE have studied its efficacy [42,43]. These studies demonstrated a reduction in the LVOT gradient at rest and after exercise, an increase in peak oxygen uptake ($pVO_2$), improvements in NYHA functional class, enhancements in the Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score, as well as improvements in NT-proBNP blood test results [40,41,44,45].

Eligible patients for this treatment are those with oHCM who are refractory to maximal pharmacological therapy and have an ejection fraction >55%. It is also suitable for patients who are candidates for SRT but prefer to avoid invasive approaches or do not have access to specialized surgical centers [46]. The efficacy of mavacamten is dose-dependent, with studies showing increased effects at higher drug concentrations.

From a safety perspective, mavacamten generally exhibits a good tolerance profile with mild side effects. The most significant adverse event is related to its negative inotropic effect, which can reduce ejection fraction and potentially lead to heart failure. In such cases, when patients reach an ejection fraction <50%, temporarily discontinuing the therapy is usually sufficient to resume contractility and recover ejection fraction [41]. Monitoring of this therapy is primarily echocardiographic, and it is particularly rigorous during both the initiation and maintenance phases of treatment and when the treatment leads to adverse events [41].

The concurrent use of disopyramide and mavacamten is contraindicated due to the negative inotropic effects of both drugs. If it is necessary to proceed with the overlap of mavacamten therapy, a gradual tapering of disopyramide during the introduction of mavacamten has been shown to be safer. As a matter of fact, in some cases where a washout of disopyramide was performed, patients exhibited



**Table 1.** Overview of main cited studies about the use of disopyramide and its effects on electrocardiogram and echocardiographic findings.

| Study | Year of publication | Main findings | ECG analysis: QTc assessment |
|---|---|---|---|
| Sherrid *et al.* [32] | 2005 | – LVOTO: reduction of 50% in 3 years<br>– NYHA: decreased from 2.3 to 1.7 | Not significant |
| Sherrid *et al.* [33] | 2013 | – LVOTO: from 63±45 to 25±32 mmHg (p<0.0001) - 60% reduction<br>– SYMPTOMS: overall reduction | Stopped when QTc>525 ms |
| Sherrid *et al.* [36] | 2012 | – LVOTO: reduction in 2/3<br>– SYMPTOMS reduction | Stopped when QTc>525 ms |
| Coppini *et al.* [31] | 2019 | – LVOTO: from 58±49 mm Hg to 25±26 mm Hg after 96 days of disopyramide (p<0.001) | QTc interval increased from 458 ms to 486 ms (p<0.001). Mean QTc prolongation was 27 ms, which corresponds to a 5.8% increase from baseline.interval (greater than the median 457 ms) had a smaller increase in QTc interval than did patients with shorter initial QTc interval (DQTc: 18 4 ms *versus* 34 8 ms, p 1⁄4 0.007). There was an inverse correlation between the initial QTc interval and the increase in QTc interval with disopyramide (Pearson r 1⁄4 0.44, p 1⁄4 0.008) |
| Maurizi *et al.* [34] | 2023 | – LVOTO: significantly reduced (72±36 mmHg *versus* 49±31 mmHg; p<0.001)<br>– NYHA: 5 (4%) patients in NYHA II class became asymptomatic; 21 (25%) patients improved their functional class from NYHA III to NYHA II | 19 (16%) patients showed reduced QTc from baseline; 19 (16%) had no difference, while 80 (68%) patients had a prolongedQTc interval |
| Topriceanu *et al.* [8] | 2023 | – LVOTO: no changeNYHA: reduction of symptoms in 86.8% and asymptomatic in 31.6% after 6 months | 2 (3.9%) QTc>500 ms |
| O'Connor *et al.* [35] | 2018 | – LVOTO: reduction of 52.8% in 8 patients but not at the last follow up | Statistically significant (p=0.004) but clinically insignificant increase in QTc. median % increase of 12.9% |
| Yedidya *et al.* [38] | 2022 | – Reduction of global longitudinal strain, segmental longitudinal strain, the base-to-apex gradient, and systolic rotational mechanics | / |

ECG, electrocardiogram; LVOTO, left ventricular outflow tract obstruction; NYHA, New York Heart Association; QTc, corrected QT interval

worse clinical outcomes and cardiac function. This effect is likely related to the different half-lives of the two drugs, with mavacamten having a half-life of 6-9 days compared to 4-10 hours for disopyramide [47]. Mavacamten shows promising results in improving cardiac contractility and has a favorable safety profile in patients with oHCM. However, its long half-life, extended wash-out period, and significant potential to interfere with the metabolism of various drugs due to its influence on multiple P450 cytochromes make it less than ideal. Moreover, it remains a very costly treatment [44]. Another drug currently under study for the treatment of oHCM is aficamten. This new myosin inhibitor has demonstrated a good safety profile and significant short-term efficacy in reducing both resting and post-Valsalva LVOT gradients as early as 2 weeks after starting therapy. Overall, its effects on cardiac function are comparable to those of mavacamten. What makes aficamten promising in comparison is its rapid hemodynamic response within a few weeks of therapy initiation, shorter half-life, and lack of influence on P450 cytochromes, resulting in fewer drug-drug interactions [48-50].

The efficacy of aficamten has been investigated in the phase 2 REDWOOD-HCM trial and further extended to the FOREST-HCM trial. Currently, it is in the phase 3 SEQUOIA-HCM clinical trial. Preliminary results from SEQUOIA-HCM suggest that 24 weeks after starting therapy, aficamten increases pVO2, thereby enhancing overall myocardial efficiency. This improvement is achieved by reducing hypercontractility and improving diastolic function in patients with oHCM. Furtheremore, aficamten has been shown to reduce LVOT pressure gradients by up to 30 mmHg and alleviate symptoms in patients with oHCM, leading to an improvement in NYHA class. Additionally, its short half-life also allows for rapid discontinuation and quick washout in case of adverse effects [50,51].

## Conclusions

Disopyramide has demonstrated significant utility in the management of pediatric oHCM, primarily through its ability to reduce LVOT and mitigate symptoms. Despite its efficacy, its use in pediatric populations requires careful consideration due to its side effect profile. The landscape of oHCM treatment is evolving with the emergence of novel agents such as mavacamten and aficamten. Early clinical trials in adult populations have shown encouraging results, suggesting these therapies may offer superior efficacy and a favorable safety profile compared to traditional treatments. However, specific studies focusing on the pediatric population are essential to prove safety, optimal dosing, and long-term outcomes.

Integrating these innovative therapies into clinical practice could revolutionize the management of pediatric oHCM. Future research should prioritize rigorous clinical trials involving pediatric patients to establish robust evidence for the use of mavacamten and aficamten in this cohort [48]. Moreover, comparative studies are needed to evaluate their effectiveness relative to existing treatments like disopyramide and to determine their role in combination therapy.

Continued research, careful patient monitoring, and a tailored approach to treatment will be crucial in exploring new therapeutic options to optimize outcomes for pediatric patients affected by oHCM.

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