CJC Open 6 (2024) 811–817

Review

# Does Disopyramide Still Have a Place in the Management of Obstructive Hypertrophic Cardiomyopathy?

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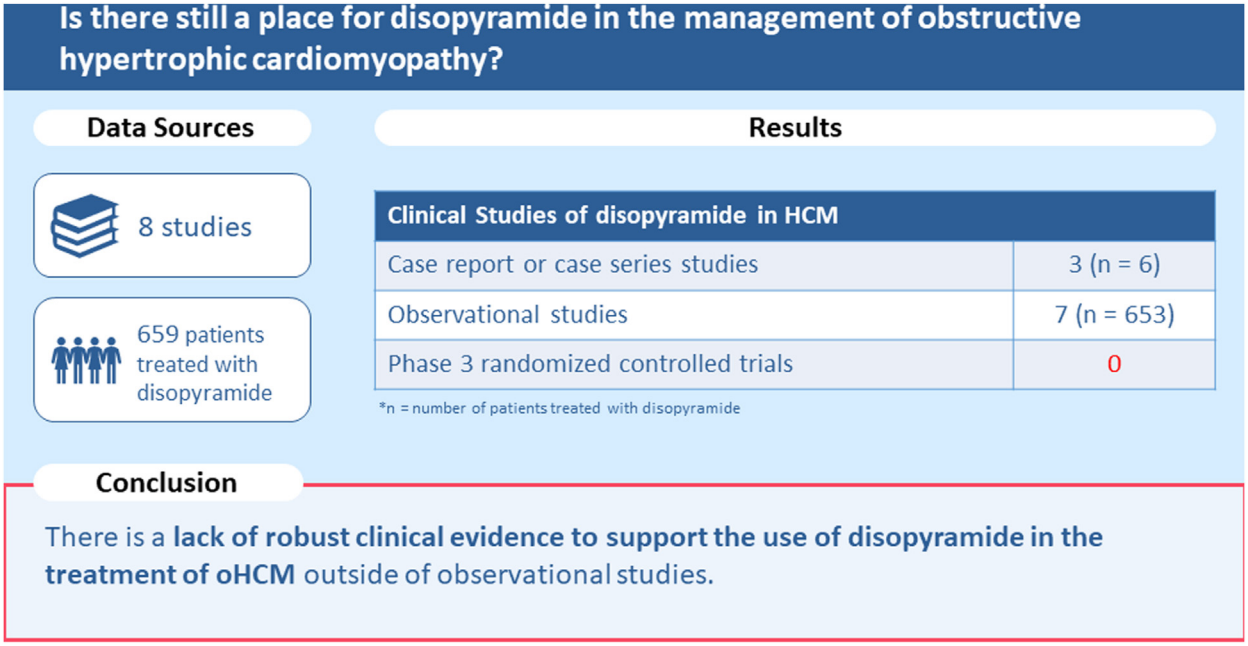


**ABSTRACT**

**Hypertrophic cardiomyopathy (HCM) is a relatively common inherited cardiac disorder associated with a left ventricular hypertrophy that cannot be explained by another cardiac or systemic disorder. One of the core pathophysiology features is left ventricular outflow tract obstruction (obstructive HCM [oHCM]), and this pathology could lead to complications, including sudden cardiac death and heart failure. Current treatment strategies for symptomatic oHCM consist of historical pharmacologic agents that are often based on nonrandomized, limited data or expert opinion. This article presents a critical appraisal of**

**RÉSUMÉ**

**La cardiomyopathie hypertrophique (CMH) est une maladie cardiaque congénitale relativement fréquente associée à une hypertrophie ventriculaire gauche qui ne peut s'expliquer par un autre trouble cardiaque ou général. L'une des principales caractéristiques physiopathologiques est l'obstruction à l'éjection du ventricule gauche (CMH obstructive [CMHo]), une pathologie qui peut entraîner certaines complications, comme la mort subite d'origine cardiaque et l'insuffisance cardiaque. Les stratégies thérapeutiques actuelles pour prendre en charge la CMHo symptomatique utilisent des agents pharmacologiques classi-**

Hypertrophic cardiomyopathy (HCM) is a relatively common inherited cardiac disorder, with an estimated prevalence of 1:500.[1,2] Obstructive HCM (oHCM) is a primary myocardial disorder defined by left ventricular (LV) hypertrophy associated with nondilated ventricular chambers that cannot be explained by another cardiac or systemic disease.[3-6] Core

https://doi.org/10.1016/j.cjco.2024.03.006

**disopyramide, one of the pharmacologic options available in Canada for managing oHCM. The author concludes that robust clinical evidence supporting the use of disopyramide in treating oHCM is lacking, and that disopyramide should be reserved as a last resort for nonresponders to pharmacologic treatment and for those in whom invasive therapies are not indicated.**

**ques et reposent sur des données limitées, recueillies dans le cadre d'études sans répartition aléatoire, ou sur l'avis de spécialistes. Cet article fournit une évaluation critique du disopyramide, l'une des options pharmacologiques offertes au Canada pour prendre en charge la CMHo. Les auteurs concluent que faute de données cliniques robustes à l'appui de l'utilisation du disopyramide dans le traitement de la CMHo, cette option devrait être utilisée en dernier recours chez les patients qui ne répondent pas au traitement pharmacologique ou chez qui les traitements invasifs ne sont pas indiqués.**

pathophysiological features include hypercontractility, impaired relaxation, and dynamic LV outflow tract obstruction.[6] The obstruction accounts for up to 70% of cases, based on current estimates.[5] Patients with oHCM are at risk of sudden cardiac death due to lethal ventricular arrhythmias, progression to end-stage heart failure (HF), and atrial fibrillation (AF) with concomitant risk of thromboembolism.[7] Based on the degree of obstruction and systolic anterior motion of the mitral valve with insufficiency, patients may also suffer significant morbidity, with limited exercise capacity and the development of presyncope or frank syncope.[8]

Due to limited evidence from randomized controlled trials, current treatment strategies for symptomatic oHCM are historical pharmacologic agents that are often based on nonrandomized, limited data or on expert opinion.[3] Only a paucity of data are available for most pharmacologic options that are being used with recommendations based on observational evidence. In the last 6 decades before the arrival of emergent treatments, Spoladore et al. report less than 50 studies that enrolled no more than 2000 patients.[9] This article aims to assess the role of disopyramide, one of the currently available therapeutic options in Canada, in the treatment algorithm of oHCM and present a critical appraisal of disopyramide as part of standard of care.

## Current Guideline Recommendation for Treatment of oHCM

Based on current treatment guidelines, pharmacotherapies for oHCM are based on empirical data aimed at improvement of symptoms and functional classification.[3] For patients with resting or inducible symptomatic oHCM, beta-blockers (BBs), titrated to effectiveness or maximally tolerated doses, are recommended as a first-line treatment, and calcium-channel blockers (CCBs) are recommended for patients in whom BBs are not tolerated or are ineffective (American Heart Association [AHA]/American College of Cardiology guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy, class Ib-NR [non-randomized]).[3] However, these therapies have limited efficacy and have not been shown to prevent disease progression or treat the underlying mechanisms of disease. Guidelines recommend that for patients with oHCM who are still symptomatic despite BBs or non-dihydropyridine CCBs, septal reduction therapies (SRTs; by experienced surgeons or interventionalists in expertise centres) or a third-class pharmacologic option (class Ia antiarrhythmics), such as disopyramide, may be considered (AHA guideline, class 1B-NR; European Society of Cardiology [ESC] guideline, class 1 level B).[3,10,11] More recently, the European guidelines included the new cardiac myosin inhibitor, suggesting that it should be recommended when a BB and/or a CCB and/or disopyramide are inefficient or not tolerated (class 2a, level A).[11]

Disopyramide is a class Ia antiarrhythmic, first developed and used in the treatment of atrial and ventricular arrhythmias. Primarily due to its negative inotropic effects, disopyramide was used in oHCM to reduce LV contractility and LV outflow tract (LVOT) gradient. Use of disopyramide in HCM requires careful monitoring due to the potential for both proarrhythmias and adverse anticholinergic events. Currently, guidelines suggest that disopyramide be considered in addition to either BBs or verapamil in patients who do not respond to either alone (class IIa, AHA).

## Data Supporting the Use of Disopyramide for Treatment of HCM

Table 1 summarizes the literature on the treatment of HCM with disopyramide. Points to note are as follows:

1. No randomized controlled trials are available; the 3 largest studies were retrospective, open-label, and prone to selection bias, and 2 of the 3 were conducted at a single centre.
2. The posology of disopyramide is not consistent across the literature.
3. Initiation of disopyramide is recommended as an in-patient administration in an expertise centre.
4. The main adverse events with disopyramide include an anticholinergic effect, HF, and a prolonged QT interval corrected for heart rate (QTc); no clear definition or consistent reporting of adverse events has come from the 3 largest studies.
5. The majority of patients were also taking BBs.
6. Of the cited studies, only 3 are cited in the American guidelines[3] in support of the recommendation, and 3 studies are cited in the 2023 ESC guidelines.[12]

## Use of Disopyramide as a Comparator for Emergent Therapies Such as Cardiac Myosin Inhibitors

The absolute contraindications to use of disopyramide are decreased LV ejection fraction, congenital long QT syndrome,

Received for publication October 19, 2023. Accepted March 3, 2024.

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**Table 1.** Clinical studies of disopyramide in obstructive hypertrophic cardiomyopathy (oHCM)

| Reference | Drug(s) studied | Study design and duration of therapy | Population (n) | | Key results |
|---|---|---|---|---|---|
| | | | oHCM at rest | oHCM provocable | |
| Pollick[18] (1982) | Disopyramide:<br>- Acute: oral (200—300 mg) or IV (100 mg)<br>- Maintenance: 150—200 mg QID | - Case series (n = 5)<br>- 4 received disopyramide | 3 | 1 | - Reduction in LVOT at rest after IV disopyramide (90-100%)<br>- Reduction in LVOT provoked after IV disopyramide (33%-72%)<br>- Improvement in exercise duration (+180, 200, 240 sec)<br>- Discontinuation rate 60%<br>- AEs: dry mouth (anticholinergic activity), mild blurring vision 100% |
| Pollick[19] (1988) | Disopyramide 150 mg QID<br>Propranolol 40 mg QID and placebo QID | - Randomized double blinded crossover design<br>- 4 times/d disopyramide, vs propranolol vs placebo<br>- (n = 10)<br>- Follow-up: 4 d | 7 | 3 | - Disopyramide decreased the rest gradient from 61 ± 20 mm Hg vs placebo 5 ± 15 mm Hg vs propranolol 30 ± 30 mm Hg<br>- Exercise capacity increased with disopyramide alone + 1 min vs placebo vs −0.5 min with propranolol<br>- No significant difference in patient drug preferences |
| Miyajima et al.[20] (1988) | Disopyramide IV dose of 50 mg | - Case report<br>- | 1 | | - oHCM patient (40 mm Hg at rest)<br>- Disopyramide widened the trigger zone of lethal ventricular tachycardia. The effective refractory period of the right ventricle was prolonged to 260 msec at the outflow tract and to 300 msec at the apex (the basic drive was 600 msec) |
| Sherrid, et al.[14] (2005) | Disopyramide 432 ± 181 mg/d<br>97% of patients on beta-blockers | - Multicentre study of efficacy and safety in oHCM<br>- Mortality observed in comparison with 373 oHCM patients not treated with disopyramide<br>- Follow-up: 3.1 ± 2.6 y | 118 | | - 78 patients (66%) were maintained on disopyramide without requiring further interventions<br>- Reduction in LVOT: 75 ± 33 mm Hg to 40 ± 32 mm Hg ($P < 0.0001$)<br>- Improvement in NYHA class: 2.3 to 1.7 ($P < 0.0001$).<br>- 40 patients (34%) required interventions<br>- All-cause annual cardiac death rate between disopyramide-treated and non-disopyramide-treated was not significant (1.4% vs 2.6%/y, $P = 0.07$)<br>- No difference in sudden death rate (1.0% vs 1.8%/y, $P = 0.08$) |
| Sherrid et al.[21] (2013) | Disopyramide 501 ± 30 mg/d (250 mg BID)<br>Added to beta-blocker or CCB (verapamil)<br>3-d hospitalization | - Prospective registry (n = 737)<br>- Refractory obstruction and symptoms resistant to beta-blockers and verapamil (n = 299 [41%])<br>- Follow-up: 4.8 y | Disopyramide: 221 | | - Reduction in resting LVOT gradient (n = 221 disopyramide-treated patients) was 63 ± 45 mm Hg to 25 ± 32 mm Hg ($P < 0.0001$)<br>- Continued pharmacologic therapy with disopyramide (n = 141 of 221; 64%)<br>- 80 patients required myectomy or alcohol septal ablation (SRT)<br>- 141 patients had an improvement in NYHA class ($P < 0.0001$)<br>- MLHF QOL score improved<br>- Survival did not differ from that in general US population |

*Continued*

**Table 1.** Continued.

| Reference | Drug(s) studied | Study design and duration of therapy | Population (n) | | Key results |
|---|---|---|---|---|---|
| | | | oHCM at rest | oHCM provocable | |
| Adler et al.[10] (2017) | Disopyramide 100 mg TID | - Single centre, data-base (n = 168) | 168 oHCM (NOS) | | - 2 patients developed a cardiac event<br>- 23% of patients developed side effects with 11% permanently discontinuing therapy<br>- Prolonged the mean QTc interval 19 ± 23 ms<br>- Among those remaining on the drug, 63% did not require SRT |
| Yedidya et al. [22] (2022) | Short-acting disopyramide | - Prospective study (n = 19)<br>- Follow-up: 1 d | 19; as high as 43 ± 28 mm Hg at rest; increasing by ∼50% with provocation (Valsalva maneuver) | | - No significant change in the rest or Valsalva gradient after disopyramide<br>- Disopyramide reduced global longitudinal strain, segmental longitudinal strain, the base-to-apex gradient, and systolic rotational mechanics |
| Maurizi et al.[12] (2023) | Initial dose of 125 mg short-acting disopyramide BID | - Retrospective study<br>- N = 1527 HCM patients<br>- n = 372 LVOTO 1−4 NYHA<br>- Follow-up: 12 mo | 372 | | - Significant decrease of LVOTO post-therapy: 72 ± 36 mm Hg vs 49 ± 31 mm Hg ($P < 0.001$)<br>- 28 (24%) were responders to therapy<br>- 45% underwent SRT (81% in NYHA class III/IV group)<br>- Atrioventricular conduction was prolonged during treatment: the mean PR interval pretreatment was 178 ± 22 msec in a total of 10 patients (8%) with AVB I vs 183 ± 24 msec in 22 patients (17%) with AVB I after treatment ($P < 0.01$)<br>- 68% patients had a prolonged QTc interval of 27 [19; 37] msec<br>- 67 of 118 (67%) discontinued treatment and underwent SRT for ineffective response or due to side effects and/or QTc interval prolongation |

AE, adverse event; AVB, atrioventricular block; BID, twice daily; CCB, calcium-channel blocker; HCM, hypertrophic cardiomyopathy; IV; intravenous; LVOT, left ventricular outflow tract; LVOTO, left ventricular outflow tract obstruction; MLHF, Minnesota Living with Heart Failure questionnaire; NYHA, New York Heart Association; oHCM, obstructive hypertrophic cardiomyopathy; oHCM NOS, hypertrophic cardiology with an obstructive gradient non otherwise specified; QID, 4 times daily; QOL, quality of life; SRT, septal reduction therapy; TID, thrice daily.

**Table 2.** Portrait of comprehensive randomized clinical trials (RCTs) in obstructive hypertrophic cardiomyopathy (oHCM)

| Current pharmacologic options | Number of phase 2–3 RCTs | Phase RCT trial names | Population of oHCM patients (n) | Key results | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Improvement in exercise capacity | Reduction in LVOT gradient | Improvement in symptoms | Improvement in QoL | References |
| Beta-blockers | 1 | TEMPO (NCT03532802) | 29 | No (exercise performance or $pVO_2$) | Yes (rest or post-exercise) | Yes | Yes | Dybro et al.[23] (2021) |
| CCBs | 0 | N/A | | | | | | |
| Disopyramide | 0 | N/A | | | | | | |
| Cardiac myosin inhibitor | 3 | • EXPLORER-HCM (NCT03470545)<br>• VALOR-HCM (NCT04349072)<br>• REDWOOD-HCM (NCT04219826) | 251<br>112<br>28 | Yes | Yes | Yes | Yes | • Olivotto et al.[24] (2020)<br>• Desai et al.[25] (2022)<br>• Maron et al.[26] (2023) |

CCB, calcium-channel blocker; EXPLORER-HCM, Clinical Study to Evaluate Mavacamten (MYK-461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy; LVOT, left ventricular outflow tract; LVOTO, left ventricular outflow tract obstruction; N/A, not applicable; oHCM: obstructive hypertrophic cardiomyopathy; $pVO_2$, mixed venous oxygen tension; QOL, quality of life; REDWOOD-HCM, **R**andomized **E**valuation of **D**osing **W**ith CD-274 in **O**bstructive **O**utflow **D**isease in **HCM**; TEMPO, **T**he **E**ffect of **M**etoprolol in **P**atients With Hypertrophic **O**bstructive Cardiomyopathy; VALOR-HCM, A Study to **Eval**uate Mavacamten in Adults With Symptomatic **O**bstructive **HCM** Who Are Eligible for Septal Reduction Therapy.

an episode of Torsade de Pointes, and pregnancy. The major side effects of disopyramide are prolongation of the QTc interval, and the cholinergic adverse effects, such as dry mouth, severe constipation, and urine retention. The risk of these side effects limits its clinical use in patients with prostate hypertrophy, urinary retention, or familial history of glaucoma, and in the elderly. Disopyramide also should be used cautiously in patients with renal or hepatic insufficiency. Beta-blockade or CCB therapy is usually maintained for both improved symptom control and reduction in risk of ventricular arrhythmias and enhanced atrioventricular conduction, a particular risk in AF, which HCM patients have an increased lifetime risk of developing.

Disopyramide is a substrate of the cytochrome P450 (CYP3A4) system that can lead to changes in plasma concentrations when it is taken with medications that induce or inhibit CYP3A4. Serious adverse events due to increased disopyramide plasma concentrations have occurred with macrolide antibiotics[13] and should be avoided in patients who also are taking protease inhibitors, antifungals, rifampin, phenytoin, carbamazapine, and other agents that affect CYP3A4.

According to the ESC guidelines, disopyramide should be avoided in patients with glaucoma, in men with prostatism, in patients taking other drugs that prolong the QT interval—such as neuroleptic agents, phenothiazines, amiodarone, and sotalol—and who are prone to AF,[4] and in patients with a risk of HF.[3]The initiation of disopyramide historically required hospitalization with continuous telemetry monitoring[14,15]] due to side effects, particularly QT interval prolongation. Further, the level of heterogeneity across institutions is high regarding the recommended practice to start disopyramide during hospitalization.[14] Adler et al. have shown that a dose of 300 mg prolonged the mean QTc interval by 19 $\pm$ 23 ms,[10] and Maurizi et al. have shown discontinuation of therapy in 6% of patients with prolongation of the QTc interval above 550 ms.[12] In addition, hospitalizations incur considerable costs and come at an inconvenience to patients.

Disopyramide use is often discontinued. Adler et al. have demonstrated, in a retrospective analysis of their registry, that the overall discontinuation rate is 44% after 3 months, with the vast majority (75%) attributed to a lack of improvement.[10] Maurizi et al. reported a discontinuation rate of 56% due to side effects, prolongation of the QTc interval above 550 ms, and for patients who underwent SRT because of ineffective response.[12]

Use of disopyramide is also limited due to supply issues of the molecule.[16] Disopyramide is not available in all countries, with some having even delisted it (eg, Australia).[17] Therefore, disopyramide is not used widely outside of the Americas. It is reserved as a last resort for patients with symptomatic oHCM, and often, patients remain on ineffective BB or CCB treatment.

Based on the following 3 facts, disopyramide does not appear to be an appropriate comparator for emergent targeted treatments for oHCM: (i) availability of disopyramide is unreliable in Canada; (ii) disopyramide has several side effects, particularly for older patients with prostate enlargement, such as anticholinergic effects and the risk of QT interval prolongation; and (iii) disopyramide efficacy is not proven with robust clinical evidence, and it is not designed for HCM.

Due to the potential risks, the need for monitoring, and the limited randomized controlled trial data demonstrating efficacy (Table 2), uncertainty remains regarding the current role of disopyramide in the treatment of oHCM in Canada. With the development and availability of effective SRTs (myectomy, alcohol septal ablation) and promising cardiac myosin inhibitors, which have demonstrated a favourable safety profile with the potential to avoid SRT and even modify the course of the disease through attenuation of left ventricular hypertrophy, the role of disopyramide requires further evaluation.

## Conclusion

Treatment of symptomatic oHCM remains a challenge, as current treatment strategies are based on historical cohorts and retrospective data. Evidence to support the use of disopyramide in the treatment of oHCM, outside of anecdotal registries and retrospectives studies, is lacking, and emergent therapies are needed to address the complex physiopathology of oHCM. In the context of new cardiac myosin inhibitors now recommended as second-line treatment after BB and/or CCB treatment,[11] we believe that disopyramide should be reserved to be used as a last resort in those who are non-responders to pharmacologic treatment and in whom invasive therapies are not indicated due to a limited level of evidence.

## Acknowledgements

The authors thank Dr Stanley Nattel, Jamila Ennaciri, and Harshila Patel for reading the manuscript.

## Ethics Statement

The research reported has adhered to relevant ethical guidelines.

## Patient Consent

The authors confirm that patient consent is not applicable to this article as it presents facts from published literature.

## Funding Sources

The authors have no funding sources to declare.

## Disclosures

S.C. is an employee of Bristol Myers Squibb. B.H. received honoraria as a consultant/speaker from Bristol-Myers-Squibb and is supported by institutional research grants. P.G. received consultant and speaking fees from Bristol Myers Squibb, Abbott, and Medtronic.

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