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CASE REPORT

Transitioning disopyramide to mavacamten in obstructive hypertrophic cardiomyopathy: A case series and clinical guide

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Abstract

Background: Hypertrophic cardiomyopathy (HCM) is a genetic disorder for which first-line treatments for obstructive HCM (oHCM) include beta-blockers, non-dihydropyridine calcium channel blockers, and disopyramide for refractory cases. Mavacamten, a selective cardiac myosin inhibitor, is indicated for symptomatic oHCM to improve functional capacity and symptoms. Use of disopyramide and mavacamten together is not recommended due to concerns of additive negative inotropic effects. Transitioning from disopyramide to mavacamten may be preferred to avoid adverse effects and frequent administration, however, the best approach for making the transition has not been established.

Cases: We present a series of seven patients with oHCM who transitioned from disopyramide to mavacamten and underwent echocardiograms mandated by a Risk Evaluation and Mitigations Strategies program. Two methods were employed. The first approach, involving washout of disopyramide before starting mavacamten, resulted in worsening of heart failure symptoms in the first two cases. The second approach, involving tapering disopyramide when starting mavacamten, was successfully implemented in the last five cases, with no adverse effects or worsening of systolic dysfunction.

Conclusion: Our method of tapering disopyramide when starting mavacamten using a stepwise approach is feasible and safe. Our report fulfills an unmet need by serving as a guide for other clinicians who seek to transition their patients from disopyramide to mavacamten.

KEY WORDS

disopyramide, hypertrophic cardiomyopathy, mavacamten

1 | INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is one of the most common cardiac genetic disorders with a disease prevalence of one case per 200 to 500 persons.¹ It is characterized by myocyte hypertrophy and disarray most commonly affecting the left basal interventricular septum, but phenotypic expression is known to be highly variable. Morphological changes within the heart lead to characteristic pathophysiological features, including diastolic dysfunction,

hypercontractility, and left ventricular outflow tract (LVOT) obstruction. In patients with obstructive hypertrophic cardiomyopathy (oHCM), the goal is to decrease the LVOT gradient and provide symptomatic relief. First-line treatments recommended in current guidelines include beta-blockers, non-dihydropyridine calcium channel blockers, and in refractory cases, disopyramide.^{2,3} Mavacamten is a first-in-class selective cardiac myosin inhibitor indicated for the treatment of adults with New York Heart Association (NYHA) classes II–III oHCM to improve functional capacity and symptoms.

The starting dose of mavacamten is 5 mg once daily with subsequent 2.5 mg-increment dose adjustments made based on follow-up Valsalva Left Ventricular Outflow Tract (VLVOT) gradient readings obtained by echocardiography.⁴ Patients receiving mavacamten are required by the United States Food and Drug Administration to be monitored with regular echocardiograms under a Risk Evaluation and Mitigation Strategy (REMS) program to detect development of heart failure (HF) secondary to systolic dysfunction. The program also intends to screen for important drug interactions that may decrease mavacamten metabolism, thereby putting patients at increased risk for systolic dysfunction.⁵ It is also recommended to avoid the use of mavacamten with specific combinations of other negative inotropes. Mavacamten can be added to a beta-blocker or calcium channel blocker in patients who have insufficient control of obstructive symptoms and can be considered in patients who are refractory to disopyramide or desiring to avoid anticholinergic side effects and frequent administration of medication. A beta-blocker or calcium channel blocker can be continued when starting mavacamten to provide additional LVOT gradient reduction. In patients, currently taking disopyramide, however, concomitant administration of mavacamten should be avoided due to a potential risk for worsening left ventricular (LV) systolic function.⁶ If these patients desire to start mavacamten, they must be transitioned off disopyramide. Methods for making this transition, however, have not been described. Here, we present a case series of seven patients with oHCM describing our method of transitioning from disopyramide to mavacamten and propose a stepwise clinical guide to achieve this goal. Detailed characteristics for each patient are shown in [Table 1](#).

2 | CASE PRESENTATIONS

2.1 | Case I

A 68-year-old female with oHCM and NYHA class III symptoms on disopyramide immediate release 100mg twice daily and verapamil 180mg daily, was scheduled to start mavacamten 5mg daily. She had been on stable doses of disopyramide and verapamil for 2 years with a baseline left ventricular ejection fraction (LVEF) and VLVOT of 66% and 196 mmHg, respectively, prior to start of mavacamten. The patient was instructed to stop disopyramide and wait 2 days prior to starting mavacamten. A 2-day washout of disopyramide was selected to allow for complete elimination of the medication which has a half-life of 4–10h.⁷ Two days after starting mavacamten, she was referred from an urgent care to an emergency department for atrial fibrillation (AF) with rapid ventricular response. A transthoracic echocardiogram revealed a normal LVEF of 70%–75%. The LVOT gradient was not measured. After confirmed absence of intracardiac thrombus by transesophageal echocardiography, she was administered intravenous amiodarone and underwent successful direct current cardioversion. She was discharged 2 days later with amiodarone 200mg twice daily, furosemide 20mg daily, and apixaban 5mg twice daily. Mavacamten 5mg daily was dose reduced to 2.5mg daily in

accordance with package insert labeling due to initiation of treatment with amiodarone, a moderate 3A4 inhibitor. Verapamil 180mg daily was continued.

Within the following 3 weeks, the patient presented to clinic complaining of worsening shortness of breath, dyspnea on exertion, cough, and fatigue requiring supplemental oxygen. She was subsequently admitted to our hospital for intravenous diuresis and further evaluation. She was in normal sinus rhythm. A new echocardiogram revealed an LVEF of 67% and LVOT gradient of 174 mmHg at rest and 232 mmHg with Valsalva. Given the severity of her symptoms and echocardiogram findings, the patient was referred for septal myectomy. Mavacamten was discontinued. Post-myectomy, her resting LVOT and VLVOT resolved, ultimately being discharged a week and a half later without further complications.

2.2 | Case II

A 57-year-old female with oHCM and NYHA class III symptoms, type 2 diabetes, stage 5 chronic kidney disease, and hypertension on disopyramide immediate release 100mg twice daily and verapamil 240mg twice daily was planned to start mavacamten 5mg daily. She had been on stable doses of disopyramide and verapamil for over a year and had a baseline LVEF of 82% with a VLVOT gradient of 47 mmHg. The patient was instructed to start mavacamten 2 days after stopping disopyramide. However, within 4 days of initiating mavacamten, the patient complained of worsening shortness of breath and dyspnea on exertion. Due to concerns for worsening LVOT obstruction, the patient was instructed to restart disopyramide 100mg twice daily and continue mavacamten 5mg daily with verapamil 240mg twice daily. A follow-up phone call was done at which time the patient reported improvement in symptoms compared to baseline.

To avoid continued concomitant administration of mavacamten, disopyramide, and verapamil, we planned to taper off disopyramide over a course of 2 to 3 weeks. Unfortunately, during this process the patient was hospitalized at an outside facility for acute diastolic HF and acute renal failure complicated by severe anion gap metabolic acidosis ultimately requiring definite renal replacement therapy. The patient underwent an echocardiogram which revealed an LVEF of 83%. The LVOT gradient was not measured. Upon discharge, her mavacamten was discontinued due to the lack of data available for its use in patients with end-stage renal disease while disopyramide was resumed in combination with verapamil.

2.3 | Case III

An 80-year-old male with a past medical history of oHCM with NYHA III symptoms, atrial fibrillation, hypertension, and hyperlipidemia presented to clinic for consideration of starting mavacamten. The patient was taking stable doses of disopyramide immediate release of 150mg three times daily and metoprolol succinate 100mg

TABLE 1 Baseline characteristics.

Patient	Case I	Case II	Case III	Case IV	Case V	Case VI	Case VII
Age	68	57	80	64	60	81	78
Sex	Female	Female	Male	Male	Female	Female	Male
eGFR (mL/min/1.73m ²)	>60	9	>60	>60	>60	>60	>60
NYHA class	III	III	III	III	III	III	III
LVMWT (mm)	22	26	20	17	29	18	18
Echocardiogram							
EF (%)	66	82	71	72	69	75	80
LVOT (mm Hg)	144	31	61	135	14	74	16
VLVOT (mm Hg)	196	47	100	164	45	113	67
Mitral valve	Severe MR SAM present	Trace MR No SAM	Mild MR SAM present	Mod MR SAM present	Mild-mod MR SAM present	Mild MR No SAM	Mod MR No SAM
Medications	Disopyramide IR 100mg BID Verapamil 180mg daily	Disopyramide IR 100mg BID Verapamil 240mg BID	Disopyramide IR 150mg TID Metoprolol succinate 100mg morning and 50mg evening	Disopyramide IR 300mg QID Metoprolol succinate 25mg BID	Disopyramide IR 200mg BID Metoprolol succinate 100mg daily	Disopyramide CR 150mg TID Metoprolol succinate 12.5mg daily	Disopyramide IR 150mg BID Verapamil 180mg daily

Abbreviations: BID, twice daily; BNP; brain natriuretic peptide; CR, extended release; EF, ejection fraction; eGFR, estimated glomerular filtration rate calculated by MDRD; IR, immediate release; LVMWT, left ventricular maximal wall thickness; LVOT, left ventricular outflow tract gradient; Mod, moderate; MR, mitral regurgitation; NYHA, New York Heart Association; QID, four times daily; SAM, systolic anterior motion of the mitral valve; TID, three times daily; VLVOT, Valsalva left ventricular outflow tract gradient.

in the morning and 50mg in the evening for over 6 months (Table 1). His baseline LVEF was 71% with a VLVOT gradient of 100mmHg. Based on his symptoms and degree of obstruction, septal reduction therapy was discussed but ultimately deferred based on patient wishes to attempt medical treatment first. Based on our experience with cases I and II described above, when mavacamten 5mg daily was started, we instructed this patient to taper disopyramide by continuing 150mg three times daily for 10days, followed by a decrease to 150mg twice daily for 10days, and then discontinue the drug (Figure 1A). Disopyramide was discontinued 2days prior to his first REMS-mandated echocardiogram which showed a 112mmHg VLVOT gradient (Figure 1A) and an LVEF of 73% (Figure 2A). The patient denied worsening of dyspnea on exertion, chest pain, palpitations, or dizziness. He reported improvement in fatigue which was thought secondary to discontinuation of disopyramide and its anticholinergic side effects. Mavacamten 5mg daily and metoprolol succinate 100mg in the morning and 50mg in the evening were continued, and follow-up echocardiograms revealed improvement in VLVOT gradient and stable LVEF above 50%.

2.4 | Case IV

A 64-year-old male with a past medical history of oHCM with NYHA III symptoms, status-post alcohol septal ablation 6years

prior, hypertension, obstructive sleep apnea, non-alcoholic steatohepatitis, and type 2 diabetes was on stable doses of disopyramide 300mg immediate release four times daily and metoprolol succinate 25mg twice daily for nearly 2years. He was also taking pyridostigmine 180mg twice daily to manage anticholinergic side effects from disopyramide. His baseline LVEF was 72% with a VLVOT gradient of 164mmHg. Due to ongoing symptoms and elevated VLVOT gradient, initiation of mavacamten was planned. Given that the patient was taking a high dose of disopyramide and reported worsening of shortness of breath on exertion when delaying a dose by a couple hours, he was given an extended taper over a month and a half (Figure 1B). After initiating mavacamten 5mg daily, the patient was advised to maintain a dosage of disopyramide 300mg four times daily for 10days. Subsequently, the dose was gradually reduced to 200mg four times daily for 10days, then to 100mg four times daily for 10days, and finally to 100mg twice daily for 10days, with discontinuation thereafter. He was also advised to stop taking pyridostigmine once he no longer experienced side effects from disopyramide. The patient had his first REMS-mandated echocardiogram at 4weeks while on mavacamten 5mg daily and disopyramide 100mg four times daily. His echocardiogram showed a 104mmHg VLVOT gradient (Figure 1B) with an LVEF of 64% (Figure 2B). The patient reported improvement in symptoms thus he was instructed to decrease the length of his final 10days of tapering of disopyramide 100mg twice daily to 7days. He also reported

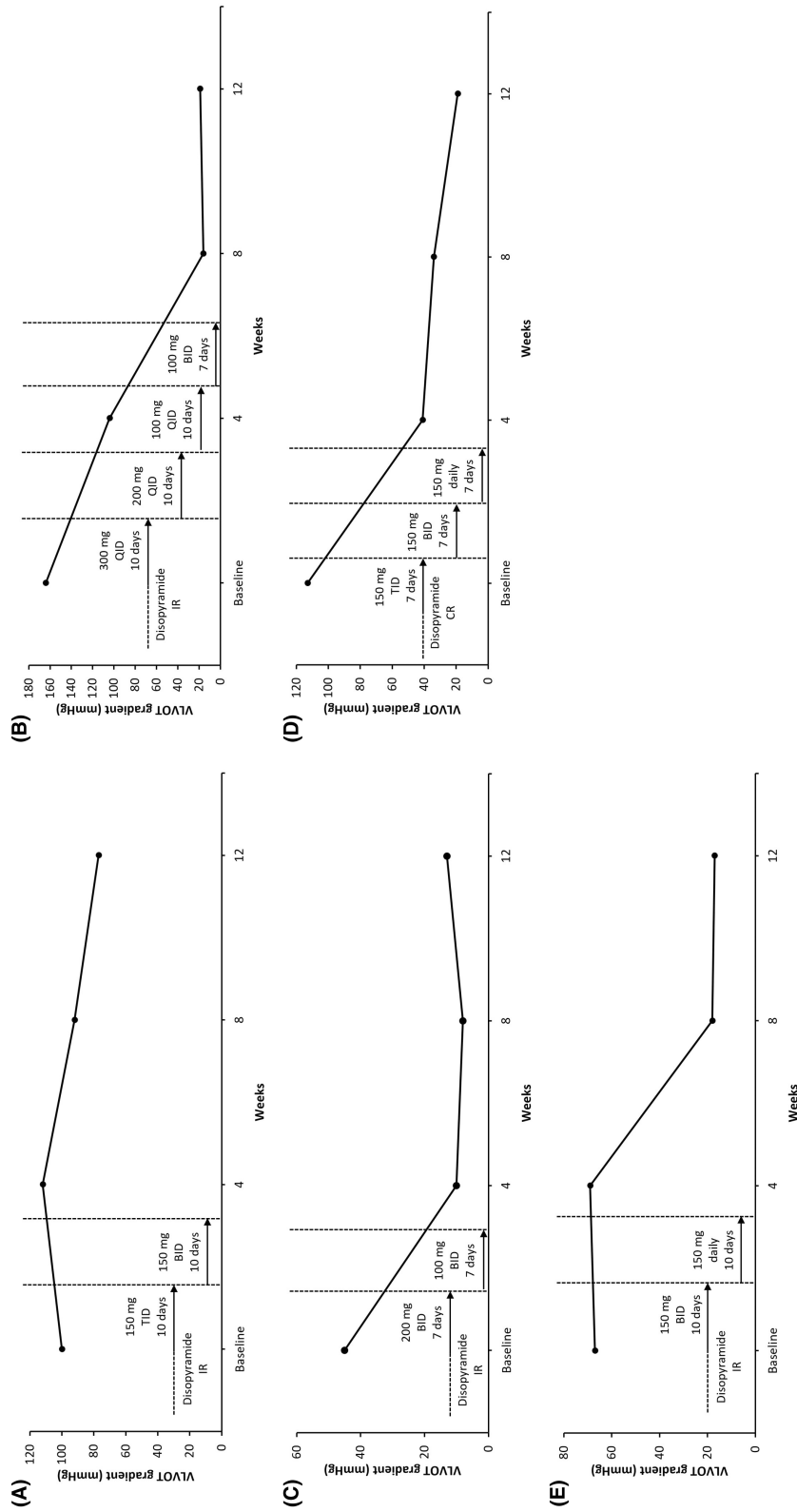


FIGURE 1 Valsalva left ventricular outflow tract gradients and disopyramide taper schedules for cases III–VII. Valsalva gradients were measured by echocardiogram every 4 weeks after initiation of mavacamten in accordance with the mavacamten REMS program. (A) shows data for case III, (B) for case IV, (C) for case V, (D) for case VI, and (E) for case VII. Case V received a dose reduction of mavacamten to 2.5 mg daily per package insert labeling on week 4. BID, twice daily; CR, extended release; IR, immediate release; QID, four times daily; TID, three times daily; VLVOT, Valsalva left ventricular outflow tract.

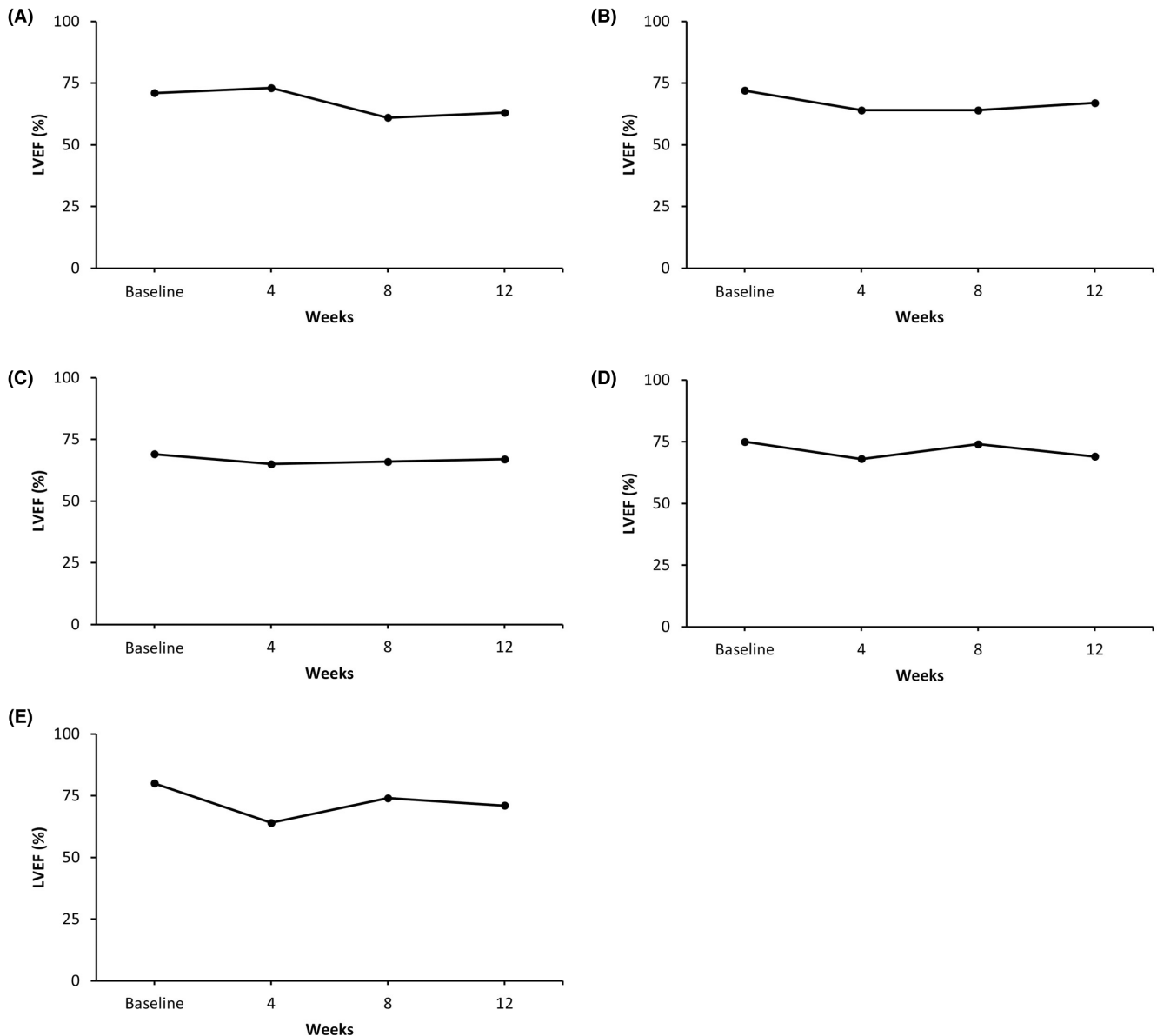


FIGURE 2 Left ventricular ejection fraction measurements for cases III-VII. Ejection fraction was measured by echocardiogram every 4 weeks after initiation of mavacamten in accordance with the mavacamten REMS program. (A) shows data for case III, (B) for case IV, (C) for case V, (D) for case VI, and (E) for case VII. LVEF, left ventricular ejection fraction.

stopping pyridostigmine at week 4. He completed the disopyramide taper approximately 2 weeks before his week 8 echocardiogram which revealed a VLVOT gradient of 16 mmHg and LVEF of 64%. The gradient and ejection fraction remained stable on the subsequent week 12 echocardiogram while on mavacamten 5 mg daily and metoprolol succinate 25 mg twice daily.

2.5 | Case V

A 60-year-old female with a past medical history of oHCM with NYHA class III symptoms, hypertension, hyperlipidemia, and type 2 diabetes was planned to start mavacamten. She was on stable doses

of disopyramide immediate release 200mg twice daily and metoprolol succinate 100mg daily for 6 months prior to starting mavacamten. Her baseline echocardiogram showed an ejection fraction of 69% and a VLVOT gradient of 45 mmHg. Once starting mavacamten 5 mg daily, the patient continued disopyramide 200mg twice daily for 7 days, followed by a decrease to 100mg twice daily for 7 days, then discontinuation of the drug (Figure 1C). She completed her taper approximately 2 weeks before her first REMS-mandated echocardiogram which showed a 10mmHg VLVOT gradient (Figure 1C) and LVEF of 65% (Figure 2C). Her dose of mavacamten was reduced to 2.5 mg daily in accordance with package insert labeling and metoprolol succinate 100mg daily was continued. She had a stable VLVOT gradient and ejection fraction over the following echocardiograms.

2.6 | Case VI

An 81-year-old female with a past medical history of oHCM with NYHA class III symptoms, hypertension, coronary artery disease status-post primary percutaneous coronary intervention 20 years prior, and hyperlipidemia was planned to start mavacamten. Her baseline medications included disopyramide extended release 150 mg three times daily and metoprolol succinate 12.5 mg daily. Before starting mavacamten, her LVEF was 75% and VLVOT 113 mm Hg. Once starting mavacamten 5 mg daily, she was instructed to continue disopyramide 150 mg three times daily for 7 days, followed by a decrease in dose to 150 mg twice daily for 7 days, followed by 150 mg daily for 7 days with discontinuation after that time. Her taper was completed 2 days before her first REMS-mandated echocardiogram which revealed a VLVOT gradient of 41 mm Hg (Figure 1D) and LVEF of 68% (Figure 2D). Her VLVOT gradient further improved and LVEF remained stable on subsequent echocardiographs while taking mavacamten 5 mg daily and metoprolol succinate 12.5 mg daily.

2.7 | Case VII

A 78-year-old male with a past medical history of oHCM with NYHA class III symptoms presented to clinic for consideration of starting mavacamten. He was on stable doses of disopyramide immediate release 150 mg twice daily and verapamil 180 mg daily. His baseline LVEF was 80% and VLVOT gradient was 67 mm Hg. Once starting mavacamten, he was instructed to continue disopyramide 150 mg twice daily for 10 days, followed by a decrease to 150 mg daily for 10 days, then stop. Five days after starting mavacamten, the patient reported he accidentally stopped taking verapamil. He reported no worsening of obstructive symptoms, thus, we advised him to continue without the verapamil. He reported taking his disopyramide as instructed and again confirmed understanding of his taper schedule. His week 4 echocardiogram showed a VLVOT gradient of 69 mm Hg (Figure 1E) and LVEF of 64% (Figure 2E). Subsequent REMS echocardiograms showed further improvement of gradient and stable LVEF while on mavacamten 5 mg daily only.

3 | DISCUSSION

In the phase 3 EXPLORER-HCM trial, treatment with mavacamten led to improved LVOT obstruction, symptom scores, NYHA functional class, and exercise capacity.⁸ The study excluded individuals on disopyramide which led to the recommendation to avoid concomitant use of the medication with mavacamten out of concern for overlapping negative inotropy and risk for LV systolic dysfunction.⁶ Whereas EXPLORER-HCM excluded patients on disopyramide, the phase 3 VALOR-HCM trial included 14 individuals on disopyramide in the mavacamten arm and found no significant differences in adverse events as compared to the placebo arm.⁹ However, the trial was limited by a small study population and a short follow-up of

16 weeks. Based on these recommendations and study limitations, we instructed the first two cases to washout disopyramide before starting mavacamten to avoid any co-administration of the two medications. Given the patients experienced worsening HF symptoms shortly after making this transition, we devised and successfully implemented a new protocol for tapering disopyramide in patients starting mavacamten.

We hypothesized for case I, that the HF symptoms were related to mavacamten-induced LV systolic dysfunction. However, this hypothesis was abrogated by the echocardiogram showing a preserved LVEF. Another plausible cause could be that mavacamten-induced AF leading to the patient's symptom presentation. In the open-label phase 2 PIONEER-HCM trial, five events of AF related to mavacamten were reported with the majority being intermittent and self-resolving.¹⁰ However, in the larger placebo-controlled randomized phase 3 EXPLORER-HCM trial, the occurrence of AF was less frequent with mavacamten compared to placebo.⁸ Thus, based on these studies, there is a low likelihood that the patient's AF and subsequent worsening of HF could have been secondary to initiation of mavacamten.

The underpinnings of these two cases with worsening HF symptoms while on mavacamten therapy can be explained by the differences in pharmacokinetic profiles between disopyramide and mavacamten. Disopyramide has a half-life of 4–10 h while mavacamten's half-life lasts 6–9 days, extending up to 23 days in those with a slower cytochrome P450 (CYP) 2C19 metabolizer status.^{6,7} The long half-life of mavacamten reflects the time required to observe significant LVOT gradient reduction as demonstrated in the PIONEER-HCM and EXPLORER-HCM trials.^{8,10} As a result, it is possible that cessation of disopyramide followed by initiation of mavacamten may result in an acute worsening of obstruction until the latter approaches steady state. With this potential mechanism at the time of case II reporting worsening symptoms, we restarted disopyramide and continued mavacamten with intent to taper disopyramide over the coming weeks. Although we do not have complete follow-up echocardiogram data for case II, this approach resulted in reported improvement in symptoms shortly after restarting disopyramide.

After observing outcomes in cases I and II, we devised the plan to taper disopyramide for cases III–VII. Taper schedules differed among the five cases but overall considered the long half-life of mavacamten and dose of disopyramide at time of mavacamten initiation. We instructed cases III, V, VI, and VII to completely taper off disopyramide before their week 4 echocardiogram since all were on lower doses of disopyramide (300–450 mg total daily dose). Considering the degree of improvement in LVOT gradient reported in the published studies, we hypothesized that mavacamten alone (i.e., without disopyramide) should suffice to relieve symptoms by week 4.^{8,10} Before starting mavacamten, case IV was taking a high dose of disopyramide at 300 mg four times daily and reported worsening of symptoms within a couple hours of being late to take medication. Because of these characteristics, we gave the patient an extended taper schedule beyond the week 4 echocardiogram

with intent to monitor closely for worsening HF symptoms and adjust the taper schedule accordingly. Case IV also had a history of hepatic impairment (non-alcoholic steatohepatitis) which could increase the half-life of disopyramide.⁷ However, the degree to which the half-life is increased is unclear thus we did not incorporate this concept into his taper schedule. None of the patients who were tapered off disopyramide had a history of renal dysfunction, a condition also expected to increase the half-life of disopyramide. How hepatic and/or renal dysfunction would affect taper outcomes is unclear given the absence of these disease states and small size of this case series. Regardless of their taper schedules and medical history, all patients reported symptom improvement by week 4. Furthermore, none of the taper patients had a decrease in LVEF to less than 50%.

Based on cases III–VII, we created a tapering guide for disopyramide discontinuation when starting mavacamten (Figure 3). The guide incorporates both the baseline dose of disopyramide and half-life of mavacamten in patients with normal CYP 2C19 metabolizer status (6–9 days). The guide can be used for both the immediate- and extended-release formulation of disopyramide. As shown in Figure 3, we recommend continuing disopyramide at the same dose for 10 days when starting mavacamten. After which, we recommend halving the dose of disopyramide every 10 days (e.g., 300mg three times daily decreased to 150mg three times daily) until the lowest capsule strength is reached (i.e., 100 or 150mg).

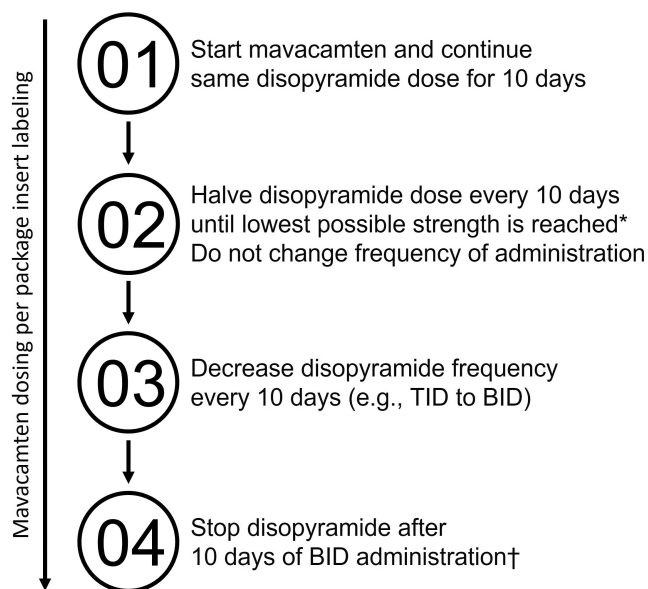


FIGURE 3 Stepwise guide to transitioning from disopyramide to mavacamten. Dose or frequency changes are made every 10 days to account for the half-life of mavacamten in patients with normal CYP 2C19 metabolizer status (i.e., 6–9 days). Disopyramide dose is decreased first (i.e., not frequency) to account for its short half-life of 4–10h. *Lowest possible strength is either a 100 or 150mg capsule, depending on what the patient is taking. †If the patient is taking disopyramide 100mg or 150mg twice daily at baseline, then continue the same dose twice daily for 10days followed by 10days of daily administration. BID, twice daily; TID, three times daily.

We first decrease the dose and not the frequency of disopyramide to account for its short half-life of 4–10h. Once the lowest capsule strength is reached, the frequency of administration should be decreased every 10 days (e.g., 150mg three times daily decreased to 150mg twice daily). After 10 days of twice daily administration, disopyramide should be discontinued. An exception to this procedure is in patients taking disopyramide 100mg or 150mg twice daily at baseline. In these patients, we recommend continuing the same dose twice daily for 10 days followed by 10 days of daily administration before discontinuation (e.g., 100mg twice daily decreased to 100mg once daily).

Although we consider doses and half-lives of mavacamten and disopyramide, our guide for tapering does not incorporate presence of CYP 2C19 polymorphisms or weak CYP 2C19 and moderate CYP 3A4 inhibitors. We follow package insert labeling recommendations for moderate 2C19 and strong 3A4 inhibitors which are contraindicated when using mavacamten. In patients with a poor CYP 2C19 metabolizer phenotype, overall exposure and half-life of mavacamten increases.⁵ The presence of 2C19 or 3A4 inhibitors are also expected to increase the exposure and half-life of mavacamten, however, the degree to which any specific inhibitor increases these parameters is unclear. We did not incorporate 2C19 polymorphisms or drug interactions because we expect our guide to result in disopyramide being tapered off before mavacamten can reach levels that, in combination with disopyramide, may put patients at risk for systolic dysfunction. Furthermore, REMS-mandated echocardiograms allow for timely dose adjustment of mavacamten to further reduce the risk of systolic dysfunction.

4 | CONCLUSION

Mavacamten, a novel cardiac myosin inhibitor, has demonstrated resolution on LVOT pressure gradient and improvement in functional capacity in those with NYHA II–III symptoms. Concomitant use of disopyramide and mavacamten is not recommended due to concerns for overlapping negative inotropic effect. However, cessation of disopyramide prior to starting mavacamten may result in an acute worsening of LVOT obstruction and subsequent HF symptoms. Real world experience in using mavacamten among patients with oHCM treated with disopyramide shows that concomitant administration is feasible with caution by tapering disopyramide when instituting mavacamten therapy. Our report highlights a simple approach to achieve this goal and provides a template for other clinicians in managing the transition from disopyramide to mavacamten in patients with oHCM.

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AW reports receiving honoraria from Bristol Myers Squibb. JSE reports receiving honoraria from Bristol Myers Squibb.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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