Mavacamten

SOP

Review date: October 2026

Mavacamten standard operating procedure document

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1.Purpose of this document:

To provide health care professionals involved in the management of obstructive hypertrophic cardiomyopathy patients with a guide on safe prescribing of Mavacamten, pharmacological properties, patients' follow up and monitoring.

2.Introduction:

Mavacamten (CAMZYOS)

> Mavacamten is a selective and reversible cardiac myosin ATPase inhibitor. It reduces the number of myosin heads in an active state, the formation of force-producing systolic and residual diastolic actin-myosin complexes. This shifts the overall myosin population towards an energy-sparing, super-relaxed state. Dysregulation of the super-relaxed state of myosin and excessive formation of actin-myosin complexes are mechanistic hallmarks of hypertrophic cardiomyopathy. These lead to myocardial hypercontractility, impaired relaxation, excessive energy consumption, and increased myocardial wall stress. Mavacamten attenuates these effects and reported in clinical trials to significantly reduce left ventricular outflow tract gradient, improve patients' symptoms, improves exercise capacity as measured by peak oxygen uptake (pVO2) as well as reducing the serum levels of cardiac biomarkers of haemodynamic and disease state including N-terminal pro B-type natriuretic peptide (NT pro BNP) and high sensitivity troponins (hs-trop) (1).

3.Hypertrophic cardiomyopathy (HCM)

HCM is a genetic disorder of cardiac myocytes leading to left ventricular hypertrophy in the absence of loading conditions. Most common mode of inheritance is an autosomal dominant pattern. Its classic form affects the basal ventricular septum although other segments of the left ventricle can also be affected. Half of the individuals carrying a pathogenic variant express the disease by the third decade of life (2). Prevalence is estimated at 1:300 – 1:600 although with improved diagnostic yield of tests, family screening and the availability of genetic testing the prevalence is expected to be as high as 1:250 (3,4). Disease-causing genetic alterations affect the structure and function of sarcomeric proteins resulting in molecular changes such as enhanced calcium sensitivity and ATPase activity of the myofibrils leading to rise in force generation and myocardial hypercontractility (5). A high dynamic systolic pressure gradient in the left ventricular outflow tract is detectable in two thirds of patients with hypertrophic cardiomyopathy and asymmetrical septal hypertrophy. This is a result of myocardial hypercontractility, the hypertrophied basal ventricular septum encroaching on the left ventricular outflow tract (LVOT), and systolic anterior motion of the mitral valve into the LVOT. Patients can present with symptoms of shortness of breath, exertional chest pain, dizziness and/or syncope. Resting LVOT pressure gradient of ≥30 mmHg is used to define raised LVOT gradient (6). However, an LVOT peak pressure gradient of ≥50 mmHg is used as the cut off for initiating treatment (6,7). A third of patients diagnosed with HCM have evidence of LVOT obstruction at rest by the third and fourth decades of life. Another third develop evidence of LVOT obstruction with exercise (8). LVOT obstruction is a strong predictor of disease progression to heart failure and mortality (9).

4.Current LVOT gradient reduction therapy

Management of patients with symptomatic LVOT obstruction includes lifestyle advice, medications with negative inotropic effect and/or invasive septal reduction therapy. Lifestyle changes include weight reduction, avoidance of dehydration and avoidance of excessive alcohol consumption. The European Society of Cardiology recommends betablockers as first line therapy (see figure 1 below), with non-dihydropyridine calcium channel blockers as a second line therapy if betablockers are either ineffective, poorly tolerated, or contraindicated. Next management step with either Disopyramide or Mavacamten (7). Septal reduction therapy with either alcohol septal ablation or surgical myomectomy is reserved for patients with significant symptomatic LVOT obstruction refractory to medical therapy (10).

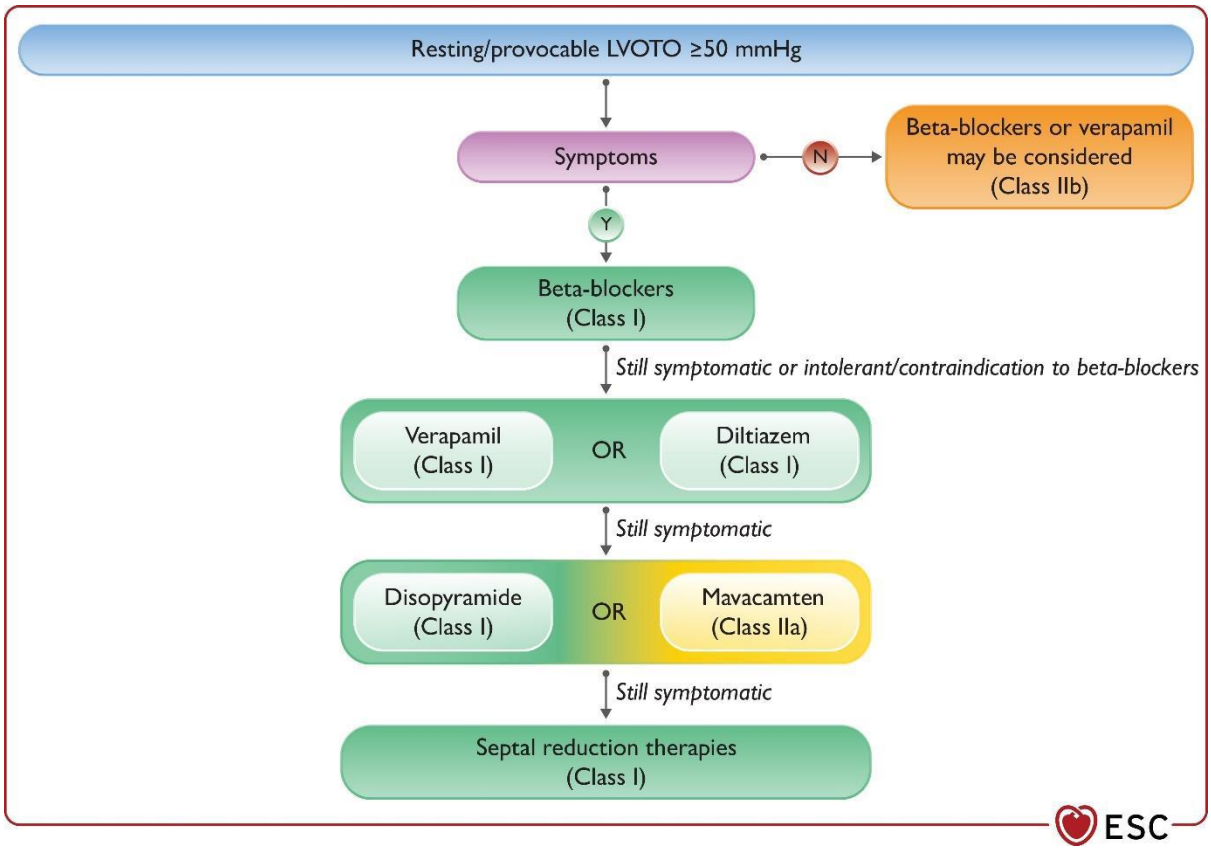


Figure 1: ESC guidelines for management of LVOT obstruction 2022

5.Roles and responsibilities

Mavacamten can only be prescribed by healthcare professionals with expertise in the management of patients with hypertrophic cardiomyopathy and inherited cardiac conditions. Treatment is to be initiated through a dedicated Mavacamten clinic to ensure appropriate review, monitoring and follow up of Mavacamten-treated patients. Mavacamten is only to be prescribed from the dedicated Mavacamten clinic and as such is categorised as a RED drug on the Hospital Formulary.

6.Licensed indication

Mavacamten is indicated for the treatment of adult patients (≥18 years of age) diagnosed with symptomatic obstructive hypertrophic cardiomyopathy with NYHA (New York Heart Association) class II-III symptoms refractory to first line therapy. Mavacamten is a black triangle drug and as such requires the completion of a yellow card for any suspected adverse reaction.

7.Contraindication

1. Hypersensitivity to the active substance or to any of the excipients.
2. During pregnancy and in women of childbearing potential not using effective contraception.
3. Concomitant treatment with strong CYP3A4 inhibitors in patients with CYP2C19 poor metaboliser phenotype or if CYP2C19 phenotype is undetermined, due to an increased risk of left ventricular dysfunction (see p13).
4. Concomitant treatment with the combination of a strong CYP2C19 inhibitor and a strong CYP3A4 inhibitor (see p13).

8.CYP genetic assessment

Mavacamten is metabolised through the hepatic enzymes CYP2C19 (74%), CYP3A4 (18%), and CYP2C9 (7.6%). CYP2C19 genotyping is required to guide Mavacamten therapy and dosing. CYP2C19 phenotype should be available prior to commencing treatment with Mavacamten.

Eligible patients with an unknown CYP phenotype require genetic testing before initiating treatment with Mavacamten. In the absence of a stored DNA sample, a 3ml EDTA blood sample should be obtained. Blood samples should be requested on ICE and sent to Ninewells Laboratory. A report will be generated and sent to the individual clinician on the request form and pre-agreed generic email (Tay.inheritedcardiacconditions@nhs.scot). CYP2C19 phenotype will be reported as either poor, intermediate, normal, or rapid metaboliser.

In CYP2C19 intermediate, normal, and rapid metabolisers; Mavacamten is primarily metabolised through CYP2C19 enzyme, and the maximum prescribed dose of the Mavacamten is 15 mg once daily. In CYP2C19 poor metabolisers, Mavacamten is metabolised primarily by CYP3A4 and the maximum prescribed dose should not exceed 5 mg once a day. The incidence of CYP2C19 poor metaboliser phenotype ranges from approximately 2-4% in Caucasian to 18% in Asian populations (11).

9.Clinic visits

Patients treated with Mavacamten will be followed up monthly during the first three months after drug initiation. At each visit, patients will undergo clinical assessment of symptoms, review of medications, and echocardiography. (see table-1 below).

After 12 weeks on treatment, patients should be reviewed every 6 months if clinically stable with satisfactory echocardiographic parameters and the dose of Mavacamten has not been changed. Otherwise, a follow-up visit should be arranged at 4 weeks (see figure 4 below).

Visit type	Clinical Assessment	Transthoracic echocardiogram	12 lead ECG	Pregnancy test – if applicable
Drug initiation visit	X	X	X	X
Week 4 visit	X	X		
Week 8 visit	X	X		
Week 12 visit	X	X	X	
Every 6 months visit on maintenance therapy	X	X	X	
Additional 4 weeks visits following dose change	X	X		

Table 1 – Clinic Visits

10.Dosage and administration/prescribed

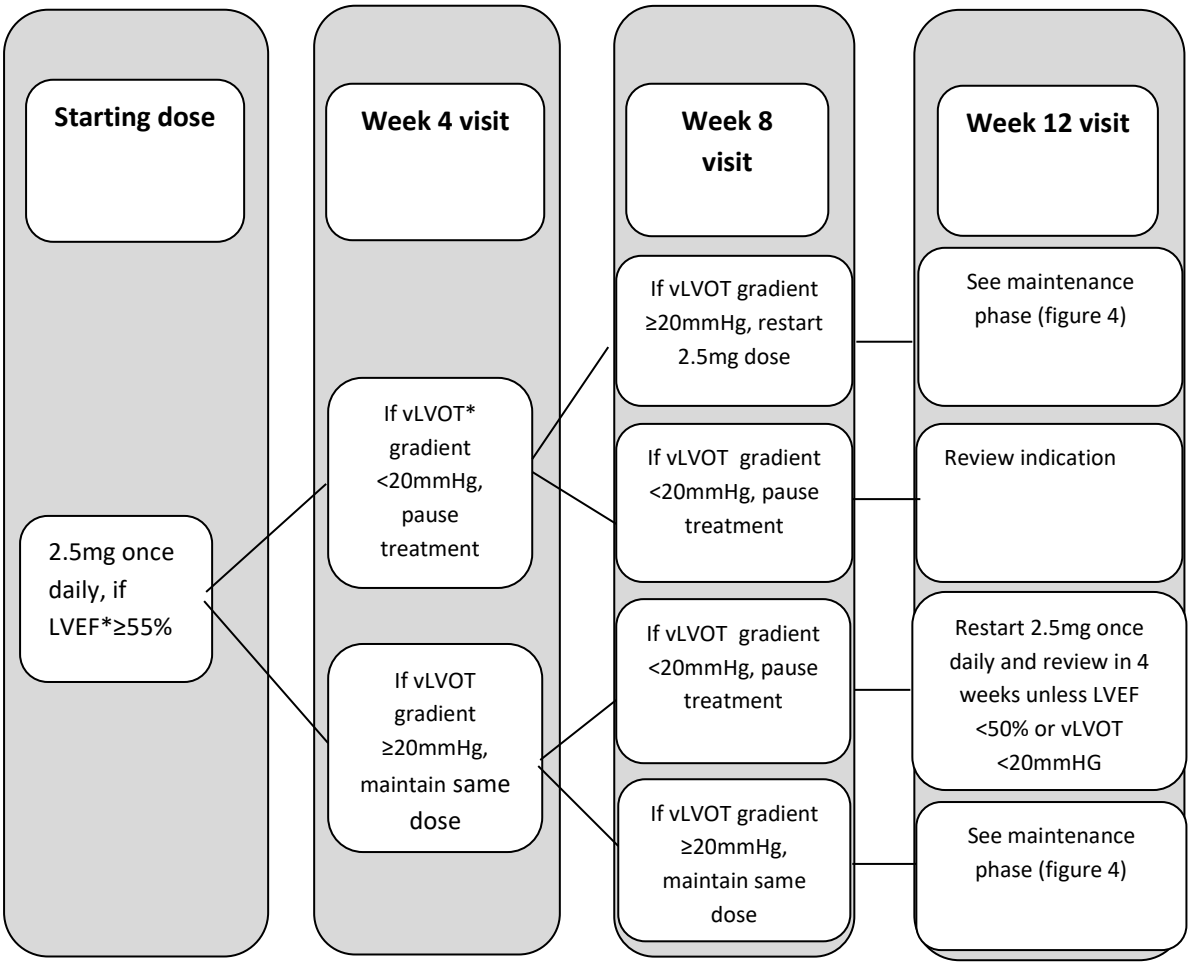
• Mavacamten should only be administered under the supervision of a physician with expertise in the management of patients with obstructive hypertrophic cardiomyopathy.
• Disopyramide and/or rate-limiting calcium channel blockers should be discontinued at least 5 days before initiating treatment with Mavacamten.
• Review the list of regular medications to identify any CYP2C19 or CYP3A4 inhibitors.
• A negative pregnancy status should be confirmed in all females of reproductive age before treatment initiation.

Initiation of therapy

A Mavacamten starting dose of 2.5mg once daily should be used in CYP2C19 poor metabolisers as well as CYP2C19 intermediate, normal, and rapid metabolisers treated with a strong CYP2C19 inhibitor.

Initiate Mavacamten treatment at a dose of 5 mg once daily in CYP2C19 intermediate, normal, and rapid metabolisers who are not treated with a CYP2C19 strong inhibitor. The capsule should be swallowed whole with water and can be taken with or without food (see figures 2 and 3 below).

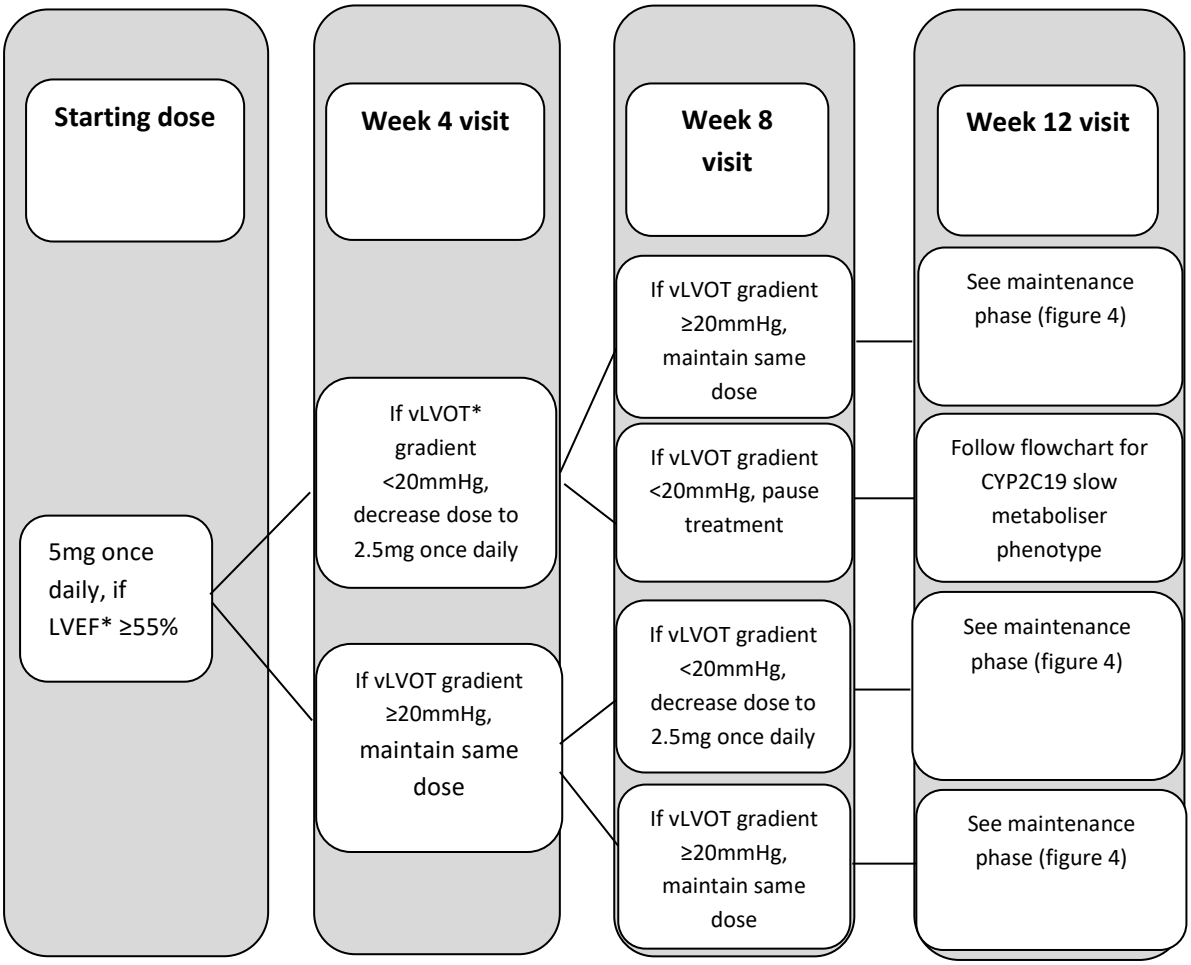
Figure 2: Treatment initiation in CYP2C19 poor metabolisers and CYP2C19 intermediate, normal or rapid metabolisers on a strong CYP2C19 inhibitor



Interrupt treatment at any point if LVEF <50%

***LVEF: left ventricular ejection fraction, vLVOT: Valsalva left ventricular outflow tract gradient.**

Figure 3: Treatment initiation in CYP2C19 normal, intermediate, and rapid metabolisers



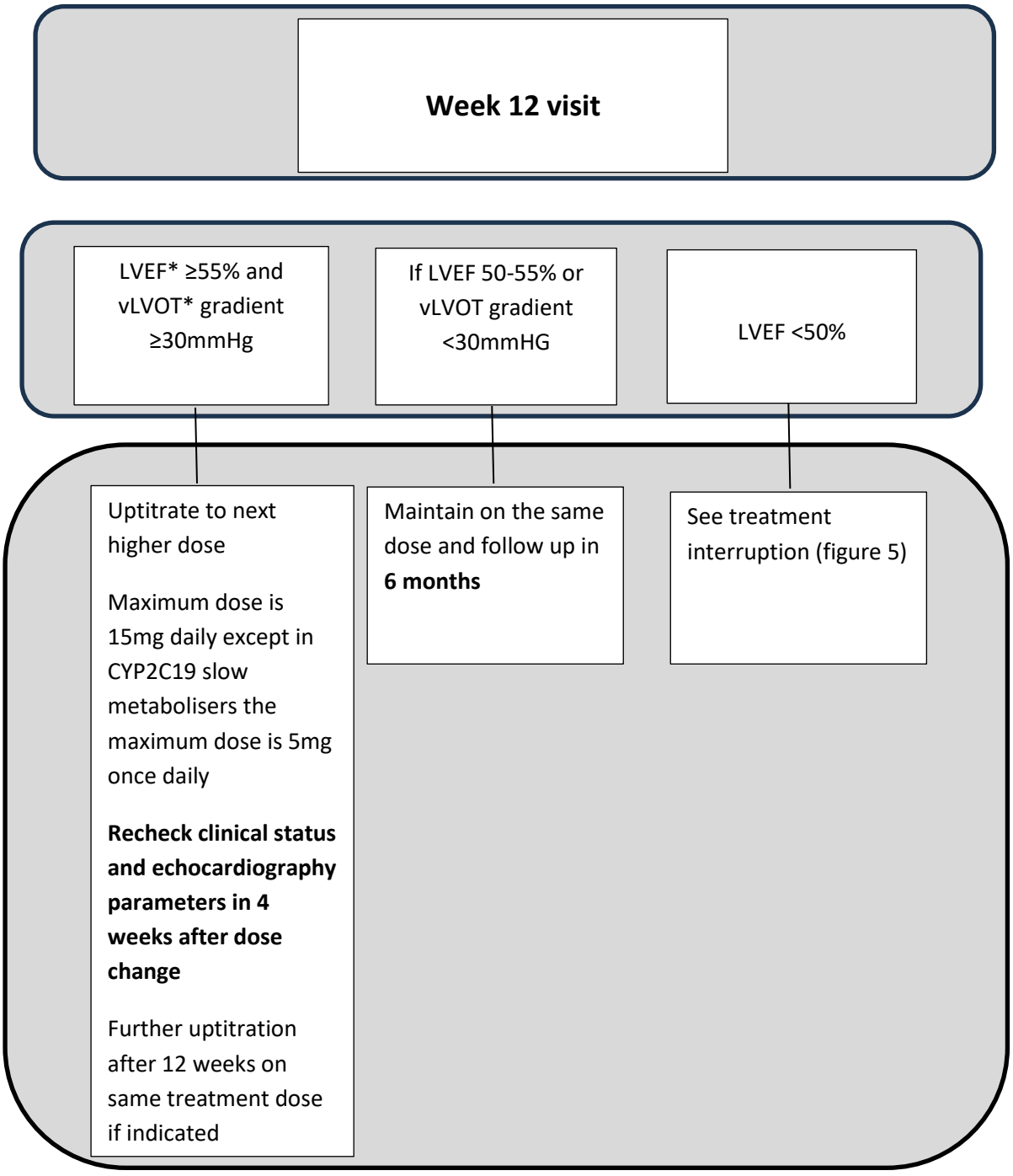
Interrupt treatment at any point if LVEF <50%

***LVEF: left ventricular ejection fraction, vLVOT: Valsalva left ventricular outflow tract gradient.**

Maintenance therapy and treatment interruption

After the initiation phase, clinical status and echocardiographic parameters should be monitored every 6 months. **If patient remains symptomatic due to LVOT obstruction while LVOT gradient with Valsalva manoeuvre is ≥ 30 mmHg and LVEF ≥55%, Mavacamten dose can be uptitrated** (see figure 4 below). Treatment should be discontinued at any point if LVEF falls to <50% (see figure 5 below).

Figure 4: Maintenance phase



***LVEF: left ventricular ejection fraction, vLVOT valsalva left ventricular outflow tract gradient**

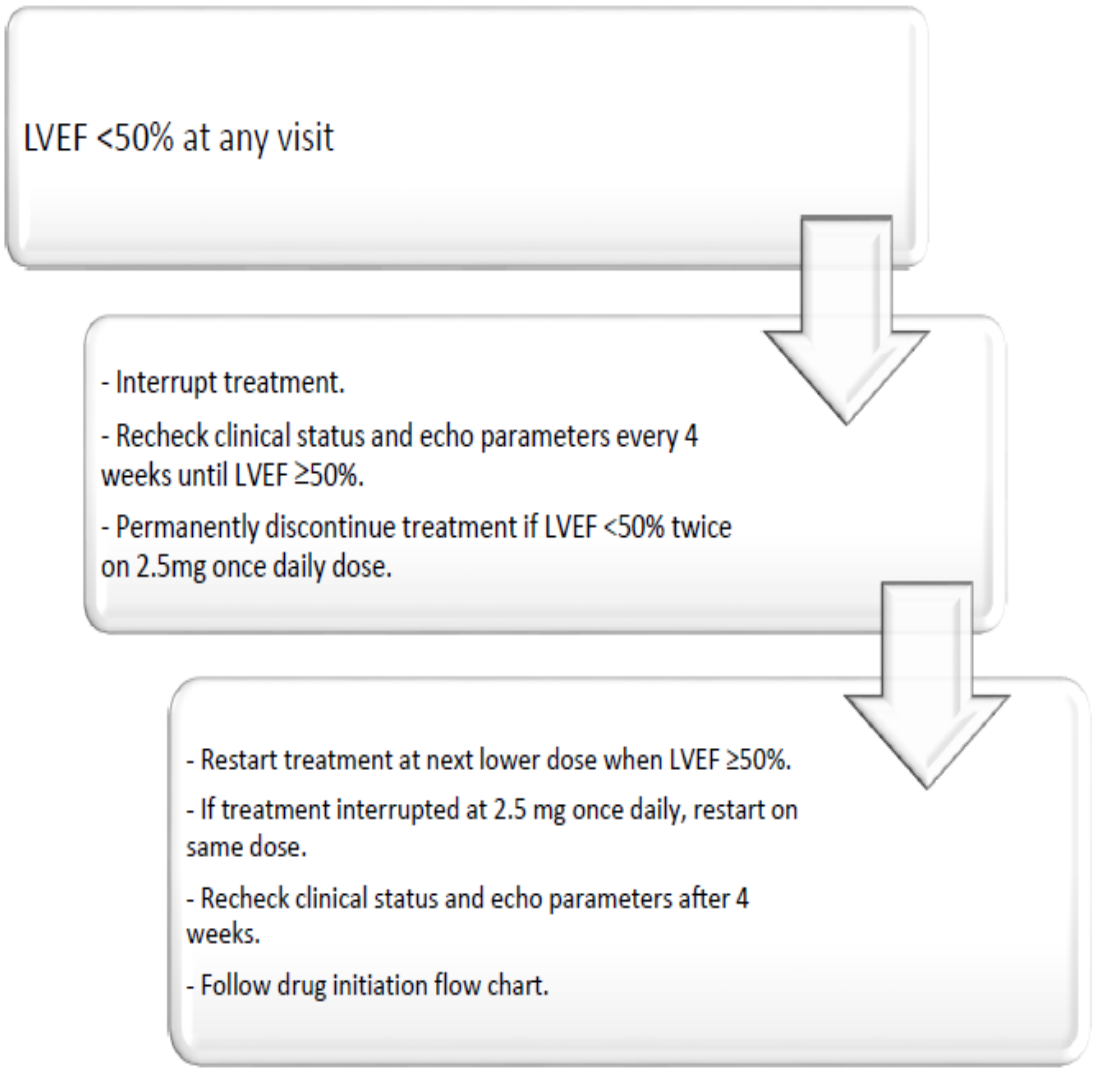


Figure 5: Treatment interruption and discontinuation of therapy

Missed dose

If a dose is missed, it should be taken as soon as possible on the same day. The next scheduled dose on the following day should be taken as usual. Two doses should not be taken on the same day.

Renal impairment

No dose adjustment is required for patients with eGFR ≥30 mL/min/1.73m$_2$. Mavacamten should be used with caution in patients with severe renal impairment (eGFR < 30 mL/min/1.73m$_2$) as it has not been studied in this population.

Hepatic impairment

Mavacamten starting dose should be 2.5 mg once daily in all patients with mild to moderate hepatic impairment (Child-Pugh class A and B). CAMZYOS is not recommended in patients with severe (Child-Pugh Class C) hepatic impairment.

Overdose

Data are very limited regarding Mavacamten overdose in humans. Left ventricular systolic dysfunction is the most likely effect. Serious adverse reaction includes vasovagal reaction, hypotension, and asystole. Treatment of an overdose includes discontinuation of the drug, close monitoring of haemodynamic state and monitoring of LVEF. Initiation of inotropic support with or without adrenergic agents may be considered in case of cardiogenic shock. Early administration of activated charcoal may also be considered, but no data are available on efficacy.

Dose modification/monitoring with concomitant medicinal products

CYP2C19 and CYP3A4 inhibitors:

1. LVEF should be assessed 4 weeks after initiating, stopping, or changing the dose of a CYP2C19 inhibitor or inducer or CYP3A4 inhibitor or inducer.
2. When starting or increasing the dose of a moderate-strong CYP2C19 inhibitor in CYP2C19 intermediate, normal, and rapid metabolisers; the dose of Mavacamten should be reduced or pause treatment if on 2.5 mg.
3. In CYP2C19 intermediate, normal, and rapid metabolisers who are treated with a strong CYP2C19 inhibitor, initiate Mavacamten at a lower dose of 2.5mg once daily.
4. CYP2C19 poor metabolisers should remain on a 2.5mg once daily dose if on a weak-moderate CYP3A4 inhibitor.

CYP2C19 and CYP3A4 inducers

1. Assessment of LVEF should be performed 4 weeks after initiating, stopping, or changing the dose of a CYP2C19 or CYP3A4 inducers.
2. In CYP2C19 intermediate, normal, and rapid metabolisers; the dose of Mavacamten should be reduced or remain on 2.5 mg once daily dose after stopping of decreasing the dose of a strong CYP2C19 inducer or a strong CYP3A4 inducer.
3. In CYP2C19 poor metabolisers, reduce the dose of Mavacamten or pause treatment after stopping or decreasing the dose of a strong CYP2C19 inducer or any CYP3A4 inducer (12).

11. Warnings and precautions

Heart failure

Mavacamten can reduce left ventricular ejection fraction. Heart failure symptoms and/or rise in NT pro-BNP should prompt assessment of left ventricular function. Factors increasing the risk of left ventricular systolic dysfunction (LVSD) include:

1. Concomitant use with Disopyramide.
2. Concomitant use in patients taking a combination of both a beta blocker and a rate-limiting calcium channel blocker.
3. Concomitant use with a CYP2C19 inhibitor or a CYP3A4 inhibitor.
4. Discontinuation or reducing the dose of a concomitantly used CYP2C19 or CYP3A4 inducer.
5. Tachyarrhythmias including atrial fibrillation.
6. Serious intercurrent illnesses such as serious infections.

Teratogenicity
Mavacamten is contraindicated during pregnancy as it may decrease embryonic viability, impair foetal growth, and cause embryo-foetal malformations.

Contraception
A negative pregnancy test is required in female patients with reproductive potential before initiating Mavacamten. Female patients with reproductive potential must be advised to use highly effective contraceptive methods (e.g. long-acting reversible contraceptives (LARC) copper intrauterine device (Cu-IUD), levonorgestrel intrauterine system (LNG-IUS) or progestogen-only implant (IMP)) during treatment with, and for 6 months after stopping Mavacamten. Studies have not been done in males taking mavacamten to find out if there is a risk to children from those taking mavacamten fathering children; therefore the risks are unknown at present.

Breast feeding
Women must not breast-feed during treatment with Mavacamten.

Driving and operating machinery
Patients should be advised not to drive or use machines if they experience dizziness.

12. Adverse reactions/side effects
Dizziness (very common), left ventricular systolic dysfunction (common), syncope (common)

13. Drug interactions

CYP2C19 inhibitors(13)

Strong inhibitors	Moderate inhibitors	Weak inhibitors
Ticlopidine	Omeprazole (TTD 40mg)	Omeprazole (TTD 20mg)
Fluconazole	Fluoxetine	Carbamazepine
Fluvoxamine	Esomeprazole	Cimetidine
Clomipramine	Voriconazole	Nortriptyline
		Citalopram
		Fenofibrate
		Topiramate

CYP3A4 inhibitors

Strong inhibitors	Moderate inhibitors	Weak inhibitors
Clarithromycin	Grapefruit juice	Omeprazole
Itraconazole	Erythromycin	Pantoprazole
Ketoconazole	Diltiazem	Esomeprazole
Voriconazole	Verapamil	Cimetidine
Tyrosine kinase inhibitors	Fluconazole	Amiodarone
Cobicistat		Cyclosporine
Idelalisib		Fosaprepitants
Ritonavir		
Ceritinib		
Tucatinib		

CYP2C19 and CYP3A4 inducers

Strong inducers	Weak and moderate CYP2C19 inducers	Weak and moderate CYP3A4 inducers
Rifampicin	Prednisolone	Primidone
carbamazepine	Norethindrone	Phenobarbital
Phenytoin	Letermovir	Cimetidine
Mitotane		Dexamethasone
Apalutamide		Bosentan
Enzalutamide		
Efavirenz		
St John's wort		

14. Monitoring

Visits' data should be recorded and saved on patient's electronic record (mava initiation or mava review documents). Patients' information leaflet should contain contact details for pharmacy or appointments queries. Clinical queries should be directed to the Inherited Cardiac Conditions team on Tay.inheritedcardiacconditions@nhs.scot during normal working hours of 9am – 4pm Monday to Friday. Out-of-hour queries should be directed to the on-call cardiology team. Left ventricular systolic function will be assessed in every visit (see appendix A below).

15. Pharmacokinetics

Mavacamten is absorbed with a median time to maximum plasma concentration of 1 hour (range: 0.5 to 3 hours) after oral administration. It has an estimated oral bioavailability of approximately 85% with plasma protein binding of 97-98%. Mavacamten is cleared from plasma primarily by metabolism through cytochrome P450 enzymes. In CYP2C19 normal metabolisers the terminal half-life is 6 to 9 days and in CYP2C19 poor metabolisers the half-life is 23 days for CYP2C19. In CYP2C19 normal metabolisers, 7% and 85% of the drug is excreted in faeces and urine, respectively.(14)

16. References

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17. Appendix A

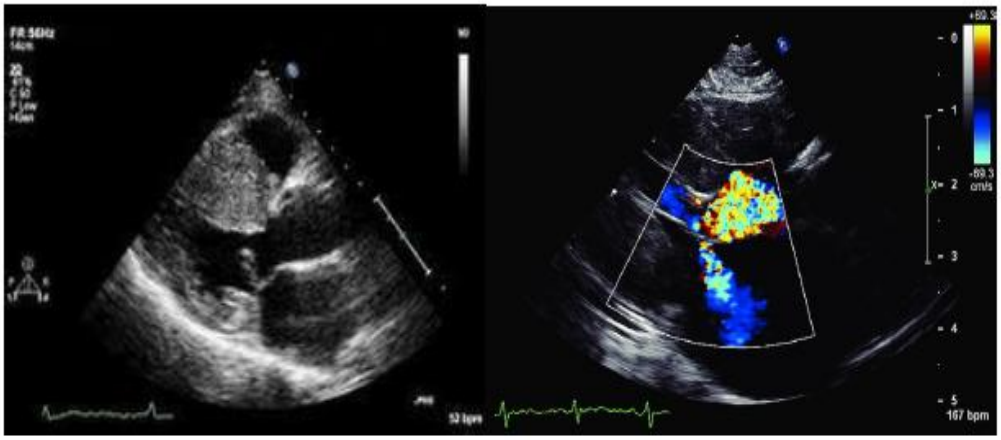
Hypertrophic Cardiomyopathy

Mavacamten Echocardiography Protocol

Parasternal Position	
1.PLAX	2D Imaging and colour flow doppler of MV and AV
2.PLAX	M-Mode of SAM
3.PSAX-MV level	2D
4.PSAX-Pap Level	2D
Apical Position	
5.AP4C	Colour Flow Doppler and MR CW doppler
6.AP5C/AP3C	CW doppler of resting LVOT gradient and with Valsalva manoeuvre
7.AP4C/AP2C	EF Simpsons biplane/Volumes
8.AP4C/AP3C/AP2C	GLS
9.AP4C – right ventricle (Baseline and every 12 months)	2D, colour doppler of TV, TR CW doppler, TAPSE, TDI, PASP

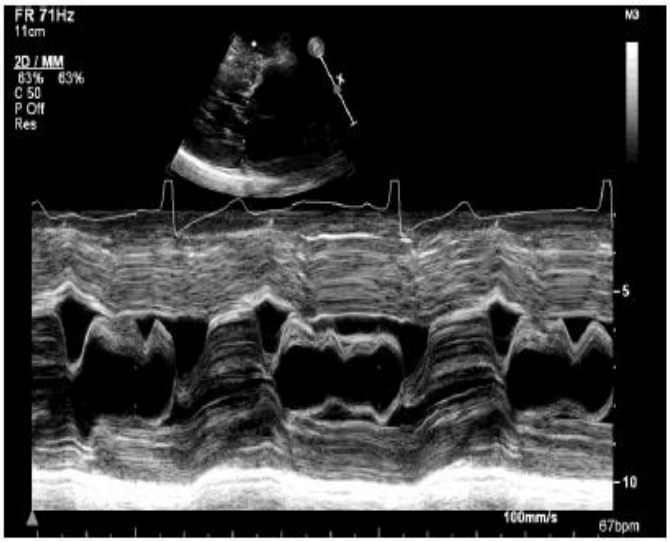
Parasternal Windows

Parasternal Long Axis (Shallow Depth): 2D Image and Colour Flow of mitral valve (MV) and aortic valve (AV)

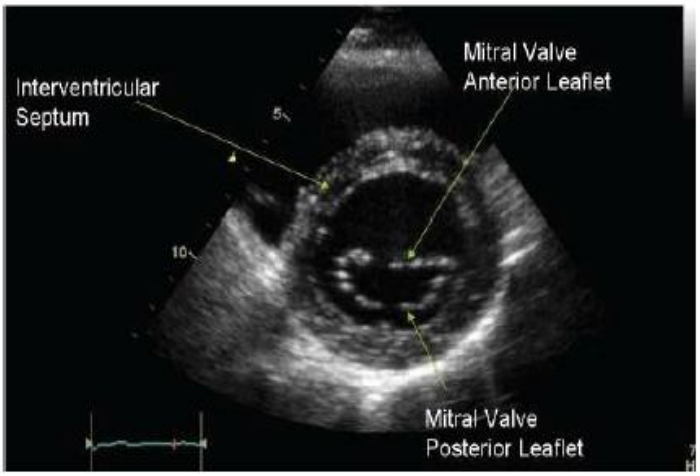


Parasternal Long Axis: Mitral valve M-Mode

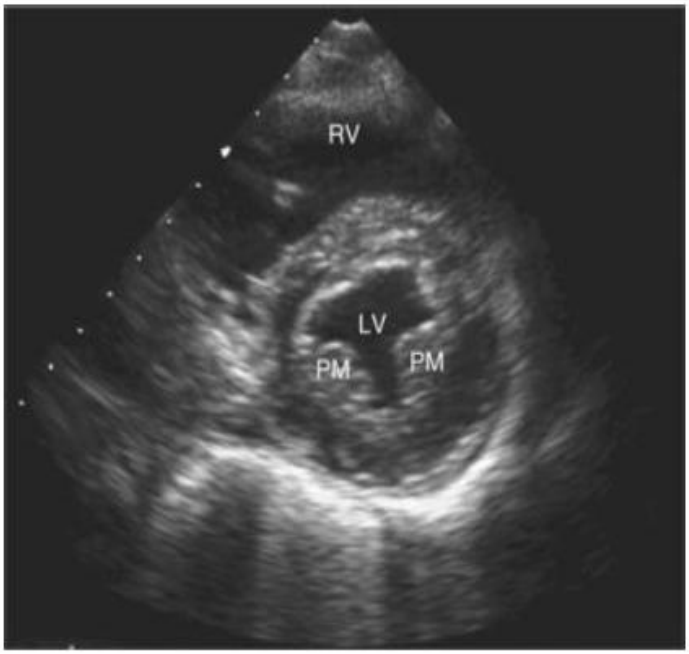
- Place M-Mode cursor through the MV leaflet tips, ensure images are on axis, involves MV leaflets and/or chordae.



Parasternal Short Axis -MV Level



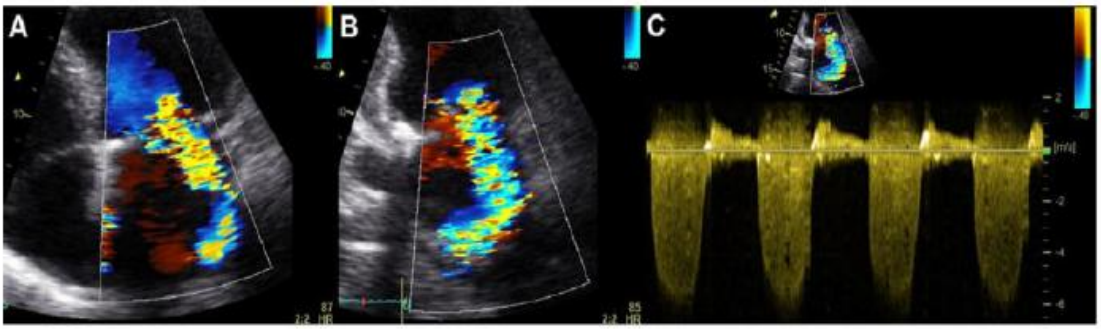
Parasternal Short Axis Pap Level



Mitral Regurgitation

View - PLAX, AP4C and AP5C

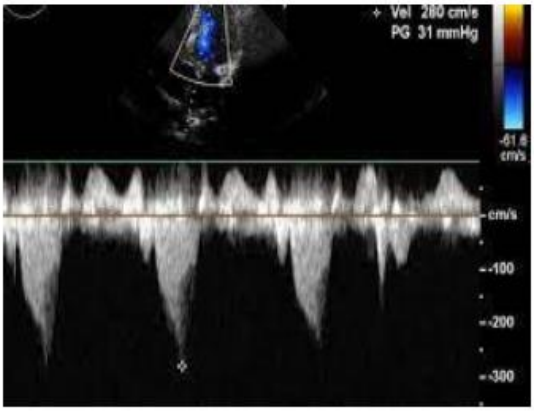
MR quantification may be limited as the PISA dome may merge with turbulent LVOT flow. MR secondary to SAM is posteriorly directed. When quantitative assessment of MR is precluded by LVOTO, other indicators of MR severity should be considered. E.g. an E velocity of <1.3m/s and an E/A ratio of <1 are strongly suggestive of non-severe MR.

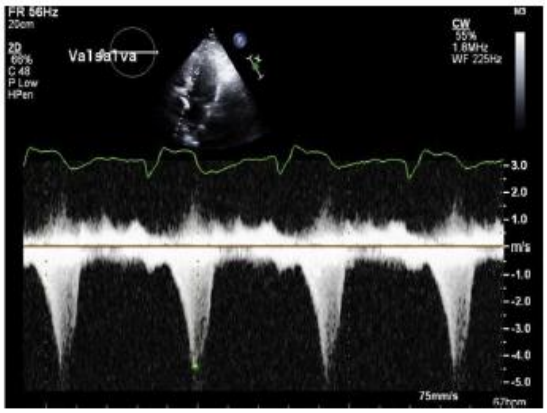


LVOT obstruction gradients

View – AP5C/AP3C

Assess obstruction gradients at rest and with Valsalva manoeuvre. Align CW doppler through entire turbulent colour flow for peak obstruction gradients.

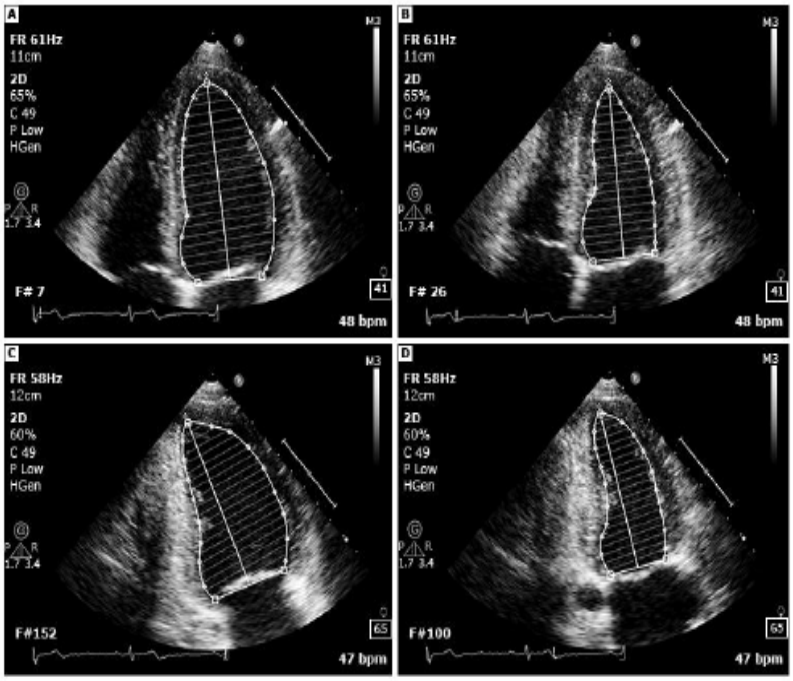




Ejection Fraction

View – AP4C and AP2C

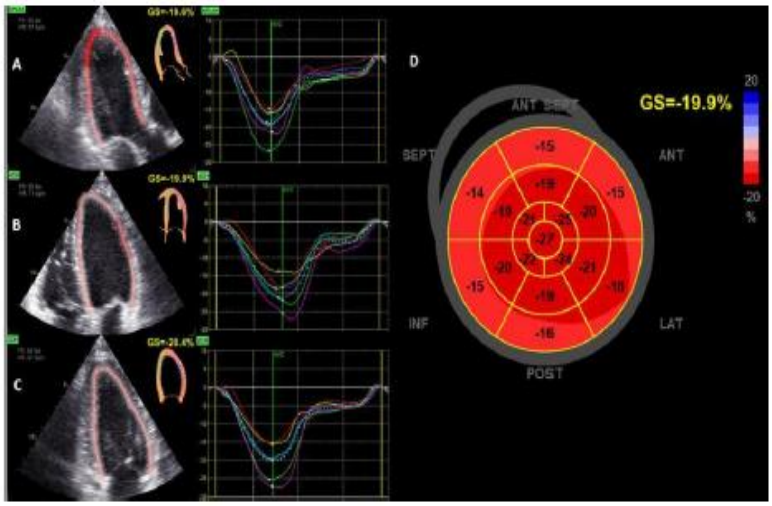
Simpsons Biplane/Volumes and LVEF



Global Longitudinal Strain Measurement

Optimal ECG signal with minimal heart rate variability will limit the calculation of GLS values, which is problematic in patients in AF. High quality image acquisition maintaining a Frame Rate of 40-90 frames/s at a normal HR is key.

Clear endocardial and epicardial definition is required to ensure adequate segment tracking throughout cardiac cycle. Use automatic tracking where possible to maintain reproducible results. Auto tracking should also be combined with a visual assessment of tracking in each view across the whole ROI. If more than two segments in any one view are not adequately tracked, the calculation of GLS should be avoided.



Focused right ventricular assessment

View – AP4C (RV centred)

A focused assessment of the right ventricle will include 2D imaging, colour doppler of the tricuspid valve/RA, CW doppler of tricuspid regurgitation, M-Mode and TDI of lateral tricuspid annulus. Assessment of the right ventricle will be carried out at the baseline visit and every 12 weeks.