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ClinicalNotes

# Subclinical Hypertrophic Cardiomyopathy: How Can This Condition Be Managed?

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Hypertrophic cardiomyopathy (HCM) is an often devastating disease of the heart muscle, affecting ≈1 in 7 cats.[1] The prevalence of this condition increases with age, and it has been linked to genetic mutations of the cardiac sarcomere in some purebred cats (eg, Maine coons, ragdolls).[1-3] Despite the staggering prevalence of this disease in the feline population, treatment options prior to the onset of severe clinical outcomes remain limited. In addition, HCM in cats can progress to congestive heart failure (CHF), sudden cardiac death (SCD), or feline arterial thromboembolism (FATE), resulting in a high degree of disease morbidity and mortality (***Figure 1***).[4]

Although most therapies employed for cats with HCM target the mitigation of already existent clinical signs, the subclinical phase of HCM represents an opportunity for early and potentially lifesaving intervention.[5] Except for antithrombotic therapies aiming to prevent or delay thromboembolism, no therapeutic intervention is widely prescribed in the subclinical period of the disease.[6] The use of clopidogrel is postulated to have a positive impact in preventing thromboembolism, despite a paucity of any evidence that initial clot prevention is impacted by its use.[7] Recently, delayed-release sirolimus was shown to halt or regress left ventricular hypertrophy in cats with subclinical HCM, leading to its reasonable expectation

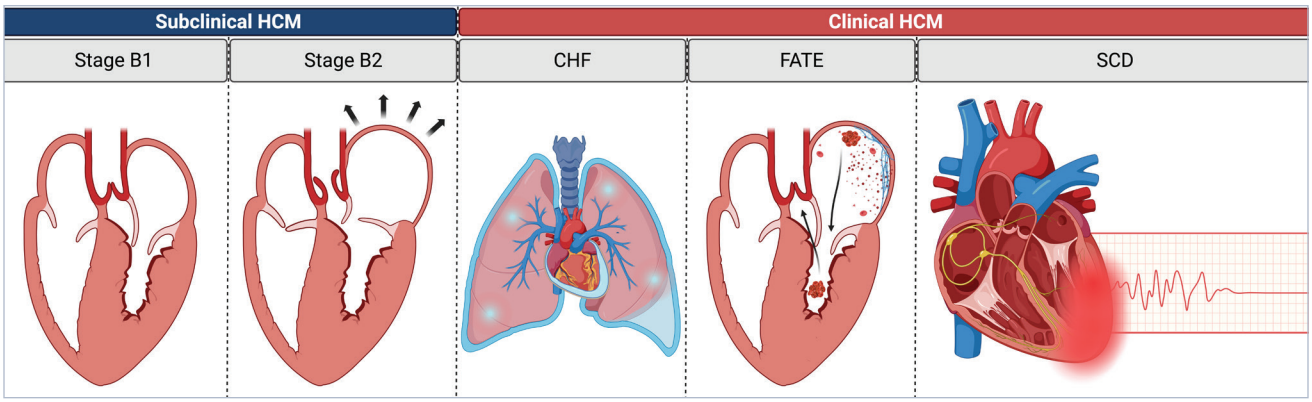


**FIGURE 1** Diagrammatic representation of the subclinical phases and clinical outcomes of feline HCM

CHF = congestive heart failure
FATE = feline arterial thromboembolism
HCM = hypertrophic cardiomyopathy
SCD = sudden cardiac death

of efficacy from the FDA and subsequent conditional approval as Felycin®-CA1.[8,9a] Although this therapy is being further explored through a pivotal clinical trial in pursuit of full FDA approval, the availability to treat the large number of cats with subclinical HCM in practice represents a major opportunity for improvement in disease management.

## Identification of Subclinical Hypertrophic Cardiomyopathy in Practice

If a paradigm shift toward managing HCM in the subclinical period is on the horizon, then a focus on subclinical HCM diagnosis is needed. Echocardiographic identification of left ventricular wall thickening (determined via the presence of a diastolic left ventricular posterior wall or an interventricular septum >6 mm) remains the gold standard.[6] However, there are several tests that can be employed by the primary care clinician to aid in understanding a cat's increased risk for disease.

A thorough physical examination is the first in a series of diagnostic evaluations that can help practitioners recognize risk for HCM in feline patients.[10,11] The presence of at least a grade 3 heart murmur or identification of an intermittent or consistent gallop sound in an apparently healthy cat should prompt the clinician to consider HCM.[1] Similarly, any ausculted arrhythmia or arrhythmia observed via electrocardiography warrants further investigation for possible HCM.[11] Chest radiography represents an insensitive mechanism for evaluation of HCM, primarily due to the heart's normal appearance until relatively late stages of disease, and radiography is thus not routinely recommended.[12] The cardiac biomarker N-terminal pro-brain natriuretic peptide (NT-proBNP) can be measured quantitatively and used to aid clinicians in understanding HCM risk.[13] Cats with abnormal NT-proBNP values (ie, >100 pmol/L) should be evaluated for HCM. False-positive NT-proBNP results are possible, particularly in the setting of concurrent renal disease,[14] making a paired serum chemistry profile alongside NT-proBNP evaluation advisable.

Finally, the use of ultrasonography in primary care is common, with 45% to 52% of >1,000 practitioners reporting the use of cardiothoracic ultrasonography in 2024.[15] Practitioners may readily identify left ventricular wall thickening with or without left atrial enlargement via fast thoracic ultrasonography. With practice, this technique represents an excellent and rapid diagnostic tool to determine whether a full echocardiogram is indicated and if HCM should remain a top differential. Once a diagnosis of definitive left ventricular wall thickening is made, other disease lookalikes, termed phenocopies, should be ruled out. These phenocopies include systemic hypertension, hyperthyroidism, transient myocardial hypertrophy seen with extreme stress, acromegaly, and other congenital heart diseases.[6]

## Risk Stratification With Subclinical Hypertrophic Cardiomyopathy

Although clinical outcomes for many cats with subclinical HCM are severe, some cats will remain subclinical for life.[4] This knowledge has led to a focus on risk stratification in subclinical HCM. This is particularly true for identifying which cats are recommended for standard or advanced antithrombotic therapies. The use of antithrombotic therapies is largely based on the presence of moderate to severe left atrial enlargement (ie, stage B2 HCM). Once cats reach obvious left atrial enlargement, the use of standard dose clopidogrel (ie, 18.75 mg/cat orally every 24 hours) is considered standard of care.[6] In the case of even more

### Key Takeaways

- Screening for HCM in clinical practice is an important first step to initiating intervention.
- Auscultation, identification of arrhythmias, NT-proBNP assessment, and fast thoracic ultrasonography are great techniques that can aid in the identification of cats that are more likely afflicted by subclinical HCM.
- A diagnosis of subclinical HCM requires the veterinarian to rule out disease phenocopies such as hyperthyroidism and systemic hypertension, among other rare conditions.
- Clopidogrel and Felycin-CA1 represent treatment options for cats with subclinical HCM that have the opportunity to alter disease outcomes.

> **Although clinical outcomes for many cats with subclinical HCM are severe, some cats will remain subclinical for life.**

[a] Conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-604.

severe left atrial enlargement (ie, presence of thrombi or smoke in the left atrium), expanded antithrombotic therapies such as concomitant rivaroxaban and clopidogrel are warranted.[16]

Beyond risk assessment for FATE, several findings have been associated with progression from subclinical to clinical HCM. Findings like severe left ventricular wall thickening, identification of thin or hypokinetic left ventricular wall segments, reduced left atrial function, and/or reduced left ventricular function place cats at increased risk.[17-22]

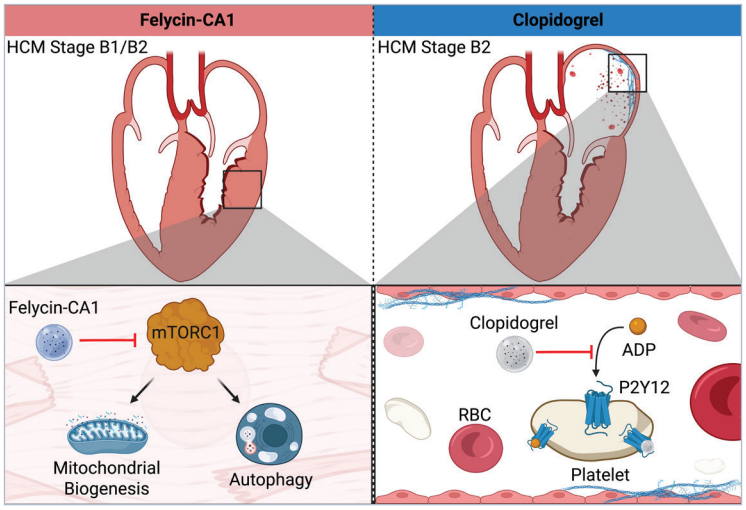


**FIGURE 2** Diagrammatic representation of therapeutic treatment options in subclinical HCM and mechanisms of action for each drug. The subclinical stage for which each therapy is recommended is shown above the representative drug's mechanism of action.

**Successful management of feline HCM takes the entire veterinary team.**

Enhance your team's approach with this companion article, **A Team Approach to Hypertrophic Cardiomyopathy in Cats**, on page X.

CHF = congestive heart failure
FATE = feline arterial thromboembolism
HCM = hypertrohpic cardiomyopathy
mTORC1 = mechanistic target of rapamycin complex 1
SCD = sudden cardiac death

## Treatment Modalities for Subclinical Hypertrophic Cardiomyopathy

Clopidogrel is an antiplatelet therapy used to reduce the risk for the potentially life-threatening complication of thromboembolism, rather than to treat the underlying HCM, and is recommended for cats with moderate to severe left atrial enlargement.[6,7] It has been shown to be well-tolerated and, in the presence of an existing blood clot, to prolong time to clot recurrence.

Felycin®-CA1 is the first and only drug conditionally approved for the management of ventricular hypertrophy in cats with subclinical HCM. It is administered once weekly and intermittently suppresses the mechanistic target of rapamycin complex 1 (mTORC1) pathway.[8,9] It has achieved conditional approval, meaning it has met all safety and preliminary efficacy requirements to be used clinically while an ongoing, large pivotal clinical trial continues to establish its full effectiveness and long-term benefits. Mechanistically, the drug targets restoration of autophagy and mitochondrial function in the left ventricle, which are deranged in the setting of HCM (***Figure 2***). Early studies suggest that regular mTORC1 modulation may slow structural remodeling of the left ventricle, potentially delaying the onset of clinical signs and improving long-term outcomes.[8] It should not be used in patients with liver disease or diabetes.

## Conclusion

Hypertrophic cardiomyopathy is an incredibly common disease of cats that can result in life-limiting disease manifestations like CHF, FATE, and SCD. Although not all cats will progress to clinical disease, the identification of subclinical disease provides an opportunity to attempt treatment and delay or halt disease progression. Many diagnostic tests can be employed in practice to more readily identify the 1 in 7 cats that may have this condition, although echocardiography remains the gold standard. Therapies like clopidogrel and Felycin-CA1 represent treatment options for consideration in the subclinical period. ●

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## Important Safety Information

Do not use Felycin®-CA1 in cats with diabetes mellitus. Discontinue immediately if a cat receiving Felycin®-CA1 is diagnosed with diabetes mellitus. Do not administer in cats with pre-existing liver disease. Administration of Felycin®-CA1 with drugs that inhibit cytochrome P-450 3A4 or P-glycoprotein, such as calcium channel blockers, amiodarone, azoles, and cyclosporine, may increase risk for toxicity. Use caution when administering in cats with the *MDR1* mutation or when administering concomitantly with another P-gp substrate. Treatment with Felycin®-CA1 could impact the cat's ability to mount an adequate immune response to vaccinations.



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**FELYCIN®-CA1 (sirolimus delayed-release tablets)**
**Cardiac drug for oral use in cats only.**
**Conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-604. It is a violation of federal law to use this product other than as directed in the labeling.** For complete prescribing information, see full package insert. **Caution:** Federal law restricts this drug to use by or on the order of a licensed veterinarian. **Indication:** for the management of ventricular hypertrophy in cats with subclinical hypertrophic cardiomyopathy (HCM). **Dosage and Administration:** Administer Felycin-CA1 at a target dose of 0.3 mg/kg orally once weekly. Tablets should be swallowed whole and not chewed. Do not split or crush tablets. Felycin-CA1 should be administered with a meal. Cats weighing less than 2.5 kg cannot be accurately dosed. **Contraindications:** Felycin-CA1 should not be used in cats with diabetes mellitus. Discontinue immediately if a cat receiving Felycin-CA1 is diagnosed with diabetes mellitus. The administration of Felycin-CA1 to a cat that developed diabetes mellitus was associated with the development of diabetic ketoacidosis and death. Do not administer in cats with pre-existing liver disease. **User Safety Warnings:** Not for human use. Keep out of reach of children. Contact a physician in case of accidental ingestion by humans. Pregnant and breastfeeding women should avoid contact with Felycin-CA1. People with known hypersensitivity to sirolimus should administer Felycin-CA1 with caution. **Animal Safety Warnings:** Administration of Felycin-CA1 with drugs that inhibit cytochrome P-450 3A4 or P-glycoprotein, such as calcium channel blockers, amiodarone, azoles, or cyclosporine, may increase risk for toxicity. Use caution when administering in cats with the MDR1 mutation or when administering concomitantly with another P-gp substrate. Treatment with Felycin-CA1 could impact the cat's ability to mount an adequate immune response to vaccinations. Concurrent administration of Felycin-CA1 did not impact the cat's ability to mount an adequate immune response to a killed rabies vaccine. The impact of Felycin-CA1 for FHV-1, FCV, FPV, and FeLV has not been evaluated. Keep Felcyin-CA1 in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose. **Precautions:** For use only in otherwise healthy cats with subclinical HCM in the absence of other causes of compensatory myocardial hypertrophy (e.g. systemic hypertension), current or historic symptoms of congestive heart failure, arterial thromboembolism, and severe LV outflow tract obstruction. Treatment with Felycin-CA1 has been associated with the elevation of the transaminase enzymes, which include alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The use of Felycin-CA1 in cats with viral disease like feline viral rhinotracheitis has not been evaluated. The safety and effectiveness of Felycin-CA1 has not been evaluated in cats with other cardiomyopathy phenotypes, in cats receiving beta blockers or corticosteroids, in cats with kidney disease, hyperthyroidism, or other significant systemic disease. The effectiveness of Felycin-CA1 has not been evaluated in sexually intact cats, therefore, should not be used in animals intended for breeding. **Adverse Reactions:** In a well-controlled pilot field study, 43 cats with subclinical HCM were administered either the label dose of Felycin-CA1 (0.3 mg/kg once weekly), twice the label dose (0.6 mg/kg once weekly), or a placebo control tablet and followed for 180 days or until removal from the study. The most frequently observed adverse reactions were cardiovascular in nature, relating to the progression of HCM, and included arrhythmia, congestive heart failure, syncope, and pericardial effusion. Other adverse reactions were lethargy, vomiting, diarrhea, and inappetence. **Clinical Pharmacology:** Sirolimus is an immunosuppressant that targets and inhibits the mammalian target of rapamycin C1 (mTORC1) protein complex, a central regulator of cell growth and nutrient response. Studies in rodent models suggest mTOR inhibition by sirolimus attenuates cardiac hypertrophy by promoting autophagy, attenuating oxidative stress and blocking proinflammatory responses, thereby resulting in an improvement in cardiac function in rodents. **Reasonable Expectation of Effectiveness:** This product is conditionally approved by FDA pending a full demonstration of effectiveness. **To obtain full product information for Felycin-CA1 please call 1-800-874-9764.**
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