Contemporary Management of Hypertrophic Cardiomyopathy

A Clinical Blueprint for Diagnosis, Risk Stratification, and Disease-Modifying Therapy.

A synthesis of ESC 2023 and AHA/ACC 2024 Guidelines — Australian Clinical Context.

The Clinical Reality

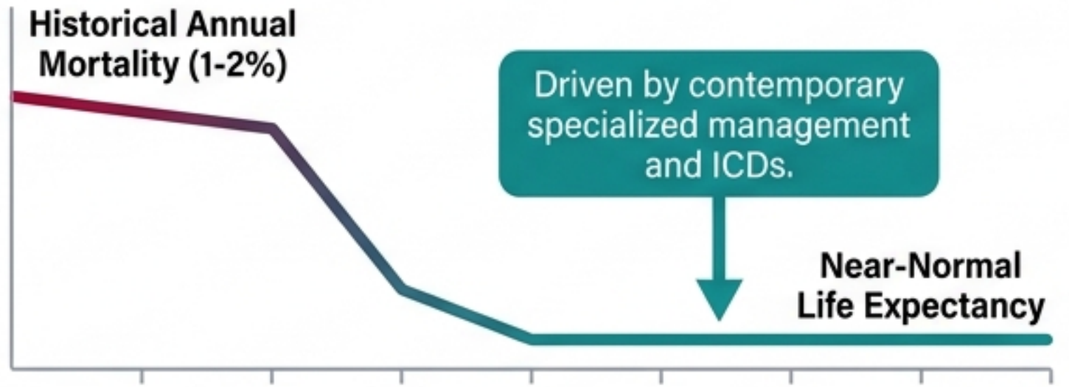
~1:500

Prevalence: (most common inherited cardiac disease).

Australian Impact:
~50,000 individuals affected (many undiagnosed).

SCD Burden:
#1 cause of Sudden Cardiac Death in the young (<35 years) and competitive athletes.

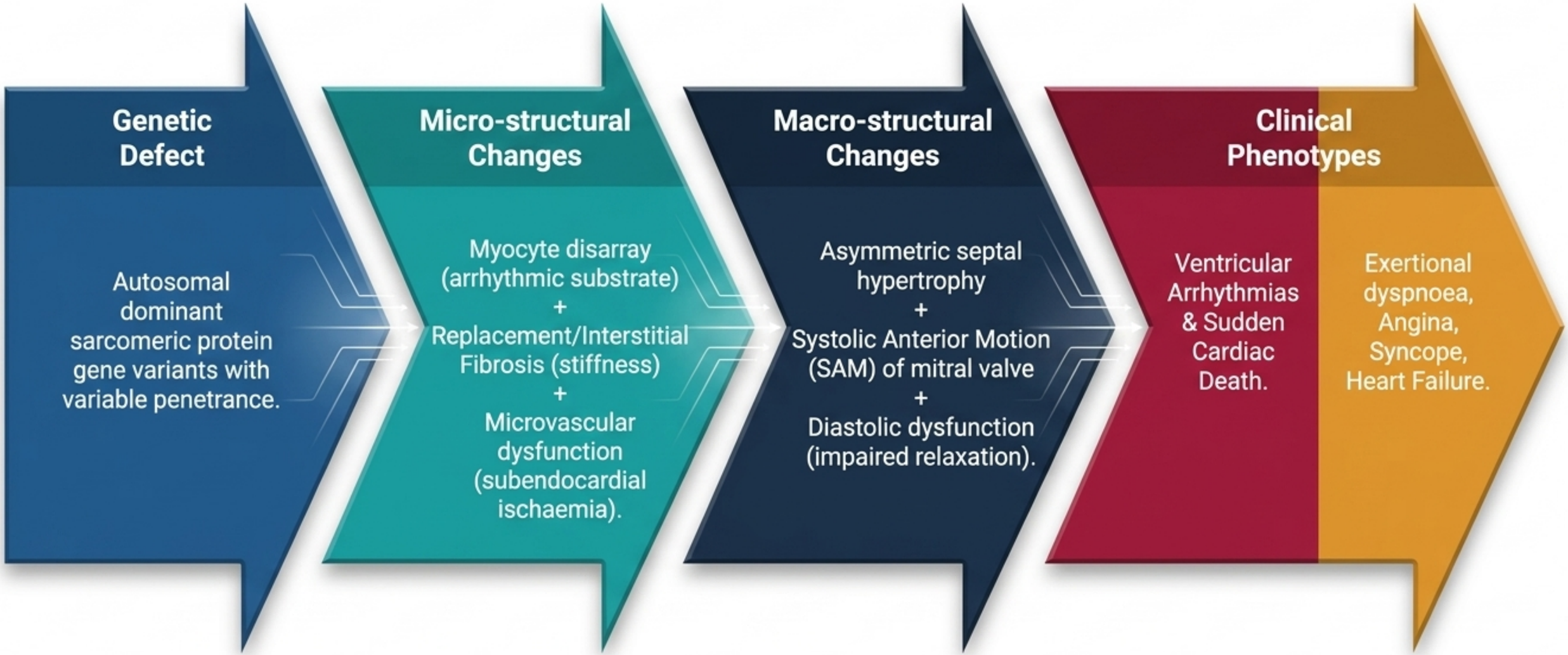
The Prognostic Shift



The Australian Context

Specialized HCM clinics and advanced diagnostics (CMR, genetic testing) are heavily concentrated in major tertiary centers (**Melbourne, Sydney, Brisbane, Perth**), creating significant access barriers for rural and remote populations.

The Pathophysiology Causal Chain



Sarcomeric Genotype-Phenotype Matrix

Gene	Protein	Frequency	Phenotypic Severity
MYBPC3	Myosin-binding protein C	~40%	Later onset, variable penetrance, frameshift/truncating.
MYH7	β-myosin heavy chain	~30–40%	Earlier onset, more severe phenotype, higher penetrance.
TNNT2	Cardiac troponin T	~5%	Mild hypertrophy but high SCD risk.
TNNI3	Cardiac troponin I	~5%	Variable severity, may cause restrictive physiology.
TPM1 / ACTC1	α-tropomyosin / Cardiac actin	<3%	Mild-moderate / Rare mid-ventricular pattern.

Genotype-Negative Phenotypes

~40% of patients have no identifiable sarcomeric variant. Must actively exclude metabolic/ infiltrative disorders (e.g., Fabry, Amyloidosis).

Diagnostic Thresholds: Maximum LV wall thickness ≥15 mm (any modality) OR ≥13 mm in genotype-positive family members.

Echocardiography (First-Line)

Assess **wall thickness, LVOT gradient** (rest ≥30 mmHg; provoked ≥50 mmHg), SAM, and **mitral regurgitation**.

(MBS Item 55116)

Cardiac MRI (Risk Stratification)

Essential for **SCD risk**. Quantifies **Late Gadolinium Enhancement** (LGE ≥15% LV mass = independent SCD predictor). Differentiates athlete's heart.

(MBS Item 63501)

12-Lead ECG & Holter (Electrical)

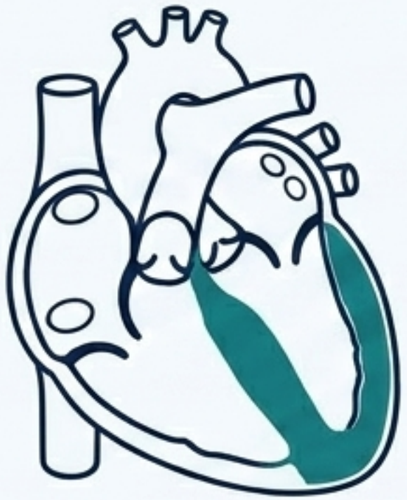
ECG abnormal in >90% (deep T-wave inversions, LVH). Holter required for SCD risk (detecting NSVT ≥3 beats at ≥120 bpm).

Genetic Panels (Cascade Prep)

Offered to all confirmed HCM. Comprehensive panels cover **sarcomeric** and mimicking-disease genes. Direct-to-consumer testing strictly not recommended.

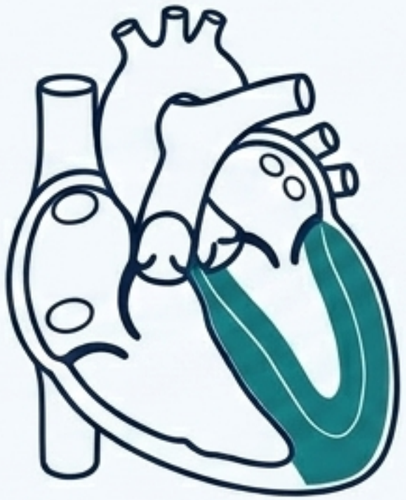
Anatomical Taxonomy and Disease Mimics

Asymmetric Septal (~70%)



Ratio >1.3:1 relative to posterior wall.

Concentric (~10-15%)

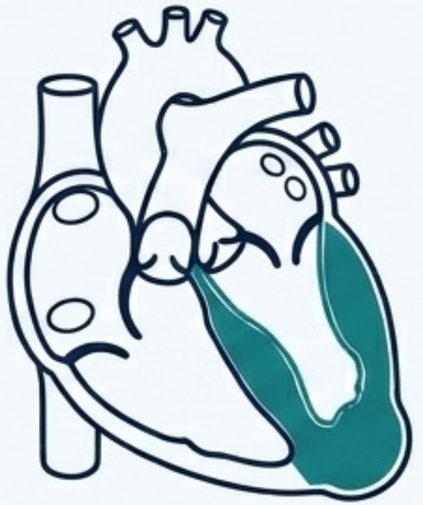


Uniform wall thickening.

Apical (~10-15%)

Apex predominant; deep T-wave inversions (V4-V6).

Mid-Ventricular



Apical aneurysm formation, higher SCD risk.

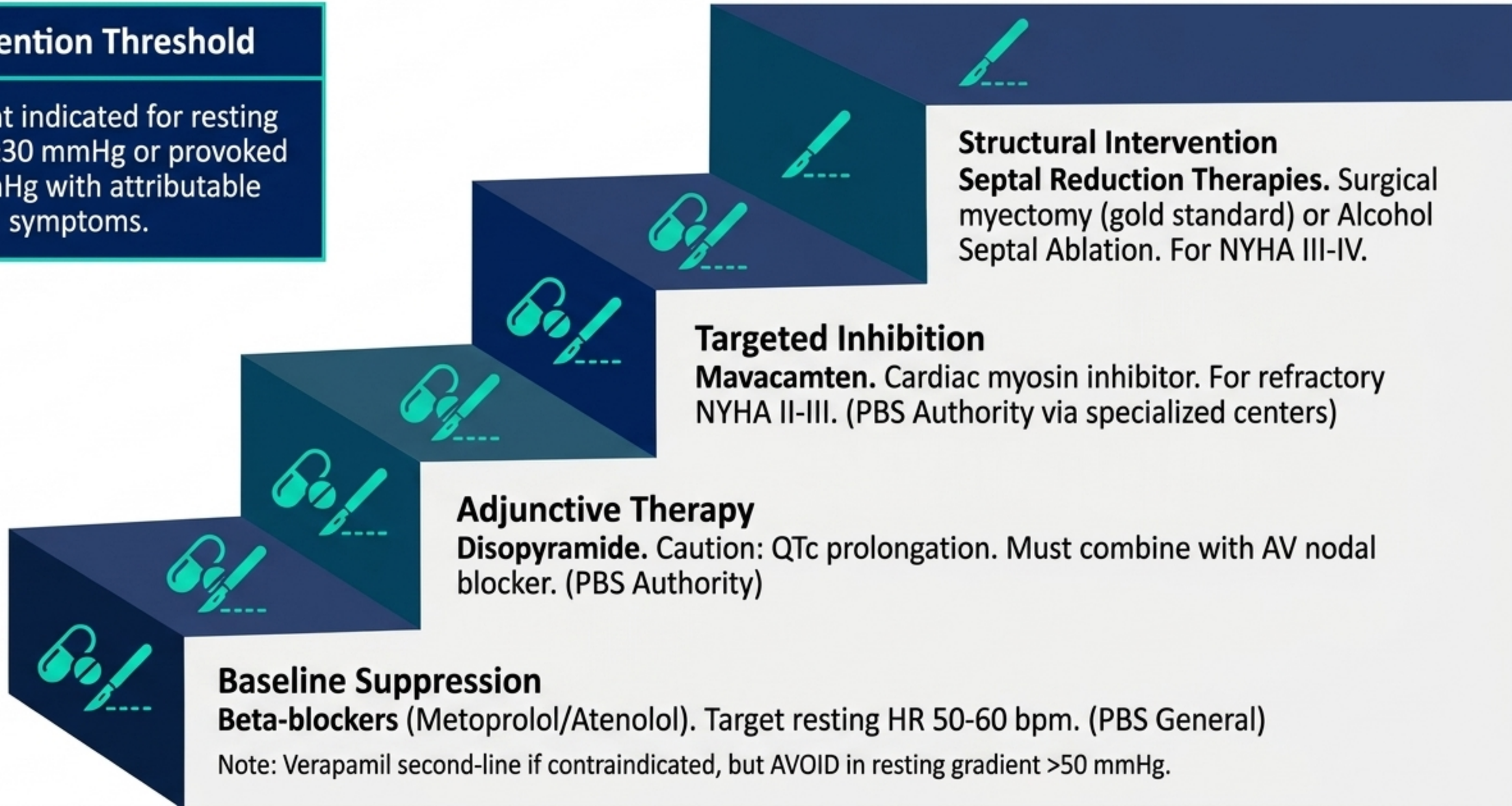
CRITICAL DIFFERENTIAL: The Mimics

Hypertension alone does NOT exclude HCM. Actively screen for **Fabry disease** (α-galactosidase A), **Cardiac Amyloidosis** (technetium-99m PYP), and **Danon disease** (LAMP-2). Treatment pathways differ completely.

Therapy Escalation Staircase: LVOT Obstruction

Intervention Threshold

Treatment indicated for resting gradient ≥30 mmHg or provoked ≥50 mmHg with attributable symptoms.



Structural Intervention
Septal Reduction Therapies. Surgical myectomy (gold standard) or Alcohol Septal Ablation. For NYHA III-IV.

Targeted Inhibition
Mavacamten. Cardiac myosin inhibitor. For refractory NYHA II-III. (PBS Authority via specialized centers)

Adjunctive Therapy
Disopyramide. Caution: QTc prolongation. Must combine with AV nodal blocker. (PBS Authority)

Baseline Suppression
Beta-blockers (Metoprolol/Atenolol). Target resting HR 50-60 bpm. (PBS General)

Note: Verapamil second-line if contraindicated, but AVOID in resting gradient >50 mmHg.

The Paradigm Shift: Mavacamten Therapy & Protocol

Mechanism: Selective allosteric inhibitor of cardiac myosin ATPase. Reduces excessive actin-myosin cross-bridge formation. Directly addresses sarcomeric hypercontractility.

The Risk: 5-7% develop LVEF <50%.
Protocol: LVEF must be ≥50% before any dose increase.

- Echo Baseline
- Echo 4 Weeks
- Echo 8 Weeks
- Echo 12 Weeks
- Echo Every 3 Months

Caution: Pharmacogenomics matters (CYP2C19 poor metabolizers have higher exposure). Contraindicated in pregnancy.

Endpoint Structural Therapies for Refractory Obstruction

Surgical Myectomy (Morrow Procedure)

Gold Standard

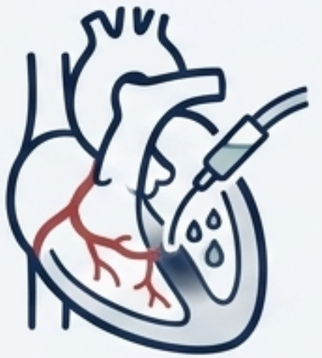
Procedure: Open-heart resection of 10-15g basal septal muscle.

Efficacy: Obstruction relief in >95%; operative mortality <1%.

Advantages: Allows concomitant mitral valve repair and addresses non-classic anatomy.

Alcohol Septal Ablation (ASA)

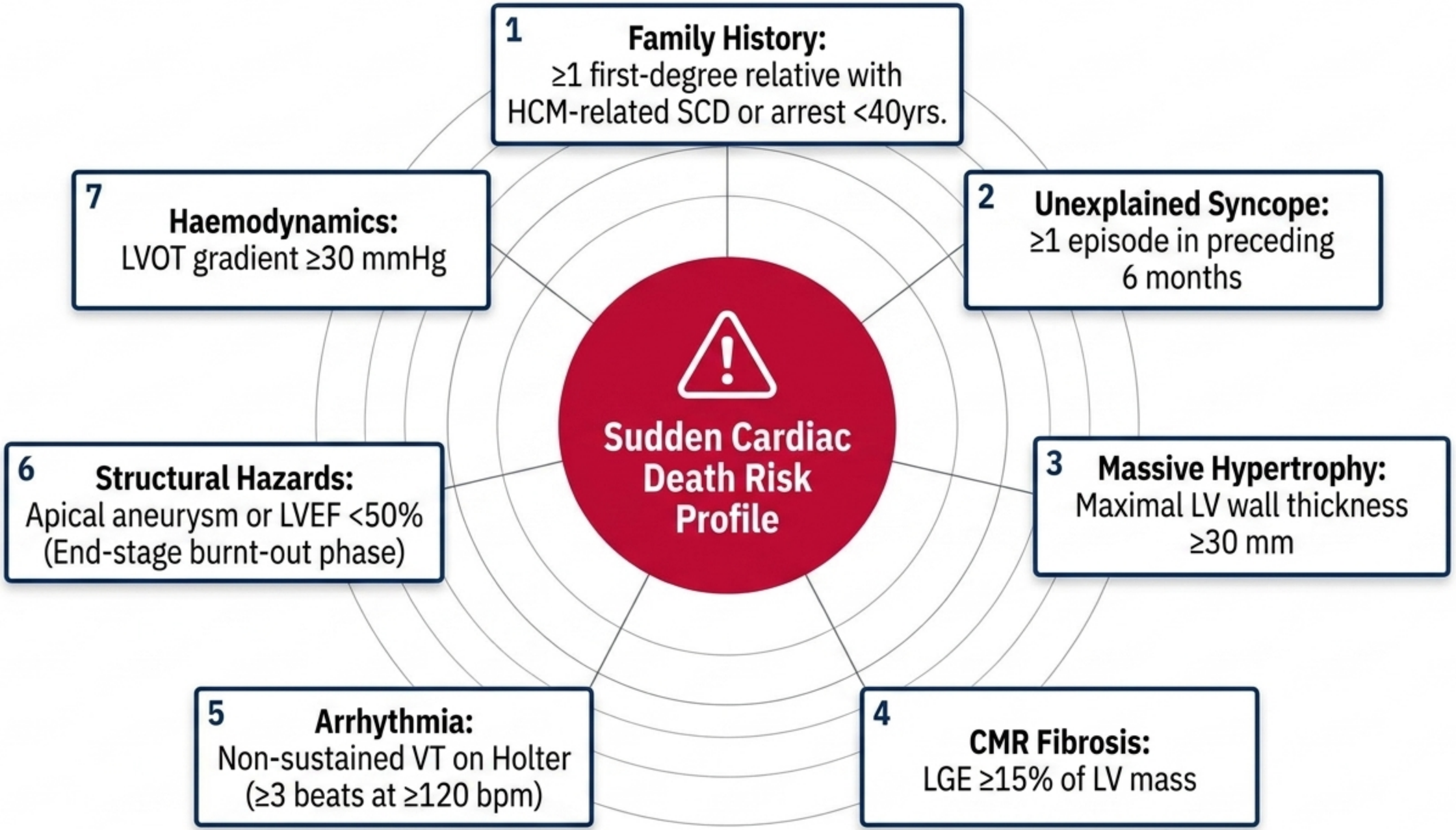
Catheter-Based Alternative



Procedure: Injection of 1-3 mL absolute ethanol into septal perforator artery to induce localized infarction.

Complications: Higher rate of permanent pacemaker implantation (10-20% vs 3-5%).

Indication: Preferred for elderly patients or those with significant surgical comorbidities. Requires suitable perforator anatomy.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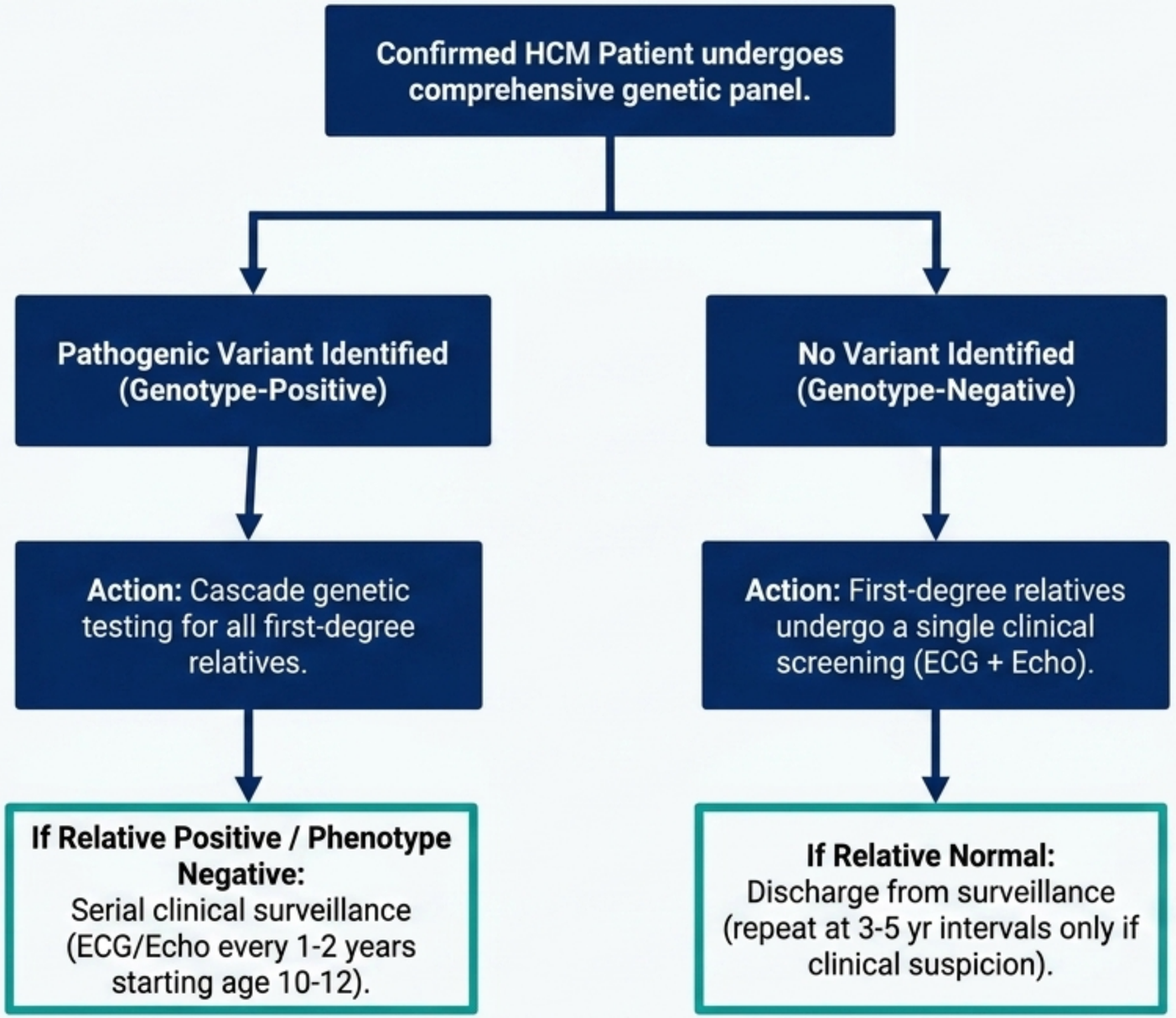
Family History:
≥1 first-degree relative with HCM-related SCD or arrest <40yrs.
2
Unexplained Syncope:
≥1 episode in preceding 6 months
3
Massive Hypertrophy:
Maximal LV wall thickness ≥30 mm
4
CMR Fibrosis:
LGE ≥15% of LV mass
5
Arrhythmia:
Non-sustained VT on Holter (≥3 beats at ≥120 bpm)
6
Structural Hazards:
Apical aneurysm or LVEF <50% (End-stage burnt-out phase)
7
Haemodynamics:
LVOT gradient ≥30 mmHg
Sudden Cardiac Death Risk Profile

ESC HCM Risk-SCD Calculator Matrix

Low Risk (<4% 5-year risk)	Intermediate Risk (4-6% 5-year risk)	High Risk (≥6% OR ≥1 Major Risk Factor)
Action: Routine clinical surveillance every 12-24 months.	**Action:** Shared decision-making integrating LGE burden, aneurysms, and genotype.	**Action:** Tertiary HCM center referral.
ICD Class III: ICD generally not recommended; risks outweigh benefits.	**ICD Class IIa:** ICD may be considered. Discuss inappropriate shock risks.	**ICD Class I:** ICD strongly recommended. Secondary prevention (prior arrest/sustained VT) is automatic Class I.

Limitation Note: The ESC calculator does NOT include LGE burden, apical aneurysm, or genetics. These must be manually integrated into clinical judgment.

Genetic Testing & Cascade Screening Protocol



Post-Mortem Note

Molecular Autopsy: Genetic testing of tissue post-SCD via Coronial systems strictly informs family screening protocols.

Contemporary Lifestyle and Exercise Parameters

The Exercise Shift

Competitive Sport

Generally contraindicated (risk of exercise-related SCD / haemodynamic stress).

Recreational Exercise

Moderate-intensity encouraged (Class I). Target 150 min/week (walking, cycling).

Heavy Resistance

Avoid Valsalva maneuvers (acutely increases LVOT gradient).

Lifestyle Parameters

Swimming Caution

Never swim unsupervised in open water. AED access required.

Medication Dangers

Avoid vasodilators (nitrates, PDE-5 inhibitors) and pseudoephedrine.

Hydration/Heat

Dehydration reduces preload, acutely worsening LVOT obstruction.

Driving

Austroads restrictions apply post-ICD (4 weeks post-implant, 6 months post-shock).

Pregnancy: Haemodynamic Stress and Management Tiers

Low Risk: Non-obstructive, no prior SCD, LVEF ≥55%	Standard obstetric care with cardiology co-management.
Moderate Risk: Obstructive (≥30 mmHg), prior ICD	Pre-conception planning, MDT heart team, epidural anaesthesia.
High Risk: Prior SCD/shock, severe obstruction, LVEF <50%	Quaternary center delivery with ECMO capability. Vaginal delivery preferred (assisted second stage to avoid Valsalva).

Pharmacological Safety Profile

Safe / Continue	Contraindicated
Metoprolol, Labetalol.	Mavacamten (teratogenic / Category D), Disopyramide (stimulates uterine contractions).

Divergence from Standard Care: Special Populations

Paediatric

- Often aggressive phenotype. Z-scores used for LV thickness.
- Beta-blockers first line; Mavacamten NOT approved.
- S-ICD preferred in older children.

Elderly (≥65y)

- Critical differentiation from hypertensive heart disease.
- High AF prevalence (~25%).
- ASA preferred over myectomy due to surgical comorbidities.

Renal Impairment

- Disopyramide is renally cleared (requires strict dose reduction; avoid if eGFR <15).
- Use macrocyclic Gadolinium for CMR.

Hepatic Impairment

- Metoprolol and Mavacamten (CYP2C19/CYP3A4) are hepatically metabolized.
- Reduce/avoid in moderate-severe impairment.

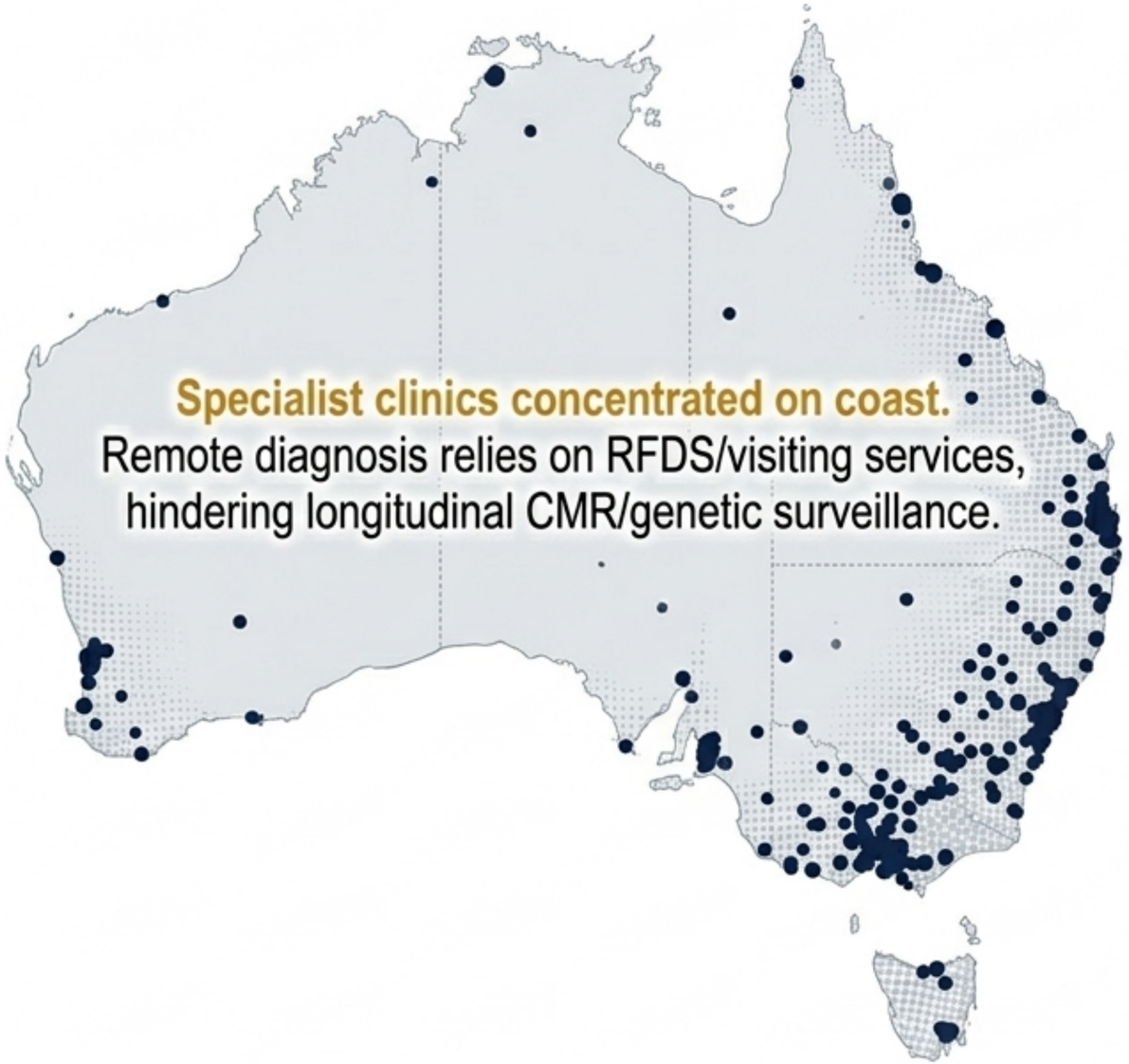
Immunocompromised

- Calcineurin inhibitors cause LVH, confounding diagnosis.
- Higher transvenous ICD infection rates.
- Rule out HIV antiretroviral cardiotoxicity.

Athletes (Screening)

- Pre-participation screening (AIS protocols) relies on baseline ECG to trigger Echo investigation.

Contextual Equity: Aboriginal and Torres Strait Islander Populations



The RHD Differential

Rheumatic Heart Disease remains highly prevalent.

Valvular loading causes secondary LVH, potentially masking primary HCM. Careful echo differentiation required.

Genetic Blind Spots

Current HCM gene panels are predominantly derived from European/North American cohorts. ATSI-specific pathogenic variants are heavily under-represented.

Culturally Safe Care

Involve Aboriginal Health Workers. Utilize yarning-based education. Navigate family screening conversations with deep sensitivity to community-level distress and kinship systems.

The Horizon: Next-Generation Therapies

Near-Term: Next Gen Inhibitors

Aficamten (Phase III SEQUOIA-HCM).

Shorter half-life (~2.5 days) allows faster reversibility of LVEF drops; potentially less intense monitoring required.

Mid-Term: Metabolic & Fibrotic Targets

N-acetylcysteine (anti-fibrotic),

Perhexiline (shifts myocardial metabolism from fatty acid to glucose oxidation in non-obstructive HCM).

Long-Term: Gene Therapies

Gene Silencing (ASO/siRNA): Targets mutant MYBPC3 mRNA to halt toxic protein expression.

CRISPR/Gene Replacement: Allele-specific editing or AAV-based delivery of functional MYBPC3.

Active trial sites available via ANZCTR and SHaRe Registry.

Contemporary HCM management has crossed a critical threshold: from purely symptomatic and palliative management to targeted, disease-modifying therapies that directly addss sarcomeric hypercontractility.

Foundational Evidence Base	
• AHA/ACC 2024 Guideline for the Management of HCM (Circulation).	• EXPLORER-HCM Phase 3 Trial (Lancet 2020 - Mavacamten).
• ESC 2023 Guidelines for the Management of Cardiomyopathies (Eur Heart J).	• SHaRe Registry Genotype-Phenotype Data (Circulation 2018).