ADVANCES IN DIAGNOSIS OF HYPERTROPHIC CARDIOMYOPATHY

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I ADVANCES IN ELECTROCARDIOGRAPHY AND ARTIFICIAL INTELLIGENCE

- **Deep-Learning Artificial Intelligence ECG (AI-ECG):** Convolutional neural networks trained on standard 12-lead ECG waveforms detect subtle, sub-visual depolarization and repolarization signatures of Hypertrophic Cardiomyopathy (HCM) with an Area Under the Curve (AUC) exceeding **0.95** (Ko et al., *JACC* 2020).
- **Clinical Utility:** Enables **pre-phenotypic screening** of genotype-positive, phenotype-negative family members, flag-alerting **Apical HCM** (which is frequently missed on routine TTE without contrast), and tracking electrophysiological reverse remodeling (rapid reductions in AI-ECG HCM probability scores and Sokolow-Lyon voltages) in patients treated with **Cardiac Myosin Inhibitors (Mavacamten / Aficamten)**.

II ADVANCES IN MULTIMODALITY ECHOCARDIOGRAPHY (ESC 2023 / AHA-ACC 2024 GUIDELINES)

- **2D Speckle-Tracking Global Longitudinal Strain (GLS) and Mechanical Dispersion:**
  - **Subclinical Systolic Dysfunction and Fibrosis Mapping:** Even when radial hypercontractility maintains a supranormal LVEF (65 to 75 percent), **regional longitudinal strain is markedly impaired (often worse than -10% to -12%) in hypertrophied septal segments**, correlating directly with histological myofibrillar disarray and replacement fibrosis (**CMR LGE**).
  - **Bull's-Eye Phenocopy Differentiation:** Polar strain maps distinguish **Sarcomeric Septal HCM** (focal septal strain loss) and **Apical HCM** (apical strain loss — "reverse cherry-on-top") from **Cardiac Amyloidosis** (relative apical sparing — "cherry-on-top") and **Fabry Disease** (basal inferolateral strain loss).
  - **Mechanical Dispersion:** Prolonged standard deviation of time-to-peak strain across 17 segments (**>60 to 65 ms**) independently predicts **Ventricular Tachycardia and Sudden Cardiac Death (SCD)**, and progressive global GLS decline warns of impending transition to **"End-Stage / Burned-Out" HCM (LVEF <50%)**.
  - **Contrast-Enhanced and 3D Echocardiography:**
  - **Ultrasound Enhancing Agents (Echo Contrast — Class I):** Mandatory whenever the apex is suboptimally visualized to unmask **Apical HCM (Yamaguchi syndrome)**, **Thin-Walled Apical Pouch / Apical Aneurysm** (a major SCD and stroke risk factor missed by unenhanced 2D TTE in >40% of cases), and apical mural thrombus.
  - **3D Echocardiography:** Eliminates geometric assumptions in asymmetric LVH mass quantification and provides **en-face surgical visualization** of intrinsic mitral valve apparatus abnormalities—specifically **elongated anterior/posterior mitral leaflets**, **anomalous direct papillary muscle insertion into the anterior mitral leaflet**, and **anteriorly displaced/bifid papillary muscles**—that drive **Systolic Anterior Motion (SAM)** even with mild septal hypertrophy (<18 mm).
  - **Physiological Exercise Stress Echocardiography (Class I):** Upright treadmill or bicycle exercise echocardiography (never dobutamine) is mandatory in symptomatic patients with resting/Valsalva gradients <50 mmHg to unmask **latent dynamic LVOT obstruction (>=50 mmHg)**.

III ADVANCES IN CARDIAC MAGNETIC RESONANCE (CMR — CLASS I REFERENCE STANDARD)

- **Quantitative Late Gadolinium Enhancement (LGE — Major SCD Risk Modifier):**
  - **Volumetric Threshold:** CMR has shifted from binary presence/absence of mid-wall patchy LGE (typically at the **RV-LV septal insertion points** and segments of maximal hypertrophy) to quantitative **percentage of total LV mass** (using the >=6 standard deviations above normal remote myocardium method).
  - **Guideline Actionability (2024 AHA/ACC & 2023 ESC): Extensive LGE comprising 15 percent or more of LV mass** confers a >2-fold increase in sudden death risk and is an established **Class IIa major risk factor for Primary-Prevention ICD implantation** (and is integrated into the 2023 ESC HCM-SCD risk refinement).
  - **Parametric Mapping (Native T1 Mapping and Extracellular Volume [ECV]) and Diffusion Tensor CMR:**
  - **Diffuse Interstitial Fibrosis: Elevated Native T1 and ECV (>28 to 30%)** quantify diffuse reactive interstitial collagen expansion *before* macroscopic replacement scar (LGE) develops.
  - **Differentiating Phenocopies on Native T1: Low Native T1** is highly characteristic of **Anderson-Fabry Disease** (intracellular glycosphingolipid storage, prior to pseudonormalization from basal inferolateral fibrosis) or iron overload, whereas **markedly elevated Native T1 (>1,100–1,150 ms) and ECV (>40%)** with nulling difficulty are diagnostic of **Cardiac Amyloidosis**.
  - **In-Vivo Diffusion Tensor CMR (DT-CMR) and Quantitative Stress Perfusion:** DT-CMR non-invasively maps **myofibrillar disarray** (reduced fractional anisotropy) in vivo, while quantitative adenosine-stress perfusion CMR detects severe **coronary microvascular dysfunction** (subendocardial hypoperfusion driving ischemia and scar).

Diagnostic Modality	Advanced Parameter / Biomarker	Actionable Diagnostic or Prognostic Cut-off (2023 ESC / 2024 AHA-ACC)
Quantitative LGE-CMR	Replacement myocardial fibrosis (% of LV mass)	**LGE >= 15% of LV mass** = Major independent **Class IIa indication for Primary-Prevention ICD**
CMR / Contrast Echo	**LV Apical Aneurysm** (with transmural apical LGE)	Independent **Class IIa indication for ICD** + **Oral Anticoagulation** for high apical thrombus/stroke risk
CMR Parametric Mapping	**Native T1 & Extracellular Volume (ECV)**	**Low Native T1** = **Fabry Disease**; **Very High Native T1 & ECV >40%** = **ATTR/AL Amyloidosis**; **Elevated ECV** = diffuse HCM fibrosis
2D STE (Strain)	**GLS & Mechanical Dispersion**	Differentiates phenocopies (polar map); **LVEF <50% ("End-Stage HCM")** = **Class IIa ICD indication**

Diagnostic Modality	Advanced Parameter / Biomarker	Actionable Diagnostic or Prognostic Cut-off (2023 ESC / 2024 AHA-ACC)
Circulating Biomarkers	**NT-proBNP & High-Sensitivity Troponin (hs-cTnI/T)**	Reflects wall stress & microvascular injury; **useful efficacy markers during Mavacamten therapy** (safety monitoring relies on echocardiographic LVEF)

IV ADVANCES IN GENOMIC MEDICINE AND PHENOCOPY EXCLUSION

- **Targeted Next-Generation Sequencing (NGS) Panels (Class I):** Identifies pathogenic variants in the eight core **sarcomeric genes** (**MYBPC3** [~40–45%, predominantly truncating/haploinsufficiency] and **MYH7** [~30–35%, predominantly missense], plus *TNNT2, TNNI3, TPM1, MYL2, MYL3, ACTC1*) in 40 to 60 percent of familial cases, enabling **cascade genetic screening** of first-degree relatives.
- **Crucial Exclusion of Actionable HCM Phenocopies ("Sarcomere-Negative LVH"):** NGS panels simultaneously screen for non-sarcomeric metabolic and infiltrative mimics that have **specific disease-modifying therapies**: **Anderson-Fabry Disease (*GLA* — treated with enzyme replacement [agalsidase] or chaperone therapy [migalastat])**, Hereditary/Wild-Type ATTR Amyloidosis (*TTR* — treated with tafamidis, acoramidis, or vutrisiran), **Danon Disease (*LAMP2* — X-linked lysosomal glycogen storage with massive LVH [often >30–40 mm], WPW pre-excitation, and rapid progression to transplant in young males)**, **PRKAG2 Cardiomyopathy** (glycogen storage + WPW + early conduction block requiring pacemaker/ICD), **Pompe Disease (*GAA*)**, **Friedreich Ataxia (*FXN* — omaveloxolone)**, and **Noonan/RASopathies (*PTPN11, RAF1*)**.
- **Polygenic Modifiers in "Genotype-Negative" HCM:** Genome-wide association studies (Harper et al., Tadros et al., *Nature Genetics* 2021) prove that the ~40 to 50 percent of HCM patients with negative sarcomere gene panels largely have **polygenic HCM** driven by a high **Polygenic Risk Score (PRS)** interacting with **diastolic blood pressure and central obesity**, which also explains why carriers of the same *MYBPC3* variant within one family exhibit vastly different wall thicknesses.

V BIOMARKER PROFILING IN SURVEILLANCE AND MYOSIN INHIBITOR THERAPY

- **High-Sensitivity Cardiac Troponin (hs-cTnT/I) and NT-proBNP:** Elevated in 30 to 70 percent of stable HCM patients; **hs-cTn** reflects ongoing subendocardial microvascular ischemia and myocyte necrosis (correlating with LGE progression and exercise hypotension), while **NT-proBNP** reflects LVOT gradient, diastolic filling pressure, and wall stress.
- **Pharmacodynamic Biomarkers for Cardiac Myosin Inhibitors:** In the **EXPLORER-HCM** (Mavacamten) and **SEQUOIA-HCM** (Aficamten, *NEJM* 2024) trials, cardiac myosin inhibition produced a rapid **65 to 80 percent reduction in NT-proBNP** and a **40 to 50 percent reduction in hs-cTnI** paralleling relief of LVOT obstruction.

KEY REFERENCES

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