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REVIEW TOPIC OF THE MONTH

Endpoint Selection in Randomized Clinical Trials for Hypertrophic Cardiomyopathy

Alberto Aimo, MD, PhD,[a,b] Iacopo Olivotto, MD,[c] Giancarlo Todiere, MD, PhD,[b] Andrea Barison, MD, PhD,[a,b] Giorgia Panichella, MD,[d] Mona Fiuzat, PharmD,[e] Cecilia Linde, MD, PhD,[f,g] Neal K. Lakdawala, MD, MSc,[h] Milind Desai, MD, MBA,[i] Faiez Zannad, MD, PhD,[j] Martin S. Maron, MD[k]

HIGHLIGHTS

- Randomized clinical trials in HCM face challenges caused by rarity and low event rates.
- Current trials focus on symptom relief, functional capacity, and cardiac remodeling as primary endpoints.
- Emerging technologies and biomarker-based endpoints hold promise for improving trial designs in HCM.
- Hierarchical composite endpoints combining mortality and HF hospitalization may enhance HCM trial designs.

ABSTRACT

Randomized clinical trials (RCTs) for hypertrophic cardiomyopathy (HCM) have long been challenging caused by the condition's rarity, low event rates, and diverse clinical presentations. However, recent advances in targeted therapies have sparked increased interest in HCM research. Despite this, designing effective RCTs remains complex, particularly in identifying clinically meaningful endpoints. HCM, often linked to sequence variation in sarcomeric protein genes like *MYH7* and *MYBPC3*, exhibits varied phenotypic expressions that influence disease progression and treatment responses. This genetic variability underscores the need for personalized approaches in clinical trials. Emerging gene therapies, such as CRISPR/Cas9, show promise in addressing these genetic factors. A major challenge in HCM RCTs is ensuring that endpoints are both statistically and clinically significant, given issues like test-retest variability and missing data. Primary endpoints often focus on symptom relief and functional improvement, while secondary and exploratory endpoints provide broader insights into treatment effects. Regulatory authorities are increasingly open to a wider range of endpoints, including patient-reported outcomes and functional measures, although the cost-risk balance is crucial, especially for high-risk interventions. Future HCM RCTs may incorporate hard clinical endpoints such as heart failure hospitalization, atrial fibrillation recurrence, and all-cause mortality, offering a more comprehensive evaluation of treatment efficacy. Integrating genetic insights and advanced technologies will be essential to improving trial design and enhancing patient outcomes in HCM. (JACC Heart Fail. 2025;13:200–212) © 2025 by the American College of Cardiology Foundation.

From the [a]Health Sciences Interdisciplinary Center, Scuola Superiore Sant'Anna, Pisa, Italy; [b]Cardiology Division, Fondazione Toscana Gabriele Monasterio, Pisa, Italy; [c]Meyer Children's Hospital IRCCS, Florence, Italy; [d]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; [e]Duke University and Duke Clinical Research Institute, Durham, NC, USA; [f]Karolinska Institutet, Department of Medicine, Cardiology Unit, Stockholm, Sweden; [g]Karolinska University Hospital, Department of Cardiology, Stockholm, Sweden; [h]Heart and Vascular Center, Brigham and Women's Hospital, Boston, Massachusetts, USA; [i]Hypertrophic Cardiomyopathy Center, Heart Vascular Thoracic Institute Cleveland Clinic, Cleveland, Ohio, USA; [j]Université de Lorraine, Nancy, France; and the [k]Hypertrophic Cardiomyopathy Center, Lahey Hospital and Medical Center, Burlington, Massachusetts, USA.

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Randomized clinical trials (RCTs) for genetic heart diseases like hypertrophic cardiomyopathy (HCM) have historically faced significant challenges because of the rarity of these conditions, the scarcity of specialized centers for patient recruitment, low event rates, and diverse clinical presentations. However, over the past decade, this perspective has shifted, driven by novel therapies targeting specific disease mechanisms, resulting in increased interest from both academia and industry. Despite this progress, designing and conducting RCTs in HCM remains complex, particularly in identifying effective markers of clinical benefit.

HCM, the most common inherited heart disease globally,[1] presents a diverse range of phenotypic expressions, with nearly any pattern and location of hypertrophy within the left ventricle (LV). Approximately 50% of HCM cases are linked to sequence variants in sarcomeric protein genes. The majority of patients exhibit left ventricular outflow tract obstruction (LVOTO) caused by mitral valve-ventricular septal contact, either at rest or with provocation. LVOTO, defined as an obstruction of ≥30 mm Hg, is a strong predictor of recurrent limiting symptoms and is associated with a 4-fold increased risk of heart failure (HF) compared with nonobstructive HCM. Negative inotropic drug therapy and septal reduction therapy (SRT) can alleviate outflow tract gradients and mitigate HF symptoms.[2]

Around one-third of HCM patients display no obstruction,[3] and 40% of them develop symptoms requiring drug therapy caused by impaired relaxation. Of these, 10% progress to end-stage HCM with associated systolic dysfunction, potentially requiring heart transplantation.[3] Additionally, HCM is a significant cause of sudden cardiac death (SCD) caused by ventricular tachyarrhythmias, driven by arrhythmic myocardial substrate related to myocyte disarray, fibrosis, and microvascular ischemia. Atrial fibrillation (AF), present in about 30% of patients, significantly affects symptom burden and stroke risk.[2]

In HCM patients, the rates of all-cause mortality and SCD are low, and cardiovascular hospitalizations are uncommon. The slow progression of symptoms and adverse cardiac remodeling over years or decades creates a challenge in demonstrating the benefit of new therapies within reasonably sized cohorts and time frames. Consequently, although improving survival and reducing hard cardiovascular outcomes remain key objectives, RCTs have primarily focused on symptom relief and enhanced functional capacity. The search for suitable endpoints that align with regulatory standards has exposed a significant gap in a field previously dominated by observational or retrospective studies.

Collaborative efforts among cardiomyopathy specialists, clinical trial experts, and regulatory authorities are advancing the field, although challenges persist. Reassessing endpoint selection in HCM RCTs could improve future trial designs. Until larger RCTs that assess harder clinical endpoints, such as a combination of HF hospitalization, new onset or recurrence of AF, and all-cause mortality, become feasible, alternative approaches are necessary. These considerations regarding endpoint selection may also be relevant for other cardiac conditions with low prevalence and slowly evolving clinical courses, including several genetic disorders.

This reassessment was initiated during discussions at the 2023 Global Cardiovascular Clinical Trials forum in Washington, DC. This paper explores the efficacy endpoints of major RCTs for HCM, evaluates the strengths and limitations of each endpoint, proposes possible new endpoints, and considers the regulatory perspective on endpoint selection.

ABBREVIATIONS AND ACRONYMS

CPET = cardiopulmonary exercise testing

HCM = hypertrophic cardiomyopathy

LVOTO = left ventricular outflow tract obstruction

PROM = patient-reported outcome measure

pVO_2 = peak oxygen consumption

RCT = randomized clinical trial

SRT = septal reduction therapy

EFFICACY ENDPOINTS EMPLOYED IN HCM TRIALS: PROPOSED CLASSIFICATION

Efficacy endpoints employed to date in HCM trials can be schematically classified as “feel” (exploring symptoms), “function” (exercise capacity), and “follow-up” (changes in structure and function) (**Central Illustration**). In this section, the application of these endpoints in HCM trials will be discussed (**Table 1**), together with their strengths and limitations (**Table 2**).

“FEEL” ENDPOINTS. Patient-reported outcome measures (PROMs) gather information from patients on a range of topics, from physical symptoms to social limitations. PROMs are reproducible in patients who are clinically stable and are sensitive to changes in clinical status.[4] However, there are several possible

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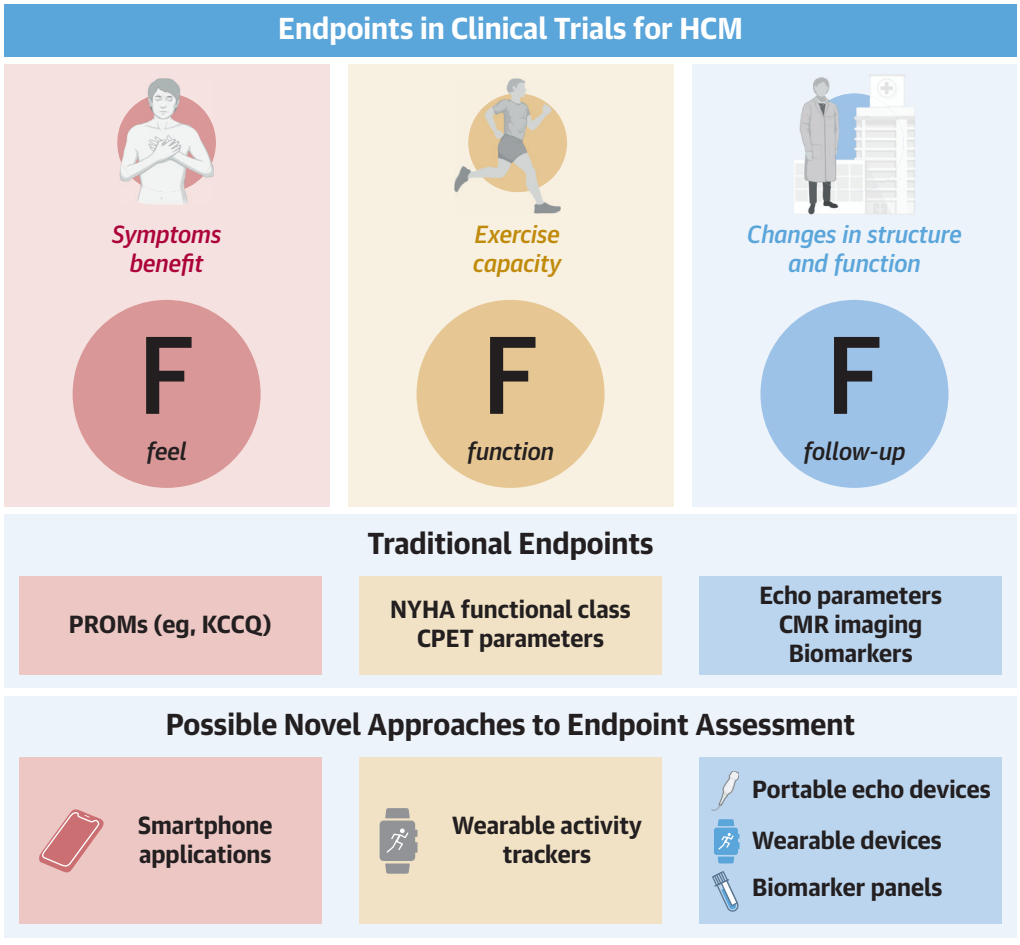
CENTRAL ILLUSTRATION **Traditional and Possible Novel Endpoints in Trials for Hypertrophic Cardiomyopathy**



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CMR = cardiovascular magnetic resonance; CPET = cardiopulmonary exercise testing; echo = echocardiography; HCM = hypertrophic cardiomyopathy; KCCQ = Kansas City Cardiomyopathy Questionnaire; PROM = patient-reported outcome measure; RCT = randomized controlled trial; STE = speckle-tracking echocardiography.

drawbacks to PROMs, including subjectivity (responses can be influenced by individual perceptions and biases), the time needed to complete the questionnaires, and selection bias (the responding population may not be representative of all patients). Additionally, PROMs sometimes use scales developed for other diseases, in heterogeneous cultural settings, and in other languages. PROMs may also fail to capture all the quality-of-life domains that patients experience, such as physical and mental/emotional symptoms, physical limitations, and social limitations.[5]

RCTs for HCM have widely employed PROMs, most commonly the Kansas City Cardiomyopathy Questionnaire-23 (KCCQ) Clinical Summary Score (CSS) (Table 1), but also the disease-specific Hypertrophic Cardiomyopathy Symptom Questionnaire-Shortness of Breath (HCMSQ-SoB).[6,7] As opposite to the heart failure (HF) setting, we are not aware of any evidence of association between KCCQ changes and meaningful clinical outcome in HCM. The EXPLORER-HCM (Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy) trial highlighted a discrepancy among changes in the KCCQ score, NYHA functional class, and functional capacity, suggesting that KCCQ may be more sensitive to symptom change.[6] In EXPLORER-HCM, changes in KCCQ scores were more strongly correlated with

improvements in peak oxygen consumption (pVO_2) than changes in NYHA functional class.[6] This suggests that the KCCQ captures nuances in patient experience and functional capacity that the NYHA functional classification might miss.

A clinically meaningful change in the KCCQ has been defined as an improvement of 5 points or more, derived from HF studies showing that such changes are associated with significant improvements in quality of life and reduced clinical events.[8,9] Further evidence is likely needed, including the intra-individual variability of score values and cutoffs that signal clinically meaningful changes and/or predict clinical outcomes in patients with HCM. Another important question is whether HCM-specific PROMs offer any added value over scales developed in the HF setting.

"FUNCTION" ENDPOINTS. The NYHA functional class is a simple and widely used method to categorize patients with heart disease, and changes in NYHA functional class are associated with clinical outcomes in HF.[10] Drawbacks include interobserver variability, possible discrepancies between the patient's perception of exercise limitation and the physician's estimate, and poor sensitivity to clinically meaningful changes, especially in patients with less severe symptoms.[10] In obstructive HCM, worsening NYHA functional class is associated with increased risks of all-cause mortality.[11] All phase 3 trials on HCM included improvement in at least one NYHA functional class as a secondary endpoint, evaluated at different time points ranging from 16 to 48 weeks (**Table 1**). One RCT also incorporated changes in NYHA functional class as part of the composite primary endpoint.[6] However, changes in NYHA functional class alone have never been proposed as a primary endpoint, likely reflecting the significant limitations of this measure as an indicator of treatment response.

Metabolic exercise testing has been considered the "gold standard" for exercise assessment in HF patients.[5] The 6-minute walking test is not employed in the setting of HCM because patients with HCM are typically younger and have a better-preserved functional capacity than other patients, such as those with HF or cardiac amyloidosis. Peak oxygen consumption (pVO_2) from cardiopulmonary exercise testing (CPET) has been demonstrated to independently predict HF severity, death, and HF hospitalizations, and also serve as a basis for the selection of transplant candidates.[5] In the setting of HCM, pVO_2 and minute ventilation relative to CO_2 production slope independently predicted all-cause mortality or cardiac transplantation.[12] Several HCM trials have indeed evaluated changes in pVO_2 as a surrogate of hard clinical endpoints (**Table 1**). Possible limitations of this CPET-derived metric include the need for dedicated equipment and specially trained personnel.[5] Furthermore, there is a need to standardize the formula for calculation[13,14] and the way CPET is performed. Regarding the latter point, a learning effect has been described, suggesting that the initial test should be used as a familiarization visit and not included in the analysis.[15] It is also unclear which variation in pVO_2 represents reflects clinically meaningful and/or prognostic change in HCM. Finally, pVO_2 is measured at peak exercise, which most HCM patients do not achieve during daily activities. Submaximal exercise parameters that are less dependent on maximal effort, such as minute ventilation to carbon dioxide production and ventilatory anaerobic threshold, have shown independent prognostic value for HF-related death or need for heart transplantation in HCM patients,[12] and have been used in some RCTs (**Table 1**).

"FOLLOW-UP" ENDPOINTS. RCTs enrolling HCM patients have often explored changes in cardiac structure and function over time to capture objective evidence of treatment efficacy. Variations in imaging findings and cardiac biomarkers were considered either as absolute changes or as dichotomous variables based on specific cutoffs.

A typical example of a "follow-up" endpoint is represented by changes in LVOT gradients, which were incorporated as primary or secondary endpoints in most RCTs on obstructive HCM (**Table 1**). LVOT gradients were mostly evaluated postexercise[6,16] or after Valsalva.[17-19] Most trials considered continuous changes in the LVOT gradient, while others used either the 30-mm Hg threshold that defines LVOTO or the 50-mm Hg threshold for SRT.[6,19] The role of the LVOT gradient as an endpoint in HCM trials has been debated.[2] Measuring the gradient provides a direct assessment of the hemodynamic burden associated with obstruction, offering a quantifiable, real-time parameter that can be tracked over time. However, the dynamic nature of gradients introduces significant variability. Gradients can fluctuate based on factors like hydration status, heart rate, and loading conditions,[20,21] making them unreliable as the sole indicator of treatment efficacy. Therefore, although LVOT gradient reduction is an important indicator, it should be used alongside other clinical outcomes to provide a comprehensive assessment of a treatment's efficacy. Additionally, regulatory agencies do not accept LVOT gradients as an endpoint, as discussed in the following text. DISCOVER-HCM (A Prospective

TABLE 1 Efficacy Endpoints in the Completed or Ongoing Phase 3 Trials on Hypertrophic Cardiomyopathy

	VALOR-HCM[16]	EXPLORER-HCM[6]	EXPLORER-CN[17]
Setting	Obstructive HCM	Obstructive HCM	Obstructive HCM
Drug tested	Mavacamten	Mavacamten	Mavacamten
Number of patients (actual/estimated)	112	429	81
Status	Completed	Completed	Completed
Primary endpoint(s)	Decision to proceed with SRT and SRT eligibility at wk 16	Improvement ≥1.5 mL/kg/min in pVO_2 and reduction of ≥1 NYHA functional class *or* improvement ≥3.0 mL/kg/min in pVO_2 with no increase in NYHA functional class	Change in post-Valsalva peak LVOT gradient over 30 wks
Secondary endpoints			
		Change in pVO_2 over 30 wks	
	≥1 NYHA functional class improvement over 16 wks	≥1 NYHA functional class improvement over 30 wks	≥1 NYHA functional class improvement over 30 wks
	Change in KCCQ-CSS over 16 wks	Changes in KCCQ-CSS over 30 wks	Changes in KCCQ-CSS over 30 wks
		Changes in HCMSQ-SoB over 30 wks	
	Change in post-exercise LVOT gradient	Change in post-exercise LVOT gradient over 30 wks	Post-Valsalva peak LVOT gradient <30 mm Hg at wk 30; peak LVOT gradient <50 mm Hg at wk 30
			Changes in resting LVOT peak gradient over 30 wks
			Change in LVMI over 30 wks
	Change in NT-proBNP over 16 wks	Change in NT-proBNP over 30 wks	Change in NT-proBNP over 30 wks
	Change in troponin over 16 wks		Change in hs-cTnI over 30 wks
Exploratory endpoints		All LVOT gradients <30 mm Hg and NYHA I at wk 30	"Changes in cardiac structure" over 30 wks
		Proportion of patients with improvement in LVOT gradients at wk 30	
		Change in hs-cTnI over 30 wks	

CPET = cardiopulmonary exercise test; CV = cardiovascular; HCMSQ-SoB = Hypertrophic Cardiomyopathy Symptom Questionnaire-Shortness of Breath; hs-cTnI = high-sensitivity cardiac troponin-I; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LAVI = left atrial volume index; LVOT = left ventricular outflow tract; LVMI = left ventricular mass index; MACE = major adverse cardiovascular events; NT-proBNP = N-terminal pro-B-type natriuretic peptide; pVO_2 = peak oxygen consumption; SRT = septal reduction therapy; VCO_2 = carbon dioxide production; VE = ventilation.

Continued on the next page

Registry Study to Assess Real-world Patient Characteristics, Treatment Patterns, and Longitudinal Outcomes in Patients Receiving Mavacamten and Other Treatments for Symptomatic Obstructive Hypertrophic Cardiomyopathy [Obstructive-HCM]; NCT05489705), the first real-world prospective registry study to characterize mavacamten safety and efficacy, will include LVOT gradients and quality of life outcomes among its secondary endpoints.

The main clinical decision in patients with obstructive HCM is whether to perform SRT. A dedicated RCT (VALOR-HCM [Mavacamten in Patients With Hypertrophic Cardiomyopathy Referred for Septal Reduction]) used the decision to proceed with SRT and SRT eligibility after 16 weeks of mavacamten treatment as its primary endpoint.[16] One study considered the "duration of eligibility for SRT" during the study duration[18] (**Table 1**). SRT eligibility as an endpoint reflects an element of subjectivity in referring a patient for an invasive therapeutic option requiring specific expertise that is not universally available.

Other imaging-based endpoints include reductions in LV mass index and changes in left atrial volume index (LAVi), which may decrease following improved diastolic function and reduced severity of mitral regurgitation. Changes in LAVi have been employed as an endpoint only in RCTs testing

TABLE 1 Continued

SEQUOIA-HCM[18]	MAPLE-HCM[19]	ODYSSEY-HCM[7]	ACACIA-HCM[22]
Obstructive HCM	Obstructive HCM	Nonobstructive HCM	Nonobstructive HCM
Aficamten	Aficamten	Mavacamten	Aficamten
282	170	420	420
Completed	Ongoing	Ongoing	Ongoing
Change in pVO_2 over 24 wks	Change in pVO_2 over 24 wks	Change in pVO_2 over 48 wks	
		Change in KCCQ-CSS over 48 wks	Change in KCCQ-CSS over 36 wks
		Time to first MACE over 120 wks	Time to first CV event
Duration of eligibility to SRT over 24 wks			
Change in total workload during CPET over 24 wks		Change in VE/VCO_2 slope over 48 wks	Change in composite of 2 Z-scores of pVO_2 and VE/VCO_2 slope over 36 wks
≥1 NYHA functional class improvement over 12 and 24 wks	≥1 NYHA functional class improvement over 24 wks	≥1 NYHA functional class improvement over 48 wks	≥1 NYHA functional class improvement over 36 wks
Change in KCCQ-CSS over 12 and 24 wks	Change in KCCQ-CSS over 24 wks		
		Change in HCMSQ-SoB over 48 wks	
Change in post-Valsalva LVOT gradient over 12 and 24 wks; post-Valsalva LVOT gradient <30 mm Hg at 12 and 24 wks	Change in post-Valsalva LVOT gradient over 24 wks		
	Change in LVMI over 24 wks		
	Change in LAVI over 24 wks		Change in LAVI over 36 wks
	Change in NT-proBNP over 24 wks	Change in NT-proBNP over 48 wks	Change in NT-proBNP over 36 wks
		Change in cardiac troponin T over 48 wks	

aficamten, namely the MAPLE-HCM (Metoprolol vs Aficamten in Patients with LVOT Obstruction on Exercise Capacity in HCM) and ACACIA-HCM (Assessment Comparing Aficamten to Placebo on Cardiac Endpoints In Adults with Non-Obstructive HCM) trials.[19,22]

Point measurements of cardiac biomarkers have been correlated with the severity of cardiac disease and patient outcomes in HCM. N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels reflect wall tension and pulmonary and systemic congestion. They correlate with LV mass, LV mass index, and late gadolinium enhancement (LGE) on CMR, as well as HF-related outcomes.[23,24] High-sensitivity cardiac troponin levels reflect ongoing cardiomyocyte damage and correlate with NYHA functional class, LVOTO, systolic dysfunction, LGE on CMR, and disease severity in HCM,[23] and independently predict adverse events.[24] To our knowledge, changes in cardiac biomarkers have not been associated with patient outcomes, which may support the choice of biomarker changes as surrogate endpoints. Nonetheless, most HCM trials have assessed continuous changes in NT-proBNP, and some trials also evaluated changes in cardiac troponins, variably considering troponin T or I.[16,17,19]

POSSIBLE NOVEL EFFICACY ENDPOINTS

Wearable technology and advanced personal devices may provide more granular, patient-centric data compared with traditional endpoints. Wearable

TABLE 2 Strengths and Limitations of Efficacy Endpoints

	Strengths	Limitations
Feel		
PROMs	• Focus on the patient's perspective • Holistic health evaluation (psychological well-being and social functioning) • Reproducibility • Sensitivity to clinical change • Improving patient-doctor communication	• Subjectivity • Time-consuming • Selection bias • Cultural and linguistic variability • Use of nonspecific scales • Incomplete capture of quality-of-life domains
Function		
NYHA functional class	• Widespread use • Ease of use • Clinical relevance • Prognostic value	• Prone to interobserver variability • Highly subjective • Poor sensitivity in stable patients • Nonspecificity • Influence by external factors (eg, psychological state, physical conditioning, or other comorbidities)
CPET	• Comprehensive assessment (eg, blood pressure response, exercise-induced LVOT obstruction, and ventricular arrhythmia) • Objective measurement • Prognostic value • Evaluation of treatment efficacy	• Technical and resource requirements • Patient compliance and safety • Lack of technique standardization • Influence by noncardiac factors (eg, motivation, physical conditioning, and neuromuscular function) • Cost • Lack of specificity for HCM
Follow-up		
Echocardiographic parameters		
Changes in LVOT gradients	• Objective and real-time measurement • Therapeutic target • Symptom correlation	• Extreme variability (eg, hydration status and heart rate) • Specific echocardiographic techniques and expertise • Poor imaging windows or technical limitations
Change in LAVI	• Indicator of diastolic dysfunction • Prognostic value	• Interobserver variability • Influence of comorbidities (eg, hypertension or valvular heart diseases) • Reflecting long-term rather than immediate changes in LV filling pressures
Reductions in LVMI	• Objective quantification of hypertrophy • Indicator of disease progression • Response to treatment	• Interobserver variability • Influence of confounding factors (eg, hypertension or aortic stenosis) • Lack of threshold for clinical significance
CMR imaging	• Detailed tissue and structure characterization (eg, LGE) • Functional assessment • Noninvasive and safe • Prognostic information • Useful in poor imaging windows	• Accessibility and cost • Contraindications (eg, metal implants, ICDs, or claustrophobia) • Requirement of specialized training and expertise • Time consuming • Quantification challenges (eg, LGE)
Indication to SRT	• Clinical relevance • Objective criteria • Direct impact on patient outcomes	• Not applicable to all patients (eg, nonobstructive HCM) • Subjectivity in clinical decision-making • Ethical and treatment bias • Delayed effects
Biomarkers		
Changes in NT-proBNP	• Indicator of pressure overload and cardiac function • Prognostic value	• Lack of specificity • Influence by other conditions (eg, kidney dysfunction and AF)
Changes in hs-cTn	• Sensitivity to myocardial injury • Monitoring disease progression	• Lack of specificity • Variable baselines

AF = atrial fibrillation; HF = heart failure; ICD = implantable cardiac defibrillator; KCCQ = Kansas City Cardiomyopathy Questionnaire; LGE = late gadolinium enhancement; LV = left ventricular; other abbreviations as in Table 1.

devices like smartwatches and fitness bands monitor physiological parameters such as heart rate, activity levels, and sleep patterns. The CHIEF-HF (Canagliflozin Impact on Health Status, Quality of Life and Functional Status in Heart Failure) trial demonstrated that daily step counts and floors climbed, as measured by a Fitbit Versa 2, were significantly linked to health status and physical limitations, highlighting the potential of wearables to complement traditional endpoints like pVO_2 and NT-proBNP.[25] Smartphone applications further enhance this landscape by collecting PROMs, tracking symptoms in real time, and monitoring medication adherence.[26] These apps streamline patient data recording and management, overcoming barriers like resource constraints and time limitations.

Incorporating these novel endpoints into trials presents unique challenges (Table 3). Ensuring that

TABLE 3 Strengths and Limitations of Possible Novel Efficacy Endpoints

	Strengths	Limitations
Feel		
Smartphone applications	• Increase efficiency in recording and monitoring PROMs • Real-time symptom tracking • Medication adherence • Educational purposes	• Resource consumption • Implementation difficulties • Verification and validation needed
Function		
Wearable activity trackers	• Continuous and objective measure of a patient's daily functioning • Small and cost-effective devices	• Lack of validation in different clinical settings • Potential issues with data blinding and integrity • Time required to manage the device and the gathered data • Need for technical expertise
Follow-up		
Optical sensors on wearable devices	• Detect irregular pulses (AF) • Identify changes in disease status missed in regular outpatient visits	• Verification and validation needed • Issues with data integrity and blinding
Handheld echocardiography devices	• On-the-go assessments of cardiac structure and function • Point-of-care LVOT gradients measurement	• Requires specific training • Lack of features (eg, Zoom, ECG synchronization, Doppler waves, frequency adjustments, and live views)
Point-of-care biomarker panels	• Correlate changes in physical function with underlying biological processes • Fast and clinically meaningful	• Verification and validation needed • May require advanced technology for point-of-care testing

ECG = electrocardiogram; PROM = patient-reported outcome measure; other abbreviations as in Tables 1 and 2.

wearable data is reproducible and reliable across different devices and settings is critical. Validation studies must compare wearable measurements with gold-standard clinical assessments to confirm their clinical relevance. Initially, wearable endpoints should be exploratory, allowing researchers to assess their feasibility and correlation with traditional endpoints before considering them for broader use in trials.

Wearable technology also includes optical sensors that detect irregular pulses, potentially identifying changes in disease status missed during routine visits. Additionally, portable echocardiography devices offer on-the-go assessments of cardiac structure and function, such as LVOT gradients, although their utility may be limited by the need for specific training and advanced features.[27]

Biomarker panels before and after CPET or other functional tests can enhance understanding of treatment effects by linking physical function changes with underlying biological processes. Point-of-care biomarker testing devices, utilizing microfluidics and nanotechnology, represent another innovative approach for quickly providing clinically meaningful endpoints.[28]

Despite the potential of wearable technology in HCM trials, challenges include ensuring data validity, reliability, and relevance, as well as addressing issues like data blinding and integrity. Early engagement with regulatory bodies is crucial to discuss the inclusion of wearable endpoints in trials, ensuring they meet the required standards of validity and clinical significance.

METHODOLOGICAL ISSUES: MISSING DATA AND STATISTICAL VS CLINICAL SIGNIFICANCE

Selecting endpoints for a randomized clinical trial in HCM is critical because of the disease's unique characteristics, including low adverse event rates and varied clinical presentations. The challenge lies in ensuring that endpoint changes are not only statistically significant but also clinically meaningful. This is closely linked to issues like test-retest variability and missing data, which can significantly affect trial design and interpretation.

Test-retest variability can stem from differences in measurement techniques, equipment calibration, and observer skills, as well as biological fluctuations in a patient's condition. For example, improvements in symptom relief, measured through PROMs like the KCCQ-CSS, must exceed natural variability to indicate a true treatment effect. Similarly, improvements in functional capacity, often measured by pVO_2, need to reflect meaningful changes in patient health beyond statistical significance.

Missing data can arise from factors like patient compliance, health status, and technology barriers, leading to bias and reduced statistical power. Simpler measures like the NYHA functional class and hard

endpoints such as death or hospitalization are less prone to these issues and provide more reliable outcomes.

To mitigate these challenges, careful trial design is essential. This includes strategies like enhancing patient engagement with simplified PROMs, using statistical techniques like multiple imputation for missing data, and incorporating a mix of subjective and objective measures. A hierarchical study design can also help by prioritizing endpoints based on their clinical significance.

REGULATORY CONSIDERATIONS AND COST-RISK BALANCE

Historically, HF trials have focused on survival and hospitalization caused by safety concerns. However, in conditions like HCM, where mortality and severe adverse events are less common, regulators have shown flexibility in accepting a broader range of endpoints.

Improvements in symptoms, physical function, and quality of life are considered valid therapeutic goals. PROMs are commonly used to capture these endpoints, reflecting the patient's perception of health status. Although improved survival remains a crucial endpoint, it is often used more as a safety endpoint in conditions like HCM. The U.S. Food and Drug Administration (FDA) does not require prior validation but encourages the use of established tools and consistent measures to ensure reliable and interpretable results. Mortality data typically support the overall safety profile of new treatments rather than serving as the primary measure of efficacy.[29] The FDA's guidance emphasizes the importance of symptom relief and functional improvement, supporting the inclusion of endpoints that reflect patients' daily experiences.[30] Moreover, the FDA is establishing a Rare Disease Endpoint Advancement Pilot Program to support novel endpoint efficacy development for drugs that treat rare diseases.[31] This approach allows for greater flexibility in designing trials that are relevant to the specific characteristics of the patient population.

Technological advancements, such as integrating continuous and patient-centric data from wearables and digital tools, offer new opportunities for dynamic endpoint assessments. These innovations align with regulatory expectations for robust evidence, supporting their inclusion in RCTs. However, when considering clinically relevant endpoints in HCM trials, it is crucial to evaluate the cost-risk balance alongside potential benefits. This is especially important when deciding whether to endorse invasive procedures or expensive therapeutics, particularly when benefits are measured primarily through PROMs rather than hard endpoints like MACE. For example, in the context of invasive procedures like SRT, the high costs and risks must be weighed against improvements in PROMs If the primary benefit observed is an improvement in symptom relief or quality of life, the justification for endorsing these procedures becomes complex. The clinical significance of these improvements must be substantial enough to justify the financial and health risks. Small gains in quality of life may not warrant the high costs and potential complications. Patient values and preferences play a crucial role, with some patients prioritizing subjective improvement in quality of life over risks, highlighting the importance of shared decision-making. Similarly, with expensive therapeutics like myosin inhibitors for nonobstructive HCM, the decision to endorse these treatments hinges on balancing their cost against clinical benefits. If trials show no significant differences in MACE but report improvements in PROMs like the KCCQ, the decision to recommend these treatments becomes challenging. Long-term data on the impact of such therapies on survival, hospitalizations, and health care costs should also be considered. The choice may differ between patients with severe symptoms, for whom quality of life improvement is paramount, and those with milder symptoms, where the cost-risk might not justify the therapy.

WHICH PERSPECTIVES FOR USING HARD CLINICAL ENDPOINTS IN HCM?

Although current trials often emphasize symptom relief and functional improvements caused by the relatively low event rates of mortality and severe adverse events, there is a strong rationale for incorporating harder clinical endpoints. These endpoints allow for a more comprehensive evaluation of the long-term efficacy and safety of new treatments. Future trials should consider including a combination of HF hospitalization, AF recurrence, and all-cause mortality as primary or secondary endpoints. This would provide a more detailed understanding of how treatments affect disease progression and patient survival, aligning more closely with the ultimate goal of improving overall survival and reducing severe adverse events in HCM patients. A promising strategy is to use hierarchical composite endpoints, similar to those employed in RCTs on cardiac amyloidosis. These endpoints prioritize the most critical outcomes, such as mortality, while also capturing relevant clinical events like HF hospitalization and AF recurrence.

This approach ensures that the most severe and impactful outcomes are given appropriate weight in the evaluation process.

Phase 4 studies conducted postapproval offer an excellent opportunity to gather data on these harder clinical endpoints. These studies can extend the observation period and increase the population size, allowing for a more comprehensive understanding of the long-term effects of treatments. This phase is particularly valuable for detecting less common adverse events and fully assessing the impact of treatment on survival and disease progression.

WHICH PRIMARY, SECONDARY AND EXPLORATORY ENDPOINTS SHOULD BE SELECTED?

Primary endpoints are key to evaluating the direct efficacy of a treatment and determining the trial's success. In the context of HCM, these endpoints may focus on symptom relief and functional improvement. Symptom relief can be assessed using PROMs such as the KCCQ-CSS, where an improvement of 5 points or more indicates a clinically meaningful enhancement in quality of life and symptom reduction. Additionally, the HCMSQ, a disease-specific tool, can evaluate symptoms like shortness of breath and chest pain. For functional capacity, pVO_2 measured during CPET serves as a surrogate for cardiovascular health, with improvements associated with better exercise tolerance and a lower risk of adverse events. Structural improvement, particularly the reduction of the LVOT gradient, is an important endpoint in trials for obstructive HCM, because it is linked to symptom relief.

Secondary endpoints provide insight into the broader impact of the treatment beyond the primary outcomes. Cardiac biomarkers, such as NT-proBNP, reflect HF severity and correlate with outcomes, with a decrease indicating reduced cardiac stress. High-sensitivity cardiac troponin levels, which indicate myocardial damage, can also serve as markers of treatment efficacy. Exercise tolerance can be assessed through submaximal exercise parameters, like ventilatory efficiency and anaerobic threshold, which provide prognostic information and are less dependent on maximal effort. Imaging endpoints, such as changes in the LAVi, may indicate improved diastolic function and reduced mitral regurgitation severity. Functional class, assessed through the NYHA functional classification, offers a simple way to evaluate physical activity limitations, despite potential interobserver variability.

Exploratory endpoints can offer additional insights into the treatment's effects, including innovative and patient-centric measures. Wearable technology, such as smartwatches, can track daily step counts, heart rate, and sleep patterns, providing real-time insights into patient health. Biomarker panels before and after CPET can help assess correlations between changes in physical function and underlying biological processes. Advanced imaging techniques allow for detailed assessments of cardiac structure and function, including fibrosis and myocardial strain.

A hierarchical study design can be utilized to prioritize endpoints based on their clinical significance, ensuring that the most critical outcomes are evaluated before those with less impact. In this design, Tier 1 focuses on primary endpoints related to symptom relief and functional improvement, including PROMs, pVO_2, and LVOT gradient reduction. Tier 2 addresses secondary endpoints, such as biomarkers and imaging changes, including NT-proBNP levels, cardiac troponins, and structural imaging findings. Tier 3 explores wearable technology and novel biomarkers, such as continuous activity monitoring and biomarker panels before and after exercise (**Figure 1**).

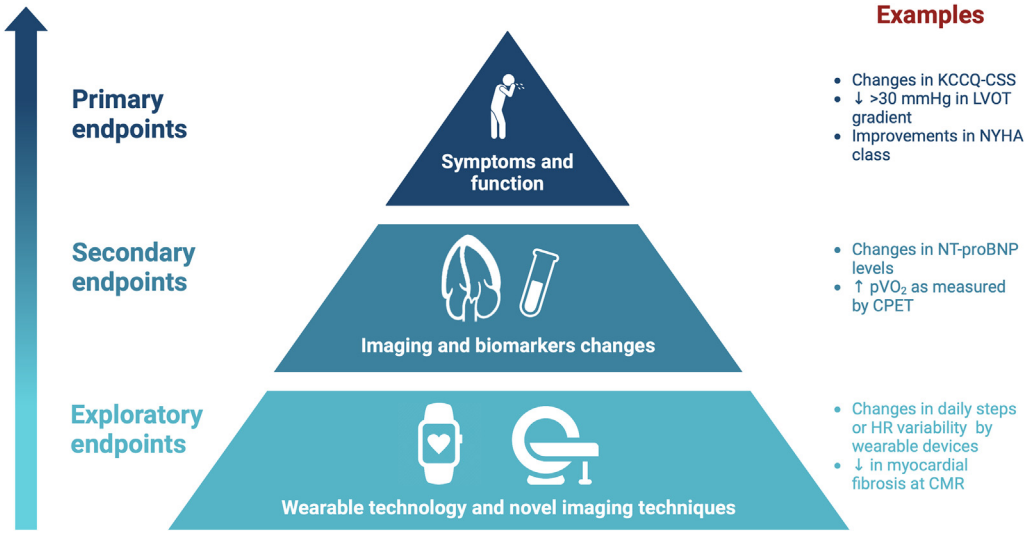
In a hypothetical trial on obstructive HCM, primary endpoints could include changes from baseline in KCCQ-CSS after 24 weeks, the reduction of more than 30 mm Hg in the LVOT gradient at 24 weeks, and the improvement by at least 1 NYHA functional class. Secondary endpoints might involve changes in NT-proBNP levels from baseline to 24 weeks and improvements in pVO_2 as measured by CPET at 24 weeks. Exploratory endpoints could include changes in daily step count and heart rate variability as tracked by wearable devices, as well as reductions in myocardial fibrosis assessed by CMR.

The hierarchical approach would first assess primary endpoints, such as PROMs and LVOT gradient reduction, for primary efficacy; followed by an evaluation of secondary outcomes, including biomarkers and exercise capacity; and finally explore wearable data and advanced imaging for additional insights.

GENETIC INSIGHTS AND EMERGING GENE THERAPIES

HCM is a complex genetic disorder, primarily driven by allelic variants in sarcomeric proteins. Understanding the genetic background is crucial for tailoring therapies and improving prognostic

FIGURE 1 A Hierarchical Endpoint Design in Trials for HCM



CMR = cardiac magnetic resonance; CPET = cardiopulmonary exercise testing; HR = heart rate; KCCQ-CSS; Kansas City Cardiomyopathy Questionnaire-Clinical Symptom Score; LVOT = left ventricular outflow tract; NT-proBNP = N-terminal pro–B-type natriuretic peptide; pVO_2 = peak O_2 consumption.

accuracy, because these variants significantly influence disease presentation, progression, and treatment response.[32] Common variants in genes such as *MYH7, MYBPC3, TNNT2*, and *TNNI3* lead to diverse phenotypic expressions, including varying degrees of hypertrophy and arrhythmia risk. For instance, *MYH7* variants often result in more severe hypertrophy and a higher risk of SCD, whereas *MYBPC3* variants may lead to a milder disease course.[32]

Genetic variability is a key prognostic factor in HCM, aiding in risk stratification and the identification of patients at higher risk for adverse outcomes.[33] This variability also affects treatment efficacy, making personalized medicine essential. For example, the effectiveness of cardiac myosin inhibitors may differ depending on the underlying sequence variation, highlighting the need for genetic stratification in clinical trials.

Gene therapy has emerged as a promising approach to treating HCM by targeting these genetic causes.[33] Techniques like CRISPR/Cas9 aim to repair or replace defective gene sequences, while gene replacement strategies use viral vectors to deliver healthy copies of genes. Current clinical trials are exploring these approaches (NCT05836259, NCT06092034). RNA interference is also being investigated to silence mutant alleles, offering another potential therapeutic option.[34]

Gene therapy holds the promise of not only managing symptoms but potentially reversing or halting disease progression by addressing the genetic roots of HCM. These therapies can be tailored to individual genetic profiles, offering a personalized treatment approach. However, challenges remain, including ensuring the long-term safety of gene editing and achieving precise delivery of therapeutic genes without off-target effects.[35]

ENDPOINTS IN HCM TRIALS: FINAL REMARKS

RCTs for HCM and other genetic heart diseases have traditionally faced challenges because of the rarity of these conditions, low event rates, and heterogeneous clinical presentations. However, the past decade has seen significant progress driven by novel therapies targeting specific disease mechanisms and increased interest from academia and industry. Despite this, designing and conducting RCTs in HCM remains complex, especially in identifying and validating effective markers of clinical benefit.

When selecting endpoints for HCM trials, balancing statistical and clinical significance is essential,

particularly given issues like test-retest variability and missing data. Primary endpoints often focus on symptom relief and functional improvement, whereas secondary and exploratory endpoints provide broader insights into treatment effects. A hierarchical approach to endpoint selection ensures that the most critical outcomes are prioritized.

Regulatory considerations are crucial in determining acceptable endpoints for HCM trials. Although survival and hard cardiovascular outcomes remain key objectives, regulatory authorities have shown flexibility in accepting a broader range of endpoints, particularly those related to PROMs and functional improvements. However, careful evaluation of the cost-risk balance is necessary, especially for expensive or high-risk interventions.

The future of RCTs in HCM holds promise for more robust assessments through the inclusion of hard clinical endpoints, such as HF hospitalization, AF recurrence, and all-cause mortality. These endpoints offer a comprehensive evaluation of long-term efficacy and safety, aligning research with the ultimate goal of improving survival and reducing severe adverse events in HCM patients.

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ADDRESS FOR CORRESPONDENCE: Dr Alberto Aimo, Interdisciplinary Center for Health Sciences, Scuola Superiore Sant'Anna, and Cardiology Division, Fondazione Toscana Gabriele Monasterio, Piazza Martiri della Libertà 33, 56124 Pisa, Italy. E-mail: a.aimo@santannapisa.it OR aimoalb@ftgm.it.

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