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HYPERTROPHIC CARDIOMYOPATHY

The “Pump”: Myocardial Conditions Affecting the Circulation in the Young

February 25, 2023

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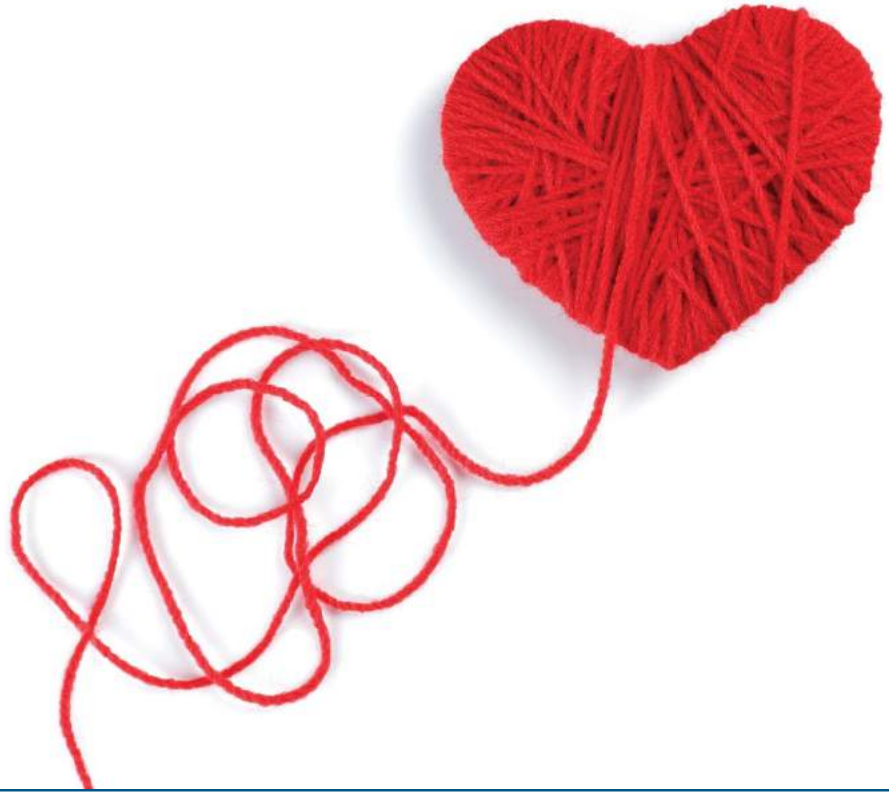

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DISCLOSURES

Unpaid consultant for Reata Pharmaceuticals, Lexio Therapeutics

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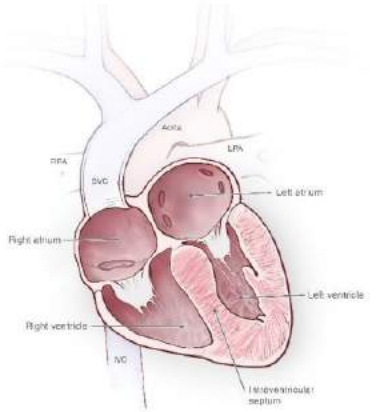
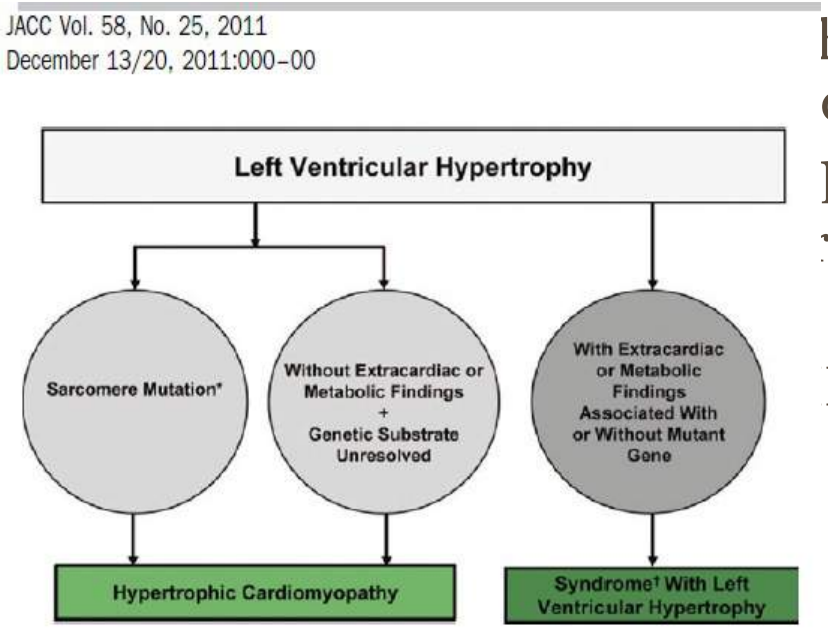
OVERVIEW – AN UPDATE ON PEDIATRIC HCM

- Disease manifestation in children
- Risk stratification tools
- New guidelines and implications for exercise
- Treatment options



HCM IN KIDS

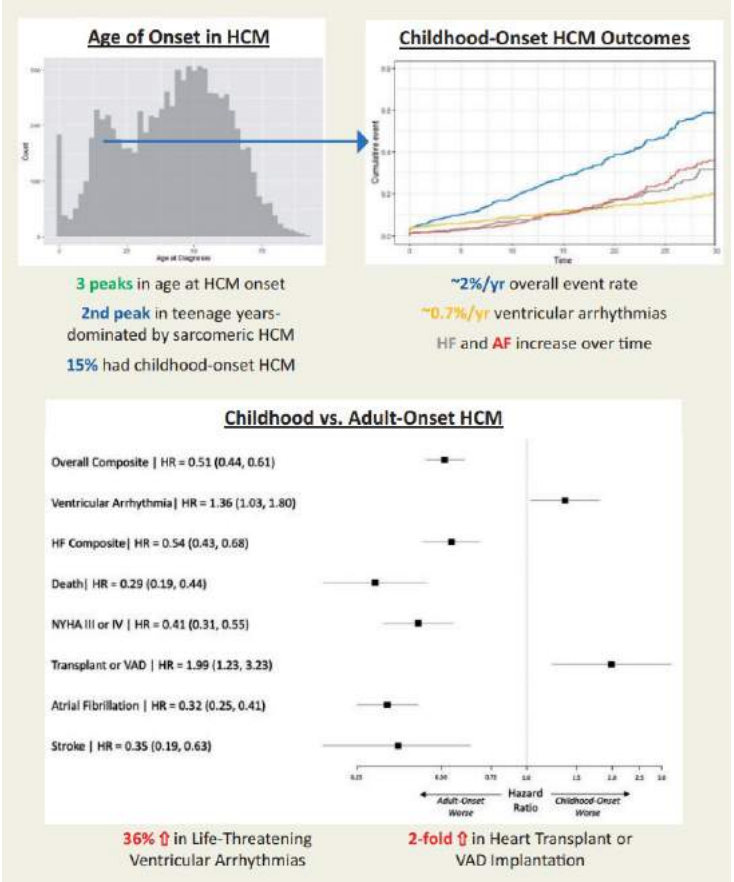
- Older classification schemes excluded genetic, metabolic or syndromic causes of LV hypertrophy in the definition of HCM
- Modern defi hypertrophied, nondilated v dynamic cause
- Hypertroph l thickness is at least 15mm, roborating z scores in children a
- Genetic test RI data may be helpful in bo



Lipshultz et al, Circ 2019 Gersh et al, JACC 2011 Elliott et al, EHJ 2014

HOW DO CHILDREN EXPERIENCE HCM?

- Kids are most often diagnosed as infants (metabolic/syndromic causes) and adolescents (sarcomere gene mutation)
- Many are largely asymptomatic
- Compared with adult-onset HCM:
  - 36% higher life-threatening arrhythmia risk
  - 2-fold higher need for advanced heart failure therapies



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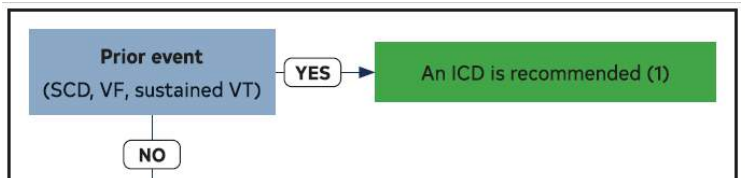
Marston et al, EHJ 2021

MANAGEMENT GUIDELINES

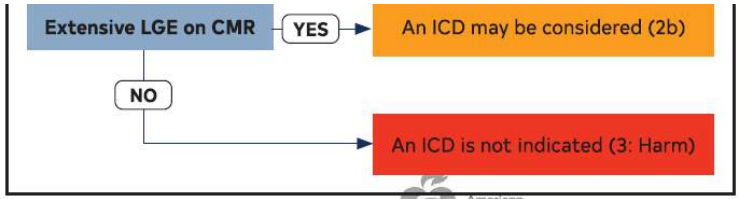
- Management of HCM symptoms is similar in the 2011 and 2020 AHA/ACC Guidelines
  - BB, CCB, disopyramide for obstructive symptoms
  - Septal myectomy for refractory symptoms
- ICD implantation criteria should be individualized in children
- Shared decision-making prominent in 2020 guidelines



4. SHARED DECISION-MAKING

Recommendation for Shared Decision-Making
Referenced studies that support the recommendation are summarized in Online Data Supplement 1.

COR	LOE	Recommendation
1	B-NR	1. For patients with HCM or at risk for HCM, shared decision-making is recommended in developing a plan of care (including but not limited to decisions regarding genetic evaluation, activity, lifestyle, and therapy choices) that includes a full disclosure of the risks, benefits, and anticipated outcomes of all options, as well the opportunity for the patient to express their goals and concerns.[1–6]



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PEDIATRIC RISK STRATIFICATION TOOLS

PRIMaCY Childhood HCM Sudden Cardiac Death Risk Prediction tool

- Age
- Height
- Weight
- Max IV septal thickness
- Max LV posterior wall thickness
- Left atrial diameter
- LV outflow tract gradient
- Non-sustained VT (prior 6 months)
- Unexplained syncope (prior 6 months)
- Genotype status

https://primacy.shinyapps.io/calculator/

HCM Risk-Kids

- Age
- Gender
- Weight
- LV max wall thickness
- LV max wall thickness Z score
- Left atrial diameter
- Left atrial diameter Z score
- LV outflow tract gradient
- Non-sustained ventricular tachycardia
- Unexplained syncope

https://hcmriskkids.org

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SHARED DECISION-MAKING

- More complicated in pediatrics as there are more stakeholders
- Generally involves more than one-time discussion
- Documentation important
- Precautions for those who proceed with sports participation:
  - Maintain hydration
  - AED present
  - Exercise with others present
  - Inform coaches, teammates, gym teachers of HCM diagnosis

TABLE 1 Steps in Shared Decision Making for Sports Participation in Athletes With HCM

Steps of Shared Decision Making	Details
1. Confirmation of Diagnosis	Often uses advanced imaging and genetic testing
2. Individualized risk stratification and treatment plans	Testing: ECG, ambulatory monitoring, stress testing, echocardiography, CMR, family history, genetic testing. Treatment: role for pharmacotherapy, intervention, and risk stratification for SCD
3. Patient and family education	Discuss potential risks/benefits, review relevant research studies, acknowledge uncertainty, provide your own expert opinion
4. Assessment of the patient's preferences and values	Discuss the role that athletics plays in their lives and athletic aspirations; gauge their risk tolerance and comfort with uncertainty
5. Synthesis of information and arrival at a shared decision	Review the treatment plan, summarize key points, discuss the balance of risks and benefits
6. Stakeholder engagement	Engage third parties, including school athletic departments, coaches, and team physicians
7. Longitudinal care and follow-up	Regular surveillance (at least yearly): monitoring for arrhythmia, stress testing, and imaging Reinforce precautions and best practices for athletes choosing to continue or returning to play and for recreational exercise

CMR = cardiac magnetic resonance; ECG = electrocardiography; HCM = hypertrophic cardiomyopathy; SCD = sudden cardiac death.

de Feria et al, JACC Case Reports 2021

EXERCISE

- The majority of adults with HCM do not meet minimum physical activity recommendations
- RESET-HCM showed us that moderate-intensity exercise can improve VO2Max in adult HCM
- Many barriers exist in improving physical activity in children with HCM

Sweeting et al, Open Heart 2016

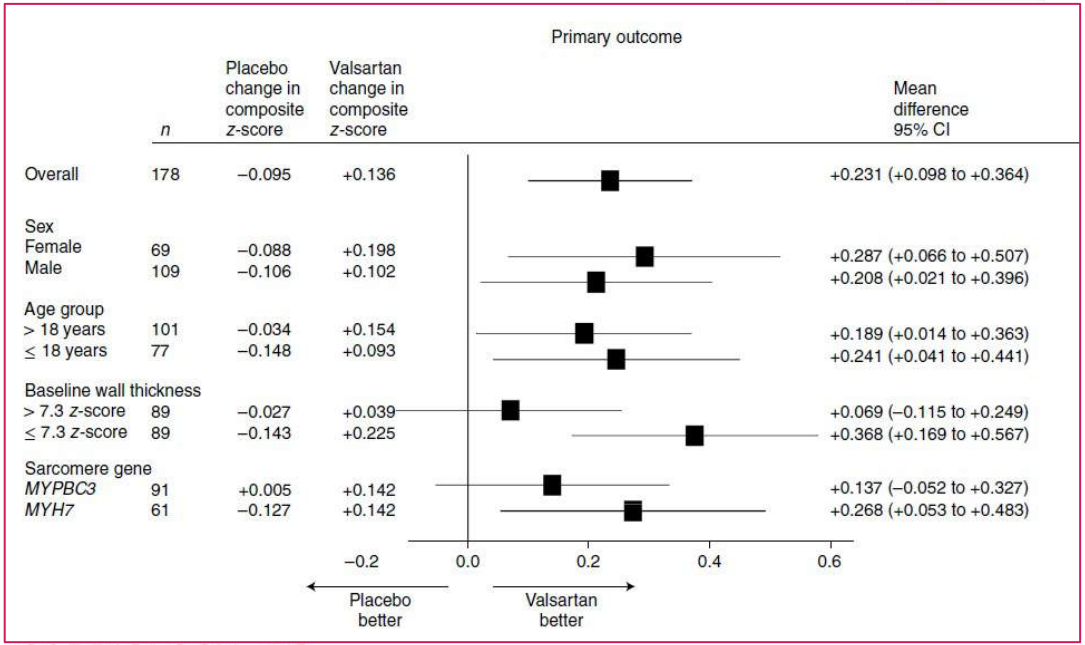
Saberi et al, JAMA 2017

	Comments from weekly phone check-ins	Completed 16-week program?	Adverse Events
Subject 1	"I've always been self-motivated. Want to get more endurance."	Yes	Chest pain, musculoskeletal, not study-related
Subject 2	Technical difficulties with MyHeart CHOP application; when fixed, still would not use app	Yes	None
Subject 3	"Didn't have time to finish," did not utilize MyHeart CHOP app regularly, lost to follow up	No	None
Subject 4	Initial exercise completed "because my mom is telling me to," difficulty with app, lost to follow up after viral illness	No	Pollen allergy, not study related
Subject 5	"Motivated by mom," missed some sessions due to "busy with school and mom working," cracked FitBit screen	Yes	None
Subject 6	Withdrew after 2 weeks because "she doesn't feel like she can keep up with such a plan that this program demands"	No	None
Subject 7	"Motivated to lose weight"	Yes	None
Subject 8	"Motivated by parents," had technical difficulties with MyHeart CHOP application	No	Chest pain, resting, not study-related

Wanner et al (unpublished), poster #25

VANISH TRIAL

nature medicine
ARTICLES
https://doi.org/10.1038/s41591-021-01505-4
Check for updates



- Showed benefit of valsartan over placebo on composite primary endpoint in early HCM
- Subjects were all positive for pathogenic or likely pathogenic sarcomere gene mutation
- Age 8–45 years, LV wall thickness 12–25 mm (or *z*-score 3–18), NYHA Class I or II, LVOTO < 30mmHg, LVEF >55%, no ICD

Ho et al, Nature Med 2021

TREATMENT OPTIONS FOR NOONAN-SPECTRUM HCM?

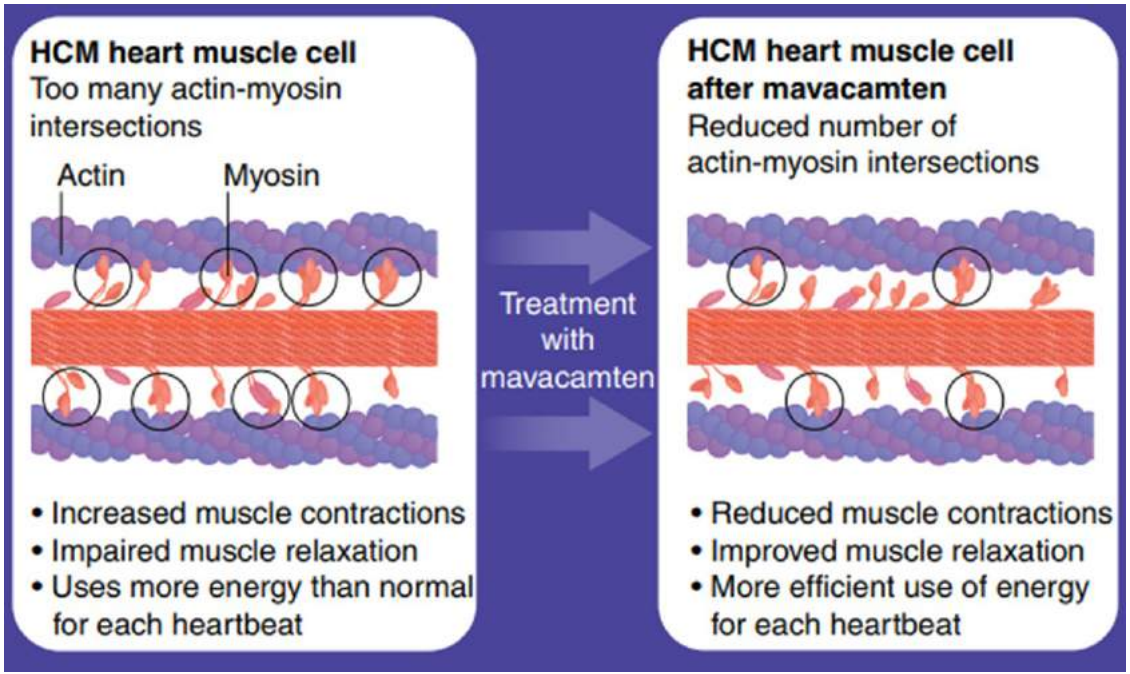
MEK-inhibitors

- Andelfinger et al 2019: 2 patients with gain-of-function RIT1 mutations successfully treated with trametinib
- Leegard et al 2022: RIT1 HCM patient successfully treated with trametinib

mTOR inhibitors

- Hahn et al 2015: NSML patient with loss-of-function PTPN11 mutation treated with everolimus, with subsequent improvement in HF but not hypertrophy

CARDIAC MYOSIN INHIBITORS



Burstein Waldman and Owens, Future Cardiol 2021

CARDIAC MYOSIN INHIBITORS

Mavacamten

- EXPLORER-HCM trial for adults with symptomatic, obstructive HCM
  - FDA approval April 2022
  - REMS program for safety monitoring
- ODYSSEY-HCM trial for adults with symptomatic, nonobstructive HCM enrolling soon

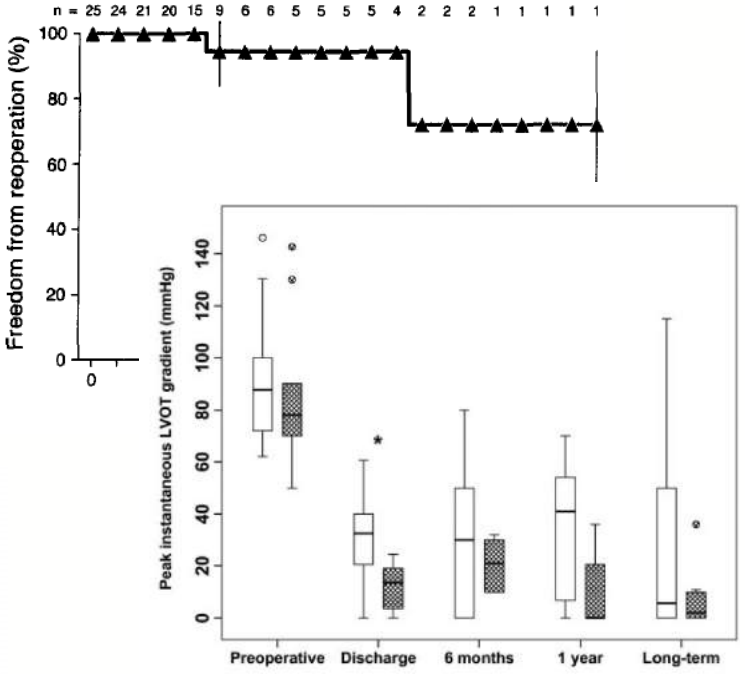
Aficamten

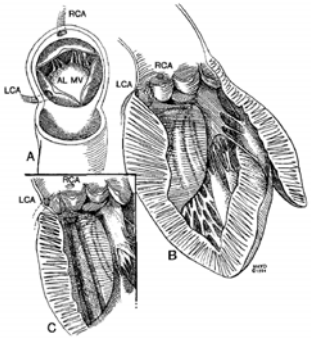
- SEQUOIA-HCM trial for adults with symptomatic obstructive HCM - enrolling now
- MAPLE-HCM trial - enrolling soon

SEPTAL REDUCTION THERAPY IN CHILDREN

- Alcohol septal ablation is not commonly performed at pediatric centers
- Septal myectomy, or even modified Konno, can be successfully performed for relief of outflow tract obstruction in children
- Younger patients have higher risk of recurrent obstruction

Schleihauf et al, EJCTS 2018





Theodoro et al, JTCVS 1996

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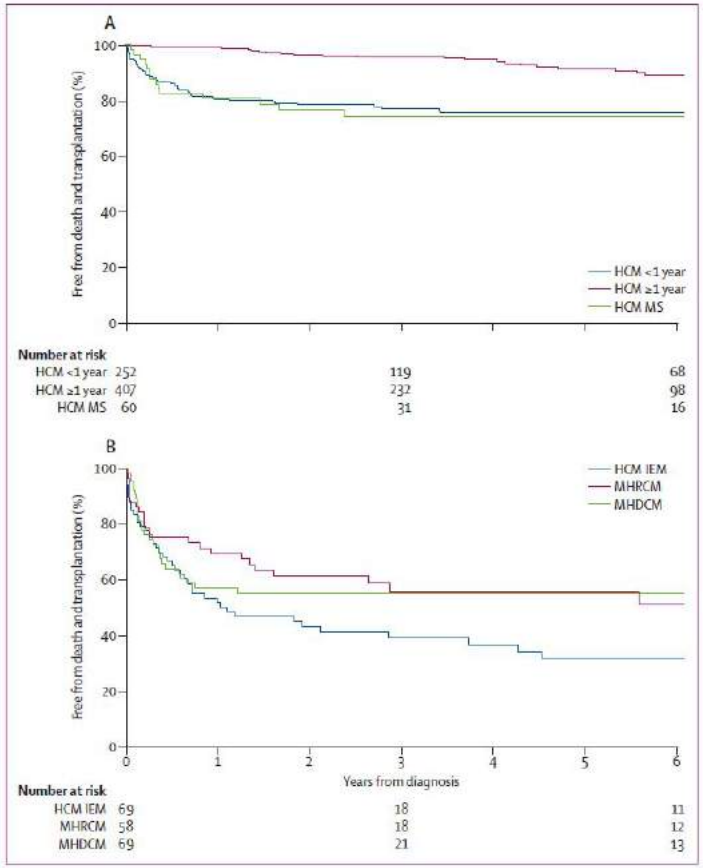
TRANSPLANT FOR PEDIATRIC HCM



- Worst survival for pediatric HCM in those with:
  - Age < 1 year old
  - Malformation syndrome
  - Inborn error of metabolism
- VAD use is low in HCM
- Waitlist and post-transplant survival equivalent to DCM patients

Lipshultz et al, Lancet 2013
Amdani et al, ATS 2021

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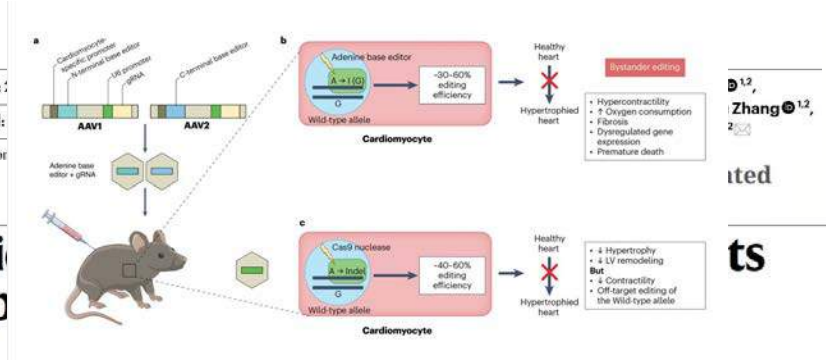
GENE THERAPY: AT THE HORIZON?

- Danon Disease: Phase 1 complete
- Friedreich Ataxia: Phase 1 underway
- MYBPC3: Phase 1 in next 1-2 years
- MHY7: Phase 1 in next 1-2 years

Base editing correction of hypertrophic cardiomyopathy in human cardiomyocytes and humanized mice



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SUMMARY

- HCM manifests in children in a variety of ways
- Consider a shared decision-making approach rather than universal activity restriction with respect to exercise
- New treatment options are on the horizon
- Genetic testing may have practical implications with respect to risk stratification and treatment options