Hypertrophic Cardiomyopathy: At the intersection of sex and race

Neal K Lakdawala, MD

Brigham and Women's Hospital

Harvard Medical School

Boston, MA

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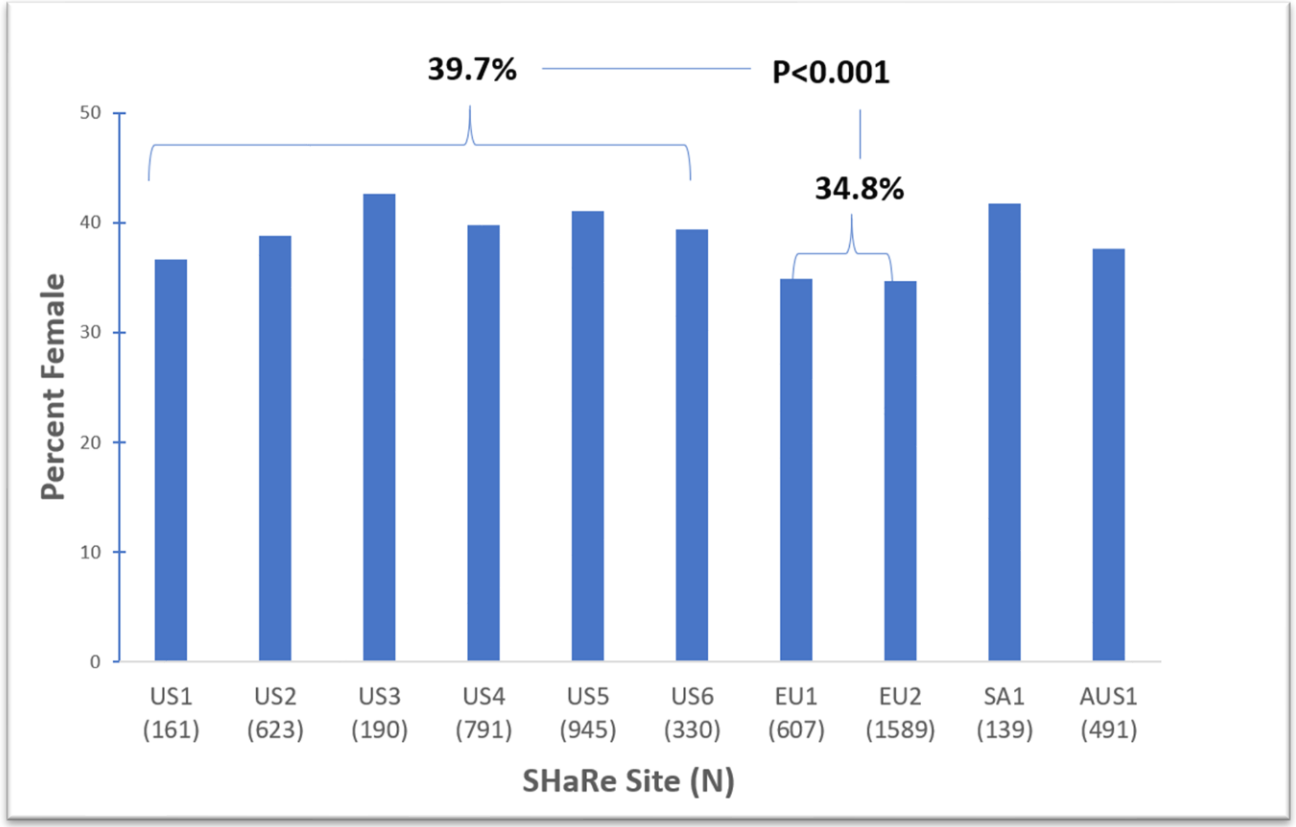
Core genetic principals of hypertrophic cardiomyopathy (HCM) 101

- HCM is the most common genetic heart disease (1:500)
- HCM is caused by sarcomere gene mutations (variants) with autosomal dominant inheritance
- The penetrance of sarcomere gene mutations is age dependent
- The expression of sarcomere gene mutations is highly variable
- The influence of sex and race on HCM penetrance and expression is incompletely understood

Women are underrepresented at HCM Centers Across the Globe

- Women account for 38% of patients at specialized HCM centers
  - Disparate access to care - ***Societal?***
  - Non-sex-based diagnostic thresholds - ***Institutional?***
  - Lower sarcomere gene penetrance - ***Biological?***



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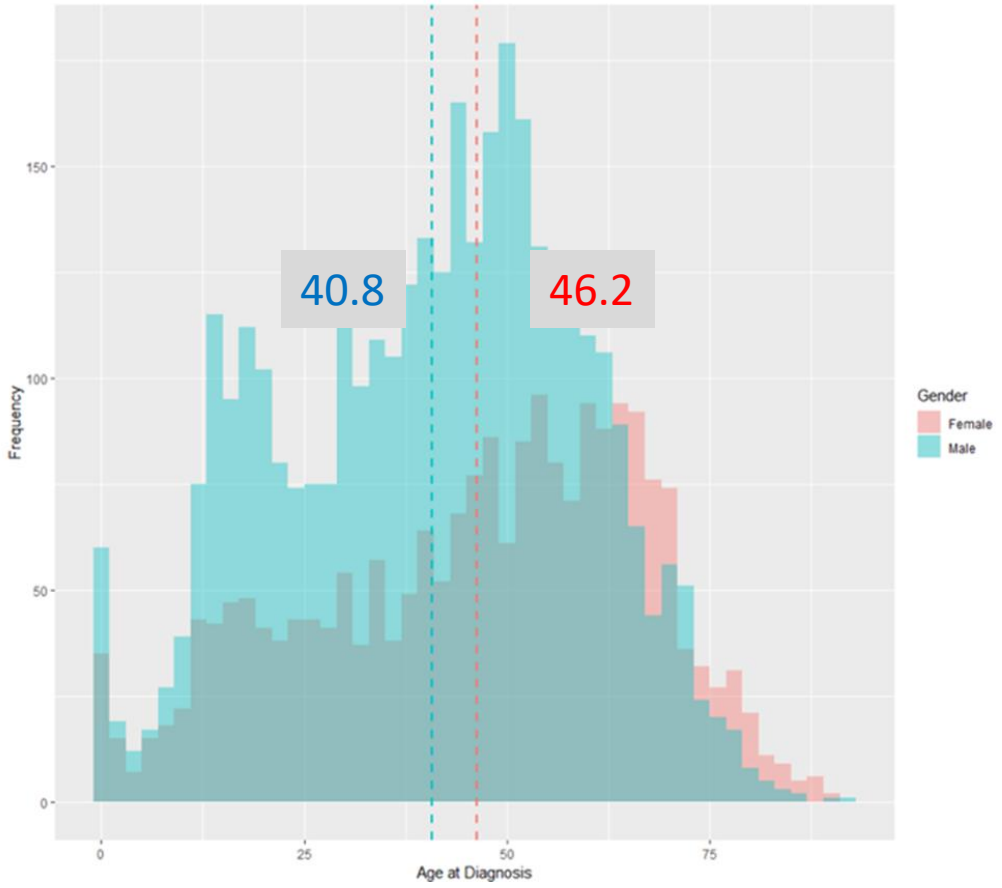
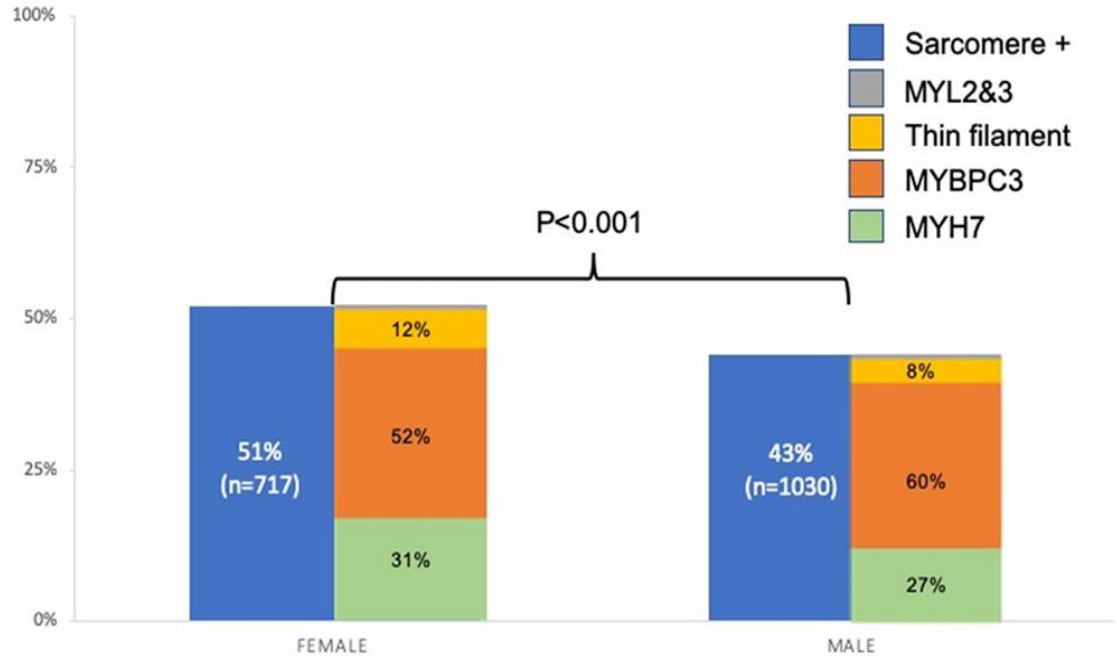
Women with HCM: Older and more likely to have a sarcomere gene mutation





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Sex based differences in the age of diagnosis vary by genetic substrate in HCM

	Female		Male		p-value
	N	Age (SD)	N	Age (SD)	
Sarc -	549	53.0 (18.6)	1039	45.9 (17.3)	<0.0001
Sarc +	701	38.7 (18.3)	1016	35.1 (16.7)	<0.0001
MYBPC3	363	41.5 (16.8)	609	36.8 (16.0)	<0.0001
MYH7	220	34.8 (19.2)	272	33.3 (16.8)	0.387
Thin filament	84	37.6 (18.3)	86	30.9 (19.4)	0.021

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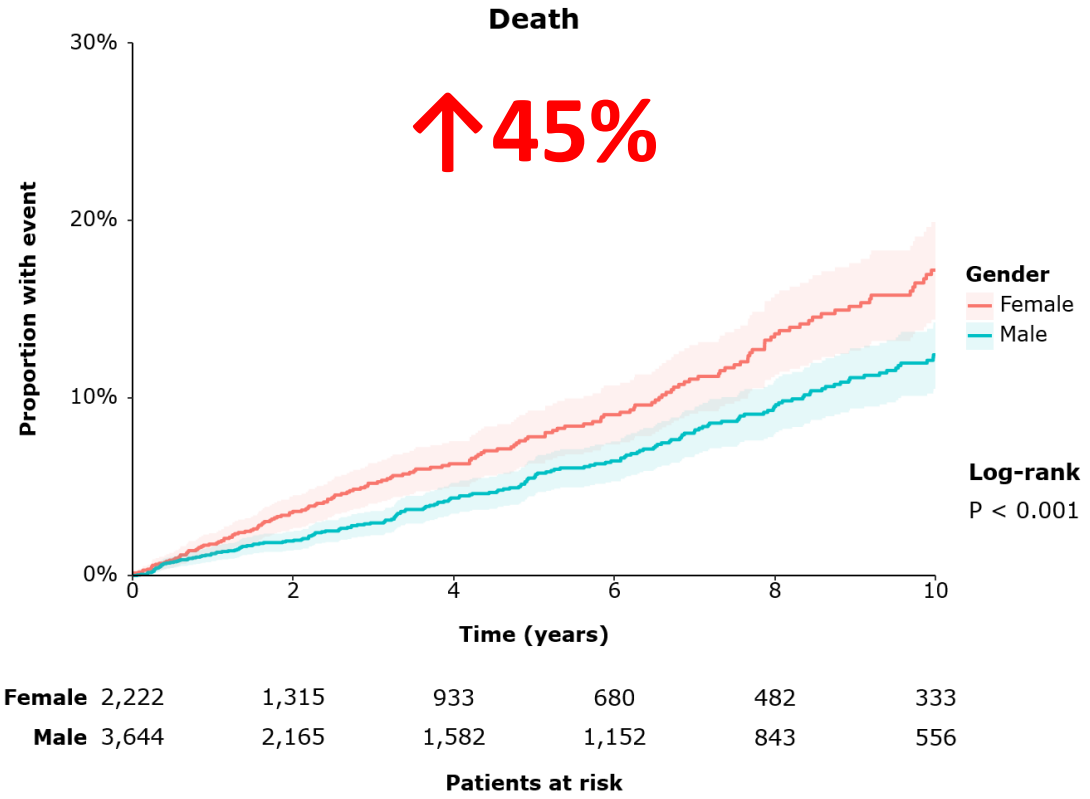
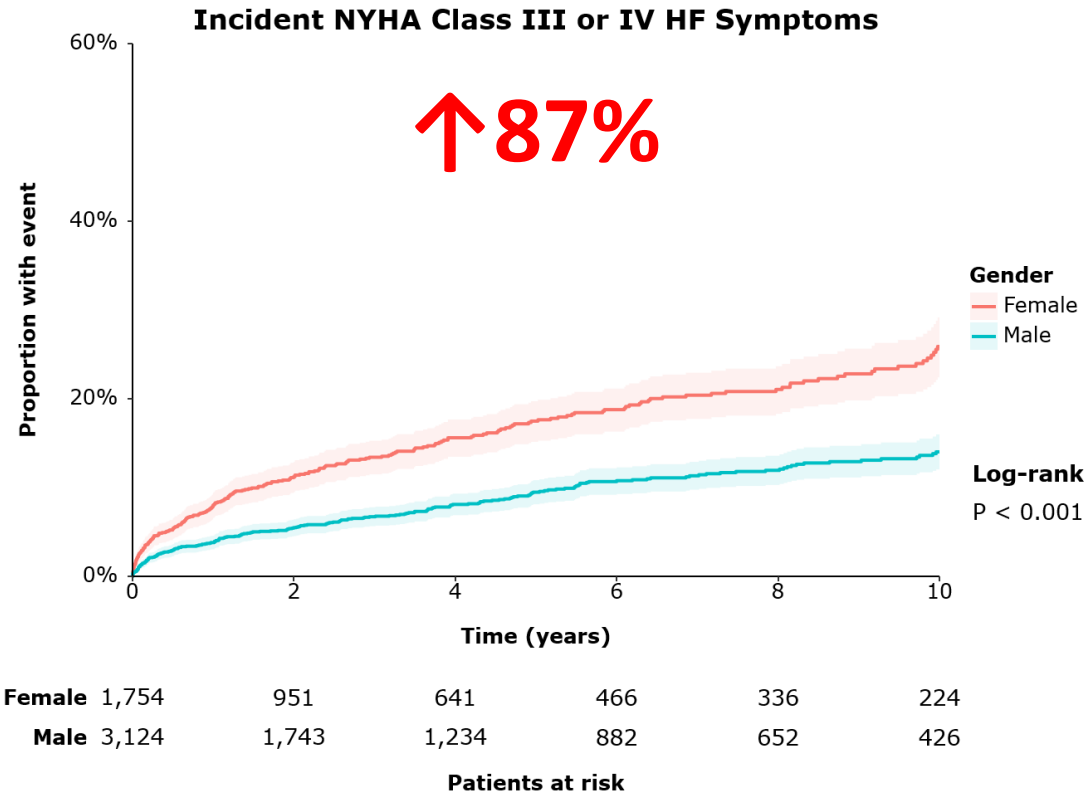
Women with HCM are more likely to die and develop advanced heart failure





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Sex-based Disparities in HCM *Where do we go?*

Model system studies: Include sex as a variable, study the effect of sex hormones

Diagnosis: Prospective studies of penetrance, improve access to specialized care, reassess diagnostic thresholds

Outcomes: Detailed studies of septal reduction therapy, myosin inhibition, and heart failure related to HCM with sex as a variable

Black Patients with HCM: Underrepresented and more symptomatic

Underrepresented: Lower representation in US HCM specialty clinics than predicted (8.3% Black, 205/2467), *29% of predicted*

Younger at diagnosis (37 vs. 42 years) with **more hypertension** (37% vs. 26%) but similar LVH and outflow tract obstruction

Less likely to have **genetic testing** (54% vs. 62%) and less likely to have (26% vs. 41%) **sarcomere mutation**

Table 3. Multivariable Model Examining Association of Race With NYHA Class III or IV Heart Failure Among 1422 Black and White Patients

Variable	Hazard Ratio (95% CI)	*P* Value
Black race	1.97 (1.34-2.88)	<.001
Age at diagnosis	1.02 (1.01-1.03)	<.001
Hypertension	1.01 (0.78-1.29)	.96
Obstruction[a]	1.81 (1.42-2.31)	<.001
Sarcomere status[b]		
Sarcomere positive	1.69 (1.30-2.20)	<.001
Sarcomere VUS	1.61 (1.08-2.39)	.02
Body mass index	1.06 (1.05-1.08)	<.001

Abbreviation: VUS, variants of unknown significance.

[a] Left ventricular outflow tract gradient >30 mm Hg on baseline echocardiography.

[b] Sarcomere-positive patients with pathogenic or likely pathogenic mutations on any of the 8 sarcomere-encoding genes; *ACTC1* (OMIM 102540), *MYBPC3* (OMIM 600958), *MYH7* (OMIM 160760), *MYL2* (OMIM 160781), *MYL3* (OMIM 160790), *TNNI3* (OMIM 191044), *TNNT2* (OMIM 191045), and *TPM1* (OMIM 191010). Sarcomere VUS is defined as patients with VUS in any of the 8 sarcomere-encoding genes. Total event rate was 304 events.

Systematic solutions for Black Patients with HCM

1

Policy makers

Improve access to specialty care

2

Cardiology community

Address preconceptions about hypertensive heart disease

3

Genomics Community

Improve the ancestral diversity of reference populations