Strain in the Assessment of Cardiomyopathies.

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Sanger Heart and Vascular Institute

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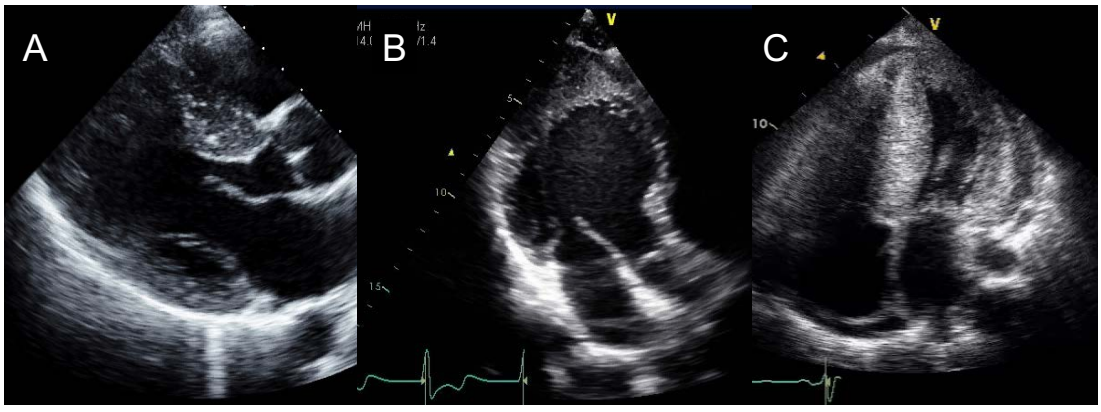
No Disclosures

1

HOCM | Apical HCM | Amyloid



What is the added utility in the assessment of CM?

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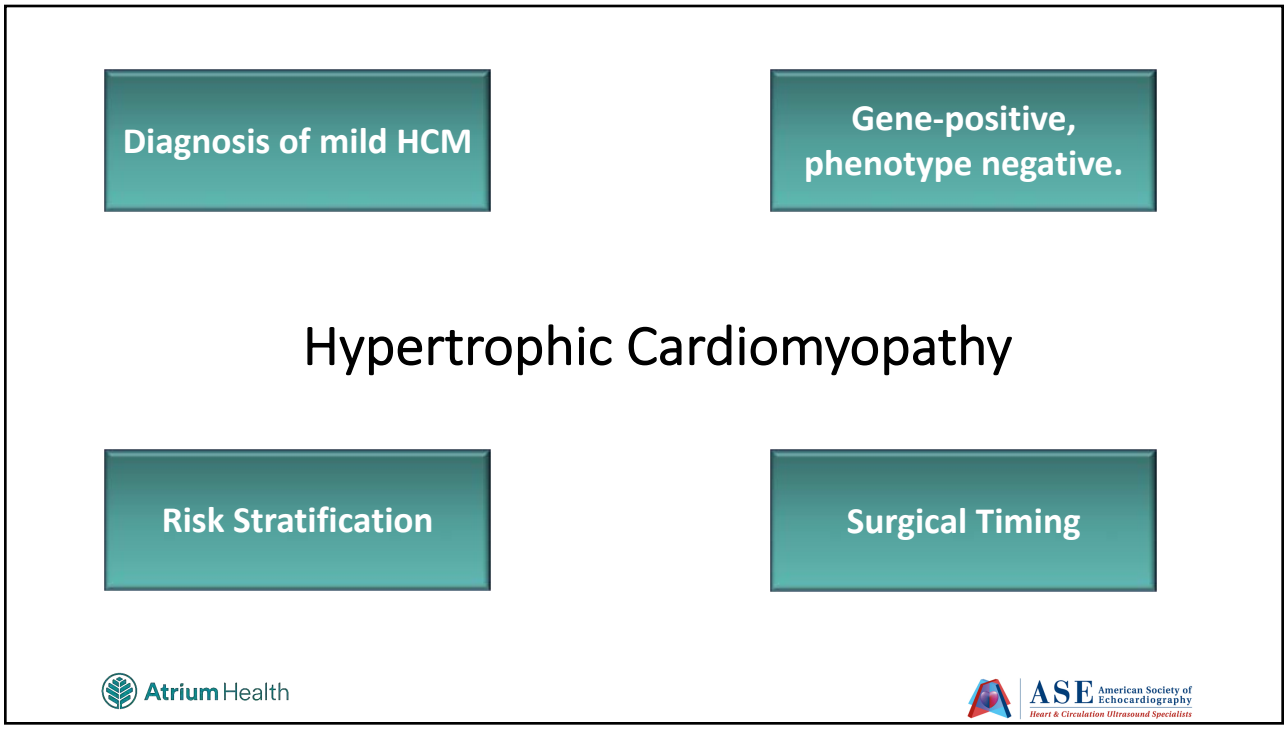
Diagnosis of mild HCM
Gene-positive, phenotype negative.
Hypertrophic Cardiomyopathy
Risk Stratification
Surgical Timing
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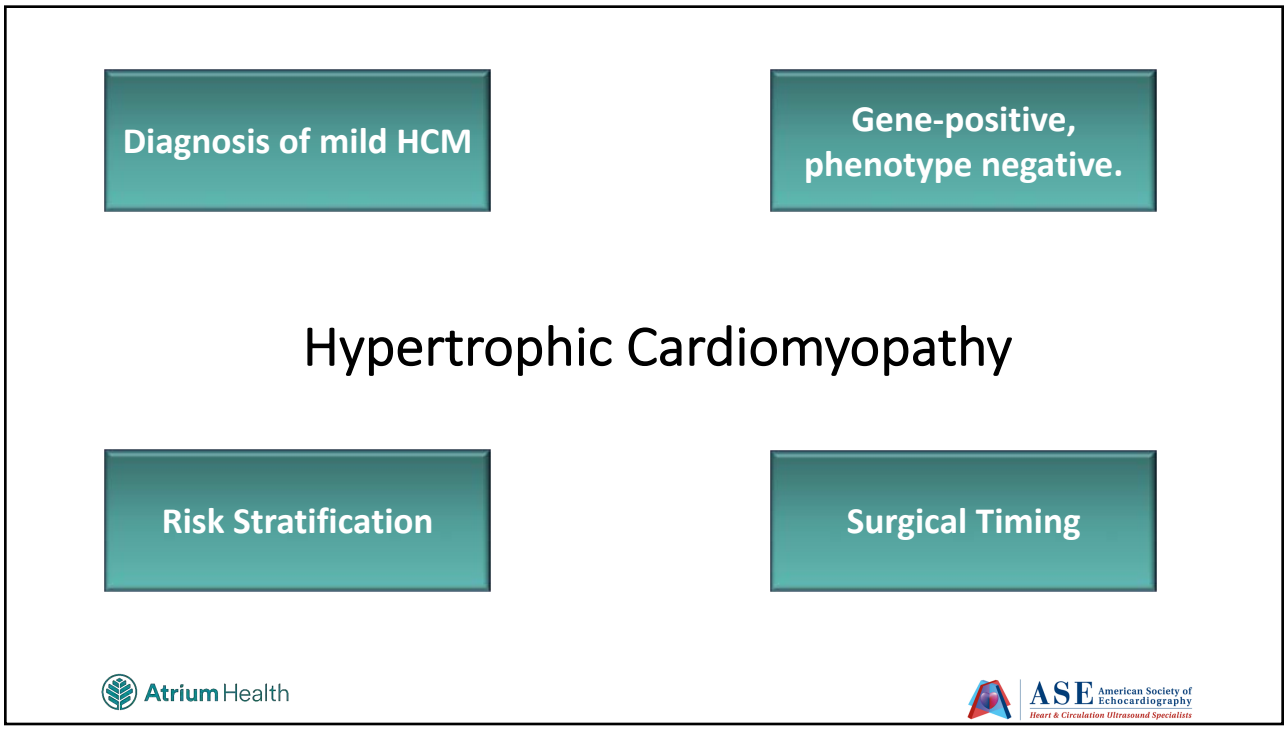
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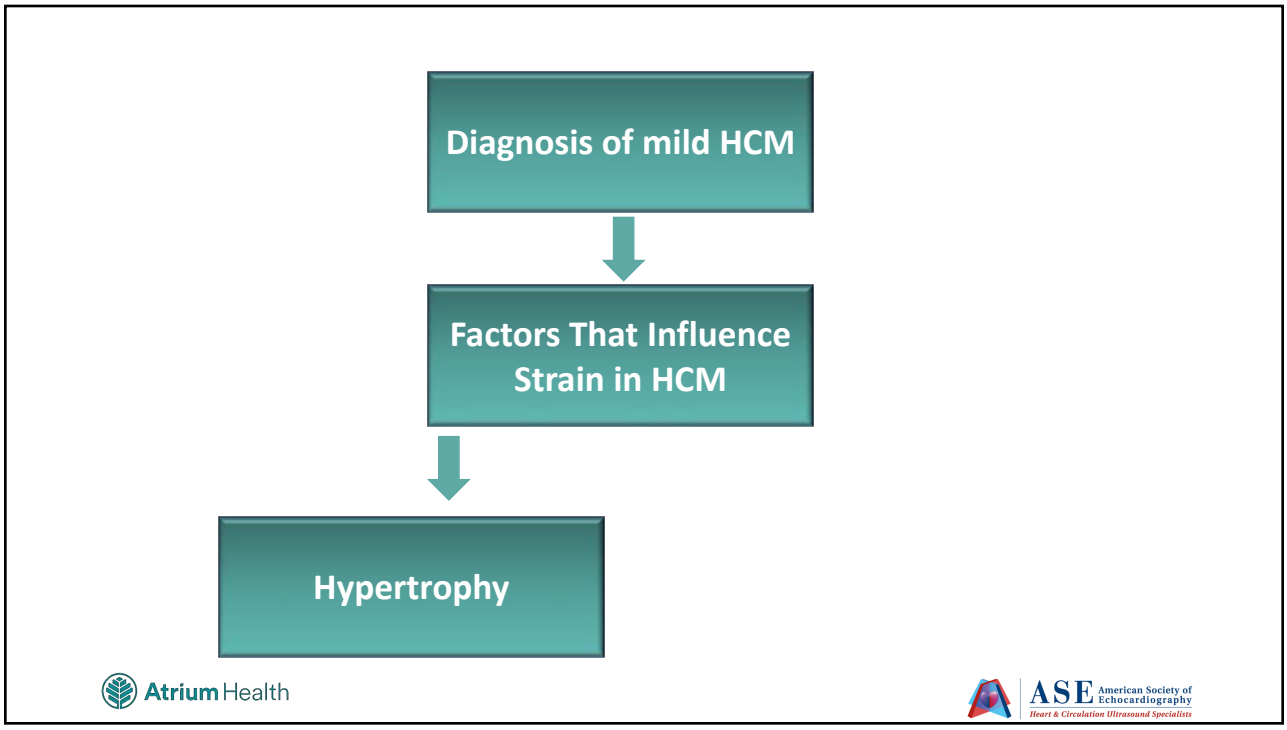

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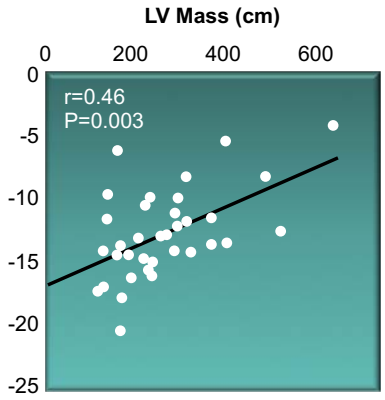
Reduction in Longitudinal Strain Correlates with LV mass



However

Strain Does not Normalize after Myectomy or Ablation

Popovic *et. al. JASE* 2008
Moravsky et al JASE 2013
Sommer European Journal of Echo 2010

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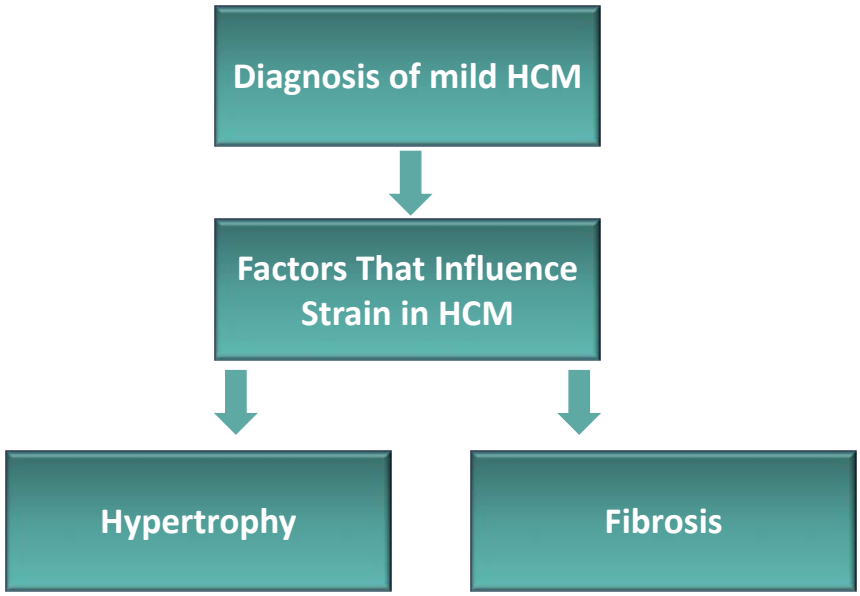

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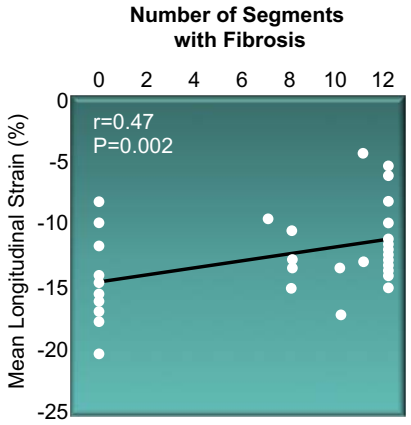
Reduction in Longitudinal Strain Correlates with LV Fibrosis



Popovic *et. al. JASE* 2008

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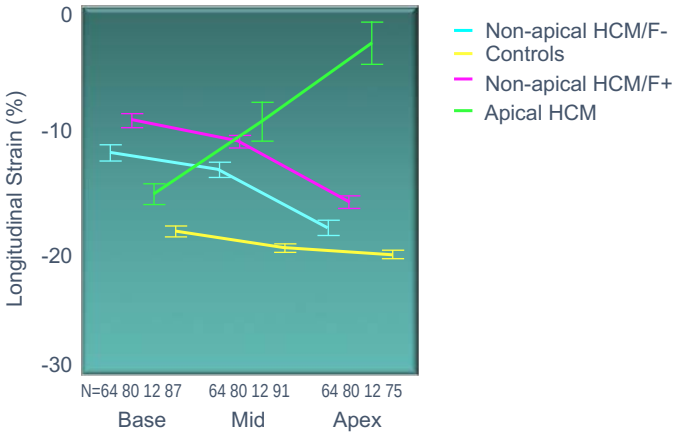
Regional Variation in Longitudinal Strain in HCM



Popovic *et. al. JASE* 2008

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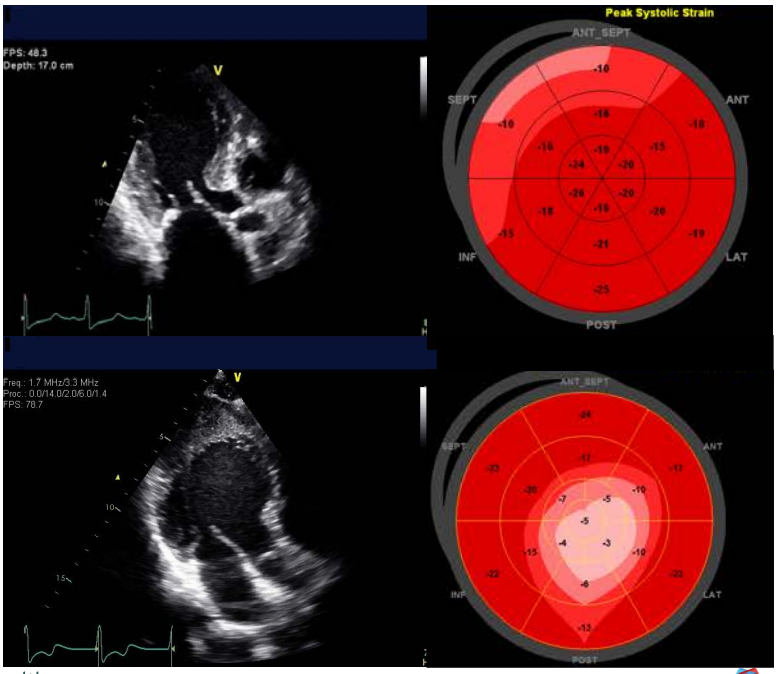

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How does LS perform in mild to moderate LVH without characteristic ECG patterns?

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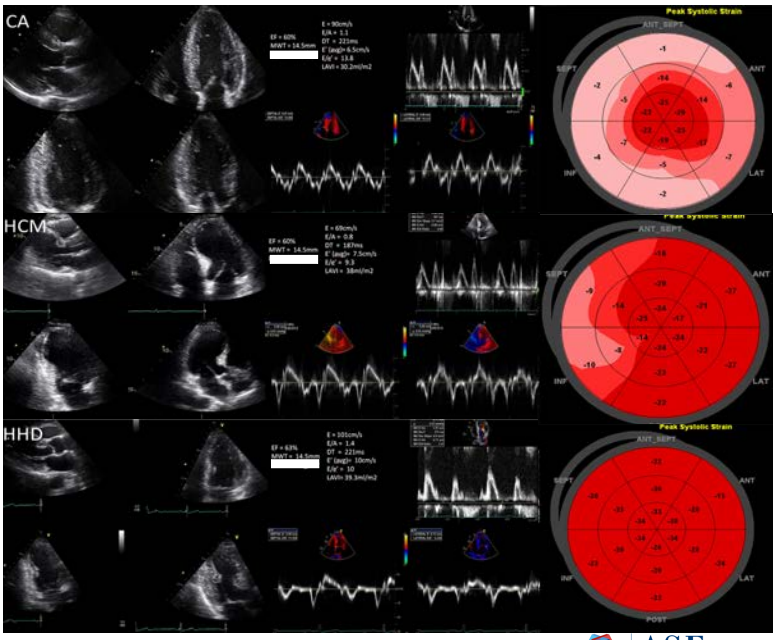
Cardiac Amyloid

HCM

HHD



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- The addition of the strain map for the diagnosis of LVH:
  - improved concordance (*K* increased from 0.28 to 0.57)
  - Improved accuracy (p<0.01)
  - 22% of cases were re-classified correctly
  - Improved reader confidence in making the correct diagnosis (p<0.01)

Table 3 Diagnostic accuracy in patients with mild to moderate LVH with and without strain polar map

Diagnosis	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
HCM					
Baseline read	44	75	65	45	73
Strain read	52	84	73	63	78
P	.054	.01	.001	<.001	.005

Phelan *et. al. JASE* 2014

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Diagnosis of mild HCM

Gene-positive, phenotype negative.

Hypertrophic Cardiomyopathy

Risk Stratification

Targeted Screening

Surgical Timing

Evaluation of Therapy

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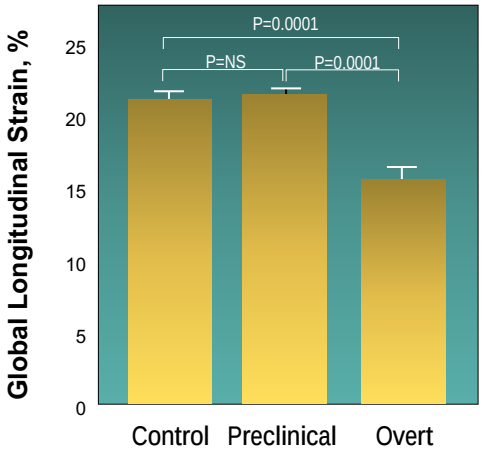
Longitudinal Strain in preclinical HCM

- 38 relatives G-/LVH-
- 68 patients with G+/LVH-
- 40 patients G+/LVH+

- All had normal EF



Ho *et. al. Circ Cardiovasc Genet*. 2009

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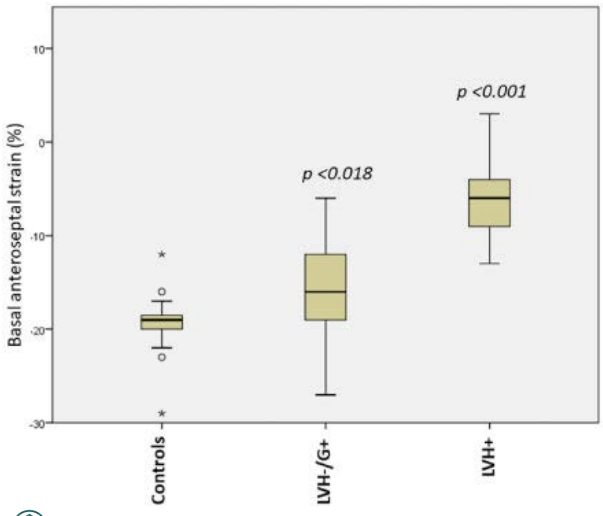
4 subsequent studies showed a mild reduction in regional strain at the basal anteroseptum in patients with pre-clinical HCM



Small Numbers

Overlap between normal and preclinical

Consistent finding in multiple labs

Baudrey et al. EHJ Cardiovascular Imaging 2019

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Diagnosis of mild HCM

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First author	Year published	n	Vendor (software)	Follow up	Average GLS for HCM	Endpoint	Major findings
Paraskevaidis et al	2009	50	GE (EchoPac)	12 months	-14 ± 4	Death and hospitalization	Strain predicted worse outcomes in univariate but not multivariate analysis.
Di Salvo et al	2010	93	GE (EchoPac)	2 years	-15.95 ± 3.24	NSVT	Patients with NSVT had lower basal and mid wall regional strain. >3 segments with peak LS of ≥-10% was predictive of outcome.
Saito et al	2012	48	GE (EchoPac)	42 ± 12 months	-12.7 ± 2.9	SCD, fatal arrhythmia, hospitalization for CHF	Significantly more events in those with GLS less than median (-12.9%).
Funabashi et al	2013	44	Philips (Qlab)	18 months	-9.89 ± 2.59	Cardiac death, syncope, sustained VT/VF, appropriate ICD discharge	Worsening GLS associated with worse outcomes. GSL significantly worse in subjects with MACE than in those without MACE (− 8.2 ± 2.0% and − 10.6 ± 2.5%, respectively, P < 0.001)
Debonnaire et al	2014	92	GE (EchoPac)	4.7 years	-13.3 ± 3.5	Appropriate ICD therapy	GLS was an independent predictors of appropriate ICD therapy on multivariate analysis. GLS ≥ -14% associated with worse outcome.
Reant et al	2015	115	GE (EchoPac)	19 ± 11 months	-16.6 ± 3.6	Death, sustained VT, appropriate ICD discharge, progression to NYHA class III/IV	Cox backward-entry selection model revealed that GLS <= 15% at rest was independently associated with an increased risk for poor outcomes.
				22			
				4.3			
				30			
						discharge, hospitalization for CHF	
Candan et al	2017	63	GE (EchoPac)	21.5 ± 6.9 months	-12.1 ± 3.4	Appropriate ICD discharge	Mechanical dispersion and GLS were found to be independent predictors of occurrence of appropriate ICD therapy
Moneghetti et al	2017	131	Philips (Qlab)	56 months	-14.3 ± 3.9	Death, worsening HF, hospitalization for CHF, heart transplantation	Global LS was predictive of outcome on univariate analysis but not multivariate analysis. The worst outcomes were observed for patients with lateral LS <16.1%.
Liu et al	2017	400	GE (EchoPac	3.1 years	-16 ± 4	Death, heart transplantation, sustained VT/VF, CHF.	Patients with GLS > -16% had significantly more events (17% vs 7%, p = 0.002). Event-free survival was significantly superior in those with GLS <= -16% versus GLS > -16% (p = 0.004). GLS was significantly associated with the composite end point on multivariate analysis.
Hiemstra et al	2017	427	GE (EchoPac	6.7 years	-15 ± 4	Death, heart transplantation, appropriate ICD discharge	Multivariable Cox regression analysis revealed GLS to be independently associated with the primary end point (hazard ratio GLS, 1.10 [1.03-1.19], P=0.007).
Tower-Rader et al	2017	1019	Philips, GE, Siemens (Velocity vector imaging)	9.4 ± 3 years	-13.7	Death or appropriate ICD discharge	61% or events occurred in patients with GLS worse than median (-13.7). Subhazard ratio for every % worsening of GLS was 1.11 (1.05-1.220) p <0.001.

Heterogenous cohorts and outcomes

Incomplete evaluation of risk

Variability in thresholds

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Incremental Prognostic Utility of Left Ventricular Global Longitudinal Strain in Hypertrophic Obstructive Cardiomyopathy Patients and Preserved Left Ventricular Ejection Fraction

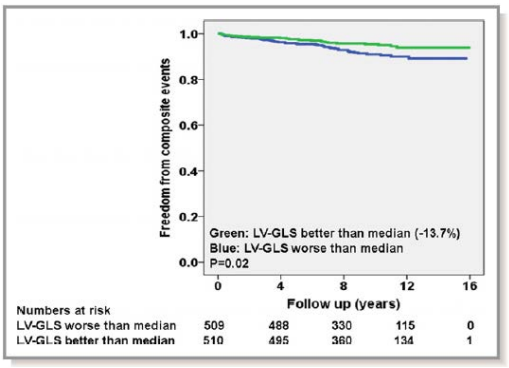
Albree Tower-Rader, MD;* Jorge Betancor, MD;* Zoran B. Popovic, MD, PhD; Kimi Sato, MD, PhD; Maran Thamilarasan, MD; Nicholas G. Smedira, MD; Harry M. Lever, MD; Milind Y. Desai, MD

1019 patients with obstructive physiology

Follow-up: 9.4 years

Outcome: death or appropriate ICD discharge

	Subhazard Ratio	*P* Value
(A) Model 1 (with standard major ACC/AHA SCD risk factors included in analysis)		
Age, y	1.04 [1.02–1.07]	<0.001
Atrial fibrillation during follow-up	1.39 [1.11–1.69]	<0.001
LV-GLS (for every % worsening)	1.11 [1.05–1.22]	<0.001
Surgical myectomy	0.44 [0.25–0.72]	<0.01
Following potential additional predictors were considered for analysis, but were not significant: standard ACC/AHA major SCD risk factors (none, 1, ≥2), sex, maximal LVOT gradient, medical therapy		
(B) Model 2 (with ESC risk score included in analysis)		
Atrial fibrillation during follow-up	1.47 [1.17–2.21]	<0.001
LV-GLS (for every % worsening)	1.13 [1.08–1.22]	<0.001
Surgical myectomy	0.42 [0.22–0.64]	<0.01
Following potential additional predictors were considered for analysis, but were not significant: ESC risk score, sex, medical therapy		



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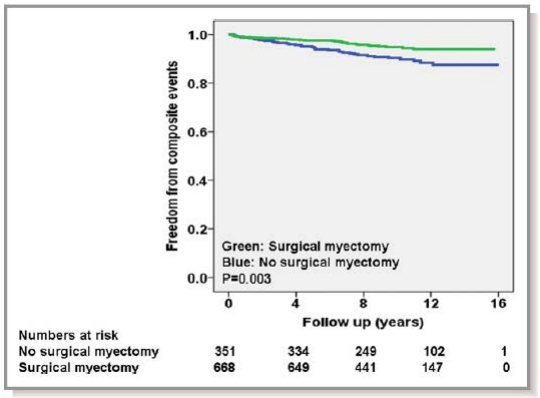
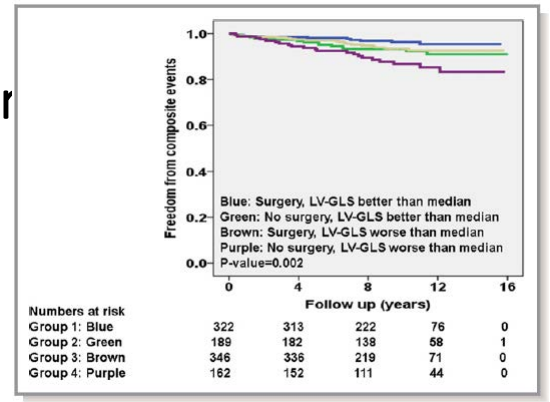
Diagnosis of mild HCM

Gene-positive, phenotype negative.



Car



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Summary Slide on Clinical Utility of Strain in HCM

- Characterized by a reduction in LS strain at the site of hypertrophy and fibrosis.
- May be helpful in diagnosing mild HCM – no pathognomonic findings
- Reduction in strain at the basal anteroseptum has been noted in gene-positive, phenotype-negative patients
- Does define risk of SCD but no reliable threshold. Largest study used a threshold of -13.7%
- Those with a gradient of >30mmHg and GLS worse than -13.7% had the worst outcome – may be considered in decisions regarding myectomy.

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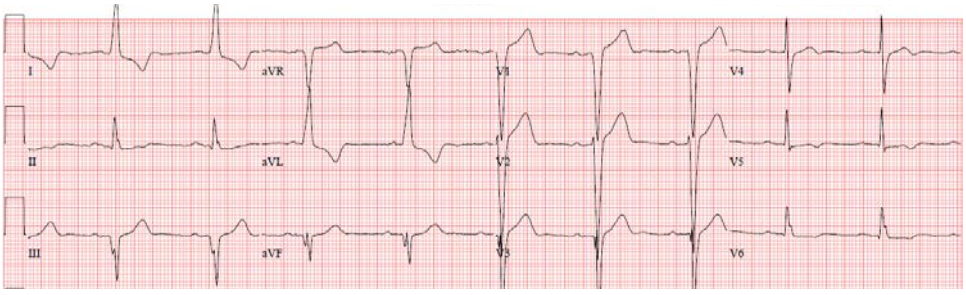
Patient

- 62 year old AA male
- CKD Stage III, proteinuria, long-standing hypertension (better control recently)
- Presents with DOE, lower extremity edema and SOB



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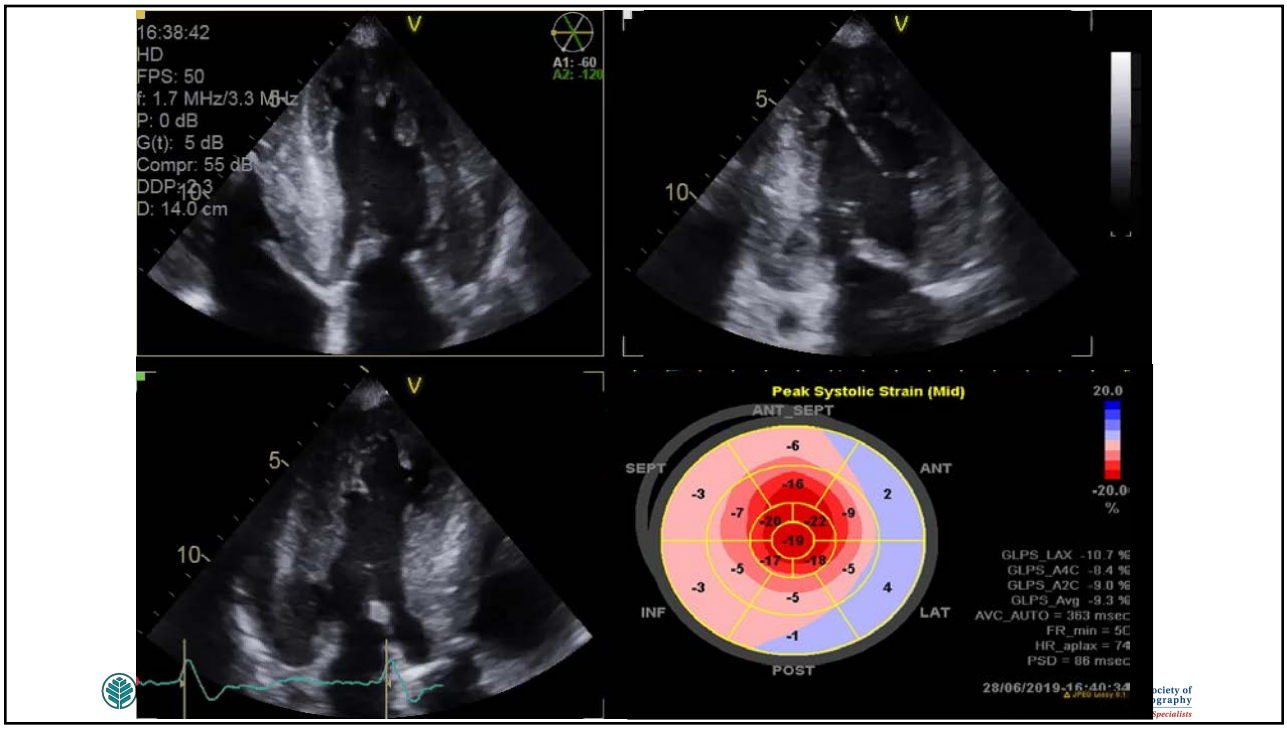

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Electrocardiography in TTR

Transthyretin CA (V122I)

n=64

- Low voltage 56%
- Pseudoinfarct 53%
- Sinus 62.5%
- A Fib 23%
- LVH 26%

Heart 2012;98:1546-1554

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Diagnosis

Prognosis

Cardiac Amyloid

Response to Therapy

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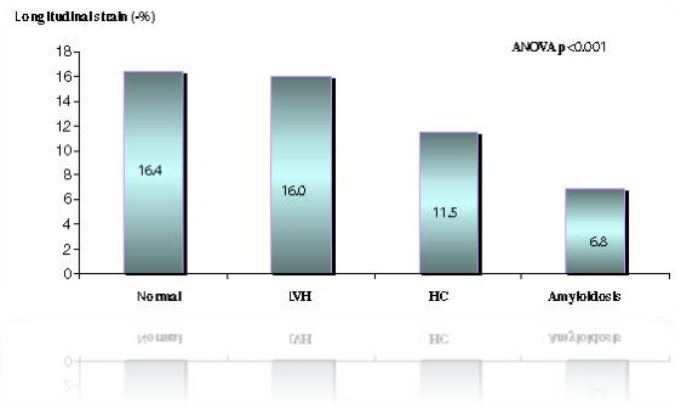
Diagnosis



Jing Ping Sun AJC 2008

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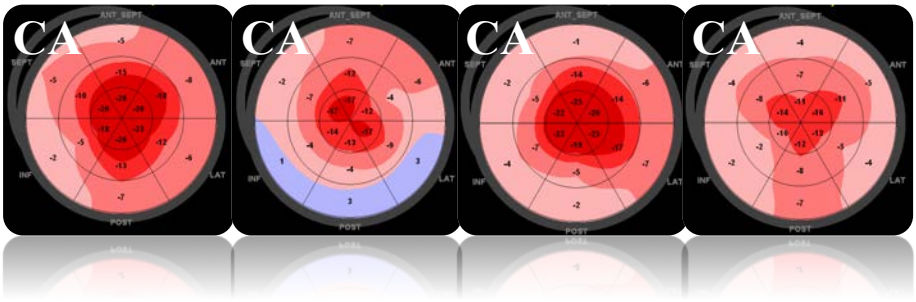
Regional Variation in LS



$$\text{Relative Regional Strain Ratio} = \frac{\text{Average apical LS}}{\text{Average basal LS + Average mid LS}}$$

Phelan *et. al. Heart* 2012

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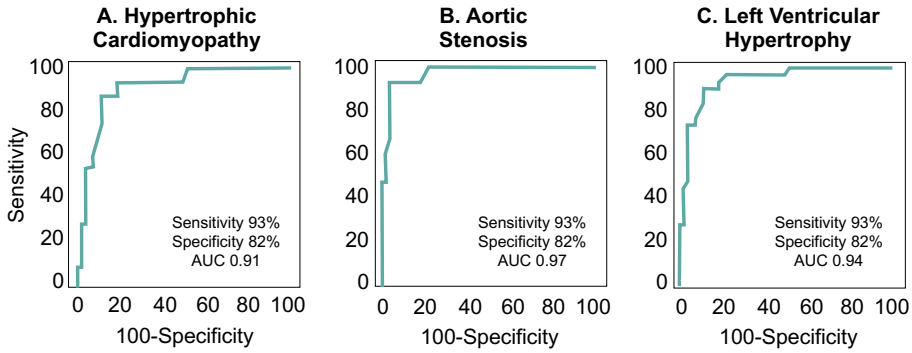
Can Regional Variation in LS differentiate CA from other froms of LVH?

Relative Regional Strain Ratio ≥ 1



Phelan *et. al. Heart* 2012

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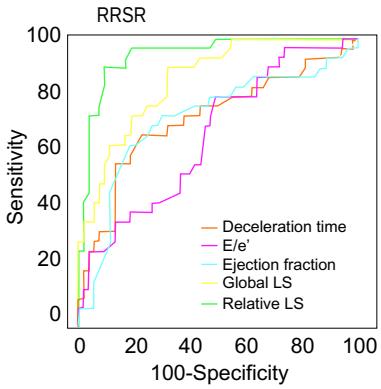

- AUC using RRSR was significantly larger than the other more traditional echocardiographic parameters used for diagnosing CA
- Relative LS was strongest predictor of CA in a multivariable Logistic regression model

Phelan *et. al. Heart* 2012

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Criteria for Diagnosis	Subtype
Histological Diagnosis of Cardiac Amyloidosis: Endomyocardial Biopsy*	
1. Endomyocardial biopsy positive for cardiac amyloidosis with Congo red staining with apple-green birefringence under polarized light; typing by immunohistochemistry and/or mass spectrometry at specialized centers	AL, ATTR, Other subtypes
Histological Diagnosis of Cardiac Amyloidosis: Extracardiac Biopsy	
1. ATTR cardiac amyloidosis is diagnosed when below criteria are met: a. Extracardiac biopsy proven ATTR amyloidosis **AND** b. Typical cardiac imaging features (as defined below)	ATTR
2. AL cardiac amyloidosis is diagnosed when below criteria are met: a. Extracardiac biopsy proven AL amyloidosis **AND** b. Typical cardiac imaging features (as defined below) **OR** c. Abnormal cardiac biomarkers: abnormal age-adjusted NT-pro BNP or abnormal	AL
1. Echo a. LV wall thickness >12 mm b. Relative apical sparing of global LS ratio (average of apical LS/average of combined mid+basal LS >1) c. ≥ Grade 2 diastolic dysfunction†	ATTR/AL
1. Echo a. LV wall thickness >12 mm b. Relative apical sparing of global LS ratio (average of apical LS/average of combined mid+basal LS >1) c. ≥ Grade 2 diastolic dysfunction†	ATTR/AL
2. CMR a. LV wall thickness >ULN for sex on SSFP cine CMR b. Global ECV >0.40 c. Diffuse LGE† d. Abnormal gadolinium kinetics typical for amyloidosis, myocardial nulling prior to blood pool nulling	ATTR/AL
3. PET: ^{18}F-florbetapir† or ^{18}F-florbetaben PET†‡ a. Target to background (LV myocardium to blood pool) ratio >1.5 b. Retention index >0.030 min^{-1}	ATTR/AL

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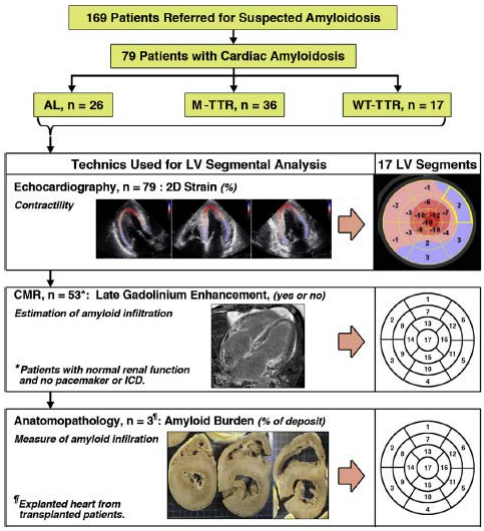
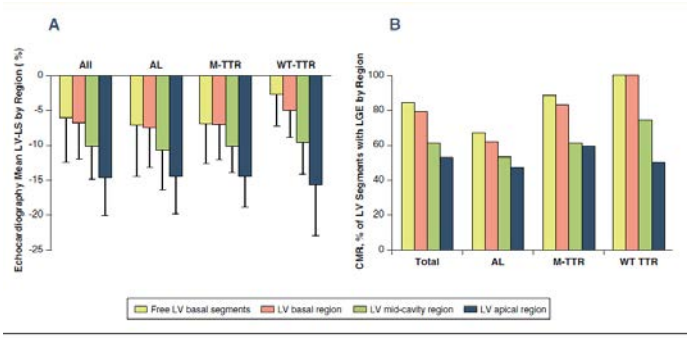
Mechanism of Apical Sparing





Ternacle et al JACC Imaging 2017

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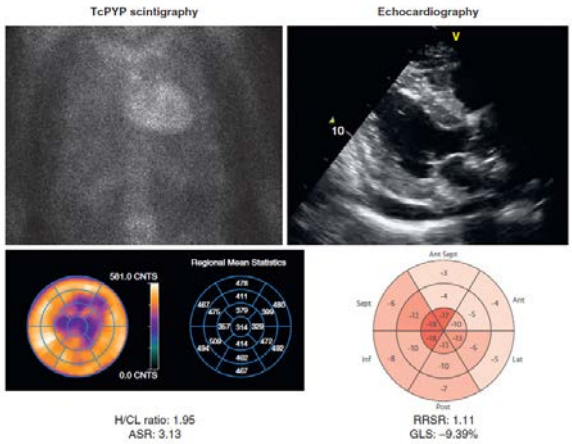
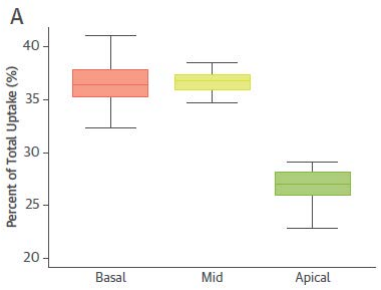
Mechanism of Apical Sparing





Sperry B et al JACC Cardiovascular Imag 2018

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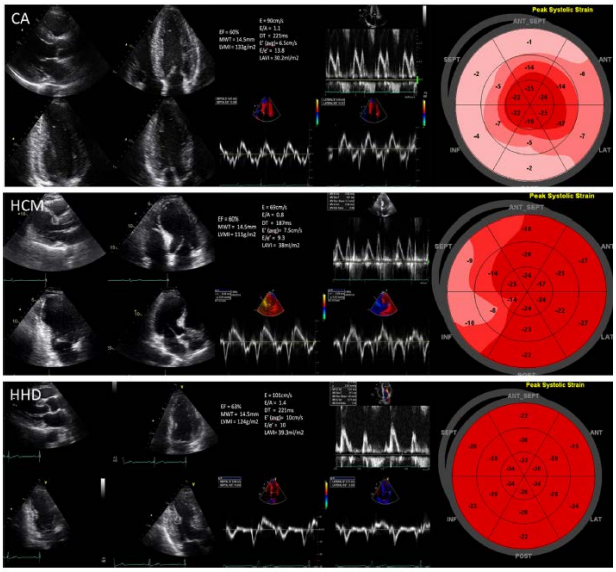
What about to differentiate patients with mild-moderate LVH?

Table 3 Diagnostic accuracy in patients with mild to moderate LVH with and without strain polar map

Diagnosis	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
CA					
Baseline read	40	84	70	55	75
Strain read	86	95	92	92	94
P	<.001	.002	<.001	<.001	<.001
HCM					
Baseline read	44	75	65	45	73
Strain read	52	84	73	63	78
P	.054	.01	.001	<.001	.005
HHD					
Baseline read	60	59	60	42	72
Strain read	70	74	73	59	84
P	.061	.002	.001	.001	.004

NPV, negative predictive value; *PPV*, positive predictive value.



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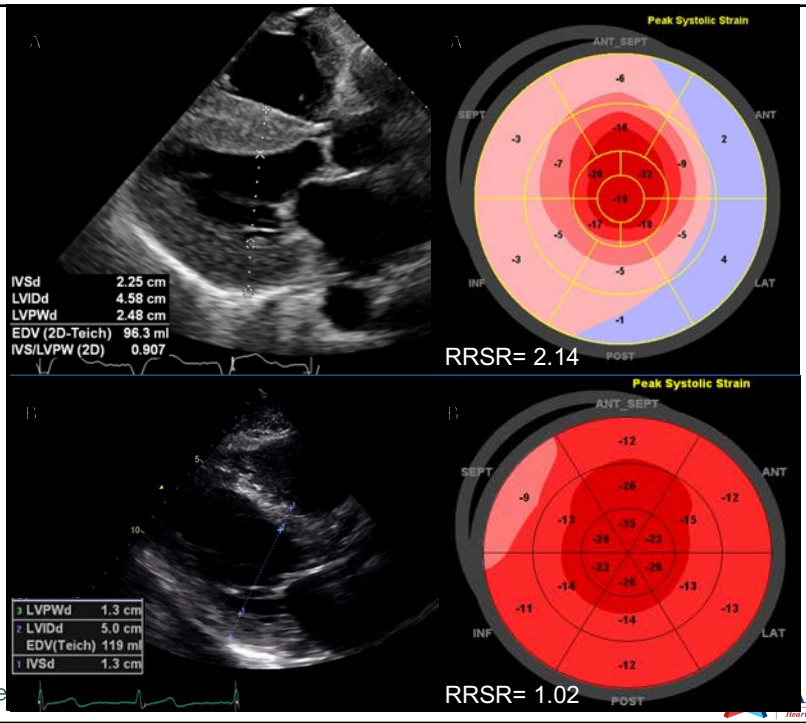

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Diagnosis

Prognosis

Cardiac Amyloid

Response to Therapy

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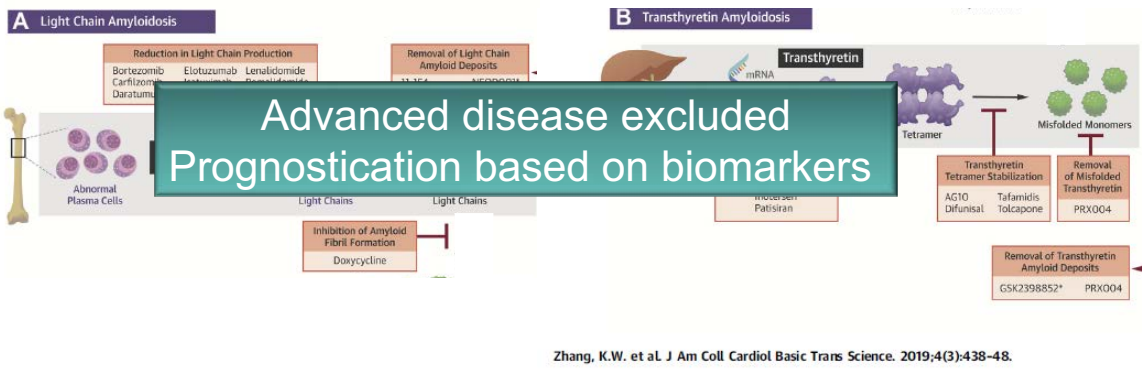
Prognosis



Advanced disease excluded
Prognostication based on biomarkers

Zhang, K.W. et al. J Am Coll Cardiol Basic Trans Science. 2019;4(3):438–48.

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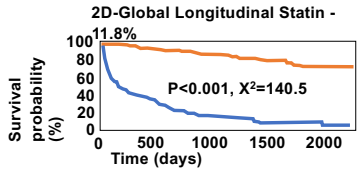
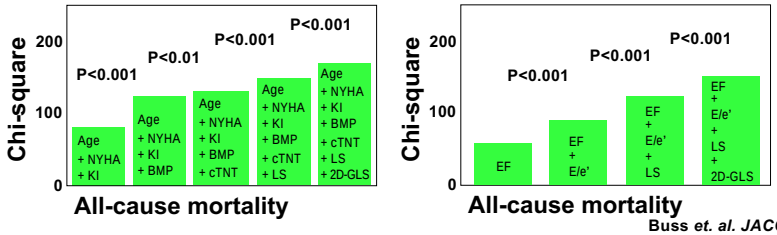
LS provides important prognostic information in CA





Buss *et. al. JACC* 2012

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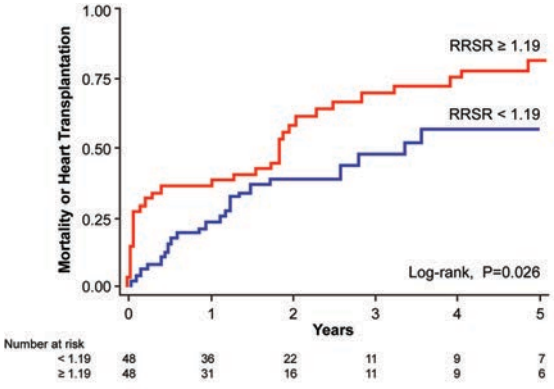
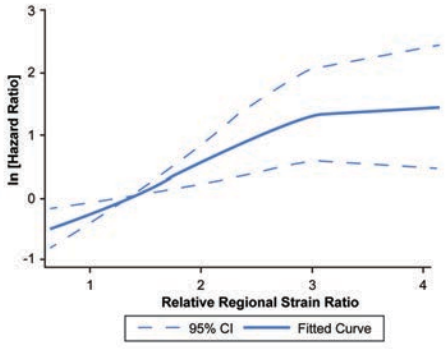
Prognositc utility of Relative Regional Strain Ratio





Phelan *et. al. Heart* 2016

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Limitations of current data to integrate strain into risk model

Heterogenous cohorts Limited data on TTR

Heterogenous Outcomes

Variability in thresholds

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Diagnosis

Prognosis

Cardiac Amyloid

Response to Therapy

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JAMA Cardiology | Brief Report

Association of Patisiran, an RNA Interference Therapeutic, With Regional Left Ventricular Myocardial Strain in Hereditary Transthyretin Amyloidosis
The APOLLO Study

Masatoshi Minamisawa, MD, PhD; Brian Claggett, PhD; David Adams, MD; Arnt V. Kristen, MD; Giampaolo Merlini, MD; Michel S. Slama, MD; Angela Dispenzieri, MD; Amil M. Shah, MD, MPH; Rodney H. Falk, MD; Verena Karsten, PhD; Marianne T. Sweetser, MD, PhD; Jihong Chen, PhD; Richard Riese, MD; John Vest, MD; Scott D. Solomon, MD

- Randomized, double-blinded, placebo-controlled, phase 3, multicenter international clinical trial
- ATTRm CA patients
- Patisiran, a small interfering RNA, or placebo.
- After 18 months the treatment group had a significant improvement in absolute GLS (least-squares mean (SE)difference , 1.4% (0.56%); 95% CI, 0.3%-2.5%, p=0.2). The greatest difference was noted in the basal segments.

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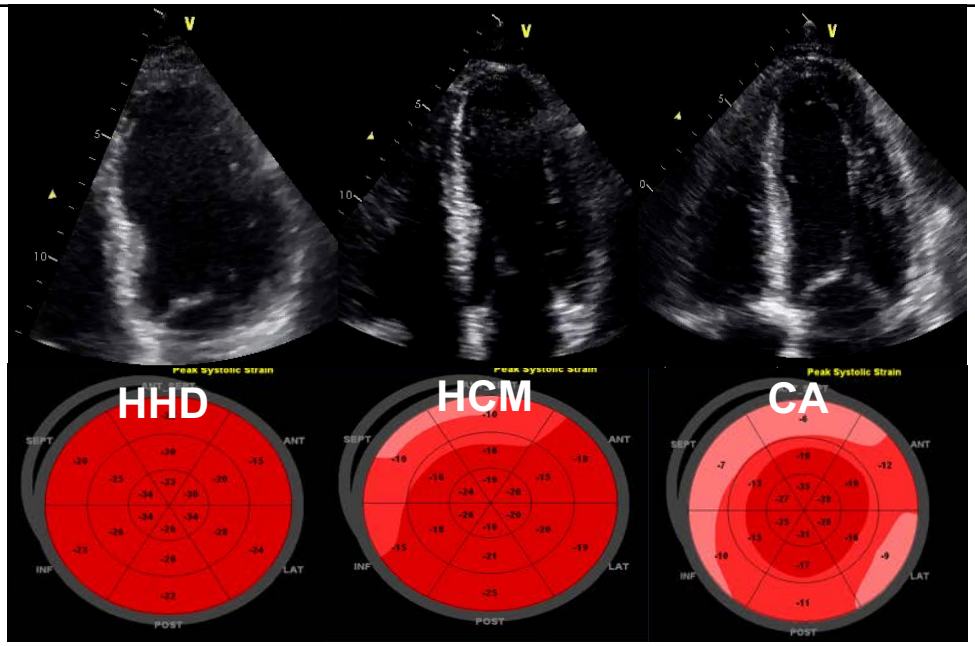

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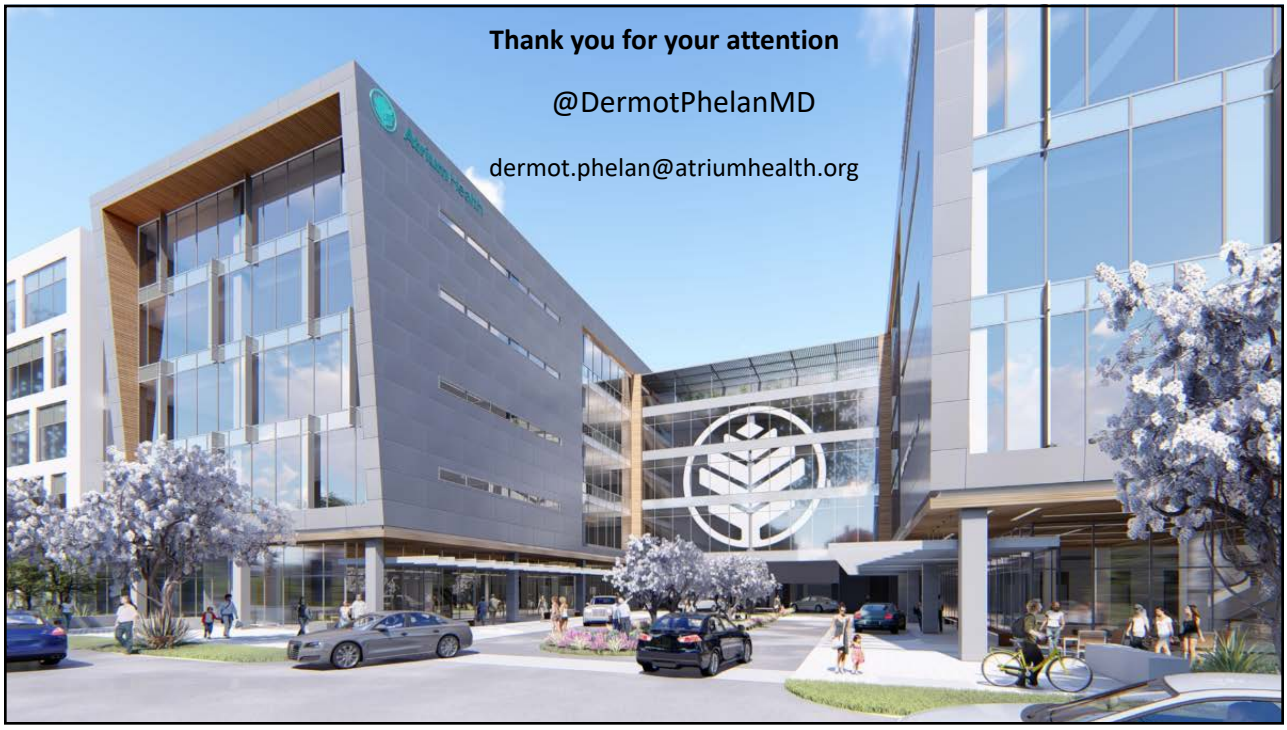
Thank you for your attention
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