UPDATE ON MANAGEMENT OF HYPERTROPHIC CARDIOMYOPATHY

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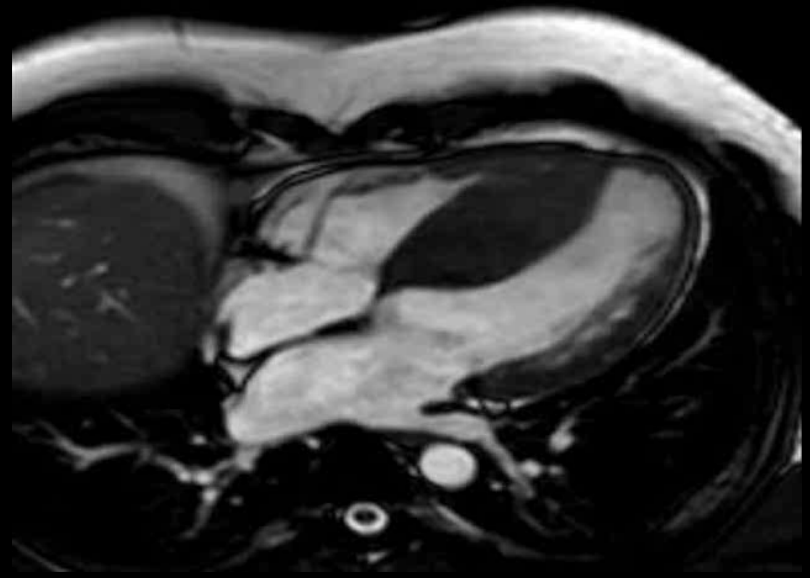
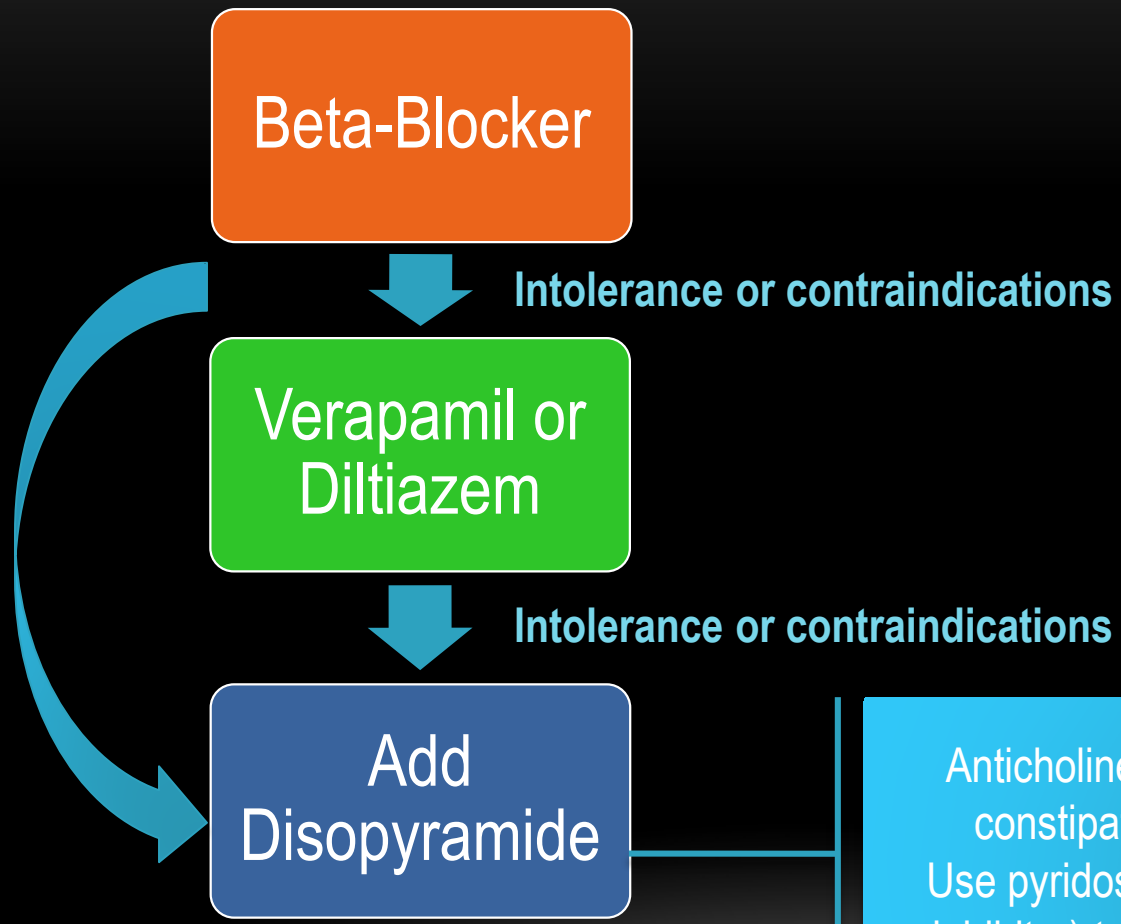


October 28, 2019

MEDICAL TREATMENT FOR LEFT VENTRICULAR (LV) OUTFLOW OBSTRUCTION IN HCM



Avoid venodilators
- Nitrates
- Amlodipine, Nifedipine
- Hydralazine
- Carvedilol

Advise Viagra and Cialis use with caution (hydrated and not in combination with alcohol).

Anticholinergic effects can cause constipation & dry everything!
Use pyridostigmine (cholinesterase inhibitor) to counteract side effects

MANAGEMENT OF SYMPTOMS IN NON-OBSTRUCTIVE HCM

Heart failure symptoms and preserved LV ejection fraction (≥ 50%) with no evidence of resting or provocable outflow obstruction

Beta-blockers, verapamil or diltiazem
Diuretics

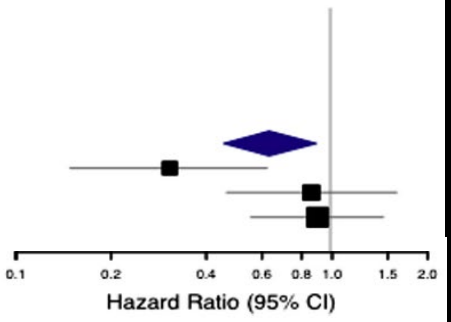
EXTRAPOLATION FROM HFpEF TRIALS

Mineralocorticoid Receptor Antagonists - Spironolactone

Primary Outcome: Composite of CV Death, HF hospitalization & Aborted SCD

TOPCAT
HF Hospitalization reduced by 17% compared with Placebo

Subgroup	Placebo No. of Events/Patients	Spironolactone No. of Events/Patients	Hazard Ratio (95% CI)	P Value for Interaction
BNP/NTBNP (n=687)				
Overall	**91/355 (25.6%)**	**57/332 (17.2%)**	**0.64 (0.46, 0.90)**	**0.017**
Tertile 1	30/117 (25.6%)	10/113 (8.8%)	0.31 (0.15, 0.63)	
Tertile 2	21/110 (19.1%)	19/120 (15.8%)	0.87 (0.47, 1.62)	
Tertile 3	40/128 (31.2%)	28/99 (28.3%)	0.91 (0.56, 1.47)	



Pitt et al. NEJM 2014;370(15):1383-1392.
Anand et al. JACC: HF 2017;5(4):241-252.

NON-MEDICATION TREATMENTS FOR OUTFLOW OBSTRUCTION

DO: Keep well-hydrated with water

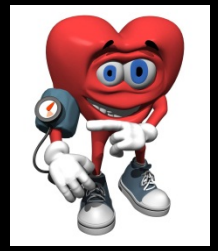
In Moderation:

- Caffeinated beverages

- Alcoholic beverages

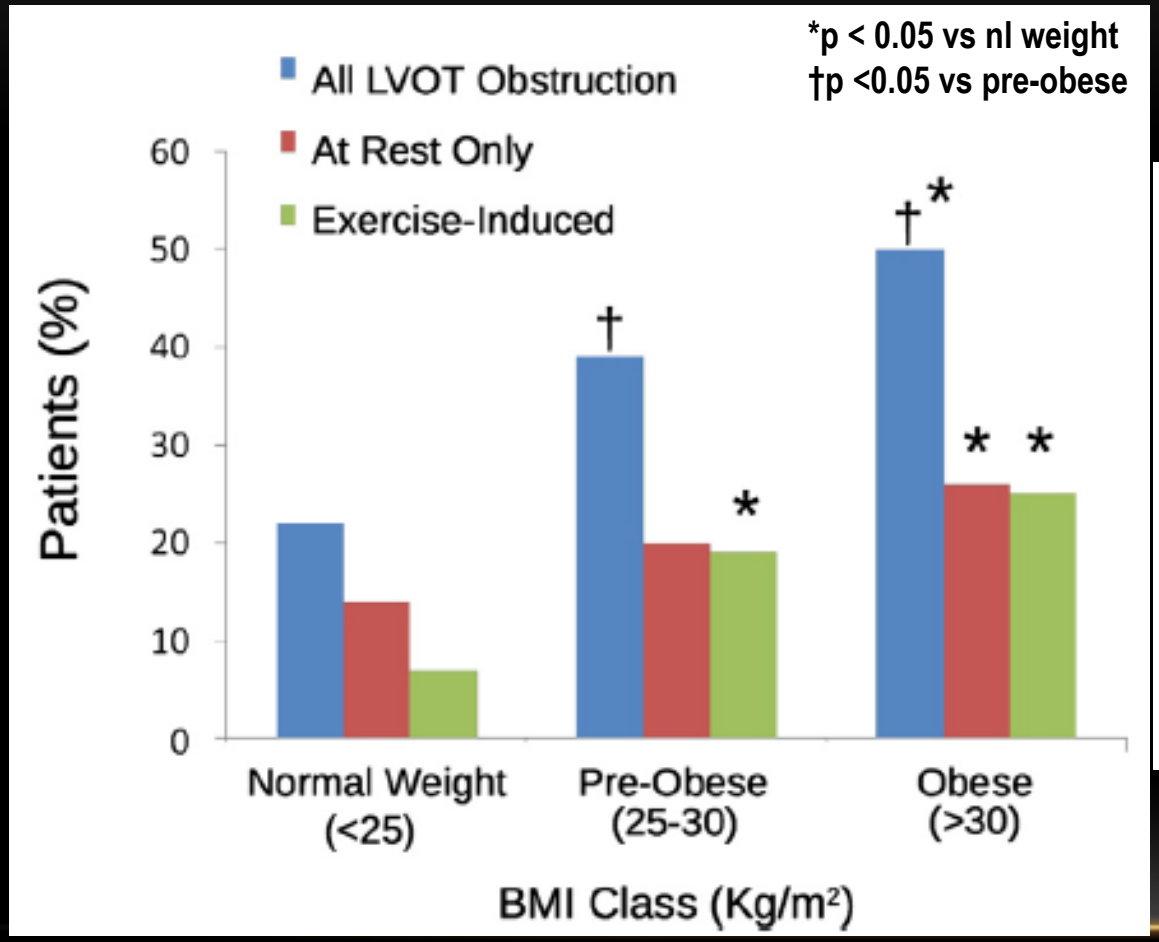
TREATMENT OF COMORBIDITIES THAT CAN EXACERBATE HCM FEATURES AND SYMPTOMS

- Control blood pressure – goal < 130/80 for most people
- Control diabetes
  - Both HTN and DM have been shown to be independent predictors of poor prognosis in HCM
- Treat OSA & CSA
  - Highly prevalent (~3/4 of HCM patients)
  - In HFpatients, CSA & OSA are independent risk factors for ventricular arrhythmias and appropriate ICD device therapies.

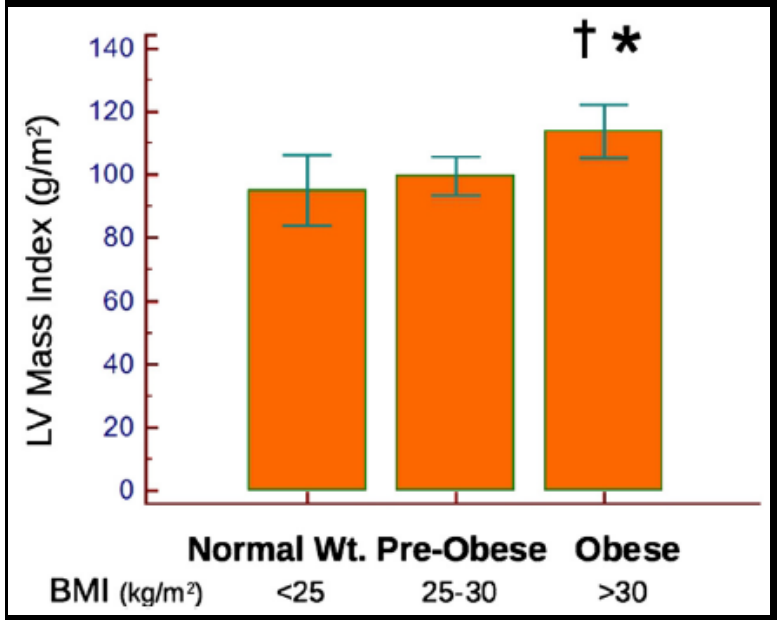


Eleid M et al. JACC. 2009;54:1805-9.
Bitter et al. Eur Heart J. 2011;32:61-74.

MANAGEMENT OF COMORBIDITIES: OBESITY



Only 25% of this study population were in the normal weight range (BMI ,25 kg/m^2)



Olivotto I et al. JACC 2013;62:449-57.

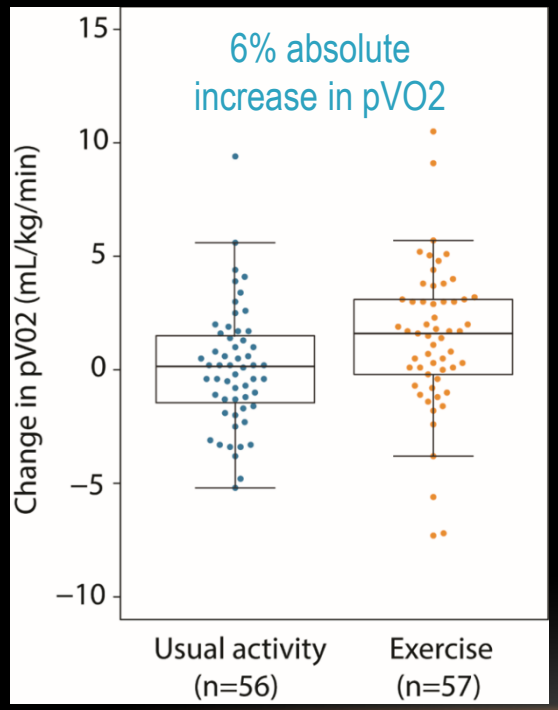
EXERCISE AS A MODE OF TREATMENT

RESET-HCM

136 patients with HCM randomized

- Usual Activity Group
- Exercise Group

16 weeks

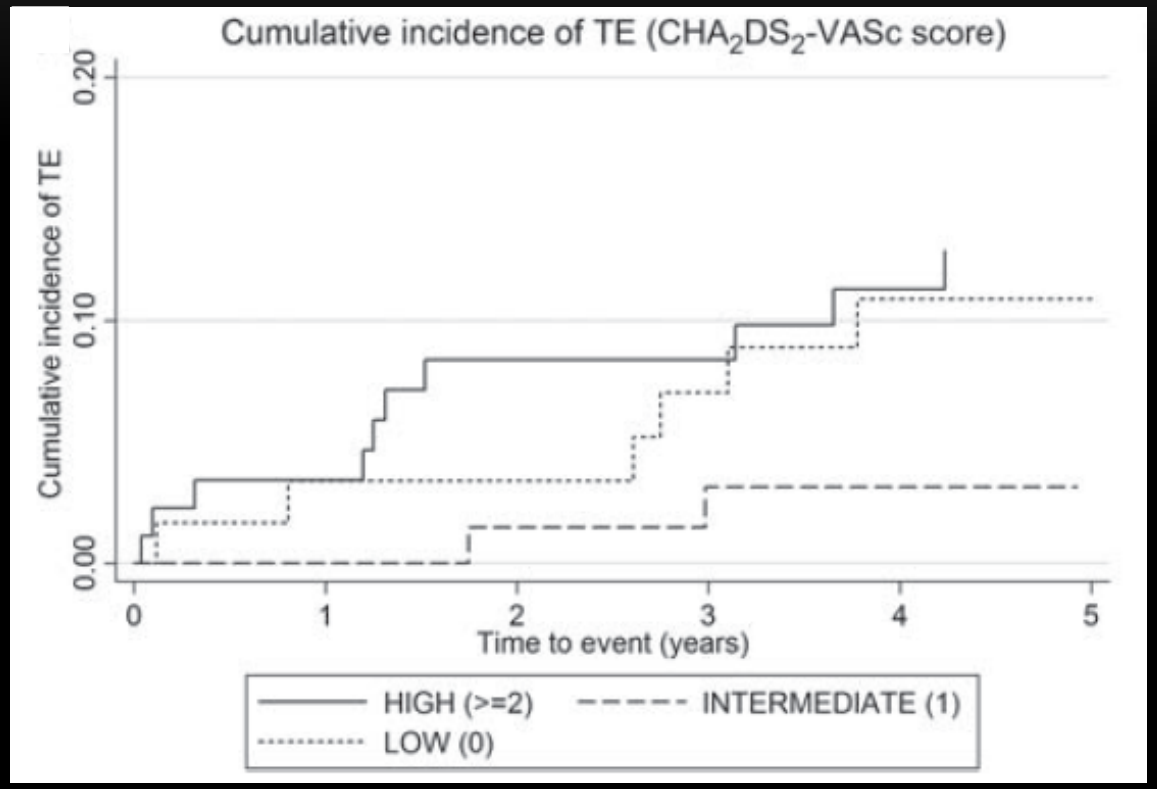


No major adverse events in either group. (death, aborted sudden cardiac death, appropriate ICD therapies, or sustained ventricular tachycardia)

Saberi S et al. JAMA 2017, April 4;317(13):1349-1357.

MANAGEMENT OF ATRIAL FIBRILLATION

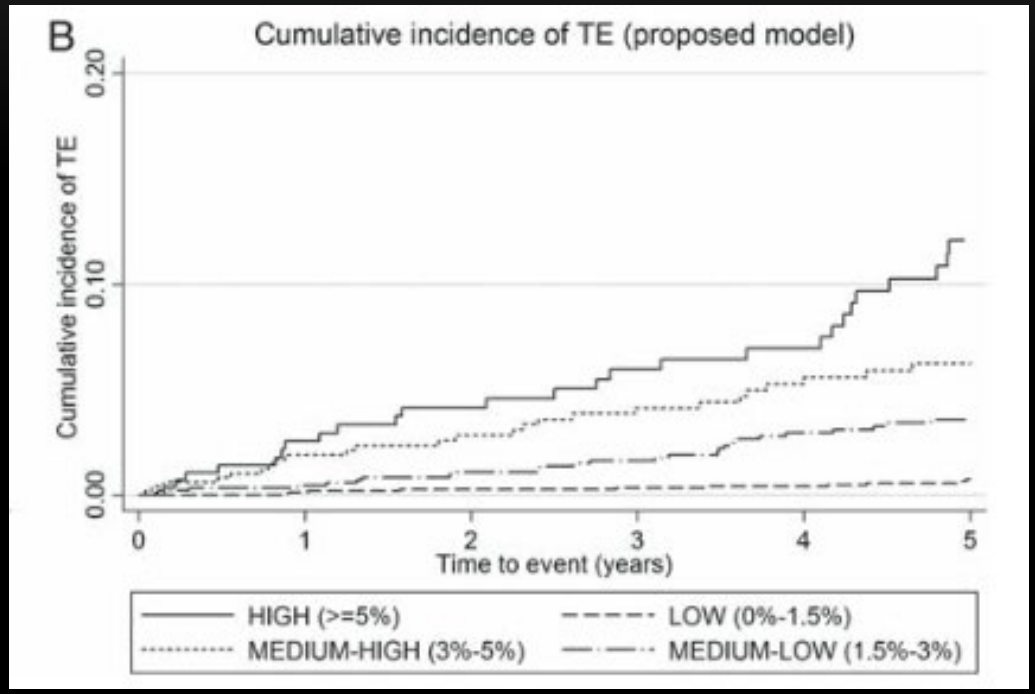
- Affects ~25% of HCM patients
  - 4-6x higher prevalence than general population
- ~2% annual stroke risk with anticoagulation vs ~10-12% without



CHADS-VASc performs poorly in HCM

Guttman et al., European Journal of Heart Failure 2015;17:837-845.

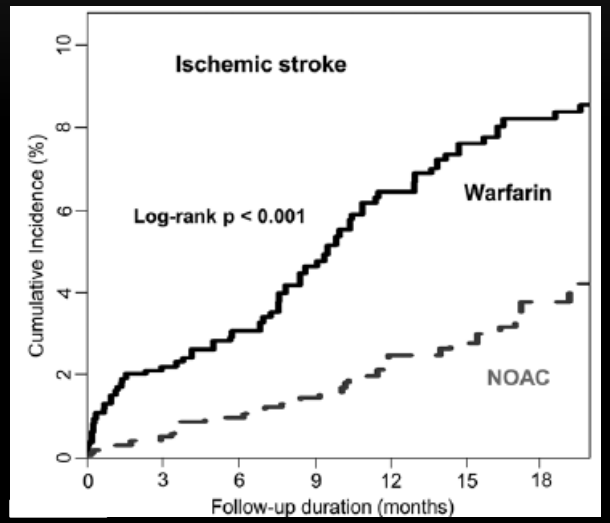
BETTER THROMBOEMBOLISM RISK PREDICTION IN HCM-ASSOCIATED ATRIAL FIBRILLATION

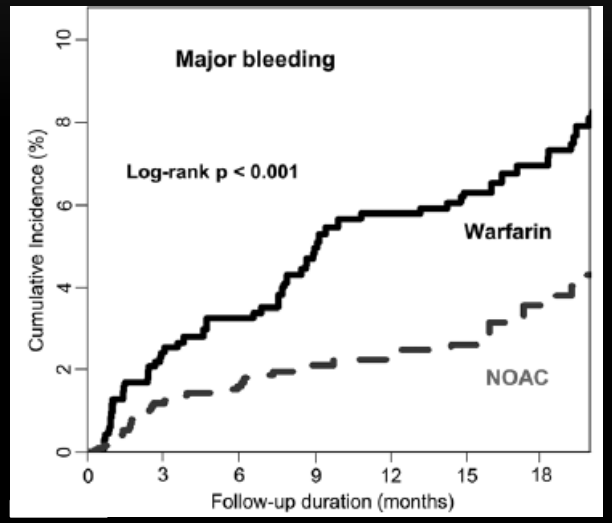


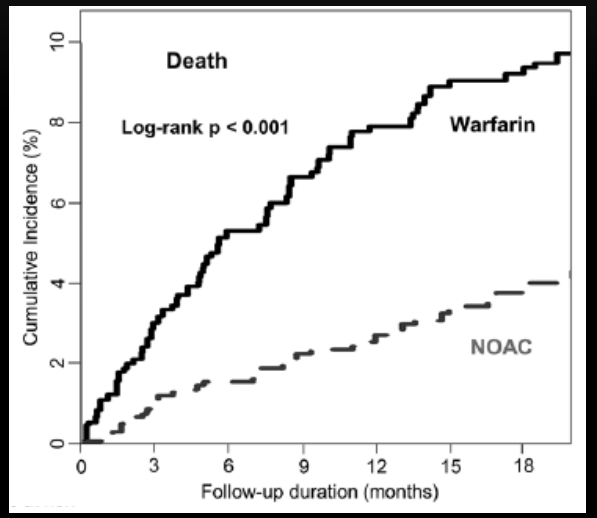
Composite of LA size, wall thickness, prior stroke/TIA, age, NYHA class discriminates risk

Guttman et al., European Journal of Heart Failure 2015;17:837-845.

ANTICOAGULATION IN ATRIAL FIBRILLATION





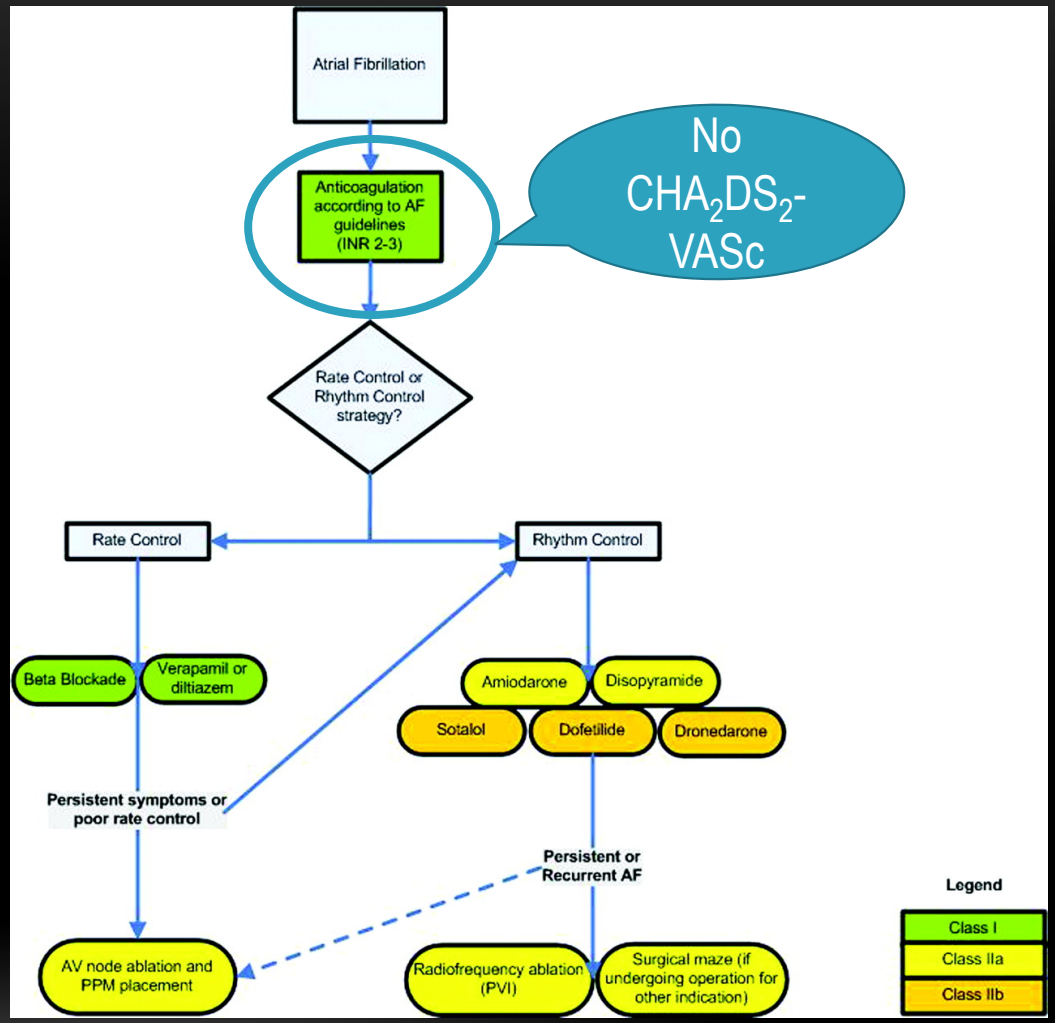


NOACs show superior effectiveness and safety compared with warfarin for primary prevention of stroke.

Lee et al., Stroke. 2019;50:2582-2586.

MANAGEMENT OF ATRIAL FIBRILLATION

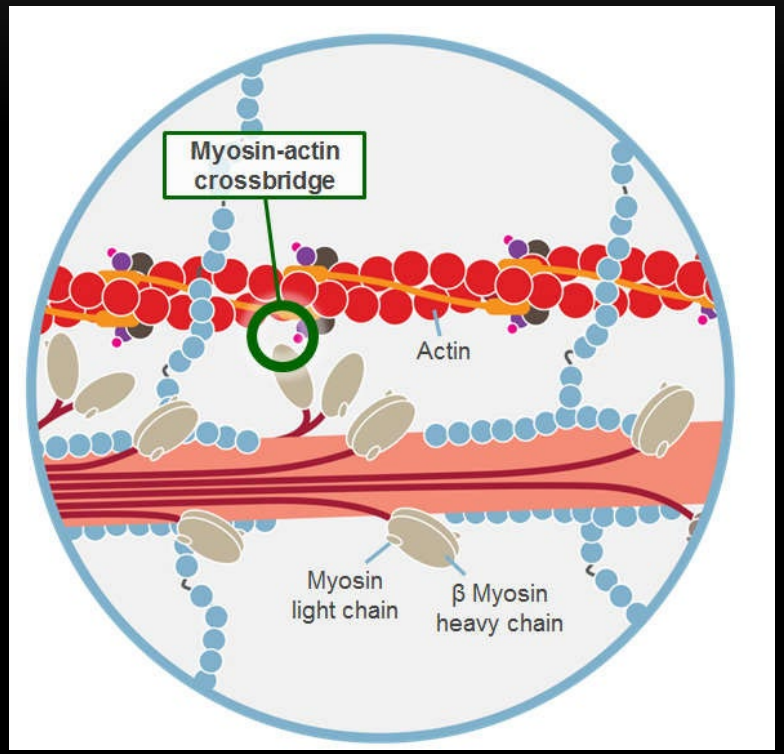
- Usually reflects more advanced stage of LV remodeling associated with increased LA pressure
- Often refractory, multiple ablations, frequent recurrence



Gersh et al. AHA/ACC guidelines, Circulation. 2011;124:e783-e831.

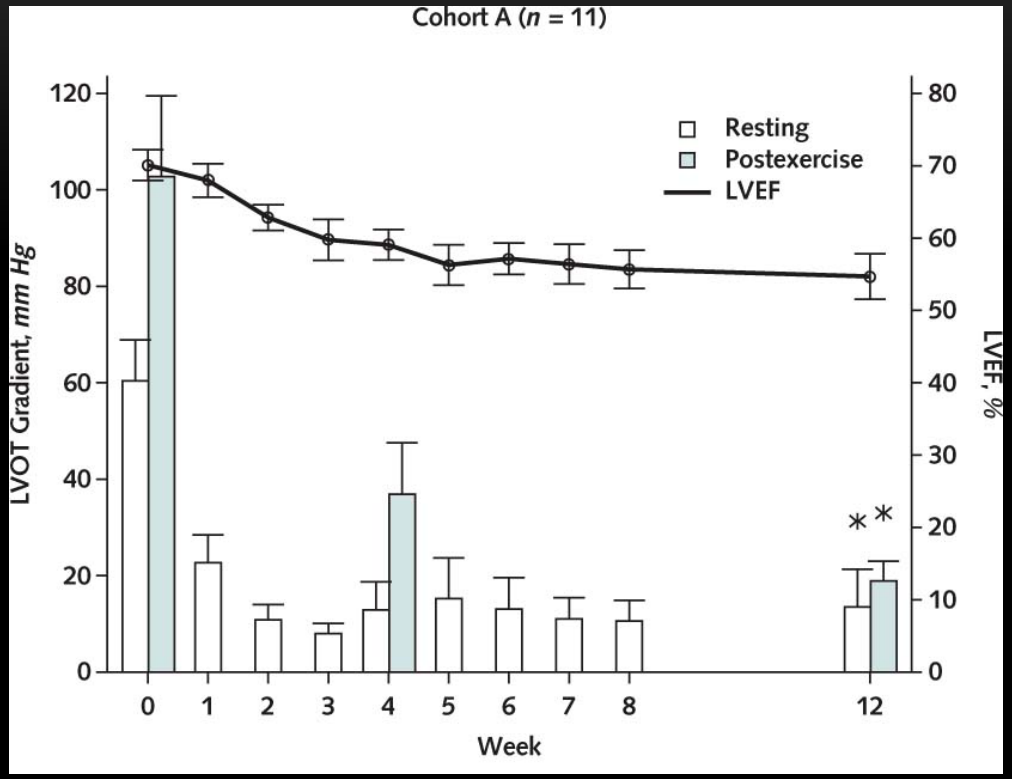
ON THE HORIZON: MAVACAMTEN (MYK-461)

- Mavacamten
  - Selective allosteric modulator of cardiac myosin ATPase
  - Stabilizes the motor in a non-force producing state
  - In HCM mutant mice, mavacamten prevented hypertrophy, reduced myocyte disarray & interstitial fibrosis compared with placebo



Green et al. Science 2016;351:617-621.

PIONEER-HCM



Dose-dependent improvement in degree of outflow obstruction and NYHA class.

Heitner et al. Ann Intern Med. 2019. doi:10.7326/M18-3016.

MAVACAMTEN

MAVERICK-HCM

- Phase 2 Double Blind RCT of Mavacamten in symptomatic non-obstructive HCM with preserved LVEF
  - 16-week course, 3 arms (low-dose, high-dose, placebo)
- 35 US sites, 60 participants, completed enrollment April 2019
- Primary Outcome: Frequency & severity of treatment-emergent adverse & serious events
- Expect results mid-2020

EXPLORER-HCM

- Phase 3 Double Blind RCT of Mavacamten in symptomatic obstructive HCM with preserved LVEF
  - 30-week course of mavacamten vs placebo
- 76 international sites (34 US), 251 participants, completed enrollment August 2019
- Primary Outcome: Effect on clinical response
  - Improvement in NYHA class + improved peak VO2 by at least 1.5 mL/min/kg
  - No worsening in NYHA class + improved peak VO2 by at least 3 mL/min/kg

ON THE HORIZON:CK-3773274

- Another cardiac myosin inhibitor
- Phase I, double-blind RCT to assess safety and tolerability among healthy participants is complete
  - Safe, well-tolerated
  - Exposure-dependent decrease in LVEF
  - No serious adverse events
  - Shallow exposure-response relationship may enable more flexible dosing than mavacamten
- Phase 2 trial in symptomatic obstructive HCM to start by end of 2019

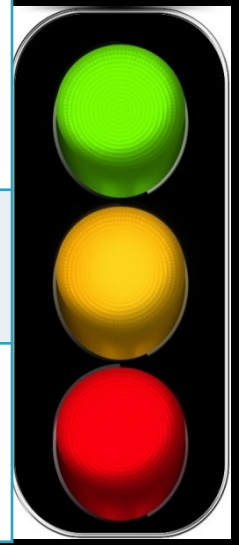
HOW MIGHT THE DIAGNOSIS OF HCM AFFECT EMPLOYMENT?

- Occupational Restrictions
  - Federal Aviation Administration – commercial pilot license
  - Department of Transportation – commercial motor vehicle drivers license
- Individualized Decision Making
  - Law enforcement
  - Emergency response personnel
  - Construction
  - Assembly line, loading dock, delivery

RISK OF PREGNANCY

Modified World Health Organization classification of maternal cardiovascular risk

Risk Class	Risk of pregnancy	Application to HCM
I	**No detectable increased risk** of maternal death or complication	
II	**Small increased risk** of maternal death or complication	**Most women with HCM:** mild to moderate obstruction; asymptomatic, well-controlled arrhythmia, EF > 45%
III	**Significantly increased risk** of maternal death or complication	Severe obstruction, symptoms or arrhythmias, moderate LV dysfunction
IV	**Extremely high risk** of maternal death or severe complication; **pregnancy contraindicated**	EF < 30%, severe symptomatic obstruction, decompensated heart failure, severe pulmonary hypertension



Thorne et al. Heart 2006;92:1520-1525.