Optimal pharmacological management of HCM by clinical manifestations

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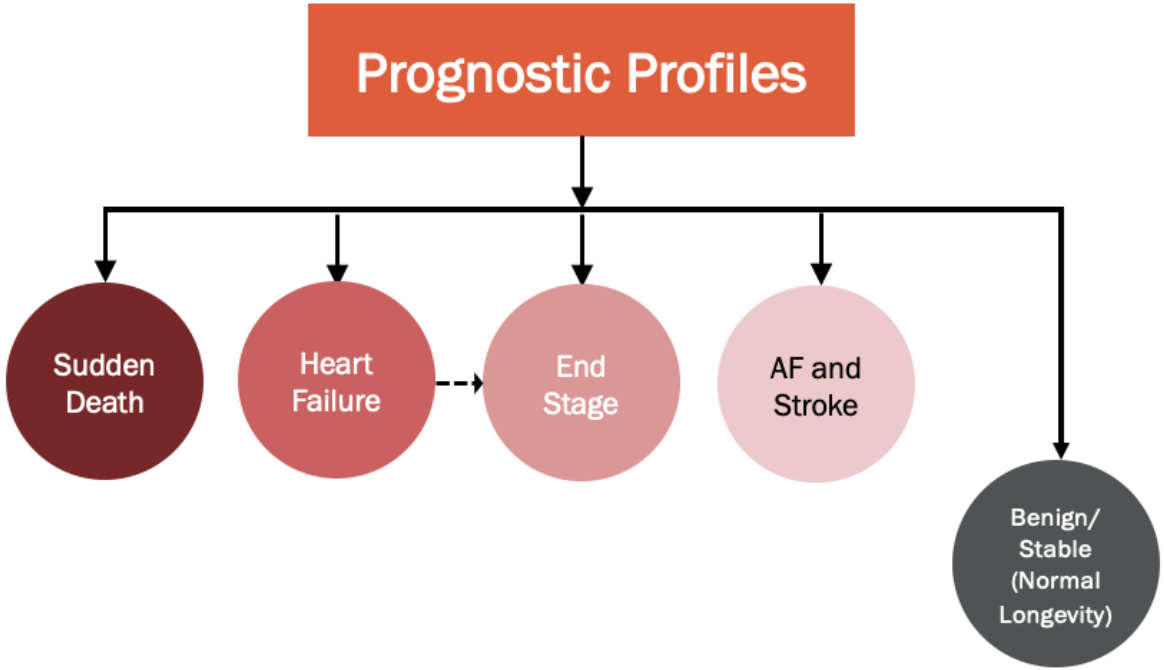
Declaration of interest

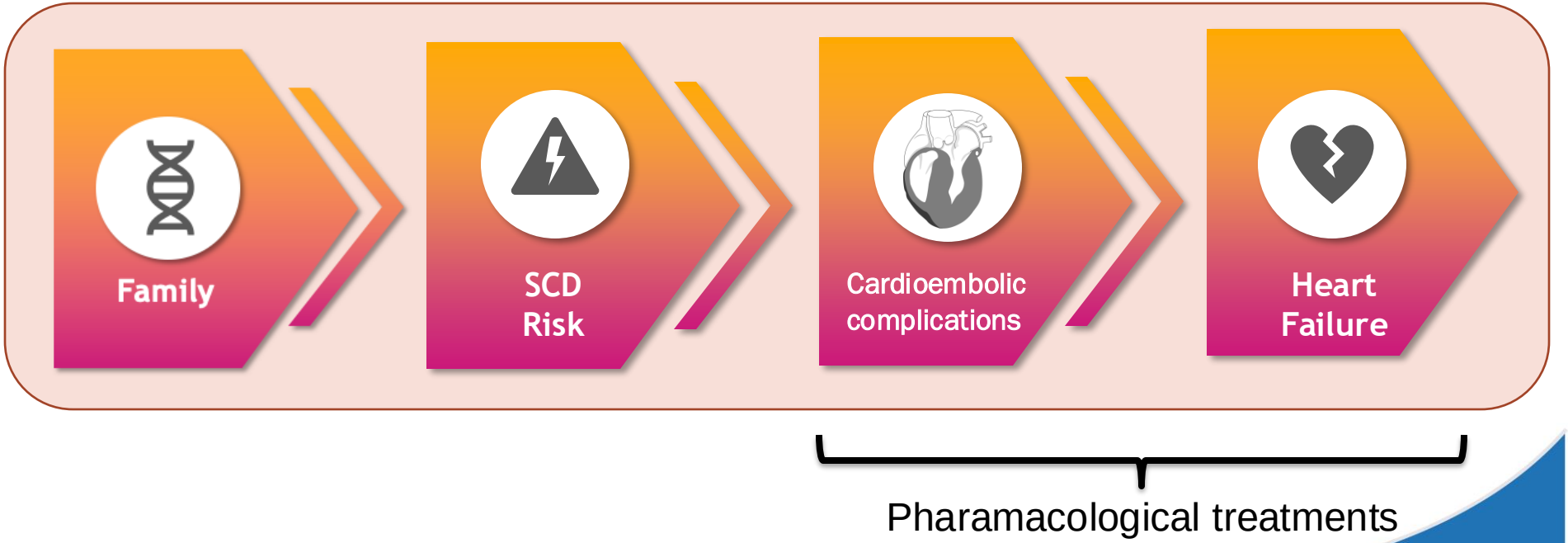
- Speaking fees from BMS
- Consulting fees from Cytokinetics and BMS.
- Clinical Trial support from Cytokinetics and BMS.

HCM Clinical Course

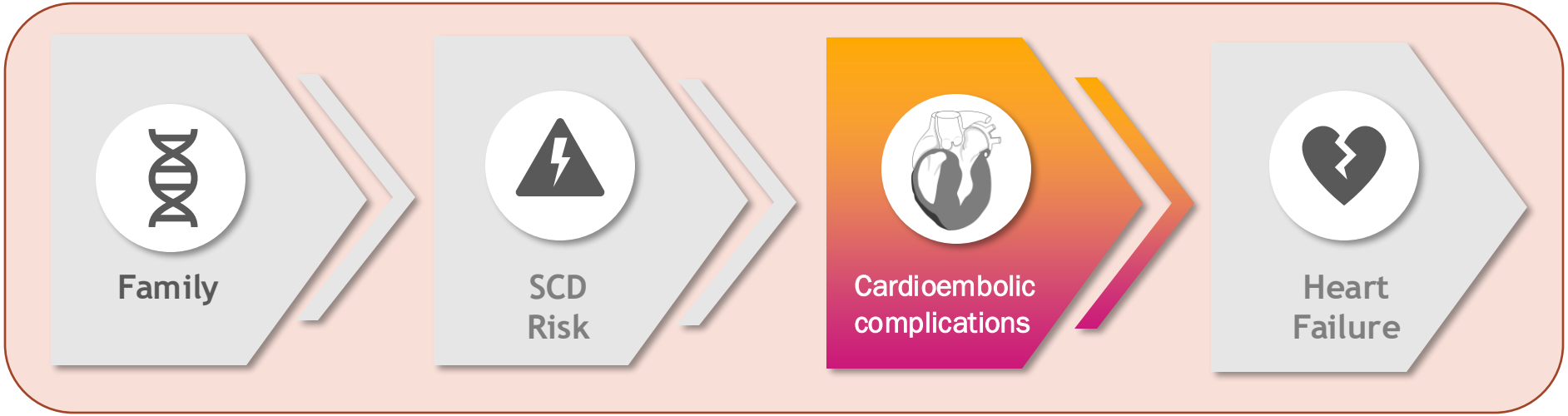


Gersh et al. Circulation 2011;124:2761-96

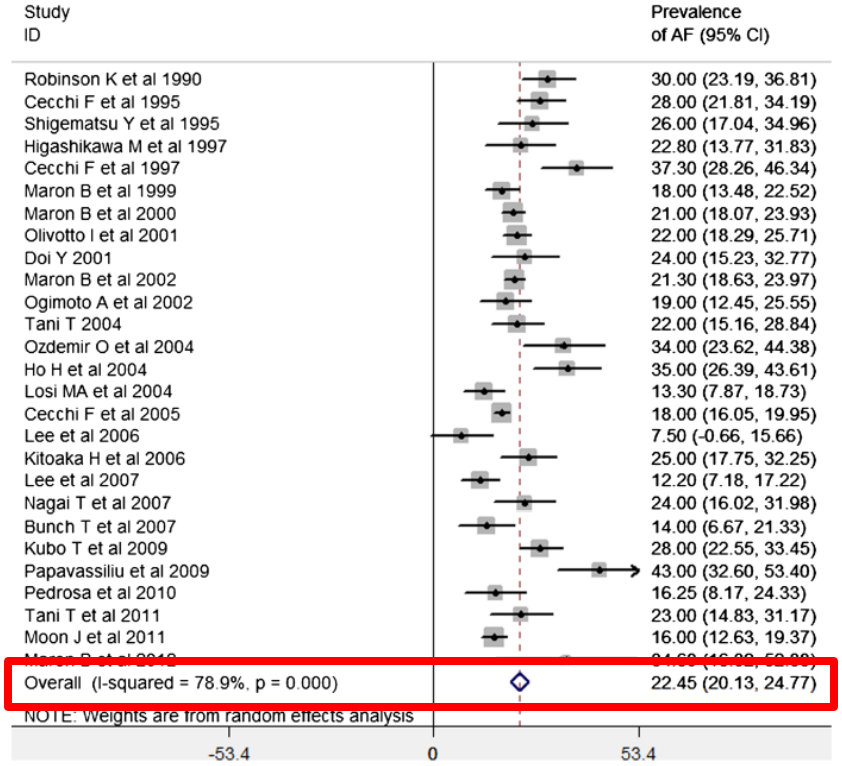
What to look for in a patient with HCM?



What to look for in a patient with HCM?



Atrial Fibrillation



Guttmann OP et al. Heart 2014;100:465-72

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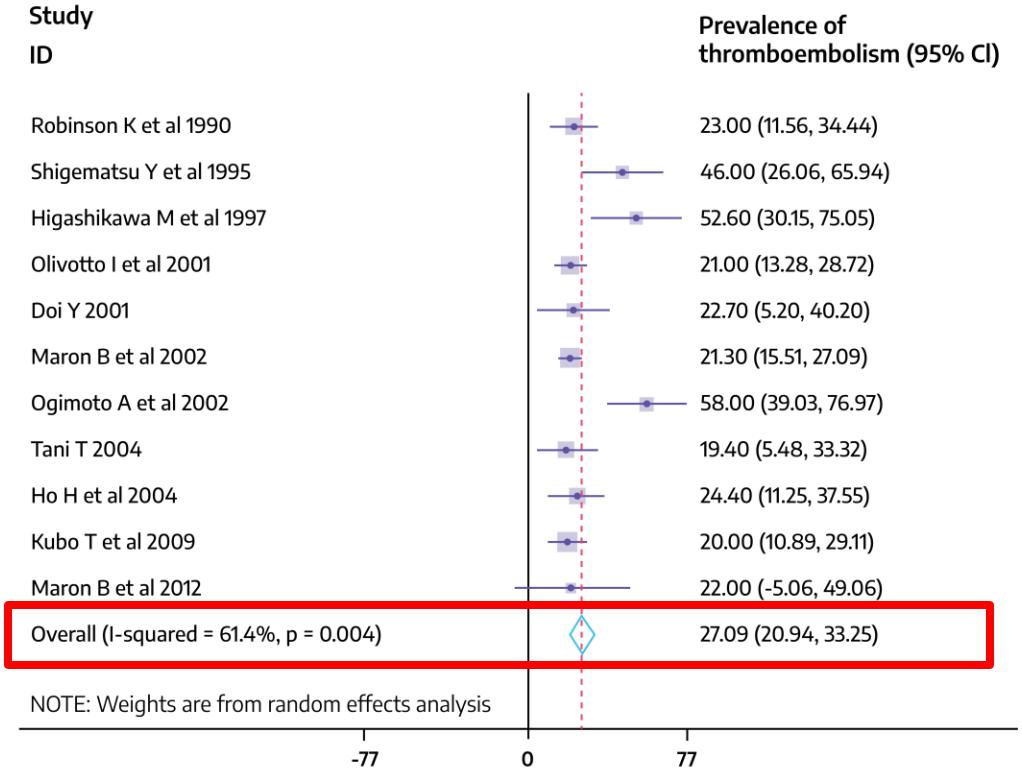
Embolic risk



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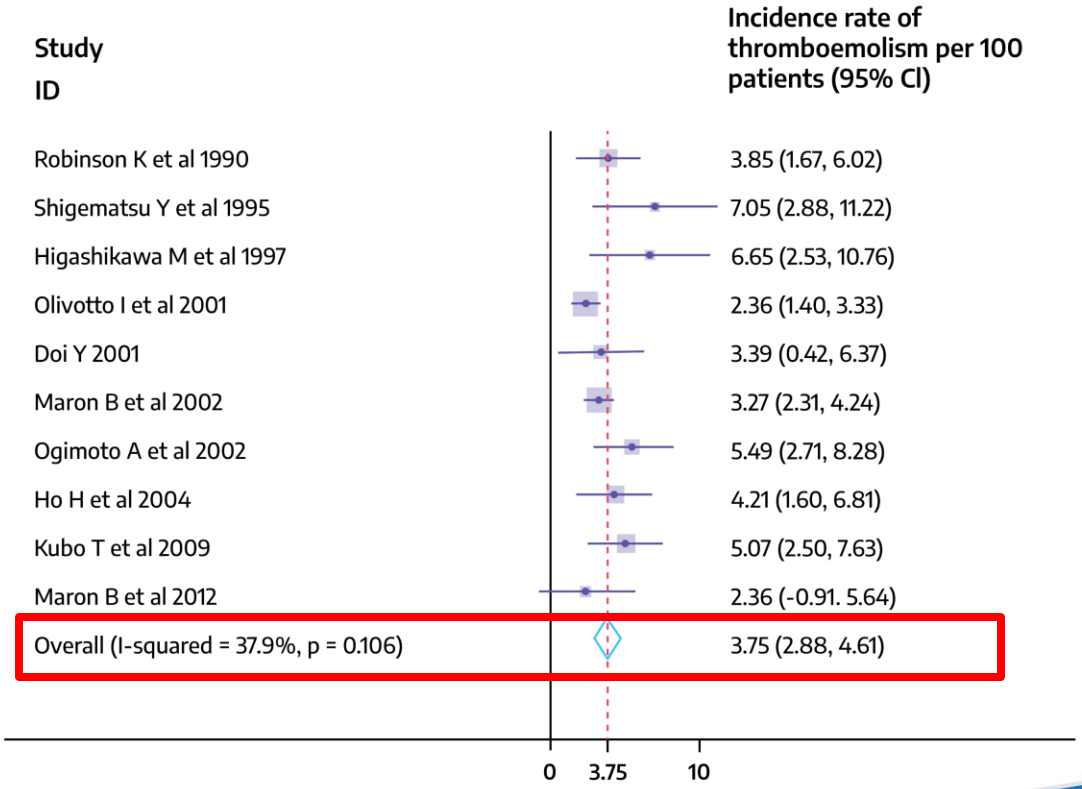


Guttmann OP et al. Heart 2014;100:465-72

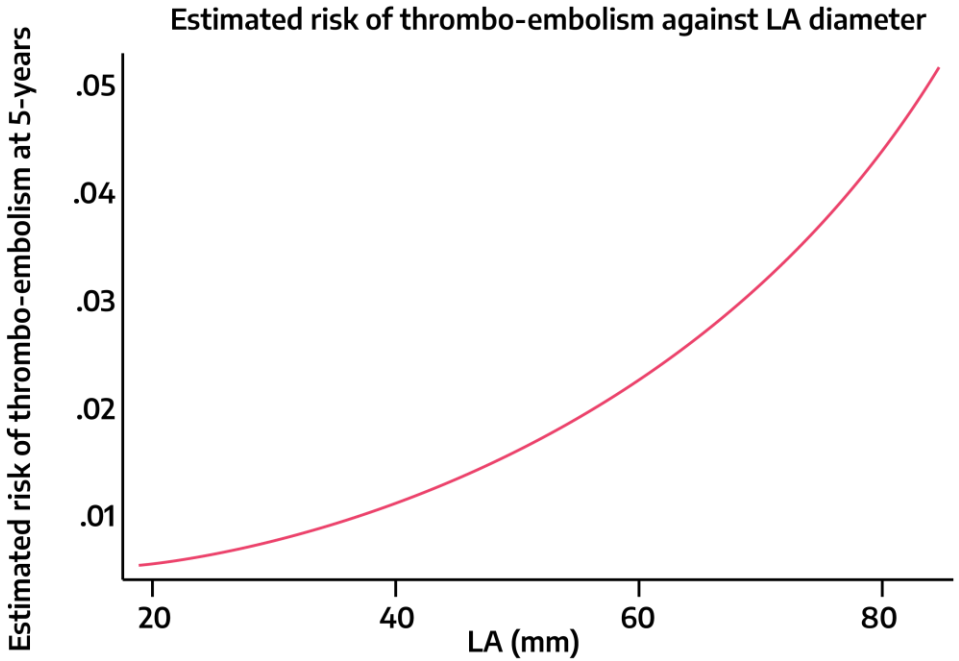
CHA_2DS_2-VASC score should not be used in HCM patients

CHA_2DS_2-VASc score does not appear to correlate well with the clinical outcome in patients with HCM and **should not be used to assess TE risk in this population**

LA size, is associated with thromboembolic complications

Guttman et al., *Eur J Heart Fail*. 2015;17(8):837–845.

Relationship between risk of thrombo-embolism and left-atrial size



Relationship appears linear up to ~45–50 mm, at which point the risk of TE rises exponentially with increasing LA diameter

Guttman et al., *Eur J Heart Fail*. 2015;17(8):837–845.

Anticoagulation in atrial fibrillation in HCM

	Doi & Kitaoka[1]	Maron et al.[2]	Olivotto et al.[3]	Guttman et al.[4]
Drug	Warfarin	Warfarin	Warfarin	Vitamin K antagonist
Patients	91	900	480	4821
% AF anticoagulated	45%	43.2%	55.1%	100%
Rate embolism	42% vs 10%	31% vs 18%	39% vs 10%	12% vs 7%

1. Doi & Kitaoka. *J Cardiol* 2001;37:133-138. **2.** Maron et al., *JACC* 2002;39:301-307. **3.** Olivotto et al., *Circulation.* 2001;104:2517–2524.
4. Guttman et al., *Eur J Heart Fail*. 2015;17(8):837–845.

Types of anticoagulation therapy for stroke prophylaxis

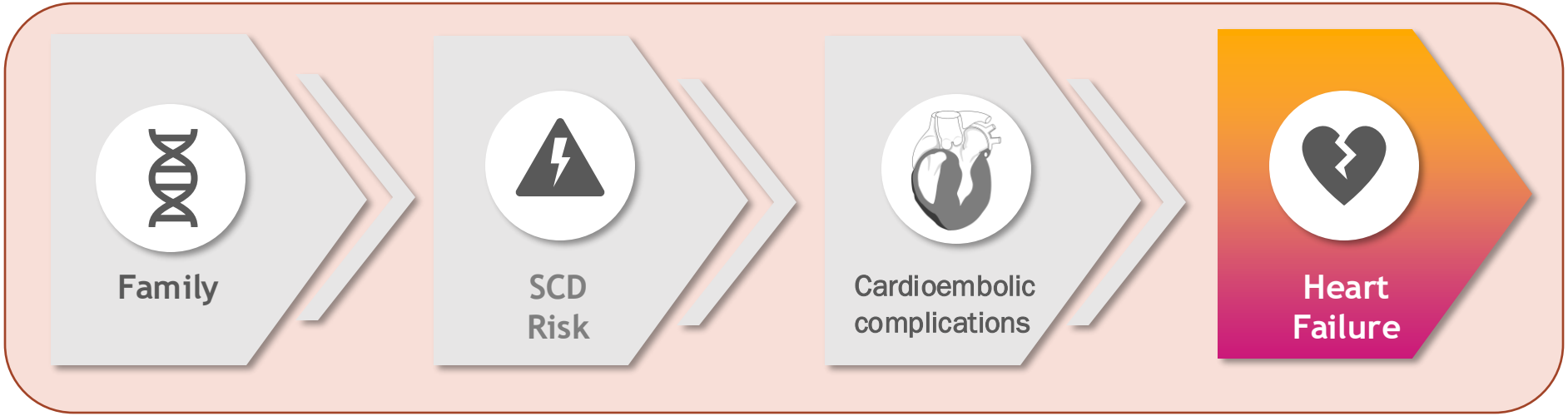
Direct oral anticoagulants

Vitamin K antagonists

- Initial evidence supports DOACs being at least equal to VKA management with a higher treatment satisfaction among patients[1]
- No difference in efficacy to date[1]
- Risk of all-cause death can be significantly reduced in patients with AF and HCM treated with DOACs than those who received VKA[2]
    - Risk of ischaemic stroke, major bleeding and intracranial bleeding not significantly different[2]

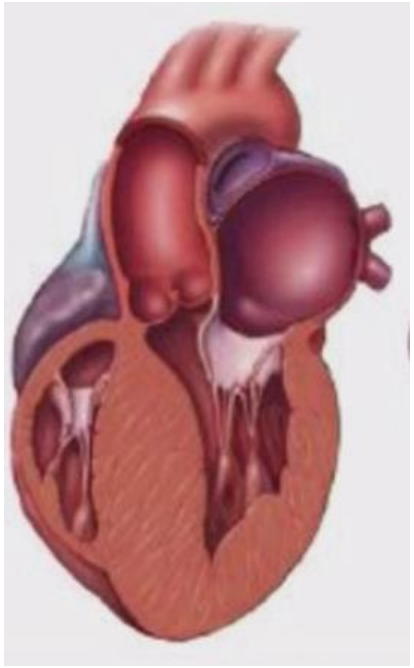
1. Dominguez et al. *Int J Cardiol*. 2017;248:232–238. **2.** Rujirachun et al., *Acta Cardiol*. 2020;75(8):724–731.

What to look for in a patient with HCM?



HF symptoms

Non-obstructive

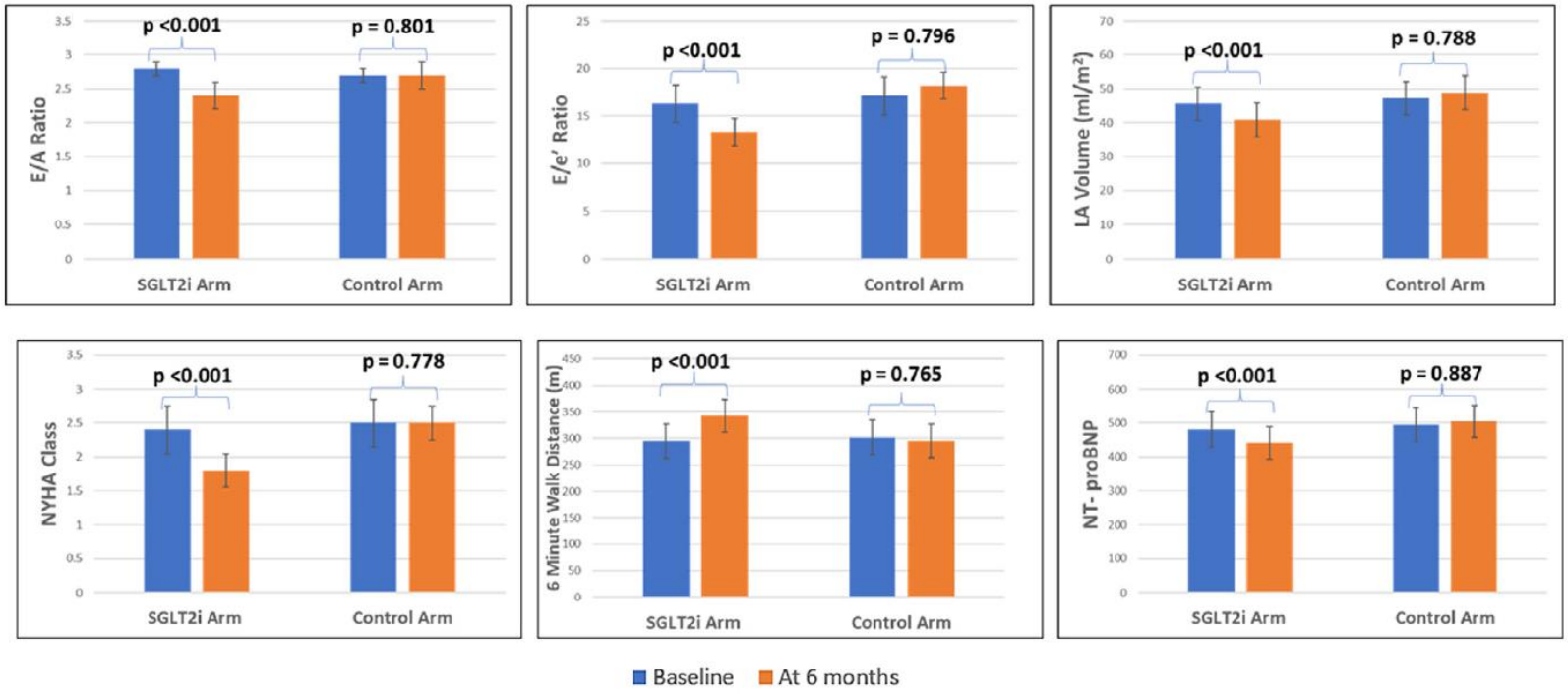


Obstructive

Pharmacological Therapies in non-obstructive HCM

- Diuretics
- Rhythm control
- Rate control: BB, Verapamil-Diltiazem, digoxin.

Observational study of non-obs HCM with diabetes treated with iSGLT2 or not (48 patients)



Subramanian et al. Am J Cardiol 2023

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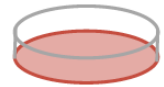
hiPSC-CM models with HCM mutations in *MYH7 and TNNT2*



2D cell culture

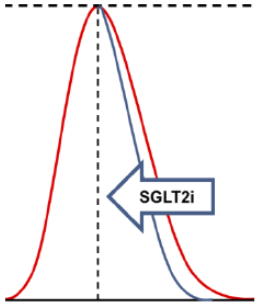
3D cell culture
engineered heart tissue

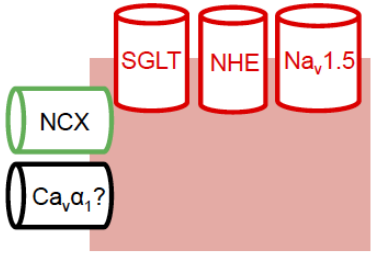
Mimick early HCM
- Impaired relaxation
- Hypercontractility

Acute SGLT2i
alter Ca^{2+} handling

SGLT2i enhance relaxation

Canagliflozin > Dapagliflozin > Empagliflozin
Long > short culture duration
HCM > control

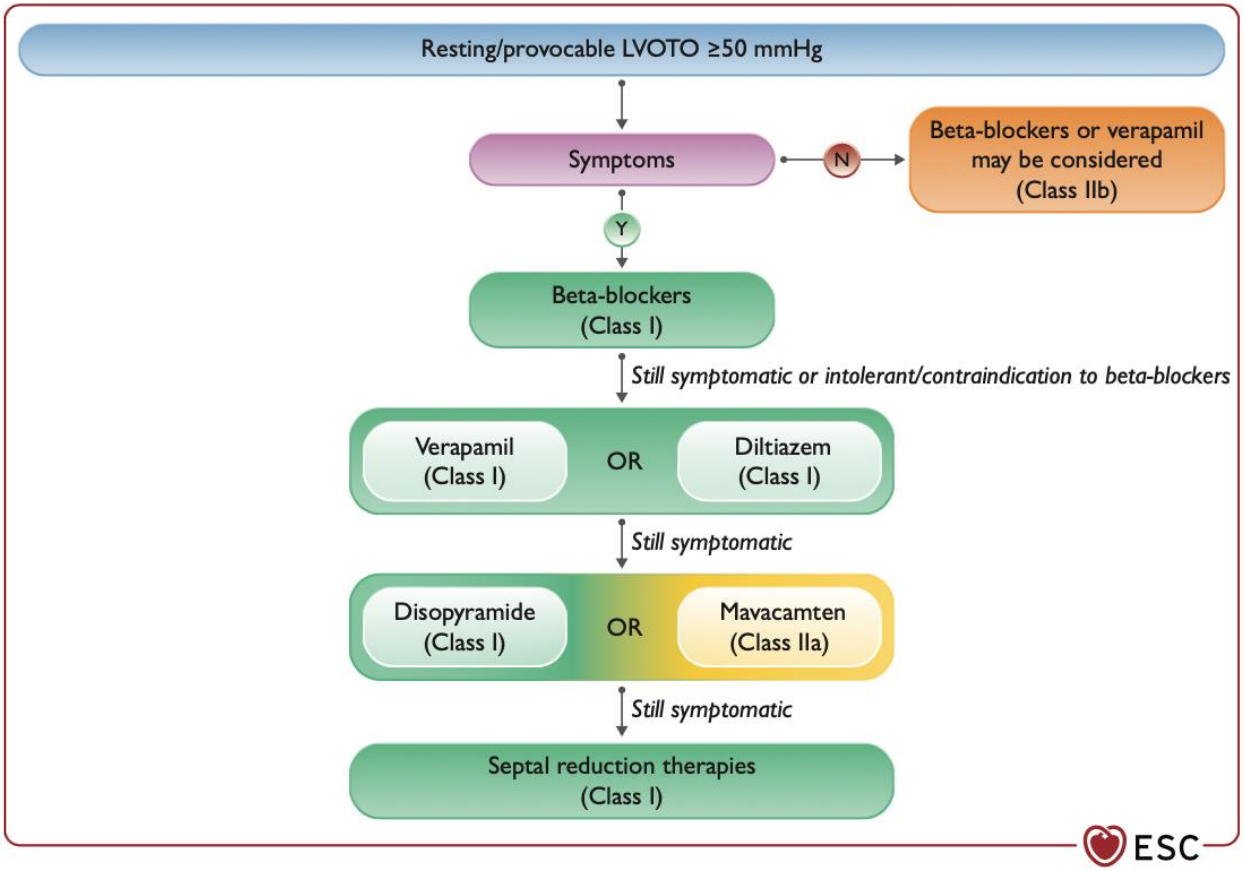




Wijnker et al. Cardiovasc Res 2024

Pharmacological Therapies in oHCM

- Beta-Blockers
- Verapamil-Diltiazem
- Dysopiramide
- Cardiac Myosin Inhibitors



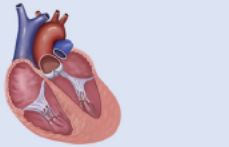
Arbelo et al.
Eur Heart J 2023

Metoprolol in oHCM

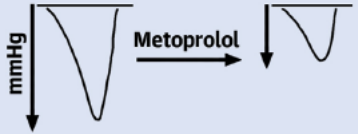
Design
Randomized Controlled Crossover Trial in 29 Patients with Obstructive Hypertrophic Cardiomyopathy

Effect of 14 Days of Metoprolol Treatment

Lower LVOT Gradients at Rest, Peak, and Post-Exercise

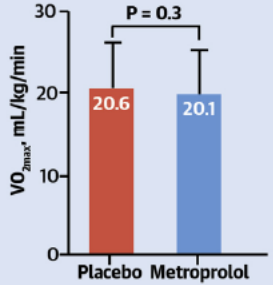


LVOT Gradients



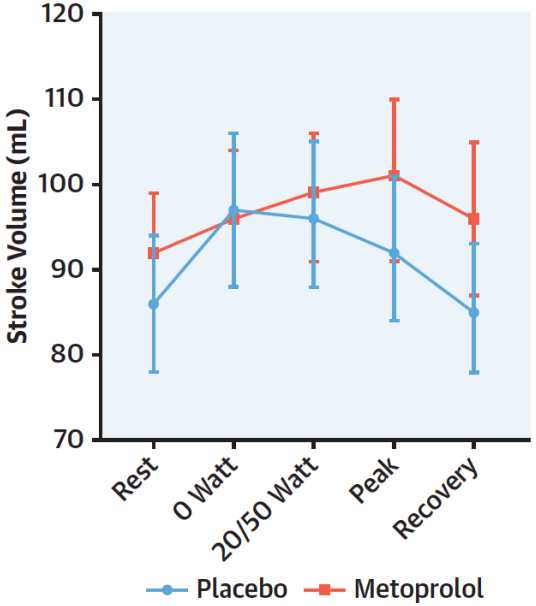
Reduce Degree of Exertional Dyspnea and Angina

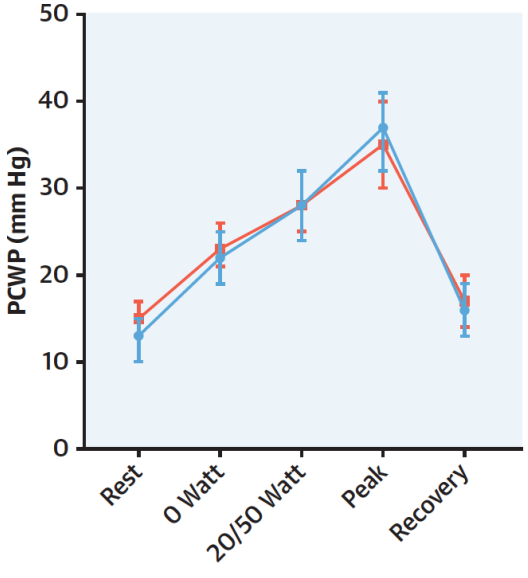
No Change in Maximum Exercise Capacity

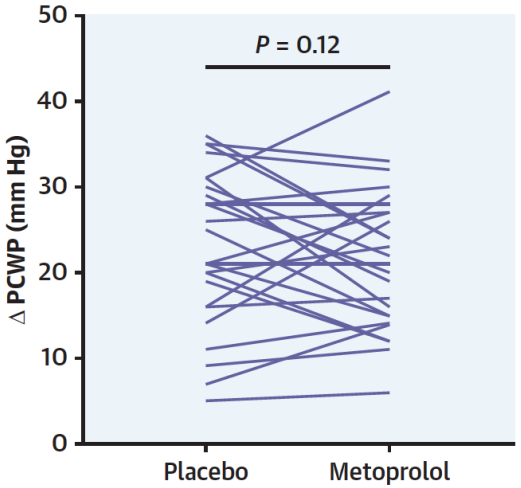


Dybro MA et al. JACC 2021

Metoprolol in oHCM

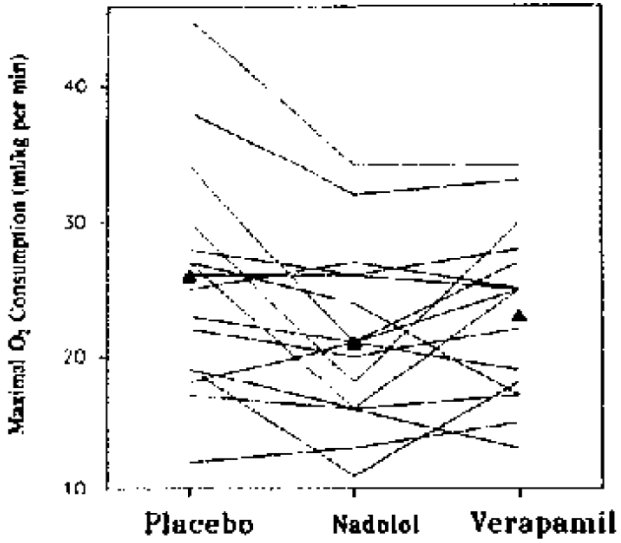






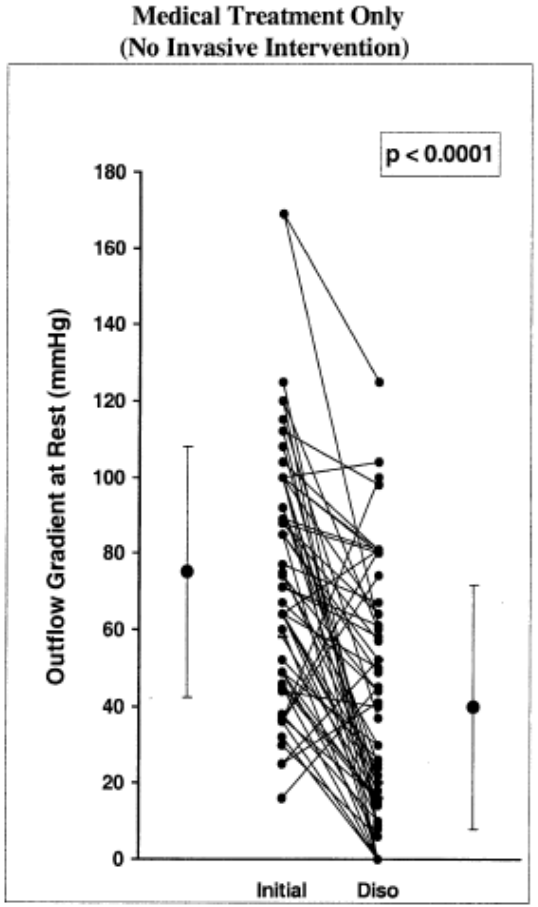
Dybro MA et al. JACC 2022

Verapamil in oHCM



16 patients
8 with LVOT grad >30 mmHg
2 with grad >50 mmHg

Guilligan et al. JACC 1993



QT prolongation
Anticholinergic side-effects
Tachyfilaxia
Periodic distribution shortage

Sherrid MV et al.
JACC 2005;45:1251-8

Allosteric modulators of Myosin ATPase

Mavacamten

Phase II
Obstructive HCM
PIONEER-HCM

Phase II
Non-Obstructive HCM
MAVERICK-HCM

Phase III
Obstructive HCM
EXPLORER-HCM

Phase III
Obstructive HCM
Valor-HCM

Phase III
Non-Obstructive HCM
ODYSSEY-HCM

Aficamten

Phase II
Obst/Non Obst HCM
REDWOOD HCM

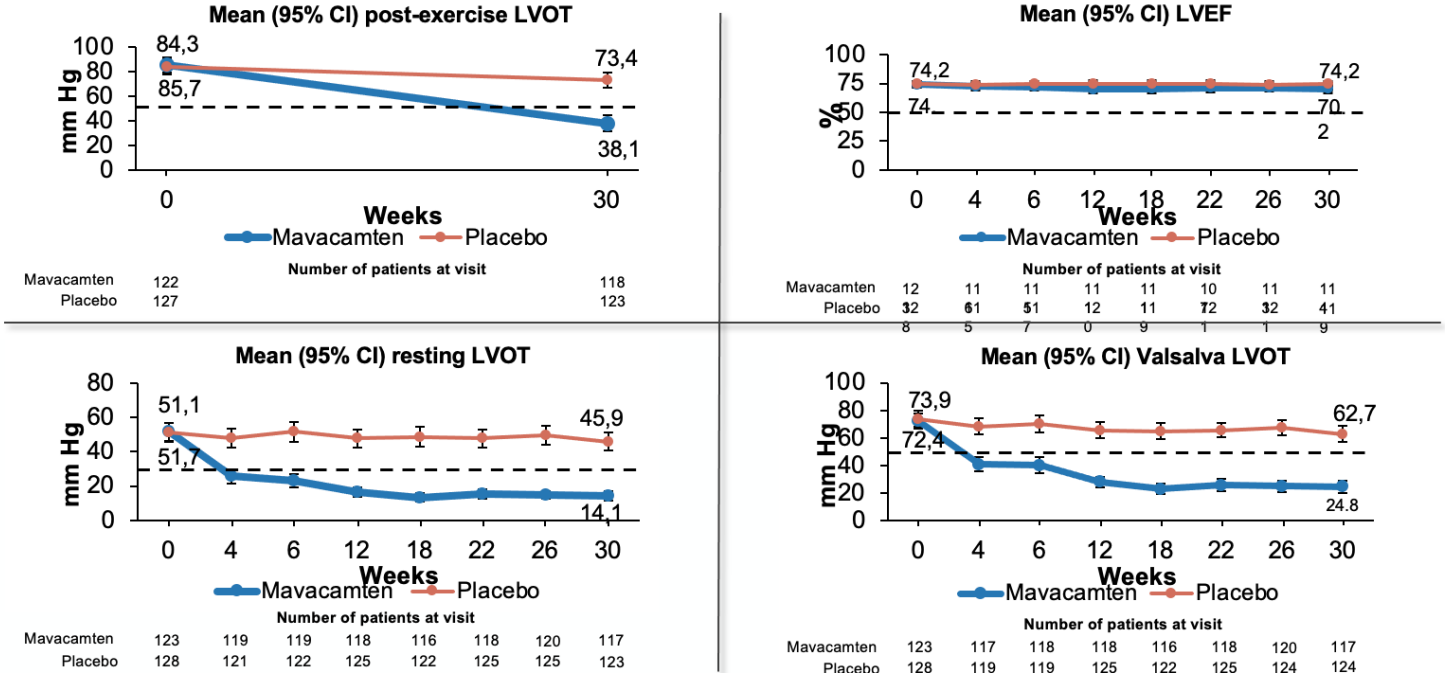
Phase III
Obstructive HCM
SEQUOIA HCM

Phase III
Obstructive HCM
(vs B-Block)
MAPLE HCM

Phase III
Non-Obstructive HCM
ACACIA HCM

Completed | Ongoing | Coming Soon

Mavacamten and LVOT Gradients and LVEF



Olivotto et al. Lancet 2020; 396:759-69

Conclusions

Pharmacological treatment of HCM is used to prevent thromboembolic complications and treat heart failure symptoms.

Diuretics and rate-limiting medications are used in patients with non-obstructive HCM

Medical treatment of obstructive HCM would probably change with progressive incorporation of myosin inhibitors.

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