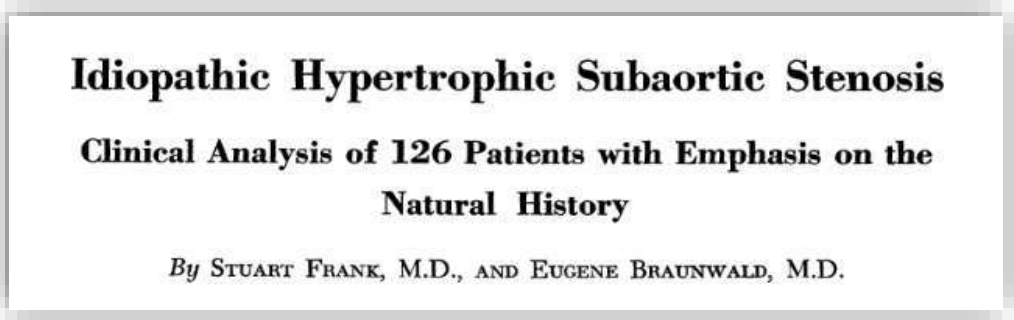
Hypertrophic cardiomyopathy: clinic predictors and outcome

Fuad Samadov

Master Course in Heart Failure

30 May – 01 June 2025

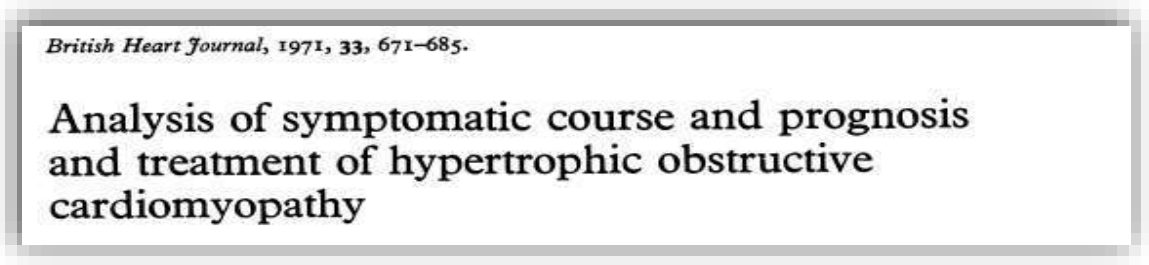
HCM is an unrelenting and malignant disease with few effective treatment options...



Idiopathic Hypertrophic Subaortic Stenosis

Clinical Analysis of 126 Patients with Emphasis on the Natural History

By Stuart Frank, M.D., and Eugene Braunwald, M.D.



British Heart Journal, 1971, 33, 671–685.

Analysis of symptomatic course and prognosis and treatment of hypertrophic obstructive cardiomyopathy

- In 1968, the Braunwald group at the National Institutes of Health described the natural history of a large (at that time) population of 126 patients with IHSS.
- During a mean FU of about 3 years, 10 patients died, 6 of SCD and 4 due to progressive heart failure.

- the Goodwin group at the Hammersmith Hospital published a study on the clinical course and prognosis of 85 patients with HCM.
- In the analysis of a 4-years FU, 12 patients died, 6 of SCD (mean age at death of 25 years) and 6 after surgery (myectomy);
- 12 patients experienced worsening of symptoms with progression to advanced NYHA functional class III/IV.

At this time, HCM is viewed as an ominous disease with an unfavourable prognosis and with an annual mortality 4-6%.

Frank S, Braunwald E. Circulation 1968;37:759–788.
Swan DA, et al. Br Heart J 1971;33:671–685.

A few years later…

1970s

- Introduction of echocardiography
- Diagnostic definition of the disease changes
- Many non-obstructive forms of HCM were identified
- The term HISS was replaced with HCM

New patients cohort are assembled, however still from referral centres.

1989

- Spirito et al. actually challenged the prognostic paradigm of HCM.
- Compared clinical course of HCM in 78 studies published in the last 5 years vs 25 pts from their center.
- 4.4 years of FU – none of 25 pts died or deteriorated
- The authors underlined that 73% of pts reported in the literature came from only two referral centres

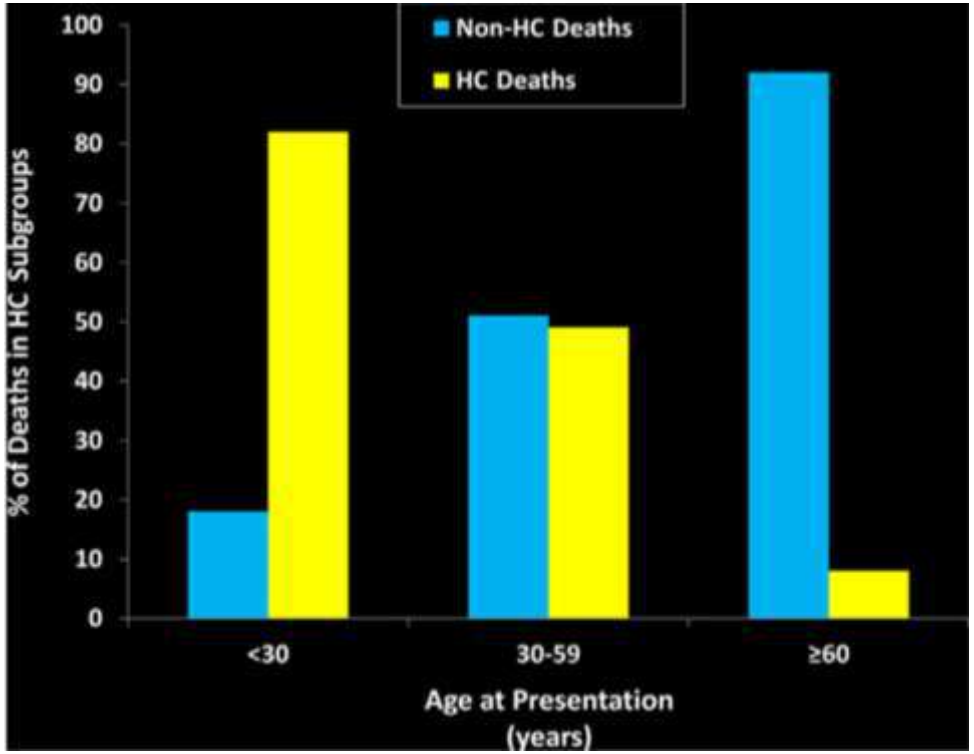
Conclusion of the study:

'The natural history of hypertrophic cardiomyopathy may be more benign than can be deduced from published studies'.

What do patients with HCM die from?

- 1,902 consecutive HCM patients (1992-2013)
- 2 HC referral centers, Minneapolis Heart Institute and Tufts Medical Center.
- 249 patients (13%) have died during 6.6 ± 5.3 years of FU
- Most deaths (72%) were unrelated to HC, cancer and predominantly in older pts.
- only 25% of pts with HC died of their disease, including predominantly those who were <30 years of age.

			Mortality		
Age at Presentation (years)	No. Patients	Survived	All Deaths	Died Non-HC	Died HC
<30	474	452 (95%)	22 (5%)	4/22 (18%)	18/22 (82%)
30-59	1000	918 (92%)	82 (8%)	42/82 (51%)	40/82 (49%)
≥60	428	283 (66%)	145 (34%)	132/145 (92%)	13/145 (8%)
Totals	1902	1653 (87%)*	249 (13%)	178/249 (72%)	71/249 (28%)



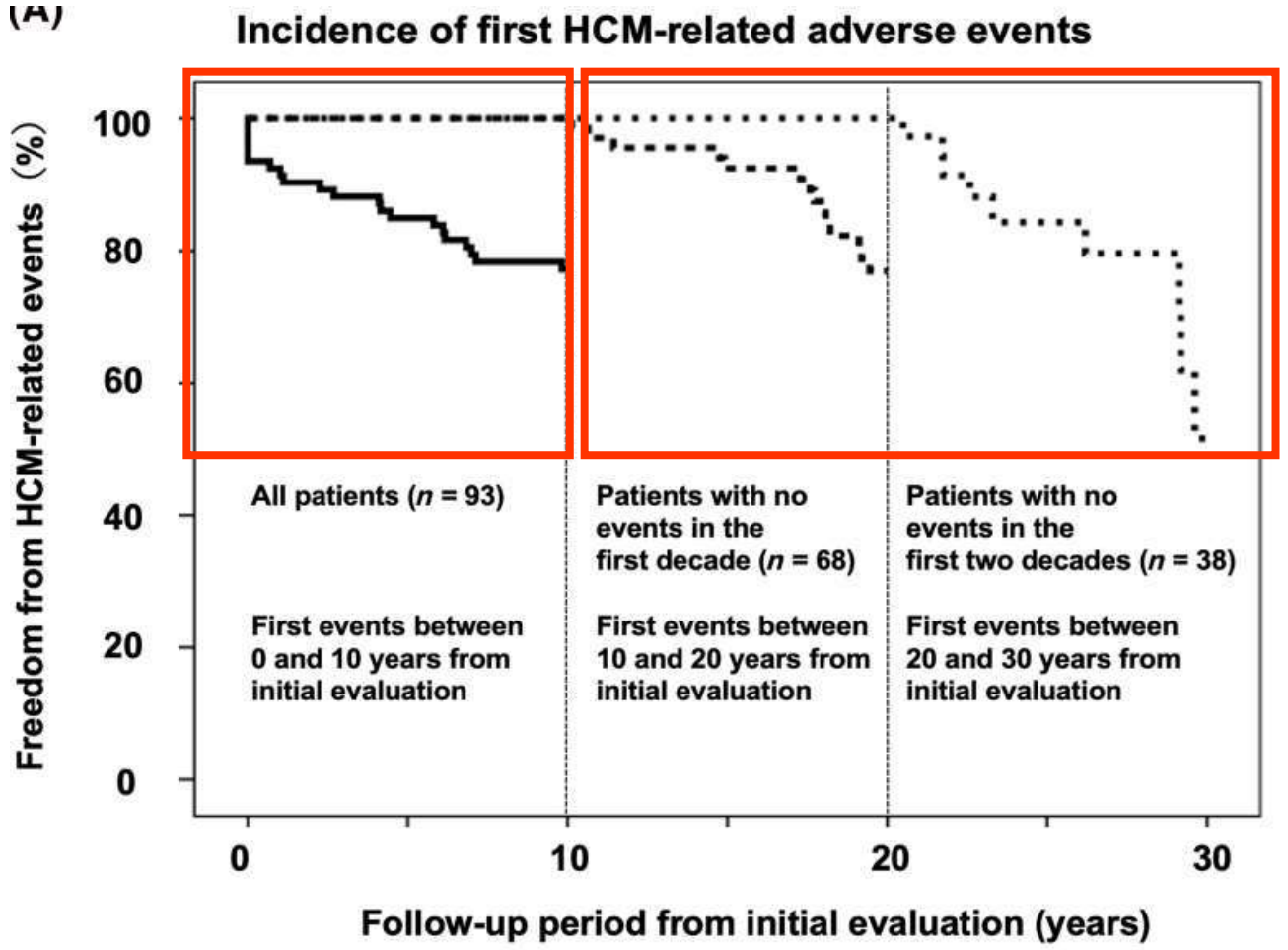
Maron, Barry J. et al.
American Journal of Cardiology, Volume 117, Issue 3, 434 - 435

What do patients with HCM die from?

- A new diagnosis of HC represents a landmark for many pts, usually unprepared for a disease often presented in the context of potentially profound clinical consequences.
- A HC diagnosis often dominates the patient perception of their overall clinical profile, even in the presence of other non-HC conditions with more profound implications.
- Indeed, it is very possible for adult patients in low HC-related risk groups to become distracted by HC and neglect preventive measures for other potentially lethal conditions such as cancer or CAD.

Maron, Barry J. et al.
American Journal of Cardiology, Volume 117, Issue 3, 434 - 435

Very long-term prognosis in patients with hypertrophic cardiomyopathy: a longitudinal study with a period of 20 years



there were no significant differences among the clinical profiles in patients with HCM-related events after the first decade and patients without HCM-related events.

- advanced age,
- symptomatic,
- presence of AF,
- more advanced LV/LA remodelling at the initial evaluation.

Sugiura, K.et al. ESC Heart Failure 2022; 9: 2618–2625

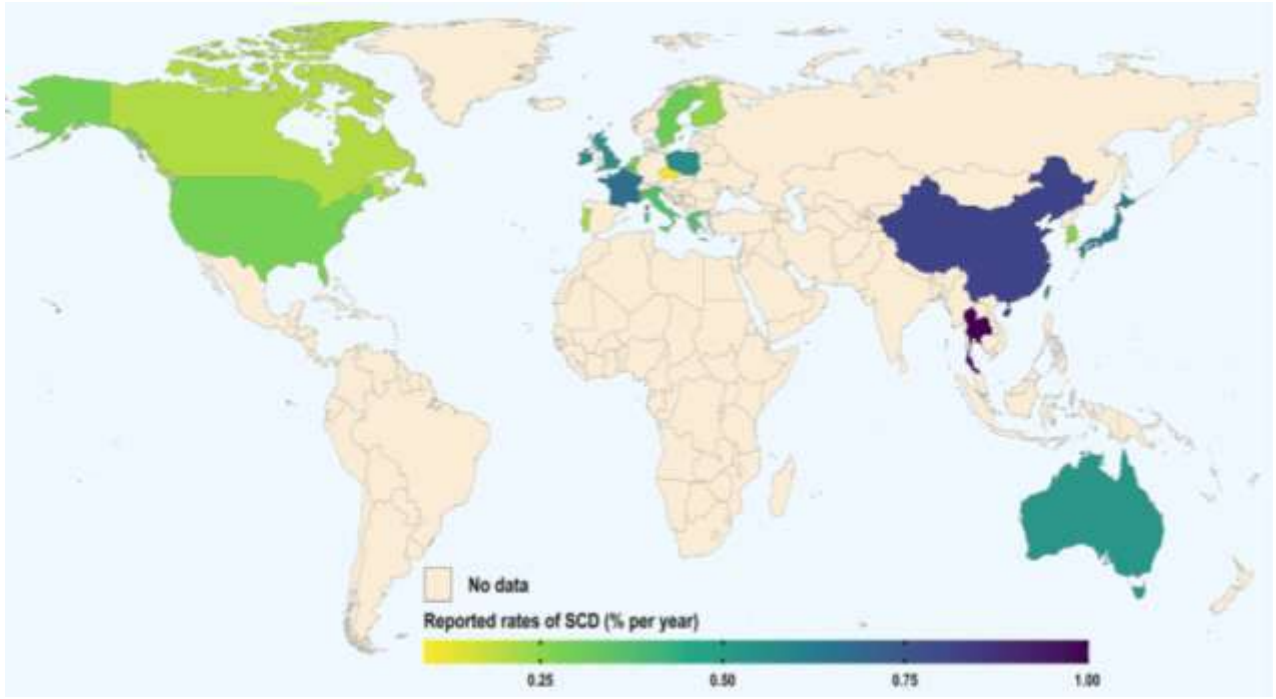
Lessons learned from this study ...

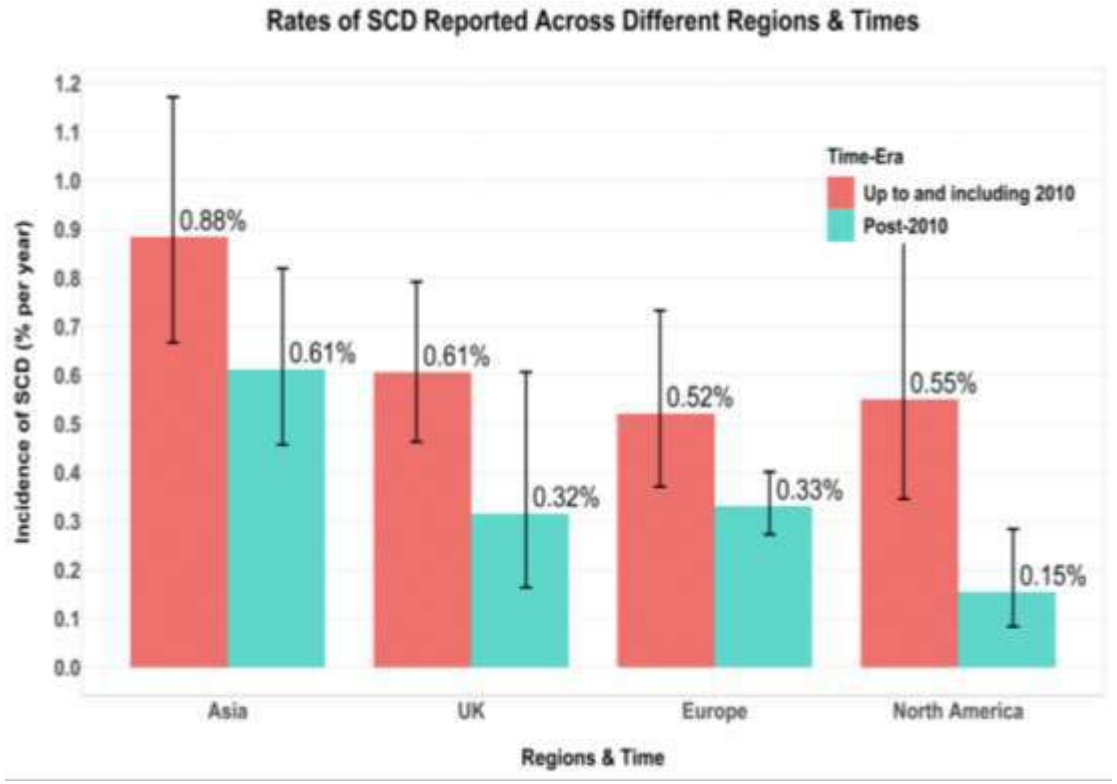
- ✓ Some patients had HCM-related adverse events for the first time even more than 20 years after diagnosis
- ✓ There are no predictors of HCM-related adverse events more than 10 years after the initial evaluation.
- ✓ HCM mortality rate - 1.1% per year, but about half of the pts suffered from serious HCM-related adverse events
- ✓ AF at diagnosis was 12%, but 51% of the pts finally had documentation of AF at the last FU.
- ✓ 24% of the patients progressed to end-stage HCM during the follow-up period of 20 years.
- ✓ 74% of the pts with AF and 86% of the pts with end-stage HCM suffered from HCM-related adverse events.

Sugiura, K.et al. ESC Heart Failure 2022; 9: 2618–2625

Temporal and Global Trends of the Incidence of SCD in Hypertrophic Cardiomyopathy

Colors represent the yearly rates of SCD as reported by studies originating from each country

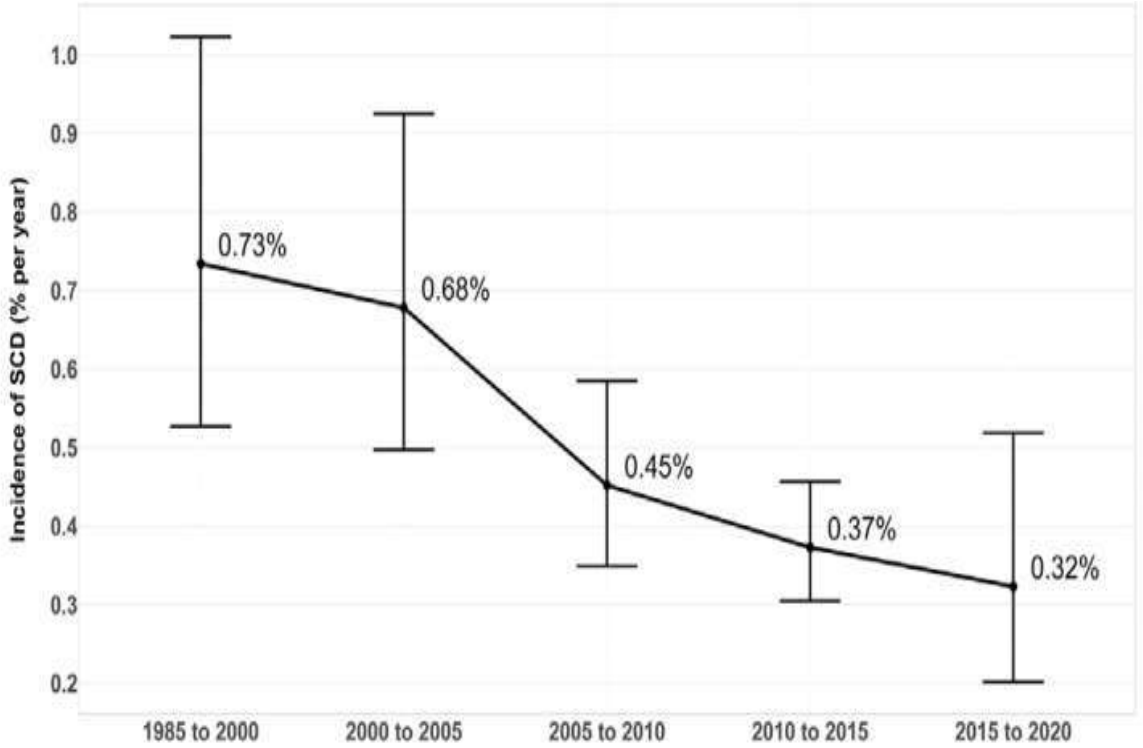




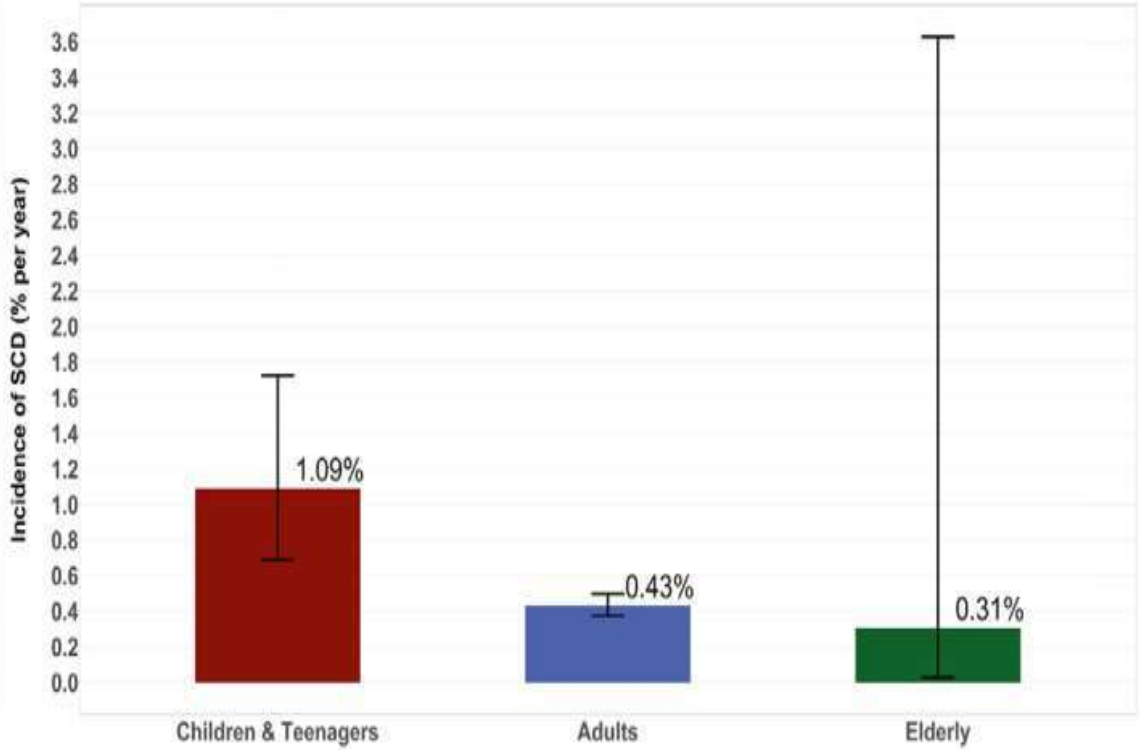
Abdelfettah, O. et al. J Am Coll Cardiol EP. 2022 Nov, 8 (11) 1417–1427

Temporal and Global Trends of the Incidence of SCD in Hypertrophic Cardiomyopathy

Rates of SCD reported across different timespans

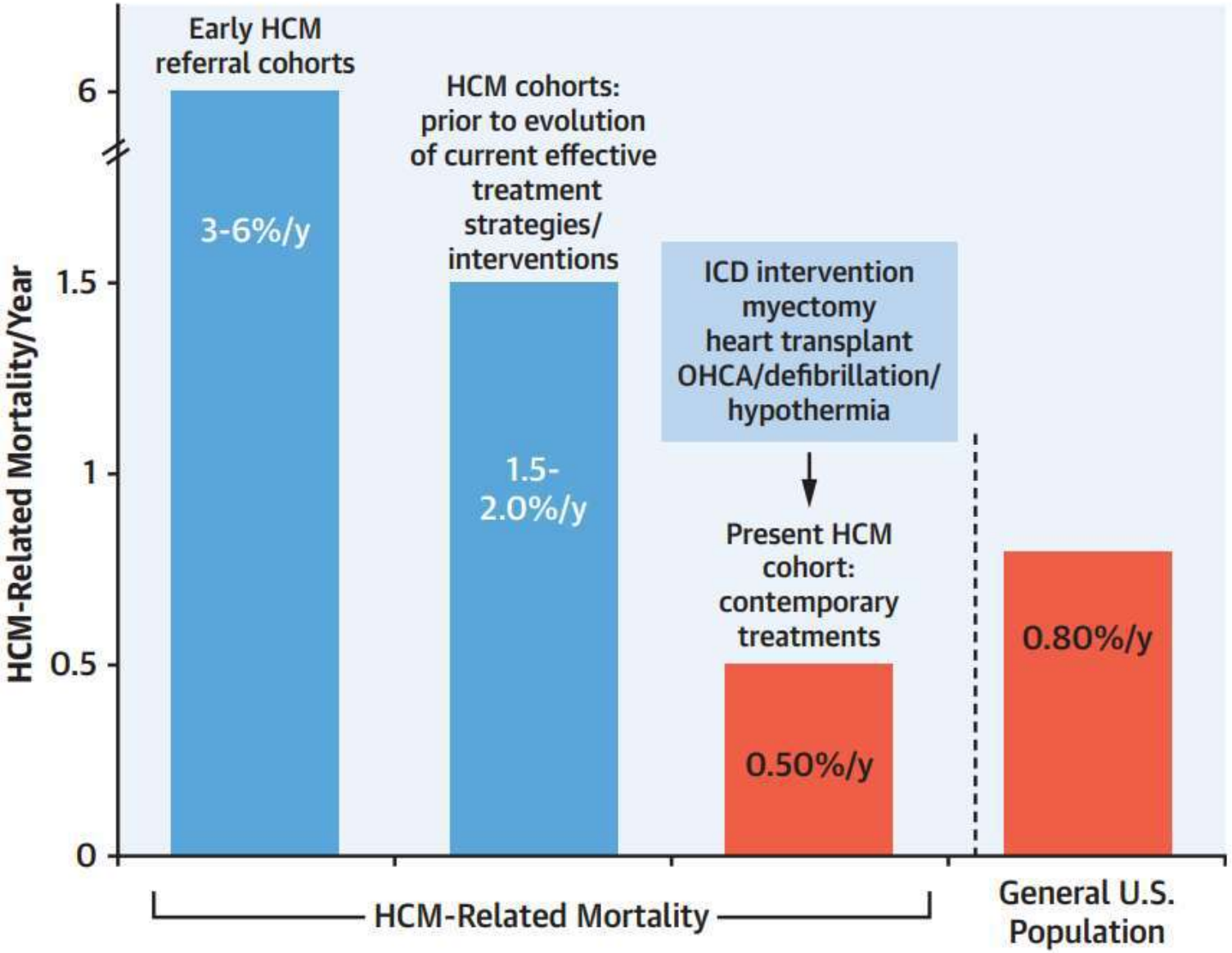


Rates of SCD reported across different age groups



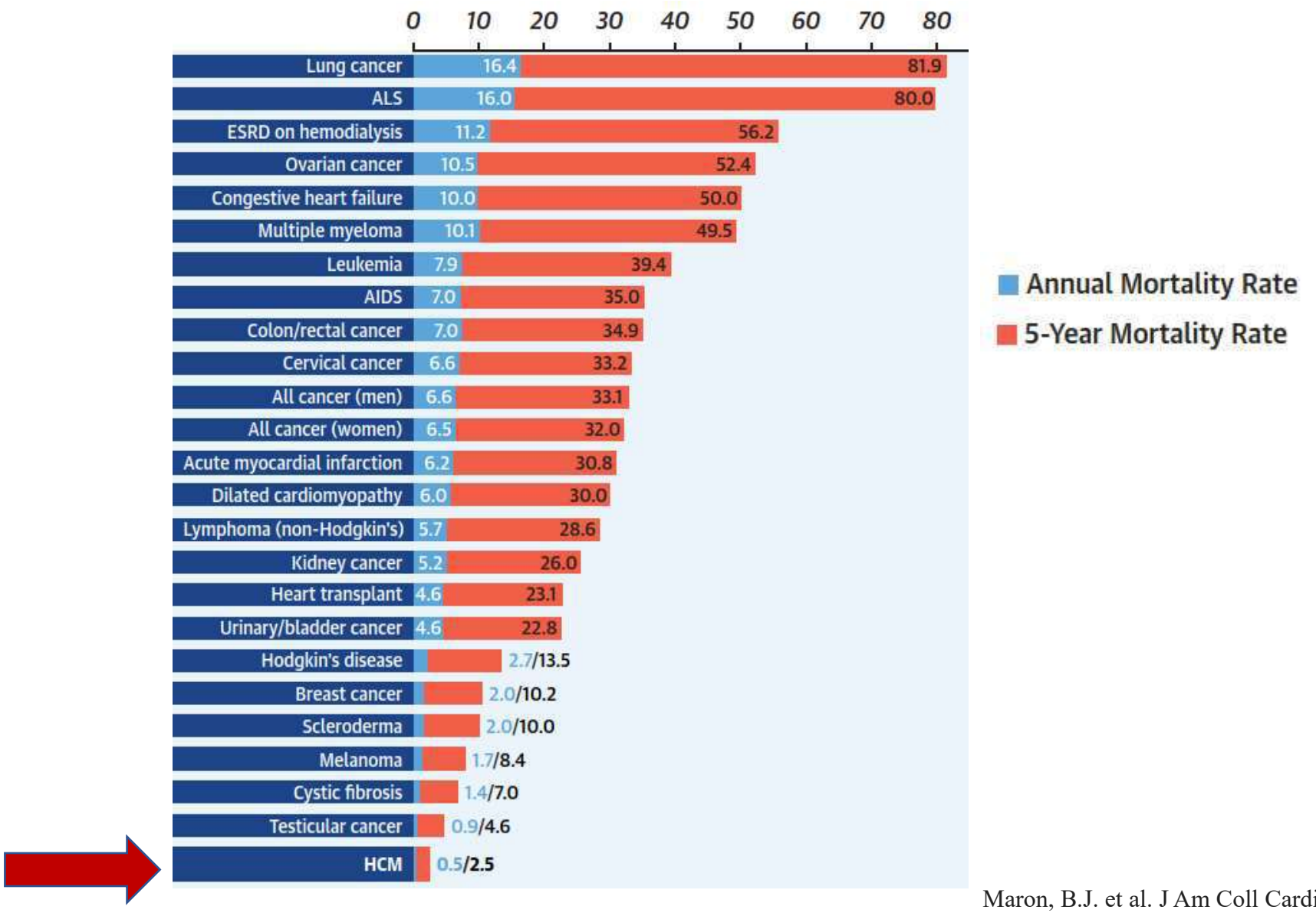
Abdelfettah, O. et al. J Am Coll Cardiol EP. 2022 Nov, 8 (11) 1417–1427

Historical progress in



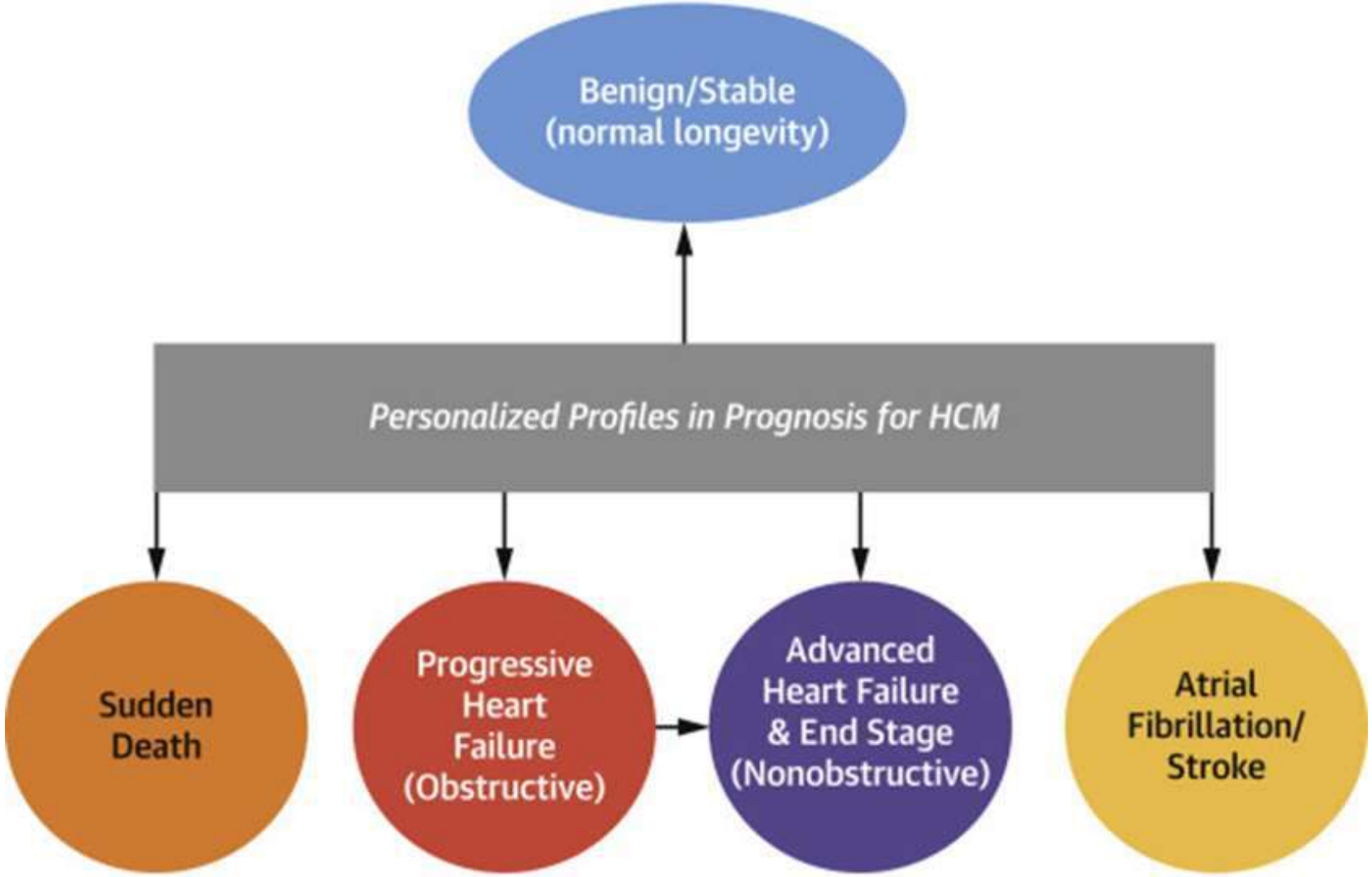
Maron, B.J. et al. J Am Coll Cardiol. 2022;79(4):390–414.

Annual and 5-year mortality rates for the most common chronic diseases that impact survival of the general population



Maron, B.J. et al. J Am Coll Cardiol. 2022;79(4):390–414.

Personalized profiles in prognosis for HCM

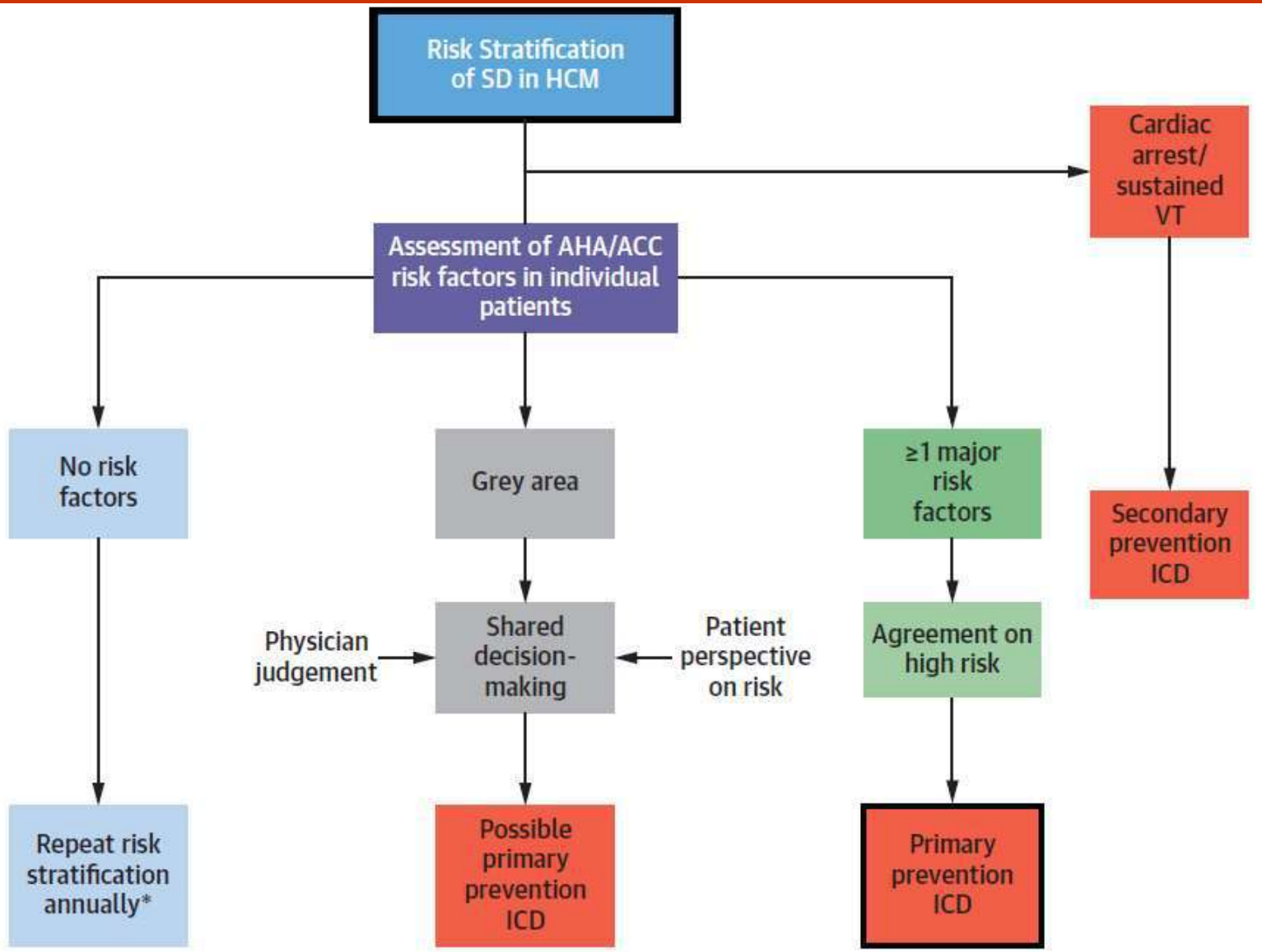


Maron, B.J. et al. J Am Coll Cardiol. 2022;79(4):390–414.

Risk stratification of SD in HCM

In grey area: ICD decision-making can rely on arbitrators including:

- extensive LGE,
- coexistent ischemic heart disease,
- prior alcohol septal ablation (ASA),
- or marked resting outflow gradient



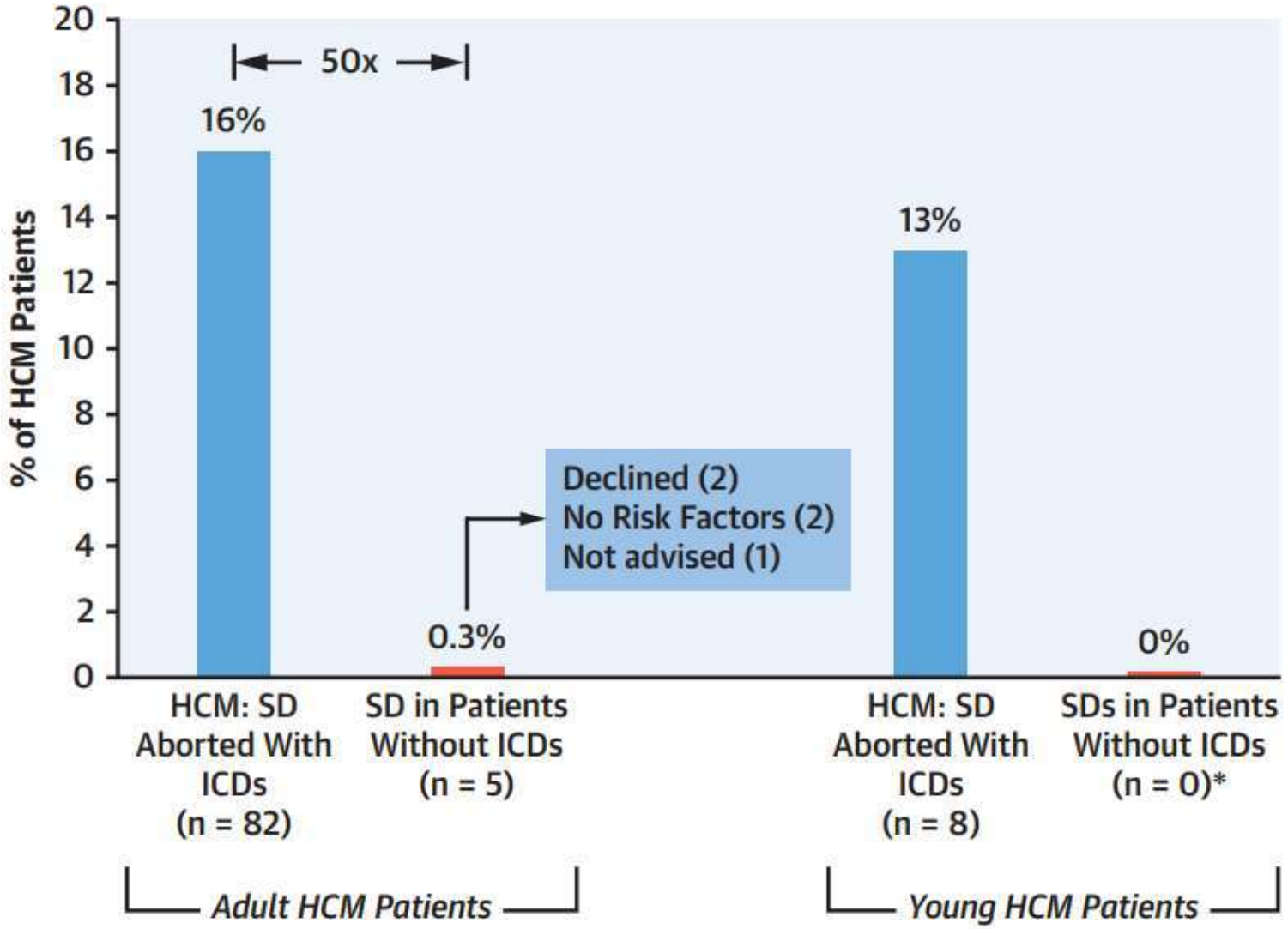
Maron, B.J. et al. J Am Coll Cardiol. 2022;79(4):390–414.

Major clinical markers recommended for current HCM risk stratification

- ✓ Family history of SCD at a young age
- ✓ Extreme LV hypertrophy
- ✓ Unexplained recent syncope
- ✓ NSVT
- ✓ LGE (fibrosis)
- ✓ End-stage HCM
- ✓ LV apical aneurysm

Ommen, S.R. et al. Circulation. 2024;149:e1239–e1311

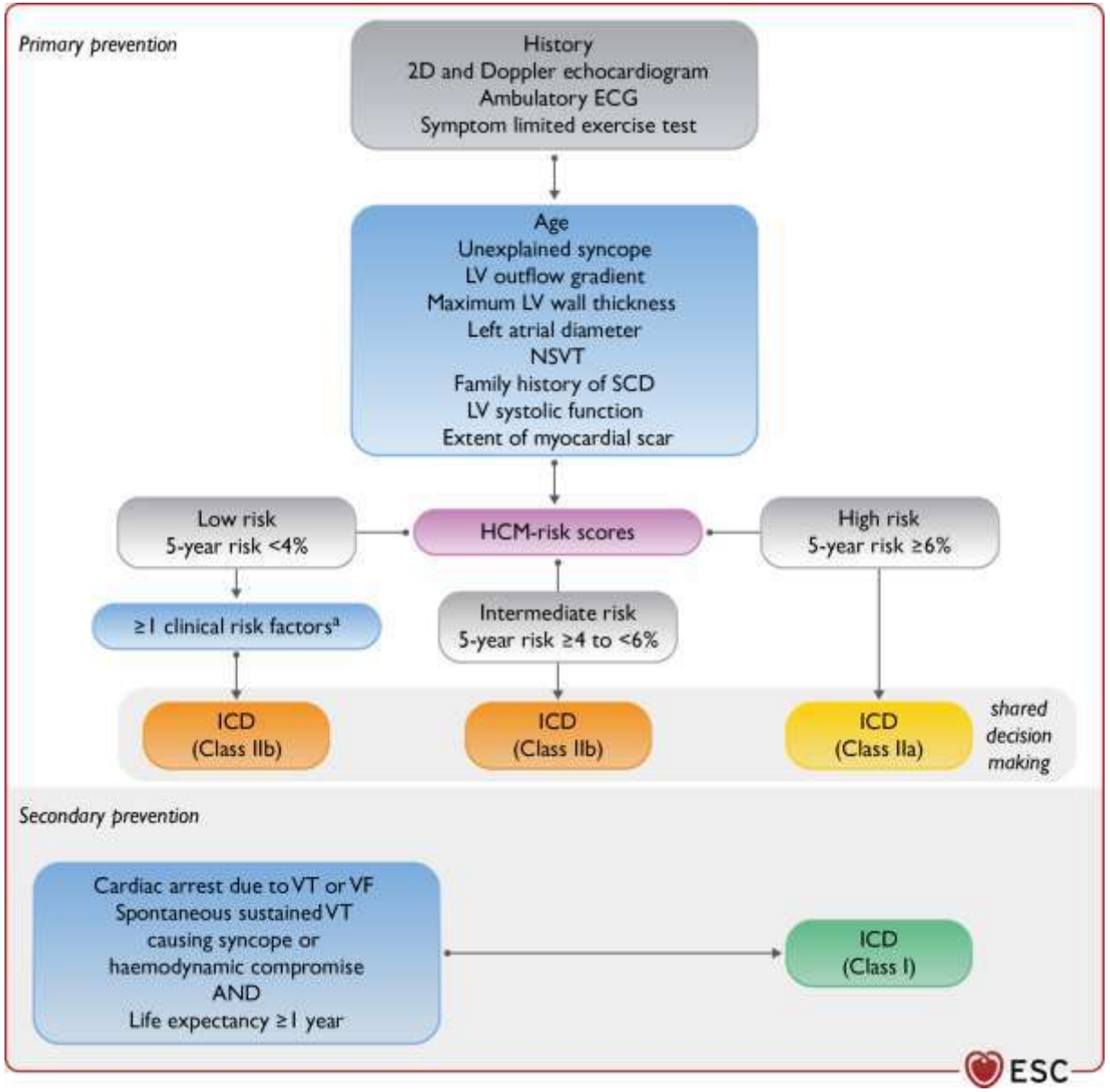
Major clinical markers recommended for current HCM risk stratification



Maron MS, et al.JAMA Cardiol. 2019 Jul 1;4(7):644-657

Figure 16

Flow chart for implantation of an implantable cardioverter defibrillator in patients with hypertrophic cardiomyopathy



2023 ESC Guidelines for the management of cardiomyopathies
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad 194)

Risk stratification of SD in HCM

- ESC score does not include CMR markers known to account for appropriate ICD therapy in 20% of patients
- When the quantitative ESC score was repeatedly tested as a primary decision-making strategy sensitivity for predicting SD events was low (average 33%, down to 10%). This is 3-fold lower than achieved with ACC-AHA risk markers, a strategy that is associated with 95% sensitivity.
- Only 1/3 of pts who experienced appropriate therapy had high scores, and about 40% had low risk scores that would have excluded an ICD recommendation.

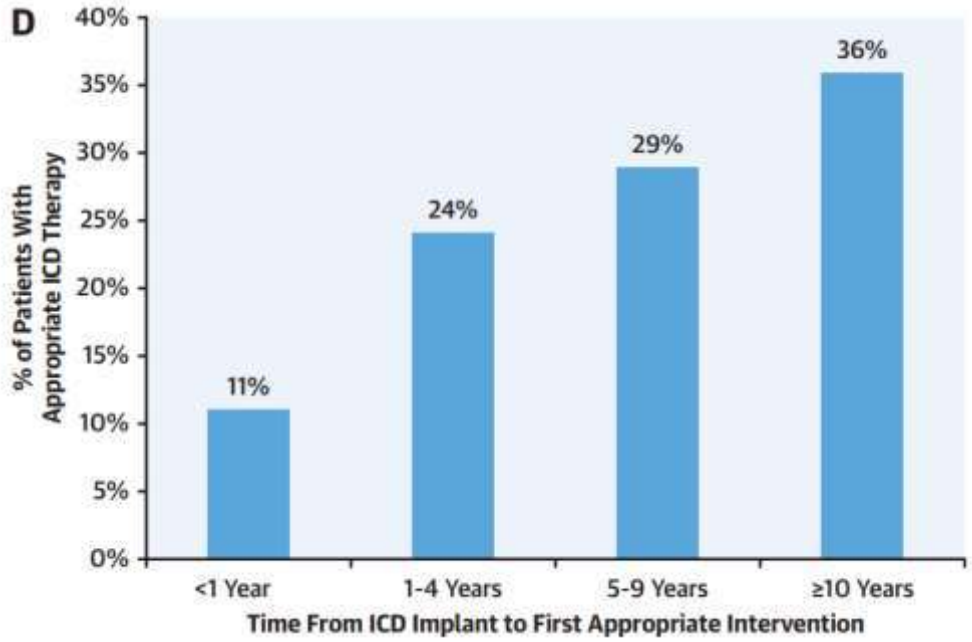
Study (reference no.)	Year	Location	No. HCM patients	No. SD events	No. SD events without high ESC score (<6%/5 yr)	Sensitivity of high ESC score (≥6%/5 yr) for SD events (%)
O'Mahony (57)	2014	Multicenter: Europe	2597	84	41	51
BJ Maron (105)	2015	Multicenter: US	1497	81	65	20
BJ Maron (11)	2016	Multicenter: US (age <30 yr)	474	40	29	27
Rowin (44)	2017	Multicenter: US (LVAA subset)	93	21	19	10
Leong (104)	2018	Single center: UK	260	14	7	50
Nakagawa (107)	2018	Single center: Japan	335	31	21	32
O'Mahony (58)	2018	Multicenter: Europe, US, Middle East, Asia	1850	44	21	52
Desai (51)	2018	Single center: US	1809	171	149	13
Choi (95)	2019	Single center: Korea	730	16	10	38
Rowin (61)	2019	Single center: US (massive LVH subset)	92	16	10	37
MS Maron (16)	2019	Single center: US	2094	91	60	34
Liu (88)	2020	Single center: China	1369	39	35	13

ESC = European Society of Cardiology; LVAA = left ventricular apical aneurysm; UK = United Kingdom; other abbreviations as in Tables 1 and 2.

Maron, J.B. Et al. Heart Rhythm 2021;18:1012–1023

Some notes about SCD/ICD in HCM patients

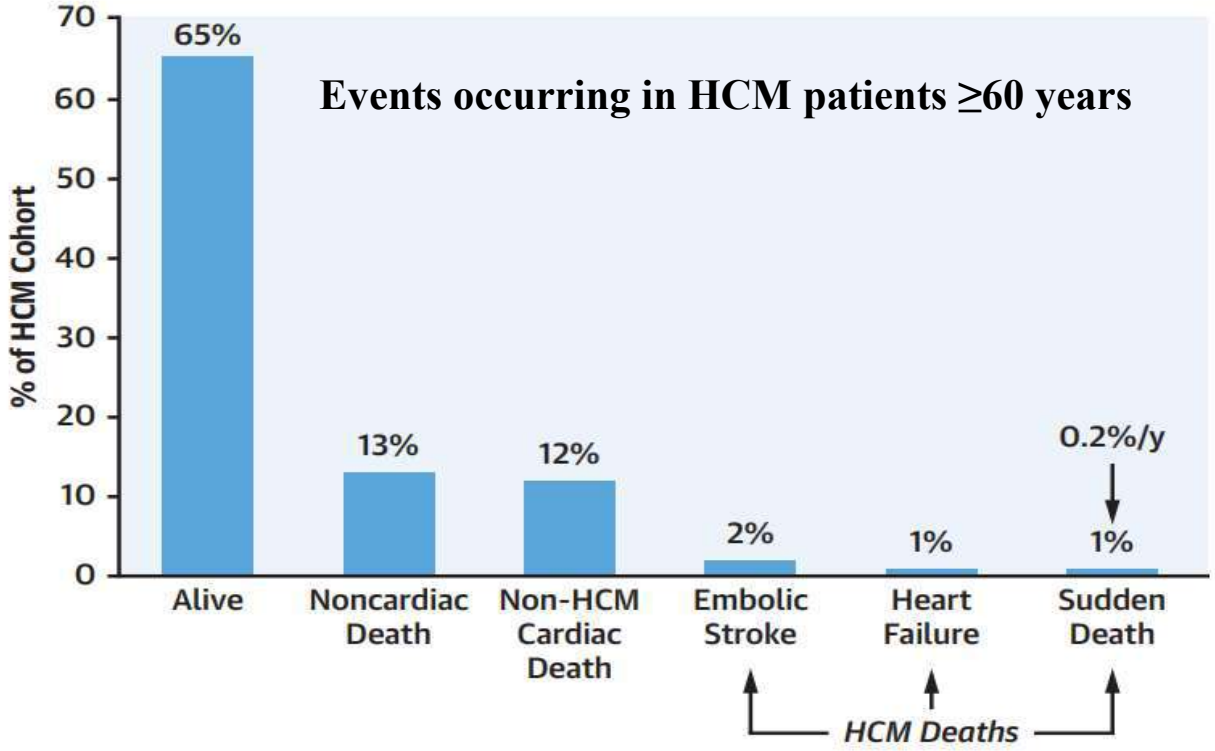
- Predicting the timing of isolated events with precision is daunting.
- There is no demonstrable circadian periodicity for ICD interventions.
- Substantial time delays can elapse between recognition of high-risk status and first VT/VF.
- Some patients survive for extended periods after cardiac arrest (up to 30 years) without subsequent events.
- In contrast to ischemic heart disease, device interventions in HCM are not associated with later disease-related morbidity/mortality such as HF, multiple hospitalizations, sudden death, psychological dysfunction



Maron, J.B. Et al. Heart Rhythm 2021;18:1012–1023

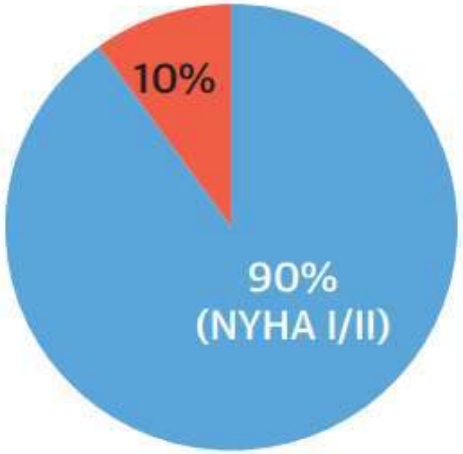
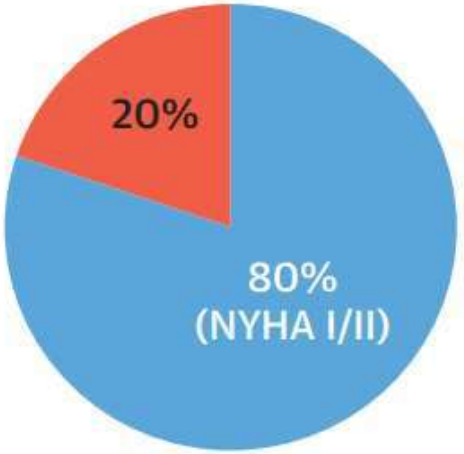
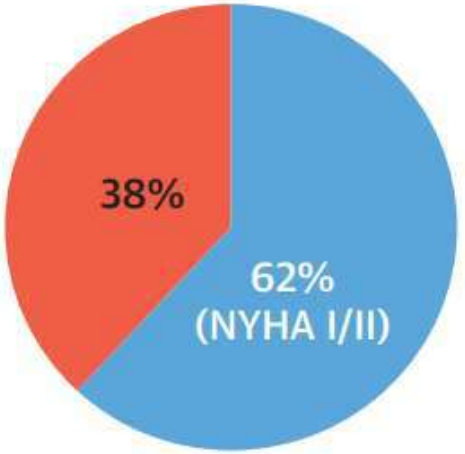
Risk stratification of SD in HCM

- For pts in the low to intermediate risk category, extensive LGE (≥15%) may be used in shared decision-making with patients about prophylactic ICD implantation.
- Primary prevention ICDs are discouraged in clinically stable patients age >60 years, given the low event rate in this age group, but may be considered on a case-by-case basis (eg, with apical aneurysm).



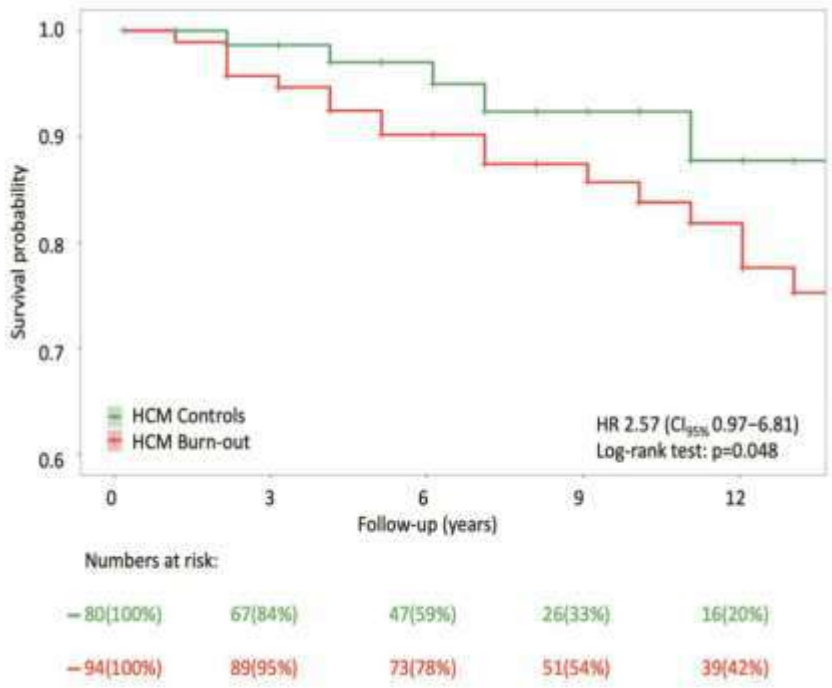
Maron, B.J. et al. J Am Coll Cardiol. 2022;79(4):390–414.

Risk stratification of SD in HCM

	Nonobstructive	*Provocable Obstruction*	*Rest Obstruction*
Proportion of Patients Who Evolved to NYHA Functional Class III/IV (red)			
Rate of Progression to NYHA Functional Class III/IV (%/y)	1.6%/y	3.2%/y	7.4%/y
Treatment for Progression to NYHA Functional Class III/IV	Transplant (CRT)	Myectomy (ASA)	Myectomy (ASA)

Maron, B.J. et al. J Am Coll Cardiol. 2022;79(4):390–414.

Clinical characteristics and prognosis of pts with end-stage HCM from a tertiary center cohort (Romania)



(i) 3.5% of pts with HCM developed systolic dysfunction, while 11.1% evolved advanced diastolic dysfunction;

(ii) 26.6% of burn-out HCM pts experienced all-cause death after a median FU of 9.0 (6.0–16.0) years,

(iii) burn-out HCM patients were significantly more symptomatic at FU

male sex, older age at diagnosis, lower LVEF, and a higher E/A ratio
were independent predictors of progression to the burn-out phase with systolic dysfunction

Afana, A.S. et al. Diagnostics 2025, 15, 1134.

Prognostic value of mitral reg in pts with HCM

From April 2008 until June 2021, prospectively included 176 patients with primary HCM (Serbia).

129 individuals (73%) had asymmetrical non-obstructive HCM, while 47 patients (27%) had HOCM.

Group 1 (n = 116), which included patients without MR or with trace/mild MR, and

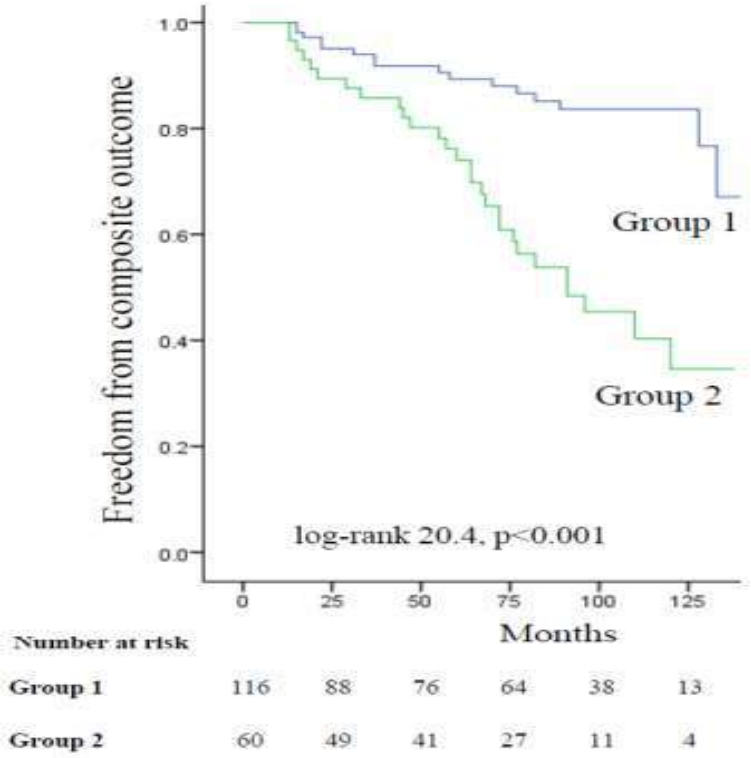
Group 2 (n = 60), which included patients with moderate or moderately severe MR.

	Group 2	Group 1	p
HCM related death	22%	8%	0.005
HF	25%	5.2%	< 0.001
New onset AF	20%	3.5%	< 0.001

Table 4. Multivariable prognostic predictors of the composite outcome.

Variables	Multivariable Analysis		
	HR	*p* Value	95% CI
Female sex	1.940	0.057	0.981–3.836
Age—years	1.000	0.987	0.976–1.025
Atrial fibrillation on Holter ECG	1.640	0.157	0.827–3.253
LAVI > 34 mL/m^2	1.546	0.248	0.738–3.239
Maximal induced LVOTG ≥ 50 mmHg	0.889	0.759	0.421–1.878
Moderate or moderately severe MR	2.788	0.015	1.221–6.364

HR: hazard ratio, CI: confidence interval, AF: atrial fibrillation, LV: left ventricular, LAVI: left atrial volume indexed for body surface area, LVOTG: left ventricular outflow tract gradient, MR: mitral regurgitation.



Tesic, M. Et al. Medicina 2023, 59, 1798.

HCM and atrial fibrillation

ATRIAL FIBRILLATION

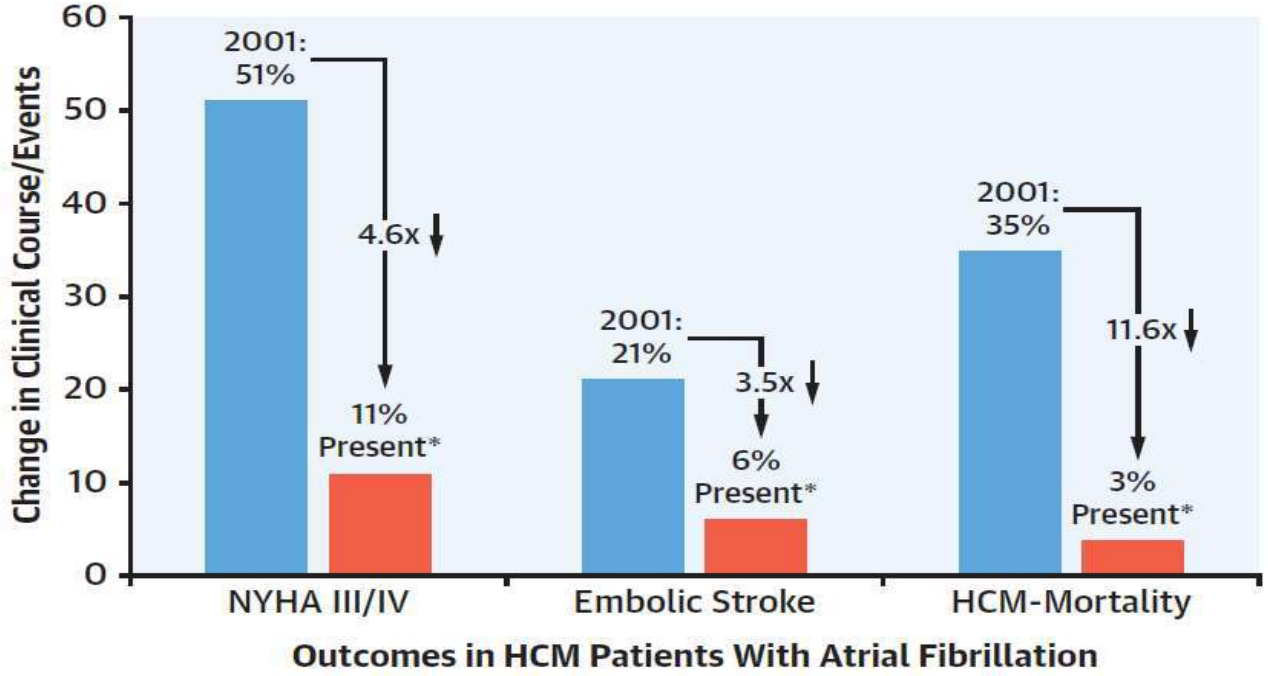
- The most common sustained arrhythmia in pts with HCM.
- Accounting for symptoms in 20% of pts at referral centers
- Age at onset, 50-55yrs
- Possibility of a primary atrial myopathy has not been excluded
- Clinically silent episodes are common and predictive of symptomatic AF
- Risk of stroke with clinically silent episodes is uncertain
- Transition from paroxysmal to permanent AF, occurs in 25% of pts

Maron BJ. N Engl J Med. 2018 Aug 16;379(7):655-668.

Much of the older HCM literature characterizes AF:

- as a decisive complication,
- inevitably a turning point and
- a marker for excess mortality and morbidity, particularly in pts with LVOT obst.[1,2]

DOACs
Maze procedure
AADs
Catheter ablation



Outcomes in HCM Patients With Atrial Fibrillation

recent analyses [2,3] of HCM patients in the contemporary treatment era failed to show AF

- to be an independent determinant of HF-related morbidity or
- to be an independent determinant of arrhythmic sudden death events,
- but rather associated with low disease related mortality (0.7%/y)

1. Olivotto I, et al..Circulation. 2001;104:2517–2524.

2. Maron, B.J. et al. J Am Coll Cardiol. 2022;79(4):390–414.

3.Rowin EJ, et al. Circulation. 2017;136:2420–2436.

Predictors of AF occurrence in HCM

Hypertrophic Cardiomypathy and Atrial Fibrillation

- CLINICAL PARAMETERS
  - Age
  - BMI
  - NYHA
- GENETIC FACTORS
  - MYH7
  - MYBPC3
  - CYP11B2
  - AGTR1
- ELECTRICAL PARAMETERS
  - P duration
  - P dispersion

Left atrial Remodeling

ATRIAL FIBRILLATION

- LEFT ATRIAL DILATATION
- LEFT ATRIAL FIBROSIS
- EPICARDIAL ADIPOSE TISSUE
- LEFT ATRIAL CONTRACTILE FUNCTION
  - LA diameter
  - LA area
  - LAVI
  - E/e'
  - LV LGE
  - EATVI
  - LA strain
  - LAEF

Dicorato, M.M. et al. J. Clin. Med. 2025, 14(6), 2018;

Predictors of AF occurrence in HCM

Electrical parameters

Pdurmax > 134.5 ms and PWD > 52.5 ms

PWD > 47.5 ms predicted AF in HCM and LA < 45 mm

Echo parameters

LA AP diam ≥ 45 mm - higher risk of AF

a LAVI ≥ 34 mL/m2 was the most sensitive and specific in predicting the PAF in 141 HCM patients,

LAEF < 38%, LAV ≥118 mL, age ≥ 40 years were independently associated with the development of AF

LA booster strain ≤ 8% and LA reservoir strain ≤ 18% were each independent determinants of AF.

LA (area exceeding 28 cm2) and a higher E/E' ratio (>17).

Other parameters

LV LGE > 15% was associated with a significant increase in AF, even in pts with LAVI below 34 mL/m2

NT-proBNP—with a cut-off value of >720 pg/ml predicts the onset of AF with good accuracy

Clinical parameters

Age
Oliviotto et al >60 years,
Maron et al ≥ 40 years,
Klopotowski et al. > 44.5 years

BMI
was a robust predictor of AF in younger patients

NYHA FC

Genetic factors

β-MHC - Higher rate (47%) of AF onset compared to that of ungenotyped familial HCM population.

3 subgroups (MYBPC3, MYH7, and "other genotypes"), with similar LA size: genotype was not correlated to AF onset or severity.

cytochrome P450 11B2 - predicted the onset of AF and was associated with higher serumaldosterone levels.

Dicorato, M.M. et al. J. Clin. Med. 2025, 14(6), 2018;

HCM-AF score

HCM-AF score		
Clinical variable	**Range**	**Points**
LA diameter, mm	24–29	+8
	30–35	+10
	36–41	+12
	42–47	+14
	48–53	+16
	54–59	+18
	60–65	+20
Age at clinical evaluation, y	10–19	+3
	20–29	+6
	30–39	+9
	40–49	+12
	50–59	+15
	60–69	+18
	70–79	+21
Age at HCM diagnosis, y	0–9	+0
	10–19	−2
	20–29	−4
	30–39	−6
	40–49	−8
	50–59	−10
	60–69	−12
	70–79	−14
Heart failure symptoms (Yes/no)*	Yes	+3
	No	+0

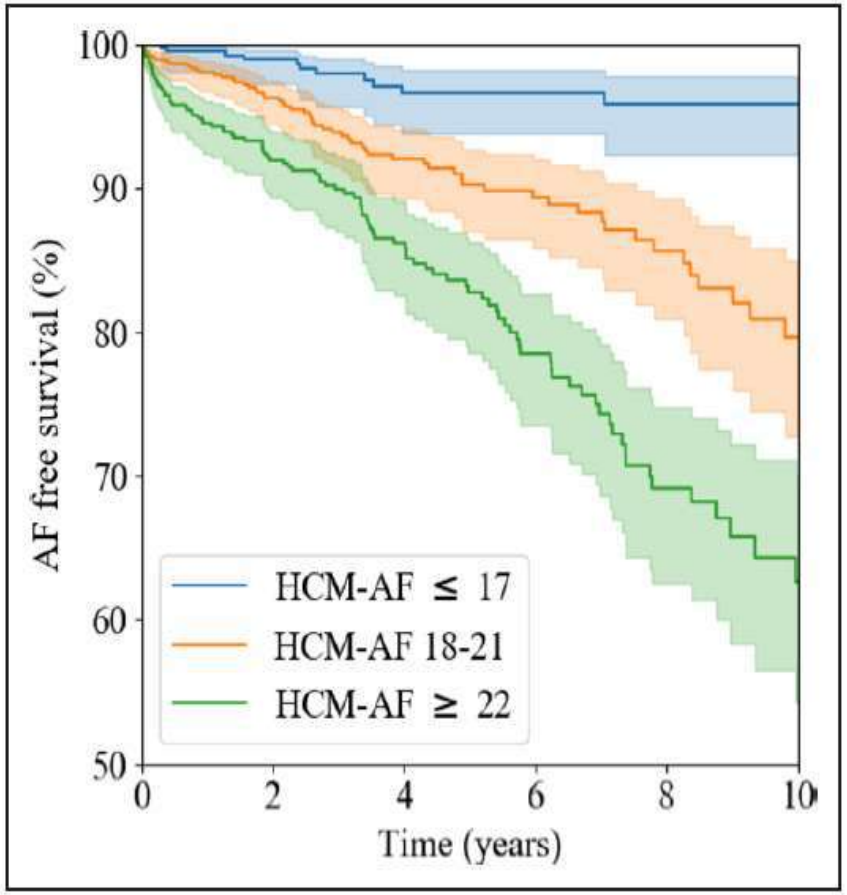


Table 6. Sensitivity, Specificity, Positive and Negative Predictive Values for Development of New-Onset AF at 5 y in 1900 Patients With HCM

	HCM-AF score ≥18*	HCM-AF score ≥ 22†	LA dimension ≥45 mm
Sensitivity (to detect patients with AF development)	95% [91–99]	58% [50–67]	35% [27–43]‡§
Specificity (likelihood detecting patients not at risk for AF)	25% [23–28]	66% [63–69]	81% [79–83]‡§
Positive predictive value	13% [11–15]	17% [14–24]	18% [13–22]
Negative predictive value	97% [94–99]	93% [91–95]	91% [89–93]‡

Table 7. Comparison of Model Discriminations for the Prediction of New-Onset Clinical AF Among 1900 Patients With HCM

	Concordance
HCM-AF score	0.70
LA size ≥45 mm	0.58
C_2HEST	0.58
CHA_2D_2VASc	0.61
CHARGE-AF	0.64

Carrick et al. Circ Arrhythm Electrophysiol. 2021;14:e009796.