HCM & HF: is your patient at risk?

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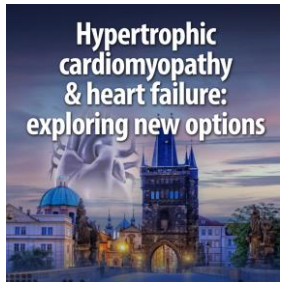

PHYSICIANS' ACADEMY FOR
PACE-CME
CARDIOVASCULAR EDUCATION

Heart failure & hypertrophic cardiomyopathy: Is your patient at risk?

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Erasmus MC
Universitair Medisch Centrum Rotterdam

PACE-CME satellite symposium, ESC Heart Failure, Sunday, May 21, 2023.
Hypertrophic cardiomyopathy & heart failure: exploring new options

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DISCLOSURES RUDOLF DE BOER

Speaker memberships/leaderships (not related to the topic)

- President, Dutch Cardiac Society
- Review coordinator of the 2021 ESC Heart Failure Guidelines
- Member Executive Committee of the *Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure* (DELIVER) trial, sponsored by AstraZeneca
- Member study group of the *Dapagliflozin Effect on Exercise Capacity Using a 6-minute Walk Test in Patients With Heart Failure With Reduced Ejection Fraction and Preserved Ejection Fraction* (DETERMINE Reduced & Preserved) trials, sponsored by AstraZeneca

Speaker research grants (paid to the institution; not related to this topic):

- Netherlands Heart Foundation (CVON grants 2017-21, 2017-11, 2018-30 & 2020B005)
- leDucq Foundation (CURE-PLaN)
- European Research Council (ERC CoG 818715, SECRETE-HF)
- Research grants/ chemicals / study / analytical help drugs from: AstraZeneca, Abbott, Boehringer Ingelheim, Cardior GmbH, Ionis Pharmaceuticals Inc, Novartis, Novo Nordisk, and Roche

Speaker personal speaker fees (not related to this topic):

- AstraZeneca, Abbott, Bayer, Bristol-Myers Squibb, Novartis, and Roche

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- # Heart Failure & hypertrophic cardiomyopathy

  - **Is it common?**
  - **Should we care?**
  - **Risk factors?**

INTRODUCTION

Maron BJ, et al. *J Am Coll Cardiol HF* 2018; **6**:353–363

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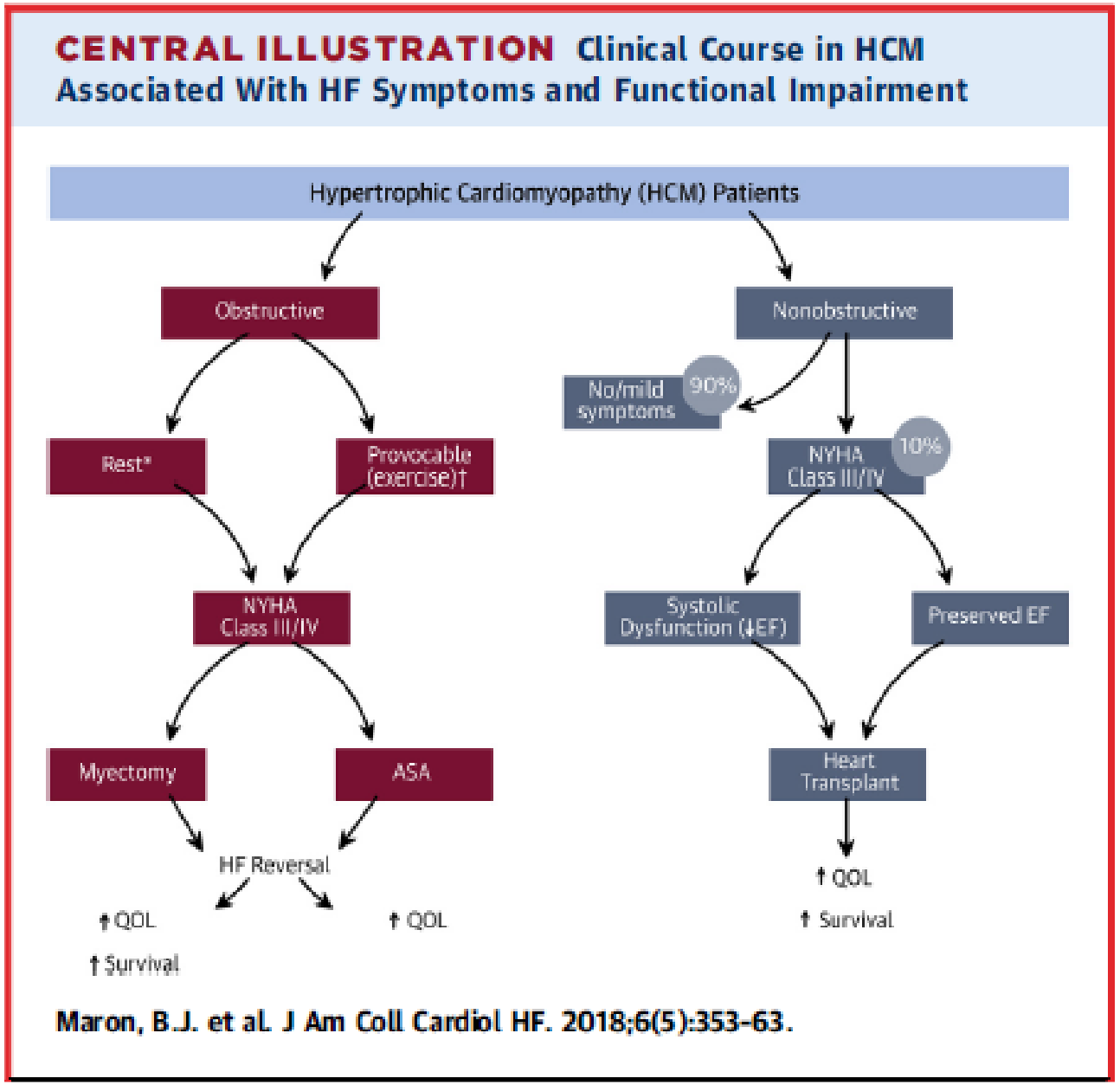

Maron BJ, et al. *J Am coll Cardiol HF* 2018; **6**:353–363

TABLE 1 Comparison of Clinical Variables Relevant to Heart Failure in HCM and Non-HCM

	Non-HCM (HFrEF/HFpEF) (23)	Obstructive HCM	Nonobstructive HCM
Annual mortality	About 10%*	0.5%	
Preserved EF	About 50%	100%	95%
Decreased EF (pump failure)	About 50%	none	About 5%
LV outflow obstruction	Absent	70% of patients with HCM (about 90% of symptomatic patients)	30% of patients with HCM (about 10% of symptomatic patients)
Reversibility	Uncommon	Symptoms reversible in majority of patients with outflow obstruction	Rare
Diastolic dysfunction	About 50%	High proportion	High proportion
Estimated prevalence in U.S.	6.5 million	700,000 to 1 million	
Hospitalization/diuresis	Very common	Virtually absent	Uncommon
Associated renovascular disease	Common	Virtually absent	Uncommon
Death due to HF	Common	Virtually absent	Rare (only end-stage patients at risk)
Comorbidities	Common	Less common; younger patient population	Less common; younger patient population
Volume overload	Very common	Virtually absent	Rare (only end-stage patients at risk)
Pulmonary/ankle edema	Common	Virtually absent	Rare (only end-stage patients at risk)
Mitral regurgitation	Common and often functional in HFrEF	Common and often secondary to obstruction	Uncommon
Symptoms: day-to-day variability	Rare	Common with obstruction	Rare
RV dysfunction	Common	Very rare	Uncommon
Pacing	Biventricular for systolic dysfunction	Dual chamber (largely abandoned)	No benefit in most
Effective drug treatments	Improved survival	No survival benefit	No survival benefit
Randomized treatment trials	Many	Very few	Very few
Transplant	2,800/y in U.S.; 0.04% of patients	Not needed	10% of nonobstructive patients eligible
LVAD	Common as bridge to transplant	Not needed	Rare/difficult

Maron BJ, et al. *J Am Coll Cardiol HF* 2018; **6**:353–363

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DATA FROM REGISTRIES

	Full HCM Cohort (n=4591)	Genotyped HCM Subset (n=2763)		
		SARC– (n=1231, 44.6%)	SARC+ (n=1279, 46.3%)	SARC VUS (n=253, 9.1%)
Baseline characteristics				
Female, n (%)	1704 (37)	419 (34)	504 (39)	85 (34)
Age at diagnosis, median (IQR), y	45.8 (30.9–58.1)	51.1 (38.3–61.8)	37.5 (23.6–49.8)	44.0 (31.4–54.1)
Mean±SD	44.3±18.5	49.0±17.4	37.3±17.1	41.9±17.9
Follow-up time, median (IQR), y	2.9 (0.3–7.9)	3.2 (0.4–7.5)	5.4 (1.5–10.6)	2.7 (0.3–7.0)
Mean±SD	5.4±6.9	5.0±6.1	7.8±8.4	5.2±6.7
Race, n (%)				
White	3911 (85)	1074 (87)	1156 (90)	205 (81)
Black	141 (3)	42 (3)	22 (2)	9 (4)
Other/not reported	539 (12)	115 (9)	101 (8)	39 (15)
Family history HCM, n (%)	1628 (35)	302 (25)	741 (58)	101 (40)
Family proband, n (%)	4039 (88)	1177 (96)	997 (78)	229 (91)
NYHA class III/IV, n (%)	597 (13)	167 (14)	134 (10)	33 (13)
Maximal LVWT, median (IQR), mm	18 (15–22)	17 (15–21)	19 (15–23)	18 (15–23)
Mean±SD	18.7±5.8	18.1±5.2	19.7±6.2	19.4±6.3
LVEF, median (IQR), %	65 (60–71)	65 (60–72)	65 (60–70)	65 (60–73)
Mean±SD	65.0±9.6	65.6±9.4	64.3±9.5	65.8±9.6
Peak gradient category, n (%)				
>30 mm Hg	1291 (28)	462 (38)	263 (21)	78 (31)
<30 mm Hg	3300 (72)	769 (62)	1016 (79)	175 (69)

without sarcomere mutations (**SARC**–), sarcomere mutation carriers (**SARC**+)

Ho CY, et al. HCM SHARE consortium *Circulation* 2018; **138**:1387–1398

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	Full HCM Cohort (n=4591)	Genotyped HCM Subset (n=2763)		
		SARC– (n=1231, 44.6%)	SARC+ (n=1279, 46.3%)	SARC VUS (n=253, 9.1%)
Patients with events, n (%)				
All-cause death	370 (8)	80 (7)	97 (8)	17 (7)
Sudden death	58 (1)	13 (1)	22 (2)	3 (1)
Resuscitated cardiac arrest	120 (3)	34 (3)	40 (3)	7 (3)
ICD present	961 (21)	224 (18)	383 (30)	68 (27)
Appropriate ICD therapy (including antitachycardia pacing)	135 (3)	30 (2)	64 (5)	10 (4)
Appropriate ICD shock (excluding antitachycardia pacing)	113 (3)	22 (2)	55 (4)	9 (4)
AF	920 (20)	254 (21)	295 (23)	58 (23)
Stroke	201 (4)	54 (4)	53 (4)	13 (5)
Transplantation or LVAD	74 (2)	10 (1)	34 (3)	1 (0)
Overall composite	1834 (41)	515 (43)	532 (42)	101 (42)
Ventricular arrhythmia composite	270 (6)	67 (5)	108 (8)	17 (7)
HF composite	996 (22)	277 (23)	290 (23)	52 (21)

- 4591 pts with HCM (2763 genotyped); mean FU 5.4±6.9 years (24,791 patient-years; median, 2.9 (IQR, 0.3–7.9) years
- Analyzed for cardiac arrest, cardiac transplantation, appropriate implantable cardioverter-defibrillator therapy, all cause death, atrial fibrillation, stroke, New York Heart Association functional class III/IV symptoms (all making up the overall composite end point), and left ventricular ejection fraction <35%.
- Outcomes were analyzed individually and as composite end points

without sarcomere mutations (**SARC**–), sarcomere mutation carriers (**SARC**+)

Ho CY, et al. HCM SHARE consortium *Circulation* 2018; **138**:1387–1398

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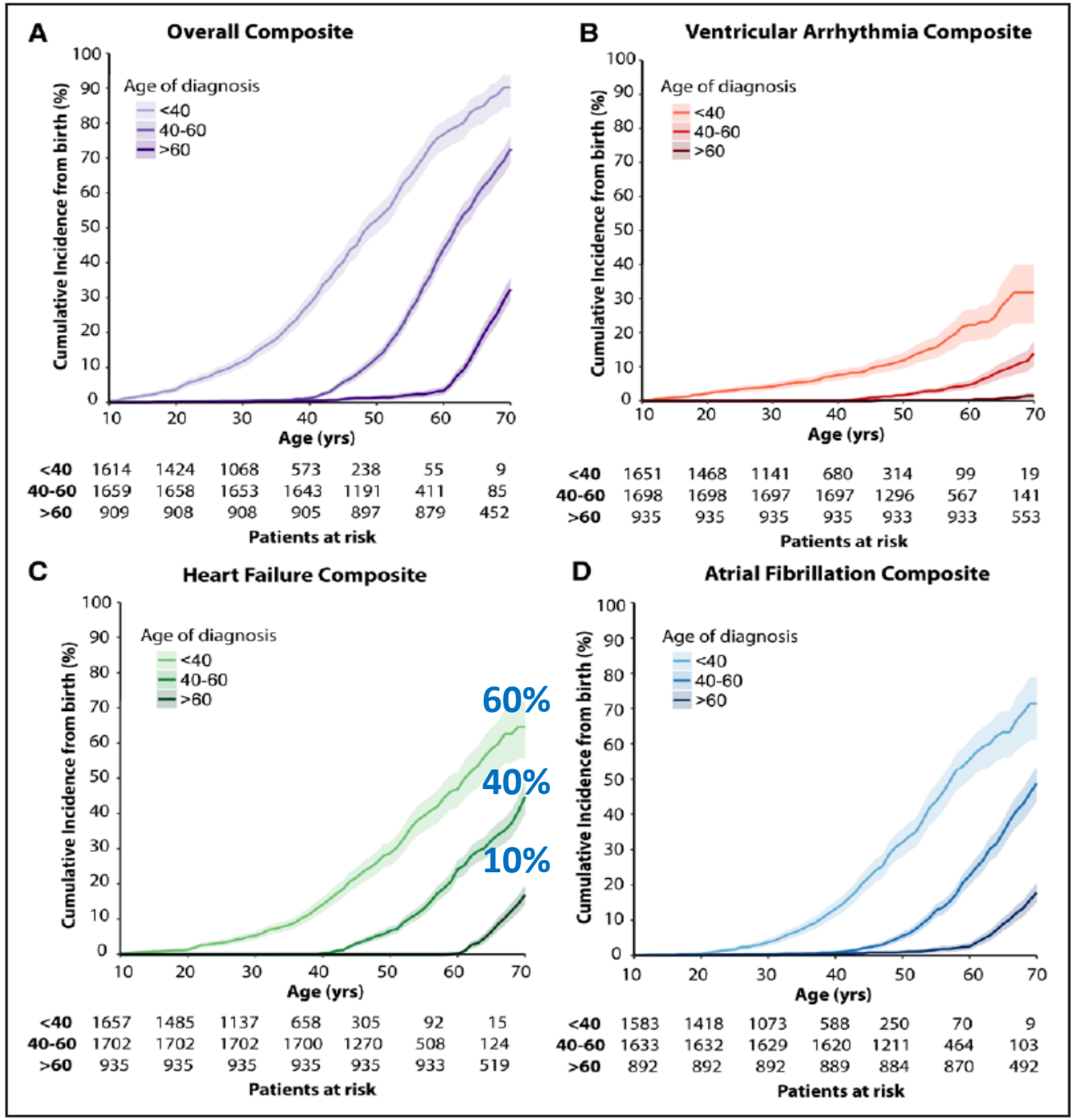

Ho CY, et al. HCM SHARE consortium *Circulation* 2018; **138**:1387–1398

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Table 2. Multivariable Models Predicting Outcomes in the Genotyped Hypertrophic Cardiomyopathy Cohort

	Overall Composite No. of Events, 1131 No. of Patients, 2631				Ventricular Arrhythmia Composite No. of Events, 187 No. of Patients, 2686				HF Composite No. of Events, 610 No. of Patients, 2692				AF No. of Events, 596 No. of Patients, 2589			
	HR	Lower 95% CI	Upper 95% CI	*P* Value	HR	Lower 95% CI	Upper 95% CI	*P* Value	HR	Lower 95% CI	Upper 95% CI	*P* Value	HR	Lower 95% CI	Upper 95% CI	*P* Value
SARC+	2.20	1.89	2.54	<0.001	2.83	2.07	3.87	<0.001	2.03	1.68	2.45	<0.001	2.41	1.98	2.94	<0.001
SARC VUS	1.57	1.22	2.02	<0.001	1.65	0.96	2.86	0.07	1.38	1.00	1.92	0.05	1.90	1.38	2.64	<0.001
Family proband	1.96	1.54	2.50	<0.001	6.65	2.72	16.26	<0.001	1.89	1.38	2.59	<0.001	1.87	1.36	2.57	<0.001
Female	0.88	0.77	1.01	0.07	0.69	0.51	0.94	<0.05	1.28	1.07	1.52	<0.01	0.72	0.60	0.87	<0.001
Nonwhite	1.01	0.80	1.90	0.91	1.50	0.96	2.34	0.08	0.99	0.73	1.34	0.94	0.92	0.66	1.28	0.63

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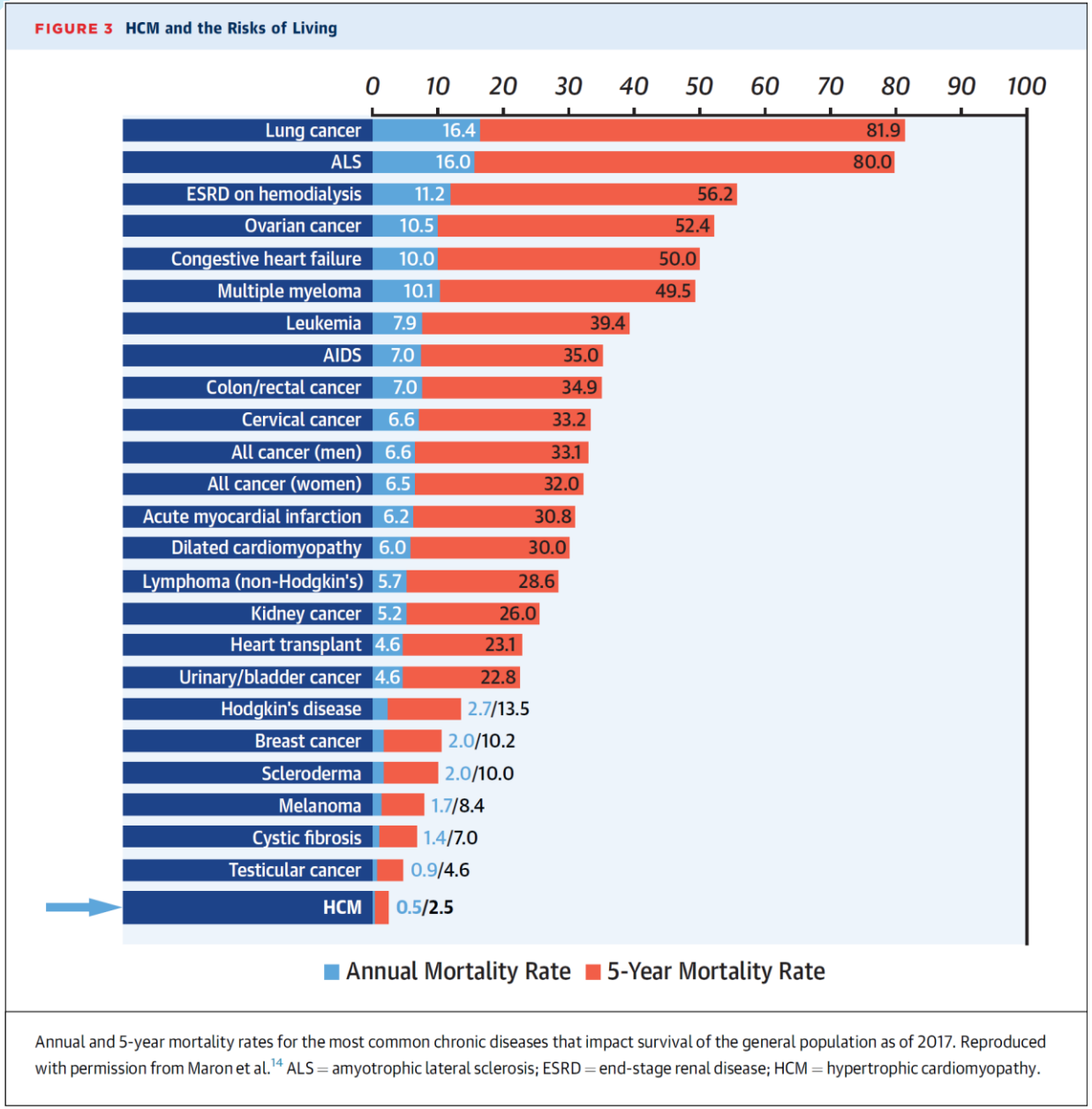
SHOULD WE CARE?



Lung cancer

CONGESTIVE HEART FAILURE

All cancer

Dilated Cardiomyopathy

Hypertrophic Cardiomyopathy

Marron BJ, et al. *J Am Coll Cardiol* 2022; **79**:390–414

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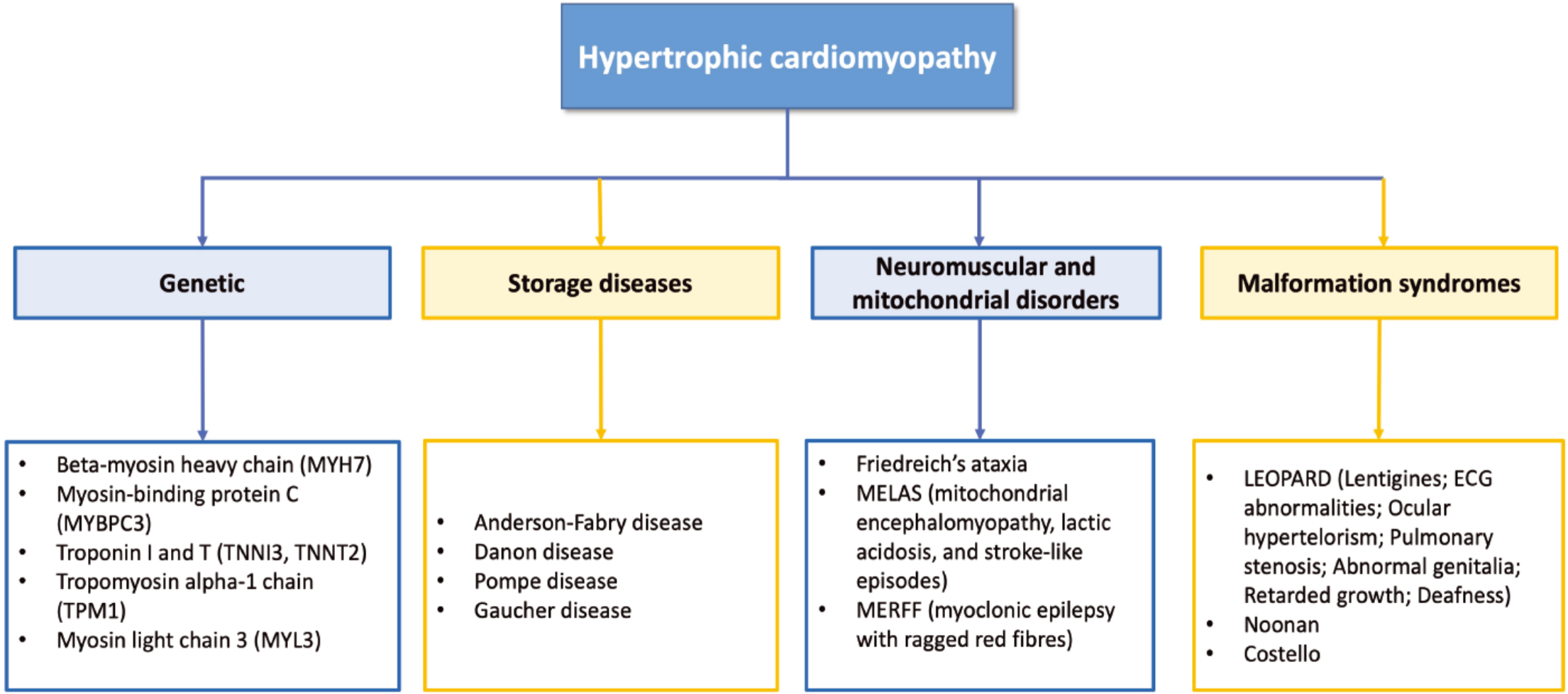
HCM: NOT JUST A DIAGNOSIS: IMPORTANCE OF PHENOTYPE



Seferovic P, et al. *J Heart Fail.* 2019: **21**:553-576

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Table 1 Summary of diagnostic subgroups at each centre

	Overall n=1697	The Heart Hospital n=987 (58%)	Bologna University Hospital n=710 (42%)
Idiopathic or sarcomeric HCM, n (%)	1288 (76)	826 (49)	462 (27)
Phenocopies, n (%)	409 (24)	161 (9)	248 (15)
AL amyloidosis, n (%)	115 (7)	6 (0.4)	109 (6)
Hereditary TTR amyloidosis, n (%)	86 (5)	6 (0.4)	80 (5)
AFD, n (%)	85 (5)	77 (5)	8 (0.5)
Wild-type or SSA, n (%)	48 (3)	8 (0.5)	40 (2)
Noonan syndrome, n (%)	15 (1)	11 (0.6)	4 (0.2)
Mitochondrial diseases, n (%)	23 (1)	21 (1)	2 (0.1)
Friedreich's ataxia, n (%)	11 (1)	9 (0.5)	2 (0.1)
GSD, n (%)	16 (1)	14 (0.8)	2 (0.1)
LEOPARD syndrome, n (%)	7 (0.4)	6 (0.4)	1 (0.1)
FHL1 mutations, n (%)	2 (0.1)	2 (0.1)	0 (0)
CPT II deficiency, n (%)	1 (0.1)	1 (0.1)	0 (0)

Rosmini S, et al. *Heart* 2017; **103**:300–306

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Table 2 Clinical and echocardiographic features at first evaluation

	Overall (n=1697)	Idiopathic or sarcomeric HCM (n=1288)	Rare phenocopies (n=409)	p Value
Male, n (%)	1160 (68)	860 (67)	300 (73)	0.012
Reason for diagnosis				
Incidental, n (%)	475 (29)	437 (36)	38 (10)	<0.0001
Cardiac symptoms, n (%)	822 (51)	660 (54)	162 (41)	
Family screening, n (%)	180 (11)	128 (10)	52 (13)	
One or more non-cardiac symptoms, n (%)	140 (9)	0 (0)	140 (35)	
Age at diagnosis of HCM, median (IQR)	50 (38–62)	49 (37–60)	58 (44–69)	<0.0001
Age at first evaluation, median (IQR)	52 (40–63)	51 (39–61)	60 (47–69)	<0.0001
NYHA III–IV at first evaluation, n (%)	241 (14)	144 (11)	97 (24)	0.013
Rhythm at first evaluation, n (%)				
Sinus rhythm	1461 (89)	1124 (87)	337 (82)	<0.0001
Atrial fibrillation/atrial flutter	124 (8)	74 (6)	50 (12)	
Paced	53 (3)	33 (3)	20 (5)	
Max LVWT at first evaluation, (mm), median (IQR)	18 (16–21)	18 (16–22)	16 (14–19)	<0.0001
LVED diameter at first evaluation, (mm), median (IQR)	45 (41–49)	45 (41–49)	45 (40–49)	0.145
EF at first evaluation (%), median (IQR)	65 (57–71)	66 (60–72)	60 (48–68)	<0.0001
EF <50% at first evaluation, n (%)	145 (9)	40 (3)	105 (26)	<0.0001
LA diameter at first evaluation (mm), median (IQR)	44 (39–49)	44 (40–49)	44 (38–48)	0.072

Rosmini S, et al. *Heart* 2017; **103**:300–306

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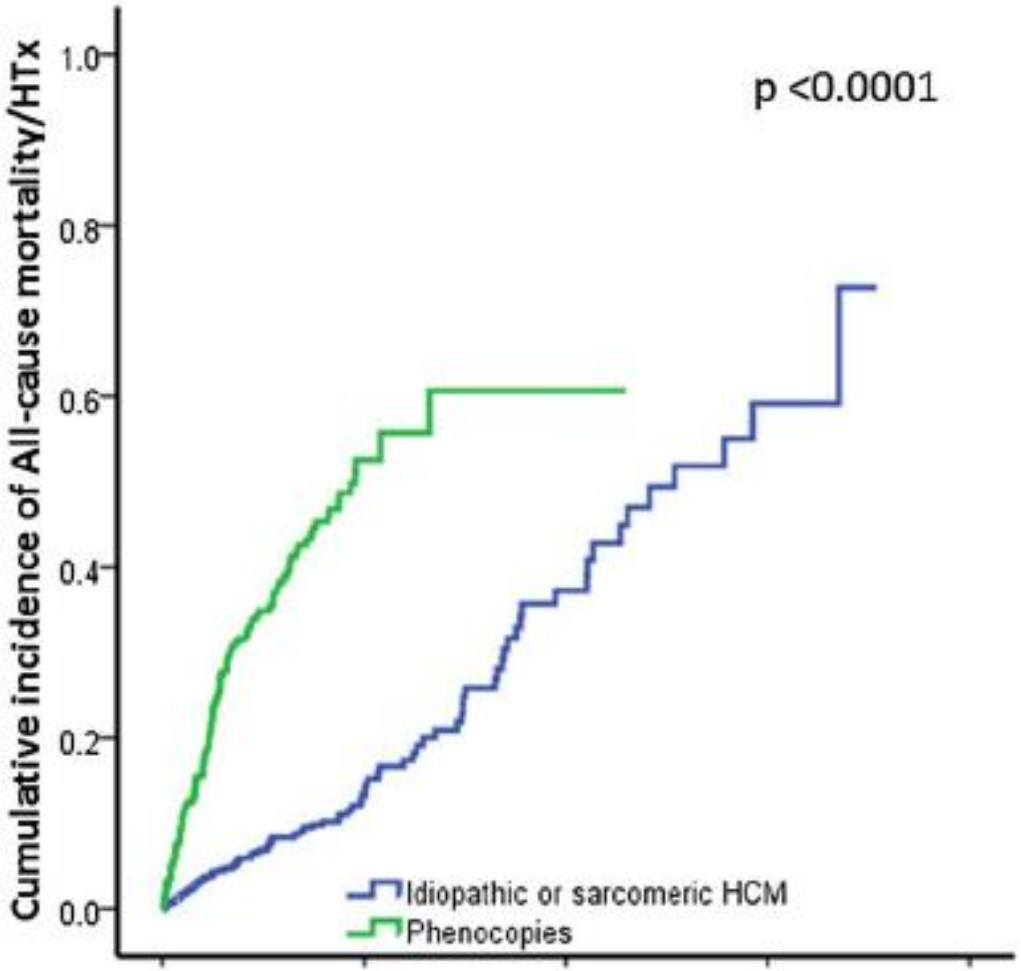
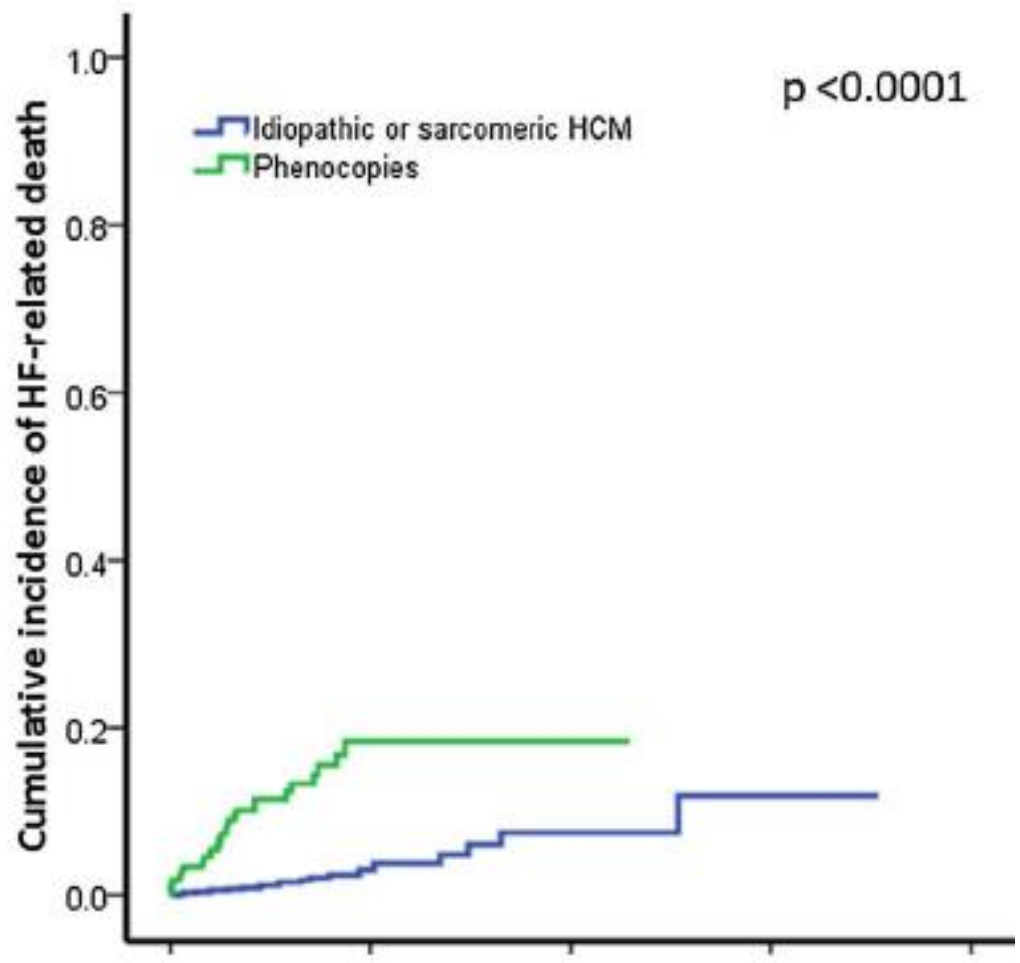
A



Time (years)	0	10	20	30	40
Total	1639	157	41	9	0
HCM	1242	135	40	9	0
Phenocopies	395	22	1	0	0

B



Time (years)	0	10	20	30	40
Total	1639	159	41	9	0
HCM	1242	137	40	9	0
Phenocopies	395	22	1	0	0

Rosmini S, et al. *Heart* 2017; **103**:300–306

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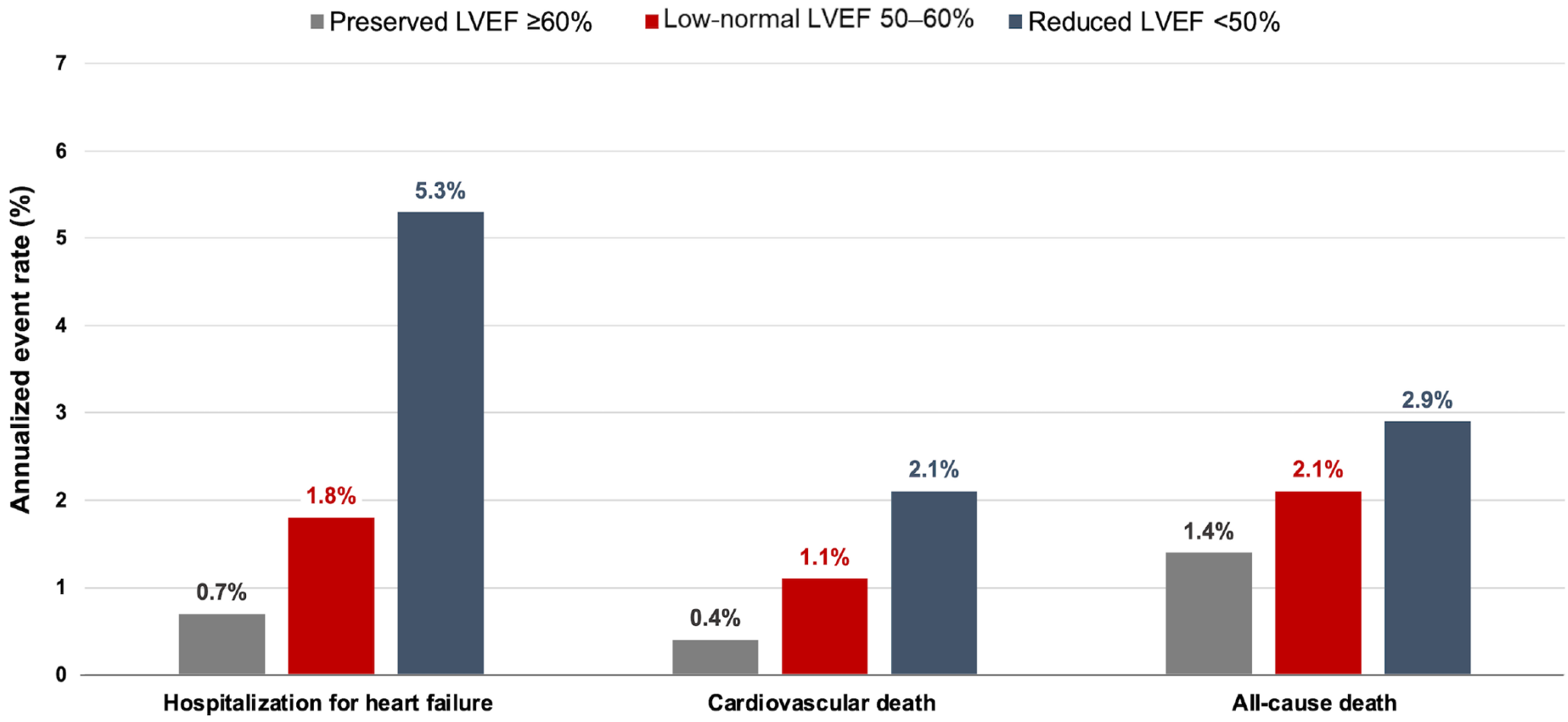
RELEVANCE OF LVEF



Secondary endpoints	Total N=1,858	LV systolic function			*p*-value
		Preserved LVEF ≥60% N=1,399	Low-normal LVEF 50–60% N=415	Reduced LVEF <50% N=44	
Hospitalization for heart failure	62 (3.3)	31 (2.2)	24 (5.8)	7 (15.9)	<0.001
Cardiovascular death	36 (1.9)	18 (1.3)	15 (3.6)	3 (6.8)	<0.001
All-cause death	98 (5.3)	65 (4.6)	29 (7.0)	4 (9.1)	0.090

Choi YJ, et al. *Heart.* 2023; **109**:771–778

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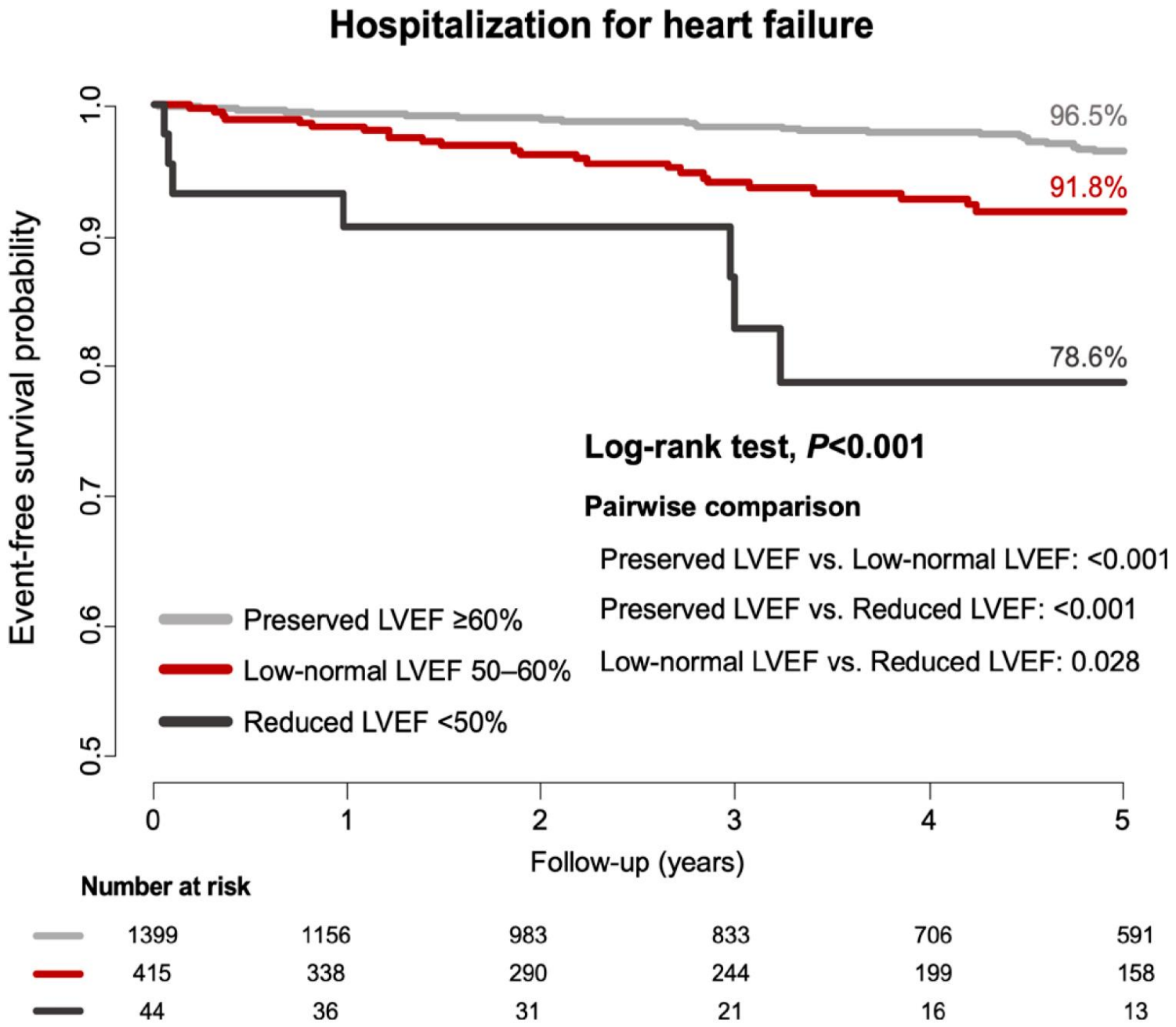

Choi YJ, et al. *Heart.* 2023; **109**:771–778

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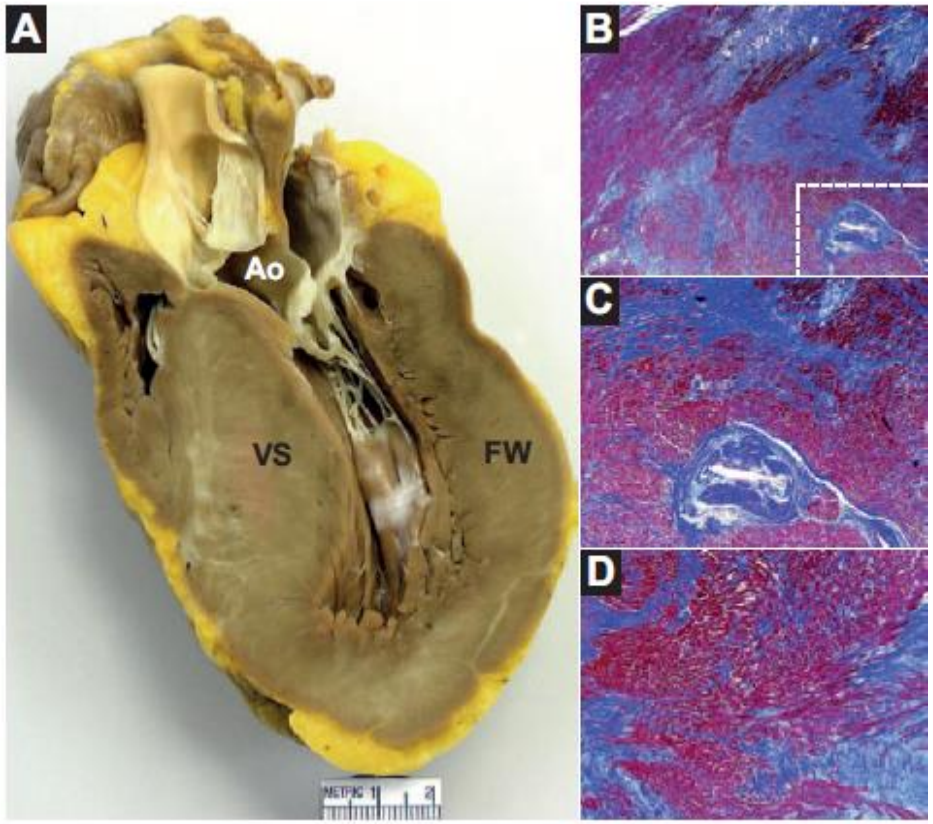
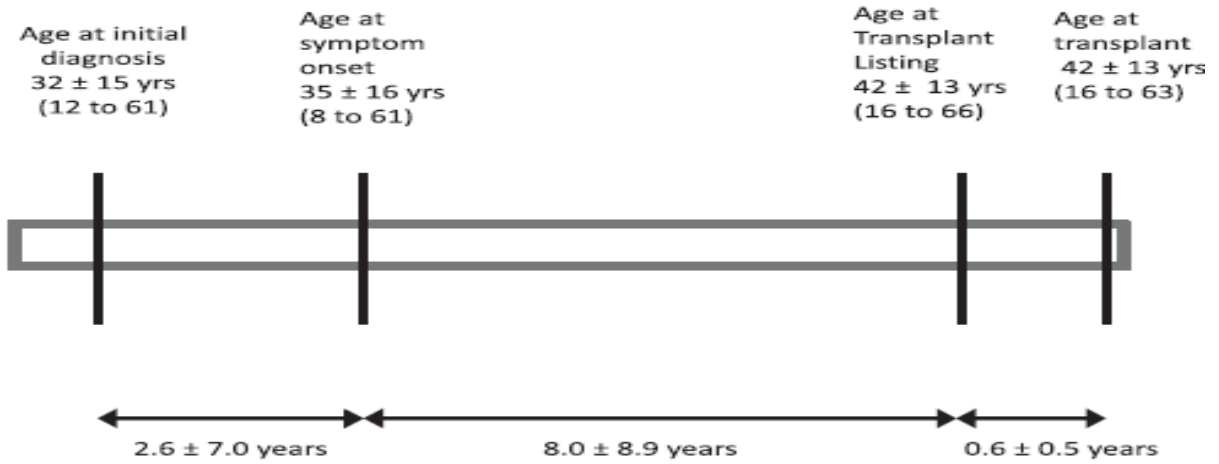
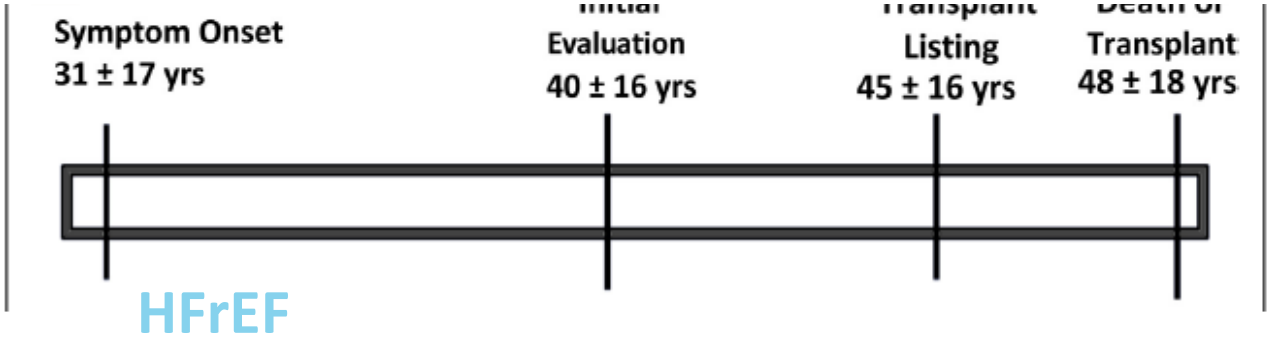
HEART FAILURE – HFREF BUT ALSO HFPEF







Rowin EJ, et al. *Circ Heart Fail* 2014; **7**:967-975

Maron BJ, et al. *J Am coll Cardiol HF* 2018; **6**:353–363

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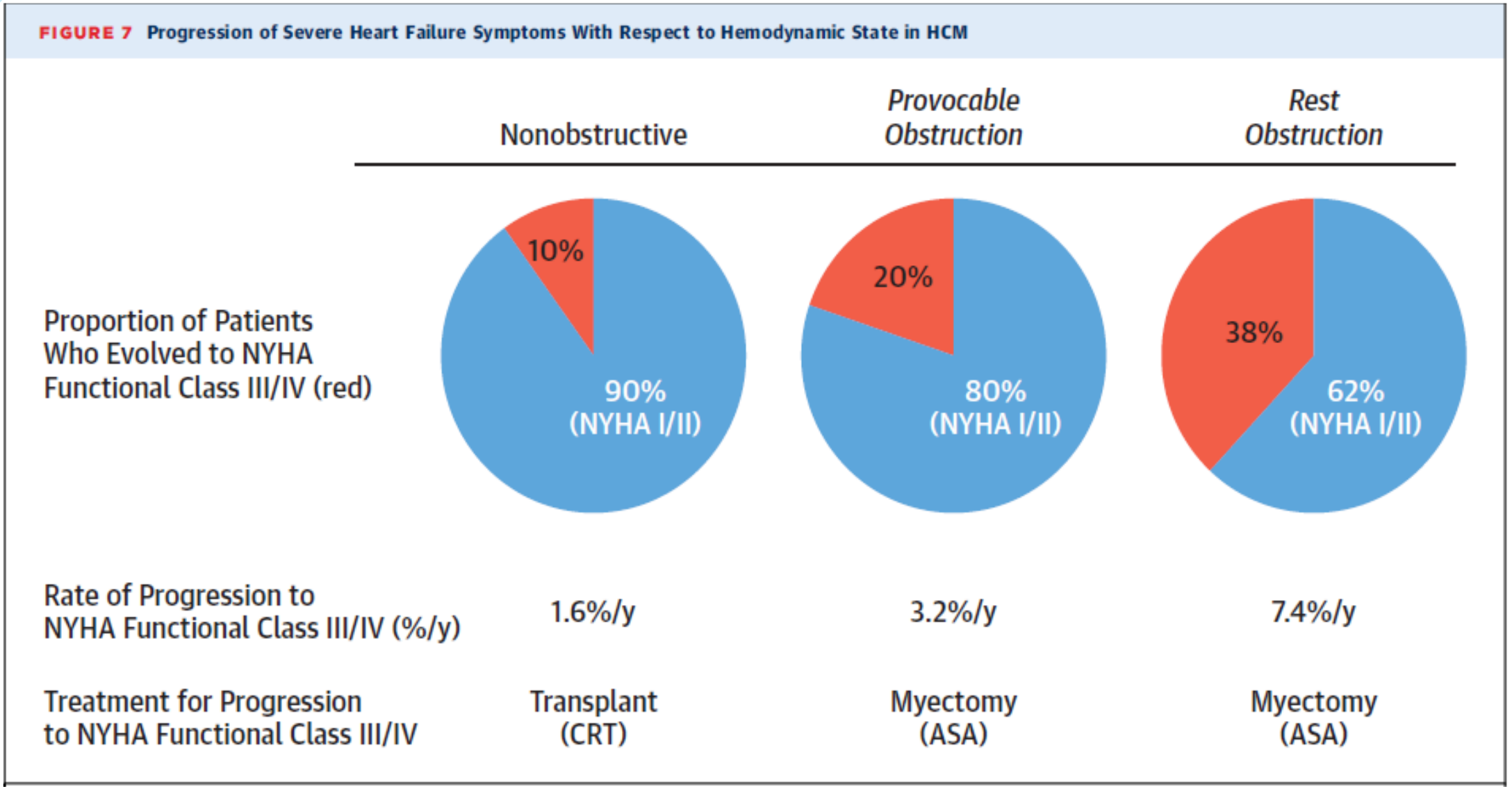
ALWAYS: THE SEVERITY OF OBSTRUCTION

CLINICAL PRESENTATION AND HF RISK

FIGURE 7 Progression of Severe Heart Failure Symptoms With Respect to Hemodynamic State in HCM



Marron BJ, et al. *J Am Coll Cardiol* 2022; **79**:390–414

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IMAGING

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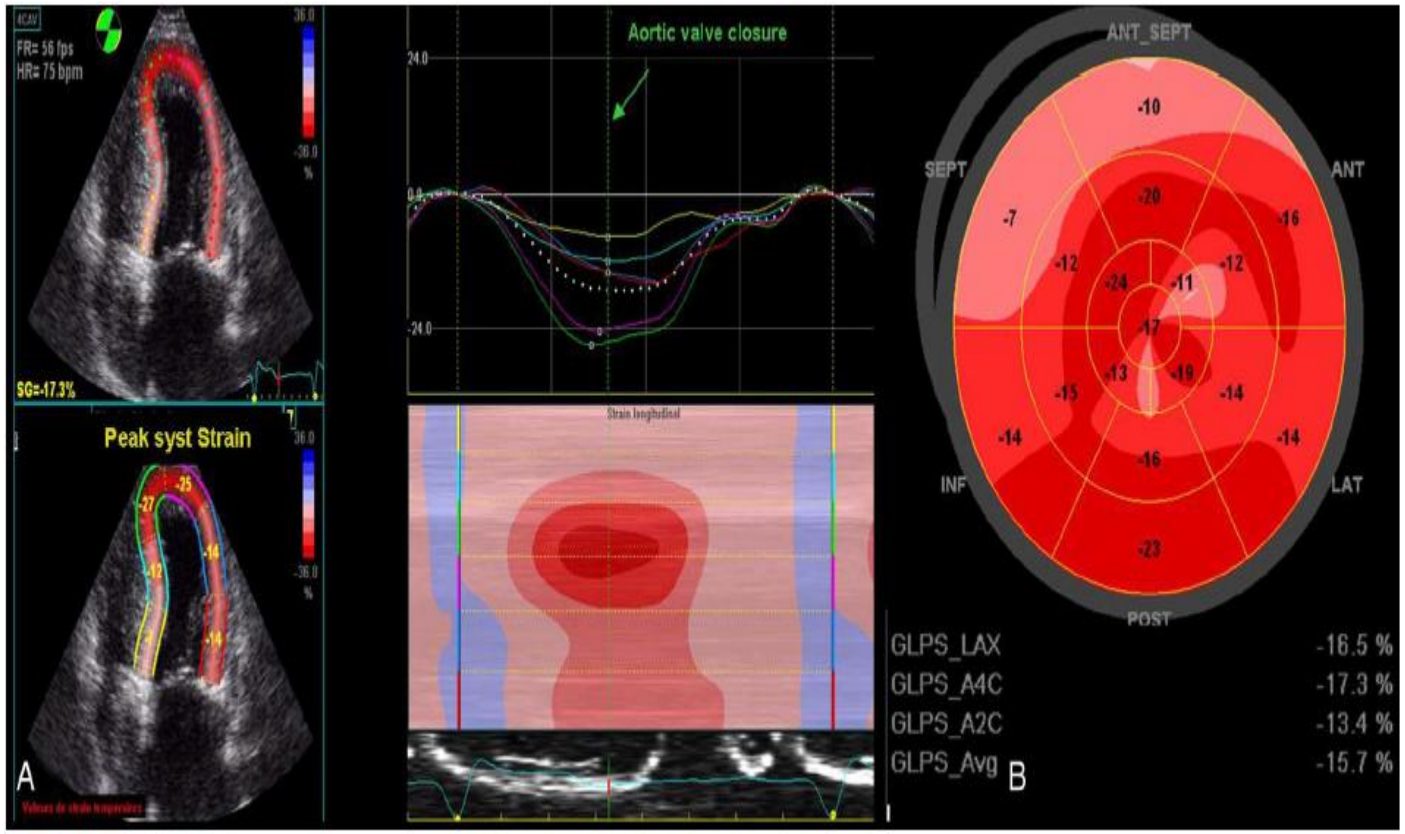
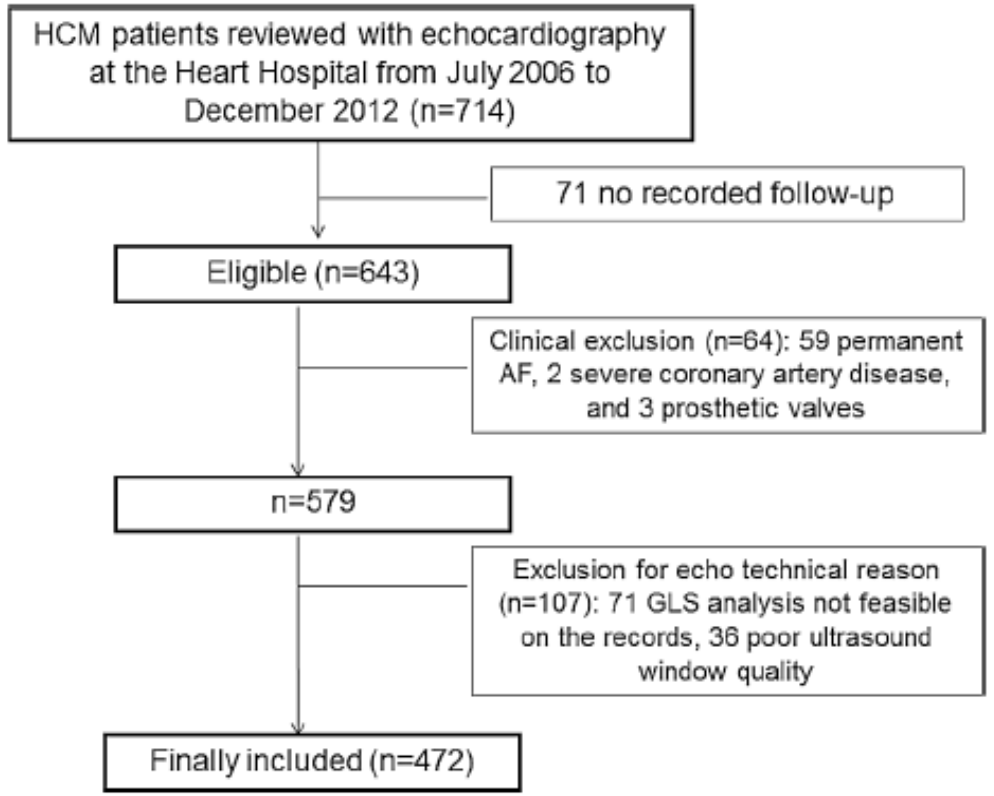
ORIGINAL ARTICLE

Global longitudinal strain is associated with heart failure outcomes in hypertrophic cardiomyopathy

Patricia Reant,[1,2] Mariana Mirabel,[1,3] Guy Lloyd,[1] Jérôme Peyrou,[2] Jose-Maria Lopez Ayala,[1] Shaughan Dickie,[1] Heeraj Bulluck,[1] Gabriella Captur,[1] Stefania Rosmini,[1] Oliver Guttmann,[1] Camelia Demetrescu,[1] Antonis Pantazis,[1] Maite Tome-Esteban,[1] James C Moon,[1] Stephane Lafitte,[2] William J McKenna[1]





Reant P, et al. *Heart.* 2016; **102**:741–747

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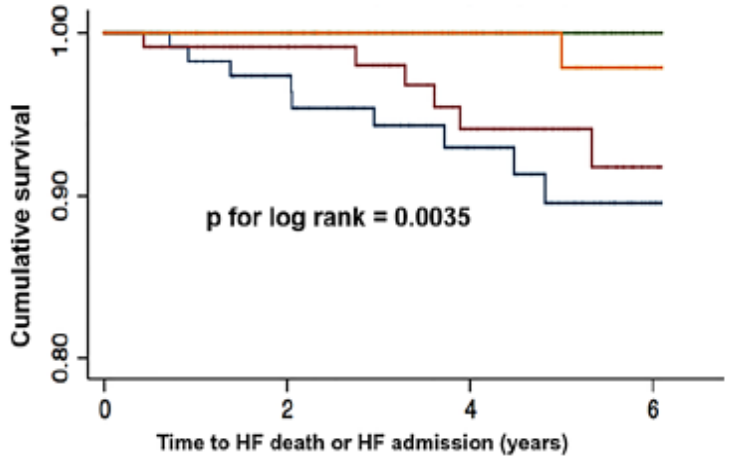
Multivariate analysis		
Factors	HR (95% CI)	p Value
Clinical variables	Primary end-point (n=37/472)	
Heart rate, bpm	1.02 (0.99 to 1.05)	0.066
NYHA class III–IV	2.40 (0.95 to 6.02)	0.065
Echocardiographic variables and age	Primary end-point (n=33/357)	
LV end-systolic volume, mL	0.95 (0.92 to 0.98)	0.001
Global longitudinal strain, %	0.90 (0.83 to 0.98)	0.018
Maximal provoked LVOT gradient, mm Hg	1.01 (1.00 to 1.02)	0.047
Age, years	1.01 (0.98 to 1.04)	0.56



No. at risk				
GLS ≤12.8%	119	101	71	28
12.9-15.5%	115	99	63	21
15.6-17.9%	119	98	70	23
GLS ≥18.0%	119	98	60	24

Multivariate analysis	HF death+HF admission (n=18/472)	
Factors	HR (95% CI)	p Value
GLS and clinical variables		
GLS, %	0.82 (0.75 to 0.90)	<0.0001
Age, years	1.03 (0.99 to 1.07)	0.10
GLS, %	0.82 (0.74 to 0.90)	<0.0001
Previous atrial fibrillation	2.84 (1.03 to 7.81)	0.043
GLS, %	0.83 (0.76 to 0.91)	<0.0001
NYHA class III–IV	4.84 (1.67 to 14.00)	0.004
GLS and other echo variables		
GLS, %	0.82 (0.75 to 0.89)	<0.0001
LV end-systolic volume, mL	0.98 (0.92 to 0.99)	0.036
GLS, %	0.83 (0.76 to 0.92)	<0.0001
Lateral E/E′ ratio	1.02 (0.97 to 0.06)	0.44
GLS, %	0.83 (0.76 to 0.90)	<0.0001
Maximal LVOT gradient at rest, mm Hg	1.01 (1.00 to 1.02)	0.040

Reant P, et al. *Heart.* 2016; **102**:741–747

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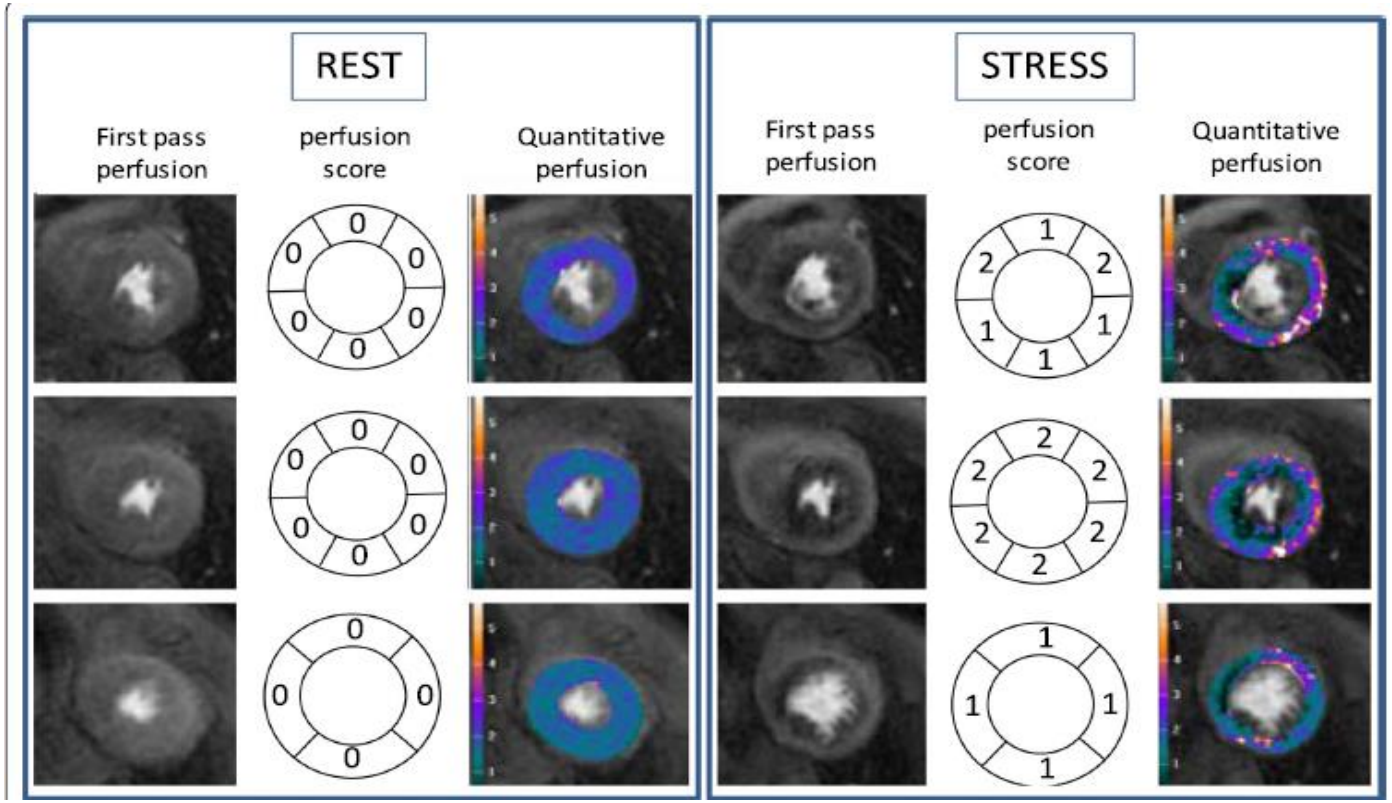
Cardiovascular magnetic resonance predictors of heart failure in hypertrophic cardiomyopathy: the role of myocardial replacement fibrosis and the microcirculation

Claire E. Raphael[1,9*], Frances Mitchell[1], Gajen Sunthar Kanaganayagam[1], Alphonsus C. Liew[1], Elisa Di Pietro[2], Miguel Silva Vieira[1], Lina Kanapeckaite[1], Simon Newsome[3], John Gregson[3], Ruth Owen[3], Li-Yueh Hsu[4], Vassilis Vassiliou[1,5], Robert Cooper[1], Aamir Ali MRCP[1], Tevfik F. Ismail[6], Brandon Wong[1], Kristi Sun[1], Peter Gatehouse[1], David Firmin[1], Stuart Cook[1,7], Michael Frenneaux[5], Andrew Arai[4], Rory O'Hanlon[8], Dudley J. Pennell[1] and Sanjay K. Prasad[1]



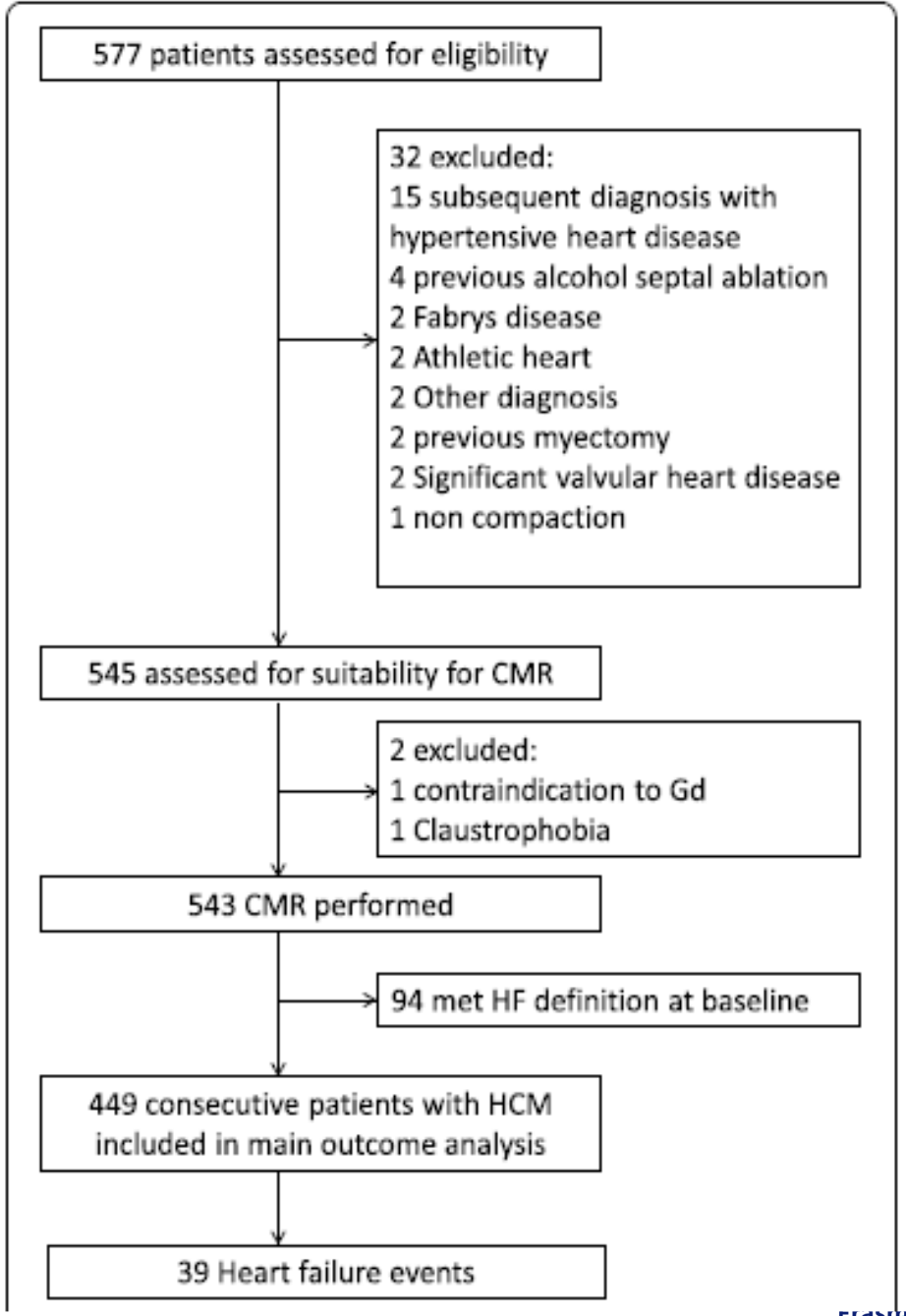


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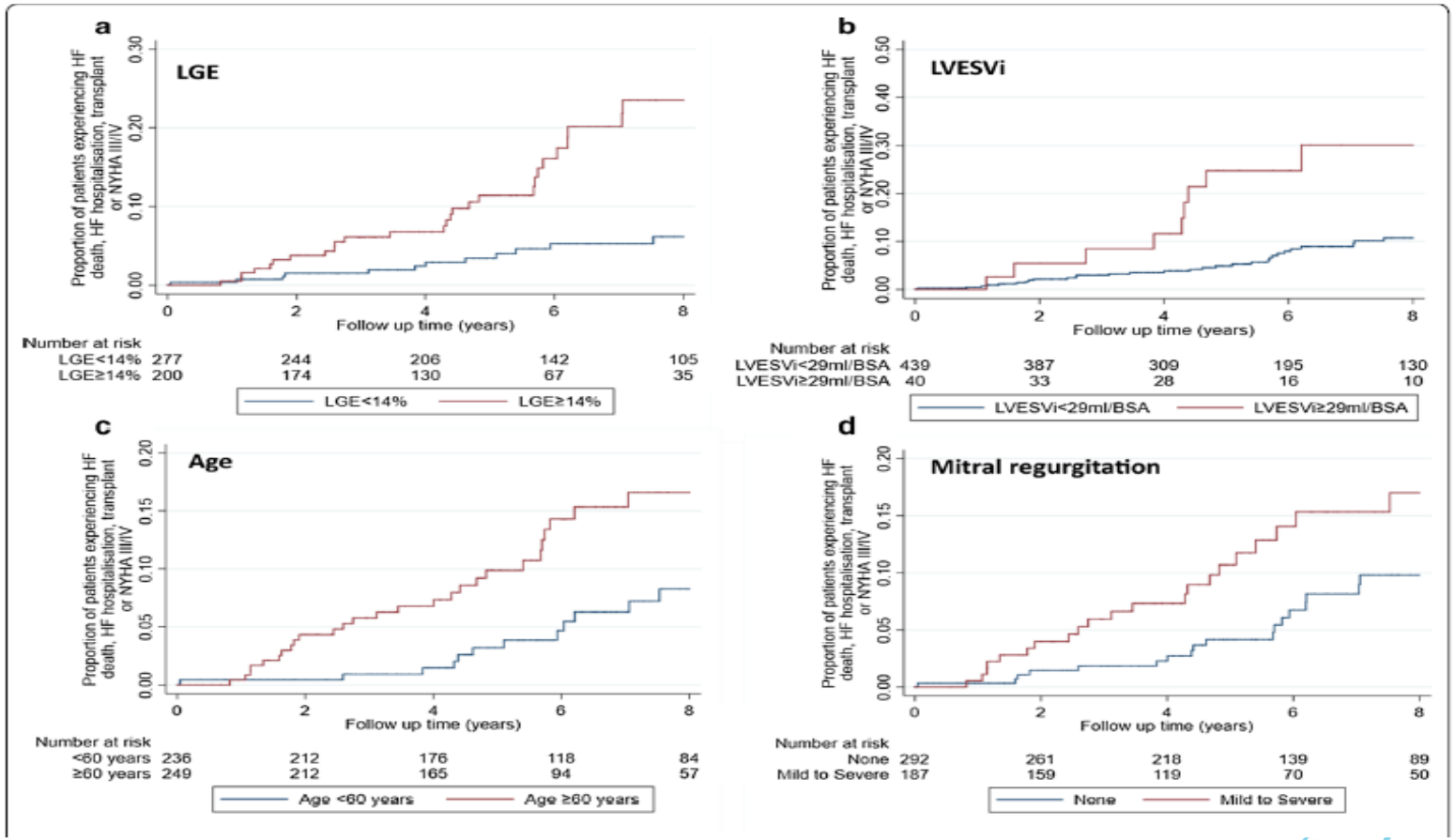
Table 3 Univariable predictors of a heart failure event

	HR (95% CI)	P
Age (per 10 years)	1.32 (1.04, 1.67)	0.02
Age at diagnosis (per 10 years)	1.16 (0.93, 1.45)	0.18
Body surface area (kg/m^2)	1.79 (0.41, 7.87)	0.44
Female	1.52 (0.78, 2.95)	0.22
Apical	0.47 (0.17, 1.32)	0.15
Atrial fibrillation	2.86 (0.88, 9.28)	0.08
LVOT gradient (≥ 30 mmHg at rest)	1.40 (0.74, 2.66)	0.3
Family history of sudden cardiac death	1.31 (0.60, 2.85)	0.5
Non sustained ventricular tachycardia	2.23 (1.02, 4.86)	0.04
Unexplained syncope	1.45 (0.69, 3.06)	0.33
Max wall thickness ≥ 30 mm	2.34 (0.83, 6.59)	0.11
CMR parameters		
Max wall thickness (mm)	1.03 (0.97, 1.09)	0.32
LVEDVI (per 10 ml/BSA)	1.19 (0.99, 1.45)	0.07
LVESVI (per 10 ml/BSA)	1.51 (1.23, 1.85)	<0.001
LAVI (per 10 ml/BSA)	1.11 (1.00, 1.22)	< 0.001
LVEF	0.95 (0.92, 0.98)	0.04
LGE (per 10%)	1.57 (1.27, 1.93)	0.001
Presence of LGE (≥ 5% of myocardial mass)[a]	3.99 (1.56, 10.22)	< 0.001
Perfusion defect	2.09 (0.74, 5.88)	0.004
Perfusion summed difference score	1.02 (0.98, 1.06)	0.16
Mitral regurgitation		
None	1	0.27
Mild	2.13 (1.10, 4.14)	0.03
Moderate/Severe	2.13 (0.72, 6.31)	0.27

	HR (95% CI)	P-value
LVESVI (per 10 ml/BSA)	1.44 (1.16, 1.78)	0.001
Mitral regurgitation		
None	Reference group	0.02
Mild	1.94 (0.99, 3.81)	
Moderate/Severe	2.55 (0.84, 7.70)	
LGE (per 10%)	1.44 (1.14, 1.82)	0.002
Age (per 10 years)	1.37 (1.06, 1.77)	0.02



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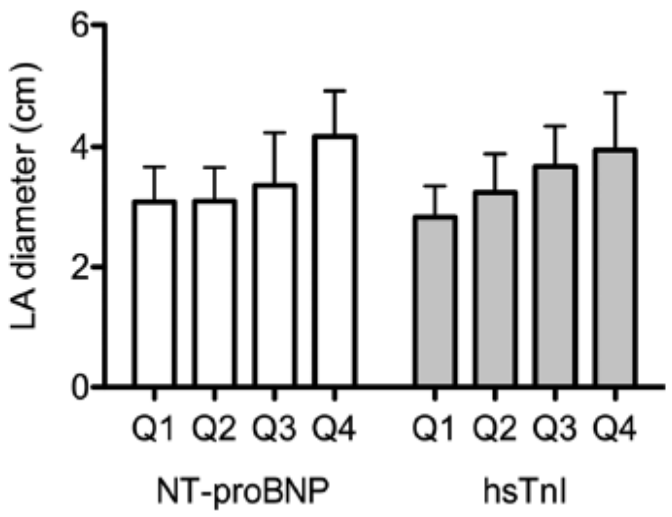
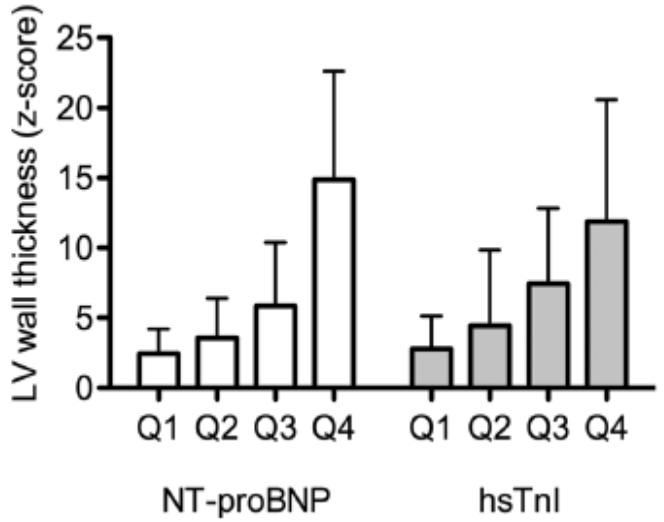
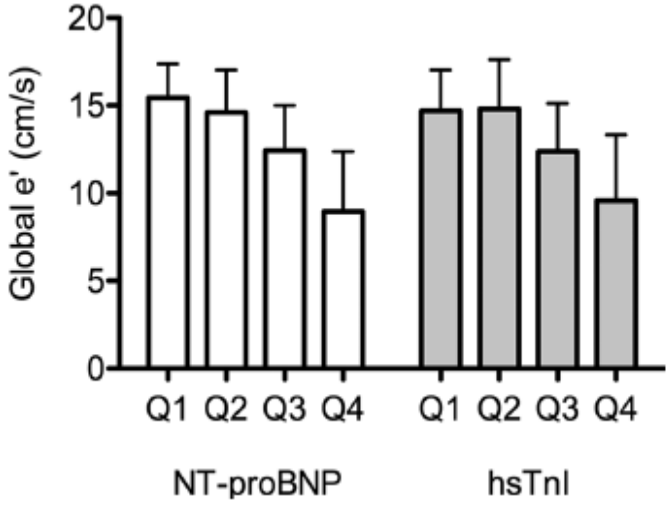
BIOMARKERS







Ho JE, et al. *Open Heart.* 2017; **4**:e000615

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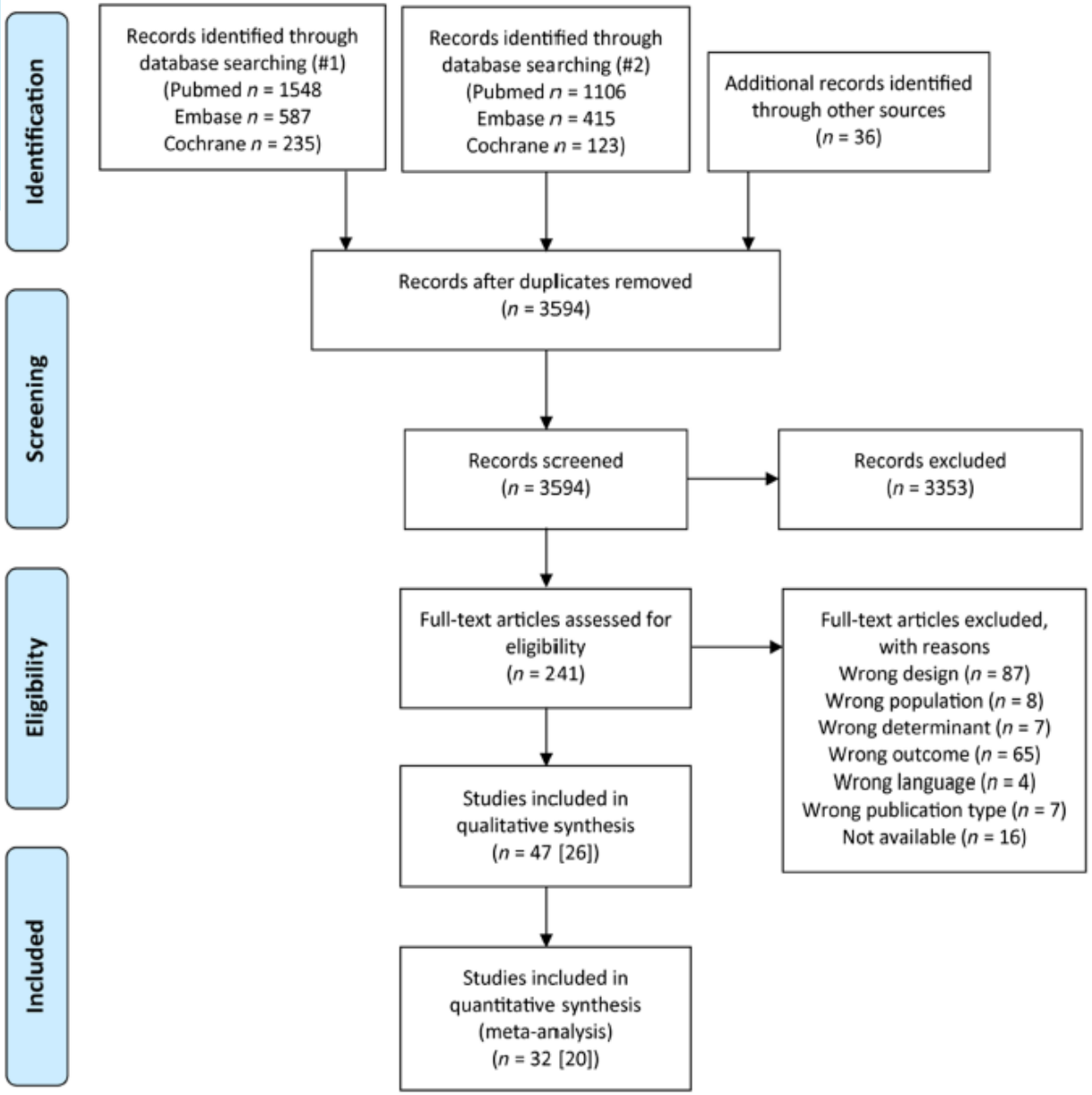

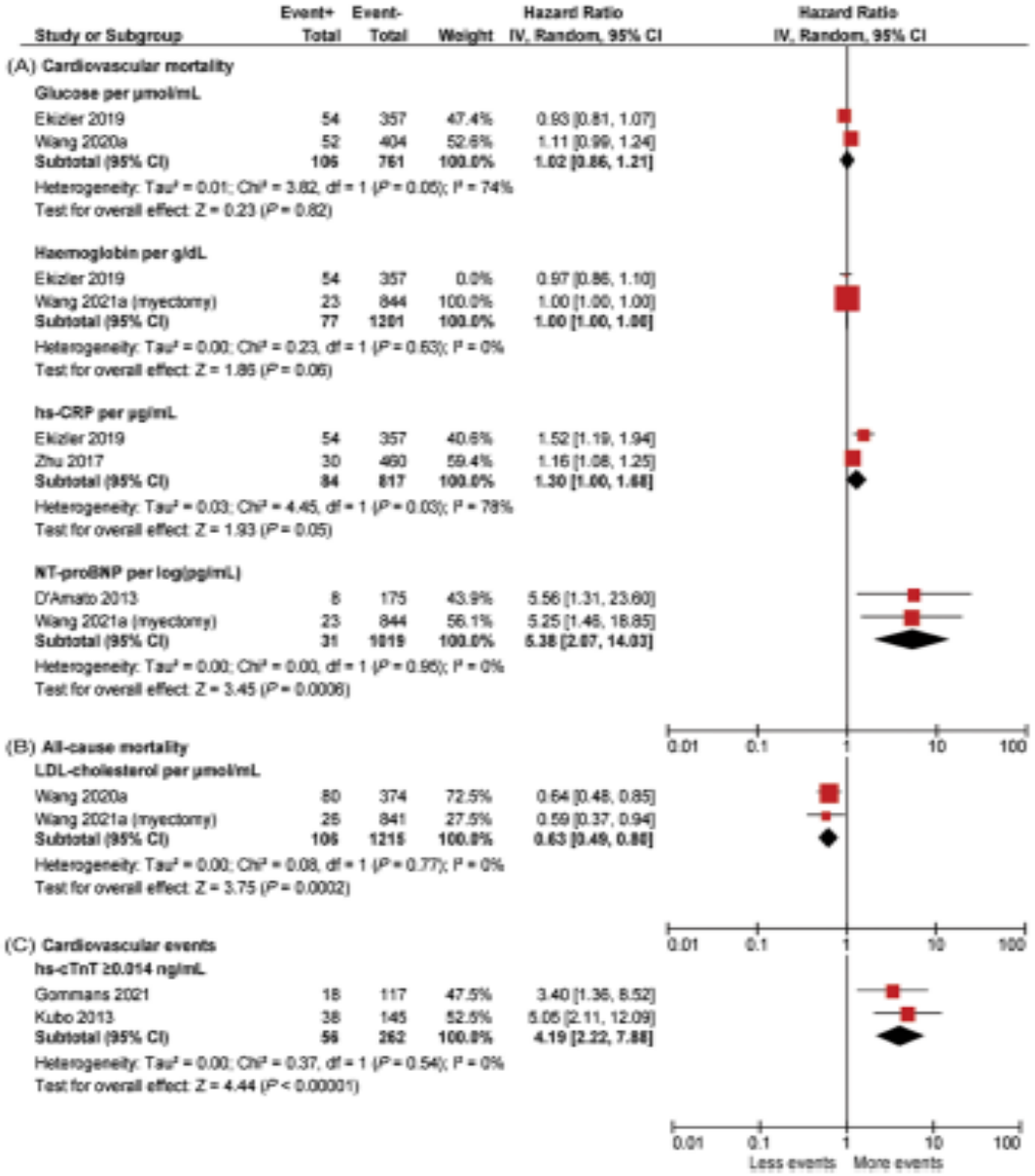

Meta analysis: poor quality, hs-TnIT/cTnI: predictor for HF, NT-proBNP predictor of mortality

Jansen M, et al. *ESC Heart Failure* 2022; **9**:3418–3434

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SUMMARY

- Heart failure often complicates HCM
- Easy rule: prognosis is good without HF and poor with HF
- Importance of etiology
- Risk factors (list likely not complete):
  - Specific sarcomere mutations/known proband
  - Female sex
  - Age of onset (young)
  - LVEF<50% (already starting LVEF <60%)
  - GLS < -18%
  - LGE (%?)
  - Rest obstruction >> provocable obstr >> no obstr
  - NT-proBNP + cTnI/cTnT (but: cut-offs values not validated)

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