



PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

ROMA

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Aritmologia Clinica e Cardiologia Interventistica in eta' pediatrica

CARDIOMIOPATIE IPERTROFICHE

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UOC di Cardiologia S. Paolo, Palidoro-S. Marinella e Aritmologia

Ospedale Pediatrico Bambino Gesù IRCCS



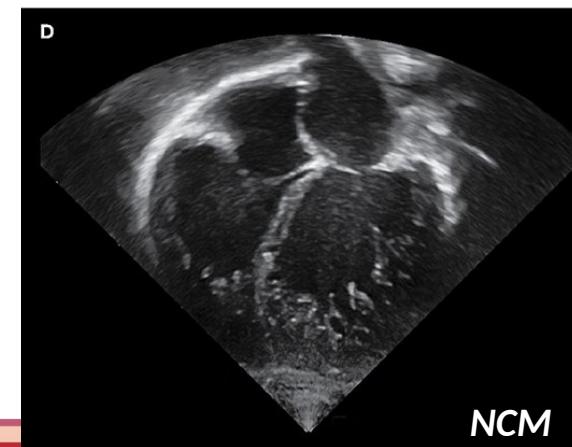
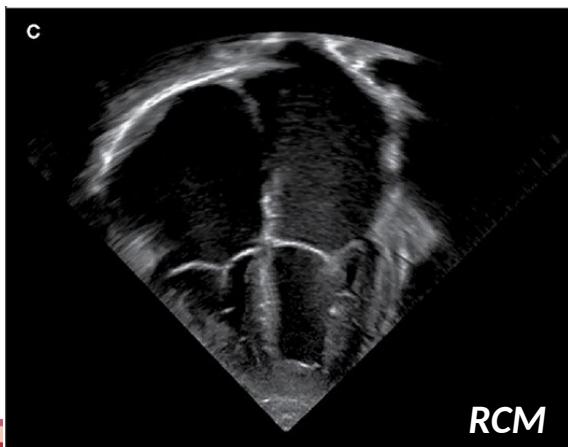
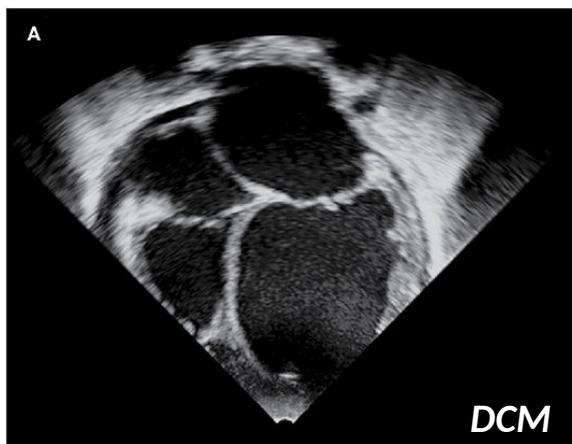
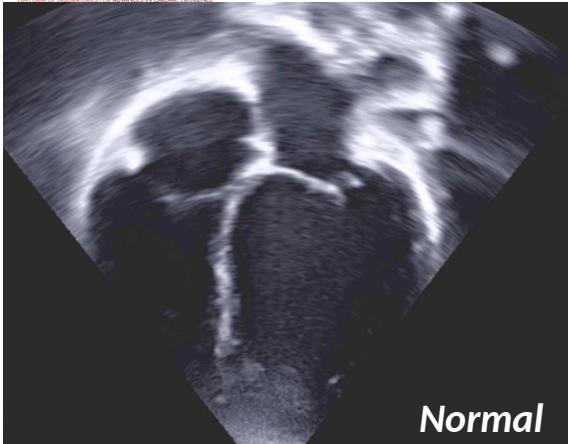
PAEDIATRIC CARDIOMYOPATHIES



A heterogenous group of rare disorders, characterized by mechanical and electrical abnormalities of the heart muscle.

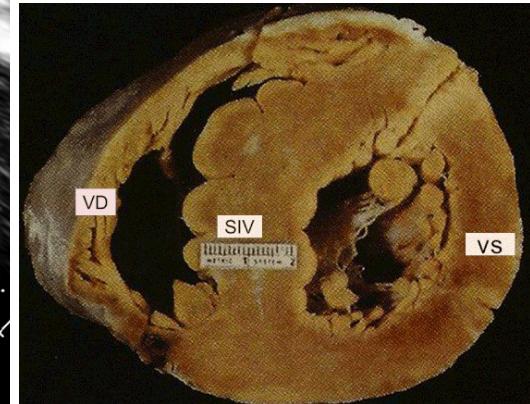
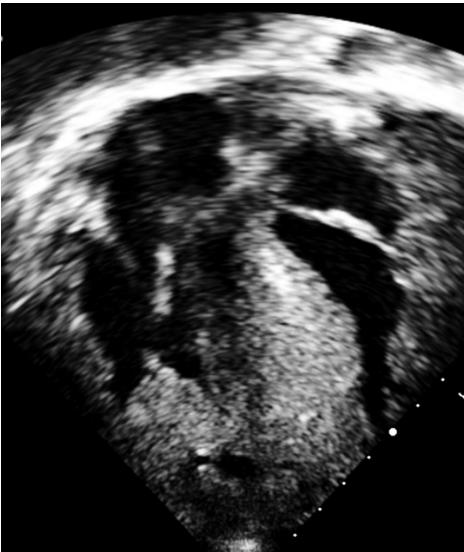
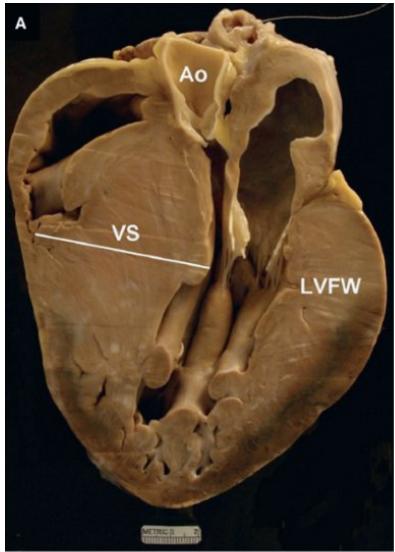
Annual incidence of childhood cardiomyopathies **1:100,000** children per year

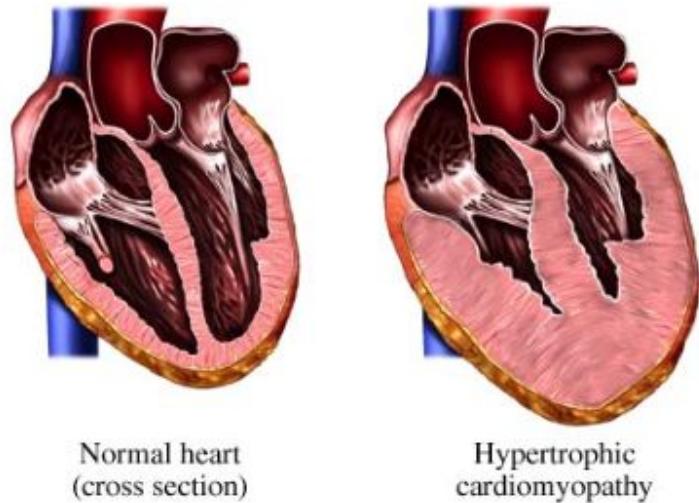
PAEDIATRIC CARDIOMYOPATHIES





HYPERTROPHIC CARDIOMIOPATHY





DEFINITION

Hypertrophic cardiomyopathy (HCM) is defined by the presence of left ventricular hypertrophy (LVH), in the absence of congenital heart disease or abnormal loading conditions sufficient to explain the observed degree of hypertrophy

Prevalence in young adults **1:500**

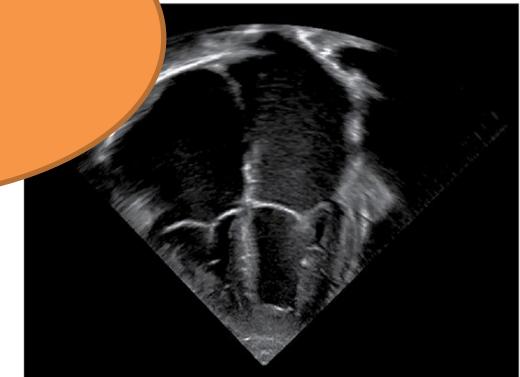
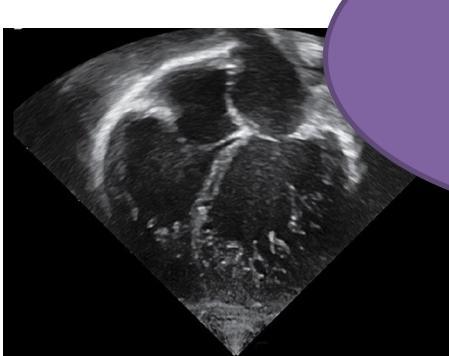
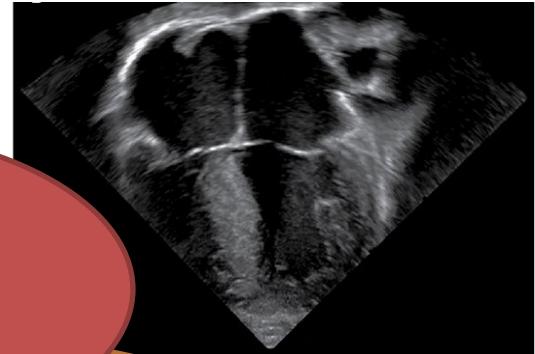
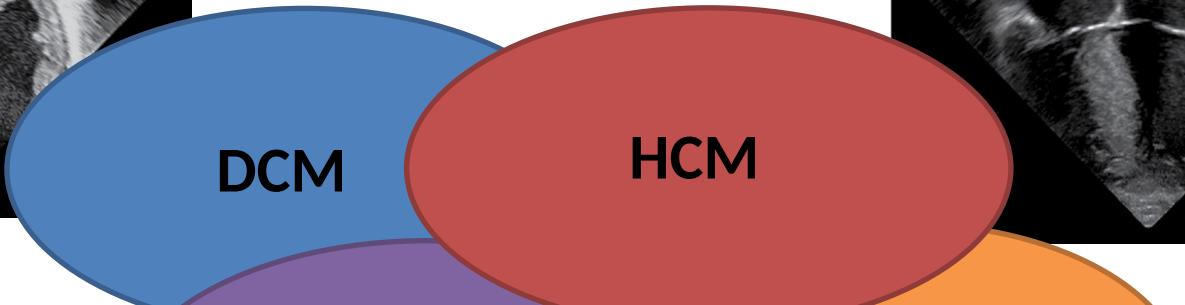
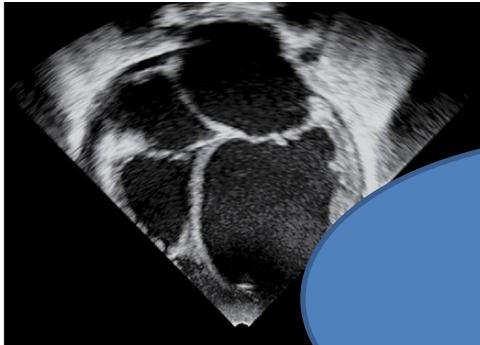
In children it has been estimated an incidence of **0.24-0.47: 100.000** by year

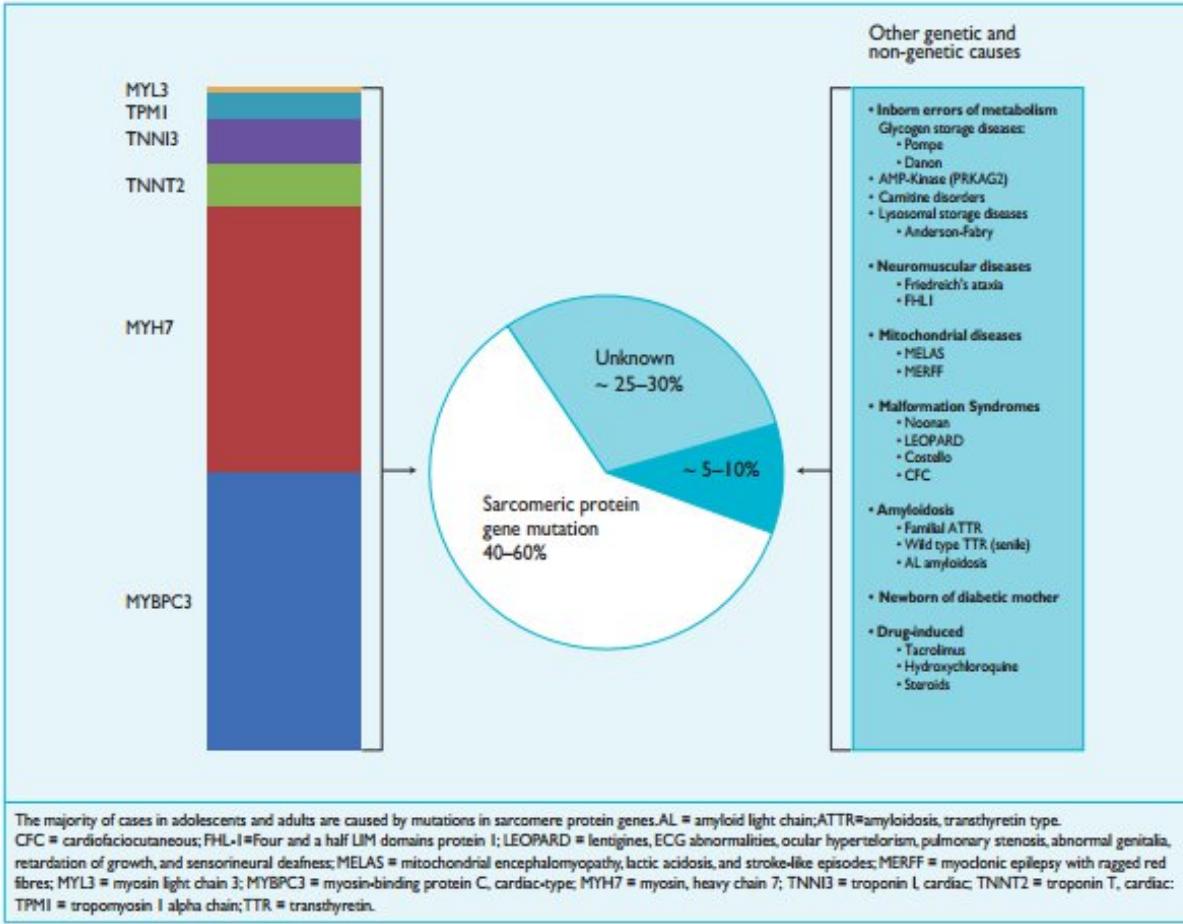
Annual incidence for cardiovascular death of **1-2%**

First cause of sudden cardiac death in young athletes

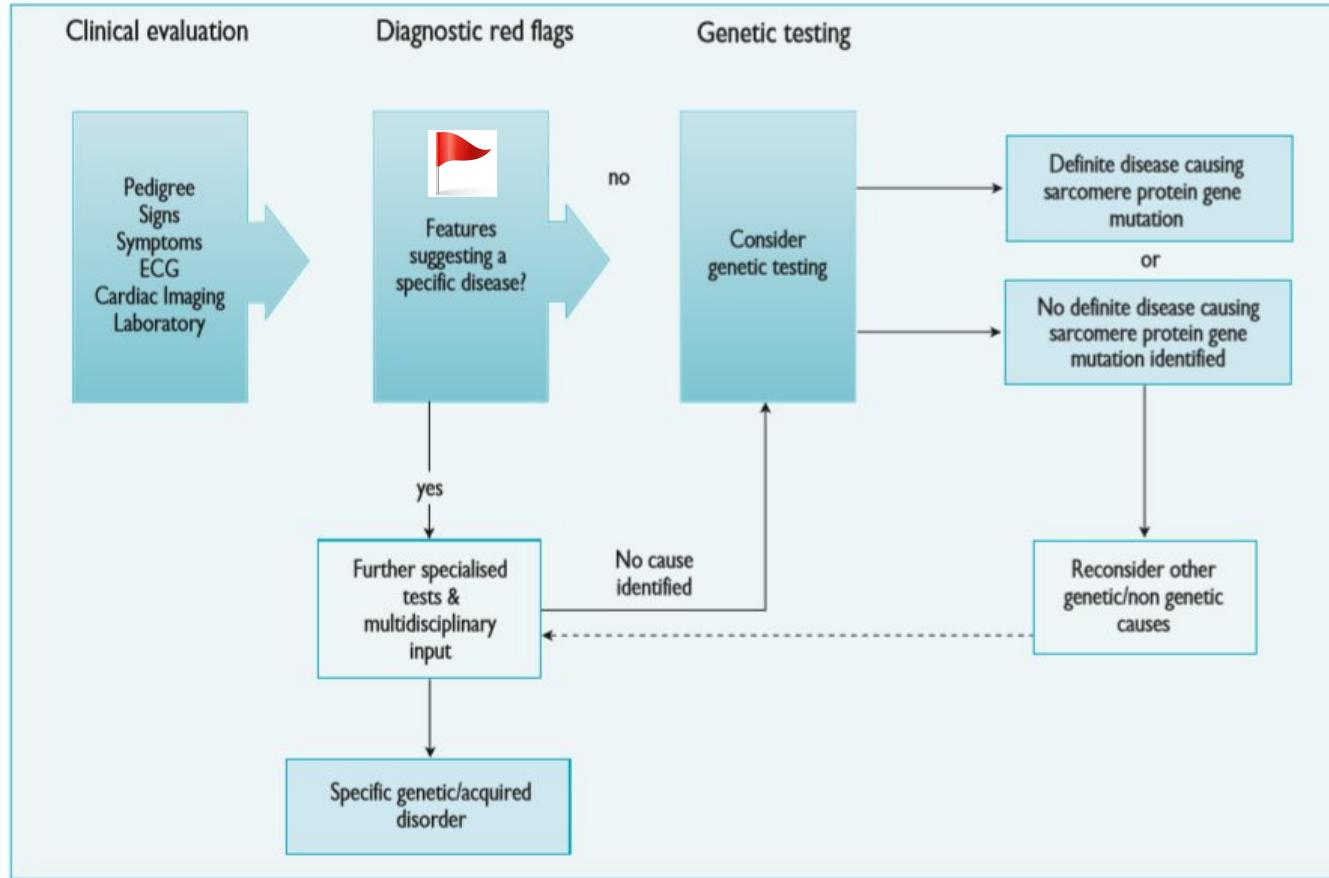
Arola A et al. Am J Epidemiol 1997; 146: 385-393.
Lipshultz SE et al. N Engl J Med 2003; 348: 1647-1655.
Nugent A et al. Circulation 2005;112:1332-1338.

PAEDIATRIC CARDIOMYOPATHIES



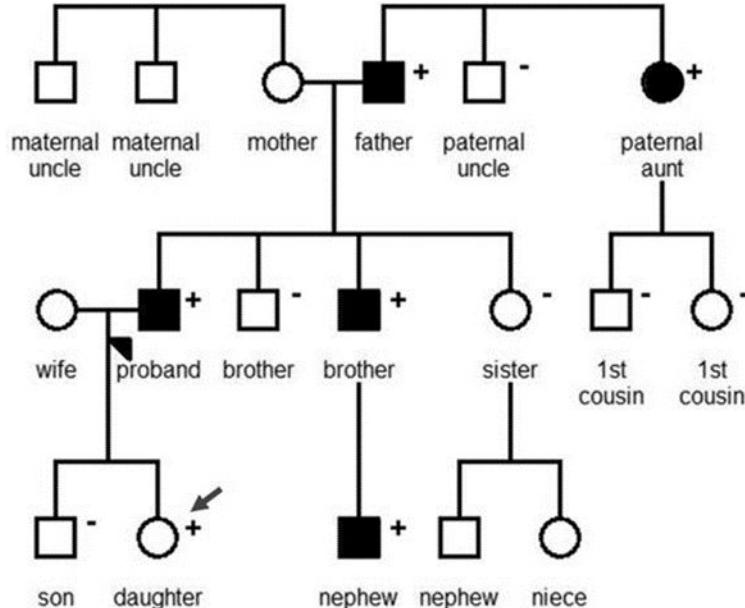


The majority of cases in adolescents and adults are caused by mutations in sarcomere protein genes. AL = amyloid light chain; ATTR=amyloidosis, transthyretin type. CFC = cardiofaciocutaneous; FHL1=Four and a half LIM domains protein 1; LEOPARD = lentigines, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERFF = myoclonic epilepsy with ragged red fibres; MYL3 = myosin light chain 3; MYBPC3 = myosin-binding protein C, cardiac-type; MYH7 = myosin, heavy chain 7; TNNI3 = troponin I, cardiac; TNNT2 = troponin T, cardiac; TPM1 = tropomyosin I alpha chain; TTR = transthyretin.





FAMILY PEDIGREE



Mode of inheritance:

- Autosomal dominant
- X-linked
- Autosomal recessive
- De novo mutations

(but apparently sporadic cases can arise because of incomplete penetrance in a parents)

CLINICAL HISTORY

- Age
- Poor growth (Infants and young children)
- Multiorgan system involvement (mitochondrial or metabolic disorders)
- Systemic myopathy (neuromuscular disorders)

SYMPTOMS

- Asymptomatic
- Heart Failure
- Chest pain
- Palpitations
- Syncope
- SCD

Infants

Older children & adolescents

- Tachypnoea
- Poor feeding
- Excessive sweating
- Failure to thrive
- Fatigue
- Dyspnoea

Table 3 Examples of signs and symptoms suggestive of specific diagnoses (modified from Rapezzi et al.⁶⁷)

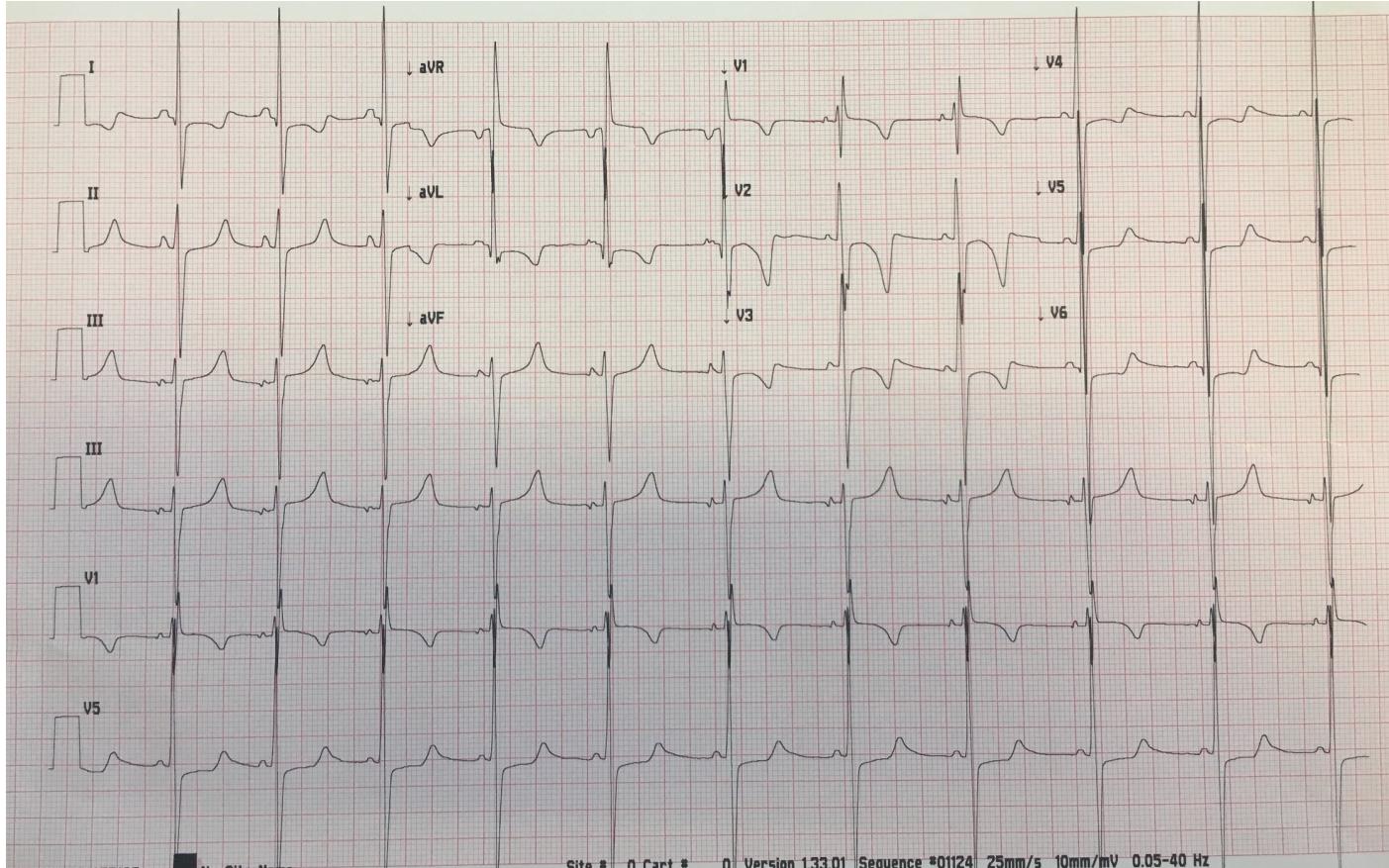
Symptom/sign	Diagnosis
Learning difficulties, mental retardation	<ul style="list-style-type: none"> Mitochondrial diseases Noonan/LEOPARD/Costello syndrome Danon disease
Sensorineural deafness	<ul style="list-style-type: none"> Mitochondrial diseases (particularly with diabetes) Anderson-Fabry disease LEOPARD syndrome
Visual impairment	<ul style="list-style-type: none"> Mitochondrial diseases (retinal disease, optic nerve atrophy) TTR-related amyloidosis (cotton wool type vitreous opacities) Danon disease (retinitis pigmentosa) Anderson-Fabry disease (cataracts, corneal opacities)
Gait disturbance	<ul style="list-style-type: none"> Friedreich's ataxia
Paraesthesia/sensory abnormalities/neuropathic pain	<ul style="list-style-type: none"> Amyloidosis Anderson-Fabry disease
Carpal tunnel syndrome	<ul style="list-style-type: none"> TTR-related amyloidosis (especially when bilateral and in male patients)
Muscle weakness	<ul style="list-style-type: none"> Mitochondrial diseases Glycogen storage disorders FHL1 mutations Friedreich's ataxia
Palpebral ptosis	<ul style="list-style-type: none"> Mitochondrial diseases Noonan/LEOPARD syndrome Myotonic dystrophy
Lentigines/café au lait spots	<ul style="list-style-type: none"> LEOPARD/Noonan syndrome
Angiokeratomata, hypohidrosis	<ul style="list-style-type: none"> Anderson-Fabry disease

ECG anomalies suggestive of underlying aetiology

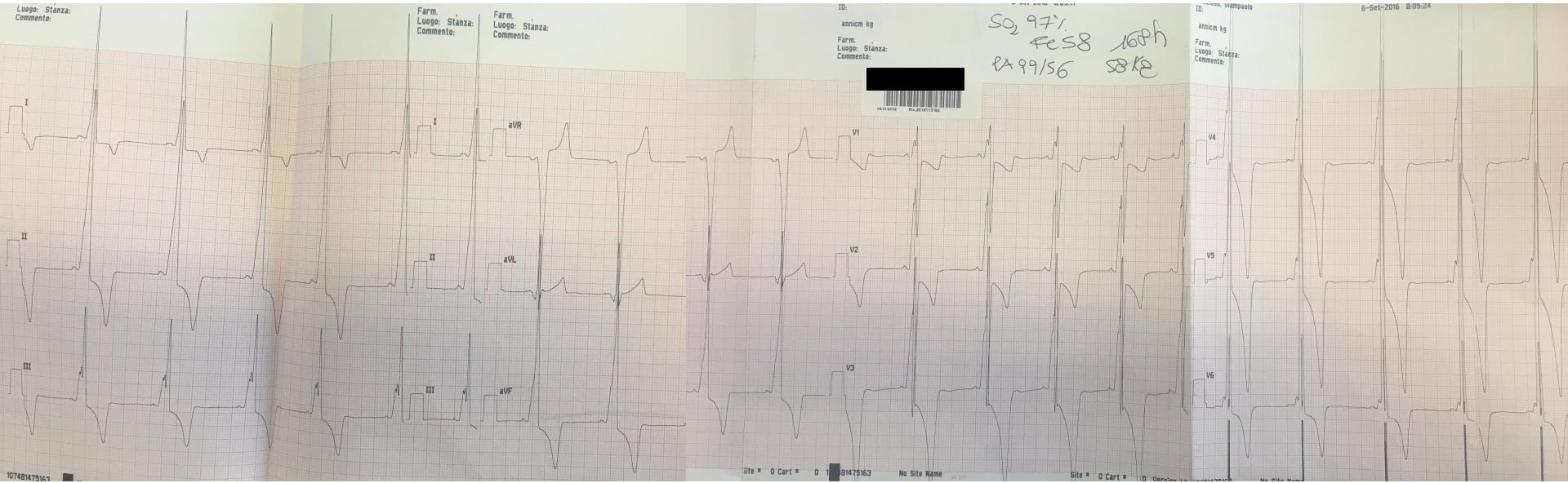


	Pompe	Danon	PRKAG2	Mitochondrial	Noonan
Short PR/pre-exitacion	✓	✓	✓	✓	
AV block		✓	✓	✓	
Superior QRS axis					✓
Extreme LVH	✓	✓			
Biventricular hypertrophy	✓				✓

Noonan Syndrome

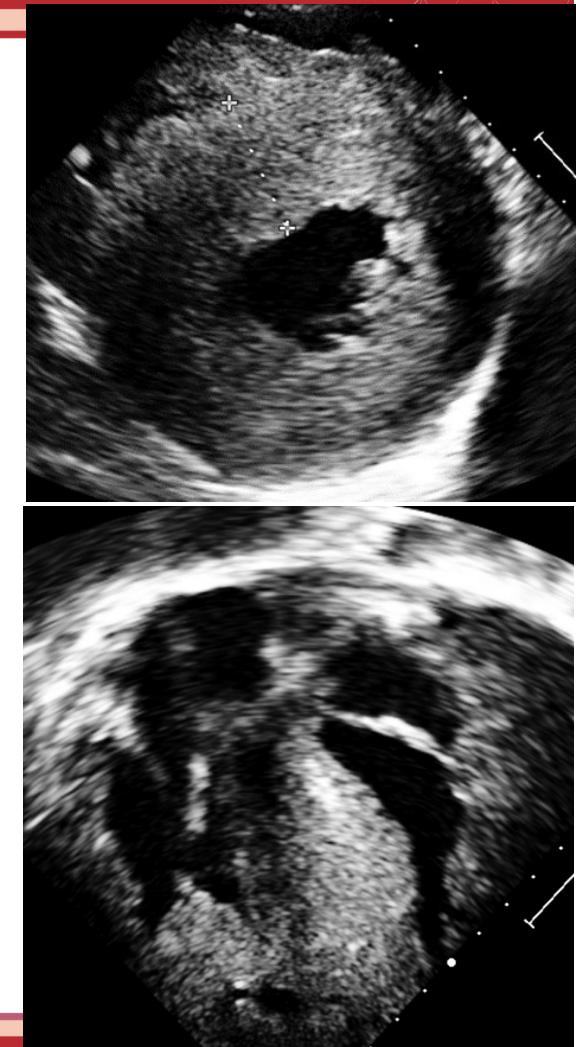


Danon Disease

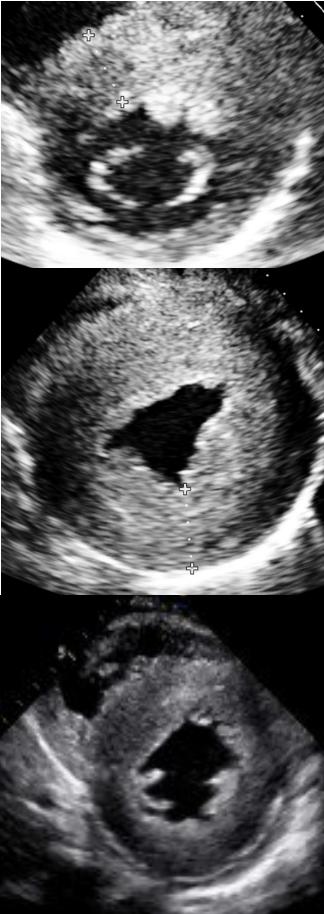


DIAGNOSIS

- **Adults:** HCM is defined by a wall thickness ≥ 15 mm in one or more LV myocardial segments
- **Children:** LV wall thickness more than two standard deviations greater than the predicted mean (z-score >2).
- **First-degree relatives :** unexplained increased LV wall thickness ≥ 13 mm in one or more LV myocardial segments, as measured using any cardiac imaging technique .



ECHOCARDIOGRAPHY



ASYMMETRIC

CONCENTRIC

(Metabolic and infiltrative disorders)



BIVENTRICULAR

(Noonan syndrome)

Laboratory Tests



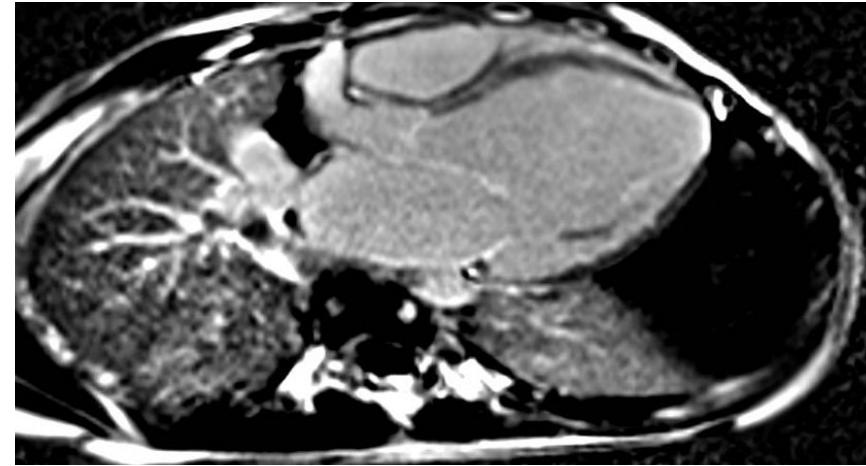
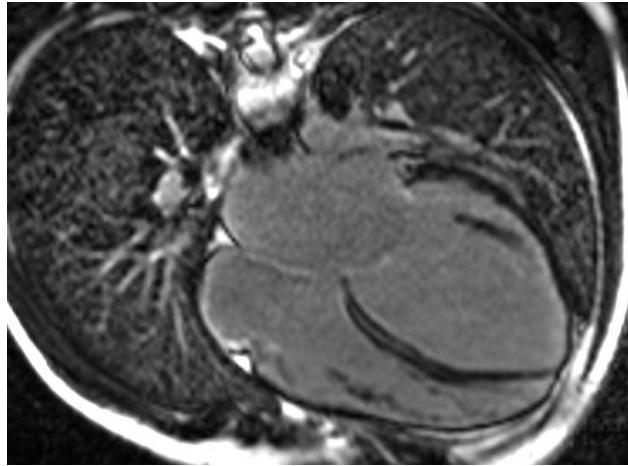
- BNP/NT-proBNP, troponin
- Blood count
- Biochemistry
- Thyroid function test
- Urine test
- Blood gas analysis, metabolic investigation
- Genetic test

- *Establishing the underlying diagnosis.*
- *Assessing the severity of heart failure and multiorgan dysfunction.*
- *Monitoring response to therapies.*

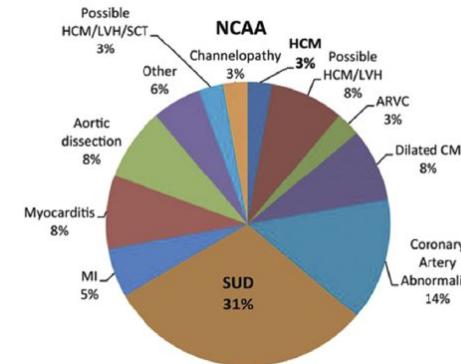
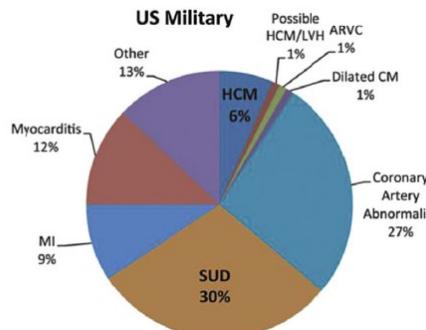
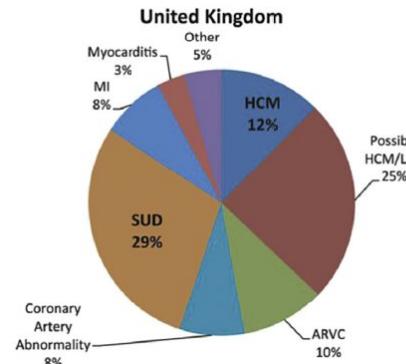
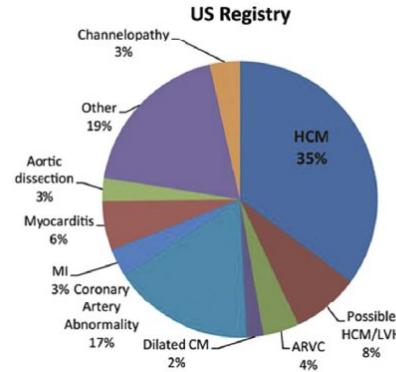
Cardiac Magnetic Resonance



- Identification of underlying disease processes.
- Evidence of fibrosis by late gadolinium enhancement.



CAUSES OF SCD IN YOUNG



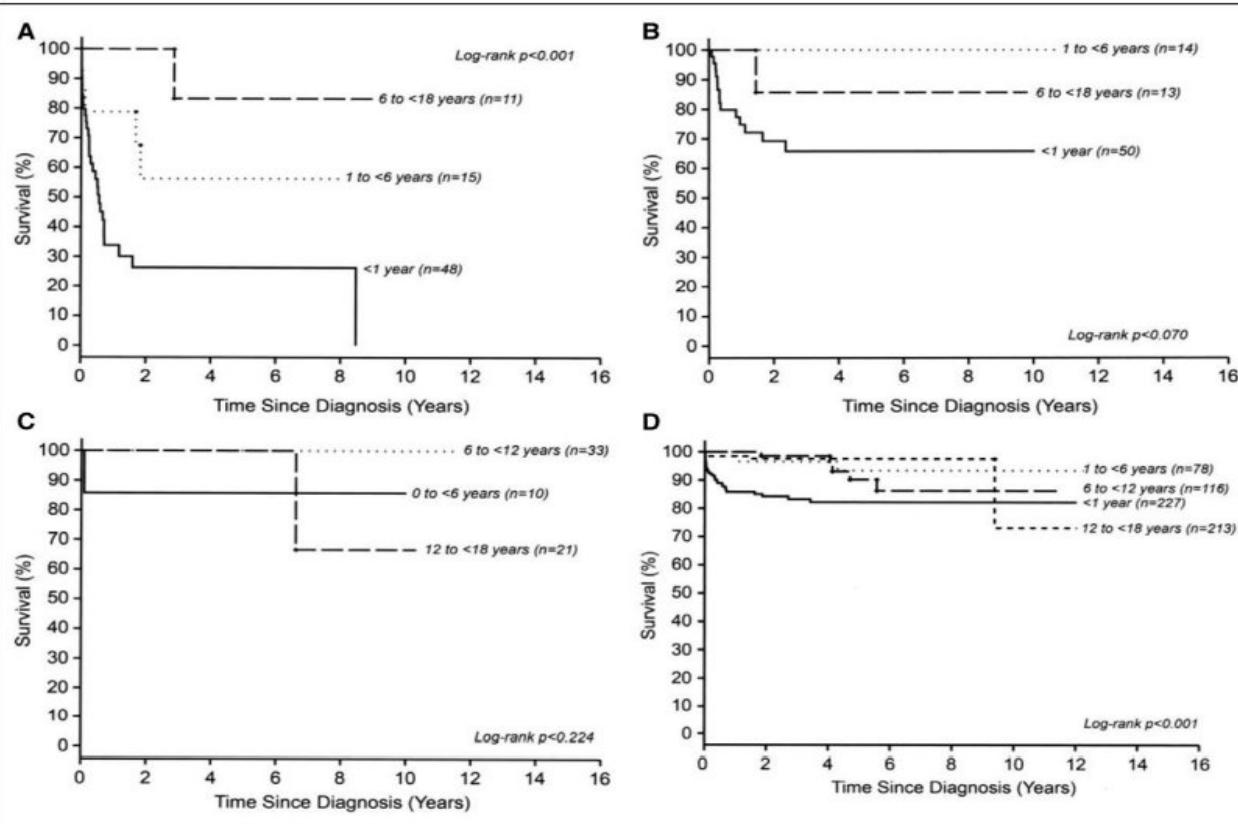


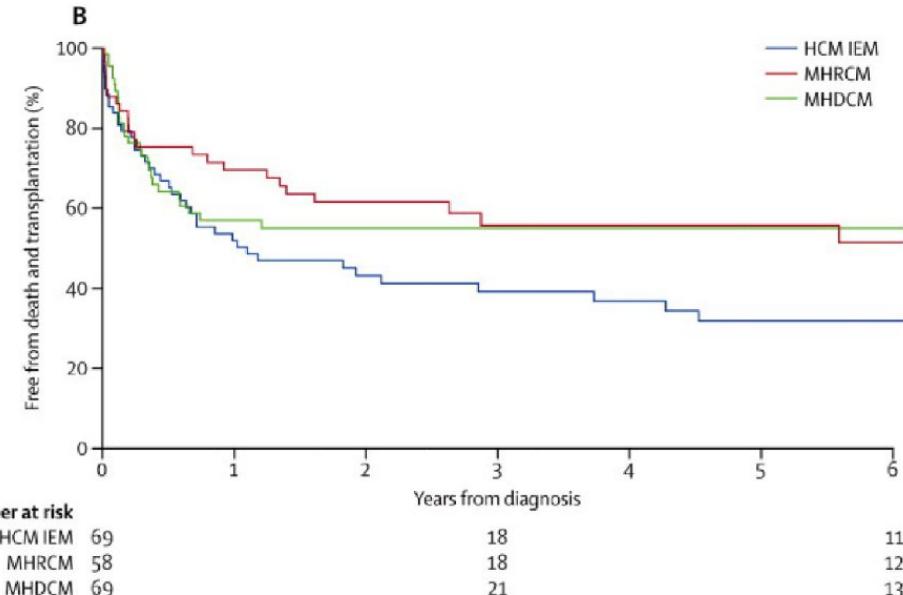
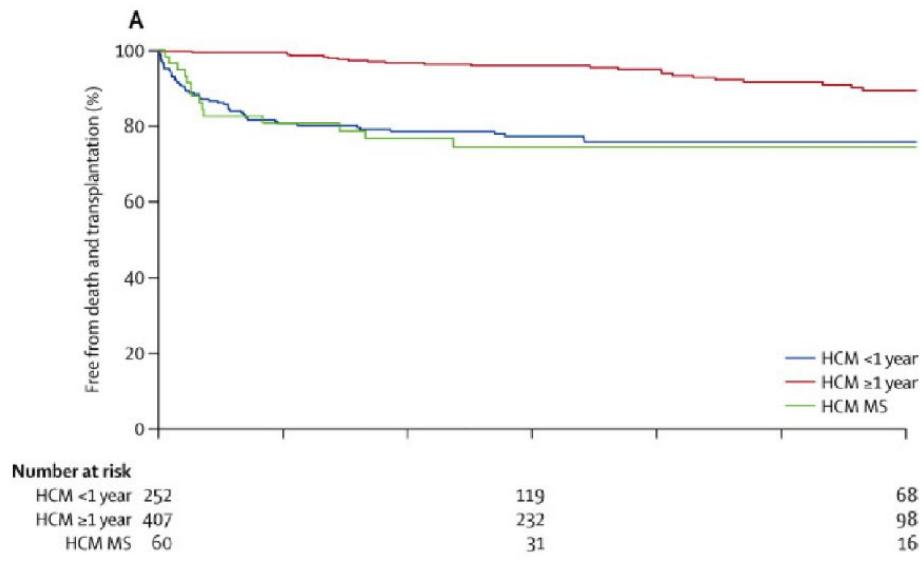
Figure 5. Survival since the diagnosis of cardiomyopathy caused by (A) inborn errors of metabolism, (B) malformation syndrome, (C) neuromuscular disorder, and (D) idiopathic hypertrophic cardiomyopathy.

Reprinted from Colan et al.⁹ Copyright © 2007, American Heart Association, Inc.

Canter et al 2007

Pediatric Cardiomyopathy Registry

Cause of death in HCM

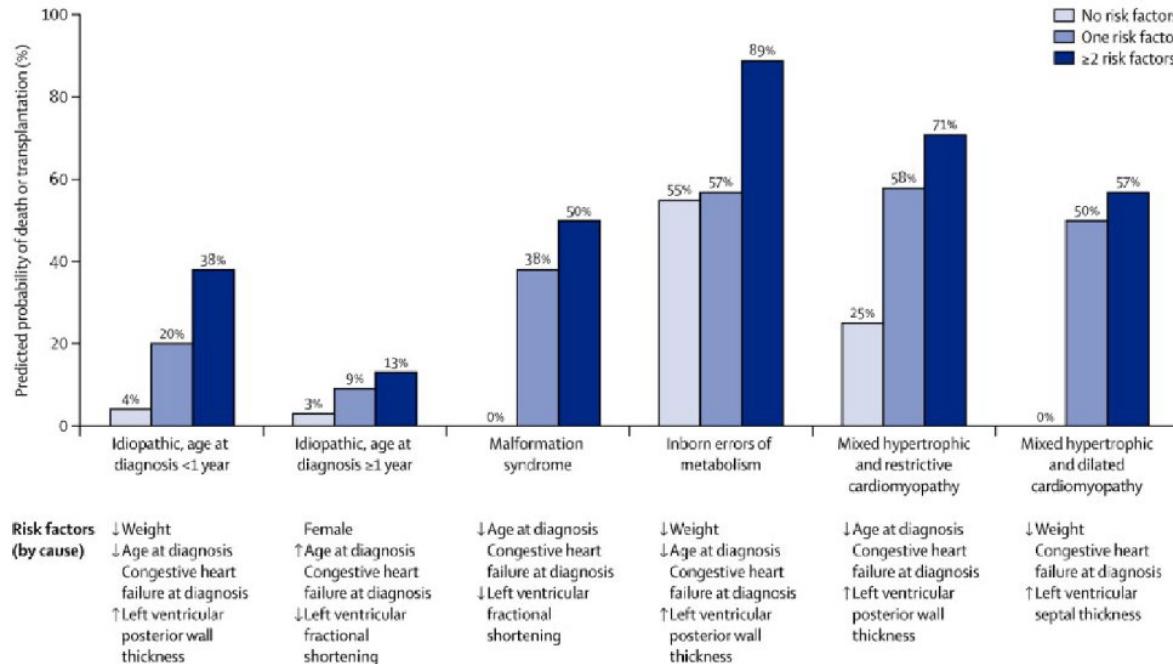


Lipschultz et al, Lancet 2013



Pediatric Cardiomyopathy Registry

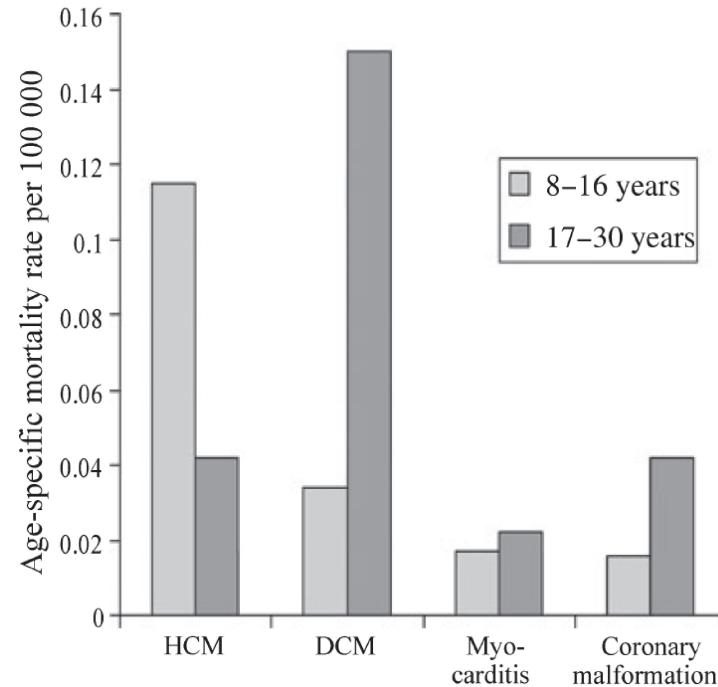
Cause of death in HCM



Lipschultz et al, Lancet 2013



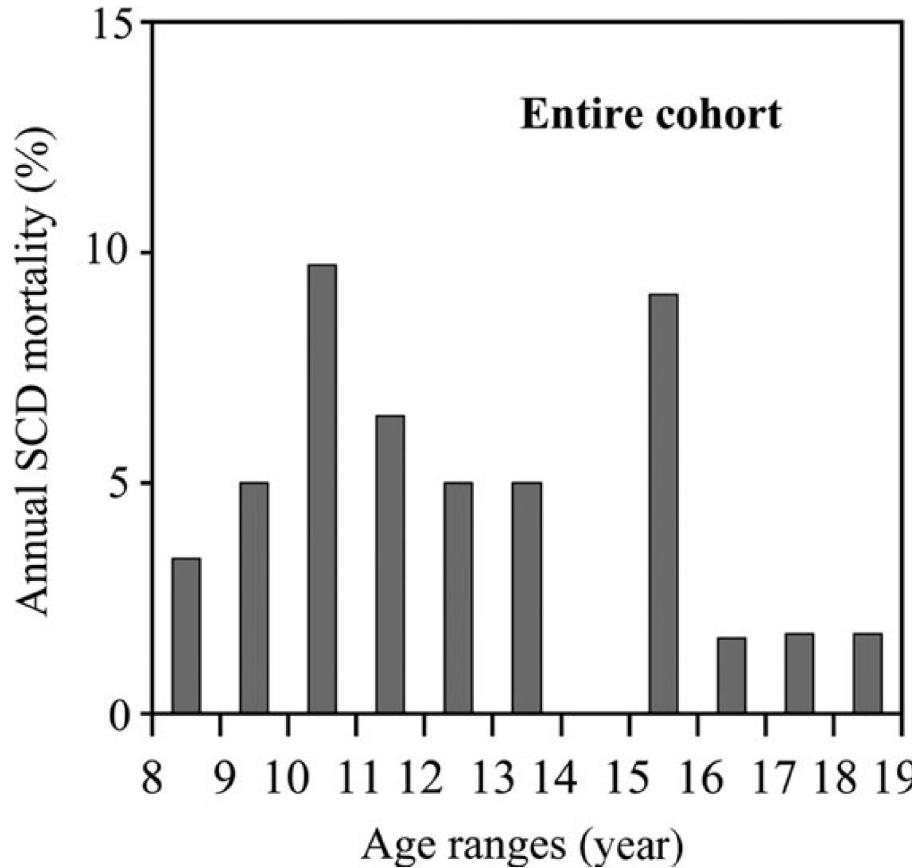
Age specific mortality rates Swedish Registry



Ostman-Smith, Eur Heart J 2008



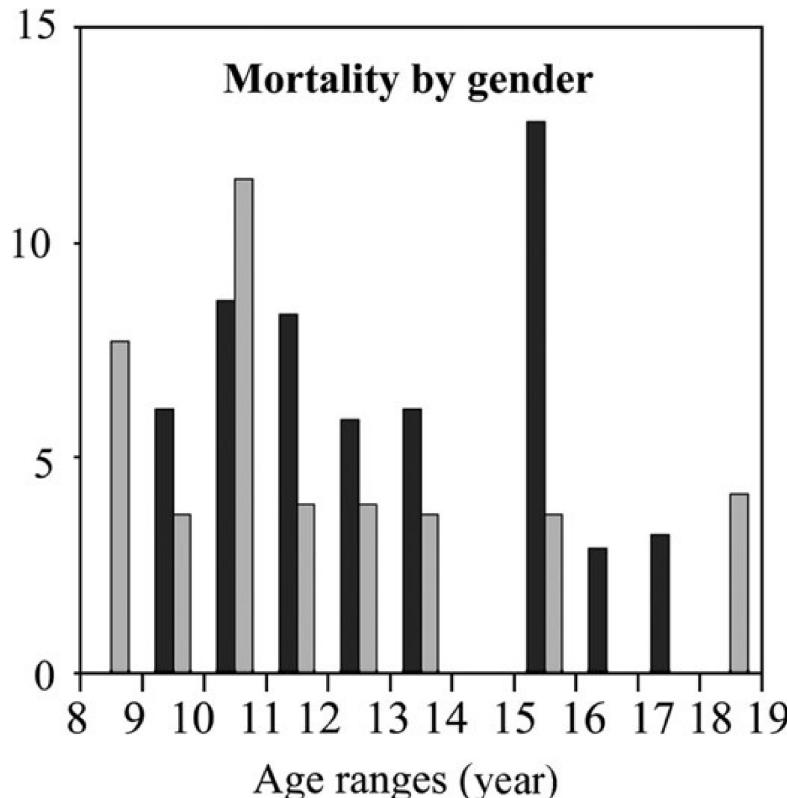
SCD in Pediatric HCM



Ostman-Smith, Eur Heart J 2008



SCD according to Gender in Pediatric HCM



Ostman-Smith, Eur Heart J 2008

A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk-SCD)

Table 7 Major clinical features associated with an increased risk of sudden cardiac death in adults

Risk Factor	Comment
Age	<ul style="list-style-type: none"> The effect of age on SCD has been examined in a number of studies^{73,82,99,244,372–374} and two have shown a significant association, with an increased risk of SCD in younger patients.^{73,99} Some risk factors appear to be more important in younger patients, most notably, NSVT,¹⁴ severe LVH⁷³ and unexplained syncope.⁹⁹
Non-sustained ventricular tachycardia	<ul style="list-style-type: none"> NSVT (defined as ≥3 consecutive ventricular beats at ≥120 BPM lasting <30 seconds) occurs in 20–30% of patients during ambulatory ECG monitoring and is an independent predictor of SCD.^{69,73,83,244,374} There is no evidence that the frequency, duration or rate of NSVT influences the risk of SCD.^{69,376}
Maximum left ventricular wall thickness	<ul style="list-style-type: none"> The severity and extent of LVH measured by TTE are associated with the risk of SCD.^{69,120,212,373} Several studies have shown the greatest risk of SCD in patients with a maximum wall thickness of ≥30 mm but there are few data in patients with extreme hypertrophy (>35 mm).^{69,73,120,247,248,373,377,378}
Family history of sudden cardiac death at a young age	<ul style="list-style-type: none"> While definitions vary,^{73,120,372,377} a family history of SCD is usually considered clinically significant when one or more first-degree relatives have died suddenly aged <40 years with or without a diagnosis of HCM, or when SCD has occurred in a first-degree relative at any age with an established diagnosis of HCM.
Syncope	<ul style="list-style-type: none"> Syncope is common in patients with HCM but it is challenging to assess as it has multiple causes.³⁷⁹ Non-neurocardiogenic syncope for which there is no explanation after investigation is associated with increased risk of SCD.^{73,83,99,244,346–348} Episodes within 6 months of evaluation may be more predictive of SCD.⁹⁹
Left atrial diameter	<ul style="list-style-type: none"> Two studies have reported a positive association between LA size and SCD.^{73,99} There are no data on the association between SCD and LA area and volume. Measurement of LA size is also important in assessing the risk of AF (see section 9.4).
Left ventricular outflow tract obstruction	<ul style="list-style-type: none"> A number of studies have reported a significant association with LVOTO and SCD.^{73,82,83,244,372,380} Several unanswered questions remain, including the prognostic importance of provokable LVOTO and the impact of treatment (medical or invasive) on SCD.
Exercise blood pressure response	<ul style="list-style-type: none"> Approximately one third of adult patients with HCM have an abnormal systolic blood pressure response to exercise characterised by progressive hypertension or a failure to augment the systolic blood pressure that is caused by an inappropriate drop in systemic vascular resistance and a low cardiac output reserve.^{381,382} Various definitions for abnormal blood pressure response in patients with HCM have been reported^{69,83,246,377;} for the purposes of this guideline an abnormal blood pressure response is defined as a failure to increase systolic pressure by at least 20 mm Hg from rest to peak exercise or a fall of >20 mm Hg from peak pressure.³⁷⁷ Abnormal exercise blood pressure response is associated with a higher risk of SCD in patients aged ≤40 years;²⁷⁷ but its prognostic significance in patients >40 years of age is unknown.

HCM = hypertrophic cardiomyopathy; LA = left atrium; LVH = left ventricular hypertrophy; LVOTO = left ventricular outflow tract obstruction; NSVT = non-sustained ventricular tachycardia; SCD = sudden cardiac death; TTE = transthoracic echocardiography.

ESC SCORE HCM Risk-SCD



HCM Risk-SCD Calculator

Age	Years	Age at evaluation
Maximum LV wall thickness	mm	Transthoracic Echocardiographic measurement
Left atrial size	mm	Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane at time of evaluation
Max LVOT gradient	mmHg	The maximum LV outflow gradient determined at rest and with Valsalva provocation (irrespective of concurrent medical treatment) using pulsed and continuous wave Doppler from the apical three and five chamber views. Peak outflow tract gradients should be determined using the modified Bernoulli equation: Gradient= $4V^2$, where V is the peak aortic outflow velocity
Family History of SCD	<input type="radio"/> No <input checked="" type="radio"/> Yes	History of sudden cardiac death in 1 or more first degree relatives under 40 years of age or SCD in a first degree relative with confirmed HCM at any age (post or ante-mortem diagnosis).
Non-sustained VT	<input type="radio"/> No <input checked="" type="radio"/> Yes	3 consecutive ventricular beats at a rate of 120 beats per minute and <30s in duration on Holter monitoring (minimum duration 24 hours) at or prior to evaluation.
Unexplained syncope	<input type="radio"/> No <input checked="" type="radio"/> Yes	History of unexplained syncope at or prior to evaluation.
Risk of SCD at 5 years (%):		
ESC recommendation:		
Reset		

2014 ESC Guidelines on Diagnosis and Management of Hypertrophic Cardiomyopathy
O'Mahony C et al Eur Heart J (2014) 35 (30): 2010-2020

HCM Risk-SCD should not be used in:

- Paediatric patients (<16 years)
- Elite/competitive athletes
- HCM associated with metabolic diseases (e.g. Anderson-Fabry disease)
- Patients with a previous history of aborted SCD or sustained ventricular fibrillation for secondary prevention.

Highest

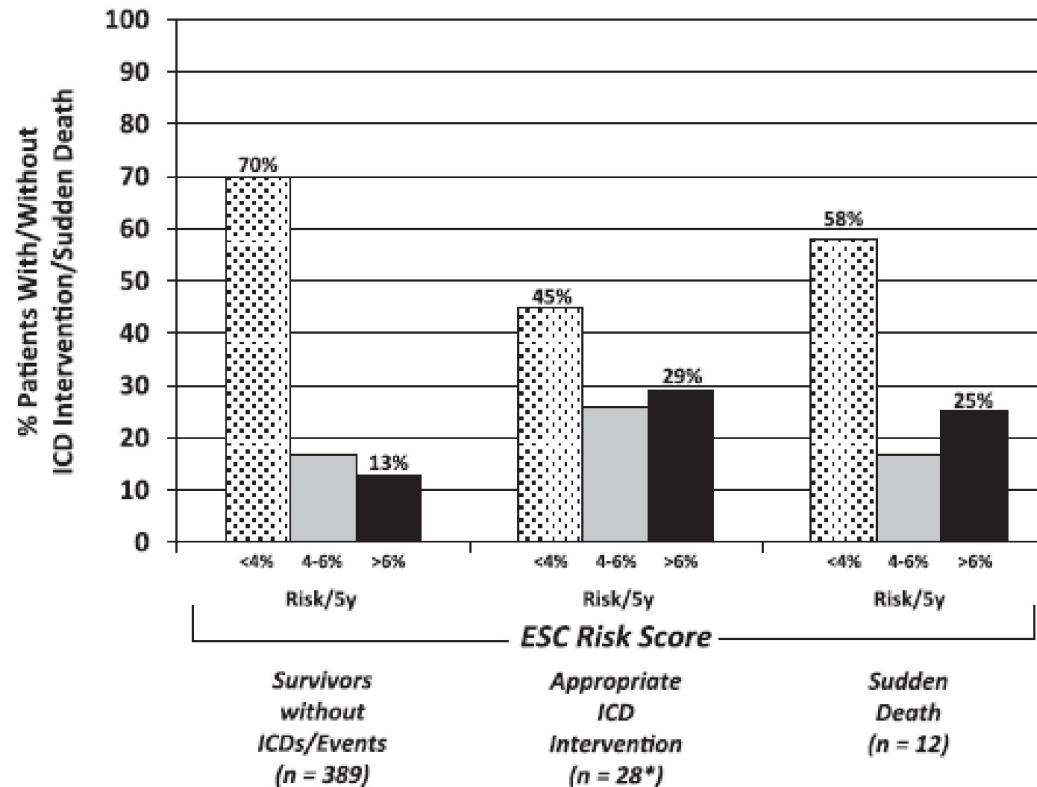
Intermediate

Lowest

ICD

O'Mahony Eur Heart J. 2014;35(30):2010-2020

ESC score in pediatric population



Circulation. 2016;133:62-73

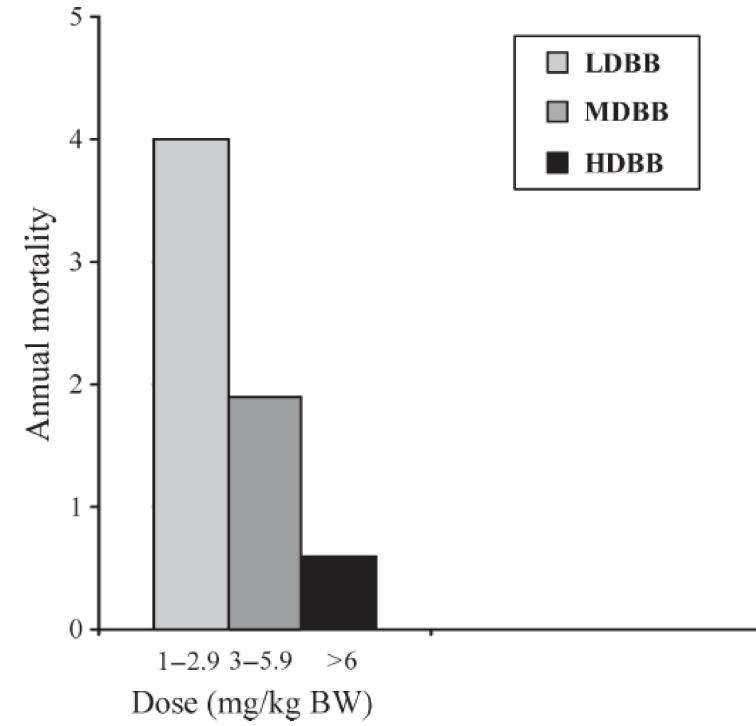
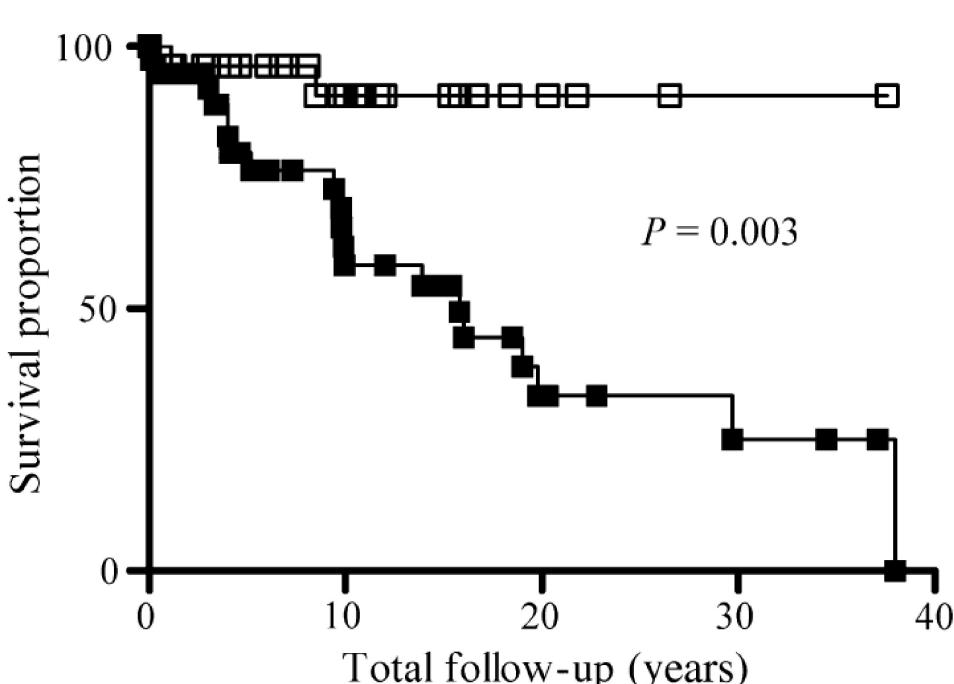


Hypertrophic Cardiomyopathy in Children, Adolescents, and Young Adults Associated With Low Cardiovascular Mortality With Contemporary Management Strategies

Barry J. Maron, MD; Ethan J. Rowin, MD; Susan A. Casey, RN; John R. Lesser, MD;
Ross F. Garberich, MS; Deepa M. McGriff, MPH; Martin S. Maron, MD

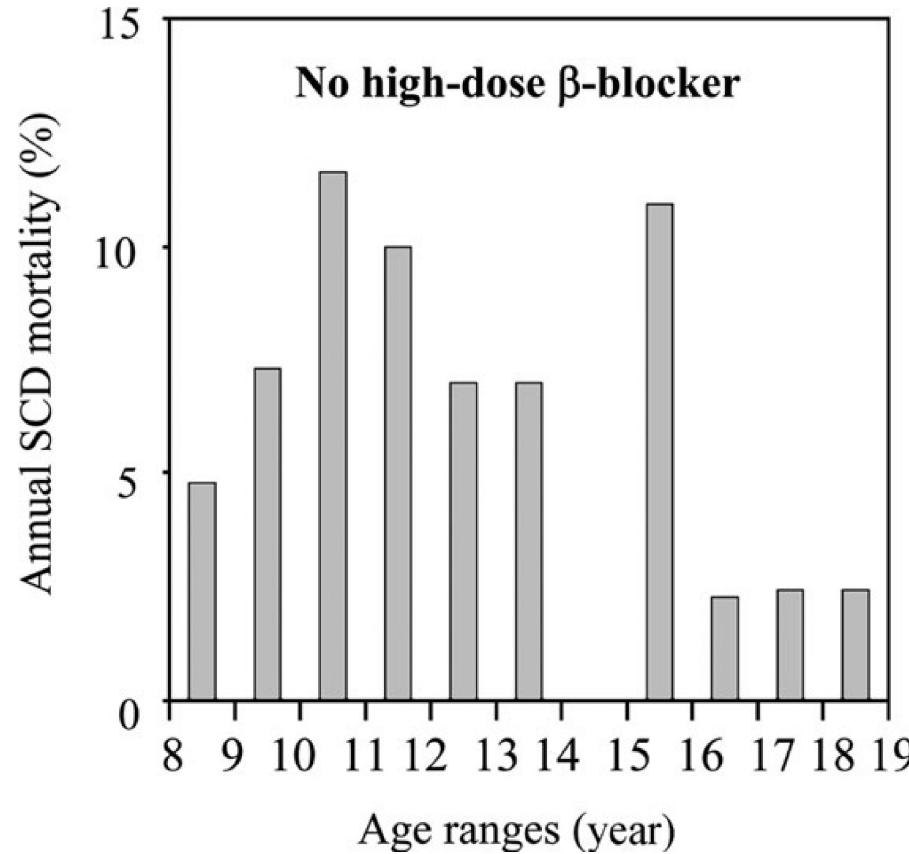


SCD and beta blockers dosage



Ostman-Smith, Eur Heart J 2008

SCD BY treatment in Pediatric HCM

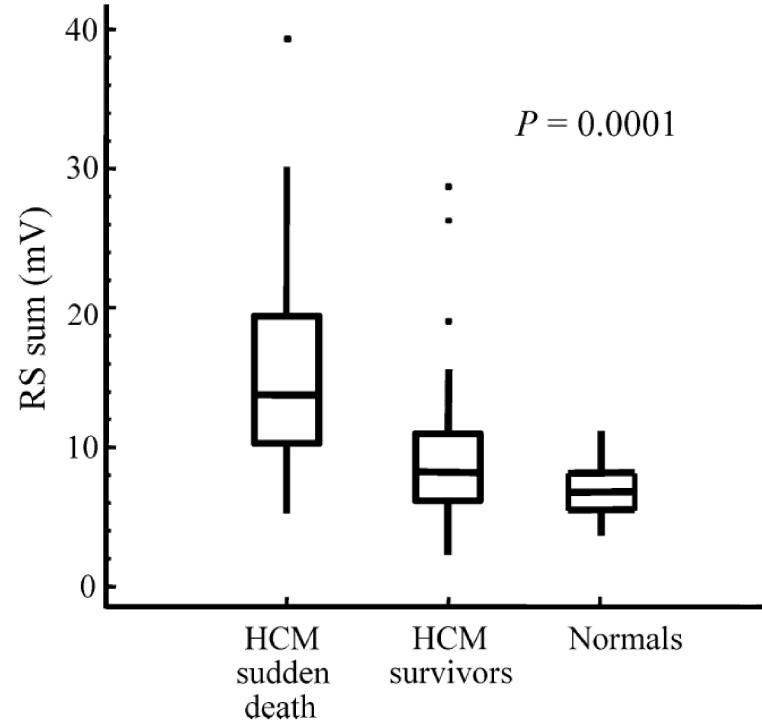


Ostman-Smith, Eur Heart J 2008



ECG score for prevention of SCD

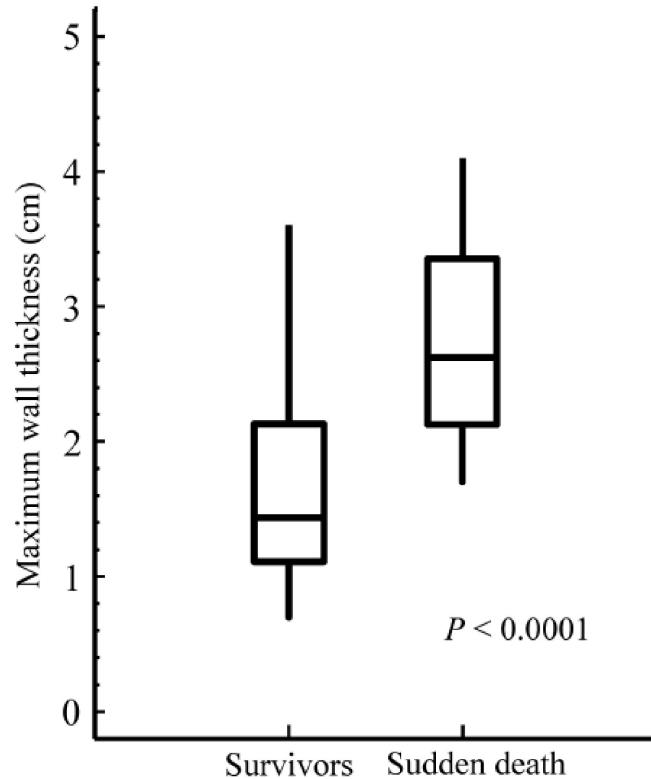
Deviation in QRS-axis present		1 point
Pathological T-wave inversion limb leads present ^a		1 point
Pathological T-wave inversion precordial leads ^b		2 points
ST-segment depression ≥ 2 mm present		2 points
S-wave greater than R-wave in V ₄		2 points
Six limb-lead QRS-amplitude sum	≥7.7 mV	1 point
	≥10.0 mV	2 points
	≥12.0 mV	3 points
Twelve-lead amplitude-duration product	≥2.2 mV.s	1 point
	≥2.5 mV.s	2 points
	≥3.0 mV.s	3 points
QTc (Bazett's formula)	≥440 ms	1 point
	Max score = 14	



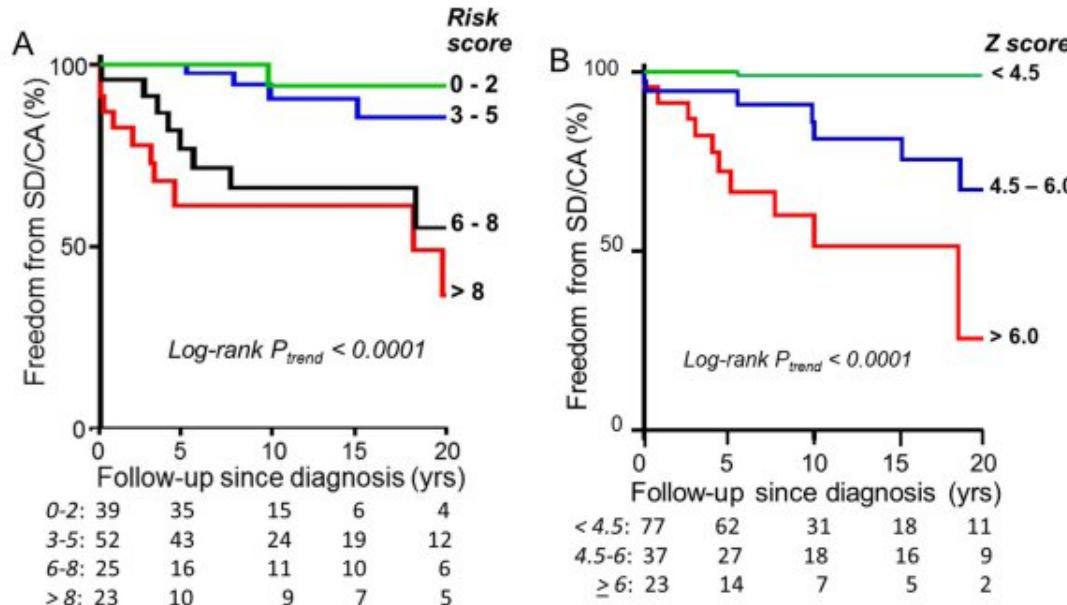
Ostman-Smith, Eur Heart J 2009



Wall thickness and SCD in Pediatric HCM

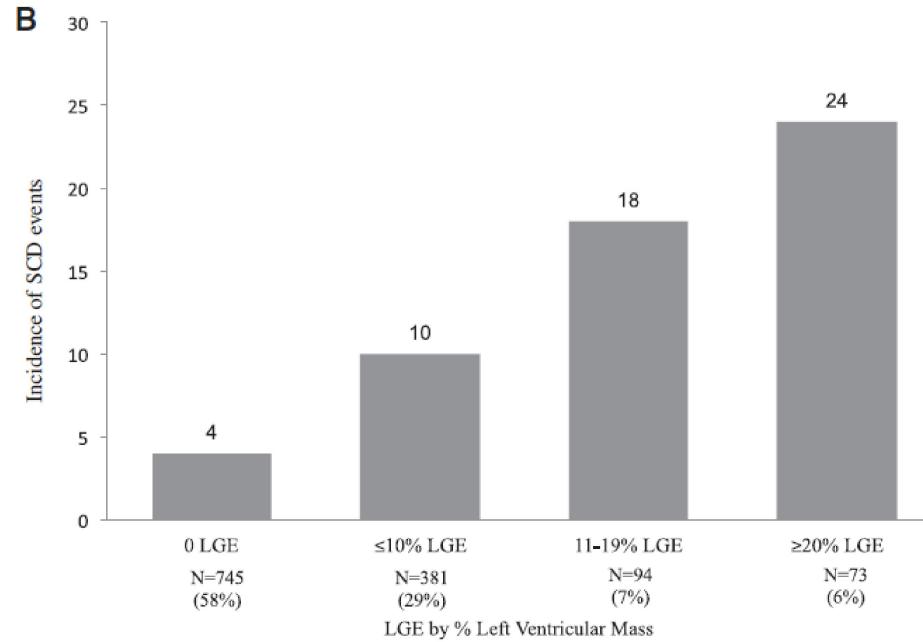
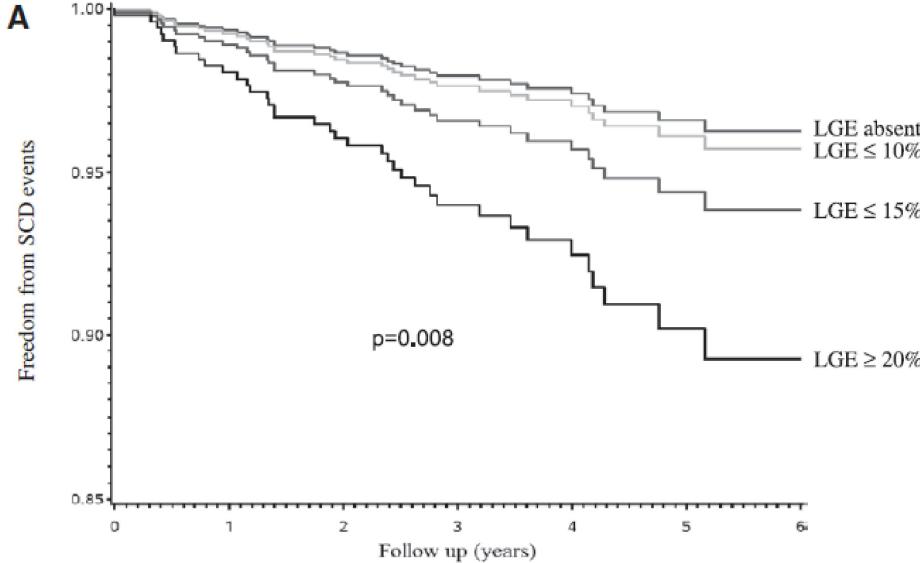


Ostman-Smith, Eur Heart J 2009


Predictors of sudden death at late follow-up (10.3% missing data in final model)

Last ECG risk score	0.279	0.089	1.321	p=0.002
Last Detroit Z-score (maximum wall thickness)	0.550	0.161	1.733	p=0.001
Beta-blocker+disopyramide therapy	-1.601	0.629	0.202	p=0.011
(Last beta-blocker dose	-0.096	0.046	0.908	p=0.037)

LGE and HCM



Chan, Circulation 2014;130:484-495



Risk factors for sudden cardiac death in childhood hypertrophic cardiomyopathy: A systematic review and meta-analysis

Gabrielle Norrish^{1,2}, Nicoletta Cantarutti^{1,3}, Eleni Pissaridou⁴, Deborah A Ridout⁴, Giuseppe Limongelli⁵, Perry M Elliott^{2,6} and Juan Pablo Kaski^{1,2}

Table 1 Risk factors for sudden cardiac death in childhood hypertrophic cardiomyopathy. Adapted from Norrish et al.

'Major' clinical risk factor ^a	Hazard ratio (95% confidence interval)
Previous aborted cardiac event	5.4 (3.67–7.95), $p < 0.001$
Non-sustained ventricular tachycardia	2.13 (1.21–3.74), $p = 0.009$
Unexplained syncope	1.89 (0.69–5.16), $p = 0.22$
Extreme left ventricular hypertrophy ^b	1.8 (0.75–4.32), $p = 0.19$
'Minor' risk factor ^c	
Left atrial diameter, Family history SCD, Gender, Age, Symptoms, ECG changes, Abnormal blood pressure response to exercise, LVOTO	

SCD RISK STRATIFICATION IN CHILDHOOD HCM





HCM Risk-Kids

[HCM RISK-KIDS MODEL](#) [COLLABORATORS](#) [CONTACT](#) [PUBLICATIONS](#)

HCM Risk-Kids model for sudden cardiac death in childhood Hypertrophic Cardiomyopathy

1. Age
2. Gender
3. Weight
4. LVMWT
5. LA
6. LVOT
7. NSVT
8. Syncope



Comment

➤ JAMA Cardiol. 2020 Mar 1;5(3):362. doi: 10.1001/jamacardio.2019.5783.

Concerns About the HCM Risk-Kids Study

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- Inadequate evidence for the surprising conclusion that a left-ventricular outflow tract gradient (LVOTG) appeared protective in the final algorithm
- A possible explanation for this paradox could be a modifying effect by β-blocker therapy

CONCLUSIONS



- Pediatric HCM is a heterogenous rare disease
- Red flags are important for heatiology
- Risk of SCD is increased in children with HCM
- Children should not been stratified with current ESC score
- Age, ECG risk score, LV mass, LGE and beta blockers dosage should be taken in account to assess the risk