Ventricular arrhythmia and sudden death in hypertrophic cardiomyopathy

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The Netherlands

Ventricular arrhythmia and sudden cardiac death in children with HCM

- Prognosis of HCM in children
- Risk stratification
  - Risk factors in adults/children
  - ESC HCM risk score
- Screening & Follow-up
- Therapies
  - (Medication)
  - ICD therapy in children with HCM
    - Indication, efficacy, role of S-ICD
  - Role of surgical myectomy

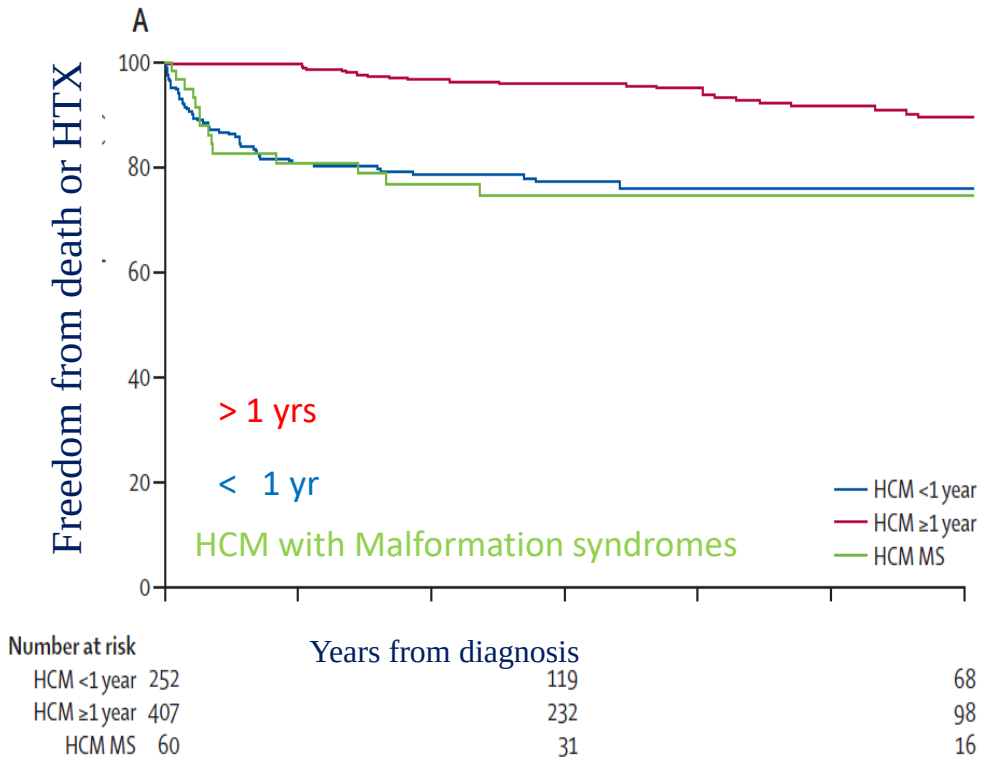
Hypertrophic cardiomyopathy

- Leading cause of SCD in the young
- 1/500 carriers of the disease, phenotypic expression highly variable
- Hallmark is myocellular disarray
- Disease of the sarcomere
- 30% HCM in children non sarcomeric disease : Noonan or Leopard syndrome, metabolic disease: also signifant risk for SCD

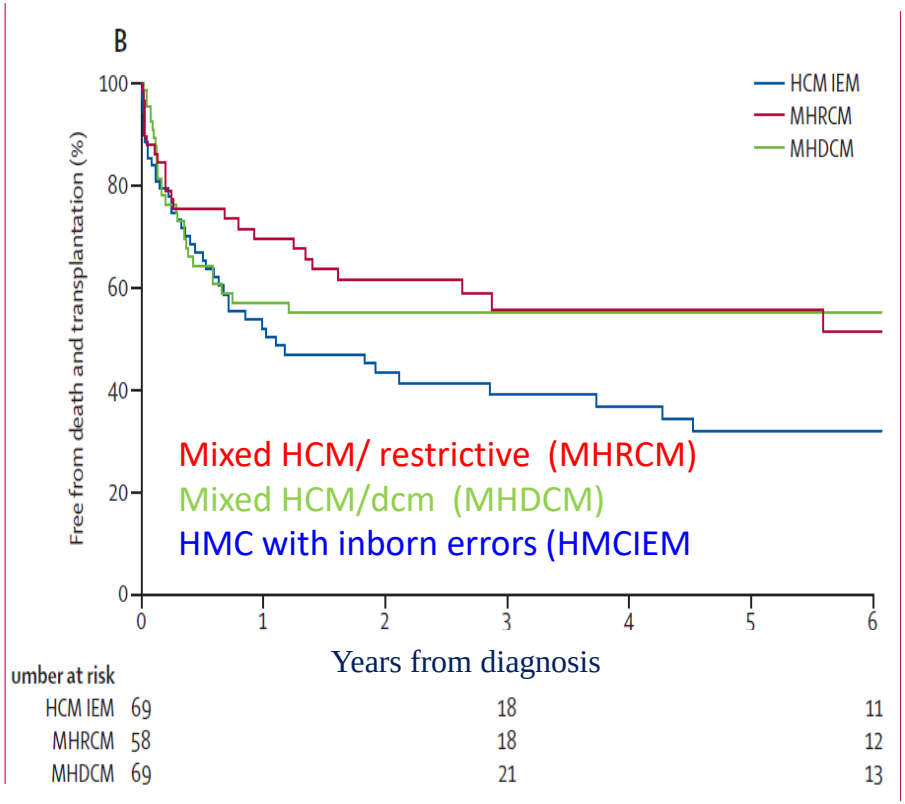
Risk stratification at diagnosis for children with hypertrophic cardiomyopathy: an analysis of data from the Pediatric Cardiomyopathy Registry

Lipshultz et Lancet 2013

HCM 719 pts

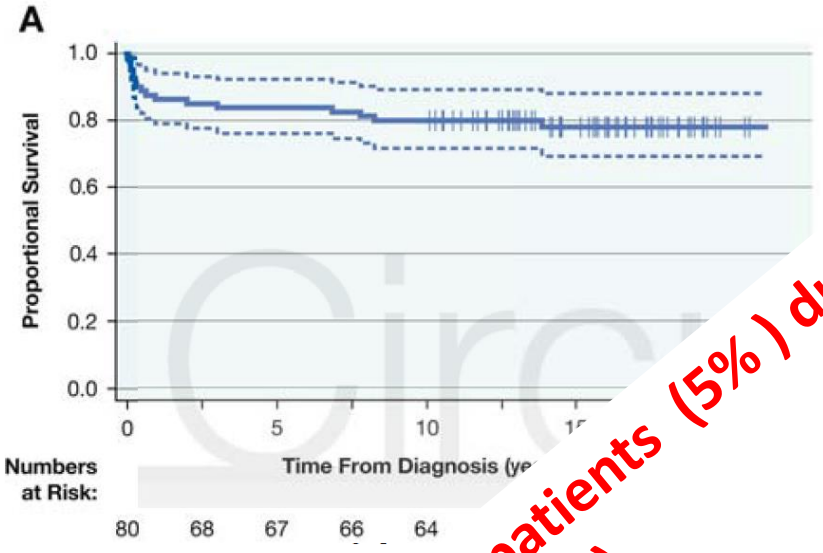


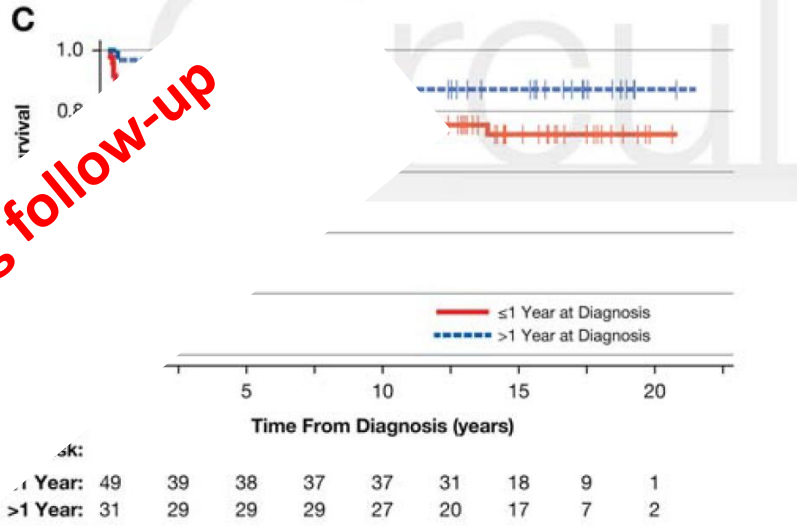
HCM mixed 196 pts



Sudden cardiac death in all groups very low (2%-3%) !!!

Children with HCM survival (Australia) 80 pts

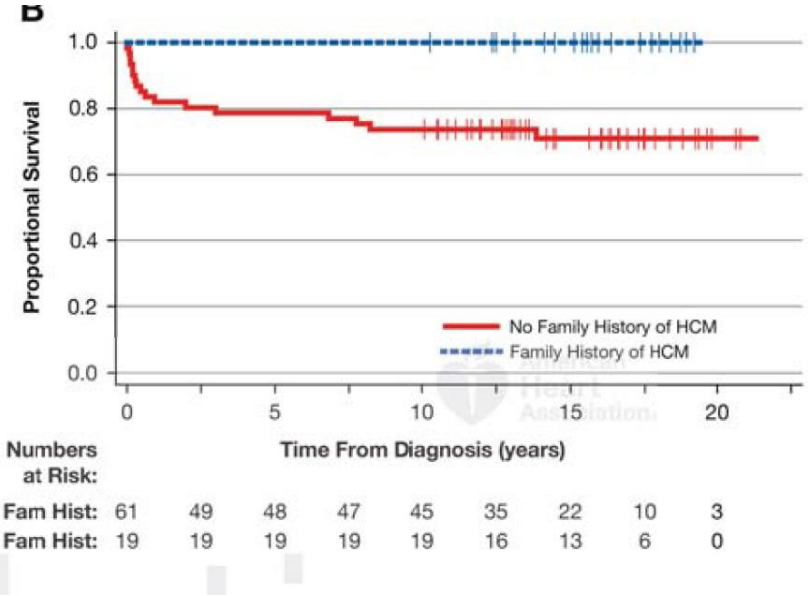




		P value
Symmetric LV hypertrophy		
Noonan syndrome	2.88 (1.02, 8.08)	0.045
Time-dependent fra[illegible] z-score	0.84 (0.74, 0.95)	0.005
Time-dependa[illegible] z-score	1.45 (1.22, 1.73)	<0.001

HR = hazard ratio; [illegible]

SCD occurred in 4 patients (5%) during follow-up (circa 3.5 % in 5 years)



Alexander et al Circulation february 2018

Pediatric HCM mutation carriers from family screening

- FU 6.9 yrs, no deaths
- 5 children had clinical HCM at screening)
- One received ICD (IVS 30 mm , and had 1 shock
- 3 more developed HCM, age 16, 25, 30 years
- Total 8 pts HCM phenotype (6.7%), 7/8 male

Table I. Clinical variables of 119 predictively tested children who were mutation positive at first clinical evaluation

Clinical variables	All mutation carriers	
Age, y	12.1 ± 3.4	119
Male	61	119 (51.3%)
Clinical diagnosis of HCM	5	119 (4.2%)
Mutated gene		
MYBPC3	95	119 (79.8%)
c.2373_2374insG	–52	95 (54.7%)
c.2827C>T	–13	95 (13.7%)
c.2864_2865delCT	–1	95 (1.1%)
MYH7	14	119 (11.8%)
TNNT2	10	119 (8.4%)
Presence of risk factors for SCD		
Extreme LVH	0	119 (0%)
NSVT	1	85 (1.2%)
Unexplained syncope	2	119 (1.7%)
Family history of SCD	11	119 (9.2%)
Cardiac events	0	119 (0%)

Vermeer et al J Pediatrics 2017

Risk factors in children

- Majority of HCM patients asymptomatic during childhood
- Current consensus (ESC 2014)
  - Screening first degree family members
  - Every 1-2 yrs > 10-20 yrs, and 2-5 years > 20 yrs
- Outcome of childhood HCM less extensively studied
  - Are adult risk factors applicable in children?
  - How should we treat children ?

Known risk factors for SCD in HCM adults

Previous cardiac arrest /VT !

Classical major risk factors

1. Familial SCD
2. Severe LVH Septal thickness > 30 mm
3. Unexplained syncope
4. Multiple-repetitive NSVT: VT run > 3 beats, > 120 bpm on 24 hr Holter
5. BP fall during exercise: BP response <20 mm Hg rise during exercise or BP fall >10 mmHg during peak exercise

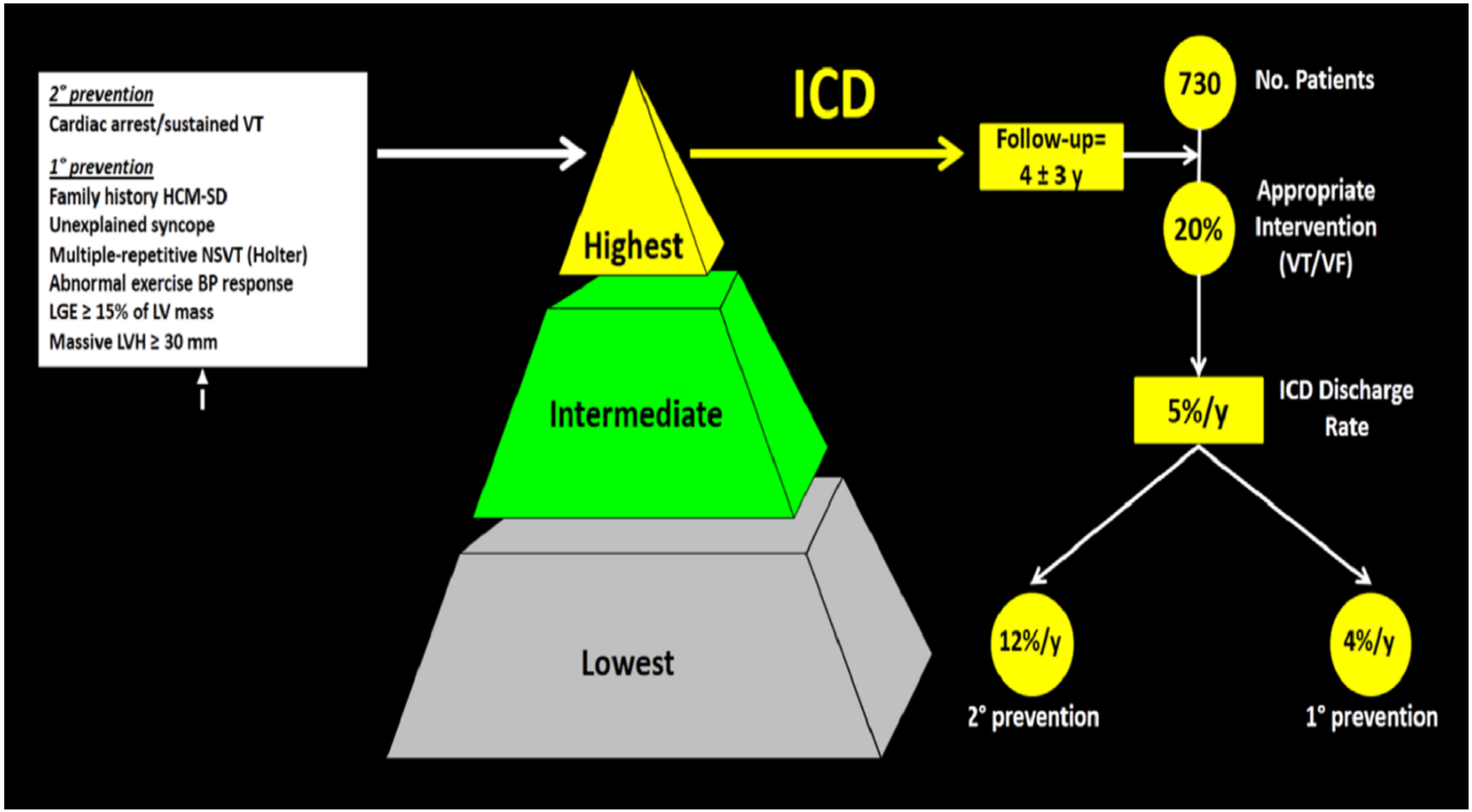
Other established risk factors

1. Age (younger age), 2. Left atrial diameter 3. LVOTO

Less well established risk factors

Delayed enhancement (MRI) (>15%) , LV apical aneurysm, specific mutations

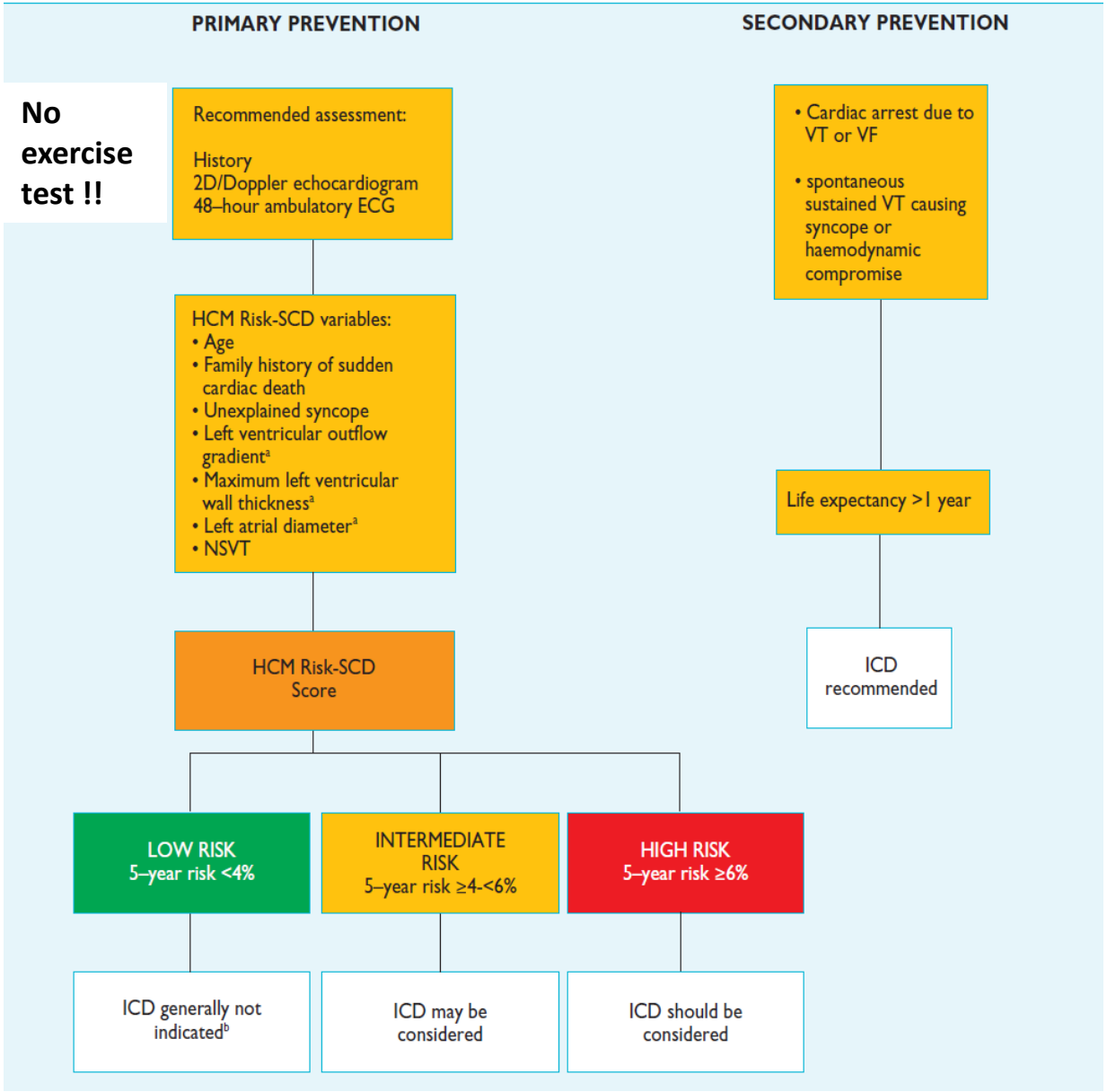
ICD therapy in adult HCM



No difference between pts with 1 or more risk factors

Maron JAMA 2007, JACC 2013

ESC guideline ICDs in patients > 16 yrs .
HCM Risk Score



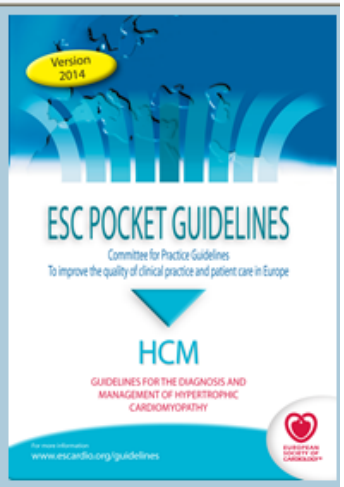
HCM Risk-SCD calculator

HCM Risk-SCD Calculator

Age	19	**Years**	*Age at evaluation*
Maximum LV wall thickness	30	**mm**	*Transthoracic Echocardiographic measurement*
Left atrial size	30	**mm**	*Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane at time of evaluation*
Max LVOT gradient	20	**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 Bernouilli equation: Gradient= $4V^2$, where V is the peak aortic outflow velocity*
Family History of SCD	◉ No ○ 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	○ No ◉ 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	◉ No ○ Yes		*History of unexplained syncope at or prior to evaluation.*

Risk of SCD at 5 years (%):	6.32
ESC recommendation:	ICD should be considered

Reset

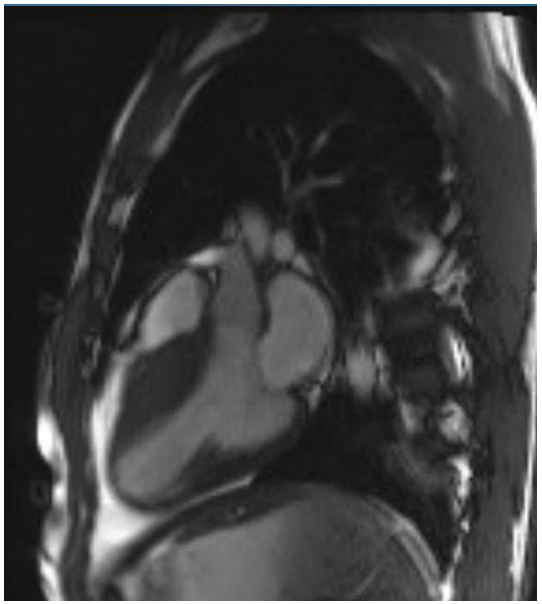


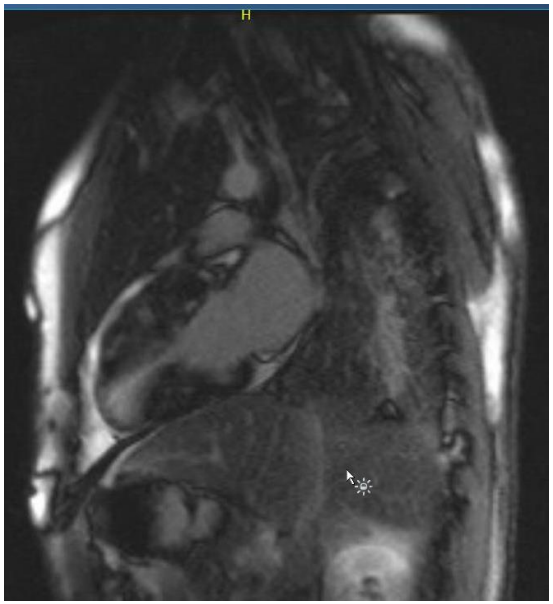
2014 ESC Guidelines on Diagnosis and Management of Hypertrophic Cardiomyopathy (Eur Heart J 2014 – doi:10.1093/eurheartj/ehu284)

O'Mahony C et al Eur Heart J (2014) 35 (30): 2010-2020

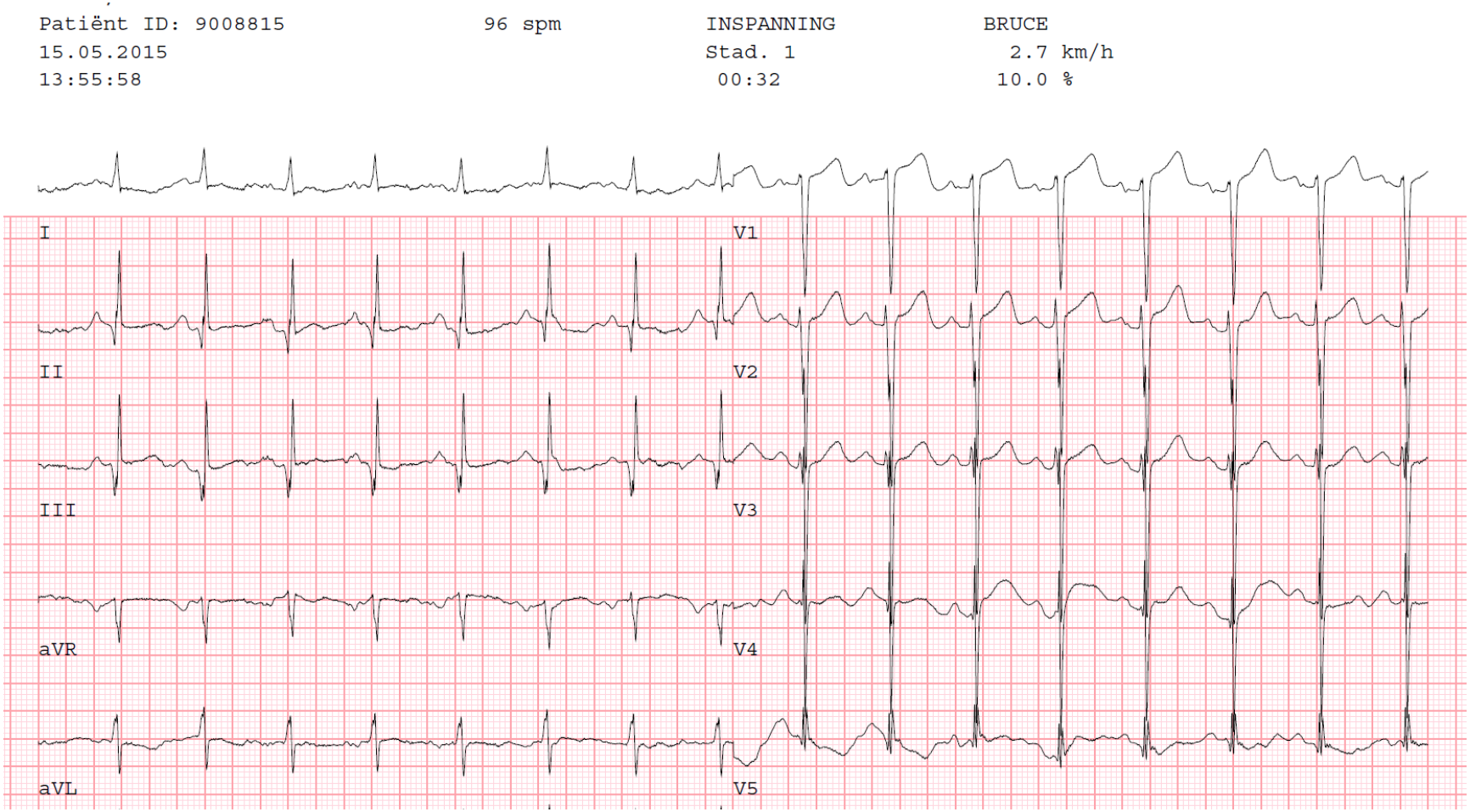
Risk factors can change in children especially during puberty

- 16 year old boy, mild HCM at age 5 (murmur) , MYH7 mutation +, FH negative, no regular check-up
- Visit at age 15 , “not feeling well during exercise”
  - Evaluation : exercise test, normal BP response normal , Holter normal, MRI assymmetrical septum max 24 mm, patchy areas of delayed enhancement, normal LV function, no LVOTO , start BB
- Age 16 : succesfully resuscitated at school : S-ICD

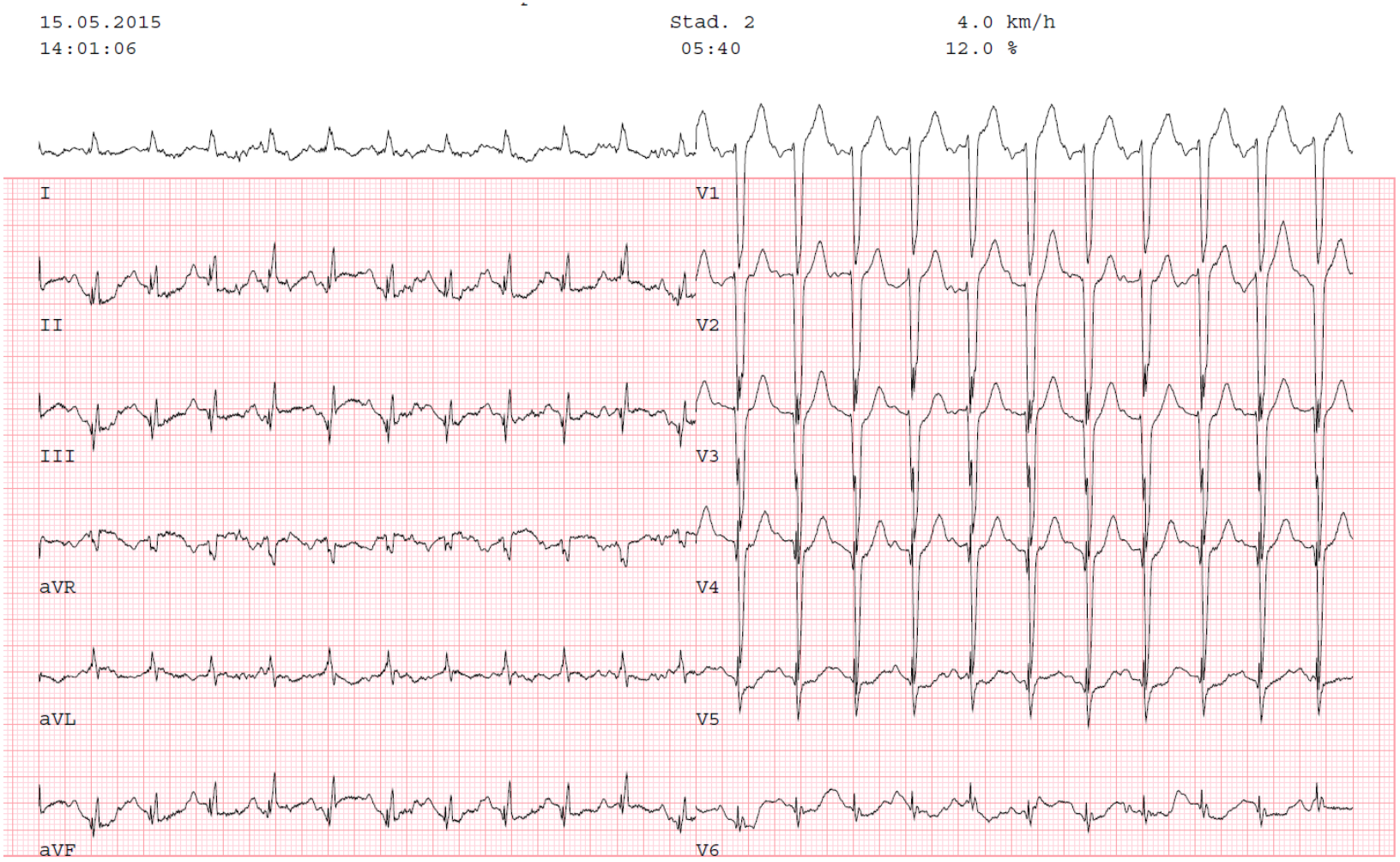




Age 17: Exercisetest repeated with S-ICD under BB therapy



HR 134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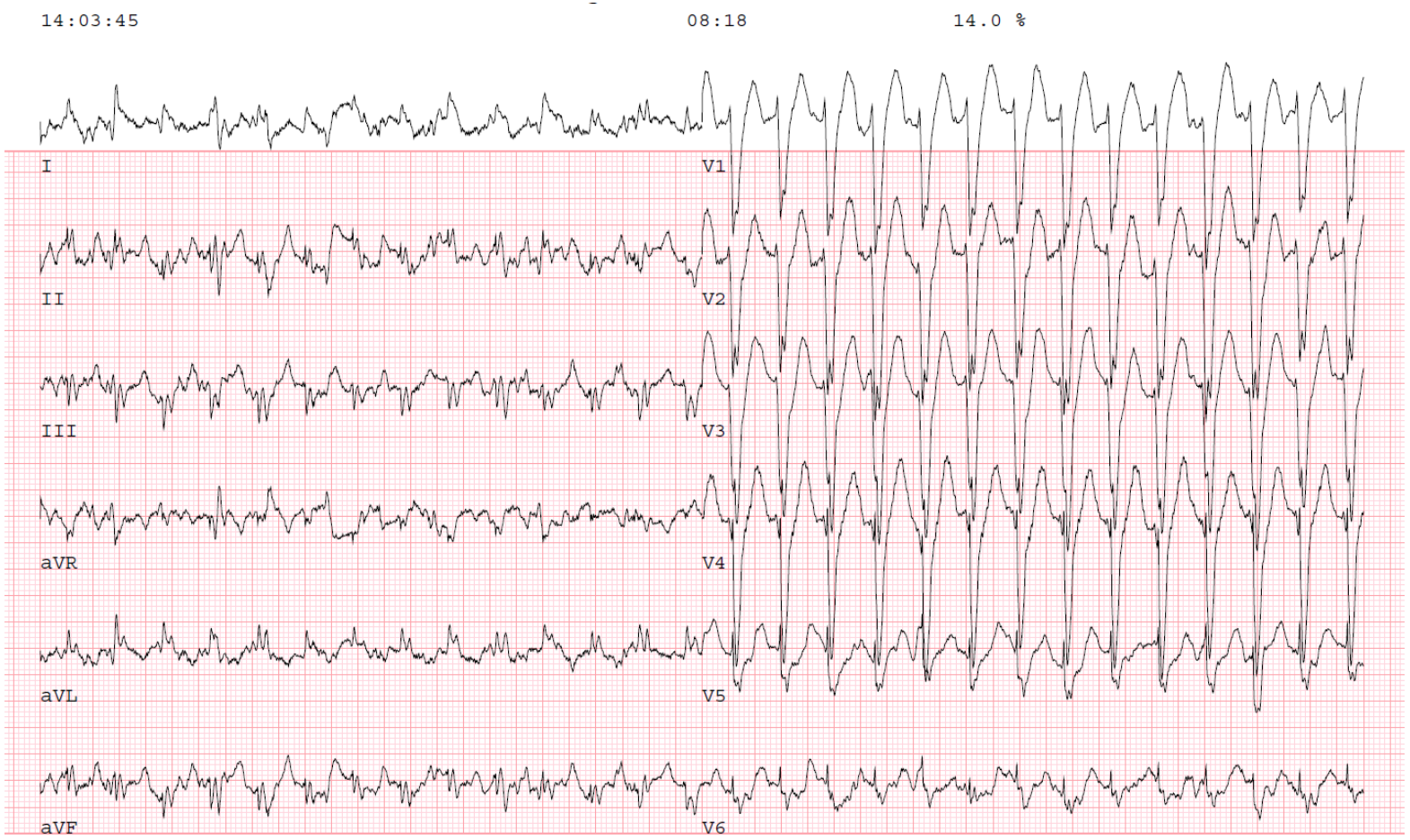
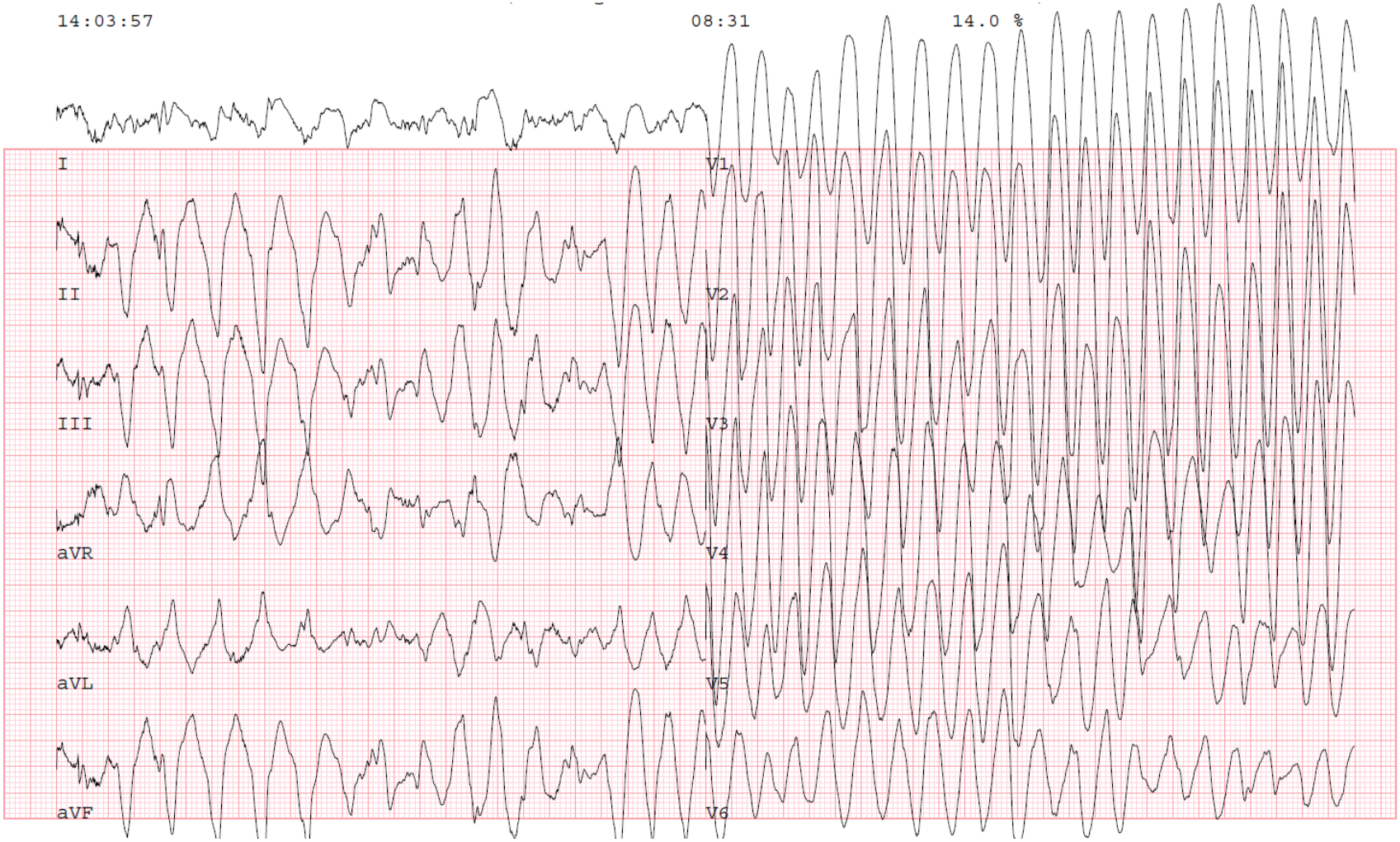
HR 167 chest pain

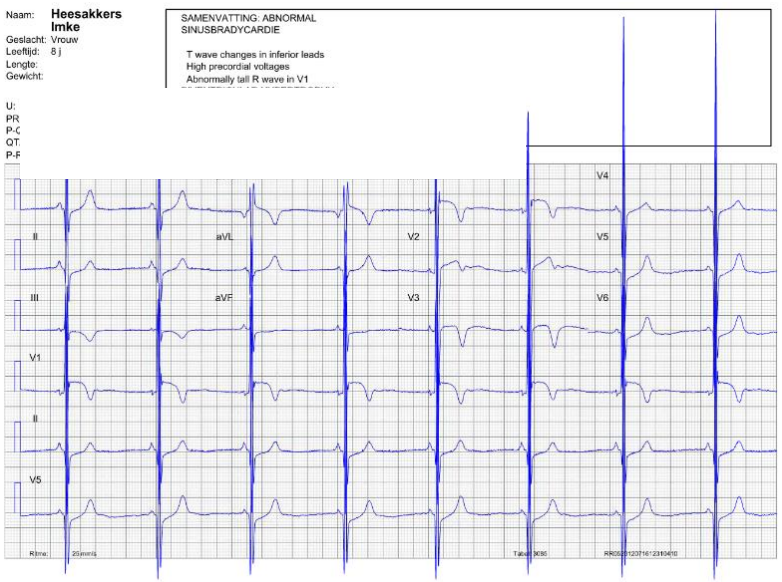


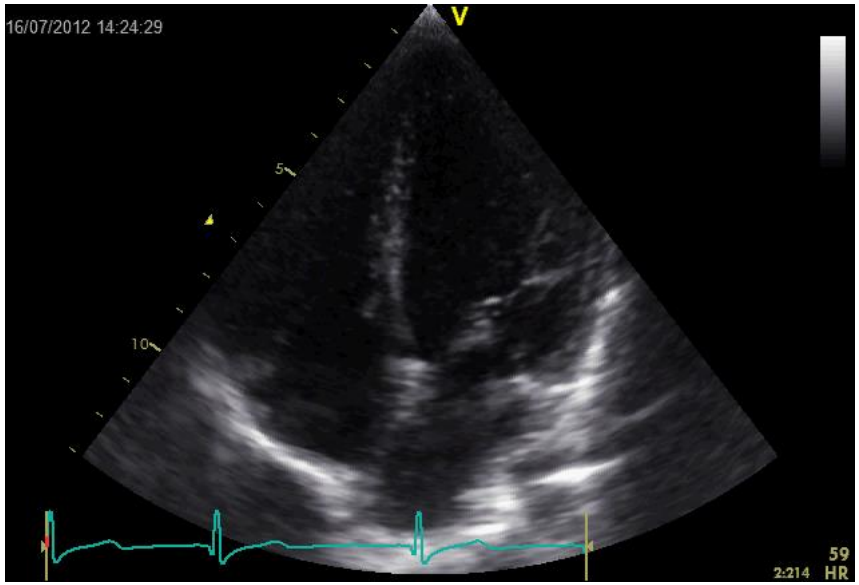
VT and ICD shock



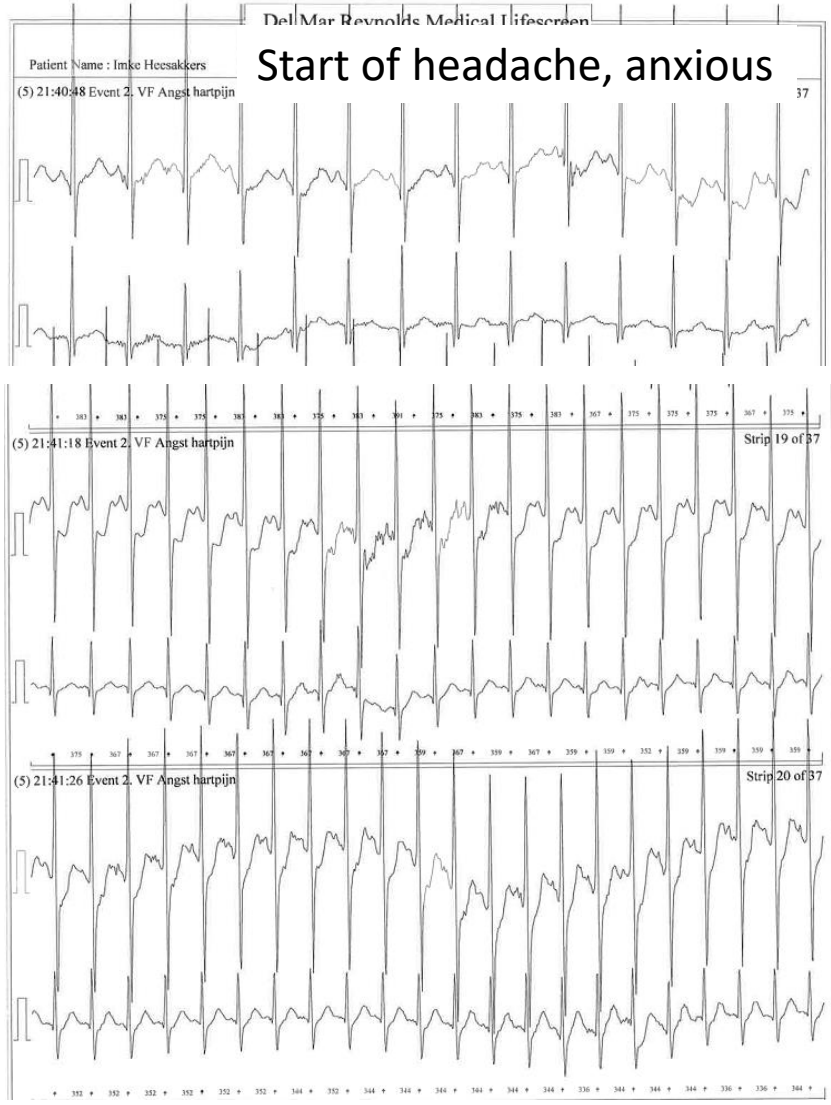
HCM in children: sometimes a severe phenotype

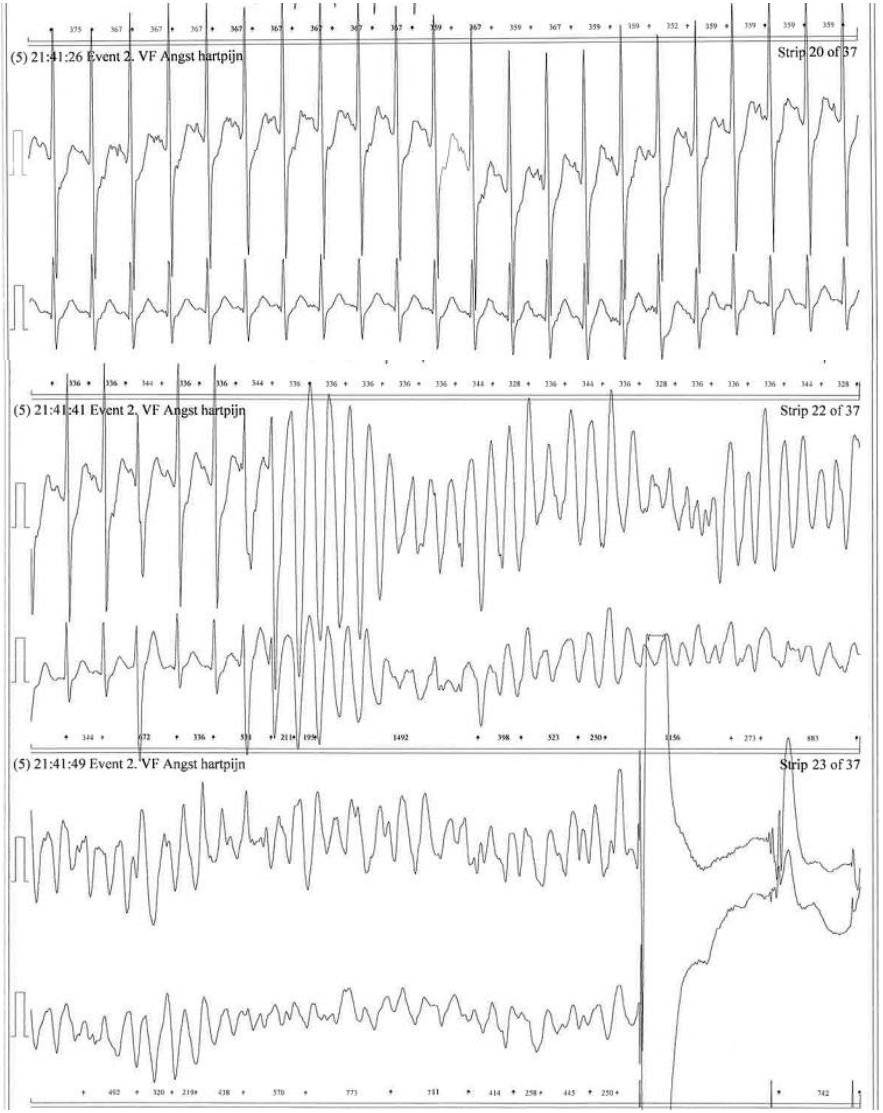
Girl 8 yrs, had a bad dream, collapsed, VF, resuscitated by father (2012)
Diagnosis: HCM (ECG) , echo /MRI almost normal, homozygous MYBP3c mutation
Therapy: nontransvenous ICD and BB
Follow-up 4 yrs: moderate exercise and/or anxiety – chest pain --ischemia ---VF
22 appropriate shocks for VF despite 200 mg metoprolol
Age 12 (2016) : psychological intervention, dysopyramide , no more shocks
Brother (14 yrs) : No symptoms, same genotype and phenotype, (one risk factor FH).
also received BB and ICD , had 2 shocks, sports restriction,





22 shocks in 4 yrs : Heartache and anxiety





Prevention of Sudden Cardiac Death With Implantable Cardioverter-Defibrillators in Children and Adolescents With Hypertrophic Cardiomyopathy

Maron et al JACC 2013

224 children with HCM

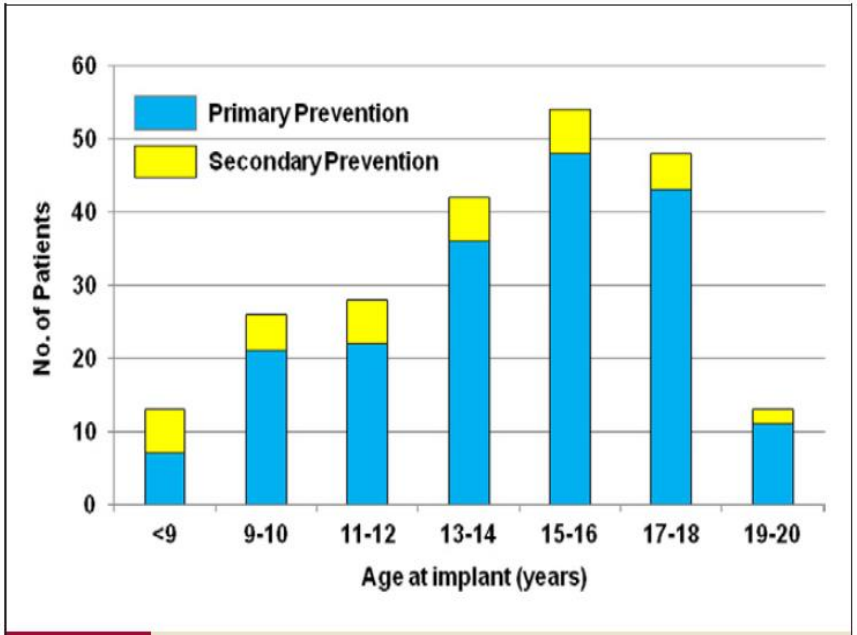


Figure 1 Patient Age at Defibrillator Implantation

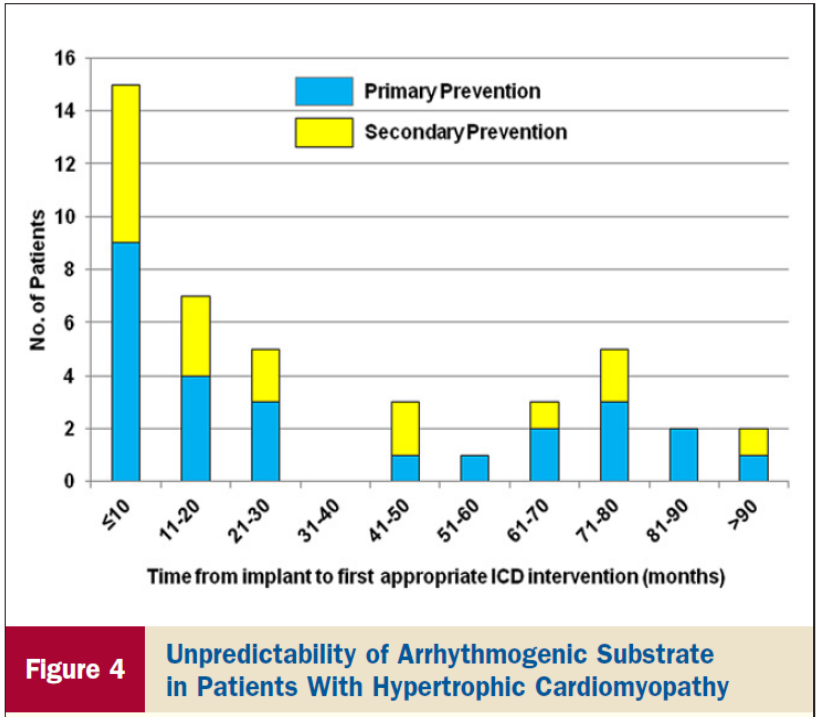


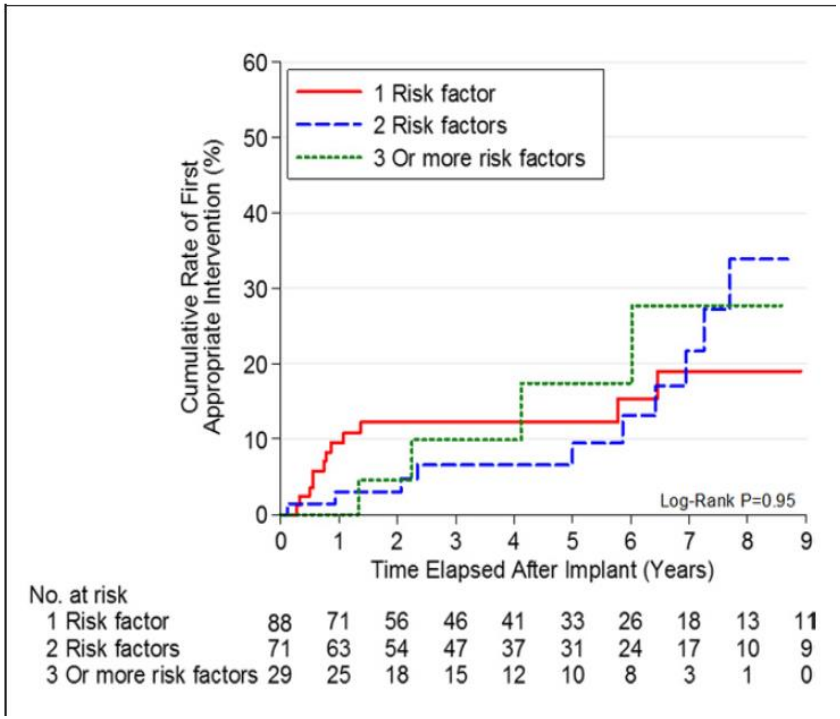
Figure 4 Unpredictability of Arrhythmogenic Substrate in Patients With Hypertrophic Cardiomyopathy

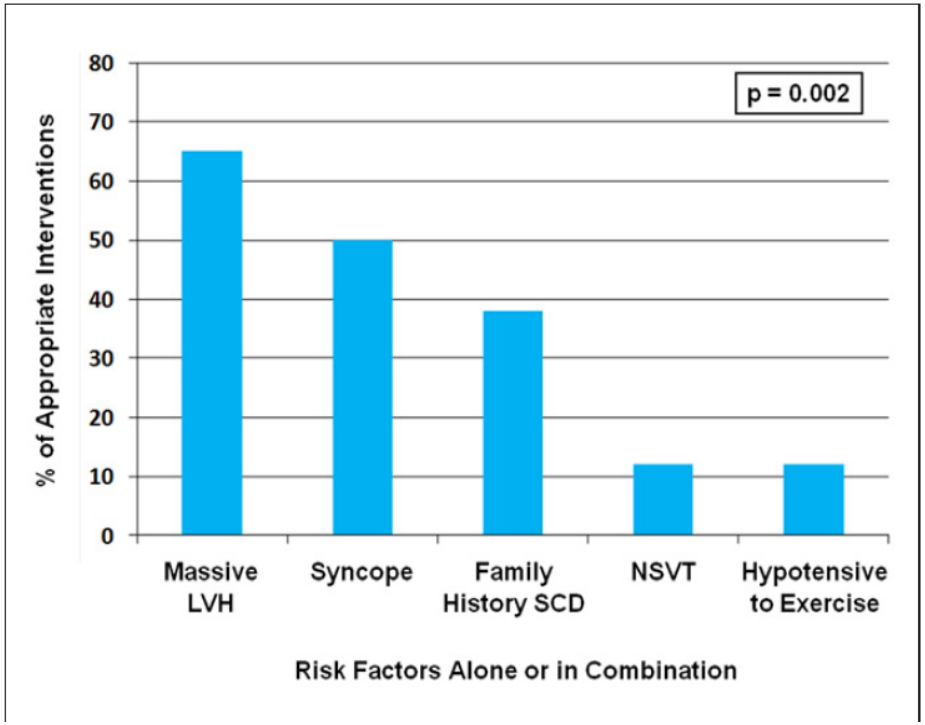
8 (4%) deaths (1 SCD with failure ICD)

41 pts myectomy, 1 alcohol ablation, 4 HTX (3 died post)

Risk factors in children for ICD shocks

Primary prevention



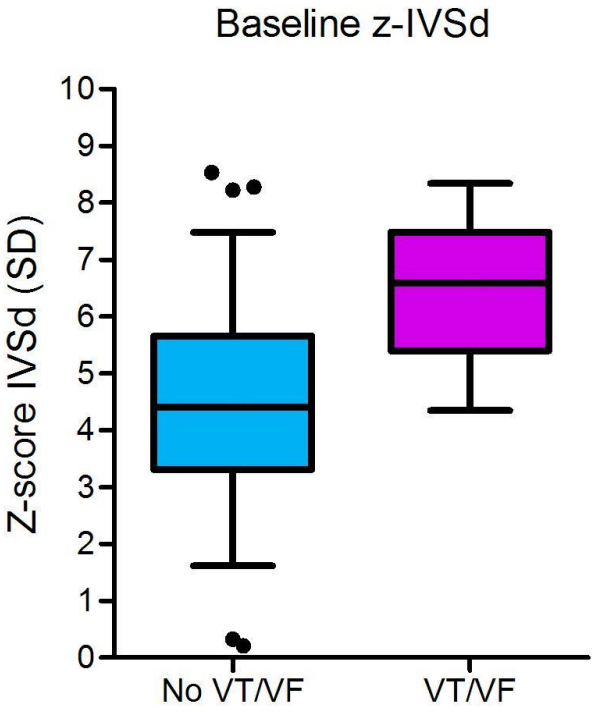


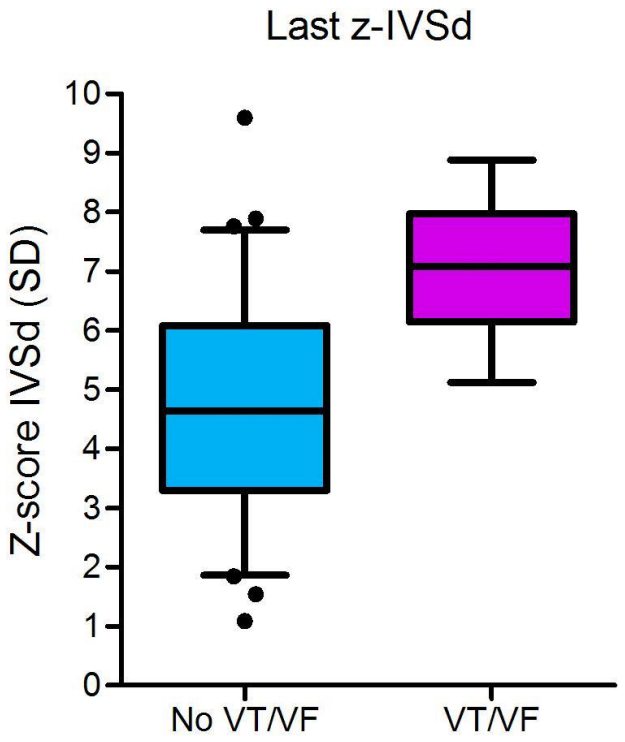
No difference between 1 or risk factors

Severe LV septal wall thickness strong RF in children (Z score > 6)

Maron et al JACC 2013

- Retrospective study 91 Dutch HCM children (excluding HCM mixed type
- Mean age at diagnosis 5.9 ±5.2 yrs
- Mean follow-up 7.3 ±5.2 yrs





- Septal thickness standardized to weight as z-score IVSd
- Baseline/at Last FU z-IVSd: $p<0.001$
- Risk VT/VF: Z-IVS > 7 specificity 0.95, sensitivity 0.45. PPV 0.56, NPV 0.92

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 Pissaridou[4], Deborah A Ridout[4], Giuseppe Limongelli[5], Perry M Elliott[2,6] and Juan Pablo Kaski[1,2]

Cardiology
2017, Vol. 24(11) 1220–1230

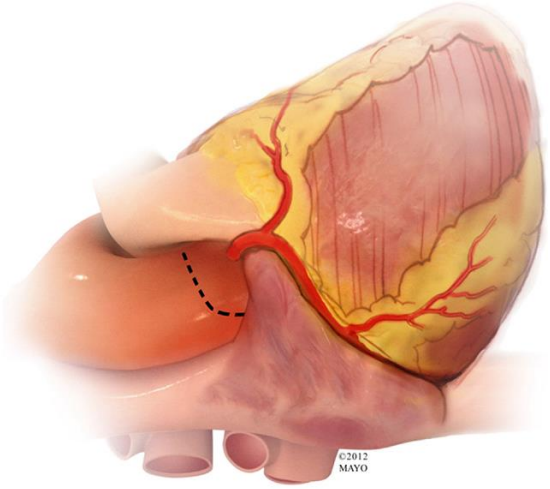
DOI: 10.1177/2047487317702519
journals.sagepub.com/home/ejpc
SAGE

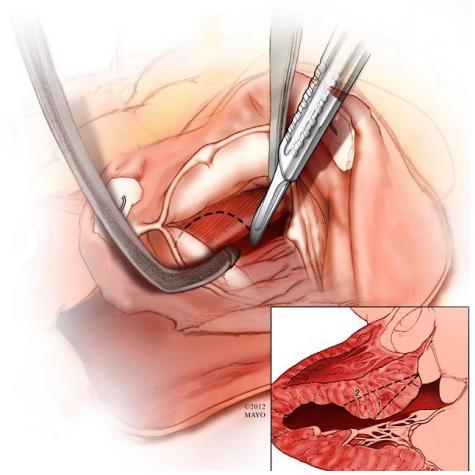
Results: Twenty-five studies (3394 patients) met the inclusion criteria. We identified four conventional major risk factors that were evaluated in at least four studies and that we found to be statistically associated with an increased risk of death in at least two studies: previous adverse cardiac event (pooled hazard ratio [HR] 5.4, 95% confidence interval [CI] 3.67–7.95, $p < 0.001$); non-sustained ventricular tachycardia (pooled HR 2.13, 95% CI 1.21–3.74, $p = 0.009$); unexplained syncope (pooled HR 1.89, 95% CI 0.69–5.16, $p = 0.22$); and extreme left ventricular hypertrophy (pooled HR 1.80, 95% CI 0.75–4.32, $p = 0.19$). Left atrial diameter did not meet the major risk factor criteria; however, this is likely to be an additional significant risk factor. 'Minor' risk factors included a family history of SCD, gender, age, symptoms, electrocardiogram changes, abnormal blood pressure response to exercise and left ventricular outflow tract obstruction.

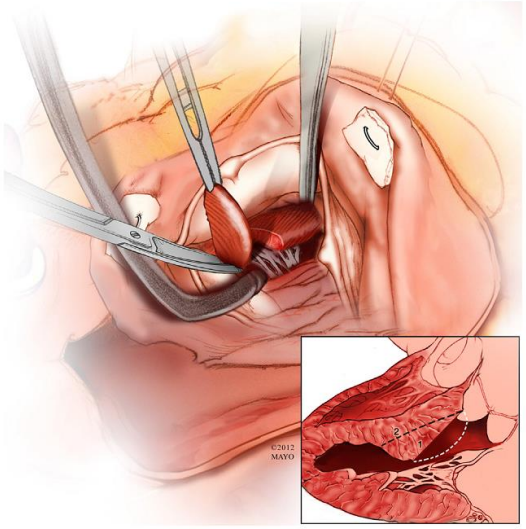
to be associated with increased risk of SCD, SCD-equivalent events or CVD. Multi-centre prospective studies are needed in order to further determine the relevance of these factors in predicting SCD in childhood hypertrophic cardiomyopathy and to identify novel risk markers.

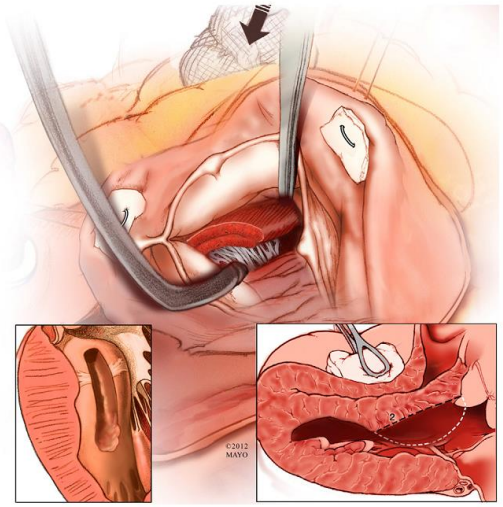
Condensed abstract: A systematic review and meta-analysis of clinical risk factors predicting sudden cardiac death in childhood hypertrophic cardiomyopathy was performed, identifying four 'major' factors: previous adverse cardiac event; non-sustained ventricular tachycardia; syncope; and extreme left ventricular hypertrophy. Well-designed multi-centre studies are required in the future in order to confirm these findings.

Role of surgery
Morrow operation







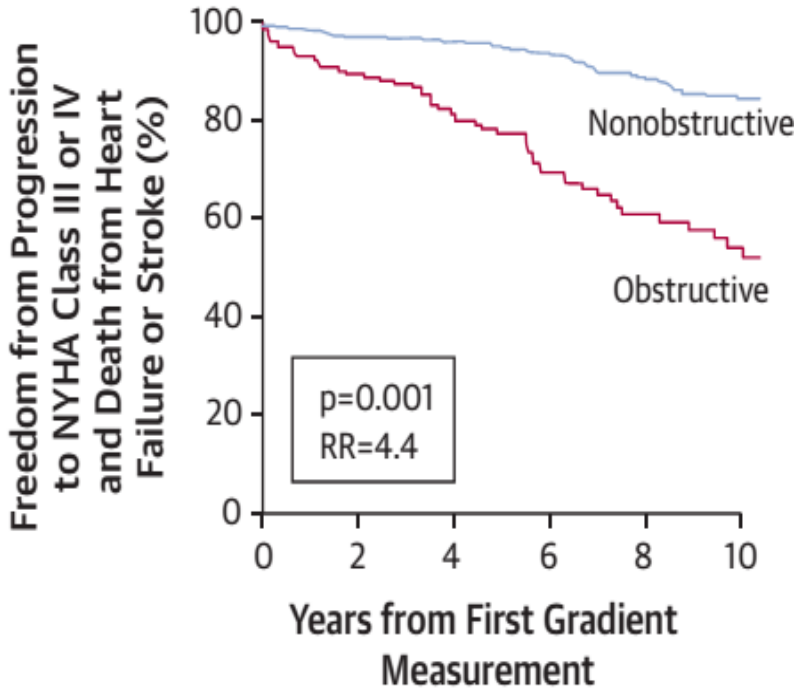


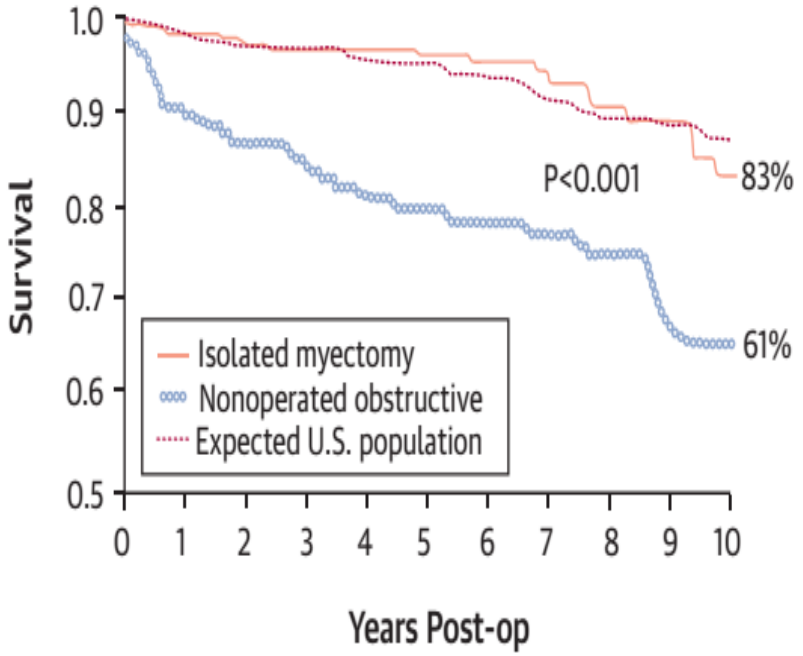
Said et sem thoracic surg 2014

Indication for surgery

- Surgical septal myectomy is indicated :
  - Pts limiting HF symptoms due to LVOTO > 50 mm Hg (at rest and/or with provocation) who are refractory to medical treatment (BB, verapamil, dysopyramide)
- Operative mortality < 1% at experienced centers
- Surgery can be combined with MV surgery
- Surgery improves QOL, improved survival (comparible to normal population)
- Alcohol septal ablation :
  - alternative to surgery in pts with advanced age, and comorbidity : High risk of AV block, repeat intervention (and ventricular arrhythmia)
  - NOT indicated in pediatric patients

The benefit of surgery



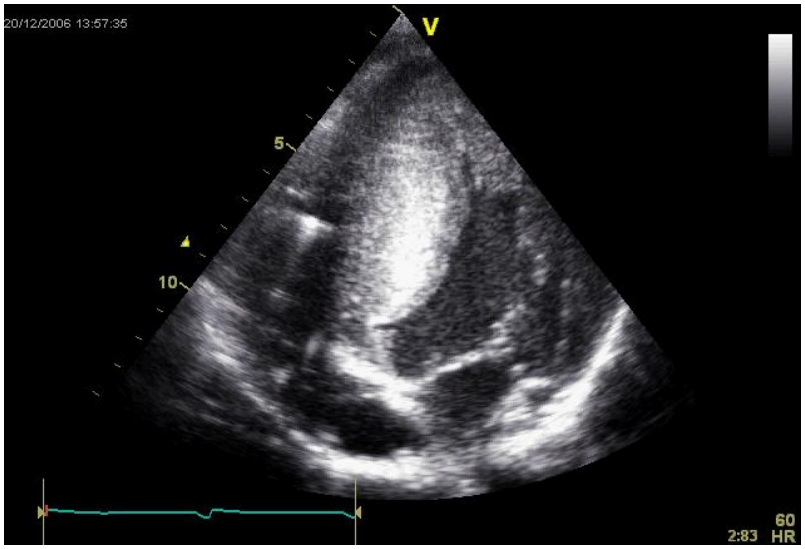


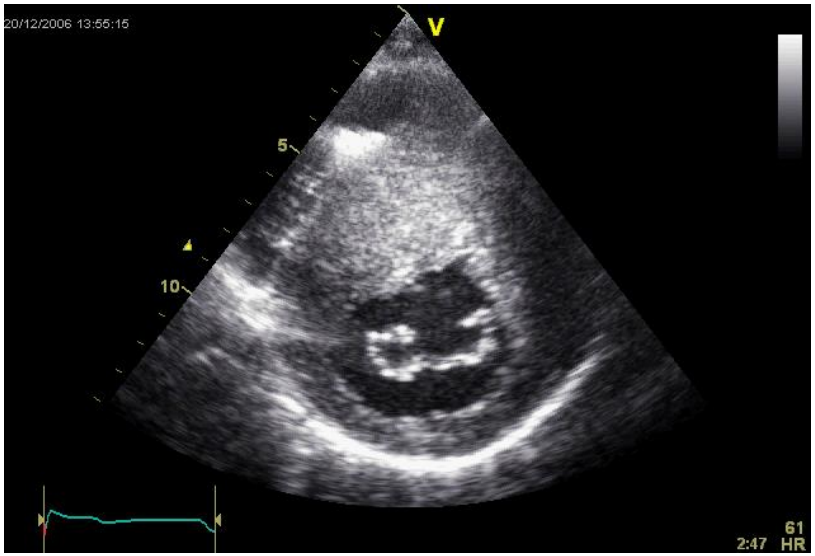
Maron JACC 2014

HCM and risk of VT/VF in children

- Asymptomatic boy 15 years
- Followed for 4 years (Family screening)
- MYBPC3 mutation
- BB therapy , LVOTO 50 mmHg
- Normal BP during exercise, no NSVT, no + FH, only IVS > 30 mm
- Collapsed during cycling
  VF , successful resuscitation
- ICD and Morrow

- Asymptomatic boy 16 yrs
  Screened for murmur
- Echo : only IVS > 30 mm , Holter normal, exercise normal,no LVOTO
- ICD implantation discussed, sports restriction
- MYBPC3 mutation
- Died suddenly during ice skating outdoor 6 weeks after diagnosis





Implantable defibrillators in children

- ICD therapy in children means decades of ICD use, including all device related morbidity/mortality

- Specific problems:
  - small size, growth
  - higher complication rate: lead fractures, endocarditis (20-30%)
  - Difficult lead removals

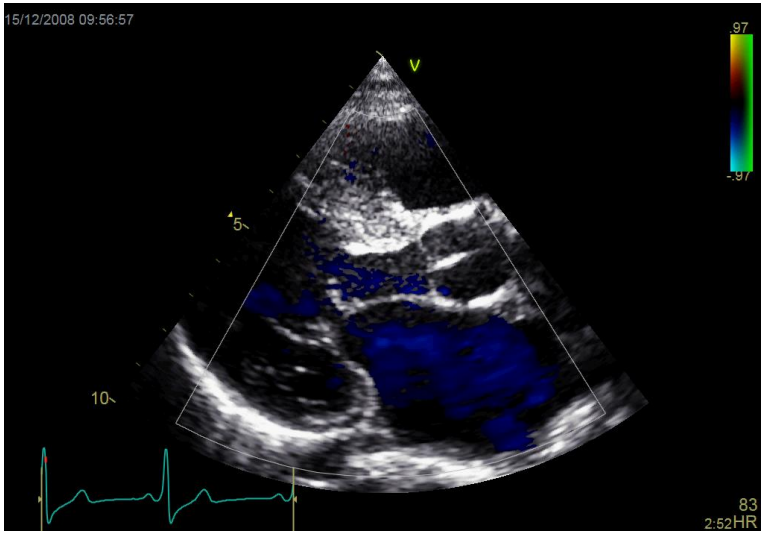
- Small children : non transvenous systems: reliability unclear during growth (DFT testing !)

- Older children: TV ICD, **preferably subcutaneous ICD**

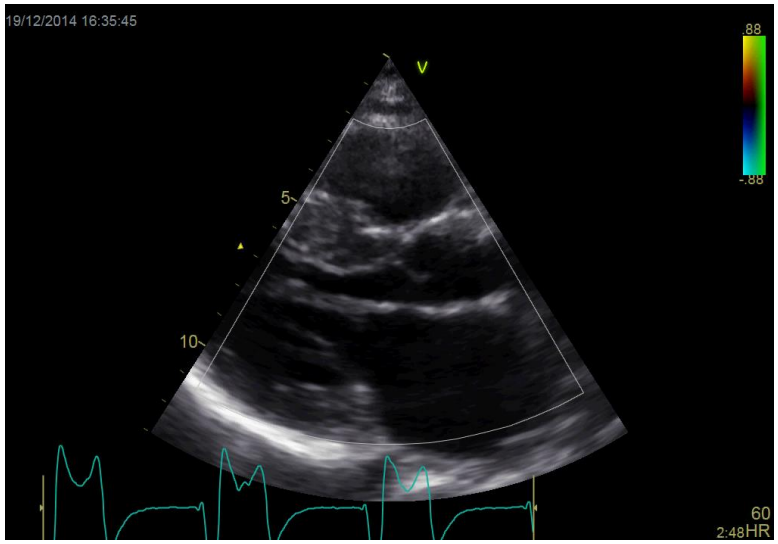
ICD related complications

- 6 year old, 1.21 , 23 kg , palpitations , dizziness
- HCM, homozygous MYH 7 gen mutation, father MYH7 + SCD age 30 yrs, mother genotype positive, phenotype negative
- IVS 19 mm (Z score +6), LVOTO 50 mmHg at rest, moderate MR , no NSVT, ST-depression during exercise, BP normal
- Age 7 Morrow, MV plasty, nontransvenous ICD (epicardial V lead, SQ array left thorax. BB therapy

preop

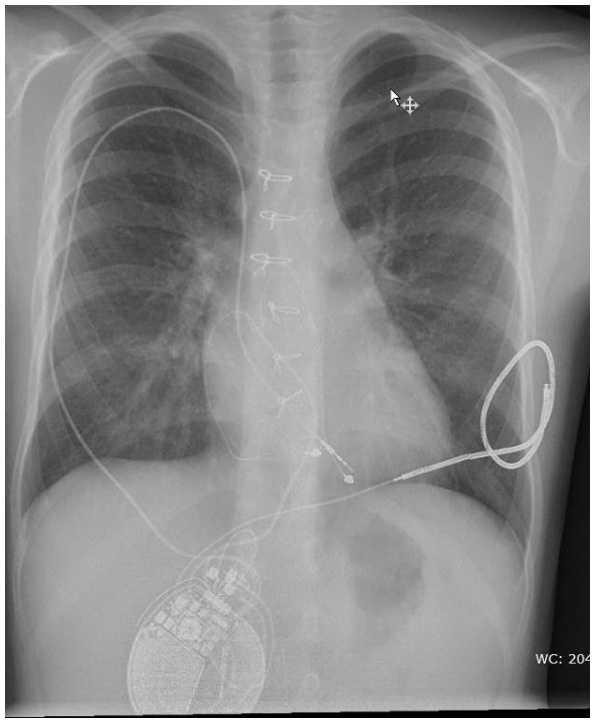


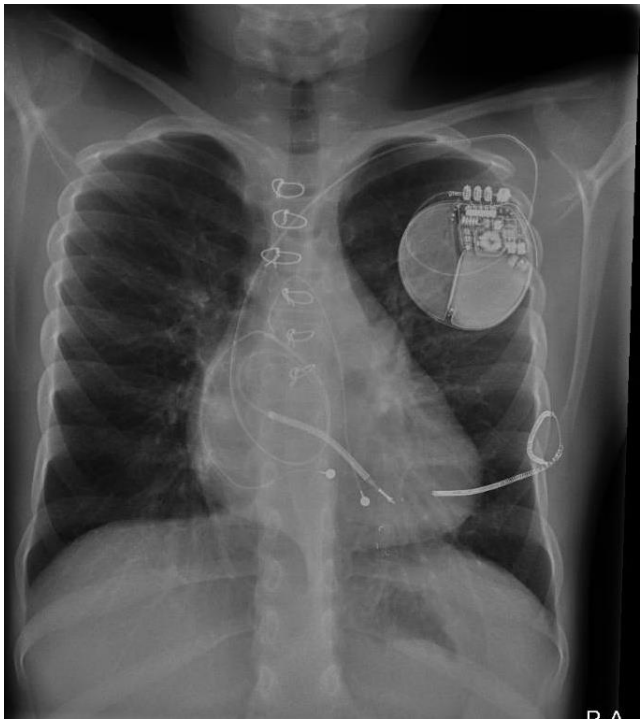
8 years postop



Case continued

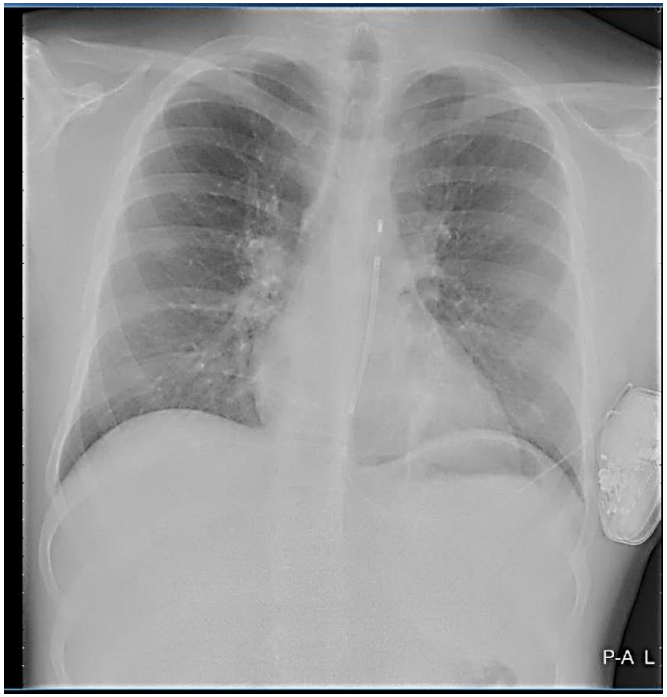
- Epicardial V lead failure after 1 yr (2010), transvenous lead right subclavian tunnelled to ICD abdomen
- Endocarditis 2012 : whole system removed
- Transvenous ICD (single chamber) 2012
- 2009-present : 9 years FU, no shocks, no VT detected !

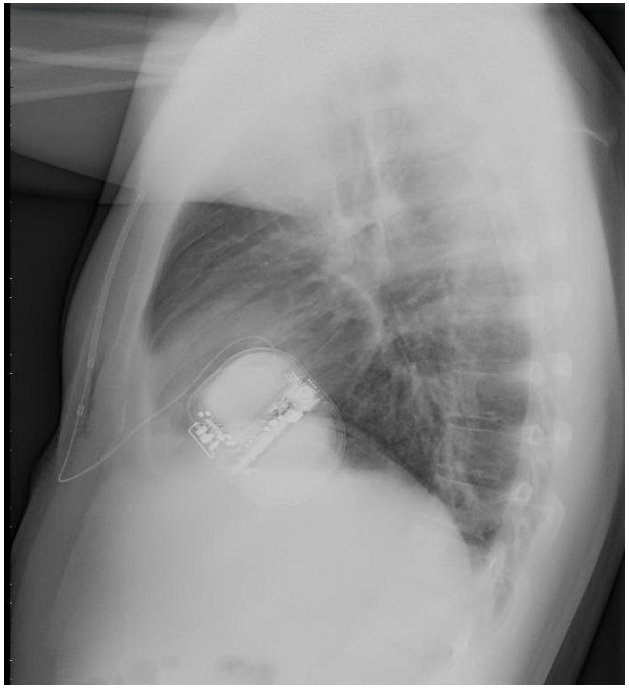




Subcutaneous ICD and HCM

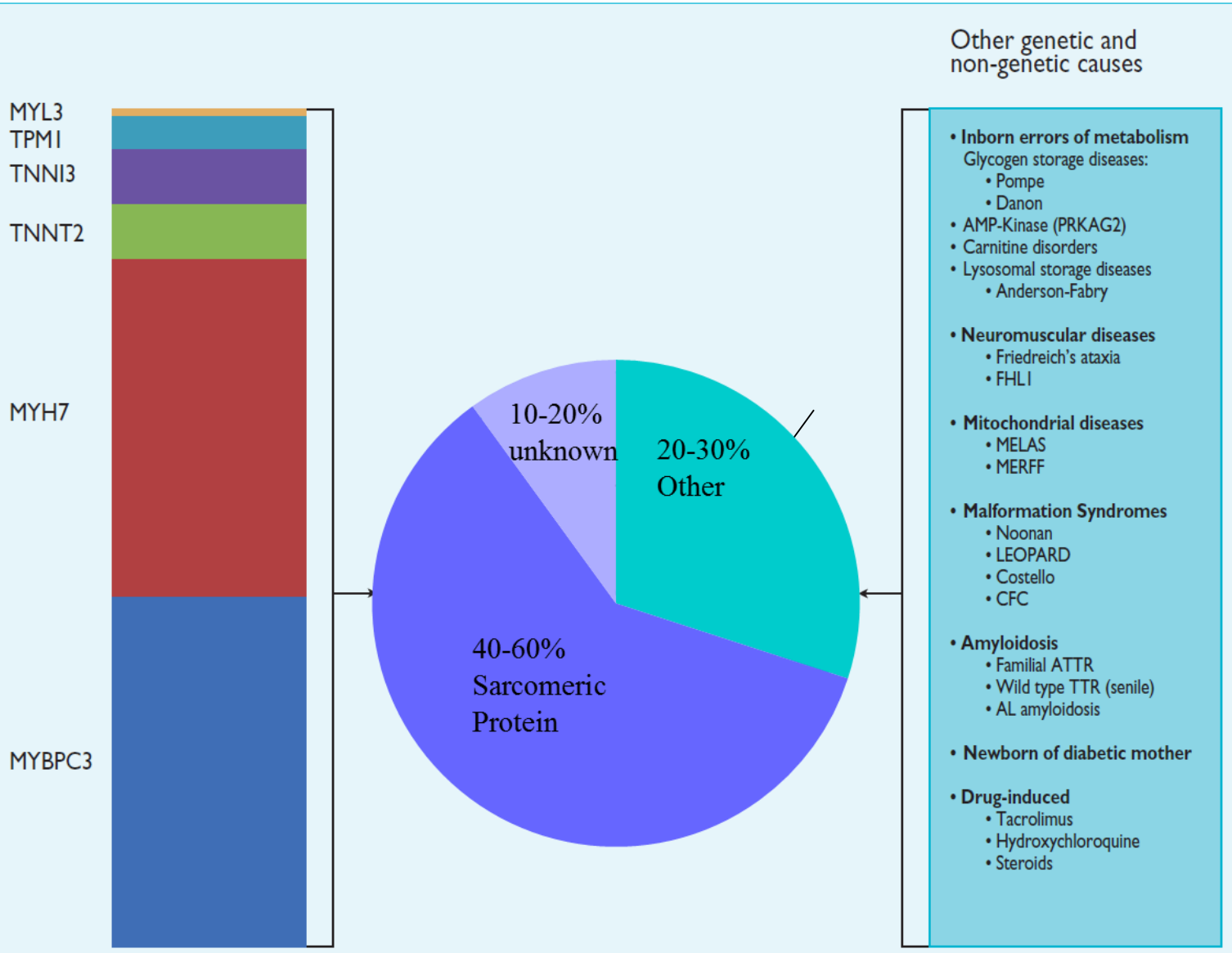
- First choice in young (HCM) patient: ideal patient population for S-ICD, no pacing indication, minimal ± weight 25 kg
- Not all HCM patients suitable for S-ICD: 16% no suitable vector with screening (high T wave voltages). T wave inversions and prior myectomy associated with screening failure (Maurizi e al HRS 2016)



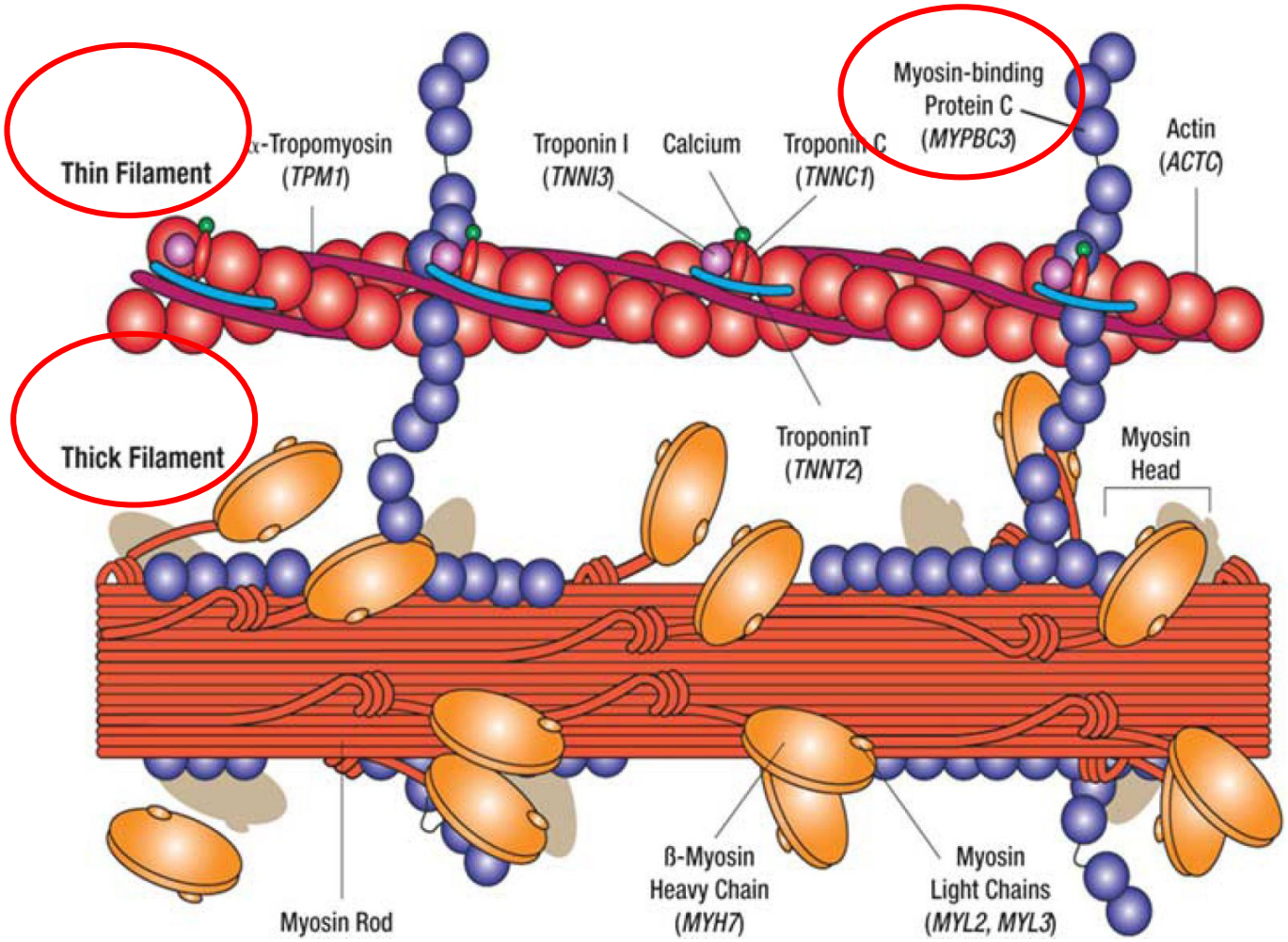


Summary management HCM in children

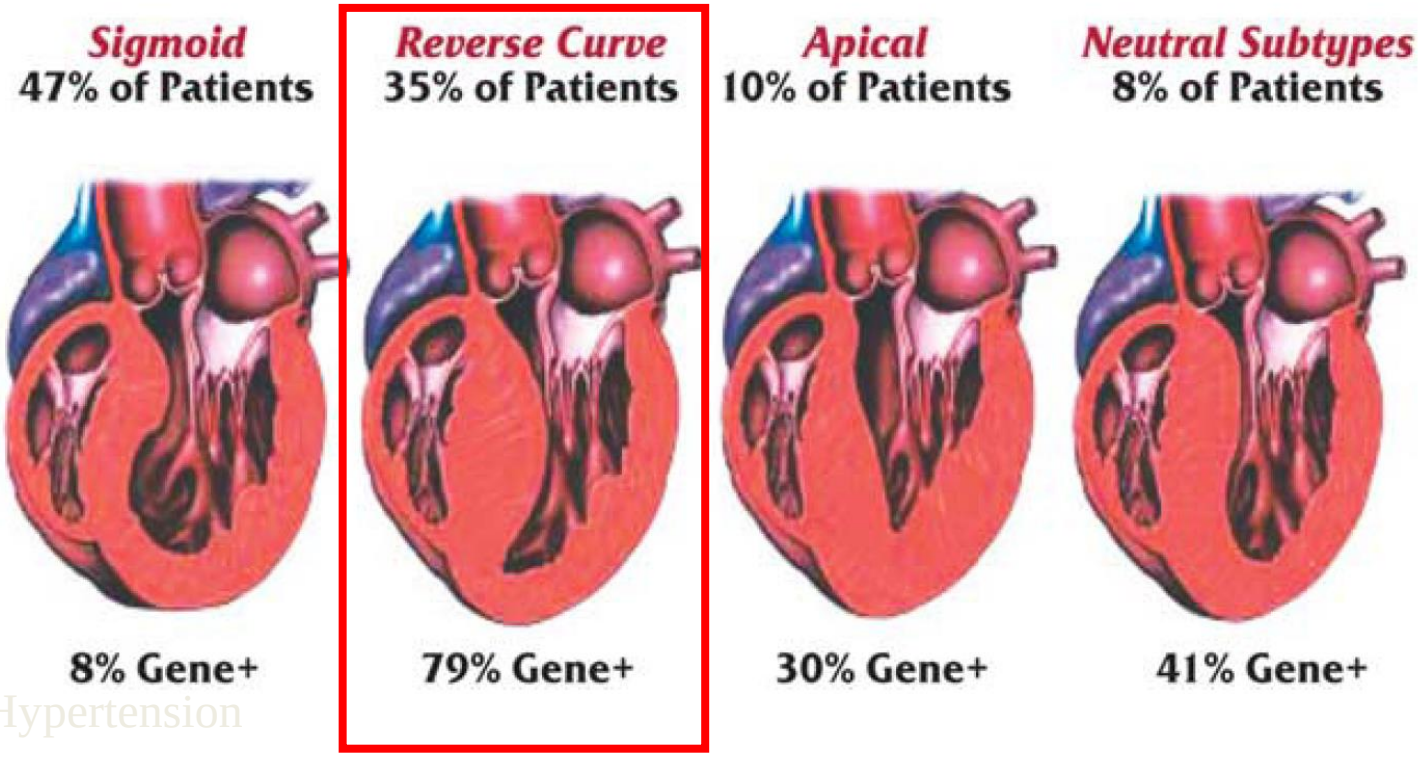
- Major paediatric risk factors : **LV wall thickness Z score > 6-7 ,** unexplained syncope, nonsustained VT , (positive FH)
- The ESC HCM risk score is not tested for children and does not seem applicable
- ICD implantation
  - Survivors of SCD or sustained VT (I)
  - Should be considered in children with 2 or more major paediatric risk factor (IIa)
  - May be considered in children with a single major risk factor (IIb)
- ICD therapy for primary prevention tailored for the individual child and family
- S-ICD has made decision making regarding ICD therapy easier in children with HCM
- Surgical myectomy is an important therapy in young patients with severe obstruction.

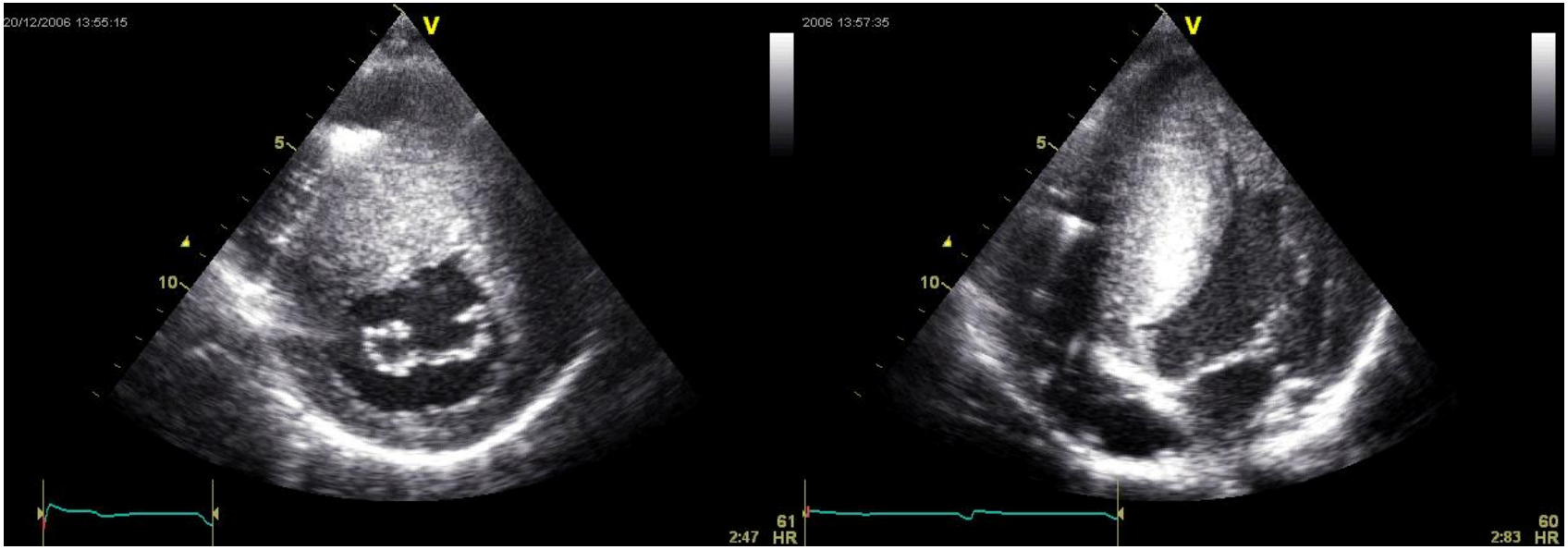


The majority of cases in adolescents and adults are caused by mutations in sarcomere protein genes. AL = amyloid light chain; ATTR=amyloidosis, transthyretin type. CFC = cardiofaciocutaneous; FHL-1=Four and a half LIM domains protein 1; LEOPARD = lentigines, ECG abnormalities, ocular hypertelorism, pulmonary 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 1 alpha chain; TTR = transthyretin.



60% have sarcomeric gene mutations





Other disease specific cardiac features

- Increased RV free wall thickness : Noonan and related disorders, Anderson-Fabry , Amyloidosis)
- Concentric LVH: glycogen storage disease, Anderson-Fabry, PRKAG mutations
- Extreme concentric LVH: Pompe disease
- LVH +global LV hypokinesia: Mitochondrial disease, PRKAG2 mutations, Danon Disease , very advanced sarcomeric HCM
- RVOTO: Noonan syndrome and related disorders

Studies on ICD therapy in HCM

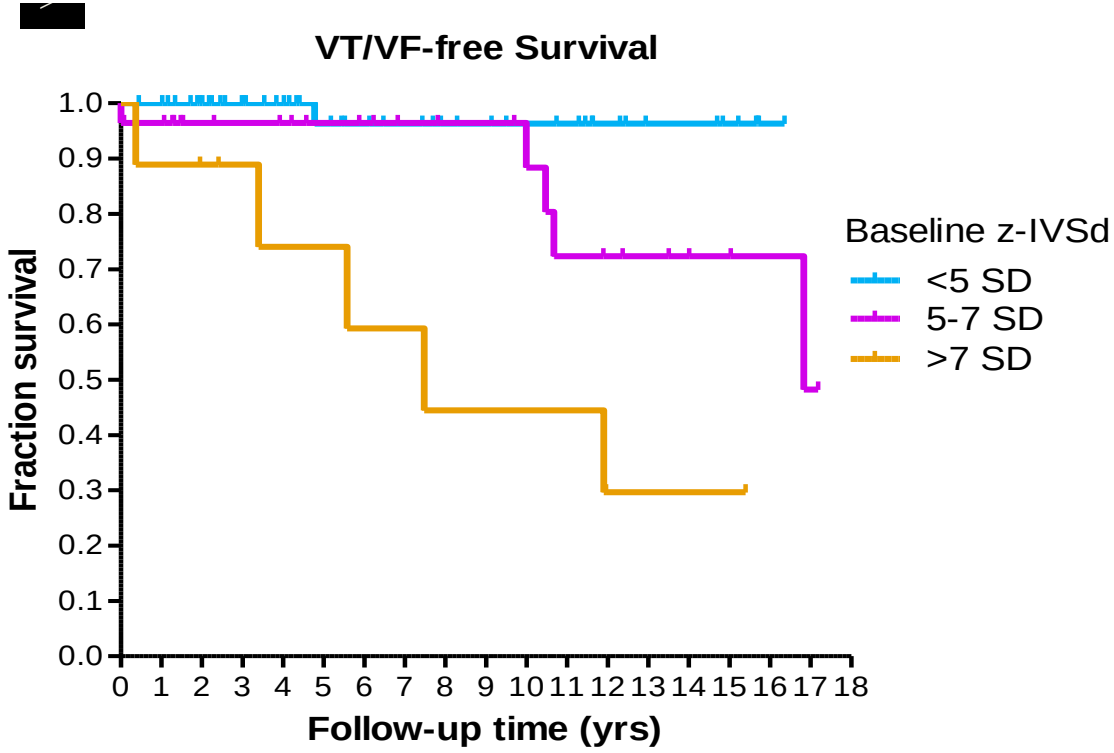
Table 1 Studies of implantable cardioverter-defibrillator therapy in patients with hypertrophic cardiomyopathy

	Year	Region	Cohort	No. patients	Mean age at implant (y)	Follow-up (y)	Secondary prevention (%/y)	Primary prevention (%/y)
Pediatric and adult HCM patients								
Maron[12]	2000	International	Multicenter	128	40	3.1	11	5
Jayatilleke[36]	2004	Australia	Single	22	—	2.9	17	10
Maron[13]	2007	International	Multicenter	506	42	3.7	11	4
Woo[32]	2007	Canada	Single	61	46	3.3	11	4
Gonzalez-Enriquez[33]	2007	Spain	Single	216	39	4.5	13	5
Syska[37]	2010	Poland	Single	104	36	4.6	8	4
Vriesendorp[35]	2013	Netherlands	Multicenter	134	47	4.2	10	5
Only pediatric HCM patients								
Kaski[40]	2006	United Kingdom	Single	22	14	1.7	71	4
Maron[39]	2013	International	Multicenter	224	14	4.3	14	3

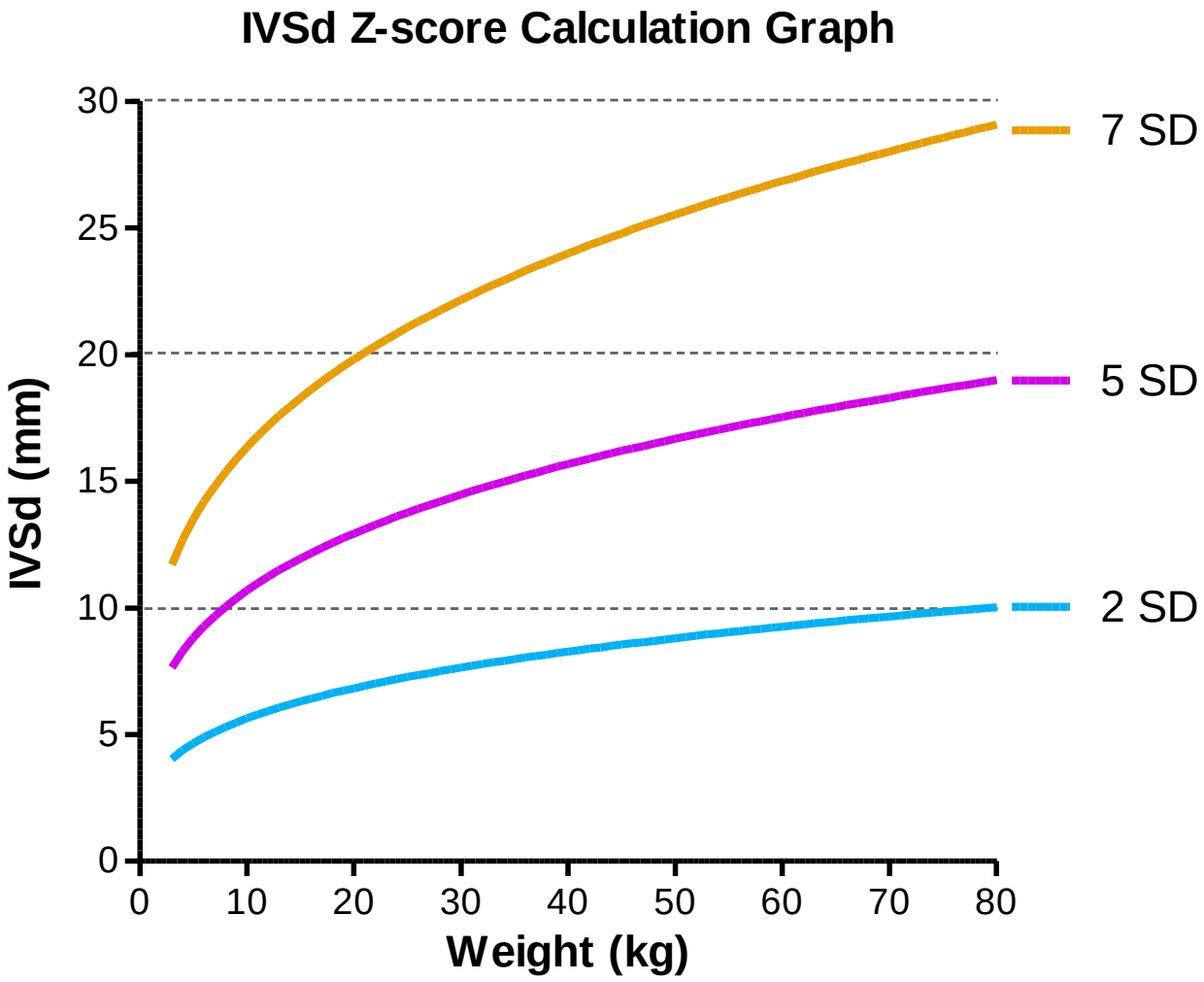
HCM = hypertrophic cardiomyopathy.

Septum cut-off values for increased risk of VT/VF

Baseline z-score IVSd	> 5 SD	> 7 SD
Sensitivity	0.91	0.45
Specificity	0.64	0.95
Pos Pred Value	0.27	0.56
Neg Pred Value	0.98	0.92



IVSd z-score Calculation Graph
7.0 SD comparable with adult cut-off value 30 mm



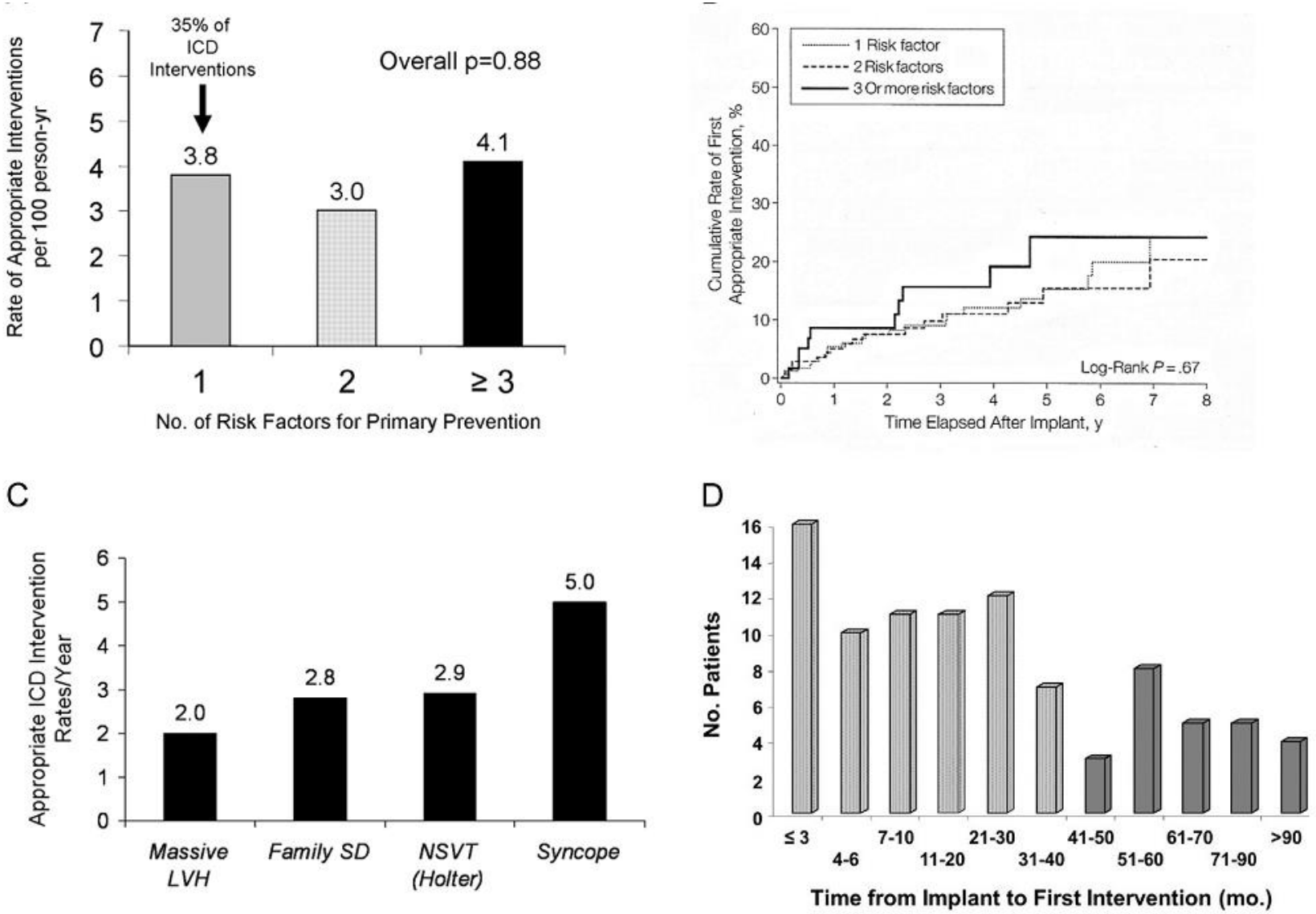
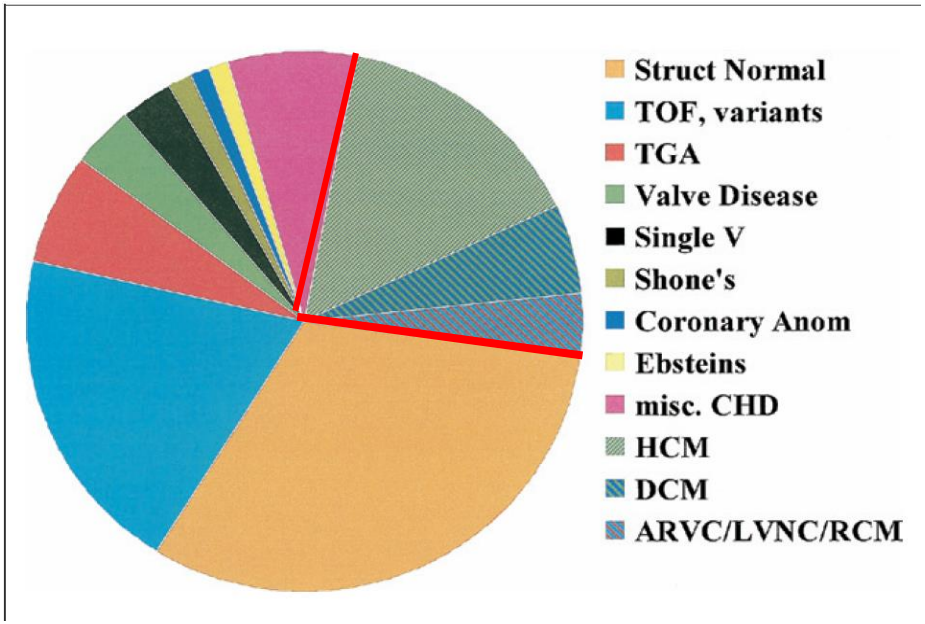


Figure 3 Strategies for prevention of sudden death (SD) in hypertrophic cardiomyopathy. **A:** Implantable cardioverter-defibrillator (ICD) intervention rates do not differ significantly with respect to implants for 1, 2, or ≥3 conventional risk factors; 35% of ICD interventions are in patients with 1 major risk factor. **B:** Cumulative rates for first device intervention with respect to 1, 2, or ≥3 risk markers. **C:** ICD intervention rates in patients implanted for only 1 risk factor. **D:** Time interval between implant and first appropriate intervention varies considerably, with some device discharges occurring after 5–10 years. From Maron et al.[13] LVH = left ventricular hypertrophy; NSVT = nonsustained ventricular tachycardia.

Cardiomyopathies in children

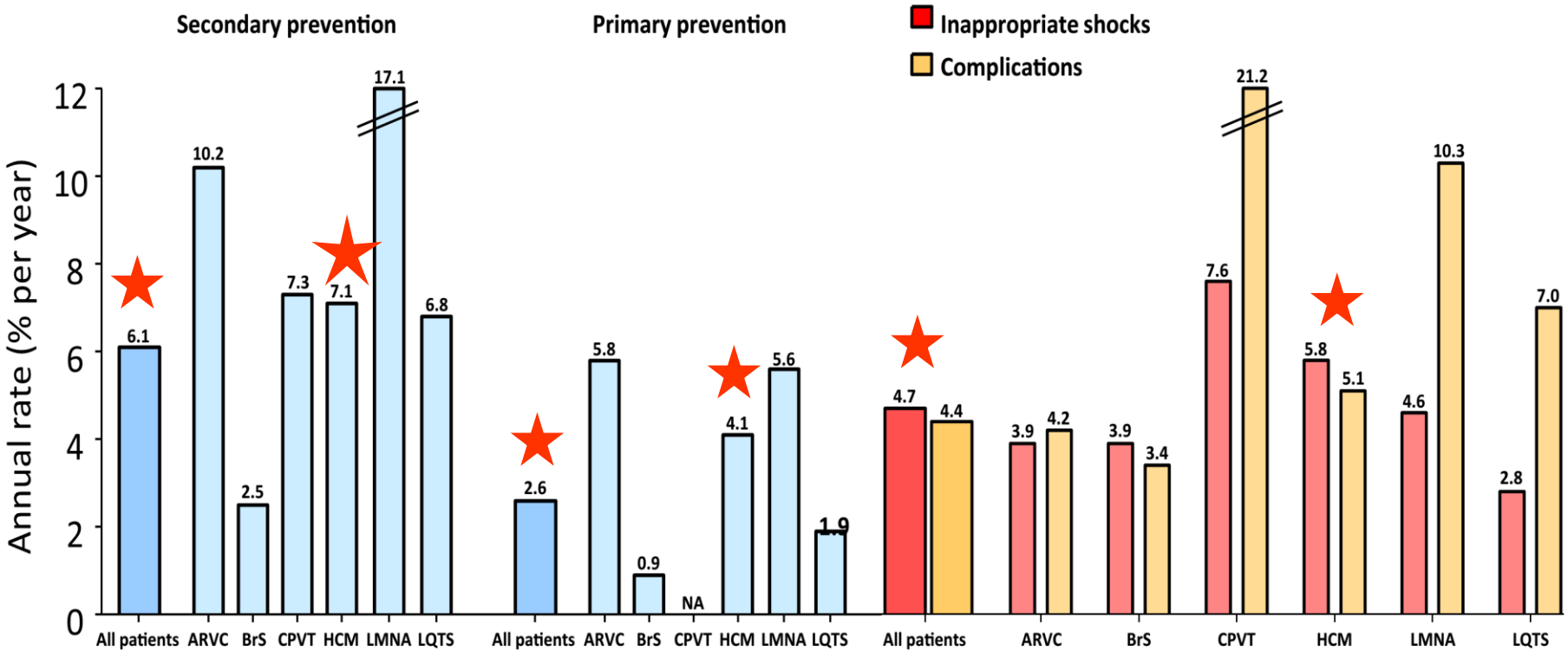
Risk of ventricular arrhythmias/sudden cardiac death

- Hypertrophic cardiomyopathy
- Dilated cardiomyopathy
- Arrhythmogenic right ventricular dysplasia
- Restrictive cardiomyopathy
- Left ventricular noncompaction



Berul, JACC 2008 n=443, 16 yrs

ICD complications in young patients inherited arrhythmia syndromes



Meta analysis 63 studies , 5000 pts, mean age 39 ± 15 yrs
Inappropriate shocks 20%, 4.7% per year
ICD related complication 22%, 4.4% per year
ICD related mortality 0.5%, 0.08% per year

Oldenordkamp 2016 HRS

Paediatric HCM data from Australia 80 pts

Alexander et al Circulation 2018

Male, n (%)	55 (69)
Age at presentation, n (%)	
≤1 year	(61)
>1 year - ≤5 years	18 (23)
>5 years	13 (16)
Noonan syndrome, n (%)	24 (30)
Familial hypertrophic cardiomyopathy, n (%)	19 (24)
Congestive cardiac failure at presentation, n (%)	6 (8)
Morphology of left ventricular involvement, n (%)	
Asymmetric septal hypertrophy with nor ss	41 (51)
Septal hypertrophy with free wall hy	39 (49)
Left ventricular fractional shortening z ation (n=74), median [IQR]	3.1 [1.2, 5.5]
Interventricular septal wall thickne sentation (n=76), median [IQR]	3.3 [1.8, 4.9]
Left ventricular outflow obstru	43 (54)
Surgical left ventricular my	19 (24)
Death or transplantatio	17 (21)
Follow-up from pre patients* (n=80), years	
Median	14.0
IQR	10.7, 17.1
Ran	0.0-21.2
Follow-u itation for all transplant-free surviving patients (n=63), years	
Media	15.7
IQR	12.9, 17.7
Range	10.1-21.2

Only a minority has typical familial HCM (sarcomeric gene mutations)