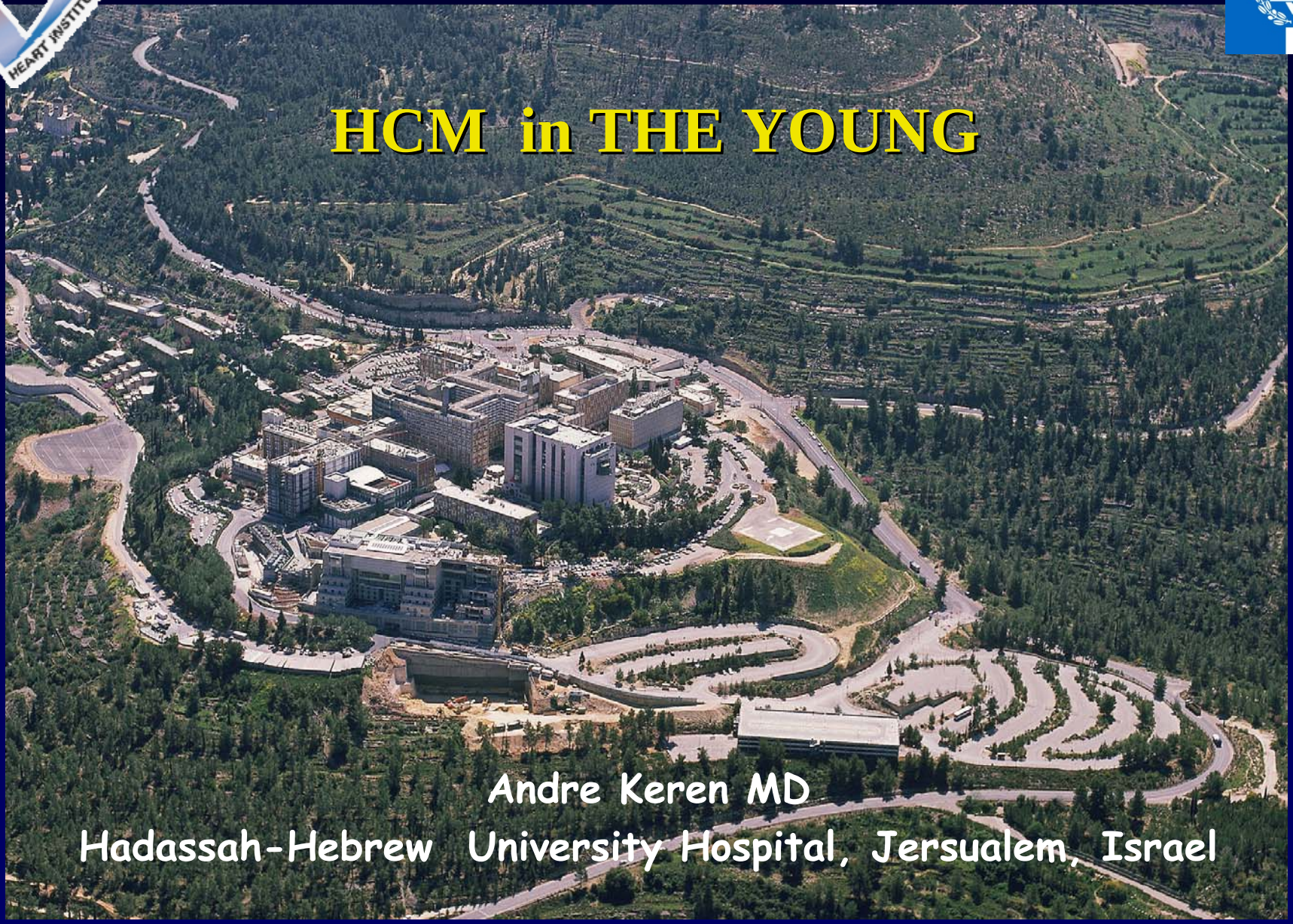
HCM in THE YOUNG



Andre Keren MD
Hadassah-Hebrew University Hospital, Jersualem, Israel

Tel Aviv 5.6.09

Hypertrophic Cardiomyopathy

Prevalence:

Author	n	Method	%
Savage 1983	3000	M mode	0.3
Hada 1987	12841	ECG	0.17
Codd 1989	3250	Echo/angio	0.02
Maron 1994	714	2D	0.5
Maron 1995	4111	2D	0.2

European Heart Journal
doi:10.1093/eurheartj/ehm342

EUROPEAN SOCIETY OF CARDIOLOGY®

Esc report

Classification of the cardiomyopathies: a position statement from the european society of cardiology working group on myocardial and pericardial diseases

Perry Elliott, Bert Andersson, Eloisa Arbustini, Zofia Bilinska, Franco Cecchi, Philippe Charron, Olivier Dubourg, Uwe Kühl, Bernhard Maisch, William J. McKenna, Lorenzo Monserrat, Sabine Pankuweit, Claudio Rapezzi, Petar Seferovic, Luigi Tavazzi, and Andre Keren*

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Received 6 March 2007; revised 27 June 2007; accepted 16 July 2007

ESC Working Group on Myocardial Pericardial Diseases (EHJ 2008)

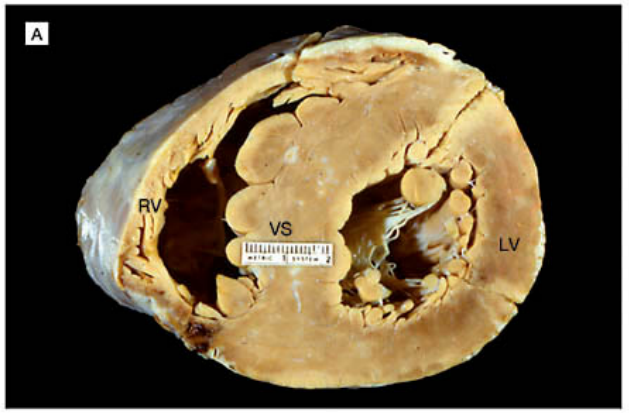
Table 1 Examples of different diseases that cause cardiomyopathies

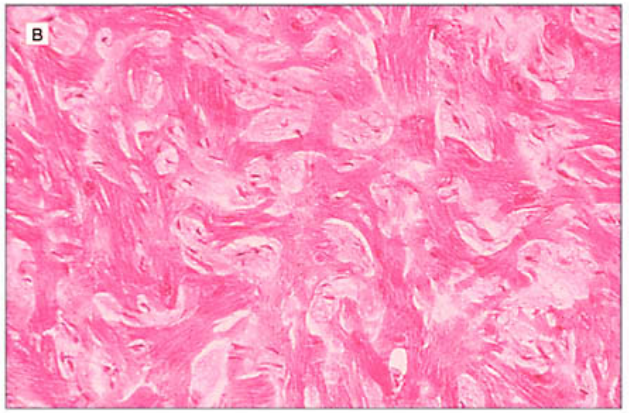
	HCM	DCM	ARVC	RCM	Unclassified
Familial	Familial, unknown gene Sarcomeric protein mutations ß myosin heavy chain Cardiac myosin binding protein C Cardiac troponin I Troponin-T α-tropomyosin Essential myosin light chain Regulatory myosin light chain Cardiac actin α-myosin heavy chain Titin Troponin C Muscle LIM protein Glycogen storage disease (e.g. Pompe; PRKAG2, Forbes', Danon) Lysosomal storage diseases (e.g. Anderson–Fabry, Hurler's) Disorders of fatty acid metabolism Carnitine deficiency Phosphorylase B kinase deficiency Mitochondrial cytopathies Syndromic HCM Noonan's syndrome LEOPARD syndrome Friedreich's ataxia Beckwith–Wiedermann syndrome Swyer's syndrome Other Phospholamban promoter Familial amyloid	Familial, unknown gene Sarcomeric protein mutations (see HCM) Z-band Muscle LIM protein TCAP Cytoskeletal genes Dystrophin Desmin Metavinculin Sarcoglycan complex CRYAB Epicardin Nuclear membrane Lamin A/C Emerin Mildly dilated CM Intercalated disc protein mutations (see ARVC) Mitochondrial cytopathy	Familial, unknown gene Intercalated disc protein mutations Plakoglobin Desmoplakin Plakophilin 2 Desmoglein 2 Desmocollin 2 Cardiac ryanodine receptor (RyR2) Transforming growth factor-β3 (TGFβ3)	Familial, unknown gene Sarcomeric protein mutations Troponin I (RCM +/− HCM) Essential light chain of myosin Familial amyloidosis Transthyretin (RCM + neuropathy) Apolipoprotein (RCM + nephropathy) Desminopathy Pseuxanthoma elasticum Haemochromatosis Anderson–Fabry disease Glycogen storage disease	Left ventricular non-compaction Barth syndrome Lamin A/C ZASP α-dystrobrevin
Non-familial	Obesity Infants of diabetic mothers Athletic training Amyloid (AL/prealbumin)	Myocarditis (infective/toxic/immune) Kawasaki disease Eosinophilic (Churg Strauss syndrome) Viral persistence Drugs Pregnancy Endocrine Nutritional — thiamine, carnitine, selenium, hypophosphataemia, hypocalcaemia Alcohol Tachycardiomyopathy	Inflammation?	Amyloid (AL/prealbumin) Scleroderma Endomyocardial fibrosis Hypereosinophilic syndrome Idiopathic Chromosomal cause Drugs (serotonin, methysergide, ergotamine, mercurial agents, busulfan) Carcinoid heart disease Metastatic cancers Radiation Drugs (anthracyclines)	Tako Tsubo cardiomyopathy

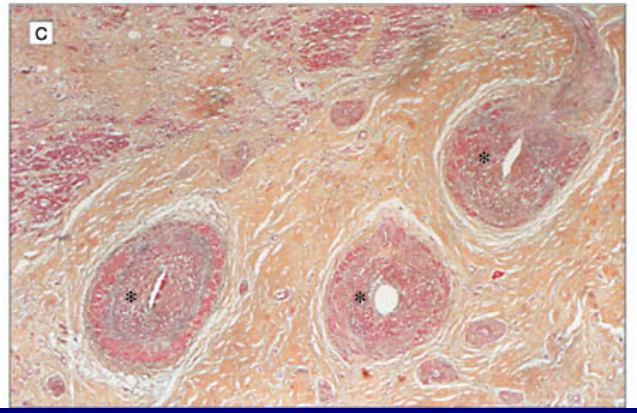
ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy.

Elliott P et al. Eur Heart J 2008;29:270-276

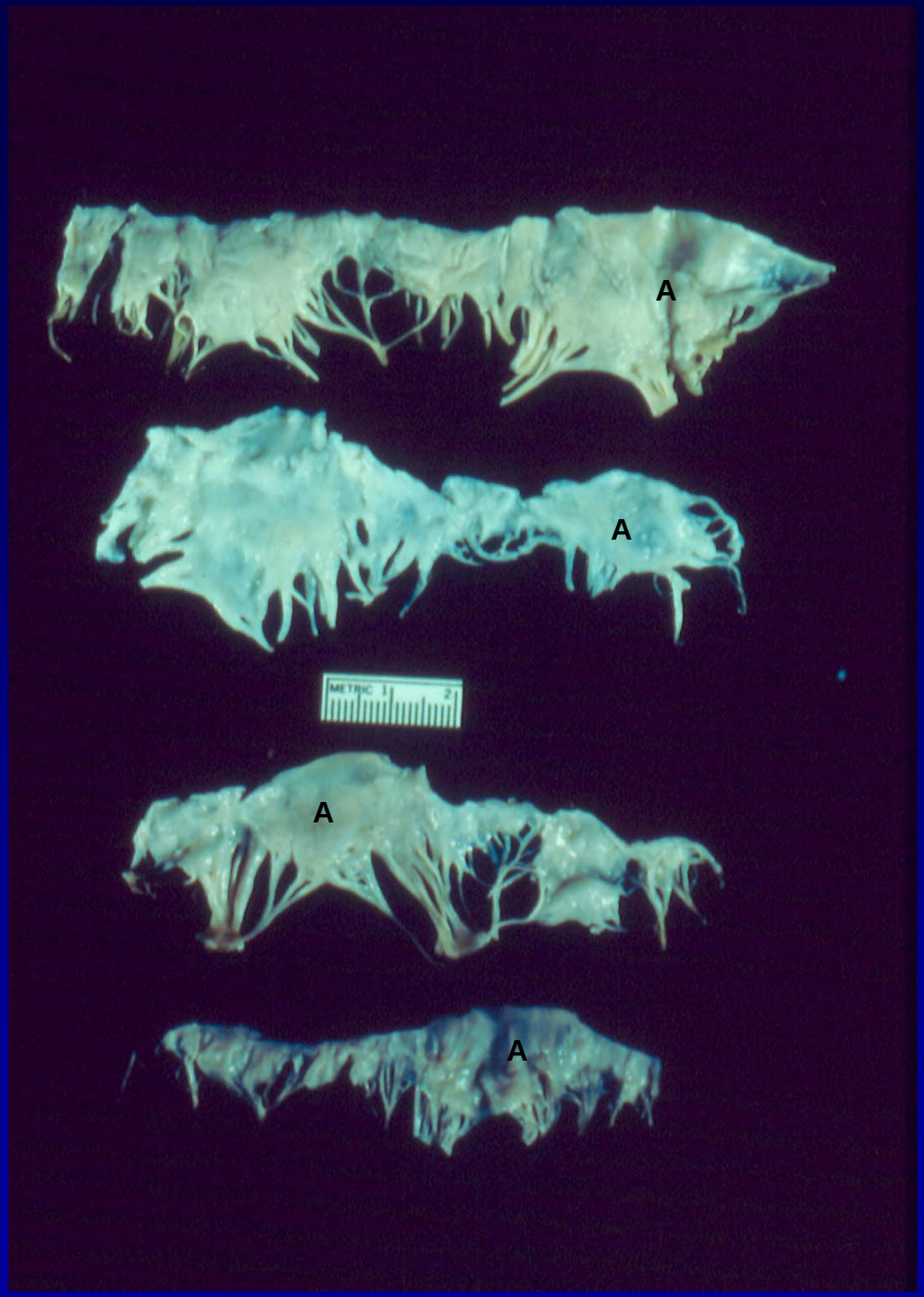
Myocardial Substrate for Sudden Death in HCM





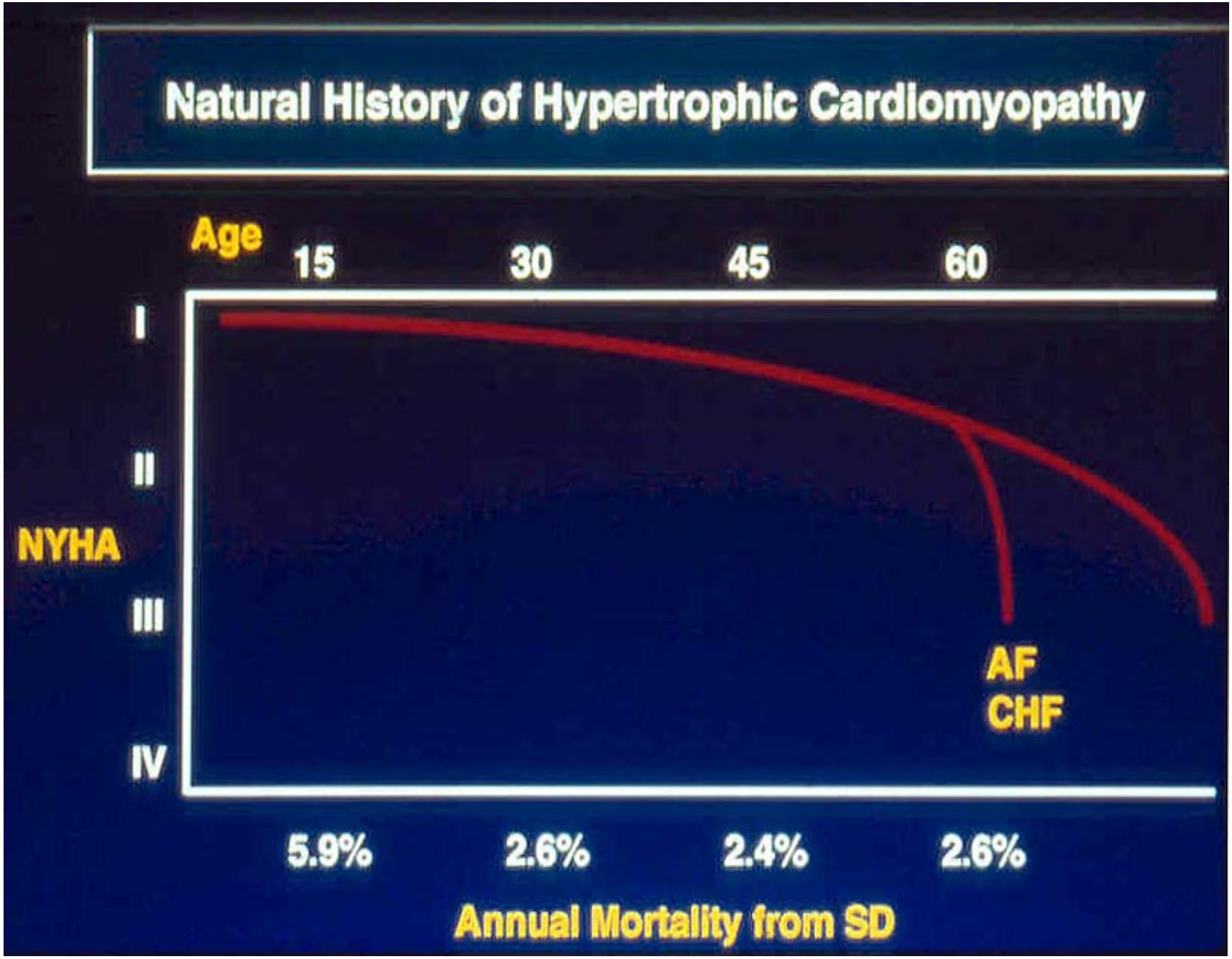


Maron BJ, JAMA 2002

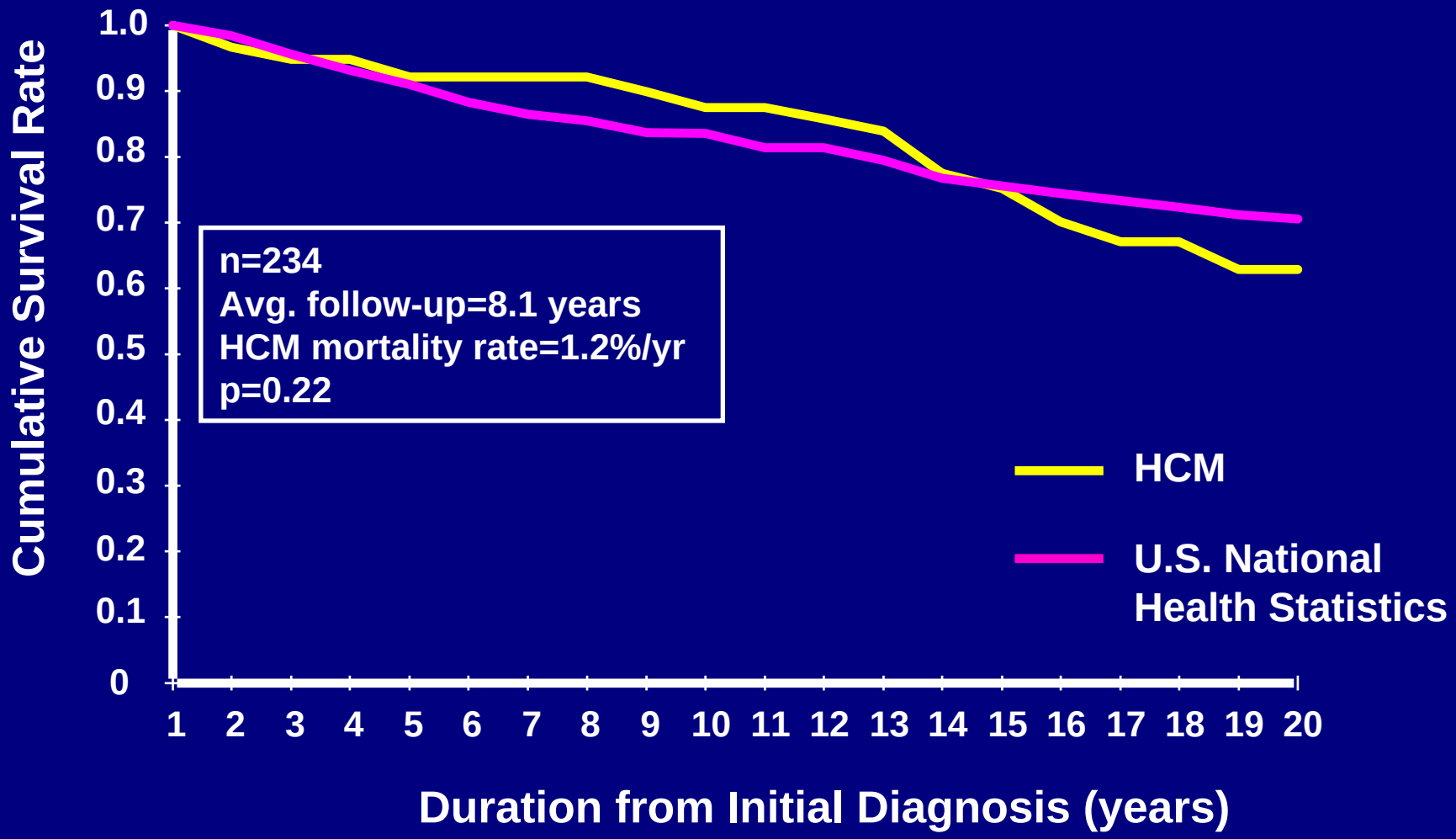


Klues HG, MaronBJ et al.

Circulation 1992;85:1651


Natural History of Hypertrophic Cardiomyopathy
Age
15
30
45
60
I
II
NYHA
III
IV
AF
CHF
5.9%
2.6%
2.4%
2.6%
Annual Mortality from SD

Survival with HCM in an Unselected Cohort of Adults (Diagnosis ≥ age 20)



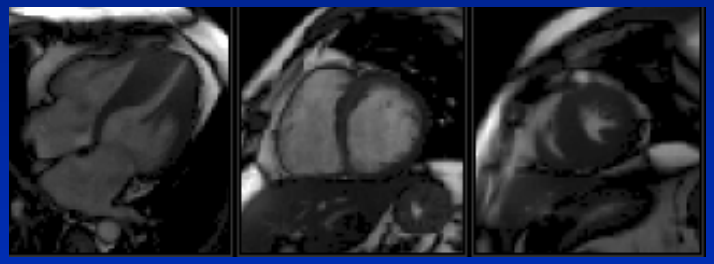
Mutations and Prognosis in HCM

Gene	Prognosis		
	Good	Intermediary	Poor
BMHC	Gly256Glu	Arg249Gln	Arg403Gln
	Leu908Val	Glu930Lys	Arg719Trp
	Val606Met	Val606Met	Arg453Cys
	Phe513Cys		Arg723Gly
	Asn232Ser		
Cardiac troponin T			
	Ser179Phe	Phe110Ile	Arg92Gln
			Arg92Trp
			Ile79Asn
			Glu160
			Ser179Pheq (homozygous)
MYBP-C	All unless listed	SASint20	
α-Tropomyosin	Asp175Asn		Val95Ala
MLC	Insufficient data		

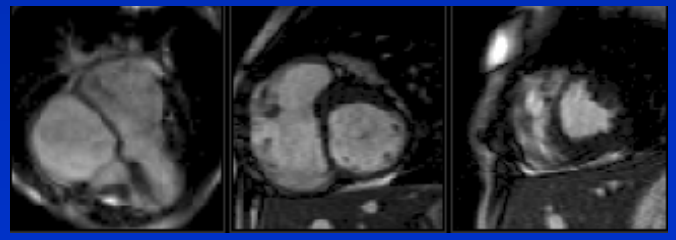
Roberts R, Sigwart U. Circulation 2001;104:21113

HCM Troponin I Mutation: Morphologic Heterogeneity

Asymmetrical Septal Hypertrophy (ASH)



Apical Hypertrophy



Restrictive Cardiomyopathy

UCLH, Heart Hospital, London, UK

Courtesy of Dr James Moon

Consensus Document:

Family Screening for HCM Dg

Prevention of Sudden Death

Family Screening and HCM Follow-up

Screening (ECG, ECHO)*:

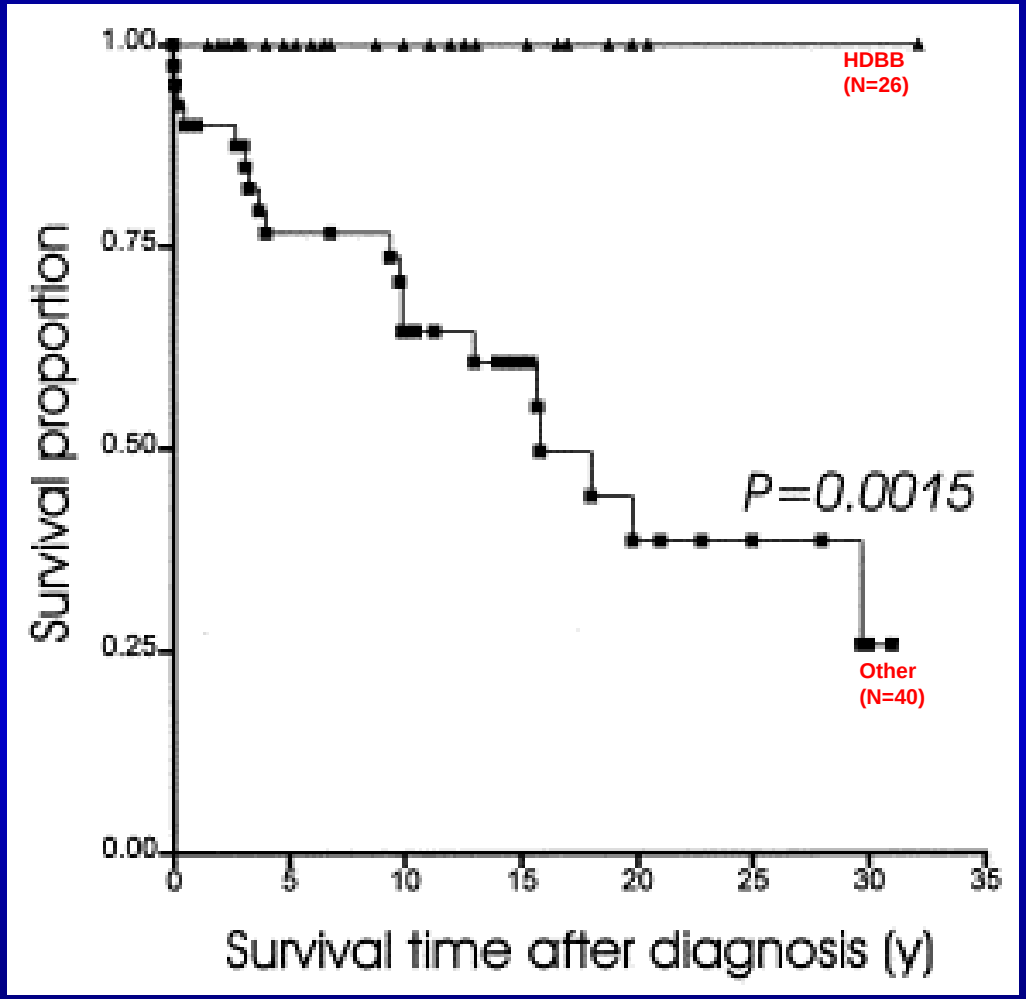
- **In ≥ 12 years old first degree relatives**

- **NO HCM: Screening / 5years**

HCM F-up (+ Holter, EXT)*:

- **Evaluation of risk for SD once / 1-1.5 years**

Comparison of Survival in the HDBB and All Other Groups (Conventional Rx)



Ostman-Smith I et al. JACC 1999;34:1813-22

Conclusion:

High-dose BB is protective in childhood HCM and reduces 5-10-fold mortality

Ostman-Smith I et al. JACC 1999;34:1813-22

Administration of massive dosses of Propranolol is not generally accepted practice.

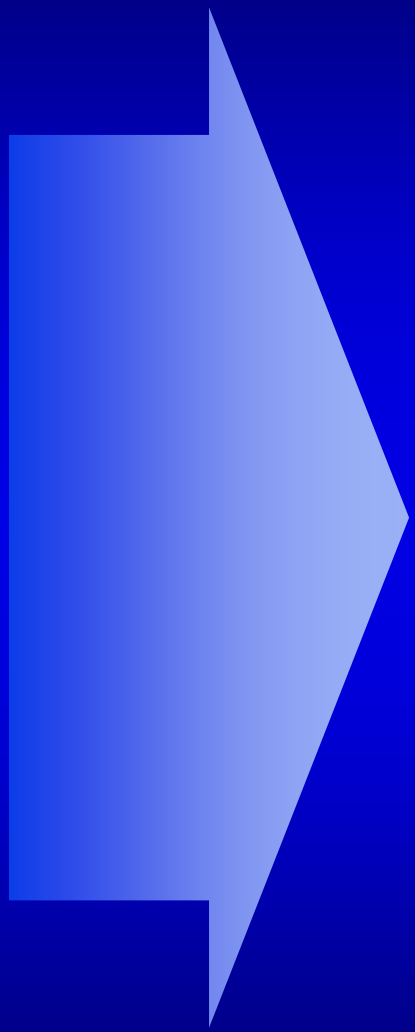
Even moderate doses of beta-blockers may affect growth in young children or impair school performance, or trigger depression in children and adolescents, and should be closely monitored in such patients.

ACC/ESC Expert Consensus on HCM, 2003

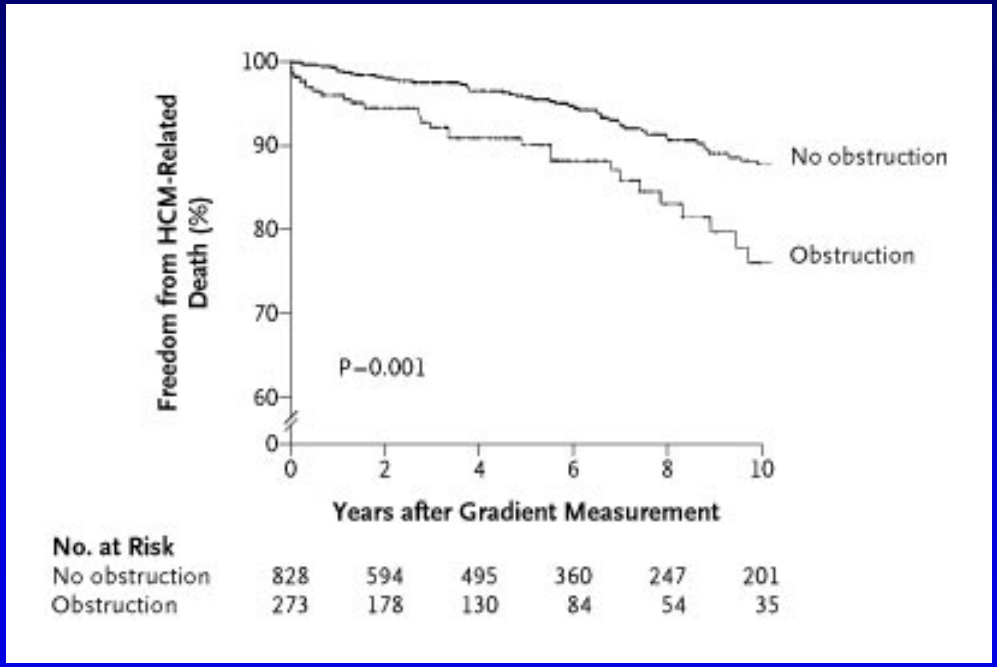
Prevention of Sudden Death

Risk Factors in HCM

Youth
Genotype
Family History
NYHA III/IV
Exercise capacity
Syncope
Severe LVH
Large gradient
Diastolic dysfunction
Abn Exercise BP
Ischaemia
Atrial fibrillation
Non-sustained VT
Inducible VT/VF
Fractionation

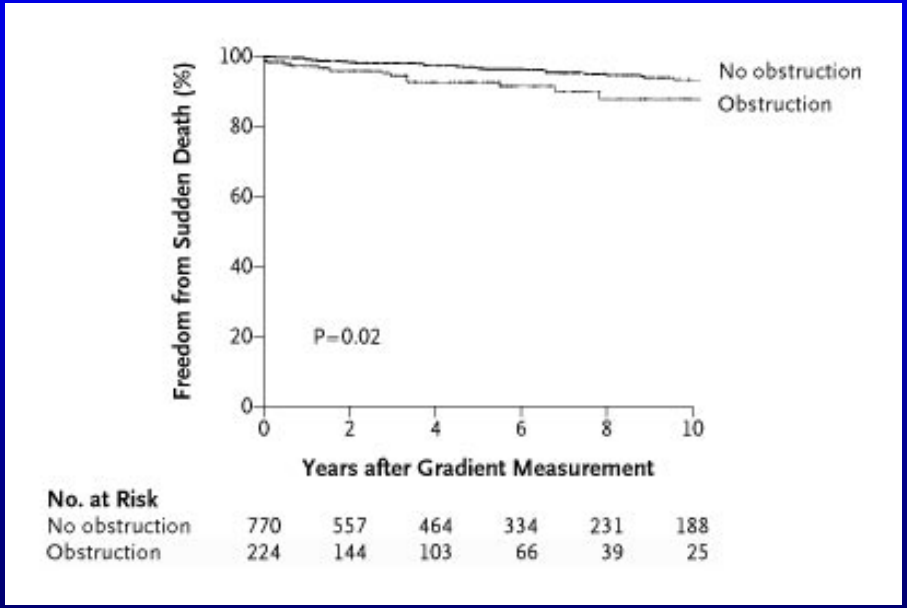


Family History
Syncope
Exercise BP
NSVT
LVH
Malignant mutation



Maron BJ ,Cecchi F et al.

NEJM 348 (4): 295, 2003



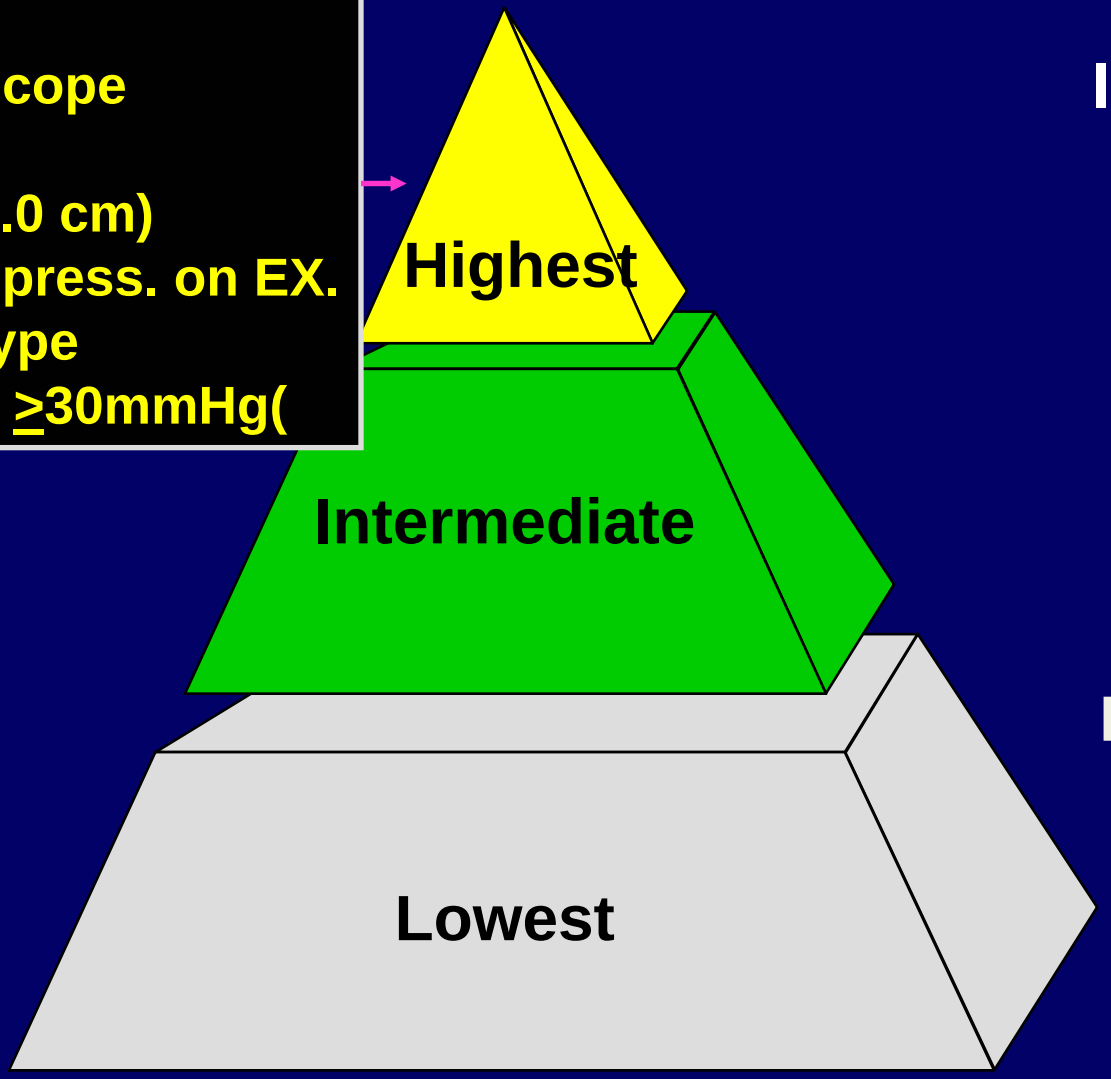
Sudden Death and Risk Markers

Risk factors	Sudden death/year
≥ 3 (5%)	6% (4 - 16)
2 (20%)	3% (0.7 - 5.5)
1 (25%)	1.2% (0.2 - 2.2)
0 (50%)	0.8% (0.2 - 1.5)

Cox Model - 368 patients. Elliott PM et al JACC 2000;36:2212-8

Strongest Risk Factors:

- Cardiac arrest/sustained VT
- Familial SD
- Unexplained syncope
- NSVT
- Massive LVH (≥3.0 cm)
- Abnormal blood press. on EX.
- Malignant genotype
- Resting gradient ≥30mmHg(



- Classical concepts of pediatric HCM
- Population based studies
- Attempt of risk stratification
- ICD in pediatric pts
- Genetics in pediatric pts

HYPERTROPHIC CARDIOMYOPATHY

- HCM presents at all ages in childhood
  - Fetus
  - Newborn/Infancy
  - Childhood
- Clinical presentation varies depending on age of onset: Newborn/Infant
  - Tachypnea
  - Dyspnea with feeds
  - Diaphoresis

HYPERTROPHIC CARDIOMYOPATHY

- Clinical presentation varies depending on age of onset: Child
  - Syncope
  - Sudden death
  - Heart failure
- Sudden death rare in infants, uncommon in childhood
- Sudden death risk increased in adolescents vs. adults

POPULATION BASED STUDIES

Population Based Studies

- **Australia (National Australian Childhood Cardiomyopathy study- NACC)**
  - 10 year period 314 new cases were identified.
  - Ann incidence 1.24: 100.000 children <10 ys
    - DCM 58.6 %
    - HCM 25.5 % (80 cases)
    - Restrictive 2.5 %
    - Left ventricular non compaction 9.2 %

Naguent AW et al. N Engl J Med. 2003;348:1639-46

Clinical Features and Outcomes of Childhood Hypertrophic Cardiomyopathy: Results From a National Population-Based Study

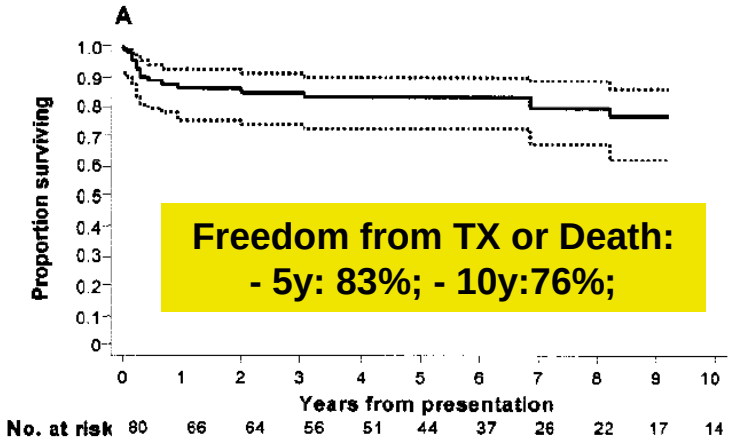
TABLE 1. Demographic Characteristics of the Patients Studied

Characteristic	
Percentage of total cases in NACCS (n=314)	25.5
Male/female, n (%)	55/25 (69/31)
Age ≤1 y at presentation, n (%)	48 (60)
Age >1 and ≤5 y, n (%)	19 (23.8)
Age >5–10 y, n (%)	13 (16.2)
Noonan syndrome, n (%)	23 (28.8)
Familial hypertrophic cardiomyopathy, n (%)	17 (21.3)
Presence of metabolic disease, n (%)	2 (2.5)
Morphology of left ventricular involvement, n (%)	
Asymmetric septal hypertrophy	56 (70)
Concentric left ventricular hypertrophy	24 (30)
Biventricular involvement, n (%)	18 (22.5)
Left ventricular outflow obstruction, n (%)	32 (40)
Surgical left ventricular myectomy, n (%)	18 (22.5)
Right ventricular outflow obstruction, n (%)	10 (12.5)
Death or transplantation, n (%)	15 (18.8)
Follow-up from presentation for all patients (n=80), y	
Median	5.25

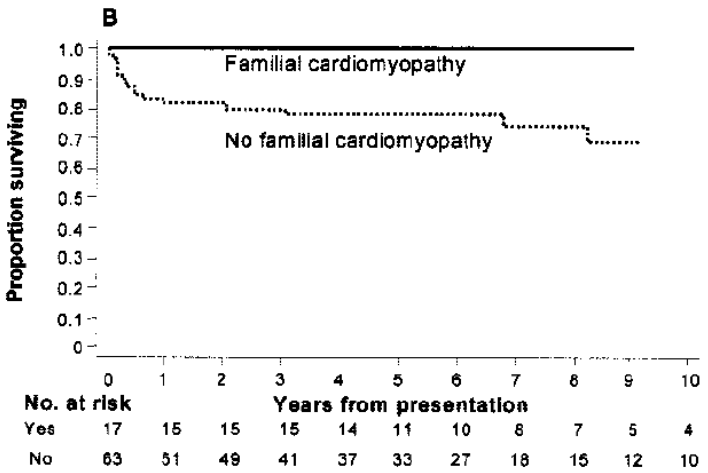
Presentation

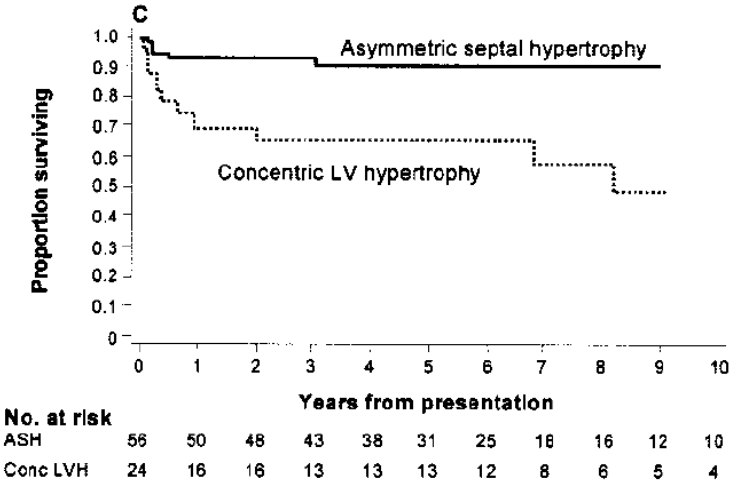
- No sudden death
- CHF in only 7%
- FH of HCM 15%
- Murmur 52%

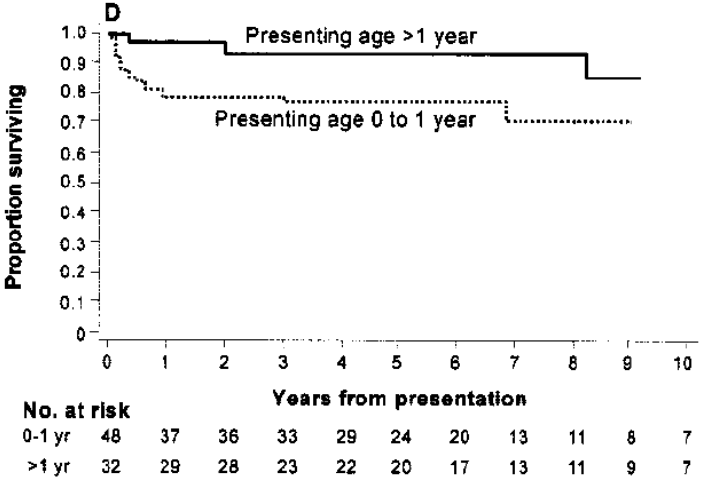
NAGUENT AW, Circulation 2005;112:1332-38



Freedom from TX or Death:
- 5y: 83%; - 10y:76%;







Naguent AW, Circulation 2005;112:1332-39

HCM

- **NACC registry*** in 10 years, 314 new cases of cardiomyopathy, 80 cases of HCM (25.5%).

***NACC excluded:**
neuromuscular disorders
inborn errors of metabolism with multiorgan involvement

- **PCMR (1994-2010)**: 855 patients with HCM <18 y
  - 74 (9%) Inborn errors of metabolism
  - 77 (9%) Malformation syndromes
  - 64 (7.5 %) Neuromuscular disorders
  - 634 (74%) Idiopathic HCM

Naguent AW et al. N Engl J Med. 2003;348:1639-46; Naguent AW, Circulation 2005;112:1332-39;
Colan SD et al. Circulation 2007;115:773-781;

Appendix, on line

Etiology	N	Median Age at Diagnosis, yrs	# Deaths
Inborn Errors of Metabolism	**74**	**0.4**	**36**
Pompe disease	25	0.3	17
Cori disease	3	3.5	0
Glycogen storage disease type IX	1	0.2	1
Glycogen storage disease with normal acid maltase	2	1.1	0
Hurler syndrome	4	6.6	2
Hunter syndrome	2	7.2	0
Morquio syndrome	1	11.2	0
Leigh disease	3	2.2	1
Complex I deficiency	3	0.2	3
Combined respiratory chain deficiencies	2	0.7	1
MELAS syndrome	6	11.1	1
Barth syndrome	2	0.4	1
Sengers syndrome	1	0.5	1
Oxidative phosphorylation disorder, other or not otherwise specified	6	0.7	4
Primary or systemic carnitine deficiency	1	0.0 (1 day)	0
Carnitine palmitoyl transferase type II deficiency	2	2.4	1
Very long chain acyl-CoA dehydrogenase deficiency	3	0.3	1
Long chain acyl-CoA dehydrogenase deficiency	3	0.3	1
Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency	2	0.6	0
Multiple acyl-COA dehydrogenase deficiency	1	0.0 (7 days)	1
Malonic acidemia	1	4.4	0

Colan SD et al. Circulation 2007;115:773-781

Etiology	N	Median Age at Diagnosis, yrs	# Deaths
Malformation Syndromes	**77**	**0.4**	**15**
Noonan syndrome	60	0.5	13
LEOPARD syndrome	1	0.0 (11 days)	0
Beckwith-Wiedemann syndrome	3	0.2	0
Rubinstein-Taybi syndrome	1	8.7	0
Total lipodystrophy, insulin resistance, leprechaunism	1	17.7	0
Costello syndrome	4	0.2	1
Macrosomia, postnatal growth and mental retardation, Costello-like features	1	1.1	0
Mental retardation, unusual facies, arthritis, deafness	1	0.0 (1 day)	0
Leber congenital amaurosis	1	1.3	0
Chromosome defect, other or not otherwise specified	4	0.2	1
Neuromuscular Disorders	**64**	**10.1**	**2**
Myotonic dystrophy	4	1.1	0
Muscular dystrophy, not otherwise specified	1	8.7	0
Minicore (multicore) myopathy	1	16.1	0
Congenital myopathy, not otherwise specified	2	0.8	1
Friedreich ataxia	56	10.3	1
Familial Isolated CM	**115**	**8.8**	**2**
Familial hypertrophic CM defect in cardiac myosin beta heavy chain (linkage to chromosome 14)	6	9.2	0
Familial hypertrophic CM linkage to chromosome 7q3 with Wolff-Parkinson-White syndrome	2	2.0	1
Familial hypertrophic CM (autosomal dominant inheritance), other or not otherwise specified	89	8.7	1
X-linked isolated cardiomyopathy, not otherwise specified	1	14.2	0

HCM Survival

- PCMR identify two main factors
  - **Age of presentation (<1 or >1 year of age)**
  - **Cause of HCM**
    - IEM
    - NMD
    - MFS
    - IHCM

Colan SD et al. Circulation 2007;115:773-781

The Pediatric CM Registry (PCMR) 1990 -2006

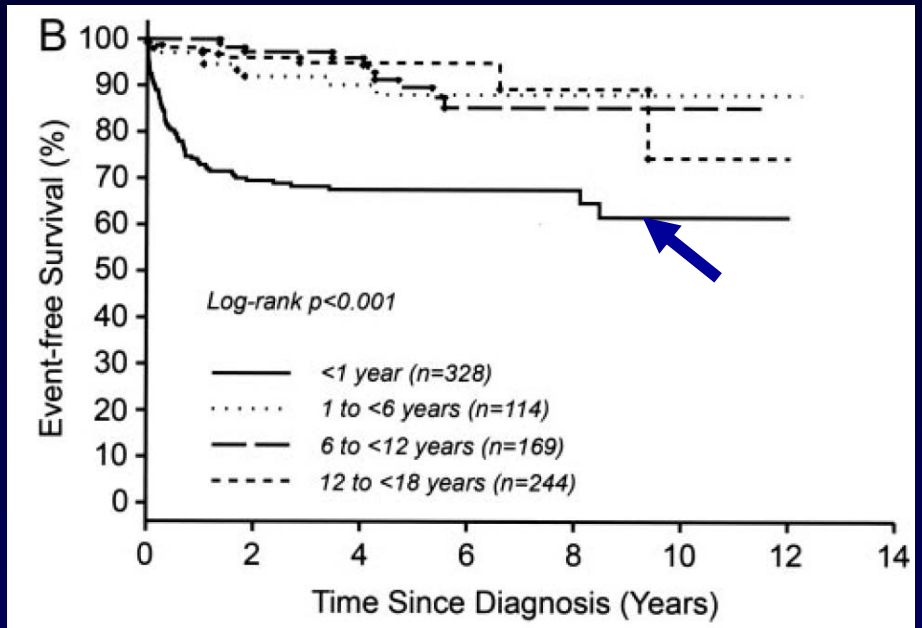


Figure 1. Survival rates from diagnosis of cardiomyopathy to death (A; log-rank $P<0.001$) and death or transplantation (B; log-rank $P<0.001$) in the combined prospective and retrospective cohorts (N=855) by age at diagnosis (<1, 1 to <6, 6 to <12, and 12 to <18 years).

Colan SD et al. Circulation 2007;115:773-781

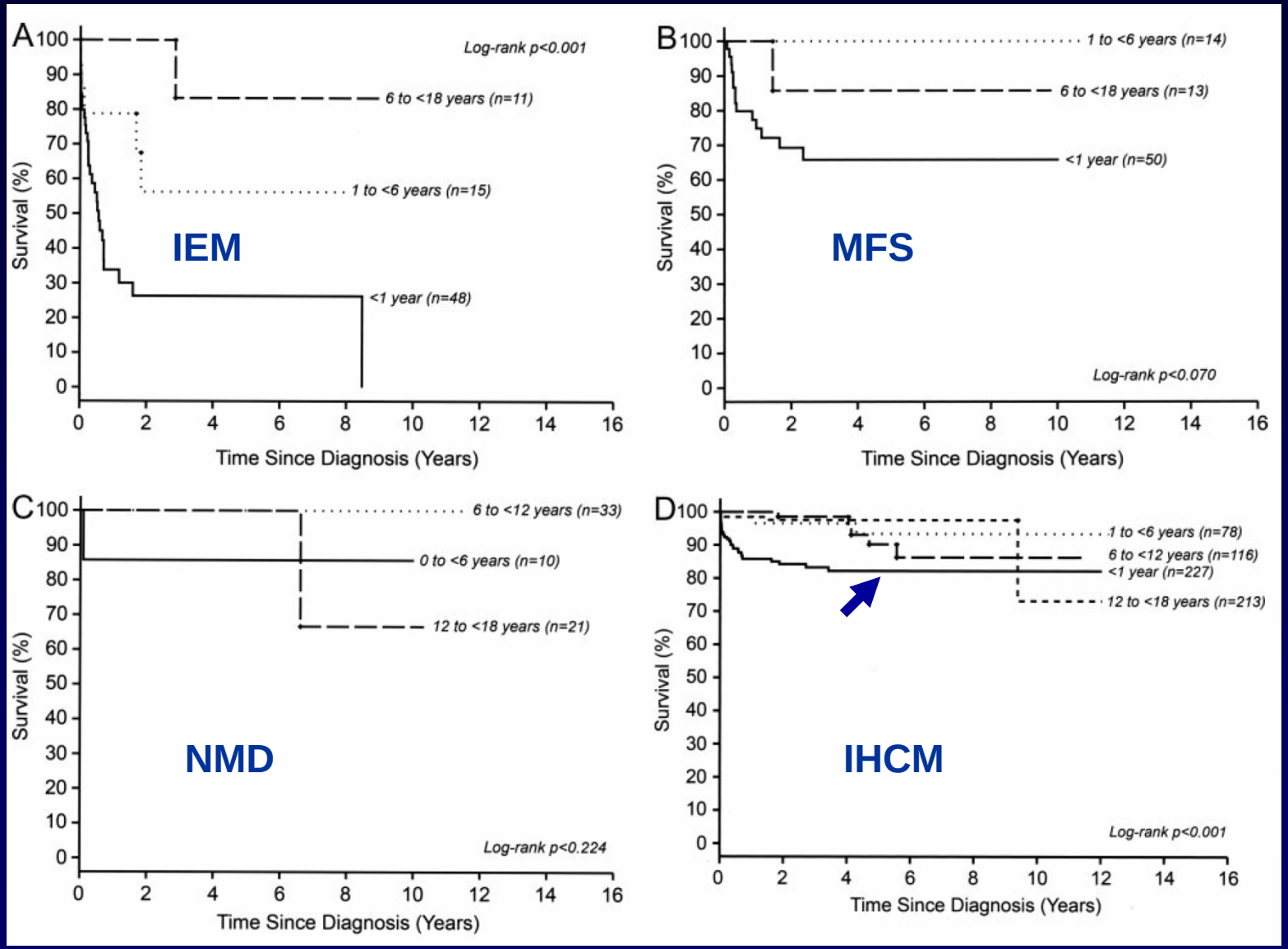
HCM Survival by Cause

TABLE 5. Survival Rate From Time of HCM Diagnosis by Etiology

	Survival Rate After HCM Diagnosis, % (95% CI)			
	1 y	2 y	5 y	10 y
IEM	53.6 (41.3 to 66.0)	44.9 (31.9 to 57.9)	41.7 (28.2 to 55.2)	*
MFS	82.4 (73.0 to 91.9)	76.6 (65.8 to 87.5)	74.4 (63.0 to 85.7)	74.4 (63.0 to 85.7)
NMD	98.2 (94.7 to 100)	98.2 (94.7 to 100)	98.2 (94.7 to 100)	91.7 (78.9 to 100)
IHCM	94.4 (92.4 to 96.4)	92.8 (90.5 to 95.1)	89.8 (86.5 to 93.1)	85.3 (77.4 to 93.2)
Infantile IHCM	85.8 (80.7 to 90.9)	84.3 (78.8 to 89.7)	82.2 (76.2 to 88.2)	82.2 (76.2 to 88.2)
Noninfantile IHCM	99.2 (98.3 to 100)	97.6 (95.7 to 99.4)	93.9 (90.0 to 97.9)	85.9 (72.7 to 99.2)

*Maximum follow-up observation in this group is only 9.0 years.

Colan SD et al. Circulation 2007;115:773-781



Colan SD et al. Circulation 2007;115:773-781

Conclusions

HCM in children is a diverse disorder with origin-specific outcomes. Infants have a worse outcome, with HCM associated with IEM and MFS having a particularly poor prognosis. Infants with IHCM have a much better survival than previously reported, however, and for those who survive beyond 1 year of age, survival rates are not different from survival rates in patients diagnosed after 1 year of age. Overall, pediatric patients with IHCM who survive beyond or are diagnosed at >1 year of age have a mortality rate of 1.0 per 100 patient-years.

Colan SD et al. Circulation 2007;115:773-781

Age- and gender-specific mortality rates in childhood hypertrophic cardiomyopathy

Ingegerd Östman-Smith[1]*, Göran Wettrell[2], Barry Keeton[3], Daniel Holmgren[1], Ulf Ergander[4], Steven Gould[5], Colene Bowker[5], and Mario Verdicchio[6]

- Cohort study from 6 regional centers of paediatric cardiology
- Population based statistics of mortality

- N=150; male 60%, Familial 40%;
- Mortality: 59 death, 39 of them sudden arrhythmic, with 31 <19 years
- Annual Sudden Death Rate:
  - Between 9-14 years 7.2%
  - After age 16 years 1.7%, p=0.025, OR 3.75 (95% CI 1.18-11.91)
  - Peaks earlier in girls than in boys

Oestman-Smith I et al. Eur HJ 2008;29:1160-1167

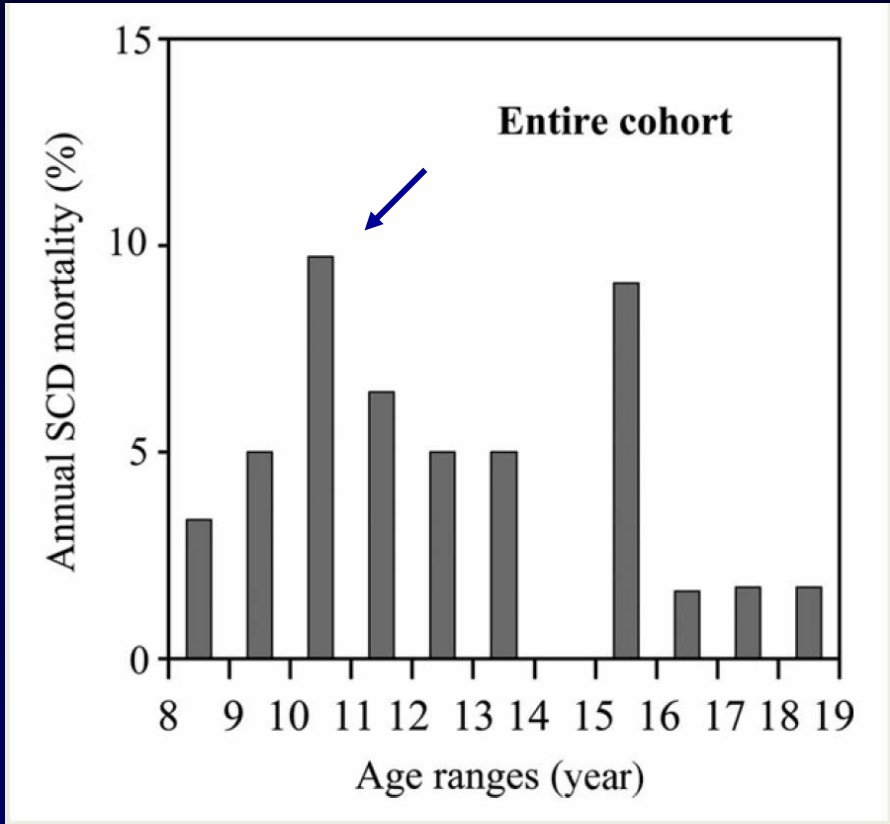


Figure 2 Dark-grey columns show sudden death mortality within age-bands expressed as annual mortality among cases known to have the disease within the age-band. Average annual mortality in the 9–12 year age range is 7.2%, and in the 16–19 year age range 1.7%. SCD, sudden cardiac death

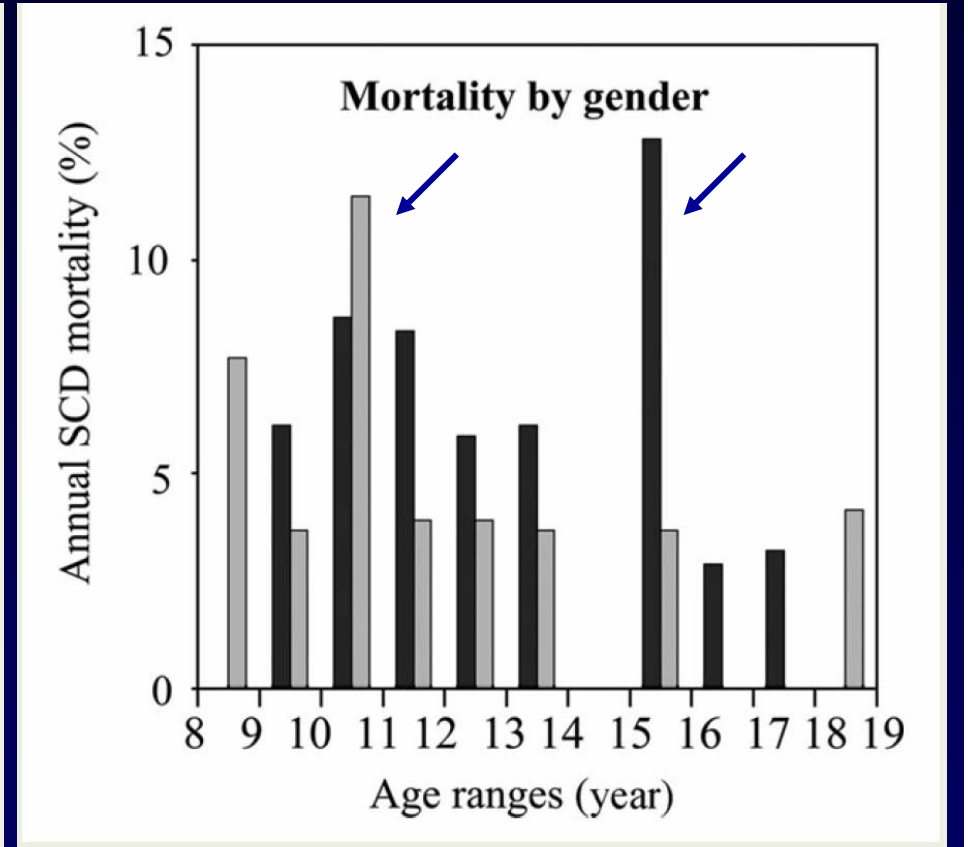


Figure 5 Annual mortality rate in age-bands separated by gender. Grey columns illustrate girls and black columns boys. Annual mortality rates peaks at 10–11 years of age in girls, and at 15–16 years of age in boys. SCD, sudden cardiac death

Ostman-Smith I et al. EHJ 2008

Table 2 Population based annual mortality per 100 000 age-specific population in Sweden according to coding on death certificates

Diagnosis	0–7 years	8–16 years	17–30 years	95% CI 17–30 year age range
HCM	0.052	0.112	0.055	0.011–0.099
DCM	0.052	0.033	0.151	0.072–0.230
Aortic stenosis	0.209	0.042	0.009	0.000–0.027
Cor. malformation	0.017	0.014	0.046	0.006–0.086
Myocarditis	0.052	0.028	0.018	0.000–0.043

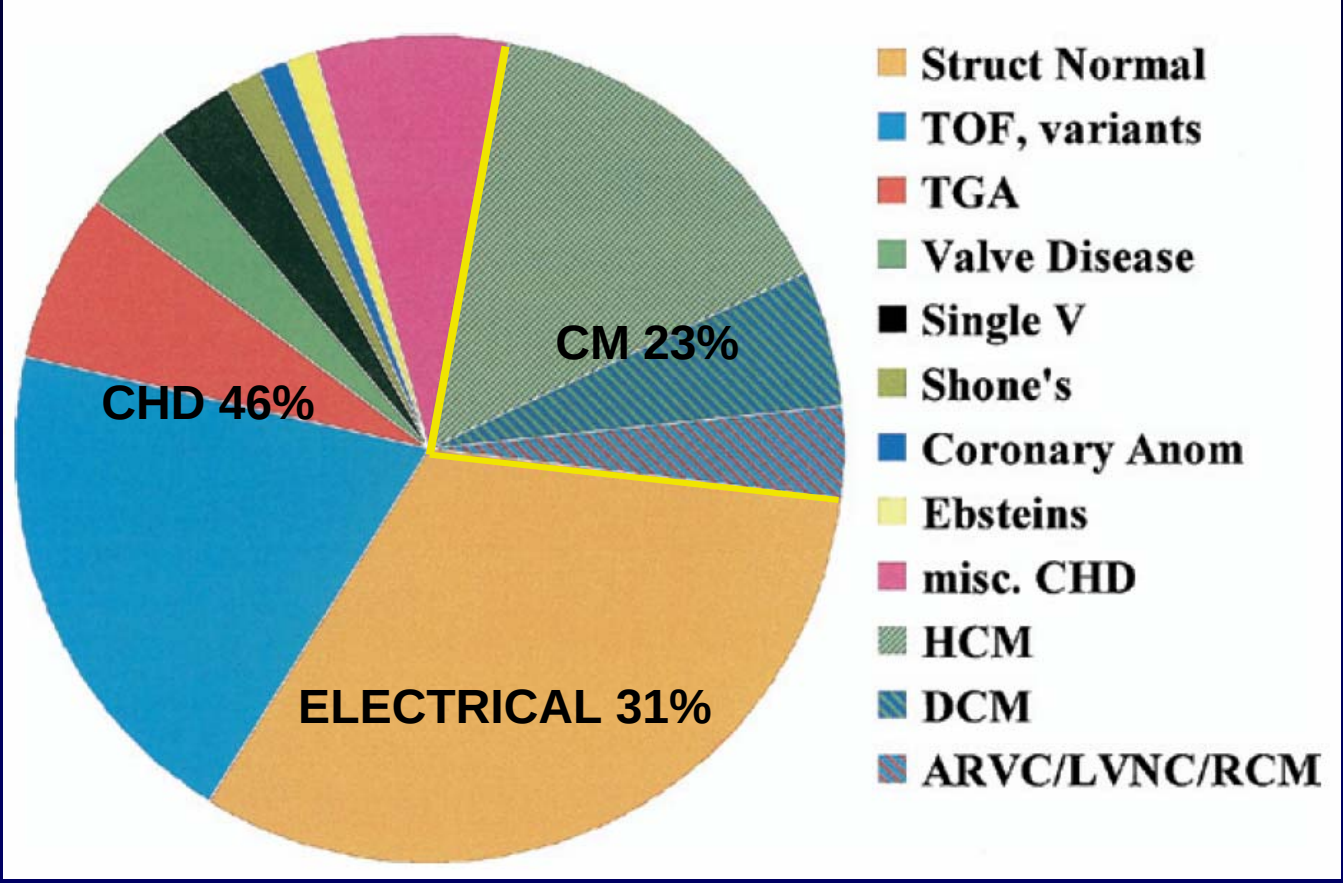
CI, confidence interval; HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; Cor, coronary.

In families with HCM children should be screened at an early age (and not =/>12years)

Ostman-Smith I et al. EHJ 2008

ICD IN PEDIATRIC PTS

ICD IN 443 PEDIATRIC AND CONGENITAL HEART DISEASE PTS



Berul CI, JACC 2008;51:1685-91

Table 2 Age at First ICD Implantation

Age (yrs)	CHD (45%)	EM (30%)	CM (25%)	Total
<1	2	2	3	7 (1.5%)
1–5	4	12	3	19 (4.2%)
6–10	9	30	14	53 (12%)
11–15	35	55	56	146 (33%)
16–21	48	35	24	107 (24%)
>21	96	4	11	111 (25%)

Totals are number of patients and percentages of total.

CHD = congenital heart disease; CM = cardiomyopathy; EM = electrical myopathy; ICD = implantable cardioverter-defibrillator.

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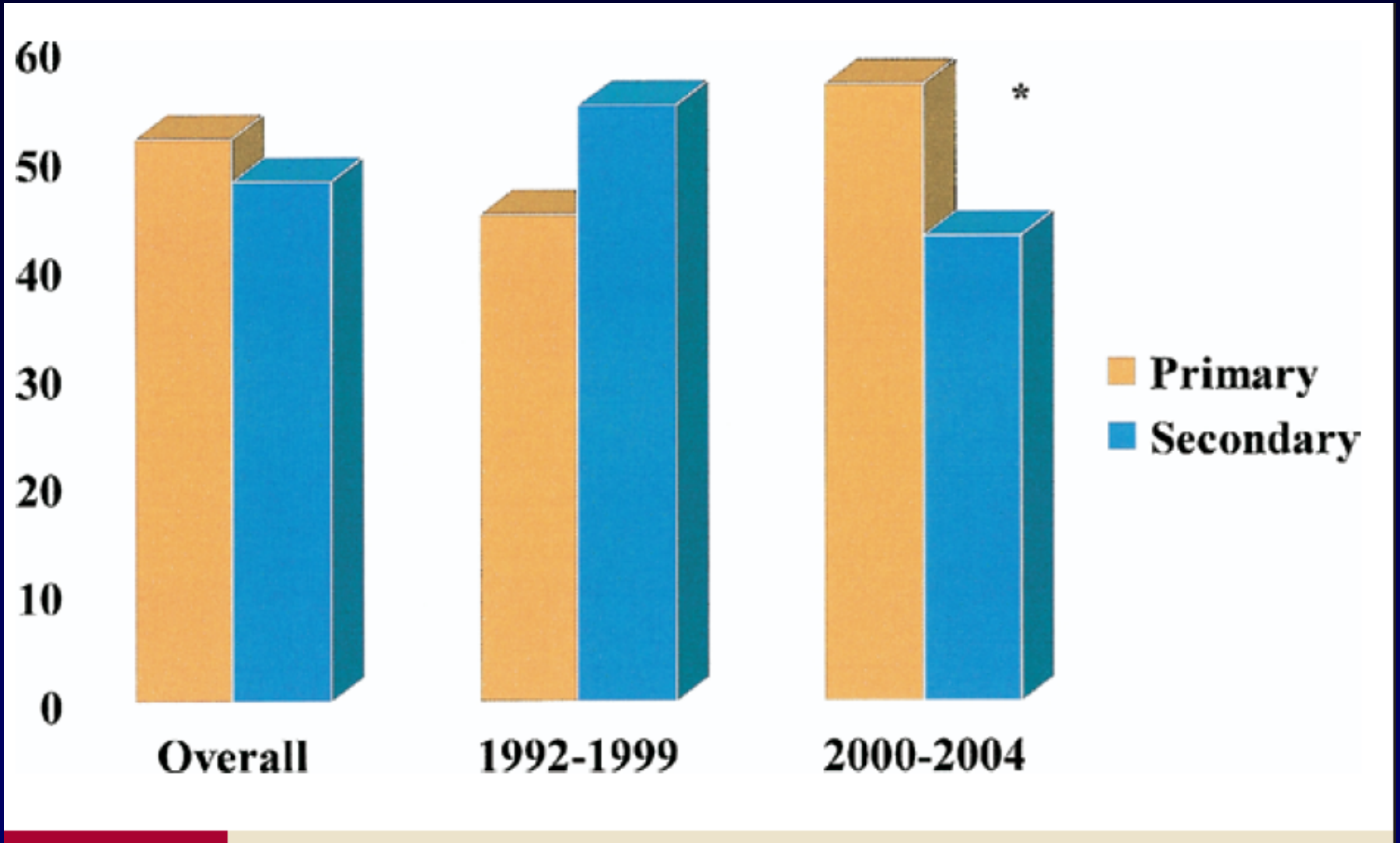

Figure 3 Indications for Implantable Cardioverter-Defibrillator Implantation, Overall and by Era

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Table 3 ICD-Related Complications

	No. of Complications
Acute Complications (Perioperative or Within 30 Days of Implant)	
Lead dislodgement	13
Inability to defibrillate or unacceptable DFT	9
Bleeding or pocket hematoma	8
Infection	7
Unsuccessful transvenous lead placement	6
Electrical storm	5
Hemothorax or pneumothorax	4
EMD/PEA	4
Skin erosion	3
SVC syndrome	2
Skin burns	2
Pneumonia and ileus	1
Total acute complications	64 (in 55 patients)
Chronic Complications (More Than 30 Days After Implant)	
Lead-related problems overall	68
Lead conductor fractures	20
Lead insulation breech	28
Lead late dislodgement	7
Lead-related change in capture, sensing, or DFT	13
Electrical storm	23
Inappropriate shocks (not related to lead failure)	22
Infection	13
Generator malfunction	2
Manufacturers' advisories/FDA recalls – device failure	1
Total chronic complications	130 (in 116 patients)
Mortality	
Periprocedural death	0
Death >30 days after implant	18 (4 known SCD)
Orthotopic heart transplantation after ICD	16
Death after orthotopic heart transplantation	3

DFT = defibrillation threshold; EMD/PEA = electromechanical dissociation/pulseless electrical activity; FDA = Food and Drug Administration; SCD = sudden cardiac death; SVC = superior vena cava; other abbreviations as in Table 2.

CONCLUSIONS

- Complications: acute in 13%; chronic in 26%
- Significant proportion of inappropriate shocks
- Lead failure was the major cause of inappropriate shocks
- Significance of psychological impact

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ICD in 22 CHILDREN with HCM

Follow up 1.7 years (1-2.3)

Table 1 Clinical characteristics at the time of implantable cardioverter-defibrillator implantation

	Whole group	PP	SP	p Value*
Demographics				
Male	13 (59.1)	8 (47.1)	5 (100)	0.05
Female	9 (40.9)	9 (52.9)	0	
Age at time of ICD implantation (years)	14 (7–16)	14 (12–16)	13 (7–16)	0.21
Age at diagnosis (years)	8 (0.3–16)	7 (0.3–15)	13 (2–16)	0.14
Symptoms and risk factors†				
Asymptomatic	4 (18.2)	2 (11.8)	2 (40)	0.21
Palpitation	9 (40.9)	9 (52.9)	0	0.05
NYHA dyspnoea class				
I	11 (50)	6 (35.3)	5 (100)	
II	8 (36.4)	8 (47.1)	0	0.04
III/IV	3 (13.6)	3 (17.6)	0	
Chest pain	12 (54.5)	11 (64.7)	1 (20)	0.14
→ Presyncope	10 (45.5)	8 (47.1)	2 (40)	1
Syncope	7 (31.8)	6 (35.3)	1 (20)	1
→ ABPR	15 (75)	13 (81.3)	2 (50)	0.25
→ FHxSCD	12 (54.5)	12 (70.6)	0	0.01
NSVT	1 (4.5)	1 (5.9)	0	1.0
→ Severe LVH	11 (50)	10 (58.8)	1 (20)	0.31
VF/polymorphic VT	5 (22.7)	0	5 (100)	NA

Kaski JP, Heart 2007;93:372-374

ICD in 22 CHILDREN with HCM

APPROPRIATE SHOCKS

- 4 pts (3SP, 1PP)
- No: 15 (11VF, 4VT)
- Median time: 3.3mo's
- Annual discharge:
  - √ 13%(70%SP, 4%PP)
  - √ 5 ys shock free survival SP 40%; PP 93%

INAPPROPRIATE SHOCKS

- 4pts (2SP, SPP)
- No: 7 (S.tach, SVT, lead frct)
- Median time: 1.2 years
- Other complications:
  - √ 1- Hematoma
  - √ 1- Anxiety/depression
  - √ 1- BE

ICDs prevent SCD in high-risk children with HCM. Complication rates are lower than previously reported, but psychological support and prevention of infection and inappropriate shocks remain important issues.

GENETICS

Shared Genetic Causes of Cardiac Hypertrophy in Children & Adults

- 84 children <15 (7+/- 6) years old, 63 boys(75%) with idiopathic HCM
- 8 sarcomeric genes (HCM), PRKAG2 and LAMP2 sequenced
- **MUTATIONS** in 25/51 (50%) without FCM
  in 21/33 (64%) with FCM
- Mutations in 75% in *MYH7 and MYBPC3*
- Sudden death, ICD implants and Tx > frequent among mutation positive and/or in those with positive family history

Morita H et al. NEJM 2008;358:1899-1908

Table 1. Clinical and Genetic Profiles of Patients with Childhood-Onset Left Ventricular Hypertrophy.*

Variable	Sporadic Disease			Familial Disease		
	Total	Mutation-Positive	Mutation-Negative	Total	Mutation-Positive	Mutation-Negative
Probands (no.)	51	25	26	33	21	12
Male sex (no.)	39	21	18	24	14	10
Age at onset (yr)	6.04±6.2	6.52±6.6	5.28±5.6	10.5±5.8	10.3±5.0	10.4±6.7
Maximum LVWT (cm)†	1.79±1.06	1.92±1.16	1.59±0.87	1.98±0.91	2.15±0.93	1.68±0.83
Fractional shortening (%)†	45±13	45±9.3	45±18	41±4	42±3	39±5
Sudden death from cardiac causes (no.)	3	3	0	0	0	0
ICD (no.)	2‡	2‡	0	8	5	3
Cardiac transplantation (no.)	4§	3§	1	1	1	0

CONCLUSION:

-Genetic causes account for about 50% of presumed sporadic and 2/3 of familial cases of childhood onset HCM

- Childhood onset LVH should prompt genetic analyses and family evaluations for sarcomeric protein mutations

Morita H et al. NEJM 2008;358:1899-1908

Major message

- The prognosis of HCM seems to be better than previously presumed
- Particularly in those diagnosed or surviving beyond the age of 1year
- Screening in FHCM should be performed in asymptomatic children at least at 12 years, perhaps earlier
- ICD implantation related complications decrease with improved technologies and experience
- A significant proportion of pts have sarcomere protein defects