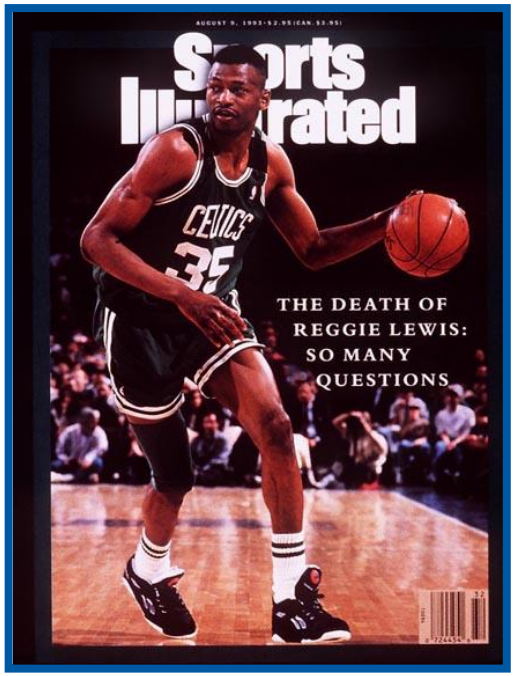
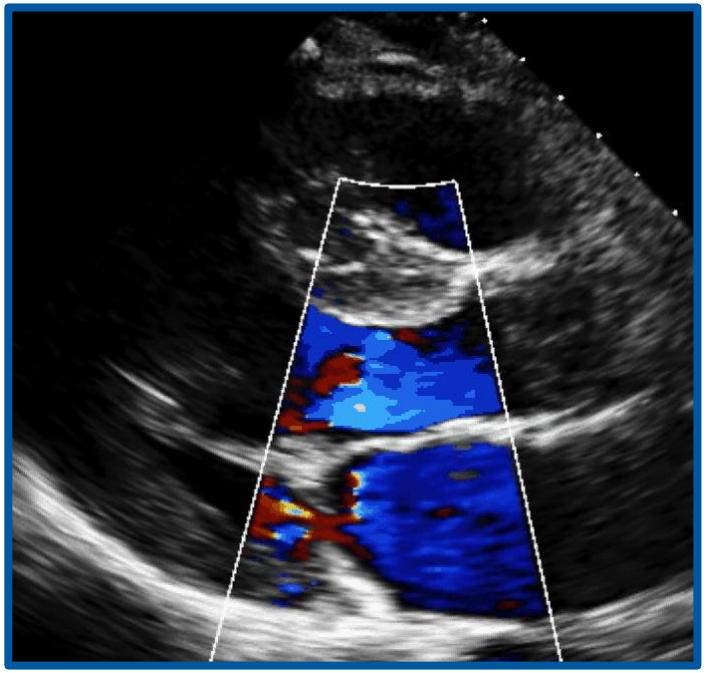
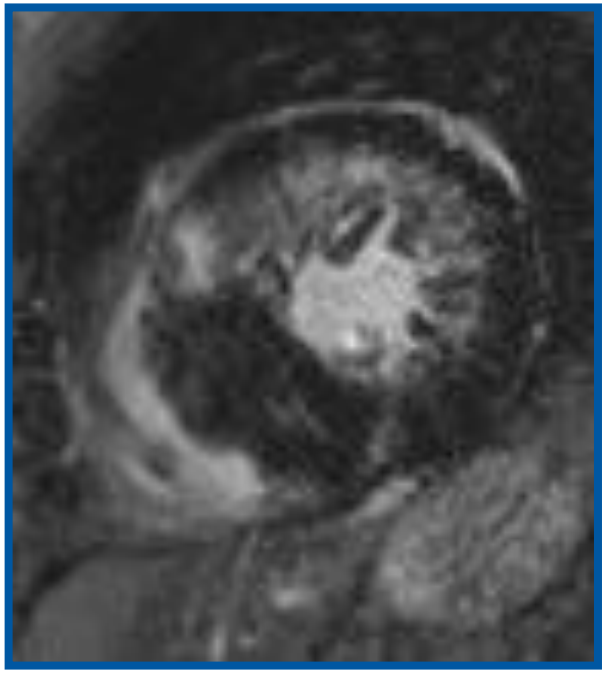
Sudden Cardiac Death in Hypertrophic Cardiomyopathy: Risk Stratification and the Role of Molecular Genetics







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Cardiology Update Davos, 2013

Christiane Gruner

OVERVIEW

Background information about HCM

Risk stratification for Sudden Cardiac Death in HCM

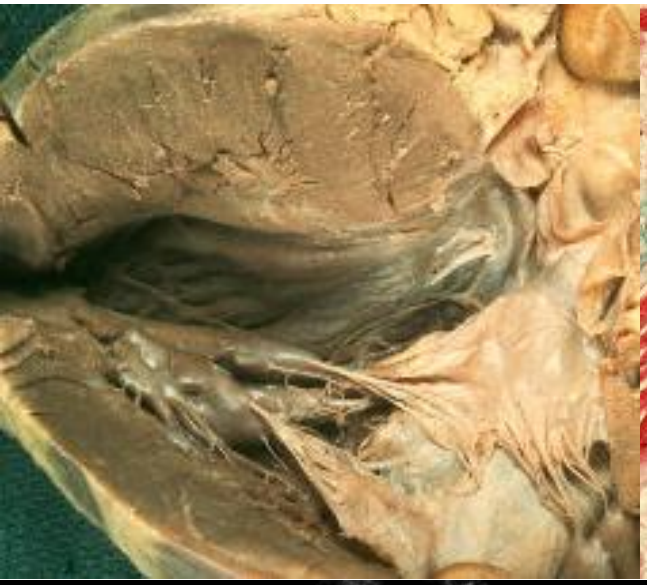
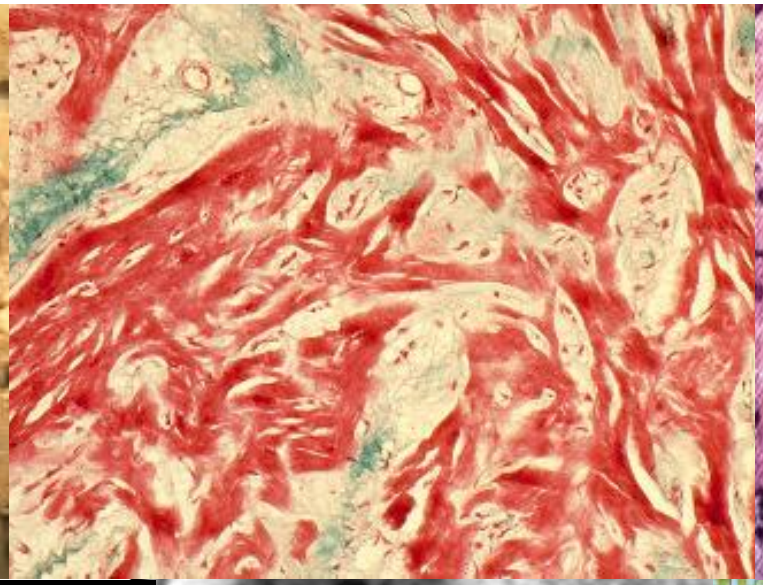
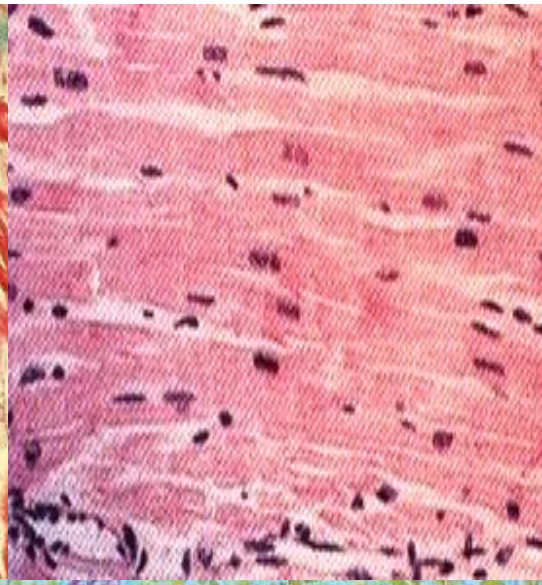
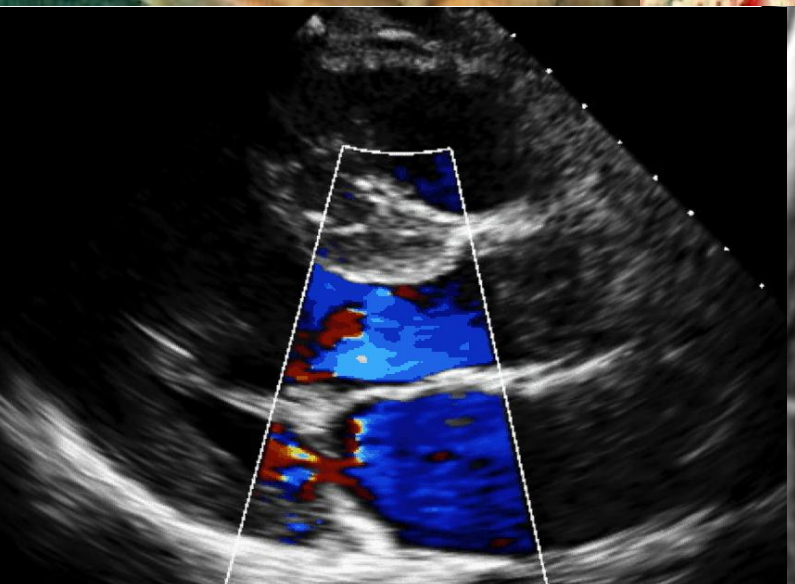
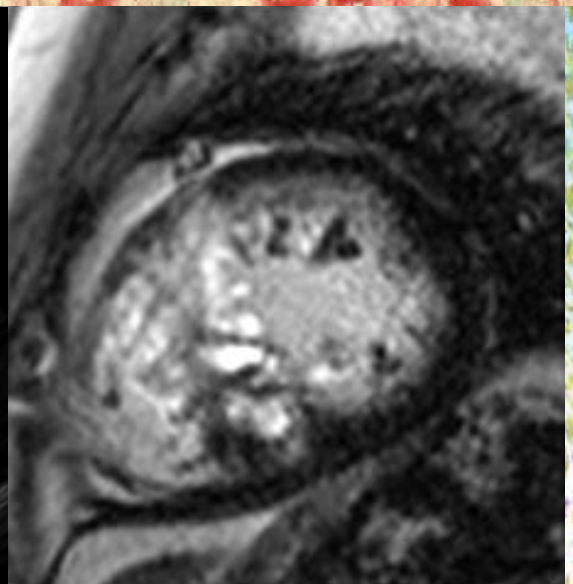
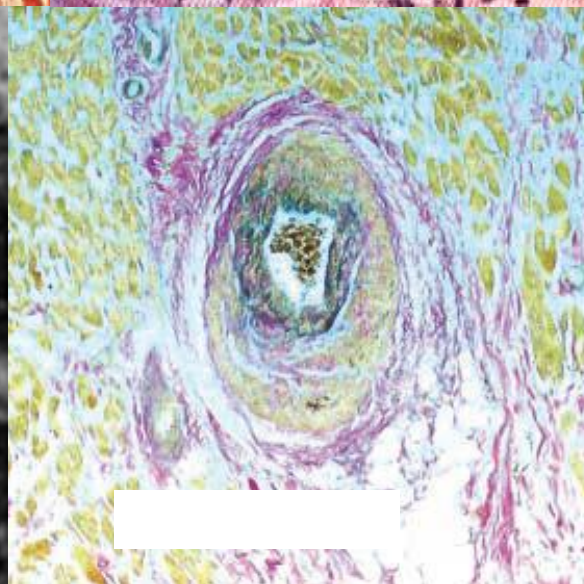
- Epidemiology
- Risk factors according to the guidelines
  - Extent of left ventricular hypertrophy
  - Fibrosis in Cardiac Magnetic Resonance Imaging

Molecular Genetics in HCM

- Genetics in HCM in general
- Influence on risk stratification for Sudden Cardiac Death

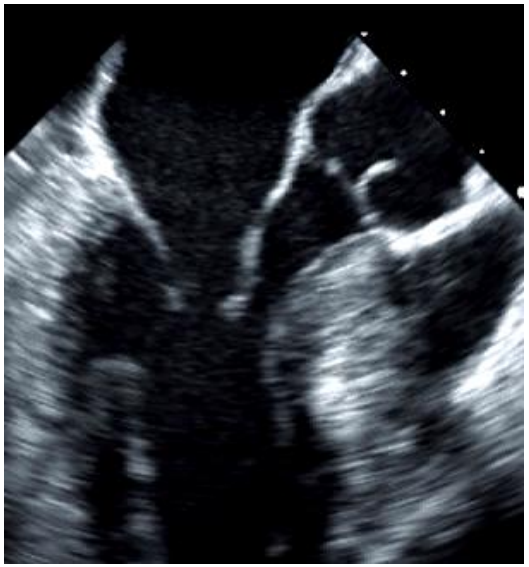
HYPERTROPHIC CARDIOMYOPATHY: HISTO-PATHOLOGY

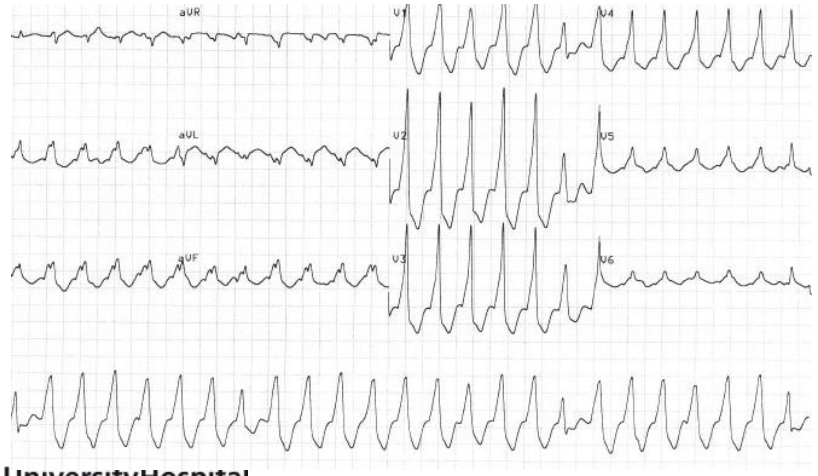
HYPERTROPHY, FIBRE DISARRAY, FIBROSIS, SMALL VESSEL DISEASE

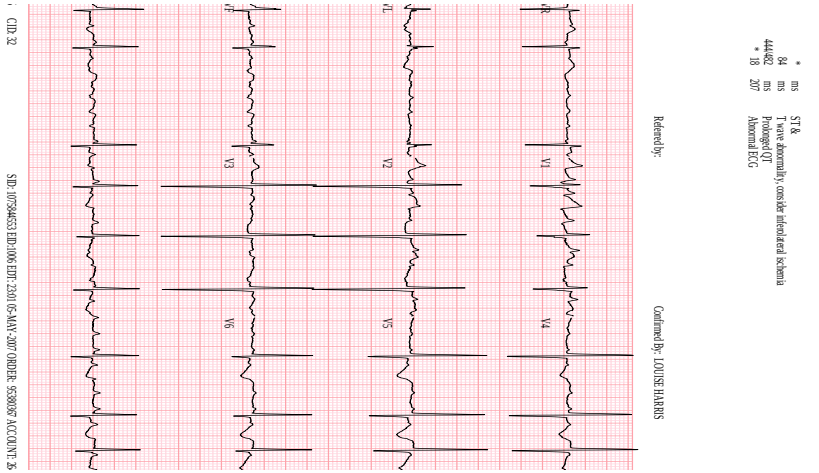







HYPERTROPHIC CARDIOMYOPATHY:
ASSOCIATED ISSUES

LVOT obstruction (25%)
Heart failure (25%)
Diastolic dysfunction (>50%) **Myocardial ischemia**
Atrial fibrillation (20%)
Sudden cardiac death (1%/year)







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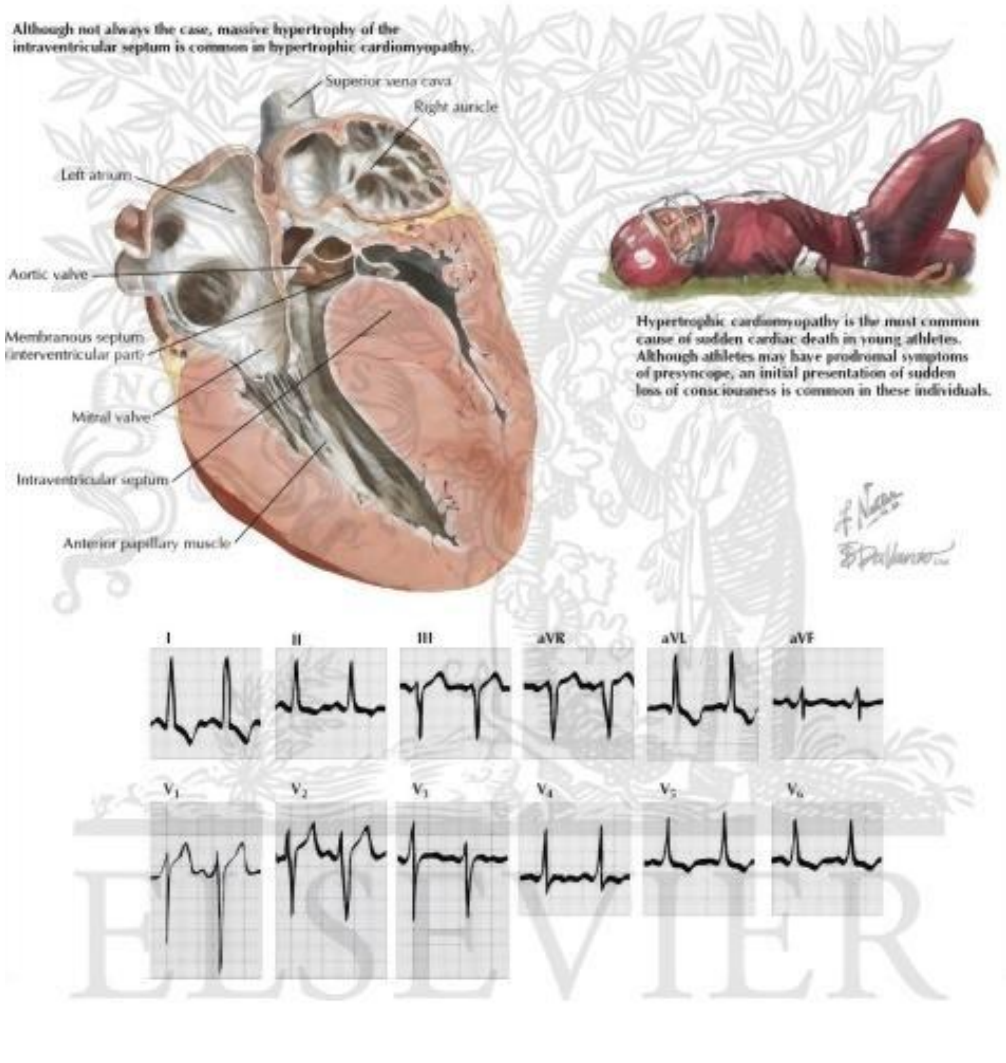
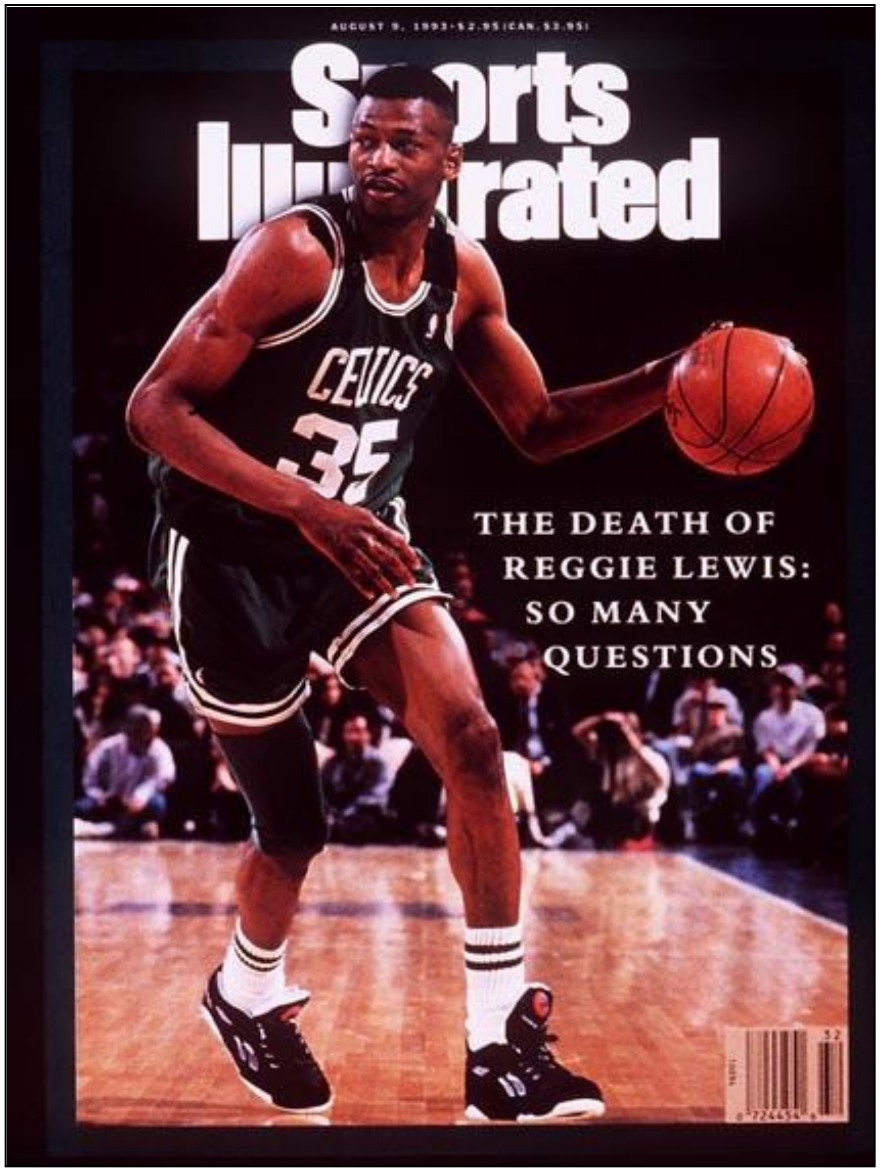
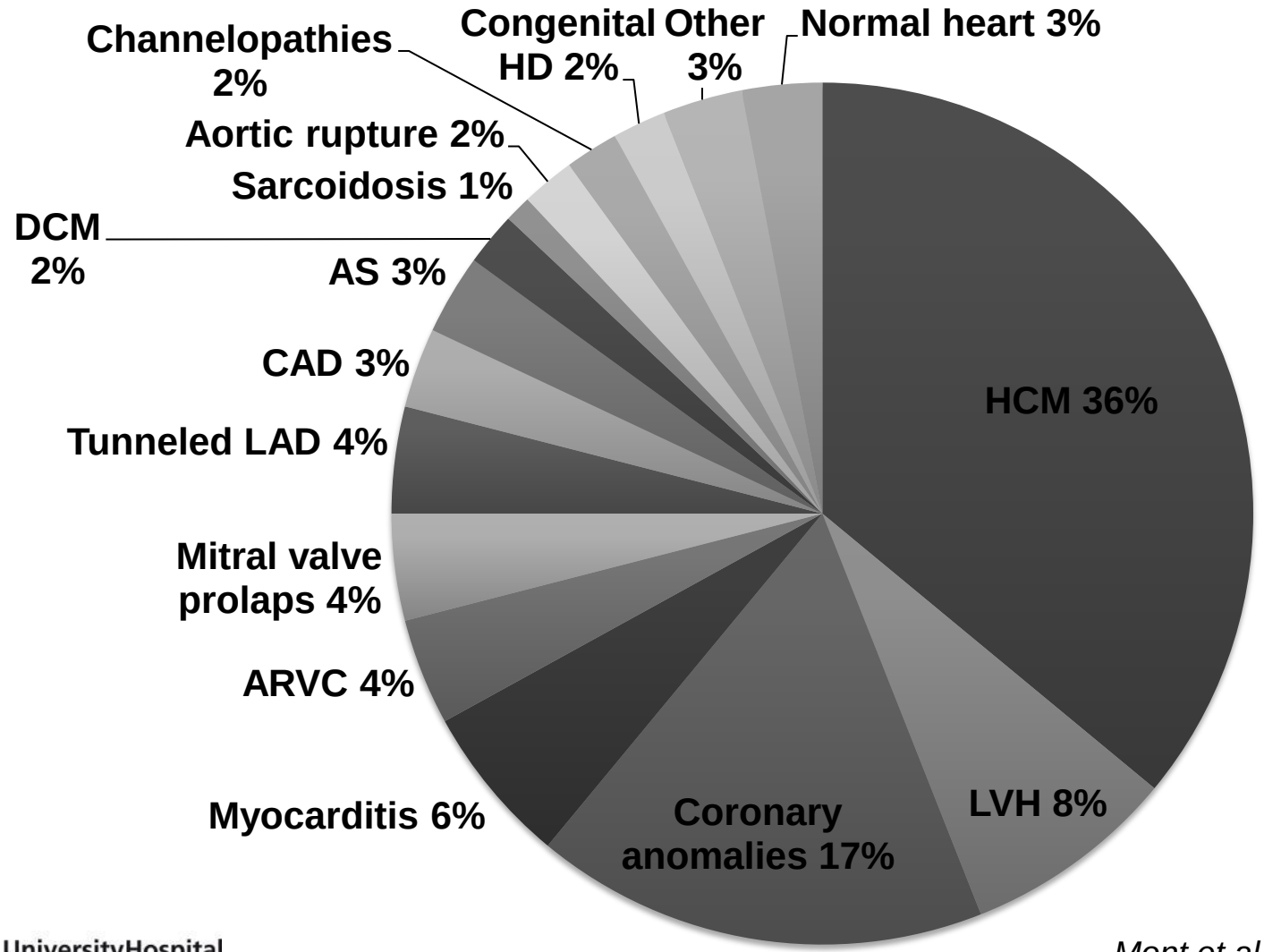
Maron et al., JAMA 1999;281(7):650-655

HYPERTROPHIC CARDIOMYOPATHY:
RISK OF SUDDEN CARDIAC DEATH





HYPERTROPHIC CARDIOMYOPATHY:
CARDIAC CAUSES OF DEATH IN ATHLETES



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Mont et al, Heart 2010, 398-405
Corrado et al, NEJM 1998: 364-369

HYPERTROPHIC CARDIOMYOPATHY:
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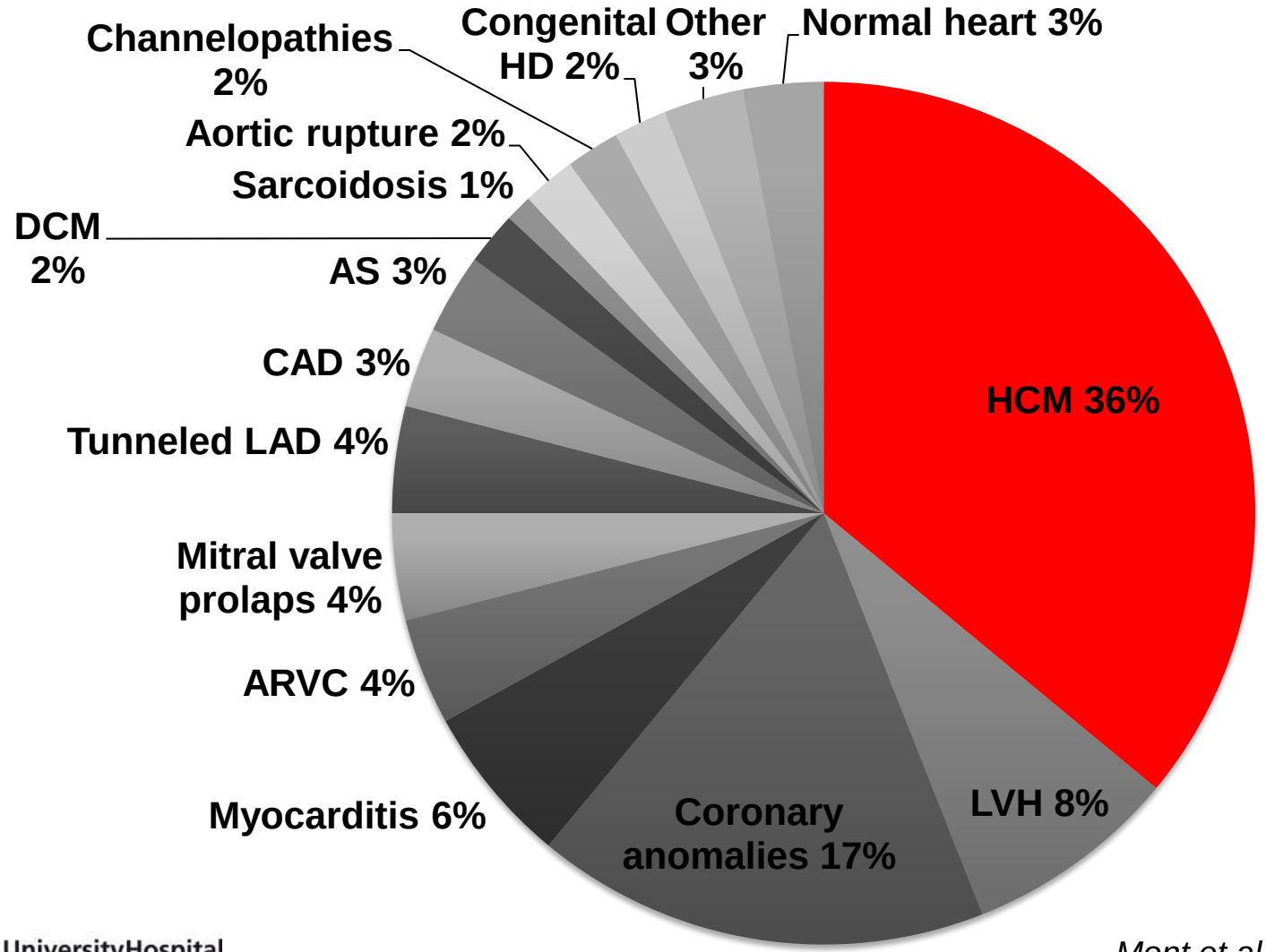

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Mont et al, Heart 2010, 398-405
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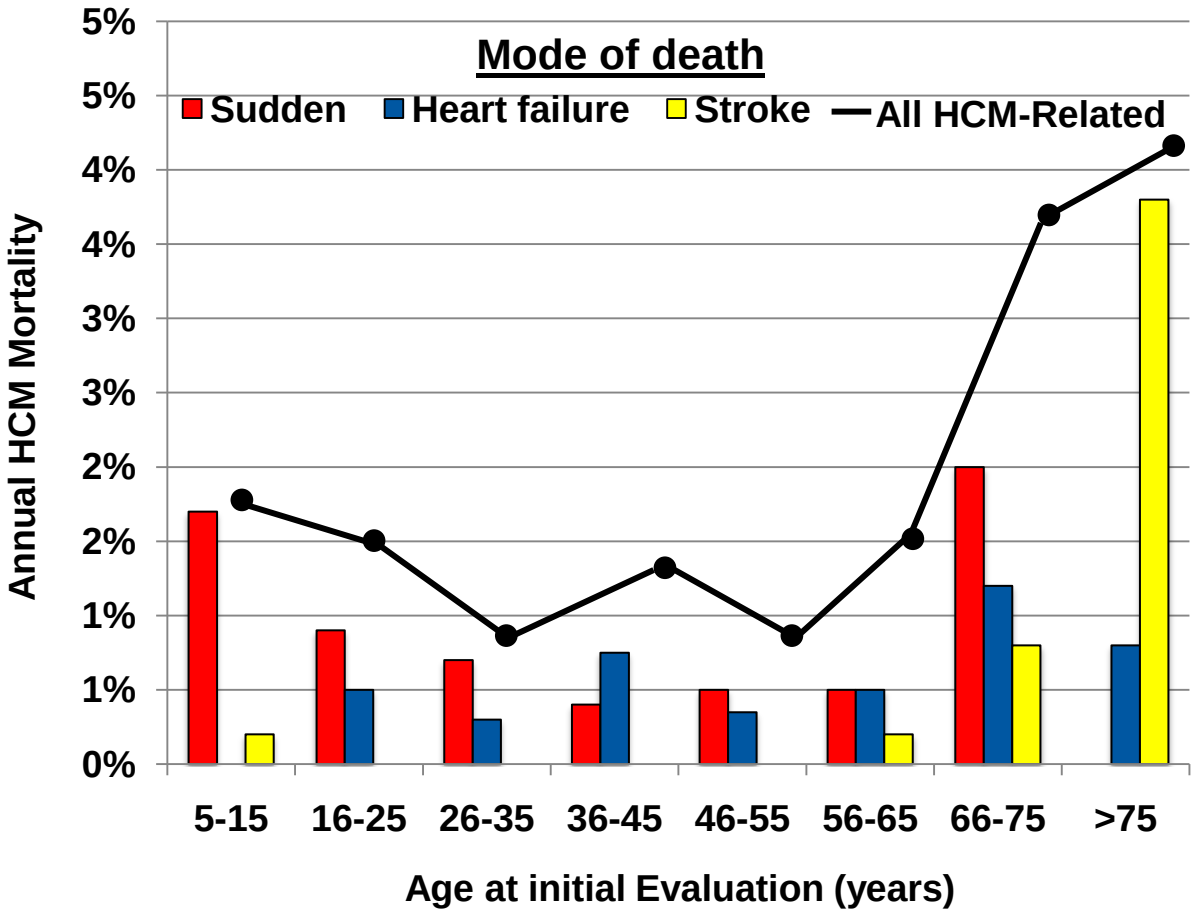
HYPERTROPHIC CARDIOMYOPATHY:
SUDDEN CARDIAC DEATH AND EPIDEMIOLOGY



n = 744; mean FU = 8 ± 7 years; annual SCD-rate = 0.7%

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Maron BJ et al, Circulation 2000;102:858-864

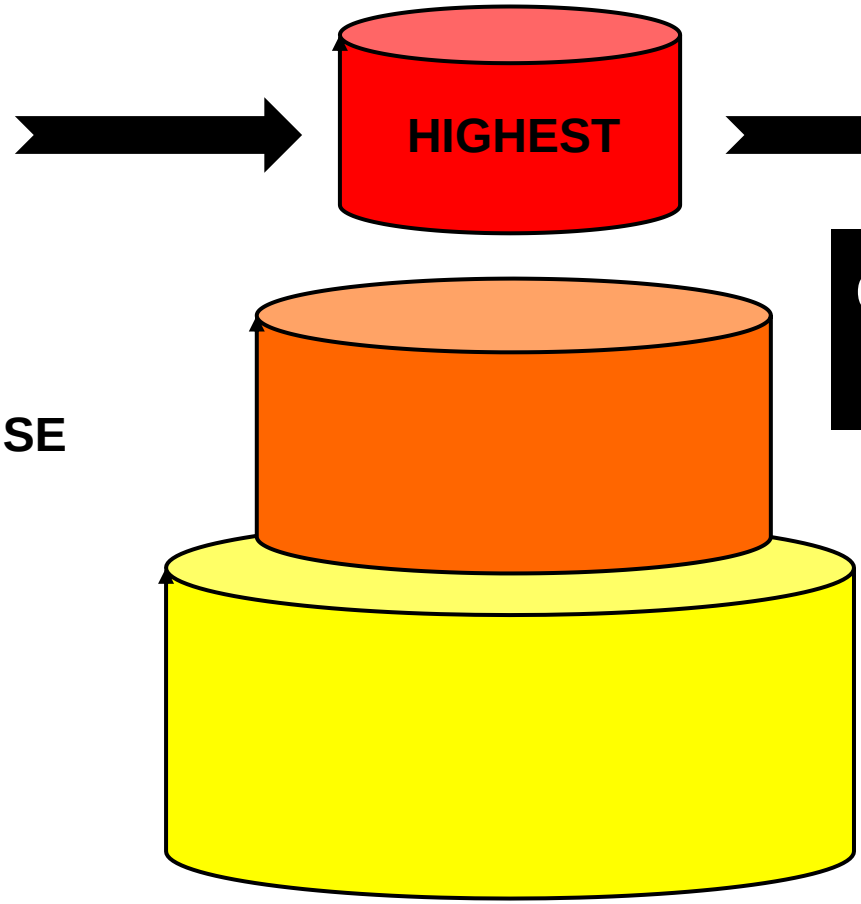
HYPERTROPHIC CARDIOMYOPATHY:
SUDDEN CARDIAC DEATH AND RISK STRATIFICATION

CARDIAC ARREST

FH FOR SCD
MASSIVE LVH
SYNCOPE

NSVT
ABNORMAL BP RESPONSE

LV APICAL ANEURYSMS
MYOCARDIAL FIBROSIS
MULTIPLE MUTATIONS
END-STAGE



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Maron BJ et al, J Cardiovasc Electrophsiol 2008;19:1118-1126

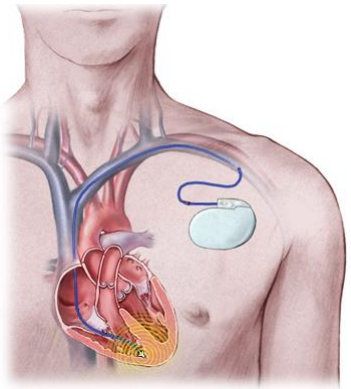
HYPERTROPHIC CARDIOMYOPATHY:
RISK STRATIFICATION FOR SUDDEN CARDIAC DEATH

Indications For ICD
- Aborted sudden death
- Sustained VT

Major Risk Factors
- LV wall thickness 30mm or greater
- First degree family member SCD
- Recent unexplained syncope

Minor Risk Factors
- Abnormal BP response to exercise
- Non sustained VT on Holter

Modifiers
- CMR: LGE
- LVOT obstruction
- Apical LV aneurysm
- Genetic mutations (double and compound)



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AHA/ACC Guidelines, Circulation 2011;124:2761-2791

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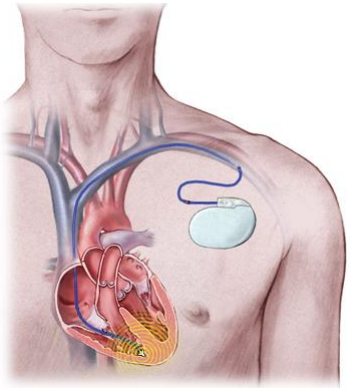

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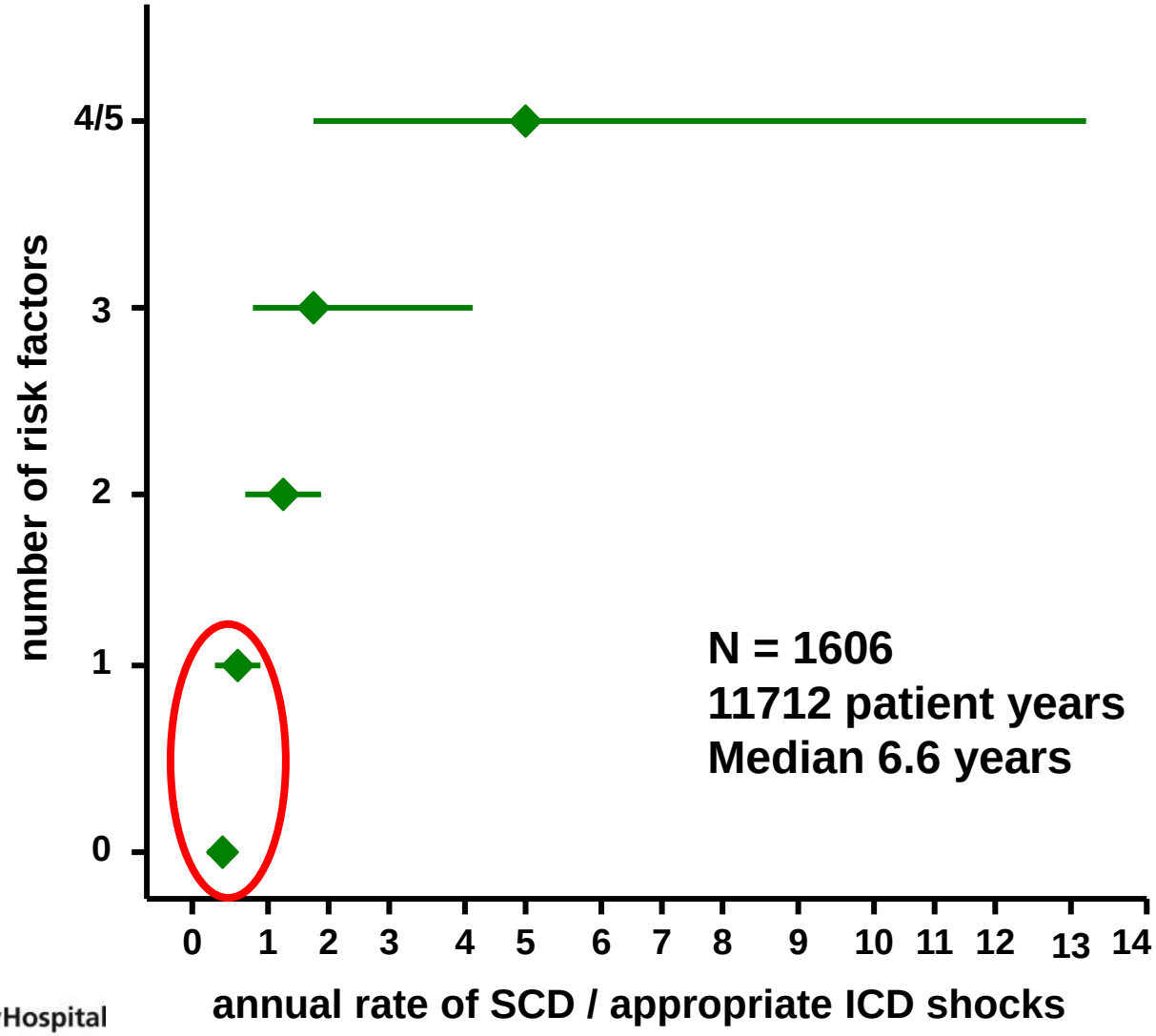
AHA/ACC Guidelines, Circulation 2011;124:2761-2791

HYPERTROPHIC CARDIOMYOPATHY:
No RISK FACTORS AND SCD EVENT RATE



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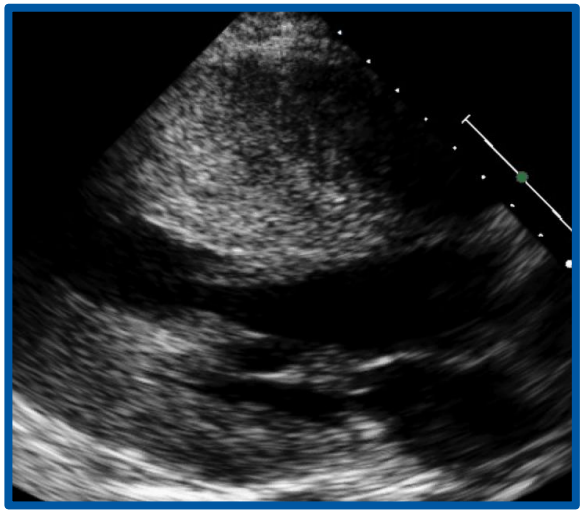
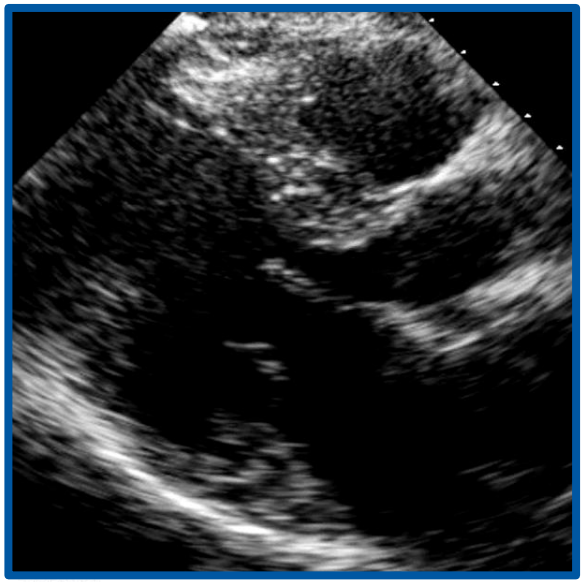
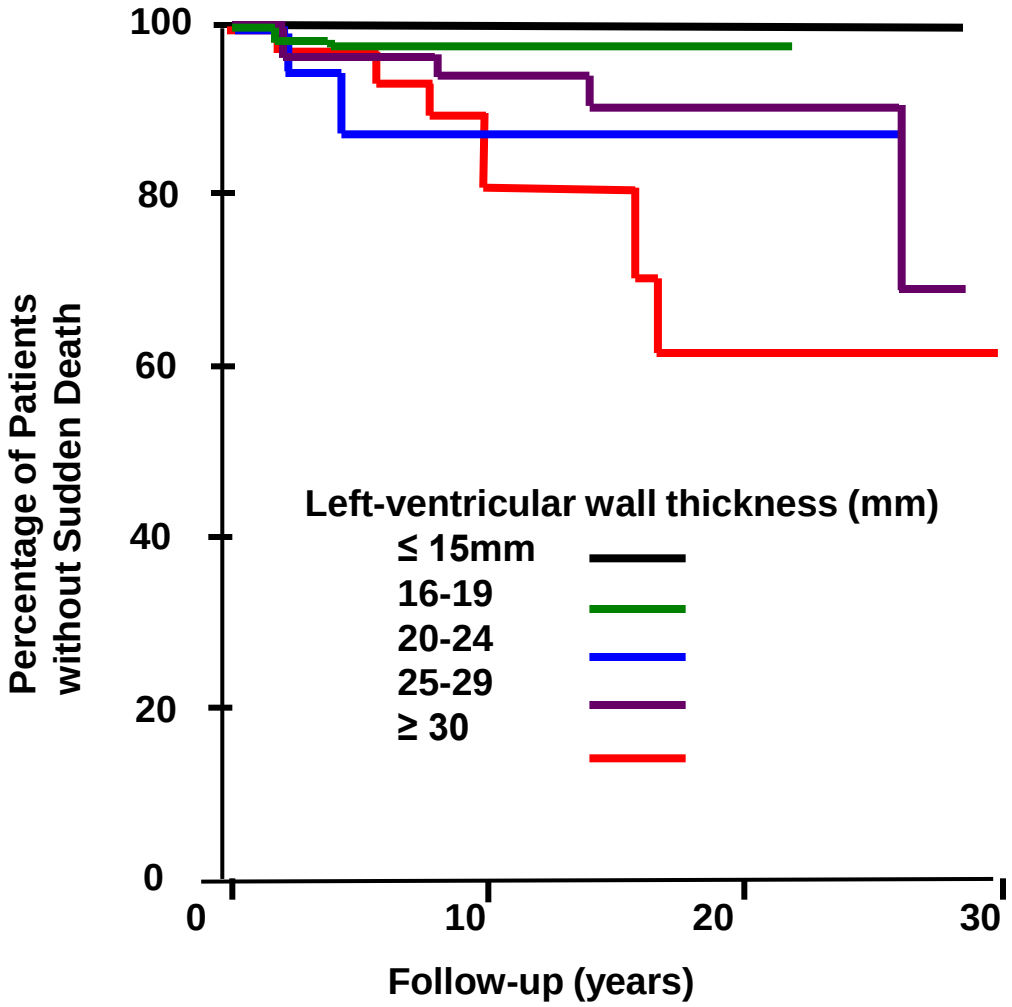
O'Mahony, Heart 2013-303271

HYPERTROPHIC CARDIOMYOPATHY:
SCD: LEFT-VENTRICULAR HYPERTROPHY

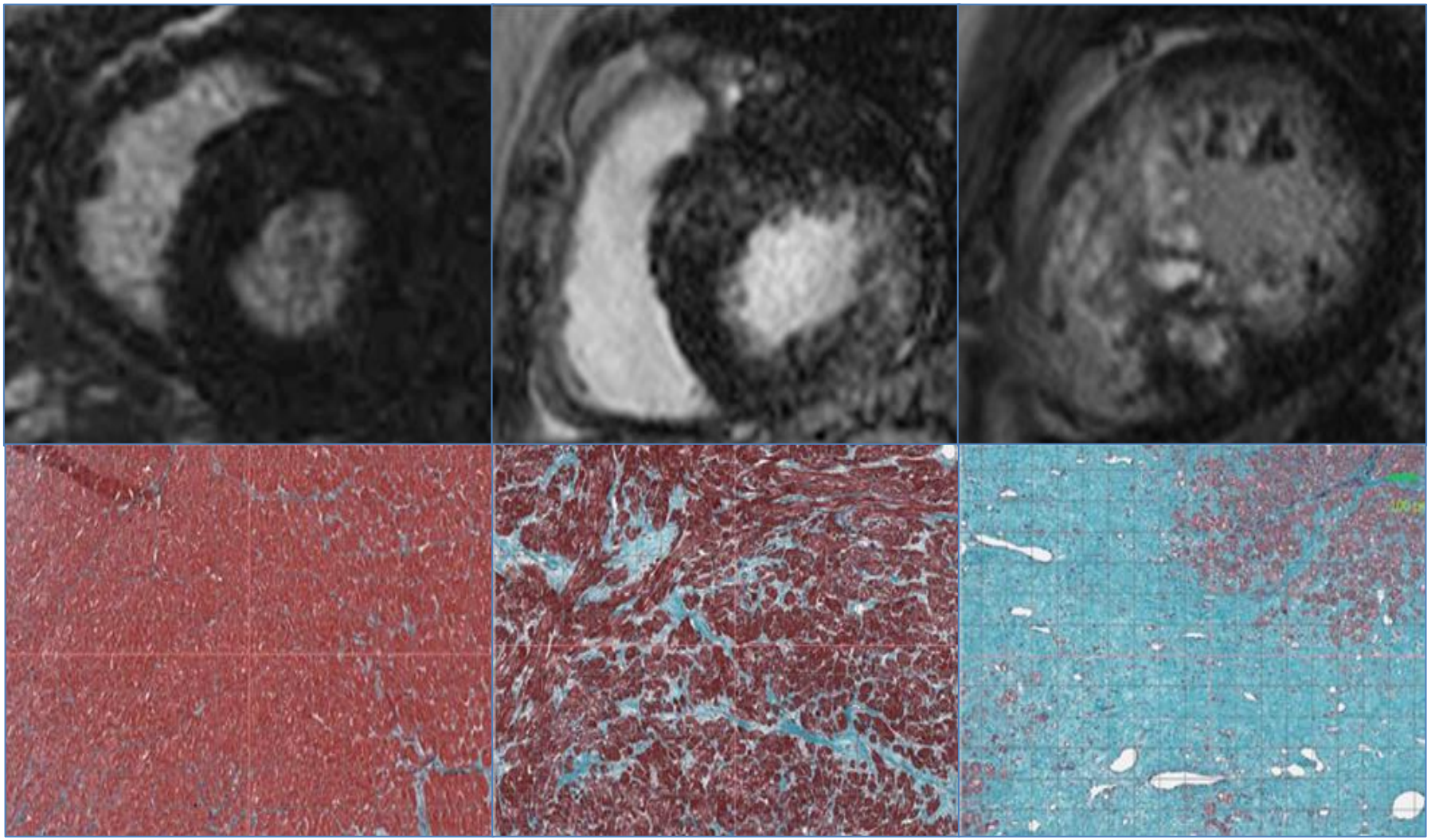






Spirito et al., NEJM 2000;342:1778-85

HYPERTROPHIC CARDIOMYOPATHY:
SUDDEN CARDIAC DEATH AND FIBROSIS



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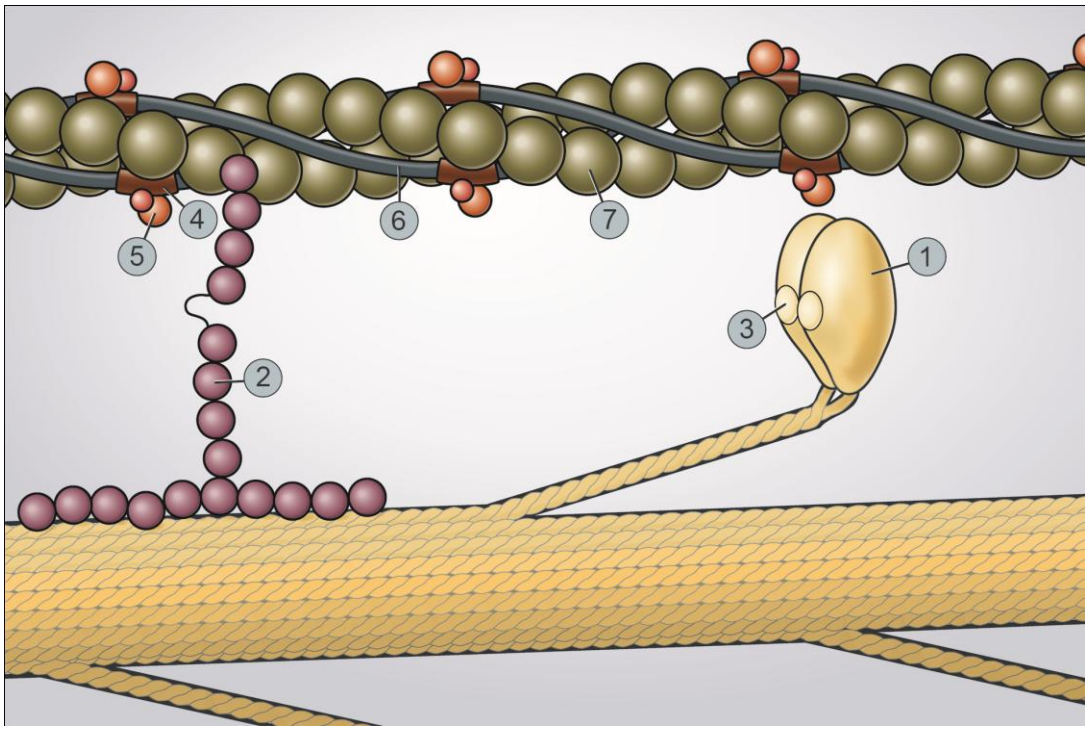
Moravsky et al, AHA 2011

HYPERTROPHIC CARDIOMYOPATHY
GENETICS BASICS

- autosomal dominant
- 1:500 with HCM in general population



1 β-Myosin heavy chain
2 Myosin-binding protein-C
3 Myosin light chain 2 and 3
4 Troponin T
5 Troponin I
6 Tropomyosin
7 Actin

Phenocopies
- Fabry's disease
- PRKAG2 cardiomyopathy
- Danon's disease

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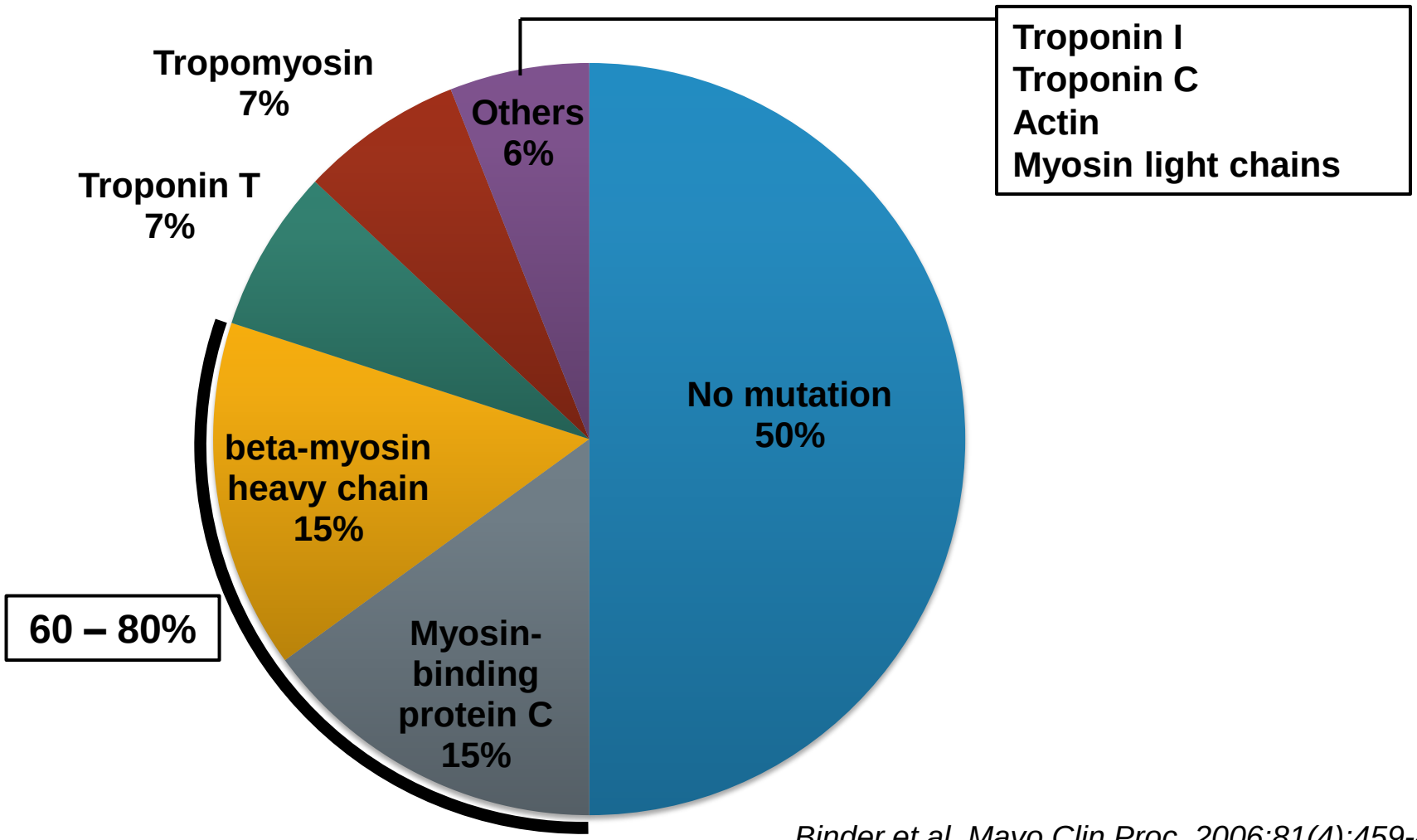
Binder et al., Mayo Clin Proc. 2006;81(4):459-467

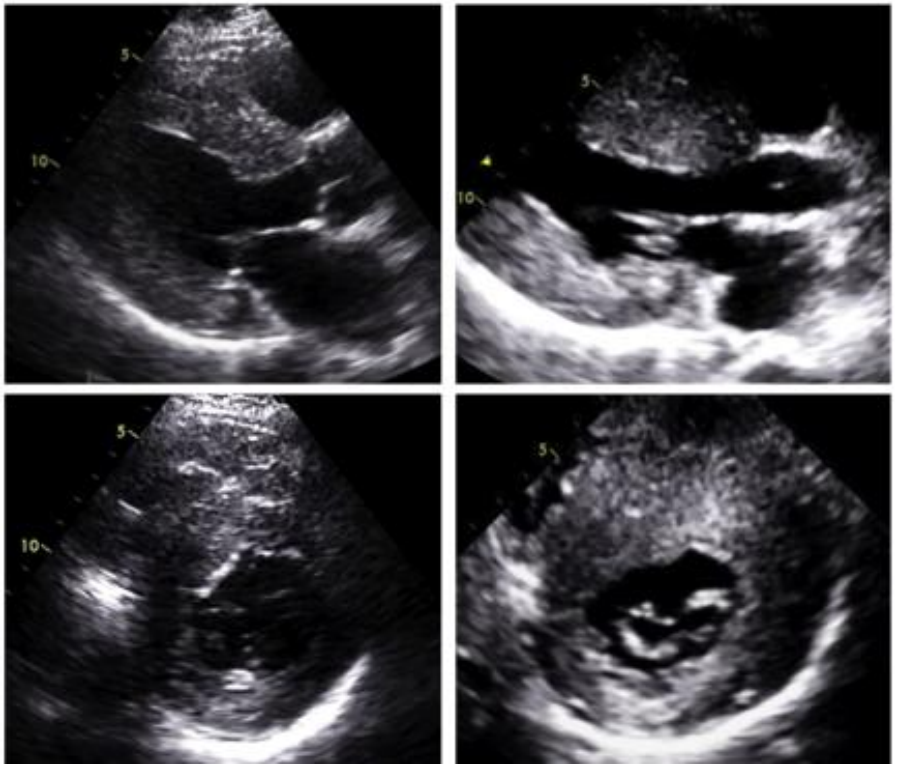
HYPERTROPHIC CARDIOMYOPATHY
GENETICS BASICS



Binder et al, Mayo Clin Proc. 2006;81(4):459-467
Maron BJ et al, JACC 2012;60:705-15
Gruner C et al, Circ CV Genetics 2012: epub

HYPERTROPHIC CARDIOMYOPATHY
CURRENT ROLES OF GENETIC TESTING

FAMILY SCREENING
Identification of family members at risk for HCM



Fabry disease

PRKAG2 cardiomyopathy

EXCLUSION OF PHENOCOPIES

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AHA/ACC Guidelines, Circulation 2011;124:2761-2791

HYPERTROPHIC CARDIOMYOPATHY
GENETICS AND RISK STRATIFICATION FOR SCD

1108 THE NEW ENGLAND JOURNAL OF MEDICINE April 23, 1992

CHARACTERISTICS AND PROGNOSTIC IMPLICATIONS OF MYOSIN MISSENSE MUTATIONS IN FAMILIAL HYPERTROPHIC CARDIOMYOPATHY

JACC Vol. 29, No. 3
March 1, 1997:549–55

Sudden Death due to Troponin T Mutations

Heart 1999;82:621–624

A new mutation of the cardiac troponin T gene causing familial hypertrophic cardiomyopathy without left ventricular hypertrophy

A Varnava, C Baboonian, F Davison, L de Cruz , P M Elliott, M J Davies, W J McKenna

HYPERTROPHIC CARDIOMYOPATHY
GENETICS AND RISK STRATIFICATION FOR SCD

Long-Term Outcomes in Hypertrophic Cardiomyopathy Caused by Mutations in the Cardiac Troponin T Gene

n Pablo Kaski, BSc, MBBS, MD;
c, FRCP, FESC; Perry Elliott, MD

	Adults (n=71)
Male	36 (51%)
Age, years	37 ± 14
NYHA I-II	59 (95%)
Obstruction	6 (9%)
Maximal wall thickness (mm)	19 ± 5
SCD in first degree relative	27 (50%)
Non sustained VTs	13 (24%)
Maximal wall thickness ≥30mm	3 (5%)
Syncope	17 (31%)
Abnormal BP response	26 (48%)

- 552 probands underwent genetic testing
- 20 probands with TNNT2 mutations
- 72 relatives with TNNT2 mutations

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Pasquale et al, Circulation CV Gen 2012;5:10-17

HYPERTROPHIC CARDIOMYOPATHY
GENETICS AND RISK STRATIFICATION FOR SCD

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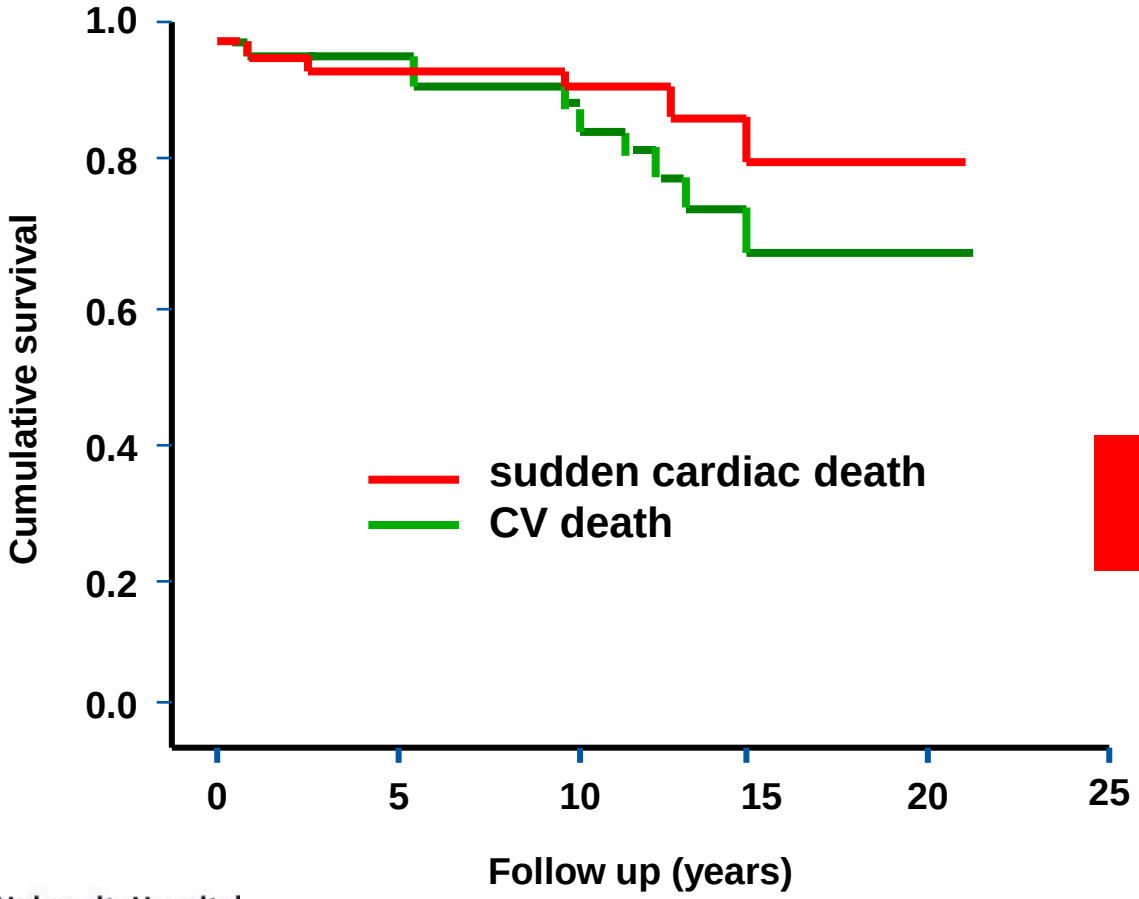

mean FU = 9.9 ± 5.2 years
annual SCD rate = 0.93%

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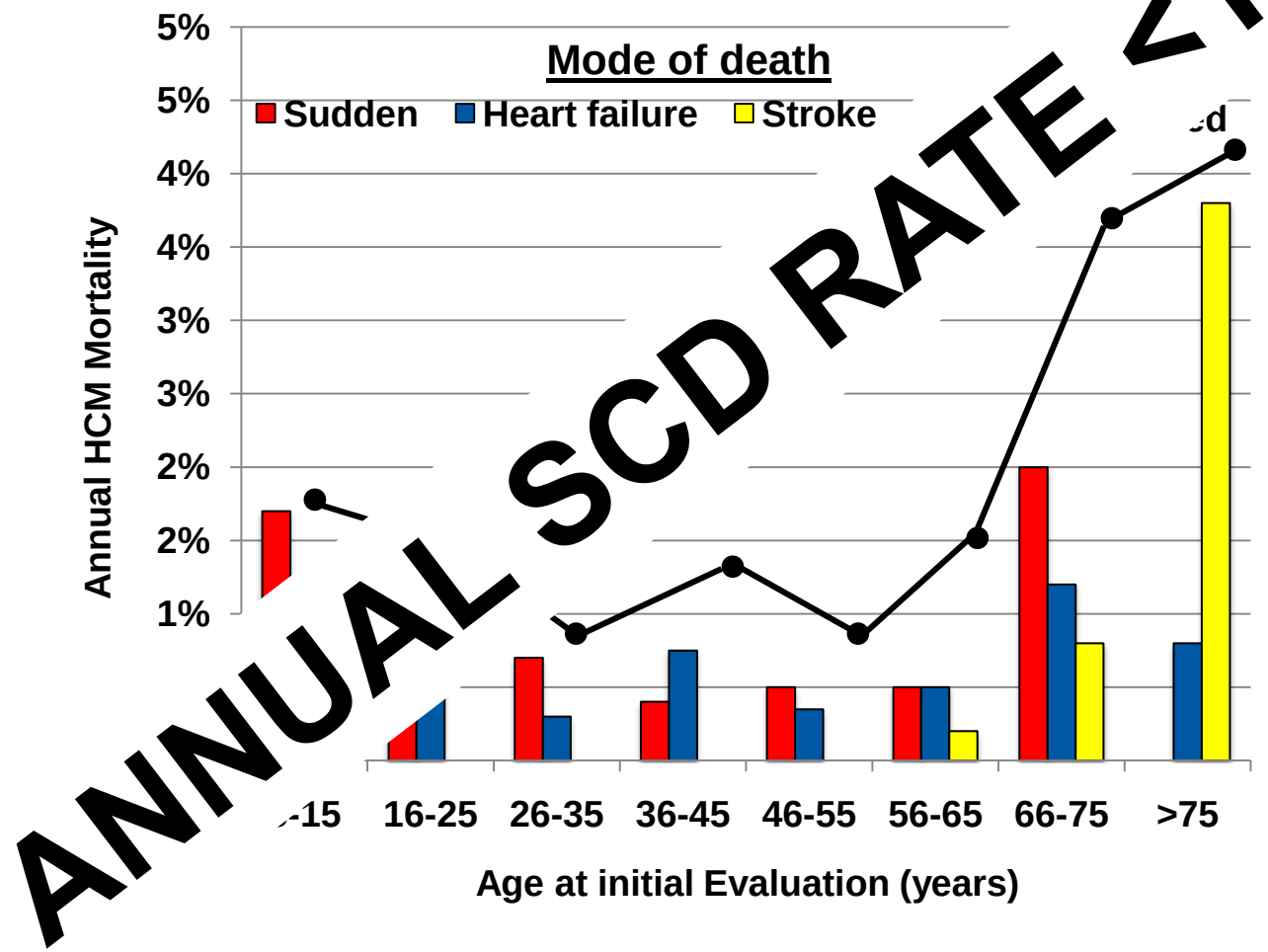
Pasquale et al, Circulation CV Gen 2012;5:10-17

HYPERTROPHIC CARDIOMYOPATHY:
SUDDEN CARDIAC DEATH AND EPIDEMIOL



n = 744; mean FU = 8 ± 7 years; annual SCD-rate = 0.7%

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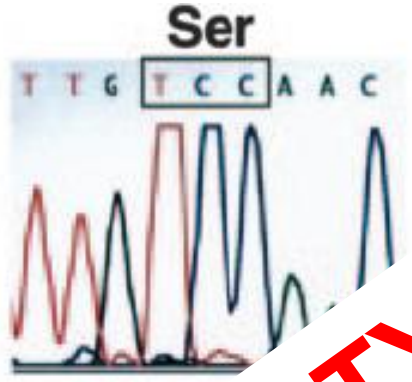
Maron BJ et al, Circulation 2000;102:858-864

HYPERTROPHIC CARDIO
GENOTYPE - PHE



NO GENOTYPE – PHENOTYPE CORRELATION

NO HIGH – RISK MUTATIONS

HYPERTROPHIC CARDIOMYOPATHY

GENETICS AND RISK STRATIFICATION FOR SCD: MULTIPLE MUTATIONS

≥ 2 disease causing sarcomere protein gene mutations (double or compound), 5% in genetically tested HCM populations

- **Early disease onset**
- **Marked left ventricular hypertrophy**
- **Advanced heart failure due to systolic dysfunction**
- **More frequent SCD events**

MULTIPLE MUTATIONS SHOULD BE CONSIDERED AS MODIFYING RISK FACTOR FOR SCD

Maron BJ et al, Heart Rhythm 2012;9:57-63
Girolami et al, JACC 2010;55:1444-53
AHA/ACC Guidelines, Circulation 2011;124:2761-2791

CONCLUSIONS

- Key role of genetics in HCM today: family screening, exclusion of phenocopies
- No genotype-phenotype correlation, essentially, genetics are not part of risk stratification for SCD in HCM, no high-risk mutations
- Multiple mutations should be considered as modifying risk factor, especially in the absence of conventional risk factors
- Classic risk factors: MWTH, unexplained syncope, positive family history for SCD, NSVTs, abnormal BP response
- Myocardial fibrosis: modifying risk factor

Thank You

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