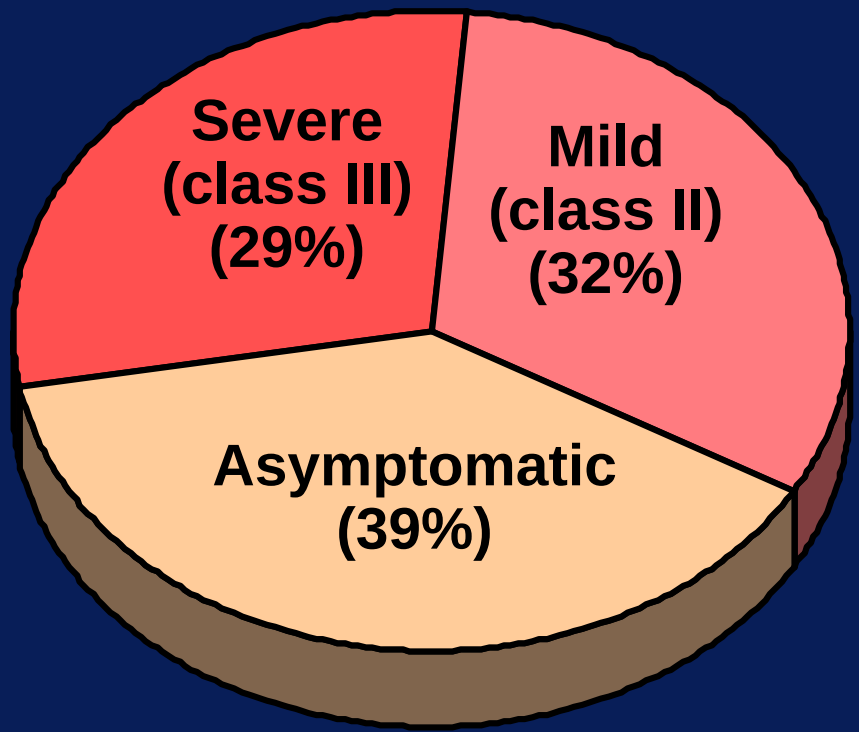
Risk Stratification for SCD in pts. with HCM

Clinical Implications of Molecular Genetics

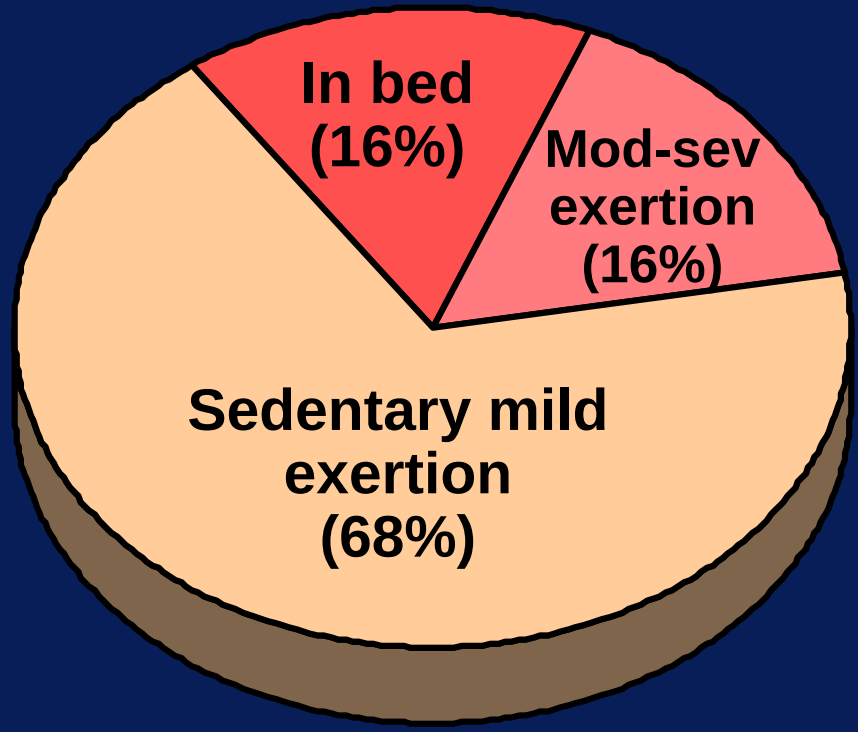
Seoul, 2005

Clinical Profile of Sudden Death
744 Patients
SCD 86 Pt (12%)

Symptom Status

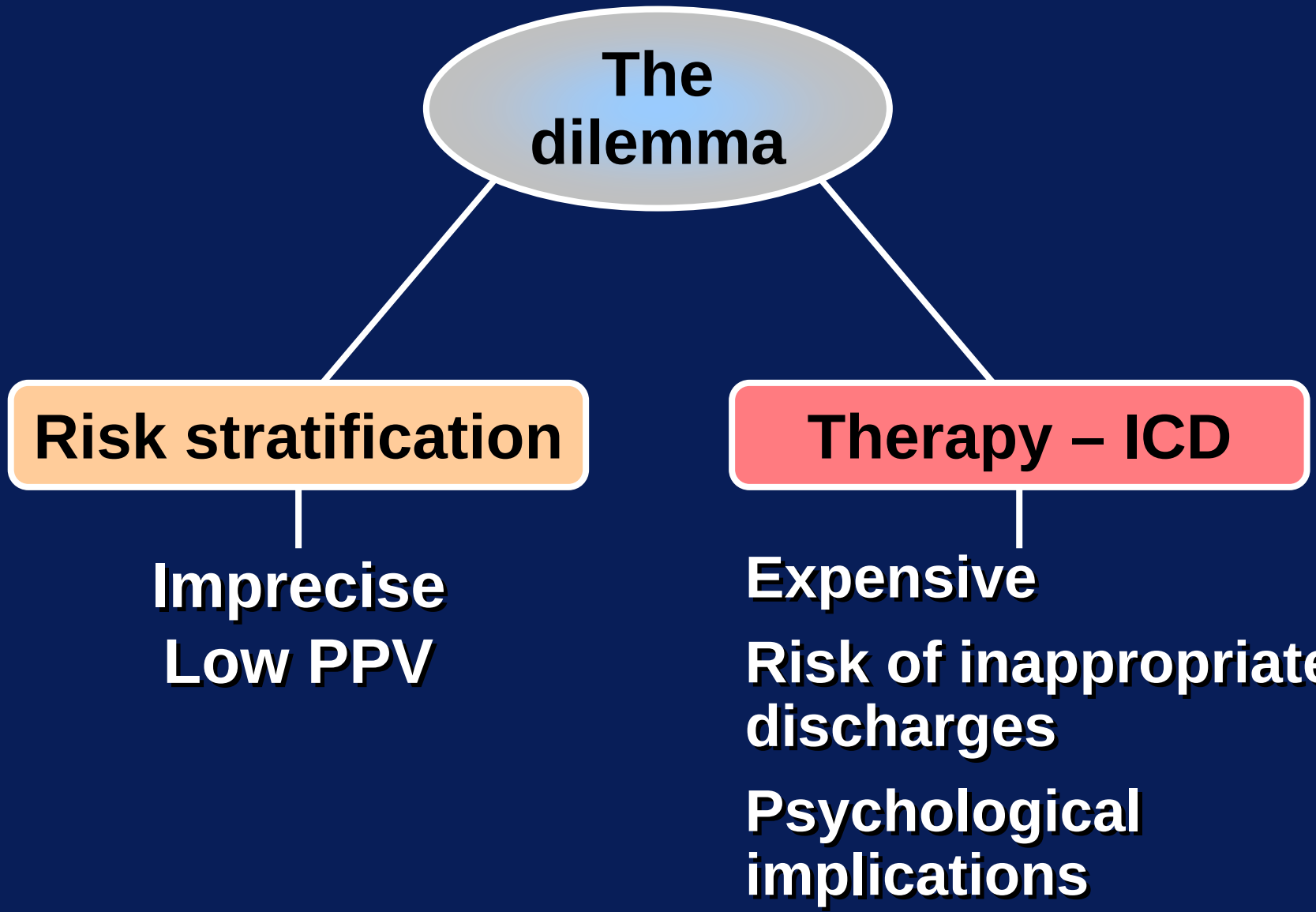


Activity Level

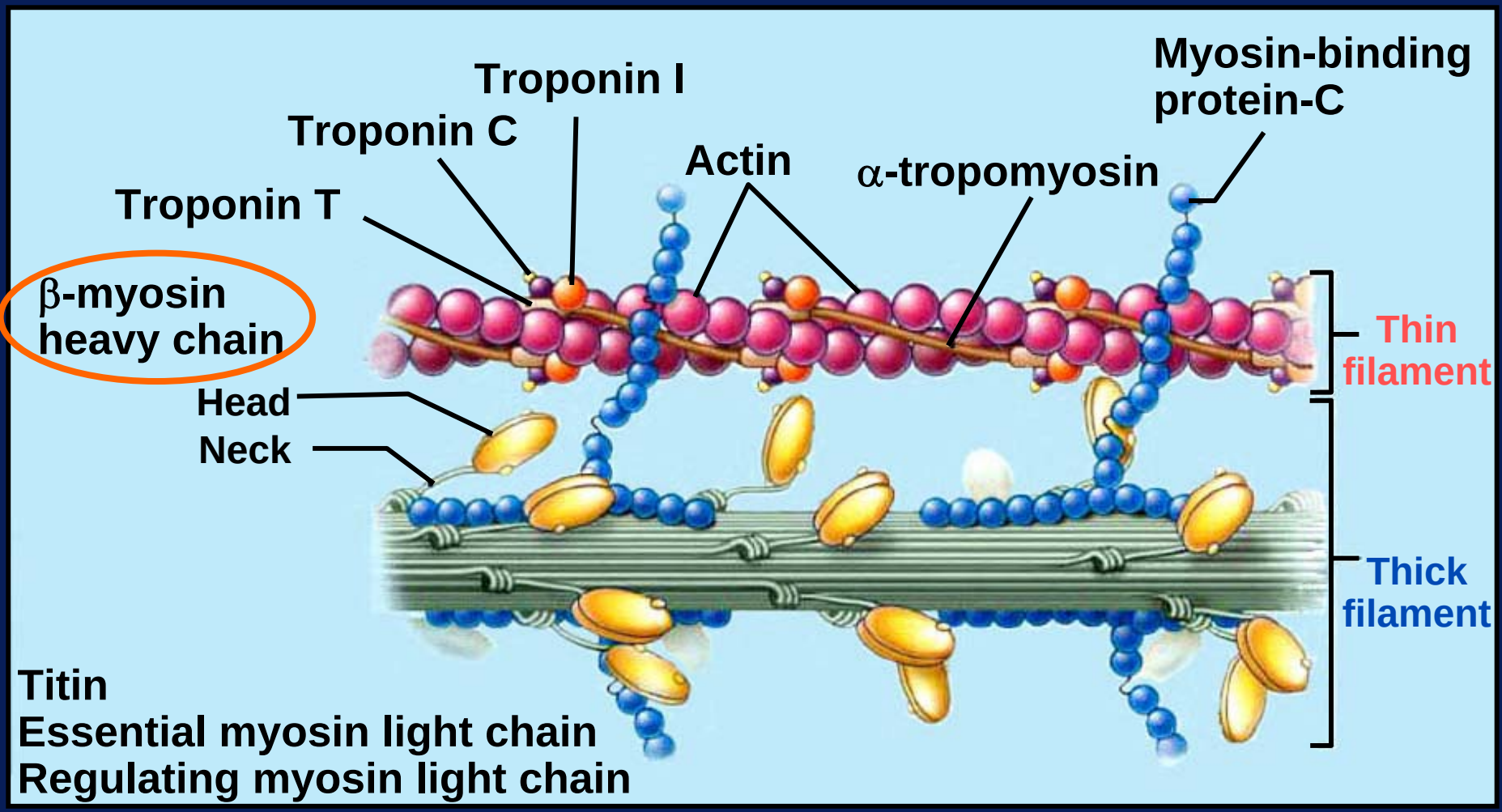


Maron et al: Circ 102:858, 2000

SCD in Hypertrophic Cardiomyopathy



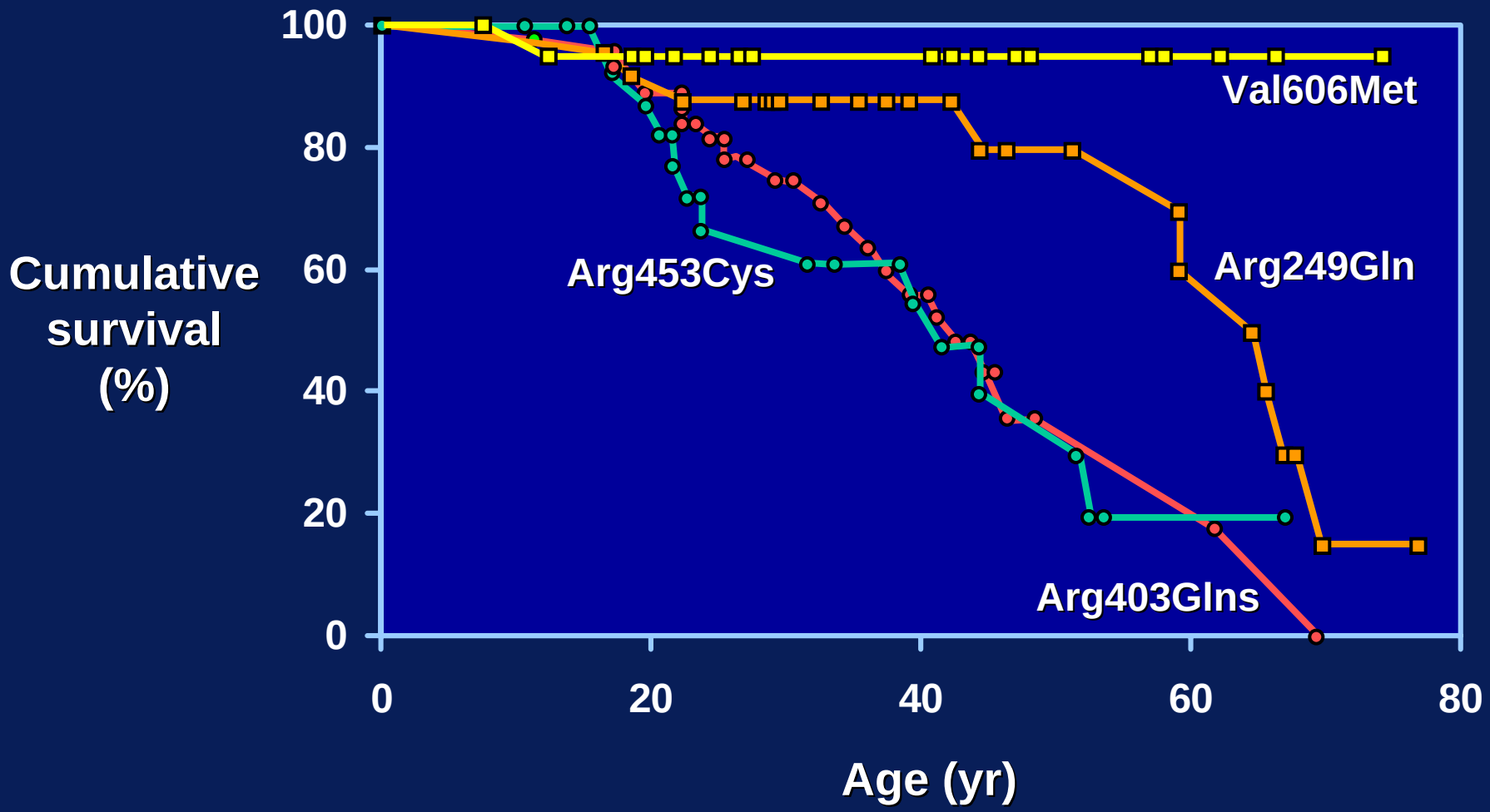
Mutations in Sarcomeric Proteins



Profound genetic heterogeneity: ≥10 genes, >400 mutations

Nabel: NEJM, 2003

Survival of Family Members According to Mutation



Watkins: NEJM, 1992

HCM – Molecular Genetics and Clinical Practice

Problem

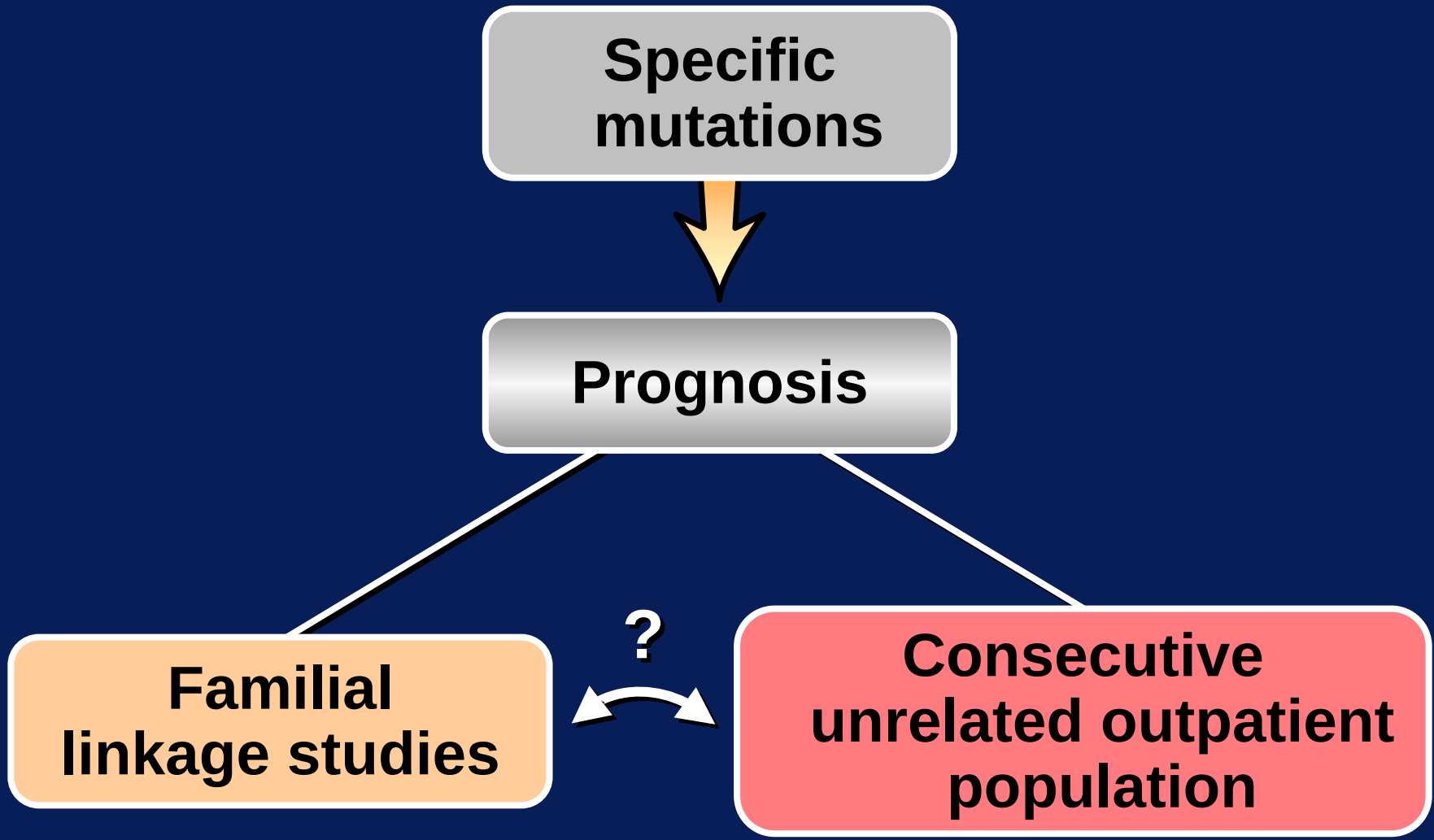
For every association there is an exception

Clinical impact

Profound for the patient who dies

mayo

Molecular Genetics and Prognosis



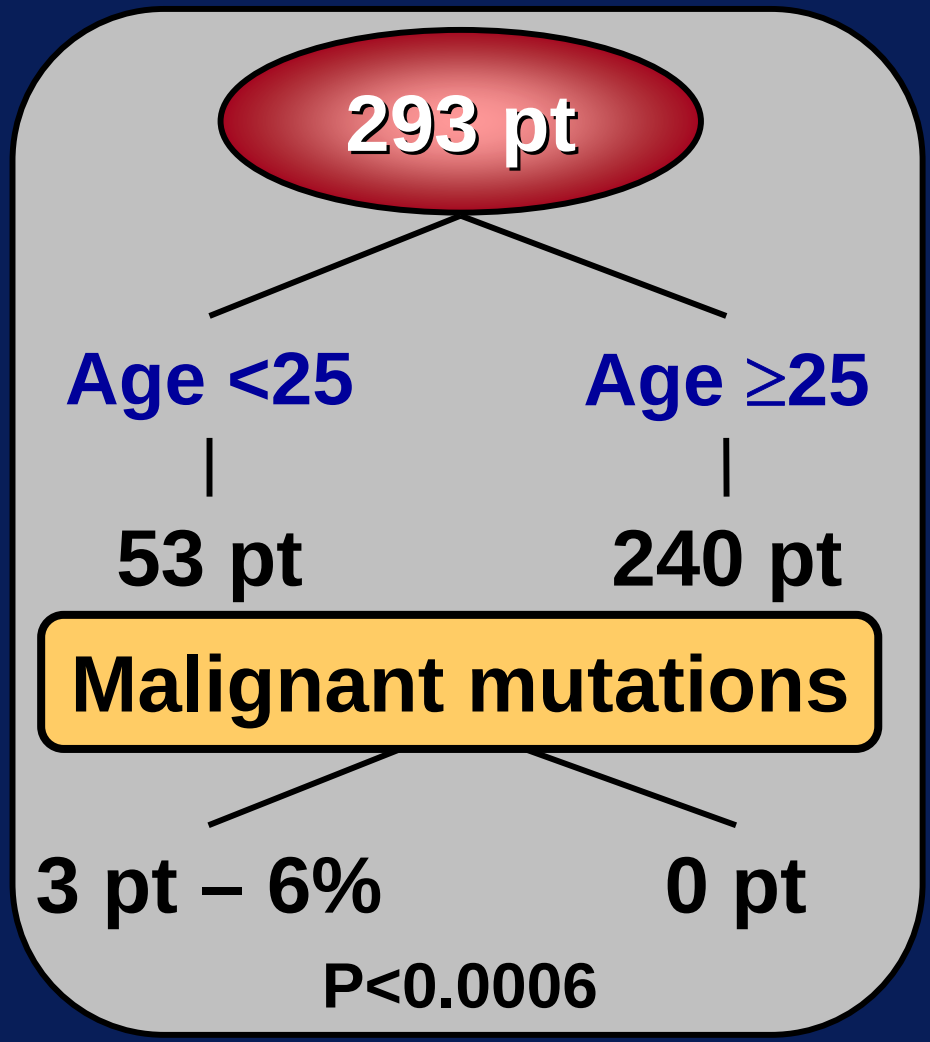
Frequency of Malignant Mutations – Clinical Perspective

βMHC, Troponin T and Alpha Tropomyosin Genes

- 293 consecutive pt – Mayo Clinic
- 1997-2000
- Mean age – 42.5 yr

Family history

- HCM – 32.4%
- SCD – 23.4%



Van Driest: JACC, 2002

"Benign" Mutations – Clinical Perspective
293 Consecutive Patients

8 benign mutations of βMHC, troponin T and alpha tropomyosin genes

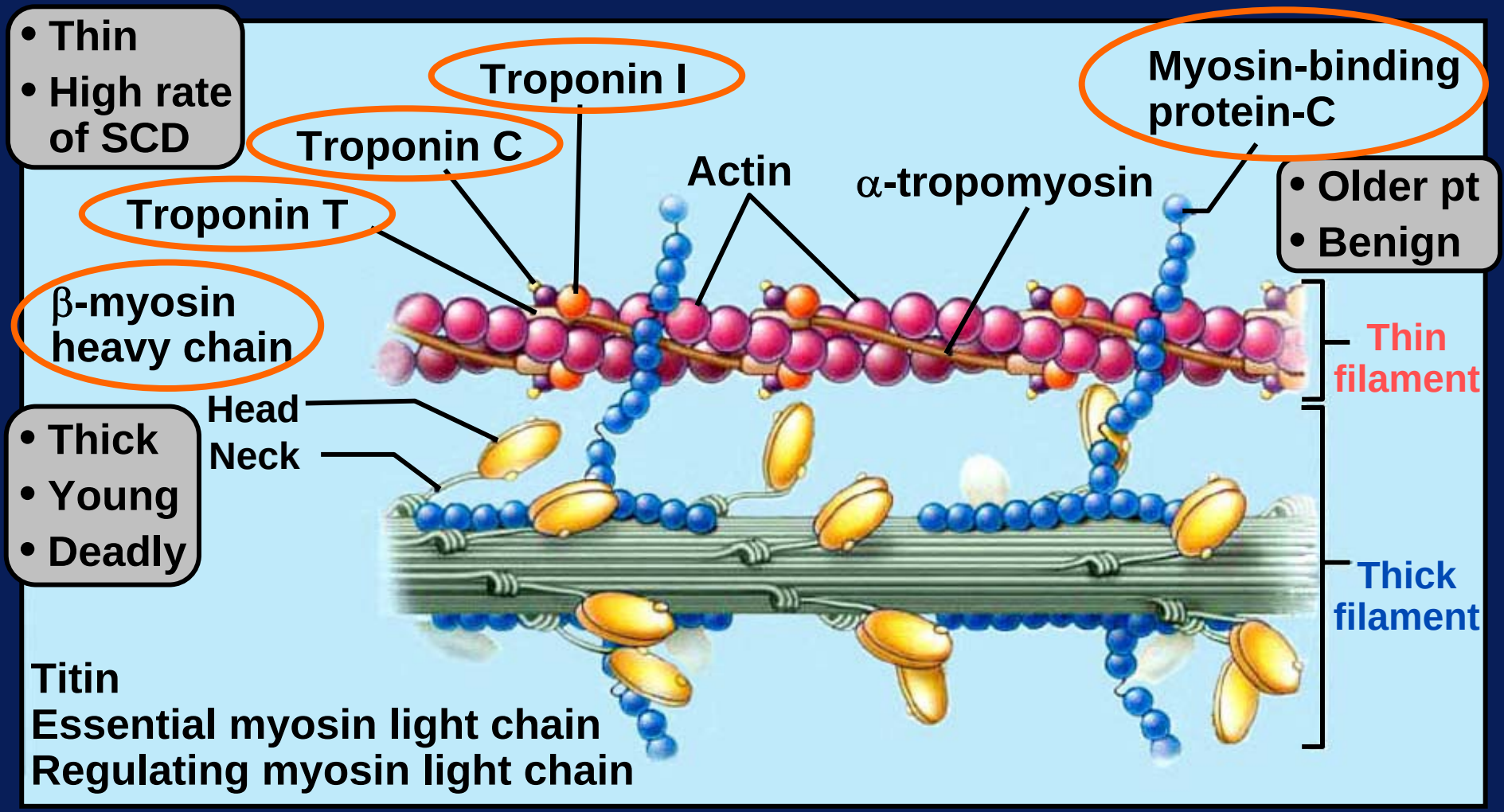
5 pt – 1.7%

How 'benign'?

- Myectomy/myotomy – 5 pt
- FH of SCD – 3 pt
- Cardiac transplant – 1 pt

Van Driest and Ackerman M: Circ, 2002

Prevailing Concepts
Phenotype/Genotype Correlations



Genetic heterogeneity ≥10 genes >150 mutations

Nabel: NEJM, 2003

Phenotypes in Genotyped HCM n=389

	MYH7	MYBPC3	TNNT2
No.	54	63	6
Age at diagnosis (yr)	33±18	38±15	44±17
FH of HCM (%)	42	43	17
FH of SCD (%)	21	16	0
LVWT (mm)	24±8	23±5	18±16

Van Driest et al
Mayo Clin. Proc. 2005t

HCM – Changing Concepts

- Sarcomeric mutations in <50% of pt

  | ?

  Novel genetic mechanisms

- Specific mutations (benign/malignant) are rare and unreliable estimates of risk

  | ?

  Novel genetic/environmental modifiers

- There are no genetic specific phenotypes

  | ?

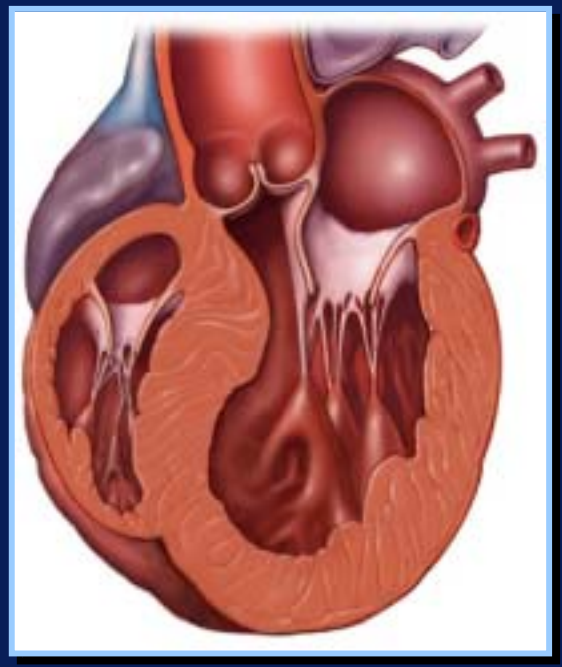
  Novel genetic/environmental modifiers

HCM of the Elderly-Same Disease ?

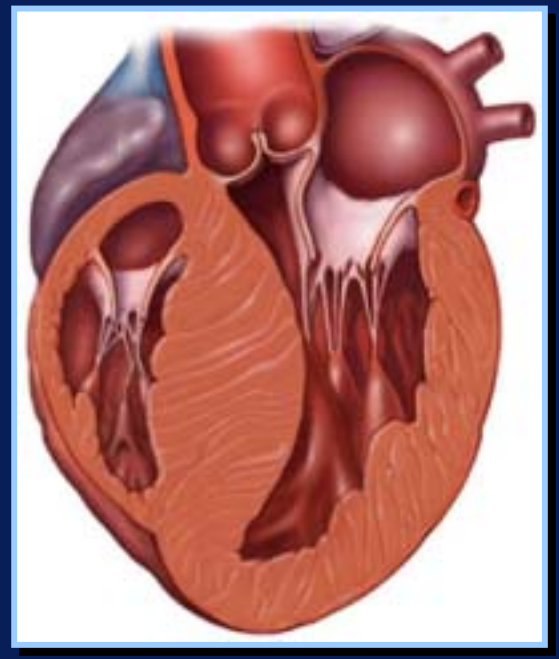
Survival similar to age- and sex-matched controls

Distinct morphology

Older patients



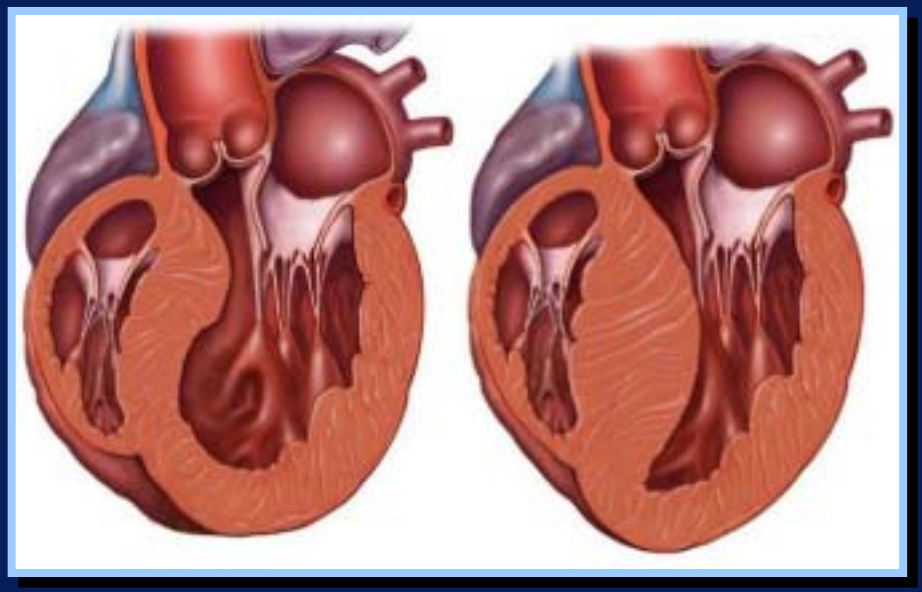
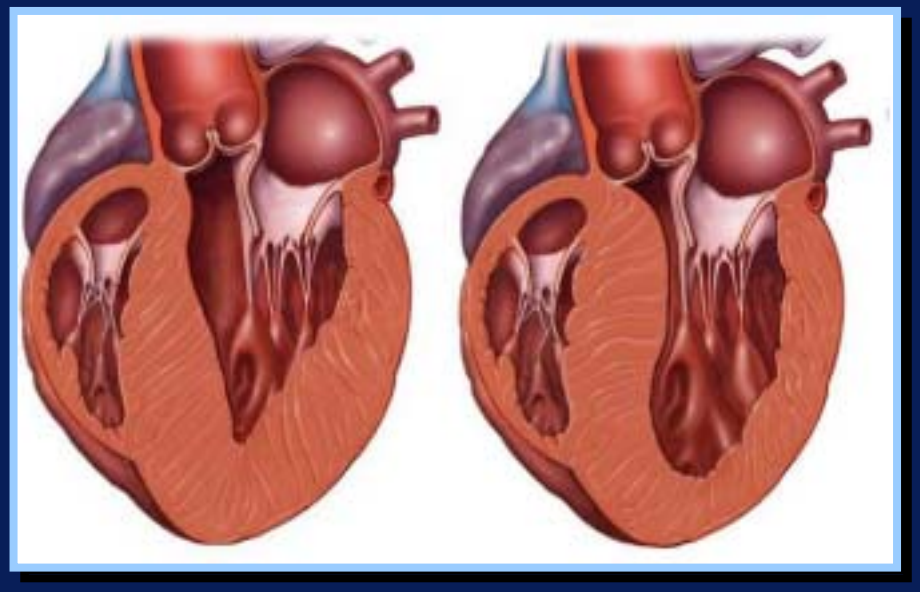
Younger patients



Fay:
JACC, 1990

Lever:
Circ, 1989

Ventricular Morphology
Myofilament Mutations

Sigmoid Septum	Reversed Septal Curvature	Apical HCM	Indeterminate
			
Gene+ 8%	Gene+ 79%	Gene+ 32%	Gene+ 41%

Binder J

HCM – Patients at High Risk for SCD

Established risk factors

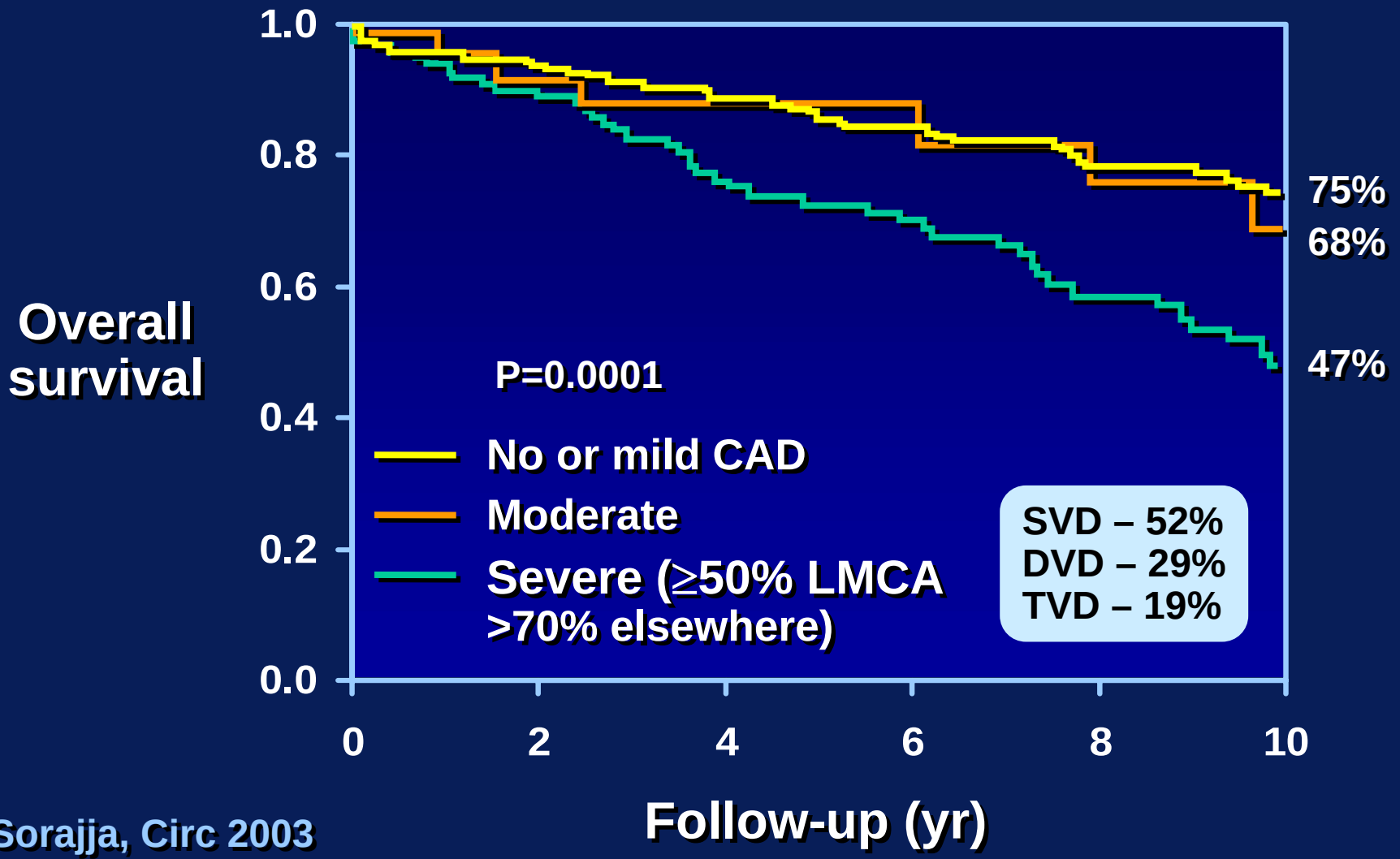
- Prior cardiac arrest
- Younger age
- Positive FH of SCD
- Unexplained syncope

- NSVT
- Exercise-induced hypotension
- LV wall thickness ≥25-30 mm

- Associated coronary artery disease – novel risk factor-
  Sorajja Circ 2003

Overall Survival – Stratified by Severity of CAD

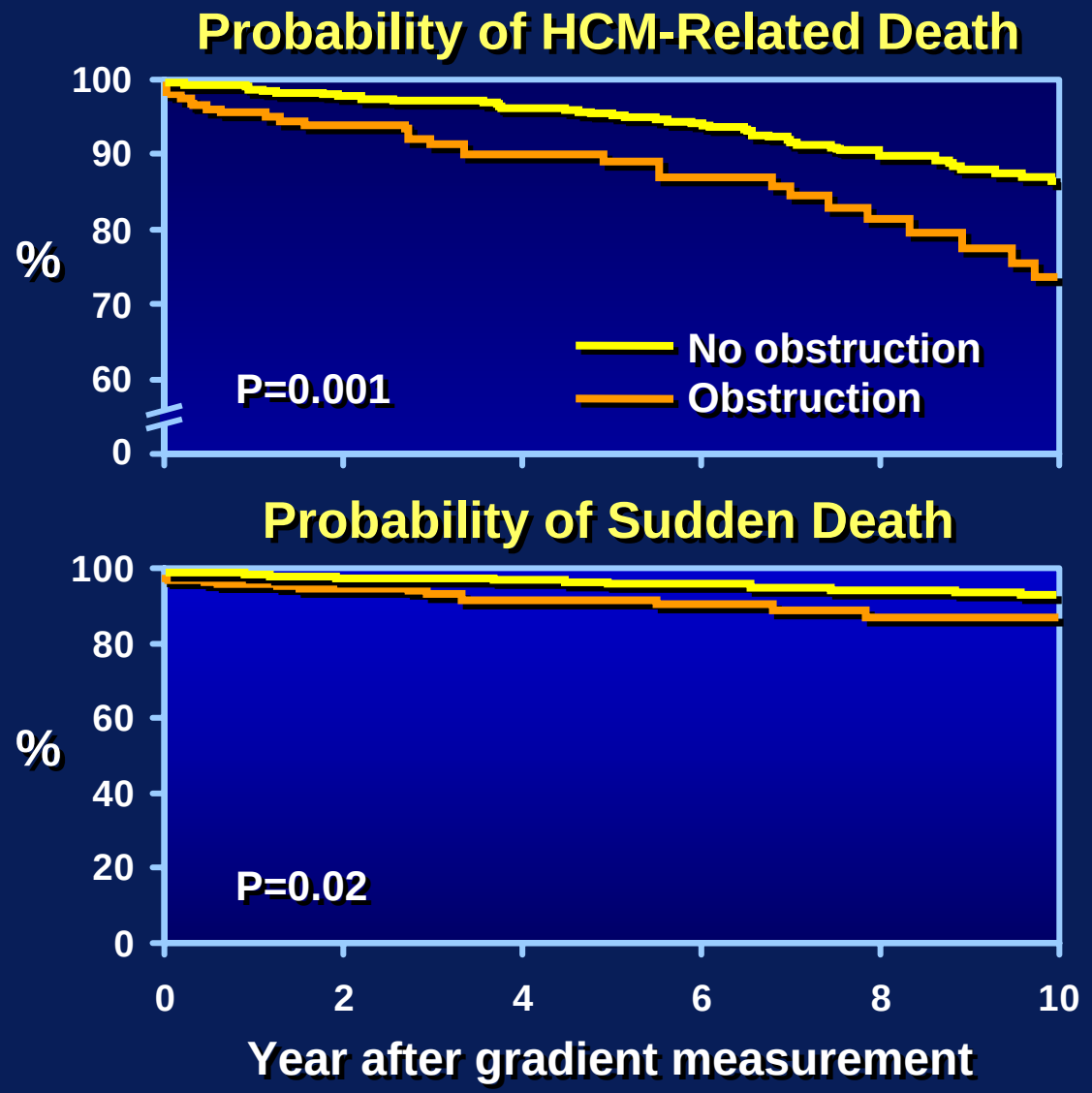
398 Patients



Sorajja, Circ 2003

Effect of LV Outflow Tract Obstruction on Prognosis

- 1,101 pt
- Florence
  Naples
  Minneapolis
- F-U 6.3±6.2 yr



Maron MS: NEJM, 2003

Risk Stratification and Therapeutic Strategies

High risk

- Young pt
- Positive FH of SCD
- Syncope
- NSVT – ?
- Exercise-induced hypotension?
- LVWT ≥25 mm?
- *Associated CAD*

Intermediate risk

- Symptomatic patients

Low risk

- Asymptomatic
- Elderly patients

Therapeutic objectives

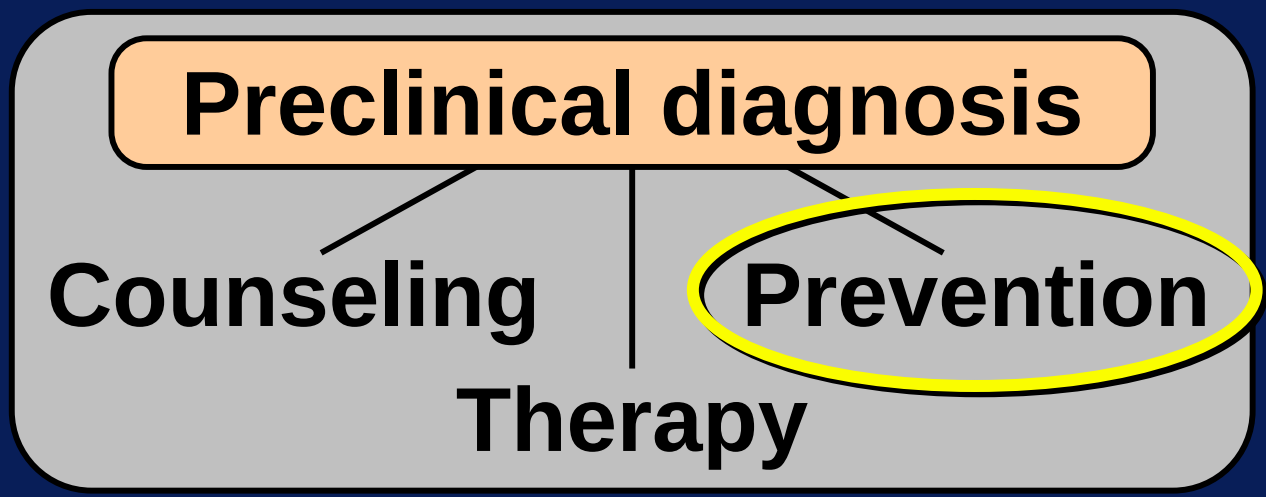
- Improved survival
- Relieve symptoms
- Reassurance
- Surveillance
- Treat hypertension

How would this be altered by genotyping?

Future of Routine Genotype Determination

Optimistic

- Establishment of disease patterns
- Risk stratification?



Prognostic Assessment – HCM

Clinical

History ECG Holter Stress test

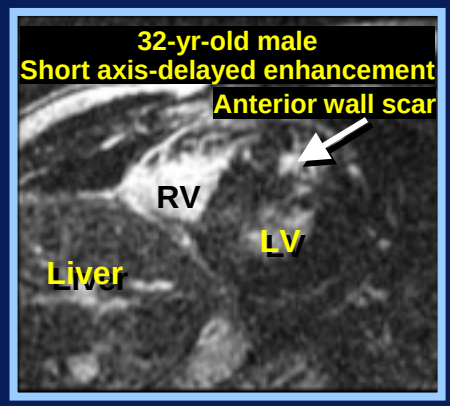
Identification for mutation positives without LVH

Reduced TD velocity

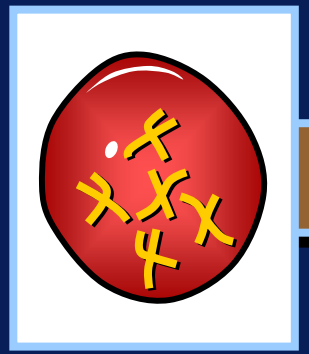
Sens 100% Spec 93%

Role of TDI?

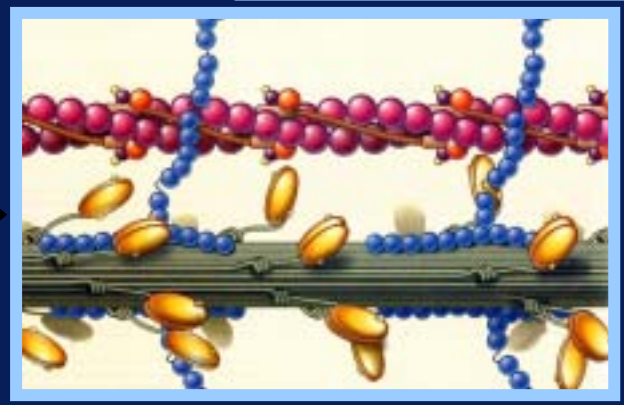
Morphologic/cellular/ scarring



Role of MRI?



Molecular

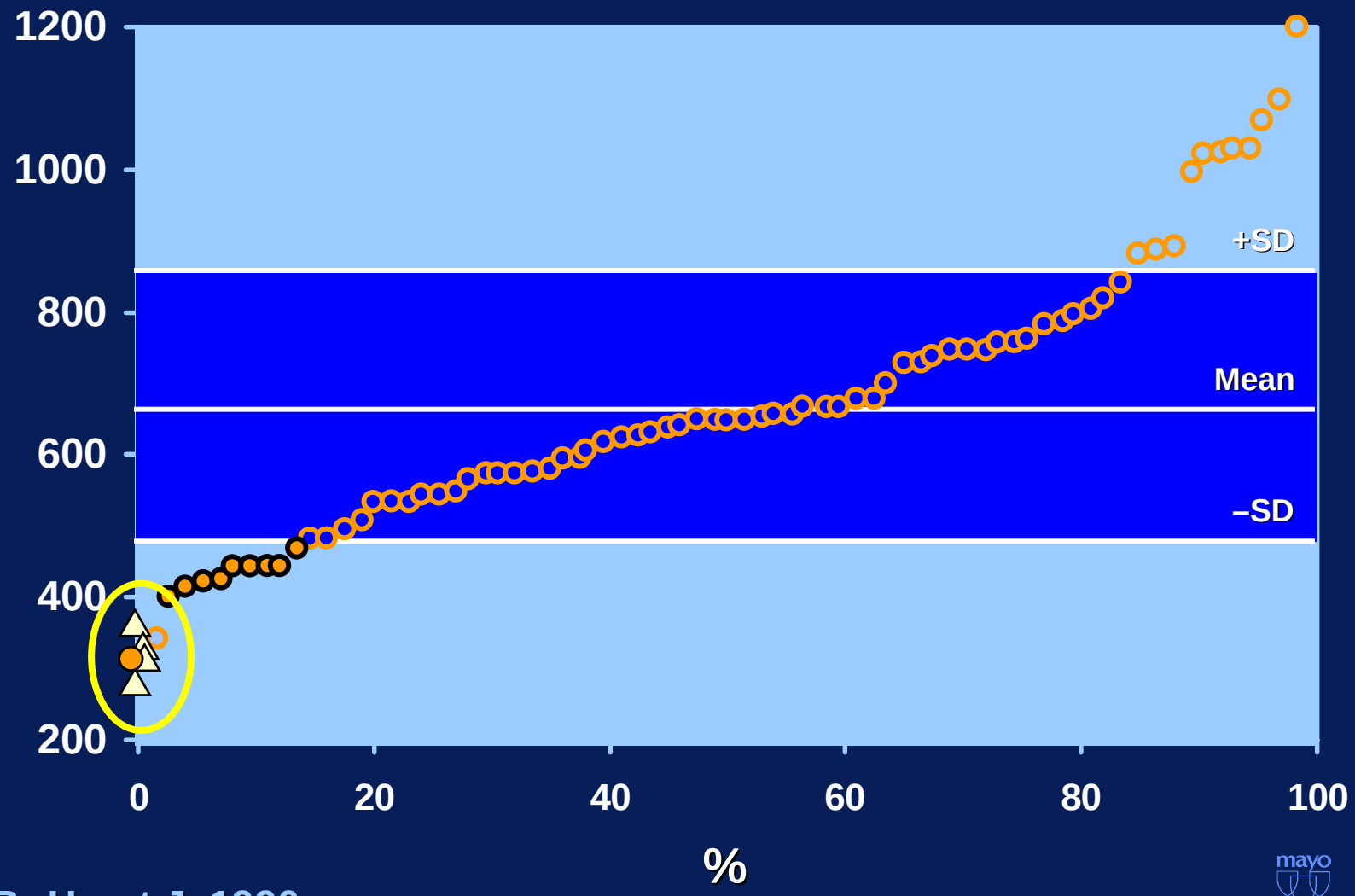


Future?

Nagueh: Circ, 2001; Valeti, 2003; Spiritto: NEJM, 1997

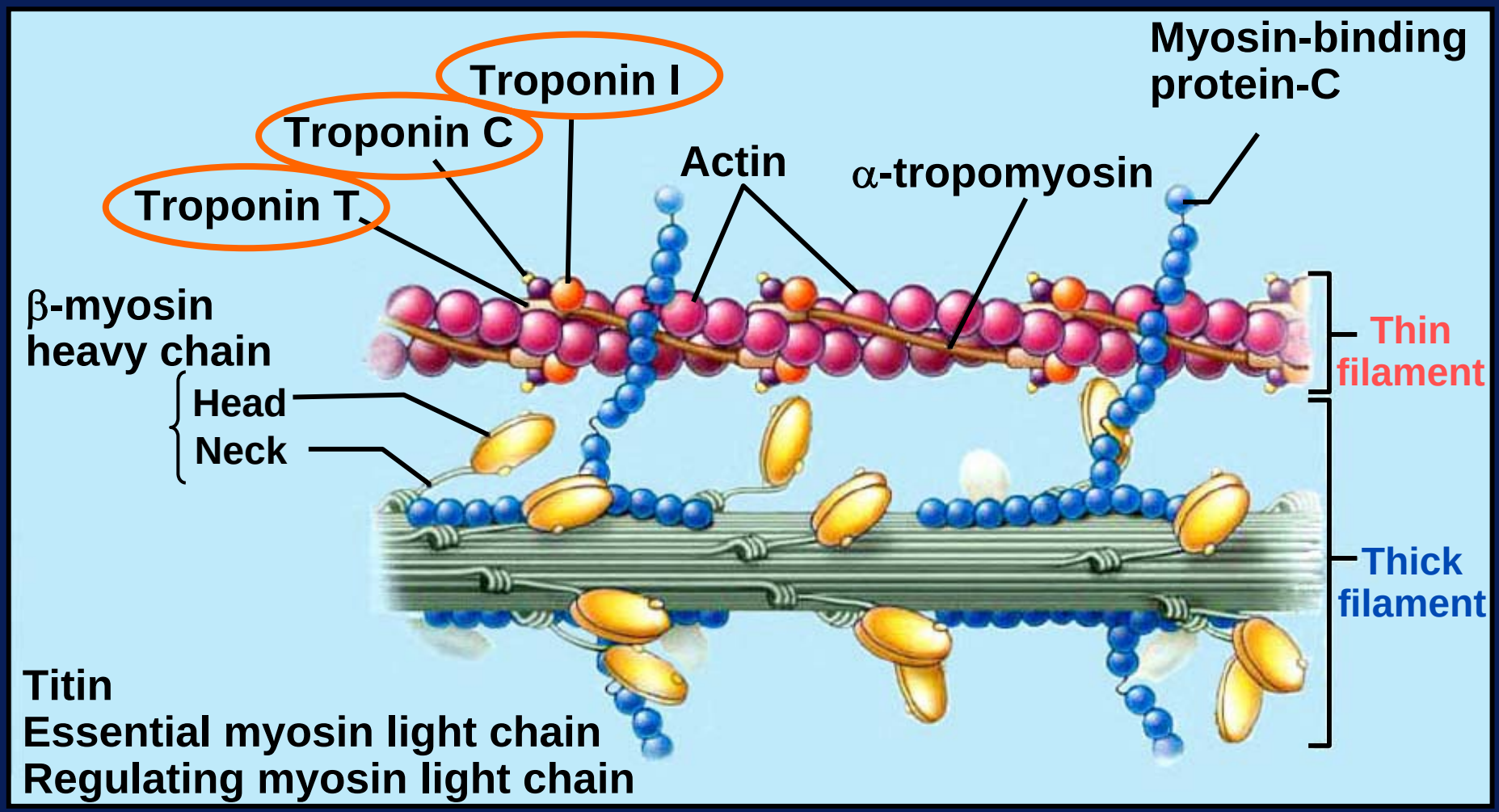
Heart Weights in HCM

Male Pts NIH Pathology Branch Registry



Maron: Br Heart J, 1990

Mutations in Sarcomeric Proteins

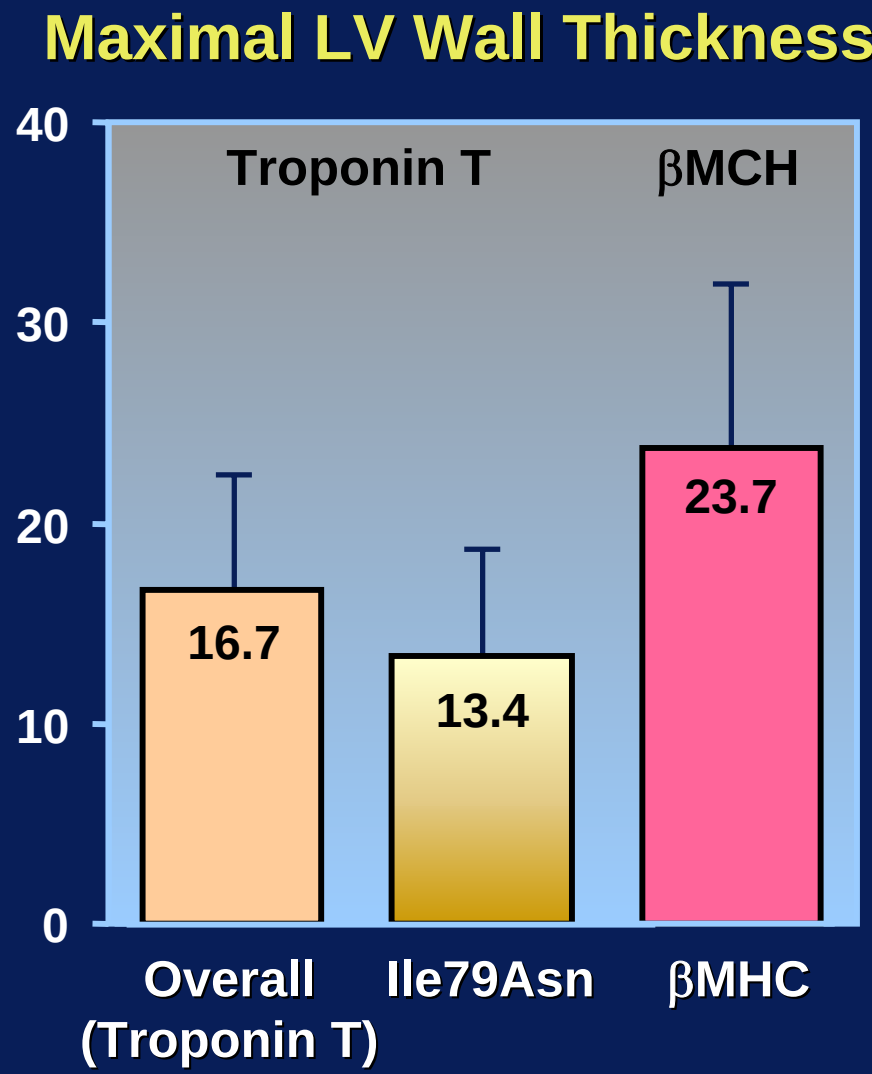


Nabel: NEJM, 2003

Mutations in Genes for Cardiac Troponin T

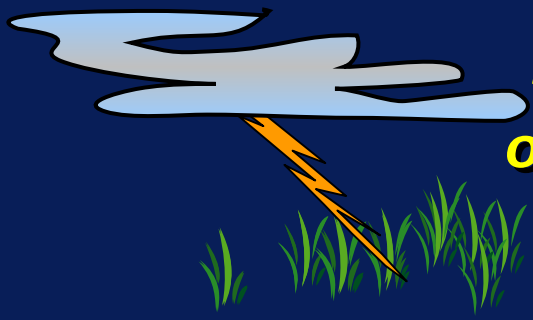
Cardiac troponin T mutations

- 7 unrelated families
- 4 mutations
- Life expectancy 35 years (SCD – 78%)



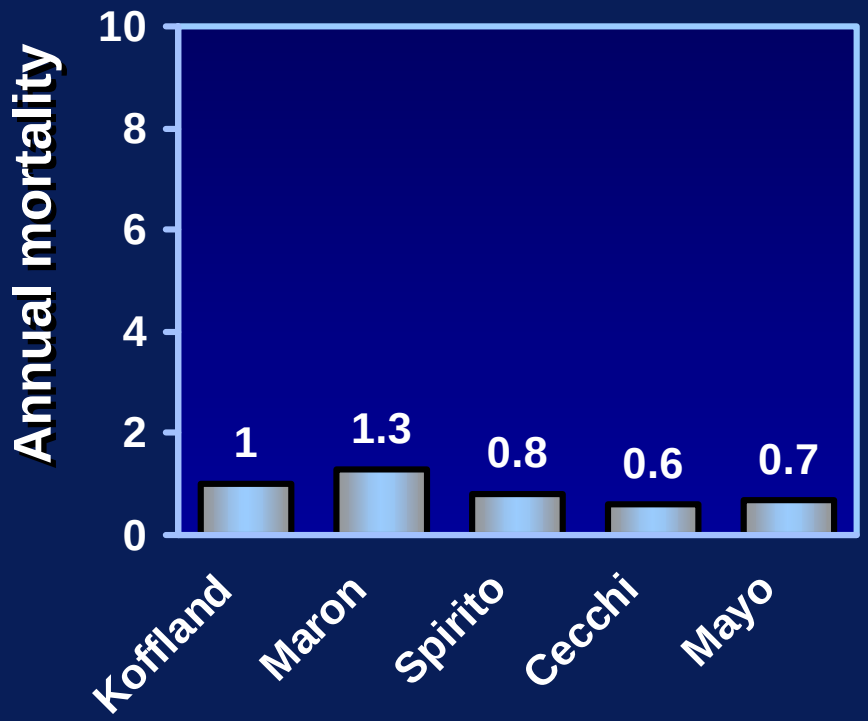
Watkins: NEJM, 1995

Sudden "Unexpected" Cardiac Death and HCM

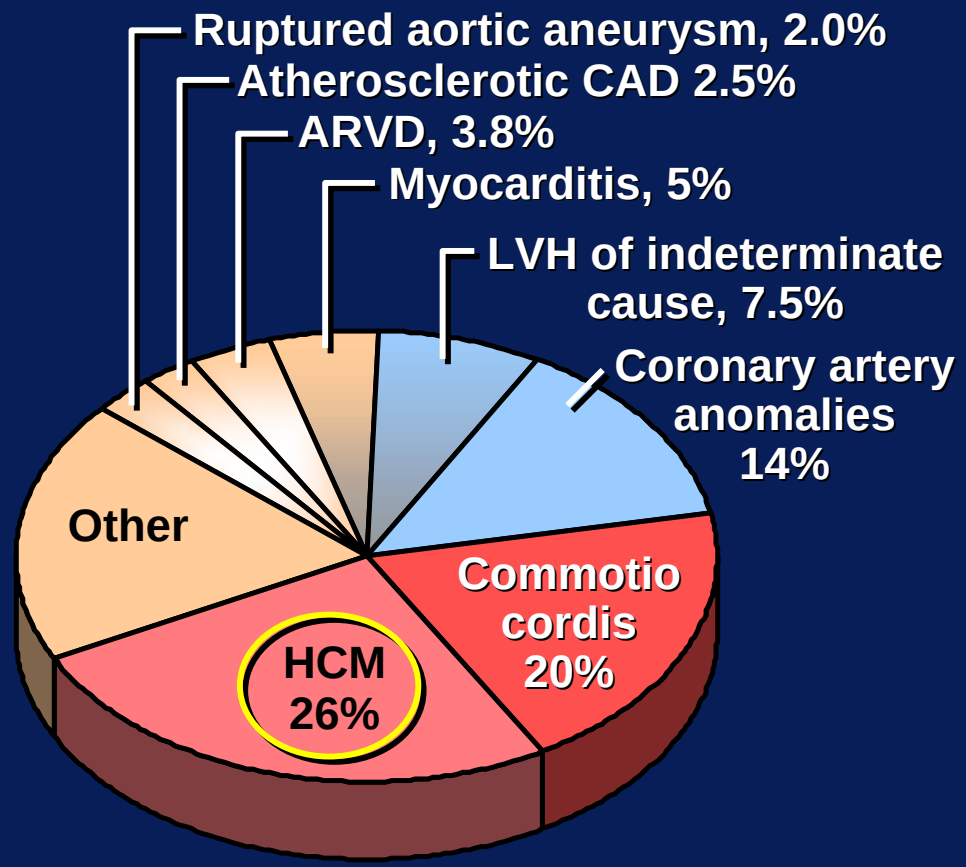


"A bolt out of the blue!"

Low Annual Mortality Overall



Causes of Death in 387 Young Athletes



Maron: NEJM, 2003

HCM in the Elderly – Unresolved Questions

Different disease?

Milder form of the same disease?

Is it an inappropriate response to stimuli to hypertrophy?

- **Mild systemic hypertension**
- **Diminished vascular compliance**
- **Decreased cardiac size**
- **Angulation of the aorta**

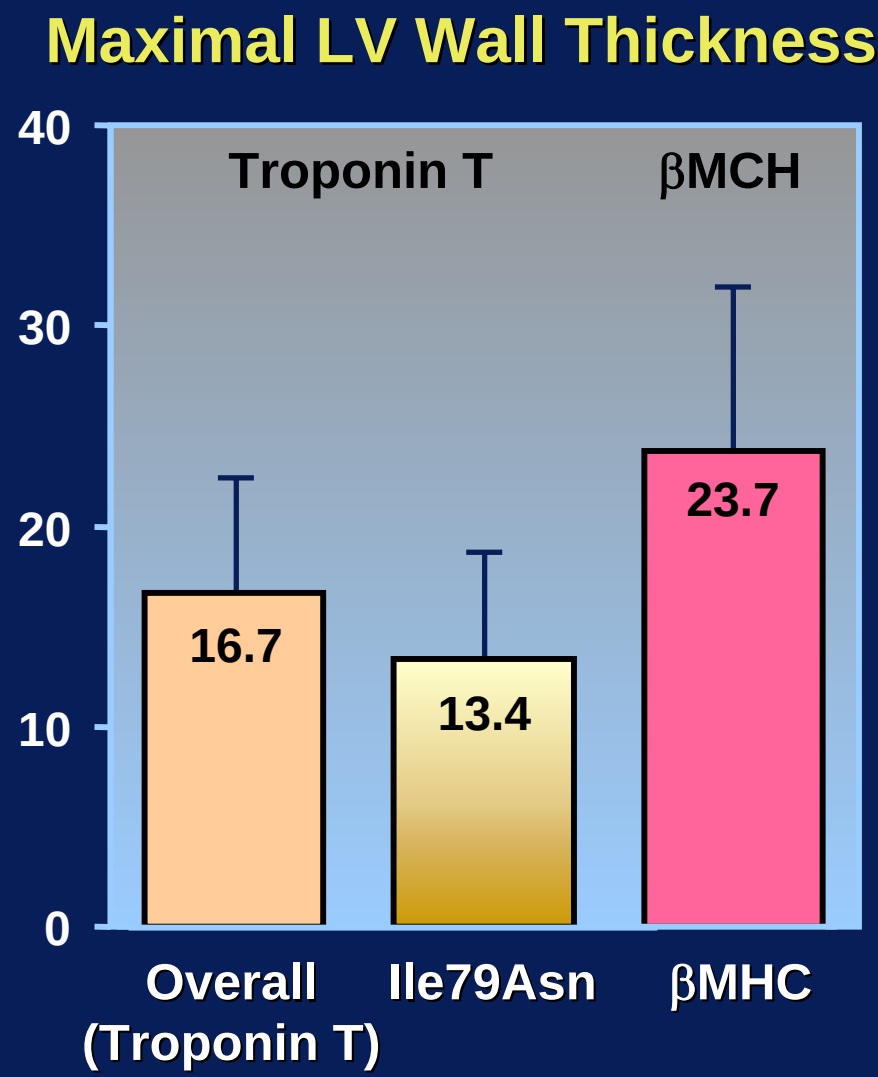
Mutations in Genes for Cardiac Troponin T

Cardiac troponin T mutations

- 7 unrelated families
- 4 mutations
- Life expectancy 35 years (SCD – 78%)

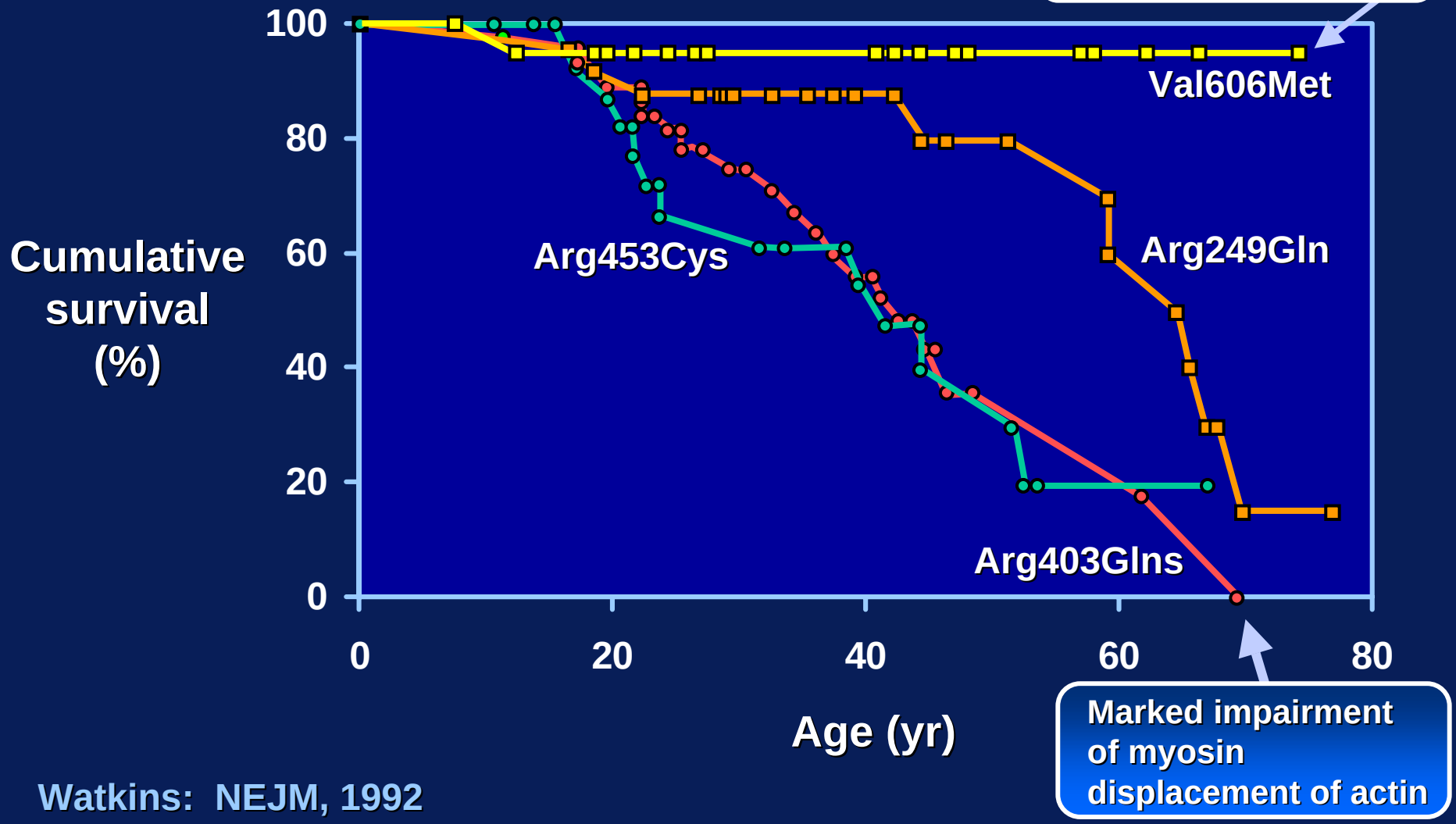
β cardiac MHC mutation

SCD – 56%



Watkins: NEJM, 1995

Survival of Family Members According to Mutation



Watkins: NEJM, 1992

CP949495-1

Results of Surgery in HOCM

Surgical pt – 353

Mayo Clinic 1983-2001

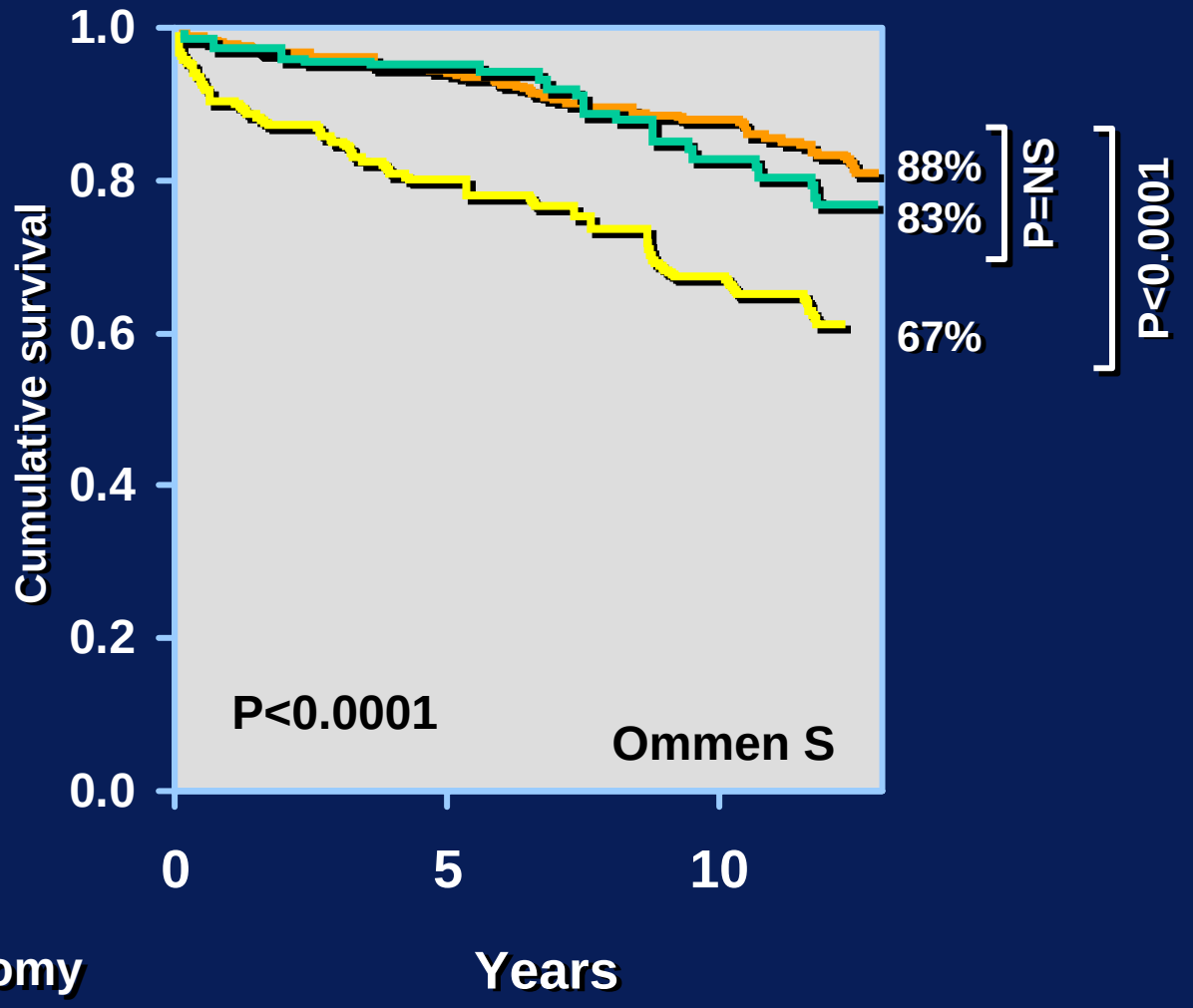
Nonoperated 1,101 pt

Florence

Naples

Minnesota

Maron: NEJM, 2003



Mayo isolated myectomy

Unoperated obstructive

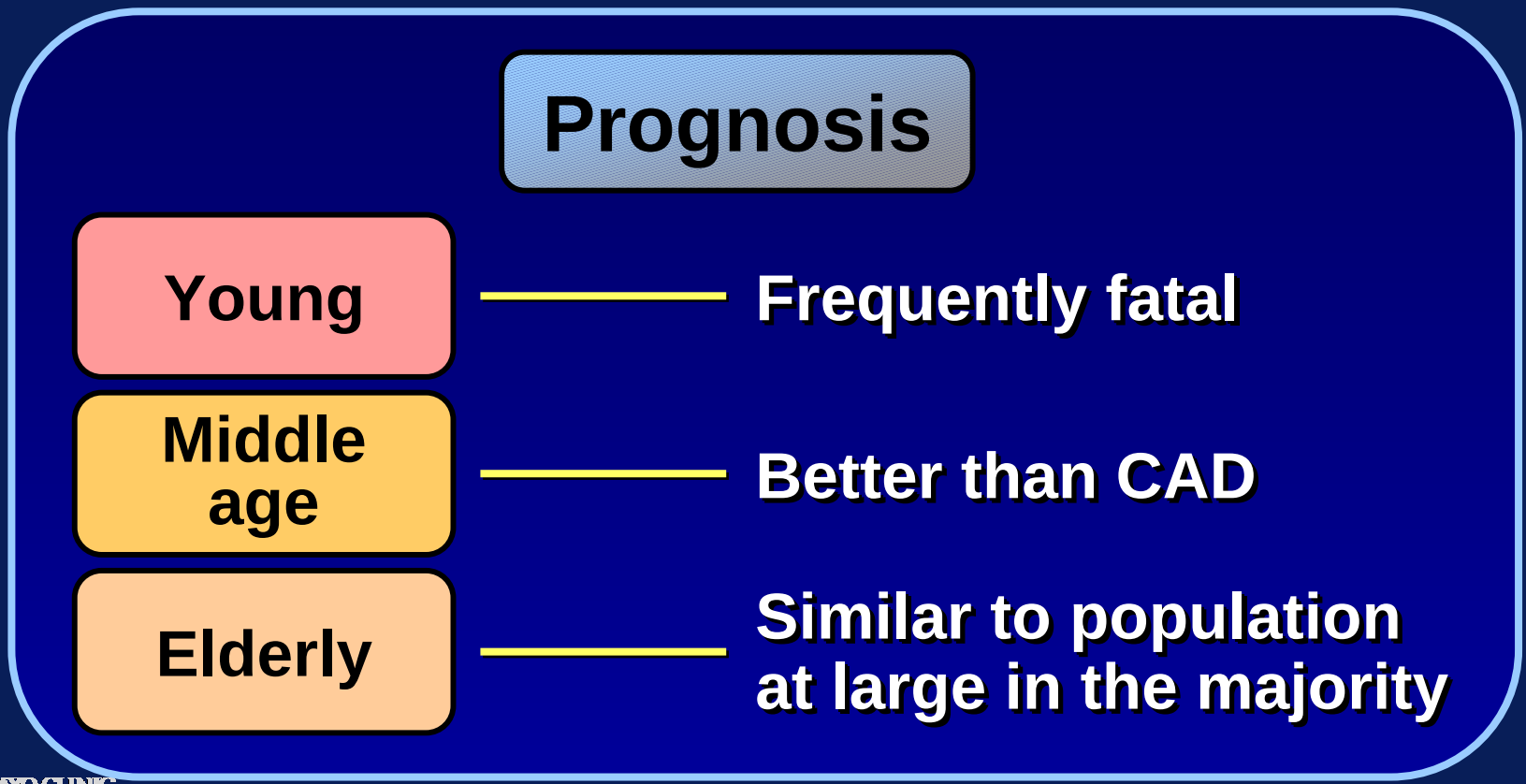
Nonobstructive

Ommen JACC 2005

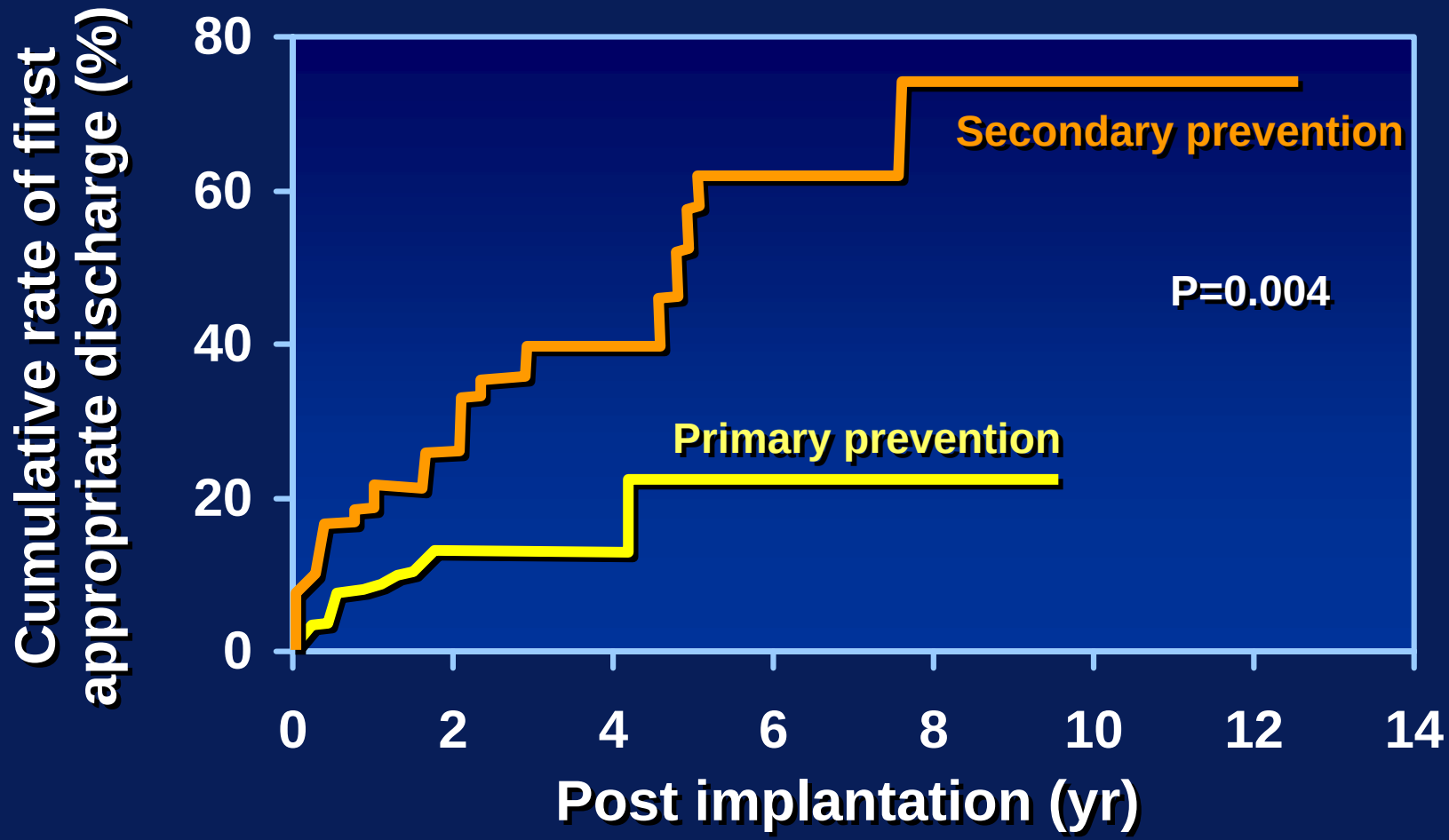
CP1119384-1

HCM – Changing Natural History

- Uncommon disease in young people
- Relatively common in older patients in community hospitals

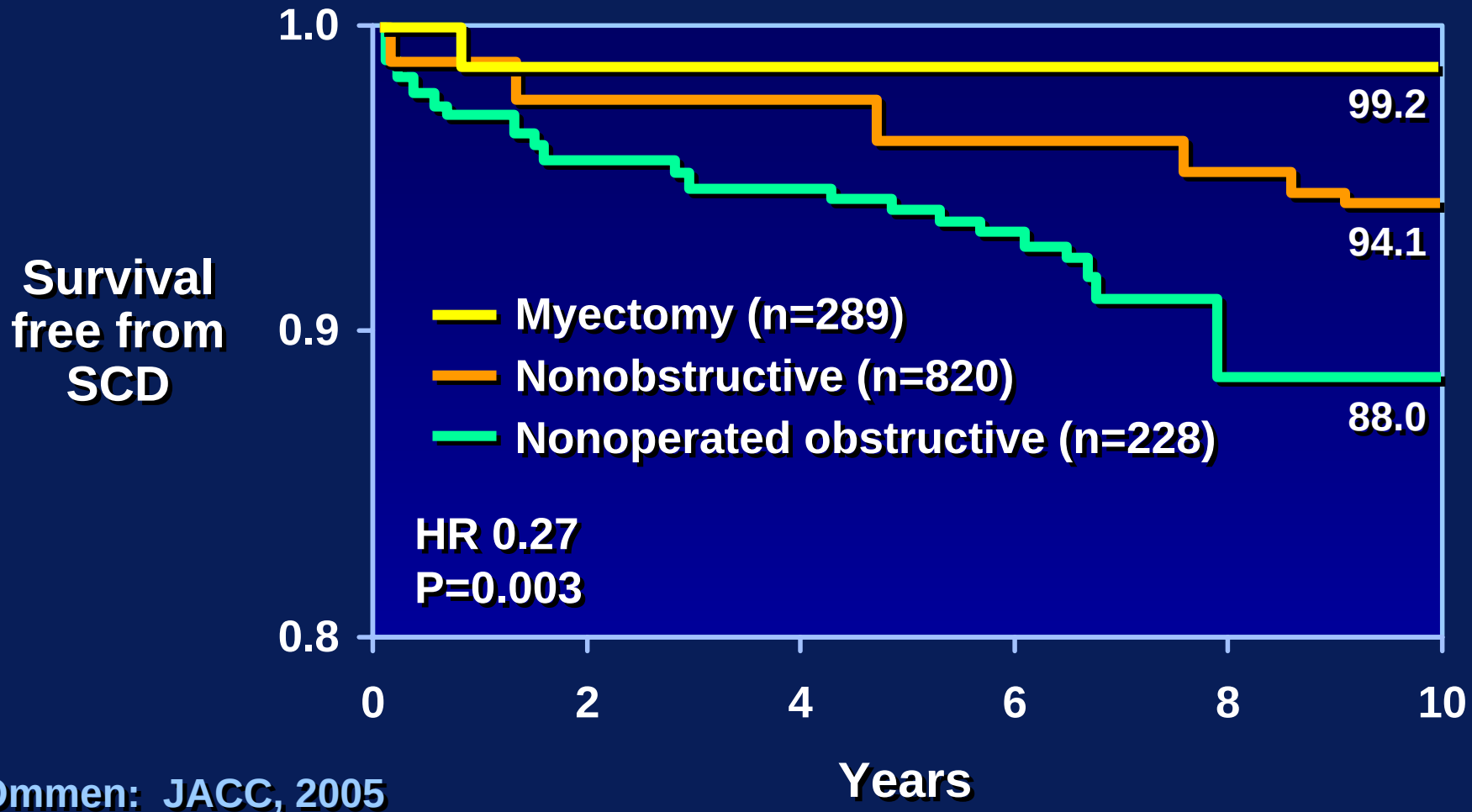


Rates of Defibrillation Discharge After Implantation for Primary and Secondary Prevention in HCM



Maron et al: NEJM 342:365, 2000

Effect of Surgery on Sudden Cardiac Death



Ommen: JACC, 2005

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CP1201810-1

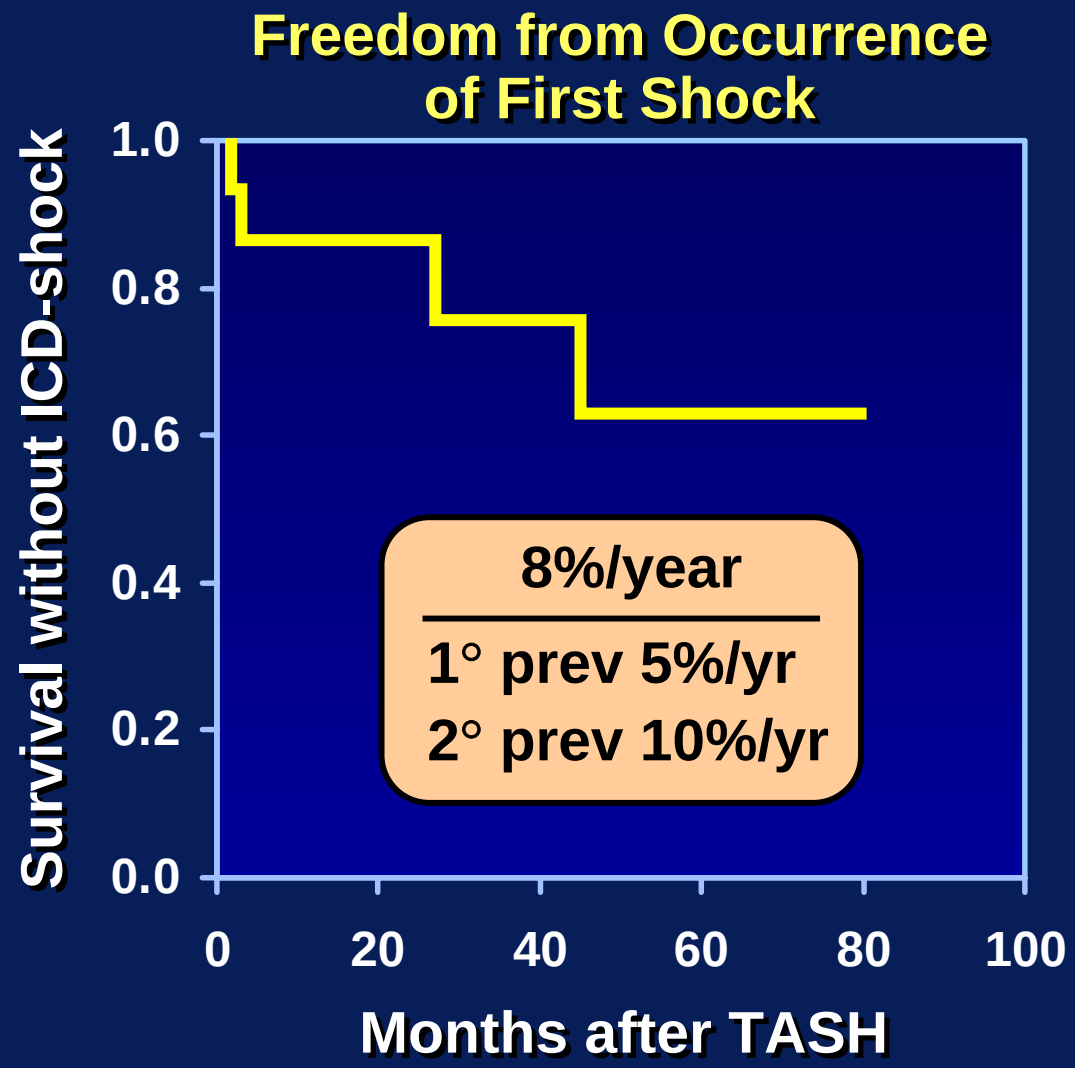
Septal Ablation and ICD Intervention

15 patients

ICD indications

Secondary prevention — 9 pt

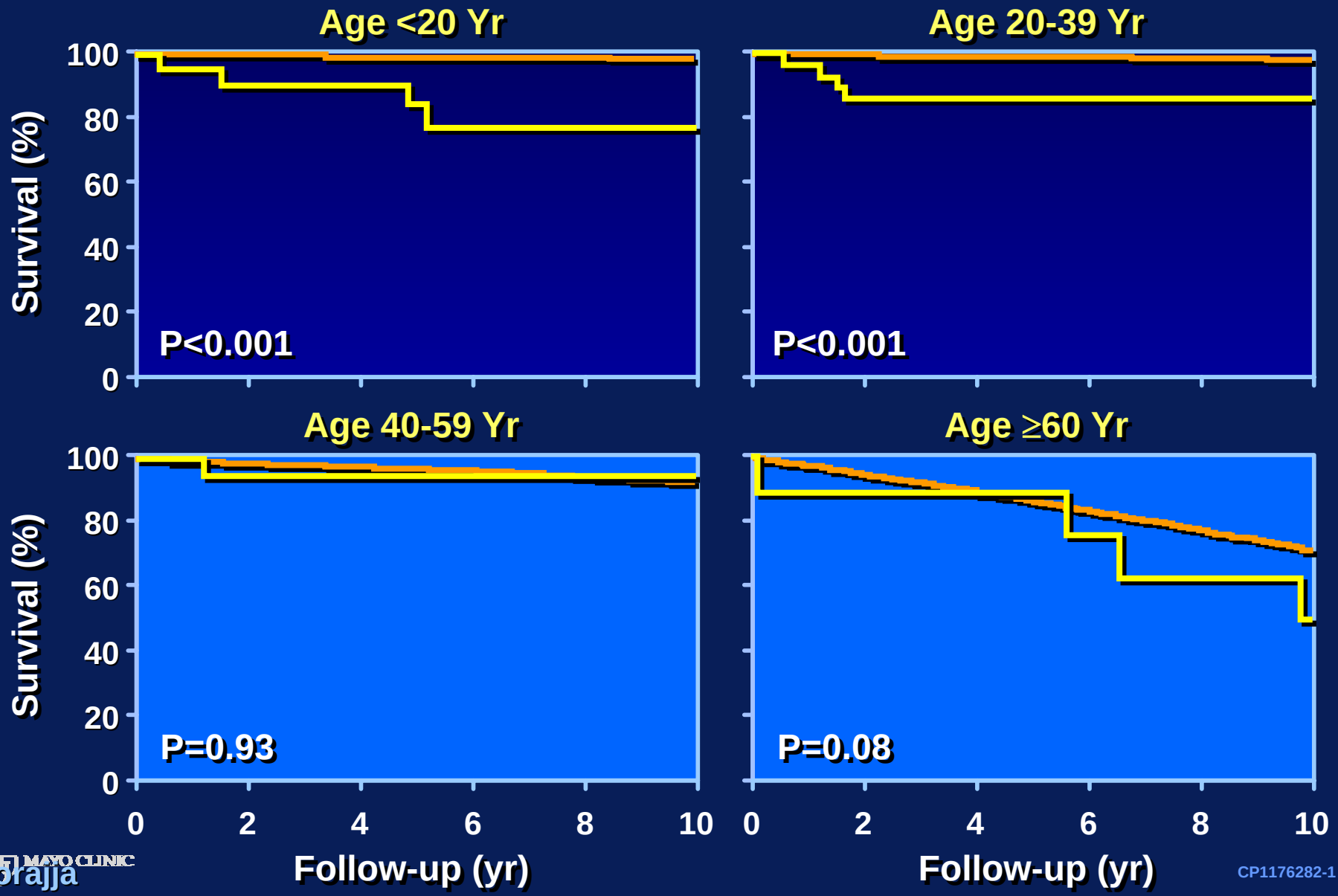
Primary prevention — 6 pt



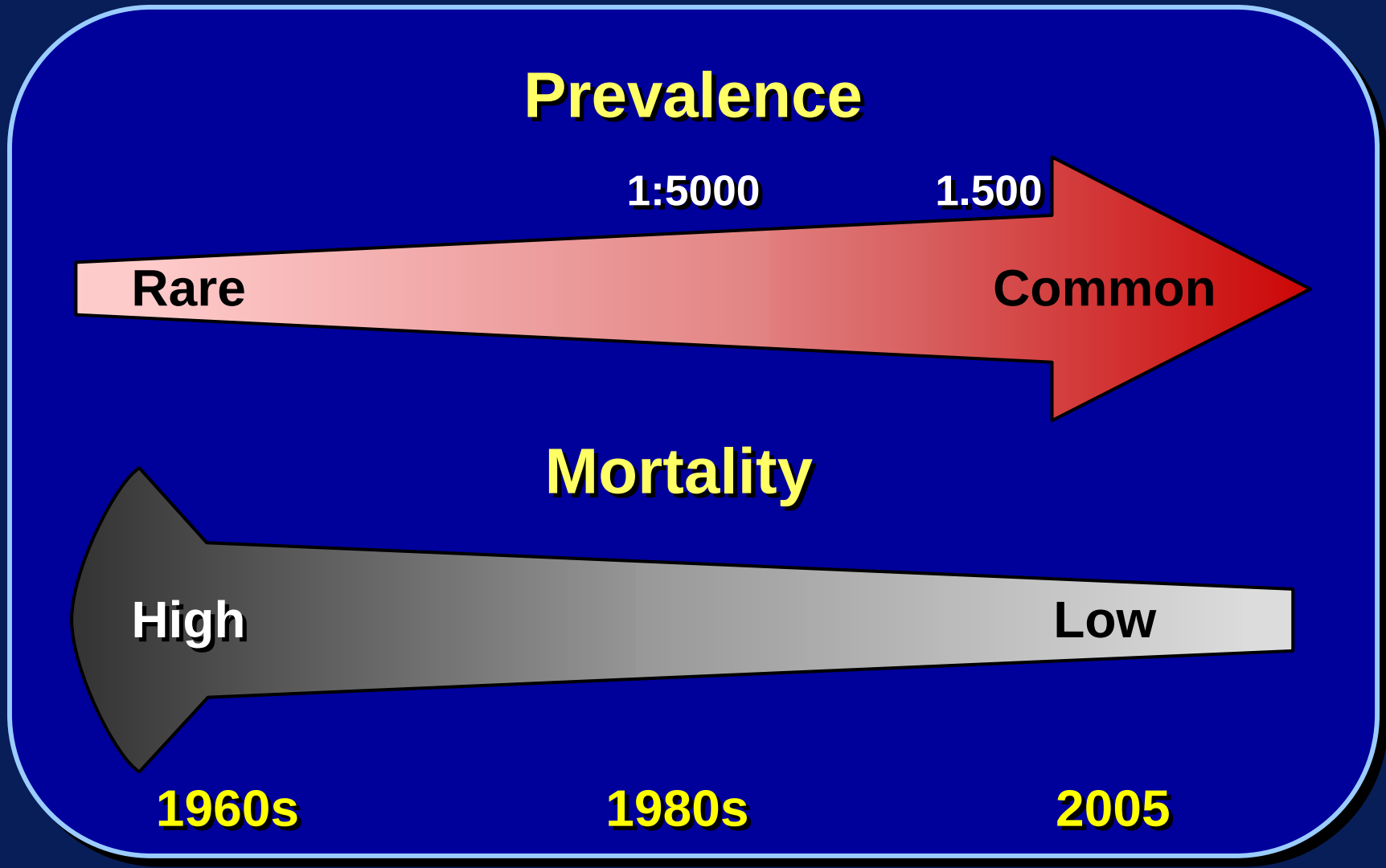
Lawrenz: PACE, 2005

Survival in 107 Patients with "Massive" LVH

Max LVWT ≥30 mm



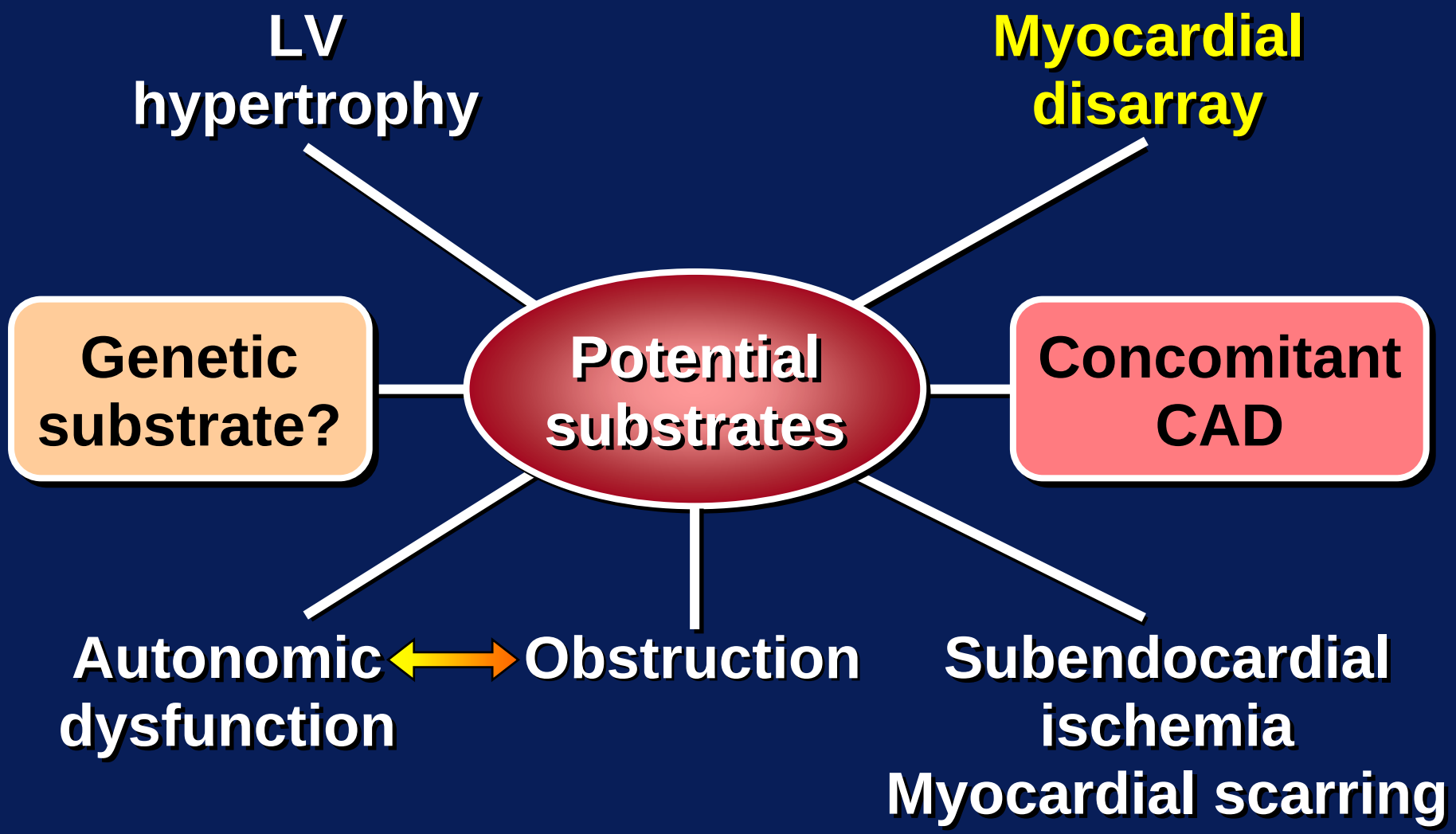
Hypertrophic Cardiomyopathy



Routine Device Interrogation

Event 2 mo previously – pt unaware of any discharges

Sudden Cardiac Death in HCM



How to save HCM lives

Courtesy of Lisa Salberg, HCMA

MAYO CLINIC College of Medicine

Sudden Cardiac Death in Familial Hypertrophic Cardiomyopathy

Are "Benign" Mutations Really Benign?

Sudden death at age 14 in a patient with Val 606 Met mutation in cardiac β MCHC gene

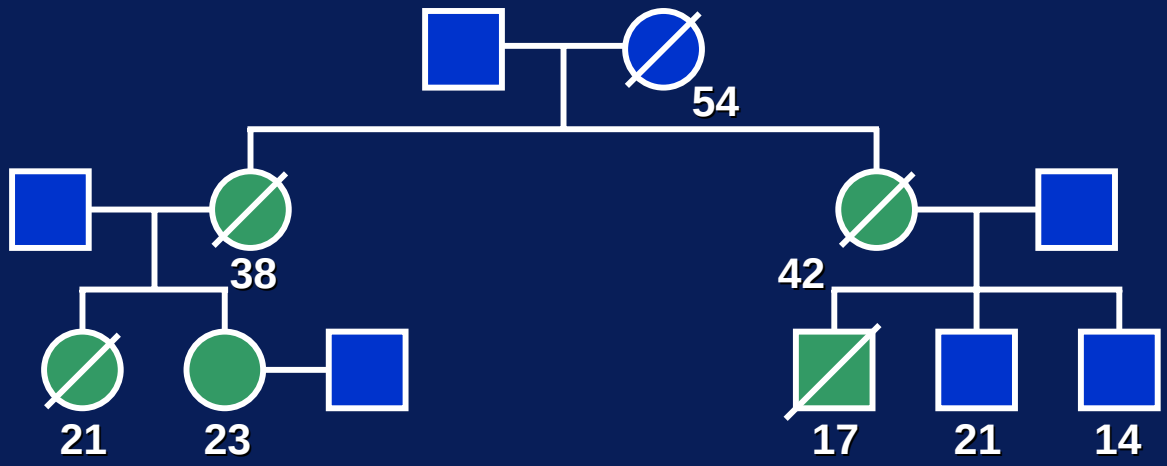
Is it the mutation alone or combinations with other genes and environmental factors ?

Semsarian C et al: Pathology 29:305, 1997

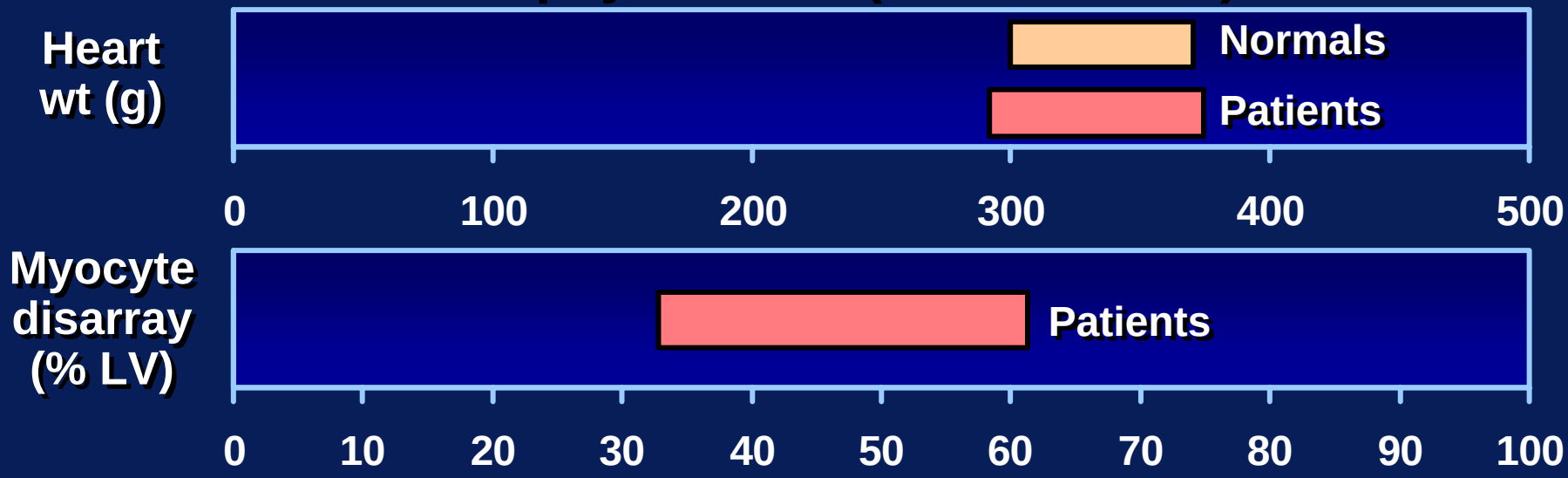
mayo

HCM Without Hypertrophy

Family Pedigree



Autopsy Results (4 Individuals)



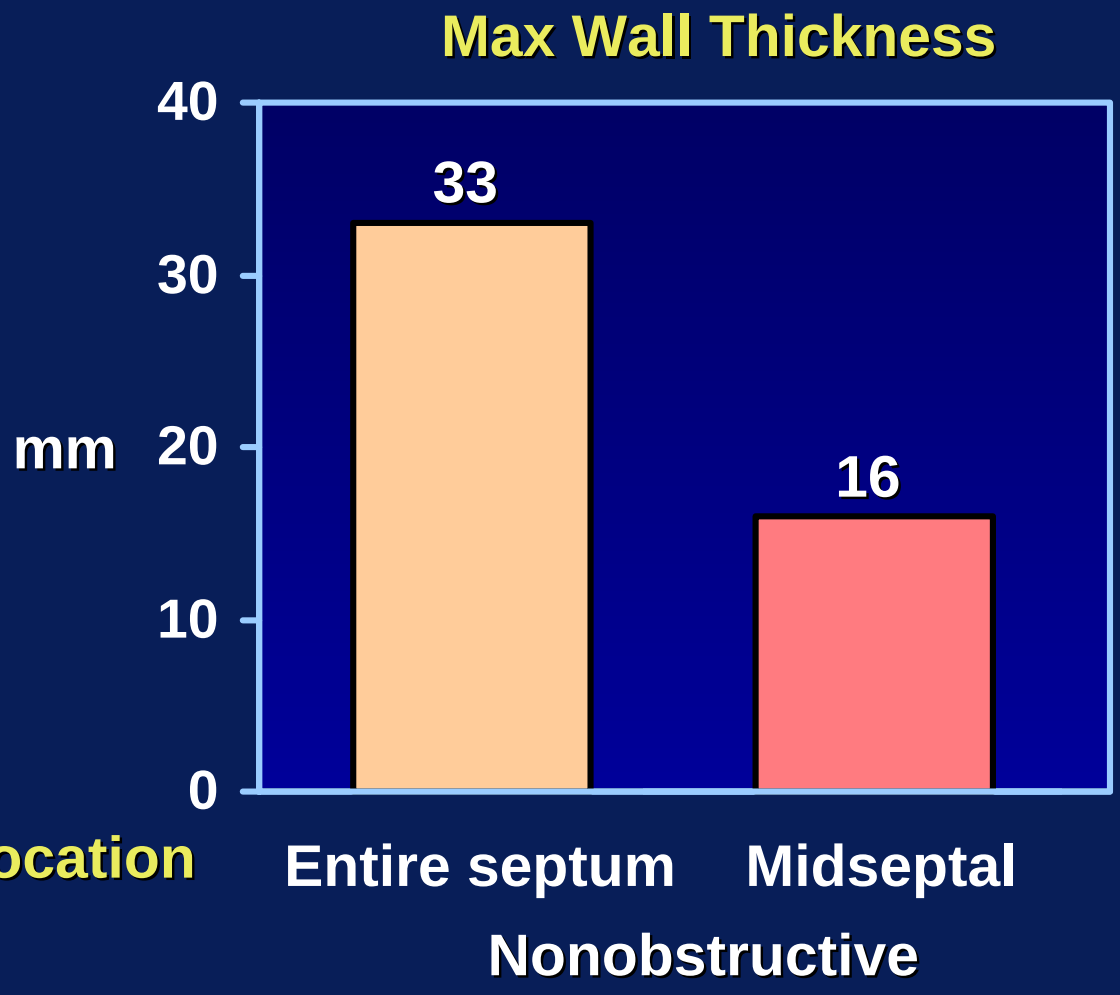
McKenna: Brit H J, 1990

Family with "Malignant" Cardiac Troponin T Mutation

R92W (Exon 9)

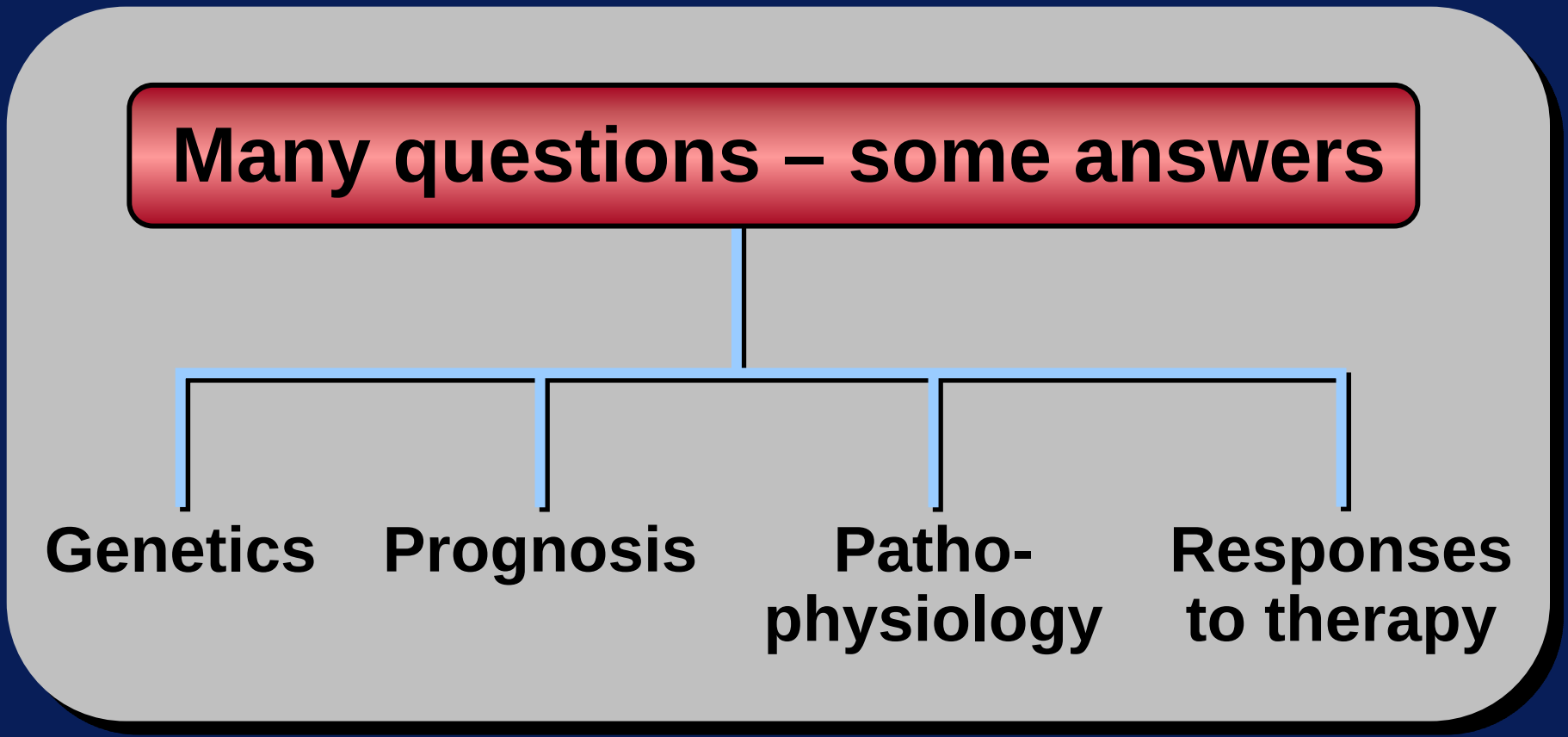
- 24-yr-old daughter
- 56-yr-old mother

FHx of SCD – negative

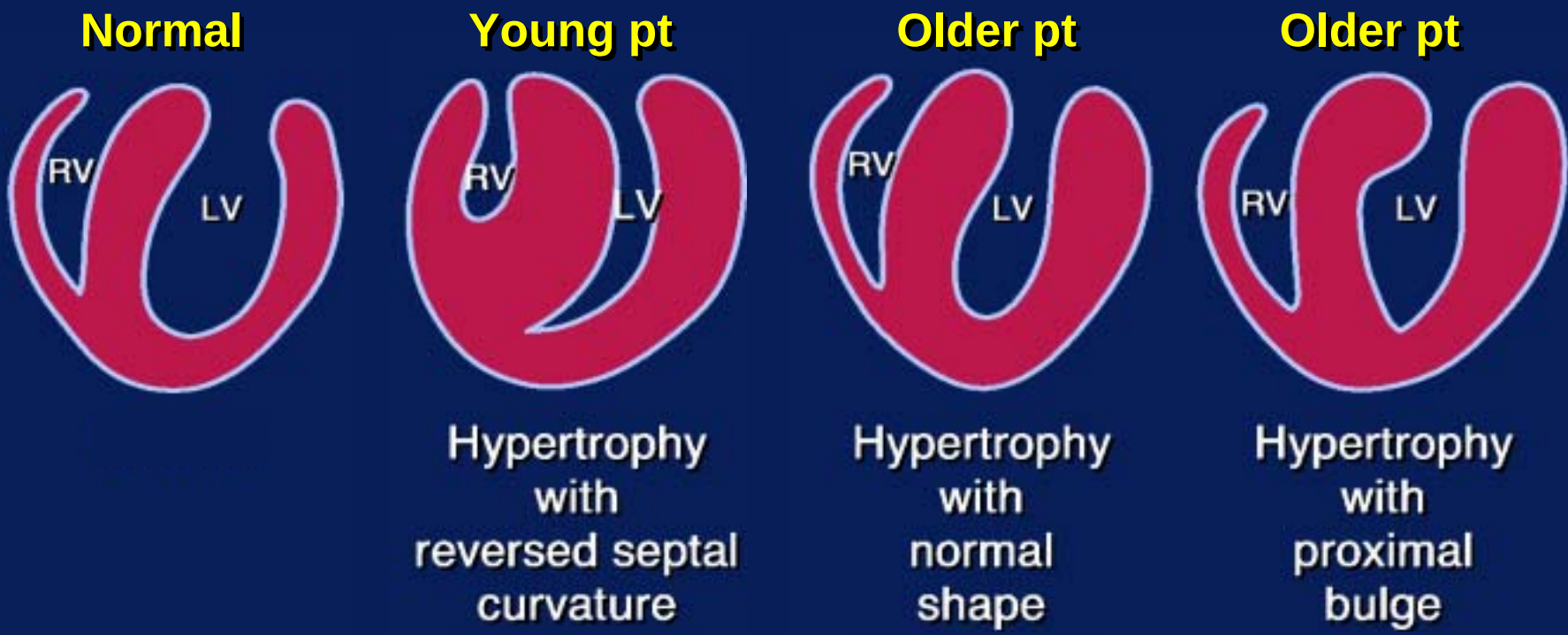


Ackerman M: JACC, 2002

HCM in the Elderly
Comparison with Younger Patients



HCM in the Elderly

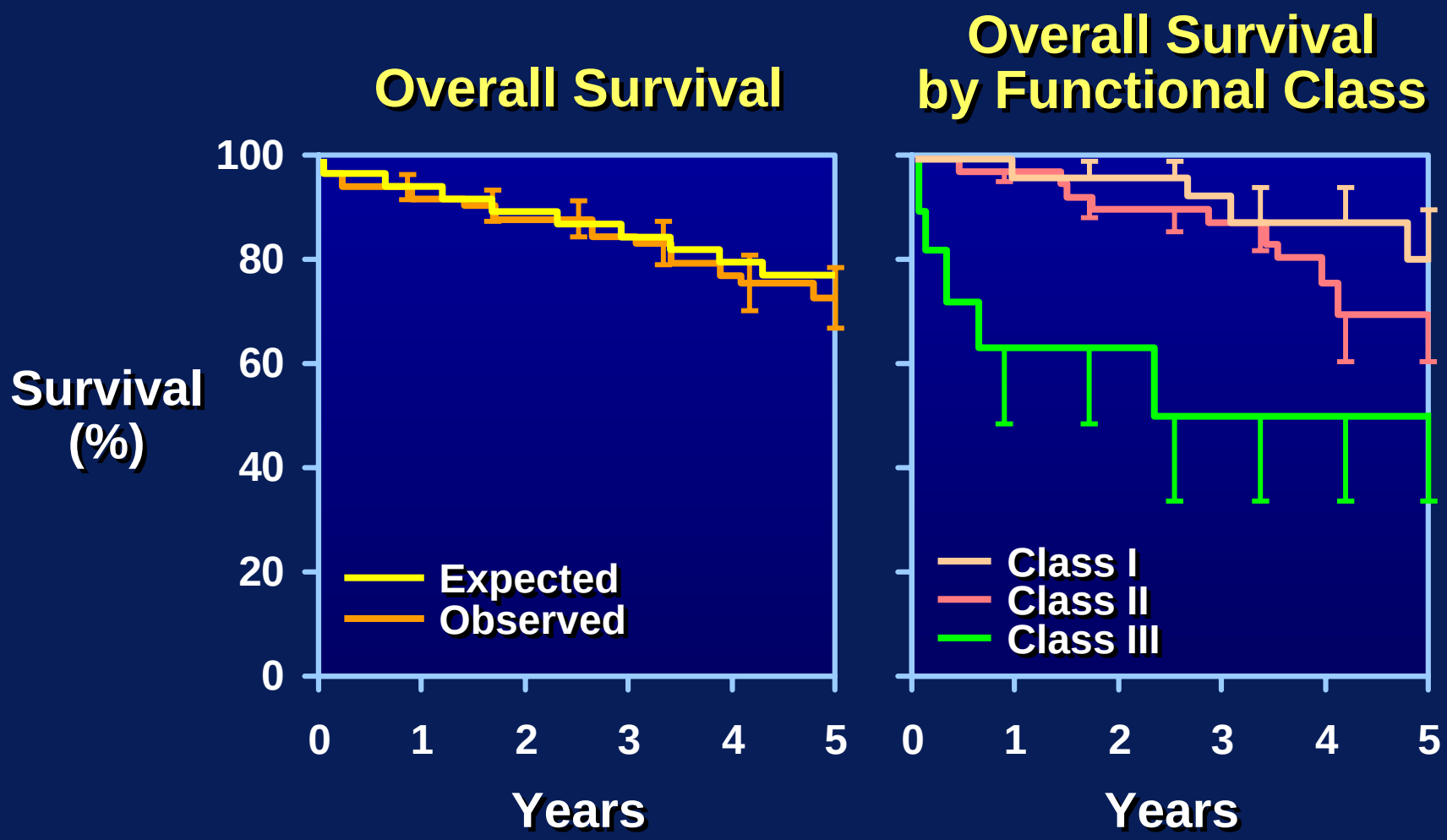


Lever H: Circ, 1989

mayo

CP939281-24

Survival
HOCM – Patients ≥65 Years Old



Fay: JACC, 1990

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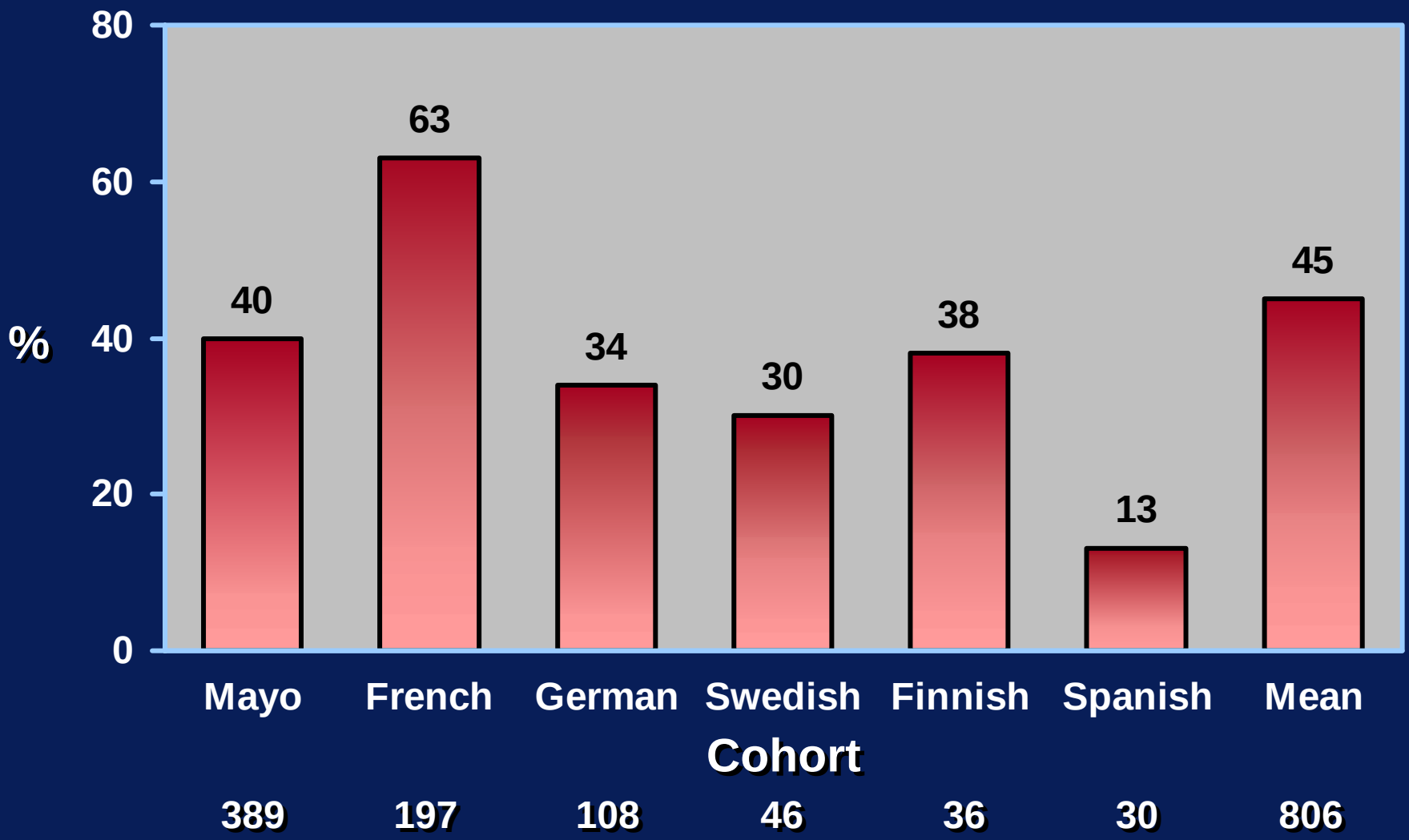
CP1183921-12

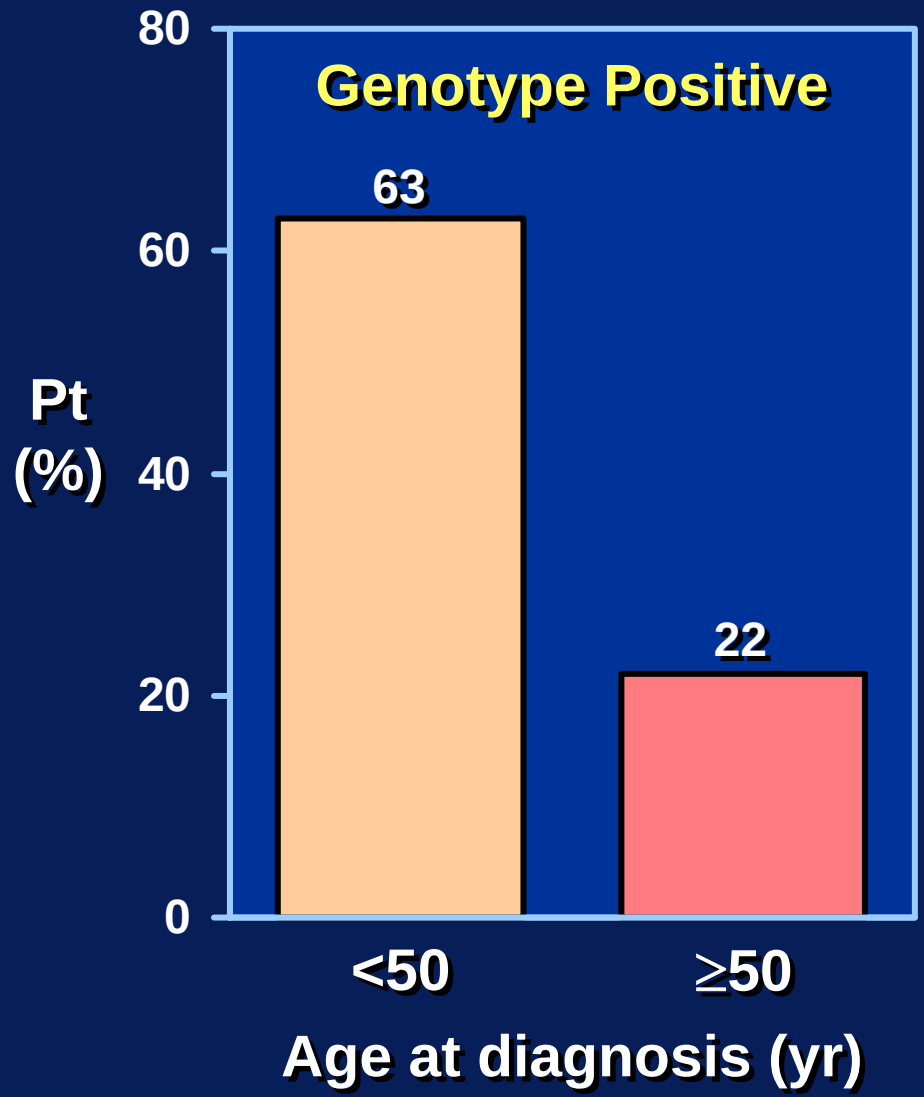
Sarcomeric Mutations Identified

7 Studies – 806 Patients



Genotype Phenotype Correlations and Age

- 382 pt
- 8 HCM-associated genes screened



Binder and Ommen

MAYO CLINIC

CP1173755-4

Genotype Phenotype Correlations and Age

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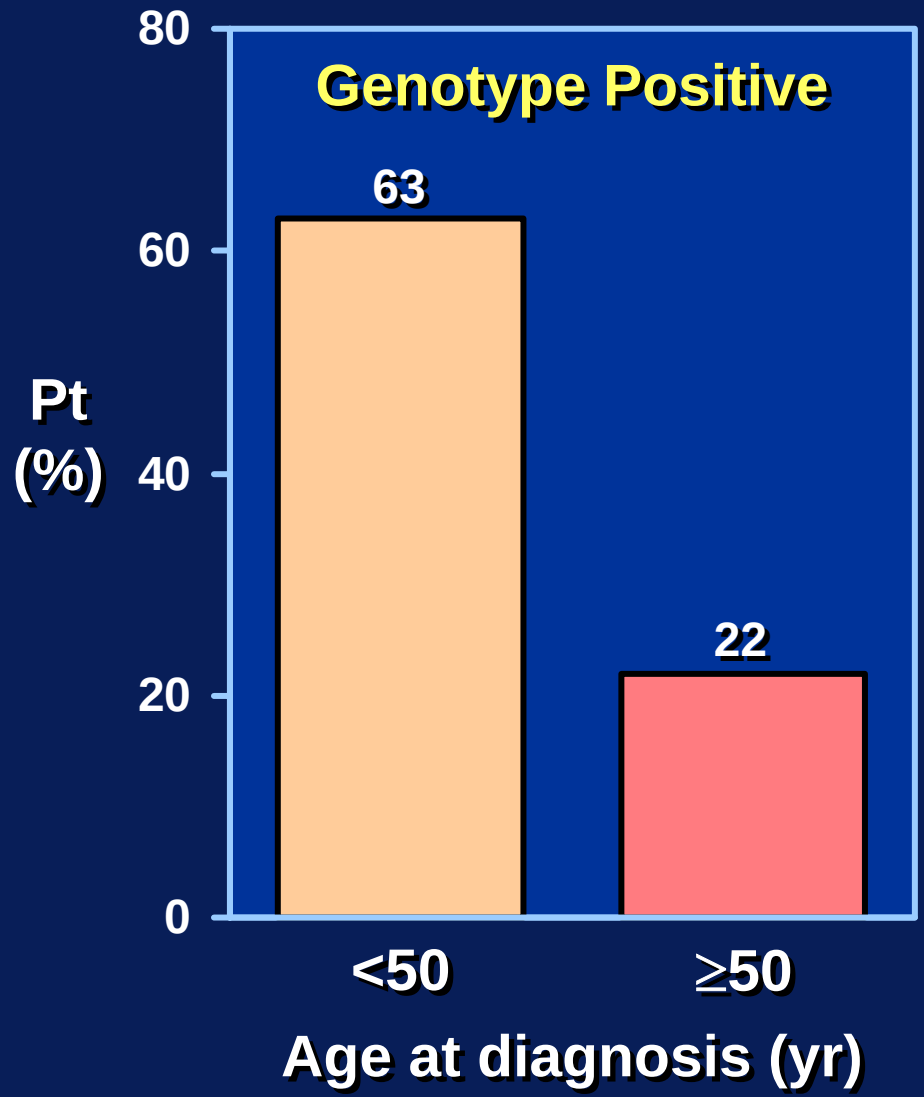
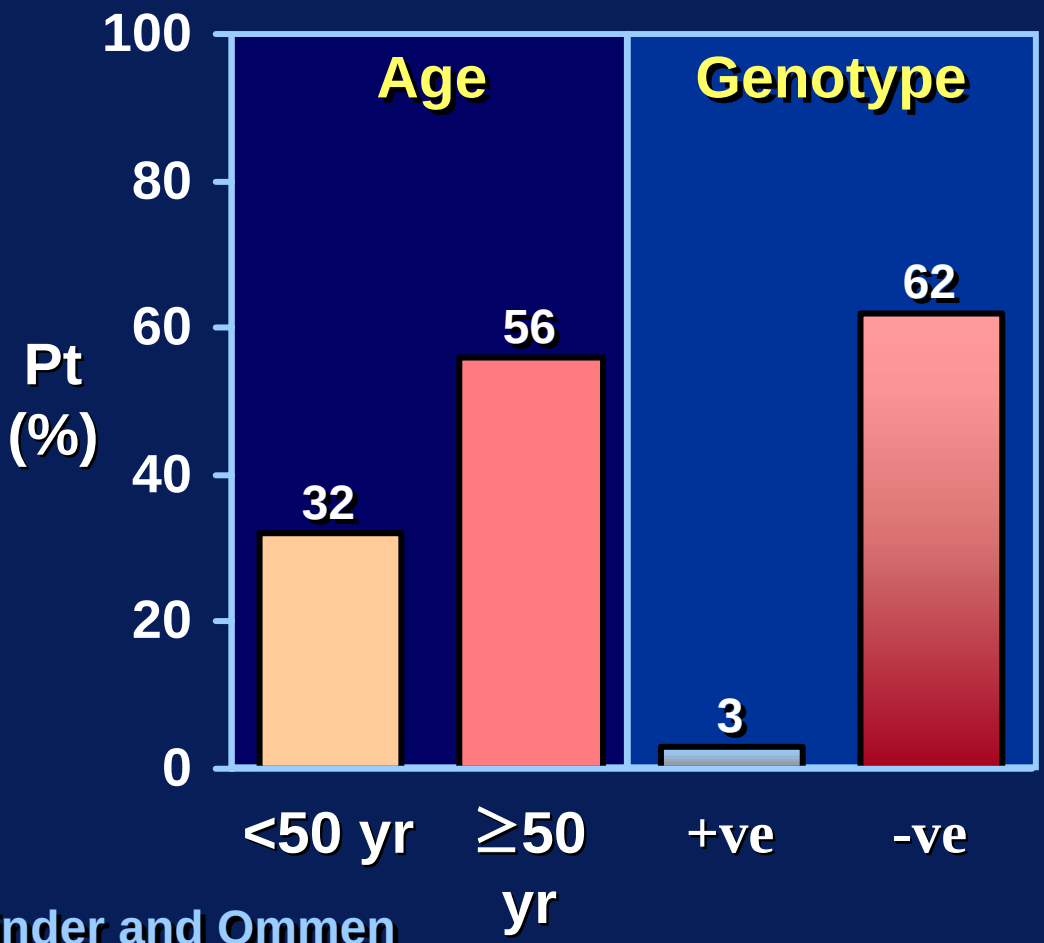


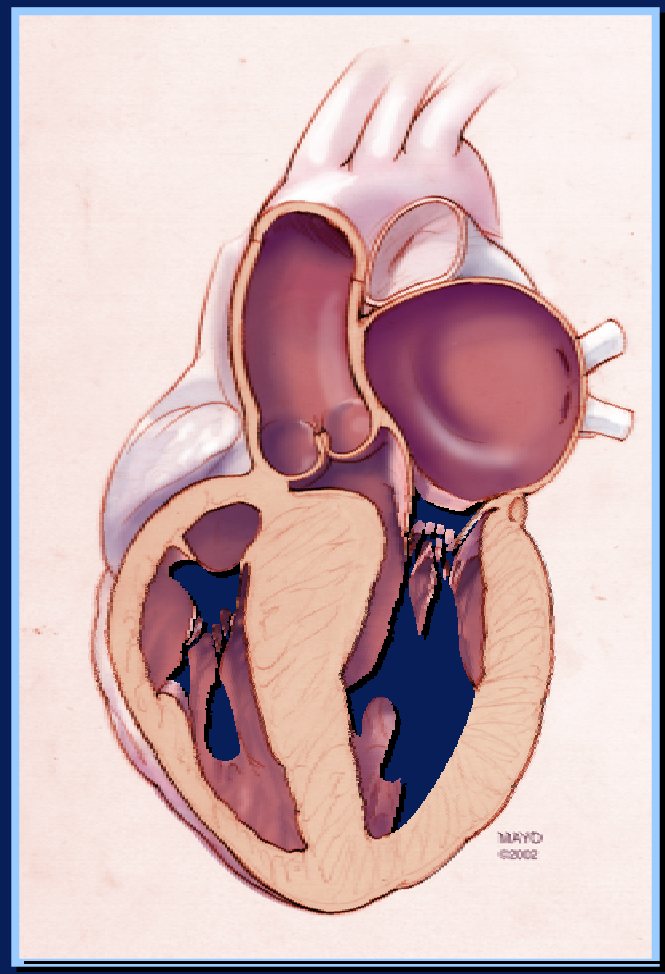
Binder and Ommen

MAYO CLINIC

CP1173755-4

"LVH" with Concave (Sigmoid) Septum (Normal LV Cavity Contour)



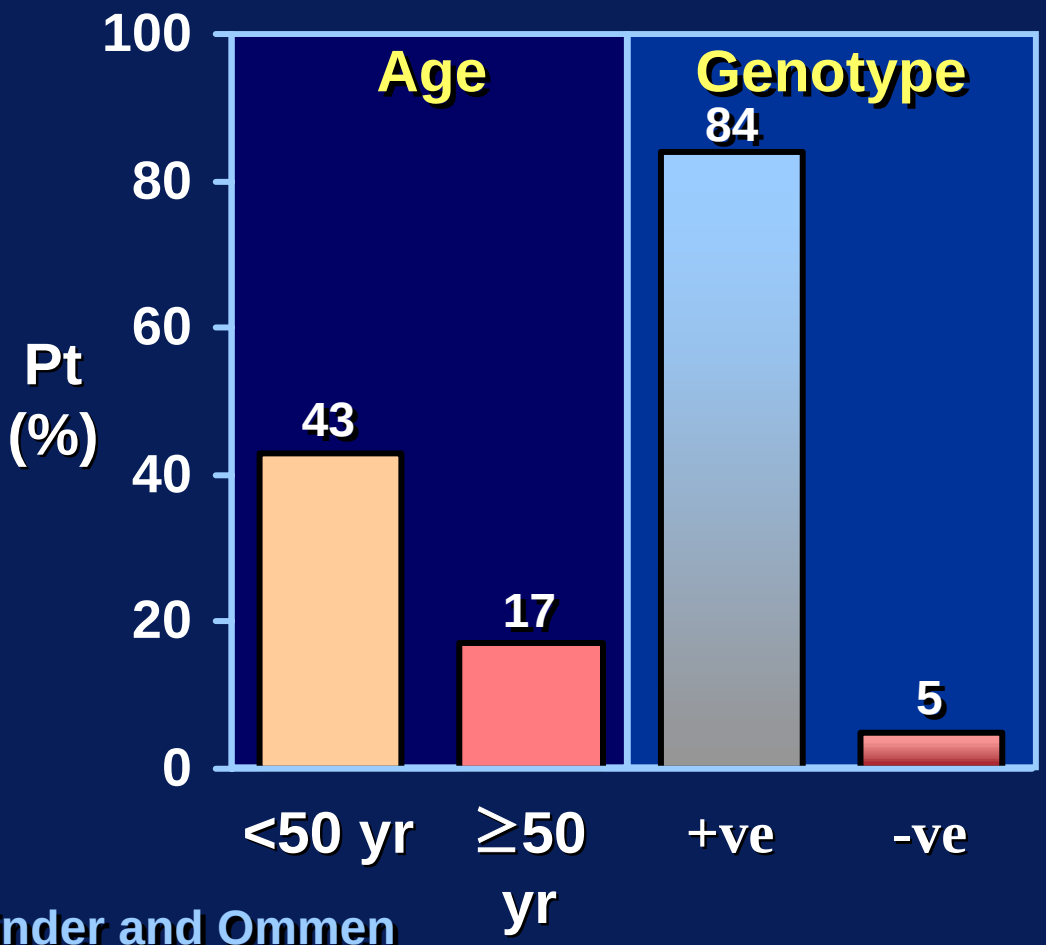


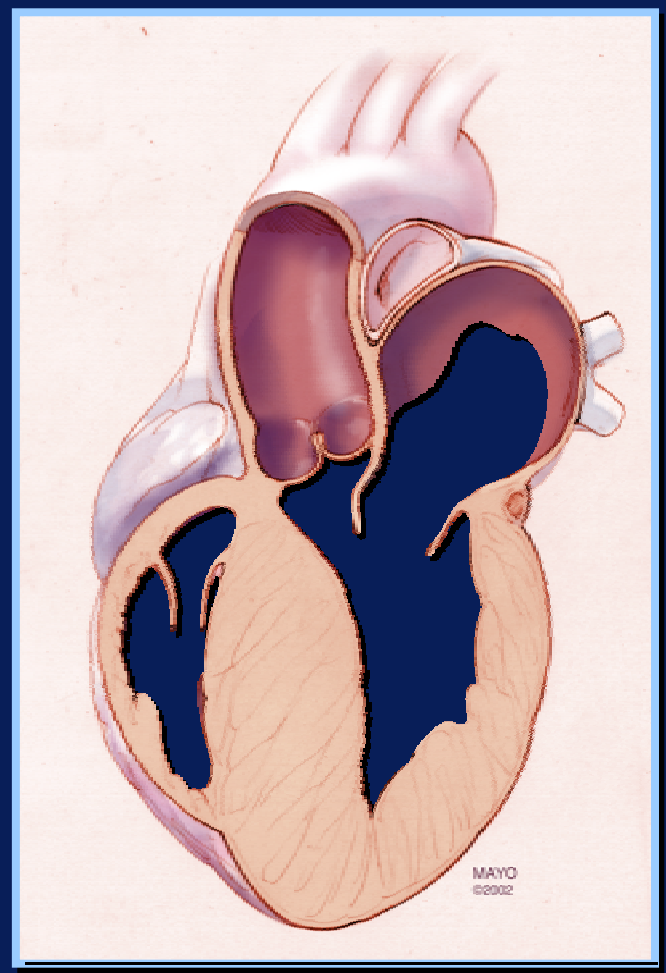
Binder and Ommen

MAYO CLINIC

CP1173755-2

"LVH" with Convex (Reversed) Septal Curvature





Binder and Ommen

Clinical experience

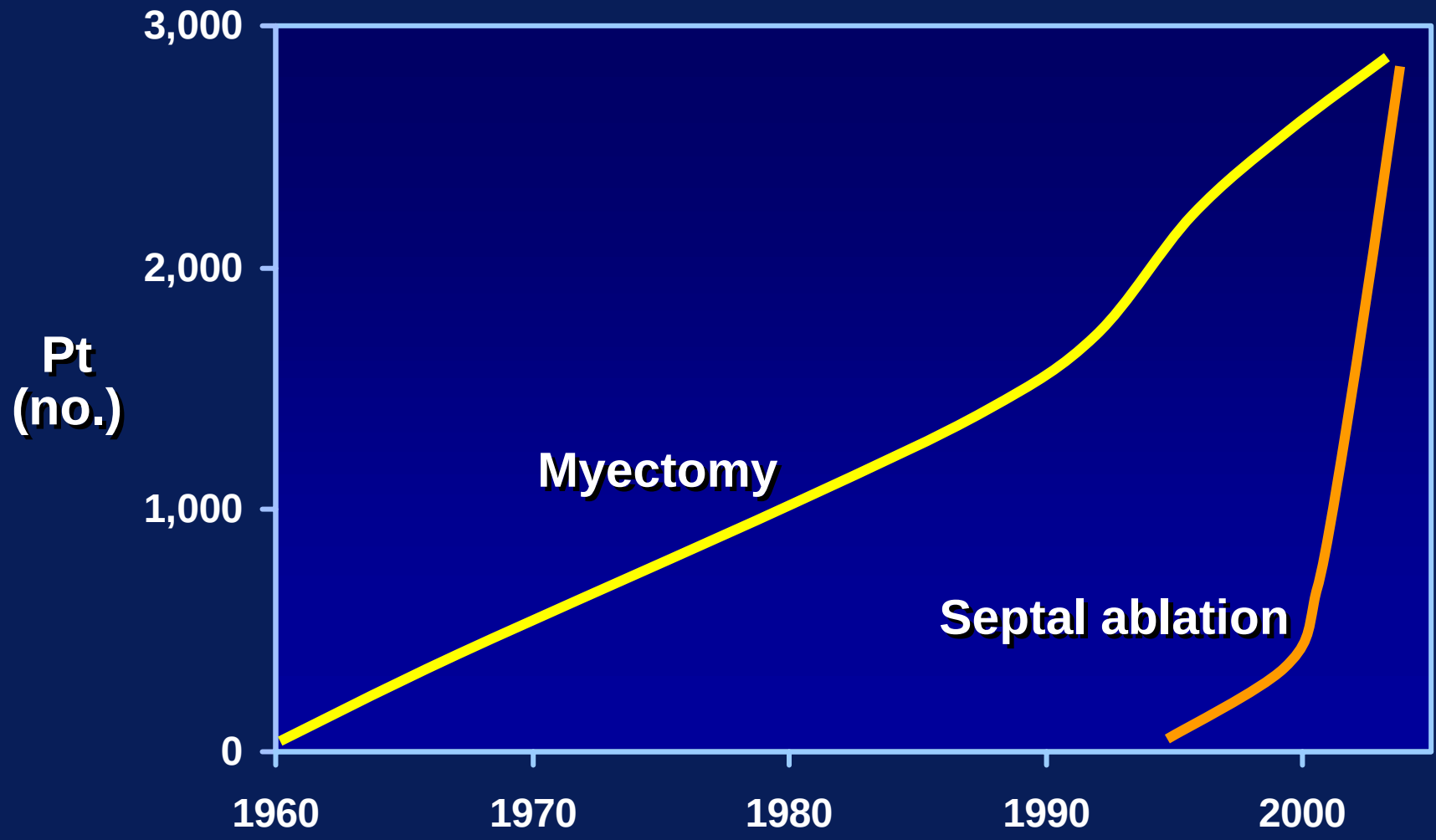
Making the same mistakes with increasing confidence over an increasing number of years

Evidence-based medicine

Making someone else's mistakes instead of your own

O'Donnell M: A Sceptic's Medical Dictionary

Patient Selection Criteria??????



Nishimura R

MAYO CLINIC

CP1140917-1

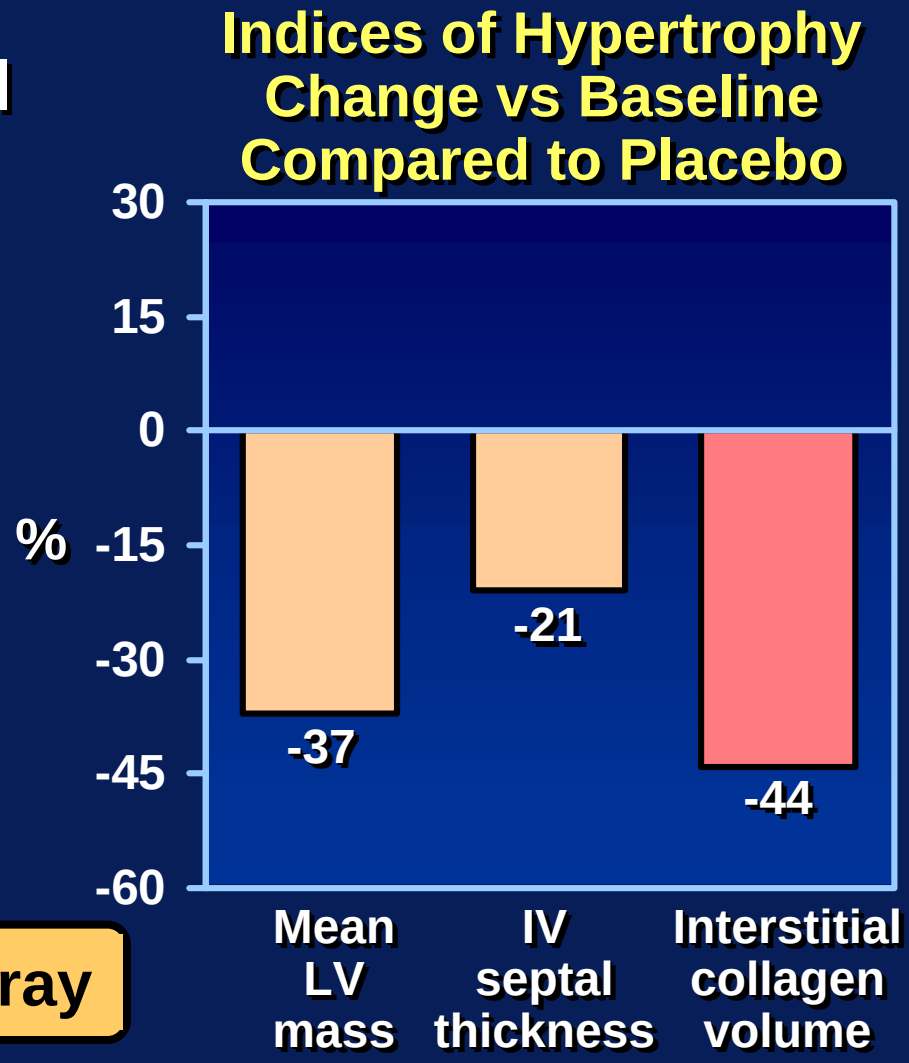
Simvastatin and Regression of LVH Experimental HCM

- Transgenic rabbit model
- β MHC mutant

Simvastatin

- Inhibits Ang-II mediated myocyte hypertrophy
- Blocks intracellular signaling molecules involved in LVH

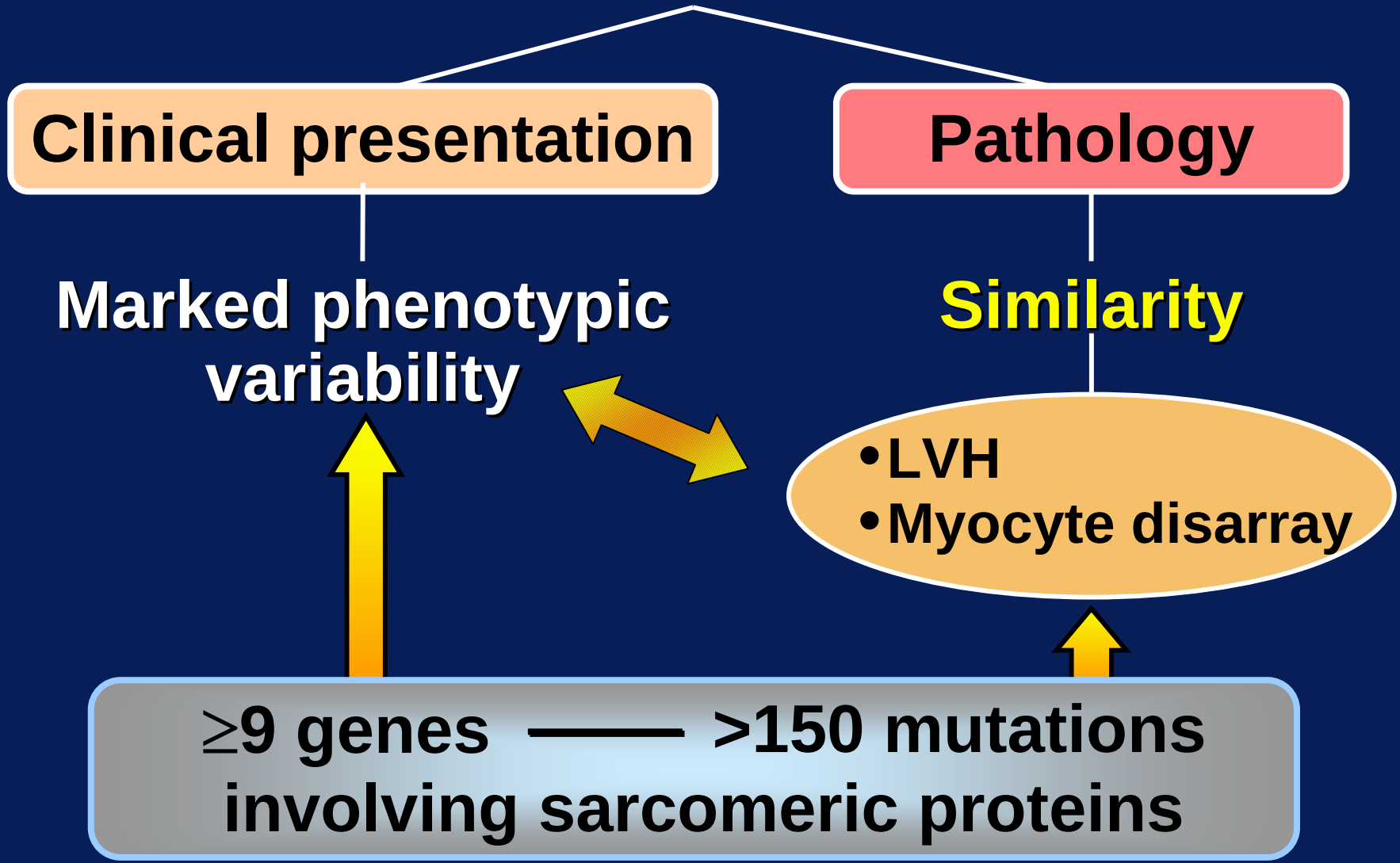
No change in myocyte disarray



Patel and Marian: Circ, 2001

Hypertrophic Cardiomyopathy

A Paradox?



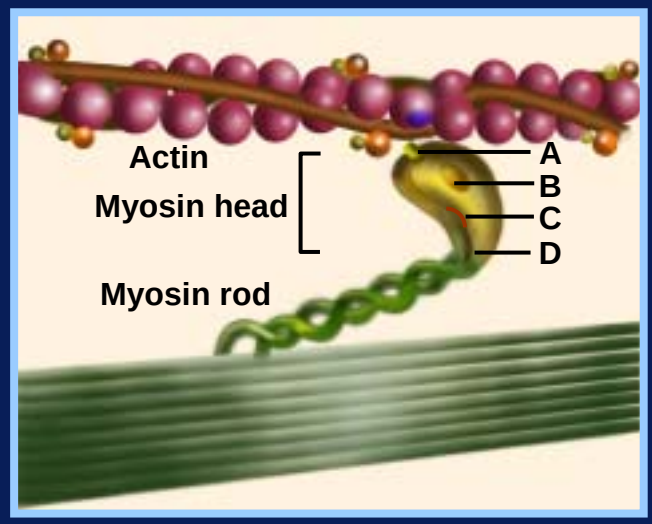
βMHC Gene Mutations and Prognosis

70 probands

βMHC mutations
21%

148 family members

Mutations
50%

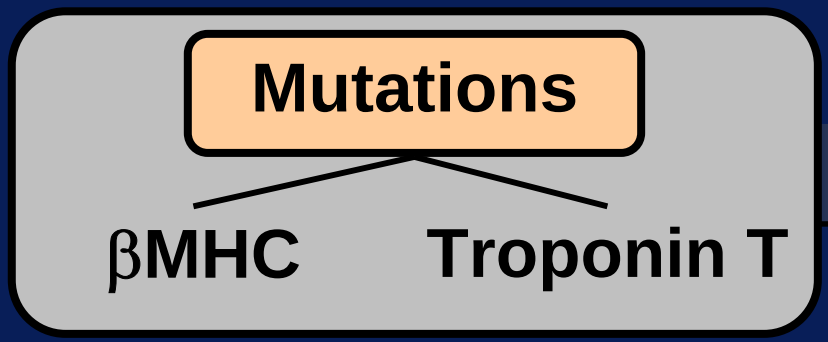


A = actin binding site
B = active ATP binding site
C = essential light chain binding site
D = head-rod junction

Predictors of mortality
Missense mutations – A P=0.003
– D P=0.03

Woo: Heart, 2003

Mutations in Sarcomeric Proteins and HCM/IDC



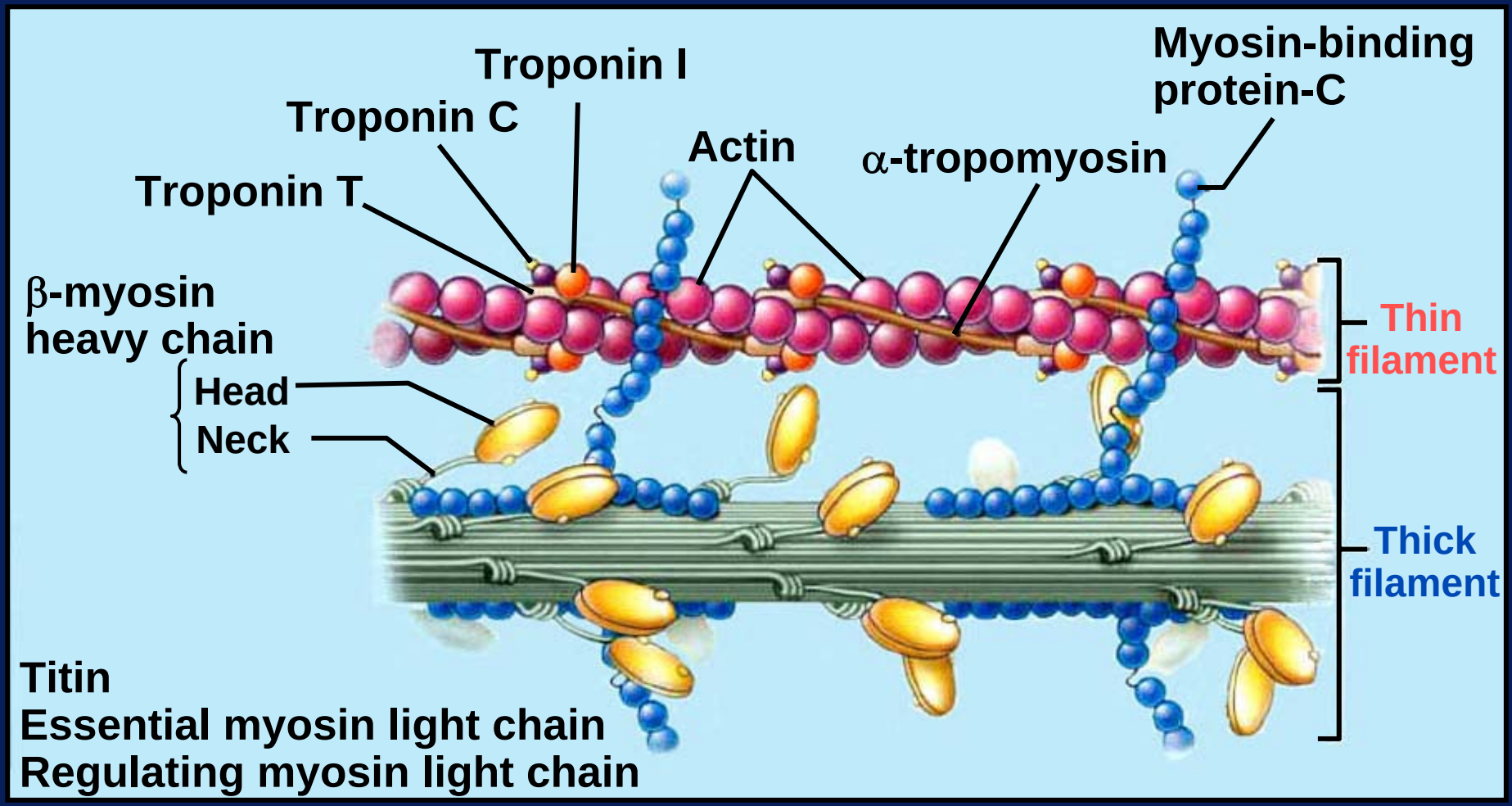
Idiopathic dilated cardiomyopathy

Li: Circ, 2001
Kamisago: NEJM, 2000

Familial HCM

Olson: J Mol Cell Cardiol, 2000

Mutations in Sarcomeric Proteins



Profound genetic heterogeneity: ≥10 genes, >400 mutations

Nabel: NEJM, 2003

Molecular Genetics

The Future

Risk Stratification and Therapeutic Strategies

High risk

- Young pt
- Positive FH of SCD
- Syncope
- NSVT – ?
- Exercise-induced hypotension?
- LVWT ≥25 mm?
- Associated CAD

Intermediate risk

- Symptomatic patients

Low risk

- Asymptomatic
- Elderly patients

How would this be altered by genotyping?

Therapeutic objectives

- Improved survival
- Relieve symptoms
- Reassurance
- Surveillance
- Treat hypertension

Risk Stratification and Therapeutic Strategies

High risk

- Young pt
- Positive FH of SCD
- Syncope
- NSVT – ?
- Exercise-induced hypotension?
- LVWT ≥25 mm?
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Intermediate risk

- Symptomatic patients

Low risk

- Asymptomatic
- Elderly patients

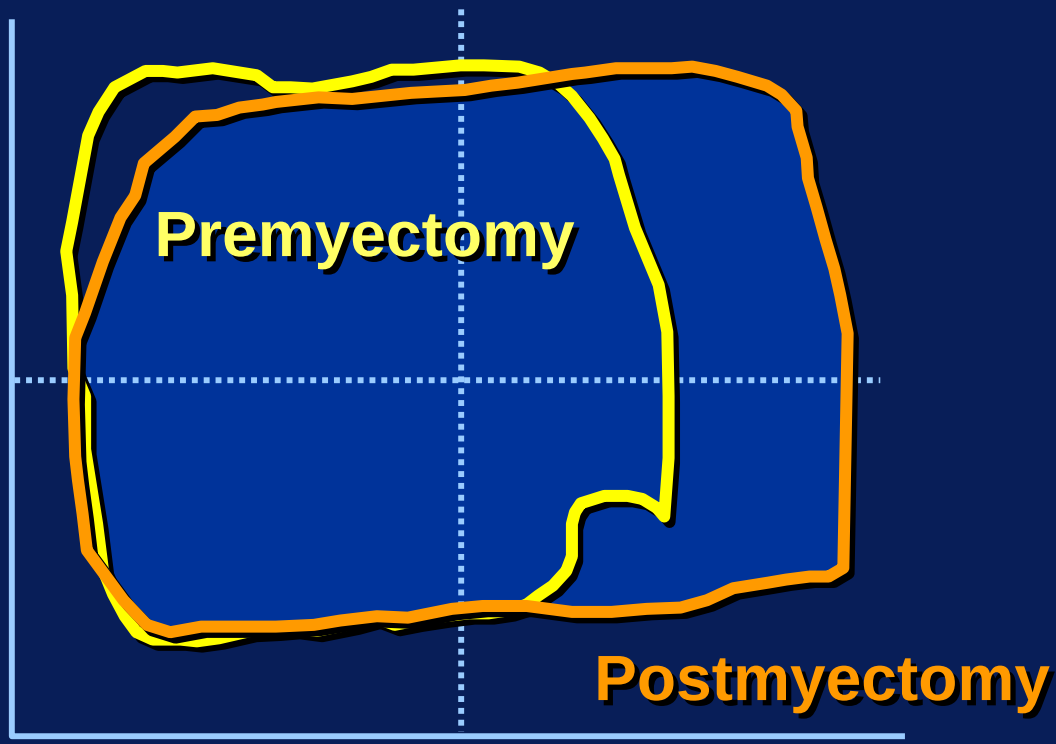
Therapeutic objectives

- Improved survival
- Relieve symptoms
- Reassurance
- Surveillance
- Treat hypertension

Surgery for Apical HCM
1996-2003 – Mayo Clinic

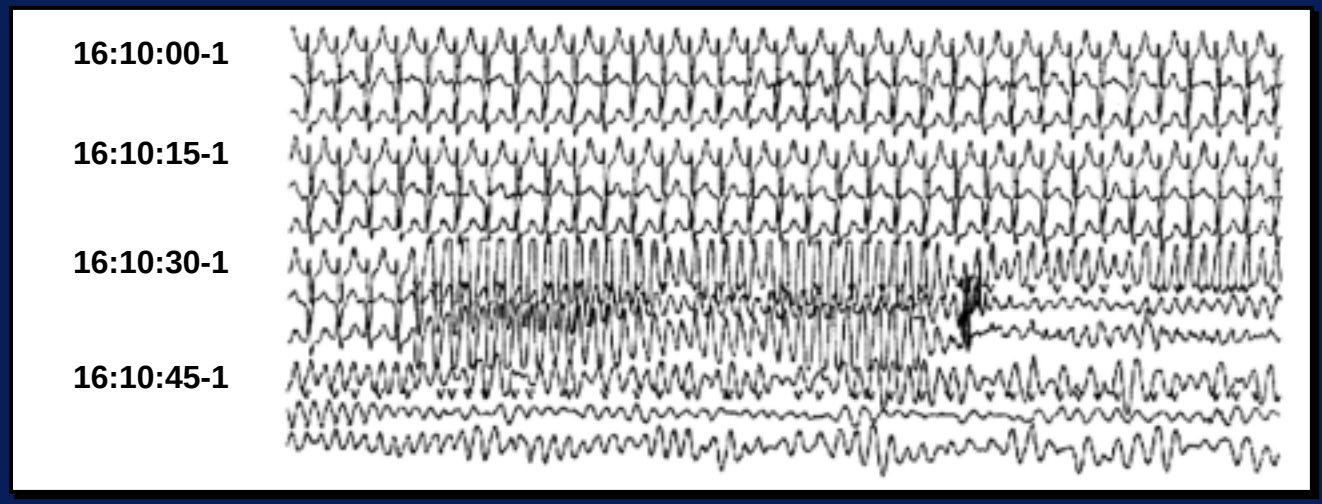
- 14 patients
- 1 perioperative death

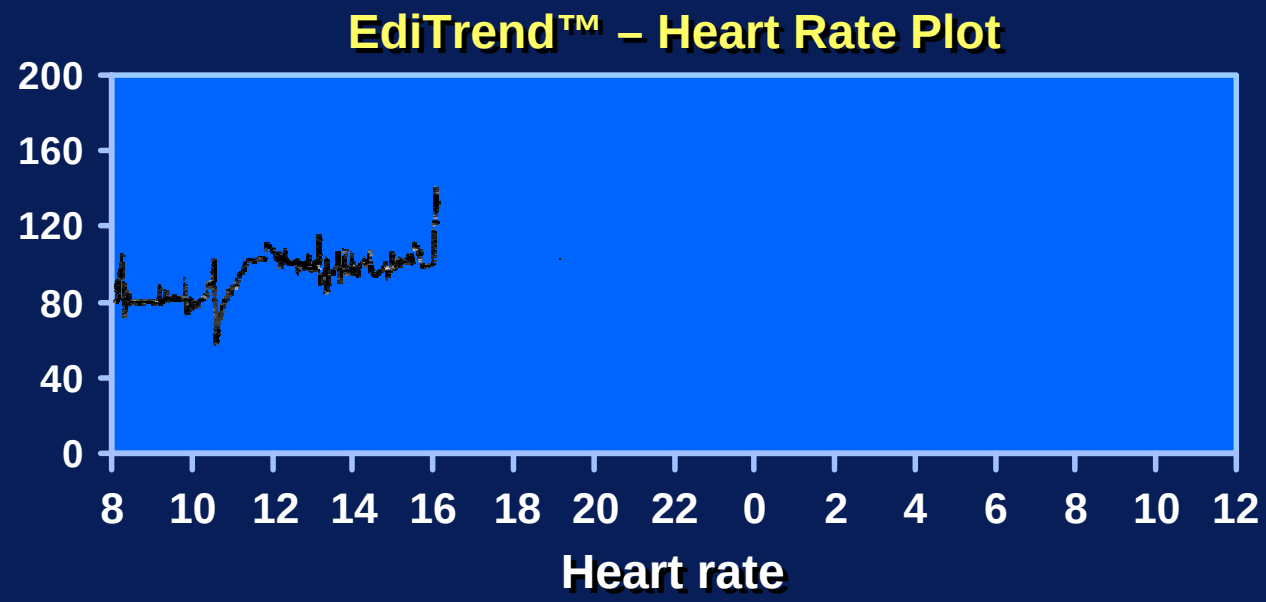
Changes in Diastolic Dysfunction

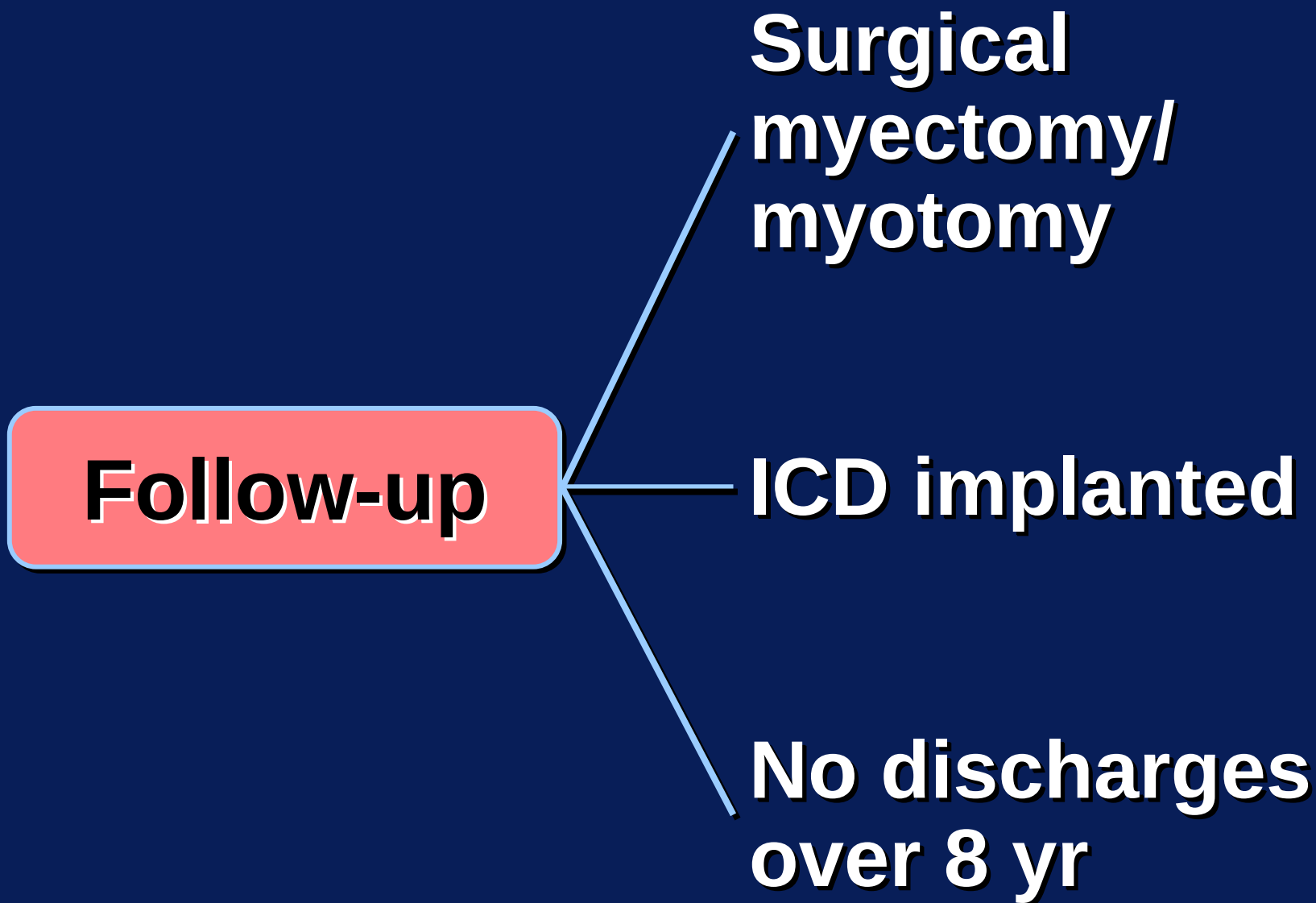


47-Year-Old Female with Angina and HCM

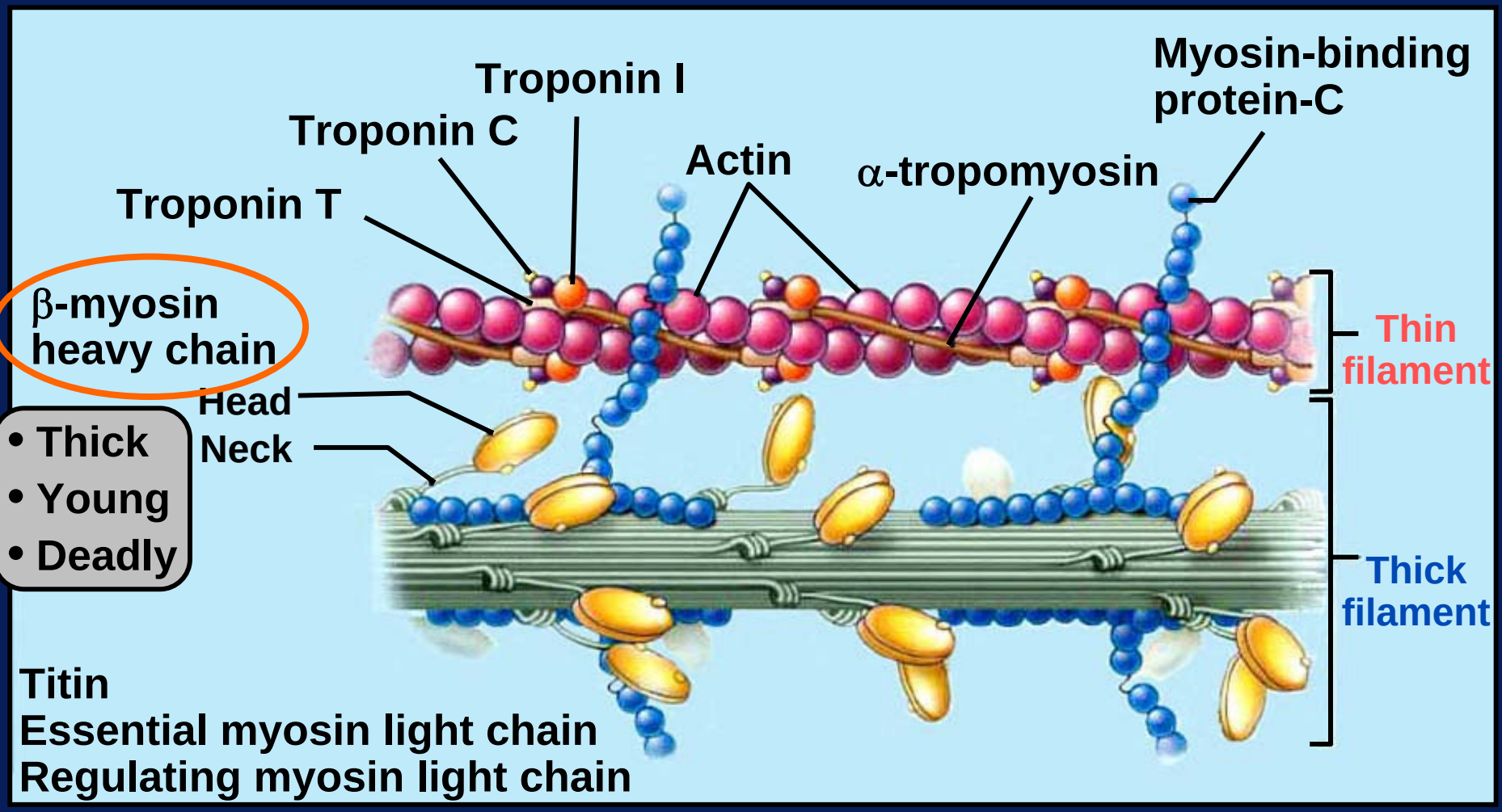
No Prior History of Syncope






Follow-up
Surgical myectomy/ myotomy
ICD implanted
No discharges over 8 yr

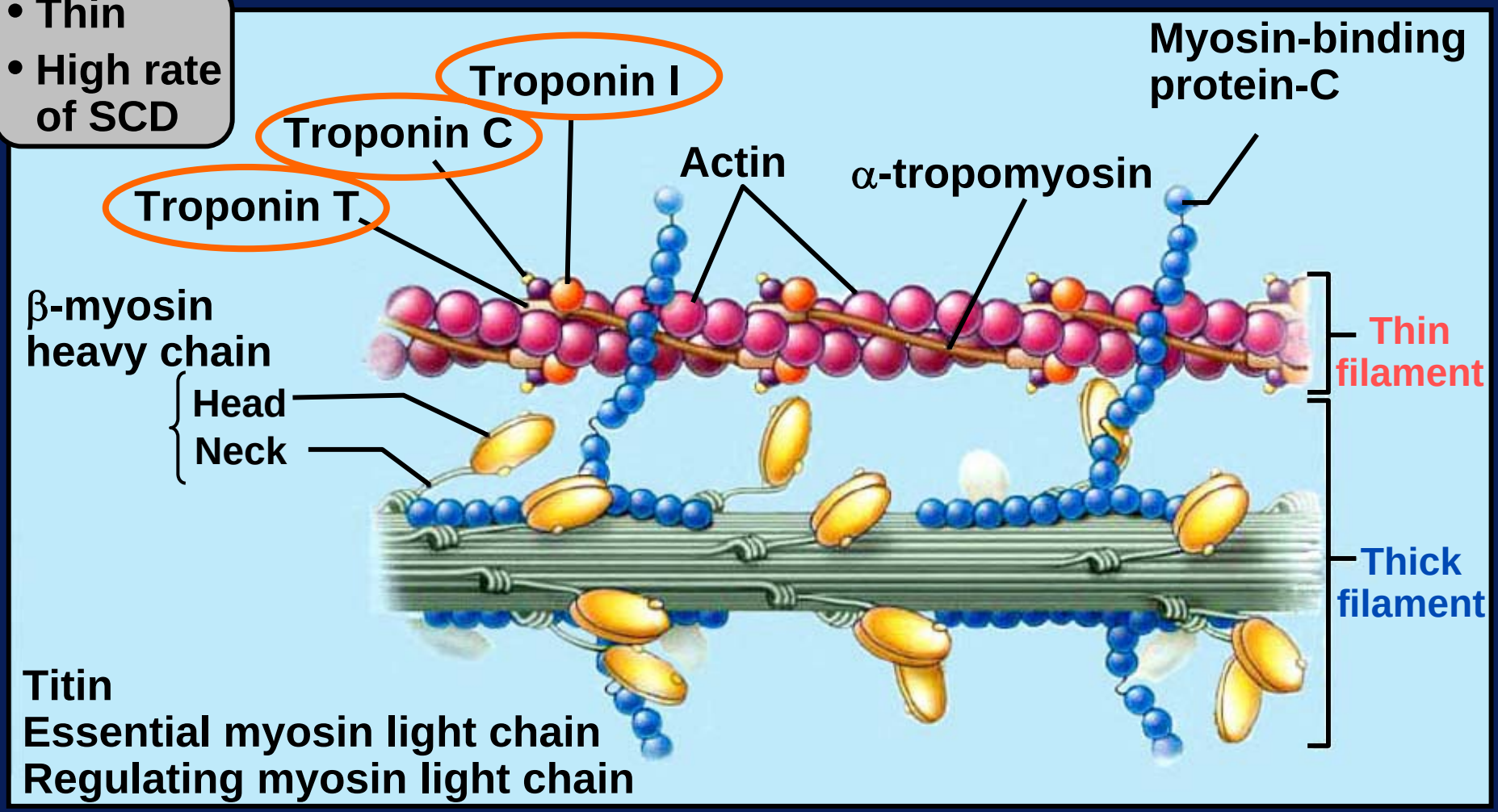
Mutations in Sarcomeric Proteins



Nabel: NEJM, 2003

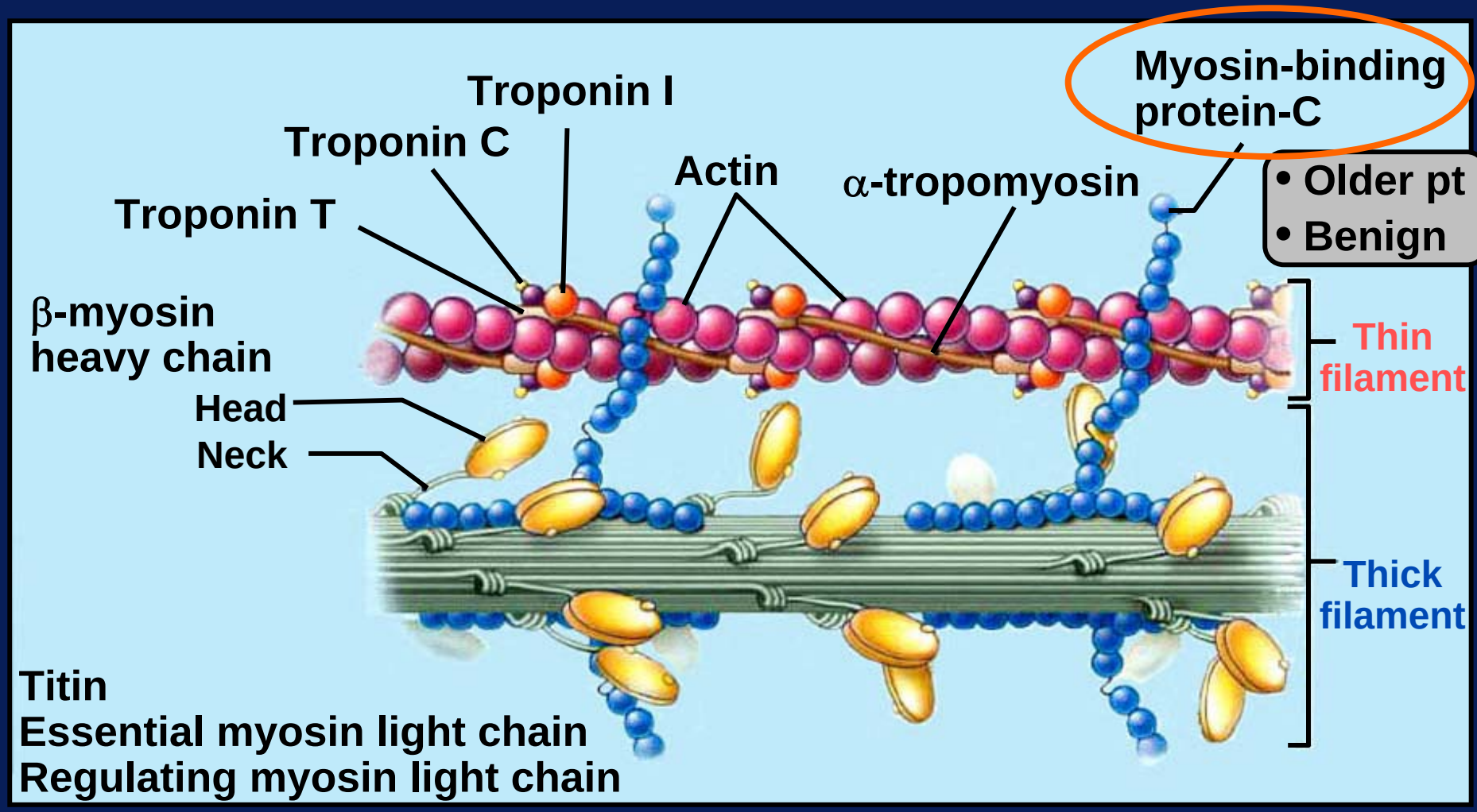
Mutations in Sarcomeric Proteins

- Thin
- High rate of SCD



Nabel: NEJM, 2003

Mutations in Sarcomeric Proteins



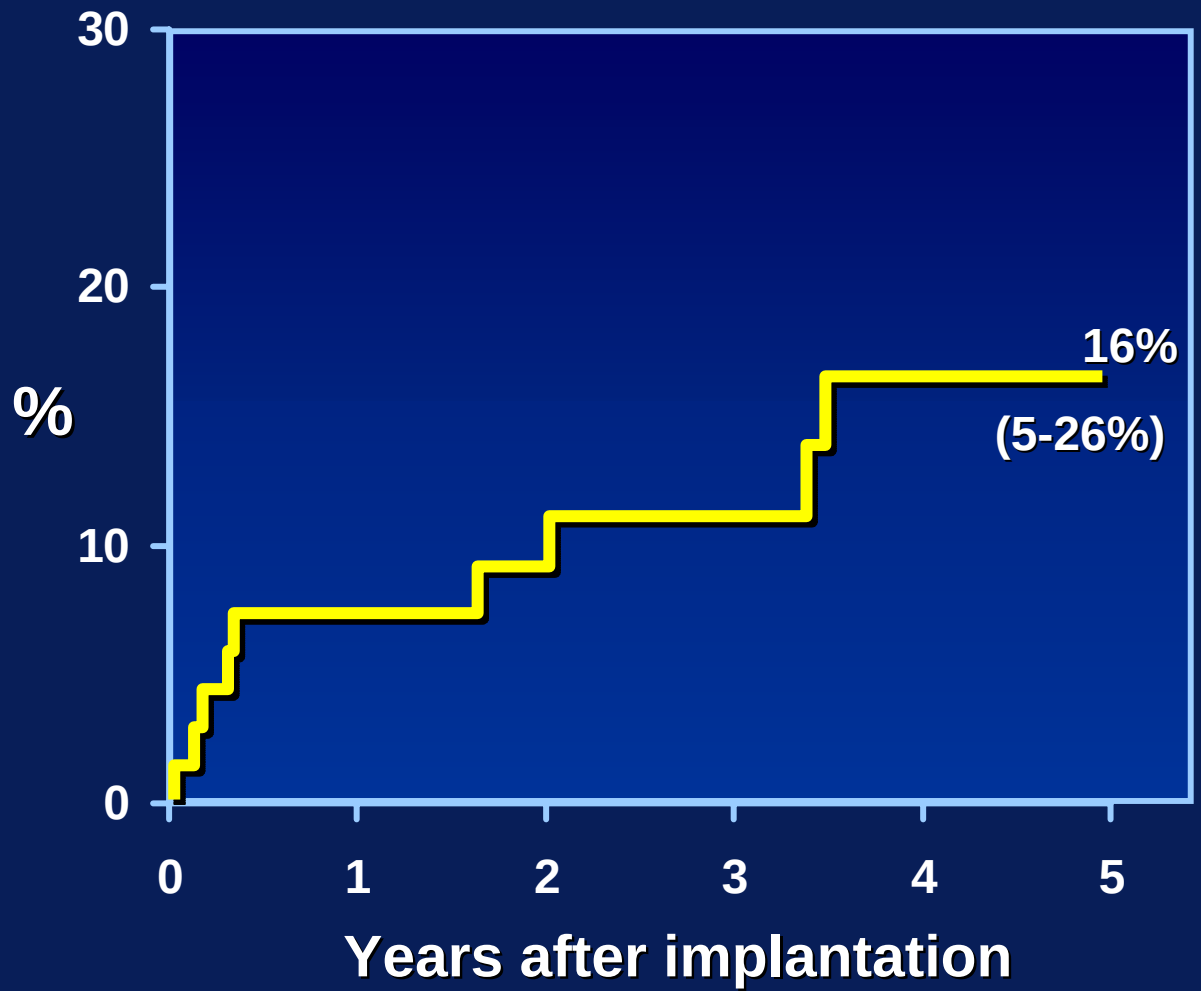
Nabel: NEJM, 2003

Cumulative Rate of First Appropriate ICD Discharges/ATP

- 68 patients

Prophylactic ICD placement

Risk factors (no.)
1 – 34%
2 – 47%
≥3 – 19%

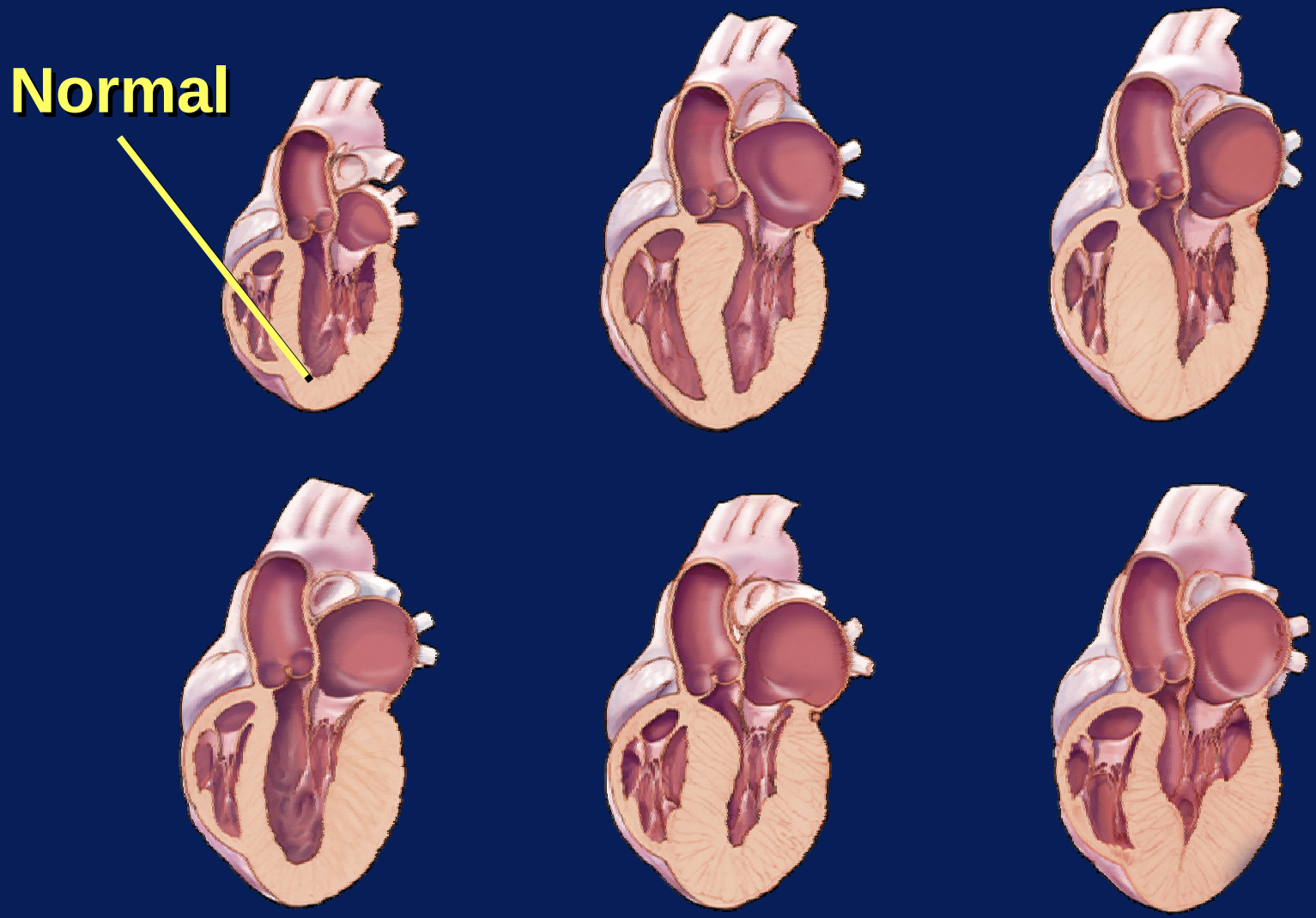


Cha, in press

MAYO CLINIC

CP1192752-8

Patterns of Hypertrophy



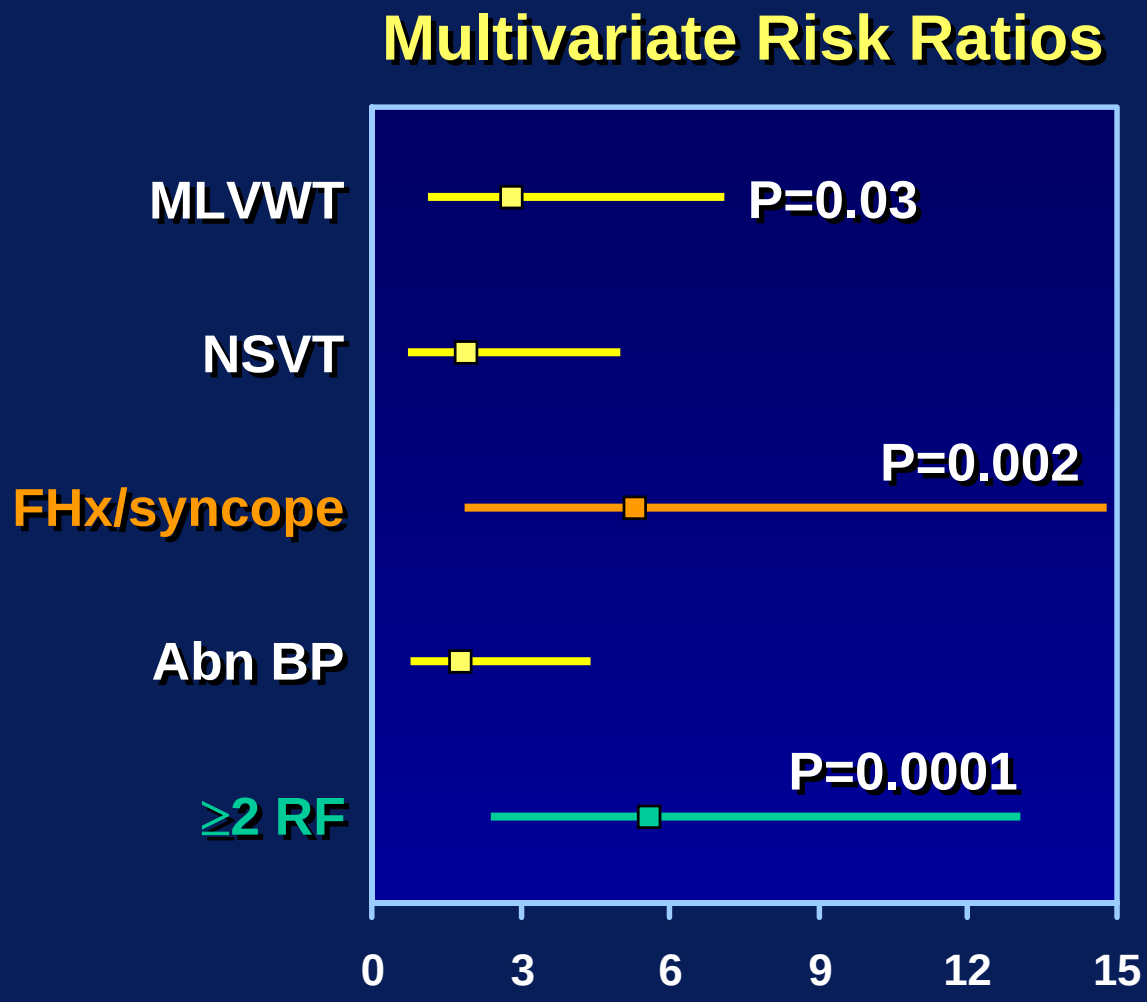
Risk of SCD in Hypertrophic Cardiomyopathy

- 368 pt
- Mean F-U 3.6±2.5 yr

Family Hx of SCD

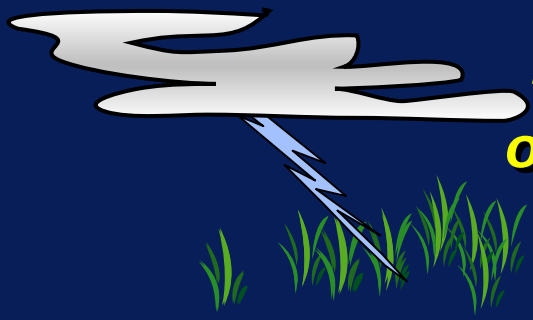
SCD in ≥2 first degree relatives <40 years old

Univariate analysis
RR 1.9 (95% CI 0.8-4.5)
P=0.15



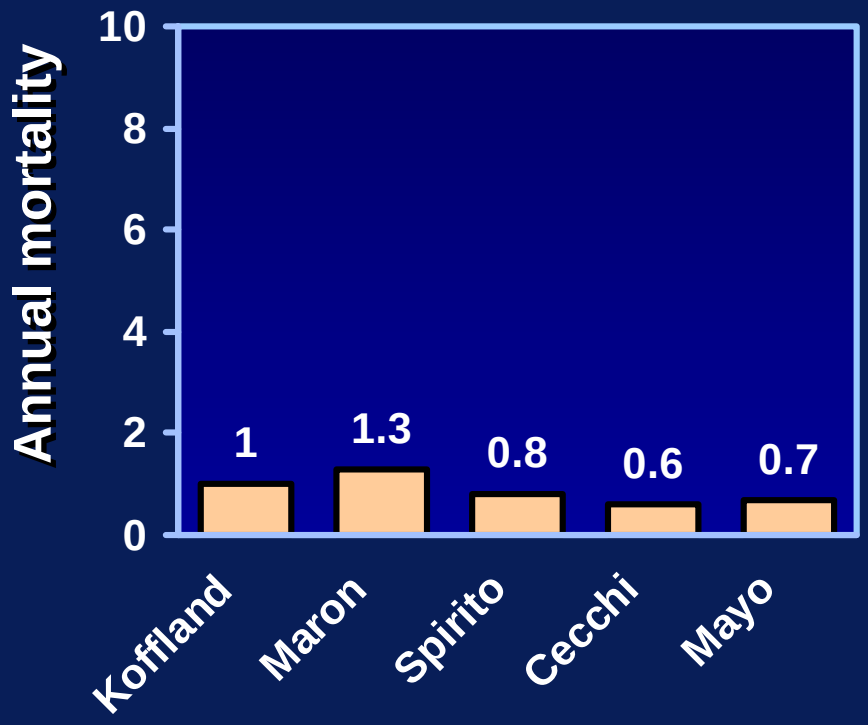
Elliott: JACC, 2000

Sudden "Unexpected" Cardiac Death and HCM

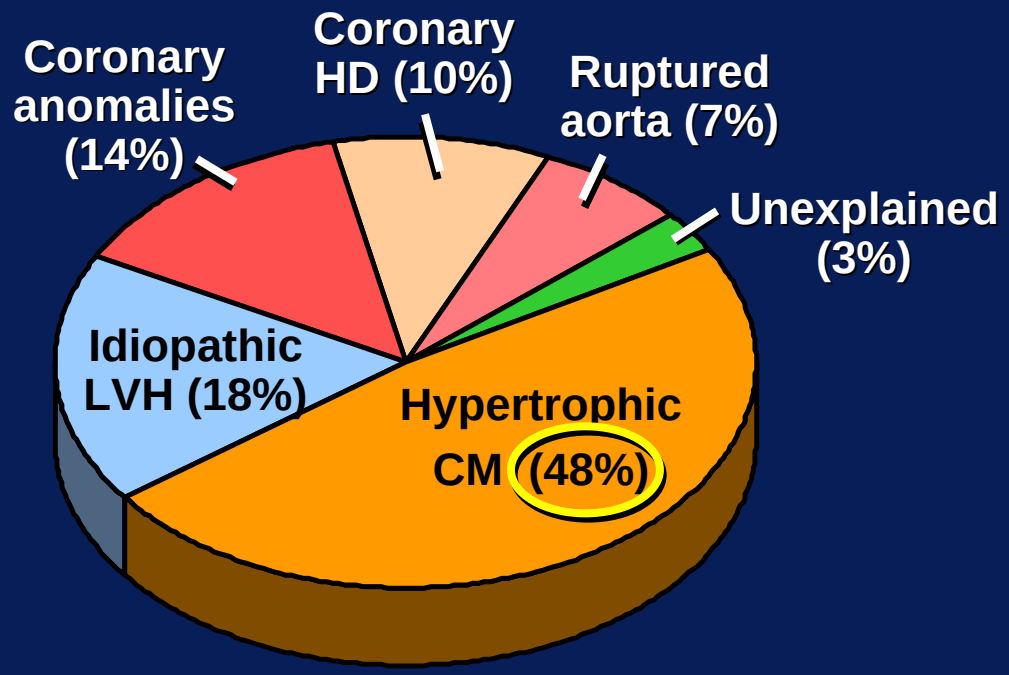


"A bolt out of the blue!"

Low Annual Mortality Overall



Causes of Death in Competitive Athletes Aged <35 yr



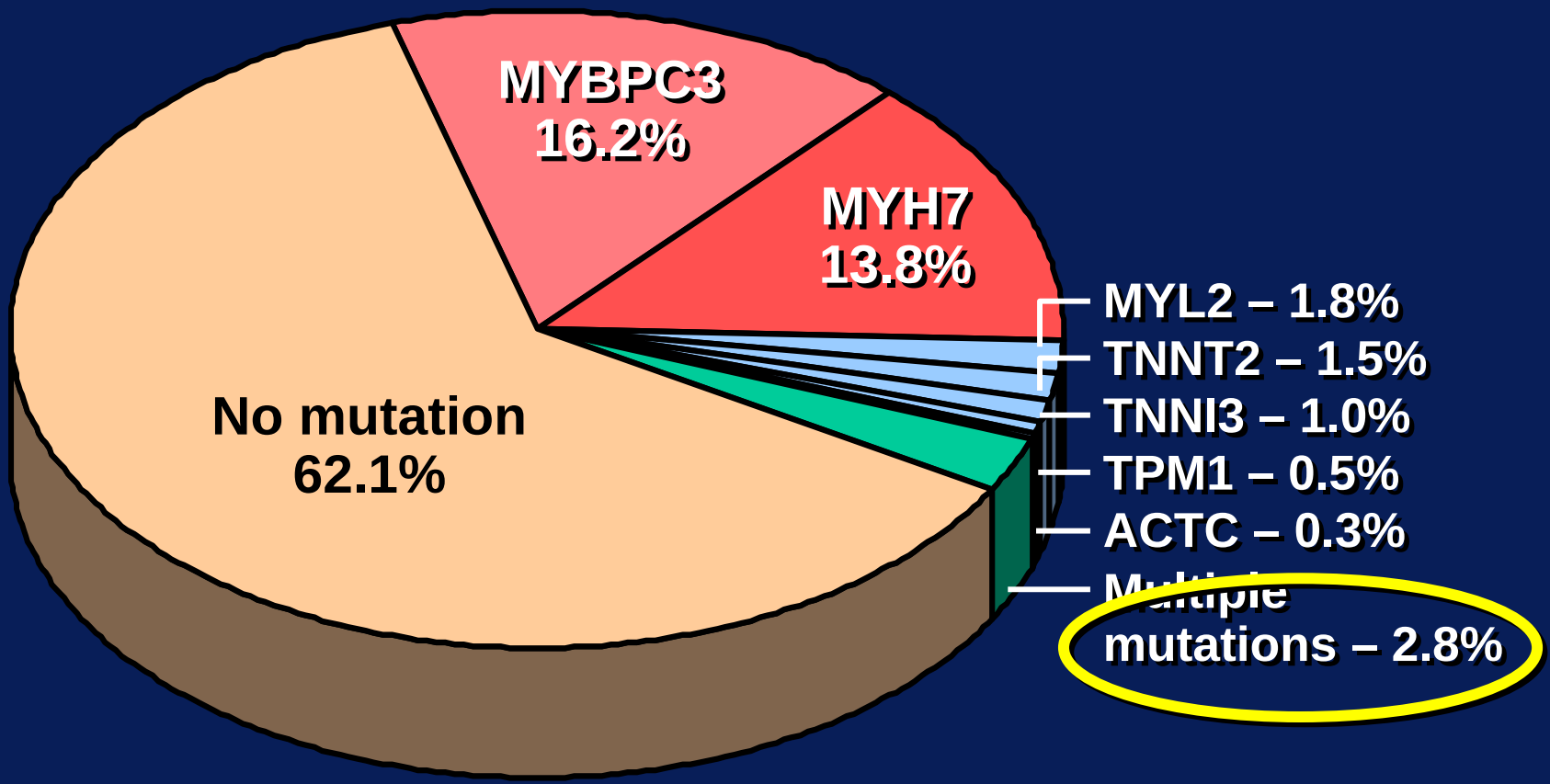
≤35 years

Maron: JACC, 1989

CP1171106-4

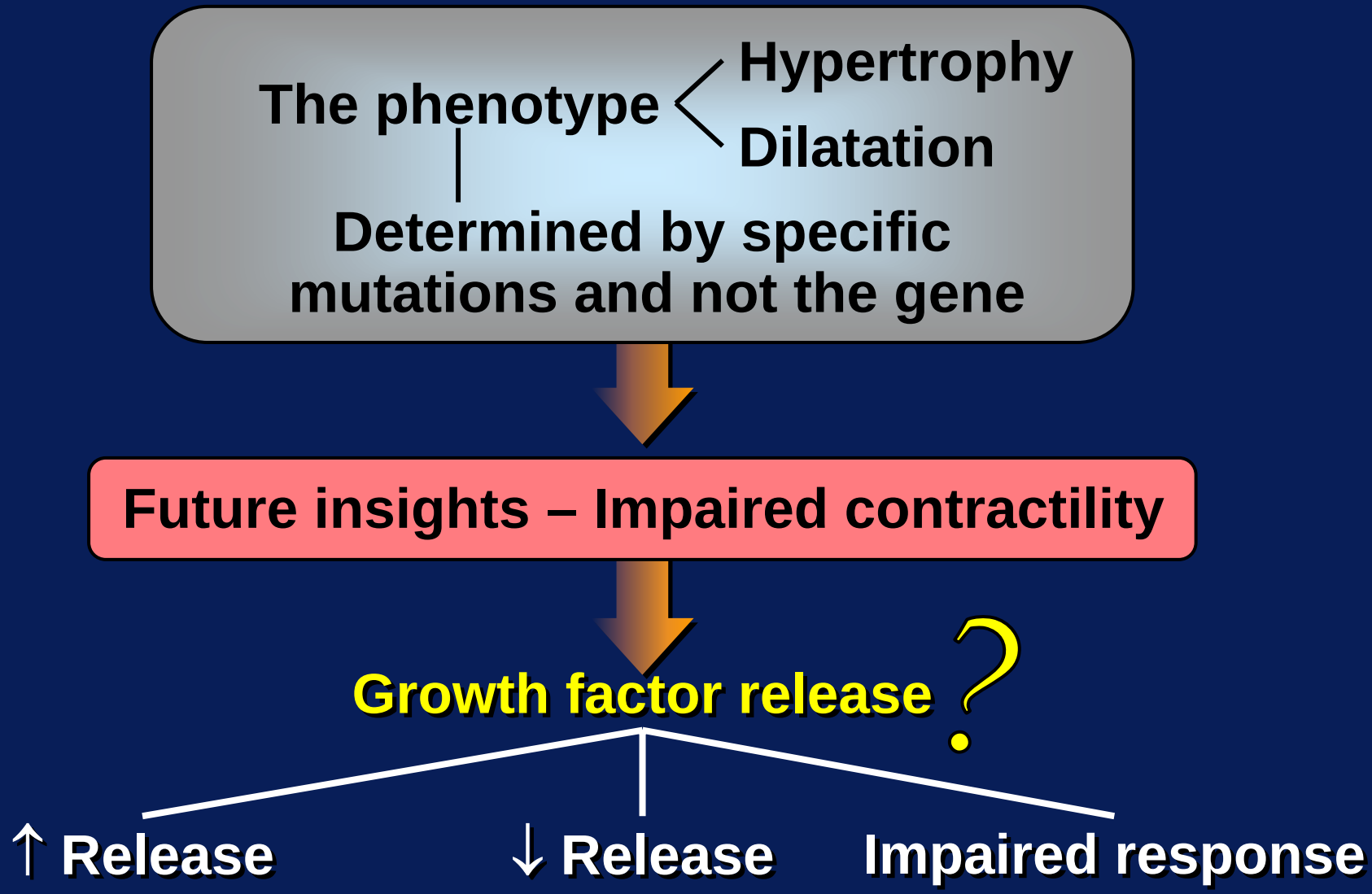
Distribution of Sarcomeric Mutations

389 Unrelated HCM Patients
Mayo Clinic 1997-2001



Van Driest and Ackerman

Mutations Causing Dilatation vs Hypertrophy



Limitations of Genotype/Phenotype Correlation Studies

Mutations

- Low frequency of each causal mutation
- Unknown roles of noncoding mutations
- Unknown sens/spec of current mutation detection technologies

Families

- Small number of families with identical mutations

Phenotypic expression

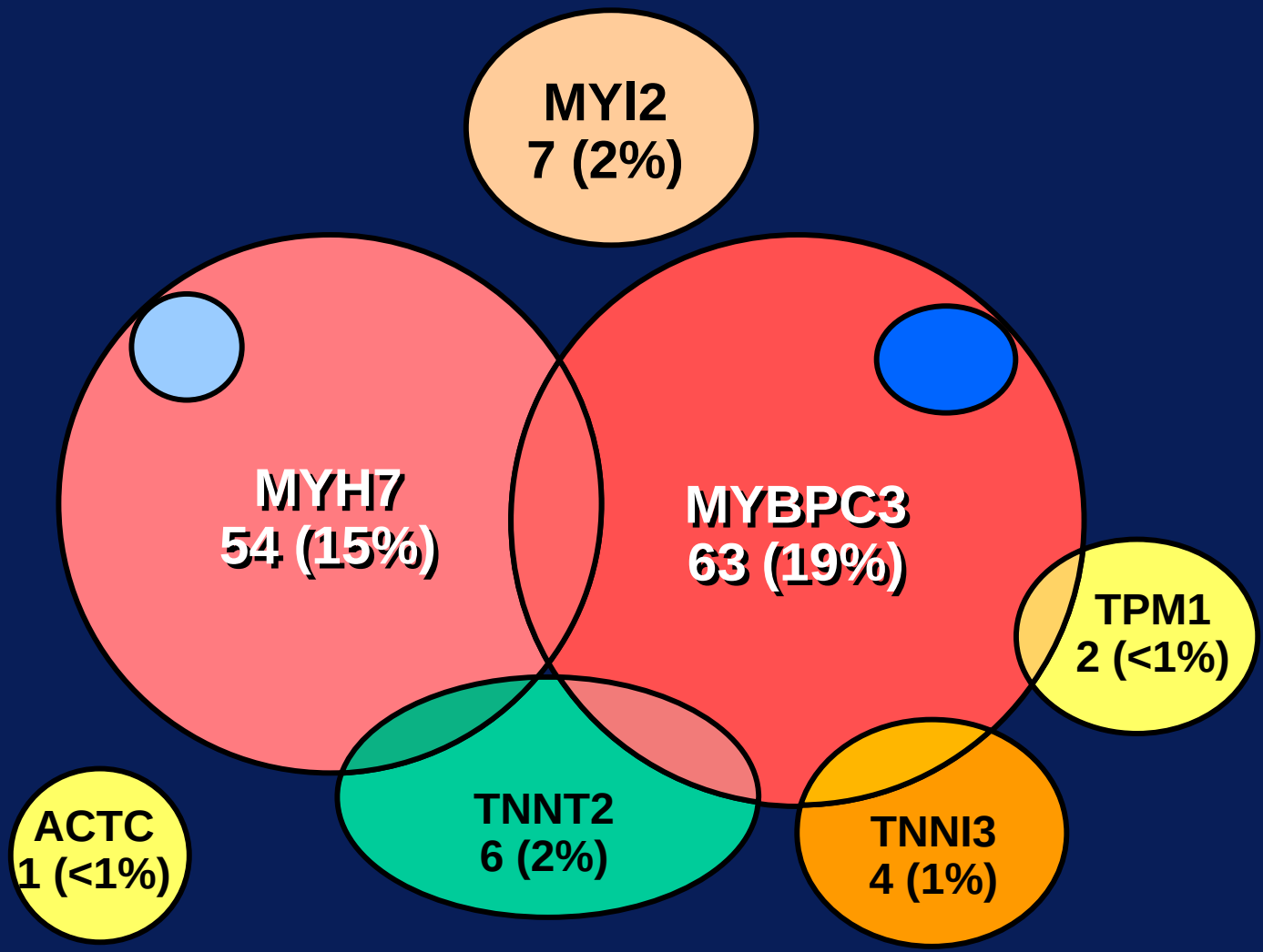
- Marked variability in affected individuals

?

Effects of modifier genes and environmental factors

Genotypes in 389 Mayo Clinic Outpatients with HCM

Genotype Positive – 35%

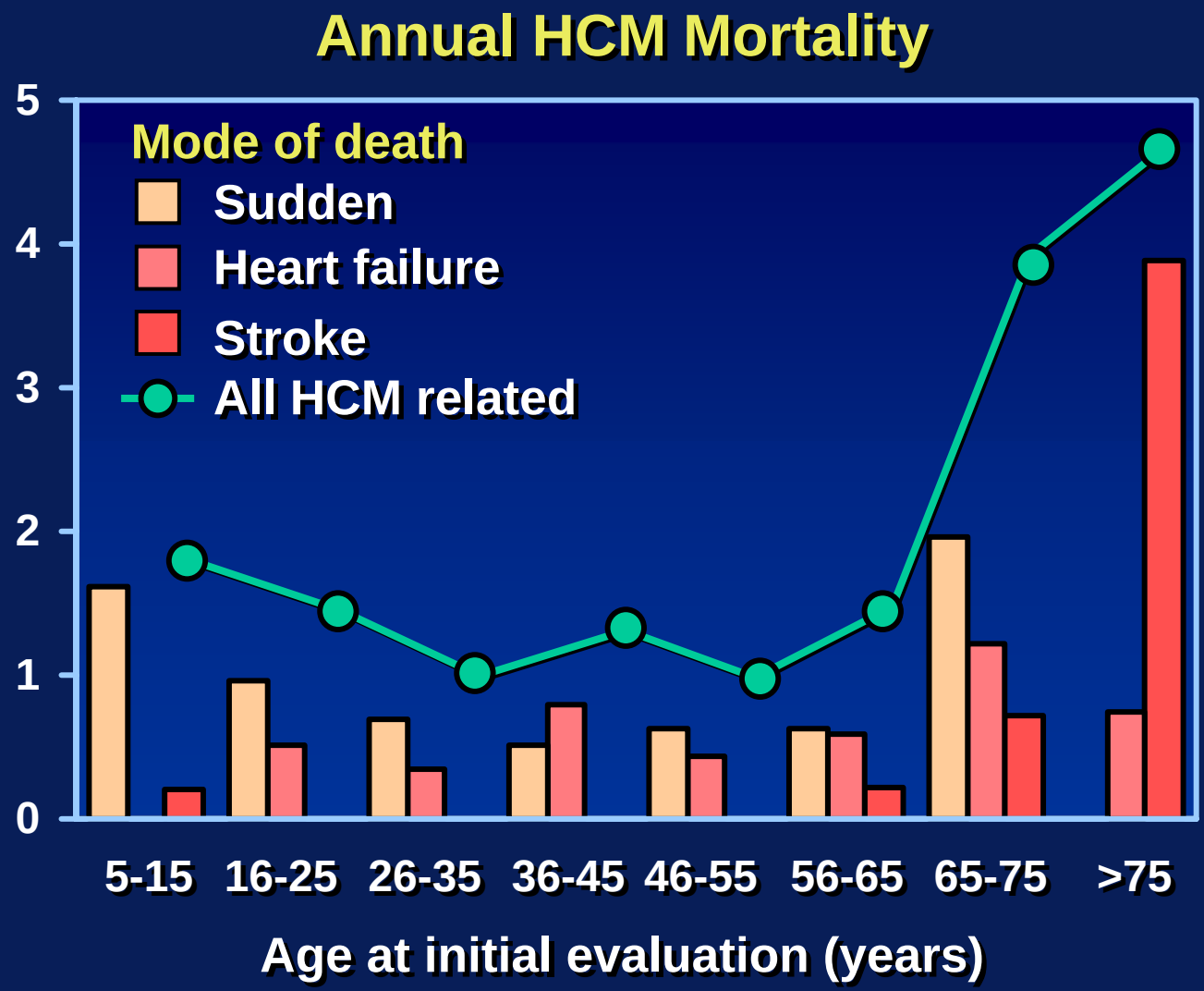


Ackerman and Van Driest, 2003

HCM-Related Mortality Stratified by Age

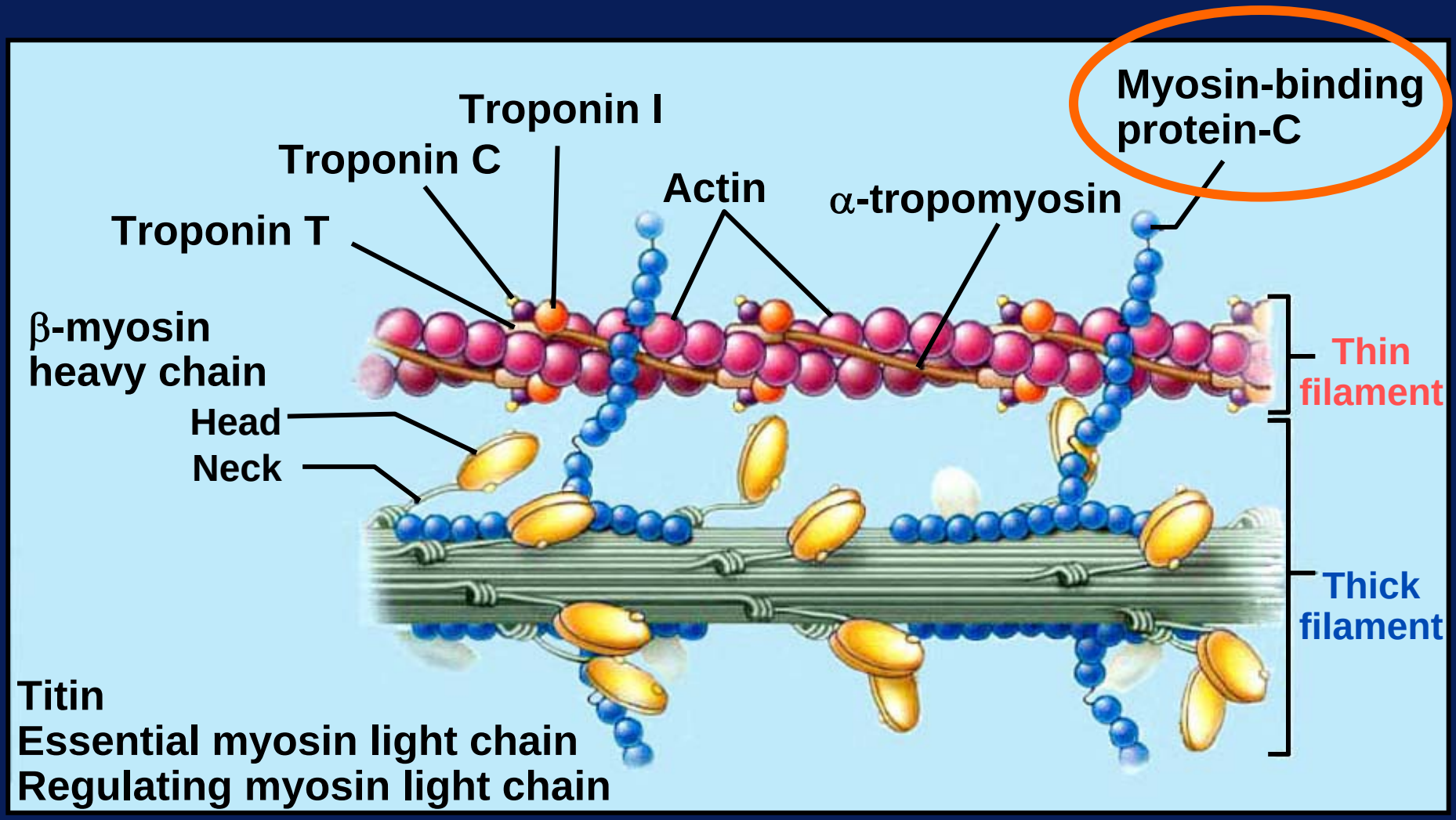
- 744 pt
- Minneapolis
- Genoa
- Florence

HCM-related death – 12% over 8 years



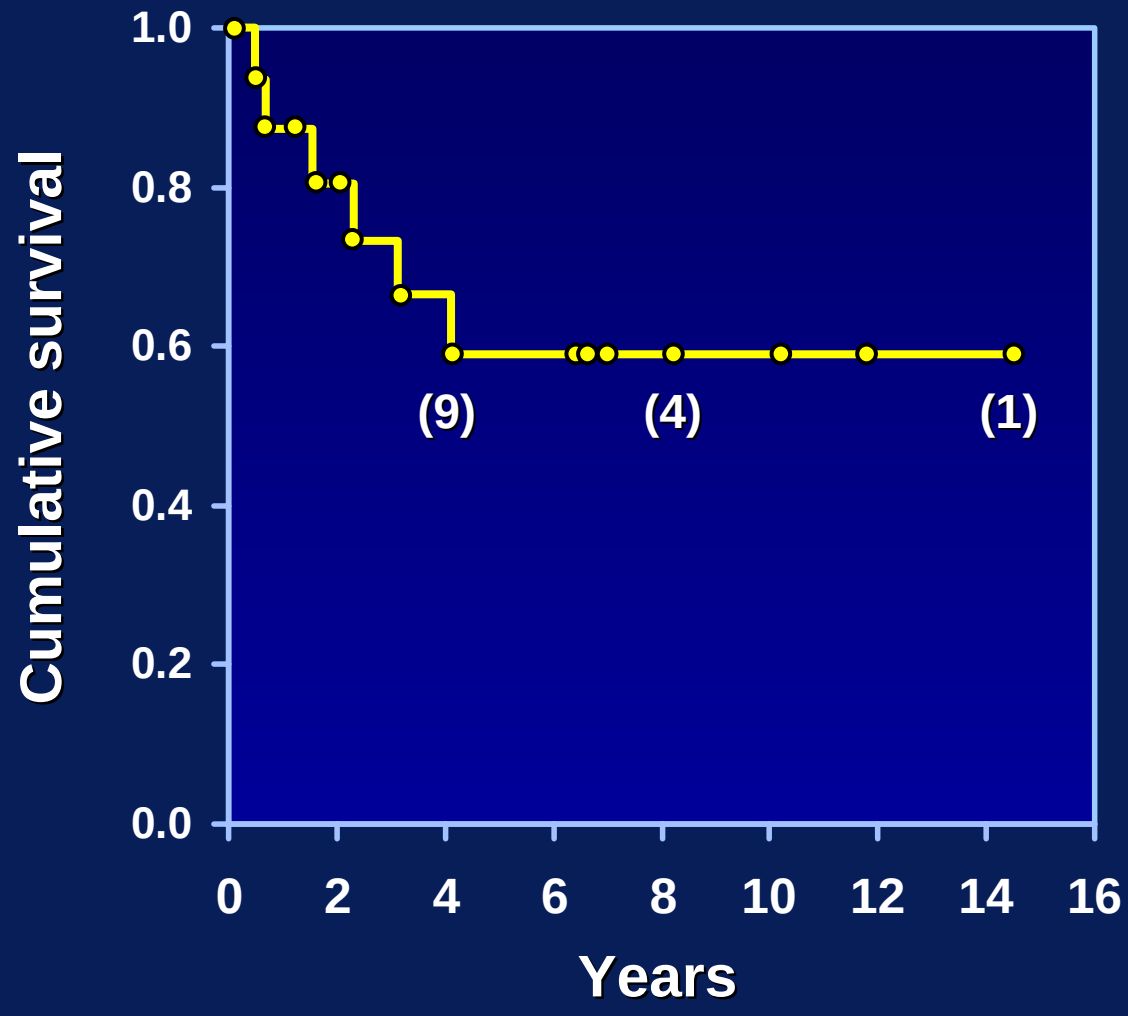
Maron: Circ, 2000

Mutations in Sarcomeric Proteins



Nabel: NEJM, 2003

Survival After Cardiac Arrest in Patients with HCM



- 16 patients
- Age 19 yr (10-36 yr)
- Sustained VT/VFib

Endpoint

Death or 1st appropriate ICD discharge

Elliott P: JACC, 1999

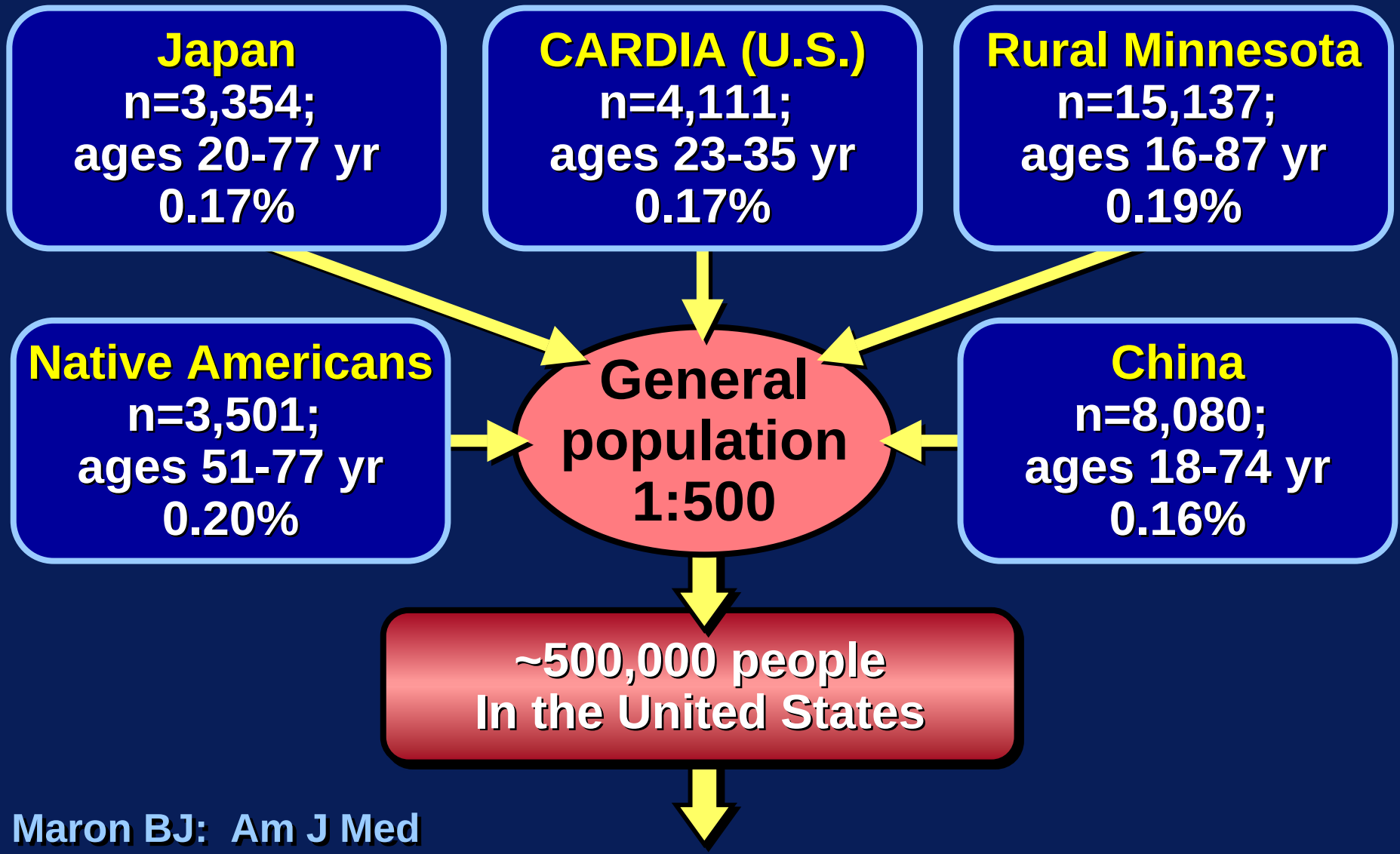
mayo

CP1016147-35

Routine Device Interrogation

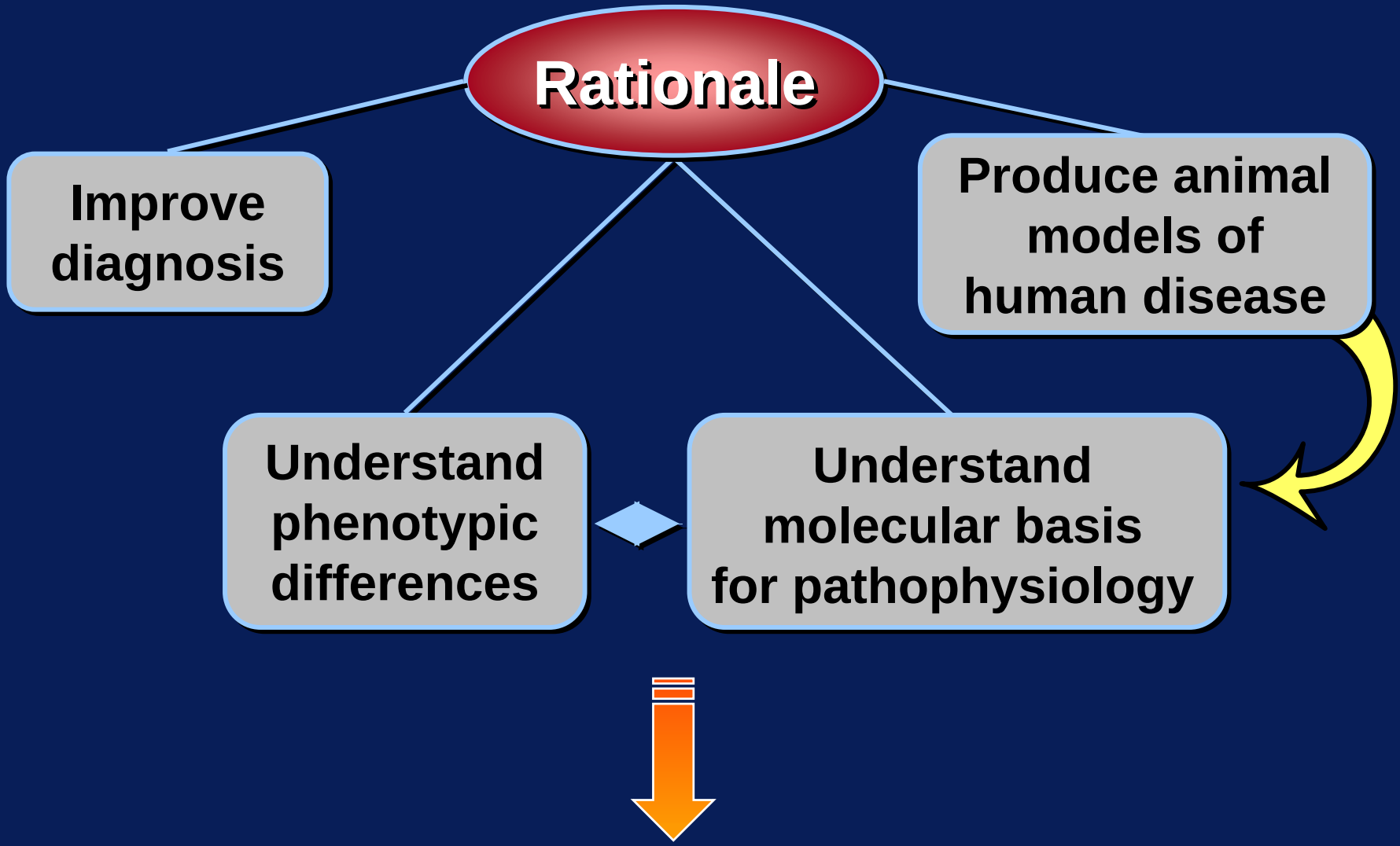
Event 2 mo previously – pt unaware of any discharges

Prevalence of HCM



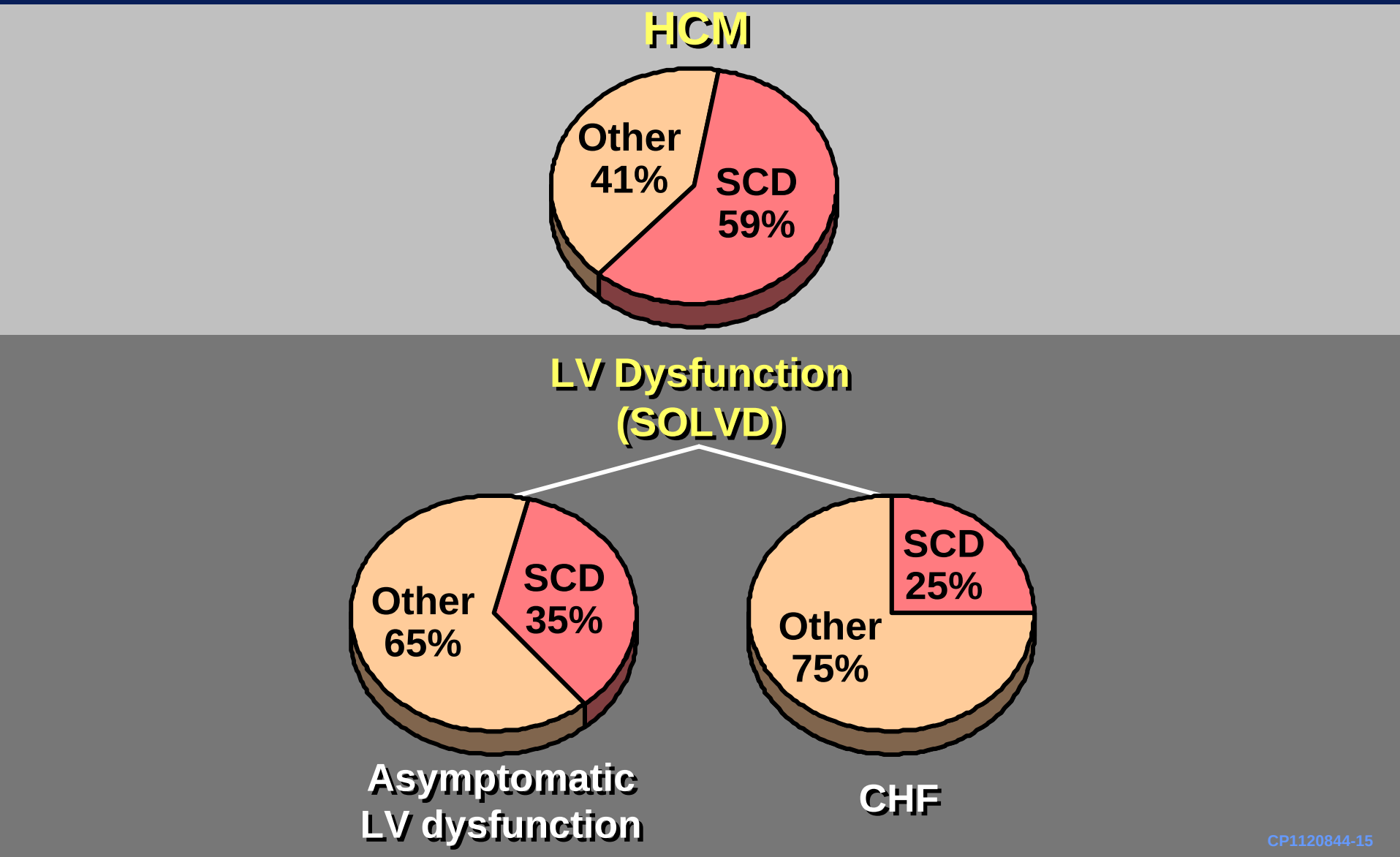
Maron BJ: Am J Med 116:63, 2004

Identification of Genes Causing Disease



Seidman C

SCD in HCM and IDC/CHF
Proportion of Overall Cardiac Deaths



Limitations of Genotype/Phenotype Correlation Studies

Mutations

- Low frequency of each causal mutation

Families

- Small size
- Small number of families with identical mutations

Phenotypic expression

- Marked variability in affected individuals
- Relationship to age

?

Effects of modifier genes and environmental factors

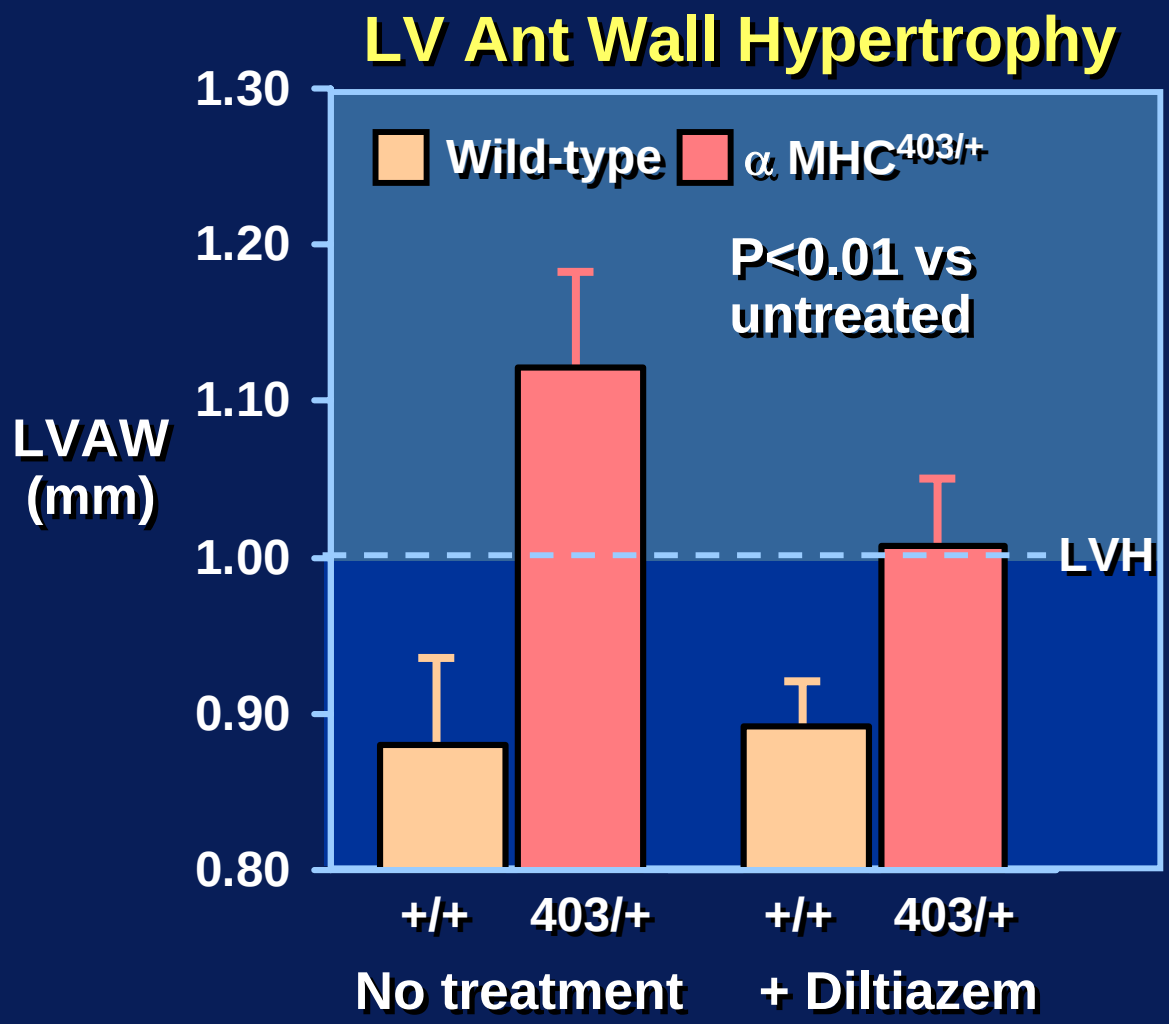
mayo

Prevention of HCM by Diltiazem in a Mouse Model

α MHC mice

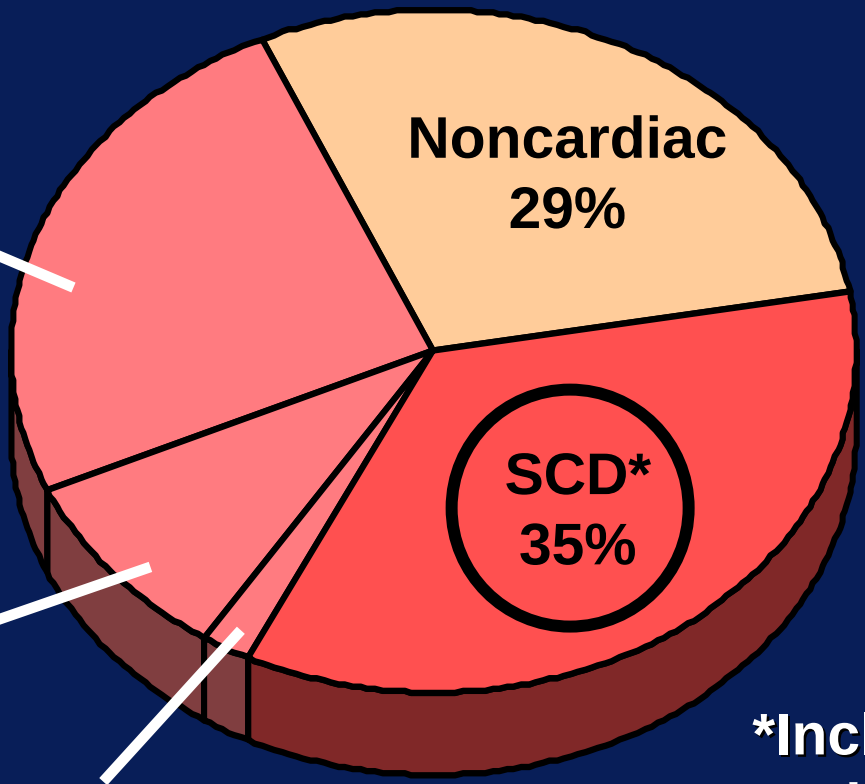
- Abnormal Ca^2 homeostasis
- Changes in Ca^2 binding levels precede LVH myocyte disarray

- Diltiazem – L-type calcium channel inhibitor vs no treatment



Semsarian: JCI, 2002

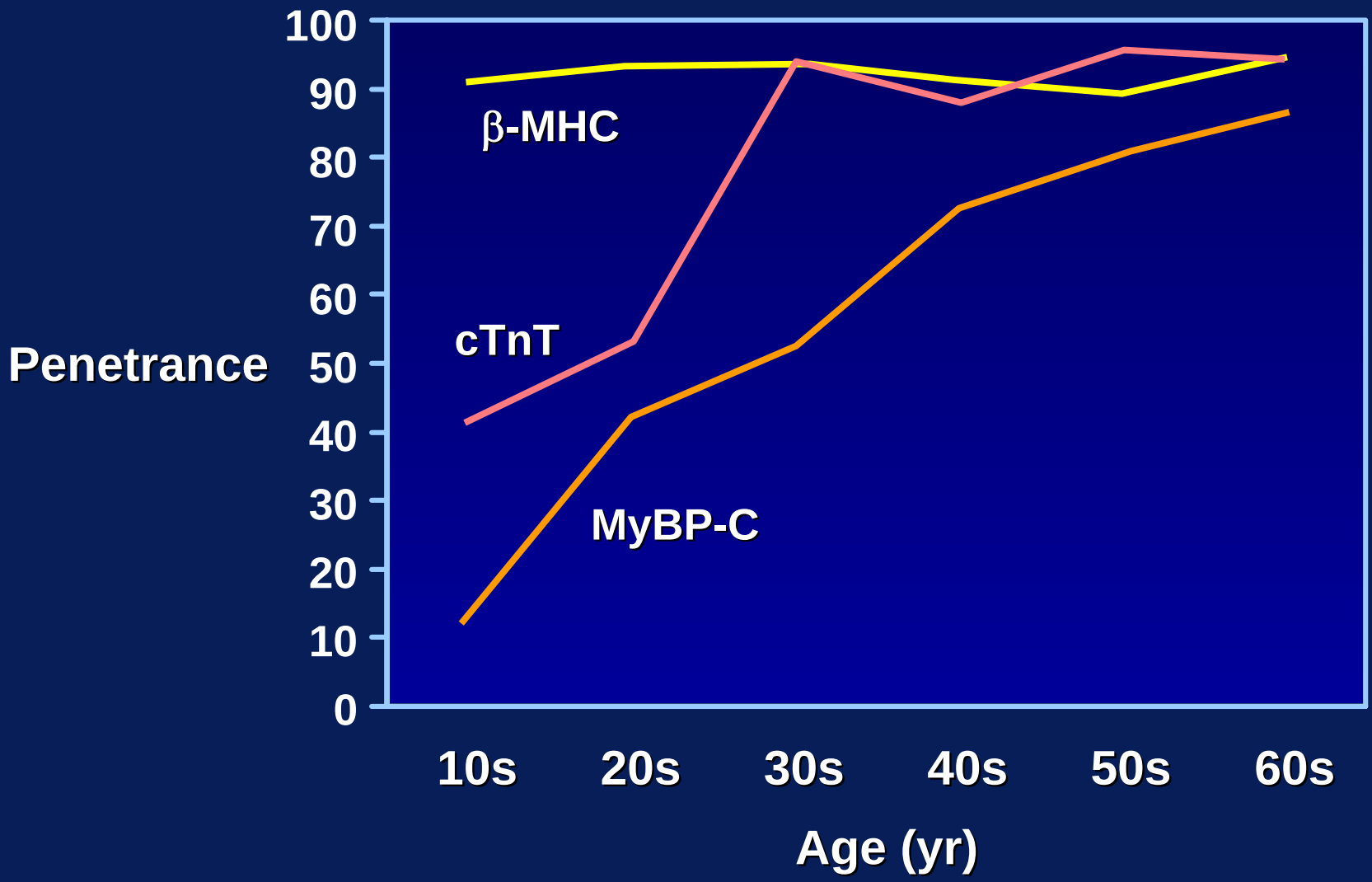
Causes of Death in HCM
744 Patients – 125 Deaths



*Incl aborted cardiac arrest and ICD discharges

Maron: Circ, 2000

Age-Related Penetrance of HCM Mutations

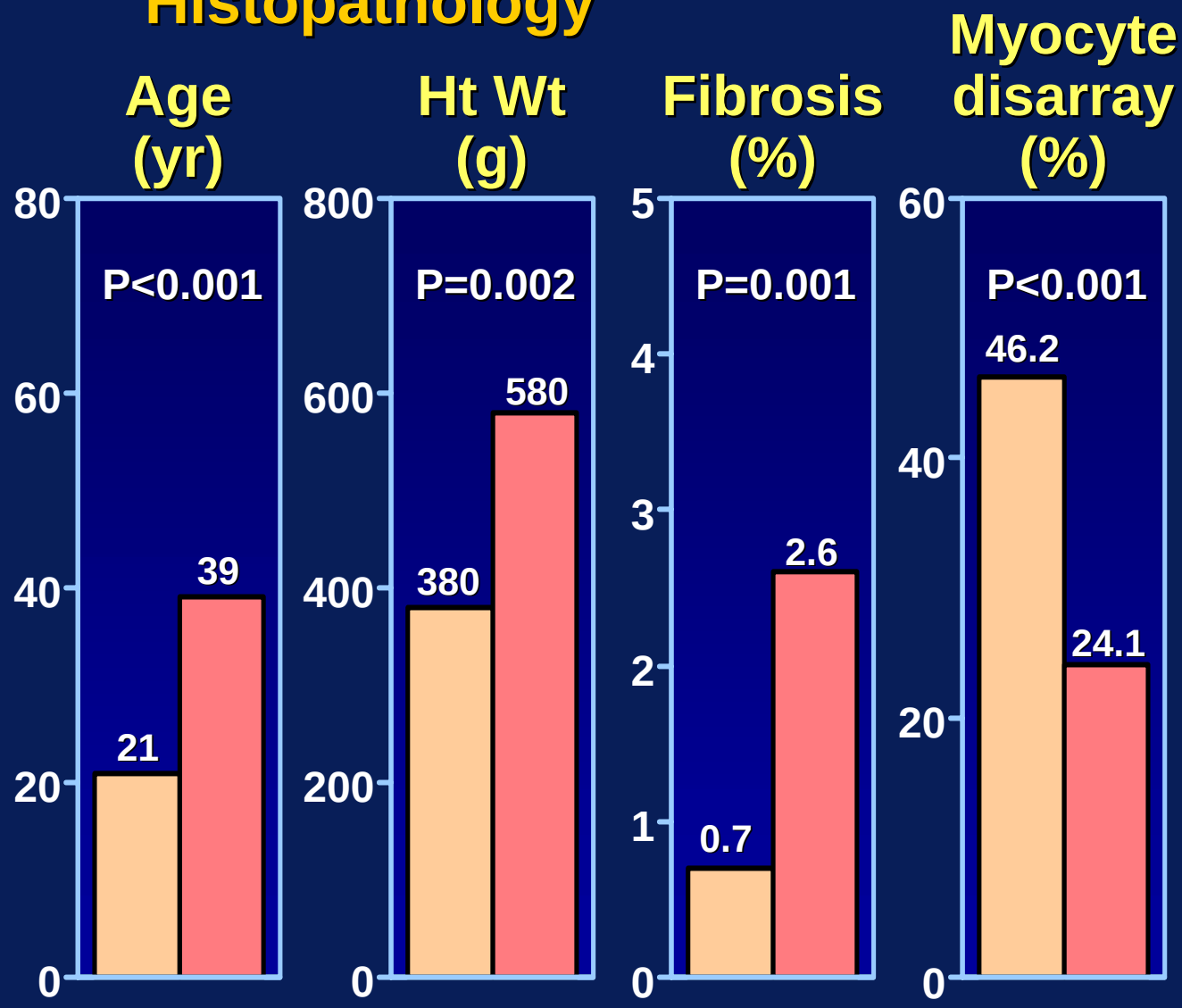


Nimura: NEJM, 1998

SCD in Cardiac Troponin T Disease

Histopathology

- 50 hearts
- DNA analysis
- Troponin T mutation 18%



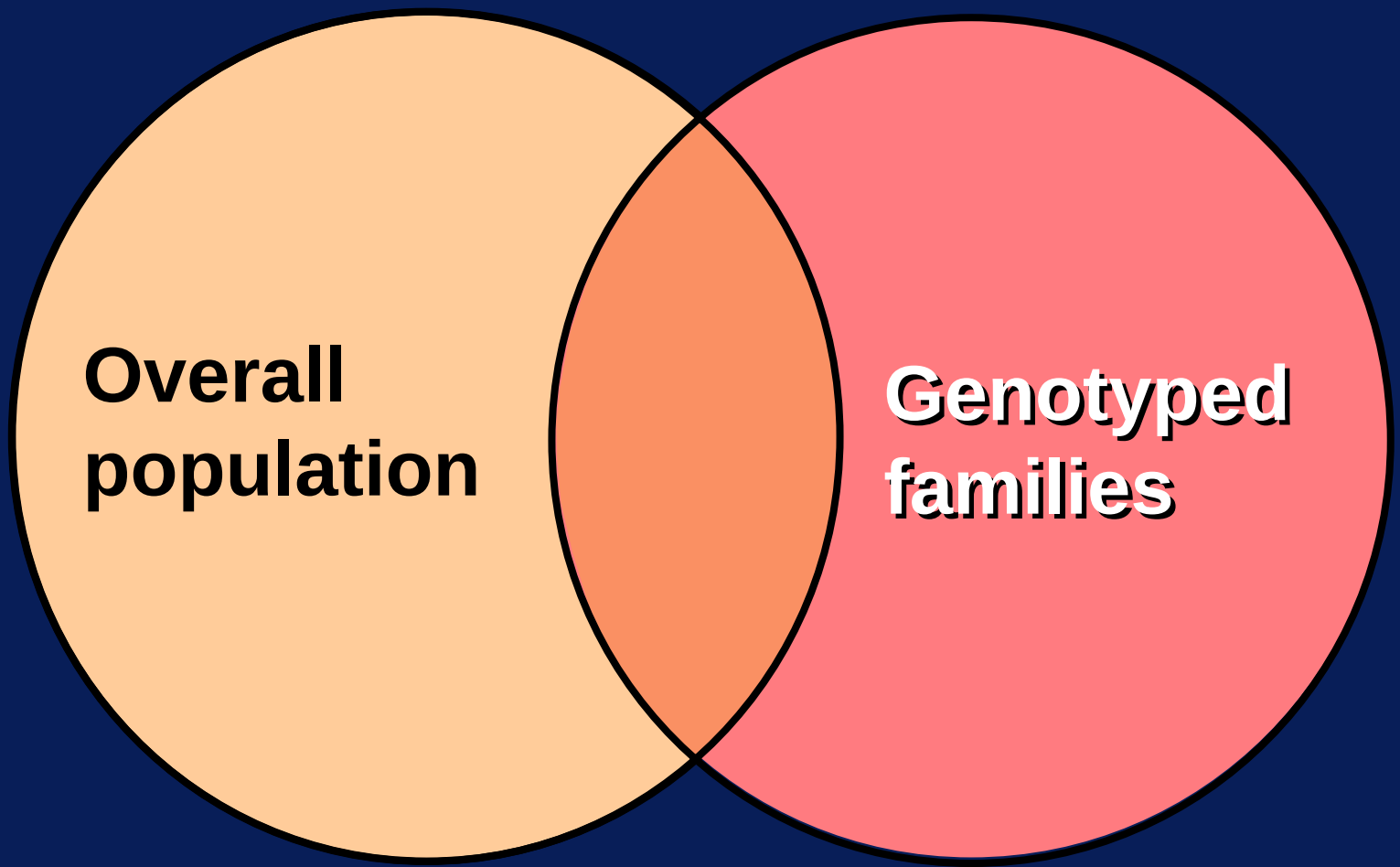
Troponin T mutation

Other HCM pt

Varnava: Circ, 2001

CP1064826-1

Genotyping in Perspective



Prevalence and Spectrum of Thin and Thick-Filament Mutations

- 395 unrelated pt
- Mayo Clinic
- 1997-2001

- βMHC mutations – 14%
- 38 mutations (63% novel)

- Thin-filament mutations – 4.8%
- 12 mutations (63% novel)

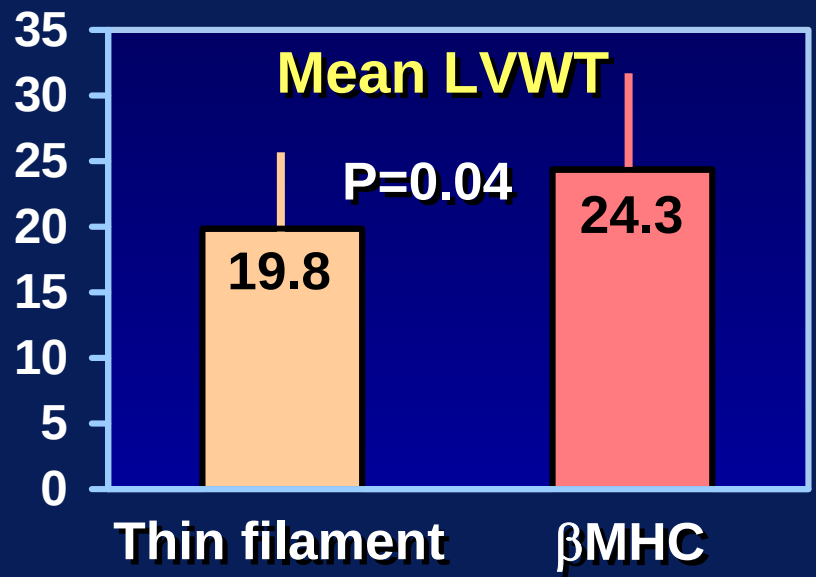
Difference – Pt with/without βMHC mutations

- Younger
- F history
- ↑ LVW thickness
- Surgery more frequent
- No difference in SCD

Van Driest and Ackerman: Circ, 2003

Prevalence and Spectrum of Thin-Filament Mutations

- 395 unrelated pt
- Mayo Clinic
- 1997-2001



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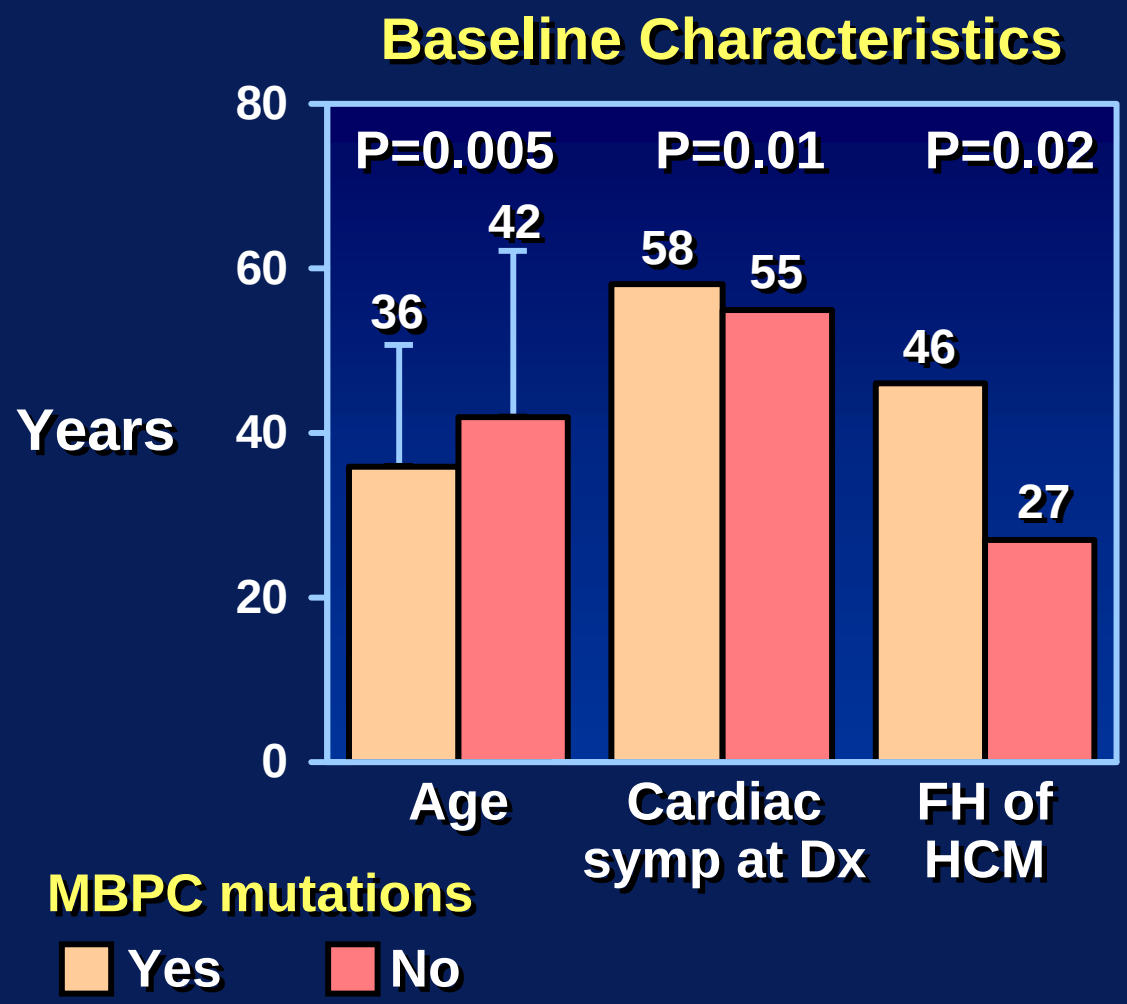
Van Driest and Ackerman: Circ, 2003

Myosin-Binding Protein-C Mutations in an Outpatient Population

389 Unrelated Patients

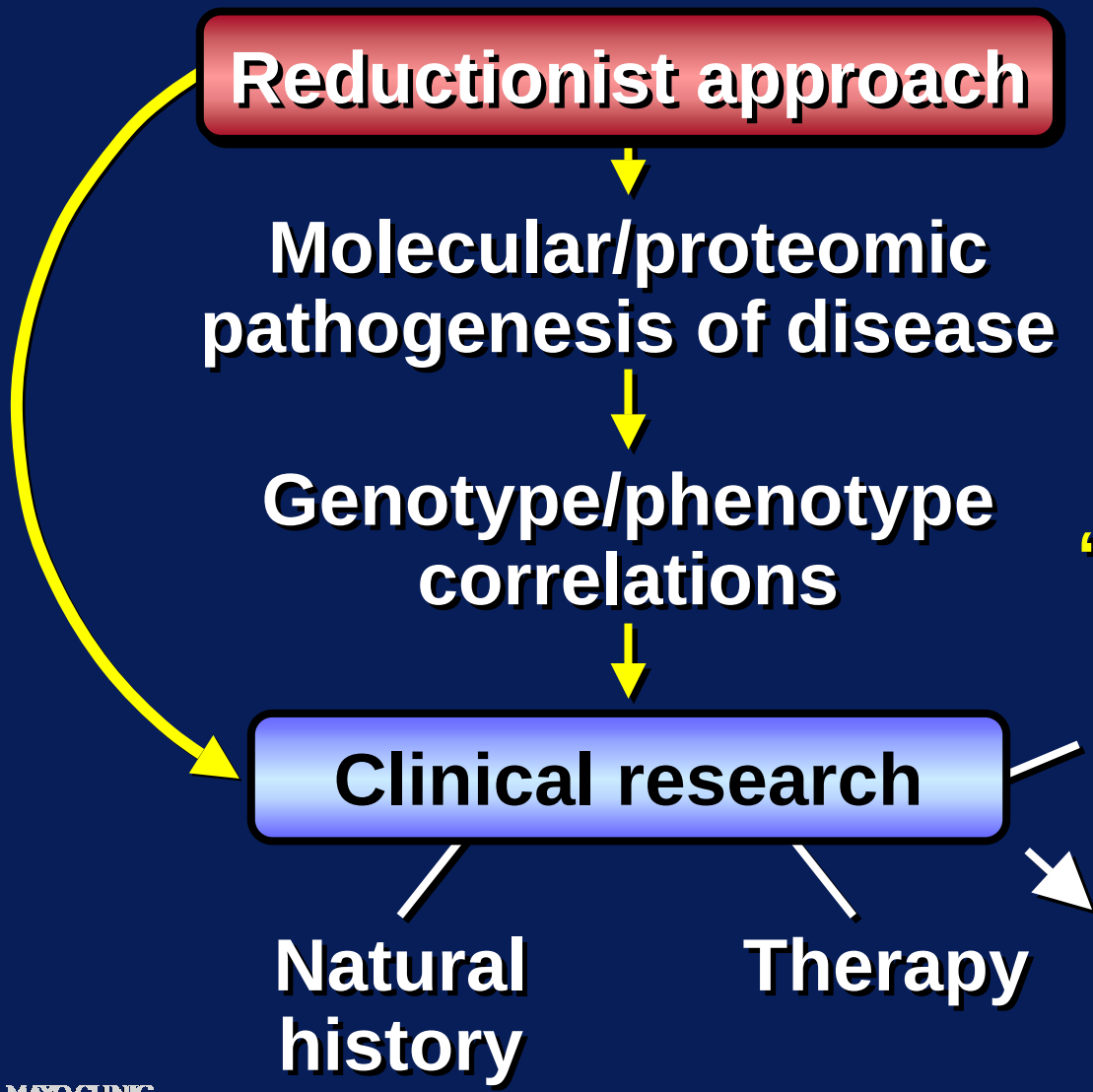
Myosin-binding protein-C

19%



Van Driest and Ackerman

Implications of Medical Genetics for Clinical Research



"Clinical research is dead in the era of molecular genetics

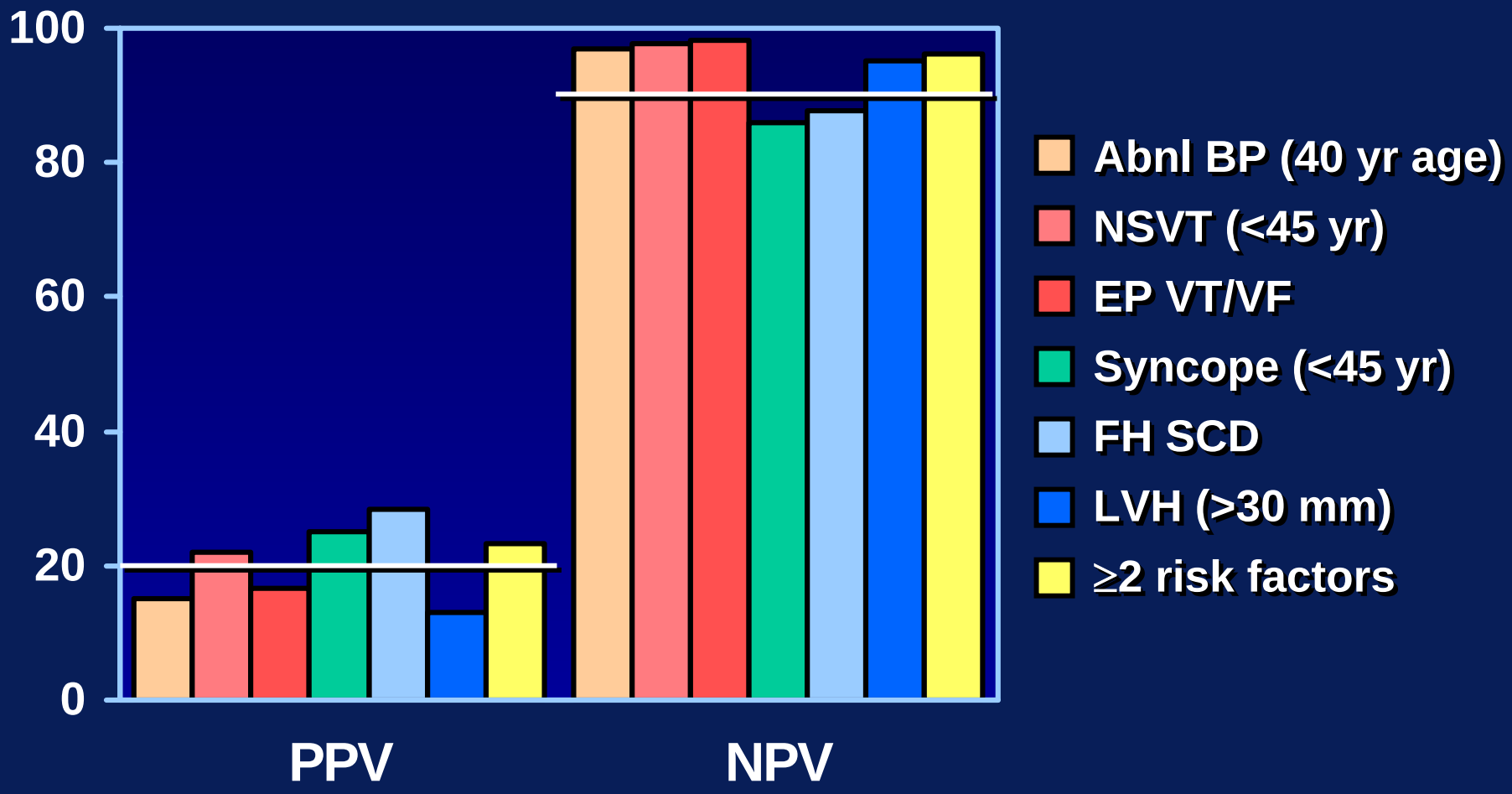
Long live clinical research"

Bell J, 2002

Molecular Genetics

The Future

Predictive Value of SCD Risk Factors



McKenna, Heart 2002

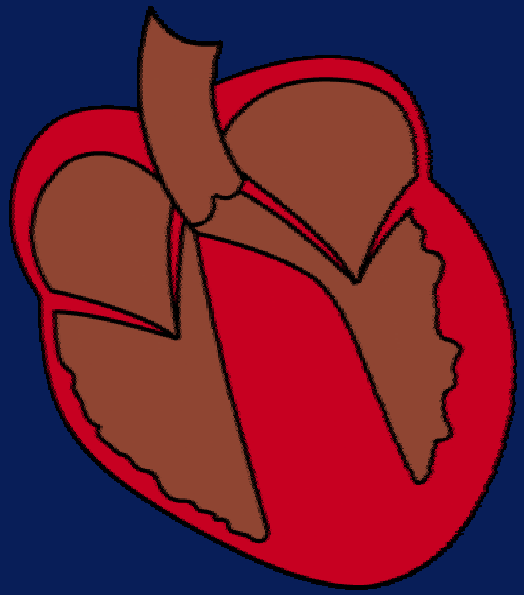
Ventricular Pressure as a Stimulus for Hypertrophy

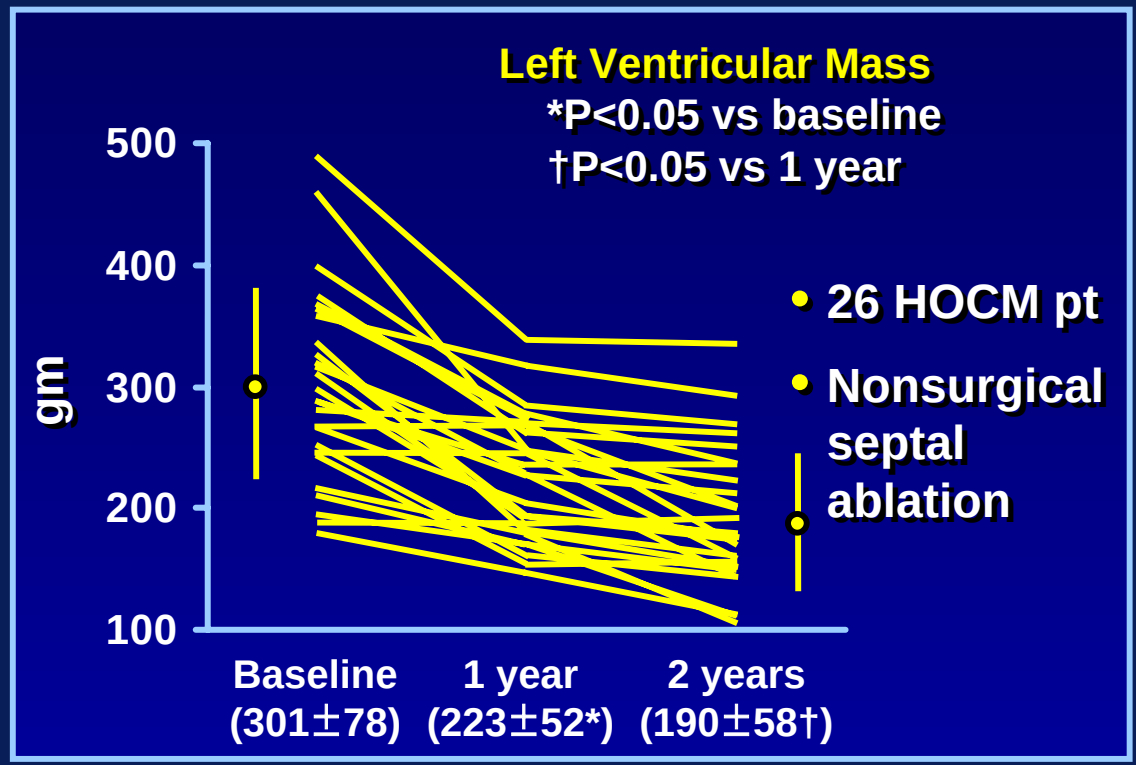
Evidence

Lack of RV involvement

Post-ablation

Regression in LV mass, LVWT and Collagen





Mazur: Circ, 2001

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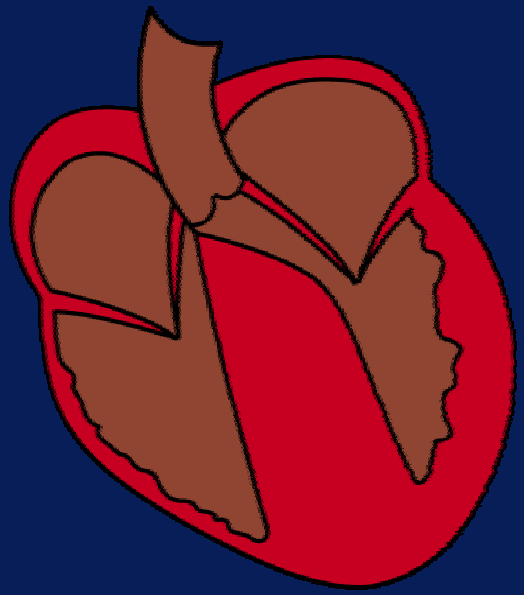
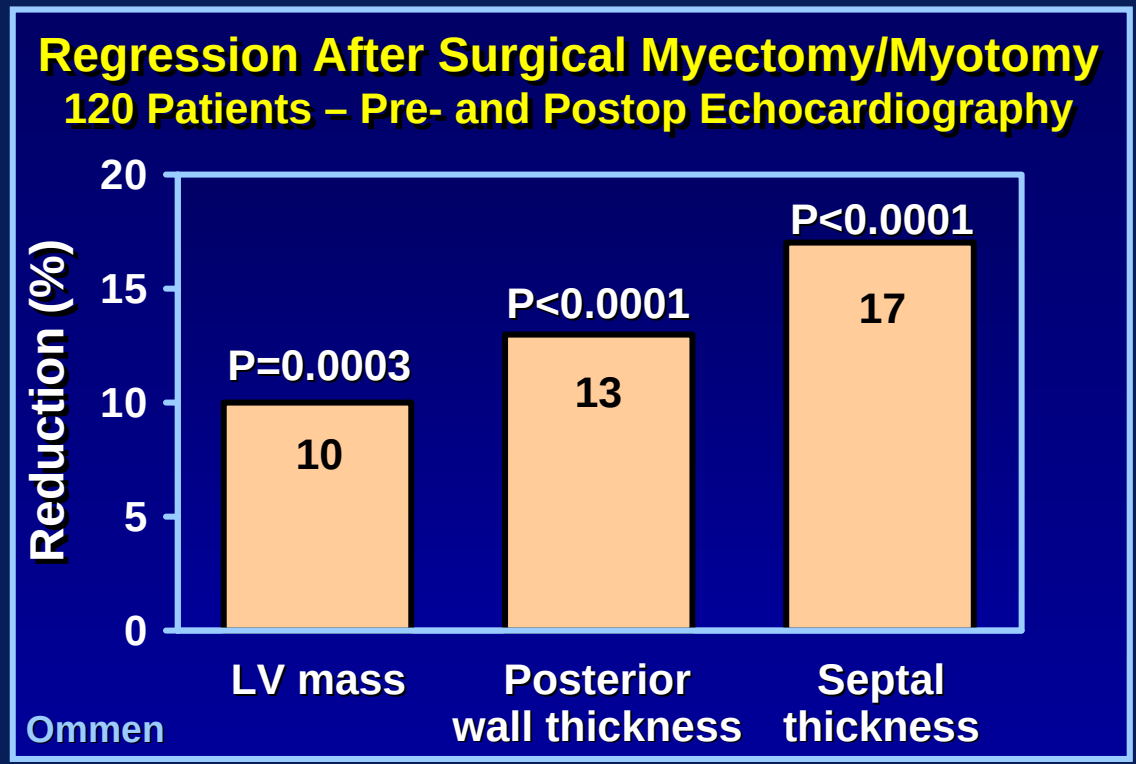




Mazur: Circ, 2001

CP1076558-30

Studies of Pts. With Severe LVH

Study	Pt (no.)	SCD rate (%)	5-yr survival (%)	Conclusions
Spirito	43	1.8	86	ICD for all
Elliott	78	2.1	88	ICD if other risk factors
Olivotto	30	0.3	87	Use other risk factors
Mayo	107	1.4	82	ICD if other risk factors

Overall death/yr = 3.5% vs 2.0%

Sudden death/yr = 1.4% vs 1.1%

NSVT on Holter and Risk of SCD

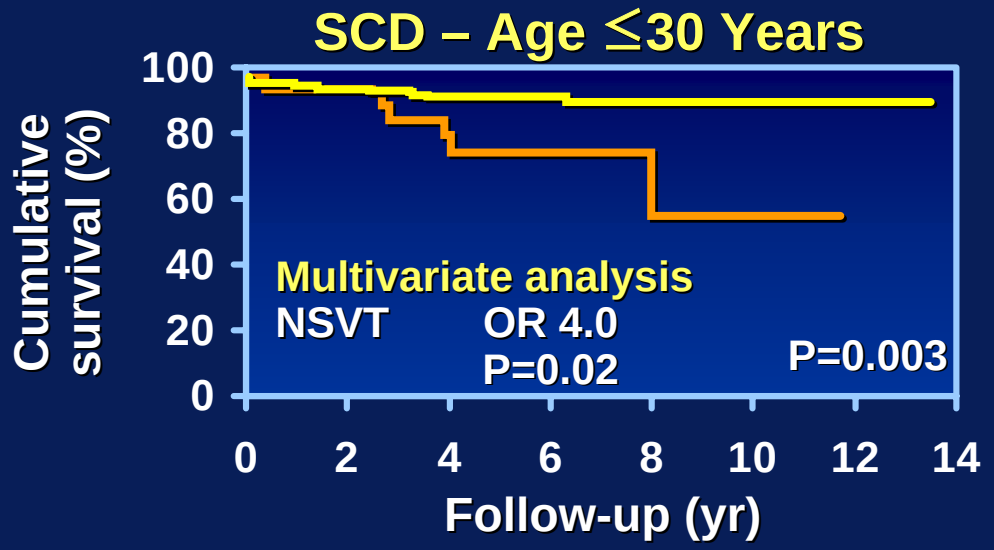
531 Patients – NSVT (19.6%)

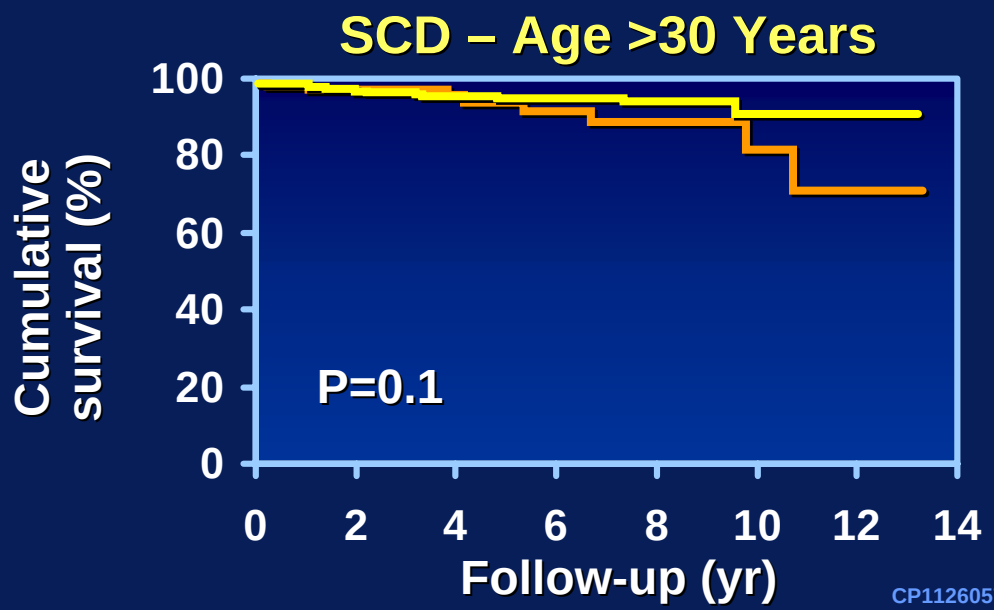
32 SCD

NSVT (13 pt)

- Prior syncope 4 pt
- MLVWT ≥30 mm 3 pt
- Abnormal BP response 4 pt

5 pt – no other risk factors





Monserrat: JACC, 2003

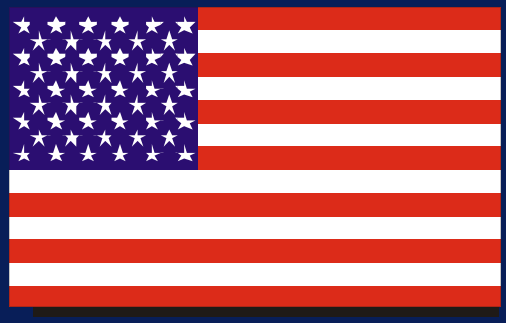
Severe LVH and Age

312 community-based patients

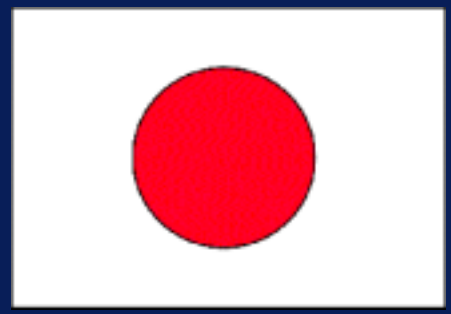
Age <75 yr 239 pt (77%)		Age ≥75 yr 73 pt (23%)	
22±6	Max LVWT mm (mean)	20.6±3	P=0.01
14	Max LVWT ≥30 mm (%)	1.4	P=0.002

Maron: JACC, 2003

Prevalence of Apical HCM in Japan and USA



Minneapolis



Kochi

• MLVW thickness		Similar	
• Apical variant	3%	P<0.0001	15%
• Giant negative T waves	2%	P<0.001	26%

Phenotypic differences
Countries and races

Genetic ? ⟷ Environmental ?

Kitaoka: AJC, 2003

Prognostic Assessment – HCM

Clinical

History ECG Holter Stress test

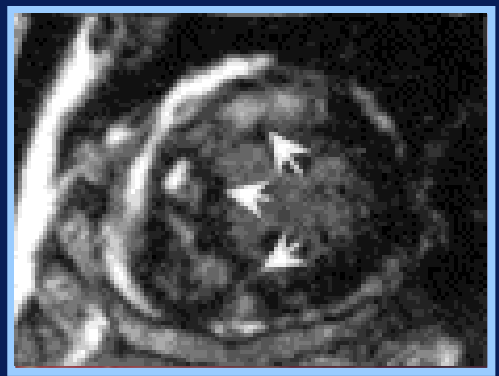
Identification for mutation positives without LVH

Reduced TD velocity

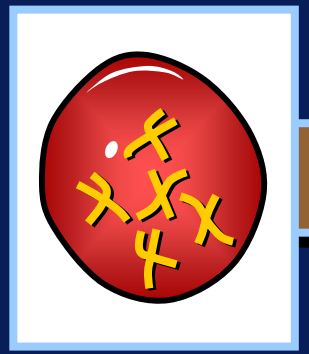
Sens 100% Spec 93%

Role of TDI?

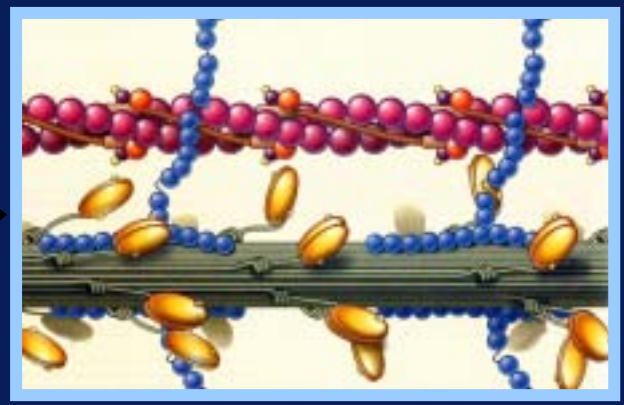
Morphologic/cellular/ scarring



Role of MRI?



Molecular

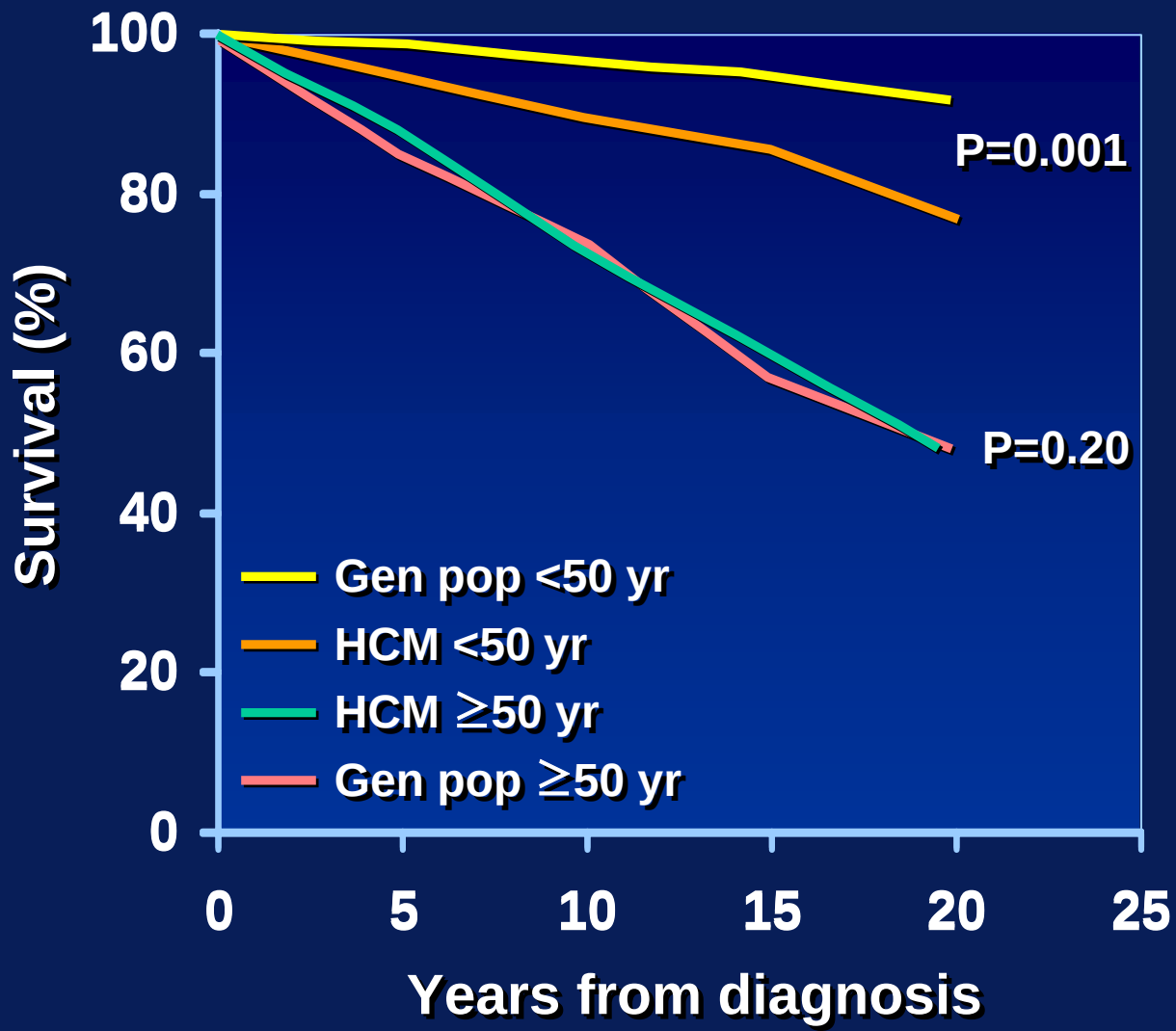


Future?

Nagueh: Circ, 2001; Choudhury: JACC, 2002; Spiritto: NEJM, 1997

Natural History of HCM in the Elderly

- 312 patients
- Community cohort
- 23% aged ≥75 yr



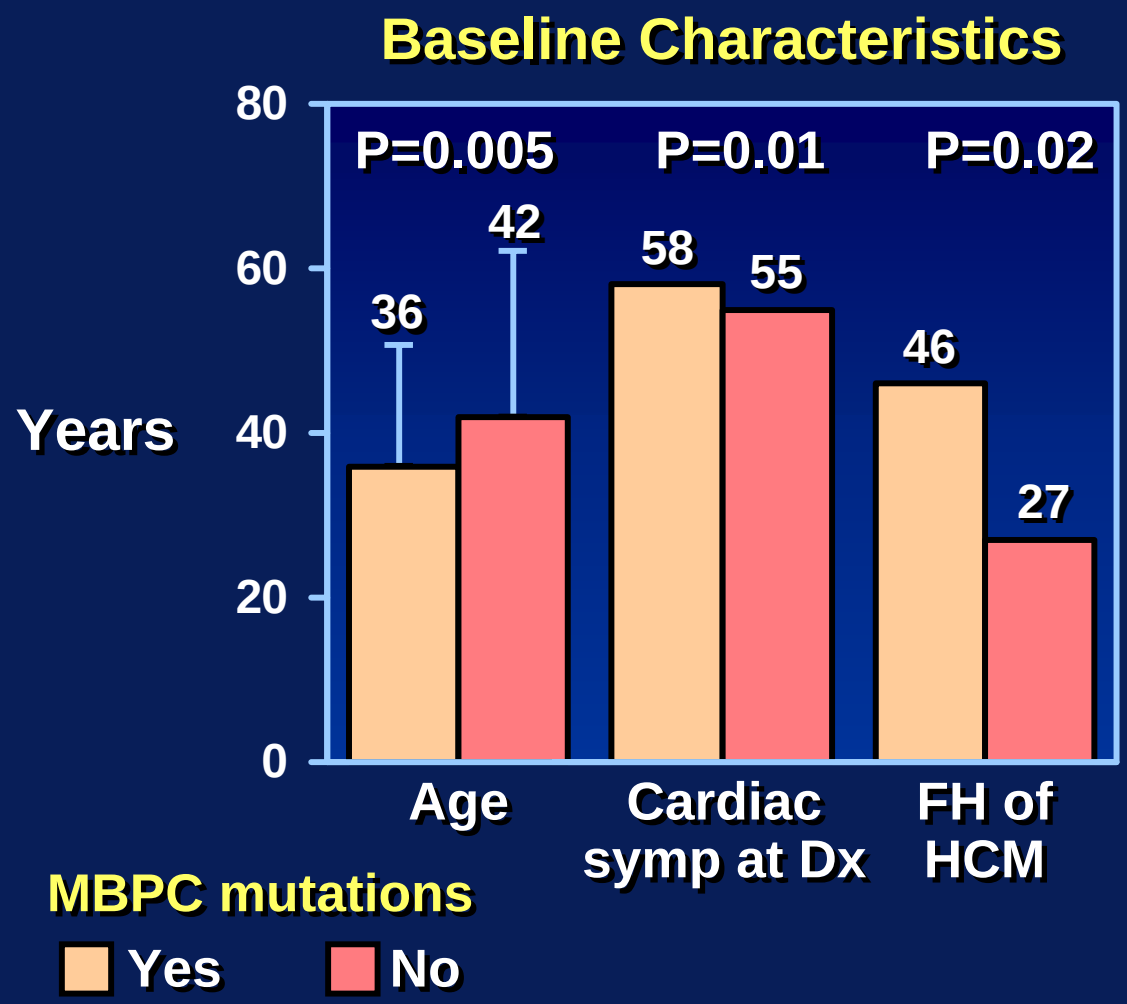
Maron: JACC, 2003

Myosin-Binding Protein-C Mutations in an Outpatient Population

389 Unrelated Patients

Myosin-binding protein-C

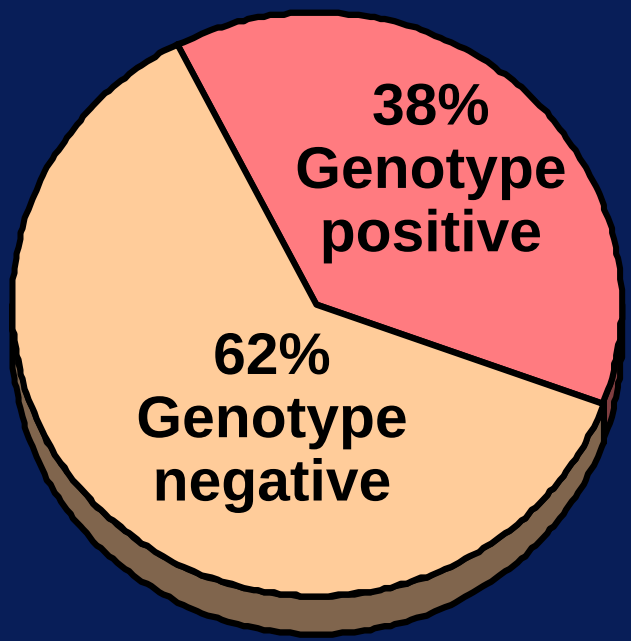
19%

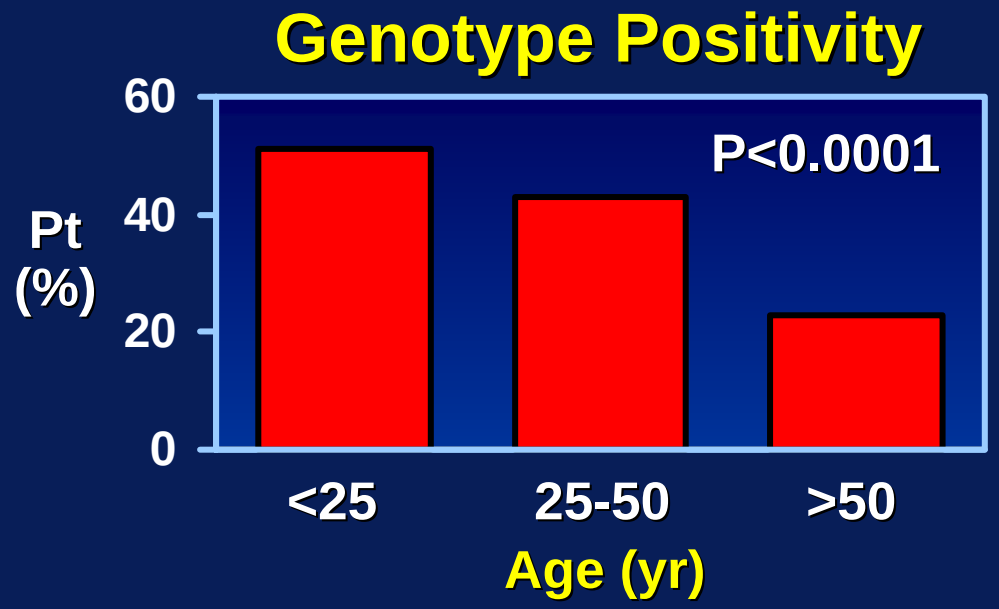


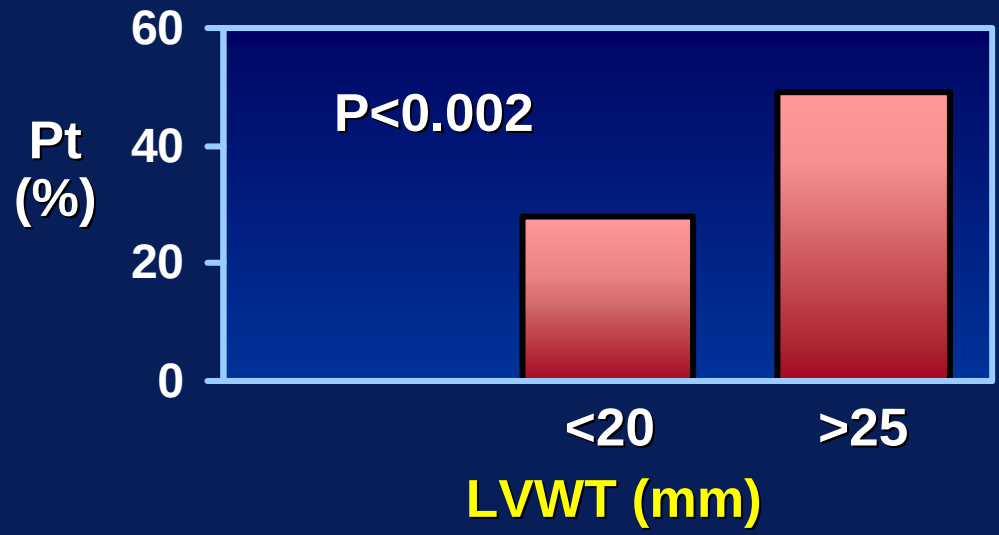
Van Driest and Ackerman

Yield of Sarcomere Gene Testing

- 389 unrelated pt
- Mayo Clinic
- 8 genes

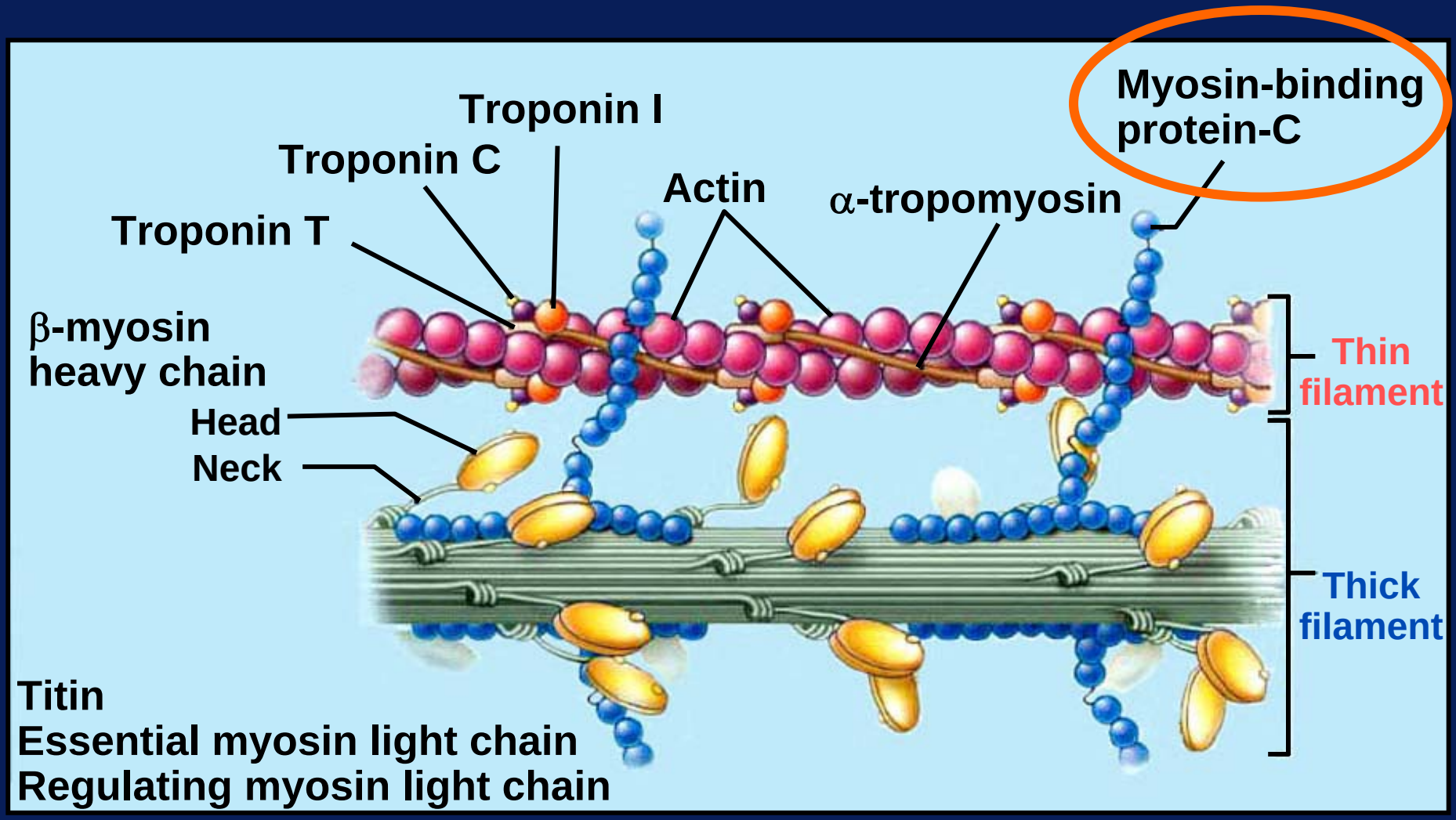






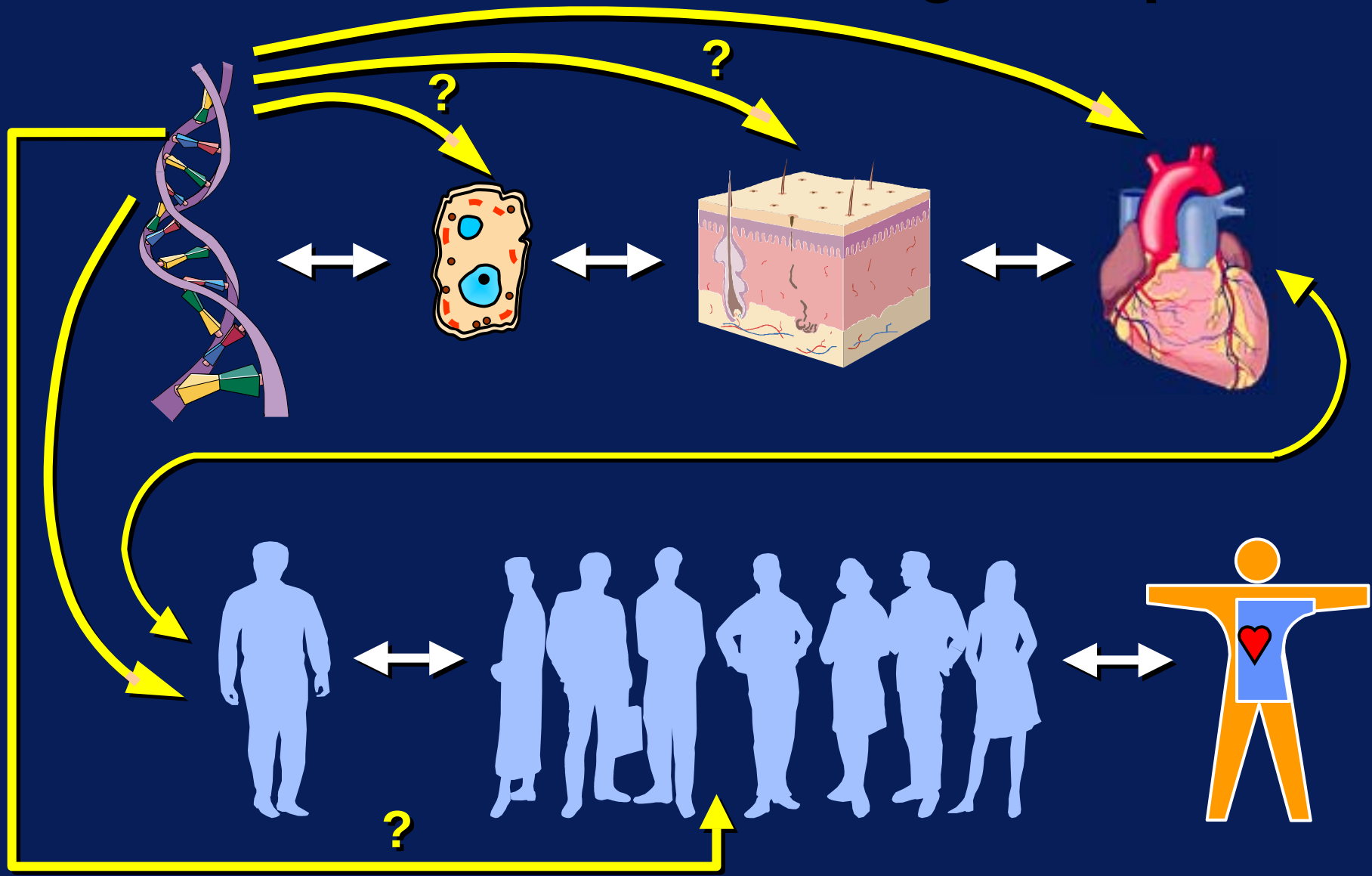
Ackerman M, 2003

Mutations in Sarcomeric Proteins



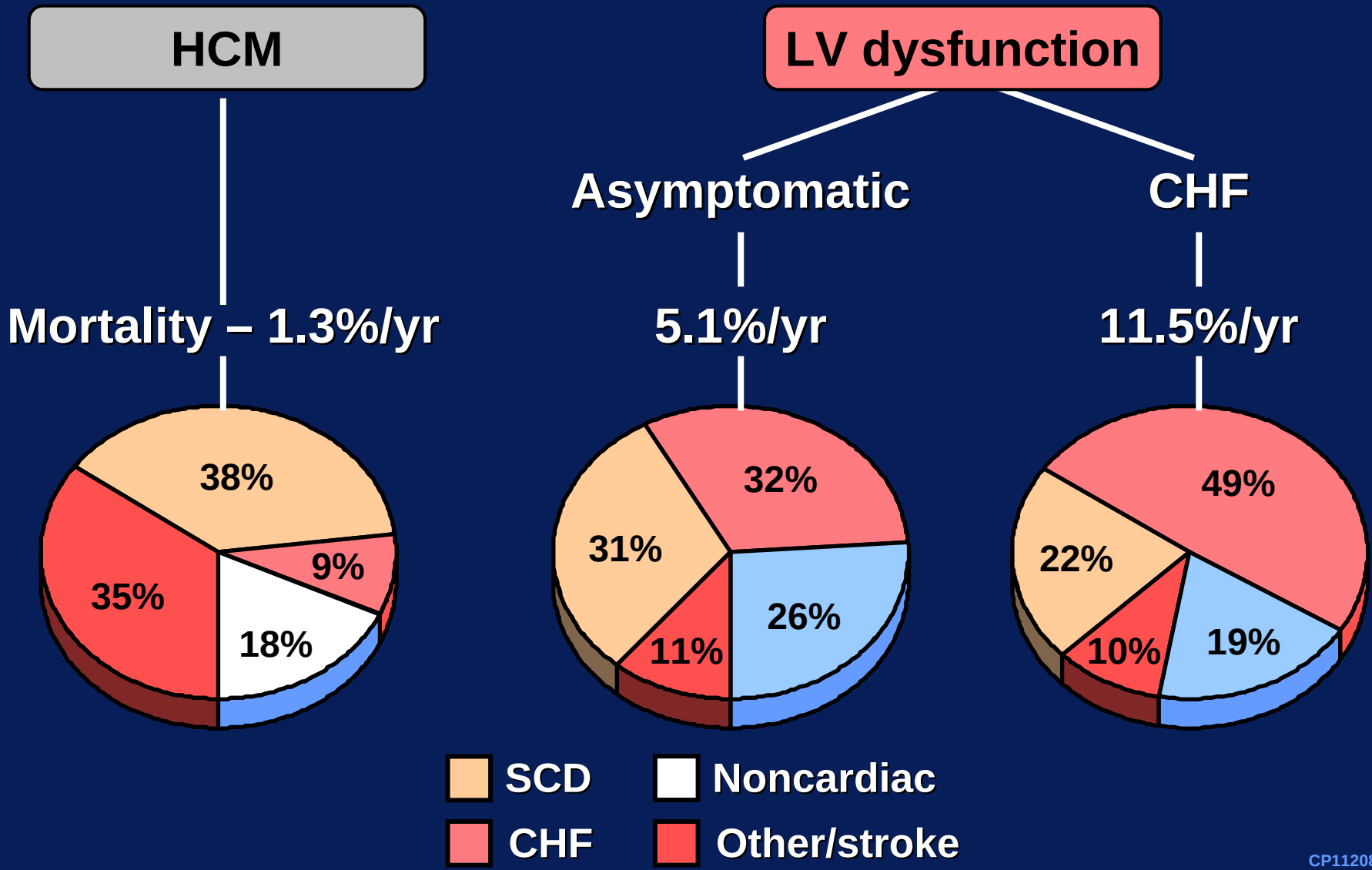
Nabel: NEJM, 2003

NHLBI SPARK Working Group



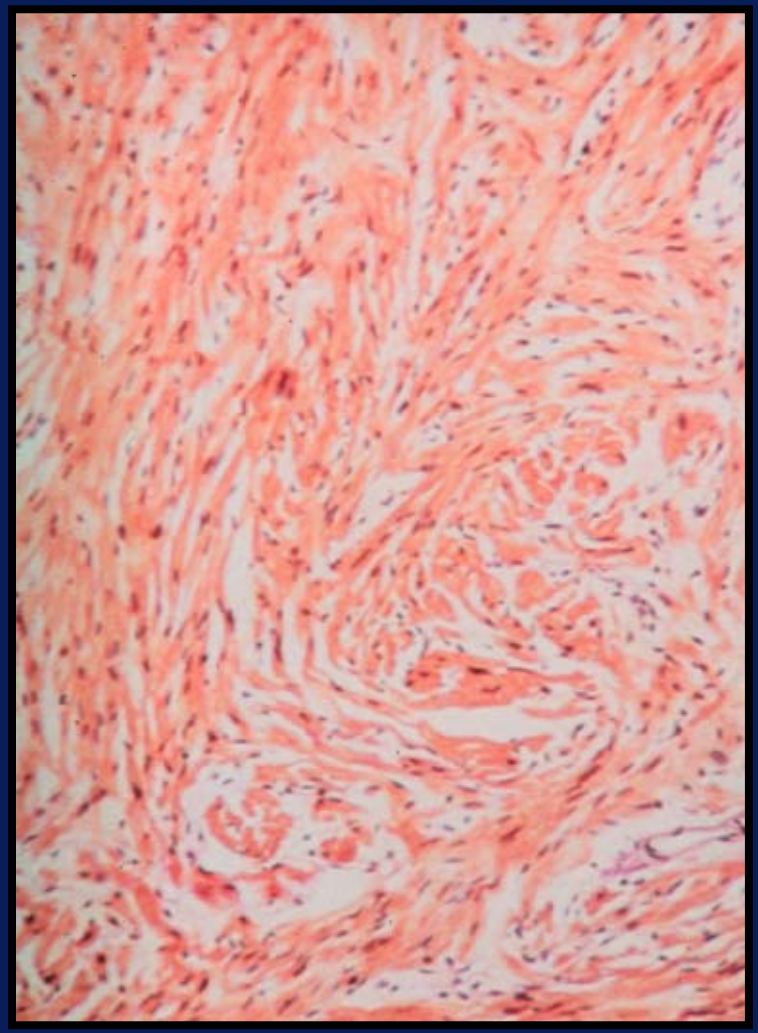
Circulation, 1999

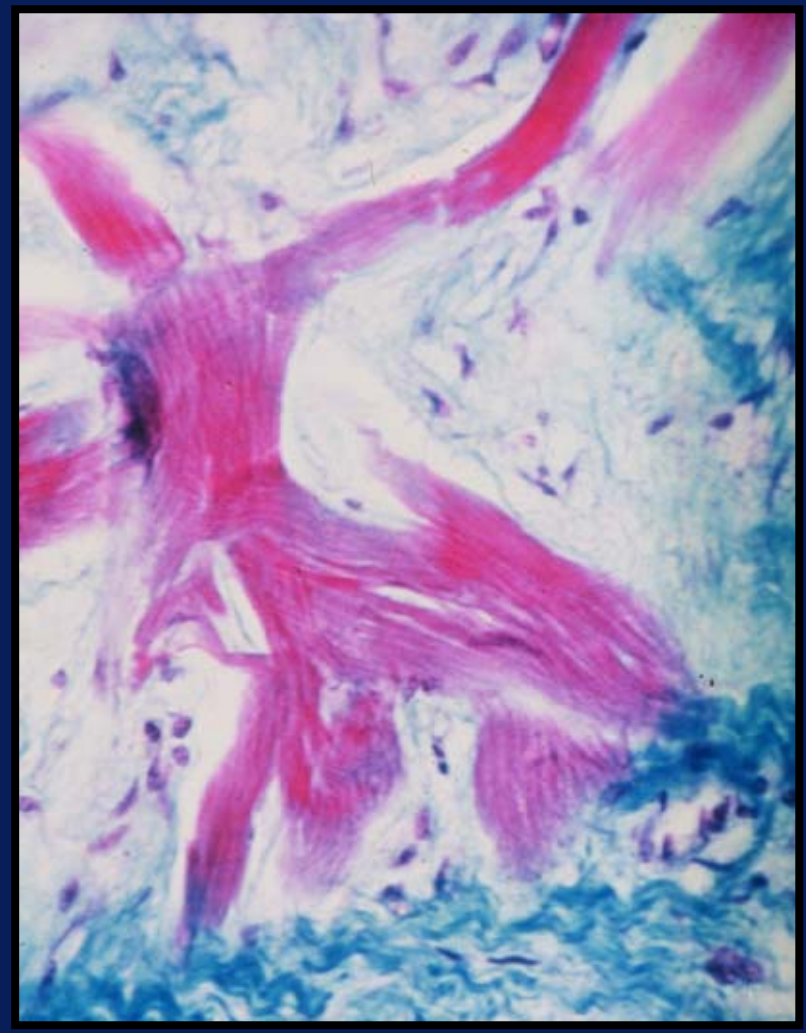
Differences in Sudden Cardiac Death in HCM and IDC



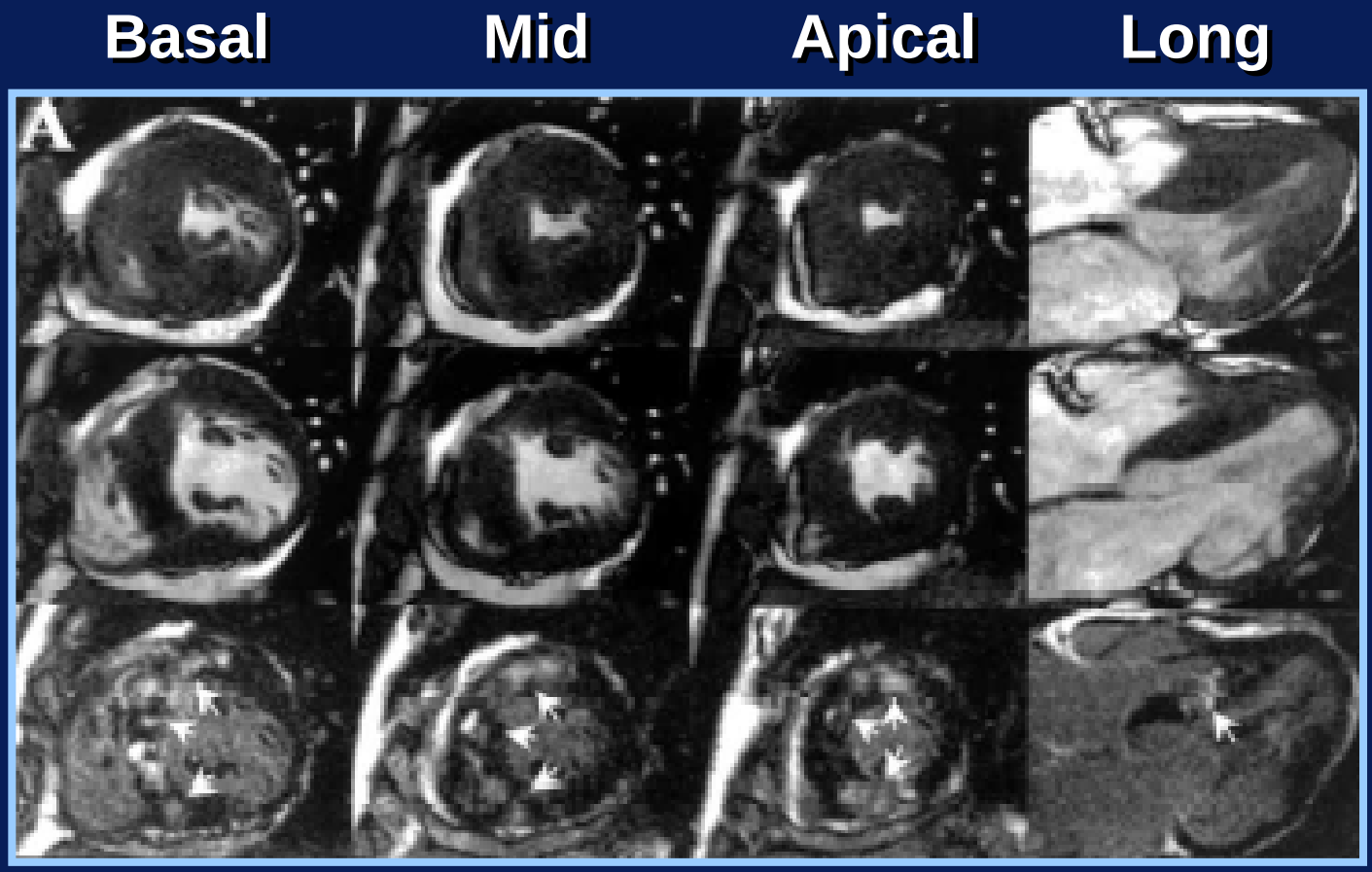
Pathology

Myocyte Disarray



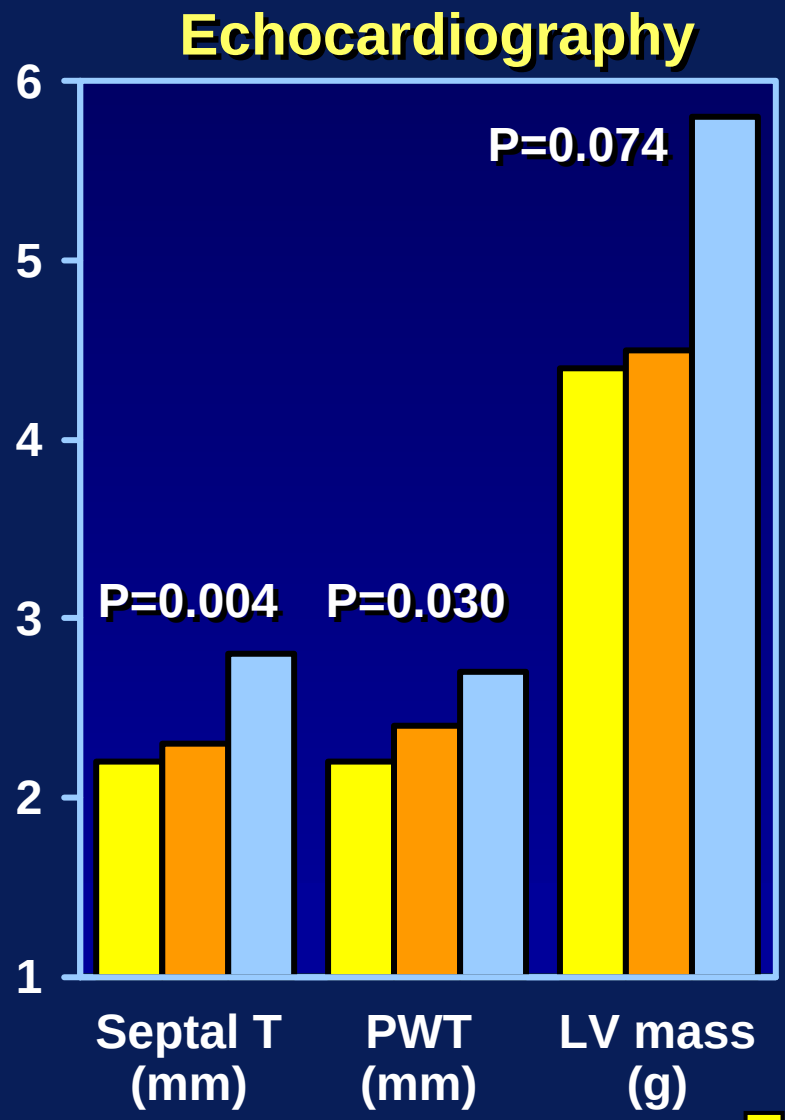


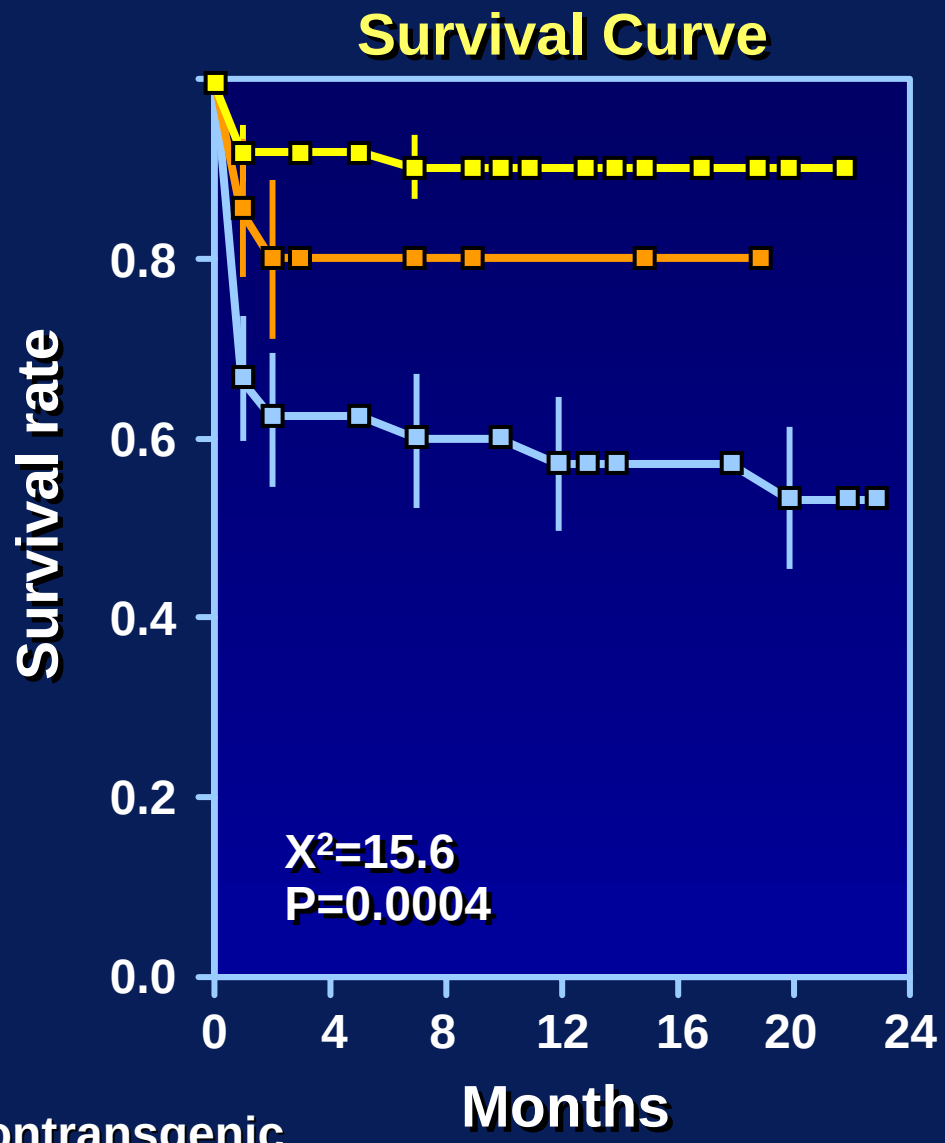
Myocardial Scar



Choudhury: JACC 40:2156, 2002

A Transgenic Rabbit Model for Human HCM





Nontransgenic
Wild-type transgenic (β-MyHC)
Mutant transgenic (β-MyHC)

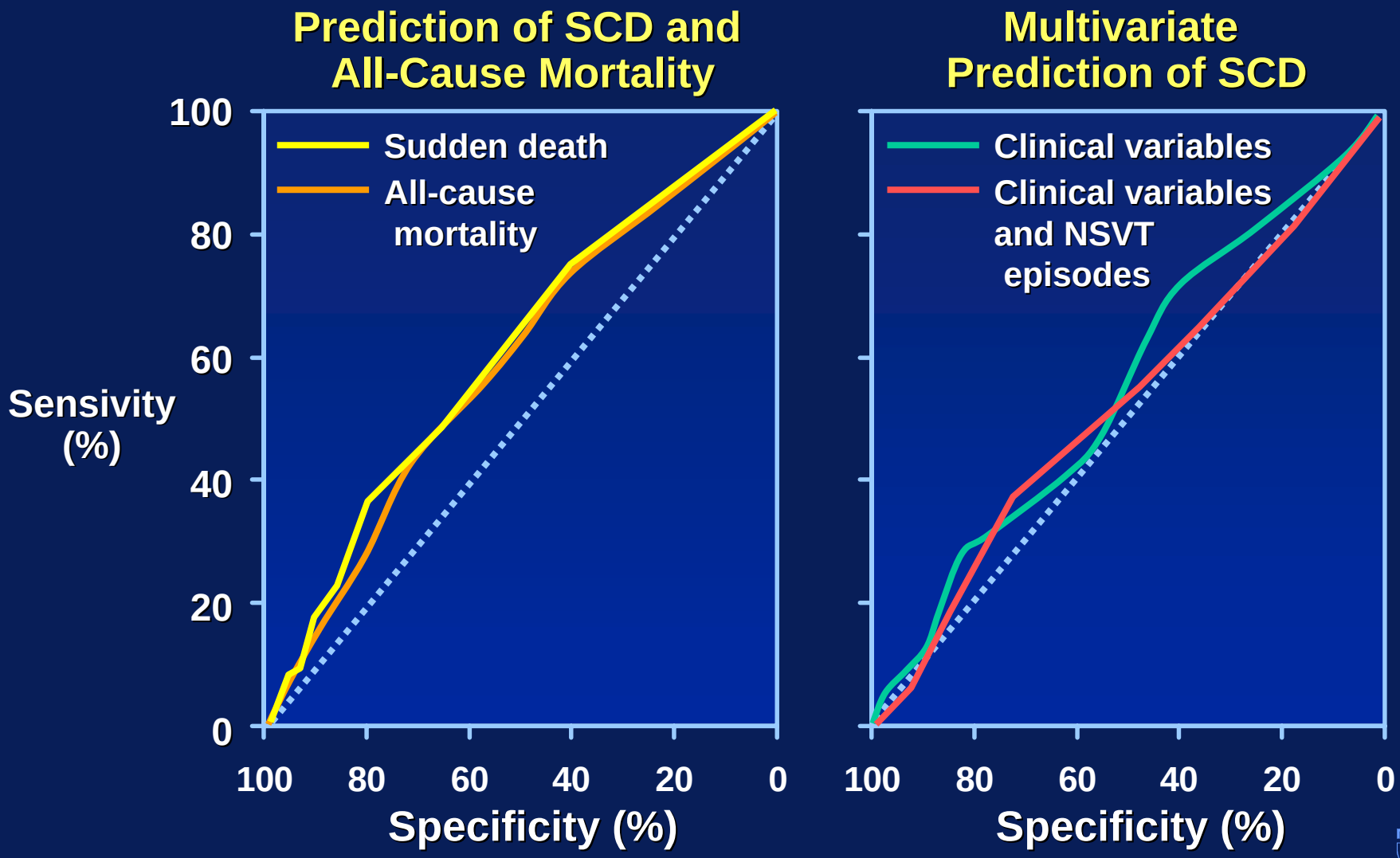
Marian AJ: JCI, 1999

MAYO CLINIC

CP1111783-3

Sensivity and Specificity of NSVT and SCD

PROMISE Trial–EF ≤35%–CAD (54%)



Teerlink: Circ, 2000

mayo

CP1016147-31

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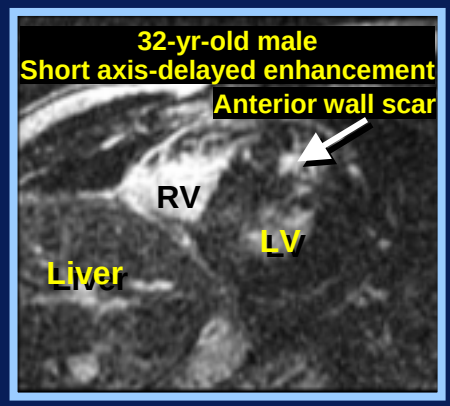

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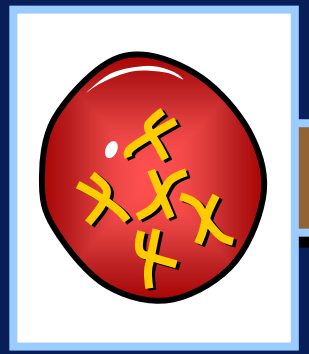

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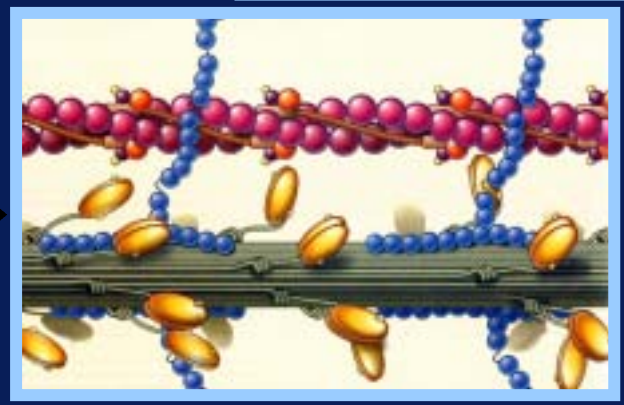

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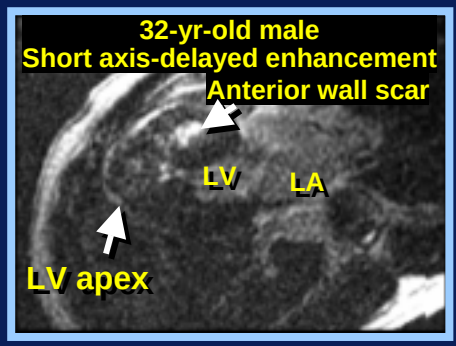

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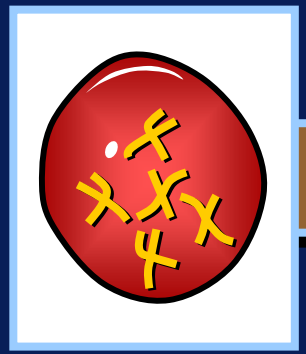

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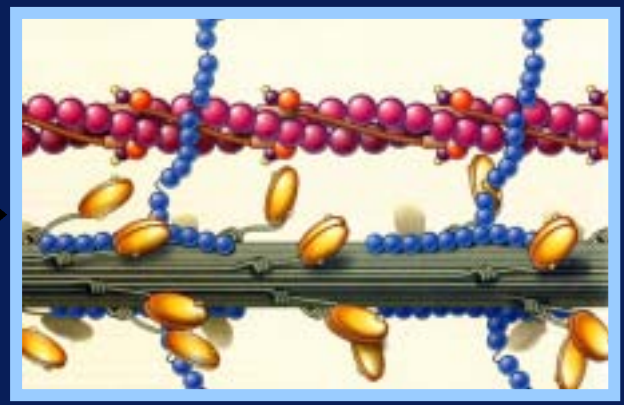

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