HCM Is A Global Disease

50 countries...all continents

General Population

1:500

600,000 people in the U.S.

AT RISK:

50,000 – 100,000?

CARDIA
N=4,111;23-35 y
0.17%

Rural Minnesota
N=15,137;16-87 y
0.19%

Japan
N=3,354;20-77 y
0.17%

Amer Indians
N=3,501;51-77 y
0.2%

China
N=8,080;18-74 y
0.16%

Tanzania
N=6,680;22-91 y
0.2%

HCM: The Tip Of The Iceberg

Identified

Unidentified
**Clinical Recognition of HCM**

- **Symptom Onset (43%)**
- **Routine Exam (33%)**
- **Acute Event (11%)**
- **Sports/Other Screening (4%)**
- **Family Screening (13%)**

Adabag et al. AJC 2006;98:1507

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**Heterogeneity**

- Asymmetrical hypertrophic cardiomyopathy
- Asymmetrical hypertrophy of the heart
- Asymmetrical septal hypertrophy
- Block's disease
- Diffuse muscular subaortic stenosis
- Diffuse subvalvular aortic stenosis
- Dynamic hypertrophic subaortic stenosis
- Dynamic muscular subaortic stenosis
- Familial hypertrophic subaortic stenosis
- Familial myocardial disease
- Functional aortic stenosis
- Functional hypertrophic subaortic stenosis
- Functional obstruction of the left ventricle
- Functional obstructive subvalvular aortic stenosis
- Functional subaortic stenosis
- Hereditary cardiovascular dysplasia
- Hypertrophic cardiomyopathy (HCM)
- Hypertrophic constrictive cardiomyopathy
- Hypertrophic hyperkinetic cardiomyopathy
- Hypertrophic infiltrative aortic stenosis
- Hypertrophic nonobstructive cardiomyopathy
- Hypertrophic obstructive cardiomyopathy
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Hypertrophic subaortic stenosis
- Idiopathic hypertrophic subvalvular stenosis
- Idiopathic muscular hypertrrophic subaortic stenosis
- Idiopathic muscular stenosis of the left ventricle
- Idiopathic myocardial hypertrrophy
- Idiopathic stenosis of the flushing chamber of LV
- Idiopathic ventricular septal hypertrophy
- Idiopathic hypertrophic cardiomyopathy
- Left ventricular muscular stenosis
- Low subaortic aortic stenosis
- Muscular aortic stenosis
- Muscular hypertrophic stenosis of LV
- Muscular stenosis of the left ventricle
- Muscular subaortic stenosis
- Muscular subvalvular aortic stenosis
- Non-dilated cardiomyopathy
- Nonobstructive hypertrophic cardiomyopathy
- Obstructive cardiomyopathy
- Obstructive hypertrophic aortic stenosis
- Obstructive hypertrophic cardiomyopathy
- Obstructive hypertrophic myocardiopathy
- Obstructive myocardial disease
- Pseudocoronary stenosis
- Sclerosis hypertrophy of the left ventricle
- Stenosis of the ejection chamber of LV
- Subaortic stenosis
- Subaortic stenosis of LV
- Subaortic subvalvular stenosis
- Subaortic subvalvular stenosis
27 yr/old female
Genotyped based on +FH (MyBPC3)/
Phenotype (-)

33 yr/old now and development of
LVH and SAM; Phenotype (+)

Age 27y

Age 33y

Maron, BJ et al. JACC 2001;38:315
Hypertrophic Cardiomyopathy

Sarcomeric Protein Mutations

Non-Sarcomeric Mutations

~ 11 Genes—
or more?

> 1000 mutations

AMP-Kinase
(PRKAG2)

Fabry Disease

Lamp2 (Danon)

Storage Diseases
Survival with HCM in an Unselected Cohort of Adults (Diagnosis > age 20)

- **n=234**
- Avg. follow-up=8.1 years
- HCM mortality rate=1.2%/yr
- p=0.22

Maron BJ et al. JAMA 2008

Age Distribution in 274 Unselected HCM Patients

- Survivors
- Died HCM Related
- Died Non-HCM Related

- 21%
HCM: A Bad Disease? ... Or a Disease That Can Be Bad?

Profiles in Prognosis for HCM

- Sudden Death Risk
- Symptom Progression
- End-Stage
- AF

ASYMMETRICAL HYPERTROPHY OF THE HEART IN YOUNG ADULTS

by DONALD YEARE

From the Department of Pathology, St. George's Hospital

"Tomatoes of the heart and pericardium have evolved an extensive literature out of all proportion to their apparent incidence and their relative importance as a cause of clinical heart disease." This opening sentence of Pomerico's chapter on cardiac tumors in "Pathology of the Heart" (Philadelphia, 1949) lies a pathologist with diligence to repeating eight men that have been seen in the last six years in a series of 40,000 autopsies.

"There is little information for metatalc tumors in young adults, and only by a review to some of the literature can the differential diagnosis, particularly of conditions that may oppose cardiac surgery. These eight cases of asymmetric hypertrophy of cardiac tumors in neonatal hearts are described in detail here, and may be among case in the its nature.
Arrhythmogenic Myocardial Substrate in HCM

Maron, BJ et al. Circulation 2000;102:858

HCM (36%)
- Other† (5%)
- MVP (4%)
- Ion Channel (4%)
- ARVC (4%)
- Aortic Rupture (3%)
- CAD (3%)
- LAD Bridge (3%)
- Dilated CM (2%)
- WPW (2%)
- Possible HCM* (8%)
- MVP (4%)
- Other† (5%)

Sudden Death in Young Athletes

Bethesda Conference # 36

Recommendations

Athletes with the unequivocal diagnosis of hypertrophic cardiomyopathy should not participate in most competitive sports, with the possible exception of those of low intensity. This recommendation includes those athletes with or without symptoms and with or without left ventricular outflow obstruction.

HCM: identification of high risk patients

follow-up duration (years)

Event-free rate

DE vs. Events

Follow-up Duration (years)

Event rate

DE (+) DE (-)

N = 202
Follow-up: 681 ± 249 days
p = 0.5
Highest

Intermediate

Lowest

ICD

2° prevention
Cardiac arrest/sustained VT

1° prevention
Familial sudden death
Unexplained syncope
Multiple-repetitive NSVT (Holter)
Abnormal exercise BP response
Massive LVH

Potential arbitrators
End-stage phase
LV apical aneurysm
Marked LV outflow obstruction (rest)
Extensive delayed enhancement
Modifiable
Intense competitive sports
CAD
Alcohol septal ablation (?)
Mutations ±

Relation Between LV Thickness & SCD in 482 HCM Patients

% Patients With SCD

<15 16-19 20-24 25-29 ≥30

Max. LV Wall Thickness (mm)
Figure 1.

Patients with LVAA (n=28):
- Aborted Cardiac Arrest (2) ✝
- Progressive Heart Failure/Death (5) ✝
- Sudden Death (2)*
- non-fatal embolic stroke (1)
- Appropriate ICD Discharge (3)*

Alive/Clinically Stable (n = 16)*

Adverse Events (n = 12)
- non-fatal embolic stroke (1)
- Sudden Death (2)
- Aborted Cardiac Arrest (1)
- Progressive Heart Failure/Death (1)
- Appropriate ICD Discharge (1)

Cardiovascular Event Rate = 11%/year

Foci For Ventricular Arrhythmias?
**Prevention of Sudden Death In HCM**
Drugs Do Not Protect Absolutely From Sudden Death in HCM

Termination of Malignant Ventricular Arrhythmias with an Implanable Cardioverter Defibrillator

35 y – Brother SD
36 y – ICD
40 y – Generator replaced
41 y – Appropriate shock #1
50 y – Appropriate shock #2
52 y – Present

HCM is *Unpredictable*

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**Circadian Variability for Appropriate ICD Shocks**

- **No. of Events**
- **Hour of Day**

---

**ICD in HCM: Age at Implant**

- **No. of Patients**
- **Age At Implant (years)**
**ICD in HCM: 2007**

- Appropriate Shocks: VT/VF (20%)
- ICD discharge rate: 5.5%/yr
- Follow-up: 3.7 ± 3 years

**High-Risk Children with HCM and ICDs**

- Implant ≤ 20 years: 83
  - Appropriate shocks: 23 (28%; 7%/yr)
  - Age at intervention: 18 ± 4 years
- Implant ≤ 15 years: 37
  - Appropriate shocks: 13 (35%; 11%/yr)
  - Age at intervention: 15 ± 3.6 years

**Rate of Appropriate Shocks**

- Overall p=0.88
- 33% of appropriate shocks

**No. Risk Factors for Primary Prevention**

- 1: 3.7
- 2: 3.0
- 3: 4.6
One Risk Factor Patients With Primary Prevention

![Graph showing appropriate shock rates/year for different risk factors]

- Massive LVH: 2.0
- Family SD: 2.8
- NSVT (Holter): 2.9
- Syncope: 5.0

Maron, BJ et al. JAMA 2007;298:

ICD in HCM - II: Time to First Shock

![Bar graph showing time to first shock by duration (months)]

- Deaths:
  - ICD Malfunction: 29 (6%)
  - HCM—Arrhythmias (nl EF): 1
  - Cancer, sepsis, renal diseases, suicide, CAD, accidents: 14
  - End-stage Embolic stroke: 14

Maron, BJ et al. JAMA 2007;298:
After the Shock?

Trading SD for CHF

Clinical Status Post—Appropriate ICD Shock

NYHA Class Initial VT/VF

NYHA Class At follow-up

90%
Management of HCM

- Beta-blocker
- Verapamil
- Beta-blocker + Diuretic
- Verapamil + Diuretic
- Disopyramide
- Diltiazem
- Beta-blocker + Verapamil

Subaortic Obstruction
Subaortic Myotomy-Myectomy
Nonobstructive
Heart Transplantation

Impact of Outflow Obstruction (≥ 30mmHg) on Progression to Severe Heart Failure - Related Symptoms and Death in 1101 HCM Patients

Maron, MS NEJM 2003:348:292

LV Outflow Gradient (mmHg)

Rest Post-Exercise
Case for Septal Myectomy: The Gold Standard

- 45 years of experience
- Low operative mortality (≤1%) & virtually zero last 10 y @ major centers) — lower than ablation
- Permanent, virtually complete reduction LVOTG to 0-10mmHg
- 85%: substantial reduction heart failure over long time
- Anatomic flexibility, under direct visualization
- Permits revision mitral / subvalvular anomalies
- No residual — no septal scar
- Monitor / revise resection w/ intraoperative echo
- Rapid reduction of obstruction
- Evidence of increased survival, possibly normal longevity

Surgical Septal Myectomy

Survival

- Isolated Myectomy
- Nonoperated obstructive
- Expected — US population

Ommen, S et. al. JACC 2006

Septal Ablation: HCM

- Images of septal ablation in a heart muscle.
**Major Issues with Alcohol Septal Ablation**

- Short follow-up: Is gradient / symptom relief long-lasting?
- Residuals common — i.e., PMK and ICD (20%)
- Relatively high rate of repeat procedures (25%)
- Often not successful w/ high gradients
- Dobutamine contamination of gradient data
- Myectomy after failed ablations is difficult
- The infarct/scar and SD risk, particularly in the young

---

**Septal Scarring**

<table>
<thead>
<tr>
<th>Post-ablation</th>
<th>Post-myectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septal Scar</td>
<td>No Scar</td>
</tr>
<tr>
<td>VS=30%</td>
<td>LV10%</td>
</tr>
</tbody>
</table>

Valeti et al. JACC 2007;49:350
Ventricular Tachyarrhythmias and Sudden Death Following Alcohol Septal Ablation

% Patients With Sustained VT/VF/SD

- Sorajja: 5%
- Cuoco: 7%
- Noseberry: 10%
- Maron: 24%
- van der Lee: 25%

Profiles in Prognosis for HCM

- Sudden Death
- Progressive Heart Failure
- End-Stage
- AF & Stroke

Clinical Pathways of Prognosis in HCM

- Normal Longevity
- SD
  - ICD
- Progressive HF
  - Drugs
  - Myectomy (alcohol ablation)
- End Stage
  - Transplant
  - Drugs
- AF & Stroke
  - warfarin
  - RFA
Sudden Death Risk
Symptom Progression

End‐Stage AF

ICD

Benign/Stable (normal longevity)

Profiles in Prognosis for HCM

Sudden Death Risk

ICD

The “Uncommon” Diseases

No. Affected / Million

HCM, Cystic Fibrosis, Multiple Sclerosis, Muscular Dystrophy, LQTS, Marfan, ALS, Brugada, Ataxia
Women With HCM

- Diagnosed less frequently
- Older when diagnosed (implying delay)
- More symptomatic when diagnosed
- Later recognition of symptoms
- More commonly have outflow obstruction

Olivotto et al. JACC 2005:46:480

HCM and Race

- Hospital-Based HCM Patients (n=1,986)
  - Competitive Athletes: HCM-related Sudden Death (n=102)
  - White (45%)
  - African-American (55%)
  - White (92%)
  - African-American (8%)

Compete Athletes: HCM-related Sudden Death (n=102) vs. Hospital-Based HCM Patients (n=1,986)
HCM is a Predominantly Obstructive Disease

- Non-Obstructive (95; 30%)
- Rest Obstruction (119; 37%)
- Provokable Obstruction (Exercise) (106; 33%)

70%

Cardiac Arrest
ICD Shock

39
Died
Survived

7
SCD (1)
End-stage (4)
Non-HCM (2)

32
No recurrence

15
If < 10 y (up to 30 y)

17
10 ≤ 8 y

ICD in HCM

• No. Patients: 506
• Centers: 42
• Sites: U.S.; Italy / W.Europe; Australia
• Age: 42±17 years
• Gender: 64% male
• LV outflow obstruction: 26%
• Follow-up: 3.7±2.8 years
• Max. LV thickness: 23±7mm

ICD: HCM vs. CAD

<table>
<thead>
<tr>
<th></th>
<th>CAD</th>
<th>HCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implant age</td>
<td>~65</td>
<td>~40</td>
</tr>
<tr>
<td>Risk period</td>
<td>short</td>
<td>long</td>
</tr>
<tr>
<td>Substrate</td>
<td>often</td>
<td>usually</td>
</tr>
<tr>
<td></td>
<td>compromised</td>
<td>intact</td>
</tr>
<tr>
<td>Intervention / yr</td>
<td>~30%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Deaths
N = 29 (6%)

• No–HCM: 14
  - cancer / sepsis
  - renal
  - suicide
  - accidents
  - CAD

• HCM: 14
  - End-stage
  - Embolic stroke

• HCM – Arrhythmia: 1
  (ICD malfunction)
Short and Long-Term Outcome After Alcohol Septal Ablation for Obstructive HCM (91 patients)

"...about one-third of HCM patients who underwent alcohol septal ablation...developed one or more cardiovascular complications over...5.6 years."

Impact of Outflow Obstruction (≥ 30mmHg) on Risk For Sudden Death in 1101 HCM Patients

Other Possible Contributing Risk Factors In Individual HCM Patients

- AF
- Myocardial ischemia
- Bridged LAD
- Alcohol Septal Ablation
- LV outflow obstruction
Clinical Implications of LAMP2 Cardiomyopathy

- Survival after age 25 years unlikely
- Requires molecular diagnosis
- Deserves consideration for heart transplantation

Strongest Risk Factors:
- Cardiac arrest
- Familial SD
- Syncope
- Multiple-repetitive NSVT
- LRP — exercise
- Massive LVH
- End-Stage
- Apical aneurysm
- Malignant genotype (?)
- Alcohol Ablation (?)

Septal Myectomy vs. Alcohol Septal Ablation: Appropriate ICD Shocks

<table>
<thead>
<tr>
<th></th>
<th>No. Pts</th>
<th>No. Appropriate Shocks</th>
<th>% Age-Adjusted</th>
<th>%/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical myectomy</td>
<td>50</td>
<td>6</td>
<td>12%</td>
<td>2.6</td>
</tr>
<tr>
<td>Alcohol septal ablation</td>
<td>17</td>
<td>4</td>
<td>24%</td>
<td>10.3</td>
</tr>
</tbody>
</table>

*p<0.01

4x
One Risk Factor Patients With Primary Prevention

- Massive LVH
- Family SD
- NSVT (Holter)
- Syncope

Appropriate Shock Rates/Year

- 2.0
- 2.8
- 2.9
- 5.0

Joshua's Implantable Defibrillator
Prizm 2 DR Model 1861 (10/4/01)

- + Backfill tube
- Short circuit
- DF Feedthrough wire
- Polyimide tubing
- *Guidant aware 2002
- *Did not inform physicians or patients

Massive LVH Family SD NSVT (Holter) Syncope

ASYMMETRICAL HYPERTROPHY OF THE HEART IN YOUNG ADULTS

BY DONALD YEAK

From the Department of Pediatrics, St. George's Hospital.

Revised January 1, 1997

"...symptoms of the heart and pericardium have evolved an extensive literature, but all precautions to their management..."
HCM: A Bad Disease?… or a Disease That Can Be Bad?
HCM Is A Global Disease

Previously Proposed Pharmacologic Therapy For Sudden Death Prevention in HCM

- β-adrenergic blockers
- verapamil
- procainamide
- quinidine
- amiodarone

no data
proarrhythmia (obsolete)
efficacy? chronic use (>3y)?
<table>
<thead>
<tr>
<th>HCM Cohorts</th>
<th>Annual Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tertiary-referral based</strong></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>4 – 6 %</td>
</tr>
<tr>
<td>Children &amp; adults</td>
<td>3 – 4 %</td>
</tr>
<tr>
<td><strong>Community-based</strong></td>
<td></td>
</tr>
<tr>
<td>non-tertiary regional unselected</td>
<td>0.5 – 1.5 %</td>
</tr>
</tbody>
</table>

![Ultrasound images](image)
End-Stage

EF ≤ 50%

LV Cavity ↑
LV Wall ↓

Death
Acute MI
VF
PNNR
ICD
Re-Intervention

Surgery
Ablation

Serruy et al. Circulation 2005; 112: 482
Rotterdam Thorax Ctr.
Over the past 40 years, based on the experience of a number of centers throughout the world, the ventricular septal myectomy operation (also known as the Morrow procedure) (8) has become established as a proven approach for alleviation of outflow obstruction and the standard therapeutic option, and the gold standard, for both adults and children with obstructive HCM and severe drug-refractory symptoms (7, 11, 14, 15, 41, 70, 78, 81, 84, 85, 90–95, 102–106, 214). The myectomy operation should be confined to centers experienced in this procedure.
The "Uncommon" Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. Affected / Million</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCM</td>
<td>2000</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>1500</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>1000</td>
</tr>
<tr>
<td>Muscular Dystrophy</td>
<td>500</td>
</tr>
<tr>
<td>LQTS</td>
<td>2500</td>
</tr>
<tr>
<td>Marfan</td>
<td>2000</td>
</tr>
<tr>
<td>ALS</td>
<td>1500</td>
</tr>
<tr>
<td>Brugada</td>
<td>1000</td>
</tr>
<tr>
<td>Ataxia</td>
<td>500</td>
</tr>
</tbody>
</table>

Sudden Death in Young Athletes

- HCM (36%)
- Indeterminate LVH - possible HCM (8%)
- Other congenital HD (17%)
- Ion channelopathies (17%)
- Aortic rupture (2%)
- Sarcoidosis (1%)
- Coronary artery anomalies (17%)
- Normal heart (3%)
Bethesda Conference # 26

Recommendations

Athletes with the unequivocal diagnosis of hypertrophic cardiomyopathy should not participate in most competitive sports, with the possible exception of those of low intensity. This recommendation includes those athletes with or without symptoms and with or without left ventricular outflow obstruction.
Theoretical Surgical Myectomy vs. Alcohol Septal Ablation Trial

- **Patients Undergoing Coronary Angiogram**
  - 25,200
  - 12,530 (50%) Clinically Eligible
  - 4,110 Eligible for Both CABG and PTCA
  - 1,629 (7%) Enrolled and Randomized

- **Exclusion Criteria**
  - 67%
  - 3,400 (10%) Refused Randomization

- **Eligible for Both Myectomy and ASA**
  - 55%
  - 2,400

- **Enrolled and Randomized**
  - 1,200 (3.5%)
  - 600 Myectomy
  - 600 ASA

- **Bypass Angioplasty Revascularization Investigation (BARI)**
  - 34,000 Patients Undergoing Coronary Angiogram
  - 3,400 (10%) Clinically Eligible
  - 2,400 Eligible for Both CABG and PTCA
  - 600 Enrolled and Randomized

- **Exclusion Criteria**
  - 30%
  - 1,829 (7%) Refused Randomization

- **Eligible for Both Myectomy and ASA**
  - 50%
  - 1,200 (3.5%)

- **Enrolled and Randomized**
  - 600 Myectomy
  - 600 ASA
Profiles in Prognosis for HCM

Sudden Death Risk

ICD

Symptom Progression

End-Stage

ICD

Sudden Heart Failure Stroke

0 10 20 30 40 50 60 70 80

Age at Death (years)

Mode of HCM Death

Hypertrophic Cardiomyopathy

Sarcomeric Protein Mutations

Non-Sarcomeric Mutations

AMP-Kinase (PRKAG2)

Lamp2 (Danon)

Fabry Disease

~ 11 Genes or more?

> 400 mutations

Storage Diseases
Case for Septal Myectomy: The Gold Standard

- 45 years of experience
- Permanent, virtually complete reduction LVOTG to 0-10mmHg
- 85%: substantial reduction heart failure over long time
- Permits revision mitral / submortal anomalies
- Monitor / revise resection w/ intraoperative echo
- Rapid reduction of obstruction
- Evidence of increased survival, possibly normal longevity

Its All About Patient Selection

**Myectomy**
- *Primary option*
- Particularly, for younger patients w/ substantial life expectancy

**Ablation**
- *Alternative option*
- Particularly, poor operative candidates
  - significant co-morbidity
  - advanced age
  - reject surgery
NYHA III/IV
Post-Op
Rest
Gradient
Post-Op
Provocable
Gradient
Late CV
Death
Failure

% of Patients

Ablation
Mystomy

59%
12%
5%
59%
0%
15%
5%
14%
15%
6%
42%
2%
2%

p < 0.001
p < 0.001
p < 0.001
p < 0.001
p < 0.001

Ralph-Edwards et al.

45 years
5 yr
~ 3,000
> 3,500

Surgery Ablation

Time
45 years
5 yr

Cases
~ 3,000
> 3,500

Ablation > Surgery by 10-35x in last 5 years
Case for Septal Myectomy: The Gold Standard

- 45 years of experience
- Permanent, virtually complete reduction LVOTG to 0-10mmHg
- 90%: substantial reduction heart failure over long time
- Permits revision mitral / submitral anomalies
- Monitor / revise resection w/ intraoperative echo
- Rapid reduction of obstruction
- Low operative mortality (≤ 1%) & virtually zero last 12 y @ major centers) --- lower than ablation

Principles

- Patients have a fundamental right to be fully informed when they are exposed to the risk of death no matter how low that risk may be perceived.
- Patients---and their physicians---are entitled to full disclosure of product information that may affect an individual’s health or safety.

Impact of Outflow Obstruction (≥ 30mmHg) on Risk For Sudden Death in 1101 HCM Patients

![](chart.png)
Consecutive Pure Myectomy Patients w/o An Operative Death

Total

Mutation Distribution - Causing Mutations in HCM Cohort

from Van Driest and Ackerman (Mayo); 2004
Obstacles From Industry

Major Issues with Alcohol Septal Ablation

- Short follow-up: is gradient / symptom relief long-lasting?
- Residuals common – ie. PMK and ICD (20%)
- Relatively high rate of repeat procedures (25%)
- Often not successful with high gradients
- Myectomy after failed ablations is difficult
- Anatomic inflexibility – perforator distribution
HCM DISEASE SPECTRUM

Marked Outflow Obstruction + Severe Symptoms (5%)

ICD in HCM: Age at Implant

Major Issues: Alcohol Septal Ablation

- Short follow-up: Is gradient / symptom relief long-lasting?
- Residuals common –ie. PMK and ICD (20%)
- Anatomic inflexibility – perforator distribution / selection
- Relatively high rate of repeat procedures (25%)
- Often not successful w/ high gradients
- Dobutamine contamination of gradient data
- Myectomy after failed ablations is difficult
- The infarct/ scar and SD risk, particularly in the young
Primary Prevention of SD in HC

1 or 2 risk factors required?

---Individualization---

“Over-treatment” vs. “under-treatment”

Imperfect risk stratification

Perceived liability

ICD is more powerful than our present ability to precisely identify all high risk patients
Family Screening Strategies to Detect HC With Echo / ECG (Absent Genetic Testing)

- **< 12 years old**
  - optional unless:
    - malignant family
    - competitive athlete
    - suspicion of early onset LVH

- **12 to 18 years old**
  - q 12 - 18 mo.

- **> 18 years old**
  - q every 5 years
  - (or until routine genetic testing available to resolve)

Glycogen Storage Cardiomyopathies (mimic HCM)

<table>
<thead>
<tr>
<th>PRKAG2 (AMP-kinase)</th>
<th>Cardiac Danon (Lamp 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ventricular pre-excitation (in some)</td>
<td>• Ventricular pre-excitation (often)</td>
</tr>
<tr>
<td>• Range in age (31 ± 15 y)</td>
<td>• Young males &lt; 25 y</td>
</tr>
<tr>
<td>• Relatively mild LVH</td>
<td>• Massive LVH (35 ± 15 mm)</td>
</tr>
<tr>
<td></td>
<td>• Tall ECG voltages</td>
</tr>
<tr>
<td></td>
<td>• Abnormal chemistries</td>
</tr>
<tr>
<td></td>
<td>† ALT / CPK</td>
</tr>
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<td>non–tertiary</td>
<td></td>
</tr>
<tr>
<td>regional</td>
<td></td>
</tr>
<tr>
<td>unselected</td>
<td>0.5 – 1.5 %</td>
</tr>
</tbody>
</table>

*Barry J. Maron, MD*

**Interventions for Obstructive HCM**

Minneapolis 1993 – 2006 (14 years)

- No. HCM Patients: 958
- Referrals for surgical myectomy: 114 (12%)
- Referred for alcohol ablation: 14 (1%)
- Total Interventions (~ 9 pts / yr): 128 (13%)
Survival With HCM According to Age at Diagnosis

- HCM
- Gen. Pup

Years From HCM Diagnosis

Percent Survival

P=0.001

P=0.20

≥ 50 yr

< 50 yr

Maron MS, Circulation, in press
Risk Stratification and ICD Decision-Making in HCM

- Current risk factors are a useful guide
- 1 risk factor can be enough (but not obligatory for device therapy)
- Risk factors cannot be summed numerically
- ICD decisions may also be based on individual physician judgment/patient autonomy considerations

Barry J. Maron, MD
Interventions for Obstructive HCM
Minneapolis 1993 – 2003 (10 years)

No. HC Patients 725
- Referrals for surgical myectomy 20 (2.8%)
- Referred for alcohol ablation 5 (0.7%)
- Total Interventions (~ 2 pts / yr) 25 (3.5%)

ICD in HCM
- No. Patients: 506
- Centers: 42
- Sites: U.S.; Italy; W.Europe; Australia
- Age: 42±17 years
- Gender: 64% male
- LV outflow obstruction: 26%
- Follow-up: 3.7±2.8 years
- Max. LV thickness: 23± 7mm
### ICD: HCM vs. CAD

<table>
<thead>
<tr>
<th></th>
<th>CAD</th>
<th>HCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implant age</td>
<td>~65</td>
<td>~40</td>
</tr>
<tr>
<td>Risk period</td>
<td>short</td>
<td>long</td>
</tr>
<tr>
<td>Substrate</td>
<td>often compromised</td>
<td>usually intact</td>
</tr>
<tr>
<td>Intervention / yr</td>
<td>~30%</td>
<td>7%</td>
</tr>
</tbody>
</table>

### The Oukrop Family

*ICD: 10/4/01*

### The “Uncommon” Diseases

![Bar chart showing various diseases](chart.png)
Other Possible Contributing Risk Factors in Individual HCM Patients

- AF
- Myocardial ischemia
- Bridged LAD
- Alcohol Septal Ablation
- LV outflow obstruction

NYHA III; EF 40%; 30% DE
NYHA I; EF 65%; 46% DE
Subsequent Events

- **June**: Guidant recalled 26,000 Prizm 2 DR ICDs.
- **June**: Guidant recalled 16,000 Contak ICDs after a patient died due to a short-circuit problem the company had identified a year earlier.
- **June**: Guidant recalled 21,000 AVT ICDs.
- **June**: Guidant recalled 46,000 Renewal ICDs.
- **July**: Guidant recalled 28,000 pacemakers that were prone to abrupt failure and runaway pacing that caused at least one death.

> 180,000 devices

Late Onset LVH

![Diagram showing the percentage of myocardium with DE at different ejection fractions (≤50, 51-59, ≥60). The p-value is 0.001.](image)

% Myocardium with DE

Ejection Fraction (%)

- ≤50
- 51-59
- ≥60

p < 0.001
**HCM and Race**

- **Hospital-based HCM Patients (n=1,986):**
  - White (45%)
  - African-American (55%)

- **Competitive Athletes: HCM-related Sudden Death (n=102):**
  - White (92%)
  - African-American (5%)

---

**Commercial Diagnostic Genetic Testing for HCM**

- **Laboratory of Molecular Medicine (Partner’s Health Care; Harvard Medical School):**
  - [http://www.hpcgp.org/lmm](http://www.hpcgp.org/lmm)
  - Tests for known and novel mutations in 10 most common HCM genes
  - 7 cc blood
  - Results: ≤ 4 weeks
  - Cost: $2800; $200 / each relative
  - Limitations:
    - cost
    - false negatives

---

**High-Risk Children with HCM and ICDs**

- **Implanted < 20 years:**
  - 83
  - Appropriate shocks: 23 (28%;7%/y)
  - Age at intervention: 18 ± 4 years

- **Implanted < 15 years:**
  - 37
  - Appropriate shocks: 13 (35%;11%/y)
  - Age at intervention: 15 ± 3.6 years
Case for Septal Myectomy: The Gold Standard

- 45 years of experience
- Low operative mortality (≤ 1%) & virtually zero last 12 y @ major centers) — lower than ablation
- Permanent, virtually complete reduction LVOTG to 0-10mmHg
- 85%: substantial reduction heart failure over long time
- Anatomic flexibility, under direct visualization
- Permits revision mitral / subvalvular anomalies
- No residual — no septal scar
- Monitor / revise resection w/ intraoperative echo
- Rapid reduction of obstruction
- Evidence of increased survival, possibly normal longevity

Septal Myectomy vs. Alcohol Septal Ablation: Appropriate ICD Shocks

<table>
<thead>
<tr>
<th></th>
<th>No. Pts</th>
<th>No. Appropriate Shocks</th>
<th>%</th>
<th>%/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical myectomy</td>
<td>50</td>
<td>6</td>
<td>12</td>
<td>2.6</td>
</tr>
<tr>
<td>Alcohol septal ablation</td>
<td>17</td>
<td>4</td>
<td>24</td>
<td>10.3</td>
</tr>
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</table>

\[ p < 0.01 \]

\[ 4x \]

Other Possible Contributing Risk Factors In Individual HCM Patients

- AF
- Myocardial ischemia
- Bridged LAD
- Alcohol Septal Ablation
- LV outflow obstruction
**Septal Scarring**

Post-ablation

- Septal Scar
  - VS = 30%
  - LV = 10%

Post-myectomy

- Septal Scar
- No Scar

---

**Septal Myectomy vs. Alcohol Septal Ablation: Appropriate ICD Shocks**

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**AGE 11**

**AGE 16**
Bethesda Conference # 36

Classification
Sports (#8)

Consensus Panels

#1 #2 #3 #4 #5 #6 #7
Congenital Valvular HCM Other CA MVP Dysrhythmia Drugs HTN CAD AED Commotio Legal

#8 #9 #10 #11 #12
Symptom Onset (43%)
Family Screening (13%)
Acute Event (11%)
Sports/Other Screening (4%)
Routine Exam (33%)

CMR Delayed
Enhancement?

Clinical Recognition of HCM