Hypertrophic Cardiomyopathy: A Contemporary And Treatable Disease in 2015

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Disclosures:
Medtronic (Grantee)
GeneDx (Consultant)
General Population 1:500

700,000 people in U.S.

AT RISK: 50,000 – 100,000 ?
Profiles in Prognosis for HCM

- Benign/Stable (normal longevity)
- Sudden Death
- Progressive Heart Failure
- End-Stage
- AF & Stroke
**U.S./Canada: ACC/AHA: 2011**

### Highest
- **2° prevention**
  - Cardiac arrest/sustained VT

### Intermediate
- **1° prevention**
  - Family history HCM-SD
  - Unexplained syncope
  - Multiple-repetitive NSVT (Holter)
  - Abnormal exercise BP response
  - LGE \( \geq 15\% \) of LV mass

### Lowest
- **Rare subgroups/potential arbitrators**
  - End-stage (EF < 50%)
  - LV apical aneurysm
  - Marked LV outflow obstruction (rest)
  - Modifiable
    - Intense competitive sports
    - CAD
    - LGE \( \geq 15\% \) of LV mass
    - Age \( \geq 60\)y
    - Alcohol septal ablation (?)
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)
U.S. Canada (ACC/AHA)

**2° prevention**
Cardiac arrest/sustained VT

**1° prevention**
Family history HCM-SD
Unexplained syncope
Multiple-repetitive NSVT (Holter)
Abnormal exercise BP response
LGE ≥ 15% of LV mass
Massive LVH ≥ 30 mm

**Rare subgroups/potential arbitrators**
End-stage (EF < 50%)
*LV apical aneurysm*
Marked LV outflow obstruction (rest)
Modifiable
  - Intense competitive sports
  - CAD
LGE ≥ 15% of LV mass
Age ≥ 60y
Alcohol septal ablation (?)
Figure 1.
HCM Related Death or Adverse Clinical Events in 70 Patients with LV Apical Aneurysms

Log-rank test p<0.001

Survival free from HCM related mortality and adverse events

HCM patients without LV apical aneurysms
HCM patients with LV apical aneurysm

1.7%/year
8.1%/year

Years from First Evaluation
**U.S./Canada: ACC/AHA**

### 2° prevention
Cardiac arrest/sustained VT

### 1° prevention
Family history HCM-SD
Unexplained syncope
Multiple-repetitive NSVT (Holter)
Abnormal exercise BP response
LGE \(\geq 15\%\) of LV mass
Massive LVH \(\geq 30\) mm

### Rare subgroups/potential arbitrators
End-stage (EF < 50%)
LV apical aneurysm
Marked LV outflow obstruction (rest)
Modifiable
- Intense competitive sports
- CAD
LGE \(\geq 15\%\) of LV mass
**Age \(\geq 60\) y**
Alcohol septal ablation (?)
Outcome of HCM Patients First Evaluated ≥ 60 Years

Aging is Good in HCM

- Alive: 65%
- Non-Cardiac Death: 13%
- Non-HCM Cardiac Death: 12%
- Embolic Stroke: 2%
- Heart Failure: 1%
- SCD: 1%

Maron BJ et. al. Circ 2013; 127: 585
Risk Stratification for Sudden Death in HCM

- Family history of sudden death
- Extreme LVH
- Nonsustained VT
- Unexplained syncope
- Abnormal BP response to Ex

No risk factors

0.5%/year
Prevalence of LGE = 55-70%
Extent of LGE vs. Sudden Death Risk in HCM

Survival vs. Follow-up (years)

- LGE (-)
- LGE < 10%
- LGE 10-20%
- LGE > 20%

Chan RH et. al. Circ 2014; 130(6): 484-95
2° prevention
Cardiac arrest/sustained VT

1° prevention
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Modifiable
  Intense competitive sports
  CAD
LGE ≥ 15% of LV mass
Age ≥ 60y
Alcohol septal ablation (?)
Genetic Testing

Prognosis

HCM (w/o LVH)

HCM (w/ LVH)

To identify

“Genotype + Phenotype -”

Follow-up
Prevention of Sudden Death in HCM
ICD Performance in HCM

Follow-up = 3.7 ± 3 years

ICD discharge rate

VT/VF

Appropriate Shocks (20%)

5.5%/y

2º prevention

11%/y

1º prevention

4%/y

Maron BJ et al. JAMA 2007; 298:405-412
No. of Risk Factors for Primary Prevention

Rate of Appropriate Interventions per 100 person-yr

- 1 Risk Factor: 3.8
- 2 Risk Factors: 3.0
- ≥ 3 Risk Factors: 4.1

Overall p = 0.88

Appropriate Shocks (35%)
Primary Prevention Decision Tree: ICD In HCM

Risk Factors

High risk

Some risk

Cardiologist

TRANSPARENCY / FULL DISCLOSURE / INFORMED CONSENT

Patient Autonomy
Evidence for Decreased HCM Mortality: 2000 Patients Presenting 10-70 years Old
MHIF/Tufts

What is Possible.....
General Population

"Historic Mortality"

Pre-ICD era

1.5%/y

86 ICD interventions

0.8%/y

Maron BJ et al. JACC 2015
General Population: 0.8%/y

"Historic Mortality": 0.8%/y
General Population "Historic Mortality" 0.8%/y

Transplants 0.8%/y

45 Transplants

% Death Per Year

0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4

General Population "Historic Mortality"
General Population: 0.8% per year

"Historic Mortality": 0.6% per year

30 OHCA (with hypothermia)
% Death Per Year

0.8%/y

161 saved

p = 0.46

0.5%/y

General Population

Current Mortality 2015
HCM-Related Mortality

Age in Years—Initial Evaluation

- ≤ 29 years (n = 474) with HCM-related mortality 0.54
- 30-59 years (n = 1000) with HCM-related mortality 0.50
- ≥ 60 years (n = 428) with HCM-related mortality 0.60
Sudden Death
Advanced HF
Paradigm Change in Causes of Death:
Advanced Heart Failure w/o Obstruction
(transplant/transplant candidates)

All HCM Patients
3%

(60%)
Early HCM Referral Cohorts

HCM Cohorts: Prior to utilization of current treatment strategies/interventions

ICD intervention
Heart transplant/myectomy
OHCA/defibrillation/hypothermia

Present HCM Cohort: Contemporary treatment

General U.S. Population

HCM-Related Mortality

% HCM Mortality

3-6%/y
1.5%/y
0.5%/y
0.8%/y
Profiles in Prognosis for HCM

Benign/Stable (normal longevity)

- Sudden Death
  - ICD
- Progressive Heart Failure (obstructive)
  - Drugs
    - Septal Myectomy (Alcohol Ablation)
- Advanced Heart Failure & End Stage (non-obstructive)
  - Transplant
- AF & Stroke
  - Drugs
    - Anticoagulants Ablation
New HCM Paradigms:

1. Contemporary Treatable Disease Compatible w/ Low Mortality & Extended/Normal Longevity

2. Rx Interventions available to Change Clinical Course of Disease
“At this time we are aware of no method of management that can specifically and favorably influence the course of a patient with idiopathic ventricular hypertrophy.”

Eugene Braunwald
Edwin C. Brockenbrough
Andrew G. Morrow

Circulation, Volume XXVI, August 1962
Assessment of ESC Sudden Death Risk Score

(n = 1649)

% Patients With/Without ICD Intervention/Sudden Death

ESC Risk Score

Appropriate ICD Intervention

<4% 4-6% >6%

Risk/5y

No Appropriate ICD Intervention

Sudden Death

<4% 4-6% >6%

Risk/5y

60% 26% 63%

9%
161 saved

Age at Presentation (years)

- **≤ 29 (n = 474)**
  - HCM-Related Death: 3.8%
  - Aborted HCM Death: 13.3%

- **30-59 (n = 1000)**
  - HCM-Related Death: 4.2%
  - Aborted HCM Death: 5.7%

- **≥ 60 (n = 428)**
  - HCM-Related Death: 2.8%
  - Aborted HCM Death: 1.2%

- **Total (n = 1902)**
  - HCM-Related Death: 3.8%
  - Aborted HCM Death: 6.6%
The ESC-HCM prediction formula for SD is as follows:

\[
\text{Probability}_{\text{SCD at 5 years}} = 1 - 0.998 \exp(\text{Prognostic index})
\]

where Prognostic index = 
\[
[0.15939858 \times \text{maximal LV wall thickness (mm)}] - [0.00294271 \times \text{LV maximal wall thickness}^2 (\text{mm}^2)] + [0.0259082 \times \text{left atrial diameter (mm)}] + [0.00446131 \times \text{maximal (rest/Valsalva) LV outflow tract gradient (mm Hg)}] + [0.4583082 \times \text{family history SCD}] + [0.82639195 \times \text{NSVT}] + [0.71650361 \times \text{unexplained syncope}] - [0.01799934 \times \text{age at clinical evaluation (years)}].
\]
ICD in HCM - II: Time to First Shock

Maron BJ et. al. JAMA 2007;298:405-412

Duration (months)

No. Patients

≤ 3 4 - 6 7 - 10 11-20 21-30 31-40 41-50 51-60 61-70 71-90 >90
HCM is *Unpredictable*
Surgical Septal Myectomy: Quality of Life/Survival

(Operative mortality: 0.4%)

Survival

Years Post-op

Ommen S et. al. JACC 2006
Advanced Heart Failure (n = 21)
SCD (n = 15)
Stroke (n=1)

0.5%/y

15 SCDs but...
5 declined ICD
7 pre-ICD era

Current Mortality
2014
Current Mortality 2014

- Advanced Heart Failure (n = 21)
- SCD (n = 15)
- Stroke (n = 1)

% Death Per Year

0.5%/y
Evidence for Decreased HCM Mortality:

2000 Patients Presenting in Mid-Life (30-59y)

MHIF/Tufts

What is Possible.....
HCM : The Tip Of The Iceberg
Unexplained LVH

Sarcomeric Protein Mutations

Non-Sarcomeric Mutations

~ 11 Genes---or more?

> 1500 mutations

AMP-Kinase (PRKAG2)

Lamp2 (Danon)

Storage Diseases

Fabry Disease
HCM Is A Global Disease

50 countries....all continents
ICD in HCM for Children / Adolescents

- No. Patients: 224
- Appropriate ICD Discharge (19%): 43
- Follow-up = 4.3 ± 3.3 yr
- Initial shock 9-23 y (mean = 17 y)

13%/yr
2° prevention

3%/yr
1° prevention

Maron BJ et. al. JACC 2013; 61:1527-35
25-Year Contemporary Initiatives in Hypertrophic Cardiomyopathy

Genetic (molecular) Single sarcomere mutation hypothesis

“Clinicians”

Lives Saved 0

Improved Quality of Life 0

Thousands

Many thousands
TERMINATION OF MALIGNANT VENTRICULAR ARRYTHMIAS WITH AN IMPLANTED AUTOMATIC DEFIBRILLATOR IN HUMAN BEINGS


The development of a clinically applicable, automatic, implantable defibrillator has been described previously. This electronic device is designed to monitor cardiac electrical activity, to recognize ventricular fibrillation and ventricular tachyarrhythmias with a sinusoidal wave form, and then to deliver corrective defibrillatory discharges. It is intended to protect patients at particularly high risk of sudden death whenever and wherever they are stricken by these lethal arrhythmias.

After extensive preclinical testing, a pilot study of this new technique was recently initiated at The Johns Hopkins Hospital. This article describes the first three patients in whom the automatic defibrillator was implanted to manage recurrent ventricular tachyarrhythmias that were refractory to medical therapy. Our results suggest that the device can successfully identify and reverse these malignant arrhythmias in human beings.

CLINICAL SUMMARIES

Case 1
A 57-year-old woman had an inferior myocardial infarction complicated by ventricular fibrillation eight years before the most recent admission; intractable angina associated with ventricular arrhythmias then developed. Coronary-artery bypass improved the angina but the arrhythmias remained refractory to propranolol, digitalis, quinidine, and procainamide. Two months before admission, ventricular fibrillation occurred outside the hospital and required multiple defibrillations. There was no evidence of acute myocardial infarction.

Case 2
A 16-year-old boy was resuscitated from ventricular fibrillation four years before the most recent admission. Physical examination was unremarkable. Although the coronary arteries and left ventricular function were normal on cardiac catheterization, the papillary muscles were prominent. Ventricular tachycardia was induced during electrophysiologic testing. A demand pacemaker was implanted, and the patient was treated with quinidine, phenytoin, lidocaine, propranolol, procainamide, disopyramide, tocainide, and amiodarone.

Case 3
A 43-year-old man with a 10-year history of asymmetric cardiomyopathy had two episodes of ventricular fibrillation outside the hospital and was treated with propranolol, sepral myectomy, and a pacemaker. Two months after the operation, progressive dyspnea developed and another episode of ventricular fibrillation occurred. Electrocardiographic and pressure data indicated.

Sudden Death in Young Athletes

- HCM (36%)
- Coronary Anomalies (17%)
- Dilated CM (2%)
- WPW (2%)
- AS (3%)
- Aortic Rupture (3%)
- CAD (3%)
- LAD Bridge (3%)
- MVP (4%)
- Ion Channel (4%)
- ARVC (4%)
- Myocarditis (6%)
- Possible HCM* (8%)
- Other† (5%)

K.K. 23 Years with ICD and HCM

BD: 2/19/56

35
Brother SD (HCM)

36
ICD implant

41
Shock Polymorphic VT (203/min)

50
VF x2 shocks (2 mo. apart)

58
AF* (cardioverted)

60
Xeralto

* preceded by asymptomatic AF on ICD (3 weeks)
Septal Scarring

Post-ablation

Septal Scar

VS = 30%
LV 10%

Post-myectomy

No Scar

Valeti et. al. JACC 2007;49:350
LGE as the Only Risk Factor

Maron BJ et al. AJC 2008; 101(4):544-7
HCM—ICD Registry

Deaths

29 (6%)

No HCM

HCM

HCM- Arrhythmias (nl EF)

ICD Malfunction

14

Cancer, sepsis, renal diseases, suicide, CAD, accidents

14

End-stage Embolic stroke

1

Maron, BJ et. al. JAMA 2007;298:405
Profiles in Prognosis for HCM

- Sudden Death Risk
- Symptom Progression
- End-Stage
- AF
Impact of Outflow Obstruction (≥ 30mmHg) on *Progression to Severe Heart Failure* - Related Symptoms and Death in 1101 HCM Patients

![Graph showing cumulative survival in NYHA Class I-II (%)](image)

- Nonobstructive
- Obstructive

Cumulative survival in NYHA Class I-II (%)

Years from First Gradient Measurement

*p=0.0001  RR= 4.4*

Maron, MS NEJM 2003:348:295
Cardiovascular Societies & HCM Consensus Panels for Myectomy vs. Alcohol Ablation

<table>
<thead>
<tr>
<th>Panel</th>
<th>Year</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC</td>
<td>2003</td>
<td>Myectomy</td>
</tr>
<tr>
<td>ESC</td>
<td>2003</td>
<td>Myectomy</td>
</tr>
<tr>
<td>ACC</td>
<td>2011</td>
<td>Myectomy</td>
</tr>
<tr>
<td>AHA</td>
<td>2011</td>
<td>Myectomy</td>
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</table>
ASYMMETRICAL HYPERTROPHY OF THE HEART IN YOUNG ADULTS

BY

DONALD TEARE

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

Received January 7, 1957

“Tumours of the heart and pericardium have evoked an extensive literature out of all proportion to their uncommon incidence and their relative unimportance as a cause of clinical heart disease.” This opening sentence of Friedberg’s chapter on cardiac tumours in Diseases of the Heart (Friedberg, 1949) fills a pathologist with diffidence in reporting eight cases that have been seen in the last six years in a series of 16,000 autopsies.

Primary tumours of the heart are undoubtedly a rarity and according to Mahaim (1945) 413 had been recorded up to 1945. There is little justification for recording rarities in young adults unless they have some relation to fitness for military service or confuse the differential diagnosis, particularly of conditions that may respond to cardiac surgery. These eight cases of asymmetrical hypertrophy or benign tumour of the heart have occurred in a large group where sudden death and indeed cardiac incapacity, particularly among men, is rare.
The “Uncommon” Diseases

No. Affected / Million

- HCM
- Cystic Fibrosis
- Multiple Sclerosis
- Muscular Dystrophy
- LQTS
- Marfan
- ALS
- Brugada
- Ataxia
## CONTEMPORARY HCM MORTALITY
### BY AGE: MHIF/Tufts
#### 2015

<table>
<thead>
<tr>
<th>Age</th>
<th>No. Patients</th>
<th>HCM Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;29 y</td>
<td>474</td>
<td>0.5%/y</td>
</tr>
<tr>
<td>30-59 y</td>
<td>1000</td>
<td>0.5%/y</td>
</tr>
<tr>
<td>&gt;60 y</td>
<td>428</td>
<td>0.6%/y</td>
</tr>
<tr>
<td>Total</td>
<td>1902</td>
<td><strong>0.5%/y</strong></td>
</tr>
</tbody>
</table>
Clinical Course in 70 HCM Patients with LV Apical Aneurysms

- 70 HCM patients with LV Apical Aneurysms
- 41 Alive without Events
- 11 Deaths
- 18 Alive with HCM Events

HCM related death/event rate = 8.1% / year

- 5 HF Death
- 2 SCD
- 4 Non-cardiac
- 1 Thromboembolic event 6 years prior to death

- 1 ICD interventions
- 2 OOHCA
- 2 Transplant listing
- 2 Transplant
- 3 Thromboembolic event
## Operative Mortality Associated with Septal Myectomy* at North American Hypertrophic Cardiomyopathy Centers, 2000-2014

<table>
<thead>
<tr>
<th>Institution</th>
<th>No. Myectomies</th>
<th>Age (years)</th>
<th>% Male</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo Clinic (Rochester, MN)</td>
<td>1411</td>
<td>51 ± 14</td>
<td>55</td>
<td>4†</td>
<td>0.3</td>
</tr>
<tr>
<td>Cleveland Clinic</td>
<td>1470Δ</td>
<td>55 ± 14</td>
<td>55</td>
<td>6</td>
<td>0.4</td>
</tr>
<tr>
<td>Tufts Medical Center‡ (Boston)</td>
<td>348</td>
<td>52 ± 15</td>
<td>56</td>
<td>4</td>
<td>1.1</td>
</tr>
<tr>
<td>Toronto General</td>
<td>306</td>
<td>49 ± 13</td>
<td>62</td>
<td>2</td>
<td>0.6</td>
</tr>
<tr>
<td>Mount Sinai-St. Luke’s (NYC)</td>
<td>160</td>
<td>53 ± 14</td>
<td>48</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td>3,695</td>
<td>54 ± 14</td>
<td>55</td>
<td>17</td>
<td>0.4</td>
</tr>
</tbody>
</table>

### Symbols:
- * does not include myectomy associated with valve replacement, coronary artery bypass grafting or resection of a subaortic membrane
- ** within 30 days of the myectomy
- † includes 2 patients with prior alcohol septal ablation; with these 2 patients considered non-pure myectomies, the Mayo mortality rate would be only 0.15%
- ‡ newest myectomy center with operations performed over only 11 years with first procedure in 2004, while data for the other centers encompasses 15 years
- Δ includes 19% of patients with mitral valve repair

### Abbreviations:
- MN = Minnesota; NYC = New York City
HCM is Unpredictable
2nd prevention
Cardiac arrest/sustained VT

1st prevention
Family history HCM-SD
Unexplained syncope
Multiple-repetitive NSVT (Holter)
Abnormal exercise BP response
LGE ± 15% of LV mass
Massive LVH ± 30 mm

Rare subgroups/potential arbitrators
End-stage (EF < 50%)
LV apical aneurysm
Marked LV outflow obstruction (rest)
Modifiable
Intense competitive sports
CAD
LGE ± 15% of LV mass
Age ≥ 60y
Alcohol septal ablation (?)

35 y - Brother SD
36 y - ICD
5 y:
40 y - Generator replaced
41 y - Appropriate Shock #1
9 y:
60 y - Appropriate Shock #2
60 y - Present

Follow-up = 3.7 ± 3 years
5.5% / yr
ICD Discharge Rate
11%/y
2nd prevention
4%/y
1st prevention

224 No. Patients
43 Appropriate ICD Discharge for VT/VF (19%)
Follow-up = 4.3 ± 3.3 years
4.4% / yr
ICD Discharge Rate
13%/y
2nd prevention
3%/y
1st prevention
HCM Mortality

Early HCM Referral Cohorts

HCM Cohorts: Prior to utilization of current treatment strategies/interventions

ICD intervention
Heart transplant/surgical myectomy
RCA/defibrillation/hypothermia

Present HCM Cohorts: Contemporary treatment

General U.S. Population

HCM-Related Mortality

% HCM Mortality

3-6%/y
1.5%/y
0.5%/y
0.8%/y
Annual Mortality (%/year)

- 86 ICD Interventions: 1.5%/y
- 45 Heart Transplants: 0.8%/y
- 30 RCA (+ hypothermia): 0.6%/y
- Current Mortality: 0.5%/y
- General Population: 0.8%/y
Profiles in Prognosis for HCM

- Sudden Death
  - ICD
- Progressive Heart Failure (obstructive)
  - Drugs
  - Septal Myectomy (Alcohol Ablation)
- Advanced Heart Failure & End Stage (non-obstructive)
  - Transplant
- AF & Stroke
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  - Anticoagulants RF Ablation

Benign/Stable (normal longevity)
2° prevention
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