How Hypertrophic Cardiomyopathy Became a Contemporary Treatable Genetic Disease With Low Mortality Shaped by 50 Years of Clinical Research and Practice

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Boston, MA

Disclosures:
Medtronic (Grantee)
GeneDx (Consultant)
First Principle:  
**HCM is a disease compatible with normal longevity without disability or need for intervention...**
Major Adverse Disease Pathways in HCM

- No adverse pathway: 56%
- Progressive HF: 32%
- AF: 16%
- SD events: 8%

% of Patients vs. Major Treatment End-Point Pathways
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

**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**

### Intermediate

**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 (??)

### Lowest

ICD
Relation Between LV Thickness & SCD in 482 HCM Patients

Max. LV Wall Thickness (mm)

% Patients With SCD

<15  16-19  20-24  25-29  ≥30

Max. LV Wall Thickness (mm)
**U.S./Canada: ACC/AHA 2011**

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LGE ≥ 15% of LV mass
**Age ≥ 60y**
Alcohol septal ablation (?)
Outcome of HCM Patients First Evaluated ≥ 60 Years

Aging is Good in HCM

% of HCM Cohort

% of HCM Cohort

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

High
Moderate
Low Risk
**U.S./ Canada (ACC/AHA) 2011**

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   - CAD
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   - Age ≥ 60y
   - Alcohol septal ablation (?)
HCM with Apical Aneurysm and Scar
HCM Related Death or Adverse Clinical Events in 93 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

Years from First Evaluation

- 1.7% / year
- 8.1% / 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**
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 (?)
Prevention of Sudden Death in HCM
ICD Performance in HCM

506

Follow-up = 3.7 ± 3 years

103

Appropriate Shocks (20%) VT/VF

5.5%/y

ICD discharge rate

11%/y

2º prevention

4%/y

1º prevention

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

Rate of Appropriate Interventions per 100 person-yr

- Appropriate Shocks (35%)
  - 1 Risk Factor: 3.8
  - 2 Risk Factors: 3.0
  - ≥ 3 Risk Factors: 4.1

Overall p=0.88
Primary Prevention Decision Tree: ICD in HCM

Risk Factors

High risk

Some risk

Cardiologist

TRANSPARENCY / FULL DISCLOSURE / INFORMED CONSENT

Patient Autonomy
NEW PARADIGM IN HYPERTROPHIC CARDIOMYOPATHY
Evidence for Decreased HCM Mortality:
2000 Patients Presenting 10-70 years Old
Tufts Medical Center

What is Possible.....and Role of HCM Centers
General Population

"Historic Mortality"

Pre-ICD era

1.5%/y

86 ICD interventions

% Death Per Year

0.8%/y

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

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

0.8%/y  
0.8%/y  

% Death Per Year
General Population

"Historic Mortality"

0.8%/y

0.6%/y
General Population: 0.8%/y

"Historic Mortality" (OHCA w/hypothermia): 0.6%/y

30 OHCA (w/hypothermia)
Current Mortality

\[
\begin{align*}
\text{General Population} & : 0.8\% / \text{y} \\
\text{Current Mortality 2014} & : 0.5\% / \text{y}
\end{align*}
\]

\[p = 0.46\]

161 lives saved
Current Mortality 2014

- Advanced Heart Failure (n = 21) - 0.5%/y
- SCD (n = 15)
- Stroke (n = 1)
Current Mortality
2014

0.5%/y

Advanced Heart Failure
(n = 21)

SCD
(n = 15)

Stroke (n=1)

15 SCDs but...
5 declined ICD
7 pre-ICD era
Sudden Death
Advanced HF
Paradigm Change in Causes of Death: Advanced Heart Failure w/o Obstruction
(transplant/transplant candidates)

- All HCM Patients: 3%
- Current Causes of HCM Mortality (2015): (60%)
Surgical Myectomy: Quality of Life/Survival Reversal Form of HF

Survival over Years Post-op:
- Isolated Myectomy
- Nonoperated obstructive
- Expected --- US population

Survival rates:
- Isolated Myectomy: 83%
- Nonoperated obstructive: 61%

Survival curve shows a significant difference between groups (P < 0.001).

Oommen S et al. JACC 2006
## Major Surgical Myectomy Centers 2000-2016 (North America)

<table>
<thead>
<tr>
<th>Center</th>
<th>No. Myectomy</th>
<th>Mort.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo</td>
<td>1525</td>
<td>0.3%</td>
</tr>
<tr>
<td>Cleveland</td>
<td>1550</td>
<td>0.4%</td>
</tr>
<tr>
<td>Tufts</td>
<td>425</td>
<td>0.9%</td>
</tr>
<tr>
<td>Toronto</td>
<td>315</td>
<td>0.6%</td>
</tr>
<tr>
<td>NYU</td>
<td>185</td>
<td>0.6%</td>
</tr>
<tr>
<td></td>
<td>4000</td>
<td>0.4%</td>
</tr>
</tbody>
</table>
WHO SHOULD DO IT?
(Operative Mortality)

• Community Hospitals
  8%

• HCM Centers
  0.4%
### Relation of Progressive Heart Failure to Outflow Obstruction

<table>
<thead>
<tr>
<th></th>
<th>Non-Obstructive</th>
<th>Provocable Obstruction</th>
<th>Rest Obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Patients</td>
<td>249</td>
<td>220</td>
<td>104</td>
</tr>
<tr>
<td>Proportion of patients who developed NYHA class III/IV</td>
<td>10%</td>
<td>20%</td>
<td>38%</td>
</tr>
<tr>
<td>Rate of Progression to NYHA Class III/IV, (%/y)</td>
<td>1.6%/y</td>
<td>3.2%/y</td>
<td>7.4%/y</td>
</tr>
</tbody>
</table>
• ITS PROBABLY BETTER TO BE NONOBSTRUCTIVE …..UNLESS YOU GET REALLY SICK
Early HCM Referral Cohorts

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

- 3-6%/y
- 1.5%/y

HCM Cohorts:
- ICD intervention
- Heart transplant/myectomy
- OHCA/defibrillation/hypothermia

Present HCM Cohort: Contemporary treatment
- 0.5%/y
- 0.8%/y

General U.S. Population
Most HCM Patients Do \textit{Not} Die of HCM

75\% of HCM Patients Die of Other, Most Commonly Non-Cardiac, Conditions

Most HCM-Related Deaths occur in Younger Patients
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 Are Available That Change Clinical Course of the Disease
Survival to Advanced Age in HC

% HCM Patients

70 years: 19%
75 years: 14%
80 years: 8%
90 years: 2%

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

Duration (months)

- ≤ 3
- 4 - 6
- 7 - 10
- 11 - 20
- 21 - 30
- 31 - 40
- 41 - 50
- 51 - 60
- 61 - 70
- 71 - 90
- > 90

No. Patients

Maron BJ et al. JAMA 2007;298:405-412
Age at Presentation (years)

- ≤ 29 (n = 474): 3.8%
- 30-59 (n = 1000): 4.2%
- ≥ 60 (n = 428): 2.8%
- Total (n = 1902): 6.6%

161 saved
“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
LGE as the Only Risk Factor
Assessment of ESC Sudden Death Risk Score
(n = 1649)

% Patients With/Without ICD Intervention/Sudden Death

<table>
<thead>
<tr>
<th>Risk/5y</th>
<th>&lt;4%</th>
<th>4-6%</th>
<th>&gt;6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESC Risk Score</td>
<td>&lt;4%</td>
<td>4-6%</td>
<td>&gt;6%</td>
</tr>
<tr>
<td>Appropriate ICD Intervention</td>
<td>60%</td>
<td>26%</td>
<td>9%</td>
</tr>
<tr>
<td>No Appropriate ICD Intervention</td>
<td>63%</td>
<td>9%</td>
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</table>

Sudden Death
How Hypertrophic Cardiomyopathy Became a Contemporary Treatable Genetic Disease With Low Mortality Shaped by 50 Years of Clinical Research and Practice

Barry J. Maron, MD; Ethan J. Rowin, MD; Susan A. Casey, RN; Martin B. Maron, MD

Hypertrophic cardiomyopathy (HCM) is a relatively common genetic heart disease encumbered throughout much of its almost 60-year history by a large measure of misunderstanding and the perception of a grim outcome without effective treatment options. However, it is now apparent that the majority of patients affected with HCM can achieve normal or near-normal life expectancy without disability, and usually do not require major treatment interventions. Nevertheless, for those patients with HCM who are at risk for (or experience) disease-related complications, a constellation of comprehensive nonpharmacologic management strategies have evolved over the last 15 years, altering the natural history and disease course for many. Including implantable defibrillators, heart transplant, external defibrillation therapy, and plasmapheresis, advances in surgical myectomy, alcohol ablation, and more recently, drug therapy using current management strategies and therapeutic measures have shown that it is now possible to achieve significantly improved survival with low HCM-related mortality of 0.5% per year across all ages, and including children and young adults characterized with the most aggressive disease course. These clinical management initiatives, instituted by the practicing cardiology community, have succeeded in preserving life and restoring an active lifestyle for thousands of patients with HCM, while providing many with a measure of reassurance and a reasonable expectation for an extended (of normal) life span.

Almost since its inception, hypertrophic cardiomyopathy (HCM) has been regarded as a clinically and morphologically heterogeneous genetic heart disease often associated with generally unfavorable prognosis, unrelenting progression, premature death, and encumbered by ineffective treatment strategies. Although this perspective is becoming less entrenched, contrary myths persist, and new management approaches, as yet, may not have penetrated systematically into the consciousness of the practicing community. In this review, the treatment advances that are now available to patients with HCM, and that have reduced disease-related mortality and improved quality of life, are presented and discussed.

Historical Perspective on the Evolution of Treatment Modalities for HCM

Hypertrophic cardiomyopathy was first described at autopsy in 195817 and subsequently came to be regarded as the most common nontraumatic cause of sudden death among young adults. This disease emerged as a clinical entity largely through the work of Braunwald et al17 at the National Institutes of Health in the 1970s. Interest in the disorder grew from 1960 to 1968, which began the formative investigative era for HCM.

Initially, HCM was regarded as a disease of left ventricular (LV) outflow obstruction, largely without management strategies that could favorably influence its course.24 However, the ventricular septal myectomy operation to relieve obstruction and reverse heart failure symptoms was soon introduced first at the National Institutes of Health and subsequently elsewhere, including Mayo Clinic.32,33 The myectomy operation was gradually recognized as an important treatment for heart failure symptoms, despite periodic misguided efforts that casted doubt on the pathophysiologic significance of the subaortic gradient.32 In 1964, pharmacologic therapy to mitigate symptoms with beta blockers was introduced to patients with HCM by Braunwald24 and it persists as a first-line therapy, even now, and was later followed by the calcium antagonist verapamil22 and the negative inotropic/antiarhythmogenic disopyramide.23 Beginning in the early 1990s, a few patients with nonobstructive HCM and unrelenting heart failure were referred for heart transplantation.23 However, the devastating and highly visible complication of unexpected arrhythmic sudden death remained, without any preventive strategies, as the greatest source of anxiety.
% of Patients

No. of End-Point Pathways

- 0: 56%
- 1: 33%
- 2: 9%
- 3: 1%
1 Adverse Pathway

Pathway End-Point

Progressive HF

AF

SD Event

Outcome

Death – HCM
Survived

Death – non-HCM

718

476

21

52

403

6

19

121

6

1

26

1

69
2 Adverse Pathways

204 (9%)

HF + SD

154

Death - HCM

37

Death - non-HCM

109

Survived

HF + AF

38

10

Death - HCM

4

Death - non-HCM

24

Survived

SD + AF

12

2

Death - HCM

1

Death - non-HCM

9

Survived
HCM Diagnosis (SD in 2 brothers)

1. ICD implant
2. Heart failure
3. Myectomy
4. Asymptomatic ICD interventions
3 Adverse Pathways

- 27 (1%) Died
- 7
  - 6 HCM-related
  - 1 Non-HCM-related
- 20 Survived
  - NYHA I/II = 16
  - NYHA III = 4
Proportion of Patients Surviving

Time (years)

Pathway = 0
Pathway = 1
Pathway = 2
Pathway = 3

1.1 %/year
1.2 %/year
2.4 %/year

p=0.38
Patients with LVAA (n=28)

- Alive/Clinically Stable (n = 16)*

Adverse Events (n = 12)

- Sudden Death (2)*
- Aborted Cardiac Arrest (2)†
- Progressive Heart Failure/Death (5)†
- Appropriate ICD Discharge (3)∗

Cardiovascular Event Rate = 11%/year
ICD in HCM for Children / Adolescents

- **224** No. Patients
- **43** Appropriate ICD Discharge (19%)
- Follow-up = 4.3 ± 3.3 yr
- **4.4% / 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
ICD in HCM - II: Time to First Shock

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<tr>
<td>&gt; 90</td>
<td>2</td>
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Maron BJ et. al. JAMA 2007;298:405-412
HCM is *Unpredictable*
Profiles in Prognosis for HCM

- Sudden Death Risk
- Symptom Progression
- End-Stage
- AF
AT RISK: 50,000 – 100,000?

General Population 1:500

700,000 people in U.S.

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

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

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

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

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

Tanzania N=6,680;22-91 y 0.2%
Prevalence of LGE = 55-70%
Genetic Testing

To identify

“Genotype +

Phenotype -”

Follow-up

HCM (w/o LVH)

Prognosis

HCM (w/ LVH)
Evidence for Decreased HCM Mortality:
2000 Patients Presenting in Mid-Life (30-59y)
MHIF/Tufts

What is Possible.....
Unexplained LVH

Sarcomeric Protein Mutations

~ 11 Genes---or more?
> 1500 mutations

Non-Sarcomeric Mutations

amp-Kinase (PRKAG2)

Lamp2 (Danon)

Storage Diseases

Fabry Disease
HCM Is A Global Disease

50 countries...all continents
TERMINATION OF MALIGNANT VENTRICULAR ARRHYTHMIAS 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 in-

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...

Case 3

A 43-year-old man with a 10-year history of asymmetric cardiologyopathy had two episodes of ventricular fibrillation outside the hospital and was treated with propranolol, septal myectomy, and a pacemaker. Two months after the operation, progressive dyspnea developed and another episode of ventricular fibrillation occurred. Electrophysiologic testing did not reveal...

Sudden Death in Young Athletes

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

K.K. 23 Years with ICD and HCM

BD: 2/19/56

- Brother SD (HCM)
- ICD implant
- Shock Polymorphic VT (203/min)
- VF x2 shocks (2 mo. apart)
- AF* (cardioverted)

Amio 200 mg
Xeralto

* preceded by asymptomatic AF on ICD (3 weeks)
25-Year Contemporary Initiatives in Hypertrophic Cardiomyopathy

Genetic (molecular) Single sarcomere mutation hypothesis

Lives Saved 0
Improved Quality of Life 0

“Clinicians”

Thousands
Many thousands
Septal Scarring

Post-ablation

Post-myectomy

Septal Scar

VS = 30%
LV 10%

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

No HCM

HCM

HCM-Arrhythmias (nl EF)

ICD Malfunction

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

End-stage Embolic stroke

Maron, BJ et. al. JAMA 2007;298:405
Impact of Outflow Obstruction ($\geq 30\text{mmHg}$) on *Progression to Severe Heart Failure* - Related Symptoms and Death in 1101 HCM Patients

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

ACC  2003  Myectomy
ESC  2003  Myectomy
ACC  2011  Myectomy
AHA  2011  Myectomy
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.
HCM : The Tip Of The Iceberg

Identified

Unidentified

?
The “Uncommon” Diseases

No. Affected / Million

HCM
Cystic Fibrosis
Multiple Sclerosis
Muscular Dystrophy
LQTS
Marfan
ALS
Brugada
Ataxia
<table>
<thead>
<tr>
<th>Age Group</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>0.5%/y</td>
</tr>
</tbody>
</table>

CONTEMPORARY HCM MORTALITY
BY AGE: MHIF/Tufts
2015
Clinical Course in 70 HCM Patients with LV Apical Aneurysms

70 HCM patients with LV Apical Aneurysms

- 11 Deaths
  - HF Death
  - SCD
  - Non-cardiac
  - Thromboembolic event 6 years prior to death

- 18 Alive with HCM Events
  - 1 Transplant listing
  - 2 Thromboembolic event
  - ICD interventions
  - OOHCA
  - Transplant

- 41 Alive without Events
  - 9 Apical thrombus identified without thromboembolic history

HCM related death/event rate = 8.1% / year
### 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>1470^</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>Totals</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*
HCM Mortality

Early HCM Referral Cohorts:
3-6%/y

HCM Cohorts: Prior to utilization of current treatment strategies/interventions:
1.5%/y

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

Present HCM Cohorts: Contemporary treatment:
0.5%/y

General U.S. Population:
0.8%/y
**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 (?)
Interventions

- 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

Annual Mortality (%/year)
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
  - Drugs
    - Anticoagulants
    - RF Ablation

Benign/Stable (normal longevity)