Preventing Sudden Cardiac Death in HCM

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Outline

• SCD
  – Definition
  – Prevalence in HCM
  – Role of substrate
• Treatment and Prevention
• Risk prediction tools in HCM
• Summary
What is Sudden Cardiac Death?

- Sudden or unexpected collapse occurring < 1 hour from the onset of symptoms in patients who had previously experienced a relatively stable or uneventful clinical course
  - Documented VF during cardiac arrest
    - Appropriate ICD shocks have been considered surrogate endpoints
      - This is reasonable for SCD; controversial for total mortality
    - Adjudication/classification a perennial challenge for clinical trials
- Clinical spectrum of patients with HCM is broad
  - “SCD intertwined with HCM”; a subset of all HCM patients
  - “Most devastating complication”

Maron BJ  Circulation 2010; 121:445-456
Maron BJ et al Circulation 2000; 102: 858-464
Modes of Death
N= 744; Centers in US Midwest, Central and Coastal Italy
1975-1998

- Modes of death change as age increases
- Stroke related to embolic events associated with paroxysmal or chronic atrial fibrillation

HCM Patients Experiencing Sudden Death

- More likely to be minimally symptomatic
  - NYHA Class not predictive
- More patients died after sedentary or mild activity vs. moderate to severe exertion
- May occur at any age; but more commonly in the young

Figure 4. Clinical profile of sudden death. Symptomatic state before death based on NYHA functional class (left) and activity level at time of collapse (right) in 44 HCM patients who died suddenly (or survived cardiac arrest or had appropriate ICD interventions).

Why: The Substrate

- Abnormal sarcomere proteins with hypertrophy, disarray, fibrosis, small vessel changes

Normal myocardium

- Abnormal myocardium ➔ dispersion of refractoriness ➔ ventricular arrhythmias

Maron BJ  Circulation 2010; 121:445-456

Ho and Seidman Circulation 2006

Maron Circulation 2010
ICDs in HCM: The Formative Paper

• Retrospective multicenter series of ICD patients
• 19 centers US and Italy
• N=128
• F/U
• Appropriate shock rates
  – 1° 5% /yr
  – 2° 11% /yr

Maron BJ,…Bardy GH et al NEJM 2000; 342:365-73
ICD Efficacy: Polish Series

- N= 104 from a single center
  - Primary 75%
  - Secondary 25%

- Number of risk factors did not impact the incidence of appropriate ICD interventions in the primary prevention group
  - NSVT greatest HR for appropriate ICD shock

ICD Meta Analysis 2012

• N= 2190 patients from 27 observational articles
• F/U  3.7 years
• 311 patients with appropriate ICD interventions (14%)
• Cardiac mortality 3%
  – 0.6% per year
• Non-cardiac mortality 2%
  – 0.4% per year

Schinkel AFL et al Circulation Heart Failure 2012; 5: 552-559
Non-pharmacologic Treatment: Alcohol Septal Ablation or Surgery

All Cause Mortality | Sudden Death Mortality

<table>
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<tr>
<th>Study</th>
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Leonardi FA et al Circ Cardiovasc Interventions 2010
AA Drugs in HCM

- Amiodarone most common
- Sotalol and disopyramide used less frequently

<table>
<thead>
<tr>
<th>Series</th>
<th>Pts on AA drug, %</th>
<th>Approp ICD shock rate in those pts on AA drug, %</th>
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<td>Maron <em>Circ 2000</em></td>
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<td>Syska <em>JCE 2010</em></td>
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ICD Eligibility: Risk Factors for SCD in HCM

Secondary prevention: Cardiac arrest/sustained VT

Primary 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

Maron BJ  Circulation 2010; 121:445-456
Wall Thickness in HCM and Sudden Death

N = 480; mean f/u 6.5 years

Maximal Left-Ventricular-Wall Thickness (mm)

0 2.6 7.4 11.0 18.2

Incidence of Sudden Death (per 1000 person – yr)

Spirito P. et al. NEJM 2000:342;1781
Other Mitigating Factors

LVOT obstruction
Maron ME et al NEJM 2003

Delayed gadolinium enhancement by MR

Figure 1. Probability of Hypertrophic Cardiomyopathy (HCM)–Related Death among 273 Patients with a Left Ventricular Outflow Gradient of at Least 30 mm Hg under Basal Conditions and 828 Patients without Obstruction at Entry.
2011 ACCF/AHA HCM Guidelines

Figure 4. Indications for ICDs in HCM. *SCD risk modifiers include established risk factors and emerging risk modifiers (Section 6.3.1.2). BP indicates blood pressure; ICD, implantable cardioverter-defibrillator; LV, left ventricular; SCD, sudden cardiac death; SD, sudden death; and VT, ventricular tachycardia.

Regardless of the level of recommendation put forth in these guidelines, the decision for placement of an ICD must involve prudent application of individual clinical judgment, thorough discussions of the strength of evidence, the benefits, and the risks (including but not limited to inappropriate discharges, lead and procedural complications) to allow active participation of the fully informed patient in ultimate decision making.
• Selection of patients for primary prevention ICD implant is challenging due to heterogeneity of the disease

• Variable effect of each of the risk factors

• “.. A clinical risk prediction model that provides patients and physicians with an individualized absolute risk prediction for SCD should be developed”
  – O’Mahoney et al Circulation 2013
ICD not recommended unless there other clinical features that are of potential prognostic importance and when the likely benefit is greater than the lifelong risk of complications and the impact of an ICD on lifestyle, socioeconomic status and psychological health.
Independent Assessment of ESC SCD Risk Model

Figure 1. ESC prognostic risk categories with respect to clinical outcome and end points in subgroups of patients with HC. y = year; *Includes 12 patients with resuscitated cardiac arrest.

Maron BJ, Casey SA, Chan RH Garberich RF, Rowin EJ and Maron MS. Am J Cardiol 2015; 116: 757-764
CIEDs: Complications

- Multiple trials have described ICD procedural and longer term complications
  - Battery longevity impacts replacement procedures
  - Complications from replacement procedures prospectively described in REPLACE Registry
  - Complications greater if lead revisions required
    - Cohort 1 vs Cohort 2

- Potential for lead failures lifelong concern for any ICD patient

- Inappropriate shocks
  - Atrial arrhythmias
  - Lead malfunction

Poole JE, Gleva MJ, Mela F et al Circulation 2010
Although ICD therapy terminates potentially life-threatening ventricular arrhythmias to prevent SCD and prolong life, it is not without risk.

Meta-analysis done to examine cardiac and non-cardiac mortality, appropriate and inappropriate shock rates and complications.

N= 27 studies; 2190 patients; 3.7 yr follow-up

Appropriate Shocks: 3.3%

Inappropriate Shocks: 4.8%

Latest series 2010 pre MADIT RIT
## ICD Complication Rates

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<thead>
<tr>
<th>Event Rate (95% CI)</th>
<th>Lead Malfunction</th>
<th>Infection</th>
<th>Lead Displacement</th>
<th>Psychological</th>
<th>Any</th>
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<td>6.2 (4.1-8.3)</td>
<td>3.1 (1.2-5.0)</td>
<td>2.7 (1.6-3.9)</td>
<td>3.8 (0.5-7.1)</td>
<td>14.9 (9.9-19.9)</td>
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<thead>
<tr>
<th>Annualized Rate (95% CI)</th>
<th>Lead Malfunction</th>
<th>Infection</th>
<th>Lead Displacement</th>
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<td>1.5 (0.9-2.1)</td>
<td>0.6 (0.1-1.0)</td>
<td>1.0 (0.5-1.4)</td>
<td>0.8 (-0.8-2.3)</td>
<td>3.4 (2.5-4.3)</td>
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<td>(95% CI)</td>
<td>(4.1-17.5)</td>
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**Note:** NA indicates not available; ICD, implantable cardioverter defibrillator; HCM, hypertrophic cardiomyopathy; NIH, National Institutes of Health.
Contemporary Areas of Exploration

• **Treatment: Subcutaneous ICD**
  - Single lead under skin and generator in axilla
  - EFFORTLESS registry
    - 58 patients with HCM
      Lambiase PE et al Eur H J 2014

• **Treatment: Cardiac resynchronization therapy to reduce LVOT gradient**
  - N=12 pts; mean QRS 103 msec, NYHA Class III, mean LVEF 68%; 30 mmHg reduction in gradient by 1 yr
    Berruezo A et al HR 2011;8: 221-227

• **Risk Stratification: Age > 60 yrs**
  Maron BJ Circulation 2013:127:585-593

• **MRI and DE**
Genetic Testing

- N= 552 UK HCM pts
- Screened for TNNT2 mutations
- 92 patients with mutation
- Follow-up available in 75 pts
  - Mean f/u 10 + years
- Figure show survival for individual mutations
- Two mutations assoc with increased SCD at younger age
  - Exon 8
  - Exon 9
- Myosin binding protein C
  Christiians I et al Eur H J 2010 31:341-348

1. The usefulness of genetic testing in the assessment of risk of SCD in HCM is uncertain. (Level of Evidence: B)
ACCF/AHA HCM Guidelines

• Class I
  • SCD risk stratification at initial evaluation for all patients
    – VF, VT, SCD, Fm Hx SCD including ICD shocks for VA, unexplained syncope, NSVT >3 beats at 120 bpm, LV wall thickness ≥ 30 mm

• Class II
  • A: BP response to exercise; re-evaluate risk periodically
  • B: CMR with late GE; double compound mutations, LVOT obstruction

• Class III
  • EPS
Conclusions

• All patients with HCM should undergo evaluation of SCD risk

• The ICD is the only therapy to date that reduces arrhythmic death
  • No trials of ICD vs meds or ICD vs placebo

• Transvenous ICDs have adverse effects; impacts consent discussions
  • Inappropriate shocks; may be reduced with appropriate programming
  • Need for subsequent procedures

• Role of genetic testing in SCD risk assessment is evolving
For Further Reading

• Maron BJ  Circulation 2010; 121:445-456
• Maron BJ et al Circulation 2000; 102: 858-464
• Maron BJ,…Bardy GH et al NEJM 2000; 342:365-73
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