Preventing Sudden Cardiac Death in HCM

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DISCLOSURE

Marye J. Gleva M.D. has financial interests to disclose.
Potential conflicts of interest have been resolved.

Research Support / Grants	BIOTRONIK
Stock/Equity (any amount)	None
Consulting / Employment	None
Speakers Bureau / Honoraria	BIOTRONIK Medtronic
Other	None

Outline

- SCD
  - Definition
  - Prevalence in HCM
  - Role of substrate
- Treatment and Prevention
- Risk prediction tools in HCM
- Summary

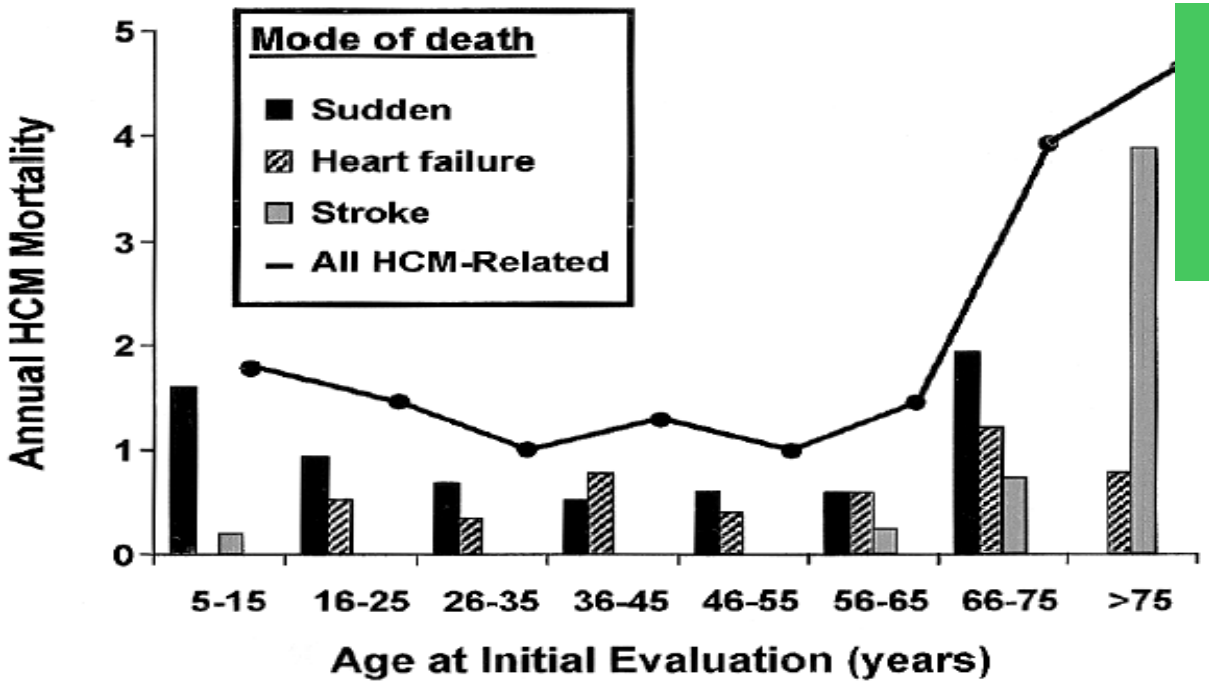
What is Sudden Cardiac Death?

- 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



Annual rate of death	**1.4%**
Sudden death	**0.7%**
HF death	**0.5%**
Stroke	**0.2%**

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

Maron BJ et al. Circulation 2000; 102: 858-864

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

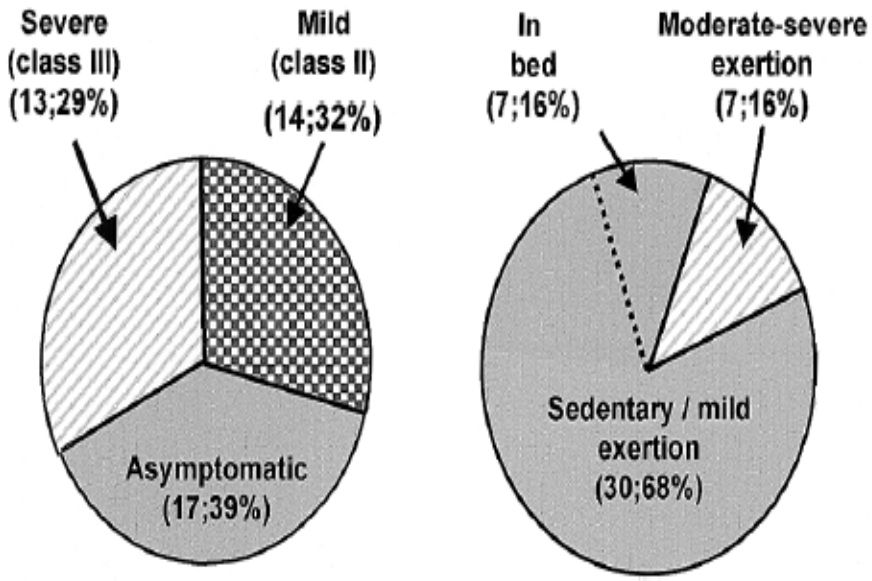


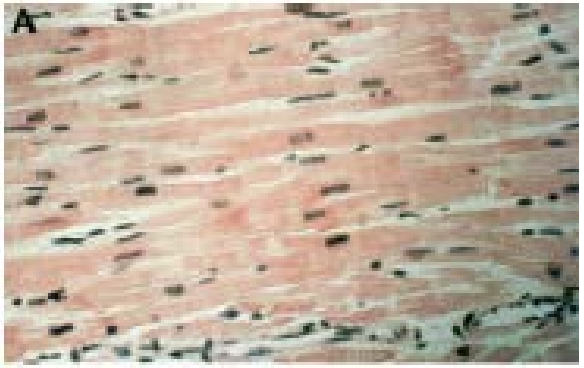
Figure 4. Clinical profile of sudden death. Symptomatic state before death based on NYHA functional class *(left)* and activity level at time of collapse *(right)* in 44 HCM patients who died suddenly (or survived cardiac arrest or had appropriate ICD interventions).

Maron BJ et al. Circulation 2000; 12:858-864

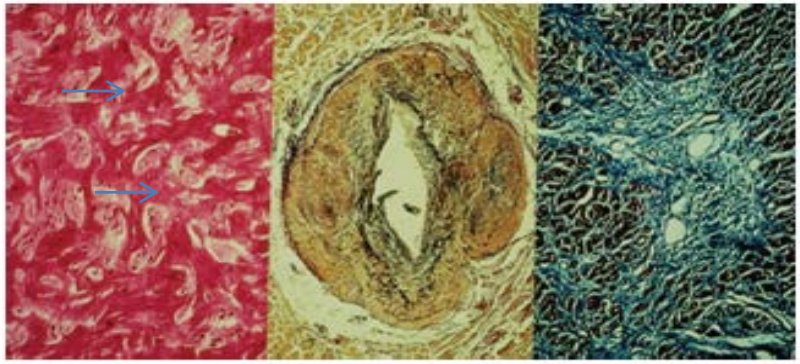
Why: The Substrate

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

Normal myocardium



Ho and Seidman Circulation 2006



Maron Circulation 2010

- Abnormal myocardium → dispersion of refractoriness → ventricular arrhythmias

Maron BJ Circulation 2010; 121:445-456

ICDs in HCM: The Formative Paper

The New England Journal of Medicine

VOLUME 342 FEBRUARY 10, 2000 NUMBER 6

EFFICACY OF IMPLANTABLE CARDIOVERTER–DEFIBRILLATORS FOR THE PREVENTION OF SUDDEN DEATH IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

BARRY J. MARON, M.D., WIN-KUANG SHEN, M.D., MARK S. LINK, M.D., ANDREW E. EPSTEIN, M.D., ADRIAN K. ALMQUIST, M.D., JAMES P. DAUBERT, M.D., GUST H. BARDY, M.D., STEFANO FAVALE, M.D., ROBERT F. REA, M.D., GIUSEPPE BORIANI, M.D., N.A. MARK ESTES III, M.D., AND PAOLO SPIRITO, M.D.*

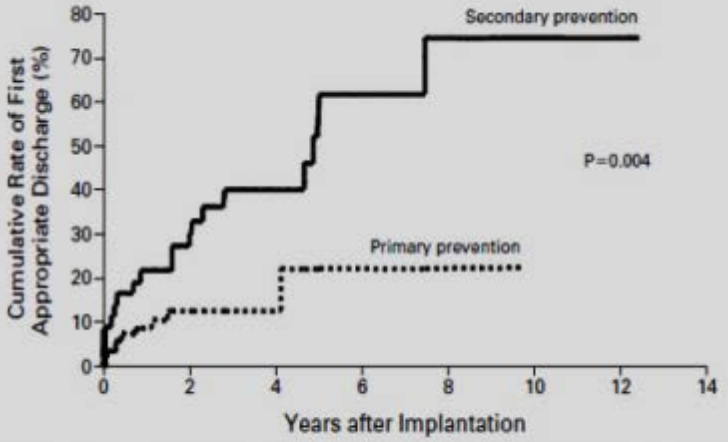


Figure 4. Estimated Cumulative Rates of First Appropriate Discharges, Calculated Separately for the 85 Patients with Defibrillators for Primary Prevention and the 43 Patients with Defibrillators for Secondary Prevention.

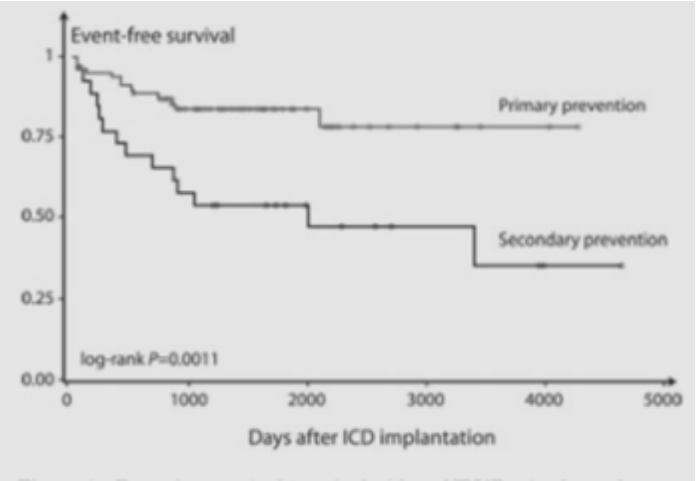
- Retrospective multicenter series of ICD patients
- 19 centers US and Italy
- N=128
- F/U
- Appropriate shock rates
  - 1° 5% /yr
  - 2° 11% /yr

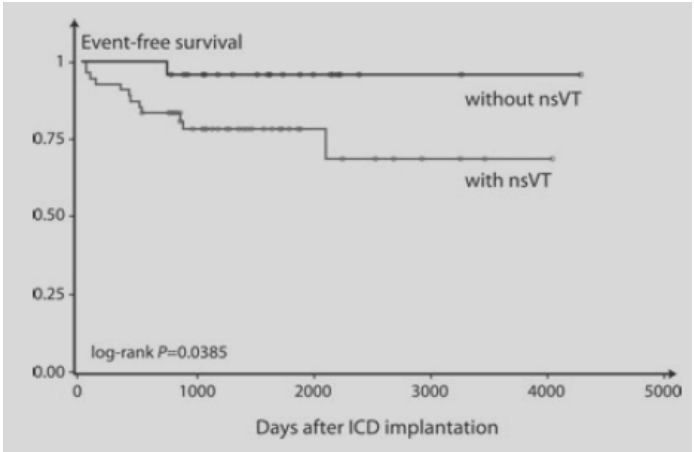
Maron BJ,…Bardy GH et al NEJM 2000; 342:365-73

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





Syska P et al JCE 2010; 21: 883-889

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

	Surgical Myectomy % per pt.-year OR (95%CI)	ASA % per pt.-year OR (95% CI)
All-cause Mortality	1.8 (1.2 -2.6)	2.1 (1.7-2.7)
SCD	0.3 (0.2-0.6)	0.4(0.3-0.6)

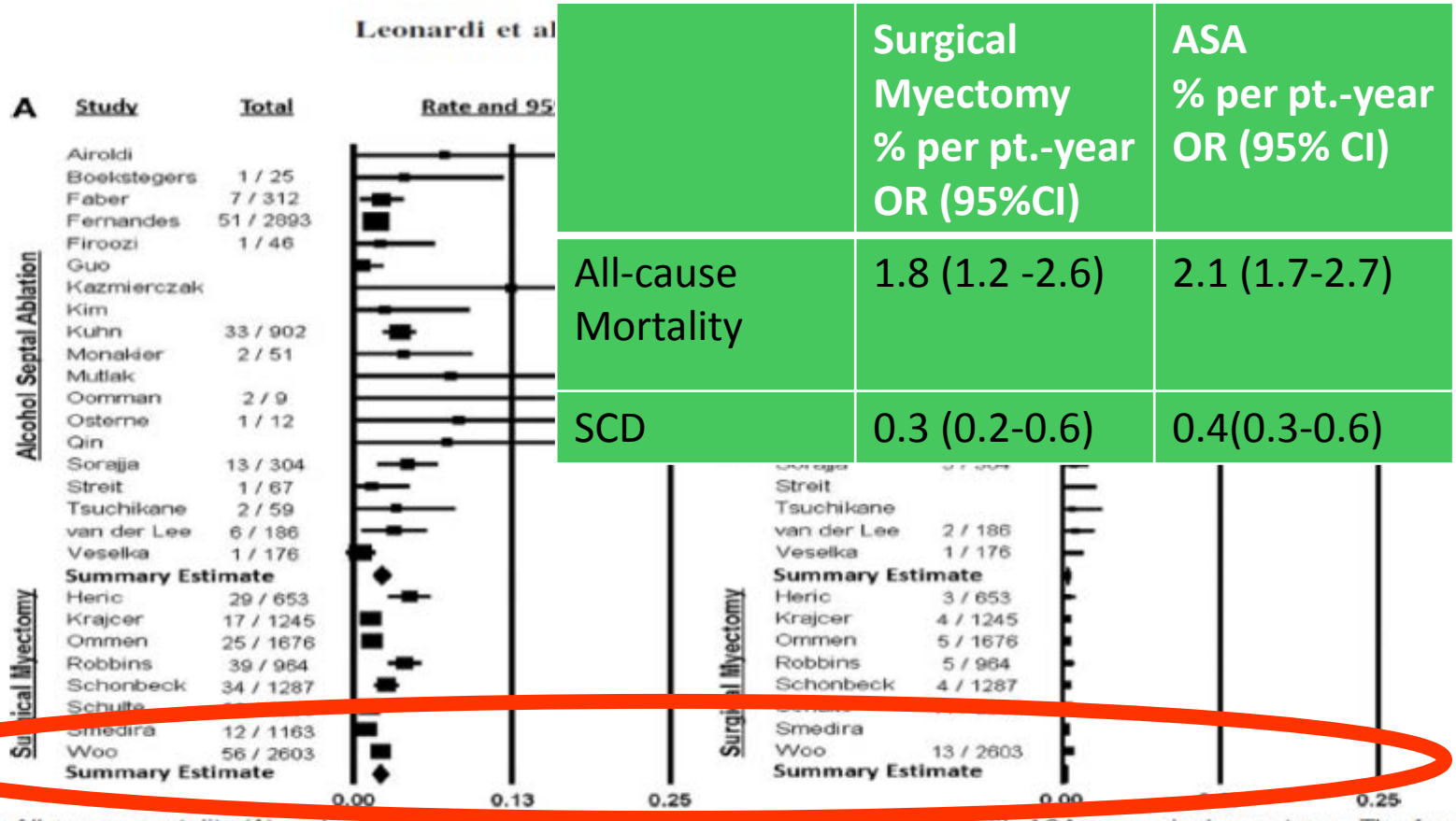


Figure 2. All-cause mortality (A) and sudden death (B) rates among HCM cohorts treated with ASA or surgical myectomy. The forest plots show the variability between studies and their relative contributions to the overall results. The Total column reports the number of all-cause or sudden deaths. Studies with no value in the Total column had 0 deaths.

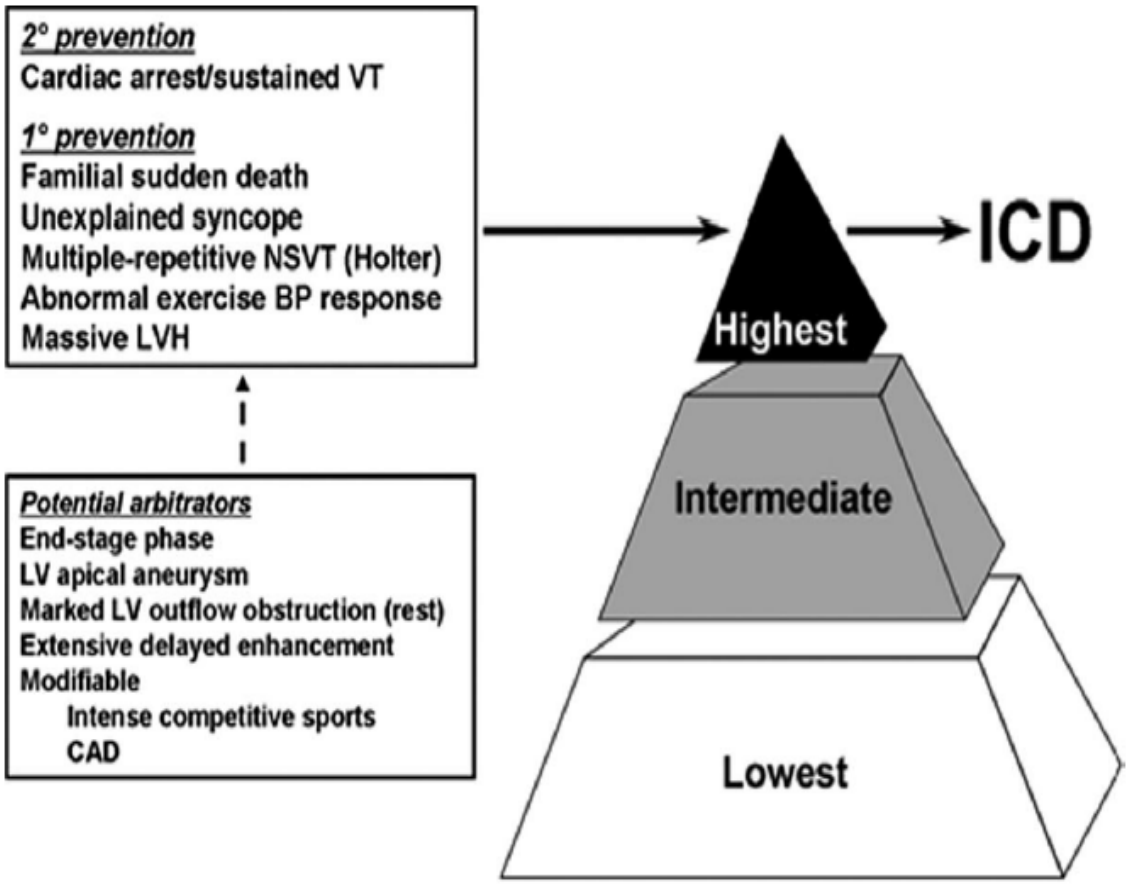
Leonardi FA et al Circ Cardiovasc Interventions 2010

AA Drugs in HCM

- Amiodarone most common
- Sotalol and disopyramide used less frequently

Series	Pts on AA drug, %	Approp ICD shock rate in those pts on AA drug, %
Maron *Circ 2000*	14	16
Maron *NEJM 2000*	41	52
Syska *JCE 2010*	15.4	56
Schinkel Circ HF 2012	nr	nr

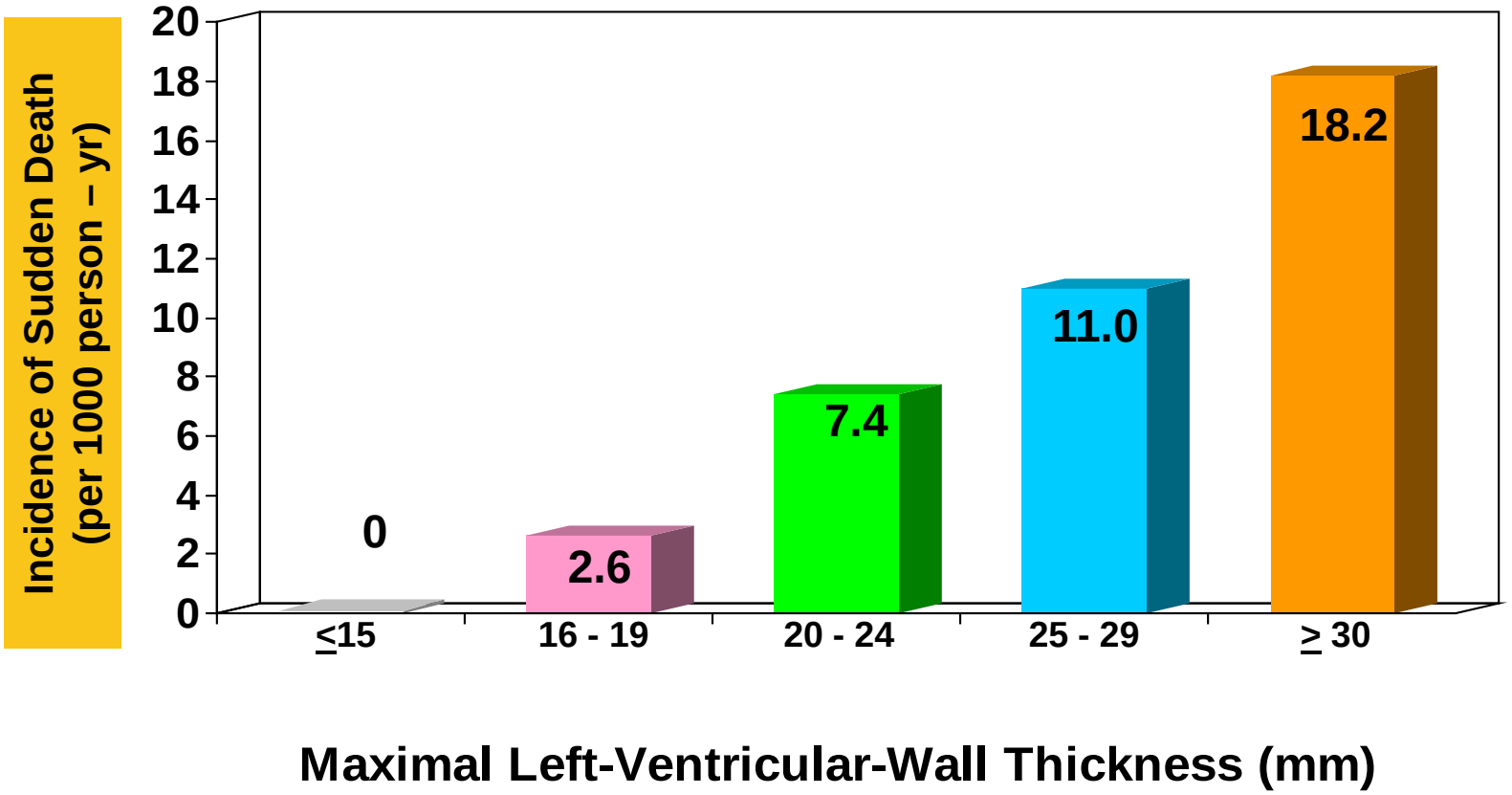
ICD Eligibility: Risk Factors for SCD in HCM



Maron BJ Circulation 2010; 121:445-456

Wall Thickness in HCM and Sudden Death

N= 480; mean f/u 6.5 years



Spirito P. et al. NEJM 2000:342;1781

Other Mitigating Factors

LVOT obstruction

Maron ME et al NEJM 2003

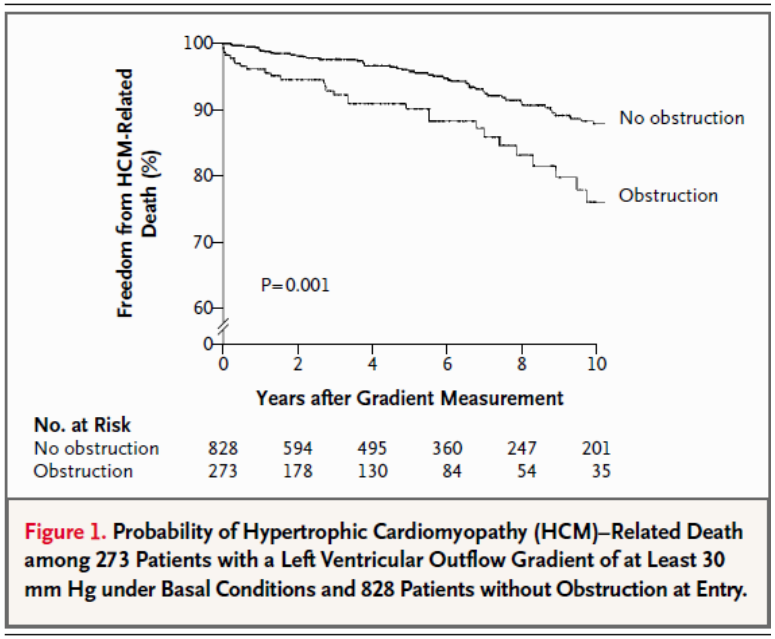
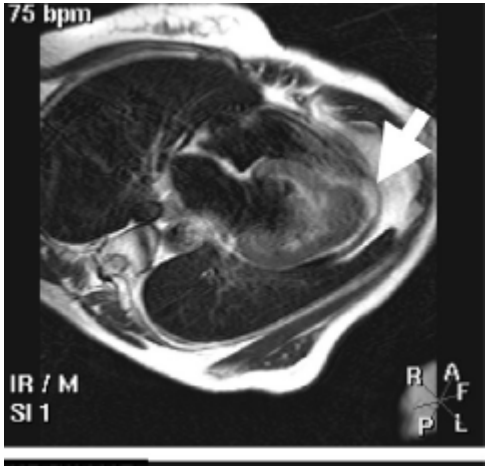


Figure 1. Probability of Hypertrophic Cardiomyopathy (HCM)–Related Death among 273 Patients with a Left Ventricular Outflow Gradient of at Least 30 mm Hg under Basal Conditions and 828 Patients without Obstruction at Entry.

Delayed gadolinium enhancement by MR



2011 ACCF/AHA HCM Guidelines

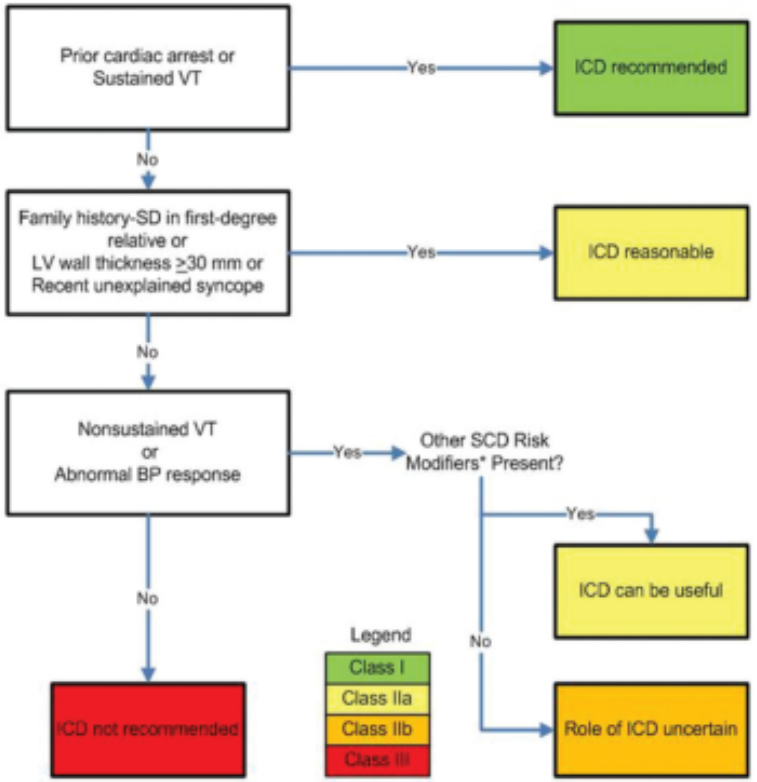


Figure 4. Indications for ICDs in HCM. *SCD risk modifiers include established risk factors and emerging risk modifiers (Section 6.3.1.2). BP indicates blood pressure; ICD, implantable cardioverter-defibrillator; LV, left ventricular; SCD, sudden cardiac death; SD, sudden death; and VT, ventricular tachycardia.

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.

ESC: SCD Risk Assessment

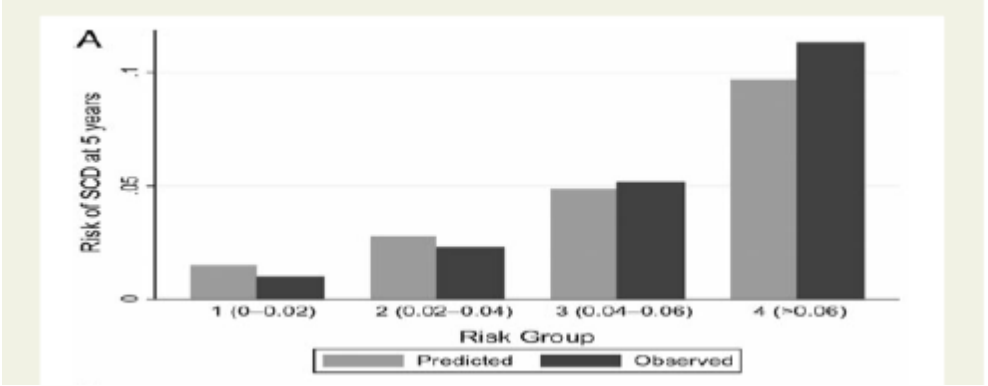
- Selection of patients for primary prevention ICD implant is challenging due to heterogeneity of the disease
- Variable effect of each of the risk factors
- ".. A clinical risk prediction model that provides patients and physicians with an individualized absolute risk prediction for SCD should be developed"
  - O'Mahoney et al Circulation 2013

•Retrospective multi-center longitudinal cohort study
- **•Cox proportional hazard model**
- **•Bootstrapping**
- **•External validation**

•N= 3675 patients; 6 European centers
•F/U 24313 patient years

$$\hat{P}_{\text{SCD at 5 years}} = 1 - 0.998^{\exp(\text{Prognostic Index})},$$

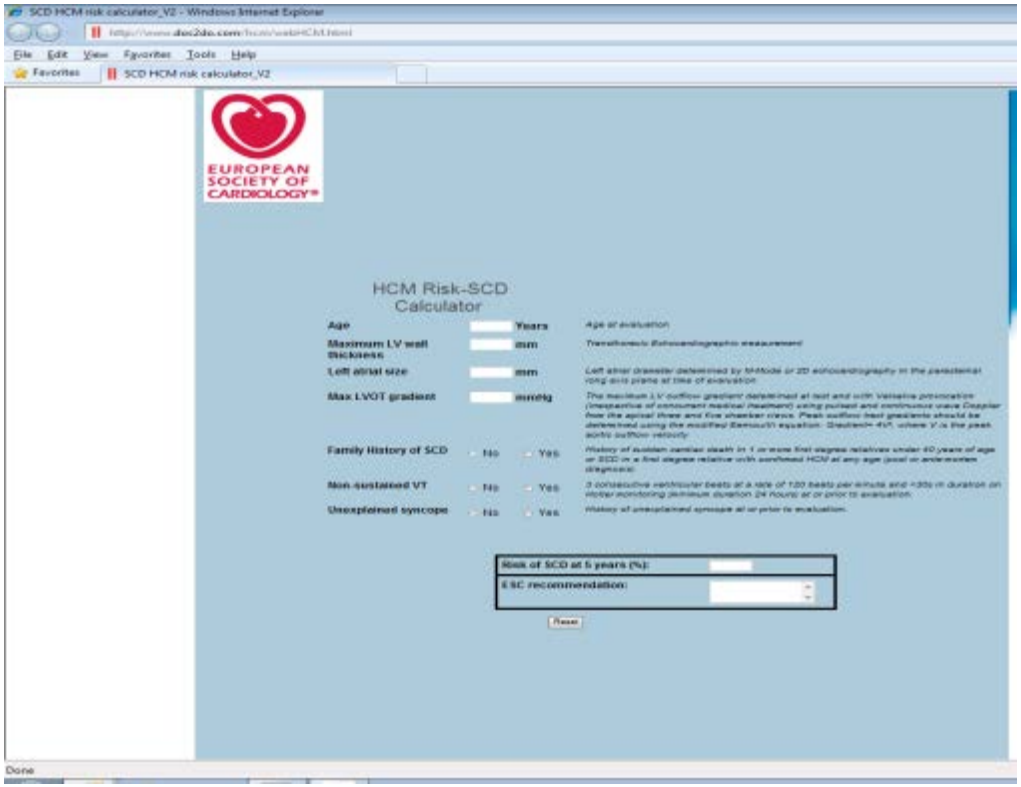
where Prognostic Index = 0.15939858*Maximal wall thickness (mm) − 0.00294271*Maximal wall thickness^2 (mm^2) + 0.0259082* Left atrial diameter (mm) + 0.00446131*Maximal left ventricular outflow tract gradient (mmHg) + 0.4583082*Family history SCD + 0.82639195*NSVT + 0.71650361*Unexplained syncope −0.01799934*Age at clinical evaluation (years).



O'Mahoney C et al Eur HJ doi10.1093/eurheartj/ehj439

ESC: SCD Online Risk Assessment Tool

- Age
- Maximum LV wall thickness
- LA size
- Max LVOT gradient
- Fm Hx SCD
- NSVT
- Unexplained syncope



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.

www.esccardio.org/guidelines

Independent Assessment of ESC SCD Risk Model

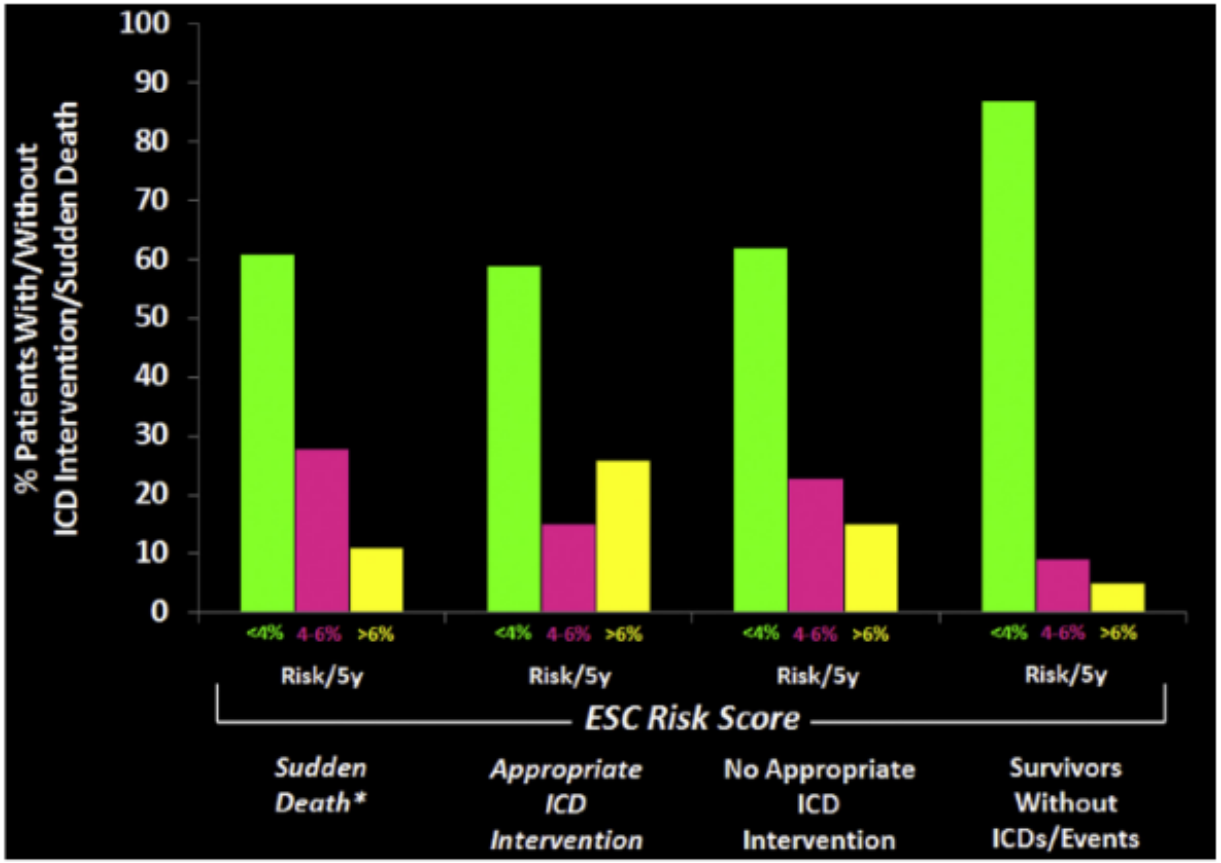
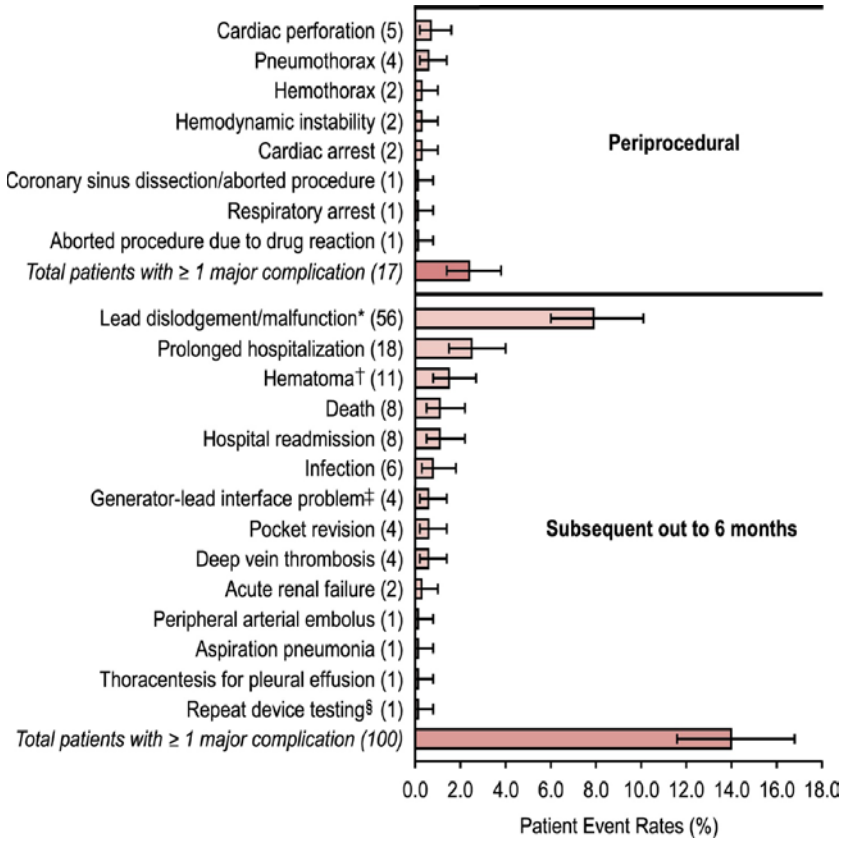


Figure 1. ESC prognostic risk categories with respect to clinical outcome and end points in subgroups of patients with HC. y = year; *Includes 12 patients with resuscitated cardiac arrest.

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

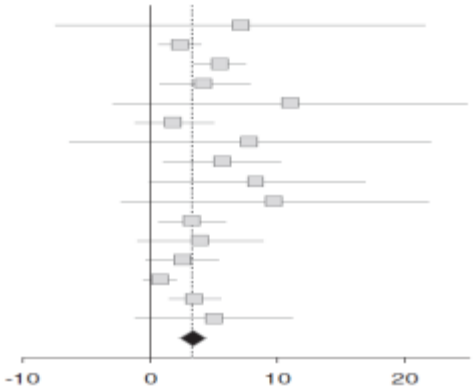
HCM: Appropriate and Inappropriate Shocks

- 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
- Appropr Shocks: 3.3%
- Inapprop Shocks: 4.8%
- Latest series 2010 pre MADIT RIT

Appropriate ICD Shocks

Author	Rate	95% CI
Primo	7.1	-7.4 – 21.6
O'Mahony	2.3	0.7 – 4.0
Maron	5.5	3.5 – 7.5
Begley	4.3	0.7 – 7.8
Jayatilleke	11.0	-2.9 – 24.8
Almquist	1.9	-1.2 – 4.9
Lawrenz	7.8	-6.3 – 21.9
Syska	5.6	1.1 – 10.2
Marin	8.3	-0.1 – 16.8
Medeiros	9.7	-2.3 – 21.7
Lin	3.3	0.6 – 5.9
Woo	3.9	-1.0 – 8.9
Cuoco	2.5	-0.3 – 5.3
Saumarez	0.8	-0.5 – 2.1
Hauser	3.5	1.4 – 5.5
Prinz	5.0	-1.2 – 11.2
Summary estimate	**3.3**	**2.2 – 4.4**

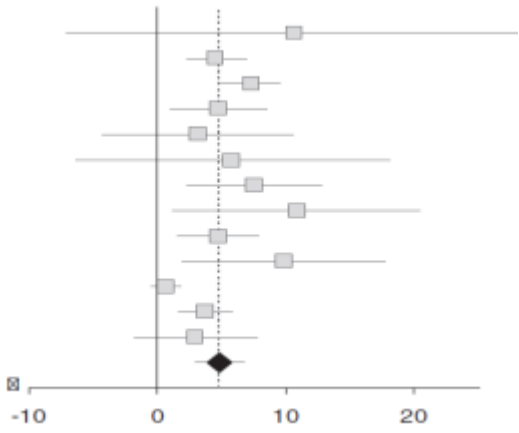
Random effects model Q = 11.6 I^2 = 0%



Inappropriate Shocks

Author	Rate	95% CI
Primo	10.7	-7.1 – 28.4
O'Mahony	4.6	2.3 – 6.9
Maron	7.3	4.9 – 9.6
Begley	4.7	1.0 – 8.4
Jayatilleke	3.1	-4.3 – 10.5
Lawrenz	5.9	-6.4 – 18.1
Syska	7.5	2.3 – 12.8
Marin	10.8	1.2 – 20.5
Lin	4.7	1.6 – 7.9
Woo	9.8	2.0 – 17.7
Saumarez	0.6	-0.5 – 1.8
Hauser	3.7	1.6 – 5.8
Prinz	3.0	-1.8 – 7.8
Summary estimate	**4.8**	**2.9 – 6.7**

Random effects model Q = 7.3 I^2 = 0%



Schinkel AFL et al Circulation Heart Failure 2012; 5: 552-559

ICD Complication Rates

	Lead Malfunction	Infection	Lead Displacement	Psychological	Any
Event Rate (95% CI)	**6.2 (4.1-8.3)**	**3.1 (1.2-5.0)**	**2.7 (1.6- 3.9)**	**3.8 (0.5-7.1)**	**14.9 (9.9-19.9)**
Annualized Rate (95% CI)	**1.5 (0.9 -2.1)**	**0.6 (0.1-1.0)**	**1.0 (0.5-1.4)**	**0.8 (-0.8-2.3)**	**3.4 (2.5-4.3)**

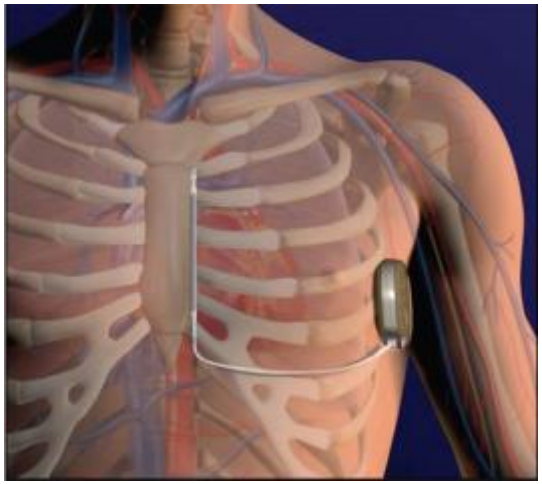
Minneapolis, Rochester	Bos et al[29]	2010	4.6	14	27	NA	NA	NA	NA	NA	3	5	NA
Bad Oeynhausen	Prinz et al[30]	2010	2.0	10	6	NA	NA	NA	NA	NA	NA	NA	NA
Event rate (95% CI)				13.7 (9.9–17.5)	19.0 (12.6–25.4)	6.2 (4.1–8.3)	3.1 (1.2–5.0)	2.7 (1.6–3.9)	3.8 (0.5–7.1)	14.9 (9.9–19.9)	2.2 (1.5–2.8)	1.4 (0.8–1.9)	2.2 (1.3–3.0)
Annualized event rate (95% CI)				3.3 (2.2–4.4)	4.8 (2.9–6.7)	1.5 (0.9–2.1)	0.6 (0.1–1.0)	1.0 (0.5–1.4)	0.8 (−0.8 to 2.3)	3.4 (2.5–4.3)	0.6 (0.2–0.9)	0.4 (0.09–0.7)	0.5 (0.1–1.0)

NA indicates not available; ICD, implantable cardioverter defibrillator; HCM, hypertrophic cardiomyopathy; NIH, National Institutes of Health.

Contemporary Areas of Exploration

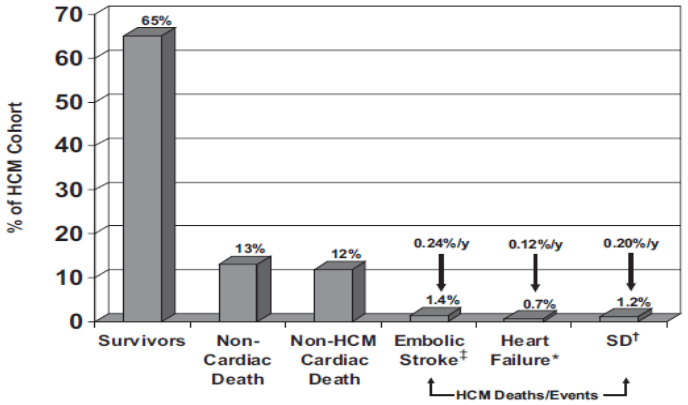
- **Treatment: Subcutaneous ICD**
  - Single lead under skin and generator in axilla
  - EFFORTLESS registry
    - 58 patients with HCM

    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



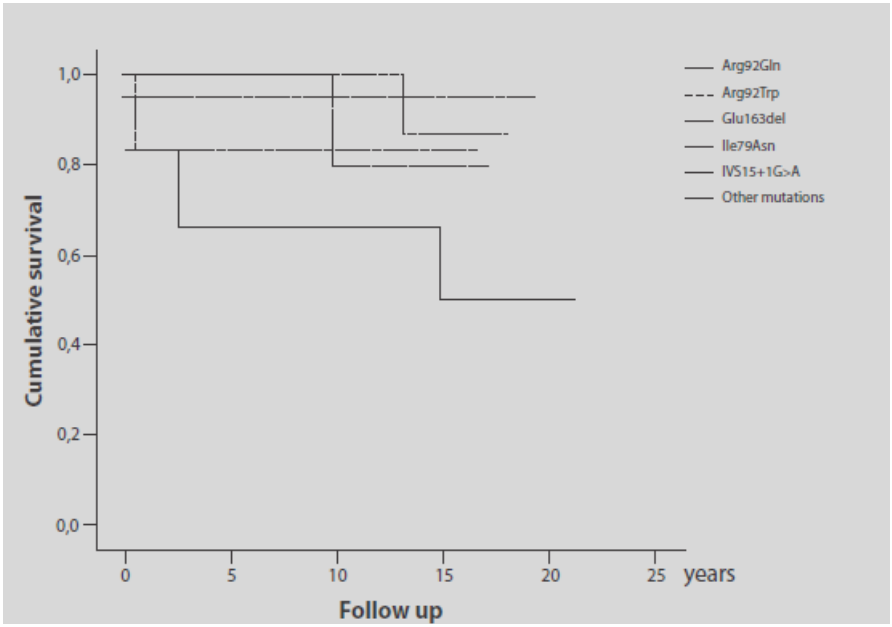
- **Risk Stratification: Age > 60 yrs**

  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
  - Pasquale F et al Circ Cardiovasc Genet. 2012; 5:10-17
- Myosin binding protein C
  Christiians I et al Eur H J 2010 31:341-348



Class IIb

1. The usefulness of genetic testing in the assessment of risk of SCD in HCM is uncertain.[107,108] *(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-evaulate 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
- Schinkel AFL et al Circulation Heart Failure 2012; 5: 552-559
- Leonardi FA et al Circ Cardiovasc Interventions 2010
- Spirito P. et al. NEJM 2000:342;1781
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- Poole JE, Gleva MJ , Mela F et al Circulation 2010
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