How to Optimize Primary Prevention ICD Programming? MADIT-RIT Trial

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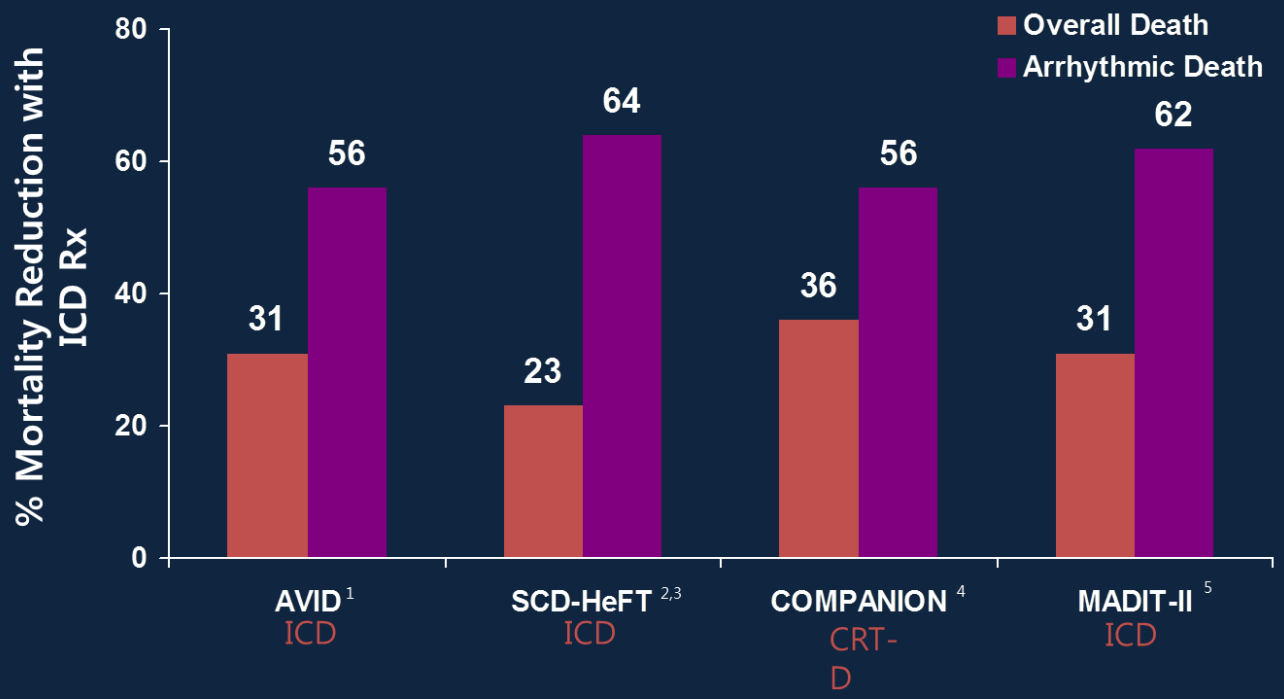
ICD (Implantable Cardioverter-Defibrillator)

- Highly effective in reducing mortality due to cardiac arrhythmia in high-risk cardiac patients.



[1] The AVID Investigators. *N Engl J Med.* 1997;337:1576-1583.

[2] Bardy GH, et al. *N Engl J Med.* 2005;352:225-237.

[3] Packer DL. *Heart Rhythm.* 2005;2:S38-S39.

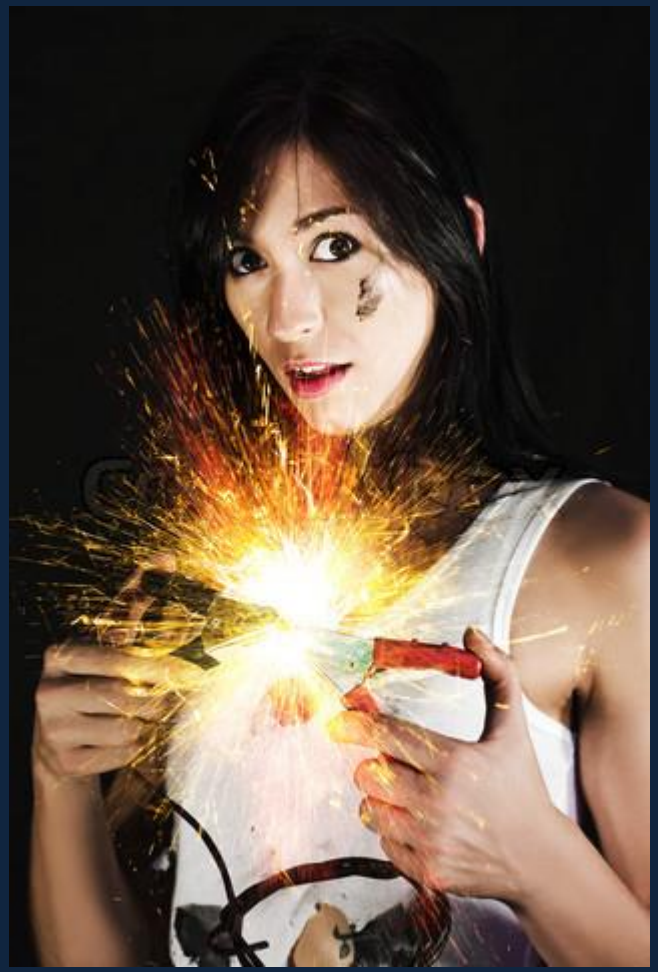
[4] Bristow MR, et al. *N Engl J Med.* 2004;350:2140-2150.

[5] Moss AJ, et al. *N Engl J Med.* 2002;346:877-883.

ICD Indication Expansion for Primary Prevention

- Ischemic CMP
  - MADIT
  - MADIT II
  - CABG Patch
  - MUSTT
  - SCD-HeFT
  - DINAMIT
  - IRIS
- Non-ischemic CMP
  - CAT and AMIOVIRT
  - SCD-HeFT
  - DEFINITE

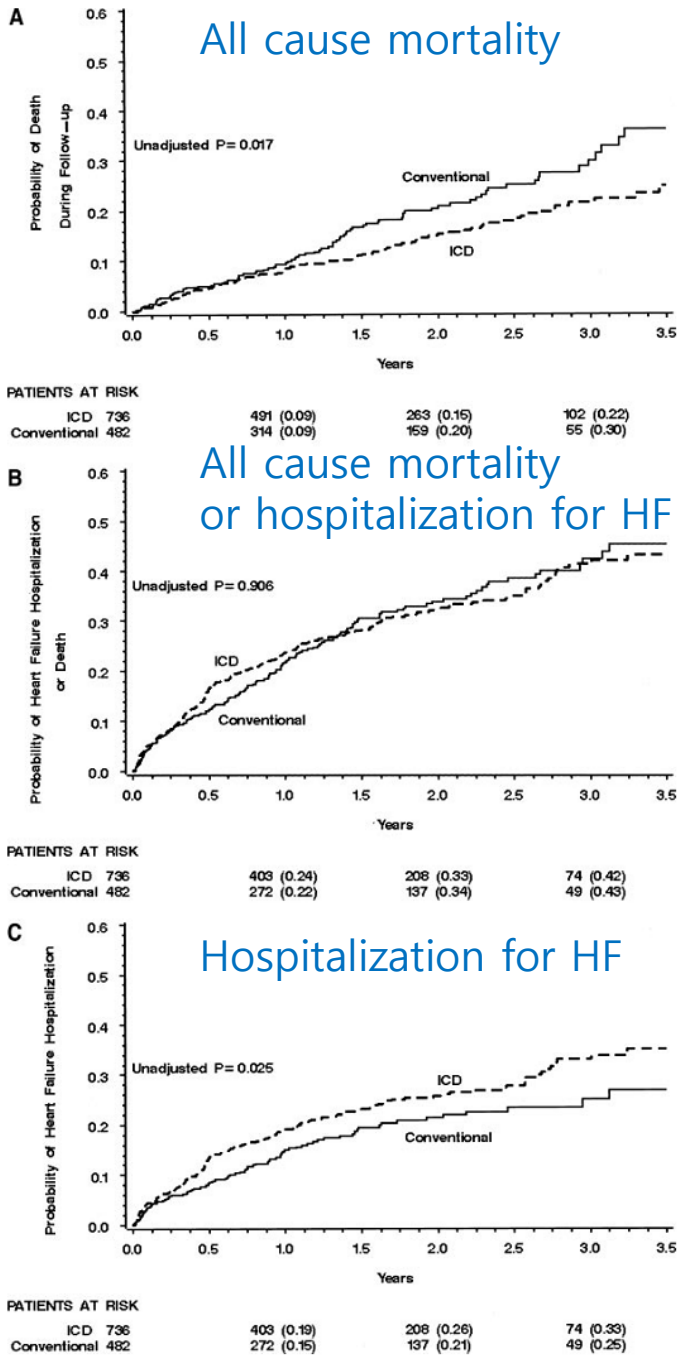
Issue of ICD shock



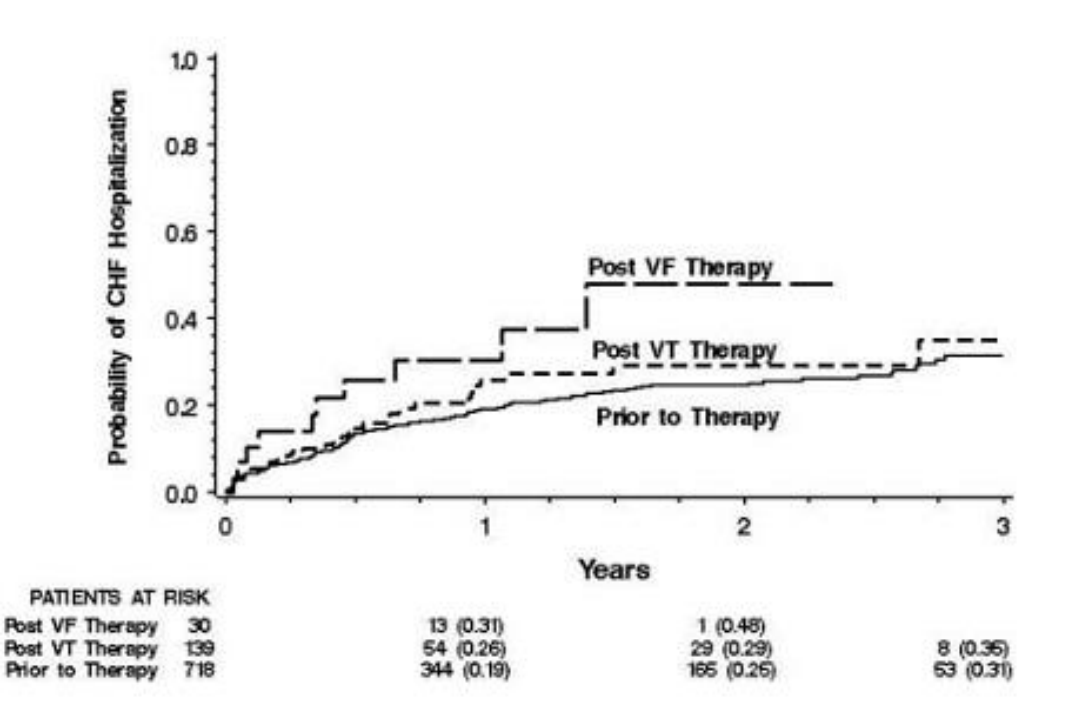
From MADIT II Trial

- Chronic ischemic heart disease who are treated with ICD have improved survival.
- But ICD arm have more increased risk of heart failure (HF).

Circulation . 2006;113:2810-2817



From MADIT II Trial

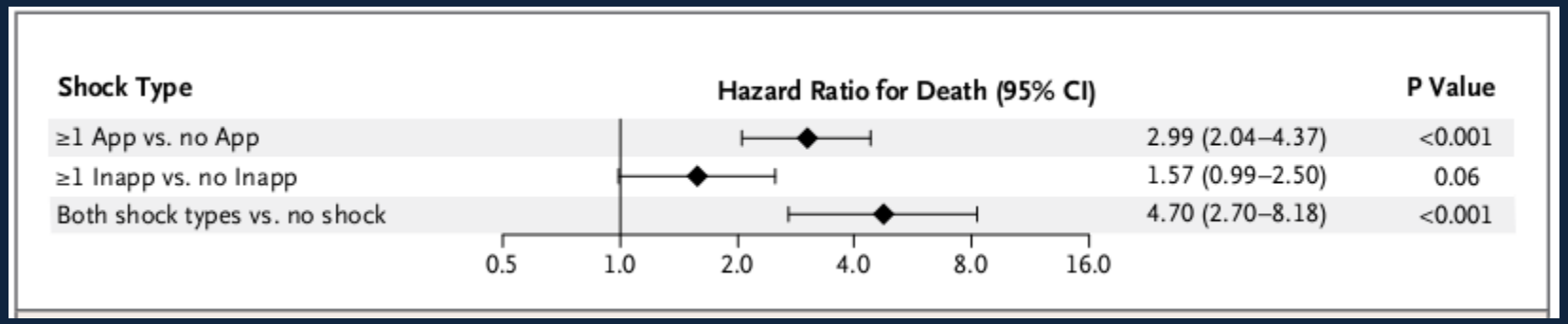


Patients who experienced appropriate shock therapy had more increased risk of CHF hospitalization

Circulation . 2004;110:3760-3765

From SCD-HeFT study

- Appropriate shock : 3 X increased risk of death
- Inappropriate shock : 1.5 X increased risk of death

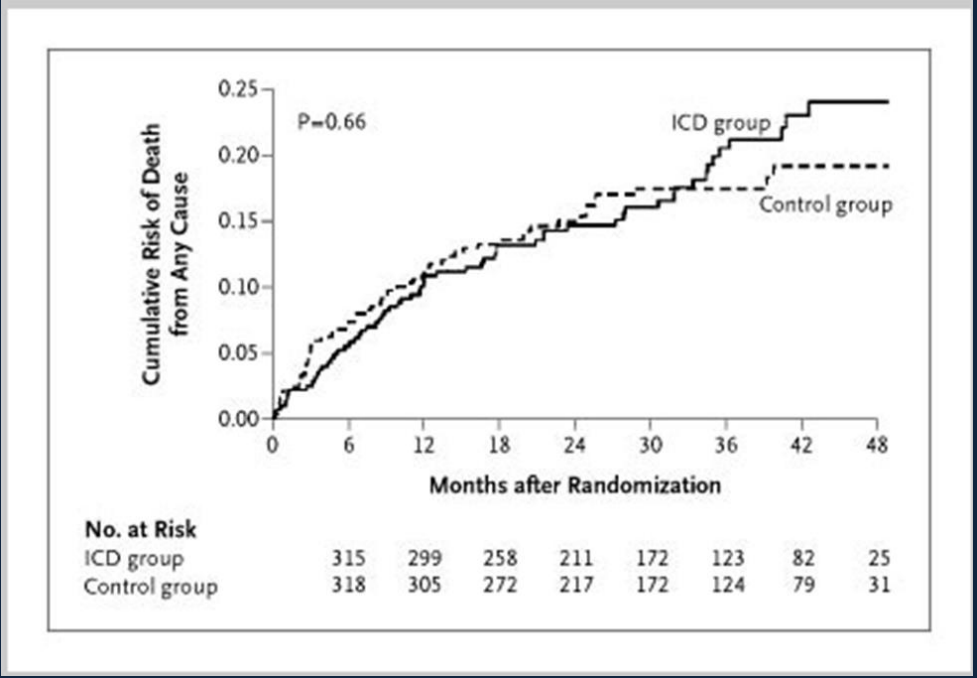


Hazard Ratios for the Risk of Death among patients who survived at least 24 hours after a First ICD Shock

N Engl J Med. 2008 September 4; 359(10): 1009–101

Defibrillation in Acute Myocardial Infarction Trial (DINAMIT).

- randomized 653 patients with EF <35%, recent MI (6 to 40 days), and low heart rate variability or high resting heart rate to primary prevention ICD (311) or medical therapy (342).



N Engl J Med 2004;351:2481-8.

From DINAMIT study

- In patients randomized to an ICD, sudden deaths were reduced, but non-arrhythmic mortality was increased, which was confined to the ICD subgroup that recorded electric therapies (mostly shocks) for VTA

Circulation . 2010;122:2645-2652

Risk for Death by Rhythm and Therapy Types in Primary Prevention Trials

Electrical Therapy Type	Hazard of Death			
	MADIT-II	SCD-HeFT	DINAMIT	COMPANION
Appropriate shock only Ischemic HF Nonischemic HF	3.4 (2.0-5.6)	5.7 (4.0-8.1) 8.7 (5.7-13.4) 2.61 (1.4, 4.8)	4.9 (2.4-10.2)	1.7-2.4
Inappropriate shock only	2.3 (1.2-4.7)	2.0 (1.3-3.1)	Not reported	Not reported
Appropriate ATP only	0.4(0.2-1.2)	NA (all shocks)	Not reported	Not reported
Inappropriate ATP only	0.7 (0.2-2.5)	NA (all shocks)	Not reported	Not reported

1.Conditioning rhythm type influences shocked episode risk
   1. Shocked VTA mortality risk > shocked SVT mortality risk
   2. Shocked VF mortality > shocked VT mortality risk
2.Risk is greater in ischemic HF
3.ATP does not increase VTA or SVT episode risk

Paradox of shock therapy

Sudden Cardiac Death Prevention

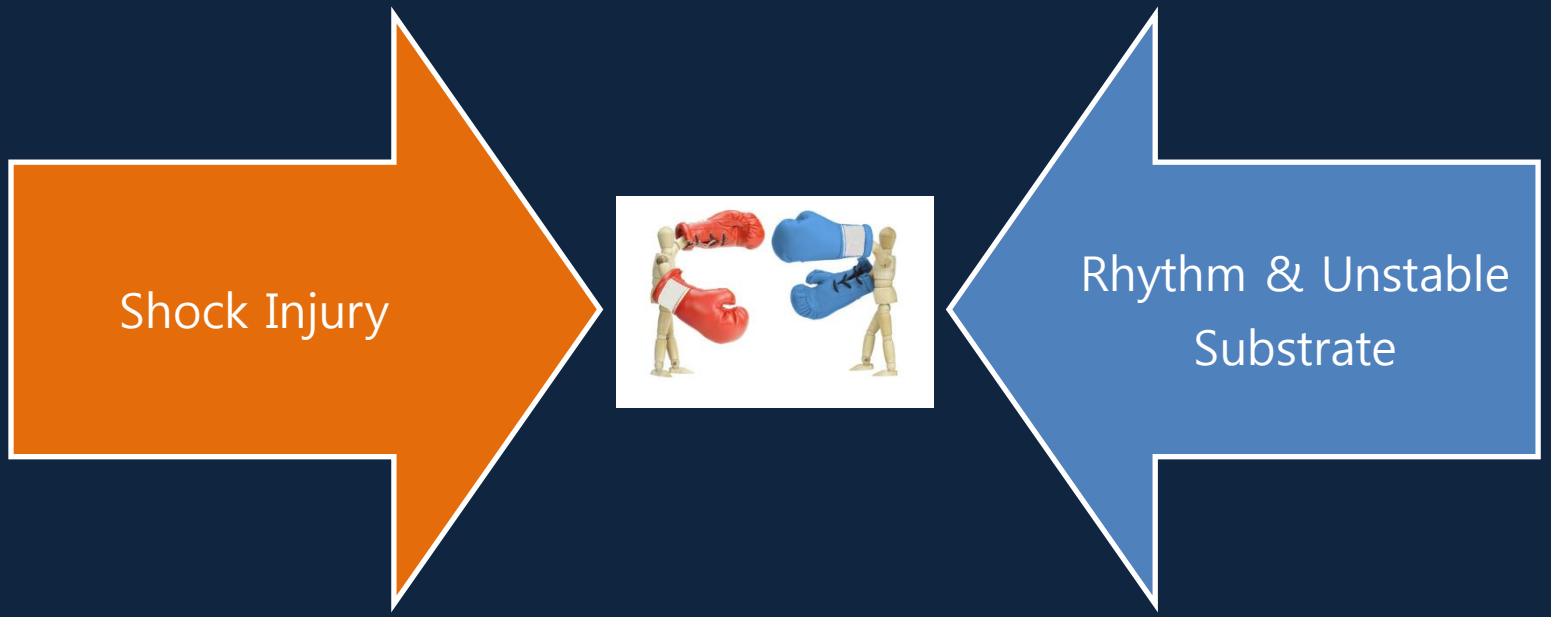
V.S.

Heart failure death acceleration

Cause of higher mortality in shocked patient ?

- Direct myocardial injury by high voltage shock.

- patients with **VTA** and **shocks** are at higher risk for death, and the former is a marker for, but mechanistically unrelated to, the latter.



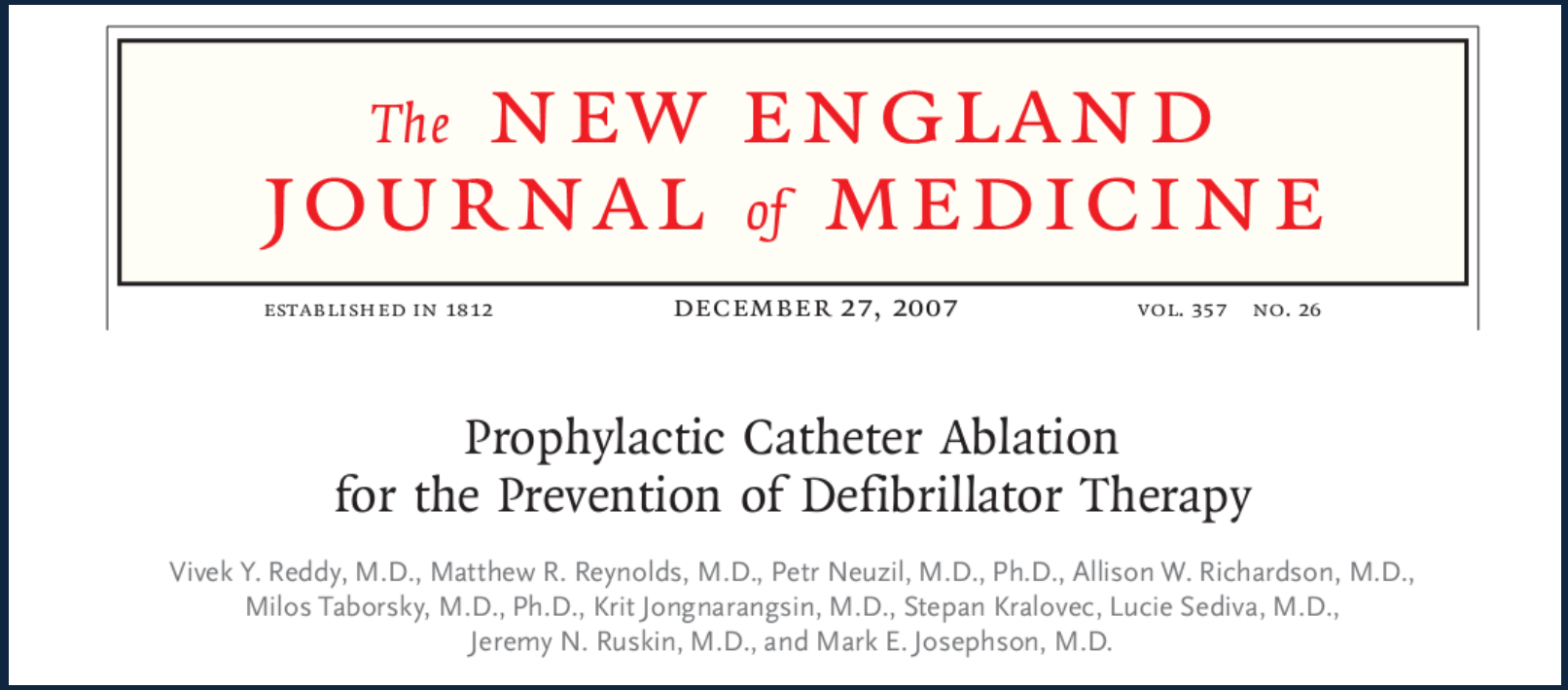
Morbidity of shock

- Psychological problem
- Reduce quality of life
- Heart failure acceleration
- Proarrythmia (rare)

To minimize inappropriate and unnecessary shocks

- ICD Programming
  - rate and duration for initial detection
  - SVT-VT discrimination (algorithm, SC vs DC)
  - ATP and shock strength
  - Sensing enhancements (T wave oversensing)
- Lead Fracture surveillance
- Remote Monitoring

Circ Arrhythm Electrophysiol 2011;4;778-790



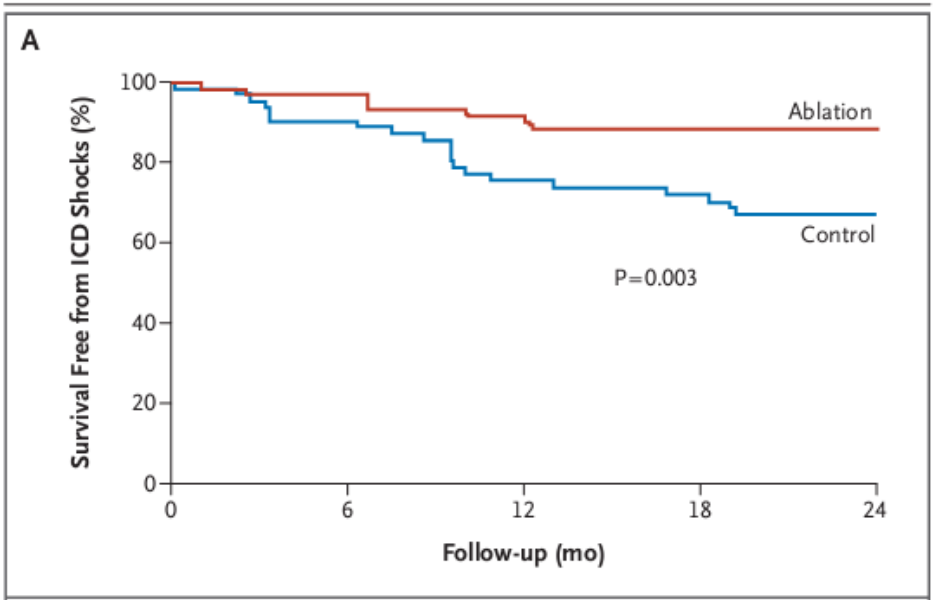
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 27, 2007 VOL. 357 NO. 26

Prophylactic Catheter Ablation for the Prevention of Defibrillator Therapy

Vivek Y. Reddy, M.D., Matthew R. Reynolds, M.D., Petr Neuzil, M.D., Ph.D., Allison W. Richardson, M.D., Milos Taborsky, M.D., Ph.D., Krit Jongnarangsin, M.D., Stepan Kralovec, Lucie Sediva, M.D., Jeremy N. Ruskin, M.D., and Mark E. Josephson, M.D.

- Eligible patients with a history of a MI with ICD for spontaneous VT or VF.
- Control v.s. adjunctive catheter ablation (64 patients in each group)
- The primary end point: survival free from any appropriate ICD therapy



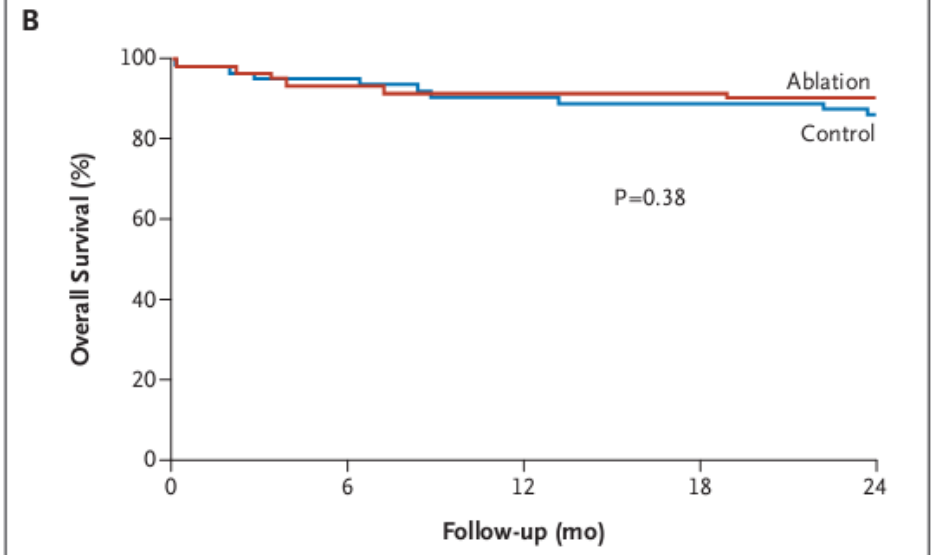


Figure 3. Kaplan–Meier Estimates of Secondary End Points.
ICD denotes implantable cardioverter–defibrillator.

a 65% reduction in the risk of receiving ICD therapy

a trend toward decreased mortality in the ablation group (9% vs. 17%, P = 0.29)

Before MADIT-RIT

CONTEMPORARY REVIEW

Implantable cardioverter-defibrillator shock prevention does not reduce mortality: A systemic review

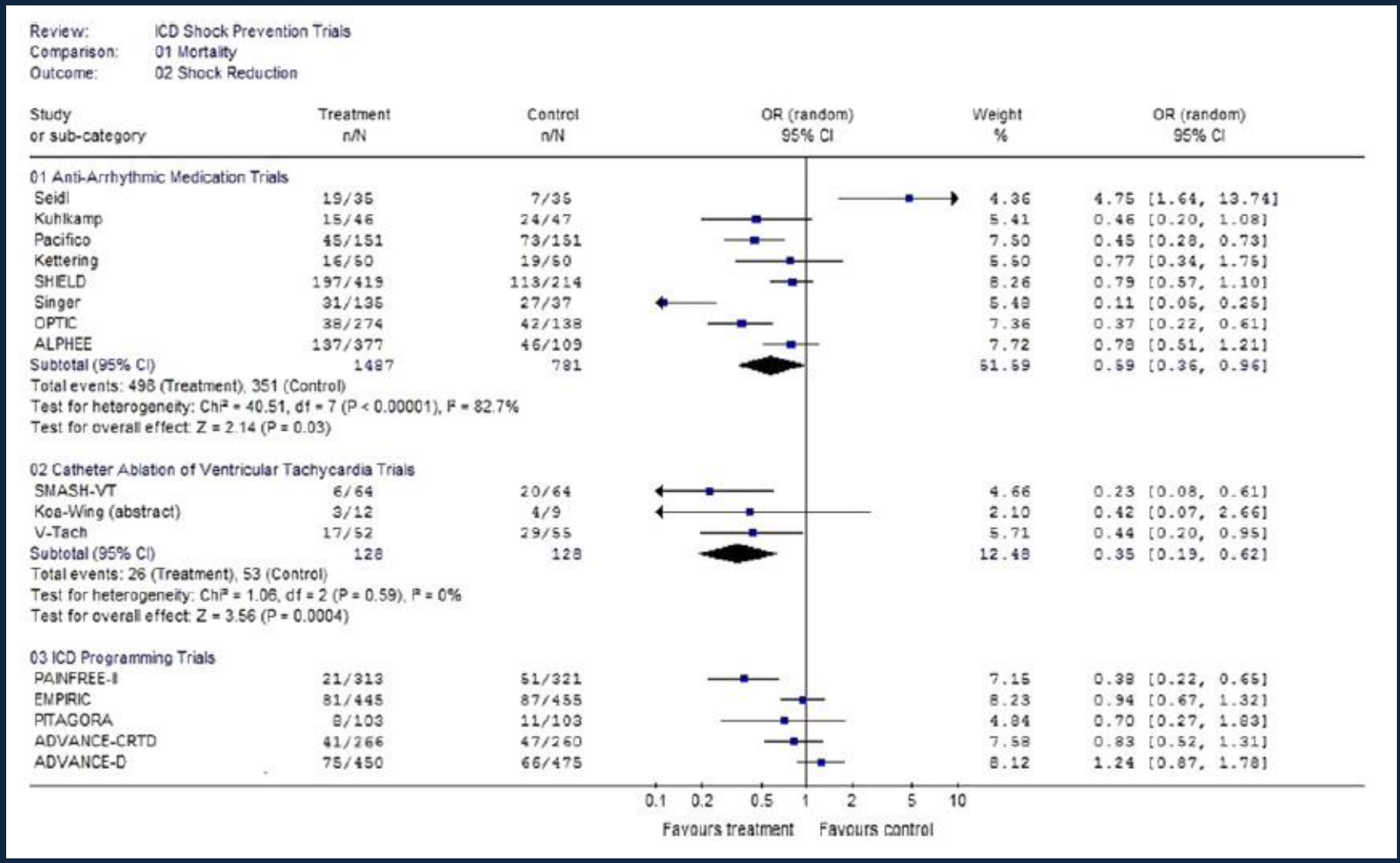
Andrew H. Ha, MD,* Inje Ham, BSc,* Girish M. Nair, MBBS,† Stuart J. Connolly, MD,† Paul Dorian, MD,‡ Carlos A. Morillo, MD, FHRS,† Jeff S. Healey, MD, MSc, FHRS†

*From the *McMaster University, Hamilton, Ontario, Canada, †Population Health Research Institute, Hamilton, Ontario, Canada and ‡St. Michael's Hospital, Toronto, Ontario, Canada.*

- 17 randomized trials were included in this analysis, including 5875 patients.

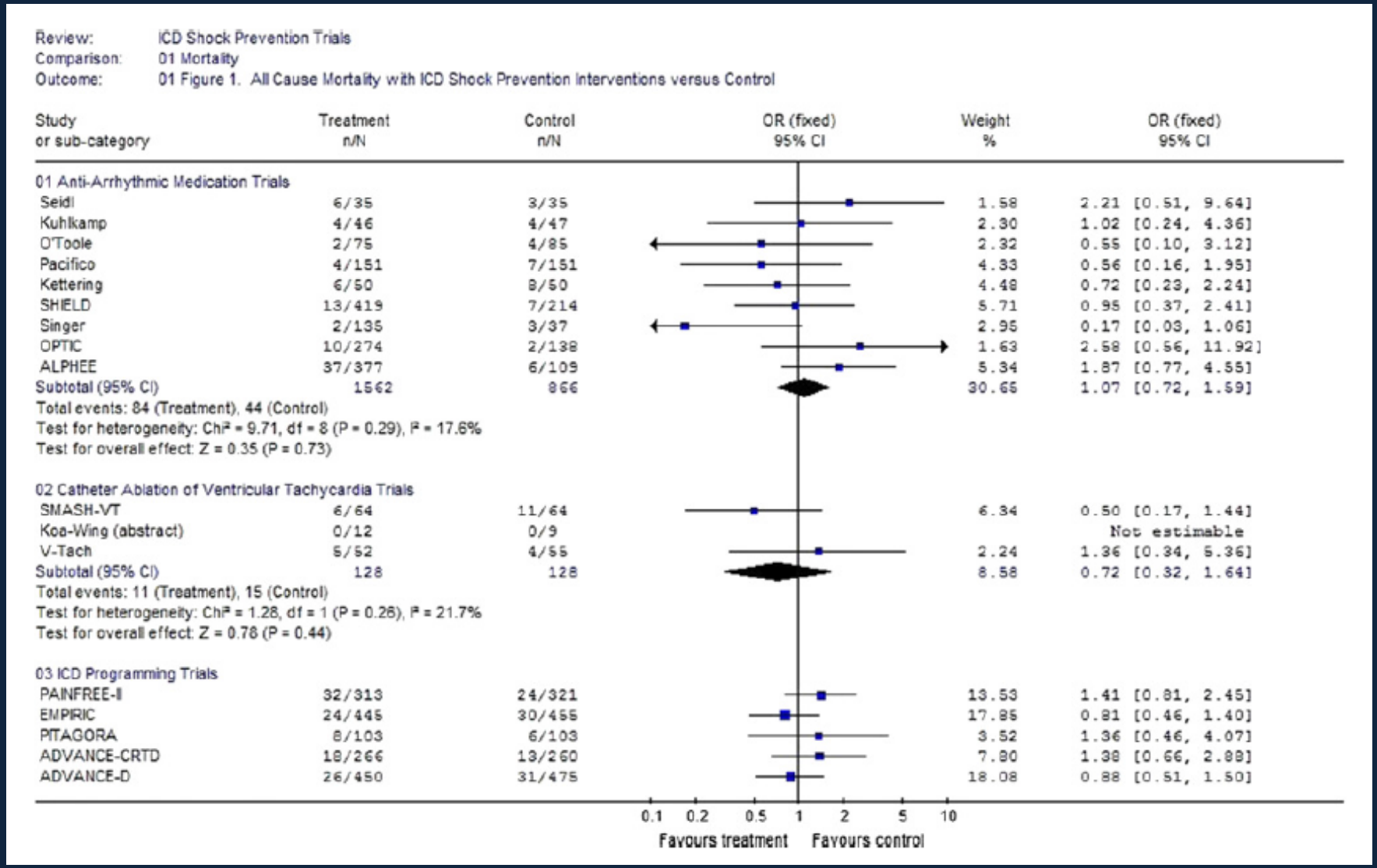
Heart Rhythm 2012;9:2068–2074

Result of shock reduction



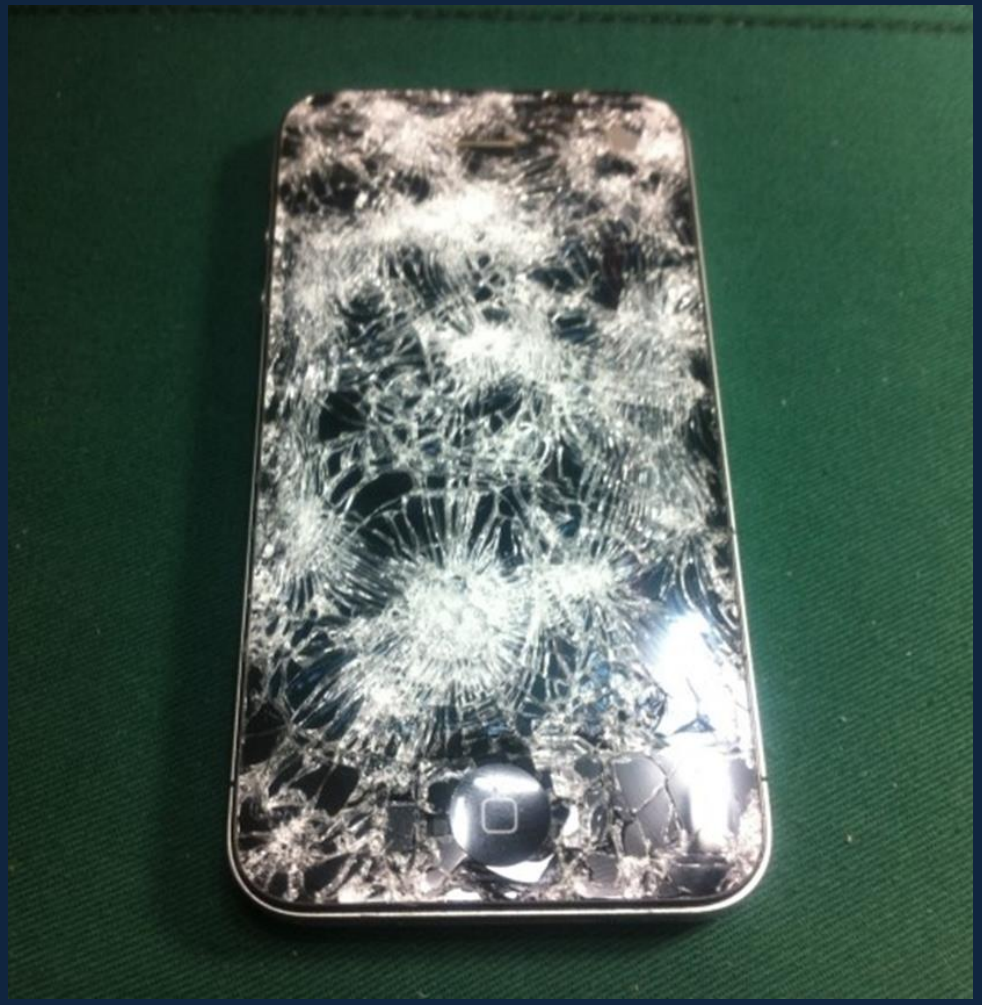
Heart Rhythm 2012;9:2068–2074

Result of all cause mortality



Heart Rhythm 2012;9:2068–2074

Shock Prevention v.s. Mortality



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 13, 2012 VOL. 367 NO. 24

Reduction in Inappropriate Therapy and Mortality through ICD Programming

Arthur J. Moss, M.D., Claudio Schuger, M.D., Christopher A. Beck, Ph.D., Mary W. Brown, M.S., David S. Cannom, M.D., James P. Daubert, M.D., N.A. Mark Estes III, M.D., Henry Greenberg, M.D., W. Jackson Hall, Ph.D.,* David T. Huang, M.D., Josef Kautzner, M.D., Ph.D., Helmut Klein, M.D., Scott McNitt, M.S., Brian Olshansky, M.D., Morio Shoda, M.D., David Wilber, M.D., and Wojciech Zareba, M.D., Ph.D., for the MADIT-RIT Trial Investigators†

Adapted from 2012 AHA Late Breaking Trial Results Presented by

Arthur J. Moss, MD

Professor of Medicine

University of Rochester Medical Center

November 6, 2012

Los Angeles, CA USA

MADIT-RIT

Background

Can ICD devices be reprogrammed to reduce inappropriate therapies?

MADIT-RIT

Study Overview

Study Design: Randomized, 3-arm study of patients randomized 1:1:1 to either conventional, high-rate cutoff, or duration-dela y programming with dual chamber ICD or CRT-D

Primary Endpoint: First episode of inappropriate therapy (defined as shock or ATP)

B arm vs. A arm

C arm vs. A arm

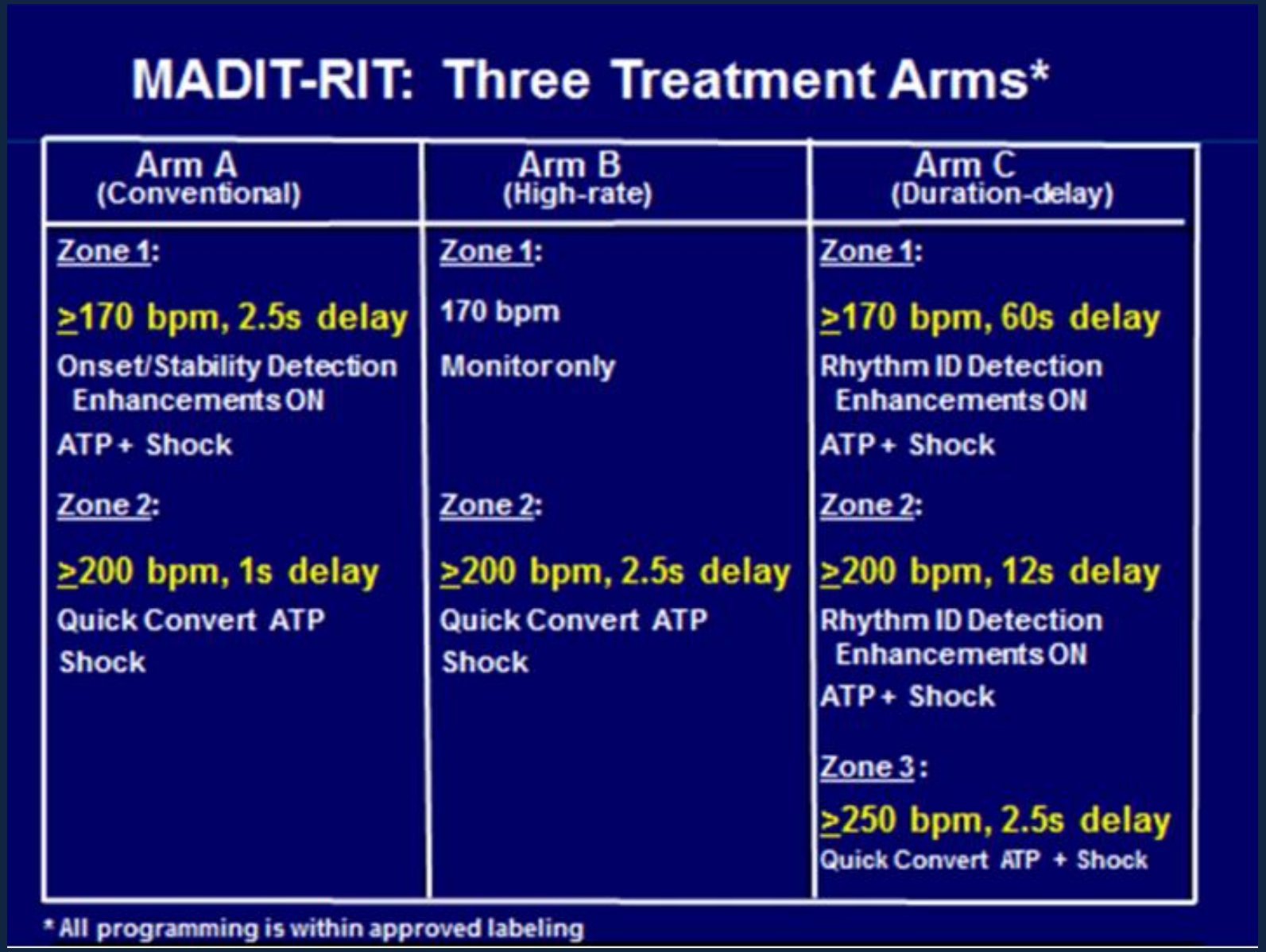
Secondary Endpoints: All-cause mortality

Syncope

Number of Patients: 1500 from 98 centers

US, Canada, Europe, Israel and Japan

MADIT-RIT



*All programming is within approved labeling. Rhythm ID® and Quick Convert™ are trademarks of Boston Scientific Corporation

MADIT-RIT

Eligibility

Inclusion Criteria

- Primary prevention patients with no Hx of VT/VF
- Sinus rhythm at enrollment; Hx PAF ok
- Pt. on stable, optimal pharmacologic therapy
- Age >21 yrs; informed consent

Exclusion Criteria

- Pt. with pacemaker, ICD or CRT-D device
- CABG or PTCA in past 3 months
- MI (enzyme +) or AF in past 3 months
- 2nd or 3rd degree heart block
- NYHA IV
- Chronic AF
- Renal disease: BUN>50mg/dlor Creatinine>2.5mg/dL

MADIT-RIT

Pre-specified End Points

Primary

- First episode of inappropriate therapy (defined as shock or ATP)
  - B arm vs. A arm
  - C arm vs. A arm
- Rationale for first inappropriate therapy (IT)
  - Expect reprogramming to be common after IT
  - Protocol allows reprogramming after IT

Secondary

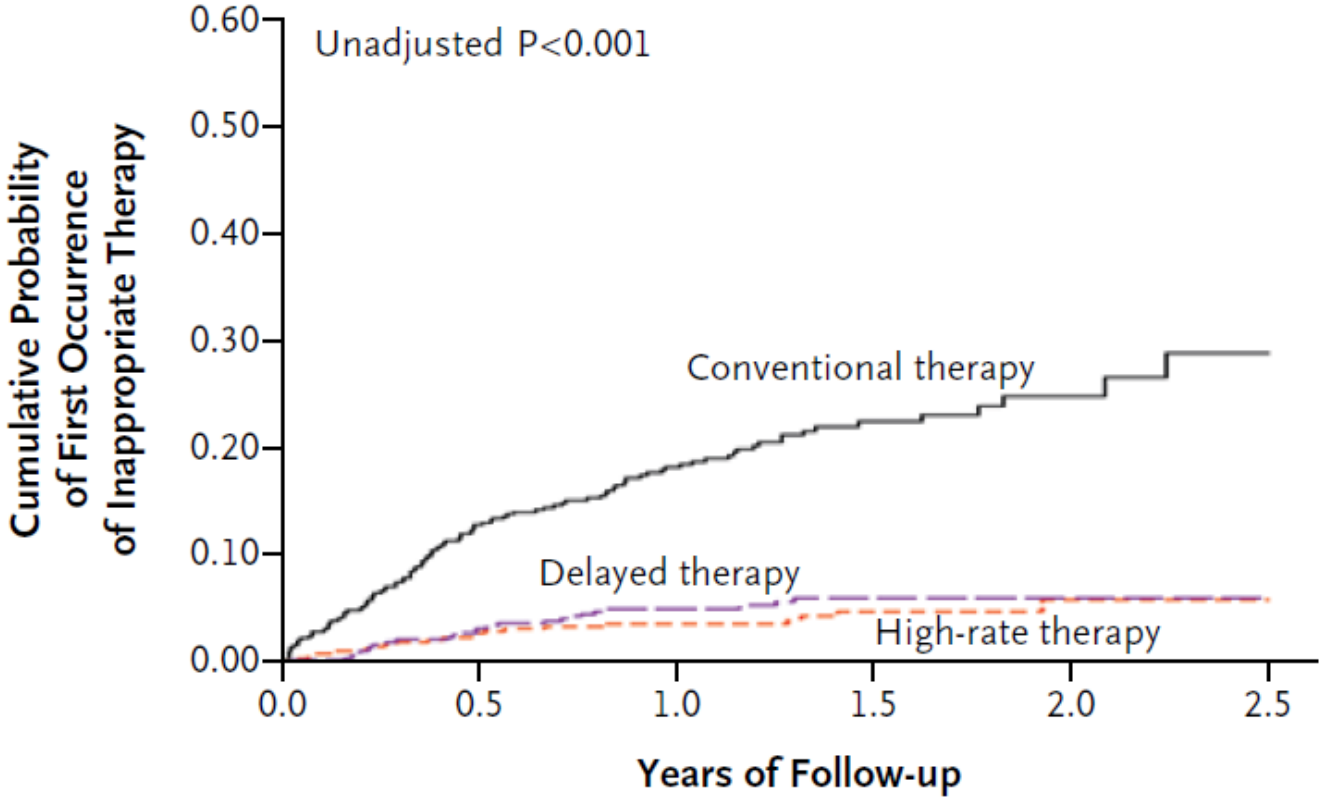
- All-cause mortality
- Syncope

Baseline Demographic and Clinical Characteristics

	Therapy Group		
	A	B	C
	Conventional ≥170bpm	High-rate ≥200bpm	Duration-Delay ≥170bpm
	n=514	n=500	n=486
Age, yrs	64	63	62
Male, %	70	71	72
Ischemic, %	53	54	52
EF, %	26	26	26

No significant differences in 22 variables among the 3 Rx groups

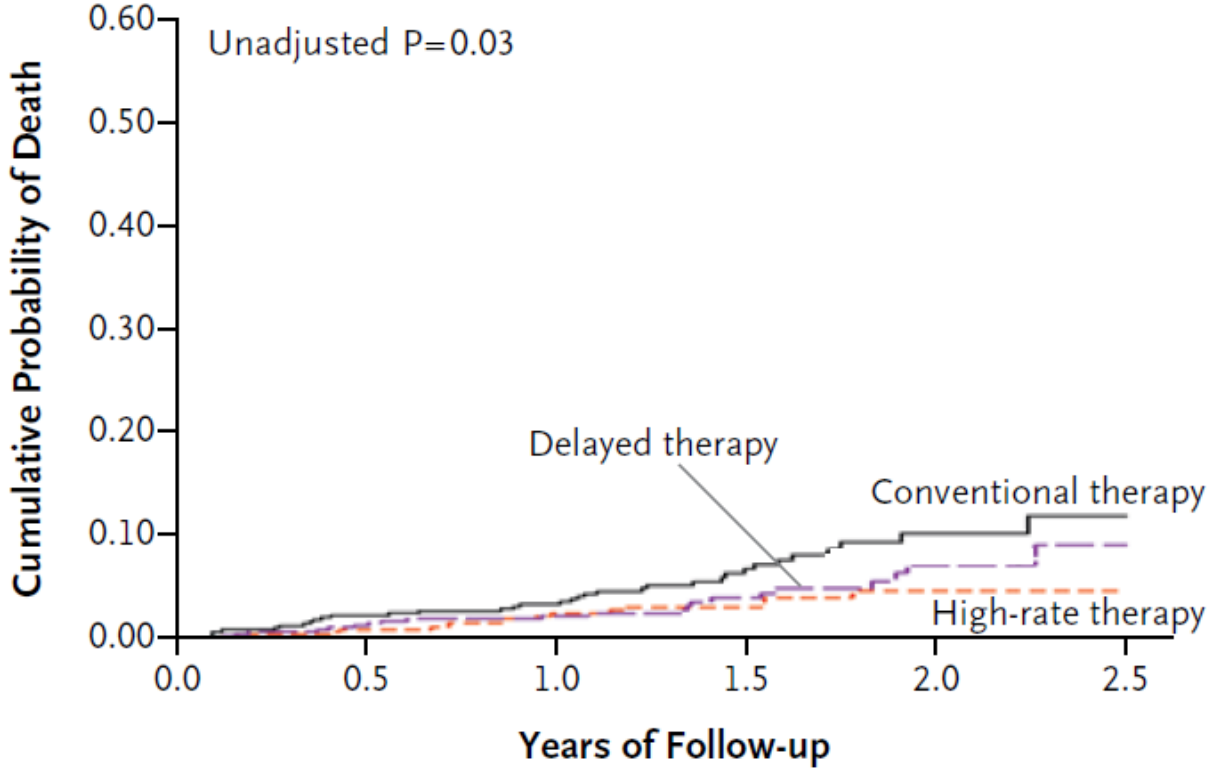
Cumulative Probability of First Inappropriate Therapy by Treatment Group



No. at Risk

Conventional therapy	514	420 (0.13)	305 (0.18)	149 (0.22)	56 (0.25)	8 (0.29)
High-rate therapy	500	454 (0.03)	339 (0.04)	191 (0.05)	70 (0.06)	17 (0.06)
Delayed therapy	486	445 (0.03)	342 (0.05)	177 (0.06)	82 (0.06)	13 (0.06)

Cumulative Probability of Death by Treatment Group



No. at Risk

Conventional therapy	514	490 (0.02)	392 (0.03)	219 (0.07)	89 (0.10)	14 (0.12)
High-rate therapy	500	478 (0.01)	372 (0.02)	221 (0.03)	90 (0.05)	21 (0.05)
Delayed therapy	486	471 (0.01)	375 (0.02)	205 (0.04)	99 (0.07)	14 (0.09)

Frequency and Hazard Ratios for Inappropriate Therapy, Death, and Syncope by Treatment Group

	Treatment Groups			Treatment Group Comparisons			
	# of patients			B vs A		C vs A	
	A	B	C	Hazard Ratio	P-value	Hazard Ratio	P-value
Events	n=514	n=500	n=486				
1st Inapp Therapy	105	21	26	0.21	<0.001	0.24	<0.001
Death	34	16	21	0.45	0.01	0.56	0.06
1st Syncope	23	22	23	1.32	0.39	1.09	0.80

A : conventional therapy
B : high-rate therapy
C : duration delay therapy

Arrhythmias Triggering First Inappropriate Therapies

	Treatment Group		
	A	B	C
Arrhythmias	# Patients 1st Inappropriate Therapies		
At Fib/Flut	24	11	5
Regular SVT	78	9	17
Other	3	1	4

A : conventional therapy
B : high-rate therapy
C : duration delay therapy

Note: marked reduction in patients with1st inappropriate therapies in High-rate (B) and Duration-delay (C) groups for At Fib/Flut and Regular SVT when compared to Conventional therapy (A).

Any Appropriate and Inappropriate Therapy by Treatment Group

Treatment Groups					
	# of Patients (% of Rx Group)				
	A	B	C		
	n=514	n=500	n=486	P-Value	
Any Appropriate Therapy				B vs A	C vs A
Shock	28 (5)	26 (5)	19 (4)	0.86	0.25
ATP	111 (22)	38 (8)	20 (4)	<0.001	<0.001
Any Inappropriate Therapy					
Shock	31 (6)	14 (3)	15 (3)	0.01	0.03
ATP	104 (20)	20 (4)	25 (5)	<0.001	<0.001

A : conventional therapy
B : high-rate therapy
C : duration delay therapy

MADIT-RIT

Summary

Improved ICD programming to high-rate (>200 bpm) or 60sec duration-delay is associated with:

1) ~75% reduction in 1st inappropriate therapy;
2) ~50% reduction in all-cause mortality

Dr. Moss and his co-authors speculated that the decrease in m ortality in this trial could have been related to the reduction in inappropriate shock and ATP therapies

Although controversial, defibrillator shocks can cause myocardial damage, and the shocks have been associated with increased mortality

Summary

- ICD shock was related to increased mortality among ICD patients.
- To reduce shock therapy, antiarrhythmic drug, catheter ablation and ICD reprogramming had been applied.
- Before MADIT-RIT study, there was no strong evidence that shock therapy reduction have beneficial effect on survival.

Conclusion

- MADIT-RIT study showed that optimized programming of ICD therapies was associated with reductions in inappropriate therapy and all-cause mortality during long-term follow-up.

Korea University Arrhythmia Center

Young-Hoon Kim, Sang- Weon Park, Hong -Euy Lim, Jong-Il Choi, Jae Min Shin, Dae In Lee, Hyun-Soo Lee, Kyung-Jeong Ko, Ju-Yong Sung, Ra-Seung Lim, Bu-Kyung Han, Jung-Hoon Che, Chul-Min Moon, Soon-Hwa Shin, Eun-Hee Kim, So-Young Kweon, Ji-Hae Yoon, Soo- Jeong Ko, Yeon-Hee Lee