Reducing Inappropriate and Appropriate Therapy in Primary Prevention Patients

Jonathan S. Steinberg, MD

Director, Arrhythmia Institute

Valley Health System

Professor of Medicine (adj)

University of Rochester School of Medicine and Dentistry

New York, NY and Ridgewood, NJ, USA

October 16 - 18
14th EDITION 2015

MY CONFLICTS OF INTEREST ARE:

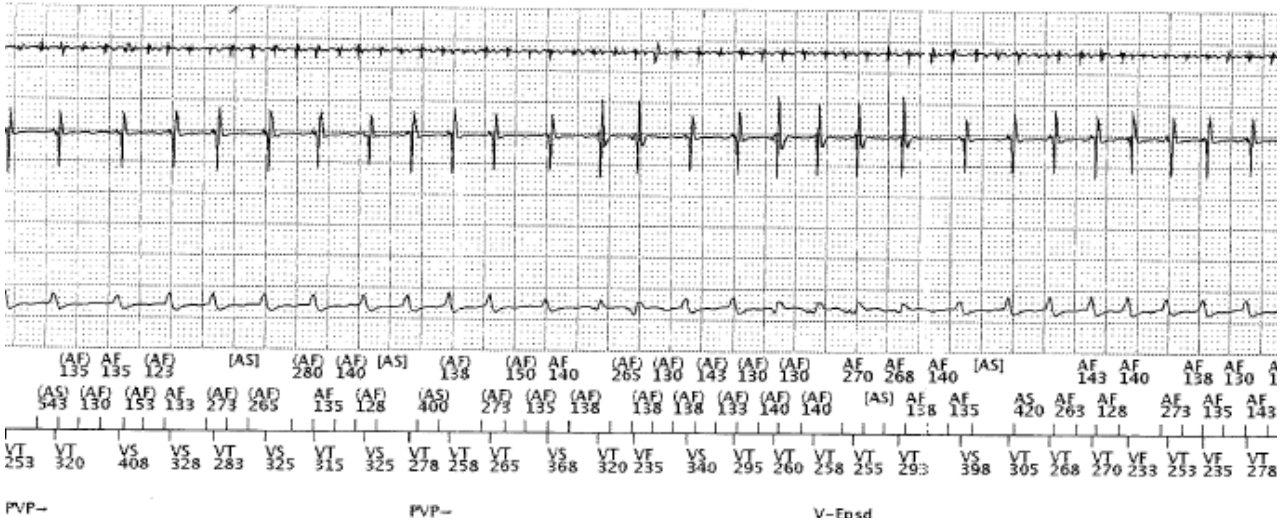
Medtronic, Boston Scientific, Biosense Webster (consultant); Medtronic, Biosense Webster (research grant)

Inappropriate ICD Therapy

Atrial electrogram

Ventricular EGM

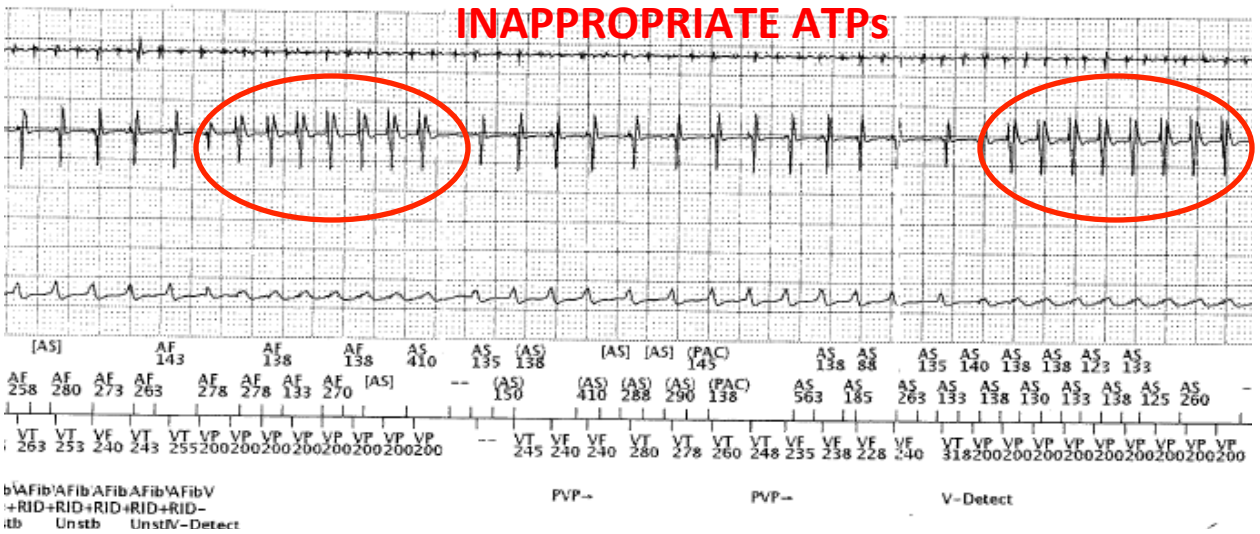
Shock EGM



Atrial electrogram

Ventricular EGM

Shock EGM

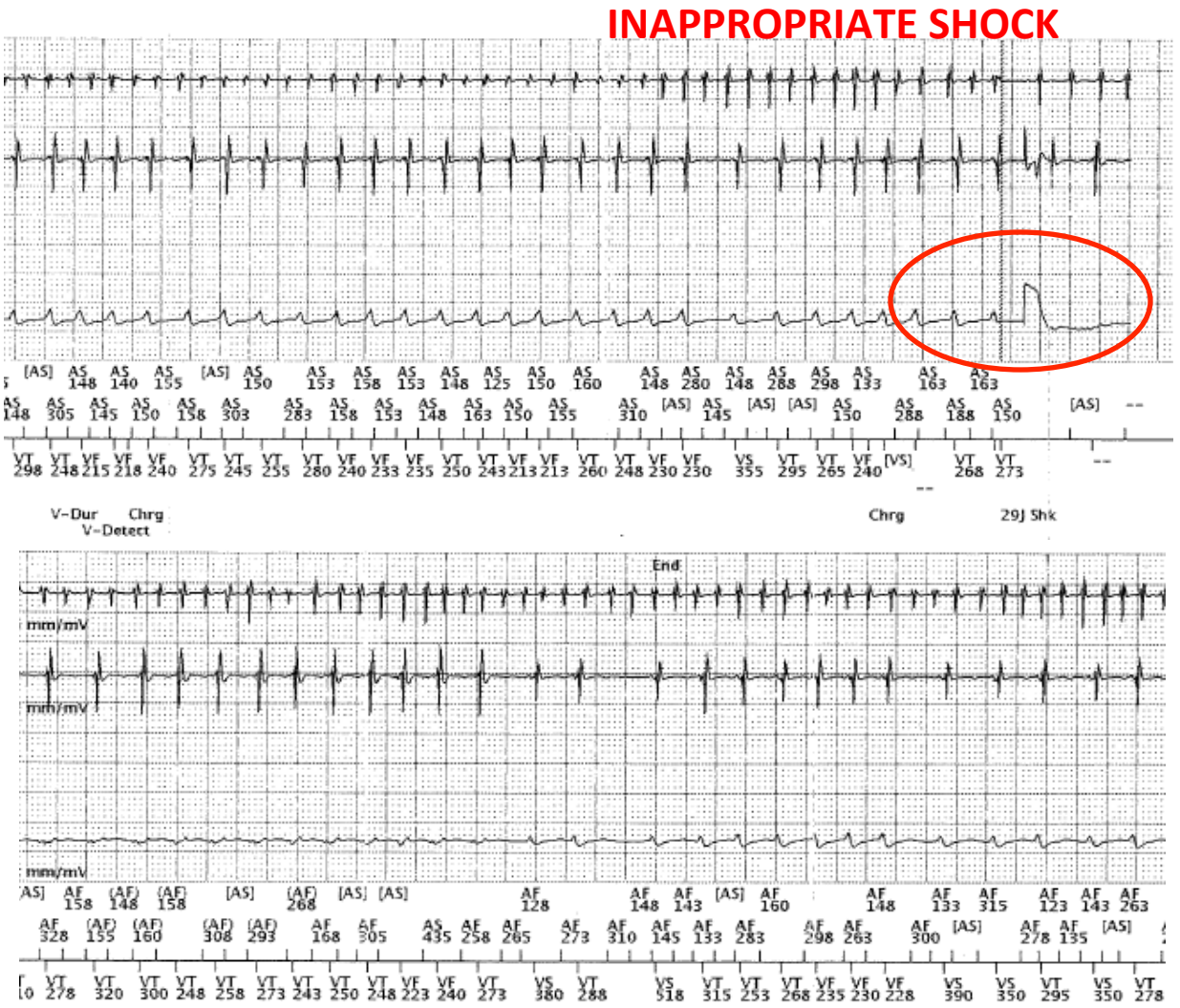


Inappropriate ICD Therapy

Atrial electrogram

Ventricular EGM

Shock EGM



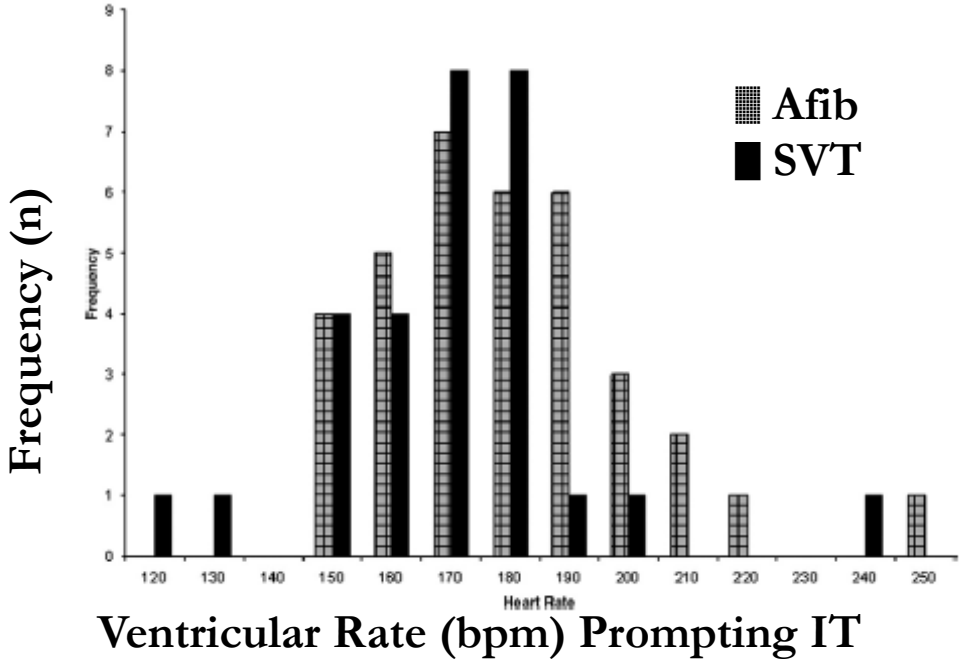
Atrial electrogram

Ventricular EGM

Shock EGM

MADIT-II: Incidence of Inappropriate Therapy

- Incidence: 12% (n=83)
  - 31.2% of all shocks
  - 38.6% had ≥ 1 shock (mean 2.2 ± 2.5)
- Cause:
  - Afib 44%
  - SVT 36%
  - Abnormal sensing 20%



Daubert et al. JACC 2008;51:357

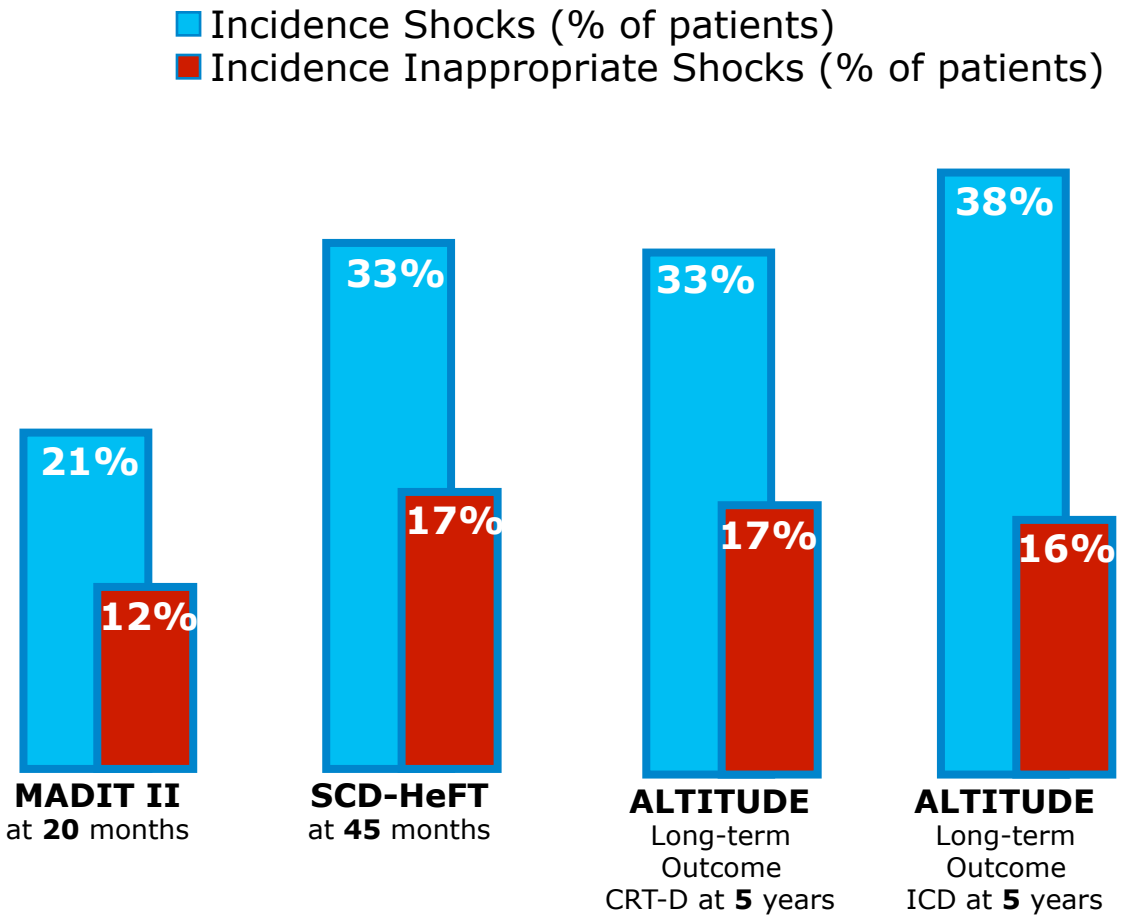
MADIT-II: Inappropriate Therapy and Mortality

Table 6 Predictors of All-Cause Mortality by Cox Proportional Hazards Regression Analysis

Variable	Hazard Ratio	95% Confidence Interval	p Value
Baseline characteristics			
Blood urea nitrogen >25	2.07	1.38–3.11	<0.01
No beta-blocker	1.64	1.09–2.47	0.02
Interim events			
Interim CHF hospitalization	4.23	2.70–6.62	<0.01
Appropriate and inappropriate shock	4.08	1.71–9.75	<0.01
Appropriate shock only	3.36	2.04–5.55	<0.01
Inappropriate shock only	2.29	1.11–4.71	0.02
Appropriate and inappropriate therapy	3.12	1.38–7.03	<0.01
Appropriate therapy only	2.53	1.54–4.15	<0.01
Inappropriate therapy only	2.01	0.97–4.13	0.06
Appropriate ATP but not shock	0.412	0.148–1.150	0.0903
Inappropriate ATP but not shock	0.729	0.213–2.496	0.6145

Daubert et al. JACC 2008;51:357

Incidence of Shocks and Inappropriate Shocks



[1] Daubert JP, et al. Inappropriate ICD Shocks in MADIT II. *JACC* 2008; 51:1357-1365.
[2] Bardy GH,et al. SCD-HeFT. *NEJM* 2005; 352;3:225-237.
[3] Saxon, Leslie et al. COMPANION Trial. *Circulation* 2006; 114; 2766-2772.
[4] Saxon Leslie et al. The ALTITUDE Survival Study. *Circulation* 2010; 122:2359-2367
[5] Van Rees et al JACC 2011;57(5):556

Incidence of Inappropriate ICD Therapy and Subsequent Outcome

- ICD therapy is highly efficient in reducing mortality in high-risk cardiac patients

- Inappropriate ICD therapy commonly occurs (12%- 17%) and is mainly delivered for regular SVT or atrial fib/flutter

- Inappropriate ICD therapy is associated with an adverse clinical outcome (increased mortality)

Pre-ICD Considerations

- Prior AF
  - Pattern: paroxysmal, persistent or permanent
  - Ventricular rate patterns
    - Holter
  - Medical therapy
    - Beta blocker
      - Maximal dosing
    - Digoxin
    - Avoid calcium channel blockers
    - Antiarrhythmic drugs
  - Prior interventions
    - Ablation
    - Surgical maze
- No prior AF
  - Still substantial risk of new AF: be proactive!

Routine Programming Considerations

- Common strategies
  - Higher rate cutoff as clinically appropriate
  - ATP preferred to shock therapy (in VT and VF zones)
  - Delayed time to detection
  - Enroll patient in remote monitoring
- Single chamber ICD
  - Two or more zones
  - Stability (eg 20-40 ms)
  - Morphology criterion (with auto updates if possible)
- Dual chamber ICD
  - As above +
  - AV relationship (AF detection)
  - Chamber of initiation

➢ The reality is that these efforts were inconsistently effective, although did not appear to delay presumed lifesaving therapy for VT.

Why the Limited Benefits of Device Programming to Prevent Inappropriate Shock for AF?

- Variable or reduced specificity of device algorithms
- Inconsistent atrial sensing of local egrams, or sensed events falling in blanking period
- Farfield oversensing of ventricular events on atrial channel
- Rapidly conducted AF may be relatively regular and foil stability calculation
- Lower than desired VT rate cutoff may be programmed
- Unnecessary programming of timeout feature

MADIT Randomized Trial to Reduce Inappropriate Therapy (MADIT-RIT)

MADIT-RIT: Hypothesis

Dual-chamber ICD or CRT-D devices with:

- **high-rate cutoff (≥200bpm)**

or

- **duration-delay (initial 60sec delayed therapy @≥170bpm) plus Rhythm ID® detection**

will be associated with fewer 1st inappropriate therapies than standard/conventional programming (2.5sec delay @ ≥170bpm) without increase in mortality

Randomized, 3-arm study using Boston Scientific devices

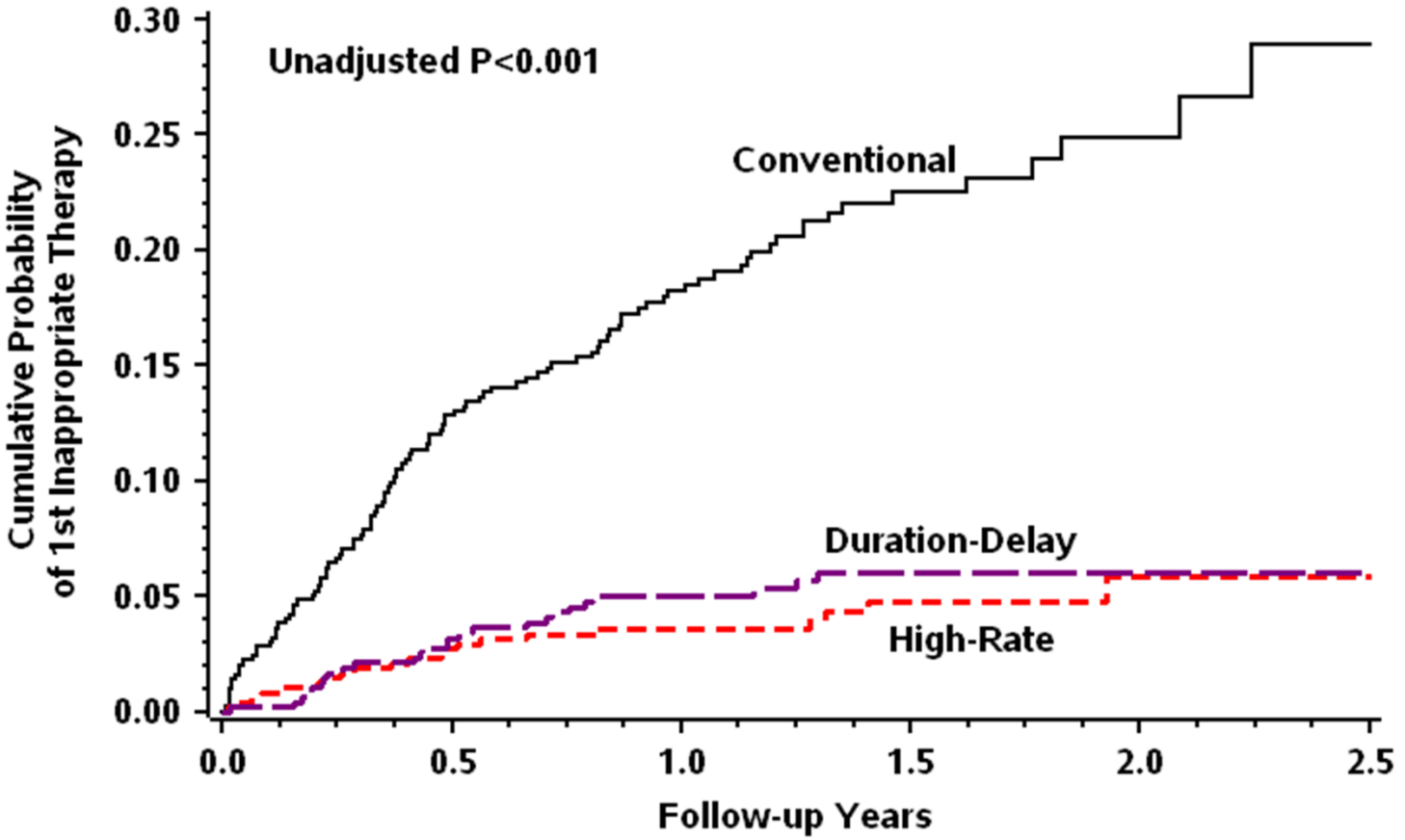
MADIT-RIT: Three Treatment Arms*

Arm A (Conventional)	Arm B (High-rate)	Arm C (Duration-delay)
Zone 1:	Zone 1:	Zone 1:
≥170 bpm, 2.5s delay	170 bpm	≥170 bpm, 60s delay
Onset/Stability Detection Enhancements ON	Monitor only	Rhythm ID Detection Enhancements ON
ATP + Shock		ATP + Shock
Zone 2:	Zone 2:	Zone 2:
≥200 bpm, 1s delay	≥200 bpm, 2.5s delay	≥200 bpm, 12s delay
Quick Convert ATP	Quick Convert ATP	Rhythm ID Detection Enhancements ON
Shock	Shock	ATP + Shock
		Zone 3 :
		≥250 bpm, 2.5s delay
		Shock

* All programming is within approved labeling

Moss et al, NEJM 2012

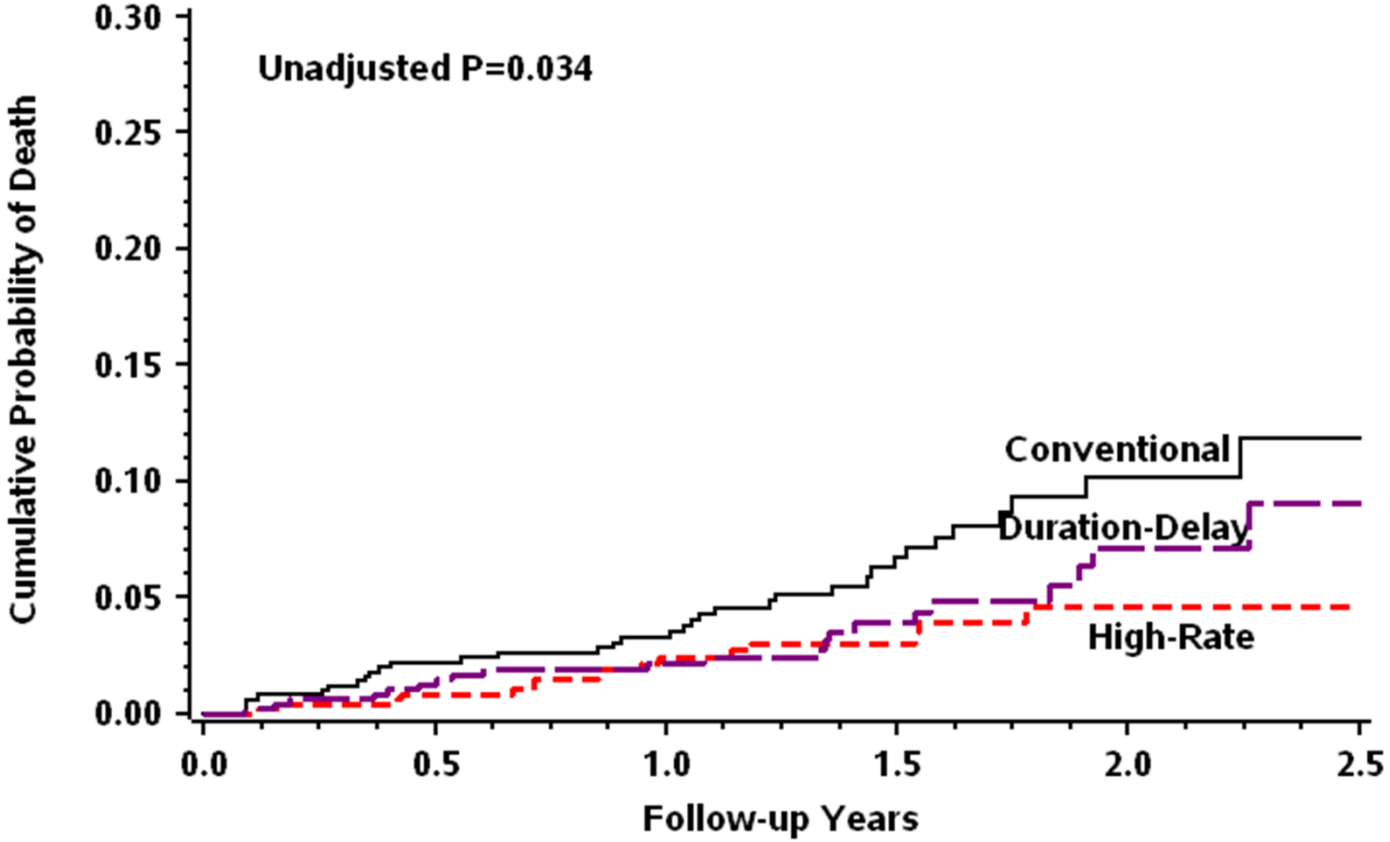
Cumulative Probability of First Inappropriate Therapy by Treatment Group



Patients at Risk						
Conventional	514	420 (0.13)	305 (0.18)	149 (0.22)	56 (0.25)	8 (0.29)
High-Rate	500	454 (0.03)	339 (0.04)	191 (0.05)	70 (0.06)	17 (0.06)
Duration-Delay	486	445 (0.03)	342 (0.05)	177 (0.06)	82 (0.06)	13 (0.06)

Moss et al, NEJM 2012

Cumulative Probability of Death by Treatment Group



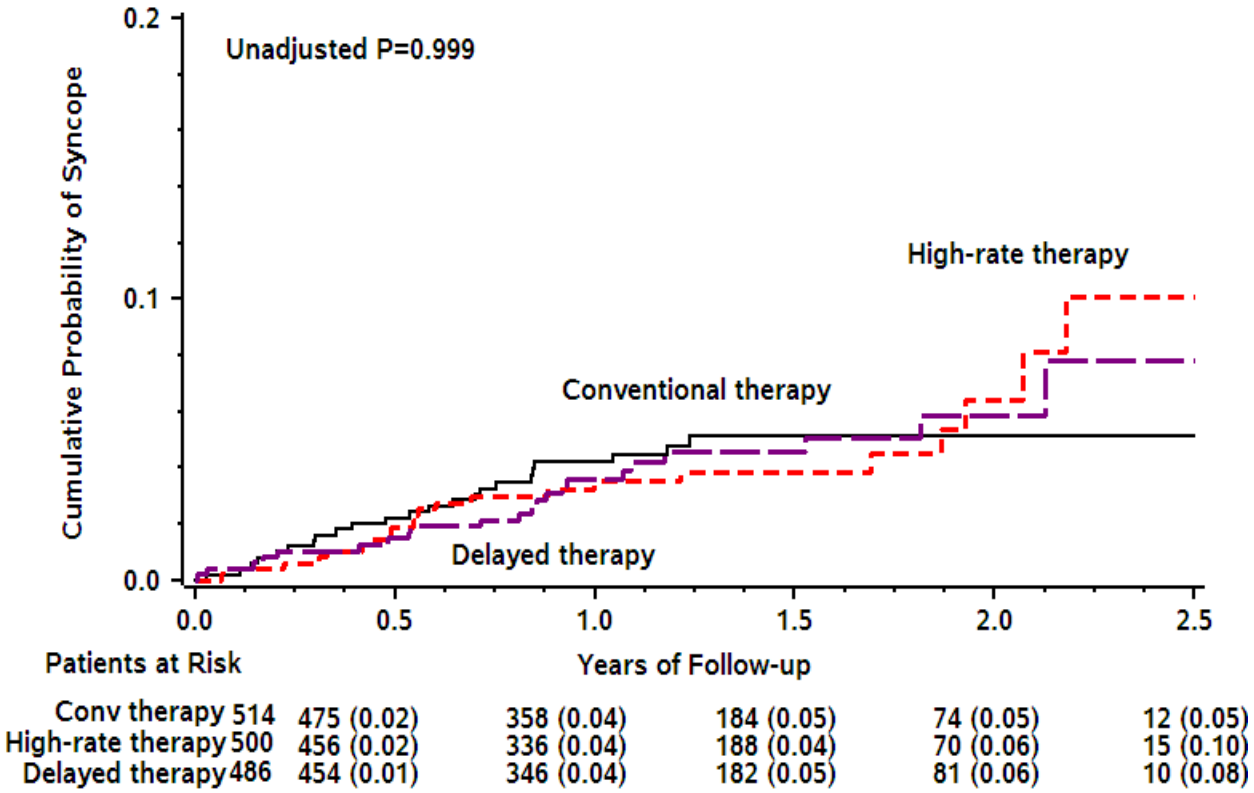
Patients at Risk						
Conventional	514	490 (0.02)	392 (0.03)	219 (0.07)	89 (0.10)	14 (0.12)
High-Rate	500	478 (0.01)	372 (0.02)	221 (0.03)	90 (0.05)	21 (0.05)
Duration-Delay	486	471 (0.01)	375 (0.02)	205 (0.04)	99 (0.07)	14 (0.09)

Moss et al, NEJM 2012

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	
Events	A n=514	B n=500	C n=486	Hazard Ratio	P-value	Hazard Ratio	P-value
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

Syncope

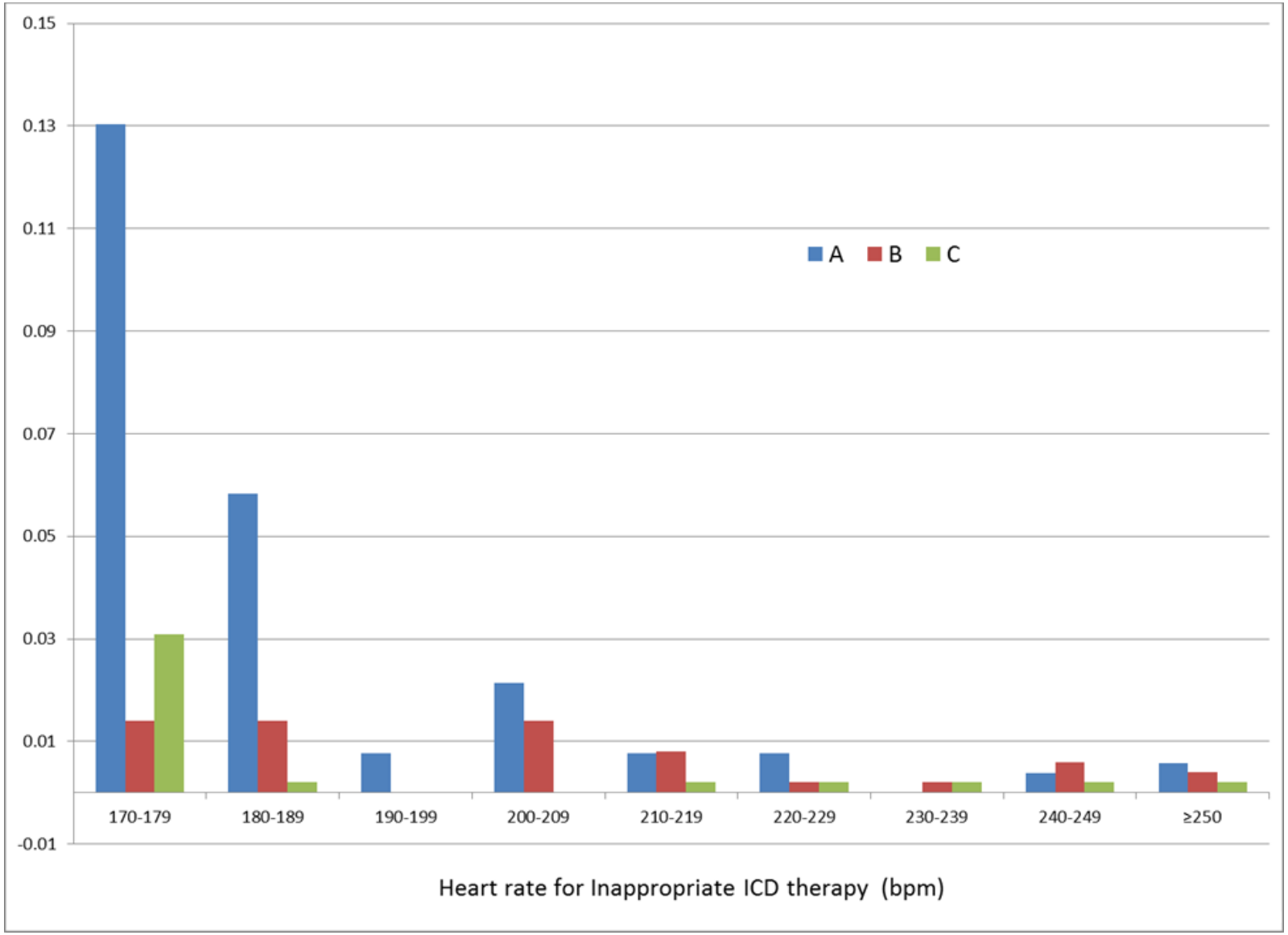

Unadjusted P=0.999
Cumulative Probability of Syncope
0.2
0.1
0.0
High-rate therapy
Conventional therapy
Delayed therapy
0.0
0.5
1.0
1.5
2.0
2.5
Years of Follow-up
Patients at Risk
Conv therapy 514 475 (0.02) 358 (0.04) 184 (0.05) 74 (0.05) 12 (0.05)
High-rate therapy 500 456 (0.02) 336 (0.04) 188 (0.04) 70 (0.06) 15 (0.10)
Delayed therapy 486 454 (0.01) 346 (0.04) 182 (0.05) 81 (0.06) 10 (0.08)

Any Appropriate and Inappropriate Therapy by Treatment Group

	Treatment Groups # of Patients (% of Rx Group)			P-Value	
	A n=514	B n=500	C n=486		
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

Moss et al, NEJM 2012

Distribution of Inappropriate ICD Therapy by Heart Rate and Programming Arm



Primary Results of MADIT-RIT

Improved ICD programming at high-rate (≥200 bpm) or with delayed therapy (60sec at ≥170bpm) is associated with significant:

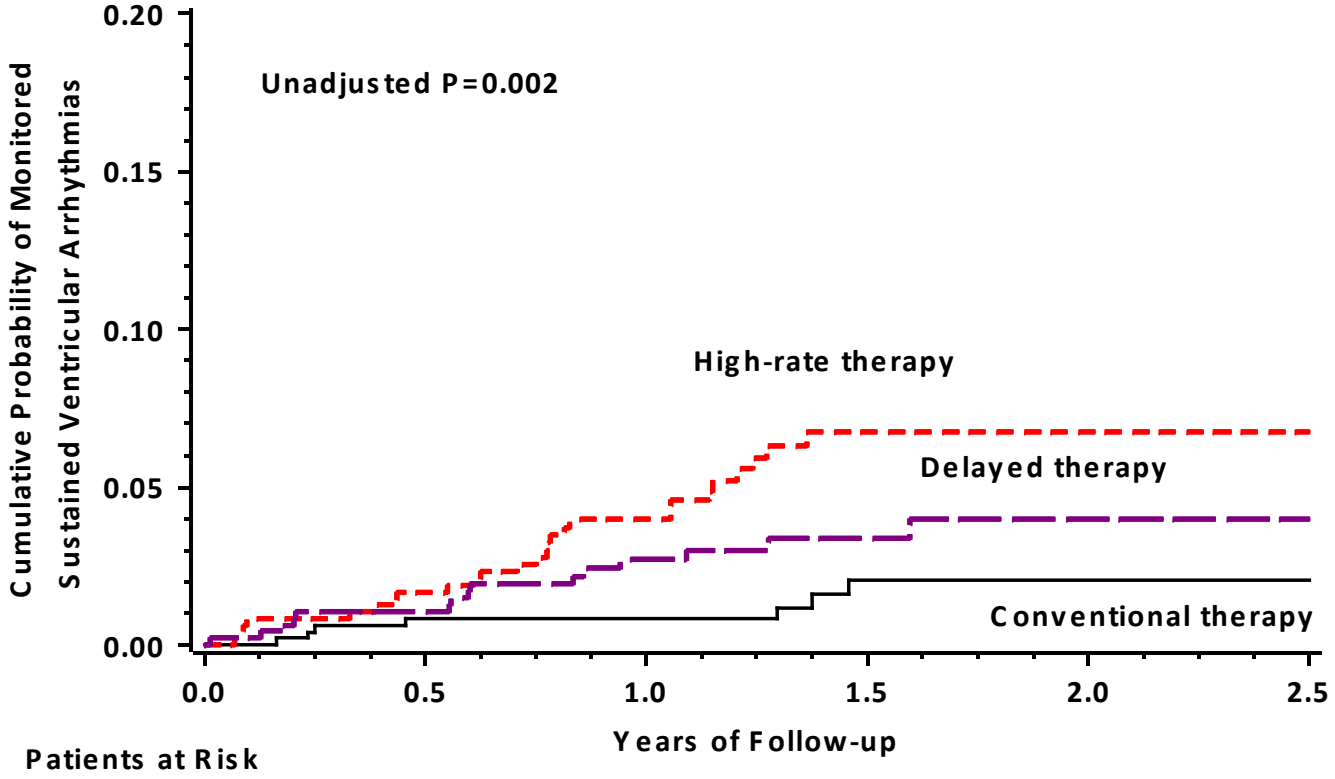
1) ~75% reduction in 1st inappropriate therapy;
2) ~50% reduction in all-cause mortality
3) Significant reduction in appropriate therapy

The Effect of Appropriate and Inappropriate ICD Therapy on Mortality

Therapies	HR	95% CI	p-value
Inappropriate shock	2.90	1.02-8.20	0.046
Inappropriate ATP	3.60	1.49-8.72	0.005
Appropriate shock	5.86	2.91-11.78	<0.001
Appropriate ATP	0.23	0.03-1.69	0.148

Unpublished data

Incidence of Monitored Sustained VTs by Programming Arm

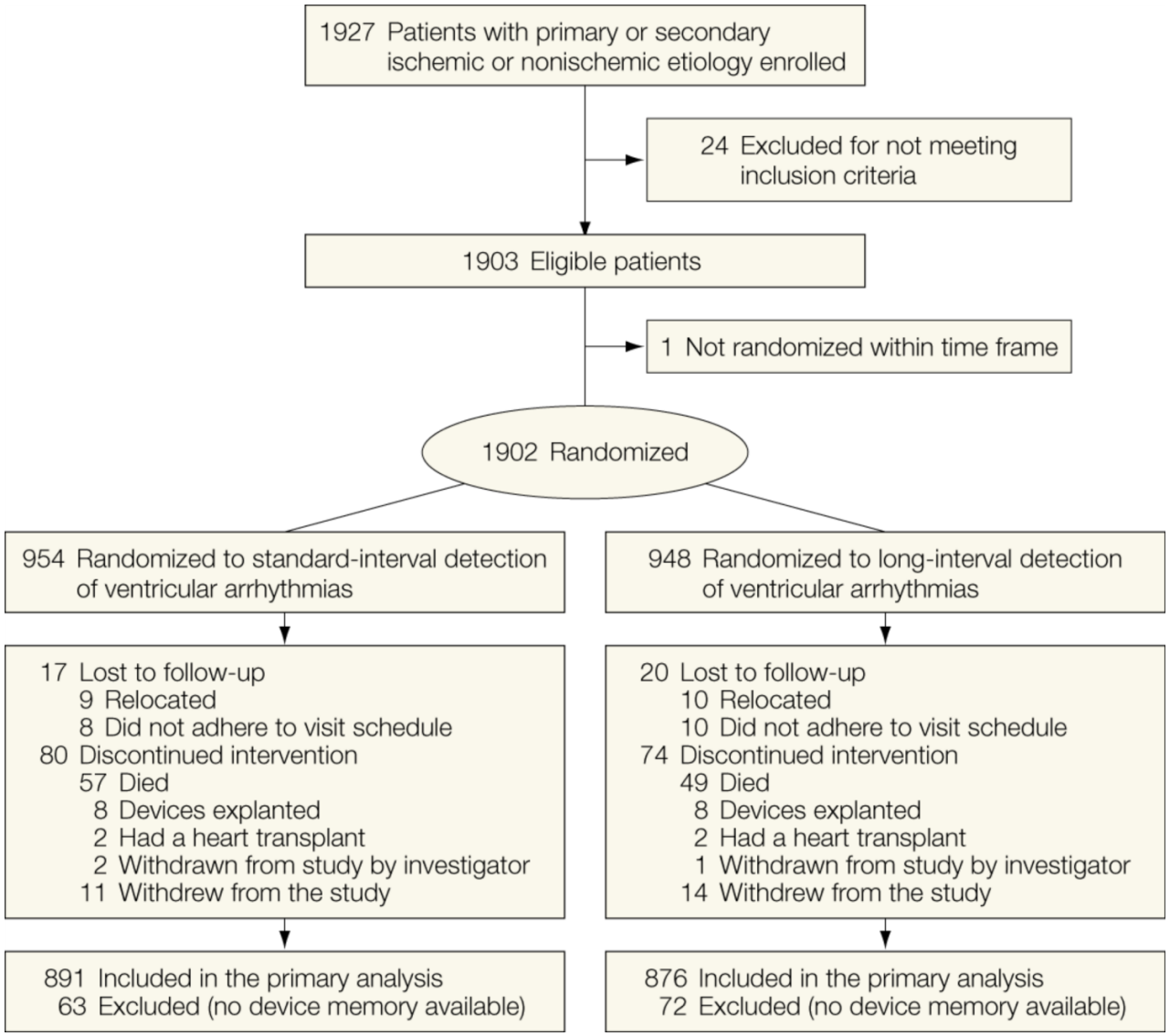


Patients at Risk

Conv. therapy	514	478 (0.01)	368 (0.01)	186 (0.02)	76 (0.02)	13 (0.02)
High-rate therapy	500	457 (0.02)	336 (0.04)	182 (0.07)	67 (0.07)	17 (0.07)
Delayed therapy	486	453 (0.01)	348 (0.03)	182 (0.03)	82 (0.04)	13 (0.04)

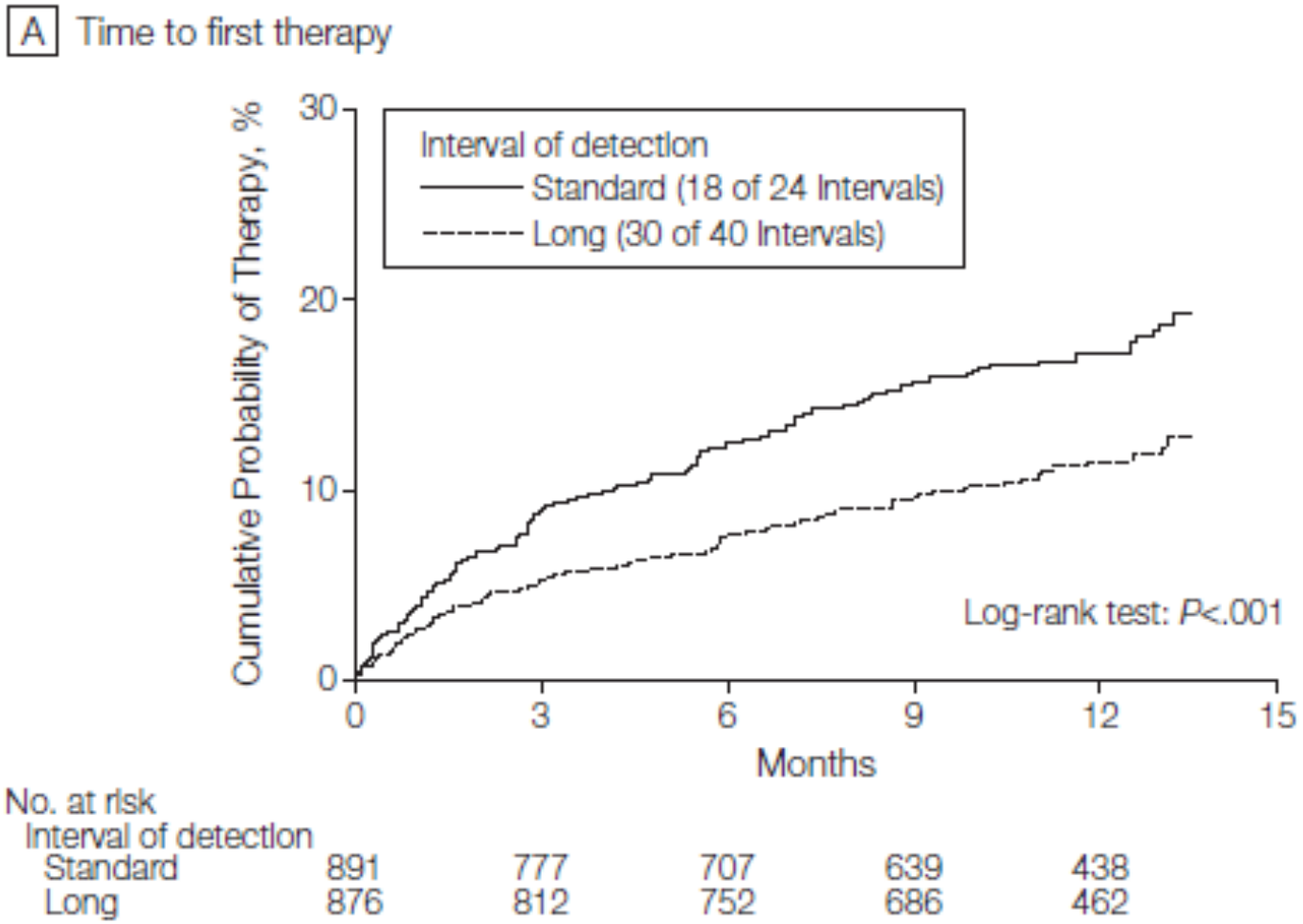
Unpublished data

ADVANCE III: Randomized Trial Comparing 30/40 to 18/24 at Cycle Length ≤320 ms (≥188 bpm)



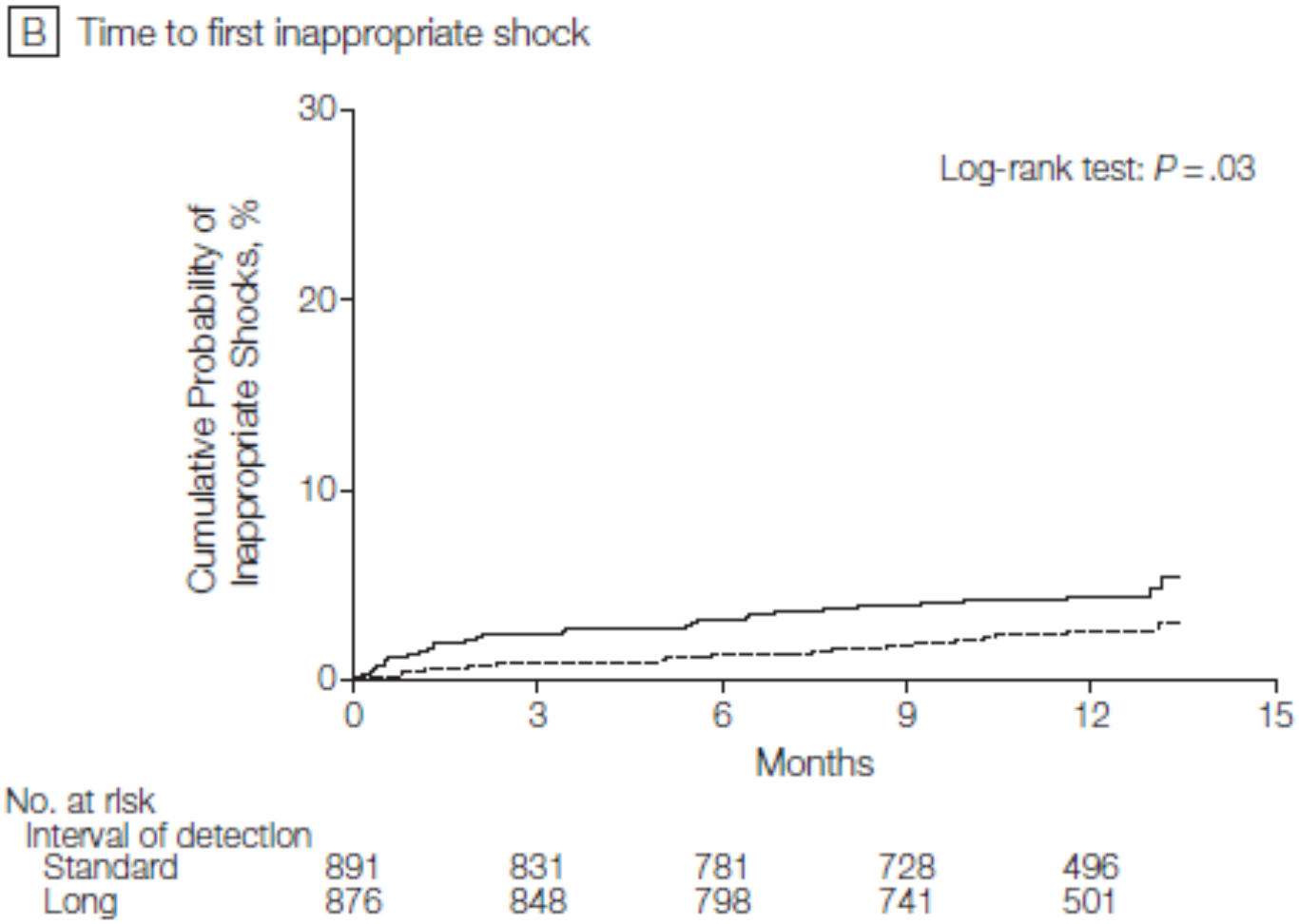
Gasparini et al. JAMA. 2013;309:1903-1911.

ADVANCE III: Time to First Therapy



Gasparini et al. JAMA. 2013;309:1903-1911.

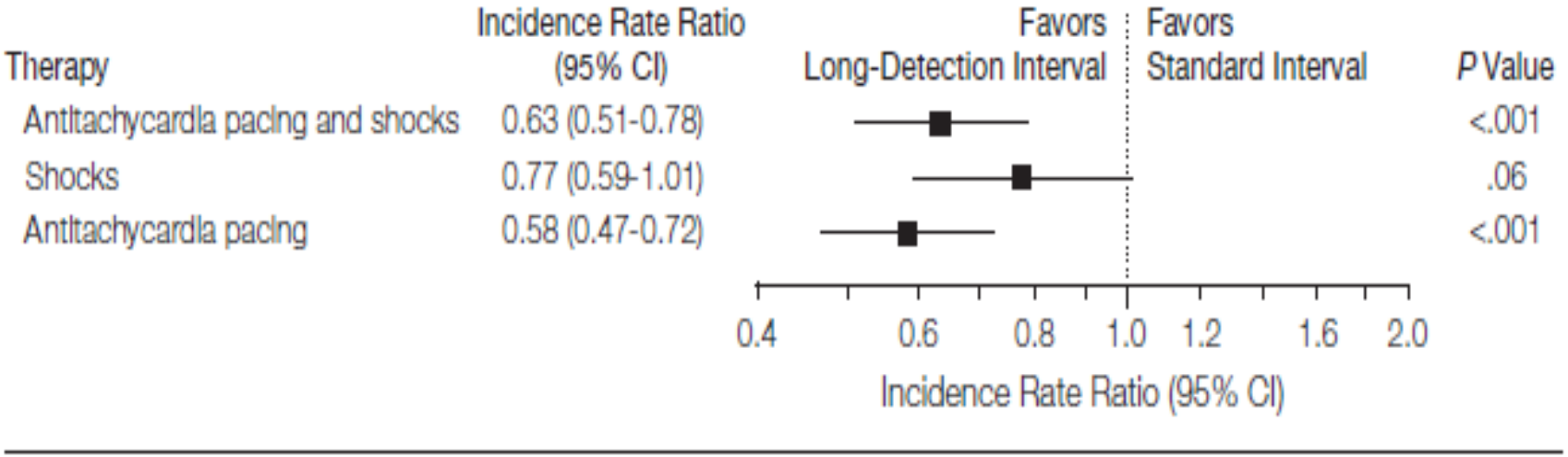
ADVANCE III: Time to First Inappropriate Shock



Gasparini et al. JAMA. 2013;309:1903-1911.

ADVANCE III: Time to First Therapy and Time to First Inappropriate Shock (18/24 vs. 30/40)

Figure 2. Treatment Effect Regarding the Primary End Point and Its Components



Gasparini et al. JAMA. 2013;309:1903-1911.

Additional Interventions as Needed

- AVJ ablation for ultimate rate control
  - Best if permanent AF and ventricular rates uncontrollable
  - Consider upgrade to CRT device
- Pharmacologic rhythm control
  - Amiodarone
    - IV for rapid effects and accelerated loading
    - PO for long-term maintenance
    - Also provides effective rate control
    - Concern re increased defibrillation threshold in some patients
  - Other AAD options
    - Dofetilide
    - Sotalol
  - Avoid class I AADs and dronedarone

Summary of Strategy to Manage Inappropriate Shocks Due to AF

1. Always program device as if the patient has had an inappropriate shock already.
2. Enroll in remote monitoring.
3. Maximize β-blocker dose.
4. Employ MADIT-RIT programming routinely.
5. Pursue aggressive AF treatment should inappropriate shocks occur, including IV rate control agents and amiodarone.
6. Consider AVJ/CRT upgrade for permanent AF with difficult to control ventricular rate.
7. Consider PVI for recurrent AF despite AAD, with appropriate sensitivity to device/lead function.

Thank you!