ICD Shocks: A risk factor or a risk marker for total mortality?

Jeff Healey MD, MSc, FRCPC
Population Health Research Institute
McMaster University
Hamilton, Canada

EUROPEAN Heart Rhythm ASSOCIATION
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Disclosures

- **Research Grants**
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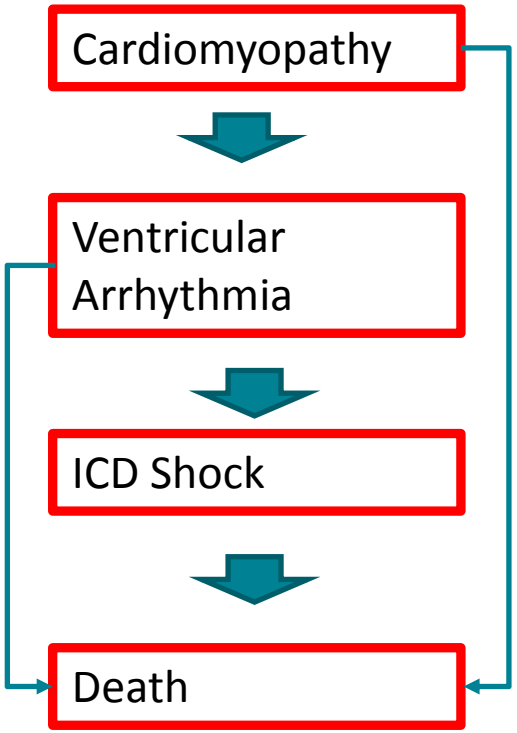
  - Medtronic, Boston Scientific, St. Jude Medical, Boehringer-Ingelheim, Bayer, Bristol-Meyers-Squibb

Criteria for Causation: Sir Austin Bradford Hill

Factor	ICD Shocks and Mortality
Strength	Very strong risk factor
Consistency	Appropriate shocks, shocks for AF, shocks for noise
Specificity	
Temporality	High mortality in weeks following shocks
Biological gradient	Increased mortality with VT storm, possibly multiple shocks
Plausibility	
Coherence	
Experimental	Many more data than for AF
Analogy	

A simplistic relationship between events



ORIGINAL ARTICLE

Prognostic Importance of Defibrillator Shocks in Patients with Heart Failure

Jeanne E. Poole, M.D., George W. Johnson, B.S.E.E., Anne S. Hellkamp, M.S., Jill Anderson, R.N., David J. Callans, M.D., Merritt H. Raitt, M.D., Ramakota K. Reddy, M.D., Francis E. Marchlinski, M.D., Raymond Yee, M.D., Thomas Guarnieri, M.D., Mario Talajic, M.D., David J. Wilber, M.D., Daniel P. Fishbein, M.D., Douglas L. Packer, M.D., Daniel B. Mark, M.D., M.P.H., Kerry L. Lee, Ph.D., and Gust H. Bardy, M.D.

N ENGL J MED 359;10 WWW.NEJM.ORG SEPTEMBER 4, 2008

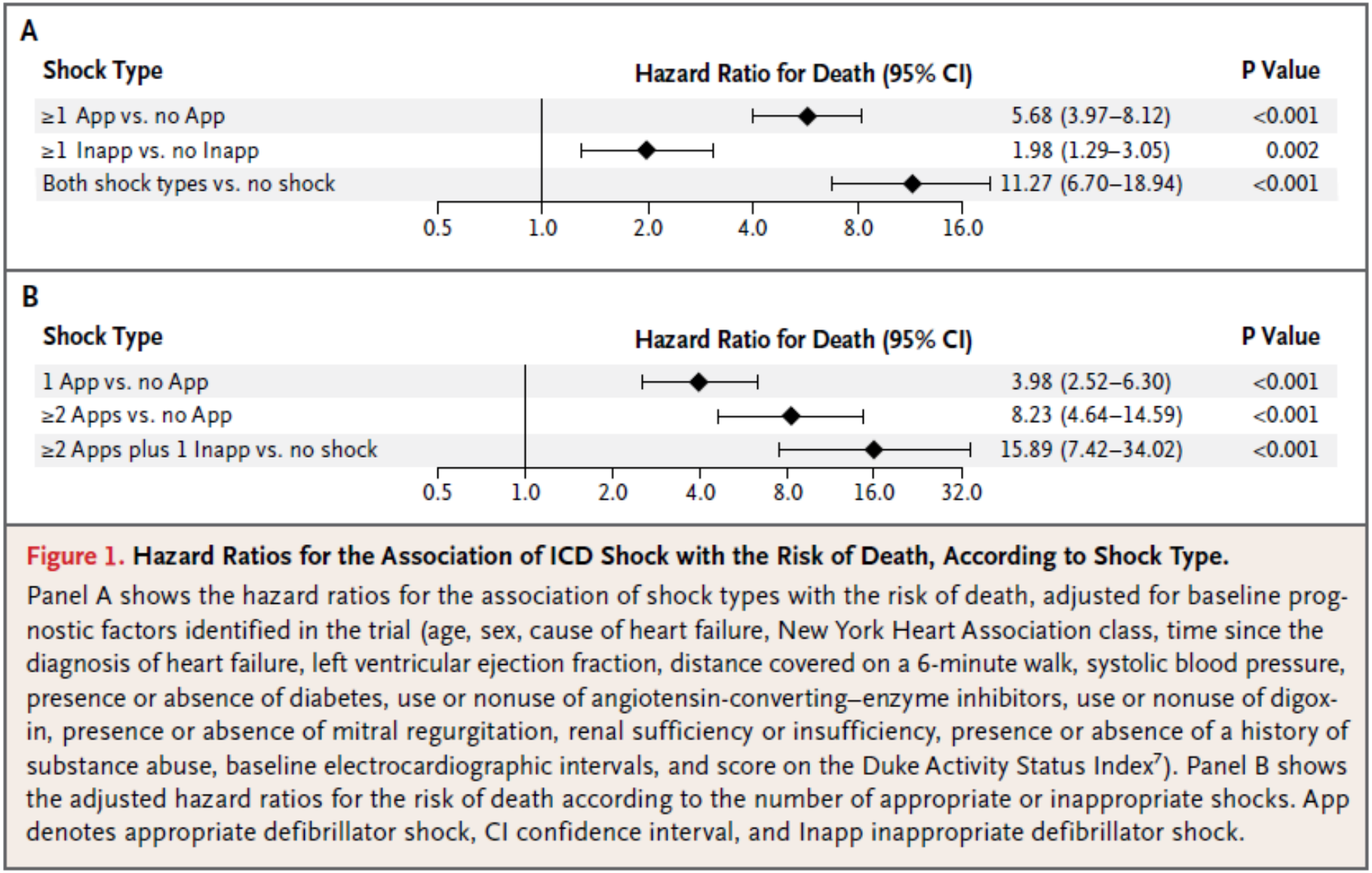


Figure 1. Hazard Ratios for the Association of ICD Shock with the Risk of Death, According to Shock Type.

Panel A shows the hazard ratios for the association of shock types with the risk of death, adjusted for baseline prognostic factors identified in the trial (age, sex, cause of heart failure, New York Heart Association class, time since the diagnosis of heart failure, left ventricular ejection fraction, distance covered on a 6-minute walk, systolic blood pressure, presence or absence of diabetes, use or nonuse of angiotensin-converting–enzyme inhibitors, use or nonuse of digoxin, presence or absence of mitral regurgitation, renal sufficiency or insufficiency, presence or absence of a history of substance abuse, baseline electrocardiographic intervals, and score on the Duke Activity Status Index[7]). Panel B shows the adjusted hazard ratios for the risk of death according to the number of appropriate or inappropriate shocks. App denotes appropriate defibrillator shock, CI confidence interval, and Inapp inappropriate defibrillator shock.

N ENGL J MED 359;10 WWW.NEJM.ORG SEPTEMBER 4, 2008

Table 2. Time from ICD Shock to Death among Patients Who Received at Least One Shock.*

Type of Shock	All Patients	Patients Who Died	Time from Shock to Death			Kaplan–Meier Survival Rate 1 Year after Shock
			Median	Interquartile Range	Full Range	
			days			%
Any shock	269	77	204	1–630	0–1872	82.5±2.4
One or more inappropriate shocks only	87	10	294	28–509	0–735	94.9±2.5
One or more appropriate shocks	182	67	168	1–797	0–1872	76.9±3.2
NYHA class II	117	31	206	1–977	0–1872	84.0±3.5
NYHA class III	65	36	168	7–626	0–1343	64.2±6.1
Ischemic heart failure	93	49	96	0–443	0–1872	62.6±5.2
Nonischemic heart failure	89	18	622	204–908	1–1785	91.6±3.0
First shock for ventricular fibrillation	77	33	3	0–622	0–1872	74.6±5.0
First shock for ventricular tachycardia	105	34	258	59–797	0–1785	78.5±4.2

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Table 3. Cause of Death According to Type of Shock.

Type of Shock	All Patients	Patients Who Died*	Cause of Death				
			Sudden Arrhythmia	Heart Failure	Other Cardiac Causes	Noncardiac Causes	Unknown
			number of patients				
Any shock	269	77	16	33	9	17	2
Any appropriate shock	182	67	14	29	8	14	2
Inappropriate shock only	87	10	2	4	1	3	0
No shock	542	86	13	34	6	29	4

* Ten additional patients whose ICDs were removed during the study died.

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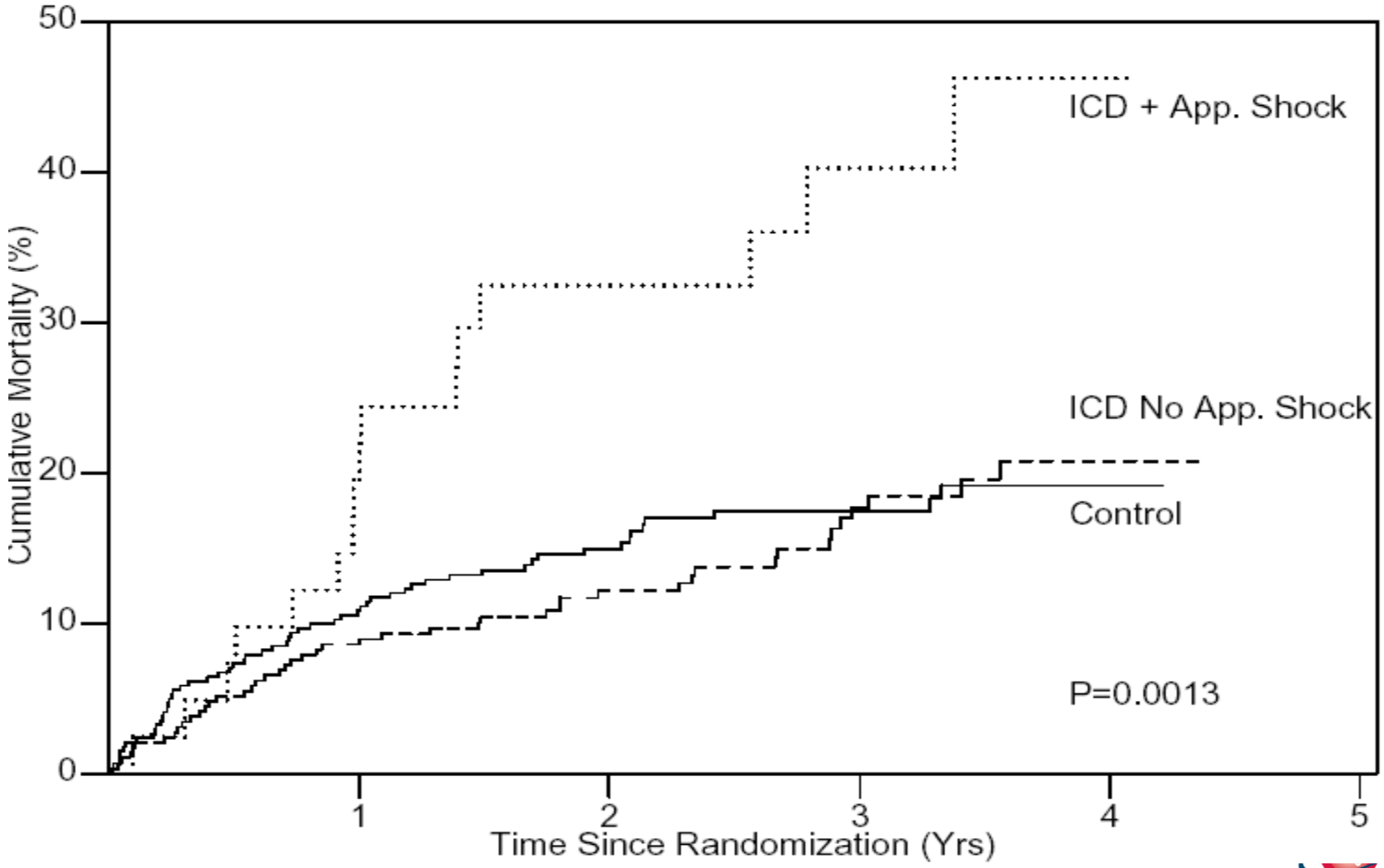
The NEW ENGLAND JOURNAL of MEDICINE

Life and Death after ICD Implantation

Jeff Healey, M.D., and Stuart Connolly, M.D.

- **6-fold increase in mortality after appropriate shock**
- **30% of these deaths within 24 hours of the shock**
- **Excluding these patients with "imminent" death, risk still increased 3-fold**

Total Mortality



ICES Ontario ICD Registry, competing risks

- **All new ICD implants in Ontario Canada**
- **February 2007 – March 2011**
- **N=3445**
- **Fine-Gray sub-distribution hazard model**
- **Outcomes**
  - Appropriate shock: 3.6/100 person-years
  - Death 4.9/100 person-years
- **DS Lee et al…**

ICES Ontario ICD Registry, competing risks

Appropriate Shock Predictor	Category	Hazard Ratio	95% CI	p-value
Age	Per 10 years	0.82	0.72 - 0.94	0.004
Sex	Male	1.52	1.00 - 2.30	0.047
Nonsustained VT		1.48	1.01 - 2.17	0.044
Atrial fibrillation		1.61	1.17 - 2.21	0.003
Pre-existing pacemaker system		2.05	1.07 - 3.93	0.030
Smoker		0.72	0.54 - 0.96	0.026
Digoxin		1.54	1.13 - 2.08	0.006
Amiodarone		0.47	0.25 - 0.90	0.023
Creatinine*	Per 1 mg/dL	1.21	1.05 - 1.39	0.007
Hemoglobin <12.0	vs. ≥12 g/dL	0.45	0.25 - 0.82	0.009
|QRSd - 130|	Per 10 msec	0.86	0.76 - 0.97	0.012

Death Predictor	Category	Hazard Ratio	95% CI	p-value
Age	Per 10 years	1.57	1.36 - 1.81	< .001
Ischemic disease	vs. nonischemic	1.62	1.14 - 2.31	0.007
Prior revascularization procedure	PCI or CABG	0.74	0.55 - 0.98	0.038
Prior HF hospitalization	Within 3 years	1.86	1.45 - 2.40	< .001
NYHA heart failure class III-IV	vs. I-II	1.43	1.10 - 1.85	0.007
Pre-existing pacemaker system		2.02	1.23 - 3.32	0.006
Systolic blood pressure	Per 20 mmHg	0.73	0.61 - 0.88	< .001
Diabetes	Insulin or oral agent	1.46	1.13 - 1.88	0.004
Smoker		1.65	1.26 - 2.15	< .001
Chronic obstructive lung disease		1.43	1.05 - 1.95	0.023
Home oxygen therapy		4.34	2.11 - 8.93	< .001
Cancer		1.43	1.00 - 2.06	0.051
ACE inhibitor or ARB		0.70	0.49 - 0.99	0.042
Creatinine*	Per 1 mg/dL	1.23	1.15 - 1.32	< .001
Serum sodium ≤138	vs. >138 mEq/L	1.56	1.21 - 2.01	< .001
Hemoglobin <12.0	vs. ≥12 g/dL	1.49	1.12 - 1.98	0.006

Randomized Trials of ICD Shock Prevention

Speaker

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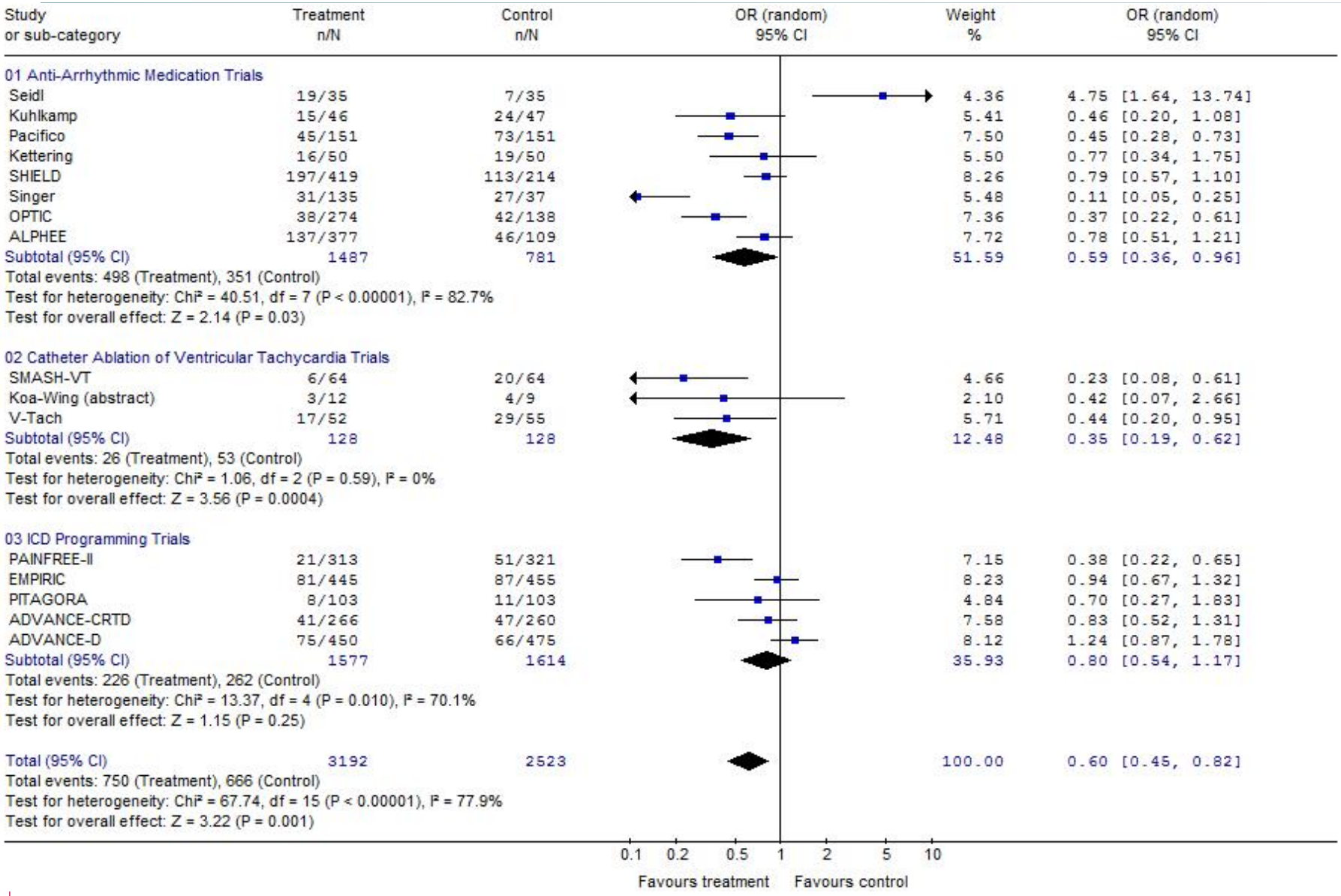
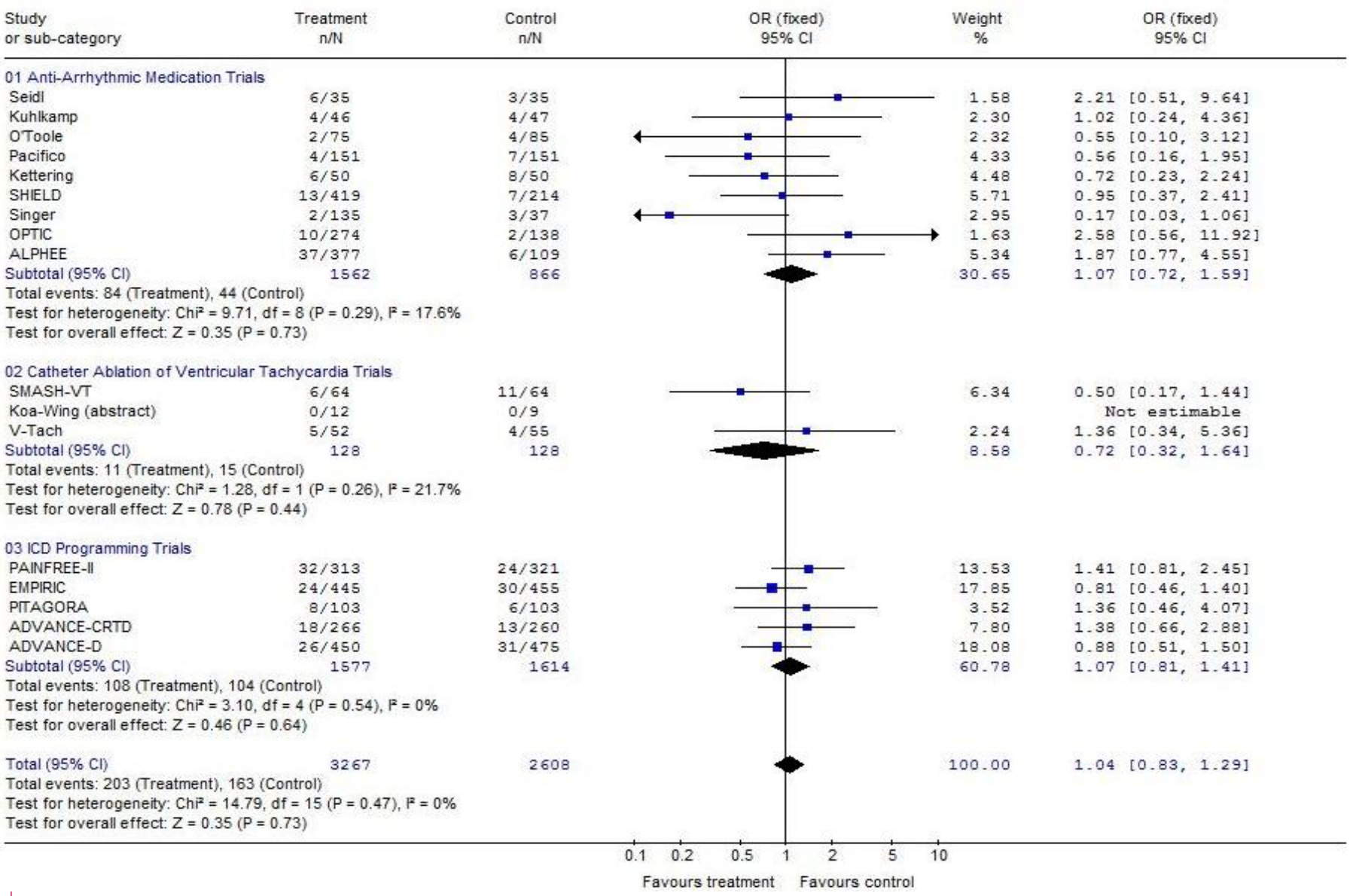
ICD shock burden

Ha A. Heart Rhythm 2012

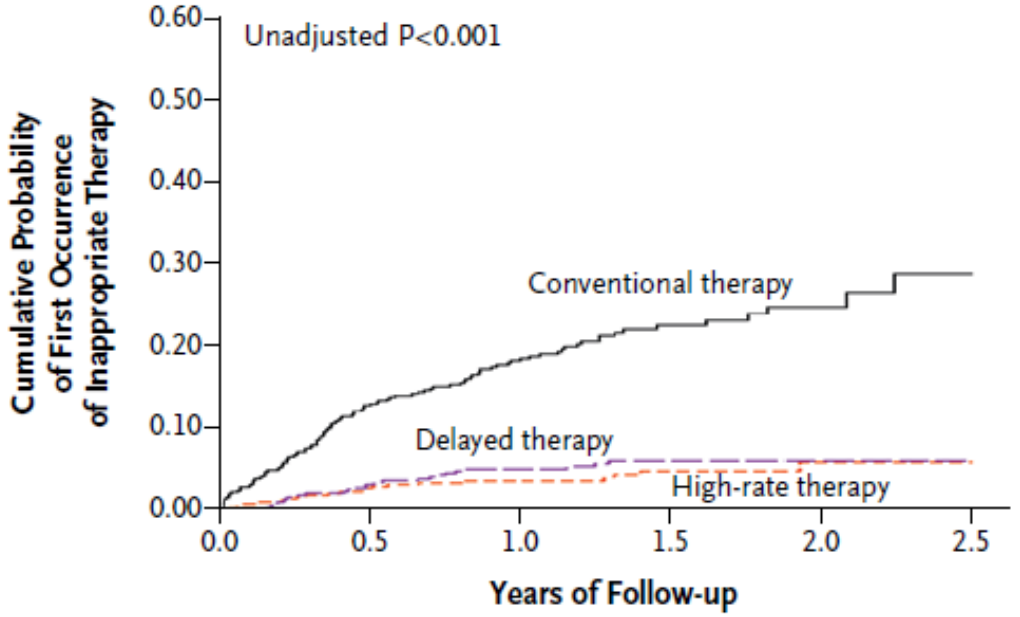


Mortality

Ha A. Heart Rhythm 2012



MADIT-RIT: Moss AJ, NEJM 2012



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)

Figure 1. Cumulative Probability of First Occurrence of Inappropriate Therapy According to Treatment Group.

MADIT-RIT: Moss AJ, NEJM 2012

Table 3. Hazard Ratios for a First Occurrence of Inappropriate Therapy, Death, and a First Episode of Syncope According to Treatment Group.

Variable	Conventional Therapy (N=514)	High-Rate Therapy (N=500)	Delayed Therapy (N=486)	High-Rate Therapy vs. Conventional Therapy		Delayed Therapy vs. Conventional Therapy	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	no. of patients						
First occurrence of inappropriate therapy	105	21	26	0.21 (0.13–0.34)	<0.001	0.24 (0.15–0.40)	<0.001
Death	34	16	21	0.45 (0.24–0.85)	0.01	0.56 (0.30–1.02)	0.06

Table 2. First Occurrence, Any Occurrence, and Total Occurrences of Appropriate and Inappropriate Device Therapy According to Treatment Group.*

Variable	Conventional Therapy (N=514)	High-Rate Therapy (N=500)	Delayed Therapy (N=486)	P Value for High-Rate Therapy vs. Conventional Therapy	P Value for Delayed Therapy vs. Conventional Therapy
First occurrence of therapy — no. of patients (%)					
Appropriate therapy	114 (22)	45 (9)	27 (6)	<0.001	<0.001
Shock	20 (4)	22 (4)	17 (3)	0.68	0.74
Antitachycardia pacing	94 (18)	23 (5)	10 (2)	<0.001	<0.001
Inappropriate therapy	105 (20)	21 (4)	26 (5)	<0.001	<0.001
Shock	20 (4)	11 (2)	13 (3)	0.12	0.28
Antitachycardia pacing	85 (17)	10 (2)	13 (3)	<0.001	<0.001

SIMPLE: Healey JS, Lancet 2015

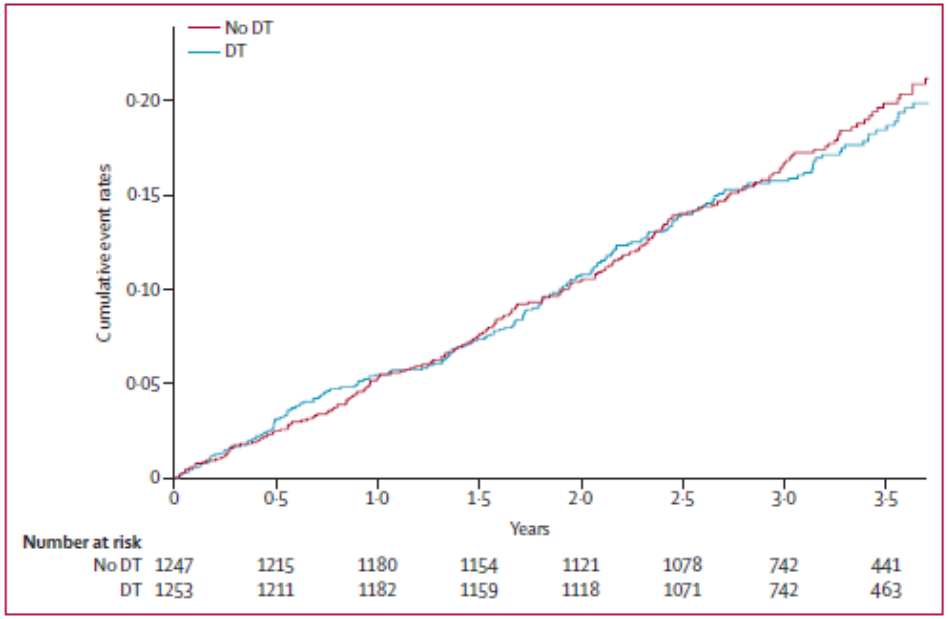


Figure 3: **Total mortality**
DT=defibrillation testing. Mortality curve was constructed with the Kaplan-Meier method.

	No defibrillation testing (n=1236)	Defibrillation testing (n=1242)	p value
Primary safety Composite*	69 (5·6%)	81 (6·5%)	0·33
Secondary safety composite†	39 (3·2%)	56 (4·5%)	0·08
Death	7 (0·6%)	5 (0·4%)	0·56
Stroke	3 (0·2%)	3 (0·2%)	1·00
Non-CNS systemic embolism	1 (0·1%)	2 (0·2%)	0·57
Pulmonary embolism	0 (0·0%)	2 (0·2%)	0·50
Myocardial infarction	4 (0·3%)	1 (0·1%)	0·18
Heart failure needing inotropes or diuretics	20 (1·6%)	28 (2·3%)	0·25
Intraoperative hypotension	6 (0·5%)	9 (0·7)	0·44
Need for chest compression	0 (0·0%)	5 (0·4%)	0·06
Non-elective intubation	1 (0·1%)	7 (0·6%)	0·03
Aspiration pneumonia	0 (0·0%)	1 (0·1%)	1·00
Unplanned stay in ICU	4 (0·3%)	1 (0·1%)	0·18
Pneumothorax	18 (1·5%)	16 (1·3%)	0·72
Pericarditis, cardiac perforation, or cardiac tamponade	11 (0·9%)	11 (0·9%)	0·99
Device infection	7 (0·6%)	3 (0·2%)	0·20
Arterial-line complication	0 (0·0%)	2 (0·2%)	0·50
Anoxic brain injury	0 (0·0%)	0 (0·0%)	..

ICU=intensive-care unit. *Includes all adverse events listed in the table. †Includes all adverse events listed in the table apart from other anoxic brain injury, aspiration pneumonia, pneumothorax, pericarditis or cardiac tamponade, and device infection. Two patients had both non-elective intubation and chest compressions.

Table 3: **Safety outcomes**

Conclusions

- **As always, causality is difficult to prove in all cases**
- **However; in most cases, ICD shocks seem to be risk marker rather than a risk factor**
- **This conclusion is based on:**
  - Different clinical predictors of these two outcomes
  - The fact that shock prevention does not appear to reduce mortality
  - The fact that giving shocks (i.e. DFT) does not measurably increase mortality
- **Shock prevention is still an important clinical goal**