Predicting ICD-treated VT/VF and Pharmacological Management of VT/VF

Wojciech Zareba, MD, PhD

Professor of Medicine/Cardiology
University of Rochester Medical Center
Rochester, NY

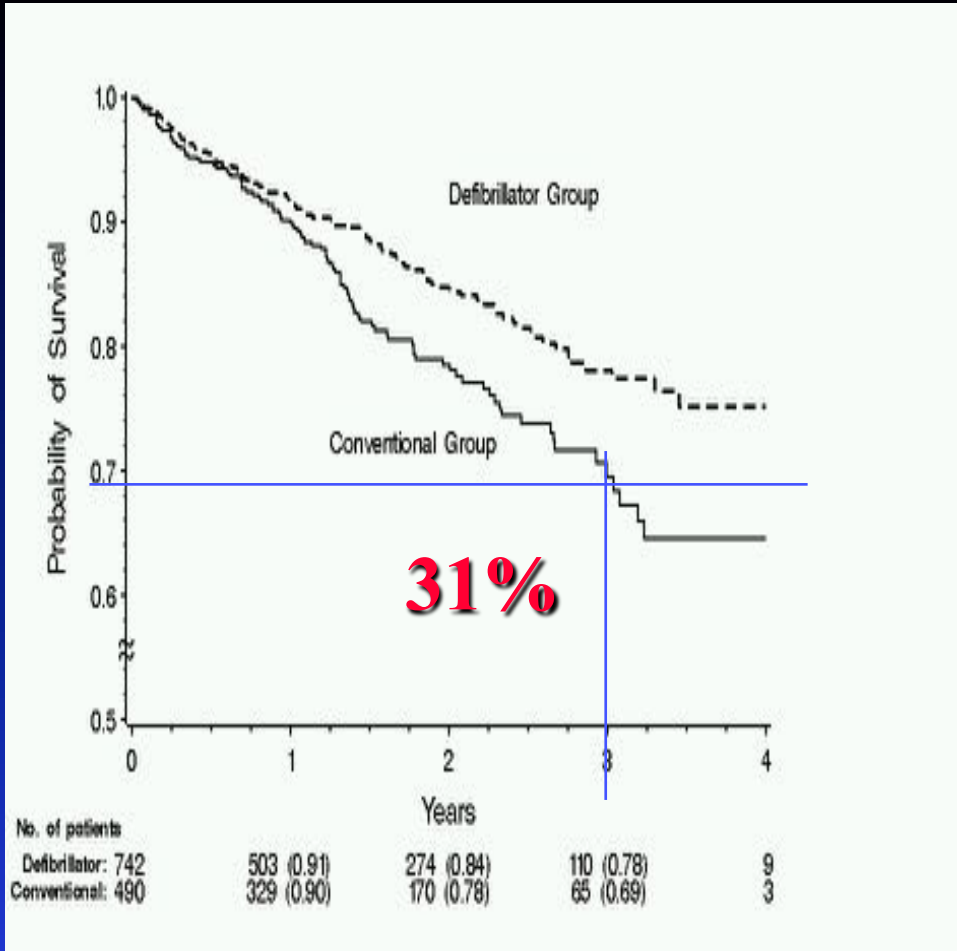
October 16 - 18
14th EDITION 2015

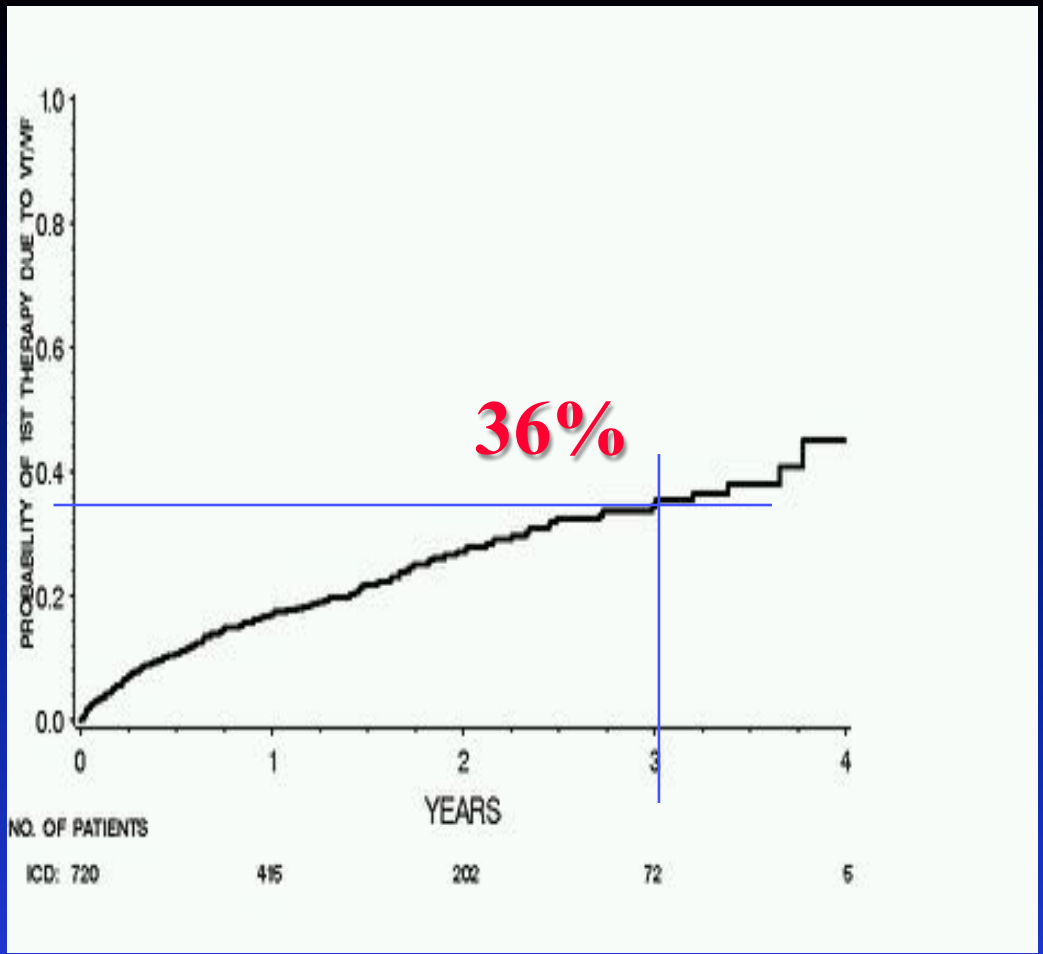
CONFLICT OF INTEREST TO DECLARE

Research Grants:

Boston Scientific
Zoll Inc.
Gilead Sciences

MADIT-II

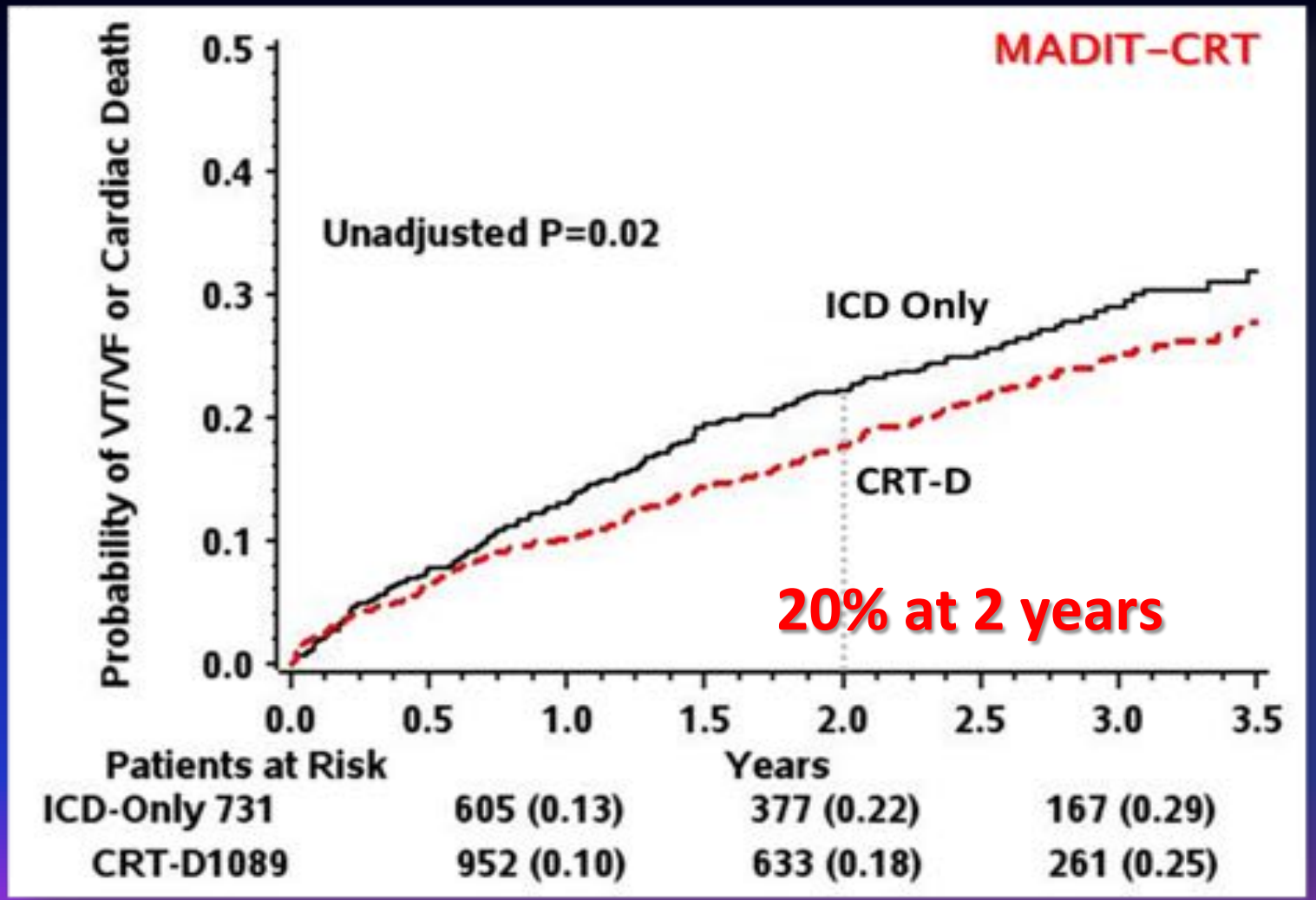




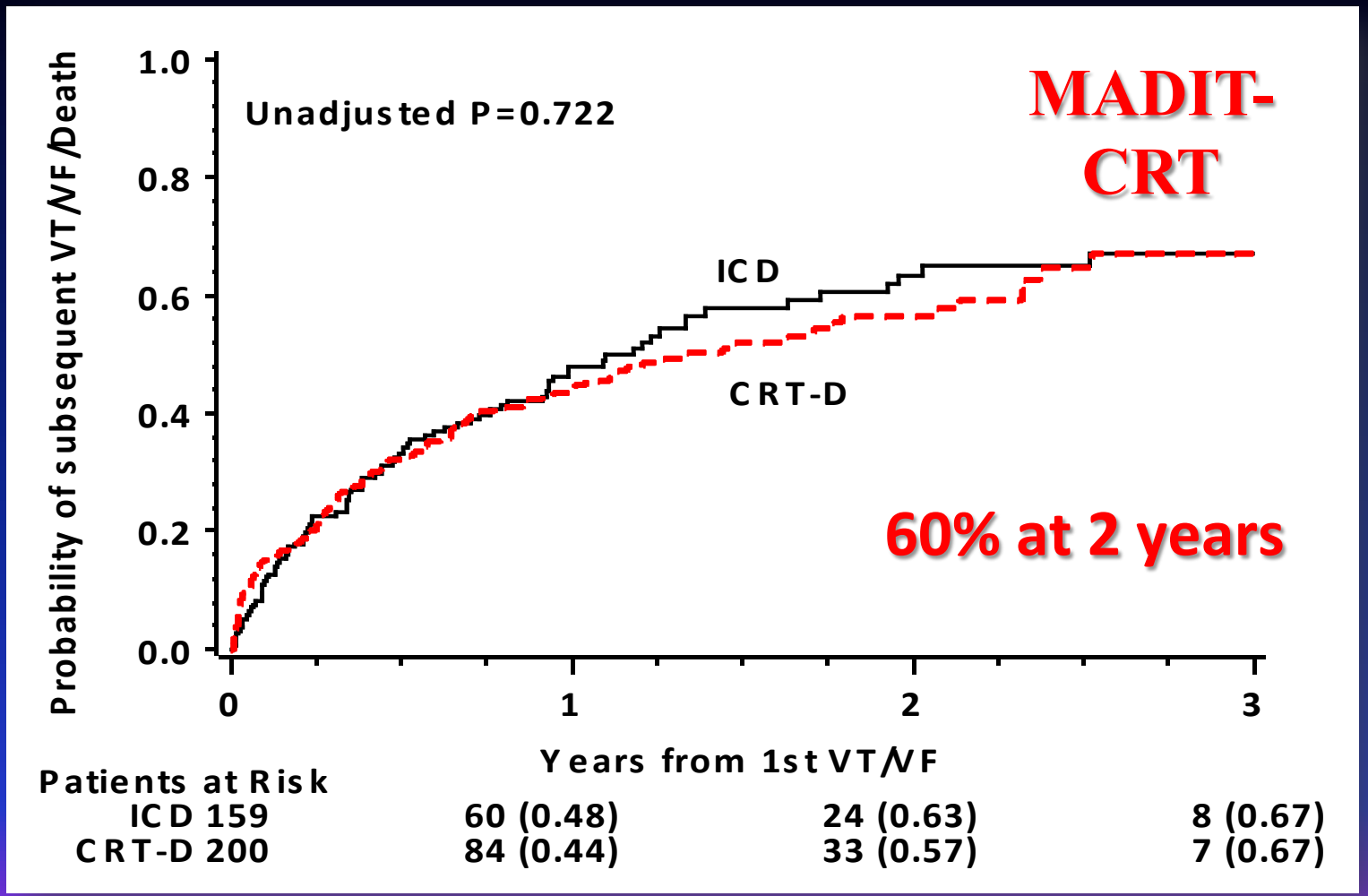
31% cumulative probability of mortality in the conventional arm at 3 years

36% cumulative probability of appropriate ICD therapy at 3 years

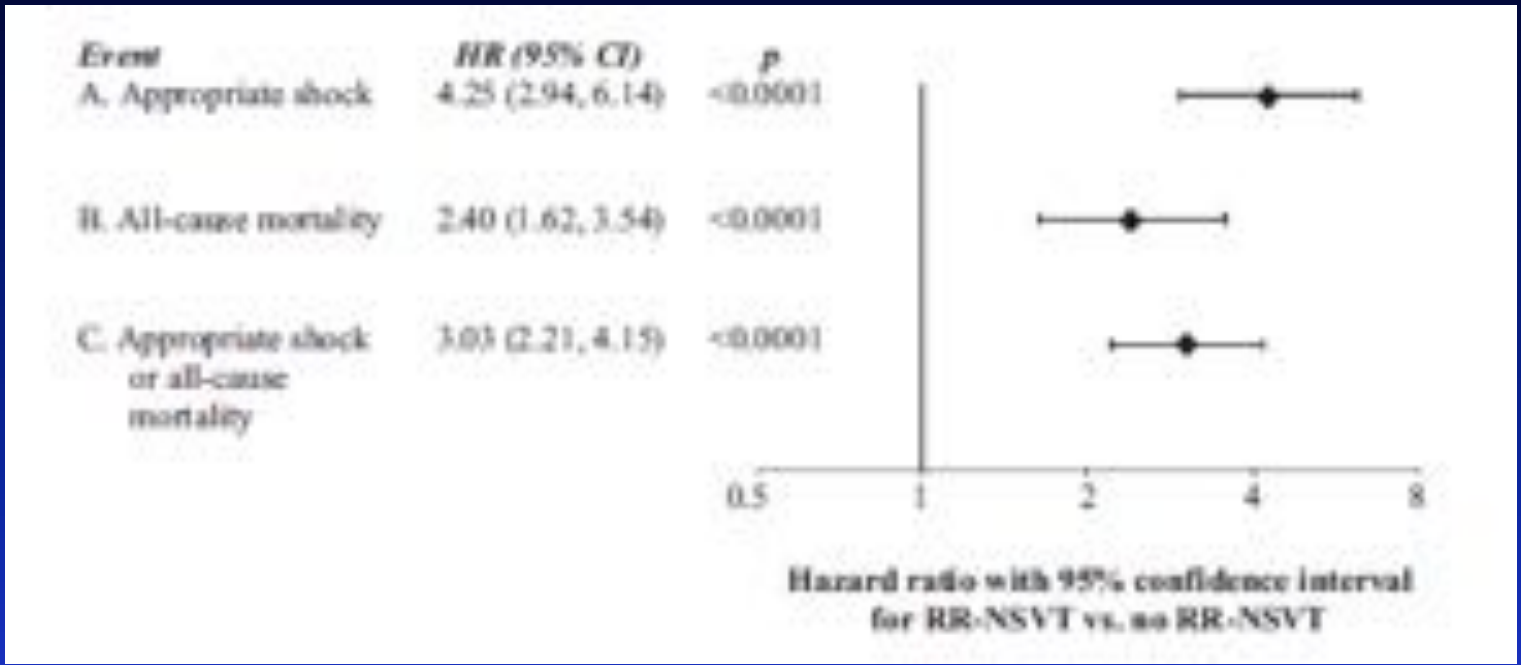
Risk of VT/VF/Death in MADIT-CRT Patients



VT/VF/Death after first VT/VF requiring appropriate ICD therapy



Association of Rapid Rate NSVT with Cardiac Events in SCD-HeFT



Rapid Rate NSVT (RR-NSVT) ≥188 bpm

Chen et al. J Am Coll Cardiol 2013;61:2161–8

MADIT-CRT: Endpoints in Patients with and without VT/VF

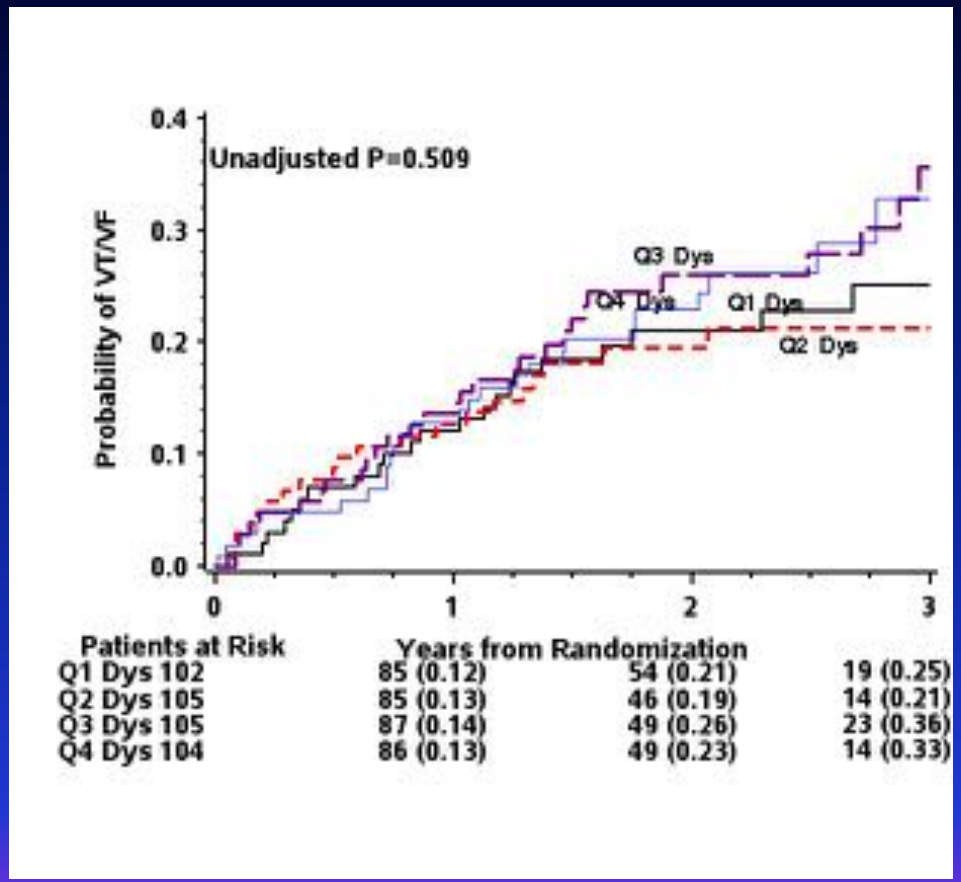
Endpoint	no VT/VF (N = 1454)	VT/VFP value (N = 366)	
CHF	208 (14%)	115 (31%)	<0.001
CHF or Death	251 (17%)	126 (34%)	<0.001
Death	87 (6%)	40 (11%)	<0.001

The occurrence of interim time-dependent VT/VF was predictive of both death (HR=2.34, p<0.001) and HF/Death (HR=2.02, p<0.001).

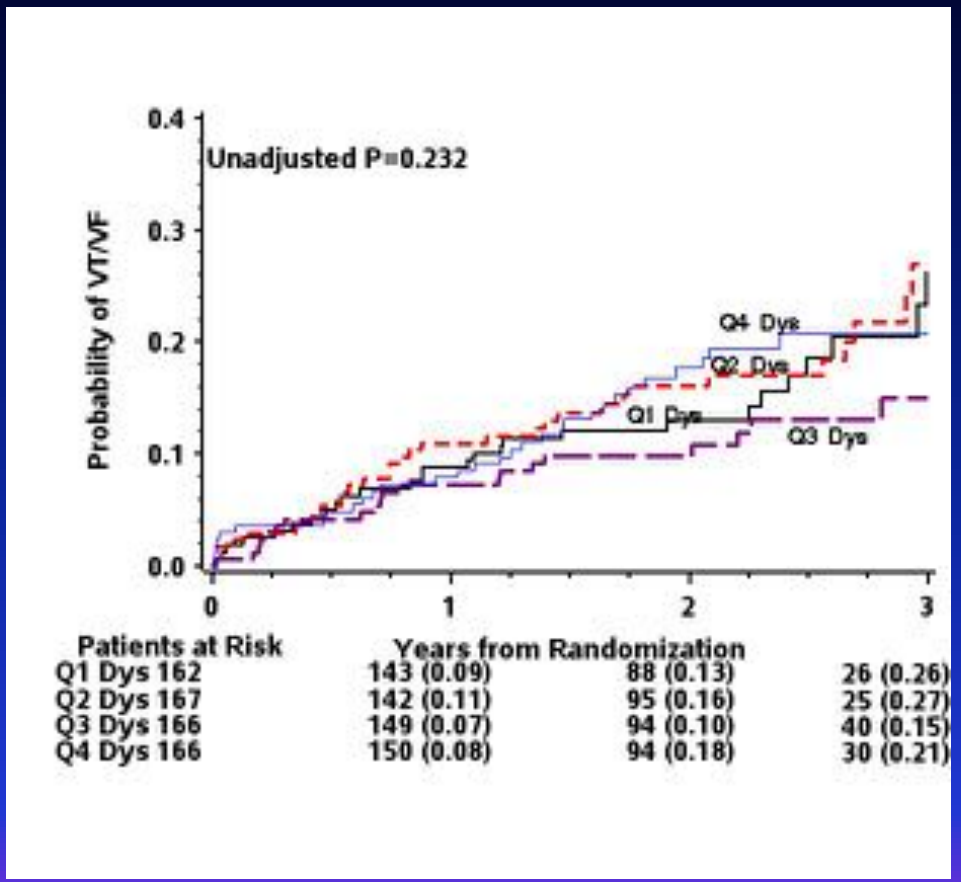
MADIT-CRT: Baseline Clinical Characteristics of Patients with and without VT/VF

Variable	no VT/VF (N = 1454)	VT/VFP value (N = 366)	
Age (yrs)	65±11	63±11	<0.001
Males	395 (27%)	58 (16%)	<0.001
Prior MI	588 (41%)	187 (52%)	<0.001
EF (%)	24.1±5.1	22.6±5.6	<0.001
QRS (ms)	159±20	156±21	0.006
LVESV (ml)	174±48	191±57	<0.001

Probability of VT/VF in Relationship to Baseline Dyssynchrony



ICD Arm



CRT-D Arm

NSVT in Predicting Clinical Endpoints in Ischemic and Non-Ischemic MADIT-CRT Patients

Clinical Endpoint	*Ischemic (n=462)*		*Non-Ischemic (n=382)*	
	HR	*P value*	*HR*	*P value*
HF Event of Death	*0.83 (95% CI: 0.53-1.31)*	*0.42*	*2.59 (95% CI: 1.25-5.3)*	*0.01*
HF Event	*0.91 (95% CI: 0.55-1.50)*	*0.70*	*3.17 (95% CI: 1.37-7.38)*	*0.007*
ICD Documented VT > 180 bpm of VF	*2.7 (95% CI: 1.82-4.02)*	*<0.001*	*3.56 (95% CI: 1.95-6.49)*	*<0.001*

Mittal et al. ACC 2011

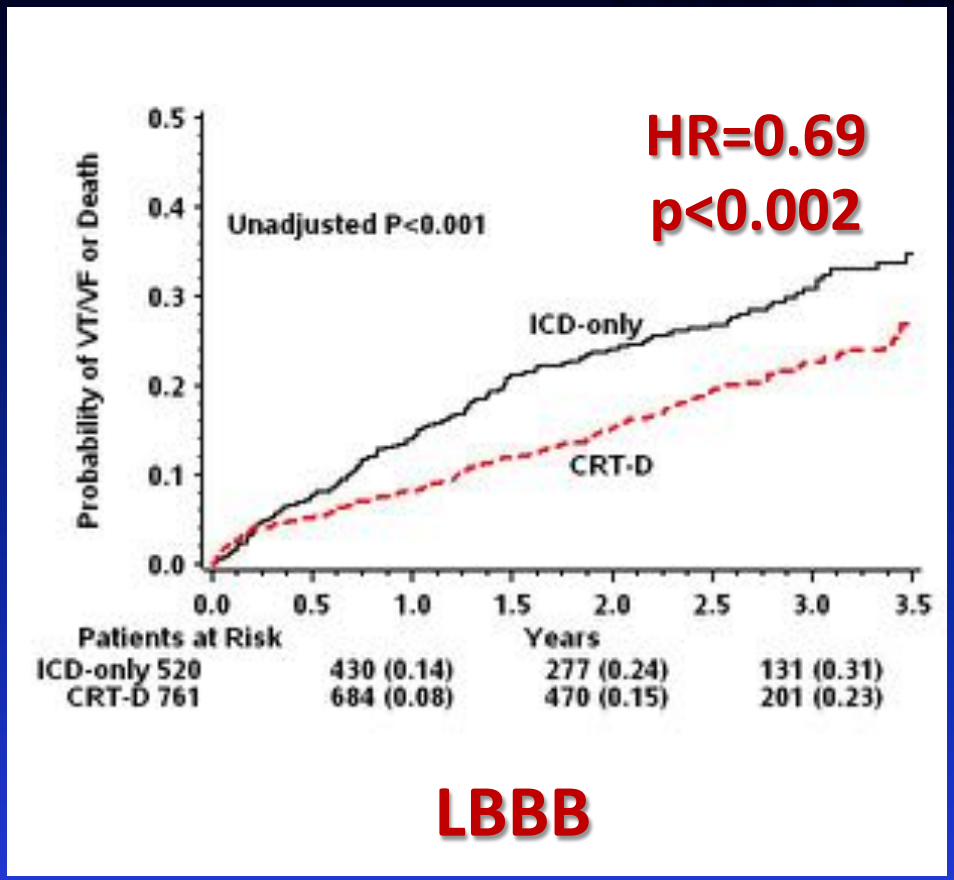
Antiarrhythmic Therapy in Patients with VT:

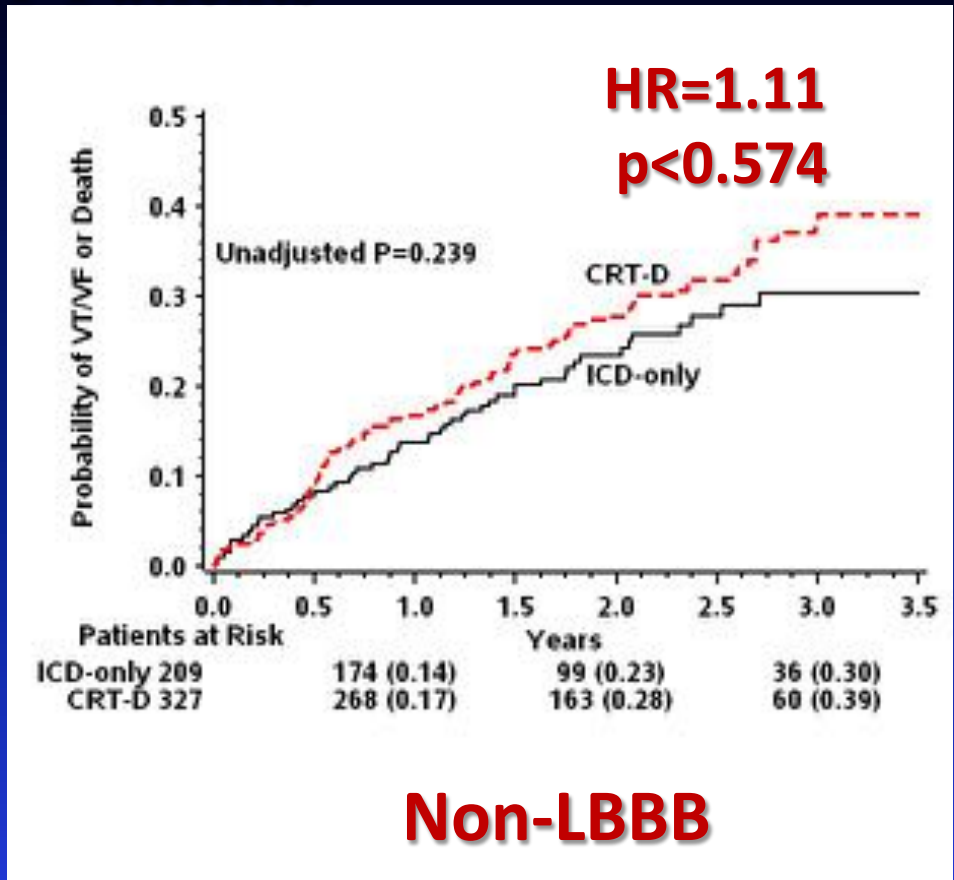
- Cardiac Resynchronization Therapy
- Pharmacological Therapy
- Device programming
- VT Ablation
- Cardiac sympathetic Denervation

Antiarrhythmic Therapy in Patients with VT:

- Cardiac Resynchronization Therapy
- Pharmacological Therapy
- Device programming
- VT Ablation
- Cardiac sympathetic Denervation

VT/VF or Death by Treatment (CRT-D vs. ICD only) in patients with LBBB and Non-LBBB QRS Pattern in MADIT-CRT Patients

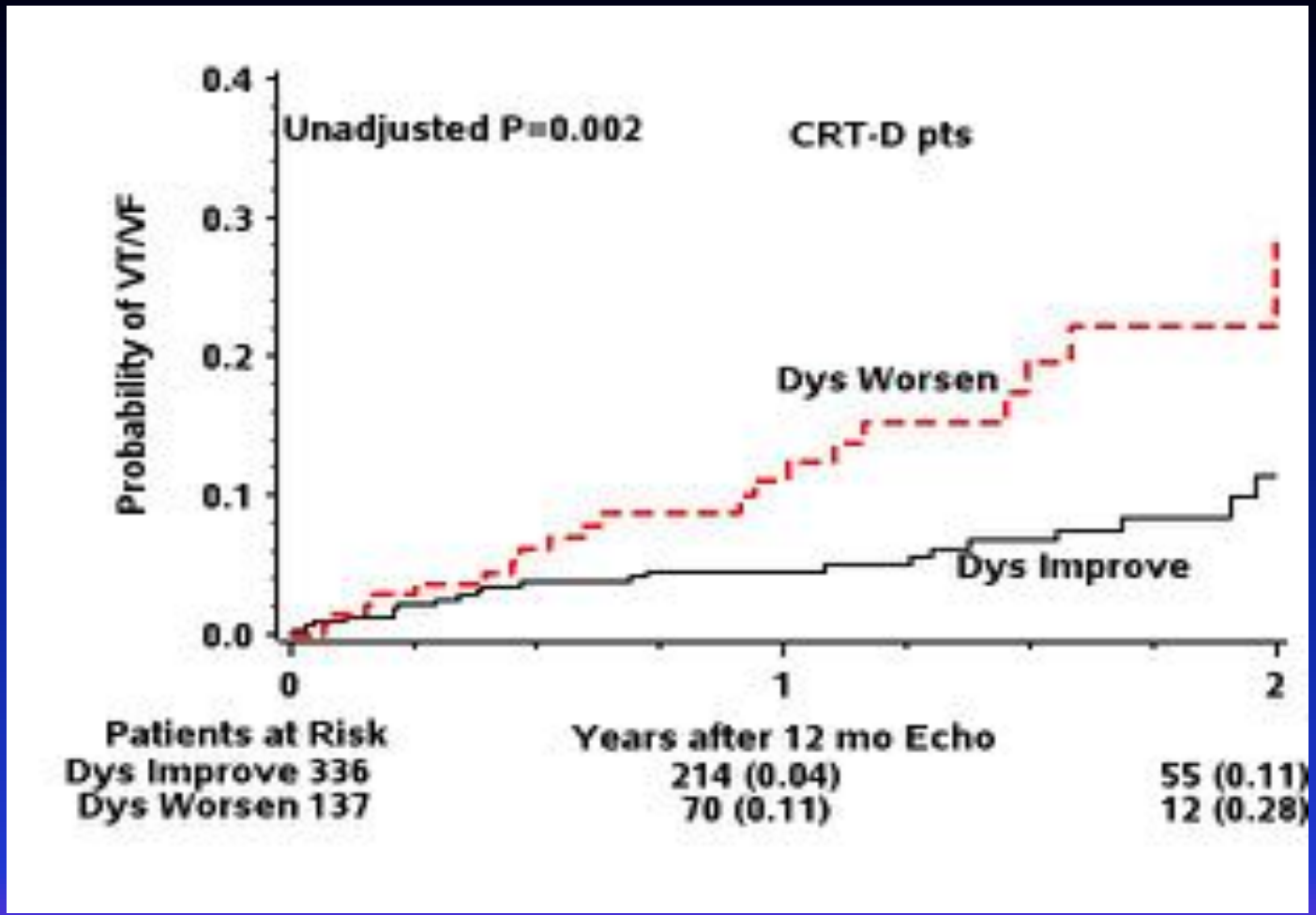




Zareba et al. Circulation 2011;123:1061-1072

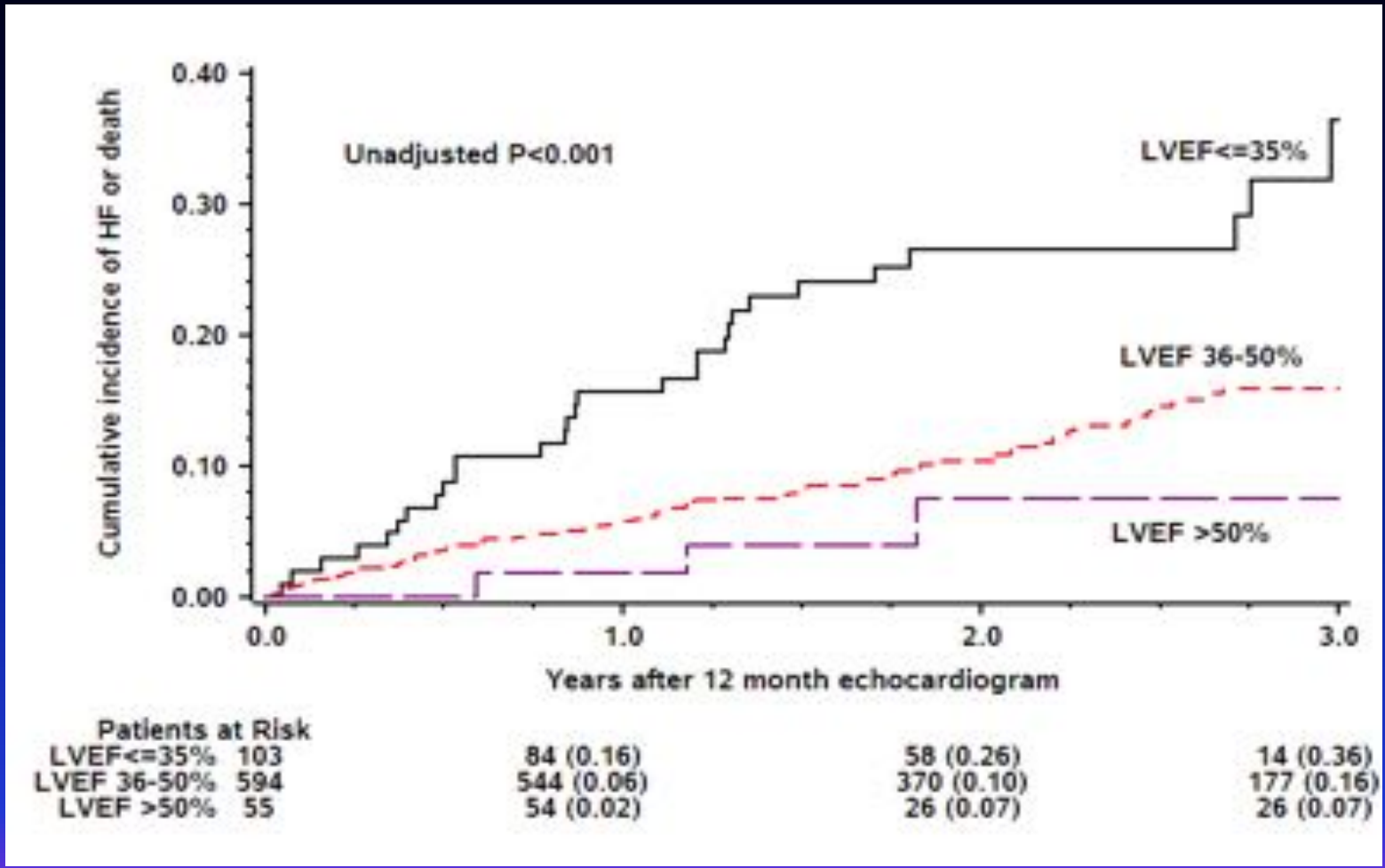
P value for interaction = 0.028

Probability of VT/VF in Relationship to CRT-D Dyssynchrony Response in MADIT-CRT Patients



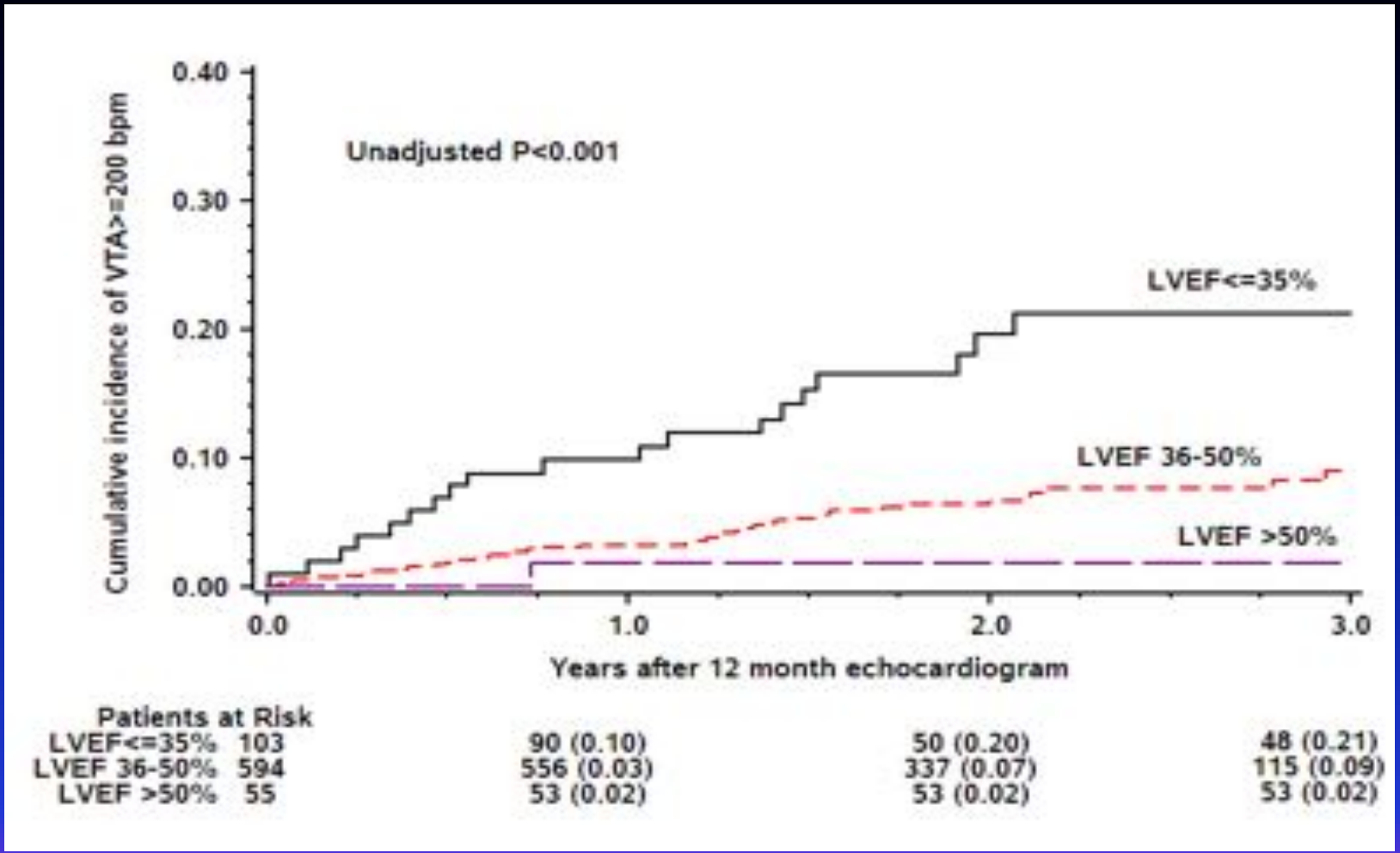
Kutyifa … Zareba JACC CI 2013

MADIT-CRT: Cumulative incidence of HF or death by LVEF groups after 12-month echocardiogram



Ruwald M …Zareba W. Circulation 2014

MADIT-CRT: Cumulative incidence of VTA≥200 bpm by LVEF groups after 12-month echocardiogram



Ruwald M …Zareba W. Circulation 2014

Antiarrhythmic Therapy in Patients with VT:

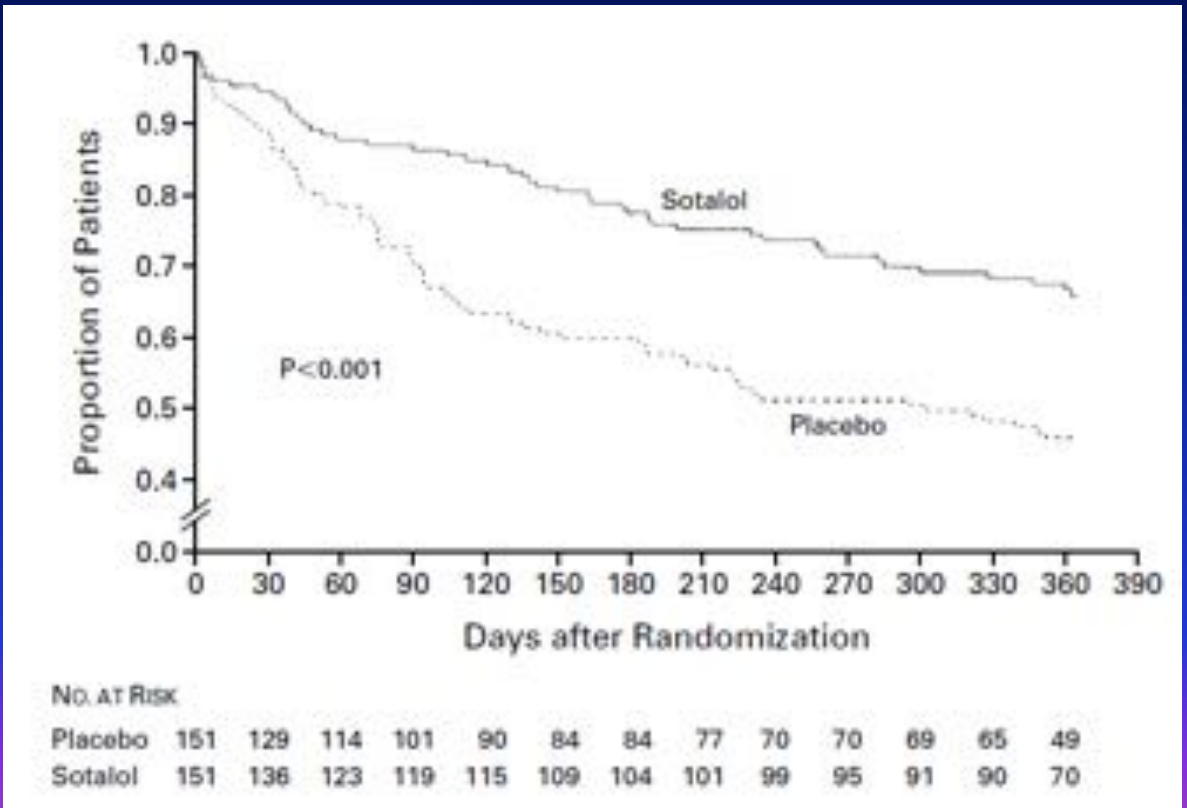
- Cardiac Resynchronization Therapy
- Pharmacological Therapy
- Device programming
- VT Ablation
- Cardiac sympathetic Denervation

PREVENTION OF IMPLANTABLE-DEFIBRILLATOR SHOCKS BY TREATMENT WITH SOTALOL

ANTONIO PACIFICO, M.D., STEFAN H. HOHNLOSER, M.D., JOHN H. WILLIAMS, M.D., BEN TAO, M.SC., SANJEEV SAKSENA, M.D., PHILIP D. HENRY, M.D., AND ERIC N. PRYSTOWSKY, M.D., FOR THE *d,l*-SOTALOL IMPLANTABLE CARDIOVERTER–DEFIBRILLATOR STUDY GROUP*

N Engl J Med 1999;340:1855-62

Time to Death from Any Cause or the Delivery of a First Shock for Any Reason



No. at Risk													
Placebo	151	129	114	101	90	84	84	77	70	70	69	65	49
Sotalol	151	136	123	119	115	109	104	101	99	95	91	90	70

SHIELD: Number of VT/VF Episodes in Patients Treated with Azimilide 125 mg, Azimilide 75 mg or Placebo.

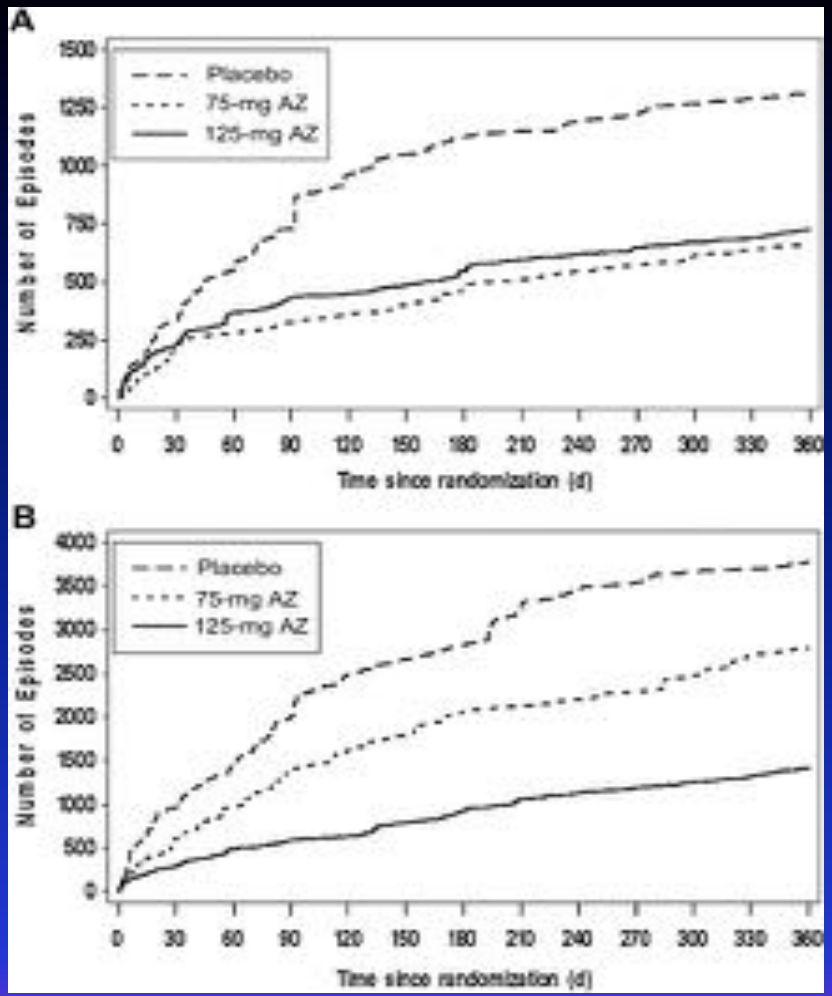


TABLE 2. Recurrent Symptomatic Arrhythmias (Shocks or ATP), Stratified Intention-to-Treat Analysis

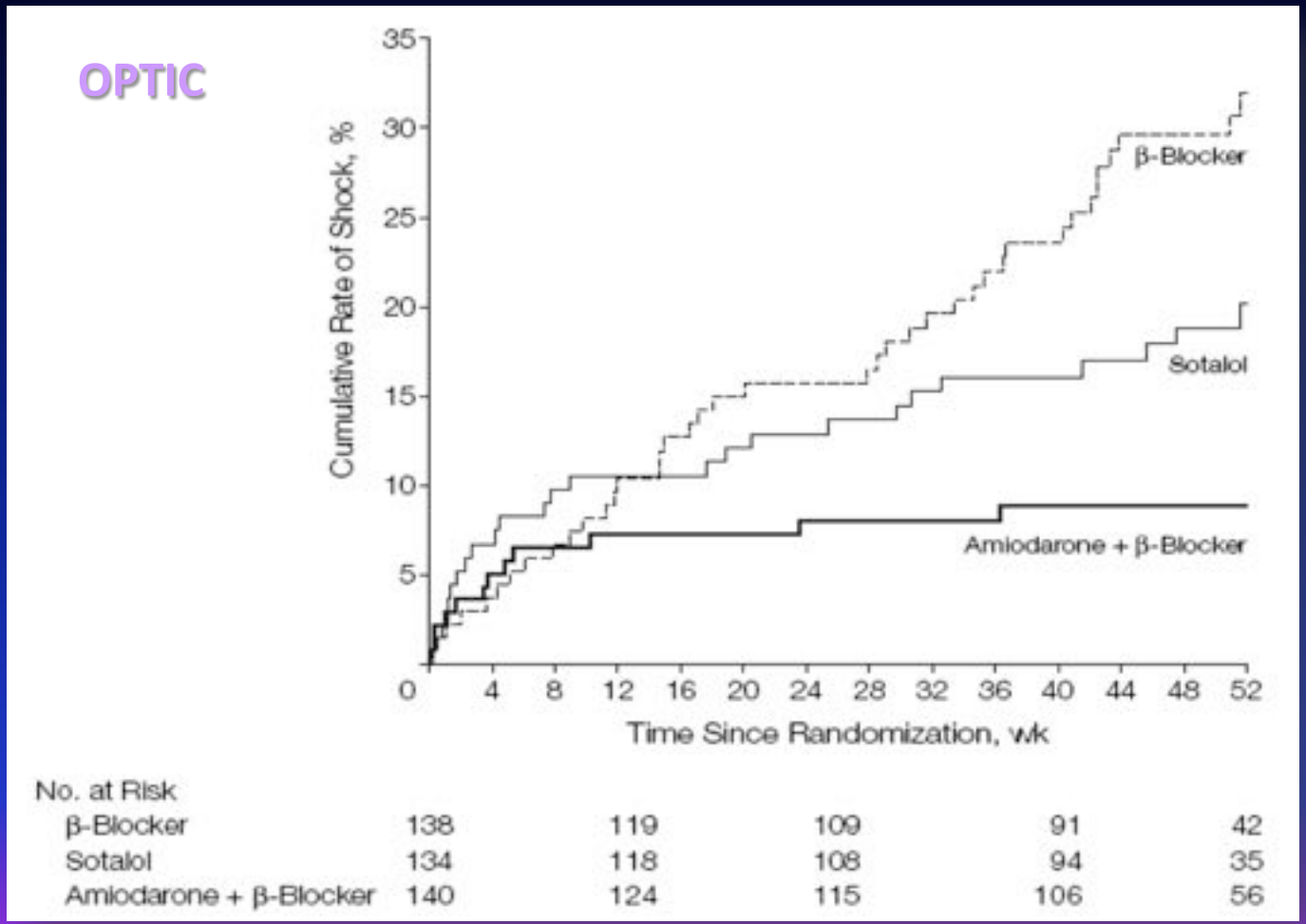
End-Point Treatment	N	n (%)	Total Events	HR	95% CI	P
All-cause shocks plus symptomatic tachyarrhythmias terminated by ATP*						
Placebo	214	134 (58)	1459			
Azimilide 75 mg	220	114 (52)	665	0.43	0.26 to 0.69	0.0006
Azimilide 125 mg	199	100 (50)	737	0.53	0.34 to 0.83	0.0053
All-cause shocks*						
Placebo	214	113 (53)	613			
Azimilide 75 mg	220	106 (48)	472	0.72	0.47 to 1.10	0.13
Azimilide 125 mg	199	91 (46)	480	0.83	0.55 to 1.24	0.36

N indicates number of patients randomized to treatment group; n(%),number and percentage of patients who experienced at least 1 event.
*Primary end points

Dorian et al. Circulation 2004;110:3646

OPTIC: Cumulative probability of ICD Shock for 3 treatment group in the OPTIC Study

421 patients with ICDs (AVID, MADIT, MUSTT type of patients)



Connolly et al. JAMA 2006;295:165–171

Amiodarone or an Implantable Cardioverter–Defibrillator for Congestive Heart Failure

Gust H. Bardy, M.D., Kerry L. Lee, Ph.D., Daniel B. Mark, M.D., Jeanne E. Poole, M.D., Douglas L. Packer, M.D., Robin Boineau, M.D., Michael Domanski, M.D., Charles Troutman, R.N., Jill Anderson, R.N., George Johnson, B.S.E.E., Steven E. McNulty, M.S., Nancy Clapp-Channing, R.N., M.P.H., Linda D. Davidson-Ray, M.A., Elizabeth S. Fraulo, R.N., Daniel P. Fishbein, M.D., Richard M. Luceri, M.D., and John H. Ip, M.D., for the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators*

N Engl J Med 2005;352:225-37.

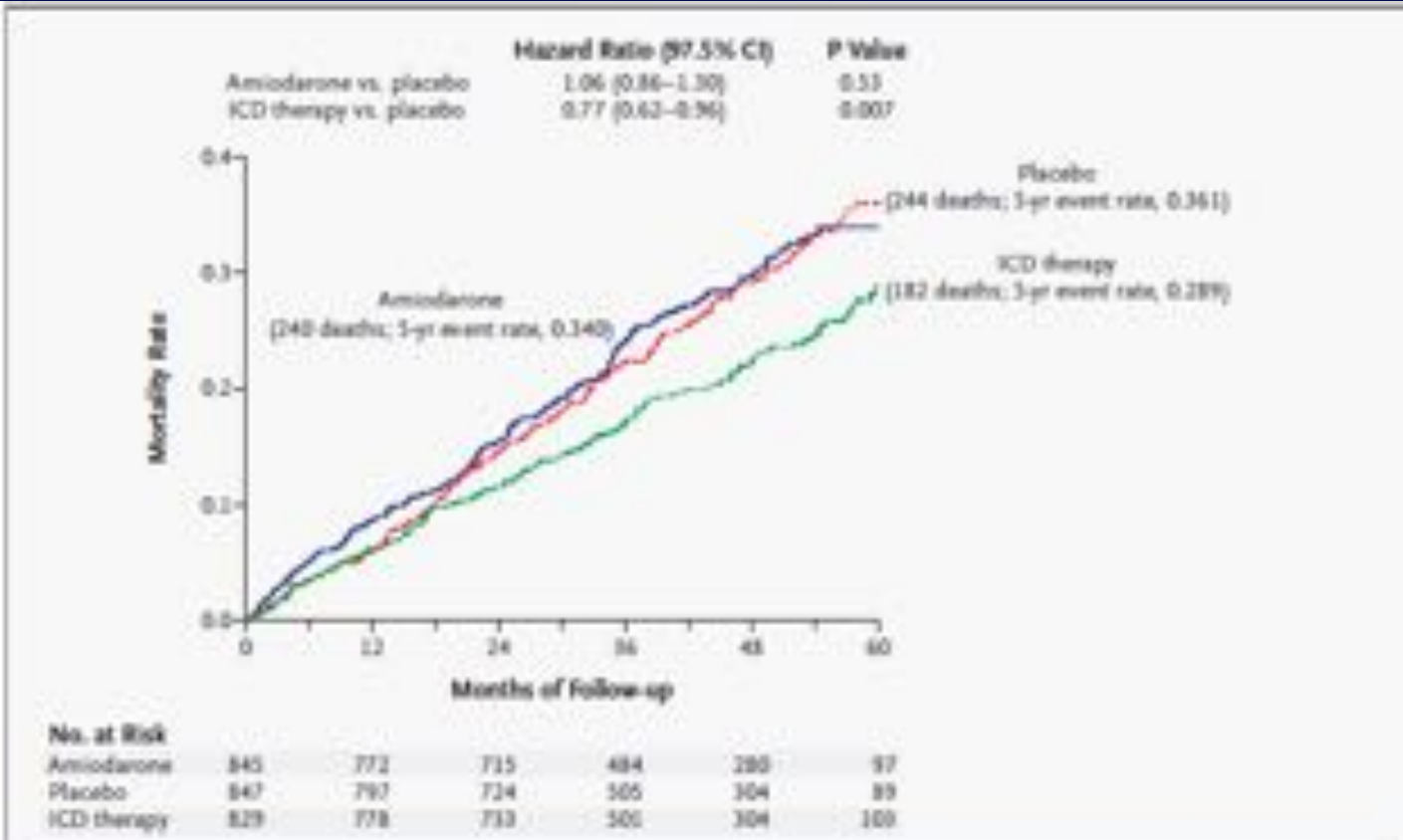
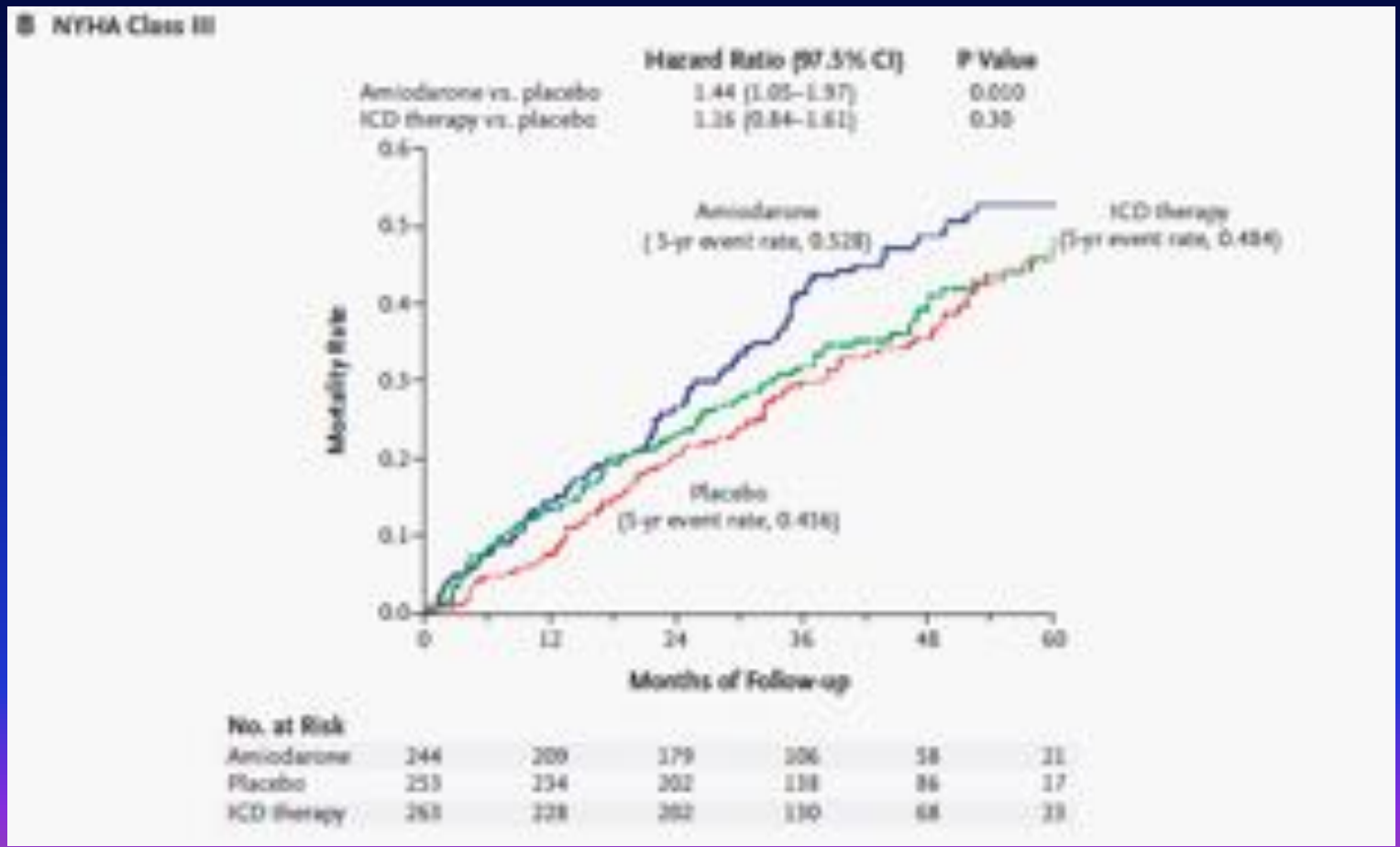


Figure 1. Kaplan–Meier Estimates of Death from Any Cause.

Amiodarone or an Implantable Cardioverter–Defibrillator for Congestive Heart Failure

Gust H. Bardy, M.D., Kerry L. Lee, Ph.D., Daniel B. Mark, M.D., Jeanne E. Poole, M.D., Douglas L. Packer, M.D., Robin Boineau, M.D., Michael Domanski, M.D., Charles Troutman, R.N., Jill Anderson, R.N., George Johnson, B.S.E.E., Steven E. McNulty, M.S., Nancy Clapp-Channing, R.N., M.P.H., Linda D. Davidson-Ray, M.A., Elizabeth S. Fraulo, R.N., Daniel P. Fishbein, M.D., Richard M. Luceri, M.D., and John H. Ip, M.D., for the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators*

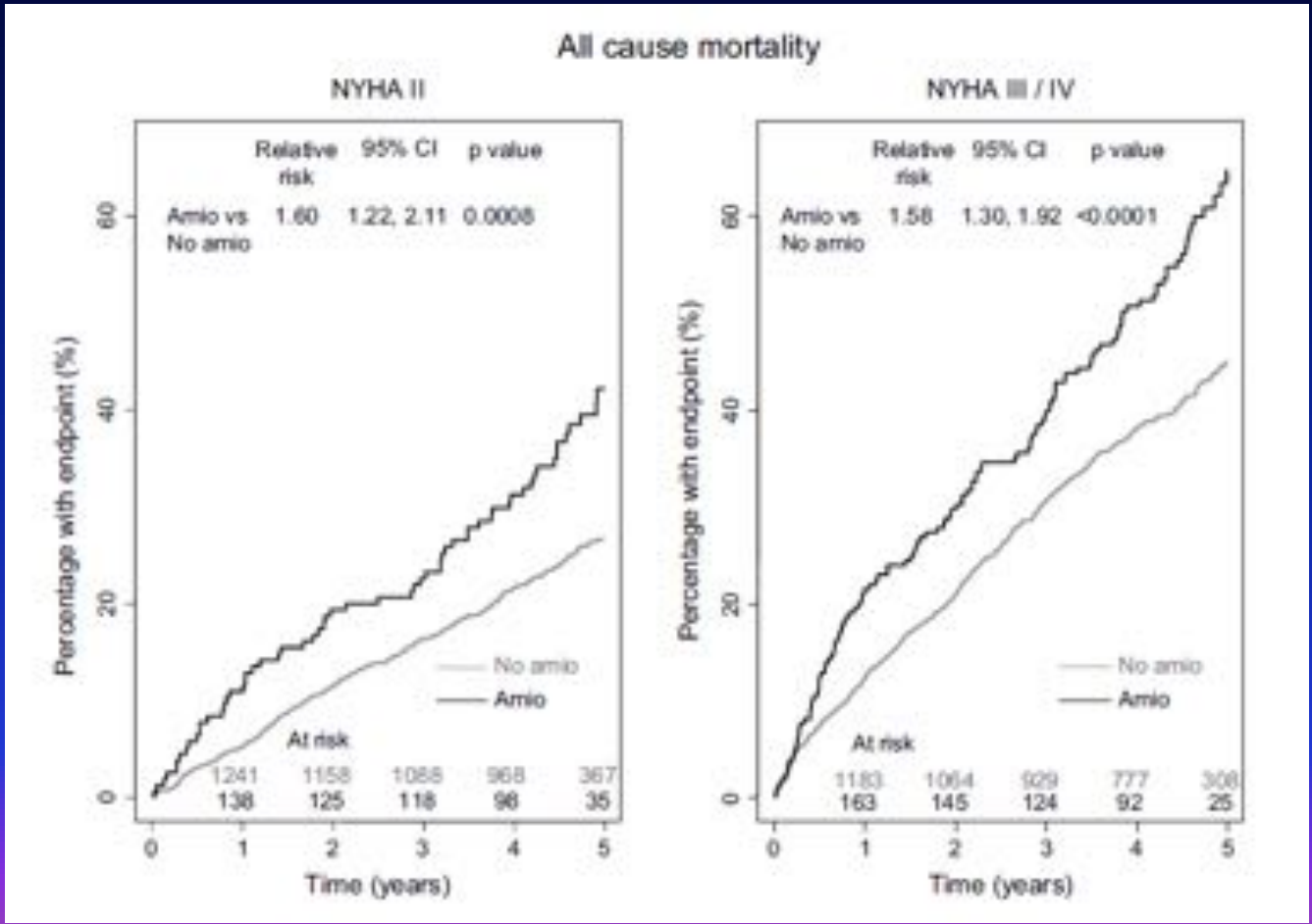
N Engl J Med 2005;352:225-37.



The Safety of Amiodarone in Patients With Heart Failure

Journal of Cardiac Failure Vol. 13 No. 5 2007

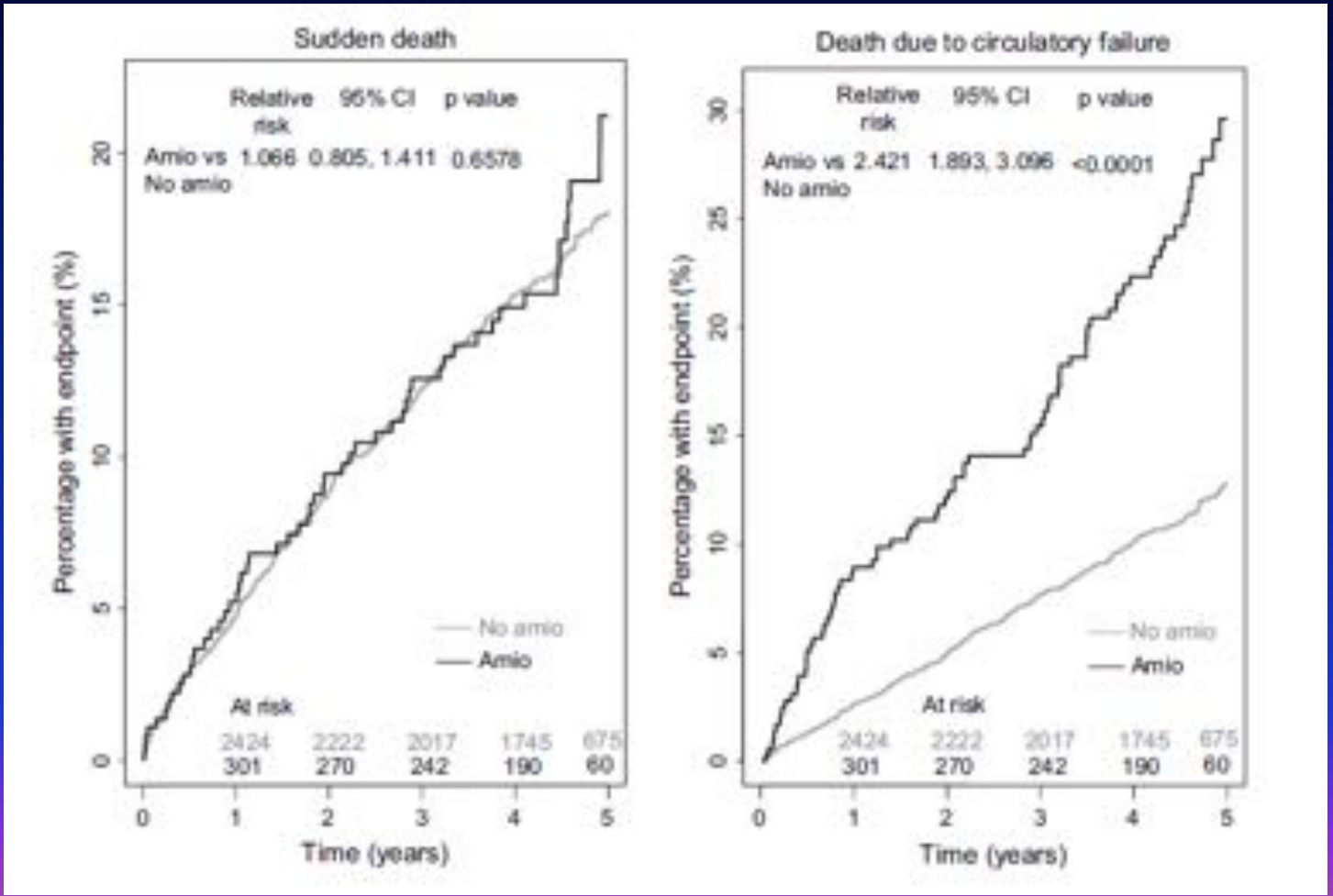
CHRISTIAN TORP-PEDERSEN, MD,[1] MARCO METRA, MD,[2] PHILIP SPARK, PhD,[3]
MARY ANN LUKAS, MD,[4] CHRISTINE MOULLET, MD,[5] ARMIN SCHERHAG, MD,[6]
MICHEL KOMAJDA, MD,[7] JOHN G.F. CLELAND, MD,[8] WILLEM REMME, MD,[9]
ANDREA DI LENARDA, MD,[10] KARL SWEDBERG, MD,[11] AND PHILIP A. POOLE-WILSON, MD,[12,*]
FOR THE COMET INVESTIGATORS



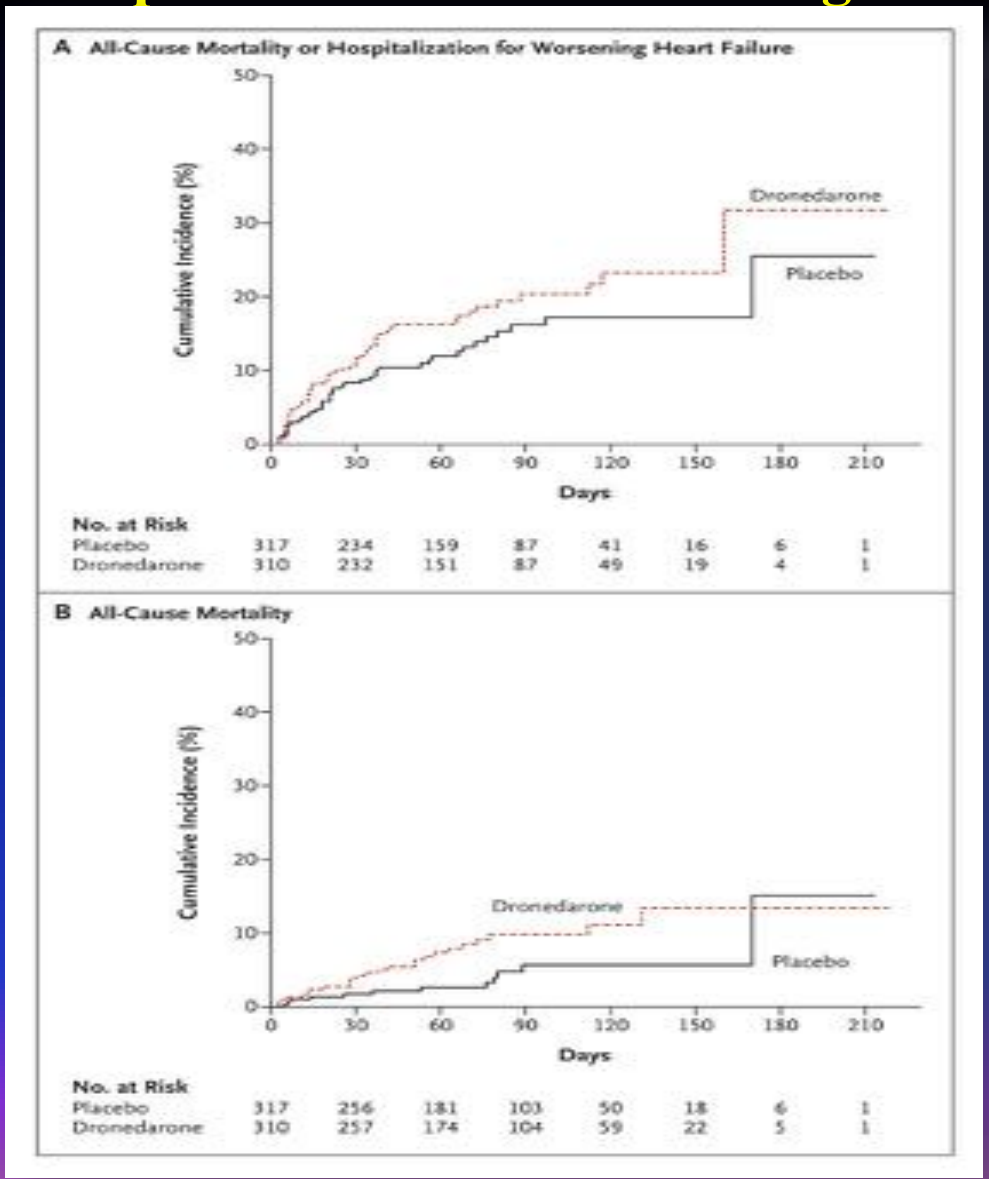
The Safety of Amiodarone in Patients With Heart Failure

Journal of Cardiac Failure Vol. 13 No. 5 2007

CHRISTIAN TORP-PEDERSEN, MD,[1] MARCO METRA, MD,[2] PHILIP SPARK, PhD,[3]
MARY ANN LUKAS, MD,[4] CHRISTINE MOULLET, MD,[5] ARMIN SCHERHAG, MD,[6]
MICHEL KOMAJDA, MD,[7] JOHN G.F. CLELAND, MD,[8] WILLEM REMME, MD,[9]
ANDREA DI LENARDA, MD,[10] KARL SWEDBERG, MD,[11] AND PHILIP A. POOLE-WILSON, MD,[12,*]
FOR THE COMET INVESTIGATORS



DRONEDARONE: Cumulative Incidence of All-Cause Mortality or Hospitalization for Worsening Heart Failure.

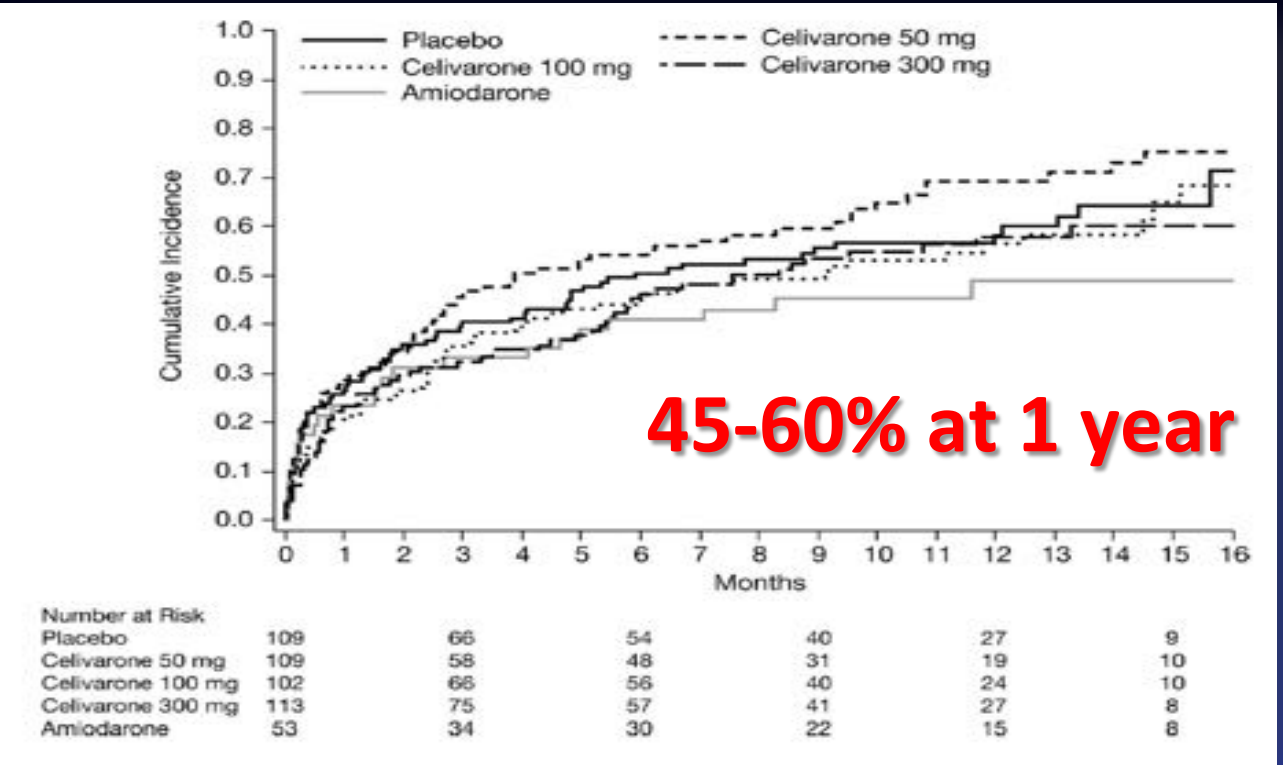


Hazard ratio = 1.38
95% CI, 0.92 to 2.09
P=0.12

Hazard ratio = 2.13
95% CI, 1.07 to 4.25
P=0.03

Kober L et al. N Engl J Med 2008;358:2678-2687

Cumulative incidence to first VT/VF–triggered ICD intervention or sudden death in ALPHEE trial.



ALPHEE

Kowey et al.
Circulation 2011;124:2649-60

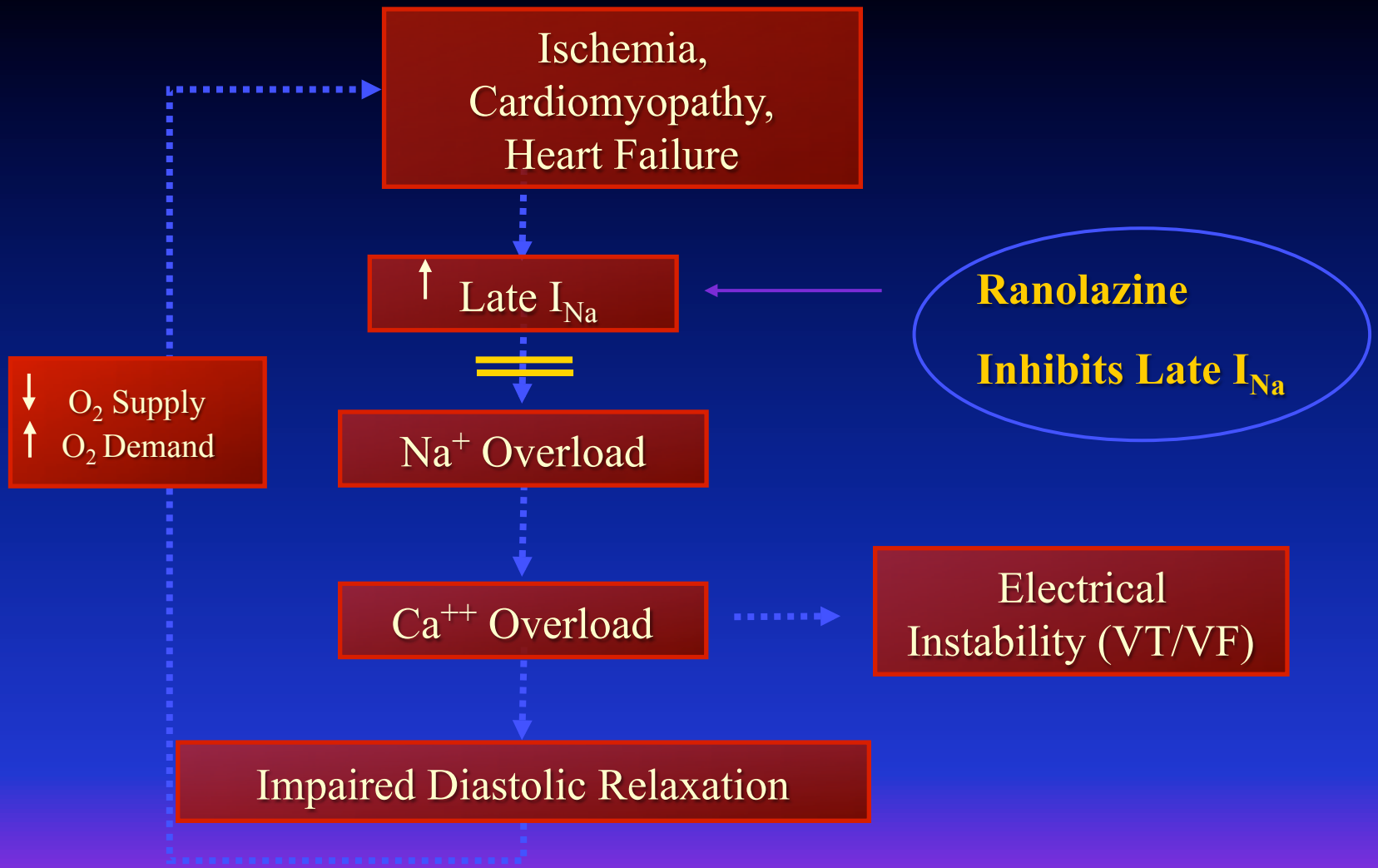
There was no apparent dose effect in the celivarone groups, **but the number of deaths in the amiodarone group was notably higher than in the placebo group (17.0% versus 5.5%).**

Reduction in Cardiac Events in Carvedilol vs. Metoprolol Treated Patients from MADIT-CRT

Study population	HF/death			VT/VF		
	HR	95% CI	P-value	HR	95% CI	P-value
MADIT-CRT	0.70	0.57-0.87	0.001	0.80	0.63-1.00	0.050
CRT-D and LBBB	0.51	0.35-0.76	<0.001	0.57	0.39-0.85	0.005

Ruwald M et al. J Am Coll Cardiol. 2013 Apr 9;61:1518-26

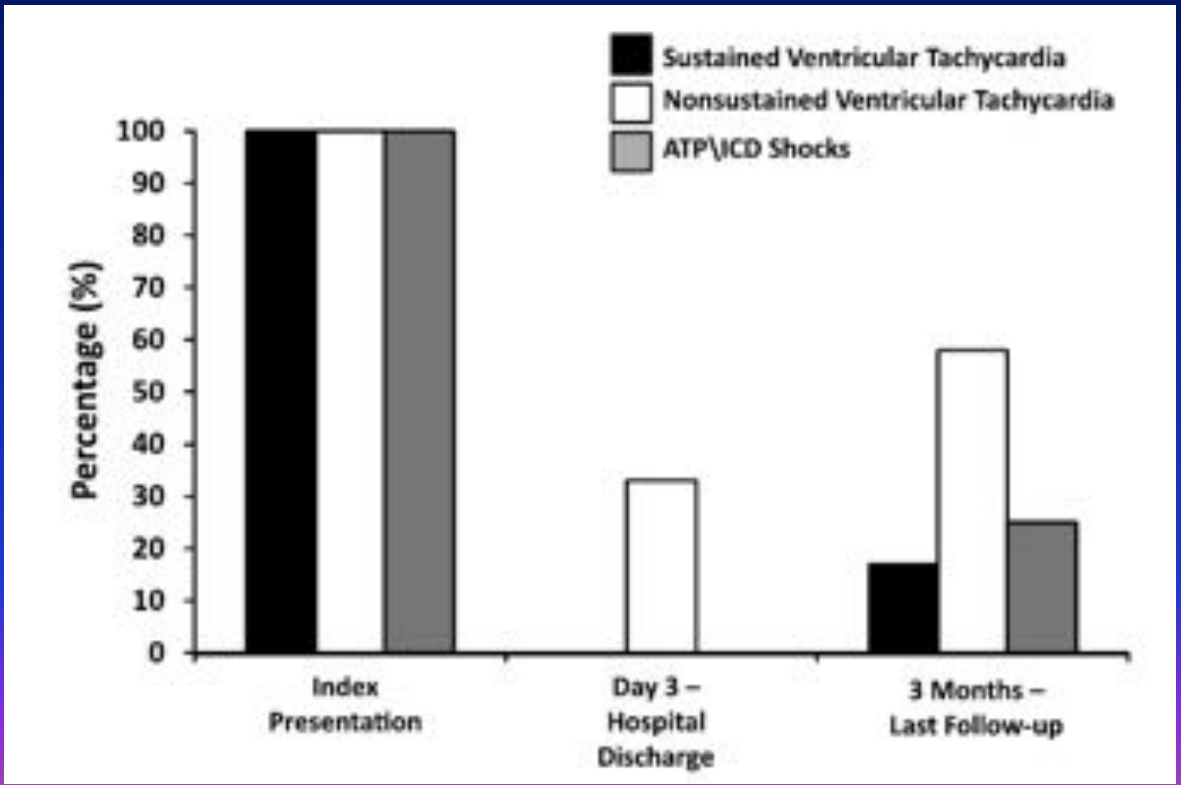
Ranolazine: Mechanism of Action



Ju YK, et al. *J Physiol.* 1996. Murphy E, et al. *Circ Res.* 1991. Jansen MA, et al. *Circulation*. 2004. Min JY, et al. *J Pharmacol Exp Ther*. 1999. Fraser H, et al. *J Mol Cell Cardiol*. 2006. Crossman DC. *Heart.* 2004. Meyer M, et al. *J Mol Cell Cardiol*. 1998.

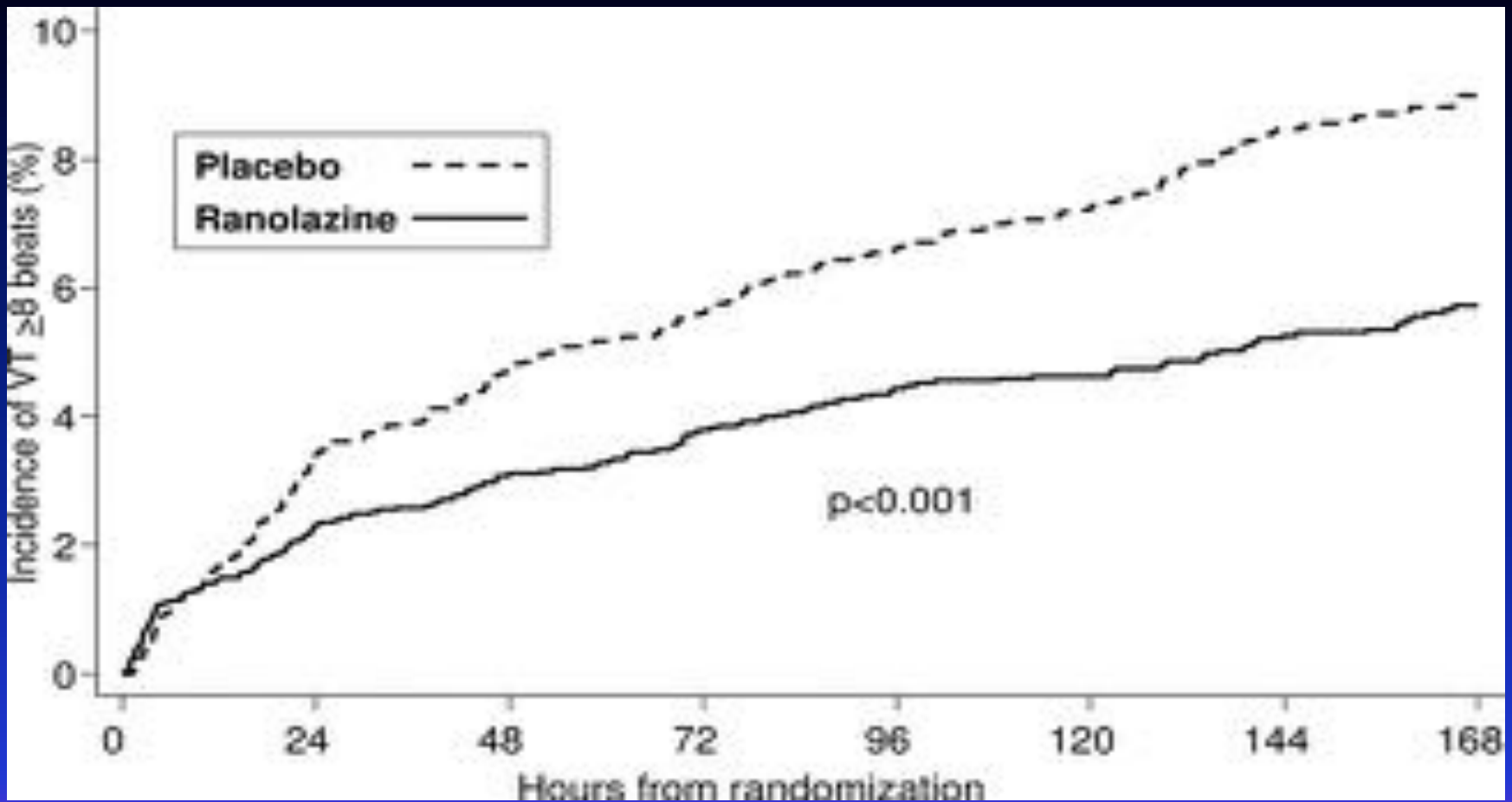
Ranolazine Reduces Ventricular Tachycardia Burden and ICD Shocks in Patients with Drug-Refractory ICD Shocks

T. JARED BUNCH, M.D.,*,† SRIJOY MAHAPATRA, M.D.,‡ DAVID MURDOCK, M.D.,§ JAMIE MOLDEN, M.D.,¶ J. PETER WEISS, M.D.,* HEIDI T. MAY, PH.D.,† TAMI L. BAIR, R.N.,† KATY M. MADER, PHARM.D,† BRIAN G. CRANDALL, M.D.,*,† JOHN D. DAY, M.D.,*,† JEFFREY S. OSBORN, M.D.,*,† JOSEPH B. MUHLESTEIN, M.D.,† DONALD L. LAPPE, M.D.,† and JEFFREY L. ANDERSON, M.D.†



PACE 2011

MERLIN: Kaplan-Meier estimated rates of the first occurrence of an episode of ventricular tachycardia lasting at least 8 beats



Scirica BM, et al. *Circulation.* 2007.

RAID Trial – Ranolazine in High Risk ICD Patients
(NIH – PI: W. Zareba)

Significance: The only pharmacological phase III trial in the world testing new antiarrhythmic agent for ventricular arrhythmias

Primary Aim: to determine whether ranolazine administration will decrease the likelihood of a composite arrhythmia endpoint consisting of ventricular tachycardia or ventricular fibrillation (VT/VF) requiring ICD therapy (ATP or shocks) or death

Study Population: 1,440 patients enrolled in >80 sites

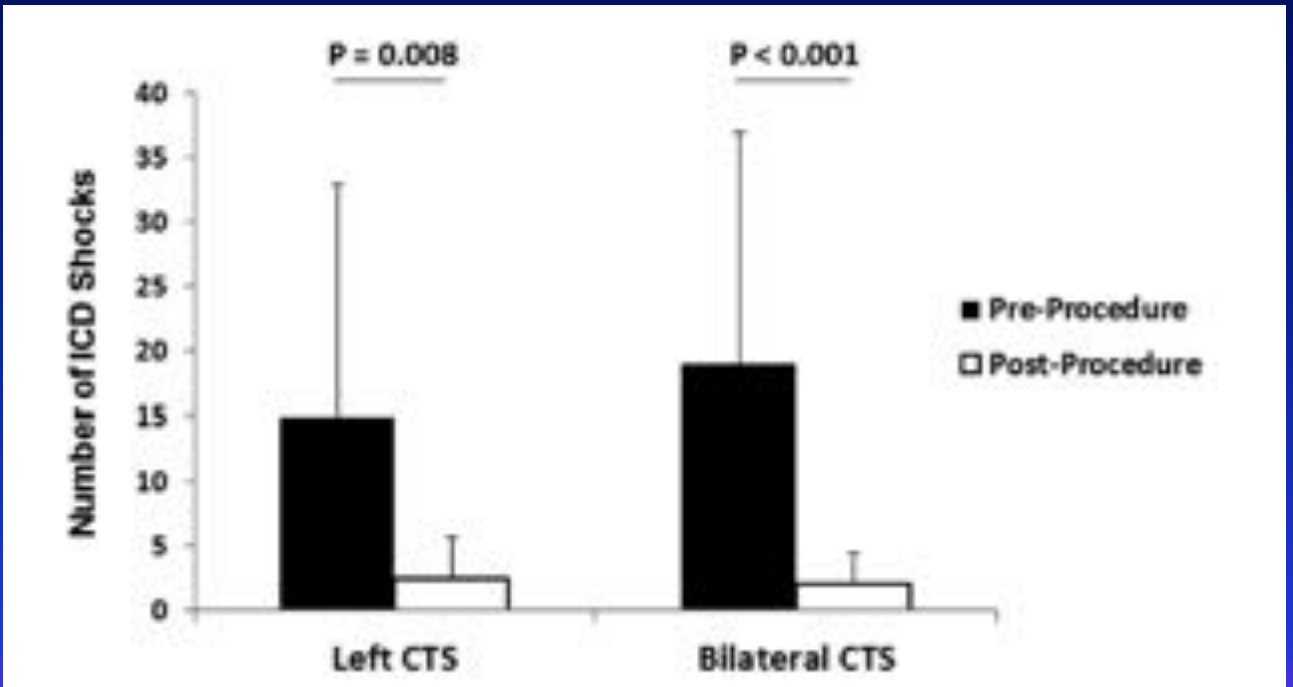
Expected Completion: 2016

Antiarrhythmic Therapy in Patients with VT:

- Cardiac Resynchronization Therapy
- Pharmacological Therapy
- Device programming
- VT Ablation
- Cardiac sympathetic Denervation

Cardiac sympathetic denervation in patients with refractory ventricular arrhythmias or electrical storm: Intermediate and long-term follow-up

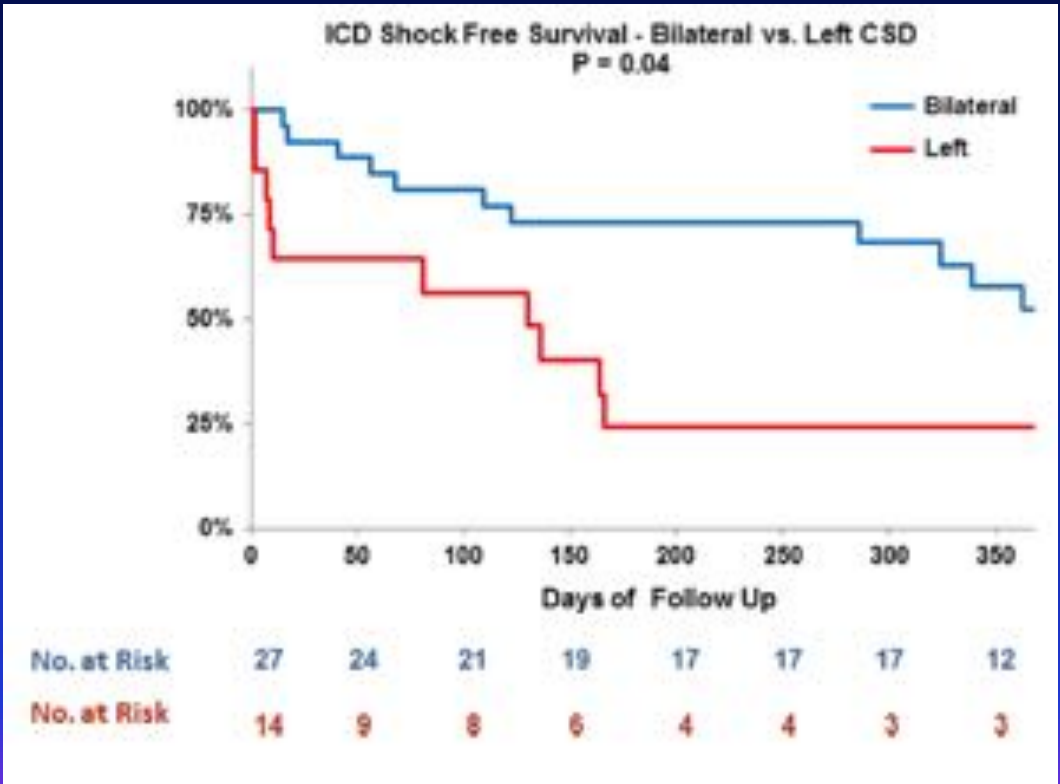
Marmar Vaseghi, MD, MS,[*] Jean Gima, RN, MSN, NP,[*] Christopher Kanaan, BS,[*] Olujimi A. Ajijola, MD, PhD,[*] Alexander Marmureanu, MD,[*†] Aman Mahajan, MD, PhD,[*‡] Kalyanam Shivkumar, MD, PhD, FHRS[*]



Heart Rhythm 2014;11:360–366

Cardiac sympathetic denervation in patients with refractory ventricular arrhythmias or electrical storm: Intermediate and long-term follow-up

Marmar Vaseghi, MD, MS,* Jean Gima, RN, MSN, NP,* Christopher Kanaan, BS,* Olujimi A. Ajijola, MD, PhD,* Alexander Marmureanu, MD,*† Aman Mahajan, MD, PhD,*‡ Kalyanam Shivkumar, MD, PhD, FHRS*



Heart Rhythm 2014;11:360–366

Antiarrhythmic Therapy in Patients with VT:

- Cardiac Resynchronization Therapy
- Pharmacological Therapy
- Device programming
- VT Ablation
- Cardiac sympathetic Denervation