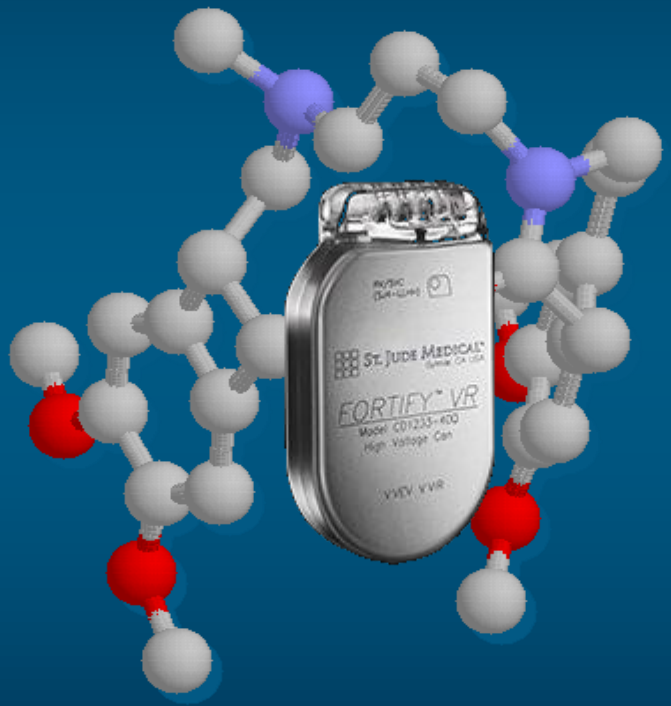
Cardiology Update 2015

Davos, Switzerland: 8-12th February 2015

Ventricular Arrhythmias



Ventricular Tachycardia

Drugs versus Devices

John Camm

St. George's University of London, UK

Imperial College, London, UK

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Declaration of Interests

Chairman: NICE Guidelines on AF, 2006; ESC Guidelines on Atrial Fibrillation, 2010 and Update, 2012; ACC/AHA/ESC Guidelines on VAs and SCD; 2006; NICE Guidelines on ACS and NSTEMI, 2012; NICE Guidelines on heart failure, 2008; NICE Guidelines on Atrial Fibrillation, 2006; ESC VA and SCD Guidelines, 2015

Steering Committees: multiple trials including novel anticoagulants

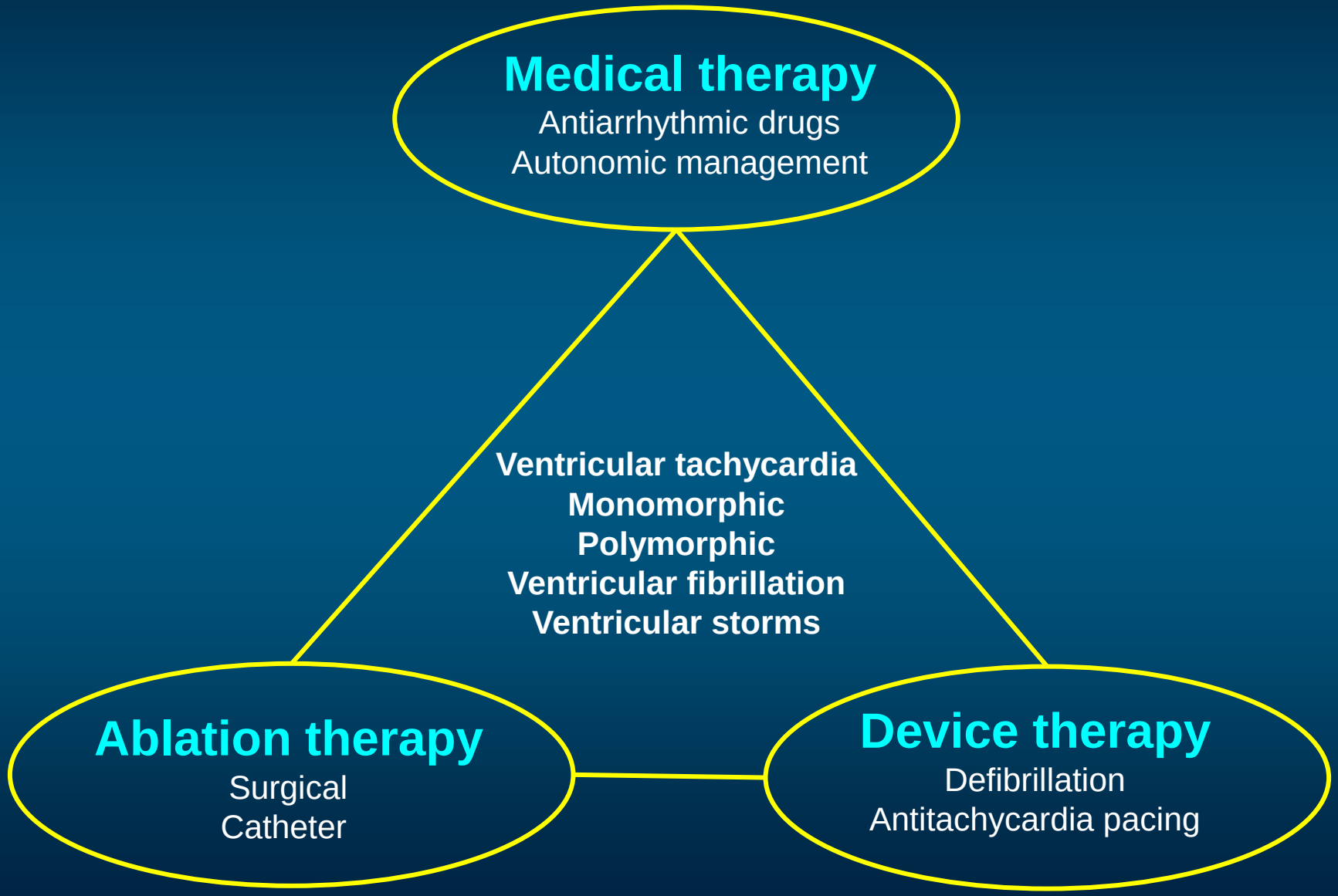
DSMBs: multiple trials including BEAUTIFUL, SHIFT, SIGNIFY, AVERROES, CASTLE-AF, STAR-AF II, INOVATE, and others

Events Committees: one trial of novel oral anticoagulants and multiple trials of miscellaneous agents with CV adverse effects

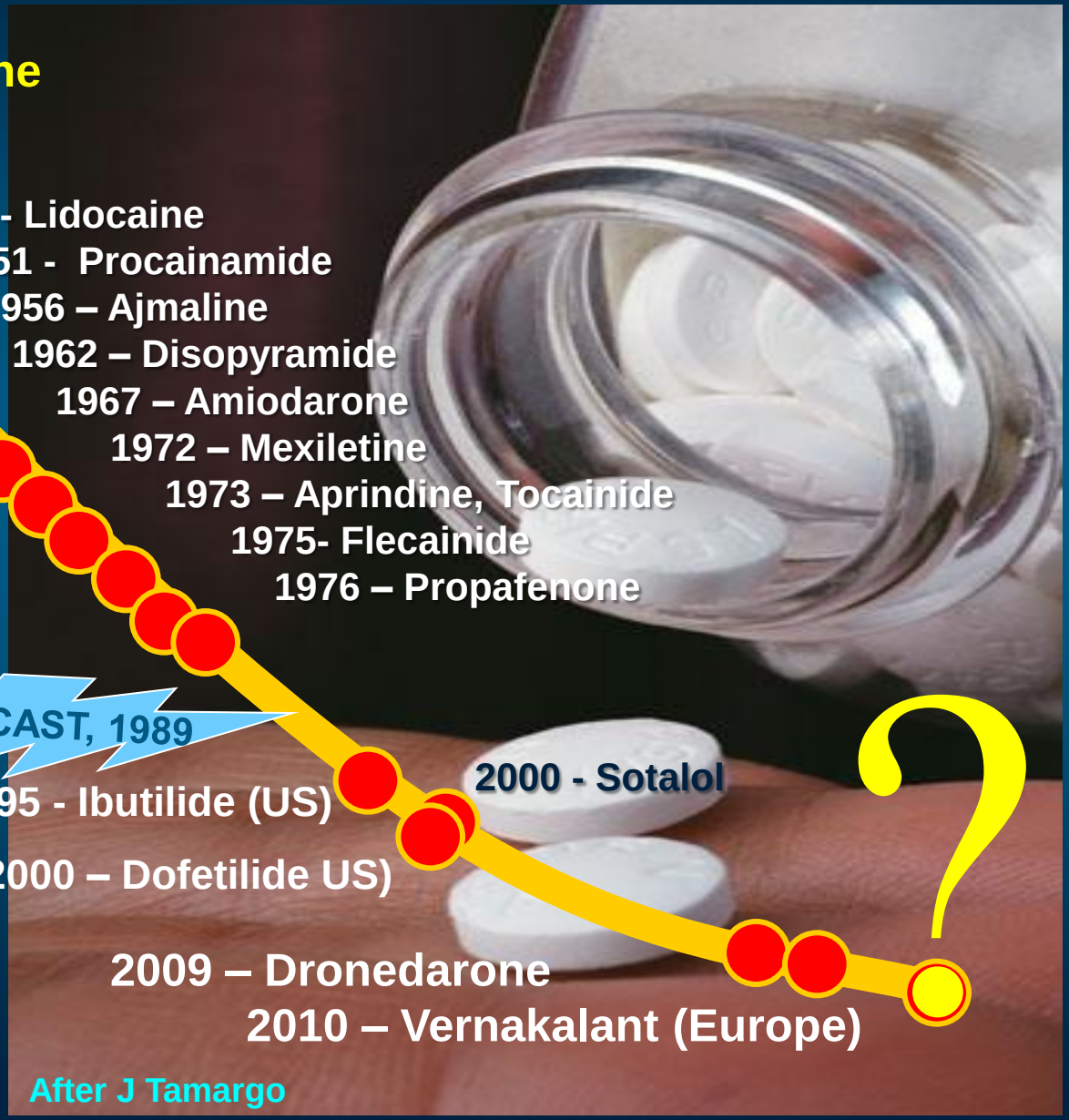
Editorial Role: Editor-in-Chief, EP-Europace and Clinical Cardiology; Editor, European Textbook of Cardiology, European Heart Journal, Electrophysiology of the Heart, and Evidence Based Cardiology

Consultant/Advisor/Speaker: Astellas, Astra Zeneca, ChanRX, Gilead, Merck, Menarini, Otsuka, Sanofi, Servier, Xention, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, Boston Scientific, Biotronik, Medtronic, St. Jude Medical, Actelion, GlaxoSmithKline, InfoBionic, Incarda, Johnson and Johnson, Mitsubishi, Novartis, Takeda

Therapy for Ventricular Tachycardia



History of Antiarrhythmic Drugs



1914 - Quinidine

1946 – Digitalis
1962 - Verapamil
1964 - Propranolol
1965 – Bretylium
1969 - Diltiazem

1950 - Lidocaine
1951 - Procainamide
1956 – Ajmaline
1962 – Disopyramide
1967 – Amiodarone
1972 – Mexiletine
1973 – Aprindine, Tocainide
1975- Flecainide
1976 – Propafenone

CAST, 1989

Encainide
Etmozine
D-sotalol
Recainam
Indecainide
Etc.

1995 - Ibutilide (US)

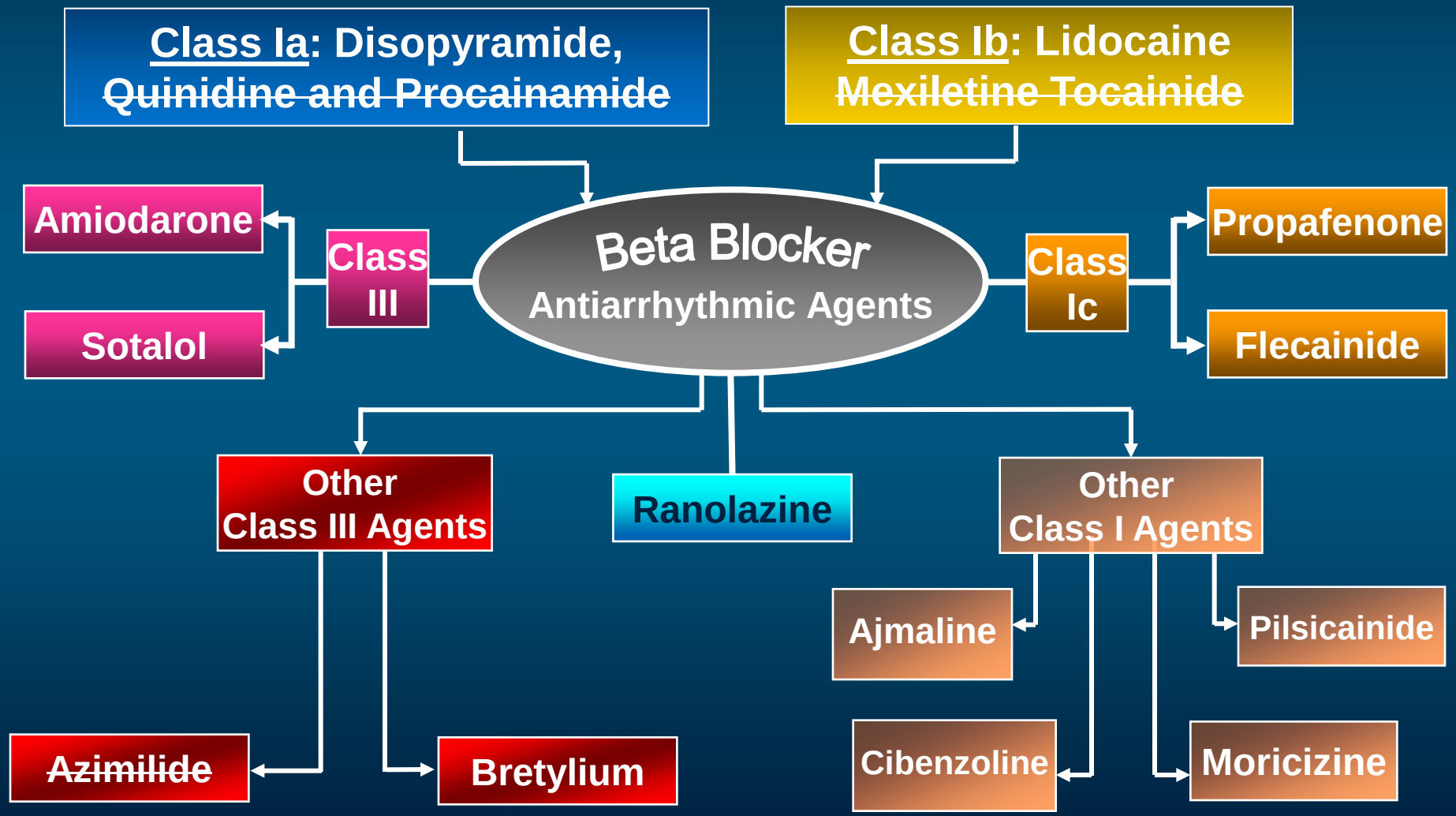
2000 - Sotalol

2000 – Dofetilide US)

2009 – Dronedarone
2010 – Vernakalant (Europe)

After J Tamargo

Ventricular Tachycardia
Antiarrhythmic Medical Therapies



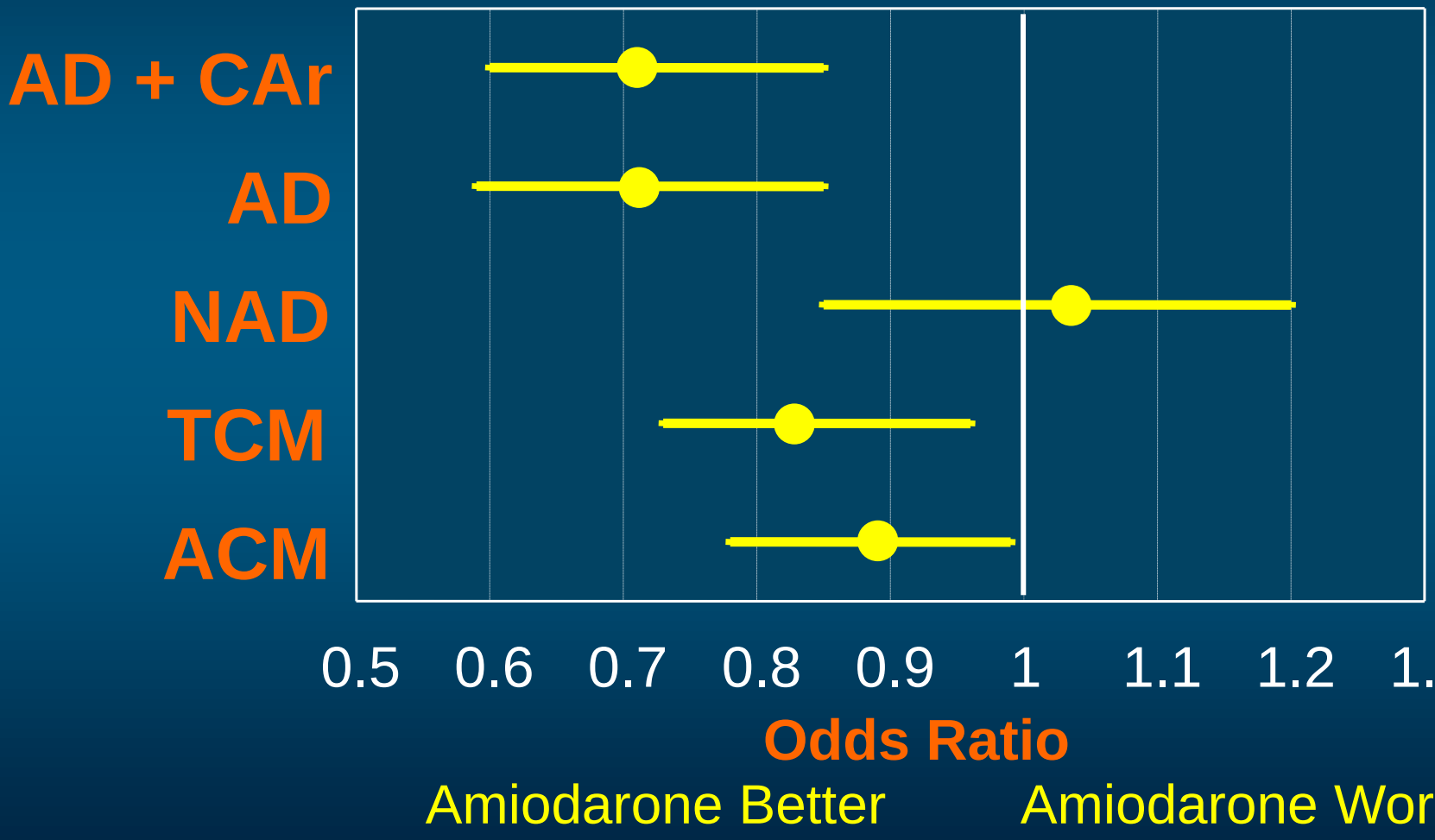
Landmarks for AADs and VT

- **IMPACT, SWORD and CAST**
  - Class 1 AADs proarrhythmic post MI
- **EMIAT and CAMIAT**
  - Amiodarone reduces sudden death but not ACM after MI
- **DIAMOND and ALIVE**
  - Azimilide and dofetilide “safe” after MI and in CHF
- **ESVEM**
  - PES/Holter does not predict outcome & sotalol superior
- **CASCADE**
  - Amiodarone better than class 1 AADs

Then, AVID CIDS, CASH and .....SCD-HeFT

Amiodarone Meta-Analysis

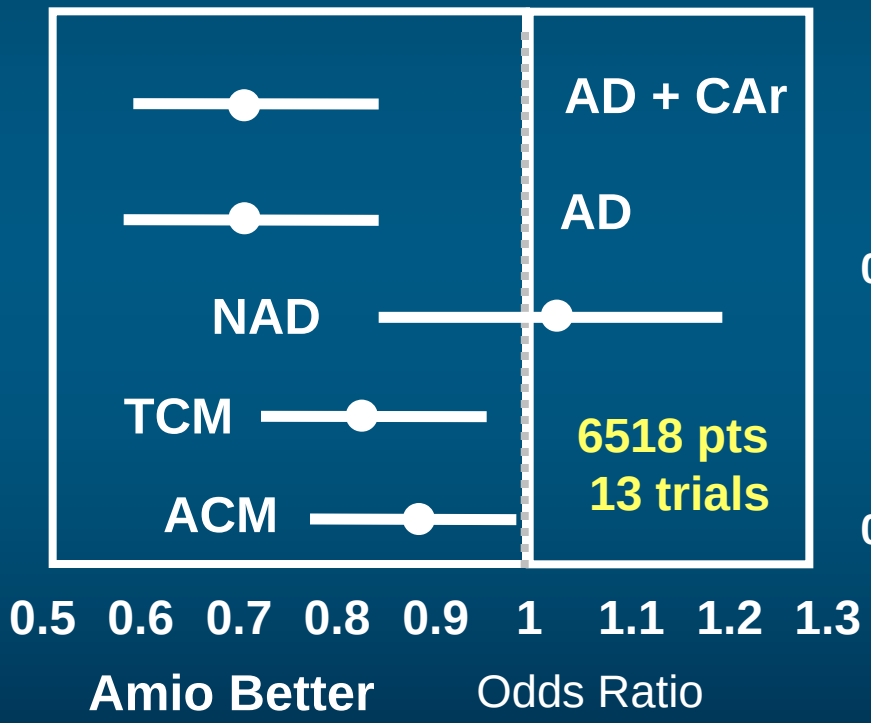
(6518 patients, 13 trials)



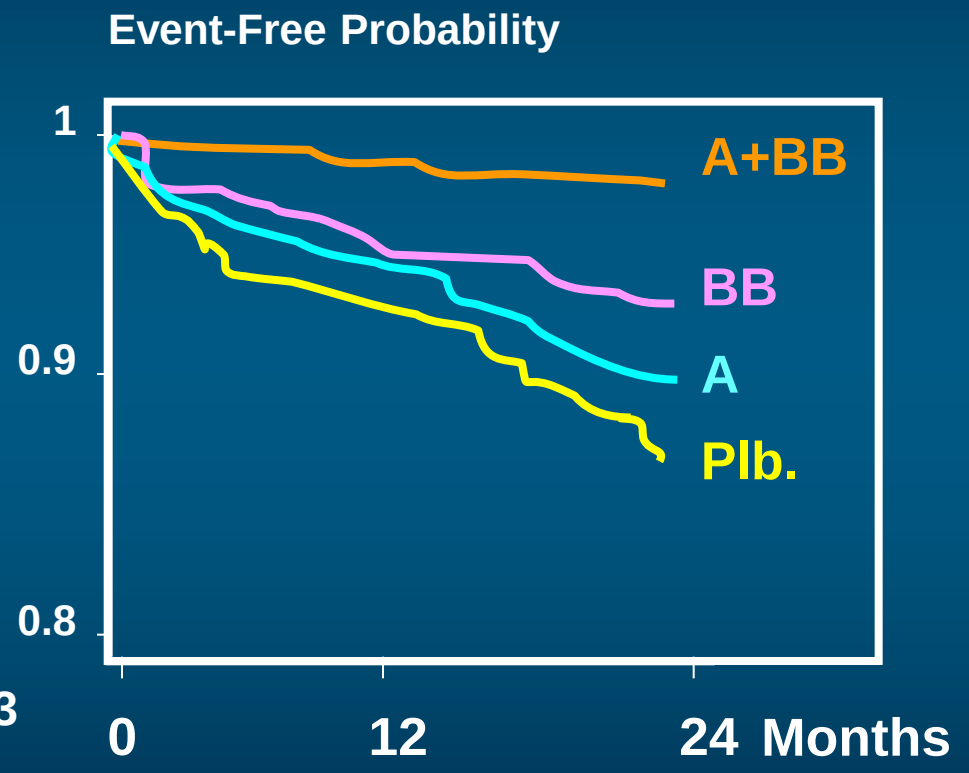
The ATMA Group, 1996

Amiodarone

Metanalyses



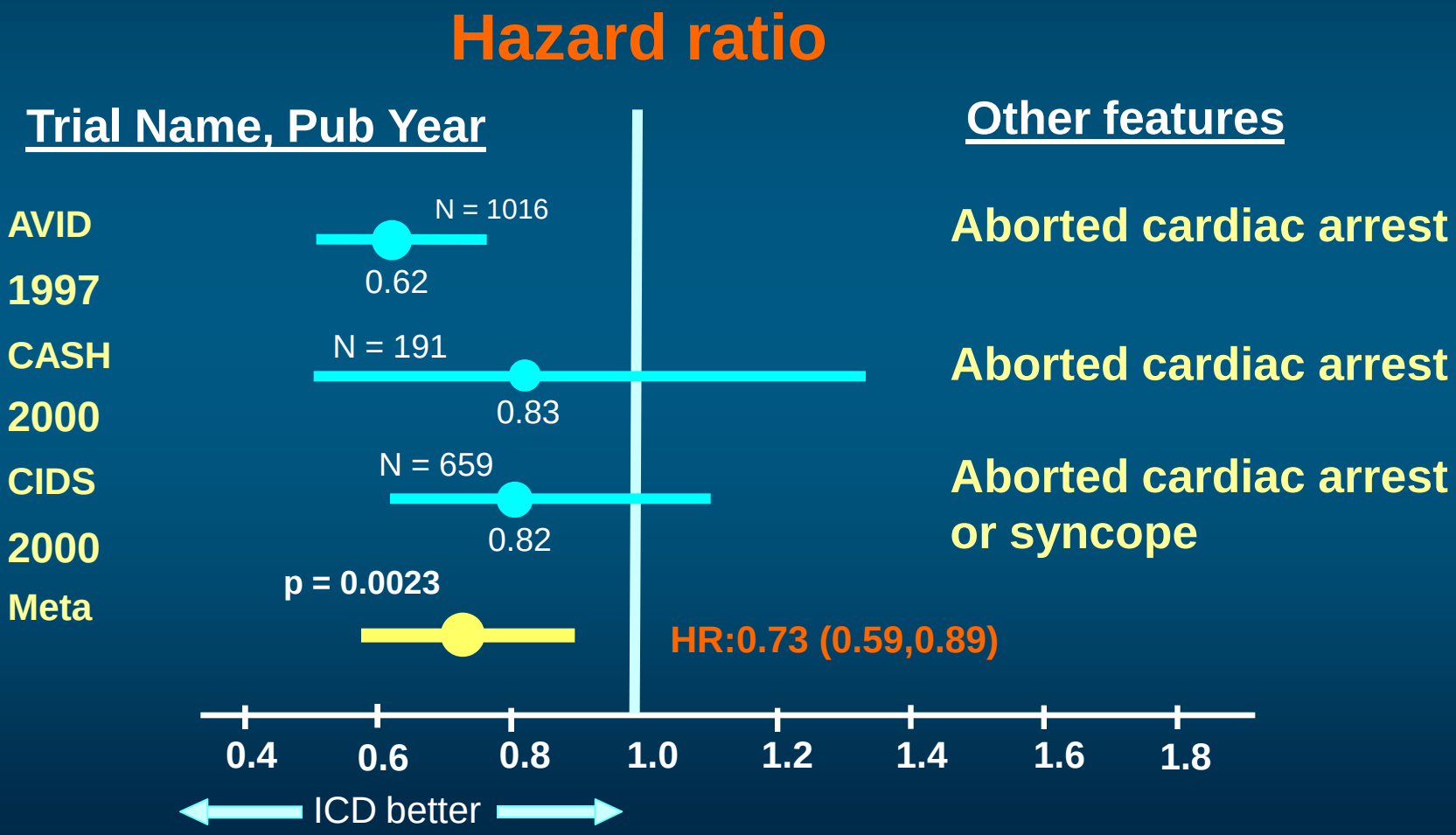
The ATMA Group, 1996



ECMA

Boutitie et al, 1999

2^0 Prevention ICD Trials

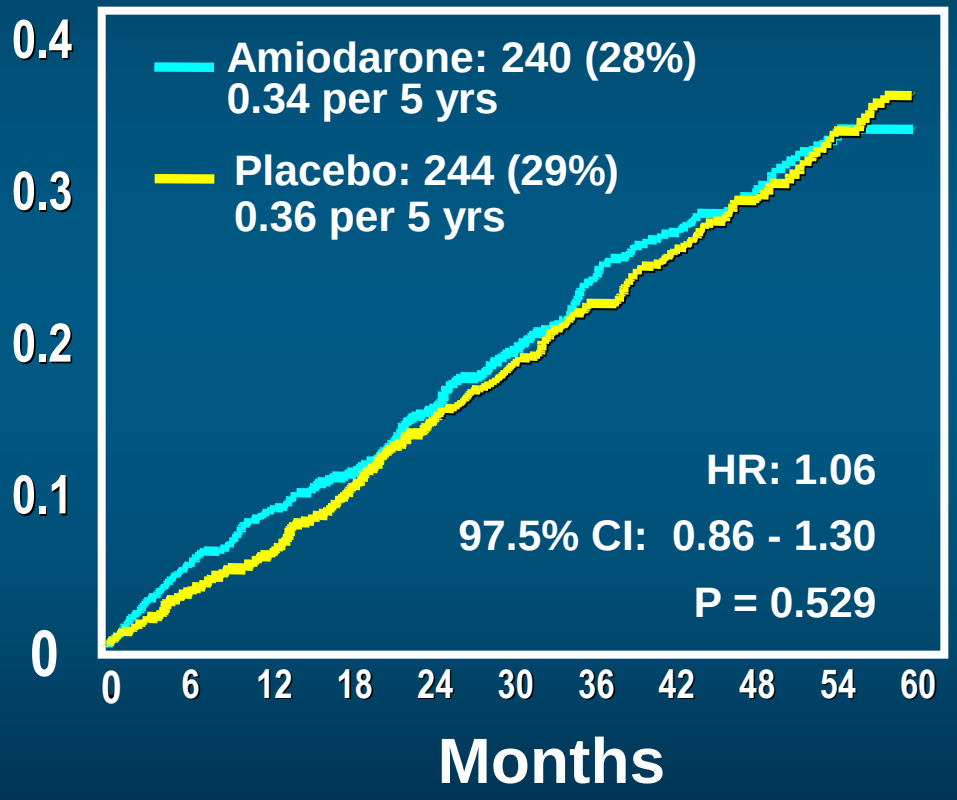


Amiodarone in CHF: The SCD-HeFT

- N = 2521 (Amio 845, Pla 847)
- LVEF ≤ 35% (mean 25%)
- NYHA Class II (70%) or III
- IHD 52%
- Median follow-up 45.5 mos

5-year ACM rates	Amio	Placebo
NYHA II	0.264	0.32
HR (95% CI)	0.85 (0.65 - 1.11) p=0.17	
NYHA III	0.528	0.456
HR (95% CI)	1.44 (1.05 - 1.97) p=0.17	

All-cause mortality



Bardy G, et al. NEJM 2005

Amiodarone Recommendations

- Class IIa Recommendation
  - Amiodarone, often in combination with beta blockers, can be useful for patients with LVD due to prior MI and symptoms due to ***VT unresponsive to beta-adrenergic blocking agents*** (Level of Evidence: B)
  - Amiodarone is reasonable therapy to reduce symptoms due to recurrent hemodynamically stable VT for patients with LVD due to prior MI ***who cannot or refuse to have an ICD implanted*** (Level of Evidence: C)
- Class IIb Recommendation
  - Amiodarone may be reasonable therapy for patients with LVD due to ***prior MI with an ICD indication***, as defined above, in patients ***who cannot, or refuse to have an ICD implanted***. (Level of Evidence: C)

Procainamide and Lidocaine Efficacy Terminating Sustained MMVT

Author	Year	No. of patients	Termination rate
Procainamide			
Wellens	1977	12	83%
Callan	1992	15	93%
Gorgels*	1996	15	80%
Present study	2009	70	76%
Total		**112**	**80%**
Lidocaine			
Armengol	1989	20	19%
Griffith	1990	24	30%
Ho*	1994	33	18%
Somberg*	2002	11	27%
Marill	1997	35	29%
Present study	2009	20	35%
Total		**143**	**26%**

* Randomised control study

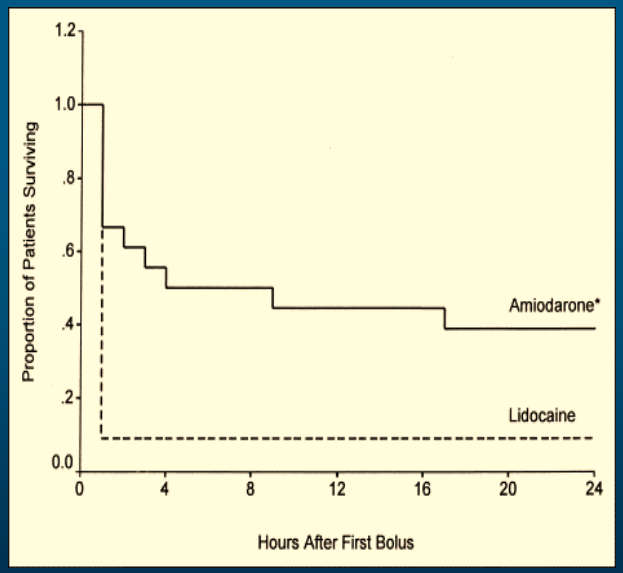
Komura S, et al. Circ J 2010;74:864–869

Intravenous Amiodarone for Incessant (shock resistant) VT

- Double-blinded parallel design
- Randomized to receive up to 2 boluses of either 150 mg iv amiodarone or 100 mg lidocaine
- If first assigned medication failed to terminate VT, the patient was crossed over

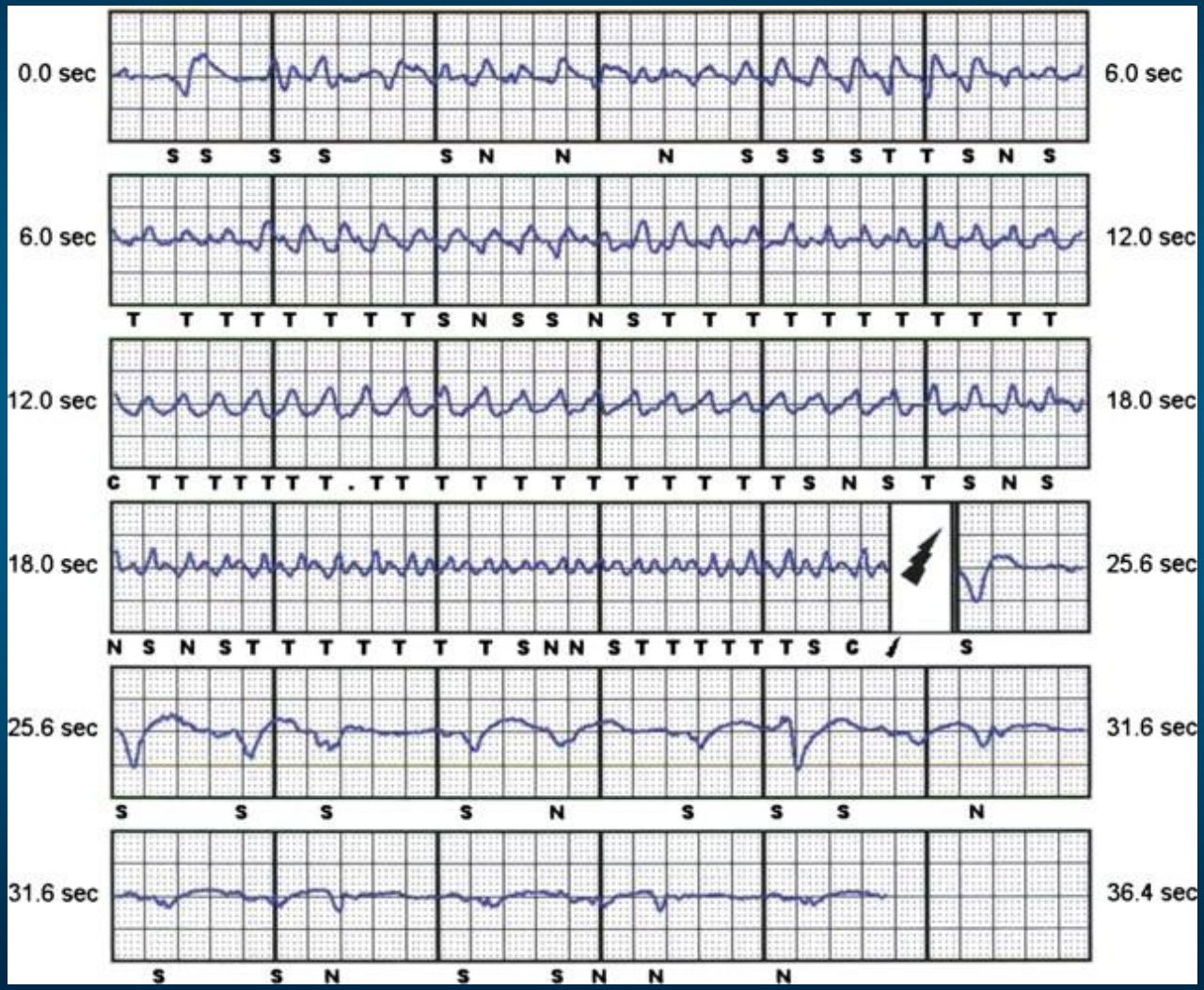
	Lidocaine (n = 11)	Amiodarone (n = 18)	p Value
VT termination	3 (27%)	14 (78%)	<0.05*
1-hour survival	1 (9%)	12 (67%)	<0.01*
24-hour survival	1 (9%)	7 (39%)	<0.01†
Crossed over	9 (82%)	7 (39%)	0.05*

* Fisher's exact test; † Kaplan-Meier test



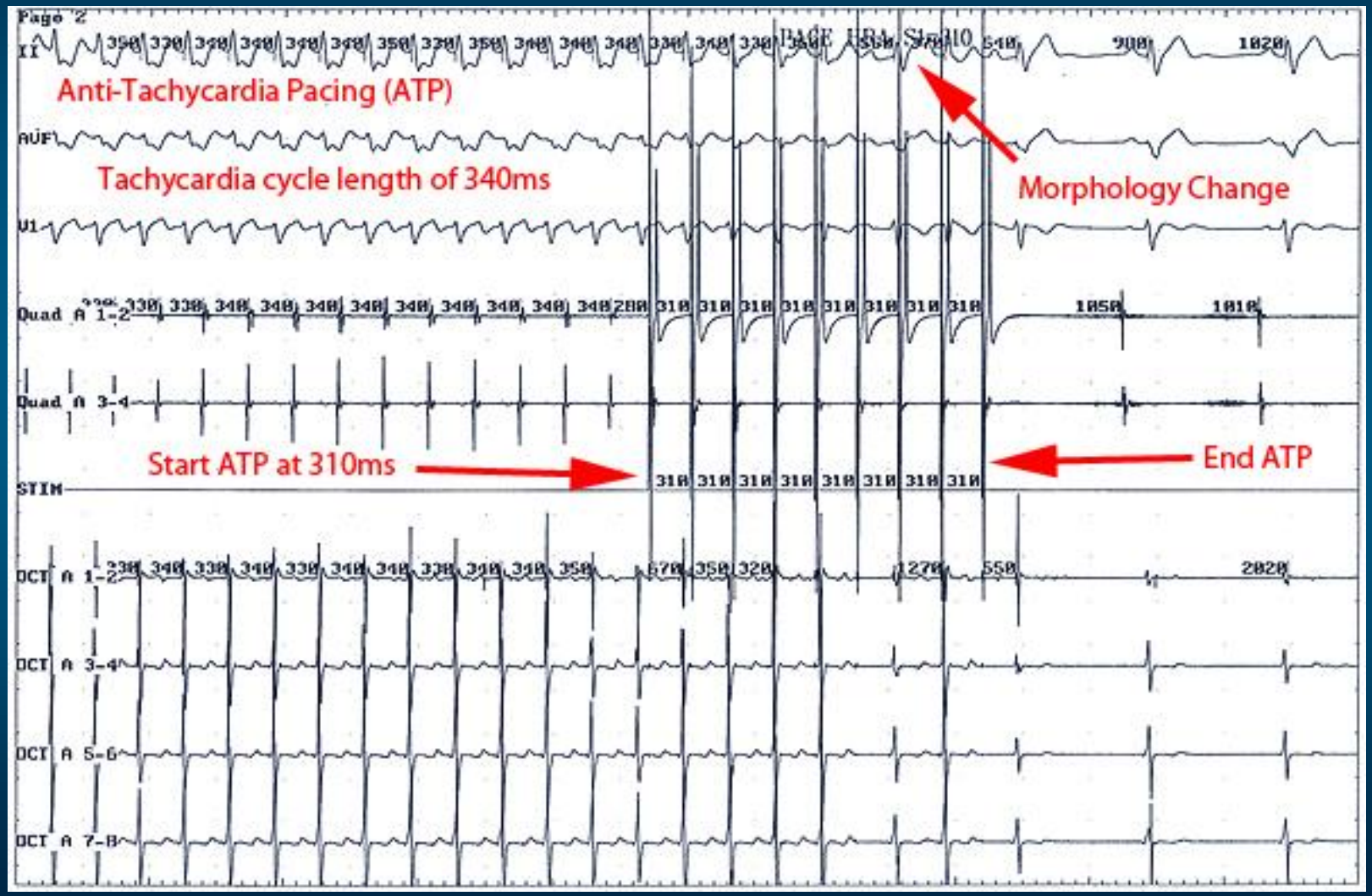
Somberg JC, et al. Amer J Cardiol 2002;90:853 - 859

Sub-cutaneous ICD (S-ICD)
Detection/Conversion of Ventricular Fibrillation



Köbe J, et al. Heart Rhythm, Volume 10, Issue 1, 2013, 29 - 36

Antitachycardia Pacing to Interrupt Ventricular Tachycardia



ATP in MADIT-RIT

The NEW ENGLAND JOURNAL of MEDICINE

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
Any occurrence of therapy — no. of patients (%)					
Appropriate therapy					
Shock	28 (5)	26 (5)	19 (4)	0.86	0.25
Antitachycardia pacing	111 (22)	38 (8)	20 (4)	<0.001	<0.001
Inappropriate therapy					
Shock	31 (6)	14 (3)	15 (3)	0.01	0.03
Antitachycardia pacing	104 (20)	20 (4)	25 (5)	<0.001	<0.001
Total occurrences of therapy — no. of occurrences					
Appropriate therapy	517	185	196	<0.001	<0.001

8% of patients in high rate and 4% of patients in delayed therapy required ATP for VT/VF

80% reduction in the need for ATP with delayed therapy

Variable	Conventional Therapy (N=514)	High-Rate Therapy (N=500)	Delayed Therapy (N=486)		
		> 220 bpm with 2.5 s delay	60s delay		
Any occurrence of therapy — no. of patients (%)					
Appropriate therapy					
Shock	28 (5)	26 (5)	19 (4)	0.86	0.25
Antitachycardia pacing	111 (22)	38 (8)	20 (4)	<0.001	<0.001

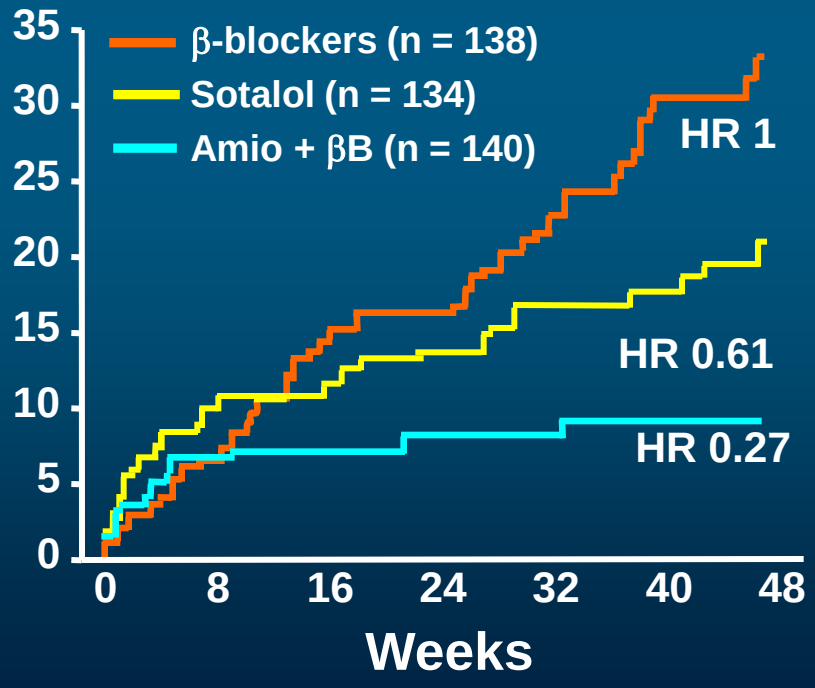
Moss, A, et al. NEJM 2012; 367:2275-2283

AADs and Shocks

OPTIC *Connolly et al, 06*

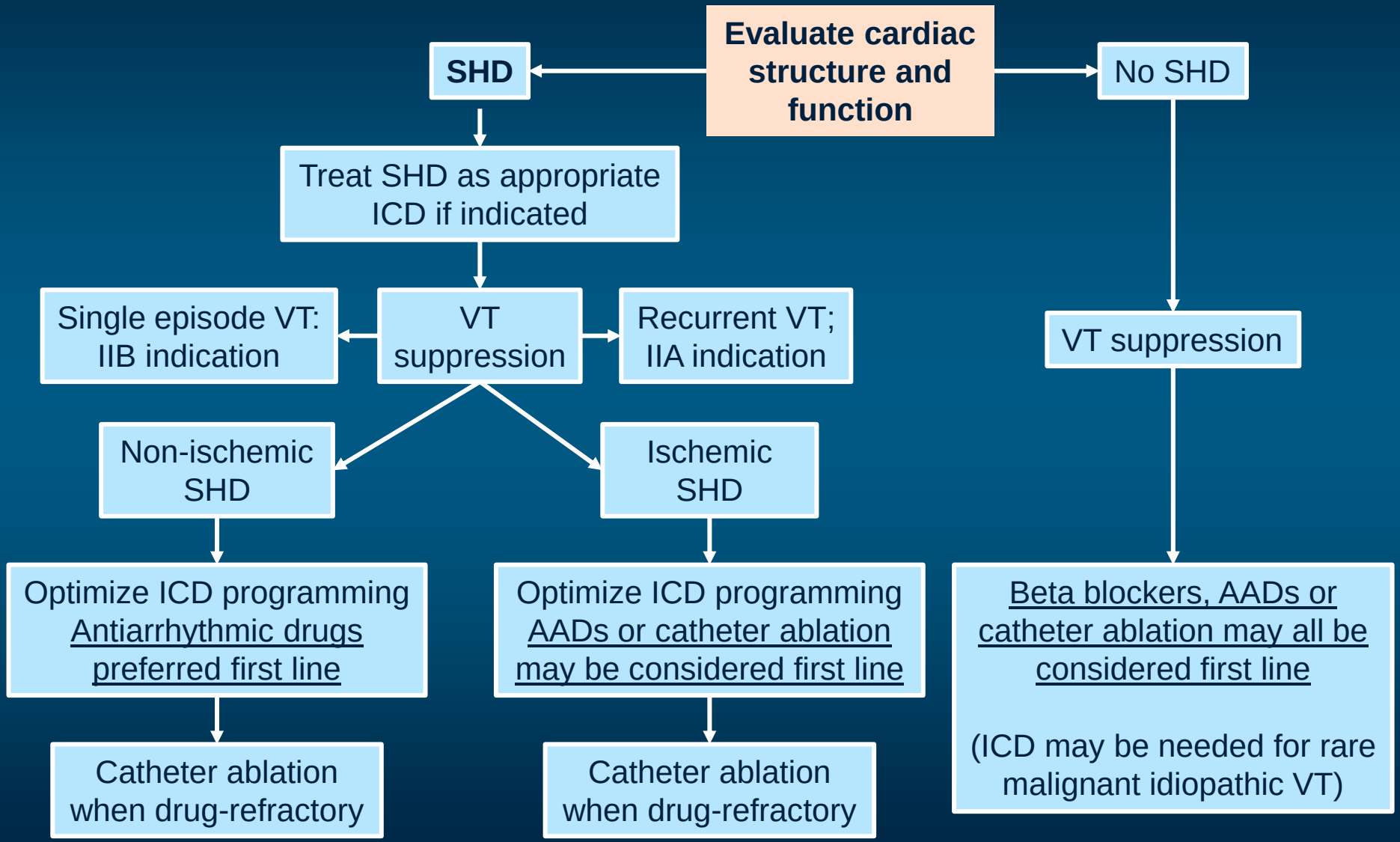
Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients

Cumulative risk of shock [%]



	Beta blocker	Amiod-arone + ßß	Sotalol
	(n=138)	(n=140)	(n=134)
Any shock			
# events	41	**12**	26
Annual rate	**38.5**	**10.3**	**24.3**
HR	1.00	**0.27** (0.14-0.52)	0.61 (0.37-1.01)
Appropriate shock			
# events	25	**8**	17
Annual rate	**22.0**	**6.7**	**15.1**
HR	1.00	**0.30** (0.14-0.68)	0.65 (0.25-1.30)
Inappropriate shock			
# events	18	**4**	11
Annual rate	**15.4**	**3.3**	**9.4**
HR	1.00	**0.22** (0.07-0.64)	0.52 (0.31-0.88)

Sustained Monomorphic Ventricular Tachycardia
Evaluation and Management



Pedersen C T et al. Europace 2014;16:1257-1283

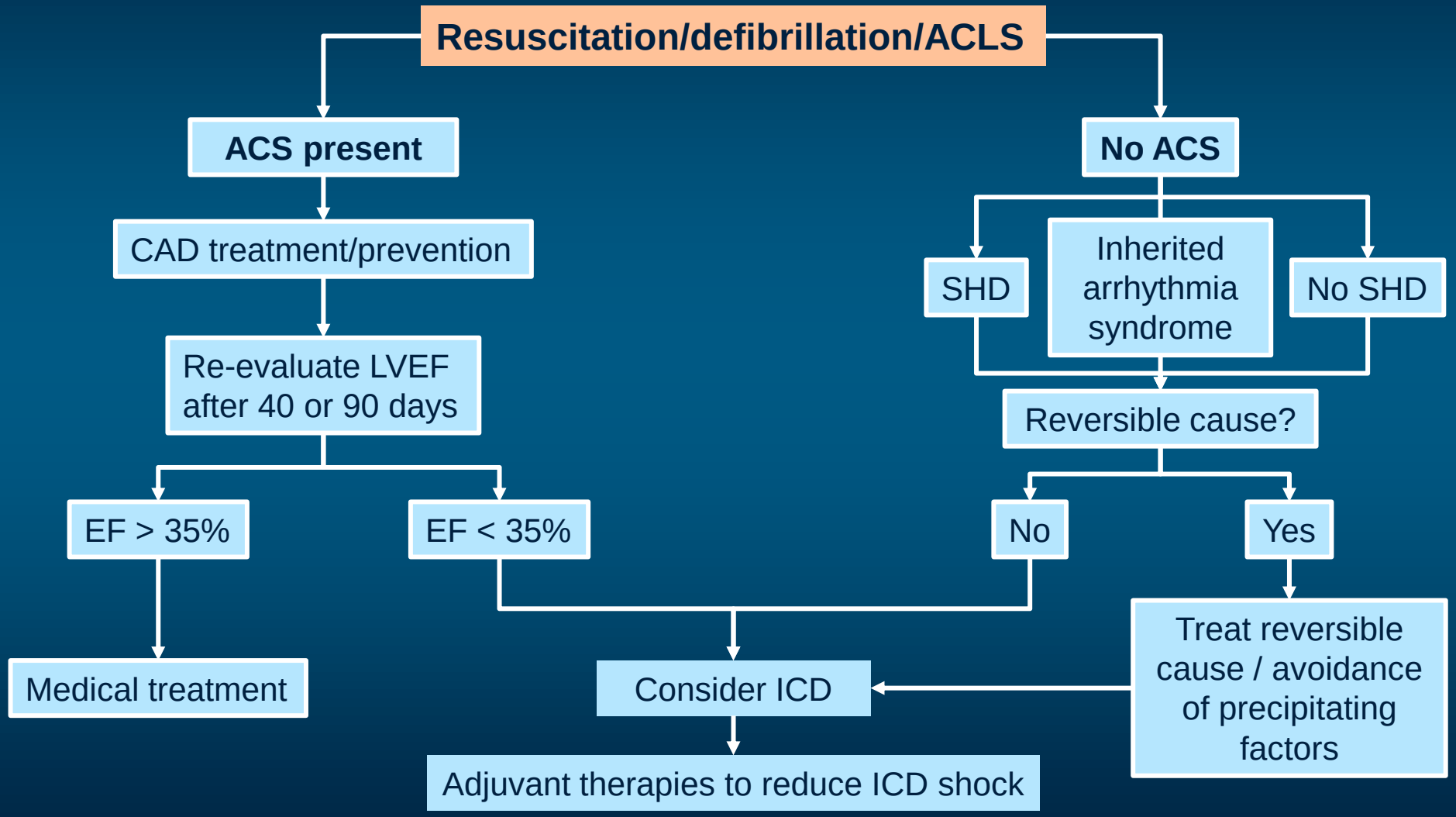
Expert Consensus Recommendations
Sustained Monomorphic Ventricular Tachycardia

1. For patients with SHD and SMVT, an ICD is recommended in the absence of contraindications. (I) LOE A

2. For patients with SHD and recurrent SMVT, specific treatment of VAs with AADs (amiodarone, mexiletine, or sotalol), catheter ablation, and/or antitachycardia pacing (ATP) from an ICD should be considered in addition to an ICD. Treatment of the underlying SHD or ischaemia will in most cases not be sufficient to prevent monomorphic VT (MMVT) recurrences. (IIa) LOE B

3. For patients with an ICD as primary prophylaxis, programming to a long VT detection interval and a high VF detection rate should be considered. (IIa) LOE A.

Sustained Polymorphic Ventricular Tachycardia/Ventricular Fibrillation



Pedersen C T et al. Europace 2014;16:1257-1283

Sustained Polymorphic VT

1. Specific antiarrhythmic therapies, e.g:
   - **Quinidine in patients with idiopathic VF**
   - **Sodium channel blocker therapy in patients with LQTS III**
   - **Intensive autonomic inhibition in patients with catecholaminergic VTs**
   - **Quinidine in Brugada syndrome**

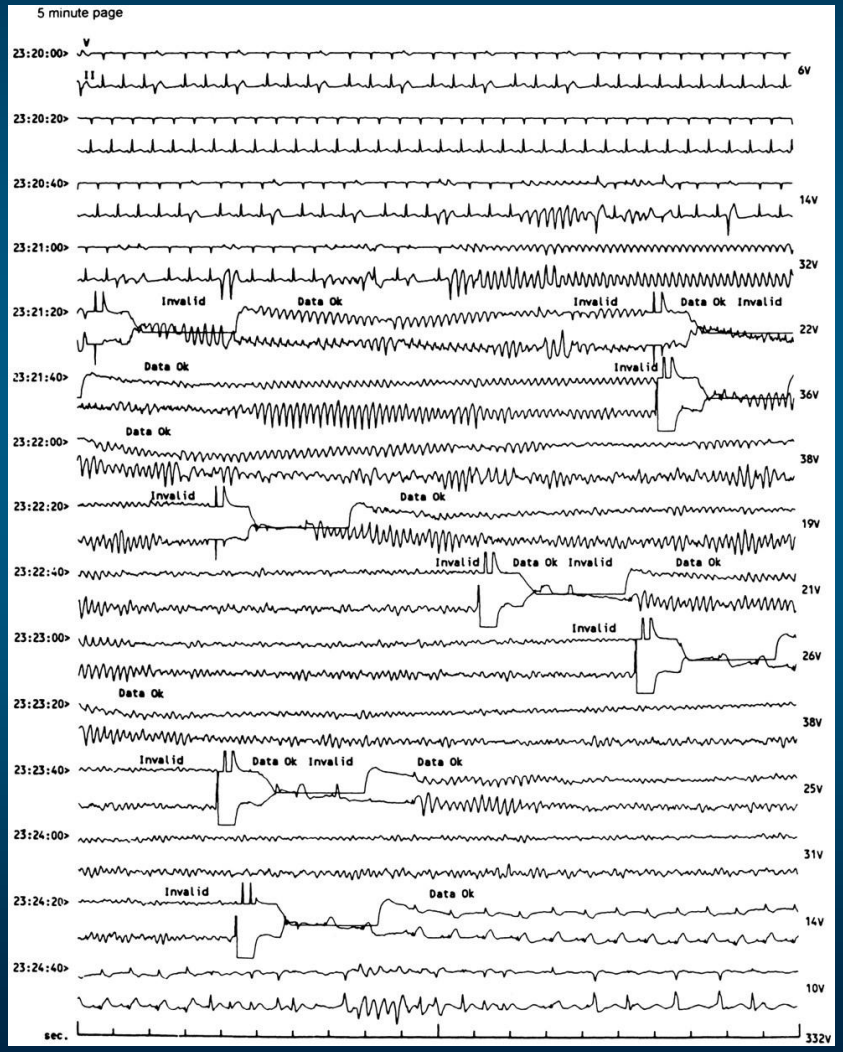
   should be considered …….. as an adjunct ICD therapy in survivors of polymorphic VAs.

1. **Pharmacological suppression of VT/VF storm with beta-adrenergic blockers, amiodarone, and/or lidocaine *should be considered* in all patients. (IIa) LOE C**
2. **For patients with VT/VF storm in whom pharmacological suppression has not been effective and who are unstable, neuraxial modulation, mechanical ventilation, catheter ablation, and/or anaesthesia *may be considered*. (IIb) LOE C**

Pedersen C T et al. Europace 2014;16:1257-1283

Ventricular Storm

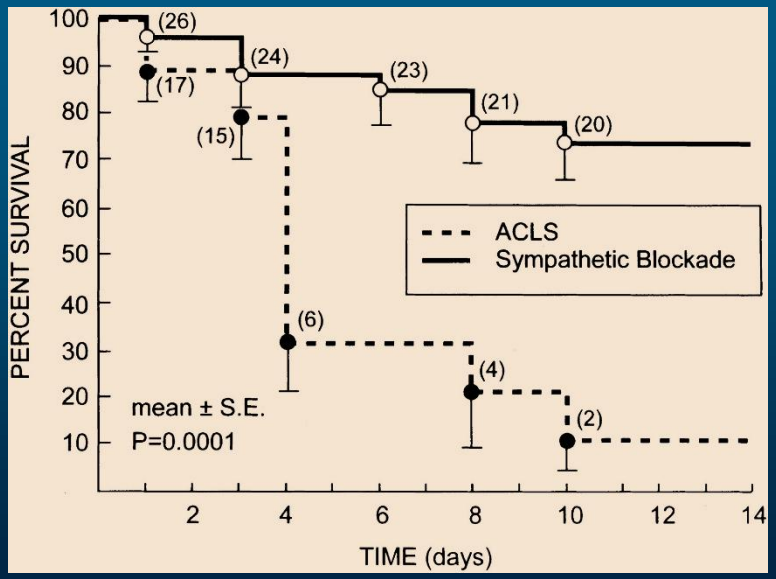
ES associated with a Recent Myocardial infarction



49 patients (36 men, 13 women, mean age 57±10 years)

Group 1 (n=27) received sympathetic blockade treatment: 6 left stellate ganglionic blockade, 7 esmolol, and 14 propranolol.

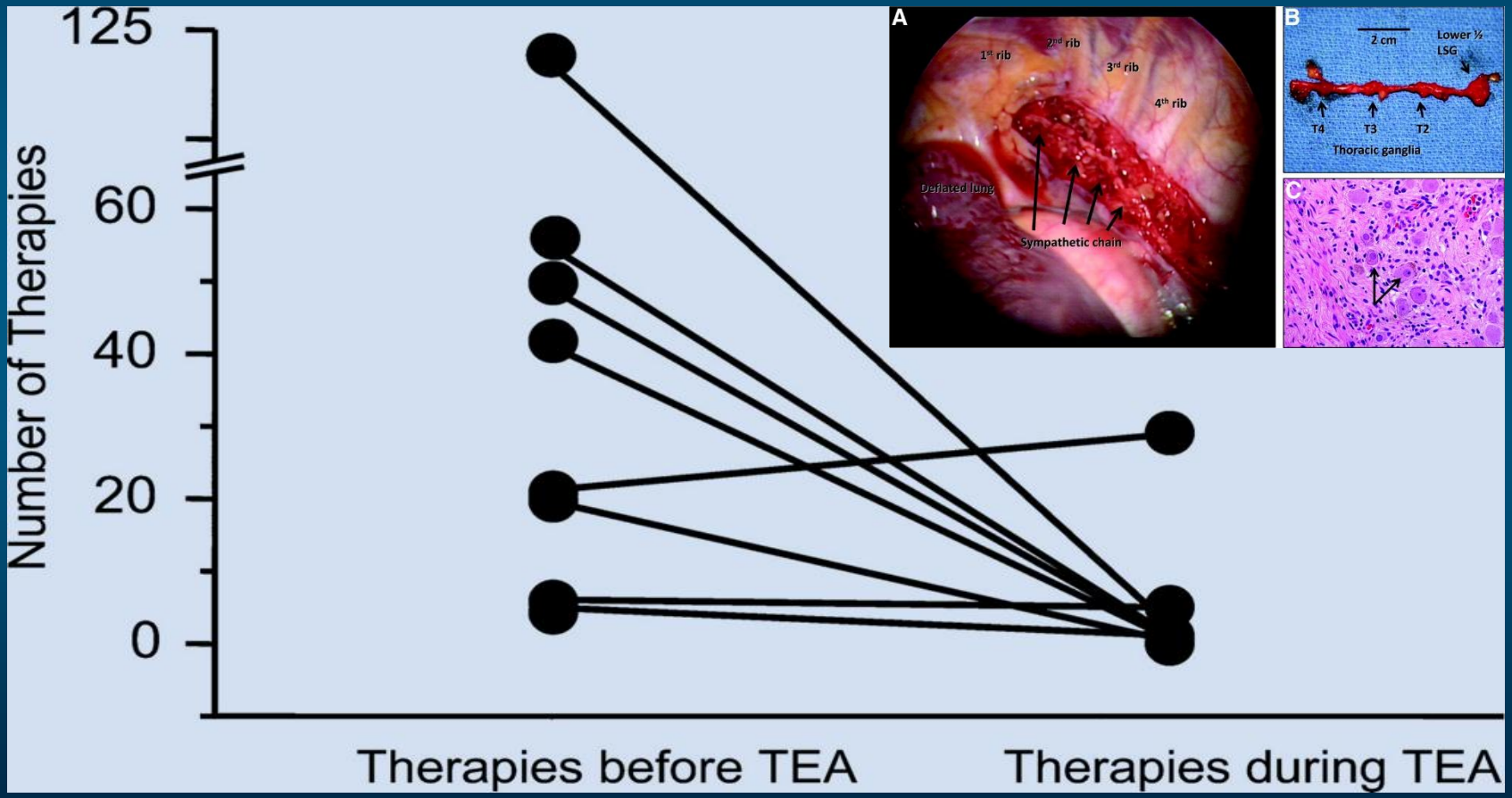
Group 2 (n=22) received antiarrhythmic medication as per ACLS guidelines.



Nademanee K et al. Circulation. 2000;102:742-747

Neuraxial Modulation for Refractory Ventricular Arrhythmias

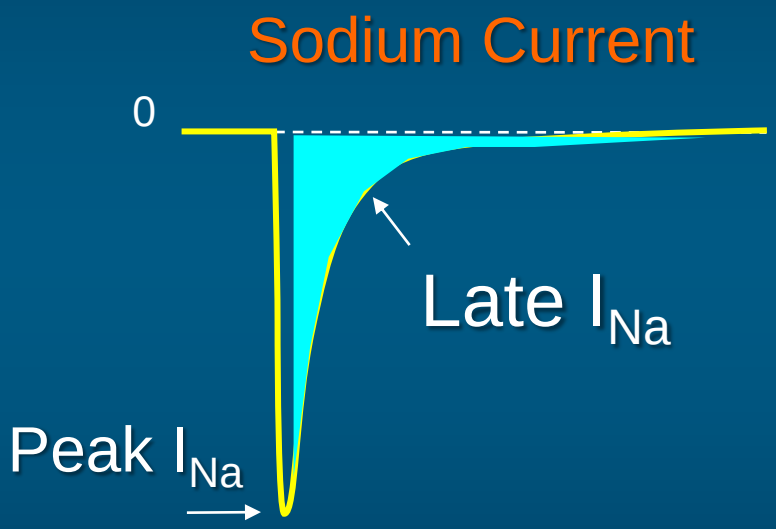
Effect of TEA. Number of VT therapies both before and during TEA infusion



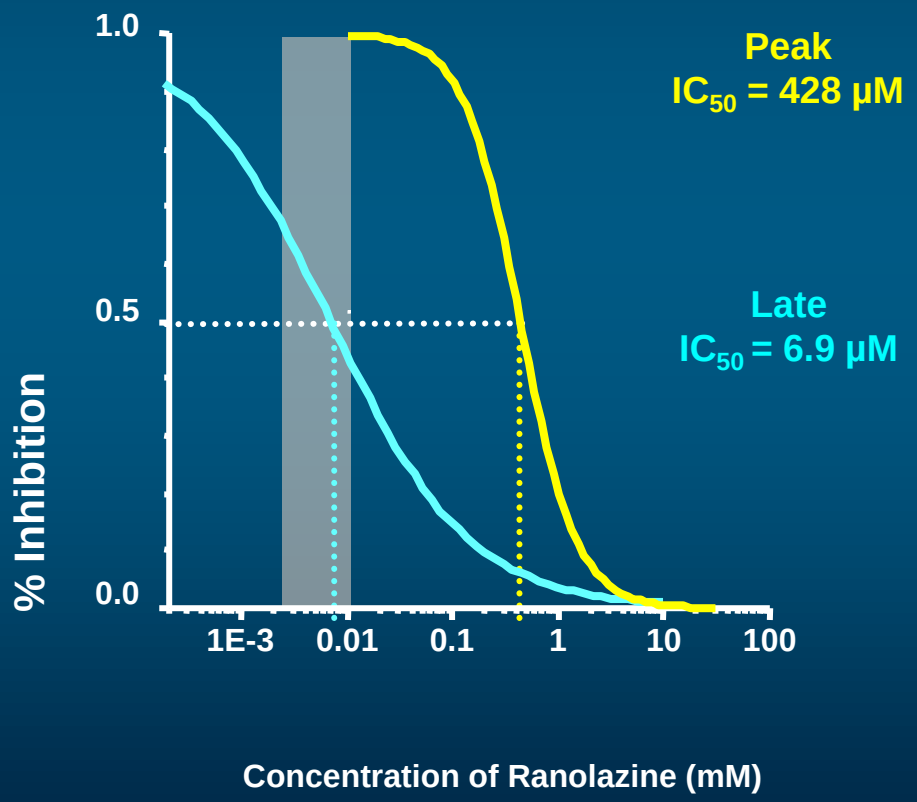
Bourke T et al. Circulation. 2010;121:2255-2262

TEA: thoracic epidural anaesthesia

Ranolazine

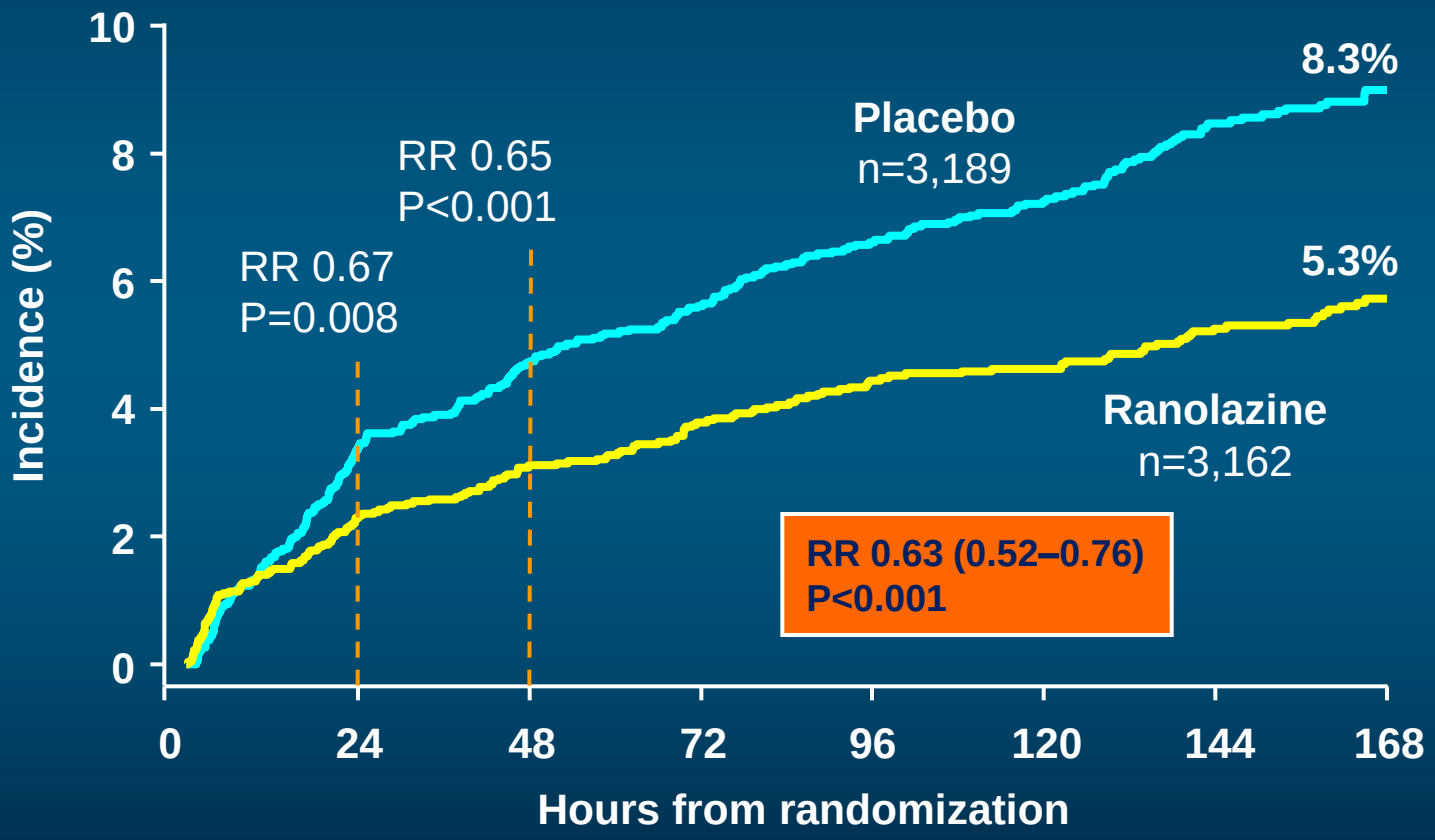


Human Cardiac NaCh in HEK293 Cells



Rajamani S., et al., Eur Heart J. 28(1) 2007

MERLIN-TIMI 36:
Reduction in VT lasting ≥8 beats



MERLIN-TIMI 36=Metabolic Efficiency With Ranolazine for Less Ischaemia in Non-ST-Elevation Acute Coronary Syndrome [MERLIN]-Thrombolysis in Myocardial Infarction [TIMI] 36; VT=ventricular tachycardia

Scirica BM, et al. Circulation 2007;116:1647–52

Ranolazine and Refractory VT

Limited options for patients who present with antiarrhythmic-drug (AAD)-refractory ventricular tachycardia (VT) with recurrent implantable cardioverter defibrillator (ICD) shocks

- 12 patients (age 65 ± 9.7 years) were treated with ranolazine.
- 11 (92%) were male, and 10 (83%) had ischemic heart disease
- Average ejection fraction of 0.34 ± 0.13
- All patients were on a class III AAD (11 amiodarone, one sotalol), with six (50%) receiving mexilitene or lidocaine

5 patients had a prior ablation and 2 were referred for a VT ablation at the index presentation

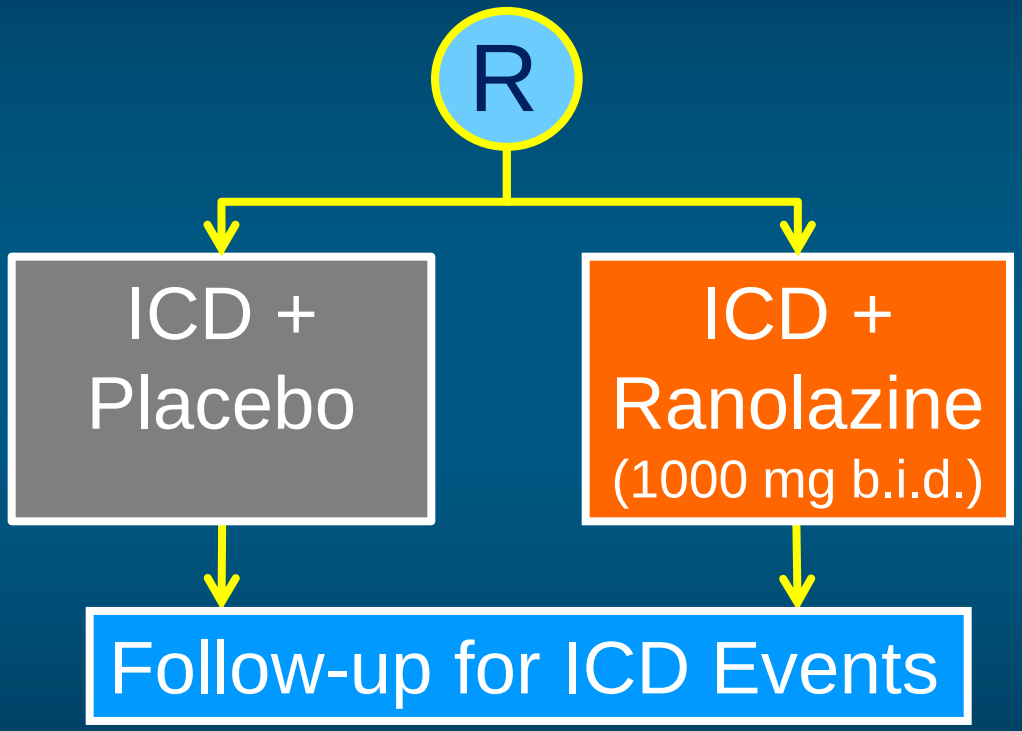
Over a follow-up of 6 ± 6 months, 11 (92%) patients had a significant reduction in VT and no ICD shocks were observed. VT ablation was not required in those referred

Bunch TJ, et al. Pacing Clin Electrophysiol 2011 Dec;34(12):1600-6

The RAID Trial
Ranolazine And Implantable Defibrillator

Ischaemic or non-ischaemic cardiomyopathy qualified for ICD

Wojciech Zareba



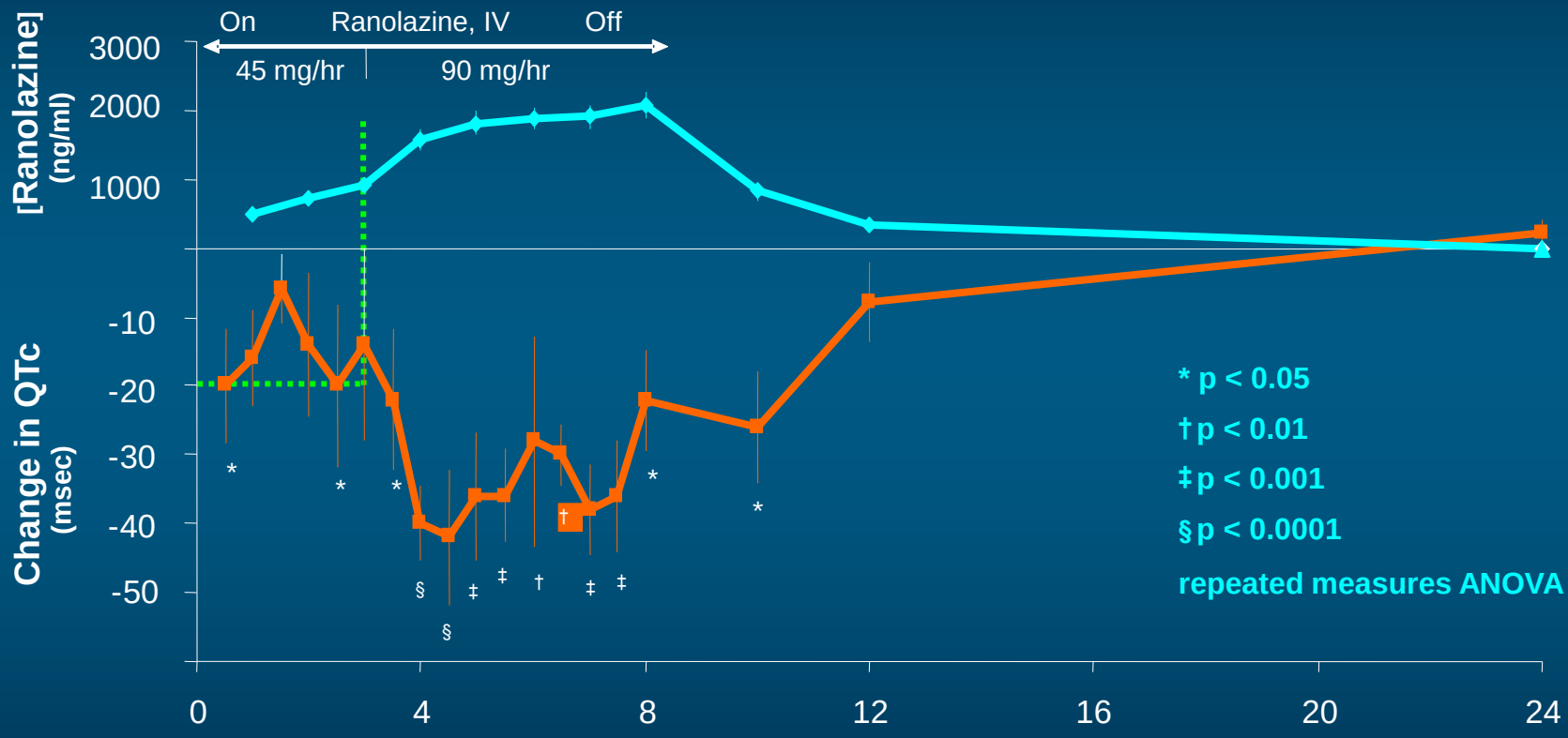
Estimated Enrollment:	1440
Study Start Date:	September 2011
Estimated Study Completion Date:	October 2015

Available at: http://clinicaltrials.gov/ct2/show/NCT01215253

ICD=implantable cardioverter defibrillator

Effect of Ranolazine on QTc interval in LQT3

LQT3 due to KPQ mutation leading to increased SCN5A – activation of Late Na current



Values are mean ± SE from 5 patients

QTc (Fridericia) change from baseline

ΔQTc vs. [RAN] plasma
r = 0.7 ± 0.22
slope = 24.1 msec/1,000 ng/ml
(P = 0.008)

Moss et al., J. Cardiovasc. Electrophysiol., 2008, 19(12):1289-1293

Conclusions

- The management of ventricular tachycardia involves three major modalities of treatment: medical, device and ablation and very often hybrid therapy is required
- Antiarrhythmic drugs have been recognized to be inadequately effective, and complicated by negative inotropic and proarrhythmic effects
- Device based therapy is often needed as a safety net to allow antiarrhythmic therapy, conversely antiarrhythmic therapy may be needed to reduce device interventions
- No new drugs have been developed for management of ventricular arrhythmias, but ranolazine and new late sodium channel blockers are being investigated at present
- For patient with sustained MMVT delayed intervention (30-60 seconds) by devices is recommended