Novel Methods to Stratify Arrhythmia Risk Using Digital Electrocardiography

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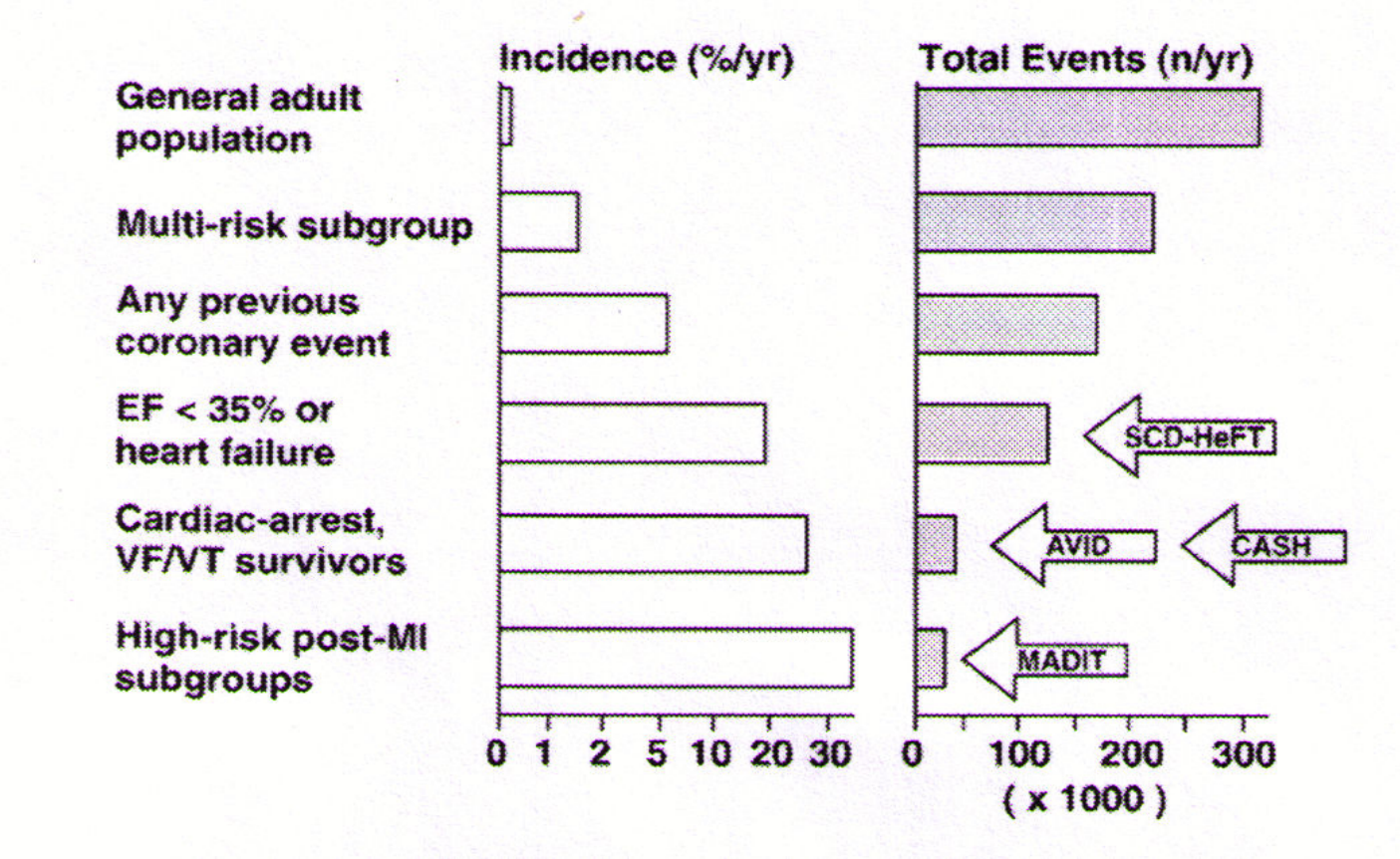
Target Population for Risk Stratification

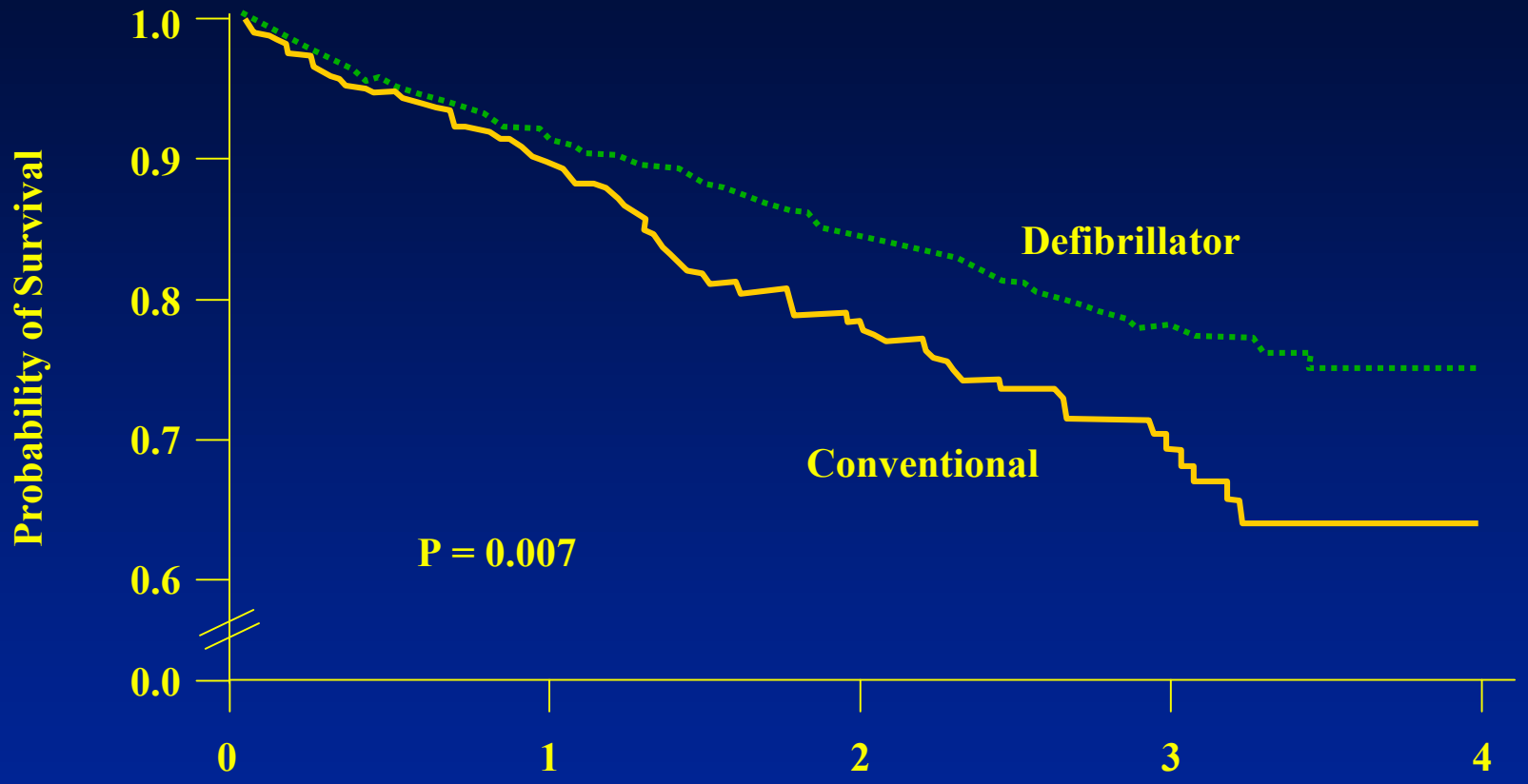


MADIT-II Inclusion Criteria

- Q-wave MI $\geq$ 4 weeks
- LVEF $\leq$ 0.30
- $\geq$ 21 years of age; no upper age limitation
- No requirement for NSVT or EPS

Moss AJ. *N Engl J Med*. 2002;346:877-83.

MADIT-II Survival Results



No. At Risk					
Defibrillator	742	502 (0.91)	274 (0.94)	110 (0.78)	9
Conventional	490	329 (0.90)	170 (0.78)	65 (0.69)	3

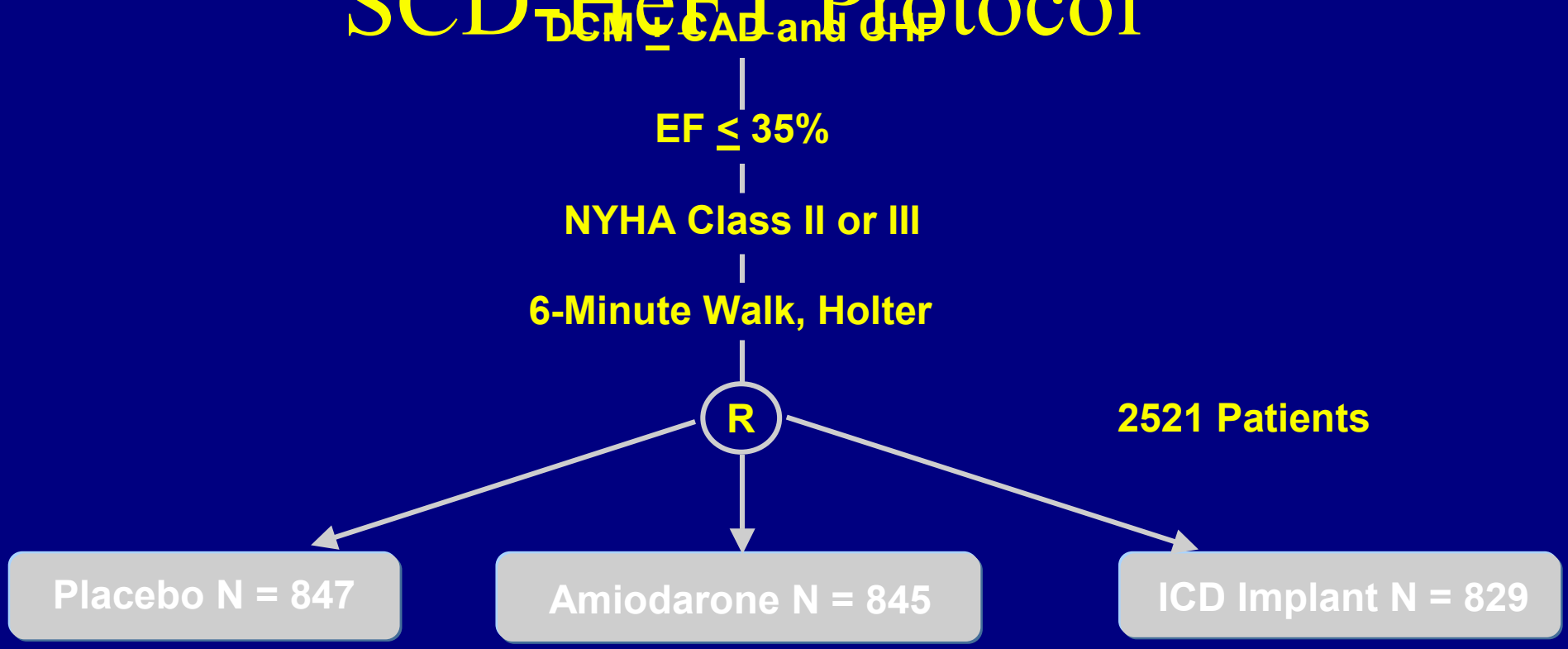
Moss AJ. *N Engl J Med*. 2002;346:877-83.

SCD-HeFT Inclusion Criteria

- Symptomatic CHF (NYHA Class II and III) due to ischemic or non-ischemic dilated cardiomyopathy
- LVEF ≤ 35%
- ≥ 18 years of age; no upper age limitation
- CHF ≥ 3 months
- On optimal medical therapy for > 3 months
  - Appropriate dose of ACE-I
  - Beta blocker, if tolerated

Bardy GH. *N Engl J Med.* 2005;352:225-237.

SCD-HeFT Protocol

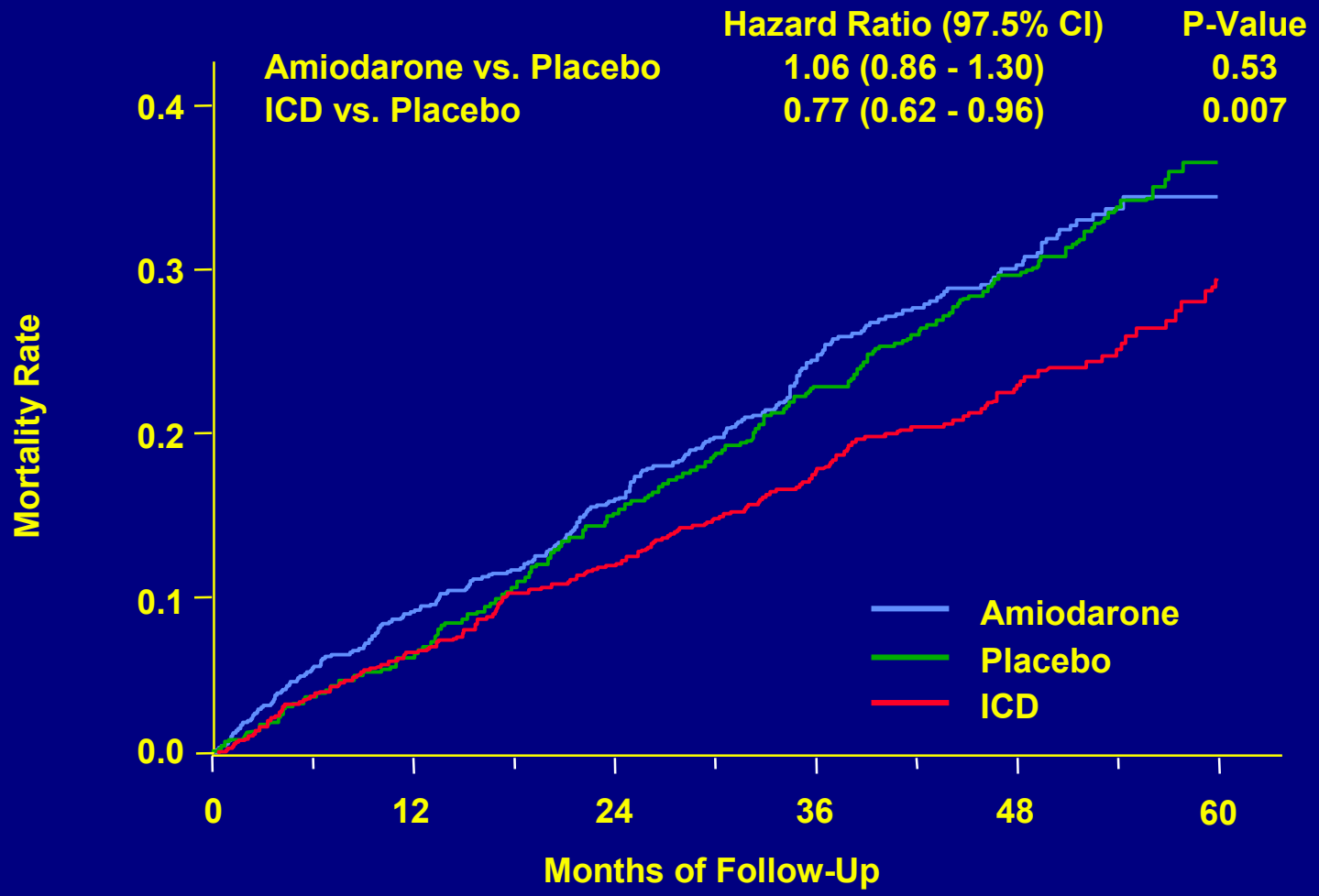


Minimum of 2.5 years follow-up required

45 months average follow-up
Optimized βB, ACE-I, Diuretics

Bardy GH. *N Engl J Med.* 2005;352:225-237.

SCD-HeFT Mortality Rate Overall Results



No. at Risk						
Amiodarone	845	772	715	484	280	97
Placebo	847	797	724	505	304	89
ICD	829	778	733	501	304	103

Bardy GH. *N Engl J Med.* 2005;352:225-237.

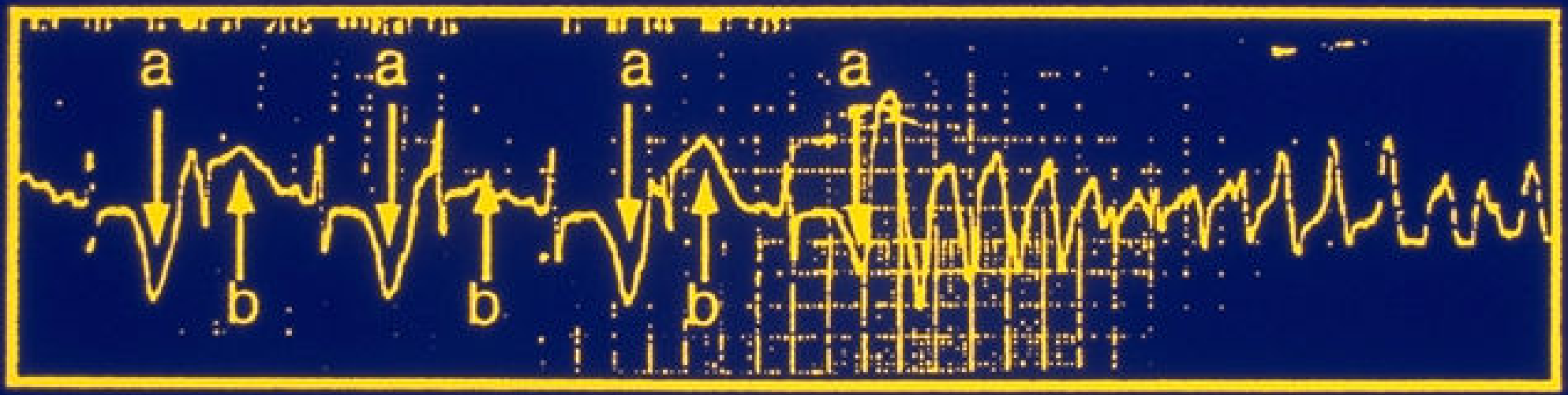
Why Not Implant an ICD?

- Cost considerations
- Inappropriate shocks
- Recalls of pulse generators and leads
- Implant-related complications
- Minority of patients in MADIT-II and SCD-HeFT received appropriate shocks
  - Risk stratification needed to identify low risk patients that may not require ICDs

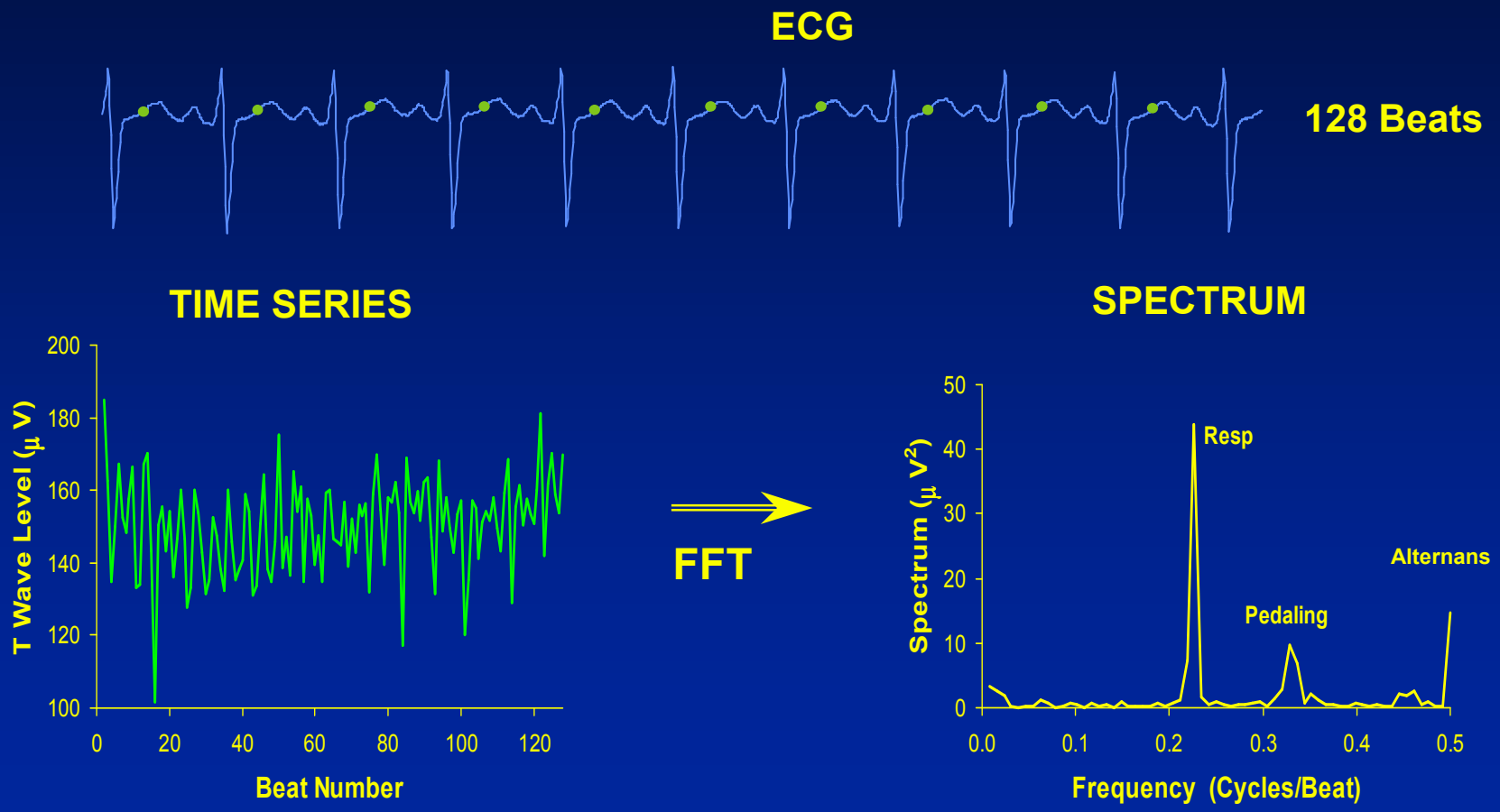
Risk Stratification Methods

- T wave alternans
- Holter-based methods
  - Heart rate variability
  - Heart rate turbulence
  - QT variability (QT length)
  - T wave variability (T wave amplitude)
  - Signal-averaged ECG

Electrical Alternans Preceding Ventricular Fibrillation

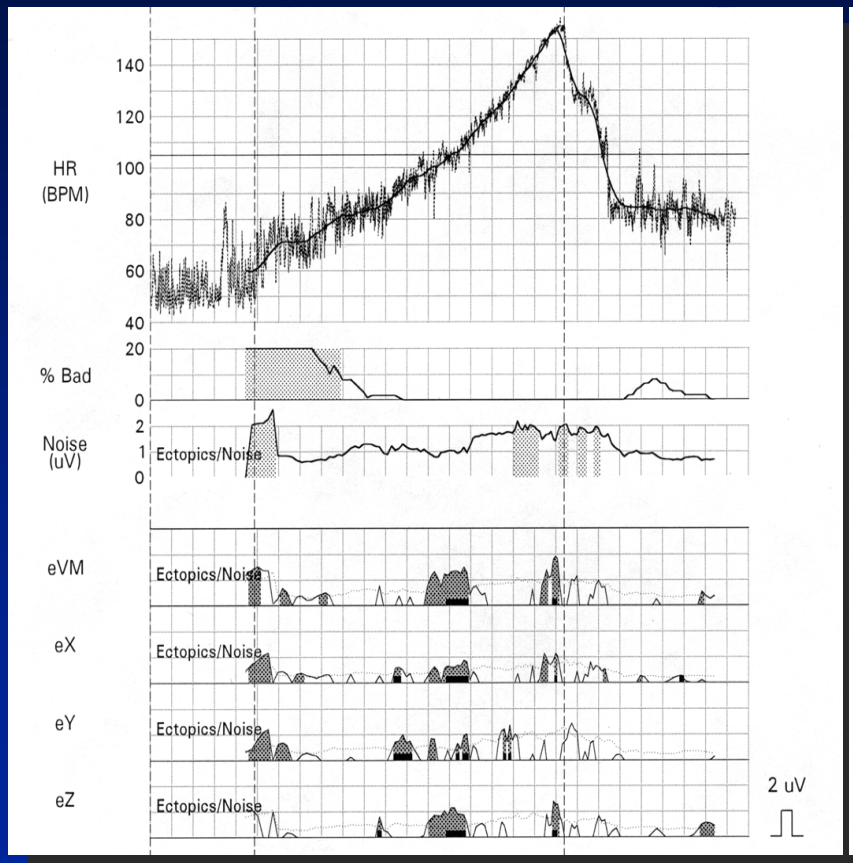


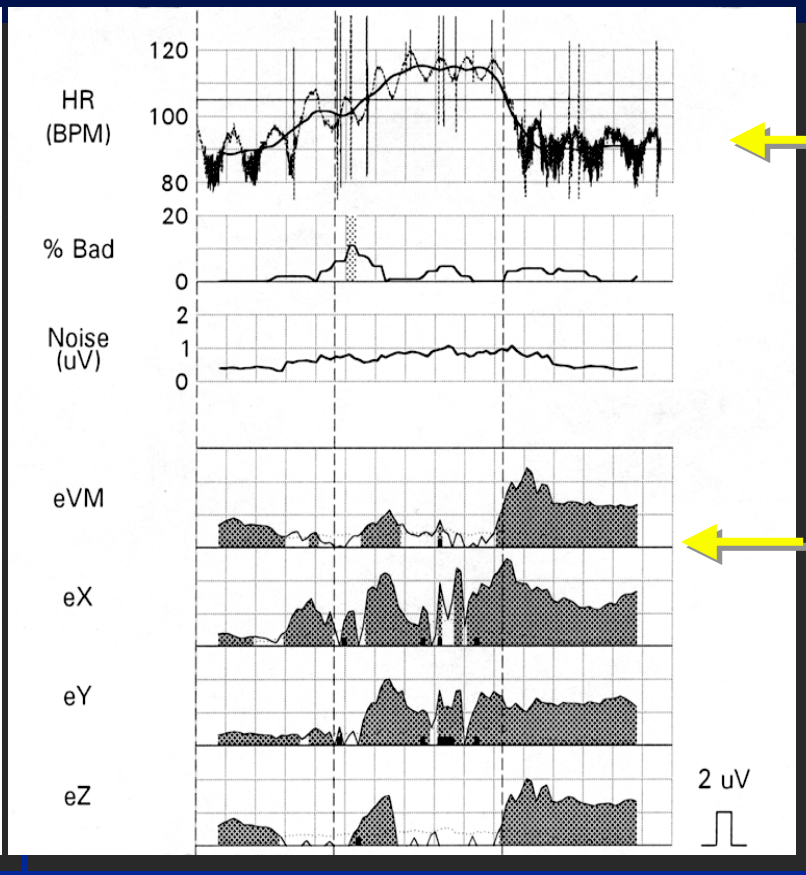
T-Wave Alternans Measurement: Spectral Method



Negative

Positive

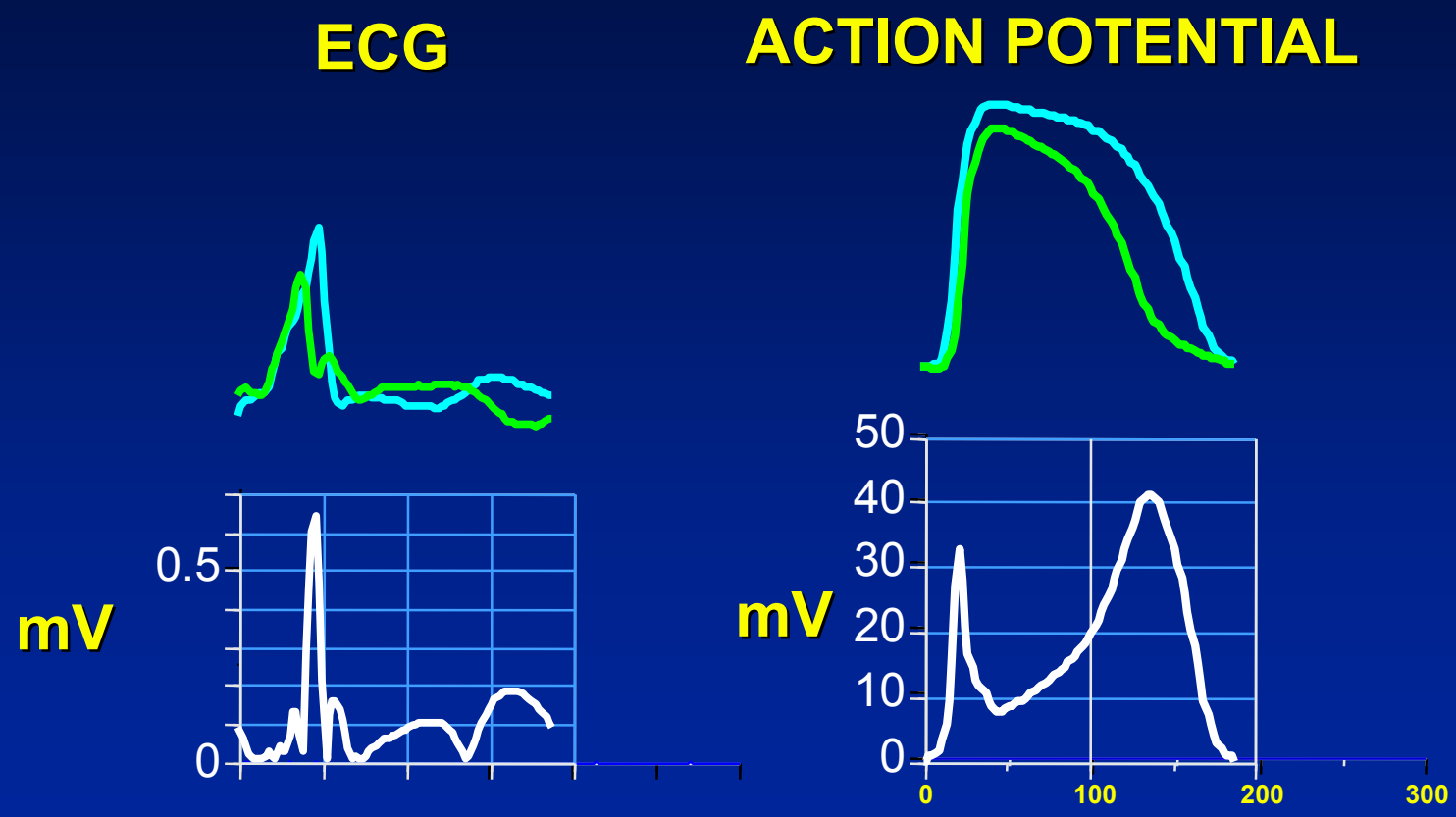




Heart Rate

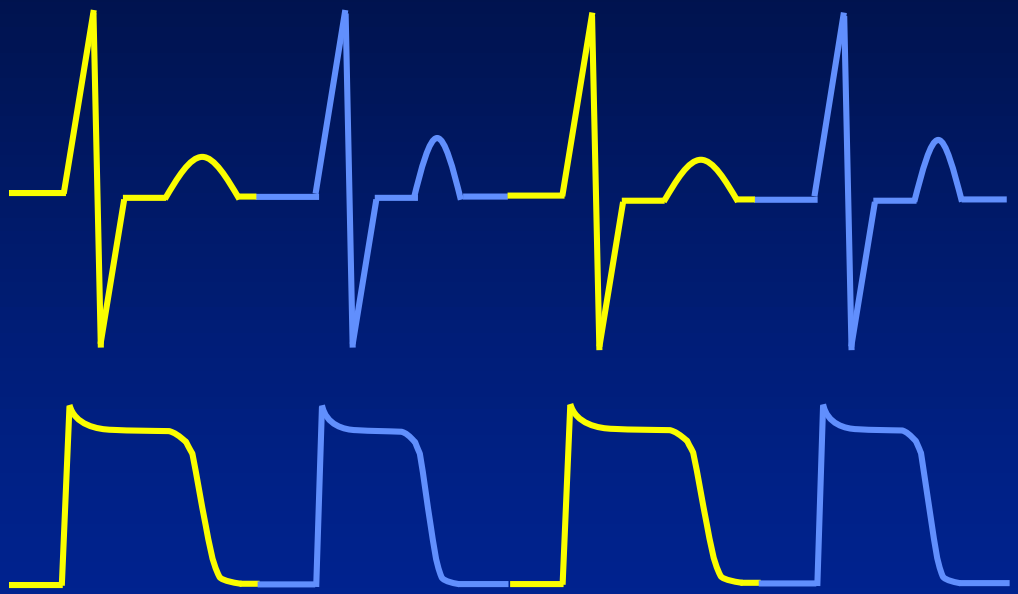
T-Wave Alternans

RELATION BETWEEN ECG AND ACTION POTENTIAL



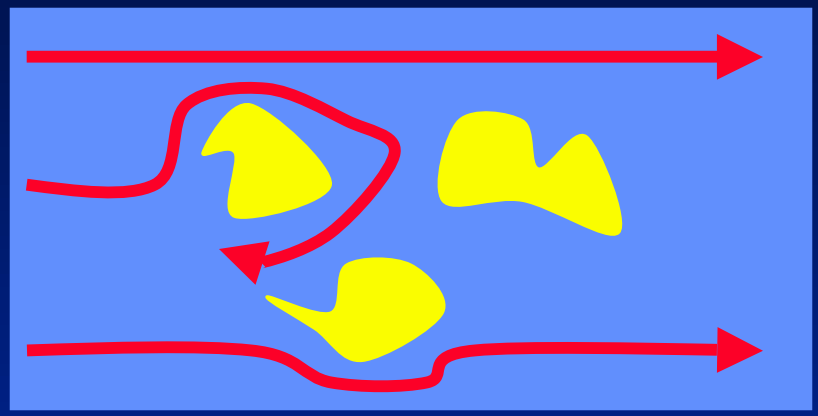
Pastore et al. Circulation 1999;99:1385-1394

Mechanism Linking TWA to Ventricular Arrhythmias



Long APD Short APD Long APD Short APD

Action Potential Alternans Leads to T-Wave Alternans



Long APD Region

Short APD Region

Spatially Discordant Alternans Leads to Dispersion of Recovery, Wave Front Fractionation, and Reentry

University of Maryland ICM Study

- Prospective evaluation of 251 patients
- Inclusion Criteria
  - Documented CAD
  - LVEF $\leq$ 0.40
  - Normal Sinus Rhythm
  - Indication for EPS
- Exclusion Criteria
  - Atrial fibrillation or frequent ectopy
  - Antiarrhythmic drug use at time of study

Rashba et. al., JCE 2002; 13: 845-850

TWA Testing Modality

- Choice of testing modality was determined by exercise capacity as well as patient and physician preference, since exercise and pacing were reported previously to yield concordant results
- Testing modality
  - Exercise only (n= 72)
  - Pacing only (n=107)
  - Both tests (n= 71)

Patient Population

	Pacing	Exercise
Age (yrs)	66±11	64±10
Male (%)	81	79
Mean EF (%)	26±8	28±8
NYHA II/III (%)	88	92
ICD (%)	68	71
Outcome event (%)	35	35

p = NS for all comparisons

Comparison of Exercise and Pacing TWA

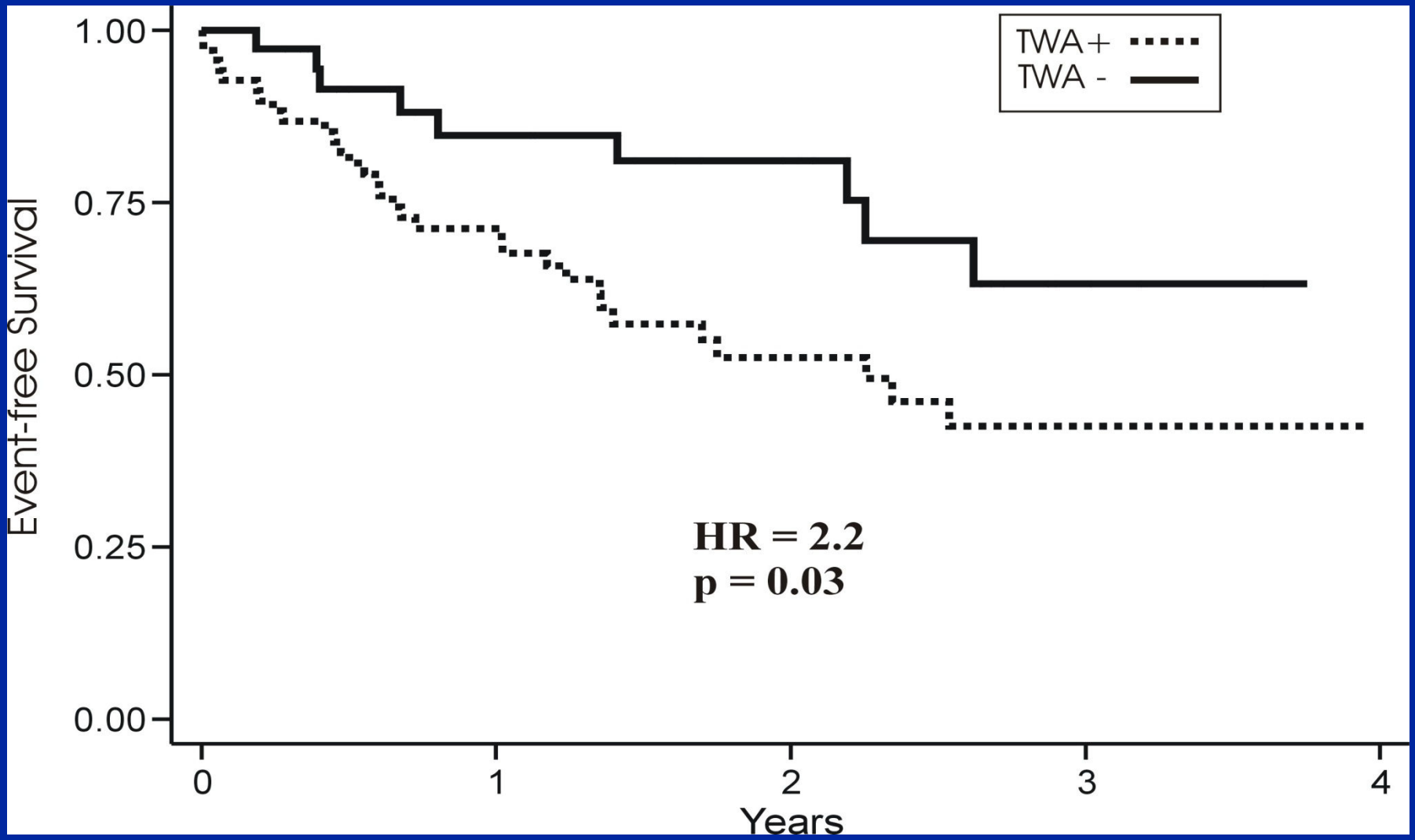
TWA Results	Pacing (n=178)	Exercise (n=143)	
Positive (%)	65	49	
Negative (%)	27	26	
Indeterminate (%)	8	25	*

* $p < 0.001$

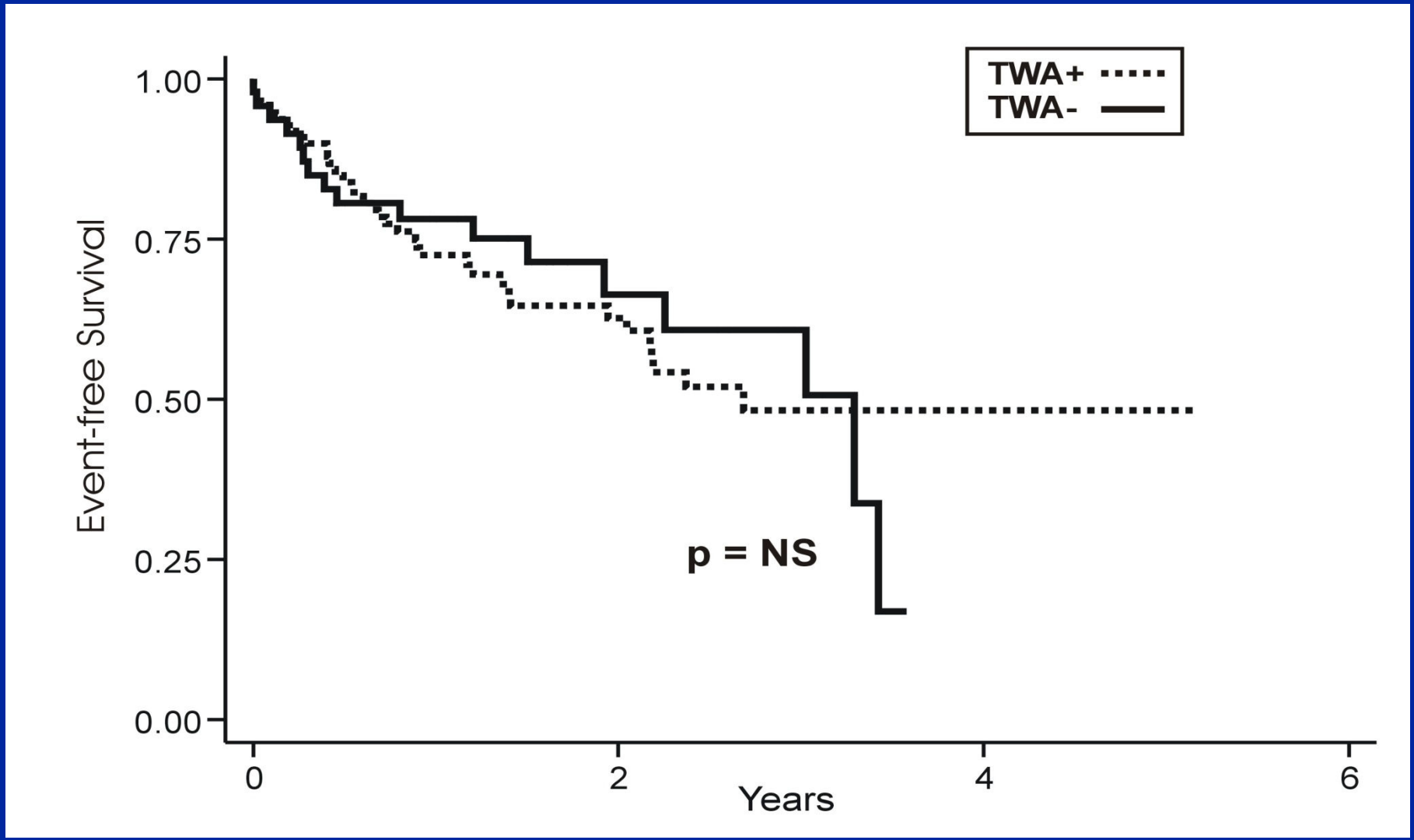
Clinical Follow-up

- Mean follow-up 499 ± 395 days
- There were 88 events (35% of pts)
  - **Appropriate ICD therapy 50**
  - **VT/VF 2**
  - **Death 35**
  - **Cardiac arrest 1**

Exercise TWA Prediction of Endpoints



Pacing TWA Prediction of Endpoints

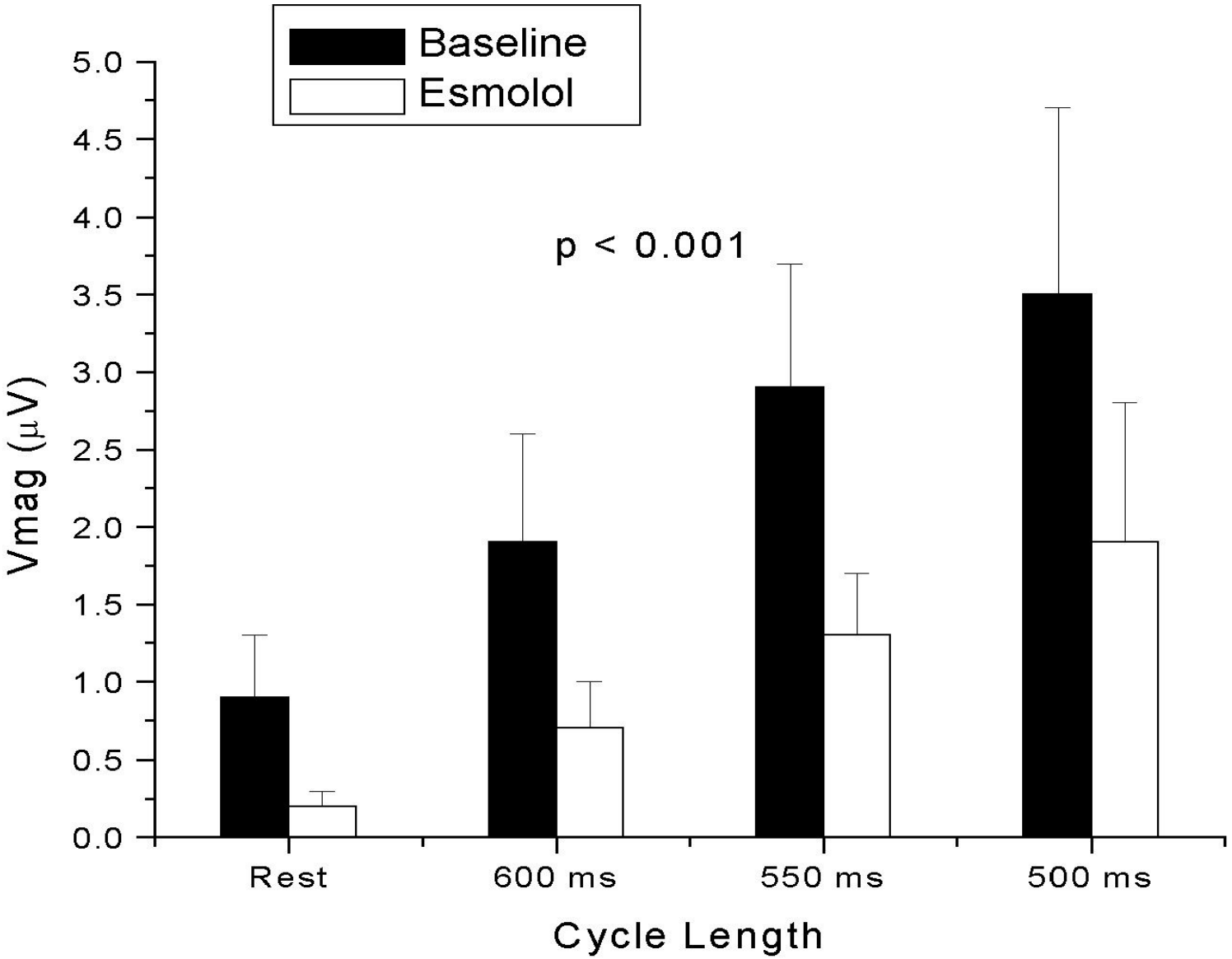


Effects of selective autonomic blockade on TWA

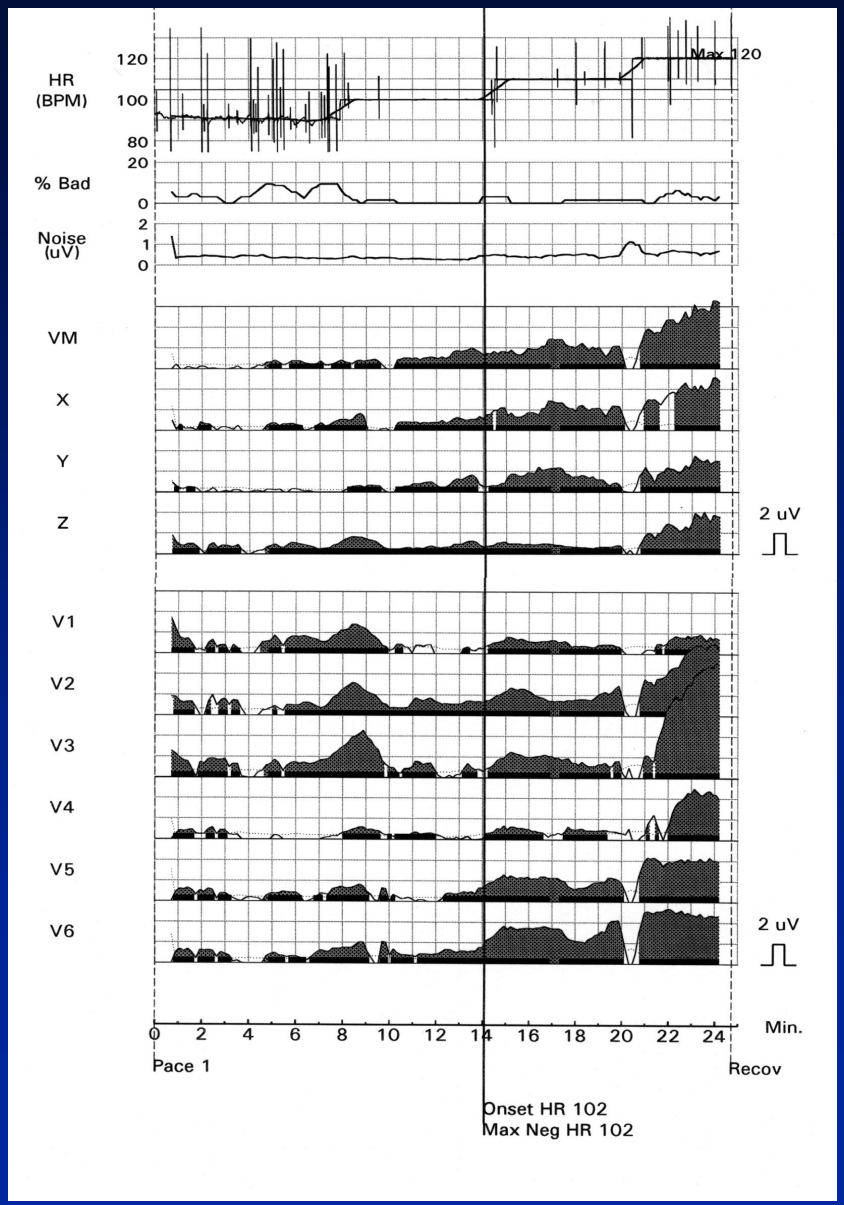
Methods

- Prospective evaluation of 74 patients with inducible SMMVT
- 14 pts excluded due to indeterminate TWA tests
- TWA measured after completion of EPS by spectral method (Cambridge Heart Inc.)
- Oral beta blockers withheld > 24 hours
- TWA measured during atrial pacing (100, 109, 120 bpm) at baseline and following infusion of either atropine (n=20), esmolol (n=20), or no drug (n=20, control)

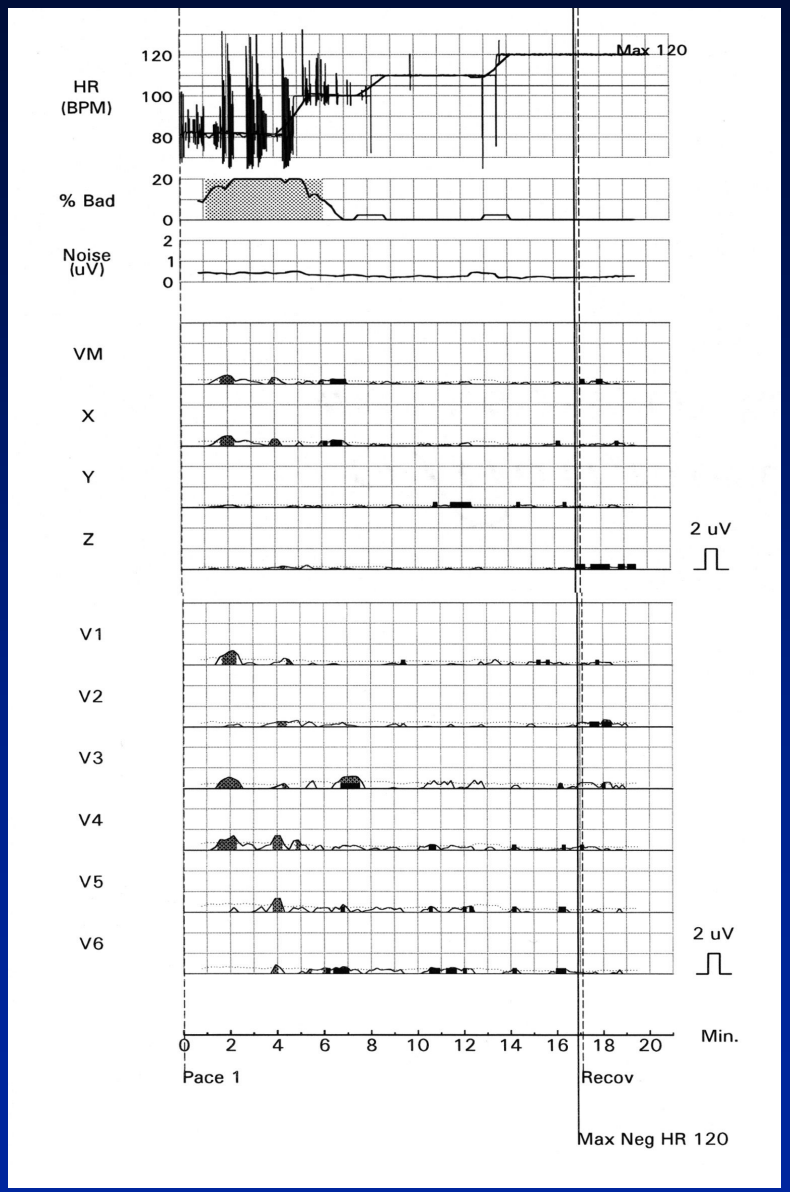
Rashba et. al., Circulation 2002; 105: 837-42


Baseline
Esmolol
p < 0.001
Vmag (μV)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Rest
600 ms
550 ms
500 ms
Cycle Length

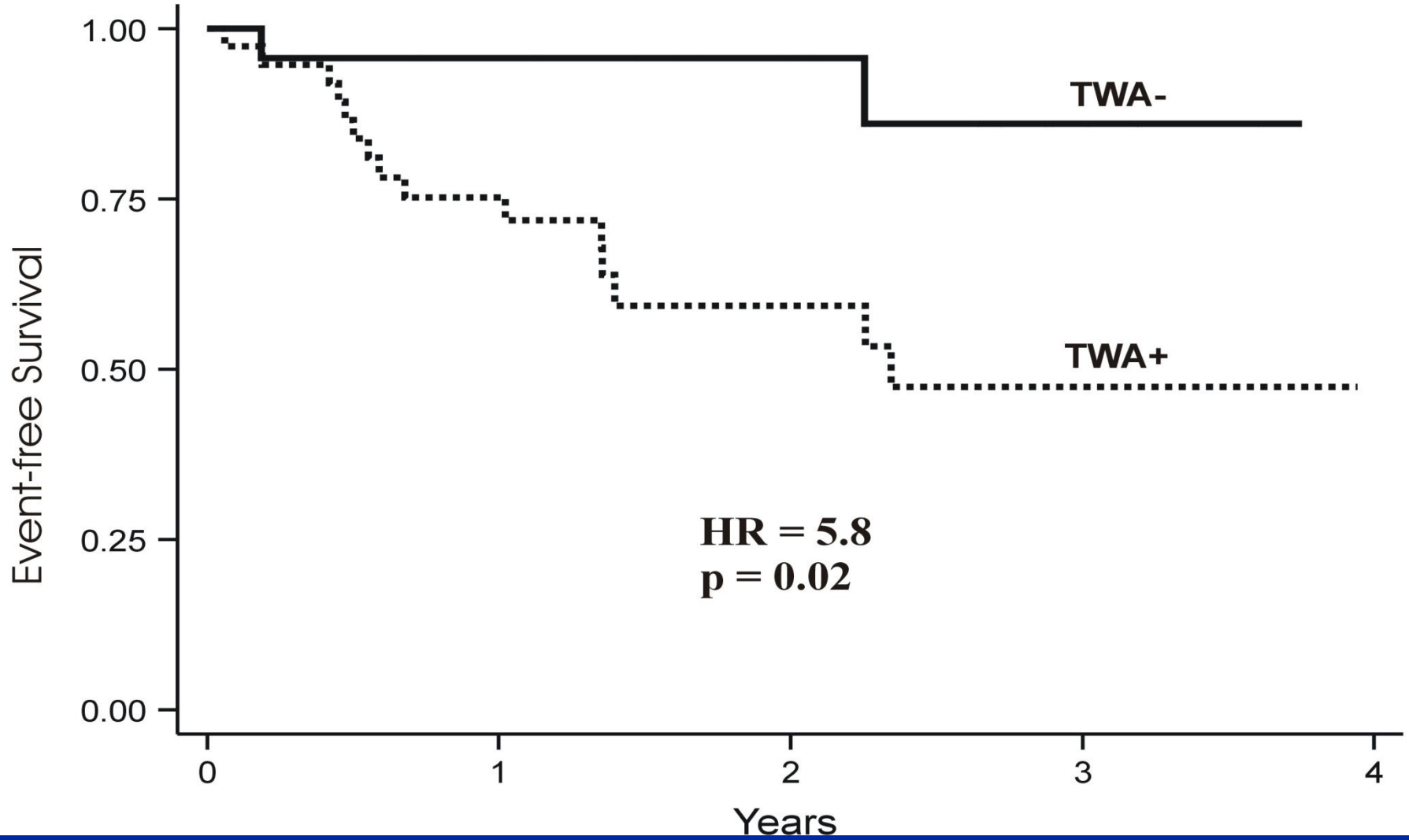
Baseline



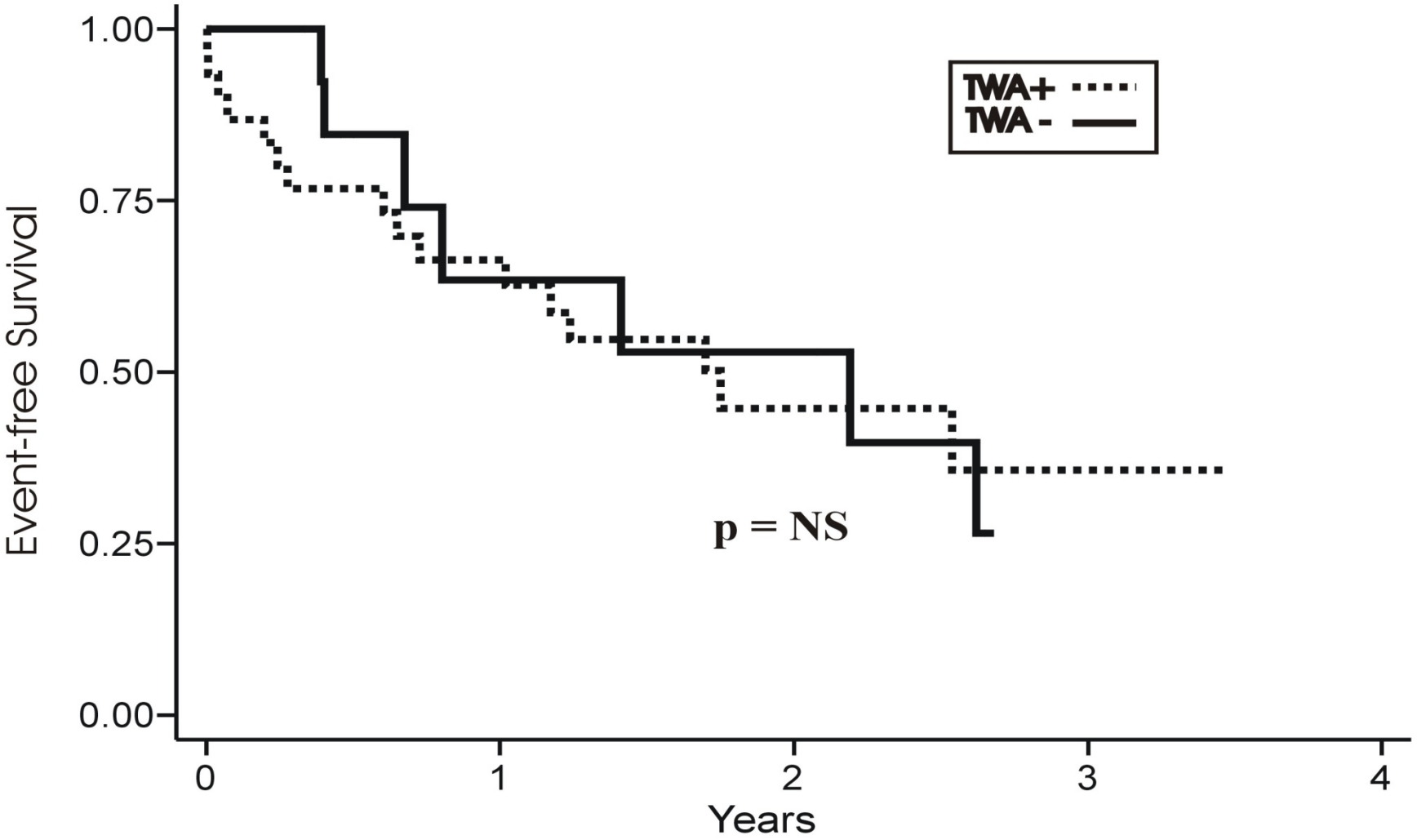
Esmolol



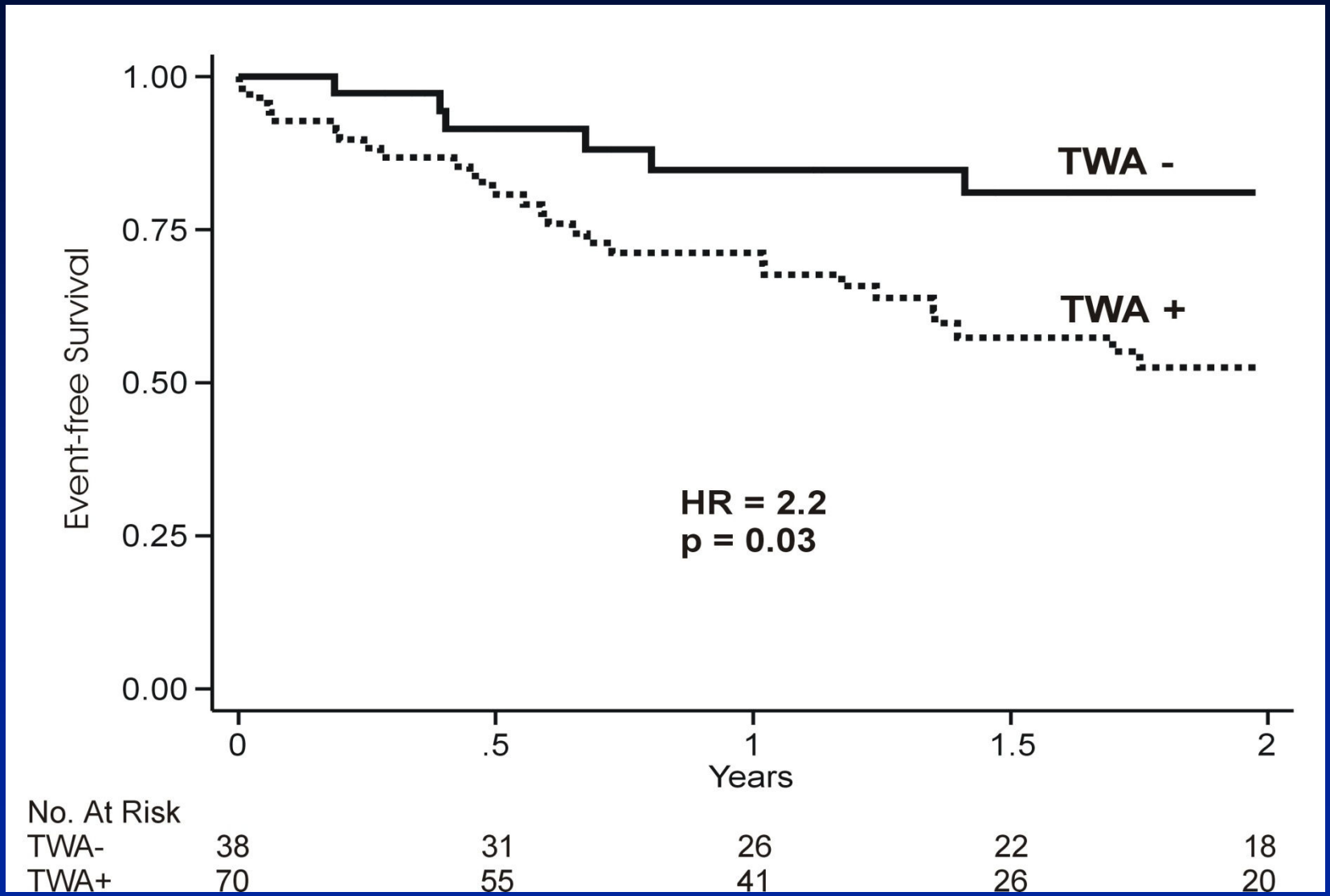
Predictive Value of TWA (QRS < 120 ms)



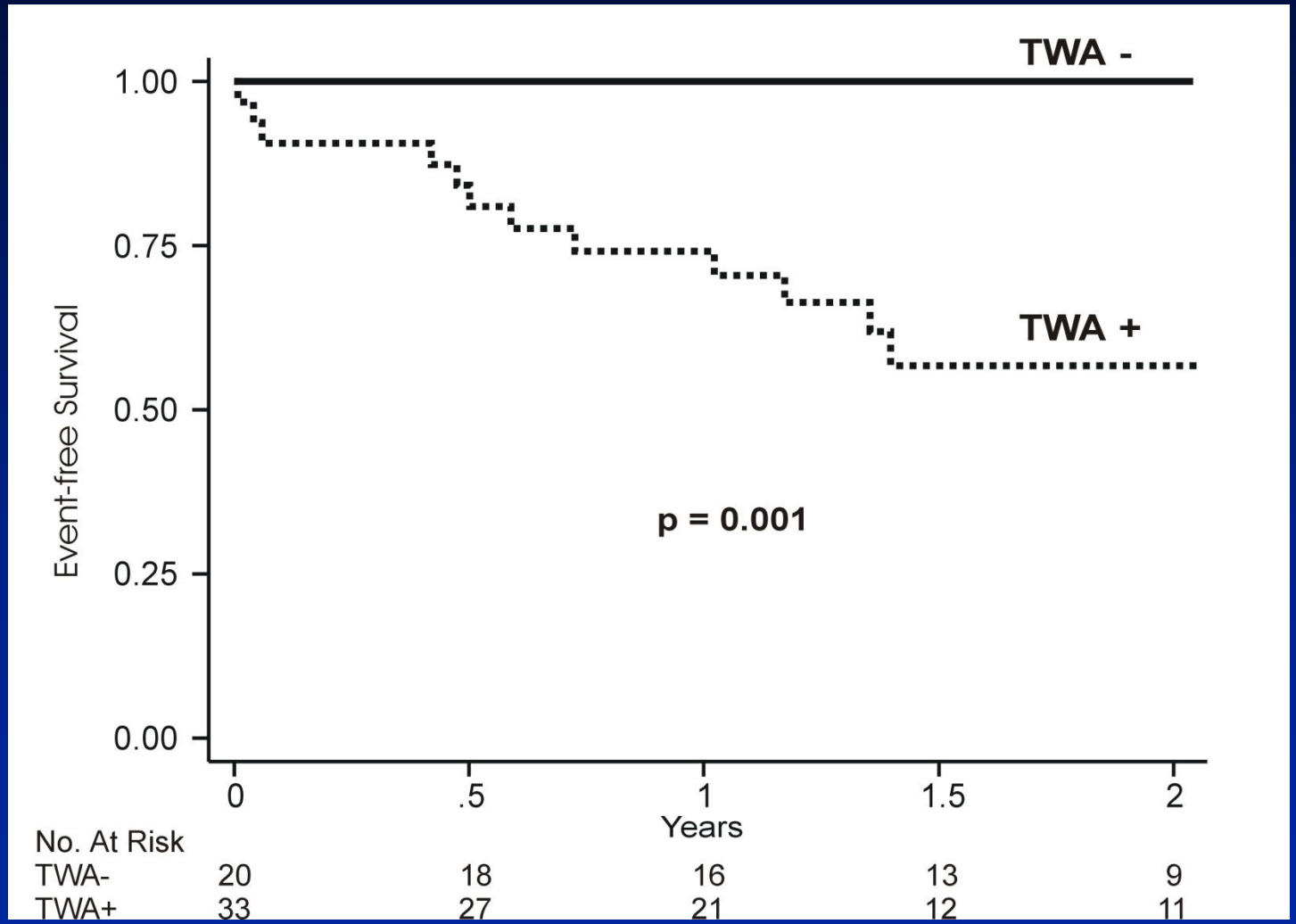
Predictive Value of TWA (QRS ≥ 120 ms)



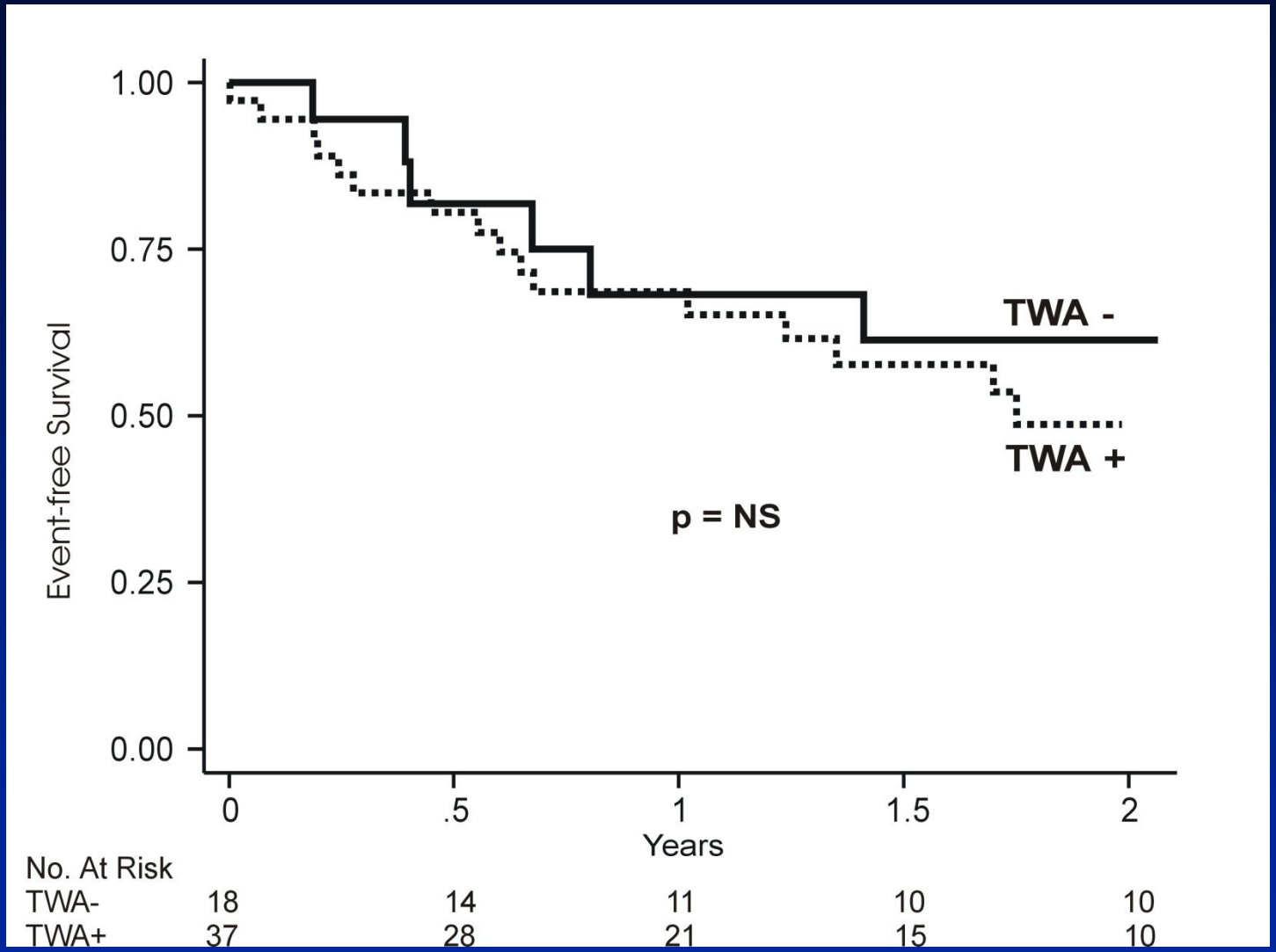
Prognostic value of TWA



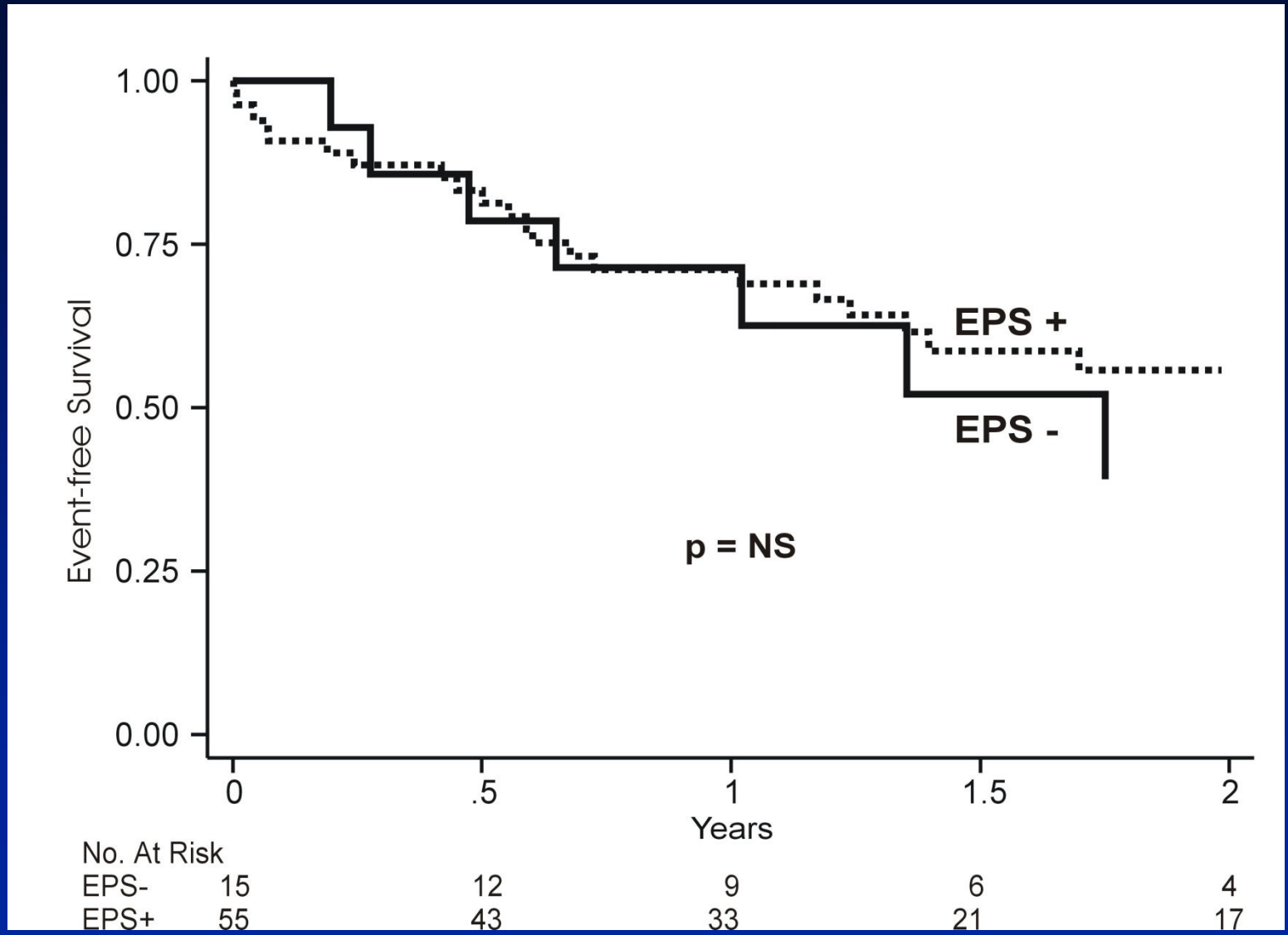
TWA, if LVEF 30-40%



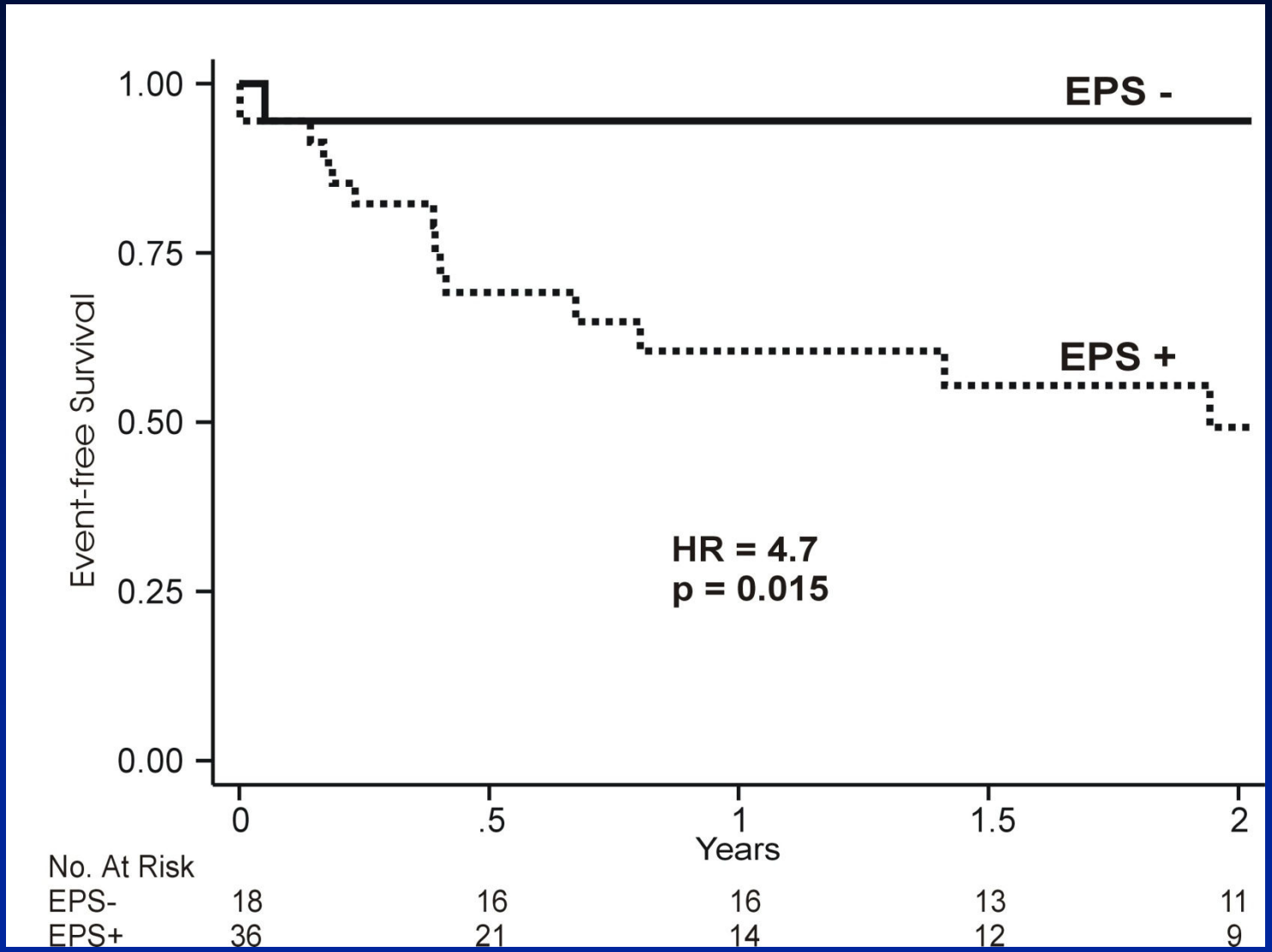
TWA, if LVEF < 30%



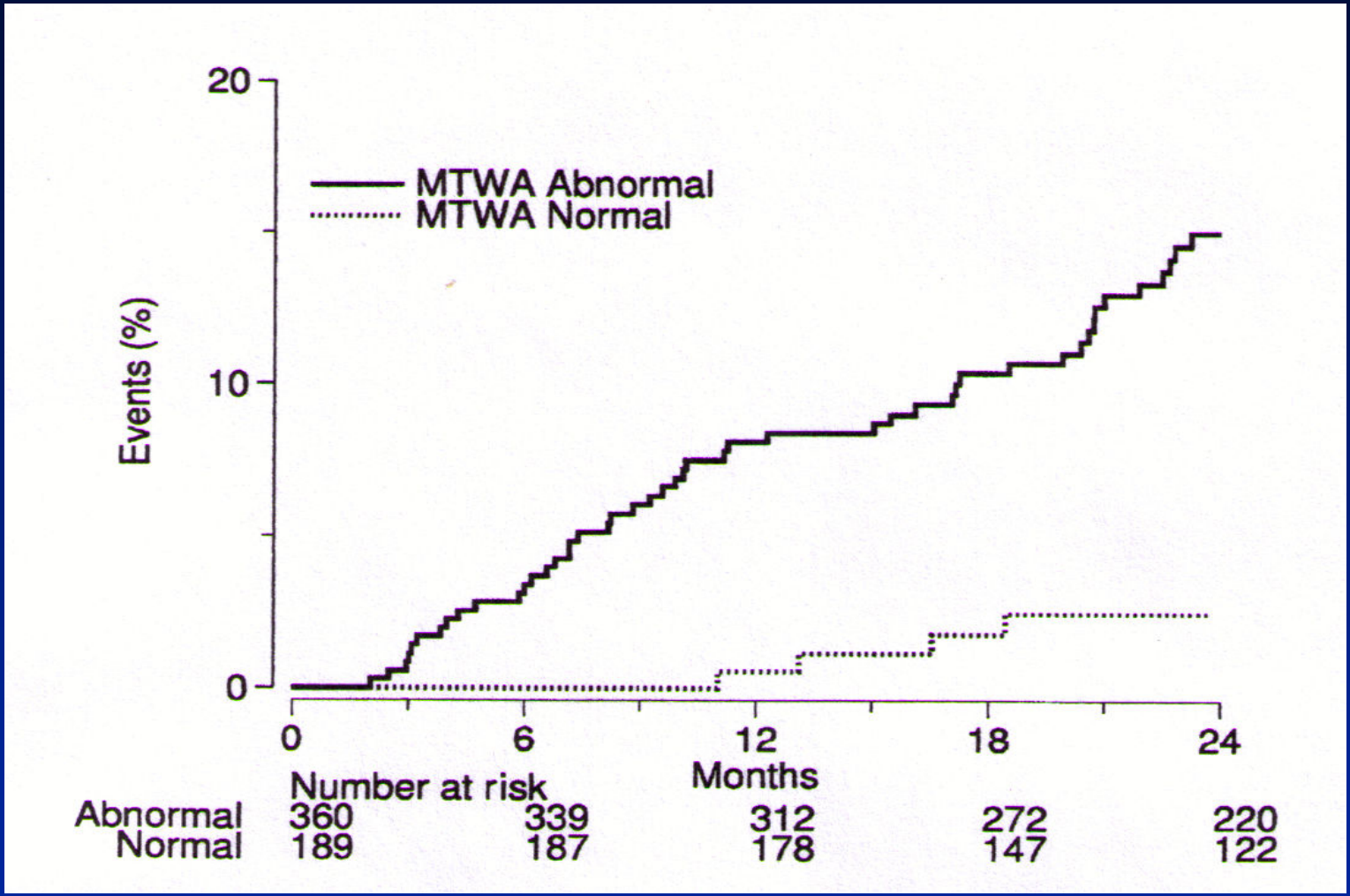
EPS, if TWA+


1.00
0.75
0.50
0.25
0.00
Event-free Survival
EPS +
EPS -
p = NS
0
.5
1
1.5
2
Years
No. At Risk
EPS- 15 12 9 6 4
EPS+ 55 43 33 21 17

EPS, if TWA- and LVEF < 30 or IND TWA



TWA in CHF



Bloomfield et. al. JACC 2006; 47: 456-63

Is TWA Testing All That We Need?

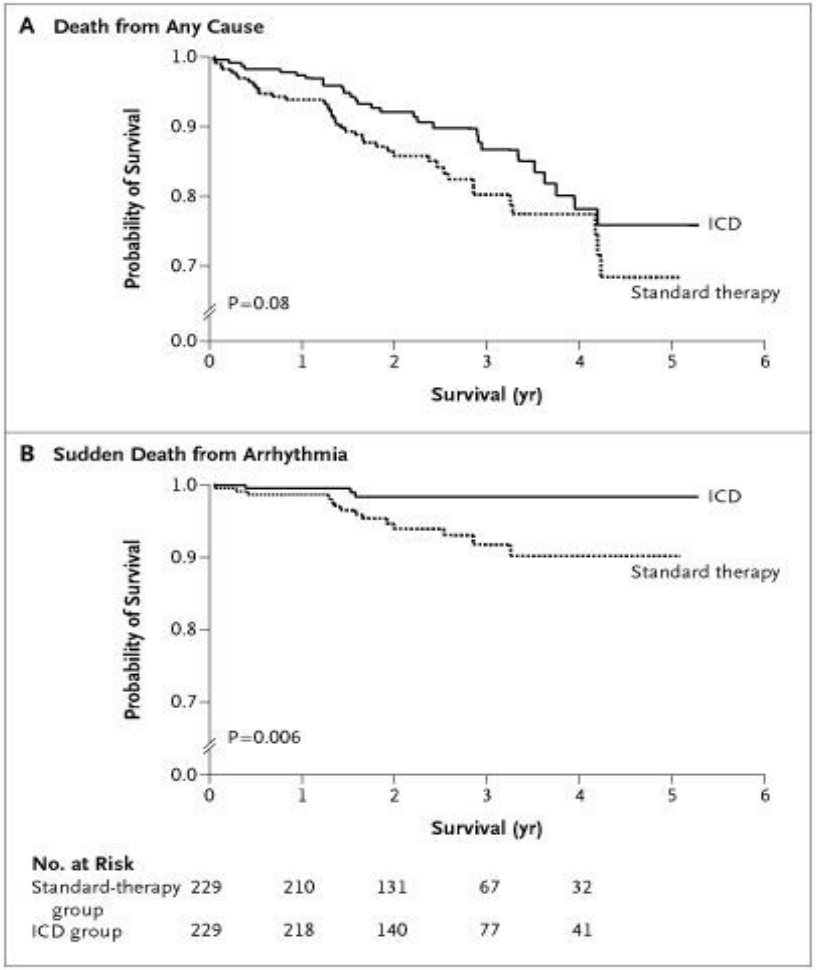
- Patients excluded from TWA testing:
  - Atrial fibrillation (20-30% of CHF pts)
  - Poor functional capacity
- Ineligibility or inability to complete TWA testing may identify high risk patients
- Extending ICD indications to broader population (EF 35-45%) may require multiple tests to achieve sufficient PPV
- Digital Holter applicable to more patients

Preserved HRV Identifies Low Risk Nonischemic Cardiomyopathy Patients: Results from the DEFINITE Trial

Eric J. Rashba, N.A. Mark Estes, Paul Wang, Andi Schaechter, Adam Howard, Wojciech Zareba, Jean-Philippe Couderc, Juha Perkiomaki, Joseph Levine, and Alan Kadish for the DEFINITE Investigators

Funded by NIH K23 HL67198

Kaplan-Meier Estimates of Death from Any Cause (Panel A) and Sudden Death from Arrhythmia (Panel B) among Patients Who Received Standard Therapy and Those Who Received an Implantable Cardioverter-Defibrillator (ICD)



Kadish A et al. N Engl J Med 2004;350:2151-2158

The NEW ENGLAND JOURNAL of MEDICINE

DEFINITE HRV Substudy

- Hypothesis: Low-risk pts with preserved HRV may not require an ICD
- First DEFINITE pt enrolled July 9, 1998
- Digital Holter equipment obtained August 1999 (Burdick 6632)
- 24-hour Holter obtained at baseline or at earliest possible follow-up visit

Methods

- Manual editing to exclude ectopy/noise
- SDNN = primary HRV variable
- Pre-specified analytic plan:
  - SDNN data split into tertiles, pts with AF or frequent ectopy (>25% of beats) analyzed in a separate group

Methods (2)

- Clinical characteristics of enrolled and excluded pts compared using unpaired t tests, Chi square test
- Kaplan-Meier analysis to examine relation of SDNN with outcome
- Events committee unaware of treatment assignment
- Endpoints:
  - All cause mortality
  - Cardiac mortality
  - Sudden death + appropriate ICD shocks
  - Appropriate ICD shocks

Results

- 303/458 patients enrolled
- 31/40 enrolling centers participated
- 29 pts excluded (<18 hours analyzable data)
- AF present in 16%, frequent ectopy 7%
- Timing of Holter after randomization
  - < 3 months 42% of patients, mean 7 ± 10 months
  - F/U for outcome analyses starting at Holter date

Clinical Characteristics

	Holter (n=274)	No Holter (n=184)
Age (years)	59 ± 12	58 ± 13
Male gender	199 (73%)	127 (69%)
Non-white *	56 (22%)	62 (36%)
Diabetes	64 (23%)	41 (22%)
LVEF (%)	21 ± 6	22 ± 6

* $p < 0.05$

Clinical Characteristics

	Holter (n=274)	No Holter (n=184)
NYHA Class *		
I	71 (26%)	28 (15%)
II	149 (54%)	114 (62%)
III	54 (20%)	41 (22%)

* $p < 0.05$

Cardiovascular Medications

	Holter (n=274)	No Holter (n=184)
ACE inhibitor	235 (86%)	157 (85%)
ARB	31 (11%)	20 (11%)
Beta Blockers *	245 (89%)	144 (78%)
Amiodarone	14 (5%)	9 (5%)

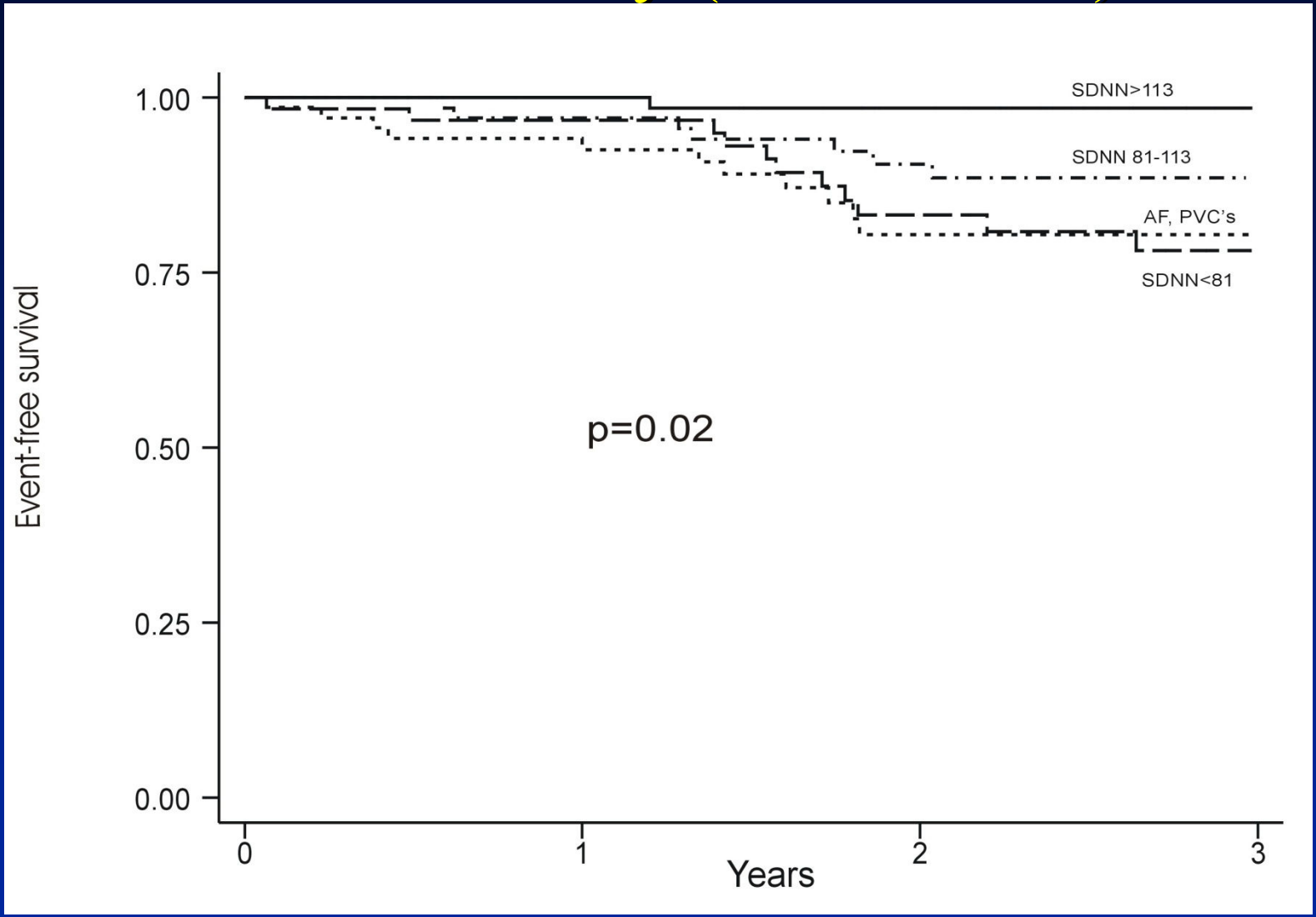
* $p < 0.05$

Clinical Outcome

	Holter (n=274)	No Holter (n=184)
Total mortality *	26 (9%)	42 (23%)
Sudden cardiac	4 (2%)	13 (7%)
Cardiac, not sudden	10 (4%)	11 (6%)
Non-cardiac	12 (4%)	14 (8%)
Unknown	0 (0%)	4 (2%)
ICD shocks	22 (15%)	13 (16%)

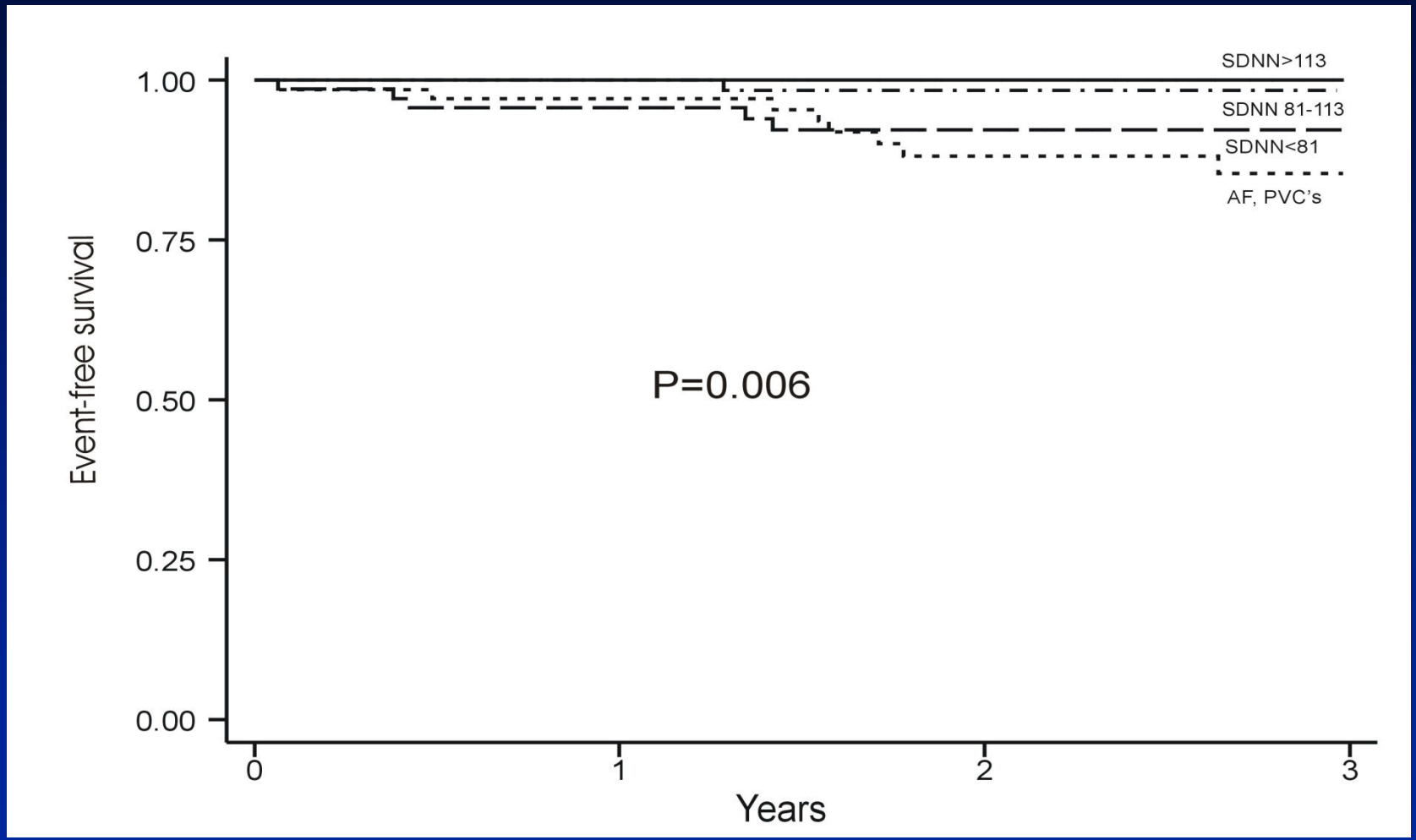
* $p < 0.05$

Total Mortality (ICD + STD)

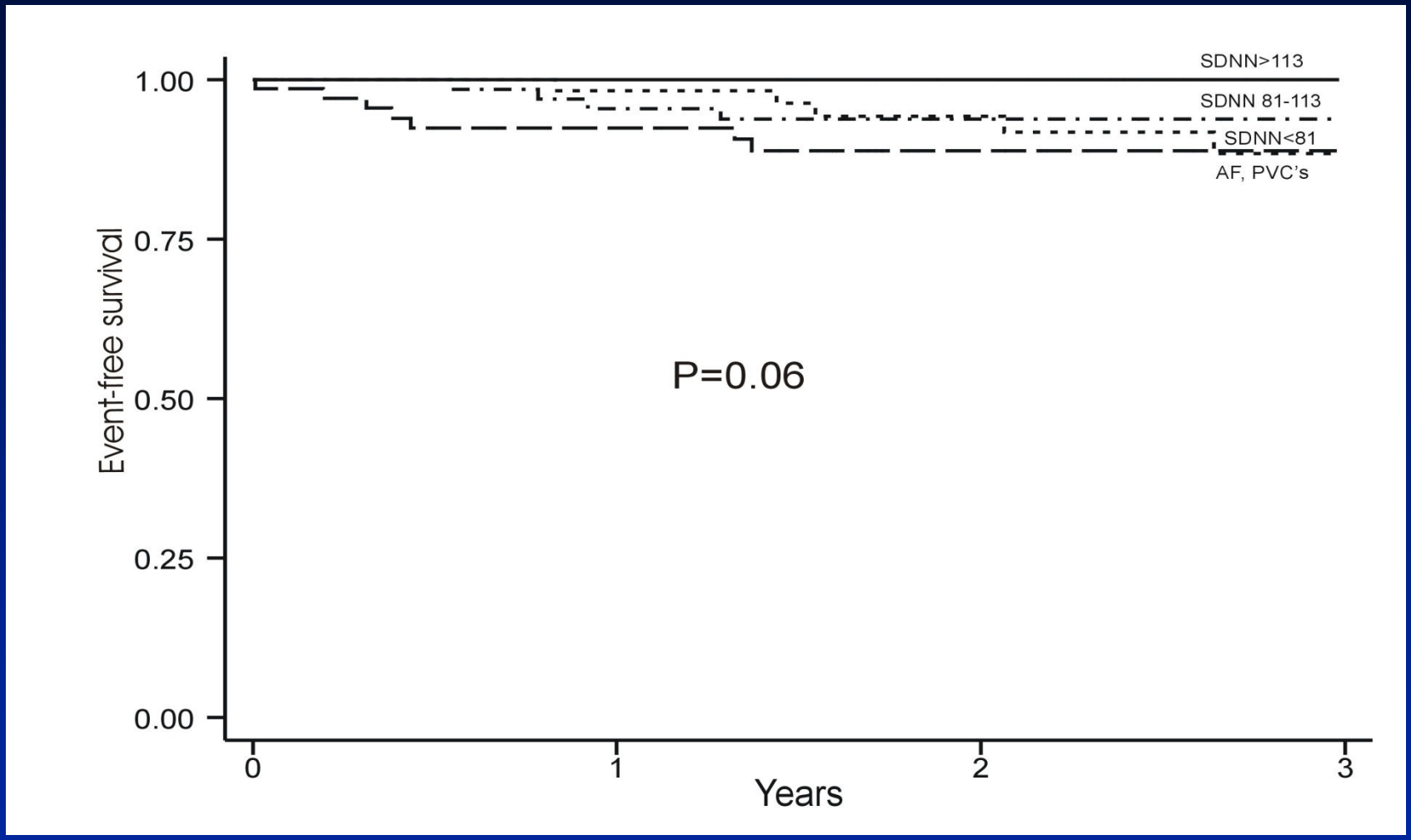


Rashba EJ, Mark Estes NA, Wang P, et al. *Heart Rhythm*. 2006;3:281-286.

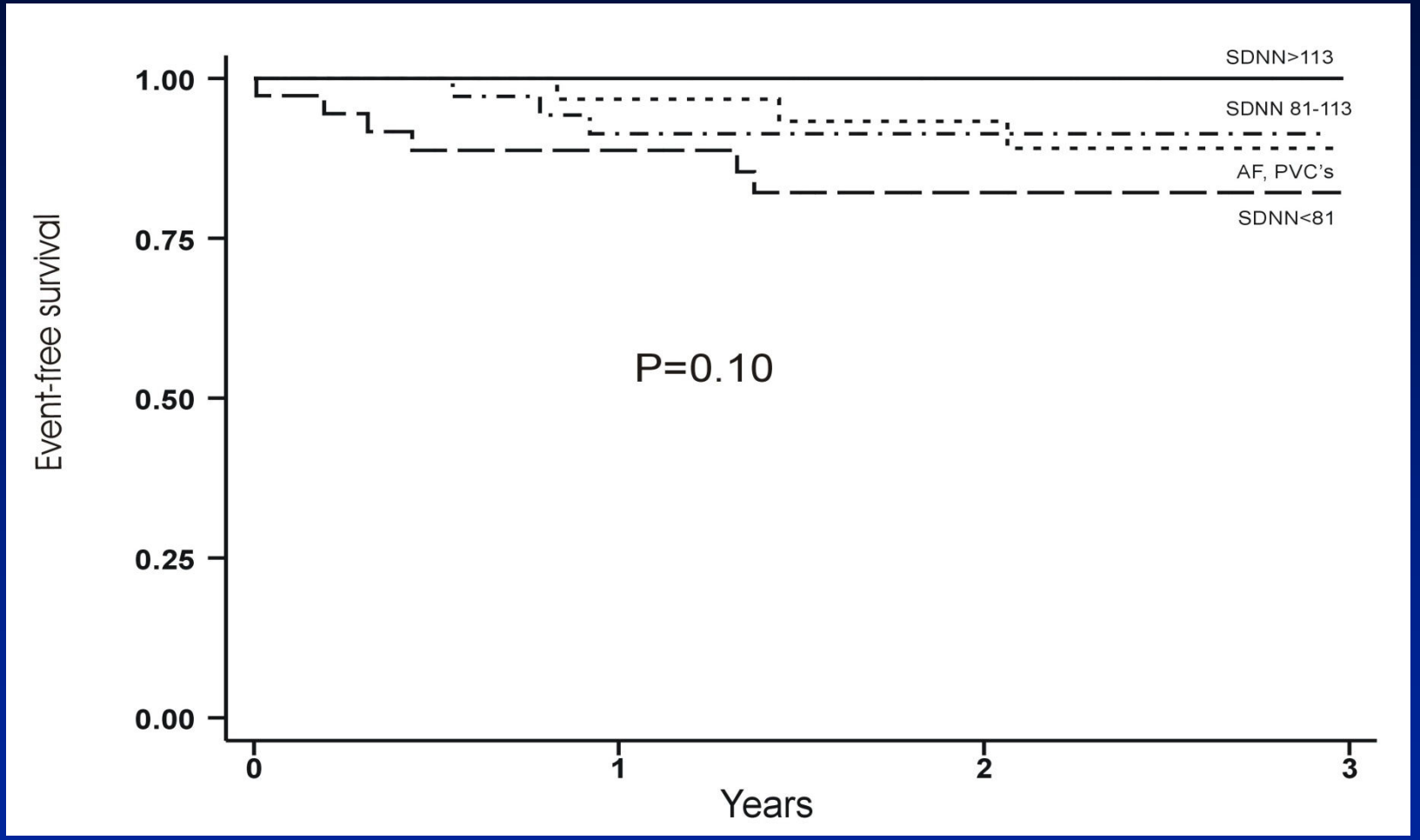
Cardiac Mortality (ICD + STD)



SCD + ICD shocks (ICD + STD)



Appropriate ICD shocks



Limitations

- Substudy pts were at lower risk than pts who did not have a Holter
- Holters not performed at enrollment in all pts
- Missed events before Holter could be performed, especially in STD therapy patients
- Favorable risk profile of substudy patients facilitates identification of low risk

Conclusions

- NIDCM pts with preserved HRV are at low risk for cardiac events
- NIDCM pts excluded from HRV analysis due to AF/PVCs are at high risk
- Prospective verification of these findings required before considering withholding ICD therapy from NIDCM patients

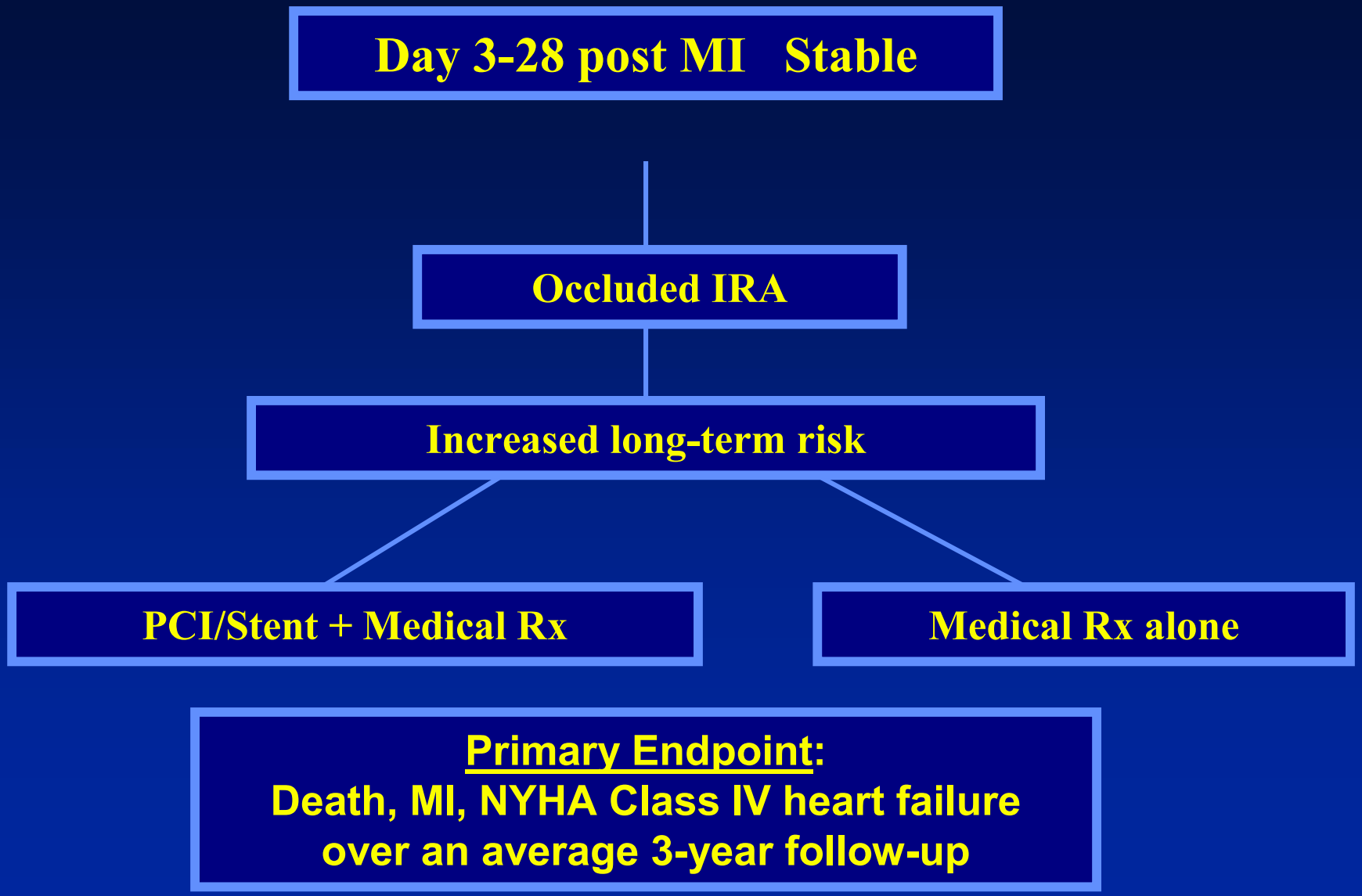
Electrophysiological Effects of Late PCI After MI: The OAT-EP Trial

Eric J. Rashba, Judith S. Hochman, Jean-Philippe Couderc, Gervasio A. Lamas, Sharri M. Hollist, Vladimir Dzavik, Warren Cantor, Carlos Vozzi, Christopher Buller, Sandra Forman, Lisa Aronson Friedman, John R. Ross, Antonio Carlos Carvalho on behalf of the OAT-EP Investigators

Rationale for Late Reperfusion

- Late open artery hypothesis suggests that PCI of occluded IRAs after the acute phase of MI would improve prognosis
- Mechanisms of potential benefit
  - Recruitment of hibernating myocardium
  - Prevention of LV enlargement
  - Source for collateral flow
  - **Stabilization of electrical substrate**
    - Limited data suggest association between patent IRA and improved HRV, SAECG and QT interval dispersion
    - No data available from large randomized controlled trials

OCCLUDED ARTERY TRIAL



OAT Eligibility

Confirmed Index MI + **Total IRA Occlusion** + **High Risk**

Confirmed by 2 out of 3

1. Ischemic symptoms ≥ 30 minutes
2. Elevated cardiac markers
3. EKG criteria: STEMI or NSTEMI, Q or Non Q wave MI

TIMI Flow 0 or 1 in IRA

3-28 days post MI

EF <50%

and/or

Proximal Occlusion of a major epicardial vessel supplying ≥25% LV

Major Exclusion Criteria

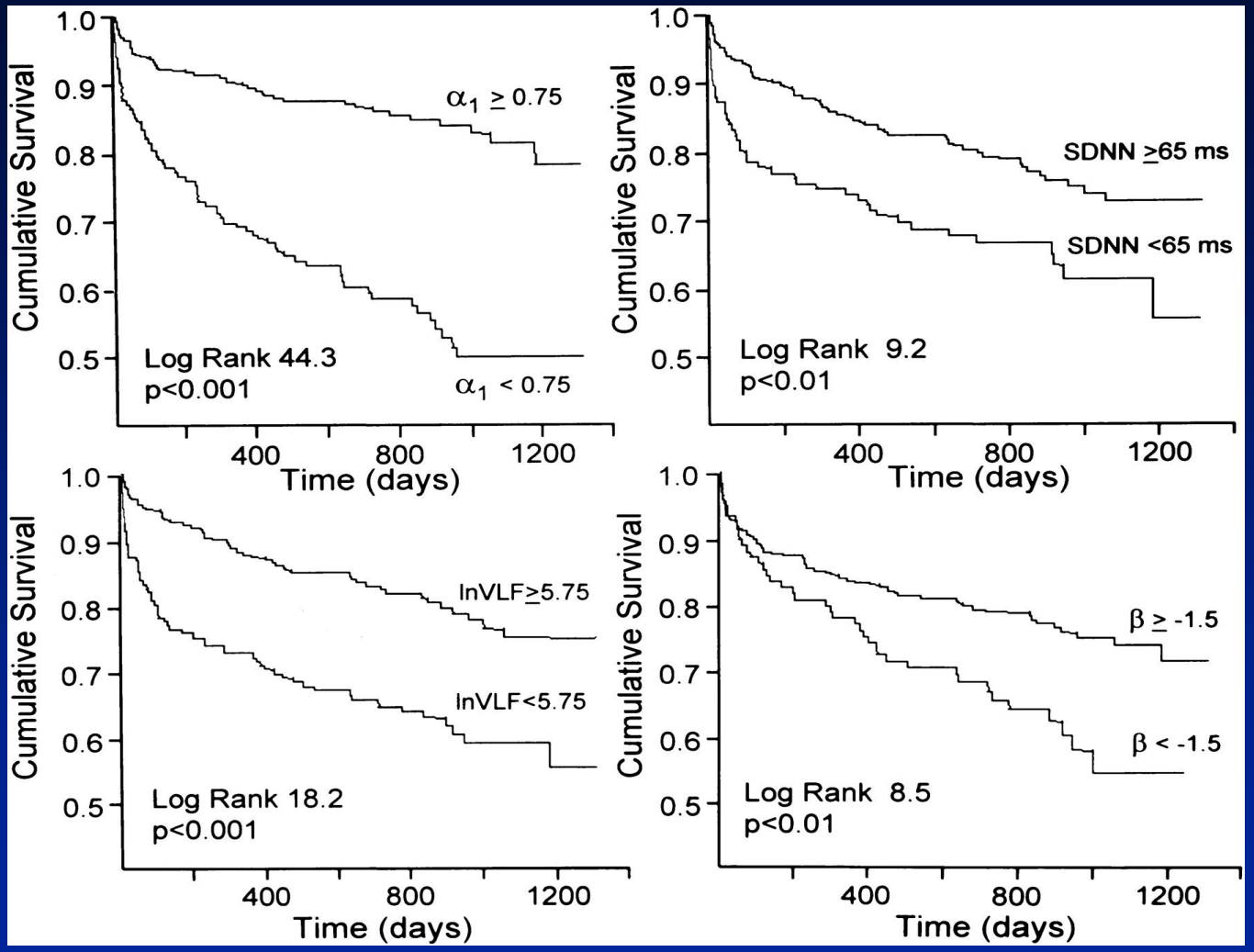
- Significant left main or 3 vessel CAD
- Hemodynamic or electrical instability
- Rest or low-threshold angina
- NYHA Class III-IV HF or shock

OAT Study Results

- Sustained IRA patency at 1 year in 83% of PCI patients vs 25% Med Rx (TOSCA-2 ancillary study)
- Baseline SPECT: moderately preserved infarct zone viability in 69% of 124 pts (OAT-NUC ancillary study)
- No effect on composite endpoint of death, MI or NYHA Class IV CHF (OAT Trial)

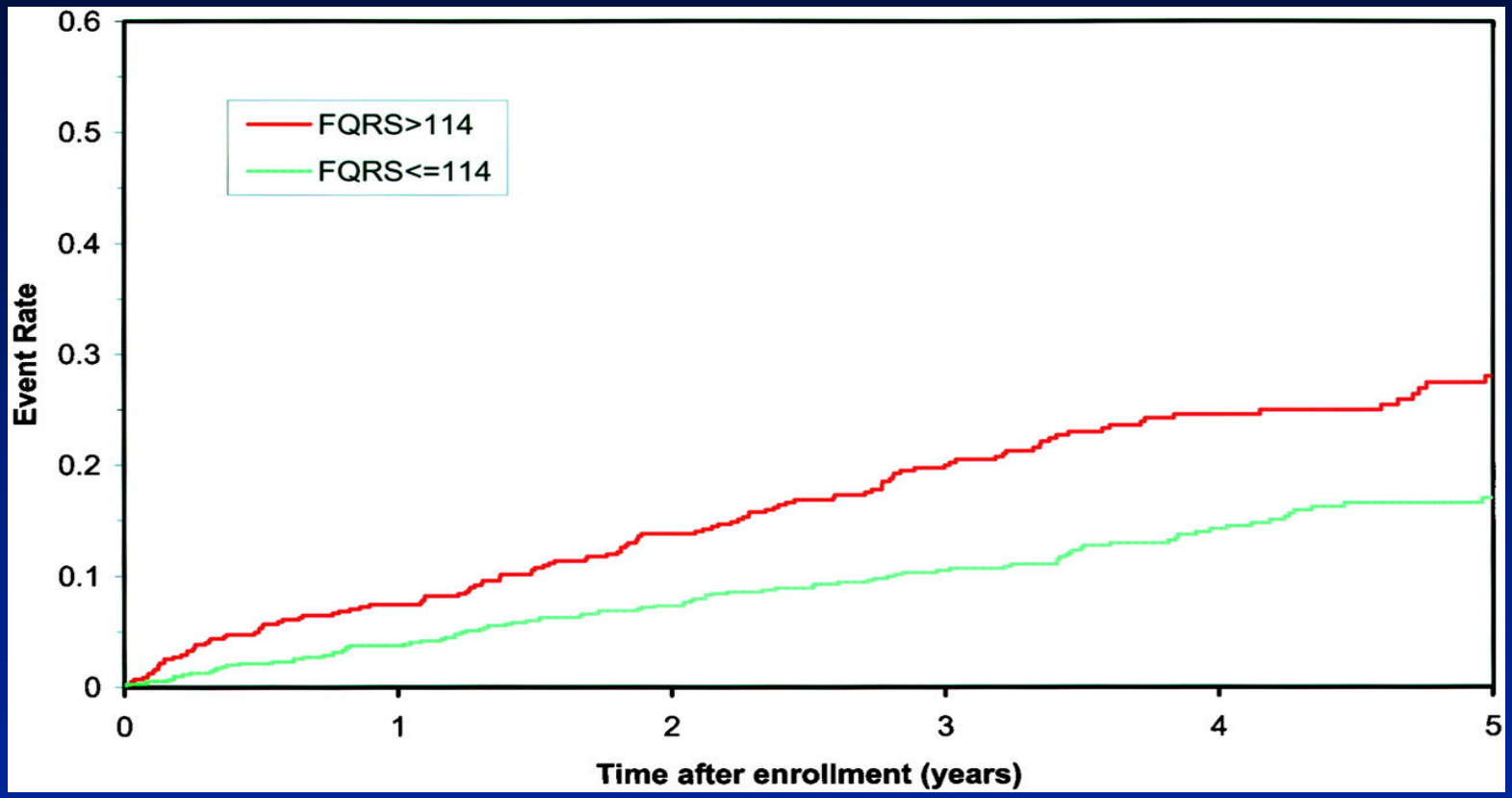
OAT-EP Study Aims

- Primary Aim
  - Characterize effects of late PCI on the autonomic nervous system (HRV)
    - $\alpha 1$ nonlinear HRV, superior prognostic value in post MI patients with LV dysfunction (Huikuri Circulation 2000; 101: 47-53)
    - Primary endpoint: change in $\alpha 1$ from baseline to 1 year
- Secondary Aims
  - Characterize effects of late PCI on
    - Impulse conduction (SAECG)
      - fQRS potent predictor of mortality (MUSTT)
    - Ventricular repolarization (TWV)
      - Beat-to-beat variability in T wave morphology
      - Independent predictor of arrhythmic events in MADIT-2
    - Secondary endpoints: change in fQRS and TWV from baseline to 1 year



Huikuri, H. V. et al. Circulation 2000;101:47-53

Kaplan-Meier estimates of arrhythmic death or cardiac arrest by SAECG result



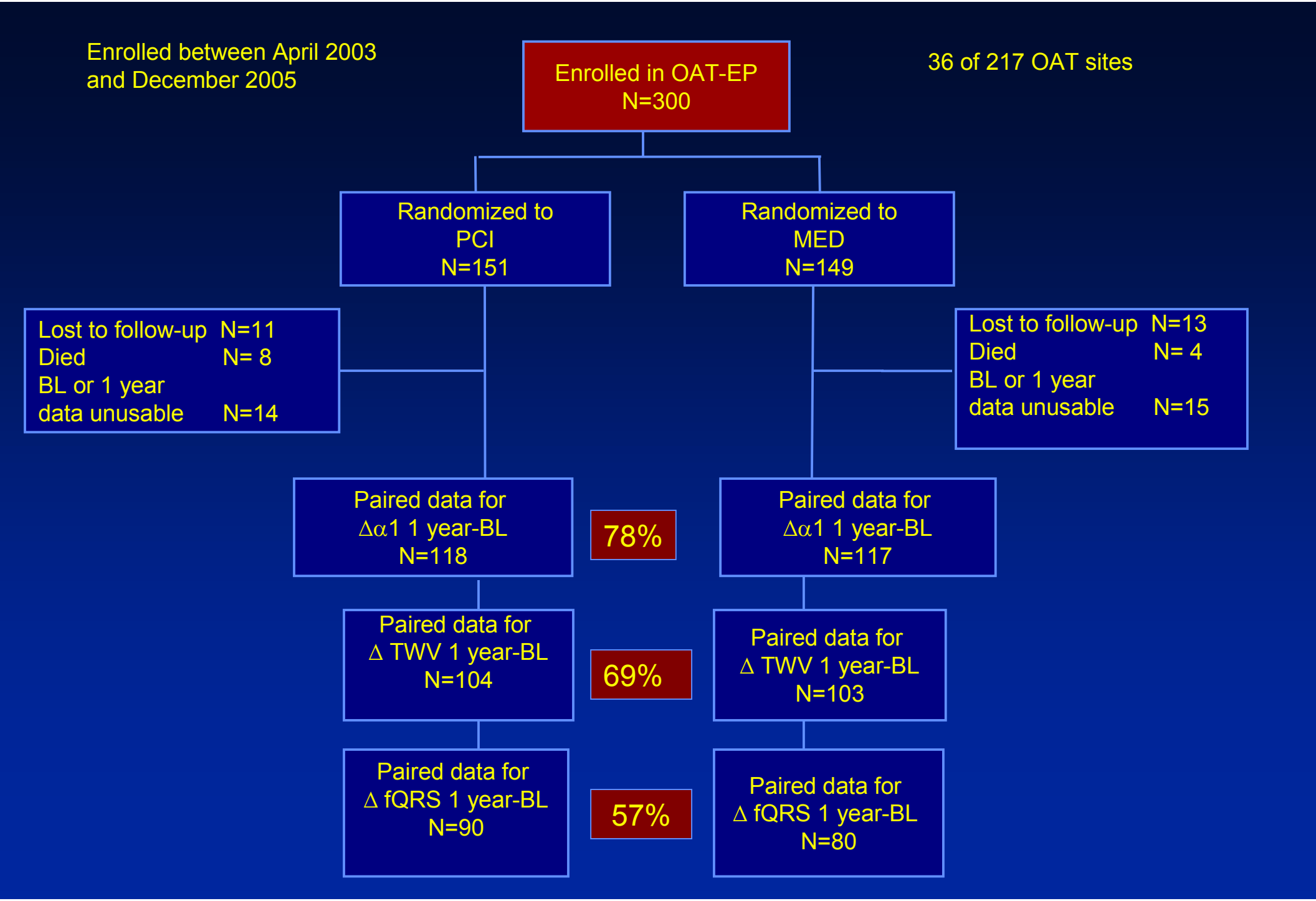
Gomes, J. A. et al. Circulation 2001;104:436-441

OAT-EP Study Design

- Must meet all OAT eligibility criteria
- Normal sinus rhythm
  - HRV and TWV measurement
- Narrow QRS (<120 ms)
  - SAECG measurement

OAT-EP Methods

- Ten minute digital Holter prior to randomization and at one year
- Data acquired at 1000 Hz using Burdick 92510 digital Holter recorder
- All data centrally analyzed at core lab
- SAECGs excluded if noise > 1 μV
- Excluded from TWV analysis if HR unstable, excessive ectopy or noise


Enrolled between April 2003
and December 2005
Enrolled in OAT-EP
N=300
36 of 217 OAT sites
Randomized to
PCI
N=151
Randomized to
MED
N=149
Lost to follow-up N=11
Died N= 8
BL or 1 year
data unusable N=14
Lost to follow-up N=13
Died N= 4
BL or 1 year
data unusable N=15
Paired data for
Δα1 1 year-BL
N=118
78%
Paired data for
Δα1 1 year-BL
N=117
Paired data for
Δ TWV 1 year-BL
N=104
69%
Paired data for
Δ TWV 1 year-BL
N=103
Paired data for
Δ fQRS 1 year-BL
N=90
57%
Paired data for
Δ fQRS 1 year-BL
N=80

Statistical Considerations

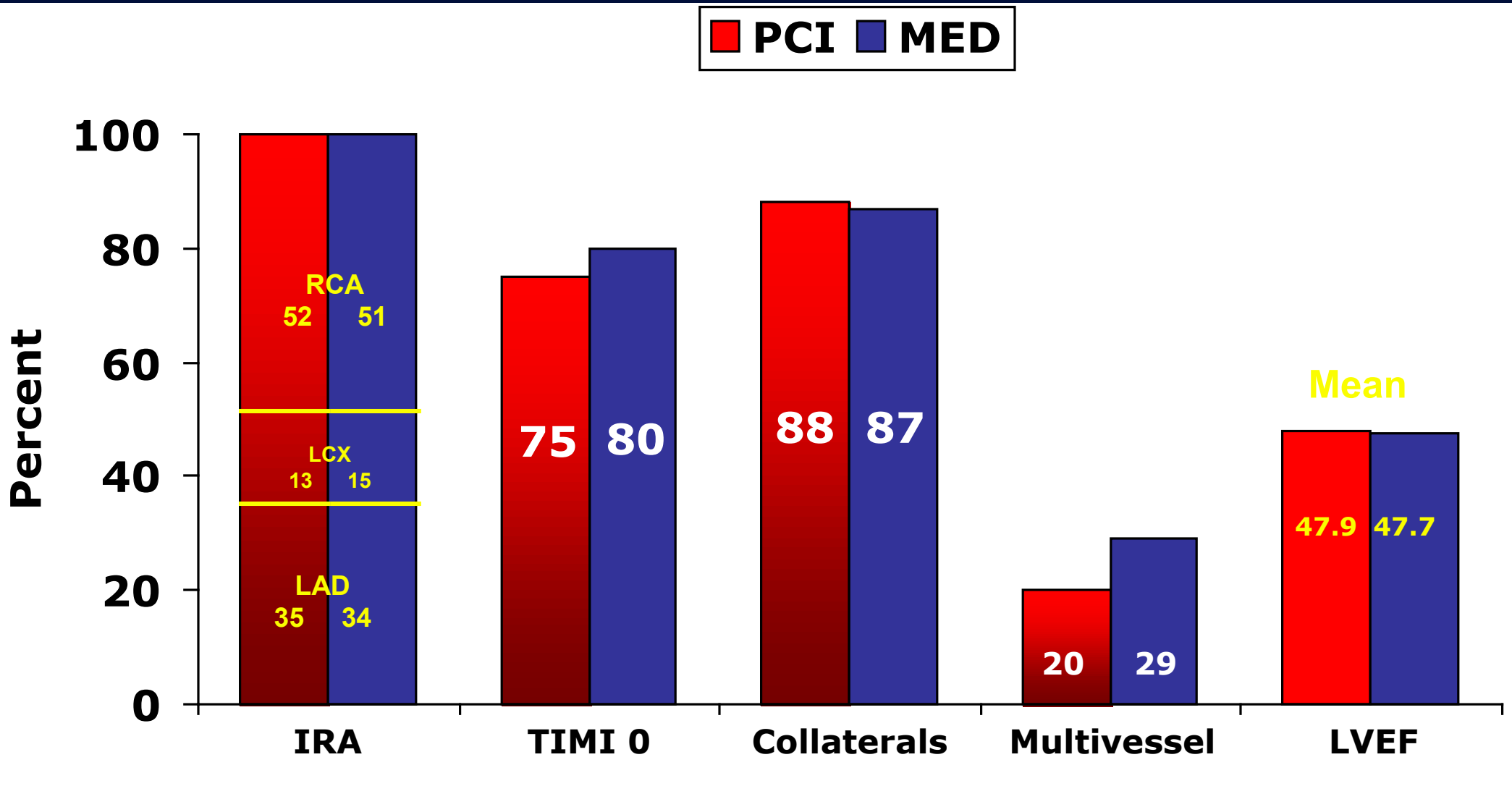
- Power based on actual numbers of analyzable pairs
  - Primary endpoint - change in $\alpha 1$ (HRV)
    - 80% to detect a difference between groups of 0.1
  - Secondary endpoint - change in fQRS (SAECG)
    - 99% power to detect a difference of 10 ms
    - 80% power to detect a difference of 5.5 ms
  - Secondary endpoint – change in TWV
    - 91% power to detect a difference of 10 μV
    - 80% power to detect a difference of 8 μV
- $p < 0.05$ required for statistical significance

Baseline Characteristics

	PCI (N=151)	MED (N=149)
Age mean ± SD, years	57.6±10.5	57.2±10.5
Male *	74.5	84.1
Prior angina	18.8	19.9
Prior MI	6.7	6.6
Diabetes *	14.8	26.5
NYHA Class I at the time of randomization	84.6	80.8
EKG - ST elevation or Q-wave or R-wave loss	88.6	88.7
Thrombolytic therapy for index MI	13.4	14.6
Days from MI to randomization Median (25,75%)	11 (6, 20)	12 (6,21)
Hypertension	54.4	62.3
Caucasian Race	77.2	77.5

* $p<0.05$

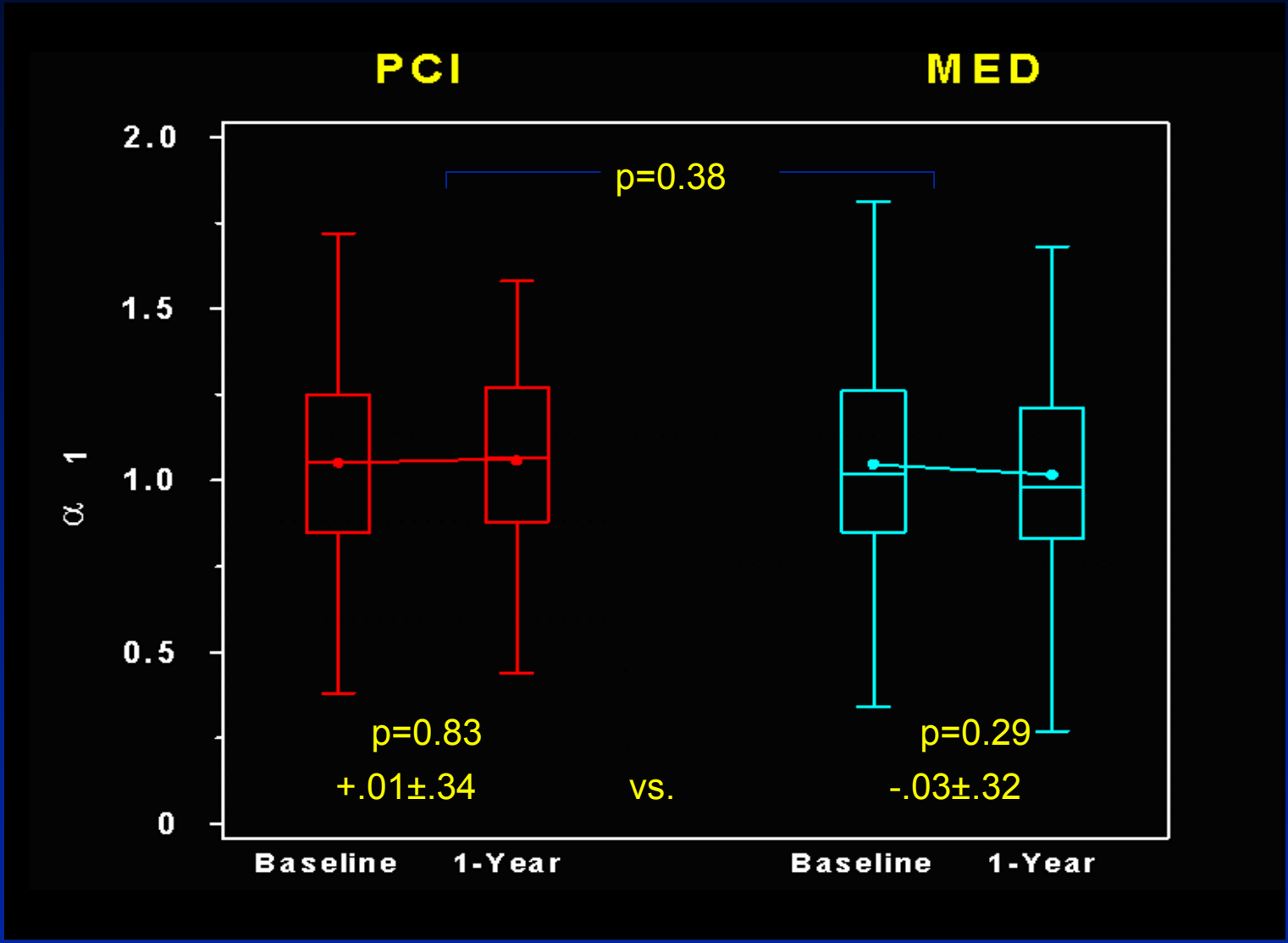
Angiographic Characteristics



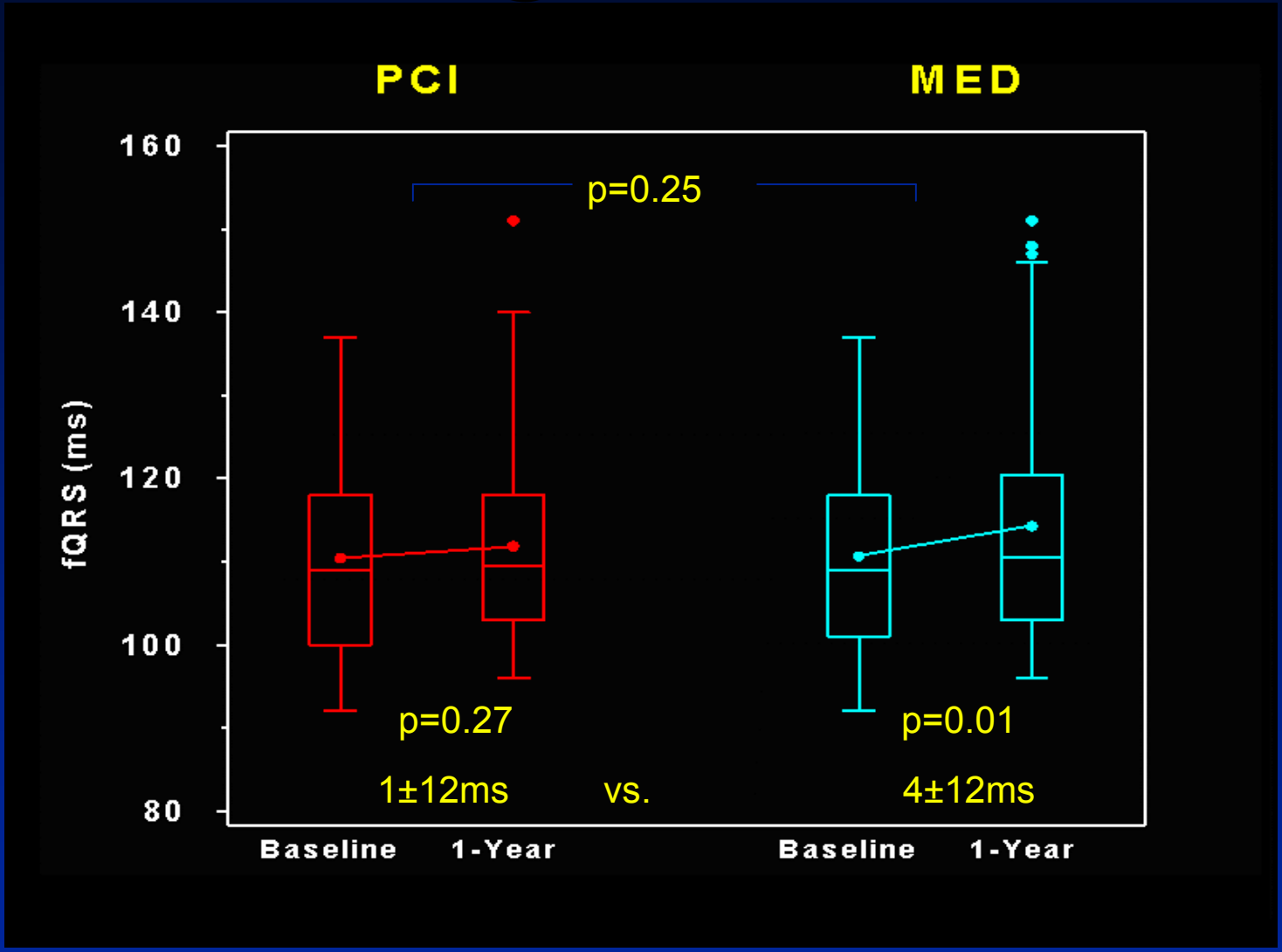
Medical Therapy

Agent	Baseline		1-Year	
	PCI (N=149)	MED (N=149)	PCI (N=126)	MED (N=132)
ACE Inhibitor	80.5	81.2	74.6	79.5
Angiotensin Receptor Blocker	3.4	2.0	7.1	6.8
β-Blocker	89.3	92.6	88.9	93.2
Calcium Channel Blocker	5.4	7.4	5.6	10.6
Diuretic	16.1	20.1	18.3	24.2
Anti-arrhythmics	1.3	2.7	3.2	1.5

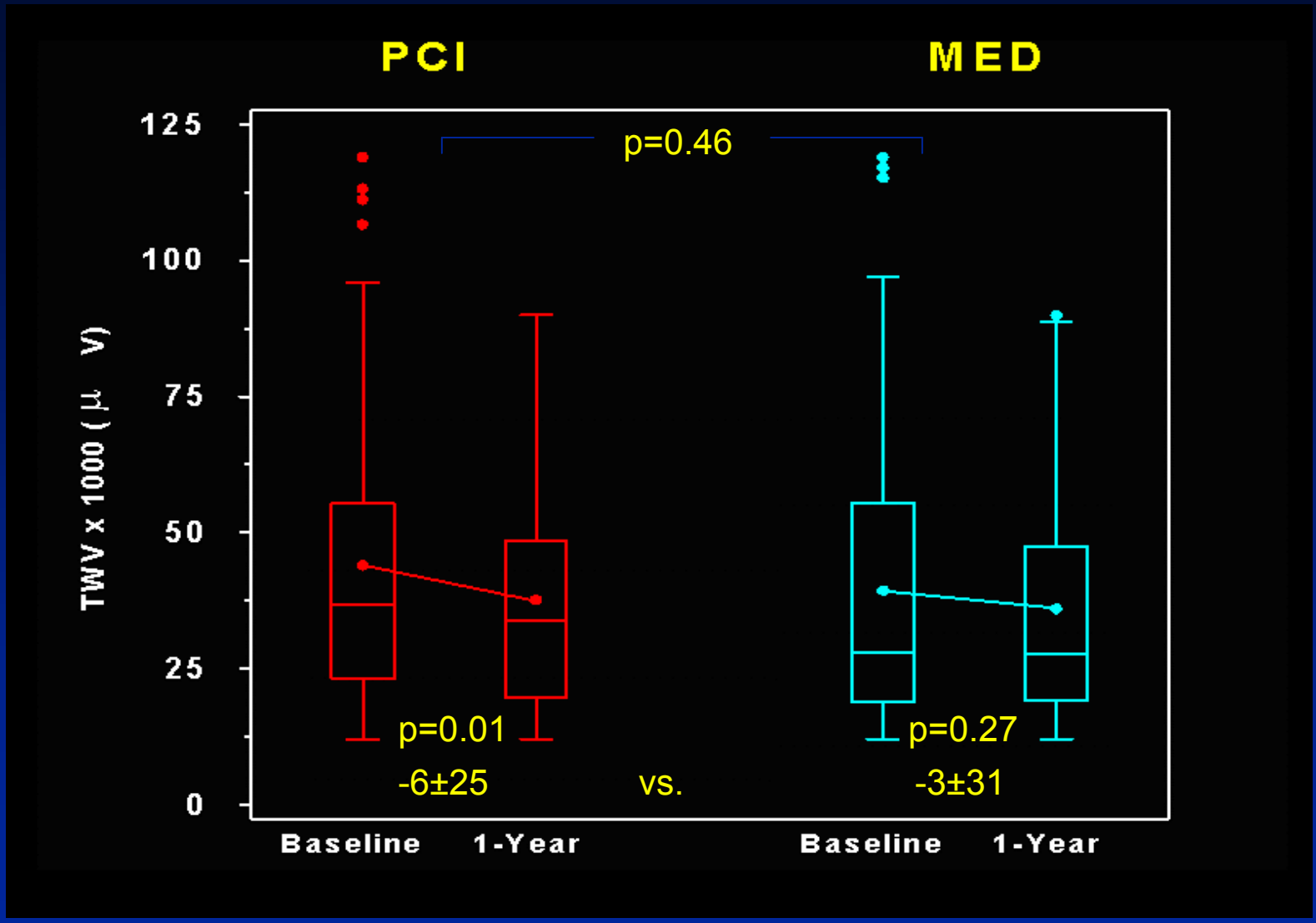
Changes in α1



Changes in fQRS



Changes in TWV



INDEPENDENT PREDICTORS OF CHANGE IN α1

Variable	Direction of Effect	P Value
PCI Group	—	0.52
ß-Blockers at 1 year	↓	0.03
Male	↓	0.04
Ejection Fraction	↓	0.04

INDEPENDENT PREDICTORS OF CHANGE IN fQRS

Variable	Direction of Effect	P Value
PCI Group	—	0.14
Prior MI	↓	0.01
Hypertension	↓	0.03
ACEI at Baseline	↑	0.05

INDEPENDENT PREDICTORS OF CHANGE IN TWV

Variable	Direction of Effect	P Value
PCI Group	—	0.38
Age	↑	0.04
Multivessel Disease	↓	0.06
Thrombolytics	↑	0.02
EKG - ST elevation or Q-wave or R-wave loss	↓	0.09

Conclusion

Despite:

- Excellent 1-year patency after PCI
- Retained viability

PCI did not reduce markers of arrhythmia vulnerability

- No effect on
  - autonomic nervous system (HRV)
  - ventricular repolarization (TWV)
  - impulse conduction (SAECG)

Limitations of Holter-based methods

- Exclusion of ~33% of patients
- Validated cutpoints for abnormal results not available for all tests
- Automated data processing and test interpretation not available

Goals of Risk Stratification

- Exclude low risk SCD-HeFT patients
  - TWA may not be as good as advertised
  - Annual reassessment mandatory
  - Multiple tests for sufficient NPV
- Identify new candidates for prophylactic ICD (e.g. LVEF 35-45%)
  - TWA insufficient
  - Multiple tests for sufficient PPV