

Primary Prevention in Arrhythmogenic Cardiomyopathy (ACM)

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No disclosures

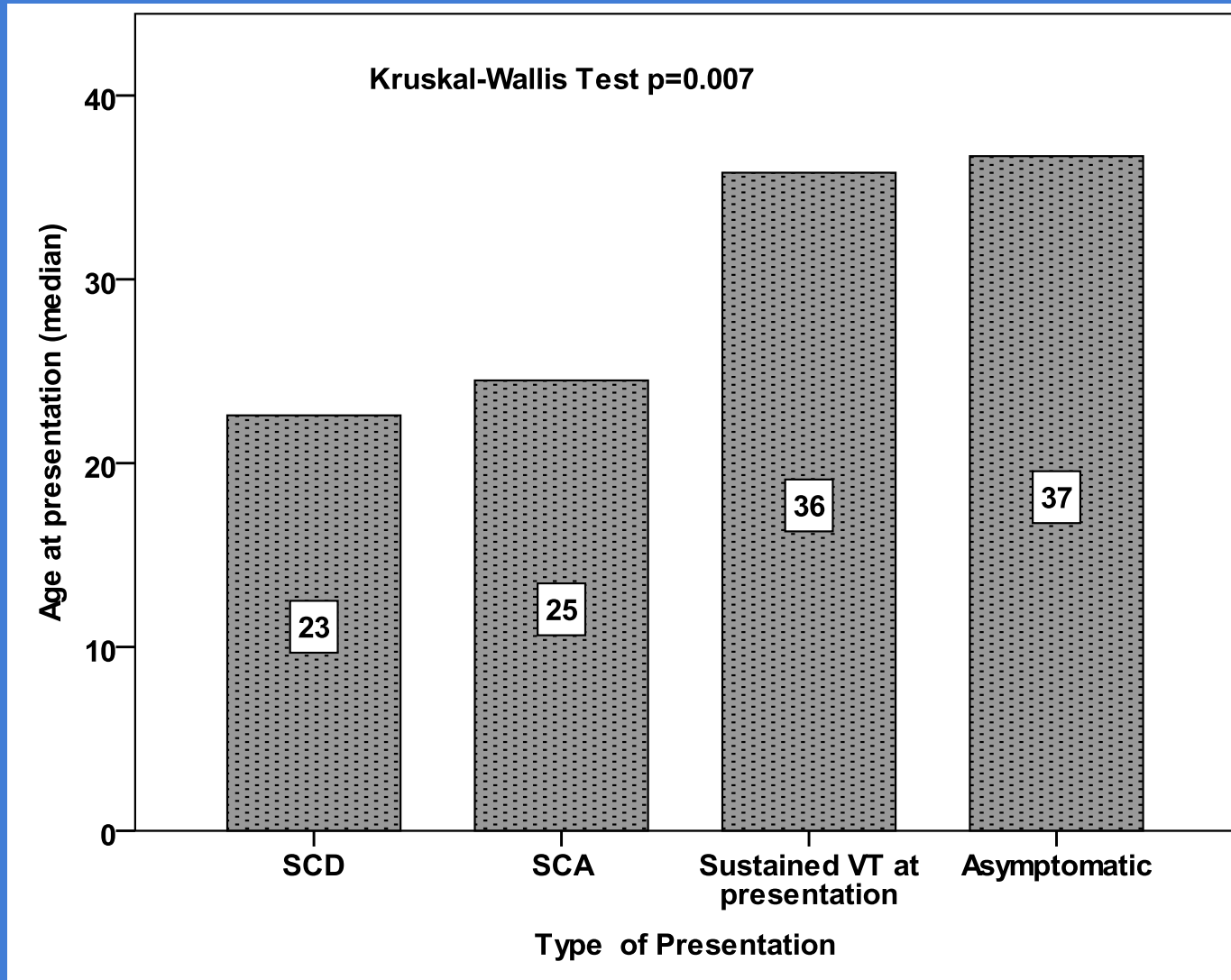
DEFINITION

Heart muscle disease *starting with ventricular arrhythmias* in the *early stage*, followed by structural and functional disorder at later stages

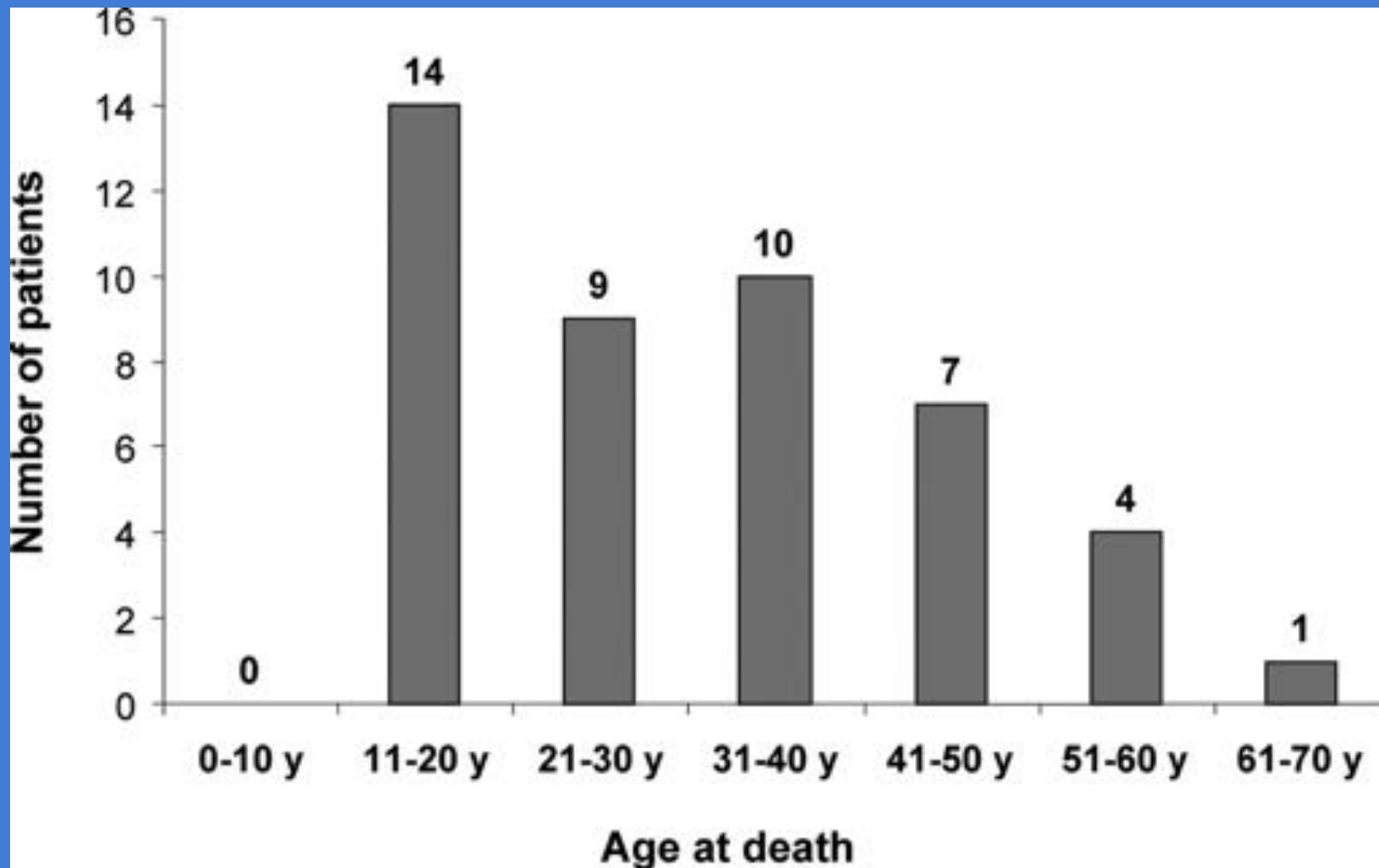
Median Age at Presentation

JHU-ICIN merged database 2014, n=577 ARVD/C mutation carriers

A. Bhonsale et al. Eur Heart J 2015;36 :847



Age at sudden cardiac death of the 45 patients with pathologically proven arrhythmogenic right ventricular cardiomyopathy

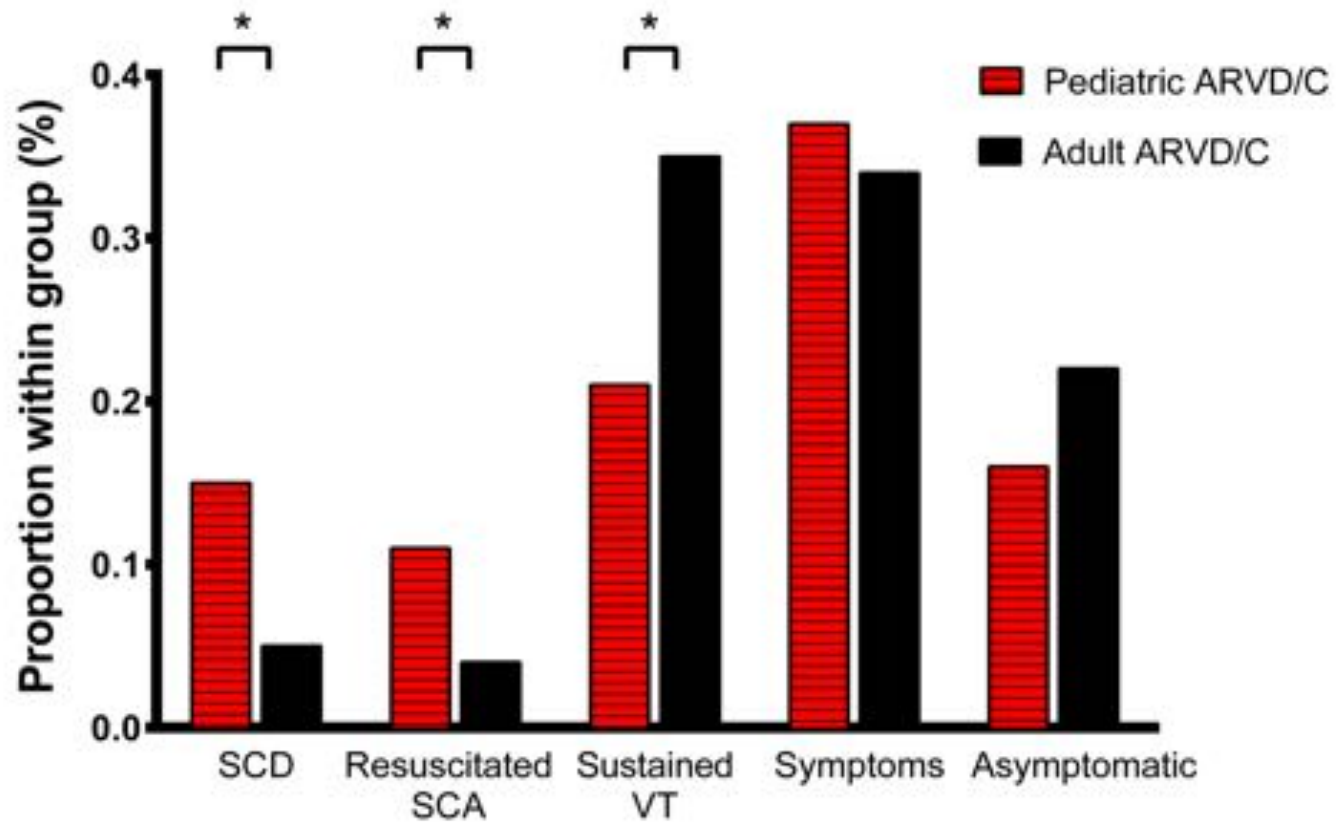


Quarta G et al. *Circulation*. 2011;123:2701-2709

Presentation in ARVD/C

Pediatric vs Adult

A.S. te Riele et al JACCEP 2015



Pediatric

15%

11%

21%

37%

16%

Adult

5%

4%

35%

34%

22%

p-value

0.003

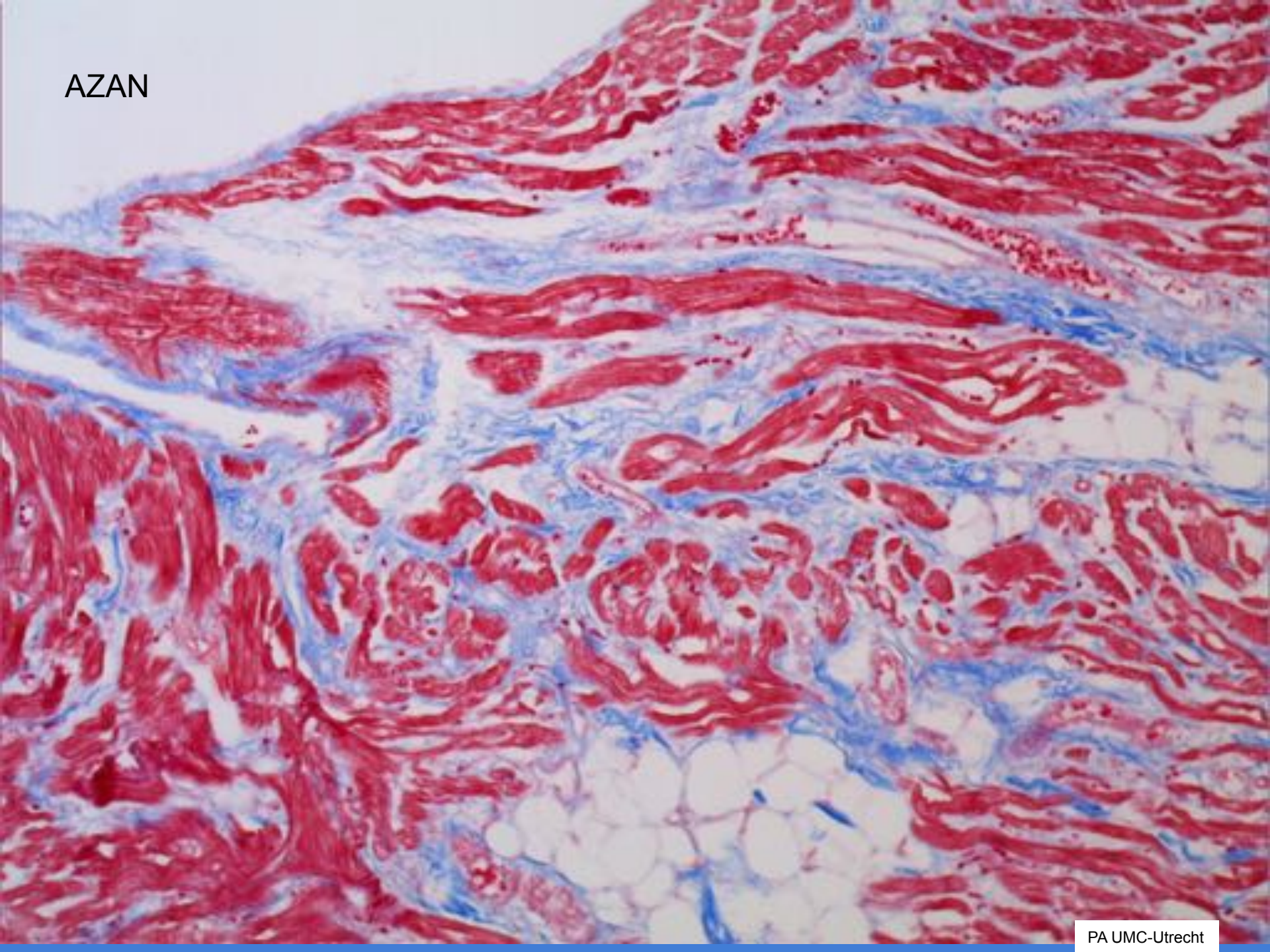
0.010

0.017

0.517

0.239

AZAN



Before Primary Prevention

- **Diagnosis at different disease stages**
- **Appropriate number of subjects**
- **Long-term follow-up**
- **Prognosis**
- **Risk markers and risk stratification**

ICIN-Johns Hopkins Collaboration in ARVD/C (ACM)

Aims

- **Merged database for Genotype-Phenotype correlation (large numbers)**
- **Improvement of diagnosis, beyond Task Force Criteria**
- **Prognosis and risk stratification, particularly in early disease stage**

Background JHU-ICIN Database

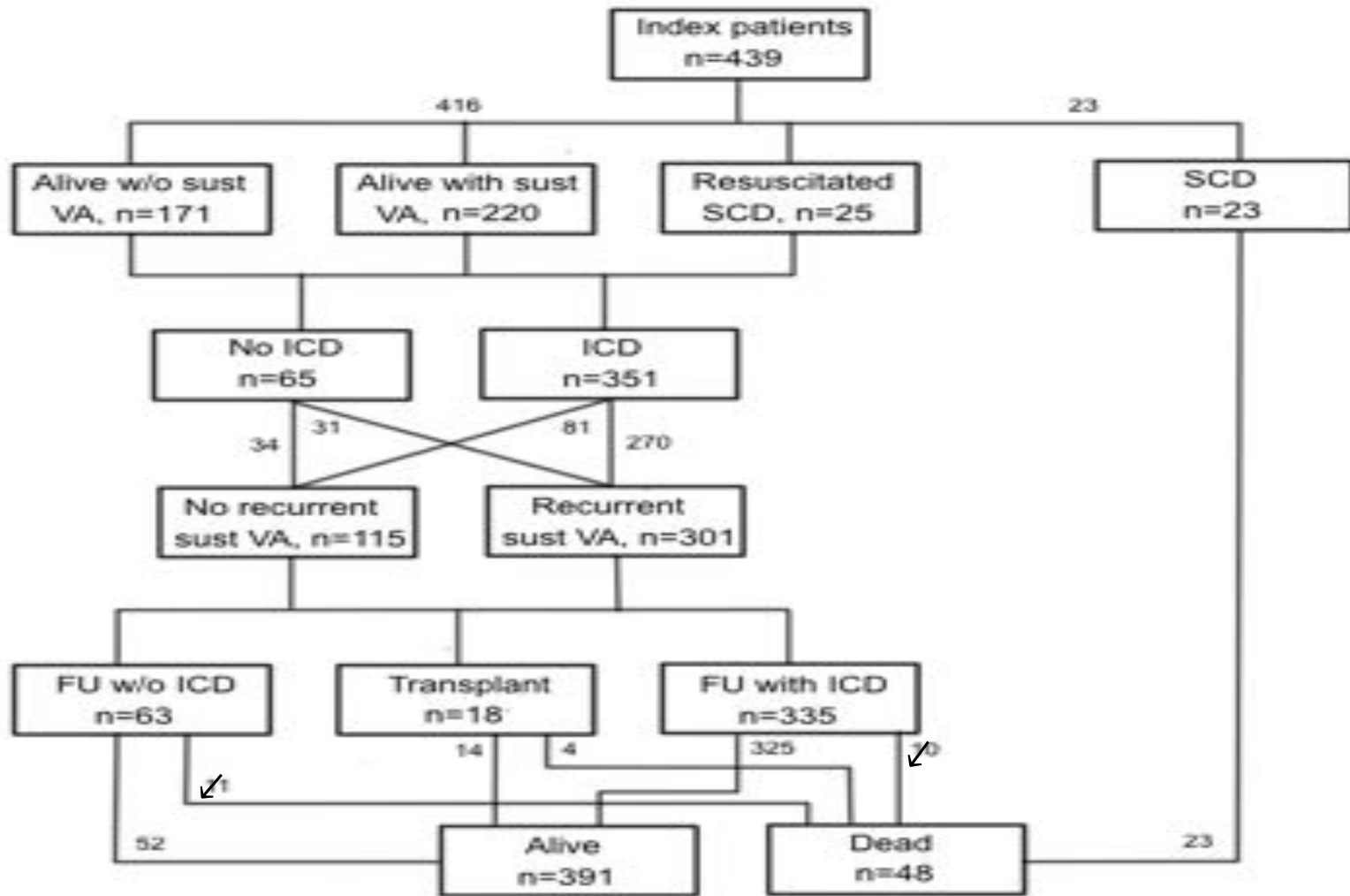
(n=1001; JHU 511, ICIN 490, index 439, relatives 562)

- Fulfillment of revised 2010 Task Force Criteria for ARVD/C diagnosis **in All Index Patients**
- DNA analysis of All Desmosomal Genes **in All Index Patients**
- Cascade Screening **in Relatives** with screening of Pathogenic Mutations identified in Index Patients

Index Patients (n=439)

Presentation, Clinical Course, Outcome

J.A. Groeneweg et al. *Circ Cardiovasc Genet* 2015;8:437



Index Patients (n=416)

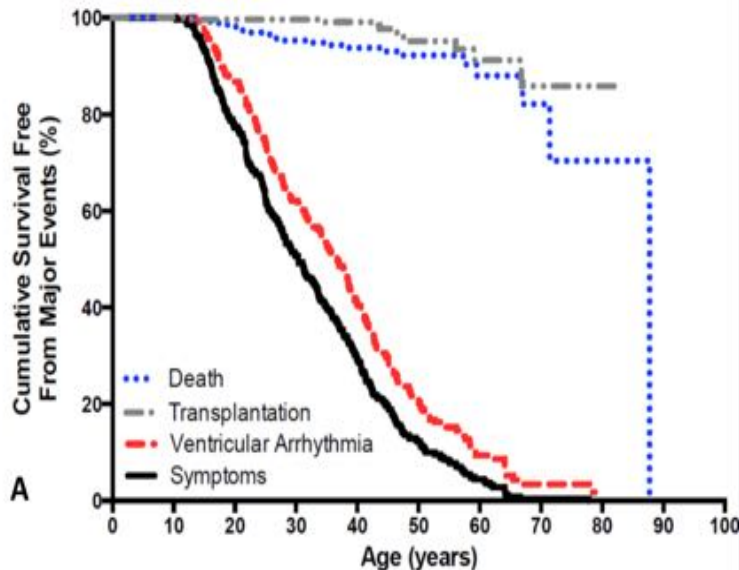
With (63%) vs Without Mutation

(JHU-ICIN database, n=1001)

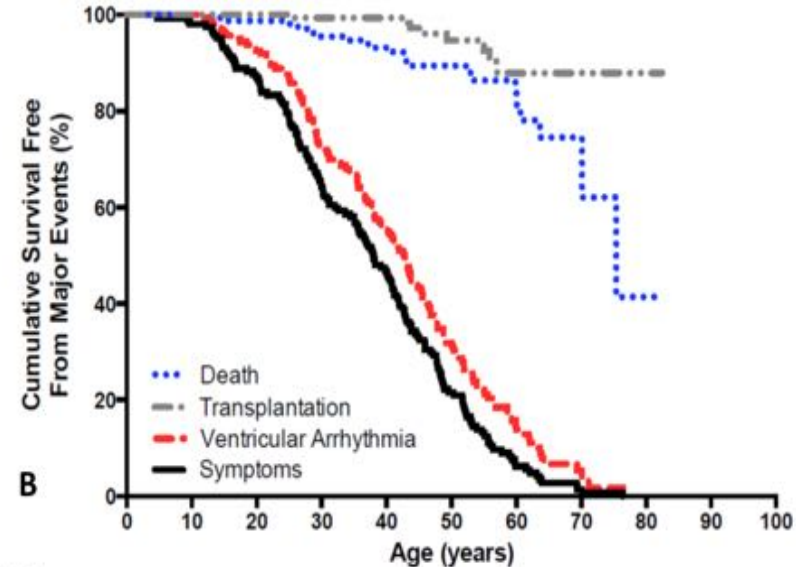
J.A. Groeneweg et al. *Circ Cardiovasc Genet* 2015;8:437

mutation + (n=264)

mutation - (n=152)



Number at risk	0	10	20	30	40	50	60	70	80	90
Death	264	264	253	209	161	94	35	8	1	0
Transplantation	264	264	253	209	161	94	35	8	1	0
Ventricular arrhythmia	264	264	229	159	99	44	13	2	0	0
Symptoms	264	264	206	137	79	33	11	1	0	0

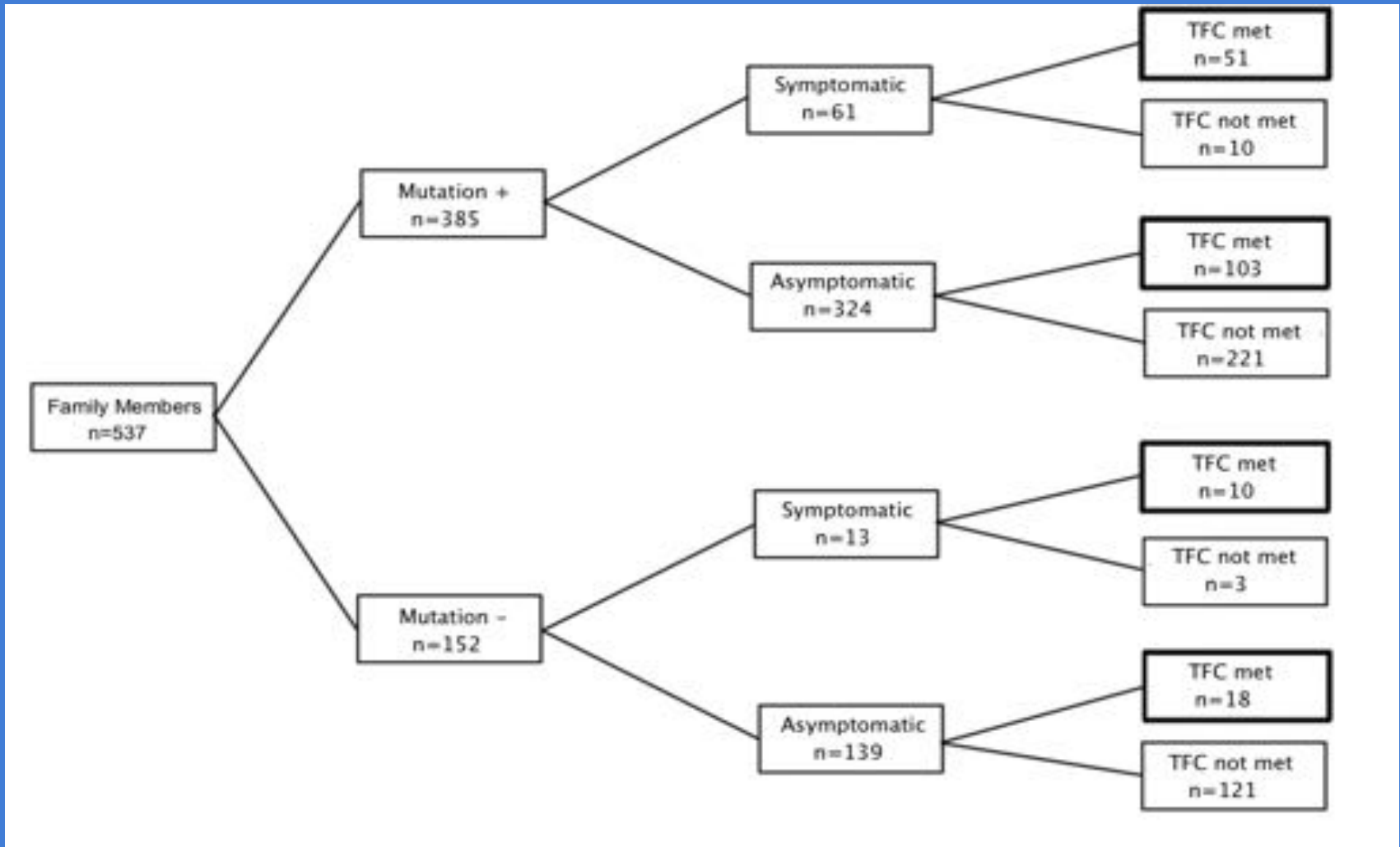


Number at risk	0	10	20	30	40	50	60	70	80	90
Death	152	152	149	132	107	66	28	5	2	0
Transplantation	152	152	149	132	107	63	24	5	2	0
Ventricular arrhythmia	152	152	141	106	80	38	13	2	0	0
Symptoms	152	149	132	97	70	31	7	1	0	0

Disease Penetrance in 537 Relatives

(JHU-ICIN database, n=1001)

J.A. Groeneweg et al. *Circ Cardiovasc Genet* 2015;8:437



Relatives (n=537)

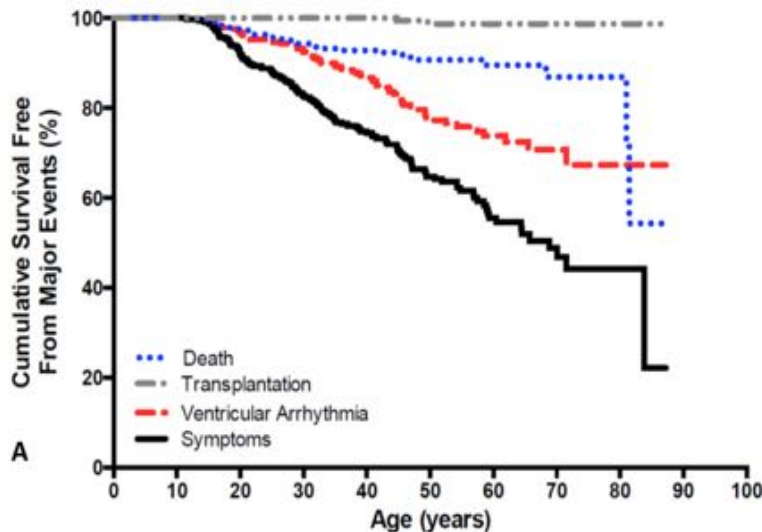
With vs Without Mutation

(JHU-ICIN database, n=1001)

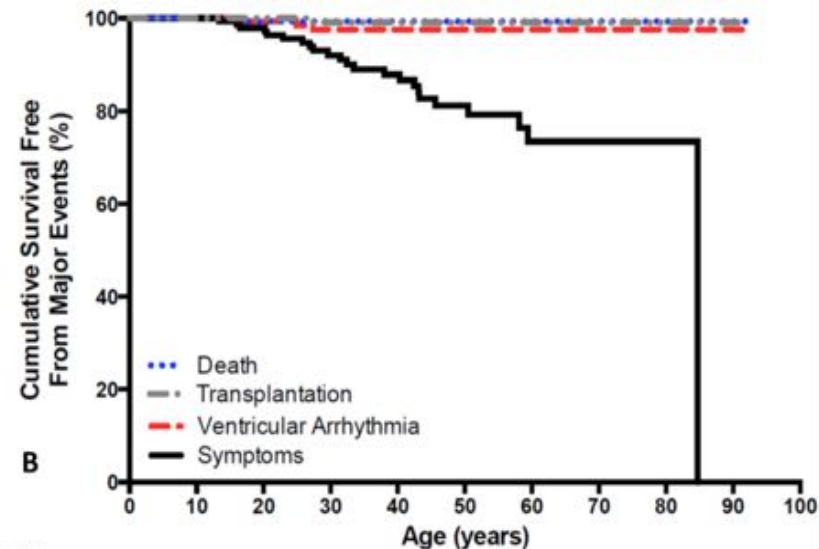
J.A. Groeneweg et al. *Circ Cardiovasc Genet* 2015;8:437

mutation + (n=385)

mutation - (n=152)



Number at risk	0	10	20	30	40	50	60	70	80	90	100
Death	385	372	318	258	205	134	70	27	6	0	0
Transplantation	385	372	318	258	205	132	69	27	5	0	0
Ventricular Arrhythmia	385	372	316	256	198	121	65	27	5	0	0
Symptoms	385	369	298	230	178	115	59	25	5	0	0



Number at risk	0	10	20	30	40	50	60	70	80	90	100
Death	152	149	129	104	78	48	28	13	2	1	0
Transplantation	152	149	129	103	78	48	28	13	2	1	0
Ventricular Arrhythmia	152	149	129	102	78	48	28	13	2	1	0
Symptoms	152	149	128	98	74	44	25	13	2	0	0

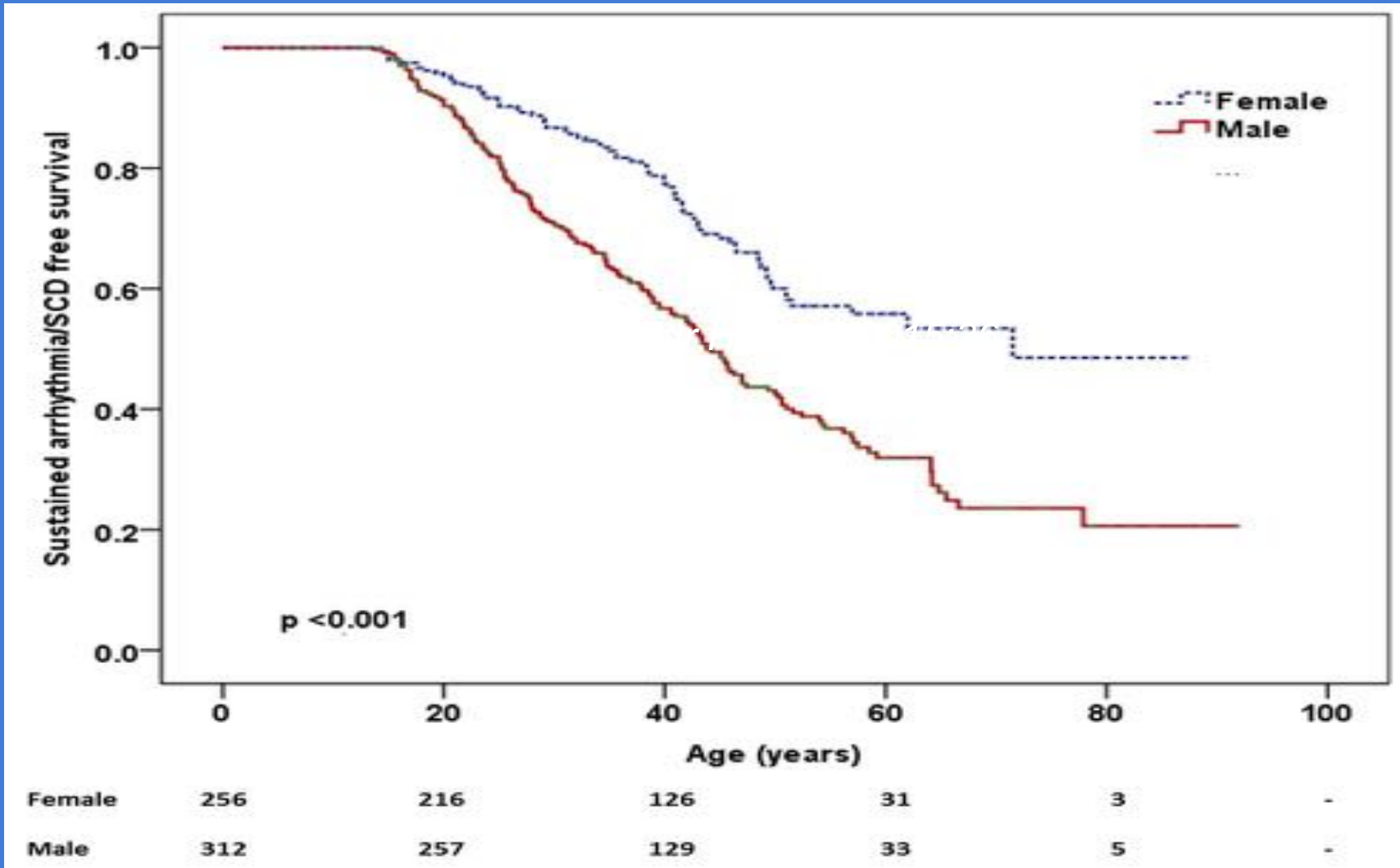
Pathogenic Mutation Carriers (n=577)

- **JHU** n=259 (probands 102, relatives 157)
- **ICIN** n=318 (probands 128, relatives 190)
- Presentation with **sudden death** n=36
(29 (80%) *PKP2*, 4 *DSP*, 1 *DSG2*, 1 *PLN*, 1 multiple)
- Presentation **alive** n=541 (probands 220, relatives 321 (443 (80%) *PKP2*, 15 *DSP*, 30 *DSG2*, 8 *DSC2*, 2 *JUP*, 31 *PLN*, 1 *TMEM43*, 21 multiple)

Sex and Outcome in Mutation Carriers

(JHU-ICIN database, n=577)

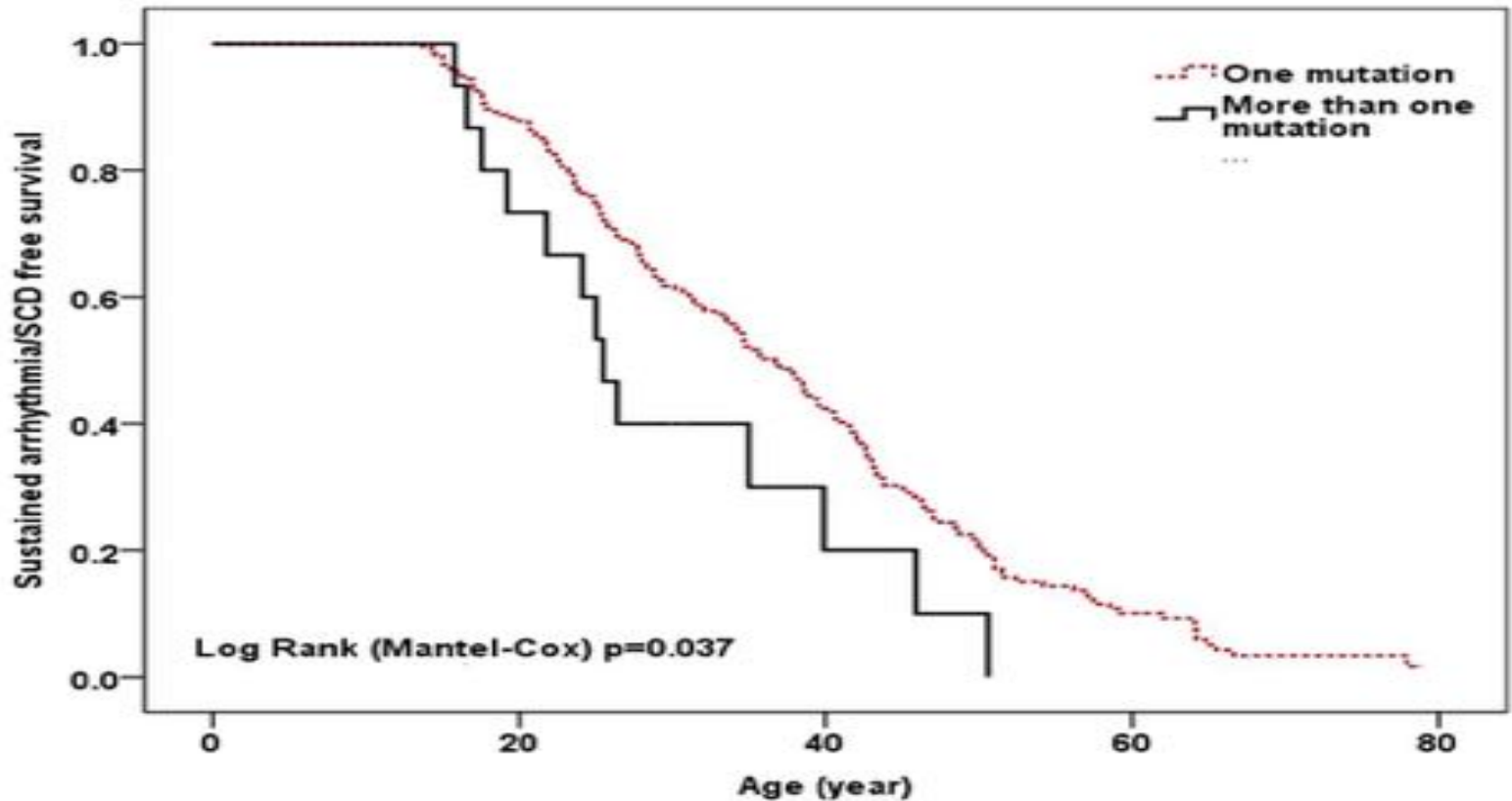
A. Bhonsale et al. *Eur Heart J* 2015;36 :847



Single vs Multiple Mutations in Index Patients

(JHU-ICIN database, n=577)

A. Bhonsale et al. *Eur Heart J.* 2015;36 (14):847

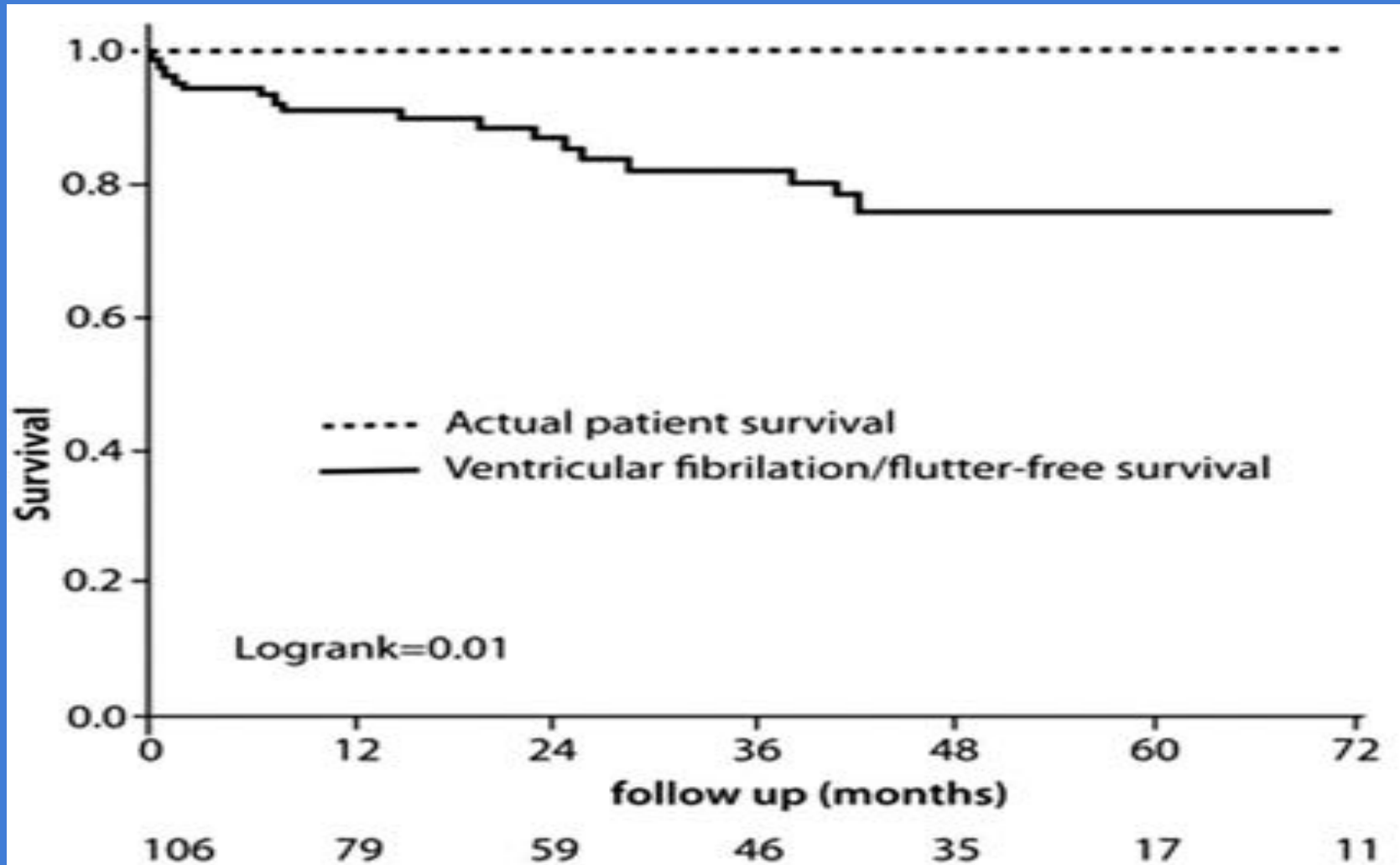


One mutation	215	186	80	14	-
More than one mutation	15	11	2	-	-

ARVD/C Presentation Without Sust VT/VF n=106

Cumulative Survival from ICD Therapy

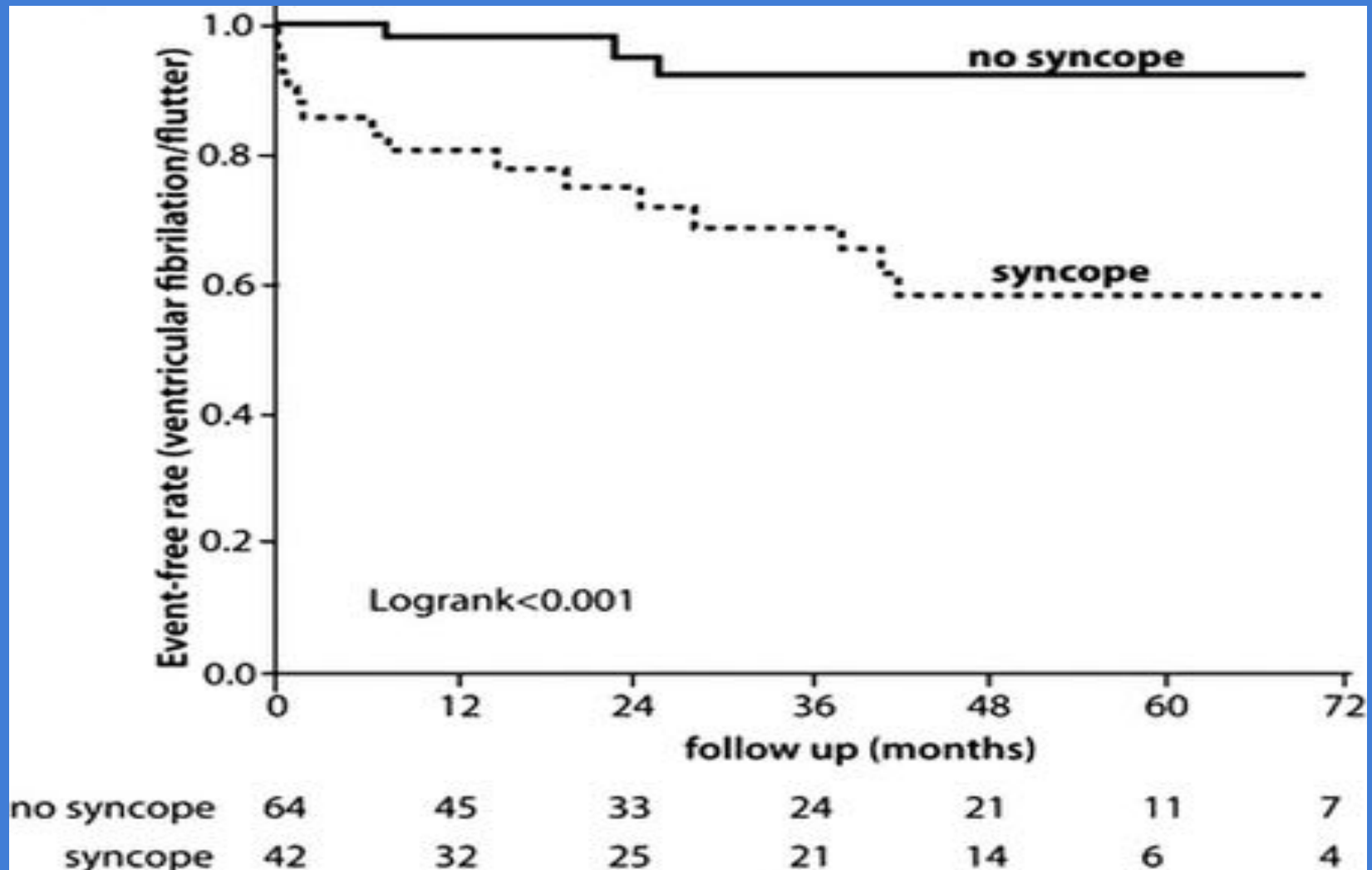
Corrado et al. *Circulation* 2010;122:1144



ARVD/C Presentation Without Sust VT/VF n=106

Cumulative Survival from ICD Therapy for VF/Vfl

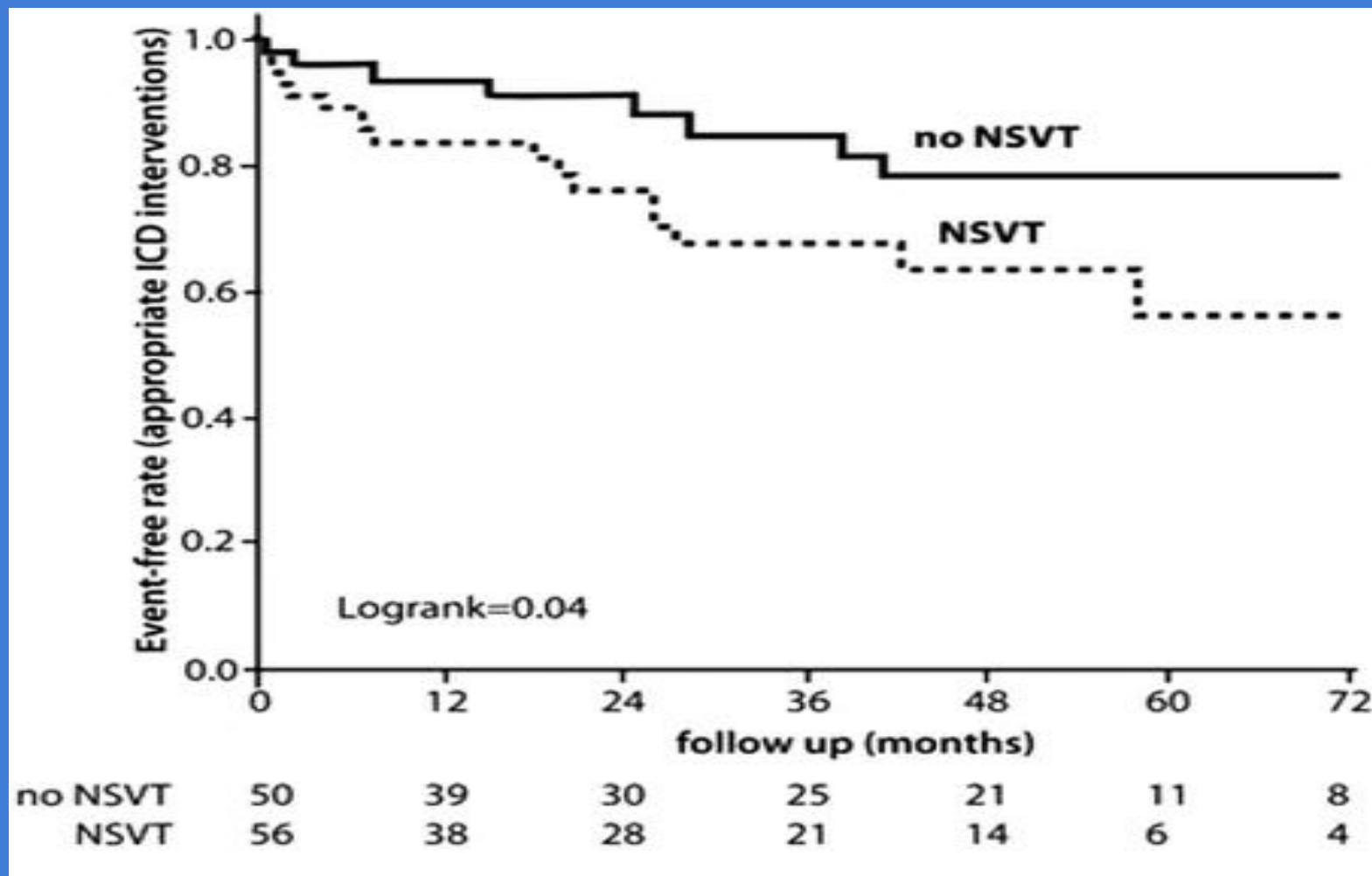
Corrado et al. Circulation 2010;122:1144



ARVD/C Presentation without sust VT/VF n=106

Cumulative survival from ICD therapy

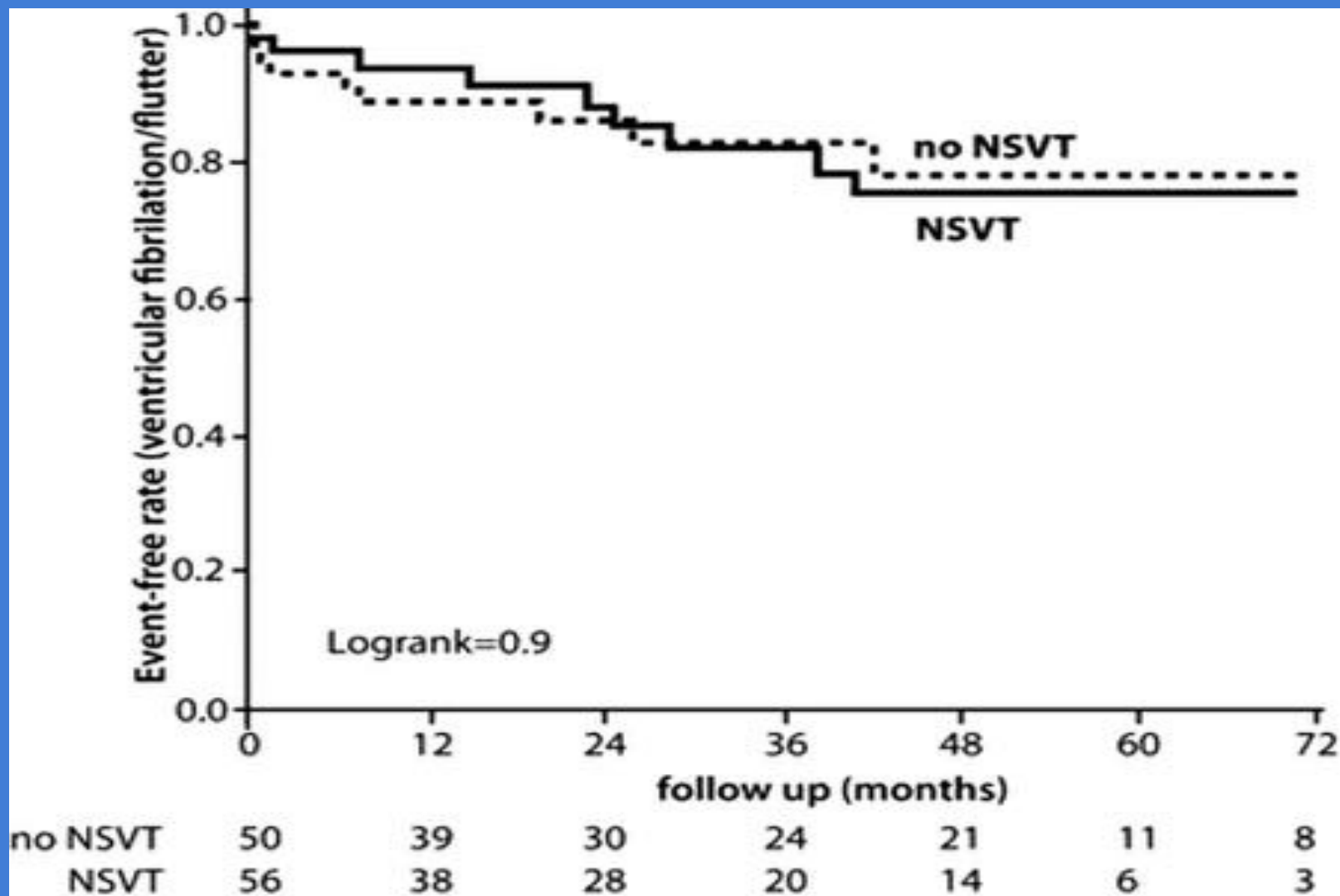
Corrado et al. Circulation 2010;122:1144



ARVD/C Presentation without sust VT/VF n=106

Cumulative Survival from ICD Therapy for VF/Vfl

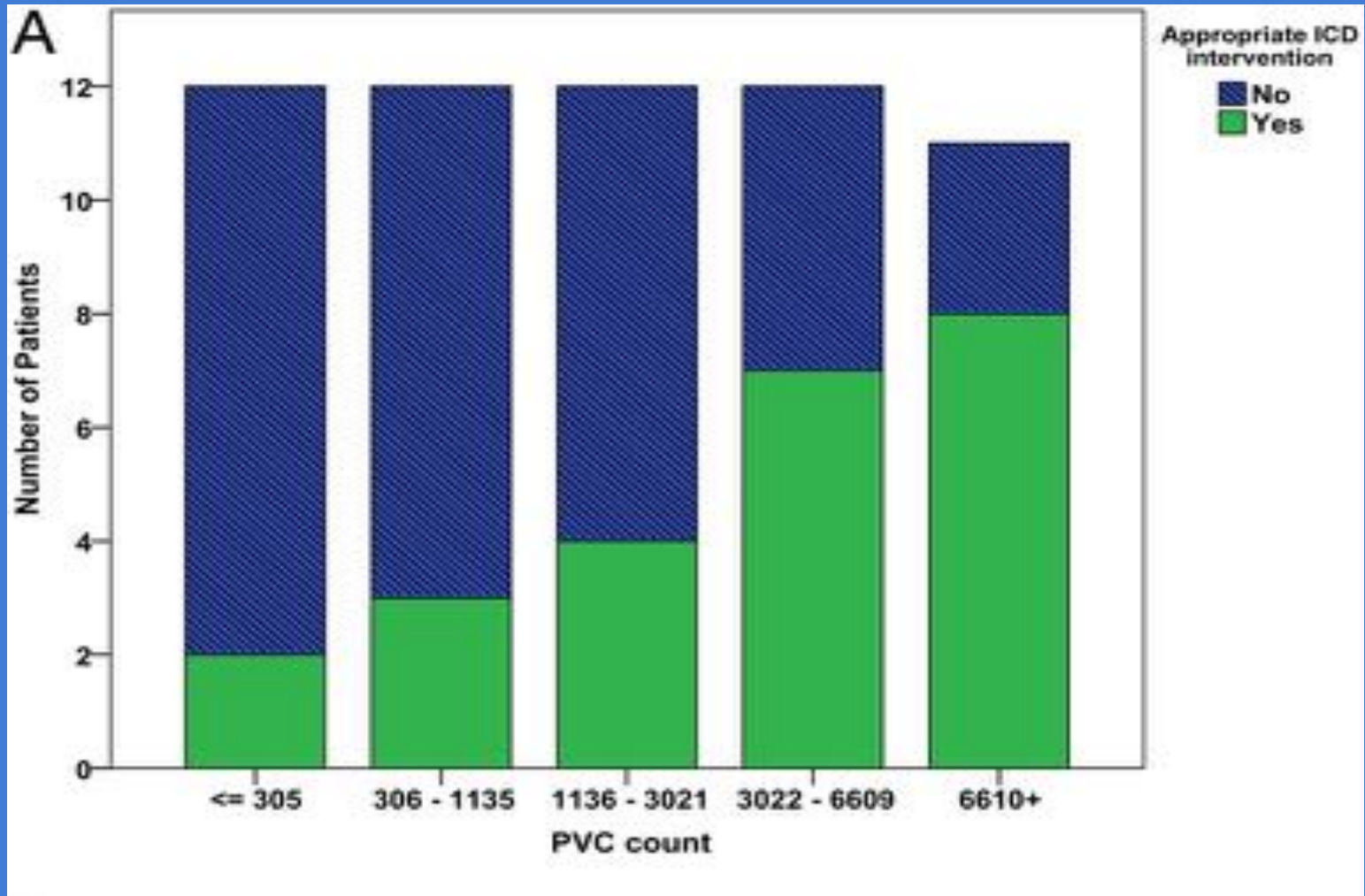
Corrado et al. Circulation 2010;122:1144



Primary Prevention in ARVD/C n=84

PVC count and ICD therapy

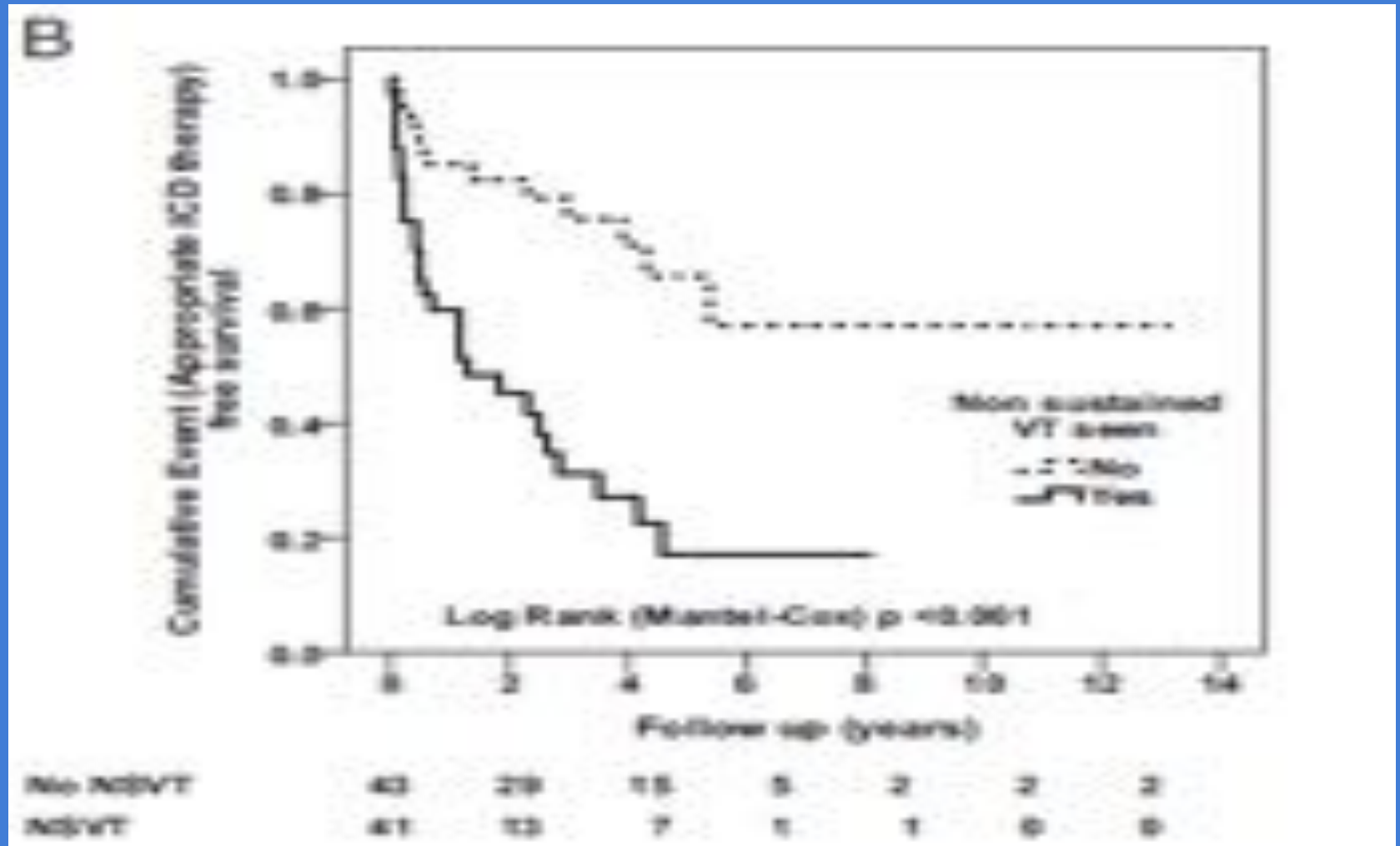
Bhonsale et al. J Am Coll 2011;58:1485



Primary Prevention in ARVD/C n=84

Cumulative Survival from ICD Therapy

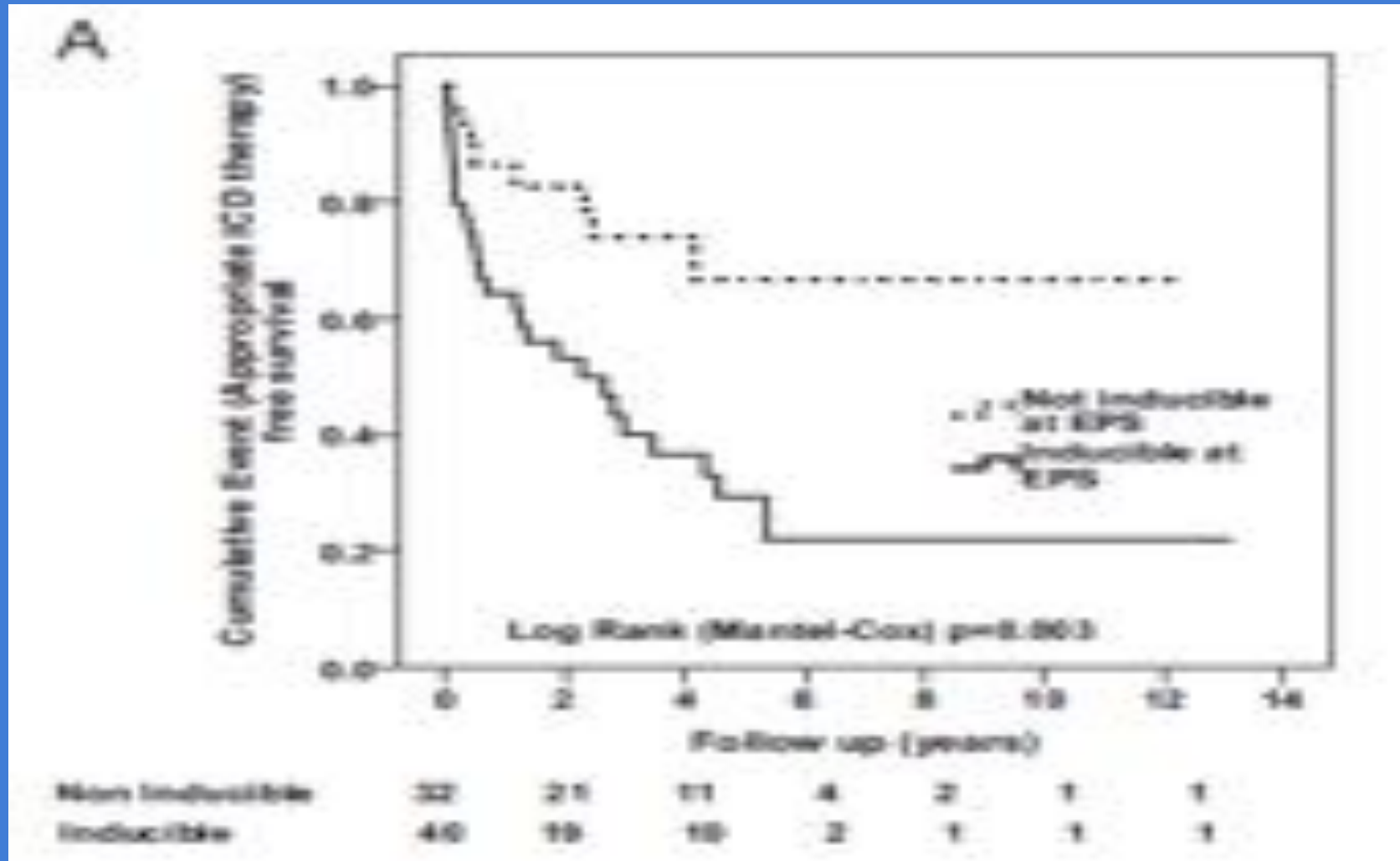
Bhonsale et al. J Am Coll 2011;58:1485



Primary Prevention in ARVD/C n=84

Cumulative Survival from ICD Therapy

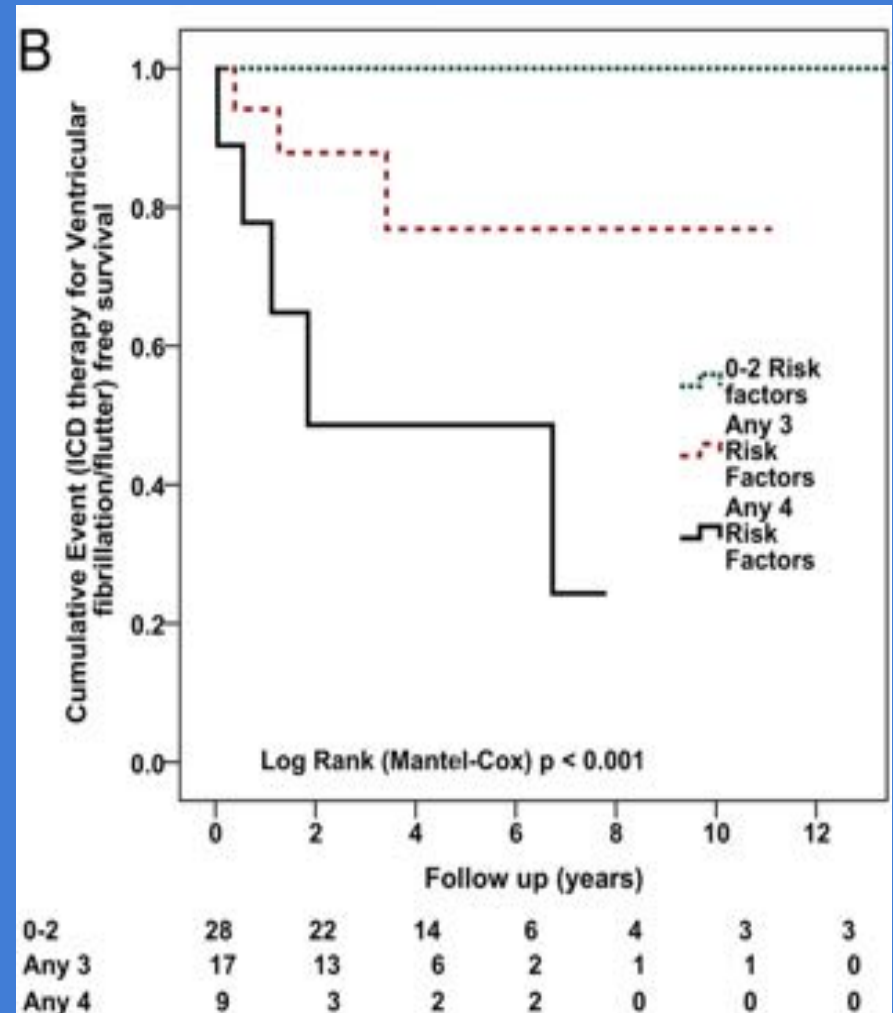
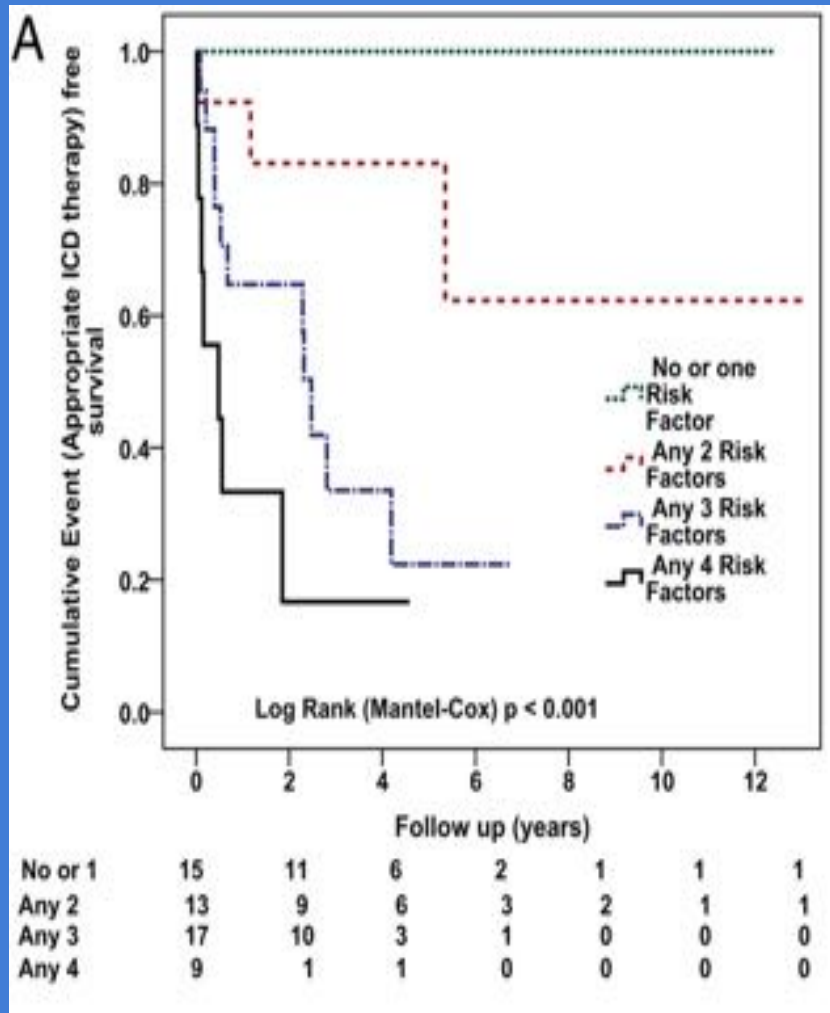
Bhonsale et al. J Am Coll 2011;58:1485



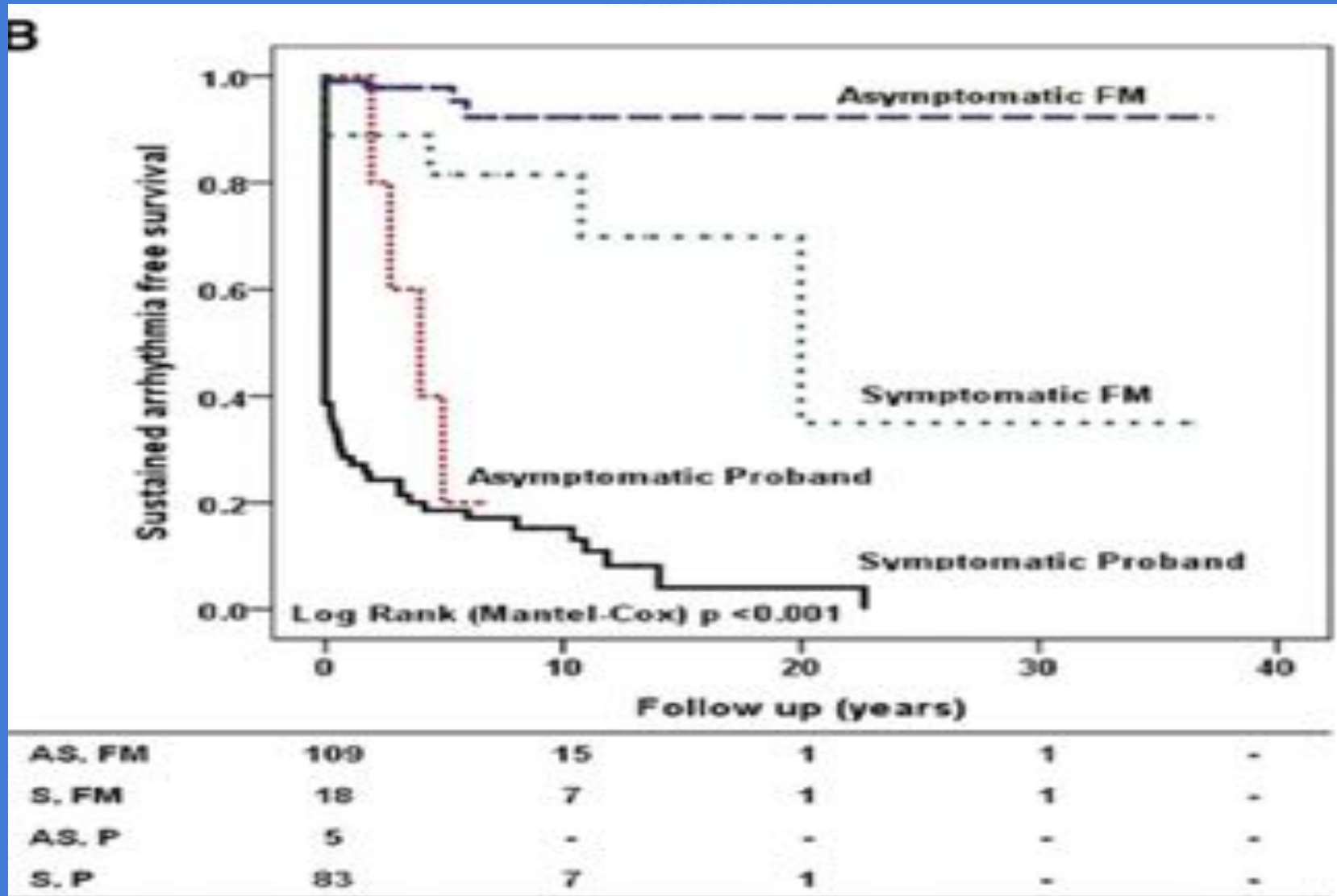
Primary Prevention in ARVD/C

Cumulative effect of risk factors

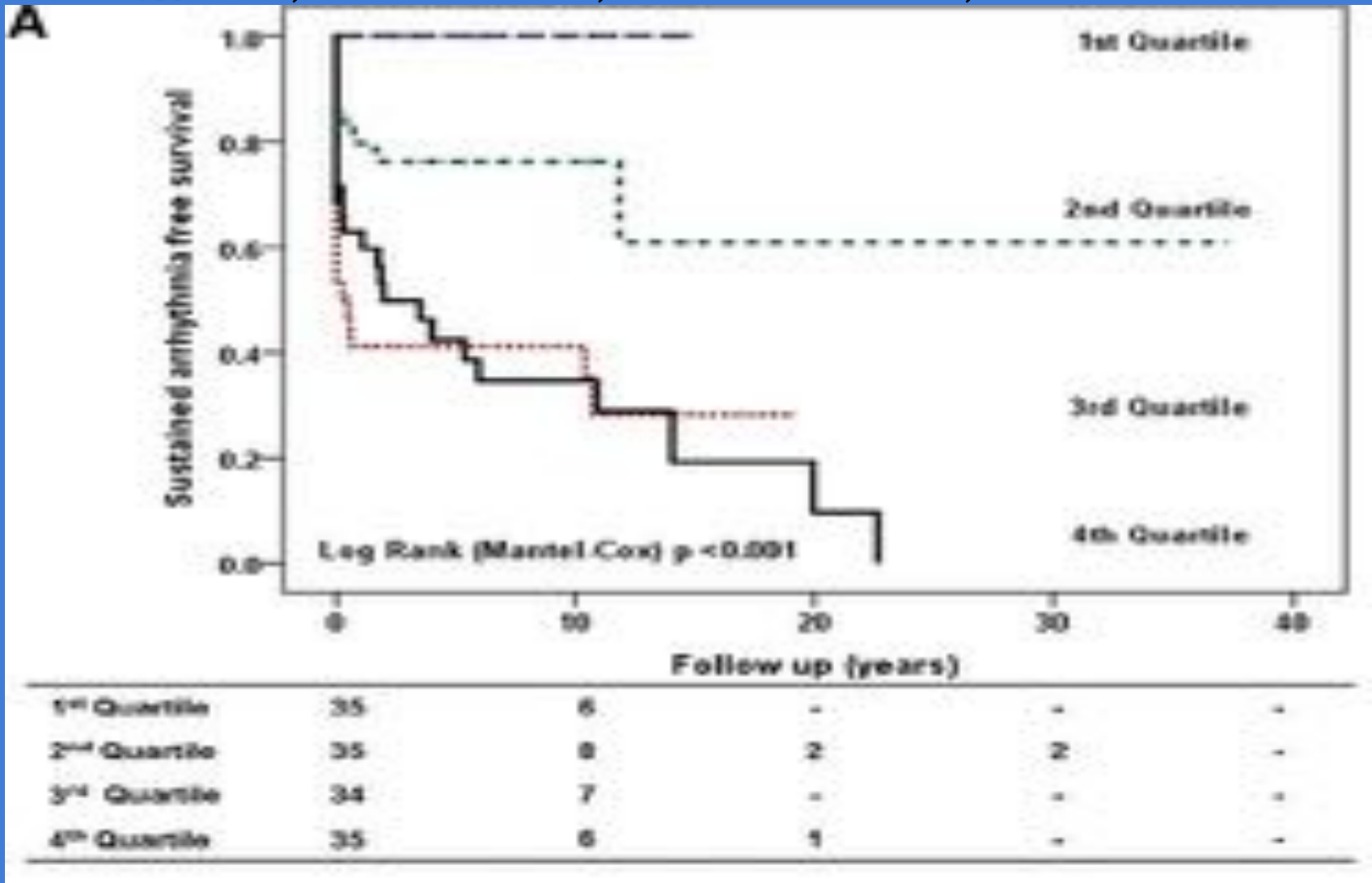
Bhonsale et al. J Am Coll 2011;58:1485



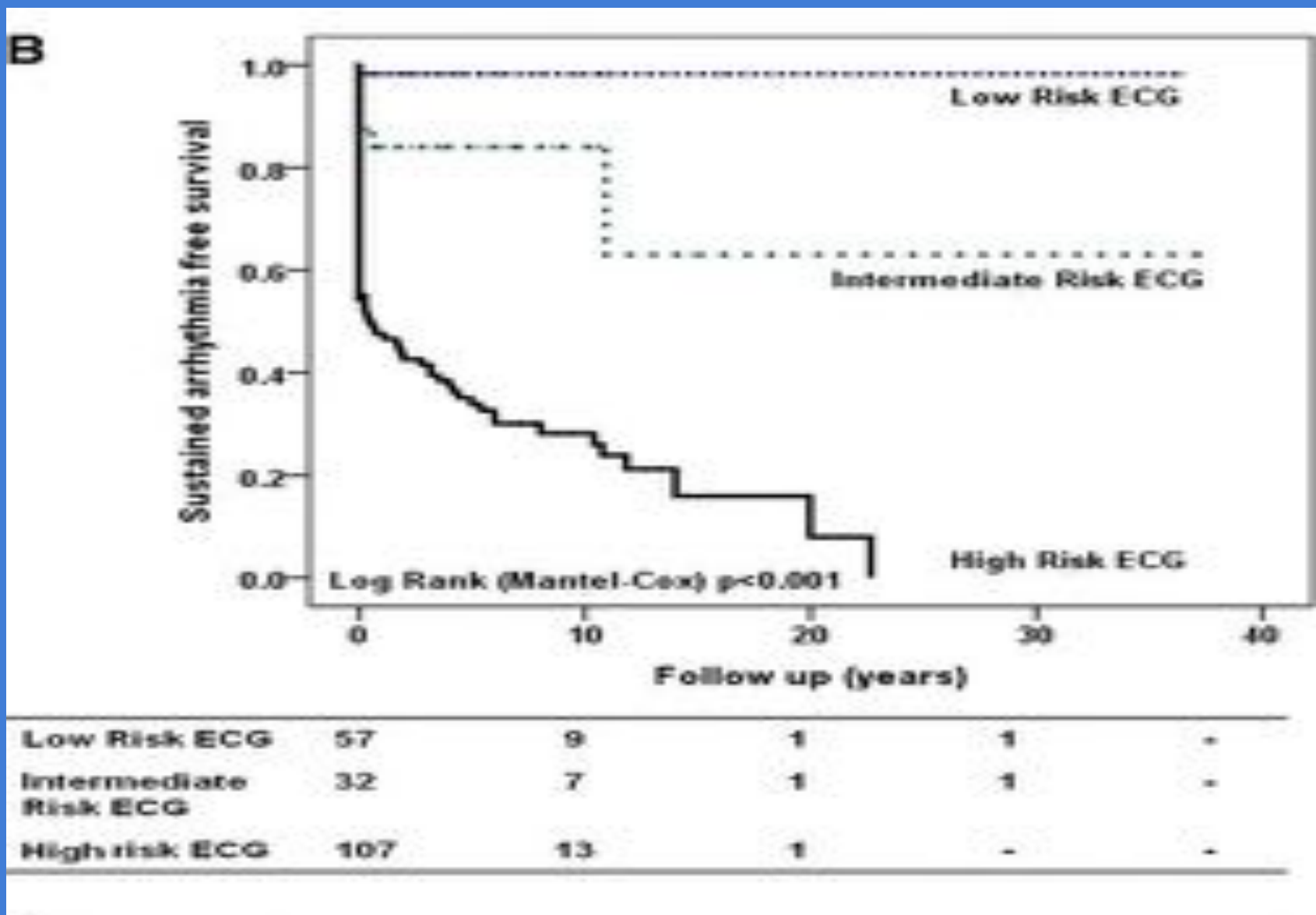
Cumulative Survival Without Sustained VT/VF n=215 Probands vs Relatives



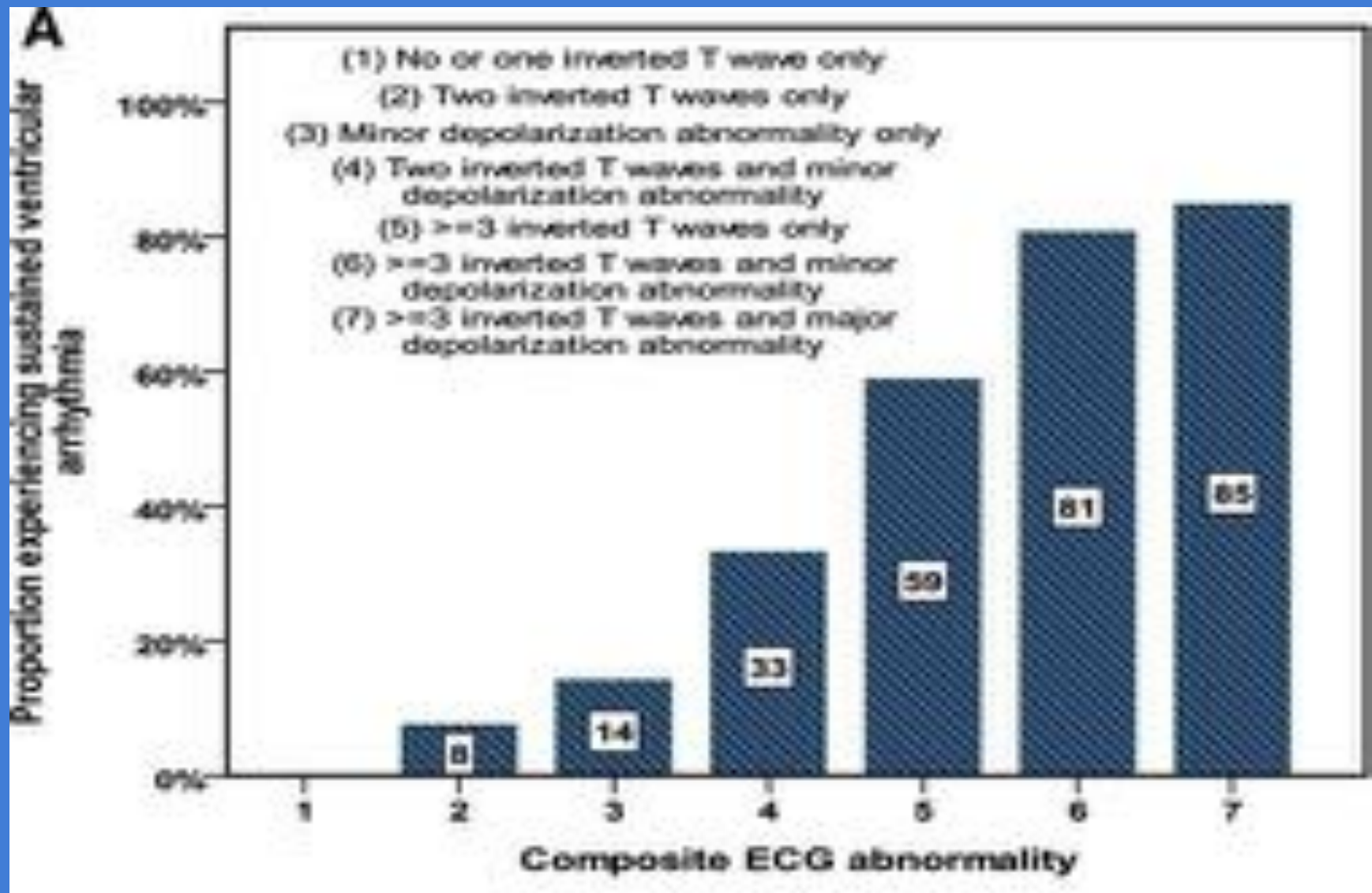
PVC Count (Quartiles) and Cumulative Survival Without Sustained VT-VF
1st ≤ 10 , 2nd 10–760, 3rd 760–3560, 4th > 3560



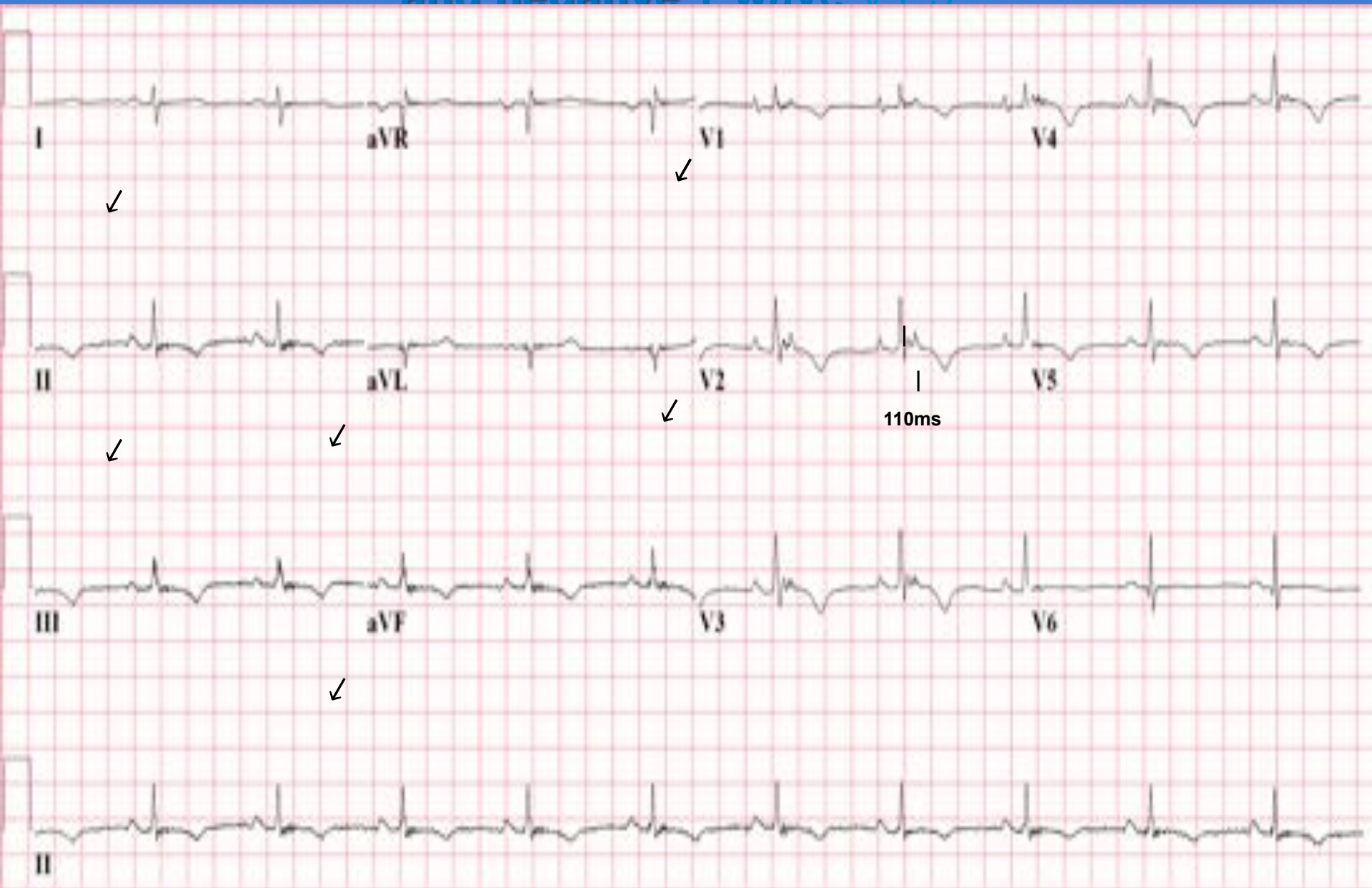
Cumulative Survival Without Sustained VT/VF and 12-lead ECG



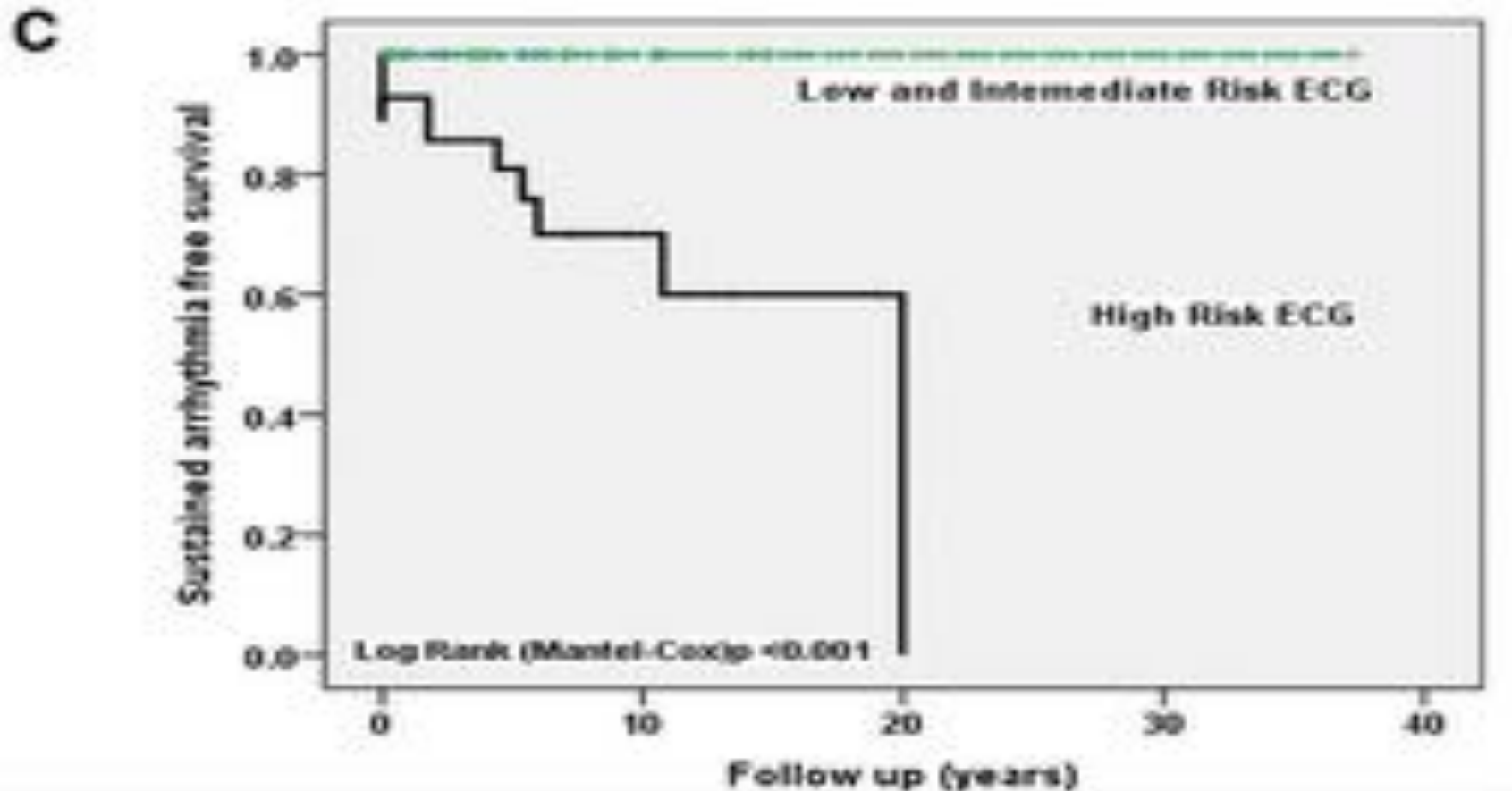
Risk of sustained VT/VF related to 12-lead ECG markers



Prolonged TAD, Epsilon Waves, Negative T in V1-5 and negative T wave V1-5



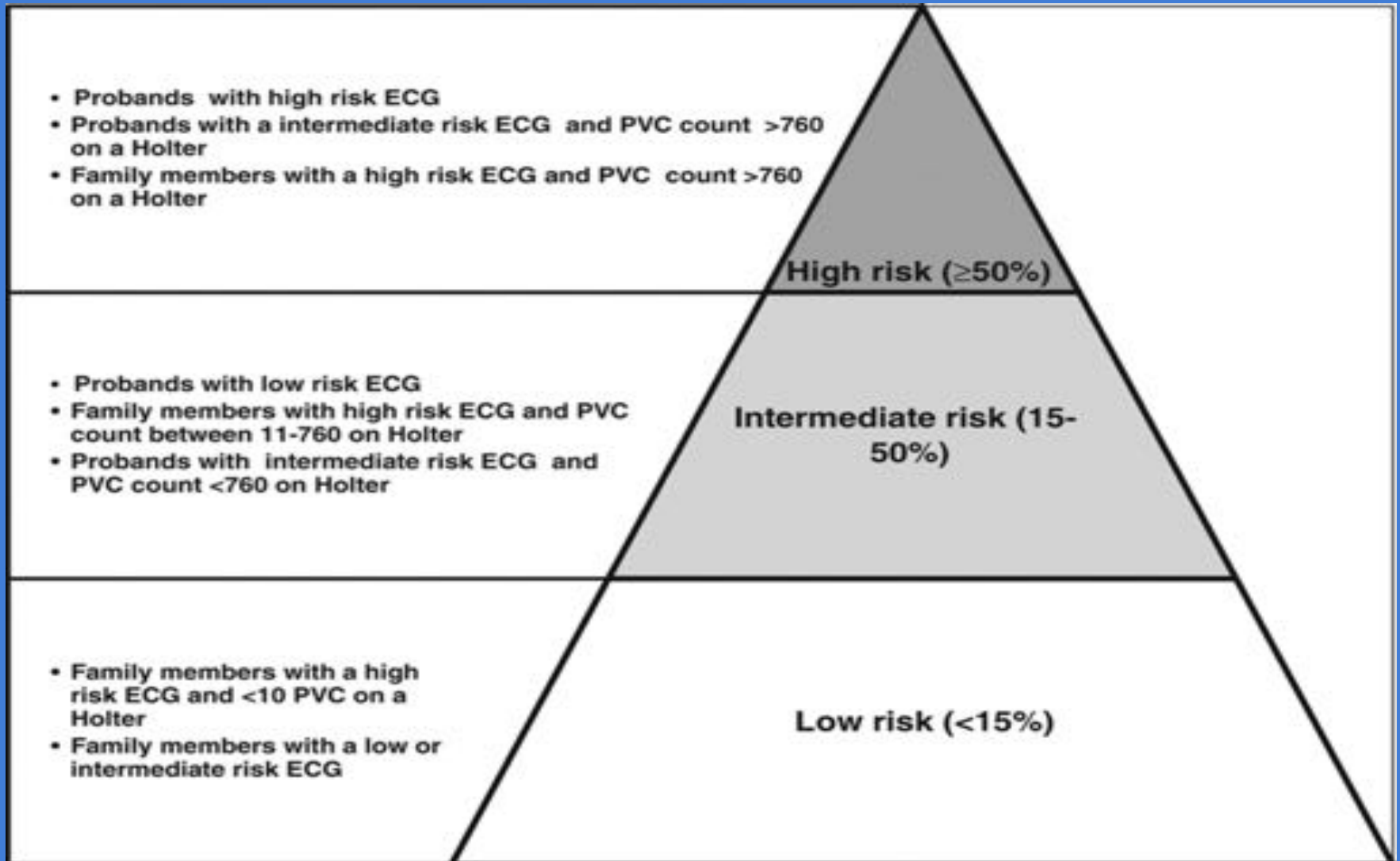
ECG and Cumulative Survival Without Sustained VT/VF in Relatives



Low Risk ECG	56	9	1	1	-
Intermediate Risk ECG	24	6	1	1	-
High risk ECG	28	7	-	-	-

Risk Stratification in ARVD/C Mutation Carriers (n=215)

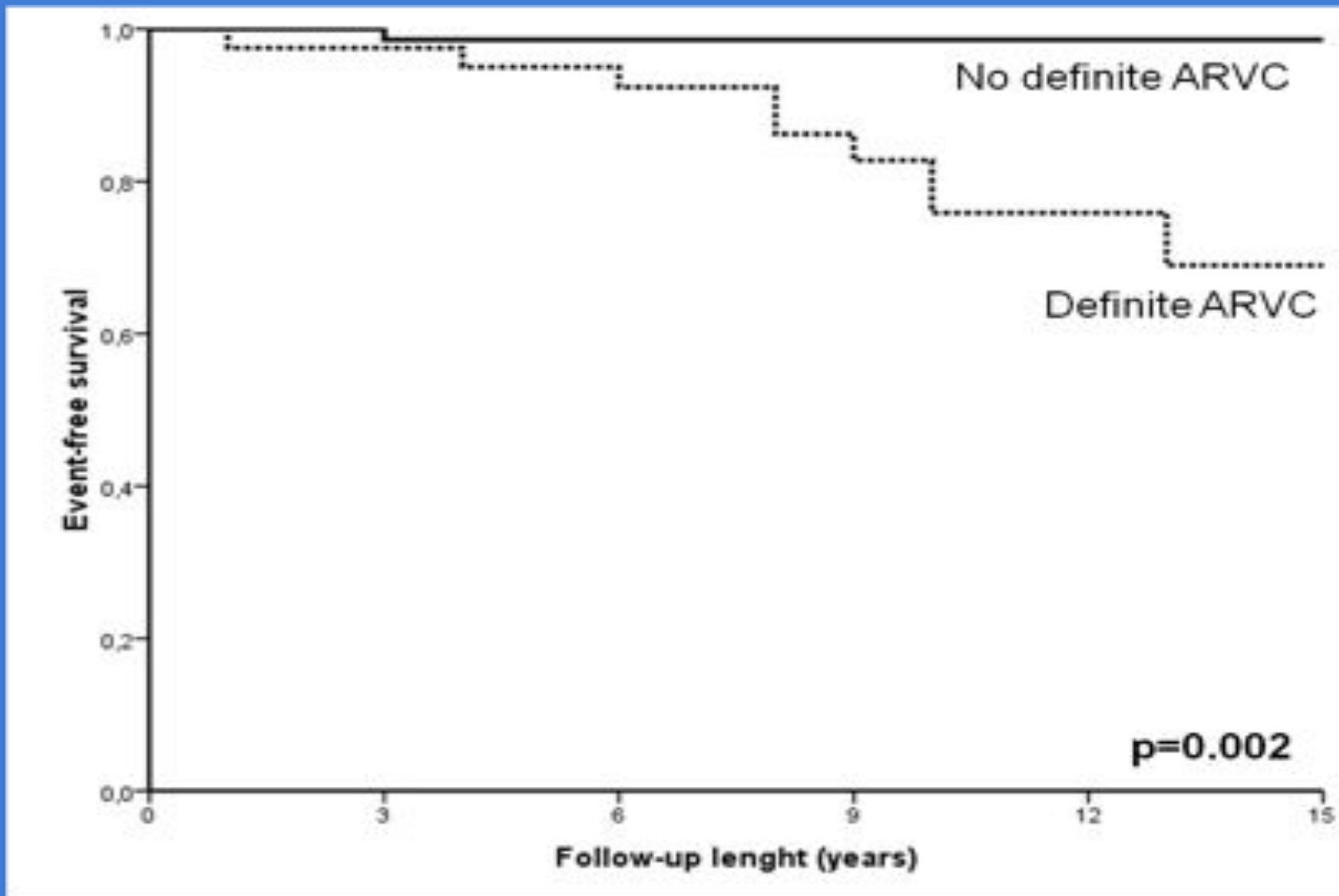
Presentation, ECG, and Holter Monitoring



ACM Mutation Carriers Without VT/VF

Definite (n=40) vs Borderline (n=19) and no (n=57) ACM

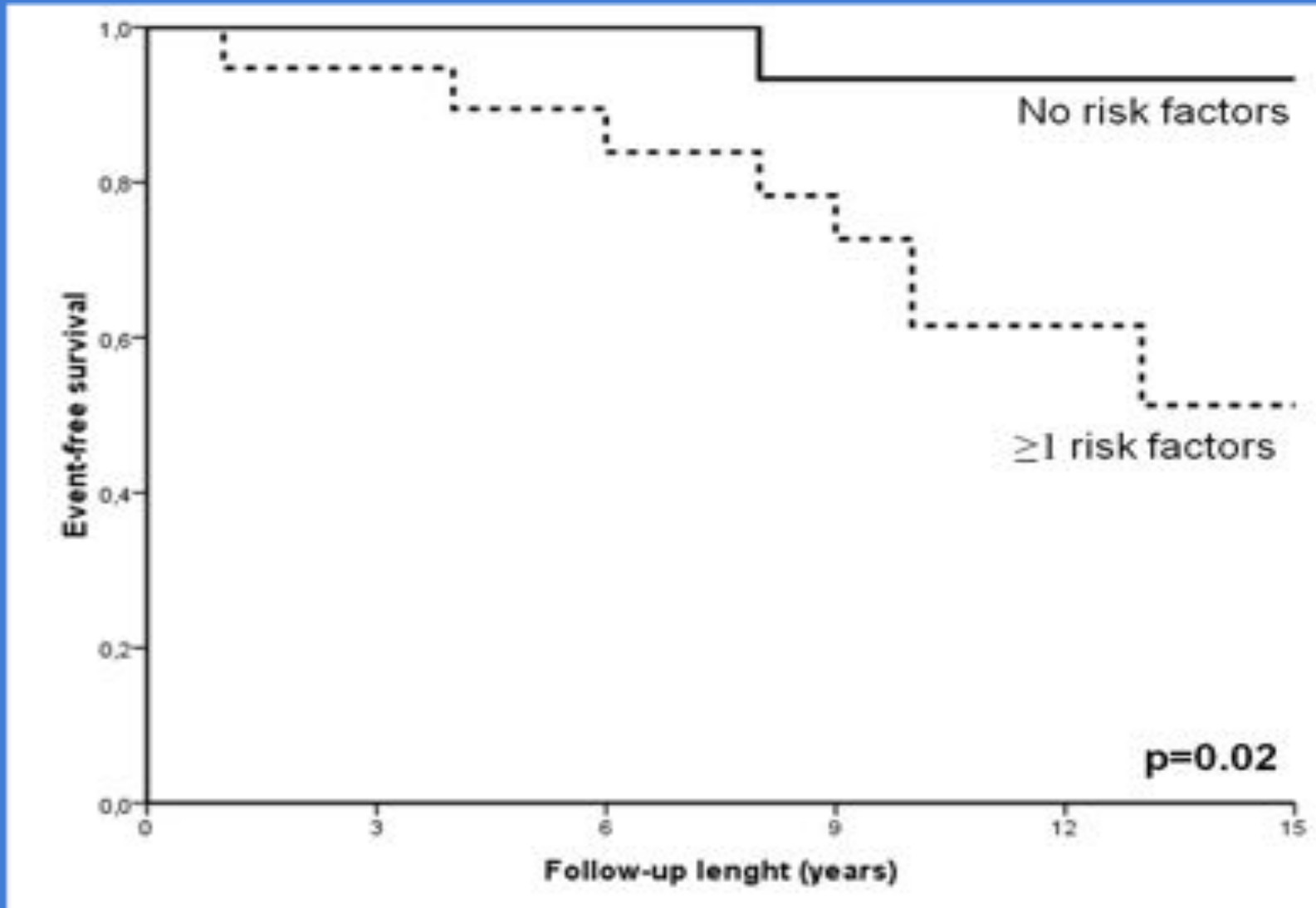
Zorzi et al. *Europace* 2015



Definite ACM (Mut +) Without VT/VF

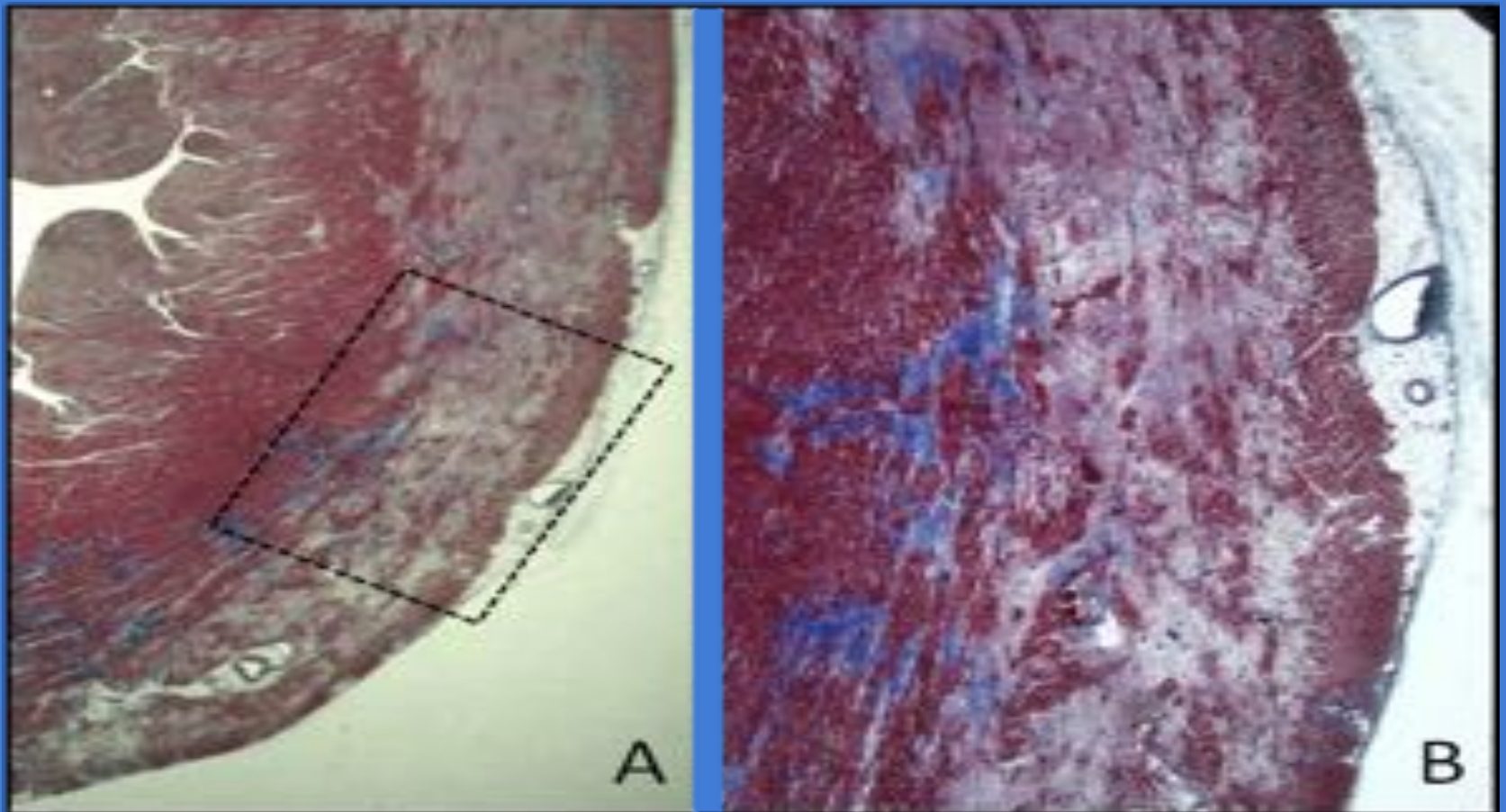
Absent (n=21) vs ≥ 1 Risk Factors (n=19)

Zorzi et al. Europace 2015



LV Histology of 15 yr Old SCD Victim with *DSP* mutation

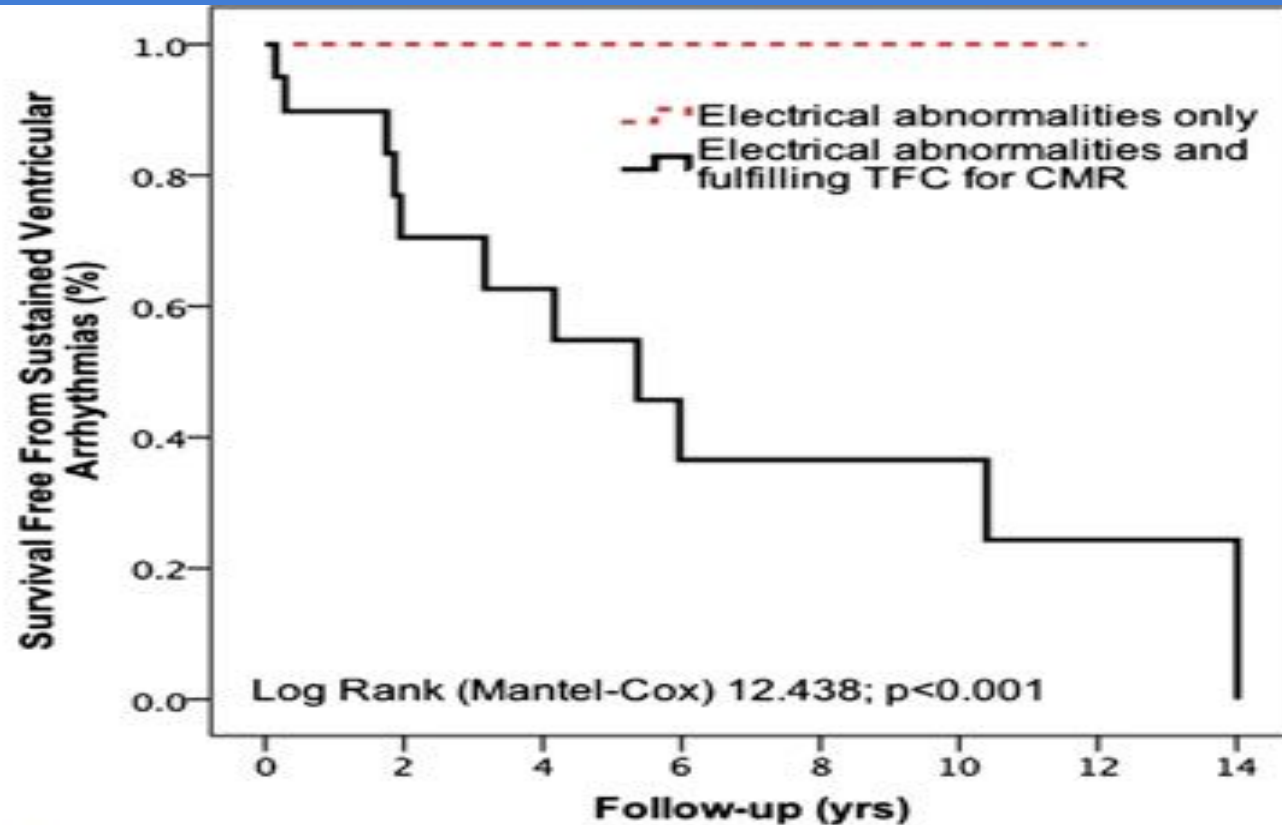
Zorzi et al. *Europace* 2015



ACM Mut+ Without VT/VF at Baseline

VT During 5.8 yrs Follow-up Related to ECG/Holter at Baseline

A.S. te Riele et al. JACC 2013; 62:1761



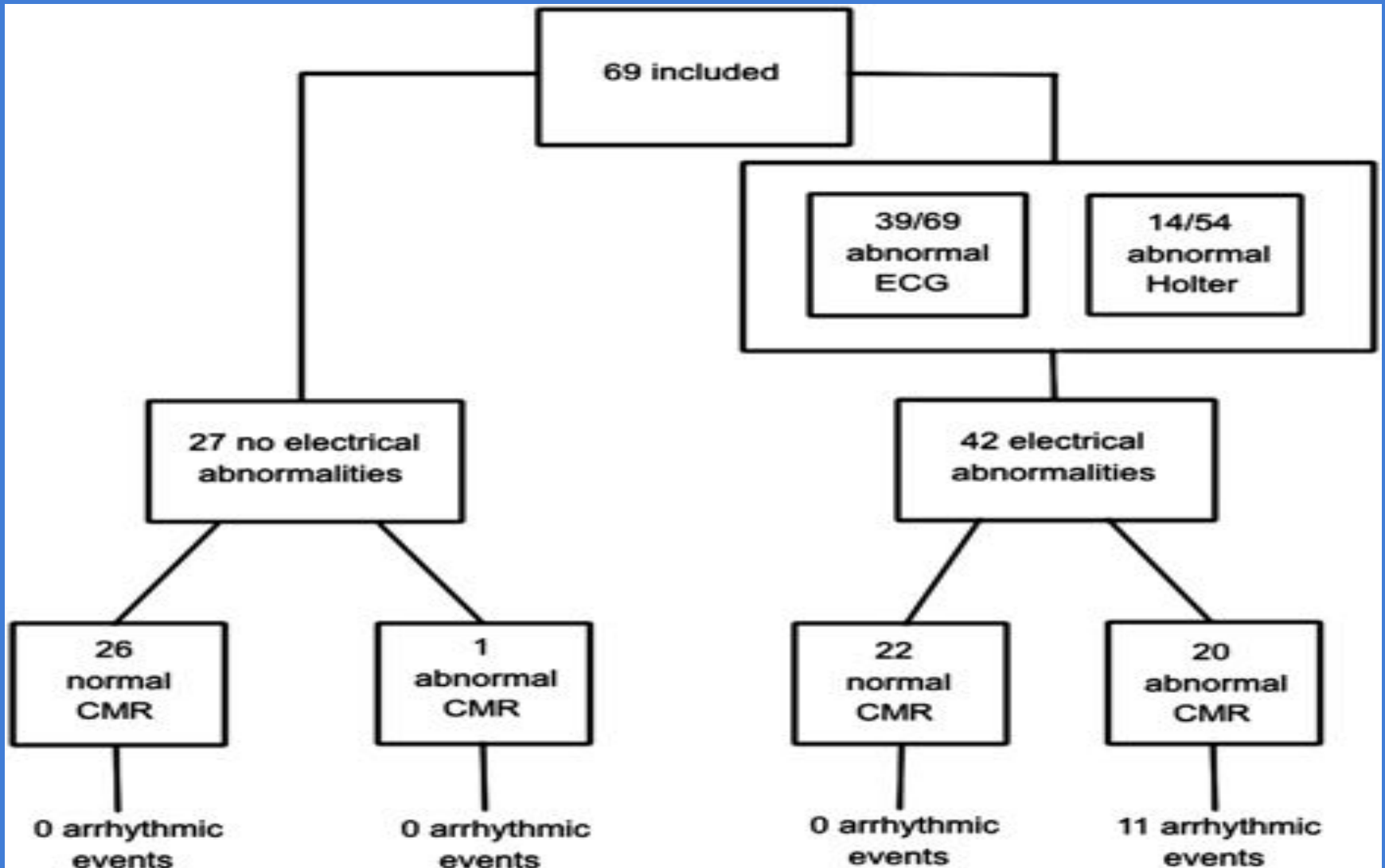
Number at risk

Electrical abnormalities only	22	14	10	8	5	4	0	0
Electrical abnormalities and fulfilling TFC for MRI	20	11	8	4	3	3	2	1

ACM Mut+ Without VT/VF at Baseline

VT During 5.8 yrs Follow-up Related to ECG/Holter at Baseline

A.S. te Riele et al. JACC 2013; 62:1761

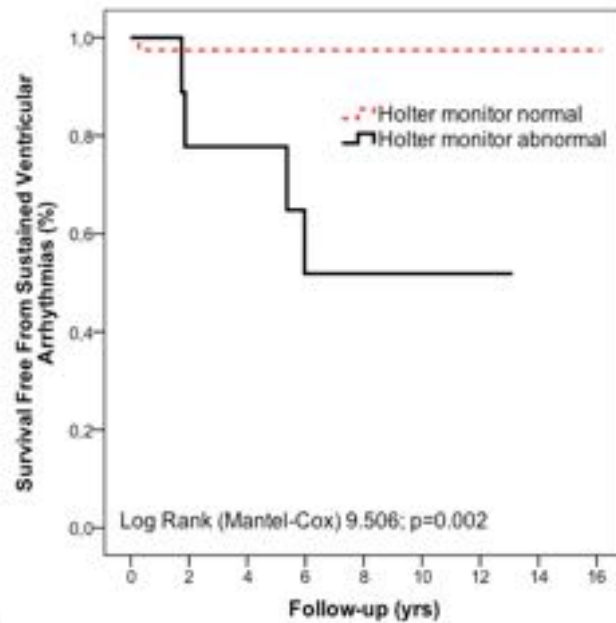


Summary

- **Primary Prevention Hampered by SCD at First Presentation in Young Subjects**
- **Arrhythmic Risk in Probands Presenting Alive is Primarily Management and ICD Therapy Related**
- **Arrhythmic Risk in Family Members Related to Pathogenic Mutation (DSP, Multiple mutations!), Symptoms at Presentation, and ECG, Holter and Structural Parameters (Syncope, PES-induced VT)**
- **Consider Primary Prevention ICD in Probands and Relatives with Phenotypic Risk Factors, or high risk mutation(s)**

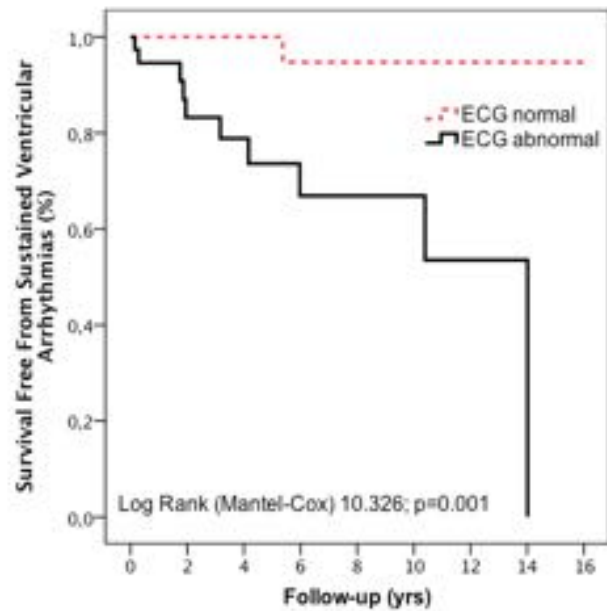
Sudden Cardiac Death in Pediatric ARVD/C

	Sex	Age at SCD	Family status	Circumstance of SCD	Prior medical evaluation	Mutation*	Autopsy findings	Symptoms prior to SCD
1	Female	15	Proband	Playing basketball	No	<i>PKP2</i> ; p.Q74fsX84	No records	None
2	Male	17	Proband	Playing hockey	No	<i>PKP2</i> ; p.A733fsX740	Biventricular hypertrophy, fibrofatty RV replacement, aneurysm RV free wall	"Chest discomfort"
3	Male	16	Proband	Playing basketball	No	<i>PKP2</i> ; p.IVS10-1G>C	Biventricular dilatation with fatty infiltration RV>LV	No records
4	Male	16	Proband	Playing basketball	No	<i>PKP2</i> ; p.IVS12+1G>A	Macroscopic fatty infiltration of basal anterior and inferior RV and posterolateral LV	No records
5	Female	13	Proband	Rest	No	None	Fatty infiltration of RV subepicardial until endocardium, with areas of fibrosis and strands of normal heart tissue	None
6	Male	15	Family member (brother of proband)	Hunting	No	<i>PKP2</i> , p.A733fsX740	Inflammatory changes in RV	No records
7	Male	16	Family member (brother of proband)	Getting up to go to bathroom	No	<i>PKP2</i> ; p.Q74fsX84	No records	None
8	Female	14	Family member (sister of proband)	Playing basketball	No	<i>PKP2</i> : mutant splice product	RV dilatation with wall thinning and fibrofatty replacement	No records
9	Female	16	Family member (sister of proband)	In bed	No	None	No records	None
10	Male	14	Family member (son of proband)	Playing soccer	No	<i>PKP2</i> ; p.IVS12+1G>A	Fibrofatty RV (and to lesser extent, LV) infiltration with focal absence of myocardium	No records
11	Male	17	Family member (brother of proband)	Gym class	No	<i>PKP2</i> ; p.V406SfsX4	No records	Presyncope during exercise



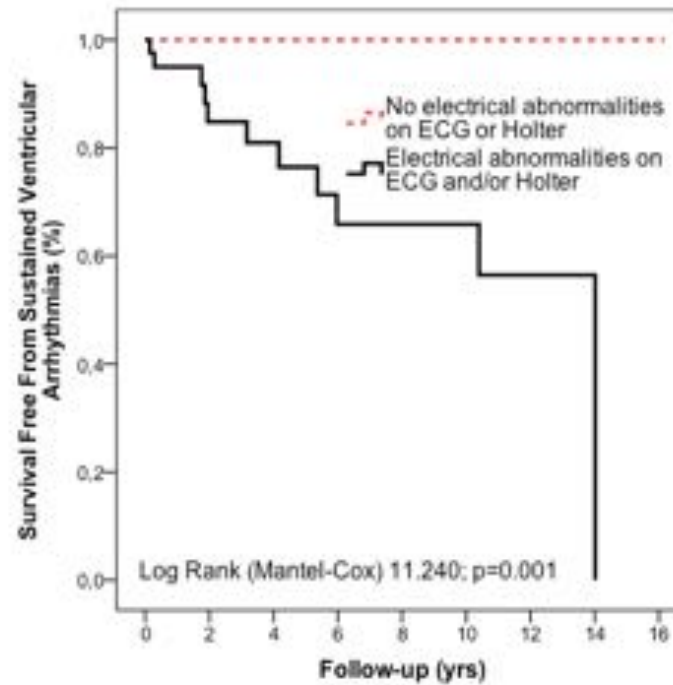
Number at risk

Holter monitor normal	40	31	25	19	12	9	3	3	1
Holter monitor abnormal	14	7	6	4	3	3	1	0	0



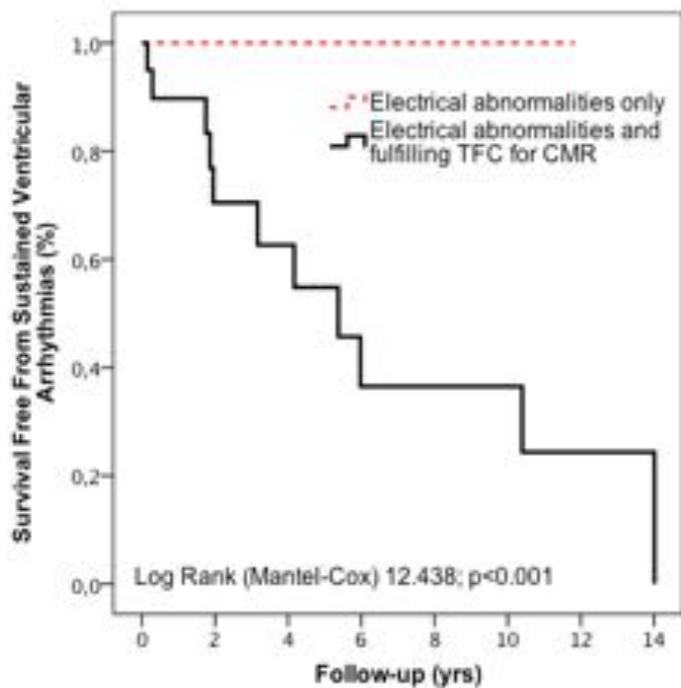
Number at risk

ECG normal	30	26	22	17	12	9	3	3	0
ECG abnormal	39	22	15	10	6	5	2	1	0



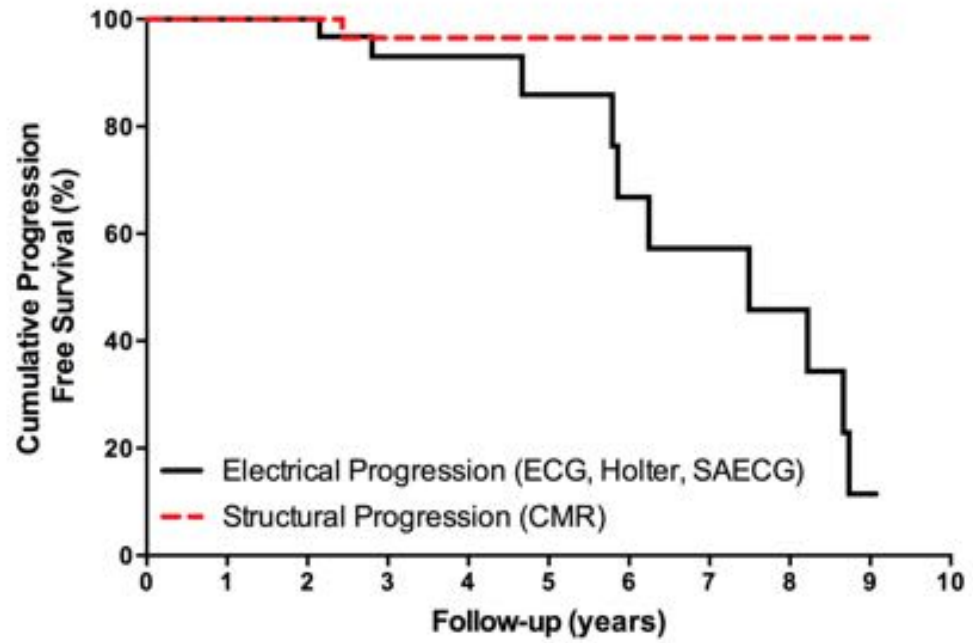
Number at risk

No electrical abnormalities (ECG, Holter monitor)	27	23	19	15	10	7	3	3	1
Electrical abnormalities (ECG, Holter monitor)	42	25	18	12	8	7	2	1	0



Number at risk

Electrical abnormalities only	22	14	10	8	5	4	0	0
Electrical abnormalities and fulfilling TFC for MRI	20	11	8	4	3	3	2	1



Number at Risk* 37 37 31 24 16 12 7 6 4 1 0

