ADVANCES IN CARDIAC ARRHYTHMIAS AND GREAT INNOVATIONS IN CARDIOLOGY – XXVI GIORNATE CARDIOLOGICHE TORINESI

Sudden death in ischemic cardiomyopathy: is ejection fraction the only reliable risk factor?

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European Heart Journal Advance Access published May 5, 2014

European Heart Journal
doi:10.1093/eurheartj/ehu176

SPECIAL ARTICLE

Risk stratification for sudden cardiac death: current status and challenges for the future†

	% of all SCD	Predictability
Not diagnosed with heart disease	45	Poor
History of heart disease: LVEF >40%	40	Limited
History of heart disease: LVEF <40%	13	Possible
Genetically based arrhythmic disease	2	Limited

SCD, sudden cardiac death; LVEF, left ventricular ejection fraction.

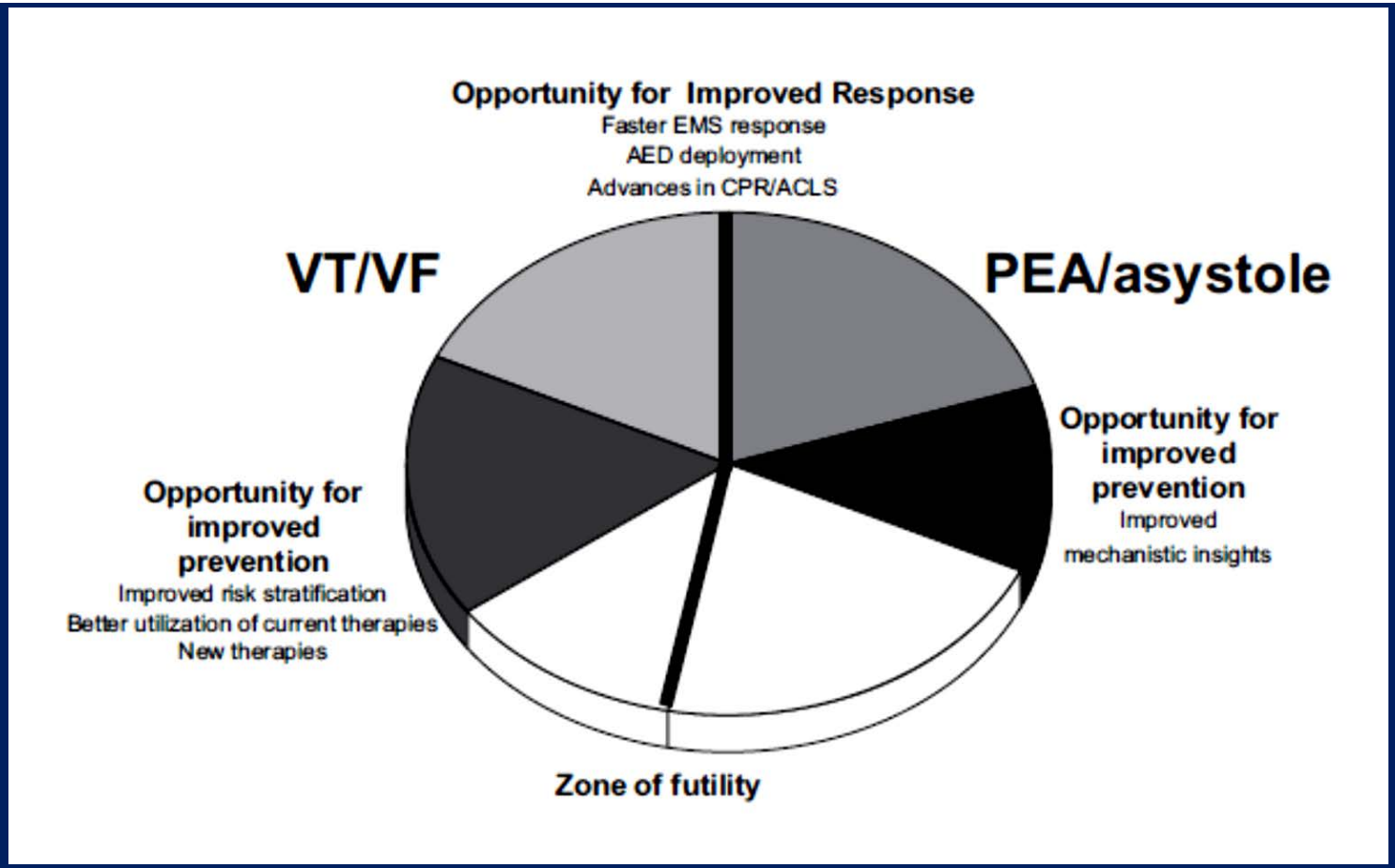
Wellens et al, 2014

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association

Special Report

Risk Stratification for Sudden Cardiac Death
A Plan for the Future



Goldberger et al, 2014

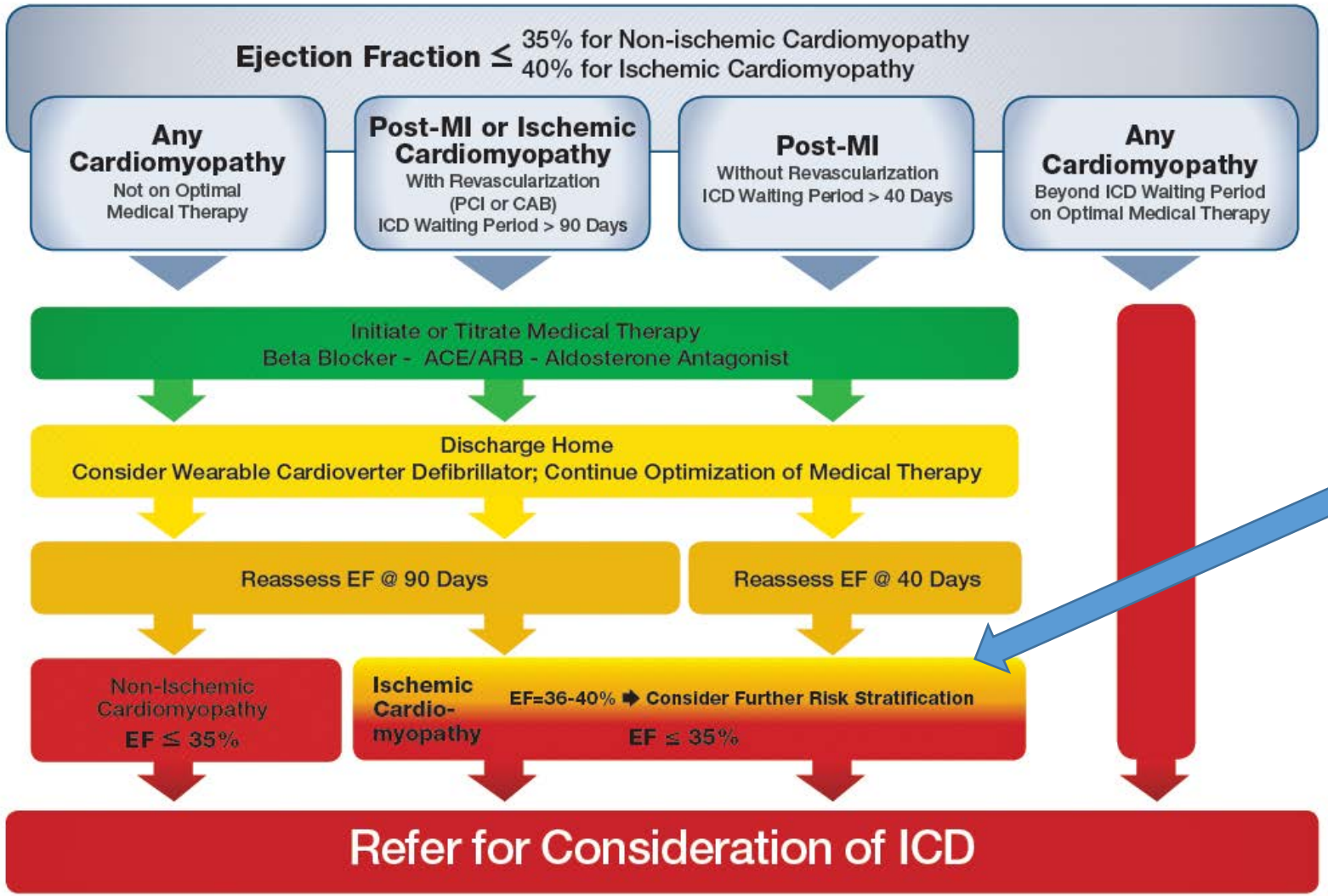
Three main concepts:

1) Sudden cardiac death my be the first and unique manifestation of ischemic heart disease.

2) Ventricular fibrillation is often but not always the cause of sudden cardiac death

3) Sudden cardiac death frequently occurs in patients with preserve or slightly reduced LVEF

Sudden Cardiac Death Primary Prevention Protocols

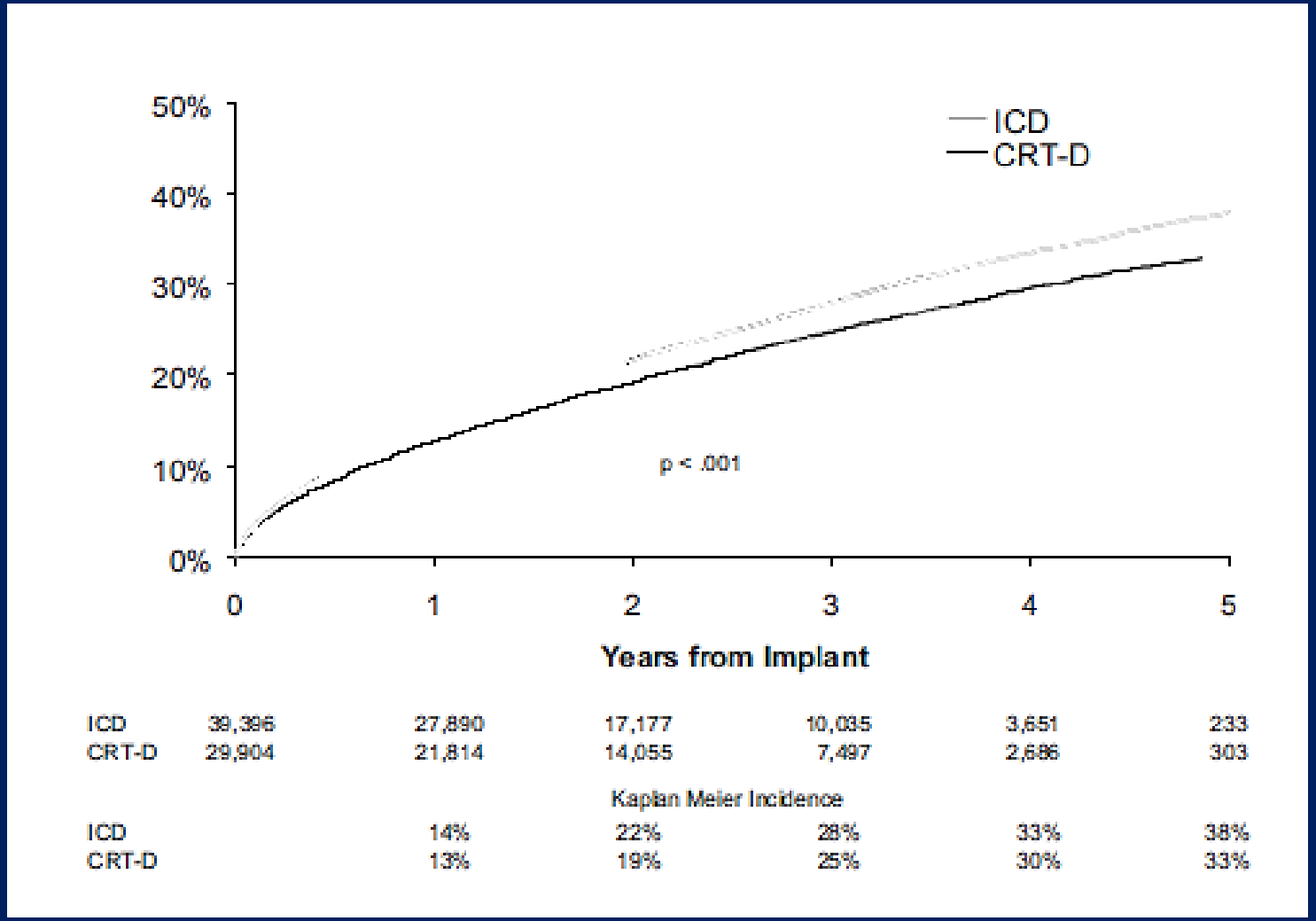


Learn more at www.HRSonline.org

Recommended by SCA Prevention Protocols Working Group (Review Date: 9/10/2012)

Heart Rhythm Society℠

Annual incidence of shock by device type: the Altitude survival trial: total networked N°= 69300 pts



ICD	39,396	27,890	17,177	10,035	3,651	233
CRT-D	29,904	21,814	14,055	7,497	2,686	303

Kaplan Meier Incidence

ICD	14%	22%	28%	33%	38%
CRT-D	13%	19%	25%	30%	33%

Saxon et al, Circulation 2010

CONVENTIONAL RISK STRATIFIERS FOR Cardiac mortality and SCD

Electrophysiologic surrogates

Measures of myocardial conduction disorders
- ECG, QRS fractionation, …….
- Signal averaged ECG
- Electrophysiologic Study

Measures of dispersion of repolarization
- QT dispersion & variability
- T-wave alternans & Variability

Measures of autonomic imbalance
- Resting Heart Rate
- Heart Rate Variability
- Baroreflex Sensitivity
- Heart rate turbulence
- Post Extrasystolic Potentiation
- Deceleration Capacity
- Myocardial Sympathetic Innervation

Measures of electrical instability
- VPCs
- NSVT

Functional contractile surrogates

NYHA CLASS

Left Ventricular Ejection Fraction

Left Ventricular Volume

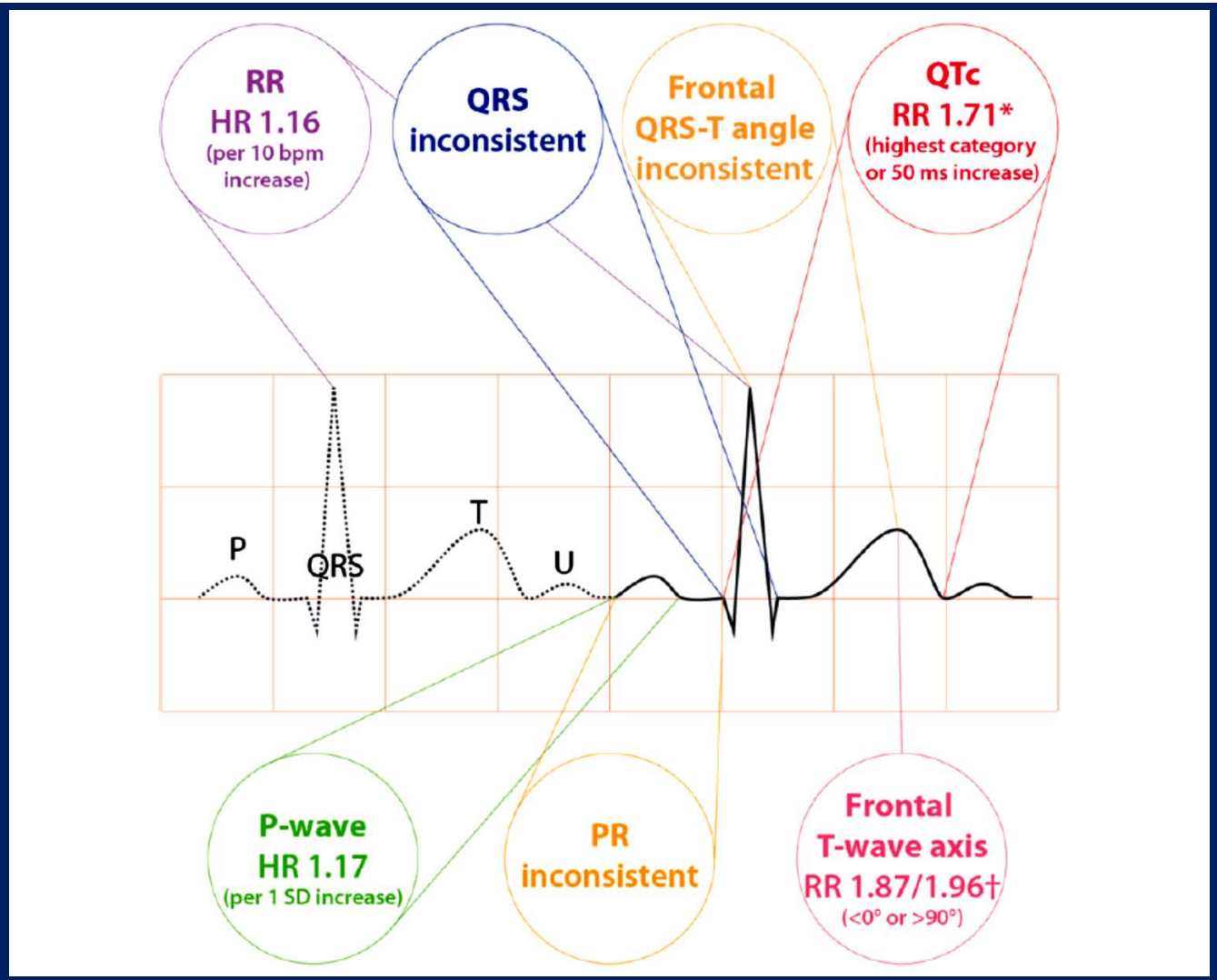
Peak Oxygen Consumption

Brain Natriuretic Peptide

European Heart Journal (2014) **35**, 1303–1305
doi:10.1093/eurheartj/ehu120

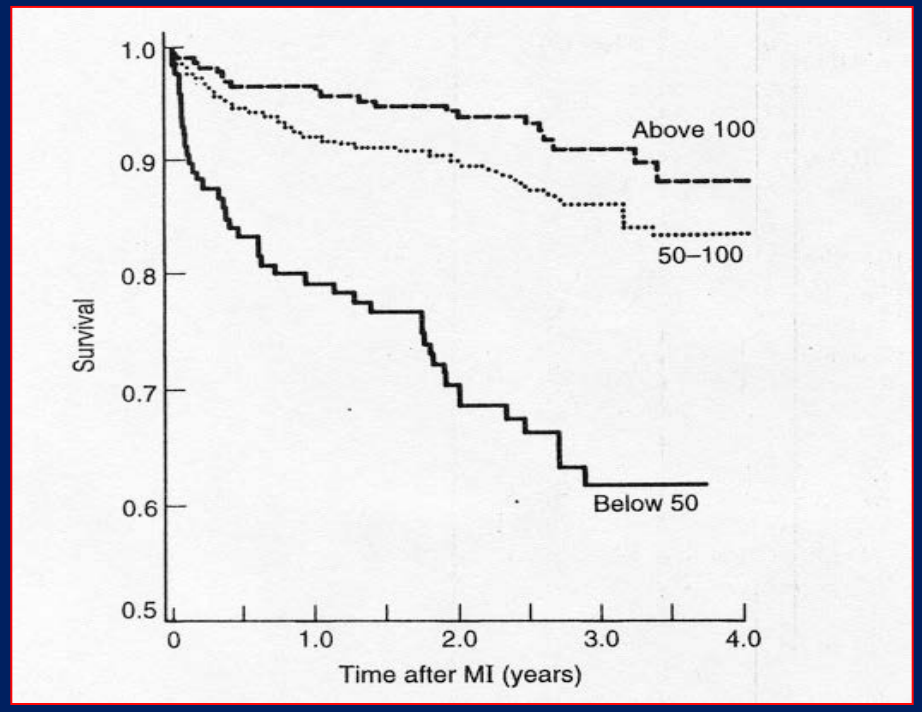
EDITORIAL

Using the electrocardiogram as a crystal ball for cardiovascular and all-cause mortality

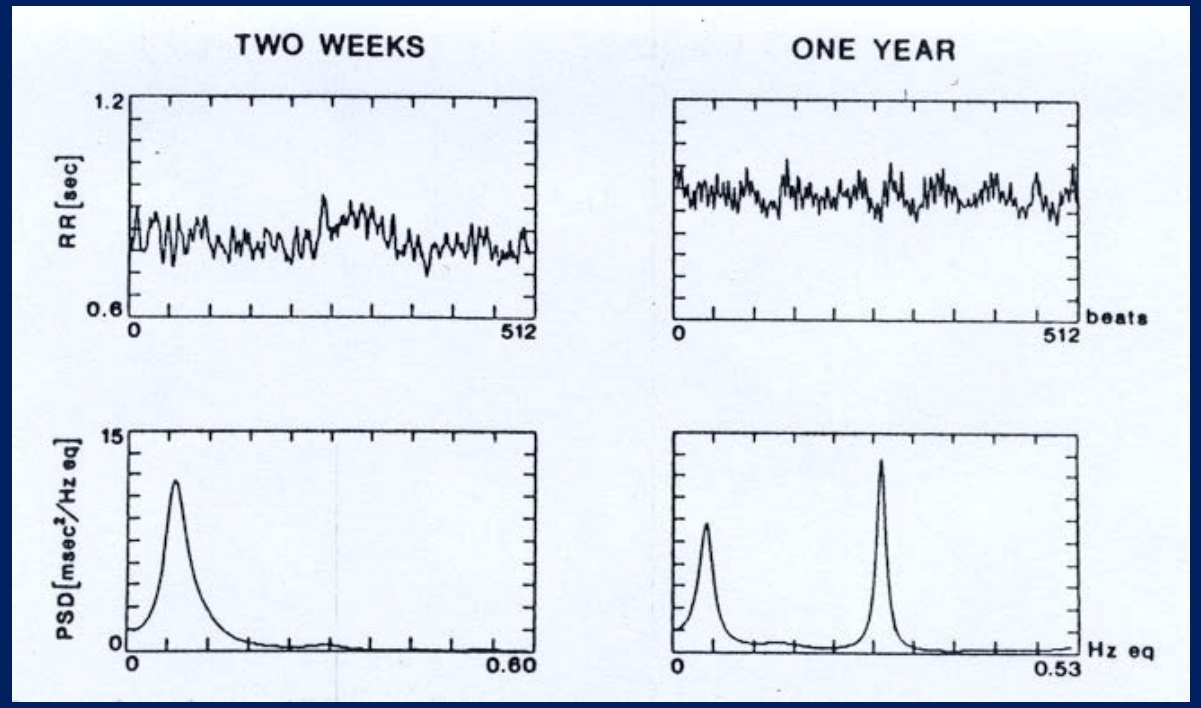


Van der Werf & Postema, 2014

Altered HRV and cardiac mortality after MI: the pro-arrhythmic role of sympathetic activation and reduced vagal tone



Kleiger et al. Am J Cardiol 1987



Lombardi et al. Am J Cardiol, 1987

European Heart Journal Advance Access published May 5, 2014

European Heart Journal
doi:10.1093/eurheartj/ehu176

SPECIAL ARTICLE

Risk stratification for sudden cardiac death: current status and challenges for the future†

Autonomic nervous system markers contribute to SCD risk stratification. Arrhythmic risk is enhanced whenever markers of vagal activity decrease or markers of sympathetic activity increase. Both RR and QT variability may provide useful and complementary information. Reflex autonomic responses are more informative than baseline measurements. The limited use of ANS tests is partially due to their complexity. Analyses derived from tests as simple as an exercise stress test are more likely to impact on clinical practice.

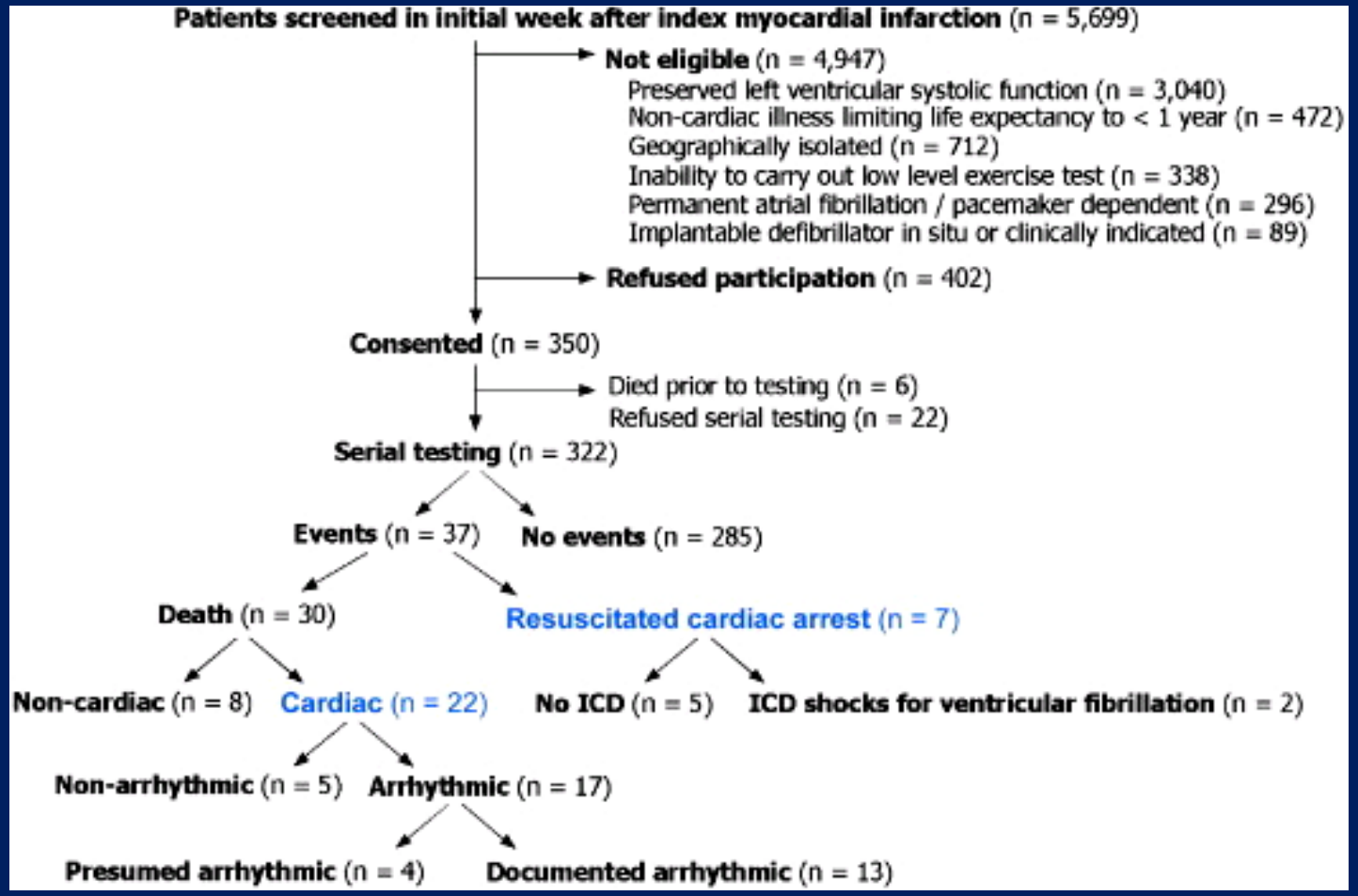
Noninvasive Risk Assessment Early After a Myocardial Infarction

The REFINE Study

LVEF: < 50%

HRV, HRT, BRS; SAECG and BRS were determined 2-4 and 10-14 weeks after MI.

Primary outcome: cardiac death or resuscitated cardiac arrest.



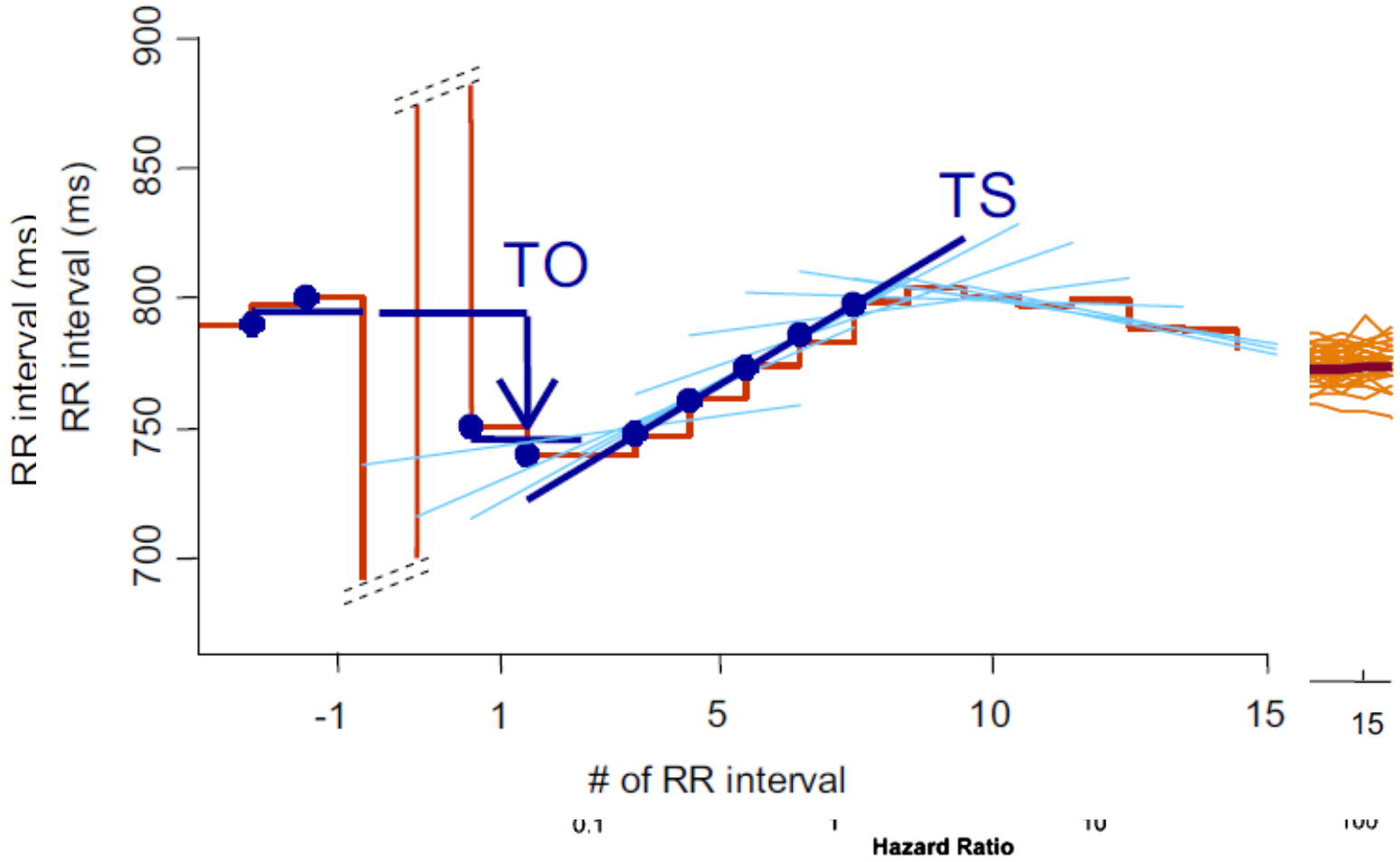
Exner et al. 2007

Adjusted HR for the capacity of individual parameters to predict primary outcome

Impairment	Hazard Ratio* (95% Confidence Interval) p Value	
	2 to 4 Weeks After Index MI	10 to 14 Weeks After Index MI
Autonomic tone		
Heart rate variability (SDNN <105 vs. ≥105 ms)	1.24 (0.50–3.27)	2.15 (0.95–4.87)
	0.65	0.066
Baroreflex sensitivity (<6.1 vs. ≥6.1 ms/mm Hg)	2.01 (0.76–5.27)	2.71 (1.10–6.67)
	0.16	0.030
Heart rate turbulence (abnormal onset or slope vs. both normal)	1.42 (0.54–3.75)	2.91 (1.13–7.48)
	0.47	0.026
Electrical substrate		
Exercise repolarization alternans (non-negative vs. negative)	2.42 (0.96–7.71)	2.75 (1.08–7.02)
	0.060	0.034
Holter repolarization alternans (≥5 vs. <5 μV)	2.09 (0.95–4.60)	2.94 (1.10–7.87)
	0.067	0.031
QRS width (≥114 vs. <114 ms)	1.35 (0.54–3.36)	1.75 (0.76–3.99)
	0.53	0.19
History of diabetes	2.68 (1.21–5.92)	2.72 (1.23–5.99)
	0.014	0.013
Left ventricular ejection fraction (≤0.30 vs. >0.30)	3.06 (1.39–6.74)	3.30 (1.43–7.63)
	0.005	0.005

Exner et al. 2007

Prediction of fatal or near-fatal cardiac arrhythmia events in patients with depressed left ventricular function after an acute myocardial infarction†



Huikuri et al, EHJ 2009

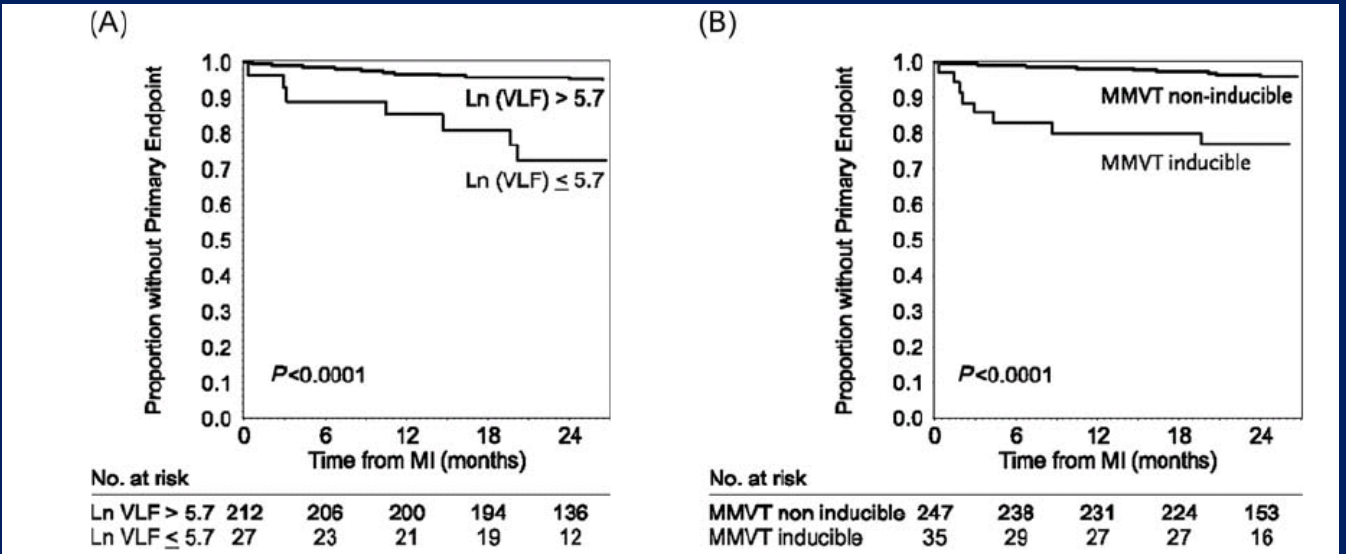


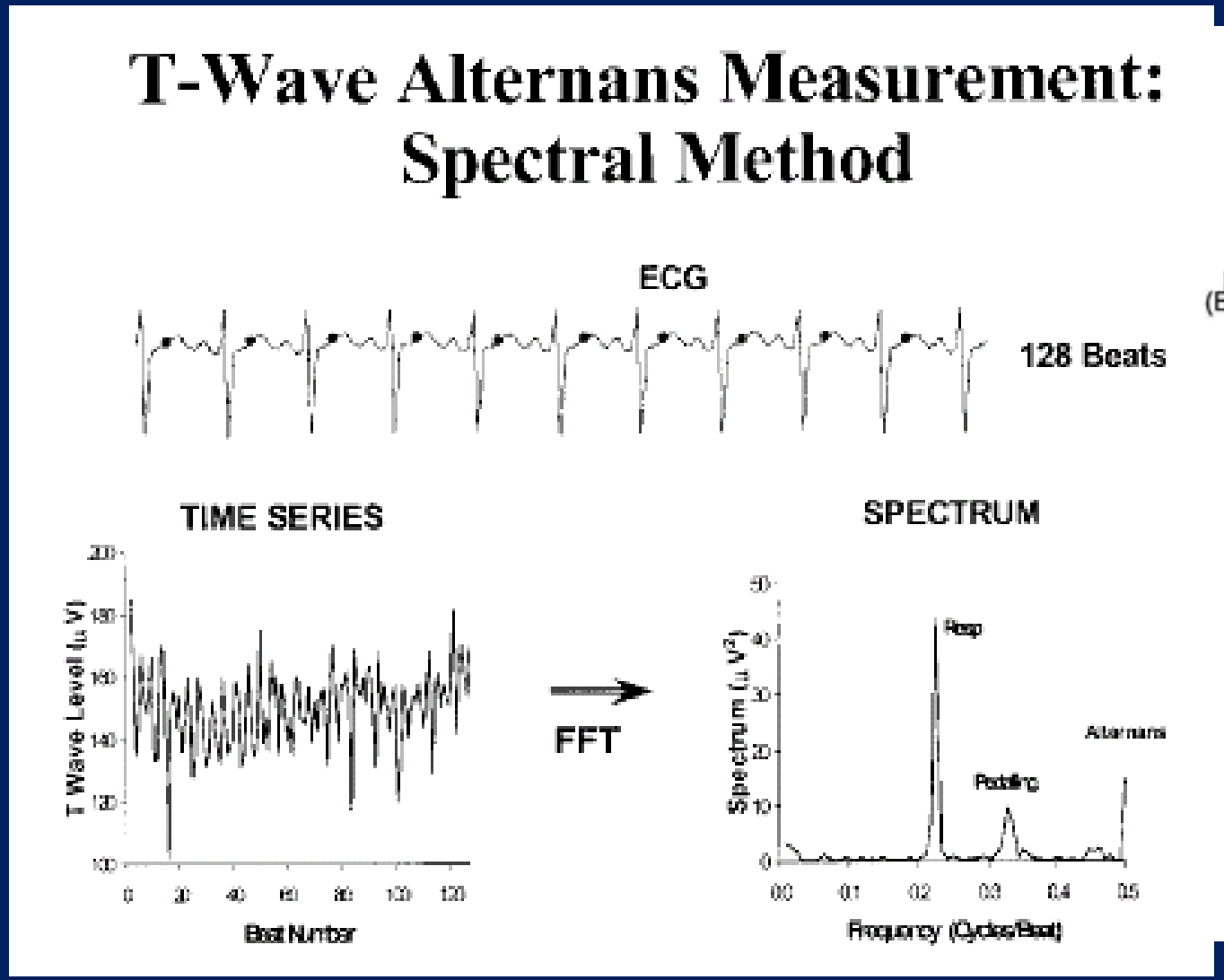
Table 4 Sensitivity, specificity, and predictive accuracy of predefined values of individual variables in predicting primary endpoint

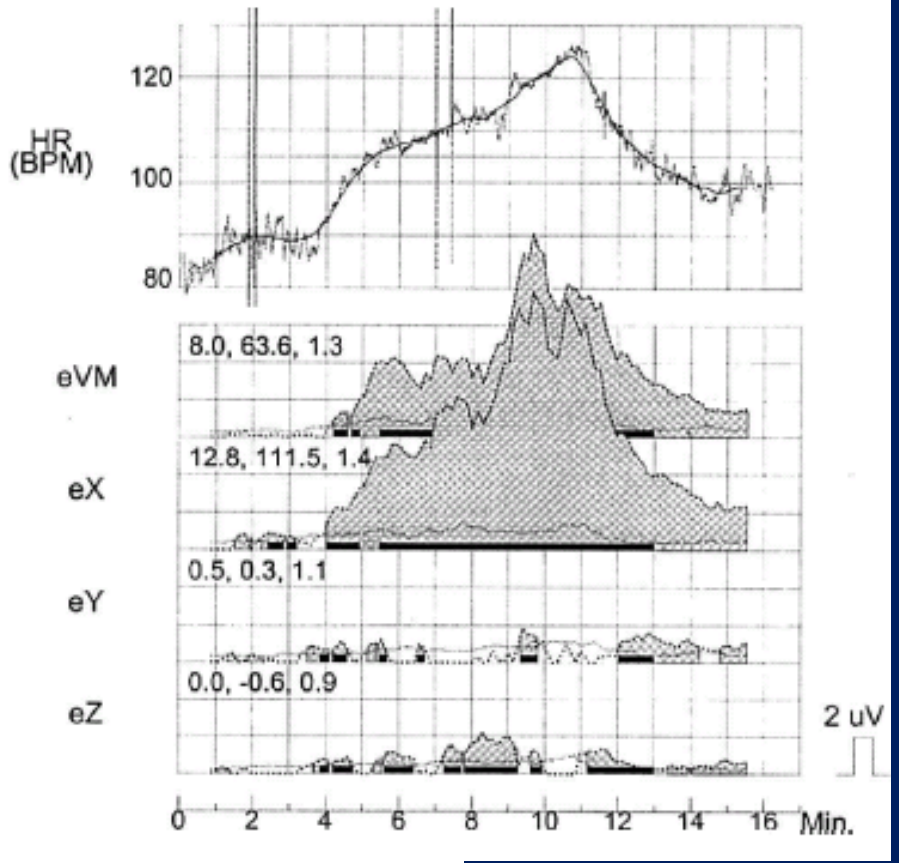
Name of variable	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
LVEF < 0.35	57 (36–78)	53 (47–59)	9 (4–13)	94 (90–98)
SDNN <70 ms	35 (13–58)	90 (86–94)	21 (6–35)	95 (92–98)
VLF spectral component ln ≤5.7 ms^2	41 (18–65)	91 (87–95)	26 (9–42)	95 (92–98)
Fractal scaling exponent <0.75	65 (42–87)	71 (65–77)	15 (7–23)	96 (93–99)
Heart rate turbulence slope <2.5 ms/RRi	53 (29–77)	74 (68–80)	14 (5–22)	95 (92–99)
QRS-width on SAECG >120 ms	44 (21–67)	85 (80–90)	20 (7–32)	95 (92–98)
Induction of sustained MMVT by PES	47 (23–71)	90 (86–93)	23 (9–37)	96 (95–99)
Induction of VT/VF by PES	53 (29–77)	78 (73–83)	14 (5–22)	96 (94–99)

NPV, negative predictive value; PPV, positive predictive value. For other abbreviations see *Table 3*.

Huikuri et al, EHJ 2009

Clinical utility of microvolt T-wave alternans testing in identifying patients at high or low risk of sudden cardiac death





Merchant et al, HR 2012

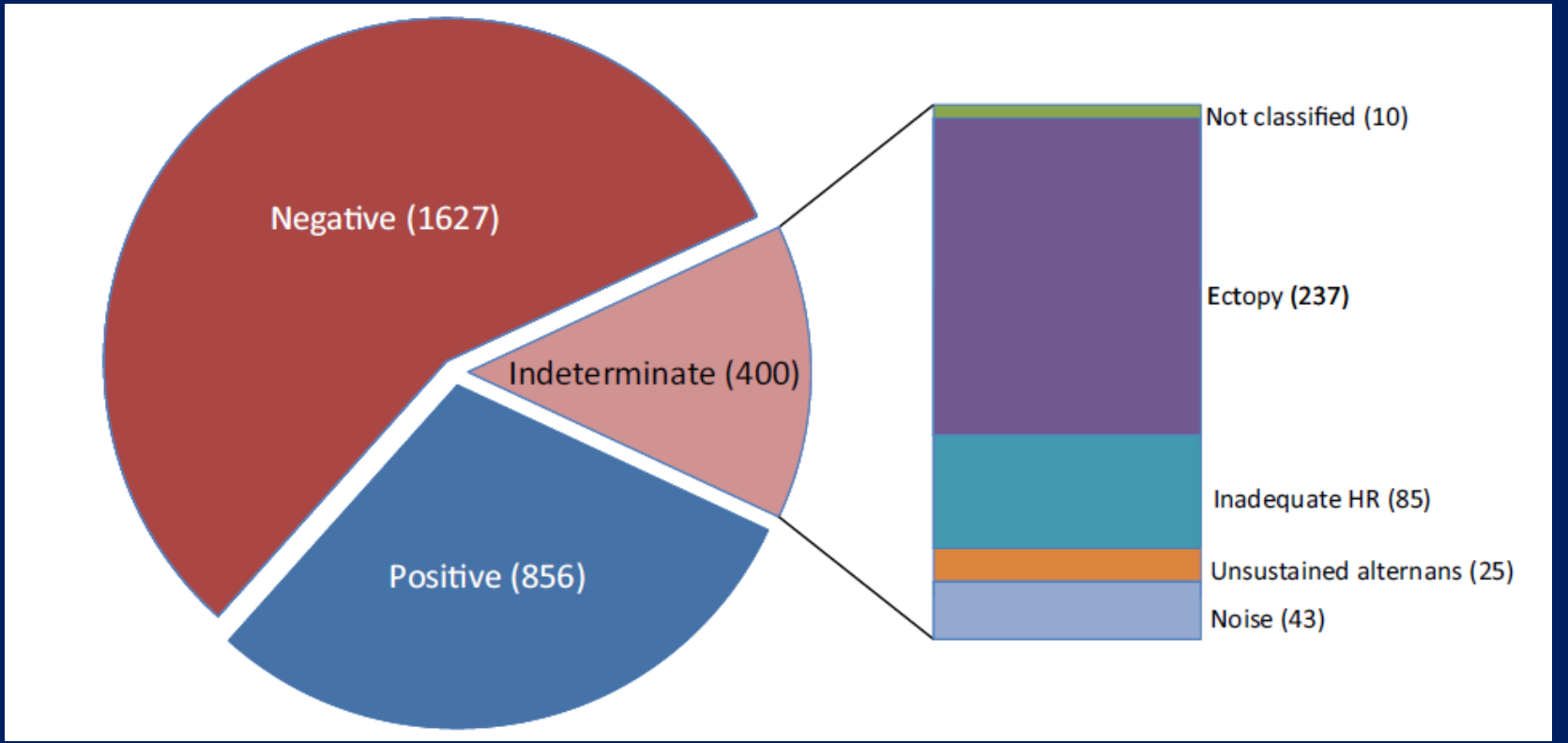


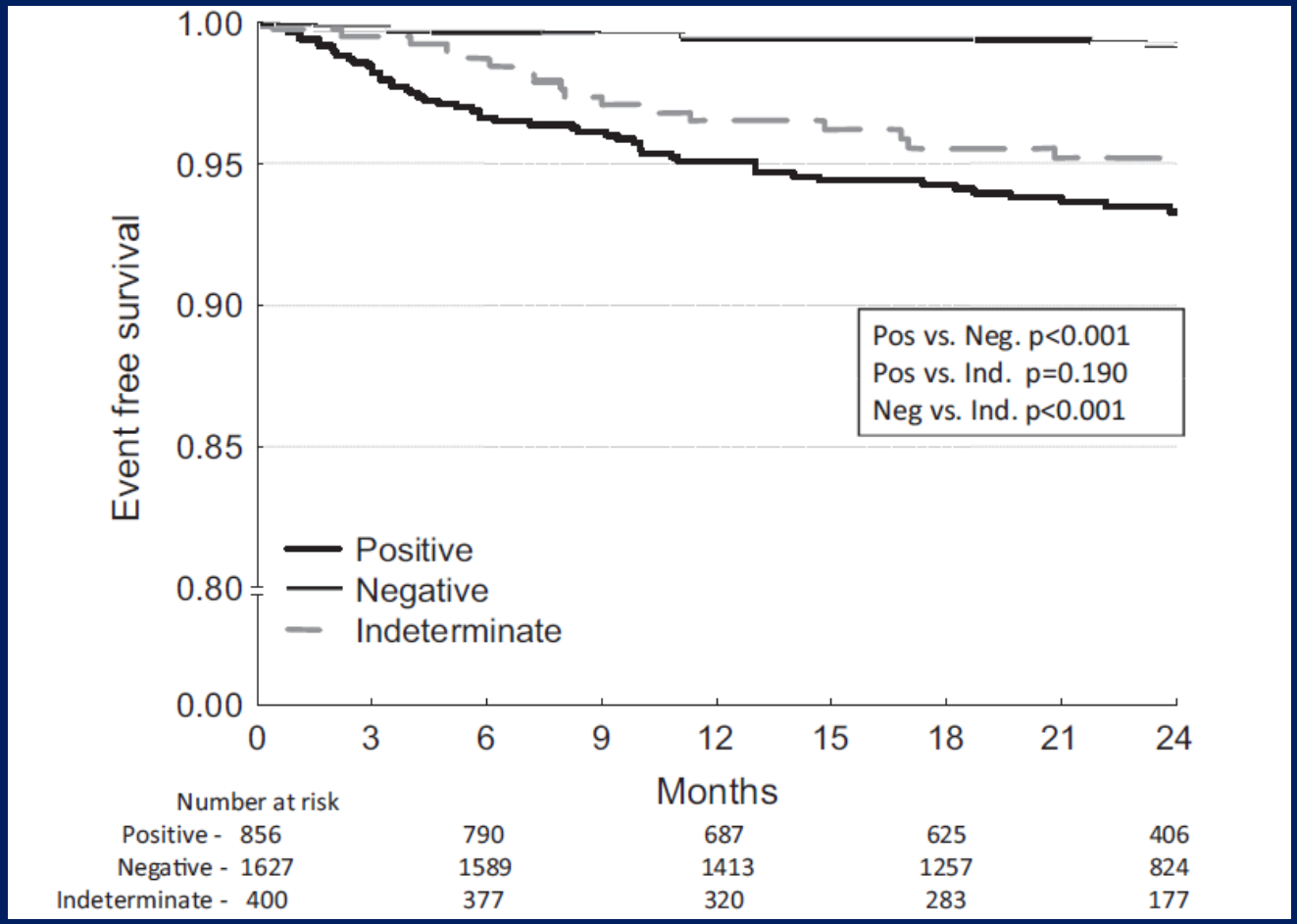
Table 2 Baseline characteristics stratified by MTWA test result

	Positive (n = 856)	Negative (n = 1627)	Indeterminate (n = 400)	*P*
Age (y), mean ± SD	62.4 ± 11.2	62.5 ± 10.8	64.5 ± 11.3	.010
Male sex, n (%)	706 (82)	1287 (79)	311 (78)	.763
Ischemic cardiomyopathy, n (%)	631 (74)	1407 (86)	279 (70)	.021
LV ejection fraction (%), mean ± SD	39.2 ± 15.4	47.9 ± 14.8	39.5 ± 15.2	<.001
Beta-blocker therapy at enrollment, n (%)	421 (49)	603 (37)	207 (52)	.079

LV = left ventricle; MTWA = microvolt T-wave alternans; SD = standard deviation.

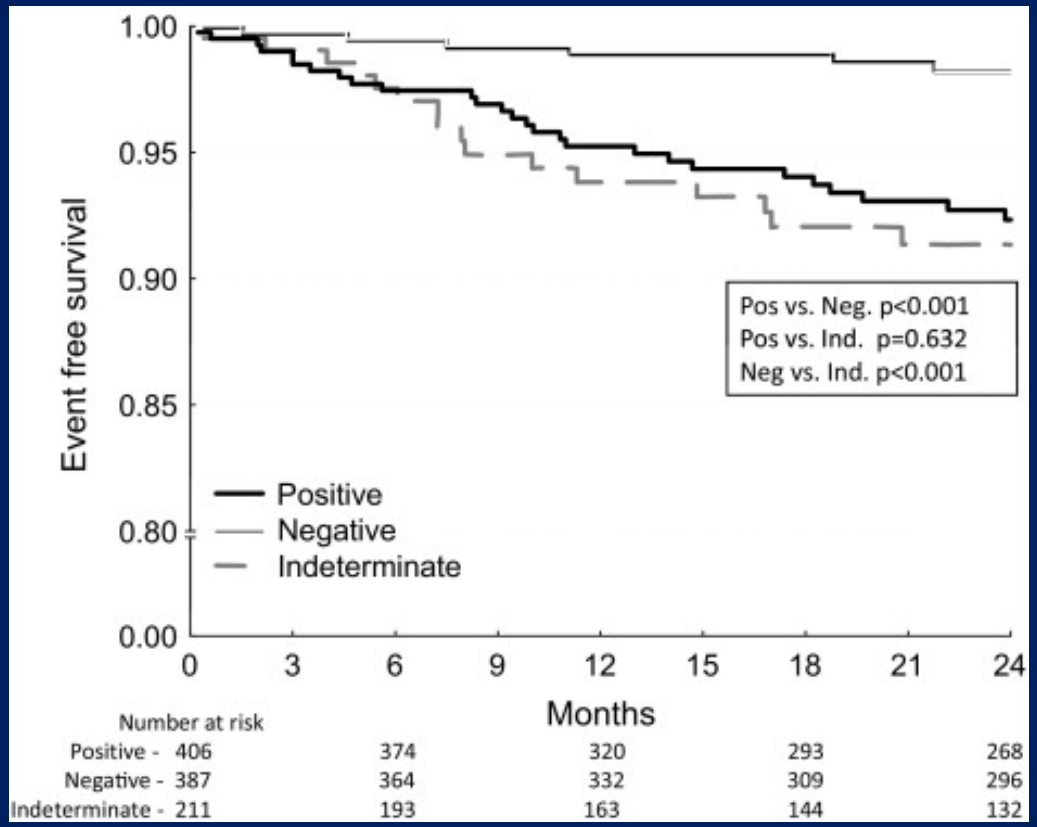
Merchant et al, HR 2012

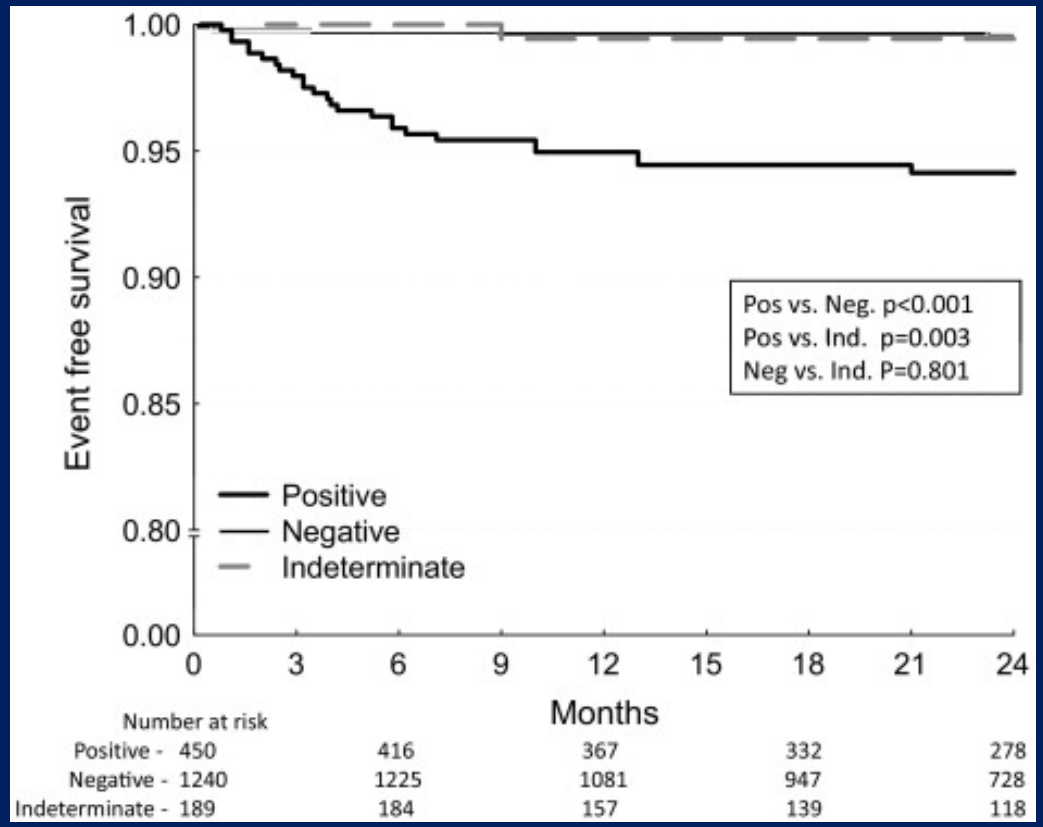
Kaplan-Meier event-free survival curves for the primary end point of arrhythmic mortality/sudden cardiac death stratified by MTWA test result for the entire pooled cohort.



Merchant et al, HR 2012

Kaplan-Meier event-free survival curves for the primary end point of arrhythmic mortality/sudden cardiac death stratified by MTWA test result among patients with an LVEF of ≤ or > 35%.





Merchant et al, HR 2012

Sudden Cardiac Death Risk Stratification in Patients With Nonischemic Dilated Cardiomyopathy

2,362 articles with 'non-ischemic' or 'idiopathic dilated' cardiomyopathy in Ovid MedLine

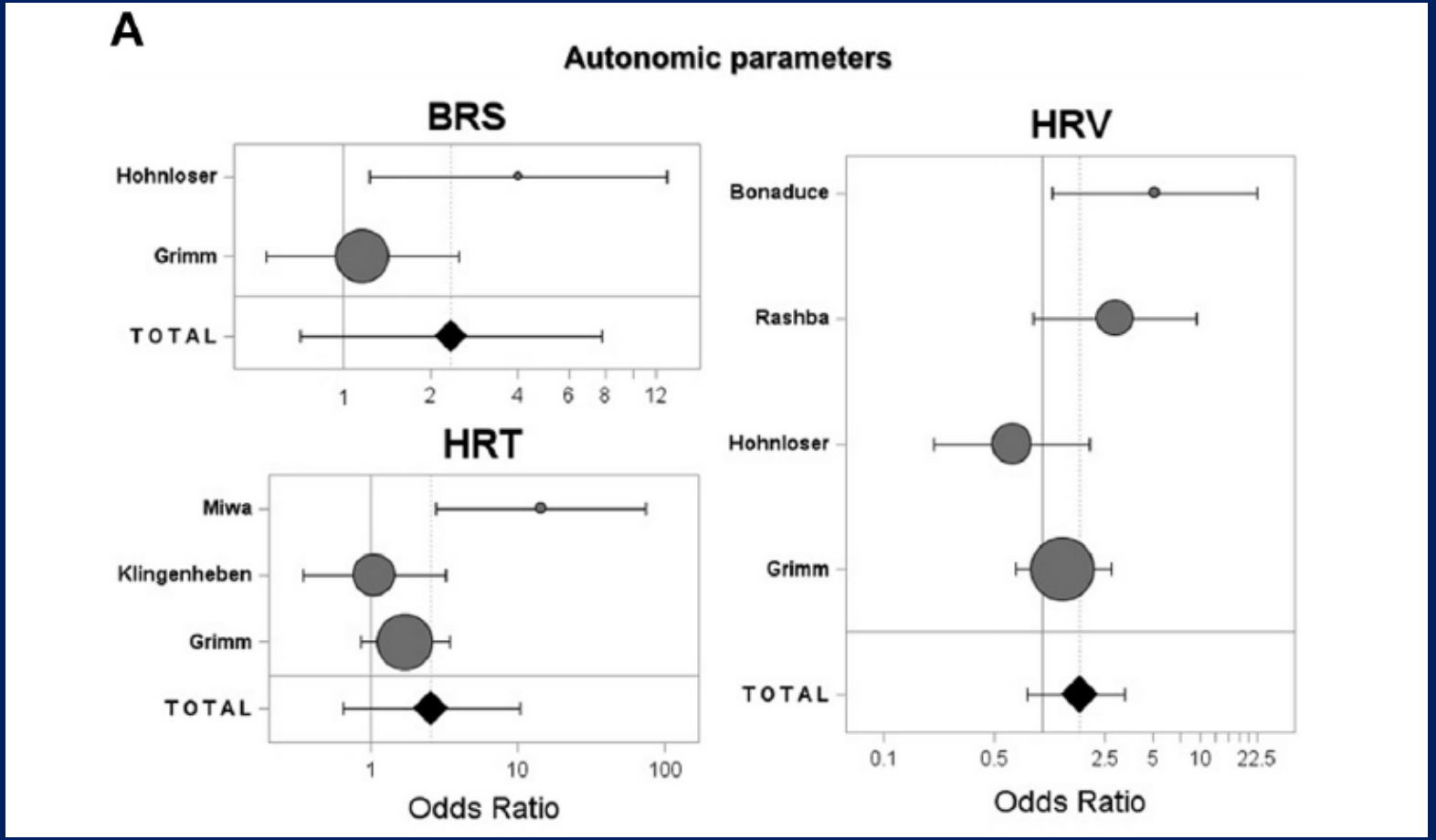
485 with BRS, EPS, HRT, HRV, LVEDD, LVEF, NSVT, QRS, QRS-T, Fragmented QRS, SAECG, TWA

348 abstracts reviewed

80 full-text articles reviewed

43 studies with valid data identified

45 studies included in the final report



Goldberger et al, JACC 2014

Table 2 Meta-Analytic Summaries of Test Performance by Predictor Category

Predictor	Studies	Events/n (%)	Calculated 3-Yr Event Rate (%)	Prev. (%)	Sens. (%)	Spec. (%)	PPA (%)	NPA (%)	RR (95% CI)
Autonomic									
BRS	2	48/359 (13.4)	17.0	52.9	64.6	48.9	16.3	89.9	1.80 (0.63–5.16)
HRT	3	66/434 (15.2)	18.6	32.3	47.0	70.4	22.1	88.1	2.12 (0.77–5.83)
HRV	4	83/630 (13.2)	15.6	43.1	55.4	58.8	16.9	89.7	1.52 (0.84–2.75)
Functional									
LVEDD	4	62/427 (14.5)	17.1	42.9	66.1	61.1	22.4	91.4	2.85 (1.70–4.79)
LVEF	12	293/1,804 (16.2)	16.9	53.1	71.7	50.5	21.9	90.2	2.34 (1.85–2.96)
Arrhythmia									
EPS	15	146/936 (15.6)	21.5	15.4	28.8	87.1	29.2	86.9	2.09 (1.30–3.35)
NSVT	18	403/2,746 (14.7)	15.7	45.5	64.0	57.7	20.7	90.3	2.45 (1.90–3.16)
Depolarization									
QRS/LBBB	10	262/1,797 (14.6)	14.7	35.7	45.4	65.9	18.5	87.6	1.43 (1.11–1.83)
SAECG	10	152/1,119 (13.6)	19.9	36.9	51.3	65.4	18.9	89.5	1.84 (1.18–2.88)
Frag. QRS	2	65/652 (10.0)	11.8	25.6	61.5	78.4	24.0	94.8	5.16 (3.17–8.41)
Repolarization									
QRS-T	1	97/455 (21.3)	25.0	62.2	74.2	41.1	25.4	85.5	1.75* (1.16–2.65)
TWA	12	177/1,631 (10.9)	15.8	66.8	91.0	36.2	14.8	97.0	3.25 (2.04–5.16)

Goldberger et al, JACC 2014

Improved Stratification of Autonomic Regulation for risk prediction in post-infarction patients with preserved left ventricular function (*ISAR-Risk*)

Characteristic	
CABG [*n* (%)]	39 (2)
Aspirin [*n* (%)]	2298 (98)
β-Blocker [*n* (%)]	2210 (94)
ACE inhibitors [*n* (%)]	2132 (91)
Statins [*n* (%)]	2057 (88)
Diuretics [*n* (%)]	926 (40)

Table 2 **Endpoints at 5 years**

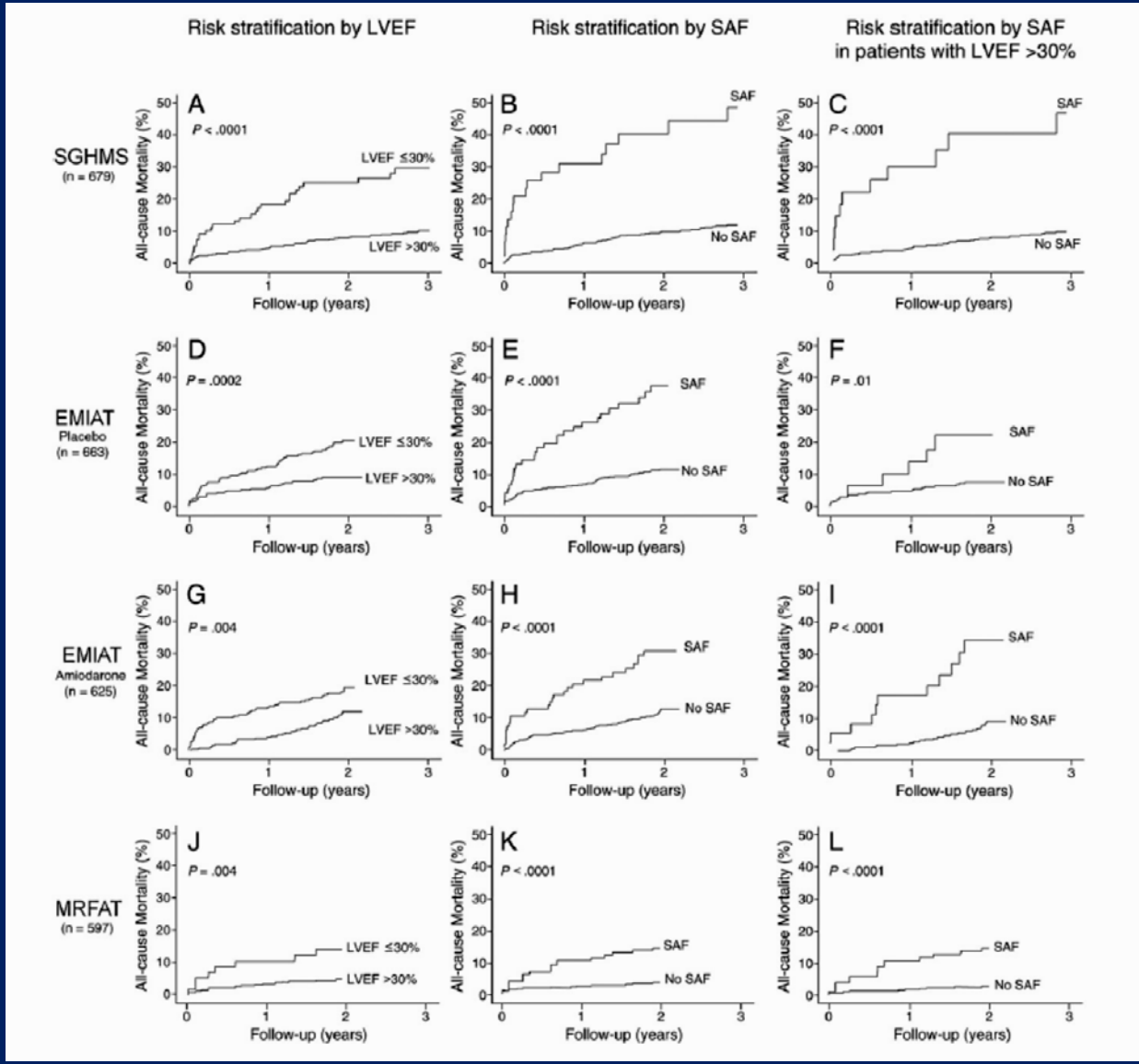
Group	Total	All-cause deaths	Cardiac deaths	Sudden cardiac deaths	Death not specified
LVEF ≤ 30%	120	39	29	12	3
SAF	152	52	40	16	3
LVEF > 30% and SAF	117	37	27	14	3
Others (=LVEF > 30% and no SAF)	2106	105	48	29	8
Total	2343	181	104	55	14

LVEF left ventricular ejection fraction; SAF severe autonomic failure.

Bauer et al, EHJ 2009

Risk prediction by heart rate turbulence and deceleration capacity in postinfarction patients with preserved left ventricular function retrospective analysis of 4 independent trials

Heart rate turbulence and DC were obtained by 24-hour Holter recordings.
Patients with both abnormal HRT and DC were considered suffering from SAF and prospectively classified as high risk.



Bauer et al, J Electrocardiol 2009

The ABCD (Alternans Before Cardioverter Defibrillator) Trial

Strategies Using T-Wave Alternans to Improve Efficiency of Sudden Cardiac Death Prevention

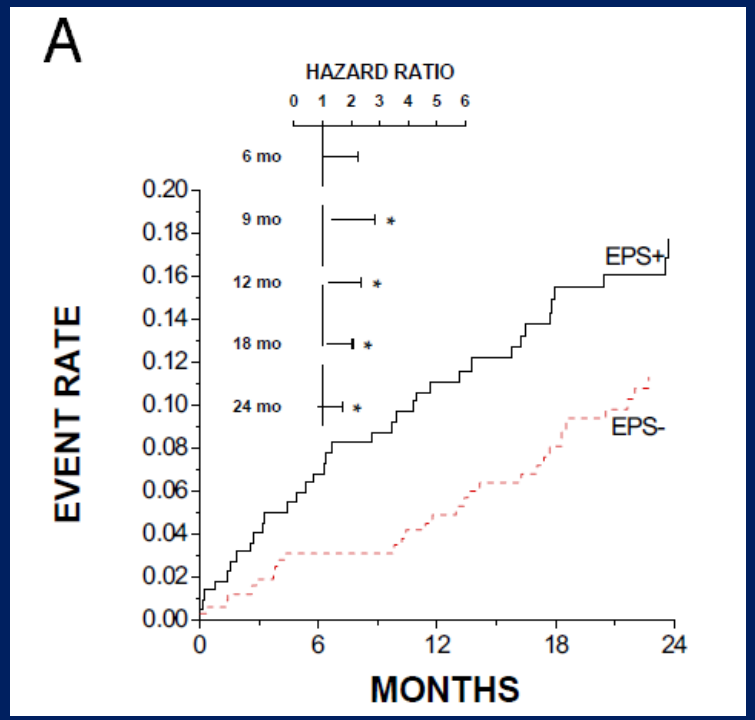
Screened 629 subjects with CAD
LVEF < 0.40, NSVT, No previous VT/VF

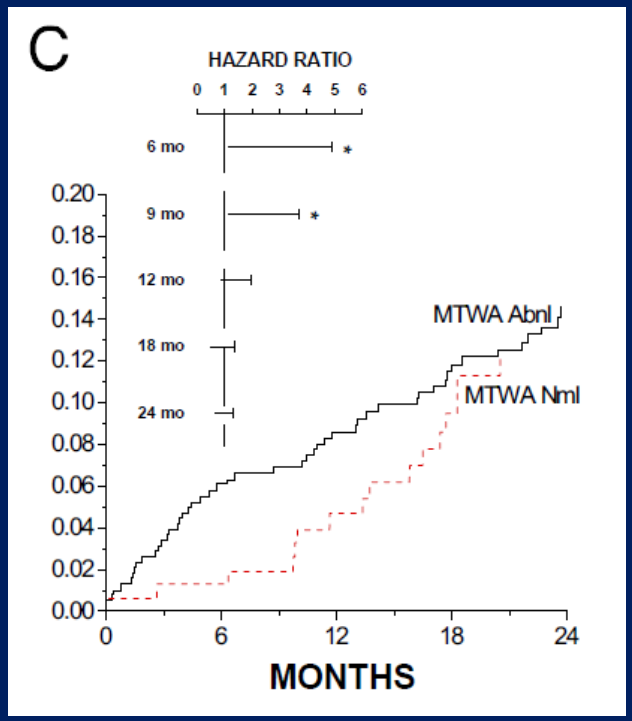
→ 63 Excluded

EPS and MTWA risk stratification in 100% (n=566)

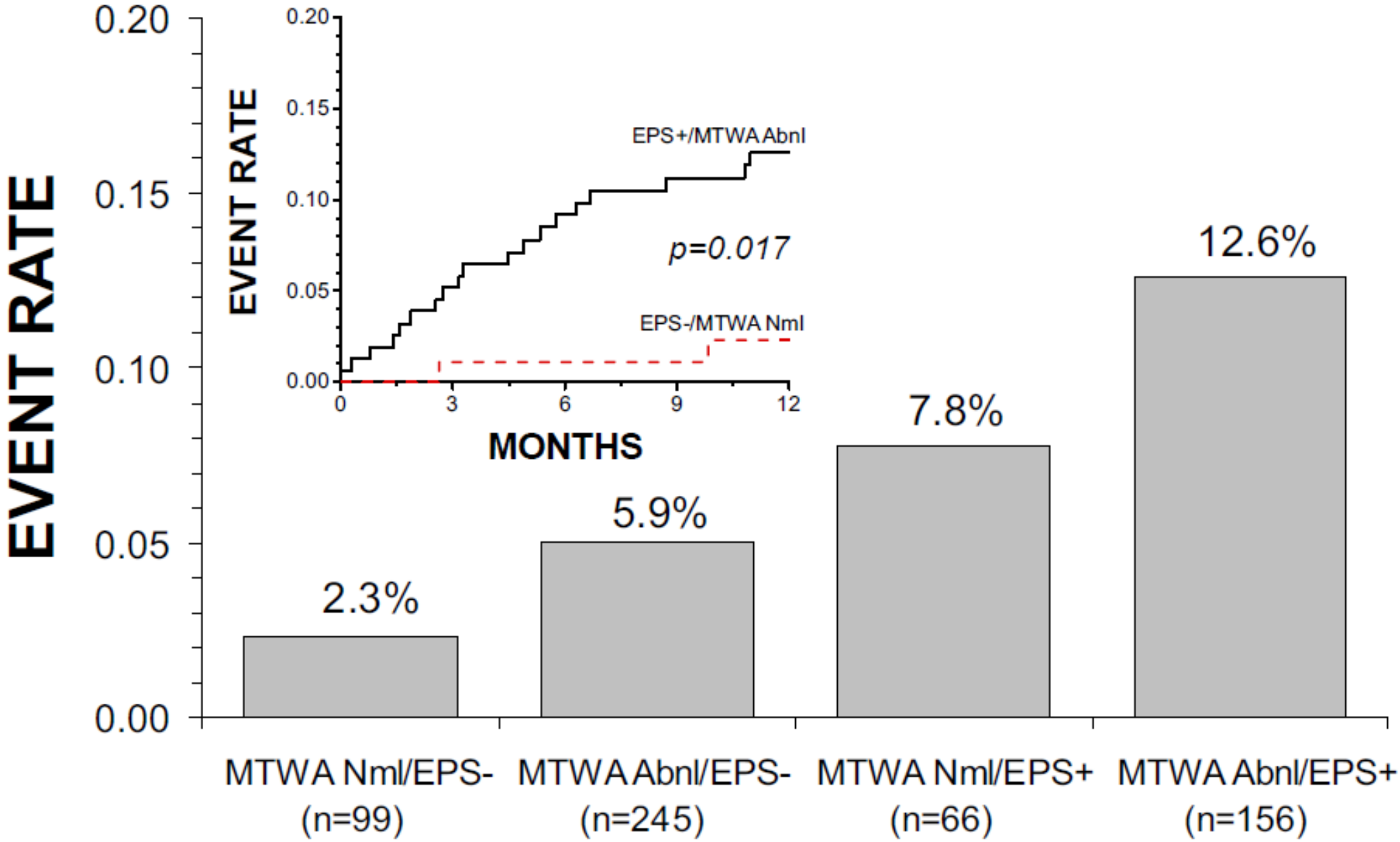
ICD Implant required in EPS+ or TWA+ patients (97%)

Follow up for events (n = 566)



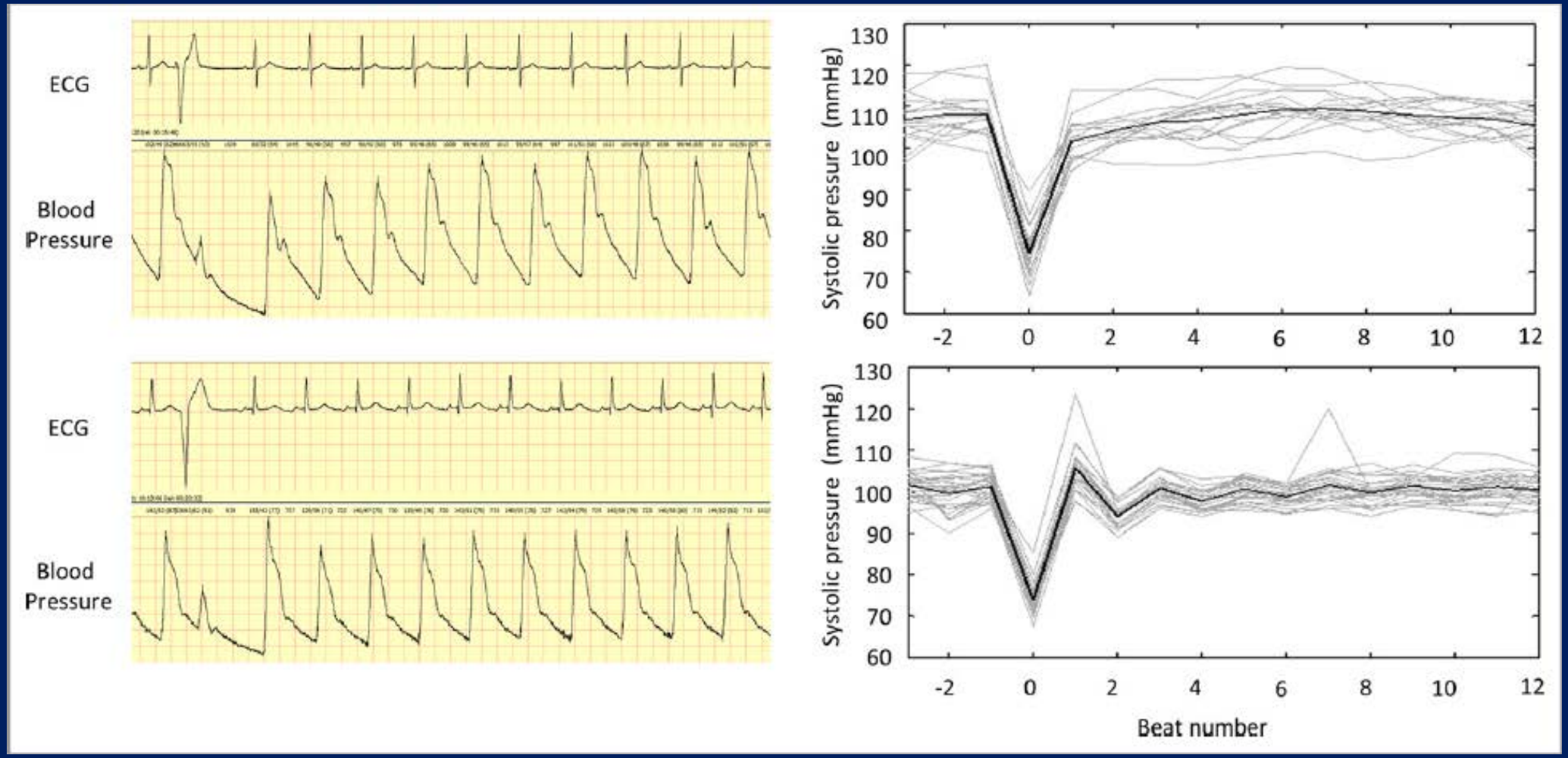


Costantini et al, JACC 2009

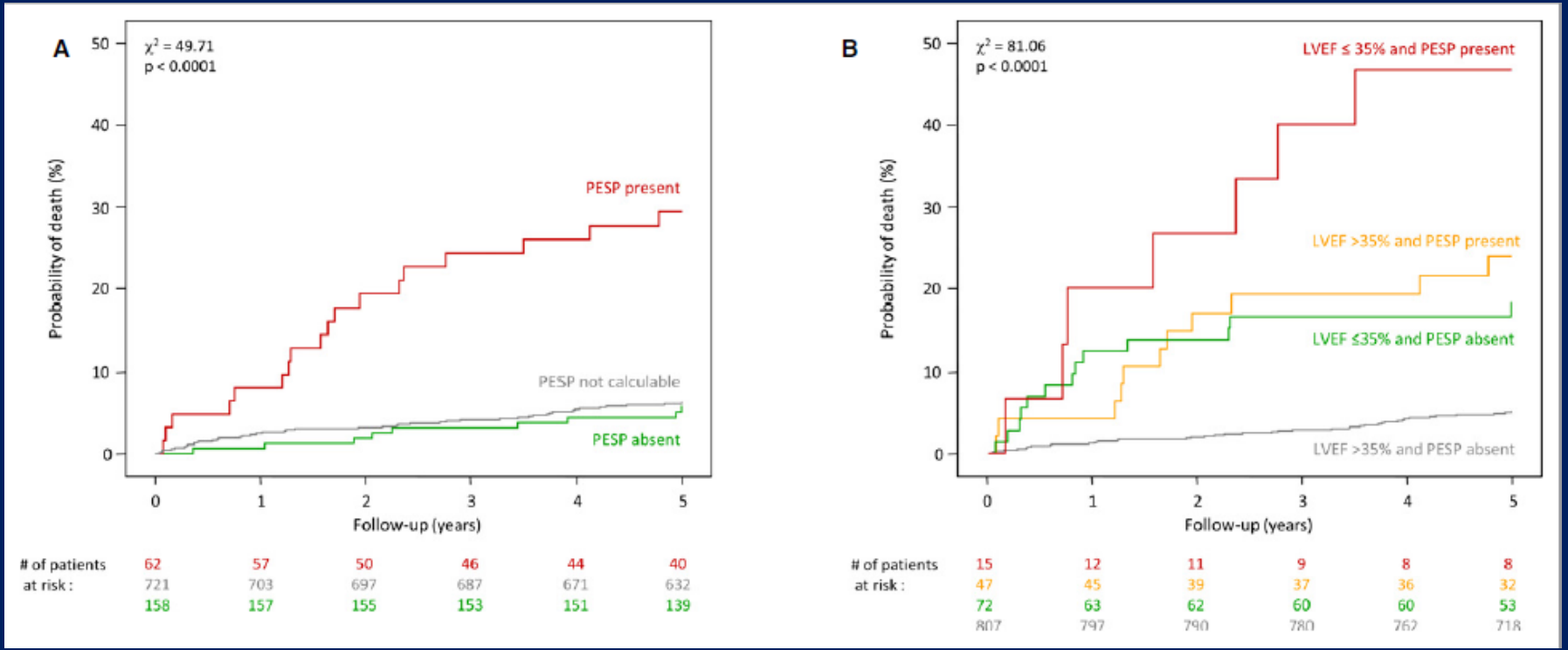


Costantini et al, JACC 2009

Postextrasystolic Blood Pressure Potentiation Predicts Poor Outcome of Cardiac Patients



Sinneker et al, JAHA 2014



Risk-Stratification Criterion	e/n	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
LVEF ≤35% alone	20/87	27.8	92.3	23.0	93.9
LVEF ≤35% or LVEF >35% and PESP present	31/134	43.1	88.1	23.1	94.9

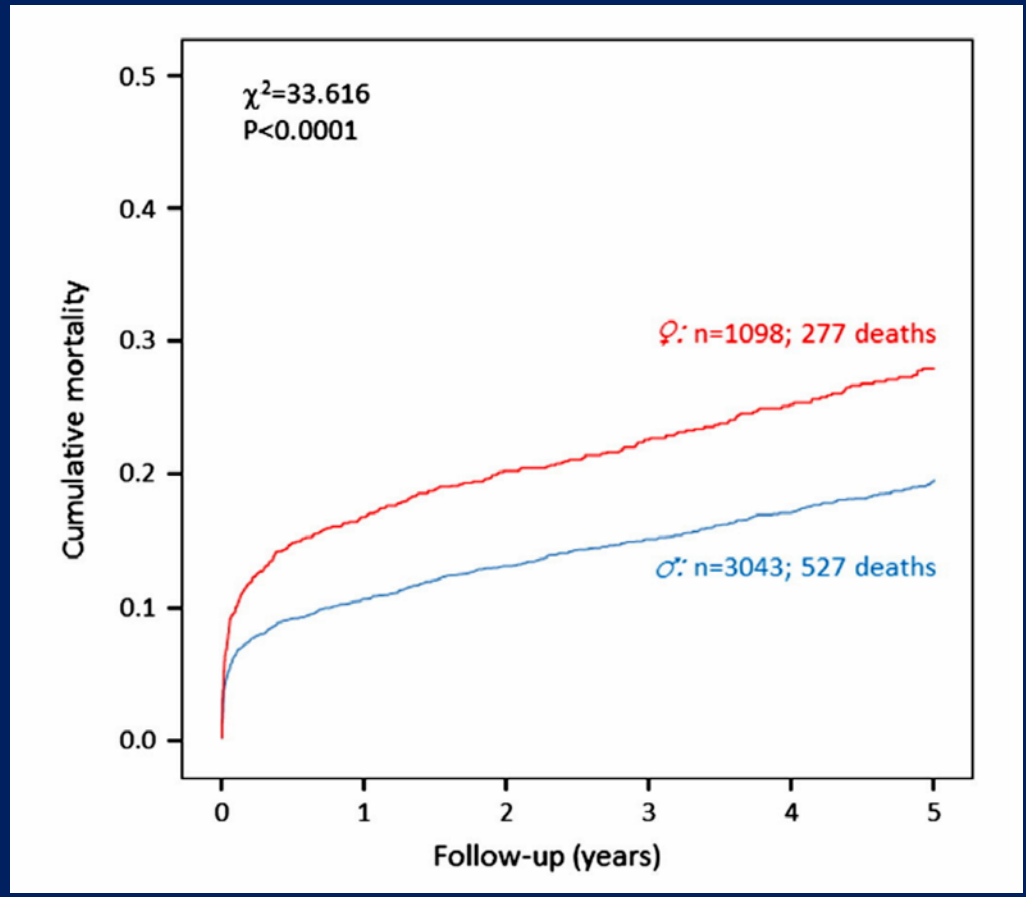
Sinneker et al, JAHA 2014

Sex differences in the non-invasive risk stratification and prognosis after myocardial infarction

Cohort A
n=4141
♀ 1098 (26.5%)
♂ 3043 (73.5%)

30-day mortality 287 (6.9%) ←
No Holter 859 (20.7%) ←
secondary ICD indication 44 (1.1%) ←

Cohort B
n=2951
♀ 724 (24.5%)
♂ 2227 (75.5%)



Sinneker et al, JElectr. 2014

Sex-specific multivariable Cox models for 5-year all-cause mortality.

Women (n = 724)

Variable	χ^2	HR (95% CI)	p
Non-SR	37.6	7.64 (3.99–14.65)	<0.001
Age ≥ 78 years	26.7	2.83 (1.91–4.20)	<0.001
LVEF ≤ 30%	14.0	2.39 (1.51–3.77)	<0.001
HRVTI ≤ 20	12.3	2.32 (1.45–3.71)	<0.001
QRS ≥ 116 ms	5.8	1.84 (1.12–3.02)	0.016
DC ≤ 4.08	14.0	2.69 (1.60–4.52)	<0.001

Men (n = 2227)

Variable	χ^2	HR (95% CI)	p
Non-SR	24.8	3.24 (2.04–5.14)	<0.001
Age ≥ 69 years	42.5	2.59 (1.95–3.45)	<0.001
LVEF ≤ 30%	30.7	2.55 (1.83–3.54)	<0.001
Mean heart rate ≥ 71 bpm	4.0	1.35 (1.01–1.82)	0.045
HRVTI ≤ 15	9.9	1.75 (1.23–2.48)	0.002
HRT: TO and TS abnormal	24.9	2.62 (1.80–3.83)	<0.001
DC ≤ 3.32	10.5	1.73 (1.24–2.41)	0.001

Sinneker et al, Jelectr. 2014

Development and validation of a risk score to predict early mortality in recipients of implantable cardioverter-defibrillators

Table 1 Variables of study population

Variable	PG (n = 905)	VG (n = 1812)	Entire cohort (n = 2717)	*P* value*
Age	65.6 ± 14.5	64.3 ± 14.6	64.5 ± 14.5	.200
Male (%)	78.3	76.7	77.2	.3231
Primary prevention (%)	75.8	74.2	74.7	.5747
White (%)	91.9	90.7	91.1	.2977
CHF (%)	67.9	64.6	67.7	.0881
ICM (%)	58.9	57.7	58.1	.5606
DCM (%)	25.3	24.1	24.5	.4979
HCM (%)	4.3	6.1	5.5	.0507
Channelopathy (%)	1.3	1.2	1.3	.8048
LVEF (mean)	31.1	31.4	31.3 ± 14.6	.5538
LVEF < 20 (%)	28.3	26.5	27.1	.3205
Creatinine (mean)	1.26	1.24	1.25 ± 0.61	.4988
Cr > 2.0 (%)	6.5	5.7	6.0	.3863
PAD (%)	8.9	9.4	9.2	.6511
AF (%)	39.2	36.0	37.1	.0989
CHF III or IV (%)	26.6	25.3	25.8	.4657
Diabetes (%)	35.8	32.4	33.5	.0763
COPD (%)	16.0	12.1	13.4	.0052

AF = atrial fibrillation; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; Cr = creatinine; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; ICM = ischemic cardiomyopathy; LVEF = left ventricular ejection fraction; PAD = peripheral arterial disease; PG = prediction group; VG = validation group.

**P* value for comparison between PG and VG.

Kramer et al, HR 2012

Table 2 Clinical follow-up and mortality

Group	Follow-up (years ± SD)	Deaths overall, n (%)
PG	3.17 ± 1.83	125 (13.8)
VG	3.06 ± 1.81	296 (16.3)
Overall	3.10 ± 1.82	421 (15.5)
P for comparison	0.1278	0.867

PG = prediction group; VG = validation group.

Table 4 Results from multivariate logistic regression

Risk factor	Adjusted odds ratio	95% CI
PAD	5.506	2.026–14.969
LVEF ≤ 20	3.106	1.153–8.370
Cr ≥ 2.0	8.626	3.295–22.580
Age ≥ 70	2.981	1.078–8.244

CI = confidence interval; Cr = creatinine; LVEF = left ventricular ejection fraction; PAD = peripheral arterial disease.

Table 3 Unadjusted analysis of effects eligible for entry into regression model

Variable	χ^2	*P*
Secondary prevention	1.2400	.2655
Gender	0.0975	.7548
ICM	1.4287	.2320
DCM	0.0362	.8491
HCM	1.0038	.3164
PAD	15.8012	<.0001
HF	0.6462	.4215
NYHA Class III or IV	1.3517	.2450
LVEF ≤ 20	2.4411	.1182
LVEF ≤ 25	1.1791	.2775
LVEF ≤ 30	2.4923	.1133
LVEF ≤ 35	1.0243	.3115
AF	2.6725	.1021
Diabetes	0.3665	.5449
Creatinine ≥ 2.0	34.4221	<.0001
COPD	0.0597	.8069
Age ≥ 65 y	4.7609	.0291
Age ≥ 70 y	6.4535	.0111
Age ≥ 75 y	2.2727	.1317
Age ≥ 80 y	4.6900	.0303

AF = atrial fibrillation; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; HF = heart failure; ICM = ischemic cardiomyopathy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PAD = peripheral arterial disease.

Kramer et al, HR 2012

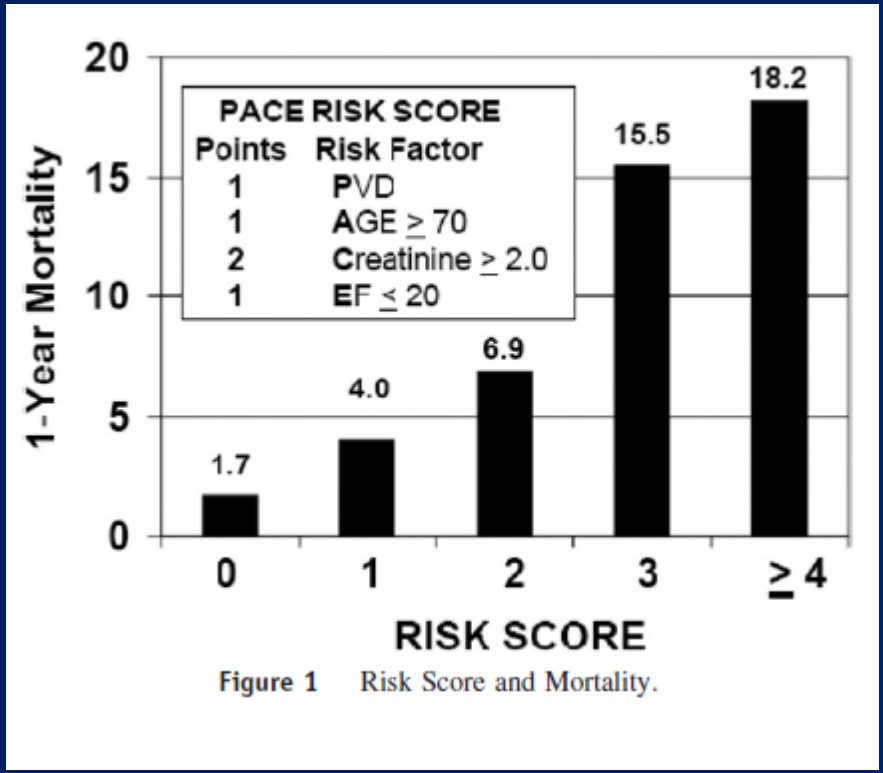


Figure 1 Risk Score and Mortality.

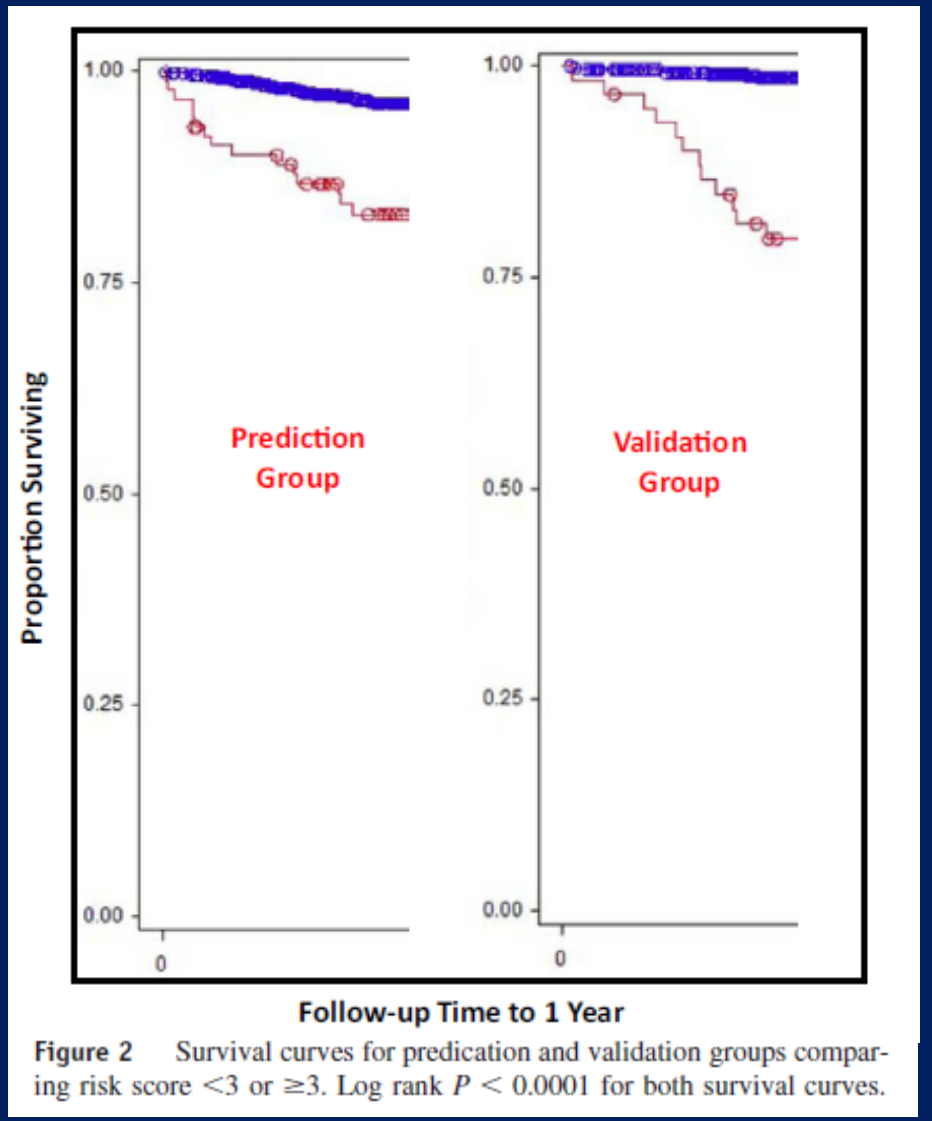


Figure 2 Survival curves for predication and validation groups comparing risk score <3 or ≥3. Log rank $P < 0.0001$ for both survival curves.

Kramer et al, HR 2012

REFINE ICD - INTRODUCTION TO THE STUDY

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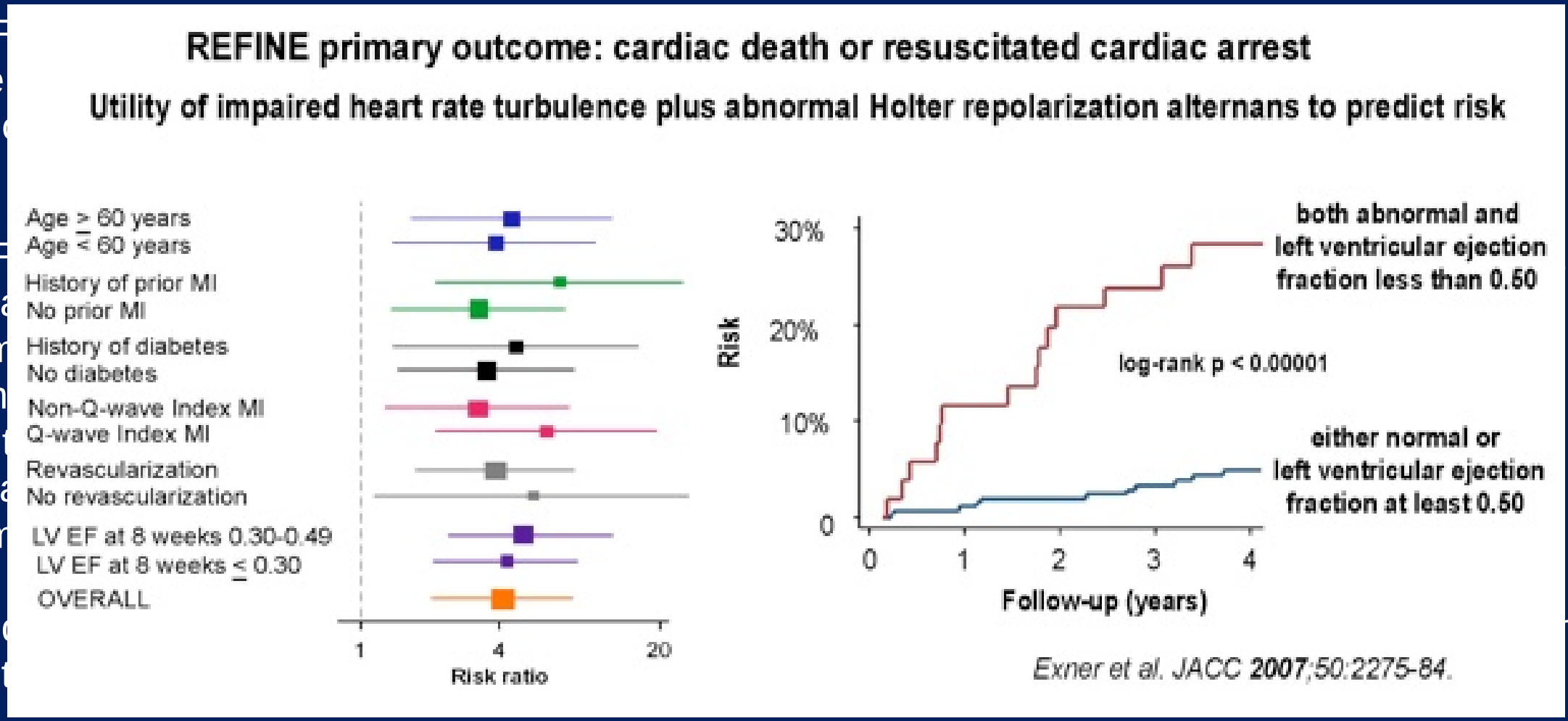

European Heart Journal Advance Access published May 5, 2014

European Heart Journal
doi:10.1093/eurheartj/ehu176

SPECIAL ARTICLE

Risk stratification for sudden cardiac death: current status and challenges for the future†

Several reports[20,21] suggest that no single test alone is likely to provide adequate risk stratification. The utility of combining tests or performing risk stratification in a sequential manner has been demonstrated.[22,23] Based on the findings of the Risk Estimation Following Infarction, Noninvasive Evaluation (REFINE) study,[24] the REFINE-ICD trial is evaluating the efficacy of the ICD to reduce mortality in postinfarction patients with ejection fraction of 36% to 49% and abnormal T wave alternans and heart rate turbulence. The ideal combination of parameters, as well as time(s) for evaluation, need to be determined.

Wellens et al, 2014