Sudden cardiac death:

Non-invasive sudden cardiac death risk stratification in 2016

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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

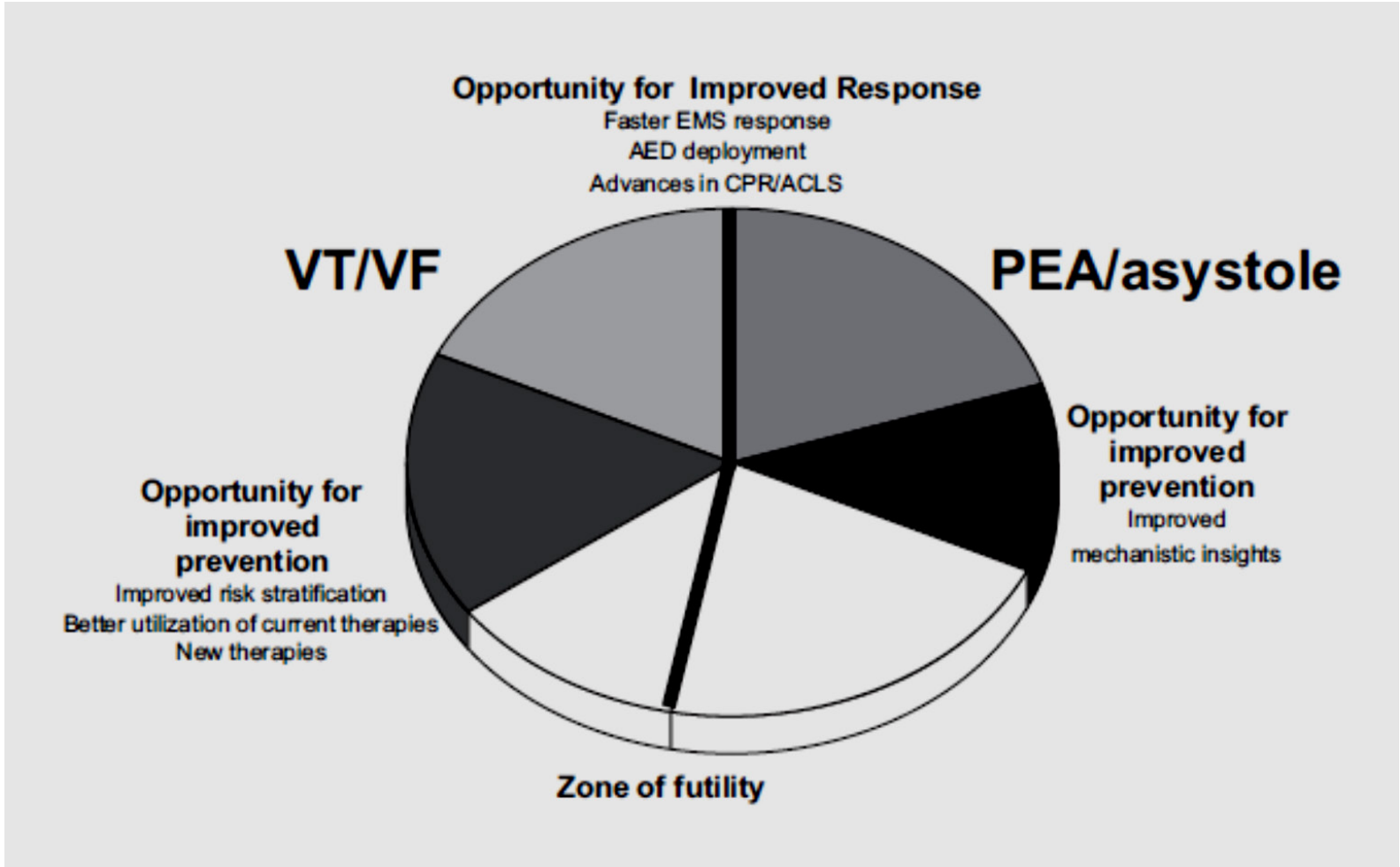
Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Special Report

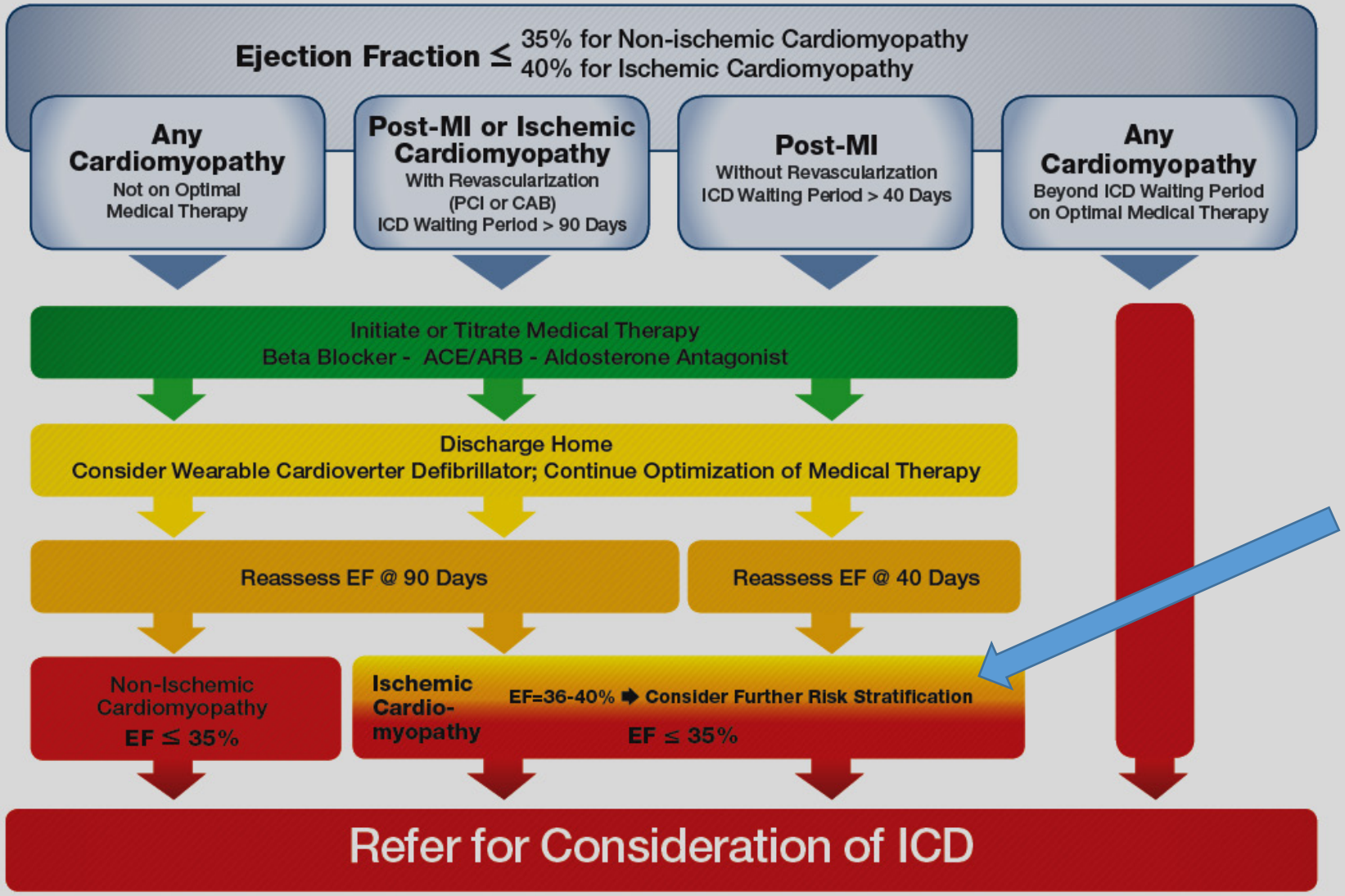
Risk Stratification for Sudden Cardiac Death

A Plan for the Future



Goldberger et al, 2014

Sudden Cardiac Death Primary Prevention Protocols

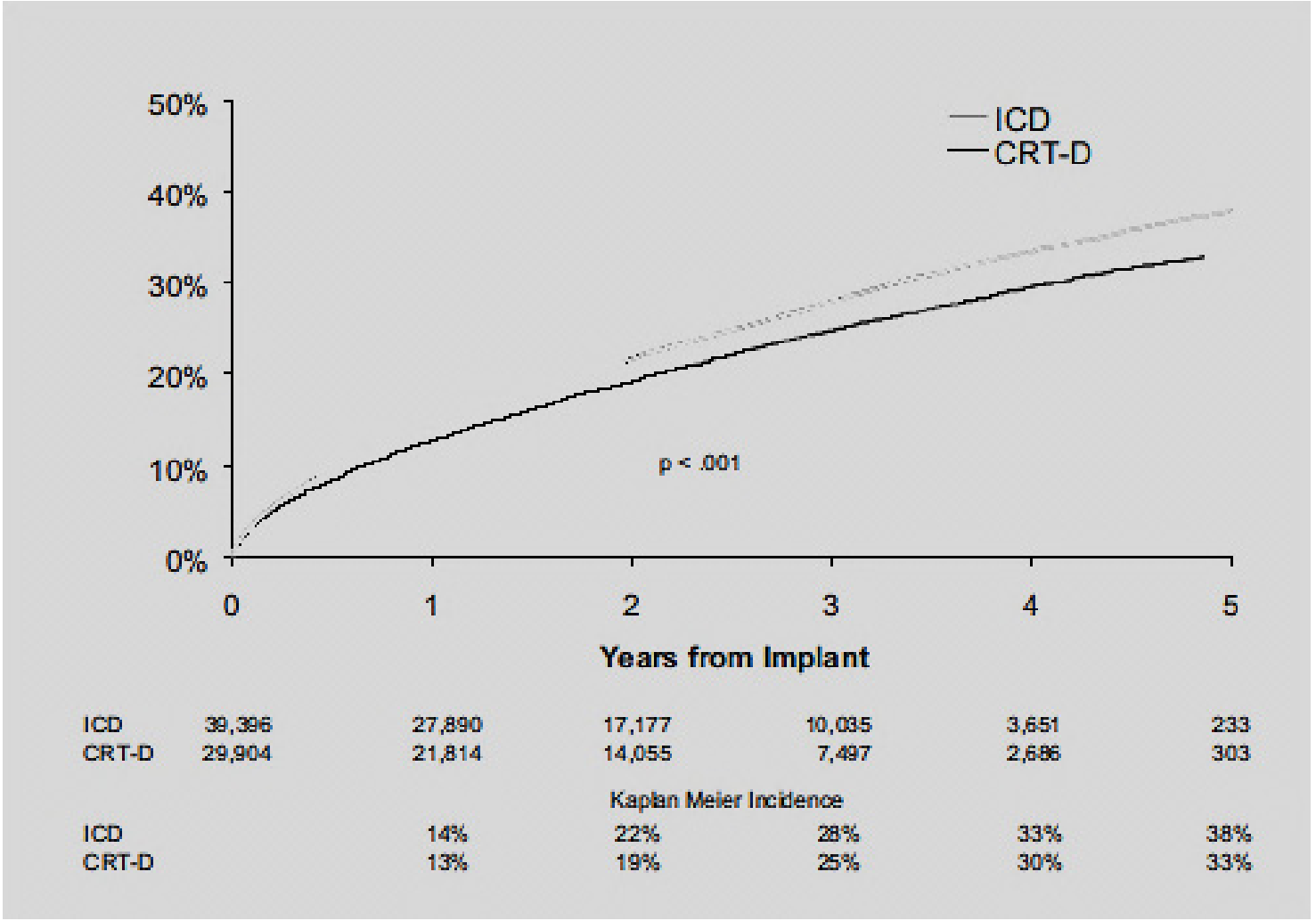


Learn more at www.HRSonline.org

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

Risk stratifiers for Sudden Cardiac Death and/or Cardiac Mortality

Electrophysiological 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
- Deceleration Capacity
- Myocardial Sympathetic Innervation

Measures of electrical instability
- VPCs
- NSVT

Functional surrogates

NYHA CLASS

Left Ventricular Ejection Fraction

Left Ventricular Volume

Peak Oxygen Consumption

Brain Natriuretic Peptide

Myocardial fibrosis assessment by LGE

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

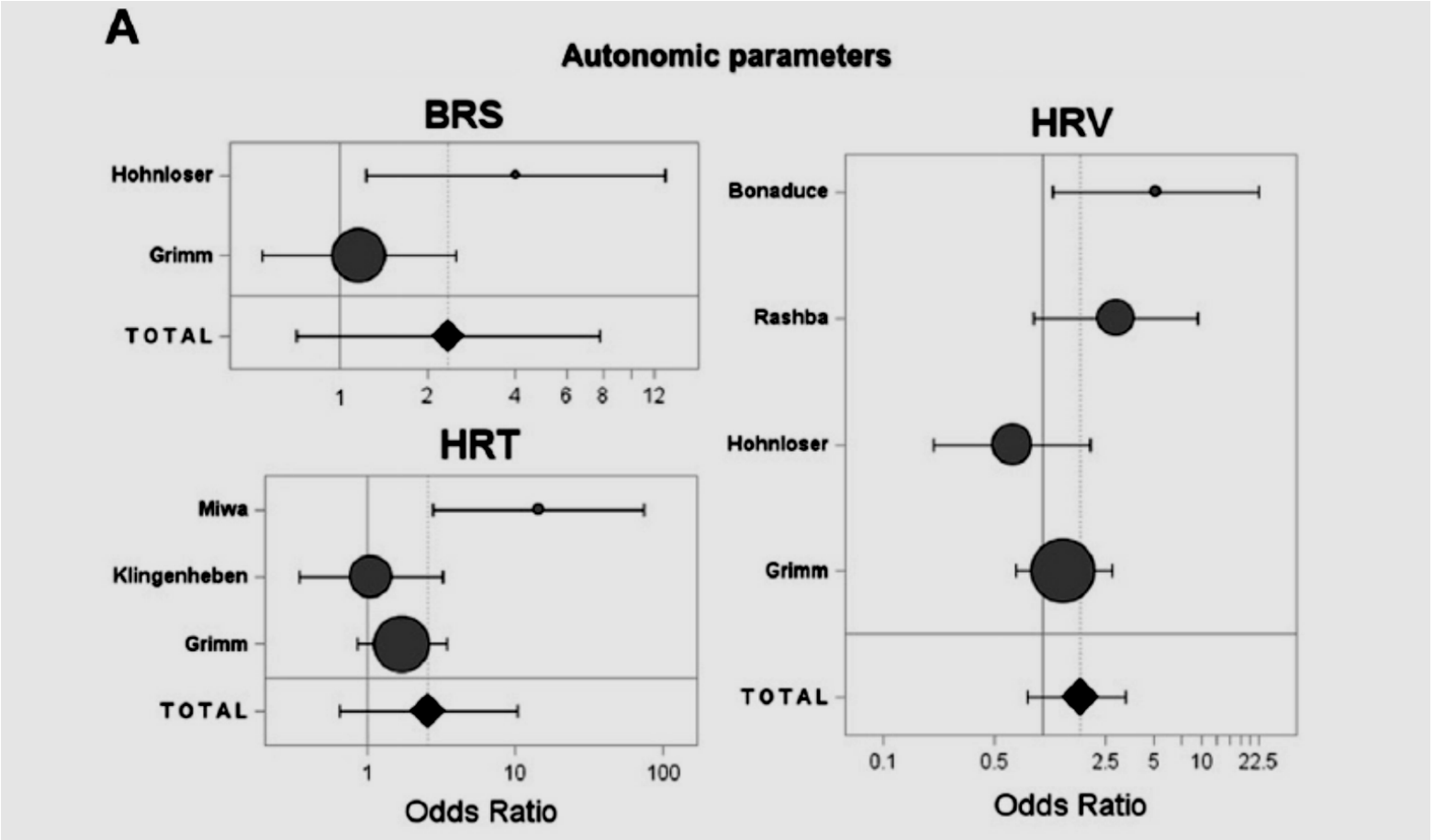
348 abstracts reviewed

80 full-text articles reviewed

43 studies with valid data identified

45 studies included in the final report

Sudden Cardiac Death Risk Stratification in Patients With Nonischemic Dilated Cardiomyopathy



Goldberger et al, JACC 2014

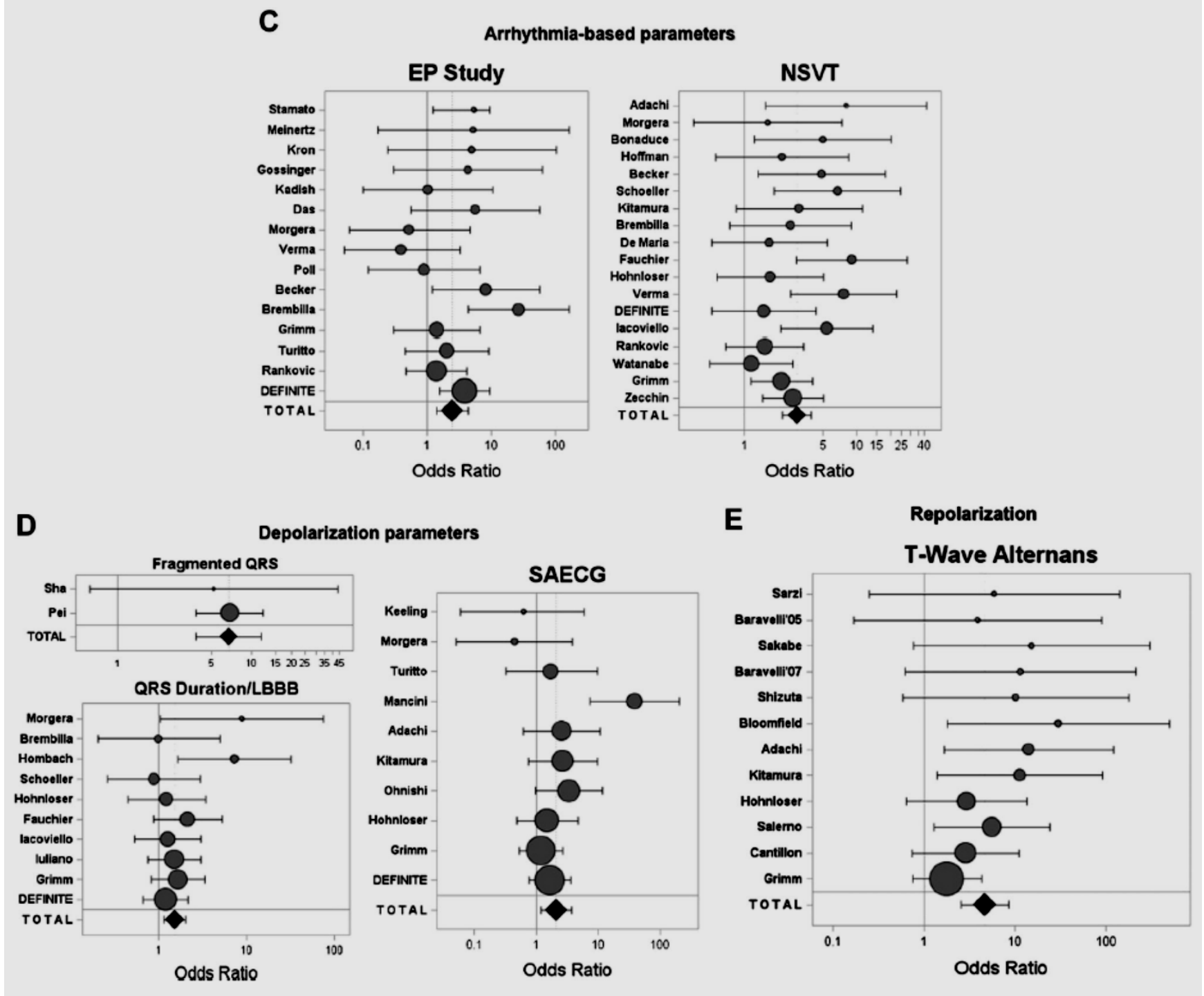

C
Arrhythmia-based parameters
EP Study
Stamato
Meinertz
Kron
Gossinger
Kadish
Das
Morgera
Verma
Poll
Becker
Brembilla
Grimm
Turitto
Rankovic
DEFINITE
TOTAL
0.1
1
10
100
Odds Ratio
NSVT
Adachi
Morgera
Bonaduce
Hoffman
Becker
Schoeller
Kitamura
Brembilla
De Maria
Fauchier
Hohnloser
Verma
DEFINITE
Iacoviello
Rankovic
Watanabe
Grimm
Zecchin
TOTAL
1
5
10
15
25
40
Odds Ratio
D
Depolarization parameters
Fragmented QRS
Sha
Pei
TOTAL
1
5
10
15
20
25
35
45
QRS Duration/LBBB
Morgera
Brembilla
Hombach
Schoeller
Hohnloser
Fauchier
Iacoviello
Iuliano
Grimm
DEFINITE
TOTAL
1
10
100
Odds Ratio
SAECG
Keeling
Morgera
Turitto
Mancini
Adachi
Kitamura
Ohnishi
Hohnloser
Grimm
DEFINITE
TOTAL
0.1
1
10
100
Odds Ratio
E
Repolarization
T-Wave Alternans
Sarzi
Baravelli'05
Sakabe
Baravelli'07
Shizuta
Bloomfield
Adachi
Kitamura
Hohnloser
Salerno
Cantillon
Grimm
TOTAL
0.1
1
10
100
Odds Ratio

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)

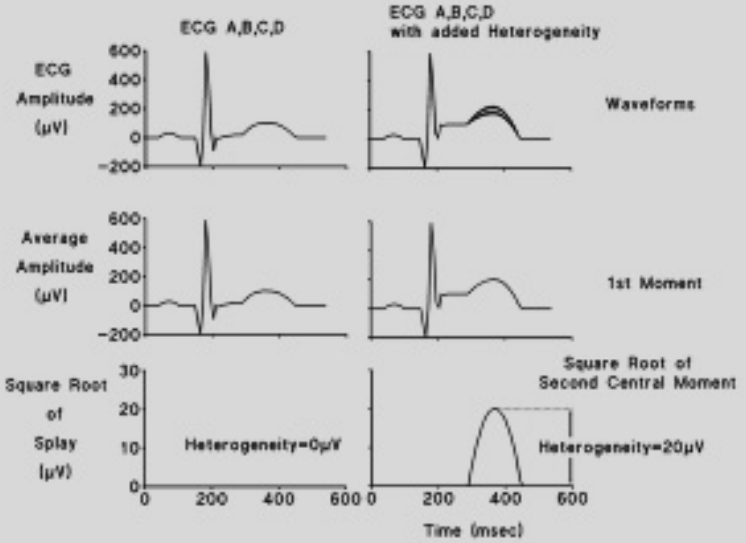
Goldberger et al, JACC 2014

Prediction of sudden cardiac death with automated high-throughput analysis of heterogeneity in standard resting 12-lead electrocardiograms

Study population

The participants in this study were drawn from the Health 2000 Survey (http://www.terveys2000.fi/indexe.html), which is a cross-sectional, general population–based epidemiological survey conducted in Finland between 2000 and 2001.[12] The study enrolled a sample of 8028 Finnish adults aged ≥ 30 and < 80 years representative of the entire Finnish adult population. After baseline participant interviews, health examinations, and exclusion of subjects with preexcitation syndrome, complete bundle branch block, paced rhythm, atrial fibrillation or flutter, low-quality ECG, and use of QT-prolonging medication or digoxin, a total of 5618 eligible participants remained in the cohort.

Multilead Template-Derived Residua of Surface ECGS for Quantitative Assessment of Arrhythmia Risk



Annals of Noninvasive Electrocardiology
Volume 20, Issue 3, pages 273-281, 18 SEP 2014 DOI: 10.1111/anec.12205
http://onlinelibrary.wiley.com/doi/10.1111/anec.12205/full#anec12205-fig-0002

Kentta et al, Heart Rhythm 2016

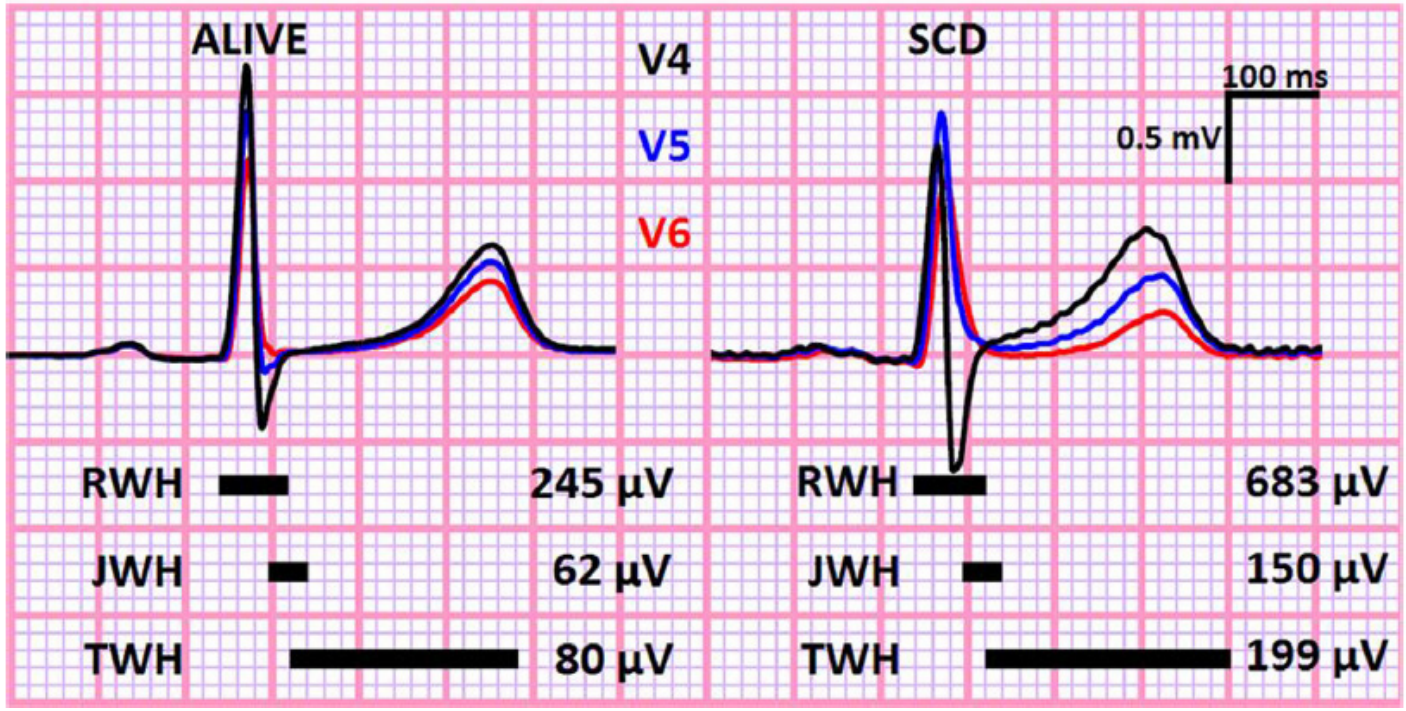
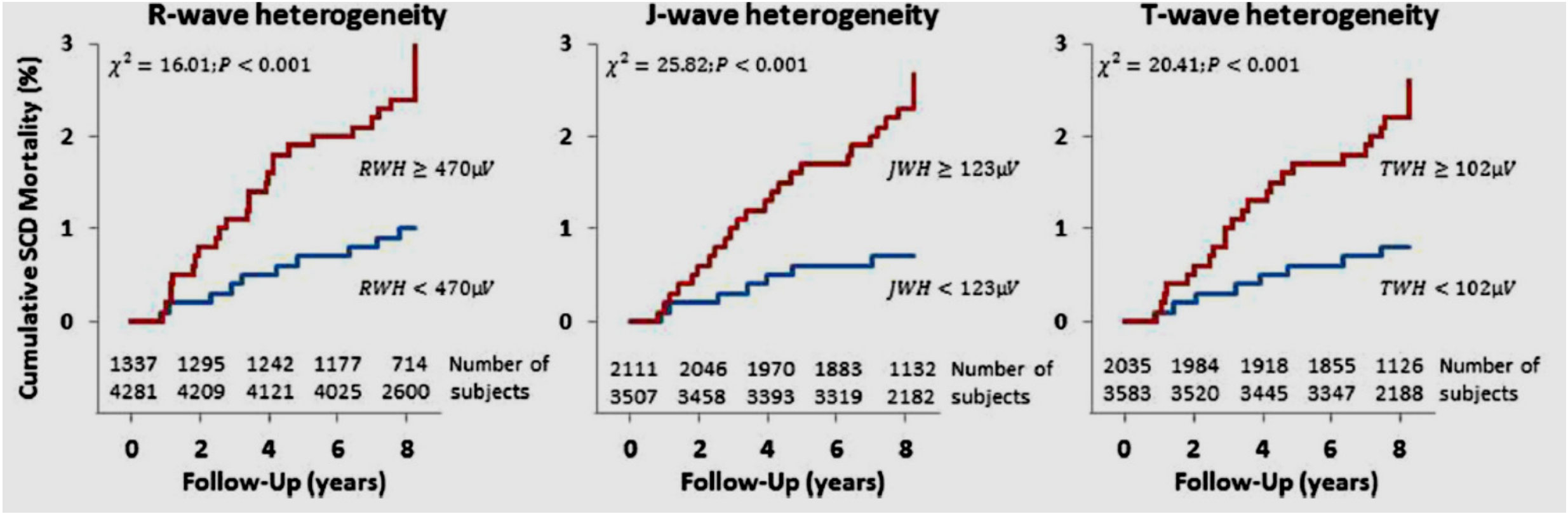


Table 3 Unadjusted and adjusted hazard ratios for left precordial depolarization and repolarization heterogeneities per increment of 1 SD

		Hazard ratio (95% CI) per increment of 1 SD		
End point	ECG parameter	Unadjusted	Age- and sex-adjusted	Multivariate adjusted
All cause mortality	R-wave heterogeneity	1.4 (1.3–1.5)‡	1.2 (1.1–1.3)‡	1.2 (1.1–1.3)‡
	J-wave heterogeneity	1.4 (1.3–1.6)‡	1.1 (1.0–1.3)*	1.2 (1.0–1.3)†
	T-wave heterogeneity	1.4 (1.3–1.6)‡	1.2 (1.1–1.4)‡	1.2 (1.1–1.4)‡
Cardiac death	R-wave heterogeneity	1.5 (1.3–1.7)‡	1.2 (1.0–1.4)*	1.1 (0.9–1.3)NS
	J-wave heterogeneity	1.6 (1.3–2.0)‡	1.2 (1.0–1.4)NS	1.2 (1.0–1.4)NS
	T-wave heterogeneity	1.8 (1.5–2.2)‡	1.5 (1.2–1.8)‡	1.4 (1.2–1.8)‡
Sudden cardiac death	R-wave heterogeneity	1.5 (1.3–1.7)‡	1.2 (1.0–1.4)*	1.1 (0.9–1.4)NS
	J-wave heterogeneity	1.8 (1.4–2.3)‡	1.3 (1.1–1.6)*	1.3 (1.0–1.6)*
	T-wave heterogeneity	1.9 (1.5–2.4)‡	1.4 (1.1–1.8)†	1.4 (1.1–1.8)†

Kentta et al, Heart Rhythm 2016

Kaplan-Meier curves of R-wave, J-wave, and T-wave heterogeneity for sudden cardiac death with number of events.



Kentta et al, Heart Rhythm 2016

Conclusion

The present study demonstrates that increased spatial heterogeneity measured with RWH, JWH, and TWH in standard 12-lead resting ECGs is a powerful, electrophysiologically sound, independent predictor of SCD. An ultrarapid automated assessment of spatial heterogeneity in left precordial leads could prove useful as a screening tool for stratifying risk for life-threatening arrhythmias even in low-risk populations.

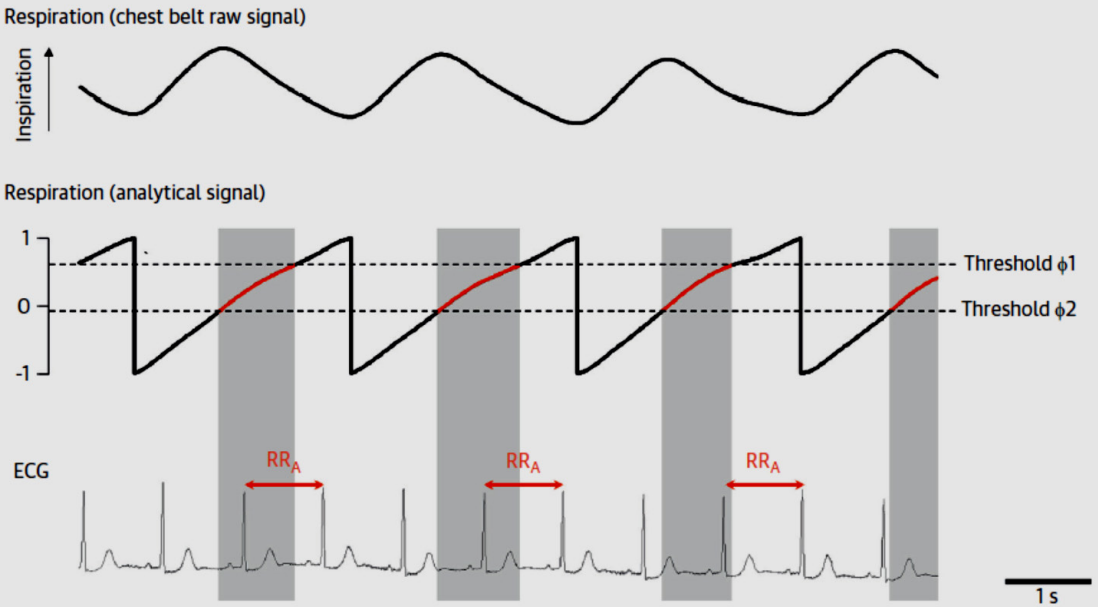
Kentta et al, Heart Rhythm 2016

Expiration-Triggered Sinus Arrhythmia Predicts Outcome in Survivors of Acute Myocardial Infarction

TABLE 1 Clinical Characteristics of the Study Cohort (N = 941)

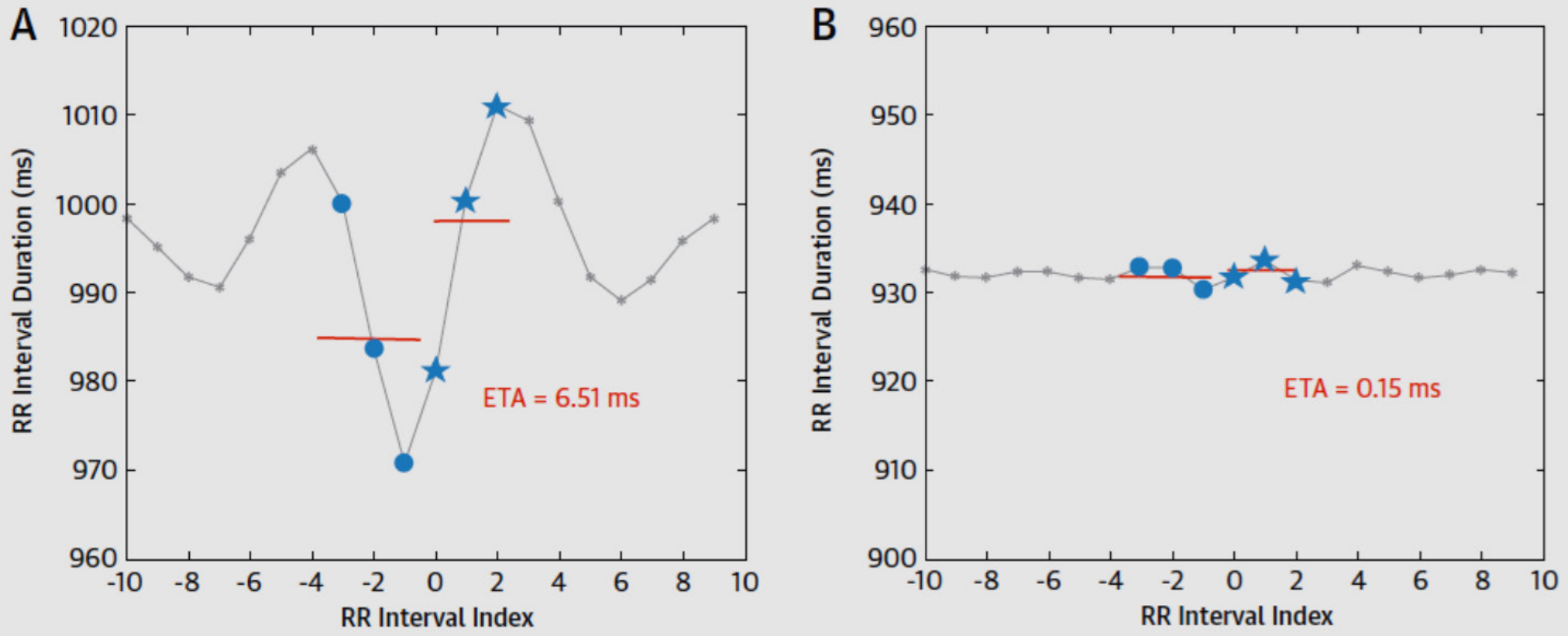
Age, yrs	61 (52-69)
Females	182 (19.3)
Diabetes mellitus	184 (19.6)
History of previous MI	90 (9.6)
Hypertension	682 (72.5)
Smoking	488 (51.9)
History of COPD	39 (4.1)
CK max, U/l	1,302 (647-2,465)
LVEF, %	53 (45-60)
Localization of AMI	
Anterior wall	391 (41.6)
Posterior wall	435 (46.2)
Lateral wall	102 (10.8)
Unclassified	12 (1.3)
BMI, kg/m^2	27 (24-29)
Serum creatinine, mg/dl	1.1 (0.9-1.3)
Cardiogenic shock/CPR	41 (4.4)
Intervention	
PCI	878 (93.3)
Thrombolysis	14 (1.5)
CABG	6 (0.6)
No revascularization possible	43 (4.6)
Aspirin	913 (97.0)
Clopidogrel	920 (97.8)
Beta-blockers	897 (95.3)
ACE inhibitors	885 (94.0)
Statins	879 (93.4)
Diuretics	415 (44.1)

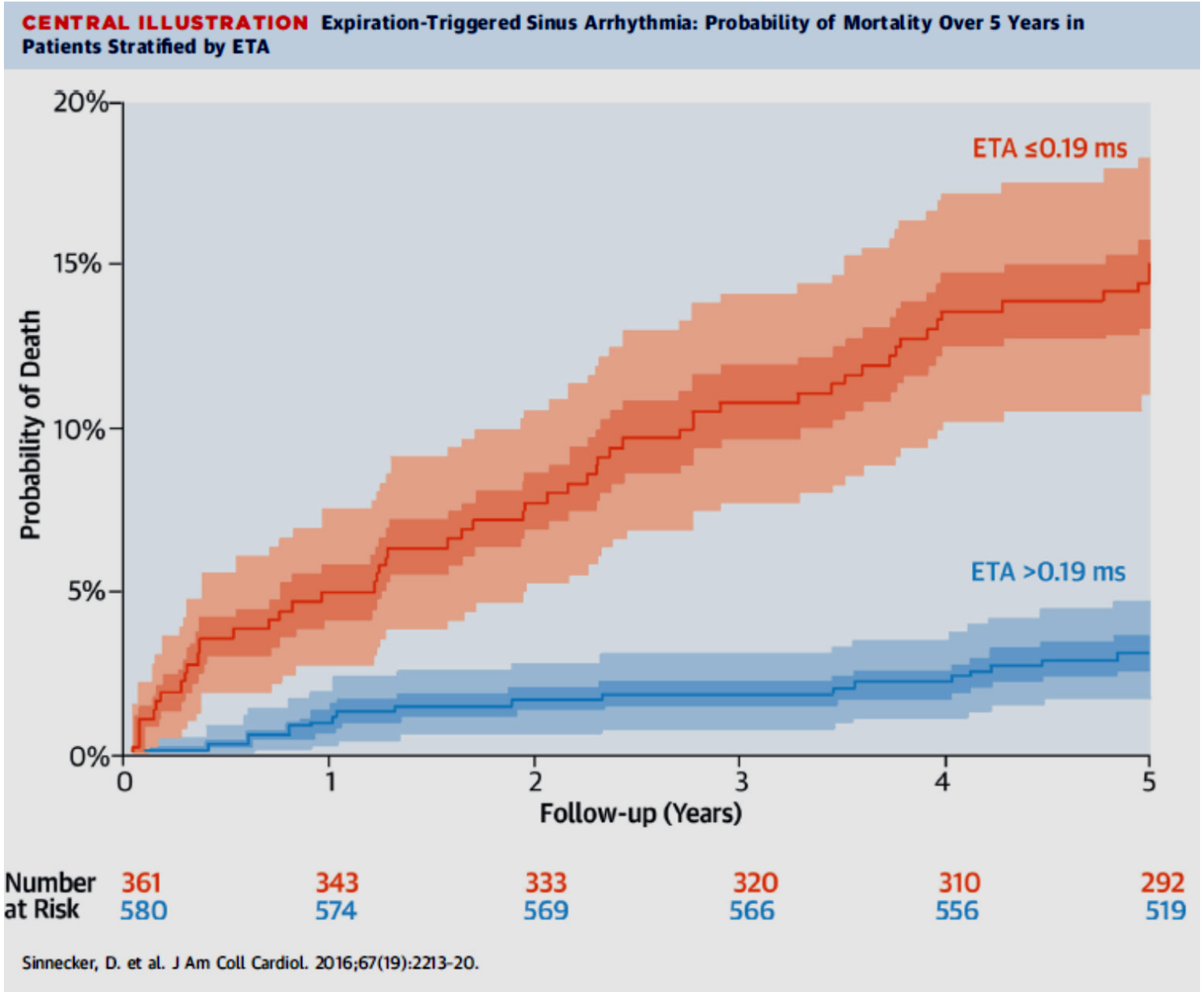
FIGURE 1 Calculation of Expiration-Triggered Sinus Arrhythmia From ECG and Respiratory Signals



Sinnecker et al, JACC 2016

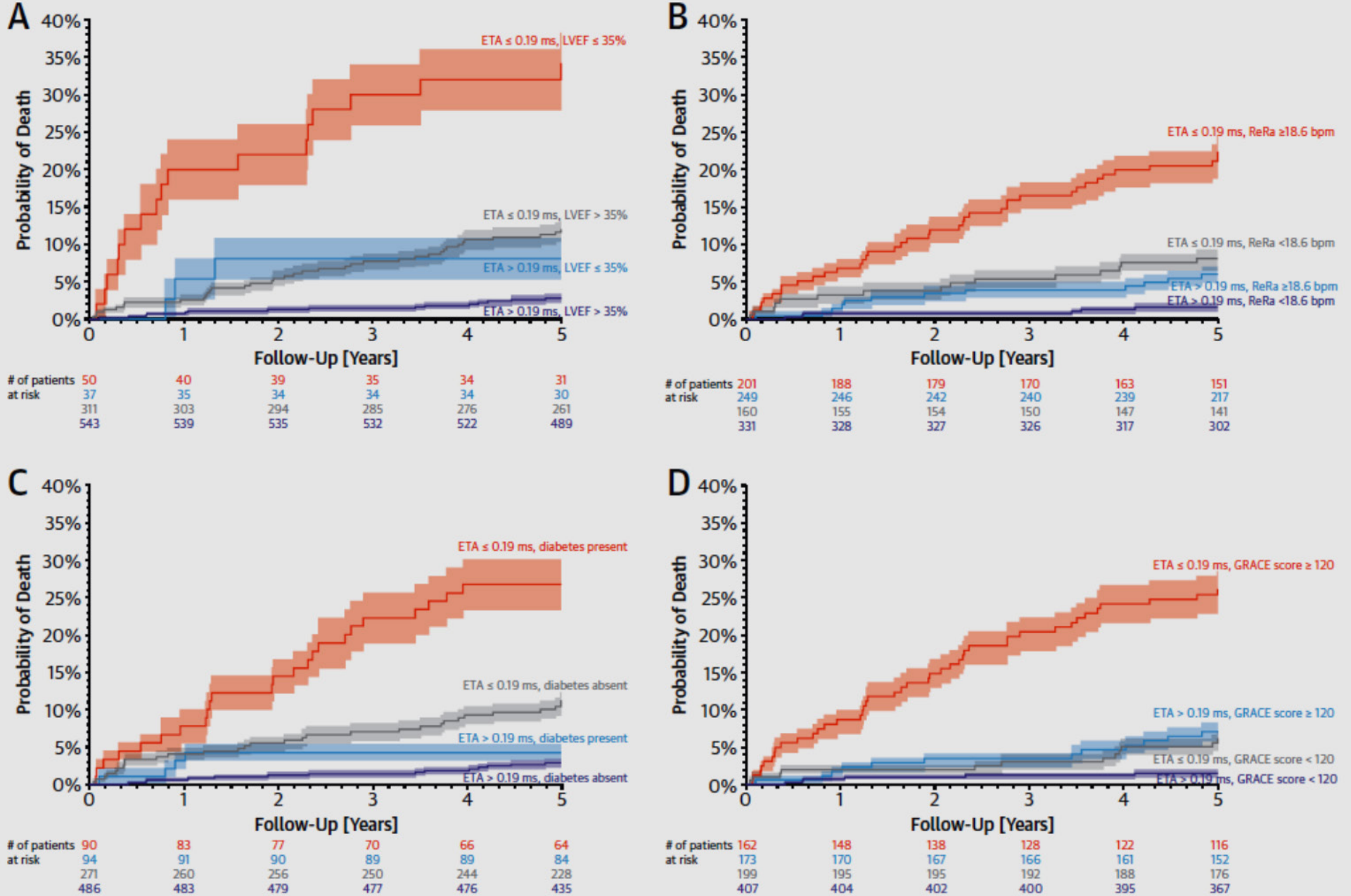
FIGURE 2 Phase-Rectified and Averaged RR Interval Tachograms Centered on Expiration





Sinnecker et al, JACC 2016

FIGURE 3 Risk Stratification by ETA in Combination With Other Risk Predictors



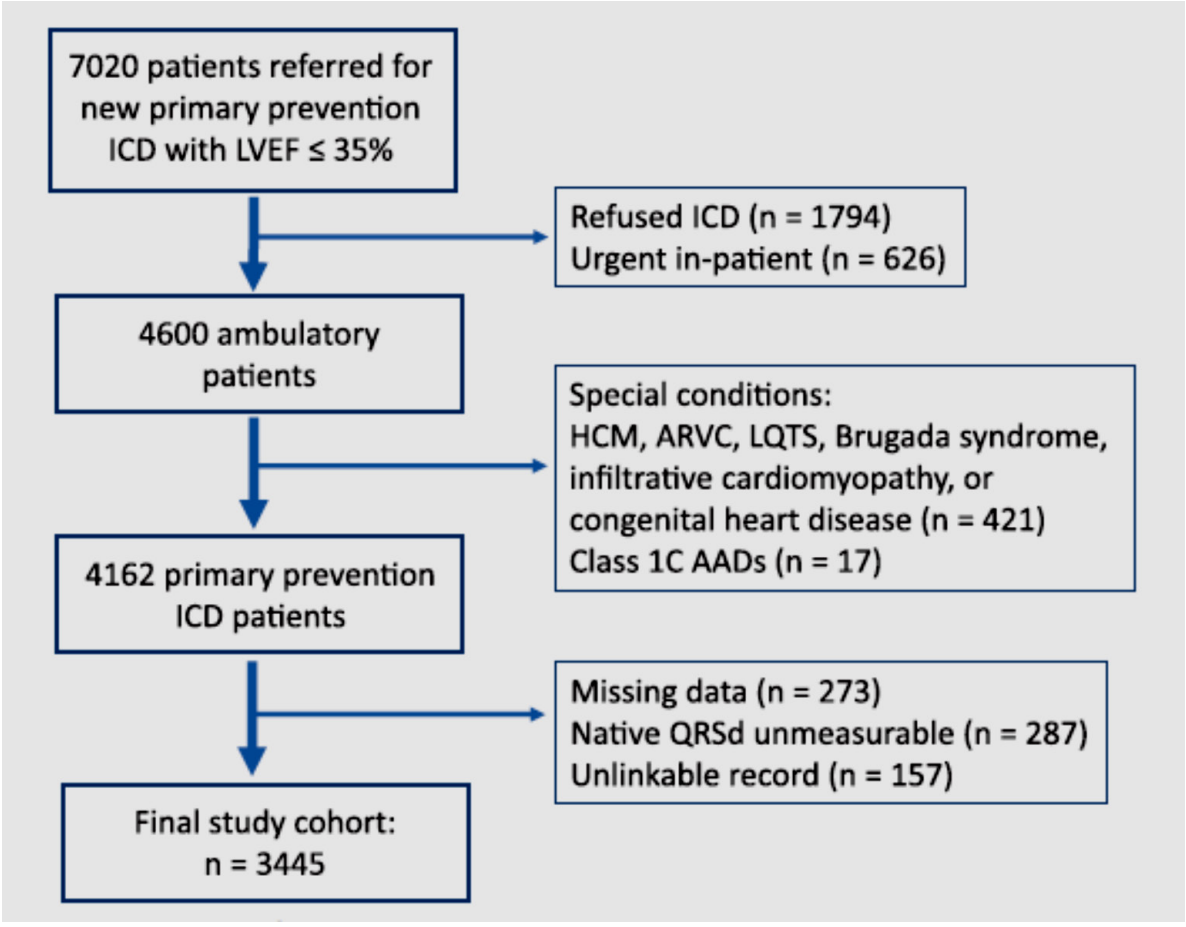
CONCLUSIONS

ETA appears to be a potent risk marker in post-infarction patients. The association of ETA and mortality is independent of other established risk factors, indicating that inclusion of ETA in risk stratification models will significantly improve the predictive power of these models.

Sinnecker et al, JACC 2016

Clinical Risk Stratification for Primary Prevention Implantable Cardioverter Defibrillators

Ontario ICD database 2007-2012



Lee et al, Circ Heart Fail 2015

Predictor Variables

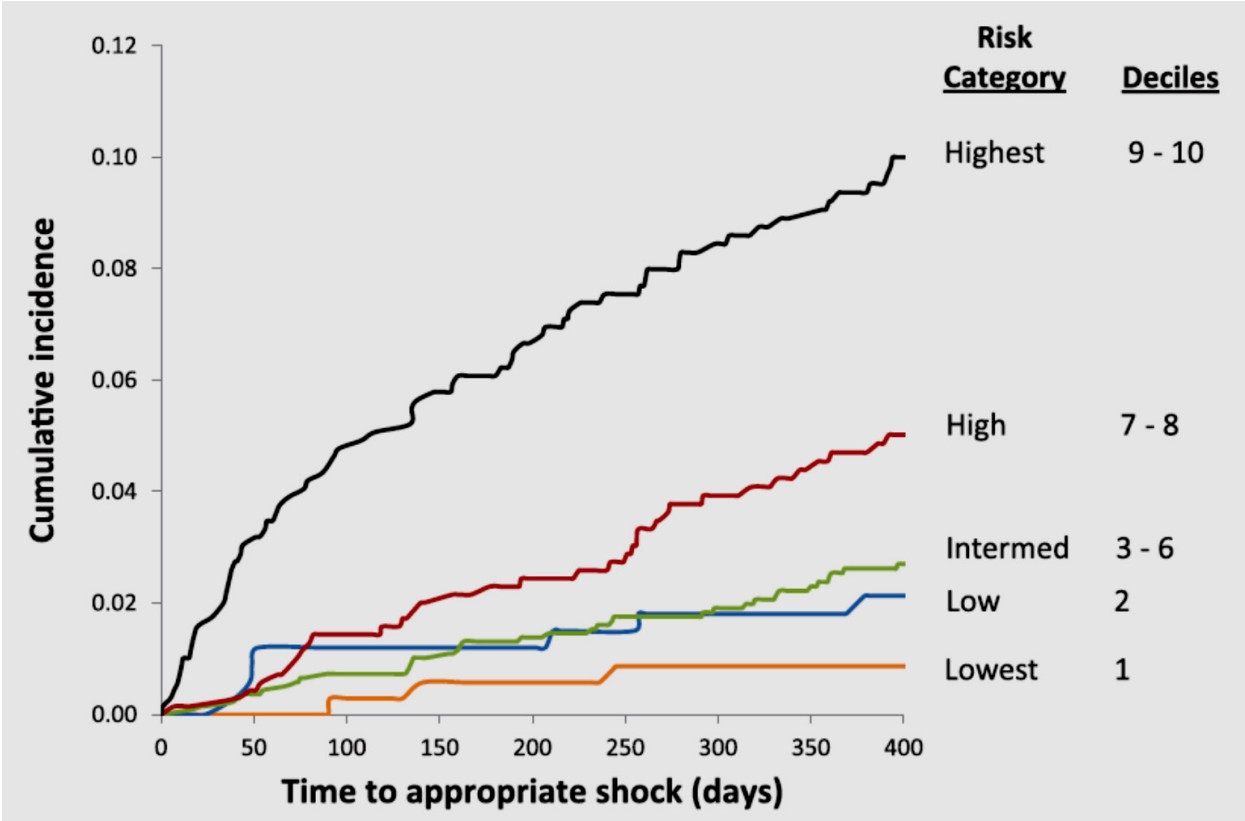
Two separate models were developed for predicting the outcomes of appropriate shock or death. Potential predictors for these models included demographics (age and sex), ventricular arrhythmia history (nonsustained VT, and syncope), disease pathogenesis (eg, ischemic versus cardiomyopathy versus other), coronary revascularization procedures (eg, percutaneous coronary intervention or coronary artery bypass graft surgery), previous heart failure (HF) hospitalizations, Canadian Cardiovascular Society angina class, New York Heart Association classification, pre-existing pacemaker system, and previous or current atrial fibrillation. We also examined the following noncardiac factors: diabetes mellitus, stroke or transient ischemic attack, cigarette smoking (current or past), peripheral vascular disease, chronic obstructive lung disease, cognitive impairment, and home oxygen use. We examined the use of cardiac medications (eg, β-adrenoreceptor antagonists, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker [ARB], loop diuretic, digoxin, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor, and amiodarone), and laboratory investigations, including QRSd, LVEF, left ventricular end-systolic dimension, left atrial size, serum creatinine, serum sodium, hemoglobin concentration, body weight, and

During 5918 person-years of follow-up, appropriate shock occurred in 204 patients (3.6 shocks/100 person-years) and 292 died (4.9 deaths/100 person-years).

Table 3. Point Score for Appropriate Shock

Variable Type	Predictor	
Demographic	Age, y	–0.2×Age
	Male	4
Rhythm status	Nonsustained VT	4
	Atrial fibrillation	5
	Amiodarone	–8
General cardiac status	Digoxin	4
	Pre-existing pacemaker	7
	Smoker	–3
Laboratory variables	QRSd (ms)	–0.2 × |QRSd-130|
	Hemoglobin <12 g/dL	–8
	Creatinine, mg/dL*	0.02×Creatinine×88.4
Sum total		Shock Score

QRSd indicates QRS duration; and VT, ventricular tachycardia.
*For creatinine in SI units, creatinine score=0.02 × Creatinine (in μmol/L).



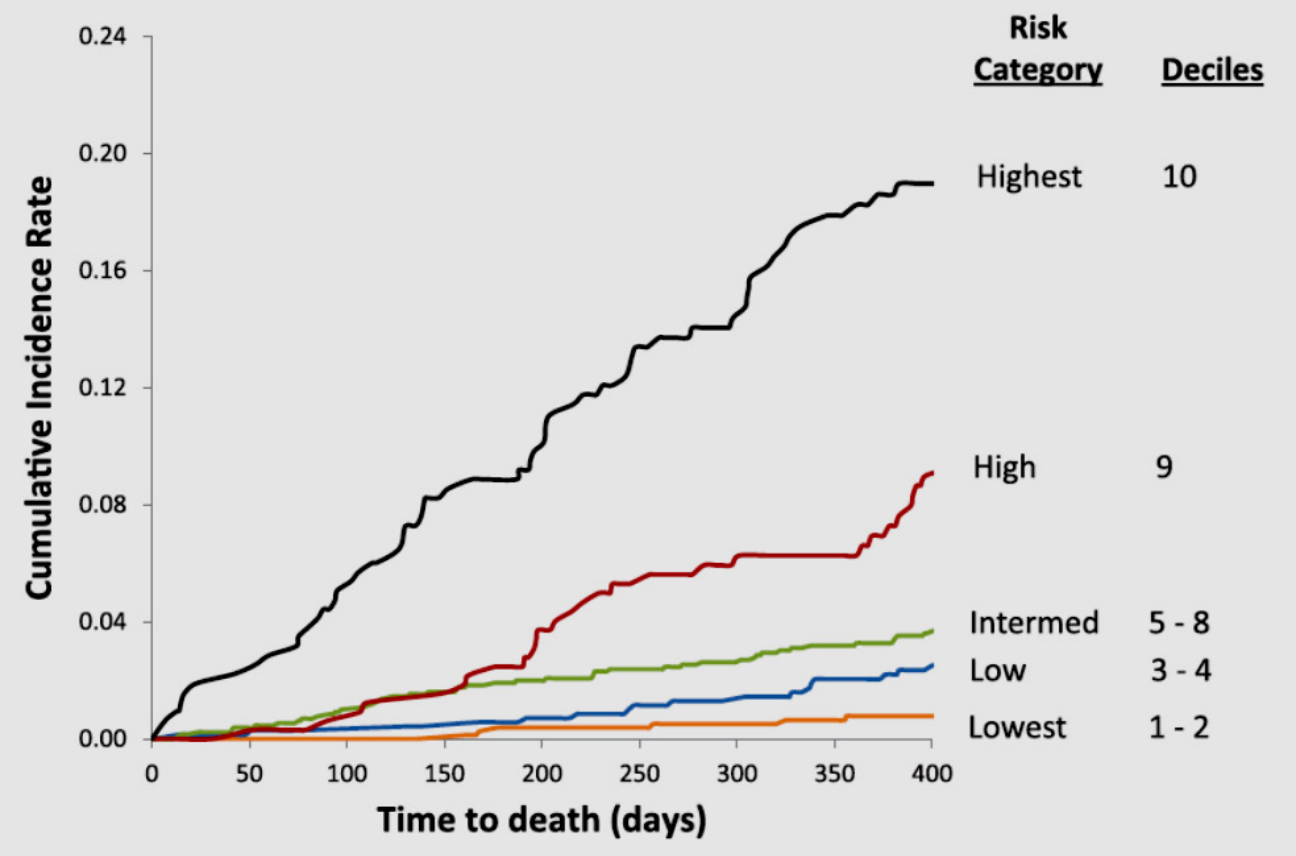
Lee et al, Circ Heart Fail 2015

Table 4. Point Score for Death

Variable Type	Predictor	
Demographic	Age, y	0.2×Age
Ischemic disease and CVD risk factors	Ischemic disease	2
	Previous coronary revascularization	−1
	Diabetes mellitus (insulin or oral agent)	2
	Smoker	2
HF status	Previous HF hospitalization	3
	NYHA class III–IV vs I–II	2
	SBP, mm Hg	−0.07×SBP
	Serum sodium ≤138	2
	ACE inhibitor or ARB	−2
Comorbid conditions	Chronic obstructive pulmonary disease	2
	Home oxygen use	7
	Pre-existing pacemaker system	3
	Any cancer	2
	Hemoglobin <12 g/dL	2
	Creatinine, mg/dL*	0.01×Creatinine×88.4
Sum total		Mortality Score

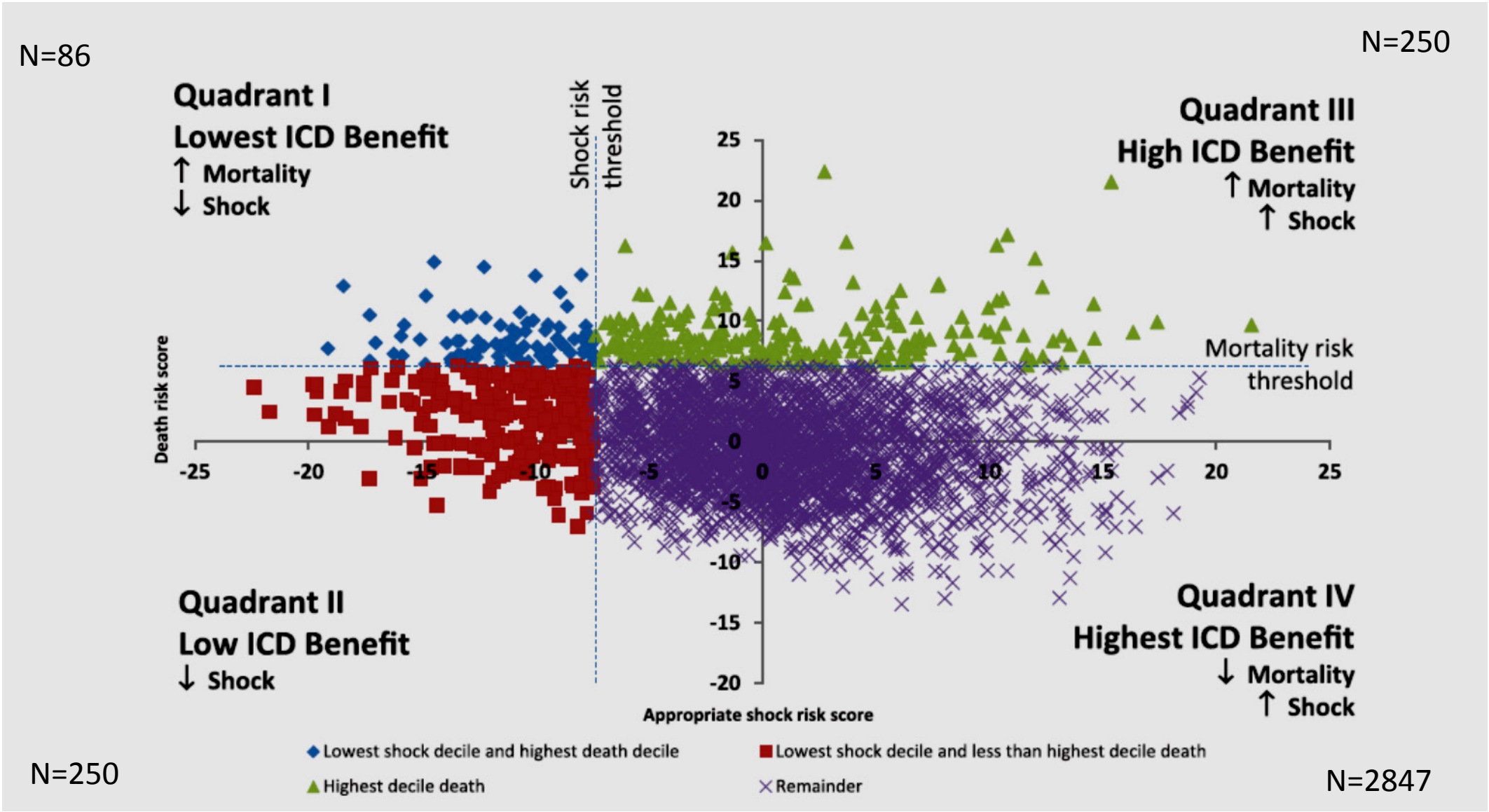
ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CVD, cardiovascular disease; HF, heart failure; NYHA, New York Heart Association; and SBP, systolic blood pressure.

*For creatinine in SI units, creatinine score=0.01×creatinine (in μmol/L).



Lee et al, Circ Heart Fail 2015

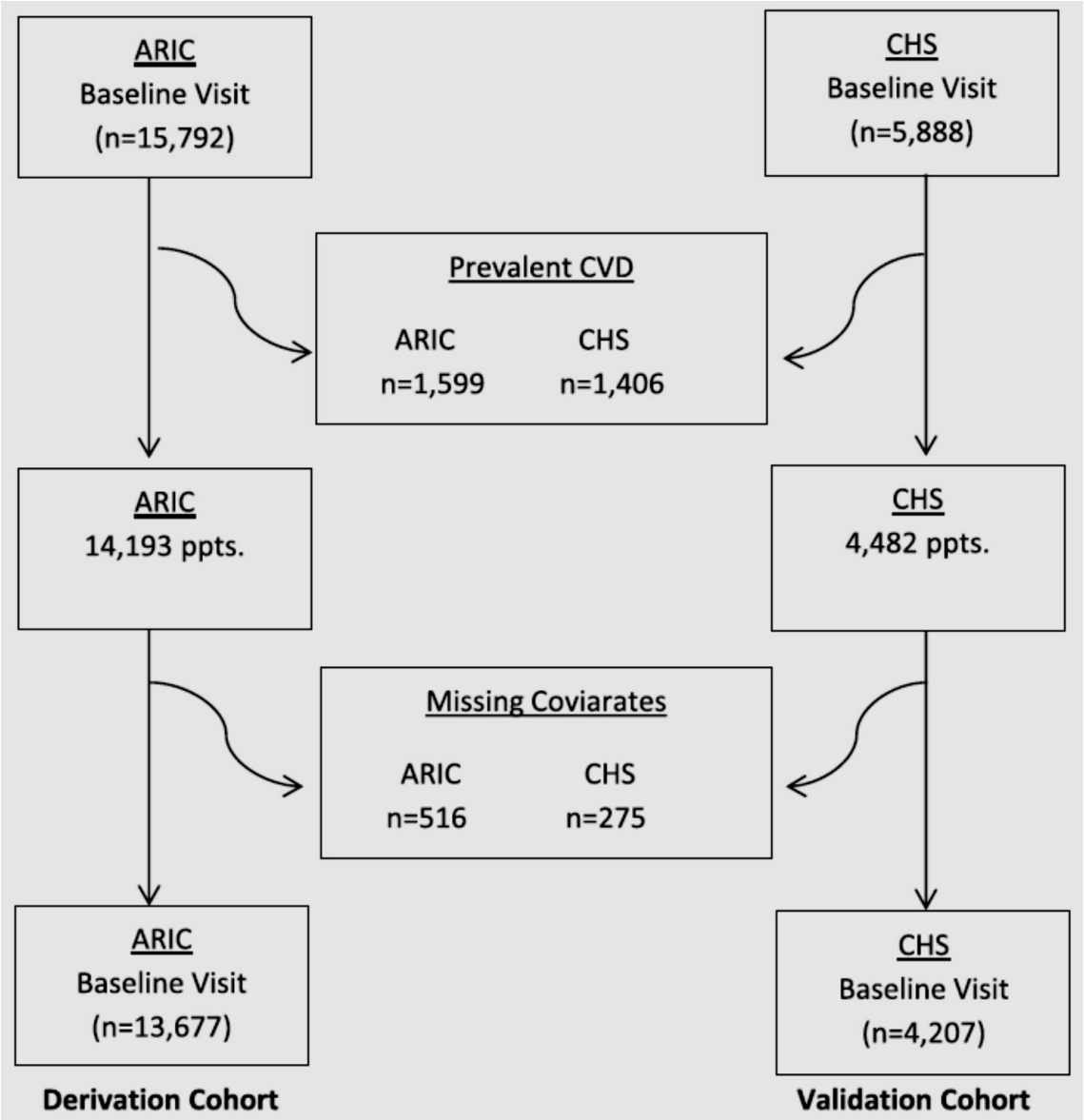
Depiction of conceptual model of predicted risks of appropriate shocks vs death using quadrants



Lee et al, Circ Heart Fail 2015

Development and Validation of a Sudden Cardiac Death Prediction Model for the General Population

Participants in the ARIC study (Atherosclerosis Risk in Communities) (n=13 677) and the CHS (Cardiovascular Health Study) (n=4207) who were free of baseline cardiovascular disease were considered.



RESULTS: There were a total o
345 adjudicated SCD events in
our analyses, and the 12
independent risk factors in the
ARIC study included
age, male sex, black race,
current smoking, systolic bloo
pressure, use
of antihypertensive medicatio
diabetes mellitus, serum
potassium, serum
albumin, high-density
lipoprotein, estimated
glomerular filtration rate,
and QTc interval.

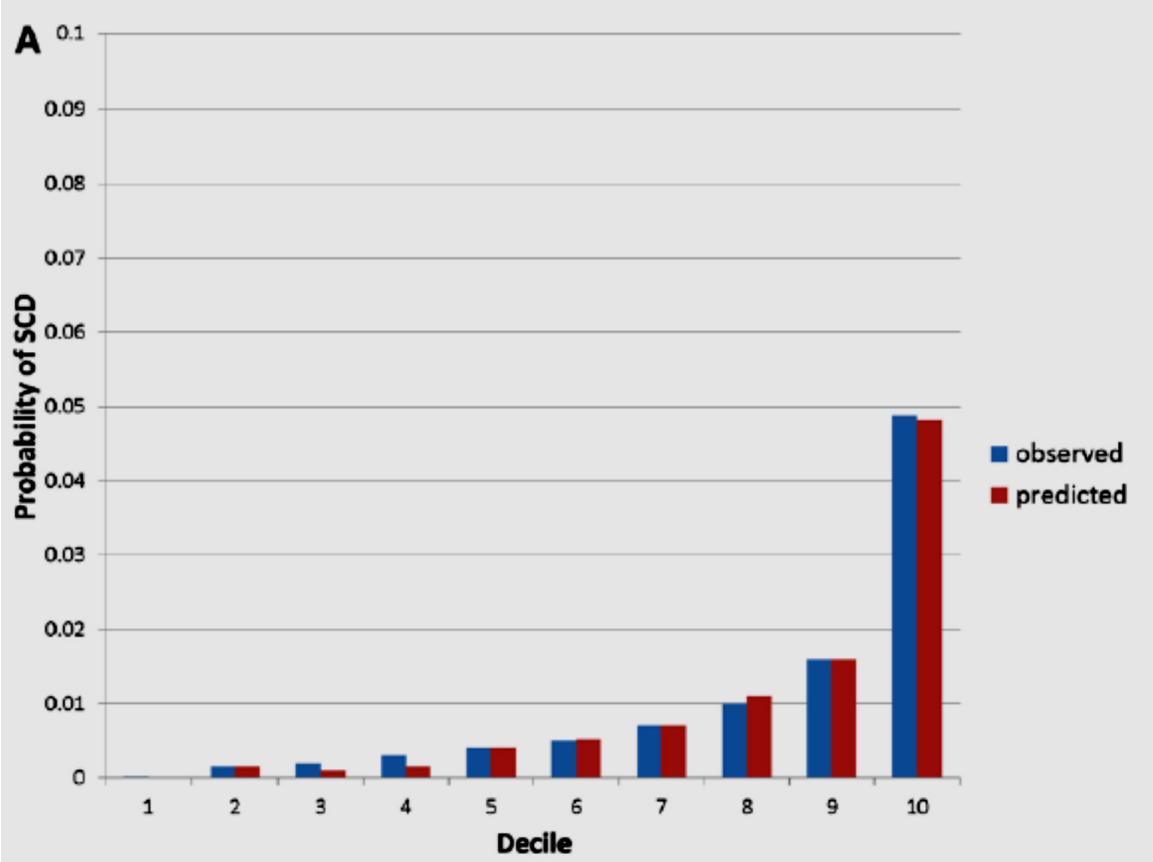
Deo et al, Circulation 2016

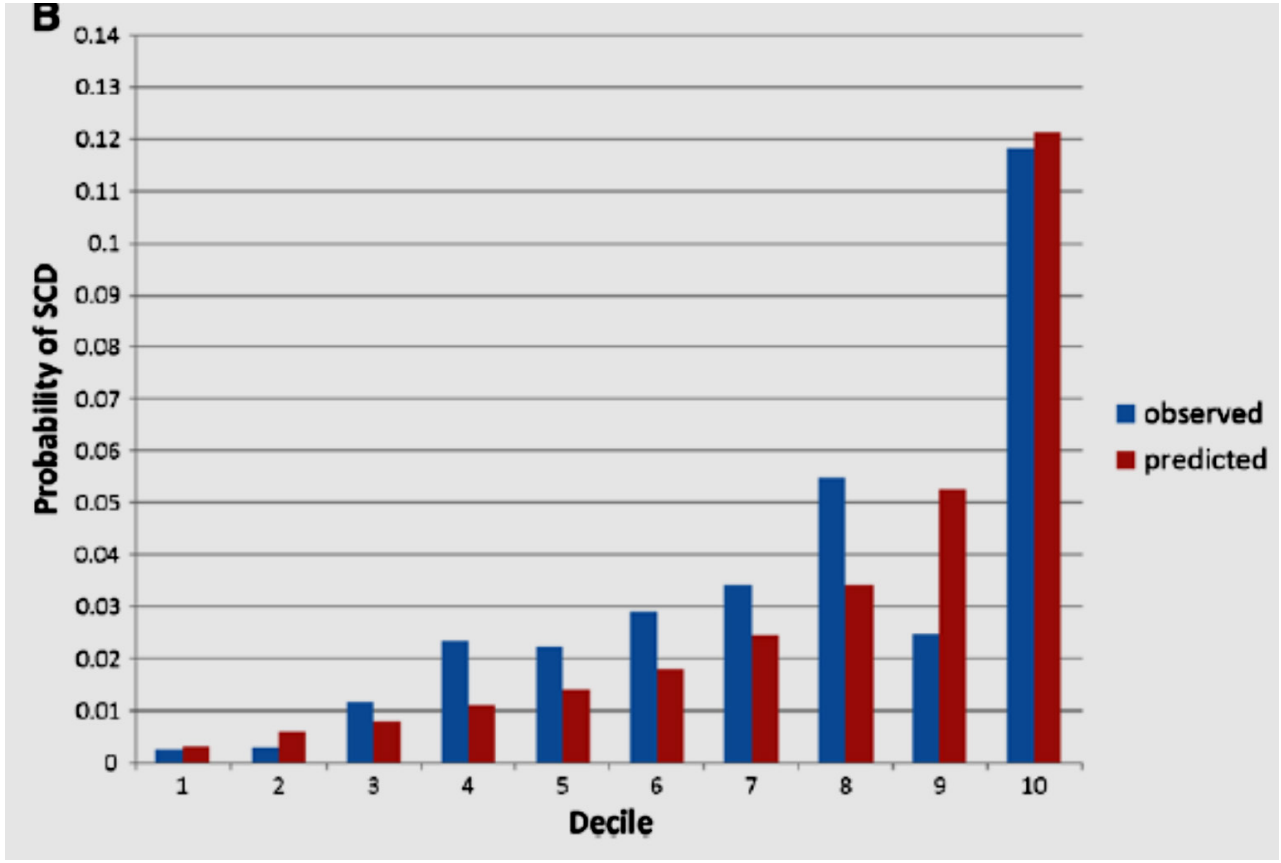
Table 2. Estimated β Coefficients in the Derived SCD Prediction Model

	Estimated β	Standard Error
Demographics		
Age (centered at 54, per 1 y increase)	0.043	0.014
Male	0.858	0.175
Black	0.597	0.179
CVD risk factors		
Current smoker	0.881	0.159
Systolic blood pressure (per 1SD increase)	0.347	0.062
Antihypertensive medication use	0.322	0.171
Diabetes mellitus	0.792	0.181
Serum measures		
Potassium (centered at 4.4, per 0.5 mmol/L increase)	–0.004	0.007
Quadratic potassium term	0.0009	0.0003
Albumin (per 0.3 g/dL decrease)	0.253	0.081
HDL (per SD decrease)	0.202	0.097
eGFR 60–90 mL/min/1.73m^2	0.315	0.175
eGFR <60 mL/min/1.73m^2	0.849	0.348
QT_c interval (per SD increase)	0.158	0.052

Deo et al, Circulation 2016

A, ARIC study 10-year calibration plot using sudden cardiac death prediction model and B, CHS 10-year calibration plot using the SCD prediction model





Deo et al, Circulation 2016

Association of Biomarkers With Sudden Cardiac Death in CHS

	Biomarker Quintiles						Linear Model
	1	2	3	4	5	Per Doubling	*P* value
CRP							
CRP range (mg/L)	<1.05	1.05–1.99	2.00–3.18	3.19–5.68	>5.68		
Unadjusted; HR (95% CI)	1.00 (ref)	0.77 (0.45, 1.32)	1.08 (0.66, 1.78)	1.14 (0.69, 1.89)	1.50 (0.92, 2.46)	1.10 (0.93, 1.30)	0.275
Adjusted*; HR (95% CI)	1.00 (ref)	0.75 (0.44, 1.29)	1.04 (0.63, 1.72)	0.92 (0.54, 1.56)	1.19 (0.71, 1.99)	1.03 (0.87, 1.23)	0.712
NT-proBNP							
NT-proBNP range (pg/dL)	<51	51–91	92–156	157–298	>298		
Unadjusted; HR (95% CI)	1.00 (ref)	1.13 (0.63, 2.01)	1.62 (0.93, 2.81)	1.88 (1.09, 3.27)	2.96 (1.65, 5.33)	1.18 (1.00, 1.39)	0.045
Adjusted*; HR (95% CI)	1.00 (ref)	1.10 (0.61, 1.96)	1.51 (0.86, 2.66)	1.56 (0.87, 2.79)	1.83 (0.95, 3.50)	1.14 (0.90, 1.28)	0.418
High sensitivity troponin T							
High sensitivity troponin T range (pg/mL)	<3.00	3.00–5.44	5.45–8.16	8.17–12.94	>12.94		
Unadjusted; HR (95% CI)	1.00 (ref)	0.53 (0.25, 1.14)	1.51 (0.86, 2.64)	1.97 (1.16, 3.37)	3.75 (2.24, 6.26)	1.50 (1.25, 1.81)	<0.001
Adjusted*; HR (95% CI)	1.00 (ref)	0.41 (0.19, 0.89)	0.96 (0.54, 1.72)	1.03 (0.58, 1.83)	1.39 (0.76, 2.55)	1.14 (0.88, 1.49)	0.327

*The final multivariable model selected based on the summary estimates from the derivation cohort: age, male sex, black race, current smoker, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, potassium, albumin, high-density lipoprotein, estimated glomerular filtration rate, and QT_C

Deo et al, Circulation 2016

Myocardial Fibrosis Assessment by LGE Is a Powerful Predictor of Ventricular Tachyarrhythmias in Ischemic and Nonischemic LV Dysfunction

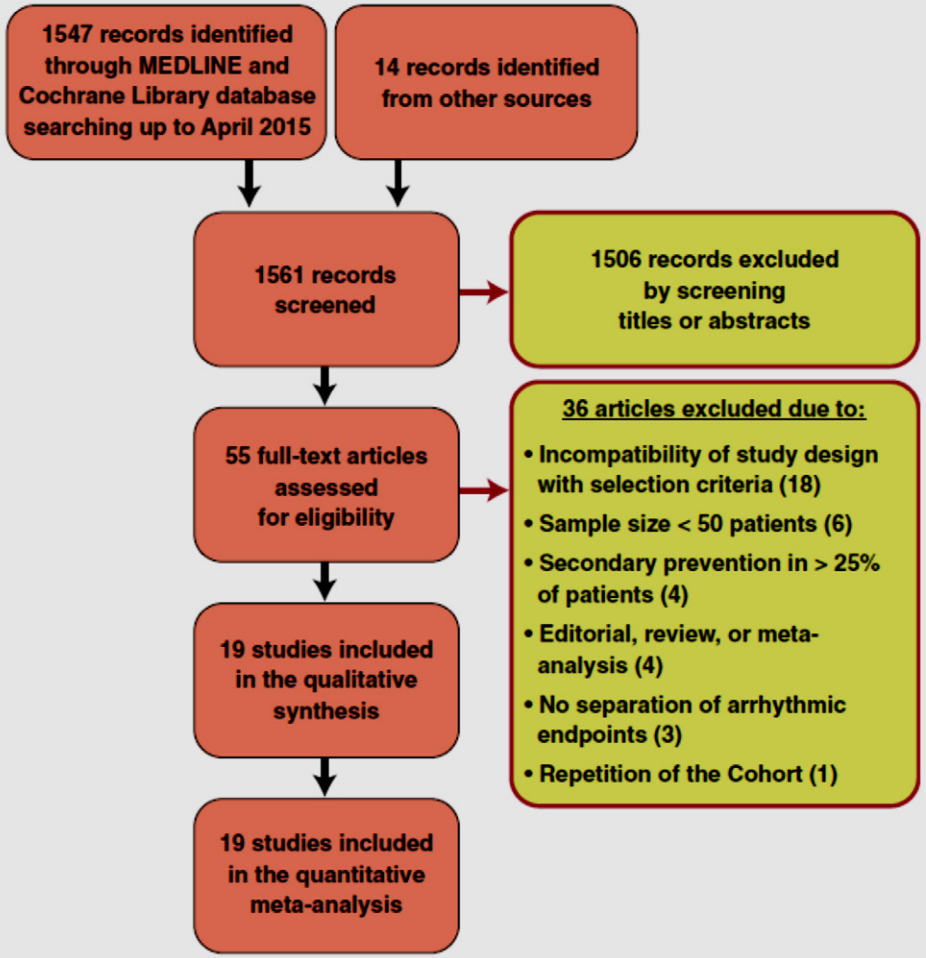


TABLE 3 Tachyarrhythmic Event Rate and Odds Ratio in the Different Subgroups of Studies

Subgroups	Studies	Patients	% AER	LGE-CMR % of LGE+ AER*	LGE-CMR % LGE− AER*	OR (95% CI)	p Value
Total	19	2,850	5.3	8.6	1.7	5.62 (4.20-7.51)	<0.00001
ICM	5	358	8.9	13.2	3.3	5.05 (2.73-9.36)	<0.00001
NICM	8	1,443	3.7	7.6	1.3	6.27 (4.15-9.47)	<0.00001
Mixed population	6	1,049	6.8	8.8	1.8	4.92 (2.70-8.98)	<0.00001
Mean EF ≤30%	11	1,178	6.6	10.3	1.2	9.56 (5.63-16.23)	<0.00001
Mean EF >30%	8	1,672	4.6	7.4	2.0	4.48 (3.17-6.33)	<0.00001

Values are n or %. *LGE+/− test results based on the criteria reported in Table 1.

AER = annualized event rate; ICM = ischemic cardiomyopathy; NICM = nonischemic cardiomyopathy; OR = odds ratio; other abbreviations as in Table 1.

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TABLE 4 Performance of the LGE-CMR Test in Predicting the Composite Arrhythmic Endpoint in the Different Subgroups of Studies*

Subgroups	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)
Total	85.5% (78.7-90.5)	53.2% (44.6-61.7)	1.83 (1.57-2.13)	0.27 (0.19-0.38)
ICM	84.3% (75.5-90.4)	52.5% (44.9-59.9)	1.77 (1.48-2.13)	0.30 (0.18-0.49)
NICM	79.7% (68.1-87.9)	66.0% (57.7-73.4)	2.35 (1.88-2.93)	0.31 (0.19-0.49)
Mixed population	92.4% (79.0-97.5)	36.7% (24.2-51.3)	1.46 (1.20-1.77)	0.21 (0.08-0.54)
Mean EF ≤30%	92.9% (83.1-97.2)	52.9% (41.2-64.3)	1.97 (1.58-2.45)	0.13 (0.06-0.30)
Mean EF >30%	78.3% (69.1-85.4)	54.4% (41.6-66.6)	1.72 (1.38-2.13)	0.40 (0.30-0.52)

*Parameters were estimated by a bivariate generalized linear mixed model.

CI = confidence interval; EF = ejection fraction; ICM = ischemic cardiomyopathy; NICM = nonischemic cardiomyopathy; NLR = negative likelihood ratio; PLR = positive likelihood ratio.

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CONCLUSIONS

This meta-analysis showed that the assessment of ventricular fibrosis by LGE-CMR is a powerful predictor of ventricular tachyarrhythmic events in both ICM and NICM patients. The prognostic power of LGE is particularly strong in patients with severely depressed EF. LGE testing may thus improve the appropriateness of ICD implantation in patients with severely depressed EF by identifying a lower-risk group unlikely to benefit from ICD. However, to be put into practice, LGE-CMR protocols need to be standardized with respect to execution modalities and the setting of diagnostic thresholds.

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Conclusions:

- Identifications of potential SCD victims remains a difficult task due to the limited positive predictive value of available techniques.
- In the past years several approached have been developed and tested focusing on either autonomic modulation, substrate alterations, biomarkers or clinical parameters.
- As a result different algorithms have been proposed without a consensus on which to prefer.
- We are still searching for a predictor easy to use, reproducible, comparable in different settings and with a strong positive predictive value. The multifactorial origin of sudden cardiac death in different patient populations make this search extremely difficult.