Clinical Significance of T Wave Alternance and Heart Rate Turbulence

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COI Disclosure

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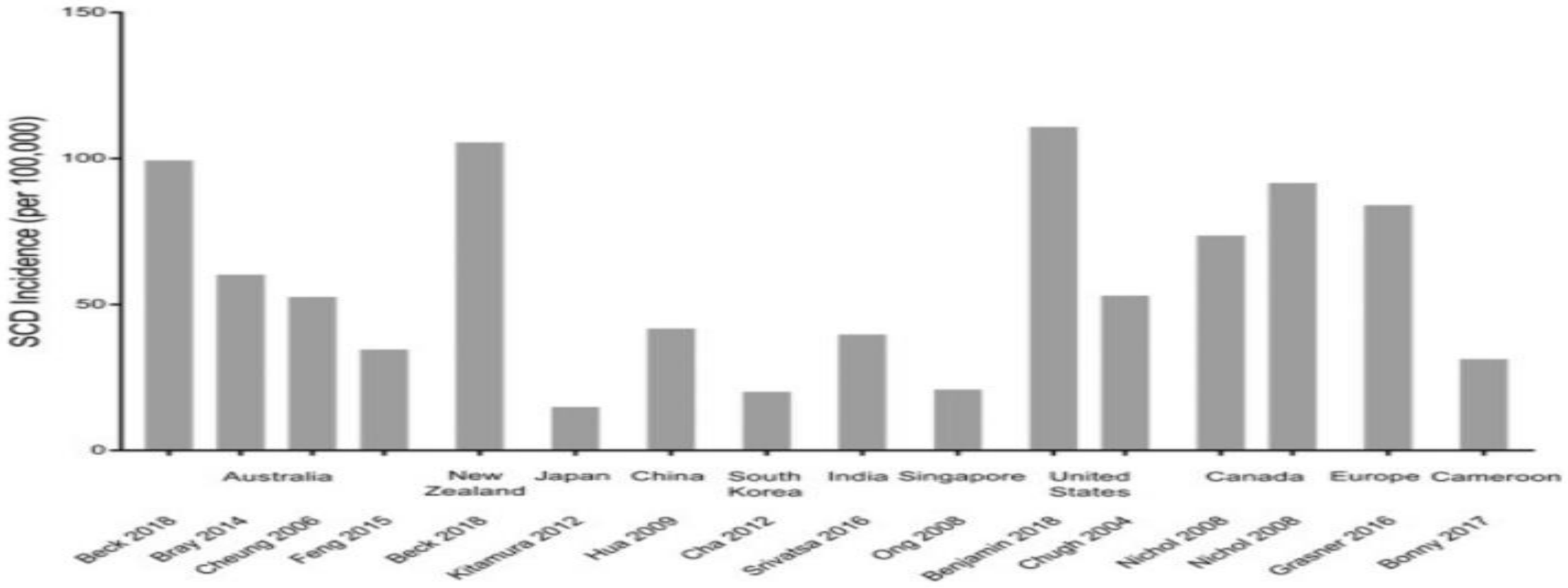
The authors have no financial conflicts of interest to disclose concerning the presentation

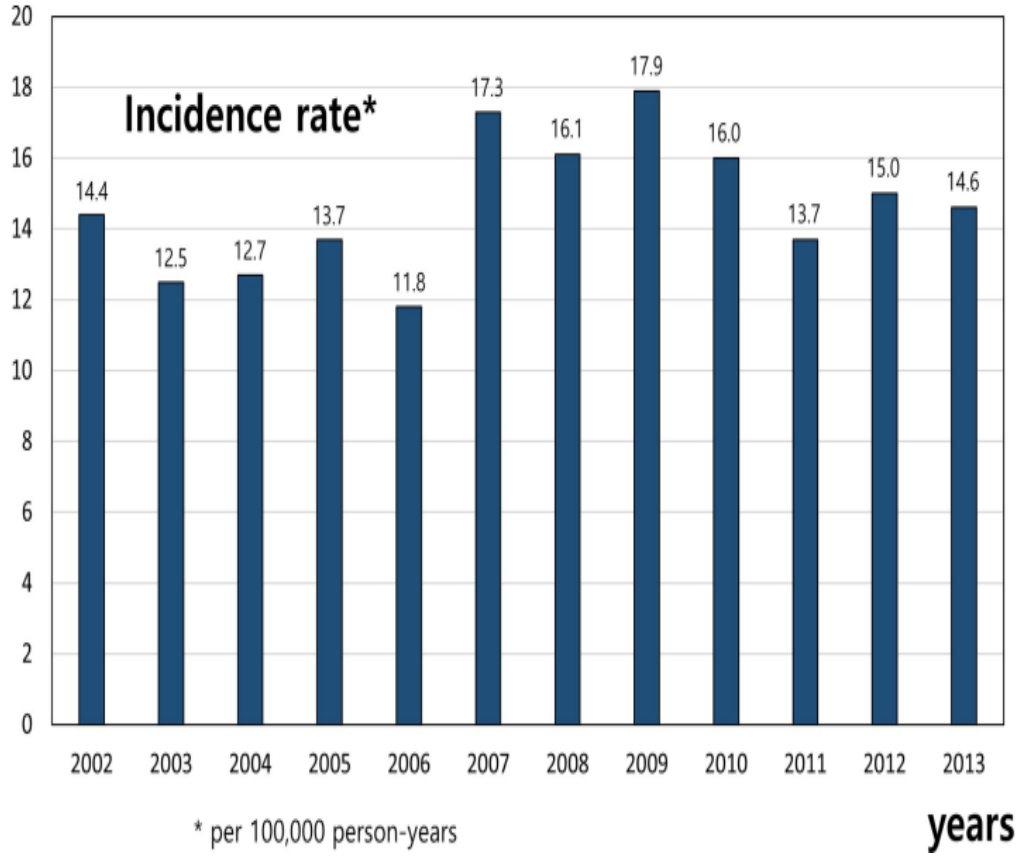
Global incidence of SCD

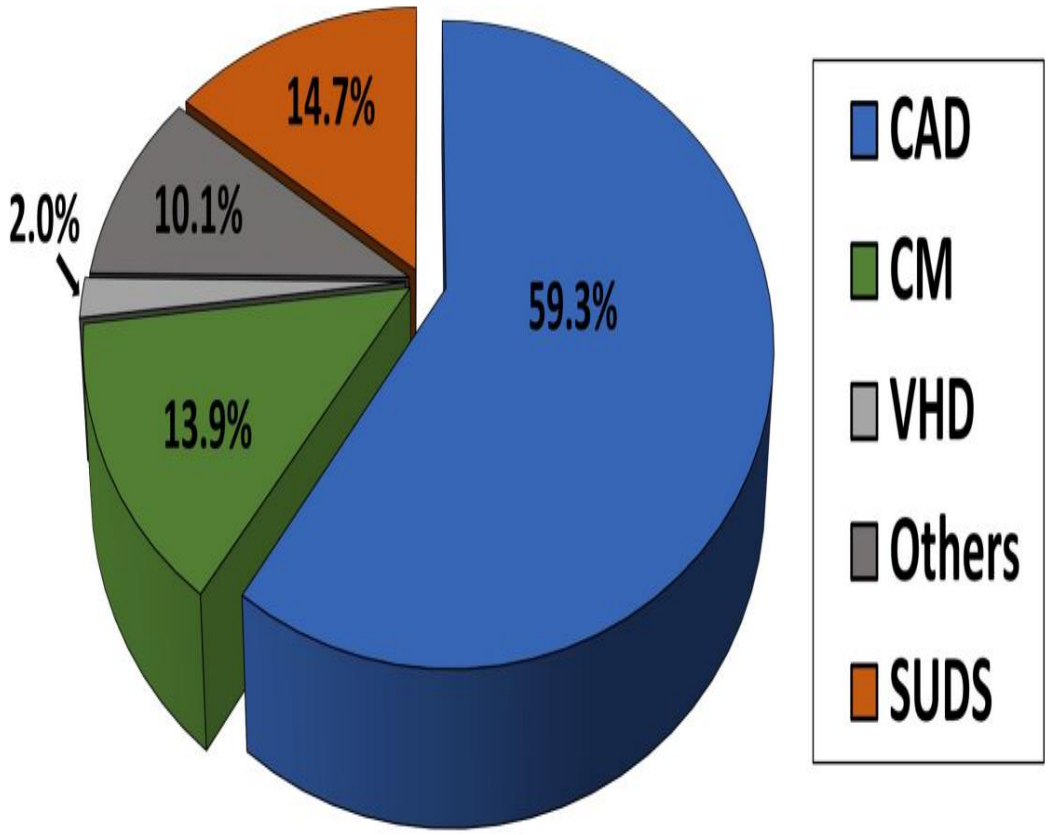


- Sudden cardiac death (SCD) is a leading cause of mortality
- SCD the cause of 15–20% of death.

Heart Lung Circ. 2019. PMID: 30482683 Review

Sudden cardiac death in Korea

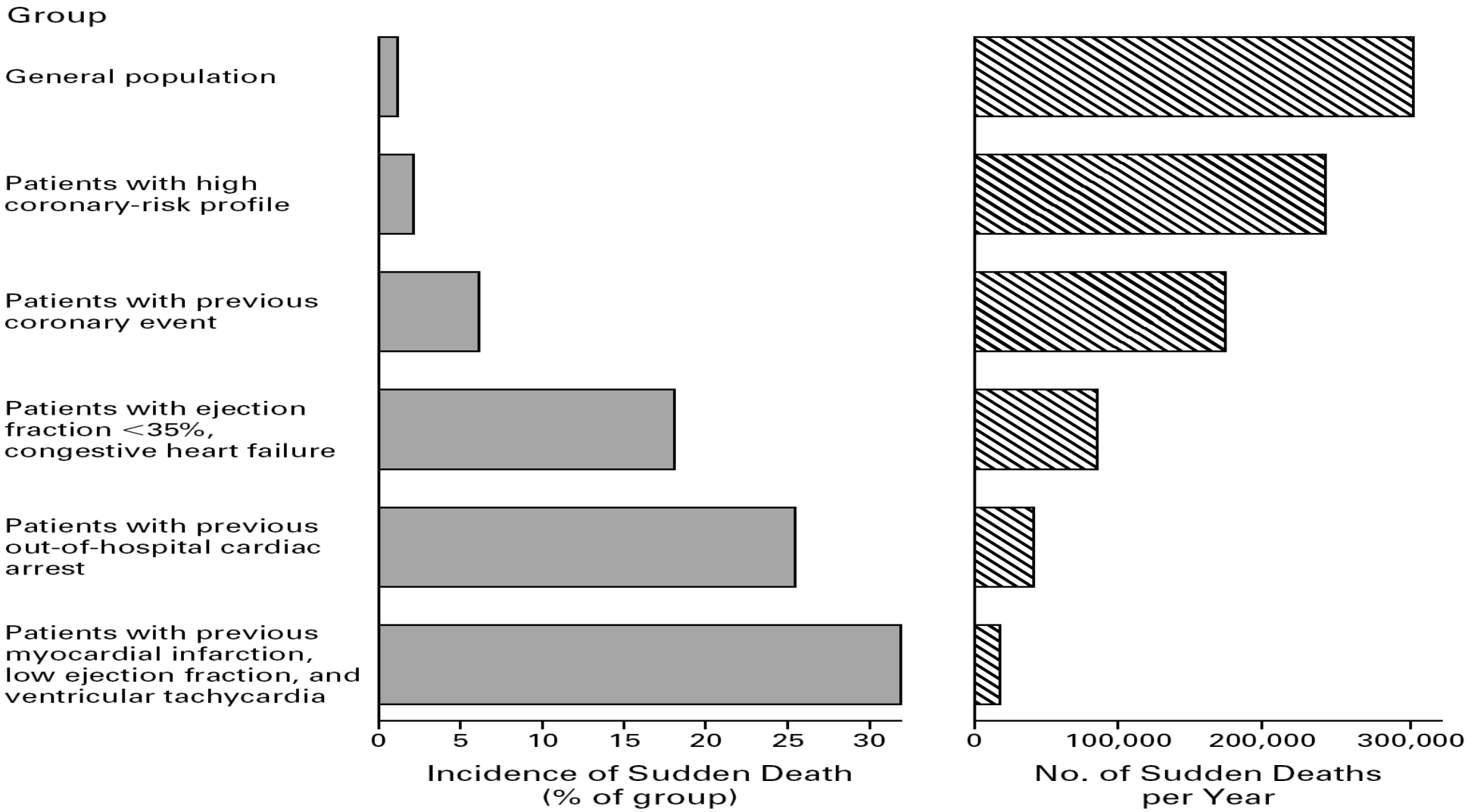




- The incidence of primary SCA was 16.1 per 100,000 person-years
- CAD was the most common cause of SCA (59.3%)
- Sudden unexplained death syndrome accounted for 14.7% of SCA.

PLoS One. 2020 Nov 25;15(11):e0242799

SCD Incidence & Prevalence



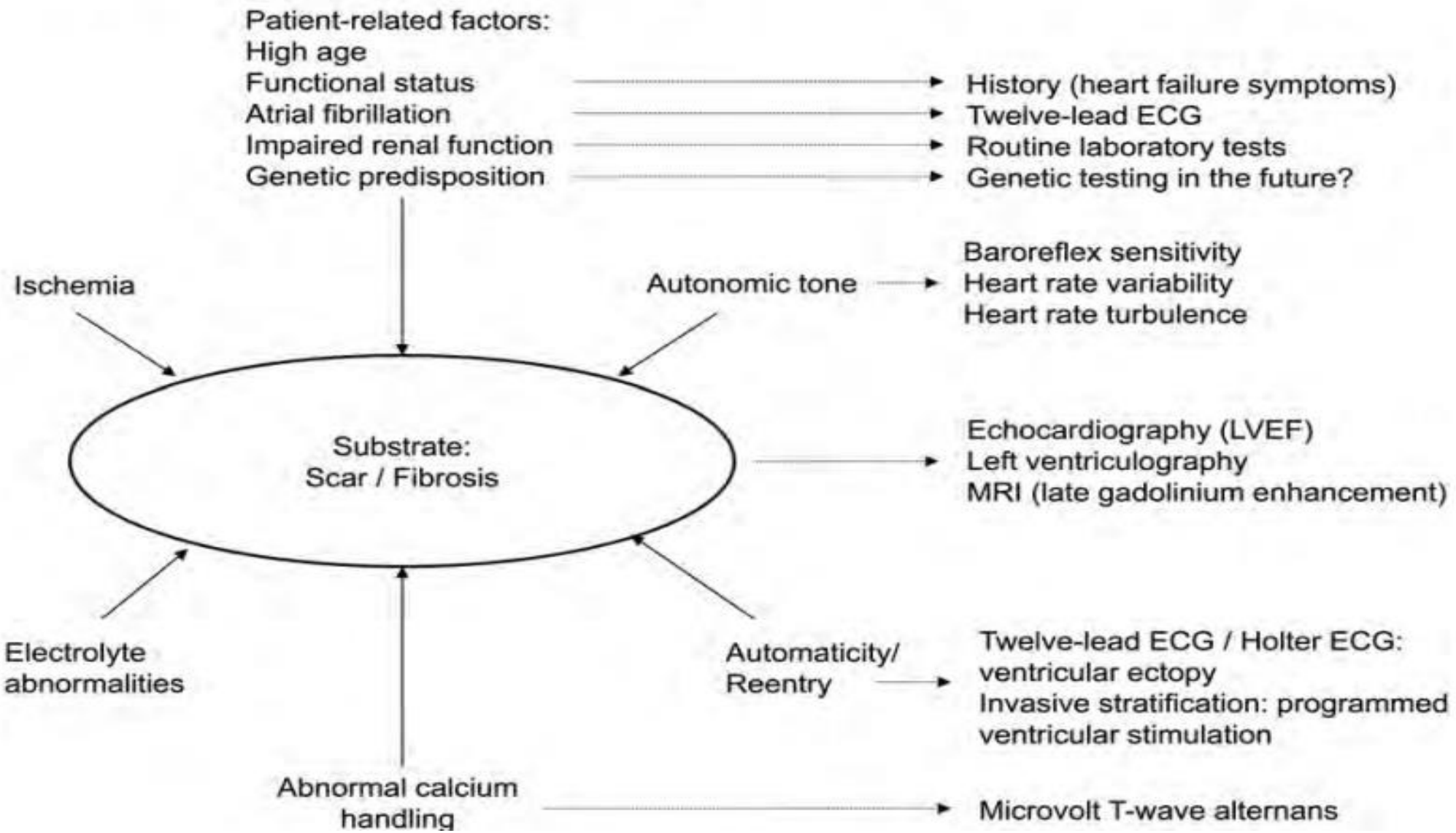
Myerburg, et al. Circ 1998;97:1514-1521

Ejection fraction(EF) is not a good predictor of SCD

	Sabbag et al.[33]	van Welsenes et al[30]	Aonuma et al.[37]	Kabutoya et al.[51]	Kotake et al.[31]	Yokoshiki et al.[36]	Cho et al.[4]
n	2,349	2,134	171	392	985	17,564	305
Year	2015	2011	2022	2021	2021	2020	2020
Country	Israel	the Netherlands	Japan	Japan	Japan	Japan	Korea
Primary/secondary, %	75/25	61/39	100/0	42/58	54/46	26/74	55/45
ICM/NICM, %	84/16	70/30	42/58	100/0	42/58	36/64	43/57
Appropriate ICD therapy/ ICD shock	3.9/1.1 (1 y)	37 (5 y)/20 (5 y)	10 (24 mo)/NA	20 (20 mo)/9 (20 mo)	22 (36 mo)/NA	NA	18/12 (31 mo)

JACC Asia. 2023 Apr 25;3(3):335-345

SCD prediction factors

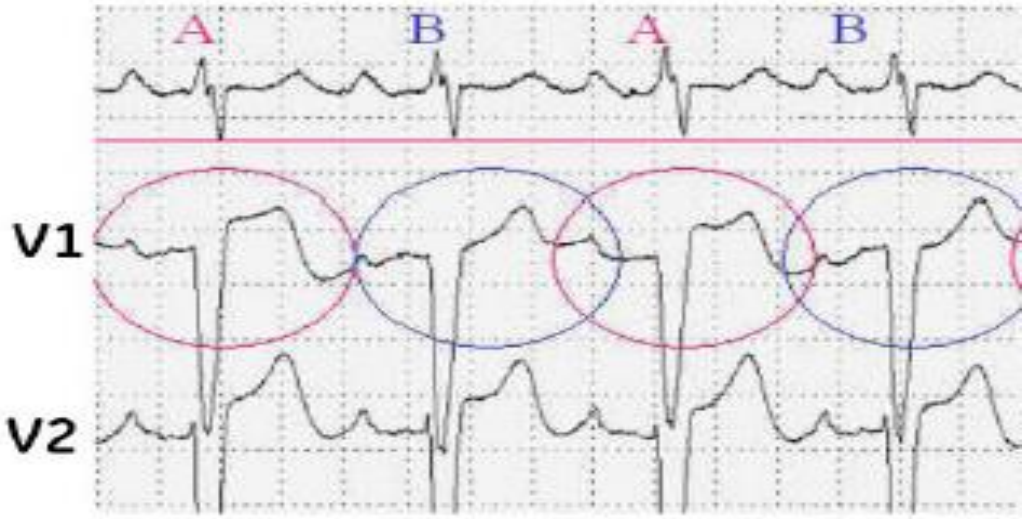


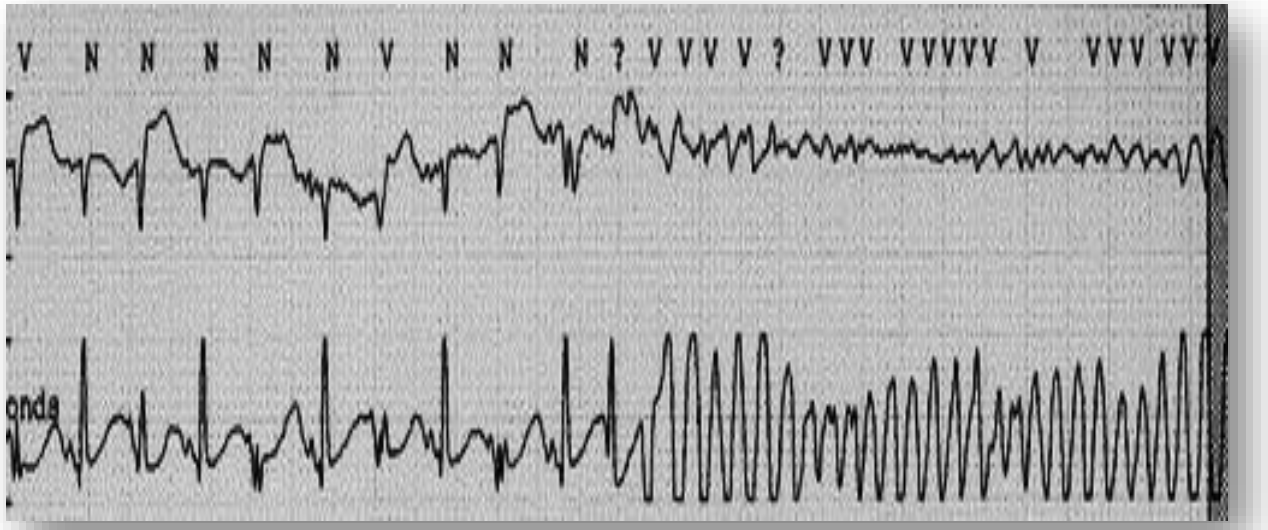
Eur Heart J. 2013 Jul;34(26):1964-71

T wave alternans?

T-Wave Alternans(TWA)?

- Beat-to-beat variability in the timing, shape, and/or amplitude of T-waves on the surface ECG
- Indicator of cardiac electrical instability, vulnerability of VT/VF
- Used for SCD risk stratification





The Spectral Method

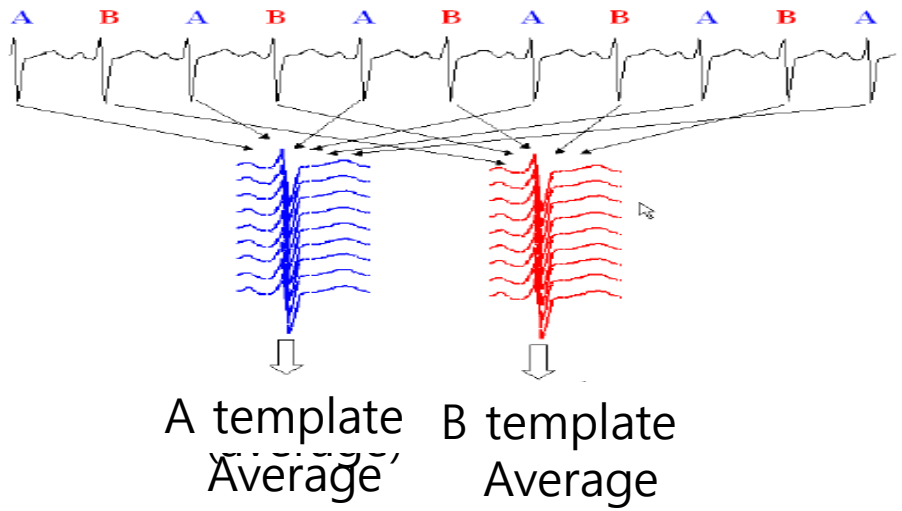
- Target HR 105-110 beats using specialized exercise protocol, pharmacological agents or atrial pacing.

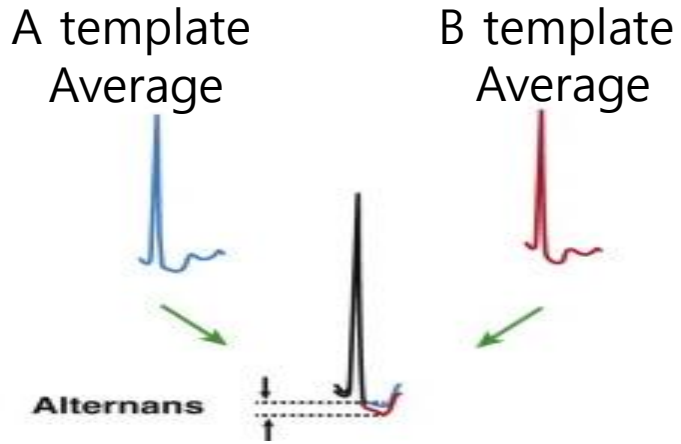
- Fast fourirer transform(FFT) technique to beat- to beat series of amplitude measurements along the 128 consecutive QRS ECG complexes

Modified Moving Average (MMA) Method

- Continuously streams odd and even beats into separate bins and creates median complexes.

- These complexes are then superimposed, and the maximum difference between the odd and even median complexes at any point within the JT segment

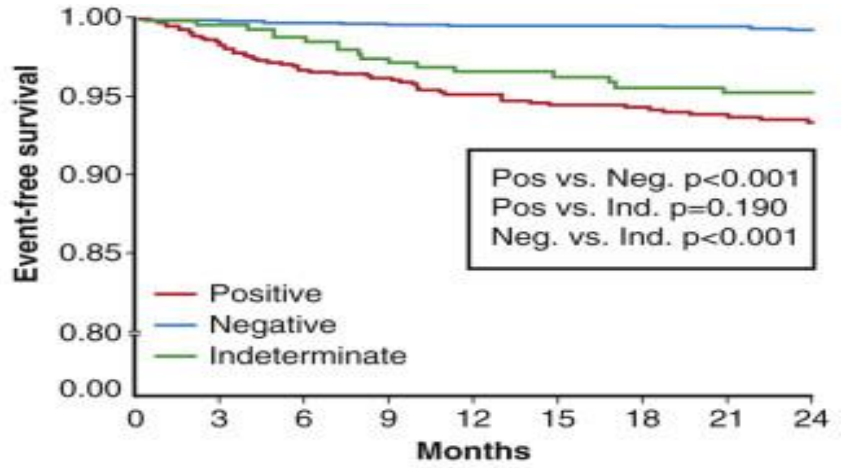




Risk stratification of patients with ICMP

:2883 patients without history of previous ventricular tachyarrhythmias

Arrhythmic mortality/sudden death

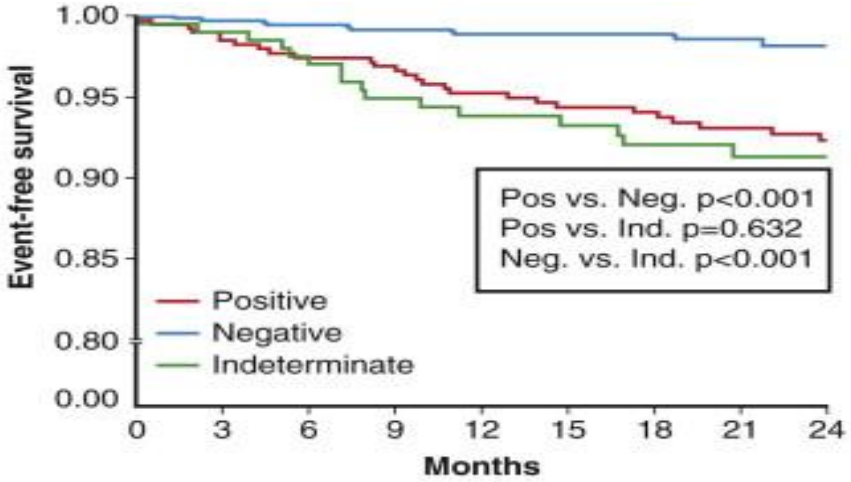


Number at risk

Positive –	856	790	687	625	406
Negative –	1627	1589	1413	1257	824
Indeterminate –	400	377	320	283	177

A

Patients with an LVEF ≤0.35



Number at risk

Positive –	406	374	320	293	268
Negative –	387	364	332	309	296
Indeterminate –	211	193	163	144	132

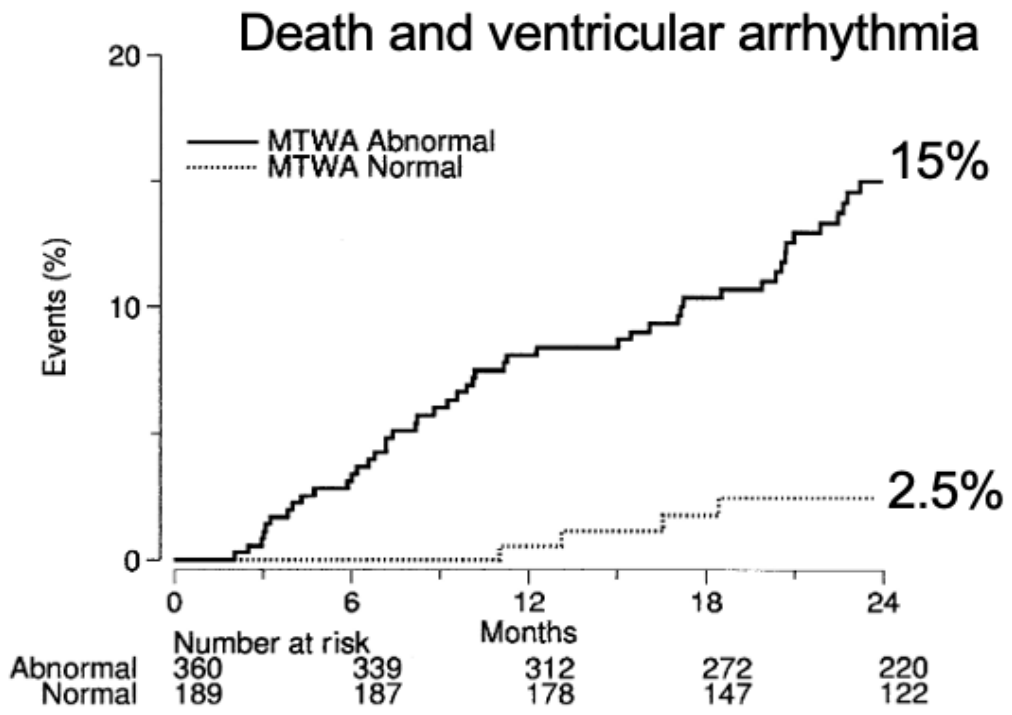
B

- 514 (67%) patients with a non-negative MTWA test
- Non-negative MTWA test was associated with a significantly higher risk for all-cause death
- Non-negative MTWA test was also associated with a higher risk for all-cause mortality in patients with low EF

J Am Coll Cardiol.2006;47:1820–1827

Risk stratification of patients with HFrEF

:549 patients with HF EF<40%, EF 25%



Variable	N	2-Year Event Rate	Hazard Ratio (95% CI)	p Value*
MTWA				
Abnormal	360	15.0		
Normal	189	2.5	6.53 (2.35–18.11)	<0.001
Age (yrs)				
≥65	126	16.0		
<65	421	9.0	1.59 (0.88–2.84)	0.120
Gender				
Male	390	12.9		
Female	159	5.3	2.67 (1.20–5.93)	0.016
Race				
White	289	11.2		
Non-white	260	10.1	1.13 (0.65–1.96)	0.670
Cardiomyopathy				
Ischemic	267	12.6		
Non-ischemic	282	8.9	1.38 (0.79–2.40)	0.254
Past CHF admission				
Yes	310	14.9		
No	229	5.1	3.12 (1.56–6.23)	0.001
NYHA functional class				
II to III	358	12.7		
<II	191	6.8	1.78 (0.93–3.41)	0.079
LVEF				
<0.31	405	12.0		
0.31 to 0.40	144	7.3	1.81 (0.88–3.73)	0.105
QRS duration				
>120 ms	150	14.0		
≤120 ms	394	9.2	1.64 (0.93–2.91)	0.088
Beta-blockers				
No	100	27.2		
Yes	434	6.8	4.24 (2.43–7.40)	<0.001

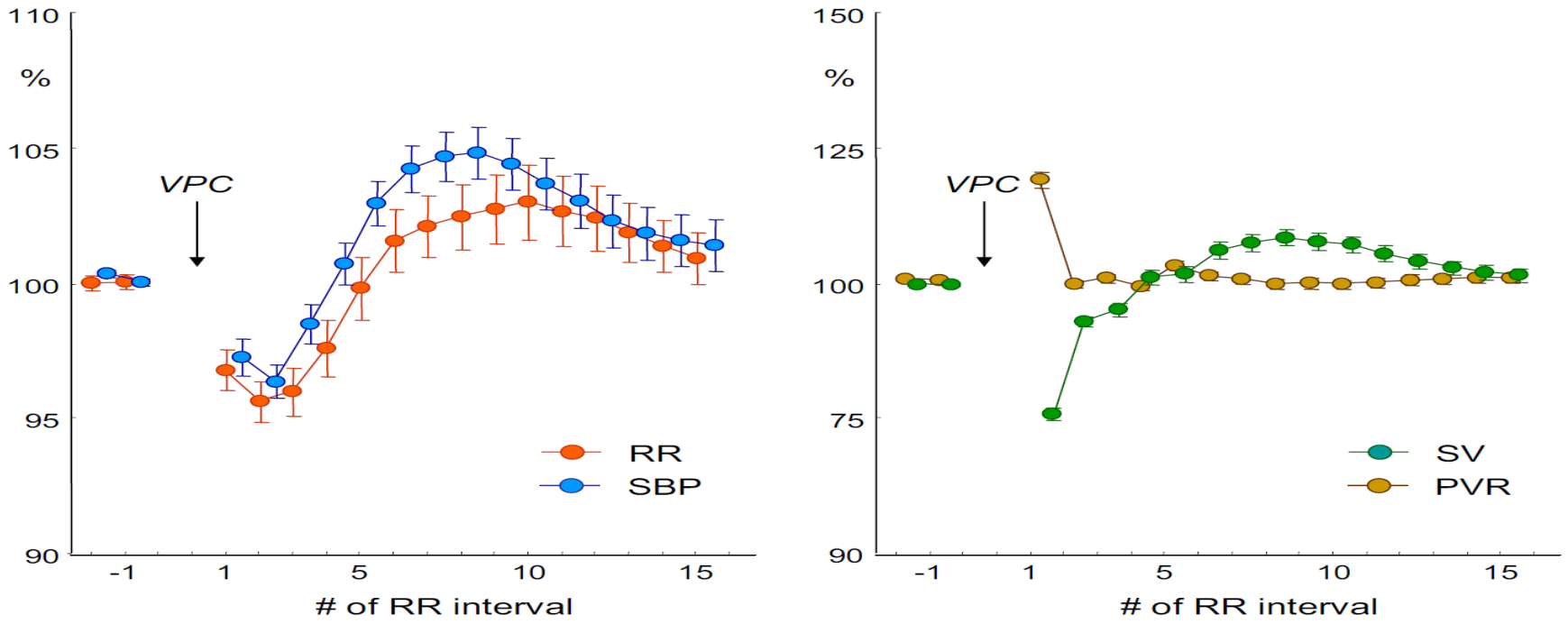
- Event rate was 15.0% in the patients with an abnormal MTWA and 2.5% in those with a normal
- MTWA was an good risk predictor of Death or ventricular arrhythmia

J Am Coll Cardiol. 2006;47:456–463

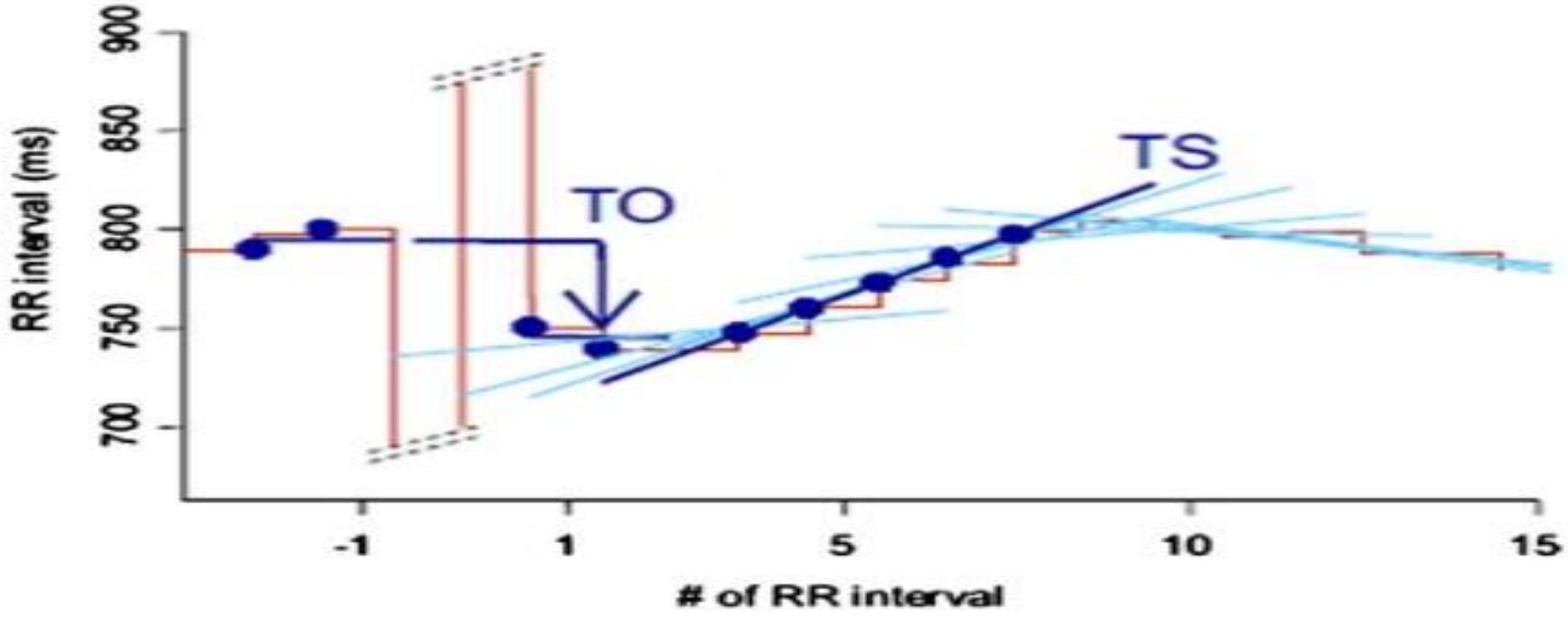
Heart rate turbulence?

Heart rate turbulence(HRT)

- Short-term fluctuations in sinus RR interval after VPC
- Indirect assessment of Cardiac Autonomic Function



Turbulence onset(TO), Turbulence slope(TS)



The values of TO > 0% and TS < 2.5 ms/RR interval were defined abnormal, respectively

HRT predict CV death in patients with AMI

:481 patients with AMI

Variable	Alive (n = 432)		CV Death (n = 49)		p Value (alive vs CV death)
	No. of Subjects	Mean ± SD	No. of Subjects	Median ± SD	
TO	359	−0.0067 ± 0.0220	44	0.0011 ± 0.0160	0.024
TS	359	3.86 ± 5.29	44	2.96 ± 3.40	<0.001
LVEF (%)	432	35 ± 6	49	32 ± 8	0.001
>30	344	80%	29	59%	
≤30	88	20%	20	41%	
SDNN (ms)	414	84 ± 40	48	78 ± 48	NS
VPC (total)	432	Median 16 (interquartile range 100)	49	61 (interquartile range 446)	0.009
VPC/h	432	Median 0.67 (interquartile range 5)	49	2.57 (interquartile range 19)	0.011
Age (yrs)	432	61 ± 16	49	67 ± 16	<0.001
Men	317	74%	31	63%	
Women	115	26%	18	37%	
Diabetes	99	23%	17	35%	NS

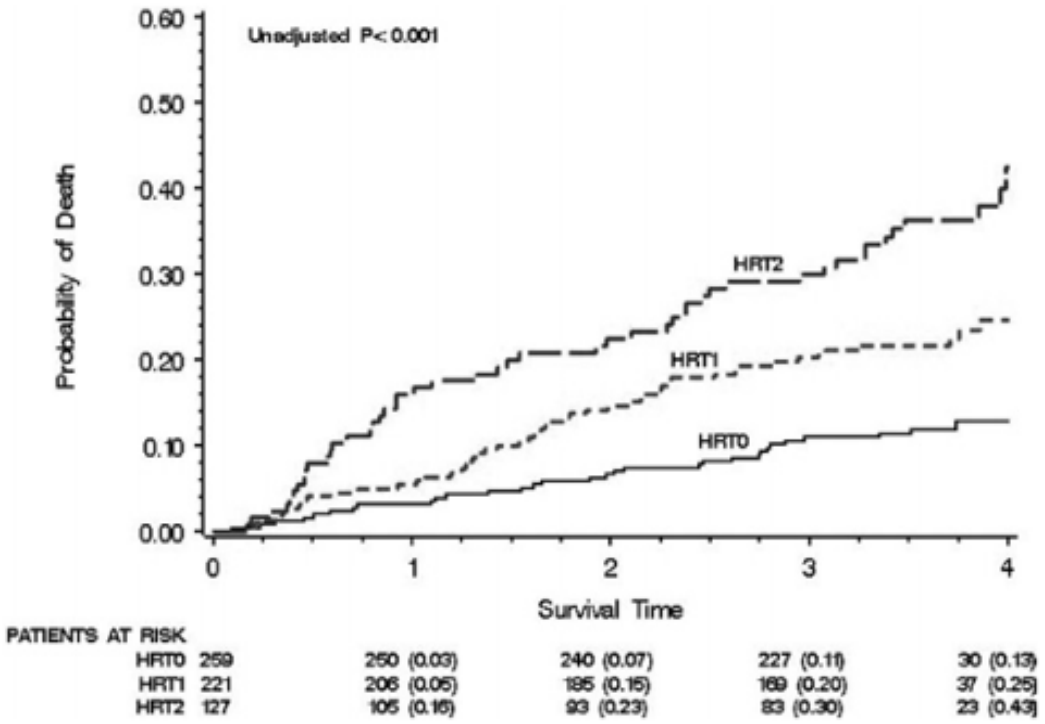
- TS and TO and left ventricular ejection fraction, VPC were independently predicted CV death

Am J Cardiol. 2009 Jun1;103(11):1495-9

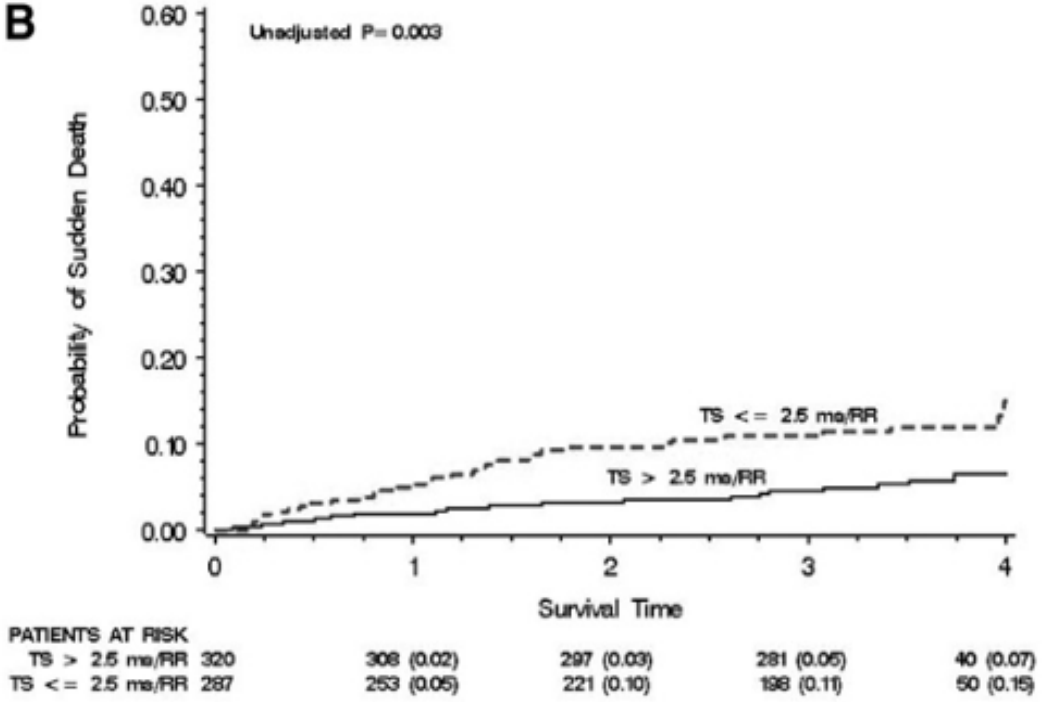
HRT predict death in patients with HF

:607 patients with HF, EF 37%

All cause death



Sudden cardiac death

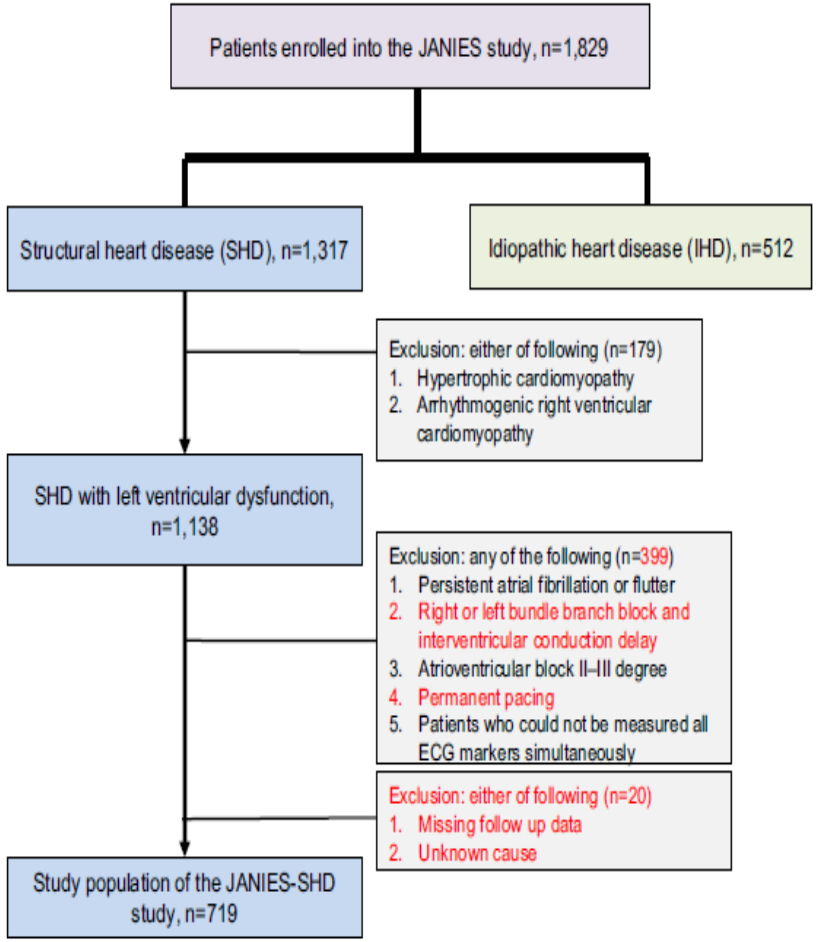


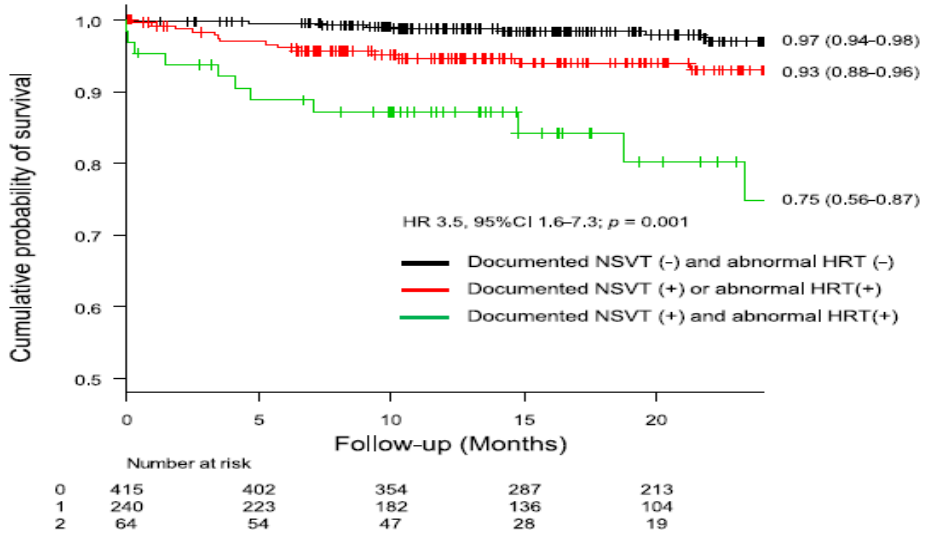
- Abnormal TS and TO were independently associated with increased all-cause mortality, SCD

Heart Rhythm. 2008 Aug;5(8):1095-1102

Recent studies

Risk stratification for cardiac mortality using ECG markers





	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
All-cause mortality				
Documented NSVT	51	80	13	97
Abnormal HRT	59	72	11	97
Documented NSVT and abnormal HRT	28	92	17	96
Fatal arrhythmic events				
Documented NSVT	56	80	13	97
Abnormal HRT	53	72	8.9	97
Documented NSVT and abnormal HRT	33	92	19	96

- NSVT and abnormal HRT were significantly associated all cause mortality
- The combined assessment of two ECG markers improved predictive accuracy

J Cardiol. 2020 Feb;75(2):155-163

Arrhythmic risk stratification using multiple factors

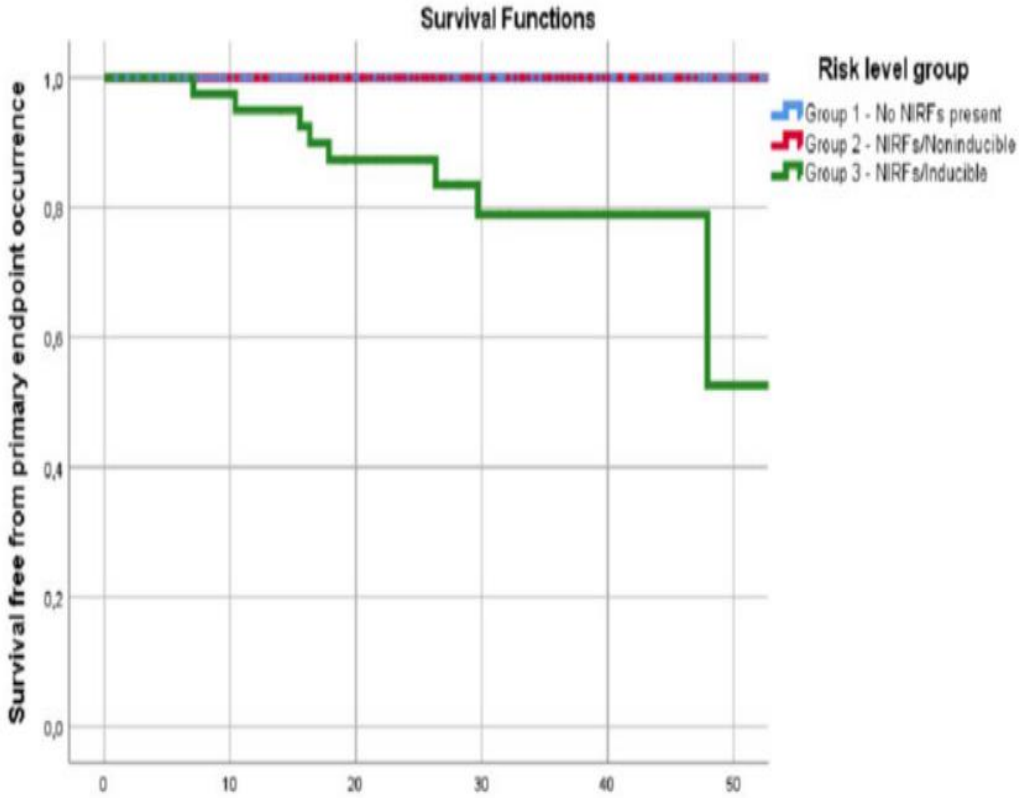
1st screening step: NIRFs

At least one of the following:

- 30 PVCs/hour
- NSVT episode(s) /24hr
- 2/3 positive criteria for LPs
- QTc >440ms(♂) or QTc >450ms (♀),
- Ambulatory T wave alternans (TWA) ≥65μV
- SDNN ≤75ms
- Deceleration Capacity ≤4.5ms AND Heart Rate Turbulence (HRT) Onset ≥0% AND HRT slope ≤2.5ms

2nd screening step: Invasive assessment

- Inducibility upon Programmed Ventricular Stimulation



Number at risk	10 months	20 months	30 months	40 months	50 months
Group 1	337	291	209	104	31
Group 2	110	95	62	28	12
Group 3	38	31	15	6	2

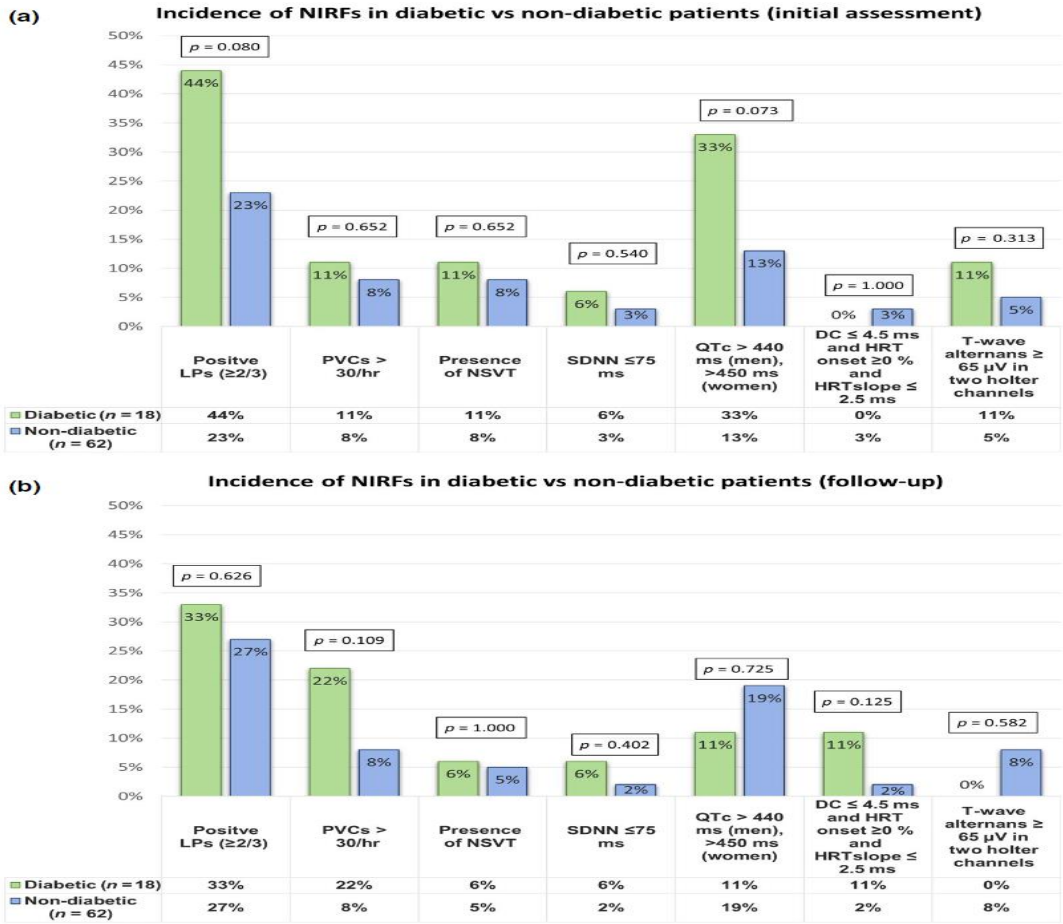
Ann Noninvasive Electrocardiol. 2022 Mar;27(2):e12923

.

Temporal changes of risk factors for SCD

:PRESERVE-EF trial post MI 80 patients with EF ≥ 40%

Noninvasive risk factors	First assessment	Second assessment	*p*-value
LPS			
fQRS (ms)[a]	97 (89, 104)	99 (90, 108)	.4223
LAS (ms)[a]	32 (24, 39)	34 (26, 40)	.3296
RMS μV[a]	36 (17, 69)	28 (15, 69)	.3936
LPS positive (%)	27.5	28.8	.8604
PVCs[a]	12 (2, 139)	19 (2, 343)	.5227
>30 PVCs/hr (%)	8.8	11.3	.5982
NSVT (%)	8.8	5	.3486
SDNN (ms)[a]	127 (108, 148)	128 (112, 154)	.7548
Abnormal SDNN (%)	3.8	3.8	1.0000
QTc (ms)[b]	425 ± 19	426 ± 16	.8853
QTc > 440 ms men, >450 ms women (%)	17.5	17.5	1.0000
TO (%)[a]	−0.02 (−0.04, −0.01)	−0.02 (−0.04, −0.01)	.6720
TS (ms/rri)[a]	9.7 (5.5, 14.9)	8.8 (4.6, 17.4)	.8631
DC (ms)[a]	6.7 (4.75, 8.8)	6.9 (5.1, 8.1)	.8417
Abnormal HR turbulence/DC (%)	2.5	3.8	1.0000
T-wave alternans (≥65 μV) (%)	6.3	6.3	1.0000



Ann Noninvasive Electrocardiol. 2020 Jan;25(1):e12701

KHRS 2023

Current guidelines

2017 AHA guideline

A 12-lead ECG may indicate the presence of structural heart disease such as prior MI or chamber enlargement that would increase the likelihood that a patient's symptoms might be due to VA, or it may provide evidence of the underlying substrate for documented VA. An ECG may also reveal evidence of inherited arrhythmia disorders, such as long QT syndrome, Brugada syndrome, and arrhythmogenic right ventricular cardiomyopathy. In patients with structural heart disease, QRS duration and the presence of conduction abnormalities provide prognostic information.[S4.2.1-7–S4.2.1-14] Data on the use of microvolt T wave alternans and the signal averaged ECG are inconclusive, as such these tests are not routinely used in clinical practice[S4.2.1-15–S4.2.1-19]; the one exception is the potential use of signal averaged ECG in patients with arrhythmogenic right ventricular cardiomyopathy (see Section 7.3).

2022 ESC guideline

5.1.3. Non-invasive and invasive tests

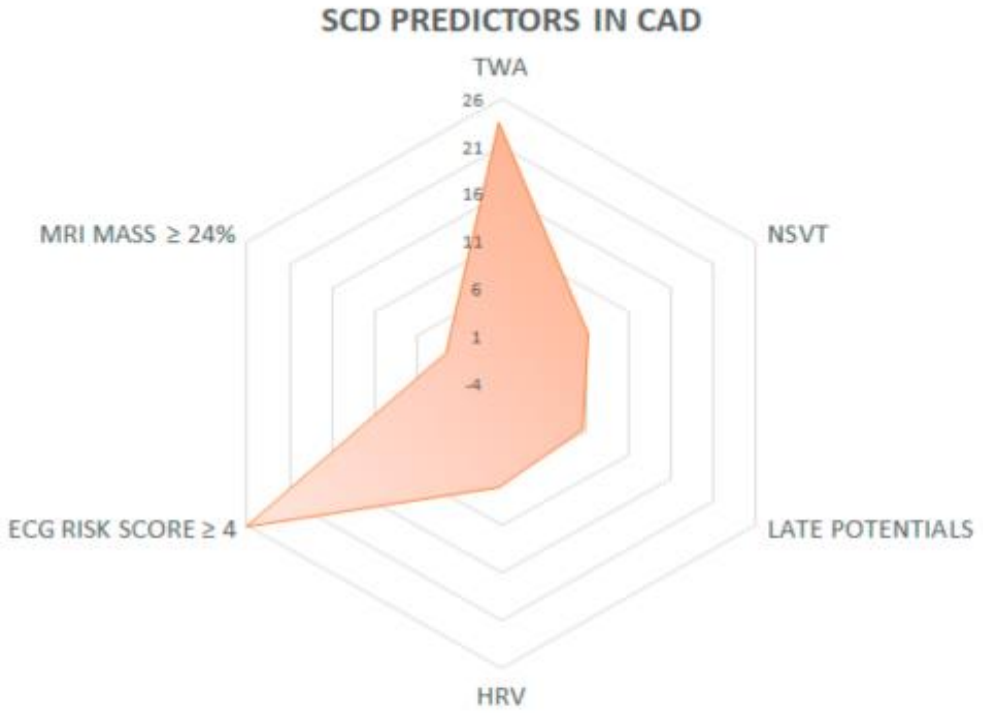
5.1.3.1. Electrocardiogram and ambulatory electrocardiographic monitoring[2]

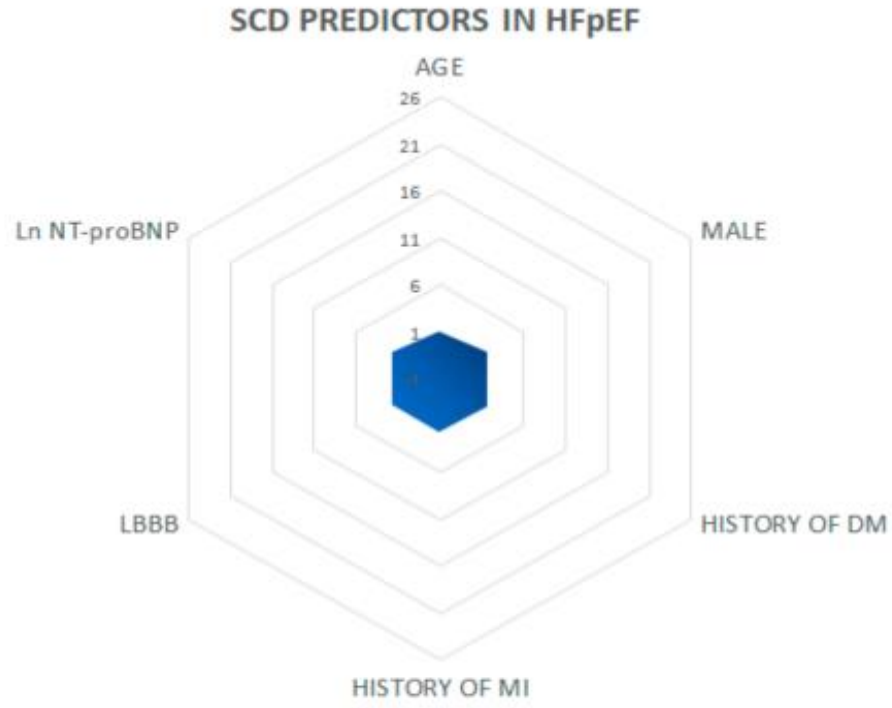
The 12-lead ECG is an important tool for the diagnosis of underlying disease, for risk stratification in selected populations, and for the diagnosis of the VA subtype, if captured. Documentation of arrhythmias related to symptoms is clinically pivotal but may be challenging with sporadic events. The type of ECG-monitoring device and the recording time should therefore match the frequency of clinical events. Monitoring over a period of 24–48 h (typically 'Holter recording') is appropriate for daily arrhythmias,[112] while intermittent monitoring over a longer period, with patient-activated ECG recorders (or mobile-health/smartphones), should be preferred for infrequent events.[113] Implantable loop recorders (ILR) can be useful in diagnosing arrhythmias in patients with potentially life-threatening symptoms, such as unexplained syncope.[114]

5.1.3.2. Signal-averaged electrocardiogram

Signal-averaged electrocardiogram (SaECG) can detect very low amplitude signals ('late potentials') in the terminal QRS segment[115] using three time-domain measurements: QRS duration, low-amplitude (<40 μV) signal duration and root mean square voltage of terminal 40 ms QRS.[112] Abnormalities in the SaECG can also be assessed by frequency-domain analysis.[112] SaECG can contribute to the diagnosis of ARVC.[116]

Predictors of sudden cardiac death





CAD SCD PREDICTORS	HR	C.I.	P-value	Reference
TWA	23.5	6.8 - 81.0	< 0.0001	Ikeda et al., JACC, 2006
NSVT	6.2	2.5 - 15.8	0.0001	Ikeda et al., JACC, 2006
LATE POTENTIALS	5.8	2.2 - 15.9	0.0006	Ikeda et al., JACC, 2006
HRV	7.0	2.4 - 20.3	< 0.01	Huikuri et al., Eur Heart J, 2009
ECG RISK SCORE ≥4	26.1	9.9 - 68.5	< 0.001	Aro et al., Eur Heart J, 2017
MRI MASS ≥ 24%	2.42	1.17 - 5.02	0.017	Bello et al., J MRI, 2011

HFpEF SCD PREDICTORS	HR	C.I.	P-value	Reference
AGE	1.03	1.01 - 1.05	0.005	Adabag et al., EJHF, 2014
MALE	1.79	1.35 - 2.38	0.0001	Adabag et al., EJHF, 2014
HISTORY OF DM	1.80	1.35 - 2.40	0.0001	Adabag et al., EJHF, 2014
HISTORY OF MI	1.60	1.20 - 2.13	0.001	Adabag et al., EJHF, 2014
LBBB	1.65	1.11 - 2.45	0.014	Adabag et al., EJHF, 2014
Ln NT-proBNP	1.63	1.45 - 1.83	0.0001	Adabag et al., EJHF, 2014

J Clin Med. 2021 Apr 22;10(9):1823.

Trial	Complete Title	Principal Investigator	Study Design	Estimated Enrollment (Patients)	Aim of the Study	Estimated Study Completion Date
PROFID-Preserved	Personalised Risk Score for Implantation of Defibrillators in Patients with Preserved LVEF > 35% and a High Risk for Sudden Cardiac Death	Gerhard Hindricks, MD	Non-commercial, investigator-driven, prospective, parallel-group, randomized, open-label, blinded outcome assessment, multi-center, superiority trial	1440	The objective of the study is to demonstrate that in post-MI patients with preserved LVEF > 35% but high risk for SCD according to a personalized risk score, the implantation of an index group (ICD) is superior to optimal medical therapy (control group) with respect to all-cause mortality.	31 December 2024
ReCONSIDER Study	Arrhythmic Risk Stratification in Nonischemic Dilated Cardiomyopathy	Konstantinos A Gatzoulis, MD	Prospective observational multicenter	675	This trial aim to integrate several approaches to arrhythmic risk stratification in nonischemic dilated cardiomyopathy in patients with preserved LVEF > 35% in a tiered, multifactorial, approach, in which noninvasive risk factors are combined with electrophysiologic studies.	1 May 2025
SMART-MI	Implantable Cardiac Monitors in High-Risk Post-Infarction Patients with Cardiac Autonomic Dysfunction	Axel Bauer, MD; Stefan Kaeaeb, MD	Randomized, interventional trial with parallel assessment	400	There is a large body of evidence that presence of cardiac autonomic dysfunction is associated with an increased susceptibility to malignant brady- and tachyarrhythmias eventually culminating in SCD in post-MI patients with LVEF >35%. SMART-MI will assess the occurrence and prognostic implications of serious arrhythmic events in this newly identified high-risk group by remote monitoring with ICM.	July 2021

Predictors of sudden cardiac death

ECG-based AI algorithm for predicting sudden cardiac death (SCD)

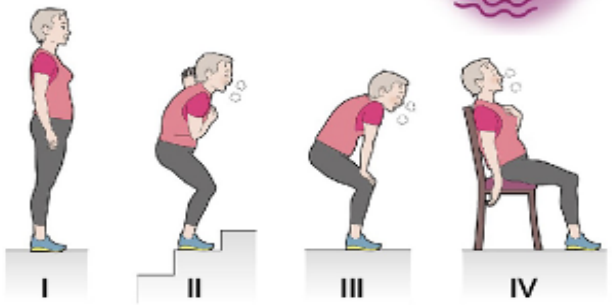
A report from the West Tokyo Heart Failure (WET-HF) registry

2559 patients

hospitalized heart failure with a recent episode of acute decompensation

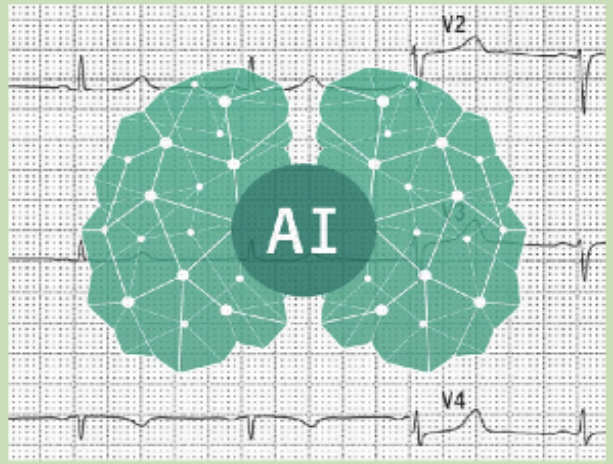
Guideline-based ICD indication

LVEF ≤ 35% &
NYHA II to III



ROC-AUC = 0.59

Guideline-based ICD indication + ECG-based AI index



ROC-AUC = 0.66

Discriminative ability for predicting SCD

Net reclassification improvement, 36% (9–64%, p = 0.009)

Europace. 2023 Mar 30;25(3):922-930.

KHRS 2023

Conclusion

- **Currently, the predictive power of risk stratification of SCD is not sufficient.**
- **TWA is an indicator of cardiac electrical instability, predict SCD**
- **HRT s an indicator of cardiac autonomic function, predict SCD**
- **In recent studies, TWA and HRT have limitations in predicting SCD by showing high NPV and low PPV.**
- **SCD prediction using AI or combining various non-invasive risk stratifications is being studied.**

Thank you for your attention