

TWA, HRT의 임상적 의의

연세원주의과대학 심장내과
박영준

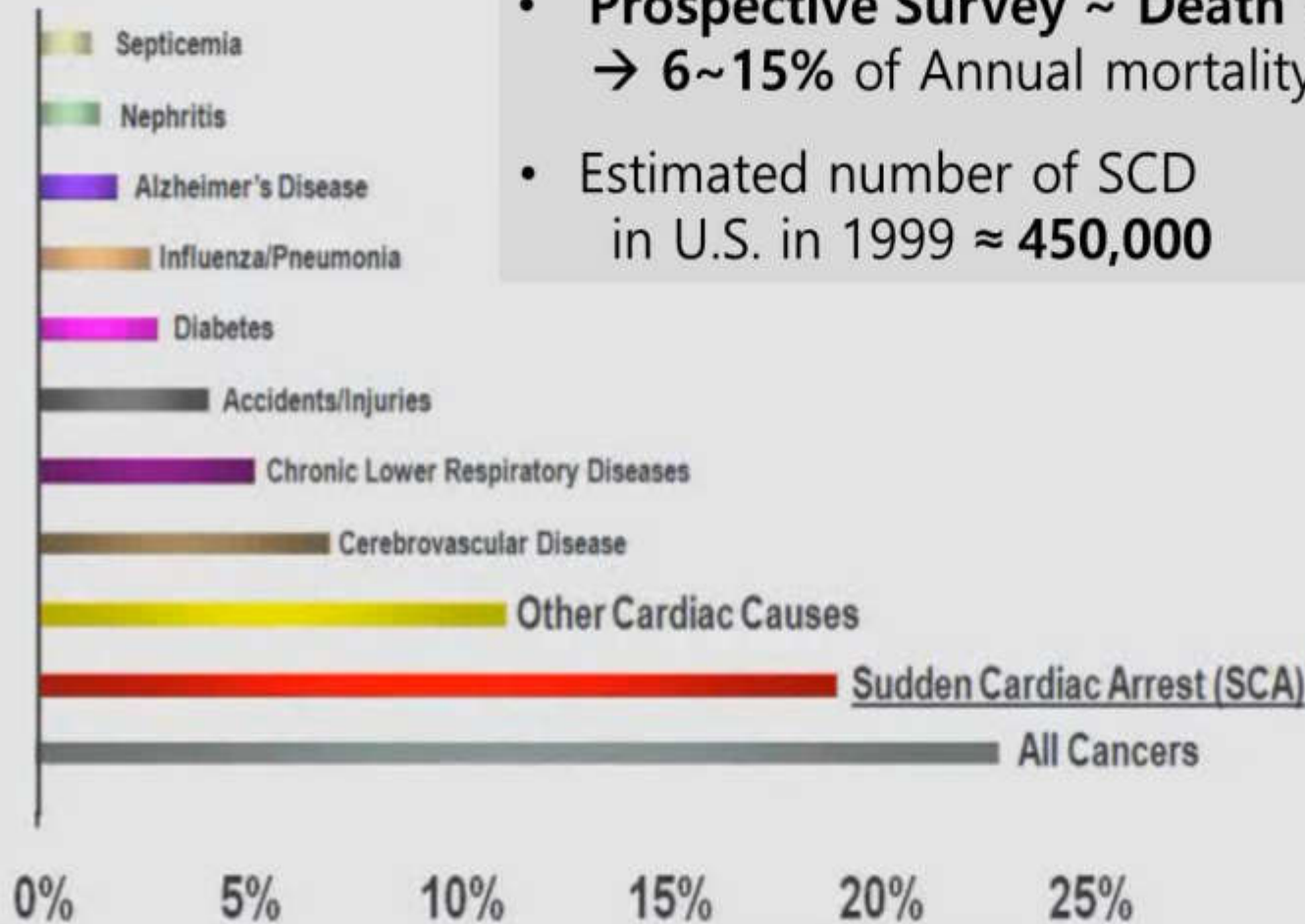


Background

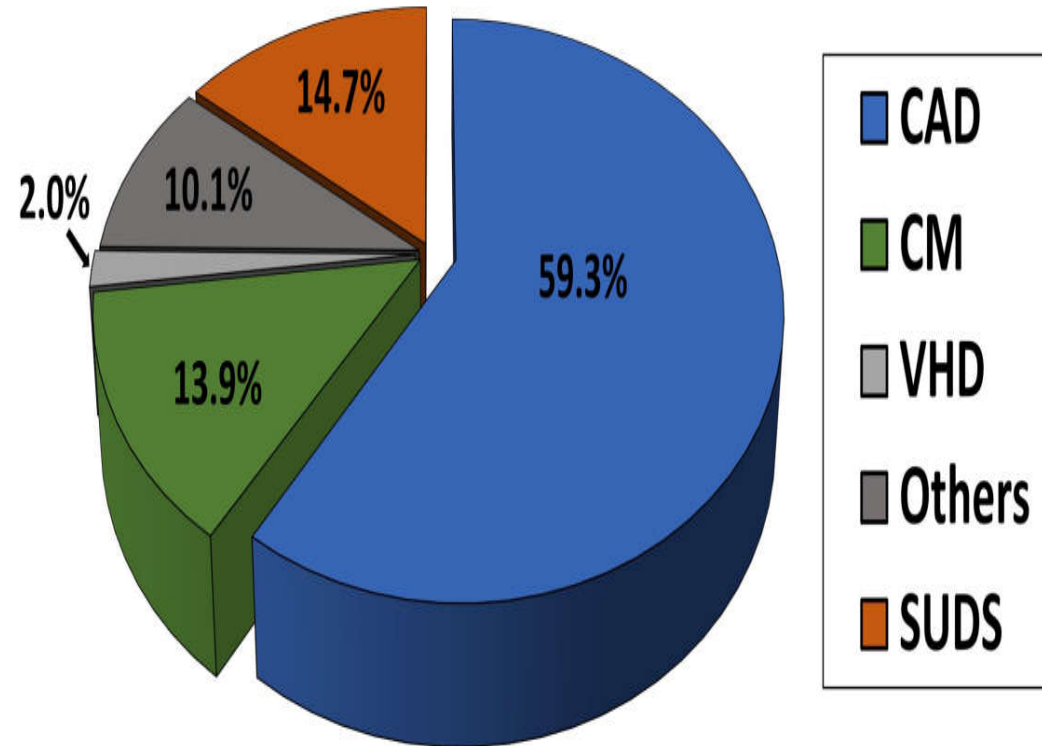
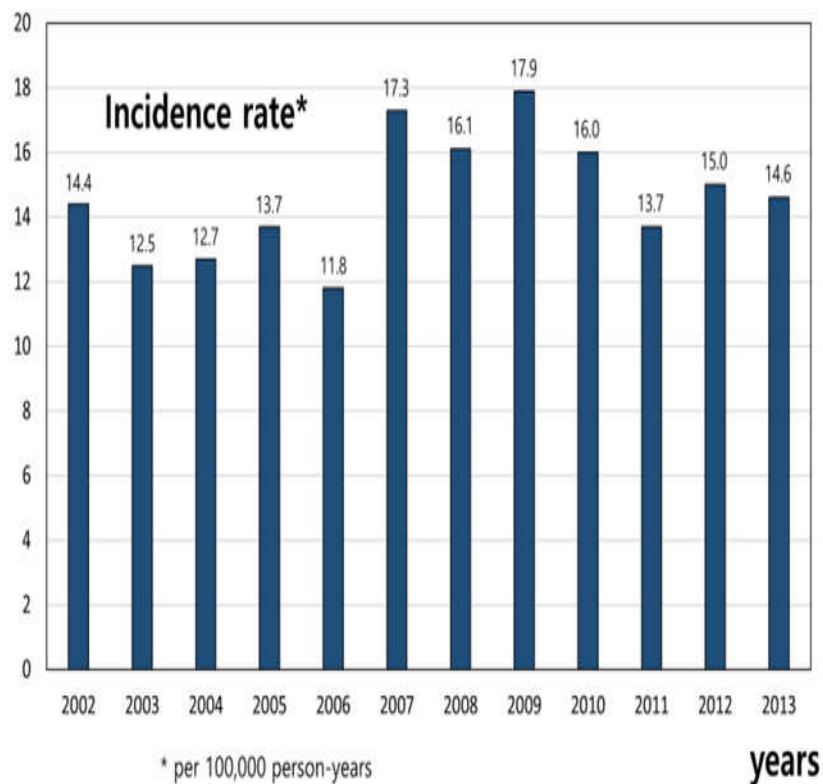


SCD is a leading cause of death

- Prospective Survey ~ Death Certificate Data
→ 6~15% of Annual mortality
- Estimated number of SCD
in U.S. in 1999 ≈ **450,000**

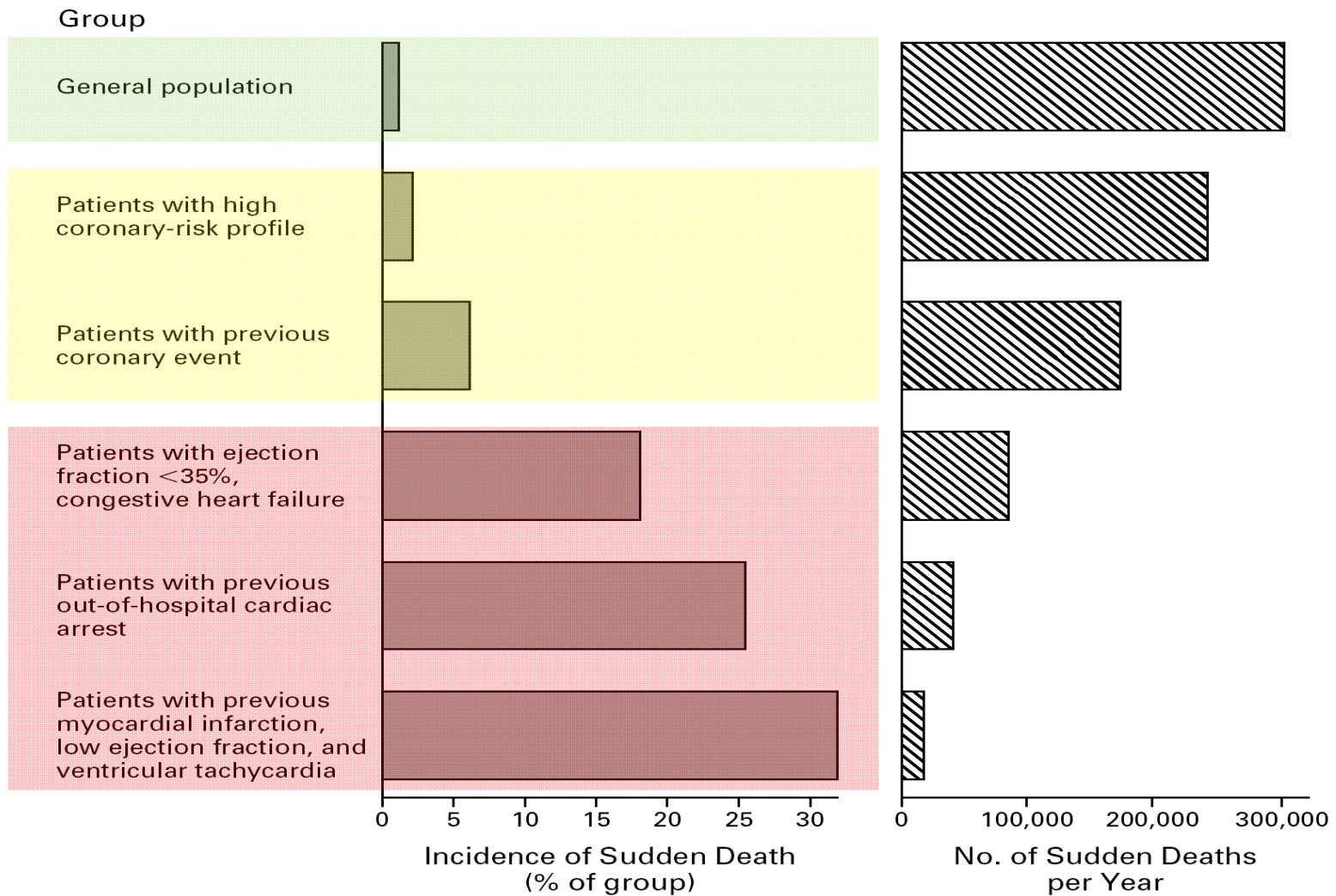


Sudden cardiac death in Korea



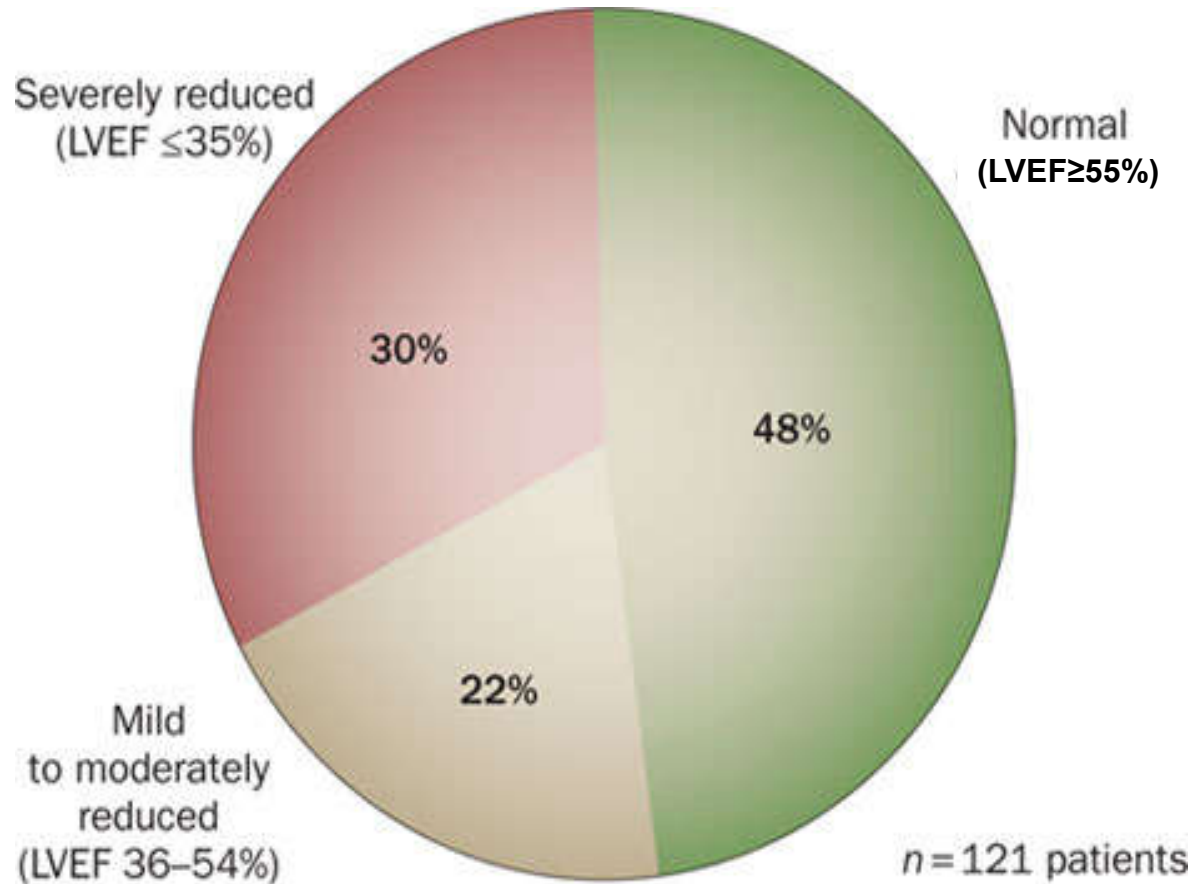
- The incidence of primary SCA was 16.1 per 100,000 person-years
- CAD was the most common cause of SCA (59.3%)
- Sudden unexplained death syndrome accounted for 14.7% of SCA.

SCD Incidence & Prevalence



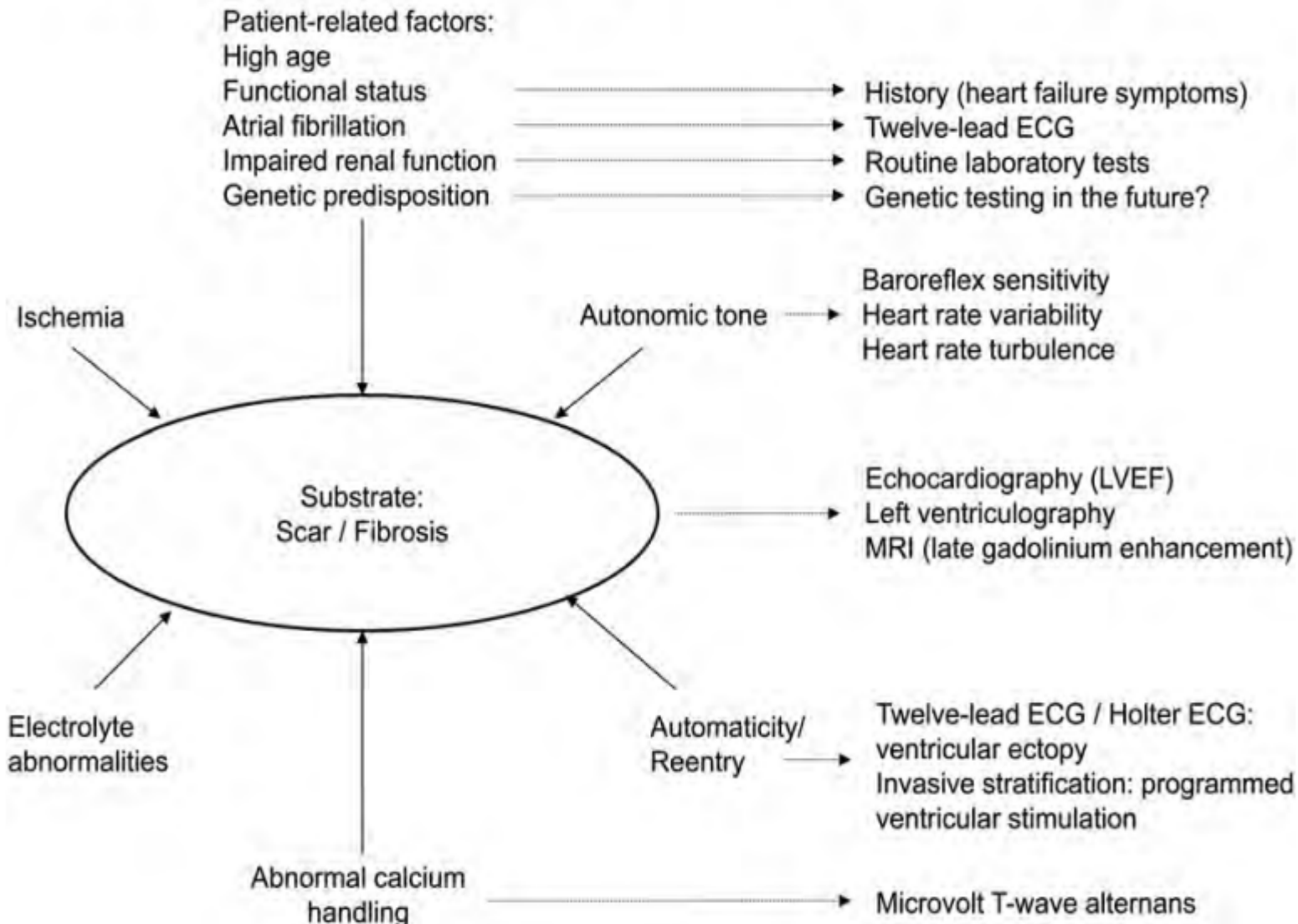
Ejection fraction(EF) is not a good predictor of SCD

findings from *the Oregon Sudden Unexpected Death Study*



Substrate and modulating factors for sudden cardiac death after myocardial infarction

Major corresponding diagnostic methods

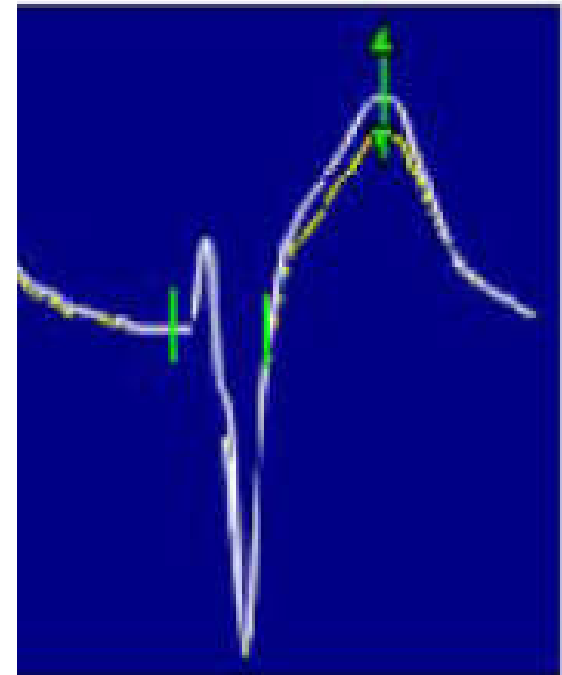
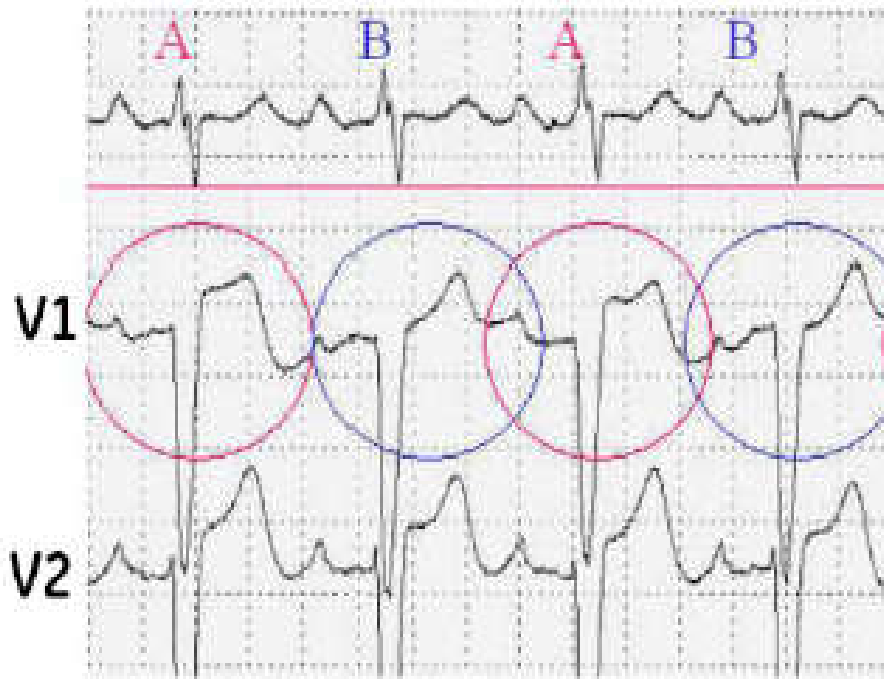


T wave alternans?



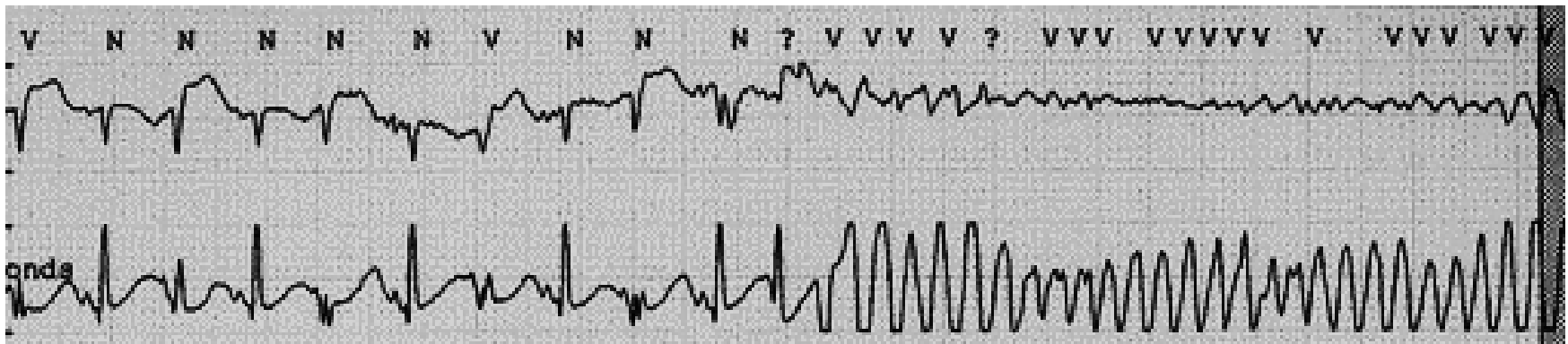
T-Wave Alternans(TWA)?

- **Beat-to-beat variability** in the timing, shape, and/or amplitude of **T-waves** on the surface ECG



Why is TWA is important?

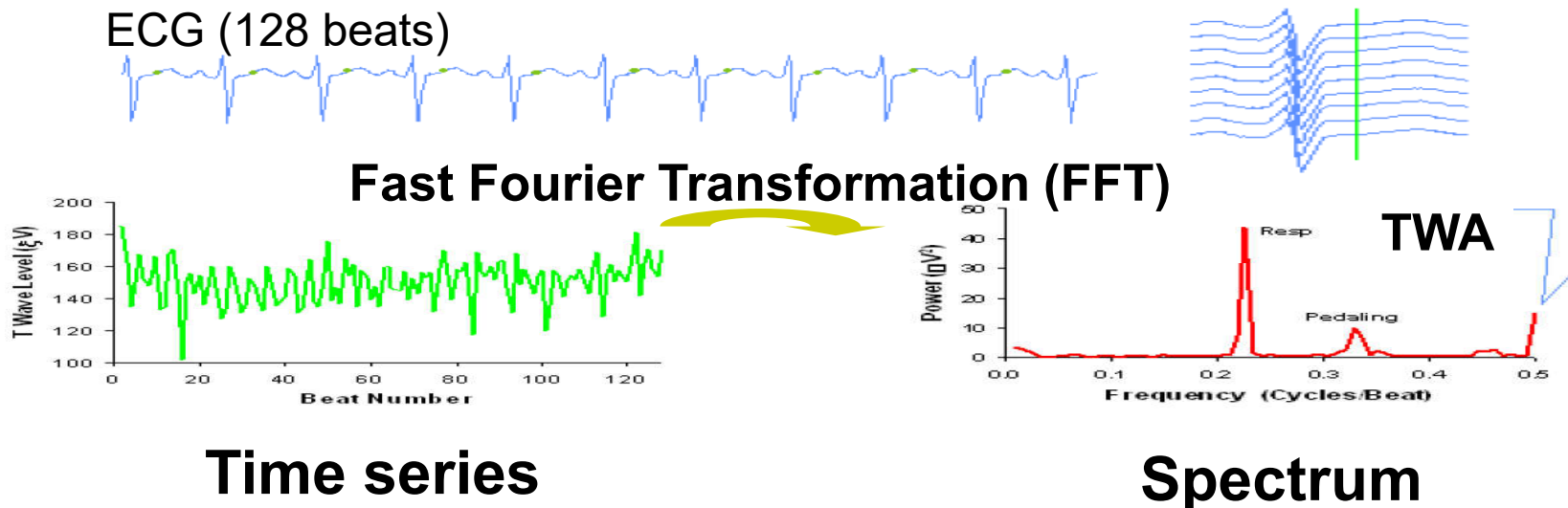
- Indicator of **cardiac electrical instability**
- Indicator of vulnerability of VT/VF



- Used for **SCD risk stratification**

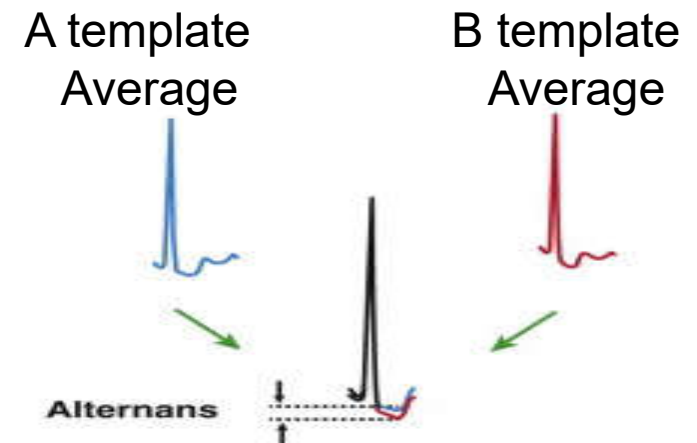
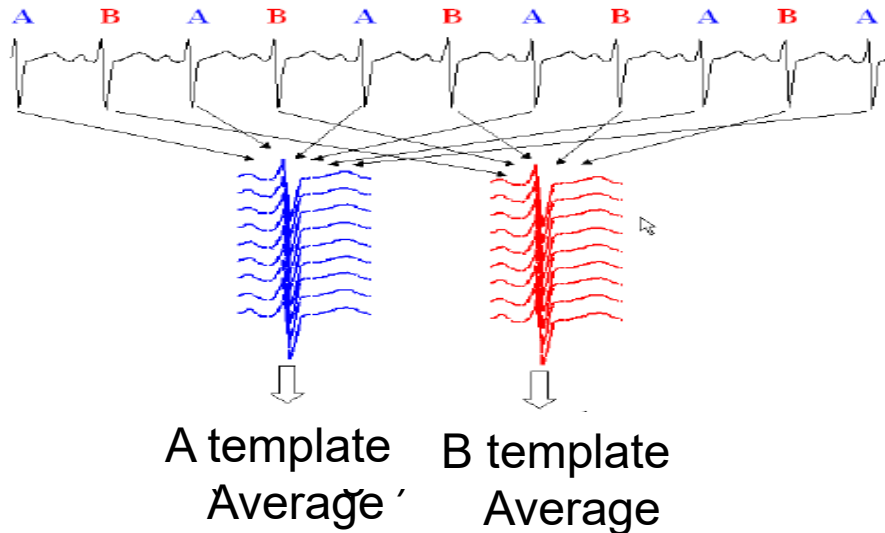
The Spectral Method

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



Clinical implication of TWA?

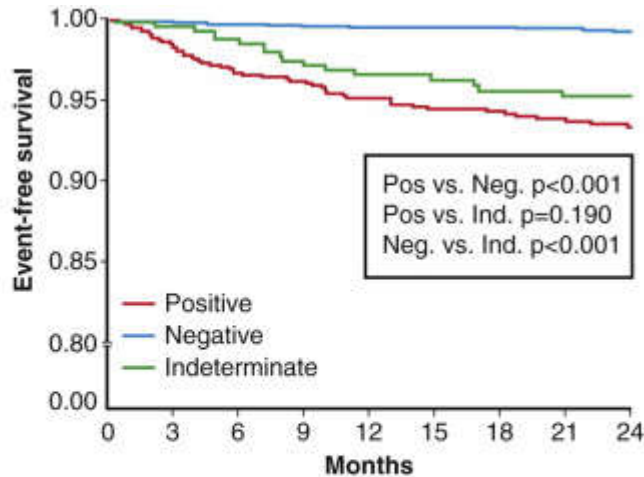


STUDY	PATIENT POPULATION (ENROLLMENT, DISEASE)	MEAN LVEF	HAZARD RATIOS FOR TWA
Predictive Studies			
Cardiomyopathy			
Kitamura et al. 2002 ²⁹	104 patients with DCM	37%	11.9 (1.53–92.59) ^a for SCD, VF, or sustained VT at 21 ± 14 months
Hohnloser et al. 2003 ³⁰	137 patients with DCM, LVEF ≤35%	29% ± 11%	3.44 for ventricular tachyarrhythmic events at 14 ± 6 months
Chow et al. 2007 ³¹	514 patients with ischemic cardiomyopathy, LVEF ≤35%, no previous sustained ventricular arrhythmia and positive or indeterminate TWA test results	26%–29%	2.24 (1.34–3.75) for all-cause mortality; 2.29 (1.00–5.24) for arrhythmic mortality; NS for nonarrhythmic mortality
Salerno-Uriarte et al. 2007 (ALPHA) ³²	446 patients with DCM, LVEF ≤40%	29.5%	4.0 (1.4–11.4) for cardiac death and life-threatening arrhythmias at 18 months
Chow et al. 2006 ³³	768 patients with ischemic cardiomyopathy, LVEF ≤35%, no previous sustained ventricular arrhythmia	26%–29%	2.27 (1.22–4.24) for all-cause mortality in patients without an ICD; 2.42 (1.07–5.41) for all-cause mortality or appropriate ICD discharge in patients with an ICD
Chan et al. 2008 ³⁴	768 patients with ischemic cardiomyopathy, LVEF ≤35%, no previous sustained ventricular arrhythmia (same patients as Chow et al. 2007 ³⁵)	26%–29%	2.19 (1.1–4.34) for all-cause mortality and appropriate ICD shocks at 1 year; 3.36 (1.28–8.83) at 2 years
Costantini et al. 2009 (ABCD) ²⁸	566 patients with ischemic cardiomyopathy, LVEF ≤40%, and NSVT	28% ± 8%	2.1 for SCD or appropriate ICD discharge at 1 year
Congenital Heart Disease			
Alexander et al. 2006 ³⁶	304 consecutive pediatric patients with congenital heart disease, myopathy, syncope, or history of cardiac arrest	Not stated	7.9 (2.2–28.1) for ventricular arrhythmia; 6.7 (1.6–28.1) for cardiac arrest at <3 years
Depressed LVEF			
Rashba et al. 2002 ³⁵	108 consecutive patients with CAD and LVEF ≤40%	28% ± 7%	2.2 (1.1–4.7) for death, sustained ventricular arrhythmias, appropriate ICD discharge at 18 ± 13 months in patients with normal QRS segment; NS in patients with prolonged QRS segment
Rashba et al. 2004 ³⁷	144 patients with CAD and LVEF ≤40%	28% ± 7%	2.2 (1.1–4.7) for death, sustained ventricular arrhythmia, or appropriate ICD discharge at 17 ± 13 months; NS in patients with LVEF <30%; ∞ in patients with LVEF >30%

Risk stratification of patients with ICMP

2883 patients without history of previous ventricular tachyarrhythmias

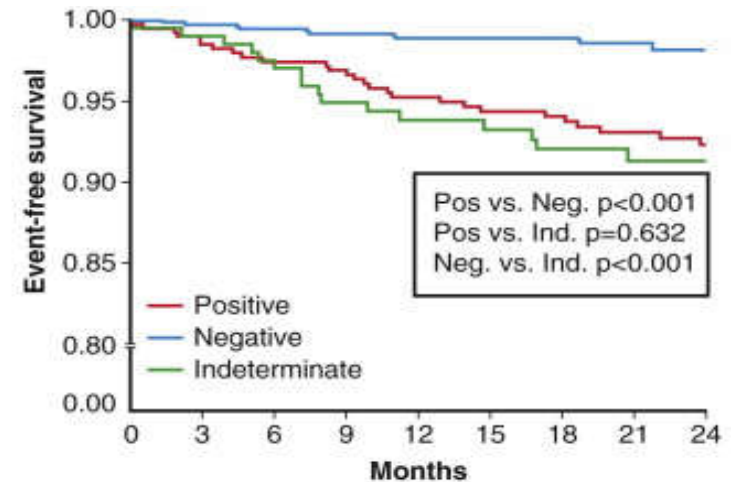
Arrhythmic mortality/sudden death



Number at risk

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

Patients with an LVEF ≤0.35

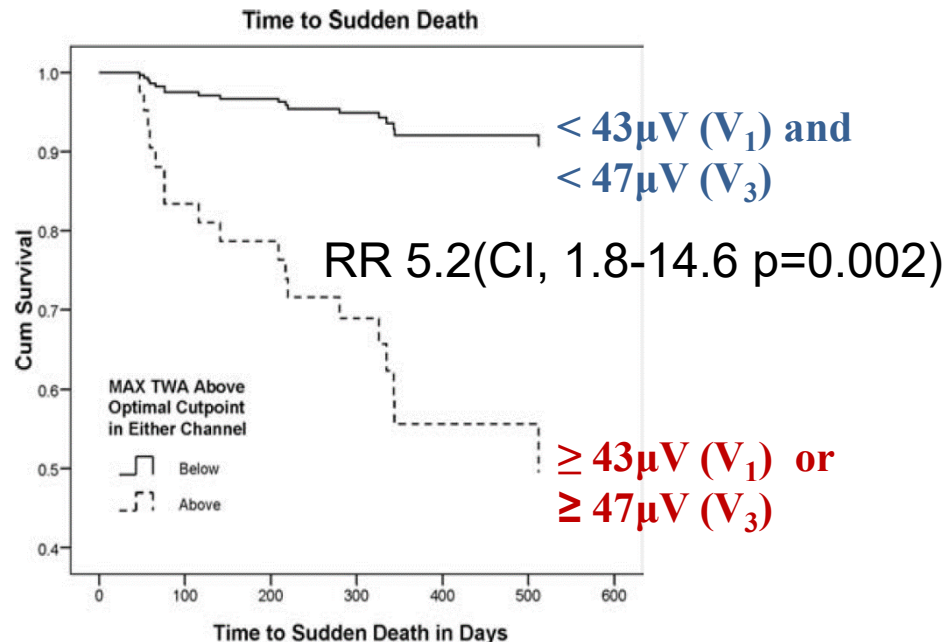


Number at risk

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

Elevated TWA predict SCD in MI patients

493 patients
 Post-MI day 2~10
 TWA (Ambulatory ECG-based)
 500 days f/u



	Alive (N = 92)	SCD (N = 18)	Non-SCD (N = 28)	Alive vs SCD P-value	Alive vs Non-SCD P-value
Lead V ₁					
HR max (bpm)	72 ± 10	72 ± 9	82 ± 15	NS	<0.0001
TWA max (µV)	29 ± 11	38 ± 12	26 ± 8	0.002	NS
Time (hours:min)	12:41 ± 4:02	12:30 ± 4:11	11:02 ± 4:31	NS	NS
Lead V ₃					
HR max (bpm)	72 ± 10	73 ± 12	83 ± 15	NS	<0.0001
TWA max (µV)	33 ± 25	45 ± 19	33 ± 13	0.054	NS
Time (hours:min)	13:30 ± 4:14	12:41 ± 4:28	13:25 ± 4:13	NS	NS
24-hour averaged HR (bpm)	71 ± 9	71 ± 8	82 ± 14	NS	<0.001

TWA in patients with patients with HFrEF

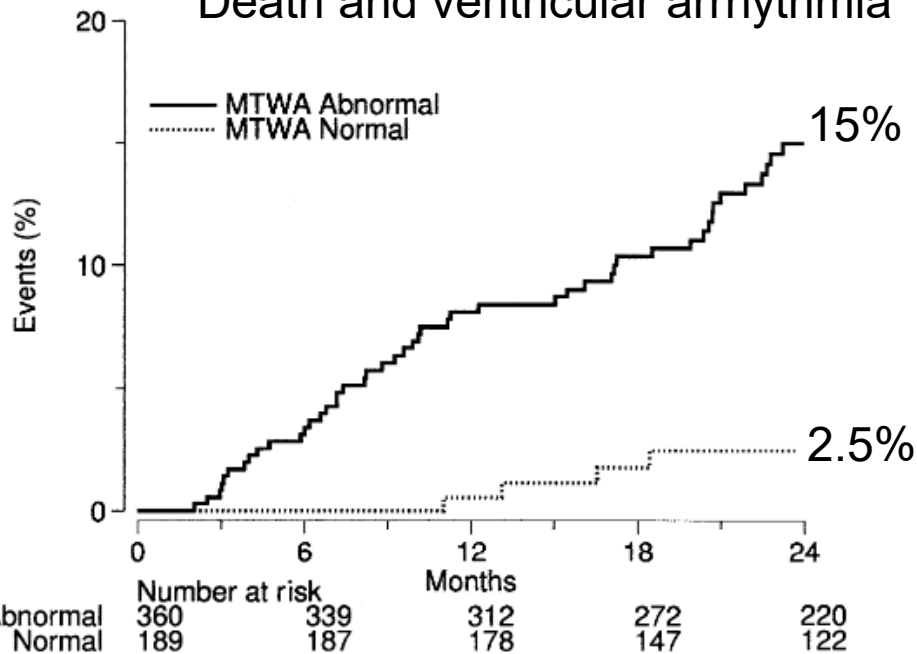
549 patients with EF \leq 40%

Age $56 \pm 10\%$

Mean EF $25 \pm 6\%$

2 years f/u

Death and ventricular arrhythmia



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

Elevated TWA predict SCD in HFrEF patients

195 patients(100 ICM, 95 NICM)

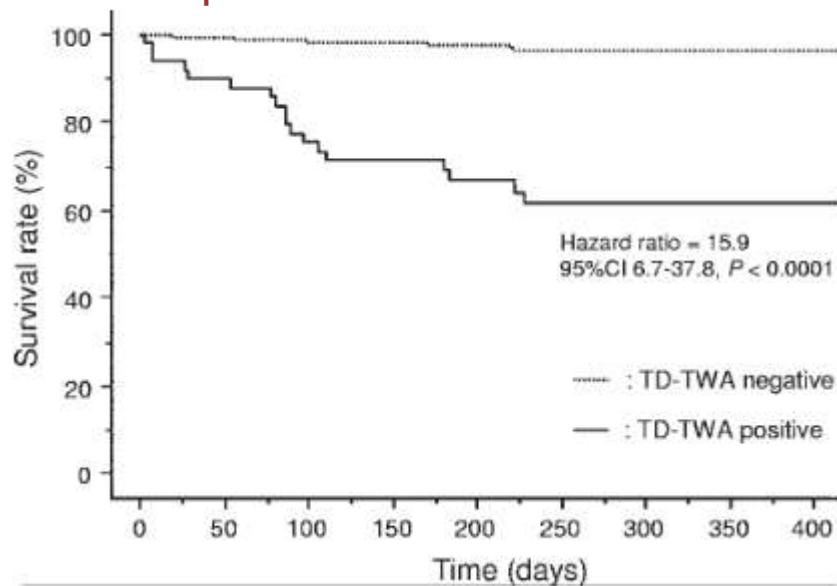
EF < 40%

Age $66 \pm 16\%$

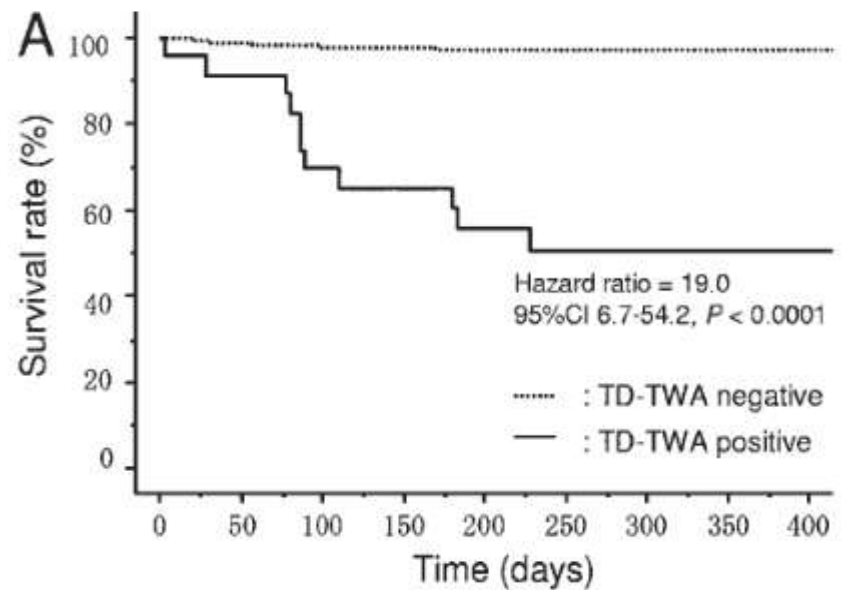
Mean EF $35 \pm 6\%$

Cut off value $65 \mu\text{V}$

All patients



NICM patients

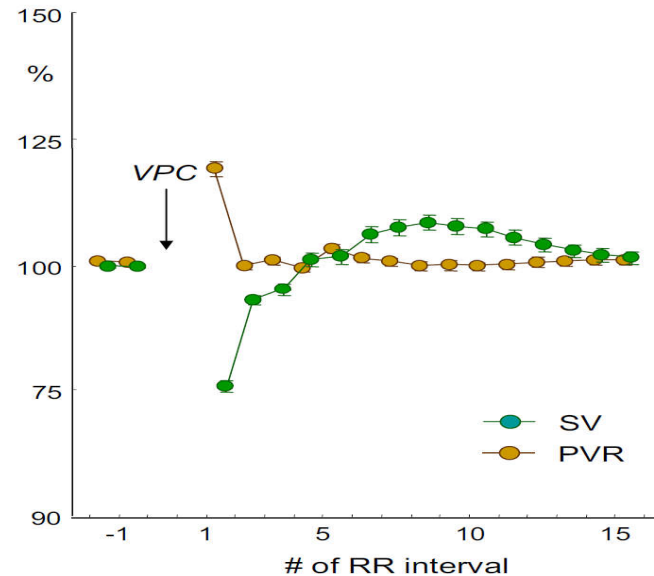
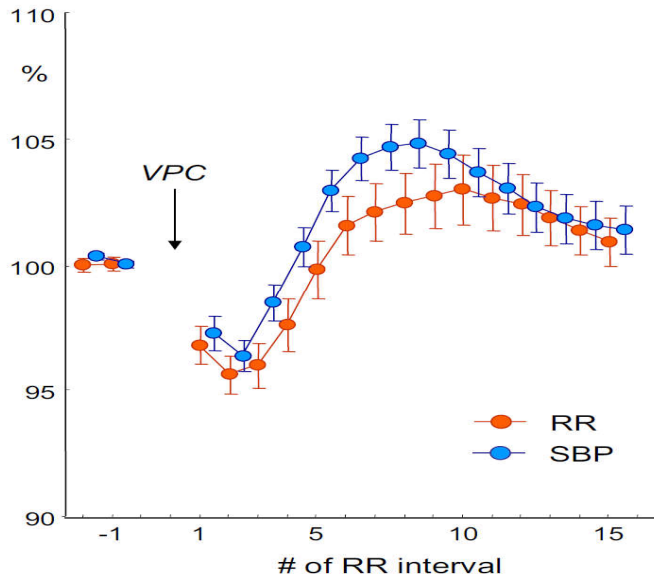


Heart rate turbulence?

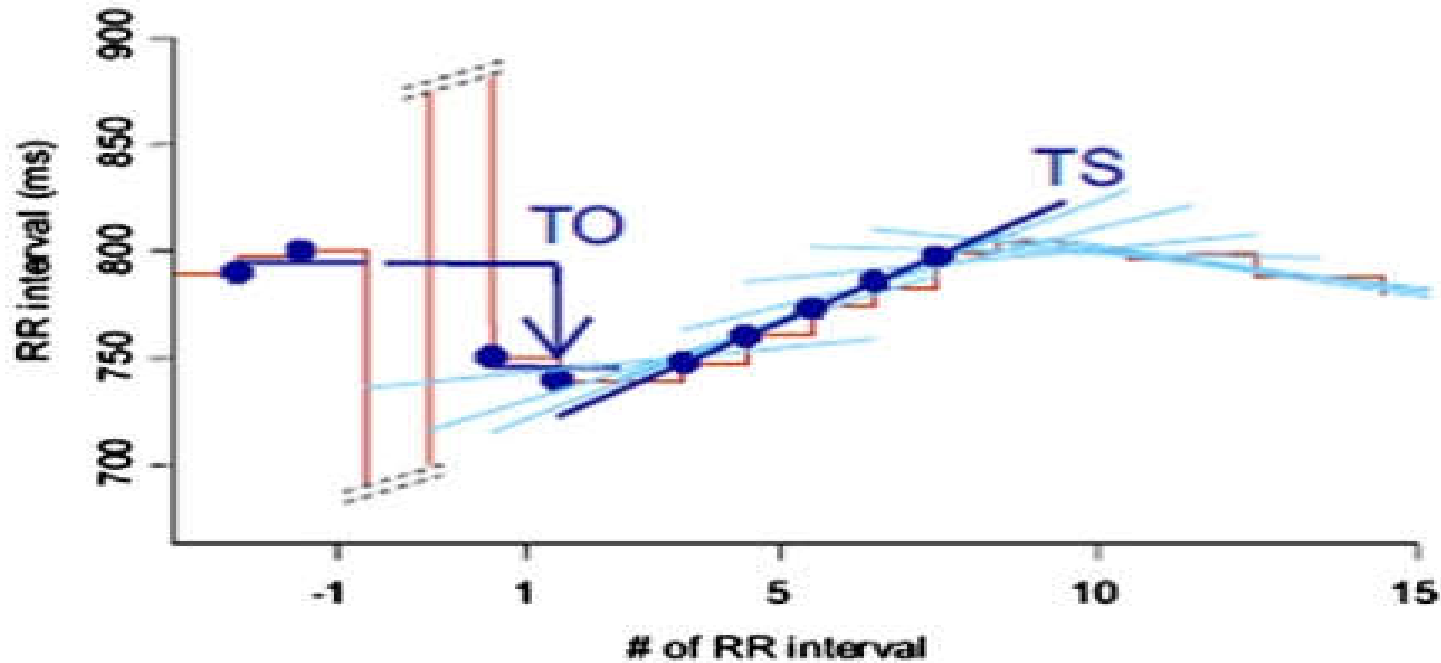


Heart rate turbulence(HRT)

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



Turbulence onset(TO), Turbulence slope(TS)

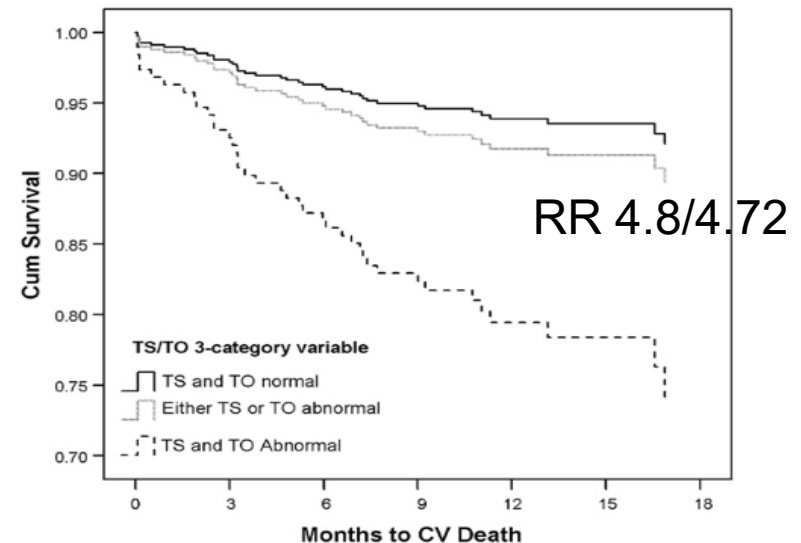


- The values of $TO > 0\%$ and $TS < 2.5 \text{ ms/RR interval}$ were defined abnormal, respectively

HRT predict CV death in patients with AMI

481 patients with AMI
2~10days after AMI.
18 months f/u

Cutoff : TS ≤ 3.0 ms/RR, TO ≥ 0



Variable	Alive (n = 432)		CV Death (n = 49)		p Value (alive vs CV death)
	No. of Subjects	Mean \pm SD	No. of Subjects	Median \pm SD	
TO	359	-0.0067 \pm 0.0220	44	0.0011 \pm 0.0160	0.024
TS	359	3.86 \pm 5.29	44	2.96 \pm 3.40	<0.001
LVEF (%)	432	35 \pm 6	49	32 \pm 8	0.001
>30	344	80%	29	59%	
≤ 30	88	20%	20	41%	
SDNN (ms)	414	84 \pm 40	48	78 \pm 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 \pm 16	49	67 \pm 16	<0.001
Men	317	74%	31	63%	
Women	115	26%	18	37%	
Diabetes	99	23%	17	35%	NS

HRT predict death in patients with HF

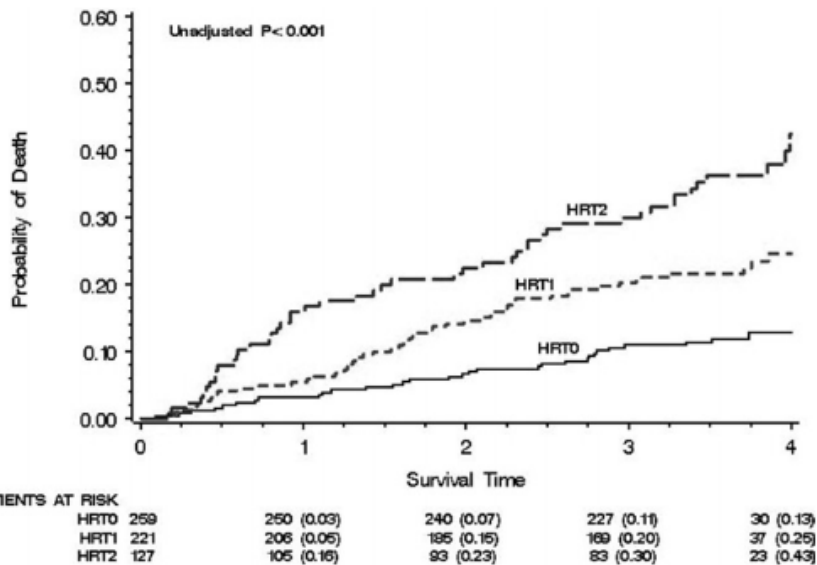
507 patients with HF

Age $63 \pm 12\%$

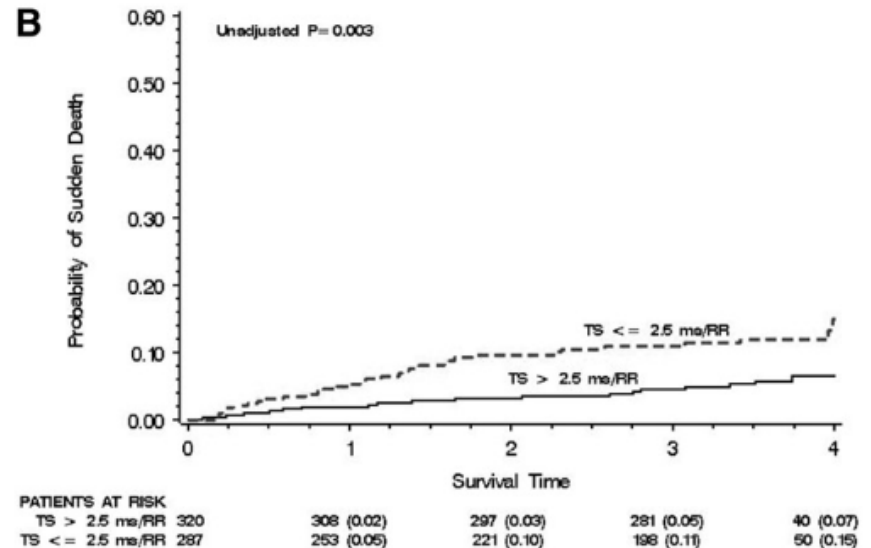
Mean EF $37 \pm 14\%$

3 years f/u

All cause death



Sudden cardiac death

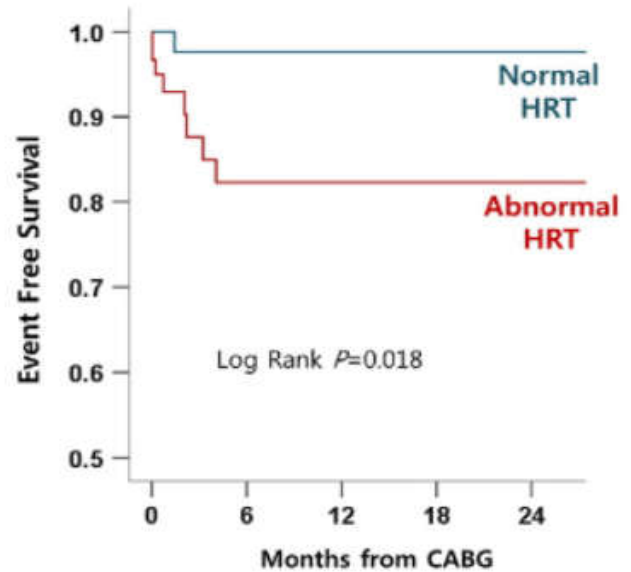
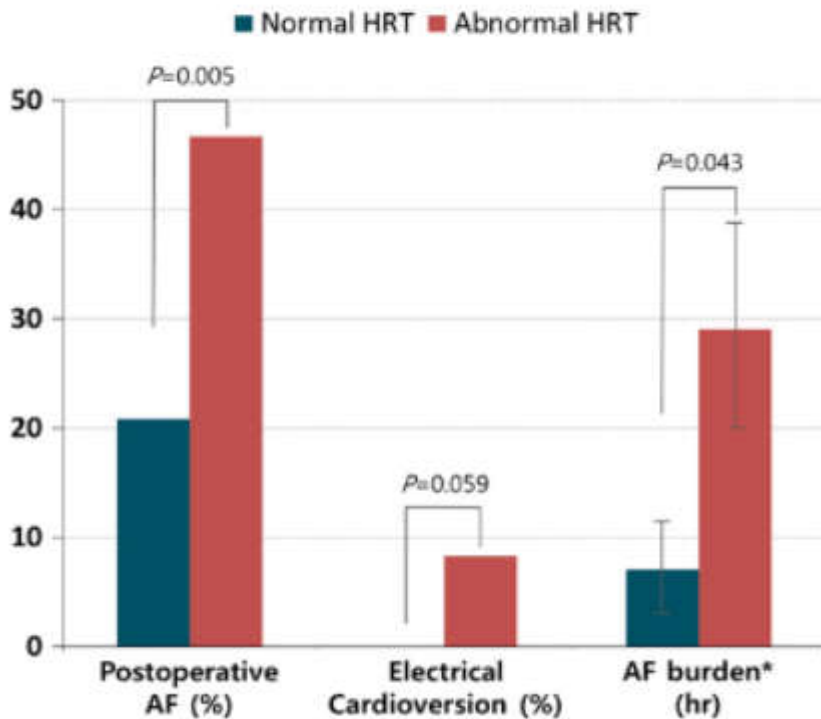


HRT predict new-onset AF

172 patients

HRT measurement prior to CABG

Without AF



	No. at risks					No. of events
	0	6	12	18	24	
Normal HRT	53	34	25	12	9	1
Abnormal HRT	60	24	20	17	12	8

Arrhythmic risk stratification

*Post MI with preserved EF
(n=575)*

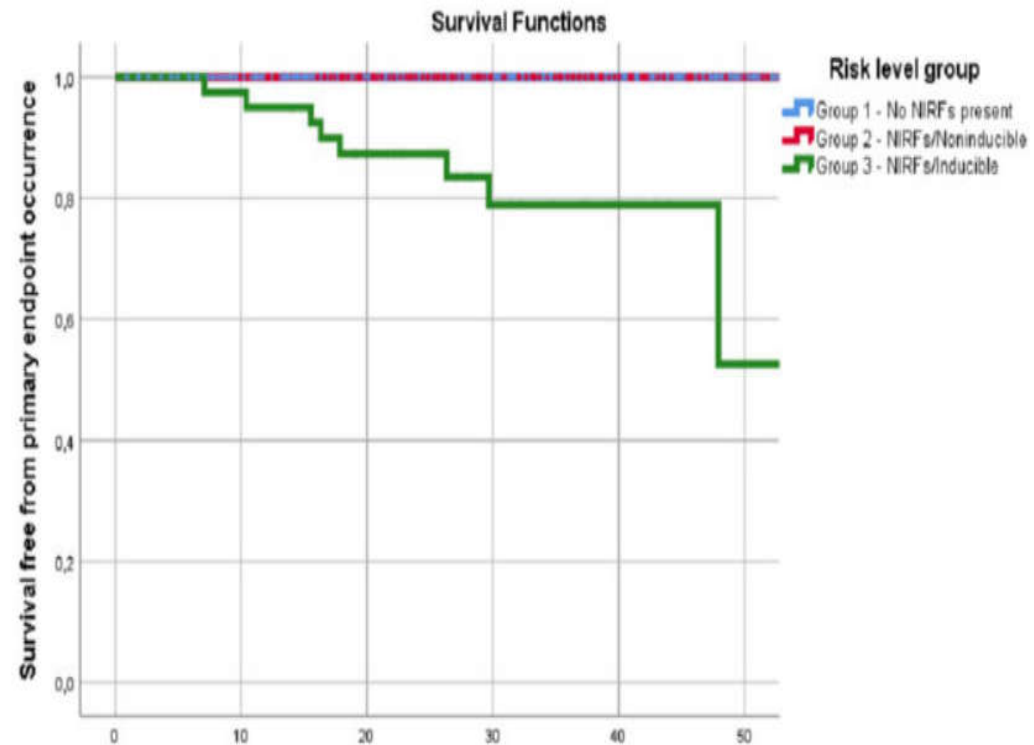
1st screening step: NIRFs

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) $\geq 65\mu V$
- SDNN $\leq 75ms$
- Deceleration Capacity $\leq 4.5ms$ AND Heart Rate Turbulence (HRT) Onset $\geq 0\%$ AND HRT slope $\leq .5ms$

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

Current guidelines

2015 ESC guideline

Non-invasive evaluation of patients with suspected or known ventricular arrhythmias

Recommendations	Class ^a	Level ^b	Ref. ^c
Resting 12-lead ECG			
Resting 12-lead ECG is recommended in all patients who are evaluated for VA.	I	A	1
ECG monitoring			
Ambulatory ECG is recommended to detect and diagnose arrhythmias. Twelve-lead ambulatory ECG is recommended to evaluate QT-interval changes or ST changes.	I	A	93
Cardiac event recorders are recommended when symptoms are sporadic to establish whether they are caused by transient arrhythmias.	I	B	94
Implantable loop recorders are recommended when symptoms, e.g. syncope, are sporadic and suspected to be related to arrhythmias and when a symptom–rhythm correlation cannot be established by conventional diagnostic techniques.	I	B	95
SA-ECG is recommended to improve the diagnosis of ARVC in patients with VAs or in those who are at risk of developing life-threatening VAs.	I	B	96,97

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).

Case



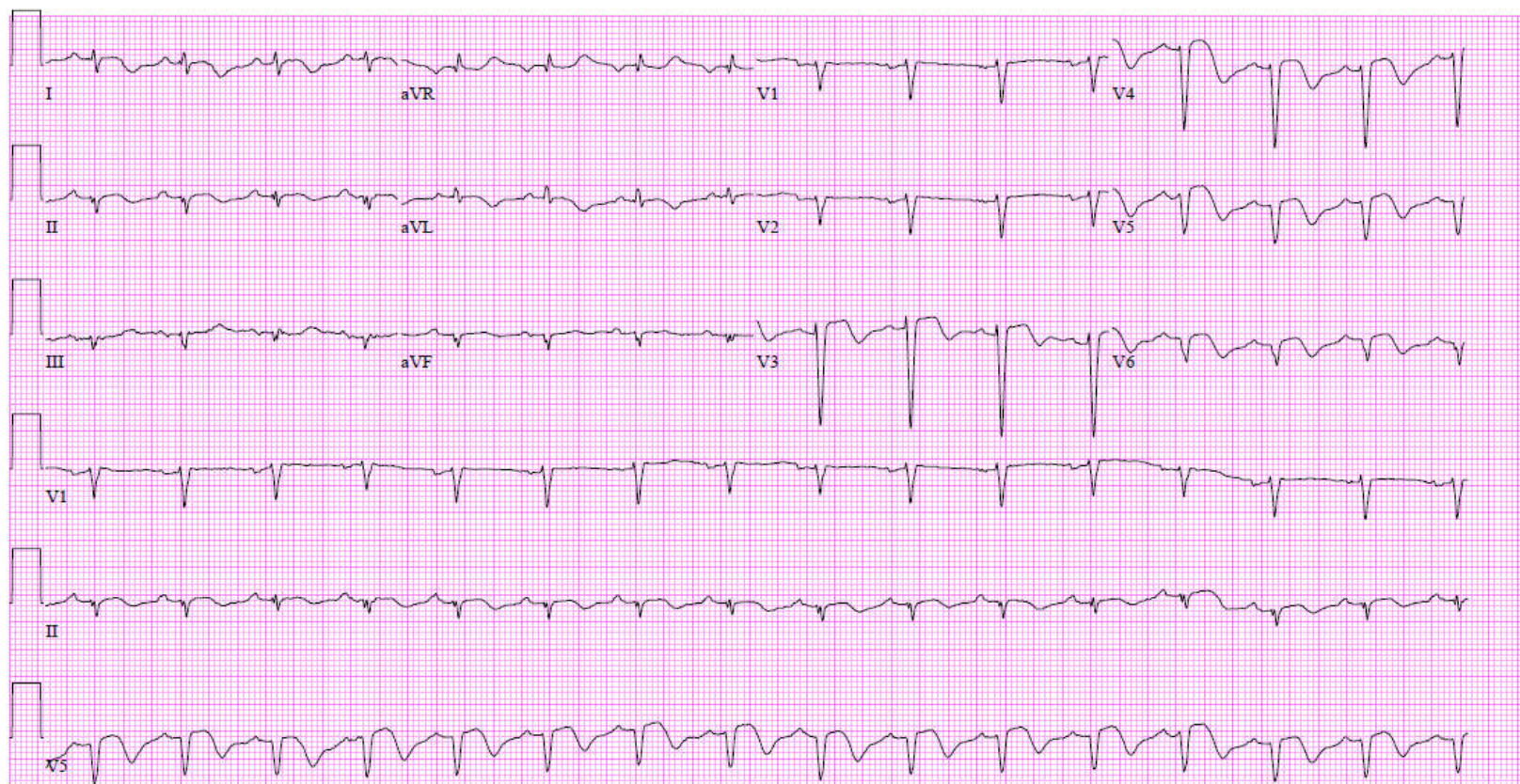
68/M chest pain

Chest pain 1 weeks ago

HTN/DM(+/+)

Cr 0.7 Hb 14.1

Troponin 5897

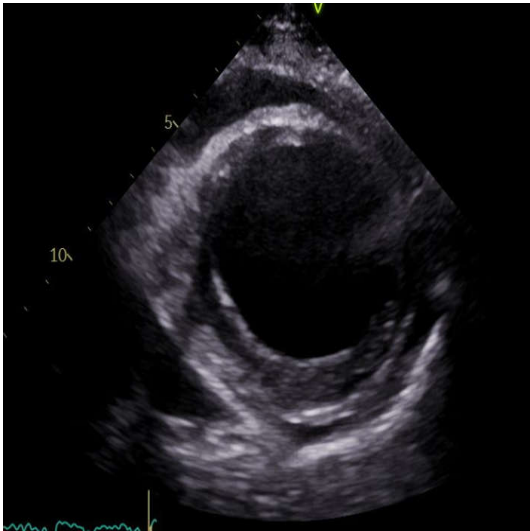


Coronary angiography

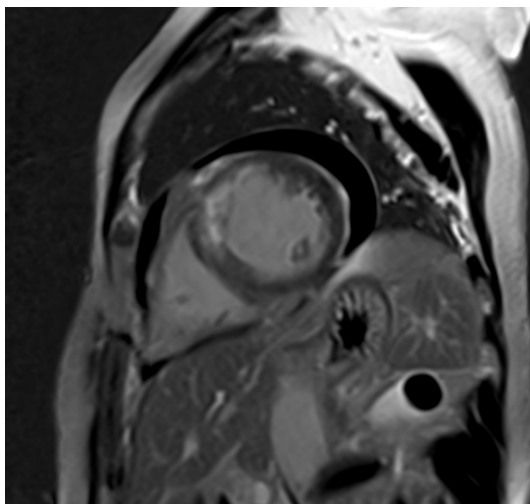


LAD PCI

Echocardiography & cardiac MRI



1. RWMA: compatible with LAD territory
 - Akinesia on IVS, AW, IW from mid to apex,
2. Reduced LV systolic function (EF: 27%).
3. moderate amount of pericardial effusion



- Old transmural MI with extensive apical aneurysm in LAD territory
- severe LV systolic dysfunction
 - large amount of pericardial effusion

68/M chest pain

BEAT COUNTS

QRS complexes: 121202
Paced: 0
Ventricular ectopics: 15 < 1% of QRS complexes
Supraventricular ectopics: 121 < 1% of QRS complexes

HEART RATES

Minimum: 54 at: 03:34:07 09-Jun-2021
Maximum: 134 at: 06:51:51 09-Jun-2021
Average: 85

VENTRICULAR ECTOPY

Isolated: 13 beats LONGEST at: bpm
Couplets: 1 beats FASTEST at: bpm
Runs: 0
Total beats: 0
Bigeminal: 0

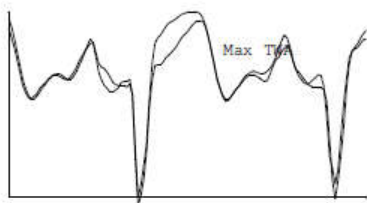
SUPRAVENTRICULAR ECTOPY

Isolated: 119 beats LONGEST at: bpm
Couplets: 1 beats FASTEST at: bpm
Runs: 0
Total beats: 0

Longest RR: 1.132 sec at: 03:36:54 09-Jun-2021
Acq duration: 23:51

INTERPRETATION

Basically sinus rhythm.
Occasional APCs.
Rare VPCs.

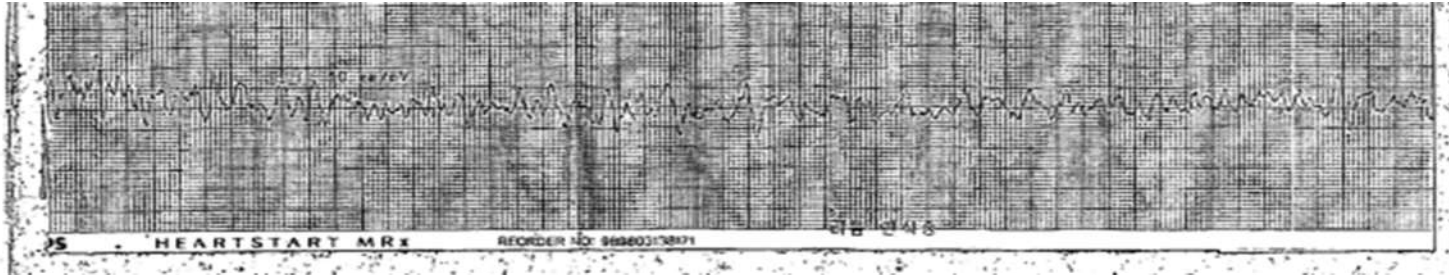


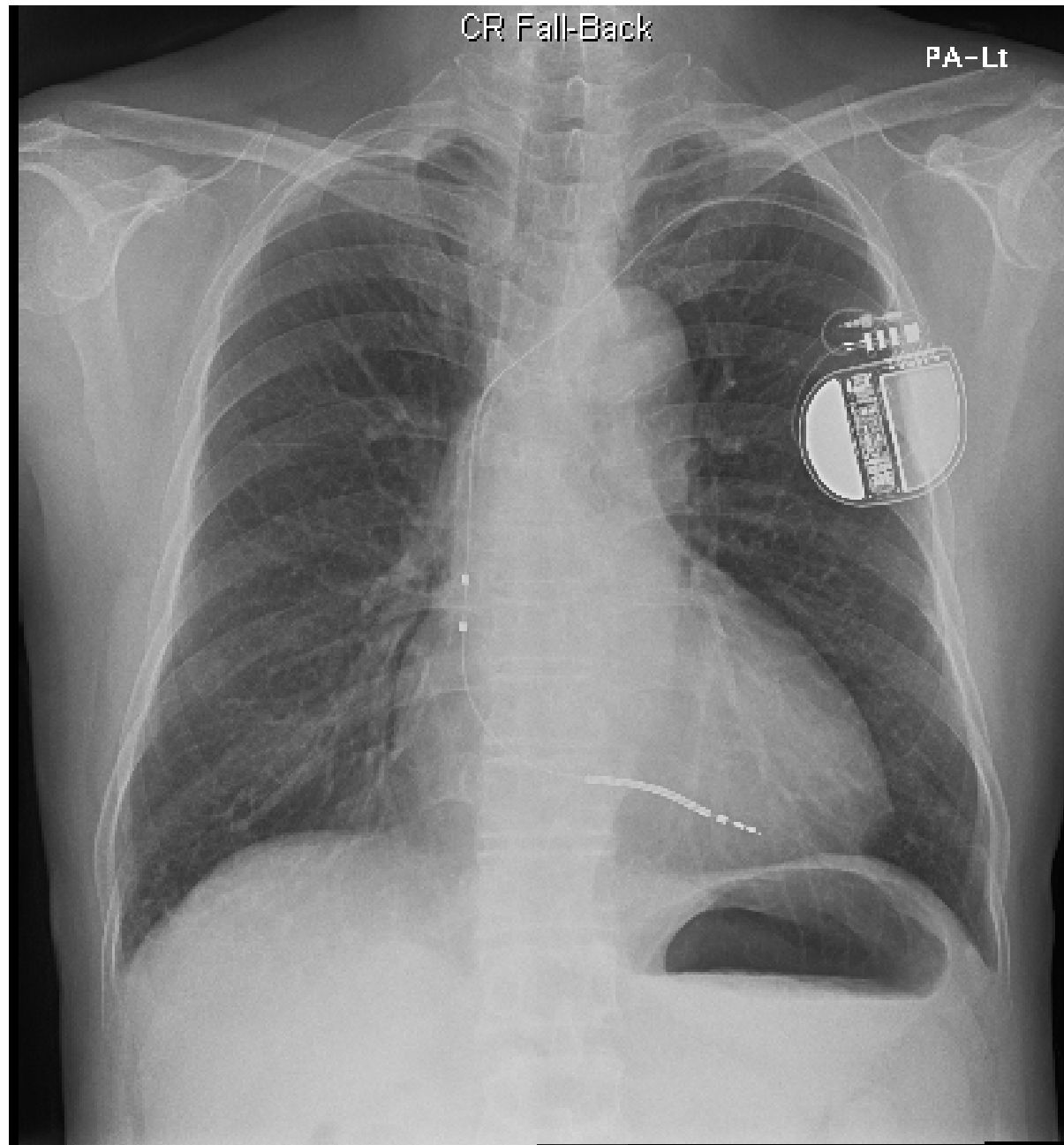
TWA Channel 1 72uV
Channel 2 87uV
Channel 3 92uV



Peak ST Even/Odd display not available

Cardiac arrest after 2 weeks





Summary

- TWA is an indicator of cardiac electrical instability, can predict SCD in patients with HF, ischemic heart disease.
- HRT s an indicator of cardiac autonomic function, can predict SCD, all cause death, new-onset AF.
- Combined non-invasive risk stratification approach can be effectively addressed SCD.

