KHRS2019, June 20-22, Seoul, Korea

The Future of Risk Stratification in Channelopathy

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COI:

The Future of Risk Stratification in Channelopathy

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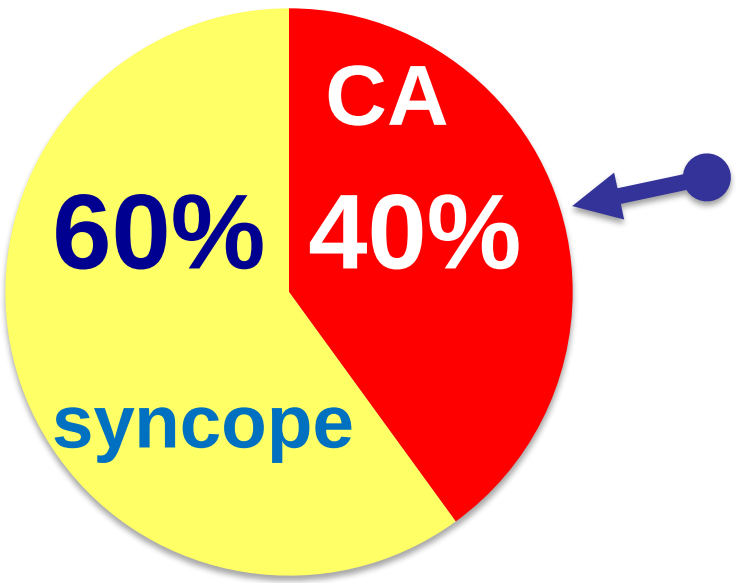
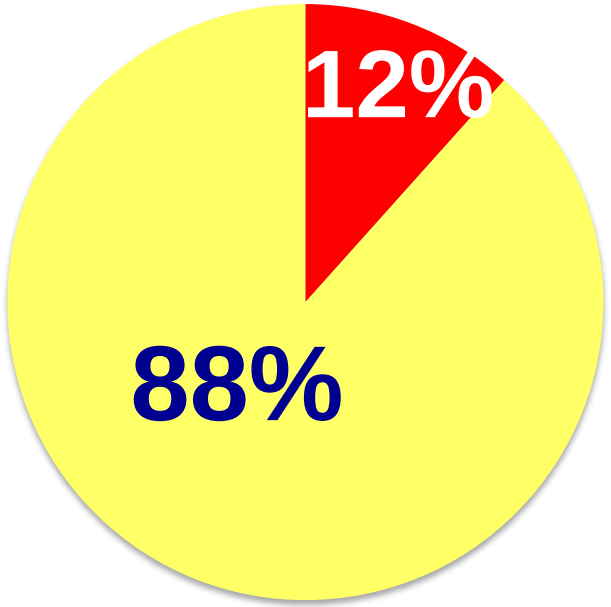
None to declare in regard to this presentation

Q1: As to SYMPTOMS, which patient presents more cardiac arrest (CA)?

Brugada or long QT syndrome?





Brugada syndrome:

Data for 1217 patients

Paul: *Eur Heart J* 2007

Long QT syndrome:

Data for 3015 patients

Goldenberg: *Circulation* 2008

Q2: How many percent of pts experienced CA without warning syncope?

Most recently published Shanghai Scoring System for BrS diagnosis is also valid for Risk Stratification.

Priori SG et al: Natural history of Brugada syndrome. *Circulation* 2002: 105(11):1342

Shanghai Score for Diagnosis of Brugada Syndrome

Antzelvitch et al. J-Wave syndromes expert consensus conference report. 2016

I. ECG (12-Lead/Ambulatory)	
A. Spontaneous type 1 Brugada ECG pattern at nominal or high leads	3.5
B. Fever-induced type 1 Brugada ECG pattern at nominal or high leads	3
C. Type 2 or 3 Brugada ECG pattern that converts with provocative drug challenge	2

**Only award points once for highest score within this category. One item from this category must apply.*

II. Clinical History*	
A. Unexplained cardiac arrest or documented VF/polymorphic VT	3
B. Nocturnal agonal respirations	2
C. Suspected arrhythmic syncope	2
D. Syncope of unclear mechanism/unclear etiology	1
E. Atrial flutter/fibrillation in patients o30 years without alternative etiology	0.5

**Only award points once for highest score within this category.*

Shanghai Score for Diagnosis of Brugada Syndrome

III. Family History	
A. First- or second-degree relative with definite BrS	2
B. Suspicious SCD (fever, nocturnal, Brugada aggravating drugs) in a first- or second-degree relative	1
C. Unexplained SCD < 45 years in first- or second- degree relative with negative autopsy	0.5
**Only award points once for highest score within this category.*	
IV. Genetic Test Result	
A. Probable pathogenic mutation in BrS susceptibility gene	0.5

SCN5A

Score (requires at least 1 ECG finding)

≥ 3.5 points: Probable/definite BrS

2–3 points: Possible BrS

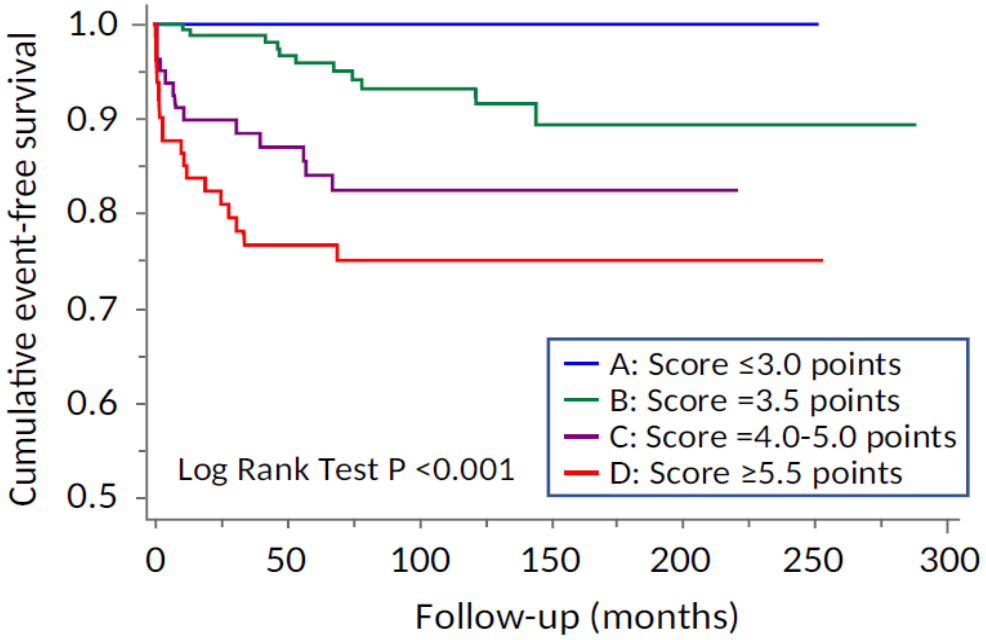
< 2 points: Nondiagnostic

Antzelvitch et al. J-Wave syndromes expert consensus conference report. 2016

Shanghai scoring system is useful for risk stratification.

Kawada, Morita, …. et al. JACC, 2018.

FIGURE 2 Cumulative Event-Free Survival as a Function of Score



Numbers at risk

A: Score ≤3.0 points	45	42	36	17	6	2	—
B: Score =3.5 points	186	131	78	36	12	3	—
C: Score =4.0-5.0 points	81	60	43	16	4	—	—
D: Score ≥5.5 points	81	53	34	15	6	2	—

393 consecutive Jpn Brugada pts at a single hospital. Mean f/u 97.2 months

Probable/definite BrS

Three major categories in Shanghai score system for risk stratification:

- ECG features

  type 1 Brugada pattern: most powerful

  only this? ER? QRS fragmentation…….
- Clinical history

  Unexplained CA or documented VF/pVT
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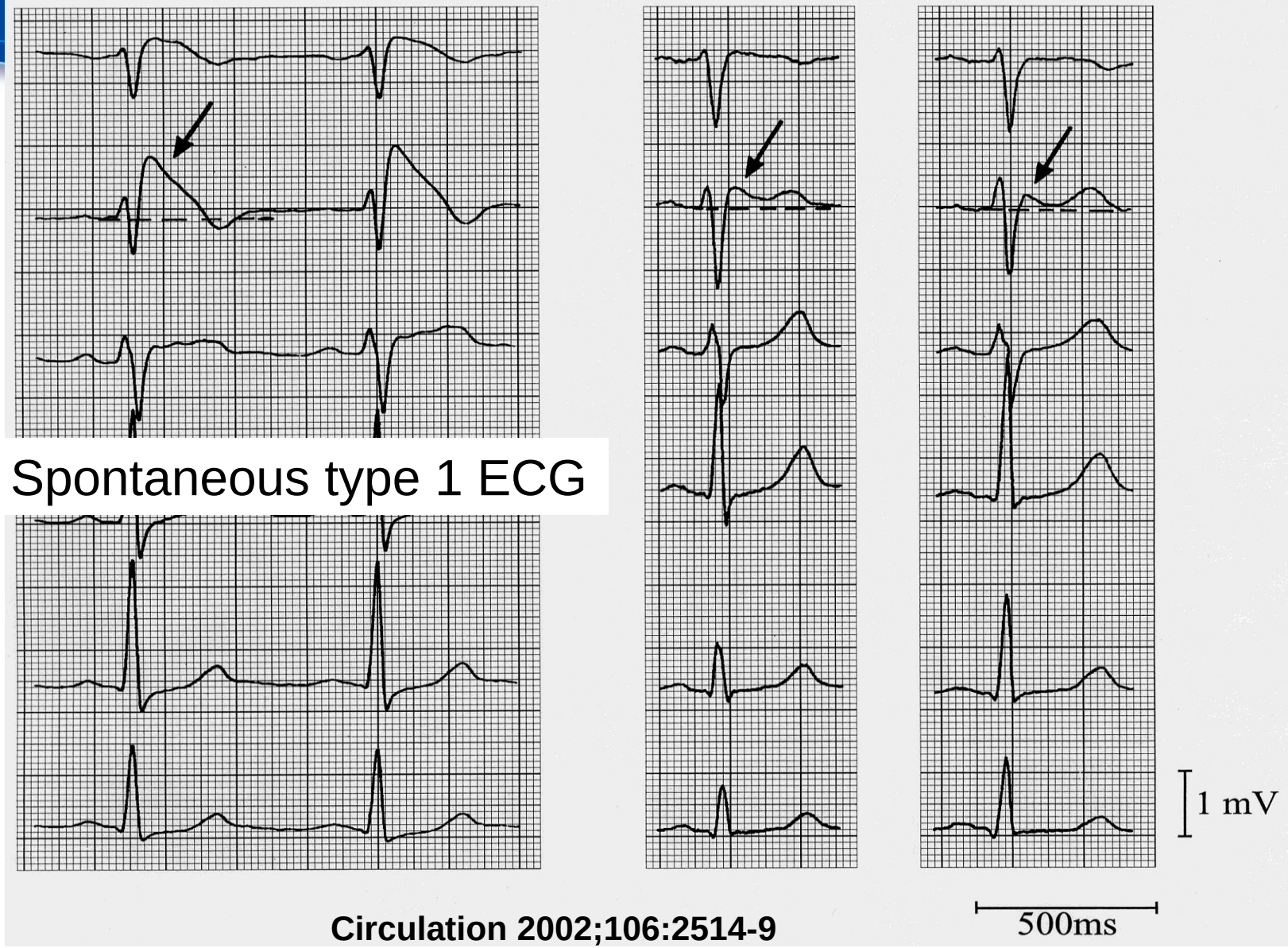
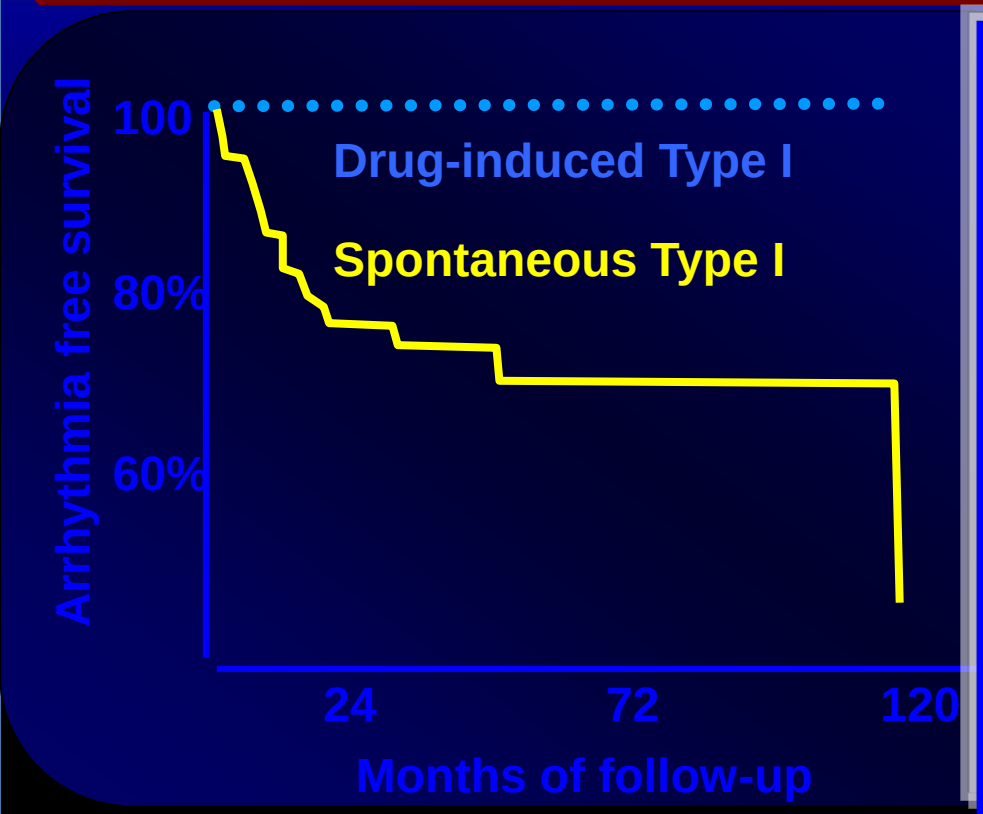
Type 1 50mm/sec speed Type 2 & 3

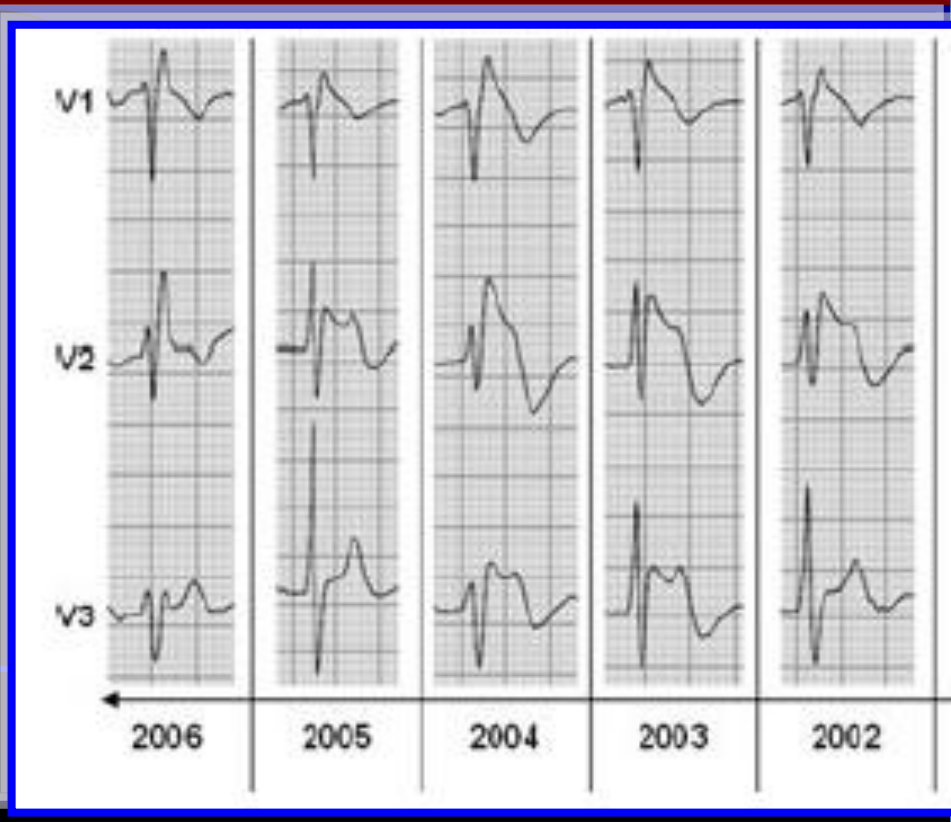


Spontaneous type 1 ECG

Circulation 2002;106:2514-9

Variability of the Diagnostic ECG Pattern in an ICD Patient Population with Brugada Syndrome





In patients with spontaneous coved-type ECG, only every third ECG is diagnostic and every third ECG normal.

You should record at least 3 ECG in a single patient.

Richter, *JCE* 2009

Other ECG features as Risk Predictors

- ✓ aVR sign (Babai et al, 2007)
- ✓ fragmented QRS in the right precordial leads (Morita et al, 2008; Priori et al, 2012)
- ✓ prolonged r-J interval in lead V_2 and QRS duration in lead V_6 (Takagi et al, 2007)
- ✓ Early repolarization patterns in other leads.
- ✓ precordial ST elevation during recovery of exercise test (Makimoto et al, 2010)
- ✓ amplitude (depth) of negative T wave in lead V_1 (Miyamoto et al, 2014)
- ✓ wide and/or deep S wave in lead I (Calo et al. 2016)
- ✓ minimum amplitude of late R' plus S < 0.8 mV (Nagase et al, 2018)

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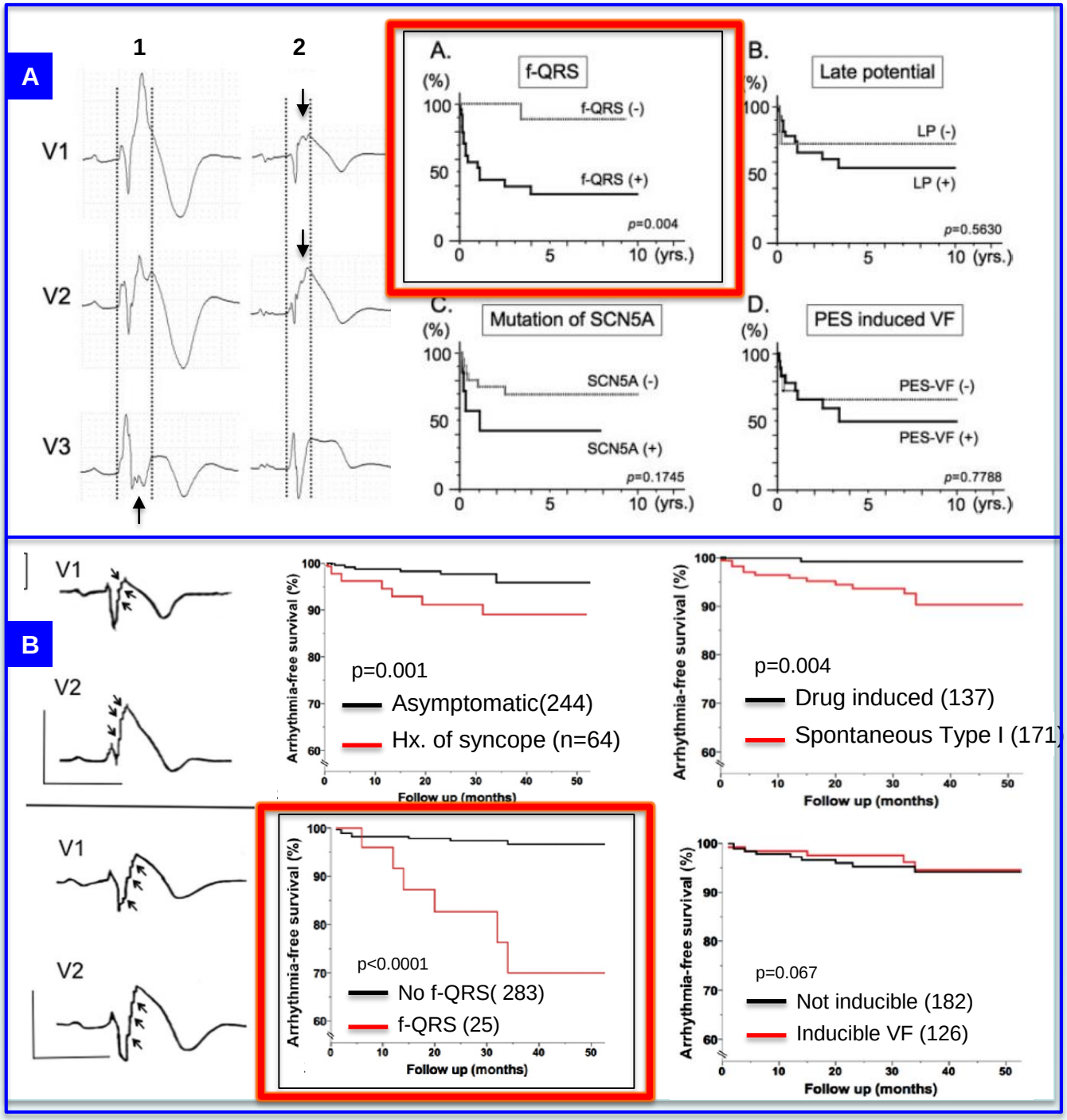


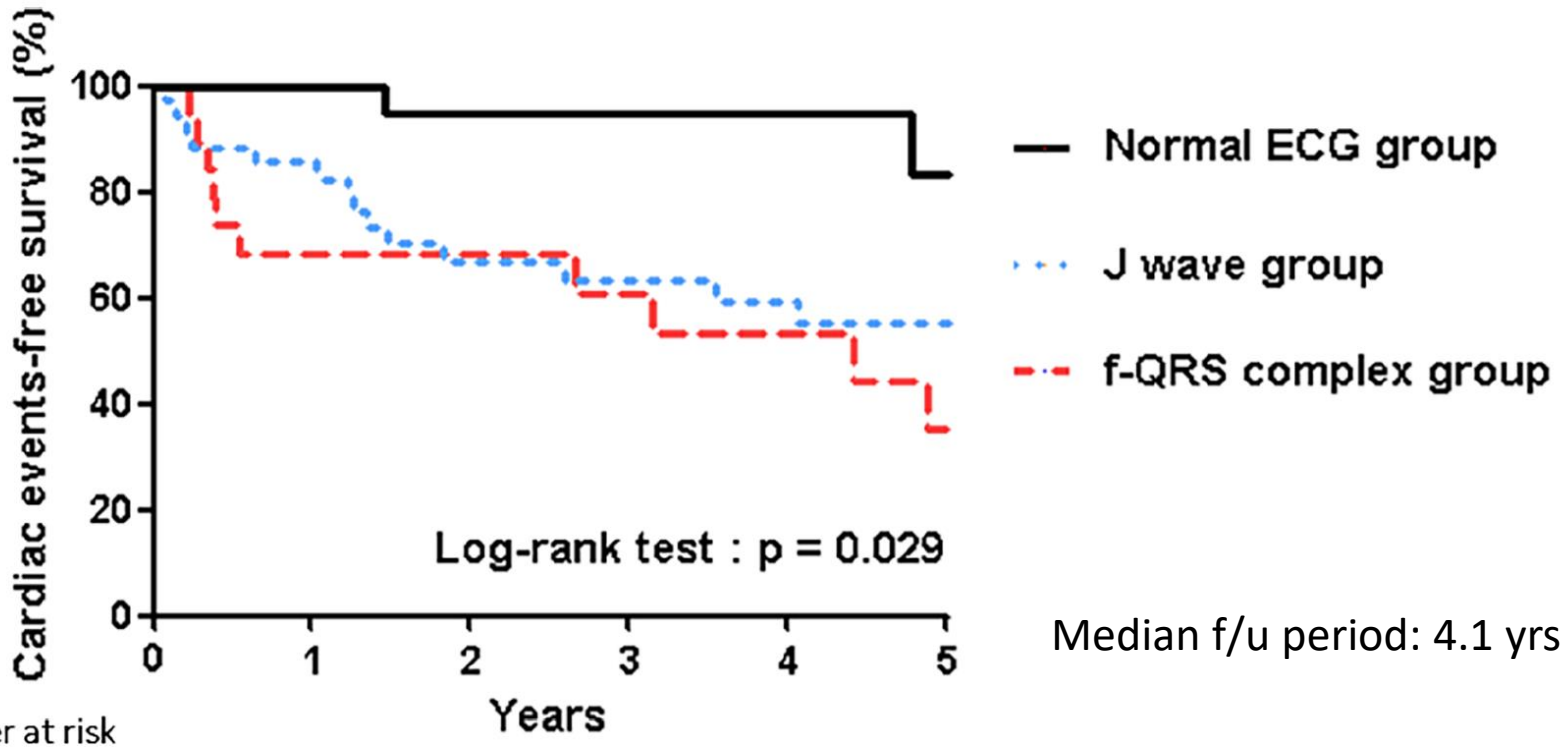
fragmented QRS in the right precordial leads

Morita, *Circulation* 2008

Priori, *JACC* 2012

IN 81 IVF patients implanted with ICD (CS Seong … YK On, PlosONE 2018)

f-QRS = fragmented QRS complexes



Number at risk						
Normal ECG	20	12	10	8	6	4
J wave	35	28	20	16	14	10
f-QRS	26	24	14	11	10	6

Median f/u period: 4.1 yrs

Low-Voltage Type 1 ECG Is Associated With Fatal Ventricular Tachyarrhythmia in Brugada Syndrome

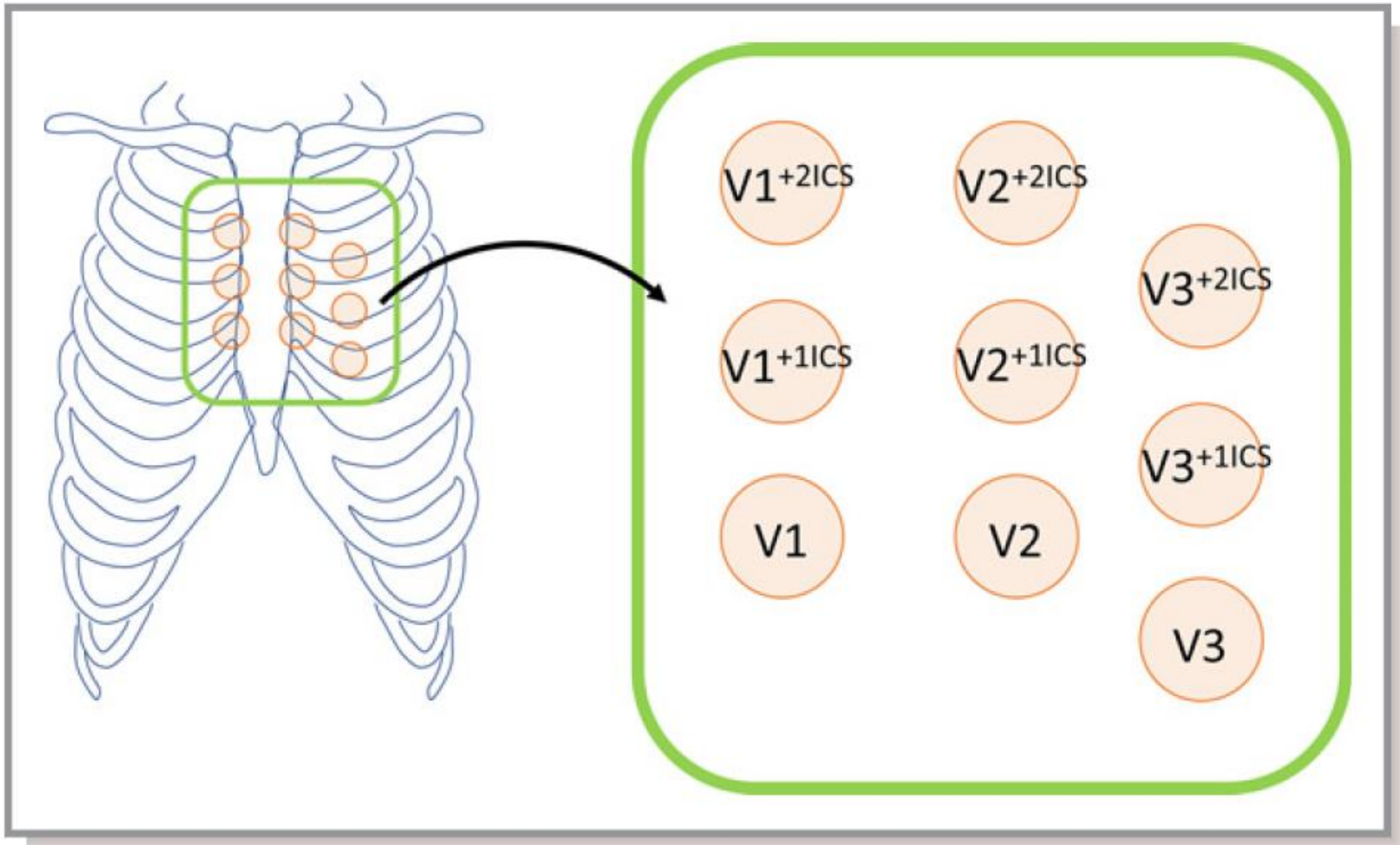
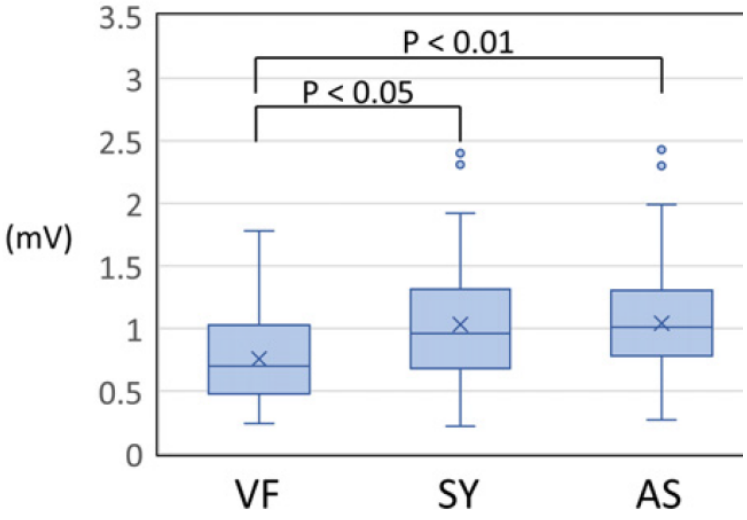
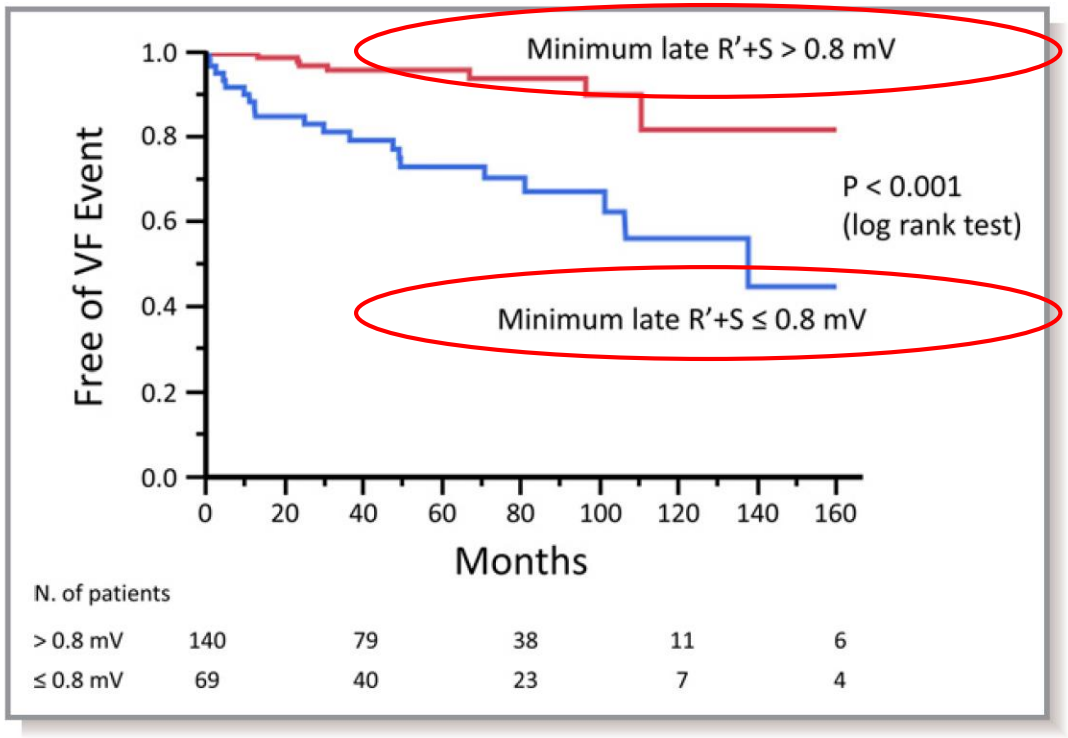


Figure 2. Measurements of ECG parameters in leads showing type 1. Among the 9 right precordial leads, the amplitudes of late R′, S, and late R′ plus S were evaluated in each ECG lead showing type 1.

Late R’ plus S = 0.78 mV was optimized cutoff point to predict VF episodes.



VF = ventricular fibrillation
SY = syncope
AS = asymptomatic



As the minimum amplitude of late R’ plus S wave was smaller, the risk for VF recurrence during f/u increased.

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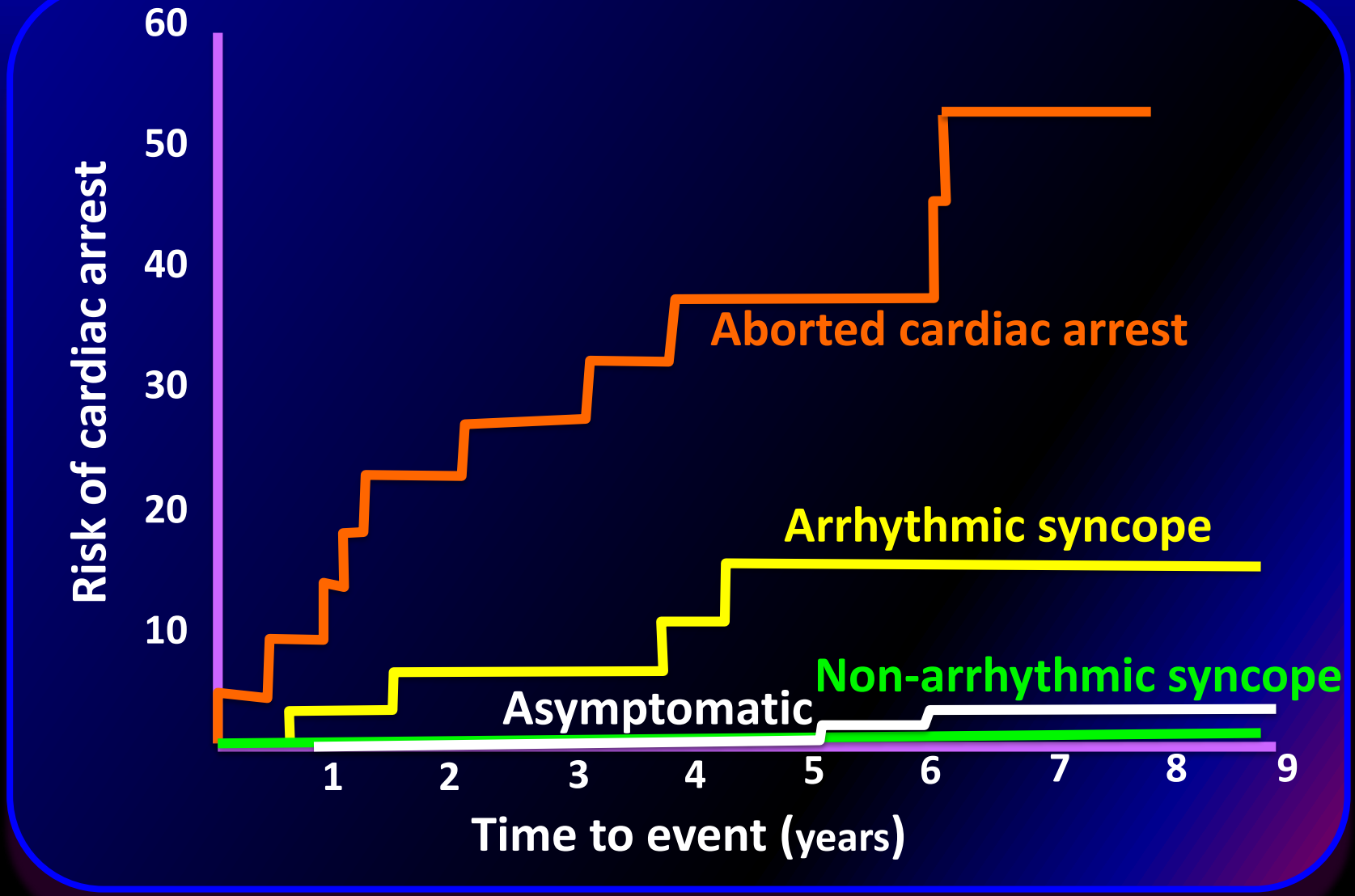
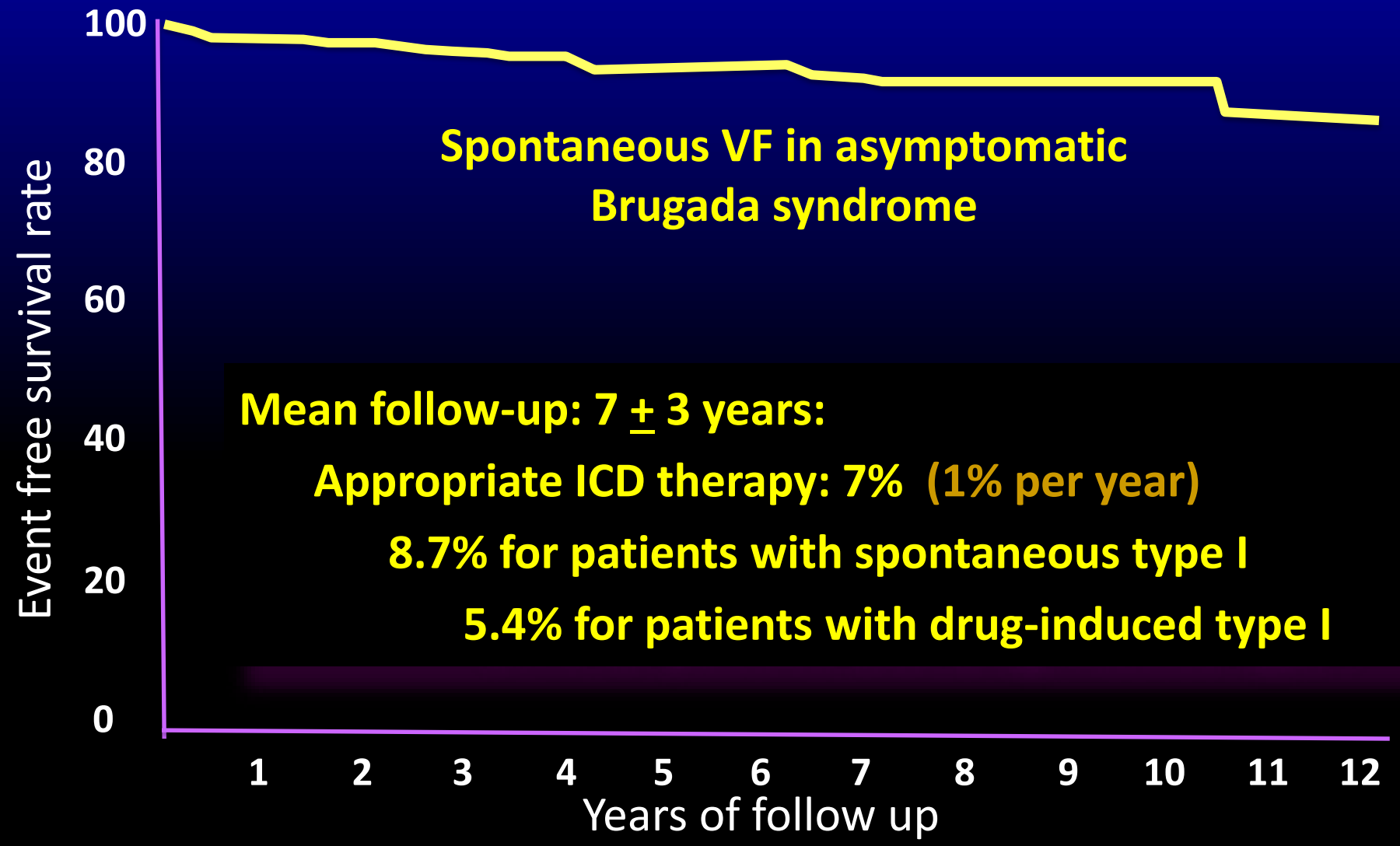
Risk of cardiac arrest in Brugada patients presenting with syncope



Olde-Nordkamp, Heart*Rhythm* 2015

Long term follow-up of 166 patients with asymptomatic Brugada who underwent ICD implantation (because of inducible VF in 84%)



Sacher, Haissaguerre et al. *Circulation* 2013

Value of VF inducibility in asymptomatic Brugada syndrome

Data for 703 patients who had EP studies.

Japanese study	FINGER	PRELUDE
Inducible VF 52 → 1 VF	Inducible VF 137 → 4 VF	Inducible VF 97 → 3 VF
Negative EPS 39 → 2 VF	Negative EPS 232 → 3 VF	Negative EPS 146 → 4 VF

Spontaneous VF if INDUCIBLE 8 of 286 = 2.7%

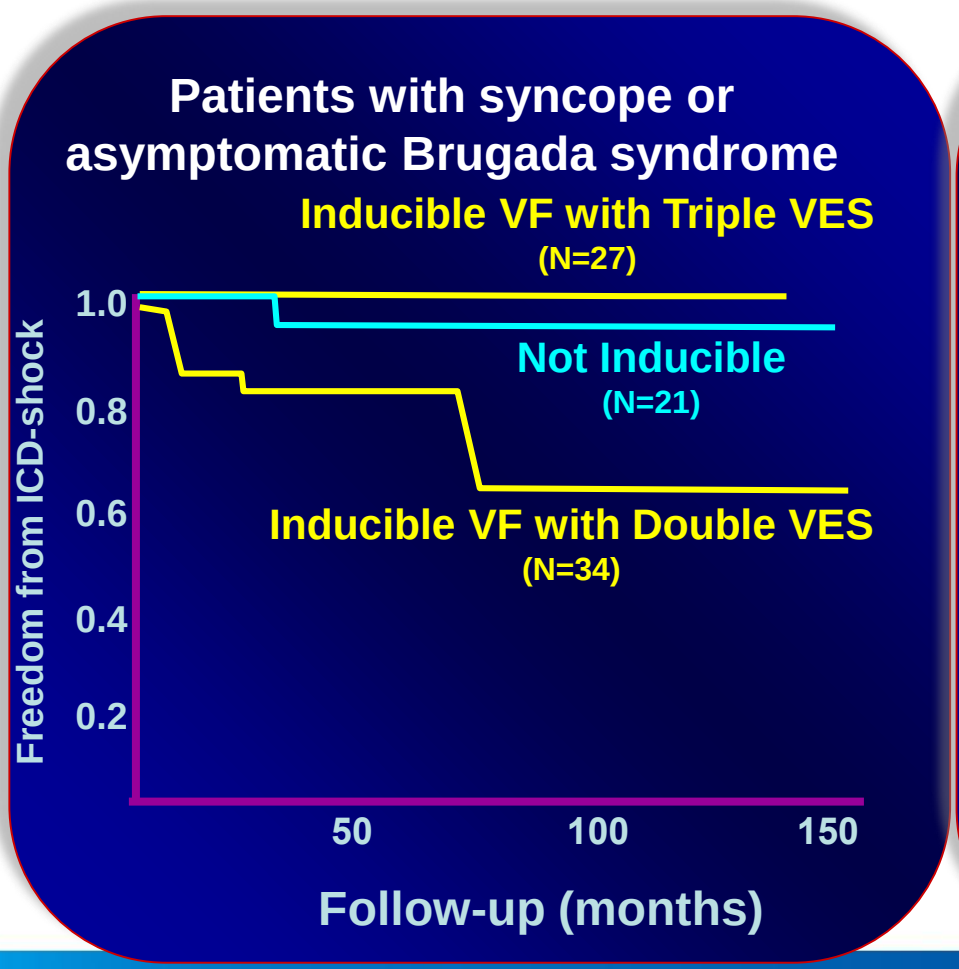
P=0.56

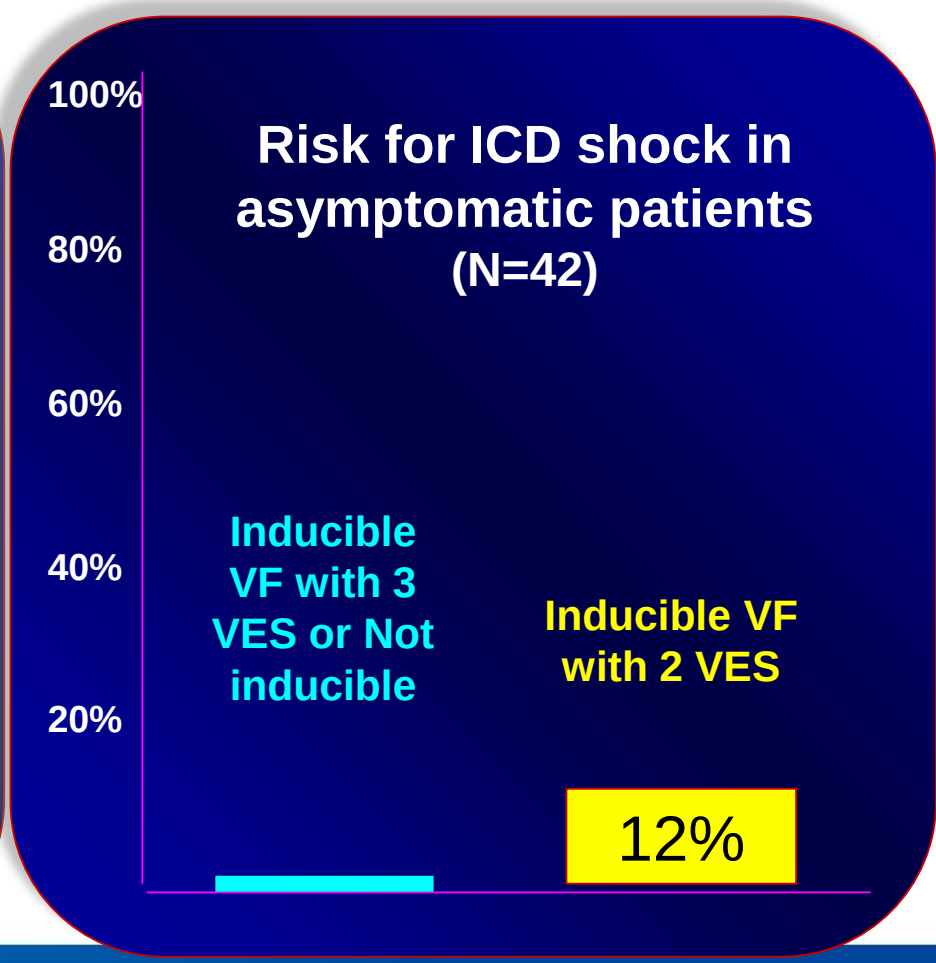
Spontaneous VF if EPS negative 9 of 417 = 2.1%

Clinical Impact of the Number of Extrastimuli in Programmed Electrical Stimulation in Patients with Brugada Syndrome.

108 consecutive patients with Brugada syndrome (VF=26, syncope=40, asymptomatic=42).
EPS: One cycle length (500 msec) and up to 3 VES (first RVA and then RVOT);
Coupling interval ≥ 180 msec.

Makimoto et al. Heart*Rhythm* 2011

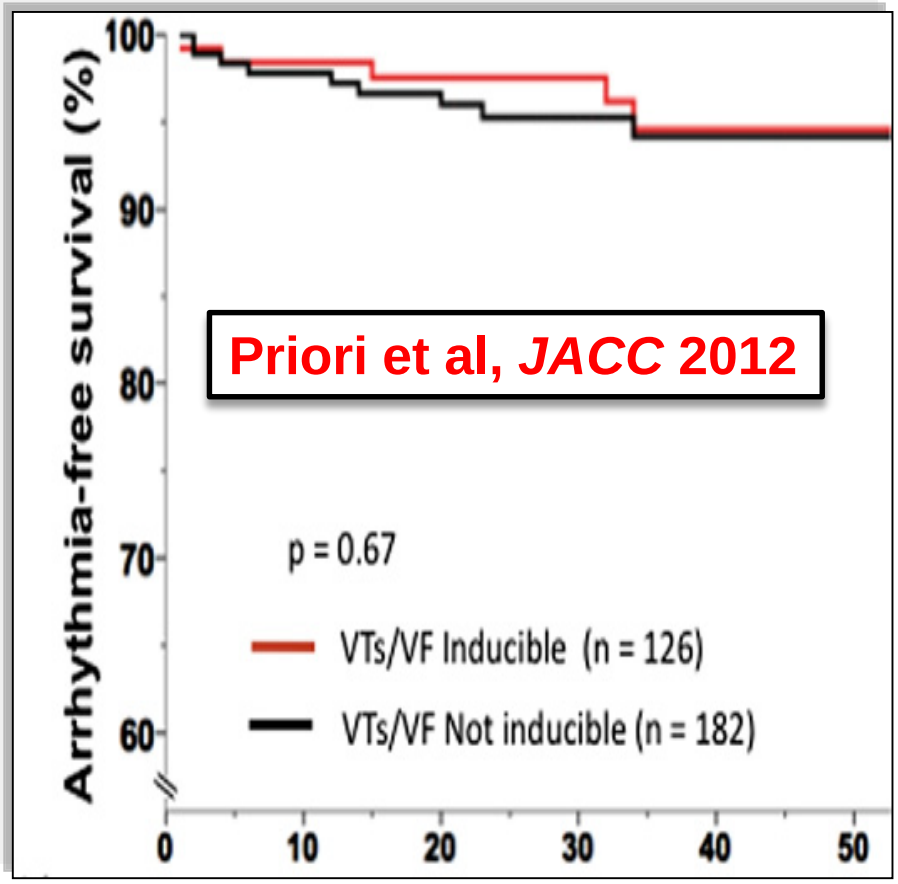




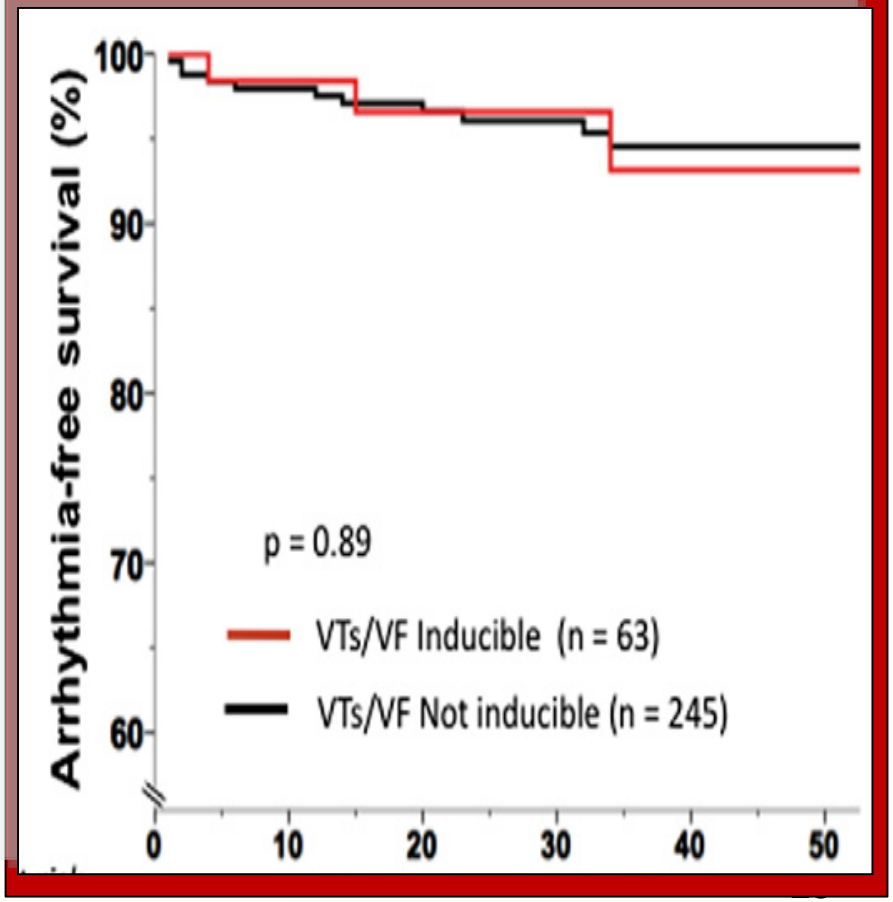
PRELUDE: 308 patients with no history of cardiac arrest (56% with type I ECG)

Inducible VF: Single 2%, double 19%, triple 26%. Total 41%

ALL PATIENTS



WITH DOUBLE VES



Takagi et al. Europace. 2018

The prognostic impact of single extra-stimulus on programmed ventricular stimulation in Brugada patients without previous cardiac arrest: multi-centre study in Japan.

Aims:

The prognostic value of programmed electrical stimulation (PES) in Brugada syndrome (BrS) remains controversial. One of the reasons for discrepant results may be due to the selection of stimulation protocol. We evaluated the prognostic value of a positive PES result (PES+) according to the inducible pacing sites and the number of extra-stimuli in BrS patients without previous cardiac arrest (CA).

Methods and results:

We enrolled 224 consecutive BrS patients without previous CA (mean age 51 ± 14 years, 209 males), who underwent PES with the identical protocol. Clinical outcomes of development of CA were explored in the patients with and without PES+ according to sites and number of extra-stimuli. During a mean follow-up period of 76 months, 12 cardiac events (CE: sudden cardiac death or documented VF) occurred (8 with and 4 without PES+). The incidence of CE was not different in patients with and without PES+, those with PES+ from RVA (n = 72) or RVOT (n = 60), and those with and without PES+ by up to 2 extra-stimuli (n = 58). However, in patients that were PES+ by a single extra-stimulus (n = 8) the incidence of CE was significantly higher than in those without PES+ (8.8 vs. 0.6%/year, $P < 0.0001$). On univariate analysis, syncope, spontaneous type 1 ECG, and PES+ by a single extra-stimulus were associated with CE.

The prognostic impact of single extra-stimulus on programmed ventricular stimulation in Brugada patients without previous cardiac arrest: multi-centre study in Japan

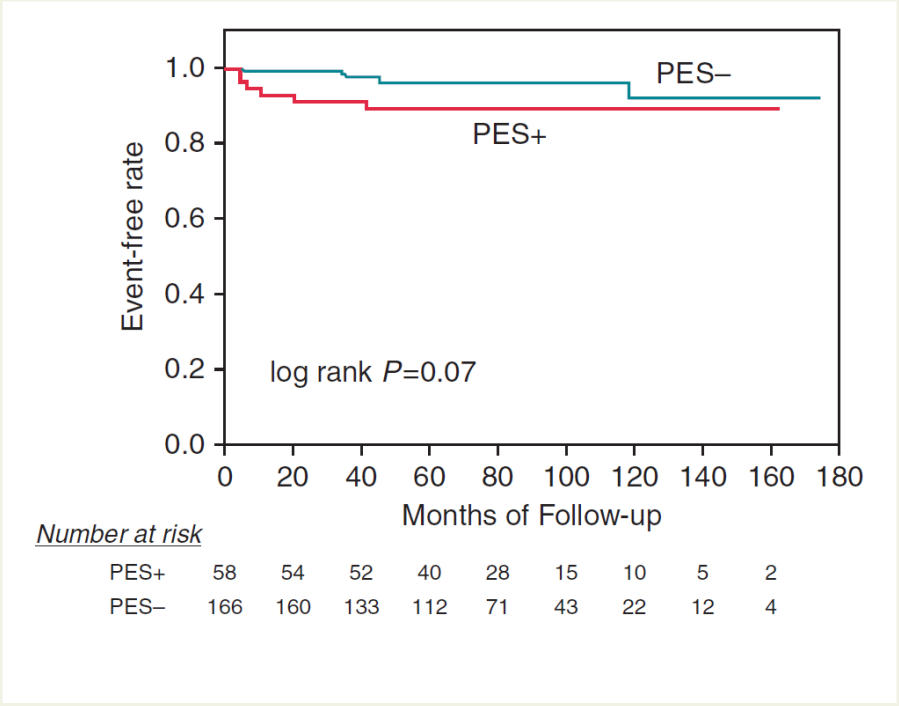


Figure 1 Survival rate according to the number of extra-stimuli. Kaplan–Meier curves for cardiac events by up to 2 ventricular extra-stimuli from right ventricular apex (RVA) or outflow tract (RVOT).

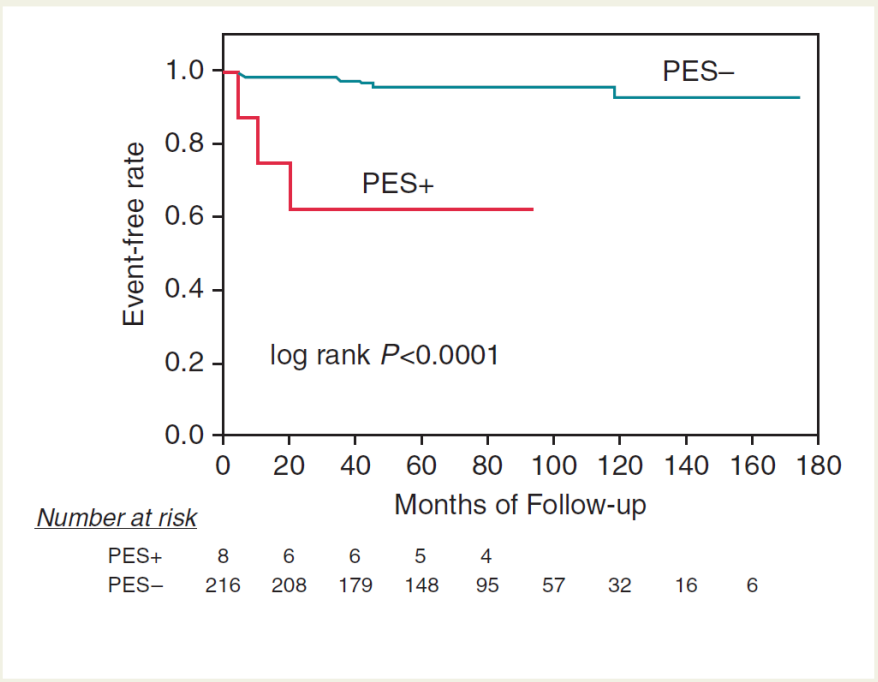


Figure 2 Survival rate according to single ventricular extra-stimuli. Kaplan–Meier curves for cardiac events by single ventricular extra-stimuli from RVA or RVOT.

(Takagi et al, Europace 2018)

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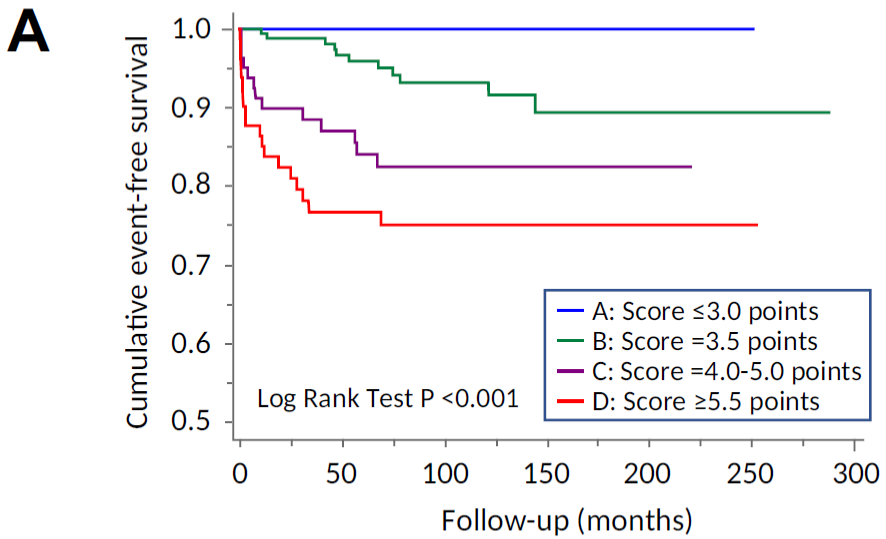
Prof. Ohno will talk about this in detail.

Shanghai scoring system is useful for risk stratification.

Kawada et al. JACC, 2018. **393 Brugada pts at a single hospital.**

FIGURE 2 **Cumulative Event-Free Survival as a Function of Score**



Numbers at risk

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D: Score ≥5.5 points	81	53	34	15	6	2	—

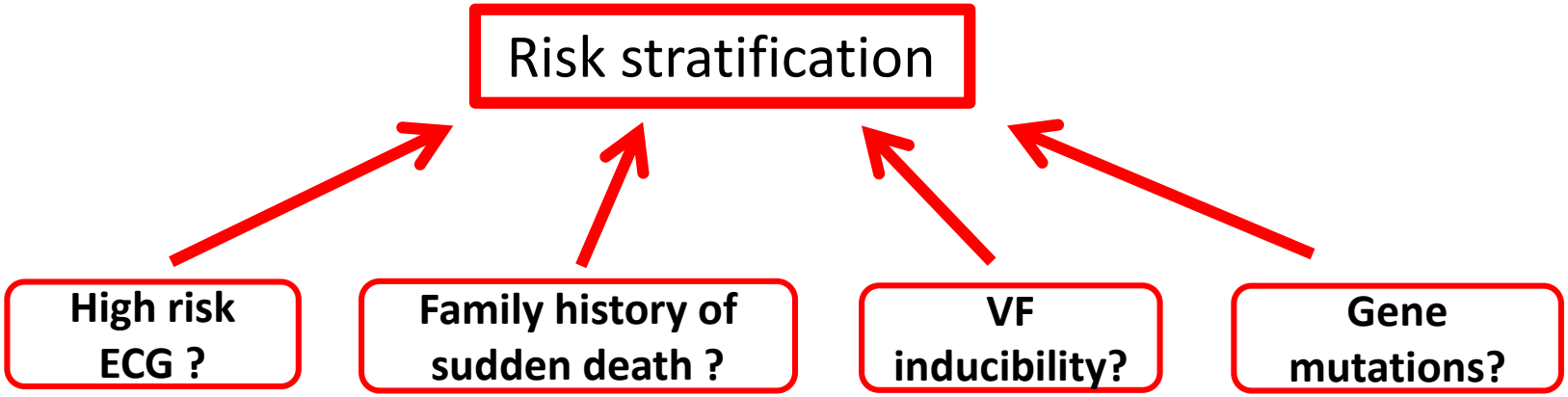
Patient Management of JWS including BrS

1. Secondary prevention

- ER resuscitated from VF ← **ICD** (Class I indication)
- ・Quinidine (adjuvant therapy)
- ・ISP (VF storm)

2. Primary prevention

- Asymptomatic individuals with ER
- ER with unexplained syncope



In summary

- As the first symptom can be cardiac arrest in Brugada syndrome, the risk stratification of asymptomatic pts is of paramount importance.
- Risk can be assessed based on 3 major categories of Shanghai scoring system: ECG, clinical history, and genetic background.

In summary

- As to the future measure, several ECG criteria would be included to the scoring system, as well as positive VF inducibility by a single extra-stimulus.
- Pathogenic SCN5A variants are currently underscored (personal opinion).

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