Sudden cardiac death in the setting of cardiac channellopaties
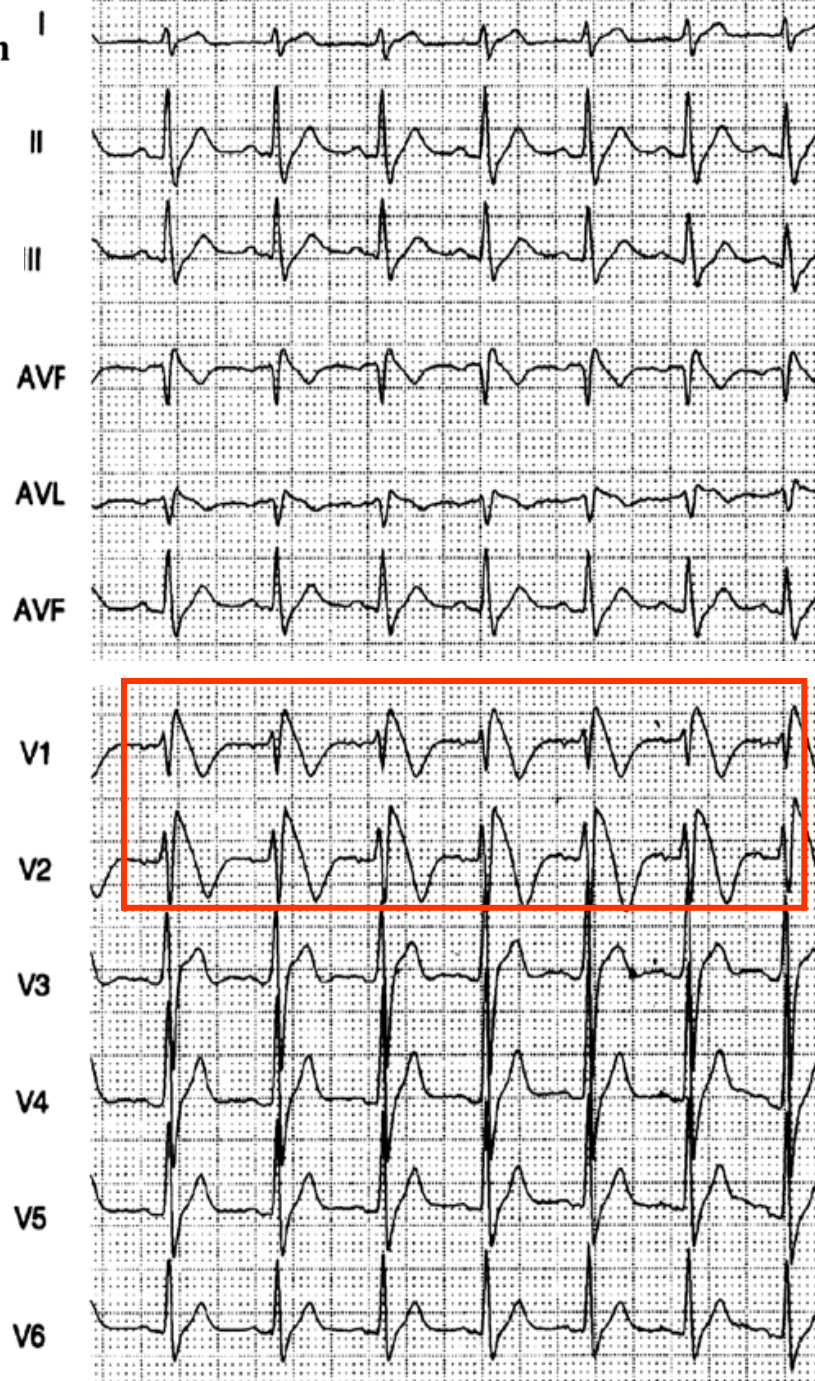
Asymptomatic Brugada Syndrome

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Right Bundle Branch Block, Persistent ST Segment Elevation and Sudden Cardiac Death: A Distinct Clinical and Electrocardiographic Syndrome

A Multicenter Report

PEDRO BRUGADA, MD, JOSEP BRUGADA, MD*†

- 1st patient identified in 1986
- 1st abstract including 4 patients in 1991 *(Brugada P, Brugada J. PACE 1991)*
- 1st paper including 8 patients in 1992 *(Brugada P, Brugada J. J Am Coll Cardiol 1992; 20, 1391-6)*

Ventricular arrhythmias in Brugada Syndrome

Table 4. Age- and Gender-Standardized Mortality of 32 Subjects With a Brugada-Type Electrocardiogram and 4,756 Control Subjects

	Brugada-Type ECG Cases (n)	Control Subjects (n)	Odds Ratio	95% Confidence Interval
Mortality from unexpected death	7	20	52.63	22.78–127.75
Mortality excluding unexpected death	9	1227	1.40	0.37–3.11
Total mortality	16	1247	2.17	1.33–3.55

Matsuo K et al. J Am Coll Cardiol 2001;38:765-770

Diagnosis
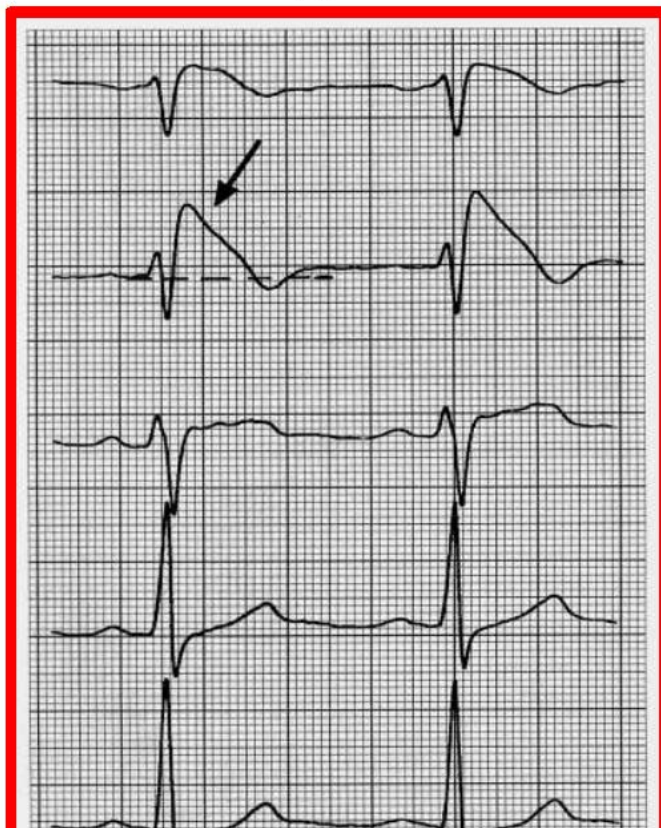
Type 1

Type 2 & 3

	Type 1
J wave amplitude	≥2 mm
T wave	negative
ST-T configuration	coved type
ST segment (terminal portion)	gradually descending
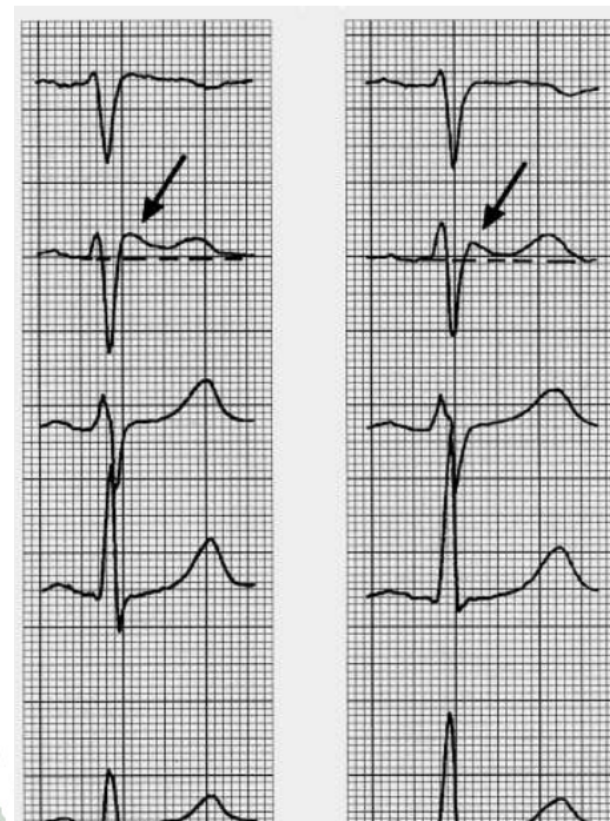
	Type 2	Type 3
	≥2 mm	≥2 mm
	positive or biphasic	positive
	saddleback	saddleback
	elevated ≥1 mm	elevated <1 mm

1 mV

500ms

Wilde A et al. Circ 2002;106:2514-19.

Diagnosis

•**Spontaneous fluctuation**:

   •33% of patients with initially positive ECG and non-diagnostic ECG in follow-up (17 months).

   •19% of patients with initially normal ECG and diagnostic ECG in follow-up (17 months).

•**Changes in the ECG pattern**:

Factors that increase ST elevation:
- **Vagal predominance → ↓ Ca, ↑ K**
- **High temperature → ↓ Na**
- **Drugs that inhibit Na^+ or Ca^{2+} channels or K openers**

Antiarrhythmic:
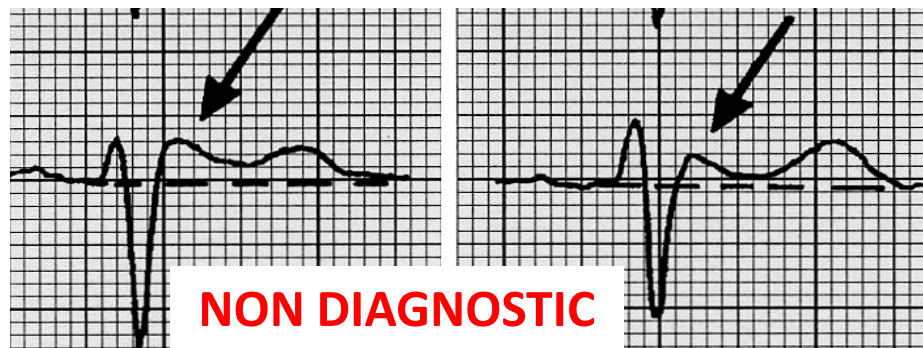- Na-blockers
- Ca-blockers
- b-blockers
Psychotropic agents
Other: anti-H_1

Veltmann et al. Eur Heart J 2006

Dumaine et al. Circ Res 1999;85:803-809

Antzelevitch. Pacing Clin Electrophysiol 2006

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Diagnosis

Type 1 "Coved"
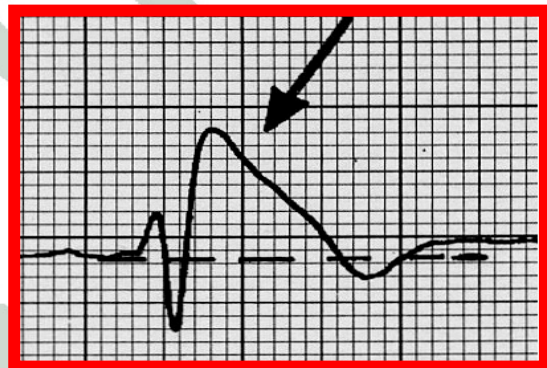
Type 2 & 3 "Saddle back"

**NON DIAGNOSTIC**

Brugada syndrome should be considered:
- Type 1 ECG pattern spontaneously (± sodium blockers), **AND**
- ≥1 of the following clinical manifestations:
  - Sudden death.
  - Documented PVT/VF.
  - Non-vasovagal syncope / nocturnal agonic respiration.
  - Family history of SD in patients <45.
  - Type 1 ECG pattern in families.

Atzelevich C. et al Circulation. 2005;111:659-670

Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes

Silvia G. Priori, (HRS Chairperson)[1], Arthur A. Wilde, (EHRA Chairperson)[2], Minoru Horie, (APHRS Chairperson)[3], Yongkeun Cho, (APHRS Chairperson)[4], Elijah R. Behr[5], Charles Berul[6], Nico Blom[7*], Josep Brugada[8], Chern-En Chiang[9], Heikki Huikuri[10], Prince Kannankeril[11‡], Andrew Krahn[12], Antoine Leenhardt[13], Arthur Moss[14], Peter J. Schwartz[15], Wataru Shimizu[16], Gordon Tomaselli[17†], Cynthia Tracy[%18]

Type 1 "Coved"
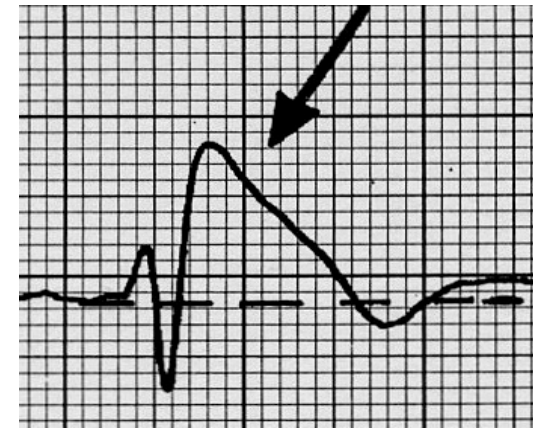
1. BrS **is diagnosed** in patients with ST segment elevation with **type 1** morphology ≥2 mm in ≥ 1 lead among the right precordial leads V1,V2, positioned in the 2nd, 3rd or 4th intercostal space occurring either spontaneously or after provocative drug test with intravenous administration of Class I antiarrhythmic drugs.

2. BrS **is diagnosed** in patients with type 2 or type 3 ST segment elevation in ≥ 1 lead among the right precordial leads V1,V2 positioned in the 2nd, 3rd or 4th intercostal space when a provocative drug test with intravenous administration of Class I antiarrhythmic drugs induces a **type 1** ECG morphology
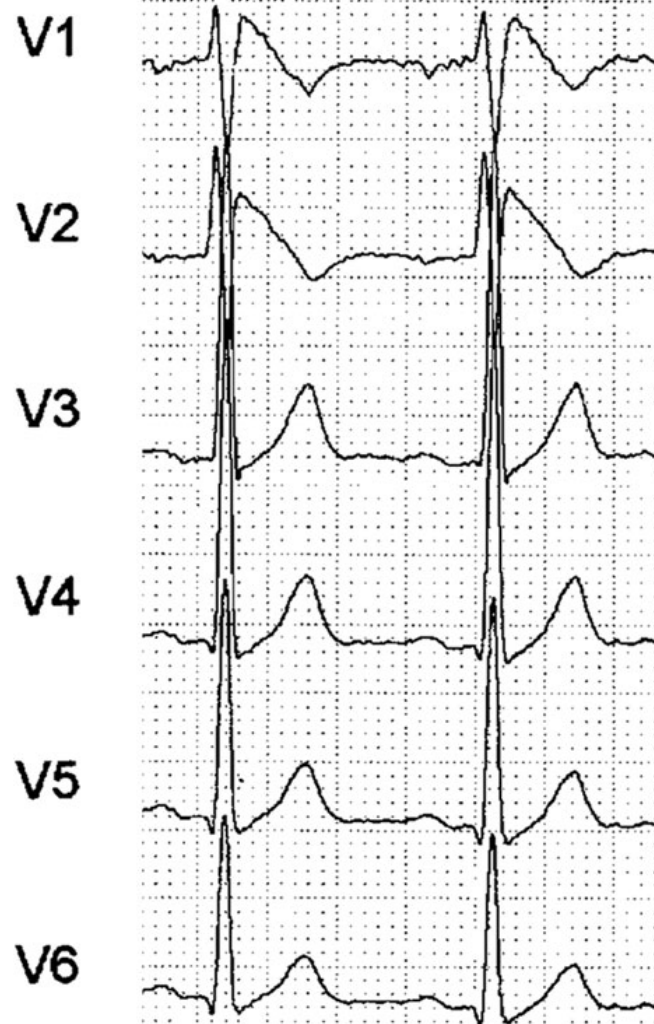
Diagnosis

4th intercostal space (non-diagnostic) — V1, V2, V3, V4, V5, V6
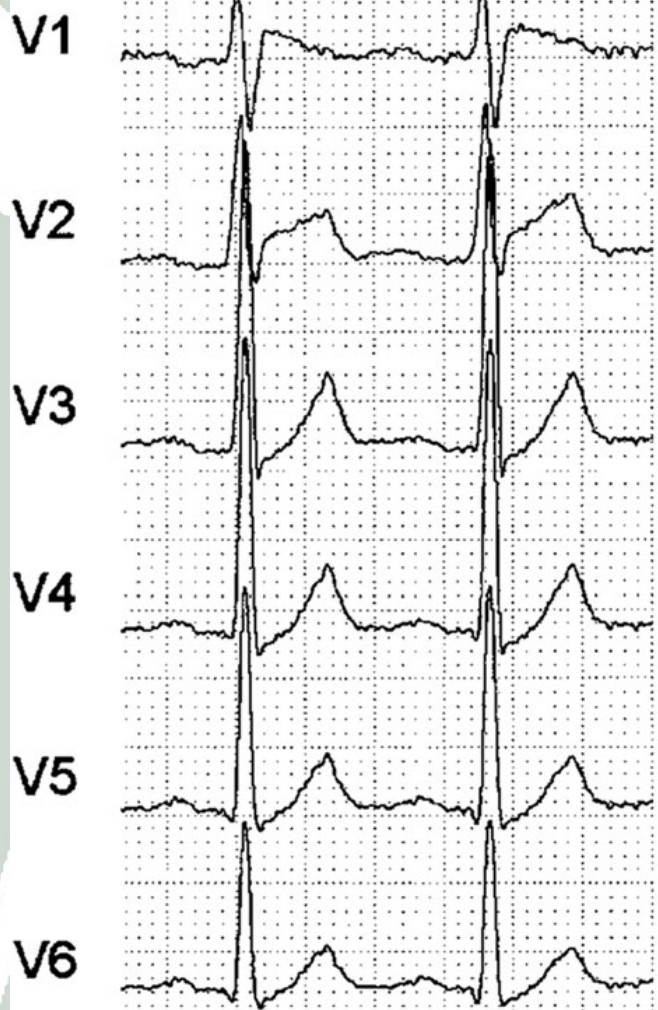
3rd intercostal space (diagnostic) — V1, V2, V3, V4, V5, V6

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Diagnosis

Pharmacological Tests

Suspicion of BrS and a non-diagnostic ECG

⬇

Drug challenge tests

Drug	Dosage and Administration
Ajmaline	1 mg/kg over 5 min, IV
Flecainide	2 mg/kg over 10 min, IV (400 mg, PO)
Procainamide	10 mg/kg over 10 min, IV
Pilsicainide	1 mg/kg over 10 min, IV

Ajmaline infusion

Baseline
V1
V2
V3
V4
V5
V6

Minute 5
V1
V2
V3
V4
V5
V6

Hong K et al. Circ 2004;110:3023–7.

Meregalli PG et al. J Cardiovasc Electrophysiol 2006;17:857–64.
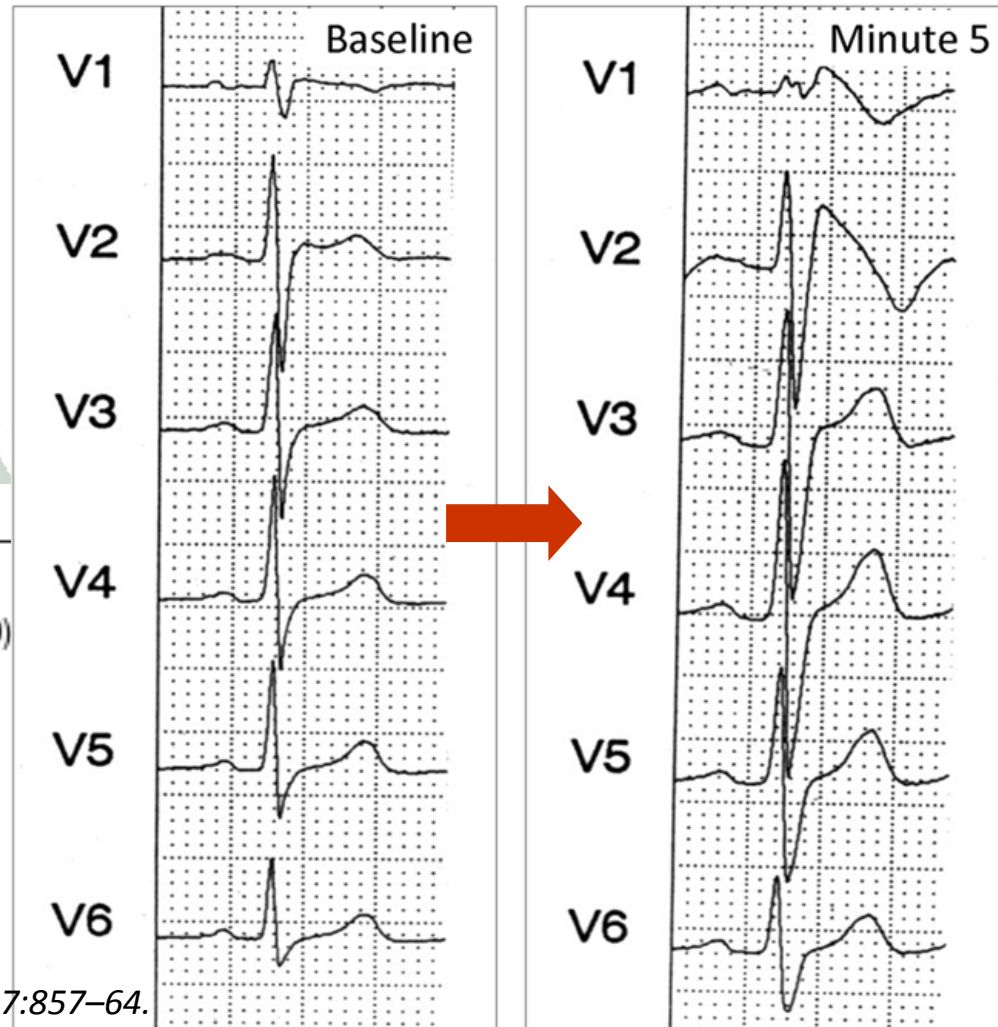
proband
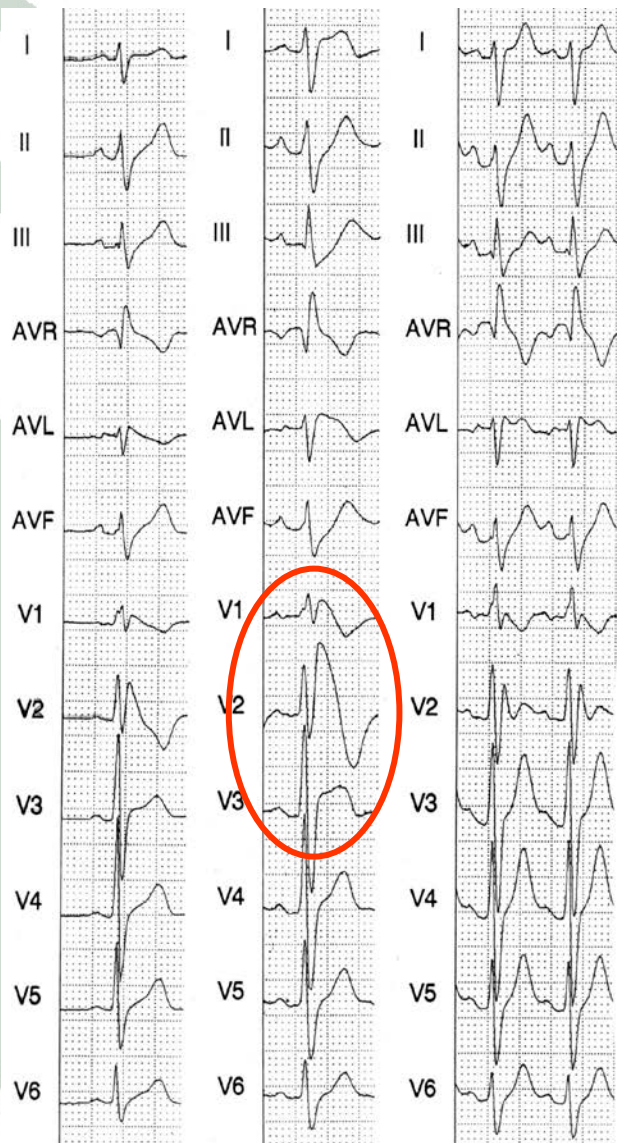
brother

basal ajmaline isoprot
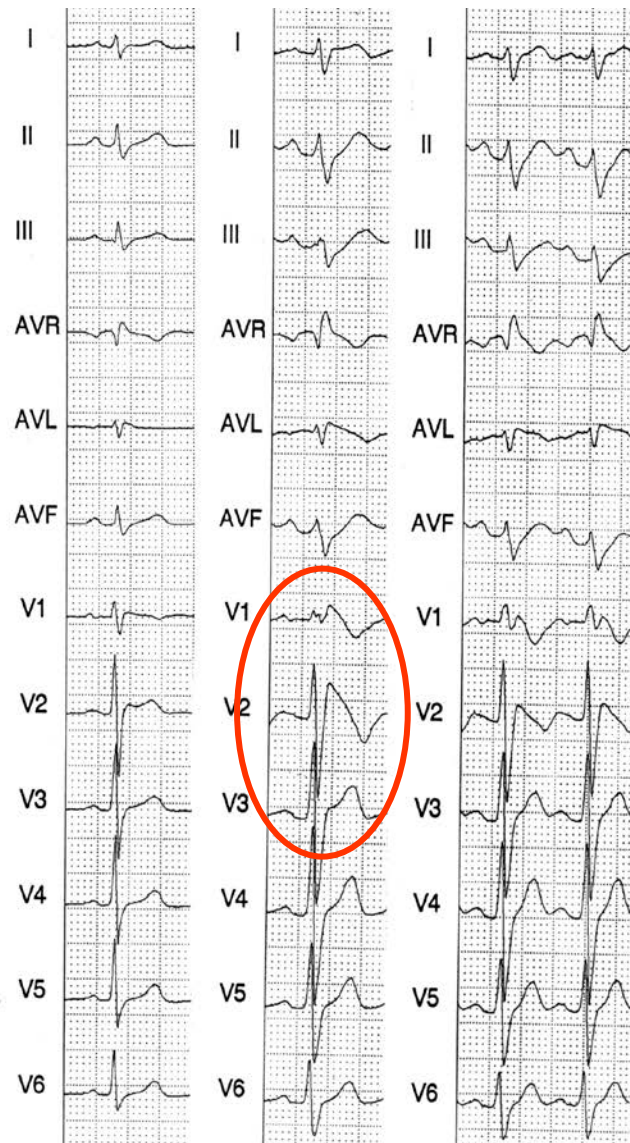
basal ajmaline isoprot

Risk Stratification
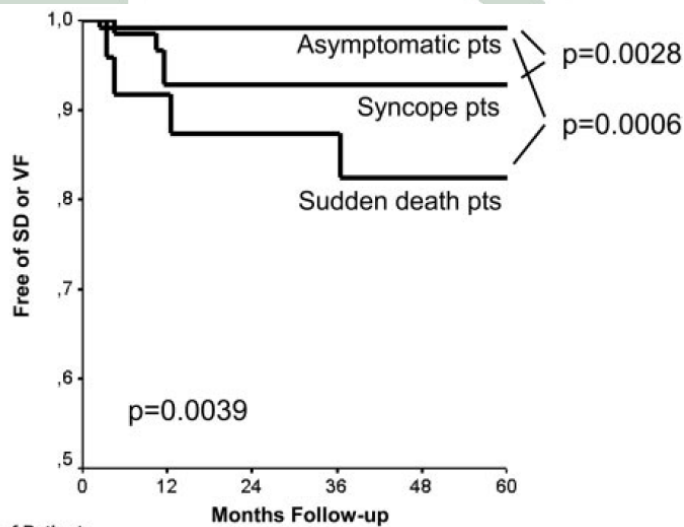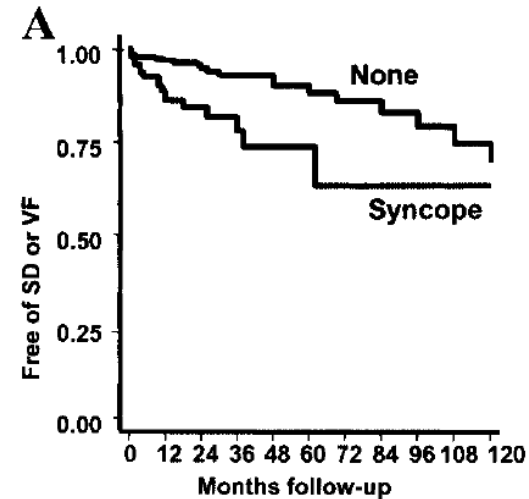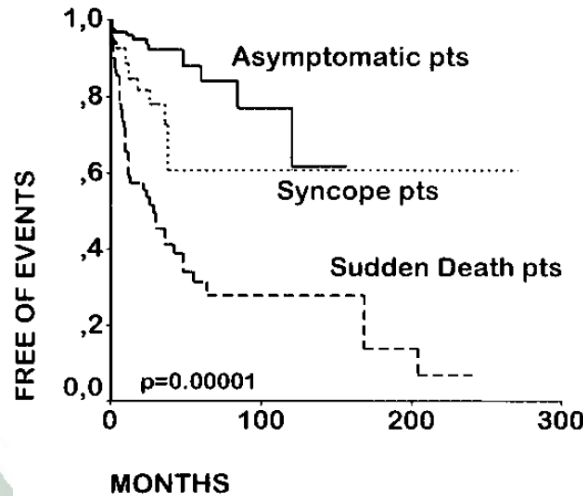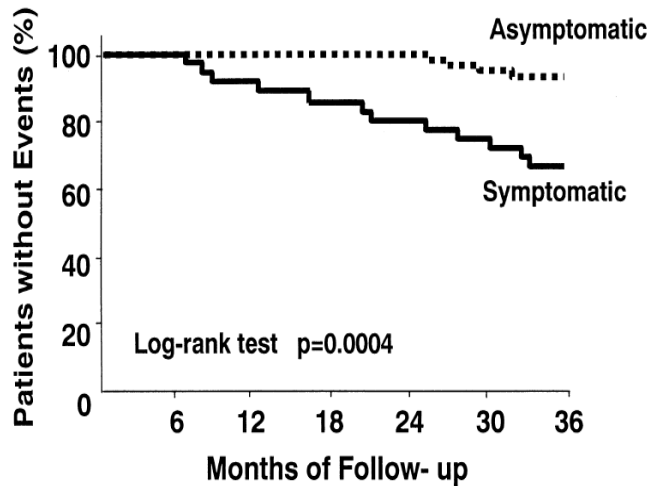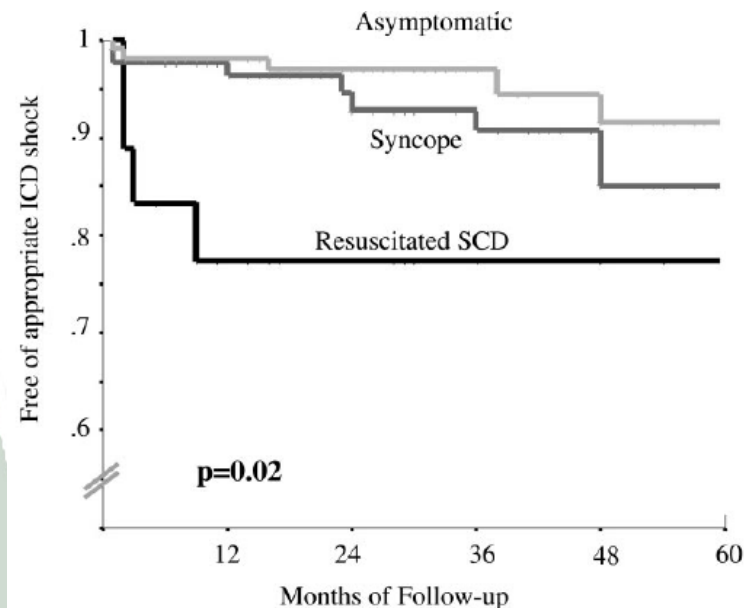
Atarashi H, et al. J Am Coll Cardiol 2001;37:1916-1920
Brugada J, et al.Circ 2002;105:73-78
Brugada J, et al. Circ 2003;108:3092-3096

Eckardt L, et al. Circ 2005;111:257-263
Sacher F, et al. Circ 2006;114:2317-2324

Risk Stratification

Asymptomatic patients with a spontaneous type 1 ECG with events
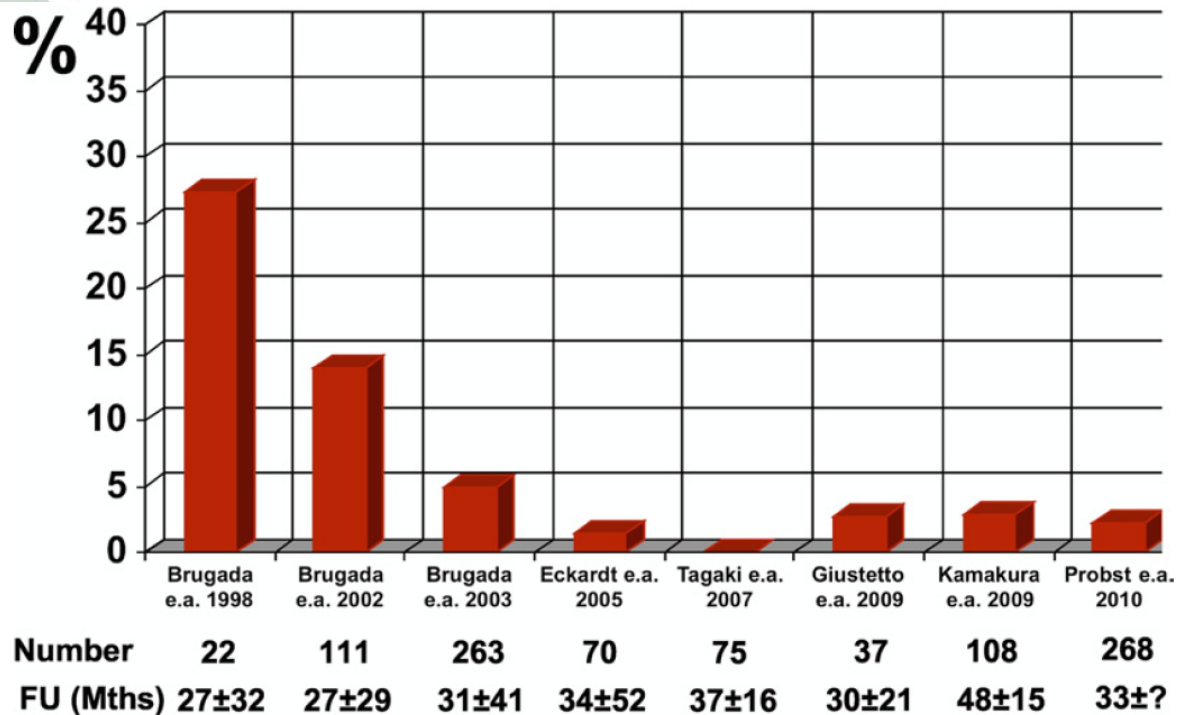
	Brugada et al. (11), 2003	FINGER (14)*	PRELUDE	Delise et al. (15), 2011
n	547	967	308	320
Average follow-up (months)	24	32.5	36	40
Number of patients with syncope before enrollment (%)	124 (23%)	313 (32%)	64 (21%)	105 (34%)
Spontaneous type 1 ECG (%)	391 (71%)	437 (45%)	171 (56%)	174 (54%)
Arrhythmic events at follow-up	45 (8.2%)	29 (2.9%)	14 (4.5%)	17 (5.3%)
Annual arrhythmic event rate	4.1%	1.1%	1.5%	1.6%
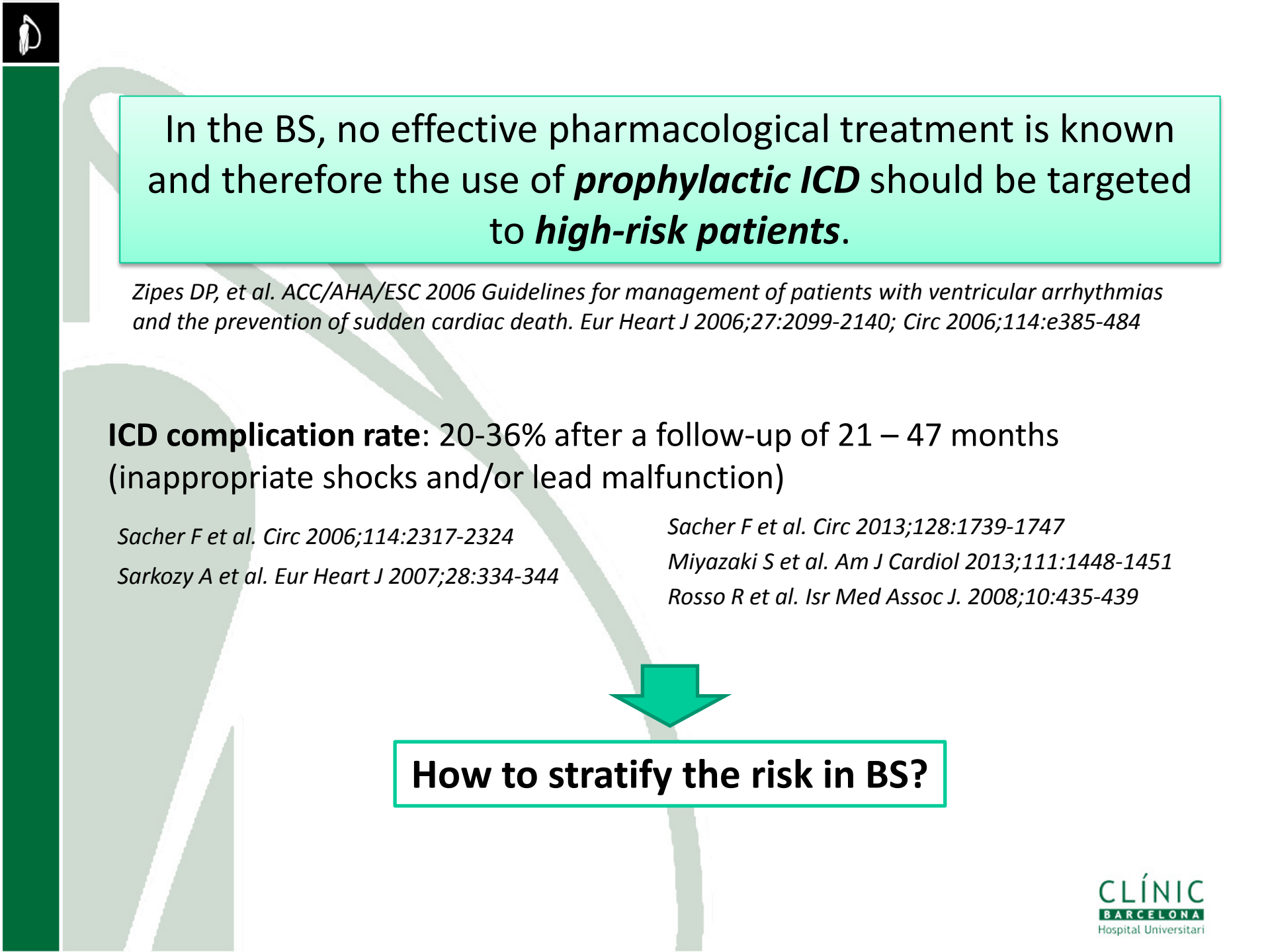
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Risk Stratification

Asymptomatic patients with a spontaneous type 1 ECG with events

- ✓ 1-2% annual risk of adverse event (SCD/VF).

- ✓ 50% of patients the first symptom will be SCD/VF.

How to manage this patients?

- ✓ A 1-2% risk of events is too high → ICD for everyone?

- ✓ A 1-2% risk of events is acceptable → Clinical follow-up?

- ✓ A 1-2% risk of events is not too high, nor acceptable → What to do???

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In the BS, no effective pharmacological treatment is known and therefore the use of *prophylactic ICD* should be targeted to *high-risk patients*.

Zipes DP, et al. ACC/AHA/ESC 2006 Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J 2006;27:2099-2140; Circ 2006;114:e385-484

ICD complication rate: 20-36% after a follow-up of 21 – 47 months (inappropriate shocks and/or lead malfunction)

Sacher F et al. Circ 2006;114:2317-2324

Sarkozy A et al. Eur Heart J 2007;28:334-344

Sacher F et al. Circ 2013;128:1739-1747

Miyazaki S et al. Am J Cardiol 2013;111:1448-1451

Rosso R et al. Isr Med Assoc J. 2008;10:435-439

How to stratify the risk in BS?

Prognostic Value of electrophysiologic Investigations in Brugada Syndrome

252 individuals with an ECG diagnostic of Brugada syndrome

116 symptomatic   FU 34±32   136 asymptomatic

inducible 73%   **P = 0.0001**   **inducible 33%**

44/54 (81.5%) resuscitated from near sudden death

7.5% developed recurrent arrhythmic events

41/62 (66%) syncopal episodes of unknown origin

39% developed recurrent arrhythmic events

Programmed electrical stimulation:
- Sensitivity 94%
- Specificity 59.5%
- Overall accuracy of 67%

Brugada P et al. J Cardiovasc Electrophysiol 2001;12(9):1004-7.

Prognostic Value of electrophysiologic Investigations in Brugada Syndrome

Statistical Data on the Predictive Value of Programmed Ventricular Stimulation in Patients with Brugada Syndrome Depending on Presenting Symptoms

	Asymptomatic	Symptomatic	Syncope	Near SCD	Total
N	136	116	62	54	252
Sensitivity (%)	86	95.5	92	97	94
Specificity (%)	70	41	41	41	59
Positive predictive value (%)	13	50.5	29	70	37
Negative predictive value (%)	99	93.5	95	90	97
False-positive rate (%)	30	59	59	59	40
False-negative rate (%)	14	4.5	7	3	6
Overall accuracy (%)	70.5	62	51	74	67
RR	2.8	1.6	1.6	1.6	2.3
95% CI of RR	1.9–4.2	1.3–1.9	1.2–2.1	1.1–2.3	1.9–2.8
P value	0.005	<0.0001	0.022	0.001	<0.0001

1. **Inducibility of sustained ventricular arrhythmias is a good predictor of outcome in Brugada syndrome.**
2. **Symptomatic patients** → ICD even if not inducible.
3. **Asymptomatic patients** → reassured if noninducible.

Longer HV in the asymptomatic individuals who became symptomatic during follow-up compared with those who did not develop symptoms (59 ± 8 ms vs 48 ± 11 ms; P = 0.04).

Brugada P et al. J Cardiovasc Electrophysiol 2001;12(9):

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Natural History of Brugada Syndrome
Insights for Risk Stratification and Management

200 probands (152 men; mean age, 43 years)
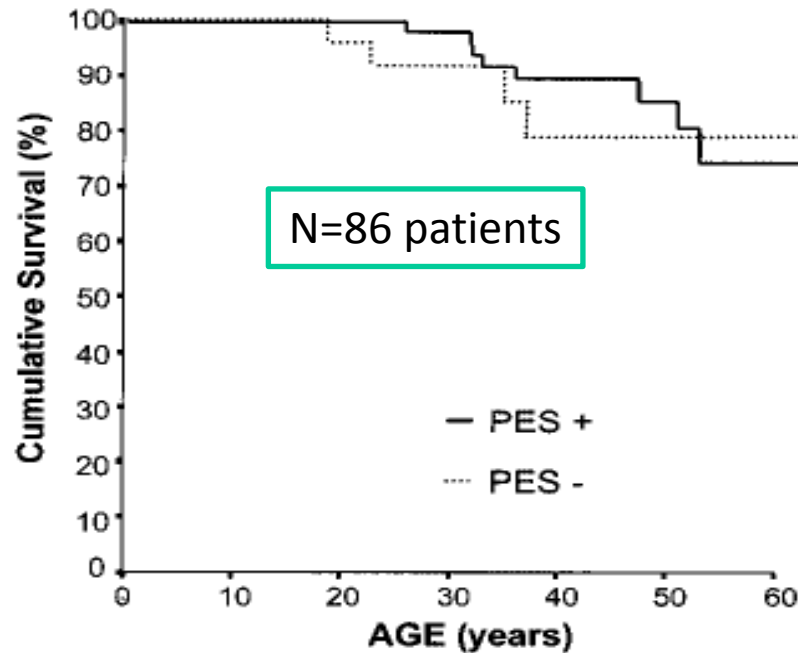
N=86 patients

N. of Patients:

PES +: 58	56	54	48	30	17	9
PES -: 29	27	25	20	11	6	1

✓ Evaluation of cardiac events that occurred between birth and the last follow-up (mean 41 y)
✓ the stimulation protocols of PES were not identical
✓ Induction of VF or sustained polymorphic ventricular tachycardia in 66%

2 premature stimuli
- Sensitivity = 75%
- Specificity = 36%

3 premature stimuli
- Sensitivity = 50%
- Specificity = 33%

Patients inducible at PES <u>do not have increased risk </u>of cardiac arrest as compared with noninducible individuals.

Priori S et al. Circ 2002;105:1342-1347

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Natural History of Brugada Syndrome
Insights for Risk Stratification and Management

Cox regression analysis of cumulative survival from cardiac arrest

→ syncope with negative ECG pattern at baseline

↘ history of syncope

↘ positive ECG at baseline only

↘ positive ECG at baseline + history of syncope

HR, 6.4; 95%
(CI 1.9-21; *P* 0.002)

Significant increase of the risk of death, even after adjustment for sex, family history of SD, and presence of a *SCN5A* gene mutation

Priori S et al. Circ 2002;105:1342-1347

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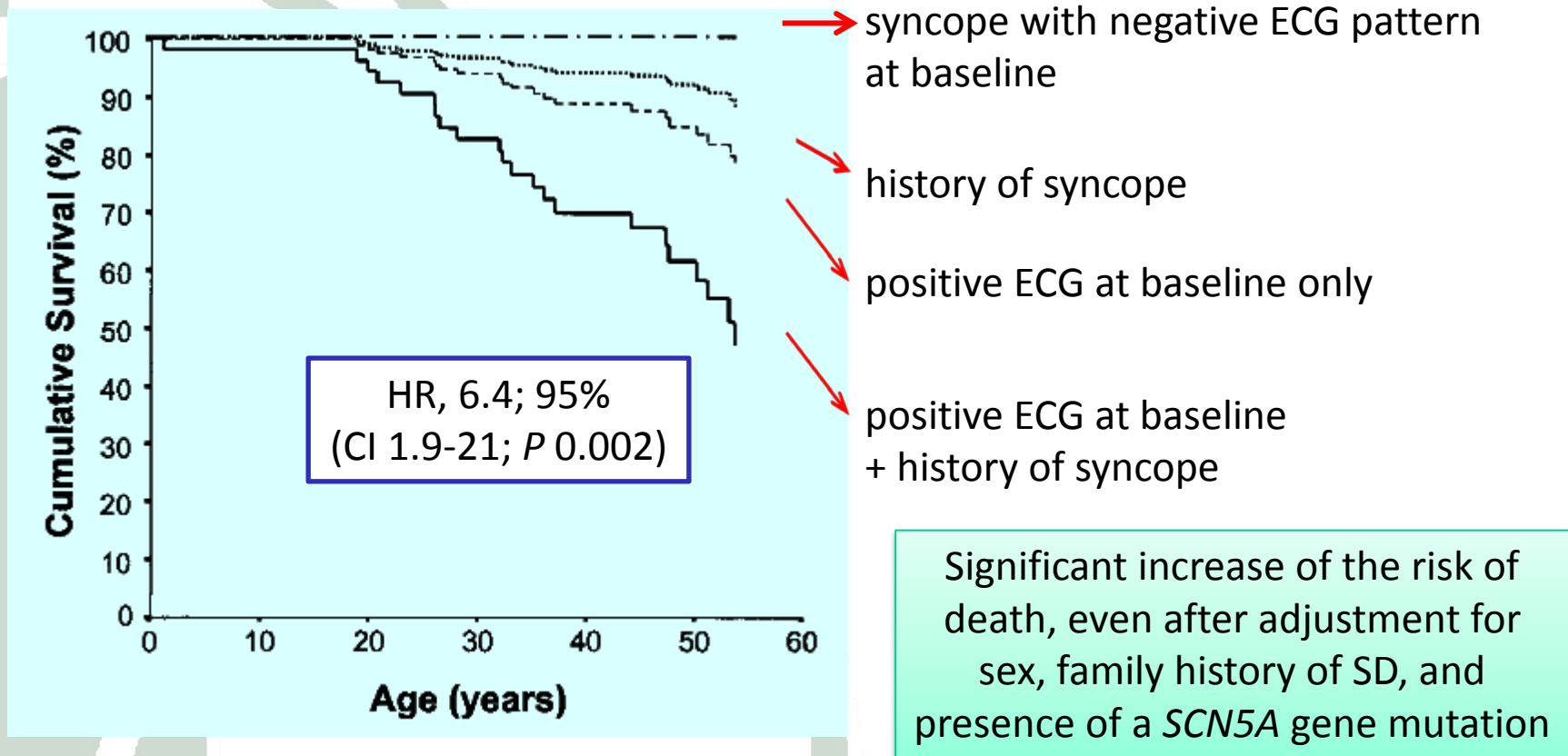
Natural History of Brugada Syndrome
Insights for Risk Stratification and Management

Risk stratification according to distribution of clinical variables in BS
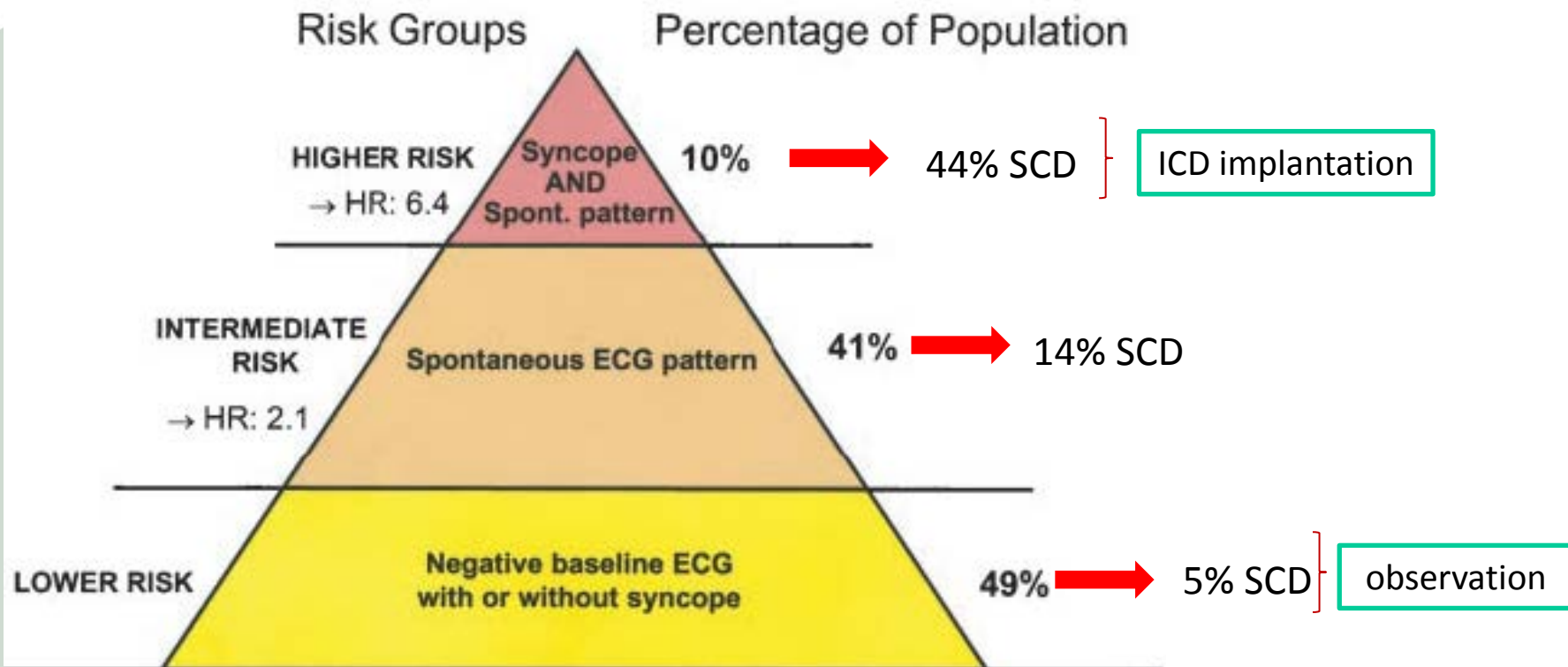
Risk Groups | Percentage of Population

HIGHER RISK → HR: 6.4 — Syncope AND Spont. pattern — 10% → 44% SCD — ICD implantation

INTERMEDIATE RISK → HR: 2.1 — Spontaneous ECG pattern — 41% → 14% SCD

LOWER RISK — Negative baseline ECG with or without syncope — 49% → 5% SCD — observation

Priori S et al. Circ 2002;105:1342-1347

Determinants of Sudden Cardiac Death in Individuals With the Electrocardiographic Pattern of Brugada Syndrome and No Previous Cardiac Arrest

547 individuals with an ECG compatible with Brugada syndrome and no demonstrable structural heart disease

mean follow up 24±33 months

Cardiac events 8.2%
SCD (n=16) or VF (n=29)
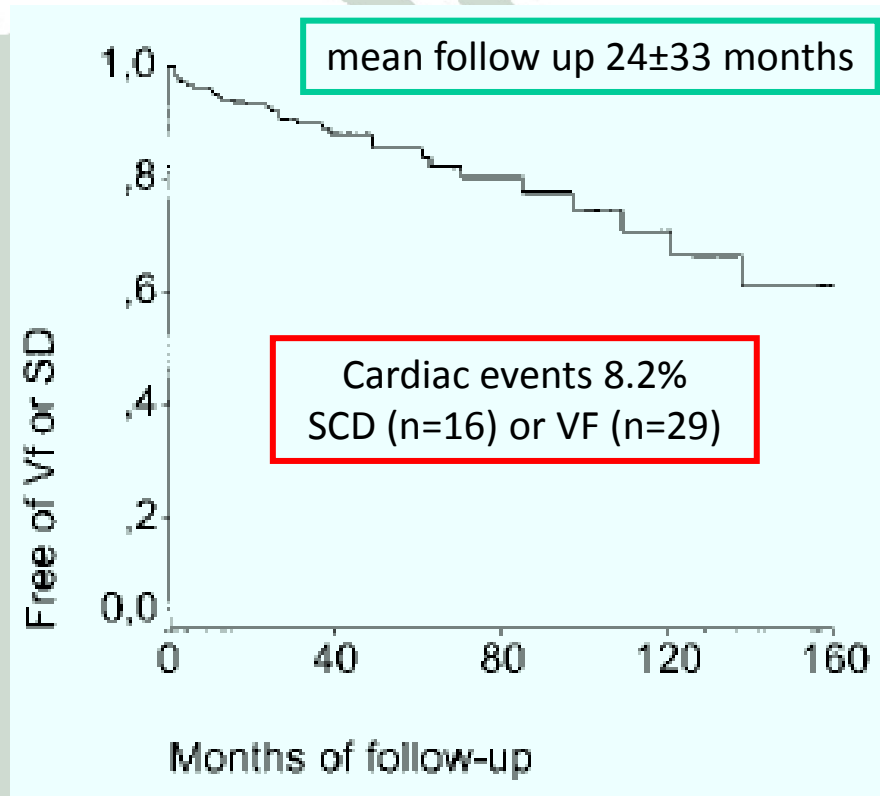
- **Electrophysiological study**:
  - ✓ basal measurements of conduction intervals + programmed ventricular stimulation.

- **Protocol**:
  - ✓ single site of stimulation (right ventricular apex),
  - ✓ 3 basic pacing cycles (600, 500, 430 ms), and induction of 1, 2, and 3 ventricular premature beats (minimum 200 ms).

Brugada J et al. Circulation 2003;108:3092-3096.

Determinants of Sudden Cardiac Death in Individuals With the Electrocardiographic Pattern of Brugada Syndrome and No Previous Cardiac Arrest

TABLE 2. Probability of Sudden Death or Ventricular Fibrillation During Follow-Up Depending on Clinical and Electrophysiological Variables

	Univariate Analysis			Multivariate Analysis		
	Hazard Ratio	95% CI	P	Hazard Ratio	95% CI	P
Inducible	8.33	2.8–25.0	0.0001	5.88	2.0–16.7	0.0001
Noninducible	1	…	…	1	…	…
Syncope	2.79	1.5–5.1	0.002	2.50	1.2–5.3	0.017
No syncope	1	…	…	1	…	…
Basal ECG	7.69	1.9–33.3	0.0001	2.86	0.7–12.3	0.103
AAD ECG	1	…	…	1	…	…
Male	5.26	1.6–16.6	0.001	…	…	…
Female	1	…	…	…	…	…
Family history	1.29	0.7–2.4	0.406	…	…	…
No family history	1	…	…	…	…	…

Basal ECG indicates spontaneously abnormal ECG; AAD ECG, abnormal ECG only after antiarrhythmic drug administration.

Brugada J et al. Circulation 2003;108:3092-3096.

Determinants of Sudden Cardiac Death in Individuals With the Electrocardiographic Pattern of Brugada Syndrome and No Previous Cardiac Arrest

TABLE 3. Logistic Regression Analysis: Probability of Events (Sudden Death or Documented Ventricular Fibrillation) During Follow-Up

	Noninducible, % (CI)	Inducible, % (CI)
Spontaneously abnormal ECG		
Syncope	4.1 (1.4–11.7)	27.2 (17.3–40.0)
No syncope	1.8 (0.6–5.1)	14.0 (8.1–23.0)
ECG abnormal only after antiarrhythmic drug challenge		
Syncope	1.2 (0.2–6.6)	9.7 (2.3–33.1)
No syncope	0.5 (0.1–2.7)	4.5 (1.0–17.1)

risk of SCD during FU 27.2%

risk of SCD during FU 0.5%

Lowest-risk group:
- ✓ Drug-induced type 1 ECG
- ✓ Not inducible during PVS
- ✓ No previous syncope

Highest-risk group:
- ✓ Spontaneous (baseline) type 1 ECG
- ✓ VF/VT inducible during PVS
- ✓ ≥1 syncopal episode.

Brugada J et al. Circulation 2003;108:3092-3096.

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Registries	N	Patient type	Follow-up (months)	Rate of events
Giustetto et al	166	ECG type 1 43% spontaneous 57% drug-induced	30 ± 21	2.2 /100 person-year SD: 60% Syncope: 8.6% Asymptomatic: 1%
Kamakura et al	330 245 pts with ECG type 1	ECG type 1 71% spontaneous 29% drug-induced	48.7 ± 15	SCD: 10.2%/y Syncope: 0.6/y Asymptomatic: 0.5%/y
Probst et al (FINGER)	1029	ECG type 1 45% spontaneous 55% drug-induced	32 (14 - 54)	Annual event rate: 1.1% SCD: 7.7%/y Syncope: 1.9%/y Asymptomatic: 0.5%/y
Delise et al	320	No SCD or VT ECG type 1 54% spontaneous 46% drug-induced	40 (20 - 67)	Annual event rate: 1.6% SCD: -- (not included) Syncope: 3%/y Asymptomatic: 0.8%/y
Priori et al (PRELUDE)	308	No SCD or VT ECG type 1 56% spontaneous 44% drug-induced	36 ± 8	Annual event rate: 1.5%

Giustetto C et al. Europace 2009;11:507-513

Kamakura S, et al. Circ Arrhyth Electrophysiol 2009;2:495-503

Probst V et al. Circ 2010;121:635-643

Priori SG, et al. J Am Coll Cardiol 2012;59:37-45

Delise P et al. Eur Heart J 2011;32:169-176

Risk stratification of the patients with Brugada type electrocardiogram: a community-based prospective study

N=166

EPS
N= 135 (81%)

No EPS
N= 31 (19%)

Aborted SCD
N= 4 (3%)

Syncope
N= 50 (37%)

Asymptomatic
N= 81 (60%)

**3 (75%)
(+) EPS**

**26 (52%)
(+) EPS** *

**17 (21%)
(+) EPS**

Inducibility EPS (Log.Reg.)
Syncope (OR=4.24; p=0.001)
Male   (OR= 11.1; p= 0.02)

(+) EPS: 46 / 135 (34%)

RV Apex N= 15 (33%)

RVOT   N= 31 (67%)

(◆ p= 0.0001)

* *No difference according to prodromes*

Giustetto C et al. Europace 2009;11:507-513
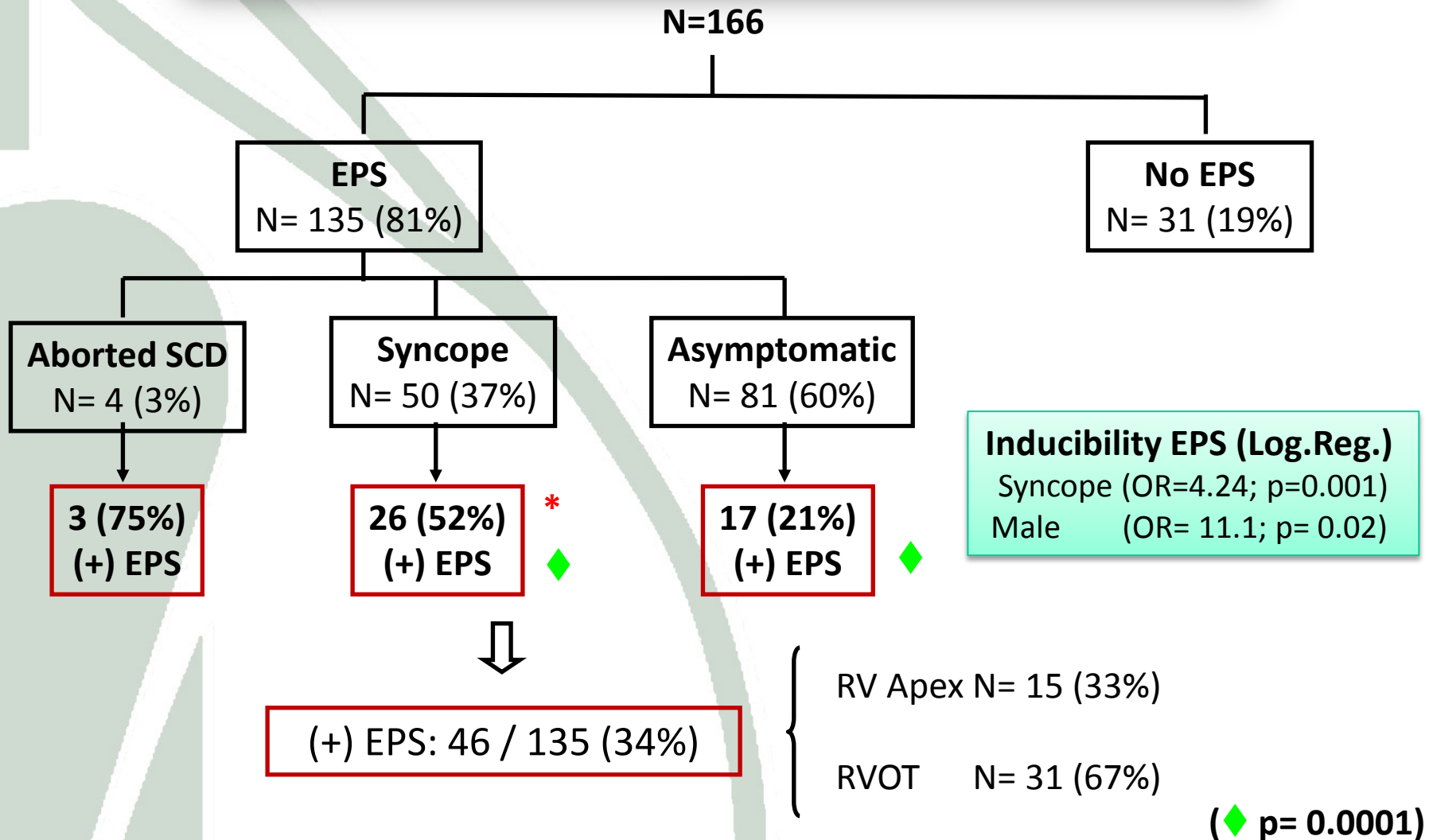
Events during follow-up
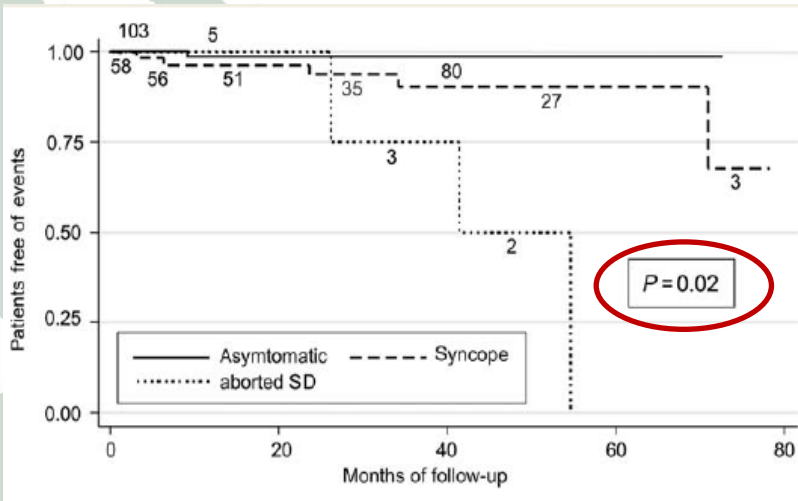
- ✓ SCD   3/5   (60%)
- ✓ Syncope *   5/58   (8.6%)
- ✓ Asymptomatic   1/103   (1%)
  (basal type 1 ECG)

* *No difference according to prodromes*

Inducibility (EPS)

- ✓ EPS (-)   0/89   (0%)
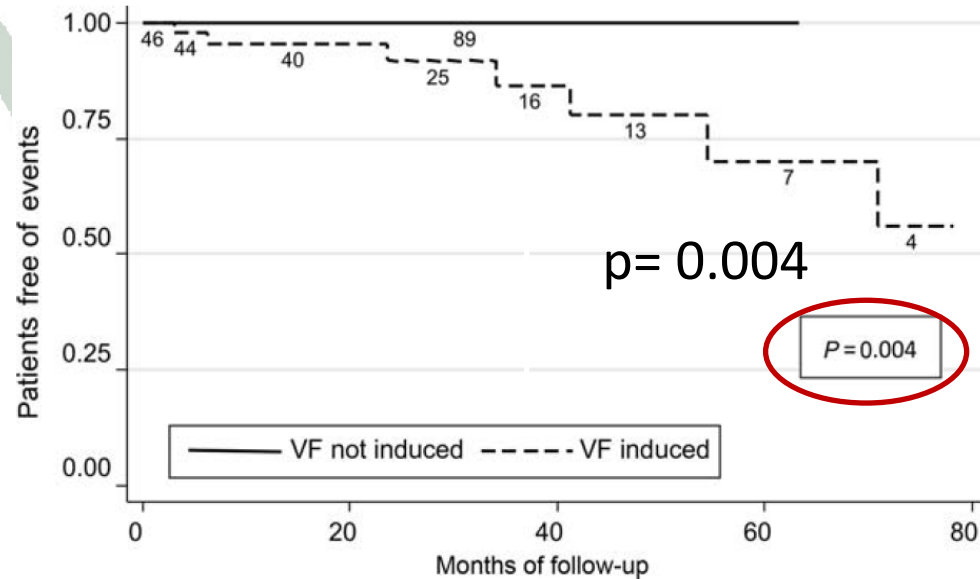- ✓ EPS (+)   7/46   (15%)

p= 0.004

Giustetto C et al. Europace 2009;11:507-513

Follow-up: 30 ± 21 months

N=166

EPS
N= 135 (81%)

No EPS
N= 31 (19%)

EPS (+)
N= 46 (34%)

EPS (−)
N= 89 (66%)

3 (10%) ICD
1 (3%) Loop recorder

44 (96%) ICD
1 (2%) Loop recorder

7 VF (15%) interrupted by the ICD

0 Arrhythmic events

1 (3%) SCD Asymptomatic Basal Type 1 ECG

1 VF (3%)interrupted by the ICD

Giustetto C et al. Europace 2009;11:507-513

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Risk stratification of the patients with Brugada type electrocardiogram: a community-based prospective study

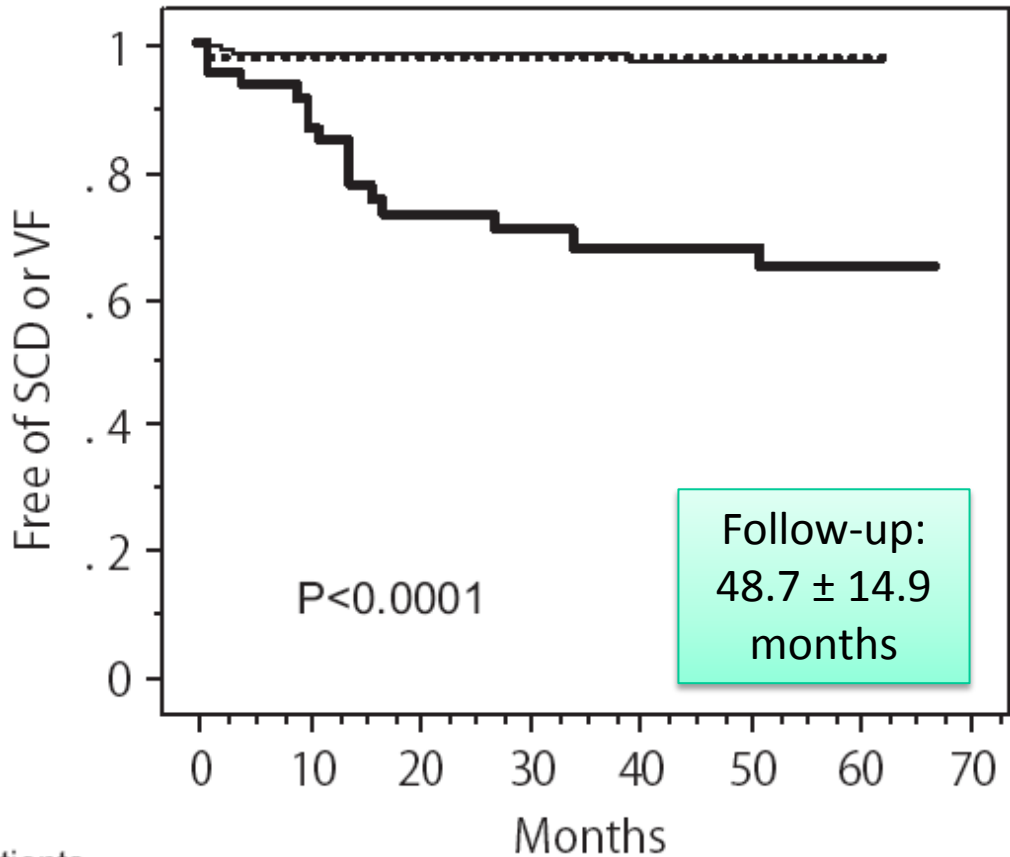| Patients	Events (%)	Patients	Events (%)	P
With aSD	3 (60)	Without aSD	6 (3.7)	0.001
With syncope	5 (8.6)	Asymptomatic	1 (1.0)	0.02
Syncope with prodromes	3 (9.7)	Syncope without prodromes	2 (7.4)	0.9
Male	9 (6.5)	Female	0	0.4
ECG Type 1	5 (6.9)	Type 2–3	4 (4.2)	0.5
Family history of SD	2 (5.1)	No Family history	7 (6.1)	0.9
PES+	7 (15)	PES−	0	0.001
Type 1 ECG with fever	0	Type 1 ECG at baseline	5 (6.9)	0.62
With supraventricular arrhythmias	1 (5.3)	Without supraventricular arrhythmias	8 (5.4)	0.73

Long-Term Prognosis of Probands With Brugada-Pattern ST-Elevation in Leads V_1–V_3

	Type 1 (n=245)		
	VF	Syncope	Asympt
No.	45	46	154
Age, y	48.2±17.8	52.5±15.6	52.3±13.1
Men, n (%)	44 (98)	44 (96)	146 (95)
FH of SCD, n (%)	11 (24)	8 (17)	17 (11)
Event at night, n (%)	37/45 (82)	15/45 (33)	
Inferolateral ER, n (%)	8 (18)	3 (7)	15 (10)
Prevalence of AF, n (%)	19 (42)	7 (15)	21 (14)
VF/VT inducibility, n (%)	27/41 (66)	31/40 (78)	52/91 (57)

Kamakura S, et al. Circ Arrhyth Electrophysiol 2009;2:495-503

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ECG type 1

Legend:
- Asymptomatic group
- Syncope group
- VF group

P<0.0001

Follow-up: 48.7 ± 14.9 months

N. of patients							
Asymptomatic	154	152	142	123	113	90	48
Syncope	46	45	42	35	33	26	10
VF	45	40	31	27	25	23	13

Kamakura S, et al. Circ Arrhyth Electrophysiol 2009;2:495-503

Long-Term Prognosis of Probands With Brugada-Pattern ST-Elevation in Leads V_1–V_3

Table 3. Probability of Sudden Death or VF During Follow-Up Depending on Clinical and Electrophysiological Variables in All Probands (Type 1 and Non–Type 1 Groups)

|	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Prior VF	21.46	8.00–57.53	<0.0001	17.48	6.22–49.11	<0.0001
FH of SCD	6.35	2.84–14.19	<0.0001	3.28	1.42–7.60	0.005
Inferolateral ER	4.14	1.71–10.00	0.001	2.66	1.06–6.71	0.03
AF	2.15	0.92–5.03	0.07	0.87	0.36–2.09	0.75
Syncope	0.35	0.08–1.09	0.15			
Sp. type1	2.31	0.67–7.94	0.18			
VF induc. (apex/OT)	1.81	0.72–4.70	0.20			
VF induc. (apex)	1.58	0.60–4.11	0.34			
Male		NA				

FH indicates family history; inferolateral ER, inferolateral early repolarization; AF, atrial fibrillation; Sp. type 1, spontaneous type 1 ST-elevation on 12-lead ECG at baseline; VF induc. (apex/OT), VF induction by programmed pacing at the RV apex or RV outflow tract; and VF induc. (apex), VF induction by programmed pacing at the RV apex.

Long-Term Prognosis of Patients Diagnosed With Brugada Syndrome
Results From the FINGER Brugada Syndrome Registry

FINGER (France, Italy, Netherlands, Germany)

N = 1029

P 0.001

SCD vs asympt: HR 11 (4.8 - 24.3; P 0.001)
Syncope vs asympt HR 3.4 (1.6 - 7.4; P 0.002)
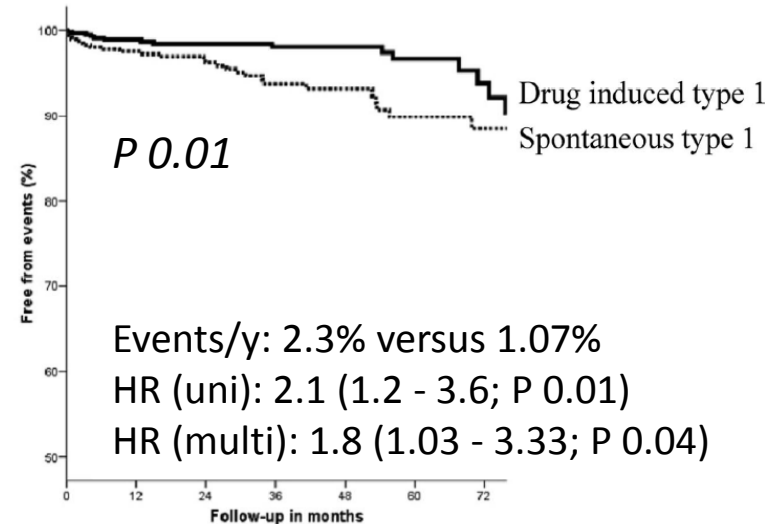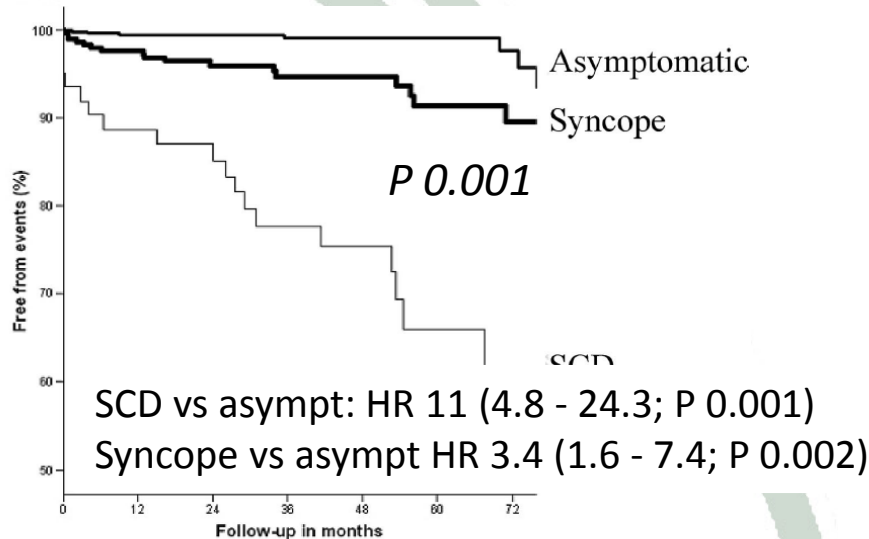
	0	12	24	36	48	60	72
group A	62	54	47	36	29	18	15
group B	313	244	192	148	99	73	49
group C	654	505	379	275	195	109	54

P 0.01

Events/y: 2.3% versus 1.07%
HR (uni): 2.1 (1.2 - 3.6; P 0.01)
HR (multi): 1.8 (1.03 - 3.33; P 0.04)

	0	12	24	36	48	60	72
type1	468	350	269	200	135	88	58
no type 1	561	453	349	259	188	112	60

Probst V et al. Circ 2010;121:635-643

Long-Term Prognosis of Patients Diagnosed With Brugada Syndrome
Results From the FINGER Brugada Syndrome Registry

FINGER (France, Italy, Netherlands, Germany)
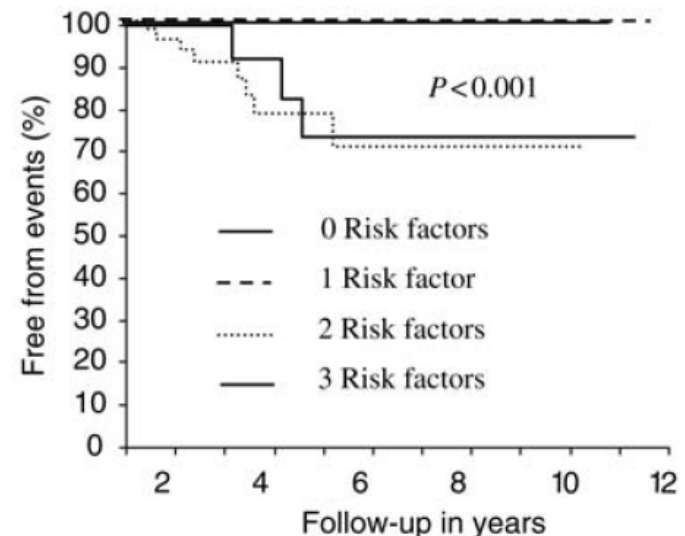
N = 1029

Probst V et al. Circ 2010;121:635-643

Risk stratification in individuals with the Brugada type 1 ECG pattern without previous cardiac arrest: usefulness of a combined clinical and electrophysiologic approach

Figure 1 Kaplan–Meier survival curves in the entire population of 245 patients who underwent electrophysiologic study (EPS). Risk factors considered were: family history of sudden death, syncope, and positive EPS. Curves are plotted according to the presence of 0, 1, 2, or 3 risk factors.
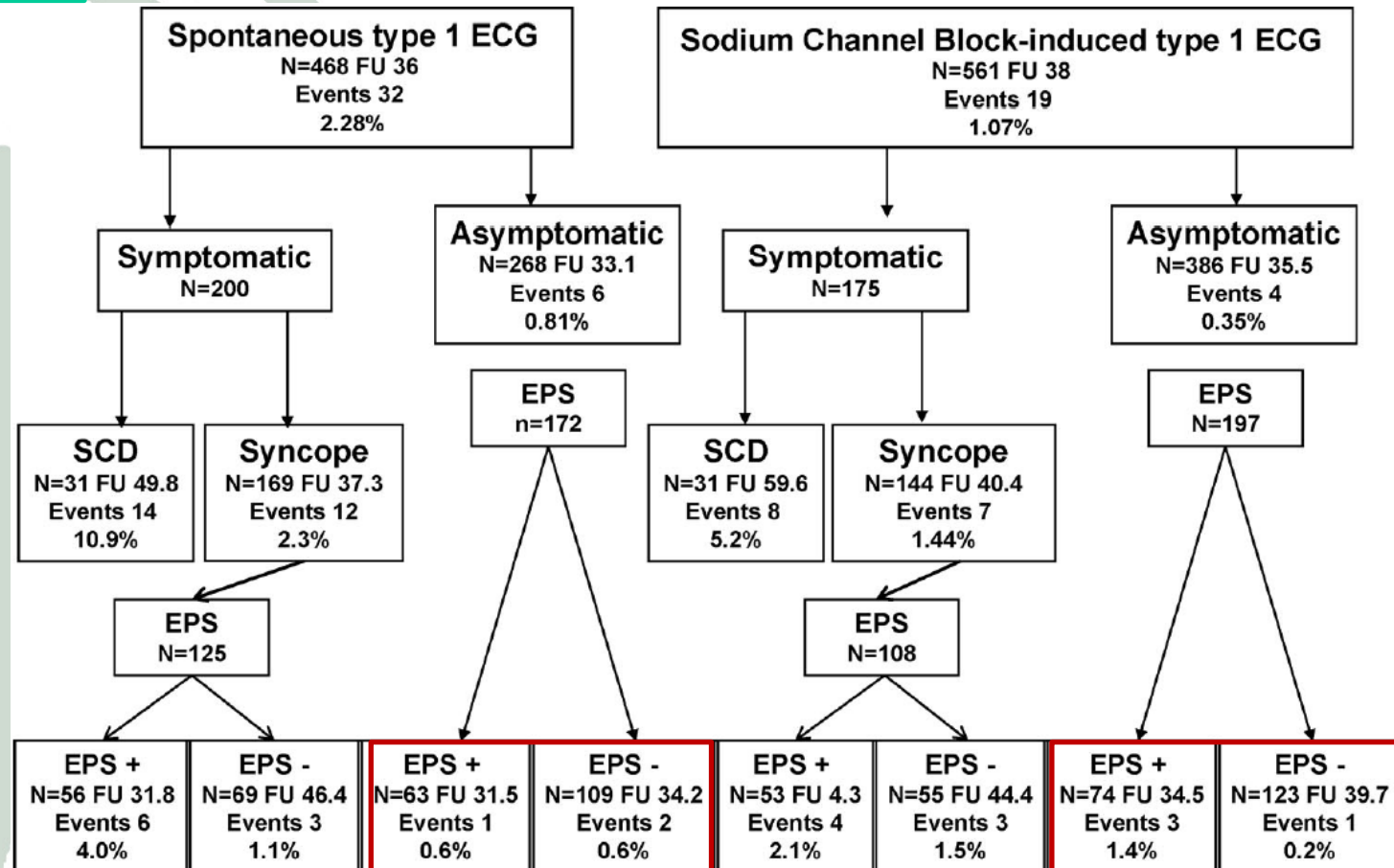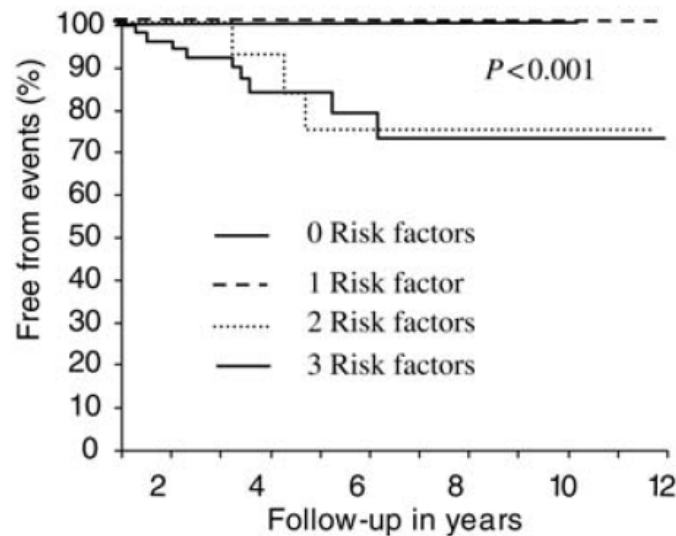
	0	2	4	6	8	10	12
Group 0	73	53	31	10	7	1	0
Group 1	94	73	52	30	14	7	1
Group 2	64	45	25	11	9	4	1
Group 3	14	12	10	4	3	2	1

Figure 2 Kaplan–Meier survival curves in the population of 140 patients with basal type 1 ECG who underwent electrophysiologic study (EPS). Risk factors considered were: familial history of sudden death, syncope, and positive EPS. Curves are plotted according to the presence of 0, 1, 2, or 3 risk factors.

	0	2	4	6	8	10	12
Group 0	32	24	12	5	4	1	0
Group 1	54	41	30	16	9	3	1
Group 2	42	29	14	6	5	1	0
Group 3	12	11	7	3	2	1	1

Delise P et al. Eur Heart J 2011;32:169-176

Risk stratification in individuals with the Brugada type 1 ECG pattern without previous cardiac arrest: usefulness of a combined clinical and electrophysiologic approach

Table 5 Outcome rate per year by risk factor in the entire population of 320 patients

	Events rate per year (%)	P-value
Age		
>43 years	1.9	0.47
<43 years	1.3	
Male	1.7	0.41
Female	0.9	
Syncope	3.0	0.004
No syncope	0.8	
Basal type 1 ECG	2.6	0.004
1C ECG	0.4	
Family history	2.2	0.27
No family history	1.3	

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P-value
Age (per year)	0.9	0.8–1.0	0.19	–	–	–
Male	2.1	0.6–13.3	0.28	–	–	–
Syncope	3.1	1.2–9.2	0.01	2.8	1.1–8.1	0.03
Basal type 1 ECG	6.6	1.8–41.8	0.001	6.2	1.8–39.9	0.002
Family history of SD	1.9	0.7–4.8	0.22	–	–	–

Delise P et al. Eur Heart J 2011;32:169-176

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Risk Stratification in Brugada Syndrome

Results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) Registry

Table 3   **Prognostic Accuracy of Predictors of Outcome**
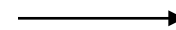
	Inducibility* (Full Protocol)	Inducibility (With 1 or 2 Extra Stimuli)	Spontaneous Type 1 ECG Pattern	History of Syncope	Spontaneous Type 1 ECG and Syncope	QRS-f	VRP <200 ms
Sensitivity	35.7 (14–64)	25.0 (5.8–50)	92.9 (65–99)	50.0 (25–76)	42.9 (19–69)	42.9 (20–69)	78.6 (49–94)
Specificity	58.8 (58–60)	74.2 (78–81)	45.7 (45–47)	80.6 (79–82)	90.5 (89–92)	93.5 (92–95)	62.9 (62–64)
NNT	102.3 (20–200)	—	14.5 (12–58)	12.4 (6.7–108)	6.8 (3.7–26)	4.7 (2.7–14)	13.2 (9.4–50)
Univariate log-rank (p value)	0.67	0.89	0.004	0.011	0.000105	0.000001	0.002

Values are % (95% confidence intervals). *Inducibility = inducibility of VTs/VF during programmed electrical stimulation.
NNT= number needed to treat; other abbreviations as in Table 1.

VT/VF inducibility unable to predict events
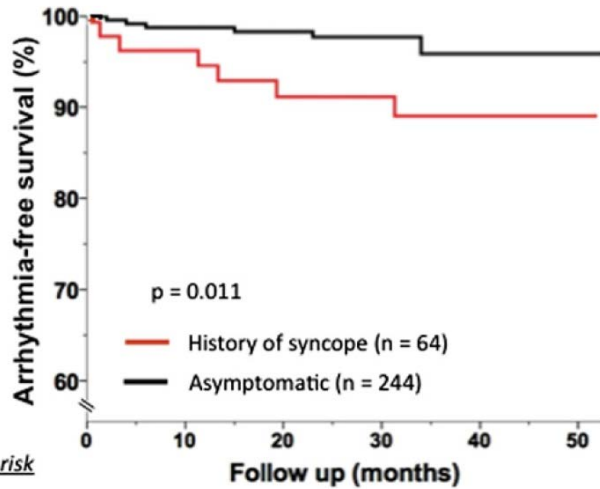
ECG pattern unmasked by a provocative drug test   ⟶   high NPV

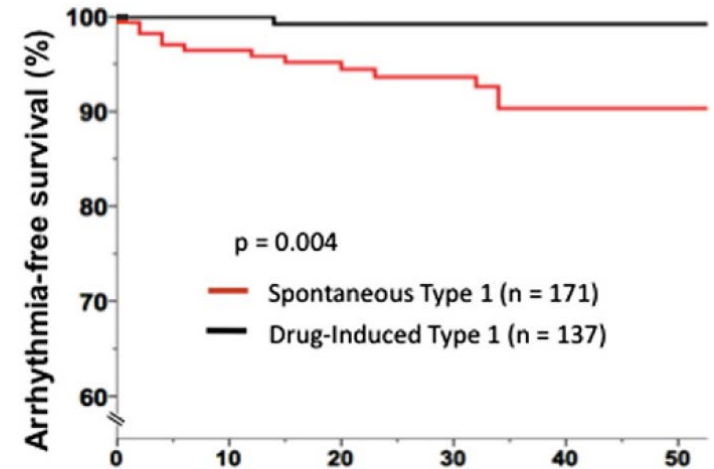2 novel clinical indicators of increased risk of life-threatening events: QRS-f short VRP

Priori SG, et al. J Am Coll Cardiol 2012;59:37-45

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Priori SG, et al. J Am Coll Cardiol 2012;59:37-45
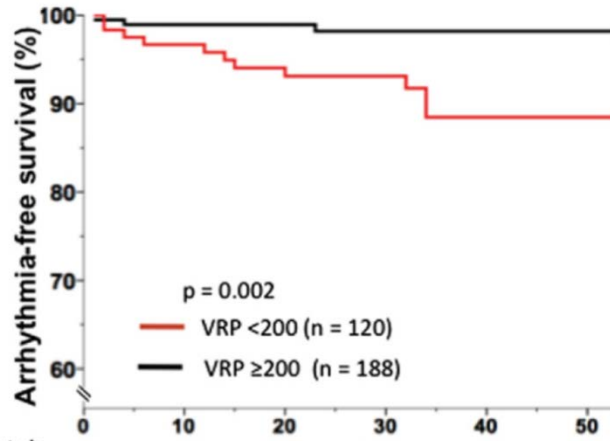
Risk Stratification in Brugada Syndrome

Results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) Registry

Table 4	Cox Multivariate Models			
			95% CI	
	p Value	HR	Lower	Upper
Independent effects				
Inducibility	0.559	0.721	0.241	2.159
Spontaneous type 1 and syncope	0.001	6.406	2.211	18.558
Inducibility	0.835	0.890	0.298	2.661
Ventricular refractory period	0.008	5.666	1.578	20.346
Inducibility	0.972	1.020	0.337	3.091
QRS-fragmentation	0.000	8.898	3.040	26.038
Backward elimination—likelihood ratio				
Step 1				
Spontaneous type 1 and syncope	0.012	4.198	1.378	12.788
QRS-fragmentation	0.007	4.928	1.540	15.776
Ventricular refractory period	0.045	3.908	1.030	14.824
Inducibility	0.959	1.030	0.336	3.155
Step 2				
Spontaneous type 1 and syncope	0.011	4.205	1.382	12.791
QRS-fragmentation	0.007	4.902	1.560	15.402
Ventricular refractory period	0.045	3.903	1.030	14.786

Priori SG, et al. J Am Coll Cardiol 2012;59:37-45

Risk Stratification

Registries	N	Family history of SCD	Syncope	Spontaneous ECG type 1	EP study (PVS)
Giustetto et al	166	?	+	+	+
Kamakura et al	330	+	-	+	
Probst et al (FINGER)	1029	-	+	+	-
Delise et al	320	-	+	+	-
Priori et al (PRELUDE)	308	?	+	+	-

Still controversy

Still controversy

Giustetto C et al. Europace 2009;11:507-513
Kamakura S, et al. Circ Arrhyth Electrophysiol 2009;2:495-503

Probst V et al. Circ 2010:121:635-643
Priori SG. et al. J Am Coll Cardiol 2012:59:37-45
Delise P et al. Eur Heart J 2011;32:169-176

Risk Stratification

Other predictors of outcome

✓ **QRS >120 ms in V2.** *Juntila MJ et al. J Cardiovasc Electrophysiol 2008:118:380-3.*

✓**Early repolarization in inferolateral leads.** *Kamakura S, et al. Circ Arrhyth Electrophysiol 2009;2:495-503.*

✓**QRS fragmentation.** *Morita H et al. Circ 2008;118:1697-704; Priori SG, et al. J Am Coll Cardiol 2012;59:37-45.*

✓ **Ventricular refractory period <200 ms.** *Priori SG, et al. J Am Coll Cardiol 2012;59:37-45.*

✓ **ST elevation during recovery phase of excercise.** *Makimoto H et al. J Am Coll Cardiol 2010;56:1576-84.*

Need for large registries

Management

ICD

Class	ICD Recommendations
Class I	ICD implantation **is recommended** in patients with a diagnosis of BrS who: • Are survivors of a cardiac arrest, and/or • Have documented spontaneous sustained VT with or without syncope.
Class IIa	ICD implantation **can be useful** in patients with a spontaneous diagnostic Type I ECG who have a history of syncope judged to be likely caused by ventricular arrhythmias.
Class IIb	ICD implantation **may be considered** in patients with a diagnosis of BrS who develop VF during programmed electrical stimulation (inducible patients).
Class III	ICD Implantation **is not indicated** in asymptomatic BrS patients with a drug induced type 1 ECG and on the basis of a family history of SCD alone.

Priori S et al. Europace. 2013;15:1389-1406 - Heart Rhythm. 2013;10:e85-e108

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Asymptomatic patients with a spontaneous type 1 ECG with events

✓ 1-2% annual risk of adverse event (SCD/VF).

✓ 50% of patients the first symptom will be SCD/VF.

How to manage this patients?

✓ A 1-2% risk of events is too high → ICD for everyone?

✓ A 1-2% risk of events is acceptable → Clinical follow-up?

✓ A 1-2% risk of events is not too high, nor acceptable → prophilactic quinidine *(Viskin S et al. Heart Rhythm. 2009;6:401-404)*?

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Management

Pharmacological Treatment

Class	Quinidine Recommendations
Class IIa	Quinidine can be useful in patients with a diagnosis of BrS and history of arrhythmic storms defined as more than two episodes of VT/VF in 24 hours. Quinidine can be useful in patients with a diagnosis of BrS: • Who qualify for an ICD but present a contraindication to the ICD or refuse it, and/or • Have a history of documented supraventricular arrhythmias that require treatment.
Class IIb	Quinidine may be considered in asymptomatic patients with a diagnosis of BrS with a spontaneous type 1 ECG.

Priori S et al. Europace. 2013;15:1389-1406 - Heart Rhythm. 2013;10:e85-e108

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Empiric quinidine therapy for asymptomatic Brugada syndrome: Time for a prospective registry

Sami Viskin, MD,* Arthur A. M. Wilde, MD,[†] Hanno L. Tan, MD,[†] Charles Antzelevitch, PhD, FHRS,[‡] Wataru Shimizu, MD,[§] Bernard Belhassen, MD*
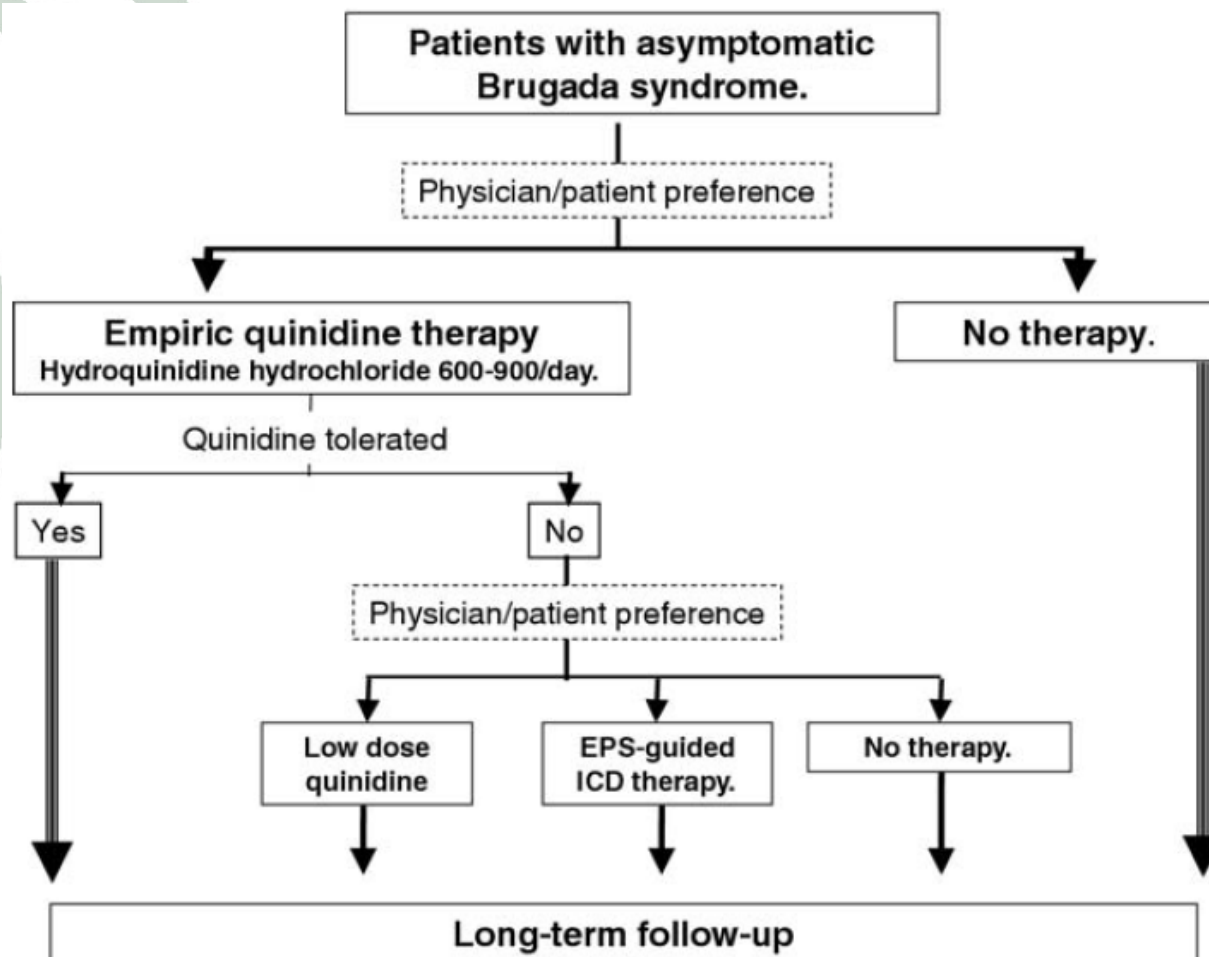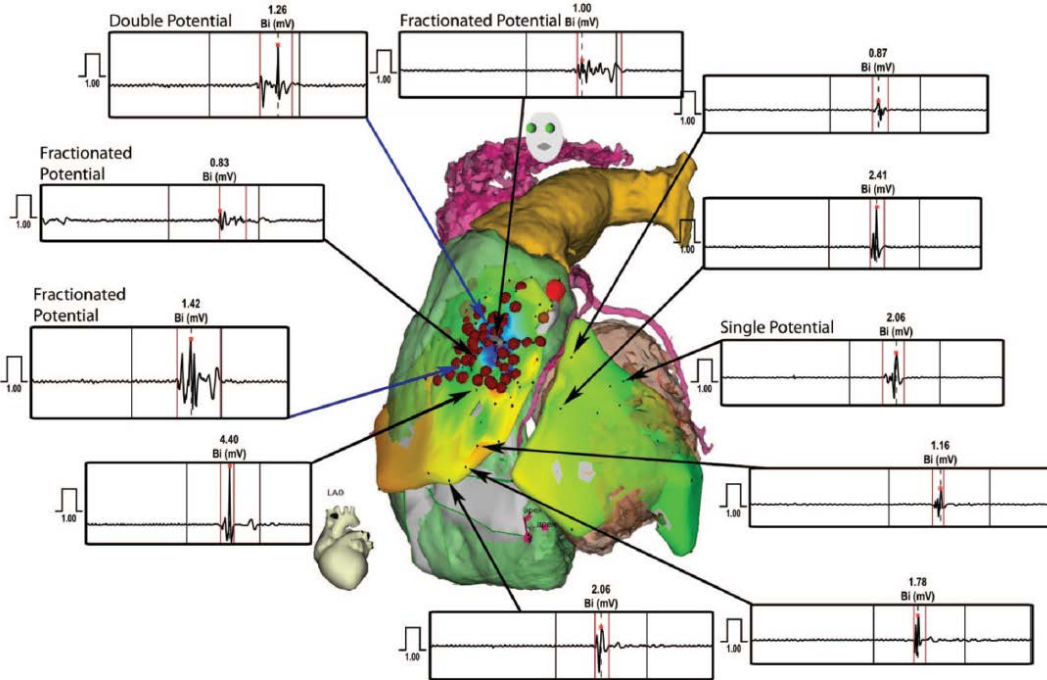
Management

Catheter Ablation

Class	Catheter Ablation Recommendation
Class IIb	Catheter ablation *may be considered* in patients with a diagnosis of BrS and history of arrhythmic storms or repeated appropriate ICD shocks.

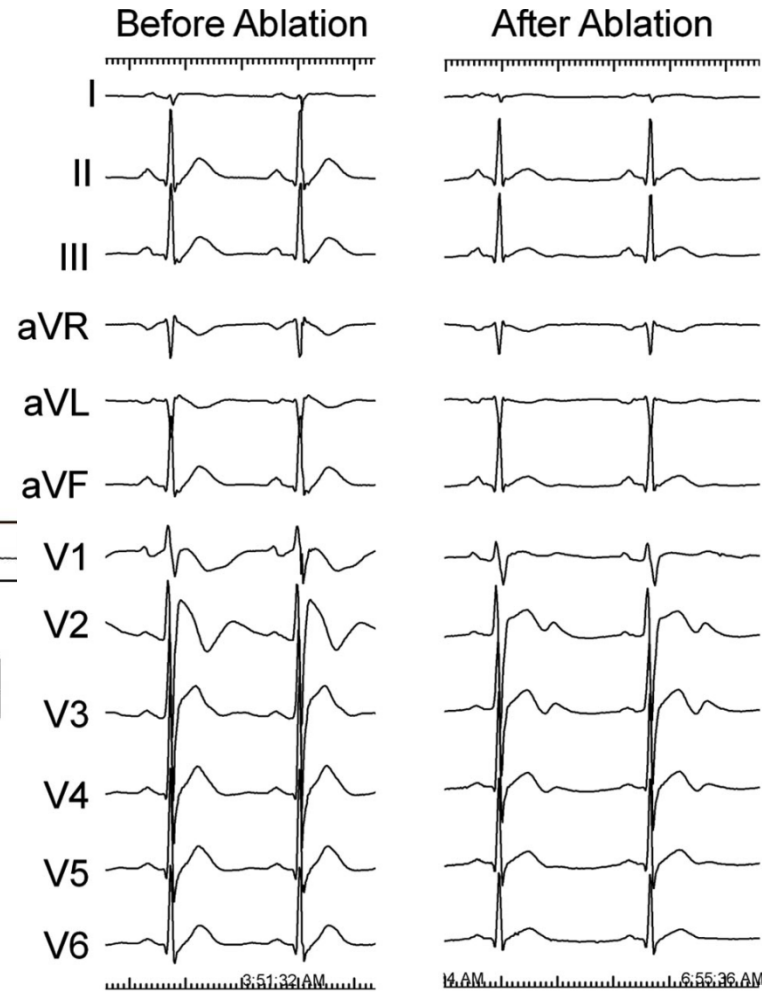*Priori S et al. Europace. 2013;15:1389-1406 - Heart Rhythm. 2013;10:e85-e108*

Management

Catheter Ablation

Non-inducible: 7 of 9 patients

FU: 20±6 months ⟶ No recurrence

Nademanee K et al. Circulation. 2011;123:1270-1279

Conclusions

- ✓ **<u>Symptoms and spontaneous type 1 EGC</u>** remain the only consistent predictors of risk.

- ✓ The relevance of <u>family history and programmed ventricular stimulation</u> remains still controversial.

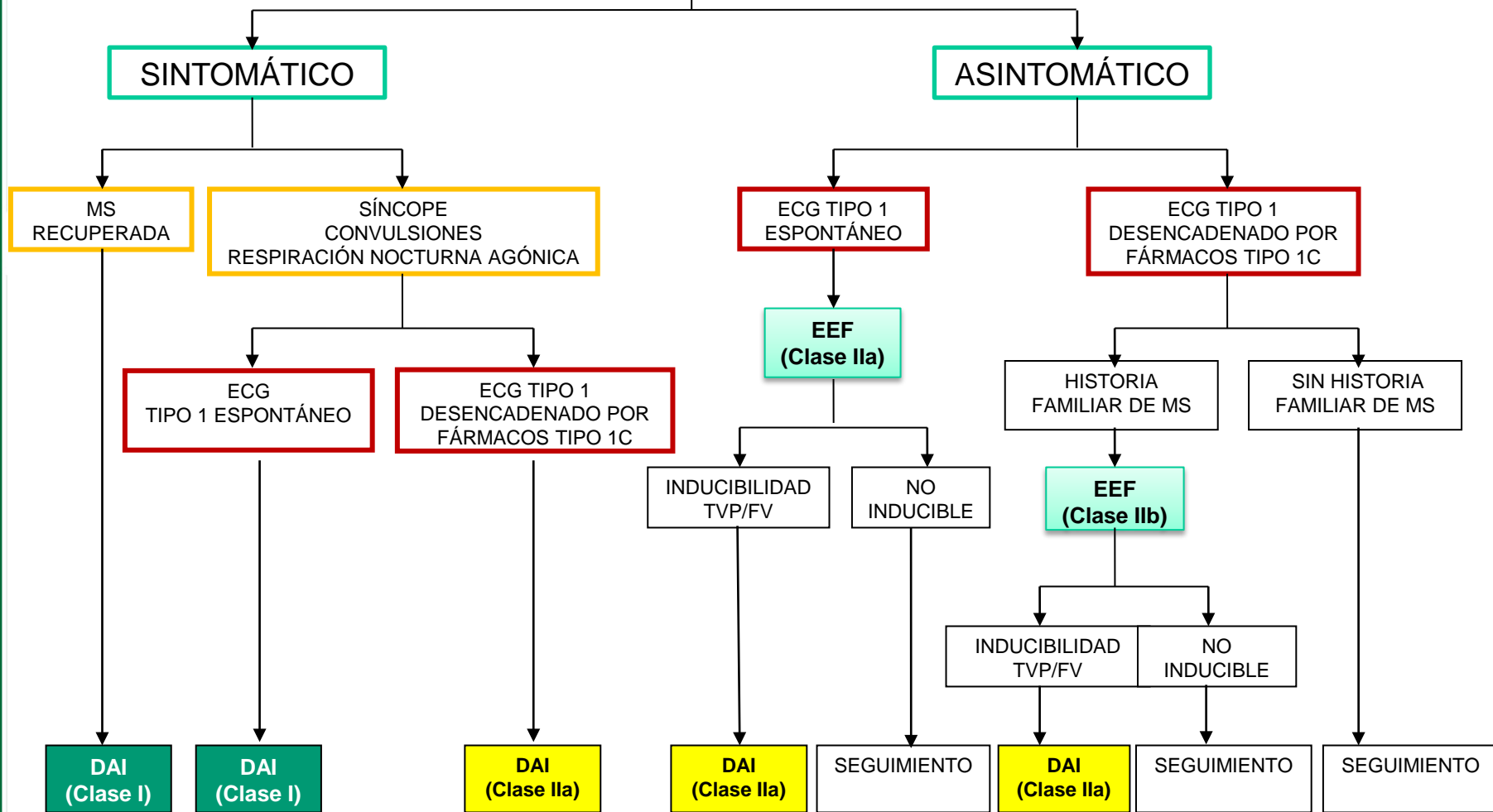- ✓ <u>No reliable prognostic marker to stratify asymptomatic patients</u> (apart from baseline EGC).

Need for large registries

Thank you

ECG TIPO 1 DE SÍNDROME DE BRUGADA

SINTOMÁTICO

- MS RECUPERADA
- SÍNCOPE CONVULSIONES RESPIRACIÓN NOCTURNA AGÓNICA
  - ECG TIPO 1 ESPONTÁNEO
  - ECG TIPO 1 DESENCADENADO POR FÁRMACOS TIPO 1C

DAI (Clase I)

DAI (Clase I)

DAI (Clase IIa)

ASINTOMÁTICO

- ECG TIPO 1 ESPONTÁNEO
  - **EEF (Clase IIa)**
    - INDUCIBILIDAD TVP/FV → **DAI (Clase IIa)**
    - NO INDUCIBLE → SEGUIMIENTO
- ECG TIPO 1 DESENCADENADO POR FÁRMACOS TIPO 1C
  - HISTORIA FAMILIAR DE MS
    - **EEF (Clase IIb)**
      - INDUCIBILIDAD TVP/FV → **DAI (Clase IIa)**
      - NO INDUCIBLE → SEGUIMIENTO
  - SIN HISTORIA FAMILIAR DE MS → SEGUIMIENTO

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Management

Expert Consensus Recommendations on BrS Therapeutic Interventions

Class I
1. The following lifestyle changes *are recommended* in all patients with diagnosis of BrS:
   a. Avoidance of drugs that may induce or aggravate ST-segment elevation in right precordial leads (e.g., Brugadadrugs.org)
   b. Avoidance of excessive alcohol intake
   c. Immediate treatment of fever with antipyretic drugs.
2. ICD implantation *is recommended* in patients with a diagnosis of BrS who:
   a. Are survivors of a cardiac arrest *and/or*
   b. Have documented spontaneous sustained VT with or without syncope.

Class IIa
3. ICD implantation *can be useful* in patients with a spontaneous diagnostic type I ECG who have a history of syncope judged to be likely caused by ventricular arrhythmias.
4. Quinidine *can be useful* in patients with a diagnosis of BrS and history of arrhythmic storms defined as more than two episodes of VT/VF in 24 hours.
5. Quinidine *can be useful* in patients with a diagnosis of BrS who:
   a. Qualify for an ICD but present a contraindication to the ICD or refuse it *and/or*
   b. Have a history of documented supraventricular arrhythmias that require treatment.
6. Isoproterenol infusion *can be useful* in suppressing arrhythmic storms in BrS patients.

Class IIb
7. ICD implantation *may be considered* in patients with a diagnosis of BrS who develop VF during programmed electrical stimulation (inducible patients).
8. Quinidine *may be considered* in asymptomatic patients with a diagnosis of BrS with a spontaneous **type I** ECG.
9. Catheter ablation *may be considered* in patients with a diagnosis of BrS and history of arrhythmic storms or repeated appropriate ICD shocks.

Class III
10. ICD implantation *is not indicated* in asymptomatic BrS patients with a drug-induced **type I** ECG and on the basis of a family history of sudden cardiac death (SCD) alone.