Drug induced Brugada Syndrome: how high (or low) is the risk?

Torino, 24th October 2014

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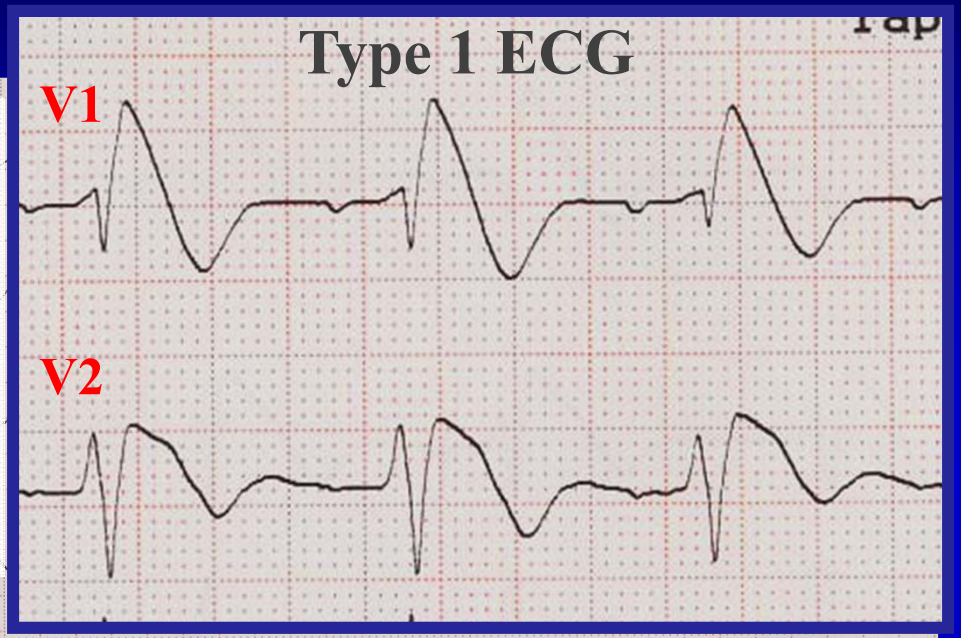
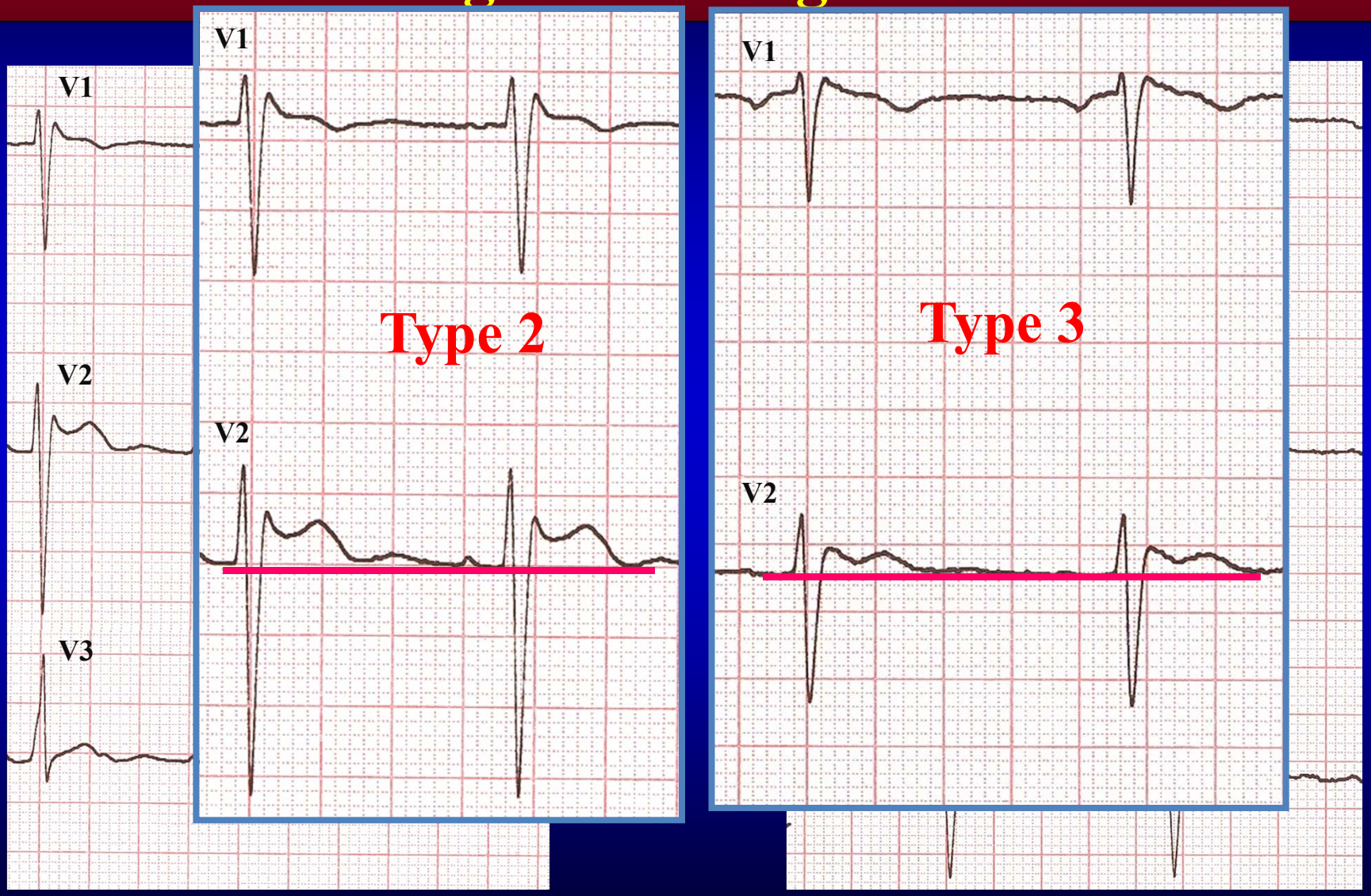
Brugada syndrome

- ✓ J point ≥ 2mm
- ✓ Coved type ST segment elevation
- ✓ Negative T wave

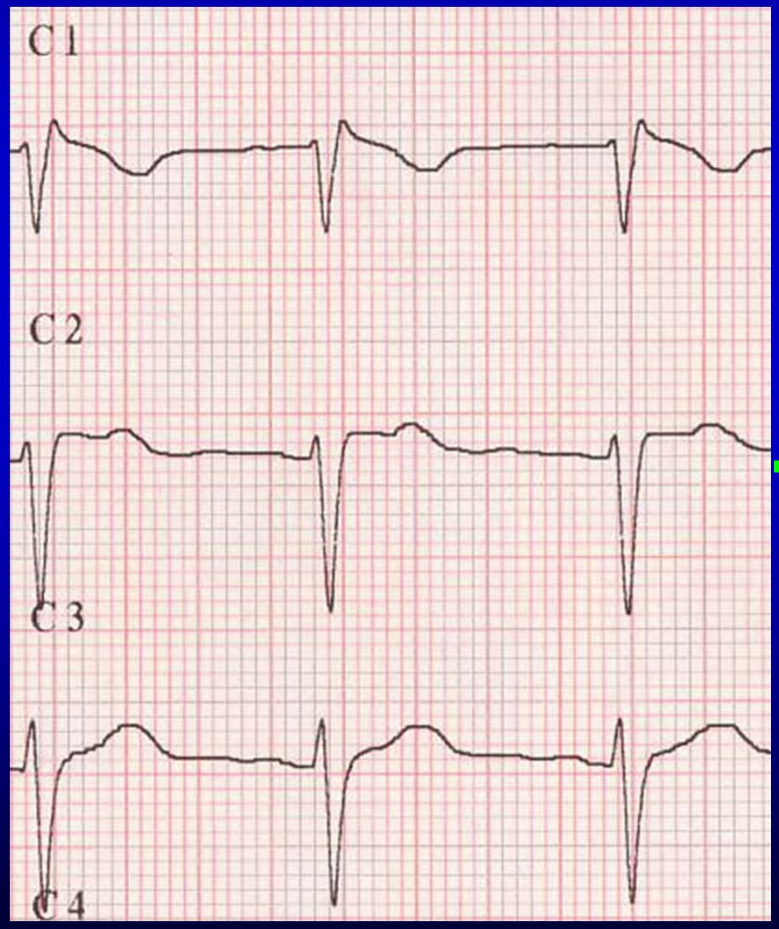


Non-diagnostic Brugada ECGs

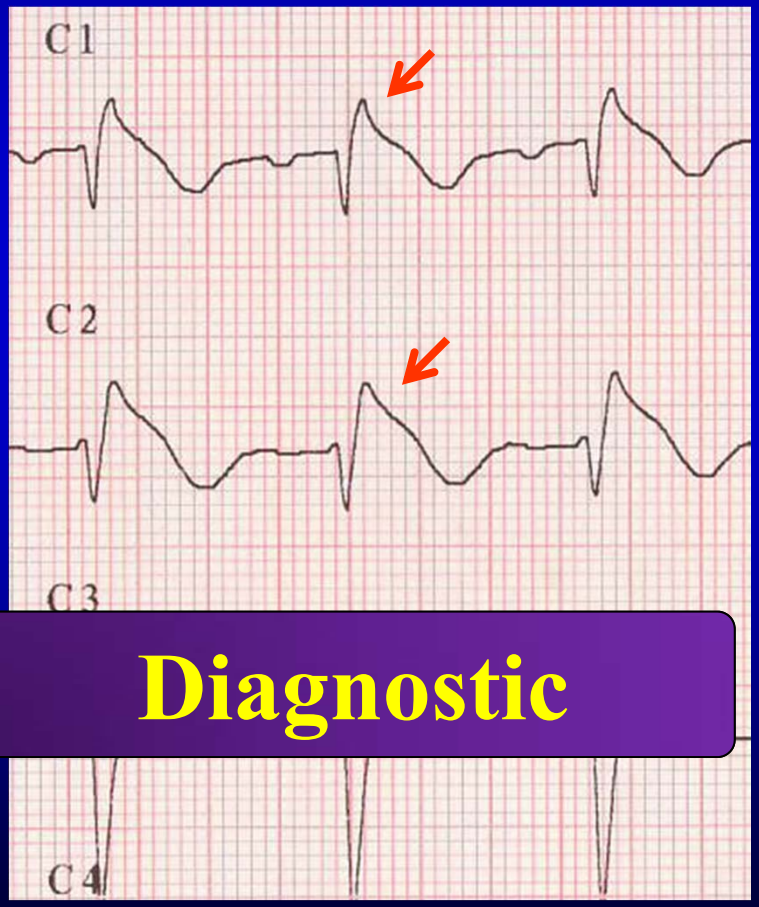


Drug challenge with Na^+ channel blockers

Basal ECG

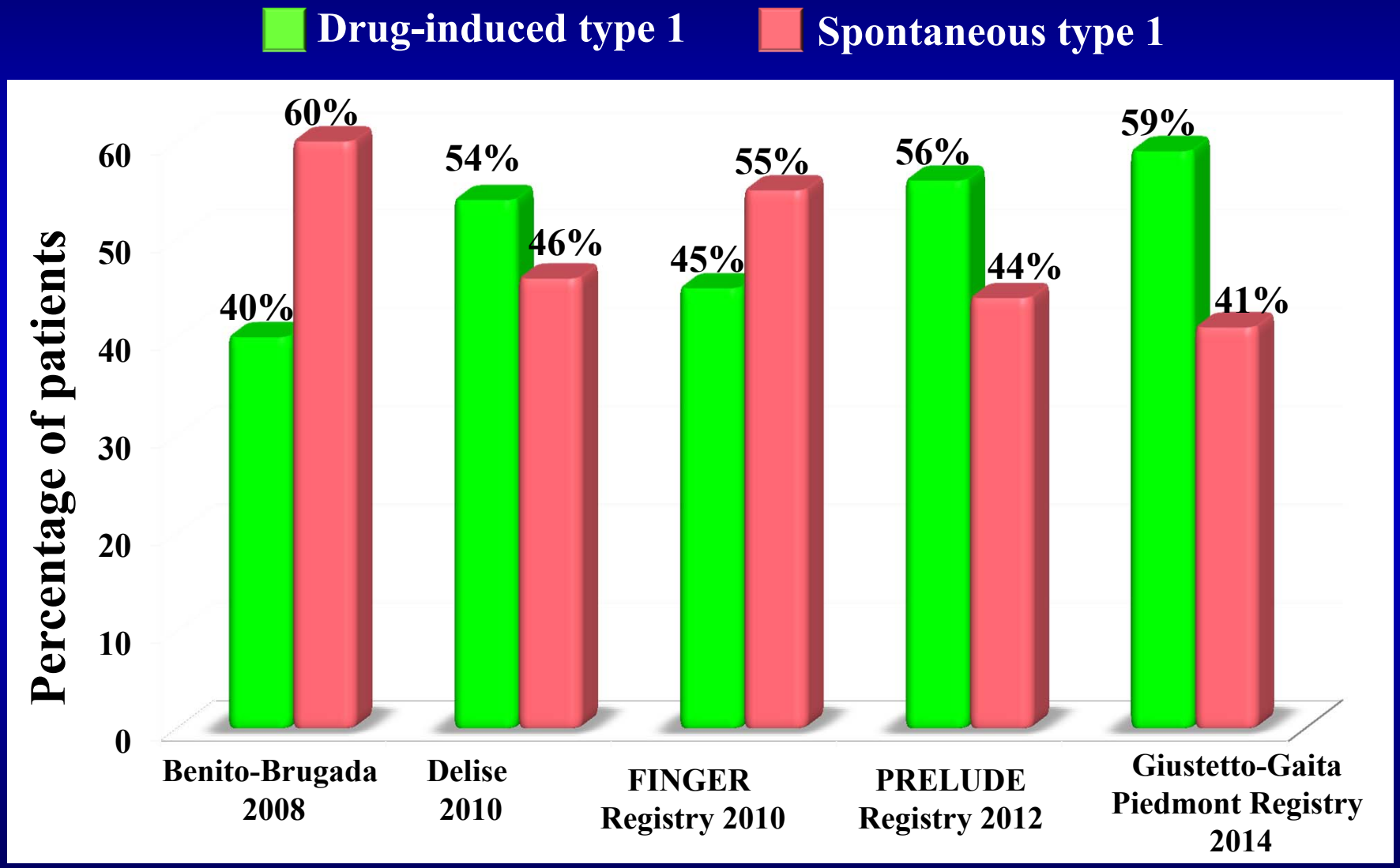


After **ajmaline** infusion
(1mg/kg in 5 min)



Diagnostic

Prevalence of drug-induced type 1 Brugada ECG



Spontaneous type 1 is a predictor of arrhythmic events

190 asymptomatic pts, 27 months f-up, 8% arrhythmic events

Probability of Sudden Death or Ventricular Fibrillation During Follow-up

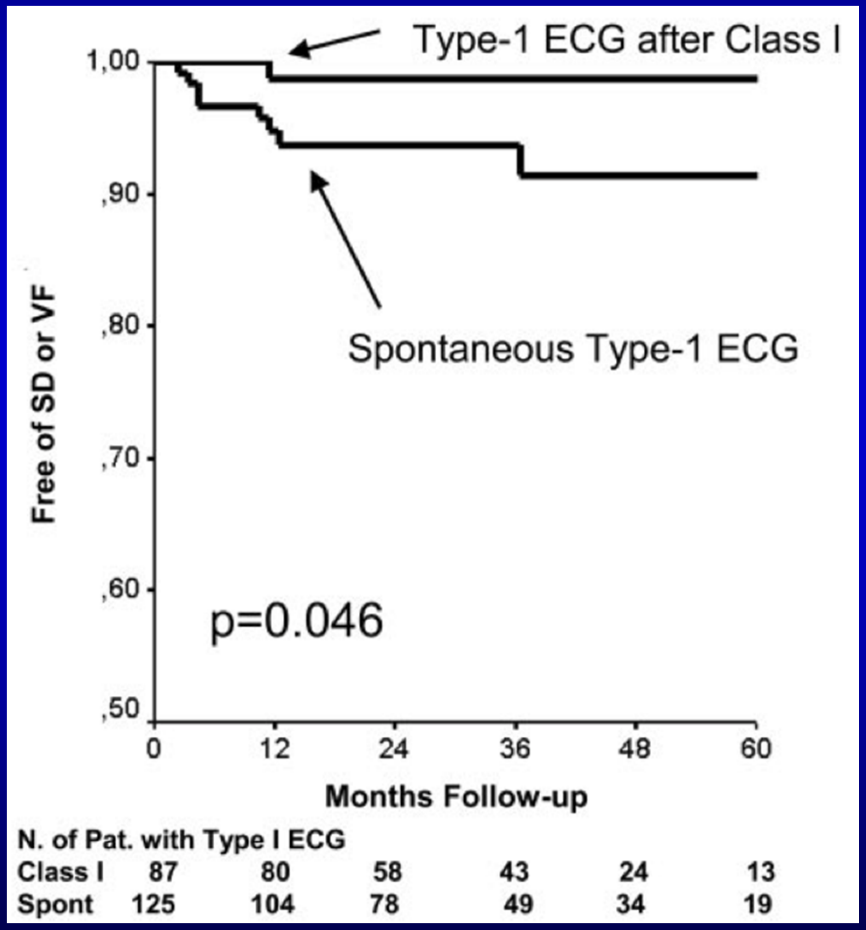
	Univariate Analysis			Multivariate Analysis		
	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
Inducible	8.33	2.8–25.0	0.0001	5.88	2.0–16.7	0.0001
Noninducible	1	...	...	1	...	...
Syncope	2.79	1.5–5.1	0.002	2.50	1.2–5.3	0.017
No syncope	1	...	...	1	...	...
Basal ECG spontaneous type 1	7.69	1.9–33.3	0.0001	2.86	0.7–12.3	0.103
AAD ECG drug-induced type 1	1	...	...	1	...	...

Prognosis seems better in asymptomatic individuals who require an antiarrhythmic drug challenge to uncover the abnormal ECG.

Brugada et al, Circulation. 2003;108:3092-96

Spontaneous type 1 is a predictor of arrhythmic events

212 pts, 40 months f-up, 4% arrhythmic events (overall incedence)



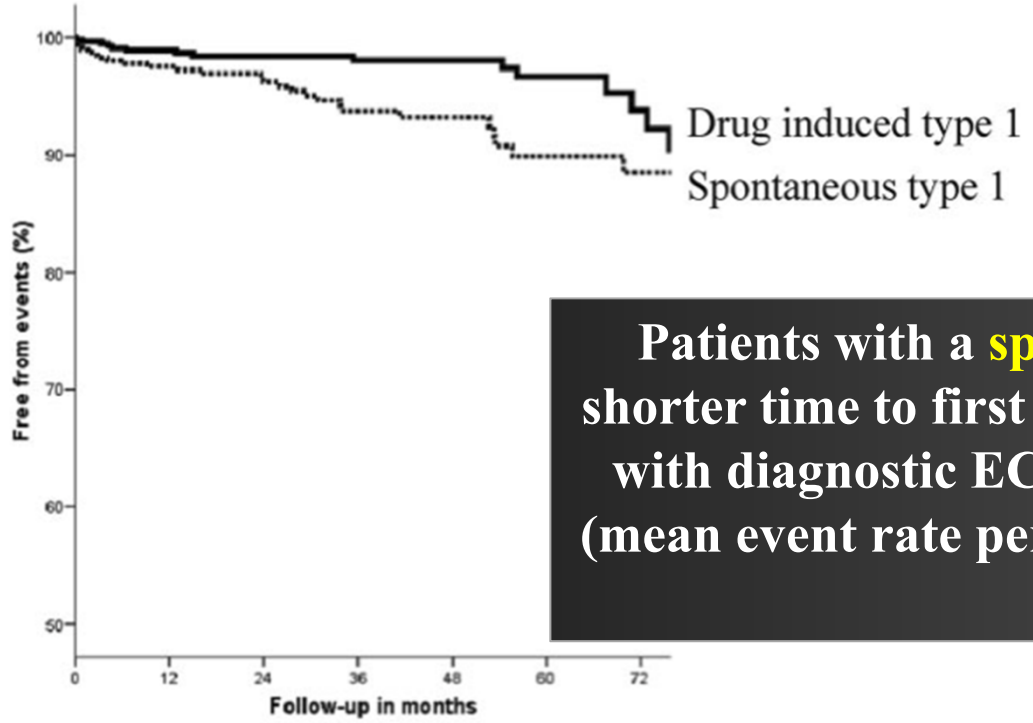
All asymptomatic individuals (n=53) and sudden death patients (n=9) with a transient type 1 ECG pattern were free of events at follow-up (32 and 78 months, respectively).

Only 1 of 40 patients with a prior syncope and a drug-induced type 1 ECG had VF during f-up.

Eckardt et al, Circulation. 2005;111:257-263

Spontaneous type 1 is a predictor of arrhythmic events

1029 pts, 32 months f-up, 5% arrhythmic events (overall incidence)



	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

Patients with a spontaneous type 1 ECG had a shorter time to first arrhythmic event than patients with diagnostic ECG only during drug challenge (mean event rate per year: 2.3% vs 1.07%; HR 2.1; p=0.01)

Probst et al, FINGER Registry, Circulation. 2010; 121:635-643

Spontaneous type 1 is a predictor of arrhythmic events

320 pts, 40 months f-up, 5% arrhythmic events (overall incidence)

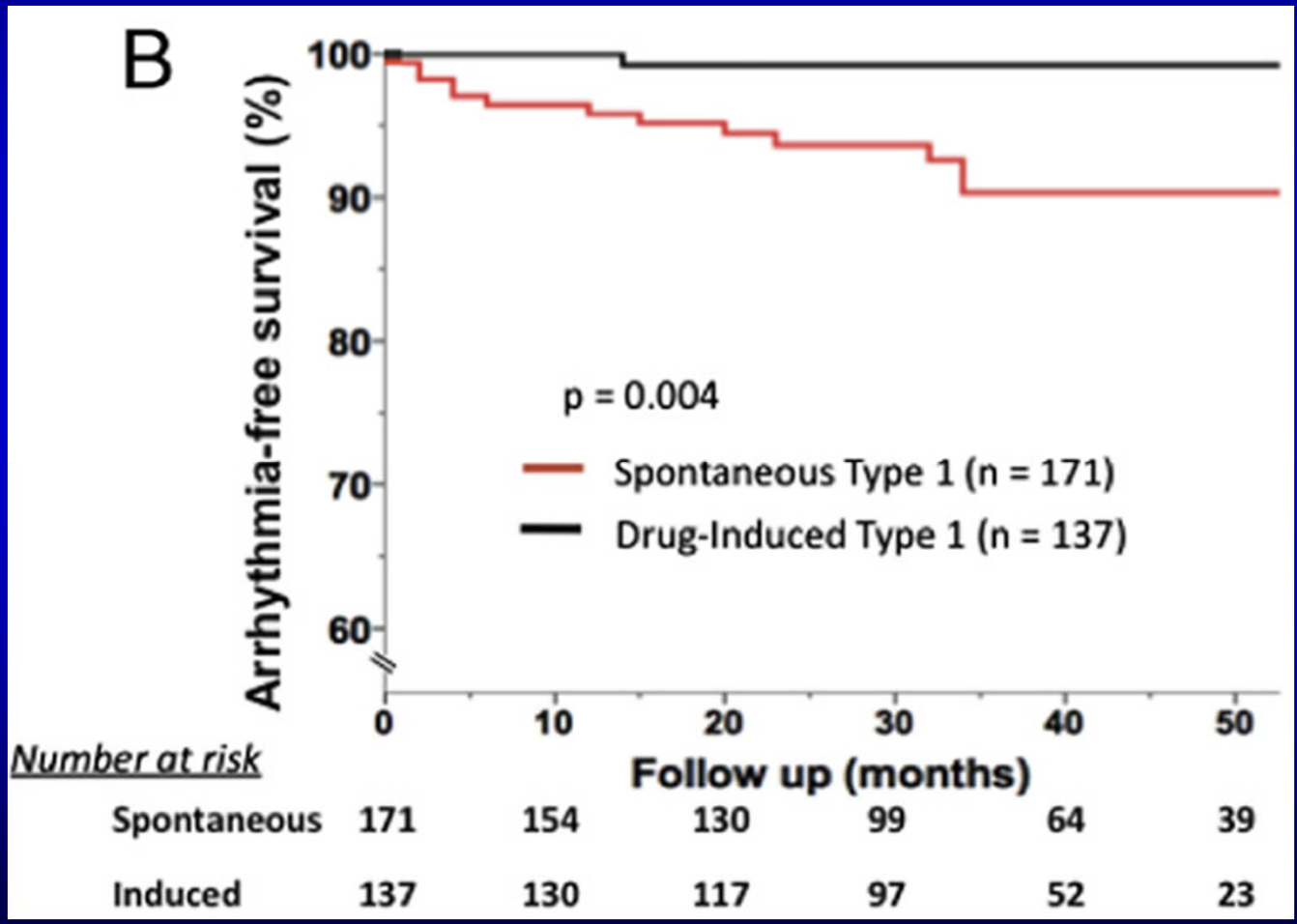
Outcome rate per year in the entire population

	Events rate per year (%)	*P*-value
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	

Delise et al, Eur Heart J 2011; 32:169–176

Spontaneous type 1 is a predictor of arrhythmic events

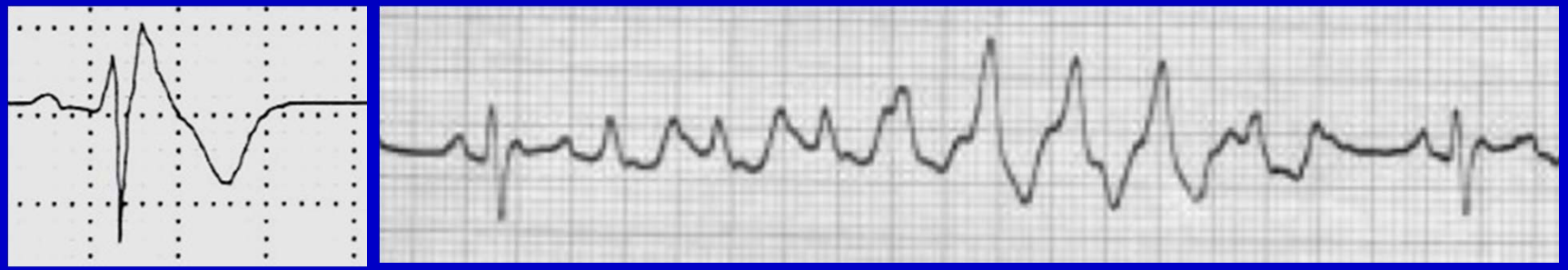
308 pts, 34 months f-up, 5% arrhythmic events (overall incidence)



Priori et al, PRELUDE registry, J Am Coll Cardiol 2012;59:37–45

Spontaneous type 1 is a predictor of arrhythmic events in children

30 pts < 16 years
37 months f-up, 10% arrhythmic events (overall incidence)



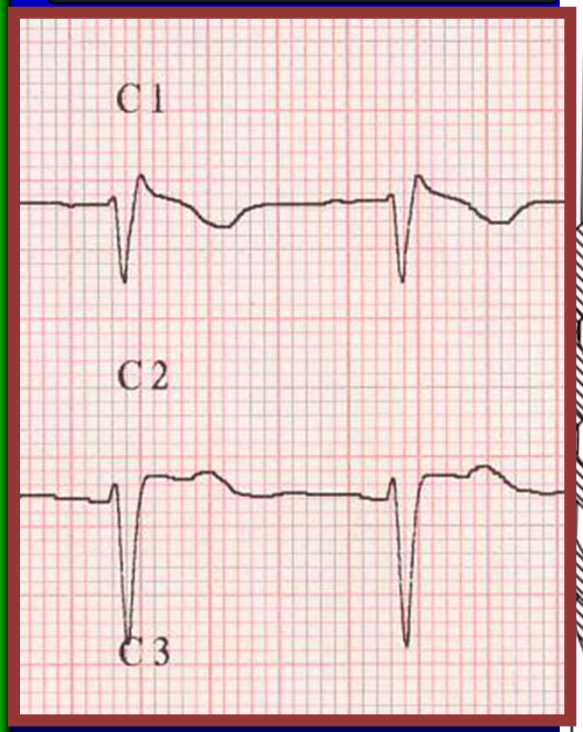
Fever was the most important precipitating factor for arrhythmic events and, as in the adult population, the risk of arrhythmic events was higher in previously symptomatic patients and in those displaying spontaneous type 1 ECG.

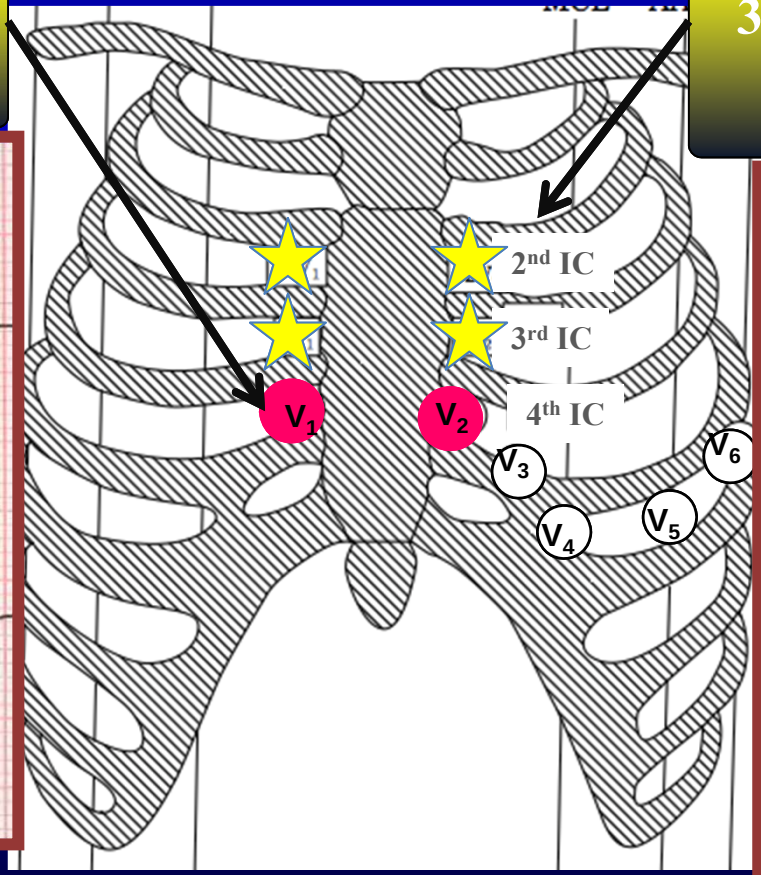
Probst et al, Circulation 2007; 115:2042-2048

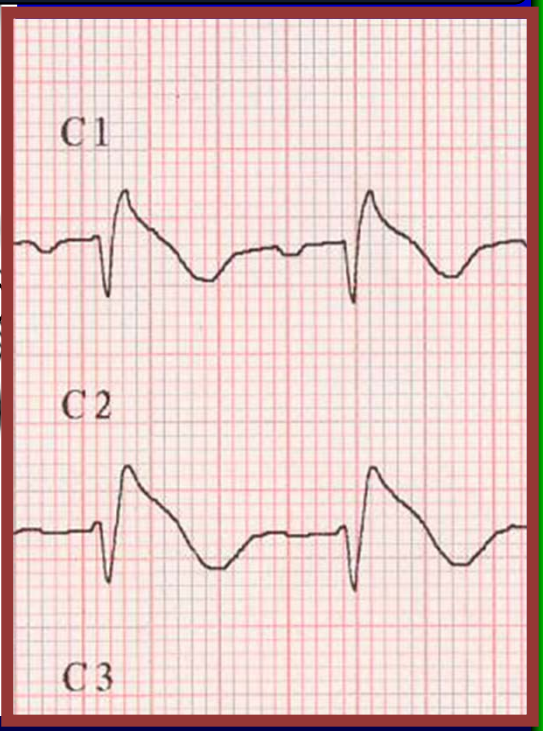
Increased sensitivity with higher electrodes (V_1-V_2) position

Standard leads:
4th intercostal space

Additional leads:
3rd and 2nd intercostal space

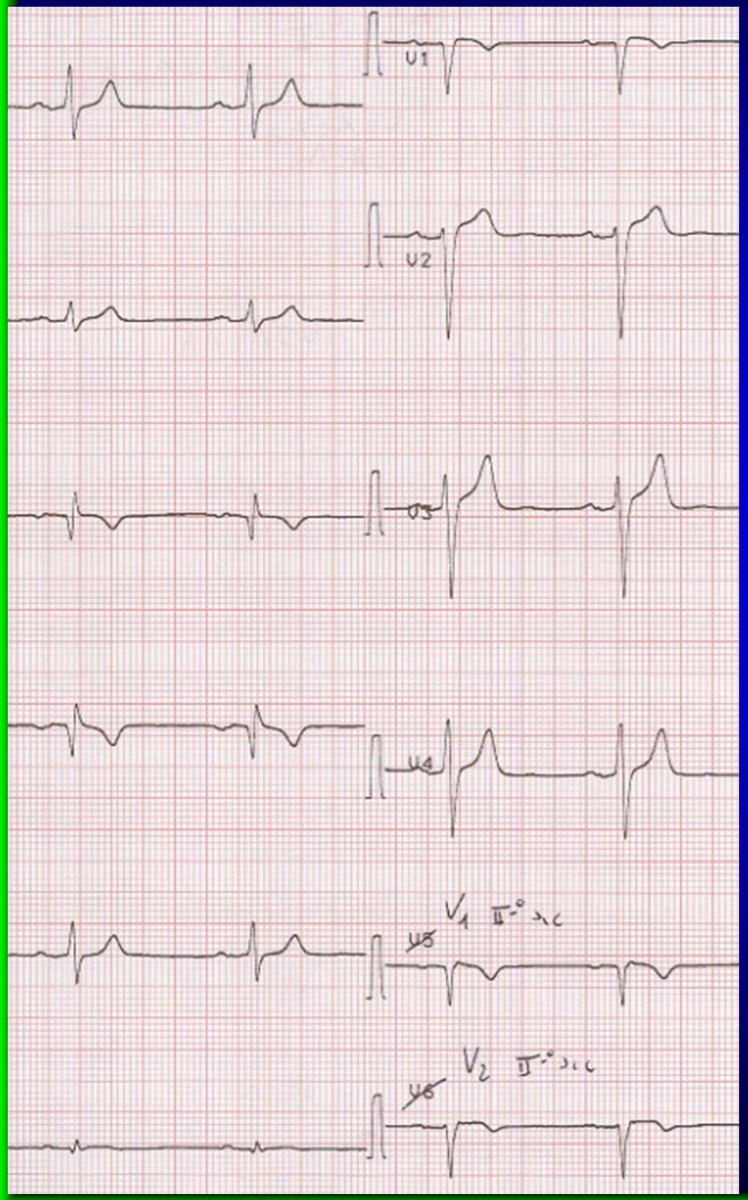


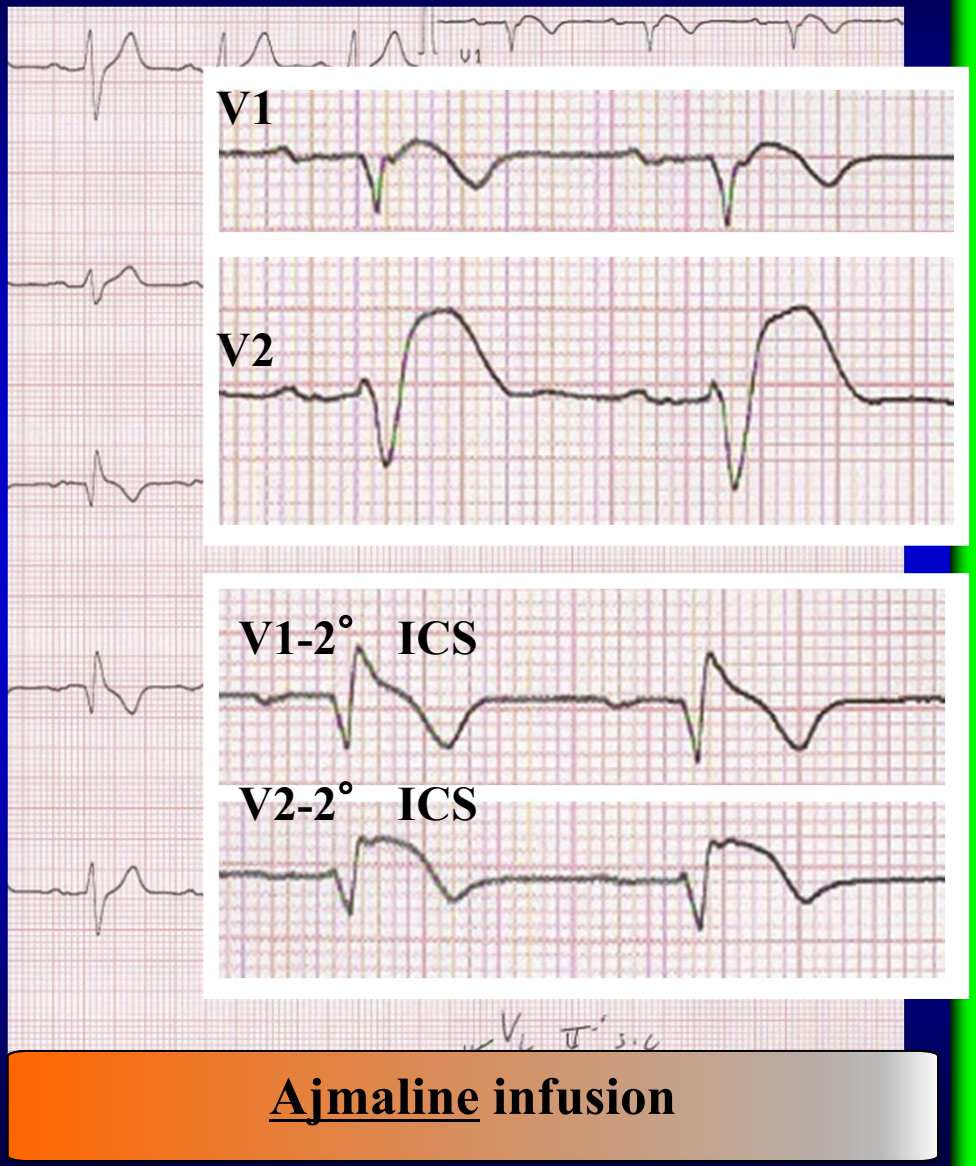




Antzelevitch C et al, Second Consensus Conference. Circulation 2005; 11: 659-670

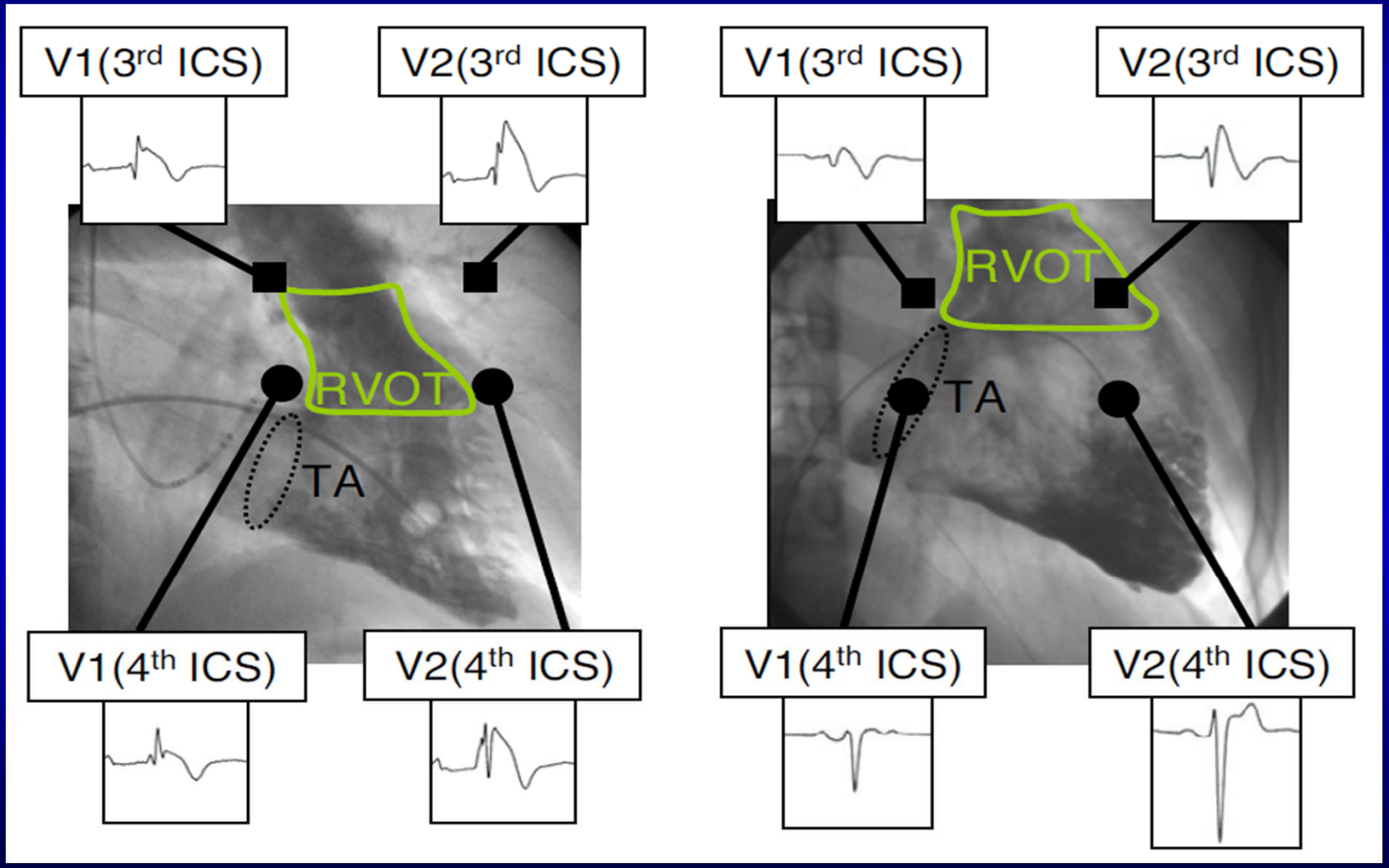
Drug challenge: ajmaline 1 mg/kg





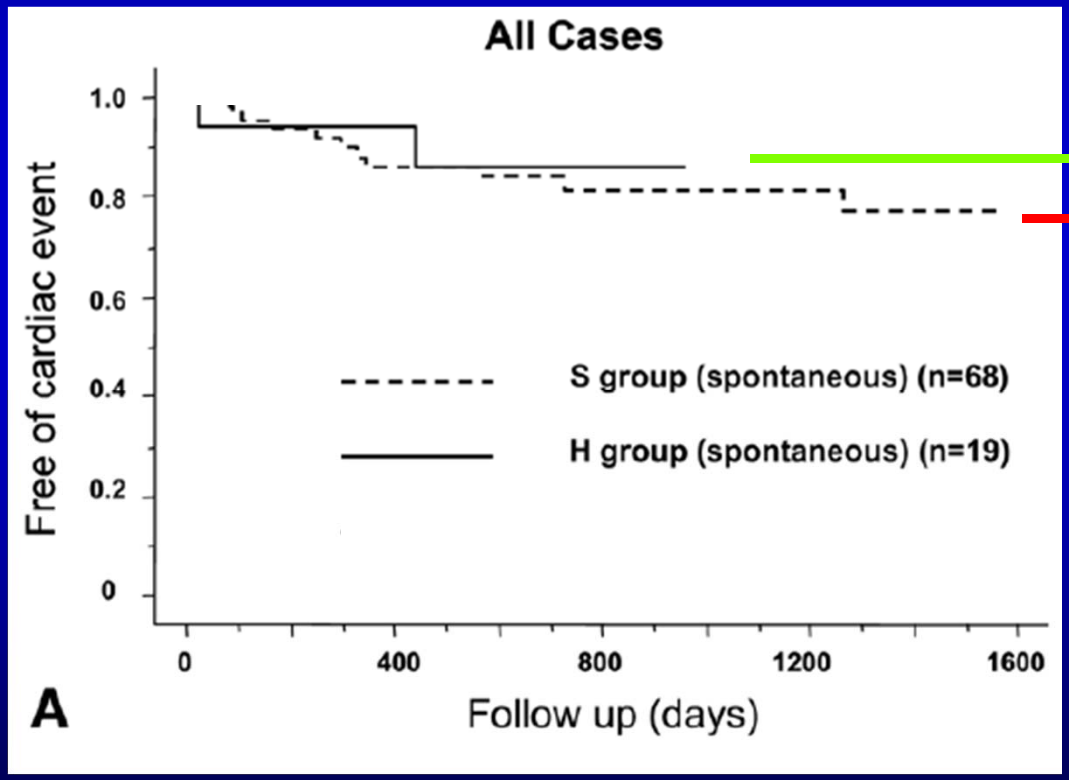
Ajmaline infusion

Correlation between RVOT position and exploring electrodes



Nagase et al, JACC 2010, 56: 2143-45

Brugada type 1 pattern recorded at an higher inter-costal space (2^{nd}-3^{rd}) showed similar prognostic values as standard recordings



High leads

Standard leads

Mean f-up 20 months

Adapted from Miyamoto et al. Am J Card 2007, 99: 53-57

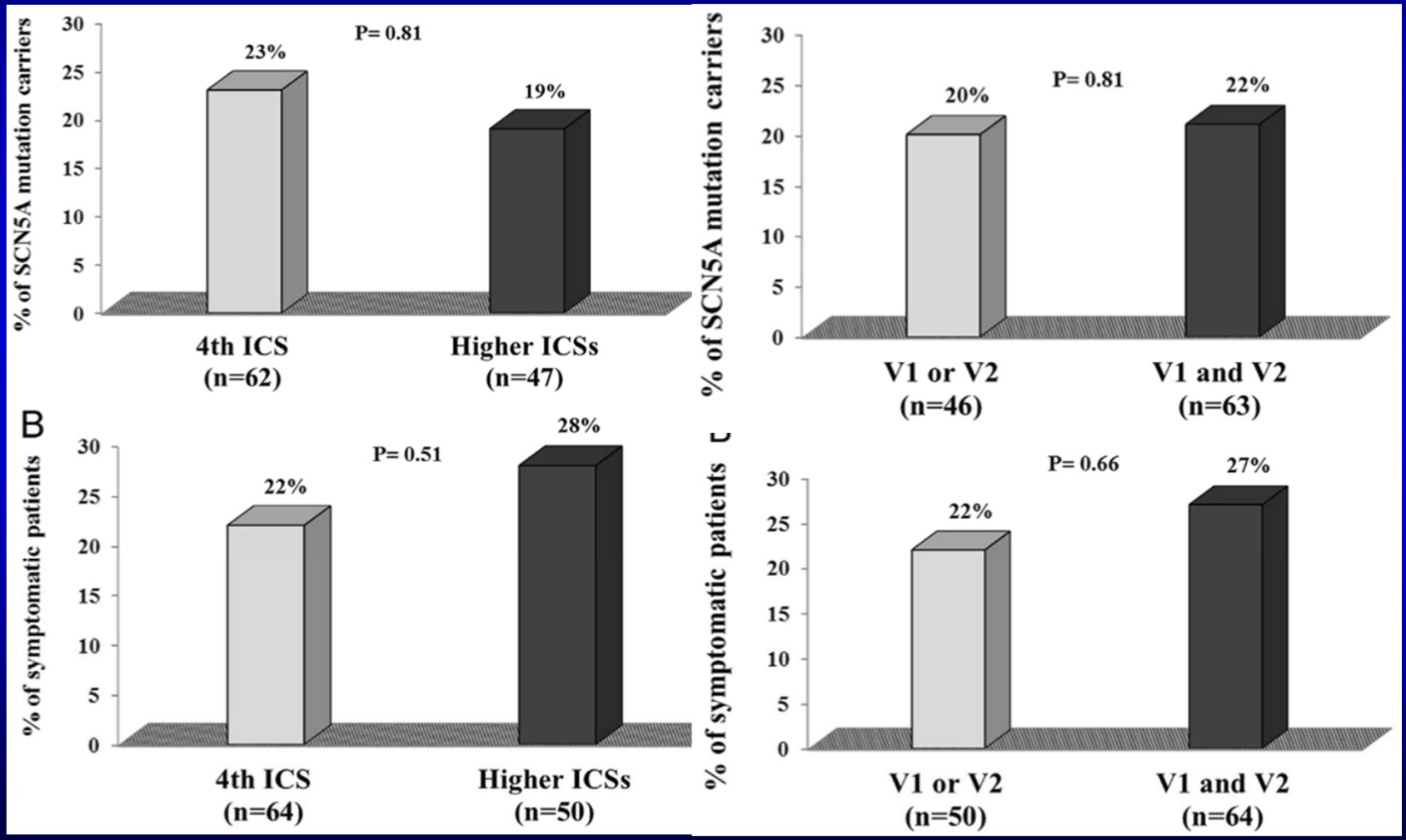
Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes

Expert Consensus Recommendations on ***BrS Diagnosis***

BrS ***is diagnosed*** in patients with ST-segment elevation with **type I** morphology $\geq$2 mm in $\geq$1 lead among the right precordial leads V_1,V_2 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.

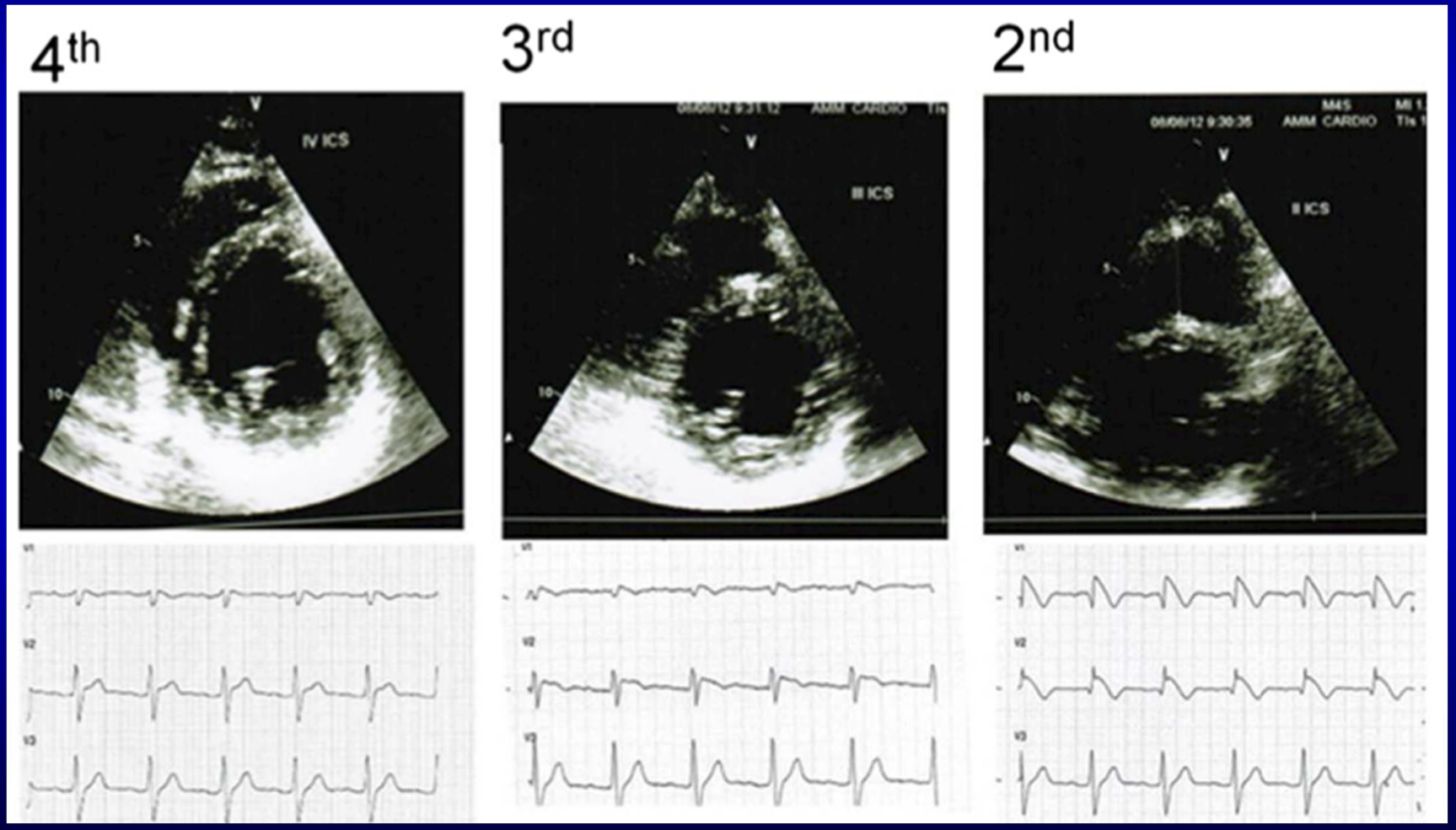
Europace 2013; 15: 1389–1406

The percentage of **mutation carriers** (MCs) and the **event rate** were **similar regardless of the diagnostic ICS** (fourth vs high ICSs) **and the number of diagnostic leads** (1 vs ≥2).

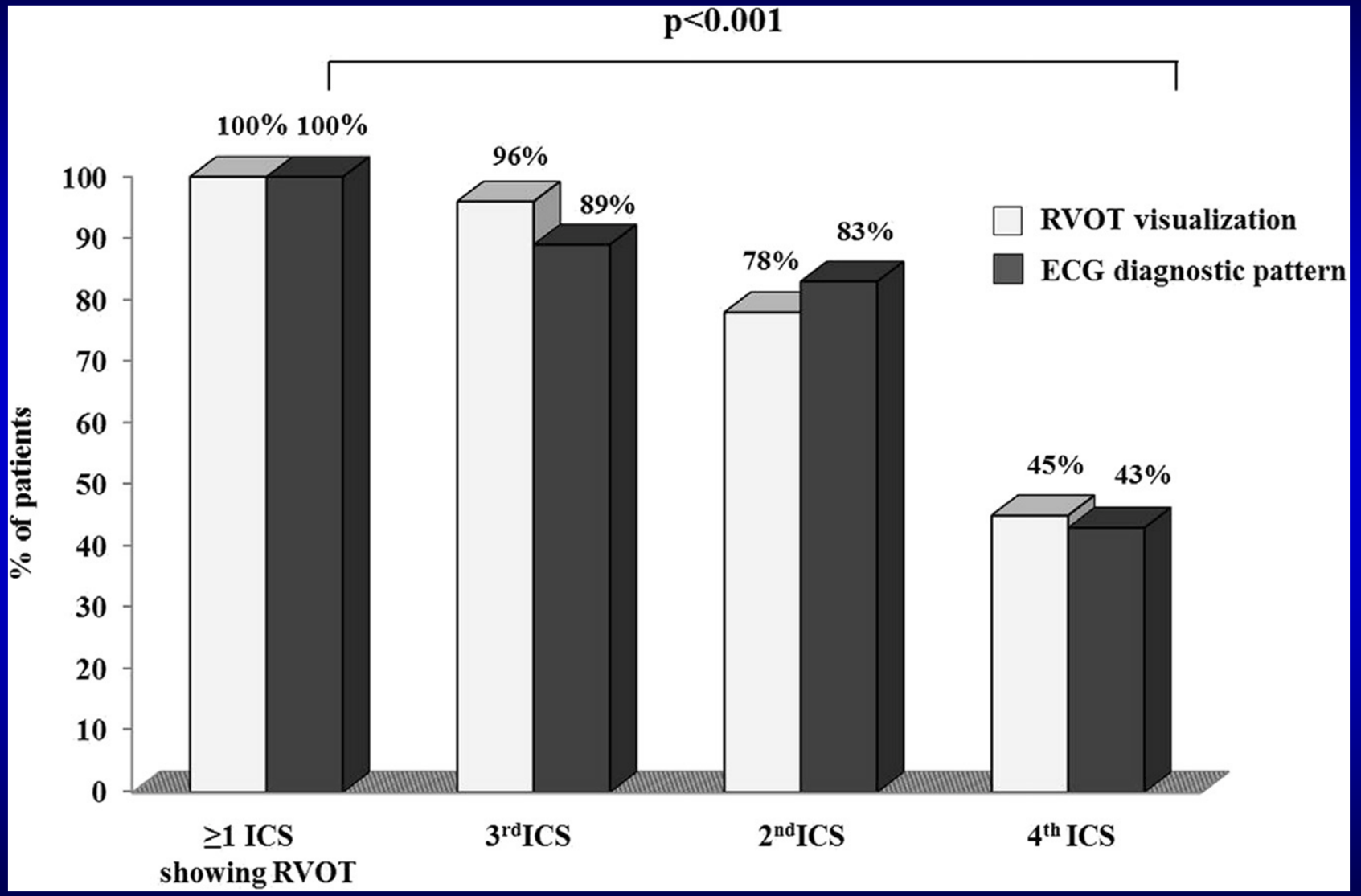


Savastano S, Schwartz PJ et al, Heart Rhythm 2014;11:1176–1183

The anatomical location of RVOT, evaluated through echocardiography, revealed a concordance between RVOT and the diagnostic intercostal space of 86%.



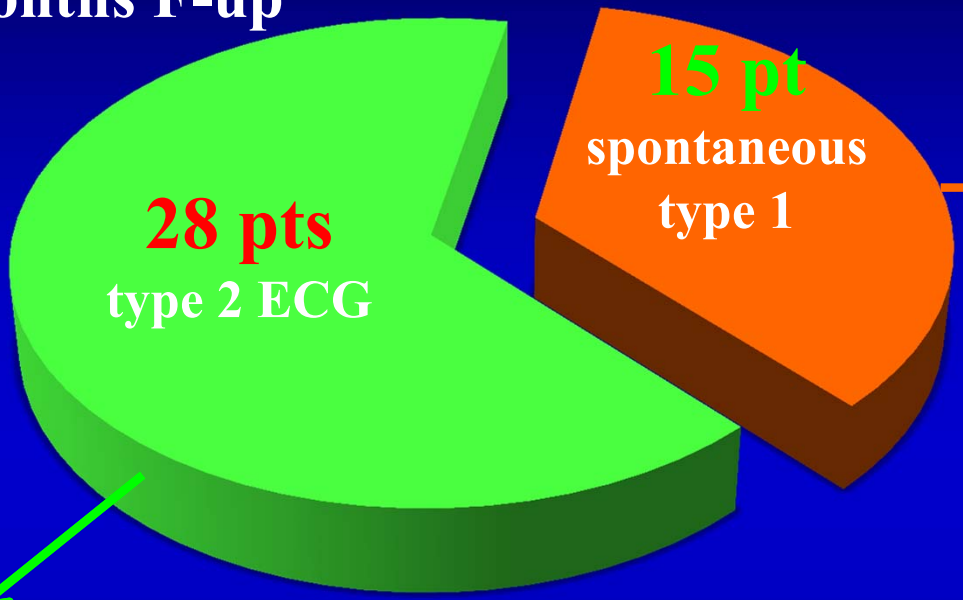
Savastano S, Schwartz PJ et al, Heart Rhythm 2014;11:1176–1183

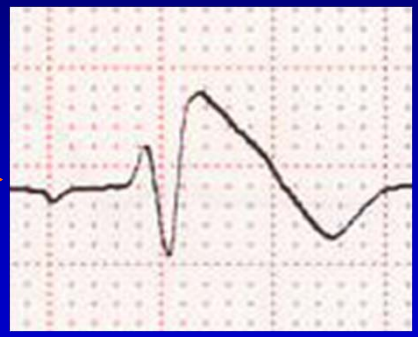


Savastano S, Schwartz PJ et al, Heart Rhythm 2014;11:1176–1183

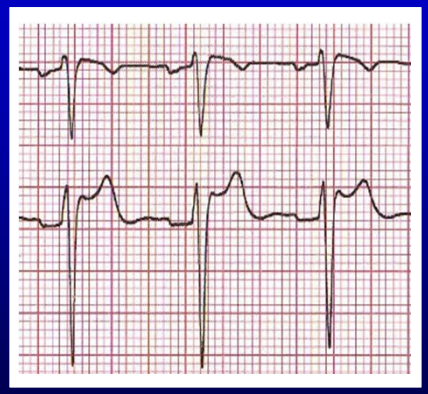
ECG fluctuations in Brugada pts

17 months F-up





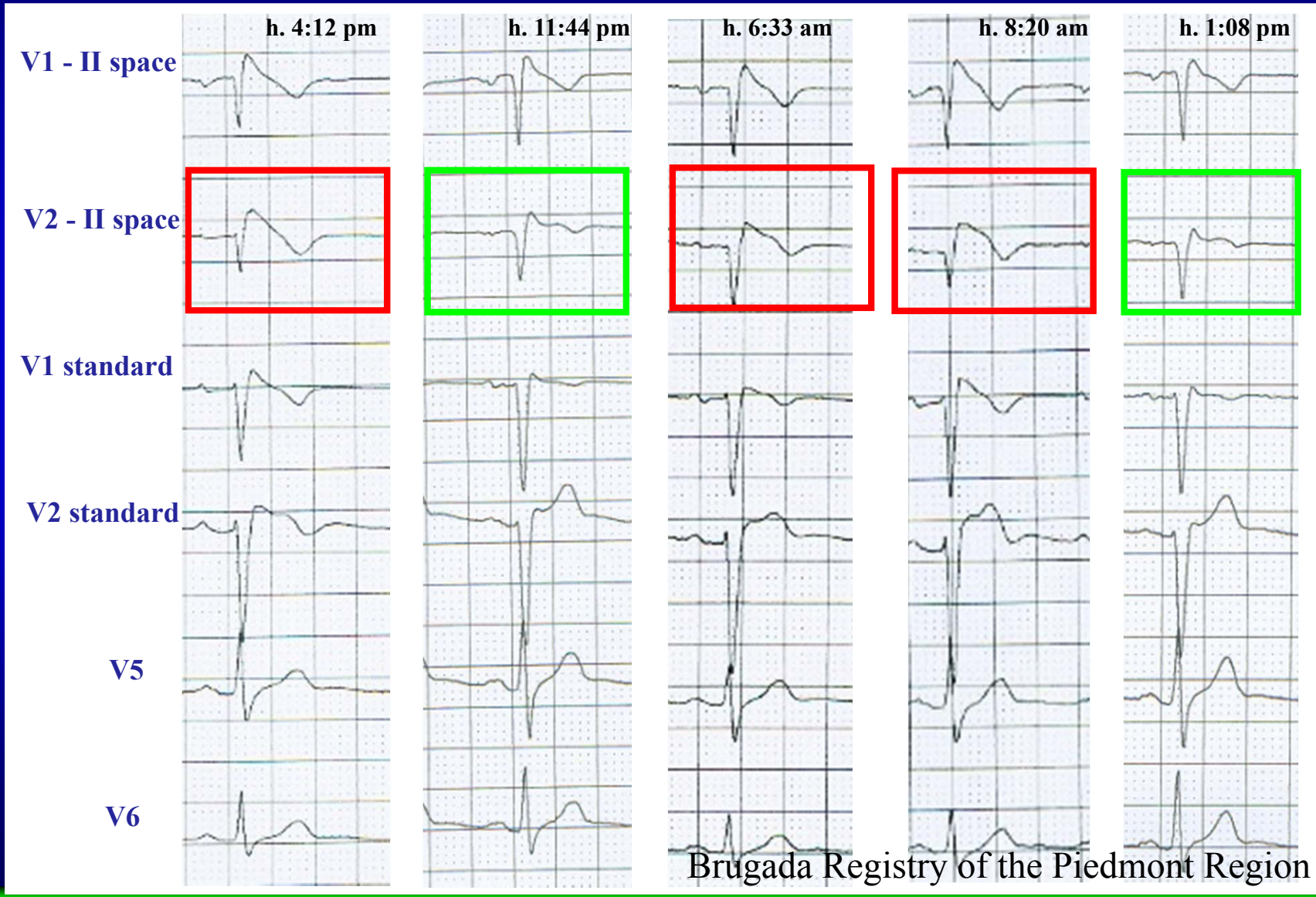
only 1 pt
had persistent type 1 ECG at follow-up



8 pts (29%)
with at least one spontaneous type 1 ECG at follow-up

Veltmann C, Borggrefe M. et al, Eur Heart J 2006

Intermittent spontaneous type 1 Brugada pattern at 12-lead 24-hour Holter monitoring



Brugada Registry of the Piedmont Region

ACCEPTED MANUSCRIPT

The American Journal of Cardiology

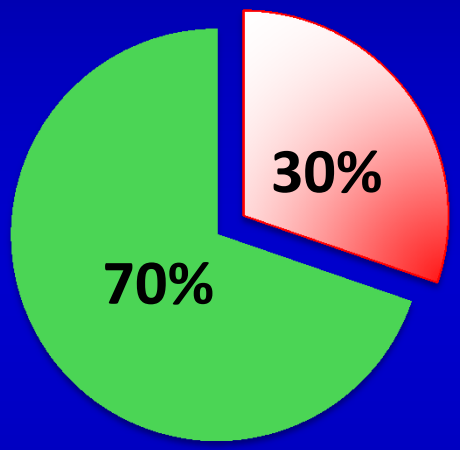
Prevalence of Type 1 Brugada Electrocardiographic Pattern Evaluated by 12-Lead 24-Hour Holter Monitoring.

Natascia Cerrato,[a1] MD, Carla Giustetto,[a1] MD, Elena Gribaudo,[a] MD, Elena Richiardi,[b] MD, Lorella Barbonaglia,[c] MD, Chiara Scrocco,[a] MD, Domenica Zema,[a] MD, and Fiorenzo Gaita,[a] MD.

Am J Cardiol 2014, doi: 10.1016/j.amjcard.2014.10.007

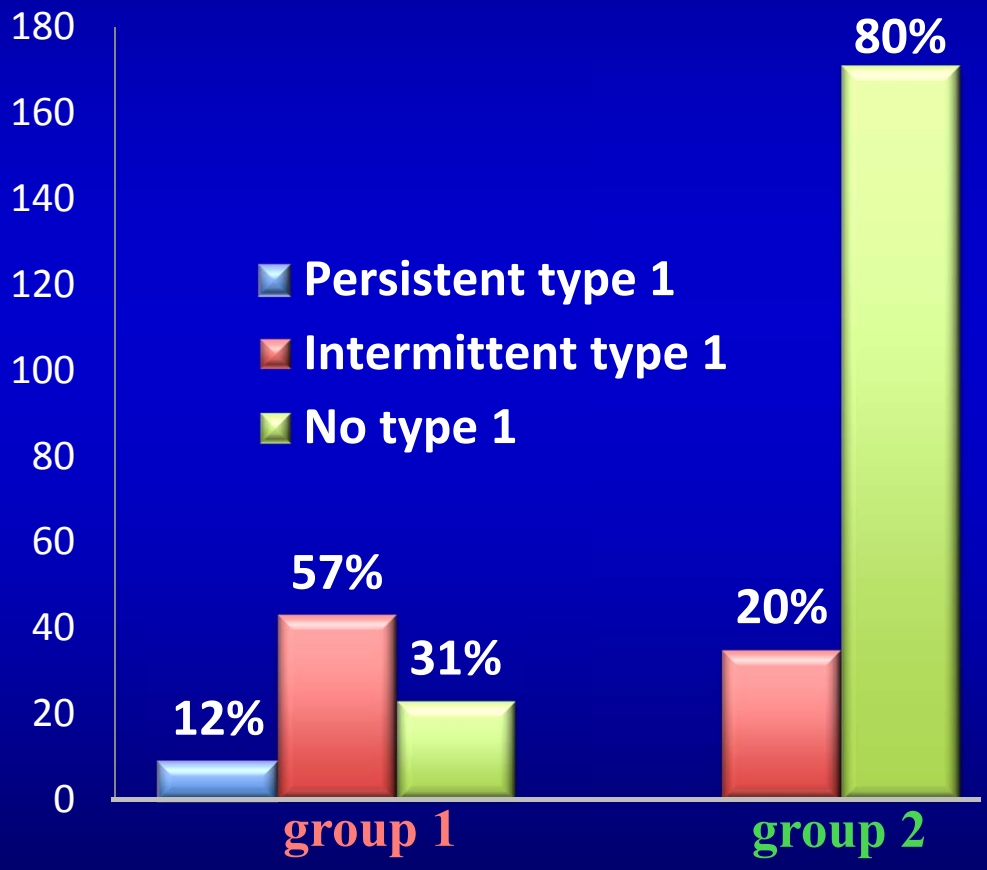
Brugada Piedmont Registry 684 patients

12 Lead - 24 hour Holter
251 patients



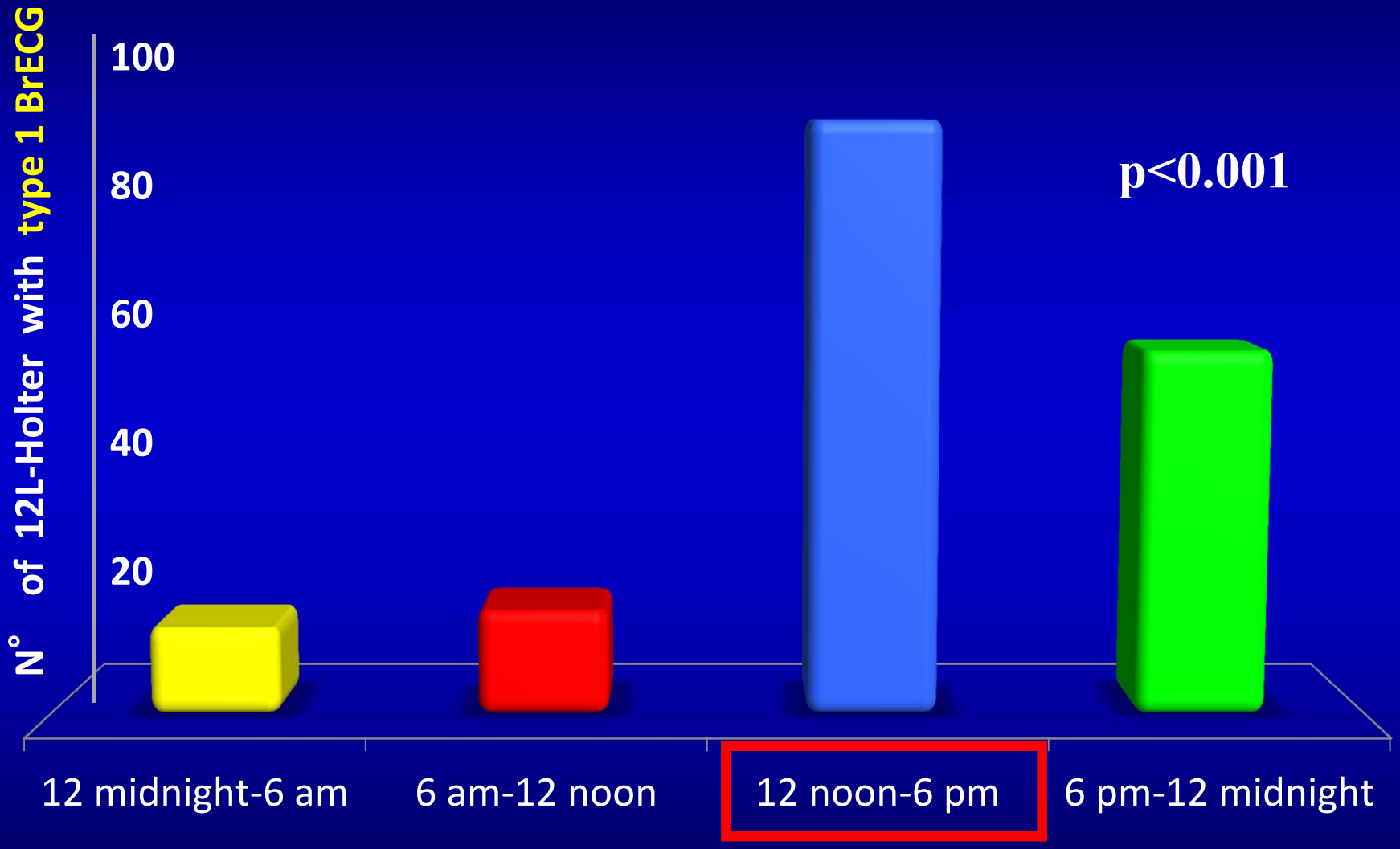
spontaneous type 1 at basal ECG (group 1)

drug-induced type 1 (group 2)



Cerrato N, Giustetto C, Gaita F, et al. Am J Cardiol 2014, doi: 10.1016/j.amjcard.2014.10.007

Circadian fluctuations of Brugada ECG pattern



Cerrato N, Giustetto C, Gaita F, et al. Am J Cardiol 2014, doi: 10.1016/j.amjcard.2014.10.007

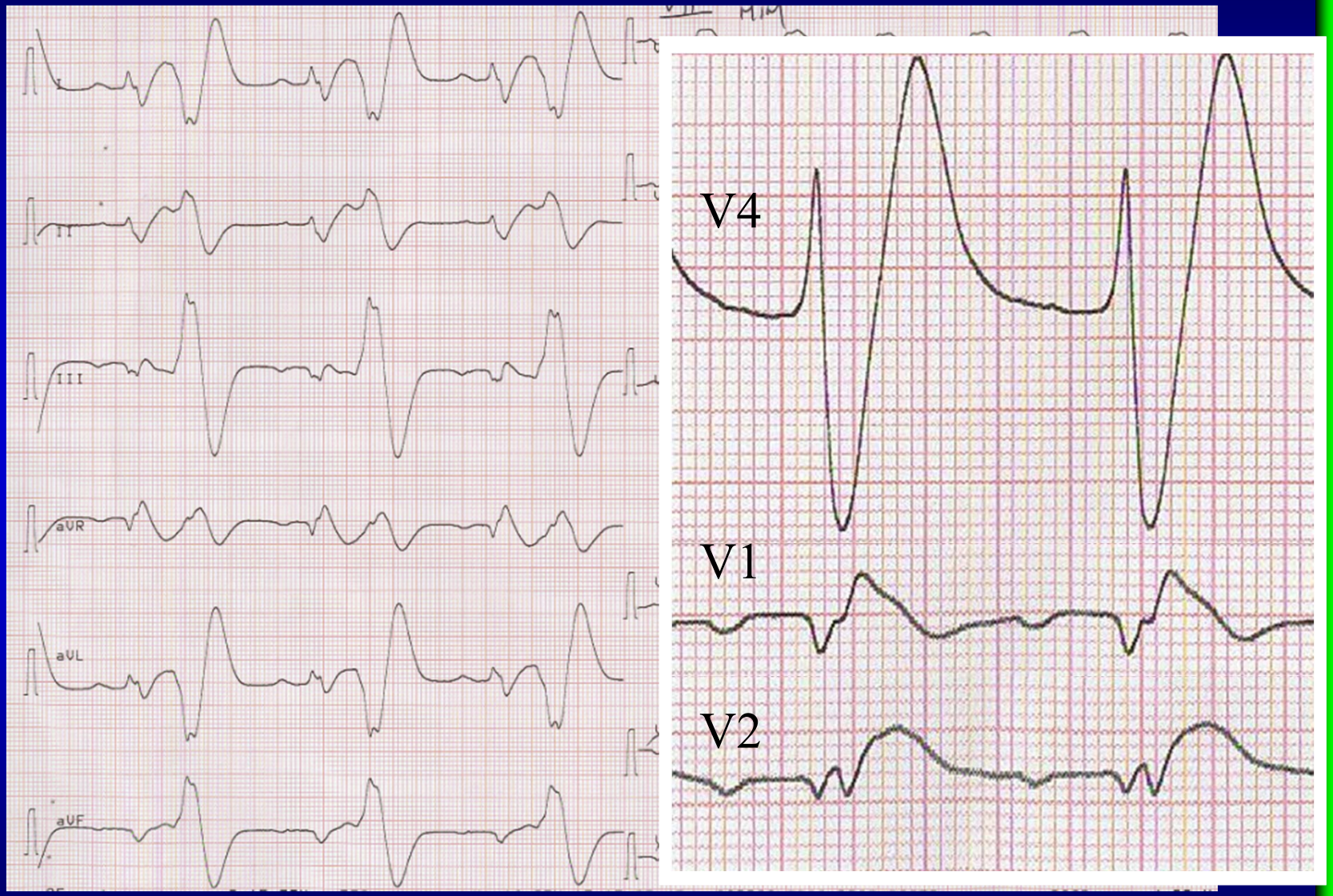
12 lead Holter monitoring:

- ✓ allows to identify, in group 2, at least **20% of subjects with spontaneous type 1**, who would have been considered at low risk, based only on periodic 12-lead ECGs

- ✓ might be the first screening test, in **alternative to pharmacological test**, which is not without risks, particularly in children, in presence of a borderline-diagnostic basal ECG and in the evaluation of family members

Cerrato N, Giustetto C, Gaita F, et al. Am J Cardiol 2014, doi: 10.1016/j.amjcard.2014.10.007

Arrhythmias during ajmaline challenge (5th minute)



1st degree AV block, QRS widening (180 ms), premature ventricular beats

Drug challenge with Na^+ channel blockers is not without risk

1043 ajmaline challenges performed from 1992 to 2013

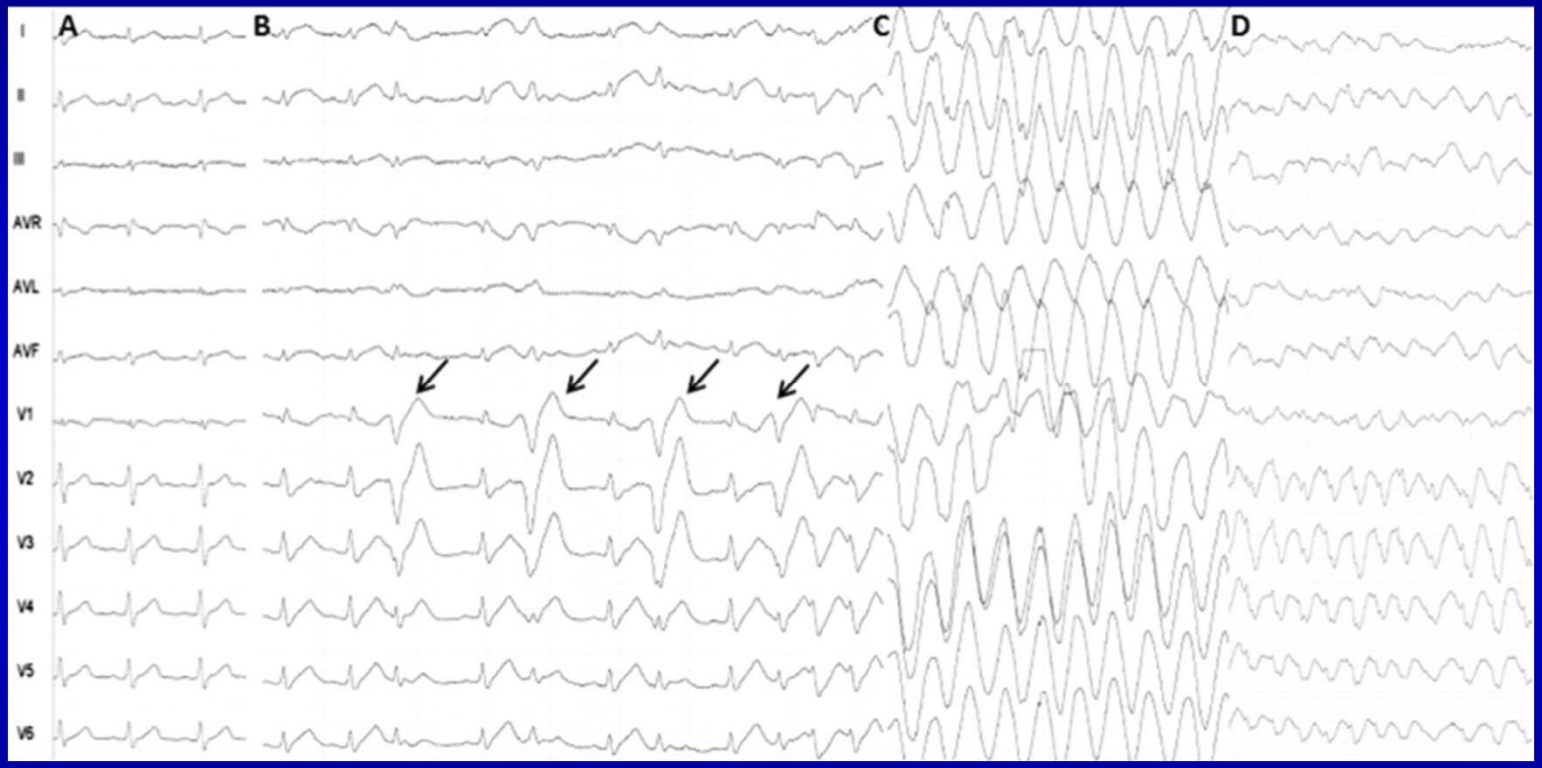
503 patients had an ajmaline-induced diagnosis of Brugada and 9 of them (1.8%) developed a life-threatening ventricular arrhythmia (VA) during the drug infusion.

- **Mean age of pts with VA: 26 ±18 years**
- **Three patients (33%) were children (6, 7, and 11 years)**

Age at the time of ajmaline challenge was significantly lower in patients with life-threatening VAs compared with patients without VAs (26 years *vs* 41 years; P < 0.01)

Conte G, Brugada P, et al, Heart Rhythm 2013;10:1869–1874

Drug challenge with Na^+ channel blockers is not without risk



Despite its challenging acute treatment, ventricular arrhythmias provoked by ajmaline test in patients with BrS might not predict a higher risk of further arrhythmic events.

Conte G, Brugada P, et al, Heart Rhythm 2013;10:1869–1874

Drug challenge

(ajmaline 1 mg/kg in 5 min or flecainide 2 mg/Kg in 10 min)

1) Continuous ECG recording during the test (standard and higher intercostal space)

1) Interruption when:
2) diagnostic Type 1 ST-segment elevation develops;
3) ST segment in Type 2 increases by ≥2 mm;
4) premature ventricular beats or other arrhythmias develop;
5) QRS widens to ≥130% of baseline.

3) Isoproterenol and sodium lactate may be effective antidotes.

Antzelevitch, PACE 2006; 29:1130–1159.
Conte G, Brugada P. et al, J Am Coll Cardiol 2014;63:2272–9

Ajmaline should NOT be used for drug test in subjects <16 years old

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Prevalence of Type 1 Brugada Electrocardiographic Pattern Evaluated by 12-Lead 24-Hour Holter Monitoring.

Natascia Cerrato,[a1] MD, Carla Giustetto,[a1] MD, Elena Gribaudo,[a] MD, Elena Richiardi,[b] MD, Lorella Barbonaglia,[c] MD, Chiara Scrocco,[a] MD, Domenica Zema,[a] MD, and Fiorenzo Gaita,[a] MD.

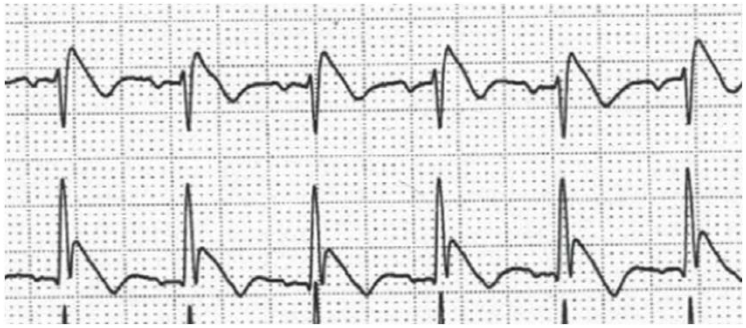
In our study, the 6 patients who came to the observation for spontaneous type 1 BrECG recorded during fever, never exhibited type 1 at 12L-Holter nor in other 12-lead ECGs recorded during the follow-up.

Cerrato N, Giustetto C, Gaita F, et al. Am J Cardiol 2014, doi: 10.1016/j.amjcard.2014.10.007

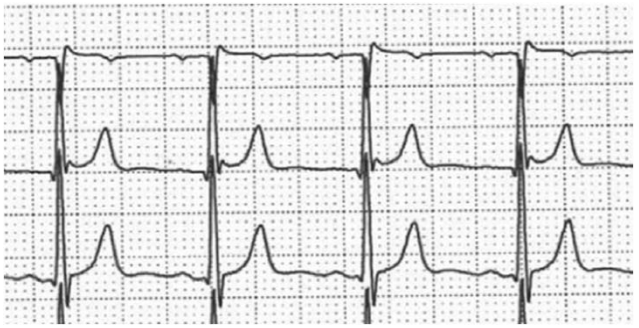
Fever-induced Brugada pattern: How common is it and what does it mean?

Arnon Adler, MD,[*] Guy Topaz, BMedSc,[*] Karin Heller, MD,[†] David Zeltser, MD,[‡] Tami Ohayon, MD,[†] Uri Rozovski, MD,[§] Amir Halkin, MD,[*] Raphael Rosso, MD,[*] Shay Ben-Shachar, MD,[¶] Charles Antzelevitch, PhD, FHRS,[‖] Sami Viskin, MD[*]

ECGs of 402 patients with fever and 909 without were evaluated. Type 1 Brugada pattern was 20 times more common in the febrile group (8 pts) than in the afebrile group (1 pt), 2% *vs* 0.1%, P =0.0001.



Temp 38.5° C

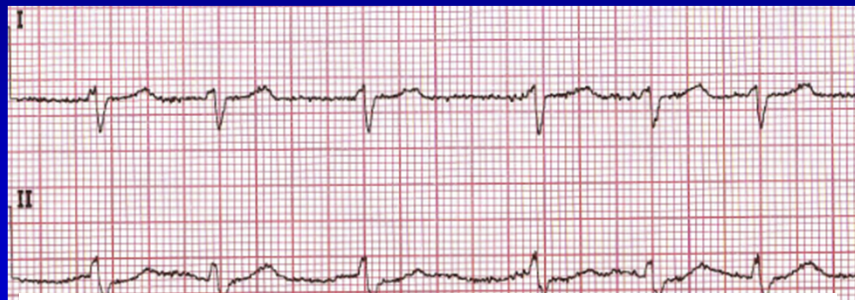


Afebrile

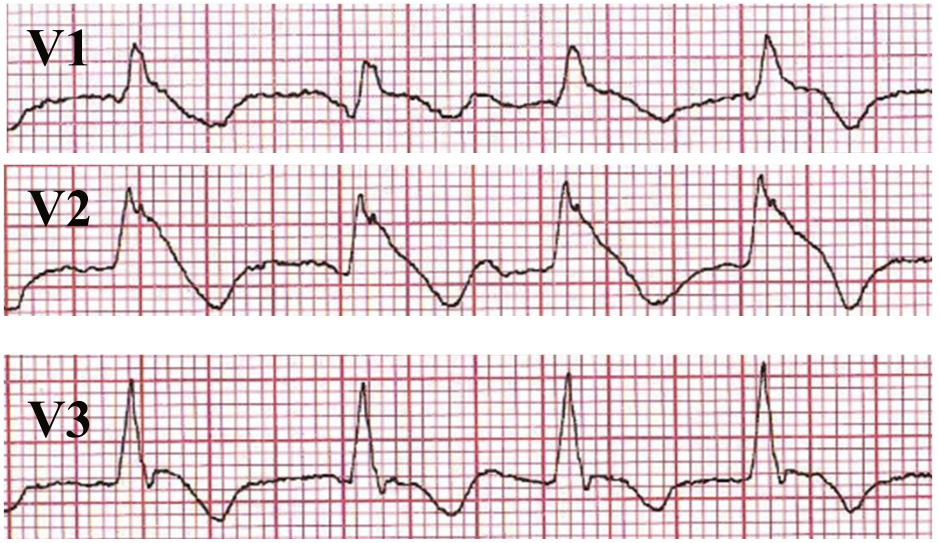
All patients with fever-induced type 1 Brugada pattern were asymptomatic and remained so during 30 months of follow-up.

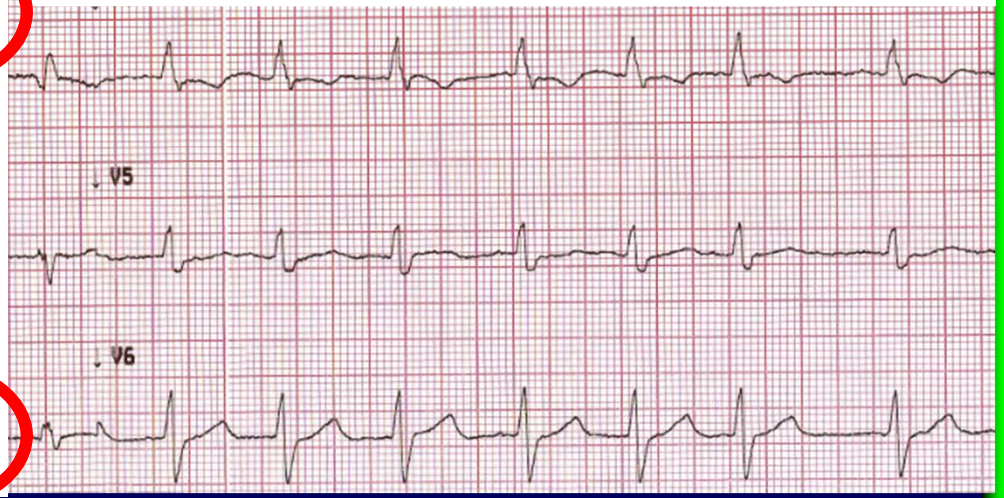
Heart Rhythm 2013;10:1375–1382

Prevalence of atrial fibrillation in subjects with Brugada ECG pattern

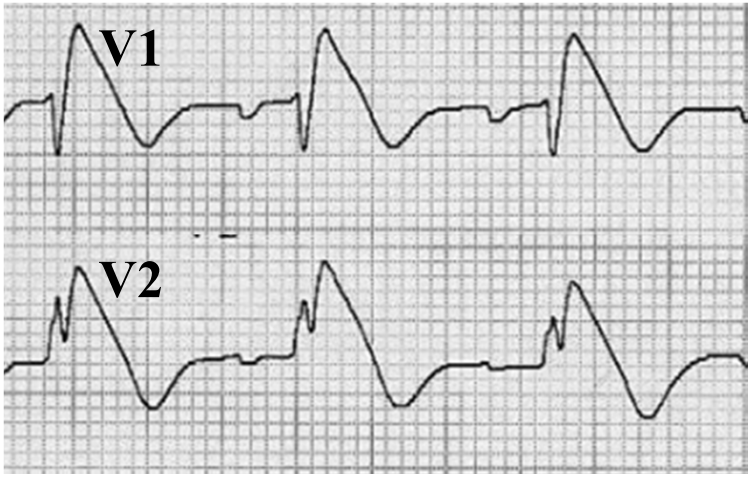


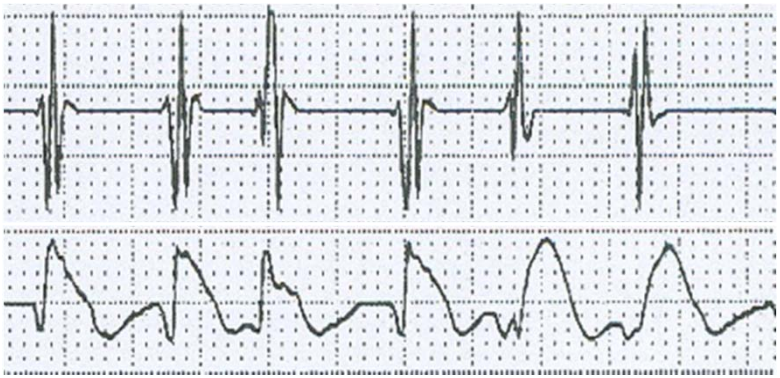
Brugada et al, 1992	25%
Itoh et al, 2001	30%
Morita et al, 2002	39%
Bordachar et al, 2004	19%
Letsas et al, 2007	20%
Schimpf, Gaita et al 2008	11%
Giustetto, Gaita et al, 2009	10%





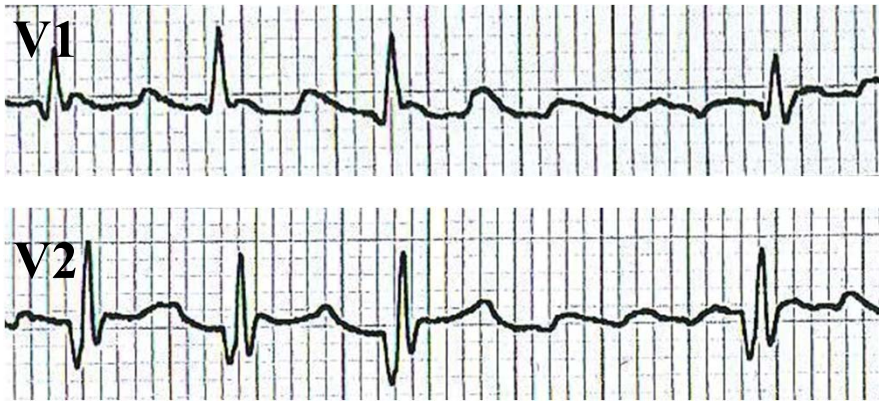
Patients in whom AF/AFl were documented after the diagnosis of Brugada ECG





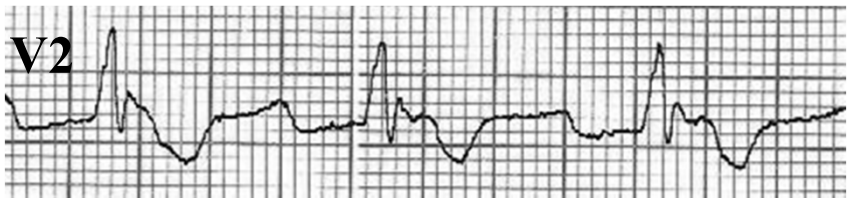
(ICD recording)

Patients with AF/AFL who developed Brugada pattern during Class IC antiarrhythmic therapy



"… patients identified as a consequence of sodium channel inhibitors assumption for atrial fibrillation presented a different clinical profile compared with the other enrolled patients."

Gaita F, Giustetto C, et al. Europace 2009; 11 (4): 507-513



Atrial fibrillation in a large population with Brugada electrocardiographic pattern: Prevalence, management, and correlation with prognosis

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BACKGROUND A high prevalence of atrial fibrillation/atrial flutter (AF/AFl) has been reported in small series of Brugada patients, with discordant data.

OBJECTIVE The purpose of this study was to analyze, in a large population of Brugada patients, the prevalence of AF/AFl, its correlation with prognosis, and the efficacy of hydroquinidine (HQ) treatment.

METHODS Among 560 patients with Brugada type 1 ECG (BrECG), 48 (9%) had AF/AFl. Three groups were considered: 23 patients with BrECG pattern recognized before AF/AFl (group 1); 25 patients first diagnosed with AF/AFl in whom Class IC antiarrhythmic drugs administered for cardioversion/prophylaxis unmasked BrECG (group 2); and 512 patients without AF/AFl (group 3). Recurrence of AF/AFl and occurrence of ventricular arrhythmias were evaluated at follow-up.

RESULTS Mean age was 47 ± 15 years, 59 ± 11 years, and 44 ± 14 years in groups 1, 2, and 3, respectively. Seven subjects (32%) in group 1 had syncope/aborted sudden death, 1 (4%) in group 2, and 122 (24%) in group 3. Ventricular arrhythmia occurred in three patients in group 1, none in group 2, and 10 in group 3 at median follow-up of 51, 68, and 41 months, respectively. Nine patients in group 1 and nine in group 2 received HQ for AF/AFl prophylaxis; on therapy, none had AF/AFl recurrence.

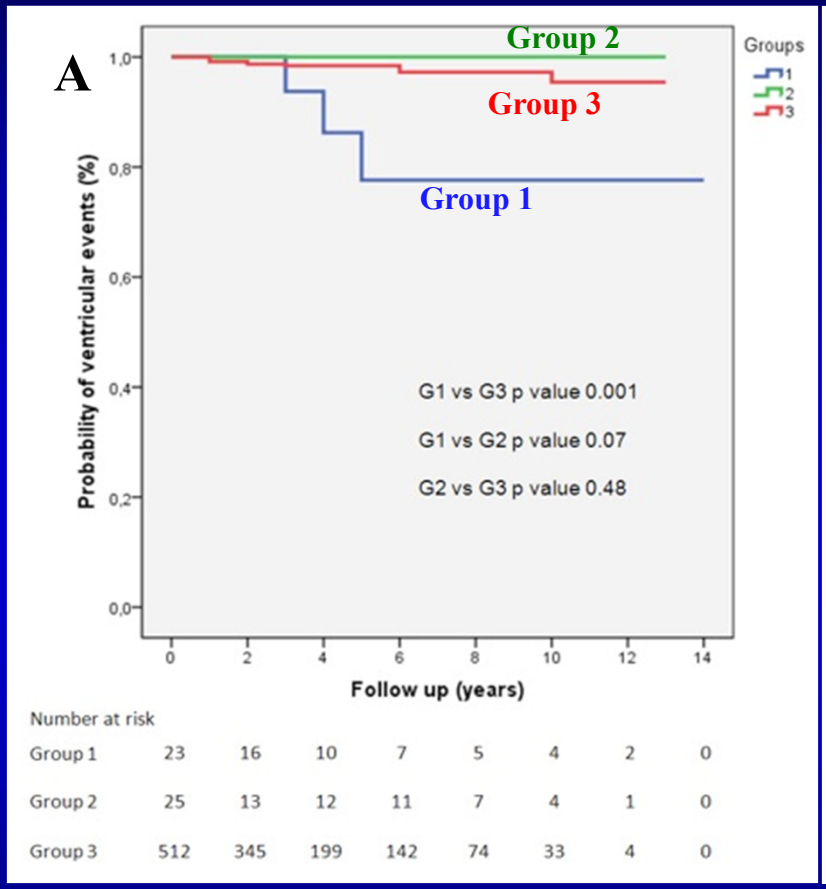
CONCLUSION Prevalence of AF/AFl in Brugada patients is higher than in the general population of the same age. Patients in group 1 are younger than those in group 2 and have a worse prognosis compared to both groups 2 and 3. HQ therapy has proved useful and safe in patients with AF/AFl and BrECG.

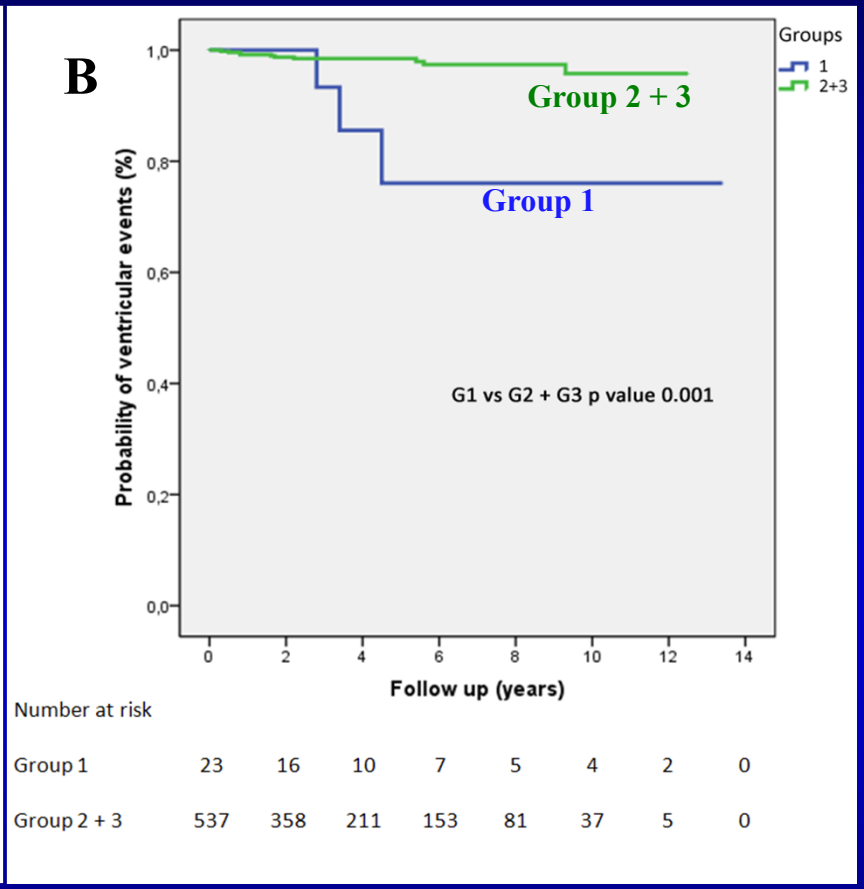
KEYWORDS Brugada syndrome; Atrial fibrillation; Hydroquinidine; Ventricular arrhythmia; SCN5A; SCN1B; Class IC antiarrhythmic drug

ABBREVIATIONS **AF** = atrial fibrillation; **AFl** = atrial flutter; **aSD** = aborted sudden death; **BrECG** = Brugada type 1 electrocardiographic pattern; **HQ** = hydroquinidine; **ICD** = implantable cardioverter-defibrillator; **IQR** = interquartile range; **VF** = ventricular fibrillation

(Heart Rhythm 2014;11:259–265)

Pts in group 1 are younger than those in group 2 and have a worse prognosis compared to both groups 2 and 3





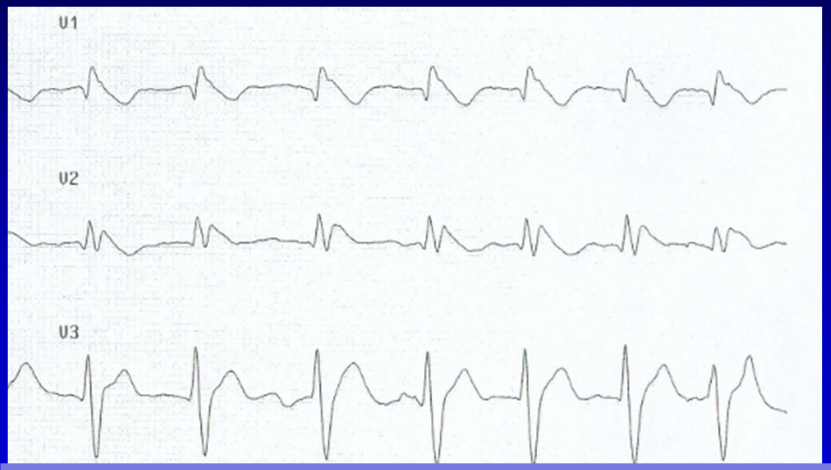
Group 1: BrECG pattern recognized before AF/AFl

Group 2: BrECG appeared for the first time after IC drugs given for AF/AFl

Group 3: pts of the Brugada Registry without AF/AFl

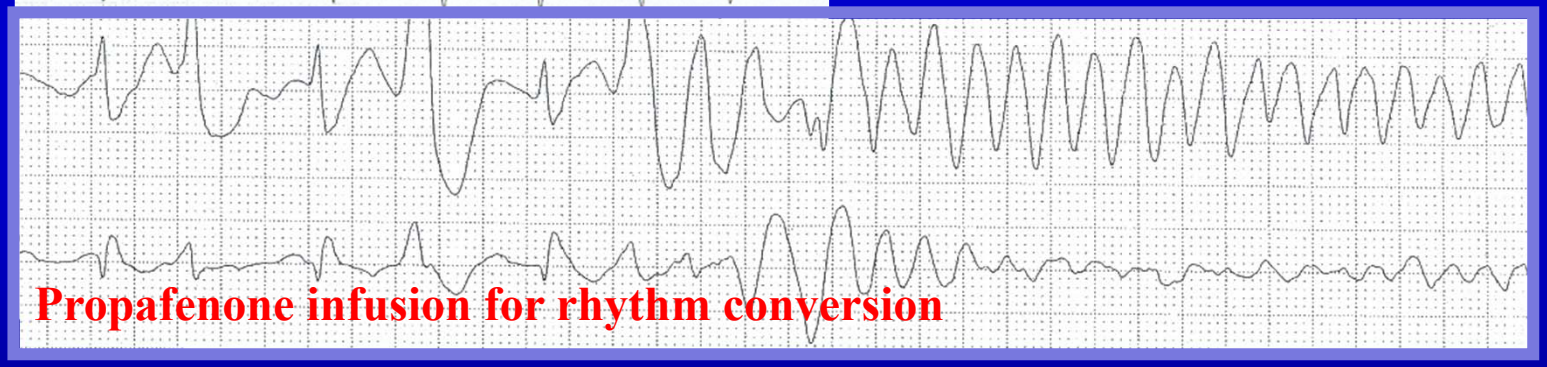
Giustetto C, Gaita F. et al, Heart Rhythm 2014;11:259–265

AF and Brugada ECG: which antiarrhythmic drug?



Class IC drugs, amiodarone, Ca^{+} - channel blockers are not indicated, as they can increase ST segment elevation and induce ventricular arrhythmias.

(Postema et al, Heart Rhythm 2009;6:1335)



In our study HYDROQUINIDINE was effective and safe in patients with BrECG and concomitant AF/Afl . It should be considered the antiarrhythmic of choice in this specific subgroup of patients.

Giustetto C, Gaita F. et al, Heart Rhythm 2014;11:259–265

Conclusions:

In the subjects with drug induced Brugada ECG, spontaneous type 1 ECG should be searched also in leads V1- V2 in 2^{nd}-3^{rd}intercostal space and with 12-lead Holter monitoring

These patients have a low arrhythmic risk

provided they avoid the use of drugs that may induce or enhance ST elevation (www.brugadadrugs.org)

and treat immediately fever with antipyretic drugs

DRUGS TO BE AVOIDED

Antiarrhythmic drugs: Ajmaline, Flecainide, Pilsicainide, Procainamide, Propafenone

Psychotropic drugs: Amitriplyline, Clomipramine, Desipramine, Lithium, Loxapine, Nortriptyline, Oxcarbazepine, Trifluoperazine

Anesthetics / analgesics: Bupivacaine, Procaine, Propofol

Other substances: Acetylcholine, Alcohol (toxicity), Cocaine, Ergonovine

DRUGS PREFERABLY AVOIDED

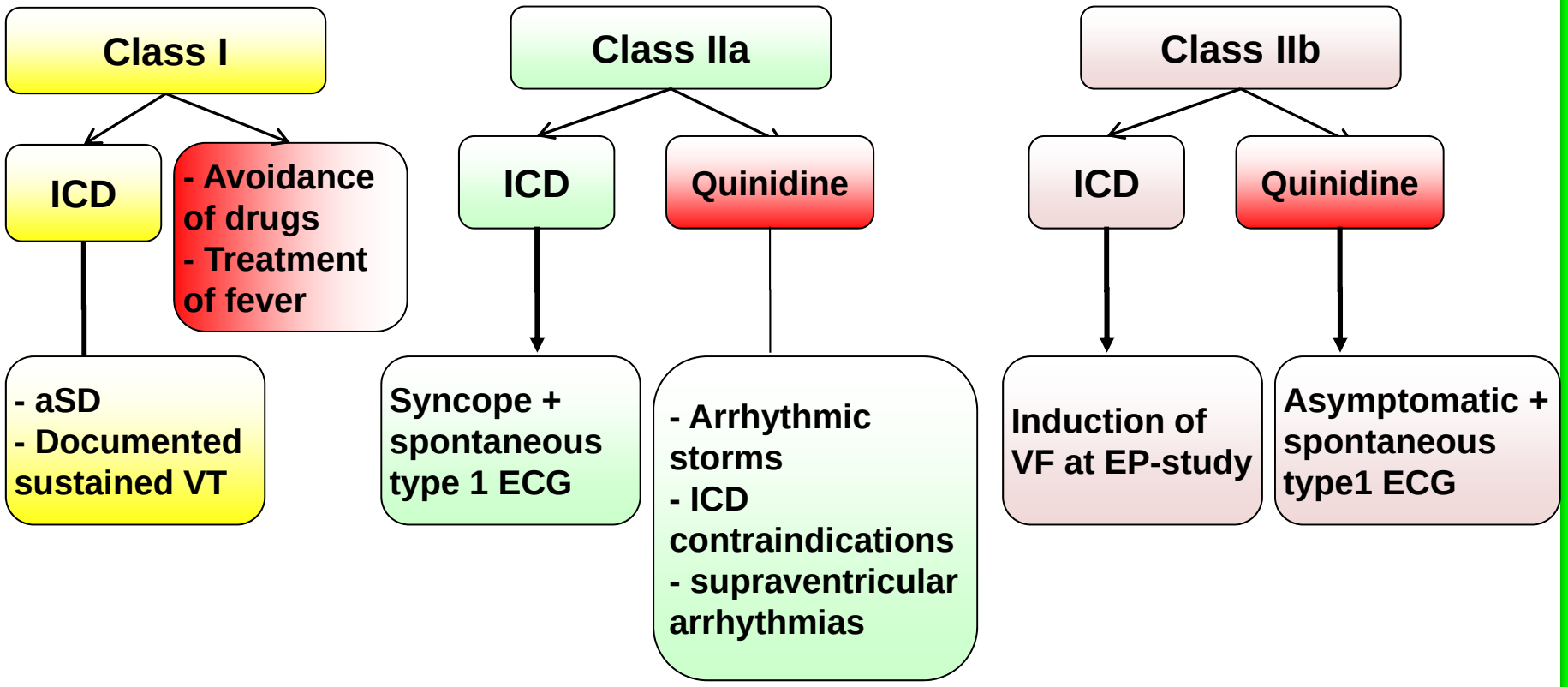
Antiarrhythmic drugs: Amiodarone, Cibenzoline, Disopyramide, Lidocaine*, Propranolol, Verapamil

Psychotropic drugs: Carbamazepine, Clothiapine, Cyamemazine, Dosulepine, Doxepine, Fluoxetine, Fluvoxamine, Imipramine, Maprotiline, Paroxetine, Perphenazine, Phenytoin, Thioridazine

Anesthetics / analgesics: Ketamine, Tramadol

Other substances: Demenhydrinate, Diphenhydramine, Edrophonium, Indapamide, Metoclopramide, Terfenadine/Fexofenadine

HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes



class III → ICD is NOT INDICATED in asymptomatic + drug-induced type 1 ECG

Priori SG et al, Heart Rhythm 2013, 10; 19321963