Drug-induced Brugada syndrome: clinical and therapeutic implications

Venice Arrhythmias 2015

Pieter G. Postema, MD, PhD
AMC Amsterdam

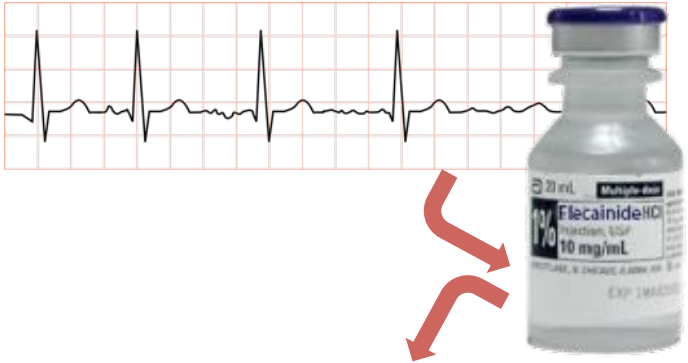
Disclosures

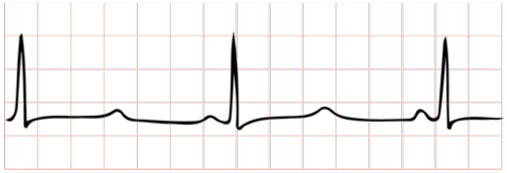
October 16 - 18
14th EDITION 2015

MY CONFLICTS OF INTEREST ARE:

I am the chair of BrugadaDrugs.org

Do we have a problem?





Viskin ea. Heart Rhythm 2009

Risk stratification

- Brugada ECG ≠ ICD …
- Risk stratification to guide therapy

Conservative

- Majority

?

Drugs / invasive

- Minority

Current guideline

2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)

Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC)

Authors/Task Force Members: Silvia G. Priori* (Chairperson) (Italy), Carina Blomström-Lundqvist* (Co-chairperson) (Sweden), Andrea Mazzanti† (Italy), Nico Blom* (The Netherlands), Martin Borggrefe (Germany), John Camm (UK), Perry Mark Elliott (UK), Donna Fitzsimons (UK), Robert Hatala (Slovakia), Gerhard Hindricks (Germany), Paulus Kirchhof (UK/Germany), Keld Kjeldsen (Denmark), Karl-Heinz Kuck (Germany), Antonio Hernandez-Madrid (Spain), Nikolaos Nikolaou (Greece), Tone M. Norekvål (Norway), Christian Spaulding (France), and Dirk J. Van Veldhuisen (The Netherlands)

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

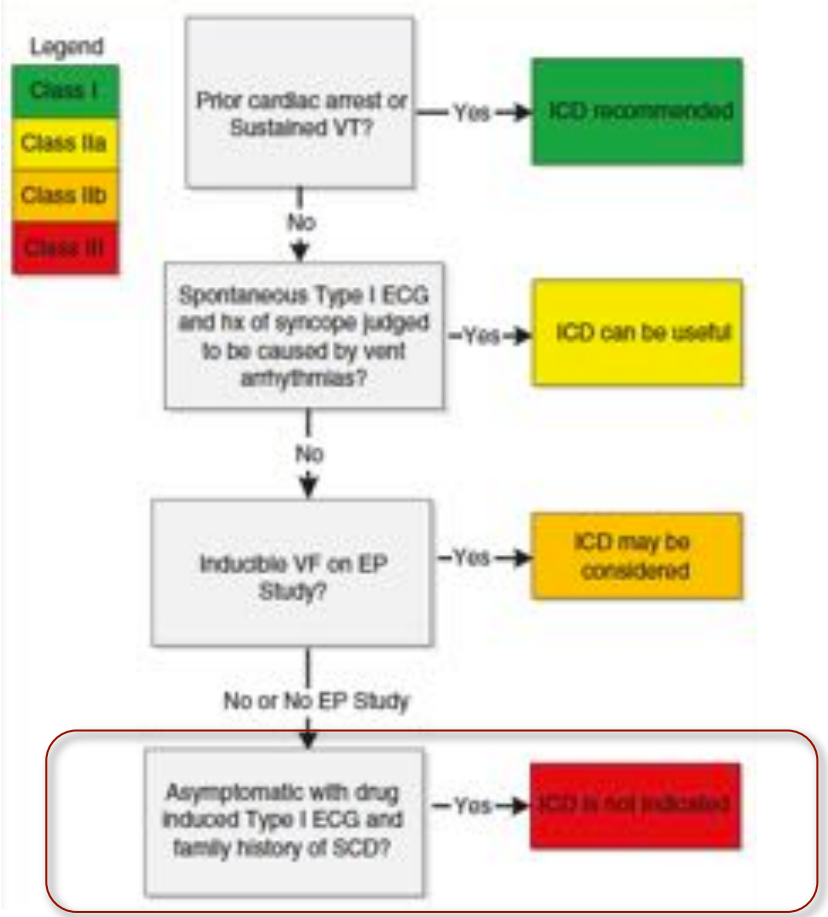
Silvia G. Priori, (HRS Chairperson)[1], Arthur A. Wilde, (EHRA Chairperson)[2], Minoru Horie, (APHRS Chairperson)[3], Yongkeun Cho, (APHRS Chairperson)[4], Elijah R. Behr[5], Charles Berul[6], Nico Blom[7*], Josep Brugada[8], Chern-En Chiang[9], Heikki Huikuri[10], Prince Kannankeril[11‡], Andrew Krahn[12],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

Priori, Wilde ea. Europace 2013, Priori ea. Europace 2015

Risk stratification and management in Brugada Syndrome

Recommendations	Class[a]	Level[b]	Ref.[c]
The following lifestyle changes are recommended in all patients with a diagnosis of Brugada syndrome: (a) Avoidance of drugs that may induce ST-segment elevation in right precordial leads (http://www.brugadadrugs.org) (b) Avoidance of excessive alcohol intake and large meals (c) Prompt treatment of any fever with antipyretic drugs.	I	C	This panel of experts
ICD implantation is recommended in patients with a diagnosis of Brugada syndrome who (a) Are survivors of an aborted cardiac arrest and/or (b) Have documented spontaneous sustained VT.	I	C	451

Current guideline



ICD implantation should be considered in patients with a spontaneous diagnostic type I ECG pattern and history of syncope.	IIa	C	451
Quinidine or isoproterenol should be considered in patients with Brugada syndrome to treat electrical storms.	IIa	C	453
Quinidine should be considered in patients who qualify for an ICD but present a contraindication or refuse it and in patients who require treatment for supraventricular arrhythmias.	IIa	C	454
ICD implantation may be considered in patients with a diagnosis of Brugada syndrome who develop VF during PVS with two or three extrastimuli at two sites.	IIb	C	120
Catheter ablation may be considered in patients with a history of electrical storms or repeated appropriate ICD shocks.	IIb	C	201, 455

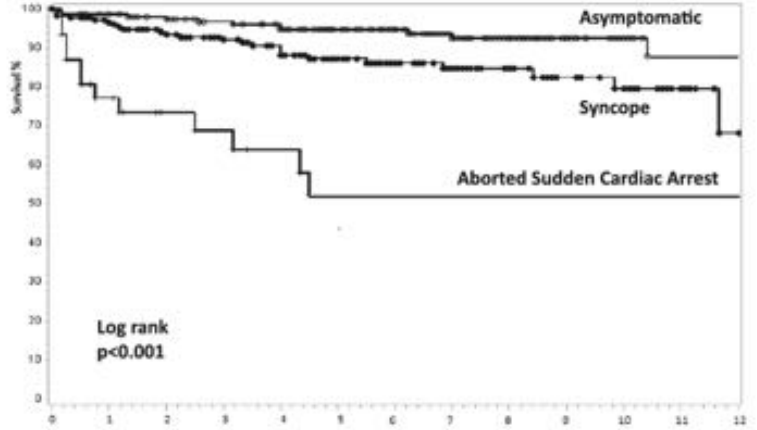
Priori, Wilde ea. Europace 2013, Priori ea. Europace 2015

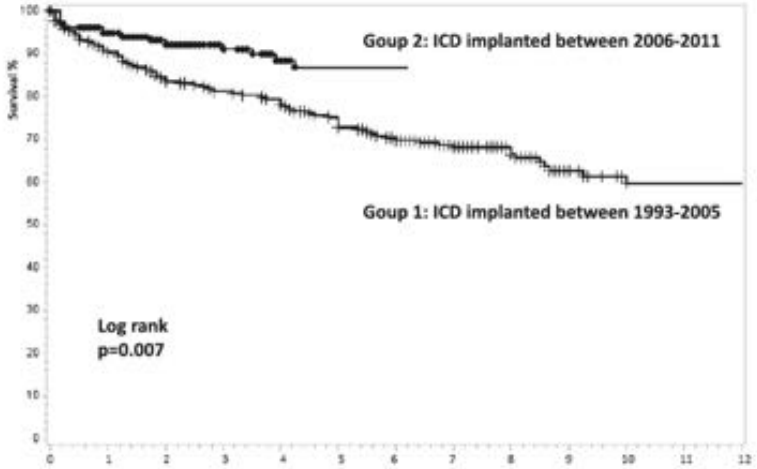
But every supposed benefit…

Table 3. Rate of Events After ICD Implantation

Year	Appropriate Shock Rate, %			Inappropriate Shock Rate, %	Lead Failure Rate, %
	Aborted SCA	Syncope	Asymptomatic		
1	25	3	1	8	1
2	30	6	2	13	2
3	36	7	4	15	5
4	41	10	6	18	7
5	48	11	6	23	13
10	48	19	12	37	29

ICD indicates implantable defibrillator-cardioverter; and SCA, sudden cardiac arrest.





Sacher ea. Circ 2013

May also cause harm…

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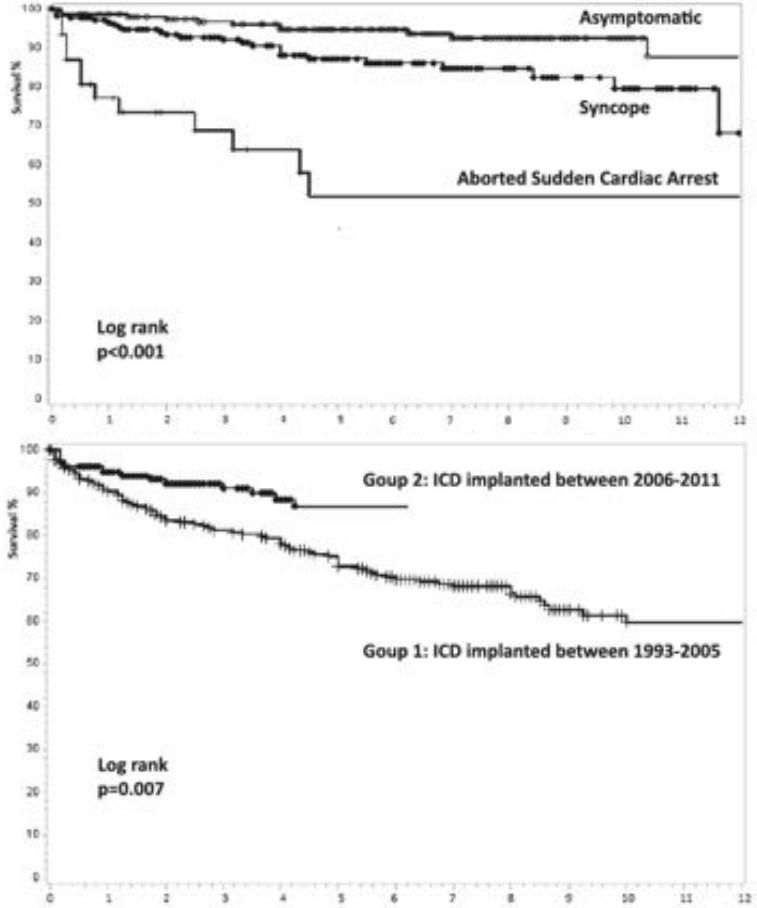


Sacher ea. Circ 2013

May also cause harm…

Either without ICD

2 asymptomatic subjects with Brugada pattern diagnosed during the period of the study but not implanted with an ICD died suddenly. The first patient was a 21-year-old man diagnosed after an ajmaline test because of familial BrS screening. He had a negative EPS (2 sites, 2 cycles, 3 extrastimuli down to 200 milliseconds) but died suddenly during his sleep 8 months later. The second patient, a 56-year-old asymptomatic man, underwent ajmaline test after a routine preoperative ECG performed before surgery showed a type 2 ECG pattern. He had no family history of SCA and did not undergo EPS. He died suddenly during sleep 16 months later. No autopsy was performed on either patient.

Drug induced Brugada ECG

Or with ICD

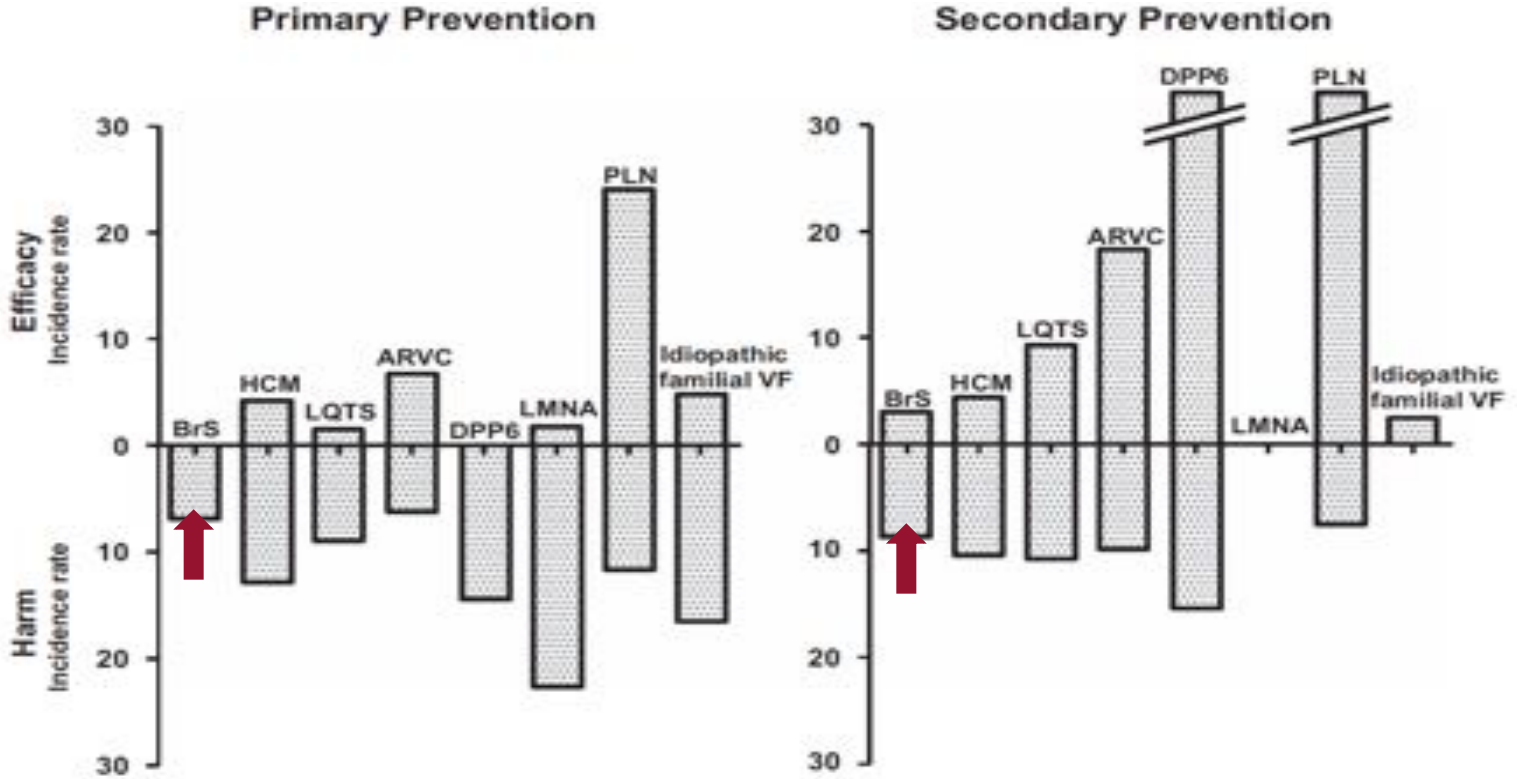
During a mean follow-up of 77±42 months (median, 76 months; range, 6–220 months) after ICD implantation, 15 patients (4%) were lost to follow-up, and 7 patients (1.8%) died. Mean age at death was 59±12 years, with causes of death including malignancy (n=3), suicide (n=2), severe trauma without preceding syncope (n=1), and inappropriate ICD discharge resulting from lead failure (n=1).

Two patients developed VF as a result of an inappropriate shock that could not be terminated by the device because of lead failure. One patient survived owing to prompt resuscitation maneuvers, but the second patient died.

Drug induced Brugada ECG

Sacher ea. Circ 2013

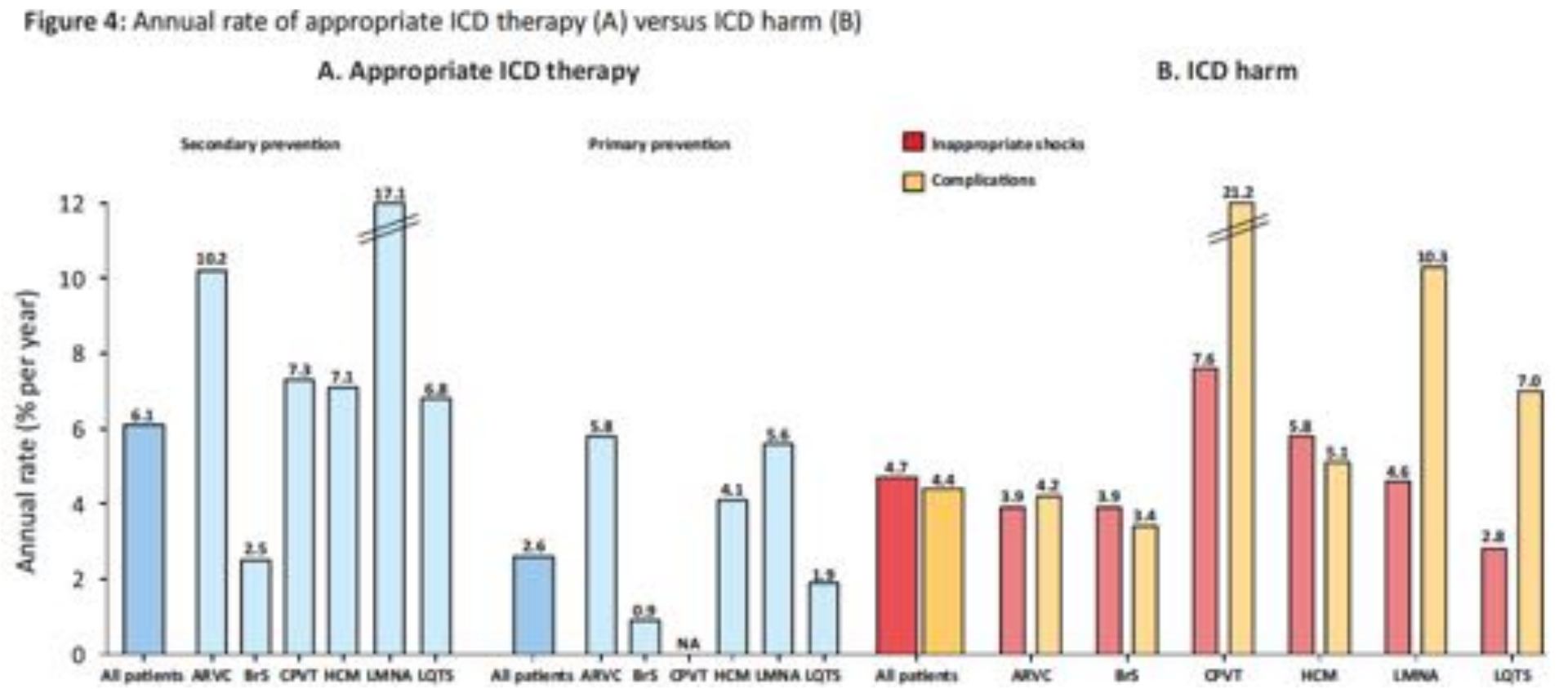
Benefit or harm in whom?



	Primary Prevention								Secondary Prevention							
	BrS	HCM	LQTS	ARVC	DPP6	LMNA	PLN	Idiopathic familial VF	BrS	HCM	LQTS	ARVC	DPP6	LMNA	PLN	Idiopathic familial VF
Total (N)	29	36	14	14	30	23	12	8	46	31	41	33	2	1	8	5
Median follow-up (months)	48	30	46	32	35	28	39	33	65	68	61	64	69	65	55	88
Appropriate shocks (N)	0	4	1	3	0	1	6	1	7	7	15	18	2	0	6	1
Serious harm (N)	8	10	3	3	9	9	4	3	18	13	16	13	1	0	2	0

Olde Nordkamp ea. Circ AEP 2013

Benefit or harm in whom?



Systematic review & meta-analyse of 63 studies comprising 4916 patients (1037 with Brugada)

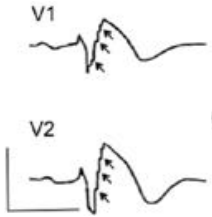
Olde Nordkamp, Postema ea. Heart Rhythm 2015 in press

Risks in patients without VT/VF

Non-invasive parameters

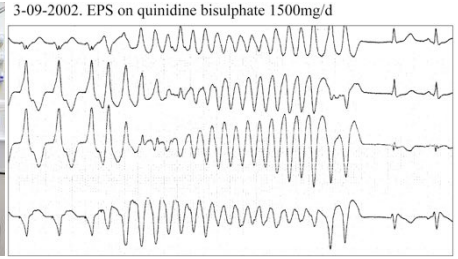
- Symptoms, triggers, ECG indices, genetics?



Invasive parameters

- EP study?

Risks in asymptomatic patients?

Risk of what?

Cardiac arrest without ICD or appropriate shock / death with ICD?

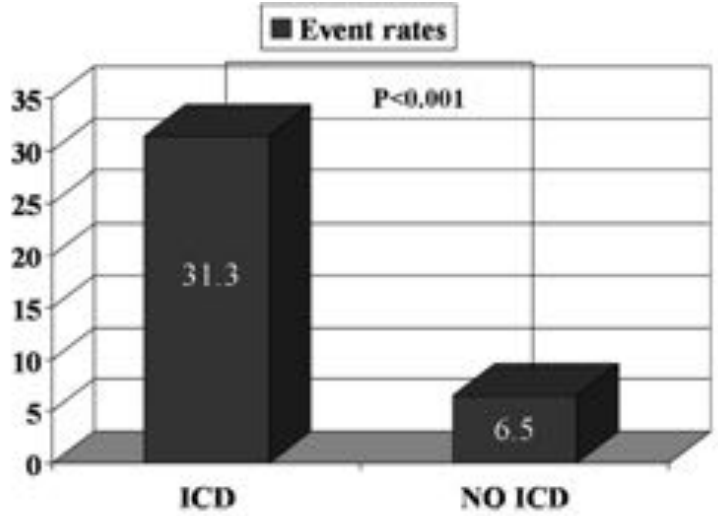


Figure 1 Event rates per 1000 patient-years of follow-up in the cumulative analysis of articles listed in Table 2. ICD = implantable cardioverter-defibrillator.

For patients without an ICD, only in 3 studies[10,12,13] could the prevalence of risk factors be established in patients with these events. These studies recorded 5 cases of SD in 491 patients. A spontaneous type 1 ECG pattern was present in 5 of 5, familial SD in 1 of 5, syncope in 0 of 5, and EPS was unavailable in 4 and negative in 1. Thus, few data on the prediction of SD are available and, paradoxically, with the exception of spontaneous type 1 ECG pattern, the risk factors considered seem to be of little use.

Delise ea. Heart Rhythm 2014

Risks in asymptomatic patients?

Table 3: Clinical characteristics patients presenting arrhythmic events during follow-up

	Event	Gender	Age	Proband	Family History of SCD	Spontaneous type I	Inducible VA	f-QRS
1	SCD	Male	39.2	Yes	No	No	No	No
2	SCD	Female	47.0	No	Yes	No	Patient refused EPS	No
3	Aborted SCD	Male	53.8	Yes	No	No	No	Yes
4	ICD shock	Male	10.7	No	Yes	No	Yes	No
5	ICD shock	Male	57.5	No	Yes	Yes	Yes	No
6	ICD shock	Male	47.8	Yes	No	Yes	Yes	Yes
7	ICD shock	Male	62.6	No	No	Yes	Yes	No
8	ICD shock	Female	43.2	No	No	No	Yes	No
9	ICD shock	Male	69.8	No	Yes	No	No	No

SCD: sudden cardiac death, Inducible VA: indicates if a ventricular arrhythmia was induced during electrophysiological study, EPS: electrophysiological study, f-QRS: fragmentation of QRS complex, ICD: implantable cardioverter defibrillator.

Sieira ea. Circ AEP 2015 in press

Risks in patients without VT/VF?

Table 2 Patients With Events at Follow-Up

Patient ID #	Sex	Age (yrs)*	Family History of SCD	Spontaneous Type 1 ECG	History of Syncope	Inducibility	VRP <200 ms	QRS-f	*SCN5A* Mutation	Event Type
4	M	43	–	+	–	+	+	–	–	ICD shock
10	M	35	–	+	–	–	–	–	+	ICD shock
174	M	69	+	+	+	+	+	+	N.A.	ICD shock
22	M	40	–	+	+	–	+	–	–	ICD shock
46	M	45	–	+	+	–	+	+	–	ICD shock
51	M	57	+	–	+	–	+	+	–	ICD shock
58	M	32	–	+	–	+	–	–	N.A.	ICD shock
63	M	23	–	+	–	–	+	+	N.A.	Resuscitated CA
73	F	58	–	+	+	–	+	+	N.A.	ICD shock
86	M	43	+	+	–	–	+	+	–	ICD shock
132	F	66	+	+	+	+	–	–	N.A.	ICD shock
195	F	33	+	+	+	–	+	+	+	ICD shock
214	M	50	–	+	–	–	+	–	–	ICD shock
264	M	42	–	+	–	+	+	–	+	ICD shock

*Age at enrollment.
CA = cardiac arrest; ICD shock = appropriate implantable cardioverter-defibrillator intervention; N.A. = deoxyribonucleic acid not available; SCD = sudden cardiac death; other abbreviations as in Table 1.

Priori ea. JACC 2012

Risks with drug-induced type-1?

Table 3 Variables Related to the Occurrence of Cardiac Events During Follow-Up in the Entire Population (Cox Regression Model)

	Overall Population					
	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	p Value	HR	95% CI	p Value
Gender	4.45	1.36-14.58	0.014	2.82	0.64-12.41	NS
Previous AF	2.63	1.24-5.58	0.012	2.16	0.93-5.03	0.07
Symptoms at diagnosis						
Syncope	3.43	1.5-7.83	0.003	1.86	0.7-4.97	NS
Aborted SCD	11.59	5.01-26.79	<0.001	8.45	3.17-22.55	<0.001
Spontaneous type-1 ECG	2.7	1.3-5.58	0.008	1.4	0.59-3.33	NS
Inducibility of VF (EPS)	5.33	2.34-12.15	<0.001	2.93	1.14-7.55	0.02

	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				

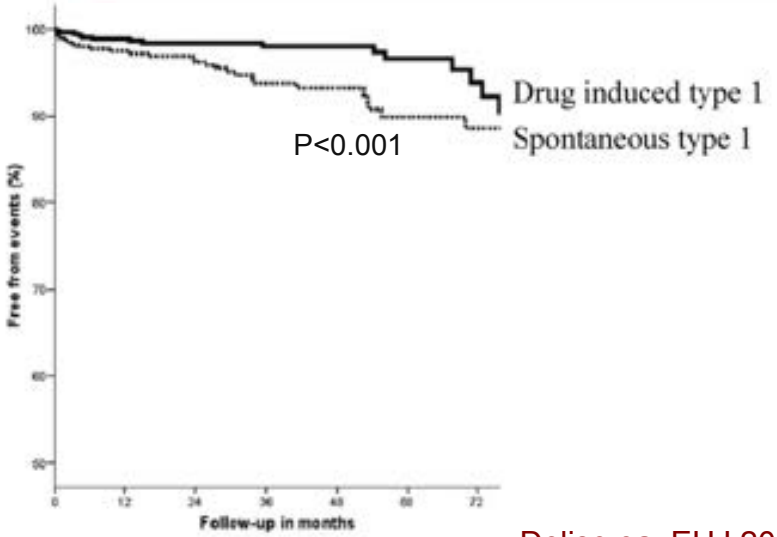
FH indicates family history; inferolateral ER, inferolateral early repolarization; AF, atrial fibrillation; Sp. type 1, spontaneous type 1 ST-elevation on 12-lead ECG at baseline; VF induc. (apex/OT), VF induction by programmed pacing at the RV apex or RV outflow tract; and VF induc. (apex), VF induction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

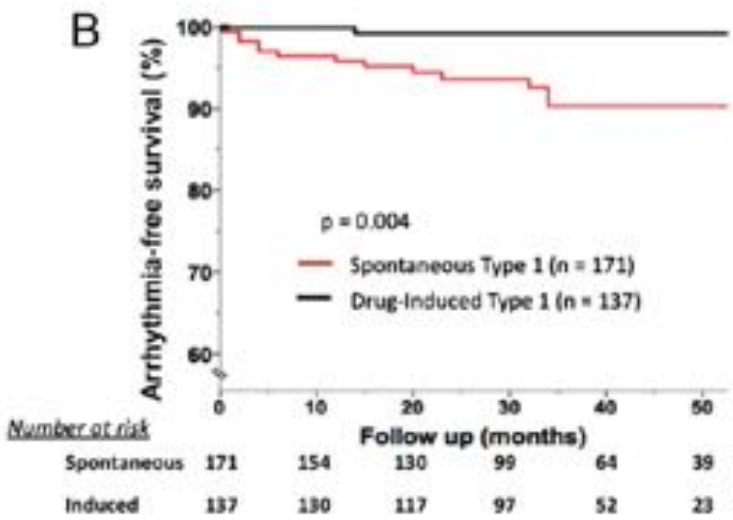
Benito ea. JACC 2008, Kamakura ea. Circ AEP 2009

Risks with drug-induced type-1?

Table 6 Univariate and multivariate analysis in the entire population of 320 cases

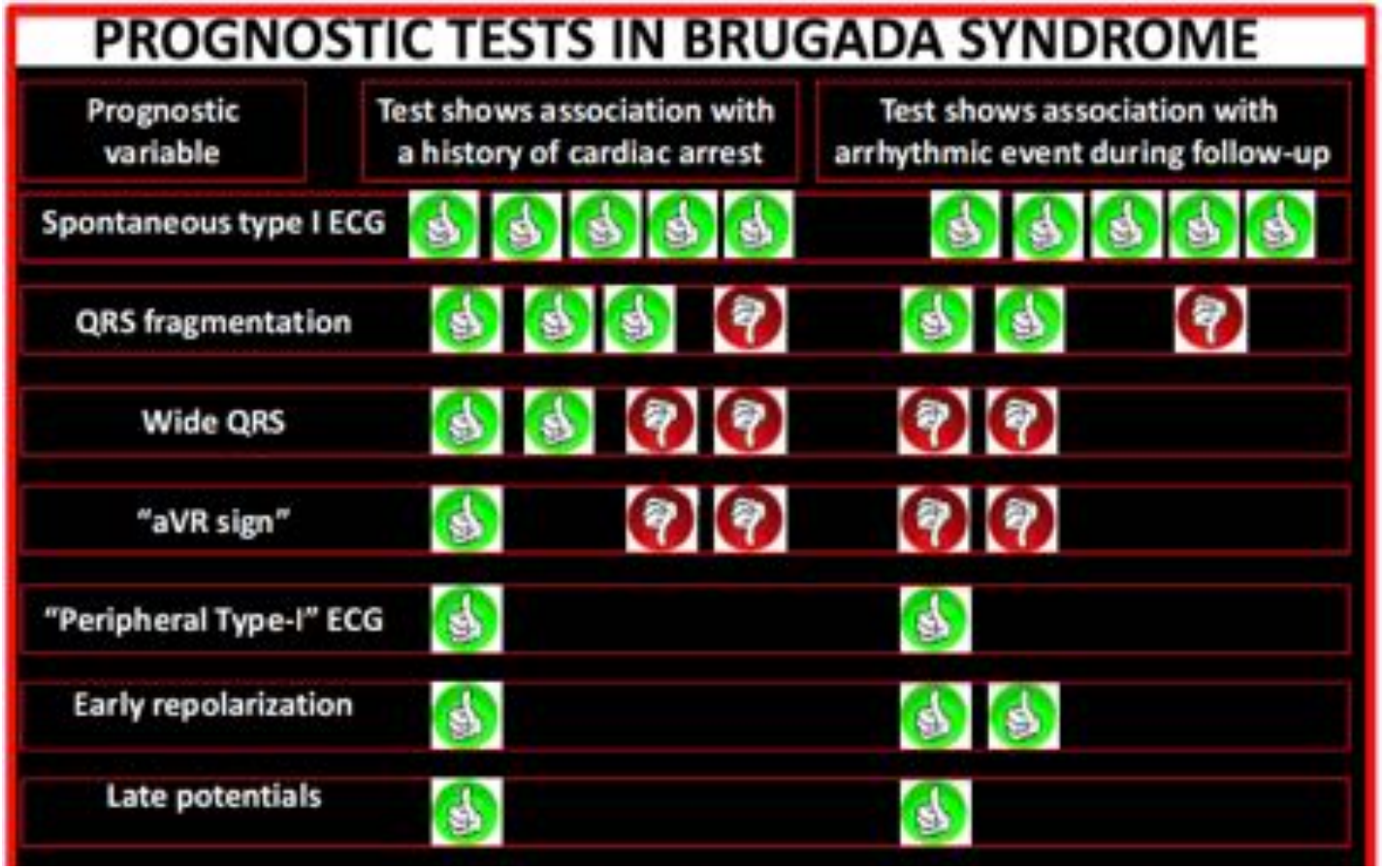
	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P-value
Age (per year)	0.9	0.8–1.0	0.19	–	–	–
Male	2.1	0.6–13.3	0.28	–	–	–
Syncope	3.1	1.2–9.2	0.01	2.8	1.1–8.1	0.03
Basal type 1 ECG	6.6	1.8–41.8	0.001	6.2	1.8–39.9	0.002
Family history of SD	1.9	0.7–4.8	0.22	–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





Delise ea. EHJ 2010, Probst ea. Circ 2010, Priori ea. JACC 2012

Other ECG markers?

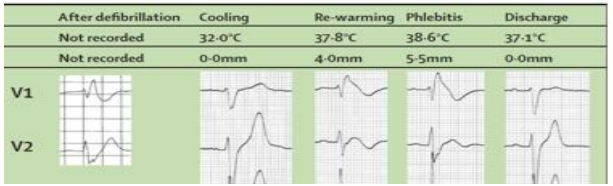


Adler ea. Heart Rhythm 2015 in press

Triggers

- Can these be avoided?
  - Drugs

  - Fever
    - ECG or admission & monitoring with (anticipated) fever, particularly in children with *SCN5A* mutations, (e.g. after vaccination / in fever-sensitive families)
    - Anti-pyretics
      - Paracetamol, cooling



Postema ea. Heart Rhythm 2009, Chockalingam ea. Pediatrics 2011, Tan ea. Lancet 2007, Matsuo ea. PACE 2003

Note on fever

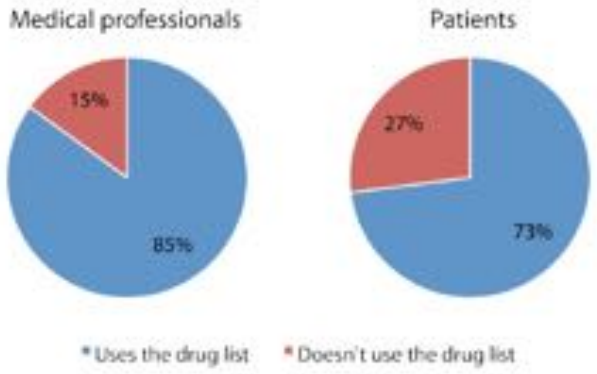
Chockalingam ea. Pediatrics 2011

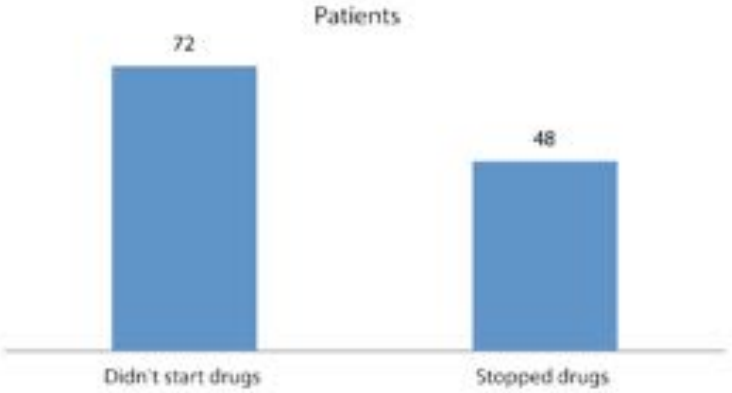
Notes on drugs

Drug lists

You can find lists of the drugs that are (preferably) avoided by Brugada syndrome patients below. Just click on the bar and you will be taken to the appropriate page. Also you can choose to see potential anti-arrhythmic drugs, diagnostic drugs including ECG examples and a page with summary letters in many different languages which list all the drugs that need to be (preferably) avoided. A translation tool is also provided, and you can find frequently asked questions here.

- Drugs to be avoided
- Drugs preferentially avoided
- Potential anti-arrhythmic drugs
- Diagnostic drugs
- Patient letter





Postema ea. Europace 2013

Notes on drugs

"At your age, people get anxious about taking so many pills, but I can prescribe something for that."

Appropriate use criteria for the use of drugs in Brugada syndrome and Long QT syndrome

WRITING COMMITTEE MEMBERS

Chair:
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In preparation

Your cooperation appreciated

Future

Better insights in pathophysiological mechanisms

Better risk stratification and indications for the different treatment modalities

Meanwhile in Brugada syndrome

- Aborted arrest

- Syncope

- Spontaneous type-1

- Asymptomatic/drug-induced

Many thanks

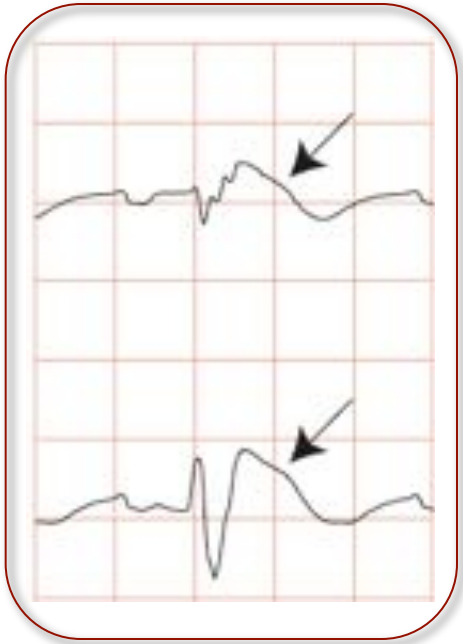
for your kind attention

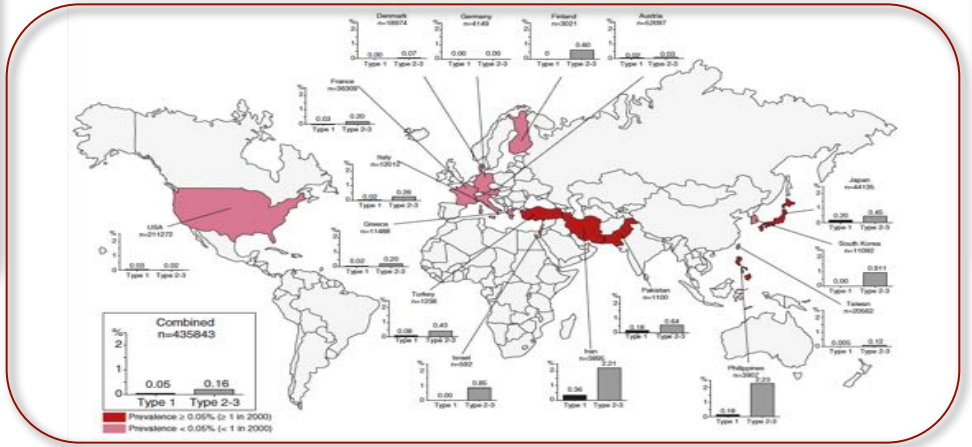
Venice Arrhythmias 2015

Pieter G. Postema, MD, PhD

AMC Amsterdam

Brugada syndrome in short

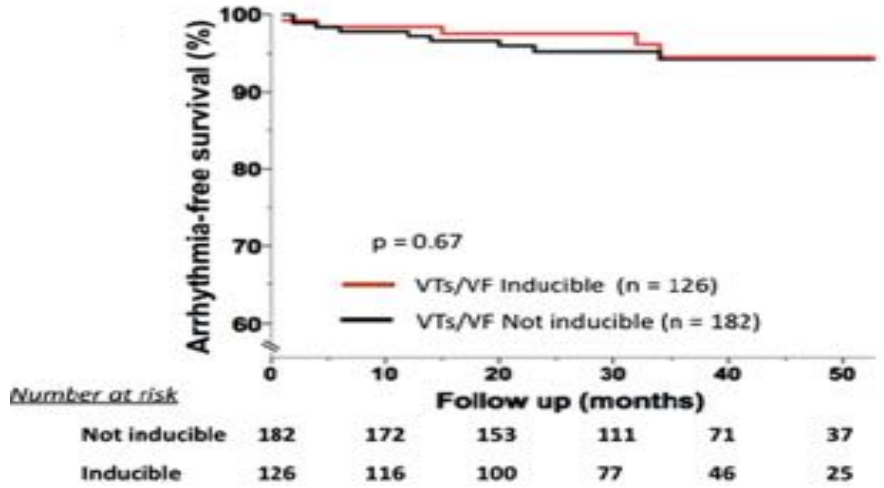




Priori ea. Heart Rhythm 2013, Postema ea. Heart Rhythm 2009, Postema ea. Europace 2012, Catalano ea. EHJ 2009

EP study?

- Controversial: Brugada et al. vs. 'the rest'
- Only randomized prospective study: negative
- V-ERP<200?
- Negative EPS?



Priori ea. JACC 2012

EP study?

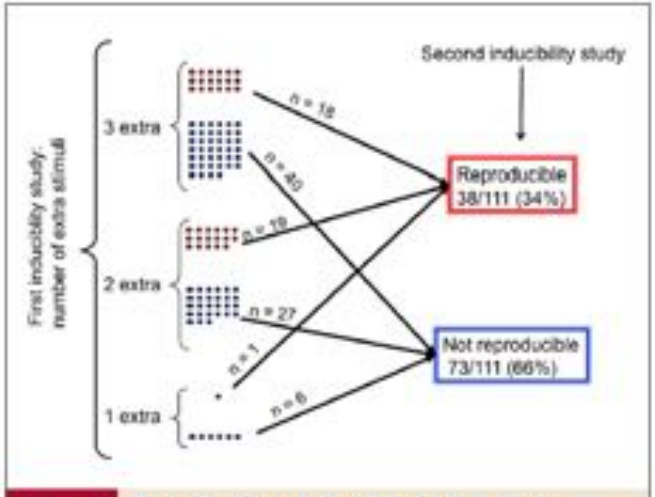
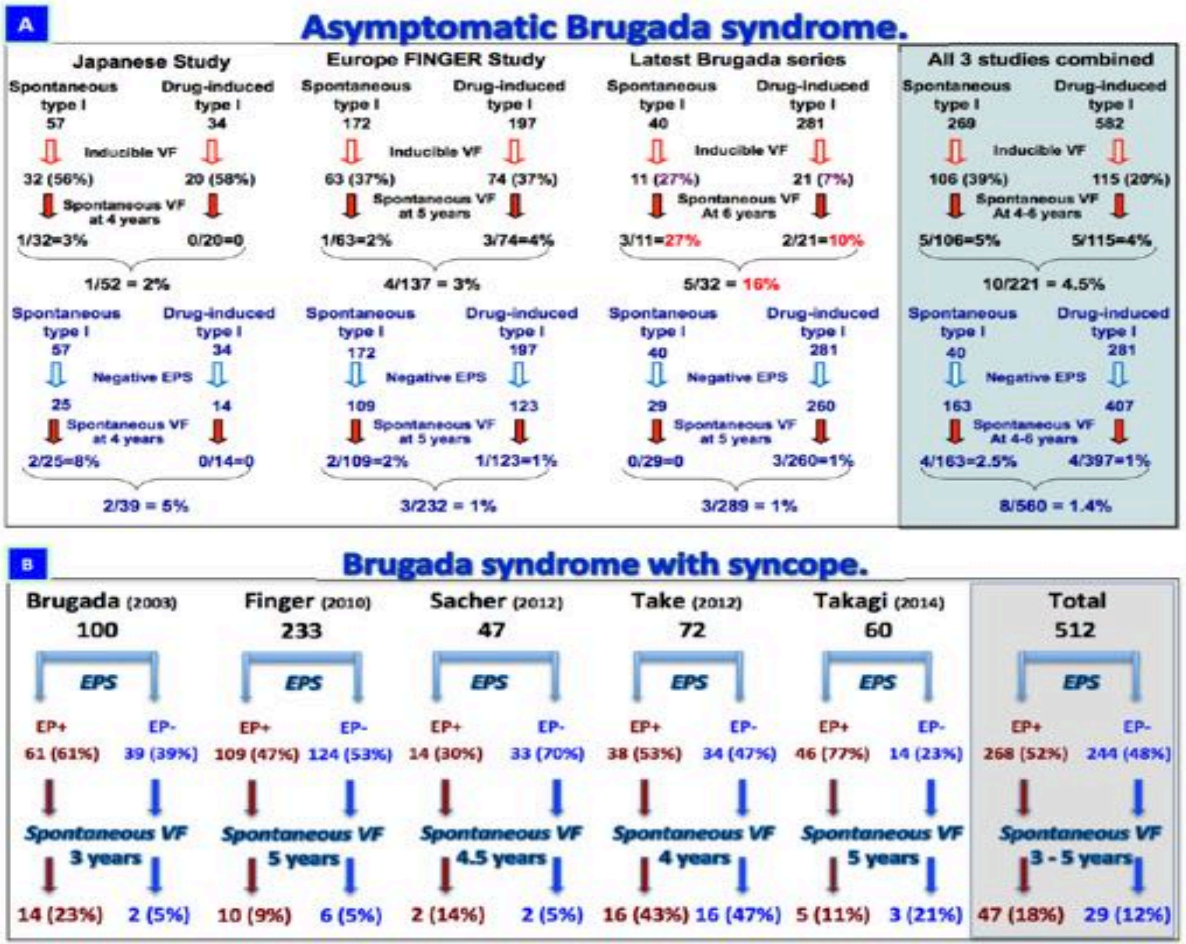


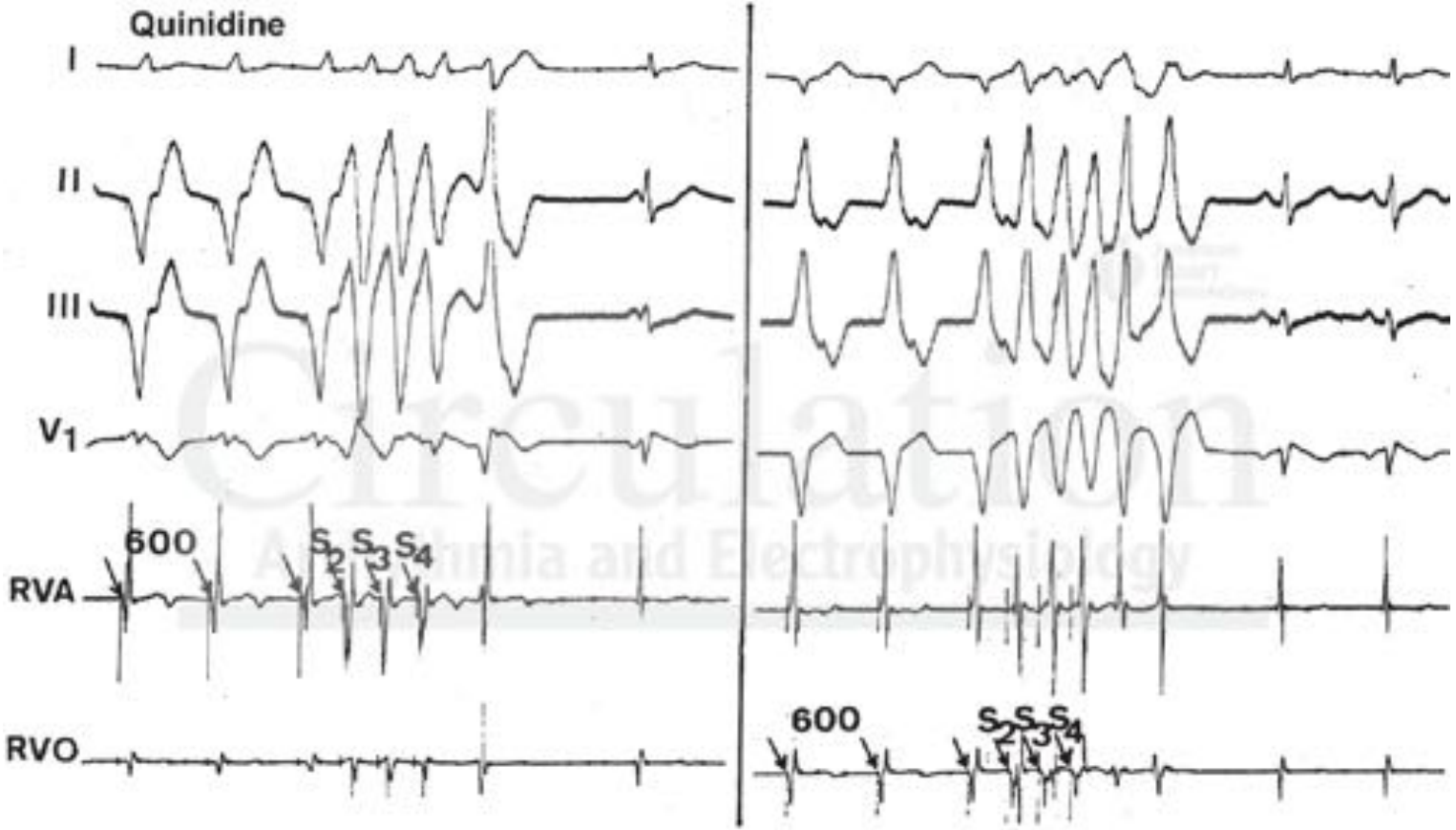
Figure 2 Reproducibility of VTs/VF Inducibility Study in 111 Patients Enrolled in the PRELUDE Registry

Patients are divided in 3 groups according to the number of extra-stimuli required for induction during the first inducibility study. Each **dot** represents 1 patient. **Red dots** indicate patients with reproducible results of inducibility study, whereas **blue dots** represent patients with non-reproducible results of inducibility study. Arrhythmia inducibility was reproducible in 1 of 7 (14%) patients induced with a single premature beat, in 19 of 46 (41%) patients induced with 2 premature beats, and in 18 of 58 (31%) patients induced with 3 premature beats. VTs/VF = sustained ventricular tachycardia/ventricular fibrillation.

Priori ea. JACC 2012
Adler ea. Heart Rhythm 2015 in press



EP study?



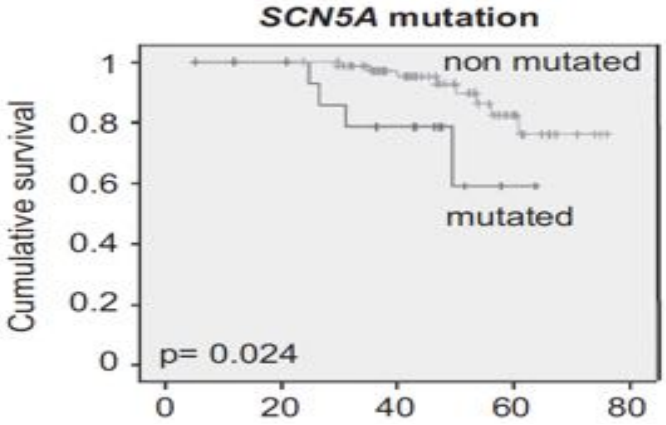
Belhassen ea. Circ AEP 2015 in press

Genetics or familial SCD?

As opposed to some small studies, in all large studies there is no (positive) prognostic value in *SCN5A* mutations or familial SCD

Table. Patient Characteristics According to Their Clinical Presentation

	Cardiac Arrest Group	Syncope Group	Asymptomatic Group	*P*
No. of patients	62	313	654	
Index patients, %	98	93	70	<0.001
Male, n (%)	55 (89)	238 (76)	452 (69)	0.01
Age at diagnosis, y	43 (35–54)	46 (37–57)	45 (35–55)	0.19
Family history of SCD, n (%)	6 (10)	63 (20)	195 (30)	<0.001
SCN5A mutations, n (%)	12/49 (24)	53/203 (26)	120/398 (30)	0.92



Probst ea. Circ 2010, Sommariva ea. Eur J Human Genet 2013

Symptoms: syncope

Table 1 Prognosis of Brugada syndrome patients in the largest studies

Study	Benito et al.[2]	Kamakura et al.[3]	Probst et al.[4]	Priori et al.[5]
Year	2008	2009	2010	2012
Location	Spain Belgium Canada	Japan	France Germany The Netherlands Italy	Italy
Average follow-up (months)	58	49	32	34
Total no. of patients	384	245	1029	308
History of aborted SCA	18 (5%)	45 (18%)	62 (6%)	Excluded
Events during follow-up[a]	11 (61%)	15 (33%)	22 (35%)	–
Annual event rate (%)	13	8	8[b]	–
History of syncope	65 (17%)	46 (19%)	313 (30%)	64 (21%)
Events during follow-up[a]	10 (15%)	1 (2%)	19 (6%)	7 (11%)
Annual event rate (%)	3	0.5	2	4
Asymptomatic	301 (78%)	154 (63%)	654 (64%)	244 (79%)
Events during follow-up[a]	13 (4%)	3 (2%)	10 (2%)	7 (3%)
Annual event rate (%)	0.9	0.4	0.6	1

[a]Either appropriate ICD shock or (aborted) sudden cardiac death.
[b]This subgroup had longer follow-up than average.
SCA, sudden cardiac arrest; ICD, implantable cardioverter defibrillator.

Postema Europace 2012

Symptoms: syncope

Syncope questionnaire filled by Brugada syndrome patients.

A. Syncope History

1. At what age did you suffer your first spell of loss of consciousness (syncope)?
- Age in years: ____

2. How many episodes of syncope did you have before you were diagnosed with Brugada syndrome?
- 1
- More than one: specify number _____

B. Description of Syncope

3. What circumstances, if any, are associated with your spells of loss of consciousness (check all that apply)?
- Rest
- Activity (specify type): _____
- Daytime
- Night time
- Exertion
- Emotional Stress

4. What symptoms do you notice before you lose consciousness?
- Sweating, paleness, dizziness, dimmed vision, clamminess
- Chest palpitations
- Anxiety
- Other (specify): _____

5. Were you injured as a result of losing consciousness?
- Yes
- No

6. If yes, did the injury result in hospitalization?
- Yes
- No

7. Did someone else witness your spell?
- Yes: how did they describe the event to you? _____
- No

8. Approximately how long were you unconsciousness?
- Less than 1 minute
- 1 to 5 minutes
- More than 5 minutes

9. How did you regain consciousness?
- Spontaneously (no assistance)
- Someone stimulated you (shaking, tapping)
- Needed CPR (chest compressions)

10. Was the episode associated with any of:
- Biting your tongue?
- Losing control of your bladder?
- Prolonged fatigue after regaining consciousness?
- Difficulty speaking or moving arm(s) and/or leg(s)?
- None of these

C. Further episodes

11. Have you experienced loss of consciousness since you were diagnosed with Brugada syndrome?
- Yes
- No

12. If Yes, was this episode(s) similar to the previous one(s)?
- Yes
- No

13. If you have an implantable defibrillator (ICD), have you received a shock associated with an episode of loss of consciousness?
- Yes
- No
- Not applicable

D. Treatment

14. What treatment(s) have been prescribed by your cardiologist for management of Brugada syndrome?
- Implantable defibrillator
- Medications (specify): _____
- Counselling regarding avoiding future syncope

15. Do you worry about future episodes of syncope?
- Yes
- No

Figure 2 Syncope questionnaire.

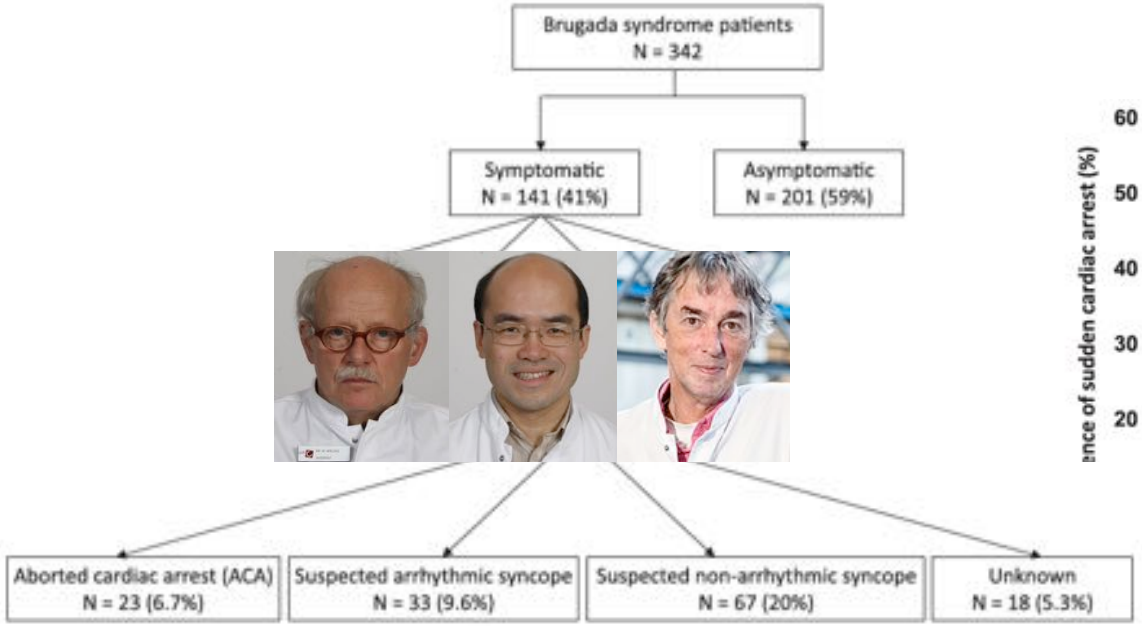
1. Absent or brief (<10 sec) prodrome
2. Absence of specific triggering circumstance
3. Brief loss of consciousness (<1 min)
4. Fast return to consciousness

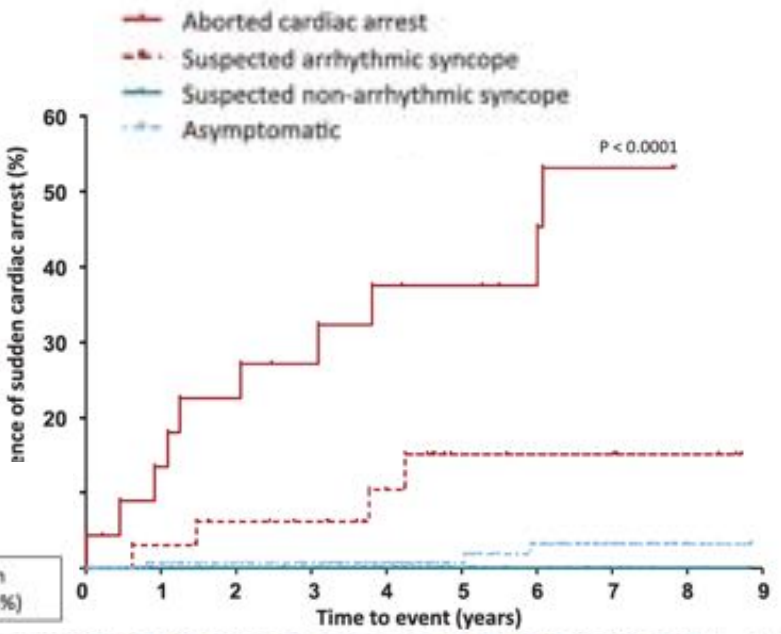
Table 3 Outcome during follow-up in the 3 groups

	Group 1 arrhythmic syncope	Group 2 nonarrhythmic syncope	Group 3 doubtful syncope	Total	*P* value
No.	23	17	17	57	
Follow-up, mean (months)	57 ± 34	80 ± 46	60 ± 45	65 ± 42	.2
Median (range) (months)	72 (46–106)	57 (39–77)	44 (19–108)	53 (36–93)	.2
Outcome [n (%)]					
Recurrent syncope	4 (17%)	7 (41%)	9 (53%)	20 (35%)	.05
Similar features	2 (50%)	7 (100%)	3 (33%)	12 (60%)	
Different features	2 (50%)	0 (0%)	6 (66%)	8 (40%)	
Asymptomatic	14 (60%)	9 (53%)	7 (41%)	30 (52%)	
Ventricular arrhythmia	6 (26%)	0	0	6 (10%)	
With syncope	2 (33%)	0	0	2 (3%)	
Death	1 (5%)	1 (6%)	1 (6%)	3 (5%)	
Patients with ICD [n (%)] %	23 (100%)	3 (18%)	6 (35%)	32 (56%)	.01
No syncope	19 (83%)	2 (66%)	4 (66%)	25 (78%)	
Appropriate shock	5	0	0	5 (16%)	
Inappropriate shock	7	0	1	8 (25%)	
Antitachycardia pacing	1	0	0	1 (3%)	
Patients with ILR [n (%)] recorder, n %	0	0	6 (35%)	6 (10%)	.01
Syncope	0	0	2 (33%)	2 (33%)	

Sacher ea. Heart Rhythm 2012

Symptoms: syncope

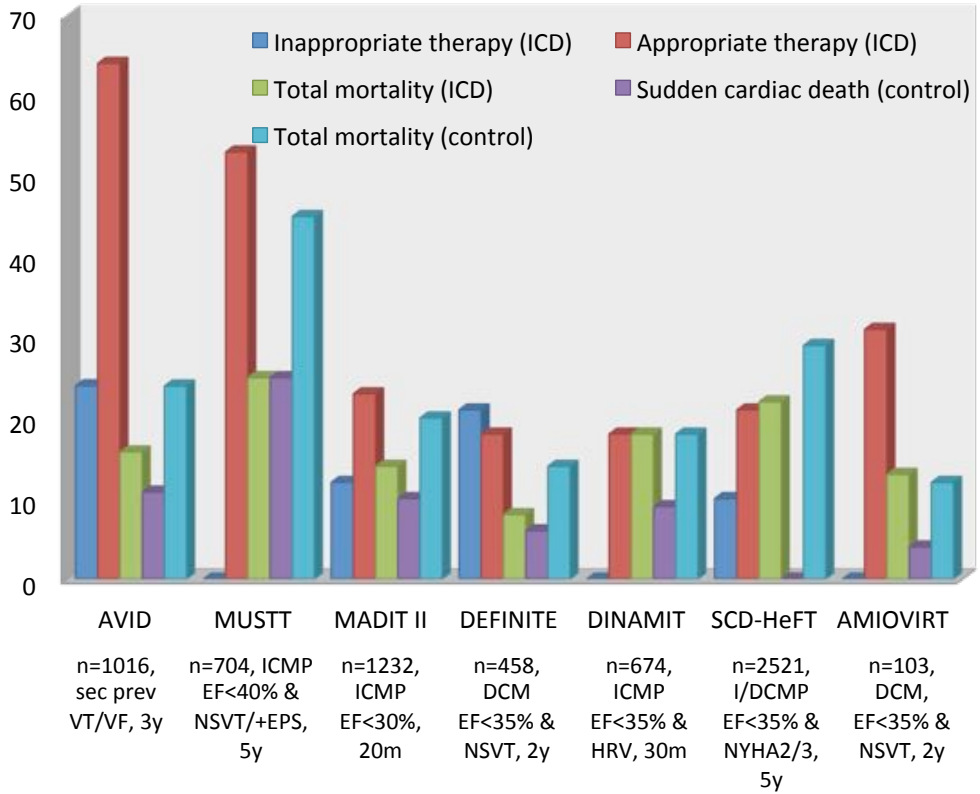


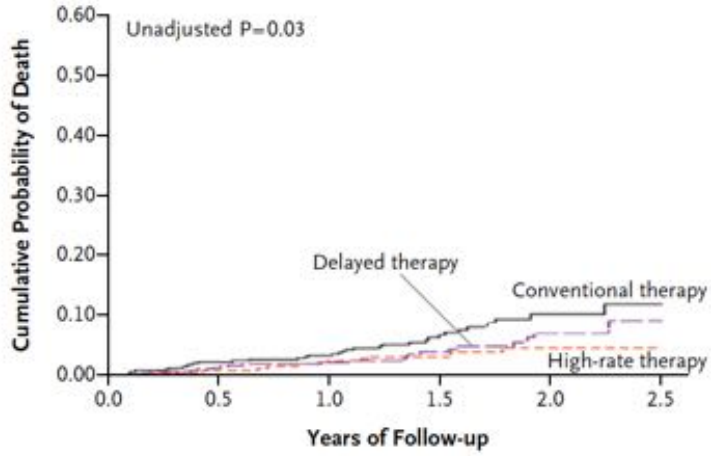


ACA during follow-up occurred in 43% (10/23) ACA patients (8.7% per year) and in 12% (4/33) suspected arrhythmic syncope patients (2.2% per year). ACA did not occur in suspected nonarrhythmic syncope patients. ACA occurred in 1.5% of patients (3/201) who were asymptomatic at diagnosis (0.3% per year). One of these patients (baseline type 1 BrS ECG) had a suspected arrhythmic syncope during follow-up, for which he received ICD placement and multiple appropriate ICD shocks 5 years later. The 2 other patients (no baseline type 1 BrS ECG) had suspected arrhythmic syncope and underwent implantable loop recorder placement, which recorded sustained VT in 1 (followed by ICD placement), and symptomatic AV block and sinus node dysfunction in the other (followed by pacemaker implantation).

Olde Nordkamp ea. Heart Rhythm 2014

Shock paradox





No. at Risk						
Conventional therapy	514	490 (0.02)	392 (0.03)	219 (0.07)	89 (0.10)	14 (0.12)
High-rate therapy	500	478 (0.01)	372 (0.02)	221 (0.03)	90 (0.05)	21 (0.05)
Delayed therapy	486	471 (0.01)	375 (0.02)	205 (0.04)	99 (0.07)	14 (0.09)

Figure 2. Cumulative Probability of Death According to Treatment Group.
The values in parentheses are Kaplan–Meier estimates of the cumulative probability of death.

Tung ea. JACC 2008, Moss ea. NEJM 2012