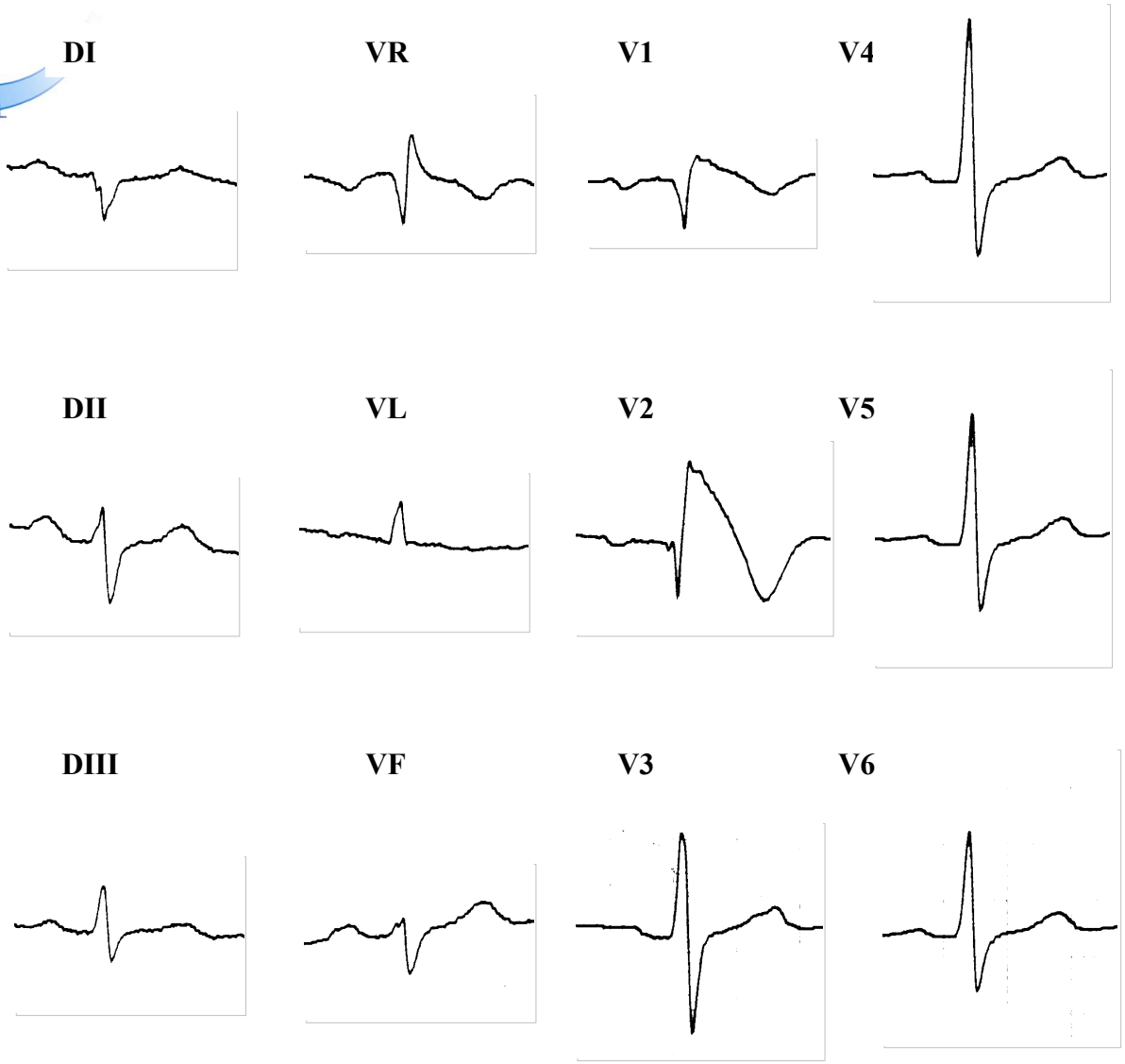
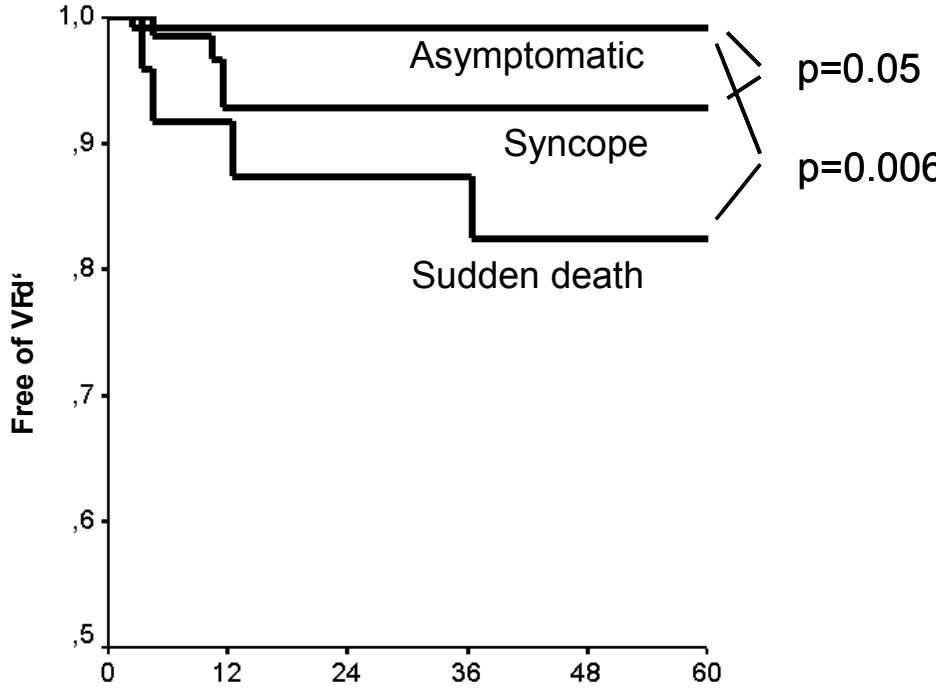
Brugada syndrome: What do we know in 2015?

Vincent Probst,MD, PhD
Reference centre for hereditary arrhythmic diseases,
Nantes, France



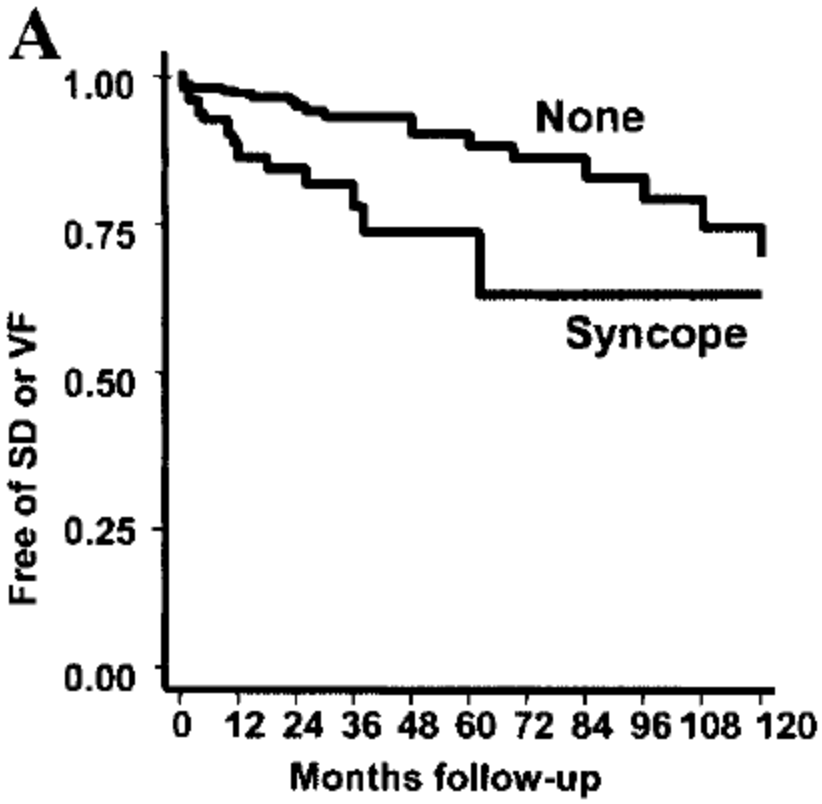
Type 1 ST-segment elevation spontaneously or after sodium channel blocking agent in at least one right precordial leads (V1 and V2) in a standard or

Prognostic regarding to the symptoms



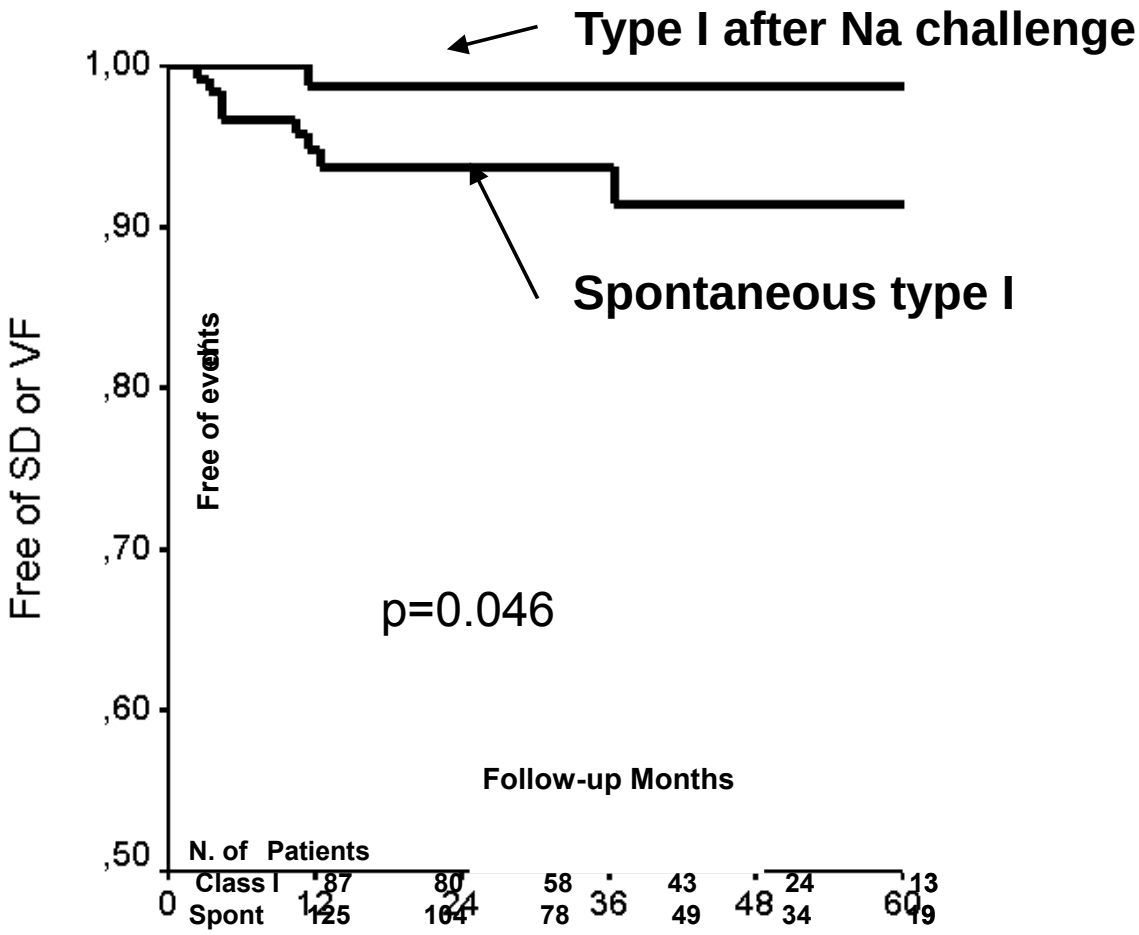
N. de Patients						
Asympto	123	108	73	43	19	6
Syncope	65	51	41	27	19	9
MS	24	22	18	18	16	13

Eckart, Circ 2005



Brugada J, Circ 2003

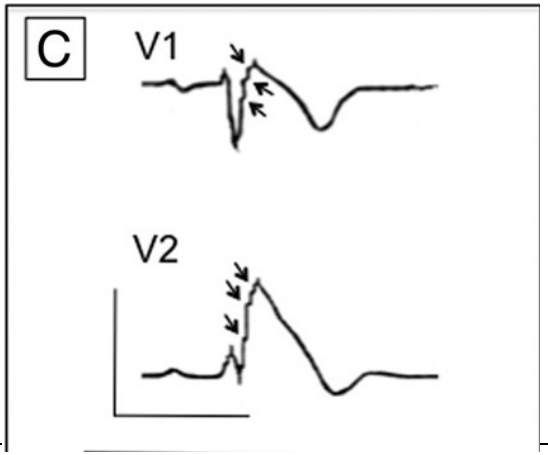
Prognostic regarding to the ECG pattern



Eckart, Circ 2005

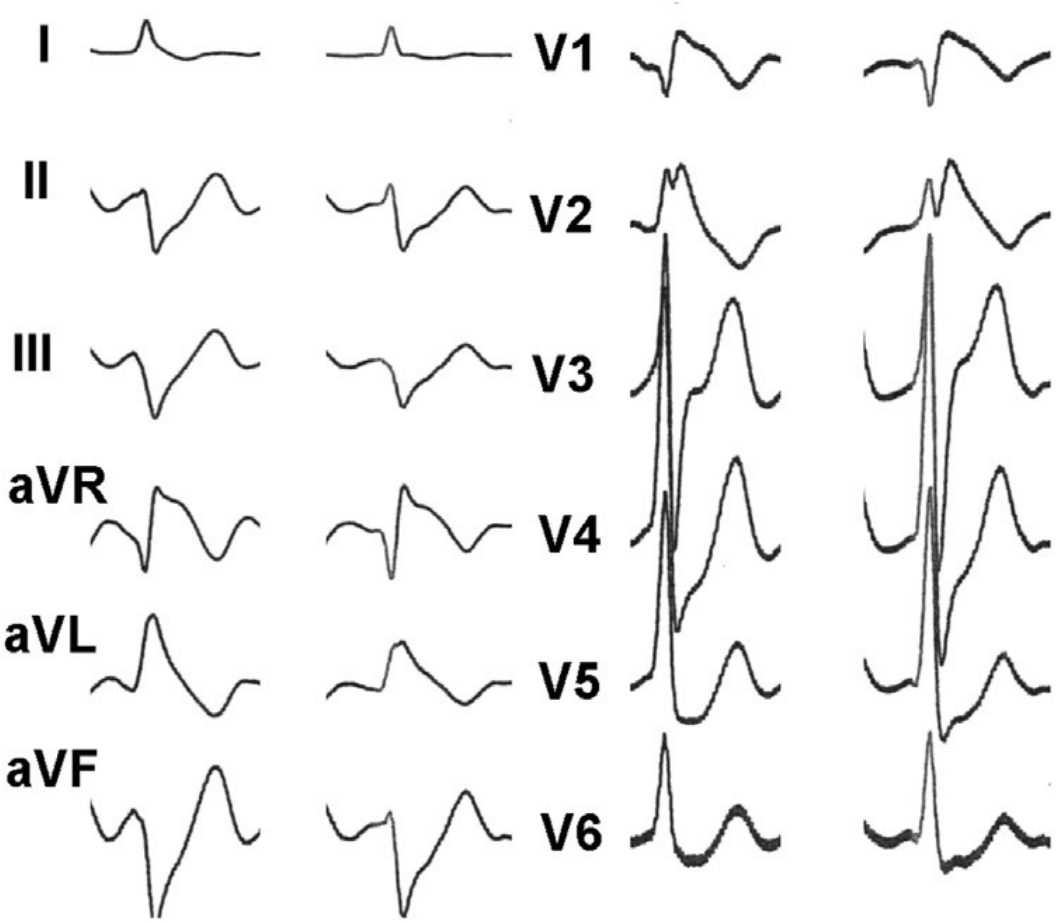
ECG pattern

- Presence of late potential
- SDANN and ultra low frequency component were decrease in symptomatic Brugada patients
- Augmented ST-segment elevation during recovery from exercise
- Fractionned QRS



Babai Bigi MA, Heart rhytm 2007
Hermida JS, Eur heart J 2003
Makimoto H, JACC 2010
Priori S, JACC 2012

ST segment elevation in the peripheral leads



Rollin A,Heart rhythm 2013

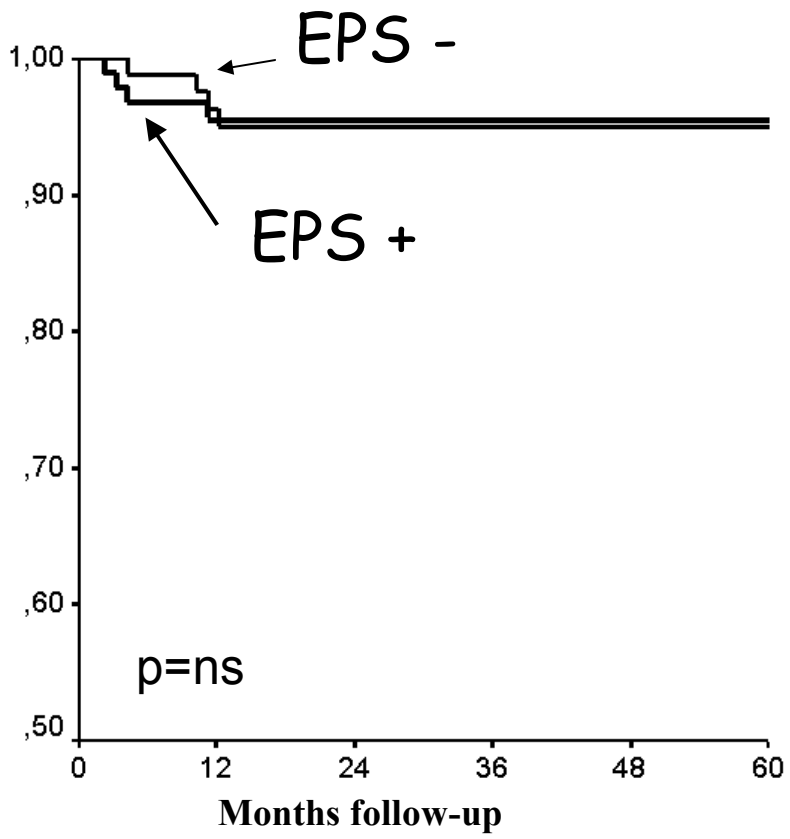
Predictive value of the different parametres: 323 patients

Table 4 Parameters related to SCD and/or AT in univariate and multivariate analyses

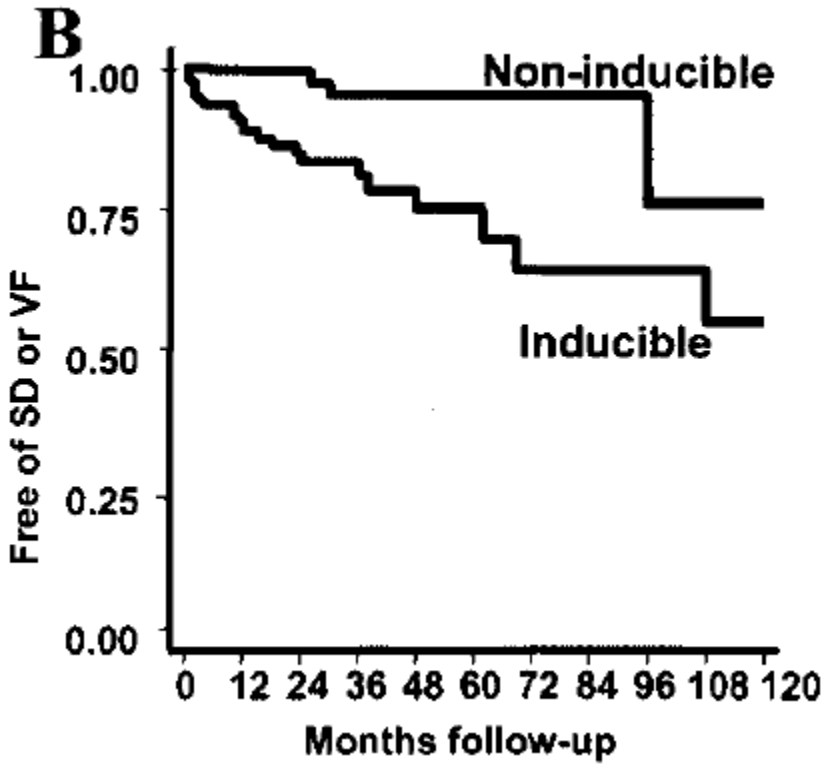
Parameters	OR (95% CI)	*P*
Univariate analysis		
Type 1 ST elevation in the peripheral leads	5.55 (2.17–14.21)	.0003
Syncope	3.12 (1.39–7.04)	.006
Spontaneous type 1 ST elevation	2.63 (1.13–6.10)	.023
SCN5A mutations	3.06 (1.06–8.80)	.037
Familial SCD	2.27 (1.01–5.12)	.047
Inducibility	2.39 (0.83–6.31)	.10
Multivariate analysis		
Type 1 ST elevation in the peripheral leads	4.58 (1.70–12.32)	.0025
Spontaneous type 1 ST elevation	2.43 (1.01–5.84)	.047
Syncope	2.34 (0.99–5.50)	.051
Familial SCD	1.99 (0.84–4.69)	.11

Rollin A,Heart rhythm 2013

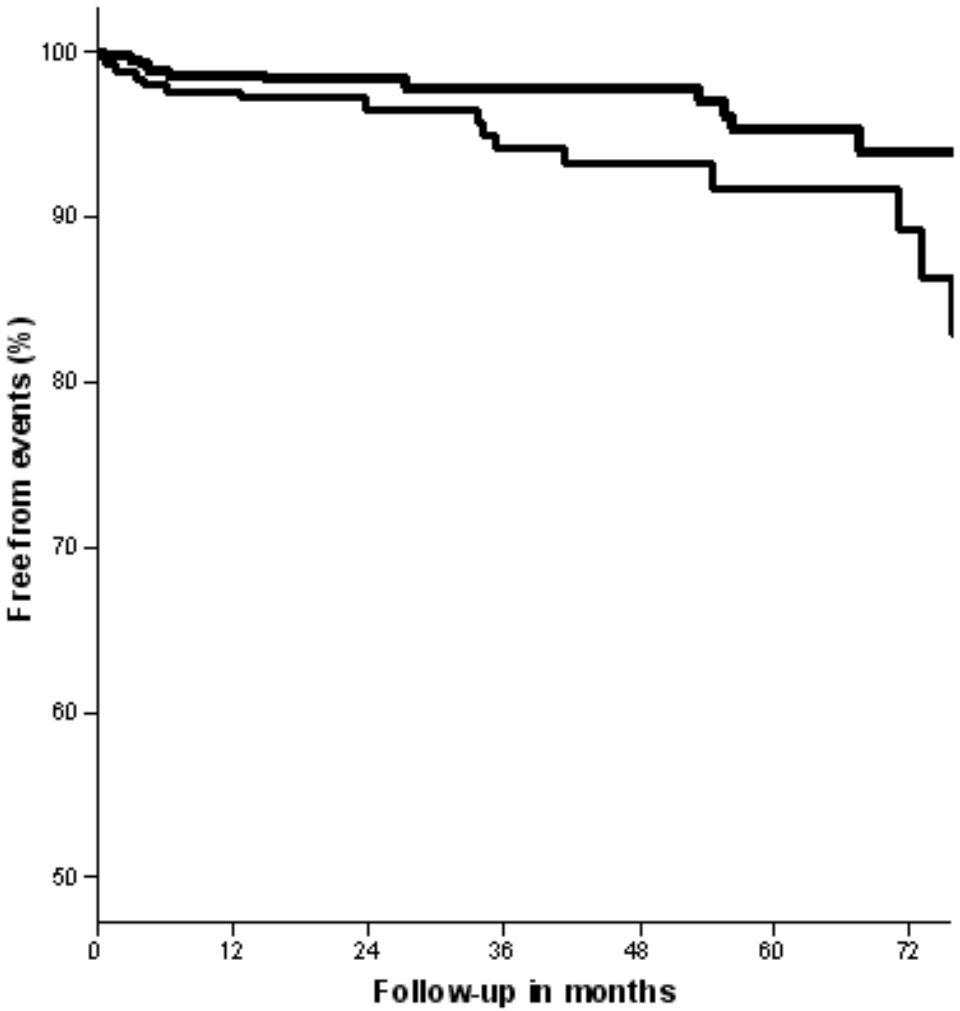
Prognostic regarding to the EPS



Eckart, Circ 2005



Brugada J, Circ 2003



gative

sitive

	0	12	24	36	48	60	72
negative	376	301	237	187	136	94	59
positive	262	212	161	113	81	52	34

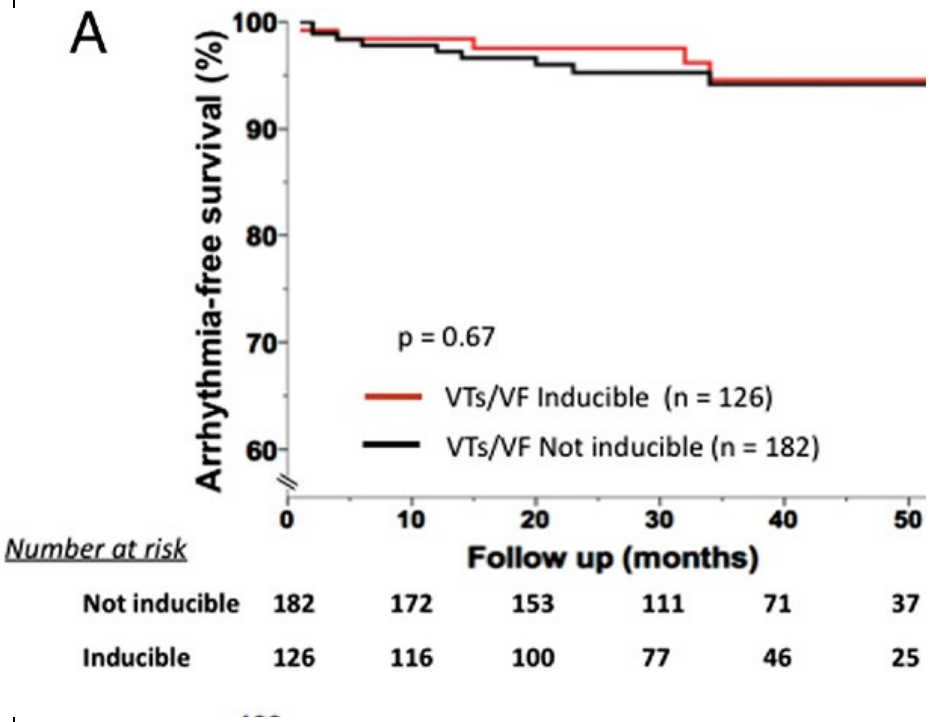
Probst, Circ 2010

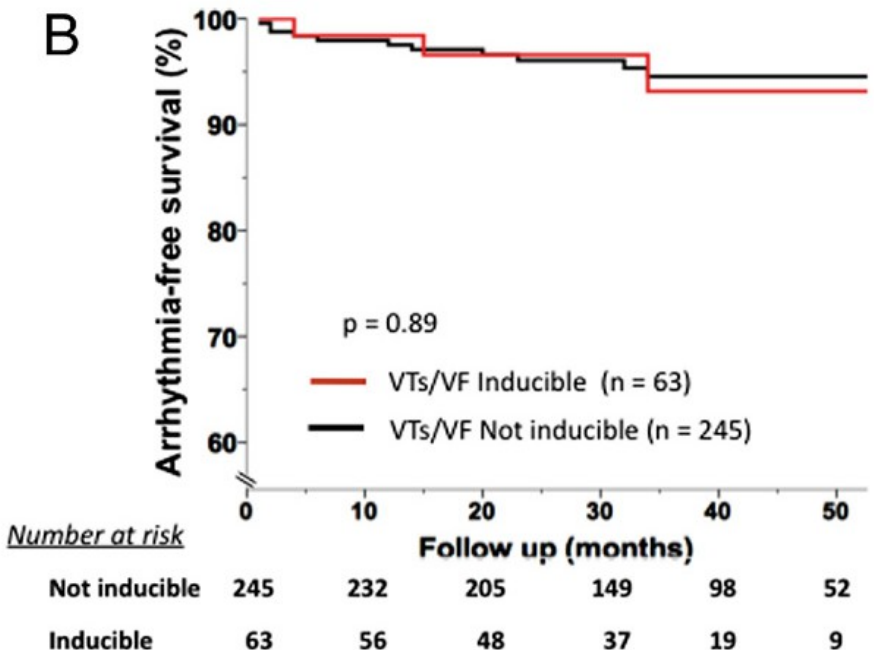
Multivariate analysis

- Symptoms before inclusion (p=0.0001)
  - ✓ SCD vs asymptomatic (p<0.0001)
  - ✓ Syncope vs asymptomatic (p=0.0002)
- Spontaneous type-1 ECG (p=0.04)
- The results of the EPS (p=0.71) and gender (p=0.63)
  - ✓ not predictive for arrhythmic events.
- ICD implantation (p=0.01) was found as predictor of arrhythmic events.

Probst, Circ 2010

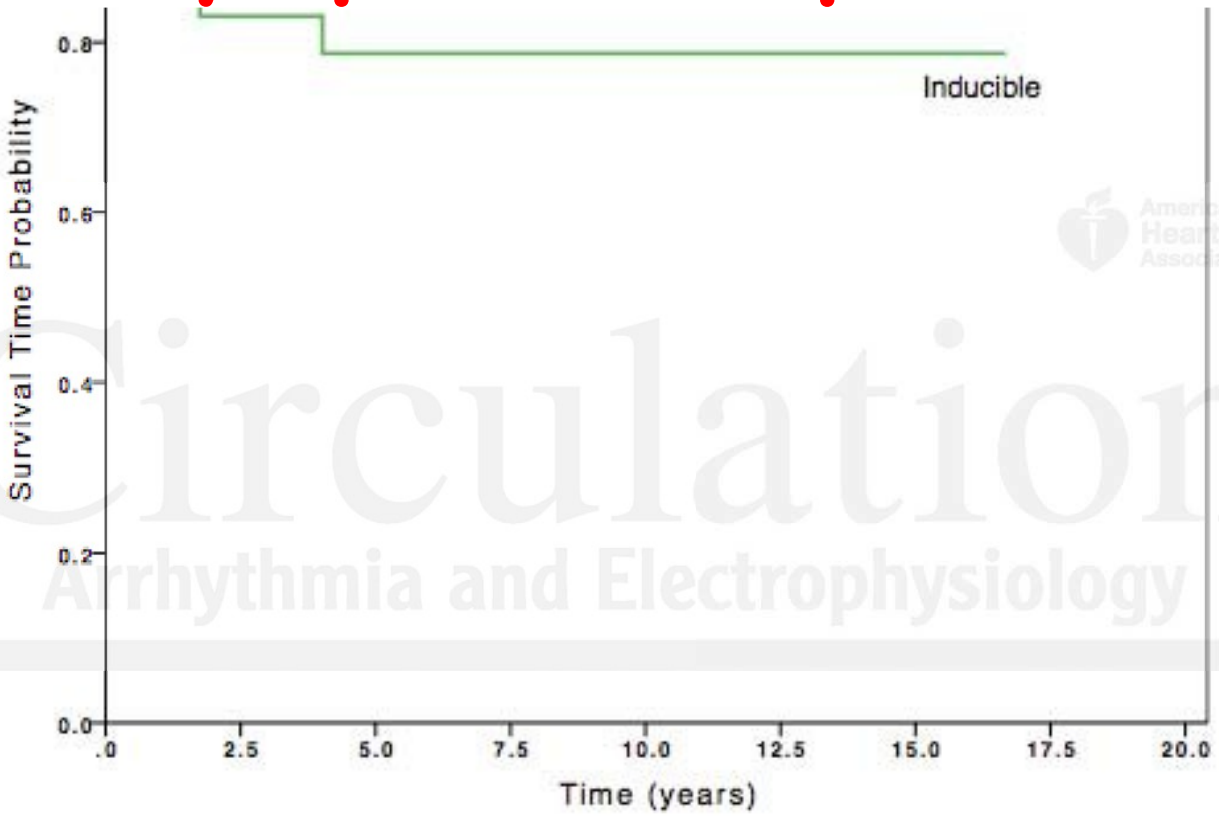
Prognostic regarding to the EPS: prelude study





Priori S, JACC 2012

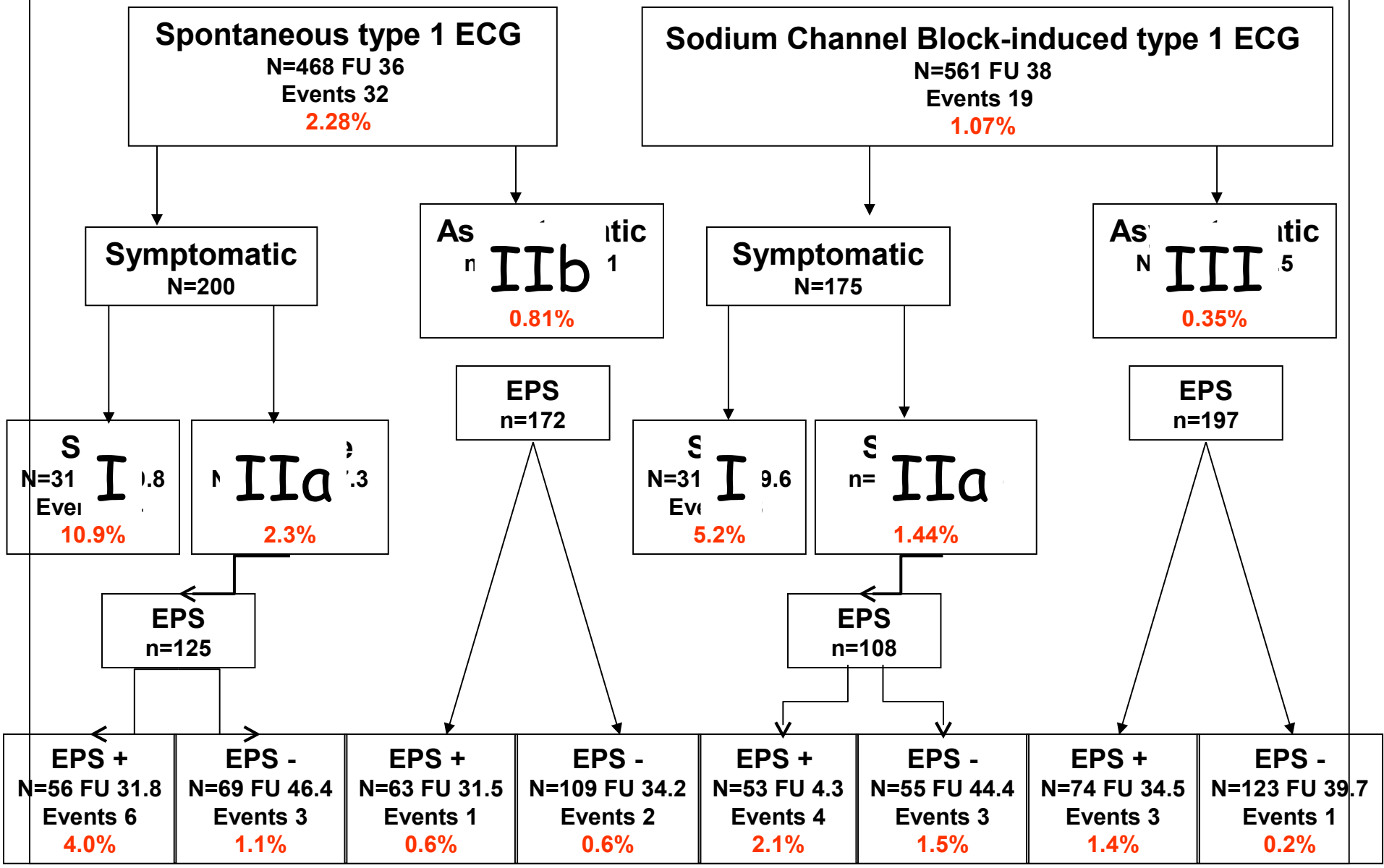
Event free survival in asymptomatic patients



Patients at risk									
Inducible	31	21	17	13	5	3	1	0	0
Non Inducible	237	145	102	72	47	14	3	0	0

Sierra j, Circ Arrht elec, 2015

Mean rate of event per year and per patient



ICD in Brugada syndrome

- 220 patients (34 ±27 month)
- Annual rate of appropriate shocks in asymptomatic patients 1,5 %
- Annual rate of inappropriate shocks 3.75%

Sacher F, Probst V Circulation 2006.

ICD in Brugada syndrome

	Resucitated SCD (n=18)	Syncope (n=85)	Asymptomatic (n=108)	p-value between the 3 groups	Total (n=211)
Median of Follow-up * (months)	90	97	92	NS	93
Patients with Appropriate shocks	9 (50%)	14 (16%)	11 (10%)	p<0.001	34 (16%)
Median delay to first shock (months)	*14*	*48*	*38*	*p=0.016*	*33*
Median of shock	1	2	2	NS	2
Patients with Inappropriate shocks	5 (28%)	31 (36%)	35 (32%)	NS	71 (34%)
Median delay to first shock (months)	22	34	29	NS	32
Median of shock	2	3	2	NS	3
Lead Failure	3 (17%)	20 (24%)	21 (19%)	NS	44 (21%)
Median delay (months)	62	60	63	NS	60
Death	0 (0%)	2 (2%)	4 (4%)	NS	6 (3%)

Sacher F, Probst V Circulation, 2013.

ICD in Brugada syndrome Evolution over time

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

Inapropriated shocks

- In patients
  - ✓ with good implantation parameters (R wave amplitude >5mV at implantation)
  - ✓ optimal programming (long NID, single high VF zone>210-220bpm)
  - ✓ close follow-up with remote monitoring
- Inappropriate shocks (0.7%/year compared to 3.7%/year in the general BrS population).

Sacher F, Probst V Circulation, 2013.

Psychological impact of Brs and ICD

Table 2 Results of the 36-item short-form health survey in the 3 groups

		Physical functioning	Physical role	Bodily pain	General health	Vitality	Social functioning	Emotional role	Mental health
G1—ICD symptomatic patients	*n*	61	60	60	60	59	61	60	59
	Mean	82.17	67.59	77.14	58.96	52.68	80.84	72.92	56.76
	SD	17.83	32.35	26.75	23.95	24.10	24.31	36.04	24.31
G2—ICD asymptomatic patients	*n*	77	74	74	77	76	77	72	74
	Mean	88.15	74.92	76.23	63.94	54.40	83.36	73.96	62.99
	SD	13.52	27.59	25.88	23.96	19.92	20.22	32.35	21.88
G3—No ICD asymptomatic patients	*n*	52	51	52	51	52	51	51	52
	Mean	87.24	72.66	83.28	66.09	58.05	81.50	71.81	60.13
	SD	17.58	34.55	23.49	20.57	20.60	24.01	36.98	24.19
P value		0.081	0.39	0.27	0.24	0.41	0.79	0.94	0.31

ICD, implantable cardioverter defibrillator; *n*, number of patients; SD, standard deviation.

Probst V, Europace 2011.

News from genetic

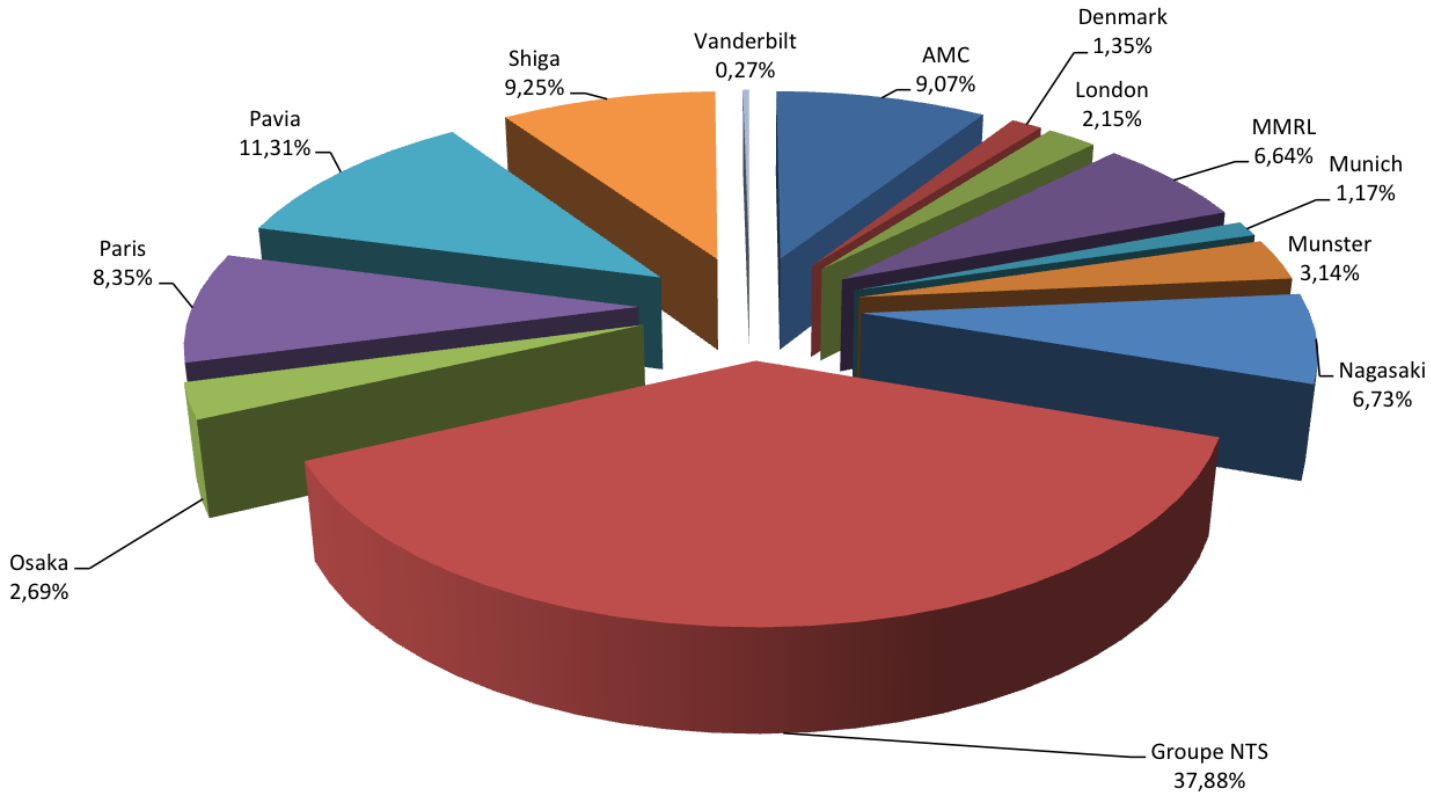
Evaluation of the role of the different genes

Gene	BrS cases (n = 167)	Internal controls (n = 167)	p-value 1	UK10K controls (n = 881)	p-value 2
SCN5A	20.4% (34)	2.4% (4)	**1.4×10^{-7} ***	2.4% (21)	**1.7×10^{-15} ***
SCN10A	6% (10)	2.4% (4)	0.170	3.5% (31)	0.131
CACNA1C	3% (5)	6.6% (11)	0.199	2% (18)	0.395
PKP2	3% (5)	2.4% (4)	1	1.7% (15)	0.348
CACNB2	1.8% (3)	1.2% (2)	1	0.9% (8)	0.396
KCNH2	1.2% (2)	3.6% (6)	0.283	1.6% (14)	1
TRPM4	1.2% (2)	3% (5)	0.448	1.9% (17)	0.754
KCND3	0.6% (1)	1.2% (2)	1	1.6% (14)	0.488
CACNA2D1	0.6% (1)	0.6% (1)	1	3.3% (29)	0.072
HEY2	0.6% (1)	0.6% (1)	1	0.1% (1)	0.293
SCN2B	0.6% (1)	0.6% (1)	1	0.5% (4)	0.581
SCN3B	0.6% (1)	0.6% (1)	1	0.5% (4)	0.581
ABCC9	-	3% (5)	0.061	1.1% (10)	0.379
SCN1B	-	1.8% (3)	0.248	0.3% (3)	1
RANGRF	-	0.6% (1)	1	0.2% (2)	1
FGF12	-	-	-	0.7% (6)	0.597
GPD1L	-	-	-	0.1% (1)	1
HCN4	-	-	-	1.6% (14)	0.144
KCNE1L	-	-	-	1% (9)	0.369
KCNE3	-	-	-	0.1% (1)	1
KCNJ8	-	-	-	0.5% (4)	1

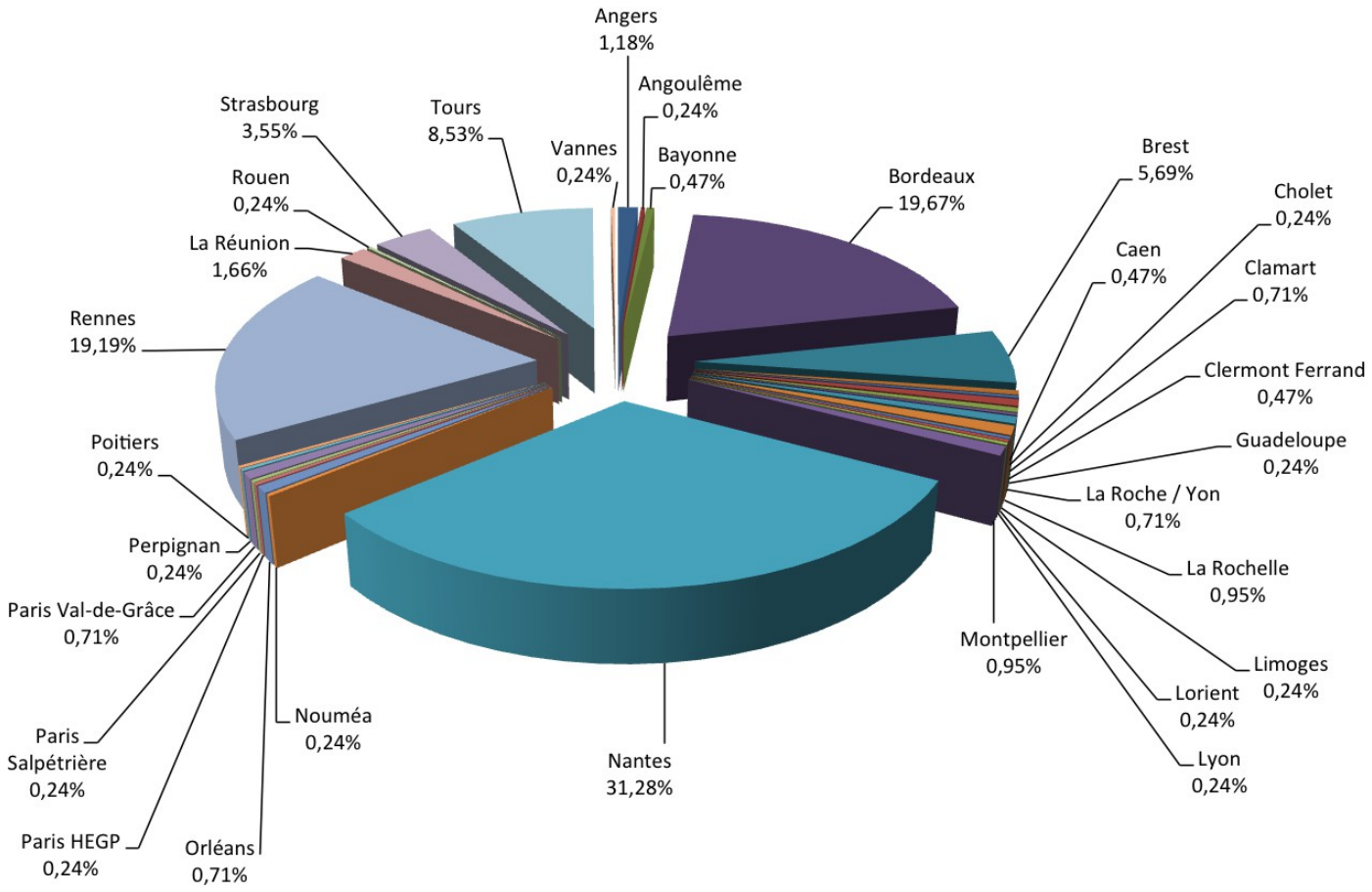
Le Scouarnec, Hum Mol Genet, 2015

1114 spontaneous type 1 index cases

Contributing Centers

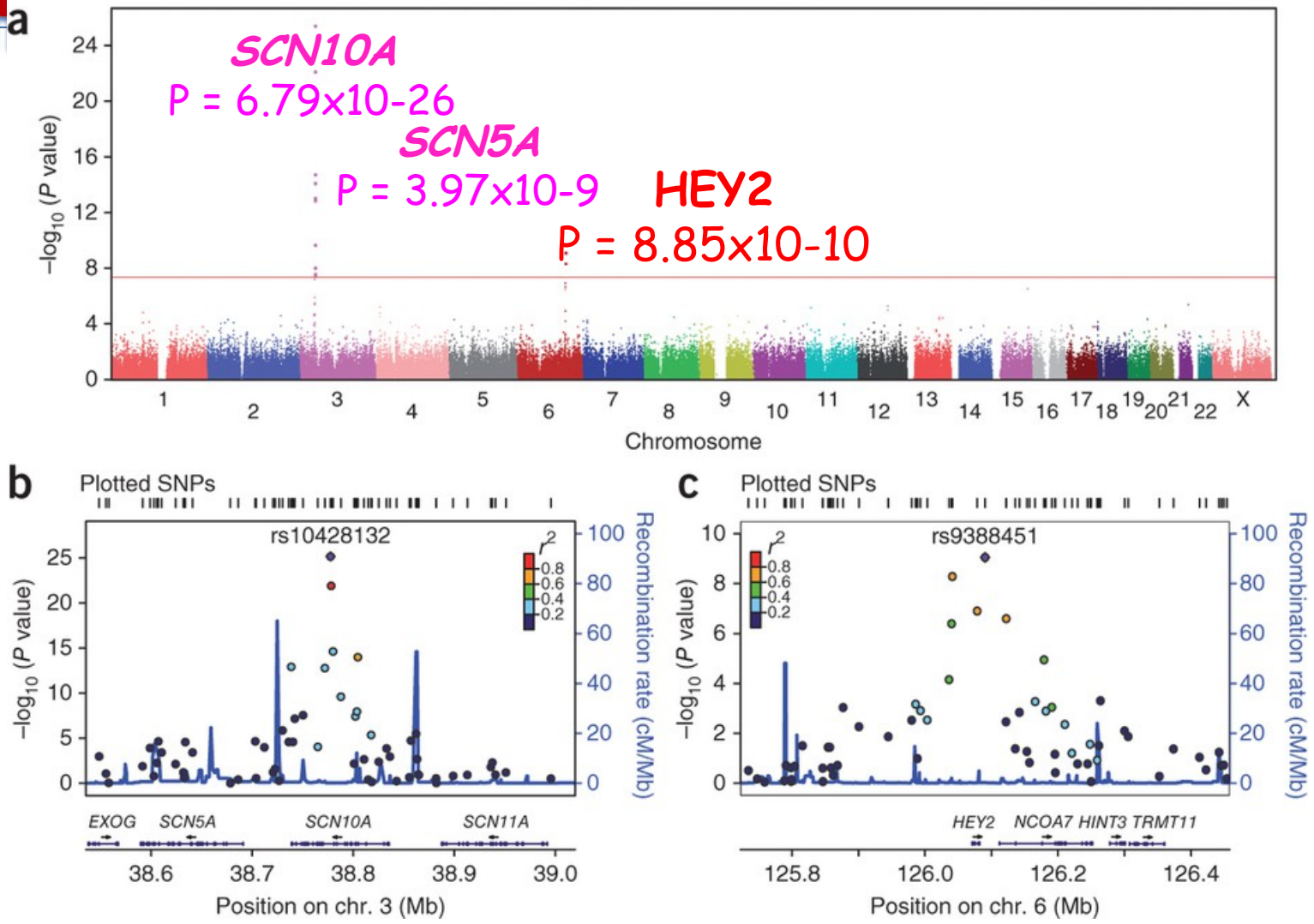


GROUPE Nantes (n=422) GWAS



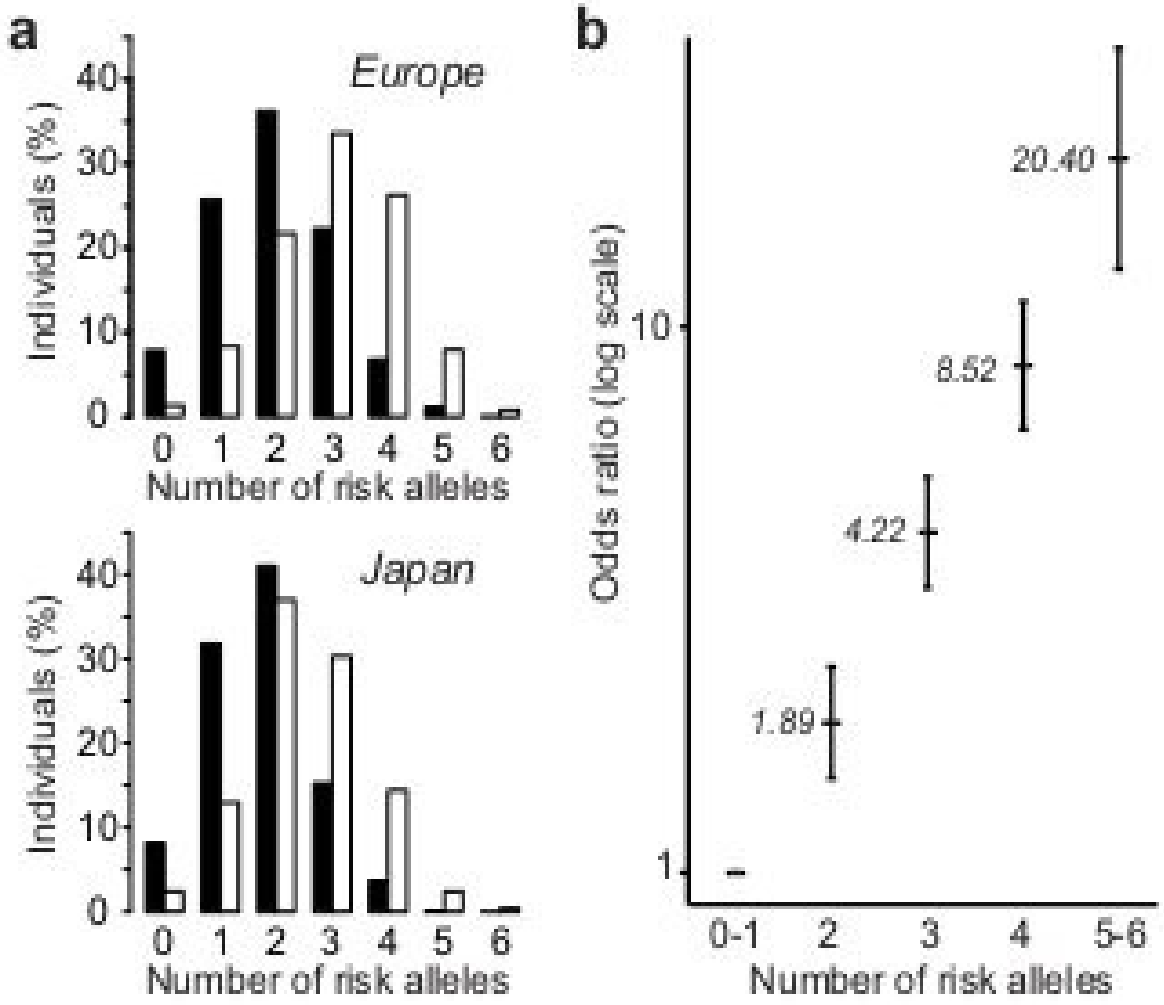
l'Institut du thorax

Results : Manhattan plot



Bezzina, Nature Genet 2013

Cumulative Risk of Brugada syndrome



Bezzina, Nature Genet 2013

Therapy in BS

- Hydroquinidine seems to be effective to treat patients with electrical storm or frequent recurrence of VF (IIa)
- Value in asymptomatic patients has still to be demonstrated (IIb)
- A double blind randomized prospective study is currently in course in France (QUIDAM study)
- Clear interest of ablation of the substrate in this situation

Hermida, JACC 2004
Marquez, heart rhythm 2012

Conclusion

- Prognosis of the asymptomatic patients is "relatively" good (12% risk at 10 years in spontaneous type 1 patients)
- Predictive value of inducibility of ventricular tachyarrhythmias during EP-study are still under discussion
- ICD implantation leads to relatively high level of complications that can be improved with a good ICD programming and remote monitoring
- The problem of leads failure should be solved by S-ICD that appears as a very attractive possibility in these patients with intermediate risk but long life expectancy