

# Clinical outcome of patients with the Brugada type 1 electrocardiogram without prophylactic implantable cardioverter defibrillator in primary prevention: a cumulative analysis of seven large prospective studies

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## Aims

Patients with the Brugada type 1 ECG (Br type 1) without previous aborted sudden death (aSD) who do not have a prophylactic ICD constitute a very large population whose outcome is little known. The objective of this study was to evaluate the risk of SD or aborted SD (aSD) in these patients.

## Methods and results

We conducted a meta-analysis and cumulative analysis of seven large prospective studies involving 1568 patients who had not received a prophylactic ICD in primary prevention. Patients proved to be heterogeneous. Many were theoretically at low risk, in that they had a drug-induced Br type 1 (48%) and/or were asymptomatic (87%). Others, in contrast, had one or more risk factors. During a mean/median follow-up ranging from 30 to 48 months, 23 patients suffered SD and 1 had aSD. The annual incidence of SD/aSD was 0.5% in the total population, 0.9% in patients with spontaneous Br type 1 and 0.08% in those with drug-induced Br type 1 ( $P=0.0001$ ). The paper by Brugada *et al.* reported an incidence of SD more than six times higher than the other studies, probably as a result of selection bias. On excluding this paper, the annual incidence of SD/aSD in the remaining 1198 patients fell to 0.22% in the total population and to 0.38 and 0.06% in spontaneous and drug-induced Br type 1, respectively. Of the 24 patients with SD/aSD, 96% were males, the mean age was  $39 \pm 15$  years, 92% had spontaneous Br type 1, 61% had familial SD (f-SD), and only 18.2% had a previous syncope; 43% had a positive electrophysiological study. Multiple meta-analysis of individual trials showed that spontaneous Br type 1, f-SD, and previous syncope increased the risk of SD/aSD (RR 2.83, 2.49, and 3.03, respectively). However, each of these three risk factors had a very low positive predictive value (PPV) (1.9–3.3%), while negative predictive values (NPV) were high (98.5–99.7%). The incidence of SD/aSD was only slightly higher in patients with syncope than in asymptomatic patients (2% vs. 1.5%,  $P=0.6124$ ). Patients with SD/aSD when compared with the others had a mean of 1.74 vs. 0.95 risk factors ( $P=0.026$ ).

## Conclusion

(i) In patients with Br type 1 ECG without an ICD in primary prevention, the risk of SD/aSD is low, particularly in those with drug-induced Br type 1; (ii) spontaneous Br type 1, f-SD, and syncope increase the risk. However, each

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of these risk factors individually has limited clinical usefulness, owing to their very low PPV; (iii) patients at highest risk are those with more than one risk factor.

## Keywords

Brugada type 1 ECG • Aborted sudden death • Prophylactic ICD

### What's new?

- Patients with the Brugada type 1 electrocardiogram (Br type 1 ECG) who do not have a prophylactic implantable cardioverter defibrillator (ICD) in primary or secondary prevention constitute a very large population whose outcome is poorly known
- Brugada type 1 patients without an ICD constitute a heterogeneous population: most of them theoretically are at low risk, a few refuse ICD implantation even when it is suggested by physicians.
- The risk of sudden death (SD) in these patients is low: 0.22% per year, in the total population, 0.38 and 0.06% per year in those with spontaneous and drug-induced Br type 1 respectively
- Patients at risk of SD have more than one risk factor (spontaneous Br type 1, familial SD, syncope): 1.74 vs. 0.95 ( $P = 0.026$ ).
- This is the first study in a large population of Br type 1 patients without ICD which tested risk factors against SD alone, and not against possibly misleading combined end-points.

## Introduction

Patients with the Brugada type 1 electrocardiogram (Br type 1 ECG) without previous aborted sudden death (aSD) who do not undergo prophylactic implantable cardioverter defibrillator (ICD) implantation constitute a large population.<sup>1</sup> According to some authors,<sup>2</sup> they account for at least two-third of patients with Br type 1 ECG. The outcome of these patients, and particularly the characteristics of those who suffer sudden death (SD) or aSD during follow-up, are little known. Indeed, all prospective studies evaluating the outcome of patients with Br type 1 ECG have considered a combined end-point composed of fast ventricular arrhythmias (FVA) recorded by ICD and sudden death (SD) in subjects without ICD.<sup>1,3–23</sup> No previous prospective studies have reported data on patients with SD/aSD alone, simply because each single study registered only a few cases of SD/aSD during follow-up in patients without ICD.

In a previous study,<sup>1</sup> we made a cumulative analysis of five published studies involving patients with Br type 1 without previous cardiac arrest, in which we separated patients who had ICD from those without ICD. In patients with ICD, we analysed the prevalence of risk factors and their sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV). In patients without ICD, however, this analysis was not possible, because in the original papers the characteristics of patients without ICD who suffered SD during follow-up were not available in most cases.

In the present study, we made a cumulative analysis of seven large published prospective studies after obtaining from the authors themselves their original data on patients with Br type 1 ECG who did not receive a prophylactic ICD for primary prevention. The purpose of our study was to evaluate the incidence of SD/aSD and risk factors in this patient population.

## Methods

We considered large prospective studies (>49 patients) published between 2003 and 2013 which involved patients with Br type 1 ECG without previous cardiac arrest.

Studies were selected when, in the total population (patients with and without ICD), it was possible to separately analyse the characteristics of those without ICD and to obtain data on their follow-up. If original papers did not satisfy the inclusion criteria, we asked the authors to send us their aggregate original data. Authors who did so were included as co-authors. Studies were excluded if patients with and without ICD were cumulatively analysed and/or the authors did not supply original data.

To avoid the double-counting of patients, studies which were subsequently included in larger (single- or multi-centre) registries were excluded.<sup>13–18</sup> For example, the study by Giustetto *et al.*<sup>18</sup> was excluded because a number of patients were included in the study by Probst *et al.*<sup>9</sup>

In the selected studies,<sup>6–12</sup> all available potential risk factors were analysed: spontaneous Br type 1 ECG, familial SD (f-SD), syncope, positive electrophysiological study (+EPS), *SCN5A* defects and, in more recent papers, fragmented QRS (f-QRS), and early repolarization (ER) pattern.

In all these studies Br type 1 ECG was defined as a J-point elevation of  $\geq 2$  mV with a slowly descending segment followed by flat or negative T wave (coved type) in at least two right precordial leads.

In multicentre studies of Kamakura *et al.*,<sup>8</sup> Probst *et al.*,<sup>9</sup> Delise *et al.*,<sup>10</sup> and Priori *et al.*<sup>11</sup> all ECG's were sent to a coordinating Center to validate the diagnosis.

In these studies, f-SD was generically defined as a family history of unexplained SD. Only in one paper<sup>10</sup> was an age-limit of 40 years adopted. In various studies, EPS was carried out according to non-homogeneous protocols; i.e. some studies adopted aggressive protocols (such as triple extra stimuli and/or premature ventricular beats reaching the ventricular refractory period),<sup>6–8,10–12</sup> while others used less aggressive stimulation protocols.<sup>9</sup>

Moreover, not all studies evaluated and/or reported all the above-mentioned risk factors (e.g. +EPS, ER etc.). Therefore, the total number of patients varies when single risk factors are considered.

## Statistical analysis

We conducted an aggregate meta-analysis of summary statistics from the individual trials. For each study, data regarding SD mortality and all risk factors, defined as spontaneous type 1 ECG, f-SD, and syncope, were used to generate risk ratios (RRs) and 95% confidence intervals (CIs). Electrophysiological study was excluded from the meta-analysis because stimulation protocols were non-homogeneous. Since each response

**Table 1** Seven selected large studies published between 2003 and 2013. Patients were excluded if they had previous aborted sudden death (aSD) or an ICD for primary prevention or were included in at least one of the other studies

Studies	Total number of patients with type 1 ECG	Pts excluded owing to previous aSD	Pts excluded owing to ICD in primary prevention	Pts excluded because included in other studies	Pts enrolled without previous aSD and without ICD
Brugada <sup>6</sup>	547	0	177	0	370
Mok <sup>7</sup>	50	8	6	0	36
Kamakura <sup>8</sup>	245	45	70	0	130
Probst <sup>9</sup>	1029	62	388	0	579
Delise <sup>10*</sup>	320	0	110	111	99
Priori 11	308	0	137	0	171
Takagi 12	460	84	193	0	183
Total	2959	199	1081	111	1568

measure was used in a number of different studies, we calculated effect sizes for each response measure and performed a separate analysis on each measure. Study-specific estimates were combined by using inverse variance-weighted averages of logarithmic RRs in random-effect models. The study by Priori *et al.* was excluded from all the meta-analyses owing to lack of information. The study by Mok *et al.* was excluded from the meta-analysis regarding f-SD and syncope owing to lack of information.

Between-study heterogeneity was analysed by means  $\chi^2$   $P \leq 0.10$  deemed statistically significant and  $I^2$  for the measure of variation in RR attributable to heterogeneity. To deal with the problem of zero cells in the  $2 \times 2$  table, we used the standard correction by adding 0.5 to all cells with 0 before analysis. Sensitivity analyses were also performed to assess the contribution of each study to the pooled estimate by excluding individual trials according to zero cells, where possible. All analyses were performed by means of the statistical software StataSE 12.0 (StataCorp, College Station, TX, USA).

Cumulative analysis of homogeneous studies was made by calculating the sensitivity, specificity, PPV, and NPV of risk factors, expressed as both percentages and proportions.

When considering each risk factor (e.g. spontaneous type 1 ECG), we classified the presence/absence of this risk factor in patients with SD/aSD as true positive (TP) and false negative (FN), respectively. Conversely, in patients without SD/aSD, the presence/absence of this risk factor was classified as false positive (FP) and true negative (TN), respectively.

Sensitivity was calculated as  $TP/TP + FN$ , Specificity as  $TN/TN + FP$ , PPV as  $TP/TP + FP$ , and NPV as  $TN/TN + FN$ .

In all statistical tests, a value of  $P < 0.05$  was considered statistically significant (when not specified, the  $P$ -value should be considered two-tailed).

## Results

The seven selected studies<sup>6–12</sup> collected a total of 2959 patients. Of these, 199 patients were excluded because they had had a previous aSD; 1081 were excluded because they had received an ICD in primary prevention; 111 belonging to the study by Delise *et al.*<sup>10</sup> were excluded because were included in another study<sup>9</sup> (Table 1). The remaining 1568 patients, who had not had a previous cardiac arrest and had not received an ICD in primary prevention, were enrolled. The characteristics of these patients are listed in Table 2. Males numbered 1189 (76%) and the mean age was  $44 \pm 14$  years.

This population mainly comprised patients theoretically at low risk. Indeed, 48% had a drug-induced type 1, 69% had no family history of SD, 87% were asymptomatic and 83% had a negative EPS. Nevertheless, a significant number had risk factors: 724 (52%) had a spontaneous Br type-1 ECG, 420 (31%) f-SD, 183 (13%) previous syncope, and 155 (17%) +EPS. Regarding other potential risks factors, two patients (0.7%) had fQRS, 49 (11%) ER and 100 (31%) SCN5A defects. The characteristics of patients who suddenly died ( $n = 23$ ) or had an aSD ( $n = 1$ ) are listed in Table 3.

The incidence of sudden death was 1.5% (24/1568) over a follow-up ranging from 30 to 48 months. The annual incidence of SD/aSD was 0.53% in the general population, 0.9% in patients with spontaneous Br type 1 ECG and 0.08% in those with drug-induced Br type 1 ECG ( $P = 0.0001$ ).

Performing a subanalysis (sensitivity analysis) without the paper of Brugada<sup>6</sup> it emerged that two-thirds of the patients who suffered SD/aSD were reported in his paper; the event rate reported by these authors (16/370) was over six times higher than in the remaining studies (8/1198) (4.3% vs. 0.66%,  $P < 0.001$ ).

As a consequence, in the absence of the paper by Brugada *et al.*<sup>6</sup> the annual incidence of SD/aSD among the remaining 1198 patients fell to 0.22% in the total population, and to 0.38 and 0.06% in those with spontaneous and drug-induced Br type 1 ECG, respectively.

Sudden death generally occurred during the night (90%), at least in cases in which this datum was available.

On the basis of multiple meta-analysis (including all studies), spontaneous Br type 1 ECG, f-SD, and syncope significantly increased the risk of SD/aSD. When data from trials were pooled by means of a random-effects model, spontaneous Br type 1 ECG was associated with a RR = 2.83 increase (95% CI 0.92–8.71,  $P = 0.07$ ), f-SD with a RR = 2.49 (95% CI 1.07–5.80;  $P = 0.035$ ), and syncope with a RR = 3.03 (95% CI 1.20–7.67;  $P = 0.019$ ), as shown in Figure 1A–C. On excluding trials with zero cells, spontaneous Br type 1 ECG reached statistical significance (RR = 5.1 increase, 95% CI 1.00–25.95,  $P = 0.05$ ).

There was no trial heterogeneity except for the higher incidence on SD/aSD in the paper of Brugada.<sup>6</sup>

On considering the common risk factors (spontaneous Br type 1 ECG, f-SD, syncope) individually, SD/aSD occurred in 2.9% of

**Table 2** Characteristics of patients in selected prospective studies without previous aSD or with ICD in primary prevention

Studies	n. pts (males)	FU (months)	Age	Sp. Type 1 ECG	F-SD	Syn.	+EPS/EPS	fQRS	ER	SCN5A
Brugada 6	370 (277)	37 ± 30	40 ± 14	231/370	200/370	22/370	25/231	NA	NA	NA
Mok 7	36 (33)	30 ± 13	55 ± 14	31/36	NA	NA	NA	NA	NA	NA
Kamakura 8	130 (124)	48 ± 15	52 ± 12	92/130	9/130	14/130	39/64	NA	NA	NA
Probst 9	579 (382)	32 (14–54)	45 (37–57)	212/579	151/579	102/579	25/295	2/282#	28/282#	100/322#
Delise 10 <sup>a</sup>	99 (77)	40 (20–67)	43 (33–54)	49/99	29/99	19/99	4/58	NA	NA	NA
Priori 11	171 (137)	36 ± 8	47 ± 12	NA	NA	NA	28/171	NA	NA	NA
Takagi 12	183 (169)	44 ± 30	54 ± 14	109/183	31/183	26/183	34/85	NA	21/183	NA
Total	1568 (1199, 76%)		44 ± 14	724/1397	420/1361	183/1361	155/904	2/282	49/465	100/322
				52%	31%	13%	17%	0.7%	10.5%	31%

Sp. Type 1 ECG, spontaneous type 1 ECG; F-SD, family history of juvenile SD; syn., n. pts with syncope; +EPS/EPS, positive EPS (FV induction)/total number of EPS performed; fQRS, fragmented QRS; ER, early repolarization; SCN5A, positive/performed; NA, not available.

<sup>a</sup>Data excluding cases from Giustetto *et al.*; #original unpublished data provided by authors.

**Table 3** Characteristics of patients without previous cardiac arrest who did not have an ICD and suffered SD or aSD during follow-up

Studies	n. pts (males)	n. SD/aSD (M)	Noct. SD	Age	Sp. type 1 ECG	F-SD	Syn.	+EPS/EPS	fQRS	ER	SCN5A
Brugada <i>et al.</i> <sup>6</sup>	370 (277)	16 (15)	NA	41 ± 15	15/16	11/16	3/16	2/2	NA	NA	NA
Mok <i>et al.</i> <sup>7</sup>	36 (33)	1 (1)	NA	NA	1/1	NA	1/1	1/1	NA	NA	NA
Kamakura <i>et al.</i> <sup>8</sup>	130 (124)	1 (1)	1	45	1/1	1/1	0/1	0/1	0/1	0/1	1/1
Probst <i>et al.</i> <sup>9</sup>	579 (382)	2 (2)	1	24,49	1/2	1/2	0/2	0/1	0/1	0/1	NO
Delise <i>et al.</i> <sup>10 a</sup>	99 (77)	1 (1)	NA	39	1/1	0/1	0/1	NA	NA	NA	NA
Priori <i>et al.</i> <sup>11</sup>	171 (137)	1 aSD	NA	23	1/1	0/1	0/1	0/1	NA	NA	NA
Takagi <i>et al.</i> <sup>12</sup>	183 (169)	2 (2)	2	45, 52	2/2	1/2	1/2	0/1	NA	1/2	NA
Total	1568 (1199)	24 (23)	4/5	39 ± 15	22/24	14/23	5/24	3/7	0/2	1/4	1/1
%		M 96%	90%		92%	61%	21%	43%	0%	25%	100%

n. pts, total number of pts who did not have an ICD; M, males; n.SD/aSD, number of pts who had SD or aSD; Noct. SD, nocturnal SD; Sp.Type 1 ECG, spontaneous type 1 ECG; F-SD, family history of juvenile SD; syn., n. pts with syncope at baseline; +EPS/EPS, positive EPS (FV induction)/total number of EPS performed; fQRS, fragmented QRS; ER, early repolarization; SCN5A, positive/performed; NA, not available.

<sup>a</sup>Data from Giustetto *et al.* (included in Probst) excluded.

patients with a spontaneous Br type 1 ECG vs. 0.3% of those with a drug-induced Br type 1 ECG ( $P = 0.0001$ ), in 3.3% of those with f-SD vs. 0.8% of those without f-SD ( $P = 0.006$ ), and in 2% vs. 1.5% of those with/without syncope ( $P = 0.6124$ ) (Figure 2). The sensitivity of the risk factors ranged between 18.2% (syncope) and 91.3% (spontaneous type 1 ECG). Specificity ranged from 48.8% (spontaneous Br type-1 ECG) to 86.6% (syncope). Positive predictive value ranged between 1.9% (+EPS) and 3.3% (fSD). Negative predictive value ranged from 98.5% (syncope) to 99.7% (spontaneous type-1 ECG) (Table 4).

In other words, with the exception of spontaneous Br type 1 ECG, sensitivity was quite low, particularly that of previous syncope (18.2%). In addition, each risk factor displayed low specificity and very low PPV. In contrast, all risk factors had high NPV.

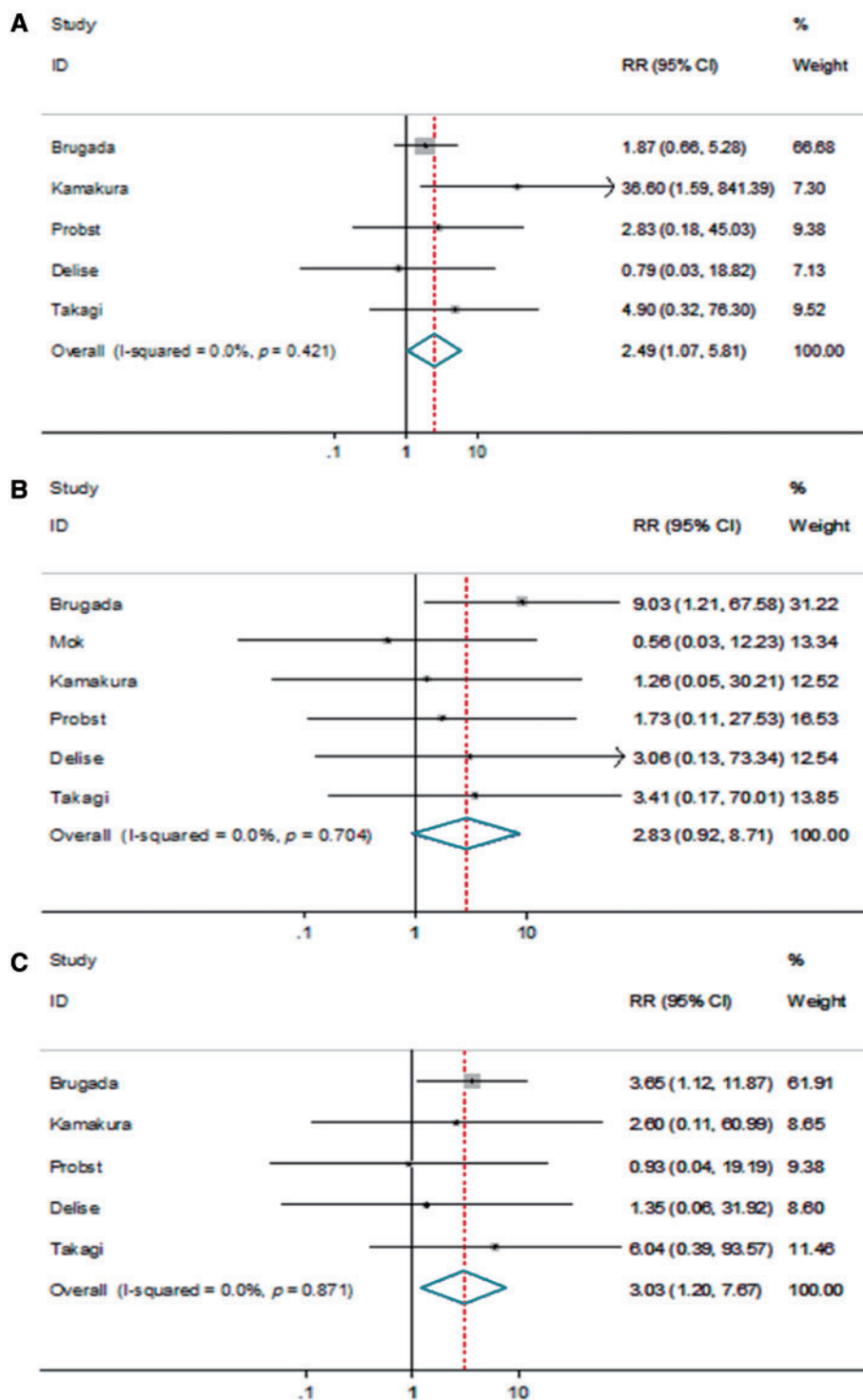
Focusing on patients who suffered SD/aSD (Table 5, Figure 3), it can be noted that the vast majority of patients with SD/aSD were males (96%) and had a spontaneous Br type 1 ECG (92%). Most (61%) had f-SD, while only a few (18.2%) had had syncope before SD/aSD. +EPS was present in a minority of cases (43%).

Of note, patients who suffered SD/aSD, when compared with those who had not SD/aSD, had a mean number of risk factors (Spont. type1 ECG, f-SD, syncope) of 1.74 vs. 0.95 ( $P = 0.026$ ). Including among risk factors also +EPS, the mean number of risk factors raised respectively to 2.2 vs. 1.1 ( $P = 0.011$ ).

## Discussion

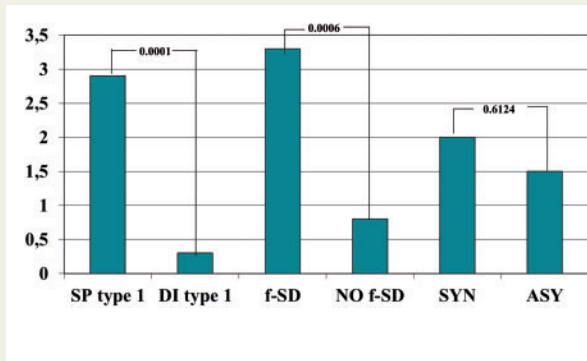
Patients with the Brugada type 1 ECG without previous aSD and who do not have an ICD for primary prevention constitute a very large population, accounting for at least two-third of patients with the Br type 1 ECG.<sup>1</sup> The outcome of these patients is poorly known.

Patients without an ICD for primary prevention constitute a heterogeneous population. Indeed, some of these patients do not receive an ICD because, on the basis of currently considered risk factors, they are deemed to be at low risk. Others refuse ICD implantation even when it is suggested by physicians.



Size of the data marker corresponds to the relative weight assigned in the pooled analysis using random-effects models. RR, risk ratio; CI, confidence interval.

**Figure 1** Meta-analysis of studies regarding spontaneous Br type 1 ECG (A), family history of SD (B), and syncope (C). (A) Sudden death among patients with family history of sudden death. (B) Sudden death among patients with Spontaneous Type 1 ECG. (C) Sudden death among patients with history of syncope. Size of the data marker corresponds to the relative weight assigned in the pooled analysis using random-effects models. RR, risk ratio; CI, confidence interval.



**Figure 2** Incidence of SD/aSD according to a spontaneous (sp) or drug-induced (DI) Br type 1 ECG, familial SD (f-SD), no familial SD (No f-SD), previous syncope (Syn), and no previous syncope (Asy).

**Table 4** Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of main risk factors

Parameter	Spont. type 1 ECG	Familial SD	Syncope	+EPS
Sensitivity	91.3%	63.6%	18.2%	42.9%
Specificity	48.8%	69.7%	86.6%	83.1%
PPV	2.9%	3.3%	2.2%	1.9%
NPV	99.7%	99.1%	98.5%	99.5%

In the present study, the first group includes the majority of patients. Indeed 87% were asymptomatic and only 17% had a +EPS. In addition, 48% had a drug-induced type 1 and 69% had no family history of SD. Nevertheless, the population analysed included also a significant number of patients with risk factors such as spontaneous Br type 1 ECG, f-SD, syncope, and +EPS.

This population of patients without ICD offers a unique opportunity to test risk factor against SD/aSD alone, offering data which are not available in the literature. Indeed, all published prospective studies<sup>1-18</sup> have used a combined end-point composed of FVA recorded by ICD and SD/aSD in patients without ICD.

In reality, however, ICD-recorded FVA are only a surrogate of SD, as they may be self-terminating and do not lead necessarily to death.<sup>19,20</sup>

All the above-mentioned prospective studies have identified a spontaneous type 1 ECG pattern and syncope as risk factors. In contrast, they have demonstrated a low risk in asymptomatic patients particularly with a drug-induced Br type 1.<sup>2-18</sup> Other risk factors have also been evaluated. Familial SD (f-SD) has proved to have a controversial prognostic value.<sup>2-18,21</sup> The usefulness of EPS has also been considered controversial for a long time, owing to the different protocols employed in various studies.<sup>2-18</sup> More recently, after performing a meta-analysis of large studies, Sroubeck et al.<sup>22</sup> stated that EPS did have a prognostic value, particularly when non-aggressive stimulation protocols were employed.

**Table 5** Prospective studies analysing non-ICD patients without (No SD) or with (SD) sudden death during follow-up

	No SD		SD		*p
	n	%	n.	%	
Cases	1544	100%	24	100%	
Males	1166/1544	75%	23/24	96%	0.0179
Age	45 ± 14		39 ± 15		0.27
Nocturnal SD	–	–	4/5	80%	–
Spontaneous type-1	703/1374	51%	22/24	92%	0.0001
Familial SD	409/1339	31%	14/23	62%	0.0015
Previous syncope	179/1339	13%	5/24	21%	0.2502
+EPS/EPS	153/898	17%	3/7	43%	0.0694
f-QRS	2/281	0.7%	0/2	0%	0.6981
ER	49/462	11%	1/4	25%	0.3752
SCN5A	105/358	29%	1/1	100%	0.1189
Mean of four classic RF		1		2.2	

Four classic risk factors were: spontaneous type 1 ECG, familial SD, previous syncope, and +EPS.

Finally, some new intriguing risk factors have recently been proposed: fragmented QRS, early repolarization, S wave in lead I, increased ST after effort, ST segment elevation on the peripheral leads, conduction disturbances.<sup>11,12,15,17,23-28</sup>

However, again, none of these studies has been able to test risk factors against SD/aSD alone.

In the present study, we collected only patients without previous cardiac arrest who had not received an ICD. The results of our cumulative study showed that this population of patients had a low risk of SD/aSD that is annual incidence of about 0.5%. Our results also confirm that the risk is significantly different according to whether the type 1 ECG is spontaneous or drug-induced. Indeed, in the former case, the annual incidence of SD/aSD proved to be 0.9% per year, while it was 0.08% in the latter.

However, in the paper by Brugada et al.<sup>6</sup> included in this study, the incidence of SD/aSD was over six times higher than in the other studies. This particularly high incidence of SD probably reflects a selection bias, as Brugada's centre, before 2003, collected complex cases from all over the world.

Our opinion is confirmed by a recent paper of the Group of Brugada<sup>29</sup> itself which has demonstrated that the incidence of events in their patients fell down to about one fourth after 2002 in respect to the population diagnosed before 2002.

On excluding the paper by Brugada from the cumulative valuation, the annual rate of SD/aSD fell to 0.22% in the total population and to 0.38 and 0.06% in patients with spontaneous and drug-induced Br type 1, respectively. The latter data probably represent the real actual incidence of SD/aSD in patients without ICD in primary prevention.

As a consequence, the conservative approach adopted in this population seems to have been appropriate. For example, in hypertrophic cardiomyopathy, a prophylactic ICD is not recommended in patients with a theoretical risk of SD <5% in 5 years, that is <0.8% per year.<sup>30</sup>

In the few patients who died in our cumulative study, multiple aggregate meta-analysis showed that spontaneous Br type 1 ECG, f-SD and syncope significantly increased the risk of SD/aSD. No meta-analysis on EPS was performed, owing to the heterogeneous stimulation protocols employed in different studies.<sup>6-12</sup>

Unfortunately, the clinical usefulness of all the above-mentioned risk factors appeared to be limited, except when they were absent. In fact, all classic risk factors had very high NPVs, ranging between 98.4% (syncope) and 99.7% (spontaneous type 1 ECG). In contrast, when present, all risk factors displayed low specificity and, above all, a very low PPV (ranging from 1.9 to 3.3%). In particular, the incidence of SD/aSD was only slightly higher in patients with syncope than in those who were asymptomatic (2% vs. 1.5%,  $P=0.6124$ ) (Figure 2). In addition the sensitivity of syncope was only 18.2%.

These data regarding prognostic value of syncope are rather surprising. Indeed, most prospective studies<sup>2-18</sup> have suggested that syncope is a useful marker of risk.

The similar incidence of SD/aSD in patients with and without syncope probably reflects a high prevalence of vaso-vagal syncope in this population without ICD.<sup>31</sup> And, conversely, patients with syncope clinically considered of cardiac origin did not take part to this population because they had ICD implantation.

As to the low sensitivity of syncope it is not easy to explain although our finding is in agreement with that of Raju *et al.*,<sup>32</sup> who reported that, of 45 subjects with familial Brugada Syndrome who suddenly died, only 9 (20%) had had syncopal episodes before the fatal event.

In our study, the high sensitivity of f-SD conflicts with the results of some studies.<sup>2-18,21</sup> However, it is in agreement with a previous study by our group,<sup>10</sup> which showed that f-SD increases the risk when associated to other risk factors. It is also possible that this discrepancy with other authors may depend from the different end points of our and other studies (again, SD/aSD alone and ICD interventions + SD/aSD respectively).

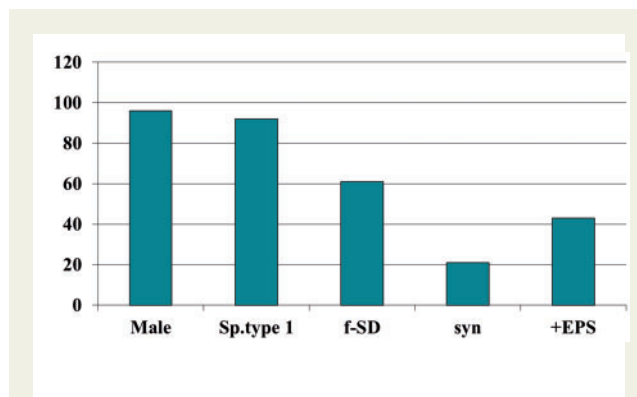
As stated above, the usefulness of EPS could not be fully evaluated owing to the heterogeneous stimulation protocols used by the various authors.

Regarding other risk factors, such as fragmented QRS, early repolarization, increased ST after effort, ST segment elevation on the peripheral leads and conduction disturbances, S in I lead which have been analysed in many studies,<sup>11,12,15,17,23-28</sup> no conclusion could be drawn in our study, owing to the paucity of data available.

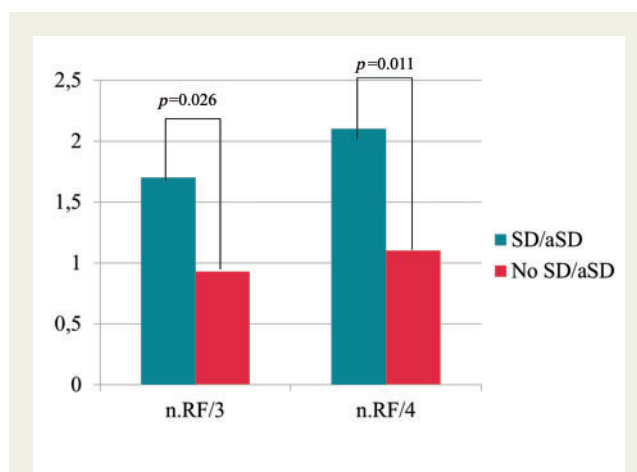
Finally, with regard to patients who suffered SD/aSD, it emerged that SD/aSD generally occurs during night, in males with a spontaneous Br type 1 ECG, and at a mean age of around 40 years. These patients frequently had familial SD, and only rarely had syncopal episodes before the life-threatening event (Figure 3).

A very important feature of these patients is that they had more than one risk factor among spontaneous type 1 ECG, f-SD and syncope (mean 1.75 vs. 0.95) (Figure 4). This latter observation confirms what was suggested by us in 2011 (10) and by Okamura *et al.* in 2015.<sup>33</sup>

The recent paper by Sroubeck *et al.*<sup>22</sup> also emphasizes the usefulness of multifactorial risk evaluation including EPS. Indeed, in his study, a +EPS (with up to two extrastimuli) increased the weight of risk factors such as spontaneous type 1 ECG and previous syncope.



**Figure 3** Prevalence of risk factors in patients who suffered SD<sup>23</sup> or aborted SD<sup>1</sup> during follow-up.



**Figure 4** Number of risk factors in patients with and without SD/aSD during follow-up. In the left columns three risk factors (n. RF/3) were considered (spontaneous type 1 ECG, f-SD, and syncope). In the right columns four risk factors (n. RF/4) were considered (including, in addition to spontaneous type 1 ECG, f-SD, and syncope, also +EPS). The differences between with and without SD/aSD during follow-up were statistically significant ( $P=0.026$  and 0.011 respectively).

In conclusion, in patients with the Brugada type 1 ECG without prior cardiac arrest who do not undergo ICD implantation, the prognosis is fairly good. The few patients who suffer SD/aSD are not easy to identify because they are generally asymptomatic.

The patients at highest risk have more than one risk factor: spontaneous Br type 1, familial SD and/or syncope. Patients with multiple risk factors should therefore be convinced to undergo ICD implantation, whether they have symptoms or not. By contrast, in patients without risk factors, or with only single risk factors, including spontaneous Br type 1, a conservative approach seems reasonable.

### Limitations of the study

As a limit of any meta-analysis there was no allocation of ECG's by central reading

In this study, we performed three aggregate meta-analyses to evaluate the heterogeneity of studies and the relative risks of the main risk factors. While meta-analysis of individual patient data (IPD) would be preferable, IPD were not available in some studies. However, since aggregate data were obtained from the authors themselves (in one case from the published paper), we did not expect significant differences between aggregate meta-analysis and an individual participant data meta-analysis. For these reasons, we decided to use standard aggregate-data meta-analysis techniques in the manuscript.

Patients without an ICD analysed in this study are not representative of the general population of patients with the Br type 1 ECG, in that those at highest risk (with previous cardiac arrest and/or significant risk factors) generally undergo ICD implantation for secondary or primary prevention. So the conclusions of this study cannot be extended to all patients with Brugada Syndrome.

The low incidence of sudden death was probably influenced by the relatively short follow-up (a mean/median of 30–48 months).

Paradoxically, as in no patient who died autopsy was available, the risk of SD might have been overestimated. However, other causes of SD in this relatively young population appear unlikely.

As the present study was not a true prospective study, but a cumulative analysis of previously published studies, many interesting data were not available. For example, the number of subjects who were probands and how many family members were affected.

The relatively short follow-up period available for the meta-analysis did not allow us to predict the risk over a longer period. It is therefore impossible to say whether this risk is centred around the age of 40 years (the mean age of the population), or may be cumulative over time, as suggested by Sacher et al.<sup>20</sup>

Finally, the small number of events<sup>22</sup> is a limitation when evaluating the prognostic value of risk factors. However, the small number of cases of SD exactly reflects the 'real-world' situation in a very large population of over 1500 cases.

## Conclusion

This is the first study to test risk factors against sudden death alone, and not against possibly misleading combined end-points.

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