Event rates and risk factors in patients with Brugada syndrome and no prior cardiac arrest: A cumulative analysis of the largest available studies distinguishing ICD-recorded fast ventricular arrhythmias and sudden death

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BACKGROUND All available studies that have addressed the issue of risk stratification in patients with type 1 Brugada electrocardiographic (ECG) pattern have considered a combined end point constituted by implantable cardioverter-defibrillator–recorded fast ventricular arrhythmias (ICD-FVA) and sudden death (SD) in patients without ICD.

OBJECTIVE As ICD-FVA are only a surrogate of SD, we tried to focus on the prognostic value of classical risk factors by separating patients with ICD-FVA from those without ICD who suffered SD.

METHODS We made a cumulative analysis of the largest available studies. Studies were selected in which the incidence of FVA and SD could be determined in patients with and without ICD separately. In addition, we tried to analyze the prognostic value of risk factors in patients with and without ICD separately.

RESULTS A total of 2176 patients were recruited from 5 studies, about one-third of whom had an ICD and two-thirds did not. Event rates per 1000 patient-years of follow-up were 31.3 (25–39) and 6.5 (4–10) in patients with and without ICD, respectively ($P < .001$). When considering FVA in patients with ICD, each single risk factor (spontaneous type 1 ECG pattern, familial juvenile SD, and +EPS) displayed limited clinical value, mainly owing to its low specificity (21%–61%) and low positive predictive value (9%–15%).

CONCLUSIONS In patients with type 1 Brugada ECG pattern, most arrhythmic events occur in patients with an ICD while SD is rare in patients without an ICD. While we have an acceptable ability to predict ICD-FVA, we have insufficient data to predict SD.

KEYWORDS Brugada syndrome; Ventricular arrhythmias; Risk stratification; Sudden death; Implantable cardioverter-defibrillator

ABBREVIATIONS **ECG** = electrocardiogram/electrocardiographic; **+EPS** = positive electrophysiologic study; **−EPS** = negative electrophysiologic study; **ICD** = implantable cardioverter-defibrillator; **ICD-FVA** = implantable cardioverter-defibrillator–recorded fast ventricular arrhythmias; **PPV** = positive predictive value; **NPV** = negative predictive value; **SD** = sudden death

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Introduction

Patients with type 1 Brugada electrocardiographic (ECG) pattern may suffer malignant arrhythmias and sudden death (SD). The real incidence of sudden SD in patients with type 1 Brugada ECG pattern is uncertain, as is risk stratification in these patients. Indeed, all published prospective studies[1–16] are registry-based population studies. There have been no randomized studies allocating patients with risk factors to an implantable cardioverter-defibrillator (ICD) or no-ICD groups. Furthermore, all studies have evaluated a combined end point constituted by implantable cardioverter-defibrillator–recorded fast ventricular arrhythmias (ICD-FVA) and SD in patients without ICD. Finally, as ICD-FVA and SD have a low incidence, most studies[1–8,10–16] have involved a relatively low number of cases.

In order to collect a large population, we performed a cumulative analysis of the largest published studies in which patients with an ICD could be separated from those without an ICD. Our purpose was to establish the incidence of events in patients with and without an ICD, respectively. Furthermore, we tried to evaluate the prognostic value of classical risk factors with respect to ICD-FVA and to SD separately.

Methods

Study selection

We first conducted a literature search by means of the PubMed database in order to identify articles published

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between 2003 and 2012 that addressed the problem of the prognostic stratification of patients with type 1 Brugada ECG pattern without previous cardiac arrest. Study selection was first based on the possibility to compare event rates (incidence of ICD-FVA and SD) in patients with and without an ICD. Furthermore, articles were selected when they had a prospective design and included more than 150 patients. The arbitrary choice of a cutoff of 150 patients was made in order to exclude small studies, which could be affected by a selection bias.

A further requirement was the possibility of establishing the prevalence of classical risk factors (spontaneous type 1 ECG pattern, familial juvenile SD, syncope, and +EPS) in patients with and without an ICD and their prognostic value with respect to the incidence of ICD-FVA and SD in patients with and without ICD, respectively.

On the basis of this research, we selected 6 large studies (Table 1).[1,2,10–13] Two other studies[8,9] that initially did not fulfill all inclusion criteria were added because authors send us their raw data that were not available in their original published articles.

Finally, in order to gather more data on patients with ICD, 2 further studies by Sacher et al[17] and Sarkozy et al[18] were selected that analyzed only patients with ICD in detail (Table 2). The article by Sarkozy was admitted, although it referred to only 47 patients.

The homogeneity of the available studies was tested by using a heterogeneity test. In addition, the Begg test was used to evaluate any predominant effect.

Statistical analysis

When performing cumulative analyses, we excluded any studies that also had been part of multicenter investigations in order to avoid the double counting of patients. Event rates (ICD-FVA and SD) were expressed per 1000 patient-years of follow-up, with 95% confidence intervals. Follow-up durations that were expressed as median values were changed to means and variances by using the method described by Hozo et al.[19]

The cumulative analysis of homogeneous studies was done by calculating the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of risk factors, expressed as both percentages and proportions. When considering each risk factor (eg, spontaneous type 1 ECG pattern), we classified the presence and absence of this risk factor in patients with events as true positive and false negative, respectively. Conversely, in patients without events, the presence and absence of this risk factor was classified as false positive and true negative, respectively.

All analyses were performed by means of the StataSE 12.0 statistical software (StataCorp, College Station, TX). Two sample-proportion tests were used to calculate statistical differences between group percentages. Event rates were compared between groups by means of incidence rate (incidence density or person-time) data. In all statistical tests, a value of $P < .05$ was considered statistically significant (when not specified, the P value should be considered 2-tailed).

Table 1 Features of the largest studies published between 2003 and 2012

Study	No. of patients	Sex: males	Type 1 ECG pattern	Familial juvenile SD	Syncope	+EPS	ICD implantation	Mean follow-up (mo)	Total events	ICD-FVA	SD (no ICD)
Brugada et al[4]	547	408	71%	55%	23%	40%	32%	36	8.2%	5.3%	2.9%
Eckardt et al[7]	188	130	59%	30%	35%	41%	47%	26–39	2.7%	2.7%	0%
Takagi et al[8]	155	145	86%	10%	37%	79%*	50%	39	2.2%	1.5%	0.7%
Kamakura et al[9]	200	190	69%	13%	23%	63%	35%	48	2%	1.5%	0.5%
Giustetto et al[10]	161	138	–	–	36%	34%	31%	30	3.7%	3%	0.7%
Probst et al[11]	967	690	45%	–	32%	41%	40%	32.5	3%	2.3%	0.7%
Delise et al[12]	320	258	54%	29%	34%	39%	32%	40	5.3%	4.3%	1%
Priori et al[13]	308	247	56%	–	21%	41%	45%	36	4.6%	4.6%	0%
Min-max (%)	155–967	130–690	45–71	10–55	21–37	34–79	31–50	26–40	2–8.2	1.5–5.3	0–2.9

In the studies by Eckardt et al,[7] Probst et al,[11] and Giustetto et al,[10] we excluded those patients who had a history of previous cardiac arrest. Therefore, the no. of patient refer only to patients symptomatic for syncope or asymptomatic. The demographic characteristics and the prevalence of main risk factors, percentage of patients with an ICD, and the mean duration of follow-up are reported, as are the incidence of FVA interrupted by ICD, of SD and the sum of these events.

ECG = electrocardiographic; +EPS = positive electropysiologic study; ICD = implantable cardioverter-defibrillator; ICD-FVA = fast ventricular arrhythmias recorded by implantable cardioverter-defibrillator; SD (no ICD) = sudden death in patients without implantable cardioverter-defibrillator.

*Including nonsustained ventricular tachycardia.

Table 2 Prevalence of risk factors in patients without previous cardiac arrest who underwent ICD implantation

Study	No. of patients	Type 1 ECG pattern	Familial SD	Syncope	+EPS/EPS performed	Follow-up (mo)	No. of events (ICD-FVA)*
Sarkozy et al[14]	47	62% (29)	55% (26)	55% (26)	83% (38/46)	Median 47 (IQR 4.5–156)	7 (7)
Sacher et al[17]	202	61% (124)	42% (85)	35% (70)	82% (153/187)	Mean 38 ± 27	14 (14)
Kamakura et al[9]	70	66% (44)	23% (16)	46% (32)	87% (58/67)	Mean 50 ± 13	3 (3)
Delise et al[12]	110	74% (82)	38% (42)	58% (64)	85% (90/106)	Median 40 (IQR 20–67)	14 (10)
Priori et al[13]	137	–	–	–	72% (98/137)	Mean 36 ± 8	13 (13)
Total no. of cases	566	279/429 (65%)	169/429 (39%)	192/429 (45%)	437/543 (80%)		51 (44)

ECG = electrocardiographic; +EPS = positive electropysiologic study; ICD = implantable cardioverter-defibrillator; ICD-FVA = implantable cardioverter-defibrillator–recorded fast ventricular arrhythmias; IQR = interquartile range; SD = sudden death.

*The numbers in brackets refer to patients who had undergone EPS.

Published data and original databases

We asked all authors of the included studies to check their respective data in our text and tables and, if possible, to provide further data. The authors found only minimal errors in our analysis of data pooled from their original articles. All errors were corrected.

The original articles by Eckardt et al,[7] Takagi et al,[8] Kamakura et al,[9] Giustetto et al,[10] and Probst et al,[11] also included patients with previous cardiac arrest. In all these studies, our analysis was limited to patients who were symptomatic for syncope or asymptomatic.

In the original study by Sacher et al,[17] 18 of 514 patients had a history of previous cardiac arrest. These 18 patients could not be excluded from the analysis of sensitivity, specificity, PPV, and NPV of classical risk factors because, in the original article, data from patients with previous cardiac arrest were pooled with those of patients who only had syncope or were asymptomatic. This problem was solved by the authors, who sent us original data that excluded patients with previous cardiac arrest.

In the original article by Brugada et al,[4] the mean follow-up reported was 24 ± 32 months. When these authors sent us their original data, they reported an updated follow-up of 36 ± 31 months.

In the multicenter study published by our group in 2011,[12] a number of cases provided by Giustetto et al[10] had previously been included in the article by Probst et al.[11]

Therefore, when we performed a cumulative analysis of both our article[12] and that of Probst et al[11] (Table 2) to avoid double counting of patients, patients from the study of Giustetto et al who had been included in the article by Probst et al were excluded from our original database. Therefore, in Table 2, the total numbers of patients and events are lower than those in our original article.[12]

Results

Preliminary analysis of the largest studies

The 8 selected large studies and the characteristics of their patients are listed in Table 3. The number of patients in these 8 studies[1,7–13] ranged between 155 and 967. All studies included patients with both spontaneous and drug-induced type 1 ECG patterns. The composition of the various populations was similar in terms of the prevalence of spontaneous type 1 ECG pattern (with the exception of the study by Brugada et al, Takagi et al, and Kamakura et al that had a 71%–86% prevalence vs 45%–59% in other studies),

Table 3 Cumulative analysis of studies in which events were compared in patients with and without ICD

Study	No. of patients	Follow-up (mo)	ICD implanted/not implanted	ICD-FVA	SD (no ICD)
Brugada et al[4]	547	Mean 36 ± 31	177/370	29/177	16/370
Kamakura et al[9]	200	Mean 48 ± 15	70/130	3/70	1/130
Probst et al[11]	967	Median 32 (IQR 14–54)	379/588	22/379	7/588
Delise et al[12]	154	Median 40 (IQR 20–67)	47/107	8/47	2/107
Priori et al[13]	308	Mean 36 ± 8	137/171	14/137	1/171
Total	2176		810/1366	76/810	27/1366

The study by Eckardt et al[7] was excluded from this analysis because some patients were also included in the multicenter study by Probst et al.[11] The study by Giustetto et al[10] was also excluded because some patients were also included in the multicenter study by Delise et al.[12]

*Finally, in the multicenter article published by our group[12] in 2011, 166 cases from Giustetto et al[10] had been previously included in the article by Probst et al.[11] Those patients from Giustetto et al[10] who had taken part in the study by Probst et al[11] were therefore excluded from our original database. Thus, the present analysis included only 154 cases instead of the 320 cases in our original article.

ICD = implantable cardioverter-defibrillator; ICD-FVA = fast ventricular arrhythmias recorded by implantable cardioverter-defibrillator; IQR = interquartile range; SD (no ICD) = sudden death in patients without implantable cardioverter-defibrillator.

syncope, +EPS, and number of patients with ICD. Follow-up ranged from 26 to 40 months.

With regard to outcome, all studies considered total events, calculated as the sum of ICD-FVA and SD occurring in those without an ICD. Total events ranged from 2.6% to 8.2%. SD in all studies ranged from 0% to 1%, with the exception of the study by Brugada et al,[4] which reported a value of 2.9%.

All 8 selected studies unanimously recognized spontaneous type 1 ECG pattern and syncope as risk factors. The significance of familial SD, however, was controversial. Moreover, the prognostic value of a +EPS proved to be highly controversial. Indeed, Brugada et al[4] and Giustetto et al[10] suggested that it had a significant prognostic value while Eckardt et al[7], Probst et al,[11] and Priori et al[13] denied that it had any value. Delise et al[12] suggested a prognostic value only in combination with other risk factors.

While these conflicting results may be partially explained by nonhomogeneous stimulation protocols, other factors were probably at work. For example, in the PRELUDE study,[13] most events (9 of 14) occurred in patients with –EPS. However, in 182 patients with –EPS, major events occurred in 20% (8 of 39) of the patients with an ICD and only in 0.6% (1 of 143) of those without an ICD ($P < .0001$). Furthermore, in 126 patients with +EPS, all events occurred in patients with ICD (5 of 98 vs 0 of 28; $P = .58$).

Other risk factors recently have been recognized in single studies: QRS fragmentation,[13,15] the occurrence/increase of ST-segment elevation after exercise,[16] and the presence of J wave.[20] However, these risk factors, except QRS fragmentation in the PRELUDE study,[13] were not analyzed in the selected 8 largest studies.

Finally, both the studies by Brugada et al[4] and by Delise et al[12] suggested that patients at the highest risk of events were those with spontaneous type 1 ECG pattern and at least 2 adjunctive risk factors (syncope, +EPS, and familial SD). Other studies did not analyze the prognostic significance of multiple risk factors and their combinations.

Event rates in patients with and without ICD

We performed a cumulative analysis of 5 of the aforementioned 8 selected largest studies.[4,9–11,16] The study by Eckardt et al[7] was excluded from this analysis because part of their population was included in the multicenter study by Probst et al.[9] The study by Giustetto et al[10] was also excluded because part of their population was included both in the multicenter study by Probst et al[9] and in that by Delise et al.[12] The study of Takagi et al[8] was also excluded because part of their population was included in the multicenter study of Kamakura et al.[9]

The final analysis included 2176 patients, about one-third of whom had an ICD and two-thirds did not (Table 3).

Event rates per 1000 patient-years of follow-up were 31.3 (25–39) and 6.5 (4–10) in patients with and without ICD, respectively ($P < .001$; Figure 1).

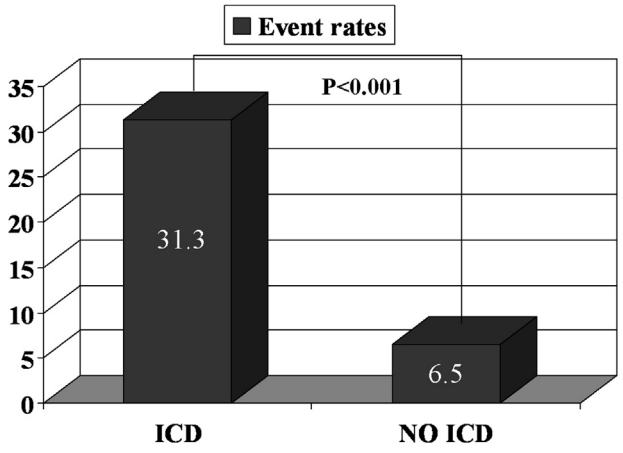

Figure 1 Event rates per 1000 patient-years of follow-up in the cumulative analysis of articles listed in Table 2. ICD = implantable cardioverter-defibrillator.

Prevalence of risk factors in patients with and without ICD implantation in various studies

The prevalence of risk factors in patients with ICD was not available from the studies by Brugada et al[4] and Probst et al[11] listed in Table 2. These data were available from Kamakura et al,[9] Delise et al,[12] and partially from Priori et al.[13] In addition, the studies by Sacher et al[17] and Sarkozy et al,[18] which analyzed only patients with ICD in detail, were selected (Table 1).

The prevalence of risk factors in patients without an ICD was not available from all the studies listed in Table 2. No data were available from the study by Probst et al,[11] and only partial data were available from those of Brugada et al[4] and Priori et al[13] (Table 4).

On analyzing the characteristics of patients who had an ICD (Table 1), the prevalence of classical risk factors was 65% for spontaneous type 1 ECG pattern, 39% for familial SD, 45% for syncope, and 80% for +EPS. Overall, the mean number of risk factors per patient was 2.3 (1.5 excluding +EPS).

By contrast, on analyzing the prevalence of the same risk factors in patients who had not undergone ICD implantation (in studies in which these data were available; Table 4), a spontaneous type 1 ECG pattern was present in 54%, familial SD in 18%, syncope in 16%, and +EPS in 22%. Overall, the mean number of risk factors was 1.1 (0.88 excluding +EPS).

The prevalence of risk factors was significantly higher in patients with ICD than in those without ICD: spontaneous type 1 ECG pattern, 279 of 429 vs 183 of 340 ($P = .002$); familial SD, 169 of 429 vs 61 of 340 ($P < .001$); syncope, 192 of 429 vs 55 of 340 ($P < .001$); +EPS, 437 of 543 vs 98 of 442 ($P < .001$) (Figure 2).

Prognostic value of classical risk factors in studies evaluating patients with ICD in detail

Five studies were selected[9,12–14,17]; these are listed in Table 1. Two of the 5 specifically addressed the outcome of patients with Brugada syndrome who had ICD.[14,17] All 4 studies addressed the prognostic value of classical risk

Table 4 Prevalence of risk factors in patients without previous cardiac arrest who were not candidates for ICD

Study	No. of patients*	Type 1 ECG pattern	Familial SD	Syncope	+EPS/EPS performed
Brugada et al[4]	370 (68)	NA	NA	NA	25/68
Kamakura et al[9]	130 (64)	92/130	9/130	14/130	39/64
Delise et al[12]	210 (139)	92/210	52/210	41/210	6/139
Priori et al[13]	171 (171)	NA	NA	NA	28/171
Total no. of cases	881 (442)	184/340 (54%)	61/340 (18%)	55/340 (16%)	98/442 (22%)

ECG = electrocardiographic; +EPS = positive electrophysiologic study; ICD = implantable cardioverter-defibrillator; SD = sudden death.
*Patients who did not undergo implantation; the values in parentheses present patients without ICD who underwent EPS.

factors. From these studies, a total population of 566 patients with ICD was recruited. During follow-up, 51 (9%) patients had ICD-FVA. Table 5 shows true-positive, false-positive, true-negative, and false-negative results for each risk factor.

Best sensitivity was obtained by spontaneous type 1 ECG pattern and +EPS (86% and 79%, respectively), although their specificity was extremely low. All risk factors showed a low PPV (ranging from 9% to 15%). All risk factors showed a high NPV (ranging from 89% to 95%), the highest NPV being observed for a spontaneous type 1 ECG pattern.

Prognostic value of classical risk factors in studies evaluating patients without ICD in detail

Six of the 8 largest studies listed in Table 1 prospectively reported cases of SD[4,8–10,12] and 1 of resuscitated cardiac arrest.[11] However, only in 3 studies[10,12,13] could the prevalence of risk factors be established in patients with these events. These studies recruited 5 cases of SD in 491 (1%) patients. A spontaneous type 1 ECG pattern was present in 5 of 5, familial SD in 1 of 5, and syncope in 0 of 5. EPS was unavailable in 4 and negative in 1.

From these data, we can deduce a sensitivity of 100% for spontaneous type 1 ECG pattern, 20% for familial SD, and 0% for syncope. Furthermore, we can deduce a PPV of 0% for syncope and of 0%–2% for familial SD.

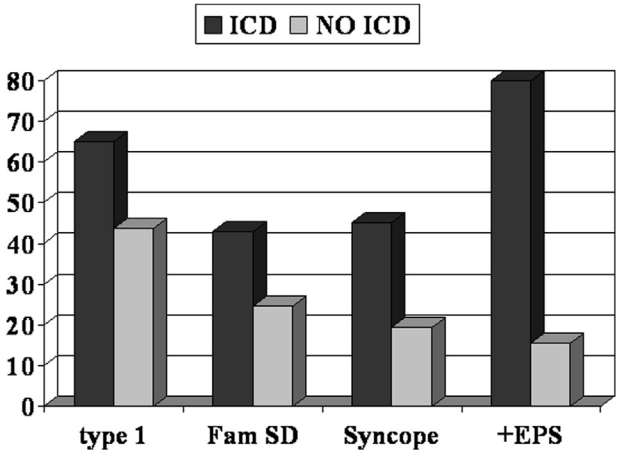

Figure 2 Prevalence of risk factors in patients with and without ICD. Patients with ICD had a mean of 2.3 risk factors while those without an ICD had a mean of 1.1 risk factors. +EPS = positive electrophysiology study; Fam SD = familial sudden death; ICD = implantable cardioverter-defibrillator; type 1 = spontaneous type 1 electrocardiographic pattern.

A cumulative analysis including specificity and NPV was not possible, as no study (except ours[10]) reported the characteristics of patients without ICD separately. All these data, however, should be considered with caution owing to the small number of patients.

Discussion

Patients with type 1 Brugada ECG pattern may suffer SD. Correct risk stratification in these patients is therefore important both to prevent SD and to avoid unnecessary ICD implantation. Indeed, patients with ICD may suffer from several complications (infections, catheter damage, and inappropriate discharge) that are deleterious, especially in young patients.

All studies that have addressed the issue of risk stratification in patients with type 1 Brugada ECG pattern[1–16] are registry-based population studies. There have been no randomized studies allocating patients with risk factors to ICD or no-ICD groups. Furthermore, all prospective studies that have tried to stratify risk in patients with type 1 Brugada ECG pattern have evaluated a combined end point constituted by FVA-ICD and SD in patients without ICD. ICD-FVA are only a surrogate of SD, as nonlethal arrhythmias may be counted. Therefore, the real incidence of SD in patients with type 1 Brugada ECG pattern is uncertain. Moreover, the prognostic value of single risk factors with regard to ICD-FVA and SD in patients without ICD is also uncertain. Finally, as ICD-FVA and SD have a low incidence, most studies have recruited a relatively small number of cases.

In the present study, we analyzed the largest available studies that have tried to stratify risk in patients with type 1

Table 5 Sensitivity, specificity, PPV, and NPV of the various risk factors according to the data from the 5 studies listed in Table 3 (Sacher et al[17], Sarkozy et al[14], Kamakura,[9] Delise et al,[12] and Priori et al[13])

Parameter	Spontaneous type 1 ECG pattern	Familial SD	Syncope	+EPS
Sensitivity	86%	39%	61%	79%
Specificity	36%	61%	52%	21%
PPV	15%	11%	14%	9%
NPV	95%	89%	91%	90%

ECG = electrocardiographic; +EPS = positive electrophysiology study; PPV = positive predictive value; NPV = negative predictive value; SD = sudden death.

Brugada ECG pattern. A preliminary analysis of the 8 largest studies[4,7–13] shows that most events occur in patients with ICD while SD in patients without ICD is rare over a follow-up ranging from 20 to 40 months. An exception is constituted by the study by Brugada et al[4] (2.9% SD rate), which probably recruited patients at the highest risk.

Our cumulative analysis of 2176 patients revealed that the incidence of events (ICD-FVA) in patients with an ICD proved to be over 5 times higher than that of SD or aborted SD in patients without an ICD (Table 2 and Figure 1). This conclusion emerges from 5 studies[4,9,11–13] that were homogeneous in terms of the prevalence of classical risk factors, including +EPS, and the proportion of patients in whom ICD were implanted (about one-third; Table 2).

We also made a cumulative analysis of studies that evaluated the prognostic value of risk factors separately in patients with and without ICD. With regard to patients with an ICD, 5 studies were selected[9,12–14,17] that recruited a population of 566 patients. An analysis of these patients revealed the limited clinical value of any single risk factor in predicting ICD-FVA. Indeed, no classic risk factor proved to be a prognostic gold standard. Sensitivity ranged from 39% (familial SD) to 86% (spontaneous type 1 pattern). Specificity was extremely low, ranging from 21% to 61%. In addition, all risk factors displayed a low PPV, ranging from 9% (+EPS) to 15% (spontaneous type 1 ECG pattern). By contrast, their NPV was high (89%–95%), with type 1 spontaneous ECG pattern displaying the highest value.

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.

Other new risk factors have recently been proposed—QRS fragmentation,[13,15] the occurrence/increase of ST-segment elevation after effort,[16] and the presence of J wave[20]—which should have interesting clinical application. However, most of these studies[15,16,20] in which these risk factors have been investigated were not part of our cumulative analysis, as they did not satisfy our inclusion criteria.

The main finding to emerge from our study is that in patients with type 1 Brugada ECG pattern without previous cardiac arrest, most events occur in patients with ICD while SD is rare in those without ICD. This raises the question "Why?" Two hypotheses can be advanced:

1. The first hypothesis is that, in clinical practice, candidates for ICD implantation are well stratified. This hypothesis is supported by the modality of selection adopted by all authors. Indeed, our cumulative analysis of available studies showed that patients who had undergone ICD implantation had a mean of more than 2 risk factors, the most common being +EPS (80%), followed by spontaneous type 1 ECG pattern (65%), syncope (45%), and familial SD (39%). By contrast, patients who had not undergone implantation had a mean of 1.1 risk factor; specifically, only 22% had +EPS, 54% type 1 ECG pattern, 16% syncope, and 18% familial SD. These data demonstrate that, in clinical practice, when the decision to implant an ICD was made, a polyparametric approach was adopted.

2. The second hypothesis is that the number of events recorded by ICD overestimates the risk of SD because potentially self-terminating and nonlethal arrhythmias may be counted.[21] There is no proof of this assumption; indeed, in patients without an ICD, we have no data on the incidence of self-terminating arrhythmias, regardless of whether asymptomatic or causing presyncope or syncope but not SD. Nevertheless, this hypothesis is intriguing and could explain why in the PRELUDE study,[13] in 126 patients with +EPS all events occurred in patients with ICD (5 of 98 vs 0 of 28; $P = .58$) while in 182 patients with –EPS major events occurred in 20% (8 of 39) of the patients with ICD and only in 0.6% (1 of 143) of those without an ICD ($P < .0001$). Moreover, if this hypothesis is true, the high prevalence of events and of +EPS in patients with ICD could mean that EPS predicts ICD-FVA that may not necessarily be lethal.

Study limitations

This study is not a multicenter prospective study, but a retrospective cumulative analysis of the largest published studies.

The data obtained from our analysis were checked by the respective authors who provided some data that were unavailable in their original articles. However, we did not obtain all original data. Consequently, we were unable to make further analyses that would have been interesting.

Conclusions

The available data show that in patients with type 1 Brugada ECG pattern and without previous cardiac arrest, we currently have an acceptable ability to predict ICD-FVA but have insufficient data to predict SD. In any case, all these data suggest that SD is rare in Brugada syndrome, particularly in patients without ICD, who account for two-thirds of the total population.

In addition, ICD-FVA are rare in patients without spontaneous type 1 ECG (ie, with only drug-induced type 1) pattern, such as in those who are asymptomatic, those without familial SD, and those with –EPS, thanks to the extremely high NPV of all these factors.

Consequently, an extensive indication for ICD implantation should be avoided in patients without risk factors or with only single risk factors (including +EPS). By contrast, ICD implantation should be proposed in the presence of multiple risk factors (syncope, familial SD, and +EPS), particularly in patients with spontaneous type 1 ECG pattern, as suggested by Brugada et al[4] in 2003, by Antzelevitch et al[6] in 2005, and by Delise et al[12] in 2011.

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