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Long-term prognosis in patients with non-type 1 Brugada electrocardiogram: Results from a large Japanese cohort of idiopathic ventricular fibrillation

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Abstract

Background: Brugada syndrome (BrS) is diagnosed in patients with ST-segment elevation with spontaneous, drug-induced, or fever-induced type 1 morphology. Prognosis in type 2 or 3 Brugada electrocardiogram (Br-ECG) patients remains unknown. The purpose of this study is to evaluate long-term prognosis in non-type 1 Br-ECG patients in a large Japanese cohort of idiopathic ventricular fibrillation (The Japan Idiopathic Ventricular Fibrillation Study [J-IVFS]).

Methods: From 567 patients with Br-ECG in J-IVFS, a total of 28 consecutive non-type 1 patients who underwent programmed electrical stimulation (PES) (median age: 58 years, all male, previous sustained ventricular tachyarrhythmias [VTs] 1, syncope 11, asymptomatic 16) were enrolled. Cardiac events (CEs: sudden cardiac death or sustained VT/ventricular fibrillation) during the follow-up period were examined.

Results: During a median follow-up of 136 months, four patients (14%) had CEs. None of patients with PES- have experienced CEs. There was no statistically significant clinical risk factor for the development of CEs. Using the Kaplan–Meier method, the event-free rate significantly decreased in a group with all 3 risk factors (symptom, wide QRS complex in lead V_2, and positive PES) ($p = .01$).

Conclusions: Our study revealed long-term prognosis in patients with non-type 1 Br-ECG. The combination analysis of these risk factors may be useful for the risk stratification of CEs in non-type 1 Br-ECG patients. The present study suggests that the patients with all these parameters showed high risk for CEs and need to be carefully followed.

KEYWORDS

Brugada syndrome, cardiac arrest, sudden death

Tetsuji Shinohara and Masahiko Takagi contributed equally to this study.

1 | INTRODUCTION

The Brugada syndrome (BrS) is generally associated with a high risk of sudden cardiac death (SCD) due to ventricular fibrillation (VF; Antzelevitch et al., 2017) The diagnosis of Brugada electrocardiogram (Br-ECG) has been based on the Brugada Consensus Report, published in 2002, in which 3 patterns of ST-segment elevation were proposed (Wilde et al., 2002). Type 1 Br-ECG is considered to be linked to a higher incidence of VF and SCD because it is frequently recognized just before and after episodes of VF (Atarashi et al., 2001). On the other hand, non-type 1 Br-ECG (type 2 and type 3 Br-ECGs) without drug-induced or fever-induced type 1 Br-ECG has been considered normal variants rather than specific predictors of VF occurrence (Junttila et al., 2004). According to the 2013 consensus report, only type 1 Br-ECG is the main criterion for the diagnosis of the BrS, whereas non-type 1 Br-ECG is excluded (Priori et al., 2013). As a result, unlike type 1 Br-ECG, the significance of non-type 1 Br-ECG has not been fully examined. Kamakura et al. reported that non-type 1 Br-ECG had high risk of SCD as similar as type 1 Br-ECG (Kamakura et al., 2009). However, it was possible that non-type 1 Br-ECG group might contain masked type 1 Br-ECG patients because high intercostal ECG recordings were not recommended as the diagnostic criteria at the time and, in some cases, the ST-segment morphology might not be fixed with daily fluctuation. A recent report showed that non-type 1 Br-ECG without the type 1 morphology even during drug provocation test and in high intercostal ECG recording was a risk factor for VF recurrence in patients with early repolarization syndrome (ERS; Kamakura et al., 2020). As a result, unlike type 1 Br-ECG, the significance of non-type 1 Br-ECG is still controversial and long-term prognosis in patients with non-type 1 Br-ECG without drug-induced type 1 Br-ECG has not been fully examined.

The Japan Idiopathic Ventricular Fibrillation Study (J-IVFS) is a multicenter prospective survey of patients with idiopathic VF, including BrS. This registry was launched in 2002 prior to the 2013 consensus report (Priori et al., 2013[)], which defined only spontaneous, drug-induced, or fever-induced type 1 Br-ECG as BrS. Therefore, most of the patients in J-IVFS registry are those with diagnostic type 1 Br-ECG, whereas few patients with non-type 1 Br-ECG without drug-induced or fever-induced type 1 Br-ECG have been included. In this study, we focused on only 28 consecutive non-type 1 patients who underwent programmed electrical stimulation (PES) with uniform protocol.

The purpose of this study is to evaluate a long-term prognosis and to seek cardiac events (CE: SCD or persistent ventricular tachycardia [VT] / VF) in patients with non-type 1 Br-ECG who are no longer diagnosed with BrS by current diagnostic criteria.

2 | METHODS

2.1 | Study population

Consecutive patients with Br-ECG (type 1, 2, or 3) including high intercostal spaces (third and/or second) (n = 567, mean age: 50 ± 15 years, 541 males) were enrolled in J-IVFS between February 2002 and August 2018.

A cohort in the present study was as same as that described in previous publication.(Takagi et al., 2018) The patients were probands from 567 different families that were followed for a period of > 1 year and met the following inclusion criteria: (a) normal findings upon physical examination, chest radiography, and echocardiography; (b) no administered antiarrhythmic drugs; and (c) no electrolyte abnormalities at the time of ECG recording and other examinations.

Of these patients, the present study registered a total of 28 consecutive patients with non-type 1 Br-ECG without drug-induced or fever-induced type 1 Br-ECG including the records at high intercostal spaces (median age: 58 years [range: 50 to 65 years], all males). All these patients have observed no type 1 Br-ECG on multiple ECG recordings, including high intercostal ECG recordings, in different days. We defined them as patients with non-type 1 Br-ECG because current diagnostic criteria do not diagnose as BrS. They underwent PES using uniform protocol. We defined a wide QRS complex when the QRS duration was greater than 90ms. J wave in inferolateral leads and late potentials on signal-averaged ECG were defined as we previously reported (Takagi et al., 2013, 2018). This study was approved by the Ethics Review Committee of each participating institution and was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients.

2.2 | Drug provocation test

Drug provocation tests were conducted with pilsicainide (1 mg/kg body weight injected at a rate of 5 to 10 mg/min) or flecainide (2 mg/kg, 10 mg/min) during standard and high intercostal ECGs recordings. The ECG recordings were recorded at 25 mm/s and 10 mm/mV. All of them were confirmed and analyzed by three cardiologists (M.T., Y.Y., and N.A.).

2.3 | Programmed electrical stimulation protocol

Stimulation protocol consisted of two drive pacing cycles (600 and 400 ms) and introduced up to three ventricular extra-stimuli down to a minimum of 200 ms from the right ventricular apex (RVA) and the right ventricular outflow tract (RVOT), respectively. The order of pacing sites and the number of extra-stimuli at both drive pacing cycles were single stimulus from RVA, double from RVA, single from RVOT, double from RVOT, triple from RVA, and then triple stimuli from RVOT (Takagi et al., 2018). Positive PES (PES+) was defined as induced VF or sustained polymorphic syncopal VT requiring direct current shock by PES. The decision to perform PES on patients with non-type 1 BrS was based on each physician's clinical judgment. Most of the patients performed PES had one of the previous defined risk factors such as syncope, family history of SCD, or wide QRS in lead V_2.

2.4 | Clinical course

Enrolled patients were monitored for ECG recordings and clinical events, at least, once every 12 months and the incidence of CEs (appropriate implantable cardioverter-defibrillator [ICD] shock therapy for fast polymorphic VT or VF > 200 beats/min in patients with ICD or documented fast VT, VF, or SCD in patients without ICD) was determined. ICD implantation was based on physician's clinical judgment according to the Japanese Circulation Society (JCS) guidelines for BrS. Each CE in patients with ICD was evaluated by analyzing intra-cardiac ECG stored in the ICD and confirmed as appropriate therapy for fast VT or VF.

2.5 | Statistical analysis

Clinical characteristics were presented as the mean ± *SD*, median (range) or with the number of patients with percentage, as appropriate. The Wilcoxon's rank sum test is used to compare the continuous values. Fisher's exact test is used for categorical variables to compare the proportion of subjects. Event-free survival between two groups was presented using Kaplan–Meier plot and compared using log rank test. Univariate and multivariate Cox proportional hazards regression analyzes were performed to estimate independent predictors of CEs. Inter- and intra-observer variability was assessed. For all tests, $p < .05$ were considered statistically significant. All computations were conducted using JMP v13.2.1 (SAS) on Windows™ 10 (Microsoft).

All authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the article as written.

3 | RESULTS

3.1 | Baseline clinical characteristics

Of the 28 patients enrolled, 12 cases (43%) had symptoms including 11 syncope (presumed arrhythmogenic) and one with history of VF, and 9 cases (32%) had history of atrial fibrillation (AF). Four cases (14%) had family history of SCD. PES + was noted in 19 cases (68%), who had induced VF and implanted ICD in all 19 cases. The median follow-up periods in all 28 patients were 136 months (range: 44 to 181 months).

3.2 | Clinical course

During follow-up periods, four of 28 patients (14%) had experienced CEs and their annual incidence was 1.5%. All of them had received ICD implantation and experienced appropriate ICD shocks for VF. There were no specific circumstances such as high fever in patients with CEs. The CEs occurred in 4 of 19 patients with PES+, in none of 9 patients with PES-. The positive predictive value of PES was 21%, and the negative predictive value was 100%. The annual incidence of CEs in patients with PES+ was 2.0%. However, Kaplan–Meier analysis demonstrated that the incidence of CEs was not significantly different between patients with PES+ and PES- ($p = .199$, Figure 1). Clinical and electrocardiographic characteristics on PES were neither different between patients with PES+ and PES-, except for the number of the patients with ICD implantation (Table 1).

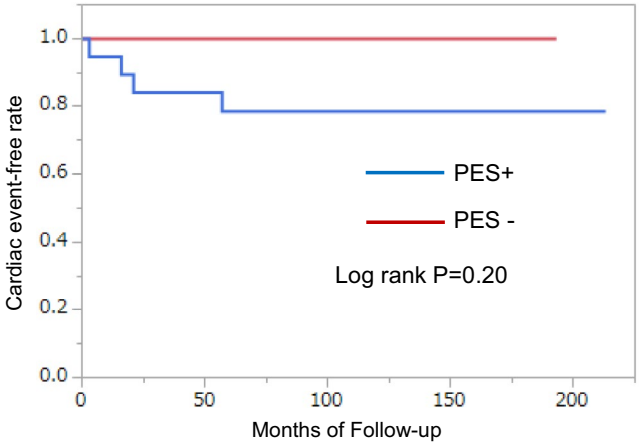

FIGURE 1 Kaplan–Meier cardiac event-free survival analysis in patients with PES+ and PES-. Kaplan–Meier curves indicate the incidence of cardiac events in patients with PES+ and PES-. PES, programmed electrical stimulation

3.3 | Predictors for cardiac event

Clinical, electrocardiographic, and electrophysiological characteristics in patients with and without CE are presented in Table 2 ($n = 4$ and $n = 24$, respectively). There were no significant differences between the two groups in any parameter. Patients with CE tended to be younger and have more symptom, wider QRS complex in lead V_2, higher inducibility compared to those without CE. Clinical characteristics in all four patients with CE are presented in Table 3. None of the patients had family history of SCD. Symptom and wide QRS complex in lead V_2 were both positive in three patients (75%). All of them had PES-induced VT/VF and ICD implantation.

3.4 | Risk factor combinations

Based on these results, we evaluated clinical significance of risk factor combinations using three risk factors (symptom, wide QRS complex in lead V_2, and PES-induced VT/VF). Three of 5 patients (60%) with three risk factors, none of 8 patients (0%) with two factors, one of 10 patients (10%) with one factor, and none of five patients (0%) without any risk factors have experienced CEs. Using the Kaplan–Meier method according to the number of risk factors, the

TABLE 1 Clinical and electrocardiographic characteristics on programmed electrical stimulation

	Induced VT/VF (PES+) *N* = 19	Non-induced VT/VF (PES−) *N* = 9	*p* value
Median age (years)	57 (38–61)	58 (52–71)	0.22
Symptom, *n* (%)	9 (47)	3 (33)	0.69
AF, *n* (%)	7 (37)	2 (22)	0.67
Family history of SCD, *n* (%)	3 (16)	1 (11)	1.00
J wave in inferolateral leads, *n* (%)	2 (11)	0 (0)	1.00
Wide QRS complex in lead V2 (>90 ms), *n* (%)	9 (50)	1 (13)	0.10
Fragmented QRS, *n* (%)	0 (0)	1 (11)	0.32
Positive late potential, *n*/*N* (%)	9/14 (64)	2/7 (29)	0.18
ICD implantation, *n* (%)	17 (89)	2 (22)	<0.001
Median follow-up periods (months)	144 (57–199)	50 (34–154)	0.15

Abbreviations: AF, atrial fibrillation; ICD, implantable cardioverter-defibrillator; PES+, positive programmed electrical stimulation; PES−, negative programmed electrical stimulation; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

TABLE 2 Clinical, electrocardiographic, and electrophysiological characteristics depended on cardiac event

	Cardiac event (+) *N* = 4	Cardiac event (−) *N* = 24	*p* value
Median age (years)	42 (30–57)	58 (51–65)	0.11
Symptom, *n* (%)	3 (75)	9 (38)	0.29
AF, *n* (%)	2 (50)	7 (29)	0.57
Family history of SCD, *n* (%)	0 (0)	4 (17)	1.00
J wave in inferolateral leads, *n* (%)	0 (0)	2 (8)	1.00
Wide QRS complex in lead V2 (>90 ms), *n* (%)	3 (75)	7 (32)	0.26
Fragmented QRS, *n* (%)	0 (0)	1 (4)	1.00
Positive late potential, *n*/*N* (%)	2/3 (67)	9/18 (50)	1.00
PES-induced VT/VF, *n* (%)	4 (100)	15 (63)	0.27
ICD implantation, *n* (%)	4 (100)	15 (63)	0.27

Abbreviations: AF, atrial fibrillation; ICD, implantable cardioverter-defibrillator; PES, programmed electrical stimulation; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

event-free rate in a group with all three risk factors significantly reduced compared to the other groups ($p = .01$, Figure 2). In addition, the results were similar even when patients with family history of SCD ($n = 4$) or history of VF ($n = 1$) were excluded ($p = .01$, Figure 3).

4 | DISCUSSION

4.1 | Main findings

Main findings in the present study were as follows: First, we revealed long-term prognosis during more than 10 years follow-up in patients with non-type 1 Br-ECG without drug-induced or fever-induced type 1 Br-ECG including high intercostal spaces. Four of 28 non-type 1 Br-ECG patients (14%) enrolled in this study have experienced CEs during median follow-up periods of 136 months (1.5%/year). Second, the VT/VF inducibility by PES showed high negative predictive value for CEs. None of patients with PES- have experienced CEs. Third, the combination analysis using 3 risk factors (symptom, wide QRS complex in lead V_2, and PES-induced VT/VF) revealed good prediction of CEs, even when patients with family history of SCD or history of VF were excluded. To the best of our knowledge, we first demonstrated that the combination analysis of above 3 risk factors is an effective tool for the risk stratification of CEs in patients with non-type 1 Br-ECG.

4.2 | Incidence of cardiac events in non-type 1 Br-ECG patients

We showed the incidence of CEs in patients with non-type 1 Br-ECG was 14% during a median follow-up of approximately 10 years. Non-type 1 Br-ECG is generally considered to be an ECG finding with a good prognosis, but no prospective prognostic study has been reported. Recently, a retrospective study reported that coexistence of non-type 1 Br-ECG, which did not show type 1 Br-ECG even during drug provocation test and in high intercostal ECG

TABLE 3 Clinical, electrocardiographic, and electrophysiological characteristics in four patients with cardiac event

	Case 1	Case 2	Case 3	Case 4
Gender (male)	+	+	+	+
Age at enrollment	58	30	30	54
Symptom	−	+	+	+
AF	−	+	+	−
Family history of SCD	−	−	−	−
J wave in inferolateral leads	−	−	−	−
Wide QRS complex in lead V2 (>90 ms)	−	+	+	+
Fragmented QRS	−	−	−	−
Positive late potential	Positive	Negative	n..a	Positive
PES-induced VT/VF	+	+	+	+
ICD implantation	+	+	+	+
Months of follow-up at cardiac event	21	4	16	56

Abbreviations: AF, atrial fibrillation; ICD, implantable cardioverter-defibrillator; n.a., not applicable; SCD, sudden cardiac death.

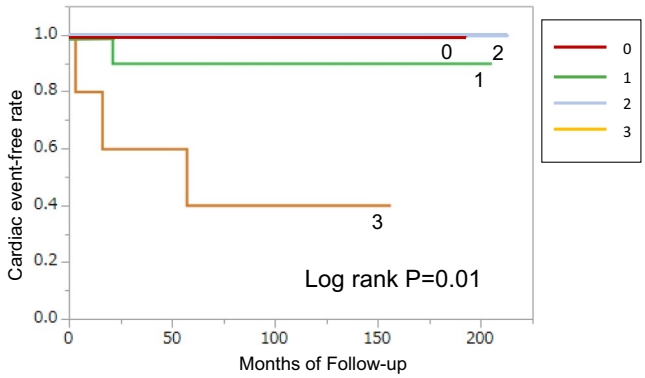

FIGURE 2 Incidence of cardiac events depending on the number of combined risk factors. Kaplan–Meier curves show the incidence of cardiac events depending on the number of risk factors in all patients ($n = 28$). Risk factors include: (a) symptom, (b) wide QRS complex in lead V_2 (>90 ms), and (c) PES-induced VT/VF

recording, was a key predictor of poor outcome in ERS patients (Kamakura et al., 2020). Their results may suggest that some studies in ERS patients with prior VF might include patients with non-type 1 Br-ECG. Tsuneoka et al. demonstrated in their retrospective study that the incidence of SCD was only 1.2% in participants with

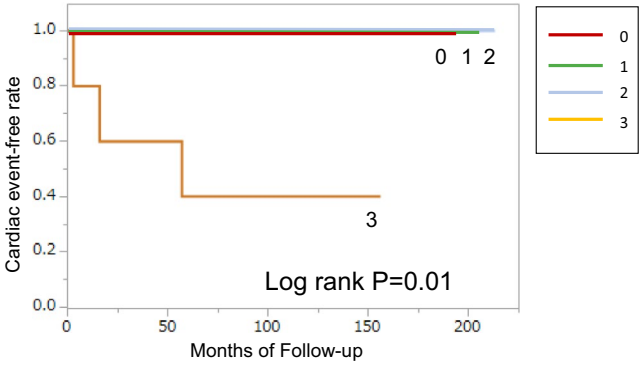

FIGURE 3 Incidence of cardiac events depending on the number of combined risk factors in patients without family history of SCD or history of VF. Kaplan–Meier curves show the incidence of cardiac events depending on the number of risk factors in patients without family history of SCD or history of VF ($n = 23$). The risk factors are the same as in Figure 2

non-type 1 Br-ECG during a median follow-up of 18.7 years in individuals with health check-up (Tsuneoka et al., 2016), which was much fewer than that in this study. This discrepancy may be due to following reasons: First, both studies might be biased at the case registration stage. In our study, it may be possible that patients with high risk of CE and/or with ECG abnormality were predominantly enrolled in our study. Actually, many patients enrolled in our study received ICD implantation (68%). The study by Tsuneoka et al. enrolled apparently healthy middle-aged participants (age range 40–64 years) who underwent health checkups. Secondly, as a result of high incidence of ICD implantation in our study, the incidence of CE could be accurately evaluated compared to the other report with check-up with the health examination once a year, although appropriate ICD shocks for VT/VF might overestimate the incidence of true SCD. The incidence of true SCD in patients with non-type 1 Br-ECG needs to be estimated carefully in those without ICD during long-term follow-up.

4.3 | Prognostic value of PES

Previous studies have shown conflicting results regarding prognostic value of PES in patients with BrS. Several studies have indicated that PES had a high negative predictive value as a tool for risk stratification (Brugada et al., 2003; Delise et al., 2011). However, prognostic value of PES in non-type 1 Br-ECG has not been fully evaluated. The present study revealed that PES had a high negative predictive value (100%) as a tool for risk stratification in patients with non-type 1 Br-ECG. On the other hand, PES did not show prognostic value of VT/VF inducibility for future CEs. The patients with PES+ tended to be higher incidence of CEs than those with PES-. Further continuing study to accumulate a larger number of patients may improve our understanding of prognostic value of VT/VF inducibility.

4.4 | Predictors for cardiac events by combination of risk factors

Although clinical, electrocardiographic, and electrophysiological characteristics in patients with and without CE were not different between the 2 groups, we found that patients with CE tended to be younger and have more symptom (syncope), wider QRS complex in lead V_2, higher inducibility compared to those without CE. Therefore, we analyzed the predictors of CEs by multiparametric approach. Several reports stressed the utility of combinations of several risk factors in patients with BrS (Delise et al., 2011; Kawazoe et al., 2016; Sieira et al., 2017). Delise et al. stressed that patients with a spontaneous type 1 ECG and at least 2 of 3 risk factors (syncope, family history of SCD, and positive PES) were at a higher risk (Delise et al., 2011). Sieira et al. proposed in a recent longest follow-up study that a combination of specific risk factors, such as spontaneous type 1 ECG, early familial SCD, inducible PES, syncope, sinus node dysfunction, and aborted SCD, could accurately predict the risk of arrhythmic events in BrS patients (Sieira et al., 2017). Furthermore, we previously reported that the combination analysis of a history of syncope, spontaneous type 1 Br-ECG, and PES by a single ventricular extra-stimulus was useful for predicting CEs in BrS patients without previous cardiac arrest (Takagi et al., 2018). The present study demonstrated, for the first time, the risk stratification of CEs in non-type 1 Br-ECG patients using a combination analysis in a large-scale survey. The combination analysis of risk factors (symptom, wide QRS complex in lead V_2 and PES-induced VT/VF) may be useful for the risk stratification of CEs in non-type 1 Br-ECG patients. The patients with all these parameters showed high risk for CEs and should be carefully followed. Larger scaled studies and longer follow-up periods are needed to validate this evaluation system for risk stratification in an independent dataset in the future.

4.5 | Study limitations

The present study has several limitations. First, only 28 patients were evaluated in the study, because PES had been rarely performed in non-type 1 Br-ECG patients. It is difficult to lead to definitive conclusion due to small number. In particular, the number of patients with CEs during follow-up was low. However, although our study had a small number of patients, we believe that the 4 patients who experienced CEs causing SCD should not be ignored. Second, patients with PES-induced VT/VF are more susceptible to implant ICD (Priori et al., 2012; Sroubek et al., 2016). In fact, the present study showed that PES+ patients had more ICD implantation than PES- patients. Appropriate ICD shocks for VT/VF in patients with ICD may include episodes terminating spontaneously, which does not result in SCD. Thus, the presence of ICD may have affected the outcome of prognosis between PES+ and PES- groups. Third, the waveform of Br-ECG has a daily fluctuation. Therefore, we diagnosed non-type 1 Br-ECG based on multiple ECG recordings in different days. Nonetheless, this study may include some patients with masked type 1 Br-ECG. Fourth, currently, PES is not commonly performed in patients with non-type 1 Br-ECG. In this study, the implementation of PES to non-type 1 Br-ECG patients was based on the clinical judgment of each physician, because non-type 1 Br-ECG patients with inducible VT/VF had been possible to be implanted ICD until the Guidelines for Non-Pharmacological Therapy of Cardiac Arrhythmias (JCS, 2006) was published in 2006. We enrolled only non-type 1 Br-ECG patients who underwent PES with uniform protocol to evaluate the utility of PES as risk factor. It cannot be denied that there may have been some bias at that point. The patients enrolled in this study may not represent the general non-type 1 Br-ECG population because we did not include non-type 1 Br-ECG patients who did not undergo the PES.

5 | CONCLUSIONS

Our large-scaled multicenter study revealed long-term prognosis in patients with non-type 1 Br-ECG. The combination analysis of symptom, wide QRS complex in lead V_2, and PES-induced VT/VF may be useful for the risk stratification of CEs in non-type 1 Br-ECG patients. The present study suggests that the patients with all these parameters showed high risk for CEs and need to be carefully followed.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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