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ORIGINAL RESEARCH

CLINICAL ELECTROPHYSIOLOGY

The Clinical Significance of Atrial Fibrillation in Non–High-Risk Brugada Syndrome

The BruFib Study

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ABSTRACT

BACKGROUND Atrial fibrillation (AF) occurs in up to 20% of patients with Brugada syndrome (BrS), yet its risk factors and prognostic implications remain uncertain.

OBJECTIVES This study sought to identify risk factors for AF in patients with non-high-risk BrS and to evaluate the impact of AF on ventricular arrhythmias (VAs), sick sinus syndrome (SSS), and stroke in non-high-risk BrS.

METHODS This was a multicenter, retrospective study conducted across 20 international centers. Non-high-risk BrS patients were stratified based on the presence or absence of AF. The primary endpoint was the occurrence of VAs, defined as sustained ventricular tachycardia, ventricular fibrillation, or arrhythmic sudden cardiac death.

RESULTS A total of 686 BrS patients were analyzed (39.3 years of age, 33.1% female, 31.8% spontaneous type 1 electrocardiogram, 36.0% pathogenic/likely pathogenic *SCN5A* variant), including 280 with AF (40.8%). Proband status and older age were associated with AF at Cox regression analysis. Over a median follow-up of 48.8 months, the incidence of VAs was 0.26% per year, with no significant difference between patients with and without AF (HR: 0.67; $P = 0.58$). Early-onset AF (<20 years) was associated with significantly higher risk of VAs ($P < 0.001$). SSS was twice as prevalent in BrS patients with AF (10.0% vs 6.2%; $P = 0.047$), and stroke occurred exclusively in the AF group (2.5%), despite low CHA_2DS_2-VA (mean 0.5).

CONCLUSIONS The presence of AF in non-high-risk BrS does not identify patients with higher risk of VAs. However, early-onset AF (<20 years) defines a distinct subgroup with elevated risk. Patients with AF and BrS have a significantly higher risk of SSS and stroke. (JACC Clin Electrophysiol. 2025;11:2471–2480) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

BrS = Brugada syndrome

ECG = electrocardiogram

ICD = implantable cardioverter-defibrillator

P/LP = pathogenic/likely pathogenic

SSS = sick sinus syndrome

VA = ventricular arrhythmia

Brugada Syndrome (BrS) is an inherited cardiac disease associated with life-threatening ventricular arrhythmias (VAs) and sudden cardiac death.[1] Beyond the ventricular involvement, BrS also predisposes to atrial arrhythmias, including atrial fibrillation (AF), atrial flutter, and atrial tachycardia.[2] The high prevalence of atrial arrhythmias, particularly AF, has been well documented in BrS, with studies reporting a lifetime incidence of up to 20%.[3,4]

An important area of investigation is whether AF correlates with VAs or whether atrial and ventricular arrhythmias represent 2 independent phenotypes of the disease. This distinction is crucial for elucidating the pathophysiology of BrS and improving risk stratification for non-high-risk patients with both BrS and AF. Early evidence suggests that AF is more common in high-risk BrS patients, implying that AF could serve as a marker of elevated risk in BrS.[5] However, several limitations in prior studies do not allow us to draw definitive conclusions: 1) small sample sizes, with most studies including <50 patients with BrS and AF; and 2) the presence of implantable cardioverter-defibrillators (ICDs) in the high-risk group may have biased the results by increasing the detection of AF through continuous rhythm monitoring, whereas AF may have been underdiagnosed in the non-high-risk group.[4]

These limitations highlight the need for more robust investigations to address unresolved questions: What are the risk factors for AF in BrS? What is the prognostic significance of AF in non-high-risk BrS patients? How does AF influence the risk of stroke and sick sinus syndrome (SSS) in BrS?

To address these questions, we conducted a large, multicenter study focusing on non-high-risk BrS patients. The primary objectives were 3-fold: 1) to identify risk factors for AF in BrS patients; 2) to assess the prognostic value of AF in predicting subsequent VAs in non-high-risk BrS patients; and 3) to evaluate the prevalence of stroke and SSS.

METHODS

STUDY DESIGN. This is a retrospective, multicenter study. A total of 20 interventional centers in 8 countries were involved. The study was approved by the local ethics committee (Swiss Ethics, approval

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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number: BASEC 2019-00754/CE 3476) and conforms to the Declaration of Helsinki. The data sets generated and/or analyzed during the current study are not publicly available to maintain patient confidentiality but are available from the corresponding author on reasonable request, and after the agreement of all the co-authors.

PATIENT POPULATION. The diagnosis of BrS was based on the latest guidelines.[6-8] Specifically, patients were included if their Shanghai score was ≥3.5 points. Consecutive BrS patients were divided into 2 groups: patients with AF (BrS AF+ group) and patients without AF (BrS AF− group). The diagnosis of AF required documentation on a 12-lead electrocardiogram (ECG) or other ECG recording device, with a minimum duration of 30 seconds, in accordance with current AF management guidelines. For patients equipped with a continuous rhythm monitoring device, asymptomatic episodes were required to last ≥6 minutes.[9] Patients were only included in the BrS AF− group if they had an implantable loop recorder for continuous rhythm monitoring.

Patients with previous VAs, previous syncope of suspected arrhythmic etiology, or implanted with an ICD were considered high-risk BrS patients and were excluded from the analysis to minimize selection bias in the AF cohort. SSS was defined as presence of: 1) symptomatic sinus arrest of 3-6 seconds, or asymptomatic arrest >6 seconds; or 2) chronotropic incompetence requiring pacemaker implantation.

ENDPOINTS. Follow-up started with the diagnosis of BrS. The primary endpoint was the prevalence of VAs defined as sustained ventricular tachycardia/ventricular fibrillation or arrhythmic sudden cardiac death. Secondary endpoints were unexplained death (ie, sudden death without evidence of arrhythmic death), cardioembolic stroke/transient ischemic attack, and SSS. Risk factors associated with AF and VA were also assessed.

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD when normally distributed or otherwise median (Q1-Q3). Comparisons between groups were undertaken with parametric (Student's *t*) or nonparametric (Mann-Whitney *U*) tests, respectively. The comparison between categorical variables was performed with the chi-square test and the Fisher exact test, as indicated. Event-free survival probability was estimated using the Kaplan-Meier method. Cox regression analysis (HR and 95% CI) and logistic regression analysis (OR and 95% CI) were used to estimate the association between baseline characteristics and arrhythmic events. A 2-sided $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS (version 23.0, IBM Corp).

TABLE 1 Baseline Characteristics

	BrS AF+ (n = 280)	BrS AF- (n = 406)	*P* Value
Age at BrS diagnosis, y	48.7 ± 17.5	30.4 ± 18.4	<0.001
Age at first AF diagnosis, y	48.3 ± 17.4		
Female	87 (31.2)	144 (35.5)	0.25
Proband status	184/240 (77.6)	204/374 (54.5)	<0.001
Family history of BrS	16/52 (31.4)	167/391 (42.7)	0.13
Family history of SCD	70 (25.0)	103/412 (25.4)	0.98
Family history of AF	14/141 (9.8)	1/12 (8.3)	0.89
Spontaneous Brugada type 1 ECG	82/265 (31.8)	129/398 (32.4)	0.86
Shanghai score	4.0 (2.0-5.0)	4.0 (2.0-4.0)	0.65
Sierra score	1 (0-2)	1 (0-1)	0.93
PR interval, ms	166.9 ± 25.7	158.6 ± 25.8	0.033
QRS interval, ms	102.0 ± 19.1	100.2 ± 17.2	0.23
SCN5A P/LP variant	22/58 (37.9)	91/256 (35.5)	0.76
Risk factors for AF			
Hypertension	49/153 (32.2)	1/91 (1.1)	0.035
Hyperthyroidism	7/140 (4.9)	0	0.89
Alcohol abuse	1/143 (0.7)	0	0.88
Endurance sport	17 (6.1)	2/83 (2.4)	0.66
CHA_2DS_2-VASc	1 (0-2)	0 (0-1)	0.87
Left atrial diameter, mm	38 (35-41)	34 (32-37)	0.48

Values are mean ± SD, n (%), n/n (%), or median (Q1-Q3).
AF = atrial fibrillation; AF+ = with atrial fibrillation; AF− = without atrial fibrillation; BrS = Brugada syndrome; ECG = electrocardiogram; P/LP = pathogenic/likely pathogenic; SCD = sudden cardiac death.

RESULTS

BASELINE CHARACTERISTICS. The study sample consisted of 686 consecutive patients with BrS (median age at diagnosis: 38.9 years; Q1-Q3: 19.9-54.0 years), 33.7% of whom were female. Among these, 280 patients (40.8%) had BrS with AF (BrS AF+), whereas the remaining 406 patients (59.2%) had BrS without AF (BrS AF−). Baseline characteristics are summarized in Table 1.

A spontaneous type 1 ECG pattern was observed in 32.0% of the cohort, and 36.0% had a pathogenic or likely pathogenic (P/LP) *SCN5A* variant. Patients in the BrS AF+ group were significantly older, more often probands, had longer PR interval, and more frequently affected by hypertension. Persistent AF was present in 10.2% of BrS patients with AF, whereas the remaining 89.8% were paroxysmal.

TABLE 2 Characteristics of BrS Patients With AF, Stratified According to Age of Onset of AF (Before or After 20 Years Old)

	BrS AF+ (<20 y) (n = 22)	BrS AF+ (>20 y) (n = 257)	*P* Value
Female	5 (22.7)	82 (31.9)	0.25
Proband status	14 (63.6)	170 (79.1)	0.087
Family history of BrS	5/10 (50.0)	11/41 (26.8)	0.25
Family history of SCD	9 (40.9)	61 (24.3)	0.12
Family history of AF	3/6 (50.0)	11/138 (8.0)	0.013
Spontaneous Brugada type 1 ECG	10/21 (47.6)	72/232 (31.0)	0.14
Shanghai score	4.0 (2.0-5.0)	4.0 (2.0-4.0)	0.65
PR interval, ms	158.2 ± 25.3	169.1 ± 25.7	0.23
QRS interval, ms	101.1 ± 18.1	108.1 ± 28.1	0.083
SCN5A P/LP variant	5/9 (55.6)	17/49 (34.7)	0.27
Risk factors for AF			
Hypertension	0	49/152 (32.2)	0.031
Endurance sport	2 (20.0)	15/142 (10.6)	0.31
CHA_2DS_2-VASc	0 (0-0)	1 (0-2)	0.87

Values are mean ± SD, n (%), n/N (%), or median (Q1-Q3).
Abbreviations as in Table 1.

TABLE 3 Predictors Events

	Univariable Analysis			
		95% CI		
	HR	Lower	Upper	*P* Value
Predictors of atrial fibrillation				
Spontaneous type 1 ECG	1.02	0.73	1.43	0.85
SCN5A P/LP variant	1.09	0.61	1.94	0.74
Female	0.84	0.60	1.16	0.26
Proband status	2.75	1.95	3.89	<0.001
Family history of BrS	0.63	0.35	1.16	0.14
Family history of SCD	1.00	0.70	1.42	0.95
Family history of AF	1.16	0.15	9.12	0.88
Sick Sinus Syndrome	1.73	1.02	2.97	0.045
LA diameter	1.13	0.98	1.30	0.069
Hypertension	5.89	0.79	44.2	0.087
Age at BrS diagnosis (per year increase)	1.05	1.04	1.07	<0.001
Predictors of ventricular events				
Female	1.18	0.28	4.98	0.82
Age at BrS diagnosis (per year increase)	0.95	0.92	0.99	0.027
Proband status	1.73	0.34	8.67	0.50
Family history of BrS	1.06	0.23	4.84	0.94
Family history of SCD	0.41	0.05	3.94	0.41
Spontaneous type 1 ECG	3.60	0.85	15.2	0.041
SCN5A P/LP variant	4.60	0.88	24.1	0.047
Atrial fibrillation	1.42	0.36	5.87	0.59
AF <20 years	22.4	5.17	96.8	<0.001

Univariable Cox regression analysis for predictors of arrhythmias.
AA = atrial arrhythmias; AF = atrial fibrillation; BrS = Brugada syndrome; P/LP = pathogenic/likely pathogenic; SCD sudden cardiac death.

A comparison of the baseline characteristics according to AF occurrence before or after the age of 20 years is provided in Table 2.

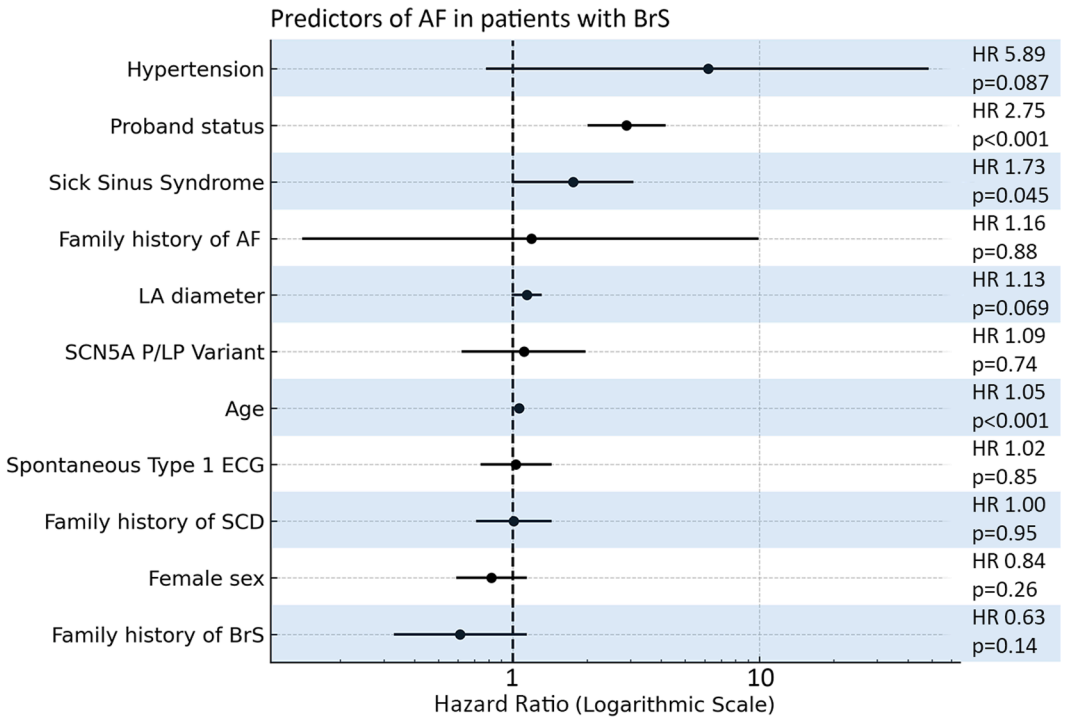
RISK FACTORS FOR AF AND VAs. Risk factors for AF and VAs are reported in Table 3, Figure 1, and the Central Illustration. In univariable Cox regression analysis, older age at BrS diagnosis and proband status were associated with higher risk of AF. Younger age, *SCN5A* P/LP variant, and a spontaneous type 1 ECG pattern were associated with higher risk of VAs in the entire BrS population at univariable Cox regression analysis.

PROGNOSTIC ROLE OF AF. Over a median follow-up of 48.8 months (Q1-Q3: 20.7-82.4 months), with no significant difference between AF+ and AF− patients, the annual incidence of VAs was 0.26% (95% CI: 0.01%-0.52%). (Figures 2 and 3, Table 4). No significant difference in the incidence of VAs was observed when comparing BrS AF+ and BrS AF− groups (HR: 0.67; $P = 0.58$). Similarly, sudden cardiac death rates did not differ significantly. To account for potential clustering by country, we performed a sensitivity analysis by including the country of inclusion as a categorical covariate in the regression model. HRs and levels of statistical significance did not substantially change, indicating that country-level variability did not affect the observed associations. Country-specific data are reported in Supplemental Table 1. A subgroup analysis stratifying patients with AF at baseline and those who developed AF during follow-up was performed to account for the immortal bias. The incidence of VA was 0.30% per year among patients with AF at baseline, whereas in those who developed AF during follow-up, the incidence was 0.24% per year. HR for the association between AF at baseline and VA was 0.69 (95% CI: 0.32-1.47; $P = 0.33$), whereas for AF occurring during follow-up, the HR was 0.66 (95% CI: 0.28-1.51; $P = 0.31$).

Stroke or transient ischemic attack occurred in 6 patients (2.5%) in the BrS AF+ group and was absent in the BrS AF− group. Among those with stroke, 50% had a CHA_2DS_2-VASc score of 0, whereas the other 50% had a score of 1. SSS was twice as prevalent in patients with AF (10.0% vs 6.2%; $P = 0.047$). No association was found between the occurrence of stroke and the presence of SSS or severity of sinus node dysfunction.

Among patients with AF diagnosed before the age of 20 years, the occurrence of SSS was significantly higher (36.3%) compared to those diagnosed later in life (7.8%; $P < 0.001$).

FIGURE 1 Risk Factors for AF in Patients With BrS



The graph illustrates the HR for each variable, with the dotted line indicating HR = 1.00. ORs are displayed on a logarithmic scale to enhance visualization. AF = atrial fibrillation; BrS = Brugada syndrome; ECG = electrocardiogram; LA = left atrium; P/LP = pathogenic/likely pathogenic; SCD = sudden cardiac death.

AF was treated with antiarrhythmic medications in 40.7% of the BrS AF+ patients (2.7% sotalol, 18.5% quinidine, 15.7% beta-blockers or calcium channel blockers, 3.7% amiodarone) and 69.4% were on oral anticoagulants. During follow-up, 43 patients (15.4%) underwent pulmonary vein isolation.

VAs AND AGE AT AF ONSET. The incidence of VAs by age group is shown in **Figure 4**. The onset of AF before the age of 20 years was associated with significantly higher risk of VAs during follow-up (HR: 22.4; $P < 0.001$). Among patients with BrS AF−, the incidence of VAs remained stable at approximately 0.6% per year until the age of 40 years, after which it progressively declined. In contrast, among BrS AF+ patients, the incidence of VAs peaked between the ages of 0 and 20 years and subsequently aligned with the rates observed in BrS AF− patients.

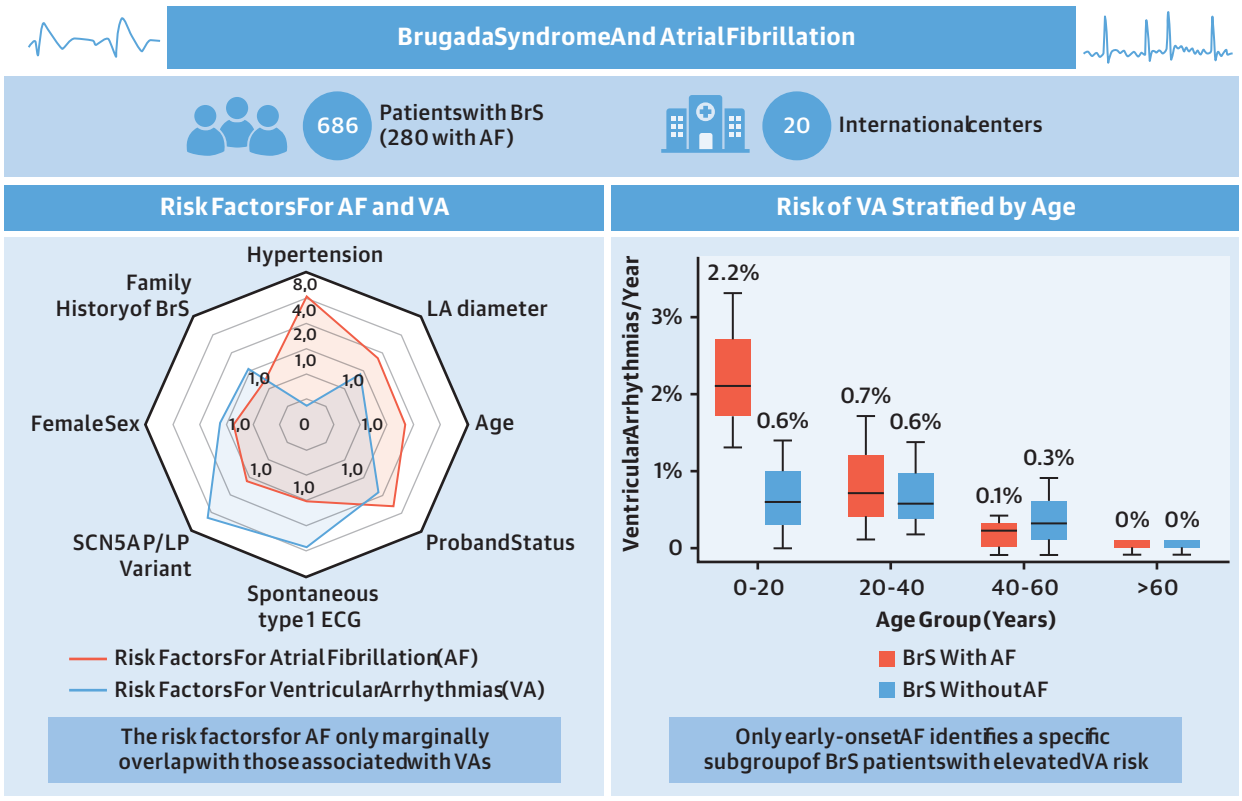
DISCUSSION

This study describes the largest cohort of non-high-risk BrS patients with AF. A key strength lies in the inclusion of a control group of patients with continuous rhythm monitor (implantable loop recorders), ensuring a reliable exclusion of AF.

The main findings are the following. 1) Among patients with BrS, risk factors for VAs are not associated with risk factors for AF. Whereas younger age at BrS diagnosis, *SCN5A* P/LP variant, and spontaneous type 1 ECG are associated with higher risk of VAs, proband status and older age at BrS diagnosis are associated with higher risk of AF. 2) The presence of AF in non-high-risk BrS patients is not independently associated with an increased risk of VAs. However, if AF occurs before the age of 20 years, the risk of VAs is significantly higher. 3) The presence of AF is likely a marker of an underlying diffuse atrial disease (atrial phenotype) with relatively high incidence of SSS (10%) and stroke (2.5%), despite the young age and absence of risk factors.

AF IN BrS: PREDICTORS OF AF OCCURRENCE. BrS patients are known to have a higher prevalence of supraventricular arrhythmias,[10] especially AF,[11,12]

CENTRAL ILLUSTRATION Brugada Syndrome and Atrial Fibrillation



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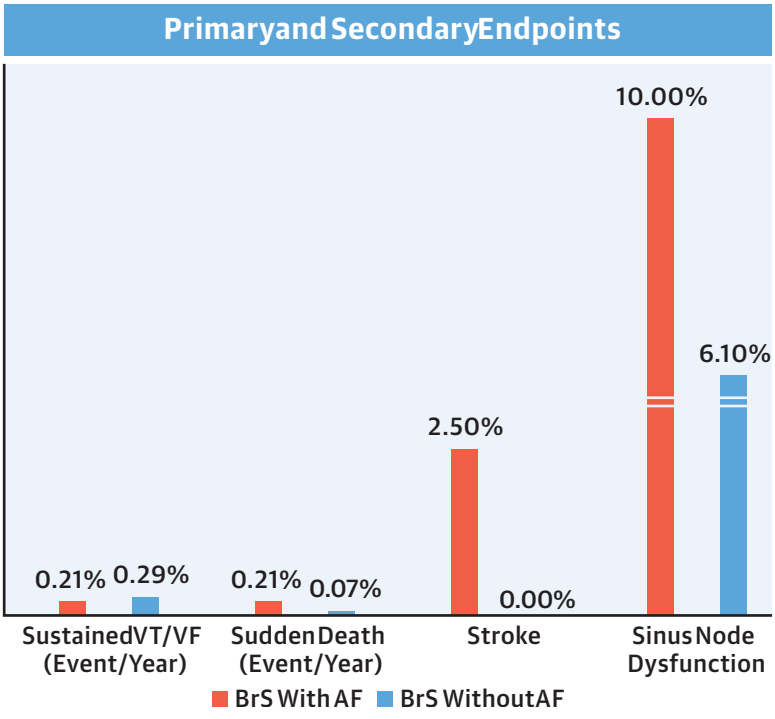
A total of 686 Brugada syndrome (BrS) patients from 20 international centers were included. Patients with BrS and atrial fibrillation (AF) were compared with patients with BrS and without AF. (Left) The chart illustrates risk factors for both AF and ventricular arrhythmias (VAs), presented in an overlaid format. The HR increases radially from the center octagon to the corners, ranging from 0 to 8, with a thicker line marking HR = 1.00. Points within the 0-1 range indicate protective factors, whereas points in the 1-8 range indicate predisposing factors. (Right) This graph displays the yearly risk of ventricular arrhythmias, stratified by the age of AF onset for patients with AF and the age of BrS diagnosis for patients without AF. ECG = electrocardiogram; LA = left atrium; P/LP = pathogenic/likely pathogenic.

with reported rates ranging from 9% to 30%.[3,4] The role of genetic variants in predisposing to AF is still controversial: whereas *SCN5A* P/LP variants have been associated with AF susceptibility,[13,14] particularly in early-onset cases, Amin et al[15] suggested that *SCN5A* P/LP variants may both promote intra-atrial conduction slowing providing a consistent substrate for AF maintenance and reduce atrial ectopic activity inhibiting triggers for AF, suggesting a simultaneous facilitatory and inhibitory effect of *SCN5A* P/LP variant on AF occurrence,[16-18] Consistent with these findings, other studies have shown that *SCN5A* P/LP variants are associated with AF induction during electrophysiological studies, but not necessarily with spontaneous AF.[19] Additionally, syncope, documented ventricular fibrillation, and spontaneous type 1 ECG have been identified as clinical predisposing factors for spontaneous AF in BrS patients, in small-to-medium-sized retrospective studies.[19-21] Previous studies often focused on high-risk BrS populations showing that ICD carriers had higher incidence of AF than patients without ICD, suggesting an aggressive ventricular phenotype among patients with AF.[4] A critical limitation of these earlier studies, however, was the low number of patients with AF and BrS, often <30. Moreover, ICD carriers can rely on constant rhythm monitoring, differently from people without ICD, increasing the chances to detect asymptomatic and otherwise misdiagnosed arrhythmic episodes.

Our study aligns with these findings, demonstrating a higher prevalence of *SCN5A* variants only in patients with early-onset AF.[22] With advancing age, conventional risk factors such as hypertension,

FIGURE 2 Incidence of Primary and Secondary Endpoints



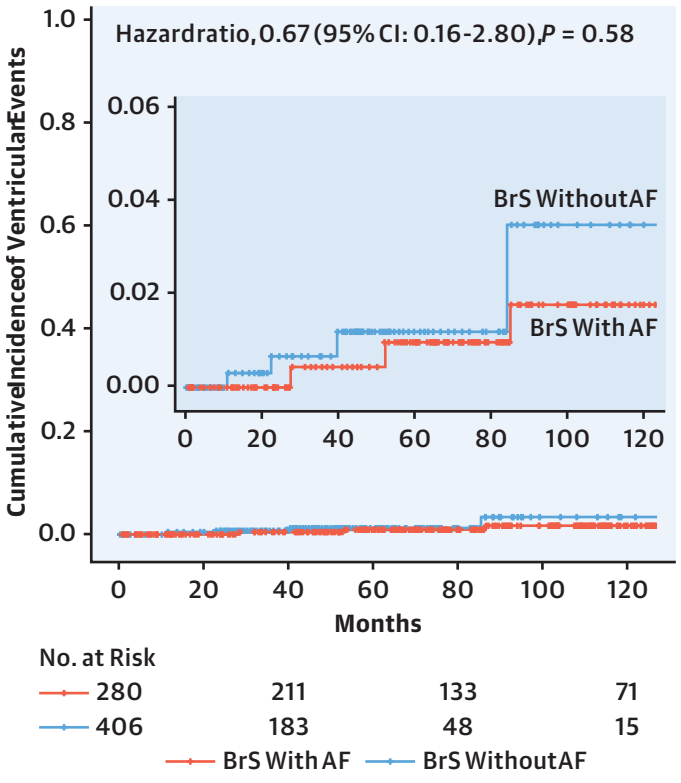
The histogram illustrates the incidence of primary and secondary endpoints, stratified by the presence or absence of AF. VF = ventricular fibrillation; VT = ventricular tachycardia; other abbreviations as in Figure 1.

atrial size, and age itself seem to predominate. A key strength of our study is the exclusion of high-risk patients (ie, ICD candidates and carriers), which minimized selection bias. This approach prevented an over-representation of AF patients in the high-risk group due to continuous rhythm monitoring in these patients. It also allowed us to analyze the prognostic impact of AF on VA in patients without known high-risk features. This has significant clinical relevance, because risk stratification in patients who are already high risk plays a marginal role, whereas it becomes crucial in non-high-risk patients and those without a clear ICD indication.

AF IN BrS: CLINICAL IMPLICATIONS. The occurrence of AF in BrS has often been considered a risk factor for worse prognosis because it may be a marker of a more aggressive phenotype.[22] However, there is no consensus on this association. A 2019 meta-analysis of 6 studies that included 1,703 BrS patients found that AF was associated with a 2-fold increased risk of VAs, even if 1 of the included studies reported a negative correlation between AF and VAs.[5,23-25] A Chinese cohort presented no higher risk of arrhythmic events in BrS patients with AF, with 80% of those who developed ventricular tachycardia/ventricular fibrillation not having AF.[26] Notably, Michowitz et al[27] observed that atrial arrhythmias increased the risk of recurrent major arrhythmic events particularly in children under 12 years old. Our study provides further insights, showing that early-onset AF before age 20 is linked to a more aggressive form of BrS, warranting closer monitoring. In contrast, AF that develops later in life may share common risk factors with conventional AF and may not carry a higher arrhythmic risk. This aligns with our findings and suggests that an atrial phenotype in BrS does not necessarily predict a more severe ventricular phenotype, and AF should be contextualized based on the age of its occurrence.[28,29]

STROKE AND SSS IN BrS PATIENTS WITH AF. The risk of stroke in BrS patients with AF is not well established, because an unexpected high risk (up to 13%) of cardioembolic stroke has been described in patients with BrS and atrial fibrillation.[30,31] Our study found a relatively low but significant incidence of stroke (2.5%), despite the lack of traditional stroke risk factors. Notably, one-half of these patients had a CHA_2DS_2-VASc score of 0, and the other half had a

FIGURE 3 Kaplan-Meier Analysis of the Primary Endpoint



The graph depicts the Kaplan-Meier analysis for the primary endpoint, stratified by the presence or absence of AF. w = with; w/o = without; other abbreviations as in Figure 1.

score of 1, underscoring the CHA_2DS_2-VASc score's limited predictive value in this cohort. These findings suggest that anticoagulation decision-making in BrS patients with AF may fall outside the conventional indications typically applied to the general AF population. Although our study is not powered to provide definitive treatment recommendations, a shared decision-making approach with each patient and their family appears reasonable, given the significant stroke risk observed in this cohort and the lack of applicable evidence from studies in non-BrS populations. BrS is also associated with SSS, especially in children, with earlier studies confirming the link between *SCN5A* variants and familial SSS.[32-35] Our study extends this knowledge, showing that SSS was more prevalent in BrS patients with AF (10.0% vs 6.2%), and that especially early AF onset was significantly associated with a higher prevalence of SSS (36.3%). These findings highlight the need for a comprehensive diagnostic approach to syncope in BrS patients with AF, as was previously described in the BruLoop (Implantable Loop Recorders in Patients With Brugada Syndrome) study.[36]

This study enhances our understanding of the complex relationship between AF and BrS, emphasizing the need for a multidisciplinary approach to diagnosis and management in this patient population. The results suggest that early-onset AF in BrS may indicate a more severe bradyarrhythmic and tachyarrhythmic phenotype, whereas later-onset AF may not significantly alter the arrhythmic risk. Furthermore, the high incidence of stroke and SSS in this cohort warrants careful clinical evaluation and tailored management strategies.

STUDY LIMITATIONS. Being a retrospective multicenter study, our research has inherent limitations. The median follow-up period of 4 years may be considered short and not fully representative of the lifelong arrhythmic risk in this young patient population. The exclusion of ICD candidates and ICD carriers may introduce a selection bias. However, including ICD patients might have resulted in an even greater selection bias, because the continuous rhythm monitoring significantly increases the likelihood of AF detection as compared to patients without ICDs. This could disproportionately raise the percentage of AF cases in the high-risk group, thereby creating an inhomogeneous AF cohort with an over-representation of high-risk subjects. Although previous studies have demonstrated that non-missense and loss-of-function SCN5A variants

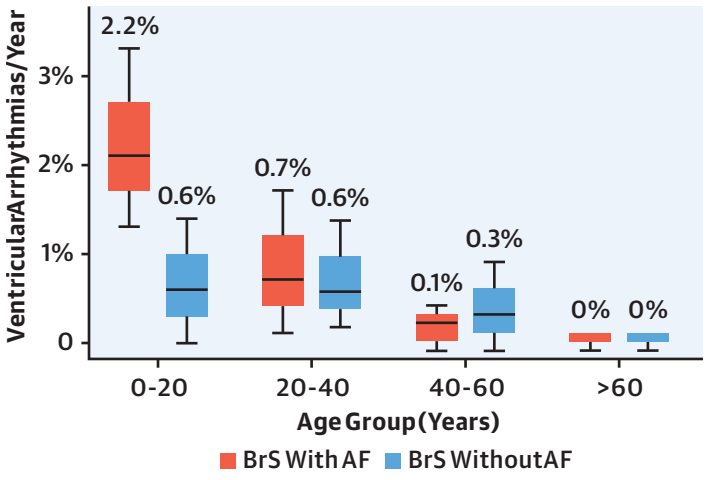
TABLE 4 Follow-up Outcomes Comparison

	BrS AF+ (n = 280)	BrS AF− (n = 406)	HR[a]/OR	Lower 95% CI	Upper 95% CI	*P* Value
Ventricular events,[a] events/y	0.21 (0.01-0.42)	0.29 (0.01-0.57)	0.67[a]	0.16	2.80	0.58
Sudden death, events/y	0.21 (0.01-0.42)	0.07 (0.01-0.21)	5.17	0.57	46.5	0.14
ICD implantation, overall events	9 (3.2)	14 (3.6)	0.9	0.38	2.10	0.81
Stroke, overall events	6 (2.5)					
Sick sinus syndrome, overall events	28 (10.0)	25 (6.2)	1.76	1.01	3.08	0.047

Values are % (95% CI) or n (%). Univariable Cox regression ([a]) and logistic regression analysis for predictors of primary and secondary outcomes, comparing patients with AF and those without AF.

ICD = implantable cardioverter-defibrillator, other abbreviations as in Table 1.

FIGURE 4 Incidence of VAs: Comparison Between Different Age Groups



The analysis compares the incidence of ventricular arrhythmias (VAs) across different age groups. Age groups are defined by the age at AF diagnosis for patients with AF and by the age at BrS diagnosis for patients without AF. Abbreviations as in Figure 1.

are associated with worse prognosis, we were unable to perform a detailed genetic analysis due to the lack of information on specific SCN5A mutations in our data set.[22,37] Our study did not evaluate the outcomes of AF recurrence in this population. Whether BrS confers a higher risk of recurrence, as suggested by other studies involving AF ablation in young patients, remains to be investigated.[38] A limitation of our study is the potential for immortal time bias due to the inclusion of patients with AF diagnosed both before and after the start of follow-up. To mitigate this bias, we performed an additional analysis comparing patients with AF at baseline to those who developed AF during follow-up, accounting for the timing of AF onset. The consistent results from this analysis support the robustness of our findings despite this limitation.

CONCLUSIONS

The presence of AF in non-high-risk BrS does not identify patients with higher risk of VAs. However, early-onset AF (<20 years) defines a distinct subgroup with elevated risk. Patients with AF and BrS have a significantly higher risk of SSS and stroke despite the young age and low risk profile.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This international study of 686 non-high-risk BrS patients found that whereas AF overall did not increase the risk of VAs, early-onset AF (<20 years) was associated with significantly higher VA risk. AF was also linked to increased rates of SSS and stroke, despite low CHA_2DS_2-VA scores. These findings support closer monitoring in BrS patients with AF, particularly those with early-onset AF.

TRANSLATIONAL OUTLOOK: Early-onset AF may define a high-risk BrS subgroup requiring refined risk stratification for the prevention of sudden cardiac death. Future studies should clarify its prognostic value and guide tailored stroke prevention strategies in BrS patients with AF.

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KEY WORDS atrial arrhythmias, atrial fibrillation, Brugada syndrome, sick sinus syndrome, stroke, sudden cardiac death, ventricular arrhythmias

APPENDIX For a supplemental table, please see the online version of this paper.