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CLINICAL RESEARCH

aTrial arrhythmias in inhEriTed aRrhythmIa Syndromes: results from the TETRIS study

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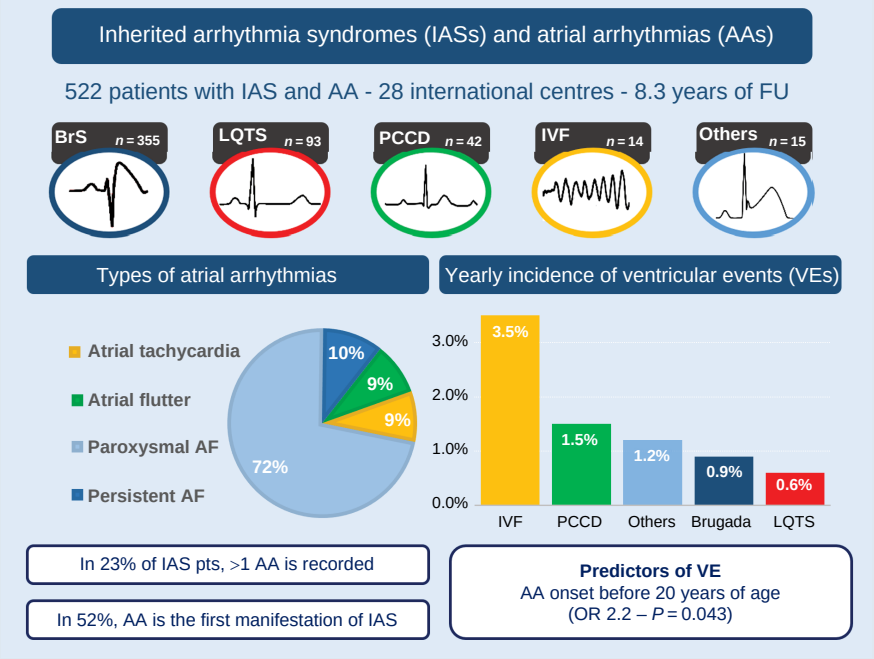
Aims Little is known about the distribution and clinical course of patients with inherited arrhythmia syndrome (IAS) and concomitant atrial arrhythmias (AAs). The aim of the study is (i) to characterize the distribution of AAs in patients with IAS and (ii) evaluate the long-term clinical course of these patients.

Methods and results An international multicentre study was performed and involved 28 centres in 16 countries. Inclusion criteria were (i) IAS and (ii) electrocardiographic documentation of AAs. The primary endpoint was a composite of sudden cardiac death, sustained ventricular arrhythmias (VAs), or appropriate implantable cardioverter defibrillator (ICD) interventions. Strokes, inappropriate ICD shocks due to AAs, and the occurrence of sinus node dysfunction were assessed. A total of 522 patients with IAS and AAs were included. Most patients were diagnosed with Brugada syndrome ($n = 355$, 68%) and long QT syndrome ($n = 93$, 18%). The remaining patients ($n = 71$, 14%) presented with short QT syndrome, early repolarization syndrome, catecholaminergic polymorphic ventricular tachycardia, progressive cardiac conduction diseases, or idiopathic ventricular fibrillation. Atrial fibrillation was the most prevalent AA (82%), followed by atrial flutter (9%) and atrial tachycardia (9%). Atrial arrhythmia was the first clinical manifestation of IAS in 52% of patients. More than one type of AA was documented in 23% of patients. Nine patients (3%) experienced VA before the diagnosis of IAS due the use of anti-arrhythmic medications taken for the AA. The incidence of the primary endpoint was 1.4% per year, with a two-fold increase in patients who experienced their first AA before the age of 20 (odds ratio 2.2, $P = 0.043$). This was consistent across the different forms of IAS. Inappropriate ICD shock due to AAs was reported in 2.8% of patients, strokes in 4.4%, and sinus node dysfunction in 9.6%.

Conclusion Among patients with IAS and AAs, AA is the first clinical manifestation in about half of the cases, with more than one form of AAs present in one-fourth of the patients. The occurrence of AA earlier in life may be associated with a higher risk of VAs. The occurrence of stroke and sinus node dysfunction is not infrequently in this cohort.

Graphical Abstract



* **Others** includes: catecholaminergic polymorphic ventricular tachycardia (CPVT), early repolarization syndrome (ERS) and short QT syndrome (SQTS).

BrS, Brugada syndrome; LQTS, long QT syndrome; SQTS, short QT syndrome; ERS, early repolarization syndrome; CPVT, catecholaminergic ventricular tachycardia; PCCD, progressive cardiac conduction disease; IVF, idiopathic ventricular fibrillation; Afib, atrial fibrillation; VE, ventricular events.

Keywords Inherited arrhythmia syndrome • Channelopathies • Sudden cardiac death • Brugada syndrome • Long QT syndrome • Atrial arrhythmias • Atrial fibrillation • Ventricular arrhythmias

What's new?

- This is the largest registry of patients with inherited arrhythmia syndromes (IAS) and atrial arrhythmias (AAs) reported so far.
- In about half of the patients, AA is the first clinical manifestation of the disease.
- One in four patients presents with multiple types of AAs.
- Early onset of AAs (before 20 years of age) is related with a higher risk of ventricular arrhythmias.
- Despite young age and lack of typical risk factors, patients with IAS and AAs face a substantial risk of stroke and sinus node dysfunction.

Introduction

The inherited arrhythmia syndromes (IAS) are a heterogeneous group of genetically determined conditions, associated with an increased risk of ventricular arrhythmias (VAs) and sudden cardiac death (SCD).[1] The vast majority of IAS present on the 12-lead electrocardiogram (ECG) with a specific ventricular phenotype, characterized by abnormal depolarization and/or repolarization, abnormal QTc interval duration, and/or impaired atrioventricular (AV) conduction.[1]

Over the past three decades, the understanding of IAS has been enriched by a considerable number of studies defining genetic and molecular features predisposing to VAs.[2] In contrast, no substantial advances have been made in the assessment of the causative role of genetically determined ion channel dysfunctions leading to different forms of atrial arrhythmias (AAs). An ion channel dysfunction can lead to the presence of specific atrial phenotypes associated with a predisposition for AAs, including atrial fibrillation (AF).[3–5] Indeed, while the prevalence of AF in young adults (age <50 years) is low, its prevalence in patients with IAS is substantially higher, ranging from 2% for patients with long QT syndrome (LQTS) to 20–30% for Brugada syndrome (BrS) or short QT syndrome (SQTS).[3–8]

Very little is known about the distribution of the different forms of AAs in patients with IAS, and their long-term outcomes remain poorly characterized. The therapeutic options may differ significantly from the standard of care, and, importantly, AAs may be the first hint of the underlying genetic disease, allowing for an early diagnosis before the occurrence of fatal events. The prognostic value of AAs in patients with IAs is debated, and there is no specific information on predictors of VAs.

The purpose of this study was to (i) characterize the distribution of AAs in patients with different forms of IAS and (ii) to investigate the clinical features, and long-term outcomes of these patients.

Methods

Study design

An international retrospective registry was established at Cardiocentro Ticino Institute, Lugano (Switzerland), involving 28 centres across 16 countries in 3 continents. Centres were requested to retrieve all consecutive cases of IAS who were concomitantly affected by AAs. Data were collected in accordance with regulations set by the local Institutional Ethics Committee (2019-00754). The study was carried out according to the principles of the Declaration of Helsinki.

Patient population

Patients with an established diagnosis of IAS and ECG documentation of AA were considered eligible and included in this study. The exclusion criteria included the absence of information on the exact form of AAs and IAS and follow-up duration shorter than 12 months.

Information on medical history, family history of SCD, AF-associated risk factors (hypertension, diabetes, obesity, endurance sport, and alcohol intake), drug therapy, 12-lead ECG parameters, and 2D echocardiography were obtained.

Definitions

The diagnosis of IAS included one of the following diseases: BrS, LQTS, SQTS, ERS, catecholaminergic polymorphic ventricular tachycardia (CPVT), progressive cardiac conduction disease (PCCD), and idiopathic ventricular fibrillation (IVF).[1]

The diagnosis of IAS was established according to current international guidelines.[1] Atrial arrhythmia was considered in the presence of AF, atrial flutter (AFL), or atrial tachycardia (AT).[9]

Follow-up

Follow-up evaluations were based on clinical visits, including physical examination, ECG, ECG Holter monitoring, cardiac implantable electronic device, or implantable loop recorders controls performed at least every 12 months. Patients were followed until the last available follow-up examination.

Endpoints

The primary endpoint was a composite of ventricular events, defined as occurrence of SCD, sustained VA, or appropriate ICD interventions. Appropriate interventions were defined as shocks or anti-tachycardia pacing delivered for VT or VF. Cerebrovascular accidents (CVAs), inappropriate shocks due to AAs, sinus node dysfunction, and anti-arrhythmic drug-induced arrhythmias were also assessed. Inappropriate shocks due to AAs were defined as therapies delivered for AA with fast ventricular conduction.

Statistical analysis

All data are analysed using Stata 17 (StataCorp, College Station, TX, USA). A two-sided $P < 0.05$ is considered statistically significant. Continuous data are presented as mean and standard deviation (SD). Categorical data are presented as counts and per cents. Event rate is presented as event number per 100 person years. Logistic regression is fitted to assess the relationship between age at AA onset and VE.

Results

Study population

The study population consisted of 522 patients from 28 international centres. Baseline characteristics are shown in *Table 1*. The mean age was 56.8 years, and 68.0% were males. Twenty-six patients (4.6%) experienced their first AA at 16 years of age or before. Brugada syndrome was the most represented IAS ($n = 355$, 68.0%), and 107 (30.1%) had spontaneous Type I ECG. Family history of SCD and family history of AAs were reported in 27.2 and 17.4% of patients, respectively. A genetic test was performed in 336 patients (66.8%), and a pathogenic/likely pathogenic variant was found in 73 patients (21.7%). No patients with an overlapping syndrome were reported. Nine patients (3%) had a history of VA before the diagnosis of IAS, due to the use of anti-arrhythmic medications taken for the AA. In all these patients, this also led to the diagnosis of IAS.

Baseline characteristics: atrial arrhythmias

Paroxysmal AF was the most common form of AA at presentation (72.1%) (*Graphical Abstract*). The specific distribution of AA according to the underlying IAS is reported in *Table 2*. Atrial arrhythmia was the first clinical manifestation of the underlying IAS in more than half of patients (52.0%). Moreover, 22.8% of the patients (76/333) had more than one form of AAs.

As shown in *Table 1*, apart from arterial hypertension, conventional AF-associated risk factors were infrequent in the study population.

Table 1 Baseline characteristics of patients with IAS and AAs

Baseline characteristic	Total *N* = 522	BRS *N* = 355	LQTS *N* = 93	SQTS *N* = 3	ERS *N* = 6	CPVT *N* = 6	PCCD *N* = 42	IVF *N* = 14
Age, mean (SD), years	56.8 ± 19.8	59.0 ± 18.1	54.9 ± 24.0	31.7 ± 23.7	41.4 ± 14.5	47.9 ± 25.5	65.9 ± 14.3	56.9 ± 17.4
Male sex, no. (%)	351 (67.4)	257 (72.4)	46 (49.5)	2 (66.7)	5 (83.3)	4 (44.4)	25 (59.5)	12 (85.7)
Age at IAS diagnosis, mean (SD), years	48.8 ± 19.4	49.2 ± 17.2	45.0 ± 22.4	28.0 ± 23.1	36.0 ± 11.7	40.3 ± 28.2	57.9 ± 25.1	50.6 ± 16.9
Age at 1st AA, mean (SD), years	47.1 ± 18.8	49.4 ± 10.5	44.5 ± 8.4	24.6 ± 9.6	34.5 ± 7.1	33.8 ± 9.6	50.2 ± 5.8	49.8 ± 6.9
Additional atrial arrhythmias	76 (22.8%)[a]	50 (22.7%)	10 (11.8%)	1 (33.3%)	1 (20.1%)	4 (44.4%)	9 (40.6%)	1 (7.1%)
Previous aborted cardiac arrest, *n* (%)	57 (10.9)	25 (7.0)	14 (15.0)	0	4 (66.7)	2 (33.3)	0	12 (85.7)
ICD implantation, *n* (%)	206 (39.4)	148 (41.7)	29 (30.1)	0	5 (83.3)	5 (55.6)	7 (16.7)	13 (92.9)
Family history and genetic								
Family history of SCD, *n* (%)	138 (27.2)	96 (27.0)	27 (29.0)	1 (33.3)	1 (16.7)	4 (44.4)	8 (19.0)	1 (7.1)
Family history of AA, *n* (%)	54 (17.4)	27 (7.6)	12 (12.9)	0	0	2 (22.2)	12 (28.6)	1 (7.1)
Genetic test performed, *n* (%)	336 (66.8)	218 (61.4)	84 (90.3)	3 (100)	1 (16.7)	9 (100)	15 (35.7)	6 (42.9)
Pathogenic/likely pathogenic variant, *n* (%)	73 (21.7)	21 (9.6)	42 (45.2)	0	0	5 (55.5)	5 (33.3)	0
Proband status, *n* (%)	338 (74.5)	256 (72.1)	46 (49.5)	2 (66.7)	5 (83.3)	7 (77.8)	10 (23.8)	12 (85.7)
Risk factors for AA								
Endurance sport	38 (9.2%)	28 (7.9%)	2 (2.2%)	1 (33.3%)	0	2 (22.2%)	3 (7.1%)	2 (14.3%)
Alcohol abuse	7 (1.7%)	4 (1.1%)	3 (3.2)	0	0	0	0	0
Hypertension	148 (35.4%)	88 (24.8%)	29 (31.2%)	0	0	2 (22.2%)	23 (54.8%)	6 (42.9%)
Hyperthyroidism	14 (3.4)	9 (2.5%)	1 (1.1%)	0	1 (16.7%)	1 (11.1%)	1 (2.4%)	1 (7.1%)
Left atrial diameter	37.5 ± 19.1	38.6 ± 21.2	35.2 ± 8.5	26.0 ± 12.5	31.8 ± 5.3	25.3 ± 4.0	31.9 ± 5.8	35.9 ± 8.2

Continuous variables are shown as mean ± SD or median and IQR. Discrete variables are presented as numbers and percentages (%).
AA, atrial arrhythmia; AF, atrial fibrillation; AVNRT, atrioventricular nodal re-entrant tachycardia; AVRT, atrioventricular re-entrant tachycardia; BrS, Brugada syndrome; CPVT, catecholaminergic ventricular tachycardia; ERS, early repolarization syndrome; IAS, inherited arrhythmia syndrome; IQR, interquartile range; IVF, idiopathic ventricular fibrillation; LQTS, long QT syndrome; PCCD, progressive cardiac conduction disease; SCD, sudden cardiac death; SD, standard deviation; SQTS, short QT syndrome.
[a]This value was calculated based on the number of patients with available data for this variable (*N* = 333).

Table 2 Atrial arrhythmia characterization

	BRS $n = 355$	LQTS $n = 93$	SQTS $n = 3$	ERS $n = 6$	CPVT $n = 6$	PCCD $n = 42$	IVF $n = 14$
AAs at presentation							
Atrial fibrillation, no. (%)	292 (82.3)	83 (89.2)	1 (33.3)	6 (100)	6 (100)	28 (66.6)	13 (65.0)
Paroxysmal AF	262 (73.8%)	73 (78.5%)	–	5 (83.3%)	6 (100%)	18 (42.9%)	11 (55.0%)
Persistent AF	30 (8.5%)	10 (10.8%)	1 (33.3%)	1 (16.7%)	–	10 (23.8%)	2 (10.0%)
AFL, no. (%)	33 (9.3)	3 (3.2)	–	–	–	11 (26.2)	–
AT, no. (%)	30 (8.5)	7 (7.5)	2 (66.7)	–	–	3 (7.1)	1 (5.0)
Anti-arrhythmic medication							
Class IA (quinidine)	70 (19.7%)	0	0	0	0	2 (4.7%)	1 (7.2%)
Class IC (e.g. flecainide)	0	2 (2.2%)	0	0	0	1 (2.4%)	0
Class II (beta-blockers)	48 (13.5%)	90 (96.7%)	1 (3.3%)	2/4 (50%)	6 (100%)	16 (38.1%)	8 (57.1%)
Class III (sotalol, amiodarone)	26 (7.3%)	0	0	0	0	5 (11.9%)	2 (14.4%)
Class IV (calcium antagonist)	7 (1.2%)	0	0	0	0	0	1 (7.2%)

Discrete variables are presented as numbers and percentages (%).
AF, atrial fibrillation; AVNRT, atrioventricular nodal re-entrant tachycardia; AVRT, atrioventricular re-entrant tachycardia; BrS, Brugada syndrome; CPVT, catecholaminergic ventricular tachycardia; ERS, early repolarization syndrome; IVF, idiopathic ventricular fibrillation; LQTS, long QT syndrome; PCCD, progressive cardiac conduction disease; SQTS, short QT syndrome.

Table 3 Primary and secondary endpoints

	Number of events (%)
Primary outcome	
Composite ventricular events	61 (11.7)
Outcome components	
Ventricular tachycardia	7 (1.3)
Ventricular fibrillation	13 (2.5)
Appropriate ICD shocks	40 (7.7)
Sudden death	11 (2.1)
Secondary outcomes	
Stroke or TIA	23 (4.4)
Inappropriate shocks	50 (9.6)
Inappropriate shocks due to AA	15 (2.8)
Sinus node dysfunction	60 (11)
AAD-induced arrhythmias	9/299 (3.0)
Overall death	45 (9.0)

Continuous variables are shown as mean ± SD or median and IQR. Discrete variables are presented as numbers and percentages (%).
AA, atrial arrhythmia; AAD, anti-arrhythmic drug; ICD, implantable cardiac defibrillator; IQR, interquartile range; TIA, transient ischaemic attack.

Classes IC and III were infrequently used ($n = 45$, 10.2%), and 39.7% of patients were under oral anticoagulants ($n = 178$).

Events at follow-up: ventricular events

Patients were followed for a median of 8.3 years (4.6–12.3 years). Death occurred in 45 patients {9.0%—yearly incidence of 1.1% [95% confidence interval (CI) 0.7–1.2]}. Sudden death occurred in 11 patients [2.1%—yearly incidence of 0.2% (95% CI 0.1–0.24)]. A total of 61 patients (11.7%) experienced the primary endpoint, corresponding to a yearly rate of VA-related events of 1.4% (95% CI 0.8–1.2) (*Table 3* and *Figure 1*). The median time to the primary endpoint was 3.1 years (0.3–6.9 years).

As shown in *Figure 1* and *Table 3*, the primary outcome was mainly driven by appropriate ICD shocks, which occurred more frequently in patients with early repolarization syndrome (ERS), IVF, and PCCD. The event rate in patients with BrS and LQTS was <1%/year. Patients with PCCD experienced the highest rate of sudden death.

Events at follow-up: atrial events

Fifteen patients (2.8%) experienced inappropriate shocks due to AAs, and 11.0% had a diagnosis of sinus node dysfunction. A CVA was reported in 4.4% of patients. The rate of inappropriate shocks was especially high in IVF, CPVT, and ERS. Conversely, no inappropriate shocks were reported in patients with LQTS and PCCD. Sinus node dysfunction ranged from 10% in patients with BrS and LQTS to 20% in patients with CPVT and PCCD. Stroke was equally more prevalent in these forms of IAS, being reported in 14.3 and 11.1% of patients with PCCD and CPVT, respectively.

Age at atrial arrhythmia onset and risk of ventricular arrhythmia

Patients who had their AA onset before the age of 20 had double the risk of experiencing VE during follow-up (21.1 vs. 11.4%, odds ratio 2.2—*P*-value 0.043) (*Figure 2*). This finding was consistent across the different forms of IAS (except for LQTS), as shown in *Figure 2*.

Discussion

This is the largest registry of patients with IAS and AAs reported so far. The main findings of this study are the following: (i) among patients with concomitant IAS and AAs, the AA is the first clinical manifestation of the IAS in about half of the patients; (ii) one out of four patients with concomitant IAS and AA presents with multiple forms of AAs; (iii) the occurrence of AA earlier in life is associated with a higher risk of VAs; and (iv) the risk of stroke and sinus node dysfunction among

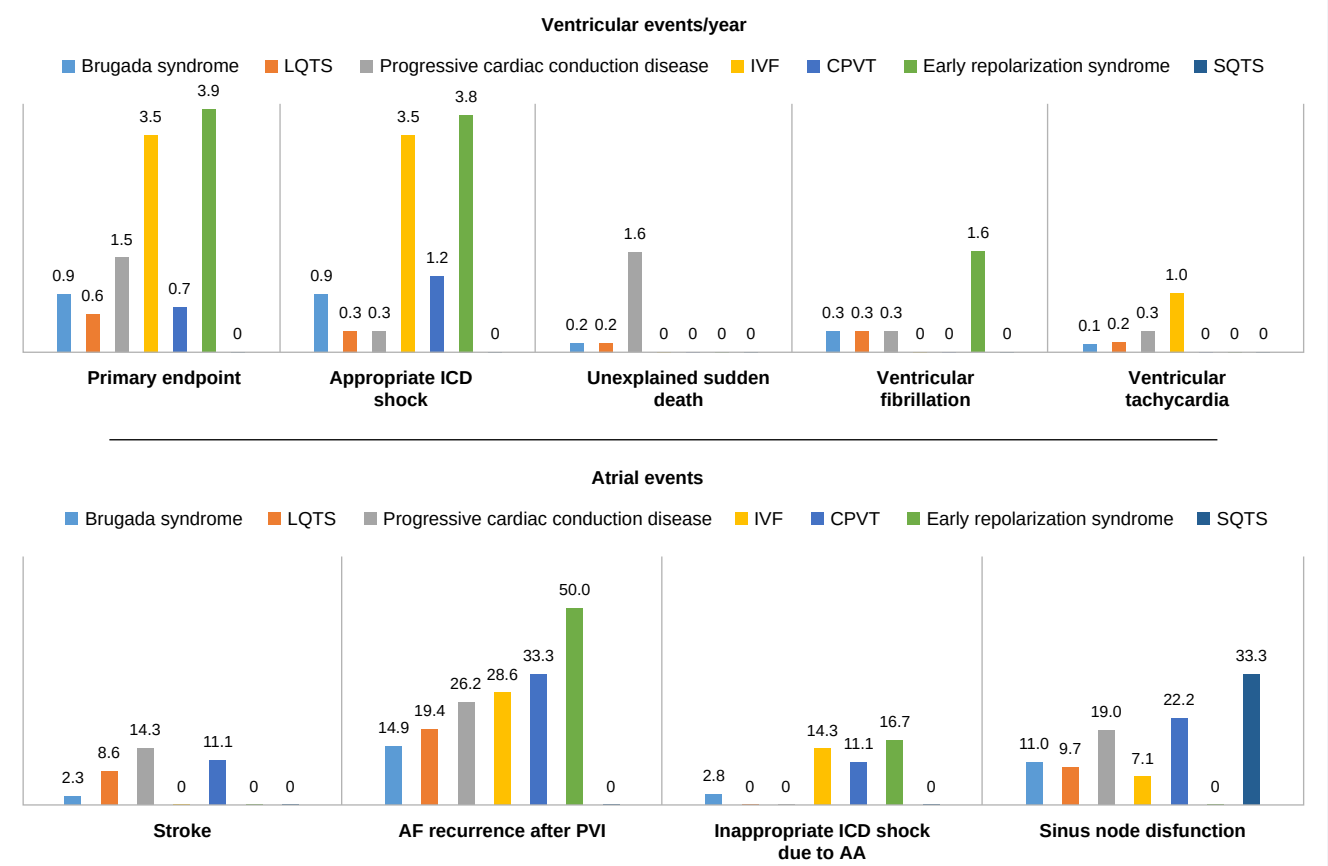


Figure 1 Primary and secondary outcomes. Inherited arrhythmia syndrome–specific distribution of the composite primary endpoint, its component, and the secondary endpoints. AA, atrial arrhythmias; AF, atrial fibrillation; BrS, Brugada syndrome; CPVT, catecholaminergic ventricular tachycardia; ERS, early repolarization syndrome; IVF, idiopathic ventricular fibrillation; LQTS, long QT syndrome; PCCD, progressive cardiac conduction disease; SQTS, short QT syndrome.

patients with IAS and AA is substantial despite the young age and lack of risk factors. This is especially true for patients with PCCD.

Atrial arrhythmias and inherited arrhythmia syndrome: prevalence and distribution

Over the last two decades, few studies have sought to describe the association between AAs and IAS.[1,5,10–14] These studies, mainly of medium size, focused on the prevalence of AAs across various IAS subtypes or the occurrence of different IAS types in patients with AA at a young age.[1,5,8,10,11] From this body of work, the incidence of AAs, particularly AF, in the context of IAS has been well documented. A critical limitation of these earlier studies, however, was their small sample sizes, often including <50 patients with both IAS and AAs, which constrained their findings.[1,5,10,11,15] Additionally, a notable gap in previous research was the exclusive focus on the prevalence of AF, with other types of AA being largely neglected. Our study addresses this gap by providing sufficient data to explore it further. The distribution of specific IAS reported in our study reflects the IAS distribution in the general population. Brugada syndrome and LQTS are the two most common IAS with a prevalence of 1:2000 and an AF risk of 20 and 2%, respectively.[1] Conversely, SQTS and CPVT are the two rarest IASs with a prevalence of 2.7:100 000 and 1:10 000, respectively.[1] Short QT syndrome is the IAS with the highest risk of AF (30%) while AAs in CVPT are mostly anecdotal.[1,10] Early repolarization syndrome has been associated with AF when associated with specific genetic variants.[11] Our findings also point towards the fact that AF is not the sole AA present in these patients, with ~25% experiencing other forms of AA (such as AFL and AT) and another 25% presenting with more than one AA during their life. Additionally, our study highlights the impact of AA on IAS, demonstrating the increased rate of inappropriate ICD shocks due to AA episodes, as well as the risk of anti-arrhythmic drug-induced VAs. Furthermore, the risk of stroke, which is typically expected to be low in this population, reached up to 4%, creating dilemmas regarding the initiation or withholding of anticoagulation therapy. Additionally, the presence of sinus node dysfunction in 10–20% of cases underscores the widespread nature of the atrial disease. This information can significantly aid in decision-making when considering ICD implantation, encouraging the selection of a dual-chamber rather than a single-chamber device.

Overall, our study enriches the existing literature by providing a comprehensive characterization of the various AA subtypes and their consequences within the diverse classes of IAS.

Atrial and ventricular events: predictors

Our research corroborates findings from smaller studies and case series, indicating that AA may serve as an initial indicator of underlying IAS.[3–7] This early sign allows for prompt diagnosis, which can be crucial in preventing fatal arrhythmic events.[3–7] Furthermore, recognizing the presence of IAS in patients experiencing AA is crucial as it significantly

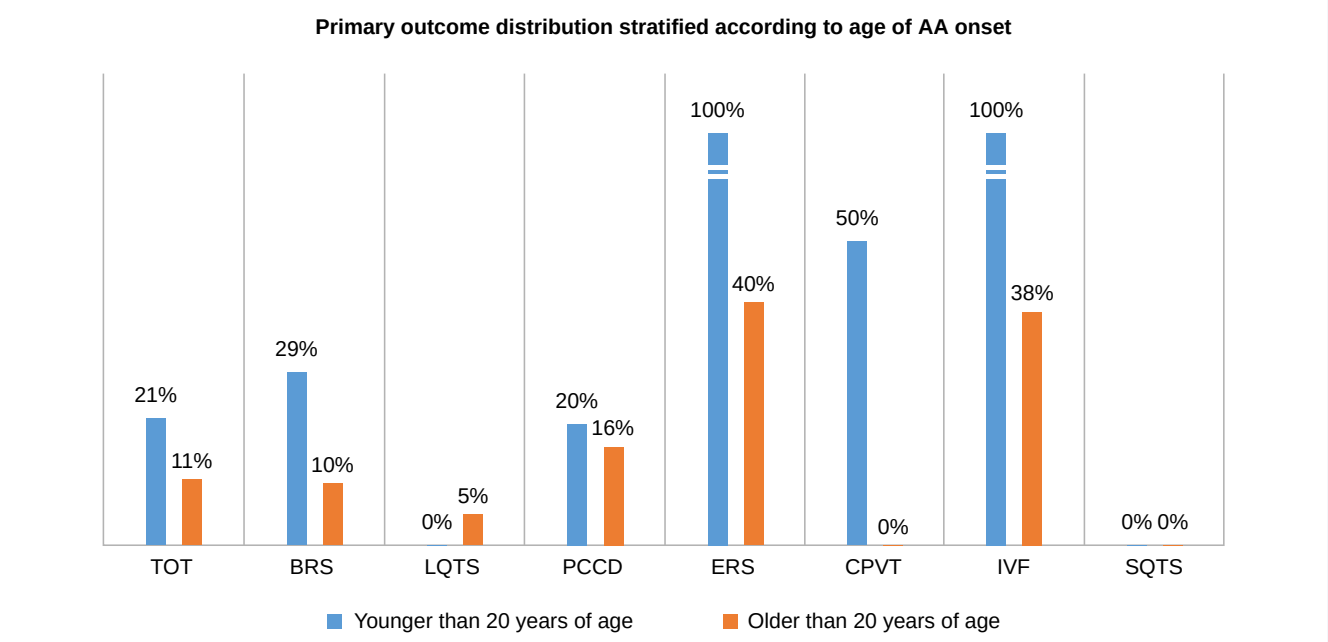


Figure 2 Primary outcome distribution stratified according to the age at atrial arrhythmia onset. AA, atrial arrhythmias; BrS, Brugada syndrome; CPVT, catecholaminergic ventricular tachycardia; ERS, early repolarization syndrome; IVF, idiopathic ventricular fibrillation; LQTS, long QT syndrome; PCCD, progressive cardiac conduction disease; SQTS, short QT syndrome.

influences the approach to rhythm management. Conventional ablation strategies (i.e. pulmonary vein isolation for AF) may have poorer outcomes.[12] Traditional drug therapies are not universally applicable in this patient group: for instance, Class IC anti-arrhythmic drugs can be life threatening for BrS syndrome patients, while sotalol and amiodarone pose risks for patients with LQTS. Our study does not include a comparative cohort of patients with and without AAs. Therefore, no conclusions can be drawn regarding the prognostic significance of AAs. However, we demonstrated that patients who develop AF earlier in life may have a more aggressive form of the disease, warranting closer monitoring. Conversely, those developing AF later in life probably share risk factors with conventional AF and may not necessarily be classified as higher risk.

Genetic basis of atrial arrhythmias

In the general population, research has identified rare genetic variants linked to AF that affect genes responsible for cardiac gap junctions and ion channels.[16,17] These studies primarily find variants in genes related to proteins that control cardiac depolarization or repolarization, which increases the risk of developing AF.[18] Despite identifying numerous genes associated with AF, current medical guidelines do not recommend genetic testing for AF alone due to the very low prevalence of pathogenic variants.[1] This situation changes markedly in patients who have both AF and IASs. In our study population, genetic testing was conducted on 357 patients, revealing pathogenic variants in 20% of these cases. This rate is significantly higher compared with that in patients with lone AF at a young age and aligns more closely with the prevalence seen in patients with IAS.[19,20] The question of whether the presence of pathogenic variants in patients with both IAS and AA is the same as in patients with IAS and without AA remains an intriguing area for further research.

There is considerable overlap among the genes involved in IAS and AF. However, prior studies indicate that the manifestation of an atrial phenotype does not consistently correlate with ventricular events.[17,18,21] Our findings support and extend these observations, showing that a more pronounced atrial phenotype does not necessarily lead to a more severe ventricular phenotype. The reasons for this—whether due to variations in the distribution of affected ion channels or the presence of different genetic variants that predispose individuals to one type of arrhythmia over another—remain to be determined.

Limitations

Our study has a certain number of limitations. It is a retrospective multicentre experience conducted, due to the rarity of the condition, in a population with heterogeneous clinical characteristics. Given the retrospective nature of case selection, case consecutiveness cannot be assessed with certainty. Furthermore, a median follow-up of 8 years can be considered short and not representative of the lifelong risk of arrhythmias among these young patients. The diagnostic approach to patients with IAS and follow-up in our study was heterogeneous and variable throughout centres. The severity of AAs may be influenced by the follow-up strategy (ECG Holter monitoring, loop recorder, and ICD) with patients with ICD experiencing more AA because of more accurate detection.

Conclusions

Among patients with IAS and concomitant AAs, the AA is the first clinical manifestation of the underlying disease in about half of the cases. More than one type of AA is recorded in one-fourth of these patients. The occurrence of AAs early in life (before the age of 20) seems to be associated with an increased risk of VAs across various IASs. However, larger studies focusing on each specific IAS are needed to confirm this observation.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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