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

Short title: "Atrial arrhythmias and inherited arrhythmia syndromes"

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The authors declare that all illustrations and figures in the manuscript are entirely original and do not require reprint permission.

Funding: This study was fully supported by a research grant of the Swiss National Science Foundation (SNSF) (PZ00P3_180055).

Conflict of interest: JTH has been consultant for Johnson and Johnson, Boston, MicroPort, Solid Bioscience, Cytokinetics and Leo Pharma. 'All remaining authors have declared no conflicts of interest.

Data Availability Statement: the data underlying this article will be shared on reasonable request to the corresponding author.

Word count: 2820

Abstract

Background: Little is known about the distribution and clinical course of patients with inherited arrhythmia syndrome (IAS) and concomitant atrial arrhythmias (AAs).

Aim: 1) to characterize the distribution of AAs in patients with IAS and 2) evaluate the long-term clinical course of these patients.

Methods: An international multicenter study was performed and involved 28 centers in 16 countries. Inclusion criteria were: 1) IAS and 2) ECG documentation of AAs. The primary endpoint was a composite of sudden cardiac death, sustained VAs or appropriate ICD interventions. Strokes, inappropriate ICD shocks due to AAs, and the occurrence of sinus node dysfunction were assessed.

Results: 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 (ERS), catecholaminergic

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polymorphic ventricular tachycardia (CPVT), progressive cardiac conduction diseases, or idiopathic ventricular fibrillation. Atrial fibrillation (AF) was the most prevalent AA (82%), followed by atrial flutter (9%) and atrial tachycardia (9%). AA was the first clinical manifestation of IAS in 52% of patients. More than one type of AAs 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 twofold increase observed in patients who experienced their first AA before the age of 20 (OR 2.2, p=0.043). This was consistent across the different forms of IAS. Inappropriate ICD shock due to AAs were reported in 2.8% of patients, strokes in 4.4% and sinus node dysfunction in 9.6%.

Conclusions: 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 ventricular arrhythmias. The occurrence of stroke and sinus node dysfunction is not-infrequently in this cohort.

Keywords: inherited arrhythmias syndrome, channelopathies, sudden cardiac death, Brugada syndrome, long QT syndrome, atrial arrhythmias, atrial fibrillation, ventricular arrhythmias.

ABBREVIATION LIST

(AF)	Atrial fibrillation
(AFL)	Atrial flutter
(AT)	Atrial tachyarrhythmias
(AVNRT)	Atrio-ventricular nodal reentrant tachycardia
(AVRT)	Atrio-ventricular reentrant tachycardia
(BA)	Bradyarrhythmias
(BrS)	Brugada syndrome

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(CIED) Cardiac implantable electronic devices

(CPVT) Catecholaminergic polymorphic ventricular tachycardia

(ERS) Early repolarization syndrome

(IAS) Inherited arrhythmia syndrome

(ICD) Implantable cardioverter-defibrillator

(IVF) Idiopathic ventricular fibrillation

(LQTS) Long QT syndrome

(PM) Pacemaker

(PSVT) Paroxysmal supraventricular tachycardia

(P/LP) Pathogenic/likely pathogenic

(PCCD) Progressive cardiac conduction disease

(SCD) Sudden cardiac death

(SQTS) Short QT syndrome

(VA) Ventricular arrhythmia

(VF) Ventricular fibrillation

(VT) Ventricular tachycardia

Introduction

The inherited arrhythmia syndromes (IASs) 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 IASs 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

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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) in patients with IAS. An ion channel dysfunction can lead to the presence of specific atrial phenotypes associated with a predisposition for atrial arrhythmias (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: 1) characterize the distribution of AAs in patients with different forms of IAS, 2) investigate the clinical features, the course and long-term outcomes of these patients.

Methods

Study design

An international retrospective registry was established at Cardiocentro Ticino Institute (CCT), Lugano (Switzerland) involving 28 centers across 16 countries in 3 continents. Centers 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. Data Availability Statement: the data underlying this article will be shared on reasonable request to the corresponding author.

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Patient population

Patients with an established diagnosis of IAS and ECG documentation of AA were considered eligible and included in this study. Exclusion criteria included 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, ER syndrome, 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] AAs 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, CIEDs or ILRs 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 (ATP) delivered for ventricular tachycardia (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.

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Statistical analysis

All data are analyzed using Stata 17 (StataCorp, College Station, TX, USA). A 2-sided p-vale<0.05 is considered statistically significant. Continuous data are presented as mean and standard deviation. Categorical data are presented as counts and percent. Events rate per 100 person year. Logistic Regressions 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 centers. 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. BrS 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 was reported in 27.2% and 17.4% patients, respectively. A genetic test was performed in 336 patients (66.8%) and a pathogenic/likely pathogenic variant was found in 21.7% of cases. No patients with an overlapping syndrome was reported. Nine patients (3%) had 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%) (Central Illustration). The specific distribution of AA according to the underlying IAS is reported in Table 2. AA was the first clinical manifestation of the underlying IAS in more than half of the patients (52.0%). Moreover, 23.2% of the patients had more than one form of AAs.

As shown in Table 1, conventional AF-associated risk factors were infrequent in the study population. Class IC and III were unfrequently used (n= 45, 10.2%) and 39.7% of patients were under oral anticoagulants (n=178).

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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% 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 VAs-related events of 1.4% (95% CI 0.8-1.2) (Table 3 – Figure 1). 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 ERS, IVF and PCCD. The event rate in patients with BrS and LQTS was less than 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 shock 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 AA onset and risk of VA**

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%, OR 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: 1) Among patients with concurrent IAS and AAs, the AA is the first clinical

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manifestation of the IAS in about half of the patients 2) one out of four patients with concurrent IAS and AA presents with multiple forms of AAs; 3) The occurrence of AA earlier in life is associated with a higher risk of ventricular arrhythmias; 4) the risk of stroke and sinus node dysfunction among 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 examining 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 less than 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 reflect the IAS distribution in the general population. BrS and LQTS are the two most common IAS with a prevalence 1:2000 and AF risk of 20% and 2%, respectively.[1] Conversely, SQTS and CPVT are the two rarest IAS with a prevalence of 2.7:100.000 and 1:10.000, respectively.[1] SQTS is the IAS with the highest risk of AF (30%) while AAs in CVPT are mostly anecdotal.[1,10] ERS 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 about 25% experiencing other forms of AA (such as atrial flutter, atrial tachycardia) 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 antiarrhythmic drug-induced ventricular arrhythmias. Furthermore, the stroke risk, which is typically expected to be low in this population, reached up to 4%, creating dilemmas regarding

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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 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 antiarrhythmic drugs can be life threatening for BrS syndrome patients, while sotalol and amiodarone pose risks for patients LQTS. Our study does not include a comparative cohort of patients with and without AA, so no conclusions can be drawn regarding the prognostic significance of having AA. However, we demonstrated that patients who develop AF earlier in life likely have a more aggressive form of the disease and may warrant 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

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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 inherited arrhythmia syndromes (IAS). 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 to 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 multicenter 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 centers. The severity of AA may be influenced by the follow-up strategy (Holter, Loop Recorder and ICD) with patients with ICD experiencing more AA because of more accurate detection.

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Conclusions

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

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Figure Legend

Central Illustration:

Abbreviation List: 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

Figure 1: Primary and secondary outcomes

IAS-specific distribution of the composite primary endpoint, its component and the secondary endpoints.

Abbreviations: AA atrial arrhythmias, 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, AF atrial fibrillation.

Figure 2: Primary outcome distribution stratified according to the age at Atrial arrhythmia onset

Abbreviations: AA atrial arrhythmias, 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.

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1 Table 1

TABLE 1: BASELINE CHARACTERISTICS OF PATIENTS WITH INHERITED ARRHYTHMIA SYNDROME (IAS) AND ATRIAL ARRHYTHMIAS (AA)

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), yr	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), yr	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), yr	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%)	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%)
Hypertyroidism	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 ± Standard Deviation (SD) or Median and (Inter Quartile Range) (IQR). Discrete variables are presented as numbers and percentages (%).
Abbreviation List: IQR interquartile range, SD standard deviation, SCD sudden cardiac death, AA atrial arrhythmias, 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, AF atrial fibrillation, AVNRT atrioventricular nodal re-entrant tachycardia, AVRT atrioventricular re-entrant tachycardia

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1 Table 2

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TABLE 2: ATRIAL ARRHYTHMIAS (AAS) 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 (%).
Abbreviation List: 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, AF atrial fibrillation, AVNRT atrioventricular nodal re-entrant tachycardia, AVRT atrioventricular re-entrant tachycardia

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1 Table 3

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TABLE 3: PRIMARY AND SECONDARY ENDPOINT	
	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 ± Standard Deviation (SD) or Median and (Inter Quartile Range) (IQR). Discrete variables are presented as numbers and percentages (%).
Abbreviation List: AAD anti-arrhythmic drugs, TIA transient ischemic attack, AA atrial arrhythmias, ICD implantable cardiac defibrillator

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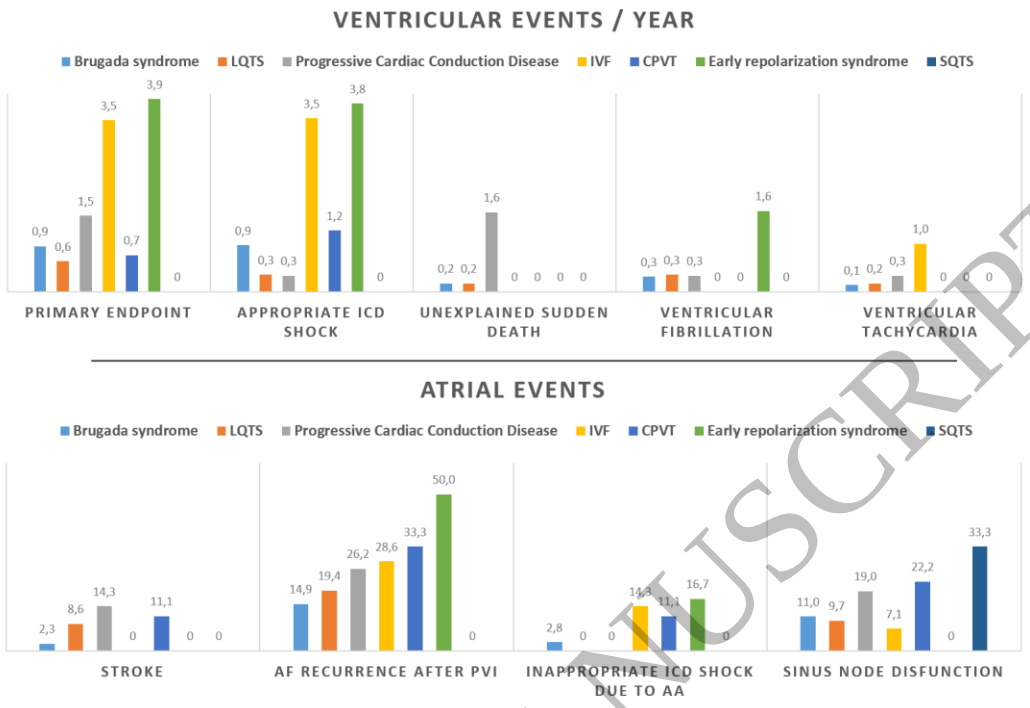

Figure 1
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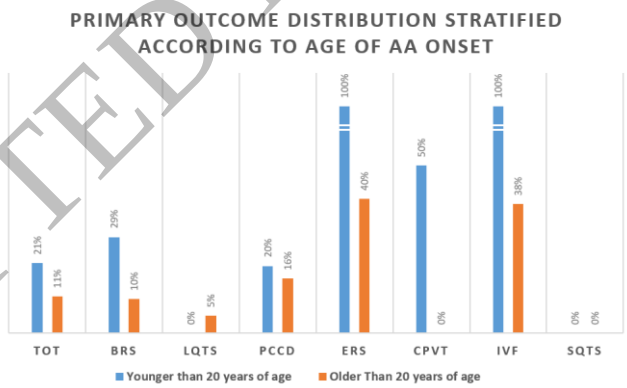

Figure 2
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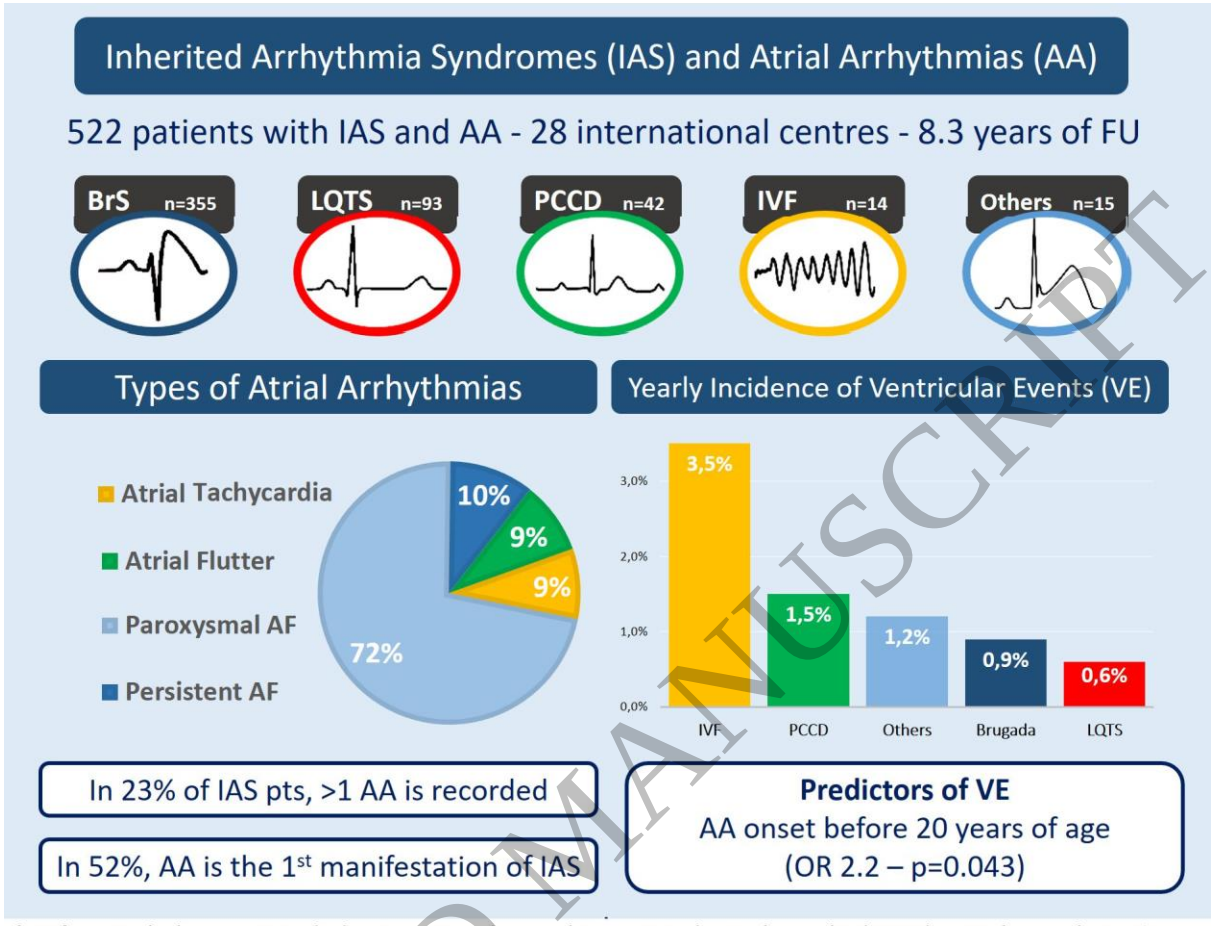

* **Others** includes: Catecholaminergic polymorphic ventricular tachycardia (CPVT), Early repolarization syndrome (ERS) and short QT syndrome (SQTS).

Graphical Abstract
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