The Importance of Dedicated Units for the Management of Patients with Inherited Arrhythmia Syndromes

Running title: *Conte et al.; Dedicated units for inherited arrhythmia syndromes*

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Nonstandard Abbreviations and Acronyms

IAS inherited arrhythmia syndromes

SCA sudden cardiac arrest

LQTS long-QT syndrome

BrS Brugada syndrome

ERS early repolarization syndrome

CPVT catecholaminergic polymorphic ventricular tachycardia

IVF idiopathic ventricular fibrillation

VT ventricular tachycardia

VF ventricular fibrillation

The inherited arrhythmia syndromes (IAS) are a group of genetic heart diseases predisposing to sudden cardiac arrest (SCA).[1] Patients with IAS and their family members receive diagnostic and therapeutic management, which is heterogeneous across centres and suboptimal with regard to adherence to current guidelines. In particular, genetic testing, which is of utmost importance for its implications in the treatment of some IAS (i.e. long-QT syndrome, LQTS), is not always performed.[2, 3]

The data that support the findings of this study are available from the European Heart Rhythm Association (EHRA) upon reasonable request. Additionally, IRB approval was obtained by EHRA.

The aim of this European Heart Rhythm Association (EHRA) survey analysis was to evaluate the relationship between the presence of dedicated IAS units, center volume and management of patients with IAS. The EHRA Scientific Initiatives Committee conducted the present survey in collaboration with the European Cardiac Arrhythmia Genetics' Focus Group

(ECGen) and ERN GUARD-Heart. A center-based on-line questionnaire was constructed to collect information about presence of dedicated IAS units, center volume and diagnostic and therapeutic management of patients with the following diseases: Brugada syndrome (BrS), long-QT syndrome (LQTS), early repolarization syndrome (ERS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and idiopathic ventricular fibrillation (IVF). Dedicated IAS unit was defined by the presence at a given Institution of a structured multidisciplinary service, including electrophysiologists specialized in IAS, device specialists, genetic counsellors, and psychiatric support, for the management of patients and their family members who have a confirmed diagnosis or who are seeking an opinion regarding a possible diagnosis of IAS. The link was sent out to the EHRA Research Network Centres and ECGen members. Forty-four European centers were included in the analysis: 27 (61%) had a dedicated unit for the management of IAS patients while there was no dedicated unit in the remaining 17 (39**%**) (Table 1). Out of 27 centers with dedicated units, 10 (37%) managed more than 100 patients in the previous 12 months, whereas all centers without a dedicated unit had lower volumes. Moreover, centers without a dedicated unit were more likely to have very low volumes (<20 patients/year) of adults (7% vs 47%, p<0.01) and pediatric patients (41% vs. 87%, p: 0.03). There were no significant differences between centres on the use of pharmacological challenges in the diagnostic assessment of IAS. However, centers without a dedicated unit performed less genetic testing for all the different types of IAS, including those where a genetic diagnosis can influence therapeutic choices. Specifically, genetic testing for LQTS was performed in 92% and 59% of centres with and without dedicated units, respectively (p: 0.01). Centers with a dedicated unit were more likely to perform an electrophysiology study with programmed ventricular stimulation for risk stratification (71% vs. 41%) and substrate ablation procedures (82% vs. 53%) for patients with Brugada syndrome.

In conclusion, dedicated IAS units frequently combine specialized care for adult and pediatric patients, genetic testing and specific diagnostic and therapeutic procedures more frequently compared to centers with a low volume. However, treatment/outcome superiority of IAS units was not examined in this survey. In the 2011 HRS/EHRA consensus statement on the state of art of genetic testing and 2013 HRS/EHRA/APHRS expert consensus on the diagnosis and management of IAS, genetic testing was recommended for probands with a clinical diagnosis and for all family members of a successfully genotyped proband (Class I recommendation).[1, 2] In LQTS, the risk of life-threatening arrhythmic events, which is modulated by the duration of QTc interval and the genetic substrate, is not equal for all patients.[4] Specific gene mutations are associated with different arrhythmic risk and potential therapeutic benefits. Therefore, genetic testing in these patients has important prognostic implications due to the interplay between genetic substrate, QTc duration, and arrhythmia risk and impact on the response to pharmacotherapy.[4] Patients with LQTS not undergoing genetic testing may therefore not receive an appropriate therapeutic approach. Moreover, genetic testing, including pre- and post- genetic testing counselling, is valuable for identifying variants within genes known to be associated with increased risk for disease features and allows for predictive testing of at-risk family members.[2, 3, 5] According to this survey's results, underuse of genetic testing is more likely to occur in centers without dedicated IAS units. Therefore, we make strong plea for institutions to commit the creation and implementation of dedicated IAS units or, otherwise refer these patients to dedicated centers where they and their families can be seen in a multidisciplinary setting.[3] Further efforts to improve patient care in this setting are strongly warranted.

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Table 1. Patient volume of centers with and without IAS units and the related patients' management.

	Centers with IAS units (N=27)	Centers without IAS units (N=17)	p-value
Number of adult patients seen in the last 12 months			
<20	2 (7%)	8 (47%)	*<0.01*
20-50	7 (26%)	7 (41%)	*0.33*
50-100	8 (30%)	2 (12%)	*0.27*
>100	10 (37%)	0	*<0.01*
Number of centres managing pediatric patients	22 (81%)	8 (47%)	*0.02*
Number of pediatric patients seen in the last 12 months			
<20	9/22 (41%)	7/8 (87.5%)	*0.03*
20-50	6/22 (27%)	1/8 (12.5%)	*0.63*
50-100	5/22 (23%)	0	*0.28*
>100	2/22 (9%)	0	*1.00*
Brugada syndrome			
- *Pharmacological challenge*	26/27 (96%)	15/17 (88%)	*0.54*
- *Genetic testing*	24/27 (89%)	9/17 (53%)	*0.05*
- *Electrophysiology study*	20/27 (74%)	7/17 (41%)	*0.05*
- *Ventricular arrhythmogenic substrate ablation*	22/27 (82%)	9/17 (53%)	*0.09*
- *AF ablation*	18/27 (67%)	13/17 (76%)	*0.73*
Long-QT syndrome			
- *Pharmacological challenge*	4/27 (15%)	1/17 (6%)	*0.63*
- *Genetic testing*	25/27 (92%)	10/17 (59%)	*0.01*
Early repolarization syndrome			
- *Pharmacological challenge*	5/27 (18%)	0/17	*0.13*
- *Genetic testing*	12/27 (44%)	1/17 (6%)	*<0.01*
Catecholaminergic polymorphic VT			
- *Pharmacological challenge*	6/27 (22%)	2/17 (12%)	*0.45*
- *Genetic testing*	23/27 (85%)	5/17 (29%)	*<0.01*
Idiopathic VF			
- *Pharmacological challenge*	14/27 (52%)	7/17 (41%)	*0.54*
- *Genetic testing*	21/27 (78%)	3/17 (18%)	*<0.01*

IAS inherited arrhythmia syndromes; VT ventricular tachycardia; VF ventricular fibrillation