

COVERING LETTER

To
The Registrar,
SCTIMST, Trivandrum

Dear Sir,
I am submitting the thesis titled "**CLINICAL OUTCOMES & SURVIVAL ANALYSIS IN INTRACARDIAC DEFIBRILLATOR RECIPIENTS WITH GENETIC CARDIAC ARRHYTHMIA SYNDROMES.**" Incorporating all the corrections & suggestions as advised by my guide.

The following corrections are made-

1. HCM & ARVD patients are excluded from the study.
2. The aim of the study also includes survival analysis.
3. In the literature review, recent data on cardiac arrhythmia syndromes are included.

Thanking you,

Yours sincerely,



Dr. Harsh kumar Pandey
PDF, Cardiac electrophysiology,
SCTIMST, Thiruvananthapuram.

**SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL
SCIENCES AND TECHNOLOGY THIRUVANANTHAPURAM**

**DEPARTMENT OF CARDIOLOGY
(Cardiac Electrophysiology division)**



**CLINICAL OUTCOMES AND SURVIVAL ANALYSIS IN INTRACARDIAC DEFIBRILLATOR
RECIPIENTS WITH
GENETIC CARDIAC ARRHYTHMIA SYNDROMES**

A THESIS SUBMITTED FOR

Post-Doctoral Fellowship in Cardiac Electrophysiology

Dr. HARSH KUMAR PANDEY

November 2022



DEPARTMENT OF CARDIOLOGY, SCTIMST, TRIVANDRUM CERTIFICATE

I hereby certify that the work in this dissertation titled "**clinical outcomes & survival analysis in Intracardiac defibrillator recipients with genetic cardiac arrhythmia syndromes**" is a certified record of original research work undertaken by Dr. Harsh Kumar pandey in the Department of Cardiac electrophysiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology in partial fulfillment of the requirement for the award of Post Doctoral fellowship degree.

Forwarded

The candidate, **Dr. Harsh Kumar pandey**, has carried out the minimum required project.

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DEPARTMENT OF CARDIOLOGY SCTIMST, TRIVANDRUM

DECLARATION BY CANDIDATE

I, Dr. Harsh Kumar Pandey, hereby declare that the project in this book, titled "**Clinical outcomes & survival analysis in Intracardiac defibrillator recipients with genetic cardiac arrhythmia syndromes**" was undertaken by me under the supervision of the faculty, Department of Cardiac electrophysiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

Thiruvananthapuram

Dr. Harsh Kumar Pandey

Date: 30/11/2022

EP fellow

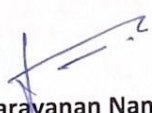


DEPARTMENT OF CARDIOLOGY SCTIMST,
TRIVANDRUM

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I hereby certify that the work in this dissertation titled " **Clinical outcomes & survival analysis in Intracardiac defibrillator recipients with genetic cardiac arrhythmia syndromes** " is a certified record of original research work undertaken by Dr. Harsh Kumar Pandey in the Department of Cardiac electrophysiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology in partial fulfillment of the requirement for the award of Post Doctoral fellowship in cardiac electrophysiology degree under my guidance and supervision.

Guides


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TITLE

"Clinical outcomes & survival analysis in Intracardiac defibrillator recipients with genetic cardiac arrhythmia syndromes "

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Finally, my sincere thanks to all the AICD recipients who were included in the study.

Dr. Harsh Kumar Pandey

ABBREVIATIONS

AICD	Automated Intracardiac defibrillator
ICD	Intra-cardiac defibrillator
SC/DC ICD	Single chamber/Dual Chamber ICD
VT/VF	Ventricular tachycardia/Fibrillation
SCD	Sudden cardiac death
AF	Atrial fibrillation
VA	Ventricular arrhythmia
SVT	Supraventricular tachycardia
LVEF	Left ventricle ejection fraction
ECG	Electrocardiography
RBBB	Right bundle branch block
LBBS	Left bundle branch block
NYHA	New York heart association
HCM	Hypertrophic cardiomyopathy
ARVD	Arrhythmogenic right ventricular dysplasia
IQR	Interquartile range
BrS	Brugada Syndrome
LQT	Long QT
SQT	Short QT

Synopsis



Background

Primary arrhythmia syndromes with known [long QT syndrome (LQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), short QT syndrome (SQTS)] or unknown [early repolarization syndrome (ERS), idiopathic ventricular fibrillation (IVF)] ion-channel mutations are responsible for the 10% of sudden deaths in young individuals(1). Indications for primary prevention for implantable cardioverter-defibrillator (ICD) therapy in patients with inherited cardiac channelopathies stem from retrospective observational studies and are uncertain. This study assesses the efficacy and complication rate of AICD implantations for primary prevention compared with secondary prevention in cardiac channelopathies.

Aim

- To assess shock (appropriate & inappropriate) & survival analysis in patients who underwent ICD therapy in primary & secondary prevention in genetic cardiac arrhythmia syndrome.

Methods

This is a descriptive single-center study with retrospective case enrolment and cross-sectional follow-up. Inherited Cardiac arrhythmia patients who underwent ICD implantation from January 2007 to October 2022 were identified by searching an institutional database. The study population was grouped by type of prevention (secondary or primary) for sudden cardiac death. Device interrogation was checked for appropriate and inappropriate shocks. The last follow-up data were acquired in October 2022. Patients with 12 months of missing data were considered lost to follow-up.

Results

Brugada syndrome (BrS)

Eighteen patients with BrS (94% male; mean age, 46.6 ± 11.7 years) received an ICD. ICDs were implanted for primary prevention in 8 (45%) patients, and secondary prevention in 10 (55%). Inducible sustained ventricular arrhythmia with EPS was the most common indication for primary prevention ($n=5$, 62%). With a median follow-up of 109 (interquartile range [IQR], 76–109) months, 2 primary prevention patients and 2 secondary prevention patients received an appropriate ICD shock ($P=0.79$). None of the evaluated predictors came out to be significant for appropriate ICD shock. The incidence rate of appropriate shocks was 2/100 per patient-years for primary & for secondary prevention. 1 patients died on follow up. (of non cardiac cause)

Short Coupled VPC/Idiopathic VF

Six patients (50% male; mean Age, 47 ± 16 years) received an ICD because of idiopathic VF. ICDs were implanted for secondary prevention in all 6 patients (100%) patients. With a median follow-up of 75 (IQR, 62.5–117) months, 3 of 6 secondary prevention patients received appropriate shocks. The incidence rate of appropriate shocks was 6/100 patient-years & incidence rate of inappropriate shock was 4/100 patients years.

Long QT

Two patients with LQTS (0% male; mean age, 50 ± 2.2 years), had an ICD implanted. ICDs were implanted for secondary prevention. Average follow-up of 59.9 (± 4.5) months. All of them were on beta-blocker. One patient had an appropriate ICD shock. The incidence rate of appropriate shocks was 10/100 patient-years

CPVT

One patient (male) was implanted for primary prevention at 30 years of age. However, he did not receive ICD therapy for 126 months of follow-up.

Complications rates:

Over a median follow-up of 102 months (12-126) of the entire cohort, the incidence of lead-related complications was 14% (1.7/100 patients years). The infection rates leading to reimplantation were 3% (0.1/100 patient-years). Only one patient died in the entire cohort, which was of non-cardiac cause.

Conclusion

During long-term follow-up, the secondary prevention group showed a higher incidence of appropriate shocks. Inappropriate shocks were similar in both groups. Complication rates were high on long-term follow-up.

INTRODUCTION



Introduction

Cardiac channelopathies are associated with an increased probability of sudden cardiac death (SCD). In addition, inherited primary arrhythmias, namely Brugada syndrome, congenital long QT syndrome, and (CPVT) catecholaminergic polymorphic ventricular tachycardia, account for a significant proportion of sudden cardiac deaths in young individuals. Therefore, genetic analysis has an integral role in the diagnosis, risk stratification, and treatment of index cases and family members.

Inherited primary arrhythmia syndromes are electrical abnormalities of the heart. The flow of ions in the cardiac myocyte is so delicately balanced that neither a loss nor a gain of the ionic channel function is tolerated by the intricately functioning electrical system of the heart. Based on whether the functional derangement is caused by the underlying genetic abnormality. The channelopathies are categorized as either loss-of-function or a gain-of-function mutation. The 3 main groups of channelopathies are congenital long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and Brugada syndrome (BrS) and related phenotypes; the less common entities being short QT syndrome (SQTS), early repolarization syndrome (ERS) and idiopathic ventricular fibrillation(2) These are typically monogenic disorders, that is, disorders that follow a clear Mendelian pattern of inheritance. However, for some of them, a more complex pattern of genetic substance.

Death in young, active, and previously healthy individuals with no identifiable cause on autopsy, termed sudden arrhythmic death syndrome (SADS), constitutes up to 5% of SCD in the general population aged 16-64 years and almost 25-35% of sudden deaths in <40 yrs of age (3). 90% of sudden cardiac death is caused by coronary artery disease, valvular, congenital, cardiomyopathy, and infiltrative cardiac disorders. The remaining 10% of SCD is caused by Primary arrhythmia syndrome(4). As per the Indian data, the risk of SCD is 39.7/100000 population >35 years of age(5). The increasing awareness and diagnosis of patients with genetic channelopathy for SCD have augmented the number of young patients with AICD. In these groups of patients, the appropriate selection criteria for ICD implantation is ill-defined, as fewer prospective studies & rely on consensus statements. ICD therapy is a class I indication in survivors of ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) because of the

risk of recurrence. Indications for prophylactic device implantation in patients without spontaneous VT/VF are uncertain, but there might be overuse regardless of risk stratification in specific disease categories.

Patients with genetic cardiac arrhythmic syndromes are likely to encounter device-related complications, like inappropriate shocks or lead-related issues, during follow-up (6), which might lead to reduced quality of life(7).

The Indian data on mortality and ICD therapy rates for arrhythmic genetic disorders during long-term follow-up are scarce. Therefore, This study was formulated to assess the differences in mortality & shock pattern (appropriate & inappropriate) between secondary and primary ICD recipients in genetic cardiac arrhythmia syndrome.

Review of literature



Brugada syndrome

Brugada syndrome (BrS) is a genetic cardiac channelopathy that manifests with a characteristic ECG pattern. Recent studies in electroanatomical mapping and imaging suggest an increased structural component rather than being exclusively an electrical disease. The highest prevalence noted in Southeast Asian populations, reaching 0.5–1 per 1000 (8). Recent advances have demonstrated structural abnormalities with electroanatomical mapping demonstrating predominantly RVOT epicardial abnormal signals (9).

Structural changes and electrical remodeling are predominantly noted in the epicardial RVOT area which plays an important role in the pathogenesis of malignant VA events. Biopsy specimens from surgical ablation and autopsy studies also show marked epicardial and interstitial myocardial fibrosis, which correlates with low-voltage, prolonged, fractionated electrograms on EPS (9). In addition, a recent autopsy study of 28 decedents showed increased biventricular fibrosis with a higher proportion of fibrosis in the epicardial RVOT (10). VAs occur at a mean age 41 ± 5 years, with increased prevalence during rest or sleep (11).

Risk stratification in BrS

In BrS, risk prediction to guide primary prevention of ICD implantation included a history of syncope and the 12-lead ECG characteristics at rest. Other risk factors that have shown to be prudent include EPS, genetic testing, and signal-averaged ECG. Recent smaller studies have suggested current guideline-accepted clinical risk markers carry low predictive accuracy for SCD (12). Previous sudden cardiac arrest and a spontaneous type 1 ECG pattern in patients who experienced a probable arrhythmia-related syncope carry higher rates of cardiac adverse events. Annual rates of 7.7% for malignant VA in those with a history of cardiac arrest and 1.9% in those with a history of syncope from the FINGER Registry (13). Asymptomatic BrS individuals generally have low event rates, with 12% experiencing appropriate ICD therapy at ten years (14). Although the decision to implant an ICD should be dependent on the presence of certain characteristics, the strength of data supporting this for current patient factors remains limited. Results of genetic testing have not been found to influence risk assessment thus far. Twelve-lead parameters such as fragmented QRS and effective refractory period < 200 ms on EPS have also been investigated as risk prognosticators (15), (16).

The role of EPS in risk stratification has been studied. A study of 1312 BrS patients without previous arrest demonstrated a 2- to 3-fold increased risk of VA on inducible VT on EPS. However, noninducibility of VT did not ensure a low risk, primarily when these patients had associated high-risk clinical features (spontaneous type 1 BrS pattern and a history of unexplained syncope) (17).

A recent multicenter international cohort has shown syncope, spontaneous type 1 pattern, and early repolarization pattern in the peripheral leads have shown the strongest association for future events. This study also produces a risk model, incorporating the four main factors with the sensitivity of 71.2% and specificity of 80.2% in predicting the 5-year risk of VA/SCD (18). However, data remains limited concerning risk stratification in asymptomatic BrS patients. Further research is warranted.

AICD indications

ICD implantation is a class I indication for survivors of sudden cardiac arrest, in patients with those previously documented spontaneous sustained monomorphic VT even without syncope (Class 1 indication in both European & North American guidelines). Patients with type 1 ECG pattern who experienced a probable arrhythmia-related or unexplained syncope (Class 2a for both guidelines). The subcutaneous ICD represents an attractive option, considering the possibility of lifetime lead failure with transvenous leads(14). A study of BrS noted a highly inappropriate morphology on device EGM analysis of 18% compared with 5% in other channelopathies(19).

Optimum AICD parameters

As AF/atrial tachycardia is a potential cause of inappropriate shock, therapy zones should be programmed accordingly(20). Studies have demonstrated inappropriate shock rates (24%0 twice as high as appropriate (12%)(14). As there are no recommended guidelines, a single VF detection zone with a high cutoff rate is considered for programming.

LQTS

Long QT syndrome encompasses a heterogeneous family of disorders characterized by delayed cardiac repolarization and a propensity to syncope and SCD(21). The estimated prevalence of LQTS is 1:2000 in the western world. Torsades de Pointes (TdP) is the mechanism behind the transient syncope in affected patients. So far, sixteen genes have been identified as associated with LQTS.13 The three main genes, KCNQ1 (LQT1), KCNH2 (LQT2) and SCN5A (LQT3) account for 75% of LQT cases(22).

Implantable cardioverter-Defibrillator (ICD) in long QT

ICD therapy is class I indication in patients who are resuscitated from cardiac arrest or documented ventricular arrhythmia. ICD is often favored in patients with LQTS-related syncope who also receive beta-blockers. Primary ICD therapy should be considered in very high-risk patients, such as symptomatic patients with two or more gene mutations(23). ICD therapy has lifetime implications. Complications are not infrequent, especially in the younger age group.

CPVT

An adrenergic-mediated disorder characterized by bidirectional or polymorphic ventricular tachycardia in a setting of a high adrenergic state. CPVT is a highly penetrant autosomal dominant disorder(24). SCD often being the first symptom; hence family screening is of paramount importance to catch the disease early and to initiate treatment. Mutations in the cardiac ryanodine receptor (RYR2) gene is the most common, are present in 55-65% of probands, whereas cardiac calsequestrin (CASQ2) gene mutations, inherited in an autosomal recessive manner, account for about 2% of cases.

ICD in CPVT

In CPVT patients who do not respond to optimal medical therapy and when LCSD is not possible, ICD should be considered. It should be ensured that patients with an ICD have also received optimal medical treatment(24).In patients who have experienced an aborted cardiac arrest before initiation of therapy, an

ICD should be implanted along with beta-blockers, or beta-blockers, and flecainide should be considered(23).

Short QT syndrome (SQTS),

It's a rare channelopathy characterized in the presence of a QTc <330 ms. or a QTc <360ms with one or more of the following: a familial history of SQTS, familial history of sudden death at age < 40, pathogenic mutation, , survival of a ventricular arrhythmic episode in the absence of heart disease(3)

ICD implantation is currently a class II b indication in asymptomatic individuals with a diagnosis of SQTS and a family history of SCD.

Idiopathic ventricular fibrillation (IVF),

It refers to spontaneous ventricular fibrillation in patients with structurally normal hearts, the cause of which remains unknown. However, recent studies showed SCN5A DPP6 as a founder mutation causative of a highly lethal form of familial IVF(25).

AIM & HYPOTHESIS



AIM

- To assess shocks (appropriate and inappropriate) & survival analysis in patients who underwent ICD therapy in primary & secondary prevention groups of genetic cardiac arrhythmia syndromes.

Hypothesis

- Patients who receive an AICD for primary prevention have fewer appropriate shocks.
- ICD recipients for genetic cardiac arrhythmia syndrome may receive a higher number of device-related complications in terms of inappropriate ICD shock & lead-related complications.

STUDY OBJECTIVE

1. All-cause mortality was considered the primary endpoint
2. Appropriate AICD shock was considered as the secondary endpoint.

MATERIALS & METHOD



Design: Retrospective cohort and cross-sectional study

Setting: Tertiary referral center, a university-level hospital (SCTIMST)

Inclusion Criteria:

All genetic cardiac arrhythmia patients who underwent AICD insertion for SCD prevention between January 2007 to October 2022 were identified by a search of an institutional database and included in the study

Exclusion Criteria

- Patients with less than 12 months of follow up

Sample size: All 27 patients of genetic cardiac arrhythmia syndromes who underwent AICD insertion for SCD prevention between January 2007 and October 2022

Methodology

This is a single-center retro-prospective study. Patients who received an ICD at our hospital between January 1, 2007, and October 2022, for Brugada syndrome (BrS), long QT syndrome (LQTS), CPVT, Short QT, and Idiopathic VF were included.

Patient data on follow-up, such as an electrocardiogram (ECG), and device interrogation, were collected from the institutional database and analyzed. All patients on follow-up who were contacted by telephone were advised for a routine device interrogation. Patients who were unable to visit the SCTIMST OPD were advised to undergo the investigations at a nearby hospital and email the reports to the investigator.

- The data of ICD implants was extracted from medical records. Which included clinical parameters (Age at onset, family history of SCD/Ventricular arrhythmia, medical therapy), ECG data, echocardiography, and electrophysiological studies. ICD-related data, indication for implant, and device interrogation data.

► Definitions

- Brugada syndrome was defined by ECG characteristics of ST-segment elevation ≥ 2 mm directly followed by a negative T-wave (type 1 ECG) in >1 right precordial lead (V1-V3)
- LQTS was defined according to criteria described by Schwartz et al. The QT interval was assessed from lead II/V5 and corrected for heart rate using the Bazett formula.
- Appropriate ICD shock: if it resulted from sustained ventricular arrhythmia, assessed by device interrogation.
- Inappropriate ICD shock: In the absence of ventricular arrhythmia.
- Electric storm : Occurrence of 3 or more separate episodes of ventricular arrhythmia requiring shock therapy within a 24-hour period.
- Secondary prevention: ICD implant after resuscitated cardiac arrest, sustained ventricular arrhythmia or syncope deemed of cardiac origin.
- primary prevention: Absence of a secondary prevention indication as defined.
- A family history of SCD was defined as a sudden death <60 years of ≥ 1 family members of first or second degree.

Inclusion criteria:

- All consecutive patients who underwent ICD implantation for cardiac arrhythmia syndrome will be included in this study.

Exclusion criteria:

- Patients who underwent ICD at other hospitals.
- Patients who are not on regular follow-up(<12 months of follow up).

Data analysis:

Data analysis will be done by the primary investigator with assistance from a statistician.

Variables will be presented as mean $\pm$ SD.

categorical variables will be presented as percentages.

All the relevant data will be recorded in Excel worksheet.

Data analysis will be done using latest version of SPSS software

Logistic regression analysis will perform to elucidate the factors predictive ICD shocks

For all tests, a P value of <0.05 is considered significant



RESULTS



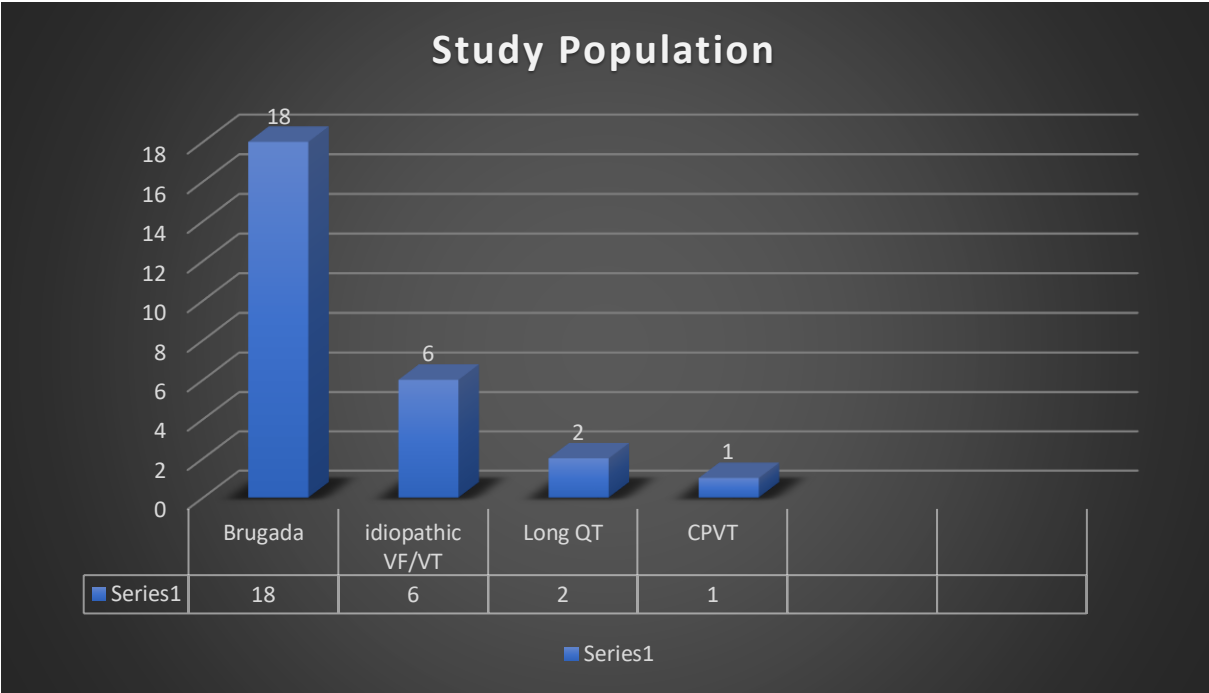


Table 1: Brugada syndrome:

Total N=18	Primary 8 (45%)	Secondary 10(55.5%)	P value
Male n(%)	7(87%)	10(100%)	
Type 1 n(%)	8 (100%)	7(70%)	
Type 2 n(%)	0	3(30%)	
VT/VF n(%)	0	4 (40%)	
Resuscitated Cardiac arrest n(%)	0	8 (80%)	
Family H/o SCD n(%)	3(33%)	1 (10%)	0.1
NSVT n(%)	2(22%)	-	
Palpitations n(%)	3 (36%)	4(40%)	0.9
Syncope, n(%)	6 (75%)	3(30%)	0.8
Presyncope, n(%)	3 (36%)	2(20%)	0.4
ECG			
QRSd (ms) (SD)	115(14)	111(10.8)	0.5
QTc(ms) (SD)	396(37)	386 (20)	0.4
LVEF (%) (SD)	70%(7)	67%(7.8)	0.4
Average age at implantation (years) (SD)	48(10)	45(13)	0.5
Average Follow up (months+/- 2SD)	82(51)	116(33)	0.1

Table 2: EP study for VT induction in brugada Patients.

EP study	Primary (8)	Secondary (10)
EPS for VT induction	5(55%)	5(50%)
Inducible VT	4 (80%)	4(80%)

Table 3: Shock pattern in Brugada syndrome

Brugada 18	Primary 8	Secondary 10	P value
<u>Appropriate shock</u>	<u>2 (25%)</u>	<u>2 (20%)</u>	<u>NS</u>
<u>Inappropriate shock</u>	<u>1 (12.5%)</u>	<u>0</u>	<u>NS</u>

Table 4: Predictors of Shock in Brugada Syndrome

Total N=18	Shock (4) (22.2%)	No shock 14 (77.7%)	P value
Type 1 n(%)	3(75%)	12(85%)	0.6
Type 2 n(%)	1(25%)	2(14%)	0.6
VT/VF	0	4(28%)	
Resuscitated Cardiac arrest n(%)	2(50%)	6(42%)	0.7
Family H/o SCD n(%)	1(7%)	3(21%)	0.8
Syncope, n(%)	2(50%)	7(50%)	1.0
Inducibility n(%)	2(50%)	5(35%)	0.6
Average age at implantation (years)	52(18.2)	45.1(9.6)	0.2

Table 5: idiopathic VT/VF patients with ICD

Total N=6	Secondary (6)
Male n(%)	3(50%)
Resuscitated Cardiac arrest n (%)	6 (100%)
Family H/o SCD n(%)	1(16%)
ECG	
QRSd ms average (SD)	95(16.9)
QTc ms average (SD)	413(26)
LVEF (%) (SD)	64%(5.89)
Average age at implantation (years)	47(16.6)
Median Follow up (months)	75.5(62-117)

Table 6: Shock pattern in idiopathic VT/VF

Idiopathic VF/VF 6	Secondary 3(50%)
<u>Appropriate n(%)</u>	<u>3 (50%)</u>
<u>Inappropriate n(%)</u>	<u>2(33%)</u>

Table 7: ICD in long QT syndrome patients

Total N=2	Secondary (2)(100%)
Male n(%)	0(0%)
Resuscitated Cardiac arrest(%)	0 (0%)
VT/TDP	2(100%)
Family H/o SCD n(%)	(0%)
ECG	
QRSd ms average(SD)	95(16.9)
QTc ms average(SD)	520(16.9)
LVEF (%) (SD)	64%(5.5)
Average age at implantation (years)	51.5(2.1)
Average Follow up (months)	59.5(4.9)

Table 8 Shock pattern in idiopathic long QTS

Long QT syndrome n=2	Secondary 2(100%)
<u>Appropriate n(%)</u>	<u>1 (50%)</u>
<u>Inappropriate</u>	<u>0</u>

Table 9: CPVT patients with ICD

Total N=1	Primary 1
Male n(%)	1(100%)
Resuscitated Cardiac arrestn(%)	0 (0%)
VT/TDP	-
Family H/o SCD n(%)	-
Syncope	1(100%)
TMT	Induced Polymorphic VPC
ECG	
QRSd ms	100
QTc ms	377
LVEF (%)(SD)	66%
Age at implantation (years)	30
Follow up (months)	128

Table 10: Shock pattern in the entire cohort.

27	Primary 9(33%)	Secondary 18(67%)	P value
<u>Appropriate (8)</u>	<u>2 (22%)</u>	<u>6(33%)</u>	<u>0.35</u>
<u>Inappropriate 3</u>	<u>1(11%)</u>	<u>2(11%)</u>	<u>0.96</u>

Table 11: Predictors of Appropriate ICD shock in the entire cohort.

Total N=27	Shock (8) (29.6%)	No shock 19 (70.4%)	P value
Male	5(62%)	15(%)	0.37
VT	4(50%)	8(85%)	0.7
Family H/o SCD	3(36%)	2(15%)	0.5
Symptoms(Syncope, presyncope) n(%)	6(75%)	16(84%)	0.30
The average age at implantation (years)	47.8(14.2)	48(12)	0.80

Figure :1

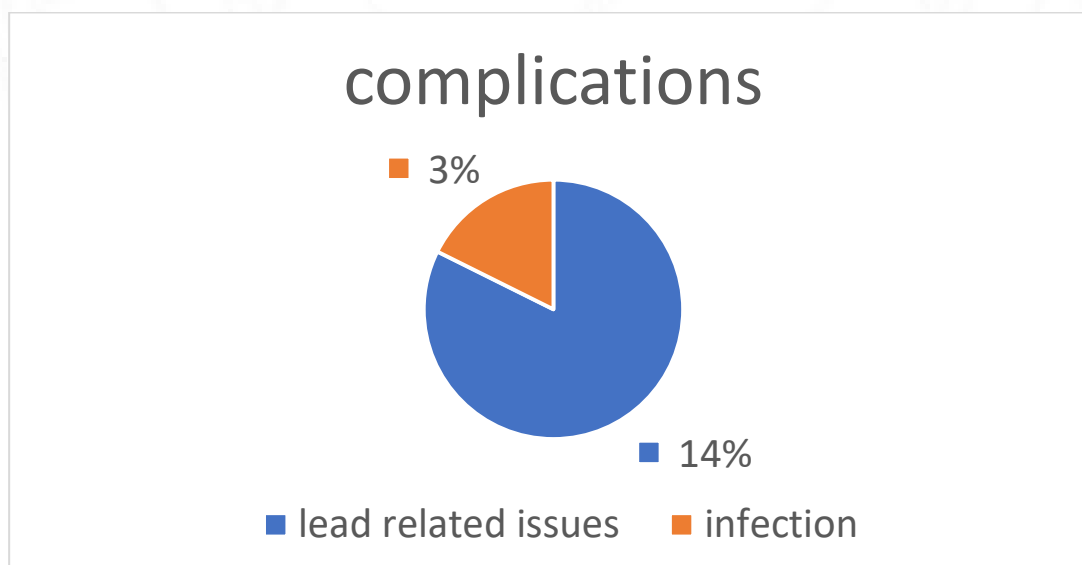


Figure 2: Kaplan Meier analysis for Appropriate ICD shocks

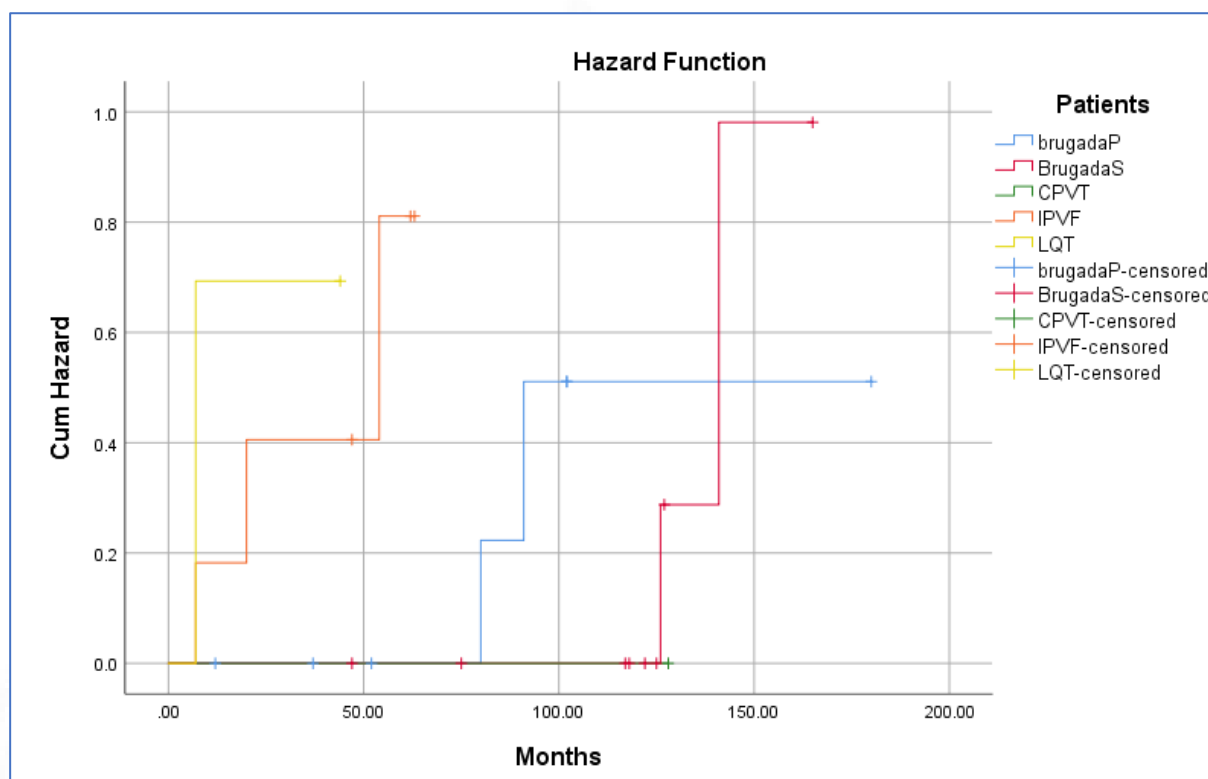
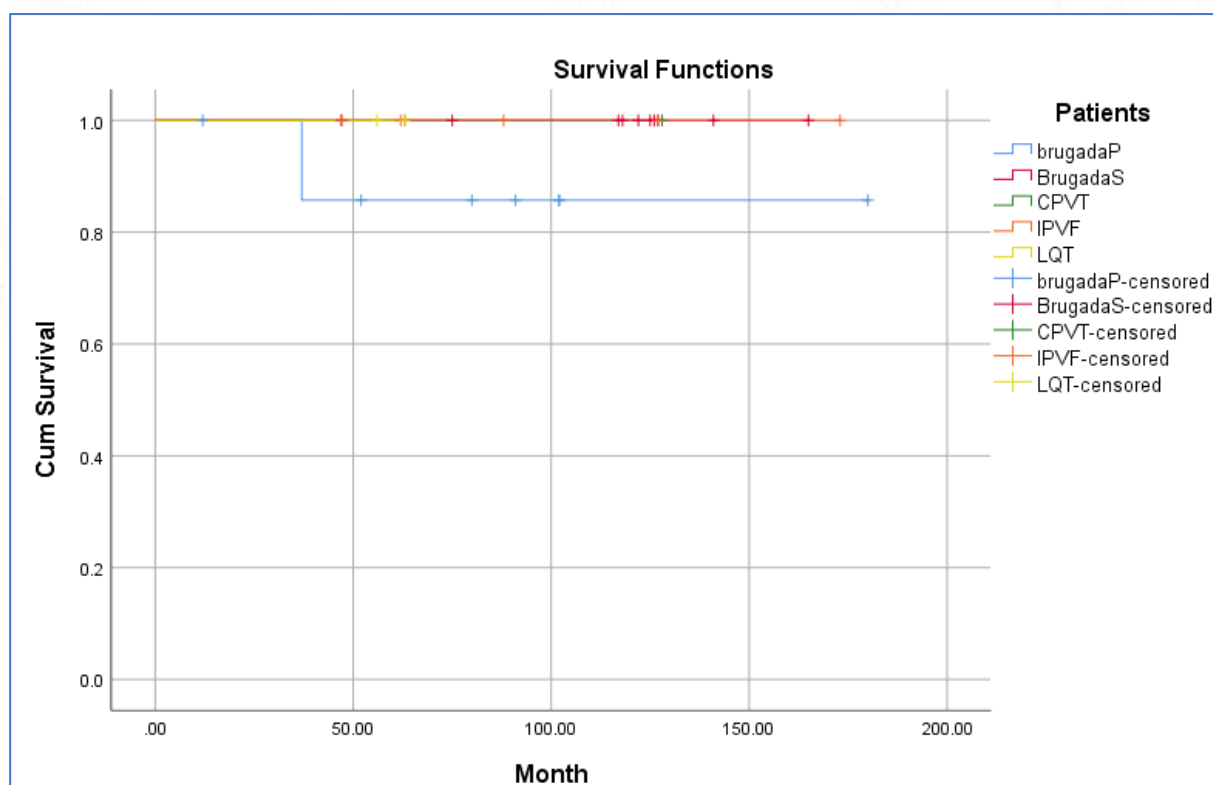


Figure 3: Kaplan Meier analysis for survival



Discussion

Main Findings

Implantable cardiac defibrillators have been used in patients with inherited arrhythmia syndromes to prevent sudden cardiac death but have also been associated with relatively high device-related complication rates.

In this study of inherited arrhythmic syndromes patients who had an ICD for the prevention of SCD, the salient findings are:

1. Appropriate shocks are frequent in inherited arrhythmia patients with an ICD.
2. Appropriate shock is more frequent in patients with secondary prevention groups than in primary prevention groups.
3. Device-related complications are high on long-term follow-up.
4. Inappropriate ICD shocks were lower on long-term follow-up.

The risk of appropriate shocks in BrS, LQT, and Idiopathic VF, CPVT patients implanted for primary prevention was (29%), 3/100 patient-years). 14% (1.7/100 patient-years) of our study population had ICD-related complications. In addition, 11% of patients had inappropriate ICD shocks (1/100 patient-years). All inappropriate shocks were due to SVT (AF). Only one mortality was observed in the entire cohort on the non-cardiac cause. There were no predictors of appropriate ICD shock.

Secondary Prevention

Previous studies have demonstrated the higher discharge rate of ICDs in patients with genetic cardiac arrhythmia syndromes for secondary prevention (4-24/100 patients years). (13) This study also showed a similar occurrence of appropriate (3.9/100 patients years) ICD discharge rates, which reconfirms that the ICDs are efficacious in patients with a history of sustained ventricular arrhythmia. The idiopathic VF and long QT syndrome group had ICD only for secondary prevention. None of the idiopathic VF and long QT patients received an ICD for primary prevention. Suggested a more malignant nature of the genetic arrhythmia associated with these disorders.

Primary Prevention

The reported incidence of Appropriate shock is around 2.5% (3.8/100 patients) in primary prevention of BrS (14). Our study's discharge rates in BrS were lower than in other prophylactic ICD trials (2.6/100 patient-years). Only two of the primary prevention BrS patients received appropriate shocks.

Our indications for prophylactic ICD in inherited cardiac arrhythmia syndromes are more conservative. Asymptomatic patients with BrS are not considered for ICD implantation if they have only a family history of SCD. However, we demonstrate a substantial proportion of patients (22%) receiving appropriate ICD interventions, which shows the discrepancy between the indications and

predictors for appropriate shocks in primary prevention for sudden cardiac death in cardiac arrhythmia syndromes.

Kaplan Meier analysis showed a significant early incidence of appropriate ICD shock in the LQT group compared to other genetic cardiac arrhythmia syndrome groups. Survival analysis does not show any difference in survival among all genetic cardiac arrhythmia syndrome groups.

Complications

Inappropriate shocks and lead-related complications rate in our study was 11% and 14%, respectively. The incidence rate of inappropriate shocks of 1.3/100 patient-years found in this study is lesser than the other studies (range, 2.4%–6.9%)(26)(27). Dual-chamber devices were very few in our study. Therefore, the incidence rate of lead-related complications of 1.7/100 patient years is lesser than that found in other studies (range, 3.3– 9.3)(28). 3% of patients have a device-related infection that causes device explantation(0.4/100patient years). 3% mortality was noted on a median of 102 (12-126) months of follow-up. Considering that patients with genetic arrhythmia syndromes with AICD recipients have a better life expectancy than those with ischemic cardiomyopathy groups, these young AICD patients are more likely to face a substantial burden of future device-related complications.

Summary

1. N=27 genetic cardiac arrhythmia syndrome
2. Average follow up= 8+/-3.5yrs
3. Primary prevention in 33.3%
4. Secondary prevention in 66.6%
5. The appropriate shock was observed in 29% of the entire cohort. (3.6/100 patient-years)
6. The inappropriate shock was observed in 11% of the entire cohort. (1/100 patient-years)
7. Total lead-related complications: 14% of the entire cohort (1.7/100 patient-years)
8. The infection rate was 3% of the entire cohort (0.4/100 patient-years)
9. Total mortality was 3% of the entire cohort (0.4/100 patient-years)

Limitations

1. The study consists a small cohort and heterogeneous study population make drawing definite conclusions difficult regarding predictors of future events.
2. Retrospective data collection.
3. Single center study
4. Absence of a control population without an AICD.

Conclusion

- The observed rate for appropriate ICD shocks & lead-related complications was high in inherited cardiac arrhythmia syndromes.
- The appropriate therapy rates were higher in the secondary prevention group compared to the primary prevention group.
- Very less mortality of non-cardiac causes was documented in this group of patients.
- The different genetic makeup of these cardiac arrhythmia syndromes with variable expressivity of their genes makes them a more vulnerable group to the risk of sudden cardiac death & hence the need for an ICD.

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Appendix

PROFORMA	
CLINICAL OUTCOMES AND SURVIVAL ANALYSIS IN INTRACARDIAC RECIPIENTS WITH GENETIC CARDIAC ARRHYTHMIA SYNDROMES.	
HOSP ID: _____	
BASELINE CHARACTERISTICS	
AGE: _____(years) SEX: M ☐ F ☐ HEIGHT _____cm WEIGHT _____kg BMI _____ kg/m ²	DM ☐ HTN ☐ SYNCOPE ☐ DYSLIPIDEMIA ☐ FAMILY HISTORY OF SUDDEN CARDIAC DEATH
NYHA FUNCTIONAL CLASS I ☐ II ☐ III ☐	DRUGS Amiodarone ☐ Sotalol ☐ Beta blockers ☐ MEXILETINE FLECAINIDE
Indication Primary ☐ Secondary ☐ ☐	
VT induction -Pre RFA, ☐ ☐	
ECHO parameters LVEF, LVOT gradients, RVOT Diameter	ECG-AF LBBB RBBB QRS WIDTH/Epsilon wave, TWI,Flecainide challenge test
Type of Brugada. Syncope/Persyncope/Palpitations/ESC SCD score/	
GENETIC STUDY FINDINGS	ICD THERAPY
SURVIVAL OUTCOMES	

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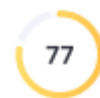
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by harsh pandey

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Institutional Ethics Committee
 (IEC Regn No. ECR/189/Inst/KL/2013/IR-21)

SCT/IEC/1894/AUGUST-2022 24.08.2022

Dr. Harsh Kumar Pandey
 PDF, Department of Cardiology
 SCTIMST, Thiruvananthapuram

Dear Dr. Harsh Kumar Pandey,

The project proposal with the title "CLINICAL OUTCOMES AND SURVIVAL ANALYSIS IN INTRACARDIAC DEFIBRILLATOR RECIPIENTS WITH GENETIC CARDIAC ARRHYTHMIA SYNDROMES" submitted to Institutional Ethics Committee (IEC) has been reviewed in the IEC Meeting held on 6th August, 2022 and assigned number as IEC/1894.

List of documents submitted:

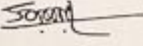
1. Covering letter addressed to the Chairman, IEC, SCTIMST	6. Patient Information Sheet and Consent Form in English and Malayalam
2. Checklist Form	7. CV of PI and Co-PIs
3. Declaration Form	8. Data Collection Sheet
4. IEC Application Form	9. Application for TCMC Registration
5. Project Proposal	10. SRC Recommendation Letter

IEC Recommendations

- The study intends to assess the performance of the implanted device with reference to the type of therapy in the context of the family history of sudden cardiac deaths.
- The design of the study is not clearly spelt out.
- As the assessment will be done during consecutive visits to the hospital, it needs to be clarified whether these visits are part of the follow up or additional visits and if so the patient needs to be informed of the frequency of visits in advance. Patient Information Sheet should be revised accordingly.
- The following statement is included in the section III of the IEC application. "A violation of confidentiality is unlikely to be of any major consequence to the subjects". This has to be either modified or deleted.
- Benefit of the study to be mentioned as a more generalized one, than offering personal benefits.
- IEC Secretary's contact details to be included
- Will minors be included in the study, if so, parental consent is required, if, no, it has to be specified in the recruitment criteria.

One set of all the documents including those revised are to be submitted to the IEC Office. The covering letter should indicate the revisions made.

Sincerely,


Dr. G. Srinivas
 Member Secretary, IEC



Master chart

IPVF SSECONDARY

NAME	H/N	comp	age of imp	indi	DATE IMP	LAST VISIT	F/P durati	MORTALIT	DATE	MORTA
Thara Shibu	274032	M	30	PVT	14-06-2008	22-11-2022	173	0		0
shankara pilla	436583	S	77	pvt	11-08-2017	22-11-2022	63	0		0
Ashamol	437416	BIO	34	PVT	21-09-2017	22-11-2022	62	0		0
elsy george	461486	M	48	PVT	05-12-2018	22-11-2022	47	0		0
lilly thomas	310409	S	50	PVT+SSS?	13-04-2010	22-11-2022	127	0		0
maheswari S	398897	B	43	TDP	28-07-2015	22-11-2022	88	0		0

BRUGADA PRIMARY

H/N	TYPE	comp	FLECAINID	DATE IMP	AGE AT IMP	LAST VISIT	F/P durati	SHOCK	shock dur	app sh
263873	1 M		0	06-10-2007	32	17.8.22	180		180.00	
359663	1 B		0	06-06-2013	46	12.7.16	37		37.00	
379787	1 B		0	26-08-2014	58	30.5.14	12		12.00	
364655	1 B		1	23-09-2014	47	30.5.22	102		102.00	
389558	1 M		0	23-12-2014	52	30.5.22	102		102.00	
395793	1 B		1	12-05-2015	49	28.4.22	91	03-09-2015	4.00	
453455	1 M		0	02-07-2018	39	22.11.22	52		52.00	
410241	1 M		0	28-03-2016	64	22.11.22	80	09-06-2020	63.00	15-06

CPVT PRIMARY

NAME	H/N	company	age at imp	syncope	AGE	TMT	DATE IMP	LAST VISIT	F/P durati	SHOCK
Jojo josep	252830	S	30	1	30	multi VPC	#####	22.11.22	128	0

BRUGADA SECONDARY

H/N	type	RESUS ARF	VT/VF	flecainide	acomany	age of im	syncope	FSCD	DATE IMP	LAST VISIT
298259	1	1	0	0	S	43	0	0	16-07-2009	22-11-2
330032	1	1	0	0	S	27	0	0	23-07-2011	22-11-2
342983	1	1	0	0	B	47	0	1	10-04-2012	22-11-2
342664	2	1	0	0	M	67	0	0	10-05-2012	22-11-2
346113	1	1	1	0	M	30	0	0	14-06-2012	22-11-2
349805	1	1	0	0	B	38	0	0	05-09-2012	22-11-2
355854	1	1	1	0	S	51	1	0	10-01-2013	22-11-2
354318	2	1	0	1	S	65	1	0	21-03-2013	22-11-2
417869	2	0	1	0	M	37	0	0	03-08-2016	22-11-2
460805	1	0	1	0	M	47	1	0	04-12-2018	22-11-2

LQT SECONDARY

NAME	H/N	comp	age of imp	indi	DATE IMP	LAST VISIT	F/P duration	MORTALITY	DAT
KADIYAMU ALI AHAMMED	437623	B	50	2:1 TDp+brady	25-08-2017	22-11-2022	63.00	0	
kumari sheela	390807	sjm	53	VT lqt	25-03-2018	22-11-2022	56	0	

