Effects of Flecainide on Cardiac Arrhythmias in ARVC Patients

Sponsor:	University of Rochester
Clinical Trials.gov:	NCT 03685149
Funding Body:	NHLBI
Indication:	Patients with ARVC and ventricular arrhythmias
Intervention:	Flecainide
Study Type:	Randomized clinical trial
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Protocol Version/Date:	Version 2.0 / December 4, 2018

Abbreviations

ARVC – arrhythmogenic right ventricular cardiomyopathy

CMRI – cardiac magnetic resonance imaging

DCC – Data Coordinating Center

ECG – electrocardiogram

ICD – implantable cardioverter-defibrillator

IDS – Investigational Drug Services

VF – ventricular fibrillation

VPBs – ventricular premature beats

VT – ventricular tachycardia

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1. PURPOSE OF THE STUDY AND BACKGROUND

1.1. Background

1.1.1. Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy characterized by fibrofatty replacement primarily of right ventricular muscle. The resultant heterogeneous structure of the RV myocardium results in ventricular arrhythmias, including ventricular premature beats (VPBs), nonsustained or sustained ventricular tachycardia (VT) or ventricular fibrillation (VF). ARVC is uncommon disorder (1 in 5000 individuals) but may account for up to 20% of cases of sudden death among young individuals (Marcus et al. 1982, Calkins 2013, Corrado 2017). As shown in Figure 1 from the Johns Hopkins and the Dutch ARVC registries described by Bhonsale et al. (2015), about 60% pf ARVC patients develop life-threatening arrhythmic event or SCD by the age of 30 years. Figure 2 from an Italian cohort described by Mazzanti et al. (2016), about 20% died from cardiovascular causes by the age of 30 years.

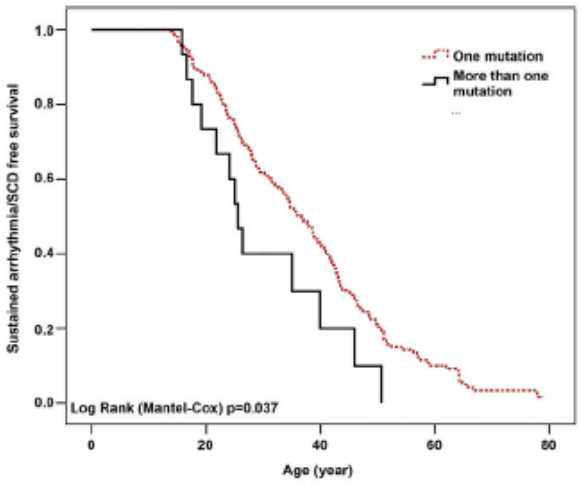


Figure 1: The risk of sustained arrhythmias or SCD in 200 ARVC patients with single and 15 patients with double mutations (Bhonsale 2015).

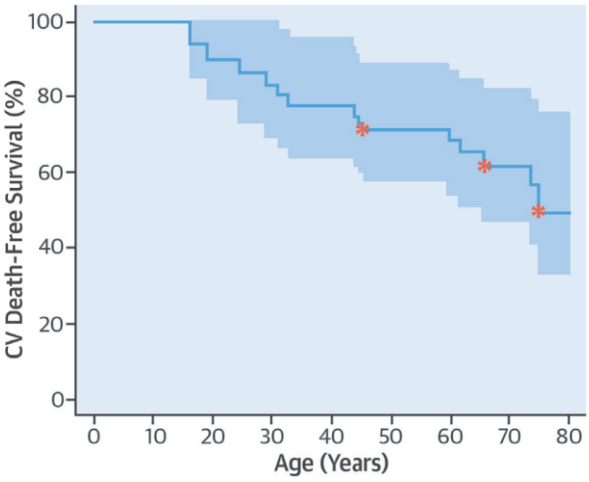


Figure 2: The risk of cardiovascular death in 198 ARVC patients (Mazzanti, et al. 2016).

Figure 3 from the North American ARVC Registry, which enrolled newly diagnosed ARVC patients, showed that about 40-50% of men and women with ARVC and implanted ICD developed arrhythmic events or did die within 2 years after implant of the device. The risk of fast VT, VF or

death is higher in males than females: 27% vs. 11%, respectively at 2 years (Choudhary et al. 2016). The John Hopkins and Dutch registries showed significantly higher lifetime risk of sustained arrhythmias or SCD in 312 males than in 256 females (Bhonsale et al. 2015).

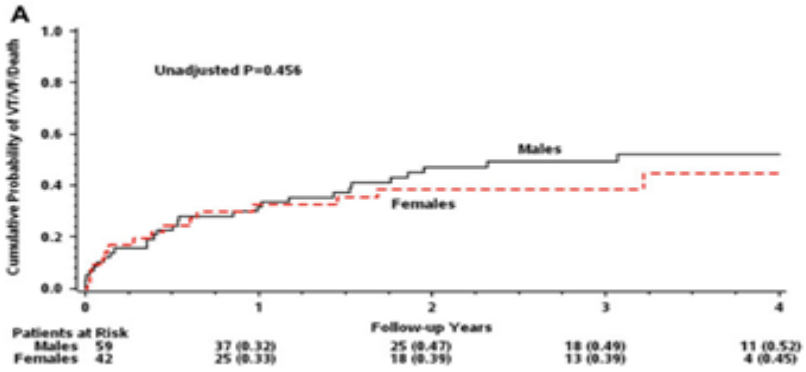


Figure 3: The risk of VT/VF or death in ARVC patients with ICD's by sex (Choudhary, et. al. 2016).

ARVC is caused by mutations in the genes encoding for desmosomal proteins which are found in about 50% of patients (Groeneweg et al. 2015). In the remaining 50%, genes are unknown. Desmosomal genes include: plakophilin-2 (PKP2), plakoglobin, desmoplakin, desmoglein-2, and desmocollin-2 but mutations in several non-desmosomal genes including phospholamban and TMEM43-encoding transmembrane protein 43 have also been reported to cause ARVC (Bhonsale et al. 2015, Groeneweg et al. 2015). In the Johns Hopkins and the Dutch ARVC registry, among 575 ARVC patients with known mutations 463, (80%) carried a single copy of a *PKP2* mutations (Bhonsale et al. 2015).

Prevention of sudden cardiac death with implantable cardioverter defibrillator (ICD) is the primary management in ARVC. Several studies of ARVC patients who received an ICD showed appropriate interventions during follow-up in about 50% of patients (Dalal et al. 2005, Corrado et al. 2010, Bhonsale et al. 2011, Link et al. 2014). Of these, approximately 40% were considered life-saving based on the presence of rapid VT/VF with a rate of >240 bpm. Predictors of appropriate therapy included previous VF arrest, syncope, severe RV dilation, LV dysfunction, young age, and definite disease by Task Force criteria. However, ICD therapy does not reduce the frequency of recurrent arrhythmias and antiarrhythmic pharmacological therapy or catheter ablation of VT is prescribed to diminish the risk of arrhythmic events and death. Frequent shocks are associated with psychological effects and decreased quality of life and every effort needs to be made to reduce their frequency.

1.1.2. Antiarrhythmic Pharmacological Treatment in ARVC

Beta-blockers are currently recommended for all patients with ARVC, for both prevention of arrhythmias and reduction of right ventricular wall stress (Corrado et al. 2015). In patients with ventricular arrhythmias, antiarrhythmic drug therapy offers the potential to ameliorate symptoms, although there is no proof that it confers protection against sudden cardiac death (Ermakov and Scheinman 2015, Corrado 2017). Analysis of the effects of antiarrhythmic medications in 95 patients from the North American ARVC Registry (Marcus G et al. 2009) showed that 61% received beta-blockers, and these medications were not associated with an increased or decreased risk of ventricular arrhythmias. Sotalol was associated with a greater risk of any clinically relevant ventricular arrhythmia as defined by sustained ventricular tachycardia or ICD therapy (hazard ratio [HR]: 2.55, p=0.045), but this was not statistically significant after adjusting

for potential confounders. An increased risk of any ICD shock and first clinically relevant ventricular arrhythmia while the patients were taking sotalol remained significant after multivariable adjustment. Amiodarone seemed to be more effective but there were only 10 patients receiving this medication. An independent analysis of a large cohort from Italy (Mazzanti et al. 2016) showed that none of the arrhythmic medications had a beneficial effect on the rate of events when comparing matched periods before and after administered drugs (Table 1). There is no good data indicating that common antiarrhythmic medications reduce VT/VF in ARVC patients. The same is true for catheter ablation in the analysis shown in Table 1; although some data show that catheter ablation might reduce VTs in select patients (Riley et al. 2010, Santangeli et al. 2015). Therefore there is a great need to explore the efficacy of other antiarrhythmic medications. Experimental data on flecainide are promising.

Table 1: Matched- Periods Analysis for the Efficacy of Antiarrhythmic Drugs and Transcatheter Ablation (Mazzanti, et.al. 2016).

Treatment	Time	n	Person-Yrs	LAE	Rate	95% CI	p Value
Beta-blockers†	Before	67	218	7	0.032	0.015-0.068	0.107
	After	67	218	15	0.069	0.033-0.145	
Sotalol	Before	37	220	3	0.014	0.003-0.060	0.062
	After	37	220	16	0.073	0.030-0.178	
Amiodarone	Before	15	88	1	0.011	0.002-0.083	0.048
	After	15	88	9	0.102	0.047-0.223	
Ablation	Before	27	170	16	0.094	0.035-0.253	0.644
	After	27	170	20	0.117	0.069-0.200	

1.1.3. Flecainide

Flecainide is a class 1C antiarrhythmic drug that blocks sodium channels. Flecainide is used to suppress cardiac tachyarrhythmias including paroxysmal atrial fibrillation and supraventricular tachycardia. Flecainide is also used to treat LQT3 patients and patients with Ca2+-mediated, catecholaminergic polymorphic ventricular tachycardia (CPVT). Flecainide can have proarrhythmic effects after myocardial infarction (Echt et al. 1991). These divergent actions result from its physiological and pharmacological actions at multiple, levels of cellular organization (Salvage et al. 2017). These properties of flecainide were studied in murine genetic models with modified Nav channel or intracellular ryanodine receptor (RyR2)-Ca2+ channel function (Watanabe et al. 2009). Flecainide accesses its transmembrane Nav1.5 channel binding site during activated, open states, producing a use-dependent antagonism. Closing either activation or inactivation gates traps flecainide within the pore. An early peak INa related to activation of Nav channels followed by rapid de-activation, causes action potential upstrokes and their propagation. This is diminished in pro-arrhythmic conditions reflecting loss of function of Nav1.5 channels, such as in the Brugada syndrome that may be exacerbated by flecainide. In contrast, the pro-arrhythmic effects attributed to prolonged action potential recovery by abnormal late INaL following gain-of-function modifications of Nav1.5 channels in LQT3 are reduced by flecainide. Anti-arrhythmic effects of flecainide that reduce triggering in CPVT mediated by sarcoplasmic reticular Ca2+ release could arise from its primary actions on Nav channels indirectly decreasing [Ca2+]i by a reduced [Na+]i and/or direct open state antagonism of the RyR2-Ca2+ channel. The consequent [Ca2+]i alterations could also modify action potential propagation velocity and therefore arrhythmic substrate through its actions on Nav1.5 channel function. This is consistent with the paradoxical differences between flecainide actions on Na+ currents, AP conduction and arrhythmogenesis under circumstances of normal and increased RyR2 function.

In a small randomized trial flecainide was effective in reducing ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia, a condition linked to RyR2 mutations causing increased SR release and triggered arrhythmias (Kannankeril 2017). This study reported a significant reduction of all forms of ventricular arrhythmias recorded during exercise in CPVT patients. ARVC patients show high prevalence of catecholamine-facilitated focal VT that is associated with ventricular premature beats observed at diagnosis and with induced sustained VT (Philips et al. 2013). Ventricular arrhythmogenicity during isoproterenol testing was further proven by Dr. Haissaguerre's group from Bordeaux who demonstrated that induction of sustained and nonsustained VT episodes by isoproterenol was highly sensitive (91.4%) for ARVC diagnosis in 41 patients with the disorder and predictive of follow-up events (Denis et al. 2014).

Experimental data using a novel murine model with cardiac-specific tamoxifen induced PKP2 deficiency indicate that enhanced triggered activity and increased sarcoplasmic reticulum (SR) calcium release via RyR2 channels could contribute to adrenergic-induced arrhythmias in an experimental model of ARVC (Cerrone et al. 2017, Van Opbergen et al. 2017). This study also reported that flecainide effectively prevented the arrhythmias observed in the experimental animals. Separate preclinical and anecdotal clinical reports also suggest that flecainide, probably through a block of the RyR2 receptor is a promising antiarrhythmic approach in ARVC. The arrhythmia burden was tested in 6 animals in the presence of a single dose of 40 mg/kg of flecainide (Cerrone et al, 2012). In contrast with results in untreated animals, flecainide-treated PKP2-cKO mice showed an absence of ISO-induced arrhythmia burden in the total recording period of 20 minutes. These results further support the notion that arrhythmias in PKP2-cKO animals may result from dysregulation of intracellular calcium cycling via increased RyR2-dependent calcium release.

Recent analysis of 8 ARVC patients with recurrent VT/VF events, who were treated with flecainide after several attempts with other antiarrhythmic medications, showed that 6 out of 8 of these patients had arrhythmias eliminated (Ermakov and Scheinman 2017). It is important to stress that patients with variants other than PKP2 and those cases with no known mutation responded to flecainide in this small series.

Clinical data from the Johns Hopkins Registry (Orgeron et al. 2017), in 312 ARVC patients with ICDs showed that patients with ventricular flutter or VF had frequent VPBs ≥1000 /24 hours, with hazard ratio of 4.39 (p=0.016). Other predictors included syncope (HR: 1.85; p=0.021), age ≤30 years at presentation (HR: 1.76; p=0.036), and male sex (HR: 1.73; p=0.046). Therefore, treatment with flecainide in patients with frequent VPBs will address a high-risk subset of patients.

1.1.4. Significance of Pilot Project

There is no known effective antiarrhythmic treatment in ARVC patients. Flecainide is a promising option, but there are no clinical trials to prove its efficacy and safety in ARVC patients. The pilot study will assess the effect of flecainide on cardiac arrhythmias detected by long-term ECG monitoring and will provide preliminary data that might lead to a larger study with stringent endpoints consisting of ICD-documented VT, VF or death during long-term follow-up. Assessing safety of this therapy is of major importance in view of the results of the CAST trial that showed increased mortality in patients with ischemic heart disease treated with antiarrhythmic drugs including flecainide (Echt et al. 1991). This is the reason we are taking precautions of including only ARVC patients with ICDs and excluding patients with significant left ventricular dysfunction and significant heart failure, who constitute a small minority of ARVC patients. Importantly, as documented in the secondary analyses from the CAST trial, proarrhythmic effects of flecainide in studied patients with depressed or preserved ejection fraction was eliminated by concomitant administration of beta-blockers (Kennedy et al. 1994: Kennedy 1997). If the pilot study documents a significant reduction in ECG-recorded arrhythmias and if a subsequent trial show long-term

effectiveness of this therapy, it would be a major therapy in the treatment of ARVC patients.

1.2. Purpose of the Study

The primary specific aim of this pilot trial is to determine whether flecainide administration is associated with a significant reduction in the number of ventricular premature beats (VPBs) in ARVC patients with ICDs.

The secondary aims are to:

1) Assess safety of flecainide administration with particular emphasis on pro-arrhythmic response measured by:
    a. VPBs on ECG monitoring
    b. Nonsustained and sustained VT/VF episodes documented on ICD interrogation
    c. Effects of flecainide on QRS morphology and duration.
2) Assess the effects of flecainide on the number of VT runs in 7-day ECG recordings.
3) Assess the effects of flecainide on the frequency of atrial premature beats in 7-day ECG recordings.
4) To demonstrate feasibility of enrollment of rare arrhythmia ARVC patients in a randomized study in preparation for the planned future large clinical trial with VT/VF as the primary endpoint.

2. STUDY DESIGN

2.1. Overview

This is a randomized double-blinded placebo-controlled crossover trial on the effect of flecainide on the frequency of ventricular arrhythmias of 38 ARVC patients. The crossover design requires a 10-week treatment with each patient receiving flecainide 100 mg bid and placebo in a blinded randomized order.

2.2. Rationale for Study Design

The cross over design of this study is suitable for the ARVC population, as the disease is chronic and the proposed intervention is not curative for the disease. The innovation of this trial is the concept of randomized trial in ARVC patients to test antiarrhythmic therapy. To date there has not been a randomized trial in ARVC patients to evaluate any therapy including ICD therapy, ventricular tachycardia ablation, or pharmacological drugs. As indicated, prior publications regarding pharmacological therapies including antiarrhythmic therapies have shown conflicting results.

2.3. Rationale for Dosage

Based on clinical experience and safety profile of flecainide a uniform dose of 100 mg of flecainide bid will be used. This dose is recommended in FDA-approved prescription information. This also was initial dose in the catecholaminergic polymorphic ventricular tachycardia trial although the median dose was 150mg bid (Kannankeril 2017). In the study “Safety and efficacy of flecainide in subjects with Long QT-3 syndrome with delta KPQ mutation” (Moss et al. 2005) an average 100 mg per day dose produced significant effects on late sodium current that caused significant QTc shortening.

3. CHARACTERISTICS OF THE RESEARCH POPULATION

3.1. Subject Characteristics

a) **Number of Subjects:** This trial will enroll 38 subjects at 10 enrolling sites who meet study inclusion and exclusion criteria as described in Section 3.2.
b) **Gender and Age of Subjects**: Male or female subjects aged 18 years or older.
c) **Racial and Ethnic Origin**: There are no restrictions on race or ethnicity in this study.

3.2. Inclusion and Exclusion Criteria

Inclusion criteria:

- Age ≥ 18 years.
- Subjects who have been diagnosed with ARVC and meet 2010 Modified Task Force Criteria for ARVC as affected.
- At minimum 500 VPBs on the most recent 24-hour Holter monitor recording prior to consent or after consent if a subsequent recording is required after 5 day washout following discontinuation of anti-arrhythmic medication.
- Functioning implanted cardioverter defibrillator with remote interrogation capability.
- Subjects should be on a beta-blocker including metoprolol, propranolol, atenolol, nadolol, carvedilol or bisoprolol unless contraindication to beta-blockers exists.
- Persons prescribed quinidine, procainamide, propafenone, disopyramide, dronedarone phenytoin, mexilitene, may be included after 5 day washout period with subsequent 24-hour Holter obtained after washout period.
- Persons prescribed sotalol may be included after 5 day washout period during which another beta-blocker may be administered with subsequent 24-hour Holter obtained.
- Subject and personal physician and or cardiologist must agree not to use any antiarrhythmic medications during the 10 weeks of participation, unless needed for management of life-threatening arrhythmias.
- All subjects must agree to use medically acceptable contraceptive measures during participation unless documented as surgically sterile or post-menopausal (no menstrual periods for more than one year).

Exclusion criteria:

- Prescribed amiodarone or dofetilide at the time of consent.
- Left ventricular ejection fraction ≤40% by any imaging modality: echocardiography, angiography, CMRI, or cardiac nuclear test on the most recent test.
- NYHA heart failure class III or IV at time of consent.
- Prior myocardial infarction at any time in the past.
- Pacemaker dependent rhythm at the time of consent.
- Renal impairment (GFR <30 mL/min/m2).
- Prior diagnosis of severe hepatic impairment.
- Pregnant or plan to become pregnant during the course of the trial (Flecainide has not been adequately studied in pregnant women). Pregnancy test is required for women of child-bearing potential prior to randomization.
- Participating in any other interventional clinical trial.
- Unwilling or unable to cooperate with the protocol.
- Lives at such a distance from the clinic that travel for the consent visit would be unusually difficult.
- Decisionally impaired adults, those of questionable capacity, those who cannot manage taking the study drug per the prescribed regimen, and those who cannot consent for themselves will not be recruited for this study.
- Unwilling to sign the consent for participation.

3.3. Discussion of Subject Population

There is no known effective antiarrhythmic treatment in ARVC patients. Flecainide is a promising option, but there are no clinical trials to prove its efficacy and safety in these patients. The proposed pilot study to assess the effect of flecainide on cardiac arrhythmias detected by long-term ECG monitoring will provide preliminary data. Assessing safety of this therapy is of major importance in view of the results of the CAST trial that showed increased mortality in patients with ischemic heart disease after myocardial infarction treated with antiarrhythmic drugs including flecainide (Echt et al. 1991). To assure the safety of subjects the study is including only ARVC patients with ICDs and excluding patients with significant left ventricular dysfunction and significant heart failure, who constitute a small minority of ARVC patients.

4. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT

4.1. Method of Subject Identification and Recruitment

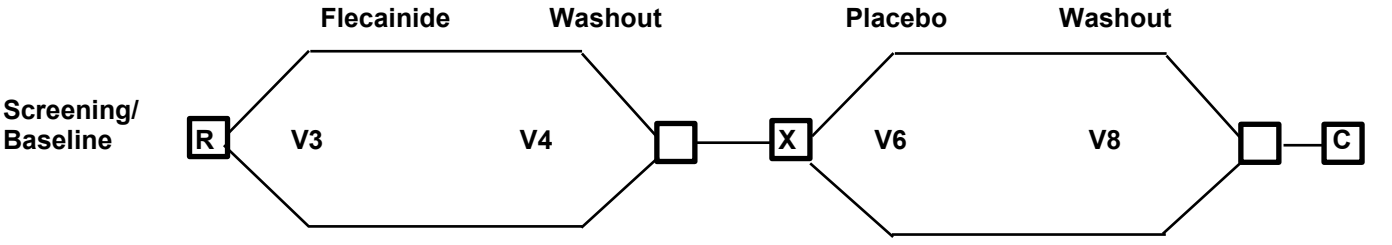
Subjects will be recruited from US enrolling centers.

4.2. Process of Consent

The site investigator and/or study coordinator will consent subjects in this study. The consent document will be used as a guide for the verbal explanation of the study and will be the basis for a meaningful exchange between the investigator and the potential subject. The subject's signature provides documentation of agreement to participate in a study, but is only one part of the consent process. The consent document will not serve as a substitute for discussion and the potential subject will be invited to ask any questions or concerns that will be answered by the study team members. Once a participant indicates that he or she does not want to take part in the research study, this process stops. The potential subject will be given sufficient opportunity to consider whether or not to participate. Refusal to take part or withdraw from the study at any time will not interfere with the future medical treatment of the potential subject.

5. METHODS AND PROCEDURES

This is a randomized double-blinded placebo-controlled crossover trial on the effect of flecainide on the frequency of ventricular arrhythmias of 38 ARVC patients. The crossover design shown below requires a 10-week treatment with each patient receiving flecainide 100 mg bid for 28 days and placebo for 28 days in a blinded randomized order. The Figure 4 and Table 2 below show the study design and the schedule of activities.



R – randomization
X – crossover, ICD interrogation
V3 and V6 - remote ICD Interrogation
V4 and V8 – in home with ECG, blood draw, 7 day ZIO-Patch
C – closeout, ICD interrogation

Figure 4: Design of the trial.

Table 2. Schedule of Activities.

	Visit 0[a]	Visit 1[a]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
	Screen	Ran-domize	Drug Initia-tion				Second Drug Bottle				Close-out
Start Medication Weeks	-4-0 weeks	-4-0 weeks	0	1 week ± 2 days	3 weeks ± 2 days	4 weeks ± 2 days	5 weeks ± 2 days	6 weeks ± 2 days	8 weeks ± 2 days	9 weeks ± 2 days	10 weeks ± 2 days
In person visit	Yes in clinic	No	No By phone	No by phone	In home or in clinic[d]	No by phone	No by phone	No by phone	In home or in clinic[d]	No by phone	No by phone
Study Periods			**Period 1**				**Period 2**				
Informed Consent	✓										
Pregnancy Test [b]	✓										
Medical History	✓										
Holter Monitor [c]	✓										
ECG	✓				✓				✓		
Randomization		✓									
Blood Sample					✓				✓		
7-day ECG Monitor					✓				✓		
Remote ICD interrogation				✓				✓			✓
Adverse event				✓	✓	✓	✓	✓	✓	✓	✓
Drug Dispense/Accountability			✓				✓			✓	
Stop and return study drug and ZIO-Patch						✓				✓	
Study Closeout											✓

a - Visits 0 and 1 could be done on the same day.
b - Pregnancy test must be obtained prior to randomization
c – Holter Monitor for subjects have had a washout of antiarrhythmic therapy
d - Visit at home will be done by specialized services with: ECG recording and blood draw; ZIO-Patch could be self-applied by subject or by study staff member. These visits could take place in a clinic if this is what subject and investigator are agreeable to.

5.1. Visits

5.1.1. Visit 0: Subject Screening and Consent

Each potential subject will have inclusion and exclusion criteria verified by study personnel prior to approaching a potential subject for consent. The consent process begins with the protocol described to them by one of the physicians or research coordinators at the enrolling site. Potential subjects will sit down with the coordinator or physician and have the opportunity to ask questions. Those who meet inclusion/exclusion criteria will then be asked to sign consent for study participation. At this time they will sign an "informed consent" form that is fully approved by the local IRB following local IRB consent administration regulations. It is the responsibility of the investigator to ensure that subjects are eligible to participate in the study prior to enrollment and throughout the study. Once informed consent has been obtained, all screening tests and procedures have been assessed and study eligibility has been confirmed, subjects will be assigned a unique subject identification number. The enrolling site will enter data in the web base system and the system will assign the subject ID after study eligibility criteria are met. The scheme for assigning subject ID is as follow: first 2 numbers are assigned for enrolling site and will not change for duration of the study. Next two numbers are specific to a randomized subject in the enrolling site.

The principal investigator ensures that informed consent from each potential research participant will be obtained by an IRB approved consent designee and documented. The following persons may obtain consent: the principal investigator, sub-investigators, or study team members listed on the IRB application form as a consent designee. Each individual who will interact with potential research participants to obtain consent will submit evidence of human subject compliance training per local IRB regulations.

After written informed consent is obtained, a medical history and an ECG will be obtained from the subject. Any woman of childbearing age must have a negative pregnancy urine or blood test prior randomization, unless the woman is surgically sterile or post-menopausal (no menstrual periods for more than one year). Investigators will verify that subjects must use a medically acceptable method of birth control prior to study entry and while participating in the study.

Subjects are expected to be on one of the following beta-blockers unless contraindicated: metoprolol, propranolol, atenolol, nadolol, carvedilol or bisoprolol. Subjects on antiarrhythmic medications including: sotalol, mexilitene, flecainide, quinidine, procainamide, propafenone, disopyramide, dronedarone, or phenytoin will require washout lasting a minimum of 5 days and a subsequent 24-hour Holter recording demonstrating at least 500 VPBs prior to being considered for randomization. Study sites are provided with dedicated Holter recorders to be used if needed. Patients should return Holter recorders in person or by mail to the enrolling site personnel who will upload Holter files into the University of Rochester Box.com system for analysis. Enrolling centers will be informed about the results of 24-hour Holter analysis within 2 business days. Subjects not meeting eligibility criteria of at least 500 VPBs in 24-hour Holter after washout of medication used prior to the study drug initiation will be withdrawn and replaced.

5.1.2. Visit 1: Randomization (Visit 1 could take place on the same day as Visit 0):

During this study visit:

- Study personnel will confirm subject's eligibility if not possible during Visit 0. No patient contact is needed if subject remains eligible.
- Study personnel will randomize subject via computer entry of the study data which will trigger the University of Rochester IDS to ship study drug, diary, ZIO-Patch with instructions, blood drawing kit, and prepaid return envelope for next day delivery via Federal Express to subject. The Zio-Patch is identified only by a serial number and will be sent to the manufacturer to retrieve information regarding ECG findings.
- For subjects requiring a 24-hour Holter recording after washout from antiarrhythmic medication, eligibility will need to be reconfirmed based on number of VPBs found on holter monitoring
- If subject is found to have less than 500 VPBs in 24-hour Holter, the subject will be informed that he/she will be withdrawn from the study.

5.1.3. Visit 2: Phone Visit (within 7 days from Visit 1)

The following tasks will be performed and documented at the Visit 2:

- Enrolling site staff member will confirm receipt of study shipment and review contents with subject.
- Review study drug prescribing regimen, diary and emphasize importance of compliance with subject. Instruct patient to begin taking study drug and record the date of the subject's first dose of study medication.

5.1.4. Visit 3: Phone visit (One week after initiating study drug**)**

During this follow-up visit:

- An ICD interrogation (with a manual transmission by patient, if system is not automatic) from remote device monitoring system should be obtained.

- Study drug prescribing regimen, diary and importance of compliance will be reviewed with subject.
- Adverse events will be assessed and reported.

5.1.5. Visit 4: **In person visit in home or in clinic** (Three weeks after initiating study drug)

During this follow-up visit:

- A standard 12-lead ECG recording will be performed.
- Blood sample will be drawn for flecainide levels. A teaspoon (5ml) of blood is needed for this sample. This blood sample will be sent to a specialized lab. Paper copy of ECG will be uploaded to the Box.com at the University of Rochester.
- A ZIO-Patch (a small, adhesive, water-resistant one lead ECG recorder) will be applied to the chest for a continuous 24-hour monitoring over 7 days. ZIO-Patch could be self-applied or applied by study staff member. At the end of the 7 days the patch must be removed and returned to the University of Rochester
- Review study drug prescribing regimen, diary and importance of compliance will be reviewed with subject.
- Adverse events will be assessed and reported.

5.1.6. Visit 5: **Phone visit** (Four weeks after initiating study drug)

During this follow-up visit study:

- Patient will be reminded to:
    - stop study drug from first bottle (begin wash out period)
    - remove ZIO-Patch
    - return the medication bottle, diary and ZIO-Patch in a pre-paid mailer to the University of Rochester.
- Adverse events will be assessed and reported.

5.1.7. Visit 6: **Phone visit** (Five weeks after initiating study drug)

During this follow-up visit:

- Enrolling site will confirm receipt of study shipment and review contents with the subjects. Shipment will include: second bottle of study drug, diary, Zio-Patch with instructions, blood drawing kit and prepaid return envelope for next day delivery via Federal Express.
- Study drug prescribing regimen, diary and importance of compliance will be reviewed with subject.
- Instruct patient to begin taking study drug and record the date of the subject's first dose of study medication from second bottle. Adverse events will be assessed and reported.

5.1.8. Visit 7: **Phone visit** (Six weeks after initiating study drug)

During this follow-up visit:

- An ICD interrogation (with a manual transmission by patient, if system is not automatic) from remote device monitoring system will be obtained.
- Study drug prescribing regimen, diary and importance of compliance will be reviewed with subject.
- Adverse events will be assessed and reported.

5.1.9. Visit 8: **In person visit in home or in clinic home visit** (Eight weeks after initiating study drug)

During this follow-up visit:

- A standard 12-lead ECG recording will be performed.
- Blood sample will be drawn for flecainide levels. A teaspoon (5ml) of blood is needed for

this sample. This sample will be sent to a specialized lab for analysis and paper copy of ECG will be sent to the University of Rochester.

- A ZIO-Patch (a small, adhesive, water-resistant one lead ECG recorder) will be applied to the chest for a continuous 24-hour monitoring over 7 days. ZIO-Patch could be self-applied or applied by study staff member. At the end of the 7 days the patch must be removed and returned to the University of Rochester
- Study drug prescribing regimen, diary and importance of compliance will be reviewed with subject.
- Adverse events will be assessed and reported.

5.1.10. Visit 9: **Phone visit** (Nine weeks after initiating study drug)

During this follow-up visit study:

- Patient will be reminded to:
  - stop study drug from second bottle
  - remove ZIO-Patch
  - return the medication bottle, diary and ZIO-Patch in a pre-paid mailer to the University of Rochester.
- Adverse events will be assessed and reported.

5.1.11. Visit 10: Phone visit (Ten weeks after initiating study drug)

During this follow-up visit:

- An ICD interrogation (with a manual transmission by patient, if system is not automatic) from remote device monitoring system will be obtained.
- Adverse events will be assessed and reported.
- Subject will be informed by study personnel regarding subsequent medical management regarding antiarrhythmic medications to be taken after the closeout of the study as per decision of enrolling center physician.
- Close out the study participation of the subject.

5.2. Treatment Dosage and Administration

Each subject will take 1 blinded capsule of study drug (flecainide or a placebo) dose BID per randomization scheme for 28 days. After 28 days there will be a 7-day washout period. At the end of the washout period, each subject will then take 1 blinded capsule of study drug (flecainide or placebo) for the next 28 days.

5.3. Efficacy Assessments

During this pilot clinical trial, efficacy of flecainide on cardiac rhythm will be assessed by 7-day ECG monitoring with ZIO-Patch to determine overall burden of premature ventricular contractions. In addition, remote ICD monitoring of the subjects previously implanted ICD device will be used to account for episodes of ventricular tachycardia ventricular fibrillation.

5.4. Safety Assessments

The assessments that will be performed to evaluate safety include medical history, standard 12-lead ECG, implanted device interrogation and the use of the 7-day ZIO-Patch monitor and will be quantified by:

a) VPBs on 7-day ECG monitoring to determine the possibility of proarrhythmia defined as a 3-fold increase in number of VPBs;

b) Total burden of nun-sustained and sustained (ICD treated and untreated) VT episodes on interrogation of ICDs evaluated after the first week and after the fourth week of study drug administration with a 5-fold increase in number of VT episodes defining proarrhythmia.

c) QRS prolongation on ECG defined as >40ms in comparison to baseline and the new presence of the Brugada pattern of the ECG. We expect 17-29% prolongation of the QRS but prolongation >30% (40ms) will be unusual. The appearance of cove-type Brugada pattern will be monitored.

5.5. Assessment of Subject Compliance

Study drug compliance will be emphasized during each contact with the study subject. Compliance will also be assessed by count of returned study drug and plasma concentrations of flecainide.

5.6. Costs to the Subject

Study drug, the ZIO-Patch monitor, ICD interrogation, ECG during in person visit and serum flecainide level will be paid for by study funds**.**

5.7. Payment for Participation

Subjects will not be paid for participation.

5.8. Return of Individual Research Results

Research results will not be provided to subjects.

6. CONCOMITANT AND DISALLOWED MEDICATIONS

Subjects will be allowed to take any prescribed beta-blocker including: propranolol, metoprolol, atenolol, nadolol, carvedilol, and bisoprolol. Disallowed antiarrhythmics medications include: sotalol, quinidine, procainamide, disopyramide, lidocaine, phenytoin, mexilitene, propafenone, dofetilide, ibutilide, amiodarone, dronedarone, verapamil, diltiazem. Subjects and their physician treating them for ARVC must agree to discontinue use of these medications to participate in this study for their safety. These medications could be administered after participation of a subject is completed per physician discretion.

7. SUBJECT WITHDRAWALS

Subjects will be advised in the written informed consent forms that they have the right to withdraw from the study at any time without prejudice. Subjects may be withdrawn as lost to follow-up by the investigator if they do not follow-up after 4 documented attempts to contact the subject. These subjects will not undergo any additional study activities prior to withdrawal.
Subjects not meeting eligibility criteria of at least 500 VPBs in 24-hour Holter after washout of medication used prior to study drug initiation will be withdrawn and replaced.

8. STUDY DRUG ADMINISTRATION/ASSIGNMENT

8.1. Study Drug

This study is IND exempt per FDA; meeting the criteria set forth in 21 CFR 312.2(b) and 320.31(b). The University of Rochester Investigational Drug Service (IDS) will prepare and dispense the study medication. All capsules of study drug will be identical in appearance (same size and color). Blinded capsules will be prepared via over-encapsulation. Active doses will

consist of 2 x 50 mg flecainide tablets placed inside larger opaque colored capsules and backfilled with lactose. Placebo doses will consist of the same opaque colored capsules filled with inert powder (lactose). Study subjects will be instructed to swallow all capsules whole and not to open them. Each subject will be dispensed 56 blinded doses per treatment period, per randomization (2 doses/day x 28 days = 56 doses per period). The University of Rochester Investigational Drug Service (IDS) will receive the subject randomization assignment and prepare and ship study drug directly to the subject for next day delivery via Federal Express. At the time of crossover and at the study closeout, bottles will be collected for study drug accountability. Subjects will be provided a pre-paid mailer to return unused study drug to the University of Rochester IDS.

8.2. Dosage of Study Drug

The active dosage of study drug is two 50 mg tablets of flecainide over encapsulated. The matching placebo will be filled with inert lactose.

8.3. Subject Enrollment/Randomization

The University of Rochester IDS will package the capsules into blinded labeled bottles. Site personnel will randomize subjects by using a computer by entry of subject data to confirm eligibility in the study electronic data capture system. If all conditions are satisfied in the computer, the subject is randomized by checking a field on the eligibility form. The site will then send via facsimile subject contact information to the University of Rochester IDS. University of Rochester IDS will dispense study medication per the randomization assignment and ship study drug via Federal Express for next day delivery.

8.4. Accountability of Investigational Supplies

At the time of crossover and at the study closeout, the study subject will ship the study drug containers back to the University of Rochester IDS for study drug accountability.

8.5. Subject Withdrawal of Study Drug

This is intention to treat trial. If the subject decides not to take study drug, the subject may remain in the study and continue study procedures for the duration of their participation.

8.6 Emergency Drug Disclosure

In the event of a clinical emergency, provisions have been made for the enrolling site Principal Investigator to obtain quick disclosure of treatment assignment for an individual subject in the study. A clinical emergency is defined as any clinical event or laboratory test that the enrolling investigator (in consultation with Dr. Hugh Calkins from The John Hopkins University the Clinical Director and Co-PI of this study) determines requires immediate disclosure of the assigned treatment group (flecainide versus placebo) to which the subject has been assigned in order to treat the adverse event. Emergency disclosure is not required to determine study drug causality of a serious or non-serious adverse event.

Disclosure of treatment assignment does not require a subject to be withdrawn from the study. The subject may remain in the study, and be provided the necessary treatment required for their condition as prescribed by their private physician.

9. DEVIATIONS

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the Data Coordinating Center (DCC) and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which

affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the DCC using the EDC system. Sites may also be required to report deviations to the IRB, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including notification, enrolling site re-training, or discontinuation) will be put into place by the DCC.

10. SAFETY AND REPORTABLE EVENTS

10.1. Adverse Event Definition

An adverse event is any symptom, sign, illness, or experience that develops or worsens during the course of the study whether or not considered drug-related. An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action. All serious and unexpected adverse events must be reported per definition in Section 9.2. Diagnostic and therapeutic invasive and non-invasive procedures (including surgeries) should not be reported as adverse events. However, the medical condition for which the procedure was performed should be recorded if it meets the criteria for an adverse event.

10.1.1. Serious Adverse Event

A serious adverse event is defined as any adverse medical experience that results in any of the following outcomes:

- death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in permanent impairment of a body structure, a body function or cancer;
- requires medical or surgical intervention to prevent permanent impairment or damage;
- is due to overdose;
- leads to fetal distress, fetal death or a congenital abnormality or birth defect**.**

10.1.2. Unexpected Adverse Drug Experience

This is defined as an adverse drug experience that is not listed in the current labeling for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

10.2. Recording Adverse Events

At each subject contact the site study staff will assess adverse events per definition in Section 10.1 by recording all voluntary complaints of the subject and by assessment of clinical

and laboratory features. At each study visit, the subject should be questioned directly regarding the occurrence of any adverse experience since his/her last contact.

All adverse events, whether observed by the Investigator, elicited from or volunteered by the subject, should be documented on or following randomization date and within 5 calendar days of date reported to the enrolling site. Ventricular tachyarrhythmias will be documented in the ICD interrogations. Each adverse event will include a brief description of the experience, the date reported to the enrolling site, the date of onset, the date of resolution, the duration and type of experience, the severity, and relationship to subject condition or study drug, contributing factors, and any action taken. Event status if not resolved will be tracked at each follow-up with final status indicated at the conclusion of study participation e.g., resolved, ongoing, unresolved.

10.3. Responsibilities for Reporting Serious and Unexpected Adverse Events

The Investigator will record all adverse events per Section 10.1 definition that occur during the study period in the appropriate source documents and/or AE case report form with 15 calendar days of the date reported to the enrolling site for serious events and 15 days for other adverse events. The study period for reporting adverse events (e.g., from the time of randomization to final study visit) will be 10 weeks, the local IRB will be notified by the enrolling site per local IRB regulations. The Investigator will comply with local regulations regarding the reporting of adverse events. Adverse events reported by enrolling sites will be promptly reported to Data Coordinating Center Institutional Review Board, NIH, and FDA per local regulations. Similar to other clinical trials conducted by University of Rochester investigators, adverse events will be immediately reported to the Data Coordinating Center (DCC) via dedicated web-based case report forms to the PI (Dr. Zareba). The DCC will be forwarding relevant reports to the Chair of DSMB for review and Chair will determine whether individual case will require immediate assessment by full DSMB committee or it could be assessed during electively scheduled DSMB meeting. The main point of assessment by DSMB will be to judge whether given adverse event could be related to study drug.

11. RISK/BENEFIT ASSESSMENT

11.1. Potential Risks

11.1.1. Potential Risks to Patients Undergoing Treatment with Flecainide

Flecainide is an antiarrhythmic drug approved by the Food and Drug Administration in the US since 1982 to suppress cardiac arrhythmias and is predominantly used for atrial arrhythmias. Flecainide was studied in the CAST trial (Echt et al. 1991) in patients after myocardial infarction with ventricular arrhythmias and was associated with a higher incidence of mortality or non-fatal cardiac arrest (19/323) as compared with its matching placebo (7/318). The most serious adverse reactions reported for flecainide in patients with ventricular arrhythmias were new or exacerbated ventricular arrhythmias which occurred in 6.8% of patients and new or worsened congestive heart failure which occurred in 3.9% of patients. In some patients, flecainide treatment has been associated with episodes of unresuscitatable ventricular tachycardia or ventricular fibrillation. There have also been instances of second- (0.5%) or third-degree (0.4%) AV block. A total of 1.2% of patients developed sinus bradycardia, sinus pause, or sinus arrest. The frequency of most of these serious adverse reactions probably increases with higher trough plasma levels, especially when these trough levels exceed 1.0 µg/mL, unlikely to occur with our propose dose of 100 mg bid.

Patients with structural heart disease, treated with flecainide for supraventricular arrhythmias, may be at increased risk for proarrhythmia and cardiac adverse events. The use of

flecainide in these patients has been associated with life-threatening and occasionally fatal ventricular arrhythmias. Therefore, in these patients, especially in the presence of impaired left ventricular function with ejection fraction ≤ 40%, flecainide should be used with extreme caution, preferably after other antiarrhythmic drugs have been tried or considered inappropriate. Because flecainide has a mild negative inotropic effect, it may cause or worsen congestive heart failure, particularly in patients with cardiomyopathy, pre-existing severe heart failure (NYHA functional class III or IV) or ejection fractions ≤ 40%. Flecainide should therefore be used cautiously in patients who are known to have a history of congestive heart failure or myocardial dysfunction. When used per current FDA approved prescription information flecainide is considered a safe drug.

The use of flecainide in this study had been approved by FDA with the Investigational New Drug (IND) exempt. The study team will carefully monitor studied patients regarding any side effects of the study drug. One of important secondary aims of this study is to evaluate safety of flecainide administration in ARVC patients and our design involving only patients with ICD implanted provides a safety measure in case of proarrhythmia.

The most commonly reported non-cardiac reactions experienced by patients with ventricular arrhythmias taking 200 mg/day were dizziness 11%, visual disturbance 5.4% (includes blurred vision, diplopia, visual field effects, photophobia), headache 4.5%, nausea 4.9% and dyspnea 5.2%.

11.1.2. Blood Draws: Blood draws may cause pain, redness, bruising or very rarely infection at the site of the needle stick. Rarely some people faint.

11.1.3. ECG, ZIO-Patch and Holter Monitoring (if needed)**:** Other than possibly experiencing some minor skin irritation from the electrodes there are no anticipated risks related to complete the electrocardiogram, ZIO-Patch or holter monitor.

11.1.4. Loss of confidentiality: As this study involves the use of identifiable, personal information, there is a chance that a loss of confidentiality will occur. The researchers have procedures in place to lessen the possibility of this happening. All personal information obtained from subjects is removed and subjects are given a unique study ID number. Access to study records is limited and any information that may potentially identify a subject will not be used in publications or reports.

11.1.5. Pregnancy: If a subject or their partner becomes pregnant during this study, there are unforeseeable risks to the unborn baby.

11.2. Protection against Risks

To minimize the risks of flecainide administration in ARVC patients, all enrolled subjects must have an implanted functioning defibrillator. Their cardiac left ventricular ejection fraction must be ≥ 40% by any cardiac imaging modality. These subjects may continue concomitant use of beta blocker therapy, as pro-arrhythmic effects of flecainide in studied patients with depressed or preserved ejection fraction was eliminated by concomitant administration of beta-blockers (Kennedy et al. 1994: Kennedy 1997).

11.3. Potential Benefits to Subjects

There is no direct benefit to the subjects.

11.4. Alternatives to Participation

If a subject does not want to participate in the study, they will receive standard medical care for their condition

12. CONFIDENTIALITY OF DATA AND INFORMATION STORAGE

Efforts will be made to maintain confidentiality of study data. All study data will be coded with an unidentifiable study code. The study coordinator for each enrolling site will locally maintain an internal key linking the subject's name with study data which will not be shared outside of the enrolling site. Subjects' personal information will be kept confidential and will not be released without his/her written permission, except as described in this section or as required by local law. Subject's personal information may be shared, to the extent necessary, among the research staff, with the Institutional Review Board and for research oversight as dictated by local regulations.

All information and data collected concerning subjects or their participation in this investigation will be considered confidential by the DCC. No social security numbers or direct identifiers will be collected by the DCC. Study data collected during this investigation may be used by the DCC for the purposes of this investigation, publication, to support future research and/or other business purposes. HIPAA authorization will be obtained from each subject by every enrolling site per local regulations and enrolling sites are expected to follow all local regulations related to data collection.

All data will be submitted using a password protected electronic data capture system with access limited to only those authorized by the Principal Investigator at each enrolling site per an electronic access request document with delegation signed by the Principal Investigator. All study data will be coded with a study subject number that is assigned at the time of treatment randomization and cannot be linked to the patient's identify except by internal records maintained at the individual enrolling sites. Source document records to support event adjudication or core laboratory analysis will be redacted of all PHI before being sent to the coordinating center and only the subject ID will be recorded to link the subject to this data. The electronic data will be directly extracted from web system for data collection.

13. RESEARCH INFORMATION IN MEDICAL RECORDS

Indication of study participation in medical records will be left to local enrolling site standards of documentation of study participation

14. DATA ANALYSIS AND MONITORING

14.1. Sample Size Determination

Enrolling 38 subjects and allowing for up to 10% drop-out due to withdrawal or death, we expect at least n=34 fully evaluable subjects in the study. As shown in Table 2 below, this sample size will provide >90% power to detect a relative reduction of 40% in VPB burden, using a two-sided 0.05 level paired t-test, assuming the correlation between VPB is at least 0.5. If the correlation is 0.7, the power to detect a more modest 30% relative reduction will be 84%.

Power	Relative Reduction in VPB	Correlation between VPB burden
84%	30%	0.7
62%	30%	0.5
99%	40%	0.7
90%	40%	0.5

Detecting a relative reduction of 30-40% in VPB frequency (flecainide vs placebo) is equivalent to detecting a shift of 0.515-0.737 units in $\log_2$ (VPB), which has an estimated standard deviation (SD) of 1.28 based on our pilot data. If the correlation between VPB

measures (before and after crossover) were at least 0.5, then the SD of the change in $\log_2$ (VPB) would be at most 1.28, whereas if the correlation were 0.7 the SD of the change would be 0.99. An evaluable sample size of n=34 patients provides 90% power to detect a 40% reduction in VPB frequency using a 2-sided 0.05 level paired t-test applied to $\log_2$ (VPB), assuming the correlation is 0.5. Accounting for 10% loss to follow-up, we will randomize n=38 patients. Power of the proposed linear mixed effects model analysis will be slightly higher, since it can accommodate partial information from any subjects who might be lost to follow-up.

14.2. Planned Statistical Analysis

The effect of flecainide on $\log_2$(VPB) will be analyzed using a linear mixed effects analysis of variance model with fixed effects for treatment and period and a random effect for subject. The estimated treatment effect, with a 95% confidence interval (CI), will be exponentiated to back-transform to the original scale, resulting in an estimated relative reduction in VPB along with 95% CI. The mixed effects model incorporates available data from all randomized subjects and accommodates missing data in an appropriate way under the "missing at random" assumption. The analyses will be repeated including only subjects who complete both treatment periods, but these analyses will be considered as secondary sensitivity analyses. It is anticipated that the withdrawal rate in this trial will be minimal and that the two methods of analysis will yield consistent results. Similar methods will be used to analyze secondary outcome variables. Adverse events will be tabulated by treatment, severity, and perceived relationship to study drug.

14.3. Data and Safety Monitoring

A data and safety monitoring board (DSMB) will be appointed to independently monitor the conduct and the outcome of the trial. The DSMB will be responsible for monitoring the safety and well-being of the patients participating in this study and ensuring the ethical conduct of the trial. The safety endpoints consist of ECG and ICD-derived measures of ventricular arrhythmogenicity. The main focus of DSMB activity will be to monitor events obtained from ICD interrogations obtained after 1 week and after 4 weeks of each treatment, data from 7 day ECG monitoring and clinical adverse events that could be related to the study medication. Data on clinical events including adverse events, HF hospitalizations, ventricular tachyarrhythmias requiring ICD therapy, and death will also be collected and provided to the DSMB for evaluation of risks associated with the drug therapy.

In the above capacities, the DSMB will be advisory to the Executive Committee responsible for overseeing the design, conduct, and data collection/analysis of the trial. The Executive Committee for the trial consists of: the trial Principal Investigator, the Co-Principal Investigator the Biostatistician and two site investigators.

The board will be comprised of 3 independent members: (1) a statistician with experience in clinical trials; (2) 1 cardiologist with expertise in drug clinical trials; and (3) 1 electrophysiologist with expertise in device implantation and experience antiarrhythmic drugs. The DSMB will meet before trial commencement and 2 times in year 1 and three times in year 2. It is anticipated that these meetings will take place via conference call. One of the clinical cardiologists will be selected to chair the committee and will serve as the principal representative of the group.

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