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# Late Sodium Current Blockade in High-Risk ICD Patients

## Ranolazine ICD Trial (RAID)

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## A. SPECIFIC AIMS

Patients with implantable cardioverter-defibrillators (ICDs) who develop ventricular tachyarrhythmias requiring appropriate ICD therapy are at significantly increased risk of mortality, recurrent arrhythmias, and hospitalization for CHF and other cardiac causes.[1-3] There are limited treatment options for patients at high risk of arrhythmic events. Beta-blockers alone do not provide enough protection, sotalol has limited effectiveness, and amiodarone although effective in some groups of patients is used infrequently due to its side effects and limitations of a long-term use.[4-8]

Ischemia and cardiomyopathies are associated with a sodium overload of myocardial cells and the late sodium current plays a pivotal role in this process.[9-14] Sodium overload leads to calcium overload of myocardial cells. The consequence of this overload is increased vulnerability of myocardium to ventricular tachyarrhythmias as well as increased impairment of diastolic relaxation of myocardium thereby augmenting the risk of ischemia and myocardial damage.[9,10,13]

Ranolazine is a novel drug with anti-ischemic and antiarrhythmic properties that uniquely blocks late sodium current, decreases intracellular calcium overload, and improves diastolic relaxation of the ventricles.[15-18] Ranolazine is a piperazine derivative with a molecular structure similar to lidocaine. Ranolazine inhibits late sodium current without a significant effect on peak sodium current (no QRS changes), and also inhibits $I_{Kr}$, $I_{Ca}$, and $I_{Ks}$.[16] The $I_{Kr}$ blocking effect contributes to minor action potential duration prolongation and QT prolongation. However, it does not causes early after depolarizations and ventricular tachyarrhythmias (similarly to antiarrhythmic profile of amiodarone) [16]. The antiischemic and antiarrhythmic properties of ranolazine might decrease the likelihood of arrhythmic events and improve the clinical course of ICD patients. Improvement of diastolic myocardial relaxation has been observed with ranolazine in preclinical conditions, heart failure patients, and in LQT3 patients.[13,19,20] Diabetic patients have shown improvement in glycemic control on ranolazine to further contribute to the beneficial effect of the drug. We propose a double-blind placebo-controlled clinical trial randomizing high-risk ICD patients who will be treated with ranolazine or placebo in addition to optimal medical therapy.

**Primary aim of the study is:**
To determine whether ranolazine administration will decrease the likelihood of a composite arrhythmia endpoint consisting of ventricular tachycardia or ventricular fibrillation (VT/VF) requiring antitachycardia pacing (ATP), ICD shocks, or death;

In addition to the above primary specific aim, there are several secondary aims that will be addressed in this trial by utilizing data from detailed records of arrhythmia episodes provided by implanted devices, and comprehensive data on hospitalizations during follow-up.

**Specific secondary aims are as follows:**
1. to determine whether ranolazine administration will decrease the likelihood of a composite arrhythmia endpoint consisting of VT or VF requiring ICD shock or death (while excluding VT/VF requiring just ATP)
2. to determine whether ranolazine administration will decrease the likelihood of composite primary endpoints consisting of hospitalization for cardiac causes (including not only hospitalization for heart failure, but also hospitalizations related to cardiac arrhythmias, myocardial infarction or ischemia) or death, whichever occurs first.
3. to determine whether ranolazine administration will decrease the likelihood of a composite secondary endpoint consisting of CHF hospitalization or death;
4. to determine whether ranolazine therapy will decrease the number of repeated hospitalizations for cardiac causes.
5. to determine whether ranolazine administration will decrease the likelihood of repeated ICD therapies (not just first therapy)
6. to determine whether ranolazine administration will decrease the likelihood of inappropriate shocks (a decrease in episodes of atrial fibrillation triggering inappropriate therapy) evaluating the risk of first and risk of repeated inappropriate shocks.

7. to determine whether ranolazine therapy will be associated with improvement in exercise capacity measured by the 6-minute walk test (6MWT) and in the quality of life measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ)

8. to evaluate the safety of ranolazine therapy utilizing ICD interrogation data documenting all types of ventricular tachyarrhythmias (including torsade de pointes).

## B. BACKGROUND AND SIGNIFICANCE

### B.1. Population at High Risk of Cardiac Events

Over the last 15 years, several key clinical trials were conducted evaluating strategies to reduce mortality in high-risk patients defined based on prior history of cardiac arrest or documented ventricular tachyarrhythmias (secondary prevention of mortality) or in patients without history of arrhythmic events but with clinical characteristics indicating high risk for arrhythmias and mortality (primary prevention of mortality).[21-25] Most of these trials showed that ICD therapy reduced mortality more effectively when compared to either amiodarone or conventional therapy. As a consequence of these clinical trials, an evidence based medicine is currently being practiced with over 100,000 ICDs implanted every year in the US and about 250,000 worldwide. However, as documented by these pivotal clinical trials and by reports in independent patients' cohorts, the long-term mortality of patients with ICD devices remains high.[21-25]

Our MADIT II data analyses[1,21] documented that of 720 patients with an ICD, 169 patients received 701 antiarrhythmic device therapies including antitachycardia pacing or ICD shock for ventricular tachyarrhythmias (VT) or ventricular fibrillation (VF). The probability of death 1 year after first therapy for VT or VF was 20%. The hazard ratios for the risk of death due to any cause in those who survived appropriate therapy for termination of VT and VF were 3.4 (P<0.001) and 3.3 (P=0.01), respectively, compared with those who survived without receiving ICD therapy (Figure 1).
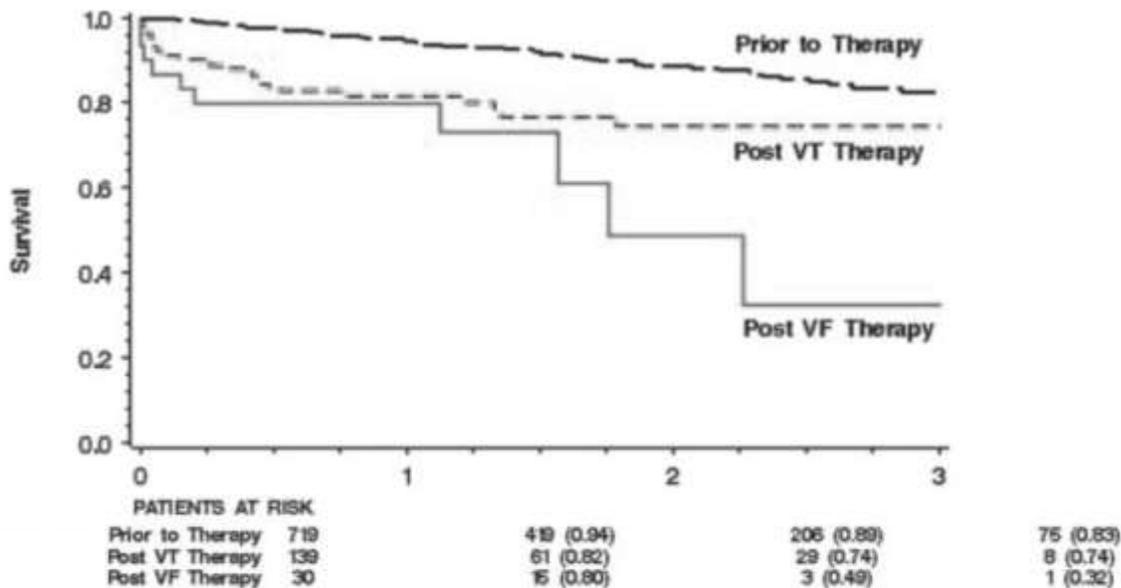


**Figure 1. Kaplan-Meier estimates of probability of survival before and after first appropriate ICD therapy for VT or VF.[1]**

Recent data from the SCD-HeFT trial demonstrated that patients with at least one appropriate ICD shock have a 3-fold higher risk of death than patients with no appropriate shocks (Figure 2).[3] One or more appropriate ICD shocks were experienced by 182 patients of whom 67 died with median time from shock to death equal to 168 days, less than 6 months. Kaplan-Meier based survival at 1 year after shock was 77%. Patients in NYHA class II had an 84% 1-year survival whereas those in NYHA class III had a 64% 1-year survival.

| Shock Type | Hazard Ratio for Death (95% CI) | | P Value |
|---|---|---|---|
| ≥1 App vs. no App | | 2.99 (2.04–4.37) | <0.001 |
| ≥1 Inapp vs. no Inapp | | 1.57 (0.99–2.50) | 0.06 |
| Both shock types vs. no shock | | 4.70 (2.70–8.18) | <0.001 |
| | 0.5  1.0  2.0  4.0  8.0  16.0 | | |

**Figure 2. Hazard ratios for the risk of death among patients who survived at least 24 hours after a first ICD shock.[3]**

Survival after shock for ventricular tachycardia was similarly poor to survival after ICD shock for ventricular fibrillation.[3]

These two independent ICD cohorts provide very similar data indicating that patients developing arrhythmic events are at very high risk of subsequent arrhythmic events and death. It is worth emphasizing that the majority of patients who qualify for ICD therapy do not receive ICDs for a variety of reasons including patients' hesitant to have a device, their preference to rely on pharmacological therapy, sometimes their insufficient knowledge of the risk, and frequently physicians' bias toward non-device management of their patients. Such patients as well as those with ICDs at high risk would greatly benefit from a pharmacological therapy reducing risk of arrhythmic events and death.

Recent, yet unpublished data from the MADIT-CRT trial demonstrate that patients who received their first appropriate ICD therapy for VT/VF have the following risk of VT/VF/Death: 45% at 1 year and 60% at 2 years after initial VT/VF episode. The risk was similar in ICD and CRT-D arm of the study. This observation together with data from prior studies and trials including AVID and OPTIC indicate that patients with prior history of VT/VF have very high risk of subsequent VT/VF/Death.

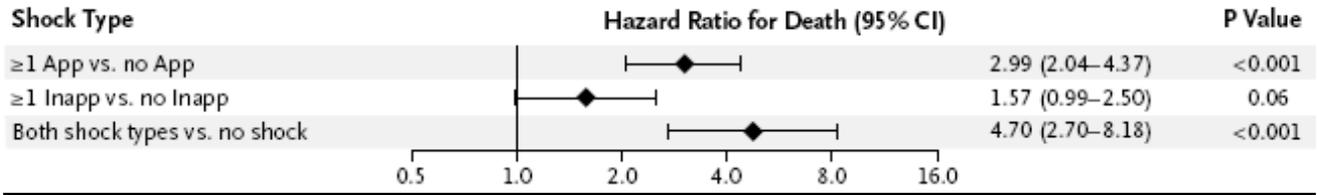It is important to emphasize that high-risk patients with ICDs include not only those who already developed arrhythmic events (either prior or after implantation) but also a large number of patients without evidence for arrhythmic events but with clinical characteristics indicating very high likelihood of developing life-threatening ventricular arrhythmias and death. There are numerous publications in the literature indicating that different risk stratification methods are able to identify high-risk cohort of patients fulfilling ICD indications. We tested numerous clinical and ECG/Holter parameters in the MADIT II patients to risk stratify patients with increased risk of cardiac events and arrhythmic events. Among numerous variables of interest, clinical variables including age, NYHA class, BUN level, atrial fibrillation and QRS duration were found the most useful and most practical. Figure 3, shows the data from the conventional arm of the MADIT II indicating that patients with BUN>25 mg/dl have the 2-year mortality of 34% in comparison to patients with BUN≤25 mg/dl with 17% mortality.
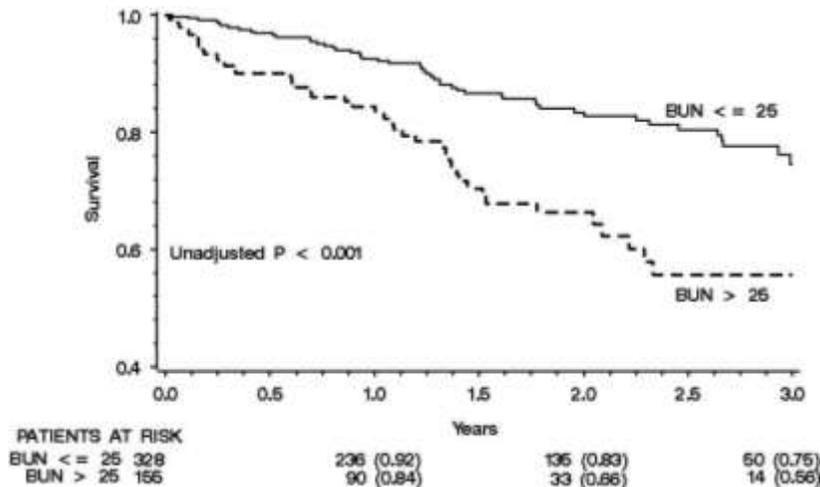


**Figure 3. Survival in the MADIT II patients by the BUN levels (Zareba et al.[28]).**

Furthermore yet unpublished analysis of data from MADIT-CRT trial indicate that unselected patients who do not have arrhythmic events during first 2 years of the trial still present significant risk of subsequent VT/VF/Death: 10% at 3rd year of follow-up and 19% at 4th year follow-up.

Our data from the MADIT-CRT Holter substudy[26] also demonstrate that patients with non-sustained VT (NSVT) have significantly higher risk for arrhythmic events than patients without NSVT.
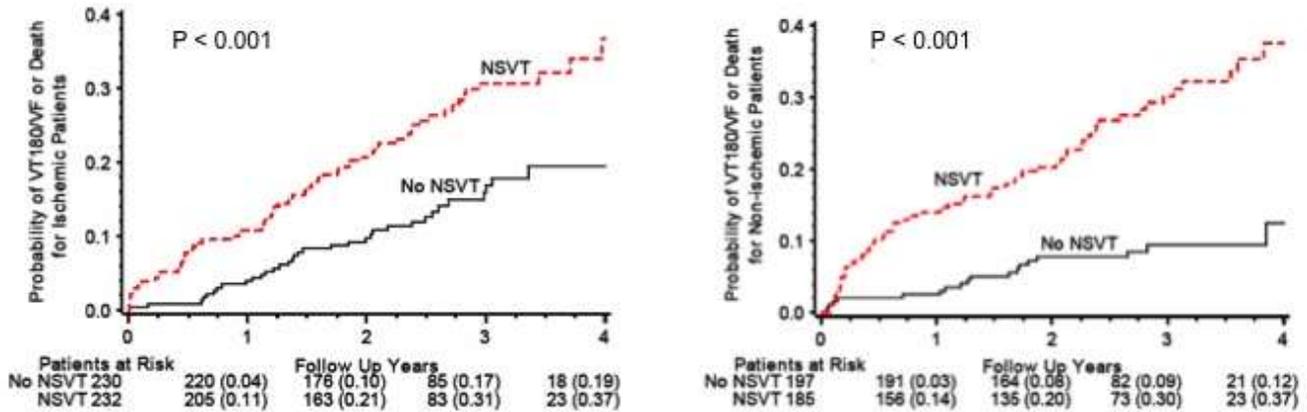


**Figure 4. Risk of VT/VF or death in the MADIT CRT patients by presence or absence of NSVT in ischemic and nonischemic population. (Mittal et al.[26]).**

We also recently completed and presented at HRS meeting in May 2013 (Zareba et al. HRS 2013)[27] results of a Risk Stratification Study in ICD Patients (called M2Risk Study) in which we also found that frequent VPBs>500 per 24 hour (or >20/hour on average) in Holter recording indicate increased risk of VT/VF in ischemic ICD patients.
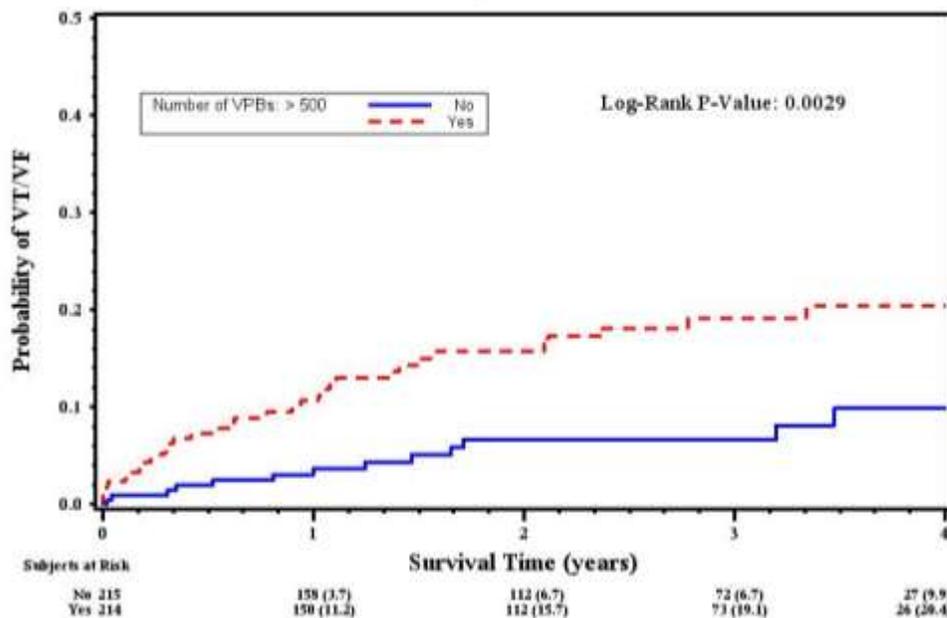


**Figure 5. Risk of VT/VF in ischemic ICD patients by presence or absence of frequent >500 VPBs on 24-hour Holter NSVT in ischemic ICD patients. (Zareba et al.[27]).**

Recent analysis of data from the SCD-HeFT (Chen et al. JACC 2013; 61:2161-8) document further that presence of NSVT detected on ICD interrogation was associated with a hazard ratio of 3.03 for predicting ICD shock or death and with hazard ratio of 4.25 for predicting ICD shock.

## B.2. Treatment Options for High-Risk Patients

The ICDs reduce mortality by detecting life-threatening ventricular tachyarrhythmias and delivering therapy in form of antitachycardia pacing and/or shocks. Clinical trials demonstrated that a significant reduction of mortality by ICDs is achieved on top of optimal medical therapy usually consisting of high use of beta-blockers, ACE-inhibitors, and statins.[21-25] These commonly used pharmacological treatments aim to decrease adrenergic activation, reduce adverse myocardial remodeling, decrease disease progression, decrease myocardial ischemia, and reduce vulnerability of plaque rupture, just to name few key mechanisms. Unfortunately, high-risk patients with ICDs frequently develop arrhythmic events and signs and symptoms of a progression of underlying disease despite this comprehensive pharmacological treatment.[1-3]
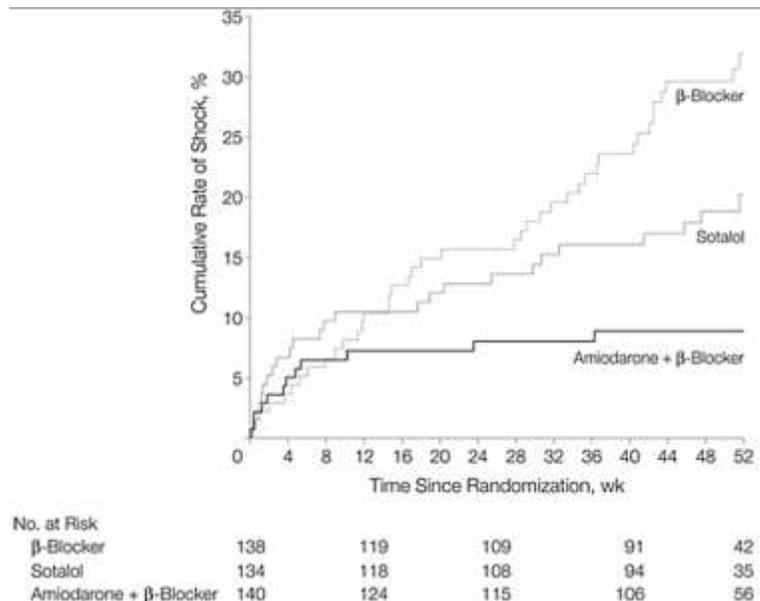


**Figure 6. Cumulative probability of ICD shock for 3 treatment group in the OPTIC Study.[7]**

The last two decades witnessed several failures of different antiarrhythmic drugs administered to reduce the risk of ventricular tachyarrhythmias and death in high-risk patients who nowadays qualify for ICD therapy. However, there are ongoing efforts to test existing and novel therapies that aim to decrease risk of arrhythmic events and decrease mortality in high-risk patients who usually present with signs and symptoms of heart failure. The therapies considered in such high-risk patients might include antiarrhythmic drugs,[6,7,29] cardiac resynchronization therapy,[30-32] or ablation of arrhythmogenic foci in the diseased myocardium.[33] Among anti-arrhythmic drugs used in the high-risk ICD patients, sotalol when compared to placebo was shown to significantly reduce risk of ventricular tachyarrhythmia requiring ICD shocks or death by 48%.[6] Beta-blockers were used in 23-37% of patients in that trial and when analyses were confined only to patients on sotalol versus no beta-blockers, reduction in endpoints was not statistically significant. Three other trials,[4,5,7] compared sotalol with beta-blockers and none of them (despite some trends) was able to demonstrate significant the reduction in endpoints; more importantly they showed conflicting results. Therefore sotalol did not gain the status of the drug of choice for high-risk patients.

In the OPTIC trial,[7] amiodarone in combination with beta-blocker significantly decreased (HR=0.27; p<0.001) the risk of arrhythmic events when compared with patients on beta-blocker alone (Figure 6). Amiodarone is currently used less and less frequently in high-risk patients due to its side effects. In a study evaluating the long-term clinical course of patients enrolled in the Canadian Implantable Defibrillator Study,[8] 82% of patients on amiodarone developed side effects and 50% required discontinuation or dose reduction. Figure 7 from a meta-analysis of drug trials in ICD patients, shows the high likelihood of discontinuation of antiarrhythmic therapy with sotalol and amiodarone.[33]

Regarding newer drugs, [34] the SHIELD trial[35] showed that azimilide was successful in reducing arrhythmic events in high-risk ICD patients. However, when analyses were performed with a combined endpoint of ICD

shock or death, hazard ratios were not significant: for 75 mg dose of azimilide 0.91 (95% CI: 0.76-1.10) and for 125 mg dose of azimilide 0.90 (95% CI: 0.74-1.09). The azimilide administration in high-risk patients was recently studied in the SHIELD II trial and in April 2013 the trial was stopped by the sponsor presumably for financial reasons although no formal statement was presented to date. Recently published trial with the new promising compound dronedarone,[29] showed increased mortality in heart failure patients assigned to this drug in comparison to placebo.

The SMASH-VT (Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia) trial[33] showed that patients randomized to substrate-based catheter ablation of arrhythmogenic ventricular foci had appropriate ICD shocks reduced from 33% to 15%. Although very promising and requiring confirmation in a larger trial, this invasive strategy could only be implemented in highly specialized centers that limit its widespread application.

Based on the above evidence, the majority of high-risk patients are still managed mostly with beta-blockers and sometimes with amiodarone with all its limitations.
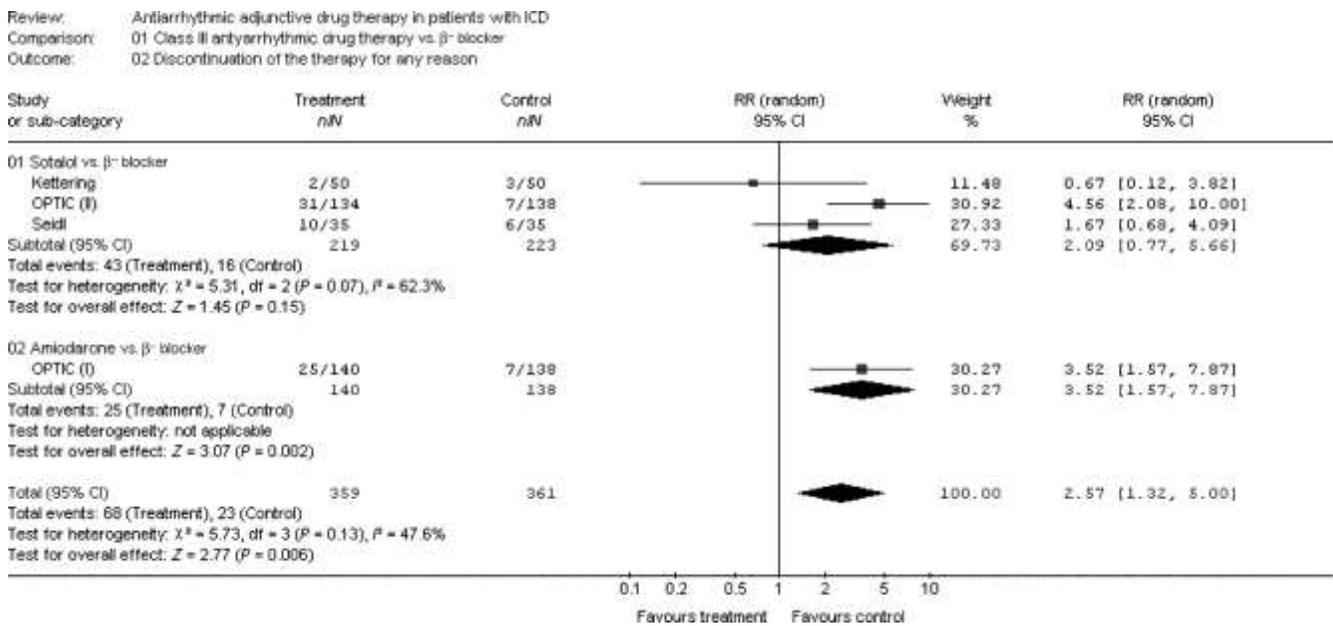


**Figure 7. Discontinuation of the therapy for any reason in studies comparing Class III antiarrhythmics with beta-blockers.[33]**

## B.3. Late Sodium Currant Blockade

Ion channels mediating the peak sodium current responsible for depolarization of myocardial cells are activated and inactivated within a few milliseconds and remain closed and non-conducting throughout the plateau phase of the cardiac action potential. In certain pathologic conditions including mutations in the sodium channel gene SCN5A associated with the long QT-3 syndrome or disease states such as hypoxia, heart failure, and post-myocardial infarction remodeling, sodium channels remain open or open again during the action potential plateau.[9-16] The late channel openings allow a sustained current off sodium ions to enter myocardial cells throughout systole.[7] This current has been referred to as late, sustained or persistent to distinguish it from the peak or transient $I_{Na}$. The amplitude of late $I_{Na}$ is less than 1% of peak $I_{Na}$ but it is sufficient to prolong action potential duration (APD).[40] Thus, although the amplitude of late $I_{Na}$ is small, because it persists for hundreds of milliseconds the influx of sodium by this mechanism may be substantial.[41] Transmural heterogeneity in the magnitude of late $I_{Na}$ can cause transmural heterogeneity of APD that may have pathophysiological significance as a mechanism of ventricular tachyarrhythmias.[41]
Ischemia and cardiomyopathies are associated with a sodium overload of myocardial cells and the late sodium current plays a pivotal role in this process.[9-13,43] Sodium overload leads to calcium overload of myocardial cells with consequent increased vulnerability of myocardium to ventricular tachyarrhythmias as well as increased

impairment of diastolic relaxation of myocardium further augmenting risk of ischemia and myocardial damage (Figure 8).

Breaking this pathway by late sodium channel blockers might bring numerous benefits to jeopardized myocardium. The entire class I of antiarrhythmic drugs consists of sodium channel blockers and none of them was proven to be effective in preventing arrhythmic events. But none of them had unique abilities to block selectively late sodium channel without significantly affecting peak current. Ranolazine, a FDA-approved anti-angina drug, was recognized over the last few years as a unique late sodium channel blocker which might have antiarrhythmic properties and properties toward reducing mechanical dysfunction of the left ventricle with long-term benefits in high-risk patients with cardiomyopathies. There is no clinical trial evaluating ranolazine (the only late sodium channel blocker on the market) in high-risk ventricular arrhythmia patients and we believe that such a trial is very much needed to advance treatment modalities for management of patients at risk for ventricular arrhythmias and to elucidate further mechanisms leading to adverse outcome in heart failure patients.
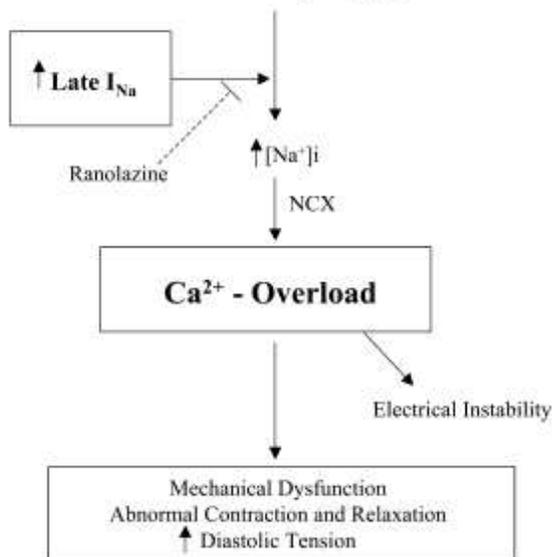


**Figure 8. Increases in intracellular sodium concentration ($[Na^+]i$) in ischemic cardiac myocytes cause calcium ($Ca^{2+}$) overload via the $Na^+$-$Ca^{2+}$ exchanger (NCX) leading to contractile dysfunction and cellular injury. A pathologically enhanced late $Na^+$ current (late $I_{Na}$) contributes to the $[Na^+]i$-dependent $Ca^{2+}$ overload. Ranolazine, by decreasing the magnitude of the pathologically enhanced late $I_{Na}$, prevents or reduces $Ca^{2+}$ overload and attenuates the accompanying deleterious consequences[43]**

## B.4. Significance of the Trial

We believe that the trial with late sodium channel blockade ranolazine in high-risk ICD patients is very much needed since there is no safe and effective treatment for a large number of patients with high risk of ventricular tachyarrhythmias. It is of interest to clinicians, NHLBI, and patients to improve the very low survival of patients at increased risk of ventricular tachyarrhythmias. The sooner we learn about the potential antiarrhythmic benefits of late sodium current blockade in a clinical trial, more patients will have their lives saved and prolonged (assuming that our hypothesis will be confirmed).

High-risk patients with ICDs in place constitute a unique group of patients in whom antiarrhythmic properties of this new drug could be very well documented by interrogating implanted devices with stored information on arrhythmic events occurring during a long-term follow-up. Simultaneously, ICDs provide a safety measure just in case of unlikely (based on preclinical and clinical experience) possibility of drug-induced proarrhythmia in studied patients.

It is worth stressing that late sodium current blockade represents a new scientifically attractive concept of antiarrhythmic therapy after two decades of no significant developments in pharmacologic treatment of ventricular arrhythmias. Conducting such a trial might open the door to the development of an entire line of compounds targeting the late sodium current as their main mode of antiarrhythmic action.

The use of ranolazine in the proposed study does not need an IND since ranolazine is currently marketed and the route, dose level, and patient population do not significantly alter risk and the study will be conducted in keeping with IRB and consent requirements. The regulations are designed to not encumber reasonable studies of approved drugs. FDA provided the letter confirming that IND is not needed.

## C. PRELIMINARY STUDIES

### C.1. Prior Studies Documenting High Risk of Cardiac Events in ICD Patients

There is vast evidence for high risk of cardiac events in high-risk patients who are qualified for ICD therapy for secondary or primary prevention of mortality. The sections below document event rates in populations of interest for this project and illustrate that there is a tremendous need of developing therapies to reduce the excessive risk of arrhythmic events and mortality, which cannot be addressed by ICD therapy alone.

### C.1.1. Secondary Prevention of Mortality

The Antiarrhythmics vs. Implantable Defibrillator (AVID) trial was the first study that documented significant reduction of mortality with ICD therapy in patients with cardiac arrest, documented ventricular tachycardia or ventricular fibrillation.[22] Individual patient data from the AVID trial, and two similar studies: the Cardiac Arrest Study Hamburg (CASH) trial, and the Canadian Implantable Defibrillator Study (CIDS) trial were merged to perform a meta-analysis of a total of 1,866 patients evaluated regarding measures aiming to reduce secondary prevention of mortality.[44] As shown in Figure 9, ICD therapy was associated with a significant reduction in mortality, however, long term mortality in the ICD arm remained high indicating that these patients require additional modes of therapies in addition to ICDs.
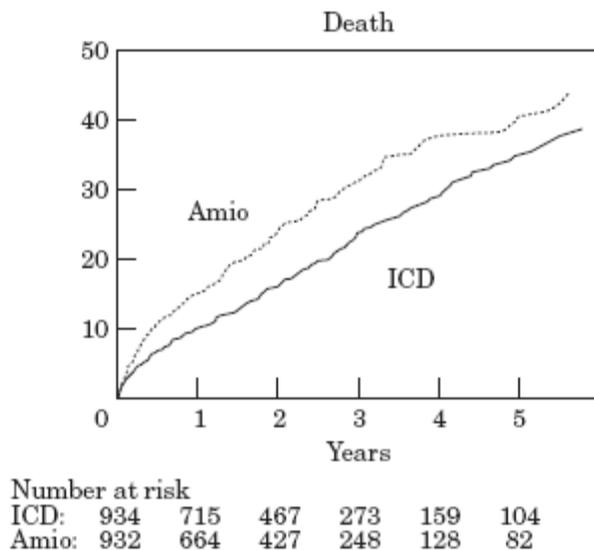
**Figure 9. Cumulative probability of death in 1,866 patients enrolled in clinical trials AVID, CIDS and CASH by treatment arm: amiodarone or ICD therapy.[44]**

Much newer data regarding the clinical course of patients qualified for secondary prevention of mortality with ICDs were presented by the OPTIC Study.[7] The OPTIC Study was designed to determine whether amiodarone plus beta-blocker or sotalol are better than beta-blocker alone for prevention of ICD shocks in patients with predominantly secondary prevention indications for ICDs. Patients were randomized to receive treatment with amiodarone plus beta-blocker, sotalol alone, or beta-blocker alone for one year. The OPTIC study population consisted of 421 patients who had implanted ICDs within the past 21 days for inducible or spontaneous VT/VF (AVID, MADIT, MUSTT type of patients). Over 70% had spontaneous VT/VF (secondary prevention following AVID indications), and the remaining 30% of patients had induced VT/VF (primary prevention following MADIT/MUSTT indications). Figure 6 (presented in section B.2) graphically shows that patients treated with beta-blockers have about 30% 1-year probability of developing VT/VF requiring ICD therapy.

Data from the control group of the Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia (SMASH-VT) trial demonstrated 33% 2-year mortality in secondary prevention patients who received their ICD for documented ventricular tachyarrhythmias or in primary prevention patients who experienced at least one arrhythmic event after implantation of device.[33]

Therefore, there is substantial evidence documenting a very high risk of mortality and arrhythmic events in patients qualified to ICD therapy for secondary prevention of mortality.

### C.1.2. Primary Prevention of Mortality in Ischemic Cardiomyopathy

In the section B.1, we referenced our MADIT II data,[1] documenting the high risk of recurrent events in patients who received appropriate ICD therapy for their first ventricular tachyarrhythmic episode. Additional analyses performed purposefully for this application in these 169 patients demonstrated that a 2-year probability of a combined endpoint of VT/VF requiring ICD therapy or death was reached by 57% of patients who survived at least one appropriate ICD therapy (Table 1).

| Table 1. Probability of Cardiac Events in 169 MADIT II Patients with ICDs after First VT/VF Requiring ICD Therapy | | |
|---|---|---|
| Event Type | 1 year rate | 2 year rate |
| ICD Therapy for VT/VF | 27% | 49% |
| ICD Therapy for VT/VF or Death | 33% | 57% |
| ICD Therapy for VT/VF, CHF Hosp or Death | 41% | 66% |

It is worth emphasizing that among MADIT II patients there is a substantial proportion of patients who should be considered as high-risk at baseline (without need for documented arrhythmic events). Figure 10 shows the data from the MADIT II cohort fulfilling the entry criteria proposed for this application. The 2-year cumulative probability of ICD shock for VT/VF or death was 37%.
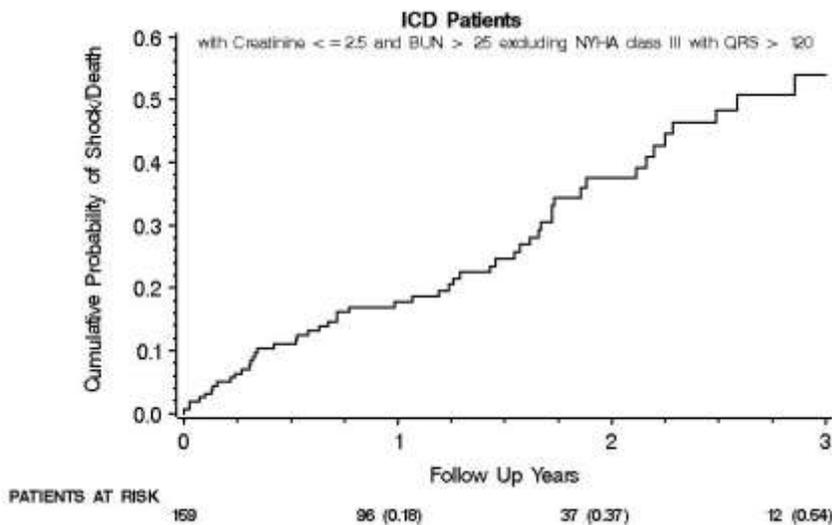


**Figure 10. Cumulative 2-year probability of ICD shock for VT/VF or death in MADIT II patients with BUN>25mg/dl.**

When considering the composite endpoint of CHF hospitalization or death, Figure 11 shows cumulative probability of CHF hospitalizations or death reaching 40% at 2 years. The analysis of cardiac hospitalizations or death in these patients revealed 55% 2-year risk of this cardiac event.

Our secondary endpoints also include analyses of repeated ICD therapies and repeated hospitalizations for cardiac causes. Figure 12 shows the intensity plot used for the analyses based on the Anderson-Gill method, reflecting repeated hospitalizations for cardiac causes in MADIT II patients with ICDs. There were 55 hospitalizations for 100 patients in year 1 and 100 hospitalizations per 100 patients in year 2 (averaging 1 hospitalization per patient over 2-year period). Regarding repeated ICD shocks, there were 23 shocks per 100

person-years, when counting one shock per day. When separate arrhythmia episodes (5-minute apart) were counted, this rate increases to 34 per 100 person-years. The above preliminary data indicate high morbidity of patients with ICDs, which might be reduce by pharmacological treatment targeting ventricular arrhythmias and also influencing diastolic function of the left ventricle.
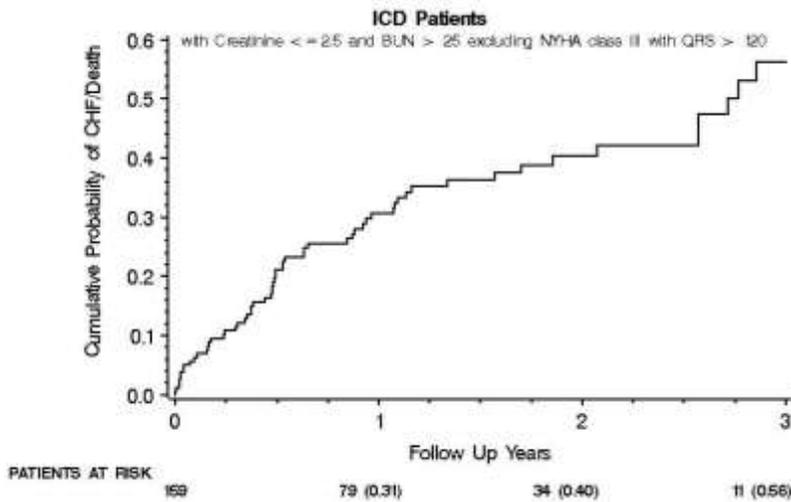


**Figure 11. Cumulative 2-year probability of CHF hospitalization or death in MADIT II patients with BUN>25mg/dl.**

As mentioned earlier, the SCD-HeFT trial (which enrolled about one-half ischemic and one-half nonischemic cardiomyopathy patients in NYHA class II or III with EF≤35%),[3] also documented high rates of mortality in patients with ventricular tachycardia or ventricular fibrillation requiring ICD therapy.
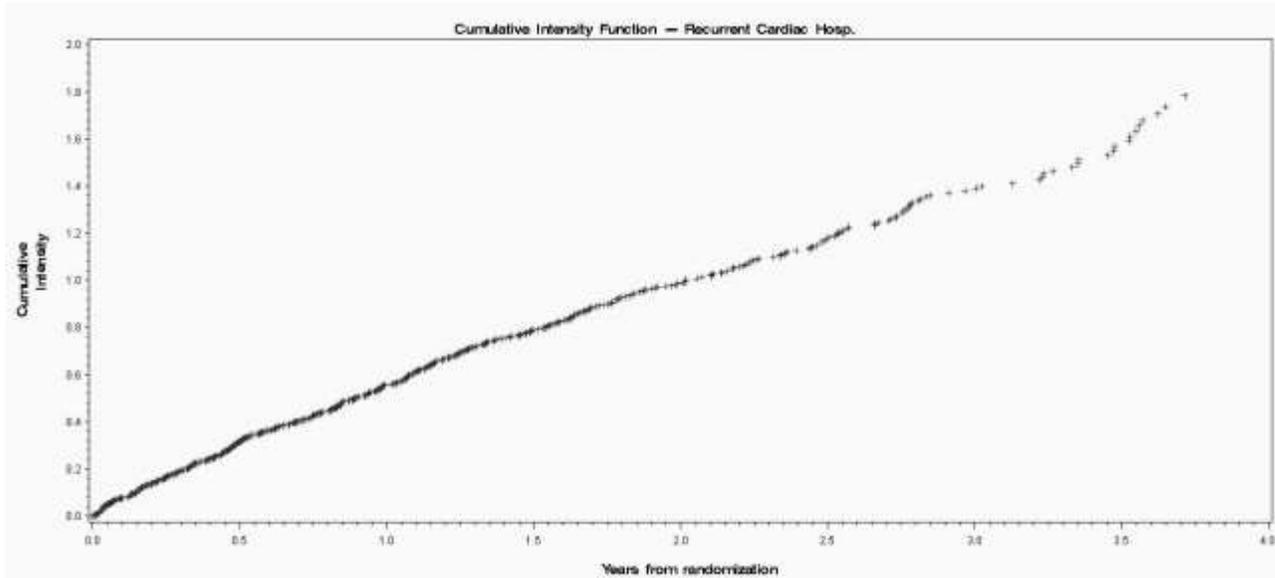


**Figure 12. Cumulative intensity of repeated hospitalization for cardiac causes in MADIT II patients with ICDs. There were 55 hospitalizations at 1 year and 100 hospitalizations at 2 years per 100 patients (intensity 0.55 and 1.0 respectively).**

### C.1.3. Nonischemic Cardiomyopathy Patients

The DEFINITE trial documented a beneficial role of ICD therapy in patients with nonischemic cardiomyopathy and low ejection fraction.[24] In the DEFINITE trial, 16% of patients in the NYHA class II and 33% of patients in the NYHA class III reached the combined endpoint of ventricular tachycardia or ventricular fibrillation requiring ICD shock or death during a mean 30-month follow-up (Dr. Alan Kadish – unpublished data - personal communication on September 18, 2008).

In the MUSIC Study,[45] which enrolled congestive heart failure patients in class II and III NYHA, we analyzed data for 263 patients with nonischemic etiology of cardiomyopathy with EF≤35%. There were 63 (24%) deaths over a median 44-month follow-up. In 58 NYHA class III patients there were 21 (35%) deaths whereas in 205 NYHA class II patients there were 42 (20%) deaths (hazard ratio for NYHA class III vs. class II = 1.99 (95% CI: 1.18-3.36; p =0.010).

The estimated 2-year mortality rates were 22% in NYHA class III and 10% in NYHA class II (Figure 13). There were no data on arrhythmic events in this patient population, but mortality rates in NYHA class III patients indicate a high likelihood of a 30% 2-year event rates when considering combined arrhythmic endpoint considered for the proposed trial.
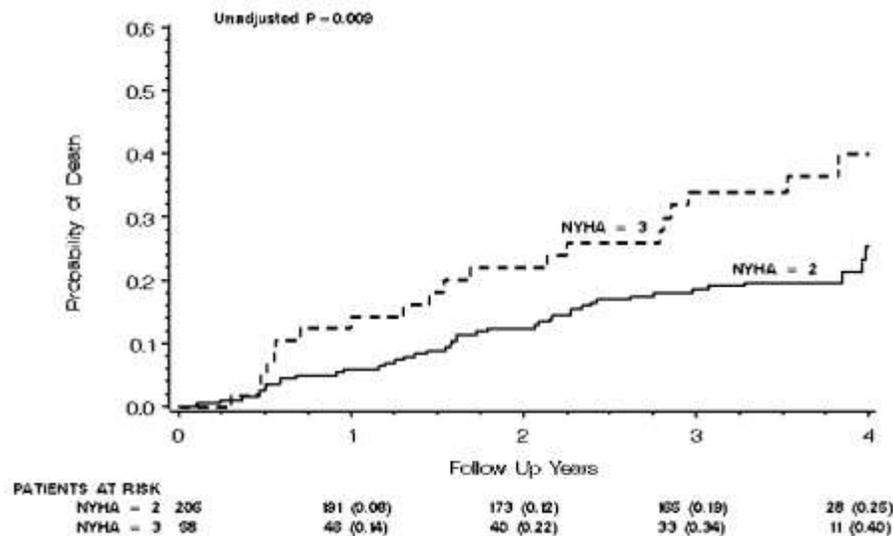


**Figure 13. Cumulative probability of survival in 263 patients with nonischemic cardiomyopathy by NYHA class enrolled in the MUSIC study**

Similarly, when using the 75th percentile of the BNP levels as a cut-off in the MUSIC patients, there was a 2-fold increase in mortality in patients with BNP in the upper quartile of the distribution than in lower three quartiles (unpublished data).

Both the DEFINITE and MUSIC studies document that nonischemic cardiomyopathy patients in NYHA class III are at high risk of mortality. In addition, DEFINITE documented a high (21%) risk of appropriate ICD therapy in NYHA class III patients. These data indicate that nonischemic cardiomyopathy patients with NYHA class III should be considered as a very high-risk subgroup of these patients.

## C.2. Ranolazine as Antiarrhythmic Compound (In Vitro Data)

Blockade of sodium channels by antiarrhythmic drugs is the principal mechanisms of action by class I antiarrhythmic drugs with all of them affecting the peak sodium current in addition to late sodium current. Ranolazine, a piperazine derivative with a molecular structure similar to lidocaine, was patented in 1986 and was developed as an anti-angina drug. Ranolazine is a novel sodium channel blocker which inhibits late sodium current without significant effect on peak sodium current (no QRS changes). In isolated ventricular myocytes of dogs with chronic heart failure, ranolazine was found to inhibit peak $I_{Na}$ and late $I_{Na}$ with potencies (50%inhibitory concentrations) of 244 and 6.5 µmol/l, respectively.[18] Ranolazine is about 38-fold more potent in inhibiting late $I_{Na}$ than peak $I_{Na}$[18]. For comparison, amiodarone is about 13-fold more potent in inhibiting late than peak $I_{Na}$.[17]

Ranolazine decreases APD, measured at either 50% or 90% of repolarization ($APD_{50}$ or $APD_{90}$, respectively), and abolishes early after depolarizations (EADs) of guinea pig ventricular myocytes treated with ATX-II (Figure 14).[15] Ranolazine has been shown to have antiarrhythmic effects in a guinea pig in vitro model of the long QT-

3 syndrome.[46] Ranolazine similarly antagonized the proarrhythmic actions of combinations of ATX-II and either the $I_{Kr}$ blocker E-4031 or the slow delayed-rectifier current ($I_{Ks}$) blocker chromanol 293B.[6] In the same long QT-3 model, ranolazine was found to suppress spontaneous and pause-triggered ventricular arrhythmic activity caused by a diverse group of $I_{Kr}$ blockers (that is, moxifloxacin, cisapride, quinidine and ziprasidone).[46]

Beat-to-beat variability of APD are often observed in myocytes from failing dog hearts, in ischemic preparations and in myocytes exposed to either ATX-II or to drugs that prolong the QT interval. An increased dispersion of repolarization is associated with electrical and mechanical alternans and is proarrhythmic.[2] There are data indicating that late $I_{Na}$ contributes to beat-to-beat variability of APD.[8] Ranolazine reduces the variability of APD in single ventricular myocytes from dogs with heart failure[10] and in myocytes exposed to ATX-II.[15] Thus, inhibition of late $I_{Na}$ with ranolazine and other sodium channel blockers suppresses EADs and decreases dispersion and variability of repolarization.[15,16,46,47.]
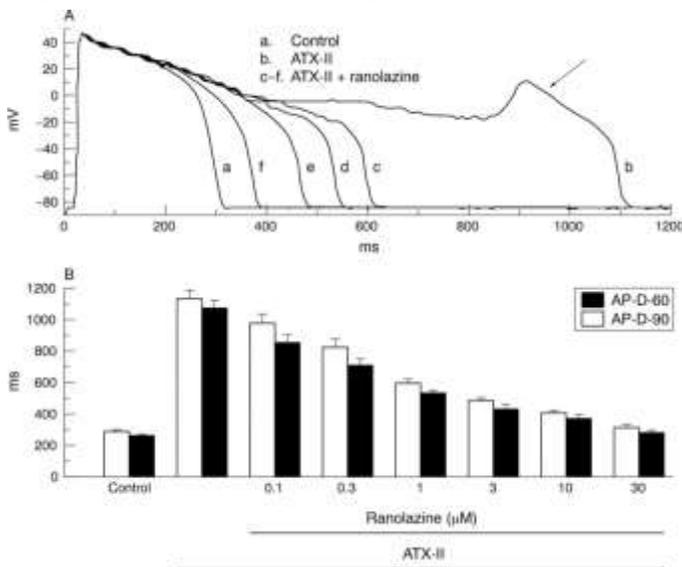


**Figure 14. Ranolazine attenuates the effects of the Anemonia sulcata toxin (ATX-II) on APD and EADs in guinea pig ventricular myocytes.**

**(A) Recordings of action potentials from a ventricular myocyte in the absence of drug (control, (a)), in the presence of 10 nM ATX-II (b), and in the presence of ATX-II and increasing concentrations (1, 3, 10 and 30 {micro}M) ranolazine (c-f). An EAD is indicated by the arrow in recording (b).**

**(B) Concentration-response relationship for ranolazine to decrease APD in the presence of 10 nM ATX-II. All values of APD in the presence of ranolazine are significantly different from ATX-II alone (p < 0.01).[15]**

Impaired left ventricular relaxation and increased left ventricular end-diastolic pressure are early manifestations of myocardial ischemia, caused in part by calcium overload. In ischemic myocardium, ranolazine has the potential to disrupt the consequences of cell hypoxia by reducing excess late $Na^+$ influx, thereby reducing calcium overload and ultimately reducing the concomitant increase in left ventricular wall tension. Reduction in diastolic left ventricular wall tension would decrease myocardial oxygen requirements and reduce vascular compression, allowing more coronary blood flow to the affected area. Since this calcium overload is coupled to an increase in sodium due to an enhanced late $I_{Na}$, inhibition of this increased late $I_{Na}$ by ranolazine attenuates the LV mechanical dysfunction associated with ischemia and cardiomyopathies. Ischemia increases LV diastolic pressure, a phenomenon attributed to calcium overload triggered by a rise in $[Na^+]_i$. In rabbit and rat isolated perfused hearts, ranolazine has been shown to significantly reduce ischemia-related increases in LV diastolic pressure and creatine kinase release (Figure 15). [9]
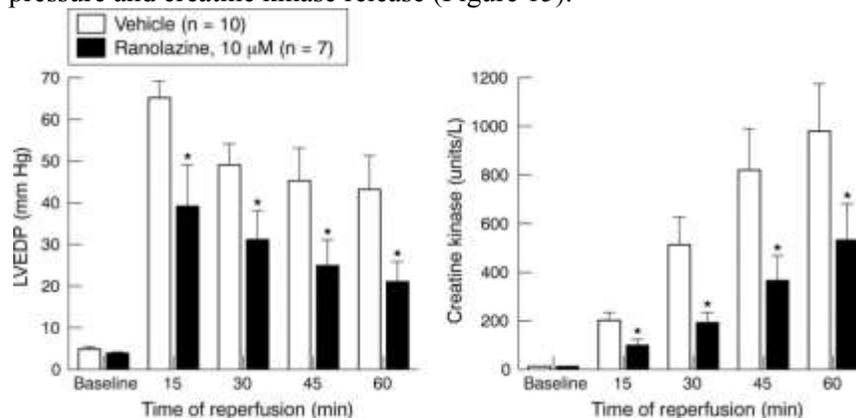


**Figure 15. Effect of ranolazine on the left ventricular end diastolic pressure (LVEDP) and creatine kinase release of rabbit isolated Langendorff-perfused hearts. Values significantly different (p < 0.05) from drug vehicle.[49]** The anti-ischemic and antiarrhythmic properties of ranolazine are believed

to be related to its ability to block late sodium current, decrease intracellular calcium overload, and improve diastolic relaxation of the ventricles. Ranolazine also inhibits $I_{Kr}$, $I_{Ca}$, and $I_{Ks}$. The $I_{Kr}$ blocking effect contributes to minor action potential duration prolongation and QT prolongation. However, it does not cause early after depolarizations and ventricular tachyarrhythmias (similar to the antiarrhythmic profile of amiodarone).

Importantly, increased activity of late sodium current with subsequent calcium overload and antiarrhythmic and functional effects of ranolazine have been documented in myocardium from failing human hearts from patients who underwent cardiac transplantation for dilative nonischemic cardiomyopathy.[13] Therefore, both ischemic and nonischemic cardiomyopathy patients might benefit from late sodium channel blockade, since sodium and calcium overload is present in both these conditions.
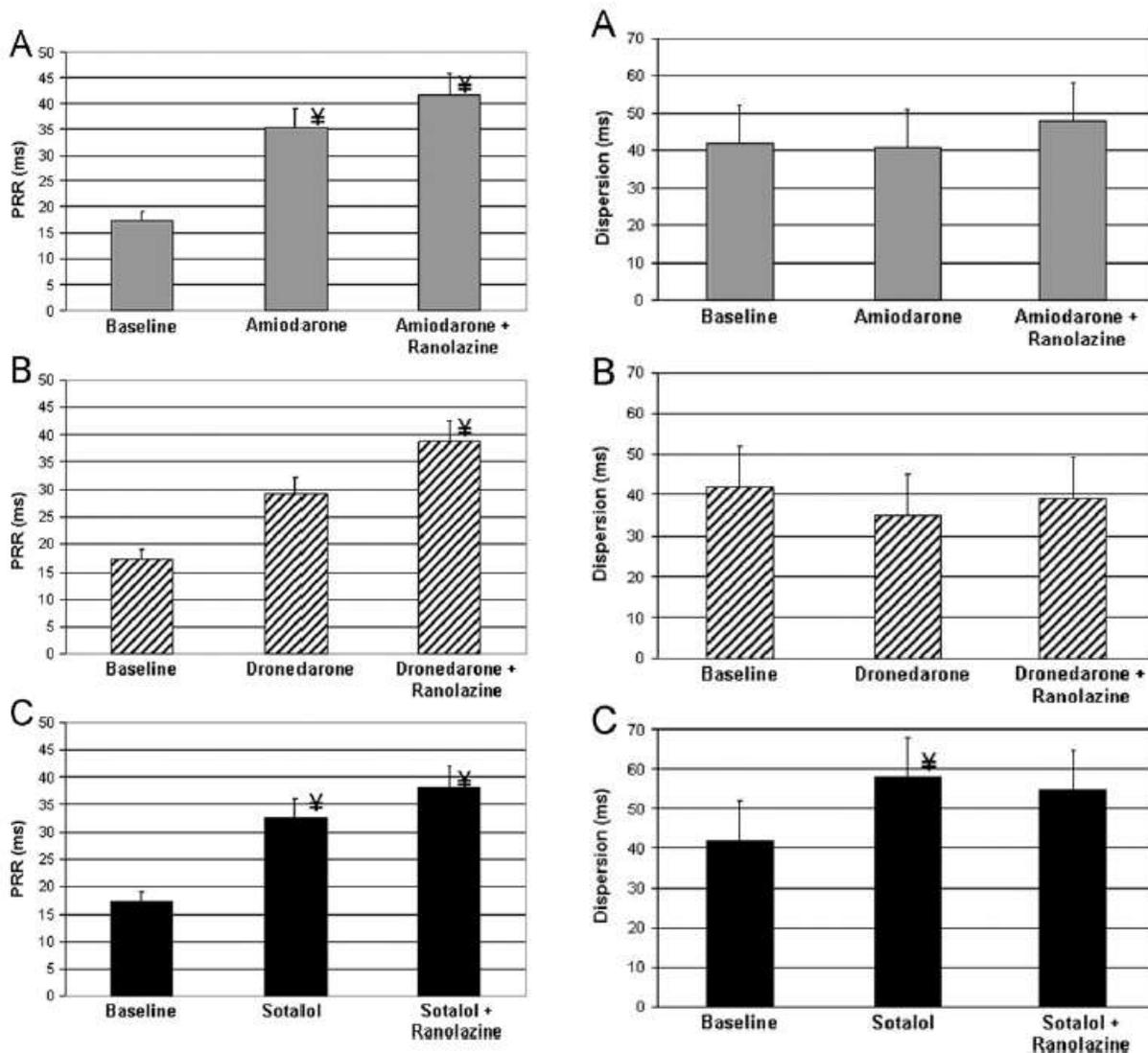


Figure 16. Post repolarization refractoriness (PRR) – left panel, and overall dispersion of repolarization – right panel in (A) amiodarone, (B) dronedarone, and (C) sotalol groups. f P o .05  as compared with baseline  (A) amiodarone, (B) dronedarone, and (C) sotalol groups. P<0.05 as compared with baseline (Frommeyer et al. [50]).

In December 2012, Frommeyer et al.[50] reported data on concomitant use of ranolazine with amiodarone, dronedarone, and sotalol in rabbit hearts. Ranolazine increased post-repolarization refractoriness as compared with amiodarone or dronedarone alone. In contrast to amiodarone and dronedarone, acute application of sotalol increased dispersion of repolarization. Additional treatment with ranolazine did not further increase spatial or temporal dispersion (Figure 16). Additional treatment with ranolazine reduced the number of VT episodes in sotalol-treated hearts and did not cause proarrhythmia in combination with amiodarone or dronedarone.

**C.3 Data Regarding Clinical use of Ranolazine**

Large clinical trials conducted with ranolazine to date were focused on evaluating predominantly anti-ischemic and anti-angina properties of the drug. The Monotherapy Assessment of Ranolazine in Stable Angina (MARISA)[52] and subsequent Combination Assessment of Ranolazine in Stable Angina (CARISA)[51] trials enrolled patients with chronic effort angina and documented exercise-induced ischemia. The primary efficacy end point for both studies was symptom-limited exercise duration at trough plasma concentrations at 12 hours after dosing. MARISA was a monotherapy study that tested a 3-fold dose range of ranolazine.[52] All 3 doses resulted in a significant increase in exercise duration compared with placebo ($P \leq 0.005$) in a dose-dependent fashion. The CARISA study tested 823 patients with chronic angina once-daily atenolol (50 mg), once-daily diltiazem (180 mg), or once-daily amlodipine (5 mg).[51] The results showed that, compared with placebo, ranolazine significantly increased symptom-limited exercise duration. The ERICA study[53] evaluated the average number of angina attacks per week. During the 6-week treatment, the mean number of angina episodes per week decreased to 3.2 in the placebo group and 2.8 in the ranolazine group ($P=0.028$). Mean nitroglycerin use per week decreased to 2.6in the placebo group and 2.0 in the ranolazine group ($P=0.014$) without a significant change in heart rate or blood pressure.

The Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndrome(MERLIN TIMI 36)[54] study was a large double-blind placebo controlled trial of patients with an acute coronary syndrome receiving contemporary therapy, who have had chest pain within the 48 hours before randomization, ST depression or abnormal biomarkers, diabetes mellitus, or a TIMI risk score $\geq 3$. The primary end point of the trial was the composite of cardiovascular death, myocardial infarction, or recurrent ischemia. Intravenous administration of the drug was followed by oral ranolazine or placebo. The MERLIN trial did not show significant difference in the primary endpoint with hazard ratio = 0.92 (95% CI: 0.83-1.02; p=0.11). There was no difference in mortality between groups and there was a significant reduction in the episodes of recurrent ischemia (HR = 0.87; 95% CI: 0.76-0.99; p=0.030). The MERLIN trial confirmed safety of a long-term administration of ranolazine, addressing initial concerns related to QT prolonging effects of the drug.

In a subanalysis of the MERLIN trial, ranolazine contributed to a significant decrease in risk of VT episodes lasting 8 beats or longer in overall study population (Figure 17).[55]
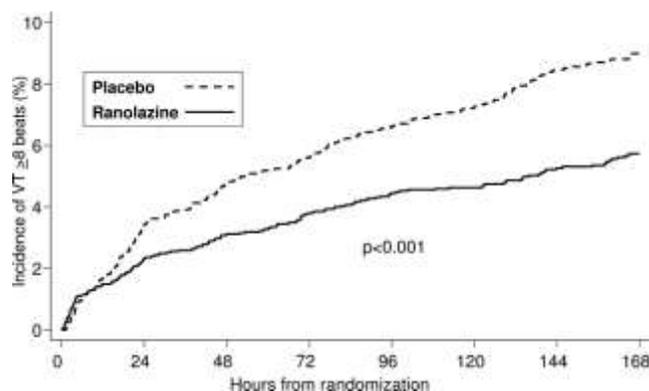


**Figure 17. Kaplan-Meier estimated rates of the first occurrence of an episode of ventricular tachycardia lasting at least 8 beats.[55]**

Relevant to this proposal that aims to evaluate the effects of ranolazine in predominantly heart failure patients, the MERLIN trial showed that in 585 patients with EF<40%, the 7-day Holter revealed a significant decrease in episodes of VT of least 8-beat duration in those treated with ranolazine (8.8%) vs. placebo (16.6%); hazard ratio = 0.53 (95% CI 0.34-0.84); p=0.005. A similar hazard ratio was reported for 1,069 patients with a prior history of heart failure.[55] Additional analyses of MERLIN data showed that in patients who had BNP>80 pg/ml, ranolazine contributed to a significant reduction of the primary endpoint.

The effects of ranolazine were evaluated in 4,543 patients from the MERLIN-TIMI 36 trial who had measured plasma levels of BNP at baseline.[56] Patients were stratified using BNP>80 pg/ml. The primary endpoint was a composite of cardiovascular death, myocardial infarction, or recurrent ischemia. There were 1,935 patients with elevated BNP and in these ranolazine reduced the primary endpoint (HR 0.79; 95%CI 0.66 – 0.94, p=0.009)

contrasting with the lack of detectable effect in those with a negative BNP result (Figure 18; p-interaction = 0.05). It is believed that in our proposed study the majority of randomized patients will have elevated BNP levels.
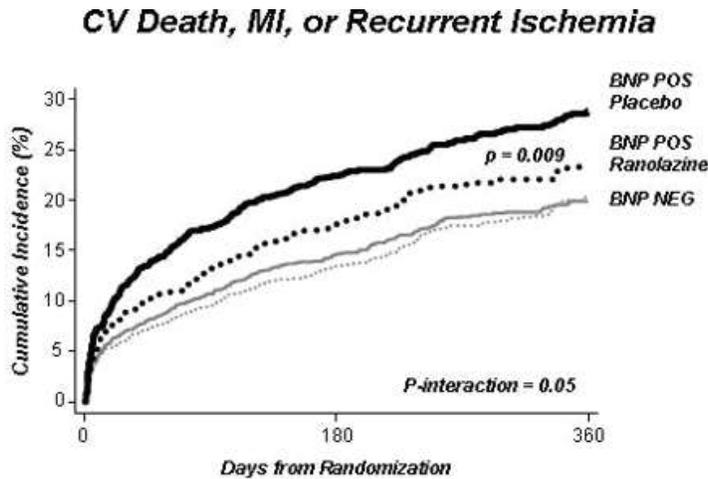


**Figure18. Cumulative probability of cardiac event defined as cardiovascular death, recurrent ischemia or myocardial infarction in patients with and without elevated BNP on ranolazine or placebo.**

Concomitant use of ranolazine with amiodarone, have been reported by Fragakis et al.[57] in 51 consecutive patients with AF eligible for pharmacologic cardioversion. Patients were randomized to intravenous amiodarone for 24 hours or to intravenous amiodarone plus oral ranolazine 1,500 mg at time of randomization. Conversion within 24 hours was achieved in 22 patients (88%) in amiodarone plus ranolazine group versus 17 patients (65%) in amiodarone alone group. There was no evidence for QTc prolongation associated with adding ranolazine to amiodarone.

Bunch et al.[58] in a small study documented that ranolazine proved effective in reducing VT burden and ICD shocks in patients with VT refractory to antiarrhythmic treatment. Ranolazine was given on top of amiodarone therapy in 11 subjects and on top of sotalol in one subject. Addition of ranolazine was effective in controlling acute arrhythmia.
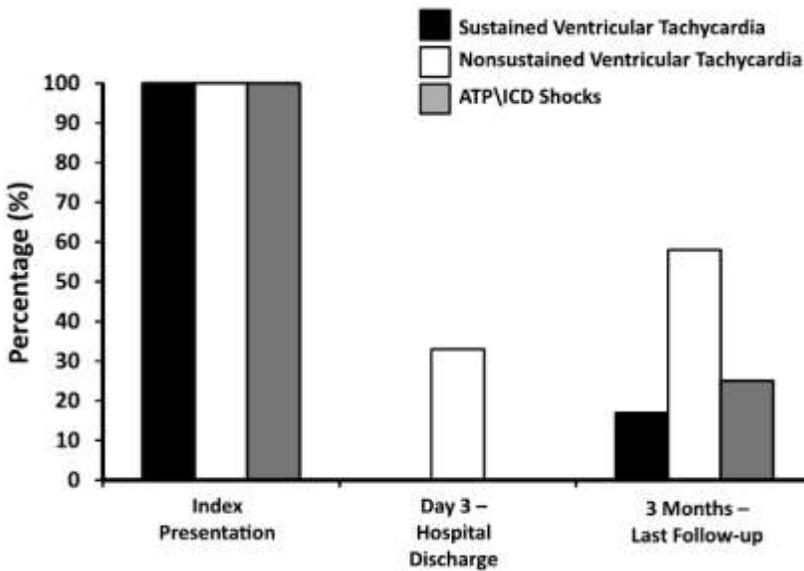


**Figure 19.** The time-based outcomes of patients treated with ranolazine. Three time periods are shown: the index hospitalization, the steady state (day 3) to hospital discharge, and 3 months to last follow-up. All patients presented with ICD therapies and both sustained and nonsustained VT. Sustained VT, nonsustained VT, and ICD therapies were all reduced during the study observation period (Bunch et al.[58]).

At the same time, there were no significant changes in QRS duration 128±31 ms vs. 133±31 ms and no significant changes in QTc: 486±32 ms vs. 495±31 ms. In those patients with ischemic substrate, recurrent VT was observed after hospital dismissal during antiarrhythmia drug dose

reduction or if the ranolazine was discontinued due to side effects. Long term effects (Figure 19) were very encouraging.

## C.4. Safety of Ranolazine

Ranolazine blocks $I_{Kr}$ current and might cause mild QT prolongation. In the dose range of 500 to 1000 mg twice daily, ranolazine increases the QTc (Fridericia) by an average of 2 to 5 ms.[59] The incidence of "QTc outliers" in lead II with the use of the Fridericia correction for a QTc of > 500 ms was 0.7% at the 1000 mg twice daily dose, and a QTc increase of > 60 ms was observed in 2.3% patients. Ranolazine is contraindicated in patients with preexisting QT prolongation, on QT-prolonging drugs, or with hepatic impairment.

Despite QT prolongation there is no evidence for ranolazine causing torsade de pointes ventricular tachycardia. Data from several clinical trials (MARISA, CARISA, ERICA, MERLIN) [51-53, 54-56] with over 4,000 patients on ranolazine treated for a long time showed that there was no evidence for torsadogenic effects of ranolazine. Especially, the MERLIN trial[54] well documented that there was no increase in mortality in patients taking ranolazine, and there was a significant decrease in the risk and rate of complex ventricular arrhythmias.

These clinical observations are in agreement with pre-clinical data from Dr. Antzelevitch's group showing that ranolazine acts similarly to amiodarone which also prolongs the action potential duration and QT interval, but reduces transmural heterogeneity of repolarization and eliminates earlyafterdepolarizations.[16]

We evaluated the safety of ranolazine in patients long QT syndrome type 3 caused by mutations of the SCN5QA gene and as shown in Figure 20, incremental plasma concentration of ranolazine was associated with progressive dose dependent QT shortening (by 26±3ms on average) further clinically confirming a late sodium blockade mechanism of this novel drug.[20]
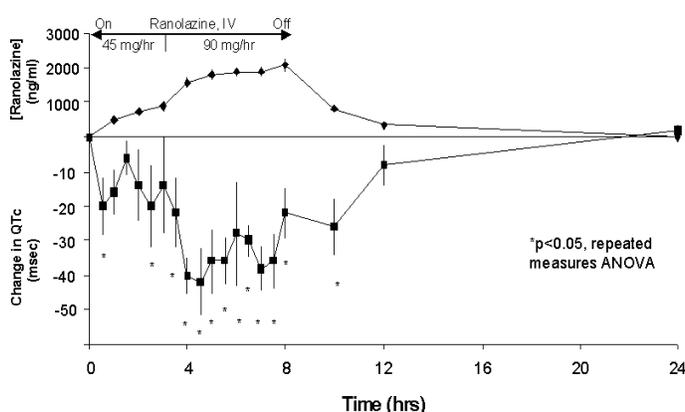


**Figure 20. Dose-dependent QTc shortening in LQT3 patients in response to ranolazine.[20]**

Additional unpublished data from the MERLIN trial database support that concomitant use of ranolazine with antiarrhythmic medication seems safe (Dr. Luiz Belardinelli and Dr. Ewa Prokopczuk from Gilead Sciences – personal communication from September 12, 2013). There were 25 patients who took amiodarone and ranolazine for prolonged period of time of several months. In parallel, 48 took amiodarone and placebo for a prolonged period of time. There were 4 deaths (all sudden deaths) in 48 amiodarone plus placebo treated patients and none in 25 amiodarone plus ranolazine treated patients. Regarding sotalol, 6 patients were taking sotalol with ranolazine for a prolonged time of several months. In parallel, 8 patients were on sotalol and placebo for a prolonged time. There were 2 death (both sudden) among sotalol and placebo patients and none in 6 sotalol and ranolazine patients. These are still anecdotal data, but there is no indication of harm due to this combination.

## C.5. Prior Experience of Investigators

This application is prepared by a group of investigators experienced in conducting clinical trials and studies (more information is provided in clustered application describing Data Coordination Center). Major studies conducted and coordinated by our group include:

- International Long QT Syndrome Registry – an ongoing multicenter collaborative project aiming to advance knowledge about this genetic disorder characterized by abnormal repolarization in the ECG and a propensity to ventricular tachyarrhythmias and sudden cardiac death. Over 1,200 proband-identified families are enrolled in the registry with over 15,000 family members.
- Multicenter Automatic Defibrillator Trials II (MADIT II) – multicenter trial of 1,232 post infarction patients with EF≤30% which demonstrated the benefit of implantable cardioverter-defibrillators in primary prevention of cardiac death (31% reduction in mortality).
- Multicenter Automatic Defibrillator Trial – Cardiac Resynchronization Therapy (MADIT – CRT) – This trial with 1,820 subjects already randomized and currently in a long-term follow-up aims to determine whether cardiac resynchronization therapy combined with ICD (CRT-D) is superior to ICD therapy alone in preventing progression of heart failure in patients with ICD indications but in NYHA class I or II (which is not currently approved indication for CRT).
- Multidisciplinary Study of Right Ventricular Dysplasia -This NIH study, aims to establish improved diagnostic criteria for identifying patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. Over 140 probands were enrolled in the study with significant complexity of core lab operations.
- Risk Stratification in MADIT II Type Patients – NIH-funded study aiming to determine risk factor for predicting cardiac events in patients qualified for ICD therapy for primary prevention of sudden death.

There are over 80 original papers published over the last 5 years by our group in relationship to the above and other related studies.

## D. RESEARCH DESIGN AND METHODS

### D.1. Introduction

Prevention of sudden death by an ICD therapy is applied to a large number of patients (>100,000 per year only in the US) who are at increased risk of mortality and arrhythmic events including patients after cardiac arrest (secondary prevention of mortality), post infarction patients with low ejection fraction, and nonischemic patients with depressed left ventricular function (primary prevention of mortality). In a population of patients with implanted ICDs, there is a substantial proportion of patients who are at high risk of developing arrhythmic events and who remain at high risk of death despite implanted devices.[1-3,6-7] It is well documented that patients who develop ventricular tachycardia/fibrillation requiring ICD therapy present with high likelihood of repeated arrhythmia episodes requiring ICD therapies.[1-7] As documented by the MADIT II and SCD-HeFT sub studies, the risk of death in patients with documented ICD therapy is a 2-3-fold higher than in patients with no arrhythmic events.[1,3]

High-risk individuals with ICDs might benefit from pharmacological therapies aiming to decrease the risk of arrhythmic events and to decrease the likelihood of hospitalizations for cardiac causes and death. Late sodium current blockade is a novel pharmacological approach that could be used in patients at high risk for ventricular arrhythmias and high risk for cardiovascular morbidity and mortality. This trial will test the hypothesis that administration of ranolazine, a unique late-sodium current blocker, will reduce the rate of a composite primary endpoint consisting of arrhythmia endpoint consisting of ventricular tachycardia or ventricular fibrillation (VT/VF) requiring antitachycardia pacing (ATP), ICD shocks or death.

### D.2. Specific Aims of the Proposed Trial

### D.2.1. Primary aim of the study

To determine whether ranolazine administration will decrease the likelihood of a composite arrhythmia endpoint consisting of ventricular tachycardia or ventricular fibrillation (VT/VF) requiring ATP therapy, ICD shocks, or death.

In addition to the above primary specific aim, there are several secondary aims that will be addressed in this trial by utilizing data from detailed records of arrhythmia episodes provided by implanted devices, and comprehensive data on hospitalizations during follow-up.

### D.2.2. Secondary aims of the study

1. to determine whether ranolazine administration will decrease the likelihood of a composite arrhythmia endpoint consisting of VT or VF requiring ICD shock or death (while excluding VT/VF requiring just ATP)
2. to determine whether ranolazine administration will decrease the likelihood of composite primary endpoints consisting of hospitalization for cardiac causes (including not only hospitalization for heart failure, but also hospitalizations related to cardiac arrhythmias, myocardial infarction or ischemia) or death, whichever occurs first.
3. to determine whether ranolazine administration will decrease the likelihood of a composite secondary endpoint consisting of CHF hospitalization or death;
4. to determine whether ranolazine therapy will decrease the number of repeated hospitalizations for cardiac causes.
5. to determine whether ranolazine administration will decrease the likelihood of repeated ICD therapies (not just first therapy)
6. to determine whether ranolazine administration will decrease the likelihood of inappropriate shocks (a decrease in episodes of atrial fibrillation triggering inappropriate therapy) evaluating the risk of first and risk of repeated inappropriate shocks.
7. to determine whether ranolazine therapy will be associated with improvement in exercise capacity measured by the 6-minute walk test (6MWT) and in the quality of life measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ)
8. to evaluate the safety of ranolazine therapy utilizing ICD interrogation data documenting all types of ventricular tachyarrhythmias (including torsade de pointes).

## D.3. Overall Design of the Trial

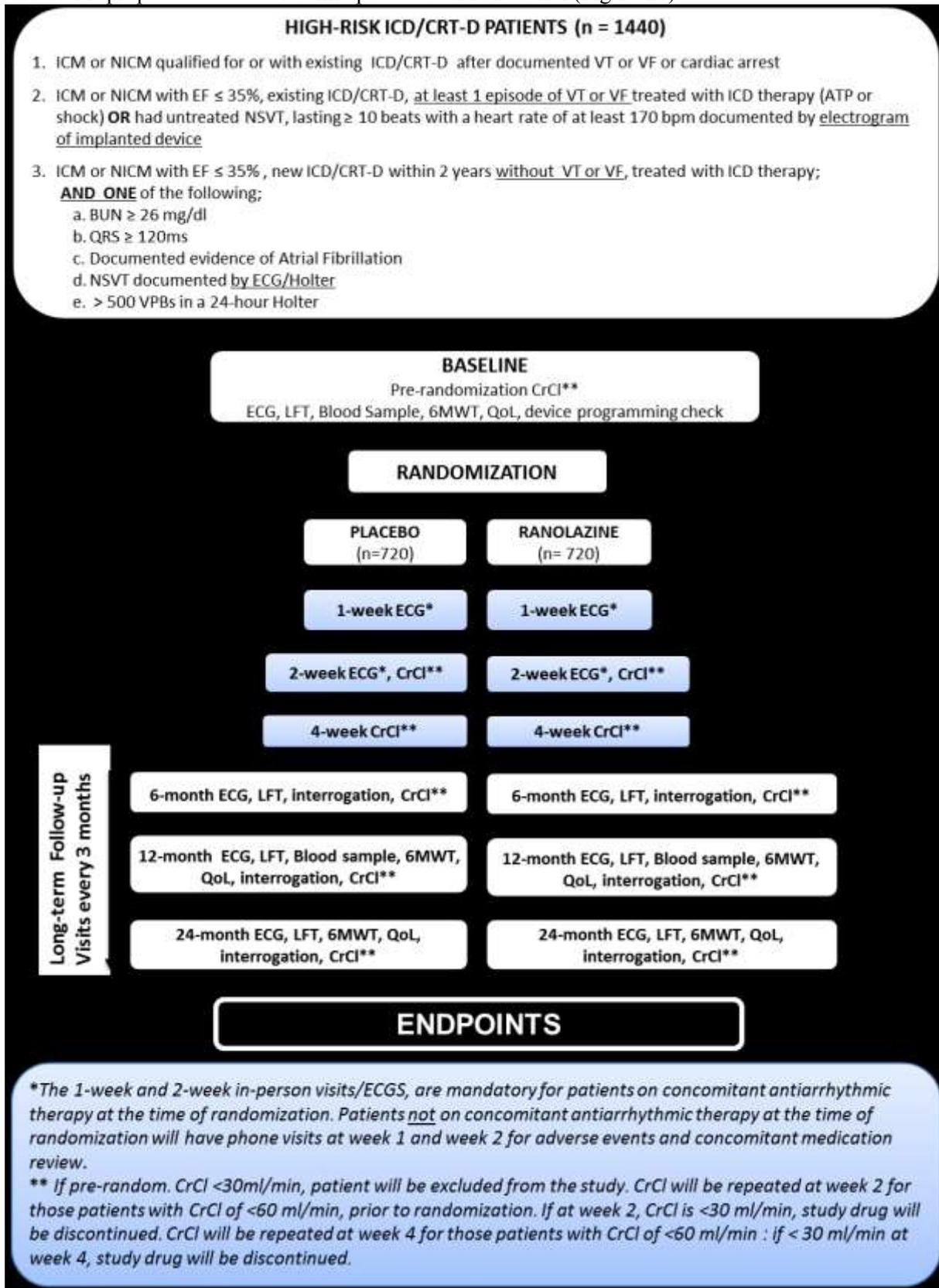This trial is proposed as a double-blind placebo-controlled trial (Figure 21).



 **Figure 21. Design of trial.**

**Study Drug Assignment:** At randomization, patients will be assigned to the ranolazine or placebo study medication treatment group. Study drug must be initiated within one calendar day following randomization. The dose of 1000 mg twice daily of ranolazine will be used in the active drug arm. However, as recommended for clinical use, each patient will be started on a 500 mg twice daily dose at baseline, for 1 week, with subsequent increase to 1000 mg twice daily after 1 week.

**QT Prolongation:** For patients on anti-arrhythmic therapy at the time of randomization, their ECG will be checked after 1 week on 500 mg twice daily dose. If there is evidence of QTc prolongation > 60ms after 1 week of therapy with 500 mg twice daily, the subject will remain in the study off study drug. The ECG will be checked again at week 2 on 1000 mg twice daily dose and the dose will be adjusted to 500mg twice daily, if there is a significant (> 60ms) prolongation of QTc in comparison to pre-dose ECG (pre-implant ECG for newly implanted ICD patients or post-implant ECG in newly implanted CRT-D patients; baseline study ECG in patients with older devices. In a large MERLIN trial,[51] with 3,279 patients randomized to ranolazine only 31 (0.9%) patients required dose adjustment due to prolongation of QT.

**Creatinine Clearance (CrCl):**

a. **Prior to Randomization**, CrCl will be performed <u>prior</u> to randomization to assess renal function. If CrCl is < 30ml/min, the patient will be excluded from the study. If CrCl is ≥ 30 ml/min, study drug will be initiated per protocol.

b. **Week 2**: CrCl will be repeated at week 2 for those patients who have a CrCl of < 60 ml/min, prior to randomization. If at the week 2 visit, their CrCl is < 30 ml/min, study drug will be discontinued but patient will remain in the study for follow-up. If CrCl is ≥ 30ml/min, study drug will be continued at their current dose, per protocol.

c. **Week 4**: CrCl will be repeated at week 4 for those patients who have a CrCl of < 60 ml/min: if ≥ 30 ml/min they can remain on their current dose of study drug, as per protocol. If CrCl < 30 ml/min, study drug will be discontinued, but patient will remain in the study for follow-up.

d. **Months 6, 12 and 24**: CrCl will be repeated at months 6, 12 and 24 for all patients taking study drug in the trial. If CrCl < 30 ml/min the study drug will be discontinued, but patient will remain in the study for follow-up. If CrCl ≥ 30 ml/min patients will remain on their current dose of study drug, as per protocol. If a patient develops severe renal impairment (< 30ml/min) anytime during the study, the patient will be taken off study drug, but patient will remain in the study for follow-up.

**<u>Liver function tests (LFTs):</u>** LFTs (AST and ALT only) will be performed at baseline, months 6, 12 and 24 with concomitant acquisition of ECGs to determine whether patients with elevated LFTs have evidence for QTc prolongation. Patients should be on optimal medical therapy including high usage of beta-blockers, ACE-inhibitors, and statins, in addition to antiarrhythmic therapy as recommended at the time consent is obtained. Patients and their primary physicians will be informed regarding potential for interactions of ranolazine with other drugs/substances that might be affected by ranolazine administration including strong CYP3A inhibitors including ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir and saquinavir; and moderate CYP3A inhibitors including diltiazem, verapamil, aprepitant, erythromycin, fluconazole and grapefruit juice or grapefruit-containing products.

**<u>Concomitant Medications:</u>**

CYP3A Inhibitors: Although, strong and moderately strong CYP3A inhibitors will exclude a patient from enrolling in the study we will allow randomized subjects who require strong CYP3A inhibitors (including ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir and saquinavir), or moderate CYP3A inhibitors (including diltiazem, verapamil, aprepitant, erythromycin, fluconazole and grapefruit juice or grapefruit-containing products), during their participation, to remain in the study: Randomized subjects, who require a strong CYP3A inhibitor, will be taken off study drug while on these class of drugs. Randomized subjects who require a moderate CYP3A inhibitor during the course of the trial will be administered ranolazine in the dose of 500 mg twice daily, while taking these classes of drugs.

**CYP3A Inducers:** Patients who require inducers of CYP3A such as rifampin, rifabutin, rifapentin, phenobarbital, phenytoin, carbamezepine and St.John's wort should be excluded from the study at the time of consent, or if already randomized, should be taken off study drug while on these class of drugs.

**Digoxin:** Concomitant use of Ranolazine and digoxin results in increased exposure to digoxin**.** Therefore, in patients taking digoxin, the dose of digoxin will be decreased in half (See section E.4.2 for further details).

**Statins:** The plasma levels of simvastatin, a CYP3A substrate, and its active metabolite are each doubled in healthy subjects receiving 80mg once daily and Ranexa 1000 mg twice daily. Therefore the dose of simvastatin in patients on any dose of Ranexa will be limited to 20mg once daily, when ranolazine is co-administered. Mean exposure to atorvastatin (80 mg daily) is increased by 40% following co-administration with Ranexa (1000 mg twice daily) in healthy volunteers. Therefore the dose of study drug in patients on 80 mg daily of atorvastatin will be limited to 500 mg twice daily, at the time of randomization. These patients will therefore not require a week 2 ECG to check QTc prolongation if they are also on an antiarrhythmic medication. Patients who may require 80 mg of atorvastatin during the study will also be limited to 500 mg twice daily while taking this medication. Patients on < 80mg atorvastatin do not require a dose reduction in study drug.

**Metformin:** In subjects with type 2 diabetes mellitus, concomitant use of Ranexa (1000 mg twice daily) and metformin results in increased plasma levels of metformin. Patients on > 1700 mg/day will have their dose of study drug limited to 500 mg twice daily during the study. Patients on > 1700 mg/day of metformin, at the time of randomization, will have their dose of study drug limited to 500 mg twice daily during the study. These patients will therefore not require a week 2 ECG to check QTc prolongation, if they are also on an antiarrhythmic medication. Patients who may require > 1700 mg/day of metformin during the study will also be limited to 500 mg twice daily while taking this medication. Patients on <1700mg/day metformin do not require a dose reduction in study drug .

**Liver Cirrhosis:** Patients who develop liver problems and/or scarring (cirrhosis) of your liver should be taken off study drug for the remainder of the study.

### D.3.1. Device Programming

The programming of implantable devices was revised to accommodate uniform approach to identification of arrhythmic endpoints. The following pre-specified ICD tachyarrhythmia programming parameters must be followed:

A. Tachyarrhythmia Programming

Primary Prevention ICD Indication Patients, without Prior VT/VF treated with ATP or shock, or prior ICD documented NSVT consisting of at least 10 beats at heart rate of at least 170 bpm:

- Monitoring zone 170-190 bpm [no therapy including no ATP]
- VT zone 190-220 bpm; initial duration of 5 seconds for Boston Scientific devices or equivalent in number of beats for other devices (See table below for details); ATP x1; 2nd therapy: shock (DFT +10J or max)
- VF zone >220 bpm with ATP turned off and shock after initial duration of 2.5 seconds for Boston Scientific devices or equivalent in number of beats for other devices
- RV pacing set at 40 bpm when programmed in VVI mode

Secondary Prevention ICD Indication Patients, or Primary Prevention Patients with Prior VT/VF treated with ATP or shock, or with untreated ICD-documented NSVT:

- Monitoring zone 170-190 bpm [no therapy including no ATP]
- VT zone 190-220 bpm; detection initial duration of 2.5 seconds for Boston Scientific devices or equivalent in number of beats for other devices**(see table below for details); ATP x1; 2nd therapy: shock (DFT +10J or max)

*__If evidence for documented VT or NSVT < 190 bpm: VT zone ≤20 bpm below clinical VT and ATP x1;
2nd therapy: shock after 5 seconds__*
- VF zone >220 bpm with ATP turned off and shock after initial duration of 2.5 seconds for Boston Scientific devices or equivalent in number of beats for other devices
- RV pacing set at 40 bpm when programmed in VVI mode

B. Antibradycardia Programming

Antibradycardia programming should follow best practice and seek to minimize ventricular pacing in patients without CRT devices.
- In patients without sinus or AV node disease, antibradycardia pacing should be programmed to VVI 40.
- In patients with complete heart block, rate-responsive pacing should be programmed as appropriate: VVIR for those with permanent AF and DDDR for those with sinus rhythm.
- In patients with sinus node dysfunction and prolonged AV conduction: DDI or DDD (or DDIR or DDDR) with lower rate of between 40-60 bpm with a long AV delay to limit right ventricular pacing; AAI<-->DDD (Medtronic) or SafeR (Sorin) or AV Search+ (or Reverse Mode Switch in Boston Scientific) or Ventricular Intrinsic Preference (VIP® Extension) (St. Jude).
- In those with CRT, the device should be programmed to optimize % BiV pacing. A lower rate limit of 40-60 bpm and optimization of AV delays (consistent with local standard practice) should be considered.

**Programming of delay in VT/VF zones by manufacturer**

| Manufacturer | Primary Prevention No Prior VT/VF | | Secondary Prevention or Primary Prevention with Prior VT/VF or ICD documented NSVT | |
|---|---|---|---|---|
| | VT zone[1] (190-220 bpm) | VF zone[1] (>220 bpm) | VT zone[1]** (190-220 bpm) | VF zone[1] (>220 bpm) |
| Total Duration* | 7 sec | 4.5 sec | 5 sec | 4.5 sec |
| Boston Scientific | Initial Duration = 5 sec | Initial Duration = 2.5 sec | Initial Duration = 2.5 sec | Initial Duration = 2.5 sec |
| Medtronic | **VT** initial beats to detect = 24 | **VF** initial beats to detect = 18/24 | **VT** initial beats to detect = 16 | **VF** initial beats to detect = 18/24 |
| St. Jude Medical | 24 | 18 | 16 | 18 |
| Biotronik | 24 | 18/24 | 16 | 18/24 |
| Sorin/ELA | 8/12 (Y=12;X%=75%) VT Persistence = 16 | 8/12 (Y=12;X%=75%) VF Persistence = 10 | 8/12 (Y=12; X%=75%) VT Persistence = 8 | 8/12 (Y=12; X%=75%) VF Persistence = 10 |

* Includes detection time and initial duration or respective number of beats

**If evidence for documented VT *or NSVT* < 190 bpm: VT zone ≤20 bpm below clinical VT

[1] cut off heart rates for respective devices:
- BSci 170 / 190 / 220
- MDT 171 / 188 / 222
- SJM 171 / 190 / 222
- Biotronik 171 / 188 / 222
- Sorin/ELA 170 / 190 / 220

These stringent programming criteria will ensure that only severe arrhythmias are treated.

### D.3.2. In –Person and Telephone Follow-up visits

Patients will be followed for 24 months on average (ranging from 6 months to 36 months) with in person follow-up visits scheduled 1 and 2 weeks (for patients on anti-arrhythmic therapy only, at the time of randomization) after randomization and subsequently every 6 months. Additional visits will be conducted every 3 months either via telephone or in person. It is expected that on average randomized patients will have two additional unscheduled visits related to unexpected adverse drug experiences (i.e. adverse drug experiences not consistent with the drug package insert). Table 2 shows the schedule of data collection and testing.

**Table 2: Data Collection and Study Testing Acquisition Schedule**

| Reportable Data Items | In Person Visit | Telephone or In Person Visit | | | In Person Visit | | | | Telephone or In Person Visit | In Person Visit |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | 1 Week Visitς | 2 Week Visitς | 4 week visit | 6 month Visit | 12 Month Visit | 24 Month Visit | 18/30/36 Month Visits | Remaining visits every 3 months (3, 9, 15, 21, 27, 33) | Unscheduled Visits* |
| | | 7+3 days | 14+3 days | 28+3 days | +14 days | +14 days | +14 days | +14 days | +14 days | |
| Creatinine Clearance (Blood Sample) | ✓**** | | ✓**** | ✓**** | ✓ | ✓ | ✓ | | | |
| Clinical/Device Data | ✓ | | | | | | | | | |
| Review of Concomitant Medications | ✓** | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Study drug dispensing | ✓ | | | | ✓ | ✓ | ✓ | ✓ | ✓ | |
| Physical Assessment | ✓ ** | | | | ✓ | ✓ | ✓ | ✓ | | ✓ |
| 6 Minute Walk Test | ✓** | | | | | ✓ | ✓ | | | |
| Kansas City Cardiomyopathy Questionnaire | ✓** | | | | | ✓ | ✓ | | | |
| ECG *** | ✓** | ✓ς | ✓ς | | ✓ | ✓ | ✓ | | | |
| Liver Function Tests (Blood Sample) | ✓** | | | | ✓ | ✓ | ✓ | | | |
| Pregnancy test † | ✓** | | | | | | | | | |
| BNP & Future Storage (Blood sample ) | ✓** | | | | | ✓ | | | | |
| Device Interrogation | ✓§ | | | | ✓ | ✓ | ✓ | ✓ | | ✓ |
| Adverse Events ‡ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

\* It is expected that additional unscheduled visits will occur in relation to unexpected adverse drug experiences (i.e. adverse drug experiences not consistent with the drug package insert).

\*\* Obtain prior to start of study medication (can be obtained prior to randomization).

\*\*\* Required pre-implant ECG can we copied from patient's chart and required post-implant pre-drug ECG can be obtained from patient chart or recorded during baseline visit.

\*\*\*\* Obtain prior to randomization. Only required at week 2 if CrCl < 60 ml/min at baseline. If CrCl < 30ml/min at week 2, patient will discontinue study drug. Only required at week 4 if CrCl <60 ml/min at week 2. At week 4, if <30 ml/min the study drug needs to be stopped. .If ≥30 ml/min they remain on current dose of study drug per protocol.

†Women at age <55 years old will be required to undergo pregnancy test to rule out pregnancy.

‡ Information regarding adverse events will be collected throughout the study apart from pre-specified visits.

§ Initial Device Check to reconfirm programming of implanted device.

ᶜ The 1-week and 2-week in-person visits/ECGs are mandatory, for patients on concomitant antiarrhythmic therapy at the time of randomization. Patients not on concomitant antiarrhythmic therapy at the time of randomization will have phone visits at week 1 and week 2 for adverse events and concomitant medication review.

## D.4. Study Population: Inclusion and Exclusion Criteria

The study population will consist of 1,440 high-risk patients with ischemic or nonischemic cardiomyopathy who receive their ICDs as standard of care for primary or secondary prevention of mortality following approved indications for ICD therapy. High-risk patients will be defined as:

A. Secondary Prevention Patients

Subjects with ischemic or nonischemic cardiomyopathy, qualified for or with existing ICD (or CRT-D) after documented VT/VF or cardiac arrest (secondary prevention of mortality).

Secondary prevention subjects with existing implants are eligible regardless of when the implant was received (subjects could be recruited from outpatient clinics or from inpatient activity including during re-implant or other procedures).

B. Primary Prevention Patients

The following two groups of primary prevention patients are eligible:

1. Patients with primary prevention indications for ischemic or non-ischemic cardiomyopathy with EF ≤ 35%, with existing devices (ICD/CRT-D), regardless of when the device was implanted, who have experienced at least ONE episode of VT/VF appropriately treated with ICD therapy (ATP or shock) or had untreated NSVT lasting at least 10 beats with heart rate of at least 170 bpm, documented by electrogram of their implanted device.

   Untreated NSVT documented by ICD interrogation should be identified based on electrogram, not just based on non-verified count/log of the device. Local physician's diagnosis of NSVT of at least 10 beats in a row with a heart rate of at least 170 bpm is required to avoid qualifying patients with atrial arrhythmias identified by the device as NSVT.

2. Patients with ischemic or non-ischemic cardiomyopathy with EF ≤ 35%, who have been implanted within the last 2 years (initial ICD/CRT-D implants, including upgrades from pacemakers) who have NOT experienced VT/VF treated with ICD therapy (ATP or shock), AND who have ONE of the following additional criteria:

   a. BUN ≥ 26 mg/dl
   b. QRS ≥ 120ms
   c. Documented evidence of Atrial Fibrillation,
   d. NSVT documented by ECG/Holter
   e. >500 Ventricular Premature Beats (VPBs) documented  in a 24-hour Holter.

Patients receiving ICDs (or CRT-Ds) for primary prevention of mortality constitute a high-risk subset of the overall patient population with MADIT II and SCD-HeFT indications for ICDs, as described in section C of this application.

   a. **BUN:** BUN level is frequently obtained at the time of device implantation as part of routine pre-procedure evaluation. Most recent BUN within 2 calendar years prior to date consent obtained should be used. If BUN level is not available, it should be performed as part of the screening for the study.

   b. **QRS:**  Current (pre-implant or most recent) ECG obtained within 2 calendar years prior to implant with a non-paced rhythm, should be used to determine QRS duration based on automatic ECG readout.

c. **Atrial fibrillation:** documented evidence for existing atrial fibrillation or atrial flutter rhythm on ECG or documented ECG evidence for paroxysmal atrial fibrillation during past 2 calendar years prior to date consent obtained. For patients with preexisting pacemaker with ventricular pacing, paced QRS duration will not be used as a criterion qualifying patients with primary prevention (only non-paced beats could be used to employ QRS duration criterion). Patients with atrial fibrillation or history of atrial fibrillation on antiarrhythmic therapy are eligible to be enrolled.

d. **NSVT:** Documentation of NSVT on ECG/Holter/telemetry within 2 years prior to implant of device or after implant of device.

e. **VPBs:** Frequent >500 VPBs per 24 hour, Holter recording should be performed within 2 years prior to implant of device or after implant of device.

## D.4.1.Inclusion Criteria

Patients who meet all of the following criteria at the time of consent could be included in this clinical investigation:

− Secondary or primary prevention patients with ischemic or nonischemic cardiomyopathy  who meet current guidelines for ICD or CRT-D device therapy and meet the above definition of high-risk patients
− Patient on stable optimal pharmacologic therapy for the cardiac condition, including use of anti-arrhythmic therapies such as (but not limited to) amiodarone, sotalol, dronedarone, and dofetilide.
− Patient greater than or equal to 21 years of age without upper limit

## D.4.2. Exclusion Criteria

Since the study will enroll and subsequently randomize patients who are routinely implanted with ICD devices, exclusion criteria will be limited mostly to conditions precluding or limiting implantation of devices based on currently approved indications..

Specifically, patients who meet any one of the following criteria at the time of consent will be excluded from this clinical investigation:

• Patients receiving first device with coronary artery bypass graft surgery within the last 3 calendar months prior to date consent obtained
• Patients receiving first device with percutaneous coronary intervention within the last 1 calendar month prior to date consent obtained
• Patients receiving first device with enzyme-positive myocardial infarction with the past 3 calendar months prior to date consent obtained
• Patients receiving first device with angiographic evidence of coronary disease who are candidates for coronary revascularization and are likely to undergo coronary artery bypass graft surgery or percutaneous coronary intervention in the foreseeable future
• Patients in NYHA Class IV
• Patients receiving prophylactic ablation of ventricular substrate
• Patients with preexisting QTc prolongation >550ms
• Patients on strong CYP3A inhibitors (including ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir and saquinavir and moderate CYP3A inhibitors, including, diltiazem, verapamil, aprepitant, erythromycin, fluconazole and grapefruit juice or grapefruit-containing products.
• Patients on CYP3A inducers such as rifampin, rifabutin, rifapentin, phenobarbital, phenytoin, carbamezepine and St.John's wort
• Patients with inherited arrhythmia disorders such as Brugada's, ARVD, LQTS or hypertrophic cardiomyopathy
• Patients who are pregnant or plan to become pregnant during the course of the trial (patients at child bearing age who use prescribed pharmaceutical contraceptives could be enrolled)
• Patients with irreversible brain damage from preexisting cerebral disease
• Patients with presence of any disease, other than the patient's cardiac disease, associated with a reduced likelihood of survival for the duration of the trial, e.g., cancer, uremia, liver failure, etc.

- Patients with chronic renal disease with creatinine ≥2.5 mg/dl or creatinine clearance <30 ml/min.
- Patients participating in any other clinical trial
- Patients unwilling or unable to cooperate with the protocol
- Patients who live at such a distance from the clinic that travel for follow-up visits would be unusually difficult
- Patients who do not anticipate being a resident of the area for the scheduled duration of the trial
- Patients who are decisionally impaired adults, those of questionable capacity, and those who cannot consent for themselves will not be recruited for this study.
- Patients unwilling to sign the consent for participation

### D.4.3. Inclusion of women

Inclusion of women and minorities in the trial is discussed in more detail in Section E.9. Women at age <55 years old will be undergoing pregnancy test to rule out pregnancy (unless they underwent hysterectomy).

### D.5. Follow-up and Endpoints

In addition to 1- and 2-week initial visits, (mandatory in-person clinic visit for those patients on anti-arrhythmic therapy at the time of randomization) patients will have long-term follow-up clinic visits scheduled every 6 months and follow-up visits either in person or via telephone every 3 months. The follow-up clinic visit will include dispensing study medication, acquisition of clinical information regarding cardiac events and changes in medication or device programming and data on arrhythmias from interrogated ICDs. Floppy disks or other electronic storage media with interrogation data will be forwarded to the Rochester Clinical Core Laboratory for central reading and interpretation. The ICD Interrogation Committee will adjudicate all arrhythmic events. The Endpoint Adjudication Committee will review and categorize all cardiac hospitalizations and death cases and will have access to data from the ICD Interrogation Committee.

Primary endpoint of the study will be defined as a composite endpoint consisting of VT/VF requiring ATP therapy, ICD shock, or death, whichever occurs first

Secondary endpoints will include:
- ICD shock for VT or VF or death, whichever occurs first
- hospitalization for cardiac causes or death, whichever occurs first;
- CHF hospitalization or death, whichever occurs first;
- number of repeated hospitalizations for cardiac causes over time;
- number and frequency of repeated arrhythmic events (VT/VF) over time;
- inappropriate therapy;
- functional capacity measured by the 6-minute walk test;
- quality of life assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ).

Hospitalizations for cardiac causes will include all hospitalizations related to the following frequent conditions: heart failure, ventricular tachyarrhythmias, unstable angina, myocardial infarction, atrial fibrillation/flutter or atrial tachyarrhythmias, high blood pressure, ICD related hospitalizations, pulmonary embolism, and other cardiac conditions not listed here.

Information regarding all cardiac events including all hospitalizations, arrhythmia episodes, and death cases will be provided by enrolling centers to central database and designated endpoint adjudication committees will categorize these events. There will be an endpoint committee adjudicating hospitalizations and death and a separate committee adjudicating arrhythmia episodes documented by ICDs. The committees will be blinded regarding randomization of evaluated patients. We considered using remote device monitoring, but since the study medications need to be dispensed to the patients every 3 months we rely on this personal visits to acquire data from interrogated ICDs. The events that occur after final visit but prior to withdrawal or death will be obtained.

When already enrolled, patients with VT/VF events observed during follow-up will be allowed to be treated with antiarrhythmic medications (as per physician discretion) to be added on top of the study drug (ranolazine or placebo). Similarly, patients requiring antiarrhythmic medications for supraventricular arrhythmias including atrial fibrillation will be allowed to be treated with antiarrhythmic medications.

### D.6. Planned enrollment and randomization

The trial will randomize 1,440 patients in approximately 100 enrolling centers over a period of approximately 27 months following enrollment (date consent obtained). This rate of randomization is equal to about 0.67 patients per month per center on average and is comparable to our recently completed MADIT-CRT trial of 1820 randomized patients where the average randomization rate per center per month was around 0.65 patients per month. We chose to use conservative estimates regarding the rate of randomization. However, we believe that our study could randomize 2-3 patients per month per center on average since volume of ICD implants is high in select enrolling centers.

### D.7 Timeline of the Study

The first 6 months of the study will be devoted to start-up activity needed to establish the organization of the study, the database, and to obtain RSRB approvals in all the enrolling centers. The enrollment activity with subsequent randomization is planned for subsequent 27 months with up to 20 additional months of follow-up allowed for (uncertain due to the stopping rule) and 1 month for final adjudication of events. The last 6 months will be devoted to closeout activities and final data analyses (Table 3):

**Table 3. Timeline of Planned Activity for the Trial**

| Activity | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Start-up | XXXX | | | | |
| Enrollment | XXXX | XXXXXXX | XXXXXXX | XXXXX | |
| Follow-up | XXXX | XXXXXXX | XXXXXXX | XXXXXXX | XXXXX |
| Closeout | | | | | XXXX |
| Final data analysis | | | | | XXXX |

### D.8. Quality of Life

Quality of life data will be acquired at baseline and after 12 and 24 months of therapy using the Kansas City Cardiomyopathy Questionnaire (KCCQ).[60,61] It is hypothesized that quality of life measures will improve after treatment with ranolazine in comparison to placebo.

### D.9. The 6-minute Walk Test (6MWT)

The 6MWT is routinely used in evaluating functional status in heart failure studies,[62,63] and will provide additional insight regarding the effect of tested drugs on functional/physical capacity of randomized patients. The 6MWT will be performed at baseline and repeated at 12-month- and 24-month follow-up visits. It is hypothesized that there will be improvements in the distance achieved during the 6MWT for patients assigned to ranolazine relative to those on placebo.

### D.10. Blood Samples for BNP and Future Research

Blood samples in the amount of 10 ml (2 teaspoons) will be collected in all randomized patients at baseline and at the 12-month follow-up visit to determine changes in levels of Brain Natriuretic Peptide (BNP) over time and, if the patient consents, an additional 10 ml (2 teaspoons) will be collected at baseline and the 12-month follow-up visits for future research on heart failure. It is hypothesized that ranolazine with its expected beneficial effects on LV systolic and diastolic function will contribute to a significant decrease in levels of BNP, a marker of heart failure advancement, and marker of risk in heart failure patients. The core lab for analyzing BNP will be at the University of Rochester Medical Center Laboratories. Blood samples will be sent directly to URMC Laboratories, where they will be analyzed using the FDA cleared Elecsys Pro-BNP Immunoassay method. Methodology of blood drawing, shipping and storing will follow standard procedures in operations for years in clinical trials coordinated by the University of Rochester Medical Center.

The budget of the trial allows for the analysis of the BNP levels, which could provide an objective insight into the effect of treatment. However, the budget does not cover analyzing numerous other biochemical markers or genetic markers of interests. Using the same blood samples, when the data and blood collection is completed, we intend to apply for additional funding specifically focused on testing novel biochemical and genetic markers, and at that time we will outline full detailed plan of such analyses. The blood samples will be stored for future additional analyses pending future funding. These analyses might include additional biochemical, metabolic markers and genetic markers identifying patients with cardiac events and/or identifying patients with differential response                                        to                                        ranolazine                                        therapy.

Among several possible future biomarkers, we intend to study: 1) serum markers of increased collagen synthesis, primarily procollagen type III N-terminal amino peptide (PIIINP) is the best overall index for detecting increased collagen synthesis and myocardial fibrosis in heart failure; 2) inflammatory markers including interleukin-6, interleukin-1β; and transforming growth factor-β1; 3) genetic polymorphisms of genes reflecting variation in the CYP3A enzymatic system metabolizing ranolazine; 4) genetic polymorphisms of the SCN5A sodium channel gene and genes influencing function of sodium homeostasis in myocardial cell; 5) genetic polymorphisms of the ryodine receptor genes and other known and newly identified genes related to intracellular calcium handling. The final list of the biomarkers of interest will be established few years from now when the study is completed and when there will be a possibility of taking advantage of newly identified biomarkers.

## D.11. TRIAL DESIGN; POWER, DURATION AND STATISTICAL ANALYSIS

### D.11.1. Endpoint Event Rates

Based on recent preliminary unpublished data from the MADIT Risk Stratification Study and from the MADIT-CRT trial, we revised our estimate of the 2-year cumulative endpoint rate to be 25% in the placebo arm of the trial (instead of original 30%). We maintain the same level of reduction of primary events: for the ranolazine arm (R), we expect at least a 25% reduction in risk, after allowing for the possibility of 10% cumulative crossovers to placebo (within 2 years) — that is, a hazard ratio (HR) of 0.75. This implies a 2-year cumulative event rate in R of 19% [= $1 - (1 - 0.25)^{0.75}$], representing a 24% reduction in 2-year cumulative event rates. We expect no crossovers from P to R. We allow for losses to follow-up at the rate of 5% per year.

### D.11.2.Significance Level and Power

The null hypothesis is that the true cumulative probability curves for time to first endpoint event are identical in the R and P arms (implying a HR of 1.0). The alternative hypothesis is that the curve for the R arm is below that for the P arm, implying a reduction in risk of a first endpoint event. Power computation is focused on a constant hazard ratio (HR) of 0.75, a 25% reduction in ongoing risk, an amount deemed worthy as clinically relevant, although a HR of 0.667 is considered quite possible. The trial is designed to have a significance level of 0.05 (2-sided) and 80% power at a constant HR of 0.75. See the table below for resulting power at other HRs; power is 98% at a HR of 0.667.

### D.11.3. Recruitment and Randomization

We will randomize 1440 patients in approximately 100 centers. The randomization is expected to require 33 months at an average rate of 44 per month, or 0.54 patients per center per month. Consented patients will be randomized equally to the R and P arms, with randomization stratified by enrolling center, by type of device (ICD vs. CRT-D), within center, and by prior history of VT/VF/cardiac arrest within device type. No further stratification is really feasible. We assume balance between treatments within each device type is more critical than within ischemic and non-ischemic patient groups, or other possible risk categories.

### D.11.4. Sequential stopping rule

A trial that continues follow-up until a pre-specified number of endpoints have accumulated, and based on a log rank test, would require 380 endpoint events. At the anticipated randomization rate, loss rate and endpoint event rates, a larger sample size and/or longer follow-up time would be required.

We have chosen instead a sequential stopping rule with triangular stopping boundaries, similar to that used in the MADIT and MADIT-II trials.[21] The expected number of events needed to reach a termination boundary is greatly reduced, although some risk of a longer trial is encountered. We chose a specific boundary as provided by PEST software[64] (as well as our own) that would meet the significance level and power requirements.

The trial is to be monitored by periodically fitting a proportional-hazards regression model with treatment arm and six presumed risk factors as covariates (see ANALYSIS section below) and stratified by enrolling center. The resulting score-test statistic, $Z$, for testing nullity of a treatment effect, when plotted against its variance V, behaves like a Brownian motion with $\beta$, the regression coefficient for treatment effect, as its drift [65] The statistic Z quantifies any difference between treatment arms R and P in estimated time-to-endpoint curves. Its variance $V$ (roughly equal to the accumulated event count divided by 4) quantifies statistical information. This computation will be done monthly, once 20 events have been accumulated, and submitted to the DSMB chair and statistician. A plot of $Z$ versus $V$, starting at the origin, will continue until it reaches one of the two boundaries:

$14.8153 + 0.101103*V$ (upper)    and    $-14.8153 + 0.303309*V$ (lower)

and truncated at $V = 130$. (The boundaries may be adjusted to recognize the discrete-time monthly monitoring.[65]) Upon reaching a boundary, the trial is to be terminated in favor of R if $Z$ reaches the upper boundary and therefore p ≤ 0.05. If $Z$ first reaches the lower boundary with p ≤ 0.05 (that is, prior to $V =$ 18.585), the trial will be terminated with a conclusion that P is superior to R — i.e., that ranolazine increases risk of endpointing. If $Z$ reaches the lower boundary with p > 0.05 ($V >$ 24.24), or along the vertical strip at $V =$ 130, the null hypothesis of no difference between R and P cannot be rejected. The p-value is appropriately adjusted for the stopping boundary.[60]Theplot should vary around a line from the origin with slope $\beta = -log$(HR), with HR the hazard ratio for treatment effect (R:P)

Power at various true HRs is given in column 2 of the table below. In column 3 are given the numbers of events expected upon reaching termination. Also listed are the associated expected trial durations. [See the Technical Note below.] Computations of duration assume recruitment of 1440 patients in 33 months, a cumulative event rate in the placebo arm of 25% at 2 years, and losses to follow-up occurring at an annual rate of 5%

## D.11.5. Trial Power and Duration[@]

| True HR | Power (in %)* | Events** at Termination | Estimated Trial Duration (months) | | | | Upper Quartile[##] | Total Duration[##] |
|---|---|---|---|---|---|---|---|---|
| | | | Recruit | Add'l F-u | Extra[#] | Total | | |
| 1.00 | 2.5 | 191 | 27 | 0 | 1 | 28 | 250 | 35 |
| 0.90 | 17 | 248 | 33 | 2 | 1 | 36 | 320 | 42 |
| 0.85 | 35 | 270 | 33 | 4 | 1 | 38 | 346 | 45 |
| 0.80 | 58 | 273 | 33 | 5 | 1 | 39 | 350 | 46 |
| **0.75** | **80** | **253** | **33** | **4** | **1** | **38** | **322** | **44** |
| 0.70 | 93 | 271 | 33 | 1 | 1 | 35 | 271 | 40 |
| 0.65 | 99 | 177 | 39 | 0 | 1 | 30 | 220 | 36 |

[@] All durations are measured from July 1, 2012. Due to the delayed start-up, and according to the revised Accrual Milestones, we act as if recruitment is carried out evenly over the 33 month period July 2012 through March 2015, with 130 patients every 3 months.

* probability of a positive trial

** in the two arms together. The actual number is random and highly variable, depending on how the trial develops; what is tabled is the expected number to reach a stopping boundary (that is, averaged over many such trials under the same conditions). However, any particular trial can require as many as 130*4=520 events ($V = 130$), although it is highly unlikely ─ with probability < 0.001.

[#] The extra month is allowance for endpoint adjudication time. Again, total duration is the expected duration under the stated conditions, but actual duration may vary. `Duration' is measured from the time enrollment is underway at most centers until the trial ends.

[##] The last two columns give the upper quartile of the number of events at termination and the corresponding trial duration.

As seen in the table, under the stated assumptions, whatever the true hazard ratio, the trial is expected to require at most 38 months once the speed up of randomization begins, with the trial estimated to end in August 2015 leaving time to allow for closeout and analysis; 44 months duration would still allow closeout and analysis within a one-year no-cost extension. However, these computations are based on the very conservative assumption of a 25% 2-year event rate in the placebo arm whereas the revised eligibility will likely lead to a higher event rate since higher proportion of patients with prior VT/VF will be expected. Any increase in the event rate will speed up termination of the trial. Also, a smaller HR will shorten duration of the trial.

## D.11.6. Analysis

At the end of the trial, a p-value for the primary hypothesis, an estimate of the true hazard ratio for treatment effect, and 95% confidence limits for the true hazard ratio will be determined, by methods adjusted to the sequential stopping rule.[65] The primary analysis will be a statistical test of treatment effect based on a Cox proportional-hazards regression analysis stratified by enrolling center ─ as used in the sequential monitoring ─ with six additional baseline covariates: ejection fraction, creatinine, age (all three numerical), ischemic status (binary), antiarrhythmic medication at enrollment (binary) and a 3-level variable identifying the following groups: - ICD and no history of VT/VF/cardiac arrest at enrollment; - CRT-D and no history of VT/VF/Cardiac Arrest at enrollment; - history of VT/VF/cardiac arrest, whether prior to implantation of device or afterwards. Device type is not expected to have an effect on risk in this third subgroup. (This last subgroup does not distinguish between device types as they are not expected to have an effect on risk once VT/VF or a cardiac arrest has been experienced. These risk factors were chosen as being those found to be relevant in corresponding (unpublished) analyses of data from the MADIT-II and MADIT-CRT trials. Computations will be done by software developed at the University of Rochester, and will be confirmed by use of PEST software.[64] Some additional events will likely be reported after formal trial termination (events that occurred prior to termination), and these will be incorporated in the final adjusted p-value, hazard ratio and confidence limits computations.[66]

### D.11.7. Validation and Assumptions

Computations of p-values are broadly valid, but estimation of HRs presume a (near) constant hazard ratio. Hence, interpretation of the HR estimates in the primary analysis depends on validating the proportional hazards assumption. This will be done by computing HRs by both 3- and 6-month intervals, with tests for differences among the time-specific HRs.

### D.11.8. Sensitivity Analysis

- Baseline covariate balance between arms: The primary analysis will be repeated including each (one at a time) baseline covariate in the regression model that is out of balance between arms.
- Evaluation of various combinations of the 3 components of the composite endpoint: A competing-risk analysis for separate components of the endpoint, determining a hazard ratio R:P for each, will be carried out,[67] in particular, for VT/VF requiring ATP, for ICD shock, for death, and for the first of ICD shock and death. The last of these provides an evaluation of the original composite endpoint without inclusion of the VT/VF requiring ATP component. Power for the others is not predicted, but power for the latter – namely ICD shock /death – is estimated to be 80% at a hazard ratio of 0.72.

### D.11.9. Treatment Interactions

The primary analysis will be repeated (without adjustment for the stopping rule), adding each of a pre-specified list of covariates (if not already in the regression model), one at a time, and their interaction with treatment arm to the regression model, and tests for interaction carried out. This will identify, to the extent feasible, different treatment effects of Ranolazine across subgroups identified by the covariate.
- CRT versus ICD groups
- Primary versus secondary prevention groups
- Ischemic versus non-ischemic groups
- Females versus males
- Older versus younger
- BNP> versus <= median
- Diabetes mellitus (yes versus no)
- Antiarrhythmic medication at baseline
- Large centers versus small centers

### D.11.10. Technical Note

The formula for the number $N$ of events expected in a single arm of the trial, assuming recruitment of $n$ patients to the arm in $m$ months and then an additional $f$ months of potential active follow-up, a monthly rate $b$ of losses, and a monthly rate $r$ of endpoint events, may be shown to be

$$N = n*(r/s)*\{1 – [\exp(-s*f) – \exp(-s*d)]/(m*s)\} \text{ with } s = r + b \text{ and } d = m + f.$$

(Derivation involves integration over exponentially distributed endpoints and losses and over uniformly distributed randomization.) Computing $N$ using the rate $r$ for the P arm, and again with $r$ replaced by HR*$r$ for the R arm, and adding, gives the number of events expected in a trial of duration $d$ months. For the P arm, $r$ = [-log(1-0.22)]/24 = 0.0103526; and $b$ = [-log(1-0.05)]/12 = 0.004274, $n$ = 720 and $m$ = 27. Carrying out this computation for a list of $f$ values, and various values of HR, provides corresponding pairs of values for total duration $d$ and the corresponding total number of events. This analysis ignores any potential effect of including six risk factors in the regression analysis, and is hence conservative.

PEST software (or other sequential trial software) can provide the number of events expected at termination of a sequential trial, in column 3 of the table above. Using the list of event-duration pairs, this leads to corresponding total duration (after adding in the additional month for adjudication time) for each row of the table. The number 720 of patients in each arm was found by trial and error as that value $n$ needed to assure satisfactory total duration times. The last two columns of the table were similarly determined.

**D.11.11. Secondary Analysis**

The primary analyses with primary endpoints are planned with 80% power to detect specified differences between the ranolazine and placebo arms. Secondary aims will likewise require power of 80% (or more), where possible.

The first three secondary aims (see Section D.2) are similar to the primary aim except with different composite endpoints. Hence, analysis of each will be similar to that for the primary aim, except that no adjustment for the sequential stopping rule will be feasible (as stopping is based on the primary composite endpoint).

1. Secondary aim #1, as mentioned above, power for ICD shock /death is estimated to be 80% at a hazard ratio of 0.72.
2. Secondary aim #2, in which hospitalizations for cardiac causes or death is the secondary endpoint, it is expected that at least 30% of patients in the placebo arm will reach this endpoint, leading to considerably more power than for the primary endpoint, namely 80% at a 25% reduction in the ongoing risk.
3. Second aim #3 addresses the effect of ranolazine on the composite endpoint consisting of CHF hospitalization or death. We assume that a 2-year probability of this endpoint in the placebo arm should reach at least 20%, resulting in power exceeding 80% for detecting a 30% reduction in the ongoing risk of this endpoint.
4. Secondary aim #4 is about repeated hospitalization for cardiac causes; for it, an Anderson-Gill regression analysis (comparable to Cox analysis for a first event), but with death as a competing risk,[67,68] will be carried out to assess any difference in ongoing risk of repeated therapy in the two arms of the trial. Power at comparable risk reductions should exceed that for secondary aim #2; this is confirmed by analysis of comparable subsets in the MADIT II data.
5. Secondary aim #5 is about repeated ICD therapies; for it, again (see aim #4 above) an Anderson-Gill regression will be carried out to assess any difference in ongoing risk of repeated therapy in the two arms of the trial. Power at comparable risk reductions should exceed that for the primary endpoint; this is supported by results from the azimilide SHIELD trial.
6. Secondary aim #6 is about inappropriate shocks. For first inappropriate shocks, a Cox regression analysis will be done while for repeated shock episodes, an Anderson-Gill analysis will be done; each of these will need to treat death as a competing risk.[67,68] The rate of first inappropriate shocks at 2 years is expected to be 16% (or more), allowing 80% power to detect a HR of 0.70. Power to detect similar effects for repeated shock episodes will be greater.
7. Secondary aim #7 is about safety of ranolazine therapy; each type of safety issue will be individually analyzed by use of ICD interrogation data, and summary statistics will be compiled.
8. Secondary aim #8 is about quality of life (QoL ─ see Section D.8). For each patient having both baseline and 2-year QoL data, the change in QoL from baseline to 2 years will be determined and averaged over patients in each arm. Comparison of mean changes in the two arms will be evaluated by a t-test. We expect at least 500 patients in each arm to have the needed 2-year QoL data (at least those recruited during the first 13 months). Earlier experience with the Kansas City Cardiomyopathy Questionnaire suggests a standard deviation for a single change in scores to be approximately 20. This should allow 80% power to detect a difference between arms in mean scores of 2.5 points and 90% power to detect difference of 3.0 points. Mean scores are expected to be in the neighborhood of 30 to 40.

For the 6MWT, we will compare distance achieved by patients at baseline and at 2-year follow-ups, again limited to those with both 6MWTs, as measure of physical functioning. The primary analyses will be focused on the 2-year time-point and similarly to the quality of life analyses, we expect that at least 500 patients will have these tests performed. Based on prior studies, a standard deviation for a single change in the distance of the 6MWT is expected to be approximately 50 meters. This should allow 80% power to detect a difference between arms in mean distance of 6.5 meters and 90% power to detect a 7.5-meter difference in mean distance of 350 meters.

## D.12 ORGANIZATION AND KEY PERSONNEL

This proposal consists of two applications originating from the University of Rochester Medical Center, Rochester, NY: 1) Clinical Core (CC) managing the overall study, activity of enrolling centers and core labs, and 2) Data Coordination Center (DCC) responsible for data management and data analyses. The Clinical Core application will serve as the Leading Application with Dr. Wojciech Zareba as overall PI of the trial and CC with Suzanne Robertson, PhD as Program Manager. Dr. James P. Daubert will serve as Co-PI of Clinical Core. The Data Coordination Center (DCC) will be independent from the main study operation and will be directed by Dr. Arthur Moss with Mary Brown, MS, as Program Manager and Dr. Chris Beck, PhD, as :. Dr. David Huang will be chairing the ICD Interrogation Adjudication Committee and Dr. Jeffrey Alexis, MD will chair the Events Committee.
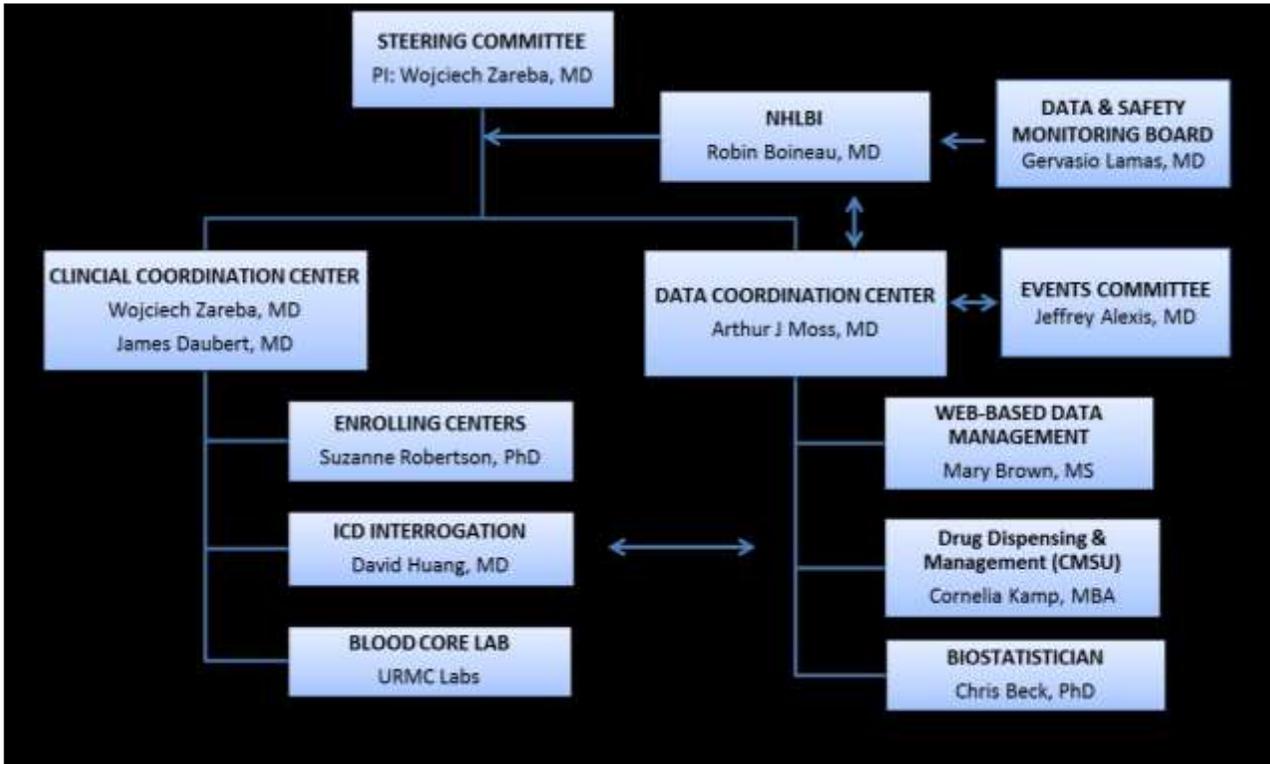


**Figure 18. Organizational Structure of the Trial.**

Similarly to other studies (including line of MADIT trials) conducted by the Heart Research Follow-up Program at University of Rochester Medical Center, the independence of the data coordination center and other operational components will be ensured by setting strict rules regarding access to the data. The steering committee consisting of several experts in the field will play a key role in overall oversight of the trial (Figure 18).

## D.13.SHARING RESEARCH DATA

The investigators of this research project and the University of Rochester will provide sharing of the research data in a manner that protects the privacy of study participants and is consistent with NIH guidelines on resource sharing with other investigators.

Data will be shared with collaborators as soon as available, with local colleagues at seminars and talks, and with the scientific community at large by presentations at local, regional, national and international scientific meetings. Publications will be prepared in timely manner. Press interviews on important publications will be arranged through the University of Rochester, Office of Public Affairs.

We welcome collaboration of scientist interested in utilizing data from this study. The de-identified data sharing with colleagues and organizations not participating in the study will be arranged based on the Data Sharing

Agreement ensuring: (1) a commitment to using the data only for research purposes; (2) a commitment to securing the data using appropriate computer technology; and (3) a commitment to destroying or returning the data after analyses are completed; 4) a commitment to sharing results of these analyses with the Executive Committee of the study.

We extensively exercise policy of sharing data for ongoing and past projects. As examples, the MADIT II data were shared with many researchers affiliated directly with the trial and with those not participating in the trial. As a result, there are over 30 original papers already published or in press exploring this reach database. A similar activity relates to data from the NIH-funded LQTS studies where data were widely shared and were used for publishing over 30 papers in last few years. Similar productivity and sharing was exercised in case of the NIH-funded THROMBO study, for which over 25 papers were published or in press.

## E. PROTECTION OF HUMAN PATIENTS

### E.1. Ranolazine

Ranolazine is a piperazine derivative that was patented in 1986 and is an FDA approved an anti-angina drug. Ranolazine (Ranexa; CV Therapeutics Inc., Palo Alto, California) is manufactured in a sustained-release form that has a prolonged absorption phase with maximal plasma concentrations (Cmax) typically seen 4 to 6 hours after administration. The average terminal elimination half-life is about 7 hours after multiple dosing to steady state, and the peak/trough difference is 1.6-fold with dosing of 500 to 1000 mg twice daily. Steady state is generally achieved within 3 days of twice-daily dosing. Ranolazine plasma concentrations that are therapeutically effective for chronic angina are in the range of 2 to 6 µmol/L.

Regarding the mechanism of action, ranolazine is a novel sodium channel blocker which inhibits late sodium current without significant effect on peak sodium current (no QRS changes). In isolated ventricular myocytes of dogs with chronic heart failure, ranolazine was found to inhibit peak $I_{Na}$ and late $I_{Na}$ with potencies (50%inhibitory concentrations) of 244 and 6.5 µmol/l, respectively.[18] Ranolazine is about 38-fold more potent in inhibiting late $I_{Na}$ than peak $I_{Na}$.[18]. For comparison, amiodarone is about 13-fold more potent in inhibiting late than peak $I_{Na}$.[17]

### E.2. Risk to the Patients

### E.2.1. Adverse Reactions: Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. A total of 2,018 patients with chronic angina were treated with ranolazine in controlled clinical trials. Of the patients treated with ranolazine, 1,026 were enrolled in three double-blind, placebo controlled, randomized studies (CARISA, ERICA, MARISA) of up to 12 weeks duration. In addition, upon study completion, 1,251 patients received treatment with ranolazine in open-label, long-term studies; 1,227 patients were exposed to ranolazine for more than 1 year, 613 patients for more than 2 years, 531 patients for more than 3 years, and 326 patients for more than 4 years.

At recommended doses, about 6% of patients discontinued treatment with ranolazine because of an adverse event in controlled studies in angina patients compared to about 3% on placebo. The most common adverse events that led to discontinuation more frequently on ranolazine than placebo were dizziness (1.3% versus 0.1%), nausea (1% versus 0%), asthenia, constipation, and headache (each about 0.5% versus 0%). Doses above 1000 mg twice daily are poorly tolerated.

In controlled clinical trials of angina patients, the most frequently reported treatment-emergent adverse reactions (> 4% and more common on ranolazine than on placebo) were dizziness (6.2%), headache (5.5%), constipation (4.5%), and nausea (4.4%). Dizziness may be dose-related. In open-label, long-term, treatment studies, a similar adverse reaction profile was observed.

## E.2.2. QT Prolongation

Ranolazine blocks $I_{Kr}$ current and might cause mild QT prolongation. In the dose range of 500 to 1000 mg twice daily, ranolazine increases the QTc (Fridericia) by an average of 2 to 5 ms.[59] The incidence of "QTc outliers" in lead II with the use of the Fridericia correction for a QTc of >500 ms was 0.7% at the 1000 mg twice daily dose, and a QTc increase of >60 ms was observed in 2.3% patients. Ranolazine is contraindicated in patients with preexisting QT prolongation, on QT-prolonging drugs, or with hepatic impairment.

Despite QT prolongation there is no evidence for ranolazine causing torsade de pointes ventricular tachycardia. Data from several clinical trials (MARISA, CARISA, ERICA, MERLIN)[51-53,56] with over 4,000 patients on ranolazine treated for a long time showed that there was no evidence for torsadogenic effects of ranolazine. Especially, the MERLIN trial[56] well documented that there was no increase in mortality in patients taking ranolazine, and there was a significant decrease in the risk and rate of complex ventricular arrhythmias.

These clinical observations are in agreement with pre-clinical data from Dr. Antzelevitch's group showing that ranolazine acts similarly to amiodarone which also prolongs the action potential duration and QT interval, but reduces transmural heterogeneity of repolarization and eliminates earlyafterdepolarizations.[16] We evaluated the safety of ranolazine in patients long QT syndrome type 3 caused by mutations of the SCN5QA gene and as shown in Figure 19, incremental plasma concentration of ranolazine was associated with progressive dose dependent QT shortening (by 26±3ms on average) further clinically confirming a late sodium blockade mechanism of this novel drug.[20]
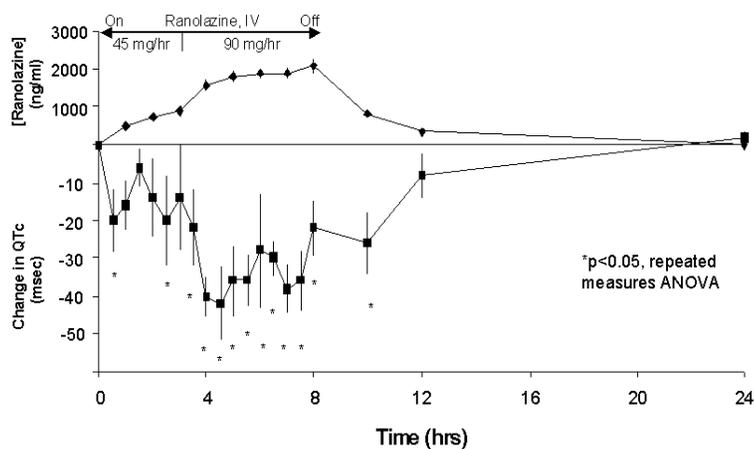


**Figure 19. Dose-dependent QTc shortening in LQT3 patients in response to ranolazine.[20]**

## E.2.3. Drug-drug Interactions

The interactions with other drugs which need to be emphasized are as follows. Drugs such as diltiazem, a moderate CYP3A inhibitor increase ranolazine plasma levels, about 50 to 130 %; ranolazine has no significant effect on diltiazem pharmacokinetics. Ranolazine is a substrate and an inhibitor of P-glycoprotein. Verapamil, a drug that inhibits P-glycoprotein, increases the absorption of ranolazine with a 100% increase in ranolazine plasma levels. The drug label indicates that ranolazine is contraindicated in patients taking strong inhibitors of CYP3A, including ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir, and saquinavir; inducers of CYP3A, such as rifampin, rifabutin, rifapentin, phenobarbital, phenytoin, carbamazepine, and St. John's wort; and patients with liver cirrhosis. Concomitant use of ranolazine and digoxin results in increased exposure to digoxin. The dose of digoxin should be adjusted. Ranolazine increases digoxin concentrations 50% in healthy volunteers receiving Ranexa 1000 mg twice daily and digoxin 0.125 mg once daily. The plasma levels of simvastatin, a CYP3A substrate, and its active metabolite are each doubled in healthy subjects receiving 80 mg once daily and Ranexa 1000 mg twice daily. The dose of simvastatin in patients on any dose of Ranexa should be limited to 20 mg once daily, when ranolazine is co-administered. Dose adjustment of other sensitive CYP3A substrates (e.g., lovastatin) and CYP3A substrates with a narrow therapeutic range (e.g., cyclosporine, tacrolimus, sirolimus) may be required as Ranexa may increase plasma concentrations of these drugs. The exposure to CYP2D6 substrates, such as tricyclic antidepressants and antipsychotics, may be increased during co-administration with Ranexa, and lower doses of these drugs may be

required. In subjects with type 2 diabetes mellitus, concomitant use of Ranexa 1000 mg twice daily and metformin results in increased plasma levels of metformin. When Ranexa 1000 mg twice daily is co-administered with metformin, metformin dose should not exceed 1700 mg/day. Metformin exposure was not significantly increased when given with Ranexa 500 mg twice daily. Therefore patients on >1700 mg/day will have their dose of study drug limited 500 mg twice daily at the time of randomization and at any time during the study. Mean exposure to atorvastatin (80 mg daily) is increased by 40% following co-administration with Ranexa (1000 mg twice daily) in healthy volunteers. Therefore the dose of study drug in patients on 80 mg daily of atorvastatin will be limited to 500 mg twice daily, at the time of randomization, and at any time during the study.

### E.3. Recruitment and Informed Consent

Each patient will have the protocol described to them by one of the physicians or research coordinators at the enrolling centers. Potential patients who meet inclusion/exclusion criteria will sit down with the coordinator or physician and have the opportunity to ask questions. . If the patient agrees to participate in the study, the patient will sign an "informed consent" form that is fully approved by the local IRB following local IRB consent administration regulations and then be randomized to a study medication treatment group provided all required pre-study drug initiation testing is performed. Study drug must be initiated within one calendar day following randomization.

### E.4. Protection Against Risk

The following measures will be implemented which are similar to currently approved recommendations regarding clinical use of ranolazine.

### E.4.1. ECG monitoring

At randomization, patients will be assigned to ranolazine or placebo. The dose of 1000 mg twice daily of ranolazine will be used in active drug arm. However, as recommended for clinical use, each patient will be started on a 500 mg twice daily dose for one week with subsequent increase to 1000 mg twice daily at 2 weeks. For each ECG will be checked at 1 week on 500 mg dose and next at 2 weeks on 1000 mg dose and the dose will be adjusted if there is a significant (>60ms) prolongation of QTc in comparison to baseline ECG. In a large MERLIN trial,[56] with 3,279 patients randomized to ranolazine only 31 (0.9%) patients required dose adjustment due to prolongation of QT.

Since impairment of liver metabolism of ranolazine might increase its level and contribute to more pronounced QT prolongation, we will measure liver function tests in relationship to concomitantly acquired ECGs for QT measurements performed at baseline prior to study drug initiation and 3 times during follow-up (, months 6, 12 and 24).

### E.4.2. Drug interaction

Patients and their primary physicians will be informed regarding potential for interactions of ranolazine with other drugs/substances that might be affected by ranolazine administration per Ranexa package insert.

To minimize the risk of digoxin toxicity, patients on digoxin will have decreased dose of this drug by 50% (i.e., 0.250 mg to 0.125 mg). Based on the retrospective data from the DIG trial, digoxin might be beneficial if administered in lower doses. However, data from newer cohorts indicate that if heart failure patients are treated with beta-blockers and ACE-inhibitors, following current guidelines, digoxin administration is not associated with significant increase or decrease of the risk of mortality or combined endpoint of CHF hospitalization or mortality. In the recent study of 347 patients with long-term follow-up,[71] hazard ratios for use of digoxin for the above endpoints were (HR=1.03; p=0.85 and 1.11; p=0.52, respectively. These observations might indicate that even decreasing the dose of digoxin in patients randomized to placebo (in our proposed trial) should not have negative impact on their outcome.

### E.4.3. Implantable Cardioverter Defibrillators

All patients randomized in this study will have implantable cardioverter defibrillators (ICDs) in place. This treatment and monitoring modality will provide detailed data regarding arrhythmic events occurring during treatment. Simultaneously, ICDs provide a safety measure just in case of unlikely (based on preclinical and clinical experience) possibility of drug-induced proarrhythmia in randomized patients. In this regard, this patient population will be protected much more effectively than in usual drug studies conducted in non-ICD patients.

### E.4.4. Privacy

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 center will maintain a key linking the patient's name with study data. The Rochester DCC will also maintain a master key in a password protected data form separate from the main database. Medical records collected to determine study eligibility will be used only for this purpose and shredded when no longer needed. This system has been used in the previous grant and has provided an adequate means for protecting patient identities.

All information and data collected concerning patients or their participation in this investigation will be considered confidential by the DCC. No social security numbers will be collected by the DCC. All data will be handled in accordance with applicable local laws. 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. All DCC data used in the analysis and reporting of this investigation will be without identifiable reference to specific patient name or other patient identifiers. HIPAA authorization will be obtained from each patient by every enrolling center per local regulations.

### E.5. Data and Safety Monitoring Plan

An Independent Data Safety and Monitoring Board (DSMB) will meet periodically, or as needed, to review the results of the trial and to evaluate any safety and efficacy issues that may arise during the course of the study. The ongoing trial data will be transmitted to the DSMB on a monthly basis. The Board will carry out periodic data review and will inform the study Principal Investigator on any safety concerns. The DSMB may recommend termination of the study at any time should prospective ethical or safety guidelines not be met. The DSMB will consist of individuals who are not involved in the trial. The above plan has been exercised from last 30 years in numerous clinical trials conducted by our research group, the last of the trial which followed the same schema was recently completed the MADIT-CRT. Based on this experience, we are confident that we will be able to address proper management of data and execution of the DSMB responsibilities for the trial.

A DSMB will consist of NIH-nominated individuals that are not involved with the study. The data will be transmitted to the board on a monthly basis; and a review of the data will be done every 4 months. The DSMB will meet in person once per year; remaining two meetings during each year will be organized as conference calls. The DSMB may terminate the study at any time they foresee increased risk to subjects, or any safety concern.

### E.6. Adverse Drug Experience Reporting

The DSMB, Steering Committee and PIs will be responsible for ensuring prompt reporting of adverse drug experience findings to IRBs and the NIH that might indicate concerns regarding safety of tested therapy in randomized patients. This reporting will be performed following routines established at our organization for numerous past trials. Since this study is IND exempt following review by the FDA, post market reporting requirements as defined in 21 CFR 314.80 will be followed in this study.

### E.6.1. Definition of Adverse Drug Experience per 21 CFR 314.80

Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: 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.

Adverse experience reports will be collected at each clinic follow-up for all randomized patients in the electronic database. Patients will be provided with enrolling center contact information to report adverse experiences between follow-up visits to avoid delays if serious events occur.

These can include but not limited to events meeting the definition of an adverse event that are:
- Intercurrent illnesses
- Significant worsening (change in nature, severity, or frequency) of the disease under study or other preexisting conditions
- Adverse events occurring during diagnostic procedures
- A laboratory or diagnostic test abnormality occurring after the start of the study (once confirmed by repeat testing) that results in the withdrawal of the participant from the study, requires medical treatment or further diagnostic work-up, or is considered by the study investigator to be serious and/or clinically significant.
- Abnormalities in physical examination or vital signs that require clinical interventions or further investigations (after repeated confirmatory test) or are considered by the study investigator to be serious and/or clinically significant.
- ECG, arrhythmias found on defibrillator interrogation and echocardiogram abnormalities that require clinical intervention (device reprogramming, invasive intervention, inpatient admission or pharmaceutical treatment).

Preexisting conditions should be recorded at screening in the source documentation at the enrolling center (medical history) but should not be reported as adverse events unless the condition worsens (increases in frequency or severity to meet the serious adverse event definition described below) after randomization. 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.

### E.6.2. Serious Adverse Drug Experience

Adverse events are classified as either serious or non-serious. A serious adverse drug event (SAE) is any adverse event occurring at any dose, which results in any of the following outcomes or actions:

- Death
- Life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity (disruption of a person's ability to conduct normal life functions)
- Congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Patients should be unblinded only if (1) knowledge of the treatment assignment will change management or (2) the treating physician feels the information is critical for patient safety. Prior to disclosing a subject's treatment assignment, the enrolling investigator will page the Clinical Monitoring Director to determine if disclosure is absolutely necessary. Disclosure of individual treatment assignment will be made by the enrolling investigator responsible for the care of the particular subject or by a physician designated specifically by the enrolling investigator only after disclosure has been determined to be the best course of action.

### E.6.3. 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.

### E.6.4. 15-Day Reporting

The enrolling center shall report each adverse drug experience to the CCC that is serious as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the center.

### E.7. Discontinuation Criteria/Early Termination

If the DCC or NIH makes a decision to discontinue the study (e.g., slow randomization, unanticipated adverse event, or other scenario), the DCC will promptly inform all Investigators and IRBs as required along with detailed information on how randomized patients should be managed thereafter. All randomized patients in the trial will continue to be followed according to the protocol unless the DCC notifies the investigational centers otherwise. No non-FDA approved treatment is being used in this study so the patient's care should not be compromised if the study is terminated for any reason since all treatment is available to the patient external to the study.

### E.8. Data Tracking Including Enrollment, Randomization and Withdrawals

Electronic data will be entered at the enrolling centers and transmitted to the DCC. This database permits data expansion, easy updating, and rapid retrieval; it has simplified report-generating routines; an audit trail component; and analysis data sets can be easily produced for transmission to the biostatisticians and the DSMB for analysis.

All data will be subject to an extensive computer edit checking process for completeness, internal consistency, numerical values outside specified rational limits, invalid codes, subject identification errors, and date errors. Errors detected in the edit check process will be corrected before the data are transferred to the definitive data management system that is used for final data analysis or reports. The DCC will implement requirements for standardization of observations and objective application of definitions, and it will institute other measures of quality control as required. It will provide monthly reports evaluating the study performance to the PI, enrolling centers and NIH as required. In summary:

- Enrollment, randomization, withdrawal and follow-up data (deaths, adverse events, etc.) will be submitted to the DCC. The DCC is responsible for the security and privacy of data with the electronic data entry system only accessible by unique username and password which can only be authorized by the DCC.
- The DCC is responsible for verification of data completeness, progress of enrollment and randomization, statistical analysis, and summary reports.

All case report forms (CRFs) must be entered into the electronic data entry system provided by the DCC. Original source documents (e.g., worksheets, programmed parameters) must remain at the center in the patient binder.

Any changes to the reported data should be reported to the DCC and should be entered into the electronic data management system provided by the DCC.

### E.9. Participation of Women and Minorities

The data from the Heart Disease and Stroke Statistics 2008 Update[69] published in Circulation in January 2008 reported that in 2004, coronary disease death rates per 100,000 people were 194.2 for white males and 223.9 for black males; 114.7 for white females and 148.7 for black females, 119.2 for Hispanics or Latinos, 106.5 for American Indians or Alaska Natives, and 84.1 for Asians or Pacific Islanders. Between 70 percent and 89 percent of sudden cardiac deaths occur in men, and the annual incidence is three to four times higher in men than in women. However, this disparity decreases with advancing age. Data relevant for ICD-eligible population are provided in a study by Hernandez et al. published in 2007 JAMA.[70] An observational analysis of13 034 patients admitted with heart failure and left ventricular ejection fraction of 30% or less and discharged alive from 217 hospitals was conducted.

Eligible patients consisted of 34% of women (11.8% black and 22.5% white), and 66% of men (17.6% black and 48.1% white). Among patients eligible for ICD therapy, 4615(35.4%) had ICD therapy at discharge (1614 with new ICDs, 527with planned ICDs, and 2474 with prior ICDs). ICDs were used in 375 of 1329 eligible black women (28.2%), 754 of 2531 white women (29.8%), 660 of 1977 black men (33.4%), and 2356 of 5403white men (43.6%) (P < 0.001). After adjustment for patient characteristics and hospital factors, the adjusted odds of ICD use were 0.73 (95% confidence interval, 0.60-0.88) for black men, 0.62 (95% confidence interval, 0.56-0.68) for white women, and 0.56 (95% confidence interval, 0.44-0.71) for black women, compared with white men. The differences were not attributable to the proportions of women and black patient sat participating hospitals or to differences in the reporting of left ventricular ejection fraction.

Based on these data it is expected that women will constitute a one-third of eligible patients. A pro-active approach will be utilized in this trial to ensure that women are appropriately included in the study population. We will enrich proportion of women eligible for randomization to reach at least 33% of women in this study. Enrollment of women will be accomplished by establishing close collaboration between center PI (electrophysiologist) and its congestive heart failure physicians who usually follow large number of women eligible for ICD therapy. In order to force the proportion of females in the study population to be at least 25%, the following rule will be imposed at each enrollment center: The proportion of females randomized at the center will be monitored; at any time when this proportion is below 25% (and after four patients have been randomized), only females will be eligible for randomization at that center. Efforts to increase recruitment of minorities will also be made, but no formal rule like that for females can be imposed due to variations in minority populations. However, center-specific targets for minorities will be established and monitored. Interpreter services made available to ensure adequate information, consent, and ongoing discussion.

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