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Rationale and Design of a Randomized Clinical Trial Comparing Stress Reduction Treatment to Usual Cardiac Care: The Reducing Vulnerability to ICD Shock-Treated Ventricular Arrhythmias (RISTA) Trial

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Abstract

Objective—Present the design of a multicenter randomized trial testing the effects of Stress Reduction Treatment (SRT) on the prevalence of shock treated ventricular arrhythmias among patients with an implantable cardioverter defibrillator (ICD). Significant adjustment problems secondary to ICD shock can increase the likelihood of arrhythmias requiring shock for termination. Whether SRT can reduce arrhythmias requiring shock for termination in patients with ICDs has not been tested in clinical trials.

Methods—New ICD recipients and previous recipients who have received an appropriate therapeutic shock in the past 6 months (n=304) will be enrolled and randomized to either SRT or usual cardiac care. Participants complete a psychosocial questionnaire and undergo laboratory mental stress testing and 24-hour holter monitoring with diary at study entry and approximately 4 months later. Follow-ups are completed at 6-, 12-, and 24-months post randomization to assess occurrence of ICD shock for ventricular arrhythmias (primary outcome), ATP events, medication changes, hospitalizations, deaths, and quality of life.

Results—Log-rank test and Cox proportional hazards model will be used to test the effects of SRT on time to first shock treated ventricular arrhythmia, with exploratory analyses testing the effects on overall frequency of ventricular arrhythmia. Secondary analyses will test the effects of SRT on lab stress induced and 24-hour arrhythmogenic electrophysiological indices from pre- to post-treatment, and both quality of life and measures of anger across the 2-years of the study.

Conclusions—The RISTA Trial is the first large scale randomized clinical trial designed to evaluate the effect of SRT on the prevalence of shock-treated arrhythmias among patients with an ICD. Results may demonstrate a treatment that can reduce vulnerability to arrhythmia provoked shock and improve quality of life.

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Keywords

implantable cardioverter defibrillator; arrhythmia; stress; treatment; randomized clinical trial

Upwards of 294,000 people in the US experience out-of-hospital cardiac arrest annually(1), and the implantable cardioverter-defibrillator (ICD) has transformed the care of patients at risk for these potentially fatal cardiac arrhythmias. The results of recent clinical trials have demonstrated the benefit of the ICD, not only for the patients with a history of spontaneous (2) or induced (3) life-threatening ventricular arrhythmias - the original targets of this therapy - but also for primary prevention in patients with impaired left ventricular (LV) function due to either ischemic or non-ischemic cardiomyopathies accompanied by congestive heart failure (4-6). These trials have led to expansions of the initial indications for ICD therapy, and with the recent approval by Centers for Medicare and Medicaid Services, it is now estimated that over 500,000 patients will receive these devices annually (7).

While ICDs can be lifesaving, a recent critical appraisal of the literature on ICD therapy concluded that the risks associated with ICDs may not always outweigh the potential benefits of getting the device (8). Significant adjustment problems may arise after implantation as shown by the clinically meaningful levels of anxiety and depression, and alterations in quality of life (9,10). Although minimal differences and/or improvement have been found in the quality of life in patients with an ICD as compared to those on medication therapy (11-13), overall, researchers have found that patient quality of life has declined after ICD implantation in patients who receive shocks from the device. Specifically, the frequency and severity of adjustment problems, as defined by anxiety, depression, and decreased quality of life, have been found to increase as a function of the number of ICD shocks that patients receive (12-14). Furthermore, these adjustment problems may increase the likelihood of arrhythmias requiring shock for termination (15). When patients experience frequent therapeutic ICD shocks, suppressive treatment with anti-arrhythmic medication is likely initiated (16). These medications have many, often profound and life-threatening side effects (17). Therefore, the testing of alternative approaches to reduce vulnerability to ICD shock-requiring arrhythmias is urgently needed.

We have previously found in both the laboratory setting and in daily life that the experience of anger and other strong emotions can increase the likelihood of ventricular arrhythmias requiring shock for termination (18-22), particularly in patients whose psychological profile is described by the experience and expression of anger when under such stress (21). We have also found that emotion/stress-triggered arrhythmias are particularly malignant in morphology (20), and therefore more likely to require shock for termination. Thus, we have identified a potential target for treatment – mental/emotional stress - to reduce vulnerability to arrhythmias requiring shock for termination in patients with an ICD.

Stress reduction treatments, offered individually and in groups, have long been a part of secondary prevention after acute coronary syndrome (ACS) events (23). These approaches are successful at reducing vulnerability to emotion and stress-triggered ischemia in the natural setting and during laboratory protocols (21,22), and improve event free survival after ACS (24). There have also been three small studies with ICD patients, each utilizing some form of group-based cognitive behavior therapy with elements of relaxation training (25,26) and/or cognitive reframing (25-27). While study samples were small (n=22, 49, and 70, respectively), benefits were seen on measures of anxiety (25-27), and on depression, quality of life, activity level, and sexual functioning, particularly among those patients who received ICD shock during the course of the study (25,26). Furthermore, one study (27) found a positive effect of cognitive therapy on ICD treated arrhythmias at three-months, though this benefit was no longer seen at twelve month follow-up. Thus while promising, these therapies have not yet been tested in

large clinical trials to determine whether they can reduce risk for ventricular arrhythmias requiring shock for termination in patients with ICDs.

The Reducing Vulnerability to ICD Shock Treated Ventricular Arrhythmias (RISTA) Trial aims to test the effects of a stress reduction intervention (SRT) on the prevalence of shock treated ventricular arrhythmia among patients with an ICD. It is hypothesized that, compared to usual care: 1) SRT will be associated with reduced relative risk of ventricular arrhythmias requiring shock for termination; 2) SRT will be associated with a decrease in arrhythmogenic electrophysiological changes (e.g., T-wave alternans) seen in response to acute stress in the laboratory and during 24-hour holter monitoring; and 3) SRT will be associated with better quality of life after ICD implantation.

Methods

The RISTA Trial will randomize 304 patients who have received an ICD to either SRT or a usual care (UC) control over a 24-month period. The recruitment period began in February 2008 and will run until January 2010. The time of study participation is 2-years post randomization (see fig. 1).

Eligibility criteria

Similar to previous studies of modalities to decrease ICD shocks (28), study participants are either new recipients of an ICD based upon current guidelines or previous recipients of an ICD who have received appropriate ICD therapy (shock, anti-tachycardia pacing) for a ventricular arrhythmia within the past 6 months (a group at higher risk for subsequent arrhythmias). Additional inclusion criteria are: 1) age 21 years and older; 2) diagnosis of ischemic cardiomyopathy or non-ischemic (dilated) cardiomyopathy; and 3) cognitive and physical ability to participate in the study intervention. There are no protocol defined ICD program parameters, thus, all patients with an ICD meeting the above inclusionary criteria will be screened for the exclusionary criteria regardless of how their ICD is programmed. Patients are excluded if they have: an incapacitating illness (e.g. stage IV congestive heart failure) that would interfere with participation, life expectancy less than 2 years (e.g. metastatic cancer), arrhythmia without underlying ischemic or non-ischemic dilated cardiomyopathy (e.g. long QT syndrome, hypertrophic cardiomyopathy, Brugada Syndrome), moderate to severe cognitive impairment demonstrated by 4 or more errors on the Short Portable Mental Status Questionnaire (29), meet criteria for current alcohol abuse with the modified Alcohol Use Disorders Identification Test (30), or meet diagnostic criteria for substance abuse or psychotic disorder.

Recruitment, Enrollment, Informed Consent

Prospective study participants are identified shortly before or at the time of implant by the patient care coordinators, and by subsequent examination of medical records after the patients are admitted to cardiac care units. Patients who have previously received an ICD are identified as prospective participants when they call their treating electrophysiologist's office after receiving an ICD shock, or if a routine ICD interrogation indicates an ICD-treated arrhythmia. The study electrophysiologist reviews the patient's ECG to determine if the shock was appropriate. The recruitment staff approaches patients who are deemed medically eligible at either hospital bedside, at the patient's first follow-up visit in clinic, or over the phone. The study is described, and patients are briefly interviewed to ascertain whether they meet any exclusionary criteria. Upon determining a patient is eligible, informed consent and HIPAA (Health Insurance Portability Authorization Act) authorization is obtained.

Psychological Assessment

Study participants complete a battery of psychosocial measures that assesses: anger and hostility with the Spielberger Trait Anger Scale (31), the Spielberger Anger Expression Scale (32), and the Cook Medley Hostility Scale (33); quality of life (a secondary outcome) with the SF-36 (34); depression with the Center for Epidemiological Studies Depression scale (35); anxiety with the Hospital Anxiety and Depression Scale, anxiety component (36,37); perceived social support (38); perceived stress (39); and ICD total concerns (25). Participants are then scheduled for a baseline laboratory mental stress session.

Laboratory Mental Stress and 24-Hour Holter Monitoring of ECG

After consent and prior to randomization, participants undergo laboratory mental stress testing following a standard protocol that includes mental arithmetic and anger-recall stress interspersed with resting baseline. Each task lasts 5 minutes, with a 20 minute rest and 5 minute baseline period in between (18,19). During the laboratory session, a holter monitor captures ECG for ascertainment of repolarization indices (e.g., T-wave alternans) and heart rate variability (19), a secondary outcome. Heart rate and blood pressure is also monitored during the rest, baseline and stress periods, and blood is drawn at the end of baseline and stress for catecholamine analysis.

Participants undergo 24-hour holter monitoring on a subsequent day to assess heart rate variability and electrophysiological parameters. During this period an electronic diary is utilized by the participant for ecological momentary assessment of mood and activity. The personal digital assistant-based diary prompts the patient to complete entries every 30-minutes on average.

Randomization

After completion of the baseline laboratory visit and 24-hour holter monitoring, participants are randomized to either SRT or UC, with the condition assignment determined via a computer generated and managed algorithm. A block randomization scheme is employed, balancing the time of ICD implant (New ICD vs. Therapeutic Shock), medical facility, gender, history of arrhythmia, and score (upper quartile vs. lower 3 quartiles) on trait anger. The patient is informed by phone of their condition assignment, and questions are solicited and answered. The intervention is described to SRT assigned participants, they are scheduled into a treatment group, and an information and confirmation letter is sent to them (i.e. schedule, directions, parking). Participants assigned to UC are informed they will be contacted in approximately 3 months to schedule a 4-month laboratory session.

Stress Reduction Treatment

The SRT protocol developed for RISTA is modeled after the group therapy component of the intervention used in the ENRICHD Clinical Trial (40) and consists of eight, 90 minute psychoeducational group sessions delivered over a 10-week period by a licensed clinical psychologist or social worker. Each group is comprised of three to eight participants. The small group setting provides for vicarious learning, whereby lessons are reinforced by group members and their experiences. Since circumstances can preclude travel to group sessions, provision is made for participation by conference call.

The protocol contains treatment elements found by others to improve event-free survival in patients with ischemic heart disease (24,41-46). It utilizes a cognitive-behavioral model of stress that emphasizes the interactive relationship of cognition, emotion, physiology and behavior. The SRT is designed to target each aspect of this model to provide patients with several different tools they can utilize to prevent or reduce the stress they experience during

their daily routine. Treatment sessions include agenda setting; a brief relaxation exercise; a review of homework to provide opportunities for participants to demonstrate acquisition of core skills and discuss questions; and the specific content material for the session. Content material is presented in a didactic format with skill guidelines and in-session exercises and includes: cognitive stress model; relaxation strategies (e.g. diaphragmatic breathing, breath counting meditation, progressive muscle relaxation, visualization, self-hypnosis, and autogenic training); cognitive restructuring; and skills training in problem solving, communication and assertiveness, and goal setting/time management. Homework assignments are presented at the end of each session to facilitate practice of new skills. Participants are provided with workbooks that include both information sheets on material covered in session, and monitoring forms to facilitate acquisition of skills and home practice.

Therapy Quality Assurance Procedures

All SRT therapy sessions are digitally recorded and therapists receive one hour of weekly supervision to ensure adherence to the study protocol. In addition, a random selection of 10% of the recordings from each therapist are reviewed by the study psychologist (MMB), with feedback provided to the therapist.

Usual Care

Participants assigned to UC are referred back to their physicians, where they receive the routine cardiologic care that their physician provides and any other treatment that the physician feels is warranted; receipt of treatment is monitored at follow-up assessments, and includes any out of study treatment. In this way, the effects of the trial intervention can be evaluated against the standard of care delivered to patients after ICD placement.

Measurement and Data Collection

Follow-up assessments are conducted 4-, 6-, 12-, and 24-months after randomization. The initial 4-month follow-up is for a repeat of the laboratory mental stress session, the 24-hour holter monitoring with electronic diary, and the psychosocial questionnaire. This assessment will be used to determine the proximal effects of SRT on electrophysiological activity under conditions of acute stress. Subsequent follow-ups include review of ICD interrogations for shock and ATP events, and both chart review and patient interview to determine hospitalizations, out of study treatment (medical, psycho-social, and psychopharmacological), and medication changes. The study electrophysiologist will review all electrograms obtained during the course of the trial to determine whether they meet the endpoint criteria (ICD-treated ventricular arrhythmias). Table 1 summarizes the measures and indicates the schedule of collection. *Sample Size, Power Calculations, and Data Analysis*

The primary hypothesis relies on the intent to treat principle and tests the effects of SRT on 2-year event-free survival, where the event is first ventricular arrhythmia requiring shock for termination. Kaplan-Meier survival curves will be generated to graphically display the survival experience of SRT vs. UC as a function of time, and the difference between curves will be tested using the log-rank test. A Cox proportional hazards model that includes treatment group as the primary predictor and age at enrollment as a covariate will be used for the primary test of this hypothesis. Sensitivity analyses will investigate whether the conclusion is altered when we additionally control for those factors (if any) on which the two groups differ at baseline.

The expected relative risk for the population used for power calculations was based on: a) an event rate of 60% at 2 years in the early “AVID” trial for patients with a history of ventricular arrhythmias (secondary prevention) (2); b) an event rate of 26% at 2-years in subsequent “MADIT” primary prophylaxis trials examining patients with a history of myocardial infarction and decreased ejection fraction (4); c) an event rate of 10% at 2-years for the most

recent “SCD-HeFT” primary prophylaxis trial in patients with CAD and non-ischemic cardiomyopathy, heart failure, and decreased ejection fraction (5). We conservatively assumed a 2-year event rate of 20% to 22% in the UC group under current guidelines for ICD patients. With this assumption, a sample size of 304 patients with an alpha level of 0.05, provides 80% power or greater to detect an effect if the event rate in the INT group is 6%-9%, assuming 20% dropout (final sample of 252). This represents a reduction of more than 50% from the event rate expected in a typical clinical sample (e.g., the UC group). This range of effect is consistent with that found for comparable treatments on 48-hour ambulatory myocardial ischemia (24), and on 3-month prevalence of shock treated ventricular arrhythmias in a pilot study of ICD patients (27). Given that ICD shock is a key predictor of subsequent adjustment problems, including clinical depression and anxiety disorders, we believe such a reduction in events would have important clinical relevance.

In addition to the testing of this primary hypothesis, a patient’s participation in the study provides for the collection of data concerning cumulative ICD activity (e.g., all shock and anti-tachycardia pacing) over the two years of study participation. Thus, we will be able to conduct exploratory analyses concerning the effects of SRT on this variable as well. This will provide additional insights concerning the effects of SRT on cumulative ventricular arrhythmia for this at risk population over a longer time frame.

For the effect of SRT on quality of life, we will specifically focus on the mental component of the SF-36. We will employ a two-group t-test to test for differential change from pre to post treatment in average quality of life, using data collected in concert with the laboratory studies. Based upon extant SF-36 data from studies of patients with ICD (c.f., 10,13), we anticipate the sd of change scores will be 12.85, for which 252 subjects with complete data will provide >90% power to detect a differential change of 6 points, corresponding to an effect size of $d' = 0.467$, for a two-sided, 0.05-level test of significance. Multiple regression models with change in mental component summary score as the dependent variable and treatment group as the primary predictor will also be used, to evaluate the sensitivity of the results when we control for factors on which the two groups differ at baseline.

Secondary and exploratory hypotheses concern the effects of SRT on the potentially arrhythmogenic electrophysiological indices observed during laboratory mental stress and 24-hour holter monitoring, each of which is collected in concert with the two laboratory studies. For example, change scores from baseline to stress are computed for electrophysiological indices (e.g., T-wave alternans) collected during laboratory study. Differences in change score from lab session 1 to lab session 2 between the INT and UC groups will be compared by repeated measures ANOVA, controlling for factors on which the two groups differ at baseline. Similarly, indices of HRV will be computed from the collected 24-hour holter monitoring data. INT and UC groups will then be compared by the same repeated measures ANOVA approach.

Beyond these analyses we also intend to explore the effects of SRT on measures of anger and hostility that we have previously found predictive of shock incidence cross-sectionally and of anger triggered arrhythmia requiring shock for termination (21). In addition, we will test the long term effect of SRT on quality of life. Repeated measures ANOVA will be used to test the effects of SRT on change in these measures from baseline to lab session 2, and to 12- and 24-month follow-ups (3 contrasts). Full information maximum likelihood (FIML) estimates of the model parameters will be obtained, using the SAS PROC MIXED procedure, in order to use all available data and Dunnett’s test will be used to control for the risk of a Type I error when testing for treatment effects across the three time intervals. FIML estimates are valid under the assumption that missing data are “missing at random”, which is a substantially *less* restrictive than that required by traditional least-squares estimation procedures that completely ignore those subjects that are missing any data. The study has over 88% power to detect a differential

change of $d' = .45$ sd in anger or hostility scores associated with SRT, at a two-tailed alpha of 0.05.

Missing Data

In all clinical trials, patient drop-out and missing data can compromise data analytic plans. While the recruitment plan provides for 20% drop-out, we anticipate that a far smaller number of patients will be lost once they have completed their first laboratory session and been randomized. Implantation with an ICD requires regular monitoring by a physician, which provides a strong impetus for the patient. Primary outcomes are based on the ICD device interrogations that occur at regular follow-up appointments, and these data can therefore be collected from patients who are otherwise lost to follow-up. With regard to secondary outcomes and exploratory analyses, reliance on full information maximum likelihood (FIML) estimates of the model parameters with SAS PROC MIXED procedures provides a robust approach for dealing with missing data.

Study Organization

The RISTA trial is underway at three separate facilities. The project coordinating center is in Yale University School of Medicine. Recruitment will take place at Yale New Haven Hospital, Hartford Hospital, and Columbia Presbyterian Hospital. Prior to the initiation of recruitment, the protocol was reviewed and endorsed by the attending electrophysiologists and approved by the institutional review board at each participating institution. The RISTA trial is sponsored by the National Heart, Lung and Blood Institute and is registered at www.clinicaltrials.gov, registration number: NCT00627263.

Conclusions

The RISTA Trial is the first large scale randomized trial to evaluate the effect of a SRT on the prevalence of ICD-treated arrhythmias among patients with an ICD. Results may demonstrate a safe, non-invasive, self-managed treatment that can reduce vulnerability to arrhythmia provoked ICD shock. Additionally, the performance of the laboratory mental stress protocol, the 24-hour holter monitoring, and the quality of life assessment will help to increase our knowledge of the pathways by which the treatment program has its effects. If hypotheses articulated for this study are supported, the findings may form the basis of a new approach to the treatment of arrhythmia vulnerability in this patient population. This could lead to SRT becoming part of the standard of care for patients receiving ICDs, thereby reducing the amount of anti-arrhythmic medication prescribed and improving the overall quality of life for this growing patient population.

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Appendix A: The RISTA Investigators

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Glossary

RISTA	Reducing Vulnerability to ICD Shock-Treated Ventricular Arrhythmias
ICD	implantable cardioverter defibrillator
SRT	stress reduction treatment
UC	usual care
LV	left ventricular
ATP	anti-tachycardia pacing
ACS	acute coronary syndrome
IV	intravenous
ECG	electrocardiogram
HIPAA	Health Insurance Portability Authorization Act
CAD	coronary artery disease
AVID	Antiarrhythmics versus Implantable Defibrillators
MADIT	Multicenter Automatic Defibrillator Implantation Trial
SCD-HeFT	Sudden Cardiac Death–Heart Failure Trial
ANOVA	Analysis of Variance

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Figure 1.
RISTA trial design.

Table 1**Study Measures and Schedule of Administration**

Measures	Screen	Baseline	Post-Randomization	
			4-Months	6-, 12-, 24-Months
General Measures				
Demographics		X		
Patient Contact Inform.		X		
Screening Form	X			
Psychological Measures				
Short Portable Mental Status Questionnaire				
Modified Alcohol Use Disorders Identification Test	X		X	X
Spielberger Trait Anger Inventory	X		X	X
Anger Expression Inventory		X	X	X
Cook-Medley Hostility Scale		X	X	X
Moss Short Form-36 (SF-36)		X	X	X
Spielberger Trait Anxiety Scale		X	X	X
Hospital Anxiety and Depression Scale Anxiety Subscale (HADS-A)		X	X	X
Perceived Social Support Scale		X	X	X
ICD Patient Concerns Questionnaire		X	X	X
Clinical Measures				
Medical Eligibility	X			
Medical History		X		
Physiological Measures - Lab				
Repolarization Indices		X	X	
Catecholamines		X	X	
Physiological Measures - Ambulatory				
24-hr Heart Rate Variability		X	X	
Medical Outcomes				
Shock Treated Ventricular Arrhythmias			X	X
Hospitalizations			X	X
Deaths			X	X
Medication Changes			X	X