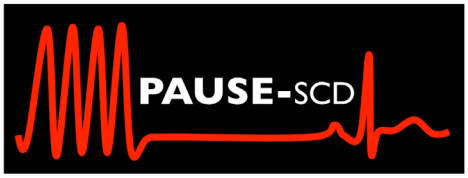
STUDY PROTOCOL

Pan-Asia United States PrEvention of Sudden Cardiac Death Catheter Ablation Trial



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Study Coordinating Site:

University of Chicago
Heart Rhythm Center
5758 Maryland Ave
Chicago, IL, 60637
T: +1 773-702-5988

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STUDY COORDINATING SITE CONTACT INFORMATION

Hemal Nayak, MD
5841 S Maryland Avenue MC9024
Chicago, IL 60637
University of Chicago Medical Center
hnayak@bsd.uchicago.edu
Tel: +1 773-702-5988
Fax: +1 773-702-4666

Yi (Dalise) Dai (Dalise Shatz)
5841 S Maryland Avenue M559 MC9024
Chicago, IL 60637
University of Chicago Medical Center
ydai1@medicine.bsd.uchicago.edu
Tel: +1 773 834-5781
Fax: +1 773 702-8577

PARTICIPATING CENTERS/PRINCIPAL INVESTIGATORS

CHINA:

Yao Yan, MD; Fuwai Cardiovascular Hospital; Beijing, China

Minglong Chen, MD; The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Shulin Wu, MD; Guangdong Provincial People's Hospital, Guangzhou, China

Chenyang Jiang, MD; Sir Run Run Shaw Hospital, Hangzhou, China

Jiang Jian, MD; West China Hospital, Chengdu, China

SOUTH KOREA:

Young Hoon Kim, MD PhD; Korea University, Seoul, South Korea

JAPAN:

Akihiko Nogami, MD PhD; Tsukuba University, Tsukuba, Japan

Shiro Nakahara, MD PhD; Dokkyo Medical University, Saitama Medical Center, Saitama, Japan

Akiko Ueda, MD PhD and Kyoko Soejima, MD; Department of Cardiology, Kyorin University Hospital, Tokyo, Japan

Kazuhiro Satomi, MD, PhD; Tokyo Medical University, Tokyo, Japan

TAIWAN:

Shih-Ann Chen, MD; Taipei Veterans General Hospital, Taipei, Taiwan

1. PROTOCOL SUMMARY

2. INTRODUCTION

2.1 BACKGROUND AND RATIONALE

2.2 STUDY PURPOSE

3. STUDY DESIGN

3.1 STUDY OBJECTIVE

3.2 STUDY ENDPOINTS

3.3 CLINICAL CENTERS

3.4 SUBJECT SELECTION

3.4.1 INCLUSION CRITERIA

3.4.2 EXCLUSION CRITERIA

3.5 STUDY DESIGN OVERVIEW

3.5.1 RANDOMIZATION

3.6 STUDY POPULATION

3.6.1 RANDOMIZED SUBJECTS

3.6.2 REGISTRY SUBJECTS

3.6.3 DISCONTINUED SUBJECTS

4. STUDY PROCEDURES

4.1 CENTER PERSONNEL

4.2 SUBJECT SCREENING AND INFORMED CONSENT

4.3 SCHEDULE OF VISITS AND PROCEDURES

4.4 PRE-ABLATION

4.5 ABLATION PROCEDURE (ABLATION ARM ONLY)

4.5.1 MAPPING OF VENTRICULAR SUBSTRATE

4.5.2 ABLATION APPROACH AND STRATEGY

4.5.3 PROCEDURAL ENDPOINTS

4.5.4 ICD PROGRAMMING

4.5.5 DATA COLLECTION DURING ABLATION

4.5.6 EPICARDIAL MAPPING AND ABLATION

4.6 PRE-DISCHARGE

4.6.1 PRE-DISCHARGE EVALUATION

4.6.2 CONCOMITANT MEDICAL THERAPY

4.7 FOLLOW-UP

4.7.1 SCHEDULED VISITS

4.7.2 UNSCHEDULED VISITS

4.8 DATA COLLECTION AND REPORTING

4.9 SOURCE DOCUMENTATION REQUIREMENTS

5. ADVERSE EVENTS

5.1 DEFINITIONS

5.1.1 ADVERSE EVENTS DEFINITION (AE)

5.1.2 SERIOUS ADVERSE EVENTS DEFINITION (SAE)

5.1.3 ANTICIPATED ADVERSE EVENTS

5.1.4 UNANTICIPATED ADVERSE DEVICE EVENTS (UADE)

5.2 HANDLING AND REPORTING OF ADVERSE EVENTS

5.3 SUBJECT DEATH

6. PROTOCOL DEVIATIONS

7. EXPLANATIONS OF RISKS AND MITIGATION TO SUBJECTS

7.1 RISKS

7.2 MITIGATION OF RISKS

7.3 POTENTIAL BENEFITS

8. DATABASE AND CONFIDENTIALITY

9. STATISTICAL ANALYSIS

9.1 SAMPLE SIZE AND POWER CALCULATION

9.2 PRIMARY ENDPOINT

9.3 PRIMARY ENDPOINT ANALYSIS

10. MONITORING

11. INSTITUTIONAL REVIEW BOARD AND ETHICS COMMITTEE

12. STATEMENT OF COMPLIANCE

13. REFERENCES

1. PROTOCOL SUMMARY

Title: Pan-Asia United States PrEvention of Sudden Cardiac Death Catheter Ablation Trial (PAUSE-SCD)

Objective:
1) To assess the incidence of sudden cardiac death and impact of ablation and ICD therapy vs. ICD therapy alone in Asia, which has not been studied in randomized trials except in the US and Europe.
2) To explore the impact of preemptive VT ablation alone in patients at risk for sudden death (observational registry cohort).

Sample Size: Pilot study sample size of 120 randomized patients (60 ICD and 60 ICD+ablation). Registry is reserved for patients who refuse randomization and received ablation only.

Design: Prospective, multi-center randomized, controlled study.

Clinical Sites: Approximately 8-12 ablation centers in Asia (China, Korea, Japan) will participate in the study. Additional centers may be considered based on the discretion of the principal participating centers. The anticipated enrollment duration is 24 months for the initial pilot enrollment Additional associated centers may be used for referrals, clinically indicated ICD implantation, NIPS study, and ICD follow up. Due to the COVID19 global pandemic, China centers were shut down and complete access for patient follow-up will require an additional 6-12 months. Therefore, we are requesting one extra year extension for follow up due to these unanticipated circumstances. No statistical review or analysis was performed, as follow-up remains incomplete as of April,28th , 2020.

Inclusion Criteria:
- Patient is receiving a new ICD or CRT-D implant, that has study required programing capabilities and is appropriate for remote monitoring. Patient who has received the ICD / CRT-D within 90 days of enrollment can also be enrolled.
- Patient who has a high risk of ICD shock as shown by documented Monomorphic VT (MMVT) by one or more of the following:
  - Spontaneous MMVT
  - Inducible MMVT during EP Study,
  - Inducible MMVT during NIPS Study

Inducible MMVT is defined as MMVT > 30 seconds or requiring electrical termination (ATP or cardioversion)

- Patient has EF < 50% or RV dysfunction
- Patient has a cardiomyopathy with structural heart disease of any cause
- 18 years of age or older
- Patient has been informed of the nature of the study and has agreed to its provisions and provided written informed consent approved by the Institutional Review Board.

Exclusion Criteria:

- Any history of debilitating stroke with neurologic deficit
- ST elevation MI or previous cardiac surgery within 60 days prior to enrollment
- Patient is pregnant or nursing
- Patient has chronic NYHA class IV heart failure
- Patient has incessant VT necessitating immediate treatment
- Patient has VT/VF thought to be from channelopathies
- Limited life expectancy (less than one year)
- Patient has current class IV angina
- Recent CABG or PCI (< 45 days)
- Patient is currently participating in another investigational drug or device study
- Patient is unable or unwilling to cooperate with the study procedures
- Known presence of intracardiac thrombi
- Prosthetic mitral or aortic valve or mitral or aortic valvular heart disease requiring immediate surgical intervention
- Major contraindication to anticoagulation therapy or coagulation disorder
- Left Ventricular Ejection Fraction < 15%
- Patient has had a previous ablation procedure for VT, excluding remote (> 3 months) outflow tract tachycardia
- Patient has GFR < 30 mL/min/1.73m^2
- Patient has peripheral vascular disease that precludes LV access
- Patient is thought to have idiopathic outflow VT as only VT
- Patient has a PVC or VT induced cardiomyopathy that is expected to resolve with ablation and will not require an ICD
- Patient has reversible cause of VT
- Patient does not meet criteria for ICD or CRT-D

Intervention:

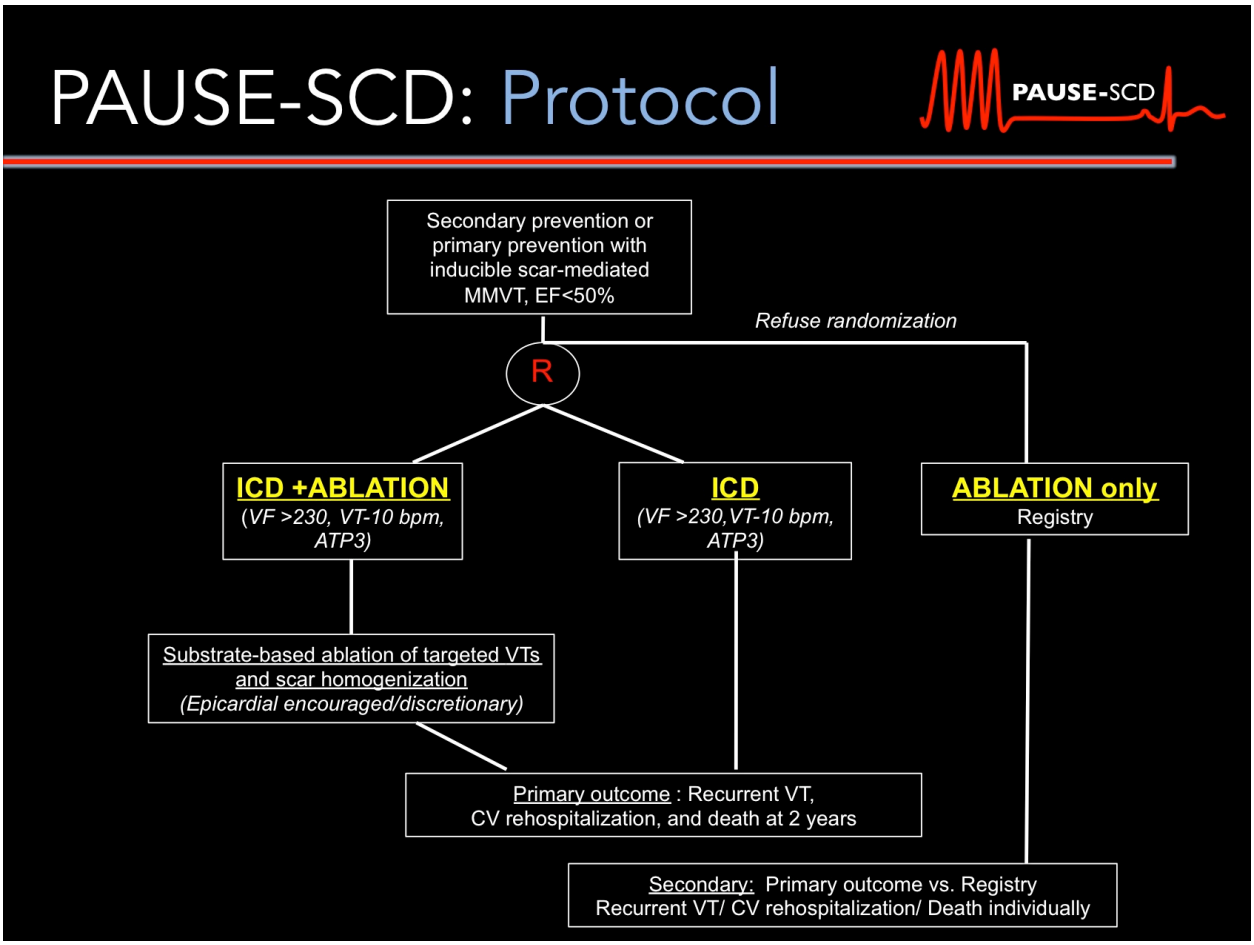
1) ICD with medical management

2) ICD with catheter ablation. Main strategy is scar-based ablation with targeting of late potentials defined as low voltage potentials with fractionated, split, or delayed components

3) Registry on non-randomized patients undergoing ablation only.

Study Endpoint: The primary endpoint is defined as a composite of recurrent VT, cardiovascular rehospitalization, and death. Prespecified secondary endpoints include each of the individual components of the primary endpoint. Comparison of the ablation-only registry with the randomized patients will serve as an additional secondary outcome measure.

Length of Study: The trial consists of a 2-3 year recruitment and randomization phase with a 2 year follow-up period. Due to the COVID19 global pandemic, China centers were shut down and complete access for patient follow-up will require an additional 6-12 months. Therefore, we are requesting one extra year extension for follow up due to these unanticipated circumstances. No statistical review or analysis was performed, as follow-up remains incomplete as of April,28th , 2020.



2. INTRODUCTION

2.1 Background and Rationale

Sudden cardiac death (SCD) remains the leading cause of death in the United States, totally over 440,000 cases annually. The incidence of SCD in Asia is unknown and the population potentially at risk is over four times the size of the Unites States. ICD implantation remains the most effective abortive strategy to decrease mortality in the secondary and primary prevention setting. However, the penetration and acceptance of ICD therapy into routine medical practice and guidelines in Asia is incomplete with significant unrealized potential. In 2011, an estimated 800 ICDs were implanted in China, compared to half a million in the United States.

The barriers to widespread adoption of ICD implantation across Asia are multifactorial, including financial, cultural, and scientific factors. In China, the cost of the device is not covered by national insurance, making the technology cost- prohibitive for many

patients who are likely to derive benefit. Cultural biases include aversion to surgery and implantation of devices, in addition to attitudes that reflect culture-specific disease progression. Additionally, the vast majority of scientific evidence and randomized studies that support current ICD guidelines have been performed in US and Europe, outside of Asia. The relative efficacy of ICD therapy in the Asian population has not been formally tested and lack of generalizable data is one factor that impedes widespread adoption among practicing physicians, which has a significant impact on how patients are counseled. Continuity and clinical follow-up are challenges in such vast Asian countries, and the implantation of an ICD offers a potential means of improving upon these limitations. In this current state, Asia serves as the ideal environment and setting to test the efficacy of both ICD therapy and catheter ablation in patients at risk for ventricular arrhythmias and sudden death. Further, mortality impact from both ICD and ablation can be further studied as the majority of patients with structural heart disease referred for VT ablation in Asia do not have an ICD.

ICD therapies have been strongly associated with increased hospitalization and all-cause mortality. As catheter ablation of VT has been demonstrated to decrease recurrent VT and ICD therapies, it is biologically plausible that ablation may have an impact on mortality. A recent multicenter study of 2,061 patients by the International VT Ablation Center Collaboration demonstrated that recurrent VT after catheter ablation was associated with a 7-fold subsequent risk for mortality and across all stages of heart failure, patients that had successful ablation experienced improved survival.(1) Only two randomized studies have been completed to date, SMASH VT (2)and VTACH(3), demonstrating that early preemptive ablation results in statistically significant reduction in subsequent ICD shocks. A trend towards improved survival was seen in the ablation group in SMASH VT.

2.2 Study Purpose

The purpose of this study is to demonstrate that scar-based VT ablation in subjects who are clinically indicated for new ICD or CRT-D implantation and are at high risk of ICD shock with spontaneous monomorphic VT or inducible monomorphic VT during EP or NIPS study results in a superior clinical outcome compared to ICD with standard medical therapy. Additionally, the registry arm which will enroll patients that refuse ICD will assess the efficacy of catheter ablation in the absence of background ICD therapy.

Additionally, secondary goals of this study include:

1) Increasing SCD awareness in Asia and improving clinical follow-up of patients at risk.
2) Assessing whether SCD is less prevalent in Asia than US and Europe and prospectively determine the relative magnitude of benefit of both ICD and ablation.
3) Determining the composition and etiology of patients referred for ICD and ablation in Asia. Patients with ischemic cardiomyopathy represent a

disproportionately small proportion of patients referred for VT ablation, despite a high prevalence of coronary artery disease and myocardial infarction. Biological and cultural differences in scar patterns may account for variations in arrhythmogenicity

3. STUDY DESIGN

3.1 Study Objective

The study is a prospective, multi-center, randomized controlled trial evaluating the efficacy of ICD plus catheter ablation vs. ICD alone in preventing recurrent VT, cardiovascular rehospitalization, and death in patients with primary and secondary indications for ICD implantation.

3.2 Study endpoints

The primary efficacy endpoint is defined as freedom from recurrent VT, cardiovascular rehospitalization, and all-cause mortality through a period of 2 years after the procedure (ablation) or randomization (standard medical therapy). Recurrent VT is defined as any appropriate ICD therapy (shock or ATP) or documented sustained monomorphic VT >30 seconds. Cardiovascular rehospitalization is defined as a hospital admission after the randomized procedure for heart failure, procedure-associated complication, or arrhythmia-related causes during the follow-up period.

3.3 Clinical Centers

We anticipate enrollment of 120 patients for this pilot study at 8-12 institutions with extensive experience in complex ablation procedures. As a conservative estimate, enrollment will occur over a 2 year period, with 60 patients per year (7-8 patients/year at each institution). Additional centers may be considered based on clinical competency and experience.

3.4 Subject Selection

The Principal Investigator at each center has the responsibility of screening potential candidates to determine if they meet all the entry criteria. Subjects receiving new ICDs and at high-risk of ICD therapy are to be included. Those subjects receiving new ICDs (within 90 days of the study enrollment) for standard clinical reasons who also have documented MMVT will be considered for inclusion. MMVT may be evidenced using an EP study or Non-Invasive Programmed Stimulation study (NIPS) unless documented

spontaneous MMVT is available. Subjects who refuse ICD and undergo ablation will be included in a prospective registry arm.

3.4.1 Inclusion Criteria

- Patient is receiving a new ICD or CRT-D implant that has study required programing capabilities and is appropriate for remote monitoring. Patient who has received the ICD / CRT-D within 90 days of enrollment can also be enrolled.
- Patient who has a high risk of ICD shock as shown by documented Monomorphic VT (MMVT) by one or more of the following:
    - Spontaneous MMVT
    - Inducible MMVT during EP Study,
    - Inducible MMVT during NIPS Study

  *Inducible MMVT is defined as MMVT > 30 seconds or requiring electrical termination (ATP or cardioversion)
- Patient has EF < 50% or RV dysfunction
- Patient has a cardiomyopathy with structural heart disease of any cause
- 18 years of age or older
- Patient has been informed of the nature of the study and has agreed to its provisions and provided written informed consent approved by the Institutional Review Board.

3.4.2 Exclusion Criteria

- Any history of debilitating stroke with neurologic deficit
- ST elevation MI or previous cardiac surgery within 60 days prior to enrollment
- Patient is pregnant or nursing
- Patient has chronic NYHA class IV heart failure
- Patient has incessant VT necessitating immediate treatment
- Patient has VT/VF thought to be from channelopathies
- Limited life expectancy (less than one year)
- Patient has current class IV angina
- Recent CABG or PCI (< 45 days)
- Patient is currently participating in another investigational drug or device study
- Patient is unable or unwilling to cooperate with the study procedures
- Known presence of intracardiac thrombi
- Prosthetic mitral or aortic valve or mitral or aortic valvular heart disease requiring immediate surgical intervention
- Major contraindication to anticoagulation therapy or coagulation disorder
- Left Ventricular Ejection Fraction < 15%
- Patient has had a previous ablation procedure for VT, excluding remote (> 3 months) outflow tract tachycardia
- Patient has GFR < 30 mL/min/1.73m^2

- Patient has peripheral vascular disease that precludes LV access
- Patient is thought to have idiopathic outflow VT as only VT
- Patient has a PVC or VT induced cardiomyopathy that is expected to resolve with ablation and will not require an ICD
- Patient has reversible cause of VT
- Patient does not meet criteria for ICD or CRT-D

3.5 Study Design Overview

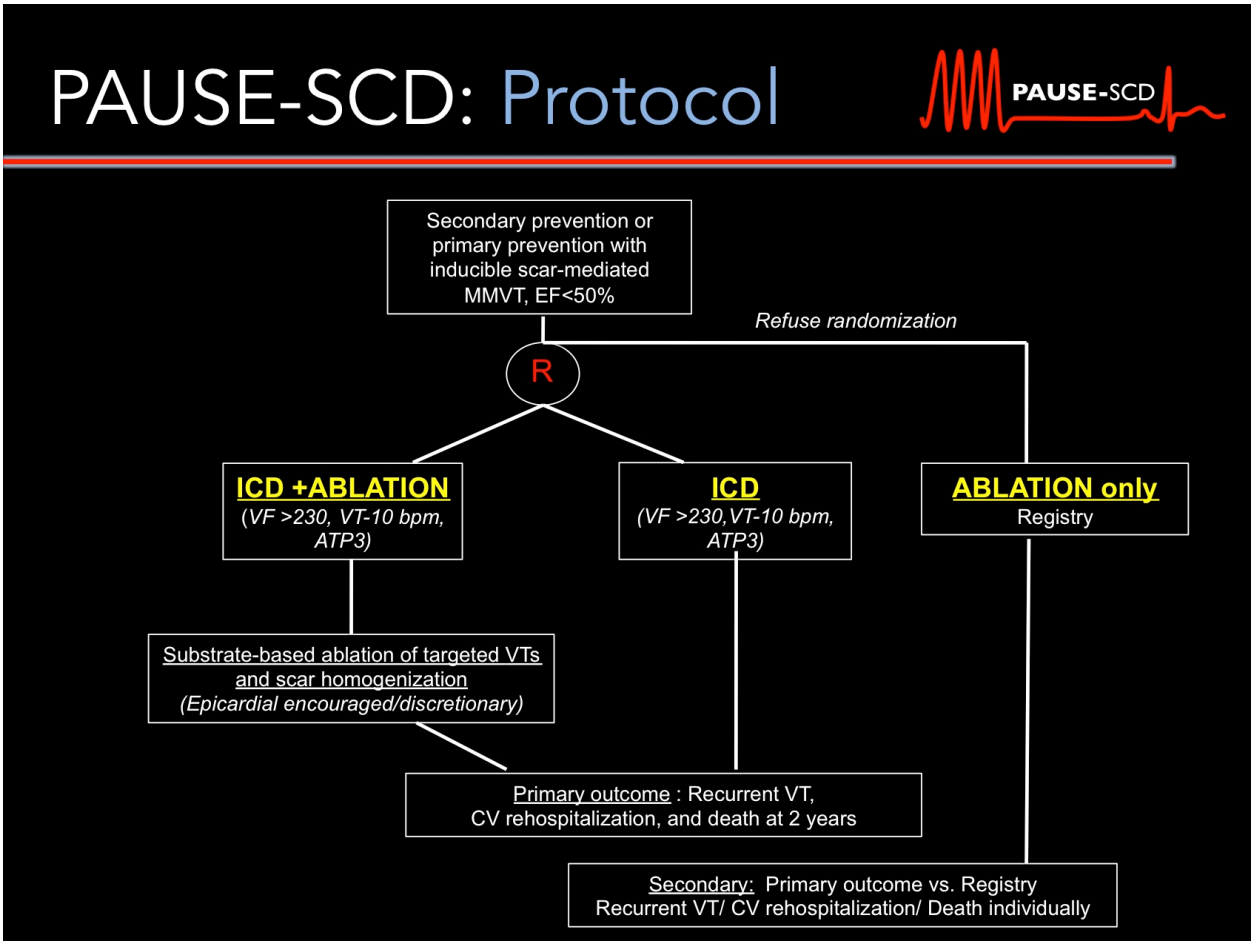
Based on assumptions from the SMASH VT trial and the AVID study, a 50% reduction in events from ablation is projected with a 50% event rate in the control arm at 2 years. 120 patients are required to achieve 80% power to detect a true difference of this magnitude with a two-sided alpha error of 0.05. The primary endpoint is a composite that includes cardiovascular rehospitalization and death, which will increase event rates at an estimated 10%/year, individually.(1,4)

3.5.1 Randomization

Subjects who meet inclusion/exclusion criteria will be entered into the randomized trial. Randomization will be 1:1 between control group and ablation group. Those randomized to the control group will receive ICD therapy and routine drug therapy (including antiarrhythmic drugs as indicated). Subjects randomized to the ablation group will receive ablation therapy plus ICD for ventricular tachycardia. Patients that refuse ICD therapy and undergo ablation only will be enrolled in a prospective registry. All primary statistical analyses will be performed on an intent-to-treat basis.

Central randomization is conducted by the coordinating site. Prior to 10/12/16, the participating sites performed randomization using a table (block size of 4) provided by the coordinating site. After additional in-house statistical review of the protocol, electronic randomization from the coordinating site was advised. Central electronic randomization commenced on 10/12/2016. 25 patients were enrolled using the original randomization table schema. The remaining patients were randomized using electronic randomization.

3.6 Study Population



3.6.1 Randomized Subjects

The **Intent to Treat (ITT)** population includes all randomized subjects. These subjects can be included in the randomized trial if they meet all other entry criteria.

3.6.2 Registry Subjects

Patients that refuse ICD implantation will not be randomized and will be approached to sign consent for inclusion into a registry if they undergo catheter ablation without ICD. Basic demographics and medical history will be collected from registry subjects upon enrollment. Registry subjects will receive a phone contact and follow-up with clinic visits and device interrogation at 3, 6, 12, 18, 24, 30 and 36 months to check on their overall status. Due to the COVID19 global pandemic, China centers were shut down and complete access for patient follow-up will require an additional 6-12 months. Therefore, we are requesting one extra year extension for follow up due to these unanticipated circumstances. No statistical review or analysis was performed,

as follow-up remains incomplete as of April,28th , 2020. Registry subjects will receive a phone contact and follow-up with clinic visits 30 and 36 months to check on their overall status

3.6.3 Discontinued Subjects

- Lost to follow-up: subjects may be lost to follow-up despite exhaustive attempts to contact them. A minimum of two (2) attempts (by telephone or mail) to contact such subjects will be made and then a certified letter will be sent to the last known address. Attempts to contact the subject will be documented.
- Subject/Family request: subjects may voluntarily decide to withdraw from the study with no penalty. If a subject chooses to discontinue participation in the study at the time of a study visit, the required assessments for that visit will be completed. If the subject notifies the clinical center by mail or phone, he/she may be requested to come in to have a final assessment.
- Subject's participation terminated by Investigator: a subject's participation may be discontinued if the Investigator considers that it is in the subject's best interest.
- Subject's participation terminated by site PI request.
- Subject Death.

If a patient is discontinued from the study, the reason for discontinuation will be documented and the data collected from this subject will be used in the final analysis and treated as censored subject.

4. STUDY PROCEDURES

4.1 Center Personnel

Study investigators and support staff will be responsible for obtaining approval from their institutional IRB and ethics committee. They will be responsible for completing case report forms and maintaining patient-level data throughout the duration of the study. All EPs performing ablation procedures must have a minimum of 3 years experience in complex ablation.

4.2 Subject Screening and Informed Consent

All patients who are being considered for enrollment into the clinical trial must be screened by the site investigator or a member of the designated study staff for study eligibility.

Patients must sign the informed consent form prior to randomization or collection of any study data. Once randomized, they will be considered enrolled in the study. The Investigator, Co-Investigator or Research Coordinator and if necessary, any witnesses should sign and date the consent as well. Consented subjects who do not satisfy entry criteria are screen failures and will not be randomized.

4.3 Schedule of Visits and Procedures

All subjects participating in the study should follow the schedule of visits as outlined in the Table provided.

4.4 Pre-Ablation

Subjects shall undergo the items outlined for Pre-ablation / baseline in Table 2.

- Informed Consent
- Inclusion Exclusion Criteria
- Medical History
- TTE (Trans-thoracic echocardiogram). This can be obtained up to six months prior to the procedure to assess EF which is standard prior to ICD implant. An MRI or TEE can be performed in lieu of a TTE
- TEE (Trans-esophageal echocardiogram) required if subject has history of LA or LV clot and recommended if subject has AF with a CHADS score >1
- A CT or MRI is strongly recommended within 3 month prior to the ablation procedure to allow for anatomy fusion
- 12-lead ECG within 6 months prior to the consent visit
- Assessment of current AAD medication
- Assessment of current anti-coagulation medication

4.5 Ablation Procedure (Ablation Arm Only)

4.5.1 Mapping of Ventricular Substrate

High-density mapping will be performed with NAVX system (Ensite Velocity, St Jude Medical). Multipolar catheters such as duodecapolar multielecrode (Livewire 2-2-2 mm spacing) are strongly encouraged to facilitate high-density mapping.(5) A minimum of 500 points is strongly encouraged for each chamber mapped. Epicardial mapping will be performed at the discretion of the treating physician but is encouraged for patients with ARVC and NICM.
Scar will be defined as regions of low voltage <1.5 mV with dense scar as <0.5mV.

4.5.2 Ablation Approach and Strategy

Irrigated-ablation technology will be used for mapping and ablation. The choice of the catheter is up to the discretion of the physician performing the procedure. The ablation technique will be targeting of late and abnormal electrograms within scar with prioritization of those with matching pacemaps, multiple exit sites pacemaps, or demonstrated diastolic activation during VT. Slow conduction zones with isochronal crowding entering the latest zone of conduction should be targeted by using an isochronal activation timing display (Isochronal Late Activation Mapping).(6) Activation and entrainment mapping are encouraged if induced VTs are hemodynamically stable. If time allows, homogenization is the goal of the procedure, where all other local abnormal electrograms that demonstrate uncoupling are eliminated.(7)

4.5.3 Procedural Endpoints

Programmed stimulation is required before the ablation procedure with two cycle lengths (600ms and 400ms up to triple extrastimuli down to VERP or 200 ms). This may be performed through the implanted ICD (NIPS). A VT is considered clinical if there is a morphologic match by 12-lead ECG or intracardiac EGM or has a similar tachycardia cycle length. Left ventricular stimulation within scar should be performed if the patient is noninducible with RV stimulation. Substrate-based ablation strategy targeting abnormal regions of slow conduction can be performed in the event of noninducibility.

The acute procedural endpoint is noninducibility of the targeted clinical VT and elimination of abnormal electrograms within scar. Programmed stimulation will be performed in the same fashion as prior to ablation. Complete noninducibility is encouraged but not required.

4.5.4 ICD Programming

The ICD will be programmed to disable all therapies during mapping and ablation.

In the Note section of the device, type the following message:

PAUSE-SCD Trial subject. Please contact [physician or coordinator name] at [center name] at [center phone] before making any programming changes.

Protocol-mandated programmed settings should be confirmed after the device is enabled at the conclusion of ablation. VF zone of 230 bpm (ATP during charging) and VT zone 185 or 10 bpm slower than clinical VT (induced or spontaneous) with detection at 30/40 intervals. (ATPx3).

4.5.5 Data Collection during Ablation

An ablation procedure form shall be completed by the operator, which includes patient demographics, number of VTs induced and targeted, predominant strategy, number of VT morphologies terminated during ablation, duration of radiofrequency applications, hemodynamic toleration during VT, and scar location and size.

4.5.6 Epicardial Mapping and Ablation

Epicardial access is encouraged in patients with ARVC and NICM substrate through the subxiphoid percutaneous approach, provided that surgical backup is present at the time of the ablation. This can be performed as a combined strategy, where access is obtained prior to any systemic anticoagulation or after reversal of anticoagulation (documentation of ACT<150) if VT remains inducible after endocardial ablation. It is recommended to leave in an epicardial drain if >50 cc of bleeding is encountered. Coronary angiography is required prior to ablation to detail coronary artery proximity to ablation lesion set as well as high output pacing to assess for phrenic nerve location.

4.6 Pre-Discharge

4.6.1 Pre-Discharge Evaluation

It is recommended that all patients have overnight observation after ablation. In patients that undergo epicardial ablation, an echocardiogram should be performed in the following day.

Subjects shall undergo the following at Pre-Discharge:

- 12-lead ECG
- Assessment of AAD medication
- Assessment of anti-coagulation medication
- Assessment of Adverse Events

For ICD programming, the following steps will be followed:

1) Program the device per guidelines outlined: VF zone of 230 bpm (ATP during charging) and VT zone 185 or 10 bpm slower than clinical VT (induced or spontaneous) with detection at 30/40 intervals. (ATPx3).

2) If the device is not programmed according to the settings recommended and unless at discretion of the physician for subject's benefit, a Deviation Form and any other applicable forms (i.e. Adverse Event or Hospitalization Form) must be completed if not previously submitted.

3) Print out the following reports to be included with procedure form:
    i. Wrap-Up Overview

ii. Parameters Printout

4.6.2 Concomitant Medical Therapy

Subject cardiac medications will be documented and tracked over the duration of the study. All subjects with heart failure should have their heart failure medications optimized including use of beta-blockers and ACE inhibitors. A consult with a heart failure specialist is encouraged especially for optimization of drugs and for diuresis after ablation. Subjects in both the ablation and no ablation arm must be maintained on their pre-procedure anti-arrhythmic drug (AAD) unless clinical events dictate otherwise. Anti-arrhythmic medications after ablation are at the discretion of the treating physician.

Subjects who have significant LV endocardial ablation and have LV dysfunction should receive anticoagulation for four weeks post-procedure per current guidelines. Other subjects with LV endocardial ablation should be considered for ASA. Also any subject who requires anticoagulation for other reasons (e.g. AF) should be maintained on therapeutic anticoagulation.

4.7 Follow-Up

Follow-ups will be scheduled according to the Table provided:

Study Activity	Baseline	Procedure	3 m	6 m	12 m	18 m	24 m	30m	36m	Unscheduled
Informed Consent	x									
Demographics	x									
Inclusion/Exclusion	x									
Medical History	x									
AAD/Medications	x	x	x	x	x	x	x	x	x	x
TTE	x			x	x		x			
CT/MRI	x									
12 lead ECG	x									
Randomization	x									
ICD implant		x								
Ablation Procedure		x								
ICD Interrogation		x	x	x	x	x	x	x	x	x
Adverse Events										
Death/Withdrawal								x	x	
Protocol Deviations										
Registry Subject	x		x	x	x	x	x	x	x	x

4.7.1 Scheduled Visits

The following shall be evaluated at every visit:

- Assessment of AAD medication
- Assessment of anti-coagulation medication

- Assessment of Adverse Events
- ICD Interrogation and event printout
- An Echocardiogram will be performed at 6 months, 1 year, and 2 years if not already performed for routine clinical evaluation.

4.7.2 Unscheduled Visits (as clinically warranted)

The following shall be evaluated at unscheduled visits:

- Assessment of AAD medication
- Assessment of anti-coagulation medication
- Assessment of Adverse Events
- ICD Interrogation and event printout

To accommodate subject referrals from remote hospitals, follow-up visits and device interrogations may be performed by the referring physician. It is the investigators responsibility to obtain the completed Case Report Forms (CRF).

4.8 Data Collection and Reporting

All required data, including subject's medical history for this trial are collected on standardized Case Report Forms (CRFs). CRFs were designed to balance the need for comprehensive data collection and to ease the process of data acquisition at the clinical center. The study coordinating site will provide each site with template CRFs to assist with data collection.

Components of the CRF:

- Subject selection criteria
- Medical History
- Medications
- Preoperative baseline subject demographics
- Ablation Procedure forms
- Device Operation Form
- ICD implantation information
- Pre-discharge hospital summary (including post-procedural complications, etc.)
- Assessment data at follow-up
- Adverse event/ Serious adverse event
- Unanticipated Adverse Device Effect
- Report of Death
- Subject Withdrawal
- Protocol Deviations

4.9 Source Documentation Requirements

Data recorded on CRFs must be verifiable by source documentation at the research center such as procedure reports, progress notes, discharge summaries, medication logs, and laboratory reports. Each site is responsible for its own data monitoring.

5. ADVERSE EVENTS

Adverse events will be monitored and reported in the source documents and on the appropriate case report form, including seriousness, action taken and relationship to investigational system at every visit. If adverse events occur, the first concern will be the safety of the study participants.

5.1 Definitions

5.1.1 Adverse Events Definition (AE)

An adverse event is any undesirable clinical occurrence or experience in a subject during the course of the study, whether or not it is related to the device or procedure.

Each adverse event will be classified by the respective site investigator as serious or non-serious. This classification of the event determines the reporting procedures to be followed. The Investigator will also assess the possible relationship between the adverse event and the investigational device. Adverse events will be followed until they are adequately resolved or deemed unresolvable.

5.1.2 Serious Adverse Events Definition (SAE)

A serious adverse event is defined as an adverse event that results in:

A. Death
B. Serious deterioration in the health of the subject that:
    1) Results in a life-threatening illness or injury;
    2) Results in permanent impairment of a body structure or a body function;
    3) Requires inpatient hospitalization > 24 hours or prolongation of existing hospitalization;
    4) Results in medical or surgical intervention to prevent permanent impairment to body structure or a body function.

5.1.3 Anticipated Adverse Events

The anticipated adverse events provided in section 7.1 (Risks) are believed to represent

adverse events and complications experienced in either animal and/or clinical studies to date with ablation procedures reported in the literature.

5.1.4 Unanticipated Adverse Device Effects (UADE)

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in this Investigational Plan; or any other serious problem associated with a device that relates to the rights, safety, or welfare of subjects. All UADE events should be reported to the coordinating center as soon as possible (within 24 hours), but in no event later than 10 days after the investigator first learns of the event.

5.2 Handling and Reporting of Adverse Events

Adverse events should be recorded in the source documents and on the Adverse Events Form. Non-serious adverse events will be reported to the IRB/EC as required by the respective site's IRB/EC.

If a serious adverse event or unanticipated adverse device effect occurs, the Investigator should do the following:

1) Notify the coordinating center within 24 hours of awareness of death, within 48 hours of awareness of a UADE and within 3 business days of awareness of an SAE.
2) Obtain and maintain applicable medical records such as procedure summary, diagnostic procedure report, discharge summary, etc. in the treatment and follow-up of the subject.
3) Provide the coordinating center a complete case history along with the adverse event form.
4) Inform the governing IRB/EC of the serious adverse event, in accordance with the IRB/EC's reporting requirement.

If the site investigator believes that a serious adverse effect is related to study procedures, the coordinating site should be notified within 10 days of the site investigator's knowledge. While the coordinating site will not be responsible for safety conduct at the sites, the study team would like remain aware of any unexpected outcomes or risks.

5.3 Subject Death

Notification of death should include a detailed statement of the pertinent events and be signed by the site investigator in addition to the appropriate CRF(s). It is the site investigator's responsibility to notify the appropriate IRB/EC, in accordance with the

IRB/EC's reporting requirements.

If the site investigator believes that the death is related to study procedures, the coordinating site should be notified within 24 hours of the site investigator's knowledge. While the coordinating site will not be responsible for safety conduct at the sites, the study team would like remain aware of any unexpected outcomes or risks.
Data communicated should include:

- Date of death;
- Primary cause (if known);
- Temporal course of death (if known);
- Any other circumstances surrounding the death;
- Whether it was device or procedure related.
- Autopsy report (if available)

If available, also provide clinical notes and witness statements. Appropriate CRFs must also be completed.

6. PROTOCOL DEVIATIONS

A protocol deviation is defined as a study related activity that is not in compliance with the protocol or the Investigator Agreement. Protocol deviations should be tracked and managed by each site, and reported according the site's IRB/EC policies.

Examples of deviations include but are not limited to: a required test not being done or not being done within the specified time-frame, a subject enrolled who did not meet the inclusion/exclusion criteria, a missed follow-up visit or missed visit window or enrollment of a subject without appropriate consent.

7. EXPLANATIONS OF RISKS AND MITIGATIONS TO SUBJECTS

7.1 Risks

The following complications have been reported for commercially available ablation catheters or in published literature and are expected to be similar to those anticipated in this study. The list of complications includes but is not limited to:

- Death
- Cardiogenic shock
- Complete Heart Block
- New incessant VT/VF
- Acute MI
- Stroke
- Pericarditis
- Cardiac perforation causing pleural effusion or tamponade

- Adverse effects on implantable pacemakers, cardioverters, and defibrillators
- Coronary artery occlusion
- Heart Valve injury
- Acute Pulmonary edema
- Pulmonary embolism
- Vascular access complications
- Phrenic nerve injury
- Arterial/venous thrombus: Clot formation in the artery or vein.
- AV fistula: An abnormal passageway between an artery and a vein.
- Catheter insertion site hematoma
- Hemopneumothorax
- Hypoxia
- Infection: Localized or systemic
- Peripheral venous thrombosis
- Phrenic nerve damage
- Pneumonia
- Pseudoaneurysm
- Radiation injury resulting in dermatitis
- Respiratory failure
- Radiation exposure during the fluoroscopic imaging of the catheters may slightly increase the lifetime risk of developing a fatal malignancy or a genetic defect in offspring
- Fluid overload resulting in pulmonary edema and exacerbation of congestive heart failure (these risks are specific to open irrigated ablation catheters)

Additional risks related to Epicardial Ablation:

- RV puncture
- Pericardial bleeding
- Hemoperitoneum
- Coronary Artery Damage
- Phrenic Nerve Damage
- Pleural Damage
- Myocardial Infarction
- Abdominal Bleeding
- Pericarditis

7.2 Mitigation of Risks

Cardiac ablation procedure is performed by physicians thoroughly trained in the technique of VT mapping and radiofrequency catheter ablation, greater than 3 years out of fellowship, have complex ablation experience (typically >50 per year) and in a fully equipped electrophysiology lab. In addition operators and centers should have experience in epicardial ablation. Catheter advancement is carefully performed under fluoroscopic guidance in conjunction with internal electrograms and impedance

monitoring to minimize the risk of cardiac damage. The physician take great care not to use excessive force to advance or withdraw the catheter when resistance is encountered. Since pacemakers and implantable defibrillators can be affected by RF signals, temporary external sources of pacing and defibrillation are available during the ablation procedure. The subject's fluid balance and hemodynamic status is continuously monitored during ablation. Various displays and alarms are used as precautionary measures to warn the physician of the possibility of any undesirable event occurring.

7.3 Potential Benefits

The major benefit of undergoing treatment with ICD and catheter ablation is the reduction and possible elimination of ventricular arrhythmias that may result in death or ICD therapy and shocks. The information gathered from the study will add to the understanding of the treatment options for subjects with ventricular tachycardia. This knowledge may advance medical science and have a benefit on other subjects with a similar arrhythmia.

8. DATABASE AND CONFIDENTIALITY

Conventional data management processing techniques will be used to by each center as they enter the data. The coordinating site and all participating centers are dedicated to maintaining the confidentiality and privacy of subjects who volunteer to participate in the study. Subject identifiers should be removed from any data that is shared with the coordinating site. Subject identifiers include, but are not limited to: subject's name, social security number / unique identification number, and medical record number. Study documents will identify the subject by a subject study identification number.

9. STATISTICAL ANALYSIS

9.1 Sample size and power calculation

Based on assumptions from the SMASH VT trial and the AVID study, a 50% reduction in events from ablation is projected with a 50% event rate in the control arm at 2 years. 120 patients are required to achieve 80% power to detect a true difference of this magnitude with a two-sided alpha error of 0.05. The primary endpoint is a composite that includes cardiovascular rehospitalization and death, which will increase event rates at an estimated 10%/year, individually.

9.2 Primary Endpoint

The primary efficacy endpoint is defined as freedom from recurrent VT, cardiovascular rehospitalization, and all-cause mortality through a period of 2 years after the procedure (ablation) or randomization (standard medical therapy). Recurrent VT is defined as any appropriate ICD therapy (shock or ATP) or documented sustained monomorphic VT >30 seconds. Cardiovascular rehospitalization is defined as a hospital admission after the randomized procedure for heart failure, procedure-associated complication, or arrhythmia-related causes during the follow-up period.

Prespecified secondary endpoints include each of the individual components of the primary endpoint. Comparison of the ablation-only registry with the randomized patients will serve as an additional secondary outcome measure.
Prespecified subgroup analysis will be performed for patients with RV cardiomyopathy.

9.3 Primary Endpoint Analysis

The primary endpoint analysis will be a time to event analysis and account for censored observations for all randomized subjects. Intention to treat analysis will be used for this endpoint; the analysis will be “analyzed as randomized” regardless of the actual treatment patients receive during the follow-up period. Kaplan-Meier (1958) estimates of the primary endpoint and overall survival will be generated along with 95% confidence intervals for the median time to event or death (Brookmeyer and Crowley, 1982).(8,9) Log-rank test will be used to compare the hazard functions between the two groups. Cox (1972) regression models will be fit to assess and adjust for baseline covariates.(10) The median time to VT recurrence as well as the 95% confidence intervals will be reported for both groups. The event free survival probability as well as the 95% confidence intervals at the 24-month follow-up for both groups will be presented. Adverse events will be tabulated by type and level of severity and compared between groups using chi-square or Fisher exact tests.

Secondary analyses comparing outcomes in the ICD+ablation and ICD arms vs. the registry patients (ablation only) will be performed in a similar manner to those described above.

Interim analyses will be generated by the coordinating center annually. A Peto-Haybittle efficacy monitoring boundary will be used: if the p-value for the difference between groups is <0.001, early stopping of the trial will be considered. Using this monitoring bound, the p-value for statistical significance at the final analysis will remain at the nominal 0.05 level.

10. MONITORING

Each participating center is responsible for study execution, data collection and monitoring for protocol compliance and conduct. The coordinating site may be consulted regarding any questions specific to protocol conduct.

The coordinating site will collect a copy of the IRB/EC approval letter for each site, as well as a copy of the final approved informed consent before randomization can begin. The coordinating site will collect a final complete data set from each site, and may work with the sites regarding any questions or outstanding data elements.

Upon inspection of the final data set, the coordinating site may request to see source documentation, reports of protocol deviations or adverse events if needed to verify data elements.

11. INSTITUTIONAL REVIEW BOARD AND ETHICS COMMITTEE

The study protocol must be reviewed and approved by the appropriate Institutional Review Board/Ethics Committee before subject enrollment may begin. Proposed changes to the protocol must be reviewed by the coordinating site PI land significant changes must be approved in writing as well as the Institutional Review Board / Ethics Committee. A significant change is one which may increase risks or present a new risk to the subject, or which may adversely affect the scientific validity of the study. Each investigator must sign the protocol amendment before implementing the change at his/her center.

IRB/EC approval is required for each institution participating in this investigation. Prior to enrollment, a signed copy of the Institutional Review Board approval letter addressed to the investigator must be submitted to the coordinating site certifying study approval. Investigators are responsible for obtaining and maintaining approval of the study by the IRB/EC. Annual review and approvals for continuation of the trial at each center must also be forwarded to the lead site where they will be submitted to coordinating site's IRB at the time of continuing review, per IRB policy. Correspondence with the IRB/EC should be retained at the center. Adverse events and protocol deviations must be reported per IRB/EC requirements.

12. STATEMENT OF COMPLIANCE

The clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and ISO 14155.
These principles protect the rights, safety, and well-being of human subjects, which are the most important considerations and shall prevail over interest of science and society. These principles shall be understood, observed, and applied at every step in the clinical investigation.

Protocol required investigational activities shall not begin until the required approval, or favorable opinion from the Institutional Review Board (IRB) or Ethics Committee (EC) or regulatory authority has been obtained and any additional requirements imposed by the IRB or EC or regulatory authority shall be followed.

13. REFERENCES

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