Continuation of Antiarrhythmics continuation Following caThEteR ablation for Ventricular Tachycardia (AFTER-VT) trial: Study protocol for a pilot randomized clinical trial.

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1. Background

Ventricular tachycardia (VT) is an important cause of morbidity and mortality in almost all forms of heart disease[1, 2]. Most of the patients with structural heart disease will have implantable cardioverter defibrillators (ICDs), which reduce the risk of sudden cardiac death[3]. Although ICDs are effective in terminating VT and preventing sudden cardiac death, shocks from ICDs reduce quality of life, and multiple shocks are associated with post-traumatic stress disorder[4, 5]. Most importantly, ventricular arrhythmia episodes and ICD shocks are also associated with increased overall-mortality and progression of heart failure, although the extent to which arrhythmia recurrences actually contribute to adverse outcomes or are simply markers for deteriorating cardiac status remains unclear[6]. Anti-arrhythmic drugs (AADs) are usually the first line therapy for VT. Of all AAD classes, the most commonly used for long-term prevention of VT recurrence are the Vaughan Williams class III AADs (sotalol, amiodarone and dofetilide). Unfortunately, AADs are often insufficient in suppressing VT and they carry a significant adverse effect profile. In cases of recurrent VT, catheter ablation (CA) has been shown to be a safe and effective treatment modality [7]. However, patients with structural heart disease who undergo CA still have substrate that predisposes them to VT recurrences. In addition, catheter ablation lesions heal and evolve over days to weeks, resulting in VT recurrences that are particularly associated with poor outcomes[8-10].

Although most patients undergoing VT ablation are on AADs, it is currently unknown the best management strategy of AADs following VT ablation, i.e., it is unclear if these patients should continue AADs or not.

2. Rationale and Specific Aims

Catheter ablation is a valuable option to control recurrent VT in patients with structural heart disease [3, 7]. However, after VT ablation the VT substrate remains and ablation lesions heal and evolve over days to weeks, such that some patients will suffer recurrent VT that is associated with worse mortality than patients who remain free of VT. Currently, it is not known if continuation of AADs following VT ablation can prevent these recurrent VT episodes. Of the currently available AADs, class III have the strongest antiarrhythmic profile, however, their significant adverse effect profile limits their use. Therefore, there is equipoise in clinical practice that benefits of class III AADs preventing recurrent VT outweighs the risks of their toxicities.

The specific aim of this pilot study is to obtain preliminary data to evaluate whether the strategy of continuation of class III AADs following CA for VT, improves VT-free survival and reduces readmissions. The goal of this study will be to answer the following question:

Among patients with structural heart disease who undergo VT ablation, does continuation of class III AADs 3 months after ablation, increases VT-free survival compared to discontinuation of antiarrhythmic drug therapy?

3. Hypothesis

We hypothesize that VT-free survival after catheter ablation is greater with continuation of class III AADs.

4. Inclusion/Exclusion Criteria

1. Age >18 years.
2. Able to give written, informed consent
3. Structural heart disease.
4. Implanted and normally functioning ICD or undergoing ICD implant at index admission.
5. Undergoing radiofrequency ablation procedure for sustained monomorphic VT.
6. Primarily on class III AADs for VT.
7. No clinically relevant VT inducible at the end of VT ablation
8. No clinically relevant VT inducible on non-invasive programmed stimulation following VT ablation.

Exclusion Criteria:

1. LV assist device in place
2. Decompensated heart failure and/or requiring continuous inotropic therapy and/or awaiting cardiac transplantation
3. Ongoing acute coronary syndrome.
4. Mechanical prosthetic aortic and mitral valves.
5. Pedunculated or mobile left ventricular thrombus.
6. Persistency of clinically relevant VT at the end of catheter ablation.
7. Absolute contraindications for amiodarone.
8. Participation in other trial.
9. Clinical VT induced on NIPS after VT ablation.
10. Another reason for continuation of class III AADs (i.e., atrial fibrillation).

5. Enrollment/Randomization

A patient will be identified as a candidate for participation in this study while receiving care at Vanderbilt University Medical Center. The clinical team will contact the patient in-person while being evaluated for VT ablation. The clinical team will ask the patient if they are interested to discuss participation in the clinical trial. If yes, information about participation will be provided by approved research staff. The patient may sign the consent document, decline, or defer until the day prior to ablation. At that time, research staff will again be available to

provide further information and/or obtain consent. Patients who decline participation will continue to receive usual care and the decision to not participate will not interfere with their medical care. Each candidate will receive a copy of the signed consent form. The consent form is presented in Appendix 1.

Patients will have VT ablation. Those with no evidence of clinical VT inducibility after ablation will then undergo Non-Invasive Programmed Stimulation (NIPS) prior to discharge. NIPS will be performed as there is evidence that patients with inducible clinical VT on NIPS after VT ablation have greater risk of VT recurrence [11] and might not be appropriate to withhold anti-arrhythmic therapy for those with inducible VT in NIPS.

Patients that meet inclusion criteria and agree to participate will be randomized and allocated to continue class III AADs or discontinuation using block randomization, stratified by type of AADs used until goal enrollment is achieved. The randomization sequence will be created using STATA 14.2 (StataCorp, College Station, TX, USA) statistical software.

Adherence to study-assigned group will be achieved by clinician education and reminders in routine daily meetings performed by the electrophysiology service.

Before enrollment begins, approval from the Institutional Review Board of Vanderbilt University Medical Center will be obtained, and the trial will be registered in ClinicalTrials.gov.

6. Outcome measures

The primary outcome will be VT-free survival, a composite of all-cause mortality and VT recurrence one year after VT ablation. Secondary outcomes will be all-cause mortality, VT recurrence, incidence of VT storm, and readmission for heart failure for one year after VT ablation. Both self-terminating sustained VTs (>30 seconds or hemodynamic instability) and VT requiring device therapies for termination will be considered as recurrences when considering VT recurrence.

Subgroup analysis.

The primary and secondary outcomes will also be investigated according to type of cardiomyopathy (ischemic vs dilated) and according to type of AADs.

7. Study Procedures

Enrollment:
At the time of enrollment, baseline information pertaining to symptoms and details clinical presentation, imaging, and heart catheterization procedures will be obtained from examination of their medical record and recorded in a Redcap database

VT ablation procedure

Ablation will be performed according to our usual practice. When feasible, prior to ablation class III AADs will be held for 72 hours prior to ablation per usual practice in our institution.

Ablation will be standardized and performed in all participants per usual care and without any differences in protocol. Briefly, in fasting state patients are taken to the electrophysiology laboratory and are continuously monitored during the ablation with external surface EKG leads.

The procedure will be performed with the usual sterile preparation under moderate sedation or general anesthesia. The left ventricular endocardial cavity will be accessed via either retrograde aortic or trans-septal access. A hexapolar catheter will be positioned in the right ventricular apex. A mapping catheter or a multi-polar mapping catheter will be used to collect voltage and activation data from the left ventricle during sinus rhythm or RV apical pacing. Areas of slow conduction with crowding of isochrones will be outlined.

Programmed stimulation for initiation of VT will be performed at the start of the procedure after catheter are placed and use 1, 2, and then 3 extrastimuli during 2 paced cycle lengths from 2 RV sites. Systemic anticoagulation with heparin will be required for LV mapping and dosed per usual protocol. After induction of VT the specific extra-stimulus protocol (site, drive cycle length and extra-stimuli) will be recorded. A comprehensive endocardial substrate map will then be created during sinus rhythm or RV apical pacing to capture both voltage and activation to the offset of the local electrogram. Areas of interest on the basis of pace-mapping or electrogram characteristics will be tagged. If at any point during this procedure, the origin of VT is located in the epicardial surface, pericardial access will be obtained and an epicardial substrate map will be generated. After completion of the substrate map repeat programmed stimulation for initiation of VT will be performed using the same protocol as the start of the case.

Then, ablation will be performed to target all clinically relevant VTs, which will be defined as all sustained monomorphic VTs having a cycle length within 20 ms longer than the fastest VT documented prior to ablation. Ablation of VTs of shorter cycle lengths will be performed whenever feasible and clinically indicated. Anticoagulation following catheter ablation will follow usual practice.

Non-Invasive Programmed Stimulation

Patients with no evidence of clinical VT being inducible at the end of ablation and no spontaneous VT recurrence will undergo NIPS prior to hospital discharge, according to our usual practice. Patients will need to provide written informed consent on the day of or before of this procedure as done in usual practice. If the patient refuses to consent will be excluded from the study.

Briefly, under fasting condition, patients will undergo NIPS via the right ventricle ICD per usual protocol**,** which is the protocol used as usual practice in our division when NIPS is performed, under monitored anesthesia care (MAC) and continuous external surface EKG lead monitoring.

Response to these stimuli will be categorized as “inducible clinical VT” and “No clinical VT inducible”. Patients with inducible clinical VT will be excluded of our study.

ICD programming guidelines:
After catheter ablation, patient’s ICD programming to detect and treat VT will be adjusted as per usual practice in our division based on published guidelines[7]. VT detection will be programmed depending on clinical VT rate.

- **If VT is 200 bpm or faster,** detection will be set at 165-171 bpm but without therapy programmed unless HR is > 200 bpm.
- **If VT is slower than 200 bpm,** detection programmed at 20 bpm slower than the known VT cycle length.
- **If the known VT is 140-150 bpm**, set detection at 130 bpm.
- **If the known VT is slower than 140 bpm**, detection should be programmed 10 bpm slower than the known VT.

In addition, will allow delay in therapy of 6-12 seconds. Anti-tachycardia pacing is recommended in all zones.

Follow-up
Patients will be evaluated per usual care after VT ablation by their treating electrophysiologist. This is at two to four weeks after ablation, and then at three months intervals (either in clinic or via remote ICD interrogation) for one year. ICD interrogations will be performed in each visit and we will ask to receive alarms for episodes of VT/VF and therapies delivered. Changes in medical therapy and ICD settings will be at the discretion of the treating electrophysiologist. Our consent form will include request of consent to access remote as well as in-office ICD interrogations. Most of these patients will likely have been already enrolled in a VT registry maintained by the arrhythmia service and this will route us the interrogations with no need to have the patient come for specific appointments with us for this trial.

8. Risks of Investigational Agents/Devices (side effects)

The added risks of continuation of class III AADs include risk of hyperthyroidism, hypothyroidism, hepatotoxicity, pulmonary fibrosis, corneal deposits, optic neuropathy, skin deposition, tremors and increased defibrillator thresholds, polymorphic ventricular tachycardia, torsades des pointes, bradycardia, fatigue, weakness, headache, edema, depression, thrombocytopenia, angioedema, skin rash.

However, most of these patients have been already tolerating these medications over several months/years. Furthermore, we expect that in the long-term, preventing VT will result in reduction of out-of-hospital VT/VF leading to ICD shocks which are associated with reduced quality of life and increased mortality.

9. Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Any unanticipated adverse events will be reported by the Principal Investigator according to applicable IRB policy. The PI is fully engaged in the performance of the study and this ensures that adverse events would be readily known by the PI and reported in a timely manner.

10. Study Withdrawal/Discontinuation

If an individual decides to withdraw their consent by informing study staff in writing or verbally, we will withdraw the participant. Contact information for the PI and study staff will be made available to the participant upon enrollment in the consent document.

11. Statistical Considerations and analysis plan

No studies have previously addressed this question; therefore we have no clear expectation on possible effect size and plan to perform this trial as a pilot study aimed at including all patients possible in a time frame of 12-24 months to then inform power size calculations for a larger and blinded clinical trial. We plan to enroll 75 patients per arm.

An intention to treat analysis will be performed. Analysis for the primary outcome will be accomplished by using log-rank statistic. Cox proportional-hazards regression will be used to estimate relative risks and 95% confidence intervals and adjust for differences in baseline outcome predictors. Differences in secondary outcomes will be calculated using log-rank statistic and cox proportional-hazards regression for all-cause mortality, VT-free survival, hospital readmissions and with unpaired t test for VT storm.

Interim analysis of the primary endpoint and drug adverse events will be planned every 6 months from study initiation. An independent statistician blinded to the treatment groups will perform the analysis and report findings to the data and safety monitoring committee who will decide the continuation of the study.

12. Privacy/Confidentiality Issues

A variety of measures will be utilized to ensure participant privacy:

Data will be stored in REDCap using the participant's study ID. Their REDCap data record may contain some identifying information. Subjects will be tracked using their study ID. The identifiable data, excluding date of procedures, will reside as a separate form under the data entry sections labeled "Registration/PHI" within our REDCap database which will allow us to exclude access to the identifiable information, excluding date of procedures, if necessary. Minimal paper records will be kept, and they will be kept locked in a cabinet.

Researchers are trained in HIPAA privacy regulations and other applicable privacy policies at Vanderbilt University. No information will be released, nor will participation in the research be acknowledged, to any party except where compulsory according to law or Vanderbilt policy. There may be unknown or unanticipated adverse effects from participation in this trial for which the PI and study team will remain observant.

13. Follow-up and Record Retention

Patients will be evaluated per usual care after VT ablation by their treating electrophysiologist. This is at two to four weeks after ablation, and then at three months intervals (either in clinic or via remote ICD interrogation) for one year. ICD interrogations will be performed in each visit and we will receive remote alarms for episodes of VT/VF. Changes in medical therapy and ICD settings at follow up will be at the discretion of the treating provider.

Data will be retained indefinitely. Electronic data may be destroyed earlier at the request of the participant. If so, electronic records will be deleted from the REDCap database, paper copies will be deposited into locked containers designated for shredding of confidential patient information.

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