-STandardized ultra-conservative **O**r **P**hysician-directed ICD programming for **SHOCK** reduction among patients on continuous flow **LVAD** support: a randomized controlled trial (**STOP SHOCK LVAD study**)

Study Design	Randomized unblinded clinical trial
Planned Number of Patients	280 patients; 140 per treatment arm
Randomization Method	REDCap
Treatment Arms	A) Ultraconservative ICD programming for maximal shock avoidance (see table at end of protocol) B) Physician Discretion
Primary Endpoints	Any ICD shock Mortality Syncope
Secondary Endpoints	Time to first ICD shock Time to first ICD shock for VT/VF Quality of Life questionnaire Hospitalizations; including HF and ventricular arrhythmia
Inclusion Criteria	- >18 years of age - Pre-existing ICD
Exclusion Criteria	- Non-functional ICD system - Uncontrolled ventricular arrhythmias ≤7 days of enrollment (defined as VT/VF >30 seconds and/or causing hemodynamic instability and/or symptoms or pre-syncope or syncope)
Follow-up schedule	Routine post-LVAD care; no additional study visits Remote ICD monitoring encouraged
Study Duration	2 years

INTRODUCTION

The proposed study will evaluate the utilization of an ultra-conservative programming strategy to reduce shocks for ventricular arrhythmias (VA) in heart failure (HF) patients with an implantable cardioverter-defibrillator (ICD) and a continuous-flow (CF) left ventricular assist device (LVAD). The survival benefit of ICDs with VA detections and therapies enabled has been established in HF patients with reduced ejection fraction (EF) without LVAD, as well as HF patients with older-generation, pulsatile-flow (PF) LVADs. However, newer studies do not demonstrate the same benefit of VA tachy-therapy in patients with current-generation CF LVAD devices, potentially due to better hemodynamic tolerability of VA. In addition, ICD shocks are known to worsen clinical outcomes while causing patients psychosocial harm. Recent studies have applied extended-detection programming to successfully reduce ICD shocks in non-LVAD HF patients. However, shock reduction strategies have not been previously evaluated in LVAD patients in an adequately-powered, randomized clinical trial. This study will prospectively randomize HF patients with pre-existing ICDs to programming at the discretion of their EP provider versus "ultra-conservative" ICD programming, in which a single ventricular fibrillation (VF) zone will be programmed using the maximum rate cutoff allowable across all ICD manufacturers (250 beats per minute [bpm]), as well as the manufacturer-specific maximum detection intervals. In the ultra-conservative arm, a monitor-only zone will be programmed at 150 bpm. The primary endpoint will be the percentage of patients receiving an ICD shock at 2-year follow-up with planned interim analyses at 6 months and 1 year. Secondary endpoints include time to first ICD shock, time to first VT/VF shock, and Quality Life questionnaires. Data collected will include mortality, syncope, LVAD-related hospitalizations (including HF, VA), and the percentage of patients receiving inappropriate ICD shocks at 2-year follow-up. The study hypothesis is that the standardized application of ultra-conservative ICD programming will reduce shocks and improve quality of life without an increase in mortality, syncope, or hospitalizations compared to physician discretion programming in CF LVAD patients.

Study Rationale

The current International Society for Heart and Lung Transplantation (ISHLT) guidelines provide a class I recommendation for tachy-therapy re-activation in patients with ICDs undergoing LVAD implantation [1]. However, these guidelines reflect a survival benefit observed in cohorts comprised primarily of older-generation PF LVADs [2, 3]. While the overall VA prevalence in the LVAD population exceeds 50% [4-6] with VA usually occurring >200 beats per minute [7], VA are generally well-tolerated both hemodynamically and symptomatically. Observed LVAD flows do decrease during sustained VA [8, 9], but there are multiple case reports of LVAD patients remaining awake and asymptomatic despite hours of ventricular fibrillation [10-12] and a large case series reported no deaths and rare syncope due to VA in CF LVAD patients [7]. Contrary to guidelines, contemporary evaluations restricted to CF LVADs show no clear ICD survival benefit in single center studies [7, 13] nor a large, pooled meta-analysis [14]. In fact, propensity-matched analyses of CF LVAD patients in the INTERMACS [15] and UNOS [16] registries have demonstrated increased mortality and more hospitalizations among patients with an active ICD and treated VA.

It is unclear in the CF LVAD population whether ICD shocks themselves are harmful or rather identify a higher-acuity patient subgroup. In the general HF population, however, shocks have consistently been associated with worse outcomes [17-21]. Shock reduction programming resulted in reduced mortality in the MADIT-RIT trial [22], suggesting shocks may be directly harmful and not only a marker of substrate

severity. In addition, repeated ICD shocks have been clearly linked to psychological harm [23-26] in the form of post-traumatic stress disorder (PTSD).

Despite signals towards physical and psychological harm, the predominant U.S. practice pattern is to maintain active ICD tachy-therapy in CF LVAD patients. In a nationwide single-vendor study, 93% of LVAD patients retained active ICDs. While only 5% were re-programed in a strategy aimed to minimize shocks, >50% were programmed in a manner more likely to deliver tachy-therapy than in a non-LVAD, primary prevention HF population [Kiehl HFSA 2017]. This discordance triggered a small, single-center study that prospectively evaluated multiple-zone ultra-conservative ICD programming in CF LVAD patients [27]. While no reduction in shocks was observed, there was also no signal towards clinical harm. Nevertheless, by programming multiple zones for ventricular tachycardia (VT) and VF, detection rates and intervals were not fully maximized. The authors concluded that a prospective trial of a monitor-only programming strategy was needed, however this remains impossible due to vendor-locked programming restrictions. The proposed study aims to evaluate the most "ultra-conservative" VA tachy-therapy currently programmable in CF LVAD patients.

OBJECTIVES AND ENDPOINTS

To evaluate the utilization of an "ultra-conservative," single-zone programming strategy for ICD tachy-therapies in CF LVAD patients as compared to a passive strategy of standard programming (at the discretion of the provider). The study hypothesis is that an ultra-conservative strategy will result in a reduction in shocks and an improvement in quality of life without increasing adverse outcomes including death, hospitalization, and syncope among patients on CF LVAD support.

Sample Size

The projected sample size is 280 enrolled subjects, 140 randomized to each programming arm. Prior observed ICD shock rates in similar CF LVAD + ICD cohorts were 21% over 11 month follow-up in a study by Richardson et al [27] and 13% over 15 month follow-up in the aforementioned internal study currently under review by Kiehl et al. We thus projected an annual ICD shock incidence of 17% (the mean of the prior 2 studies). Thus, in order to detect a 15% absolute risk reduction in shocks over 2-year follow-up with 80% power and two-tailed α=0.05, 280 patients are needed.

Statistical Plan

At the end of study enrollment, baseline characteristics will be compared with potential covariates of interest able to later be balanced either via multi-variable regression or propensity analysis if needed. For continuous outcomes, linear regression will be utilized, for categorical outcomes, logistic regression will be utilized, and for time to event outcomes, Cox regression will be utilized.

Study Population

Patients will be eligible for study enrollment and randomization if adult (>18 years old) with a pre-existing, active ICD prior to CF LVAD implantation. Possible study enrollment will be discussed with eligible patients by their treating medical teams and the dedicated study research coordinator during

their index LVAD hospitalization. Consent and randomization will occur either at the time of index hospitalization discharge or during the first post-discharge LVAD/ICD clinic visit, whichever comes first.

Inclusion:

- >18 years of age
- Pre-existing ICD

Exclusion:

- Non-functional ICD system
- Uncontrolled ventricular arrhythmias ≤7 days of enrollment (defined as VT/VF >30 seconds and/or causing hemodynamic instability and/or symptoms or pre-syncope or syncope)

Of note, the need for anti-arrhythmic (AAT) drug therapy and/or catheter ablation is not an exclusion criteria, with treatment of VA per treatment team discretion and non-protocol driven. Ventricular ectopy and/or palpitations associated with non-sustained VT also do not serve as an exclusion criteria.

Enrollment and Informed Consent

The multi-disciplinary study investigators include physicians and nurse practitioners in electrophysiology, HF, and cardiothoracic surgery. The LVAD nurse practitioners, HF physicians, and surgical team will identify eligible patients and hold a preliminary discussion with patients about the study. A research coordinator will then verify eligibility, obtain informed consent, complete randomization, direct the device clinic on assigned programming changes (if any), and coordinate research follow-up visits to coincide with clinical LVAD visits for data collection on ICD therapies, symptomatology, HF hospitalizations, and death/transplantation.

All subjects who complete the informed consent process, sign and date the informed consent form are considered enrolled in the Stop Shock LVAD study. Subjects enrolled in this investigation must be followed
per protocol.

Randomization

Randomization to ultra-conservative versus standard programming will occur at the time of study enrollment using REDCap. Radomization will be a 1:1 ratio. Neither the patient nor treatment team are blinded to the randomization or programming assignment. ICD re-programming will occur in the device clinic or patient hospital room as per the current routine care pathway.

ICD Programing

There were will be no study-related diagnostic tests, treatments, or follow-up visits beyond routine post LVAD care. The ICD re-programming will be performed during the routine pre-discharge ICD check during the LVAD implant hospitalization or at routine LVAD clinic follow-up ≤ 30 days. For patients experiencing sustained VA below the VT zone in the ultra-conservative pathway, a symptom-driven care pathway will be implemented involving same-day cardioversion with the associated routine care. In the physician-discretion arm, ICD shocks delivered for VA routinely result in emergency department visits and hospitalizations, which fall under usual care covered by private and public payers.

Data for Supplemental Protocol Document
Ultra-conservative Programming by Vendor

Manufacturer	***Monitor Zone***	***VT Zone Detection***	***VT Zone Therapy***	***VF Zone Detection***	***VF Zone Therapy***
Abbott	*Rate: 150 bpm*	*Off*	*Off*	*Rate: 250 bpm 100 intervals (25s) to detection*	*ATP x1 (prior to charge) 36J, 40J x5*
Biotronik	*Rate: 150 bpm*	*Off*	*Off*	*Rate: 250 bpm 30/40 intervals (10 s) to detection*	*ATP x 1 (prior to charge) ***J*
Boston Scientific	*Rate: 150 bpm*	*Off*	*Off*	*Rate: 250 bpm 15s to detection*	*ATP x1 (quick convert) 41J x8*
Medtronic	*Rate: 150 bpm*	*Off*	*Off*	*Rate: 250 bpm 120/160 intervals (40s) to detection*	*ATP x1 (prior to charge) 35J x6*

Proposed care pathway ICD re-programming if a) asymptomatic shock in standard programming arm; or b) symptoms prompting external cardioversion in ultra-conservative programming am

Manufacturer	**Monitor Zone**	**VT Zone Detection**	**VT Zone Therapy**	**VF Zone Detection**	**VF Zone Therapy**
Abbott	Rate: 150 bpm	Rate: 10 bpm below clinical VT 100 intervals to detection	ATP x 30 (20-pulse burst)	Rate: 250 bpm 100 intervals (25s) to detection	ATP x1 (prior to charge) 36J, 40J x5
Biotronik	Rate: 150 bpm	Rate: 10 bpm below clinical VT 32 intervals to detection	ATP x 20 (10-pulse burst)	Rate: 250 bpm 30/40 intervals (10 s) to detection	ATP x 1 (prior to charge) 40J x6
Boston Scientific	Rate: 150 bpm	Rate: 10 bpm below clinical VT 30s to detection	ATP x 60 (30-pulse burst)	Rate: 250 bpm 15s to detection	ATP x1 (quick convert) 41J x8
Medtronic	Rate: 150 bpm	Rate: 10 bpm below clinical VT 130 intervals to detection	ATP x 10 (15-pulse burst)	Rate: 250 bpm 120/160 intervals (40s) to detection	ATP x1 (prior to charge) 35J x6

Follow Up

	Screening Enrollment	1 mo	3 mo	6 mo	9 mo	12 mo	15 mo	18 mo	21 mo	24 mo
History, demographics, cardiac test results	x									
Informed Consent	x									
Randomization	x									
Office Visit	x		x	x		x		x		x
Research Visit *, including assessment for AE/SAE/QOL		x			x		x		x	
Device interrogation/data (may be remote)		x	x	x	x	x	x	x	x	x

**Can be completed in-office, by phone, medical record review and from the* Interagency Registry of Mechanically Assisted Circulatory Support/NIH registry.

All visits follow the schedule of routine LVAD follow up.

Withdrawal

All subjects enrolled in the clinical study, including those withdrawn from the clinical study or lost to follow-up, shall be accounted for and documented.

Data Monitoring

The principal investigator will be responsible for ensuring the study is being carried out per protocol and the associated data documented and submitted for analysis. Adverse events will be reviewed by the Principle Investigator.

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