Elimination of Premature Ventricular Contractions in Heart Failure (EVAC-HF)

NCT 01757067

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Data Analysis

Primary Endpoint

Left ventricular ejection fraction

Based on previous observational data, a minimum 10 percent improvement of EF is expected with successful reduction of PVC burden. We expect a successful suppression of ≥80% of PVC's in 60% of patients. We assume an attrition rate of 10% without 6 months follow- up data (in those cases of missing data the enrollment EF will be used as 6 month EF as well). As a result we expect a 10%x0.6=6% change of EF, which after accounting for a 10% attrition rate results in a 6%-0.6%=5.4% improvement of EF in the intervention group. The standard deviation for echocardiographic LV assessment is assumed to be 7 percent. As primary intention-to-treat analysis, we propose a pilot study with 80 percent power to detect a 5.4 percent improvement in LV systolic function (LVEF at 6 months – LVEF at baseline) between the two groups, at an alpha level of 0.05. Using a 1:1 randomization, we will need to randomize 56 patients (28 in each arm) to complete our assessment. Each study site will be allowed up to 10 participants. Randomization will be assigned via email contact with the coordinating site, University of Maryland Medical Center. The Permuted Block design will be utilized in assuring even distribution to the 2 arms of the study.

Fixed Scenario Elements	
Distribution	Normal
Method	Exact
Group 1 Weight	1
Group 2 Weight	1
Number of Sides	2
Null Difference	0
Alpha	0.05

Computed N Total					
Index	**Mean Diff**	**Std Dev**	**Nominal Power**	**Actual Power**	**N Total**

9	5.4	7	0.8	0.809	56

A prespecified “on successful treatment” analysis will be performed comparing patients with successful ≥80% PVC suppression with patients with unsuccessful PVC suppression.
In case of missing data due to loss of follow-up the enrollment EF will be used as the EF at 6 months assuming no improvement.
Patients in the OMT group that had to cross-over to the ablation group will be analyzed in the OMT group for the intention-to-treat analysis.
Start of anti-arrhythmic drug therapy in the OMT group during the 6 months randomized period is expected to occur only in very rare cases (as patients were stable in 3 months optimization phase). As AAD are often not able to achieve significant PVC suppression, these patients will be analyzed in the OMT group.
Uptitration of the HF medications such as beta-blocker is expected to occur only occasionally as they were optimized in the 3 months run-in period. This would be counted as protocol deviation as they could result in improvement of EF independently of studied PVC reduction strategies.
Each value will measured as the absolute change between baseline and end follow-up and compared between the 2 study groups. All echocardiographic measurements will be made by single echocardiography core center and will include calculation of left ventricular volumes and function using Simpson’s biplane method. Before and after echocardiograms will be reviewed by a single, experienced reader in a blinded fashion.

Secondary Endpoints:

A secondary primary endpoint will include

a) Echocardiography:
   Left Ventricular end-systolic volume index (LVESVI)
   Left Ventricular end-systolic dimension
   Left Ventricular end-diastolic volume
   Left Ventricular end-diastolic dimension
   All the above echocardiographic parameters assess different aspects of the cardiac function and have been used in clinical studies before.
b) Biomarker: BNP, hs-Troponin, galectin-3, soluble ST2
   All the above biomarkers assess a different pathological pathways/processes which could lead to worsening heart failure. BNP has been associated with heart failure exacerbations and morbidity. Troponin has been related to myocardial necrosis and mortality. Galectin-3 and ST2 have been associated with cardiac fibrosis and remodeling.
c) Heart Failure: 6-MWT, Kansas City Cardiomyopathy Questionnaire, Minnesota Living with Heart Failure Questionnaire, (possibly SF 12/36)
   Very few data is known about the quality of life of this patient population. Therefore the objective is to assess if the intervention (ablation ±

antiarrhythmic drug for suppression of PVCs) resulted in a change of the quality of life assessed by validated questionnaires compared to the control group.

The objective is to assess if the intervention (ablation ± antiarrhythmic drug for suppression of PVCs) resulted in a change of these parameters compared to the control group.

For each of the patients the difference of the test will be calculated to determine the delta between pre and post. We will then compare the mean between the deltas in the control and intervention group using a t-test. We assume that suppression of PVCs by >80% will result in a significant difference between pre/post measurements compared with the control group.

Specific data to be collected:

1- Patient demographics (not identified)
2- Peripheral blood samples will be collected and stored from the time of randomization and at 6 months. These samples will be send to core laboratory and assayed for relevant biomarkers including BNP, galectin-3, soluble ST2.
3- Blood samples will be collected at initial visit for genome analysis
4- Echocardiographic and electrocardiographic data
5- 24 hour Holter recordings with available HRV data
6- Procedural data such as 3-dimensional left ventricular mapping data including number and origin of PVCs and the successful ablation sites
7- Peri-procedural data collection including mode of sedation, inducibility, dose of sympathomimetic drugs, procedure duration and fluoroscopy time
8- The complications, if any, of the procedure
9- The acute and intermediate-term success rate of the procedure.
10- Procedure, medication and outpatient visit costs
11- 6 MWT at baseline and 6 months
12- Heart Failure Questionnaire at baseline and 6 months
13- Clinically performed high-resolution CMRI studies performed prior to the enrollment, during randomizatoin duration and after 6 months will be collected to assess anatomic, perfusion and delayed enhancement myocardial fibrosis.
14- Tissue samples that may become available during the study duration from clinically indicated procedures such as biopsy, LVAD placement or heart transplantation will be stored for further tissue analysis
15- Clinical data such as past medical history, medications, NYHA class, physical exam findings, hospitalizations will be assessed during the 2-years follow-up