A. Study Purpose and Rationale

Current clinical guidelines recommend ICD placement for primary prevention in selected heart failure patients based on evidence from several randomized control studies, most notably the MADIT II and SCD-HeFT trials.[1,2] Despite evidence and national guidelines, a large multi-center study has shown that only half of patients with evidence-based indications for ICD placement actually undergo ICD placement.[3] Prior studies have identified some predictors of nonadherence to guideline-based ICD use.[3,4] They have shown that older patients, female patients, and patients seen by non-cardiologists are less likely to undergo guideline-recommended ICD placement. This association exists despite the lack of evidence to suggest that these groups of patients derive no mortality benefit from ICD placement. In fact, there is evidence that older patients experience comparable mortality risk reduction despite their higher baseline risk of mortality.[5] Prior studies evaluating predictors of guideline-based ICD use have been limited by their lack of ability to reliably capture information through retrospective review of clinical documentation. These prior studies have been unable to look at variables of interest that are not routinely obtained or reliably documented for all patients, such as frailty and cognitive impairment. The objectives of this proposed study are 1) to determine if frailty and cognitive impairment predict adherence to guideline-based ICD use for primary prevention in heart failure patients and 2) to determine the relationship between ICD placement and 5-year mortality in frail and cognitively impaired patients. It is our hypothesis that these variables are significantly and independently associated with guideline adherence, and, as frailty has been shown to be correlated with age and gender,[6] may help explain some of the existing age and gender bias in ICD placement. We also predict that frail and cognitively impaired patients derive diminished mortality risk reduction from ICD placement as compared to their counterparts.

B. Study Design and Statistical Analysis

This study will be a prospective cohort study of heart failure patients from outpatient CUMC primary care or cardiology practices who qualify for ICD placement based on current primary prevention guidelines and do not yet have an ICD in place. Patients will be cohorted according to the presence of frailty (yes/no) and according to the presence of cognitive impairment (yes/no). Frailty will be defined according to The Frailty Phenotype Score which has been previously described in detail elsewhere.[6] In brief, patients will be considered frail if they have 3 or more of the following 5 characteristics: 1) self-reported weight loss of >= 10 lbs in the last year, 2) low grip strength, 3) self-reported exhaustion, 4) slow walking speed, 5) and low physical activity. Cognitive impairment will be defined as a score of less than 24 points on the Folstein Mini-Mental State Exam (MMSE).[7]

Based on prevalence data from previous studies, we predict that approximately 25% of patients with heart failure are frail[6,8] and 30% are cognitively impaired.[9,10] We will use data from a recent study by Chae and Koelling to predict the proportion of

patients in each group who will receive ICD placement at our institution.[4] This study looked at determinants of ICD use in heart failure patients at a university-based tertiary care center. While the study did not look at frailty or cognitive impairment it did look at the proportion of ICD placement in patients with common comorbidities including dementia. As frailty is associated with comorbidity, we will use the average rates of ICD implantation in patients with common comorbidities (e.g., CAD, DM, renal disease, pulmonary disease) as a proxy estimate for the proportion of frail patients expected to undergo ICD placement. The study found that approximately 60-70% patients with common comorbidities underwent ICD placement, whereas 70-80% of total patients underwent ICD placement. Similarly, as dementia and cognitive impairment are related, we will use the results for dementia as an estimate for our cognitive impairment projections. In the study by Chae, 15% of patient's with dementia underwent ICD placement. As dementia is more severe than cognitive impairment we will increase the 15% figure and estimate that 30% of patients with cognitive impairment will ultimately undergo ICD placement.

Differences in ICD placement rates stratified by frailty and cognitive impairment will be compared using chi-square tests. Based on the above projected estimates, and a 2% lost to follow-up rate, approximately 1000 patients will need to be enrolled (~25% of which will be frail) to achieve an 80% powered-study to demonstrate whether frailty is associated with ICD nonplacement. Significantly fewer subjects, approximately 70, are needed to demonstrate whether cognitive impairment is associated with ICD nonplacement.

Hierarchical logistic regression will be used to identify whether frailty and cognitive impairment are independently associated with ICD placement after accounting for other prespecified variables of clinical significance, which include patient sex, age, and physician specialty. The discrimination of the logistic regression model will be assessed with a c-index.

Crude 5-year mortality rates for patients who did and did not undergo ICD placement will be compared with chi-square tests. To assess for heterogeneity in the relationship between ICD placement and 5-year mortality in frail and cognitively impaired subgroups, stratified multivariable models will be constructed. The statistical significance of differences in these relationships will be assessed with the probability value for interaction.

C. Study Procedure

Eligible patients will be identified during their clinic visit and will be scheduled to come back to clinic within two weeks to undergo baseline testing and survey. They will be given a telephone reminder 24 to 48 hours prior to confirm their visit. Patient charts will be reviewed at baseline for basic clinical variables (eg medications) and to see if the patient has a documented LVEF in the last year.

At the return visit the patient will undergo basic testing administered by a trained research assistant. This testing will include a 15-ft walk test, grip strength, and a

questionnaire which will include but will not be limited to questions from other clinical survey tools such as the MMSE, Minnesota Leisure Times Activities Questionnaire (MLTAQ),[11] and Kansis City Cardiomyopathy Questionnaire (KCCQ).[12] A detailed list of survey questions will be presented in part F of this proposal. If the patient was identified as needing an echocardiogram (does not have a documented LVEF in the last year) an appointment will be made for it at this time. An echocardiogram is a non-invasive procedure that involves transthoracic ultrasound assessment of the size and function of the heart with little risk to the patient.

We estimate that it will take one year to recruit the 1000 patients targeted.

Six months after a patient's enrollment, his or her medical chart will be reviewed for documentation of ICD placement or contraindication to ICD placement within the last 6 months. ICD placement is not dictated by participation in the study and is done according to routine clinical management. ICD placement involves having a small stopwatch-sized electronic device implanted by a cardiologist or surgeon under the skin with wire leads extending into the heart. The procedure is generally a same-day procedure done under mild sedative anesthesia. Complications include bleeding, infection, and temporary collapse of the lung. There will be some post-operative pain and discomfort in the week following the procedure.

Patients will be contacted via phone at 6months post-enrollment to complete a brief follow-up questionnaire.

At 5 years after the completion of enrollment, mortality will be assessed by linking study data to Medicare records.

D. Study Drugs – N/A

E. Medical Device

ICDs are commercially available, approved devices that deliver shocks during certain types of ventricular arrhythmia to protect against sudden cardiac death. These devices have clear national guidelines detailing indications for their use. In the setting of primary prevention, ICD placement is indicated for 1) patients with NYHA class II or III heart failure irrespective of etiology and LVEF <= 35% or 2) patients with NYHA class I heart failure with medical hx of prior MI and LVEF <= 30%. In addition all patients must not have had an MI within the last 40 days, be optimized on medical therapy, and have expectation of >1 year survival. Efficacy has been demonstrated in several clinical trials, most notably MADIT II and SCD-HeFT.[1,2]

F. Study Questionnaire

The baseline study questionnaire will be administered in person and include the full MMSE, KCCQ, and MLTAQ. In addition it will ask for the subjective components of the frailty measurement including weight loss in the past year and self-reported exhaustion as identified by two questions from the CES-D scale.[13] In addition the questionnaire will ask the patient about his/her social supports, ability to perform activities of daily living,

and if he or she feels like there is a physician who is primarily responsible for his or her health.

The follow-up six-month questionnaire will be brief. It will ask if the patient if he or she received an ICD in the past 6 months. If the procedure was not performed at CUMC, it will ask where the procedure was done (and will be adjudicated with the performing institution). If the patient did not undergo ICD placement, the survey will ask if a physician had recommended ICD placement and if the patient had refused placement based on personal preference.

Trained research assistances will be responsible for administering both baseline and follow-up questionnaires to study participants.

G. Study Subjects

All Medicare-enrolled patients >= 65 years of age who have been seen at any of the CPMC primary care or cardiology outpatient clinics with an ICD-9 diagnosis of heart failure will be screened.

Inclusion criteria

1) patients with NYHA class II or III heart failure irrespective of etiology and LVEF <= 35% or

2) patients with NYHA class I heart failure with medical hx of prior MI and LVEF <= 30%.

Exclusion criteria

1) MI within the last 40 days

2) Not optimized on medical therapy (if a patient is not on guideline-indicated therapy documentation of contraindication must be present)

3) Less than one year survival expectancy.

This study specifically targets an elderly population as prior studies have shown that this population is less likely to undergo guideline-based ICD placement. Patients without capacity to consent to study participation will have their healthcare proxies or surrogates decide on participation.

H. Recruitment of Subjects

Eligible, suitable, and willing subjects will be identified by physicians on the day of their appointment.

I. Confidentiality of Study Data

All study data will be de-identified. However, a crossover key will be maintained in a locked safe location separate from the actual study data. The key will allow for medical chart review at various time points throughout the study. The key will also allow for ascertainment of 5-year mortality data via linking to Medicare files.

J. Potential Conflict of Interest

None of the authors have conflict of interest to report.

K. Location of the Study

The study will take place solely in clinical care areas of CPMC. Baseline surveys will be conducted in the outpatient clinics (primary care, general practice, cardiology). Echocardiograms will be performed in the echocardiography suite at CPMC.

L. Potential Risks

Because this is an observational study, potential risks to the subject are minimal. Clinical decision-making is minimally affected by participation in the study. If a patient has not had a documented measurement of LVEF in the last year he/she will undergo an additional echocardiogram, the results of which will be made available to the treating physician. The findings of this test can impact patient care in both positive and negative ways. In addition, patients will undergo frailty and cognition testing which some patients may find tiring.

M. Potential Benefits

The potential benefits to the patient are minimal and consist mainly of free heart failure education. The potential benefits to society include giving clinicians a better understanding of non-compliance with ICD guidelines. The results of the study may ultimately help to improve rates of appropriate and effective ICD placement.

N. Alternative Therapies – N/A

O. Compensation to the Subjects

Patients will receive a $20 dollar check after the completion of the follow-up questionnaire at 6 months. Patients will receive free evaluation of cognition and frailty and free heart failure education.

P. Costs to the Subjects

The cost to subjects is mainly that of time. If the patient does not have a documented estimate of LVEF within the previous year, he/she will undergo transthoracic echocardiogram at the time of the baseline study, which will be billed to the patient and his or her insurance.

Q. Minors as Research Subjects – N/A

R. Radiation or Radioactive Substances – N/A

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