IRB Submission - ICCR

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Study Purpose and Rationale:

Heart failure is a condition that at best estimate affects 5.7 million people in the United States. As the population continues to age there is trend of increasing incidence and prevalence in the population with heart failure becoming the fastest growing cardiac condition in the United States, 550,000 cases are diagnosed per year. In 2006 1.1 million patients were admitted to hospitals for management of acute decompensation of heart failure. This accounts for nearly 2% of all hospital admissions in the United States and in patient's over 65 heart failure is the most frequent reason for hospitalization (1-4).

Medication and therapy is aimed at improving symptoms, slowing disease progression and improving mortality. Over the past decade there have been many well designed trials that have examined pharmacologic intervention and it's effect on left ventricular function, re-hospitalization rates and mortality. With the overwhelming evidence in favor it is now recommended to initiate therapy with angiotensin converting enzyme inhibitors (ACE –I), if intolerant angiotensin II receptor blockers (ARBs), and Beta-blocker therapy (5-8). Although the utility of such therapy in the chronic management of heart failure is clearly defined the time to initiation of therapy upon acute presentation is not as well defined. The current guidelines recommend stabilizing a patient on an ace-I first and then starting b-blocker therapy although the data supporting that method to be equivocal (9). The beneficial nature of ace-inhibitor therapy is apparent but the role it plays in the early management of acute exacerbation of heart failure continues to be unknown. Although there is no benefit seen in patients who receive therapy immediately after a myocardial infarct there is a potential benefit in the patient presenting with an exacerbation of heart failure (13).

We propose to evaluate the safety and potential benefits of early initiation of ace inhibitor therapy as a means to improve in hospital outcomes and decrease time spent in hospital for patients admitted to manage acute decompensated heart failure.

Study Design/Statistical Analysis

This study will be a single blinded randomized control trial with a total population of 2800 patients presenting with an acute decompensation of heart failure that fit the inclusion and exclusion criteria described below. After identification of appropriate patients by primary admitting service consent will be obtained to enroll patients into the study. Randomization will then be generated by the

department of medical statistics to create two separate race, gender and age equivalent arms of 1400 patients each.

One arm will initiate ace-i therapy within the first 24 hours of admission and the other will have ace-i therapy initiated after 24 hours. In order to blind patients from will give those in the late therapy arm inert compound in lieu of ace-inhibitor. Prior literature from medicare data analysis indicates the mean length of stay for heart failure is 6.33 days with an in house mortality rate of 4.3%(13). The primary outcome for this study will be reduction in mortality and adverse event rates. Adverse events will be defined as episode of symptomatic or clinically significant hypotension (SBP <90), hyperkalemia, or incidence of acute kidney injury as defined by AKIN criteria. The secondary outcome will be assessing for change in average length of stay.

An even modest reduction in mortality or length of stay will amount to a large reduction in total cost to patients and health care system. In order to achieve 80% power with an alpha value of 0.05, assuming a clinically relevant effect of decreasing mortality by 2% and length of stay by a half day, a chi squared test calculated an n value of 1260. Assuming dropouts we will aim for a sample size of 1400 patient in each arm. Length of stay will be analyzed with an unpaired t-test if normally distributed otherwise will be analyzed by non parametric tests. Event rates will be analyzed by chi-square tests.

Study procedure:

Patients in both randomized groups will have daily monitoring of basic metabolic profiles, general nursing designated measurements of vital signs and weight. Patients will otherwise receive other standards of care monitoring and imaging including but not exclusive to ekg, and chest x-ray. Those patients with no known transthoracic echocardiography in the past 6 months will have imaging completed prior to discharge.

Study drugs:

Enalapril 2.5 mg twice daily

Medical Device:

Patients will be examined with standard chest x-rays, EKG machines, and transthoracic echocardiography upon discretion of primary medical team.

Study Questionnaire:

None

Study Subjects:

Inclusion Criteria:

-New York Heart Association Class I-III
- Primary admission diagnosis of Acute Exacerbation of Heart Failure
- Age 18 years or older

Exclusion Criteria:

- Age less than 18 years
- No ace-inhibitor or angiotensin receptor blocker therapy in past 6 months
- K >5.0
- SBP < 90
- Presence of CKD (GFR < 60mL/min per 1.73m^2)
- Absolute increase in serum creatinine of >.3g/dL or >50% increase in serum creatinine from baseline
- Prior medication allergy

Recruitment of Subjects:

Potential subjects will be identified by the emergency department and primary admitting teams. Subjects will be approached after emergency department physician or primary team has determined patient's willingness to participate in the study.

Confidentiality of Study Data:

All patient information will be uniquely coded. Coded data will only be available to study investigators.

Potential Conflicts of Interest:

None

Location of Study:

This study will be conducted on inpatient medical services at CPMC and multiple academic medical centers across the country.

Potential Risks:

Potential risks in the early initiation group include increased incidence of symptomatic hypotension, hyperkalemia with associated symptoms (weakness, fatigue, cardiac arrhythmia, and secondary sudden death), acute kidney injury and a potential increase in length of stay and mortality.

Potential Benefits:

Potential benefits include a decrease in mortality during hospitalization, decreased length of stay and improved long term outcomes. In addition there would be collateral benefit in decreasing costs accrued in the in-patient management of heart failure.

Compensation of Subjects:

No compensation to patients and routine hospital billing will apply.

Cost to Subjects:

No additional cost to subjects.

Minors as research subjects

Minors will not be included in the study.

Reference:

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