# Nesiritide in the Outpatient Setting: Reducing Risk of Hospitalization for Congestive Heart Failure

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### A. Study Purpose and Rationale

Heart failure occurs in 4.7 million persons living in the United States and acute decompensation is the discharge diagnosis for 3.5 million patients annually. Hospitalization accounts for 60% of the 10 billion dollars in annual health care expenditure for heart failure. Despite this, only one new intravenous drug, Nesiritide (Natrecor) has been approved by the FDA since 1987. The drug is a synthetic of a peptide produced by the ventricular myocardium. Naturally occurring BNP has known benefits in improving hemodynamics in patients with congestive heart failure, including arterial and venous vasodilation, enhanced sodium excretion, and suppression of the renin-angiotensin-aldosterone nervous system. Therefore, the development of the synthetic form was met with great optimism. Initial studies in patients hospitalized for advanced heart failure showed improvement in symptoms of shortness of breath and a decrease in fluid overload in the lungs. However, follow-up studies have suggested significant worsening of renal function and perhaps even an increase in mortality. Despite this, use of the drug is increasing and projected sales for nesiritide is $700 million for 2005.

Making up a large portion of these sales is an "off-label" use of the drug in the outpatient setting, wherein patients receive treatment in clinic once or twice per week over a period of several months, for what is described as an outpatient "tune-up". The cost of such infusions is considerable- $500 per dose in addition to a professional fee for observation ($172 for the first hour, then $40 each additional hour). We will attempt to answer the question of whether outpatient use of nesiritide prevents hospitalization for congestive heart failure, warranting its great monetary cost. Furthermore, we will attempt to answer the question of whether the drug is safe, measuring death and renal function in patients taking the drug vs. placebo.

### B. Study Design and Statistical Analysis

This study proposed is a randomized controlled trial of patients with Class III and IV heart failure (symptoms of short of breath at rest or with minimal activity) who had been discharged from the hospital for CHF exacerbation within the last month. The study group will be given regularly scheduled (every 2 weeks) administration of nesiritide as part of their outpatient visit. The control group will be administered a placebo infusion. Both groups will be seen by their outpatient cardiologist before and after the infusion, who will have freedom to adjust the remainder of their drug regimen as they see fit. The patient and the cardiologist will be blinded as to the study drug being administered. The patient's doctors will be able to discontinue infusion for hypotension (BP<85 systolic). The primary outcome we will measure is hospitalization for cardiovascular cause. Secondary outcomes will include death, increase in creatinine (>0.5mg/dL), improvement in shortness of breath and exercise tolerance. There will be 130 patients in both groups, a number that was obtained using an 80% power analysis aimed at detecting a 33% reduction in the 1-year risk of hospitalization in this high risk group (hospitalization rate 60% in the control and 40% in the treatment group). This number also takes into account a 20% expected mortality in this group. Because several important factors influence outcome in pts with CHF, we will use a "stratified randomization" approach using class of heart failure (III or IV), presence of absence of diabetes, and Cr<1 and Cr<2 but >1. This a priori randomization will help ensure that pts randomized to either treatment or placebo do not disproportionately possess a well known factor that will influence outcome. Patients will be randomized to group by an independent party.

The study and the control groups with respect to the primary outcome will be compared by a Chi-Square analysis. Death, proportion of patients with a significant increase in creatinine and assessment of symptoms will also be compared by a Chi-Square analysis. Death will also be compared using a Kaplan-Meier survival curve. Also for each of the end-points a Cox-proportional hazard model will be utilized. The data will be compiled and reviewed every 2 months by a safety review board. Stopping points will be a 50% increase or decrease in hospitalization, 25% increase or decrease in mortality, and 50% increase or decrease in renal dysfunction.

**C. Study Procedure**

The study participants will undergo the routine close follow-up care that is required of most patients with advanced heart failure. This will include 30 minutes of history, physical and drawing and review of laboratory tests. Routine basic metabolic profile, which includes creatinine, will be drawn in clinic prior to the outpatient visit and the results will be available at the end of the study infusion. The pt will then be seen by their cardiologist who will interview the pt and measures vital signs, including blood pressure and weight. The infusion will then be performed in the office and will require for each visit the placement of a 22G peripheral IV, preferable in the antecubital positional. The placement of the IV does incur pain and has a small risk of clot and infection. The study drug will be infused in identical bags with equal volumes to promote blinding. The drug will be prepared in the same concentration and rate used in prior studies, which is at a concentration of 10 micrograms/nil and administered as a 2 microgram/kg bolus followed by a fixed dose infusion of 0.01 micrograms/kg/min for 3 hours. Vital signs and weight will be recorded after the procedure and a required 1 hour observation period will be mandatory post infusion, wherein the pt's cardiologist will interview the patient. We plan for 6 months of drug infusion and follow-up for 1 year. This means 26 outpatients visits and 13 infusion events.

**D. Study Drugs**

The study drug is Nesiritide (Natrecor), a drug approved by the FDA in 2001 for use in patients hospitalized for acute exacerbation of heart failure. This study is aimed at determining whether a common off-label use of the drug- for outpatient "maintenance" or "tune-up" of patients with advanced heart failure, actually improves outcome and is safe. The method, route of administration and dosage regimen are based on standard practice in use of a drug that has been on the market for four years in 600,000 patients. In several clinical trials performed to date, nesiritide has been shown to reduce measures of fluid overload in the lungs ('wedge pressure") and self-reported shortness of breath. However, more recent analysis using follow-up data from these studies have suggested increase in mortality and renal dysfunction. A pooled analysis of prior studies conducted by Sacker-Bernstein et al. revealed a 30 day risk ratio of death of 1.74 (95% CI 0.97-3.12). Worsening of baseline renal dysfunction is common- the largest study conducted showed a 28% incidence of elevation in creatinine >0.5mg/dL above baseline. The final important risk of nesiritide is hypotension which has occurred at a rate of about 4%. It has been found that most cases of hypotension occur at doses higher than that which will be given in this study. Nonetheless, prior to infusion of the study drug, blood pressure will be checked and the infusion will be cancelled if BP systolic <90.

**E. Medical Device**

N/A

**F. Study Questionnaires**

For the secondary outcome "shortness of breath" we will use an unvalidated rating scale used in prior studies of nesiritide. During the clinic visit the patient will fill out a form stating whether over the last 2 weeks their symptoms are 1) improved 2) no change or 3) worse.

**G. Study Subjects**

The study subjects will be recruited from the heart failure clinics at Columbia Presbyterian Hospital. The patients must older than 21, with no age limit and have Class III/1V heart failure with discharge from the hospital for CHF exacerbation within the last month. Judgement of heart failure class will be made by the patient's cardiologist. Exclusion criteria for patients will include Cr >2, systolic BP <90, MI or unstable angina within the last 48 hours, clinically important valvular stenosis, hypertrophic or restrictive cardiomyopathy or primary pulmonary hypertension. The patients will reflect the patient population of the CHF clinic at Columbia; meaning that they will include a predominance of Hispanic and white men >60 years of age. Many of the patients will be Spanish speaking only and consent material will be offered in Spanish.

**H. Recruitment of Subjects**

Subjects will be recruited based on the recommendations of the attendings in the heart failure clinic at Columbia, with a patient base >5000. The investigators will approach patients only after recommendation by their primary cardiologist.

**I. Confidentiality of Study Data**

All study data will be coded, removing identifying information, and stored in a secure location, accessible only to the investigators.

**J. Potential Conflict of Interest**

The physicians involved in patient care will be excluded from participating in the study if they admit to having any proprietary interest in nesiritide or the company which developed the drug, Scios.

**H. Location of the Study**

The location of the study is Columbia University Medical Center, specifically the heart failure clinic located in Presbyterian Hospital. Patients will be seen and undergo drug infusion at this site. Prior to their scheduled office visit, the patients will undergo phlebotomy on the 1s` floor of the building.

**I. Potential Risks**

Both study groups will receive standard treatment for advanced heart failure, including oral diuretics, b-blockers, ACE inihibitors, spironolactone. For those patients who receive the study drug, risks will include hypotension, renal dysfunction and possibly death. Blood pressure and creatinine will be monitored closely. In terms of risk of not receiving the study medication, there has been no study showing clear benefit to patients given nesiritide, other than measures of shortness of breath and "wedge pressure"; therefore, withholding nesiritide is not considered deviation from standard of care.

**J. Potential Benefits**

There is considerable possibility that the patients who receive the study drug will incur no benefit. Potential benefits include decreased risk of hospitalization for congestive heart failure and improvement in symptoms.

**K. Alternative Therapies**

This study does not involve an experimental therapy

**L. Compensation**

There will be no compensation for participation in the study. However, a travel stipend of $10 will be available for those participants who request assistance.

**M. Costs to Subjects**

There will be no additional costs to patients for participating in the study

**N. Minors as Research Subjects**

N/A

**O. Radiation or Radioactive Substances**

N/A

**P.** References

Colucci, W. et al. Intravenous Nesiritide, a Natriuretic Peptide, in the Treatment of Decompensated Congestive Heart Failure. NEJM 2000, 343 (246-252).

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