Randomized Double-Blind Placebo-Controlled Trial of Lisinopril in Heart Failure with Preserved Ejection Fraction

Linda Rosenband

A. Study Purpose and Rationale

Congestive heart failure (CHF) is a highly prevalent disease, affecting approximately 4.8 million Americans and causing significant degrees of morbidity and mortality. Clinical outcomes for patients with CHF have markedly improved over the last 2 decades as large clinical trials have demonstrated the large mortality benefits of treatments including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta blockers, spironolactone, and implantable cardioverterdefibrillators (ICDs). However, these trials have largely been conducted in populations with evidence of decreased cardiac systolic function as measured by echocardiography. Clinically, it is found that 30-50% of patients with heart failure have a normal ejection fraction (EF) of > 50% [1]. Pathophysiologically, diastolic dysfunction occurs when there is impairment in either active distension of the myocardium during diastole (an energy-requiring process which can be impaired in ischemic heart disease) or passive ventricular relaxation during diastole (which is adversely affected by structural limitations to ventricular filling such as left ventricular hypertrophy (LVH)).

Treatment for heart failure due to diastolic dysfunction is at this point largely empiric as trial data is very limited. The ACC/AHA released guidelines for the management of heart failure with preserved systolic function in 2005 [2]. These guidelines were limited to three treatment modalties with class I indication: control of hypertension, ventricular rate control in atrial fibrillation and diuretic use to control pulmonary congestion and peripheral edema. Revascularization of coronary artery disease (CAD) thought to be contributory to CHF was thought to merit a class Ila recommendation. Other medical therapies, including use of beta blockers, ACE inhibitors, ARBs, calcium antagonists, and digitalis were classified as lib as there are no randomized trials demonstrating their efficacy in patients with CHF due to diastolic dysfunction.

ACE inhibitors have been shown to be highly effective in reducing the morbidity and mortality of CHF due to systolic dysfunction in several large randomized, prospective placebo-controlled trials [3-7]. A meta-analysis of five trials involving the use of ACE inhibitors in systolic dysfunction showed a reduction in mortality (from 27% to 23%; OR 0.8, 95% CI 0.74-0.87) and a reduction in rehospitalization for CHF exacerbation (from 19% to 14%; OR 0.67, 95% CI 0.61-0.74) [8]. Based on these data, ACE inhibtors are standard-of-care for patients with systolic dysfunction. The mechanisms by which ACE inhibitors decrease morbidity and mortality of systolic dysfunction are incompletely understood, but are thought to be related to several factors: (1) ACE inhibitors are vasodilatory and consequent reduction in cardiac afterload is thought to be beneficial. (2) CHF is associated with over-activation of the reninangiotensin system which in turn is thought to lead to deleterious myocardial hypertrophy and remodeling; by reducing the activity of angiotensin-converting enzyme and the production of angiotensin II, ACE inhibitors prevent this [9]. (3) CHF is associated with a hyper-adrenergic state. ACE inhibitors in CHF reduce norepinephrine levels and normalize cardiac response to exercise [10]. (4) ACE inhibitors increase concentrations of bradykinin by inhibiting ACE which is a kininase. This leads to improved endothelial function via improved endothelial nitric oxide synthesis and responsiveness [11], thus possibly contributing to improved cardiovascular outcomes. Other possible mechanisms of ACE inhibitors are thought to involve effects on cytokine levels, modification of hypercoagulable states, and alteration of plasma fibrinolytic activity. These mechanisms might also be contributory to improved outcomes with ACE inhibitor use after acute coronary syndromes.

It is uncertain whether ACE inhibitor use in heart failure due to diastolic dysfunction has the same benefits as in systolic dysfunction. Presumably, benefits of blood pressure control, endothelial function,

cardiac remodeling, and control of hyperadrenergic state would still be present. However, ACE inhibitors cause peripheral vasodilation. There is some concern that this might lead to hypotension due to impaired diastolic filling. Nevertheless, retrospective studies indicate that there might be improved outcomes of diastolic dysfunction with ACE inhibitor use. A retrospective analysis of 1291 patients hospitalized with CHF exacerbations found that among those with EF > 50% the 29% of patients who were treated with ACE inhibitors had better outcomes in heart failure class (2.1 +/- 0.8 vs 2.4 +/- 0.7; $p < 0.05$) though mortality rates were equivalent [12]. Another observational study of elderly Medicare beneficiaries hospitalized with heart failure exacerbations found a statistically insignificant mortality benefit associated with ACE inhibitor use [13]. However, this study included only 238 patients with preserved EF and does not report impact of ACE inhibitor use on rehospitalization. The CHARM-Preserved trial was a large, randomized, placebo-controlled study of candesartan, an ARB in over 3000 hospitalized patients with CHF and preserved systolic function. It showed a trend toward decreased hospitalization and mortality in the treatment arm of the study (22% vs 24% combined outcome), but failed to show statistical significance [14]. Although, they generally work along the same pathophysiologic pathway as ACE inhibitors, ARBs do not increase bradykinin as ACE inhibitors due and it is not clear whether they have the same beneficial effects on endothelial function. A large randomized, placebo-controlled study of ACE inhibitors in patients with CHF and preserved systolic function is required to truly determine their efficacy in this patient population.

B. Study Design and Statistical Analysis

This study is a multi-center, randomized, double-blind, placebo-controlled trial of the ACE inhibitor lisinopril in adult subjects hospitalized with heart failure exacerbations and found to have preserved ejection fraction. There will be two study groups, one receiving lisinopril and one receiving matching placebo. The primary outcome will be the percentage of patients in either group reaching a composite endpoint of rehospitalization for cardiac causes and all-cause mortality over 24 months. Secondary outcomes will include all-cause mortality, cardiovascular mortality, total number of hospitalizations in each group, and incidence of diabetes mellitus. The study will also include prespecified subgroup analyses to detect interactions between the effectiveness of lisinopril and age group (<70 vs >= 70), gender, ethnic background (white, black, other), NYHA heart failure class (II, III, IV), ejection fraction (50-60%, >60%), presence of diabetes mellitus.

Based on existing data [12,14], a primary event rate of 20-30% can be expected over 2 years. The effect of lisinopril on outcome is more difficult to predict, but a meta-analysis of ACE inhibitor use in patients with systolic dysfunction [8], showed a relative risk reduction of 28% for a similar composite endpoint. This study will be powered to detect a difference of 20% in rates of the primary outcome as this would provide a good indication of clinical significance.

As the primary outcome is a categorical variable, power was calculated for a chi-square test. With an expected event-rate in the placebo group of 20% and an expected relative risk reduction of 20% in the intervention group, the study will need to include 1987 patients in each group (i.e., 3974 patients total) to have power of 0.9 to detect a difference with a two-sided alpha level of 0.05. Subgroup analyses will take place via Cox proportional hazards methods. A Bonferroni correction for multiple comparisons will be used for the subgroup analysis.

A large, academic medical center could be expected to recruit approximately 200 patients per year to this study, so there will be 20 involved sites. Randomization will take place by random-number generation at a central coordinated study site and will be stratified by study center. Randomization will take place at time of enrollment after subject has provided informed consent. Subjects, treating physicians, and study investigators will be blinded to treatment assignment.

An independent data safety monitoring board will evaluate study data after accrual of 4000 person-years of study data. The study will be discontinued if a treatment benefit can be proven with $p<0.01$ or treatment harm with $p<0.05$. The data safety monitoring board will also review adverse events every 6 months and independently determine whether the study should be continued.

C. Study Procedure

Patients will be randomized prior to hospital discharge. A study investigator will meet with subjects at the time of enrollment to verify that patient meets study entry criteria, obtain written informed consent, draw baseline laboratory studies and schedule follow-up visits and phlebotomy. Information on past medical history and concurrent medications will be obtained at time of study enrollment. Baseline phlebotomy will include basic metabolic panel (including serum creatinine and potassium), fasting glucose level, liver function panel, and serum pregnancy test in female patients up to age 55. The blinded study investigator will also determine patients' NYHA functional class at time of enrollment. Patients' blood pressure will also be recorded.

At time of randomization, patients will be randomized to receive lisinopril or matching placebo. Doses will be titrated as follows: lisinopril 5 mg orally once a day for two weeks; if this is tolerated, dose is increased to 10 mg for two weeks, then 20 mg for two weeks, then 30 mg for two weeks then 40 mg for two weeks. Subjects will meet with a blinded study investigator at scheduled follow-up visits at 2 weeks, 4 weeks, 6 weeks, and 8 weeks, 6 months and every 6 months thereafter. At each visit, blinded study investigators will determine whether patients have been hospitalized for cardiac causes, whether patients have developed side effects from study medications, and evaluate compliance with study medication via pill count. Basic metabolic panel will be rechecked at each study visit. If serum creatinine is > 3 or potassium > 5.5, study medication will be discontinued. If systolic blood pressure is < 100 and the patient is in the early dose-titration phase of the study, study medication will not be increased. At scheduled study visits, it will be noted whether patients have discontinued study drug due to side effects or begun open-label treatment with ACE inhibitors. If patients remain eligible for study medication, a 200-day supply of medication will be issued. At the final follow-up visit, fasting glucose measurement will be repeated.

D. Study Drugs

Lisinopril (Zestril, AstraZeneca) is an oral long-acting angiotensin converting enzyme inhibitor. It is a synthetic peptide derivative, chemically described *as* a (5)-11N2-(1- carboxy-3-phenylpropy1)-L-lysylj-L-proline dihydrate. It is supplied as 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg and 40 mg tablets for oral administration.

Following oral administration, peak serum concentrations of lisinopril occur within 7 hours. Serum half-life is 12 hours. Oral bioavailability is approximately 16% and somewhat variable. It is not influenced by food in the gastrointestinal tract. Lisinopril is not metabolized and is excreted unchanged in the urine. Decreased urinary excretion of lisinopril becomes clinically significant at glomerular filtration rates below 30 mL/min.

Lisinopril is currently FDA-approved for the treatment of hypertension, heart failure due to systolic dysfunction, and for the treatment of hemodynamically stable patients 24 hours after myocardial infarction. This study would investigate the use of lisinopril in a population of patients with heart failure with diastolic dysfunction, a group for whom (as described above), there is some retrospective data that the medication might be beneficial.

Lisinopril is generally well-tolerated in controlled clinical trials involving 1969 patients with heart failure or hypertension and extensive clinical practice. In clinical trials, approximately 5% of patients discontinue ACE inhibitors due to side effects, mostly cough, renal insufficiency, or hypotension. Lisinopril is contraindicated in patients with a hypersensitivity to ACE inhibitors, in patients with previous angioedema related to ACE inhibitor use and in patients with hereditary or idiopathic angioedema. It has a black-box warning against use in pregnancy as it can cause injury and death to the developing fetus when used in the second and third trimester of pregnancy. Potential adverse events with lisinopril include head and neck angioedema which may occur at any time during treatment and may be life-threatening, hyperkalemia (4.8% with systolic dysfunction, 2.2% with hypertension),

cough (3.5%), hypotension (4.4%), dizziness (5.4%), headache (5.7%), liver function abnormalities (very rare), leukopenia/neutropenia (very rare), fetal malformations. Many other side effects (including fatigue, asthenia, diarrhea, nausea, vomiting, dyspepsia, muscle cramps, paresthesia, decreased libido, skin rash, upper respiratory infection, common cold, nasal congestion, influenza, impotence) are reported to occur, but occur at about the same rates in placebo groups.

D. Medical Device

Not applicable.

E. Study Questionnaires

Not applicable.

F. Study Subjects

Study subjects will include adults hospitalized for a heart failure exacerbation and found to have a normal EF (> 50%) on transthoracic echocardiography. Diagnosis of heart failure will be made clinically via modified Framingham criteria [15]. These criteria include 8 major criteria for heart failure (paroxysmal nocturnal dyspnea, orthopnea, elevated jugular venous pressure, pulmonary rates, third heart sound, cardiomegaly on chest X-ray, pulmonary edema on chest X-ray, weight loss of 4.5 kg or more in five days in response to treatment of presumed heart failure). Minor criteria include bilateral leg edema, nocturnal cough, dyspnea on ordinary exertion, hepatomegaly, pleural effusion, tachycardia (heart rate > 120 beats per minute), and weight loss of 4.5 kg or more in five days. Patients are classified as having heart failure if they have 2 major criteria or 1 major and 2 minor criteria concurrently. Minor criteria may be used only if they are not thought secondary to another medical condition. The blinded investigator will verify the diagnosis of heart failure via these criteria at time of enrollment.

Exclusion criteria will include unwillingness to participate in the study, EF < 50%, preexisting ACE inhibitor use, past intolerance of ACE inhibitor, class I indication for ACE inhibitor (acute myocardial infarction, stable CAD and diabetes, diabetes with microalbuminuria), contraindication to ACE inhibitor use (history of hereditary or idiopathic angioedema), women of childbearing potential who are not using reliable contraception, breastfeeding women, presence of concomitant medical condition considered to limit 5-year survival, participation in a research trial of a non-FDAapproved medication, creatinine > 2, potassium > 5, uncontrolled hypertension (SBP > 160 or DBP > 100), primary valvular heart disease, liver dysfunction as manifested by ALT or AST > 2.5 x upper limit of normal.

G. Recruitment of Subjects

Subjects will be recruited at 20 acute-care hospitals. Subjects will be identified via their heart failure physicians and referred to the study. The heart failure physician will discuss the study with potential recruits and patients will only be recruited if their treating physicians agree to their participation. Subsequent to subject identification, a study investigator will meet with subjects to discuss the study and to obtain informed consent and enroll patients if they meet entry criteria and are willing to participate.

H. Confidentiality of Study Data

All study data will be confidential. Study data will be encoded using a unique 6-digit code not related to subjects' hospital unit number, social security number, name, address, phone number, or date of birth. Data will be stored in a locked secure location. The data safety monitoring board will have

access to the data, but will not inform investigators of findings unless criteria for stopping the study have been met.

I. Potential Conflict of Interest

None

J. Location of the Study

Columbia University Medical Center + 19 other acute care facilities.

K. Potential Risks

Patients have a risk of experiencing side effects related to lisinopril use. These side effects have been well characterized in large clinical trials and in clinical experience with thousands of patients taking the medication. As the effect of ACE inhibitors on heart failure with diastolic dysfunction is unknown, there could be potential harmful effects, though retrospective data do not seem to indicate this.

L. Potential Benefits

Subjects may or may not benefit from their treatment assignment in this study. They will benefit from close monitoring for electrolyte abnormalities and blood pressure monitoring during the study. There might be a beneficial effect of lisinopril use. However, this is unknown.

Heart failure due to diastolic impairment is a very prevalent disease with high morbidity and mortality. Society would benefit from having better data about its treatment options.

M. Alternative Therapies

Several medications, including open-label ACE inhibitors, beta blockers, ARBs, digoxin, diuretics, and spironolactone are available for use in patients with heart failure and preserved systolic function. None of these medications have been studied adequately for this indication. It will be left to the discretion of the treating physician which or any of these medications to use, although open-label ACE inhibitor use would preclude entry into the study. It will be recommended that all patients' blood pressure be controlled adequately.

N. Compensation to Subjects

Patients will receive study medication free of charge. They will receive several blood tests, blood pressure checks and study visits free of charge. Patients will receive assistance for transportation to and from study sites. No other monetary or other compensation will be provided.

O. Costs to Subjects

Subjects will not incur additional costs for participating in the study. A number will be provided for subjects to call in case of adverse events.

P. Minors as Research Subjects

Not applicable.

Q. Radiation or Radioactive Substances

Not applicable.

R. References

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