

A Randomized, Double-Blind, Placebo-Controlled Trial of Spironolactone versus Eplerenone in Patients with Mild to Moderate Heart Failure

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Abstract

This paper is a first draft for a definitive study of the relative merits of spironolactone versus eplerenone versus placebo in patients with mild to moderate heart failure. Previous studies have demonstrated mortality benefits in patients with severe heart failure or patients with a recent myocardial infarction, respectively. However, the role of these therapies in the treatment of chronic mild or moderate heart failure remains undefined.

The trial is scheduled to last five years, and will enroll 4869 patients with Stage B or C heart failure who are otherwise receiving adequate therapy. Each patient is expected to be followed for three years. An independent Event Committee will be utilized to assess events related to the primary endpoint. A group of statisticians, ethicists, and clinicians will comprise a Data and Safety Monitoring Board.

The primary outcome variable is combined all-cause mortality and cardiac hospitalization. The secondary outcome measure is quality of life, since patients with less severe heart failure may need to take these drugs over a period of years. Quality of life information will also allow a cost-effectiveness analysis between the two therapies. This data is critical because eplerenone is 7-8 times the price per tablet of spironolactone. It is hoped that the results of this trial will support a treatment recommendation for patients in earlier stages of heart failure.

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1 Introduction

1.1 Background

Heart failure is a major cause of morbidity and mortality in the United States, accounting for 12 to 15 million office visits each year.¹ Approximately 5 million patients have symptomatic heart failure in the United States, and about 550,000 new cases are diagnosed per year. More patients die of heart failure on a yearly basis than from all forms of cancer combined. The financial impact of heart failure is no less staggering: the estimated annual cost is \$25.8 billion.²

Heart failure is primarily a disease of the elderly. The prevalence of heart failure is about 1% between the ages of 50-59, but progressively increases to ~10% of the US population over age 80.² It is the final common pathway to a number of insults to the heart, such as coronary artery disease, hypertension, and valvular disease. Coronary artery disease is the single risk factor most highly correlated with heart failure, and could account for more than 60% of cases.³ Because of the increasing mean age of the United States population and our ability to effectively intervene in acute conditions such as myocardial infarctions, the number of cases of heart failure is increasing steadily despite advances in treatment.

Heart failure initially develops in an asymptomatic form, most commonly from left ventricular dysfunction. Patients commonly present to physicians with a syndrome of exercise intolerance, fluid overload, or with symptoms of another cardiac or non-cardiac disorder.⁴ Because of the compensatory mechanisms, symptoms are quite variable and fluctuate over time. Some patients remain asymptomatic until relatively late in the disease. As the compensatory capacity of the heart is exceeded, the disease is inexorably progressive. The most common cause of death is refractory heart failure, but many patients also die suddenly from ventricular arrhythmias.

Hospitalization of patients with heart failure due to cardiac decompensation is extremely common. Approximately 6.5 million hospital days per year are needed by patients with heart failure.¹ The estimated costs of hospitalization account for 53% of the cost of caring for heart failure patients.² As a result, hospitalization is an important economic and prognostic variable in studies of heart failure.

Therapies for heart failure not amenable to surgery generally include both dietary and pharmacologic components. Sodium restriction and sometimes potassium supplementation are often necessary dietary changes. With respect to pharmacological agents, the most direct means of reducing sodium and water from the circulation is by using diuretics. Low doses of beta-blockers early in the course of heart failure is also known to reduce mortality and prevent cardiac remodeling associated with heart failure.⁵

The renin-angiotensin-aldosterone system (RAAS) plays an integral role in cardiovascular homeostasis through its effects on vascular tone and volume, which are mediated by aldosterone and angiotensin II. RAAS activation is associated with an increased risk of ischemic cardiovascular events,⁶ whereas interruption of the RAAS by angiotensin-converting enzyme (ACE) inhibition or angiotensin type 1 receptor blockade reduces cardiovascular mortality.^{7,8} Angiotensin II also stimulates the synthesis of the mineralocorticoid aldosterone from the zona glomerulosa of the adrenal gland.

Studies suggest that aldosterone contributes to cardiac damage in humans, independent of the effects of Angiotensin II. Clinical studies indicate a strong correlation between aldosterone concentrations and cardiovascular morbidity and mortality.⁹ Patients with primary hyperaldosteronism exhibit endothelial dysfunction, a predictor of future cardiovascular events.¹⁰ Increased plasma aldosterone concentrations are associated with decreased arterial compliance in hypertensive individuals.¹¹ Conversely, aldosterone receptor antagonism improves vasodilation in patients with congestive heart failure.¹² Yet even with chronic treatment with maximal ACE inhibition, aldosterone concentrations return toward baseline or “escape,”¹³ potentially attenuating the cardioprotective effects of these drugs.

The Randomized Aldactone Evaluation Study (RALES) evaluated the addition of spironolactone, an aldosterone receptor blocker, in patients with New York Heart Association (NYHA) class 3 or 4 heart failure who were already treated with an ACE inhibitor, diuretics, and digoxin. The primary endpoint was all-cause mortality. The study was discontinued early because interim analysis demonstrated that spironolactone significantly reduced all-cause mortality ($p < 0.001$). Similarly, the spironolactone group showed a significant decrease in morbidity as measured by hospitalization ($p < 0.001$).¹⁴ However, spironolactone, because of its interaction with other steroid receptors, is not without its limitations, which include gynecomastia, breast tenderness, menstrual irregularities, and impotence.

More recently, the Eplerenone Neurohormonal Efficacy and Survival Trial (EPHESUS) tested the effect of the addition of eplerenone to standard therapy with ACE inhibitors, beta-blockers, digoxin, and diuretics. The primary end points were all-cause mortality and the time to first occurrence of either cardiovascular mortality or hospitalization in 6200 patients with left ventricular dysfunction after a recent myocardial infarction. The results indicate that addition of eplerenone significantly reduced all cause ($P = 0.008$) and cardiovascular ($P = 0.0002$) mortality.¹⁵ Additionally, eplerenone is generally better tolerated than spironolactone. However, the retail cost of eplerenone is approximately \$3.33 higher per 25 mg pill than that of generic spironolactone.

The role of spironolactone and eplerenone in the treatment of mild or moderate heart failure remains undefined. Therefore, we propose a study designed to test spironolactone versus eplerenone versus placebo in patients with mild to moderate heart failure who are already receiving adequate treatment for heart failure. Because of the unreliability of surrogate measures such as exercise tolerance, ventricular remodeling, and stage of heart failure at predicting mortality or hospitalization, our primary endpoint will be combined all-cause mortality and cardiac hospitalization.

1.2 Motivation for this Study

Morbidity and mortality benefits of spironolactone therapy in patients with severe heart failure have been demonstrated in a randomized controlled trial. Similarly, eplerenone has been shown to reduce morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure. However, the benefits of these medications in patients with mild or moderate heart failure are unclear. Additionally, spironolactone has substantial side effects, most notably hyperkalemia and in men, gynecomastia. While eplerenone is generally better tolerated, it is substantially

more expensive than spironolactone. Therefore, demonstration of benefits in improved survival or fewer hospitalizations is necessary before routine use of either drug can be recommended in patients with mild or moderate heart failure.

2 Objectives

The objective of this study is to assess the effectiveness of spironolactone or eplerenone versus placebo in preventing mortality and hospitalization in patients with mild or moderate heart failure as a result of systolic left ventricular dysfunction. It is hoped that the results of this trial will serve as a starting point for therapeutic recommendations in patients with heart failure.

2.1 Primary Question and Response Variables

The primary endpoint in this study is combined all-cause mortality or cardiac hospitalization as assessed by an independent Event Committee, whose members are unaware of treatment assignment. Each event will be classified by two members of the committee, according to prespecified definitions. Agreement between the two will be considered final classification. If the initial two members do not agree, a third committee member will also review the event.

2.2 Secondary Question

Because the benefits of these drugs in treating mild to moderate heart failure are unclear, a secondary question will also be addressed.

- Quality of Life

The correlation between self-reported quality of life and cardiac dysfunction is generally poor in patients with heart failure, which necessitates measurement of more than clinical outcomes when assessing efficacy of new therapies. Because patients with mild to moderate heart failure may require aldosterone blockade for a prolonged period, it is important to understand how these drugs impact the quality of life. Additionally, quality of life measurements will allow a cost-effectiveness comparison of spironolactone and eplerenone at the end of the study. Quality of life will be assessed using the Minnesota Living with Heart Failure questionnaire.

2.3 Cost Determination

The goal of economic evaluation in clinical trials is to assess the economic impact of a new therapy. Performing such an evaluation requires that the following data be collected as part of a clinical trial: (1) total costs incurred after randomization for study patients; (2) clinical outcomes resulting for patients subsequent to randomization; (3) quality of life for patients who are randomized; (4) some evaluation of the utility of various health states described in the quality of life assessment.

To collect total cost data in this study, a technique similar to that used by Schulman, et al. in the FIRST Study will be adopted.¹⁶ A set of resource elements have been developed and physicians will be asked to check off the resource elements used during office visits or hospital stays. Hospital or Medicare cost data will then be employed in converting resource use into costs in dollars. Information regarding clinical outcomes will be obtained directly from case report forms collected throughout the study.

Quality of life will be assessed using the Minnesota Living with Heart Failure Questionnaire, which has been demonstrated to have good reliability and responsiveness to changes in condition.¹⁷ This questionnaire will be self-administered at baseline, and then every three months until completion of the trial to assess the patient's perceptions of the effects of congestive heart failure and its treatment on his or her life. Finally, random samples of 100 patients from each arm of the study will be selected to participate in a utilities exercise, based on the questions from the quality of life questionnaire. They will be asked to rank the health states described on the questionnaire in an interviewer conducted survey. The utilities obtained from this exercise will then be averaged, and the values will be used to develop a QALYs gained through treatment estimate in the manner of Lave, et al. in their study on the cost-effectiveness of treatment for depression.¹⁸

2.4 Subgroups

The following baseline characteristics will be assessed by treatment group to assure comparability of patients in each arm of the trial. These variables were chosen because they are known to be prognostic factors for patients with heart failure, and/or are indicators of the severity of the disease.

- Mean age (yrs)
- Race (White, Black, Other)
- Sex
- Stage of heart failure
- Mean Blood Pressure (Systolic, Diastolic)
- Mean Left Ventricular Ejection Fraction
- Cause of Heart Failure (Ischemic/Nonischemic)
- Medications (ACE Inhibitor, Beta-blockers, Diuretics, Aspirin, Digitalis, Potassium Supplements)

Accordingly, the relative risk of all-cause mortality and cardiac hospitalization will be assessed according to the following demographic and clinical characteristics.

- Median age
- LV ejection fraction
- Cause of heart failure
- Median creatinine
- Use of digitalis
- Use of ACE Inhibitor
- Sex

- Potassium
- Stage of heart failure

3 Sample Size Calculation

Our sample size calculation is based on several assumptions. The rate of mortality or cardiac-related hospitalization (our combined primary outcome) is estimated to be 32 percent in the placebo group based on data provided in the EPHEBUS trial.¹⁵ The risk of a primary event occurring is expected to be 20 percent lower in the spironolactone- or eplerenone-treated group, also based on EPHEBUS data.¹⁵ The power to detect a study difference has been set at 90 percent. Because two comparisons will be made in this study (spironolactone vs. placebo and eplerenone vs. placebo), a two-tailed .025 α level will be used, evenly splitting two-tailed .05 α between the comparisons. The data allows for the following calculation to be made:

$$2N = \frac{4(Z_{\alpha} + Z_{\beta})^2 * p(1-p)}{(p_c - p_t)^2}$$

$$2N = \frac{4(2.24 + 1.28)^2 * 0.256(1 - 0.256)}{(0.32 - 0.256)^2}$$

$$N = 1152/\text{arm}$$

Drop out rate is estimated to be 10 percent during the first year of treatment and 5 percent for the following two years, comparable to the drop out rate for the MERIT heart failure trial, which enrolled a group of patients that is expected to be clinically similar to the patient population we wish to enroll and utilized a drug with an incidence of side effects similar to that of spironolactone.⁵ A drop in rate of 3 percent per year is also assumed, based on the recent publication of the EPHEBUS trial results¹⁵ and the potential for this new data to influence physician prescribing patterns. Adjustments to the sample size are then made as follows:

$$\text{Adjustment factor} = 1/(1 - R_o - R_i)^2$$

R_o = overall drop out rate

R_i = overall drop in rate

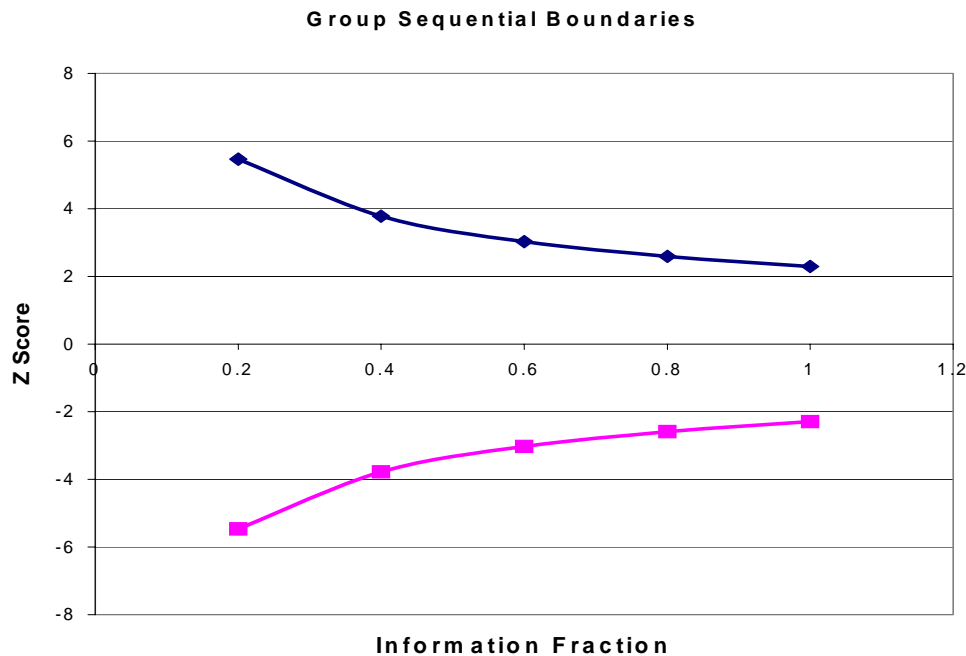
$$\text{Adjustment factor} = 1/(1 - .20 - .09)^2 = 1.41$$

$$\text{Adjusted } N = 1.41(1152) = 1623/\text{arm}$$

The adjustment in sample size due to drop-in and drop-out is large enough to also adjust for data monitoring. Utilizing Lan-DeMets¹⁹ group sequential boundaries calculations and an O'Brien-Fleming²⁰ spending function with interim analyses specified at five

(related to the five-year length of the trial and expected annual monitoring), the following boundaries calculations are obtained:

Time	Lower	Upper	Nominal Upr Alpha	Cum Alpha
0.20	-5.4633	5.4633	0.00000	0.00000
0.40	-3.7803	3.7803	0.00008	0.00016
0.60	-3.0270	3.0270	0.00123	0.00252
0.80	-2.5879	2.5879	0.00483	0.01046
1.00	-2.2959	2.2959	0.01084	0.02500



Final Z_{α} in this case is equal to 2.29, which would lead to calculation of an adjusted N of 1185/arm. The drop-out/drop-in adjustment is substantially larger, so that this calculation is unnecessary for determining final sample size.

4 Selection Criteria

4.1 Treatment Center Inclusion

Treatment centers with a substantial number of eligible heart failure patients in North America, Europe, Japan, and Latin America will be invited to participate. Participating centers must have the human and technological resources to recruit and follow patients, as well as maintain constant postal and electronic contact with the central data collection

center. Individual physician-investigators must agree to adhere to the protocol and to submit data and adverse event reports in a timely manner.

4.2 Patient Inclusion and Exclusion

Patients are eligible for this study if they have Stage B or Stage C (mild or moderate) heart failure, diagnosed at least six weeks prior to study enrollment. Patients must be able to attend one of the participating centers for regular follow-up.

4.2.1 Staging of Heart Failure

Accurate staging of heart failure is crucial prior to randomization. The staging system used in this study was developed by the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. (8) This system is summarized in the table below.

	Stage	Patient Description
A	High risk for developing HF	<ul style="list-style-type: none"> • Hypertension • Coronary Artery Disease • Diabetes Mellitus • Family history of cardiomyopathy
B	Asymptomatic HF	<ul style="list-style-type: none"> • Previous myocardial infarction • Left ventricular systolic dysfunction • Asymptomatic valvular disease
C	Symptomatic HF	<ul style="list-style-type: none"> • Known structural heart disease • Dyspnea and fatigue • Reduced Exercise tolerance
D	Refractory End-Stage HF	<ul style="list-style-type: none"> • Marked symptoms at rest despite maximal medical therapy

Table 1: Adapted from ACC/AHA Practice Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult

Only patients with Stage B or C heart failure are eligible for this study. This allows exclusion of patients with severe heart failure who are already known to benefit from aldosterone blockade, and exclusion of patients in whom heart failure may not develop (Stage A).

If candidates for this study have not had a two-dimensional echocardiogram coupled with Doppler flow studies in the past six months, one must be completed prior to randomization. Patients are eligible if they meet the following criteria:

- At least 18 years of age at randomization
- Diagnosed with Stage B or C heart failure at least six weeks before enrollment
- Receiving medication and counseling for stage of heart failure according to best practice guidelines⁴ for at least two weeks prior to randomization
- Left ventricular ejection fraction of no more than 40%, as measured no more than six months prior to enrollment
- No clinically significant intercurrent event after measurement of ejection fraction

- No contraindications for spironolactone or eplerenone therapy
- Compliance 90% or greater during the two-week single-blind washout period
- Meet none of the exclusionary criteria

Exclusion Criteria

- Primary operable valvular heart disease, other than mitral or tricuspid regurgitation due to left ventricular systolic heart failure
- Congenital heart disease
- Type 2 diabetes with microalbuminuria.
- Serum creatinine >2.0 mg/dl in males or >1.8 mg/dl in females.
- Two serial serum potassium concentrations of more than 5.0 mmol/L measured in the three months prior to enrollment
- Creatinine clearance <50 ml/min.
- Patients requiring potassium supplements or potassium-sparing diuretics
- Patients requiring strong inhibitors of CYP450 3A4 (*e.g.*, ketoconazole, itraconazole)
- Previous unstable angina within the last year
- Current or past primary hepatic or renal failure
- Active cancer of any kind
- Patients with any current life-threatening illness other than heart failure
- Patients who have undergone or are awaiting solid organ transplantation

5 Pre-Randomization Evaluation

Prior to randomization, it is important to determine baseline information about the health of each subject. Therefore, baseline variables such as age, race, current medications, and pertinent medical history will be obtained. In particular, risk factors for heart failure such as coronary artery disease, diabetes mellitus, and hypertension will be ascertained.

Patients will have a general physical examination, with measurements such as height, weight, and vital signs obtained. Blood samples will also be sent to a central laboratory to assess renal and hepatic function as well as serum electrolyte concentrations. Creatinine clearance will be measured. If the patient has not had two-dimensional echocardiogram coupled with Doppler flow studies in the past six months, one must be completed to assess left ventricular ejection fraction.

Once all information is obtained, it must be entered into the study database for review by personnel at the data management center. After the patient is determined to be eligible, a randomization number will be forwarded to the individual clinic site.

6 Randomization

If a subject is eligible and wishes to participate in the trial after the baseline evaluation, they will first participate in a single-blind, 2-week placebo run-in period. If compliance during the two-week period is 90 percent or greater, they will then be assigned into either the placebo, spironolactone or eplerenone arm of the trial. Randomization will be stratified by treatment center, so that approximately equal numbers of participants will be in each arm at each treatment center. A permuted block design with n=8 will be used, such that after every 8th assignment the numbers of participants in each group will be equal. Enrollment is expected to occur over a two-year time period.

7 Intervention and Follow Up

7.1 Intervention Summary and Schedule

Patients will be randomized to 25 mg of spironolactone, 25 mg of eplerenone or placebo once daily. Follow-up procedures are identical for each group to maintain blinding. This dose will be maintained for 8 weeks, after which the dose may be titrated up to 50 mg at the discretion of the physician investigator if the patient shows signs of worsening heart failure without evidence of hyperkalemia. If hyperkalemia develops at any time, the dose can be reduced to 25 mg every other day, but investigators are encouraged to adjust other medications first.

Follow-up evaluations and laboratory measurements will be done every four weeks for the first twelve months, every three months for the first year, and then every six months until a follow-up period of three years has been completed. Quality of life will be assessed at the beginning of the study and every three months thereafter. When patients are not coming to clinic sites for blood test, questionnaires may be mailed to participants. Study medication can be withheld in the event of serious hyperkalemia, a serum creatinine concentration over 4.0 mg/dl, or when medically necessary to protect the best interests of the patient. However, all patients will remain in the study for the purposes of tracking hospitalizations and deaths.

All blood samples will be sent to a central laboratory for analysis. Results will be forwarded to both the treating investigator and the data management center. The results of all other evaluations and treatments should be entered into the study computer system for daily forwarding.

For reference, the study procedures are presented in tabular form below:

Visit	Time
<ul style="list-style-type: none"> • Randomization to 25 mg of spironolactone or eplerenone • Quality of life Questionnaire 	Week 0
<ul style="list-style-type: none"> • Vital Signs, Blood tests 	Week 4
<ul style="list-style-type: none"> • Vital Signs, Blood tests 	Week 8
<ul style="list-style-type: none"> • Eligible to increase dose of 	Week 8 or later

medication with signs and symptoms of worsening heart failure	
<ul style="list-style-type: none"> • Vital Signs, Blood tests • Quality of life questionnaire 	Week 12
<ul style="list-style-type: none"> • Vital Signs, Blood tests • Quality of life questionnaire 	Month 6
<ul style="list-style-type: none"> • Vital Signs, Blood tests • Quality of life questionnaire 	Month 9
<ul style="list-style-type: none"> • Vital Signs, Blood tests 	Month 12 and every six months thereafter unless closer monitoring is medically necessary
<ul style="list-style-type: none"> • Quality of life questionnaire 	Month 12 and every three months thereafter (By mail when participant does not come for clinic visits.)

7.2 Subject Withdrawal Policy

Withdrawals are considered subjects that have been randomized but are deliberately omitted from the analysis. This study will be analyzed on the intention-to-treat principle, so that all subjects who are randomized will be included in the analysis. To minimize the amount of missing data, subjects will only be randomized after they have undergone appropriate diagnostic tests, eligibility has been confirmed by the statistical analysis center and placebo run-in period has been completed. If a subject is randomized but later decides to discontinue study participation, they are asked in the consent form to allow follow-up via medical record review. For further information on subjects who discontinue participation, see Section 9.2. Every effort will be made to follow all patient outcomes via medical records and/or survival data.

8 Data Monitoring

An independent data and safety monitoring committee of statisticians, cardiologists, and ethicists will oversee this study.

8.1 Schedule and Duties

The DSMB will meet to review the study prior to initiation, and then annually after the study commences. The Lan-DeMets group sequential boundaries and O'Brien-Fleming spending function described in the sample size calculations will be used in monitoring this trial. In each case, the committee will decide if recruitment is proceeding as planned, and whether it is ethically and scientifically justified to continue the trial based on analysis of the interim results.

8.2 Criteria for Early Termination

In addition to statistical criteria, the following factors should also be evaluated:

1. Due to the size and duration of this trial, missing data is almost inevitable. The committee should estimate a range of possible results based on extreme but reasonable values for the missing data.
2. Similarly, the committee should examine the range of possibilities of outcomes for patients who are not yet enrolled in the study. For example, if the study continued and all deaths occurred in one group, the committee should assess whether the current answer to the study question would change.
3. Possible differences in baseline factors between the three arms of the study should be evaluated, particularly as they pertain to the health of the participants. If the groups are unbalanced in some way, death and hospitalization rates would be expected to be lower in the healthier group.
4. Potential sources of bias should be critically assessed.
5. The committee should assess the internal consistency of results across all subgroups prior to ending the trial. If all of these results suggest one treatment over another, the results are more compelling.
6. Finally, the purpose of a clinical trial is to make recommendations for treatment practices in the general medical community. For this reason, the results and conduct of the trial must be highly credible. In the absence of very compelling evidence of harm or benefit, the focus of the trial should be on obtaining scientifically valid, generalizable results.

8.3 Criteria for Trial Extension

It is possible that the DSMB may find that the assumptions used in the design of this study were inadequate. In particular, the death and hospitalization rate may be lower than anticipated. The follow-up period, recruitment period, or sample size calculations may need to be adjusted to assure adequate power. Preliminary estimates should be assessed carefully, particularly in the first DSMB meetings after the study begins.

9 Non-Compliance Policies

9.1 Crossovers

A “crossover” patient is a subject who is assigned to one treatment, but decides of his or her own volition to cease taking the assigned treatment and instead opts for another treatment tested in the study. These patients will be included in the analysis. Appropriate statistics will be kept on all such subjects, and will be reported separately. However, they will also be included in the analysis of the group to which they were originally assigned.

9.2 Dropouts

A subject is considered to have “dropped out” of the study if they are randomized but later decide to discontinue participation. Because of the long follow-up period of this study and possible side effects of the drugs, we anticipate a combined dropout and crossover rate of 29%. Participants are asked in the consent form to allow follow-up via medical records after they drop out. Every effort will be made to ask subjects to complete a withdrawal form, which will allow us to learn more about why patients choose to leave clinical trials. As with crossover patients, all patients who drop out of the study will be included in the analysis on an intention to treat principle.

10 Statistical Analysis

10.1 Estimation of Survival Curves

The analysis of death from any cause will include all patients, according to the intention-to-treat principle. The survival curves will be estimated through use of the Kaplan-Meier conditional probability strategy, which allows for censored observations and staggered entry into the trial.²¹ This procedure assumes that the exact time of entry into a trial, event or loss to follow-up is known. If a death and loss to follow-up are recorded as having occurred at the same time, the death is then assumed to have occurred first. The total time of the trial will be divided up into intervals and the probability of surviving through a particular interval will be given by

$$p_j = (n_j - \delta_j) / n_j$$

where n_j is the number alive at the beginning of the j interval and δ_j the number who die during the j interval. $P(t)$ is then the cumulative probability of survival to three years, and it is equal to the accumulated product of the p_j .

10.2 Comparison of Survival Curves

Pair-wise comparisons of the overall eplerenone and placebo curves and spironolactone and placebo curves will be made using the Mantel-Haenszel Test. For each comparison, event times will be pooled from both groups and ranked. A 2x2 table will be calculated for each event time. The Mantel-Haenszel test statistic will be calculated as follows:

$$MH = \left(\sum_{j=1}^K \text{trt deaths in interval} - \text{expected \# trt deaths in group} \right)^2 / \sum_{j=1}^K \text{variance of trt deaths}$$

where K is the number of distinct event times. Then $(MH)^{1/2} = Z_{MH}$, which has asymptotically a normal distribution. Critical Z_{MH} will be associated with two sided $\alpha = 0.025$, which is corrected for pair-wise comparisons.

Cox proportional-hazards models will be developed to explore the effect of baseline characteristics on the estimated effects of spironolactone and eplerenone.

10.3 Comparison of Adverse Events/Quality of Life

Pair-wise comparisons of the number of adverse effects in the eplerenone vs. placebo groups and spironolactone vs. placebo groups will be accomplished through two-independent sample t-tests. Quality of life responses will be grouped into an overall quality of life score for each questionnaire and will then be pooled within treatment groups and averaged. Difference in mean quality of life score will then be calculated through paired t-tests. For both adverse event and quality of life comparisons, differences will be considered significant if $p\text{-value} > \alpha/2$ (corrected for pair-wise comparisons).

11 Conclusion

We propose a randomized, double-blind, placebo-controlled, multi-center clinical trial of the effectiveness of spironolactone or eplerenone on patients with mild to moderate heart failure. The primary outcome variable is combined all-cause mortality and cardiac hospitalization. Secondary outcome measures include death from cardiac causes and quality of life.

Clinical stage of heart failure will be evaluated prior to randomization, and only patients with Stage B or C heart failure are eligible for this study. Blood tests and quality of life questionnaires will be used to assess the effectiveness and side effect profile of the study drugs. A committee blind to treatment assignment will assess reasons for death and hospitalization. Every effort will be made to follow each participant who is randomized via medical records and vital statistics. A central data analysis center will be responsible for the integrity of all participant data.

This trial is scheduled to last approximately five years and enroll 4869 patients. Survival curves will be constructed using the Kaplan-Meier method, and compared using a log rank test. An independent data and safety monitoring committee will oversee this trial, and is responsible for participant safety and trial continuation.

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