A randomized, controlled trial comparing the efficacy of carvedilol vs. metoprolol in the treatment of atrial fibrillation

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Lay Abstract: Atrial fibrillation is a common form of irregular, rapid heart rate that causes a significant increase in hospitalization and mortality in the United States. Studies have demonstrated that slowing the heart rate with medications is an effective means of reducing complications and mortality from atrial fibrillation. Beta-blockers are one of three types of medications that are typically used for rate control. No previous studies have assessed differences between specific beta-blockers in terms of improving outcomes for patients with atrial fibrillation.

Carvedilol is a beta-blocker that also has additional anti-inflammatory and anti-hormonal properties not found in traditional beta blockers. Multiple studies have compared carvedilol with metoprolol for the treatment of heart failure, a disease marked by inflammation and increased hormonal activity. In these studies, carvedilol has been consistently shown to have an advantage in reducing deaths from heart failure. Evidence shows that atrial fibrillation is also characterized by increased hormonal activity and inflammation and these effects could be related to the increased mortality seen in this disease. Therefore, a medication such as carvedilol, with actions that extend beyond rate control, should work better to prevent deaths and hospitalizations from complications of atrial fibrillation. Several observational studies suggest that carvedilol might be a superior medicine to metoprolol in the treatment of atrial fibrillation.

We propose to conduct the first multi-center, randomized controlled trial to test the hypothesis that carvedilol will reduce mortality and hospitalizations as compared to metoprolol when used to treat atrial fibrillation. We will enroll 2100 patients with pre-existing or newly-diagnosed atrial fibrillation from hospitals and cardiology offices. They will randomly be assigned to receive metoprolol and carvedilol and will not know which treatment they are receiving. Each medication will be increased for optimal control of heart rate. Subjects will be followed for five years following enrollment and will be seen by study personnel every six months during the study period. There are no ethical issues related to the study as both of these medications are accepted treatments for atrial fibrillation. Subjects will be also be maintained on blood thinners during the study, as is recommended for the treatment of all patients with atrial fibrillation.

A. Study Purpose and Rational

Atrial fibrillation is a common cardiac arrhythmia that leads to significant morbidity and mortality. Complications of atrial fibrillation include stroke and progression of left ventricular (LV) dysfunction (1,2). Strategies to treat atrial fibrillation include controlling patients' heart rates, attempting to convert patients into sinus rhythm through medications or through electrical cardioversion, and anticoagulation with warfarin to prevent embolic strokes. The AFFIRM trial compared a strategy of rate control to rhythm control and found that mortality of patients in these two arms was statistically equivalent with a trend in favor of rate control strategy (3).

Beta-blockers are common therapeutic choices for rate control and were used by up to 68% of patients in the AFFIRM trial (3). Selective beta-blockers, such as metoprolol, act at the atrio-ventricular junction to slow down the ventricular response to a rapid atrial rate. Carvedilol is a non-selective beta-blocker that has alpha-1 blocking effects as well as antioxidant and anti-arrhythmic properties (4,5). Carvedilol has been studied extensively in congestive heart failure (CHF) and has been shown to produce a significant morbidity and mortality benefit in comparison to the use of metoprolol in CHF (6,7,8). These results are thought to be due to carvedilol's role in LV remodeling, as demonstrated by significant improvements in LV function and dimensions in patients treated with this medication (7). Data on carvedilol in the treatment of atrial fibrillation has mostly come from studies of patients with CHF. In these studies, carvedilol has shown effectiveness in reducing mortality and improving morbidity from CHF (7,9,10).

Small studies in specific patients have suggested a benefit of carvedilol over standard beta-blockers in the treatment and prevention of atrial fibrillation. Among 90 patients who had been cardioverted to sinus rhythm, carvedilol had a non-significant trend towards maintenance of sinus rhythm as compared to bisoprolol (11). In a retrospective study of 115 cardiac surgery patients, carvedilol reduced the post-operative incidence of atrial fibrillation by 32% compared to an 8% reduction seen with metoprolol (12).

Although the primary known effect of beta-blockers in atrial fibrillation is the reduction of heart rate, evidence exists that they have a benefit beyond heart rate control (14). In one large trial of patients with LV dysfunction, patients in the carvedilol group had significant reductions in the incidence of atrial fibrillation as compared to placebo (15). This suggests that carvedilol may alter the neurohormonal milieu that promotes both the development and perpetuation of atrial fibrillation. Similar to CHF, atrial fibrillation is characterized by adrenergic stimulation leading to atrial remodeling (5). Since carvedilol possesses alpha-1 blocking properties as well as antioxidant effects, we think it has a greater effect in preventing atrial remodeling, perpetuation of atrial fibrillation, development of CHF and overall morbidity and mortality. We propose to study this hypothesis in a randomized, controlled trial comparing the use of metoprolol and carvedilol in atrial fibrillation.

B. Study Design and Statistical Analysis

Patients will be recruited from participating medical centers and cardiology practices. Randomization will be stratified by site and patients will be assigned to take carvedilol or metoprolol. Both investigators and patients will be blinded as to which group the subjects have been assigned. Initial dose of metoprolol will be 12.5 mg BID and initial dose of carvedilol will be 3.125 mg BID. Each medication can be increased at discretion of each patient's physician to maximum doses of 100 mg BID of metoprolol and 25 mg BID of carvedilol. Target resting heart rate will be <70 beats per minute in each group.

Discontinuation of study medication will be allowed for symptomatic bradycardia, significant bronchospasm or failure to achieve rate control. Non-pharmacologic therapy for atrial fibrillation, such as radio-frequency ablation, pacing or surgical procedures is discouraged, but can be provided to subjects at the discretion of their physician. All patients will be maintained on warfarin throughout the study period, with a goal INR of 2-3.

We will enroll 2000 patients, which is calculated based on the rate of cardiovascular (CV) hospitalizations in the AFFIRM trial. The definition of CV hospitalizations in our trial will be any hospitalization for an arrhythmia, ischemia, angina or symptomatic heart failure. In that trial 36% of patients in the rate-control arm were hospitalized for a cardiovascular reason (15). Approximately 25% of patients in that trial had a reduced ejection fraction (EF) and this group had a hazard ratio of approximately 2.0 as compared to the patients with normal EFs (16). Therefore, extrapolating these numbers to our trial, in which patients with reduced EFs will be excluded, we estimate the rate of CV hospitalizations in our control group to be 28.8%. To show a 20% reduction in this endpoint with 80% power and an α of 0.05 , we calculated that 944 patients will be required in each arm. We will enroll an additional 150 patients to account for potential withdrawals and loss to follow-up.

All outcomes will be assessed on an intention-to-treat basis. The primary endpoint will be time to cardiovascular hospitalizations and will be assessed with a Cox proportional hazards model. Secondary endpoints will include a composite of death, non-fatal MI and non-fatal stroke. We will also assess the number of cardiovascular hospitalizations in each group, the number of patients in each group who develop symptomatic congestive heart failure (as defined by one symptom and sign of CHF and an EF<50%) and the number of bleeding events (minor and major) in each group. All comparisons will be performed with a chi-square analysis.

C. Study Procedure

As part of the enrollment process, all patients will have a transthoracic echo (TTE), which is a typical component of the work-up of atrial fibrillation but is not used in every case. This procedure poses no risk to the patient. All patients will be followed for five years following randomization. In addition to regular doctor visits, the study participants will be seen by study physicians at 6-month intervals for the entire study period. At these visits, blood will be drawn to assess specific biomarkers for use in subsequent studies (e.g. C-reactive protein and endothelin levels). Study investigators will assess compliance with medication, concurrently administered medications, outcome events and symptoms of angina or CHF. If a study physician suspects CHF, they will order a repeat TTE to assess the patient's EF. Other than inconvenience and time, these visits pose minimal risk to the patient.

D. Study Drugs

Metoprolol is a selective beta1-adrenoreceptor blocking medication that is approved for the treatment of hypertension, heart failure and supraventricular arrhythmias. Metoprolol's use in atrial fibrillation has been studied extensively and the medication has been demonstrated to be safe when used appropriately. Major side effects include bradycardia, which is dose-dependent and bronchospasm, which typically only occurs in patients with pre-existing obstructive lung disease.

Carvedilol is a non-selective beta-blocker that also possesses alpha-1 blocking properties. Carvedilol is approved for the treatment of hypertension and congestive heart failure. This medication has previously been used in patients with concurrent CHF and atrial fibrillation and has been shown to have a mortality benefit in these patients. The side effect profile of carvedilol is similar to metoprolol.

E. Study Subjects

All patients who are 65 years of age or older and who are judged to have atrial fibrillation that is likely to be recurrent will be included. We will also include patients younger than 65 with at least one risk factor for stroke (i.e. hypertension, diabetes mellitus, coronary artery disease, prior cerberovascular disease or peripheral arterial disease). Atrial fibrillation can be new onset or of prior onset, but must be documented by electrocardiogram in the six weeks prior to enrollment.

Patients who require immediate cardioversion or patients on antiarrhythmic therapy at the time of randomization will be excluded from the study. All patients will undergo TTE before randomization and patients with ejection fractions less than 50% will be excluded. Further exclusion criteria are: 1) contraindication to anticoagulant therapy (prior intracereberal hemorrhage, prior massive gastrointestinal bleeding, recent surgery), 2) allergies to beta-blockers, 3) resting heart rate <60, 4) second or third degree AV block, 5) moderate to severe asthma or COPD, 6) unstable angina, myocardial infarction, stroke or coronary revascularization in the two months prior to enrollment. Patients with mild asthma or COPD can be included if they have previously taken a beta-blocker without incident.

F. Recruitment of subjects

Patients will be recruited by study investigators at cardiology clinics and medical centers participating in the study.

G. Confidentiality

Each subject will be assigned a unique identifying number. These numbers will be used to construct a study database containing all pertinent clinical information and measurements. Study forms linking patient's names to their number will be kept in a locked location by the primary investigator at each site. Subjects will never be identified by name when results are analyzed and published.

H. Potential Risks

The primary risk to the patient is that carvedilol will not be as effective in reducing hospitalizations and mortality as metoprolol. Although carvedilol has demonstrated significant benefits in the treatment of CHF, experience with its use in atrial fibrillation is limited. However, evidence in patients with concurrent CHF and atrial fibrillation is reassuring as to carvedilol's efficacy in the treatment of atrial fibrillation. Other possible risks include the side effects and inconvenience described above.

I. Potential Benefits

The study subjects may or may not benefit from participating in this study. If carvedilol is shown to be superior to metoprolol, the patients who took carvedilol will have accrued those benefits. As this medication shows significant promise in the treatment of atrial fibrillation, the potential benefits to society from this study are numerous.

J. Compensation

Subjects will be reimbursed for any travel expenses related to follow-up visits.

K. Costs

None

L. References

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