# Effect of Low Digoxin Blood Levels on Morbidity and Mortality in Patients with Heart Failure. (the Low DIG trial)

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### A.  Study Purpose

This study aims to assess whether low blood levels of digoxin reduce mortality in patients with congestive heart failure. Digoxin i's a digitalis glycoside that exerts positive inotropic effects on the heart. It is commonly used and approved for heart failure. It was previously noted in the DIG trial that empiric digoxin did not change mortality but reduced rates of hospitalization. However, in a post-HOC analysis of that study showed that that those with lower blood levels of digoxin had a reduced mortality compared to higher levels and to placebo. Thus, I designed a double-blinded, randomized placebo controlled trial to assess for this possible improvement in mortality.

### B.  Study Subjects and Method of Recruitment

Men and women aged 21 years and older, diagnosed with heart failure, will be enrolled. To show the smallest difference of clinical interest (10% in relative risk reduction), a total of 6000 patients would need to be enrolled. This would require and multicenter trial. At CUMC subjects will be recruited until the 6000-subject mark. A letter will be written to the cardiology department inviting all cardiologists to participate in this trial. After the patients are identified by their cardiologists as potential subjects and agree to meet with the study investigator, the study investigator will contact the subjects.

#### a.  Study Procedures

During the initial encounter the following data will be collected using an initial standardized questioner: age, sex, ejection fraction, duration of CHF, N_YHA-HF class, signs and symptoms of CHF, history of previous myocardial infarction, current angina, diabetes, hypertension, digoxin use, and cause of CHF. The patient will be randomized. Blood will be drawn and sent for digoxin level, blood urea nitrogen (BUN), creatinine, magnesium, calcium and potassium levels. If not already on digoxin they will be loaded with the drug and started on a daily regimen.

Digoxin blood level would be assessed by phlebotomy weekly for 3 weeks or until achievement of the desire digoxin level, then monthly for 3 months, and then every 3 months until the end of the trial. During these meetings, the following data will be collected: changes in clinical and functional status, use of selective non-study drugs (such as: beta-blockers, angiotensin converting enzyme inhibitors, nitrates, and other vasodilators), hospitalizations, adherence to study regimens and side effects.

### C.  Issues

There is a very small risk of increase of high degree AV block in the digoxin arm. In the placebo arm there may be more hospitalizations, as active digoxin use has been shown to decrease hospitalizations in this population. The subjects will have to pay for transport to and from the study center.

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### A.  Study Purpose and Rationale

The purpose of this study is to assess the potential effect of low blood levels of digoxin in reducing mortality from heart failure. As previously reported in the DIG trial, digoxin when given to heart failure patients had no effect on mortality . However, in a post HOC analysis it was noted that mortality in the digoxin arm was inversely related to blood levels of digoxin, even after adjusting for possible

confounders 2. Those with the lowest levels (0.5-0.8ng/dL) had a reduction in mortality, those in the middle range (0.9-1.1 ng/dL) had no change, while those in the highest levels (>1.2ng/dL) had and increase in mortality compared to placebo.

The primary end point will be all cause mortality. Secondary outcomes that will be assessed are: mortality for cardiovascular causes, hospitalizations for worsening heart failure, hospitalizations for other causes, in particular for suspected digoxin toxicity, and effect of sex on mortality.

## B.  Study Design and Statistical Analysis

The subject in this will be randomized to an interventional arm, in which the subjects will receive digoxin, to be titrated to a blood level of digoxin between 0.50.8ng/dL, or to placebo.

In the DIG trial the mortality over 5 years was 29.9% in the lower digoxin level group and 35.1 in the placebo group. This represents a 5.2% absolute risk reduction (ARR) and a 14% relative risk reduction (RRR). However, a smaller risk reduction is clinically significant. Thus, in orderto detect a 10% RRR (or 3.5% ARR) with 80% power testing at P=0.05, and using the Chi-square test, we would to enroll approximately 3000 subjects on each arm (total of 6000 subjects) and follow them for about 3 years.

Given the large number of subjects needed for the study, most of the predictors for worse outcome would be expected to distribute evenly between the two groups. Thus, no stratified randomization would be necessary based on the patients' characteristics. However, patients would be stratified by center.

During the study the subjects will not cross, and if they were to cross because of a break in the study protocol, they will be analyzed on an intension-to-treat basis with two-sided p-values. A stratified log-rank statistic will be used to compare the survival distributions in the two study groups. Kaplan-Meier analysis will be used for a life-table plot. Cox proportional-hazards model will be used to calculate the 95% confidence interval.

## C.  Study Procedure

When a subject is randomized and started on the investigational drug or placebo, the drug dose and the blood level will be monitored by a study investigator unaware of the of the group assignment. To ensure blinding of the investigator, a central laboratory computer linked to the central computer (that is aware of the randomization) will produce fake digoxin blood level values for patients in the placebo group. Thus, the investigator will be prompted to titrate the placebo drug up or down, just as in the intervention arm. This is done in a similar fashion as 3 previously published warfarin trials .

Digoxin blood level would be assessed by phlebotomy weekly for 3 weeks or until achievement of the desire digoxin level, then monthly for 3 months, and then every 3 months until the end of the trial. Along with digoxin level, blood urea nitrogen (BUN), creatinine, magnesium, calcium and potassium levels would be obtained. The creatinine clearance will be calculated from the serum creatinine and the subjects's sex and age, using the standard formulas:

Males: $Ccr = (140\text{-}age)/Scr$

Females: $Ccr = ((140\text{-}age)/Scr) \times 0.85$

(Ccr=creatinine clearance). Abnormal electrolyte levels would be reported to the patient's physicians so that they can act upon them. A pill count will also be done at each visit to assess for compliance.

The initial visit will also include a height measurement to calculate ideal weight.

This frequent blood drawing is an added inconvenience to the patients, as they would have to come to the hospital to have phlebotomy and experience the minimal pain/discomfort involved with the procedure.

## D.  Study drug

Digoxin is a generic drug already approved for use in congestive heart failure (CHF). It is a digitalis glycoside that exerts positive inotropic effects on the heart. It is thought to improved contractility of the heart and, thus, the ejection fraction (EF), improve functional status, exercise capacity. Its withdrawal in patients with CHF [4] may cause worsening in those parameters .

Patients are loaded with a digoxin 10 micrograms/kg of ideal weight orally. After the loading dose, a daily schedule of initial dose should follow:

- 125 micrograms (0. 125 milligrams) once daily in patients under age 70 with good renal ftinction, or
- 62.5 micrograms (0.065 milligrams) once daily inpatients over age 70 or with impaired renal ftmction (creatinine clerarace between 20 to 50 mL/min),

Drug levels should be drawn during the post-absorptive, post-distributive phase of drug elimination, i.e., during the 8 to 24-hour interval following the previous dose. Doses may be titrated up or down by 31.25 to 125 micrograms depending on blood level. Patients who are already on digoxin will be allowed to enter the trial without a washout period. These patients will not have a loading dose. The investigator could use the previous digoxin dose and blood levels to modify the daily dose regimen. Both the initial dose and titration are half of the standard dose used in clinical practice, as the blood levels to be achieved in this study are lower than those seen in standard practice.

Patients who are already on digoxin will be allowed to enter the trial without a washout
period.

The safety and efficacy of Digoxin have been previously demonstrated in large clinical trials . Levels less than 2ng/dL are thought to be safe and have few side effects. Uncommonly some patients may experience some side effects with these levels. Higher levels are commonly associated with toxicity. These include:

- Blood: thrombocytopenia case reports, thought to be immunologically mediated
- Cardiovascular: Arrythmias: premature ventricular contractions, atrioventricular/junctional tachycardia. Toxicity may include: SA (sinoatrial) block, sinus arrest, AV (atrioventricular) block, atrial tachycardia with block, atrial fibrillation with high-grade AV block, nonparoxysmal AV junctional tachycardia, complex ventricular premature beats, and ventricular tachycardia
- Central Nervous system:
  o Neurologic: headache, encephalopathy, seizures, trigeminal neuralgia, dizziness, fatigue, lassitude, malaise, insomnia, and stupor have occurred with digoxin therapy. Often, many of these effects are associated with toxic digoxin levels.
  o Psychiatric: apathy, irritability, nightmares, psychosis including hallucinations and delirium have been reported with digoxin therapy. Often, many of these effects are associated with toxic digoxin levels.
- Endocrine: Gynecomastia has been associated with digoxin therapy. Serum estrogen levels may be increased by digoxin in both older men and women. Luteinizing hormone and testosterone concentrations have been reported to be significantly decreased in older men.
- Gastointestinal: Common adverse effects of digoxin therapy include nausea, vomiting, diarrhea, abdominal pain, and anorexia. Often, many of these effects are associated with toxic digoxin levels.
- Ocular: Blurred vision, halos around bright objects, disturbed color vision (yellow vision), disturbed visual acuity associated with ocular muscle palsies, alteration of pupillary size, retrobulbar neuritis, or central scotomas have occurred with digoxin therapy. These effects are particularly prominent with a reported incidence as high as 95% in patients who are digitalis toxic.
- Dermatologic: Digoxin has been associated with rare cases of erythematous, raised, pruritic rash, maculopapular rash, and Stevens-Johnson syndrome.
- Immunologic: Occasional allergic reactions have been reported with digoxin re-exposure.

We expect less toxicity with digoxin in this trial given that the goal for blood level are much lower than those usually associated with toxicity.

## E.  Medical Device

N/A

## F.  Study Questioners

During the initial encounter the following data will be collected using an initial questioner (still to be developed): age, sex, race/ethnic background, ejection fraction, duration of CHF, NYHA-HF class, signs and symptoms of CHF, history of previous myocardial infarction, current angina, diabetes, hypertension, digoxin use, and cause of CHF

During follow up visits at 3 weeks, then monthly, then every 3 months another questioner will be used to collect the following data in a standardized manner: changes in clinical and functional status, use of selective non-study drugs (such as: beta-blockers, angiotensin converting enzyme (ACE) inhibitors, nitrates, and other vasodilators), hospitalizations, adherence to study regimens and side effects.

## G.  Study Subjects

Patients are eligible if they have heart failure with an ejection fraction (EF) =<45% and are in sinus rhythm. The diagnosis of heart failure is based on current or past clinical symptoms (limitations of activity, fatigue, dyspnea and/or orthopnea), signs (edema, elevated jugular venous pressure, rales, S3 gallop) or radiographic evidence of pulmonary congestion. The NYHA-HF class is assessed based on severity of symptoms.

The EF is obtained from previous imaging modalities including radionucleotide left ventriculography, left ventricular contrast angiography or two-dimensional echocardiogram. If two or more EF measurements are performed, then the last one is taken into account. EF measurements <7 days from a myocardial infarction or surgery cannot be used.

Exclusion criteria are as follow:
1. Age < 21 years
2. Baseline left ventricular EF not available
3. Myocardial infarction, cardiac surgery, or percutaneous transluminal coronary angioplasty (PTCA) within 4weeks
4. Unstable or refractory angina < I month
5. 11-111 degree AV block without a pacemaker
6. Atrial fibrillation (with or without pacemaker) or atrial flutter
7. Cor pulmonale
8. Constrictive pericarditis (such patients are eligible after surgery)
9. Acute myocarditis
10. Hypertrophic cardiornyopathy
11. Amyloid cardiomyopathy
12. Complex congenital heart disease
13. Pre-excitation syndromes
14. Current treatment with intravenous inotropic agents
15. Potassium below 3.2 mmol/L or above 5.5 mmol/L
16. Need for cardiac surgery (e.g., severe valvular disease, planned coronary artery bypass graft surgery) or PTCA in the near future. (Such patients are eligible after surgery or PTCA.)
17. Patients on heart transplant list are not eligible

18. Sick sinus syndrome without pacemaker
19. Recognizable non-cardiac causes of CHF
20. Significant renal insufficiency (creatinine clearance <20 based on formulas previously described) or severe liver disease. Any noncardiac disease that shortens life expectance to less than 3 years (e.g., most cancers)
21. Patient is unlikely to comply with the protocol requirements for follow-up and drug adherance (i.e. chronic alcoholism, no fixed address) Patients from minority groups and women are encouraged to participate. Patients previously on digoxin are admitted into the trial without a washout period.

## H.  Recruitment of subjects

In order to obtain the needed number of patients necessary to complete this trial a large number of centers would need to be involved. Thus, an invitation letter will be written to centers that previous participated in the DIG trial, and to all of the cardiology departments of hospitals within the United States of America and Canada. The cardiologists within the participating centers will identify eligible patients. At each center a study investigator will then approach the patients and perform the interviews and the blood draws.

## I.  Confidentiality of Study Data

Each investigator will call the central investigator in order to assign each patient. A central computer will randomize the patient and assign a number to the patient. Each time a questioner is filled or blood is drawn and analyzed in the central laboratory, the participant's number instead of the name will be used. All data entry will be done using the number of the patient. The code to access to the central computer randomization key will be kept in a safe deposit box at City Bank. Only the principal investigator will have access to the box.

## J.  Potential Conflict of Interest

The principal investigator does not have any connection to any pharmaceutical company and would not benefit financially from the results of this investigation.

## K.  Location of the Study

The study will take place in the outpatient setting. Patients in each of the locations will be interview at their respective investigator's office. Each institution will submit an IRB protocol. In those institutions without IRB, an administrator will provide a signed approval letter.

## L.  Potential Risks

From the DIG trial, the only toxicity that was different between groups was the development of 11 or III degree AV block (1.2 vs. 0.4% in the treatment arm vs. placebo)'. More digoxin toxicity was suspected in the treatment arm as compared to the placebo arm (11.9 vs. 7.9%), and these patients were more likely to be hospitalized (16.4 vs. 11.4%). However, these side effects are likely to smaller in our trial given the lower blood level chosen as a target for digoxin.

It is possible that the patients in the placebo group will have more hospitalizations for CHF, given that digoxin therapy was associated with a fewer hospitalization for any cause in the DIG trial.

## M.  Potential Benefits

Potential benefits to the study group would be a 10- 15% decrease in mortality and hospitalizations. If this is found, the results may be applicable to a large population of patients with heart failure that would derive benefits from taking digoxin as specified in this trial. However, you may or may not benefit as a result of your participation in this study.

## N.  Alternative Therapies

There are no alternative therapies to digoxin in heart failure. Digoxin is usually added or not to a standard CHF regimen that will likely include ACE inhibitors, beta-blocker, diuretic, and possibly spiranolactone or eplerenone.

## O.  Compensation

There will be no monetary compensation to the subjects.

## P.  Cost to Subjects

The subject will incur in no cost other than transportation to and from the center where the have investigation is taking place.

## Q.  Minors as Research Subjects

N/A

## R.  Radiation or Radioactive Substances

N/A

## S.  References

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