Digoxin has been used to treat heart failure for centuries; however, not until recent years did we have clinical studies that assessed its clinical benefits and/or harms. Digoxin has a positive inotropic effect due to the inhibition of sodium-potassium ATP-ase in the sarcolemma membrane of cardiac myocytes. This results in an increase in intracellular calcium that then becomes available for contractile protein with a resultant increase in myocardial contractility. In patients with atrial fibrillation, digoxin effects electrophysiologic conduction through a vagally mediated action resulting in a reduction in ventricular rate due to increased AV nodal tissue refractoriness. Digoxin has neurohormonal activity, as evidenced by its direct sympathoinhibitory effects as well as increases in heart rate variability which is a measure of baroreceptor activity. Decreases in serum norepinephrine concentrations and plasma renin activity also occur in patients treated with digoxin. Overall the neurohormonal benefits of digoxin are seen at lower serum concentrations (< 1.4 ng/ml). Additionally, there are no apparent increases in ionotropic effects at serum concentrations above 1-2 ng/ml.

Two recent companion studies, the Prospective Randomized Study of Ventricular Failure an Efficacy of Digoxin (PROVED) and the Randomized Assessment of Digoxin on Inhibitors of Angiotensin Converting Enzyme (RADIANCE), demonstrated that the withdrawal of digoxin therapy from patients with mild to moderate heart failure (NYHA FC II-III) and treated with diuretics (PROVED) or diuretics and ACE inhibitors (RADIANCE) resulted in worsened exercise tolerance, symptoms, NYHA-FC, quality of life, and need for ER visit or hospitalization. The mean serum digoxin concentrations approximately 1.2 ng/ml for patients continuing to receive digoxin in both studies. Clinical deterioration was often delayed, occurring 6 to 12 weeks after withdrawal of digoxin. These trials demonstrated that in patients with mild to moderate heart failure already receiving therapy with digoxin, withdrawal of digoxin therapy results in worsening of heart failure. These studies were not designed to evaluate the effects of digoxin on survival.

Digoxin’s effect on survival was determined with the results of the Digoxin Investigational Group (DIG) study. The DIG study evaluated the effects of digoxin compared to placebo on mortality and morbidity in nearly 8,000 patients with symptomatic congestive heart failure, in normal sinus rhythm, and receiving therapy with diuretics and ACE inhibitors. Left ventricular ejection fractions (LVEF) were < 45% in 6,800 patients, mean LVEF for study group ~ 28%. Approximately 44% of patients were also receiving digoxin at the time of randomization and therefore were withdrawn from digoxin upon randomization to placebo. The majority of patients (84%) were NYHA FC II and III. The DIG study resulted in no difference in the primary endpoint of total mortality between digoxin (and placebo over a mean follow-up period of 37 months. There was a trend towards a reduction in death due to heart failure in the digoxin group (11.6%) compared to the placebo (13.2%) group (p<0.06); however, this was offset by an increase in mortality due to other cardiovascular causes (arrhythmia’s, CAD, etc.) in the digoxin group (15%) as compared to the placebo (13%) group (p=0.04). Digoxin did demonstrate a statistically significant reduction in CHF hospitalizations (28% risk reduction), and hospitalizations for any cause (8% risk reduction). There was a significantly increased number of admissions for suspected digoxin toxicity in the digoxin group (2%) versus the placebo (0.9%) patients (p<0.001). Subset analysis of the combined endpoint of either death or hospitalization due to CHF revealed that the greatest benefit of digoxin therapy was in patients with LVEF’s < 25% (-32%), nonischemic CM (-33%), NYHA-FC III & IV (-30%), and those with cardiothoracic ratios > 55%. The mean serum digoxin concentration at the end of 1 year was 0.8 ng/ml. An accompanying editorial estimated that 1000 patients would need to be treated for 1 year in order to prevent 9 hospitalizations due to heart failure.

Clinical guidelines for the treatment of heart failure such as those from the Agency for Health Care Policy and Research (AHCPR) state that digoxin can prevent clinical deterioration in patients with left-sided systolic
dysfunction and improve patients’ symptoms (Strength of Evidence=A). The AHCPR guidelines also state that since mortality data was unknown, digoxin should be used in patients with severe CHF and should be added to mild or moderate failure patients who remain symptomatic despite optimal management with ACE inhibitors and diuretics (Strength of Evidence=C). The American College of Cardiology and the American Heart Association (ACC/AHA) released guidelines for the evaluation and management of CHF in 1995. They recommended that digoxin be used in patients with heart failure due to systolic dysfunction not adequately responsive to ACE inhibitors and diuretics. Additionally, digoxin is indicated for patients with atrial fibrillation and a rapid ventricular response. These recommendations were Class I. A Class II recommendation was made that all patients with CHF due to LV systolic dysfunction should receive digoxin. Both of these treatment guidelines were published prior to the release of the DIG study.

Therefore, it is the recommendation of the University Hospital CHF critical pathway development team that digoxin should be initiated in those patients who remain symptomatic despite optimal management with ACE inhibitors and diuretics. Patients with atrial fibrillation and a rapid ventricular rate (>100 beats/min) should receive digoxin. Additionally, patients with NYHA-FC II-IV CHF already receiving digoxin should not have their digoxin discontinued. The desired serum concentration for digoxin should be 0.8 to 1.4 ng/ml. There is no clinical rationale for loading doses of digoxin in patients with CHF without atrial fibrillation. Serum digoxin levels should be checked after one week of therapy in patients with normal renal function and in 2 to 3 weeks for patients with renal insufficiency. For suspected toxicity, other monitoring parameters include serum potassium and magnesium, BUN, creatinine, and ECG. The potassium dose should be adjusted to keep levels between 4 to 4.5 Meq/L. Serum digoxin levels should be monitored only under the following conditions:

- Worsening heart failure
- Declining renal function
- Addition of medications likely to interact with digoxin (i.e. verapamil, amiodarone, quinidine)
- Suspected toxicity (confusion, nausea, vomiting, visual disturbances)