Response

The Contemporary Use of Digoxin for the Treatment of Heart Failure

Gary S. Francis, MD

The use of digitalis has been plagued by controversy since its initial use by Withering in 1775. We now have much more data, but it should be remembered that the Digitalis Investigator Group trial was executed when β-blockers were not widely used to treat heart failure. There are still many questions about where we currently stand with the use of digitalis. Specifically, when should one add digoxin to the medical regimen of a patient with heart failure symptoms? Another question that frequently arises is whether one should consider stopping digoxin in a patient referred for care who has chronic stable heart failure. I will briefly examine these 2 scenarios separately.

Should One Add Digoxin to a Medical Regimen in Patients With Heart Failure?

When faced with a patient demonstrating worsening symptoms of heart failure, we are trained to ask, “why is this patient worse?” Sometimes the answer is apparent, but often it is unclear. When heart failure worsens and patients begin to have more signs and symptoms, a remedial cause should be sought and corrected when possible. Often the cause is dietary indiscretion, noncompliance with medications, comorbid conditions, and unclear or misunderstood instructions about how to self-manage the condition of heart failure. However, complications directly related to the heart, such as myocardial ischemia, myocardial infarction, or arrhythmias, can occur. We know that paroxysmal and permanent atrial fibrillation (AF) occurs in a substantial proportion of patients with heart failure during the course of their illness, probably in the range of 20% to 30%. One should always consider AF as a potential cause of worsening heart failure. Unless it is an emergency (ie, acute pulmonary edema), slowing the ventricular rate rather than correcting the underlying rhythm disturbance is the preferred therapeutic pathway. In such patients, I frequently use small doses of digoxin to control rate. Precisely how one does this is more a product of local custom rather than a scientific inquiry, but several doses of digoxin (0.125 mg/day) will frequently reduce the heart rate and thus improve signs and symptoms. I prefer digoxin to intravenous β-blockers and diltiazem, as there is no negative inotropy and no excessive vasodilation or hypotension. Unless contraindicated, I consider the use of digoxin to control AF when it is observed in patients with heart failure with normal or only slightly impaired renal function. It remains unclear if restoring sinus rhythm is useful in the absence of worsening symptoms, so the threshold for using digoxin to control heart rate as opposed to cardioversion in patients with heart failure and AF may become less as time goes by. One should have a low threshold to use digoxin to slow ventricular rate in the setting of AF and heart failure, recognizing that most patients will already be receiving β-adrenergic blocking agents and that a heart rate of 60 to 80 bpm is reasonable.

Even if the patient has no evidence of AF, starting a maintenance dose of digoxin might be considered in the setting of patient’s normal sinus rhythm and signs and symptoms of New York Heart Association class II to III heart failure (Figure 1). The incidence of death or hospitalization because of worsening heart failure is less when digoxin is added to diuretics and angiotensin-converting enzyme inhibitors. The effectiveness of digoxin therapy in men with heart failure and a left ventricular ejection fraction of ≤45% may be optimal when the serum digoxin concentration is in the range of 0.5 to 0.8 ng/mL, suggesting that lower doses of digoxin may be safer. Digoxin may be less safe in women, but controversy persists, and the gender concern may be overstated. In addition to its well-known positive inotropic effect, digoxin may lessen autonomic dysfunction and have favorable long-term effects on neurohumoral mechanisms. It is possible that benefit from digoxin is related to the reduction in ejection fraction. It is unclear if digoxin is helpful for diastolic heart failure. In summary, I would favor adding digoxin to conventional therapy to control the heart rate in patients with heart failure and AF. I also favor adding a small maintenance dose of digoxin (0.125 mg/day) to aid patients with New York Heart Association class II to III heart failure and normal sinus rhythm, particularly if they remain symptomatic despite evidence-based pharmacotherapy. The role of serum digoxin concentration is well established. Serum digoxin concentrations in the range of 0.5 to 0.8 ng/mL are ideal and should not exceed 1.0 ng/mL.

Should One Discontinue Digoxin in a Patient With Stable Heart Failure?

One should never thoughtlessly change therapy in patients who are doing well. In fact, I have tended to avoid requesting such
patients to enter clinical trials. Many patients are referred to me who are on maintenance digoxin and are doing well. I will measure the serum digoxin concentration and may alter the dose accordingly, but I would not routinely withdraw digoxin from a clinically stable patient. Withdrawal of digoxin carries considerable risks for patients with chronic stable heart failure and impaired systolic function who are receiving angiotensin-converting enzyme inhibitors (Figure 2). As a matter of routine, I do not discontinue digoxin in clinically stable patients. However, there may be special circumstances where I might consider withdrawal or reducing the dose, such as in those with excessive serum digoxin concentrations. Based on the currently available data, I believe that the risk/benefit ratio of using digoxin is less than I previously believed. Measurement of serum digoxin concentrations is readily available and should be checked, especially in the setting of chronic kidney disease. Levels $\geq 1.2$ ng/mL may be harmful, and reduction in dose or, in some cases when clinical toxicity is suspected, withdrawal of the drug is appropriate. A number of points can be used as general guide-

**Figure 1.** Incidence of death or hospitalization because of worsening heart failure in the digoxin and placebo groups. The number of patients at risk each 4-month interval is shown below the figure. Reproduced with permission from *N Engl J Med* 1997;336:525–533.

**Figure 2.** Kaplan-Meier analysis of the cumulative probability of worsening heart failure in the patients continuing to receive digoxin and those switched to placebo. The patients in the placebo group had a higher risk of worsening heart failure throughout the 12-week study (relative risk, 5.9; 95% confidence interval, 2.1 to 17.2; $P<0.001$). Reproduced with permission from *N Engl J Med* 1993;329:1–7.

### Table: General Guidelines Regarding the Use of Digoxin in the Setting of Heart Failure

Digoxin is still preferred as an adjunct measure to control heart rate in patients with heart failure, atrial fibrillation, and a poorly controlled heart rate.

There is still a role for careful use of low-dose digoxin in patients with New York Heart Association class II to III heart failure with normal sinus rhythm who demonstrate impaired systolic function despite evidence-based pharmacotherapy. I am more likely to prescribe digoxin in such patients if they are not doing well.

Digoxin may reduce the need for hospitalization and lessen the chance of developing worsening heart failure in patients with impaired left ventricular function.

Serum digoxin concentrations should be monitored and levels in the range of 0.5 to 0.8 ng/mL may be optimal. Levels below 1.0 ng/mL are safer and perhaps more effective.

Digoxin is neutral with regard to mortality, although there may be increased mortality that clusters in patients with serum digoxin concentrations of $\geq 1.2$ ng/mL. Mortality may be improved when serum concentrations are low (post hoc analysis; Digitalis Investigator Group trial).

Patients with heart failure and a reduced ejection fraction who are clinically stable should not have digoxin routinely withdrawn.

### Lines regarding the use of digoxin in the setting of heart failure (Table).

On balance, there is still a role for digoxin in selected patients with chronic heart failure. Clearly, digoxin’s role is not as expansive as it once was. There are many reasons for this, some of which are nonscientific. We now know that serum digoxin concentrations are useful, lower doses of digoxin are safer and perhaps more effective, and some patients will clinically improve with digoxin use. Routine withdrawal of digoxin in stable patients with heart failure is discouraged.

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### References


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