



**SORT: KEY RECOMMENDATIONS FOR PRACTICE**

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
Digoxin is recommended for symptomatic patients with stage C or D heart failure.	A	9, 11, 12, 14
The target serum digoxin concentration should be 0.5 to 1.0 ng per mL (0.6 to 1.3 nmol per L).	B	12, 14, 15
Digoxin is not recommended for the treatment of diastolic heart failure.	B	21, 22
Digoxin should be used only as a second-line therapy for controlling the heart rates of patients with atrial fibrillation associated with heart failure.	B	10, 24
Some evidence suggests that digoxin increases mortality in women but not in men; therefore, it should be used cautiously in women with symptomatic heart failure.	B	16

*A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 542 or <http://www.aafp.org/afpsort.xml>.*

An ancillary trial included 988 patients with preserved ventricular function (i.e., ejection fraction greater than 45 percent).<sup>9</sup> The DIG investigators concluded that adding digoxin to standard heart failure therapy (i.e., ACE inhibitors plus diuretics) significantly decreased hospitalizations for worsening heart failure and improved exercise performance (number needed to treat [NNT] to prevent one hospitalization = 13 over three years). However, adding digoxin to standard therapy did not improve cardiovascular or all-cause mortality during the trial.<sup>9</sup>

American College of Cardiology (ACC) and American Heart Association (AHA) joint guidelines for managing chronic heart failure in adults recommend administering digoxin to improve symptoms in patients treated with diuretics, ACE inhibitors, and beta blockers.<sup>10</sup> Digoxin therapy may be delayed until the patient is stabilized using these agents and initiated only if the patient remains symptomatic. This recommendation is supported by findings from a meta-analysis of seven randomized trials published before the PROVED, RADIANCE, and DIG trials.<sup>11</sup> The meta-analysis showed that the NNT to prevent the clinical deterioration of one patient was nine. The presence of a third heart sound, the severity and duration of heart failure, and cardiomegaly on a chest radiograph predicted the effectiveness

of digoxin.<sup>11</sup> Digoxin is not recommended for patients with significant sinoatrial or atrioventricular block.

**Reanalysis of Digoxin Therapy for Heart Failure**

Reanalyses of the DIG trial have brought into question the safety of digoxin, including the optimal serum digoxin concentration for treating heart failure and the role of the patient's sex in digoxin therapy.

**SERUM DIGOXIN CONCENTRATIONS**

A widely used reference range for serum digoxin concentration is 0.8 ng per mL (1.0 nmol per L) to 2 ng per mL (2.6 nmol per L). This range was established to assess digoxin toxicity, not effectiveness.<sup>12,13</sup>

Retrospective subgroup analysis of the DIG trial showed increased mortality in men who received serum digoxin concentrations of more than 1.0 ng per mL (1.3 nmol per L) and showed decreased mortality in men with serum digoxin concentrations of 0.5 ng per L (0.6 nmol per L) to 0.8 ng per mL.<sup>14</sup> However, because less than one third of patients had a concentration measurement at one month, there was insufficient statistical power to determine whether digoxin use was associated with benefit or harm or had a neutral effect for women in this or any serum digoxin concentration range.<sup>14</sup>

Reanalysis of the PROVED and RADIANCE trials indicated that patients with low serum digoxin concentrations (0.5 to 0.9 ng per mL [1.2 nmol per L]) experienced similar benefits regarding symptoms of heart failure, improvement in LVEFs, and increased treadmill time compared with patients with moderate (1.0 to 1.2 ng per mL [1.5 nmol per L]) to high (more than 1.2 ng per mL) serum digoxin concentrations.<sup>15</sup>

#### ROLE OF THE PATIENT'S SEX

Another retrospective analysis of the DIG trial that included participants with only systolic heart failure, examined the effects of digoxin on mortality based on the sex of patients.<sup>16</sup> Overall, women in the DIG trial had a lower mortality rate than men (31 versus 36 percent). However, women randomized to receive digoxin had a higher mortality rate than women who received placebo (33.1 versus 28.9 percent;  $P = .034$ ; number needed to harm = 24).<sup>16</sup> The reason for this finding is unclear. Although female participants in the DIG trial were slightly older and had more comorbidities than their male counterparts, these factors are not thought to influence the effectiveness of digoxin therapy.<sup>17</sup> The instances of suspected digoxin toxicity and hospitalization were similar in men and women.<sup>16</sup>

#### Recommendations

New data questioning the effectiveness of digoxin for heart failure create a dilemma for physicians. Before these new data were published, digoxin was the only positive inotropic agent that had not been shown to increase mortality in patients with heart failure. This observation now must be reevaluated.

Although good evidence suggests that digoxin improves symptoms and reduces hospitalization in select patients with heart failure, recent data suggest that the use of higher serum digoxin concentrations in men and the use of digoxin at any concentration in women are associated with increased mortality.

#### APPROPRIATE PATIENT POPULATION

The ACC/AHA staging system for heart failure can be a useful tool when determining whether to initiate digoxin therapy. This staging system and corresponding NYHA functional classifications for heart failure are included in *Table 1*.<sup>10,18</sup>

According to ACC/AHA guidelines, patients with stage A heart failure have a high risk of heart failure based on comorbidities and medical history.<sup>10</sup> Patients with stage B heart failure have some component of structural heart disease but are asymptomatic, and patients with stage C heart failure

**TABLE 1**  
**Classification Systems for Heart Failure**

<i>ACC/AHA stages of heart failure</i> <sup>10</sup>	<i>NYHA functional classifications for heart failure</i> <sup>18</sup>
A: high risk of heart failure; no underlying structural cardiac disease (e.g., hypertension, diabetes, hyperlipidemia)	No correlation
B: asymptomatic structural heart disease (e.g., left ventricular hypertrophy)	I: no limitation of patient activities; ordinary physical activity causes no symptoms
C: structural heart disease with past or current symptoms of heart failure	II: slight or mild limitation of activity; comfortable at rest and with mild exertion III: marked limitation of activity; comfortable only at rest
D: refractory heart failure	IV: need for complete rest and confined to bed or chair; discomfort with any physical activity; symptoms occur at rest

ACC = American College of Cardiology; AHA = American Heart Association; NYHA = New York Heart Association.  
Information from references 10 and 18.

are currently symptomatic or have had previous heart failure symptoms with the same underlying structural abnormalities. Patients with stage D heart failure are refractory to conventional medical therapy and have end-stage heart failure symptoms.<sup>10</sup>

Available clinical trial data indicate that digoxin therapy for heart failure is most beneficial in symptomatic patients with enlarged hearts, poor pump function, and low ejection fractions (i.e., patients with stage C or D heart failure).<sup>9-12,14</sup> Digoxin therapy is unlikely to benefit patients with stage A or B heart failure. In these patients, it is important

to first implement risk factor reduction and then initiate therapy with ACE inhibitors and beta blockers when indicated. Therefore, it is reasonable to prescribe digoxin for symptomatic patients who are already undergoing adequate diuretic therapy and taking ACE inhibitors with or without beta blockers.<sup>10</sup>

### DOSING

Reanalysis of the DIG trial showed that mean serum digoxin concentrations of more than 1.0 ng per mL were associated with increased mortality. However, concentrations between 0.5 and 0.8 ng per mL were associated with decreased all-cause mortality.<sup>14</sup> This narrow range is based on retrospective data and would not be a practical target in a physician's day-to-day practice. A concentration range of 0.5 to 1.0 ng per mL would be a more practical goal.<sup>14,19</sup>

The recommended approach to digoxin therapy for patients with stage C or D heart failure (*Figure 1*<sup>10,15,19,20</sup>) is to empirically administer digoxin therapy without a loading dose and to use a low, once-daily dose to achieve a serum digoxin concentration between 0.5 and 1.0 ng per mL.<sup>14,15,19,20</sup>

### WOMEN

Although there was an inadequate number of women in the DIG trial to determine whether a specific serum digoxin concentration range was beneficial, or at least did not increase

mortality, it is premature to conclude that digoxin should never be used in women. It seems reasonable to initiate digoxin therapy in women only when they are clearly symptomatic despite receiving maximal treatment with more-proven agents such as diuretics (e.g., furosemide [Lasix]), ACE inhibitors or angiotensin-II receptor blockers and beta blockers.

### DIASTOLIC HEART FAILURE

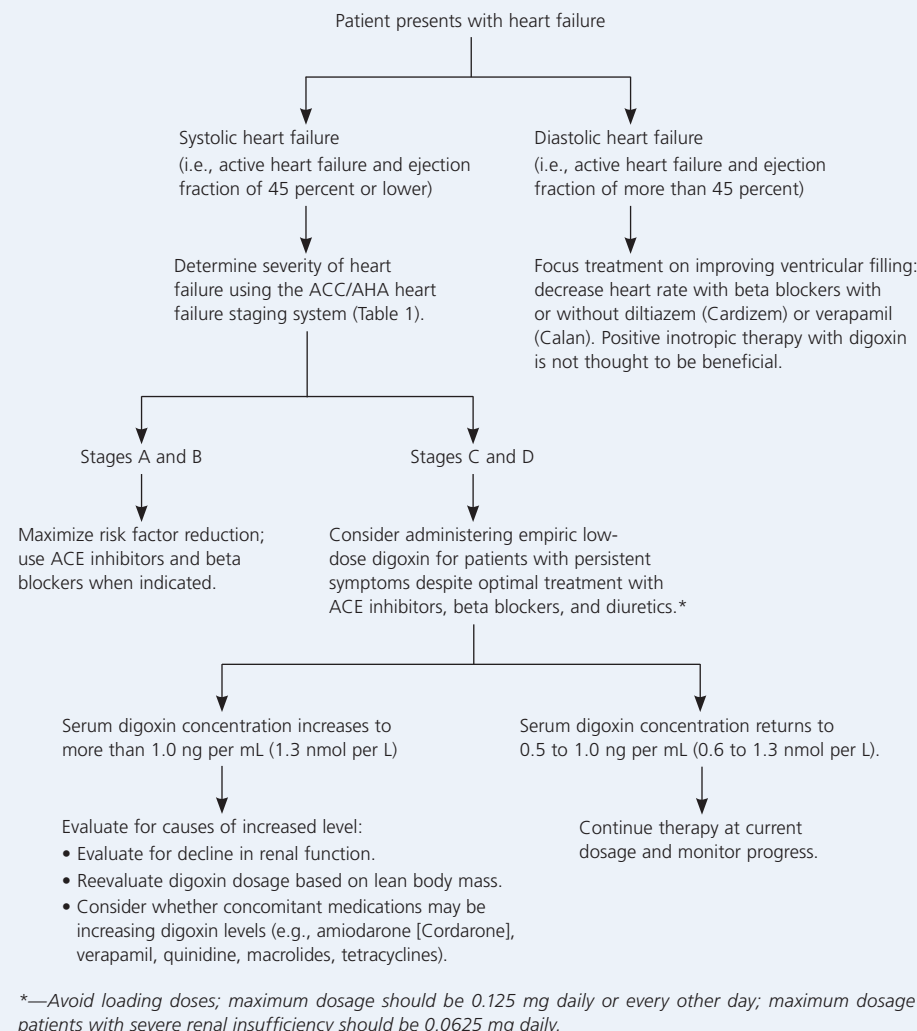
Another controversy regarding digoxin therapy is its role in the treatment of symptomatic diastolic dysfunction. The DIG ancillary trial demonstrated a trend toward decreased hospitalization and improved exercise performance in patients who received digoxin; however, these benefits were not statistically significant.<sup>9</sup> Diastolic heart failure treatment has been directed at modifying physiologic factors (e.g., decreasing heart rate, controlling blood pressure) because of the paucity of outcome data.<sup>21,22</sup> Pump function is relatively preserved in patients with diastolic heart failure, and inotropic therapy is usually not appropriate in this population. Clinical trials are underway to provide better guidelines for the treatment of diastolic heart failure; however, digoxin will not likely emerge as a standard therapy.<sup>21,22</sup>

### HEART FAILURE AND CONCOMITANT ATRIAL FIBRILLATION

Digoxin has electrophysiologic effects that decrease atrioventricular node conduction, making it potentially useful for controlling ventricular rates in patients with heart failure and concomitant atrial fibrillation. However, digoxin appears to be most effective in controlling heart rate at rest in this population. Large doses of digoxin often are required when digoxin is used alone, usually resulting in higher serum digoxin concentrations. The ACC/AHA guidelines<sup>10</sup> recommend adding a beta blocker to digoxin therapy instead of increasing digoxin doses to control atrial fibrillation with a rapid ventricular response, because higher serum digoxin concentrations are associated with increased adverse effects. Evidence suggests that using digoxin as a first-line agent for heart rate control may potentiate the shortening of the effective atrial

**Digoxin therapy for heart failure may be most beneficial in symptomatic patients with enlarged hearts, poor pump function, and low ejection fractions.**

## Digoxin Therapy for Heart Failure



**Figure 1.** Algorithm for managing heart failure with digoxin. (ACC = American College of Cardiology; AHA = American Heart Association; ACE = angiotensin-converting enzyme.)

Information from references 10, 15, 19, and 20.

refractory period, possibly facilitating short-term atrial fibrillation recurrence and increasing a patient's risk of future episodes.<sup>23</sup>

American Academy of Family Physicians (AAFP) and American College of Physicians (ACP) joint guidelines on managing newly detected atrial fibrillation do not apply to patients with NYHA class IV heart failure<sup>24</sup> but may be applied to patients with less severe symptoms. For patients with atrial fibrillation, the AAFP/ACP guidelines recommend the following drugs as first-line therapy for controlling heart rate during exercise and while at rest: atenolol (Tenormin), metoprolol (Toprol XL), diltiazem (Cardizem), and verapamil (Calan). Digoxin has only been

shown to effectively control heart rate at rest and, therefore, should only be used as a second-line therapy for heart rate control in patients with atrial fibrillation.<sup>10,24</sup>

### The Authors

SPENCER A. MORRIS, Pharm.D., B.C.P.S., is a clinical pharmacist with Georgetown (S.C.) Hospital System. He received a pharmacy degree from the University of South Carolina College of Pharmacy, Columbia, and completed a clinical pharmacy residency in family medicine at the McLeod Family Medicine Center, Florence, S.C.

H. FLOYD HATCHER, M.D., is clinical associate professor of family medicine and is associate director of residency education for the Self Regional Healthcare Family Practice Residency, Greenwood, S.C. He received a medical degree from the Medical University of South

Carolina, Charleston, and completed a family medicine residency at Self Memorial Hospital.

DEEPA K. REDDY, M.D., is a family physician in Tacoma, Wash. Dr. Reddy received a medical degree from the University of Mysore Adichunchanagiri Institute of Medical Sciences, Karnataka, India. She completed a family medicine residency at Self Regional Medical Center.

*Address correspondence to Spencer A. Morris, Pharm.D., B.C.P.S., Georgetown Hospital System, 606 Black River Rd., Georgetown, SC 29440 (e-mail: spenceamorris@aol.com). Reprints are not available from the authors.*

The authors thank William J. Hueston, M.D., and Lori M. Dickerson, Pharm.D., B.C.P.S., for their assistance in the preparation of this manuscript.

Members of various family medicine departments develop articles for "Clinical Pharmacology." This article is one in a series coordinated by Allen F. Shaughnessy, Pharm.D., and Andrea E. Gordon, M.D., of the Tufts University Family Medicine Residency, Malden, Mass.

Author disclosure: Nothing to disclose.

## REFERENCES

- Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. *J Am Coll Cardiol* 1992;20:248-54.
- Garg R, Yusuf S, for the Collaborative Group on ACE Inhibitor Trials. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure [Published correction appears in *JAMA* 1995;274:462]. *JAMA* 1995;273:1450-6.
- Foody JM, Farrell MH, Krumholz HM. Beta-blocker therapy in heart failure: scientific review. *JAMA* 2002;287:883-9.
- Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al., for the Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341:709-17.
- Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al., for the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction [Published correction appears in *N Engl J Med* 2003;348:2271]. *N Engl J Med* 2003;348:1309-21.
- The Captopril-Digoxin Multicenter Research Group. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. *JAMA* 1988;259:539-44.
- Packer M, Gheorghide M, Young JB, Costantini PJ, Adams KF, Cody RJ, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. *N Engl J Med* 1993;329:1-7.
- Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK, for the PROVED Investigative Group. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED Trial. *J Am Coll Cardiol* 1993;22:955-62.
- The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;336:525-33.
- Hunt SA. ACC/AHA 2005 guidelines for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure) [Published correction appears in *J Am Coll Cardiol* 2006;47:1503-5]. *J Am Coll Cardiol* 2005;46:e1-82.
- Jaeschke R, Oxman AD, Guyatt GH. To what extent do congestive heart failure patients in sinus rhythm benefit from digoxin therapy? A systematic overview and meta-analysis. *Am J Med* 1990;88:279-86.
- Terra SG, Washam JB, Dunham GD, Gattis WA. Therapeutic range of digoxin's efficacy in heart failure: what is the evidence? *Pharmacotherapy* 1999;19:1123-6.
- Beller GA, Smith TW, Abelmann WH, Haber E, Hood WB Jr. Digitalis intoxication. A prospective clinical study with serum level correlations. *N Engl J Med* 1971;284:989-97.
- Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM. Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA* 2003;289:871-8.
- Adams KF Jr, Gheorghide M, Uretsky BF, Patterson JH, Schwartz TA, Young JB. Clinical benefits of low serum digoxin concentrations in heart failure. *J Am Coll Cardiol* 2002;39:946-53.
- Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. *N Engl J Med* 2002;347:1403-11.
- Rich MW, McSherry F, Williford WO, Yusuf S, for the Digitalis Investigation Group. Effect of age on mortality, hospitalizations and response to digoxin in patients with heart failure: the DIG study. *J Am Coll Cardiol* 2001;38:806-13.
- The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass.: Little, Brown & Co, 1994:253-6.
- Klein L, O'Connor CM, Gattis WA, Zampino M, de Luca L, Vitarelli A, et al. Pharmacologic therapy for patients with chronic heart failure and reduced systolic function: review of trials and practical considerations [Published correction appears in *Am J Cardiol* 2003;92:1378]. *Am J Cardiol* 2003;91(9A):18F-40F.
- Shlipak MG. Pharmacotherapy for heart failure in patients with renal insufficiency. *Ann Intern Med* 2003;138:917-24.
- Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: part II: causal mechanisms and treatment. *Circulation* 2002;105:1503-8.
- Aurigemma GP, Gaasch WH. Clinical practice. Diastolic heart failure. *N Engl J Med* 2004;351:1097-105.
- Sticherling C, Oral H, Horrocks J, Chough SP, Baker RL, Kim MH, et al. Effects of digoxin on acute, atrial fibrillation-induced changes in atrial refractoriness. *Circulation* 2000;102:2503-8.
- Snow V, Weiss KB, LeFevre M, McNamara R, Bass E, Green LA, et al., for the AAFP Panel on Atrial Fibrillation; ACP Panel on Atrial Fibrillation. Management of newly detected atrial fibrillation: a clinical practice guideline from the American Academy of Family Physicians and the American College of Physicians. *Ann Intern Med* 2003;139:1009-17.