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Is digoxin a drug of the past?

■ ABSTRACT

Digoxin has been the cornerstone of the treatment of heart failure for more than 2 centuries. Now that newer therapies have been introduced that reduce the mortality rate in heart failure and recent trials have failed to prove the same for digoxin, its use has significantly decreased. But a careful review of the multiple pharmacologic actions of digoxin and closer analysis of the results of recent trials suggest that digoxin may in fact continue to be an effective treatment for heart failure.

■ KEY POINTS

In addition to its inotropic effects, digoxin has neurohormonal and autonomic actions that may play a beneficial role in heart failure.

In selected patients at higher risk, digoxin may prove an important adjunctive therapy, as it may reduce hospitalizations and treatment costs due to heart failure.

Recent subgroup analyses of the Digitalis Investigation Group trial data suggest that the same clinical benefits can be attained at lower target serum digoxin concentrations (< 1 ng/mL) than used in the past, with possible favorable effects on the mortality rates.

Digoxin is beneficial in heart failure irrespective of the patient's sex and systolic function.

CARDIAC GLYCOSIDES such as digoxin have been used for centuries, and concerns about their toxicity go back to the very beginning. Even William Withering, who discovered the medical uses of foxglove (*Digitalis purpurea*), was tentative with his conclusions when he presented his experience in his 1785 monograph *An Account of the Foxglove, and Some of its Medical Uses: With Practical Remarks on Dropsy and Other Diseases*, warning that physicians should use the drug very carefully.

Now that clinical trials have shown that angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blockers, angiotensin-receptor blockers (ARBs), and aldosterone antagonists all significantly reduce the mortality rate in heart failure—and other trials have suggested that digoxin does not—many physicians are wondering if digoxin has become a drug of the past.

We believe it has not, but to answer this question, we should first review the complex and multiple physiologic actions of digoxin, the results of the major clinical studies of digoxin, and the pathophysiology of heart failure.

■ DIGOXIN HAS MULTIPLE ACTIONS

The pharmacologic actions of digitalis and its descendants remained obscure for a long time. Withering considered digitalis a diuretic, and these drugs do have diuretic properties (see below). In 1938, Cattle and Gold first demonstrated that digitalis has direct inotropic effects, and this became the traditional understanding of its mechanism of action.

But the issue is more complex than that. Our understanding of the pathophysiology of heart failure and of the role of digitalis-type drugs in its treatment has changed drastically in recent years. In fact, digoxin has multiple hemo-

dynamic, neurohormonal, and electrophysiologic effects. These include the following:

Increases contractility. Digoxin reversibly inhibits the alpha subunit of sodium-potassium ATPase, the molecule that pumps sodium out of the cell while pumping potassium in (FIGURE 1). The normal transmembrane sodium gradient—a high concentration of sodium outside the cell, a low concentration inside—drives the action of another molecule, the sodium-calcium exchanger, which pumps calcium out of the cell. By inhibiting sodium-potassium ATPase, digoxin reduces the transmembrane sodium gradient and thus indirectly inhibits the sodium-calcium exchanger, allowing calcium to accumulate in cardiac myocytes and be taken up by the sarcoplasmic reticulum. Calcium is a key ion in muscle contraction, and with more calcium in the myocytes, the heart beats more forcefully: thus, the positive inotropic effect of digoxin.

This positive inotropic effect is more prominent in decompensated heart failure with systolic dysfunction. Stroke volume is increased, while ventricular filling pressures and end-systolic and end-diastolic volumes decrease. Digoxin is unique in that it increases contractility without increasing the heart rate.¹

Improves baroreceptor function and decreases sympathetic tone. Heart failure is characterized by decreased baroreceptor reflex sensitivity and a resultant generalized increase in sympathetic tone. Digoxin increases the sensitivity of baroreceptors, thereby leading to decreased sympathetic drive.²⁻⁴

Increases parasympathetic tone. Heart failure is also characterized by blunted parasympathetic tone. Digoxin increases parasympathetic tone,⁵ an effect that plays a key role in its electrophysiologic impact on the heart and that may have a survival benefit as well.⁶

Reduces neurohormone levels. Digoxin decreases plasma renin activity and serum aldosterone and plasma norepinephrine levels.^{7,8} These beneficial neurohormonal effects are evident even at low doses. In theory, digoxin may confer neurohormonal benefits at serum levels well below those traditionally needed for electrophysiologic or inotropic benefit and at a much lower risk of toxicity.

Reduces vascular tone. In patients with

heart failure, digoxin decreases systemic vascular resistance and venous tone.¹ This is likely an indirect effect mediated by the sympathetic activity of digoxin in heart failure. These effects are not seen in patients without heart failure, in whom digoxin has direct vasoconstrictor properties.⁹

Induces diuresis. Digoxin indirectly improves renal function by improving renal perfusion via its cardiac inotropic effects. It also has direct effects, inhibiting renal tubular sodium reabsorption by inhibiting the renal sodium-potassium ATPase pump.^{10,11}

Alters cardiac electrophysiology via a direct effect and also via its parasympathomimetic effect. The electrophysiologic properties of digoxin vary with its serum concentration. At low doses (with serum concentrations of 1–2 ng/mL) digoxin decreases automaticity, decreases atrioventricular nodal velocity, and prolongs the effective refractory period.¹² At higher (toxic) doses it increases automaticity, prolongs atrioventricular conduction, and causes bradycardia and heart block. The difference between a low and a high serum concentration is small: digoxin has a narrow therapeutic index.

■ MAJOR CLINICAL TRIALS OF DIGOXIN IN HEART FAILURE

During the last 2 decades, several nonrandomized and small randomized studies have shown digoxin to be effective in treating symptomatic heart failure. Of these, three studies stand out and have defined the way that we think about digoxin.

Digoxin withdrawal trials: PROVED and RADIANCE

The Prospective Randomized Study of Ventricular Failure and Efficacy of Digoxin (PROVED) involved 113 patients in heart failure (New York Heart Association [NYHA] functional class II or III) who already were receiving digoxin and a diuretic.¹³ In the experimental group of this randomized, double-blind study, digoxin was withdrawn and replaced by placebo. In these patients, left ventricular ejection fractions decreased, heart rates increased, serum creatinine concentrations rose, and exercise capacity fell. These

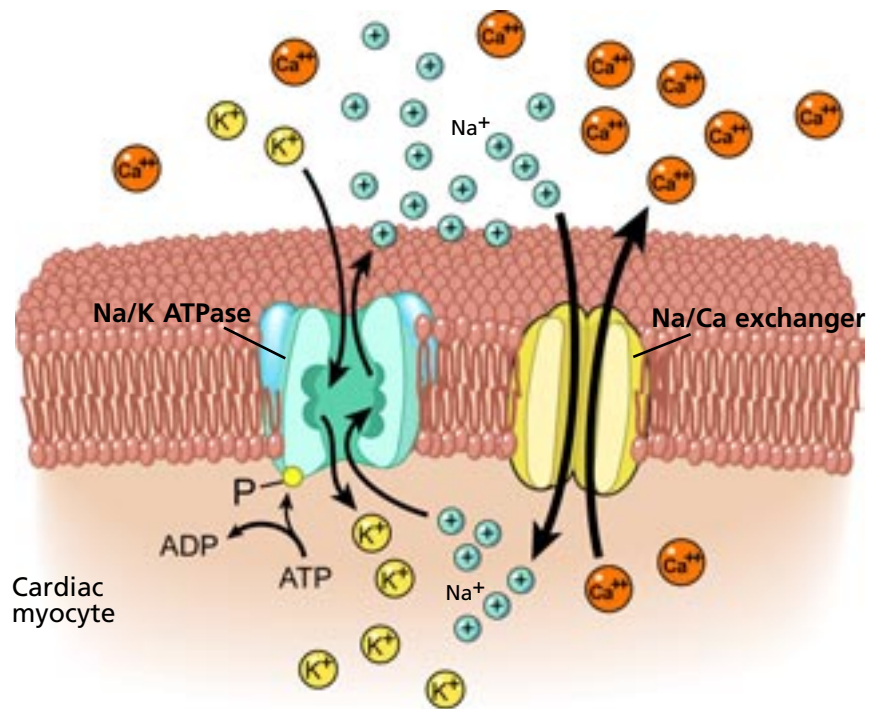
Understanding of heart failure and digoxin has changed drastically

■ Digoxin's mechanism of action

Digoxin's positive inotropic effect results from its ability to inhibit sodium-calcium exchange across the cell membrane, allowing calcium to accumulate in the myocytes. Calcium is a key ion for muscle contraction, and with more calcium in the myocytes, the heart beats more forcefully.

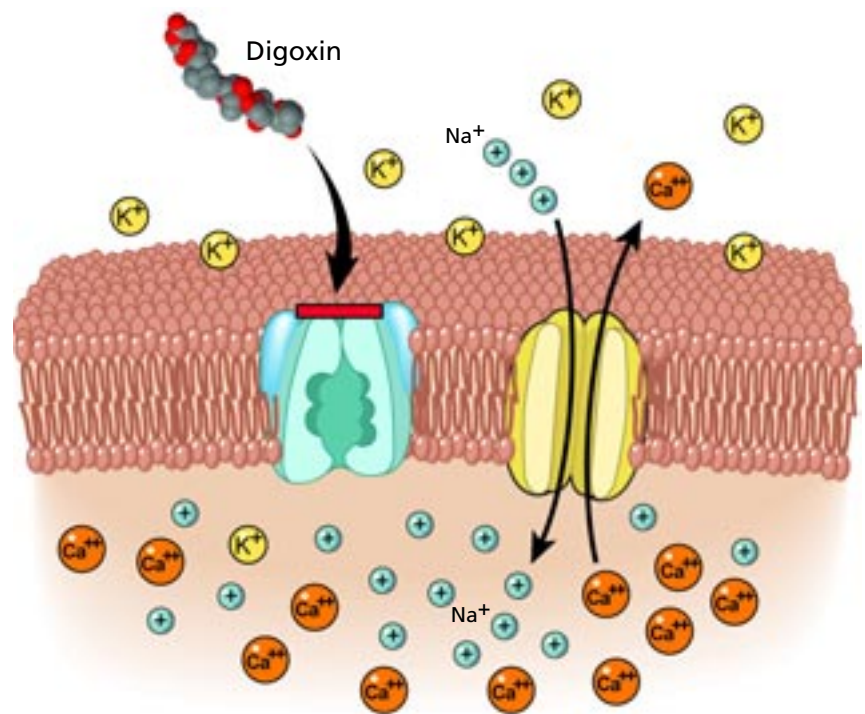
Normal physiology, calcium is removed

Sodium-potassium ATPase pumps sodium out of the cell while pumping potassium in, creating a high transmembrane sodium gradient. The transmembrane sodium gradient drives the sodium-calcium exchanger, which removes calcium from the cell.



With digoxin, calcium accumulates

Digoxin inhibits sodium-potassium ATPase, reducing the transmembrane sodium gradient and thus indirectly inhibiting the sodium-calcium exchanger, allowing calcium to accumulate in the cell.



CCF
Medical Illustrator: David Schumick ©2006

FIGURE 1

changes suggested that digoxin had been providing multiple benefits to these patients.

The Randomized Assessment of Digoxin and Inhibitors of Angiotensin-Converting Enzyme (RADIANCE), another randomized, double-blind, placebo-controlled study of digoxin withdrawal, involved 78 patients in NYHA functional class II or III heart failure who were already receiving digoxin, an ACE inhibitor, and a diuretic.¹⁴ Replacing digoxin with placebo had effects very similar to those in the PROVED trial. These observations suggested that digoxin was conferring benefits that were additive to those of neurohormonal blockade with an ACE inhibitor.

Economic assessment of PROVED and RADIANCE. In view of the adverse effects of discontinuing digoxin in these two trials, Ward et al¹⁵ assessed the theoretical cost savings of continuing digoxin treatment. They estimated that, even accounting for 12,500 cases of digoxin toxicity per year, continued digoxin treatment would result in 137,000 fewer hospital admissions and 212,000 fewer outpatient visits, at a net savings of \$406 million per year.

Only digoxin increases contractility without increasing the heart rate

The Digitalis Investigation Group (DIG) trial
The Digitalis Investigation Group (DIG) trial was the largest prospective randomized placebo-controlled trial to evaluate the effects of digoxin on clinical outcomes in heart failure patients who were in sinus rhythm.¹⁶ The main trial included 6,800 patients with left ventricular ejection fractions of 45% or less; an ancillary trial included 998 patients with left ventricular ejection fractions greater than 45%.

Notable findings (which were consistent in both groups) were:

- Most patients received an ACE inhibitor (94.4%), a diuretic (81.7%), or both (77.7%). Although the number of patients who received a beta-blocker is unknown, the DIG trial was conducted before beta-blockers became widely used in heart failure, so few patients likely received them.
- Digoxin did not reduce the rates of all-cause or cardiovascular mortality.
- There was no evidence of increased mortality due to digoxin use.
- The digoxin treatment group showed a

trend toward fewer deaths due to worsening heart failure.

- The digoxin group had statistically significantly lower rates of hospitalization for any cause and hospitalization for heart failure.
- Digoxin was more beneficial in patients who were at higher risk, ie, those with lower ejection fractions (< 25%), enlarged hearts, and in NYHA functional class III or IV.

Although fewer patients who received digoxin died of progressive heart failure, more of them died of sudden cardiac death, so that overall there was no net effect on the death rate. Nevertheless, it was good to find out that digoxin does not increase the total mortality rate, considering that all other inotropic drugs do. Digoxin was therefore established as a safe therapy to add on to baseline neurohormonal therapy, especially in patients at higher risk, with the goal of reducing heart failure hospitalizations or deaths from progressive heart failure.

Results in patients with diastolic heart failure. Heart failure with preserved systolic function (left ventricular ejection fraction > 45%) accounts for about 40% of cases of heart failure in the general population.¹⁷ In the 998 patients in the DIG trial who had left ventricular ejection fractions greater than 45%, digoxin use (in addition to an ACE inhibitor and a diuretic) resulted in an 18% risk reduction in the combined end point of death or hospitalization due to worsening heart failure.¹⁶ These results were consistent with those in the systolic dysfunction group.

■ CLINICAL USES OF DIGOXIN

Currently approved uses of digoxin are to treat atrial fibrillation (with or without heart failure) and to treat heart failure (with or without systolic dysfunction.)

Digoxin for atrial fibrillation

Digoxin is often used to control the ventricular heart rate in patients with atrial fibrillation with or without heart failure. Major benefits include once-daily dosing, low cost, and easy monitoring of blood levels, if required.

Use of digoxin as the sole agent for rate control has been losing favor because, although it reduces the resting heart rate, it

TABLE 1

Updated guidelines for the use of digoxin in heart failure: American College of Cardiology and American Heart Association, 2005

RECOMMENDATION	PREVIOUS CLASS* (2001)	UPDATED CLASS* (2005)	LEVEL OF EVIDENCE†
Digoxin should not be used in patients with low ejection fraction, sinus rhythm, and no history of heart failure symptoms because in this population the risk of harm is not balanced by any known benefit	III	III	C
Digoxin can be beneficial in patients with current or prior symptoms of heart failure and reduced left ventricular ejection fraction to decrease hospitalizations for heart failure	I	IIa	B
The usefulness of digoxin to minimize symptoms of heart failure in patients with heart failure and normal left ventricular ejection fraction is not well established	IIb	IIb	C
It is reasonable to prescribe digoxin to control the ventricular response rate in patients with heart failure and atrial fibrillation	IIa	IIa	A

*Class I: Evidence and/or general agreement in favor

Class II: Conflicting evidence and/or divergence of opinion

Class IIa: Weight of evidence/opinion is in favor

Class IIb: Usefulness or efficacy is less well established by evidence and opinion

Class III: Evidence and/or general agreement against

†Level of evidence A: Data derived from multiple randomized clinical trials or meta-analyses

Level of evidence B: Data derived from a single randomized trial, or nonrandomized studies

Level of evidence C: Only consensus opinion of experts, case studies, or standard-of-care

BASED ON HUNT SA, ABRAHAM WT, CHIN MH, ET AL. ACC/AHA 2005 GUIDELINE UPDATE 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). J AM COLL CARDIOL 2005; 46:e1-e82.

often does not control the rate during physical activity or adrenergic stress.¹⁸ However, a combination of digoxin and a beta-blocker is quite effective and is advocated for rate control in atrial fibrillation with rapid ventricular response. This combination is particularly helpful in patients with systolic dysfunction, in whom it was found to be more effective than either agent alone.¹⁹

The role of digoxin is less clear in atrial fibrillation with diastolic heart failure. Digoxin actually potentiates the shortening of the atrial effective refractory period and may predispose to short-term recurrences of atrial fibrillation and an increased risk of future episodes of atrial fibrillation,²⁰ suggesting that a beta-blocker alone may be a better choice for rate control in this situation.

Contrary to anecdotal belief, digoxin by itself clearly does not restore sinus rhythm in patients with atrial fibrillation without heart failure.²¹ Whether it has this benefit in patients with heart failure has not been studied, but it seems unlikely.²²

Digoxin for heart failure

These days, digoxin is being used less in heart failure patients than in the past, while ACE inhibitors and beta-blockers (which increase survival) are being used much more. In 1997 and 1998, when patients were enrolled in the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure,²³ 63% of them were receiving digoxin. A few years later, in the Cardiac Insufficiency Bisoprolol study (October 2002 to May 2005),²⁴ only 31% of patients were receiving it.

Although the recent update to the American College of Cardiology and American Heart Association guidelines for the management of chronic heart failure²⁵ still acknowledges a role for digoxin in controlling the heart rate in atrial fibrillation and in preventing recurrent hospitalizations in patients with heart failure, the strength of the recommendations has been weakened (TABLE 1). These changes reflect the current trends and waning enthusiasm for digoxin after the DIG trial found that it did not reduce the mortality rate.



Digoxin and the neurohormonal hypothesis of heart failure

According to the neurohormonal hypothesis, heart failure develops and progresses as a result of activation of endogenous neurohormones (eg, renin, angiotensin, aldosterone, and norepinephrine) and cytokines (eg, tumor necrosis factor alpha).^{26–28} Agents that block the excessive neurohormonal activation in heart failure, such as ACE inhibitors, beta-blockers, ARBs, and aldosterone antagonists, have consistently reduced the mortality rate, while inotropic agents such as phosphodiesterase inhibitors or beta-agonists have consistently increased it.

Digoxin, although a positive inotropic agent, is an exception, likely owing to its additional neurohormonal,⁵ negative chronotropic, and parasympathomimetic actions.^{8,29} What is unique about digoxin is that it has both inotropic effects (with potential adverse long-term consequences) and beneficial neurohormonal-blocking and autonomic properties (which may balance out the adverse effects). Digoxin therefore appears to have an ongoing role in the treatment of heart failure. While neurohormonal blockade with ACE inhibitors and beta-blockers has become the cornerstone of treatment, digoxin can still be added for additional benefit—with a few caveats.

■ DIGOXIN'S TOXICITY AND NARROW THERAPEUTIC INDEX

Digoxin's narrow therapeutic index has remained a cause of concern and is the major reason for morbidity and death associated with its use. Ventricular arrhythmias are the major cause of death due to digoxin toxicity. In the DIG trial,¹⁶ 11.9% of patients in the digoxin treatment group were found to have "suspected digoxin toxicity" compared with 7.9% in the placebo group.

Digoxin's toxicity is dose-dependent and is affected by multiple drug interactions (such as non-potassium-sparing diuretics, amiodarone, calcium channel blockers, spironolactone, and macrolide antibiotics).¹² In addition, digoxin is cleared by the kidneys, so toxicity often is the result of alterations in renal function.

Should serum digoxin levels be lower?

Would the results of these studies have been different if the serum digoxin concentrations had been lower?

Using the data from the PROVED and RADIANCE trials, Adams et al³⁰ analyzed the association between low (0.5–0.9 ng/mL), moderate (0.9–1.2 ng/mL), and high (> 1.2 mg/mL) serum digoxin concentrations and adverse clinical outcomes such as worsening heart failure, declining left ventricular ejection fraction, and declining exercise tolerance. There was no relationship between serum digoxin concentrations and any of these clinical outcomes, ie, the risk of worsening heart failure was the same at low and high serum digoxin concentrations.

These observations suggest that low or moderate serum digoxin concentrations are therapeutically as effective as high serum digoxin concentrations. This means that targeting a serum digoxin concentration lower than 1 ng/mL may provide the same clinical benefit as a serum digoxin concentration greater than 1, but with significantly less risk of the major toxic effects, which are dose-dependent (with increasing risk at concentrations greater than 1).

In the DIG trial, 1,171 men with systolic dysfunction in the digoxin treatment group were randomly selected to have their serum digoxin concentrations measured 1 month after enrollment. Using these data, Rathore et al³¹ performed a post hoc analysis to assess the clinical outcomes according to different serum digoxin concentrations. They divided these patients into three groups on the basis of three concentration ranges: 0.5 to 0.8, 0.9 to 1.1, and 1.2 ng/mL or higher. A multivariate Cox proportional hazards analysis was performed to find the independent association between the digoxin concentration and the all-cause mortality rate compared with the rate in 2,611 patients in the placebo group.

The results: at a mean follow-up of 37 months, the group with the lowest serum digoxin concentration had a 6.3% lower rate of death than in the placebo group, while those with the highest concentrations had an 11.5% higher rate than in the placebo group (TABLE 2).

If digoxin is used, it should be titrated to a serum concentration of 0.5 to 0.9 ng/mL

TABLE 2

Data from the Digitalis Investigation Group trial: Serum digoxin concentration and outcomes in patients with heart failure

	ALL-CAUSE MORTALITY (%)	CARDIOVASCULAR MORTALITY (%)	WORSENING HEART FAILURE MORTALITY (%)	ALL-CAUSE HOSPITALIZATION (%)	HOSPITALIZATION FOR WORSENING HEART FAILURE (%)	HOSPITALIZATION FOR DIGOXIN TOXICITY (%)
Placebo group	36.2	30.4	13.3	67.8	34.8	0.8
Digoxin group						
Serum digoxin concentration (ng/mL)*						
0.5–0.8	29.9 [†]	26.8	8.6 [†]	61.9 [†]	20.8 [†]	1.2
0.9–1.1	38.8	34.5	14.9	72.4	31.1	0.9
≥ 1.2	48.0 [†]	41.9 [†]	15.2	70.4	29.6	3.2 [†]

*Serum concentrations were measured at 1 month; mean follow-up was 37 months.

[†] $P < .05$ compared with placebo

ADAPTED FROM RATHORE SS, CURTIS JP, WANG Y, BRISTOW MR, KRUMHOLZ HM. ASSOCIATION OF SERUM DIGOXIN CONCENTRATION AND OUTCOMES IN PATIENTS WITH HEART FAILURE. JAMA 2003; 289:871–878.

This analysis suggests that digoxin may have a dose-dependent effect on mortality in heart failure. This makes sense: in theory, digoxin might still exert beneficial neurohormonal effects at a lower serum concentration but not be as toxic. However, as this analysis was post hoc, it is by nature limited and primarily hypothesis-generating. The patients with higher serum digoxin concentrations in this analysis were generally older and also had higher serum creatinine levels, and although these factors were incorporated into the multivariate model, other, unrecognized, confounding factors cannot be entirely ruled out. Nonetheless, it does raise the provocative possibility that titrating the digoxin dose to a serum concentration of 0.5 to 0.8 ng/mL might reduce the mortality rate.

These findings were confirmed in a more comprehensive post hoc analysis of the DIG trial data by Ahmed et al,^{32,33} who analyzed the mortality and hospitalization rates at different serum digoxin concentrations. This analysis included all patients ($n = 1,687$) for whom 1-month serum digoxin concentration data were available, including women and patients without systolic dysfunction.

Compared with patients receiving placebo, patients with serum digoxin concentrations of 0.5 to 0.9 ng/mL had lower rates of death (29% vs 33%, adjusted hazard ratio [HR]

0.77, 95% confidence interval [CI] 0.67–0.89, **FIGURE 2**); hospitalization for any cause (64% vs 67%, adjusted HR 0.85, 95% CI 0.78–0.92); and hospitalization for heart failure (23% vs 33%, adjusted HR 0.62, 95% CI 0.54–0.72).

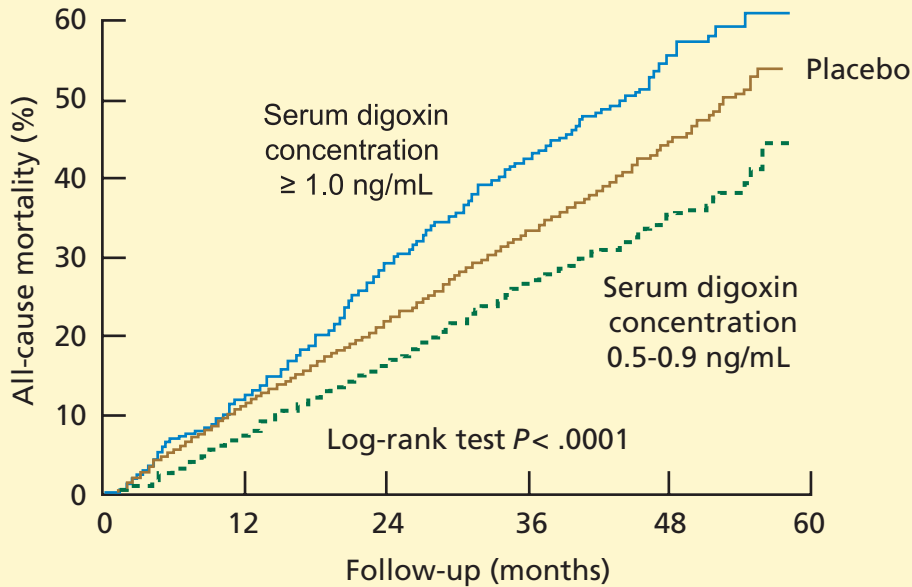
Patients with serum digoxin concentrations of 1 ng/mL or higher also had a lower rate of hospitalization for heart failure compared with patients receiving placebo. However, they did not have a lower mortality rate or a lower rate of all-cause hospitalization. In the group with concentrations of 0.5 to 0.9 ng/mL, the mortality rate was lower than in the placebo group in all subgroups studied except for nonwhites, and the effects were independent of ejection fraction.

It seems clear then that if digoxin is going to be used, it should be given in a dose to achieve a serum digoxin concentration between 0.5 and 0.9 ng/mL.

Digoxin initially distributes to the plasma and then redistributes to the tissues. In monitoring serum digoxin concentrations it is important not to draw the blood sample within 8 hours of a digoxin dose, as the level will be falsely high because this redistribution will not yet have taken place. In a recent review,³⁴ digoxin levels were found to have been erroneously obtained within this 8-hour window 32% of the time. If a true steady-state level is desired, the blood sample should be obtained



Digoxin: Beneficial at lower serum concentrations, harmful at higher concentrations?



No. at risk	0 month	12 months	24 months	36 months	48 months
Placebo	3861	3439	3080	2166	835
Digoxin 0.5-0.9	982	909	826	740	375
Digoxin ≥ 1.0	705	623	524	455	219

FIGURE 2. Kaplan-Meier plots for cumulative risk of death due to all causes by serum digoxin concentration (SDC) in the Digoxin Investigation Group (DIG) trial.

AHMED A, RICH MW, LOVE TE, ET AL. DIGOXIN AND REDUCTION IN MORTALITY AND HOSPITALIZATION IN HEART FAILURE: A COMPREHENSIVE POST HOC ANALYSIS OF THE DIG TRIAL. EUR HEART J 2006; 27:178-186. BY PERMISSION.

Digoxin levels may be falsely high if drawn < 8 hours after a dose

approximately 1 week after any change in dose, owing to the long (> 30-hour) half-life of digoxin.

Of note: all of the major trials of digoxin were performed before the use of beta-blockers in heart failure became widespread. It is therefore unknown whether digoxin exerts benefits in addition to those of beta-blockers. Since the benefits of digoxin are likely related to its neuromodulatory effects, a significant question remains as to the benefits of digoxin in the setting of beta-blockade.

■ DIGOXIN IN WOMEN VS MEN

Concerns were raised about the safety of digoxin in women when Rathore et al³⁵ performed a

post hoc subgroup analysis of the DIG trial data, showing that women who had heart failure with reduced ejection fraction who received digoxin had a higher rate of all-cause mortality than men. Using a subgroup interaction test for sex and digoxin on the primary outcome of all-cause mortality, there was a significant difference in effect between women and men (interaction $P = .034$), with women having a 4.2% higher mortality rate with digoxin treatment and men a 1.6% lower mortality rate with digoxin treatment. In the multivariate analysis, the increased risk achieved statistical significance in women (adjusted HR 1.23, 95% CI 1.02-1.47), while in men digoxin appeared mortality-neutral (adjusted HR 0.93, 95% CI 0.85-1.02).

More recently however, Adams et al³⁶ re-analyzed the DIG data using a multivariate Cox proportional hazards regression model and found that at lower serum digoxin concentrations (0.5–0.9 ng/mL), digoxin did not increase mortality in women. Moreover, low serum digoxin concentrations in women decreased the risk of hospitalization for worsening heart failure and the combined end point of mortality due to heart failure and hospitalization due to heart failure. Compared with women in the placebo group, women with concentrations greater than 1.2 ng/mL had a higher risk of death (similar to the association found in men by Rathore et al).

Practically, this analysis confirmed that the association between clinical outcomes and serum digoxin concentration in men with heart failure was also true for women treated with digoxin. It also suggested that the increased mortality in women in the DIG trial was related to higher serum digoxin concentrations in women, as suggested in an editorial that accompanied that report.³⁷

■ RECOMMENDATIONS: DIGOXIN IN HIGH-RISK PATIENTS

Although our understanding of and the treatment options for heart failure have changed since digitalis was first used in heart failure, digoxin can still be useful.

Because the DIG trial showed no lower death rate with digoxin and perhaps a higher death rate in women, enthusiasm for its use has waned. Further, the strong evidence of mortality benefit in heart failure with contemporary medical management with ACE inhibitors, beta-blockers, ARBs, and aldosterone antagonists has resulted in much less of an emphasis on digoxin and weaker recommendations for its use.

The recent, more-detailed analyses looking at the impact of serum digoxin concentrations have reopened the controversy. It remains possible that digoxin use at a low serum concentration might reduce mortality. Digoxin has complex pharmacologic properties that go well beyond inotropy and include beneficial neurohormonal and autonomic effects in heart failure. These beneficial effects are present at lower serum digoxin concentrations than traditionally used.

Where, then, should digoxin fit in the modern management of a patient with heart failure? The data for the benefit of neurohormonal-blocking agents (ACE inhibitors, ARBs, beta-blockers) are so strong that digoxin should not be considered a replacement for any of these medications. In patients with persistent heart failure symptoms, especially those who have high-risk features (left ventricular ejection fraction < 25%, markedly dilated ventricles, NYHA functional class III or IV), digoxin remains an attractive add-on agent. If carefully dosed to a serum concentration of 0.5 to 0.9 ng/mL, digoxin can reduce hospitalizations for heart failure and may additionally reduce the risk of death. It also may significantly reduce medical costs.

In heart failure patients with atrial fibrillation, digoxin plus a beta-blocker is an excellent combination for rate control.

Is digoxin a drug of the past? Considering the documented economic and clinical benefits of digoxin in reducing heart failure hospitalizations and deaths due to progressive heart failure, the suggestions of reduced mortality in some subgroups, and digoxin's cost-effectiveness and easy availability worldwide, the answer seems clear: digoxin should not be a drug of the past, but rather a drug of the present and probably of the future. ■

■ REFERENCES

1. **Mason D, Braunwald E.** Studies on digitalis: effects of ouabain on systemic vascular resistance and venous tone in normal subjects and in patients with heart failure. *J Clin Invest* 1964; 43:532–543.
2. **Hirsch AT, Dzau VJ, Creager MA.** Baroreceptor function in congestive heart failure: effect on neurohumoral activation and regional vascular resistance. *Circulation* 1987; 75:IV36–IV48.
3. **Higgins CB, Vatner SF, Eckberg DL, Braunwald E.** Alterations in the baroreceptor reflex in conscious dogs with heart failure. *J Clin Invest* 1972; 51:715–724.
4. **Thames MD, Miller BD, Abboud FM.** Sensitization of vagal cardiopulmonary baroreflex by chronic digoxin. *Am J Physiol* 1982; 243:H815–H818.
5. **Krum H, Bigger JT Jr, Goldsmith RL, Packer M.** Effect of long-term digoxin therapy on autonomic function in patients with chronic heart failure. *J Am Coll Cardiol* 1995; 25:289–294.
6. **Osterziel KJ, Hanlein D, Dietz R.** Interactions between the renin-angiotensin system and the parasympathetic nervous system in heart failure. *J Cardiovasc Pharmacol* 1994; 24(suppl 2):S70–S74.
7. **Gheorghiadu M, Hall V, Lakier JB, Goldstein S.** Comparative hemodynamic and neurohormonal effects of intravenous captopril and digoxin and



- their combinations in patients with severe heart failure. *J Am Coll Cardiol* 1989; 13:134–142.
8. **Covit AB, Schaer GL, Sealey JE, Laragh JH, Cody RJ.** Suppression of the renin-angiotensin system by intravenous digoxin in chronic congestive heart failure. *Am J Med* 1983; 75:445–447.
 9. **Ross J Jr, Waldhausen JA, Braunwald E.** Studies on digitalis. I. Direct effects on peripheral vascular resistance. *J Clin Invest* 1960; 39:930–936.
 10. **Katz AI.** Renal Na-K-ATPase: its role in tubular sodium and potassium transport. *Am J Physiol* 1982; 242:F207–F219.
 11. **Nelson JA, Nechay BR.** Effects of cardiac glycosides on renal adenosine triphosphatase activity and Na⁺ reabsorption in dogs. *J Pharmacol Exp Ther* 1970; 175:727–740.
 12. **Rocco T, Fang JC.** Pharmacologic treatment of heart failure. In: Brunton L, Lazo J, Parker K, editors. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. New York: McGraw-Hill, 2006:869–898.
 13. **Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK.** Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. PROVED Investigative Group. *J Am Coll Cardiol* 1993; 22:955–962.
 14. **Packer M, Gheorghiade M, Young JB, 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.
 15. **Ward RE, Gheorghiade M, Young JB, Uretsky B.** Economic outcomes of withdrawal of digoxin therapy in adult patients with stable congestive heart failure. *J Am Coll Cardiol* 1995; 26:93–101.
 16. **The Digitalis Investigation Group.** The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997; 336:525–533.
 17. **Adams KF Jr, Fonarow GC, Emerman CL, et al.** Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2005; 149:209–216.
 18. **Redfors A.** The effect of different digoxin doses on subjective symptoms and physical working capacity in patients with atrial fibrillation. *Acta Med Scand* 1971; 190:307–320.
 19. **Khand AU, Rankin AC, Martin W, Taylor J, Gemmell I, Cleland JG.** Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? *J Am Coll Cardiol* 2003; 42:1944–1951.
 20. **Sticherling C, Oral H, Horrocks J, et al.** Effects of digoxin on acute, atrial fibrillation-induced changes in atrial refractoriness. *Circulation* 2000; 102:2503–2508.
 21. **Falk RH, Knowlton AA, Bernard SA, Gotlieb NE, Battinelli NJ.** Digoxin for converting recent-onset atrial fibrillation to sinus rhythm. A randomized, double-blinded trial. *Ann Intern Med* 1987; 106:503–506.
 22. **Golzari H, Cebul RD, Bahler RC.** Atrial fibrillation: restoration and maintenance of sinus rhythm and indications for anticoagulation therapy. *Ann Intern Med* 1996; 125:311–323.
 23. **Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF).** *Lancet* 1999; 353:2001–2007.
 24. **Willenheimer R, van Veldhuisen DJ, Silke B, et al.** Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. *Circulation* 2005; 112:2426–2435.
 25. **Hunt SA, Abraham WT, Chin MH, et al.** ACC/AHA 2005 Guideline Update 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). *J Am Coll Cardiol* 2005; 46:e1–e82.
 26. **Francis GS, Cohn JN, Johnson G, Rector TS, Goldman S, Simon A.** Plasma norepinephrine, plasma renin activity, and congestive heart failure. Relations to survival and the effects of therapy in V-HeFT II. The V-HeFT VA Cooperative Studies Group. *Circulation* 1993; 87(suppl 6):VI40–VI48.
 27. **Francis GS.** Neurohumoral activation and progression of heart failure: hypothetical and clinical considerations. *J Cardiovasc Pharmacol* 1998; 32(suppl 1):S16–S21.
 28. **Benedict CR, Johnstone DE, Weiner DH, et al.** Relation of neurohumoral activation to clinical variables and degree of ventricular dysfunction: a report from the Registry of Studies of Left Ventricular Dysfunction. SOLVD Investigators. *J Am Coll Cardiol* 1994; 23:1410–1420.
 29. **Gheorghiade M, Ferguson D.** Digoxin. A neurohormonal modulator in heart failure? *Circulation* 1991; 84:2181–2186.
 30. **Adams KF Jr, Gheorghiade M, Uretsky BF, Patterson JH, Schwartz TA, Young JB.** Clinical benefits of low serum digoxin concentrations in heart failure. *J Am Coll Cardiol* 2002; 39:946–953.
 31. **Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM.** Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA* 2003; 289:871–878.
 32. **Ahmed A, Aban IB, Weaver MT, Aronow WS, Fleg JL.** Serum digoxin concentration and outcomes in women with heart failure: a bi-directional effect and a possible effect modification by ejection fraction. *Eur J Heart Fail* 2005; 8:409–419.
 33. **Ahmed A, Rich MW, Love TE, et al.** Digoxin and reduction in mortality and hospitalization in heart failure: a comprehensive post hoc analysis of the DIG trial. *Eur Heart J* 2006; 27:178–186.
 34. **Sidwell A, Barclay M, Begg E, Moore G.** Digoxin therapeutic drug monitoring: an audit and review. *N Z Med J* 2003; 116:U708.
 35. **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; 347:1403–1411.
 36. **Adams KF Jr, Patterson JH, Gattis WA, et al.** Relationship of serum digoxin concentration to mortality and morbidity in women in the Digitalis Investigation Group trial. A retrospective analysis. *J Am Coll Cardiol* 2005; 46:497–504.
 37. **Young JB.** Whither Withering's legacy? Digoxin's role in our contemporary pharmacopeia for heart failure. *J Am Coll Cardiol* 2005; 46:505–507.
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