Despite more than 200 years of research, the role of digoxin in contemporary medicine remains controversial. It is an old drug but with a remarkably sophisticated and rather modern pharmacological profile. It was the first neuroendocrine modulator to enhance parasympathetic tone and possibly reduce sympathetic activity. It is the only available oral inotropic agent. It is probably also a diuretic. In common with many other agents for heart failure, good dose-ranging studies have not been conducted, and the optimal dose is uncertain. Well-designed randomized controlled trials conducted in the pre-β-blocker era suggested that digoxin could improve symptoms and exercise capacity, but a large trial that enrolled patients mostly with mild symptoms suggested no overall effect on mortality, although it did report a substantial (28%) reduction in hospitalization for worsening heart failure. A small increase in sudden death was balanced by a reduction in death from worsening heart failure. Whether these benefits were mediated by changes in autonomic tone, in heart rate, in sodium balance, or through inotropic effects is unclear.

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At this time, the clinical community’s attention turned from the potential, but still equivocal, effects of digoxin on morbidity and mortality to the striking benefits of aldosterone receptor antagonists and β-blockers and, subsequently, cardiac resynchronization therapy on prognosis. Digoxin became largely ignored in discussions and debate, its use declined rapidly (Table and Figure), and the role of digoxin for managing heart failure was left unresolved.

The benefits of angiotensin-converting enzyme inhibitors, β-blockers, and aldosterone antagonists could simply be so overwhelming that any additional benefit from digoxin is swamped. However, in epidemiologically representative populations, the prognosis of heart failure remains poor. Most patients who have experienced an episode of worsening heart failure requiring hospitalization or who have an N-terminal prohormone brain natriuretic peptide that is persistently above 1500 pg/mL will be dead within 3 years. We are simply not doing as well as some would like to think. A combination of better monitoring, improved pharmacological interventions, more aggressive device strategies, and ultimately replacement of organ function or, alternatively, improved palliative care will be required to manage the growing size and complexity of the population with heart failure.

Is the role of digoxin for the contemporary management of heart failure undervalued? One potential mechanism of benefit of digoxin is simply to reduce ventricular rate. This is regarded as its principal mode of action in patients with atrial fibrillation, the group of patients in whom the benefits of digoxin are most widely accepted. The concept that β-blockers might eliminate the need for digoxin in patients with atrial fibrillation and heart failure was the rationale for the Carvedilol Atrial Fibrillation Evaluation (CAFÉ) study. However, rather than suggesting that digoxin was redundant, the study suggested that there might be synergistic benefits between digoxin and carvedilol. Circumstantial evidence of possible benefit mediated through a reduction in heart rate might come from a large ongoing trial named Systolic Heart Failure Treatment with I Inhibitor Ivabradine Trial (SHIFT) that investigates the effects of ivabradine, a sinus node inhibitor causing further reduction in heart rate in patients with heart failure already treated with β-blockers. If this study shows that further reductions in heart rate are associated with benefit, the question of whether digoxin or ivabradine is the preferred method to reduce heart rate or, indeed, whether all 3 rate-lowering agents should be used in combination, at least for those patients with inadequate rate control in sinus rhythm, will arise. Subgroup analyses of studies of β-blockers suggest that the effects of carvedilol are similar in the presence or absence of digoxin, although this seems not to be the case for β1-receptor selective agents. There were too few patients on β-blockers in the Digitalis Investigation Group (DIG) study to allow any insight into the potential benefits of adding β-blockers to digoxin for patients in sinus rhythm. There are reasons other than heart rate control to suggest that digoxin might be more effective in the presence of a β-blocker. β-blockers, especially nonselective ones that attenuate stress-induced reductions in serum potassium, might neutralize the increase in sudden death associated with the use of digoxin. Aldosterone antagonists also increase serum potassium, which may also reduce the rhythmogenic potential of digoxin. In the Randomized Aldactone Evaluation Study (RALES) trial, spironolactone tended to exert a greater reduction in mortality among patients treated with digoxin. Perhaps, concomitant therapy has at last evolved to the point where the full benefits of digoxin can be exploited, but final proof is still lacking.

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**Editors' Note**

For more information on this topic, please visit http://circheartfailure.ahajournals.org.
Although most people’s attention turned to new developments in pharmacology and device therapy, others continued to analyze the data acquired from the substantial randomized controlled trials of digoxin. These analyses suggested that lower-than-conventional doses of digoxin might deliver all the benefits of treatment and avoid toxicity. It seems that, just as with many modern drugs, the dose with optimal risk/benefit ratio is uncertain. Concomitant therapy with β-blockers and aldosterone antagonists and use of lower doses of digoxin could radically alter the risk/benefit ratio for digoxin in a favorable direction.

Digoxin, if it is effective, has some unique advantages compared with the existing heart failure medications. Provided toxicity is avoided, digoxin is remarkably free of side effects. Unlike other interventions for heart failure, except cardiac resynchronisation therapy, digoxin increases systolic blood pressure. A low arterial pressure is a bad prognostic sign. As renal autoregulation in heart failure is defective, lowering arterial pressure may impair renal function. Unlike angiotensin converting enzyme inhibitors and aldosterone antagonists, digoxin does not worsen renal function. Unlike β-blockers, it does not cause fatigue, and although the evidence that digoxin improves quality of life is not robust, the evidence for β-blockers is not that strong either.

Clearly, we need more evidence. In this issue of *Circulation: Heart Failure*, Georgiopoulou et al set out to address this need by analyzing the outcome in a population of relatively young patients with severe heart failure being assessed for heart transplantation. However, patient characteristics were quite unlike most patients included in the large randomized trials, which recruited patients who were predominantly 60 years or older and in the New York Heart Association class II/III. In the DIG study, the most striking benefits on heart failure events were in patients aged 70 years or older. None of the tests for interaction between age and the effects of digoxin were statistically significant, but there was a trend to an increase in mortality among patients aged <60 years assigned to digoxin rather than placebo, which was due to reasons other than death from heart failure, presumably an excess of sudden death. This might be assumed to reflect more aggressive dosing and higher serum digoxin concentration in this group. Data from the DIG trial support the former assumption but refute the latter. Most patients in this study who were treated with digoxin had a worse prognosis than those who were not. This did not seem to be true if the patient was in atrial fibrillation. The most likely explanation for this anomaly is that those in atrial fibrillation were treated to optimize ventricular rate control, whereas those in sinus rhythm received digoxin because they were sicker. Similar
observations have been made in large clinical trials but have been attributed to confounding by indication.\textsuperscript{53} Indeed, in the DIG study, being on digoxin before randomization was a risk factor for subsequent hospitalization for worsening heart failure regardless of assigned treatment.\textsuperscript{54} In this study, many patients stopped digoxin because they improved and many patients started digoxin because they deteriorated. Not surprisingly, a time-dependent analysis also suggested a worse outcome in patients receiving digoxin. The authors correctly identified that the adverse outcomes of patients treated with digoxin could be biased and reflect confounding by indication and tried to correct for such biases by using Seattle Heart Failure Scores and propensity analyses.

However, there is a fundamental flaw in the propensity analysis methodology, especially when it is applied to the investigation of the effects of treatment in an observational rather than a randomized study. If the intervention being studied improves patient characteristics that are also powerful predictors of outcome and then uses these to match patients who are or are not receiving the treatment, then patients with an intrinsically poorer prognosis and receiving the intervention will inevitably be matched to patients with a better prognosis. For instance, in the Cardiac Resynchronization—Heart Failure Study (CARE-HF), improvements in echocardiographic variables, reductions in natriuretic peptides, and increases in blood pressure with therapy were all associated with a better outcome but predicted only a small proportion of the impact of cardiac resynchronization on long-term morbidity and mortality.\textsuperscript{56} The same may or may not be true for digoxin.

The authors suggest use of registry data or new randomized controlled trials to determine the future role of digoxin. This article should act as a warning about the dangers of making inferences from observational data. Outcomes on treatment should not be confused with the response to therapy.\textsuperscript{57} Giving people who are well a treatment they do not need will usually be associated with a good outcome even though they have

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Table. Continued

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had no response to the intervention. On the other hand, a very sick patient may have a substantial response to an intervention but nonetheless die within 1 or 2 years. This patient has a poor outcome and, yet, if destined to die within weeks without the intervention, he/she may be considered to have had a good response. In the final analysis, further substantial randomized controlled trials are required to find out whether digoxin has a role in contemporary management of patients with heart failure in sinus rhythm. Ideally, these trials should address the issue of dose, seek surrogate measures that predict the effect of treatment on prognosis, even though previous studies have failed, and measure meaningful outcomes such as symptoms, quality of life, and longevity. A proposal for a large study that would address most of these points is currently being considered for funding in Europe.

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Disclosures

None.

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Digoxin: Quo Vadis?
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