

Does digoxin decrease morbidity for those in sinus rhythm with heart failure?

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EVIDENCE-BASED ANSWER

In patients with congestive heart failure due to systolic dysfunction who are in normal sinus rhythm, digoxin therapy reduces rates of hospitalization, as well as clinical deterioration, defined as worsening New York Heart Association (NYHA) classification or an increase in clinical signs and symptoms (strength of recommendation [SOR]: **A**, systematic review of randomized controlled trials [RCT]).¹ These benefits appear to be more pronounced for men.²

Patients treated with digoxin are at increased

risk of developing supraventricular dysrhythmias and second- or third-degree atrioventricular block (SOR: **A**, large RCT).³ It is unclear if patients with diastolic dysfunction experience similar benefits or harms (SOR: **A**, systematic review of RCTs).¹ Digoxin has not been shown to have any effect on mortality for men with congestive heart failure in sinus rhythm (SOR: **A**, systematic review of RCTs).¹ Digoxin use for women may be associated with an increased risk of mortality² (SOR: **B**, extrapolation from RCT).

CLINICAL COMMENTARY

Digoxin unlikely to benefit most patients with mild heart failure

It is clear that ACE inhibitors, diuretics, and beta-blockers should all be the first drugs chosen for therapy for patients with CHF. They have not only been shown to improve mortality and reduce symptoms but they do not carry any of the significant risks associated with digoxin toxicity.

Digoxin is unlikely to benefit patients with Class I heart failure, as their risk of clinical

deterioration and hospitalizations are low. However, for patients who cannot tolerate any of the first-line drugs or who remain symptomatic while taking them, digoxin carefully dosed and monitored is a useful adjunct in practice.

While it is true that these patients need periodic laboratory monitoring, by the time they require digoxin therapy, their visits for care are already frequent and they would likely require few, if any, additional visits.

■ Evidence summary

A recent Cochrane systematic review summarizes the clinical effects of digoxin when used for patients with heart failure in normal sinus rhythm. Thirteen studies including 7896 participants, most of whom had systolic dysfunction, met the criteria for inclusion. Ninety-four percent of all study participants came from a single large randomized placebo-controlled trial.³ Because the studies did not all measure the same outcomes, subgroup analyses were performed.

Four studies with 1096 participants contributed to the findings on clinical sta-

tus, 12 studies with 7262 participants contributed to the findings of hospitalization and 8 studies including 7755 patients contributed to the data on mortality. Patients receiving digoxin experienced reduced rates of hospitalization due to worsening heart failure (odds ratio [OR]=0.68; 95% confidence interval [CI], 0.61–0.75; number needed to treat [NNT]=13–17) and less clinical deterioration (OR=0.31; 95% CI, 0.21–0.43; NNT=3–61). The wide range in NNT for the reduction in clinical deterioration reflects varying baseline rates of worsening clinical status found among the 12

studies for patients receiving placebo. The narrow CI associated with the odds ratio for reduced rates of clinical deterioration reflects the fact that the majority of patients whose clinical status was evaluated as an outcome came from a single large study, the DIG trial.³ This trial followed 6800 patients with NYHA classifications I to III. Ninety-four percent of patients in this trial were additionally on angiotensin-converting enzyme (ACE) inhibitors and 82% were taking diuretics. Patients were followed for a mean of 37 months.

A subgroup analysis of 988 patients with diastolic dysfunction (ejection fraction >45%) in this study³ suggested no clear benefits or harms when digoxin was used in combination with other therapies vs placebo; however, it did show a positive trend towards the combined outcome of reduced hospitalizations and less clinical deterioration (relative risk [RR]=0.82; 95% CI, 0.63–1.07). Increased rates of supraventricular dysrhythmias (RR=2.08; 95% CI, 1.44–2.99; number needed to harm [NNH]=77) and second- and third-degree heart block were demonstrated for patients receiving digoxin (RR=2.93; 95% CI, 1.61–5.34; NNH=125). There was no difference in mortality between patients receiving digoxin or those receiving placebo (OR=0.98; 95% CI, 0.89–1.09).¹

A post-hoc subgroup analysis focusing only on sex-based differences in the DIG trial suggested women benefit less than men from reduced hospitalizations: -4.2% (95% CI, -8.9 to 0.5) vs -8.9% (95% CI, -11.4 to -6.5) ($P=.053$).² When a multivariable analysis was performed, digoxin use for women was associated with a higher risk of mortality (adjusted hazard ratio vs placebo=1.23; 95% CI, 1.02–1.47).²

Two randomized controlled withdrawal studies, in which patients who were being treated with digoxin had it discontinued, were also included in the systematic review. These patients' clinical outcomes were then compared with persons who had continued to receive digoxin for the duration of the trial. Six parallel design studies, in which patients taking digoxin underwent

a washout period before being randomized to either digoxin or placebo, were also included in the evaluation of digoxin's effect on clinical status. Because these patients had already demonstrated the ability to tolerate digoxin, these studies may have been biased in favor of digoxin.^{4,5}

Recommendations from others

The American College of Cardiology/American Heart Association⁶ and Heart Failure Society of America⁷ guidelines both recommend that digoxin be used in NYHA class II–III patients in sinus rhythm who remain symptomatic on standard therapy (described as ACE inhibitors, diuretics, and beta-blockers). Guidelines from the Scottish Intercollegiate Society,⁸ the European Society of Cardiology,⁹ and the American Medical Directors Association¹⁰ all offer similar recommendations. ■

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FAST TRACK

Digoxin should be used in NYHA Class II–III patients in sinus rhythm who remain symptomatic on standard therapy