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

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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. 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 status, 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. 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 study 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. ■

**References**


