Digoxin reduced hospitalizations in patients with heart failure and normal sinus rhythm


Objective
To determine the effect of digoxin on mortality and hospitalization for heart failure in patients with heart failure and normal sinus rhythm.

Design
Randomized, double-blind, placebo-controlled trial with mean 37-month follow-up.

Setting
302 clinical centers in the United States and Canada.

Patients
The main trial included 6800 patients (mean age 63 y, 78% men) with heart failure, left ventricular ejection fraction (LVEF) ≤ 0.45, and a normal sinus rhythm. Most patients were receiving angiotensin-converting enzyme (ACE) inhibitors and diuretics. 988 patients with heart failure and a LVEF > 0.45 were enrolled in an ancillary trial. Patients were included whether they had already been treated with digoxin.

Intervention
Patients were stratified by center and LVEF. In the main trial, 3397 patients were allocated to digoxin and 3403 to placebo. The initial digoxin dose was based on the patient’s age, sex, weight, and renal function. Investigators were allowed to modify the dose and were encouraged to give patients ACE inhibitors. Patients were assessed at 4 and 16 weeks and every 4 months thereafter.

Main outcome measures
The primary outcome was total mortality. Secondary outcomes were mortality from cardiovascular causes and worsening heart failure; hospitalization for worsening heart failure; and hospitalization for other causes, particularly digoxin toxicity.

Main results
Mortality (overall and from cardiovascular causes) did not differ between groups. 1181 deaths occurred in the digoxin group compared with 1194 deaths in the placebo group (34.8% vs 35.1%, P = 0.8). Compared with the placebo group, the digoxin group had lower rates of hospitalizations overall (P < 0.006), for worsening heart failure (P < 0.001), and for cardiovascular causes (P < 0.001) (Table). More patients in the digoxin group were hospitalized for digoxin toxicity than in the placebo group (P < 0.001). Subgroup analyses suggested a greater benefit among patients at high risk (i.e., those with lower LVEFs, enlarged hearts, and more severe New York Heart Association [NYHA] functional class). Ancillary trial results were consistent with the main trial.

Conclusion
Digoxin did not affect mortality but reduced hospitalizations in patients with heart failure and normal sinus rhythm.

Drug therapy in patients with congestive heart failure has been extensively studied. The Study of Left Ventricular Dysfunction (SOLVD) trial (1) showed that the ACE inhibitor enalapril reduced mortality and hospitalizations. The Evaluation of Losartan in the Elderly (ELITE) trial (2) suggested that treatment with an angiotensin II inhibitor caused reductions in morbidity and mortality. These issues were examined for the use of digoxin in this study of 6800 patients with heart failure, sinus rhythm, and an LVEF of ≤ 45%. Digoxin or a placebo was added to an ACE inhibitor (94%) and diuretics (82%). Mortality did not differ between the 2 groups. Previous studies with inotropic agents actually showed increased mortality.

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References

Abstract and Commentary also published in ACP Journal Club. 1997;127:34.