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Digoxin's effect on mortality and hospitalization in heart failure: implications of the DIG study

The DIG study showed that digoxin does not reduce the overall mortality rate, but is still useful in improving symptoms and reducing hospitalization

Cardiac glycosides (ie, digitalis and its congeners, notably digoxin) have been used for more than 200 years to treat heart failure. In recent years, the introduction of angiotensin-converting enzyme (ACE) inhibitors and beta blockers has led to controversy regarding the use of digoxin. On one hand, recent studies demonstrated that digoxin decreases symptoms, increases exercise capacity and ejection fraction, corrects neurohormonal abnormalities, improves quality of life, and decreases the need for hospitalization.[1–7] Conversely, digoxin is perceived as a potentially toxic, weak inotropic agent whose role may be redundant now that ACE inhibitors are available.[8] No study has demonstrated that digoxin increases survival in heart failure.

In a survey of American physicians, only 7% said they use digoxin as the initial drug for heart failure, one third believed that it prolongs survival, and two thirds believed that it improves exercise capacity.[9] Although digoxin is one of the most commonly prescribed drugs worldwide, its patterns of use vary from country to country: low in the United Kingdom, high in Scandinavia, and moderate in the United States.

To clarify whether digoxin reduces mortality and morbidity in heart failure, the National Heart Lung and Blood Institute and the Department of Veteran's Affairs sponsored the world's largest clinical trial in heart failure: the DIG study.[10]

DESIGN OF THE DIG STUDY

The DIG study was a double-blind, randomized, collaborative, international trial of nearly 8000 patients with congestive heart failure. The Digitalis Investigation Group (DIG) consisted of 302 clinical centers in the United States and Canada. The main trial enrolled 6800 patients with all classes of heart failure and a left ventricular ejection fraction of 45% or less. An ancillary trial enrolled 988 patients with heart failure and a left ventricular ejection fraction greater than 45%.

The diagnosis of heart failure was based on clinical assessment of low cardiac output or of congestion. Cardiac catheterization, follow-up exercise testing, and follow-up measurements of left ventricular ejection fraction were not included in the study. The primary endpoint was mortality; the secondary endpoints were deaths from cardiovascular causes, deaths from worsening heart failure, hospitalizations for worsening heart failure, and hospitalizations for other causes.

Most patients had moderate heart failure:

84% were in New York Heart Association functional class II or III. Ninety-five percent were taking an ACE inhibitor, 82% were taking diuretics, and 44% were previously treated with digoxin. The recruitment period was 3 years, and the follow-up period extended an additional 2 years.

Patients were randomly assigned to receive digoxin or placebo. An algorithm was used to determine the dose of digoxin on the basis of age, sex, weight, and renal function; the investigators were allowed to modify the dose on the basis of clinical judgment. Seventy percent of patients received 0.25 mg per day, and another 17% received 0.125 mg per day.

RESULTS OF THE DIG STUDY

Digoxin had no effect on the number of patients who died, which was approximately 35% for both groups. Survival curves for the digoxin and placebo groups were nearly identical (FIGURE). However, fewer patients in the digoxin group died of worsening heart failure, 11.6% vs 13.2%, risk ratio 0.88, $P = .06$.

Two thirds of the study patients were hospitalized during the follow-up interval. There were fewer hospitalizations for worsening heart failure in the digoxin group vs those taking placebo, (26.8% vs 34.7% of patients, risk ratio 0.72, $P < .001$) and for all cardiovascular causes. The groups did not differ in the number of hospitalizations for cardiac arrest or ventricular arrhythmias. Although twice as many patients in the digoxin group were hospitalized for suspected digoxin toxicity, its overall incidence was very low.

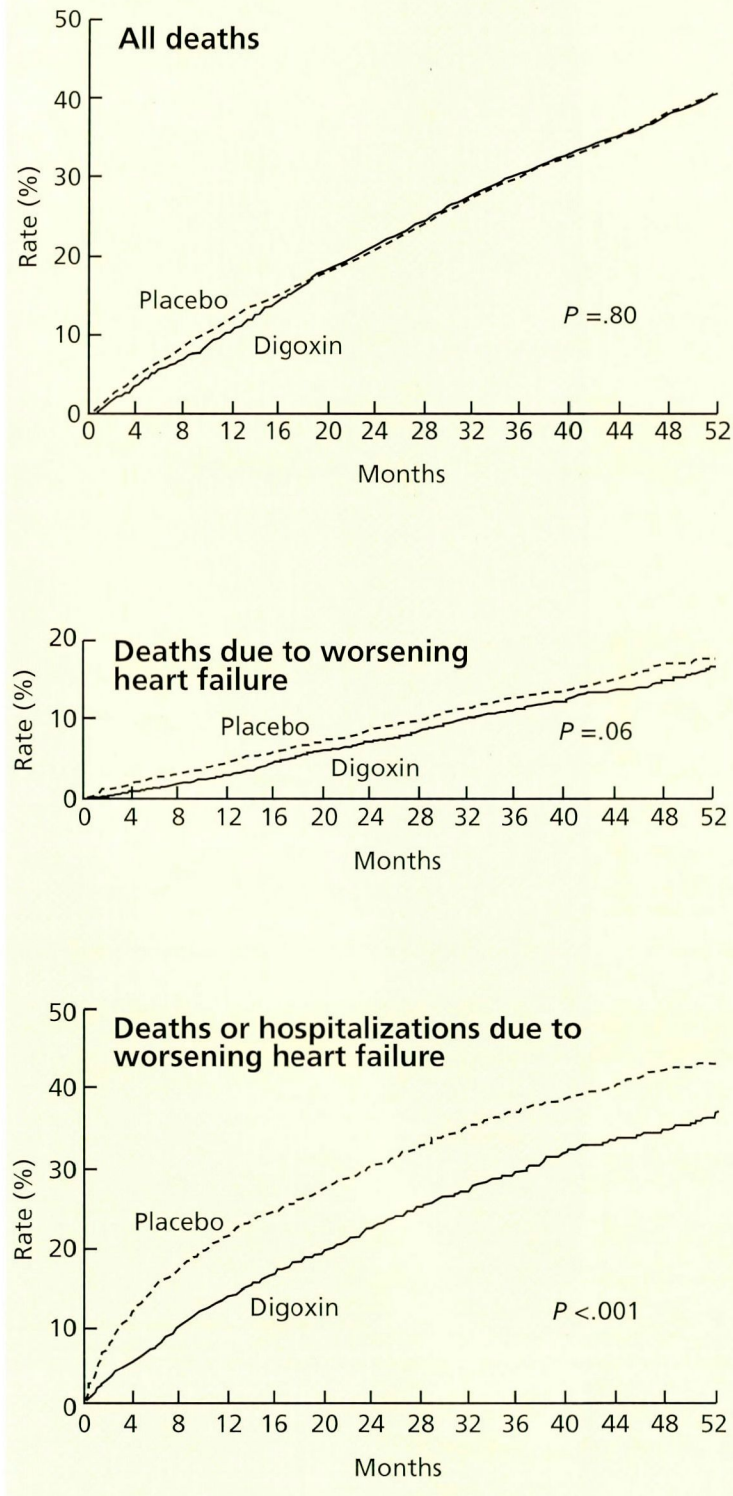
Digoxin appeared more beneficial among patients at higher risk. For example, patients with low ejection fractions, higher cardiothoracic ratios (a measure of heart enlargement), or more severe symptoms as reflected by New York Heart Association class all had higher rates of the combined endpoint of death due to worsening heart failure or hospitalization related to that diagnosis. However, these high-risk patients had greater reductions in this event rate with digoxin therapy than did patients at lower risk (TABLE).

HOW DIGOXIN WORKS IN HEART FAILURE

Digoxin is a complex drug with inotropic, neurohormonal, and electrophysiologic properties.[11] It has several direct actions on the

FIGURE

DIGOXIN IN HEART FAILURE: PRINCIPAL RESULTS



Adapted from the Digitalis Investigation Group, reference 10

TABLE

DIGOXIN IS MORE BENEFICIAL IN PATIENTS AT GREATER RISK

Measure of heart failure	Event rate* Digoxin group (%)	Event rate* Placebo group (%)	Absolute difference (%)
Ejection fraction			
< 25%	38.0	49.2	11.2
25–45%	27.0	32.3	5.3
P value†			.02
Cardiothoracic ratio			
> 0.55	37.5	48.5	11.0
≤ 0.55	27.0	32.4	5.4
P value			.02
New York Heart Association Class			
III or IV	39.2	50.0	10.8
I or II	26.4	32.2	5.8
P value			.02

*Deaths due to worsening heart failure or hospitalizations for worsening heart failure

†*P* values compare the reduction in events with digoxin use between the groups at higher risk vs the groups at lower risk

Adapted from the Digitalis Investigation Group, reference 10

Use digoxin in symptomatic heart failure

myocardium and the conducting system, and indirect actions mediated by the autonomic nervous system.

Direct actions

Digoxin directly enhances contractility, prolongs the atrioventricular (AV) nodal refractory period, and increases systemic vascular resistance. Digoxin's inotropic actions occur as a result of binding and inhibition of the enzyme sodium-potassium ATPase. This ultimately results in increased intracellular calcium levels, which enhances contractility.

Indirect actions

Digoxin also indirectly, through its effect on the vagus nerve, inhibits the sinoatrial node and prolongs AV nodal conduction. One of digoxin's major indirect actions is that it restores baroreceptor sensitivity, which decreases neurohormonal abnormalities. These combined actions of digoxin improve cardiac performance, correct neurohormonal abnormalities (sympathetic excess, renin-angiotensin activation), and modulate heart rate response.

GUIDELINES FOR USING DIGOXIN IN HEART FAILURE

Since digoxin does not prolong life, it is probably not indicated in patients with asymptomatic left ventricular dysfunction.

The initial symptoms of heart failure usually respond to ACE inhibitors and diuretics. Therefore, digoxin should not be used as the initial drug for treating heart failure. Patients with mild to moderate heart failure often become symptom-free while taking ACE inhibitors and diuretics and do not require digoxin. However, it may be added to the regimen if symptoms persist despite optimal doses of ACE inhibitors and diuretics.[12,13]

All patients with severe symptomatic heart failure should receive digoxin, because it alleviates symptoms, increases exercise tolerance, enhances quality of life, decreases the risk of hospitalization, and has a low incidence of toxicity. Although digoxin does not alter the natural history of the disease, it is safe, inexpensive, and highly effective for relieving heart failure symptoms.

Patients with atrial fibrillation and heart failure also usually benefit from using digoxin.

Cautions

Digoxin should be used with caution in patients with renal dysfunction, since it is excreted by the kidney. Diuretics and steroids may cause hypokalemia and predispose to digoxin toxicity. Drugs such as amiodarone, quinidine, verapamil, propafenone, and alprazolam may cause an increase in serum digoxin concentrations.

Most patients do not require repeated measurements of serum digoxin levels. Patients with renal dysfunction or possible drug interactions should have serum digoxin levels monitored as needed to prevent toxicity. ■

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