The New England Journal of Medicine

VOLUME 336 FEBRUARY 20, 1997 NUMBER 8

THE EFFECT OF DIGOXIN ON MORTALITY AND MORBIDITY IN PATIENTS WITH HEART FAILURE

THE DIGITALIS INVESTIGATION GROUP*

ABSTRACT

Background The role of cardiac glycosides in treating patients with chronic heart failure and normal sinus rhythm remains controversial. We studied the effect of digoxin on mortality and hospitalization in a randomized, double-blind clinical trial.

Methods In the main trial, patients with left ventricular ejection fractions of 0.45 or less were randomly assigned to digoxin (3397 patients) or placebo (3403 patients) in addition to diuretics and angiotensin-converting–enzyme inhibitors (median dose of digoxin, 0.25 mg per day; average follow-up, 37 months). In an ancillary trial of patients with ejection fractions greater than 0.45, 492 patients were randomly assigned to digoxin and 496 to placebo.

Results In the main trial, mortality was unaffected. There were 1181 deaths (34.8 percent) with digoxin and 1194 deaths (35.1 percent) with placebo (risk ratio when digoxin was compared with placebo, 0.99; 95 percent confidence interval, 0.91 to 1.07; $P=0.80$). In the digoxin group, there was a trend toward a decrease in the risk of death attributed to worsening heart failure (risk ratio, 0.88; 95 percent confidence interval, 0.77 to 1.01; $P=0.06$). There were 6 percent fewer hospitalizations overall in that group than in the placebo group, and fewer patients were hospitalized for worsening heart failure (26.8 percent vs. 34.7 percent; risk ratio, 0.72; 95 percent confidence interval, 0.66 to 0.79; $P<0.001$). In the ancillary trial, the findings regarding the primary combined outcome of death or hospitalization due to worsening heart failure were consistent with the results of the main trial.

Conclusions Digoxin did not reduce overall mortality, but it reduced the rate of hospitalization both overall and for worsening heart failure. These findings define more precisely the role of digoxin in the management of chronic heart failure. (N Engl J Med 1997;336:525-33.)

ALTHOUGH digoxin is one of the most commonly prescribed drugs for the treatment of heart failure, there is uncertainty about its long-term efficacy and safety.[1-3] Several recent short-term, randomized trials indicated that withdrawing digoxin worsens functional status, exercise capacity, and the left ventricular ejection fraction in patients with heart failure.[4,5] However, the long-term effect of digoxin on mortality and hospitalization for heart failure or other causes is unknown. We conducted a randomized, double-blind, placebo-controlled trial to evaluate the effects of digoxin (Lanoxin, Glaxo Wellcome) on mortality from any cause (the primary end point) and on hospitalization for heart failure (the secondary end point) over a three-to-five-year period in patients with heart failure and normal sinus rhythm.[6]

METHODS

Design

The rationale and design of the study and the base-line characteristics of the patients have been reported previously.[7] Patients were enrolled at 302 clinical centers in the United States and Canada. The study was organized and conducted by a Steering Committee representing the National Heart, Lung, and Blood Institute; the Department of Veterans Affairs Cooperative Studies Program; and cardiologists from the United States and Canada. An independent Data and Safety Monitoring Board monitored the progress of the study. The study was approved by the institutional review board at each participating center. All the patients gave written informed consent.

Eligibility

Patients were eligible for the main trial if they had heart failure and a left ventricular ejection fraction of 0.45 or less (6800 pa-

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*The participants in the Digitalis Investigation Group are listed in the Appendix.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY PATIENTS ACCORDING TO TREATMENT GROUP.*

CHARACTERISTIC	DIGOXIN (N=3397)	PLACEBO (N=3403)
Age (yr) — mean ±SD	63.4±11.0	63.5±10.8
Ejection fraction — mean ±SD	28.6±8.9	28.4±8.9
Median duration of CHF — mo	17	16
	% of patients	
Female sex	22.2	22.5
Nonwhite race	14.4	14.8
Age >70 yr	26.7	27.4
Method of assessing ejection fraction		
Radionuclide ventriculography	65.0	64.2
Two-dimensional echocardiography	29.5	30.0
Contrast angiography	5.5	5.8
Cardiothoracic ratio >0.55	34.6	34.4
NYHA class		
I	13.7	13.0
II	53.3	54.5
III	30.7	30.5
IV	2.2	1.9
No. of signs or symptoms of CHF†		
0	1.1	1.1
1	2.4	2.0
2	7.1	7.1
3	9.3	8.6
≥4	80.1	81.2
Medical history		
Previous myocardial infarction	64.7	65.3
Current angina	27.1	26.4
Diabetes	28.3	28.6
Hypertension	45.0	45.8
Previous digoxin use	44.1	44.6
Primary cause of CHF		
Ischemic	70.8	70.4
Nonischemic	29.0	29.3
Idiopathic	15.5	14.1
Hypertensive	8.0	9.2
Other‡	5.4	6.0
Concomitant medications		
Diuretics	81.2	82.2
ACE inhibitors	94.1	94.8
Nitrates	42.1	43.1
Other vasodilators§	0.9	1.5
Daily dose of study medication prescribed		
0.125 mg	17.5	17.4
0.250 mg	70.6	70.0
0.375 mg	10.3	11.3
0.500 mg	1.1	0.9

*CHF denotes congestive heart failure, NYHA New York Heart Association, and ACE angiotensin-converting enzyme. Because of rounding, not all percentages total 100.

†The clinical signs or symptoms studied included rales, elevated jugular venous pressure, peripheral edema, dyspnea at rest or on exertion, orthopnea, limitation of activity, S_3 gallop, and radiologic evidence of pulmonary congestion.

‡This category included valvular and alcohol-related causes of congestive heart failure.

§These drugs included clonidine hydrochloride, doxazosin mesylate, flosequinan, labetalol hydrochloride, minoxidil, prazosin hydrochloride, and terazosin hydrochloride.

tients) and were in normal sinus rhythm. Patients with heart failure and a left ventricular ejection fraction of more than 0.45 (988 patients) were enrolled in an ancillary trial conducted parallel to the main study. The diagnosis of heart failure was based on current or past clinical symptoms (limitation of activity, fatigue, and dyspnea or orthopnea), signs (edema, elevated jugular venous pressure, rales, or S_3 gallop), or radiologic evidence of pulmonary congestion. Patients were eligible for the study whether or not they were already being treated with digoxin. The left ventricular ejection fraction was assessed by radionuclide left ventriculography, left ventricular contrast angiography, or two-dimensional echocardiography. The criteria for exclusion from the study have been published previously.[7]

Randomization, Dose Titration, and Follow-up

In telephone conversations between the clinical centers and the data coordinating center from February 1991 through August 1993, the patients were randomly assigned to receive digoxin or placebo. The randomization was stratified according to center and left ventricular ejection fraction (≤0.45 or >0.45). The recommended initial dose of the study drug was determined with an algorithm that took into account the patient's age, sex, weight, and renal function.[8] The investigators were permitted to modify the dose on the basis of other factors, such as the previous dose of digoxin and the use of concomitant drugs that might alter digoxin pharmacokinetics, and they were strongly encouraged to give the patients angiotensin-converting–enzyme inhibitors. Patients who were using digoxin before entry into the study were randomly assigned to receive either digoxin or placebo without a washout period. All the patients returned for follow-up visits 4 weeks and 16 weeks after randomization and every 4 months thereafter. At each follow-up visit, data were recorded on changes in clinical and functional status, the use of selected nonstudy drugs, hospitalization, adherence to the study regimen, and side effects. When patients had worsening symptoms of heart failure, it was recommended that other therapy for heart failure be used in an optimal fashion. If the patients remained symptomatic despite efforts to optimize other forms of treatment, open-label treatment with digoxin was allowed and the study drug was discontinued.

Outcomes

The primary outcome studied in the main trial was mortality. The secondary outcomes were mortality from cardiovascular causes, death from worsening heart failure, hospitalization for worsening heart failure, and hospitalization for other causes, in particular suspected digoxin toxicity. In the ancillary trial, the occurrence of death or hospitalization due to worsening heart failure was studied as a combined primary outcome. At this writing, the vital status of 47 patients assigned to digoxin and 46 patients assigned to placebo in the main trial (1.4 percent of the total) remains unknown.

Classification of Outcomes

Each investigator classified the cause of death or the primary diagnosis leading to hospitalization without knowing the patient's study-drug assignment and after reviewing the patient's hospital chart or interviewing relatives. Deaths due to worsening heart failure were classified as such even if the final event was an arrhythmia. Suspected digoxin toxicity was diagnosed according to the judgment of the investigator.

Statistical Analysis

All the analyses were performed on an intention-to-treat basis with two-sided P values. A stratified log-rank statistic was used to compare the survival distributions in the two study groups. Kaplan–Meier analysis was used to construct life-table plots. In comparing the digoxin and placebo groups, we estimated the risk ratio associated with an event and calculated the 95 percent confidence interval from the Cox proportional-hazards model.

The Wilcoxon rank-sum test was used to determine any differences between groups in the number of hospitalizations. The Cox proportional-hazards model was also used to test for interactions between the study assignments and predefined variables that included the left ventricular ejection fraction (<0.25 vs. 0.25 to 0.45), heart size (cardiothoracic ratio, ≤0.55 vs. >0.55), the cause of heart failure (ischemic vs. nonischemic), digoxin use before the trial (any vs. none), and New York Heart Association (NYHA) functional class (I or II vs. III or IV). In this article we report primarily the results of the main trial.

The data were reviewed every six months by the Data and Safety Monitoring Board. December 31, 1995, was chosen in advance as the date on which identification of events would terminate.

Data on the 93 patients whose vital status was unknown on December 31, 1995, were censored as of the date of their most recent follow-up visit. A sensitivity analysis in which we assumed either that all the placebo patients had died or that all the digoxin patients had died did not change the overall results with respect to mortality.

RESULTS

Main Trial (Left Ventricular Ejection Fraction, ≤0.45)

Except as otherwise specified, the results reported here are those of the main trial. In that trial, there were no significant differences in base-line characteristics between the 3397 patients assigned to digoxin and the 3403 patients assigned to placebo (Table 1). The mean duration of follow-up was 37 months (range, 28 to 58).

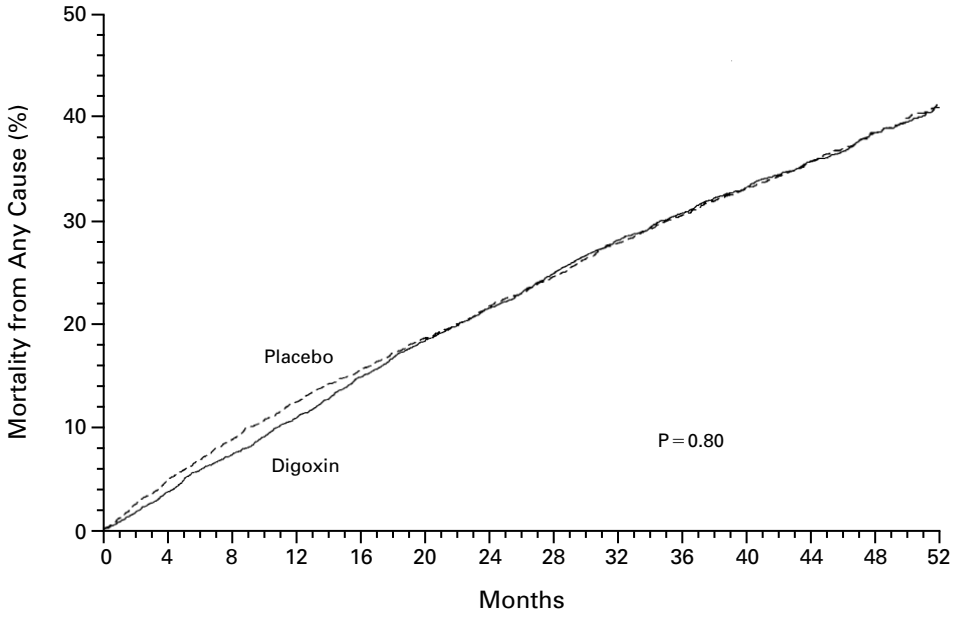
Mortality

There were 1181 deaths in the digoxin group (34.8 percent) and 1194 deaths in the placebo group (35.1 percent) (risk ratio when digoxin was compared with placebo, 0.99; 95 percent confidence interval, 0.91 to 1.07; P = 0.80) (Fig. 1 and Table 2).

There were 1016 deaths from cardiovascular causes in the digoxin group (29.9 percent) and 1004 such deaths in the placebo group (29.5 percent) (risk ratio, 1.01; 95 percent confidence interval, 0.93 to 1.10; P = 0.78). In the digoxin group as compared with the placebo group, there was a trend toward a lower risk of mortality attributable to worsening heart failure (number of deaths, 394 vs. 449; risk ratio, 0.88; 95 percent confidence interval, 0.77 to 1.01; P = 0.06) (Fig. 2).

Hospitalizations for Heart Failure and Arrhythmia

Fewer patients were hospitalized for worsening heart failure in the digoxin group (910) than in the placebo group (1180) (risk ratio, 0.72; 95 percent confidence interval, 0.66 to 0.79; P<0.001) (Table 3). In all, there were 1927 hospitalizations with worsening heart failure as the primary diagnosis in the digoxin group and 2553 such hospitalizations in the placebo group. There was no significant difference between the groups in the number of patients hospitalized for ventricular arrhythmia or cardiac arrest (142 vs. 145). The risk of death from any cause or hospitalization for worsening heart failure was lower in the digoxin group (risk ratio, 0.85; 95 per-



NO. OF PATIENTS AT RISK

Placebo	3403	3239	3105	2976	2868	2758	2652	2551	2205	1881	1506	1168	734	339
Digoxin	3397	3269	3144	3019	2882	2759	2644	2531	2184	1840	1475	1156	737	335

Figure 1. Mortality in the Digoxin and Placebo Groups.
The number of patients at risk at each four-month interval is shown below the figure.

TABLE 2. DEATHS ACCORDING TO STUDY GROUP AND CAUSE.

CAUSE OF DEATH	DIGOXIN (N=3397)	PLACEBO (N=3403)	ABSOLUTE DIFFERENCE*	RISK RATIO (95% CI)†	P VALUE
	no. of patients (%)		%		
All	1181 (34.8)	1194 (35.1)	−0.4	0.99 (0.91–1.07)	0.80
Cardiovascular	1016 (29.9)	1004 (29.5)	0.4	1.01 (0.93–1.10)	0.78
Worsening heart failure‡	394 (11.6)	449 (13.2)	−1.6	0.88 (0.77–1.01)	0.06
Other cardiac§	508 (15.0)	444 (13.0)	1.9	1.14 (1.01–1.30)	
Other vascular¶	50 (1.5)	45 (1.3)	0.1	1.11 (0.74–1.66)	
Unknown	64 (1.9)	66 (1.9)	−0.1	0.97 (0.69–1.37)	
Noncardiac and nonvascular	165 (4.9)	190 (5.6)	−0.7	0.87 (0.71–1.07)	

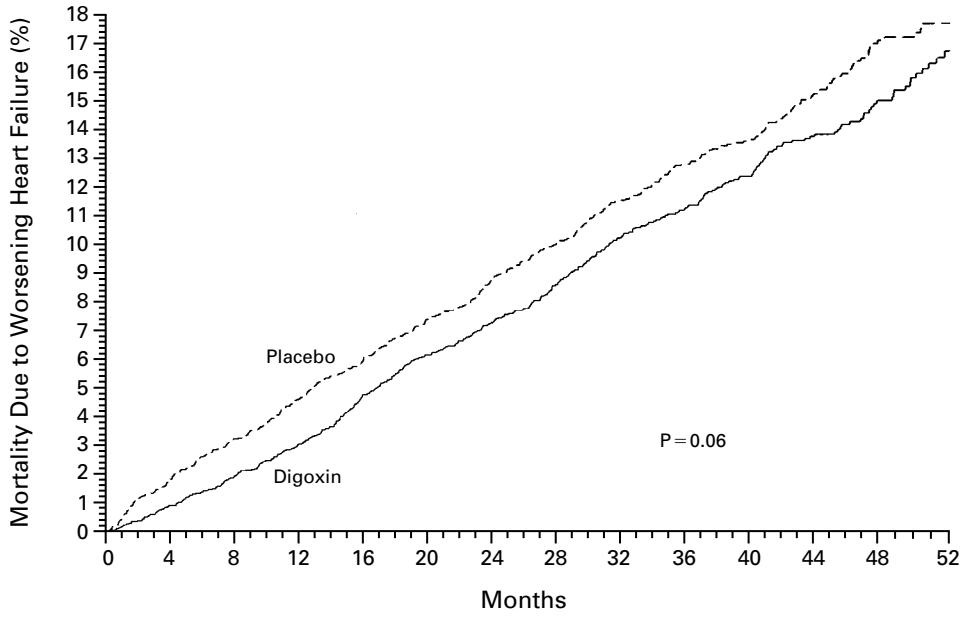
*Absolute differences were calculated by subtracting the percentage of deaths in the placebo group from the percentage of deaths in the digoxin group (before values were rounded).

†Risk ratios and confidence intervals (CI) were estimated from the Cox proportional-hazards model.

‡This category includes patients who died from worsening heart failure, even if the final event was an arrhythmia.

§This category includes deaths presumed to result from arrhythmia without evidence of worsening heart failure and deaths due to atherosclerotic coronary disease, bradyarrhythmias, low-output states, and cardiac surgery. Although this outcome was not prespecified, P=0.04 for the comparison of study groups with respect to death from other cardiac causes.

¶This category includes deaths due to stroke, embolism, peripheral vascular disease, vascular surgery, and carotid endarterectomy.



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Digoxin	3397	3269	3144	3019	2882	2759	2644	2531	2184	1840	1475	1156	737	335

Figure 2. Mortality Due to Worsening Heart Failure in the Digoxin and Placebo Groups. The number of patients at risk at each four-month interval is shown below the figure.

TABLE 3. PATIENTS HOSPITALIZED DURING THE STUDY, ACCORDING TO STUDY GROUP AND REASON FOR HOSPITALIZATION.

REASON FOR HOSPITALIZATION*	DIGOXIN (N=3397)	PLACEBO (N=3403)	ABSOLUTE DIFFERENCE†	RISK RATIO (95% CI)‡	P VALUE
	no. of patients (%)		%		
Cardiovascular	1694 (49.9)	1850 (54.4)	−4.5	0.87 (0.81–0.93)	<0.001
Worsening heart failure	910 (26.8)	1180 (34.7)	−7.9	0.72 (0.66–0.79)	<0.001
Ventricular arrhythmia, cardiac arrest	142 (4.2)	145 (4.3)	−0.1	0.98 (0.78–1.24)	
Supraventricular arrhythmia§	133 (3.9)	152 (4.5)	−0.6	0.87 (0.69–1.10)	
Atrioventricular block, bradyarrhythmia	14 (0.4)	9 (0.3)	0.1	1.56 (0.68–3.61)	
Suspected digoxin toxicity	67 (2.0)	31 (0.9)	1.1	2.17 (1.42–3.32)	<0.001
Myocardial infarction	195 (5.7)	201 (5.9)	−0.2	0.97 (0.79–1.18)	
Unstable angina	399 (11.7)	398 (11.7)	0.1	1.01 (0.87–1.16)	
Stroke	157 (4.6)	164 (4.8)	−0.2	0.95 (0.77–1.19)	
Coronary revascularization¶	83 (2.4)	71 (2.1)	0.4	1.17 (0.85–1.61)	
Cardiac transplantation	25 (0.7)	16 (0.5)	0.3	1.57 (0.84–2.94)	
Other cardiovascular‖	452 (13.3)	381 (11.2)	2.1	1.20 (1.05–1.38)	
Respiratory infection	238 (7.0)	252 (7.4)	−0.4	0.94 (0.79–1.12)	
Other noncardiac and nonvascular	1126 (33.1)	1079 (31.7)	1.4	1.06 (0.98–1.15)	
Unspecified	20 (0.6)	18 (0.5)	0.1	1.11 (0.59–2.10)	
No. of patients hospitalized	2184 (64.3)	2282 (67.1)	−2.8	0.92 (0.87–0.98)	0.006
No. of hospitalizations	6356	6777			

*Data shown include the first hospitalization of each patient for each reason.

†Absolute differences were calculated by subtracting the percentage of patients hospitalized in the placebo group from the percentage of patients hospitalized in the digoxin group (before values were rounded).

‡Risk ratios and confidence intervals (CI) were estimated from a Cox proportional-hazards model that used the first hospitalization of each patient for each reason.

§This category includes atrioventricular block and bradyarrhythmia.

¶This category includes coronary-artery bypass grafting and percutaneous transluminal coronary angioplasty.

‖This category includes embolism, venous thrombosis, peripheral vascular disease, hypertension, other vascular surgery, cardiac catheterization, other types of catheterization, pacemaker implantation, installation of automatic implantable cardiac defibrillator, electrophysiologic testing, transplant-related evaluation, nonspecific chest pain, atherosclerotic heart disease, hypotension, orthostatic hypotension, and valve operation.

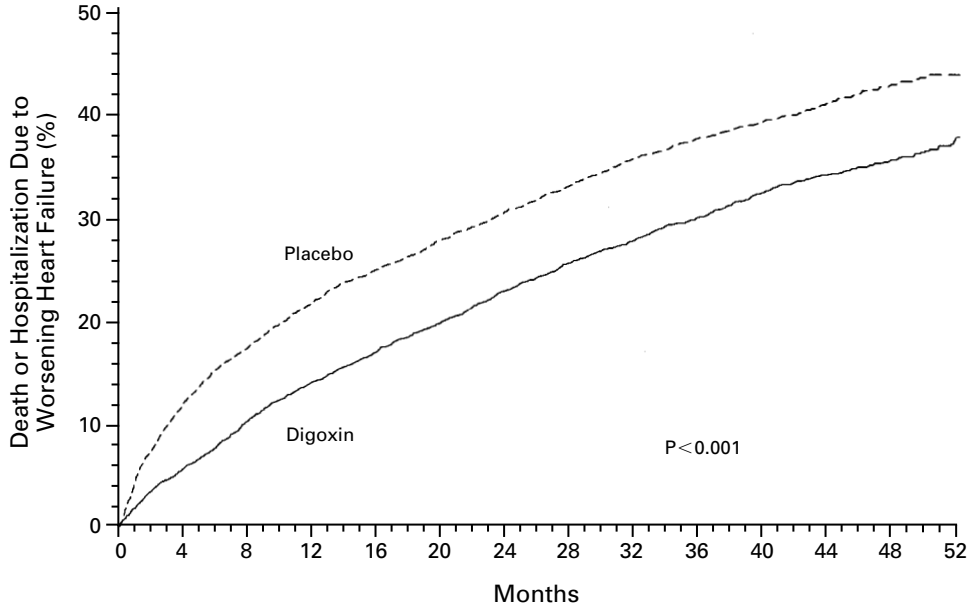
cent confidence interval, 0.79 to 0.91; P<0.001). The risk associated with the combined outcome of death due to worsening heart failure or hospitalization related to that diagnosis was lower in the digoxin group (in which 1041 patients had the outcome) than in the placebo group (1291 patients) (risk ratio, 0.75; 95 percent confidence interval, 0.69 to 0.82; P<0.001) (Fig. 3 and Table 4). These benefits were seen soon after randomization, and they persisted throughout the trial.

Other Hospitalizations

There were 6 percent fewer hospitalizations in the digoxin group than in the placebo group (6356 vs. 6777), and 10 percent fewer hospitalizations for cardiovascular causes (4106 vs. 4570). Furthermore, there were fewer hospitalizations for any reason per patient in the digoxin group than in the placebo group (P = 0.01 by the Wilcoxon test), and fewer hospitalizations per patient for cardiovascular causes (P<0.001). The difference between the groups became more apparent when the number of hospitalizations was standardized according to the duration of follow-up. In all, 64.3 percent of the patients in the digoxin group and 67.1 percent of those in the placebo group were hospitalized for all reasons combined, with cardiovascular causes as the primary reason in both groups (Table 3). There was no significant difference between the digoxin group and the placebo group in the number of hospitalizations for myocardial infarction (195 vs. 201) or unstable angina (399 vs. 398), but there were fewer hospitalizations for supraventricular arrhythmia in the digoxin group (133 vs. 152). Small proportions of patients in both groups were hospitalized with suspected digoxin toxicity, with significantly more in the digoxin group than in the placebo group (2.0 percent vs. 0.9 percent, P<0.001). The proportion of patients hospitalized for noncardiovascular reasons was similar in the two groups.

Effects in Subgroups

We examined the influence of digoxin on both the relative and the absolute reduction in the risk of a secondary outcome in prespecified subgroups. With regard to the combined outcome of mortality from worsening heart failure or a hospitalization related to that diagnosis, the benefit of digoxin appeared to be greater among patients at high risk — that is, those with lower ejection fractions or en-



No. of Patients at Risk

Placebo	3403	2915	2674	2473	2328	2197	2071	1954	1659	1397	1111	859	546	250
Digoxin	3397	3120	2888	2696	2544	2392	2241	2115	1825	1521	1188	916	578	255

Figure 3. Incidence of Death or Hospitalization Due to Worsening Heart Failure in the Digoxin and Placebo Groups.

The number of patients at risk at each four-month interval is shown below the figure.

larged hearts and those in NYHA functional class III or IV (Table 4).

Serum Digoxin Levels

Among the 1485 patients in the digoxin group for whom blood samples obtained more than six hours after the last dose were available, the mean steady-state serum digoxin level was 0.86 ng per milliliter (1.10 nmol per liter) at the 1-month visit and 0.80 ng per milliliter (1.02 nmol per liter) at the 12-month visit. At the one-month visit, the mean serum digoxin levels were 0.76 ng per milliliter (0.97 nmol per liter) in the patients receiving 0.125 mg of digoxin per day, 0.89 ng per milliliter (1.14 nmol per liter) in those receiving 0.250 mg per day, 0.88 ng per milliliter (1.13 nmol per liter) in those receiving 0.375 mg per day, and 0.88 ng per milliliter in those receiving 0.500 mg per day. At one month, 88.3 percent of the patients in the digoxin group had serum digoxin levels within the therapeutic range of 0.5 to 2.0 ng per milliliter (0.6 to 2.6 nmol per liter).

Adherence to the Study Regimen

At randomization, the median daily dose of the assigned study drug was 0.250 mg in both treatment groups. At one year, 85.6 percent of the patients in the digoxin group were taking the study drug, and 82.9 percent of the patients in the placebo group were taking placebo. At the final study visit, 70.8 percent of the surviving patients in the digoxin group were taking the study drug, and an additional 10.3 percent were taking open-label digoxin. In the placebo group, 67.9 percent of the surviving patients were taking placebo and 15.6 percent were taking open-label digoxin. Open-label digoxin was used at some time during the trial by 14.2 percent of patients in the digoxin group as compared with 22.0 percent of those in the placebo group ($P<0.001$). The primary reasons for discontinuing the study drug were the use of open-label digoxin to treat worsening heart failure (rate of discontinuation at one year, 3.0 percent in the digoxin group vs. 6.4 percent in the placebo group; by the end of the trial, 6.7 percent vs. 11.0 percent) and atrial fibrillation (rate of discontinuation at one year, 1.5 percent vs. 1.6 percent; by the end of the trial, 2.8 percent vs. 3.4 percent).

Digoxin Toxicity

More patients had suspected digoxin toxicity in the digoxin group than in the placebo group (11.9 percent vs. 7.9 percent). Among these patients, 16.5

TABLE 4. EFFECT OF THE STUDY DRUG ON THE OCCURRENCE OF DEATH OR HOSPITALIZATION DUE TO WORSENING HEART FAILURE.

VARIABLE	DIGOXIN*	PLACEBO*	ABSOLUTE DIFFERENCE (95% CI)†	RISK RATIO (95% CI)‡
	no. of patients with ≥1 event/ no. randomized (%)		%	
Ejection fraction				
0.25–0.45	613/2270 (27.0)	735/2273 (32.3)	−5.3 (−8.0 to −2.7)	0.80 (0.72 to 0.89)
<0.25	428/1127 (38.0)	556/1130 (49.2)	−11.2 (−15.3 to −7.2)	0.68 (0.60 to 0.77)
Previous use of digoxin				
Yes	550/1498 (36.7)	688/1519 (45.3)	−8.6 (−12.1 to −5.1)	0.74 (0.66 to 0.83)
No	491/1899 (25.9)	603/1884 (32.0)	−6.2 (−9.0 to −3.3)	0.77 (0.68 to 0.86)
Cause of heart failure				
Ischemic	731/2405 (30.4)	873/2398 (36.4)	−6.0 (−8.7 to −3.3)	0.79 (0.72 to 0.88)
Nonischemic	306/983 (31.1)	413/996 (41.5)	−10.3 (−14.5 to −6.1)	0.67 (0.58 to 0.77)
Cardiothoracic ratio				
≤0.55	600/2220 (27.0)	724/2233 (32.4)	−5.4 (−8.1 to −2.7)	0.79 (0.71 to 0.88)
>0.55	441/1176 (37.5)	567/1170 (48.5)	−11.0 (−14.9 to −7.0)	0.69 (0.61 to 0.78)
NYHA class				
I or II	601/2275 (26.4)	739/2296 (32.2)	−5.8 (−8.4 to −3.1)	0.78 (0.70 to 0.87)
III or IV	438/1118 (39.2)	552/1105 (50.0)	−10.8 (−14.9 to −6.7)	0.70 (0.61 to 0.79)
Overall study population	1041/3397 (30.6)	1291/3403 (37.9)	−7.3 (−9.5 to −5.0)	0.75 (0.69 to 0.82)

*Numbers of patients shown for the subgroups do not all add up to the total number in the group because of missing data for some patients.

†Absolute differences were calculated by subtracting the percentage of patients with one or more events in the placebo group from the corresponding percentage of patients in the digoxin group (before values were rounded). P values for the interaction of the variables shown with the study assignments were as follows: ejection fraction, P = 0.02; previous digoxin use, P = 0.54; cause of heart failure, P = 0.11; cardiothoracic ratio, P = 0.02; and NYHA class, P = 0.02.

‡Risk ratios and confidence intervals (CI) were estimated from the Cox proportional-hazards model that used the date of the first event. P values for the interaction of the variables shown with the study assignments were as follows: ejection fraction, P = 0.05; previous digoxin use, P = 0.60; cause of heart failure, P = 0.06; cardiothoracic ratio, P = 0.10; and NYHA class, P = 0.15.

percent of those in the digoxin group were hospitalized, as compared with 11.4 percent of those in the placebo group. The most common reasons for suspected digoxin toxicity were ventricular fibrillation or tachycardia (1.1 percent in the digoxin group vs. 0.8 percent in the placebo group; risk ratio, 1.40; 95 percent confidence interval, 0.84 to 2.30; P = 0.20), supraventricular arrhythmia (2.5 percent vs. 1.2 percent; risk ratio, 2.10; 95 percent confidence interval, 1.45 to 3.07; P<0.001), and second- or third-degree atrioventricular block (1.2 percent vs. 0.4 percent; risk ratio, 2.87; 95 percent confidence interval, 1.56 to 5.28; P<0.001). The increase in the risk of digoxin toxicity in the digoxin group was similar for all subgroups.

Ancillary Trial (Left Ventricular Ejection Fraction, >0.45)

In the ancillary trial, there were no significant differences in base-line characteristics between the 492 patients assigned to digoxin and the 496 patients assigned to placebo. There were 115 deaths in the digoxin group (23.4 percent) and 116 deaths in the placebo group (23.4 percent; risk ratio, 0.99; 95 percent confidence interval, 0.76 to 1.28). With regard to the combined outcome of death or hospitalization due to worsening heart failure, the results in the ancillary trial (risk ratio, 0.82; 95 percent confidence interval, 0.63 to 1.07) were consistent with the findings of the main trial.

DISCUSSION

In the main trial, in which patients with left ventricular ejection fractions of 0.45 or lower were studied, we found that digoxin had no effect on overall mortality when it was added to diuretics and angiotensin-converting–enzyme inhibitors to treat heart failure. There were fewer deaths due to worsening heart failure in the digoxin group. Although death attributable to other cardiac causes was not specified in advance as a study outcome, there was a statistically significant difference between the study groups (P = 0.04) with regard to that outcome. The risk of hospitalization, especially for worsening heart failure, was reduced with digoxin treatment. When the combined outcome was analyzed, the incidence of death from worsening heart failure or hospitalization for that diagnosis was markedly reduced. Smaller studies, such as the Randomized Assessment of Digoxin on Inhibitors of the Angiotensin-Converting Enzyme (RADIANCE) and Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin (PROVED) trials, have suggested that

worsening heart failure and hospitalization occurred less often in patients treated with digoxin.[4,5] Although our trial showed that digoxin had no effect on mortality, studies of other inotropic agents not related to glycosides, such as dobutamine, beta-agonists, milrinone, and enoximone, have demonstrated excess mortality.[6,9-11]

The population studied in the main trial represented a wide spectrum of patients with heart failure. A large proportion of the study patients received background therapy with angiotensin-converting–enzyme inhibitors (94.4 percent), diuretics (81.7 percent), one or the other of these classes of drugs (98.4 percent), or both (77.7 percent). Among the patients in the study, 22.3 percent were women, and patients with diverse causes of heart failure and a broad range of symptoms were included. Although only 2 percent of patients were in NYHA functional class IV, 30.6 percent were in class III. Inclusion of patients irrespective of base-line ejection fraction distinguishes this trial from prior studies.

Although there were more patients with suspected digoxin toxicity in the digoxin group (11.9 percent, as compared with 7.9 percent in the placebo group), the proportion of patients actually hospitalized was low (2.0 percent vs. 0.9 percent over a period of 3.5 years). This excess of suspected cases took the form of new episodes of ventricular tachycardia or fibrillation, supraventricular arrhythmia, and advanced atrioventricular block. The vast majority of the study patients, however (88.3 percent), had serum digoxin levels in the therapeutic range at the one-month visit, and only 2 percent had levels exceeding 2.0 ng per milliliter.

Subgroups were assessed for differences in the benefits and risks of digoxin. The reduction in the occurrence of either death or hospitalization due to worsening heart failure was seen at all levels of the left ventricular ejection fraction, but it was greatest in patients with ejection fractions of 0.25 or lower, those who had enlarged hearts, and those in NYHA functional class III or IV.

In conclusion, digoxin had no effect on overall mortality in patients receiving diuretics and angiotensin-converting–enzyme inhibitors, but it did reduce the overall number of hospitalizations and the combined outcome of death or hospitalization attributable to worsening heart failure. In clinical practice, digoxin therapy is likely to affect the frequency of hospitalization, but not survival.

We are indebted to the study patients for their willingness to volunteer for the trial; to the several hundred physicians who referred patients, for their cooperation; and to Glaxo Wellcome for supplying the drug and placebo.

APPENDIX

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