CLINICAL STUDIES

HEART FAILURE

Randomized Study Assessing the Effect of Digoxin Withdrawal in Patients With Mild to Moderate Chronic Congestive Heart Failure: Results of the PROVED Trial

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Objectives. The purpose of this study was to determine whether digoxin is effective in patients with chronic, stable mild to moderate heart failure.

Background. Digoxin has been a traditional therapy in heart failure, but methodologic limitations in earlier studies have prevented definitive conclusions regarding its efficacy.

Methods. Withdrawal of digoxin (placebo group, n = 46) or its continuation (digoxin group, n = 42) was performed in a prospective, randomized, double-blind, placebo-controlled multicenter trial of patients with chronic, stable mild to moderate heart failure secondary to left ventricular systolic dysfunction who had normal sinus rhythm and were receiving long-term treatment with diuretic drugs and digoxin.

Results. Patients withdrawn from digoxin therapy showed worsened maximal exercise capacity (median change in exercise time −96 s) compared with that of patients who continued to receive digoxin (change in exercise time +4.5 s) (p = 0.003). Patients withdrawn from digoxin therapy showed an increased incidence of treatment failures (p = 0.039) (39%, digoxin withdrawal group vs. 19%, digoxin maintenance group) and a decreased time to treatment failure (p = 0.037). In addition, patients who continued to receive digoxin had a lower body weight (p = 0.044) and heart rate (p = 0.003) and a higher left ventricular ejection fraction (p = 0.016).

Conclusions. These data provide strong evidence of the clinical efficacy of digoxin in patients with normal sinus rhythm and mild to moderate chronic heart failure secondary to systolic dysfunction who are treated with diuretics.

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Attempts to demonstrate the clinical efficacy of the digitalis glycosides in patients with congestive heart failure and normal sinus rhythm have progressed from presentations of case series to prospectively designed clinical trials (1–8). In 1982, Lee et al. (4) demonstrated for the first time in a randomized placebo-controlled trial that, compared with results achieved with placebo, digoxin resulted in improved signs and lessened symptoms in patients with heart failure who had normal sinus rhythm and were receiving maintenance therapy with digoxin and diuretics. However, this study was not totally convincing because 25% of patients had an essentially normal heart failure score at baseline. There were also a high (29%) dropout rate, small sample size, crossover design, hypertrophic cardiomyopathy in 8% of patients and normal left ventricular systolic function in 24%. In 1988 Guyatt et al. (5) demonstrated in a placebo-controlled, randomized, double-blind study in patients with

congestive heart failure and normal sinus rhythm an improvement with digoxin in submaximal (6-min walk) exercise, a decrease in treatment failures and a reduction in symptoms of dyspnea and heart failure score, as well as a decrease in cardiothoracic ratio on chest X-ray film and improvement in fractional shortening by echocardiography. As in the study by Lee et al. (4), the trial used a crossover design, and the sample size was quite small, limiting definitive conclusions. In the same year, the German-Austrian xamoterol study (6), a double-blind, placebo-controlled parallel group trial demonstrated that, compared with placebo, digoxin reduced symptoms and improved exercise capacity. Although the sample size was large (n = 433) and all patients had normal sinus rhythm, this study was seriously flawed. The extent of left ventricular systolic dysfunction in enrolled patients was not defined, the etiology of heart failure was unclear in 75% of the patients, only 23% were taking diuretic drugs, 25% were classified as having New York Heart Association class 1 heart failure, and patients with angina pectoris were enrolled. In addition, the study used a 2:1:1 randomization (xamoterol:placebo:digoxin), providing greater power to demonstrate significant effects with xamoterol than with digoxin. Finally, only patients who completed the trial were included in the analysis.

In the same year, the Captopril-Digoxin Study (8), a large (n = 300), double-blind, placebo-controlled, randomized parallel group trial, demonstrated that patients with heart failure taking digoxin with background therapy of diuretic drugs required fewer hospitalizations and emergency room visits than did patients receiving placebo with diuretic drugs. In addition, compared with the placebo group, the digoxin group showed fewer treatment failures, less need for additional diuretics, and an increase in ejection fraction. This study was biased against digoxin because most study patients had been receiving digoxin before the study and were withdrawn from digoxin therapy before randomization. A sizable percentage of patients were not entered into the randomized phase because their condition deteriorated during the withdrawal period; thus, the patients who most likely would have been responsive to digoxin were excluded from the trial. In 1989, a large, double-blind, randomized placebo-controlled parallel group trial, the milrinone-digoxin study (two arms of which represented a randomized digoxin withdrawal trial) (7) demonstrated that continued treatment with digoxin resulted in improved exercise capacity, reduced need for co-intervention, reduced incidence of treatment failures, a higher rate of study completion and improvement in ejection fraction compared with results achieved with placebo (that is, the digoxin withdrawal group).

Thus, recent data provide evidence that digoxin is, in fact, clinically effective in patients who have chronic heart failure and normal sinus rhythm. Despite this evidence, the use of digoxin in many parts of the world appears to be less frequent than one might expect. For example, in a survey of centers in the Studies of Left Ventricular Dysfunction (SOLVD) trials, digoxin use ranged from almost 80% in patients with four signs of congestive heart failure and a left ventricular ejection fraction of <0.20 to approximately 20% in patients with only one sign of congestive heart failure and an ejection fraction of 0.36 to 0.45. Overall, approximately 50% of patients with left ventricular dysfunction with or without congestive heart failure from the United States were taking digoxin compared with only 24% from Belgium and 41% from Canada. The three large clinical trials cited earlier were primarily evaluating another compound while utilizing digoxin as an active control. Some of the design elements of these studies enhanced evaluation of the primary drug in question rather than of digoxin (for example, 2:1:1 randomization in the xamoterol trial, digoxin withdrawal before randomization in the Captopril-Digoxin Study). The present study—the Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin (PROVED)—was designed to evaluate definitively and test specifically the efficacy and safety of digoxin in patients with normal sinus rhythm who had mild to moderate heart failure secondary to systolic dysfunction and were receiving maintenance therapy with digoxin and diuretics.

Methods

This study was designed as a multicenter double-blind, randomized, placebo-controlled and parallel group trial with an 8-week single-blind baseline phase (physician but not patient knowledge of the study drug, which in all cases was digoxin) and a 12-week double-blind withdrawal phase. Thirty-two centers participated, and all centers obtained Institutional Review Board approval of the protocol and informed, written patient consent. From 1 to 11 patients (median 2) were recruited at each center, with 29 centers entering <4 patients. The first patient was enrolled in June 1989 and the last in October 1990. Recruitment of patients became increasingly difficult soon after the study began, in part because of the widespread use of angiotensin-converting enzyme inhibitors. In July 1990, a decision was made before unblinding by the study sponsor with the consent of several principal investigators, including the chairman of the study's advisory committee (B.F.U.), to halt recruitment after 113 patients were enrolled in the single-blind phase and 88 patients were randomized in the double-blind phase. The last follow-up visit occurred in April 1991. A companion trial (RADIANCE) (10) with identical methodology except for the concomitant use of angiotensin-converting enzyme inhibitors was conducted during the same time period. By design, patients were limited to only those currently taking digoxin and diuretic drugs for at least 1 month before study entry. The use of an angiotensin-converting enzyme inhibitor was an exclusion criterion.

Patient entry criteria. Entry criteria included patients with mild to moderate chronic heart failure (functional class II or III) and normal sinus rhythm who were receiving digoxin and diuretics. Each patient (≥18 years old) was required to have a history of documented congestive heart failure not caused by acute ischemia with evidence of peripheral edema, jugular venous distension, X-ray evidence of interstitial edema or pulmonary congestion or a pulmonary artery wedge pressure >12 mm Hg. An ejection fraction determined by radionuclide angiography to be ≤0.35 and a left ventricular end-diastolic dimension ≥60 mm or 34 mm/m^2 by echocardiography were required for entry.

Patients were excluded if they had had a myocardial infarction within 3 months, unstable angina pectoris, a cerebrovascular accident within 12 months, primary valvular disease, hypertrophic cardiomyopathy, uncontrolled serious ventricular arrhythmias, a history of atrial fibrillation, atrial flutter or paroxysmal supraventricular tachycardia, hepatic dysfunction as manifested by an elevation of serum glutamic oxaloacetic transaminase or bilirubin twice normal or greater, abnormal renal function (serum creatinine >2.5 mg/dl), chronic obstructive pulmonary disease (forced expiratory volume in 1 s/forced vital capacity <60% predicted), exercise not limited by dyspnea or fatigue, hypertension (diastolic blood pressure >95 mm Hg), hypotension (systolic pressure <90 mm Hg), uncontrolled thyroid disease, myocarditis, amyloidosis, malignant disease or current use of

	PRE-STUDY	SINGLE BLIND BASELINE STABILIZATION						DOUBLE BLIND DIGOXIN WITHDRAWAL						
		Digoxin* + Diuretic						Placebo** + Diuretic / Digoxin* + Diuretic						
VISIT NO.	1	2	3	4	5	6	7	8	9	10	11	12	13
STUDY WEEK	0	1	2	4	6	8	8	10	12	14	16	18	20
HX	X												
PE	X					X							X
NYHA	X	X	X	X	X	X		X	X	X	X	X	X
LWHF				X		X			X				X
CHF#	X					X							X
ECHO	X					X							X
CXR	X					X							X
MUGA	X					X							X
ETT		X		X	X	X		X		X			X
ECG	X					X							X
LABS	X		X			X			X				X
6 MIN WALK			X			X			X		X	X	
[DIG]	X			X		X							X
DIG Δ		X		X									
GEP	X	X	X	X	X	X	X	X	X	X	X	X	X

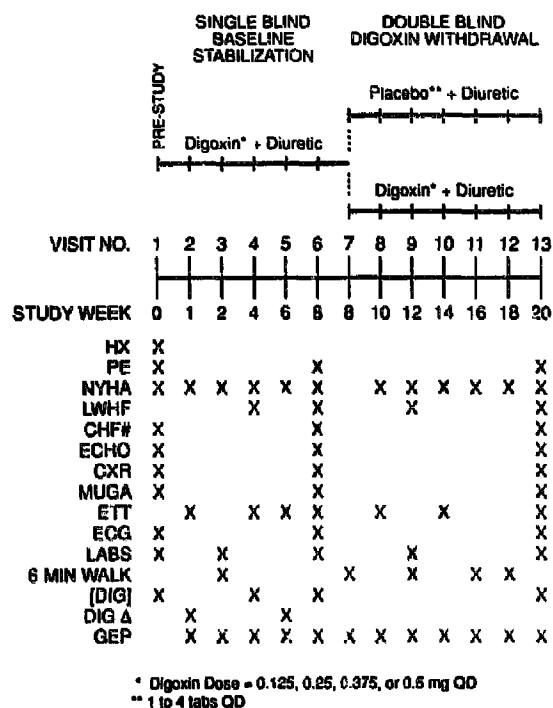* Digoxin Dose = 0.125, 0.25, 0.375, or 0.5 mg QD
** 1 to 4 tabs QD

Figure 1. The basic schema and major tests performed in the PROVED trial. The text explains the procedure and methods employed. CHF# = CHF score; CXR = chest X-ray film; [DIG] = serum digoxin concentration; DIG Δ = investigator change of digoxin dose, if required; ECG = electrocardiogram; ECHO = M-mode echocardiography; ETT = modified Naughton exercise treadmill test; GEP = 7-point Global Evaluation of Progress; HX = patient history; LABS = routine laboratory studies; MUGA = radionuclide angiography; NYHA = New York Heart Association functional class; PE = physical examination; LWHF = Living with Heart Failure questionnaire; 6 MIN WALK = 6-min walking test; QD = once daily.

concomitant medications including tricyclic antidepressants, phenothiazines, vasodilators including angiotensin-converting enzyme inhibitors and nitrates, beta-adrenergic blocking agents, calcium channel blocking agents and antiarrhythmic drugs with negative inotropic properties.

Study design. The primary end points of the study were 1) treadmill time on maximal exercise testing, 2) distance covered during a 6-min walking test (11), 3) incidence of treatment failure, and 4) time to treatment failure. Secondary end points included change in signs and symptoms of congestive heart failure, quality of life using the Minnesota Living with Heart Failure questionnaire (12), congestive heart failure score (4), 7-point Global Evaluation of Progress, left ventricular ejection fraction by radionuclide angiography, left ventricular dimensions by echocardiography, vital signs and body weight. Also, routine biochemical variables, electrocardiogram (ECG) and serum digoxin concentration were monitored as safety indexes.

To ensure clinical stability before randomization, an 8-week single-blind stabilization period was mandated (Fig. 1). During this period, serum digoxin concentration was obtained at three time points, and dose adjustments were made to ensure a serum digoxin concentration between 0.9 and 2.0 ng/ml for at least 2 weeks before double-blind randomization. At the time of double-blind randomization, the prescribed digoxin dose required to attain the specified serum digoxin concentration during the single-blind period (or a corresponding placebo dose) was provided during the double-blind period. Patients assigned to placebo therapy were therefore withdrawn from treatment with digoxin. In addition, a fixed diuretic regimen was required for at least 4 weeks before double-blind randomization. Exercise criteria for entering the double-blind study phase included walking between 2 and 12 min on the first of at least four modified Naughton treadmill tests and between 2 and 14 min at the final test, with a <60-s difference between the results of the last two exercise tests. The results of the last single-blind treadmill test were considered as the "baseline value" for comparison with subsequent tests. Patients were exercised to maximal effort, with a Borg score of ≥ 19 (13).

Patients were seen at weeks 1, 2, 4, 6 and 8 during the single-blind stabilization phase. During the double-blind phase, patients were seen every 2 weeks for 3 months. At each visit, vital signs, brief physical examination, 7-point Global Evaluation of Progress, signs and symptoms of heart failure and functional class were determined. At study weeks 1, 4, 6 and 8 of the single-blind and weeks 10, 14 and 20 (2, 6 and 12 weeks of the double-blind period), exercise treadmill tests were performed (see flow diagram, Fig. 1, for a schedule of all tests). The 6-min walking test for total distance was performed at weeks 2 and 8 of the single-blind period and at study weeks 12, 16 and 18 (4, 8 and 10 weeks of double-blind therapy). The Living with Heart Failure questionnaire was administered at 4 and 8 weeks in the single-blind phase and at 12 and 20 weeks during the double-blind period. Congestive heart failure score, echocardiogram, chest X-ray film and radionuclide angiograms were obtained before study and at weeks 8 and 20. Laboratory studies were obtained at 2, 8, 12 and 20 weeks. During the double-blind period, study staff members made semiweekly telephone calls to patients to assess the signs and symptoms of heart failure.

During the double-blind period, an increase in diuretic therapy, addition of new medications for heart failure and death or admission to an emergency room or hospital for heart failure were defined as a treatment failure. Death was not a primary end point because this was not a mortality trial.

After termination of recruitment and follow-up (and before unblinding), a subcommittee of investigators reviewed each reported treatment failure and admission to the hospital or emergency room to ascertain if the event was secondary to congestive heart failure. Each death was also reviewed in a blinded fashion to assess its cause. A consensus was reached with each case; cases deemed not related to heart failure were considered withdrawn to follow-up at that point but not a treatment failure.

The Ethics Committee reviewed and approved the final protocol and was charged to review adverse events and deaths by a priori rule after each 100 randomized patients. Because the study was terminated after 88 patients were randomized, the committee did not convene for this latter purpose.

Statistical methods. An intention-to-treat analysis based on group assignment was used for all primary end points. The number of patients to be recruited was estimated by the expectation of differences in exercise treadmill time. Assuming a difference in exercise time between digoxin and placebo groups of 50 s and an SD of 150 s, it was originally estimated that 300 patients would be required to make a conclusion with 90% power (alpha = 0.05, one-tailed). A nonparametric approach was used to analyze changes in treadmill exercise duration and 6-min walk distance. Treatment group comparisons were made using the extended Mantel-Haenszel statistic (Cochran-Mantel-Haenszel) stratified by center and adjusted for two covariates, baseline exercise time/distance and ejection fraction (14). Patients who died or were withdrawn from the double-blind phase as treatment failures with no final exercise tests had a final exercise duration of lowest rank assigned and carried forward to the remaining time points. Other patients who prematurely discontinued the study had their final double-blind exercise duration carried forward. Carry-forward analyses were also used for the 6-min walk, signs and symptoms of congestive heart failure, physical examination, patient's Global Evaluation of Progress, congestive heart failure score and quality of life. For the analysis of New York Heart Association functional class and patient's Global Evaluation of Progress, patients who died or were classified as treatment failures with missing values on the date of treatment failure were assigned the worst score (that is, functional class IV and "much worse" on the Global Evaluation of Progress). For the analysis of signs and symptoms of congestive heart failure, the worst score was not assigned because it could not be assumed that all signs and symptoms were most severe at the time of treatment failure or death; therefore, the final double-blind score was carried forward. For continuous variables such as left ventricular ejection fraction and echocardiographic variables, an analysis of covariance, using the baseline as the covariate, was performed.

The proportion of patients characterized as treatment failures and the incidence of adverse effects were compared using a Pearson chi-square test (15) and, where there were few events, the Fisher exact test. The distribution of time to treatment failure were compared between groups using the log-rank test (16). The distribution of clinical signs and symptoms and other categoric data were compared using the mean rank score version of the Cochran-Mantel-Haenszel statistic adjusted for investigator. To test the comparability of treatment groups at baseline, an analysis of variance for continuous variables (17) and a Cochran-Mantel-Haenszel test for categoric data were utilized (18). Both analyses were

Table 1. Baseline Demographic and Ventricular Function Variables of Patients Randomized to Placebo and Digoxin Treatment

	Placebo Group (n = 46)	Digoxin Group (n = 42)
Age (yr)	64 ± 2	64 ± 2
Men/women	37/9	38/4
NYHA class II or III	38/7	35/7
LVEF (%)	29 ± 2	27 ± 1
Cardiothoracic ratio	0.5 ± 0.01	0.5 ± 0.01
LVEDD (mm)	67 ± 1	67 ± 1
Duration of CHF (yr)	3.1 ± 0.5	3.6 ± 0.5
Etiology of CHF (%) (ICM/non-ICM)	67/33	60/40
Serum digoxin level (ng/ml)	1.1 ± 0.05	1.2 ± 0.05
Median digoxin dose (mg)	0.375	0.375

Continuous variables are presented as mean value ± SEM. CHF = congestive heart failure; ICM = ischemic cardiomyopathy; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association functional classification.

adjusted for investigator differences. Although sample size estimates were initially based on a one-sided hypothesis, the results of this study were tested and reported herein, using a two-sided hypothesis, with alpha = 0.05. Baseline was defined as the last value obtained before administration of the double-blind study drug.

Study patients. A total of 113 patients were entered into the single-blind phase, and 88 patients were subsequently entered into the double-blind phase. Of these, 46 patients were randomized to placebo and 42 to digoxin therapy. Of the 25 patients who withdrew during the single-blind phase, 15 patients (60%) had either an adverse event or an intercurrent event unrelated to digoxin use, 4 patients (16%) had a protocol violation, and 2 patients each (8%) were either admitted to the hospital for worsening congestive heart failure, did not meet entry requirements for the double-blind period or withdrew consent. Adverse intercurrent events during the single-blind period included two deaths (one sudden and one occurring after an acute myocardial infarction), one cardiac arrest in a patient who was resuscitated, six noncardiac events and six cardiac events not directly related to heart failure (development of atrial fibrillation in three patients who had normal sinus rhythm and worsening angina pectoris, second degree atrioventricular block or ventricular tachycardia in one patient each).

The demographic data and ventricular function were similar in the two groups (Table 1). Signs and symptoms of congestive heart failure were similar except a larger percentage (p = 0.02) of the group randomized to continued digoxin therapy than of the placebo group had jugular venous distension (45% vs. 22%). In addition, the Living with Heart Failure Questionnaire showed, at baseline, more physical impairment (p = 0.04) in the digoxin group than in the placebo group, based on a score of ≥100 (67% vs. 51%).
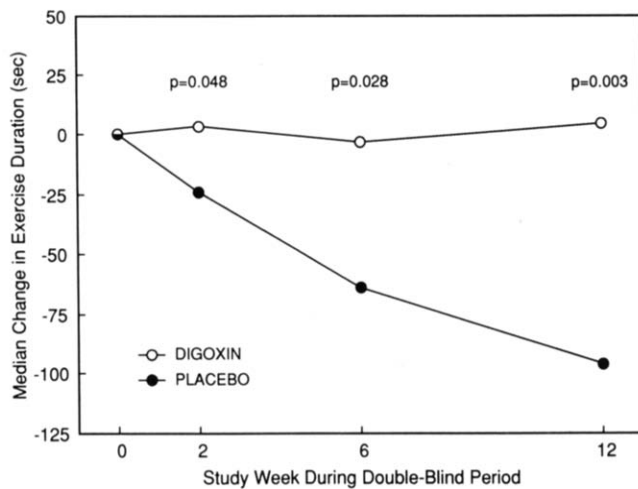
Figure 2. The change (in seconds) in maximal exercise time of patients continued on digoxin treatment compared to patients receiving placebo. The difference in this change between the two groups was highly significant. The number of study weeks represents the time from double-blind randomization.

Figure 3. The number of patients and cumulative incidence (%) of treatment failures (A) and time to treatment of heart failure (B) during the double-blind period. A highly significant increase in rate and cumulative incidence of treatment failures is observed in the placebo group compared with results in the digoxin group.

Results

Three of the four primary end points demonstrated significant differences between the two groups. Median exercise duration at baseline was 540 s in the placebo group and 494 s in the digoxin group. Patients receiving placebo demonstrated significant (p = 0.003) worsening of maximal exercise performance compared with that of patients receiving digoxin (Fig. 2). There was a median decrease of 96 s at 12 weeks in the placebo group and a 4.5-s increase in the digoxin group. Patients randomized to placebo demonstrated a higher percentage of treatment failures (39% vs. 19%, p = 0.039) and a decreased time to treatment failures (p = 0.037) (Fig. 3, Tables 2 and 3) compared with patients maintained on digoxin. Of the primary end points, only the submaximal exercise test (6-min walk) did not demonstrate a statistically significant effect of digoxin.

Of the secondary end points, left ventricular ejection fraction at the end of the double-blind period was significantly higher (p = 0.016) in the digoxin than in the placebo group (Table 4), whereas heart rate (p = 0.003) and body weight (p = 0.044) were lower in the digoxin- than in the placebo-treated group.

There were no significant differences between the two groups at the end of the double-blind period in changes in most signs and symptoms of heart failure, congestive heart failure score or the Living with Heart Failure questionnaire. However, at entry into the double-blind phase, <50% of the patients had an abnormality in most variables (for example, orthopnea and jugular venous distension) or only mild symptoms, such as dyspnea, at baseline. Thus, the ability to demonstrate improvement in these variables in the patient group was limited. However, there was clearly a trend to worsening in most variables in the placebo group as com-
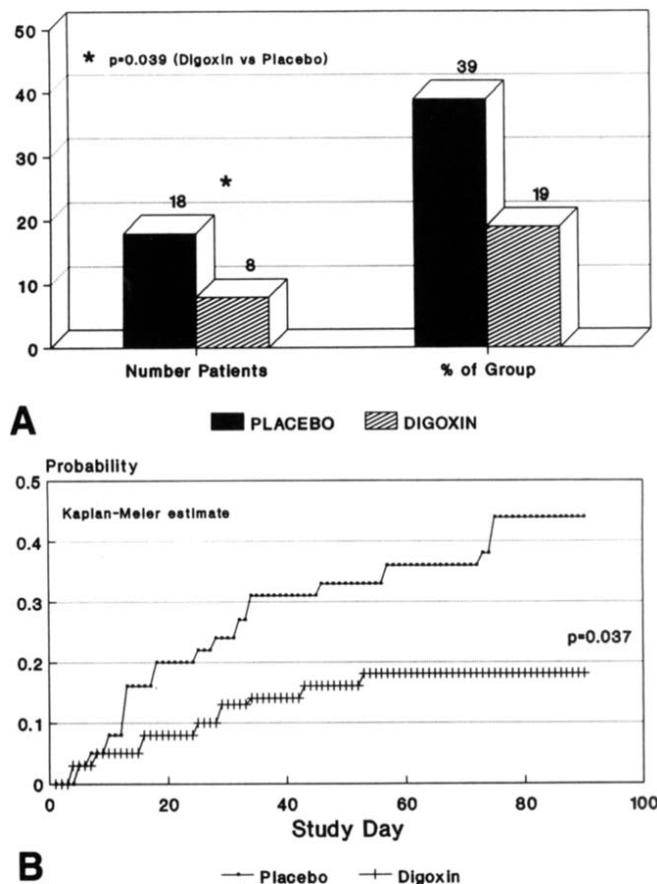
pared with the digoxin group (Fig. 4). Because a significantly higher percentage of patients in the placebo than in the digoxin group withdrew as treatment failures and because many of the secondary end points were not assessed at the time of treatment failure, it is likely that the differences would have been magnified had actual pretreatment failure values been included rather than "carry forward" values obtained at more remote times before study withdrawal. There was a trend toward an increase in left ventricular end-diastolic dimension in the placebo group (1.3 ± 1.6 mm) as compared with the digoxin group (0.4 ± 1.5 mm). The difference at the end of the double-blind period in blood urea nitrogen and serum creatinine was significant (Table 4).

The overall percentage of patients with one or more adverse experiences of any type during the double-blind period was similar in the two groups: 59% (27 of 46) in the placebo group and 69% (29 of 42) in the digoxin group.

There were no clinical episodes of digitalis toxicity. By intention-to-treat analysis, there were two deaths in the placebo group and one in the digoxin group during the double-blind period.

Table 2. Reasons for Withdrawal From the Trial

Reasons for Withdrawal	Placebo Group (n = 46) (no. [%])	Digoxin Group (n = 42) (no. [%])	p Value
Increase in drug therapy for worsening heart failure*	9 [20]	5 [12]	
Hospital admission for worsening heart failure	6 [13]	3 [7]	
Emergency room treatment for worsening heart failure	1 [2]	0 [0]	
Intercurrent/adverse events (includes death)	2 [4]	1 [2]	
Other†	3 [6]	1 [2]	
Total	21 [46]	10 [24]	0.032

*The blinded treatment failure review committee determined that one additional patient in the placebo group had worsened heart failure requiring an increase in drug therapy on the last study visit (Table 3). This patient is not included in Table 2 because the patient was not withdrawn prematurely from the trial. The committee also determined that one of the five patients in the digoxin group withdrawn because of increased drug therapy did not, in fact, have worsened heart failure (Table 3). †These patients include one patient each in the placebo group with a protocol violation, loss to follow-up, and withdrawal of consent and one patient in the digoxin group with withdrawal of consent.

Discussion

The results of this study provide strong evidence that digoxin is effective in treating patients with chronic congestive heart failure secondary to systolic dysfunction who have mild to moderate symptoms and normal sinus rhythm. Specifically, withdrawal of digoxin resulted in a significant worsening of exercise performance and an increased incidence of, and a decreased time to, treatment failure. Additional evidence of clinical efficacy was an increase in ejection fraction and a decrease in body weight and heart rate in the digoxin group.

The conclusions of this study are strengthened by the rigor employed to establish a stable baseline. The length of the single-blind baseline phase (8 weeks), the requirement of a minimum of four baseline exercise tests, the last two within 60 s of each other, and an insistence on unchanged medical therapy for 4 weeks before double-blind entry represent extremely stringent criteria for baseline stability. That such

Table 3. Treatment Failures

Causes of Treatment Failure	Placebo Group (n = 46) (no. [%])	Digoxin Group (n = 42) (no. [%])	p Value
Increased drug therapy	10 [22]	4 [10]	
Hospital admission for worsened heart failure	6 [13]	3 [7]	
Emergency room treatment for worsened heart failure	1 [2]*	0 [0]	
Death	1 [2]	1 [2]	
Total	18 [39]	8 [19]	0.039

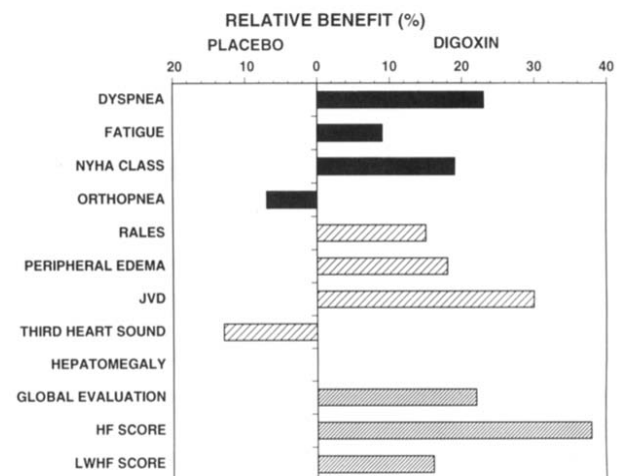*This patient later also died but is not included under Death.

Figure 4. The relative clinical benefit of digoxin at 12 weeks of the double-blind phase was calculated by measuring relative improvement of the digoxin group over that of the placebo group and subtracting the relative worsening. (Relative benefit = relative improvement minus relative worsening.) Relative improvement (worsening) for each variable was calculated as percent of digoxin-treated patients with improvement (worsening) minus the percent of placebo-treated patients with improvement (worsening). For example, in the dyspnea category improvement occurred in 24% of the digoxin group and in 11% of the placebo group. Thus, the relative digoxin improvement was 13%. Worsening occurred in 19% of the digoxin group and in 29% of the placebo group. Thus, relative worsening for digoxin was −10% (19% to 29%). Therefore, the relative benefit of digoxin in the dyspnea category was 13% (relative improvement) − (−10%) (relative worsening) = +23%. The percent of patients classified as showing "no change" is not included in either group. HF = heart failure; JVD = jugular venous distension; other abbreviations as in Figure 1.

baseline stability was, in fact, achieved is perhaps best demonstrated by the virtually unchanged maximal exercise capacity observed after randomization in patients who continued digoxin treatment (Fig. 2). In addition, strict attention to adequate digitalization was ensured before digoxin withdrawal during the double-blind phase.

A limitation of this study is the relatively small number of patients included. The nearly universal use of angiotensin-converting enzyme inhibitors made timely patient recruitment impossible. Nevertheless, the study was able to demonstrate efficacy in three of the four primary end points. In the companion trial, RADIANCE, which required angiotensin-converting enzyme inhibitors as background therapy and recruited approximately twice the number of patients included in the present PROVED study, all four primary end points showed significant treatment differences in favor of digoxin (10). In the subjective and difficult to quantify measures of signs and symptoms of heart failure, there was an internal consistency in this study with a trend toward worsening of signs and symptoms in the placebo group and a trend toward improvement in the digoxin group (Fig. 4). This trend was present even though actual values for these secondary end points were usually not obtained before patient withdrawal because of treatment failure and values at the point of pretreatment failure (which were likely to be less

Table 4. Significant Differences in Secondary End Points and Safety Variables Between Digoxin and Placebo Groups at the End of the Double-Blind Period

	Baseline		Change From Baseline		
	Placebo	Digoxin	Placebo	Digoxin	p Value
LVEF (%)	29 ± 2	27 ± 1	−3 ± 2	+2 ± 2	0.016
BW (kg)	83 ± 3	76 ± 3	0.5 ± 0.6	−0.9 ± 0.5	0.044
HR (beats/min)	73 ± 1	73 ± 2	11 ± 3	−0.2 ± 3	0.003
BUN (mg/100 ml)	19 ± 1	19 ± 1	3 ± 1	0.2 ± 3	0.003
Creat (mg/100 ml)	1.2 ± 0.05	1.2 ± 0.05	0.09 ± 0.04	−0.02 ± 0.04	0.024

All values are presented as mean value ± SEM. BUN = blood urea nitrogen; BW = body weight; Creat = serum creatinine; HR = supine testing heart rate; LVEF = left ventricular ejection fraction.

severely abnormal) were carried forward. Because most symptoms and signs of heart failure were absent or minimal in at least 50% of the patient group, it is possible that a much larger cohort than that in the PROVED trial would have been necessary to document differences in all these variables.

A frequent clinical situation is that of a patient who had an episode of congestive heart failure sometime in the past, has been clinically stable for a prolonged period on maintenance digoxin therapy and whose physician is considering whether digoxin therapy can be discontinued. The present data argue that a patient who continues to have even mild functional limitation and has both a reduced ejection fraction and left ventricular dilation, is at risk of clinical deterioration if digoxin therapy is withdrawn.

An extremely important issue is whether the results of the present withdrawal study can be applied to congestive heart failure patients for initiation of digoxin therapy. Although it may be considered a leap of faith to do so, we consider the extrapolation small, given the rigor of the study design, the strength of the positive results and the fact that the patients in the present study were originally treated with digoxin by their treating physicians to improve their clinical state and functional capacity.

One question raised by the results of this study is whether one needs to titrate to a serum digoxin concentration for clinical efficacy. In the present study, the purpose of titrating digoxin dose to serum concentration was to ensure that serum digoxin concentrations would be within the generally accepted therapeutic (0.9 to 2.0 ng/ml) and not toxic range. In fact, the mean digoxin concentration achieved in this study was in the middle of this range (1.2 ng/ml). Furthermore, the serum concentrations at the various doses before double-blind randomization were not different. The lack of digitalis toxicity suggests that this approach was effective. A secondary reason for utilizing serum digoxin concentrations was to ascertain that a reasonable concentration (>0.8 ng/ml) was present to test the efficacy of digoxin most effectively. These precautions to assure safety do not imply that the clinician must titrate to a certain serum digoxin concentration. This study did not test the relative efficacy of digoxin at different doses or at different serum concentrations to validate this approach to therapy.

The median (0.375 mg) dose of digoxin in this study may be viewed as high compared with doses most often used in

present clinical practice. This study was confined to patients with chronic heart failure, relatively normal renal function and without extremely poor systemic flow, as judged by the patient's clinical state. In patients with these problems or with acute heart failure, lower doses may be adequate to produce comparable serum concentrations.

It might be argued that these data are no longer clinically relevant because currently accepted medical therapy for chronic congestive heart failure secondary to systolic dysfunction and normal sinus rhythm includes angiotensin-converting enzyme inhibitors. The purpose of this study was to evaluate the clinical efficacy of digoxin rather than consider its efficacy as part of a therapeutic strategy including background angiotensin-converting enzyme inhibition. The latter evaluation was performed in the RADIANCE trial (10). Both studies demonstrated the clinical efficacy of digoxin with or without background angiotensin-converting enzyme inhibition.

The effect of digoxin on survival was not addressed in this study and remains an important issue to be resolved. A study sponsored by the National Heart, Lung, and Blood Institute and the Veterans Affairs Cooperative Studies Center, which plans to enroll 8,000 patients (DIG), is underway in North America to test the effect of digoxin on survival and major morbidity. Because a difference between favorable clinical effects and an adverse effect on survival has been observed with certain other agents used in congestive heart failure (7,19), it seems reasonable to proceed with this study despite the positive results of the PROVED and RADIANCE trials.

Appendix

The PROVED Trial

Clinical Investigators and Sites

Najam Awan, MD, Sacramento, CA. *Principal Investigator:* Chuck Sears, Leslie Sears, RN, *Study Coordinators.*

Tanvir Bajwa, MD, Milwaukee, WI. *Principal Investigator:* Cheryl Maglio, RN, *Study Coordinator.*

Carl Carlson, MD, Fremont, CA. *Principal Investigator:* Catherine Carlson, *Study Coordinator.*

Harry T. Colfer, MD, Petoskey, MI, *Principal Investigator*; Karen Graham, Colleen Shaw, RN, *Study Coordinators*.

Peter J. Costantini, DO, Linwood, NJ, *Principal Investigator*; Daphne Stanley, RT, Rande Mathesen, RT, *Study Coordinators*.

Alan Dauer, MD, Whittier, CA, *Principal Investigator*; Vera Holt, RN, *Study Coordinator*.

Robert Detje, MD, Clearlake, CA, *Principal Investigator*; Cathy Chisolm, RN, *Study Coordinator*.

John R. Filip, MD, Penn Valley, PA, *Principal Investigator*; Sandy Perri, *Study Coordinator*.

Michael Fisher, MD, Baltimore, MD, *Principal Investigator*; Nancy Greenberg, RN, Catherine Kritchen, RN, MS, *Study Coordinators*.

James Galyean III, MD, Memphis, TN, *Principal Investigator*; Susan Jaynes Smith, RN, *Study Coordinator*.

David Goldscher, MD, Baltimore, MD, *Principal Investigator*; Sandy De Petris, RN, *Study Coordinator*.

Lloyd Goodman, MD, Savannah, GA, *Principal Investigator*; Sarah Lanier, RN, *Study Coordinator*.

General Hilliard, MD, Oakland, CA, *Principal Investigator*; Marilou Lucero, RN, *Study Coordinator*.

Ronald Karlsberg, MD, Beverly Hills, CA, *Principal Investigator*; Sonia Maccioni, *Study Coordinator*.

Paul Pennock, MD, Newark, DE, *Principal Investigator*; Nancy Gale, RN, *Study Coordinator*.

Melissa Reynolds, MD, Vero Beach, FL, *Principal Investigator*; Betsy Screws, RN, Kathy King, RN, *Study Coordinators*.

Allen Rhodes, MD, Las Vegas, NV, *Principal Investigator*; Bob Vanselow, PA, *Study Coordinator*.

James Sandberg, MD, Allentown, PA, *Principal Investigator*; Claire Yurick, RN, *Study Coordinator*.

F. Eden Shahidi, MD, Garden City, NY, *Principal Investigator*; Jeneane Shahidi, *Study Coordinator*.

John Somberg, MD, North Chicago, IL, *Principal Investigator*; Phyllis Collins, RN, *Study Coordinator*.

Leo Spaccavento, MD, San Antonio, TX, *Principal Investigator*; Mary Jane Burns, RN, *Study Coordinator*.

Robert Stein, MD, Escondido, CA, *Principal Investigator*; Bobbie Seibert, *Study Coordinator*.

Michael Sullivan, MD, San Diego, CA, *Principal Investigator*; Karen Engstrand, *Study Coordinator*.

Alan Taranto, MD, Atlanta, GA, *Principal Investigator*; Diane Blum, RN, *Study Coordinator*.

Udho Thadani, MD, Oklahoma City, OK, *Principal Investigator*; Allyson Potts, RN, *Study Coordinator*.

Serge Tobias, MD, Long Beach, CA, *Principal Investigator*; Cindy Tayek, *Study Coordinator*.

Barry F. Uretsky, MD, Pittsburgh, PA, *Principal Investigator*; Srinivas Murali, MD, *Co-Investigator*; Tammy Tokarczyk, RN, *Study Coordinator*.

Nampalli Vijay, MD, Denver, CO, *Principal Investigator*; Melinda Washem, RN, *Study Coordinator*.

George Williams, MD, Saint Louis, MO, *Principal Investigator*; Ruth Genovely, RN, *Study Coordinator*.

Larry Yellen, MD, San Diego, CA, *Principal Investigator*; Nancy Junker, RN, Amy Clark, RN, *Study Coordinators*.

James B. Young, MD, Houston, TX, *Principal Investigator*; Marilyn Francis, RN, *Study Coordinator*.

Edward T. Zawada, MD, Sioux Falls, SD, *Principal Investigator*; Linda Williams, RN, *Study Coordinator*.

Coordinating Center

G. H. Besselaar Associates, Princeton, NJ; Lynn Gourley, RN, MS, Valerie Arneson, MS, Sarah Lowell, MS, Maria Harrison, BS, John S. Whalen, MD, Michael Klein, PhD, *Project Team*.

Sponsoring Center

Burroughs Wellcome Co., Research Triangle Park, NC; M. King Jolly, PharmD, *Project Director*; Robert L. Rolleri, PharmD, *Project Co-Director*; Mike Thorn, MS, DrPH, *Statistician*.

Ethics Committee

Gary Francis, MD, Minneapolis, MN; Richard Gorlin, MD, New York, NY; Mariell Jessup, MD, Philadelphia, PA; John Wilson, MD, Philadelphia, PA.

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