JACC Vol. 30, No. 1
July 1997:42–8

Patients With Mild Heart Failure Worsen During Withdrawal From Digoxin Therapy

KIRKWOOD F. ADAMS, JR., MD, FACC, MIHAI GHEORGHIADE, MD, FACC,*
BARRY F. URETSKY, MD, FACC,† JAMES B. YOUNG, MD, FACC,‡ SAGIR AHMED, MD,
LISA TOMASKO, MS, MILTON PACKER, MD, FACC§

Chapel Hill, North Carolina; Chicago, Illinois; Galveston, Texas; Cleveland, Ohio; and New York, New York

Objectives. **We investigated whether patients with mild heart failure due to left ventricular systolic dysfunction were at risk of worsening during digoxin withdrawal.**

Background. **Deterioration during digoxin withdrawal is often believed to be restricted to patients with moderate to severe clinical evidence of heart failure. To test this hypothesis, we studied the outcome of patients categorized by treatment assignment and a clinical signs and symptoms heart failure score in two rigorously designed clinical heart failure trials: the Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin (PROVED) and the Randomized Assessment of Digoxin and Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) trial.**

Methods. **Potential differences in treatment failure, left ventricular ejection fraction and exercise capacity were evaluated in three groups of patients: those with mild heart failure (score ≤2) who were withdrawn from digoxin (Dig WD Mild); those with moderate heart failure (score >2) who were withdrawn from digoxin (Dig WD Moderate); and patients who continued receiving digoxin regardless of heart failure score (Dig Cont).**

Results. **Heart failure score at randomization did not predict outcome during follow-up in Dig Cont-group patients. Dig WD Mild-group patients were at increased risk of treatment failure and had deterioration of exercise capacity and left ventricular ejection fraction compared with that in Dig Cont-group patients (all $p < 0.01$). Patients in the Dig WD Moderate group were significantly more likely to experience treatment failure than patients in either the Dig WD Mild or Dig Cont group (both $p < 0.05$).**

Conclusions. **Patients with systolic left ventricular dysfunction were at risk of clinical deterioration after digoxin withdrawal despite mild clinical evidence of congestive heart failure.**

(J Am Coll Cardiol 1997;30:42–8)

Historically, a number of controversies have surrounded the use of digitalis in patients with heart failure. One classical debate appears to be resolved (1). Favorable results from early studies have been confirmed by more rigorous clinical trials that support the role of digoxin in the treatment of patients with heart failure who are in normal sinus rhythm rather than atrial fibrillation (2–12). Additionally, results of the Digoxin Investigators Group (DIG) study (13) appear to resolve two important and persistent issues concerning digoxin efficacy. Benefit was evident whether digoxin was withdrawn or added to background therapy, and no adverse mortality effect was associated with digoxin use.

These trial results draw attention to the remaining unresolved issues concerning digoxin therapy in heart failure. One debate of particular clinical importance concerns the utility of digoxin in patients with significant left ventricular dysfunction but little or no clinical evidence of classical congestive heart failure (14,15). The important early clinical trials of Lee et al. (4) and Guyatt et al. (6) suggested that the favorable clinical response to digoxin in heart failure might be restricted to patients who had substantial clinical evidence of congestion and shortness of breath. Since that time, digitalis has often been considered to be ineffective in patients who, despite a history of heart failure, are lacking significant signs and symptoms of this syndrome at the time of presentation.

Despite the clinical importance of this issue, most efficacy studies have not been able to specifically investigate the therapeutic effects of digoxin in patients with mild clinical heart failure. Small sample sizes and lack of characterization of patient signs and symptoms limit conclusions from these investigations (1–9). In contrast, the combined experience

From the Departments of Medicine and Radiology, School of Medicine and Department of Biostatistics, School of Public Health, University of North Carolina, Chapel Hill, North Carolina; *Department of Medicine, Northwestern University Medical School, Chicago, Illinois; †Department of Medicine, University of Texas Medical Branch, Galveston, Texas; ‡Department of Cardiology, Cleveland Clinic Foundation, Cleveland, Ohio; and §Center for Heart Failure Research, Columbia University College of Physicians and Surgeons, New York, New York. The PROVED and RADIANCE studies were supported by a grant from Glaxo-Wellcome, Inc., Research Triangle Park, North Carolina. Work related to the present publication was supported in part by PHS Research MO1 RR00046 from the General Clinical Research Centers branch of the Division of Research Resources, National Institutes of Health, Bethesda, Maryland and by an unrestricted grant from Glaxo-Wellcome, Inc., Research Triangle Park, North Carolina.

Manuscript received December 6, 1996; revised manuscript received March 6, 1997, accepted March 20, 1997.

Address for correspondence: Dr. Kirkwood F. Adams, Jr., Division of Cardiology, University of North Carolina at Chapel Hill, CB# 7075, Burnett-Womack Building, Chapel Hill, North Carolina 27599-7075. E-mail: kfa@med.unc.edu.

Published by Elsevier Science Inc.

0735-1097/97/$17.00
PII S0735-1097(97)00133-2

Abbreviations and Acronyms

ACE	=	angiotensin-converting enzyme
Dig Cont	=	patients who continued receiving digoxin regardless of heart failure score
Dig WD Mild	=	patients with mild heart failure (score ≤2) who were withdrawn from digoxin
Dig WD Moderate	=	patients with moderate heart failure (score >2) who were withdrawn from digoxin
PROVED	=	Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin
RADIANCE	=	Randomized Assessment of Digoxin and Inhibitors of Angiotensin-Converting Enzyme

from the Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin (PROVED) (10) and Randomized Assessment of Digoxin and Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) (11) trials of digoxin withdrawal provides a unique opportunity to further investigate this issue. Detailed data concerning heart failure signs and symptoms were prospectively collected in these trials before randomization and combined into a composite heart failure score after a modification of that of Carlson et al. (16). We compared the outcome of patients with mild heart failure (score ≤2) who were withdrawn from digoxin therapy (Dig WD Mild) with that of patients who continued to receive digoxin regardless of heart failure score (Dig Cont) and patients with moderate heart failure (score >2) who were withdrawn from digoxin (Dig WD Moderate).

Methods

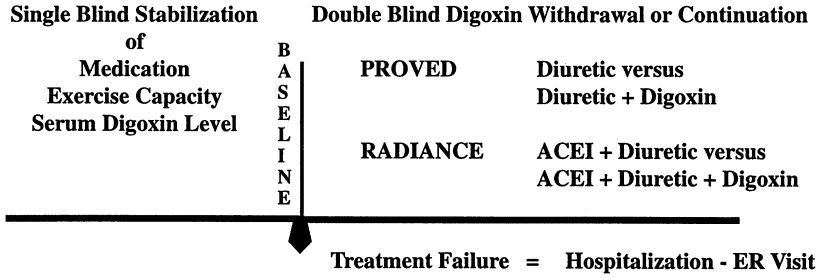
Design of protocols. The PROVED (10) and RADIANCE (11) trials shared a similar design (Fig. 1). Both studies were multicenter, double-blind, randomized, placebo-controlled parallel-group protocols. Each study began with an 8-week single-blind stabilization phase that patients had to successfully complete to be eligible for randomization. During this run-in period, the patients' background therapy for heart failure was optimized. Background therapy consisted of digoxin and diuretic drugs in the PROVED trial and digoxin, diuretic drugs and angiotensin-converting enzyme (ACE) inhibitors in the RADIANCE study. Serum digoxin concentration was obtained on several occasions, and dose adjustments were made in an attempt to achieve a serum digoxin concentration of 0.9 to 2.0 ng/ml for at least 2 weeks before randomization. The ACE inhibitor (RADIANCE) and diuretic drug doses (RADIANCE and PROVED) had to be unchanged for 4 weeks before randomization. Treadmill exercise time had to be between 2 and 12 min on the initial and final tests, and exercise duration could not differ by ≥60 s on the last two tests. Patients completing this baseline phase were randomized to continue digoxin therapy or to receive placebo instead of digoxin while trial-specific background therapy was kept constant for as long as possible during follow-up. After randomization, patients were reassessed in detail regarding clinical status, exercise capacity and ventricular function. Patients were withdrawn from either study for adverse reactions during follow-up or if their heart failure worsened sufficiently to require one of the following therapeutic interventions: change in background therapy, visit to an emergency room for increasing heart failure or hospital admission for heart failure. A committee of investigators uninvolved in the care of the specific study patients and unaware of treatment assignment classified each withdrawal in the two studies as due to worsening heart failure or an adverse reaction unrelated to heart failure status.

Entry criteria. Patients ≥18 years old with mild to moderate symptoms of heart failure (New York Heart Association functional class II or III) who were in normal sinus rhythm and had a radionuclide left ventricular ejection fraction ≤0.35 and a left ventricular end-diastolic dimension ≥60 mm or ≥34 mm/m^2 were considered for enrollment in the trials. Symptomatic heart failure was documented in all patients on the basis of evidence of peripheral edema, jugular venous distension and the presence of interstitial edema or pulmonary congestion on chest X-ray film. Reasons for exclusion from the two trials were the same and included uncorrected primary valvular disease, active myocarditis, obstructive or restrictive cardiomyopathy, exercise limited by angina, angina requiring continuous therapy or myocardial infarction within the previous 3 months. Patients with a history of supraventricular arrhythmia or sustained ventricular arrhythmia were excluded.

Analysis of end points. Data from the PROVED and RADIANCE trials were combined for purposes of this analysis. The primary objectives of both PROVED and RADIANCE were to compare patients randomized to continue or discontinue receiving digoxin with respect to the following particular end points: 1) rates of withdrawal due to worsening heart failure; 2) time to withdrawal; and 3) changes in exercise capacity as assessed by treadmill testing or the 6-min walk test. In the present analysis, end points 1 and 2 were considered together in a time-dependent analysis, and evaluation of exercise capacity was restricted to treadmill testing. In addition, we compared the change in left ventricular ejection fraction from randomization to the last measured value in the study patients.

Heart failure score. Categorization of the degree of clinical heart failure was based on a heart failure score determined from patient symptoms, signs and chest X-ray results collected at the randomization visit. A composite score was computed by a modification of the method of Carlson et al. (16) as shown in Table 1. The modified point system and signs and symptoms were similar to those investigators, except that our score did not award points for wheezing, S_3, bilateral pleural effusion or a cardiothoracic ratio >0.50, and exertional dyspnea was not divided into walking and climbing.

Statistical analysis. Various clinical characteristics were compared at randomization among groups of study patients by analysis of variance methods or the chi-square test, as appro-



Visit No	1	2	3	4	5	6	7	8	9	10	11	12	13
Study Wk	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
Echo	X					X							X
CXR	X					X							X
LVEF	X					X							X
ETT		X		X	X	X		X		X			X
6 MinWalk			X				X		X		X	X	
SDC	X			X		X							X
Chg Dig		X			X								X

Figure 1. Study schema of the PROVED and RADIANCE studies. After a single-blind stabilization period, patients were randomized to continue or discontinue digoxin with background therapy as indicated. Occurrence of treatment failure was determined by an events committee that had no knowledge of treatment assignment. ACEI = angiotensin-converting enzyme inhibitor; Chg Dig = investigator change in digoxin dose; CXR = chest X-ray film; Echo = echocardiogram; ER = emergency room; ETT = maximal treadmill exercise test; HF = heart failure; Hx = history; LVEF = left ventricular ejection fraction; Meds = medications; NYHA = New York Heart Association functional class; PE = physical examination; SDC = serum digoxin concentration; 6 MinWalk = 6-min walk test.

priate. Changes in left ventricular ejection fraction and exercise capacity were compared at the end of the follow-up period between patient groups using the Student *t* test or the Wilcoxon rank-sum test, as appropriate. The risk of treatment failure was compared between the patient groups by standard life-table methods (17) and by a multivariate Cox proportional hazards regression technique (18).

Results

Patient groups. The study analysis was based on the 258 patients in the PROVED and RADIANCE trials who completed the stabilization period and had a heart failure score determined at randomization. These patients were classified into three groups on the basis of treatment assignment and median heart failure score: 1) patients who continued receiving digoxin regardless of their heart failure score (Dig Cont); 2) patients withdrawn from digoxin who were defined as having mild heart failure on the basis of a total score of ≤2 (Dig WD Mild); and 3) patients withdrawn from digoxin who were defined as having moderate heart failure on the basis of a total score of >2 (Dig WD Moderate). Comparisons of selected baseline characteristics among these three groups of study patients revealed them to be similar in most respects (Table 2). Differences between the groups were noted only for exercise duration and left ventricular end-diastolic dimension by echocardiography.

Distribution of heart failure score. The individual components of the heart failure score at randomization in the three groups of study patients are shown in Table 3. In the Dig WD Mild group, 8 (11%) of 75 patients had a heart failure score of zero, whereas 44 (59%) of 75 had a total score of 1. Dyspnea on exertion was the predominant symptom in this group and was present in 59 (79%) of 75 patients. In contrast, no evidence of rales was found in 72 (96%) of these 75 patients. Only one patient in the Dig WD Mild group had evidence of right heart failure at randomization, and only seven had chest X-ray evidence of pulmonary congestion. In the Dig WD Moderate group, 20% of the patients had basilar rales, and 33% had chest X-ray evidence of heart failure.

Treatment failure. Worsening heart failure occurred in 11 (9%) of 122 Dig Cont-group patients. Life-table analysis demonstrated no relation between heart failure score at randomization and risk of treatment failure in this subset of study patients ($p = 0.944$) (Fig. 2). Treatment failure occurred in 6 (9.5%) of 63 patients in this Dig Cont group who had mild heart failure by clinical score (≤2) compared with 5 (8.5%) of the remaining 59 patients who had moderate heart failure score (>2).

Treatment failure occurred in 17 (23%) of the 75 patients who were in the Dig WD Mild group and in 24 (39%) of the 61 patients in the Dig WD Moderate group. Life-table analysis demonstrated that patients in the Dig WD Mild group were significantly more likely to experience worsening heart failure than those in the Dig Cont group ($p = 0.011$) (Fig. 2). Similar analysis demonstrated that patients in the Dig WD Moderate group were significantly more likely to experience treatment failure than either patients in the Dig Cont group ($p < 0.001$) or those in the Dig WD Mild group ($p = 0.028$) (Fig. 2).

Cox proportional hazards regression analysis evaluated the

Table 1. Heart Failure Score Computation

Point Value	Dyspnea	Standing HR (beats/min)	Rales	Right HF	Chest X-Ray Findings
1	Exertional	91–110	Base(s) only	JVP >6 cm H_2O	Upper zone flow redistribution
2	Nocturnal	>110	>Base(s)	JVP >6 cm H_2O + edema or hepatomegaly	Interstitial edema
3	Orthopnea	—	—	—	Alveolar edema or interstitial edema with pleural effusions
4	At rest	—	—	—	—
Max points/ category	4	2	2	2	3

Heart failure (HF) score is the total sum of the points awarded, up to the maximum (Max), for each of the five categories. The highest possible score, equal to the sum of the maximal number of points in each category is 13 and corresponds to the most severe symptomatic state of heart failure. HR = heart rate; JVP = jugular venous pulse; — = not applicable.

likelihood of treatment failure in the Dig WD Mild and Dig WD Moderate groups compared with that in the Dig Cont group after adjustment for left ventricular ejection fraction, cardiothoracic ratio and ACE inhibitor use determined at randomization (Table 4). This multivariate analysis demonstrated that both the Dig WD Mild ($p = 0.002$) and Dig WD Moderate groups ($p < 0.001$) had a significantly greater risk of treatment failure than the Dig Cont group (Table 4). In addition, the multivariate modeling suggested that patients in the Dig WD Moderate group were significantly more likely to

Table 2. Baseline Clinical Characteristics in the Three Groups of Study Patients

		Digoxin Withdrawal		
	Dig Cont Group (n = 122)	Dig WD Mild Group (n = 75)	Dig WD Moderate Group (n = 61)	p Value*
Age (yr)	63 ± 1.0	62 ± 1.4	60 ± 1.6	0.293
Male/female	94/28	59/16	51/10	0.587
Etiology				0.333
Ischemic	76	48	32	
Nonischemic	46	27	29	
Duration of HF (yr)	4.3 ± 0.5	3.3 ± 0.4	3.9 ± 0.6	0.245
HF score				
0–1	36	52	0	
2	27	23	0	
3	29	0	34	
≥4	30	0	27	
Median	2.0	1.0	3.0	
SDC (ng/ml) (wk 8)	1.2 ± 0.0	1.1 ± 0.1	1.1 ± 0.1	0.220
Supine HR (beats/min)	76 ± 1.1	74 ± 1.3	78 ± 1.7	0.268
Supine SBP (mm Hg)	127 ± 1.6	127 ± 2.2	124 ± 2.3	0.432
LVEF (U)	26 ± 0.9	30 ± 1.1	27 ± 1.3	0.053
LVEDd (mm)	69 ± 1.0	66 ± 0.9	70 ± 1.1	0.033
CT ratio	0.53 ± 0.01	0.52 ± 0.01	0.54 ± 0.01	0.137
Median ex time (s)	495	609	408	<0.001

*Reflects overall differences between patient groups assessed by analysis of variance methods or chi-square statistic, as appropriate. Data presented are mean value ± SEM, median or number of patients where appropriate. CT = cardiothoracic; Dig Cont = patients who continued receiving digoxin regardless of heart failure (HF) score; Dig WD Mild = patients with mild heart failure (score ≤2) in whom digoxin was withdrawn; Dig WD Moderate = patients with moderate heart failure (score >2) in whom digoxin was withdrawn; HR = heart rate; LVEDd = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; SBP = supine blood pressure; SDC = serum digoxin concentration taken after 4 to 8 weeks (randomization visit) of stabilization.

Table 3. Components of Heart Failure Score in the Patient Groups

		Digoxin Withdrawal	
	Digoxin Cont Group (n = 122)	Dig WD Mild Group (n = 75)	Dig WD Moderate Group (n = 61)
Total HF score (%)			
0	4	11	0
1	25	59	0
2	22	31	0
3	24	0	56
≥ 4	25	0	44
Dyspnea (%)			
0 = none	8	17	0
1 = exertional	53	79	10
2 = nocturnal	6	4	7
3 = orthopnea	31	0	82
4 = at rest	3	0	2
Standing HR (%)			
0 <91 beats/min	72	84	74
1 = 91–110 beats/min	25	16	25
2 >110 beats/min	3	0	1
Rales (%)			
0 = no rales	90	96	80
1 = bases only	10	4	20
2 >bases	0	0	0
Right HF (%)			
0 = not present	91	99	90
1 = JVP >6 cm H_2O	3	0	3
2 >6 cm H_2O+edema or hepatomegaly	6	1	7
Chest X-ray abnormality (%)			
0 = none present	72	91	67
1 = upper zone redistribution	19	8	15
2 = interstitial edema	6	1	13
3 = alveolar edema	3	0	5

Data presented are percent of patients; zero indicates absence findings (see Table 1). Abbreviations as in Table 2.

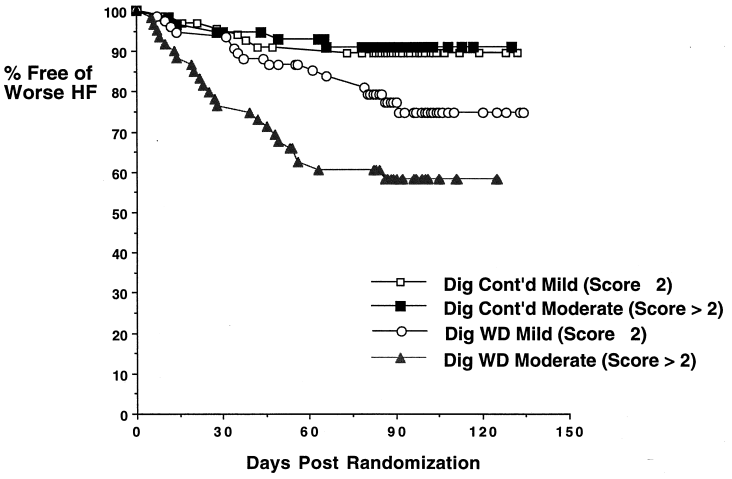


Figure 2. Likelihood of deterioration of heart failure (HF) status in patients continuing digoxin therapy (Dig Cont'd) who had mild or moderate heart failure by clinical score versus patients withdrawn from digoxin who had mild (Dig WD Mild) or moderate heart failure (Dig WD Moderate) by the same score criteria. Life-table analysis revealed no difference in the risk of treatment failure by heart failure score category in patients who continued receiving digoxin ($p = 0.944$). The risk of worsening was significantly greater in patients with mild heart failure who were withdrawn from digoxin than in all patients who continued receiving digoxin ($p = 0.011$). Patients withdrawn from digoxin who had moderate heart failure were significantly more likely to experience treatment failure during follow-up than either patients who continued receiving digoxin ($p < 0.001$) or patients in the mild heart failure group ($p = 0.028$).

experience treatment failure than patients in the Dig WD Mild group ($p = 0.026$). Finally, multivariate analysis demonstrated that patients in both the Dig WD Mild ($p = 0.001$) and Dig WD Moderate ($p < 0.001$) groups were significantly more likely to deteriorate than patients in the Dig Cont group after adjustment for baseline differences in exercise duration and left ventricular end-diastolic diameter.

Ventricular function and exercise capacity. Figure 3 demonstrates the change in left ventricular ejection fraction during the course of the follow-up period in the three patient groups. Left ventricular ejection fraction declined to a significant and similar degree in the Dig WD Mild and Dig WD Moderate groups compared to the Dig Cont group (both $p < 0.001$). Changes in exercise duration during maximal treadmill exercise testing in the three patient groups are shown in Figure 4. At the final study visit, exercise duration was significantly less in patients in the Dig WD Mild ($p = 0.009$) and Dig WD Moderate ($p < 0.001$) groups compared to Dig Cont patients. Exercise capacity also deteriorated to a significantly greater degree in the Dig WD Moderate group compared to the Dig WD Mild group ($p = 0.005$).

Discussion

We investigated the risk of clinical deterioration during digoxin withdrawal in patients with mild heart failure due to left ventricular systolic dysfunction. We found that these patients were at risk for worsening heart failure even though they had few or no symptoms or signs typical of congestive heart failure at randomization. Other clinical indexes also demonstrated that patients with mild heart failure deteriorated during digoxin withdrawal. They experienced a significant reduction in exercise capacity and left ventricular ejection fraction after discontinuing digoxin compared with patients maintained on this drug. Patients in the Dig WD Mild group remained at risk of worsening heart failure compared with patients in the Dig Cont group after adjusting for baseline ACE inhibitor use, cardiothoracic ratio and left ventricular ejection fraction.

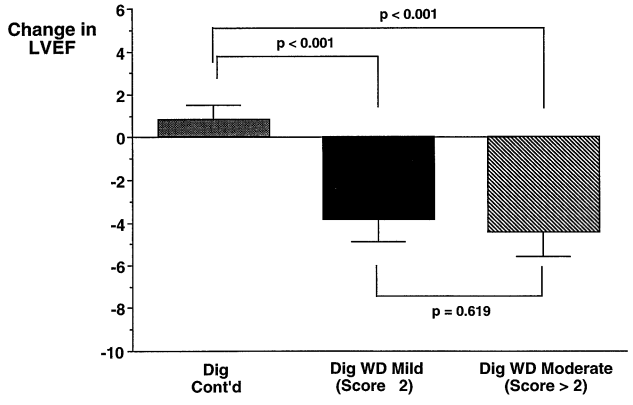
Our analysis also suggested that patients with moderate clinical evidence of heart failure were at even greater risk of treatment failure during digoxin withdrawal. Patients in the Dig WD Moderate group were more likely to experience

Table 4. Adjusted Risk of Treatment Failure: Mild and Moderate Patient Groups Versus Digoxin-Continued Patient Group

Patient Group	Hazard Ratio (95% CI)	p Value*
Dig WD Mild	3.50 (1.58–7.76)	0.002
Dig WD Moderate	7.30 (3.43–15.4)	<0.001
Dig WD Mild vs. Dig WD Moderate		0.028

*Based on a Cox proportional hazards model that adjusted for left ventricular ejection fraction, cardiothoracic ratio and angiotensin-converting enzyme inhibitor use at randomization. CI = confidence interval; other abbreviations as in Table 2.

Figure 3. Changes in left ventricular ejection fraction (LVEF) from randomization to final study visit in patients who continued receiving digoxin (Dig Cont'd) versus patients withdrawn from digoxin who had either mild (Dig WD Mild) or moderate heart failure (Dig WD Moderate) by clinical score. Left ventricular ejection fraction declined to a similar degree in both groups of patients who were withdrawn from digoxin, and both of these groups had a significant reduction in ejection fraction compared with patients who continued receiving digoxin.



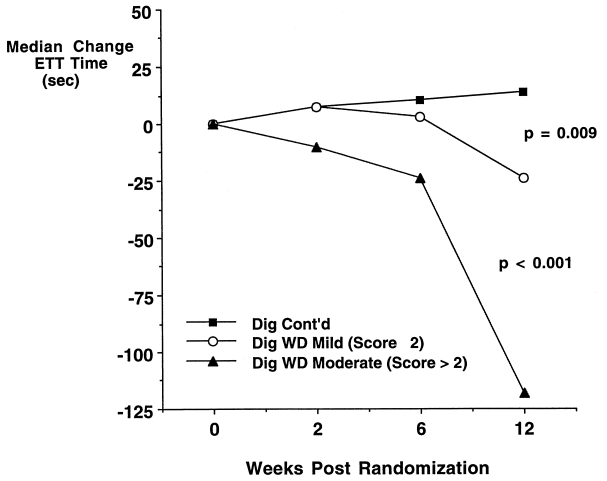


Figure 4. Changes in maximal exercise duration after randomization in patients who continued receiving digoxin versus patients who were withdrawn from digoxin and had mild or moderate heart failure by clinical signs and symptoms at randomization. The p values reflect patients withdrawn from digoxin who had either mild or moderate heart failure versus patients who continued receiving digoxin. Both groups of patients withdrawn from digoxin experienced significant deterioration in exercise capacity compared with patients who continued receiving digoxin. ETT = exercise tolerance testing; other abbreviations as in Figure 3.

treatment failure and a deterioration in exercise capacity than patients in either the Dig WD Mild group or the Dig Cont group. In contrast, a similar reduction in left ventricular ejection fraction occurred in patients with mild and moderate heart failure who were withdrawn from digoxin.

Previous work. Our work both confirms and extends the observations originally made by Lee et al. (4) and Guyatt et al. (6). We found that patients with higher heart failure scores were indeed more likely to worsen than those with few or no symptoms. However, in contrast to these investigators, we found a significant risk of worsening heart failure even in patients with few or no symptoms at the time of randomization. A number of explanations may account for the differences between our results and those of previous investigators. Our patients were characterized by significant left ventricular systolic dysfunction and cardiomegaly. Whether worsening during digoxin withdrawal would be found in patients with few or no current symptoms of heart failure and preserved left ventricular systolic function remains to be determined. Data from the Digitalis Investigation Group (DIG) trial (13) may provide important information on this point.

Our results are in agreement with the findings of van Veldhuisen et al. (19) in a subgroup of patients with mild heart failure studied in the Dutch Ibopamine Multicenter Trial (DIMT). This subgroup was composed of patients in the trial who were not receiving therapy for heart failure at study entry. Although details of the clinical heart failure score are not given, 91% of the patients were in functional class II, and only 9% were functional class III at the time of randomization. During the 6-month follow-up period, patients randomized to digoxin therapy had improved exercise tolerance and reduced plasma norepinephrine concentrations compared with patients randomized to placebo.

Study limitations. Our findings must be regarded with appropriate caution because investigation of patients with mild heart failure by clinical score was not a prespecified analysis of either study design. The follow-up period was limited to 12 weeks in the PROVED and RADIANCE studies. The risk of clinical worsening after a longer period of digoxin discontinuation in patients with mild heart failure remains to be determined.

Conclusions. Patients with mild evidence of heart failure were at risk of clinical worsening during digoxin withdrawal. They experienced significant deterioration of exercise capacity and left ventricular ejection fraction and were more likely to develop worsening heart failure than patients maintained on digoxin. Our findings support the use of digoxin therapy in patients with left ventricular systolic dysfunction even when only a few signs or symptoms of heart failure are present.

We gratefully acknowledge the efforts in manuscript preparation provided by Tyler Joscelyn.

References

1. Christian HA. Digitalis effects in chronic cases with regular rhythm in contrast to auricular fibrillation. Med Clin North Am 1922;5:1173–90.
2. Dobbs SM, Kenyon WI, Dobbs RJ. Maintenance digoxin after an episode of heart failure: placebo-controlled trial in outpatients. BMJ 1977;1:749–52.
3. Fleg JL, Gottlieb SH, Lakatta EG. Is digoxin really important in treatment of compensated heart failure? A placebo-controlled crossover study in patients with sinus rhythm. Am J Med 1982;73:244–50.
4. Lee DC, Johnson RA, Bingham JB, et al. Heart failure in outpatients: a randomized trial of digoxin versus placebo. N Engl J Med 1982;306:699–705.
5. Taggart AJ, Johnston GD, McDevitt DG. Digoxin withdrawal after cardiac failure in patients with sinus rhythm. J Cardiovasc Pharmacol 1983;5:229–34.
6. Guyatt GH, Sullivan MJ, Fallen EL, et al. A controlled trial of digoxin in congestive heart failure. Am J Cardiol 1988;61:371–5.
7. DiBianco R, Shabetai R, Kostuk W, Moran J, Schlant RC, Wright R, for the Milrinone Multicenter Trial Group. A comparison of oral milrinone, digoxin, and their combination in the treatment of patients with chronic heart failure. N Engl J Med 1989;320:677–83.
8. The Captopril-Digoxin Multicenter Research Group. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. JAMA 1988;259:539–44.
9. German and Austrian Xamoterol Study Group. Double-blind placebo-controlled comparison of digoxin and xamoterol in chronic heart failure. Lancet 1988;1:489–93.
10. Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED Trial. J Am Coll Cardiol 1993;22:955–62.
11. Packer M, Gheorghiade M, Young JB, et al., for the RADIANCE Study. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. N Engl J Med 1993;329:1–7.
12. van Veldhuisen DJ, Man in't Veld AJ, Dunselman PHJM, et al., on behalf of the DIMT Study Group. Double-blind placebo-controlled study of ibopamine and digoxin in patients with mild to moderate heart failure: results of the Dutch Ibopamine Multicenter Trial (DIMT). J Am Coll Cardiol 1993;22:1564–73.
13. Garg R, Gorlin R, Smith T, Yusuf S, for the Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336:525–33.

14. Gheorghiade M, Zarowitz BJ. Review of randomized trials of digoxin therapy in patients with chronic heart failure. Am J Cardiol 1992;69:48G–63G.
15. van Veldhuisen DJ, de Graeff PA, Remme WJ, Lie KI. Value of digoxin in heart failure and sinus rhythm: new features of an old drug. J Am Coll Cardiol 1996;28:813–9.
16. Carlson KJ, Lee DC-S, Goroll AH, Leahy M, Johnson RA. An analysis of physicians' reasons for prescribing long-term digitalis therapy in outpatients. J Chronic Dis 1985;38:733–9.
17. Lee ET. Statistical Methods for Survival Data Analysis. Belmont (CA): Lifetime Learning Publications, 1980:75–87.
18. Cox DR. Regression models and life-tables. J R Stat Soc (B) 1972;34:187–220.
19. van Veldhuisen DJ, Brouwer J, Man in't Veld AJ, Dunselman PHJM, Boomsam F, Lie KI, for the DIMT Study Group. Progression of mild untreated heart failure during six months of follow-up and clinical and neurohormonal effects of ibopamine and digoxin as monotherapy. Am J Cardiol 1995;75:796–800.