Effects of Digoxin on Morbidity and Mortality in Diastolic Heart Failure

The Ancillary Digitalis Investigation Group Trial

Ali Ahmed, MD, MPH; Michael W. Rich, MD; Jerome L. Fleg, MD; Michael R. Zile, MD; James B. Young, MD; Dalane W. Kitzman, MD; Thomas E. Love, PhD; Wilbert S. Aronow, MD; Kirkwood F. Adams, Jr, MD; Mihai Gheorghiade, MD

**Background**—About half of the 5 million heart failure patients in the United States have diastolic heart failure (clinical heart failure with normal or near-normal ejection fraction). Except for candesartan, no drugs have been tested in randomized clinical trials in these patients. Although digoxin was tested in an appreciable number of diastolic heart failure patients in the Digitalis Investigation Group ancillary trial, detailed findings from this important study have not previously been published.

**Methods and Results**—Ambulatory chronic heart failure patients (n=988) with normal sinus rhythm and ejection fraction >45% (median, 53%) from the United States and Canada (1991 to 1993) were randomly assigned to digoxin (n=492) or placebo (n=496). During follow-up with a mean length of 37 months, 102 patients (21%) in the digoxin group and 119 patients (24%) in the placebo group (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.63 to 1.07; P=0.136) experienced the primary combined outcome of heart failure hospitalization or heart failure mortality. Digoxin had no effect on all-cause or cause-specific mortality or on all-cause or cardiovascular hospitalization. Use of digoxin was associated with a trend toward a reduction in hospitalizations resulting from worsening heart failure (HR, 0.79; 95% CI, 0.59 to 1.04; P=0.094) but also a trend toward an increase in hospitalizations for unstable angina (HR, 1.37; 95% CI, 0.99 to 1.91; P=0.061).

**Conclusions**—In ambulatory patients with chronic mild to moderate diastolic heart failure and normal sinus rhythm receiving angiotensin-converting enzyme inhibitor and diuretics, digoxin had no effect on natural history end points such as mortality and all-cause or cardiovascular hospitalizations. *(Circulation. 2006;114:397-403.)*

**Key Words:** digoxin " heart failure " morbidity " mortality

There are an estimated 5 million heart failure (HF) patients in the United States. About half of these patients have diastolic HF, defined as clinical HF with normal or near-normal left ventricular ejection fraction (LVEF), and this group has substantial morbidity and mortality. Despite this high prevalence of diastolic HF, with the exception of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)–Preserved trial, these patients have generally been excluded from randomized HF trials.

Digitalis glycosides have been used in HF for >2 centuries, are inexpensive, and have been studied extensively in systolic HF. The role of digoxin in patients with diastolic HF was evaluated in the Digitalis Investigation Group (DIG) ancillary trial, which was conducted in parallel with the main DIG trial. The objective of the DIG ancillary trial was to assess the effect of digoxin on the primary combined outcome of HF hospitalization or HF mortality. We analyzed a public-use copy of the DIG dataset obtained from the National Heart, Lung, and Blood Institute (NHLBI) and present the full results of the ancillary DIG trial, which have not previously been reported.

**Clinical Perspective p 403**

The randomized DIG trial was conducted and supported by the NHLBI in collaboration with the Department of Veterans Affairs Cooperative Studies Program and cardiologists from the United States and Canada. Additional support was received from Glaxo Wellcome, which provided the study drugs, Lanoxin and placebo.

**Methods**

**Study Design**

The randomized DIG trial was conducted and supported by the NHLBI in collaboration with the Department of Veterans Affairs Cooperative Studies Program and cardiologists from the United States and Canada. Additional support was received from Glaxo Wellcome, which provided the study drugs, Lanoxin and placebo.
The purpose of the DIG trial was to evaluate the effects of digoxin on mortality and hospitalizations in ambulatory chronic HF patients with normal sinus rhythm.10 HF patients with LVEF $\geq$45\% (n=6800) made up the main trial, whereas those with LVEF $>45\%$ (n=988) were enrolled in an ancillary study conducted parallel to the main trial. The design and results of the DIG trial have been reported previously.9,10

**Patients**

In the DIG ancillary trial, 988 patients with LVEF $>$45\% and normal sinus rhythm at baseline were recruited from the United States (186 centers) and Canada (116 centers) between January 1991 and August 1993. Patients received 4 different daily doses of digoxin or matching placebo (0.125, 0.25, 0.375, and 0.50 mg) on the basis of age, sex, weight, and serum creatinine levels.11 More than 85\% of patients were receiving angiotensin-converting enzyme inhibitors, and $>$80\% were receiving diuretics.

**Outcomes**

The primary outcome in the ancillary DIG trial was the combined end point of HF hospitalization or HF mortality. Vital status of all patients was collected up to December 31, 1995, and was 98.9\% complete.12 The DIG ancillary trial did not prespecify other secondary outcomes. However, we also studied other outcomes, including all-cause and cardiovascular mortality and all-cause and cardiovascular hospitalizations. In addition, we studied the combined outcome of HF hospitalization or cardiovascular mortality, which was the primary outcome in CHARM-Preserved,7 the only other large randomized clinical trial of diastolic HF. The cause of death or the primary diagnosis leading to hospitalization was classified by DIG investigators, who were blinded to the patient’s study drug assignment.

**Statistical Analysis**

Kaplan-Meier analysis was used to construct survival plots, and a log-rank statistic was used to compare the survival distributions in the 2 study groups. To compare the effects of digoxin with those of placebo, we calculated hazard ratios (HRs) and 95\% confidence intervals (CIs) associated with primary and other outcomes using Cox proportional-hazards models. Differences in the number of hospitalizations between groups were estimated with the Wilcoxon rank-sum test. All analyses were repeated for outcomes at 2 years after randomization. Because the effect of digoxin on outcomes was expected to be more marked in the first 2 years after randomization, a separate analysis of the effect of digoxin during this period was prespecified in the DIG protocol.12 All analyses were performed on an intention-to-treat basis, with 2-sided values of $P<0.05$ considered significant, using SPSS for Windows, version 13.0.1 (SPSS Inc, Chicago, Ill).

Statistical analyses were conducted by Dr Ahmed in collaboration with Dr Love. Fidelity of the raw data was verified by Sean Coady at the NHLBI. Dr Ahmed had full access to the raw data and takes full responsibility for their integrity. All other authors had full access to the output data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

**Results**

**Patient Characteristics**

Baseline patient characteristics are presented in Table 1. Patients had a median age of 67 years; 41\% were women; 14\% were nonwhite; and 73\% had LVEF $\geq 50\%$. There were no significant differences in baseline characteristics between the 492 patients randomly assigned to digoxin and the 496 patients assigned to placebo (Table 1).

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Patient Characteristics by Treatment Group</th>
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<tr>
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<tr>
<td>Age, mean ± SD, y</td>
</tr>
<tr>
<td>Ejection fraction, mean ± SD, %</td>
</tr>
<tr>
<td>Serum creatinine, mean ± SD, mg/dL</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, mean ± SD, mL per min $\times^1.73$ m$^{-2}$</td>
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<tr>
<td>Median duration of HF, mo</td>
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</table>

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**Results**

**Patient Characteristics**

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HF Hospitalization or HF Mortality: The Primary Outcome

During a follow-up with a mean length of 37 months, 102 patients (21%) in the digoxin group and 119 patients (24%) in the placebo group experienced the primary combined outcome of HF hospitalization or HF mortality (HR for digoxin versus placebo, 0.82; 95% CI, 0.63 to 1.07; \( P = 0.136 \)) (Figure 1A and Table 2), which is consistent with the main DIG report.\(^\text{10}\) During the first 2 years of follow-up after randomization, 67 patients (14%) in the digoxin group and 90 patients (18%) in the placebo group experienced the primary combined outcome (HR, 0.71; 95% CI, 0.52 to 0.98; \( P = 0.034 \)) (Figure 1A and Table 2).

### HF Hospitalization or Cardiovascular Mortality

Hospitalizations resulting from HF or deaths resulting from cardiovascular causes, the primary outcomes used in the CHARM-Preserved trial, occurred in 142 patients (29%) in the digoxin group and 154 patients (31%) in the placebo group (HR, 0.88; 95% CI, 0.70 to 1.11; \( P = 0.269 \)) (Figure 1B and Table 2). At 2 years after randomization, 89 patients (18%) in the digoxin group, compared with 113 patients (23%) in the placebo group, experienced HF hospitalizations or cardiovascular mortality (HR, 0.75; 95% CI, 0.57 to 0.99; \( P = 0.044 \)) (Figure 1B and Table 2).

### Effect of Digoxin on Mortality

There were 115 deaths from all causes in the digoxin group (23%) and 116 deaths in the placebo group (23%) during the study (HR, 0.99; 95% CI, 0.76 to 1.28; \( P = 0.925 \)) (Figure 2A and Table 2). There were 30 deaths resulting from HF among patients randomized to receive digoxin (6%) and 34 deaths (7%) from the same cause among patients randomized to receive placebo (HR, 0.88; 95% CI, 0.54 to 1.43; \( P = 0.598 \)) (Figure 2B and Table 2). There was no difference in mortality resulting from cardiovascular causes (81 in each group; HR, 1.00; 95% CI, 0.73 to 1.36; \( P = 0.978 \)) (Figure 2C and Table 2). Effects of digoxin on mortality from various causes at 2 years are displayed in Figure 2A, 2B, and 2C and Table 2.

### Effect of Digoxin on Hospitalization

Hospitalization resulting from worsening HF occurred in 89 patients (18%) randomized to digoxin and 108 patients (22%) randomized to placebo (HR, 0.79; 95% CI, 0.59 to 1.04; \( P = 0.094 \)) (Figure 3C and Table 3). During the first 2 years of the study, 59 patients randomized to digoxin (12%) and 86 patients randomized to placebo (17%) were hospitalized as a result of worsening HF (HR, 0.66; 95% CI, 0.47 to 0.91; \( P = 0.012 \)) (Figure 3C and Table 3).

Hospital admissions for cardiovascular causes occurred in 241 patients (49%) in the digoxin group and 225 patients (45%) in the placebo group (HR, 1.10; 95% CI, 0.92 to 1.32; \( P = 0.301 \)) (Figure 3C and Table 3).

### Table 2. Mortality and Composite End Points According to Randomization to Digoxin or Placebo

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Events at Study End, n (%)</th>
<th>HR (95% CI)†</th>
<th>Absolute Risk Difference (ARD), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF hospitalization or HF mortality (primary end point)</td>
<td>119 (24.0)</td>
<td>102 (20.7)</td>
<td>-3.3</td>
</tr>
<tr>
<td>HF hospitalization or cardiovascular mortality (CHARM-Preserved end point)</td>
<td>154 (31.0)</td>
<td>142 (28.9)</td>
<td>-2.1</td>
</tr>
<tr>
<td>HF mortality</td>
<td>34 (6.9)</td>
<td>30 (6.1)</td>
<td>-0.8</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>81 (16.3)</td>
<td>81 (16.5)</td>
<td>-0.2</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>116 (23.4)</td>
<td>115 (23.4)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Absolute risk difference (ARD) was calculated by subtracting the percentage of deaths in the placebo group from the percentage of deaths in the digoxin group.
†HRs and 95% CIs were estimated from the Cox proportional-hazards models.
There were no differences in all-cause hospitalizations between the 2 groups (68% in the digoxin group, 67% in the placebo group; HR, 1.03; 95% CI, 0.89 to 1.20; \( P = 0.683 \)) (Figure 3A and Table 3). Among patients hospitalized for all causes, 332 in the digoxin group had 985 (median, 2) total hospitalizations for all reasons combined, and 330 in the placebo group had 949 (median, 2) such hospitalizations (Wilcoxon test, \( P = 0.811 \)). The effects of digoxin on various causes of hospitalizations at the end of 2 years of follow-up are displayed in Figure 3A, 3B, and 3C and Table 3. Compared with 62 patients (13%) in the placebo group, 82
patients (17%) in the digoxin group were hospitalized for unstable angina during the study period (HR, 1.37; 95% CI, 0.99 to 1.91; \( P=0.061 \); Table 3). The effects of digoxin on hospitalizations by various causes are displayed in Table 3.

### Adherence to Study Drugs

The median daily dose of the study drug at randomization was 0.25 mg for both the digoxin and placebo groups. Twelve months after randomization, 384 patients (78%) in the digoxin group and 384 patients (77%) in the placebo group were still receiving the study drug. The median daily dose of the study drug at 12 months was 0.25 mg for both treatment groups. Over the entire follow-up period, the study drug was discontinued in 323 patients (33%), of whom 159 (32%) were receiving digoxin and 164 (33%) were receiving placebo (\( P=0.802 \)). Compared with 53 patients (11%) receiving placebo, 32 patients (7%) receiving digoxin required prescription of open-label digoxin for worsening HF or atrial fibrillation (\( P<0.001 \)).

### Digoxin Toxicity

Overall, 66 patients (7%) were identified by study investigators as having suspected or confirmed digoxin toxicity during routine follow-up; 21 patients (2%) suffered suspected or confirmed digoxin toxicity during the first 2 years after randomization. As anticipated, there were more cases of suspected digoxin toxicity in the digoxin group (48, 10%) than in the placebo group (18, 4%; \( P<0.001 \)). Respective numbers for cases of suspected digoxin toxicity during the first 2 years were 15 (3.0%) in the digoxin group and 6 (1%) in the placebo group (\( P=0.049 \)). Out of the total of 66 patients with suspected or confirmed digoxin toxicity, only 1 such patient was hospitalized for that reason.

### Discussion

Results of the present analysis demonstrate that digoxin had no favorable effect on the natural history of ambulatory patients with chronic mild to moderate diastolic HF and normal sinus rhythm. Although the results of the DIG ancillary trial were briefly reported in the original DIG publication,\(^10\) the results presented here provide the first detailed analyses about the use of digoxin in diastolic HF.

### Clinical Importance

These findings are important for several reasons. Up to 50% of all HF patients experience diastolic HF, and most of these patients are older adults.\(^3\-^6\) Furthermore, with the population aging, the prevalence of diastolic HF is projected to increase disproportionately in the coming decades. Despite better survival compared with patients with systolic HF, older adults with diastolic HF suffer from multiple morbidities and frequent hospitalizations.\(^15,16\) Even so, diastolic HF patients traditionally have been excluded from clinical HF trials; thus, there are few evidence-based recommendations for these patients.\(^17\) Therefore, despite the age of the dataset used in our
analysis, the results of the present analysis have contemporary clinical relevance.

Effect of Digoxin on HF Hospitalization
The effect of digoxin on HF hospitalization in the ancillary DIG trial, although not significant, is comparable to its effect in the main DIG trial and the effect of candesartan in the CHARM-Preserved trial. Although 66 patients (7%) were identified as worsening HF,10,19 although not significant, is comparable to its effect in the main DIG trial and the effect of candesartan in the CHARM-Preserved trial.10,19 The magnitude of the digoxin-associated reduction in HF hospitalization observed in our analysis (HR, 0.79; 95% CI, 0.59 to 1.04) is similar to those observed in the main DIG trial (HR, 0.72; 95% CI, 0.66 to 0.79)10 and the CHARM-Preserved trial (HR, 0.85; 95% CI, 0.72 to 0.1.01).7 The lack of statistical significance of the effects of digoxin in the ancillary DIG trial is possibly a result of the small sample size (988 in the ancillary DIG trial, ≈7 times smaller than the 6800 in the main DIG trial and >3 times smaller than the 3023 in the CHARM-Preserved trial). In addition, >75% of participants in the ancillary DIG trial had NYHA class I to II symptoms. Hospitalization as a result of worsening HF was much lower among these patients than would be expected of diastolic HF patients in clinical practice.6,18 These relatively low event rates suggest that a larger study or a study involving patients at higher risk such as those with more advanced symptoms, age, or morbidities may have resulted in a greater reduction in the primary end point by digoxin. Despite the statistical significance of the protocol-prespecified 2-year outcomes and the fact that they are the basis of Food and Drug Administration approval of digoxin for use in HF, the results of the post hoc analyses of 2-year outcomes should be interpreted with caution. This is particularly important because digoxin had no favorable effect on the natural history of patients with HF and normal or near-normal LVEF.

An unanticipated finding of the present analysis is that digoxin use was associated with increased risk of hospitalization for unstable angina, which offset the reduction in HF hospitalization, resulting in no effect on cardiovascular hospitalizations. It is possible that the amount of viable ischemic myocardium in diastolic HF is larger than that in systolic HF. However, the increased incidence of unstable angina did not translate into increased myocardial infarction or mortality.

Comparison With CHARM-Preserved Trial
In the CHARM-Preserved trial (n=3023), at follow-up with median length of 37 months, hospitalizations resulting from HF or deaths resulting from cardiovascular causes, the primary outcomes of that trial, occurred in 333 patients (22%) in the candesartan group and 366 patients (24%) in the placebo group (HR, 0.89; 95% CI, 0.77 to 1.03; P=0.118).7 In the DIG ancillary trial, on the other hand, during a similar follow-up (median, 39 months), 142 patients (29%) in the digoxin group and 154 patients (31%) in the placebo group experienced the same outcomes (HR, 0.88; 95% CI, 0.70 to 1.11; P=0.269) (Figure 1, bottom, and Table 2).

The primary reason for discontinuation of the study drug in CHARM-Preserved was drug-related adverse events, including hypotension, hyperkalemia, or abnormal laboratory values such as an increase in creatinine, which was noted in 18% of patients in the candesartan group (versus 14% in the placebo group; P=0.001).7 In contrast, the primary reason for discontinuation of the study drug in the DIG trial was the use of open-label digoxin as a result of worsening HF.10,19 Although 66 patients (7%) were identified as having suspected or confirmed digoxin toxicity, only 1 patient was hospitalized.

Implication for Future Research in Diastolic HF
Among diastolic HF patients in the DIG trial who received placebo, only 7% died of HF and 16% died of cardiovascular causes (11% in CHARM-Preserved); overall mortality was 23%. In contrast, among systolic HF patients receiving placebo, 13% died of HF, 30% died of cardiovascular causes, and 35% died as a result of all causes combined.10 The low HF mortality in diastolic HF should be taken into consideration when future clinical diastolic HF trials are planned.15

Clinical Implications: Role of Digoxin in Diastolic HF
Digitalis is the oldest and one of the least expensive drugs for the management of HF. Digoxin has historically been thought to be contraindicated in patients with diastolic HF, often on the basis of anecdotal reports or nonrandomized studies.12,20 The exact mechanistic explanation of how digoxin may exert any potential beneficial effect in diastolic HF (as suggested by the trend in HF hospitalization reduction) is not clearly understood. Although digoxin appears to improve the active energy-dependent early myocardial diastolic function,6,21 this effect has not been well studied.12,22 The effects of digoxin in diastolic HF may be related to its favorable effects on neurohormonal profile.17,23 It is now known that, as in systolic HF, neurohormonal activation is present in diastolic HF and may contribute to disease progression.24,25 Recent evidence suggests that in addition to cardiac tissues, digitalis glycosides also inhibit the sodium-potassium adenosine triphosphatase enzyme in noncardiac tissues such vagal afferent fibers and the kidneys. Thus, digoxin may reduce sympathetic neurohormonal activity by sensitizing cardiac baroreceptors and suppress the renin-angiotensin-aldosterone system by reducing proximal renal tubular reabsorption of sodium.26–28 The trend toward an increase in hospitalization for unstable angina may be related to reported, but not well-studied, effects of digoxin on platelet and endothelial cell activation.29

Conclusions
In ambulatory patients with chronic mild to moderate diastolic HF and normal sinus rhythm receiving angiotensin-converting enzyme inhibitors and diuretics, digoxin use was not associated with any significant effect on total, cardiovascular, or HF mortality or on total or cardiovascular hospitalizations.

Acknowledgments
This manuscript has been reviewed by the NHLBI for scientific content and consistency of data interpretation with previous DIG publications, and significant comments have been incorporated before submission for publication.

We dedicate this article to the memories of Thomas W. Smith, MD (1936–1997), and Richard Gorlin, MD (1926–1997), who played a crucial role in enhancing our understanding of digoxin in HF and in the planning and conduct of the DIG trial.

Source of Funding
The DIG study was conducted and supported by the NHLBI in collaboration with the Department of Veterans Affairs Cooperative Studies Program and the DIG Investigators. Study drugs (Lanoxin and placebo) were provided by Glaxo Wellcome. Drs Fleg, Gheorghiade, Rich, and Young were investigators in the DIG trial.
Diastolic heart failure (HF), defined as clinical HF with normal or near-normal left ventricular ejection fraction (LVEF), is common and associated with substantial morbidity and mortality. Except for candesartan in CHARM-Preserved (LVEF >40%), irbesartan in the ongoing I-Preserve (LVEF ≥45%), and digoxin in the Digitalis Investigation Group ancillary trials, no drugs have been tested in these patients in randomized trials. Digoxin is an old and inexpensive HF drug that has been studied extensively in systolic HF. However, little is known about the effect of digoxin in diastolic HF. The present study reports a detailed analysis of the Digitalis Investigation Group ancillary trial in which 988 diastolic HF (LVEF >45%) patients in normal sinus rhythm were randomized to receive digoxin or placebo. Digoxin had no effect on natural history end points such as mortality and all-cause or cardiovascular hospitalizations. At follow-up with a mean length of 37 months, the primary outcome of the study, HF hospitalization or HF mortality, showed a nonsignificant 18% lower risk in patients receiving digoxin. There was a trend toward an effect of digoxin on reducing HF hospitalization (21% nonsignificant reduction; P = 0.094), but digoxin use also was associated with a nonsignificant 37% increased risk of hospitalization resulting from unstable angina (P = 0.061). Results from this study suggest that digoxin does not exert a net beneficial effect on mortality or overall cardiovascular morbidity in diastolic HF.
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