Digoxin Therapy Does Not Improve Outcomes in Patients With Advanced Heart Failure on Contemporary Medical Therapy

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Background—The impact of digoxin on outcomes of patients with advanced heart failure (HF) receiving optimal contemporary therapy is not known.

Methods and Results—We retrospectively reviewed data of 455 advanced HF patients referred for transplant evaluation (age, 52±12 years; ejection fraction, 18.3±8%); 227 (49.9%) were on digoxin at baseline. Primary outcome was death (n=101), urgent transplantation (n=14), or ventricular assist device implantation (n=4); secondary outcomes included HF and all-cause hospitalizations. Digoxin use was evaluated (1) in the original cohort; (2) in a propensity score–matched subset (n=322); (3) as a time-dependent covariate; and (4) after adjustment for Seattle Heart Failure Score. Patients were on optimal therapy: angiotensin-II modulation, 92.5%; β-blockers, 91.2%; aldosterone antagonists, 45.6%; and devices, 71.0%. After a median of 27 months, 83 of 277 (36.6%) patients treated with digoxin versus 36 of 228 (15.8%) patients without digoxin met primary outcome (hazard ratio [HR], 2.28; 95% CI, 1.51 to 3.43; P=0.001). This risk persisted in the matched subset (HR, 1.73; 95% CI, 1.09 to 2.75; P=0.021) and with time-varying digoxin use (HR, 2.05; 95% CI, 1.23 to 3.41; P=0.011). Digoxin was associated with higher risk among patients in sinus rhythm compared with atrial fibrillation. Digoxin was not associated with improvement in either all-cause or HF hospitalization rates. These results were similar across sex and race and when adjusted for Seattle Heart Failure Score and renal function.

Conclusion—This study suggests that digoxin therapy may be of no benefit in patients with advanced HF referred for cardiac transplantation who received optimal medical therapy. Treatment with digoxin should be used cautiously in such patients because of risk for adverse outcomes. (Circ Heart Fail. 2009;2:90-97.)

Key Words: heart failure ▪ digoxin ▪ outcomes ▪ prognosis ▪ morbidity ▪ mortality

Unless contraindicated, the American College of Cardiology and the American Heart Association guidelines for the management of patients with heart failure (HF) recommend the use of digoxin for symptoms.1 Digoxin use is also endorsed by the Heart Failure Society of America and the European Society of Cardiology.2,3 Although widely endorsed, these recommendations are derived mainly from smaller short-term studies assessing nonmortality outcomes, including symptoms, exercise tolerance, and quality of life in patients with mild to moderate HF.4–10 The Digitalis Investigator Group (DIG),11 a large randomized trial, showed no impact on all-cause or cardiovascular mortality with digoxin in HF patients in sinus rhythm; there was, however, a modest reduction in hospitalization rate. A substudy of the DIG trial showed no significant improvement in quality of life with digoxin use either.12 Moreover, 2 post hoc analyses of the DIG trial showed disturbing trends with the use of digoxin in specific subgroups of HF patients. In one analysis, digoxin therapy was associated with increased all-cause mortality in women.13 and in another study, there was a higher risk of adverse outcomes at serum digoxin levels which are traditionally considered therapeutic.14 However, a similar post hoc analysis of the Studies of Left Ventricular Dysfunction (SOLVD) trials failed to show any gender-specific interaction with digoxin therapy.15

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The DIG trial enrolled patients from 1991 to 1993. Although more than 90% of patients were receiving angiotensin-converting enzyme inhibitors in the DIG trial, the use of β-blockers and aldosterone antagonists was not reported and was likely very limited. Similarly, improved outcomes are also seen with cardiac devices, both defibrillators and biventricular pacemakers, which are now widely used in patients with HF. There are no studies that have assessed the impact of digoxin in patients with advanced HF already receiving contemporary optimal medical therapy.
Beyond safety and efficacy, another important issue is the impact of therapy in determining HF prognosis. A recent multimarker tool for HF prognosis determination, the Seattle Heart Failure Model (SHFM), incorporates the effect of angiotensin-converting enzyme inhibitors, β-blockers, and devices in determining HF prognosis. This model was, however, derived from the Prospective Randomized Amiodipine Survival Evaluation (PRAISE 1) trial database in which the participants were near uniformly on digoxin therapy. Thus, the utility of digoxin therapy as a potential variable for HF risk prediction could not be ascertained.

In this study, we sought to assess the utility of digoxin therapy in a cohort of patients with advanced HF referred for cardiac transplantation evaluation who were on optimal contemporary medical therapy.

Methods

Patient Population

Data on consecutive patients between January 2000 and December 2006 referred for transplantation evaluation were abstracted. Inclusion criteria were as follows: (1) adults 18 to 70 years old; (2) ejection fraction ≤30%; (3) on maximum tolerated medical therapy; and (4) New York Heart Association class II to IV symptoms. Patients with HF, secondary to congenital heart disease, and those planned to undergo cardiac surgery within 6 months were excluded. A total of 455 patients fulfilled these criteria. The institutional review board approved the study.

Data Collection

Demographic and clinical information were abstracted from medical records. For risk adjustment and to assess the utility of digoxin therapy in determining prognosis over the SHFM, data were also collected on the variables included in SHFM. If multiple laboratory data were available, values from the date closest to the date of patient achieving optimal tolerated medical therapy were used. Digoxin concentrations were collected when available. Data on all hospitalizations at any of the hospital sites affiliated with the Emory Healthcare were collected. Moreover, all medical records including outpatient notes, and hospital admission and discharge notes were reviewed to ascertain documentation of any hospitalization that may have occurred outside Emory Healthcare.

Outcomes

The primary outcome was defined as the time to death or urgent transplantation (United Network for Organ Sharing status 1A) or left ventricular assist device implantation. The secondary outcomes were (1) the composite of the primary outcome plus hospitalization for decompensated HF (time-to-event analysis); (2) the rate of all-cause hospitalizations; and (3) the rate of HF-related hospitalizations.

Subgroup Analyses

Three a priori defined subgroup analyses were performed: (1) in patients with atrial fibrillation versus in sinus rhythm; (2) in whites versus nonwhites; and (3) in sex-based subgroups.

Seattle Heart Failure Model

The SHFM score was derived for all patients based on the original equation described by Levy et al. Except for the lymphocyte count (available in 70.6%), all other data were available in >90% of observations. Missing covariates were replaced with the cohort mean for score calculation purposes.

Statistics

Baseline characteristics were compared by the Mann-Whitney rank-sum test (continuous variables) and the Fisher exact test (categorical variables). Survival curves were compared by the log-rank test. Cox proportional hazards models with bootstrap estimation (1000 replications with replacement) were used to obtain raw and adjusted hazard ratios (HR) and normal-based, bias-corrected CI. Analysis with digoxin treatment as a time-varying covariate was performed by creating serial records for each patient at 3-month intervals; the last documented digoxin treatment status (yes/no) was carried forward. For the Seattle Heart Failure Score-adjusted Cox models, the functional form of continuous covariates (linear versus nonlinear fit) was evaluated by fractional polynomials. The proportionality assumption for each Cox model was formally tested by examining the scaled Schoenfeld residuals.

The propensity score was obtained by logistic regression analysis with baseline digoxin treatment as the outcome variable and all the variables described in Table 1 as predictors. Nearest neighbor matching without replacement was performed by applying a “greedy” algorithm on the logit of the propensity score within a caliper equal to 0.25 times the pooled standard deviation of the logit. The effectiveness of matching to alleviate covariate imbalance was evaluated by (1) the likelihood-ratio test of the joint significance of all the regressors (ie, the ability of the covariates to predict treatment assignment); and (2) by the standardized difference “d” of the covariates between treatment groups:

\[
d = 100 \frac{\text{abs}(\text{mean digoxin} - \text{mean control})}{\text{SD digoxin} + \text{SD control}} / 2
\]

where SD is the standard deviation of the covariate in the corresponding treatment group. Small (<10%) values of “d” support the assumption of balance between treatment groups. Baseline characteristics after matching were also compared by the unpaired t test.

Because imputation of the cohort mean for missing values can lead to incomplete control of confounding, we performed the following sensitivity analysis. We repeated the propensity score matching process (with the same parameters) in 5 datasets in which the missing values were imputed using regression imputation by chained equations, and then estimated the effect of digoxin in each of the corresponding propensity-matched cohorts.

Analyses were performed with Stata 9.2 (StataCorp LP, College Station, Tex); propensity score matching was performed with NCSS 2007 (NCSS LLC, Kaysville, Utah). Imputation of missing values by chained equations was performed using a Stata module (ICE) written by Patrick Royston (MRC Clinical Trials Unit, United Kingdom).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patient Population

Baseline characteristics for the 227 patients on digoxin and 228 patients not on digoxin are shown in Table 1. Digoxin levels were assessed in 115 of 227 (50.7%) patients treated with digoxin at baseline. Digoxin levels were drawn only once in 87.0% of patients during the follow-up period. Median daily digoxin dose was 0.13 mg/day (25% to 75%: 0.13 to 0.19). Median digoxin level was 0.75 ng/mL (25% to 75%: 0.5 to 1.4 ng/mL). Figure 1 describes digoxin use over time and crossover rates for the 2 groups.

Among the 43 patients who were started on digoxin after baseline, the reasons for therapy initiation were documented in 32 patients and included worsening HF symptoms leading to hospitalization in 29 and inadequate rate control of atrial fibrillation in 3 patients. Among the 72 patients who discontinued digoxin after the baseline visit, the reasons were documented in 47 patients and included improved symptoms in 29, gastrointestinal side effects (nausea, anorexia) in 7, worsening renal function and/or difficulty to maintain therapeutic levels in 7, and chronotropic incompetence in 4 patients.
implantation (primary outcome) was met in 36.6% of patients on digoxin versus 15.8% in those not on digoxin (HR, 2.28; 95% CI, 1.51 to 3.43; P<0.001; Table 2, Figure 2A). The composite of primary outcome plus HF hospitalization was met in 63.0% of patients on digoxin versus 40.4% in those not on digoxin (HR, 1.71; 95% CI, 1.32 to 2.23; P<0.001; Table 2, Figure 2B). Both all-cause and HF-related hospitalization rates were higher in patients taking digoxin (Table 2).

**Seattle Heart Failure Model and Renal Function**

After adjusting for HF severity using the Seattle Heart Failure Score, digoxin use was still a significant predictor of primary outcome (HR, 1.99; 95% CI, 1.31 to 3.02; P=0.001). The Seattle Heart Failure Score does not include renal function, which is important with respect to digoxin therapy and has been associated with HF outcomes independently. When baseline renal function (serum creatinine and blood urea nitrogen level) was included along

### Outcomes and Event Rates

Total follow-up time was 1186 patient-years (median, 27 months). Overall, 101 of 455 (22.7%) patients died (annual mortality of 9.4%; 95% CI, 7.7% to 11.5%). In addition, 14 patients underwent UNOS IA heart transplantation and 4 underwent left ventricular assist device implantation. Therefore, the primary outcome was met in 119 of 455 (26.2%) patients (annual rate, 10.0%; 95% CI, 8.4% to 12.0%). There were 1098 all-cause hospitalizations (93 per 100 patient-years); of these, 573 (52.2%) were related to HF (48 per 100 patient-years).

### Digoxin Use and Outcomes

#### Original Cohort

Overall, 227 patients (49.9%) were receiving digoxin at baseline. Death, urgent transplantation, or left ventricular assist device implantation (primary outcome) was met in 36.6% of patients on digoxin versus 15.8% in those not on digoxin (HR, 2.28; 95% CI, 1.51 to 3.43; P<0.001; Table 2, Figure 2A). The composite of primary outcome plus HF hospitalization was met in 63.0% of patients on digoxin versus 40.4% in those not on digoxin (HR, 1.71; 95% CI, 1.32 to 2.23; P<0.001; Table 2, Figure 2B). Both all-cause and HF-related hospitalization rates were higher in patients taking digoxin (Table 2).

#### Propensity Matched

After adjusting for HF severity using the Seattle Heart Failure Score, digoxin use was still a significant predictor of primary outcome (HR, 1.99; 95% CI, 1.31 to 3.02; P=0.001). The Seattle Heart Failure Score does not include renal function, which is important with respect to digoxin therapy and has been associated with HF outcomes independently. When baseline renal function (serum creatinine and blood urea nitrogen level) was included along

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### Table 1. Patient Characteristics by Digoxin Use at Baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>With Digoxin (n=227)</th>
<th>Without Digoxin (n=228)</th>
<th>P</th>
<th>d, %*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>50.5±13.4</td>
<td>54.1±11.3</td>
<td>0.005</td>
<td>27.8</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>67.0</td>
<td>70.6</td>
<td>0.419</td>
<td>6.6</td>
</tr>
<tr>
<td>Race†, % white</td>
<td>51.5</td>
<td>53.5</td>
<td>0.708</td>
<td>2.1</td>
</tr>
<tr>
<td>NYHA class, % II/III/IV</td>
<td>46.3/43.6/10.1</td>
<td>51.3/41.2/7.5</td>
<td>0.325</td>
<td>11.8</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>17.5±8.0</td>
<td>19.2±8.0</td>
<td>0.006</td>
<td>21.6</td>
</tr>
<tr>
<td>Ischemic, %</td>
<td>35.2</td>
<td>39.9</td>
<td>0.333</td>
<td>8.1</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>40.1</td>
<td>31.1</td>
<td>0.051</td>
<td>17.7</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>115±19</td>
<td>115±19</td>
<td>0.803</td>
<td>0.5</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>79±14</td>
<td>76±14</td>
<td>0.021</td>
<td>19.7</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.3±0.8</td>
<td>1.5±1.2</td>
<td>0.926</td>
<td>11.3</td>
</tr>
<tr>
<td>Sodium, meq/L</td>
<td>137±3</td>
<td>138±3</td>
<td>0.004</td>
<td>24.6</td>
</tr>
<tr>
<td>Potassium, meq/L</td>
<td>4.0±0.5</td>
<td>4.1±0.6</td>
<td>0.760</td>
<td>7.5</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL</td>
<td>22.1±13</td>
<td>23.1±19</td>
<td>0.773</td>
<td>2.2</td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>8.5±1.1</td>
<td>8.4±0.7</td>
<td>0.208</td>
<td>6.6</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>159±40</td>
<td>160±37</td>
<td>0.943</td>
<td>4.4</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>39.6±5.4</td>
<td>38.9±5.8</td>
<td>0.098</td>
<td>12.8</td>
</tr>
<tr>
<td>Lymphocytes, %</td>
<td>24.8±8</td>
<td>25.7±7</td>
<td>0.118</td>
<td>13.0</td>
</tr>
<tr>
<td>Cardiac device, %</td>
<td>71.8</td>
<td>71.1</td>
<td>0.71</td>
<td>0.760</td>
</tr>
<tr>
<td>Defibrillator, %</td>
<td>29.5</td>
<td>30.7</td>
<td>0.838</td>
<td>3.7</td>
</tr>
<tr>
<td>Bi-ventricular pacer, %</td>
<td>4.8</td>
<td>1.8</td>
<td>0.072</td>
<td>17.7</td>
</tr>
<tr>
<td>Combined, %</td>
<td>37.2</td>
<td>38.2</td>
<td>0.923</td>
<td>0.5</td>
</tr>
<tr>
<td>ACE inhibitor, %</td>
<td>73.4</td>
<td>69.7</td>
<td>0.406</td>
<td>7.6</td>
</tr>
<tr>
<td>Angiotensin-receptor blocker, %</td>
<td>22.0</td>
<td>19.7</td>
<td>0.566</td>
<td>6.1</td>
</tr>
<tr>
<td>β-blockers, %</td>
<td>90.0</td>
<td>93.4</td>
<td>0.101</td>
<td>14.6</td>
</tr>
<tr>
<td>Aldosterone antagonist, %</td>
<td>52.0</td>
<td>39.0</td>
<td>0.006</td>
<td>26.3</td>
</tr>
<tr>
<td>Statine, %</td>
<td>37.0</td>
<td>49.6</td>
<td>0.008</td>
<td>25.8</td>
</tr>
<tr>
<td>Allopurinol, %</td>
<td>7.0</td>
<td>6.6</td>
<td>0.855</td>
<td>2.1</td>
</tr>
<tr>
<td>Amiodarone, %</td>
<td>21.6</td>
<td>14.9</td>
<td>0.070</td>
<td>16.7</td>
</tr>
<tr>
<td>Daily diuretic dose, mg/kg‡</td>
<td>1.2±1.3</td>
<td>0.9±1.0</td>
<td>0.009</td>
<td>26.5</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association; ACE, angiotensin-converting enzyme.

*d—standardized difference (see text for formula).

†Among non-whites, 93.5% were blacks.

‡Furosemide equivalent.16
with Seattle Heart Failure Score, digoxin use was still associated with a higher risk for the primary outcome (HR 2.03; 95% CI, 1.33 to 3.09; \( P < 0.001 \)).

**Propensity Score–Matched Subset**

The number of patients retained after propensity score matching was 322 (161 in each group, Table 1). The standardized difference in logit was reduced from 71.7% to 0.7%; the likelihood-ratio \( \chi^2 \) of the joint insignificance was reduced from 55.47 (\( P < 0.002 \)) to 4.67 (\( P = 1.000 \)) after matching (\( df = 29 \)). Median follow-up was 31 months (25% to 75%: 16 to 52) and 28 months (25% to 75%: 17 to 42) in patients with digoxin versus without digoxin. In the matched subset, 33.5% of patients in the digoxin group reached the primary outcome versus 17.4% in the control group (HR, 1.73; 95% CI, 1.09 to 2.75; \( P = 0.021 \); Table 2, Figure 2C). Secondary outcome data are shown in Table 2 and Figure 2D.

The results were similar in 5 propensity-matched cohorts obtained after imputation of missing values in the original cohort using chained equations instead of imputing the cohort mean (data not shown).

**Digoxin Treatment as Time-Varying Covariate**

In the propensity-matched subset, analysis was repeated with digoxin treatment entered as a time-varying covariate using 3-month intervals. Patients were on digoxin 49.8% of the time on average, 82.4% of the time for patients who were on digoxin at baseline (n = 161), and 13.5% for patients who were not on digoxin at baseline (n = 161). For the primary outcome, 52 events per 436 patient-years were observed on digoxin versus 30 events per 444 patient-years off digoxin (HR, 2.05; 95% CI, 1.23 to 3.41; \( P = 0.011 \); Table 2, Figure 2E). Secondary outcome data are shown in Table 2 and Figure 2F.

**Sinus Rhythm Versus Atrial Fibrillation**

In the original cohort, digoxin use was associated with a higher risk for the primary outcome among patients in sinus rhythm (n = 293; HR, 3.19; 95% CI, 1.78 to 5.72; \( P = 0.001 \) ) compared with those in AF (n = 162; HR, 1.29; 95% CI, 0.69 to 2.43; \( P = 0.421 \); \( P = 0.033 \) for interaction). This interaction was not significant in the matched subset (\( P = 0.196 \)), although digoxin was still associated with higher risk among the 204 patients in sinus rhythm (n = 161). For the secondary outcomes, similar trends were observed (data not shown).

![Figure 1. Flowchart describing the baseline patient population with respect to digoxin therapy and crossover rates.](http://circheartfailure.ahajournals.org/)

**Table 2. Primary and Secondary Outcome Results by Analytic Approach**

<table>
<thead>
<tr>
<th></th>
<th>Unmatched Cohort (N=455)</th>
<th>PSM Subset (N=322)</th>
<th>PSM Subset with Digoxin as Time-Varying Covariate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome: death or urgent transplantation or LVAD implantation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td>83 (36.6%)</td>
<td>36 (15.8%)</td>
<td>54 (33.5%)</td>
</tr>
<tr>
<td>Annual rate, %</td>
<td>13.9</td>
<td>6.1</td>
<td>11.6</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>2.28 (1.51–3.43)*</td>
<td>Referent</td>
<td>1.73 (1.09–2.75)†</td>
</tr>
<tr>
<td><strong>Secondary outcome 1: death or urgent transplantation or LVAD implantation or hospitalization for heart failure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td>143 (63.0%)</td>
<td>92 (40.4%)</td>
<td>97 (60.2%)</td>
</tr>
<tr>
<td>Annual rate, %</td>
<td>33.0</td>
<td>19.3</td>
<td>28.1</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.71 (1.32–2.23)*</td>
<td>Referent</td>
<td>1.34 (0.98–1.83)‡</td>
</tr>
<tr>
<td><strong>Secondary outcome 2: rate of all-cause hospitalizations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>675</td>
<td>423</td>
<td>474</td>
</tr>
<tr>
<td>Per 100 pt-years</td>
<td>113</td>
<td>72</td>
<td>102</td>
</tr>
<tr>
<td>IRR (95% CI)</td>
<td>1.58 (1.18–2.13)$§</td>
<td>Referent</td>
<td>1.30 (0.93–1.80)§</td>
</tr>
<tr>
<td><strong>Secondary outcome 3: rate of heart failure-related hospitalizations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>370</td>
<td>203</td>
<td>242</td>
</tr>
<tr>
<td>Per 100 pt-years</td>
<td>62</td>
<td>34</td>
<td>52</td>
</tr>
<tr>
<td>IRR (95% CI)</td>
<td>1.81 (1.17–2.80)$†</td>
<td>Referent</td>
<td>1.26 (0.77–2.06)§</td>
</tr>
</tbody>
</table>

PSM indicates propensity score–matched; HR, hazard ratio; IRR, incidence rate ratio; LVAD, left ventricular assist device.

\* \( P < 0.001 \), † \( P < 0.05 \), ‡ \( P < 0.1 \), § \( P < 0.01 \).
Sex and Race
In the original cohort, digoxin was associated with a higher risk in nonwhite (HR, 4.18; 95% CI, 2.06 to 8.49; \(P = 0.001\)) compared with white patients (HR, 1.51; 95% CI, 0.91 to 2.53; \(P = 0.114\); \(P = 0.027\) for interaction). This interaction was not present in the matched subset and in secondary outcome analyses (data not shown). No interactions with sex were observed.

Analyses Based on Crossover of Digoxin Treatment
In the original, unmatched cohort (n = 455), patients who continued receiving digoxin (n = 155) throughout follow-up (Figure 1) had 59 primary events (38.1%, annual rate 15.7%); in comparison, those who discontinued digoxin (n = 72) had 24 events (33.3%; annual rate, 11.0%; HR, 0.84; 95% CI, 0.66 to 1.06; \(P = 0.149\)). Patients who never received digoxin (n = 185) had 31 primary events (16.8%; annual rate, 6.9%); in comparison, those who were started on digoxin after the baseline evaluation (n = 43) had 5 events (11.6%; annual rate, 3.5%; HR, 0.71; 95% CI, 0.44 to 1.14; \(P = 0.151\)).

In the 340 patients (155 with digoxin, 185 without digoxin) who did not cross over, ie, were not switched on or off digoxin throughout follow-up (Figure 1), HR of digoxin use for the primary outcome was 2.21 (95% CI, 1.43 to 3.42; \(P = 0.001\)). In the propensity-matched cohort (n = 322), there were 235 patients (110 with digoxin, 125 without digoxin) who did not cross over. In these patients, HR of digoxin use for the primary outcome was 1.72 (95% CI, 1.02 to 2.89; \(P = 0.041\)).

In a separate analysis, we censored observations at the time of crossover. In this analysis, there were 90 primary events in 455 patients, 59 in those with digoxin, and 31 in those without digoxin (HR, 2.03; 95% CI, 1.32 to 3.14; \(P = 0.001\)). In the propensity-matched subset, there were 62 primary events in 322 patients, 39 in those with digoxin, and 23 in those without digoxin (HR, 1.62; 95% CI, 0.96 to 2.71; \(P = 0.070\)).

B-Type Natriuretic Peptide and Echocardiographic Data
B-type natriuretic peptide concentrations were available in 104 of 322 patients (48 with digoxin, 56 without digoxin) of the propensity-matched cohort (32.3%) at baseline. Median B-type natriuretic peptide was 475 ng/mL (interquartile
range, 169 to 790) in patients with digoxin versus 552 ng/mL (interquartile range, 177 to 1517) in patients without digoxin ($P=0.34$).

Echocardiograms at the time of evaluation (within 1 month) were available in 149 of 322 patients (71 with digoxin, 78 without digoxin) of the propensity-matched cohort (46.3%). The main echocardiographic findings in this subset are summarized in Table 3. Patients with digoxin had slightly larger left ventricles and comparable ejection fractions in the presence of more severe mitral regurgitation. These observations, however, did not reach statistical significance.

### Discussion

Unlike the results from older trials, in this study of patients with contemporary advanced HF, digoxin therapy was not associated with improved outcomes. These results are important because recent data in patients with HF and low-ejection fraction suggest that baseline digoxin use in this population ranges from 45% to 75%.24–28 If these results are replicated, it would raise questions regarding routine use of digoxin in the current era.

In the DIG trial,11 there were 6% fewer overall hospitalizations in the digoxin group but difference in hospitalization for worsening HF was more impressive (26.8% versus 34.7%; $P<0.05$). Two other trials showed that withdrawal of digoxin resulted in worsening HF symptoms.9,10 Thus, the primary reason for digoxin therapy is to improve symptoms and reduce hospitalization for HF. However, the reduction in HF hospitalizations with digoxin was shown in an era where medical therapy for HF was substantially different than contemporary care. Since the publication of the DIG trial, β-blockers, angiotensin receptor blockers, aldosterone antagonists, hydralazine/nitrates in black patients, and biventricular pacemakers have all been shown to reduce hospitalization rates among patients with HF.24–26,28 Thus, whether digoxin adds anything in the current era is an open question. Therefore, our results of no improvement in either mortality or hospitalization with digoxin therapy are theoretically plausible. A substudy of the Valsartan in Heart Failure Trial (Val-HeFT) on 6800 patients also failed to show any hospitalization benefit with the use of digoxin therapy,27 thereby further supporting our results.

One issue with retrospective outcomes analysis is always whether or not the sicker patients preferentially received a given therapy. To address this concern, we controlled for baseline differences in all available variables between the 2 groups by propensity score matching. Even after carefully matching for these variables, our results did not change. In a separate analysis, we adjusted for the SHFM, which comprehensively controls for multiple risk factors known to predict outcomes in HF, and we additionally controlled for other important variables like renal function. None of these adjusted analyses changed the results with respect to lack of benefit from digoxin therapy in our study. The same trend persisted when analysis was restricted to patients who did not switch digoxin therapy during the follow-up period (ie, patients without crossover).

Are there any theoretical explanations for these outcomes? Digoxin has modest inotropic properties, and multiple inotropes in the past have been shown to worsen outcomes in HF, especially the risk of sudden death.23 Indeed, there was a numeric increase in non-HF cardiac deaths in DIG, including arrhythmic deaths (15% versus 13%; $P=0.04$). Furthermore, B-type natriuretic peptide levels strongly correlate with mortality in HF.29 Interestingly, in a Val-HeFT substudy, there was a significantly greater lowering of B-type natriuretic peptide at 12 months among patients not on digoxin.27 The earlier reports related to digoxin and adverse outcomes may be related to the higher risk of mortality at serum digoxin levels initially thought to be “therapeutic.”14 According to these estimates, the serum digoxin concentration associated with improved outcomes ranged between 0.5 and 0.8 ng/mL. This represents a narrow therapeutic range and raises practical “real-life” management issues. Digoxin levels were available for only half the patients in our study and despite a median follow-up of over 2 years, the majority had serum digoxin concentration checked only once. Adverse outcomes in practice due to side effects with agents shown to be beneficial in clinical trials has been reported previously, for example, spironolactone.30,31 In practice, most HF patients are elderly, have impaired renal function, and take concomitant medications that may either alter renal function or have drug to drug interaction with digoxin. All these factors increase the risk of achieving higher than desired serum digoxin concentrations despite “therapeutic” doses. We contend that unlike the survival benefit seen with spironolactone in HF, which may justify close follow-up for hyperkalemia, there is no survival benefit with digoxin in HF. Moreover, reduction in hospitalization rates with digoxin in the current era has not been shown, and there are reasons to believe that this reduction may not be there because of the competing effect of other beneficial therapies. In our cohort, for example, which represents the severe end of the HF spectrum with a very low mean left ventricular ejection fraction (<20%),
use of contemporary medications and devices was very high. This may be the underlying reason for the lack of benefit from digoxin treatment in these patients. Therefore, the routine use of digoxin therapy should be cautiously re-evaluated, at least in patients with advanced HF.

The SHFM controls for multiple common variables associated with HF outcomes including medical therapy. Irrespective of the debate whether digoxin therapy is a risk marker or a risk factor, our data suggest that it adds substantially to the SHFM in predicting the risk for patients with HF. The original SHFM did not evaluate the benefit of digoxin therapy because of inherent study limitations as described previously. We recommend on the basis of our results that inclusion of digoxin use in the SHFM be considered and evaluated further, especially in patients with advanced HF; a group where risk prediction arguably is more important.

Our study has several strengths and limitations. The most important strength is that these patients were aggressively treated. More than 90% of the patients were on both angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers and β-blockers, and more than 70% had cardiac devices implanted. These characteristics differentiate our study from most other studies in the past. On the other hand, this was a retrospective study. Retrospective studies pose significant difficulties in adequately adjusting for confounding. First, propensity score can balance differences only in measured covariates. In our study, for example, we observed some differences in echocardiographic characteristics in the subset of patients with available echocardiograms at baseline. Although these observations were from a nonmatched subset of propensity-matched patients and differences did not reach statistical significance because of small numbers, it is possible that these subtle differences in underlying structural heart disease may explain part of the observed differences in outcomes between the digoxin therapy groups. Second, there are variables that are difficult to adjust for, a prime example being the time-lapse from start of digoxin therapy before entering the study. These variables are also a possible source of bias. Third, propensity score matching has its own limitations. For example, there is no consensus on what constitutes “adequate” covariate balance between groups, and importantly, inference is valid only within the limits of the propensity-matched groups (i.e., we cannot draw conclusions for populations that are not represented in the matched groups). Our approach, however, to estimate the propensity score and the treatment effect was conservative, and thus, we believe that our findings are strongly suggestive at least. Finally, our study was not designed on the basis of an expected effect of digoxin. Therefore, only a properly designed and powered clinical trial would be able to definitely address the utility of digoxin in advanced HF. However, unless certain preliminary data suggest a magnitude for the treatment effect of digoxin in advanced HF (in this case, an unfavorable treatment effect), it will not be possible to design a study with adequate power to reject or, alternatively, confirm this effect.

In conclusion, our data suggest no benefit with digoxin in patients with advanced HF on contemporary medical therapy. Patients with HF experience multiple comorbidities and take many medications33; even patients with HF alone take 4 or more HF medications routinely.34 Polypharmacy is known to be associated with an increased risk of adverse drug reactions, drug interactions, and poor compliance.35 Besides, with advances in drug and device therapy for these patients, there is currently no evidence of benefit with the use of digoxin in advanced HF. Thus, for multiple reasons related to both efficacy and safety, whether or not digoxin therapy has any role in the current management of advanced HF needs to be evaluated. How to best accomplish this task, however, is difficult to answer. One possibility is a randomized control trial. An alternative is to develop a prospective multicenter registry to collect credible prospective data, or to analyze other large contemporary clinical trials. Our data indicate that at least this step should be taken to potentially plan prospective studies.

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Disclosures
None.

References

CLINICAL PERSPECTIVE

Current heart failure management guidelines recommend use of digoxin therapy for symptomatic improvement, based on noncontemporary data. The impact of digoxin on outcomes of patients with advanced heart failure receiving optimal contemporary therapy is not known. In this retrospective study of 455 patients on optimal contemporary medical therapy referred for transplant evaluation (age, 52±12 years; ejection fraction, 18.3±8%), 227 (49.9%) patients were on digoxin at baseline. After a median follow-up of 27 months, 83 of 277 (36.6%) patients treated with digoxin versus 36 of 228 (15.8%) without digoxin met the primary outcome of death, urgent transplantation, or ventricular assist device implantation (hazard ratio, 2.28; 95% CI, 1.51 to 3.43; P<0.001). Digoxin use remained associated with increased risk for the primary outcome in a propensity score–matched subset (n=322; hazard ratio, 1.73; 95% CI, 1.09 to 2.75; P=0.021) when entered as a time-dependent covariate (hazard ratio, 2.05; 95% CI, 1.23 to 3.41; P=0.011). Adjustment for Seattle Heart Failure Score and renal function did not alter this association. Risk was higher among patients in sinus rhythm compared with atrial fibrillation. There was no improvement in either all-cause or heart failure hospitalization rates with digoxin use. These results were similar across sex and race. These results suggest no benefit with digoxin in a transplant referral patient population with advanced heart failure receiving contemporary medical therapy, indicating that digoxin should be used cautiously in these patients until its value is further assessed in a contemporary cohort.
Digoxin Therapy Does Not Improve Outcomes in Patients With Advanced Heart Failure on Contemporary Medical Therapy
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