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Relationship of Serum Digoxin Concentration to Mortality and Morbidity in Women in the Digitalis Investigation Group Trial

A Retrospective Analysis

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OBJECTIVES The purpose of this study was to investigate the relationship of serum digoxin concentration (SDC) and outcomes in women with heart failure (HF).

BACKGROUND Controversy continues concerning the clinical utility of digoxin in women with HF.

METHODS Our analysis was retrospective with data from the Digitalis Investigation Group (DIG) trial. The principal study analysis reviewed 4,944 patients with HF due to systolic dysfunction who survived for at least 4 weeks (all 3,366 patients randomized to placebo and the 1,578 of 3,372 patients randomized to digoxin who had serum concentration measured 6 to 30 h [inclusive] after the last dose of study drug at 4 weeks).

RESULTS Continuous multivariable analysis demonstrated a significant linear relationship between SDC and mortality in women ($p = 0.008$) and men ($p = 0.002$, $p = 0.766$ for gender interaction). Averaging hazard ratios (HRs) across serum concentrations from 0.5 to 0.9 ng/ml in women produced a HR for death of 0.8 (95% confidence interval [CI] 0.62 to 1.13, $p = 0.245$) and for death or hospital stay for worsening HF of 0.73 (95% CI 0.58 to 0.93, $p = 0.011$). In contrast, SDCs from 1.2 to 2.0 ng/ml were associated with a HR for death for women of 1.33 (95% CI 1.001 to 1.76, $p = 0.049$).

CONCLUSIONS Retrospective analysis of data from the DIG trial indicates a beneficial effect of digoxin on morbidity and no excess mortality in women at serum concentrations from 0.5 to 0.9 ng/ml, whereas serum concentrations ≥1.2 ng/ml seem harmful. (J Am Coll Cardiol 2005;46: 497–504) © 2005 by the American College of Cardiology Foundation

Digitalis glycosides have been used in the treatment of heart failure (HF) for over two centuries and are still one of the most common treatments prescribed for this condition (1–3); however, the proper role of these drugs in the contemporary management of HF in women remains controversial. Recent analysis of all patients with reduced ejection fraction in the Digitalis Investigation Group (DIG) trial suggested that digoxin might have limited benefits on morbidity and might increase mortality in women (4). Further review of this trial strongly suggested the effect of digoxin on mortality in men with reduced ejection fraction was dependent upon serum concentration. Higher, but not lower, serum concentrations were associated with increased risk (5). If a similar relationship exists in both genders, consideration of serum concentration would be necessary to define the effect of digoxin on mortality in women. Adjusting for concentration might have greater impact in women, because they had higher digoxin concentrations, compared with men, early in the DIG trial (6). Understanding whether digoxin is harmful in women has substantial clinical importance, given that 50% of patients with HF are female and low-cost medications are needed to ease the economic burden of this syndrome.

To address this issue, we retrospectively analyzed data from the DIG trial with continuous multivariable analysis to determine if the relationship between serum concentration and mortality differed between women and men and whether there was any evidence that digoxin, at low serum concentrations, increased mortality or failed to have a morbidity benefit in women (7).

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Abbreviations and Acronyms

CI = confidence interval
DIG = Digitalis Investigation Group
HF = heart failure
HR = hazard ratio
SDC = serum digoxin concentration

METHODS

Study design. The DIG trial dataset was obtained from the National Heart, Lung, and Blood Institute under the Limited Access Dataset Procedure and its use was approved by the University of North Carolina School of Medicine Biomedical Institutional Review Board. The design, patient population, and conduct of the main trial in this study have been well documented (7). The initial dose of study drug was determined by an algorithm that took into account the patient's age, gender, weight, and renal function (8). The investigator could modify the digoxin dose as necessary on the basis of other factors, including co-administration of drugs known to alter digoxin pharmacokinetics. Blinded serum digoxin concentrations (SDCs) were determined in an arbitrary subset of patients at their week four study visit by radioimmunoassay (lower limit of detection 0.5 ng/ml) in a core laboratory (SmithKline BioScience, Norristown, Pennsylvania).

Study population. A total of 6,738 of the 6,800 patients enrolled in the main trial survived for at least 4 weeks of follow-up. Data were reviewed in 5,209 patients within this group, including all 3,366 patients randomized to placebo and all 1,843 patients randomized to digoxin who had a serum concentration obtained at their four-week visit. The SDC was measured between 6 and 30 h (inclusive) after the last dose of study drug in 1,578 of these 1,843 patients and they, along with the 3,366 placebo patients, comprised the principal patient group for analysis in this study (N = 4,944). The SDCs were detectable in 1,451 of these 1,578 patients (1,133 men and 318 women), and a total of 1,416 patients (1,110 men and 306 women) had SDCs ≥0.5 to 2.0 ng/ml (Fig. 1).

Statistical analysis. Multivariable Cox proportional hazards regression modeling was performed to determine adjusted hazard ratios (HRs) for digoxin versus placebo for various study end points. In analyses involving SDC, detectable serum concentrations (≥0.5 ng/ml) were treated as a linear continuous variable. The linear relationship between concentration and outcome was allowed to vary by gender. Patients randomized to digoxin who had undetectable serum concentrations (<0.5 ng/ml) were included as a separate group. Interactions for gender with SDC and the significant covariates for mortality were tested. Additional modeling of the relationship of serum concentration to outcome was performed in women and men separately. To assess linearity of the relationship with SDC, a backward

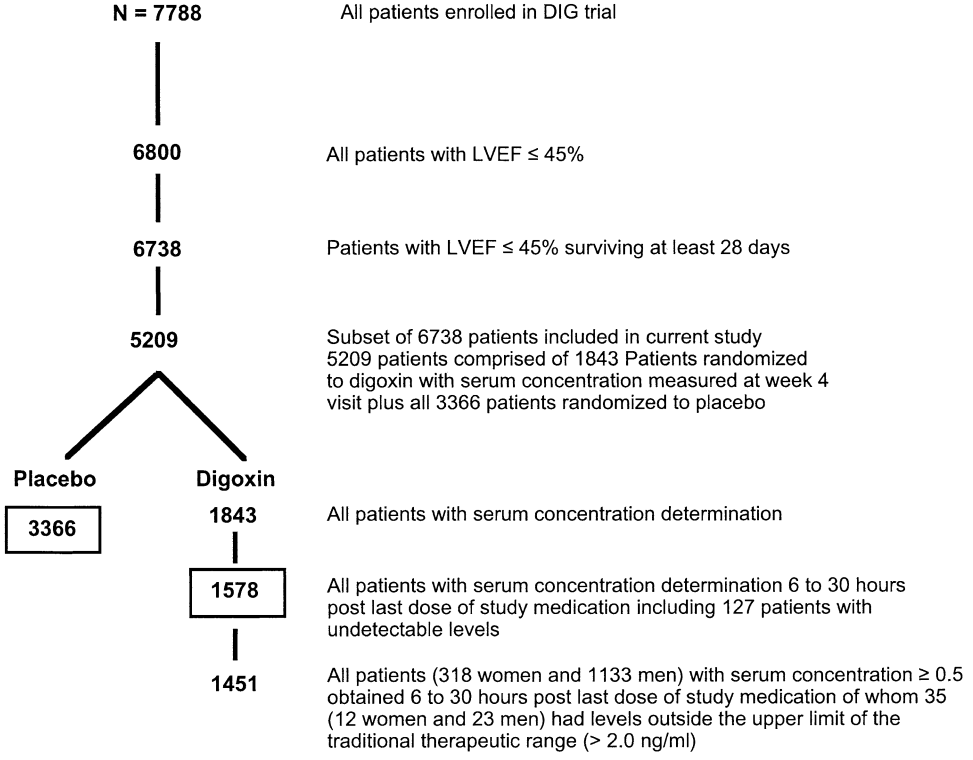

Figure 1. Diagram that shows the relationship between the original study population in the Digoxin Investigation Group (DIG) trial and the patients analyzed in the present study. LVEF = left ventricular ejection fraction.

selection of polynomial terms through the fourth order was conducted, and piecewise linear models were fitted with different slopes for lower (0.5 to 0.9 ng/ml) and higher (≥1.0 ng/ml) SDCs.

The modeling assessed the relationship between SDC at the four-week visit and either time to all-cause mortality, time to the combined end point of all-cause mortality or first hospital stay due to worsening HF, or first hospital stay due to worsening HF alone (9). The following variables, in addition to treatment assignment, were considered as potential covariates for the study end points of interest in a backward selection approach: digoxin use at baseline, race, age, gender, etiology (ischemic vs. nonischemic), body mass index, systolic and diastolic blood pressures, heart rate, resting left ventricular ejection fraction, cardiothoracic ratio, prior myocardial infarction status, current angina pectoris status, history of hypertension, history of diabetes, duration of HF, New York Heart Association functional class, diuretic use at baseline, nitrate use at baseline, vasodilator use at baseline, reported symptoms score or clinical HF score, and serum creatinine or estimated glomerular filtration rate. The clinical HF score was determined from patient symptoms, signs, and chest X-ray results collected at their baseline visit. Data on serum creatinine were captured from the week four visit or the baseline visit if not available at week four. Estimated glomerular filtration rate, expressed as ml/min/1.73 m^2 (10), was calculated from serum creatinine data with a modification of the prediction formula derived from the Modification of Diet in Renal Disease study (with all non-Caucasian patients considered as African Americans).

For descriptive and clinical purposes, HRs for ranges of SDC compared with placebo were calculated from the models by averaging HRs across the serum concentrations in a given range; ranges of interest included 0.5 to 0.9 ng/ml, on the basis of findings from the Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin (PROVED) and Randomized Assessment of Digoxin and Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) data, and 1.2 to 2.0 ng/ml, representing serum concentrations of possible harm in men (5,11). Adjusted survival curves were also generated with categories of serum concentration with the same covariates as for the continuous analysis.

Baseline characteristics were compared between women with and without SDCs measured between 6 and 30 h after the last dose of study drug and in women across categorical SDC ranges (0.5 to 0.9 ng/ml and 1.2 to 2.0 ng/ml) and placebo with chi-square statistics for categorical variables and one-way analysis of variance for continuous variables. For any baseline covariate with an imbalance across the three groups, significant pairwise comparisons were identified with a Bonferroni adjustment. Mean SDC and the time since the sample was drawn were compared between men and women by Student *t* test. Data are shown as mean ± SD.

RESULTS

Baseline characteristics. Overall, the clinical characteristics of the women randomized to placebo and those in the low serum concentration group (0.5 to 0.9 ng/ml) and the high serum concentration group (≥1.2 to 2.0 ng/ml) were comparable (Table 1). Women with low serum concentrations did have a higher estimated glomerular filtration rate and diastolic blood pressure than women with high serum concentrations ($p < 0.05$ after Bonferroni adjustment), but neither group was significantly different from placebo. Women with higher serum concentrations had greater HF scores at baseline compared with those on placebo ($p < 0.05$ after Bonferroni adjustment), but not compared with those in the low serum concentration group. The SDC was significantly greater in women compared with men (1.05 ± 0.45 ng/ml vs. 0.96 ± 0.41 ng/ml, $p = 0.003$) among patients with measurable concentrations (≥0.5 ng/ml) obtained 6 to 30 h after dosing of study drug at week 4. Overall, the baseline characteristics of women with and without SDC measurement were comparable (Table 2) and any differences found were accounted for in the multivariable modeling.

Continuous modeling of SDC, gender, and mortality. In all patients with detectable serum concentrations (women and men considered together), a significant linear relationship was observed between the adjusted relative risk of death and SDC ($p < 0.001$). Curve fitting with higher order models (second, third, and fourth order) were all nonsignificant (all $p = 0.119$), and attempts to fit a piecewise linear model with a different slope at lower (0.5 to 0.9 ng/ml) and at higher (≥1.0 ng/ml) concentrations was also nonsignificant ($p = 0.956$). The risk of mortality did not differ in the 127 patients with undetectable SDCs compared with placebo (adjusted HR of 1.01 with 95% confidence interval [CI] from 0.74 to 1.37, $p = 0.947$).

A significant linear relationship was found between SDC obtained 6 to 30 h after last dose of study medication and the risk of death relative to placebo in both women ($p = 0.0078$) and men ($p < 0.001$). Given this continuous relationship, the effect of digoxin versus placebo on mortality in either gender is best assessed by viewing point estimates for mortality across a range of serum concentrations (Fig. 2). Although there was some separation in the curves for serum concentrations above 1 ng/ml, the test for interaction with gender was not significant ($p = 0.766$, tested for equal intercepts and equal slopes), and there was wide overlap of the CIs between women and men. No significant interaction with gender was found when baseline characteristics that differed between women with and without SDC measurements were forced into the continuous, multivariable analysis ($p = 0.780$).

The validity of the model was also confirmed by testing for potential interactions between gender and each of the covariates in the final multivariable model for mortality. This analysis determined that the only covariate whose

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Table 1. Baseline Characteristics of Women in the Study Subgrouped According to SDC

Characteristic	Placebo	SDC (0.5–0.9 ng/ml)	SDC (1.2–2.0 ng/ml)	p Value
n	757	162	89	
Age (yrs)	65 ± 12	64 ± 12	65 ± 12	0.509
Race (non-white) (%)	19	19	15	0.547
BMI (kg/m^2)	27 ± 6.3	26 ± 6.2	27 ± 6.9	0.550
Previous digoxin use (%)	45	53	53	0.085
Previous MI (%)	53	52	56	0.786
Current angina (%)	29	27	22	0.387
Hypertension (%)	54	53	57	0.794
Ischemic etiology (%)	60	61	61	0.933
Diabetes (%)	34	28	35	0.318
NYHA functional class (%)				
I	9	9	12	
II	51	50	47	
III	38	40	33	
IV	2	1	8	0.961
ACE inhibitor	94	96	96	0.687
Diuretic	88	86	91	0.452
Nitrate	43	43	45	0.936
Vasodilator therapy	3.8	3.7	3.4	0.976
LVEF (U)	30 ± 9.0	29 ± 9.0	29 ± 9.4	0.309
Duration of CHF (months)	27 ± 32	28 ± 36	32 ± 32	0.303
SBP (mm Hg)	128 ± 21	130 ± 22	125 ± 20	0.188
DBP (mm Hg)	75 ± 12	77 ± 11	73 ± 10	0.031
Heart rate (beats/min)	81 ± 13	82 ± 12	80 ± 12	0.586
CT ratio (%)	0.56 ± 0.08	0.56 ± 0.07	0.58 ± 0.07	0.067
CHF score (U)	12 ± 5	12 ± 5	14 ± 6	0.012
eGFR (ml/min/1.73 m^2)	60 ± 34	64 ± 21	54 ± 20	0.032
SDC (ng/ml)	NA	0.73 ± 0.13	1.44 ± 0.22	<0.001
Time sample drawn (h)	NA	21 ± 7.4	18 ± 8.2	<0.001

SDC groups based on samples obtained within 6 to 30 h after last dose of study drug. Results shown as mean ± SD where appropriate. p values represent significance testing across all three groups (see Results for pairwise comparison testing).

ACE = angiotensin converting enzyme; BMI = body mass index; CHF = congestive heart failure; CT = cardiothoracic; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; SBP = systolic blood pressure; SDC = serum digoxin concentration.

association with mortality was influenced by gender was the history of diabetes (nominally significant with p = 0.032); however, the nonsignificance of the interaction between gender and the relationship of serum concentration to mortality was unchanged when this term was included in the modeling (p = 0.763). Additional continuous multivariable analysis with all available SDCs, regardless of the time from study drug administration, demonstrated a significant linear relationship between serum concentration and mortality similar to the primary analysis in both men (p < 0.001) and women (p = 0.001), and there was still no significant interaction with gender (p = 0.327). A significant linear relationship was also found between SDC and mortality when modeling was conducted in women alone (p = 0.007).

HRs across ranges of SDC. The HRs derived from the results of the continuous modeling were averaged across various concentration ranges to demonstrate the clinical importance of the SDC-mortality relationship in both women and men (Tables 3, 4, and 5). There was a suggestion of reduced mortality in men and no effect on mortality in women at serum concentrations from 0.5 to 0.9 ng/ml, whereas serum concentration ≥1.2 ng/ml seemed harmful in both genders. Similar relationships were observed in women when survival curves with these serum concentration ranges were compared with placebo (Fig. 3).

Serum concentration, gender, and other end points. Continuous multivariable modeling demonstrated a significant linear relationship between SDC versus placebo and the risk of the combined study end point (in women p = 0.033, and men p = 0.011; Fig. 4). In contrast, modeling did not reveal a significant linear relationship between the risk of hospital stay alone in women (p = 0.297) or men (p = 0.313), although there were trends for a greater benefit on this end point at lower compared with higher serum concentration in women and men as well (Table 3). There was no significant interaction between gender and the risk of either of these end points (combined, p = 0.679, and hospital stay alone, p = 0.306). Averaging HRs across ranges of SDC revealed substantial and similar reductions in the risk of the combined study end point and the risk of hospital stay due to worsening HF in both women and men at low serum concentrations, whereas less evidence of benefit was seen at higher concentrations (Table 3).

DISCUSSION

Our retrospective analysis of patients from the DIG trial demonstrates that the clinical effects of digoxin in women,

Table 2. Comparison of Baseline Characteristics in Women Randomized to Digoxin With and Without a Measurement of SDC at Their Week Four Visit

Characteristic	SDC Done	SDC Not Done	p Value
n	411	338	
Age (yrs)	64 ± 12	65 ± 13	0.181
Race (non-white) (%)	19	17	0.535
Prior MI (%)	54	59	0.210
Current angina (%)	26	30	0.256
Hypertension (%)	55	54	0.933
Ischemic etiology (%)	63	65	0.668
Diabetes (%)	30	36	0.140
Previous digoxin use, yes (%)	52	41	0.002*
NYHA functional class	2.3 ± 0.7	2.4 ± 0.7	0.077
BMI (kg/m^2)	27 ± 6.4	27 ± 6.4	0.634
LVEF (U)	30 ± 9.0	31 ± 8.6	0.075
Duration of CHF (months)	31 ± 37	24 ± 34	0.009†
SBP (mm Hg)	129 ± 21	127 ± 20	0.359
DBP (mm Hg)	75 ± 11	74 ± 12	0.036†
Heart rate (beats/min)	81 ± 12	82 ± 13	0.497
CT ratio	0.56 ± 0.08	0.57 ± 0.08	0.500
CHF score (U)	12.4 ± 5.1	12.4 ± 5.2	0.895
eGFR (ml/min/1.73 m^2)	61 ± 21	57 ± 20	0.012*
ACE inhibitor	96	93	0.197
Diuretic	88	87	0.740
Nitrate	43	43	0.854
Vasodilator	3.2	3.6	0.769

Results shown as mean ± SD where appropriate. *Present in original model of independent risk factors for both mortality and combined end point (Table 4); †not present in model of independent risk factors—forced to account for differences between SDC yes and no.

Abbreviations as in Table 1.

as in men, are significantly influenced by serum concentration, with divergent outcomes relative to placebo at low versus high concentrations. Specifically, there was no evidence that digoxin increased mortality in women at low serum concentrations by any of our analytical approaches. The point estimate for the relative risk of death on digoxin versus placebo was below unity for women at detectable serum concentrations <1 ng/ml. In addition, digoxin substantially reduced the risk of hospital stay for worsening HF and the risk of the combined end point of mortality and HF hospital stay in women at low SDCs (0.5 to 0.9 ng/ml). In contrast, the risk for mortality was greater than placebo when serum concentrations were ≥1.2 ng/ml, and there was no reduction in the risk of the combined end point at higher serum concentrations. Our study cannot define the mechanisms responsible for the adverse effect of higher SDCs. Increased SDC might have a pro-arrhythmic effect as seen with other positive inotropic agents even at the upper end of the traditional therapeutic range. Additional studies are needed to better define the adverse effects of inotropic agents on the failing human heart.

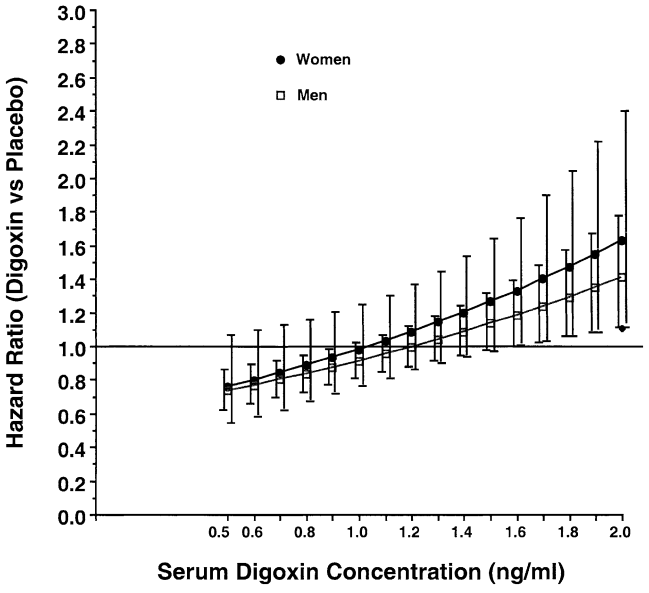

Figure 2. Plot of the adjusted point estimates and 95% confidence intervals of women and men for the hazard ratio for death on digoxin versus placebo at various serum digoxin concentrations (ng/ml) with concentration modeled as a continuous variable. The 95% confidence intervals for the women are offset to allow better depiction of results.

Our analysis concurs with the recent important findings of Rathore et al. (5) concerning the relationship between the efficacy of digoxin and serum concentration in men in the main DIG trial, with better outcomes at lower serum concentration and harm at higher concentrations. This group also reported a modest increase in mortality in women, but not men, in an analysis of all patients (N = 6,800) in the main trial (4). Several explanations could reconcile our findings with those of Rathore et al. (4) regarding the effects of digoxin on mortality in women with HF. First and most importantly, serum concentration significantly influences the effect of digoxin on mortality, not only in men, but also in women. This critical confounding factor could not be taken into account in an analysis of all

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Table 3. Risk of Study End Points for Men and Women Derived From the Continuous Multivariable Analysis Across Various SDC Ranges

	SDC 0.5–0.9 ng/ml			SDC 1.2–2.0 ng/ml		
Outcome	**HR**	**95% CI**	**p Value**	**HR**	**95% CI**	**p Value**
Mortality						
Men	0.80	0.70–0.92	0.002	1.18	0.99–1.39	0.060
Women	0.84	0.62–1.13	0.245	1.33	1.001–1.76	0.049
All patients	0.81	0.71–0.92	<0.001	1.21	1.05–1.40	0.009
Combined end point						
Men	0.70	0.63–0.79	<0.001	0.89	0.76–1.03	0.115
Women	0.73	0.58–0.93	0.011	1.01	0.79–1.28	0.961
All patients	0.71	0.64–0.79	<0.001	0.92	0.81–1.04	0.179
Hospital stay for worsening heart failure						
Men	0.59	0.50–0.69	<0.001	0.67	0.54–0.82	<0.001
Women	0.70	0.53–0.94	0.016	0.85	0.63–1.15	0.292
All patients	0.61	0.53–0.70	<0.001	0.72	0.60–0.85	<0.001

p values based on multivariable Cox proportional hazards modeling. Hazard ratio for digoxin versus placebo.
CI = confidence interval; HR = hazard ratio; SDC = serum digoxin concentration.

patients in the main trial. Measurement of serum concentration in a subgroup of patients in the trial demonstrated modestly but significantly higher SDCs in women, so that accounting for this confounding factor is even more important. In addition, because serum concentrations are not available in all patients in the main trial, the possibility of even greater gender differences in serum concentration cannot be excluded. Finally, the shape of the serum concentration outcome relationship in women suggests they might be more likely than men to have adverse effects at higher serum concentrations (Fig. 2). Formal interaction testing was negative, suggesting any difference in sensitivity is likely small, although the combination of higher SDCs and the potential for greater likelihood of an adverse effect of digoxin at serum concentrations ≥1.2 ng/ml could have also contributed to the findings of Rathore et al. (4) in the main trial population. Ultimately, the important therapeutic issue is not whether women and men differ to some degree in their responsiveness to digoxin, but whether any difference has clinical consequences after taking into account the influence of other important factors like serum concentration. Our analysis provides convincing evidence that the benefits of low serum concentration outweigh any potential differential response to digoxin by gender.

Our findings do not diminish the importance of investigating the potential for gender differences in the benefits of medications for HF. We and others have demonstrated significant differences in baseline characteristics and survival between men and women with HF, suggesting the response to medications for this condition might differ by gender (12–15). Enrollment of larger numbers of women in future clinical trials conducted in HF will help address this important issue.

As with any retrospective, nonrandomized study, well

Table 4. Multivariable Analysis of SDC as an Independent Predictor of Mortality in Patients Randomized to Digoxin Versus Placebo

Mortality End Point	**Adjusted Chi-Square**	**Hazard Ratio**	**95% CI**	**p Value**
eGFR (per 10 ml/min/1.73 m^2)	18.8	0.94	0.91–0.97	<0.001
Previous digoxin use	23.0	1.27	1.15–1.39	<0.001
Age (per 10 yrs)	36.1	1.19	1.12–1.26	<0.001
Gender (male)	44.0	1.53	1.35–1.74	<0.001
NYHA functional class	17.3	1.17	1.09–1.27	<0.001
SBP (per 5 mm Hg)	15.9	0.97	0.96–0.99	<0.001
CT ratio (per 0.05 U)	41.0	1.12	1.08–1.16	<0.001
LVEF (per 5 U)	65.2	0.89	0.86–0.91	<0.001
Diabetes	29.0	1.34	1.20–1.48	<0.001
CHF score	23.4	1.02	1.01–1.03	<0.001
BMI (per 5 kg/m^2)	9.8	0.92	0.87–0.97	0.002
Race	0.8	0.94	0.81–1.08	0.370
Nitrate	13.0	1.20	1.09–1.32	<0.001
Diuretic	13.5	1.35	1.15–1.58	<0.001
Vasodilator	6.2	1.36	1.07–1.73	0.013
Treatment	20.6	NA	NA	<0.001
SDC	21.7	NA	NA	<0.001
Undetectable SDC	<0.01	1.01	0.74–1.37	0.947

The variable race was forced into the mortality analysis. p values based on Cox proportional hazards model. SDC ≥ 0.5 ng/ml treated as a continuous variable with undetected concentrations considered as a separate group.
Abbreviations as in Tables 1 and 3.

Table 5. Multivariable Analysis of SDC as an Independent Predictor of Combined Mortality and Morbidity in Patients Randomized to Digoxin Versus Placebo

Combined End Point	Adjusted Chi-Square	HR	95% CI	p Value
eGFR (per 10 ml/min/1.73 m^2)	21.3	0.95	0.92–0.97	<0.001
Previous digoxin use	57.8	1.36	1.26–1.48	<0.001
Age (per 10 yrs)	20.3	1.11	1.06–1.16	<0.001
Gender (male)	38.5	1.38	1.25–1.53	<0.001
NYHA functional class	26.5	1.18	1.11–1.25	<0.001
SBP (per 5 mm Hg)	26.5	0.97	0.96–0.98	<0.001
CT ratio (per 0.05 U)	54.8	1.12	1.08–1.15	<0.001
LVEF (per 5 U)	86.6	0.89	0.87–0.91	<0.001
Diabetes	53.1	1.38	1.26–1.50	<0.001
CHF score	43.4	1.03	1.02–1.04	<0.001
BMI (per 5 kg/m^2)	3.0	0.96	0.92–1.01	0.085
Race	8.5	1.19	1.06–1.33	0.004
Nitrate	26.0	1.23	1.14–1.34	<0.001
Diuretic	29.9	1.44	1.26–1.64	<0.001
Vasodilator	3.7	1.22	0.99–1.50	0.056
Treatment	29.5	NA	NA	<0.001
SDC	11.1	NA	NA	0.001
Undetectable SDC	0.7	0.89	0.69–1.16	0.392

The variable race was forced into the mortality analysis. p values based on Cox proportional hazards model.
Abbreviations as in Tables 1 and 3.

known factors could have confounded our results. Our modeling analysis did investigate serum concentration as a continuous variable with arbitrary cut points only used to illustrate the clinical importance of the observed relationship. Worse outcomes in patients with high SDCs could be related to underlying renal disease or more severe clinical HF; however, our results were observed after taking into account renal function and various characteristics indicative of HF severity. We also found women in the digoxin group with and without serum concentration values to be reasonably comparable at baseline (Table 2), and including any differences found in the modeling did not alter our results. Because of the pharmacokinetics of digoxin, our primary analysis examined serum concentrations obtained within 6 to 30 h after the last dose of study medication. Our results, however, were similar when all serum concentrations were included

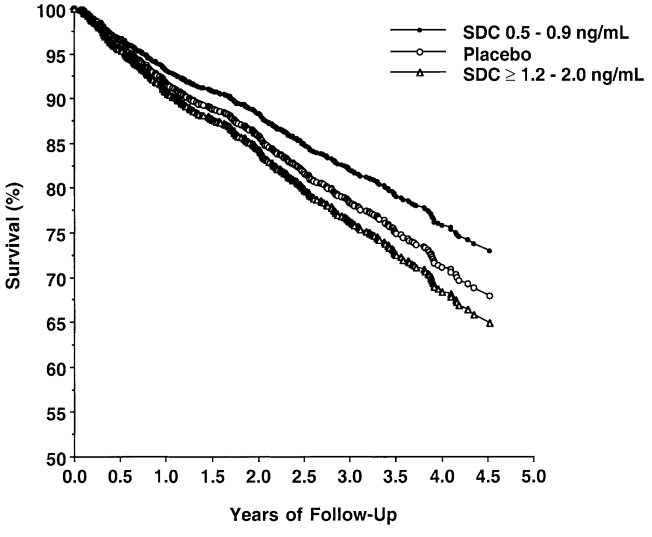

Figure 3. Plot of adjusted survival curves in placebo and various digoxin serum concentration groups. Results from this categorical analysis demonstrated that women with serum concentrations from 0.5 to 0.9 ng/ml had similar survival compared with those receiving placebo (hazard ratio 0.81, with 95% confidence interval from 0.58 to 1.14, p = 0.229), whereas women with serum concentrations from 1.2 to 2.0 ng/ml seemed to have a worse outcome (hazard ratio 1.11, with 95% confidence interval from 0.78 to 1.60, p = 0.557). SDC = serum digoxin concentration.

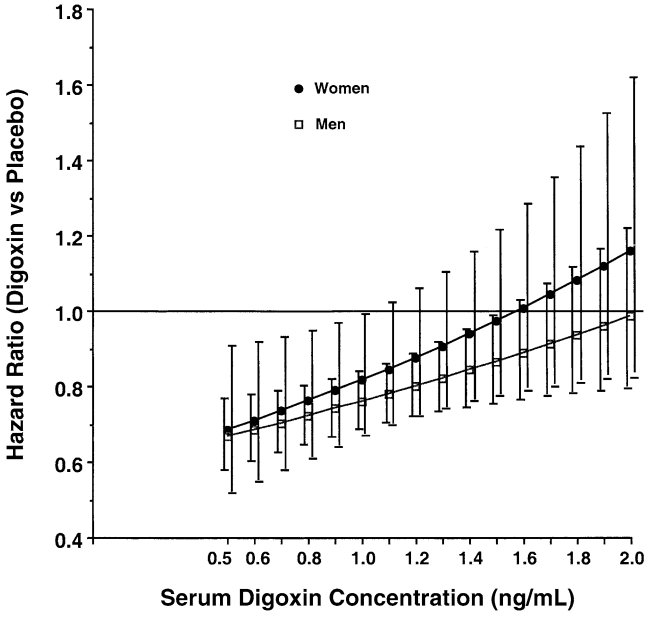

Figure 4. Plot of the adjusted point estimates and 95% confidence intervals of women and men for the hazard ratio for the combined study end point (of all-cause mortality or first hospitalization due to worsening heart failure) on digoxin versus placebo at various serum digoxin concentrations (ng/ml) with concentration modeled as a continuous variable. The 95% confidence intervals for the women are offset to allow better depiction of results.

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in the analysis. Although our findings are based on a modest number of women, their results were quite consistent with those of the men, especially with regard to the strong relationship of clinical outcome to serum concentration and the beneficial effects of digoxin at low serum concentrations on both the risk of the combined study end point and the risk of hospital stay due to HF. Some limitations concerning the generalizability of our findings should be mentioned. Only patients with symptomatic HF due to left ventricular systolic dysfunction were analyzed. Beta-blockers were not part of the usual management of HF at the time of the DIG study. Whether digoxin would exert beneficial clinical effects on outcomes at low serum concentrations in patients receiving beta blockers remains unknown.

Some might wonder why we should bother with digoxin, given recent advances in therapy for HF. But this question ignores the public health perspective concerning this drug: a familiar, well tolerated, convenient, and inexpensive agent which, in our analysis, seems to have clinical benefit in both women and men at the proper serum concentration. Integrating current biological and statistical understanding of digoxin therapy with good clinical judgment suggests a prudent strategy for the use of this drug in women with HF. Because the morbidity benefit seems greater and safety more likely at lower serum concentrations, administering low doses (0.125 mg/day or less) to achieve serum concentrations from 0.5 to 0.9 ng/ml is indicated. Dosing should always be individualized by considering age, body size, renal function, and concomitant interacting medications. Recognizing that women tend to have higher serum concentrations than expected, the steady state concentration could also be monitored after approximately four weeks. Once trough serum concentration is detectable but <1.0 ng/ml, further measurements are unnecessary unless renal function deteriorates, an interacting drug is added, or digoxin toxicity is suspected.

In conclusion, retrospective analysis of patients from the DIG trial indicates that digoxin is an effective treatment for HF in women with reduced ejection fractions when this drug is used at low serum concentrations. A beneficial effect on morbidity and no excess mortality was observed at serum concentrations from 0.5 to 0.9 ng/ml.

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