SEX-BASED DIFFERENCES IN THE EFFECT OF DIGOXIN FOR THE TREATMENT OF HEART FAILURE

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ABSTRACT

Background The Digitalis Investigation Group trial reported that treatment with digoxin did not decrease overall mortality among patients with heart failure and depressed left ventricular systolic function, although it did reduce hospitalizations slightly. Even though the epidemiologic features, causes, and prognosis of heart failure vary between men and women, sex-based differences in the effect of digoxin were not evaluated.

Methods We conducted a post hoc subgroup analysis to assess whether there were sex-based differences in the effect of digoxin therapy among the 6800 patients in the Digitalis Investigation Group study. The presence of an interaction between sex and digoxin therapy with respect to the primary end point of death from any cause was evaluated with the use of Mantel–Haenszel tests of heterogeneity and a multivariable Cox proportional-hazards model, adjusted for demographic and clinical variables.

Results There was an absolute difference of 5.8 percent (95 percent confidence interval, 0.5 to 11.1) between men and women in the effect of digoxin on the rate of death from any cause (P=0.034 for the interaction). Specifically, women who were randomly assigned to digoxin had a higher rate of death than women who were randomly assigned to placebo (33.1 percent vs. 28.9 percent; absolute difference, 4.2 percent, 95 percent confidence interval, −0.5 to 8.8). In contrast, the rate of death was similar among men randomly assigned to digoxin and men randomly assigned to placebo (35.2 percent vs. 36.9 percent; absolute difference, −1.6 percent; 95 percent confidence interval, −4.2 to 1.0). In the multivariable analysis, digoxin was associated with a significantly higher risk of death among women (adjusted hazard ratio for the comparison with placebo, 1.23; 95 percent confidence interval, 1.02 to 1.47), but it had no significant effect among men (adjusted hazard ratio, 0.93; 95 percent confidence interval, 0.85 to 1.02; P=0.014 for the interaction).

Conclusions The effect of digoxin therapy differs between men and women. Digoxin therapy is associated with an increased risk of death from any cause among women, but not men, with heart failure and depressed left ventricular systolic function. (N Engl J Med 2002;347:1403-11.)

IN 1997, the Digitalis Investigation Group reported the results of a randomized, double-blind, placebo-controlled trial evaluating the efficacy of digoxin therapy for patients with heart failure.[1] The investigators found that digoxin did not reduce overall mortality or three of the five secondary outcomes (death due to cardiovascular causes, death due to worsening heart failure, and the combined end point of death or hospitalization due to worsening heart failure in an ancillary trial). However, digoxin did decrease the risk of hospitalization for worsening heart failure and the overall risk of hospitalization during three years of follow-up. Since these results were published, the American College of Cardiology and American Heart Association,[2] the European Society of Cardiology,[3] and the Heart Failure Society of America[4] have issued clinical guidelines that strongly endorse the use of digoxin for patients with heart failure.

Although men and women differ with respect to the risk, causes, and prognosis of heart failure,[5] the Digitalis Investigation Group trial did not prespecify or report sex-specific subgroup analyses, and current clinical guidelines do not differentiate between the use of digoxin in men and the use of this agent in women. The majority of deaths attributable to heart failure occur in women,[6] even though women with heart failure have a lower risk of death than men.[7-10] Women with heart failure have more symptoms than men with similar ejection fractions,[11] are older,[8] and are more likely to have hypertension,[12] diabetes mellitus,[13] and preserved systolic function.[13] Sex-based or sex hormone–associated differences have also been documented in myocardial-cell function,[14-16] signal transduction and ion-channel activity,[15,17-20] autonomic nervous system function,[14] muscle metabolism,[21] and cardiac-cell growth.[16,22,23] Because the Digitalis Investigation Group trial enrolled nearly four men for every woman,[24] any differences in the effect of digoxin among women would have been subsumed by the effect of digoxin therapy among men. Accordingly, we assessed whether the effect of digoxin therapy varied according to the sex of the patients in the Digitalis Investigation Group trial.

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METHODS

Trial Data Base

We obtained a public-use copy of the data base of the Digitalis Investigation Group trial by submitting a written request to the National Heart, Lung, and Blood Institute. None of the authors were members of the Digitalis Investigation Group Investigators, and thus none were involved in the conduct or initial analysis of the trial.

Study Design

Details of the design and results of the Digitalis Investigation Group trial have been reported previously.[1,24] Patients who had stable heart failure were enrolled between February 1991 and August 1993 at 302 clinical centers in the United States and Canada. Patients were eligible for randomization if they had clinically confirmed heart failure, had an ejection fraction of 45 percent or less, and were in normal sinus rhythm. The diagnosis of heart failure was based on current or past clinical symptoms or signs or radiographic evidence of pulmonary congestion. A simultaneously conducted ancillary study enrolled patients who had symptomatic heart failure and an ejection fraction of more than 45 percent.

Treatment

The 6800 patients in the main trial and the 988 patients in the ancillary trial were assigned to receive digoxin or placebo therapy within each center according to a block-randomization approach. The initial recommended dose of the study drug was based on a nomogram that accounted for the patient's age, sex, weight, and renal function.[25] Modifications in dosage were permitted to account for the dose of digoxin a patient had been taking before enrollment and the use of concomitant drugs that might affect the pharmacokinetics of digoxin. To avoid the loss of blinding, investigators were discouraged from having patients' serum digoxin levels determined locally.

Outcomes

The primary study outcome was death from any cause within 37 months (range, 24 to 48) after randomization in the main trial. The five prespecified secondary outcomes in the Digitalis Investigation Group trial were death from cardiovascular causes, death from worsening heart failure, hospitalization for worsening heart failure, hospitalization for causes other than worsening heart failure, and the composite end point of death or hospitalization for worsening heart failure in the ancillary trial.[24] Causes of deaths and hospitalizations were prospectively recorded by local investigators who were blinded to the patients' treatment assignments.

Statistical Analysis

Analyses were conducted according to the intention-to-treat principle. Base-line characteristics were compared between men and women overall and stratified according to treatment-group assignment with the use of chi-square and Wilcoxon rank-sum tests. Rates of hospitalization for suspected digoxin-related toxicity and median serum digoxin levels, assessed 1 month and 12 months after randomization in a randomly selected subgroup of patients from the main trial cohort, were also compared.

Our analysis focused solely on the possible interaction between sex and digoxin therapy; no other subgroup analyses were conducted. Kaplan–Meier curves for death from any cause were plotted for the four groups represented by the combination of sex and treatment assignment — men randomly assigned to receive digoxin, men randomly assigned to receive placebo, women randomly assigned to receive digoxin, and women randomly assigned to receive placebo — and compared with use of a log-rank test.

To minimize concern about multiple testing, we based our statistical evaluation of the possible interaction between sex and digoxin therapy on the trial's primary outcome of death from any cause among patients enrolled in the main trial.[1] The existence of an interaction between sex and digoxin therapy was formally evaluated with use of the Mantel–Haenszel test of the heterogeneity of the effects of digoxin therapy according to sex and a Cox proportional-hazards model incorporating terms for the main effect of sex, the main effect of digoxin therapy, and the interaction between sex and digoxin therapy. To quantify the magnitude of the interaction, we determined the difference in the effects of digoxin therapy between men and women.[26,27]

A multivariable Cox proportional-hazards analysis was conducted to determine whether the interaction between sex and digoxin therapy was independent of other clinical factors. Patients' characteristics assessed at base line, including demographic characteristics, medical history, history of digoxin use, and current medications, were entered in a backward, stepwise Cox proportional-hazards model to identify predictors of mortality. Variables with a P value of less than 0.50 were entered into the model, and those with a P value of less than 0.10 were retained. The characteristics incorporated into the final Cox proportional-hazards model for death from any cause were age, race, body-mass index, left ventricular ejection fraction, cardiothoracic ratio, New York Heart Association (NYHA) functional class, the number of signs and symptoms of heart failure, the serum creatinine level, systolic blood pressure, and the presence or absence of diabetes, prior digoxin use, and concomitant use of diuretics, nitrates, and other vasodilators. This model was also repeated separately for men and women to estimate the sex-specific effect of digoxin therapy. The trial's secondary outcomes were also analyzed in order to identify additional interactions between sex and digoxin therapy.

RESULTS

Patients

In the main Digitalis Investigation Group trial, women as a whole were older than men and had a higher average left ventricular ejection fraction, heart rate, systolic blood pressure, and cardiothoracic ratio. A greater proportion of women had a history of diabetes, hypertension, angina, and prior use of digoxin than men or were in NYHA functional class III or IV, whereas fewer women presented with rales, a history of myocardial infarction, and ischemia as their primary cause of heart failure. Serum creatinine values and the initial dose of study medication prescribed were also lower in women (Table 1). There were no significant differences between the 2642 men who were randomly assigned to receive digoxin and the 2639 men who were randomly assigned to receive placebo or between the 755 women who were randomly assigned to receive digoxin and the 764 women who were randomly assigned to receive placebo.

Primary Outcome

As reported in the original study,[1] digoxin was not associated with a significant reduction in the rate of death from any cause (34.8 percent in the digoxin group, as compared with 35.1 percent in the placebo group; $P=0.79$; crude relative risk, 0.99; 95 percent confidence interval, 0.93 to 1.06). Women had a lower overall rate of death than men (31.0 percent vs. 36.1 percent, $P<0.001$). The rate of death was also

TABLE 1. CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	OVERALL		P VALUE	MEN		WOMEN	
	MEN (N=5281)	WOMEN (N=1519)		PLACEBO GROUP (N=2639)	DIGOXIN GROUP (N=2642)	PLACEBO GROUP (N=764)	DIGOXIN GROUP (N=755)
Median age (yr)	64	66	<0.001	64	64	66	66
Median ejection fraction (%)	28	30	<0.001	28	28	31	30
Median duration of CHF (mo)	18	12	<0.001	18	18	12	12
White race (%)	86.7	81.1	<0.001	86.5	86.8	80.6	81.6
Median body-mass index†	26.6	26.0	0.005	26.6	26.5	26.2	25.8
Method of assessing ejection fraction (%)							
Radionuclide ventriculography	67.0	56.2	<0.001	66.8	67.2	55.2	57.2
Two-dimensional echocardiography	27.8	36.5	<0.001	28.1	27.6	36.6	36.4
Contrast angiography	5.2	7.2	0.003	5.1	5.3	8.1	6.4
Median cardiothoracic ratio	0.52	0.56	<0.001	0.52	0.52	0.56	0.56
Median serum creatinine (mg/dl)‡	1.3	1.1	<0.001	1.3	1.2	1.1	1.1
Median systolic blood pressure (mm Hg)	122	128	<0.001	122	122	128	128
Median heart rate (beats/min)	78	80	<0.001	78	78	80	80
NYHA functional class (%)							
I	14.7	8.6	<0.001	14.2	15.2	8.8	8.5
II	54.8	50.7	0.005	55.7	53.9	50.4	51.0
III	28.4	38.1	<0.001	28.2	28.7	38.6	37.6
IV	2.0	2.5	0.21	1.9	2.1	2.2	2.8
No. of signs or symptoms of CHF (%)§							
0	1.3	0.5	0.02	1.2	1.3	0.5	0.5
1	2.4	1.6	0.07	2.2	2.5	1.4	1.7
2	7.5	5.7	0.02	7.4	7.6	6.4	5.0
3	9.5	7.0	0.003	8.9	10.1	7.6	6.4
≥4	79.4	85.2	<0.001	80.4	78.4	84.0	86.4
Medical history (%)							
Prior myocardial infarction	68.0	54.4	<0.001	68.9	67.2	52.8	56.0
Current angina	26.3	28.3	0.13	25.6	27.1	29.3	27.3
Diabetes	26.9	33.6	<0.001	26.8	27.0	34.6	32.7
Hypertension	42.8	54.1	<0.001	43.4	42.2	53.8	54.4
Prior digoxin use (%)	43.9	46.0	0.02	44.5	43.3	45.0	47.0
Primary cause of CHF (%)							
Ischemic	73.2	61.8	<0.001	73.5	72.9	60.0	63.6
Nonischemic	26.8	38.2	<0.001	26.5	27.1	40.0	36.4
Hypertensive	7.3	13.0	<0.001	7.5	7.1	14.7	11.3
Idiopathic	13.3	20.0	<0.001	12.6	14.0	19.5	20.5
Other¶	6.2	5.3	0.19	6.3	6.1	5.9	4.6
Concomitant medications (%)							
Diuretics	79.9	88.0	<0.001	80.4	79.3	88.2	87.8
ACE inhibitors	94.5	94.3	0.85	95.0	94.0	94.1	94.6
Nitrates	42.5	43.1	0.66	43.0	41.9	43.2	43.0
Other vasodilators‖	3.1	3.7	0.23	3.1	3.0	3.8	3.6
Dose of study medication prescribed (%)**							
0.125 mg/day	14.4	28.1	<0.001	14.2	14.5	28.5	27.7
0.250 mg/day	72.2	64.0	<0.001	72.0	72.3	63.4	64.6
0.375 mg/day	12.0	6.6	<0.001	12.5	11.5	7.1	6.1
0.500 mg/day	1.0	0.9	0.53	1.0	1.1	0.6	1.1

*Unless otherwise noted, values are expressed as proportions. Because of rounding, percentages may not total 100. None of the comparisons between men randomly assigned to digoxin and men randomly assigned to placebo or between women randomly assigned to digoxin and women randomly assigned to placebo were significant ($P>0.05$). CHF denotes congestive heart failure, NYHA New York Heart Association, and ACE angiotensin-converting enzyme.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡To convert values for creatinine to micromoles per liter, multiply by 88.4.

§The clinical signs or symptoms of CHF include rales, elevated jugular venous pressure, peripheral edema, dyspnea at rest or on exertion, orthopnea, limitation of activity, S_3 gallop, and radiologic evidence of pulmonary congestion.

¶Other causes of CHF included valvular and alcohol-related causes.

‖Other vasodilators included clonidine hydrochloride, doxazosin mesylate, flosequinan, labetalol hydrochloride, minoxidil, prazosin hydrochloride, and terazosin hydrochloride.

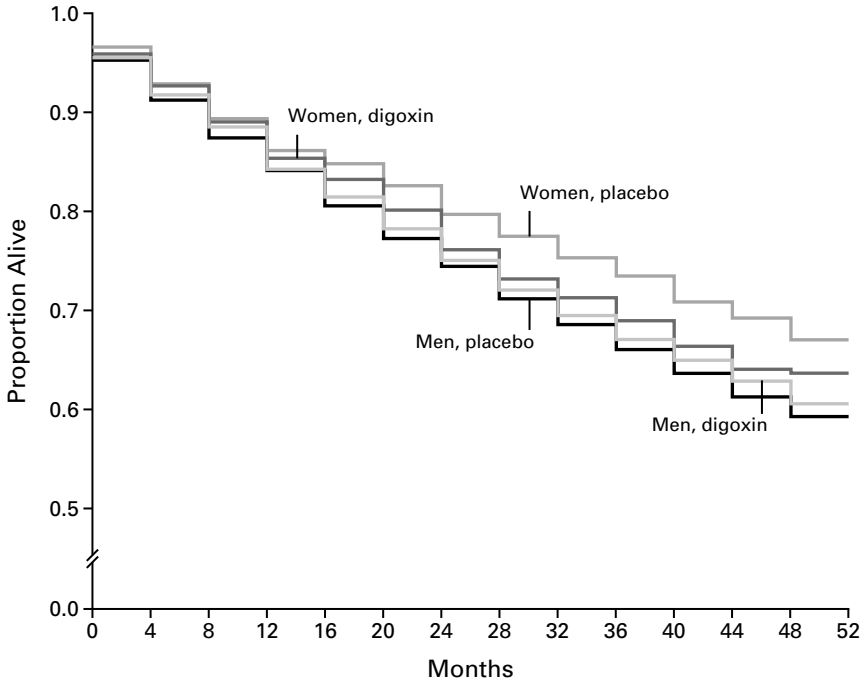
**Data on dosage were unavailable for 31 patients (24 men and 7 women).

lower among women in the placebo group than among men in this group (28.9 percent vs. 36.9 percent, $P<0.001$) and among women in the digoxin group than among men in the digoxin group (33.1 percent vs. 35.2 percent, $P=0.034$). Survival curves, however, differed significantly among the four subgroups ($P=0.002$) (Fig. 1).

The Mantel–Haenszel test of crude rates and a Cox proportional-hazards analysis identified a significant interaction between sex and digoxin therapy with respect to death from any cause. There was a 5.8 percent (95 percent confidence interval, 0.5 to 11.1) absolute difference in the effect of digoxin on the rate of death from all causes between men and women (Table 2). Digoxin therapy was not associated with a significantly increased rate of death among men (35.2 percent in the digoxin group, as compared with 36.9 percent in the placebo group; absolute difference, −1.6 percent; 95 percent confidence interval, −4.2 to 1.0), but it was associated with an increased rate of death among women that was of borderline significance (33.1 percent in the digoxin group, as compared with 28.9 percent in the placebo group; absolute difference, 4.2 percent; 95 percent confidence interval, −0.5 to 8.8; $P=0.034$ for the interaction between sex and digoxin). After multivariable adjustment, digoxin therapy was associated with a small, nonsignificant reduction in the risk of death from any cause among men (hazard ratio, 0.93; 95 percent confidence interval, 0.85 to 1.02) and a significantly increased risk of death from any cause among women (hazard ratio, 1.23; 95 percent confidence interval, 1.02 to 1.47; $P=0.014$ for the interaction between sex and digoxin) (Table 3).

Secondary Outcomes

Digoxin therapy was associated with a 4.7 percent (95 percent confidence interval, −0.6 to 10.0) smaller absolute reduction in the rate of hospitalization for worsening heart failure among women as compared with men (absolute difference between the digoxin and placebo groups, −4.2 percent [95 percent con-



No. at Risk

Men, placebo	2639	2510	2401	2301	2210	2111	2022	1944	1686	1438	1152	886	568	255
Men, digoxin	2642	2549	2449	2353	2243	2135	2047	1962	1685	1420	1129	870	572	249
Women, placebo	764	729	701	675	657	645	626	603	511	440	347	266	163	73
Women, digoxin	755	720	693	665	638	621	596	564	488	414	338	261	164	79

Figure 1. Kaplan–Meier Estimates of Survival among Men and Women, According to Whether They Were Randomly Assigned to Receive Digoxin or Placebo.

TABLE 2. RATES OF DEATH AND HOSPITALIZATION AMONG MEN AND WOMEN, ACCORDING TO TREATMENT ASSIGNMENT.*

VARIABLE	DEATH FROM ANY CAUSE	DEATH FROM CARDIOVASCULAR CAUSES	DEATH FROM WORSENING HEART FAILURE	HOSPITALIZATION FOR WORSENING HEART FAILURE	HOSPITALIZATION FOR OTHER CAUSES	DEATH FROM WORSENING HEART FAILURE OR HOSPITALIZATION FOR WORSENING HEART FAILURE IN ANCILLARY TRIAL
All patients						
Digoxin group (%)	34.8	29.9	11.6	26.8	39.0	20.7
Placebo group (%)	35.1	29.5	13.2	34.7	34.4	24.0
Absolute difference (%)	−0.3 (−2.6 to 2.0)	0.4 (−1.8 to 2.6)	−1.6 (−3.2 to −0.03)	−7.9 (−10.1 to −5.7)	4.6 (2.4 to 6.9)	−3.3 (−8.4 to 1.9)
P value	0.79	0.72	0.046	<0.001	<0.001	0.22
Men						
Digoxin group (%)	35.2	30.5	11.4	25.8	39.9	14.4
Placebo group (%)	36.9	31.1	13.6	34.7	35.0	20.3
Absolute difference (%)	−1.6 (−4.2 to 1.0)	−0.6 (−3.1 to 1.9)	−2.2 (−4.0 to −0.4)	−8.9 (−11.4 to −6.5)	4.9 (2.3 to 7.5)	−5.9 (−12.0 to 0.2)
P value	0.22	0.66	0.015	<0.001	<0.001	0.062
Women						
Digoxin group (%)	33.1	27.8	12.4	30.2	35.9	29.5
Placebo group (%)	28.9	24.1	11.9	34.4	32.2	29.5
Absolute difference (%)	4.2 (−0.5 to 8.8)	3.7 (−0.7 to 8.1)	0.5 (−2.8 to 3.8)	−4.2 (−8.9 to 0.5)	3.7 (−1.1 to 8.5)	−0.03 (−8.9 to 8.8)
P value	0.078	0.098	0.75	0.079	0.13	0.99
Interaction between sex and digoxin						
Absolute difference (%)†	5.8 (0.5 to 11.1)	4.3 (−0.8 to 9.4)	2.8 (−1.0 to 6.5)	4.7 (−0.6 to 10.0)	−1.2 (−6.6 to 4.2)	5.8 (−4.9 to 16.6)
P value‡	0.034	0.092	0.16	0.053	0.78	0.16

*Six thousand eight hundred patients (5281 men and 1519 women) were included in the evaluation of death from any cause, death from cardiovascular causes, death from worsening heart failure, hospitalization for worsening heart failure, and hospitalization for other causes, and 988 patients (581 men and 407 women) were included in the evaluation of death from worsening heart failure or hospitalization for worsening heart failure in the ancillary trial. With respect to absolute differences, a negative number indicates a lower rate among patients randomly assigned to receive digoxin than among patients randomly assigned to receive placebo.

†The absolute difference represents the absolute difference between the effect of digoxin therapy as compared with that of placebo among women and the effect of digoxin therapy as compared with that of placebo among men. A positive number indicates that digoxin is associated with a higher rate of the outcome among women than among men.

‡P values were obtained with the use of a Mantel–Haenszel test of heterogeneity.

TABLE 3. DIGOXIN-ASSOCIATED RISK OF DEATH AND HOSPITALIZATION AMONG MEN AND WOMEN.*

VARIABLE	DEATH FROM ANY CAUSE	DEATH FROM CARDIOVASCULAR CAUSES	DEATH FROM WORSENING HEART FAILURE	HOSPITALIZATION FOR WORSENING HEART FAILURE	HOSPITALIZATION FOR OTHER CAUSES	DEATH FROM WORSENING HEART FAILURE OR HOSPITALIZATION FOR WORSENING HEART FAILURE IN ANCILLARY TRIAL
Men						
Unadjusted hazard ratio (95% CI)	0.95 (0.87–1.04)	0.98 (0.88–1.08)	0.83 (0.71–0.97)	0.68 (0.62–0.75)	1.16 (1.06–1.27)	0.67 (0.45–0.99)
Adjusted hazard ratio (95% CI)†	0.93 (0.85–1.02)	0.96 (0.87–1.06)	0.79 (0.68–0.92)	0.66 (0.60–0.73)	1.17 (1.07–1.28)	0.72 (0.48–1.07)
Women						
Unadjusted hazard ratio (95% CI)	1.17 (0.97–1.40)	1.18 (0.97–1.44)	1.07 (0.80–1.42)	0.85 (0.71–1.01)	1.14 (0.96–1.36)	0.95 (0.67–1.36)
Adjusted hazard ratio (95% CI)†	1.23 (1.02–1.47)	1.24 (1.02–1.52)	1.17 (0.87–1.56)	0.87 (0.72–1.04)	1.15 (0.97–1.37)	0.92 (0.64–1.31)
Interaction between sex and digoxin‡						
Unadjusted P value	0.047	0.097	0.14	0.039	0.87	0.19
Adjusted P value†	0.014	0.035	0.026	0.011	0.91	0.32

*Hazard ratios represent the risk of the outcome among patients randomly assigned to digoxin as compared with patients randomly assigned to placebo and were obtained with use of a Cox proportional-hazards model.

†Values were adjusted for age, race, body-mass index, left ventricular ejection fraction, cardiothoracic ratio, New York Heart Association functional class, number of signs and symptoms of heart failure, serum creatinine level, systolic blood pressure, and presence or absence of diabetes, prior digoxin use, and concomitant use of diuretics, nitrates, and vasodilators.

‡P values are for the sex-and-digoxin-therapy interaction term entered in the Cox proportional-hazards model.

fidence interval, −8.9 to 0.5] for women and −8.9 percent [95 percent confidence interval, −11.4 to −6.5] for men; P=0.053 for the interaction between sex and digoxin). The effect of digoxin on the rate of death from cardiovascular causes differed by 4.3 percent (95 percent confidence interval, −0.8 to 9.4) between women and men (absolute difference between the digoxin and placebo groups, 3.7 percent [95 percent confidence interval, −0.7 to 8.1] for women and −0.6 percent [95 percent confidence interval, −3.1 to 1.9] for men; P=0.092 for the interaction between sex and digoxin). Digoxin was associated with a small, nonsignificant increase in the rate of death due to worsening heart failure among women but not among men (absolute difference between the digoxin and placebo groups, 0.5 percent [95 percent confidence interval, −2.8 to 3.8] for women and −2.2 percent [95 percent confidence interval, −4.0 to −0.4] for men; P=0.16 for the interaction between sex and digoxin). There was no interaction between sex and digoxin therapy with respect to the end point of hospitalization for causes other than worsening heart failure (P=0.78 for the interaction) or for the composite end point of death or hospitalization for worsening heart failure among patients enrolled in the ancillary trial (P=0.16 for the interaction) (Table 2).

Multivariable modeling confirmed the interaction between sex and digoxin therapy that was observed in unadjusted analyses. Digoxin was associated with an increased risk of death from cardiovascular causes among women (hazard ratio, 1.24; 95 percent confidence interval, 1.02 to 1.52) but not among men (hazard ratio, 0.96; 95 percent confidence interval, 0.87 to 1.06; P=0.035 for the interaction between sex and digoxin). Digoxin was associated with a decreased risk of death from worsening heart failure among men (hazard ratio, 0.79; 95 percent confidence interval, 0.68 to 0.92) but not among women (hazard ratio, 1.17; 95 percent confidence interval, 0.87 to 1.56; P=0.026 for the interaction between sex and digoxin). Although men who were randomly assigned to receive digoxin had a lower risk of hospitalization for worsening heart failure than men who were assigned to receive placebo (hazard ratio, 0.66; 95 percent confidence interval, 0.60 to 0.73), the benefit was smaller for women (hazard ratio, 0.87; 95 percent confidence interval, 0.72 to 1.04; P=0.011 for the interaction between sex and digoxin). Digoxin had a similar effect in men and women with respect to the end point of hospitalization for causes other than worsening heart failure (hazard ratio for men, 1.17 [95 percent confidence interval, 1.07 to 1.28]; hazard ratio for women, 1.15 [95 percent confidence interval, 0.97 to 1.37]; P=0.91 for the interaction between sex and digoxin) and the end point of death or hospitalization due to worsening heart

failure among patients enrolled in the ancillary trial (hazard ratio for men, 0.72 [95 percent confidence interval, 0.48 to 1.07]; hazard ratio for women, 0.92 [95 percent confidence interval, 0.64 to 1.31]; P= 0.32 for the interaction between sex and digoxin) (Table 3).

Medication Doses, Serum Digoxin Levels, and Suspected Digoxin Toxicity

The mean daily dose of medication prescribed at randomization was 0.25 mg in men and 0.22 mg in women (P=0.28). When the dose was standardized according to the body-mass index, men received a higher dose of digoxin than women (0.0093 mg per unit of body-mass index vs. 0.0084 mg per unit of body-mass index, P<0.001). However, the median serum digoxin level was slightly higher in a group of 475 randomly selected women than in a group of 1653 randomly selected men one month after study entry (0.9 ng per milliliter vs. 0.8 ng per milliliter, P= 0.007). The median serum digoxin level was the same 12 months after randomization among 581 randomly selected women and 2063 randomly selected men (0.6 ng per milliliter and 0.6 ng per milliliter, P=0.46). The proportion of patients who had serum digoxin levels of more than 2.0 ng per milliliter was similar among men and women 1 month after randomization (2.3 percent and 3.4 percent, respectively; P=0.20) and 12 months after randomization (2.1 percent and 1.4 percent, P=0.30). Although random assignment to digoxin therapy was associated with higher rates of hospitalization for suspected digoxin-related toxic effects in the main trial (2.0 percent, as compared with 0.9 percent in the placebo group; P<0.001), the magnitude of this effect was similar among men (1.8 percent and 0.8 percent, respectively; P=0.002) and women (2.5 percent and 1.2 percent, respectively; P= 0.053; P=0.97 for the interaction between sex and digoxin).

DISCUSSION

Our post hoc subgroup analysis of data from the Digitalis Investigation Group trial indicates that the effect of digoxin in the treatment of outpatients with stable heart failure differs between men and women. There was an absolute difference of 5.8 percent in the effect of digoxin on the rate of death from any cause between men and women. Digoxin was associated with an increased risk of death among women but not among men. Among women, digoxin therapy was also associated with an increased risk of the secondary outcomes of death from cardiovascular causes and death from worsening heart failure. Furthermore, women had a smaller digoxin-associated reduction in the rate of hospitalization for worsening heart failure than men. In the absence of other data concerning sex-based differences in the efficacy of digoxin, our findings raise strong concern about the appropriate role of digoxin therapy in women.

Subgroup analyses are generally not considered to provide definitive evidence for several reasons, including the manner in which post hoc analyses are planned and reported, the statistical methods used to identify interactions, and the spurious associations that may arise as a result of multiple testing.[28-34] Our analysis addressed each of these issues. There are sufficient clinical data concerning sex-based differences in the pathophysiology and outcomes of heart failure to justify a post hoc investigation of the effect of these differences on the efficacy of digoxin therapy. We identified the interaction between sex and digoxin therapy using formal tests of treatment interaction rather than comparing the results of significance tests within the separate strata of men and women.[30,35] We addressed concern about multiple testing[31,36] by basing our evaluation of the interaction between sex and digoxin therapy principally on the trial's prespecified primary outcome of death from any cause. The magnitude of the interaction between sex and digoxin therapy and the precision in its estimation afforded by the size of the Digitalis Investigation Group trial lead us to believe that the interaction we identified is clinically significant and probably not a statistical artifact.

To our knowledge, there are no published data concerning interactions between sex and digoxin therapy with which to compare our results, and previous randomized, controlled trials of digoxin therapy in patients with heart failure did not report sex-stratified results.[5,11,37] Although we cannot identify the mechanism of the interaction between sex and digoxin therapy, our data suggest that some hypotheses can be discounted. Instances of suspected digoxin toxicity and hospitalization for complications of digoxin therapy were infrequent, and there were no sex-based differences in digoxin-associated complications. The interaction between sex and digoxin therapy is not attributable to age, because age does not modify the efficacy of digoxin.[38] The interaction does not reflect a dosing effect, since men received higher drug doses (standardized according to the body-mass index) than women. The slightly higher serum digoxin levels in women than in men one month after randomization raises the possibility of sex-associated differences in the pharmacokinetics of digoxin. Because serum digoxin levels were measured in less than one third of patients at one month, the trial had insufficient statistical power to test whether the interaction between sex and digoxin therapy was independent of sex-based differences in serum digoxin levels.

A possible mechanism for the increased risk of death among women may involve an interaction between hormone-replacement therapy and digoxin. Proges-

tin may increase serum digoxin levels by inhibiting P-glycoprotein and thereby reducing the excretion of digoxin through the renal tubules.[39] Furthermore, the Heart and Estrogen/Progestin Replacement Study reported an interaction between digoxin and hormone-replacement therapy that was associated with a higher rate of cardiovascular events.[40] This hypothesis could not be tested because the Digitalis Investigation Group trial did not collect information about the use of hormone-replacement therapy. Other endogenous factors, which are either due to or associated with sex, may also be possible, although sex-based differences in pharmacodynamics are rare.

Although based on a post hoc analysis of the Digitalis Investigation Group trial, our study provides robust evidence of an interaction between sex and digoxin therapy and suggests an increased risk of death among women with heart failure treated with digoxin. This finding is particularly important for practice, given that the sole benefit of digoxin therapy is a small reduction in the secondary end point of hospitalization. There is no accepted method by which to balance a possible therapy-associated increased risk of death with a demonstrated therapy-associated benefit of a decreased risk of complications. However, women may not consider the potential increased risk of death associated with digoxin therapy worth the small reduction in the risk of hospitalization.

Our study underscores the importance of investigations of sex-based variations in treatment efficacy.[5,41] However, few randomized, controlled trials are designed to test for sex-specific effects, and relatively few women have been enrolled in trials of heart-failure therapies.[5,11,42] The interaction between sex and digoxin therapy can be confirmed only by a sex-stratified, randomized, controlled trial of digoxin therapy. However, such a study may not be considered ethical, since it would be designed to confirm risk and not benefit. In the absence of definitive evidence from trials and despite the lack of clear knowledge of the mechanism of the interaction of sex with digoxin, we believe that our data provide sufficient grounds for a reexamination of the use of digoxin therapy for women with heart failure.

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