ORIGINAL ARTICLE

Digitoxin in Patients with Heart Failure and Reduced Ejection Fraction

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ABSTRACT

BACKGROUND

The therapeutic efficacy of the cardiac glycoside digitoxin in patients with heart failure and reduced ejection fraction is not established.

METHODS

In this international, double-blind, placebo-controlled trial, we randomly assigned patients with chronic heart failure who had a left ventricular ejection fraction of 40% or less and a New York Heart Association (NYHA) functional class of III or IV or a left ventricular ejection fraction of 30% or less and an NYHA functional class of II in a 1:1 ratio to receive digitoxin (at a starting dose of 0.07 mg once daily) or matching placebo in addition to guideline-directed medical therapy. The primary outcome was a composite of death from any cause or hospital admission for worsening heart failure, whichever occurred first.

RESULTS

Among 1240 patients who underwent randomization, 1212 fulfilled the criteria for inclusion in the modified intention-to-treat population: 613 patients in the digitoxin group and 599 in the placebo group. Over a median follow-up of 36 months, a primary-outcome event occurred in 242 patients (39.5%) in the digitoxin group and 264 (44.1%) in the placebo group (hazard ratio for death or first hospital admission for worsening heart failure, 0.82; 95% confidence interval [CI], 0.69 to 0.98; P=0.03). Death from any cause occurred in 167 patients (27.2%) in the digitoxin group and 177 (29.5%) in the placebo group (hazard ratio, 0.86; 95% CI, 0.69 to 1.07). A first hospital admission for worsening heart failure occurred in 172 patients (28.1%) in the digitoxin group and 182 (30.4%) in the placebo group (hazard ratio, 0.85; 95% CI, 0.69 to 1.05). At least one serious adverse event occurred in 29 patients (4.7%) in the digitoxin group and 17 (2.8%) in the placebo group.

CONCLUSIONS

Treatment with digitoxin led to a lower combined risk of death from any cause or hospital admission for worsening heart failure than placebo among patients with heart failure and reduced ejection fraction who received guideline-directed medical therapy. (Funded by the German Federal Ministry of Research, Technology, and Space and others; DIGIT-HF EudraCT number, 2013-005326-38.)

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*A complete list of members of the DIGIT-HF Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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Cardiac glycosides have been used in the treatment of heart failure for two centuries.[1,2] However, evidence of benefit in patients with heart failure and reduced ejection fraction is limited. In the randomized, placebo-controlled clinical trial DIG (Effect of Digoxin on Mortality and Morbidity in Patients with Heart Failure), which enrolled patients with heart failure and reduced ejection fraction, digoxin was not superior to placebo with respect to death from any cause (the primary outcome), but it was associated with a lower incidence of hospitalization for worsening heart failure (a secondary outcome).[3] Patients with a markedly reduced ejection fraction (<25%) or with advanced symptoms of heart failure (New York Heart Association [NYHA] functional class III or IV) may benefit from digoxin.[4] In the DIG trial, low serum digoxin concentrations (0.5 to 0.9 ng per milliliter) were associated with better clinical outcomes than placebo, whereas concentrations above 1.0 ng per milliliter were associated with worse outcomes.[5-7] Because the DIG trial was conducted decades ago, background therapy for heart failure was limited to angiotensin-converting–enzyme inhibitors and diuretics, whereas currently available treatments include beta-blockers, mineralocorticoid receptor antagonists, angiotensin receptor–neprilysin inhibitors, sodium–glucose cotransporter 2 inhibitors, and cardiac device therapies, such as the use of an implantable cardioverter–defibrillator and cardiac-resynchronization therapy.[8-10]

Digitoxin is the other clinically relevant cardiac glycoside. Although the pharmacodynamics of digoxin and digitoxin are similar, the levels of enteral absorption and serum protein binding are higher with the more lipophilic digitoxin than with digoxin.[11,12] Unlike digoxin, digitoxin is effectively eliminated by enterohepatic excretion when renal function is markedly impaired.[11,12] Digitoxin concentrations in blood can remain stable without dose adjustments, even among patients with progressive renal dysfunction.[12] However, the lack of double-blind, randomized, clinical trials that use digitoxin underscores the need for further investigation. The DIGIT-HF (Digitoxin to Improve Outcomes in Patients with Advanced Chronic Heart Failure) trial was conducted to evaluate the efficacy and safety of digitoxin at low concentrations in patients with chronic heart failure and reduced ejection fraction that had been treated with current medical and cardiac device therapies.

Methods

Trial Design and Oversight

We conducted this phase 4, double-blind, randomized, placebo-controlled trial at 65 sites in Austria, Germany, and Serbia. The trial design has been published previously.[13-15] The trial protocol (available with the full text of this article at NEJM.org) was approved by the respective national authorities and ethics committees. The trial was conducted and is reported according to the principles of the Declaration of Helsinki and the guidelines for Good Clinical Practice. Trial committees are described in the Supplementary Appendix, available at NEJM.org. The six authors who had access to the data vouch for the accuracy and completeness of the data and analyses, and all the authors vouch for the fidelity of the trial and of this report to the protocol.

Patients

Patients were eligible for enrollment if they were at least 18 years old, had symptomatic chronic heart failure (specified as a left ventricular ejection fraction of ≤40% and an NYHA functional class of III or IV, or a left ventricular ejection fraction of ≤30% and an NYHA functional class of II), and had received evidence-based therapy for heart failure for a period of at least 6 months. Detailed criteria for patient selection are provided in Table S1 in the Supplementary Appendix. All the patients who underwent randomization provided written informed consent. The number of patients enrolled per site is shown in Table S2.

Trial Procedures

Patients were randomly assigned in a 1:1 ratio to receive digitoxin at a starting dose of 0.07 mg once daily or matching placebo. Dose adjustments were made according to a predefined algorithm: digitoxin concentrations in serum were measured in a blinded manner in a central laboratory 6 weeks after randomization, and if the level was found to be outside the predefined target range of 8 to 18 ng per milliliter (10.5 to 23.6 nmol per liter), the dosage was adjusted accordingly, with either a decrease to 0.05 mg once daily or an increase to 0.1 mg once daily. In the placebo group,

respective dose adjustments were randomly assigned. Further details and rationale with regard to digitoxin doses are available in the protocol.[13,14,16] Randomization was stratified according to sex, NYHA functional class (II, III, or IV), trial site, the presence or absence of atrial fibrillation, and previous treatment with cardiac glycosides (yes or no; because of the small number of patients who had previous treatment with cardiac glycosides, this variable was not included in analyses). All patients received standard care in accordance with current guidelines for the treatment of heart failure.[8-10]

OUTCOMES

The primary outcome, which was tested for superiority, was a composite of death from any cause or hospital admission for worsening heart failure, whichever occurred first. Potential primary-outcome events were adjudicated in a blinded manner by an independent committee (see the Supplementary Appendix for additional information). Key secondary outcomes included death from any cause, which was tested for noninferiority to exclude a detriment from digitoxin as compared with placebo, and a composite of death from any cause and any hospitalization due to heart failure, assessed as the total number of events. Other secondary outcomes included death from cardiovascular causes, death from noncardiovascular causes, death from heart failure, sudden death from cardiac causes, hospitalization due to cardiovascular causes, hospitalization due to noncardiovascular causes, hospitalization due to any cause, and a composite of death from cardiovascular causes or first hospitalization for heart failure. Safety outcomes included serum digitoxin concentrations, adverse and serious adverse events, and serious adverse events that appeared to be unexpected adverse reactions to digitoxin or placebo.

STATISTICAL ANALYSIS

The sample size was calculated on the basis of the assumption that a primary-outcome event would occur in 26% of patients in the digitoxin group and 31% of those in the placebo group within 24 months after randomization (exponential model; hazard ratio for death from any cause or first hospitalization for worsening heart failure, 0.811), with an overall two-sided type I error rate of 0.05 (of which 0.01 would be spent in one interim analysis conducted according to an O'Brien–Fleming design[17]), a recruitment period of 36 months, and a maximum of 48 months of follow-up. We calculated that a sample of 2190 patients and 734 events would provide the trial with 80% power to show superiority of digitoxin to placebo with respect to the primary outcome.[13] Death from any cause was assessed in a noninferiority analysis to exclude a detriment from digitoxin with respect to survival. Assuming the worst-case scenario in which digitoxin would have no effect on the incidence of death from any cause (such that the hazard ratio for death would be 1), estimating a 2-year mortality of 17% in both groups, and taking into account the aforementioned timing with regard to recruitment and follow-up, the sample of 2190 patients calculated for the primary outcome would provide the trial with 80% power to exclude a detriment from digitoxin, with noninferiority defined by a hazard ratio of no more than 1.303.

Primary and key secondary outcomes were ordered hierarchically: in the primary analysis, the superiority of digitoxin to placebo with respect to death from any cause or hospitalization for worsening heart failure, whichever occurred first, was tested in a Cox regression model with assigned group (digitoxin or placebo) and randomization strata as independent variables. The noninferiority of digitoxin to placebo with respect to death from any cause was analyzed in a Cox regression model, and the superiority of digitoxin to placebo with respect to the total number of deaths from any cause and hospitalizations for worsening heart failure was analyzed in a negative binomial model with the logarithm of the observation time per patient as an offset variable.[13,14] Both key secondary analyses included the same independent variables as the primary analysis.

Efficacy analyses were performed in a modified intention-to-treat population, which excluded patients who had undergone randomization but were confirmed to have never taken digitoxin or placebo as assigned but included all other patients who had undergone randomization (further details are provided in the Supplementary Appendix). Otherwise, patients were included in analyses according to their assigned trial group. Absolute and relative frequencies of adverse events were compared descriptively between trial groups at the patient level. In analyses of hospitalizations,

data for patients who died without being hospitalized were censored at the date of death.

Recruitment was slower than anticipated, and 40 months after the start of recruitment, the trial duration was extended. After 84 months, the number of events projected for the interim analysis had not yet occurred. The decision was made to waive the interim analysis, and the final analysis was evaluated with the full type I error rate of 0.05. A P value of less than 0.05 was considered to indicate significance.

Seven protocol amendments address the slower recruitment with the inclusion of additional centers, prolongation of the trial duration, and implications for the statistical analysis as summarized in the statistical analysis plan.[14] Additional information is available in the Supplementary Appendix.

RESULTS

PATIENTS

From May 4, 2015, to September 29, 2023, a total of 1240 patients were randomly assigned to receive either digitoxin or matching placebo. Before the data were unblinded, 25 patients who had undergone randomization but never took a dose of digitoxin or placebo were excluded from the analysis. Three patients from one trial site who had undergone randomization were excluded owing to the closure of the site due to noncompliance with quality standards for trial conduct. Therefore, the modified intention-to-treat population included 1212 patients: 613 assigned to the digitoxin group and 599 to the placebo group (Fig. S1). The final date of data collection for the double-blind period was November 29, 2024. Seventeen patients (2.8%) in the digitoxin group and 8 patients (1.3%) in the placebo group were lost to follow-up (Table S3A). Eleven (1.8%) patients in the digitoxin group and 3 patients (0.5%) in the placebo group had unknown vital status at the end of the trial period (Table S3B). Results of the worst-case analysis for loss to follow-up are shown in Table S3C. The median follow-up period was 36 months (range, 0 to 110), and the median duration of treatment was 18 months (range, 0 to 107). In the case of 54 patients in the digitoxin group and 28 in the placebo group, the treating physician, the patient, or both were made aware of the trial-group assignment (Table S4). Digitoxin or placebo was discontinued for reasons other than death in 361 patients (58.9%) in the digitoxin group and 330 patients (55.1%) in the placebo group (Table S5).

At baseline, the characteristics of the patients and the therapies for heart failure appeared to be well balanced between the trial groups (Table 1 and Table S6). The characteristics of the patients at baseline have been described previously.[15] The mean age of the patients was 66 years, and 20.4% were women. The majority of the patients had NYHA class III or IV heart failure. The mean left ventricular ejection fraction was 29%, and 27.2% of the patients had atrial fibrillation. The mean estimated glomerular filtration rate was 65 ml per minute per 1.73 m^2 of body-surface area. At enrollment, at least 93% of the patients were receiving treatment with a beta-blocker and an inhibitor of the renin-angiotensin system, including the 39.5% of patients who were taking an angiotensin receptor–neprilysin inhibitor; 76.2% of the patients were taking a mineralocorticoid receptor antagonist, and 19.3% were taking a sodium–glucose cotransporter 2 inhibitor. A total of 779 patients (64.3%) were treated with an implantable cardioverter–defibrillator, and 306 patients (25.2%) received cardiac-resynchronization therapy.[13]

EFFICACY

A primary-outcome event occurred in 242 patients (39.5%; 12.8 events per 100 patient-years) in the digitoxin group and 264 (44.1%; 15.7 events per 100 patient-years) in the placebo group (hazard ratio for death or first hospital admission for worsening heart failure, 0.82; 95% confidence interval [CI], 0.69 to 0.98; P=0.03) (Table 2, Fig. 1A, and Table S7A). Death from any cause occurred in 167 patients (27.2%; 7.8 deaths per 100 patient-years) in the digitoxin group and 177 (29.5%; 8.9 deaths per 100 patient-years) in the placebo group (hazard ratio, 0.86; 95% CI, 0.69 to 1.07; threshold for noninferiority, 1.303; P<0.001) (Table 2, Fig. 1B, and Table S7B). A first hospitalization for worsening heart failure occurred in 172 patients (28.1%; 9.1 events per 100 patient-years) in the digitoxin group and 182 patients (30.4%; 10.8 events per 100 patient-years) in the placebo group (hazard ratio, 0.85; 95% CI, 0.69 to 1.05) (Table 2 and Fig. 1C). During the trial period, the number of patients who would need to be treated with digitoxin to prevent one primary-outcome event was 22 (standard error, 14).

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Digitoxin (N = 613)	Placebo (N = 599)
Age — yr	66.0±11.1	65.8±11.4
Female sex — no. (%)	122 (19.9)	125 (20.9)
Region — no. (%)		
Germany	545 (88.9)	533 (89.0)
Austria	19 (3.1)	14 (2.3)
Serbia	49 (8.0)	52 (8.7)
NYHA functional class — no. (%)†		
II	181 (29.5)	178 (29.7)
III	408 (66.6)	399 (66.6)
IV	24 (3.9)	22 (3.7)
Left ventricular ejection fraction — %	28.4±6.9	28.9±6.7
Left ventricular ejection fraction <30% — no. (%)	315 (51.4)	278 (46.4)
Main cause of heart failure — no./total no. (%)		
Ischemic	323/608 (53.1)	310/592 (52.4)
Nonischemic or unknown	285/608 (46.9)	282/592 (47.6)
Body-mass index‡	29.3±5.7	28.9±5.6
Heart rate — beats/min	73.7±11.9	74.1±12.3
Systolic blood pressure — mm Hg	120.5±18.6	121.4±18.8
Atrial fibrillation — no. (%)	169 (27.6)	161 (26.9)
eGFR		
Mean — ml/min/1.73 m^2	65.0±23.0	65.2±23.7
≤60 ml/min/1.73 m^2 — no./total no. (%)	263/612 (43.0)	257/599 (42.9)
Device therapy — no./total no. (%)		
Implantable cardioverter–defibrillator therapy	415/613 (67.7)	364/598 (60.9)
Cardiac-resynchronization therapy	162/613 (26.4)	144/597 (24.1)
Heart failure medication — no. (%)		
Beta-blocker	593 (96.7)	567 (94.7)
Angiotensin-converting–enzyme inhibitor	222 (36.2)	213 (35.6)
Angiotensin-receptor blocker	113 (18.4)	115 (19.2)
Angiotensin receptor–neprilysin inhibitor	248 (40.5)	231 (38.6)
Mineralocorticoid receptor antagonist	466 (76.0)	458 (76.5)
Sodium–glucose cotransporter 2 inhibitor§	121 (19.7)	113 (18.9)
Cardiac glycoside	3 (0.5)	6 (1.0)

* Plus–minus values are means ±SD. Data are shown for the modified intention-to-treat population, which included all the patients who underwent randomization and received at least one dose of digitoxin or placebo. Data on body-mass index were missing for 1 patient in each group, data on heart rate were missing for 2 patients in the digitoxin group, and data on the estimated glomerular filtration rate (eGFR) were missing for 1 patient in the digitoxin group. Percentages may not total 100 because of rounding.

† The New York Heart Association (NYHA) functional classification is based on the severity of symptoms of heart failure and the associated limitations on physical activity. Classes range from I (symptoms do not limit physical activity) to IV (symptoms are present at rest).

‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Information on the use of sodium–glucose cotransporter 2 inhibitors was included in the electronic case report form after December 1, 2019.

Table 2. Primary and Secondary Outcomes.

Outcome	Digitoxin (N=613)		Placebo (N=599)		Hazard or Rate Ratio (95% CI)*
	no. (%)†	*events/100 patient-yr*	*no. (%)†*	*events/100 patient-yr*	
Primary outcome and components					
Death from any cause or first hospitalization for heart failure	242 (39.5)	12.8	264 (44.1)	15.7	0.82 (0.69 to 0.98)‡
Death from any cause	167 (27.2)	7.8	177 (29.5)	8.9	0.86 (0.69 to 1.07)§
First hospitalization for heart failure¶	172 (28.1)	9.1	182 (30.4)	10.8	0.85 (0.69 to 1.05)
Key secondary outcome					
Death from any cause and hospitalization for heart failure	537	25.1	531	26.6	0.85 (0.67 to 1.09)‖
Other secondary outcomes					
Death from cardiovascular causes	125 (20.4)	5.8	132 (22.0)	6.6	0.87 (0.67 to 1.11)
Death from heart failure	46 (7.5)	2.2	47 (7.8)	2.4	0.86 (0.57 to 1.31)
Sudden death from cardiac causes	12 (2.0)	0.6	12 (2.0)	0.6	0.89 (0.40 to 2.00)
Death from noncardiovascular causes	42 (6.9)	2.0	45 (7.5)	2.3	0.84 (0.55 to 1.29)
Hospitalization for cardiovascular causes¶	359 (58.6)	28.8	353 (58.9)	32.8	0.89 (0.77 to 1.04)
Hospitalization for noncardiovascular causes¶	263 (42.9)	18.1	255 (42.6)	18.6	0.97 (0.81 to 1.15)
Any hospitalization¶	429 (70.0)	43.9	427 (71.3)	50.4	0.90 (0.78 to 1.03)
Death from cardiovascular causes or first hospitalization for worsening heart failure	220 (35.9)	11.7	232 (38.7)	13.8	0.85 (0.71 to 1.03)

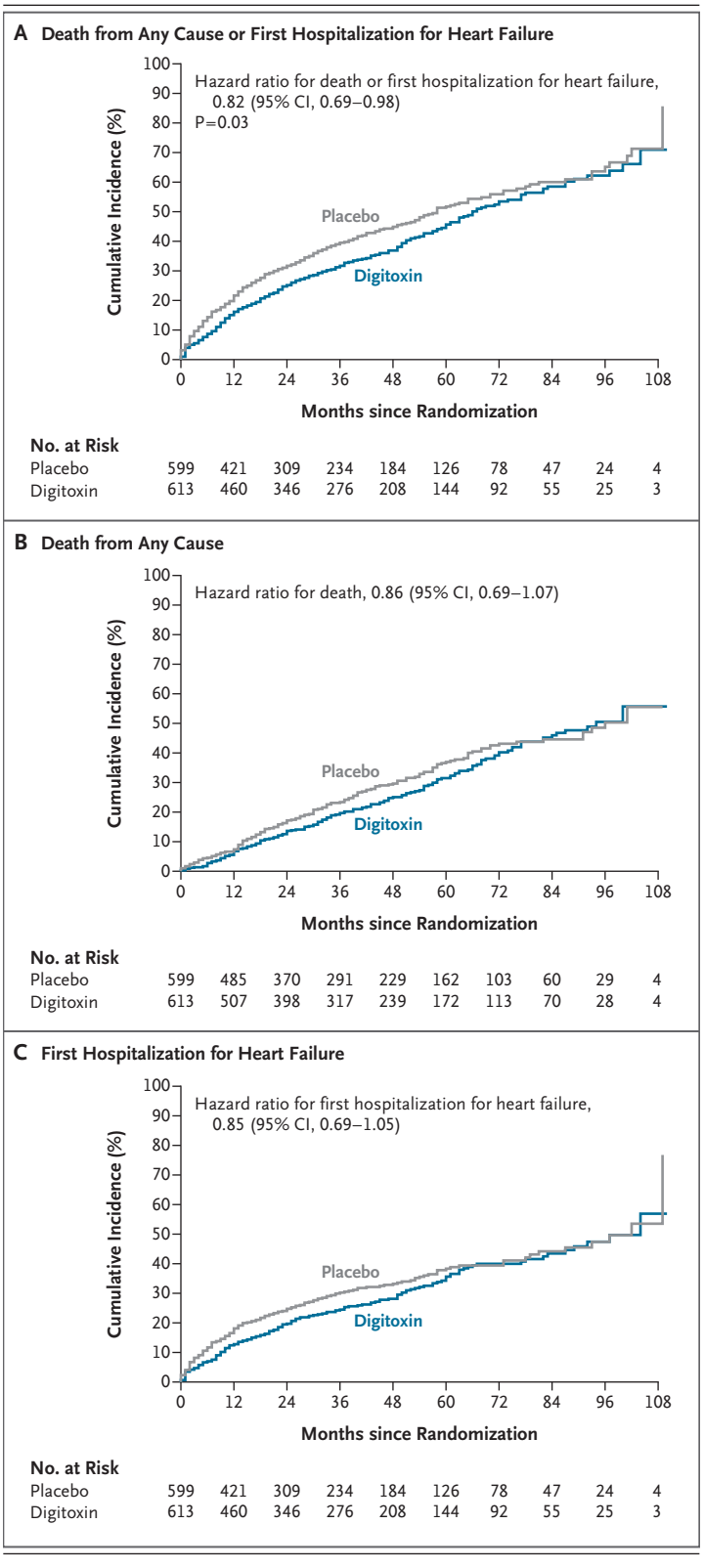
* Values shown are hazard ratios unless otherwise noted.
† Values shown are numbers and percentages of patients, except the values for the key secondary outcome, which are numbers of events.
‡ P=0.03. The P value was derived from the primary analysis of the primary outcome (a composite of death from any cause or hospitalization for heart failure, whichever occurred first) with the use of a Cox regression model adjusted according to trial site, NYHA functional class, sex, and the presence or absence of atrial fibrillation.
§ P<0.001 for noninferiority. The noninferiority of digitoxin to placebo with respect to death from any cause was predefined by a hazard ratio of no more than 1.303.
¶ Data for patients who died without being hospitalized were censored at the date of death.
‖ P=0.20. The total numbers of deaths from any cause and hospitalizations for worsening heart failure were analyzed with the use of a negative binomial model that included the same independent variables as the model used in the primary analysis; the treatment effect is reported as a rate ratio.

The total number of deaths from any cause and hospitalizations for worsening heart failure was 537 in the digitoxin group and 531 in the placebo group (rate ratio, 0.85; 95% CI, 0.67 to 1.09; P=0.20) (Table 2). The number of patients who underwent implantation of a left ventricular assist device or heart transplantation, the results of an analysis in which implantable cardioverter–defibrillator therapy was treated as a covariable, and the results of a competing-risks analysis are shown in the Supplementary Appendix (Tables S8, S9, and S10). Results for prespecified subgroups are shown in Figure 2 and Table S11, and other secondary outcomes are summarized in Table 2.

SAFETY

The mean (±SD) serum digitoxin concentration at the dose-adjustment visit 6 weeks after randomization was 17.0±5.9 ng per milliliter in 550 patients in the digitoxin group for whom data were available. At 12 months, the mean serum digitoxin concentration (determined for scientific and safety reasons only) was 13.5±5.1 ng per milliliter in 398 patients (Table S12). All deaths and hospitalization events were excluded from the reporting of serious adverse events according to the protocol and were included as part of the analyses of the primary and secondary outcomes (Table 2). At least one serious adverse event occurred in 29 patients (4.7%) in the

Figure 1. Cardiovascular Outcomes.
Panel A shows the cumulative incidence of death from any cause or first hospitalization for heart failure (the composite primary outcome). Panels B and C show the cumulative incidence of the two components of the primary outcome.



digitoxin group and 17 patients (2.8%) in the placebo group; these events included cardiac disorders in 21 patients (3.4%) and 11 patients (1.8%), respectively (Tables S13 and S14). Adverse events led to discontinuation of digitoxin or placebo in 56 patients (9.1%) and 61 patients (10.2%), respectively.

DISCUSSION

Among patients with chronic heart failure and reduced ejection fraction, the incidence of a primary-outcome event (death from any cause or hospitalization for worsening heart failure, whichever occurred first) was significantly lower with digitoxin than with placebo. The treatment effect of digitoxin on the primary outcome appeared to be consistent among prespecified subgroups.

A post hoc analysis of the DIG trial indicated a beneficial effect of digoxin at low concentrations in serum (0.5 to 0.9 ng per milliliter) with respect to death from any cause or hospitalization for worsening heart failure (a composite outcome).[6] This effect appears to be similar to the observed effect of digitoxin in our trial, and the effects appeared to be applicable to female and male patients in both trials. Digitoxin appeared to have an effect on each component of this composite outcome in our trial. Low serum digitoxin concentrations may have been associated with fewer deaths than placebo. This finding is consistent with the observed effects of low serum digoxin concentrations on mortality in the DIG trial, whereas high serum digoxin concentrations (>1.0 ng per milliliter) seemed to be harmful.[5-7] Digitoxin was also associated with fewer hospitalizations for worsening heart failure than placebo; this finding is similar to what was observed in the DIG trial, in which the effect was more pronounced at lower serum digoxin concentrations.[5-7] Overall, the data from our trial and the DIG trial underscore the importance of low se-

Subgroup	Digitoxin	Placebo	Hazard Ratio for Primary-Outcome Event (95% CI)
	no. of patients with event/total no. (%)		
All patients	242/613 (39.5)	264/599 (44.1)	0.82 (0.69–0.98)
Sex			
Male	200/491 (40.7)	217/474 (45.8)	0.84 (0.69–1.02)
Female	42/122 (34.4)	47/125 (37.6)	0.73 (0.46–1.17)
NYHA functional class			
II	57/181 (31.5)	63/178 (35.4)	0.76 (0.52–1.11)
III or IV	185/432 (42.8)	201/421 (47.7)	0.83 (0.68–1.02)
Atrial fibrillation			
Yes	67/169 (39.6)	79/161 (49.1)	0.72 (0.50–1.03)
No	175/444 (39.4)	185/438 (42.2)	0.86 (0.69–1.06)
Geographic region			
Germany and Austria	237/564 (42.0)	256/547 (46.8)	0.82 (0.68–0.97)
Serbia	5/49 (10.2)	8/52 (15.4)	0.69 (0.22–2.19)
Age			
<70 yr	116/362 (32.0)	142/350 (40.6)	0.77 (0.60–1.00)
≥70 yr	126/251 (50.2)	122/249 (49.0)	0.87 (0.67–1.14)
Ejection fraction			
<30%	127/315 (40.3)	130/278 (46.8)	0.77 (0.59–0.99)
≥30%	115/298 (38.6)	134/321 (41.7)	0.85 (0.66–1.11)
Main cause of heart failure			
Ischemic	144/323 (44.6)	140/310 (45.2)	0.97 (0.76–1.24)
Nonischemic or unknown	97/285 (34.0)	119/282 (42.2)	0.70 (0.53–0.93)
Heart rate			
<75 bpm	134/354 (37.9)	143/348 (41.1)	0.92 (0.72–1.18)
≥75 bpm	108/257 (42.0)	121/251 (48.2)	0.63 (0.48–0.83)
Systolic blood pressure			
≤120 mm Hg	131/331 (39.6)	148/300 (49.3)	0.61 (0.48–0.79)
>120 mm Hg	111/282 (39.4)	116/299 (38.8)	1.03 (0.78–1.36)
Body-mass index			
<30	142/374 (38.0)	170/369 (46.1)	0.74 (0.58–0.93)
≥30	99/238 (41.6)	94/229 (41.0)	0.91 (0.67–1.23)
Hypertension			
Yes	210/492 (42.7)	212/468 (45.3)	0.86 (0.71–1.05)
No	32/121 (26.4)	52/129 (40.3)	0.57 (0.34–0.93)
Diabetes mellitus			
Yes	106/222 (47.7)	106/231 (45.9)	0.93 (0.70–1.25)
No	136/390 (34.9)	157/367 (42.8)	0.76 (0.60–0.96)
eGFR			
≤60 ml/min/1.73 m^2	132/263 (50.2)	142/257 (55.3)	0.73 (0.56–0.94)
>60 ml/min/1.73 m^2	110/349 (31.5)	122/342 (35.7)	0.81 (0.62–1.06)
Implantable cardioverter–defibrillator therapy			
Yes	179/415 (43.1)	162/364 (44.5)	0.94 (0.75–1.16)
No	63/198 (31.8)	101/234 (43.2)	0.57 (0.41–0.80)
Cardiac-resynchronization therapy			
Yes	84/162 (51.9)	65/144 (45.1)	1.03 (0.73–1.45)
No	158/451 (35)	198/453 (43.7)	0.72 (0.58–0.90)
Mineralocorticoid receptor antagonist			
Yes	166/466 (35.6)	189/458 (41.3)	0.82 (0.67–1.02)
No	76/147 (51.7)	75/141 (53.2)	0.97 (0.68–1.38)
Angiotensin receptor–neprilysin inhibitor			
Yes	81/248 (32.7)	83/231 (35.9)	0.80 (0.58–1.11)
No	161/365 (44.1)	181/368 (49.2)	0.84 (0.67–1.05)
Sodium–glucose cotransporter 2 inhibitor			
Yes	24/121 (19.8)	32/113 (28.3)	0.70 (0.40–1.23)
No	32/98 (32.7)	36/96 (37.5)	0.59 (0.34–1.04)
Triple therapy			
Yes	159/436 (36.5)	178/422 (42.2)	0.81 (0.65–1.01)
No	83/177 (46.9)	86/177 (48.6)	0.89 (0.64–1.23)
Quadruple therapy			
Yes	20/101 (19.8)	28/99 (28.3)	0.77 (0.41–1.42)
No	36/118 (30.5)	40/110 (36.4)	0.64 (0.39–1.07)

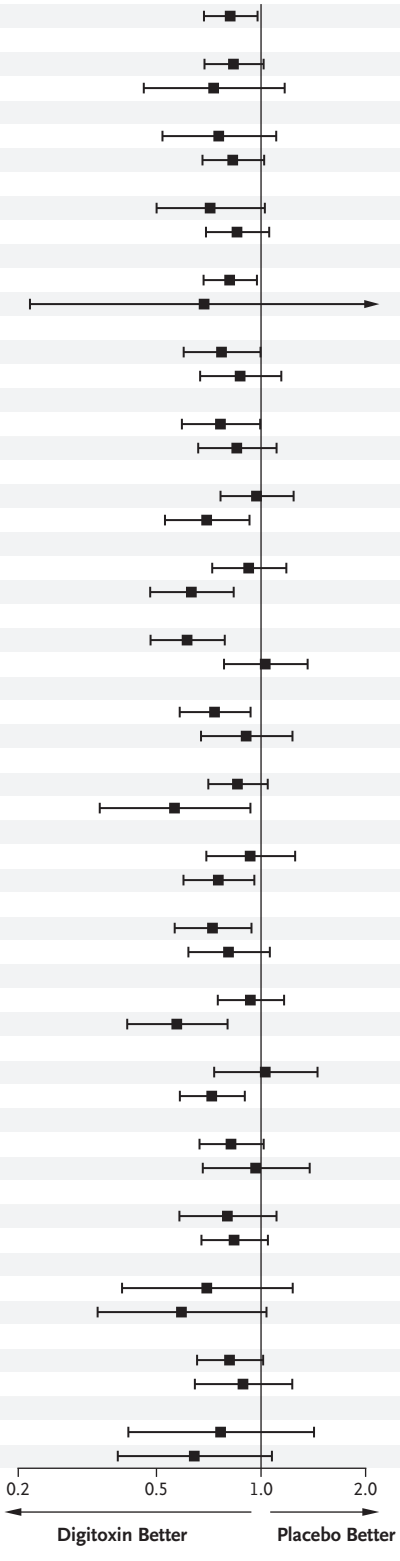


Figure 2 (facing page). Primary Outcome in Prespecified Subgroups.

The first occurrence of hospitalization for worsening heart failure or death from any cause (the primary outcome) with digitoxin as compared with placebo was analyzed among patients stratified according to prespecified subgroups. Data on the main cause of heart failure were missing for 5 patients in the digitoxin group and 7 in the placebo group; data on heart rate were missing for 2 patients in the digitoxin group; data on body-mass index (the weight in kilograms divided by the square of the height in meters) and diabetes status were missing for 1 patient in each group; data on hypertension and the use of cardiac-resynchronization therapy were missing for 2 patients in the placebo group; data on the estimated glomerular filtration rate (eGFR) were missing for 1 patient in the digitoxin group; data on the use of an implantable cardioverter–defibrillator were missing for 1 patient in the placebo group; and data on the use of a sodium–glucose cotransporter 2 inhibitor or quadruple therapy (a beta-blocker, a mineralocorticoid receptor antagonist, and a sodium–glucose cotransporter 2 inhibitor combined with an angiotensin-converting–enzyme inhibitor, an angiotensin-receptor blocker, or an angiotensin receptor–neprilysin inhibitor) were missing for 394 patients in the digitoxin group and 390 patients in the placebo group who underwent randomization before December 1, 2019, when information on the use of sodium–glucose cotransporter 2 inhibitors was added to the electronic case report form used for documentation. For purposes of analysis, patients with New York Heart Association (NYHA) class IV heart failure were grouped with those with NYHA class III heart failure, patients over 80 years of age were grouped with those 70 to 80 years of age, patients with an eGFR of less than 30 ml per minute per 1.73 m^2 of body-surface area were grouped with those with an eGFR of 30 to 60 ml per minute per 1.73 m^2, and patients with a cardiac-resynchronization therapy device were grouped with those with a cardiac-resynchronization therapy pacemaker owing to the small number of patients with a cardiac-resynchronization therapy pacemaker. Triple therapy denotes the use of a beta-blocker and a mineralocorticoid receptor antagonist combined with an angiotensin-converting–enzyme inhibitor, an angiotensin-receptor blocker, or an angiotensin receptor–neprilysin inhibitor.

rum concentrations of cardiac glycosides in patient treatment.

Our trial enrolled patients with a high burden of heart failure symptoms (70.4% of the patients had NYHA class III or IV heart failure) as compared with recent trials, such as the PARADIGM-HF (Prospective Comparison of Angiotensin Receptor Blocker–Neprilysin Inhibitor with Angiotensin-Converting–Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial,[18] the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial,[19] and EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction)[20]; in those trials, a higher percentage of patients had NYHA class II heart failure. The representativeness of our trial population is shown in Table S15. A comparison of the results of the present trial with those of the PARADIGM-HF trial (which used sacubitril and valsartan) and the DAPA-HF trial (which used dapagliflozin) showed that although the patients enrolled in our trial had a higher burden of heart failure symptoms, mortality and the incidence of a first hospitalization for heart failure appeared to be similar among the trials. This finding may be explained by better implementation of guideline-directed pharmacologic and device therapy among patients in our trial.[15] Despite the higher burden of heart failure symptoms and the better implementation of therapy in our trial, the absolute reduction in the risk of death from any cause or first hospitalization for worsening heart failure — and thus the number of patients who would need to be treated to avoid one primary-outcome event — seems to be similar to that in the PARADIGM-HF and DAPA-HF trials and EMPEROR-Reduced (which used empagliflozin).

The efficacy of digitoxin observed in the overall trial population appeared to be consistent among patients who were taking an angiotensin receptor–neprilysin inhibitor or sodium–glucose cotransporter 2 inhibitor at baseline and among patients who were taking triple or quadruple combinations of guideline-recommended medications. This additive effect of digitoxin may be explained by the known enhancement of the parasympathetic system by cardiac glycosides, such as vagally driven lowering of heart rate,[21,22] because other potential effects, such as inhibition of the sympathetic nervous system,[23,24] may have already been sufficiently masked by a well-implemented background therapy. During follow-up, many patients in our trial discontinued digitoxin for a substantial period of time, but the trial results still show efficacy, a finding that suggests that the beneficial effects of digitoxin in patients with worsening heart failure may extend for a time beyond treatment.

Treatment with digitoxin at low concentra-

tions in serum according to a simple dosage protocol appeared to be safe in our trial. This finding contradicts conclusions based on nonrandomized studies or post hoc analyses that have claimed to show harmful effects of cardiac glycosides in heart failure with and without atrial fibrillation.[25-27] Although female sex and impaired kidney function are known to be the strongest predictors of elevated serum digoxin concentrations,[7] the effects of digitoxin with respect to the primary outcome in our trial appeared to be consistent in female patients and those with impaired kidney function. This finding may be attributable to the pharmacokinetic properties of digitoxin: high serum digitoxin concentrations in patients with impaired or worsening renal function are avoided by means of compensatory enterohepatic elimination.[12]

Our trial has limitations. The results of the analysis of the prespecified subgroups must be interpreted with caution because it lacked statistical power. Results cannot be generalized to other cardiac glycosides, and a trial of digoxin — DECISION (Digoxin Evaluation in Chronic Heart Failure: Investigational Study in Outpatients in the Netherlands) — is currently ongoing.[28] Although the number of patients enrolled in our trial was lower than expected, we were able to confirm the primary hypothesis that digitoxin would be superior to placebo with respect to the incidence of death from any cause or first hospitalization for worsening heart failure. Digitoxin is available in fewer countries than digoxin, but in some countries, digitoxin has a long history of use in a substantial number of patients. Our findings can be readily implemented into clinical practice, as shown by the simple digitoxin dosage protocol[16] and by the fact that patient selection in our trial was based primarily on the burden of heart failure symptoms and the left ventricular ejection fraction rather than threshold levels of the brain natriuretic peptide biomarker.

In our trial, treatment with digitoxin led to a lower combined risk of death from any cause or hospital admission for worsening heart failure than placebo among patients with heart failure and reduced ejection fraction who received guideline-recommended medical therapy.

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