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Digoxin and 30-Day All-Cause Hospital Admission in Older Patients with Chronic Diastolic Heart Failure

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Abstract

BACKGROUND—In the main Digitalis Investigation Group (DIG) trial, digoxin reduced the risk of 30-day all-cause hospitalization in older systolic heart failure patients. However, this effect has not been studied in older diastolic heart failure patients.

METHODS—In the ancillary DIG trial, of the 988 patients with chronic heart failure and preserved (>45%) ejection fraction, 631 were 65 years (mean age, 73 years, 45% women, 12% nonwhites), of whom 311 received digoxin.

RESULTS—All-cause hospitalization 30-day post-randomization occurred in 4% of patients in the placebo group and 9% each among those in the digoxin group receiving 0.125 mg and 0.25 mg a day dosage ($p=0.026$). Hazard ratios (HR) and 95% confidence intervals (CI) for digoxin use overall for 30-day, 3-month, and 12-month all-cause hospitalizations were 2.46 (1.25–4.83), 1.45 (0.96–2.20) and 1.14 (0.89–1.46), respectively. There was one 30-day death in the placebo group. Digoxin-associated HRs (95% CIs) for 30-day hospitalizations due to cardiovascular, heart failure and unstable angina causes were 2.82 (1.18–6.69), 0.51 (0.09–2.79), and 6.21 (0.75–51.62),

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Authorship: Dr. Ahmed conceived the study hypothesis and developed the analysis plan in consultation with coauthors. Drs. Ahmed, Elbaz and Hashim wrote the first draft. Drs. Ahmed, Elbaz, Hashim and Patel conducted statistical analyses in collaboration with Drs. Morgan, McGwin, and Cutter. All authors interpreted the data, participated in critical revision of the paper for important intellectual content, and approved the final version. Drs. Ahmed, Elbaz, Hashim, Morgan and Patel had full access to the data.

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respectively. Digoxin had no significant association with 30-day all-cause hospitalization among younger patients (6% vs. 7% for placebo; HR, 0.80; 95% CI, 0.36–1.79).

CONCLUSIONS—In older patients with chronic diastolic heart failure, digoxin increased the risk of 30-day all-cause hospital admission, but not during longer follow-up. Although chance finding due to small sample size is possible, these data suggest that unlike in systolic heart failure, digoxin may not reduce 30-day all-cause hospitalization in older diastolic heart failure patients.

Keywords

Digoxin; diastolic heart failure; 30-day all-cause hospital admission

Heart failure is the leading cause for hospital readmission for older Medicare beneficiaries.¹ Despite limitations of the cost-driven metric of 30-day all-cause hospital readmission,^{2,3} nearly one in four hospitalized heart failure patients are readmitted within 30 days of index discharge.¹ Hospital readmission accounts for up to 20% of Medicare cost for inpatient care and the reduction of Medicare cost is a priority under the Affordable Care Act, the new United States health care reform law.¹ The law mandates financial penalties for hospitals with above-average readmission rates and heart failure is one of the three conditions for which the law is currently being implemented. In October, 2012, the Center of Medicare and Medicaid Services penalized over 2000 hospitals for the first time with \$300 million in fine and this is projected to increase in the coming years.⁴ Post hoc analyses of the randomized controlled *main* Digitalis Investigation Group (DIG) trial demonstrated that digoxin significantly reduced the risk of 30-day all-cause hospital admission in older patients with chronic heart failure and reduced ejection fraction or systolic heart failure without adversely affecting mortality or subsequent hospital admissions.⁵ However, the effect of digoxin on 30-day all-cause hospital admission in older patients with heart failure and preserved ejection fraction or diastolic heart failure remains unknown. The objective of the current study was to examine the effect of digoxin on 30 day all-cause hospital admission in older patients with diastolic heart failure in the *ancillary* DIG trial.

MATERIALS AND METHODS

Study Design and Patients

The DIG trial was a double-blind randomized controlled trial to evaluate the effect of digoxin on mortality and hospitalization in 7788 ambulatory adults with chronic heart failure and normal sinus rhythm recruited from 186 U.S. centers and 116 Canadian centers between January 1991 and August 1993.⁶ Heart failure was diagnosed based on current or past history of symptoms, signs or radiographic evidence of pulmonary congestion and ejection fraction was estimated using radionuclide ventriculography (69%), transthoracic echocardiogram (26%) and contrast angiography (5%).⁶ Patients with ejection fraction <45% were enrolled in the main DIG trial (n=6800) and those with ejection fraction >45% were enrolled into the ancillary DIG trial (n=988).^{6,7}

The current study focused on the 631 patients, aged <65 years enrolled in the ancillary DIG trial. Of these, 311 patients received digoxin, of which 90 received 0.125 mg a day and 221 received 0.25 mg a day. Data on serum digoxin concentration was collected after the first 30 days of randomization and was available for 118 of the 311 patients receiving digoxin, of which 68 had serum digoxin concentration of 0.5–0.9 ng/ml and 50 had serum digoxin concentration of >1.0 ng/ml. The DIG trial was sponsored by National Heart, Lung, and Blood Institute, which also provided copies of de-identified data used in the current analysis.

Outcomes

The primary outcome in the ancillary trial was the occurrence of death due to progressive heart failure or hospitalization due to worsening heart failure. In the current analysis, hospitalization due to all-causes occurring during the first 30 days after randomization was the main outcome of interest. Secondary outcomes included cause-specific hospitalizations and mortality, and the combined end point of all-cause hospitalization or all-cause mortality during the first 30 days after randomization. All outcomes were classified by DIG investigators based on reviews of medical records and interviewing patients' relatives.

Statistical Analysis

Baseline patient characteristics were compared between the two treatment groups using Pearson's Chi-square and Student's t tests. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the outcomes in the digoxin group using placebo group as the reference, and Kaplan-Meier analysis was used to plot 30-day all-cause hospitalization for patients in the digoxin and placebo groups. All analyses were repeated for patients <65 years. Subgroup analyses were conducted to examine heterogeneity of effect on outcomes only among older adults. All statistical tests were 2-tailed with a p-value <0.05 considered significant. SPSS-20 for Windows (IBM Corp., Armonk, NY) was used for statistical analyses.

RESULTS

Baseline Characteristics

The subset of older patients ≥65 years (n=631) in the DIG ancillary study had a mean age of 73 (SD±6) years, a mean ejection fraction of 56% (SD±8), 45% were women, and 12% were nonwhite. These patients were well balanced in all baseline characteristics with regards to treatment assignment (Table 1). Younger patients were also balanced on nearly all baseline characteristics except for pulmonary rales and the use of angiotensin-converting enzyme inhibitors (Table 1).

Digoxin and 30-Day All-Cause Hospital Admission

Among patients aged ≥65 years, the main endpoint of all-cause hospitalization during the first 30 days after randomization occurred in 3.8%, 8.9% and 9.0% of patients in the placebo group, and those in the digoxin group receiving 0.125 mg and 0.25 mg of digoxin a day, respectively (p=0.026). When compared with placebo, HR for 30-day all-cause admission for patients in the digoxin group as a whole was 2.46 (95% CI, 1.25–4.83; Table 2 and Figure 1). Among the 68 and 50 patients with 0.5–0.9 and ≥1 ng/ml serum digoxin concentrations, 30-day all-cause admission occurred in 5.9% and 4.0% of patients (vs. 3.8% in the placebo group; p=0.726).

This effect of digoxin was rather homogeneous across various subgroups of patients except by sex (Table 3). Compared to men in the placebo group, 4.9% of whom had 30-day all-cause hospitalization (reference), 4.9% of men in the digoxin group (HR, 1.01; 95% CI, 0.39–2.61), 2.2% of women in the placebo group (HR, 0.44; 95% CI, 0.12–1.64), and 13.4% of women in the digoxin group (HR, 2.84; 95% CI, 1.29–6.23) had 30-day all-cause hospitalization (p for interaction, 0.019; Table 3).

Digoxin and Other 30-Day Outcomes

There was only one death in the placebo group among patients aged ≥65 years. Consequently, the risk of the combined end point of 30-day all-cause hospitalization or all-cause mortality was also high in the digoxin group (HR, 2.27; 95% CI, 1.17–4.38; Table 2).

There were 6 hospitalizations due to worsening heart failure, 2 of which occurred in the digoxin group (HR, 0.51; 95% CI, 0.09–2.79) and there were 7 hospitalizations due to unstable angina, all but one occurred in the digoxin group (HR, 6.21; 95% CI, 0.75–51.62; Table 2). Associations with other outcomes are displayed in Table 2.

Digoxin and 3- and 12- Month Outcomes

During the first 3 months after randomization, among patients aged ≥ 65 years, all-cause hospitalization occurred in 12.2% and 17.0% of those in the placebo and digoxin groups, respectively (HR for digoxin, 1.45; 95% CI, 0.96–2.20). There was no interaction between digoxin and sex ($p=0.677$) – with respective HRs of 1.57 (95% CI, 0.83–2.99) and 1.33 (95% CI, 0.77–2.27) for men and women. During this period, digoxin reduced the risk of heart failure hospitalization (4.7% vs. 1.6% for digoxin; HR, 0.34; 95% CI, 0.12–0.93), but increased hospitalization due to unstable angina (0.9% vs. 4.2% for digoxin; HR, 4.53; 95% CI, 1.29–15.91). There were 5 and 6 deaths in the placebo and digoxin groups, respectively (HR, 1.24; 95% CI, 0.38–4.05).

During the first 12 months after randomization, among patients aged ≥ 65 years, all-cause hospitalization occurred in 37.8% and 40.5% of those in the placebo and digoxin groups, respectively (HR for digoxin, 1.14; 95% CI, 0.90–1.46). There was no digoxin-sex interaction ($p=0.705$) at 12-months – HRs for men and women were 1.08 (95% CI, 0.76–1.53) and 1.19 (95% CI, 0.83–1.70), respectively. Digoxin decreased the risk of heart failure hospitalization (14.4% vs. 8.4% for digoxin; HR, 0.56; 95% CI, 0.35–0.91), but increased the risk for hospitalization due to unstable angina (8.0% vs. 4.1% in the placebo group; HR, 2.06; 95% CI, 1.06–4.03). There were 27 deaths in each treatment group (HR, 1.03; 95% CI, 0.61–1.76).

Effect of Digoxin on 30-Day Outcomes in Patients <65 Years

Among the 357 patients <65 years, 30-day all-cause hospitalization occurred in 7.4% and 6.1% of patients in the placebo and digoxin groups, respectively, (HR for digoxin, 0.80; 95% CI, 0.36–1.79; Table 2 and Figure 1). Digoxin had no significant effect on any other outcomes (Table 2). There were only 4 hospitalizations due to worsening heart failure and 3 due to unstable angina, 1 of each occurring in the digoxin group, and the only death occurred in the placebo group (Table 2).

DISCUSSION

Findings from the current analysis suggest that in the ancillary DIG trial digoxin increased the risk of 30-day all cause hospital admission in ambulatory older diastolic heart failure patients, but had no effect in younger diastolic heart failure patients. Although there were more events during 3 and 12 months of follow-up, the risks of all-cause hospital admission were not significantly different by treatment group during these longer follow-up durations that included the first month. These findings are in sharp contrast to the findings from the main DIG trial in which digoxin significantly reduced the risks of all-cause hospital admission in older systolic heart failure patients during the first 30 days after randomization, an effect that also lasted during longer follow-up. The current results based on a much smaller ancillary DIG trial may represent a chance effect and thus need to be interpreted with caution. The lack of an effect of digoxin in younger patients during the first 30 days and in older patients during longer follow-up suggest that unlike in systolic heart failure digoxin may have no beneficial effect on 30-day all-cause hospital admission in diastolic heart failure.

The increased risk of 30-day all-cause admission in the digoxin group was apparently driven by an increased risk of cardiovascular hospitalization, in particular that due to unstable angina. However, while the magnitude of the risk of 30-day unstable angina hospitalization in the digoxin group was strong, it was not statistically significant, likely due to small number of events (n=7). Importantly, even as the risk of unstable angina hospitalization became significant during longer follow-up, the risk of all-cause hospitalization became weaker and non-significant, likely due to a proportionate decreased risk of heart failure hospitalization. Therefore, unstable angina is unlikely to fully explain the increased risk of 30-day all-cause hospital admission among older diastolic heart failure patients in the ancillary DIG trial. A more plausible interpretation is that unlike in systolic heart failure, digoxin has no beneficial effect on 30-day all-cause hospitalization in diastolic heart failure. This is also consistent with findings from younger patients who had higher events for all-cause hospitalization in the placebo group but no increased risk in the digoxin group. Similarly, the sex difference in the effect of digoxin on 30-day all-cause admission needs to be interpreted with caution as this was also lost during both 3 and 12 months of follow-up.

Findings from the current study are consistent with a similar lack of a long-term effect of digoxin on all-cause hospitalization in diastolic heart failure in the ancillary DIG trial.⁷ In that trial, among patients in the placebo group, there were more hospitalizations due to heart failure (n=108; 22%) than due to unstable angina (n=62; 13%) during 37 months of mean follow-up.⁷ Although digoxin significantly decreased the risk of heart failure hospitalization by 4% (from 22% to 18%), it also increased the risk of unstable angina hospitalization by 4% (from 13% to 17%) – thus, there was no net difference in all-cause hospital admission between patients in the placebo (67%) and digoxin (68%) groups.⁷ In the main DIG trial, in contrast, in patients with systolic heart failure, digoxin reduced the risk of heart failure hospitalization by 8% (35% to 27%) during 37 months of mean follow-up, but had no effect on unstable angina hospitalizations (12% in both treatment groups) – thus, there was a net 3% significant reduction in all-cause hospital admission between patients in the placebo (67%) and digoxin (64%) groups.⁶ A post hoc analysis of DIG data suggested that the risk of unstable angina hospitalization was higher among those with higher ejection fraction, so that compared with ejection fraction <35%, those with 35–55% and >55% had 17% and 57% independent higher risk, respectively.⁸ It has been suggested that viable hypertrophied myocardium with abnormal coronary microcirculation may make patients with diastolic heart failure more prone to unstable angina.^{9–11} However, it is not clear why this risk might be higher among older patients receiving digoxin, and importantly, whether this risk would be attenuated in those receiving beta-blockers.

Findings from the current study are also consistent with findings from the Alabama Heart Failure Project in which among Medicare beneficiaries hospitalized for acute decompensated heart failure, a new discharge prescription of digoxin was associated with a significant lower risk of 30-day all-cause hospital readmission among those with ejection fraction <45%, but not among those with ≥45% (p-value for interaction, 0.145), a difference that became stronger and significant during first 12-month post-discharge (p for interaction, 0.019).¹² Taken together, these findings suggest that digoxin may not reduce the risk of all-cause hospital readmission in patients with diastolic heart failure. Considering the small sample size of the current analysis based on the ancillary DIG trial (n=631) and the diastolic heart failure subset of the Alabama Heart Failure Project (n=457), these findings need to be replicated in future prospective studies of contemporary hospitalized older diastolic heart failure patients.

Findings from the current study are important as they suggest that digoxin should not be used for the sole purpose of readmission reduction in older patients with diastolic heart failure. Although digoxin is not recommended for use in these patients, it is often prescribed

for indications such as atrial fibrillation, although digoxin does not appear to reduce mortality in these patients.¹³ Because of recent findings of beneficial effects of digoxin in reducing 30-day hospital admission and its clinical effectiveness in lowering 30-day hospital readmission in systolic heart failure,^{5,12} and its beneficial effect on heart failure hospitalization in diastolic heart failure,⁷ it is possible that these data may be extrapolated to those with diastolic heart failure, especially as clinicians and hospitals are under pressure to reduce 30-day all-cause readmission in heart failure, the leading cause for readmission.¹

Our study has several limitations. Unlike the main DIG trial, the ancillary DIG trial was small and there were far fewer events during the first 30 days after randomization. Although the DIG trial was conducted on the pre-beta-blocker era of heart failure care, these drugs have not been shown to be effective in diastolic heart failure.¹⁴ The DIG trial was based on heart failure patients in normal sinus rhythm, thus limiting generalizability as atrial fibrillation is common in older diastolic heart failure patients. Data on serum digoxin concentration were collected one month after randomization,¹⁵ which precluded examination of prospective association with 30-day all-cause hospital admission.

CONCLUSIONS

Digoxin increased the risk of 30-day all-cause hospitalization in older chronic diastolic heart failure patients. Although a chance association cannot be ruled out as there were very few events during the first 30 days after randomization, no beneficial effect was observed during 3 and 12 months after randomization. Taken together with the findings from the main DIG trial and the Alabama Heart Failure Project,^{5,12} these data suggest that unlike in systolic heart failure, in which digoxin reduced the risk of 30-day all-cause hospital admission and was associated with lower 30-day all-cause hospital readmission, digoxin may have no such effect in diastolic heart failure.

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References

1. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med.* 2009; 360:1418–1428. [PubMed: 19339721]
2. Butler J, Kalogeropoulos A. Hospital strategies to reduce heart failure readmissions: where is the evidence? *J Am Coll Cardiol.* 2012; 60:615–617. [PubMed: 22818073]
3. Konstam MA. Heart failure in the lifetime of *Musca Domestica* (the common housefly). *JACC: Heart Failure.* 2013; 1:178–180.
4. Rau, J. The New York Times. New York: 2012. Hospitals Face Pressure to Avert Readmissions. http://www.nytimes.com/2012/11/27/health/hospitals-face-pressure-from-medicare-to-avert-readmissions.html?_r=0 [Access date: December 2, 2012]
5. Bourge RC, Fleg JL, Fonarow GC, Cleland JG, McMurray JJ, van Veldhuisen DJ, et al. Digoxin reduces 30-day all-cause hospital admission in older patients with chronic systolic heart failure. *Am J Med.* 2013; 126:701–708. [PubMed: 23490060]
6. The Digitalis Investigation Group Investigators. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med.* 1997; 336:525–533. [PubMed: 9036306]

7. Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, et al. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. *Circulation*. 2006; 114:397–403. [PubMed: 16864724]
8. Ahmed A, Zile MR, Rich MW, Fleg JL, Adams KF Jr, Love TE, et al. Hospitalizations due to unstable angina pectoris in diastolic and systolic heart failure. *Am J Cardiol*. 2007; 99:460–464. [PubMed: 17293184]
9. Iriarte M, Caso R, Murga N, Faus JM, Sagastagoitia D, Molinero E, et al. Microvascular angina pectoris in hypertensive patients with left ventricular hypertrophy and diagnostic value of exercise thallium-201 scintigraphy. *Am J Cardiol*. 1995; 75:335–339. [PubMed: 7856523]
10. Marcus ML, Koyanagi S, Harrison DG, Doty DB, Hiratzka LF, Eastham CL. Abnormalities in the coronary circulation that occur as a consequence of cardiac hypertrophy. *Am J Med*. 1983; 75:62–66. [PubMed: 6226197]
11. Nijland F, Kamp O, Verhorst PM, de Voogt WG, Visser CA. In-hospital and long-term prognostic value of viable myocardium detected by dobutamine echocardiography early after acute myocardial infarction and its relation to indicators of left ventricular systolic dysfunction. *Am J Cardiol*. 2001; 88:949–955. [PubMed: 11703987]
12. Ahmed A, Bourge RC, Fonarow GC, Patel K, Morgran CJ, Fleg JL, et al. Digoxin use and lower 30-day all-cause readmission for Medicare beneficiaries hospitalized for heart failure. *Am J Med*. 2013 (in press).
13. Gheorghide M, Fonarow GC, van Veldhuisen DJ, Cleland JG, Butler J, Epstein AE, et al. Lack of evidence of increased mortality among patients with atrial fibrillation taking digoxin: findings from post hoc propensity-matched analysis of the AFFIRM trial. *Eur Heart J*. 2013; 34:1489–1497. [PubMed: 23592708]
14. Hernandez AF, Hammill BG, O'Connor CM, Schulman KA, Curtis LH, Fonarow GC. Clinical effectiveness of beta-blockers in heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) Registry. *J Am Coll Cardiol*. 2009; 53:184–192. [PubMed: 19130987]
15. Ahmed A, Rich MW, Love TE, Lloyd-Jones DM, Aban IB, Colucci WS, et al. Digoxin and reduction in mortality and hospitalization in heart failure: a comprehensive post hoc analysis of the DIG trial. *Eur Heart J*. 2006; 27:178–186. [PubMed: 16339157]

Clinical Significance

In a separate document, include a maximum of 3–4 bullet points that succinctly and specifically explain the clinical significance of your manuscript. Bullets should provide readers with your manuscript’s “take home” messages for practicing internists. Do not restate information that would be considered common knowledge. Do not call for additional research in this area.

- Heart failure is the leading cause for hospital readmission and hospitals with above-average 30-day all-cause readmissions face financial penalties under the Affordable Care Act.
- Prior studies suggest that digoxin may reduce the risk of 30-day all-cause hospital admission and readmission in systolic heart failure.
- The new analysis of the ancillary DIG trial suggests that digoxin may increase the risk of 30-day all-cause hospital admission in diastolic heart failure.

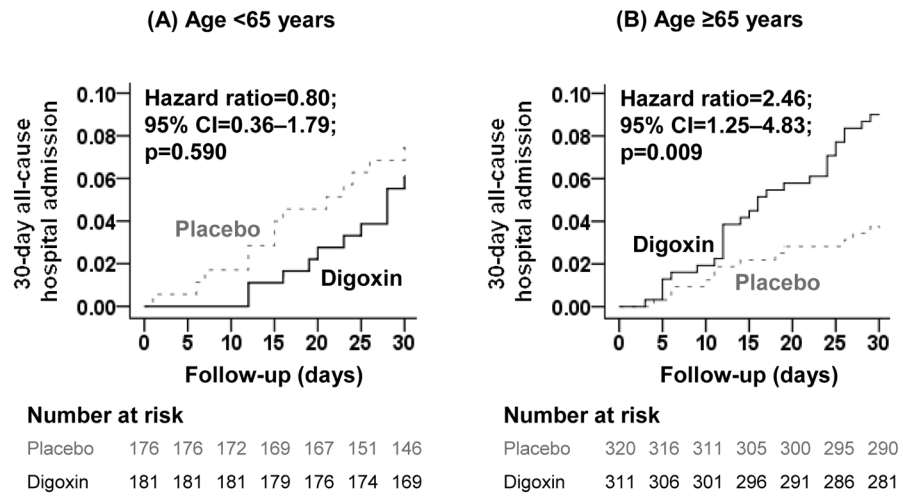


Figure 1. Kaplan-Meier plots for 30-day all-cause hospital admission for ambulatory patients with chronic diastolic heart failure randomized to receive digoxin or placebo, stratified by age <65 years (A) and ≥65 years (B). The number of patients at risk at each 5-day interval after randomization is shown below the figure. CI= confidence interval.

Table 1

Baseline Characteristics of Younger and Older Patients With Chronic Heart Failure and Ejection Fraction >45% in the Ancillary Digitalis Investigation Group (DIG) Trial, According to Randomization to Digoxin or Placebo

Variables, mean (\pm standard deviation) or n (%)	Age <65 years		Age 65 years	
	Placebo (n=176)	Digoxin (n=181)	Placebo (n=320)	Digoxin (n=311)
Age (years)**	56 (\pm 7)	56 (\pm 8)	73 (\pm 6)	73 (\pm 6)
Female**	64 (36%)	58 (32%)	136 (43%)	149 (48%)
Nonwhite**	30 (17%)	32 (18%)	36 (11%)	39 (13%)
Body mass index (kg/m ²)**	30.1 (\pm 7.1)	30.0 (\pm 7.4)	27.8 (\pm 5.5)	27.7 (\pm 5.2)
Duration of heart failure (months)	28 (\pm 33)	26 (\pm 29)	29 (\pm 38)	24 (\pm 30)
Left ventricular ejection fraction**	54 (\pm 8)	54 (\pm 7)	56 (\pm 8)	56 (\pm 9)
Cardiothoracic ratio	0.51 (\pm 0.07)	0.51 (\pm 0.08)	0.52 (\pm 0.08)	0.52 (\pm 0.08)
Cardiothoracic ratio >55%**	41 (23%)	38 (21%)	90 (28%)	94 (30%)
New York Heart Association functional class**				
I	40 (23%)	43 (24%)	62 (19%)	51 (17%)
II	106 (60%)	114 (63%)	176 (55%)	177 (57%)
III	30 (17%)	23 (13%)	74 (23%)	79 (26%)
IV	0 (0%)	1 (0.6%)	8 (3%)	3 (1%)
Signs or symptoms of heart failure				
Dyspnea at rest	30 (17%)	40 (22%)	71 (22%)	58 (19%)
Dyspnea on exertion	130 (74%)	122 (67%)	242 (76%)	228 (73%)
Jugular venous distension	11 (6%)	15 (8%)	27 (8%)	28 (9%)
Pulmonary râles**	15 (9%)	30 (17%)*	63 (20%)	47 (15%)
Lower extremity edema	39 (22%)	48 (27%)	96 (30%)	90 (29%)
Pulmonary congestion by chest x-ray	18 (10%)	18 (10%)	34 (11%)	31 (10%)
Number of signs or symptoms of heart failure [†]				
0	2 (1%)	2 (1%)	2 (<1%)	1 (<1%)
1	5 (3%)	1 (<1%)	5 (2%)	5 (2%)
2	14 (8%)	15 (8%)	18 (6%)	19 (6%)
3	16 (9%)	12 (7%)	40 (13%)	29 (9%)
4 or more	139 (79%)	151 (83%)	255 (80%)	257 (83%)
Prior myocardial infarction	92 (52%)	94 (52%)	153 (48%)	150 (48%)
Current angina pectoris	44 (25%)	57 (32%)	101 (32%)	92 (30%)
Hypertension	93 (53%)	111 (61%)	192 (60%)	194 (62%)
Diabetes mellitus**	64 (36%)	54 (30%)	86 (27%)	81 (26%)
Chronic kidney disease**	65 (37%)	55 (30%)	187 (58%)	178 (57%)
Primary cause of heart failure**				
Ischemic	103 (59%)	104 (58%)	177 (55%)	173 (56%)
Hypertensive	27 (15%)	35 (19%)	77 (24%)	83 (27%)

Variables, mean (\pm standard deviation) or n (%)	Age <65 years		Age 65 years	
	Placebo (n=176)	Digoxin (n=181)	Placebo (n=320)	Digoxin (n=311)
Idiopathic	24 (14%)	29 (16%)	29 (9%)	22 (7%)
Others	22 (13%)	13 (7%)	37 (12%)	33 (11%)
Medications				
Pre-trial digoxin use	68 (39%)	60 (33%)	112 (35%)	108 (35%)
Angiotensin-converting enzyme inhibitors	160 (91%)	153 (85%)*	267 (83%)	272 (88%)
Diuretics**	131 (74%)	128 (71%)	251 (78%)	241 (78%)
Nitrates	64 (36%)	66 (37%)	129 (40%)	130 (42%)
Heart rate (beats per minute)**	78 (\pm 13)	76 (\pm 13)	76 (\pm 12)	75 (\pm 11)
Systolic blood pressure (mm Hg)**	133 (\pm 22)	136 (\pm 21)	138 (\pm 21)	140 (\pm 21)
Diastolic blood pressure (mm Hg)**	78 (\pm 11)	79 (\pm 12)	76 (\pm 11)	76 (\pm 12)
Serum creatinine (mg/dL)	1.20 (\pm 0.35)	1.19 (\pm 0.38)	1.29 (\pm 0.40)	1.27 (\pm 0.39)
Daily dose of study medication, mg**				
0.125	16 (9%)	20 (11%)	96 (30%)	90 (29%)
0.25	127 (72%)	119 (66%)	212 (66%)	209 (67%)
0.375	33 (19%)	42 (23%)	12 (4%)	12 (4%)

* $p < 0.05$ for differences between the two treatment groups.

** $p < 0.05$ for differences between the two age groups.

† Clinical signs or symptoms included râles, elevated jugular venous pressure, peripheral edema, dyspnea at rest or on exertion, orthopnea, limitation of activity, S3 gallop, and radiologic evidence of pulmonary congestion present in past or present.

Table 2

Effect of Digoxin on Outcomes During 30 Days After Randomization Among Younger and Older Patients with Chronic Heart Failure and Ejection Fraction >45% in the Ancillary Digitalis Investigation Group (DIG) Trial

Outcomes	Age <65 years		Age ≥65 years		Hazard ratio [†] (95% CI)
	Placebo (n=176)	Digoxin (n=181)	Placebo (n=320)	Digoxin (n=311)	
	% (events)		% (events)		
Hospitalization					
All-cause	7.4% (13)	6.1% (11)	3.8% (12)	9.0% (28)	2.46 (1.25–4.83)
Cardiovascular	5.1% (9)	3.3% (6)	2.0% (7)	6.0% (19)	2.82 (1.18–6.69)
Heart failure	1.7% (3)	0.6% (1)	1.3% (4)	0.6% (2)	0.51 (0.09–2.79)
Myocardial infarction	0.6% (1)	0.6% (1)	0.0% (0)	1.0% (3)	—
Unstable angina	1.1% (2)	0.6% (1)	0.3% (1)	1.9% (6)	6.21 (0.75–51.62)
Ventricular arrhythmia/cardiac arrest	0.0% (0)	0.0% (0)	0.0% (0)	1.0% (3)	—
Supraventricular arrhythmia	1.1% (2)	0.0% (0)	0.0% (0)	0.6% (2)	—
Suspected digoxin toxicity	0.0% (0)	0.6% (1)	0.0% (0)	0.6% (2)	—
Non-cardiovascular	2.3% (4)	2.8% (5)	1.6% (5)	2.6% (8)	1.66 (0.54–5.08)
Mortality					
All-cause	0.6% (1)	0.0% (0)	0.3% (1)	0.0% (0)	—
Cardiovascular	0.6% (1)	0.0% (0)	0.3% (1)	0.0% (0)	—
Heart failure	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	—
All-cause hospitalization or All-cause mortality	8.0% (14)	6.1% (11)	4.1% (13)	9.0% (28)	2.27 (1.17–4.38)

CI=confidence interval.

[†]HRs comparing patients in the digoxin group with those in the placebo group.

Table 3

Effect of Digoxin on 30-Day All-Cause Hospital Admission in Subgroups of 631 Ambulatory Older Patients with Chronic Heart Failure and Ejection Fraction >45% in the Ancillary Digitalis Investigation Group (DIG) Trial.

Variable	Placebo % (event/total)	Digoxin % (event/total)	Hazard ratio [†] (95% CI)
Age			
70 years (n=262)	3.0% (4/135)	7.9% (10/127)	2.71 (0.85–8.94)
>70 years (n=369)	4.3% (8/185)	9.8% (18/184)	2.31 (1.01–5.32)
Sex			
Male (n=346)	4.9% (9/184)	4.9% (8/162)	1.01 (0.39–2.61)
Female (n=285)	2.2% (3/136)	13.4% (20/149)	6.43 (1.91–21.64)
Non-white			
No (n=556)	3.9% (11/284)	9.2% (25/272)	2.43 (1.19–4.94)
Yes (n=75)	2.8% (1/36)	7.7% (3/39)	2.78 (0.29–26.7)
Primary cause of heart failure			
Non-ischemic (n=281)	4.2% (6/143)	8.7% (12/138)	2.10 (0.79–5.59)
Ischemic (n=350)	3.4% (6/177)	9.2% (16/173)	2.81 (1.10–7.18)
Chronic kidney disease			
No (n=266)	5.3% (7/133)	8.3% (11/133)	1.58 (0.61–4.09)
Yes (n=365)	2.7% (5/187)	9.6% (17/178)	3.69 (1.36–10.02)
Pre-trial digoxin use			
No (n= 411)	3.4% (7/208)	9.4% (19/203)	2.85 (1.19–6.77)
Yes (n= 220)	4.5% (5/112)	8.3% (9/108)	1.92 (0.64–5.71)
Ejection fraction			
45–54% (n= 328)	3.7% (6/161)	6.6% (11/167)	1.78 (0.66–4.80)
55% (n= 303)	3.8% (6/159)	11.8% (17/144)	3.25 (1.28–8.25)
New York Heart Association functional class			
I–II (n=467)	2.1% (5/238)	8.3% (19/229)	4.06 (1.52–10.8)
III–IV (n= 164)	8.5% (7/82)	11.0% (9/82)	1.29 (0.48–3.48)
Cardiothoracic ratio >55%			
No (n=447)	3.5% (8/230)	8.8% (19/217)	2.57 (1.13–5.88)
Yes (n=184)	4.4% (4/90)	9.6% (9/94)	2.19 (0.68–7.13)
Overall	3.8% (12/320)	9.0% (28/311)	2.46 (1.25–4.83)

CI=confidence interval.

P values for the interaction of the variables shown are as follows: age, 0.830; sex, 0.019; race, 0.908; etiology of heart failure, 0.900; chronic kidney disease, 0.342; prior digoxin use, 0.957; ejection fraction, 0.381; New York Heart Association class, 0.527, and cardiothoracic ratio, 0.506.

[†]HRs comparing patients in the digoxin group with those in the placebo group.