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Digoxin Reduces 30-Day All-Cause Hospital Admission in Older Patients with Chronic Systolic Heart Failure

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Abstract

BACKGROUND—Heart failure is a leading cause of hospital admission and readmission in older adults. The new United States healthcare reform law has created provisions for financial penalties for hospitals with higher-than-expected 30-day all-cause readmission rates for hospitalized Medicare beneficiaries 65 years with heart failure. We examined the effect of digoxin on 30-day all-cause hospital admission in older patients with heart failure and reduced ejection fraction.

METHODS—In the main Digitalis Investigation Group (DIG) trial, 6800 ambulatory patients with chronic heart failure (ejection fraction <45%) were randomly assigned to digoxin or placebo. Of these, 3405 were 65 years (mean age, 72 years, 25% women, 11% non-whites). The main outcome in the current analysis was 30-day all-cause hospital admission.

RESULTS—In the first 30 days after randomization, all-cause hospitalization occurred in 5.4% (92/1693) and 8.1% (139/1712) of patients in the digoxin and placebo groups, respectively, (hazard ratio {HR} when digoxin was compared with placebo, 0.66; 95% confidence interval {CI}, 0.51–0.86; $p=0.002$). Digoxin also reduced both 30-day cardiovascular (3.5% vs. 6.5%; HR, 0.53; 95% CI, 0.38–0.72; $p<0.001$) and heart failure (1.7 vs. 4.2%; HR, 0.40; 95% CI, 0.26–0.62;

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Contributors:

AA, RCB, JLF, GCF conceived the study hypothesis and design, and AA, RCB, GCF and KP wrote the first draft. AA and KP conducted statistical analyses in collaboration with IBA. All authors interpreted the data, participated in critical revision of the paper for important intellectual content, and approved the final version of the article. AA, KP and IBA had full access to the data.

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p<0.001) hospitalizations, with similar trends for 30-day all-cause mortality (0.7% vs. 1.3%; HR, 0.55; 95% CI, 0.27–1.11; p=0.096). Younger patients were at lower risk of events but obtained similar benefits from digoxin.

CONCLUSIONS—Digoxin reduces 30-day all-cause hospital *admission* in ambulatory older patients with chronic systolic heart failure. Future studies need to examine its effect on 30-day all-cause hospital *readmission* in hospitalized patients with acute heart failure.

Keywords

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

Heart failure is a leading cause of hospital admission and readmission for Medicare beneficiaries, many of which are considered potentially preventable.^{1,2} The Patient Protection and Affordable Care Act (PPACA), the new United States healthcare reform law, has identified 30-day all-cause hospital readmission in hospitalized Medicare beneficiaries 65 years of age as a target outcome for reduction of Medicare costs.³ The law requires the Centers for Medicare and Medicaid Services to reduce payments to hospitals with excess readmissions effective for discharges beginning on October 1, 2012.⁴ The New York Times recently reported that Medicare has already imposed financial penalties against 2217 hospitals.⁵ Heart failure is one of three conditions for which the law is currently being implemented (the other two being acute myocardial infarction and pneumonia) and of the three, heart failure has the highest 30-day readmission rate.²

In the Digitalis Investigation Group (DIG) trial, digoxin led to a substantial reduction in hospitalization due to heart failure over the mean follow-up of 37 months, though its effect on all-cause hospital admission was more modest.^{6–8} However, the effect of digoxin on all-cause hospitalization during the first 30-days after randomization has not yet been reported. Although patients in the DIG trial were ambulatory and had chronic heart failure, because of digoxin's favorable effect on hemodynamics, it has been suggested that it may also improve outcomes in patients hospitalized with acute heart failure and those recently discharged after such a hospitalization.⁹ Therefore, the focus of the current analysis was to examine the effect of digoxin on 30-day all-cause hospital admission in older, potentially Medicare-eligible, adults with heart failure and reduced ejection fraction in the main DIG trial.

MATERIALS AND METHODS

Study Design and Patients

The main DIG trial was a double-blind placebo-controlled randomized clinical trial of digoxin in chronic heart failure patients with reduced ejection fraction. The rationale, design, and results of which have been previously reported.^{6,10} Briefly, in the main DIG trial, 6800 ambulatory chronic heart failure (ejection fraction <45%) patients in normal sinus rhythm from United States and Canada were randomized to receive either digoxin or placebo during 1991–1993 and were followed for an average of 37 months.⁶ The diagnosis of heart failure was based on current or past clinical symptoms, signs, or radiologic evidence of pulmonary congestion and ejection fraction was assessed by using radionuclide left ventriculography, left ventricular contrast angiography, or two-dimensional echocardiography. Most patients were receiving background therapy with angiotensin-converting enzyme inhibitors and diuretics. Although data on beta-blocker use were not collected, the rate of beta-blocker use would be expected to be low, as these drugs were not yet approved for use in heart failure. Of the 6800 patients with heart failure and reduced ejection fraction in the main trial, 3405 (50%) were 65 years of age or older. The current study is based on a public-use copy of the

DIG data obtained from the National Heart, Lung, and Blood Institute, which also sponsored the DIG trial.

Outcomes

The primary outcome in the main DIG trial was all-cause mortality. For the current analysis, we used hospitalization due to all-causes occurring during the first 30 days after randomization as our main outcome of interest. We also studied other outcomes that included 30-day cardiovascular and heart failure hospitalizations, 30-day all-cause mortality and cause-specific mortalities, and the composite outcome of 30-day all-cause hospitalization or mortality. Causes of death or hospitalization were classified by DIG investigators, who were blinded to the patient's study-drug assignment, by review of medical record and interview of patients' relatives. Vital status of patients was collected up to December 31, 1995 and was 98.9% complete.¹¹

Statistical Analysis

Baseline patient characteristics by randomization are displayed as mean ($\pm$ SD) or percentage and compared using Pearson's Chi-square and Wilcoxon rank-sum tests. Kaplan-Meier and Cox proportional hazards analyses were used to determine the effect of digoxin on various outcomes. Because patients were randomized to receive digoxin or placebo, and because the subset of older patients used in the current analysis were balanced on all measured baseline characteristics, our primary Cox regression models did not adjust for baseline covariates. However, we conducted sensitivity analyses in which we adjusted our Cox models for all key baseline demographics, morbidity and treatment characteristics presented in Table 1. In addition, to examine the effect of randomized treatment, we examined the effect of digoxin on 30-day all-cause admission in all 6800 patients with systolic heart failure in the main DIG trial that also included younger patients. Although the new health care reform law specifically targets older heart failure patients, this allowed us to examine the effect of digoxin in younger heart failure patients, who also have high rates of hospitalization. All statistical tests were two-tailed with a p-value <0.05 considered significant. SPSS-20 for Windows (IBM Corp. Armonk, NY) was used for statistical analysis.

RESULTS

Baseline Characteristics

The subset of main DIG patients 65 years or older ($n=3405$) had a mean age of 72 (SD ± 5) years, 25% were women, 11% were non-whites and 1693 (49.8%) patients were receiving digoxin. Baseline characteristics of patients assigned to digoxin and placebo were similar except for a lower body mass index amongst those assigned to digoxin (Table 1).

Digoxin and 30-day All-Cause Hospital Admission

In the 30 days after randomization, all-cause hospital admission occurred in 8.1% and 5.4% of older patients with heart failure and reduced ejection fraction assigned to placebo and digoxin, respectively (hazard ratio {HR} when digoxin was compared with placebo, 0.66; 95% confidence interval {CI}, 0.51–0.86; $p=0.002$; Table 2 and Figure 1). This effect of digoxin remained unchanged when adjusted for baseline characteristics presented in Table 1 (HR, 0.65; 95% CI, 0.50–0.85; $p=0.002$). The effect of digoxin on 30-day all-cause hospital admission in various subgroups of older patients with heart failure and reduced ejection fraction is displayed in Figure 2. Reductions in 30-day all-cause hospitalization were observed both for patients who continued pre-existing digoxin therapy or were newly initiated on digoxin compared to patients who were assigned to placebo (Figure 2). Digoxin also reduced the composite endpoint of all-cause mortality or all-cause hospitalization at 30

days after randomization (Table 2) and all-cause hospitalization at 60 days (HR, 0.76; 95% CI, 0.63–0.91; $p=0.003$) and 90 days (HR, 0.75; 95% CI, 0.63–0.88; $p<0.001$) after randomization.

Similarly, if all 6800 patients with heart failure and reduced ejection fraction in the main DIG trial are considered, regardless of age, digoxin reduced the risk of 30-day all-cause hospitalization (HR, 0.69; 95% CI, 0.57–0.83; $p<0.001$; Table 3). In particular, among the 3395 patients with heart failure and reduced ejection fraction, aged <65 years, digoxin reduced the risk of 30-day all-cause hospitalization (HR, 0.71; 95% CI, 0.55–0.93; $p=0.012$) and 30-day all-cause hospitalization or all-cause mortality (HR, 0.72; 95% CI, 0.56–0.93; $p=0.012$).

Digoxin and Other 30-day Outcomes

Older patients with heart failure and reduced ejection fraction in the digoxin group had lower risk of 30-day cardiovascular (HR, 0.53; 95% CI, 0.38–0.72; $p<0.001$) and 30-day heart failure (HR, 0.40; 95% CI, 0.26–0.62; $p<0.001$) hospitalizations, with similar trends for 30-day total mortality that did not reach statistical significance due to a low number of events (HR, 0.55; 95% CI, 0.27–1.11; $p=0.096$; Table 2). Digoxin had similar effect on all 30-day outcomes in the overall DIG population without evidence of an age interaction (Table 3). Only four patients were hospitalized due to suspected digoxin toxicity within 30 days of randomization, of which three were from the digoxin group.

30-day All-Cause Hospital Admission in High-Risk Patients

The DIG protocol pre-specified patients with ejection fraction $<25\%$, cardiothoracic ratio $>55\%$ or New York Heart Association class III-IV symptoms as a high-risk subgroup. About 67% of the older patients with heart failure and reduced ejection fraction in our study had one of the above three high-risk characteristics and these patients were more likely to have 30-day all-cause hospitalization (8.4% vs. 3.5% in the low-risk subgroup; $p<0.001$). Digoxin significantly reduced the risk of 30-day all-cause hospital admission in all 3 high-risk subgroups (Figure 2).

DISCUSSION

Findings from the current analysis demonstrate that in the DIG trial the 30-day all-cause hospital admission rate among ambulatory older patients with heart failure and reduced ejection fraction was low (8% in the placebo group, compared to 27% among hospitalized heart failure patients),² yet this rate was further reduced by about one third amongst those assigned to digoxin. Although few deaths occurred during this period, they were numerically fewer in patients assigned to digoxin; consequently, the composite outcome of all-cause hospitalization or all-cause death at 30 days was also reduced substantially. The effect of digoxin persisted during 60 and 90 days after randomization, suggesting the early benefit of digoxin was not at the cost of later harm. To the best of our knowledge, this is the first report of a significant reduction in 30-day all-cause hospital admission in older patients with heart failure and reduced ejection fraction receiving digoxin. If the beneficial effect of digoxin on hospital admissions in ambulatory patients with chronic heart failure from the pre-beta-blocker era of heart failure therapy presented in this report can be replicated in contemporary hospitalized older patients with acute heart failure, digoxin may play a role in reducing 30-day all-cause hospital readmission in patients with heart failure and reduced ejection fraction.

In the main DIG trial, digoxin reduced the risk of all-cause hospitalization by 8% during 37 months of mean follow-up.⁶ In contrast, in the current analysis digoxin reduced the risk of

30-day all-cause hospital admission by a robust 34% in older patients. This large reduction of 30-day admissions is unlikely solely an age effect as we observed that digoxin reduced this risk by 29% in those aged <65 years. A potential explanation is that the beneficial effects of digoxin may be more marked during early follow-up. For example, although digoxin had no significant effect on mortality in the main DIG trial, it reduced the risk of all-cause mortality by 13% (HR, 0.87; $p=0.043$) during the first year after randomization.¹² Another potential explanation is the preferential beneficial effect of digoxin on outcomes in high-risk subgroups.⁶ A protocol pre-specified subgroup analyses of the DIG trial demonstrated that during the first two years after randomization, digoxin reduced the risk of all-cause hospitalization by 16% (HR, 0.84; $p<0.001$) in high-risk patients, but not in those in the low-risk subgroup (HR, 1.06; $p=0.355$).¹³ Two thirds of the older patients with heart failure and reduced ejection fraction in our study belonged to the high-risk subgroups who also had higher risk for 30-day all-cause hospitalization. It is also possible that part of the differences in 30-day admissions was mediated by an adverse effect of digoxin withdrawal.^{14,15} Although there was no significant interaction, the effect of digoxin on 30-day all-cause hospital admission was more pronounced in the subgroup receiving prior digoxin therapy (Figure 2). However, prior digoxin use may also be a marker of high risk. Treatment effect is often more pronounced in subgroups with higher baseline risk,¹⁶ and the observed effect of digoxin was greater in other high-risk subgroups (Figure 2).

Few randomized clinical trials of chronic heart failure patients have examined the effect of pharmacotherapy on 30-day all-cause hospital admission after randomization and most such data are based on patients with acute decompensated heart failure. Although there is some evidence of early salutary effects of renin-angiotensin inhibition and beta-blockade on heart failure hospitalization,^{17,18} data on 30-day all-cause hospitalization are lacking. Eplerenone, a selective aldosterone blocker, tended to reduce 30-day heart failure hospitalization in patients with post-acute myocardial infarction and systolic heart failure, but its effect on 30-day all-cause hospital admission was not reported.¹⁹ In hospitalized heart failure patients, discharge prescriptions for angiotensin-converting enzyme inhibitors and beta-blockers have been shown to be associated with lower risk of 60- and 90-day post-discharge mortality or rehospitalization, but data on 30-day all-cause hospital readmission or association with digoxin use were not presented.²⁰ Findings from studies of short-term intravenous therapies in hospitalized patients with acute decompensated heart failure suggest that in general these drugs do not have beneficial effects on 30-day hospital readmission.²¹⁻²³ Many current heart failure performance measures also do not seem to be associated with lower hospital readmission rates.^{2,24}

Preventable hospital readmissions account for nearly one fifth of Medicare payments to hospitals and heart failure is the leading cause of hospital readmission in the United States.² Findings from this study suggest that digoxin, an old, inexpensive and well-tolerated drug with proven efficacy for reduction in heart failure hospitalization,⁶ also reduces 30-day all-cause hospital admission rates in ambulatory patients with chronic heart failure. However, hospitalized heart failure patients are characteristically and prognostically different from ambulatory heart failure patients. About 27% of hospitalized heart failure patients are readmitted within 30 days of hospital discharge,² which is much higher than the 8% hospitalization rate observed in the current study. Worsening heart failure is the most frequent reason for hospital readmission during the first 30 days after discharge (37%), followed by pneumonia (5%) and renal failure (4%).² In our study, worsening heart failure was also the primary reason for hospital admissions during the first 30 days after randomization accounting for 52% (72/139) of all hospital admission in the placebo group, followed by non-heart failure cardiovascular causes. In our study, patients assigned to digoxin had less than half the rate of admission for heart failure by 30 days. Considering that the effect of digoxin on heart failure hospital admission was more profound in high-risk

subgroups of ambulatory chronic heart failure patients, it is plausible that digoxin would also reduce 30-day all-cause hospital readmission in hospitalized patients with acute heart failure who would be expected to be at higher risk for hospital readmission.

Our study has several limitations. The current analysis was restricted to ambulatory older patients with heart failure and reduced ejection fraction. In the general community, over half of the hospitalized older heart failure patients have preserved ejection fraction.²⁵ Although digoxin appears to reduce the risk of heart failure hospitalization in patients with heart failure and preserved ejection fraction,²⁶ whether it would also reduce 30-day hospital readmission in such patients remains unknown. DIG participants were not receiving beta-blockers, which may limit generalizability of these findings to current practice since medical and device-based therapy for systolic heart failure has evolved since the DIG trial. However, systolic heart failure patients in early randomized clinical trials of angiotensin-converting enzyme inhibitors and aldosterone antagonists also did not receive beta-blockers,^{27,28} and yet these drugs have later been shown to improve outcomes in those receiving beta-blockers.^{29,30} Future prospective randomized clinical trials need to examine whether digoxin would also reduce the risk of 30-day all-cause hospital readmission in contemporary hospitalized older heart failure patients receiving evidence-based therapy with neurohormonal blocking agents.

In conclusion, digoxin reduced the risk of 30-day all-cause, cardiovascular and heart failure-related hospital admissions in ambulatory older adults with chronic systolic heart failure. If these findings can be replicated in hospitalized older patients with acute heart failure, digoxin may provide an inexpensive tool to reduce 30-day all-cause hospital readmission for this large and growing population.

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Number at risk

Placebo	1712	1666	1618	1566
Digoxin	1693	1659	1623	1592

Figure 1.

Kaplan-Meier plots for 30-day all-cause hospital admission by randomization to digoxin or placebo in the subset of 3405 ambulatory patients 65 years of age or older with chronic heart failure and reduced ejection fraction in the main Digitalis Investigation Group (DIG) trial

Figure 2.

Effect of digoxin on 30-day all-cause hospital admission in subgroups of 3405 ambulatory older patients with chronic heart failure and reduced ejection fraction in the main Digitalis Investigation Group (DIG) trial

Table 1

Baseline characteristics of the subset of 3405 ambulatory patients aged 65 years or older with chronic heart failure and reduced ejection fraction in the main Digitalis Investigation Group (DIG) trial, according to randomization to digoxin or placebo

Variables	Placebo	Digoxin	P-value
n (%) or mean (±SD)	(n=1712)	(n=1693)	
Age (years)	72 (±5)	72 (±5)	0.974
Female	426 (25%)	415 (25%)	0.802
Non-white	194 (11%)	180 (11%)	0.514
Body mass index (kg/m ²)	26.2 (±4.7)	25.9 (±4.5)	0.040
Duration of heart failure (months)	30 (±37)	30 (±38)	0.625
Left ventricular ejection fraction	29 (±9)	29 (±9)	0.855
Left ventricular ejection fraction <25%	541 (32%)	546 (32%)	0.684
Cardiothoracic ratio	0.54 (±0.08)	0.54 (±0.07)	0.385
Cardiothoracic ratio >55%	644 (38%)	622 (37%)	0.596
New York Heart Association functional class			
I	192 (11%)	211 (13%)	0.599
II	918 (54%)	878 (52%)	
III	563 (33%)	560 (33%)	
IV	39 (2%)	43 (3%)	
Signs or symptoms of heart failure			
Dyspnea at rest	386 (23%)	358 (21%)	0.323
Dyspnea on exertion	1323 (77%)	1306 (77%)	0.924
Jugular venous distension	259 (15%)	247 (15%)	0.658
Pulmonary râles	346 (20%)	356 (21%)	0.555
Lower extremity edema	359 (21%)	348 (21%)	0.766
Pulmonary Congestion by chest x-ray	266 (16%)	286 (17%)	0.283
No of signs or symptoms of heart failure *			
0	14 (1%)	12 (1%)	0.525
1	28 (2%)	41 (2%)	
2	109 (6%)	115 (7%)	
3	150 (9%)	141 (8%)	
4	1411 (82%)	1384 (82%)	
Comorbid conditions			
Prior myocardial infarction	1168 (68%)	1154 (68%)	0.969
Current angina pectoris	489 (29%)	465 (28%)	0.476
Hypertension	815 (48%)	784 (46%)	0.448
Diabetes mellitus	517 (30%)	488 (29%)	0.379
Chronic kidney disease	1038 (61%)	1045 (62%)	0.513
Primary cause of heart failure			
Ischemic	1293 (76%)	1278 (76%)	0.532
Hypertensive	156 (9%)	146 (9%)	

Variables n (%) or mean (±SD)	Placebo (n=1712)	Digoxin (n=1693)	P-value
Idiopathic	190 (11%)	208 (12%)	
Others	73 (4%)	61 (4%)	
Medications			
Pre-trial digoxin use	739 (43%)	744 (44%)	0.646
Angiotensin-converting enzyme inhibitors	1605 (94%)	1591 (94%)	0.784
Diuretics	1405 (82%)	1374 (81%)	0.493
Nitrates	788 (46%)	768 (45%)	0.697
Heart rate (beats per minute)	78 (±12)	78 (±12)	0.445
Systolic blood pressure (mm Hg)	128 (±20)	128 (±20)	0.643
Diastolic blood pressure (mm Hg)	74 (±11)	74 (±11)	0.782
Serum creatinine (mg/dL)	1.37 (±0.40)	1.37 (±0.39)	0.938
Daily dose of study medication, mg			
0.125	433 (25.3%)	426 (25.2%)	0.430
0.250	1197 (69.9%)	1209 (71.5%)	
0.375	69 (4.0%)	46 (2.7%)	
0.500	2 (0.1%)	2 (0.1%)	

* Clinical signs or symptoms included rales, 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

Effect of digoxin on outcomes during 30 days after randomization in the subset of 3405 ambulatory patients aged 65 years or older with chronic heart failure and reduced ejection fraction in the main Digitalis Investigation Group (DIG) trial

Table 2

Outcomes	% (events)		Absolute risk difference* (%)	Hazard ratio† (95% CI)	P-value
	Placebo (n=1712)	Digoxin (n=1693)			
30-day all-cause hospitalization	8.1% (139)	5.4% (92)	-2.7	0.66 (0.51-0.86)	0.002
30-day cardiovascular hospitalization	6.5% (112)	3.5% (59)	-3.0	0.53 (0.38-0.72)	<0.001
30-day heart failure hospitalization	4.2% (72)	1.7% (29)	-2.5	0.40 (0.26-0.62)	<0.001
30-day all-cause mortality	1.3% (22)	0.7% (12)	-0.6	0.55 (0.27-1.11)	0.096
30-day cardiovascular mortality	1.1% (19)	0.7% (12)	-0.4	0.64 (0.31-1.31)	0.222
30-day heart failure mortality	0.5% (9)	0.1% (2)	-0.4	0.22 (0.05-1.04)	0.056
30-day all-cause hospitalization or all-cause mortality	8.7% (149)	6.0% (102)	-2.7	0.69 (0.53-0.88)	0.003

* Absolute risk differences were calculated by subtracting percent events in patients receiving placebo from those receiving digoxin

† Hazard ratios comparing patients receiving digoxin versus those receiving placebo

Table 3

Effect of digoxin on outcomes during 30 days after randomization in all 6800 ambulatory patients with chronic heart failure and reduced ejection fraction in the main Digitalis Investigation Group (DIG) trial

Outcomes	% (events)		Absolute risk difference* (%)	Hazard ratio [†] (95% CI)	P-value
	Placebo (n=3403)	Digoxin (n=3397)			
30-day all-cause hospitalization	7.9% (270)	5.5% (187)	-2.4	0.69 (0.57-0.83)	<0.001
30-day cardiovascular hospitalization	6.1% (209)	3.6% (122)	-2.5	0.58 (0.46-0.72)	<0.001
30-day heart failure hospitalization	4.1% (140)	1.6% (55)	-2.5	0.39 (0.29-0.53)	<0.001
30-day all-cause mortality	1.1% (36)	0.7% (23)	-0.4	0.64 (0.38-1.08)	0.093
30-day cardiovascular mortality	0.9% (32)	0.6% (21)	-0.3	0.66 (0.38-1.14)	0.134
30-day heart failure mortality	0.4% (15)	0.1% (5)	-0.3	0.33 (0.12-0.92)	0.033
30-day all-cause hospitalization or all-cause mortality	8.5% (288)	6.0% (204)	-2.5	0.70 (0.59-0.84)	<0.001

* Absolute risk differences were calculated by subtracting percent events in patients receiving placebo from those receiving digoxin

[†] Hazard ratios comparing patients receiving digoxin versus those receiving placebo