CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Digoxin Reduces 30-day All-cause Hospital Admission in Older Patients with Chronic Systolic Heart Failure

Robert C. Bourge, MD,[a] Jerome L. Fleg, MD,[b] Gregg C. Fonarow, MD,[c] John G. F. Cleland, MD,[d] John J. V. McMurray, MD,[e] Dirk J. van Veldhuisen, MD, PhD,[f] Mihai Gheorghiade, MD,[g] Kanan Patel, MBBS, MPH,[a] Inmaculada B. Aban, PhD,[a] Richard M. Allman, MD,[h,a] Connie White-Williams, RN, PhD,[a] Michel White, MD,[i] Gerasimos S. Filippatos, MD, PhD,[j] Stefan D. Anker, MD, PhD,[k] Ali Ahmed, MD, MPH[a,h]

[a]University of Alabama at Birmingham, Birmingham; [b]National Heart, Lung, and Blood Institute, Bethesda, Md; [c]University of California, Los Angeles; [d]Hull York Medical School, Kingston-Upon-Hull, United Kingdom; [e]University of Glasgow, Glasgow, United Kingdom; [f]University Medical Centre, Groningen, The Netherlands; [g]Northwestern University, Chicago, Ill; [h]Veterans Affairs Medical Center, Birmingham, Ala; [i]Montreal Heart Institute, Montreal, Canada; [j]Attikon University Hospital, Athens, Greece; [k]Center for Clinical and Basic Research, IRCCS San Raffaele, Rome, Italy.

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 aged ≥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 trial, 6800 ambulatory patients with chronic heart failure (ejection fraction ≤45%) were randomly assigned to digoxin or placebo. Of these, 3405 were aged ≥65 years (mean age, 72 years; 25% were women; 11% were nonwhite). 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; $P = .002$). Digoxin also reduced both 30-day cardiovascular (3.5% vs 6.5%; HR, 0.53; 95% CI, 0.38-0.72; $P < .001$) and heart failure (1.7 vs 4.2%; HR, 0.40; 95% CI, 0.26-0.62; $P < .001$) hospitalizations, with similar trends for 30-day all-cause mortality (0.7% vs 1.3%; HR, 0.55; 95% CI, 0.27-1.11; $P = .096$). 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.

Published by Elsevier Inc. • *The American Journal of Medicine (2013) 126, 701-708*

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, the new United States healthcare reform law, has identified 30-day all-cause hospital readmission in hospitalized Medicare beneficiaries aged ≥65 years as a target outcome for reduction of Medicare costs.[3] The law requires the Centers for Medicare and Med-

Funding: The Digitalis Investigation Group (DIG) study was conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) and the Department of Veterans Affairs Cooperative Studies Program, in collaboration with the DIG Investigators. This article was prepared using a limited access dataset obtained from the NHLBI and does not necessarily reflect the opinions or views of the DIG Study or the NHLBI. Dr Ahmed was in part supported by the National Institutes of Health through grants (R01-HL085561, R01-HL085561-S and R01-HL097047) from the National Heart, Lung, and Blood Institute.

Conflict of Interest: See last page of article.

Authorship: See last page of article.

Requests for reprints should be addressed to Ali Ahmed, MD, MPH, UAB Center for Aging, 1720 2nd Ave South, CH19-219, Birmingham, AL 35294-2041.

E-mail address: aahmed@uab.edu

0002-9343/$ -see front matter Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.amjmed.2013.02.001

icaid Services to reduce payments to hospitals with excess readmissions effective for discharges beginning on October 1, 2012.[3,4] *The New York Times* recently reported that Medicare has already imposed financial penalties against 2217 hospitals.[5] Heart failure is 1 of 3 conditions for which the law is currently being implemented (the other 2 being acute myocardial infarction and pneumonia), and of the 3, 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, although 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 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.

CLINICAL SIGNIFICANCE

- According to the new United States health care reform law, starting October 2012, hospitals are being penalized for higher than expected 30-day all-cause hospital readmissions for older patients with heart failure.
- Digoxin, known to reduce heart failure hospitalization, also reduces 30-day all-cause hospital *admission* in ambulatory older patients with chronic systolic heart failure.
- Future studies need to examine the effect of digoxin on 30-day all-cause hospital *readmission* in acute heart failure.

MATERIALS AND METHODS

Study Design and Patients

The main DIG trial was a double-blind, placebo-controlled randomized clinical trial of digoxin in patients with chronic heart failure and reduced ejection fraction. The rationale, design, and results of the main DIG trial have been previously reported.[1,6,10] Briefly, in the main DIG trial, 6800 ambulatory patients with chronic heart failure (ejection fraction ≤45%) in normal sinus rhythm from the United States and Canada were randomized to receive 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 2-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 because 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 aged ≥65 years. 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 (± standard deviation) 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 the subset of older patients used in the current analysis was 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 patients with heart failure, this allowed us to examine the effect of digoxin in younger patients with heart failure, who also have high rates of hospitalization. All statistical tests were 2-tailed with a P value $<.05$ considered significant. SPSS-20 for Windows (IBM Corp, Armonk, NY) was used for statistical analysis.

Table 1 Baseline Characteristics of the Subset of 3405 Ambulatory Patients Aged ≥65 Years with Chronic Heart Failure and Reduced Ejection Fraction in the Main Digitalis Investigation Group Trial, According to Randomization to Digoxin or Placebo

Variables n (%) or mean (±SD)	Placebo (n = 1712)	Digoxin (n = 1693)	*P* Value
Age (y)	72 (±5)	72 (±5)	.974
Female	426 (25%)	415 (25%)	.802
Nonwhite	194 (11%)	180 (11%)	.514
Body mass index (kg/m^2)	26.2 (±4.7)	25.9 (±4.5)	.040
Duration of heart failure (mo)	30 (±37)	30 (±38)	.625
Left ventricular ejection fraction	29 (±9)	29 (±9)	.855
Left ventricular ejection fraction <25%	541 (32%)	546 (32%)	.684
Cardiothoracic ratio	0.54 (±0.08)	0.54 (±0.07)	.385
Cardiothoracic ratio >55%	644 (38%)	622 (37%)	.596
New York Heart Association functional class			
I	192 (11%)	211 (13%)	.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%)	.323
Dyspnea on exertion	1323 (77%)	1306 (77%)	.924
Jugular venous distension	259 (15%)	247 (15%)	.658
Pulmonary rales	346 (20%)	356 (21%)	.555
Lower-extremity edema	359 (21%)	348 (21%)	.766
Pulmonary congestion by chest x-ray	266 (16%)	286 (17%)	.283
No of signs or symptoms of heart failure*			
0	14 (1%)	12 (1%)	.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%)	.969
Current angina pectoris	489 (29%)	465 (28%)	.476
Hypertension	815 (48%)	784 (46%)	.448
Diabetes mellitus	517 (30%)	488 (29%)	.379
Chronic kidney disease	1038 (61%)	1045 (62%)	.513
Primary cause of heart failure			
Ischemic	1293 (76%)	1278 (76%)	.532
Hypertensive	156 (9%)	146 (9%)	
Idiopathic	190 (11%)	208 (12%)	
Others	73 (4%)	61 (4%)	
Medications			
Pre-trial digoxin use	739 (43%)	744 (44%)	.646
Angiotensin-converting enzyme inhibitors	1605 (94%)	1591 (94%)	.784
Diuretics	1405 (82%)	1374 (81%)	.493
Nitrates	788 (46%)	768 (45%)	.697
Heart rate (beats/min)	78 (±12)	78 (±12)	.445
Systolic blood pressure (mm Hg)	128 (±20)	128 (±20)	.643
Diastolic blood pressure (mm Hg)	74 (±11)	74 (±11)	.782
Serum creatinine (mg/dL)	1.37 (±0.40)	1.37 (±0.39)	.938
Daily dose of study medication, mg			
0.125	433 (25.3%)	426 (25.2%)	.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%)	

SD = standard deviation.

*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 in past or present.

RESULTS

Baseline Characteristics

The subset of main DIG patients aged ≥65 years (n = 3405) had a mean age of 72 (standard deviation ±5) years, 25% were women, and 11% were nonwhite. Baseline characteristics of patients assigned to digoxin and placebo were similar except for a lower body mass index among 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* = .002; **Table 2** and **Figure 1**). This effect of digoxin remained un-

Table 2 Effect of Digoxin on Outcomes During 30 Days After Randomization in the Subset of 3405 Ambulatory Patients Aged ≥65 years with Chronic Heart Failure and Reduced Ejection Fraction in the Main Digitalis Investigation Group Trial

Outcomes	% (Events) Placebo (n = 1712)	Digoxin (n = 1693)	Absolute Risk Difference* (%)	Hazard Ratio† (95% CI)	*P* Value
30-d all-cause hospitalization	8.1% (139)	5.4% (92)	−2.7	0.66 (0.51-0.86)	.002
30-d cardiovascular hospitalization	6.5% (112)	3.5% (59)	−3.0	0.53 (0.38-0.72)	<.001
30-d heart failure hospitalization	4.2% (72)	1.7% (29)	−2.5	0.40 (0.26-0.62)	<.001
30-d all-cause mortality	1.3% (22)	0.7% (12)	−0.6	0.55 (0.27-1.11)	.096
30-d cardiovascular mortality	1.1% (19)	0.7% (12)	−0.4	0.64 (0.31-1.31)	.222
30-d heart failure mortality	0.5% (9)	0.1% (2)	−0.4	0.22 (0.05-1.04)	.056
30-d all-cause hospitalization or all-cause mortality	8.7% (149)	6.0% (102)	−2.7	0.69 (0.53-0.88)	.003

CI = confidence interval.
*Absolute risk differences were calculated by subtracting percent events in patients receiving placebo from those receiving digoxin.
†HRs comparing patients receiving digoxin with those receiving placebo.

changed when adjusted for baseline characteristics presented in **Table 1** (HR, 0.65; 95% CI, 0.50-0.85; $P = .002$). 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 for patients who continued preexisting digoxin therapy or were newly initiated on digoxin compared with patients who were assigned to placebo (**Figure 2**). Digoxin also reduced the composite end point 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; $P = .003$) and 90 days (HR, 0.75; 95% CI, 0.63-0.88; $P < .001$) after randomization.

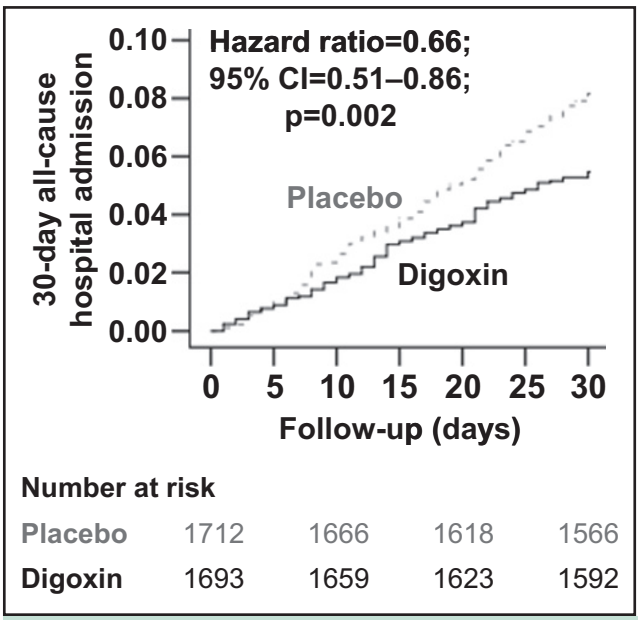

Figure 1 Kaplan-Meier plots for 30-day all-cause hospital admission by randomization to digoxin or placebo in the subset of 3405 ambulatory patients aged ≥65 years with chronic heart failure and reduced ejection fraction in the main DIG trial. CI = confidence interval.

Likewise, 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; $P < .001$; **Table 3**). In particular, among the 3395 patients aged <65 years with heart failure and reduced ejection fraction, digoxin reduced the risk of 30-day all-cause hospitalization (HR, 0.71; 95% CI, 0.55-0.93; $P = .012$) and 30-day all-cause hospitalization or all-cause mortality (HR, 0.72; 95% CI, 0.56-0.93; $P = .012$).

Digoxin and Other 30-day Outcomes

Older patients with heart failure and reduced ejection fraction in the digoxin group had a lower risk of 30-day cardiovascular (HR, 0.53; 95% CI, 0.38-0.72; $P < .001$) and 30-day heart failure (HR, 0.40; 95% CI, 0.26-0.62; $P < .001$) hospitalizations, with similar trends for 30-day total mortality that did not reach statistical significance because of a low number of events (HR, 0.55; 95% CI, 0.27-1.11; $P = .096$; **Table 2**). Digoxin had a similar effect on all 30-day outcomes in the overall DIG population without evidence of an age interaction (**Table 3**). Only 4 patients were hospitalized because of suspected digoxin toxicity within 30 days of randomization, of whom 3 were from the digoxin group.

Thirty-day All-cause Hospital Admission in High-risk Patients

The DIG protocol prespecified patients with ejection fraction <25%, cardiothoracic ratio >55%, or New York Heart Association class III-IV symptoms as a high-risk

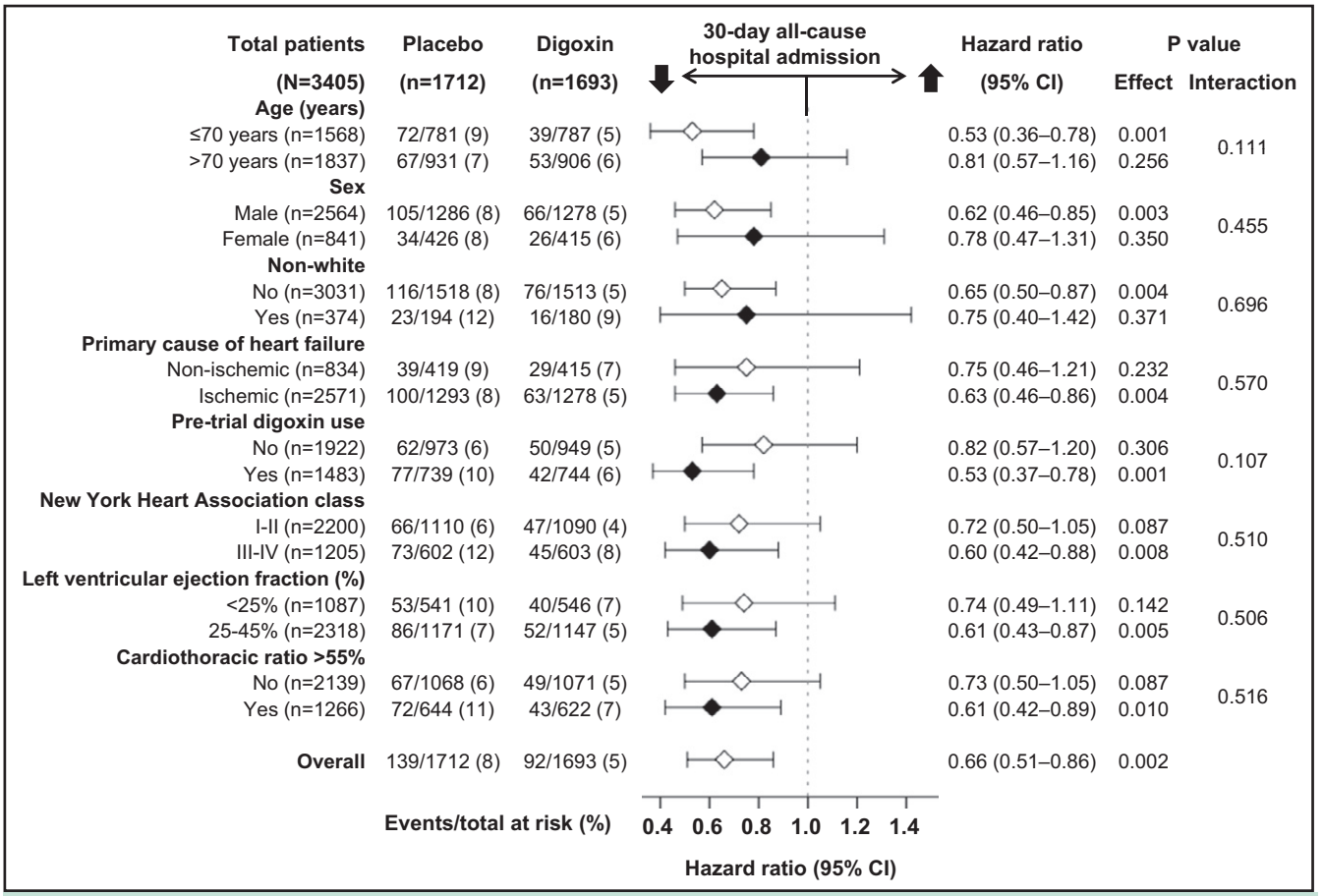

Figure 2 Effect of digoxin on 30-day all-cause hospital admission in subgroups of 3405 ambulatory older patients with chronic heart failure and reduced ejection fraction in the main DIG trial. CI = confidence interval; EF = ejection fraction.

subgroup. Approximately 67% of the older patients with heart failure and reduced ejection fraction in our study had 1 of these 3 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; $P < .001$). Digoxin significantly reduced the risk of 30-day all-cause hospital admission in all 3 high-risk subgroups (**Figure 2**).

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 Trial

	% (events)				
Outcomes	Placebo (n = 3403)	Digoxin (n = 3397)	Absolute Risk Difference* (%)	Hazard Ratio† (95% CI)	*P* Value
30-d all-cause hospitalization	7.9% (270)	5.5% (187)	−2.4	0.69 (0.57-0.83)	<.001
30-d cardiovascular hospitalization	6.1% (209)	3.6% (122)	−2.5	0.58 (0.46-0.72)	<.001
30-d heart failure hospitalization	4.1% (140)	1.6% (55)	−2.5	0.39 (0.29-0.53)	<.001
30-d all-cause mortality	1.1% (36)	0.7% (23)	−0.4	0.64 (0.38-1.08)	.093
30-d cardiovascular mortality	0.9% (32)	0.6% (21)	−0.3	0.66 (0.38-1.14)	.134
30-d heart failure mortality	0.4% (15)	0.1% (5)	−0.3	0.33 (0.12-0.92)	.033
30-d all-cause hospitalization or all-cause mortality	8.5% (288)	6.0% (204)	−2.5	0.70 (0.59-0.84)	<.001

CI = confidence interval.
*Absolute risk differences were calculated by subtracting percent events in patients receiving placebo from those receiving digoxin.
†HRs comparing patients receiving digoxin with those receiving placebo.

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 with 27% among hospitalized patients with heart failure),[2] yet this rate was further reduced by approximately one third among 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 also was 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 because 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.[12] 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; $P = .043$) during the first year after randomization.[12] Another potential explanation is the preferential beneficial effect of digoxin on outcomes in high-risk subgroups.[6] Protocol prespecified subgroup analyses of the DIG trial demonstrated that during the first 2 years after randomization, digoxin reduced the risk of all-cause hospitalization by 16% (HR, 0.84; $P < .001$) in high-risk patients, but not in the low-risk subgroup (HR, 1.06; $P = .355$).[13,14] 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 also is possible that part of the difference 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 also may 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 patients with chronic heart failure 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 patients with heart failure, discharge prescriptions for angiotensin-converting enzyme inhibitors and beta-blockers have been shown to be associated with a 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 approximately 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 patients with heart failure are characteristically and prognostically different from ambulatory patients with heart failure. Approximately 27% of hospitalized patients with heart failure are readmitted within 30 days of hospital discharge,[2] which is 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 also was the primary reason for hospital admissions during the first 30 days after randomization, accounting for 52% (72/139) of all hospital admissions in the placebo group, followed by non–heart failure cardiovascular causes. We observed that 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 patients with chronic heart failure, it is plausible that digoxin also would 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.

Study Limitations

The current analysis was restricted to ambulatory older patients with heart failure and reduced ejection fraction. In the general community, more than half of the hospitalized older patients with heart failure have preserved ejection fraction.[25] Although digoxin seems to reduce the risk of heart failure hospitalization in patients with heart failure and preserved ejection fraction,[26] whether it also would reduce 30-day hospital readmission in such patients remains unknown. DIG participants were not receiving beta-blockers, which may limit the generalizability of these findings to current practice because medical and device-based therapy for systolic heart failure has evolved since the DIG trial. However, patients with systolic heart failure 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 also would reduce the risk of 30-day all-cause hospital readmission in contemporary hospitalized older patients with heart failure receiving evidence-based therapy with neurohormonal-blocking agents.

CONCLUSIONS

Digoxin reduced the risk of 30-day all-cause hospital admission in ambulatory older adults with chronic systolic heart failure, receiving background therapy with angiotensin-converting enzyme inhibitors and diuretics. 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.

References

1. Jiang HJ, Russo CA, Barrett ML. *Nationwide Frequency and Costs of Potentially Preventable Hospitalizations, 2006. HCUP Statistical Brief #72. April 2009.* Rockville, MD: US Agency for Healthcare Research and Quality. Available at: http://www.hcup-us.ahrq.gov/reports/statbriefs/sb72.pdf. Accessed February 14, 2013.
2. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med*. 2009;360:1418-1428.
3. Stone J, Hoffman GJ. Medicare Hospital Readmissions: Issues, Policy Options and PPACA: Congressional Research Service Report for Congress. Prepared for Members and Committees of Congress. Washington, DC: Congressional Research Service; 2010.
4. The Centers for Medicare & Medicaid Services. Readmissions reduction program. Available at: http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/Readmissions-Reduction-Program.html. Accessed December 28, 2012.
5. Rau J. Hospitals face pressure to avert readmissions. *The New York Times.* November 27, 2012, page D1. Available at: http://www.nytimes.com/2012/11/27/health/hospitals-face-pressure-from-medicare-to-avert-readmissions.html?_r=0. Accessed December 2, 2012.
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.
7. Hood WB Jr, Dans AL, Guyatt GH, Jaeschke R, McMurray JJ. Digitalis for treatment of congestive heart failure in patients in sinus rhythm. *Cochrane Database Syst Rev*. 2004:CD002901.
8. Gheorghiade M, van Veldhuisen DJ, Colucci WS. Contemporary use of digoxin in the management of cardiovascular disorders. *Circulation*. 2006;113:2556-2564.
9. Gheorghiade M, Braunwald E. Reconsidering the role for digoxin in the management of acute heart failure syndromes. *JAMA*. 2009;302:2146-2147.
10. The Digitalis Investigation Group. Rationale, design, implementation, and baseline characteristics of patients in the DIG trial: a large, simple, long-term trial to evaluate the effect of digitalis on mortality in heart failure. *Control Clin Trials*. 1996;17:77-97.
11. Collins JF, Howell CL, Horney A, Invest DIG. Determination of vital status at the end of the DIG trial. *Control Clin Trials*. 2003;24:726-730.
12. Ahmed A, Waagstein F, Pitt B, et al. Effectiveness of digoxin in reducing one-year mortality in chronic heart failure in the Digitalis Investigation Group trial. *Am J Cardiol*. 2009;103:82-87.
13. Gheorghiade M, Patel K, Flippatos GS, et al. Effect of oral digoxin in high-risk heart failure patients: a pre-specified subgroup analysis of the DIG trial. *Eur J Heart Fail*. 2013 Jan 25. [Epub ahead of print]
14. Packer M, Gheorghiade M, Young JB, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. *N Engl J Med*. 1993;329:1-7.
15. Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. PROVED Investigative Group. *J Am Coll Cardiol*. 1993;22:955-962.
16. Rothwell PM. Treating individuals 2. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. *Lancet*. 2005;365:176-186.
17. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA*. 1995;273:1450-1456.
18. Krum H, Roecker EB, Mohacsi P, et al. Effects of initiating carvedilol in patients with severe chronic heart failure: results from the COPERNICUS Study. *JAMA*. 2003;289:712-718.
19. Pitt B, White H, Nicolau J, et al. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *J Am Coll Cardiol*. 2005;46:425-431.
20. Fonarow GC, Abraham WT, Albert NM, et al. Association between performance measures and clinical outcomes for patients hospitalized with heart failure. *JAMA*. 2007;297:61-70.
21. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med*. 2011;365:32-43.
22. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. *N Engl J Med*. 1991;325:1468-1475.
23. Teerlink JR, Cotter G, Davison BA, et al. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. *Lancet*. 2013;381:29-39.
24. Mulvey GK, Wang Y, Lin Z, et al. Mortality and readmission for patients with heart failure among U.S. News & World Report's top heart hospitals. *Circ Cardiovasc Qual Outcomes*. 2009;2:558-565.
25. Fonarow GC, Stough WG, Abraham WT, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. *J Am Coll Cardiol*. 2007;50:768-777.
26. Ahmed A, Rich MW, Fleg JL, et al. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. *Circulation*. 2006;114:397-403.

27. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999; 341:709-717.
28. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325:293-302.
29. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet*. 2003;362:772-776.
30. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364:11-21.

Conflict of Interest: Dr Fonarow has been consultant to Medtronic, Novartis, and Gambro. Dr Gheorghiade has been a consultant for Abbott Laboratories, Astellas, AstraZeneca, Bayer HealthCare AG, CorThera, Cytokinetics, DebioPharm S.A., Errekappa Terapeutici, GlaxoSmithKline, Ikaria, Johnson & Johnson, Medtronic, Merck, Novartis Pharma AG, Otsuka Pharmaceuticals, Palatin Technologies, Pericor Therapeutics, Protein Design Laboratories, Sanofi-Aventis, Sigma Tau, Solvay Pharmaceuticals, Takeda Pharmaceutical, and Trevena Therapeutics. All other authors reported no conflict of interest.

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

An abstract based on these findings was presented at a Late-Breaking Clinical Trials Session at the 2013 American College of Cardiology Scientific Sessions on March 11, 2013, in San Francisco, California.