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Inappropriate Use of Digoxin in Older Hospitalized Heart Failure Patients

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Background. Older adults are more likely to suffer from the adverse effects of digoxin. Studies have described the inappropriate use of digoxin in various populations. The objective of this study was to determine the correlates of inappropriate digoxin use in older heart failure patients.

Methods. We studied older hospitalized heart failure patients with documented left ventricular (LV) function evaluation and electrocardiography. Digoxin use was considered inappropriate if patients had preserved LV systolic function (ejection fraction ≥40%) or if they had no atrial fibrillation (AF). We compared baseline patient characteristics by indication for digoxin and tested statistical significance using Pearson's chi-square analysis and Student's *t* tests. Using logistic regression, we determined the correlates of inappropriate use and initiation of digoxin.

Results. Subjects ($N = 603$) had a mean age of 79 (±7) years; 59% were women, and 18% were African American. A total of 376 patients (62%) were discharged on digoxin, and 223 (37%) had no indication for its use. Half of the patients without an indication for digoxin received the drug. Of 132 patients without an indication and not already on digoxin, 38 (29%) were initiated on it. After adjustment for various patient and care characteristics, prior digoxin use (adjusted odds ratio [OR] 11.47, 95% confidence interval [CI] 5.72–23.02) and pulse ≥100/min (adjusted OR 2.33, 95% CI 1.10–4.94) were associated with inappropriate digoxin use. Pulse ≥100/min was also associated with inappropriate initiation of the drug (adjusted OR 2.95, 95% CI 1.28–6.78).

Conclusions. Inappropriate use of digoxin was common and was associated with prior use. Tachycardia was associated with inappropriate use and initiation. Electrocardiography and echocardiography should be performed in all older heart failure patients. Digoxin therapy should not be initiated or continued in patients without any evidence of LV systolic dysfunction or chronic AF.

THE only two FDA-approved and manufacturer-recommended indications for digoxin use are heart failure associated with left ventricular systolic dysfunction (LVSD) and chronic atrial fibrillation (AF) (1,2). The usefulness of digoxin in heart failure patients treated with angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and spironolactone, and especially in those who are asymptomatic on these drugs, has not yet been established (3). Digoxin has been shown to have a deleterious effect in patients with heart failure and myocardial infarct/ischemia, which is of concern because myocardial ischemia is the number one cause of heart failure (4,5). There is no role of digoxin in the management of acute (6,7) or paroxysmal AF (8,9). Digoxin is also ineffective in controlling ventricular rate during activities (10,11).

Heart failure and chronic AF are common and often coexist in old age (12–14). Digoxin is one of the most commonly prescribed drugs (15–22). In 1999, in the United States about 22 million prescriptions of Lanoxin (Glaxo Wellcome) were dispensed (ranked as the 13th most sold drug), of which about one third were new prescriptions (21). Most of these prescriptions were written for older patients. The adverse effects of digoxin are common (23–29), and the risk of adverse effects increases with age (30,31). Digoxin toxicity is also difficult to recognize in older patients (31) and often occurs in the presence of a normal serum digoxin level (32). Studies have demonstrated inappropriate use of digoxin in older community-dwelling adults (33) and in long-term care facilities (15). To our knowledge, no study has examined the factors associated with inappropriate use of digoxin in older hospitalized heart failure patients.

Methods

Subjects

The study subjects were fee-for-service Medicare beneficiaries discharged with a principal diagnosis of heart failure in 1994 from 11 Alabama hospitals of varying sizes (from 64 to 908 beds). The Alabama Quality Assurance Foundation identified the patients through the MEDPRO (administrative claims history for Medicare Part A) files. International Classification of Diseases, 9th Revision, and Clinical Modification (ICD-9-CM) codes 428 (principal discharge diagnosis of heart failure) or 402.91 (principal discharge di-

agnosis of hypertensive heart disease with congestive heart failure) and Diagnosis Related Codes (DRG) code 127 (heart failure) were used to identify patients. Trained study nurses abstracted charts of patients with the above listed codes and verified the discharge diagnoses by reviewing the chart. We further verified the diagnosis of HF by the presence of any two of the following: history of heart failure, or any presenting symptoms (dyspnea on exertion, orthopnea, or paroxysmal nocturnal dyspnea), signs (jugular venous distension, third heart sound, displaced point of maximum cardiac impulse, or pulmonary rales), or radiographic evidence (cardiomegaly, pulmonary venous congestion, or pulmonary edema) of heart failure. Patients who did not meet these verification criteria were excluded from the study (n = 17). We also excluded subjects without documentation of age and those younger than 65 years (n = 29).

Indications for Digoxin Use

Digoxin use was considered inappropriate if there was no evidence of LVSD or AF. Patients were considered to have LVSD if their left ventricular (LV) ejection fraction was less than 40% or if their LV function was described as moderate to severely depressed by a contrast left ventriculography, a multiple-gated acquisition (MUGA) radionuclide ventriculography, or an echocardiography during the index admission or in the past. Patients were considered to have AF if they had AF documented by an electrocardiography performed during the index admission. Patients who had no documentation of current or past LV function evaluation (n = 445) or who had no electrocardiography performed during the current hospitalization (n = 26) were therefore excluded from the study.

Data Abstraction

From each hospital, data from 120 randomly selected charts (all if less than 120 were available) with a principal discharge diagnosis of heart failure were abstracted between January and March 1995. Data were abstracted on patient demographics, history of heart failure, past left ventricular (LV) function evaluation, home use of digoxin, presenting symptoms and signs, laboratory values, chest radiograph and electrocardiograph findings, current LV function evaluation, and discharge use of digoxin. Comorbid conditions were ascertained from the list of secondary diagnoses on the basis of ICD-9-CM codes. The reliability and validity of the chart abstraction were verified respectively by random reabstractions of 5% of the charts by another group of nurse abstractors and expert physicians in the panel. The concordance rates for both reliability and validity on key variables were 95% or greater.

Analysis

The SPSS for Windows, Release 10 (34) was used to analyze the data. Baseline patient characteristics and digoxin use were compared by indication for the drug, and statistical significance was tested using Pearson's chi-square analysis and Student's t tests. We used logistic regression analysis to calculate crude odds ratios (OR) with 95% confidence intervals (95% CI) of digoxin use for all patients (use), for those without an indication for the drug (inappropriate use), and for those without an indication who were not receiving the drug at the time of the admission (inappropriate initiation). We created multiple logistic regression models to adjust for the confounding effects of patient and care characteristics. At first, we entered age (continuous variable), sex, and race into the model. We also entered absence of indication for digoxin into the model for all patients. Then, in a forward stepwise fashion, we entered history of heart failure, being on digoxin during admission (removed from the model for inappropriate initiation), use of a diuretic, symptoms of dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, lower extremity edema, angina, pulse rate 100 or more per minute, admission systolic blood pressure of 90 mm Hg or less (removed from the model restricted to inappropriate use because only one patient had systolic blood pressure less than 90 mm Hg), serum creatinine 2.5 mg/dl or more, serum potassium 3.5 mEq/l or less, admission by a cardiologist, and hospitalization. We categorized hospitals into small (0–99 beds), medium (100–399 beds), and large (400+ beds) and used them as dummy variables. We used the Hosmer-Lemeshow goodness-of-fit test to evaluate the overall fit of the model (35). For all analyses, a two-tailed alpha of $<.05$ was used for statistical significance.

Results

All patients (N = 603) met two of the four heart failure diagnostic criteria. Three hundred nine (51%) patients had LVSD, 152 (25%) had AF, and 81 (13%) had both. Two hundred twenty-three (37%) patients had neither of the two indications.

Patient Characteristics

Baseline patient characteristics are summarized in Tables 1 and 2. Patients without an indication for digoxin were more likely to be women and less likely to have history of heart failure and be on ACE inhibitors or digoxin before admission. They were also less likely to have cardiomyopathy or arrhythmias and were less likely to be cared for by cardiologists.

Use of Digoxin

A total of 312 (52%) patients were receiving digoxin before admission, and 376 (62%) were discharged on it. Of the 380 patients who had indications for digoxin use, 265 (70%) were discharged on it. Of the 81 patients with both LVSD and AF, 77% were discharged on digoxin (Figure 1). Of the 291 patients who were not receiving digoxin at the time of hospitalization, 42% were discharged on it. Patients (62%) receiving a daily dosage of 0.125 mg or less were older (mean age 80 years vs 76 years for those taking higher dosage; $p < .001$), more likely to be women, and more likely to have chronic renal insufficiency.

Prior use of digoxin was strongly associated with discharge use of digoxin (crude OR 5.86, 95% CI 4.06–8.45) (Table 3). Dyspnea and pulse 100 beats per minute or greater were associated with higher use of digoxin. Those with renal insufficiency were less likely to receive digoxin. However, hypokalemia was not associated with discharge use of digoxin. On the multivariate analysis, prior digoxin use, indication for digoxin, pulse $\geq$100 per minute, and se-

Table 1. Patient Characteristics by Indication for Digoxin Use

Parameter	All Patients (N = 603)	No Indication for Digoxin (n = 223)	Indication for Digoxin (n = 380)	p Value
Mean age, y	78.5 (±7.4)	77.8 (7.7)	78.9 (±7.1)	.09
Female gender	357 (59%)	159 (71%)	198 (52%)	<.001
African American	108 (18%)	40 (18%)	68 (18%)	.99
Nursing home admission	36 (6%)	9 (4%)	27 (7%)	.125
Historical features				
Heart failure	432 (72%)	145 (65%)	288 (76%)	.003
Atrial fibrillation	154 (26%)	27 (12%)	127 (33%)	<.001
Admission medications				
Angiotensin-converting enzyme inhibitors	223 (37%)	62 (28%)	161 (42%)	<.001
Diuretics	184 (31%)	75 (34%)	109 (29%)	.203
Digoxin	312 (52%)	91 (41%)	221 (58%)	<.001
Comorbidities				
Coronary artery disease	149 (25%)	47 (21%)	102 (27%)	.113
Cardiomyopathies	107 (18%)	11 (5%)	96 (25%)	<.001
Hypertension	106 (18%)	48 (22%)	58 (15%)	.051
Diabetes	150 (25%)	62 (28%)	88 (23%)	.203
Chronic Obstructive Pulmonary Disease	189 (32%)	73 (33%)	116 (31%)	.572
Pneumonia	75 (12%)	24 (11%)	51 (13%)	.340
Renal Failure	16 (3%)	5 (2%)	11 (3%)	.630
Care by cardiologist	357 (59%)	110 (49%)	247 (65%)	<.001
Hospital size				
Small (0–99 beds)	157 (26%)	70 (31%)	87 (23%)	.022
Medium (100–399 beds)	318 (53%)	115 (52%)	203 (53%)	.660
Large (400+ beds)	128 (21%)	38 (17%)	90 (24%)	.054

Table 2. Admission Characteristics by Indication for Digoxin Use

Parameter	All Patients (N = 603)	No Indication for Digoxin (n = 223)	Indication for Digoxin (n = 380)	p Value
Symptoms				
Dyspnea	543 (90%)	205 (92%)	338 (89%)	.238
Dyspnea on exertion	206 (34%)	78 (35%)	128 (34%)	.746
Orthopnea	251 (42%)	87 (39%)	164 (43%)	.319
PND	168 (28%)	62 (28%)	106 (28%)	.981
Fatigue	41 (7%)	12 (5%)	29 (8%)	.289
Angina	23 (4%)	11 (5%)	12 (3%)	.272
Leg swelling	365 (61%)	137 (61%)	228 (60%)	.728
Physical signs				
Pulse (per min)	92 (±23)	86 (±20)	96 (±23)	<.001
Systolic BP, mm Hg	148 (±30)	152 (±31)	146 (±29)	.011
Diastolic BP, mm Hg	82 (±19)	80 (±19)	83 (±19)	.104
Third heart sound	129 (21%)	46 (21%)	83 (22%)	.726
JVD	265 (44%)	84 (38%)	181 (48%)	.017
Pulmonary rales	422 (70%)	161 (72%)	261 (69%)	.364
PMI displaced	61 (10%)	19 (8%)	42 (11%)	.319
Laboratory values				
BUN, mg/dl	27 (±19)	30 (±21)	23 (±13)	<.001
Serum creatinine, mg/dl	1.5 (±0.96)	1.4 (±0.80)	1.6 (±1.0)	.004
Serum creatinine >2.5 mg/dl	57 (10%)	18 (8%)	39 (10%)	.359
Serum potassium, mEq/l	4.3 (±0.66)	4.3 (±0.63)	4.3 (±0.68)	.915
Serum potassium <3.5 mEq/l	64 (11%)	21 (10%)	43 (12%)	.446
Serum sodium, mEq/l	139 (±5.4)	139 (±4.9)	139 (±5.7)	.364
Chest radiograph				
Cardiomegaly	409 (68%)	134 (60%)	275 (72%)	.002
Pulmonary edema	181 (30%)	59 (27%)	122 (32%)	.144
Pulmonary venous congestion	173 (29%)	51 (23%)	122 (32%)	.016

Note: PND = paroxysmal nocturnal dyspnea; BP = blood pressure; JVD = jugular venous distension; PMI = point of maximum impulse; BUN = blood urea nitrogen.

rum creatinine ≥2.5 mg/dl were independently associated with discharge use of digoxin (Table 4).

Inappropriate Use of Digoxin

Half of the patients without an indication for digoxin use were discharged on the drug (Figure 1). Prior digoxin use was strongly associated with inappropriate use of the drug (OR 10.03, 95% CI 5.30–19.00) (Table 3). After adjustment for various patient and care characteristics, prior digoxin use and pulse ≥100 per minute were associated with use of digoxin (Table 4). There were no significant differences between the observed and expected number of events, suggesting a reasonable fit of the multivariate logistic regression model (Hosmer-Lemeshow goodness-of-fit test χ^2 4.45, p = .814). The expected number of events in most groups exceeded five, and none of the groups had an expected value less than 1. When we restricted our analyses to patients with incident heart failure (N = 171), we found similar results.

Inappropriate Initiation of Digoxin Therapy

Among patients who were not receiving digoxin at the time of the hospitalization (n = 312), 132 had no indication for digoxin use. Of them, 38 (29%) received digoxin at discharge. Patients with pulse rates ≥100 beats per minute had almost three times higher odds of receiving a new prescription for digoxin on discharge in the absence of any approved indications (Table 5). After adjustment for other covariates, this association remained unchanged. The multivariate logistic regression model was fit to data (Hosmer-Lemeshow goodness-of-fit test: χ^2 7.98, p = .436). The expected number of events in all the groups exceeded five, and none of the groups had an expected value less than 1.

Discussion

The results of our study demonstrate that as many as half of the older heart failure patients who had no indication for digoxin use were discharged on the drug. For patients without an indication for digoxin, being on the drug at the time of admission was the strongest predictor of being discharged on it. However, we have demonstrated that inappropriate initiation of digoxin therapy in older heart failure patients was also common. Among these patients, a higher admission pulse rate was associated with initiation of digoxin therapy. Other investigators also demonstrated high rates of inappropriate digoxin use (15,33,36,37).

These findings are important for several reasons. First, although LVSD and chronic AF are the only two FDA-approved indications for use of digoxin, it is not the drug of choice for either of these two conditions. The role of digoxin in asymptomatic LVSD patients on optimum dosage of ACE inhibitors, beta-blockers, and spironolactone and those with preserved LV systolic function has not yet been established (3,38,39). There is also concern about its

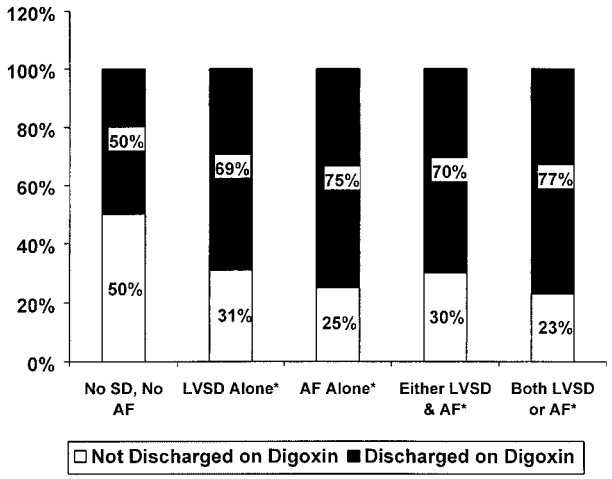

Figure 1. Proportion of patients with left ventricular systolic dysfunction (LVSD) and atrial fibrillation (AF), alone and together, and number without who received digoxin on discharge (*$p < .5$).

use in heart failure patients with myocardial infarction and coronary artery disease (4,5). Similarly, clearly, digoxin has no role in the management of acute AF, and most studies indicate that it has no role in the management of paroxysmal AF (6–9). Second, digoxin use is associated with adverse effects with the potential for fatal complications (29–31,40). Older adults are also more likely to experience adverse effects of digoxin at normal serum digoxin concentrations (32). This is particularly a concern because older adults are the users of most of the estimated more than 20 million digoxin prescriptions dispensed every year (21).

Our observation of a high prevalence of inappropriate use of digoxin has several possible explanations. Inappropriate use of drugs is not uncommon in older adults (37,41–47). Most patients receiving digoxin are older adults who also receive multiple other medications. The risk of inappropriate use of medications increases with the increase in the total number of medications prescribed (45). Second, we have demonstrated that prior digoxin use was the strongest predictor of its discharge use. Recently, Incalzia and colleagues

Table 3. Crude Odds Ratio (95% Confidence Interval) for Use of Digoxin

Parameter	All Patients ($N = 603$)	Patients Without Indication for Digoxin ($n = 223$)
Age	1.02 (1.00–1.04)	1.03 (1.00–1.07)
Female gender	0.90 (0.64–1.26)	0.64 (0.35–1.14)
African American	0.89 (0.58–1.37)	1.14 (0.58–2.26)
Absence of indication for digoxin	0.43 (0.31–0.61)	—
Preadmission digoxin use	5.86 (4.06–8.45)	10.03 (5.30–19.00)
Dyspnea	1.76 (1.03–3.00)	0.99 (0.38–2.60)
Pulse >100 beats/min	1.56 (1.09–2.23)	1.73 (0.93–3.21)
Serum creatinine >2.5 mg/dl	0.25 (0.14–0.44)	0.26 (0.08–0.83)
Serum potassium <3.5 mEq/l	0.77 (0.45–1.29)	0.74 (0.30–1.84)
Care by cardiologist	1.31 (0.94–1.84)	1.17 (0.70–1.99)

Table 4. Adjusted Odds Ratio (95% Confidence Interval) for Use of Digoxin

Parameter	All Patients ($N = 602$)	Patients Without Indication for Digoxin ($n = 223$)
Age	1.01 (0.99–1.04)	1.03 (0.98–1.07)
Female gender	0.92 (0.61–1.38)	0.49 (0.24–1.01)
African American	1.35 (0.82–2.23)	1.63 (0.72–3.69)
Absence of indication for digoxin	0.53 (0.36–0.80)	—
Preadmission digoxin use	6.19 (4.15–9.23)	11.48 (5.72–23.02)
Pulse >100 beats/min	1.64 (1.08–2.49)	2.33 (1.10–4.94)
Serum creatinine >2.5 mg/dl	0.18 (0.09–0.34)	0.23 (0.06–0.88)

Note: Also adjusted for history of heart failure, diuretic use, admission symptom of dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, lower extremity edema and angina, serum potassium of 3.5 mEq/l or less, care by cardiology, and hospitals (dummy variables for medium and large hospitals by bed size, using small hospital as the reference category).

demonstrated a similar association (37). Studies have demonstrated a general reluctance by physicians to stop a drug that a patient is already using (43,48), especially if the drug is not causing any adverse side effects, if discontinuation of the drug is believed to cause worsening of symptoms, or if it was prescribed by another physician. This is particularly true in the light of the publication in the preceding year (1993) of findings of the studies that withdrawal of digoxin resulted in worsening of heart failure symptoms (49,50). The subjects in these two studies were heart failure patients with LVSD. However, we observed a high rate of digoxin use and initiation in patients without LVSD or AF. Among patients who were inappropriately initiated on digoxin, we found that presence of tachycardia was the only predictor of digoxin use on discharge. Increase in pulse rate by one beat per minute was independently associated with 3% higher odds of inappropriate initiation of digoxin therapy (adjusted OR 1.03, 95% CI 1.01–1.05). Digoxin is not recommended for rate control in patients with supraventricular tachycardia other than chronic AF (51). To our knowledge, no other study has reported an association between tachycardia and inappropriate initiation of therapy with digoxin.

Our study has several strengths. We included patients from hospitals of various sizes and from various geographic locations. Data were collected by chart review with direct

Table 5. Crude and Adjusted Odds Ratio (95% Confidence Interval) for Initiation of Digoxin Therapy Among Patients Without Indications for its Use

Parameter	Crude Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)
Age	1.02 (0.97–1.08)	1.03 (0.98–1.08)
Female gender	0.66 (0.29–1.49)	0.56 (0.24–1.34)
African American	1.21 (0.47–3.09)	1.26 (0.47–3.41)
Pulse >100 beats/min	2.87 (1.27–6.50)	2.95 (1.28–6.78)

Note: Also adjusted for history of heart failure, admission symptom of dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, lower extremity edema and angina, serum creatinine of 2.5 mg/dl or more, serum potassium of 3.5 mEq/l or less, care by cardiology, and medium and large size hospitals (using small hospital as the reference category).

supervision by one of the coauthors (JFD) rather than from Medicare administrative files. Several limitations of the study also need to be recognized. Due to the retrospective chart review design of the study, documentation bias remains a concern. This is especially true for procedures such as echocardiography or MUGA scan performed in the past. However, we believe any such underdocumentation of past procedures would have been nondifferential to the indications for digoxin use. Moreover, when we restricted our analyses to patients hospitalized with incident heart failure, we found similar results. We have used admission electrocardiography as the criterion for AF. Events during the hospital course, such as cardioversion or the use of medications for the restoration and maintenance of sinus rhythm, might have affected physician decision not to prescribe digoxin at the time of discharge. However, we expect any such effect to be minimal. The use of sinus-rhythm–restoring drugs in outpatient settings was reportedly very low in the early 1990s (16). We were also not able to obtain data on patients' functional status. Older heart failure patients, who are more likely to have limited functional capacity, are also less likely to be symptomatic (30,52). However, in our study, symptoms were not associated with digoxin use, and adjustment for symptoms did not alter the results. Similarly, other unknown patient, family, or physician preference might also have affected digoxin use.

Although the Digitalis Investigation Group (DIG) study did not demonstrate any increased mortality (death rates of 23% for patients in both the digoxin and the placebo group; risk ratio 0.99, 95% CI 0.76–1.28) from the use of digoxin in heart failure patients with preserved LV systolic function (ejection fraction >45%) (53), routine use of digoxin in this group of patients is not recommended (38,39). In one population-based study, use of digoxin was associated with increased morbidity and mortality (54).

In conclusion, we observed a high prevalence of digoxin use among older heart failure patients who had no approved indication for its use. We also found a relative underutilization of the drug for patients who might have benefited most from the drug. Although the results of this observational study should be interpreted with caution, the study provides epidemiologic data about the high prevalence of inappropriate use and initiation of digoxin, a drug with the potential for serious complication in older patients. Electrocardiography and echocardiography should be performed in all older heart failure patients, and consideration should be given to discontinue digoxin if the absence of LVSD or chronic AF can be established. Similarly, digoxin therapy should not be initiated in the absence of these indications.

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