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Original Article

Effectiveness and Safety of Digoxin Among Contemporary Adults With Incident Systolic Heart Failure

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Background—Clinical guidelines recommend digoxin for patients with symptomatic systolic heart failure (HF) receiving optimal medical therapy, but this recommendation is based on limited, older trial data. We evaluated the effectiveness and safety of digoxin in a contemporary cohort of patients with incident systolic HF.

Methods and Results—We identified adults with incident systolic HF between 2006 and 2008 within Kaiser Permanente Northern California who had no prior digoxin use. We used multivariable extended Cox regression to examine the association between new digoxin use and risks of death and HF hospitalization, controlling for medical history, laboratory results, medications, HF disease severity, and the propensity for digoxin use. We also conducted analyses stratified by sex and concurrent β-blocker use. Among 2891 newly diagnosed patients with systolic HF, 529 (18%) received digoxin. During a median 2.5 years of follow-up, incident digoxin use was associated with higher rates of death (14.2 versus 11.3 per 100 person-years) and HF hospitalization (28.2 versus 24.4 per 100 person-years). In multivariable analysis, incident digoxin use was associated with higher mortality (hazard ratio, 1.72; 95% confidence interval, 1.25–2.36) but no significant difference in the risk of HF hospitalization (hazard ratio, 1.05; 95% confidence interval, 0.82–1.34). Results were similar in analyses stratified by sex and β-blocker use.

Conclusions—Digoxin use in patients with incident systolic HF was independently associated with a higher risk of death but no difference in HF hospitalization. **(*Circ Cardiovasc Qual Outcomes*. 2013;6:00-00.)**

Key Words: digoxin ■ epidemiology ■ heart failure ■ morbidity ■ mortality

Digitalis has been used for >200 years to treat patients with heart failure (HF). The Digitalis Investigation Group (DIG) randomized trial showed that digoxin did not lower mortality among therapy patients with systolic HF (risk ratio, 0.99; 95% confidence interval [CI], 0.91–1.07) even though it reduced hospitalizations for worsening HF (risk ratio, 0.72; 95% CI, 0.66–0.79) compared with placebo, consistent with the findings of 2 previous small, randomized studies.[1–3] Professional societies[4–6] subsequently issued clinical guidelines endorsing the use of digoxin for patients with systolic dysfunction, that is, left ventricular ejection fraction ≤40% in patients who remain symptomatic despite optimal medical therapy. However, the DIG trial enrolled patients between 1991 and 1993, before several significant advances in HF therapy and a significant shift in the epidemiology of systolic HF toward more ischemic cardiomyopathy,[7,8] which may significantly influence the effects of digoxin. In the Valsartan Heart Failure Trial (Val-HeFT), digoxin use was associated with higher risks of death and hospitalization for HF.[9] Furthermore, a retrospective analysis of 455 patients with advanced HF referred for transplantation also reported that patients treated with digoxin had a higher risk of death, urgent transplantation, or ventricular assist device implantation.[10]

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A post hoc analysis of the DIG trial suggested that digoxin was associated with a significantly higher risk of death among women but not men and that women compared with men had higher serum digoxin levels.[11] However, these findings have not been replicated consistently, and it remains unclear whether the effect of digoxin on HF symptoms and hospitalization is modified by patient sex.

To evaluate the contemporary effectiveness and safety of digoxin therapy, we examined clinical outcomes in a large, diverse, community-based cohort of adults with newly diagnosed systolic HF.

Methods

Identification and Characterization of Patients With Systolic HF

We identified all adults aged≥21 years who were diagnosed with HF between January 1, 2006, and December 31, 2008, in Kaiser Permanente Northern California (Figure 1), a large, integrated healthcare delivery system that cares for >3.2 million people who are broadly representative of the local and statewide population, except for slightly lower representation at the extremes of age and income.[12] Using information

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WHAT IS KNOWN

- The Digitalis Investigation Group (DIG) randomized trial showed that digoxin did not lower mortality among patients with systolic heart failure but did reduce hospitalizations for worsening heart failure.
- The DIG trial enrolled highly selected patients between 1991 and 1993, before several substantial advances in heart failure therapy and a significant shift in the epidemiology of systolic heart failure toward more ischemic cardiomyopathy.

WHAT THE STUDY ADDS

- In a contemporary cohort of patients with incident systolic heart failure between 2006 and 2008 within Kaiser Permanente Northern California, new digoxin use was associated with higher mortality (hazard ratio, 1.72; 95% confidence interval, 1.25–2.36) but no significant difference in the risk of heart failure hospitalization (hazard ratio, 1.05; 95% confidence interval, 0.82–1.34).
- These finding were consistent in analyses stratified by sex and β-blocker use.
- These findings suggest that the use of digoxin should be re-evaluated for the treatment of systolic heart failure in the modern era.

from comprehensive health plan databases, we defined HF as meeting either of the following criteria: ≥1 inpatient admission with a primary discharge diagnosis of HF (*International Classification of Diseases*, *Ninth Edition* code 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0, 428.1, or 428.9) or ≥3 outpatient, nonemergency department encounters for diagnosed HF.[13–15] We assigned the index date on the basis of first qualifying diagnosis and identified the subset of patients with presumed incident HF as individuals without a previous inpatient or outpatient diagnosis of HF between January 1996 and the cohort entry date.

For the present analysis, we excluded those with unknown sex, <12 months of continuous membership or drug benefit before index date, no membership after index date, or prior cardiac or renal transplantation. We selected patients who had documented left ventricular systolic dysfunction defined as left ventricular ejection fraction ≤40% or qualitative assessment of moderate or severely reduced systolic function on the basis of cardiac imaging results from the health plan databases and the electronic medical record, including echocardiography, radionuclide scintigraphy, cardiac magnetic resonance imaging, and left ventriculography during cardiac catheterization. The large majority of patients with available data had an echocardiogram as a primary source for classifying left ventricular function. Patients were further required to have no evidence of digoxin use between 1996 and their index date on the basis of data from ambulatory health plan pharmacy databases.

Institutional Review boards of the Kaiser Foundation Research Institute and Stanford University approved the study. A waiver of informed consent was obtained because of the nature of the study.

Longitudinal Exposure to Digoxin

We adopted a new user design[16] and characterized time-varying exposure to digoxin using previously validated methods on the basis of estimated day supply information per dispensed prescription and refill patterns found in health plan pharmacy databases.[17,18] Briefly, for any 2 consecutive prescriptions, we examined the time between the projected end date of the first prescription and the date of the next filled prescription. Because dose adjustment is not uncommon, we allowed a grace period of 30 days between prescriptions. Thus, if the time between the projected end date of the first prescription and the fill date of the next prescription was ≤30 days, we considered that individual to be continuously receiving digoxin therapy. If the refill interval was >30 days, we considered the individual off digoxin therapy starting the day after the projected end date of the first prescription until the date of next filled prescription, if any. Because hospitalized patients receive their medications from the inpatient pharmacy and do not use their outpatient medication supply, we subtracted the number of hospitals days from the subsequent refill interval.

Follow-Up and Outcomes

We followed up patients through December 31, 2010, for the outcomes of death and hospitalization for HF. Patients were censored at the time of health plan disenrollment or the end of follow-up. Death resulting from any cause was identified from health plan databases (inpatient deaths, proxy report of outpatient deaths), California state death certificate files, and Social Security Administration Death Master File quarterly updated data files.[19,20] Hospitalization for HF was defined as having a primary discharge diagnosis of HF on the basis of *International Classification of Diseases*, *Ninth Edition* code 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0, 428.1, or 428.9 found in hospital discharge and billing claims databases.[14,15]

Covariates

We obtained data on age, sex, and self-reported race/ethnicity from health plan databases. We ascertained relevant medical history documented ≤4 years before cohort entry and throughout follow-up using previously validated approaches on the basis of *International Classification of Diseases*, *Ninth Edition* diagnosis and procedure codes, Current Procedural Terminology codes, laboratory records, and pharmacy records.[14,17,21–25] This included cardiovascular diseases (acute myocardial infarction, unstable angina, ischemic stroke or transient ischemic attack, peripheral arterial disease, percutaneous coronary intervention, or coronary artery bypass surgery), valvular heart disease (mitral, aortic, or rheumatic heart disease), cardiac arrhythmias (atrial fibrillation or flutter, ventricular tachycardia or fibrillation), implantable cardiac devices (implantable cardioverter-defibrillators, pacemaker, cardiac resynchronization therapy, cardiac resynchronization therapy with defibrillator function), other cardiovascular risk factors (hypertension, diabetes mellitus, and dyslipidemia), and other coexisting medical illnesses (arthritis, dementia, diagnosed depression, thyroid disease, bleeding, HIV/AIDS, systemic cancer, lung disease, and liver disease). We ascertained body mass index and blood pressure ≤365 days before cohort entry and during follow-up from ambulatory visit information in the electronic medical record. We also characterized baseline renal function using serum creatinine concentration and estimated glomerular filtration rate (mL/min per 1.73 m^2) using the Chronic Kidney Disease Epidemiology Collaboration equation[26] and dipstick proteinuria from outpatient laboratory databases. We ascertained other selected laboratory test results from health plan databases ≤1 year before cohort entry and during follow-up, including low-density lipoprotein and high-density lipoprotein cholesterol, serum sodium, serum potassium, and serum digoxin concentration.

We characterized baseline and longitudinal time-varying exposure to other relevant cardiovascular medications using methods similar to those described above for digoxin on the basis of information from health plan pharmacy records for the following medications: α-adrenergic receptor antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, β-blockers, aldosterone receptor antagonists, calcium channel blockers, nitrates, hydralazine, statins, other lipid-lowering agents, antiplatelet agents, and diabetic medications.[14,15]

Finally, in addition to adjustment for all of these factors, we further attempted to account for overall health status by quantifying the number of outpatient visits in the year before cohort entry.

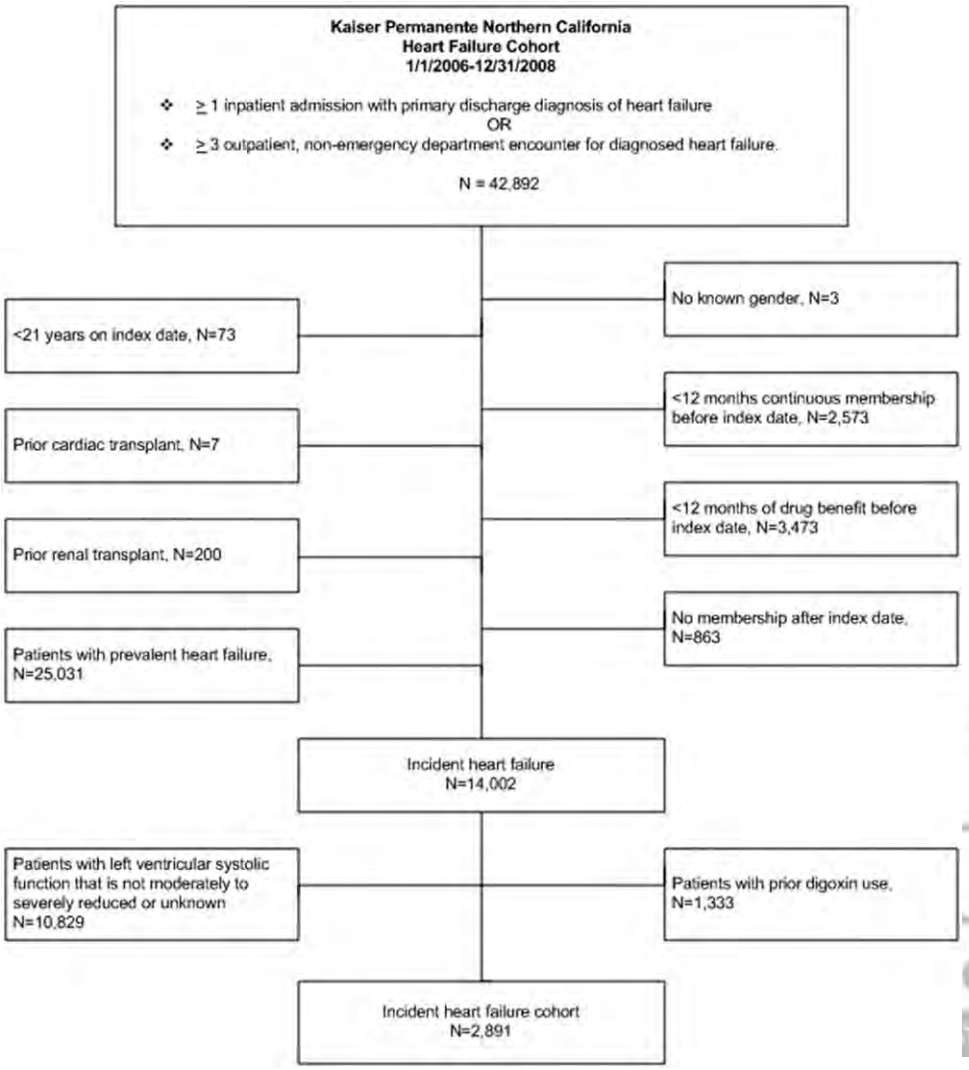

Figure 1. Cohort assembly of patients with incident systolic heart failure and incident digoxin use between January 1, 2006, and December 31, 2008.

Statistical Analysis

All analyses were performed using SAS statistical software, version 9.2 (Cary, NC). Using the new user design,[16] we compared the baseline characteristics for patients prescribed or not prescribed digoxin during follow-up using the *t* test or Wilcoxon rank-sum test for continuous variables and the χ^2 test for categorical variables.

We next calculated rates (per 100 person-years) with associated 95% confidence limits for death and hospitalization for HF for periods receiving versus not receiving digoxin therapy, overall and stratified by patient sex, and concurrent β-blocker use. We conducted multivariable extended Cox regression models to examine the independent association between current digoxin use and the risk of adverse outcomes after adjustment for time-varying medication exposure, laboratory test results, and comorbidities. Additional models were performed, stratified by patient sex and concurrent β-blocker use. We also conducted a secondary analysis using an intent-to-treat analysis approach for digoxin use rather than a time-varying exposure method. In this intent-to-treat analysis, any adverse outcome that occurred in a patient after the initiation of digoxin was considered associated with digoxin use. We considered as candidate covariates all variables listed in Table 1. We included all variables previously reported in the final models to be associated with death or hospitalization for HF, as well as any variables with differences at baseline between incident digoxin users compared with nonusers, using a cutoff of $P<0.05$. We also included a dummy variable for the primary health plan facility at which each patient received the majority of his or her medical care to account for potential unmeasured cluster effects at that level. We attempted to further control for overall health status by including a variable for the number of outpatient visits in the year before cohort entry. Finally, we conducted a sensitivity analysis in which we performed an age-, sex-, and propensity score–matched analysis (model *c* statistic, 0.70) with 1 digoxin user matched to ≤3 nondigoxin users (without replacement) and matched on age (±5 years), sex, propensity score for the initiation of digoxin (±0.05), and time between the incident HF diagnosis and the first digoxin prescription. The propensity score for the initiation of digoxin at any time during follow-up was calculated for each person using logistic regression using the baseline values for the same list of covariates as in multivariable extended Cox models.

Results

Baseline Characteristics

We identified 2891 adults who had newly diagnosed systolic HF and no prior digoxin use between January 1, 2006, and December 31, 2008, 529 (18%) of whom initiated digoxin during the study period. Patients who received digoxin were younger than those not treated with digoxin but had more severe left ventricular systolic dysfunction and more severe obesity (Table 1). Those treated with digoxin had a lower prevalence of prior myocardial infarction, hypertension, and dyslipidemia but a higher prevalence of atrial fibrillation and

Table 1. Baseline Characteristics of 2891 Adults With Incident Systolic Heart Failure Between 2006 and 2008 and No Prior Digoxin Use, Stratified by Subsequent Incident Digoxin Use

Characteristic	Overall (N=2891)	Digoxin Nonusers (n=2362)	Incident Digoxin Users (n=529)	*P* Value
Total person-years				
Median (interquartile range)	2.53 (1.42–3.49)	2.47 (1.34–3.45)	2.71 (1.62–3.57)	
Age, y				
Mean (SD)	69.5 (14.5)	69.8 (14.4)	68.2 (14.8)	0.02
Women	954 (33.0)	779 (33.0)	175 (33.1)	0.96
Race/ethnicity, n (%)				0.33
White	1981 (68.5)	1599 (67.7)	382 (72.2)	
Black	380 (13.1)	316 (13.4)	64 (12.1)	
Asian/Pacific Islander	300 (10.4)	253 (10.7)	47 (8.9)	
Native American	11 (0.4)	10 (0.4)	1 (0.2)	
Other/unknown	219 (7.6)	184 (7.8)	35 (6.6)	
Hispanic ethnicity, n (%)	384 (13.3)	324 (13.7)	60 (11.3)	0.15
Left ventricular systolic function, n (%)				0.003
Moderate	1581 (54.7)	1323 (56.0)	258 (48.8)	
Severe	1310 (45.3)	1039 (44.0)	271 (51.2)	
Cardiovascular history, n (%)				
Acute myocardial infarction	397 (13.7)	355 (15.0)	42 (7.9)	<0.001
Unstable angina	77 (2.7)	68 (2.9)	9 (1.7)	0.13
Ventricular fibrillation or tachycardia	107 (3.7)	88 (3.7)	19 (3.6)	0.88
Hospitalized ischemic stroke	62 (2.1)	55 (2.3)	7 (1.3)	0.15
Peripheral arterial disease	126 (4.4)	99 (4.2)	27 (5.1)	0.35
Mitral or aortic valvular disease	288 (10.0)	242 (10.2)	46 (8.7)	0.28
Atrial fibrillation or flutter	663 (22.9)	454 (19.2)	209 (39.5)	<0.001
Procedure history, n (%)				
Coronary artery bypass graft surgery	43 (1.5)	39 (1.7)	4 (0.8)	0.12
Percutaneous coronary intervention	156 (5.4)	146 (6.2)	10 (1.9)	<0.001
Implantable cardioverter-defibrillator	45 (1.6)	41 (1.7)	4 (0.8)	0.1
Pacemaker	56 (1.9)	49 (2.1)	7 (1.3)	0.26
Cardiac resynchronization therapy	2 (0.1)	2 (0.1)	0 (0.0)	0.5
Outpatient visits in the previous year, n				
Mean (SD)	10.4 (10)	10.6 (9.9)	9.6 (10.5)	0.05
Medical history, n (%)				
Diabetes mellitus	963 (33.3)	806 (34.1)	157 (29.7)	0.05
Hypertension	1893 (65.5)	1577 (66.8)	316 (59.7)	0.002
Diagnosed dementia	108 (3.7)	89 (3.8)	19 (3.6)	0.85
Dyslipidemia	1976 (68.4)	1647 (69.7)	329 (62.2)	<0.001
Chronic liver disease	51 (1.8)	42 (1.8)	9 (1.7)	0.9
Chronic lung disease	727 (25.1)	574 (24.3)	153 (28.9)	0.03
Diagnosed depression	397 (13.7)	321 (13.6)	76 (14.4)	0.64
Hypothyroidism	334 (11.6)	282 (11.9)	52 (9.8)	0.17
Systemic cancer	417 (14.4)	340 (14.4)	77 (14.6)	0.92
Body mass index, n (%)				0.001
≤24.9 kg/m^2	798 (27.6)	666 (28.2)	132 (25.0)	
25–29.9 kg/m^2	838 (29.0)	698 (29.6)	140 (26.5)	
30–39.9 kg/m^2	716 (24.8)	580 (24.6)	136 (25.7)	
≥40 kg/m^2	184 (6.4)	130 (5.5)	54 (10.2)	
Unknown	355 (12.3)	288 (12.2)	67 (12.7)	

Continued

Table 1. Continued

Characteristic	Overall (n=2891)	Nondigoxin Users (n=2362)	Incident Digoxin Users (n=529)	*P* Value
Systolic blood pressure, n (%)				0.14
≤120 mm Hg	1033 (35.7)	833 (35.3)	200 (37.8)	
121–129 mm Hg	491 (17.0)	391 (16.6)	100 (18.9)	
130–139 mm Hg	532 (18.4)	440 (18.6)	92 (17.4)	
140–159 mm Hg	440 (15.2)	360 (15.2)	80 (15.1)	
160–179 mm Hg	160 (5.5)	137 (5.8)	23 (4.3)	
≥180 mm Hg	59 (2.0)	55 (2.3)	4 (0.8)	
Unknown	176 (6.1)	146 (6.2)	30 (5.7)	
Baseline medication use, n (%)				
Angiotensin-converting enzyme inhibitor	1308 (45.2)	1112 (47.1)	196 (37.1)	<0.001
Antiarrhythmic	138 (4.8)	122 (5.2)	16 (3.0)	0.04
Angiotensin II receptor blocker	276 (9.5)	236 (10.0)	40 (7.6)	0.09
Diuretic, loop	1018 (35.2)	859 (36.4)	159 (30.1)	0.01
Diuretic, thiazide	650 (22.5)	504 (21.3)	146 (27.6)	0.002
Any β-blocker	1414 (48.9)	1205 (51.0)	209 (39.5)	<0.001
Any aldosterone receptor antagonist	86 (3.0)	75 (3.2)	11 (2.1)	0.18
Calcium channel blocker, dihydrophyridines	419 (14.5)	359 (15.2)	60 (11.3)	0.02
Calcium channel blocker, nondihydrophyridines	182 (6.3)	135 (5.7)	47 (8.9)	0.01
Statins	1419 (49.1)	1206 (51.1)	213 (40.3)	<0.001
Other lipid-lowering agent	104 (3.6)	84 (3.6)	20 (3.8)	0.8
Aspirin	255 (8.8)	228 (9.7)	27 (5.1)	<0.001
Antiplatelet	302 (10.4)	275 (11.6)	27 (5.1)	<0.001
Diabetic therapy	704 (24.4)	596 (25.2)	108 (20.4)	0.02
Baseline laboratory values				
Hemoglobin				
Mean (SD), g/L	13.2 (2.0)	13.1 (2.0)	13.5 (1.9)	<0.001
Missing, n (%)	526 (18.2)	416 (17.6)	110 (20.8)	0.09
Estimated glomerular filtration rate, n (%)				0.01
90–150 mL/min per 1.73 m^2	210 (7.3)	171 (7.2)	39 (7.4)	
60–89 mL/min per 1.73 m^2	944 (32.7)	774 (32.8)	170 (32.1)	
45–59 mL/min per 1.73 m^2	684 (23.7)	552 (23.4)	132 (25.0)	
30–44 mL/min per 1.73 m^2	460 (15.9)	390 (16.5)	70 (13.2)	
15–29 mL/min per 1.73 m^2	145 (5.0)	121 (5.1)	24 (4.5)	
<15 mL/min per 1.73 m^2	32 (1.1)	30 (1.3)	2 (0.4)	
Dialysis	58 (2.0)	53 (2.2)	5 (0.9)	
Missing	358 (12.4)	271 (11.5)	87 (16.4)	
Urinary dipstick protein excretion, n (%)				0.02
0 or trace	1806 (62.5)	1453 (61.5)	353 (66.7)	
≥1	1085 (37.5)	909 (38.5)	176 (33.3)	
Serum potassium				
Mean (SD), mg/dL	4.4 (0.5)	4.4 (0.5)	4.4 (0.4)	0.53
Missing, n (%)	459 (15.9)	360 (15.2)	99 (18.7)	0.05
Serum sodium				
Mean (SD), mg/dL	139.3 (3.8)	139.3 (3.7)	139.2 (3.9)	0.55
Missing, n (%)	722 (25.0)	574 (24.3)	148 (28.0)	0.08

chronic lung disease. Patients treated with digoxin were less likely to be treated at baseline with angiotensin-converting enzyme inhibitors, loop diuretics, β-blockers, dihydropyridine calcium channel blockers, antiplatelet medications, and diabetes medications but were more likely to be treated with thiazide diuretics and nondihydropyridine calcium channel blockers. Patients treated with digoxin also had higher blood hemoglobin concentrations and estimated glomerular filtration rate levels at entry. Among the 529 digoxin users, 157 patients (29.7%) had no serum digoxin concentration measured, 144 patients (27.2%) had a single level drawn (median, 38 days after starting therapy), and 228 patients (43.1) had ≥2 levels drawn (median, 25 and 86 days after starting therapy).

Outcomes According to Digoxin Exposure

There were a total of 6998 person-years of follow-up in the cohort, with a median follow-up of 2.5 years (interquartile range, 1.4–3.5 years). There were 6548 person-years of follow-up for patients during periods off digoxin and 450 person-years of follow-up for patients during periods on digoxin. There were a total of 801 deaths (737 off digoxin and 64 on digoxin). The crude rate of death was significantly higher on digoxin therapy (14.2 per 100 person-years) than off digoxin therapy (11.3 per 100 person-years; P=0.04). After adjustment for potential confounders, current digoxin use was associated with a 72% higher relative rate of death (adjusted hazard ratio [HR], 1.72; 95% CI, 1.25–2.36; Table 2; Figure 2).

During follow-up, there were 1723 hospitalizations for HF overall (1596 off digoxin, 127 on digoxin). The crude rate of hospitalization for HF was higher for patients receiving digoxin (28.2 per 100 person-years) compared with those off digoxin therapy (24.4 per 100 person-years; P=0.06). After adjustment for potential confounders, current digoxin use was not significantly associated with hospitalization for HF (adjusted HR, 1.05; 95% CI, 0.82–1.34; Table 2; Figure 2).

In a sensitivity analysis using an intention-to-treat approach, the results of the adjusted analyses were not substantially different from our primary results for death (adjusted HR, 1.36; 95% CI, 1.10–1.69), but digoxin was associated with a borderline significant increase in the risk of hospitalization for HF (adjusted HR, 1.24; 95% CI, 1.02–1.50).

In a sensitivity analysis using an age-, sex-, and propensity score–matched cohort, the results of the adjusted analyses were not substantially different from our primary results for death (adjusted HR, 1.47; 95% CI, 1.00–2.16) or hospitalization for HF (adjusted HR, 0.86; 95% CI, 0.65–1.15).

Outcomes According to Digoxin Use in Subgroups of Patient Sex

The association between digoxin use and the outcomes of death and HF hospitalization was similar in men and women. As with the overall cohort, current digoxin use was associated with a 64% higher relative rate of death in men (adjusted HR, 1.64; 95% CI, 1.09–2.46; Table 2) and a 69% higher relative rate of death in women (adjusted HR, 1.69; 95% CI, 0.98–2.90; Table 2). Also consistent with results in the overall cohort, current digoxin use was not significantly associated with HF hospitalization in men (adjusted HR, 1.11; 95% CI, 0.82–1.48; Table 2) and women (adjusted HR, 1.04; 95% CI, 0.71–1.53; Table 2). The serum digoxin level at the first measurement during follow-up was not significantly different between men (mean, 0.93 ng/mL; SD, 0.21 ng/mL) and women (mean, 1.12 ng/mL; SD, 0.32 ng/mL).

Outcomes According to Digoxin Use in Subgroups of β-Blocker Users and Nonusers

The association between digoxin use and the outcomes of death and HF hospitalization was similar among concurrent users and nonusers of β-blockers. Current digoxin use was associated with a higher rate of death in the presence (adjusted HR, 1.55; 95% CI, 1.11–2.18) or in the absence (adjusted HR, 2.49; 95% CI, 1.20–5.17) of concomitant β-blocker use. Current digoxin use was associated with no difference in the relative rate of HF hospitalization in the presence (adjusted HR, 1.08; 95% CI, 0.83–1.42) or in the absence (adjusted HR, 0.88; 95% CI, 0.46–1.69) of concomitant β-blocker use.

Table 2. Multivariable Association Between Incident Digoxin Use and Adverse Outcomes in Different Categories of Adults With Incident Systolic Heart Failure Between 2006 and 2008 With Nondigoxin Users as the Reference*

	Death From Any Cause	Hospitalization for Heart Failure
Therapy	Adjusted Hazard Ratio (95% Confidence Interval)	
Overall cohort	1.72 (1.25–2.36)	1.05 (0.82–1.34)
Men (digoxin vs nondigoxin users)	1.64 (1.09–2.46)	1.11 (0.82–1.48)
Women (digoxin vs nondigoxin users)	1.69 (0.98–2.90)	1.04 (0.71–1.53)
Concurrent β-blockers (digoxin vs nondigoxin users	1.55 (1.11–2.18)	1.08 (0.83–1.42)
No concurrent β-blockers (digoxin vs nondigoxin users	2.49 (1.20–5.17)	0.88 (0.46–1.69)

*Models adjusted for left ventricular ejection fraction, sex, race, Hispanic ethnicity, body mass index, and time-updated information on acute myocardial infarction, unstable angina, hospitalized ventricular fibrillation or ventricular tachycardia, hospitalized ischemic stroke, mitral or aortic valve disease, atrial fibrillation or flutter, coronary artery bypass surgery, percutaneous coronary intervention, implantable cardioverter-defibrillator, cardiac resynchronization therapy, diabetes mellitus, hypertension, dyslipidemia, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, β-blockers, aldosterone receptor antagonists, isosorbide dinitrate and hydralazine, calcium channel blockers, statins, diabetic therapy, aspirin, hemoglobin, estimated glomerular filtration rate, serum potassium, serum sodium, number of outpatient visits in the year before cohort entry, and propensity score for digoxin initiation.

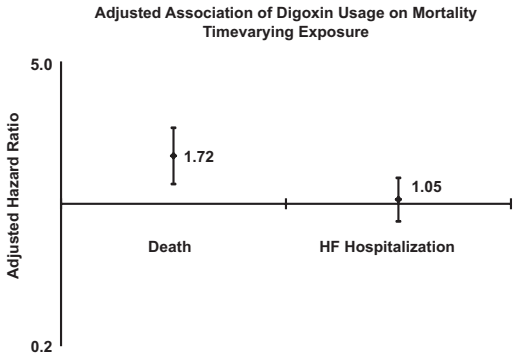

Figure 2. Adjusted hazard ratios for death and heart failure (HF) hospitalization among adults with systolic heart failure taking digoxin compared with those not taking digoxin.

Digoxin Prescription Dosages and Serum Digoxin Concentrations

Among all digoxin users, the mean daily dose of digoxin was 0.15 mg (SD, 0.05 mg). The mean daily dose of digoxin was minimally lower among those who died (0.14 mg; SD, 0.04 mg) compared with those who did not die (0.15 mg; SD, 0.05 mg) during periods exposed to digoxin (P=0.038).

Among digoxin users, the serum digoxin concentration was never measured in 30% of patients, was measured once in 27% of patients, and was measured more than once in 43% of patients. The mean serum digoxin concentration was 1.02 ng/mL (SD, 0.48 ng/mL) among all digoxin users. The mean serum digoxin concentration was not significantly different comparing those who died (1.01 ng/mL; SD, 0.46 ng/mL) compared with those who did not die (1.04 ng/ml; SD, 0.55 ng/mL) during periods exposed to digoxin (P=0.62).

Discussion

In a large, diverse, community-based cohort of adults with newly diagnosed systolic HF, we found that incident digoxin use was associated with a higher risk of death but no significant difference in hospitalization for HF. In addition, we found that these associations were consistent in men and women, in the presence or in the absence of concurrent β-blocker use, and in a sensitivity analysis using an age-, sex-, and propensity score–matched cohort.

Our results contrast with the findings of the DIG randomized trial, which showed that digoxin had no effect on the risk of death but a lower risk of hospitalization for HF, and extend reports from recent observational studies that suggested a higher risk of death with digoxin therapy in the current treatment era.[1,9,10] Multiple differences between our community-based cohort and the selected trial participants enrolled in the DIG trial may have contributed to a differential effect of digoxin on the 2 populations. Compared with the participants in the DIG trial, the digoxin users from our cohort were more likely to be older, women, persons of color, hypertensive, and diabetic and to be treated with β-blockers, but they were less likely to have a history of myocardial infarction and to be receiving concurrent HF treatment with diuretics and angiotensin-converting enzyme inhibitors. These findings suggest significant differences in systolic HF epidemiology and treatment patterns that may account for the differential effect of digoxin on death and HF hospitalization. Because both digoxin and β-blockers have atrioventricular nodal blocking activity, we hypothesized that their combination may lead to heart block or bradycardia, resulting in significant morbidity and mortality. However, we found that outcomes with digoxin were similar in the presence or in the absence of concurrent β-blocker use. Nonetheless, substantial improvements in HF treatment have occurred over the past 20 years, with greater concurrent use of β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists, and these therapies may substantially modify the independent effect of digoxin on death and HF hospitalization. Our community-based systolic HF cohort is more likely to represent patients with systolic HF in the modern era with regard to pathogenesis and treatment patterns; therefore, our results may more accurately represent the outcomes expected with digoxin for patients with systolic HF in typical contemporary practices.

Another possible explanation for the difference between our results and those of the DIG trial is that we analyzed digoxin use in a time-varying manner, so adverse events were assigned to digoxin only if patients were exposed to the medication when the event occurred, whereas the DIG trial used an intention-to-treat study design. We also performed sensitivity analyses in which adverse events were assigned to digoxin if a patient had used digoxin at any point during the study period (similar to an intent-to-treat approach) and our results were not qualitatively different other than a borderline significantly higher risk of HF hospitalization associated with digoxin. A secondary analysis of the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial similarly demonstrated that when digoxin use was treated as a time-varying exposure, it was associated with an increased adjusted rate of death (HR, 1.42; 95% CI, 1.09–1.86) in patients with atrial fibrillation.[27]

A post hoc analysis of the DIG trial by Rathore et al[28] suggested that the effectiveness and safety of digoxin may vary by serum digoxin concentration. In the DIG trial, patients had digoxin levels measured at 4 weeks and 1 year and were routinely followed up for signs of digoxin toxicity at 4 weeks, 4 months, and every 4 months thereafter. In our cohort, there was no significant difference in serum digoxin concentration between those who died and those who did not die, but levels were not checked in 30% of patients and were checked only once in an additional 27% of patients, which likely reflects the community practice of checking levels only in cases of suspected digoxin toxicity. Because many patients in our cohort did not have digoxin levels and the time from digoxin initiation to drawing a digoxin level was highly variable, we could not evaluate whether digoxin level modified the effect of digoxin on outcomes. However, differences in digoxin level testing, intensity of follow-up to assess for digoxin toxicity, and digoxin administration patterns between the DIG trial and our contemporary community-based cohort may also account for the differences in study findings.

Our results challenge the post hoc analysis of the DIG trial by Rathore et al,[11] which showed that digoxin was associated with a significantly higher risk of death among women

(HR, 1.23; 95% CI, 1.02–1.47) but not men (HR, 0.93; 95% CI, 0.85–1.02; *P*=0.014 for the interaction). The authors suggested that their results may be because of sex-associated differences in the pharmacokinetics of digoxin, which would suggest that lower dosing may be required for women to maintain an optimal serum digoxin concentration. However, differential pharmacokinetics for digoxin by patient sex has not been demonstrated in subsequent years, and our results showed that the outcomes associated with digoxin use did not vary in men and in women.

Our study results should be interpreted in the context of several important caveats. As an observational study of outcomes associated with a therapy, we cannot fully rule out the possibility of residual confounding. Digoxin is currently indicated in patients with systolic HF and persistent symptoms despite maximal medical therapy, and we may not have completely eliminated confounding by indication. However, we controlled for an extensive set of comorbid conditions, longitudinal concomitant HF-specific and other cardiovascular therapies, longitudinal measures of targeted laboratory results, and a measure of overall health status, that is, number of outpatient visits in the year before cohort entry, as well as a propensity score for digoxin initiation, in our extended Cox regression analysis. We also focused on a contemporary sample of newly diagnosed patients with HF to capture the full natural history of patients, as well as new digoxin use, to avoid biases associated with examining prevalent therapy and outcomes. Finally, even though the study was conducted within a large healthcare delivery system in northern California, the results may not be fully generalizable to other populations cared for in different settings.

In conclusion, we found that incident digoxin use was associated with a higher risk of death but no significant difference in hospitalization for HF in a large, diverse, community-based cohort of adults with newly diagnosed systolic HF. These results were consistent in men and women and in concurrent β-blocker users and nonusers. Our findings suggest that the use of digoxin should be re-evaluated for the treatment of systolic HF in the modern era.

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Disclosures

None.

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