Published in final edited form as:
Int J Cardiol. 2008 January 11; 123(2): 138–146.

Effects of Digoxin at Low Serum Concentrations on Mortality and Hospitalization in Heart Failure: A Propensity Matched Study of the DIG Trial

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Abstract

Background—In heart failure (HF), digoxin at low serum digoxin concentrations (SDC) reduces all-cause mortality and HF hospitalizations. However, the effects of digoxin on other cause-specific outcomes have not been studied in a propensity matched cohort.

Methods—The Digitalis Investigation Group trial, conducted during 1991–1993, enrolled 7788 ambulatory chronic HF patients. This analysis focuses on 4843 patients: 982 receiving digoxin with low (0.5–0.9 ng/ml) SDC at one month, and 3861 receiving placebo and alive at one month. Propensity scores for low SDC, calculated using a non-parsimonious multivariable logistic regression model, were used to match 982 low-SDC patients with 982 placebo patients. Matched Cox regression analyses were used to determine the effect of digoxin at low SDC on outcomes.

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Contributors
Ali Ahmed conceived the study hypothesis and design, and wrote the first and the subsequent drafts of the paper. Ali Ahmed did the biostatistical analyses in consultation with Thomas Love. All authors interpreted the data, participated in critical revision of the paper for important intellectual content, and approved the final version of the article. Ali Ahmed had full access to the data.

Dedication
The authors wish to dedicate this article to the memories of Thomas W. Smith, MD (1936–1997) and Richard Gorlin, MD (1926–1997) who played a crucial role in enhancing our understanding of digoxin in heart failure and in the planning and conduct of the DIG trial.

Results—All-cause mortality occurred in 315 placebo (rate, 1071/10000 person-years) and 288 low-SDC digoxin (rate, 871/10000 person-years) patients, respectively, during 2940 and 3305 years of follow up (hazard ratio {HR}, 0.81, 95% confidence interval {CI}, 0.68–0.98; p=0.028). Cardiovascular hospitalizations occurred in 493 placebo (2359/10,000 person-year) and 471 low-SDC digoxin (1963/10,000 person-year) patients, respectively during 2090 and 2399 years of follow up (HR, 0.82, 95% CI, 0.70–0.95; p=0.010). Low-SDC digoxin to placebo HR (95%CI) for HF mortality and HF hospitalizations were respectively, 0.65 (0.45–0.92; P=0.015) and 0.63 (0.52–0.77; P<0.0001). Low-dose digoxin (<=0.125 mg/day) was the strongest independent predictor of low SDC (adjusted odd ratio, 2.07, 95% CI 1.54–2.80).

Conclusions—Digoxin at low SDC significantly reduced mortality and hospitalizations in ambulatory chronic systolic and diastolic HF patients.

Keywords

Digoxin; Low Dose; Low Serum Concentration; Heart Failure; Mortality; Hospitalization

Introduction

Digoxin is the oldest and one of the least expensive heart failure drugs. It is approved by the United States Food and Drug Administration for use in heart failure. [1, 2] Digoxin reduces hospitalizations due to worsening heart failure without increasing mortality. [3–5] It is recommended by major national heart failure guidelines. [6–9] Yet, the use of digoxin is in decline, in part due to its lack of mortality benefit. [10–12] Therapeutic and toxic effects of digoxin are related to its dose and serum digoxin concentrations (SDC). [4, 13, 14] However, reports suggesting no survival benefit of digoxin or harmful effects of digoxin in women did not account for SDC. [3, 15] Digoxin at low SDC appears to reduce mortality in both men and women with heart failure. [4, 14] However, results of these post-hoc analyses were based on traditional multivariable risk adjustments. [16, 17]

A recent comprehensive post-hoc analysis of the DIG trial demonstrated that compared with heart failure patients receiving placebo, those receiving digoxin at low (0.5–0.9 ng/ml) SDC had significant reduction in all-cause mortality and all-cause hospitalizations. [4] A propensity score analysis confirmed the effect of digoxin at low SDC on mortality and heart failure hospitalization. [4] However, the effects of digoxin at low SDC on other cause-specific outcomes have not been studied in a propensity-matched cohort. As in randomization, propensity score matching allows elimination of baseline covariate imbalance without access to outcomes data. [17–20] In addition, propensity score technique allows objective estimation of bias reduction. [20, 21] The purpose of this analysis is to examine the effect of digoxin at low SDC on various cause-specific outcomes in a propensity score-matched cohort of heart failure patients.

Materials and Methods

Study Design

Retrospective propensity matched analysis of the DIG trial, which was conducted in the U.S. (186 centers) and Canada (116 centers) in the early 1990's. The design and the results of the DIG trial has been described previously. [3, 22]

Patients

Of the 7788 heart failure patients with normal sinus rhythm in the DIG trial, 6,800 had left ventricular ejection fraction (LVEF) ≤45% and 988 had LVEF >45%. Most patients were receiving angiotensin-converting enzyme (ACE) inhibitors and diuretics. Data on beta-blockers were not collected. The current analysis was restricted to 982 patients who were

receiving digoxin and had low (0.5–0.9 ng/ml) SDC at one month after randomization, and 3,861 patients receiving placebo, who were alive at one month. SDC 0.5–0.9 ng/ml has been shown to be therapeutic in prior studies. [4, 14] Specimens for SDC were analyzed in a central laboratory. [3]

Outcomes

Primary outcomes were mortality and hospitalizations due to all causes, cardiovascular causes, and worsening heart failure. Data on vital status were 99% complete. [4] Secondary outcomes included other cause-specific deaths and hospitalizations.

Bias Reduction by Propensity Score Matching

We compared baseline characteristics between treatment groups using Pearson chi-square and Wilcoxon rank-sum tests. Patients with low SDC were younger and less likely to have severe heart failure or to have chronic renal dysfunction (estimated glomerular filtration rate < 60 ml/min/1.73 square meter). [23] To achieve balance in baseline covariates, we matched all 982 low SDC patients to 982 unique patients in the placebo group, who had very similar propensities for low SDC (Figure 1). [24] We calculated propensity scores for low SDC, that is the conditional probability of developing low SDC, for all 4,843 patients using a non-parsimonious multivariable logistic regression model incorporating all measured baseline characteristics. [4, 20] To avoid inflated significance in baseline covariate imbalance in the pre-match cohort, we identified a random subset of 982 patients from the placebo group.

Assessment of Bias Reduction: Absolute Standardized Differences

Covariate imbalance before and after propensity score matching was estimated using absolute standardized differences between the two treatment groups. [4, 20, 21, 25, 26] A standardized difference of less than 10% is taken to indicate a well-balanced covariate. [20, 21, 26] The standardized difference in propensity score between placebo and low SDC patients before and after matching were respectively 48% and 0.0%, indicating substantially improved covariate balance after matching. Placebo-low SDC absolute standardized differences for age, serum creatinine, and diuretic use were respectively 10%, 32%, and 12% before matching and 1%, 0%, and 2% after matching.

Statistical analysis

We used Kaplan-Meier analysis and matched Cox proportional hazards analyses to determine association between digoxin at low SDC and various outcomes. Proportional hazards assumptions were checked using log-minus-log scale survival plots for patients in the two treatment groups. To determine whether the effect of digoxin was homogeneous, we estimated the effects of low SDC (versus placebo) on all-cause mortality in various subgroups of patients. Finally, we identified predictors of low SDC among patients receiving digoxin using logistic regression analysis. [4]

We conducted formal sensitivity analyses to describe the weight of our evidence by quantifying the degree of hidden bias that would need to be present to invalidate our main conclusions. All statistical tests were evaluated using two-tailed 95% confidence levels, and data analyses were performed using SPSS for Windows version 14. [27]

Results

Patient Characteristics

Patients had a mean age of 63 years, 21% were women, 13% non-white, and 11% had LVEF >45%. Among the 982 low SDC patients, 17%, 73% and 11% respectively were receiving

digoxin ≤0.125 mg, 0.25 mg and >0.25 mg per day, with a median dose of 0.25 mg/day. After matching, compared to placebo patients, those with low SDC were balanced in terms of all measured covariates (Table 1).

Digoxin and Mortality

During 42 months of median follow-up, 31% patients died from all causes, including 24% from cardiovascular causes, and 10% from worsening heart failure. Kaplan-Meier plots for death due to all causes are displayed in Figure 2.

Mortality due to all causes occurred in 315 patients receiving placebo during 2,940 years (1,071/10,000 person-year) and 288 patients receiving digoxin at low SDC during 3,305 years (871/10,000 person-year) of follow up (hazard ratio, 0.81, 95% confidence interval, 0.68–0.98; p=0.028; Table 2). This is consistent with our prior report of reduced all-cause mortality associated with low SDC (HR, 0.81; 95% CI, 0.67–0.97), using a somewhat different cohort of patients in the placebo group. [4]

When extrapolated to the US population, this represented a potential annual savings of about 100,000 lives if all of the estimated 5 million heart failure patients had similar characteristics to the DIG participants and were receiving digoxin at low SDC. Incidence rates and risks for cause-specific deaths in placebo and low SDC patients before and after matching are displayed in Table 2.

Our sensitivity analysis suggests that for an unmeasured binary covariate (unrelated to covariates in our propensity model) to explain away our results, that unmeasured covariate would need to increase the odds of developing low SDC by at least 48% and would also need to be a near-perfect predictor of all-cause mortality, at the $p<0.05$, suggesting that these results are at least somewhat resistant to hidden bias. An appropriate matched-samples comparison of hazard rates gave a Z-statistic of 2.20 (two-tailed P=0.028) for the comparison of low SDC to placebo.

Digoxin and Hospitalization

Overall 64% patients were hospitalized for all causes including 49% from cardiovascular causes and 26% from worsening heart failure. Kaplan-Meier plots for hospitalizations due cardiovascular causes, and heart failure are displayed in Figure 2.

Compared with 639 all-cause hospitalizations in placebo patients during 1,795 years (3,560/10,000 person-year), there were 625 all-cause hospitalizations in low SDC patients during 2,032 years (3,076/10,000 person-year) of follow up (HR, 0.92, 95% CI, 0.81–1.06; p=0.262; Table 3). Extrapolated to the US population, this would represent a potential annual reduction in total hospitalizations by over 240,000. The association between low SDC and all-cause hospitalization became significant (HR 0.83, 95% CI, 0.75–0.93; p=0.001) in a cohort with 1:3 matching (916 digoxin patients matched to 2,738 placebo patients; absolute standardized difference in propensity score=0.6%).

Cardiovascular hospitalizations occurred in 493 placebo patients during 2,090 years (2,359/10,000 person-year) and 471 low SDC patients during 2,399 years (1,963/10,000 person-year) of follow up (HR, 0.82, 95% CI, 0.70–0.95; p=0.010; Table 3). Extrapolated to the US population, this would potentially prevent about 200,000 cardiovascular hospitalizations annually.

Hospitalizations due to worsening heart failure occurs in 287 placebo patients during 2,479 years (1,158/10,000 person-year) and 229 low SDC patients during 2,934 years (781/10,000 person-year) of follow up (HR, 0.63, 95% CI, 0.52–0.77; p<0.0001; Table 3. Extrapolated to

the US population, this represented a potential reduction of about 190,000 heart failure hospitalizations in one year.

Incidence rates and risks for other cause-specific hospitalizations in patients receiving placebo and digoxin at low SDC in the propensity score-matched cohort are also displayed in Table 3.

Subgroup Analysis

Reduction in mortality associated with use of digoxin at low SDC was noted in various subgroups of patients, including both sexes (p for interaction=0.840) and regardless of LVEF (p for interaction=0.373; Figure 3). The effects of digoxin among nonwhites (versus whites; p for interaction =0.046) and those receiving diuretics (versus not receiving; p for interaction=0.027; Figure 3) were significantly different.

Predictors of Low SDC

Daily dose of digoxin was not a significant predictor of SDC in bivariate analysis. However, when adjusted for other predictors of SDC, low (≤0.125 mg/day) dose of digoxin was a significant predictor of low SDC (adjusted odds ratio, 2.07, 95% CI, 1.54–2.80; p<0.0001). Other independent predictors of SDC included age, chronic kidney disease, diuretic use, and pulmonary congestion, all of which lowered the odds of achieving a low SDC (Figure 4).

Discussion

The findings of the current analysis demonstrate that therapy with digoxin at low SDC (0.5–0.9 ng/ml) is associated with reduction in broader natural history endpoints such as all-cause mortality and cardiovascular hospitalizations in chronic heart failure. We also noted that low doses (≤0.125 mg/day) of digoxin are likely to achieve low SDC. Despite recent advances in therapy, heart failure is associated with high mortality and hospitalizations. Our data suggest that if used in low doses to achieve low SDC, digoxin can play a significant role in heart failure care.

Potential Mechanism of Action

Beneficial effects of digoxin at low SDC are primarily due to its effect on neurohormonal system. [6, 28] By inhibiting the sodium-potassium adenosine tri-phosphate pump in renal tubules and vagal afferent fibers, digoxin suppresses both the renin- angiotensin-aldosterone[29–31] and the sympathetic nervous systems. [32, 33] This also explains the beneficial role of digoxin in diastolic heart failure. [5] It is believed that the inhibitory effect of digoxin on neurohormones in heart failure is optimum at low doses and low SDC. [2, 28] Low SDC also reduce the risk of digoxin toxicity and the morbidity and mortality associated with it. [34]

Digoxin associated reduction in death due to non-cardiovascular causes may be due to misclassification of causes of death, which might also explain non-significance of its effects on cardiovascular mortality. Increased risk of coronary revascularizations among low SDC patients may be due to their longer survival. However, low SDC was not associated with myocardial infraction or unstable angina (Table 3). The less pronounced and non-significant benefit of low SDC in patients receiving (versus not receiving) diuretics may be associated with diuretic-associated subsequent increase in SDC (Figure 3).[34] Our finding of no effect of digoxin in non-white patients lacks biological basis and could be due to chance. [4]

Clinical Implications

Our findings support a more expanded role of digoxin in heart failure. Digoxin should be used in those who continue to remain symptomatic despite optimum therapy with ACE inhibitors or angiotensin receptor blocker and beta-blockers, or who cannot tolerate or afford these drugs.

This is particularly important as about half of all heart failure patients do not receive therapy with ACE inhibitors or beta-blockers. [2, 10] Because most heart failure patients are elderly and many suffer from renal dysfunction, a starting dose of 0.125 mg/day of digoxin would be reasonable for most patients. If symptoms persist, dose may be increased in young, male patients with normal kidney function. About half of the patients in our analysis were <65 years and 73% of were receiving 0.25 mg/day of digoxin, yet achieved low SDC. In patients who are elderly, female, have chronic renal dysfunction, pulmonary congestion, or are receiving diuretics, any dose increase should be guided by SDC. Heart failure patients with multiple risk factors for high SDC should receive 0.125 mg of digoxin every other day. [4] We estimated that use of digoxin at low SDC in all 5 million heart failure patients in the US would prevent over 190,000 heart failure hospitalizations (Table 3). This will likely offset any cost associated with testing of SDC in select heart failure patients.

Comparison with Prior Studies

The effect of digoxin in reducing hospitalization due to worsening heart failure is now well recognized. [3, 5] Recent evidence suggests that digoxin-associated reduction in heart failure hospitalizations at low SDC (adjusted HR, 0.62; $p<0.0001$) is not further improved at high SDC (adjusted HR, 0.68; $p<0.0001$). [4] Therefore, the long-term benefit of digoxin seems to be maximized if a low SDC can be achieved. We observed that low daily doses are strong predictors of low SDC. The findings from the current analysis based on propensity score analysis provide more robust evidence that digoxin at low SDC reduces major natural history endpoints in heart failure. DIG participants were in general a decade younger than heart failure patients seen in clinical practice and the vast majority had NYHA class I–II symptoms. Therefore, the effects of digoxin at low SDC will probably be more pronounced in real-life heart failure patients who are older and have more advanced heart failure and comorbidity burden. [35]

Strengths and Limitations

One of the strengths of our analysis is our use of propensity score matching. We assembled a cohort in which placebo and low SDC patients were balanced in all measured covariates. More importantly, our study cohort was assembled prior to occurrence of outcomes and without access to the outcomes data as would be used in a randomized trial. [17] Furthermore, propensity score technique allows objective estimation of pre-match imbalances and post-match balances in baseline covariates. When randomization is unethical or impractical, propensity score methods provide reliable, high-quality evidence using non-randomized designs. [19] A review of the 2005 ACC/AHA heart failure guidelines suggest of the 11 Class I recommendations for Stage C heart failure, 1 was based on level C evidence and 4 were based on level B evidence. Our data provide the strongest evidence to date of the benefit of low-dose digoxin at low SDC.

The key limitation of the propensity score analysis is that it cannot account for unmeasured confounders. Sensitivity analyses can determine the effect of such a potential confounder, however, it cannot determine if such a bias did in fact exist. [20, 36] Our sensitivity analysis suggest that the results of our study were fairly insensitive to potential hidden covariates. [36] Heart failure patients in the DIG trial were not receiving beta-blockers or aldosterone antagonists. However, data from the spironolactone and carvedilol trials in heart failure demonstrate that digoxin is effective when co-administered with these drugs. [37, 38] Results of our study are based on male and relatively younger patients with mild to moderate heart failure and normal sinus rhythm.

Conclusions

In conclusion, the results of our analysis based on a propensity-matched cohort of heart failure patients suggest that digoxin in low doses and at low SDC reduced major natural history

endpoints including overall mortality and cardiovascular hospitalizations. Digoxin should be used in low doses to achieve low SDC in heart failure patients who are symptomatic despite therapy with ACE inhibitors or angiotensin receptor blockers, and beta-blockers, or who cannot tolerate or afford these drugs.

Acknowledgement

"The Digitalis Investigation Group (DIG) study was conducted and supported by the NHLBI in collaboration with the DIG Investigators. This Manuscript was prepared using a limited access dataset obtained by the NHLBI and does not necessarily reflect the opinions or views of the DIG Study or the NHLBI."

Funding/Support: Dr. Ahmed is supported by the National Institutes of Health through grants from the National Institute on Aging (1-K23-AG19211-04) and the National Heart, Lung, and Blood Institute (1-R01-HL085561-01 and P-50-HL077100).

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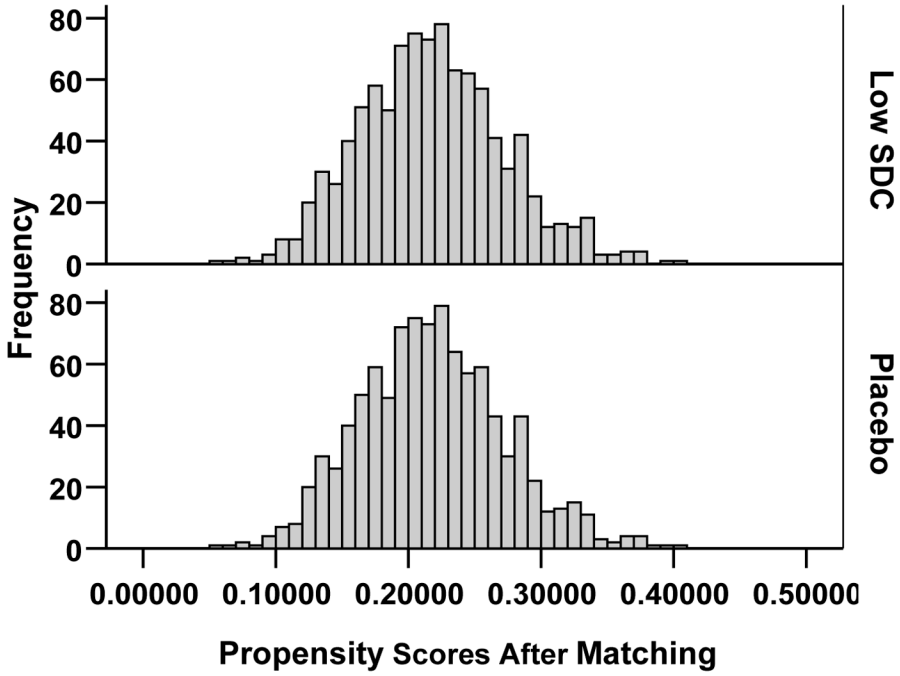
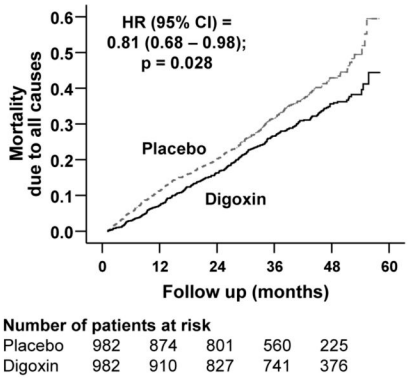


Figure 1.
Distribution of propensity score for the low serum digoxin concentrations, for patients receiving digoxin and placebo, before (a) and after (b) matching

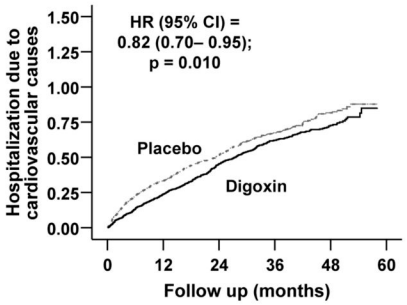
Figure 2a



Number of patients at risk

Placebo	982	874	801	560	225
Digoxin	982	910	827	741	376

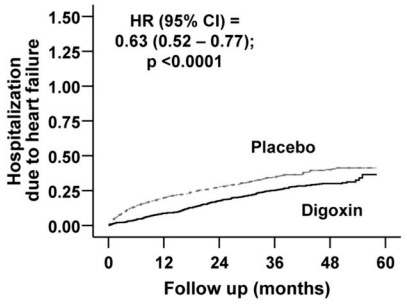
Figure 2b



Number of patients at risk

Placebo	982	668	530	341	133
Digoxin	982	734	556	444	213

Figure 2c



Number of patients at risk

Placebo	982	752	659	444	178
Digoxin	982	844	715	616	305

Figure 2.

Kaplan-Meier plots for (a) mortality due to all-causes, and hospitalizations due to (b) cardiovascular causes, and (c) worsening heart failure

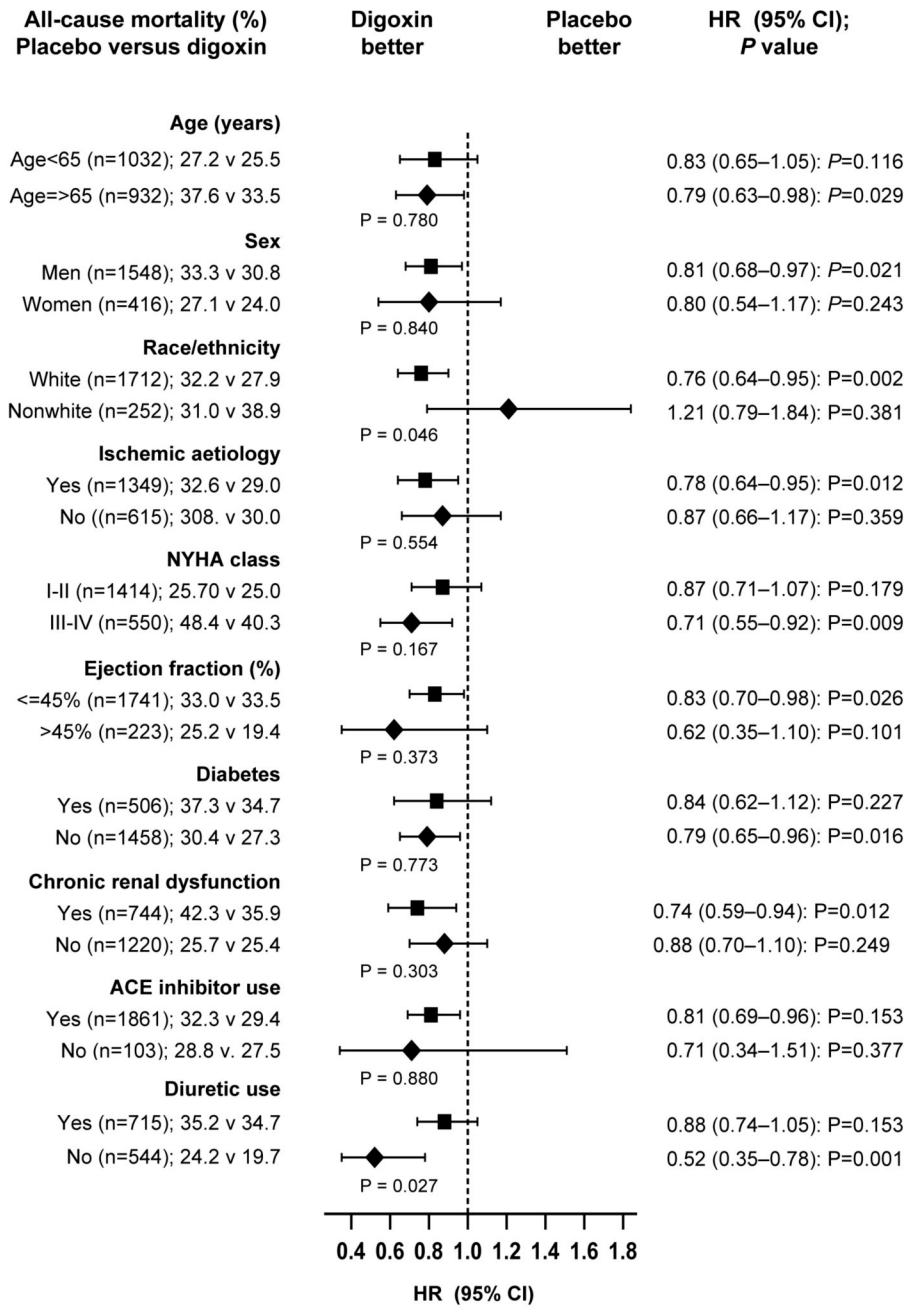


Figure 3.

Effects of digoxin at low serum digoxin concentrations (0.5–0.9 ng/ml) on all-cause mortality in subgroups of propensity score matched heart failure patients (ACE=angiotensin-converting enzyme; CI= confidence interval; HR=hazard ratio; = NYHA=New York Heart Association)

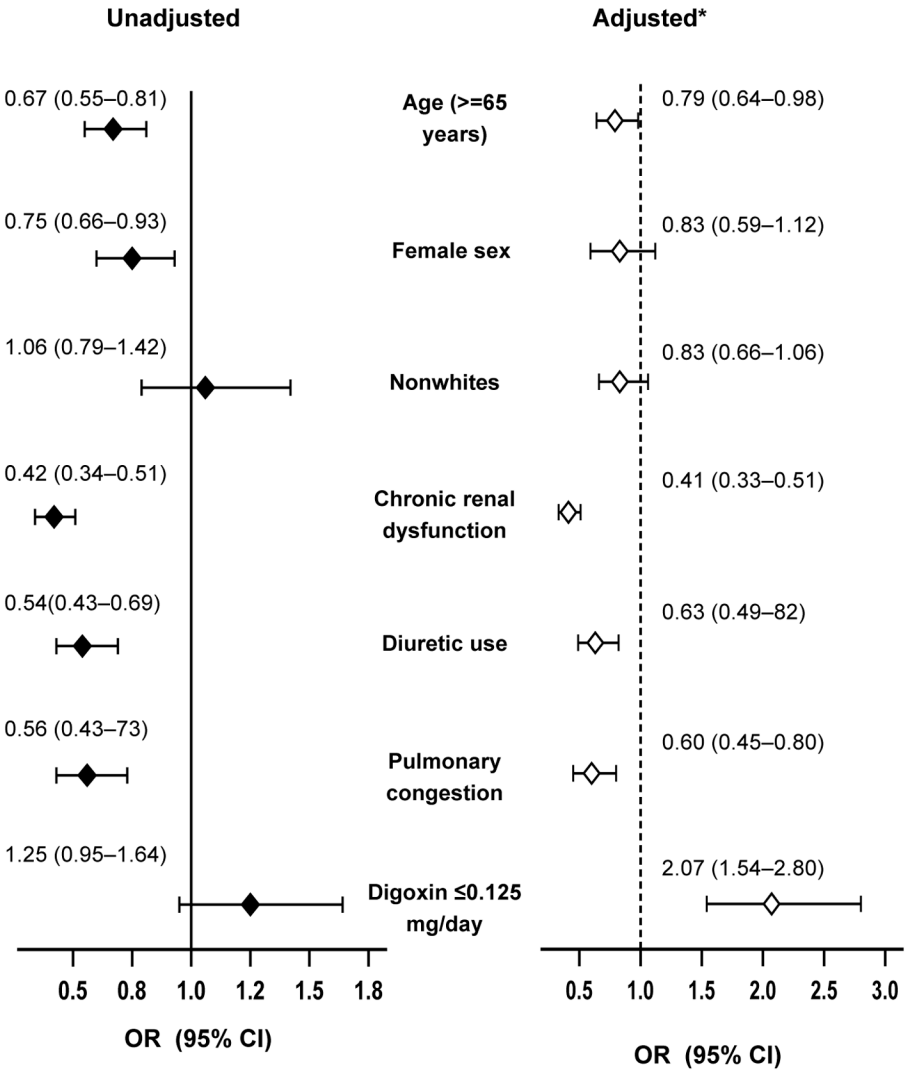


Figure 4.

Predictors of low (0.5–0.9 ng/ml) serum digoxin concentrations (SDC). An odds ratio >1 indicates increased odds of developing low SDC. For example, when adjusted for other predictors of SDC, presence of chronic renal dysfunction was associated with significant 59% lower odds of developing low SDC. Similarly, independent of other covariates, use of digoxin at ≤0.125 mg/day was associated with significant 107% higher odds of developing low SDC (*Adjusted for other covariates shown in the Figure, namely age, sex, race, chronic renal dysfunction, diuretic use, pulmonary congestion, and digoxin at ≤0.125 mg/day).
Chronic renal dysfunction was defined as estimated glomerular filtration rate <60 ml/m/1.73 sq. m. by Modification of Diet in Renal Disease methods; OR=odds ratio, CI=confidence interval

Int J Cardiol. Author manuscript; available in PMC 2009 January 11.

Table 1

Baseline Patient Characteristics, Before and After Propensity Score Matching

	Before matching			After matching	
N (%) or mean (±SD)	**Random Placebo (N=982)**	**P**	**Digoxin at SDC 0.5–0.9 (N=982)**	**P**	**Matched Placebo (N=982)**
Age (years)	64.2 (±10.8)	0.004	62.8 (±10.6)	0.834	62.7 (±11.2)
Age ≥65 years	520 (53.0%)	0.034	472 (48.1%)	0.558	460(46.8%)
Female	236 (24.0%)	0.335	217 (22.1%)	0.348	199 (20.3%)
Non-white	162 (16.5%)	0.025	126 (12.8%)	1.000	126 (12.8%)
Body mass index, kg/square meter	27.6 (±5.14)	0.080	27.2 (±5.03)	0.136	26.8 (±5.0)
Duration of HF (months)	31.1 (±38.1)	0.540	32.2 (±38.7)	0.251	30 (±37)
Primary cause of HF					
Ischemic	683 (69.6%)		672 (68.4%)		677 (68.9%)
Hypertensive	98 (10.0%)		98 (10.0%)		90 (9.2%)
Idiopathic	133 (13.5%)	0.799	148 (15.1%)	0.922	147 (15.0%)
Others	68 (6.9%)		64 (6.5%)		68 (6.9%)
Comorbid conditions					
Prior myocardial infarction	629 (64.1%)	0.851	624 (63.5%)	0.708	615 (62.6%)
Current angina	277 (28.2%)	0.479	262 (26.7%)	0.759	256 (26.1%)
Hypertension	485 (49.4%)	0.021	433 (44.1%)	1.000	432 (44.0%)
Diabetes	294 (29.9%)	0.147	265 (27.0%)	0.235	241 (24.5%)
Chronic renal dysfunctioin	460 (46.8%)	<0.0001	368 (37.5%)	0.745	376 (38.3%)
Dose of study medication	0.246 (±0.07)	0.596	0.244 (±0.07)	0.317	0.247 (±0.07)
Medications					
Pre-trial digoxin use	409 (41.6%)	0.033	457 (46.5%)	0.104	494 (50.3%)
ACE inhibitors	917 (93.4%)	0.213	931 (94.8%)	0.920	930 (94.7%)
Diuretics	768 (78.2%)	0.006	715 (72.8%)	0.650	705 (71.8%)
Symptoms and signs of heart					
Dyspnea at rest	225 (22.9%)	0.077	192 (19.6%)	0.820	188 (19.1%)
Dyspnea on exertion	736 (74.9%)	0.470	721 (73.4%)	0.760	714 (72.7%)
Jugular venous distension	133 (13.5%)	0.172	112 (11.4%)	1.000	113 (11.5%)
Third heart sound	234 (23.8%)	0.674	243 (24.7%)	0.793	237 (24.1%)
Pulmonary râles	149 (15.2%)	0.368	134 (13.6%)	0.791	129 (13.1%)
Lower extremity edema	207 (21.1%)	0.193	183 (18.6%)	0.954	185 (18.8%)
NYHA functional class					
I	141 (14.4%)		173 (17.6%)		181 (18.4%)
II	558 (56.8%)	0.273	536 (54.6%)	0.845	524 (53.4%)
III	268 (27.3%)		259 (26.4%)		259 (26.4%)
IV	15 (0.8%)		14 (1.4%)		18 (1.8%)
Heart rate (/minute),	78.3 (±12.4)	0.067	77.2 (±12.7)	0.329	77.8 (±12.5)
Blood pressure (mm Hg)					
Systolic	127.8 (±20.0)	0.171	126.6 (±19.8)	0.926	126.5 (±20.0)
Diastolic	75.2 (±11.3)	0.543	75.6 (±10.8)	0.753	75.4 (±11.1)
Chest radiograph findings					
Pulmonary congestion	128 (13.0%)	0.372	114 (11.6%)	0.780	119 (12.1%)
Cardiothoracic ratio >0.5	586 (59.7%)	0.217	558 (56.8%)	0.891	554 (56.4%)
Serum creatinine (mg/dL)	1.28 (±0.37)	<0.0001	1.21 (±0.32)	0.675	1.22 (±0.32)
Ejection fraction (%)	31.9 (±12.5)	0.958	31.9 (±12.1)	0.554	31.6 (±12.5)
Ejection fraction >45%	130 (113.2%)	0.146	108 (11.0%)	0.670	115 (11.7%)

Table 2

Effects of Digoxin at Low Serum Digoxin Concentrations (0.5 – 0.9 ng/ml) on Cause-Specific Mortalities

	Placebo (N=982)	Digoxin (N=982)	Absolute difference* (per 10,000 person-year)	Lives to be saved for ~5 million patients in one year	Hazard ratio (95% confidence interval)†	P value
	Death rates (per 10,000 person-year of follow up)					
All-cause	1,071	871	− 200	− 100,011	0.81 (0.68–0.98)	0.028
Cardiovascular	813	717	− 96	− 47,915	0.90 (0.73–1.11)	0.313
Heart failure‡	354	260	− 94	− 46,765	0.65 (0.45–0.92)	0.015
Other cardiac§	415	421	+ 6	+ 2,804	1.09 (0.83–1.44)	0.530
Other vascular¶	44	36	− 8	− 3,955	1.00 (0.42–2.40)	1.000
Non-cardiovascular	187	103	− 84	− 42,100	0.49 (0.30–0.81)	0.005
Unknown	71	51	− 20	− 9,996	0.77 (0.37–1.57)	0.467

*Absolute differences in rates of mortality per 10,000 person-year of follow up were calculated by subtracting the death rates in the placebo group from the death rates in the digoxin group (before values were rounded)

†Hazard ratios and confidence intervals (CI) were estimated from the Cox proportional-hazards models

‡This category includes patients who died from worsening heart failure, even if the final event was an arrhythmia

§This category includes deaths presumed to result from arrhythmia without evidence of worsening heart failure and deaths due to atherosclerotic coronary disease, bradyarrhythmias, low-output states, and cardiac surgery

¶This category includes deaths due to stroke, embolism, peripheral vascular disease, vascular surgery, and carotid endarterectomy

Table 3

Effects of Digoxin at Low Serum Digoxin Concentrations (0.5 – 0.9 ng/ml) on Cause-Specific Hospitalizations

Cause for hospitalization*	Placebo (N=982)	Digoxin (N=982)	Absolute difference* (per 10,000 person-year)	Reduction (−) in hospitalizations for ~5 million heart failure patients in one year	Hazard ratio (95% confidence interval)†	P value
	Hospitalization rates (per 10,000 person-year of follow up)					
All-cause	3,560	3,076	− 484	− 242,051	0.92 (0.81–1.06)	0.262
Cardiovascular	2,359	1,963	− 396	− 197,767	0.82 (0.70–0.95)	0.010
Worsening heart failure‡	1,158	781	− 377	− 188,610	0.63 (0.52–0.77)	<0.0001
Ventricular arrhythmia, cardiac arrest	128	145	+18	+8,896	1.06 (0.66–1.71)	0.808
SV arrhythmia§	150	120	− 30	− 14,947	0.80 (0.50–1.27)	0.340
AV block, bradyarrhythmias	10	15	+5	+2,479	1.50 (0.25–8.98)	0.657
Suspected digoxin toxicity	31	37	+6	+2,923	1.43 (0.54–3.75)	0.469
Myocardial infarction	173	154	− 19	− 9,374	0.78 (0.49–1.24)	0.293
Unstable angina	422	414	− 8	− 4,116	1.09 (0.82–1.46)	0.551
Stroke	167	130	− 37	− 18,338	0.68 (0.42–1.13)	0.136
Coronary revascularization¶	51	86	+35	+17,347	2.08 (1.05–4.15)	0.037
Cardiac transplantation	24	27	+3	+1,774	1.00 (0.35–2.85)	1.000
Other cardiovascular**	408	427	+18	+9,247	1.10 (0.83–1.38)	0.577
Respiratory infection	247	213	− 33	− 16,864	0.84 (0.59–1.21)	0.358
Other non-cardiovascular	1220	1226	+6	+2,959	1.07 (0.89–1.28)	0.484
Unspecified	20	15	− 5	− 2,659	0.67 (0.19–2.36)	0.530
Number of hospitalizations	10,117	8,558	− 1,559	− 779,460		

*Data shown include the first hospitalization of each patient due to each cause.

†Absolute differences were calculated by subtracting the percentage of patients hospitalized in the placebo group from the percentage of patients hospitalized in the digoxin group (before values were rounded).

‡Hazard ratios and confidence intervals (CI) were estimated from a Cox proportional-hazards models that used the first hospitalization of each patient for each reason.

§Supraventricular (SV) arrhythmias include Atrioventricular (AV) block and bradyarrhythmias

¶This category includes coronary-artery bypass grafting and percutaneous transluminal coronary angioplasty

**This category includes embolism, venous thrombosis, peripheral vascular disease, hypertension, other vascular surgery, cardiac catheterization, other types of catheterization, pacemaker implantation, installation of automatic implantable cardiac defibrillator, electrophysiologic testing, transplant-related evaluation, nonspecific chest pain, atherosclerotic heart disease, hypotension, orthostatic hypotension, and valve operation