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Digoxin Initiation and Outcomes in Patients with Heart Failure with Preserved Ejection Fraction

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Abstract

Background: Digoxin reduces the risk of heart failure hospitalization in patients with heart failure with reduced ejection fraction (HFrEF). Less is known about this association in patients with heart failure with preserved ejection fraction (HFpEF), the examination of which was the objective of the current study.

Methods: In the Medicare-linked OPTIMIZE-HF registry, 7374 patients hospitalized for HF had ejection fraction ≥50% who were not receiving digoxin before admission. Of these, 5675 had a

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heart rate ≥50 beats/minute, an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2 or did not receive inpatient dialysis, and digoxin was initiated in 524 of these patients. Using propensity scores for digoxin initiation, calculated for each of the 5675 patients, we assembled a matched cohort of 513 pairs of patients initiated and not initiated on digoxin, balanced on 58 baseline characteristics (mean age, 80 years; 66% women; 8% African American). Hazard ratios (HRs) and 95% confidence intervals (CIs) for outcomes associated with digoxin initiation were estimated in the matched cohort.

Results: Among the 1026 matched patients with HFpEF, 30-day heart failure readmission occurred in 6% and 9% of patients initiated and not initiated on digoxin, respectively (HR, 0.70; 95% CI, 0.45–1.10; p=0.124). HRs (95% CIs) for 30-day all-cause readmission and all-cause mortality associated with digoxin initiation were 0.95 (0.73–1.23; p=0.689) and 0.93 (0.55–1.56; p=0.773), respectively. Digoxin initiation had no association with 6-year outcomes.

Conclusion: Digoxin initiation before hospital discharge was not associated with 30-day or 6-year outcomes in older hospitalized patients with HFpEF.

Keywords

Heart failure with preserved ejection fraction; digoxin; readmission; mortality

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Clinical efficacy and effectiveness of digoxin in improving outcomes in patients with heart failure with reduced ejection fraction (HFrEF) are well known. In the main Digitalis Investigation Group (DIG) trial, digoxin reduced the risk of heart failure hospitalization in ambulatory patients with HFrEF but had no effect on all-cause mortality.[1, 2] Digoxin use has also been shown to be associated with a lower risk of heart failure readmission in real-world older hospitalized patients with HFrEF.[3–5] As in the main DIG trial, in the ancillary DIG trial, digoxin had no effect on all-cause mortality in patients with heart failure with preserved ejection fraction (HFpEF) but there was a trend towards a reduction in heart failure hospitalization.[6–8] However, little is known about the association between digoxin use and outcomes in hospitalized patients with HFpEF in clinical practice, the examination of which was the objective of the current analysis.

Methods

Data Source and Study Population

The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) is a national hospital-based registry of patients hospitalized with decompensated HF, the details of which have been previously described.[5, 9–11] The registry is based on 48,612 hospitalizations due to HF in 259 U.S. hospitals during 2003–2004. Extensive baseline data were collected by chart abstraction. Long-term outcomes data were obtained by linking 26,376 patients to fee-for-service Medicare data.[12] Of these, 8873 had HFpEF, defined as left ventricular ejection fraction ≥50%.[13]

Assembly of an Inception Cohort without Contraindication to Digoxin Initiation

Considering the insurmountable bias associated with prevalent use of digoxin in observational studies,[14] and the emerging evidence that associations of digoxin initiation

with outcomes approach the effects observed in the main DIG trial,[4, 5, 15, 16] we assembled an inception cohort by excluding 1499 patients receiving digoxin before admission (Figure 1).[17] Even though digoxin is not recommended in patients with HFpEF, clinicians may still take traditional contraindications into account while initiating the drug. As such, we excluded 90 patients who had a heart rate <50 beats/minute and 604 patients who either had an estimated glomerular filtration rate <30 mL/min/1.73 m^2 or received inpatient dialysis. Of the remaining 5675 patients with HFpEF, digoxin was initiated in 524 (8%) patients before hospital discharge (Figure 1).

Assembly of a Balanced Cohort

In a randomized controlled trial of digoxin, the probability of receiving digoxin would be 50% for each patient regardless of whether one receives the drug or not. However, in clinical practice, many patient and care characteristics are considered before a drug is initiated. Thus, the probability of receiving a drug in the non-randomized setting may vary between 0 to 100% and the initiation of a drug is often associated with an indication bias. However, the indication bias can be attenuated by estimating the probability of receiving the drug, which is also known as propensity scores.[18, 19] We began by estimating the propensity scores for digoxin initiation prior to hospital discharge for each of the 5675 patients using a non-parsimonious multivariable logistic regression model in which digoxin initiation was the dependent variable and 58 measured baseline characteristics were used as covariates.[3, 20–22] The propensity score for the receipt of a drug for each patient is a cohort-specific relative number. For example, a patient with a systolic blood pressure of 145 mmHg in a normotensive cohort (with a mean systolic blood pressure of 125 mmHg) may have a propensity score of 65% for the receipt of an anti-hypertensive drug. However, the same patient may have a propensity score of 25% if he/she is part of a cohort with uncontrolled hypertension (with a mean systolic blood pressure of 185 mmHg). We then used a greedy matching algorithm described elsewhere to match 513 patients who were initiated on digoxin at discharge to 513 patients who were not initiated on digoxin at discharge.[23, 24] Absolute standardized differences were estimated to assess post-match balance of all 58 measured baseline characteristics.[23, 24]

Study Outcomes

The primary outcome in this study was heart failure readmission during 30 days, 2 years, and 6 years of follow-up starting from the date of hospital discharge. Secondary outcomes include all-cause readmission, all-cause mortality, the combined endpoint of HF readmission or all-cause mortality and the combined endpoint of all-cause readmission or all-cause mortality at all 3 time-periods.

Statistical Analysis

Pearson’s chi-square and Wilcoxon rank-sum tests were used to compare baseline characteristics between patients initiated and not initiated on digoxin, as appropriate. All subsequent analyses were based on the matched cohort, in which patients initiated and not initiated on digoxin were balanced on 58 baseline characteristics. Survival plots for patients initiated and not initiated on digoxin were constructed using Kaplan-Meier analysis. Cox proportional hazard analyses were used to calculate hazard ratios (HR) and 95% confidence

intervals (CI) for outcomes associated with digoxin initiation, using patients not initiated on digoxin as the reference. Since there are no clinical indications to initiate digoxin therapy for patients with HFpEF at present, we examined the output of the logistic regression model used for the estimation of propensity scores to identify significant independent predictors of initiation of digoxin in our pre-match cohort of 5675 patients. All statistical tests were two-tailed with a p-value <0.05 considered significant. SPSS, Version 24 (IBM Corp., Armonk, NY) and SAS for Windows version 9.2 (Cary, NC) were used for data analyses.

Results

Baseline Characteristics

Patients in the matched cohort had a mean age of 80 years, 66% were women, and 7% were African American. Baseline characteristics for patients receiving and not receiving digoxin before and after propensity matching are shown in Table 1. Before matching, patients initiated on digoxin were older and twice as many had atrial fibrillation, compared to those not initiated on digoxin (Table 1). The prevalence of nearly all other comorbidities was lower in the group initiated on digoxin. The distribution of all baseline characteristics was balanced after matching (Table 1). Prior heart failure hospitalization and signs and symptoms of heart failure were similar both before and after matching. After propensity score-matching, absolute standardized differences for all 58 baseline characteristics were <10% except for peripheral arterial disease (11%), <5% for 48 and <2% for 23 of the 58 baseline characteristics (Figure 2).

Digoxin Initiation and Readmission in HFpEF

Among the 1026 matched patients with HFpEF, 30-day heart failure readmission occurred in 6% and 9% of patients initiated and not initiated on digoxin, respectively (HR, 0.70; 95% CI, 0.45–1.10; p=0.124; Table 2 and Figure 2). HRs (95% CIs) for 2-year and 6-year heart failure readmission associated with digoxin initiation were 0.80 (0.64–0.99; p=0.041) and 0.87 (0.72–1.05; p=0.149), respectively (Table 2). Digoxin initiation had no associations with all-cause readmission (Table 2).

Digoxin Initiation and Mortality in HFpEF

30-day all-cause mortality occurred in 5% and 6% of patients initiated and not initiated on digoxin, respectively (HR, 0.93; 95% CI, 0.55–1.56; p=0.773; Table 2 and Figure 2). HRs (95% CIs) for 2-year and 6-year all-cause mortality associated with digoxin initiation were 0.79 (0.65–0.96; p=0.020) and 0.90 (0.78–1.05; p=0.187), respectively (Table 2).

Predictors of Initiation of Digoxin in HFpEF

Among the 5675 pre-match patients with HFpEF who were not receiving digoxin at the time of hospital admission, significant baseline predictors of initiation of digoxin were atrial fibrillation (odds ratio, 2.27; 95% CI, (1.83–2.82); p<0.001) and warfarin use (odds ratio, 2.50; 95% CI, (2.00–3.13); p<0.001; Table 3). Other significant predictors are listed in Table 3.

Discussion

Findings from the current study demonstrate that digoxin was initiated in one in ten hospitalized patients with HFpEF, nearly half of whom did not have atrial fibrillation, and that digoxin initiation had no association with heart failure readmission during 30 days and 6 years of follow-up in patients with HFpEF. Digoxin initiation had no association with other outcomes during these two timepoints. To the best of our knowledge, this is the first study to examine the relationship between digoxin initiation with outcomes in hospitalized older patients with HFpEF. The findings from the current study suggest that despite a consistent evidence of efficacy and effectiveness of digoxin in lowering the risk of HF hospitalization in patients with HFrEF, there is currently no such evidence for patients with HFpEF.

In the ancillary DIG trial, among ambulatory patients with chronic HFpEF, digoxin did not reduce the risk of heart failure hospitalization during 4 years of follow-up (HR, 0.79; p=0.094), but did during the first 2 years of follow-up (HR, 0.66; p=0.012).[6, 25] A post hoc analysis of the ancillary DIG trial did not find any evidence that digoxin lowered the risk of 30-day heart failure hospitalization.[8] The associations of digoxin initiation and heart failure readmission observed in the current study are generally consistent, albeit more modest, with those reported in the ancillary DIG trial. The lower risk of 2-year mortality observed in our study is intriguing and cannot be explained by our current understanding of the pathophysiology of HFpEF or the mechanism of action of digoxin. Even in the larger main DIG trial, digoxin did not reduce the risk of death in patients with HFrEF, and the modest reduction in the risk of 1-year mortality was not observed in subsequent years.[1, 26]

It has been suggested that at a lower serum digoxin concentration, which may be more pronounced at lower doses,[27] digoxin may act as a neurohormonal inhibitor.[28–34] In the DIG trial, compared with propensity score-matched placebo, digoxin use at serum digoxin concentration of 0.5–0.9 ng/mL was associated with a lower risk of all-cause mortality (HR, 0.81; 95% CI, 0.67–0.97, p=0.025), which was homogeneous between patients with HFrEF and HFpEF (p for interaction, 0.834).[2] Evidence also suggest that as in HFrEF, there is also neurohormonal activation in patients with HFpEF.[35] However, none of the other neurohormonal inhibitors with proven efficacy in reducing mortality and hospitalization in HFrEF has been shown to improve outcomes in HFpEF.[10, 23, 36–42] Thus, currently there is no mechanistically plausible explanation for the unexpected finding of a lower risk of all-cause mortality during 2 years of follow-up in our study.

There are several limitations with our retrospective study. Significant associations in an observational study can be subject to confounding by an unmeasured and/or unmeasurable baseline characteristic. However, key associations observed in our study were null. Sensitivity analysis can estimate the effect of an unmeasured confounder but only when there are significant associations. Our analysis was restricted to fee-for-service Medicare beneficiaries, which may limit generalizability.

Conclusions

Unlike in HFrEF, digoxin does not appear to have associations with outcomes in patients with HFpEF. Hospitalized patients with HFpEF who were initiated on digoxin prior to hospital discharge had similar 30-day and 6-year outcomes as those who were not initiated on digoxin. The lower risk of 2-year heart failure readmission, although consistent with the lower risk of 2-year hospitalization in the ancillary DIG trial, should be interpreted with caution.

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CLINICAL SIGNIFICANCE

- In hospitalized patients with HFpEF, patients initiated on digoxin had similar 30-day and 6-year readmission and mortality as those not initiated on digoxin.
- The lower risk of 2-year heart failure readmission should be interpreted with caution.
- Key predictors of digoxin initiation included atrial fibrillation and warfarin use.
- Unlike in HFrEF, digoxin use is not associated with outcomes in HFpEF.

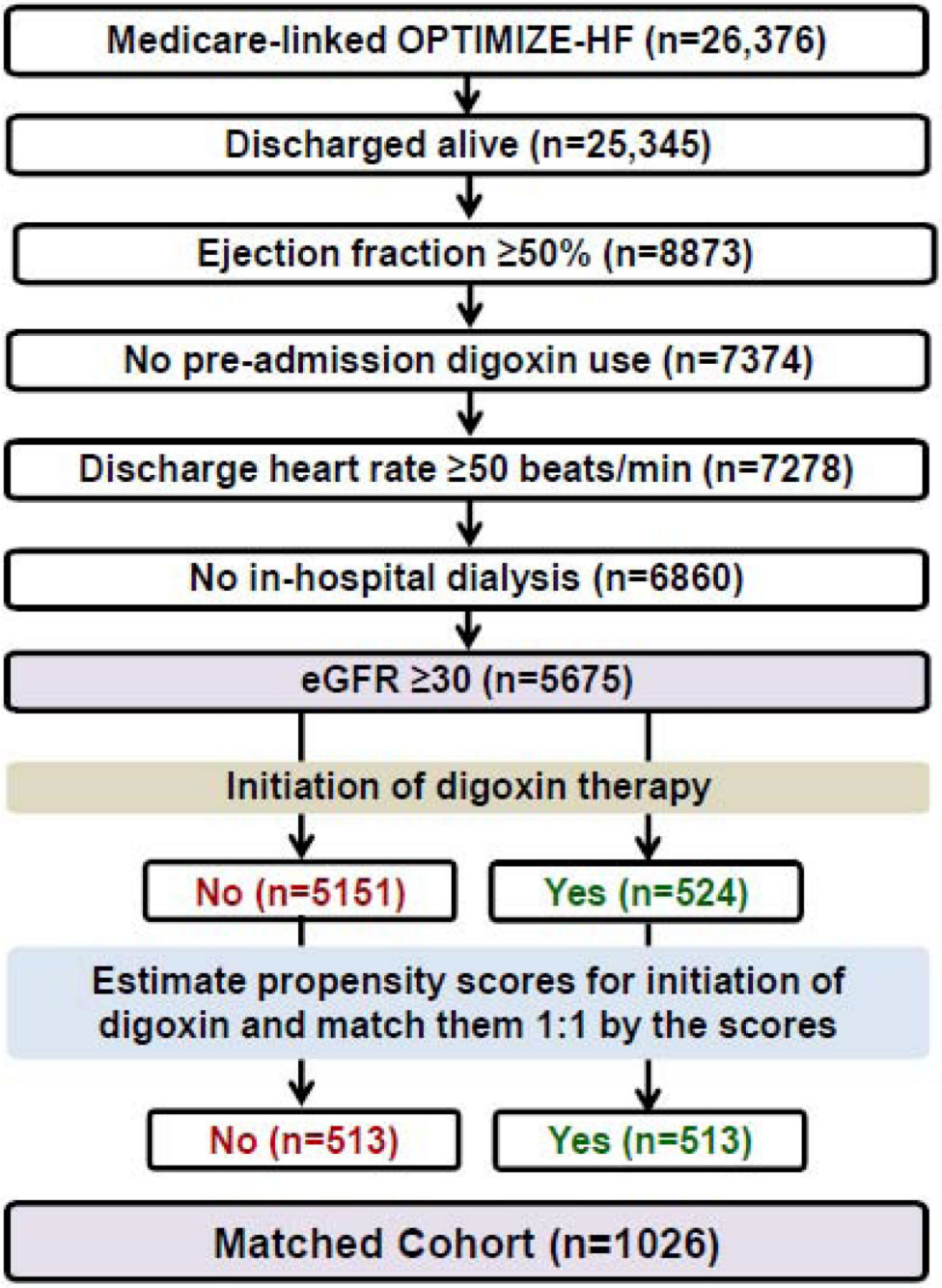

Figure 1.

Flow chart displaying assembly of matched cohorts of patients with heart failure with preserved ejection fraction, by initiation of digoxin therapy (OPTIMIZE-HF = Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure; eGFR = estimated glomerular filtration rate)

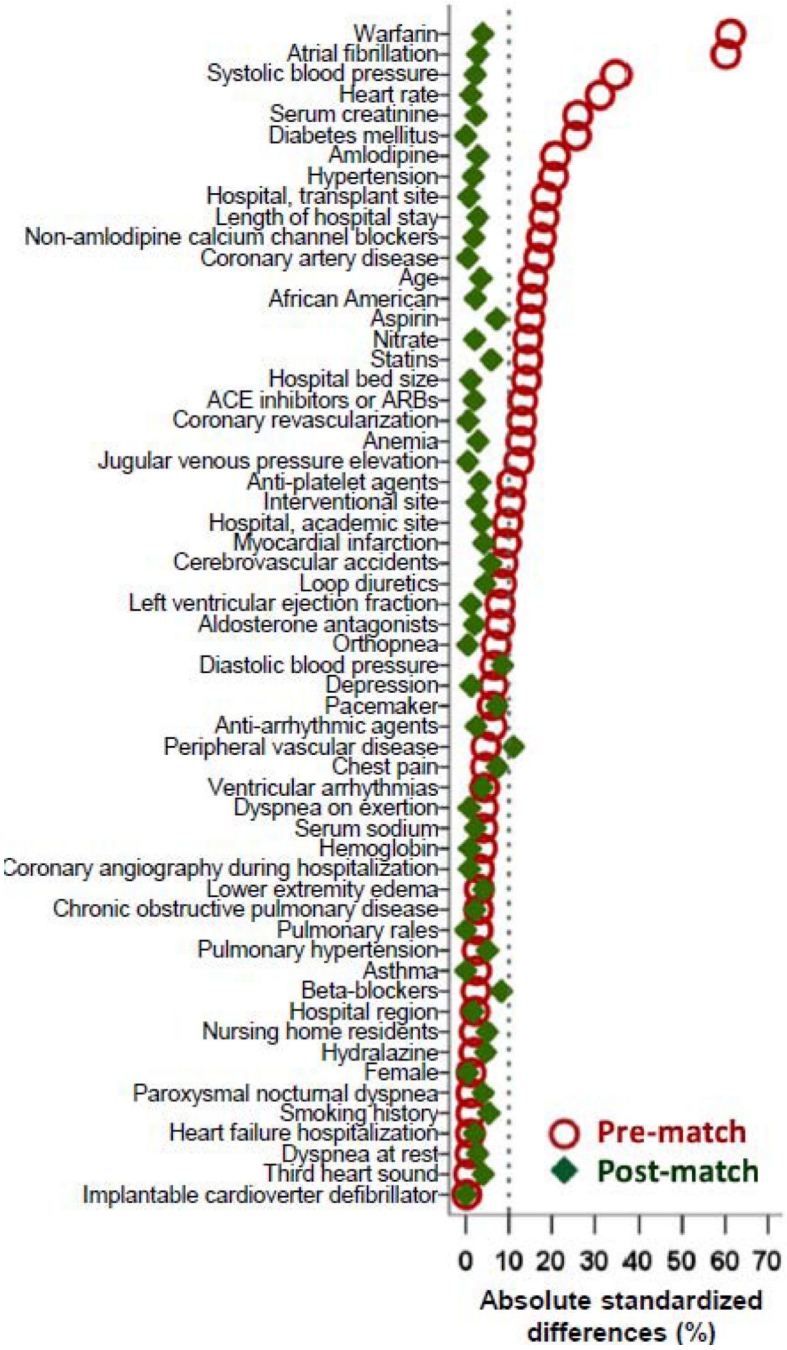

Figure 2.

Love plot displaying absolute standardized differences comparing 58 baseline characteristics of patients with heart failure and preserved ejection fraction initiated and not initiated on digoxin, before and after propensity score matching (ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blockers)

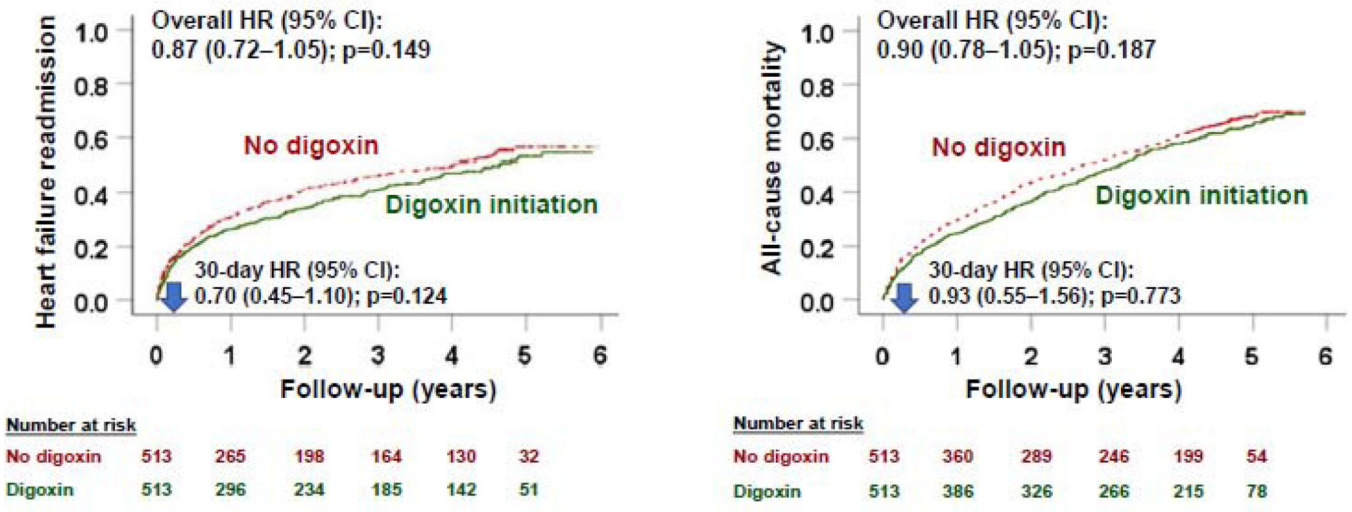

Figure 3.

Kaplan Meier plots for heart failure readmission (left) and all-cause mortality (right) during 6-years of follow up by initiation of digoxin before hospital discharge in 513 pairs of propensity score-matched patients with heart failure with preserved ejection fraction who were not receiving digoxin before hospital admission (CI = confidence interval; HR = hazard ratio)

Table 1.

Baseline characteristics by digoxin initiation before hospital discharge in patients with heart failure with preserved left ventricular ejection fraction who were not receiving digoxin prior to hospital admission

n (%) or mean (±SD)	Before propensity score matching (n=5675)			After piopensity score matching (n=1026)		
	Digoxin initiation		P value	Digoxin initiation		P value
	No (n=5151)	Yes (n=524)		No (n=513)	Yes (n=513)	
Aeb (years)	79(±10)	80 (±9)	0.001	80 (±9)	80 (±9)	0.580
Female	3431(67%)	346 (66%)	0.789	337 (66%)	336 (66%)	0.948
African American	617(12%)	39(7%)	0.002	41 (8%)	38 (7%)	0.725
Left ventricular ejection fraction (%)	59 (±7)	58 (±7)	0.089	58 (±7)	58 (±7)	0.854
Smoking within past year	559 (11%)	55 (11%)	0.803	45 (9%)	53 (10% >	0.395
Past medical history						
HF hospitalization in past 6 months	466 (9%)	49 (9%)	0.817	50 (10%)	47(9%)	0.749
Hypertension	3936(77%)	358 (6KK)	<0.001	351 (68%)	355 (69%)	0.787
Coronary artery disease	2234 (43%)	184 (35%)	<0.001	183 (36%)	184 (36%)	0.948
Myocardial infarction	818 (16%)	66 (13%)	0.048	59 (12%)	66(13%)	0.504
Coronary revascularization	1119 (22%)	87 (17%)	0.0006	88 (17%)	87(17%)	0.934
Implantable defibrillator	40 (0.8%)	4 (0.8%)	0.974	4(0.8%)	4 (0.8%)	1.000
Atrial fibrillation	1452 (28%)	297 (57%)	<0.001	293 (57%)	286 (56%)	0.659
Ventricular arrhythmias	104 (2%)	14 (3%)	0.318	11(2%)	14 (3%)	0.544
Cerebrovascular disease	901 (18%)	75 (14%)	0.066	64 (13%)	74 (14%)	0.360
Peripheral vascular disease	678 (13%)	61 (12%)	0.324	43 {8%)	60 (12%)	0.077
Diabetes mellitus	2013 (39%)	142 (27%)	<0.001	141 (28%)	141(28%)	1.000
Chronie obstructive pulmonary disease	1562 (30%)	166 (32%)	0.521	168(33%)	163 (32%)	0.738
Anemia	971 (19%)	74 (14%)	0.008	69 (14%)	74 (14%)	0.652
Admission clinical and laboratory findings						
Dyspnea on exeration	3212 (62%)	337 (64%)	0.378	332(65%)	330(64%)	0.896
Orthopnea	1267(25%)	145 (28%)	0.121	142 (28%)	143 (28%)	0.944
Paroxysmal nocturnal dyspnea	689 (13%)	68 (13%)	0.798	74 (14%)	67 {13%)	0.526
Dyspnea at rest	2246(44%)	231 (44%)	0.833	236(46%)	229(45%)	0.661
Chest pain	1198 (23%)	112 (21%)	0.330	95 (19%)	110(21%)	0.242
Jugular venous pressure elevation	1189 (23%)	149 (23%)	0.006	147(29%:	146 (29%)	0.945
Third heart sound	288 (6%)	30 (6%)	0.899	35 (7%)	30 (6%)	0.522
Pulmonary rales	3273 (64%)	340 (65%)	0.542	333 (65%)	333 (65%)	1.000
Peripheral edema	3418 (66%)	340 (65%)	0.498	327(64%)	337 (66%)	0.514
Pulse (beats per minute)	74 (±13)	79 (±16)	<0.001	79 (±14)	79 (±15)	0.854
Systolic blood presure (mm Hg)	151 (±32)	140 (±28)	<0.001	140(±29)	141 (±29)	0.727
Diastolic blood presure (mm Hg)	66 (±12)	67 (±12	0.138	66 (±12)	67 (±12)	0.173
Hemoglobin (g/dL)	12 (±3)	12 (±2)	0.461	12 (±2)	12 (±2)	0.883
Serum creatinine (mg/dL)	1.3 (±0.5)	1.2 (±4.4)	<0.001	1.2 (±0.4)	1.2 (±0.4)	0.697

n (%) or mean (±SD)	Before propensity score matching (n=5675)			After piopensity score matching (n=1026)		
	Digoxin initiation		P value	Digoxin initiation		P value
	No (n=5151)	Yes (n=524)		No (n=513)	Yes (n=513)	
Discarge medications						
ACE inhibitors or ARBs	3148 (61%)	286 (55%)	0.004	277 (54%)	282 (55%)	0.754
Beta blockers	2949 (57%)	294 (56%)	0.614	267(52%:	288 (56%)	0.188
Aldosterone antagonists	361 (7%)	48 (9%)	0.070	50 (10%)	47 (9%)	0.749
Loop diunetics	4225 (82%)	446 (85%)	0.077	445 (87%)	437 (85%)	0.472
Nitrates	1181(23%)	90 (17%)	0.003	93 (18%)	89 (17%)	0.744
Amlodipine	527 (10%)	25 (5%)	<0.001	22 (4%)	25 (5%)	0.654
Other calcium channel blockers	856 (17%)	124 (24%)	<0.001	120 (23%)	116(23%)	0767
Antiarrhythmic drugs	493(10%)	60 (12%)	0.167	63 (12%)	59 (12%)	0.700
Aspirin	2435 (−17%)	209 (40%)	0.001	223 (44%)	205 (40%)	0.254
Non-aspirin anti-platelet agent	743 (14%)	57 (11%)	0.026	51 (10%)	56 (11%)	0.610
Warfarin	1070(21%)	255 (49% j	<0.001	236(46%)	246 (43%)	0.532
Statins	1631 (32%)	132 (25%)	0.002	119(23%)	132 (26%)	0.345
Hospital characterisitics						
Length of stay (days; median, IQR)	4(4)	5(5)	<0.001	5(4)	8(5)	0.397
Bed size (numbers; median, IQR)	350 (212)	350 (205)	0.803	330 (249)	350 (205)	0.170
Academic center	2182 (42%)	197 (38%)	0.035	200(39%)	191 (37%)	0.563

Values are number (percentage) or mean ±standaed deviation. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HF=heart filure; IQR = interquaticle range

Table 2.

Association between digoxin initiation and outcomes in a propensity score-matched cohort of patients with heart failure with preserved ejection fraction

	Events (%), by digoxin initiation		Hazard ratio associated with initiation of digoxin (95%CI); P values
	No (n=513)	**Yes (n=513)**	
30-day			
Heart failure readmission	46 (9%)	33 (6%)	0.70 (0.45–1.10): pp=0.124
All-cause readmission	115 (23%)	111 (22%)	0.95 <0.73–1.23): pe=0.689
All-cause mortality	28 (6%)	27 (5%)	0.93(0.55–1.56): p=0.773
Heart failure readmission or all-cause mortality	73 (14%)	59 (12%)	0.79 (0.56–1.12): p=0.185
All-cause readmission or all-cause mortality	136 (27%)	130 (25%)	0.95 (0.75–1.21): p=0.660
2-year			
Heart failure readmission	178 (35%)	152 (30%)	0.80 (0.64–0.99): p=0.041
All-cause mortality	393 (77%)	378(74%)	0.92 (0.79–1.05); p=0.217
All-cause mortality	224 (44%)	187(37%)	0.79 (0.65–0.96): P=0.020
Heart failure readmission or all-cause mortality	315 (81%)	279 (80%)	0.83 (0.70–0.97): p=0.020
All-cause readmission or all-cause mortality	427 (83%)	426 (83%)	0.95 (0.83–1.09): p=0.451
6-year			
Heart failure readmission	216 (42%)	204 (40%)	0.87 (0.72–1.05): p=0.149
All-cause readmission	445 (87%)	432 (34%)	0.93 (0.81–1.06): p=0.277
All-cause mortality	344 (.67%)	334 (65%)	0.90 (0.73–1.05): p=0.187
Heart fauilure readmission or all-caude mortality	412 (80%)	402 (78%)	0.39 (0.73–1.02); p=0.105
All-cause readmission or all-cause mortality	488 (95%)	486 (95%)	0.95 (0.84–1.08): p=0.466

Table 3.

Predictors of initiation of digoxin therapy in a pre-match cohort of 5675 patient with heart falline with preserved ejection fraction not receiving digoxin prior to hospital admission Data from the multivariable logistic regression model for the estimation of propensity scores included the 58 baseline characteristics listed, in Figure 2 except pube and serum creatinine. which were used as categorical variables

Predictors	Odds ratios (95% confidence intervals); P value
Diabetes mellitus	0.74 (0.59–0.92): p=0.006
Atrial fibrillation	2.27 (1.83–2.82): p<0–001
Orthopnea	1.30 (1.02–1.66); p=0.037
Pulse > 70 beats/minute	1.47 (1.18—1.83); p=0.001
Amlodipine use	0.60 (0.39–0.93); p=0.023
Warfarin use	2.50 (2.00–3.13); p<0.001
Serum creatinine >1.2 mg/dL	0.63 (0. 51–0.77): p<0.001

Note: Because propensity scote models are sample-specific adjusters, these predictors may not be used for out-of-sample prediction of digoxin initiation in patients with HFpEF.