

Digoxin Discontinuation and Outcomes in Patients With Heart Failure With Reduced Ejection Fraction



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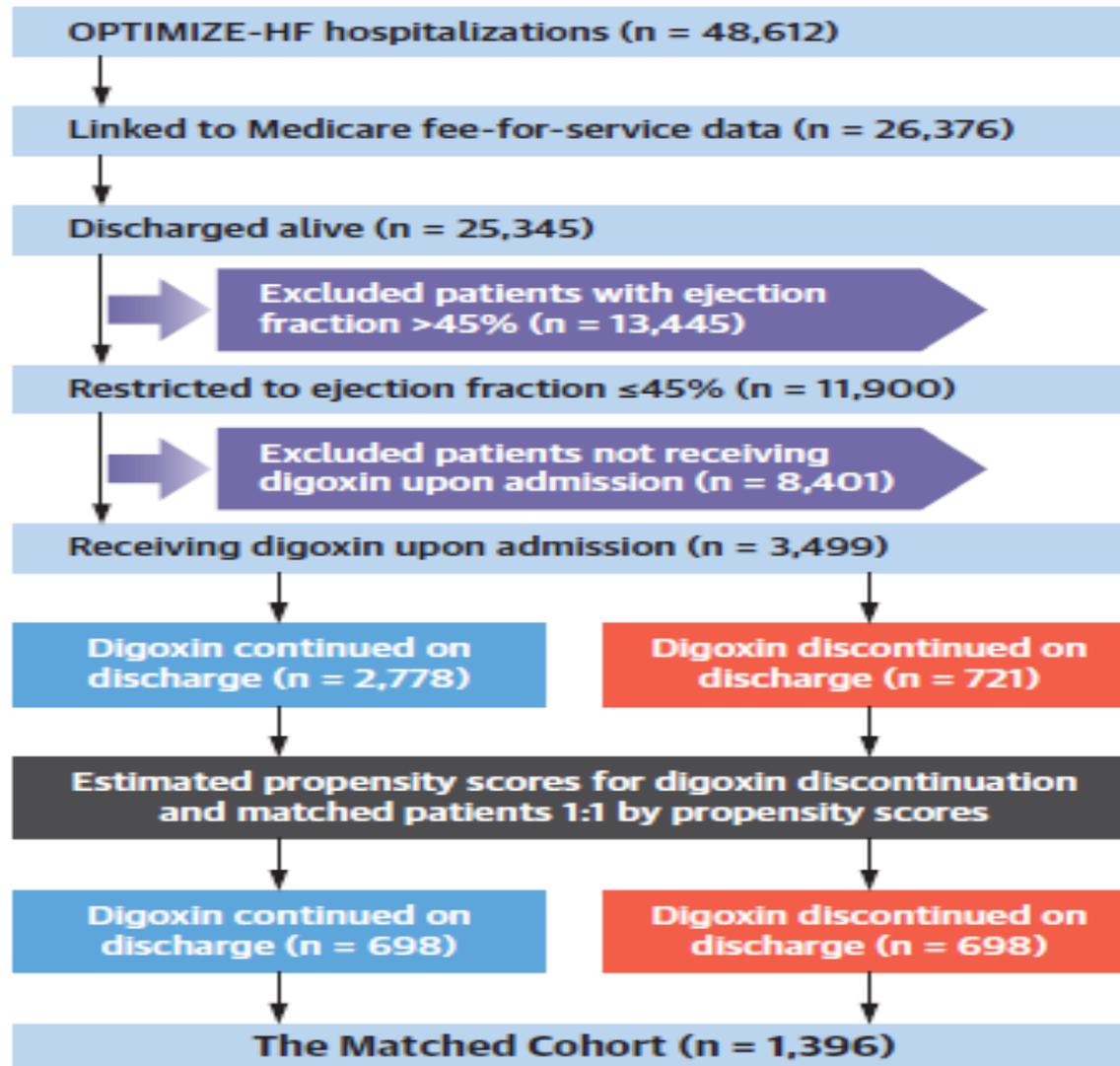
Introduction

- Heart failure (HF) is a leading cause of hospital admission and readmission.
- The efficacy and effectiveness of digoxin in lowering the risk of admission and readmission in patients with HFrEF are well established.
- However, less is known about the effect of discontinuation of digoxin in patients with HFrEF.

OBJECTIVES

- The objective of the current study was to examine the relationship between discontinuation of pre-admission digoxin therapy and outcomes in a propensity score-matched cohort of hospitalized patients with HFrEF receiving more contemporary GDMT

FIGURE 1 Assembly of the Study Cohort



Flow chart displaying assembly of a matched cohort of patients with heart failure with reduced ejection fraction, by discontinuation of digoxin therapy. OPTIMIZE-HF = Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure registry.

- **OUTCOMES DATA:**
- We examined the following outcomes: HF readmission, all-cause readmission, all-cause mortality, and the combined endpoint of HF readmission or all-cause mortality.
- All outcomes were examined at 30 days, 6 months, 1 year, and 4 years after hospital discharge.
- Data on all outcome events and times to events were collected from the Medicare data.

Results

	Before Propensity Score Matching (n = 3,499)			After Propensity Score Matching (n = 1,396)		
	Digoxin Discontinuation		p Value	Digoxin Discontinuation		p Value
	No (n = 2,778)	Yes (n = 721)		No (n = 698)	Yes (n = 698)	
Age, yrs	75 ± 11	76 ± 11	0.047	75 ± 11	76 ± 11	0.827
Women	1,086 (39)	290 (40)	0.580	287 (41)	279 (40)	0.663
African American	389 (14)	105 (15)	0.700	84 (12)	103 (15)	0.135
Left ventricular ejection fraction, %	26 ± 9	28 ± 10	<0.001	28 ± 9	28 ± 10	0.973
Smoker in past 1 yr	359 (13)	81 (11)	0.223	83 (12)	80 (11)	0.803

Past medical history

Prior heart failure	2,621 (94)	683 (95)	0.691	658 (94)	662 (95)	0.637
Prior HF hospitalization in 6 months	602 (22)	161 (22)	0.702	154 (22)	153 (22)	0.948
Hypertension	1,805 (65)	465 (64)	0.809	459 (66)	449 (64)	0.575
Myocardial infarction	872 (31)	220 (31)	0.651	228 (33)	215 (31)	0.455
Coronary revascularization	1,097 (39)	281 (39)	0.801	278 (40)	268 (38)	0.583
Diabetes mellitus	1,135 (41)	304 (42)	0.525	302 (43)	292 (42)	0.588
Stroke/transient ischemic attack	430 (15)	101 (14)	0.327	103 (15)	100 (14)	0.820
Peripheral vascular disease	438 (16)	107 (15)	0.541	106 (15)	104 (15)	0.881
Atrial fibrillation	1,271 (46)	324 (45)	0.696	313 (45)	314 (45)	0.957
Ventricular arrhythmia	299 (11)	69 (10)	0.352	60 (9)	67 (10)	0.515
Implantable cardioverter defibrillator	341 (12)	86 (12)	0.800	88 (13)	82 (12)	0.623
Biventricular pacemaker	230 (8)	50 (7)	0.236	54 (8)	49 (7)	0.609
Chronic obstructive pulmonary disease	813 (29)	179 (25)	0.018	165 (24)	176 (25)	0.493
Anemia	407 (15)	94 (13)	0.270	93 (13)	92 (13)	0.937
Depression	251 (9)	70 (10)	0.577	64 (9)	65 (9)	0.926

Admission findings

Dyspnea at rest	1,183 (43)	291 (40)	0.281	300 (43)	284 (41)	0.385
Dyspnea on exertion	1,751 (63)	433 (60)	0.142	417 (60)	421 (60)	0.827
Orthopnea	838 (30)	165 (23)	<0.001	156 (22)	165 (24)	0.567
Paroxysmal nocturnal dyspnea	503 (18)	95 (13)	0.002	87 (12)	94 (13)	0.577
Jugular venous pressure elevation	948 (34)	250 (35)	0.782	226 (32)	242 (35)	0.364
Third heart sound	378 (14)	92 (13)	0.552	83 (12)	88 (13)	0.683
Pulmonary rales	1,709 (62)	423 (59)	0.162	415 (59)	411 (59)	0.828
Peripheral edema	1,687 (61)	467 (65)	0.047	459 (66)	452 (65)	0.694
Pulse, beat/min	85 ± 20	83 ± 20	0.014	82 ± 19	83 ± 20	0.538
Systolic blood pressure, mm Hg	133 ± 28	134 ± 30	0.537	133 ± 29	134 ± 30	0.706
Diastolic blood pressure, mm Hg	74 ± 17	72 ± 18	0.006	71 ± 17	72 ± 18	0.553

Laboratory findings

Admission serum sodium, mEq/l	137 ± 10	136 ± 13	0.349	136 ± 10	136 ± 13	0.941
Admission hemoglobin, g/dl	13 ± 3	12 ± 2	0.040	12 ± 2	12 ± 2	0.795
Admission serum BNP, pg/ml	1,208 (792-1,527)	1,222 (830-1,553)	0.435	1,186 (772-1,557)	1,223 (784-1,561)	0.363
Discharge serum creatinine, mg/dl	1.6 ± 0.9	1.7 ± 1.0	0.008	1.7 ± 1.2	1.7 ± 1.0	0.729

Discharge medications

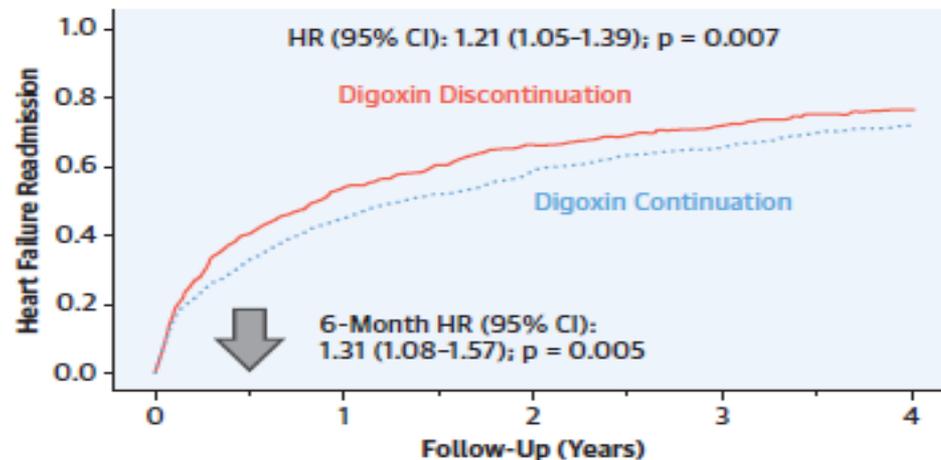
ACE inhibitors or ARBs	2,001 (72)	436 (60)	<0.001	449 (64)	429 (61)	0.268
Beta-blockers	2,027 (73)	450 (62)	<0.001	457 (65)	444 (64)	0.467
Aldosterone antagonists	559 (20)	106 (15)	0.001	105 (15)	106 (15)	0.940
Loop diuretic agents	2,354 (85)	513 (71)	<0.001	507 (73)	510 (73)	0.857
Nitrates	795 (29)	170 (24)	0.007	157 (22)	170 (24)	0.411
Amlodipine	118 (4)	43 (6)	0.050	42 (6)	40 (6)	0.820
Other calcium-channel blockers	189 (7)	39 (5)	0.176	43 (6)	39 (6)	0.649
Antiarrhythmic agents	483 (17)	127 (18)	0.886	135 (19)	123 (18)	0.408

Hospital length of stay, days	4 (3-7)	5 (3-8)	<0.001	5 (3-8)	5 (3-8)	0.332
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TABLE 2 Outcomes in 1,396 Propensity Score-Matched Hospitalized Patients With HFrEF

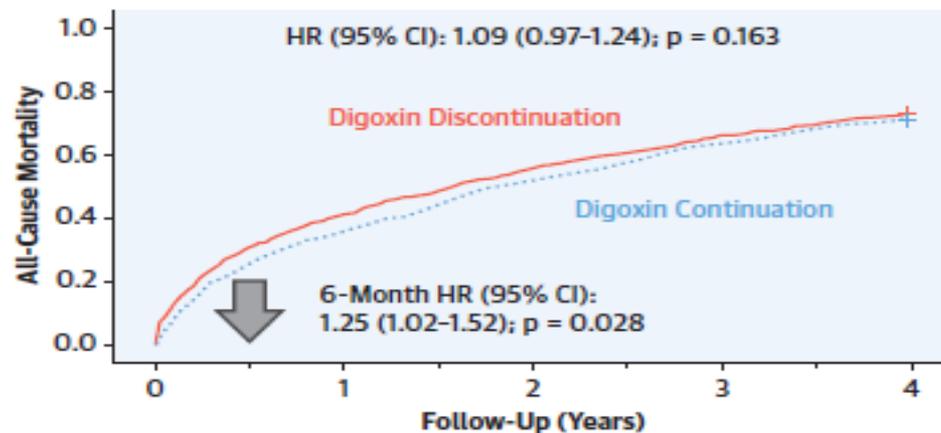
	Events by Digoxin Discontinuation at Hospital Discharge, n (%)		Hazard Ratio Associated With Digoxin Discontinuation, (95% CI); p Value
	No (n = 698)	Yes (n = 698)	
30-day outcomes			
HF readmission	89 (13)	101 (14)	1.19 (0.90-1.59); 0.226
All-cause readmission	195 (28)	193 (28)	1.03 (0.84-1.26); 0.778
All-cause mortality	47 (7)	82 (12)	1.80 (1.26-2.57); 0.001
HF readmission or all-cause mortality	131 (19)	171 (24)	1.36 (1.09-1.71); 0.007
6-month outcomes			
HF readmission	205 (29)	246 (35)	1.31 (1.08-1.57); 0.005
All-cause readmission	377 (54)	409 (59)	1.18 (1.03-1.36); 0.019
All-cause mortality	181 (26)	215 (31)	1.25 (1.02-1.52); 0.028
HF readmission or all-cause mortality	321 (46)	377 (54)	1.28 (1.10-1.48); 0.001
1-yr outcomes			
HF readmission	276 (40)	317 (45)	1.28 (1.09-1.51); 0.003
All-cause readmission	472 (68)	483 (69)	1.15 (1.02-1.31); 0.028
All-cause mortality	251 (36)	287 (41)	1.21 (1.02-1.43); 0.028
HF readmission or all-cause mortality	415 (59)	475 (68)	1.27 (1.11-1.45); <0.001
4-yr outcomes			
HF readmission	391 (56)	407 (58)	1.21 (1.05-1.39); 0.007
All-cause readmission	595 (85)	579 (83)	1.16 (1.04-1.31); 0.010
All-cause mortality	498 (71)	510 (73)	1.09 (0.97-1.24); 0.163
HF readmission or all-cause mortality	607 (87)	624 (89)	1.20 (1.07-1.34); 0.002

CENTRAL ILLUSTRATION Kaplan-Meier Plots for Outcomes by Digoxin Discontinuation



Number at risk

Digoxin Discontinuation	698	223	134	94	74
Digoxin Continuation	698	283	180	129	91



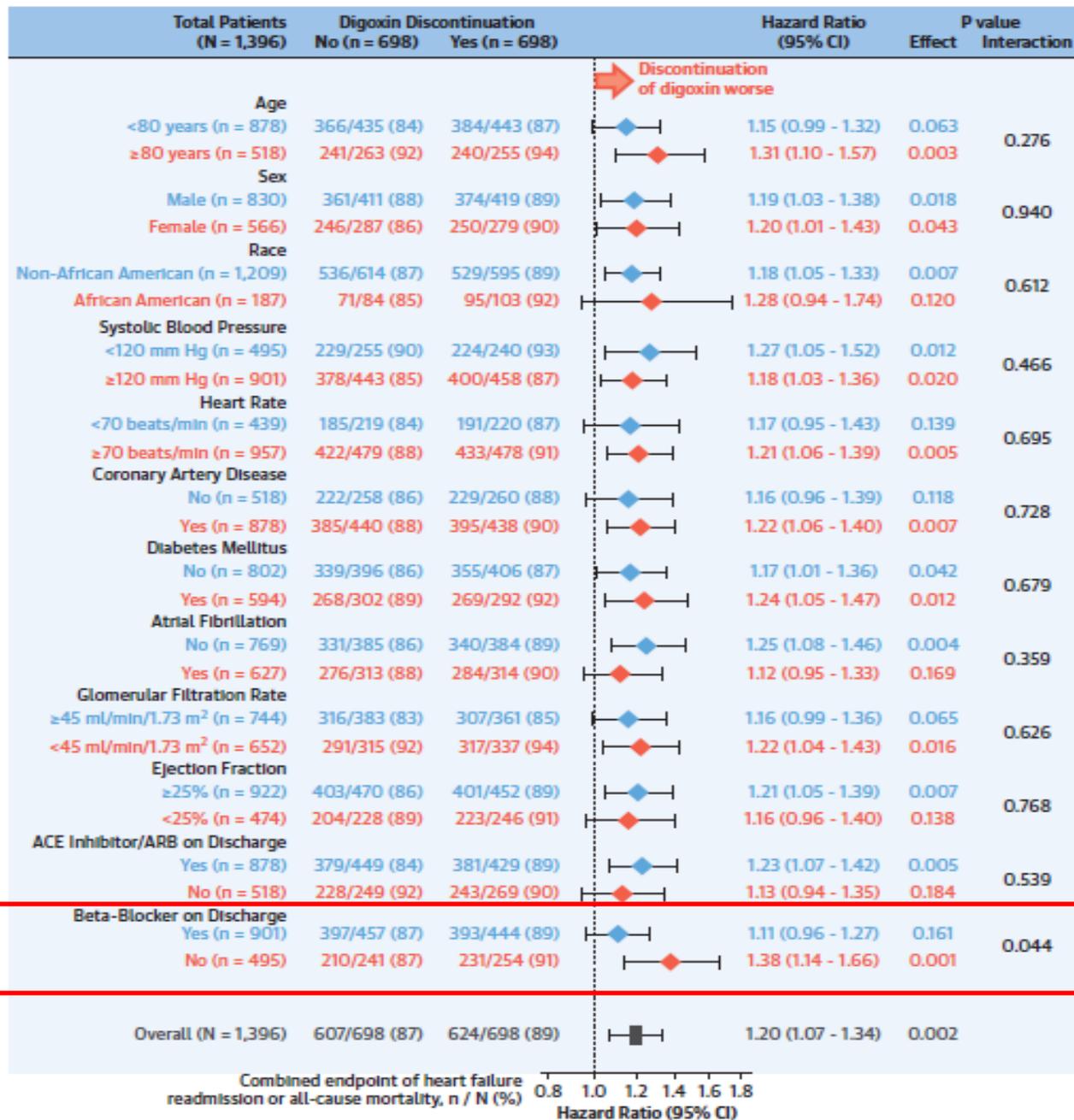
Number at risk

Digoxin Discontinuation	698	411	308	236	188
Digoxin Continuation	698	447	336	254	200

Malik, A. et al. *J Am Coll Cardiol*. 2019;74(5):617-27.

This study assessed the relationship of discontinuation of pre-admission digoxin therapy with heart failure readmission (**top**) and all-cause mortality (**bottom**) in 698 pairs of propensity score-matched patients with heart failure with reduced ejection fraction. During 4 years of follow-up, digoxin discontinuation was associated with a significantly higher risk of heart failure readmission but not of all-cause mortality, compared with patients whose digoxin therapy was continued. During the first 6 months of follow-up, digoxin discontinuation was associated with a significantly higher risk of both outcomes. CI = confidence interval; HR = hazard ratio.

FIGURE 2 Forest Plots for Subgroup Analyses of Combined Outcome by Digoxin Discontinuation



- Among the 3,499 pre-match patients with HFrEF
 - ACE inhibitors or angiotensin receptor blocker (ARBs) (OR: 0.64; 95% CI: 0.53 to 0.77; $p < 0.001$),
 - beta-blockers (OR: 0.68; 95% CI: 0.57 to 0.82; $p < 0.001$),
 - loop diuretics (OR: 0.52; 95% CI: 0.43 to 0.64; $p < 0.001$),
 - nitrates (OR: 0.76; 95% CI: 0.62 to 0.94; $p \approx 0.011$)associated with lower odds of digoxin discontinuation.
- The odds of digoxin discontinuation were also lower among patients with
 - orthopnea (OR: 0.77; 95% CI: 0.61 to 0.97; $p \approx 0.026$),
 - anemia (OR: 0.72; 95% CI: 0.56 to 0.94; $p \approx 0.016$),
 - chronic obstructive pulmonary disease (OR: 0.81; 95% CI, 0.66–0.99; $p \approx 0.038$),
- Higher among those with lower extremity edema (OR: 1.32; 95% CI: 1.10 to 1.60; $p \approx 0.003$).
- In-hospital AKI was not associated with digoxin discontinuation (OR: 0.89; 95% CI: 0.68 to 1.17; $p \approx 0.420$).

Conclusion

- Among hospitalized older patients with HFrEF receiving more contemporary GDMT including ACE inhibitors/ARBs, beta-blockers and MRAs, discontinuation of pre-admission digoxin therapy was associated with poor outcomes. Findings from this study suggest that it may be premature to abandon the use of digoxin in patients with HFrEF.