Published in final edited form as:

Am Heart J. 2018 May ; 199: 97–104. doi:10.1016/j.ahj.2018.02.004.

Prevalent digoxin use and subsequent risk of death or hospitalization in ambulatory heart failure patients with a reduced ejection fraction—Findings from the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) randomized controlled trial

Andrew P. Ambrosy, MD^{a,b,*}, Ankeet S. Bhatt, MD, MBA^a, Amanda L. Stebbins, MS^b, Lisa M. Wruck, PhD^b, Marat Fudim, MD^a, Stephen J. Greene, MD^a, William E. Kraus, MD^a, Christopher M. O'Connor, MD^{b,c}, Ileana L. Piña, MD^d, David J. Whellan, MD^e, Robert J. Mentz, MD^{a,b}

^aDuke University Medical Center, Durham, NC

^bDuke Clinical Research Institute, Durham, NC

^cInova Heart and Vascular Institute, Falls Church, VA

^dAlbert Einstein College of Medicine, Bronx, NY

^eJefferson Medical College, Philadelphia, PA

Abstract

Background: Despite more than 200 years of clinical experience and a pivotal trial, recently published research has called into question the safety and efficacy of digoxin therapy in heart failure (HF).

Methods: HF-ACTION ([ClinicalTrials.gov](https://clinicaltrials.gov) Number:) enrolled 2331 outpatients with HF and an EF $\geq 35\%$ between April 2003 and February 2007 and randomized them to aerobic exercise training versus usual care. Patients were grouped according to prevalent digoxin status at baseline. The association between digoxin therapy and outcomes was assessed using Cox proportional hazard and inverse-probability weighted (IPW) regression models adjusted for demographics, medical history, medications, laboratory values, quality of life, and exercise parameters.

Results: The prevalence of digoxin therapy decreased from 52% during the first 6 months of enrollment to 35% at the end of the HF-ACTION trial ($P < 0.0001$). Study participants were 59 ± 13 years of age, 72% were male, and approximately half had an ischemic etiology of HF. Patients receiving digoxin at baseline tended to be younger and were more likely to report New York Heart Association functional class III/IV symptoms (rather than class II) compared to those not receiving digoxin. Patients taking digoxin had worse baseline exercise capacity as measured by peak VO_2 and 6-min walk test and greater impairments in health status as reflected by the Kansas City

*Reprint requests: Andrew P. Ambrosy, MD, Division of Cardiology, Duke University Medical Center, Duke Clinical Research Institute. andrew.ambrosy@dm.duke.edu (A.P. Ambrosy).

Hector O. Ventura, MD served as guest editor for this article.

Cardiomyopathy Questionnaire. The association between digoxin and the risk of death or hospitalization differed depending on whether Cox proportional hazard (Hazard Ratio 1.03, 95% Confidence Interval 0.92–1.16; $P = .62$) or IPW regression models (HR 1.08, 95% CI 1.00–1.17; $P = .057$) were used to adjust for potential confounders.

Conclusion: Although digoxin use was associated with high-risk clinical features, the association between digoxin therapy and outcomes was dependent on the statistical methods used for multivariable adjustment. Clinical equipoise exists and additional prospective research is required to clarify the role of digoxin in contemporary clinical practice including its effects on functional capacity, quality of life, and long-term outcomes.

Digoxin is the oldest cardiac drug still in contemporary use, yet its role in the management of patients with heart failure (HF) remains controversial.^{1–3} At its peak, digoxin was prescribed to an estimated 80% of patients with HF in the United States.^{4,5} However, following the completion of the DIG (Digitalis Investigation Group) trial, which showed that digoxin reduces the risk of hospitalization but not mortality, its use declined precipitously.⁶ As a result, although the US Food and Drug Administration approved digoxin in 1997, the guidelines currently offer a secondary recommendation (ie, class IIa) for digoxin in (1) patients with HF with reduced ejection fraction (EF) experiencing persistent symptoms despite optimal medical therapy and (2) as an adjunct for rate control in patients with atrial fibrillation already receiving β -blockers and/or calcium channel blockers.^{7,8} More recently, the peer-reviewed literature and the popular press have highlighted a number of studies showing potential harm with digoxin therapy in both HF and atrial fibrillation.^{9,10}

Thus, HF-ACTION^{11–13} provides a unique opportunity to systematically describe (1) temporal trends in the prevalence of digoxin therapy, (2) patient characteristics by digoxin treatment status, (3) the association between digoxin use and exercise capacity and quality of life, and (4) the relationship between digoxin and long-term morbidity and mortality in an ambulatory HF population with a reduced EF.

Methods

Overview

The study design¹¹ and primary results^{12,13} of the HF-ACTION trial have been previously reported. Briefly, HF-ACTION was a multicenter, randomized, placebo-controlled trial designed to assess the long-term efficacy and safety of a structured exercise intervention in medically stable outpatients with chronic HF and a reduced EF. A total of 2331 patients were recruited from 82 centers in the United States, Canada, and France between April 2003 and February 2007. Enrollment criteria included an EF $\geq 35\%$, New York Heart Association (NYHA) functional class II–IV symptoms despite optimal medical therapy for at least 6 weeks duration, and the ability and willingness to exercise. Patients were excluded if they were unable to exercise, were already exercising regularly (ie, defined as more than once per week), or had experienced a major cardiovascular event in the past six weeks. Eligible participants were randomized 1:1 to aerobic exercise training versus usual care, with each group also receiving optimal background medical therapy. Exercise training consisted of 36

supervised sessions over 3 months, followed by in-home unsupervised training on a treadmill or stationary cycle of 5 or more episodes per week.

All patients were asked to return for clinic visits every 3 months for the first 2 years and then yearly for up to 4 years. To provide comparable levels of attention from study personnel to both treatment arms, all patients were called every 2 weeks for the first 9 months, monthly until 24 months of follow-up, and quarterly thereafter. All patients, regardless of treatment assignment, received self-management educational materials with information on medications, fluid/diet management, and recommendations for 30 min of moderate-intensity physical activity most days of the week as tolerated.

Exercise testing

All cardiopulmonary exercise (CPX) tests were completed following the American College of Cardiology/American Heart Association (ACC/ AHA) 2002 guideline update for exercise testing.¹⁴ Patients enrolled in the HF-ACTION trial completed CPX testing at baseline using a modified Naughton treadmill protocol.^{15,16} Tests could be terminated by the patient and/or provider any time due to general/leg fatigue, cardiac symptoms (ie, angina, etc.), musculoskeletal complaints, adverse changes in blood pressure, or electrocardiographic evidence of ischemia or serious/life-threatening arrhythmias.

The HF-ACTION protocol instructed testing personnel to exercise patients to a Borg rating of perceived exertion N16 and/or a respiratory exchange ratio (RER) (VCO_2/VO_2) >1.1, but not to terminate exercise once these targets had been reached. Two independent and blinded study physicians determined the peak VO_2 and ventilatory anaerobic threshold (VAT).

Health status

The HF-ACTION trial assessed patient self-reported health status at baseline using the disease-specific Kansas City Cardiomyopathy Questionnaire (KCCQ)¹⁷ and the general EuroQol-5 Dimensions (EQ-5D)¹⁸ survey.

The KCCQ¹⁷ is a 23-item, self-administered disease-specific questionnaire that quantifies physical function, symptoms, social function, self-efficacy/knowledge and quality of life in ambulatory HF patients. The KCCQ provides an overall summary score, as well as scores for the subscales of physical limitation, social limitation, symptom burden, and quality of life. The KCCQ is scored from 0 to 100 with higher scores representing better health status.

The EQ-5D¹⁸ is a widely used, generic, and self-administered survey designed to assess health status in adults. The instrument is comprised of two components, a descriptive profile and a single-index Visual Analogue Scale (VAS). The descriptive profile includes five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/ depression) and allows for three possible response options for each domain (no problem, some/moderate problem, or severe/extreme problem). The VAS provides a global assessment of health status ranging from 0 (ie, 'worst imaginable health state') to 100 (ie, 'best imaginable health state').

Study endpoints

The primary end point was a composite of all-cause mortality or all-cause hospitalization. Secondary end points included all-cause mortality, the composite of cardiovascular (CV) mortality or CV hospitalization, and the composite of CV mortality or HF hospitalization. Although blinding was not possible due to the nature of the exercise intervention, deaths and CV hospitalizations for each patient were adjudicated by an independent clinical events committee. Once a patient had a HF hospitalization that was confirmed by the clinical events committee, no future hospitalizations were adjudicated for that patient.

Statistical analysis

All continuous data were reported as a mean and standard deviation (SD) and/or median (25th, 75th) percentiles, and categorical data as frequencies and percentages. Patients were divided into two groups based on whether they did or did not use digoxin at the time of enrollment. Baseline clinical characteristics including demographics, medical history, laboratory values, medication use, quality of life, and exercise parameters were compared between the two groups. Comparisons for continuous variables were based on the Wilcoxon test, while categorical variables were assessed using χ^2 test or Fisher's exact test, as appropriate. Cox proportional hazards regression models were used to evaluate the relationship between baseline digoxin use and clinical endpoints. Each model was generated to assess digoxin use association with this outcome. All modeling assumptions were confirmed and transformations were carried out when necessary. Models were adjusted for covariates previously identified as being associated with clinical outcomes.¹⁹ $P < .05$ from two-sided tests were considered statistically significant. Adjustments were not made for multiple comparisons. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Funding and manuscript preparation

The HF-ACTION trial was funded via grant support provided by the National Heart, Lung, and Blood Institute ([ClinicalTrials.gov](https://clinicaltrials.gov) Number:). Database management and statistical analysis was performed by the Duke Clinical Research Institute. The authors take responsibility for the manuscript's integrity and had complete control and authority over its preparation and the decision to publish.

Results

Study population

A total of 2331 patients were enrolled in the HF-ACTION trial. Study participants were a median of 59 ± 13 years of age and 72% of the participants were male (Table I). An ischemic etiology for HF was reported in 51% of participants and the median (25th, 75th) LVEF was 25% (20%, 30%). About 35% of patients reported NYHA functional class III-IV symptoms. The vast majority of patients were prescribed a β -blocker and/or angiotensin-converting enzyme inhibitors (ACEI)/ angiotensin receptor blockers (ARB).

Prevalence of digoxin

At the time of randomization, 45% (n = 1046) of patients were receiving digoxin. The prevalence of digoxin use was greater in patients enrolled in the US (46%) as compared to patients enrolled in Canada or France (34%). The prevalence of baseline digoxin use among patients enrolled in HF-ACTION declined significantly during the enrollment period, from 54% between Nov 2003-Apr 2004 to 35% between Nov 2006-Feb 2007 (Cochran-Armitage Trend Test, $Z = 4.96$, $P < .0001$) (Figure 1).

Clinical characteristics

Patients receiving digoxin at baseline tended to be younger and were more likely to have non-ischemic etiology of HF (Table I). These patients also tended to have more advanced HF as evidenced by a lower EF and higher prevalence of New York Heart Association (NYHA) functional class III/IV symptoms (rather than class II). Patients prescribed digoxin were also more likely to report a history of atrial fibrillation/flutter (26% vs. 17%) and/or prior stroke (11% vs. 10%). Finally, although β -blocker and ACEI/ARB utilization was comparable, patients receiving digoxin therapy were more likely to be prescribed a mineralocorticoid receptor antagonist, to be taking higher doses of a loop diuretic, or to have an implantable cardioverter-defibrillator and/or biventricular (BiV) pacemaker.

Exercise testing

In general, patients prescribed digoxin had significantly worse functional capacity at baseline as assessed by CPX and 6-min walk test (6MWT) (Table II). Digoxin use was associated with lower peak VO_2 (14.7 ± 4.5 mL/kg per minute vs. 15.1 ± 4.8) despite having a similar RER. There was also a trend towards shorter exercise duration on CPX testing among digoxin-treated patients. Interestingly, there was not a clinically significant difference in the VAT (ie, a measure of submaximal exercise capacity). Finally, patients taking digoxin ambulated a significantly shorter distance on 6MWT at baseline (356 ± 101 m vs. 372 ± 107 m). Although study participants experienced a modest improvement in functional status from baseline to 3 months as assessed by CPX parameters and 6-MWT, there were no between-group differences.

Health status

Overall, patients receiving digoxin had significantly impaired disease-specific and general health status at baseline (Table III). Based on the KCCQ subscales, patients receiving digoxin were more likely to report limitations in the following domains: physical functioning, social interactions, symptom burden, and quality of life. As a result, digoxin-treated patients reported a significantly lower KCCQ summary score (65 ± 21 vs. 68 ± 21). Similarly, EQ-5D mapped utility (0.80 ± 0.14 vs. 0.82 ± 0.14) and VAS (65 ± 19 vs. 66 ± 19) scores were marginally lower among patients taking digoxin at baseline. However, disease-specific and general health status improved to a similar extent in both groups from baseline to 3 months.

Clinical outcomes

A total of 834 patients (80%) receiving digoxin at baseline and 965 patients (75%) not prescribed digoxin at baseline were hospitalized or died over a median follow-up duration of 2.6 years (1.7 years, 3.5 years).

On univariate analysis, digoxin therapy was associated with increased risk of all-cause mortality/all-cause hospitalization (HR 1.11, 95% CI 1.01–1.23; $P = .04$) (Table IV, Figure 2A). Similarly, patients receiving digoxin experienced higher unadjusted rates of all-cause mortality (HR 1.29, 95% CI 1.06–1.57; $P = .01$) (Figure 2B), CV mortality/CV hospitalization (HR 1.25, 95% CI 1.12–1.40; $P = .01$) (Figure 2C), and CV mortality/HF hospitalization (HR 1.54, 95% CI 1.33–1.79; $P = .01$) (Figure 2D).

After adjusting for confounders using Cox proportional hazards regression models, there was no association between digoxin use and all-cause mortality/all-cause hospitalization (HR 1.03, 95% CI 0.92–1.16; $P = .62$) or all-cause mortality (HR 1.15, 95% CI 0.94–1.42; $P = .17$) (Table IV, Figure 3). However, digoxin therapy remained independently associated with increased risk of the composite of CV mortality/CV hospitalization (HR 1.15, 95% CI 1.01–1.31; $P = .03$) and CV mortality/HF hospitalization (HR 1.21, 95% CI 1.02–1.44; $P = .03$).

In contrast, multivariable adjustment was repeated using IPW methods, there was an association between digoxin therapy and all-cause mortality (HR 1.19, 95% CI 1.02–1.39; $P = .03$), CV mortality/CV hospitalization (HR 1.19, 95% CI 1.09–1.30; $P = .01$), and CV mortality/HF hospitalization (HR 1.29, 95% CI 1.14–1.45; $P = .01$). In addition, there was trend towards increased risk of all-cause mortality/all-cause hospitalization (HR 1.08, 95% CI 1.00–1.17; $P = .057$) with digoxin use that approached but did not reach the threshold for statistical significance.

Discussion

This post hoc analysis of the HF-ACTION trial demonstrated that the prevalence of digoxin at baseline was higher in the US compared to abroad, though prevalence declined by approximately 20% over the timeframe of enrollment. In general, patients prescribed digoxin had more advanced HF as evidenced by a lower EF, more severe signs and symptoms, and a higher rate of utilization of MRAs and device-based therapies (ie, ICDs and/or BiV pacemakers). Similarly, digoxin-treated patients had greater impairments in baseline functional status and worse disease-specific and general health status. Although digoxin use was associated with increased risk of unadjusted CV-specific and all cause morbidity and mortality, after accounting for known confounders using two different statistical approaches, the relationship between digoxin therapy and outcomes was dependent on the method of multivariable adjustment.

Despite more than 200 years of clinical experience and a phase III trial, digoxin remains the most controversial drug in contemporary CV medicine.^{1–3} The finding that digoxin use declined precipitously over the relatively short timeframe of HF-ACTION is congruent with hospital-based registry data.^{4,5} For example, a recently published analysis of the Get with

the Guideline-Heart Failure (GWTG-HF) registry found that between January 2005 and June 2014, digoxin prescription rates have declined from 33.1% to 10.7% among patients with HF with a reduced EF.²⁰ The safety of digoxin has been repeatedly challenged since the 1970s based on retrospective analyses suggesting possible harm.²¹ However, the pivotal DIG trial, which enrolled 6800 ambulatory HF patients with a reduced EF demonstrated that digoxin reduced all-cause, CV-related, and HF-specific hospitalizations and was neutral with respect to survival.⁶ In addition, although post hoc analyses of the DIG database have raised the hypothesis that digoxin might increase mortality in subsets of patients at high-risk for digoxin toxicity (ie, women, the elderly, patients with renal insufficiency, etc.), any potential detrimental effects on survival were attenuated after adjusting for serum digoxin concentration (SDC).^{22–24}

More recently, the peer-reviewed literature and the popular press have highlighted a number of studies showing potential harm with digoxin therapy in both HF and atrial fibrillation.^{9,10} It is intriguing that the present analysis found that digoxin therapy was uniformly associated with increased risk of morbidity and mortality on univariate analysis, while the relationship between digoxin and all-cause mortality and readmissions was dependent on the statistical approach to multivariable adjustment. These findings suggest that outcome data with digoxin may be due to confounding, given the tendency of providers to prescribe digoxin to high-risk patients. The discrepancy between different statistical approaches is likely due to the inherent difficulty of comprehensively adjusting for disease severity and indication for treatment. Although CV and HF morbidity and mortality are the most likely endpoints to be favorably modified by digoxin therapy based on the results of the DIG trial, they are also the most likely to be characterized by residual confounding. Thus, while existing and future observational datasets may provide useful information regarding the real-world epidemiology and practice patterns of digoxin, definitive conclusions regarding its safety should be interpreted with caution.²⁵

It is also noteworthy that patients treated with digoxin had more advanced HF, worse functional status, poor exercise tolerance, and greater impairments in quality of life. Digoxin has many favorable properties that make it a potentially useful therapy for clinically overt HF. It is the only available inotrope capable of safely augmenting cardiac output and reducing pulmonary capillary wedge pressure without causing deleterious increases in heart rate or decreases in blood pressure.^{26,27} As a result, digoxin has been shown to improve signs and symptoms of HF and exercise capacity and reduce all-cause and cause-specific hospitalizations.^{6,28,29} In addition, exploratory analyses of the DIG database have raised the hypothesis that in certain prespecified high-risk groups (eg, New York Heart Association functional class III or IV symptoms, an EF <25%, and/or a cardiothoracic ratio <55%) and at SDCs <1 ng/mL, digoxin may improve survival.^{22–24,30} Thus, given the preponderance of safety data based on the DIG trial and the inherent difficulty of studying the clinical effectiveness of digoxin therapy in observational cohorts, there is clinical equipoise at the present time. A prospective, multicenter, double-blind, randomized, placebo-controlled clinical trial is necessary to clarify the utility of digoxin therapy in patients with HF with a reduced EF who remain symptomatic and at high-risk for admission despite optimal medical therapy in the contemporary era including newer agents such as sacubitril/valsartan and ivabradine.

There are several limitations of the data that should be acknowledged. First, this study was non-randomized and is subject to selection bias as digoxin is generally prescribed to patients with more advanced HF. As previously discussed, even with statistical adjustment techniques, it may be challenging to comprehensively adjust for disease severity and bias by indication. In addition, this analysis is based on prevalent digoxin use (ie, as opposed to incident digoxin use). Substantial differences in clinical characteristics may have emerged in the timeframe between initial prescription and study enrollment. Second, SDCs were not collected as part of the HF-ACTION protocol and therefore could not be included as a covariate in outcome models. Third, patients who were unable or unwilling to exercise were excluded, potentially limiting the generalizability to an otherwise unselected population of ambulatory HF patients with a reduced EF. Finally, due to the nature of the exercise intervention, physicians and patients necessarily were unblinded to treatment assignment, which may have led to an interaction between digoxin therapy and study endpoints. However, all outcomes were adjudicated by a blinded and independent clinical events committee.

In conclusion, the prevalence of digoxin at baseline declined from a peak of 54% to a low of 35% over the relatively short timeframe of the HF-ACTION trial. In addition, digoxin use was more common among patients with advanced HF, decreased exercise capacity, and severe impairments in disease-specific and general health status. Although digoxin therapy was associated with numerous high-risk clinical features and higher unadjusted rates of morbidity and mortality, the relationship between digoxin and outcomes was dependent on the statistical approach to multivariable adjustment. Additional double-blind, randomized, placebo-controlled trials should be conducted to assess the effects of low-dose digoxin on signs and symptoms, functional capacity, quality of life, and long-term outcomes in a contemporary cohort of ambulatory HF patients with reduced EF receiving optimal medical therapy.

Acknowledgments

Conflict of Interest: CMO reports consulting fees from Novella and Amgen; ownership/partnership/principal in Biscardia, LLC; and research support from Otsuka, Roche Diagnostics, BG Medicine, Critical Diagnostics, Astellas, Gilead, GE Healthcare, and ResMed. RJM receives research support from Amgen, AstraZeneca, BMS, GSK, Gilead, Novartis, Otsuka, and ResMed; and honoraria from Thoratec. All other authors declare no relevant financial disclosures.

Appendix A

Candidate variables: age, sex, race, history of myocardial infarction, previous revascularization, history of diabetes, history of peripheral vascular disease, smoking status, history of chronic obstructive pulmonary disease, heart failure hospitalization in the last 6 months, hospitalizations in the last 6 months, etiology of heart failure, NYHA functional class (ie, II vs. III/IV), CCS angina class, automated ICD, BiV pacemaker, pacemaker, atrial fibrillation/flutter, mitral regurgitation grade, systolic blood pressure, diastolic blood pressure, heart rate, body mass index, left ventricular ejection fraction, KCCQ total symptom score, KCCQ quality of life score, KCCQ self-efficacy score, KCCQ symptom stability score, KCCQ physical limitation score, KCCQ social limitation score, Beck Depression Index II, heart rate reserve on CPX test, rest EKG rhythm on CPX test, peak O₂

pulse on CPX test, peak respiratory exchange ratio on CPX test, ventricular conduction prior to CPX test, VE/VCO₂ slope, peak VO₂ by Weber class, distance on 6-min walk test, creatinine, sodium, blood urea nitrogen, and treatment group (ie, exercise vs. usual care).

Abbreviations: NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society; ICD, implantable cardioverter-defibrillator; BiV, biventricular; KCCQ, Kansas City Cardiomyopathy Questionnaire; CPX, cardiopulmonary exercise test; EKG, electrocardiogram; VE/VCO₂, volume of air exhaled/volume of CO₂ exhaled; VO₂, oxygen consumption

References

1. Ambrosy AP, Butler J, Ahmed A, et al. The use of digoxin in patients with worsening chronic heart failure: reconsidering an old drug to reduce hospital admissions. *J Am Coll Cardiol* 2014;63(18):1823–32. [PubMed: 24613328]
2. Ambrosy AP, Gheorghiade M. Targeting digoxin dosing to serum concentration: is the bullseye too small? *Eur J Heart Fail* 2016;18(8):1082–4. [PubMed: 27492642]
3. Ambrosy AP, Pang PS, Gheorghiade M. Digoxin for Worsening Chronic Heart Failure: Underutilized and Underrated. *JACC Heart Fail* 2016;4(5):365–7. [PubMed: 27126283]
4. Adams KF Jr, Fonarow GC, Emerman CL, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and pre-liminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2005;149(2):209–16. [PubMed: 15846257]
5. Gheorghiade M, Abraham WT, Albert NM, et al. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA* 2006;296(18):2217–26. [PubMed: 17090768]
6. Digitalis Investigation G The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;336(8):525–33. [PubMed: 9036306]
7. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;62(16): e147–239. [PubMed: 23747642]
8. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014;64(21):e1–e76. [PubMed: 24685669]
9. Gheorghiade M, Fonarow GC, van Veldhuisen DJ, et al. Lack of evidence of increased mortality among patients with atrial fibrillation taking digoxin: findings from post hoc propensity-matched analysis of the AFFIRM trial. *Eur Heart J* 2013;34(20):1489–97. [PubMed: 23592708]
10. Whitbeck MG, Charnigo RJ, Khairy P, et al. Increased mortality among patients taking digoxin—analysis from the AFFIRM study. *Eur Heart J* 2013;34(20):1481–8. [PubMed: 23186806]
11. Whellan DJ, O'Connor CM, Lee KL, et al. Heart failure and a controlled trial investigating outcomes of exercise training (HF-ACTION): design and rationale. *Am Heart J* 2007;153(2):201–11. [PubMed: 17239677]
12. Flynn KE, Pina IL, Whellan DJ, et al. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009;301(14):1451–9. [PubMed: 19351942]
13. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009;301(14):1439–50. [PubMed: 19351941]
14. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association

Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *J Am Coll Cardiol* 2002;40(8):1531–40. [PubMed: 12392846]

15. Bensimhon DR, Leifer ES, Ellis SJ, et al. Reproducibility of peak oxygen uptake and other cardiopulmonary exercise testing parameters in patients with heart failure (from the Heart Failure and A Controlled Trial Investigating Outcomes of exercise training). *Am J Cardiol* 2008;102(6):712–7. [PubMed: 18773994]
16. Keteyian SJ, Patel M, Kraus WE, et al. Variables Measured During Cardiopulmonary Exercise Testing as Predictors of Mortality in Chronic Systolic Heart Failure. *J Am Coll Cardiol* 2016;67(7):780–9. [PubMed: 26892413]
17. Green CP, Porter CB, Bresnahan DR, et al. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol* 2000;35(5):1245–55. [PubMed: 10758967]
18. EuroQol G EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16(3):199–208. [PubMed: 10109801]
19. O'Connor CM, Whellan DJ, Wojdyla D, et al. Factors related to morbidity and mortality in patients with chronic heart failure with systolic dysfunction: the HF-ACTION predictive risk score model. *Circ Heart Fail* 2012;5(1):63–71. [PubMed: 22114101]
20. Patel N, Ju C, Macon C, et al. Temporal Trends of Digoxin Use in Patients Hospitalized With Heart Failure: Analysis From the American Heart Association Get With The Guidelines-Heart Failure Registry. *JACC Heart Fail* 2016;4(5):348–56. [PubMed: 26874392]
21. Yusuf S, Wittes J, Bailey K, et al. Digitalis—a new controversy regarding an old drug. The pitfalls of inappropriate methods. *Circulation* 1986;73(1):14–8. [PubMed: 3510086]
22. Ahmed A, Rich MW, Love TE, et al. Digoxin and reduction in mortality and hospitalization in heart failure: a comprehensive post hoc analysis of the DIG trial. *Eur Heart J* 2006;27(2):178–86. [PubMed: 16339157]
23. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. *N Engl J Med* 2002;347(18):1403–11. [PubMed: 12409542]
24. Adams KF Jr, Patterson JH, Gattis WA, et al. Relationship of serum digoxin concentration to mortality and morbidity in women in the digitalis investigation group trial: a retrospective analysis. *J Am Coll Cardiol* 2005;46(3):497–504. [PubMed: 16053964]
25. Khan SS, Gheorghiade M. Digoxin use in atrial fibrillation: a critical reappraisal. *Lancet* 2015;385(9985):2330–2. [PubMed: 25749645]
26. Gheorghiade M, Hall V, Lakier JB, et al. Comparative hemodynamic and neurohormonal effects of intravenous captopril and digoxin and their combinations in patients with severe heart failure. *J Am Coll Cardiol* 1989;13(1):134–42. [PubMed: 2562844]
27. Gheorghiade M, St Clair J, St Clair C, et al. Hemodynamic effects of intravenous digoxin in patients with severe heart failure initially treated with diuretics and vasodilators. *J Am Coll Cardiol* 1987;9(4):849–57. [PubMed: 3558983]
28. Uretsky BF, Young JB, Shahidi FE, et al. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. PROVED Investigative Group. *J Am Coll Cardiol* 1993;22(4):955–62. [PubMed: 8409069]
29. Packer M, Gheorghiade M, Young JB, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. *N Engl J Med* 1993;329(1):1–7. [PubMed: 8505940]
30. Gheorghiade M, Patel K, Filippatos G, et al. Effect of oral digoxin in high-risk heart failure patients: a pre-specified subgroup analysis of the DIG trial. *Eur J Heart Fail* 2013;15(5):551–9. [PubMed: 23355060]

Figure 1.
Prevalence of digoxin use among patients enrolled in HF-ACTION over time.

Figure 2. Unadjusted Kaplan Meier curve for (A) all-cause mortality/all-cause death, (B) all-cause mortality, (C) CV mortality/CV hospitalization, CV mortality/HF hospitalization by digoxin use at baseline.

Figure 3. Unadjusted and adjusted (ie, Cox proportional hazard ratios for digoxin use at baseline and clinical outcomes).

Table I

Baseline clinical characteristics by digoxin use at baseline.

	All Patients (N= 2331)	Digoxin use at baseline		P
		No (N=1046)	Yes (N=1285)	
Demographics				
Age, years,				.02
Mean (SD)	59 (13)	60 (12)	58 (13)	
Gender (% male)	1670 (72)	926 (72)	744 (71)	.62
Race (%)				.10
Black	749 (33)	405 (32)	344 (34)	
White	1426 (62)	806 (64)	620 (60)	
Other	121 (5)	57 (5)	64 (6)	
BMI (mg/m ²)				.65
Mean (SD)	31 (7)	31 (7)	31 (7)	
Ejection Fraction (%)				<.01
Mean (SD)	25 (7)	26 (8)	25 (7)	
NYHA Class Classification (%)				<.01
II	1477 (63)	864 (67)	613 (58)	
III	831 (36)	412 (32)	419(40)	
IV	23 (1)	9 (1)	14 (1)	
Resting HR, beats/min,				.46
Mean (SD)	71(12)	71 (12)	71 (12)	
Systolic blood pressure, mmHg,				<.01
Mean (SD)	114 (18)	115 (19)	113 (18)	
Comorbidities (%)				
Ischemic etiology	1197 (51)	686 (53)	511 (49)	.03
Atrial fibrillation/flutter	488 (21)	214 (17)	274 (26)	<.01
Stroke	238 (10)	122 (10)	116 (11)	.21
Hypertension	1388 (60)	799 (62)	589 (57)	.01
Medications/devices at enrollment (%)				
ACEI/ARB	2199 (94)	1206 (94)	993 (95)	.26
β-Blockers	2203 (95)	1216 (95)	987 (94)	.78
Aldosterone antagonist	1051 (45)	485 (38)	566 (54)	<.01
Loop diuretic	1816 (78)	927 (72)	889 (85)	<.01
Furosemide equivalent dose, mg/day,				<.01
Mean (SD)	58 (77)	49 (79)	68 (73)	
AICD	938 (40)	446 (35)	492 (47)	<.01
Bi-V ICD	419 (18)	178 (14)	241 (23)	<.01
Laboratory values				
Hemoglobin, g/dL				.99
Mean (SD)	13.4 (4.5)	13.3 (2.0)	13.5 (6.3)	

	All Patients (N= 2331)	Digoxin use at baseline		<i>P</i>
		No (N=1046)	Yes (N=1285)	
Sodium, mg/L				.14
Mean (SD)	139 (5.4)	139 (5.0)	139 (5.8)	
BUN, mg/dl				<.01
Mean (SD)	25 (27.1)	25 (24.8)	25 (29.4)	
Creatinine, mg/dl				.30
Mean (SD)	1.3 (0.8)	1.4 (1.0)	1.3 (0.6)	

Abbreviations: SD, Standard deviation; *BMI*, body mass index; *NYHA*, New York Heart Association; *HR*, heart rate; *ACEI*, angiotensin converting-enzyme inhibitor; *ARB*, angiotensin receptor blocker; *AICD*, automated implantable cardioverter-defibrillator; *BiV*, biventricular; *BUN*, blood urea nitrogen.

Table II

Baseline and change from baseline to 3 months in exercise capacity by digoxin use at baseline.

	All patients (N=2331)	Digoxin Use at Baseline		<i>P</i>
		No (N=1046)	Yes (N=1285)	
Relative Peak VO ₂ (mL/kg/min)				
BL, mean (SD)	14.9 (4.7)	15.1 (4.8)	14.7 (4.5)	.03
Change in Relative Peak VO ₂ (mL/kg/min)				
BL to 3 months, mean (SD)	0.5 (2.5)	0.5 (2.6)	0.5 (2.5)	.75
Absolute Peak VO ₂ (l/min)				
BL, mean (SD)	1.4 (0.5)	1.4 (0.5)	1.3 (0.5)	.02
Change in Absolute Peak VO ₂ (l/min)				
BL to 3 months, mean (SD)	0.0 (0.2)	0.0 (0.2)	0.0 (0.2)	.66
VO ₂ at ventilator threshold (mL/kg/min)				
BL, mean (SD)	10.8 (2.7)	10.8 (2.8)	10.7 (2.5)	.29
Change in VO ₂ at ventilator threshold (mL/kg/min)				
BL to 3 months, mean (SD)	0.4 (2.0)	0.4 (2.1)	0.3 (2.0)	.61
Exercise Duration (Min)				
BL, mean (SD)	9.8 (4.0)	9.9 (4.0)	9.6 (3.9)	.10
Change in Exercise Duration (Min)				
BL to 3 months, mean (SD)	1.1 (2.3)	1.1 (2.3)	1.0 (2.3)	.98
RER				
BL, mean (SD)	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)	.03
Change in RER				
BL to 3 months, mean (SD)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)	.13
6MWT distance (m)				
BL, mean (SD)	365 (105)	372 (107)	356 (101)	<.01
Change in 6MWT distance (m)				
BL to 3 months, mean (SD)	14 (71)	16 (75)	11 (67)	.27

Abbreviations: VO₂, Oxygen consumption; BL, baseline; RER, respiratory exchange ratio; 6MWT, 6-min walk test.

Table III

Baseline and change from baseline to 3 months in KCCQ and EQ-5D measurements by digoxin use at baseline. Digoxin use at baseline

	All patients (N=2331)	Digoxin use at baseline		<i>P</i>
		No (N=1046)	Yes (N=1285)	
KCCQ overall summary score				
BL, mean (SD)	66 (21)	68 (21)	65 (21)	<.01
Change in KCCQ overall summary score				
BL to 3 months, mean (SD)	4 (14)	4 (15)	4 (14)	.57
KCCQ physical limitation score				
BL, mean (SD)	69 (22)	71 (22)	68 (22)	<.01
Change in KCCQ physical limitation score				
BL to 3 months, mean (SD)	3 (17)	3 (17)	2 (18)	.82
KCCQ social limitation score				
BL, mean (SD)	62 (28)	64 (27)	60 (27)	<.01
Change in KCCQ social limitation score				
BL to 3 months, mean (SD)	5 (22)	5 (23)	4 (22)	.78
KCCQ symptom burden score				
BL, mean (SD)	75 (21)	76 (20)	73 (21)	<.01
Change in KCCQ symptom burden score				
BL to 3 months, mean (SD)	3 (16)	3 (16)	3 (16)	.84
KCCQ quality of life score				
BL, mean (SD)	60 (25)	61 (24)	58 (25)	.02
Change in KCCQ quality of life score				
BL to 3 months, mean (SD)	6 (20)	5 (20)	6 (19)	.13
EQ-5D Mapped Utility Score				
BL, mean (SD)	0.81 (0.14)	0.82 (0.14)	0.80 (0.14)	.01
Change in EQ-5D Mapped Utility Score				
BL to 3 months, mean (SD)	0.00 (0.14)	0.00 (0.14)	0.00 (0.14)	.41
EQ-5D VAS				
BL, mean (SD)	65 (19)	66 (19)	65 (19)	.28
Change in EQ-5D VAS				
BL to 3 months, mean (SD)	5 (19)	4 (18)	5 (19)	.41

Abbreviations: *KCCQ*, Kansas City Cardiomyopathy Questionnaire; *EQ-5D*, EuroQol five dimensions questionnaire; *BL*, baseline.

Table IV

Clinical outcomes by digoxin use at baseline.

Clinical outcome	Unadjusted		Cox regression analysis		IPW analysis	
	HR for digoxin (95% CI)	P	HR for digoxin (95% CI)	P	HR for digoxin (95% CI)	P
All-cause mortality/all-cause hospitalization	1.11 (1.01, 1.23)	0.04	1.03 (0.92, 1.16) ¹	0.62	1.08 (1.00, 1.17) ⁵	.06
All-cause mortality	1.29 (1.06, 1.57)	0.01	1.16 (0.94, 1.42) ²	0.17	1.19 (1.02, 1.39) ⁶	.03
CV mortality/CV hospitalization	1.25 (1.12, 1.40)	<0.01	1.15 (1.01, 1.31) ³	0.03	1.19 (1.09, 1.30) ⁷	<.01
CV mortality/HF hospitalization	1.54 (1.33, 1.79)	<0.01	1.21 (1.02, 1.44) ⁴	0.03	1.29 (1.14, 1.45) ⁸	<.01

Abbreviations: *HR*, Hazard ratio; *CI*, confidence interval; *CV*, cardiovascular; *HF*, heart failure *CPX*, cardiopulmonary exercise; *BMI*, body mass index; *LVEF*, left ventricular ejection fraction; *BUN*, blood urea nitrogen; *CCS*, Canadian Cardiovascular Society; *VO₂*, oxygen consumption; *KCCQ*, Kansas City Cardiomyopathy Questionnaire; *VE*, ventilation; *VCO₂*, *CO₂* production.

^{*} Model adjusted for peak *VO₂* characterized by Weber class, KCCQ symptom stability score, BUN, country (ie, US or non-US), LVEF, sex, dosage of β -blocker, mitral regurgitation grade, ventricular conduction on the baseline CPX test.

[†] Model adjusted for exercise duration on the baseline CPX test, serum creatinine level, BMI, sex, dosage of loop diuretic, LVEF, CCS angina classification, and ventricular conduction on the baseline CPX test.

[‡] Model adjusted for LVEF, mitral regurgitation grade, ventricular conduction on the baseline CPX test, HR at peak exercise, BUN, race, sex, baseline use of nitrates, peak *VO₂* characterized by Weber class.

[§] Model adjusted for dosage of loop diuretic, LVEF, mitral regurgitation grade, ventricular conduction on the baseline CPX test, KCCQ symptom stability score, BUN, race, sex, age, peak *VO₂* characterized by Weber Class, and *VE/VCO₂*.

^{||} Model adjusted for peak *VO₂* characterized by Weber class, KCCQ symptom stability score, country (ie, US or non-US), BUN, LVEF, sex, dosage of β -blocker, mitral regurgitation grade, and ventricular conduction on the baseline CPX test.

[¶] Model adjusted for exercise duration on the baseline CPX, BMI, gender, LVEF, ventricular conduction on the baseline EKG, serum creatinine, dosage of loop diuretic, and CCS angina classification.

[#] Model adjusted for LVEF, mitral regurgitation grade, ventricular conduction on the baseline CPX test, BUN, race, HR at peak exercise, sex, nitrate use, and peak *VO₂* characterized by Weber class.

^{**} Model adjusted for loop diuretic use, mitral regurgitation grade, KCCQ symptom stability score, LVEF, ventricular conduction on baseline CPX, BUN, sex, race, age, *VE/VCO₂*, and peak *VO₂* by Weber Class.