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Digoxin use and subsequent outcomes among patients in a contemporary atrial fibrillation cohort

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Abstract

BACKGROUND—Although digoxin has long been used to treat atrial fibrillation (AF) and heart failure (HF), its safety remains controversial.

OBJECTIVES—This study sought to describe digoxin use over time in patients with AF stratified by presence or absence of HF; characterize predictors of digoxin use and initiation; and correlate digoxin use with outcomes.

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METHODS—Longitudinal patterns of digoxin use and its association with a variety of outcomes were assessed in a prospective outpatient registry conducted at 174 U.S. sites with enrollment from June 2010 to August 2011.

RESULTS—Among 9,619 patients with AF and serial follow-up every 6 months for up to 3 years, 2,267 (23.6%) were receiving digoxin at study enrollment, 681 (7.1%) were initiated on digoxin during follow-up, and 6,671 (69.4%) were never prescribed digoxin. Adjusting for other medications, heart rate was 72.9 beats/min among digoxin users and 71.5 among nonusers ($p < 0.0001$). Prevalent digoxin use at registry enrollment was not associated with subsequent onset of symptoms, hospitalization, or mortality (in patients with HF, adjusted hazard ratio [HR] for death: 1.04; without HF, HR: 1.22). Incident digoxin use during follow-up was not associated with subsequent death in patients with HF (propensity-adjusted HR: 1.05) but was in those without HF (propensity-adjusted HR: 1.99).

CONCLUSIONS—After adjustment for detailed clinical factors, digoxin use in registry patients with AF had a neutral association with outcomes under most circumstances. Given multiple conflicting observational reports about digoxin's safety and possible concerns in specific clinical situations, a large pragmatic trial of digoxin therapy in AF is needed.

Keywords

heart failure; mortality; patient outcome assessment; safety

Cardiac glycosides, such as digoxin, have been used for decades to treat patients with atrial fibrillation (AF) and those with heart failure (HF) to slow atrioventricular (AV) nodal conduction and increase cardiac inotropy (1). With the development of alternative treatments for AF (2) and HF (3), as well as concerns about digoxin's potential proarrhythmic properties and long-term effects on cardiac remodeling (4), digoxin prescribing has decreased and is no longer recommended as first-line therapy for either disease (3,5). Yet, there remain unmet needs for the treatment of many subgroups of AF patients, including those with HF, prompting calls for renewed use of digoxin in certain clinical situations (6).

Effectiveness and safety data for digoxin are relatively limited. The only large randomized trial of digoxin, the DIG (Digitalis Investigation Group) trial, showed no effect on mortality but digoxin did reduce hospitalization among patients with HF and reduced ejection fraction (HFrEF) (7); notably it enrolled only patients in sinus rhythm, was conducted between 1991 and 1993, and raised safety concerns at higher serum concentrations and in certain subgroups, including women (8–10). A more recent observational analysis of patients with incident HFrEF under routine care found that digoxin use was independently associated with higher mortality (11). There are no large randomized trials of digoxin in patients with AF. Two post hoc nonrandomized analyses of data from the large AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial came to conflicting conclusions (12,13). Post hoc analysis of other AF trials have shown higher mortality associated with digoxin use (14), as has real-world data from a large incident AF cohort from the Veterans Administration (15) and 2 large health maintenance organizations (16).

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Due to limited and conflicting data, we set out to describe digoxin use over time among a large contemporary cohort of patients with AF stratified by presence or absence of HF, characterize predictors of digoxin use and initiation, and clarify the association of digoxin use with heart rate, health-related quality of life (HRQOL) measures, hospitalization, and survival.

METHODS

We used data from ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) to assess the use of digoxin and its association with outcomes. Details of the ORBIT-AF study design have been published (17). Briefly, ORBIT-AF is a U.S.-based, prospective outpatient registry of AF conducted at 176 sites nationwide. The Duke Clinical Research Institute was responsible for ORBIT-AF site selection and study management. Eligible patients were 18 years of age and older with electrocardiographically-confirmed atrial fibrillation. Enrolling providers included cardiologists, electrophysiologists, and primary care providers. Site personnel entered information on demographics, medical history, cardiovascular risk factors, AF management strategy, cardiac imaging, and provider characteristics into a standardized, web-based collection form. The presence or absence of HF and New York Heart Association (NYHA) functional class were determined at baseline by medical record review. Following initial enrollment, longitudinal information was collected during clinic visits at approximately 6-month intervals for up to 36 months and included information on medication regimens, procedures, hospitalizations, quality of life, and vital status. We excluded patients missing information regarding whether or not they were taking digoxin. Written informed consent was obtained for all study participants. The Duke Institutional Review Board (IRB) approved the ORBIT-AF Registry; all participating sites obtained approval from local IRBs prior to entering patient data.

Medication use was collected prospectively at each study visit, including a field specific for digoxin. Dose and blood levels were not collected. The follow-up visit date at which digoxin was first reported was defined as the time period of initiation.

The primary outcome of interest was all-cause death. Additional outcomes of interest included heart rate, symptoms, HRQOL, all-cause hospitalization, and the composite of all-cause hospitalization and death. Symptoms were measured using the European Heart Rhythm Association (EHRA) score of AF-related symptoms (18). HRQOL was assessed by the Atrial Fibrillation Effect on Quality-of-life (AFEQT) questionnaire in a subset of patients at baseline, 12 months, and 24 months (19).

STATISTICAL ANALYSIS

Characteristics between patients were described as frequency and percent for categorical variables, medians and interquartile ranges (IQR) for continuous variables. The characteristics were compared using the chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables. The cohort was divided into those taking digoxin at study enrollment (prevalent use), those initiated on digoxin during follow-up (incident use), and those not on digoxin at any time during the study period. Characteristics

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between the groups were compared using Pearson chi-square tests for categorical variables and Wilcoxon rank sum tests for continuous variables.

To examine factors associated with prevalent digoxin use, a multivariable hierarchical logistic regression model was constructed using backward selection for the binary outcome digoxin use at baseline, beginning with Online Table 1 covariates (54 pre-specified clinical and demographic characteristics and a random effect for the enrolling site) followed by inclusion criterion of $p < 0.05$ (final model covariates, Online Table 2a). Prevalent digoxin users at baseline were excluded from this model. As digoxin use was measured at 6-month visit intervals, a second multivariable, discrete-time Cox frailty model was constructed for the time to first report of digoxin initiation (final model covariates, Online Table 2b). Patients were censored from the risk set at the time lost to follow-up (mainly due to staggered entry into the cohort). A third discrete-time Cox frailty model was constructed for digoxin discontinuation among prevalent digoxin users (final model covariates, Online Table 2c). Results were presented as odds/hazard ratios (OR/HR) with corresponding 95% confidence intervals (CI) and p values.

Baseline heart rate was compared for baseline digoxin use using a linear regression model accounting for other rate control medications (i.e., beta-blockers, verapamil, diltiazem, sotalol, and amiodarone). The adjusted mean heart rate was estimated by the model predicted heart rate, with and without digoxin, with the adjustment variables set equal to their population average.

Associations between prevalent digoxin use at baseline and subsequent all-cause death, all-cause hospitalization, cardiovascular hospitalization, and onset of symptoms were assessed in unadjusted and adjusted analysis. According to the pre-specified analysis plan, primary analyses were stratified a priori by presence or absence of HF. Time to first reported symptoms was measured at 6-month visit intervals, and a discrete-time Cox model was used for this outcome only; otherwise, exact event dates were used. The potential for clustering of patient outcomes within a site was handled by adding a random effect for site (multivariable Cox frailty model). Models were adjusted for all covariates listed in Online Table 3, which were those determined to have: 1) particular clinical relevance, determined *a priori*; or 2) a statistically significant association with *any* of the outcomes under evaluation, as previously identified by backward selection with stay criteria of 0.05. The same set of covariates was used for adjustment of all outcomes. Adjusted associations for outcomes were displayed as HRs (95% CI).

Associations between incident digoxin use in follow-up and subsequent all-cause death, all-cause hospitalization, and cardiovascular hospitalization were assessed through propensity-score matching between patients initiated on digoxin in follow-up. Among people who initiated digoxin at the final follow-up period (30 to 36 months), it was unusual to have subsequent follow-up; therefore, digoxin initiation was restricted to occur between 6 and 24 months. Analyses were conducted separately for patients with and without HF. Each case (incident digoxin use) was matched to 3 controls (noninitiators) using sequential stratification matching (20), identifying matches from the same point in follow-up at which digoxin was initiated using all available covariate information up to that point (including HF

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status). The criteria for matching was a single propensity score, obtained from a logistic regression model for digoxin initiation. Matching was conducted sequentially, starting at 6 months and moving forward through follow-up. At each visit period, patients initiating digoxin were matched to others, still under follow-up at the same time but not yet starting digoxin. The criteria for identifying a match was "closeness" on a single propensity score value calculated at each visit period. In order to be considered a match, patients had to have a difference in propensities no larger than a caliper of 20% of a standard deviation. Standardized differences were used to evaluate the success of propensity matching at achieving balance. Outcomes assessment began immediately after the time period of initiation and the model was fit using stratified Cox regression, stratified on the matched pair (21).

Pre-defined secondary analyses were performed for subgroups of patients divided by renal function (estimated glomerular filtration rate [eGFR] < and ≥60 ml/min/1.73m^2) and left ventricular ejection fraction (LVEF) (< and ≥40%).

All candidate variables had <2% missingness except for level of education (4%), serum creatinine (7%), hematocrit (10%), LVEF (11%), and left atrial diameter (14%). Missing data were handled with single imputation. Imputed values were obtained by the Markov chain Monte Carlo method or regression methods (22).

For all models, continuous variables were evaluated for nonlinearity with the outcome and when nonlinear fit with linear splines. All analyses were performed using SAS software version 9.3 (SAS Institute, Cary, North Carolina).

RESULTS

PATIENT CHARACTERISTICS AND PATTERNS OF DIGOXIN USE

Between June 2010 and August 2011, 10,132 patients were enrolled in ORBIT-AF from 176 sites; 490 patients (4.8%) were then excluded due to lack of follow-up data and 23 patients (0.2%) were excluded due to a missing response for digoxin use at baseline or follow-up, resulting in a final cohort of 9,619 patients from 174 sites. Mean follow-up was 22 months (IQR, 17 to 25). Digoxin use was reported in 2,267 patients (23.6%) at the time of study enrollment and an additional 681 patients (7.1%) were initiated on digoxin during follow-up, leaving 6,671 (69.4%) who were never on digoxin. Of those on digoxin at baseline, 794 (35.0%) patients discontinued digoxin in follow-up and, of these, 217 (27.3%) subsequently resumed digoxin.

Baseline characteristics of the overall study population stratified by digoxin use are shown in Table 1. Heart failure was present in 3,161 (32.9%) of the cohort, among whom prevalent digoxin use at baseline was present in 1,091 (34.5%) and incident use in follow-up was observed in another 268 (8.5%). Beta-blockers were prescribed in 69.6% of patients on digoxin compared with 62.4% of those never on digoxin; nondihydropyridine calcium channel blockers were prescribed in 18.6% on digoxin compared with 16.0% never on digoxin; and antiarrhythmic medications were prescribed in 17.6% on digoxin compared with 32.6% never on digoxin.

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Factors independently associated with digoxin use at baseline included: rate control strategy and absence of prior ablation; permanent AF; worse HF functional class and LVEF; sinus node dysfunction; larger left atria; lower diastolic blood pressure; better renal function; faster heart rate; history of diabetes, hyperthyroidism, or chronic obstructive pulmonary disease; and female sex (full model presented in Online Table 2a). Multivariable predictors of the initiation of digoxin in follow-up were relatively similar to those for baseline use (full model, Online Table 2b). Multivariable baseline predictors of discontinuation during follow-up were: new-onset, paroxysmal, or persistent AF; bradycardia or tachycardia; no prior myocardial infarction; prior use of an antiarrhythmic drug; lower eGFR; higher EHRA score; and higher systolic blood pressure (full model, Online Table 2c).

The overall mean heart rate at baseline was 71.9 (± 13) beats/min, with a higher unadjusted heart rate (73.1 ± 12.7 beats/min) among prevalent digoxin users compared with those not on digoxin at baseline (71.5 ± 13.1 beats/min; p for comparison < 0.001). After adjustment for other rate control medications, the adjusted heart rate remained slightly higher among digoxin users (72.9 beats/min) than nonusers at baseline (71.5 beats/min; p < 0.0001).

QUALITY OF LIFE, SYMPTOMS, AND OUTCOMES

EHRA symptom scores were not significantly different among prevalent or incident digoxin patients versus no digoxin (p = 0.09 and p = 0.58, respectively) (Table 1). In the quality of life substudy, unadjusted HRQOL was slightly lower in patients who received digoxin than those who were never on digoxin, both at baseline (AFEQT overall score median [IQR]: prevalent 78.7 [62.0 to 92.6]; incident 79.2 [64.8 to 88.9]; never 83.3 [68.5 to 93.5]; p = 0.0002) and at 1 year (prevalent 80.6 [66.7 to 91.7]; incident 79.6 [64.8 to 95.4]; never 86.6 [73.1 to 95.4]; p = 0.0001). The majority of prevalent digoxin patients who had follow-up were without symptoms, with an EHRA score of 0 in 51% to 53% of patients at 6, 12, 18, and 24 months. In multivariable analysis, digoxin use had a neutral association with the frequency of worsening AF symptoms in both patients with HF (**Central Illustration, Panel A**) and patients without HF (**Central Illustration, Panel B**).

Hospitalization for any cause occurred in 4,326 (45.0%), cardiovascular hospitalization in 2,485 (26.0%), and death in 865 (9.0%) patients. Prevalent use of digoxin at registry enrollment among patients with and without HF was not associated with all-cause hospitalization, cardiovascular hospitalization, symptoms, or death (**Central Illustration, Panels A and B**). Among patients with eGFR <60 ml/min/1.73m^2, digoxin use at enrollment had borderline association with subsequent death (adjusted HR: 1.23; 95% CI: 1.00 to 1.51) and first all-cause hospitalization (adjusted HR: 1.14; 95% CI: 1.01 to 1.28).

Incident use of digoxin during follow-up among patients with and without HF after propensity matching (Supplemental Tables 4a and 4b) was not associated with all-cause hospitalization, cardiovascular hospitalization, or symptoms (**Central Illustration, Panels C and D**). Incident digoxin use was not associated with subsequent death in those with HF (adjusted HR: 1.05; 95% CI: 0.66 to 1.65; **Central Illustration, Panel C**) but was in those without HF (adjusted HR: 1.99; 95% CI: 1.12 to 3.56; **Central Illustration, Panel D**). Similarly, the association of incident digoxin use with death was confined to those with LVEF >40% (adjusted HR: 2.21; 95% CI: 1.32 to 3.71). Among patients with eGFR <60

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ml/min/1.73m^2, incident digoxin use was not associated with death (adjusted HR: 0.96; 95% CI: 0.51 to 1.82).

DISCUSSION

Within the context of multiple recent descriptions of digoxin prescribing in a variety of patient populations, the ORBIT-AF registry provides a broadly representative and clinically detailed look at the patterns of digoxin use in patients with existing AF. Despite the growing availability of alternative treatments for AF patients with HF, prevalent use of digoxin in ORBIT-AF was 24% overall and even higher among patients with HF, lower blood pressure, higher heart rate, and female sex. Other contemporary data show similar rates of digoxin use: 23% use among incident AF (15) and 18% use among patients with incident HFrEF (11). In follow-up out to 3 years, 15% of ORBIT-AF patients either initiated or discontinued the drug, suggesting that use was dynamic. Digoxin was given with beta-blockers and other rate and rhythm control agents in the majority of patients.

DIGOXIN EFFECTIVENESS AND SAFETY

These data add to the suboptimal body of evidence regarding the effectiveness and safety of digoxin in AF patients with and without HF. All positive cardiac inotropes that act through calcium handling and sensitization – with the notable exception of digoxin – have been shown in controlled trials to promote left ventricular remodeling and adverse events (23–26). The exception, the DIG trial, demonstrated equal survival in HF patients randomized to digoxin versus placebo (7). Yet, its conduct in the early 1990s, predating most modern therapies for HFrEF, and its exclusion of patients with AF leave open many questions. Since DIG, no high-quality, large, randomized trials of digoxin have been performed. Meanwhile, a variety of post hoc analyses of trial data have found digoxin to be neutral to harmful in certain subgroups. In SPORTIF III and V (the Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation studies), digitalis use was 53% and users had a higher mortality than nonusers (14). The AFFIRM study analysis that incorporated time-dependent assessment of digoxin use found an association between incident digoxin use and mortality (12,13).

Observational data from real-world practice have generally come to similar conclusions. In a large study of 2,891 Kaiser patients with newly diagnosed HFrEF, of whom 22.9% had AF, incident digoxin use was associated with higher mortality (HR: 1.72; 95% CI: 1.25 to 2.36) but no significant difference in the risk of HF hospitalization (HR: 1.05; 95% CI: 0.82 to 1.34) (11). A propensity-score matching analysis of 14,787 Kaiser patients with incident AF and without HF, the ATRIA-CVRN (Anticoagulation and Risk factors In Atrial fibrillation-Cardiovascular Research Network) study, found that incident digoxin use was independently associated with higher risk of death (HR: 1.71; 95% CI: 1.52 to 1.93) and higher risk of hospitalization (HR: 1.63; 95% CI: 1.56 to 1.71) (16). Most recently, the TREAT-AF (Retrospective Evaluation and Assessment of Therapies in Atrial Fibrillation) study among 122,465 veterans with new-onset AF showed higher mortality in those treated with digoxin (multivariable HR: 1.26; 95% CI: 1.23 to 1.29; and propensity matching HR: 1.21; 95% CI: 1.17 to 1.25) (15).

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STUDY ADVANTAGES AND LIMITATIONS

The ORBIT-AF registry has advantages over these other studies. Unlike trial cohorts with narrow eligibility criteria and mandated systematic follow-up, ORBIT-AF captured a wide range of patients in routine care. Unlike the Kaiser and TREAT-AF studies, which relied on administrative coding for diagnoses and were absent LVEF and functional status measures, the prospective and rigorous clinical data capture in ORBIT-AF is more likely to limit misclassification and accurately measure potential confounders. This may be why the adjustment process in ORBIT-AF showed greater reduction in the unadjusted to adjusted HR for digoxin in most of the analyses performed.

Obviously, unaccounted for treatment selection biases are likely to affect observational associations. The contradictory findings from different statistical analyses of the same AFFIRM database highlight this potential (12,13). Although extensive covariates were collected and modeled in this detailed prospective ORBIT-AF registry, including LVEF, NYHA functional class, vital signs, laboratory values, and concomitant medications, unmeasured reasons for starting digoxin are likely to be at least partially confounding the association observed between digoxin and outcomes. Digoxin use is often dictated by hypotension, intolerance to more typical agents (e.g., beta-blocker), and worsening left ventricular dysfunction; all of which indicate worse disease. Digoxin is prescribed in AF largely for its ability to slow AV nodal conduction; yet, even after adjustment, digoxin was associated with higher heart rates, suggesting residual unmeasured differences or issues with medication adherence that were not measured.

Propensity matching, multivariable adjustment, and stratified analysis all help to reduce such confounding, but these methods do not completely address disease severity or many other facets of cardiac health. Ultimately, higher-quality data from randomized trial designs that can remove treatment selection biases are necessary to definitively assess the effectiveness and safety of digoxin. While another large randomized trial of digoxin like the DIG study is unlikely to be funded, evolving pragmatic clinical trial designs offer opportunities in the near future to test such a question through randomization of real-world practices (27). Since there are 33 million individuals with AF across the globe, determining whether or not digoxin is safe and effective should be a key priority in future clinical investigation.

Other limitations should be considered. ORBIT-AF participating sites were selected to be representative of the national AF population, but were not a true cross-section, such that results may not be generalizable to all patients with AF; they also purposely do not represent patients outside the United States. Dose, serum digoxin concentration, and exact timing of and reasons for digoxin initiation or discontinuation were not collected.

CONCLUSIONS

Digoxin use remains common in the contemporary treatment of AF. Overall, after statistical adjustment for detailed clinical factors, digoxin had a neutral association with a wide range of outcomes. Given ongoing questions about the safety of this commonly-used medication, high-quality data derived from a pragmatic clinical trial of real-world contemporary digoxin use is greatly needed.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS AND ACRONYMS

AF	atrial fibrillation
CI	confidence interval
eGFR	estimated glomerular filtration rate
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
HRQOL	health-related quality of life
LVEF	left ventricular ejection fraction
OR	odds ratio

REFERENCES

1. Gheorghiade M, van Veldhuisen DJ, Colucci WS. Contemporary use of digoxin in the management of cardiovascular disorders. Circulation. 2006; 113:2556–2564. [PubMed: 16735690]
2. Anderson JL, Halperin JL, Albert NM, et al. Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations): a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013; 61:1935–1944. [PubMed: 23558044]
3. 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:e147–e239. [PubMed: 23747642]
4. Kanji S, MacLean RD. Cardiac glycoside toxicity: more than 200 years and counting. Crit Care Clin. 2012; 28:527–535. [PubMed: 22998989]
5. 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:e1–e76. [PubMed: 24685669]
6. 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; 63:1823–1832. [PubMed: 24613328]

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7. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med. 1997; 336:525–533. [No authors listed]. [PubMed: 9036306]
8. 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; 27:178–186. [PubMed: 16339157]
9. 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; 347:1403–1411. [PubMed: 12409542]
10. 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; 15:551–559. [PubMed: 23355060]
11. Freeman JV, Yang J, Sung SH, Hlatky MA, Go AS. Effectiveness and safety of digoxin among contemporary adults with incident systolic heart failure. Circ Cardiovasc Qual Outcomes. 2013; 6:525–533. [PubMed: 24021697]
12. Whitbeck MG, Charnigo RJ, Khairy P, et al. Increased mortality among patients taking digoxin--analysis from the AFFIRM study. Eur Heart J. 2013; 34:1481–1488. [PubMed: 23186806]
13. 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; 34:1489–1497. [PubMed: 23592708]
14. Gjesdal K, Feyzi J, Olsson SB. Digitalis: a dangerous drug in atrial fibrillation? An analysis of the SPORTIF III and V data. Heart. 2008; 94:191–196. [PubMed: 17483128]
15. Turakhia MP, Santangeli P, Winkelmayer WC, et al. Increased mortality associated with digoxin in contemporary patients with atrial fibrillation: findings from the TREAT-AF study. J Am Coll Cardiol. 2014; 64:660–668. [PubMed: 25125296]
16. Freeman JV, Reynolds K, Fang M, et al. Digoxin and Risk of Death in Adults with Atrial Fibrillation: The ATRIA-CVRN Study. Circ Arrhythm Electrophysiol. 2015; 8:49–58. [PubMed: 25414270]
17. Piccini JP, Fraulo ES, Ansell JE, et al. Outcomes registry for better informed treatment of atrial fibrillation: rationale and design of ORBIT-AF. Am Heart J. 2011; 162:606–612 e1. [PubMed: 21982650]
18. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J. 2013; 34:2281–2329. [PubMed: 23801822]
19. Spertus J, Dorian P, Bubien R, et al. Development and validation of the Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) Questionnaire in patients with atrial fibrillation. Circ Arrhythm Electrophysiol. 2011; 4:15–25. [PubMed: 21160035]
20. Schaubel DE, Wolfe RA, Port FK. A sequential stratification method for estimating the effect of a time-dependent experimental treatment in observational studies. Biometrics. 2006; 62:910–917. [PubMed: 16984335]
21. Austin PC. Primer on statistical interpretation or methods report card on propensity-score matching in the cardiology literature from 2004 to 2006: a systematic review. Circ Cardiovasc Qual Outcomes. 2008; 1:62–67. [PubMed: 20031790]
22. Enders, CK. Applied Missing Data Analysis. New York, NY: Guilford Press; 2010.
23. Cohn JN, Goldstein SO, Greenberg BH, et al. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. N Engl J Med. 1998; 339:1810–1816. [PubMed: 9854116]
24. Oliva F, Latini R, Politi A, et al. Intermittent 6-month low-dose dobutamine infusion in severe heart failure: DICE Multicenter Trial. Am Heart J. 1999; 138:247–253. [PubMed: 10426835]
25. Cuffe MS, Califf RM, Adams KF, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure - A randomized controlled trial. JAMA. 2002; 287:1541–1547. [PubMed: 11911756]
26. Packer M, Colucci W, Fisher L, et al. Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. JACC Heart Fail. 2013; 1:103–111. [PubMed: 24621834]
27. Sugarman J, Califf RM. Ethics and regulatory complexities for pragmatic clinical trials. JAMA. 2014; 311:2381–2382. [PubMed: 24810723]

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PERSPECTIVES

Competency in Medical Knowledge

Previous studies have suggested that digoxin use might be associated with adverse events in patients with atrial fibrillation (AF), but after adjustment for patient characteristics in a contemporary cohort, there were no significant interactions across a range of outcomes.

Translational Outlook

Mixed results regarding the safety of digoxin across multiple observational analyses call for higher quality evidence derived from pragmatic clinical trials of digoxin in patients with AF.

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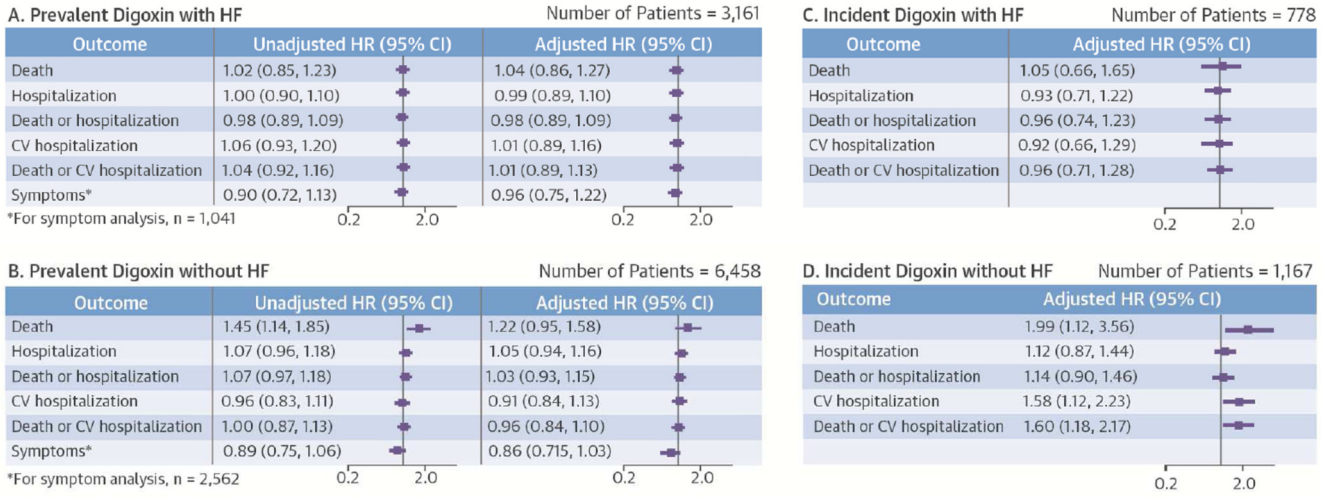

CENTRAL ILLUSTRATION Association of Digoxin Use with Subsequent Outcomes

In this assessment of longitudinal patterns of digoxin use in patients with atrial fibrillation (AF) with and without heart failure (HF), registry data were used to correlate digoxin use with outcomes. Among patients receiving digoxin at study enrollment (prevalent), digoxin use was not associated with subsequent onset of symptoms, hospitalization, or mortality in patients with **(A)** or without **(B)** HF. The same is true for patients with HF who initiated digoxin during follow-up **(C)**, although incident digoxin use in patients without HF was associated with subsequent death **(D)**. CI = confidence interval; CV = cardiovascular; HR = hazard ratio.

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TABLE 1

Selected Baseline Characteristics of Patients by Digoxin Use

	Overall (N = 9,619)	Prevalent Digoxin (n = 2,267)	Incident Digoxin (n = 681)	No Digoxin (n = 6,671)	p Value (Prevalent vs. Never)	p Value (Incident vs. Never)
Demographics						
Age, yrs	75 (67,82)	76 (67,83)	76 (68,81)	75 (67,81)	<0.0001	0.12
Female	4,088 (43%)	1,009 (45%)	299 (44%)	2,780 (42%)	0.018	0.26
Body mass index, kg/m^2	29.1 (25.4,34.0)	27.9 (24.3,32.6)	29.0 (25.4,34.4)	29.5 (25.8,34.4)	<0.0001	0.15
Heart rate, beats/min	70 (63,80)	72 (64,80)	72 (64,81)	70 (62,79)	<0.0001	<0.0001
Systolic BP, mm Hg	126 (116,138)	124 (112,136)	124 (112,136)	126 (118,138)	<0.0001	<0.001
Diastolic BP, mm Hg	72 (66,80)	70 (64,80)	70 (66,80)	72 (68,80)	<0.0001	0.006
Medical history						
Diabetes	2,837 (29%)	822 (36%)	215 (32%)	1,800 (27%)	<0.0001	0.011
Hyperthyroidism	196 (2%)	62 (3%)	21 (3%)	113 (2%)	0.002	0.010
COPD	1,581 (16%)	476 (21%)	124 (18%)	981 (15%)	<0.0001	0.015
Hyperlipidemia	6,961 (72%)	1,647 (73%)	470 (69%)	4,844 (73%)	0.98	0.045
Sick sinus syndrome	1,706 (18%)	488 (22%)	131 (19%)	1,087 (16%)	<0.0001	0.049
No HF	6,458 (67%)	1,176 (52%)	413 (61%)	4,869 (73%)		
NYHA class I HF	1,006 (10%)	326 (14%)	96 (14%)	584 (9%)	<.0001	<.0001
NYHA class II HF	1,440 (15%)	499 (22%)	109 (16%)	832 (12%)		
NYHA class III/IV HF	700 (7%)	262 (12%)	62 (9%)	376 (6%)		
Prior MI	1,547 (16%)	430 (19%)	127 (19%)	990 (15%)	<0.0001	0.008
Prior CABG	1,428 (15%)	346 (15%)	119 (17%)	963 (14%)	0.34	0.033
Studies						
LVEF, ≤40% or moderate to severely reduced	1,263 (13%)	526 (23%)	118 (17%)	619 (9%)	<0.0001	<0.0001
Left atrium, moderate or severe enlargement	3,799 (39%)	1,077 (48%)	306 (45%)	2,416 (36%)	<0.0001	<.0001
IVCD	1,062 (11%)	281 (12%)	65 (10%)	716 (11%)	0.001	0.040
RBBB	806 (8%)	201 (9%)	77 (11%)	528 (8%)		
LBBB	376 (4%)	103 (5%)	27 (4%)	246 (4%)		
eGFR, ml/min/1.73m^2	67 (53,82)	67 (54,83)	65 (51,81)	67 (53,82)	0.3853	0.1223
AF history						
New-onset AF	429 (4%)	64 (3%)	35 (5%)	330 (5%)	<0.0001	0.16
Paroxysmal AF	4,874 (51%)	862 (38%)	353 (52%)	3,659 (55%)		
Persistent AF	1,610 (17%)	461 (20%)	100 (15%)	1,049 (16%)		
Rhythm control strategy	3,043 (32%)	416 (18%)	199 (29%)	2,428 (36%)	<0.0001	<0.001
Prior cardioversion	2,907 (30%)	659 (29%)	225 (33%)	2,023 (30%)	0.26	0.14
Prior antiarrhythmic drug	4,403 (46%)	921 (41%)	311 (46%)	3,171 (48%)	<0.0001	0.35
Catheter ablation of AF	538 (6%)	75 (3%)	29 (4%)	434 (7%)	<0.0001	0.021

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	Overall (N = 9,619)	Prevalent Digoxin (n = 2,267)	Incident Digoxin (n = 681)	No Digoxin (n = 6,671)	p Value (Prevalent vs. Never)	p Value (Incident vs. Never)
AV node ablation	217 (2%)	32 (1%)	9 (1%)	176 (3%)	0.001	0.037
EHRA Scores						
No symptoms	3,676 (38%)	856 (38%)	247 (36%)	2,573 (39%)	0.09	0.58
Mild symptoms	4,332 (45%)	1,021 (45%)	323 (47%)	2,988 (45%)		
Severe symptoms	1,398 (15%)	353 (16%)	93 (14%)	952 (14%)		
EHRA score–disabling	172 (2%)	29 (1%)	13 (2%)	130 (2%)		

Values are n (%) (dichotomous variables) or median (interquartile range) (continuous variables). AF = atrial fibrillation; AV = atrioventricular; BP = blood pressure; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; EHRA = European Heart Rhythm Association; HF = heart failure; IVCD = interventricular conduction delay; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; RBBB = right bundle branch block.