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Increased Mortality Associated With Digoxin in Contemporary Patients With Atrial Fibrillation

Findings From the TREAT-AF Study

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ABSTRACT

BACKGROUND Despite endorsement of digoxin in clinical practice guidelines, there exist limited data on its safety in atrial fibrillation/flutter (AF).

OBJECTIVES The goal of this study was to evaluate the association of digoxin with mortality in AF.

METHODS Using complete data of the TREAT-AF (The Retrospective Evaluation and Assessment of Therapies in AF) study from the U.S. Department of Veterans Affairs (VA) healthcare system, we identified patients with newly diagnosed, nonvalvular AF seen within 90 days in an outpatient setting between VA fiscal years 2004 and 2008. We used multivariate and propensity-matched Cox proportional hazards to evaluate the association of digoxin use with death. Residual confounding was assessed by sensitivity analysis.

RESULTS Of 122,465 patients with 353,168 person-years of follow-up (age 72.1 ± 10.3 years, 98.4% male), 28,679 (23.4%) patients received digoxin. Cumulative mortality rates were higher for digoxin-treated patients than for untreated patients (95 vs. 67 per 1,000 person-years; $p < 0.001$). Digoxin use was independently associated with mortality after multivariate adjustment (hazard ratio [HR]: 1.26, 95% confidence interval [CI]: 1.23 to 1.29, $p < 0.001$) and propensity matching (HR: 1.21, 95% CI: 1.17 to 1.25, $p < 0.001$), even after adjustment for drug adherence. The risk of death was not modified by age, sex, heart failure, kidney function, or concomitant use of beta-blockers, amiodarone, or warfarin.

CONCLUSIONS Digoxin was associated with increased risk of death in patients with newly diagnosed AF, independent of drug adherence, kidney function, cardiovascular comorbidities, and concomitant therapies. These findings challenge current cardiovascular society recommendations on use of digoxin in AF. (J Am Coll Cardiol 2014;64:660–8) © 2014 by the American College of Cardiology Foundation.

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In atrial fibrillation/atrial flutter (AF, collectively), digoxin is one of the most widely used rate control agents worldwide and is largely accepted as a valid therapeutic option (1). Clinical guidelines currently endorse the use of digoxin in AF, despite the lack of randomized trials of digoxin in AF cohorts (2,3). In heart failure (HF) cohorts, the effectiveness and safety of digoxin has been shown to vary by serum digoxin concentrations (4–6), indicating possible moderation by kidney function (7). However, despite established arrhythmic and nonarrhythmic toxicities, there are only limited, conflicting, and mostly older observational data on the safety of digoxin in AF (8–11). We therefore investigated the association of digoxin therapy with mortality in a large cohort of patients with newly diagnosed AF from a large, national healthcare system.

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METHODS

The TREAT-AF (The Retrospective Evaluation and Assessment of Therapies in AF) study is a retrospective cohort study of patients with newly diagnosed AF treated in the U.S. Department of Veterans Affairs (VA) healthcare system (12), which is the largest integrated healthcare system in the United States. We used data from multiple VA centralized datasets, which represent claims and electronic health records from the full denominator of VA users. Linked and merged datasets include the VA National Patient Care Database, which contains demographic, outpatient, inpatient, and long-term care administrative data (13); the VA Decision Support System national pharmacy extract, which provides patient-level detail on inpatient and outpatient medications, dispensing details, and costs (14); the VA Fee Basis Inpatient and Outpatient datasets, which capture non-VA care provided to veterans (14); the VA Laboratory Decision Support System extract, which includes claims and laboratory results for serum creatinine measurement (15); and the VA Vital Status File, which contains validated combined mortality data from VA, Medicare, and Social Security Administration sources (16,17).

IDENTIFICATION OF THE STUDY COHORT. We identified patients with newly diagnosed, nonvalvular AF and seen within 90 days in an outpatient care setting. **Figure 1** illustrates our cohort inclusion criteria: 1) a primary or secondary diagnosis of AF (International Classification of Diseases-9th Revision [ICD-9] 427.31 or 427.32) associated with an inpatient or outpatient VA encounter between October 1, 2003, and September 30, 2008 (VA fiscal years 2004 to 2008); 2) a second confirmatory diagnosis between 30 and 365 days after the date of the index AF diagnosis; 3) at least 1 primary care, cardiology, women's health, nephrology, geriatric, or anticoagulation clinic outpatient visit in the 90 days after the index date; and 4) receipt of any outpatient prescriptions within 90 days after the index AF diagnosis. The requirement of a confirmatory AF diagnosis is intended to minimize the impact of rule-out diagnoses and improve specificity; this approach has been previously applied to Medicare (18,19) and VA (12) studies.

Patients were excluded if they met any of the following criteria at the index date: 1) a prior AF diagnosis, defined by any inpatient, outpatient or Fee Basis AF ICD-9 codes or Current Procedural Terminology-4th Edition (CPT-4) codes for catheter or surgical ablation in the 4 years prior; 2) history of valve disease, repair, or replacement; 3) thyroid disease; 4) kidney transplant; or 5) cardiac surgery within 30 days.

PRIMARY EXPOSURE VARIABLES AND OUTCOMES. The primary exposure variable was receipt of outpatient digoxin during a 90-day exposure ascertainment window, starting from date of the index AF diagnosis. The primary outcome was time to death, beginning from 90 days after index AF diagnosis. Death was ascertained using VA's validated Vital Status file, which has 97.6% agreement and 98.3% sensitivity for detection of deaths identified by the National Death Index (17). We assumed that patients with no record of death were alive until September 30, 2011, the last date for which vital status records from all sources were fully ascertained.

CLINICAL COVARIATES. We determined baseline patient comorbidities by calculating a Charlson comorbidity score (20,21) and by identifying comorbidity-specific ICD-9 codes up to 2 years before the index AF date, using algorithms based on the Agency for Healthcare Research and Quality's Clinical Classification System (22). Internal checking of the data indicated no substantial increase in comorbidity ascertainment by extending the claims window for more than two years prior to the index date. The $CHADS_2$ score was calculated using diagnostic algorithms previously validated in VA data (23,24). Receipt of concomitant outpatient drug therapies was ascertained using the same methods as for the primary exposure.

We estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration formula (25). We used the most recent

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation/atrial flutter

CI = confidence interval

eGFR = estimated glomerular filtration rate

HF = heart failure

HR = hazard ratio

ICD-9 = International Classification of Diseases-9th Revision

IDMS = isotope-dilution mass spectroscopy

MI = myocardial infarction

MPR = medication possession ratio

VA = U.S. Department of Veterans Affairs

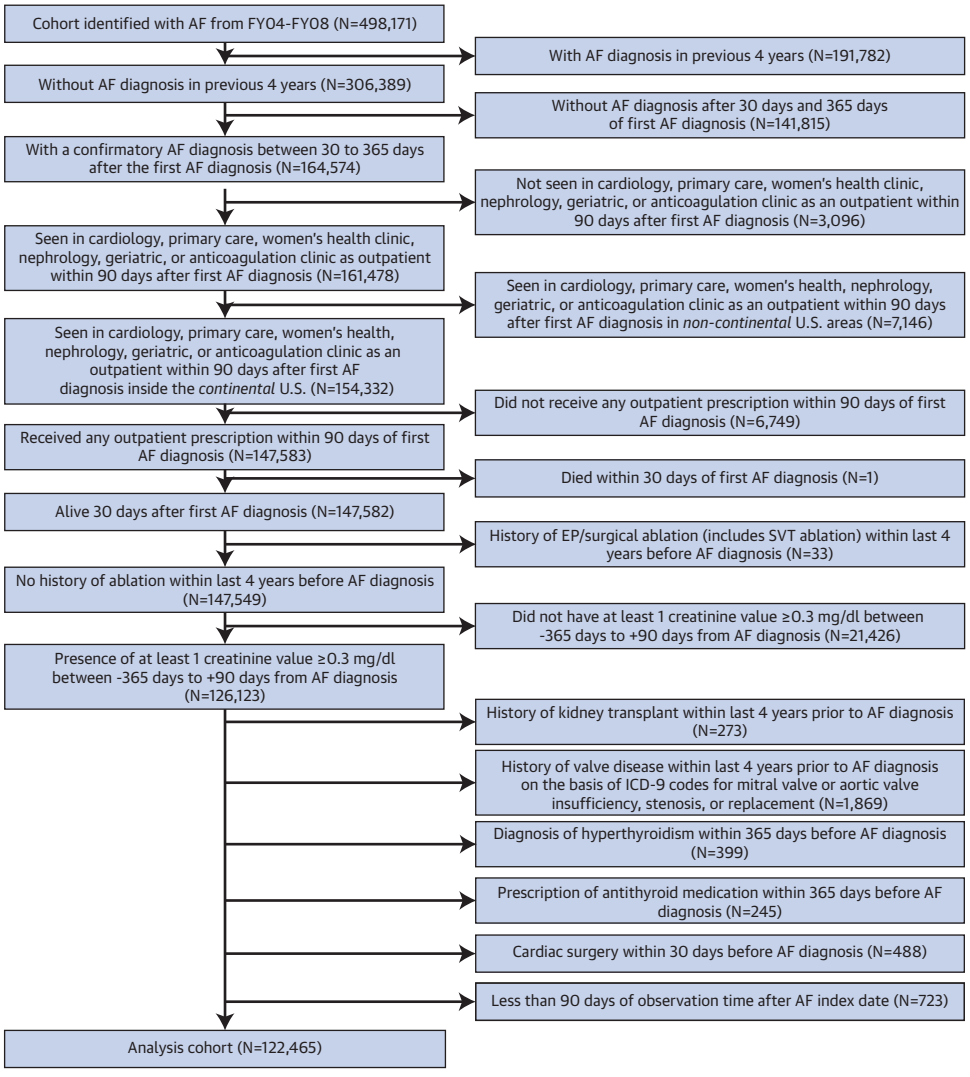


FIGURE 1 Consort Diagram

Detailed inclusion and exclusion criteria used to select the cohort of 122,465 patients studied in this analysis. AF = atrial fibrillation/atrial flutter; EP = electrophysiology; FY = fiscal year; ICD-9 = International Classification of Diseases-9th Revision; SVT = supraventricular tachycardia.

outpatient serum creatinine from 365 days before to 90 days after the index AF diagnosis. In the VA system, isotope-dilution mass spectroscopy (IDMS)-based calibration was implemented beginning in the third quarter of 2007. Because GFR can be underestimated if creatinine measurements have not been calibrated to IDMS (26), we therefore adjusted for non-IDMS standardized creatinine values by subtracting 5% from all creatinine measurements before fiscal year 2008. Kidney function was then stratified by eGFR (in ml/min/1.73 m^2) into the following groups: ≥90; <90 to ≥60; <60 to ≥45; <45 to ≥30; <30 to ≥15; and <15. A separate eGFR group for dialysis-dependent chronic kidney disease was also identified using ICD-9 and CPT-4 codes for dialysis-related procedures or diagnoses.

STATISTICAL ANALYSIS. We compared differences in baseline characteristics between digoxin-treated patients and untreated patients using chi-square tests for categorical variables and Student *t* tests for continuous variables. We performed Cox regression to estimate the risk of death, first modeling an "intention-to-treat" analysis on the basis of digoxin receipt, adjusting for age, sex, race, hypertension,

prior stroke, HF, diabetes, Charlson comorbidity score, $CHADS_2$ score, cardiovascular medications, antiarrhythmic drug therapies, and eGFR stratum.

Next, to account for variable exposure on the basis of duration and intensity of drug therapy, we performed an adherence-adjusted analysis by quantifying digoxin exposure by calculating the patient-level medication possession ratio (MPR) and performing Cox regression with MPR as a time-varying covariate. The MPR was calculated as the fraction of total outpatient days' supply of digoxin divided by the total number of days from time of AF diagnosis until date of death or censoring, truncated at 1.0. The MPR was adjusted to account for carryover of previous medication fills to avoid overestimation of drug supply. If the patient received different dosages on the same day, these were considered part of the same prescription. This approach has been validated (27,28) and used previously with VA data (29). For all Cox models, the assumption of proportional hazards was found to be valid by examining Schoenfeld residuals.

PROPENSITY MATCHING. We also performed a separate Cox regression on patients matched by the propensity scores of digoxin receipt. Propensity scores were calculated, with receipt of digoxin as the dependent variable, by using multivariate logistic regression and baseline characteristics listed in Table 1 as independent variables. We tested pairwise interactions of covariates and retained the terms that significantly improved model fit. Propensity score balance and overlap were assessed using propensity score distributions and standardized differences in observed characteristics. Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test and the C-statistic. Patients receiving the study drug were matched 1:1 with nonrecipients using nearest-neighbor matching without replacement. Finally, we used the Kaplan-Meier method to estimate cumulative incidence of death in both the full and propensity-matched cohorts, and log-rank tests to assess differences between treated and untreated groups.

STRATIFIED AND SUBGROUP ANALYSES. We tested for modification of the association between digoxin use and mortality using the chi-square test for a series of potential effect modifiers. A log-likelihood ratio test for nested models with n degrees of freedom, where n = the number of interaction terms, was used to assess model fit. Potential effect modifiers included age, sex, presence of HF, prior myocardial infarction (MI), and concomitant use of warfarin, beta-blockers, or amiodarone.

SENSITIVITY ANALYSES. We used the method of Lin et al. (30) to perform a 3-way sensitivity analysis to

TABLE 1 Baseline Characteristics

	Digoxin Prescribed Within 90 Days After AF Diagnosis		
	Yes (n = 28,679)	No (n = 93,786)	p Value
Seen in primary care	20,936 (73.0)	68,449 (73.0)	0.96
Age, yrs	71.7 ± 10.2	72.2 ± 10.3	<0.001
Female	434 (1.5)	1,546 (1.7)	0.11
Race, white	24,532 (85.5)	79,918 (85.2)	0.17
Charlson comorbidity index	1.1 ± 1.2	0.91 ± 1.1	<0.001
$CHADS_2$ score group			<0.001
$CHADS_2$ 0–1	14,536 (50.7)	43,241 (46.1)	<0.001
$CHADS_2$ 2–3	12,163 (42.4)	43,807 (46.7)	<0.001
$CHADS_2$ 4–6	1,980 (6.9)	6,738 (7.2)	0.11
Congestive HF	6,099 (21.3)	13,218 (14.1)	<0.001
Hypertension	16,010 (55.8)	61,491 (65.6)	<0.001
Age ≥75 yrs	12,934 (45.1)	44,925 (47.9)	<0.001
Diabetes	7,949 (27.7)	27,353 (29.2)	<0.001
Prior stroke/TIA	1,551 (5.4)	6,009 (6.4)	<0.001
Prior MI	1,370 (4.8)	4,149 (4.4)	0.01
eGFR group, ml/min/1.73 m^2			<0.001
eGFR ≥90	3,782 (13.2)	11,673 (12.5)	0.001
eGFR 60–89	14,611 (51.0)	47,299 (50.4)	0.13
eGFR 45–59	6,312 (22.0)	20,464 (21.8)	0.50
eGFR 30–44	3,076 (10.7)	10,207 (10.9)	0.45
eGFR 15–29	727 (2.5)	3,011 (3.2)	<0.001
eGFR <15	88 (0.31)	582 (0.62)	<0.001
Dialysis	83 (0.29)	550 (0.59)	<0.001
eGFR, ml/min/1.73 m^2	67.6 ± 19.9	66.6 ± 20.6	<0.001
Cardiovascular medications			
Aspirin	4,738 (16.5)	13,973 (14.9)	<0.001
Clopidogrel	1,499 (5.2)	4,941 (5.3)	0.78
Aspirin + clopidogrel	731 (2.6)	2,004 (2.1)	<0.001
ACE inhibitor or angiotensin receptor blockers	17,133 (59.7)	47,471 (50.6)	<0.001
Alpha-blockers	464 (1.6)	1,948 (2.1)	<0.001
Diuretic agents	16,625 (58.0)	40,422 (43.1)	<0.001
Niacin or fibrates	2,384 (8.3)	6,258 (6.7)	<0.001
Statins	15,137 (52.8)	49,661 (53.0)	0.61
Warfarin	18,045 (62.9)	50,843 (54.2)	<0.001
Antiarrhythmic drugs			<0.001
All Class I	585 (2.0)	2,031 (2.2)	0.20
Class III (sotalol/dofetilide)	810 (2.8)	3,364 (3.6)	<0.001
Amiodarone	2,849 (9.9)	8,806 (9.4)	0.006
Rate-controlling drugs			
All beta-blockers	18,246 (63.6)	53,065 (56.6)	<0.001
Metoprolol	11,923 (41.6)	34,884 (37.2)	<0.001
Carvedilol	3,331 (11.6)	4,375 (4.7)	<0.001
Atenolol	2,735 (9.5)	12,785 (13.6)	<0.001
Other	257 (0.90)	1,021 (1.1)	0.01
All calcium-channel blockers	8,742 (30.5)	28,340 (30.2)	<0.001
Diltiazem	5,175 (18.0)	12,622 (13.5)	<0.001
Verapamil	840 (2.9)	1,866 (2.0)	<0.001
Other	2,727 (9.5)	13,852 (14.8)	<0.001

Values are n (%) or mean ± SD.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation/atrial flutter; eGFR = estimated glomerular filtration rate; HF = heart failure; MI = myocardial infarction; TIA = transient ischemic stroke.

determine whether observed differences in the risk of death could be fully explained by unmeasured confounders. Using this approach, we calculated the hazard required of an unmeasured confounder to explain the result across hypothetical prevalences of the confounder in the treated and untreated groups.

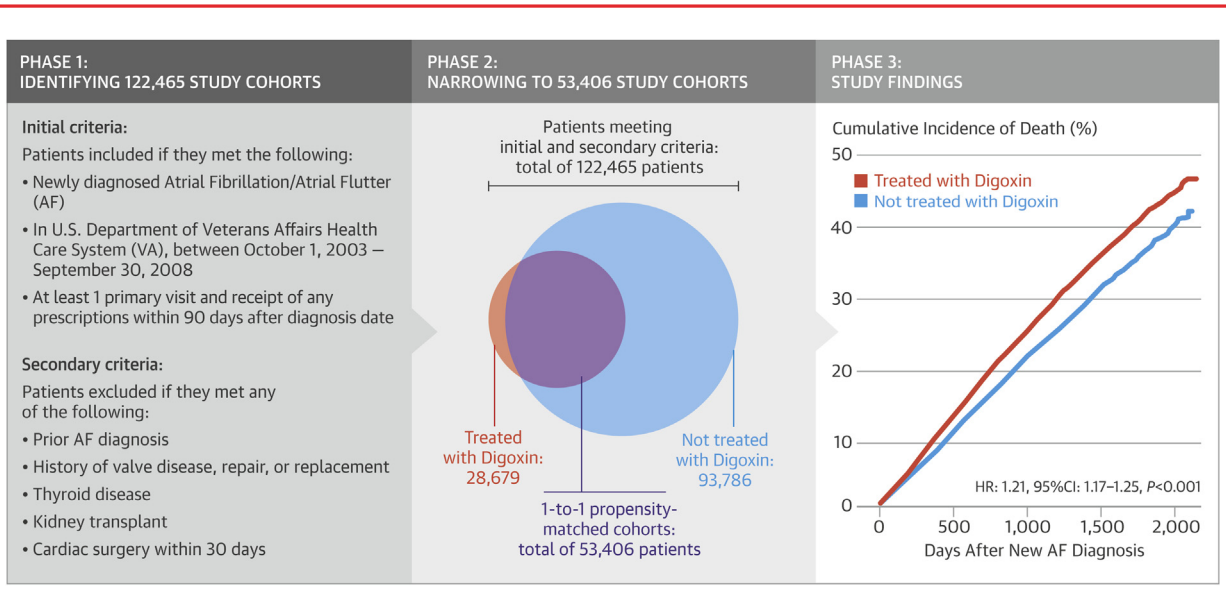
ROLE OF FUNDING SOURCE. The sponsors were not involved with study design, data assembly and analysis, or manuscript preparation. The local institutional review board approved the study. All analyses were performed using SAS version 9.1 (Cary, North Carolina) and STATA version 11.0 (College Station, Texas).

RESULTS

PATIENT POPULATION. A schema of methods and results are shown in the **Central Illustration**. The study cohort included 122,465 patients with a mean age of 72.1 ± 10.3 years; 1.6% were women, and 36.8% of patients had an eGFR <60 ml/min/1.73 m^2 or were on dialysis. Of these patients, 28,679 (23.4%) received digoxin during the first 90 days after initial AF diagnosis (**Table 1**). In patients receiving digoxin, the mean MPR was 0.79 ± 0.27, and 70% of digoxin users were on therapy 1 year after the index date. Compared with nonrecipients, digoxin recipients were of similar age but had a higher prevalence of HF and receipt of beta-blockers, angiotensin receptor blockers, antiplatelet therapy, diuretic agents, and warfarin.

PROPENSITY-MATCHED COHORT. Online Figure 1 shows the propensity distribution and overlap for recipients and nonrecipients of digoxin in the full cohort. Using 1:1 nearest-neighbor matching without replacement, 93.1% of the digoxin-treated group of patients from the full cohort were matched (Hosmer-Lemeshow goodness-of-fit test p = 0.70; C-statistic = 0.68). Standardized differences of covariates for matched patients (26,703 in each arm) demonstrated adequate balance with no standardized differences >0.10 (31); the highest standardized difference was 0.030 (Online Table 1).

OUTCOMES. Total follow-up time was 353,168 patient-years; 28,723 (23.5%) patients died during the observation period. Digoxin recipients had higher unadjusted mortality compared with nonrecipients (Online Table 2). Digoxin treatment was significantly associated with death in the multivariate Cox regression model (hazard ratio [HR]: 1.26, 95% confidence interval [CI]: 1.23 to 1.29, p < 0.001) and after propensity matching (HR: 1.21, 95% CI: 1.17 to 1.25, p < 0.001) (**Table 2**). The results were similar and significant when including digoxin MPR as a time-varying covariate with and without propensity matching (HR: 1.31, 95% CI: 1.27 to 1.36, p < 0.001 for full cohort; 1.18, 95% CI: 1.10 to 1.27, p < 0.001 for propensity



CENTRAL ILLUSTRATION **The TREAT-AF Study**

Researching the association of digoxin therapy with mortality in patients with newly diagnosed atrial fibrillation/atrial flutter (AF). CI = confidence interval; HR = hazard ratio; TREAT-AF = The Retrospective Evaluation and Assessment of Therapies in AF.

matched cohort) (Table 2). Figure 2 shows the cumulative incidence of death in the propensity-matched cohort. Cumulative incidence of death was higher in the digoxin-treated patients versus the untreated group ($p < 0.001$).

RELATIONSHIP TO KIDNEY FUNCTION. With multivariate adjustment and propensity matching, digoxin was associated with a significant increase in risk of death among nearly all strata of eGFR, except dialysis patients (Table 2). However, there was no evidence of effect modification present across strata of kidney function ($p = 0.76$).

SUBGROUP ANALYSIS. Multivariate and propensity-matched analyses are shown for 9 clinically relevant subgroups in Table 3. Overall, subgroup findings were similar to the point estimates for the full and propensity-matched cohorts. There was evidence of possible effect modification in the full cohort and increased risk in patients with prior MI ($p_{interaction} = 0.002$ in the full cohort; $p_{interaction} = 0.077$ in the propensity-matched cohort). In all other subgroups, tests for interaction were not significant ($p \leq 0.10$) in full and propensity-matched analyses.

SENSITIVITY TO UNMEASURED CONFOUNDING. We performed an analysis to determine whether an unmeasured confounder (or set of confounders) can explain the propensity-matched HR of digoxin for death (Fig. 3). The curves compare the hypothetical prevalence of the unmeasured confounder(s) within the digoxin-treated group (x-axis) and within the untreated group (curves for 5%, 10%, 20%, 30%, and 40%), showing the hypothetical HR (y-axis) for all-cause mortality that would need to be associated with this confounder. For example, if an unmeasured confounder was present in 30% of untreated patients (Fig. 3, orange line) and in 50%, 60%, or 80% of digoxin-treated patients (x-axis), then the HR required for the confounder to account for the observed difference (i.e., to shift the upper 95% HR confidence interval to 1.00) would be 2.5, 1.9, and 1.7, respectively. As an example of an unmeasured confounder, suppose that patients treated with digoxin had greater frailty and that this was not captured with the current variables. If frailty was present in 5% of untreated patients (Fig. 3, red line) and in 20% of digoxin-treated patients, then frailty could explain the observed difference only if frailty independently increased the risk of death by a factor (HR) of 2.4.

DISCUSSION

The present study was designed to evaluate the association of digoxin therapy with mortality in patients with newly diagnosed AF. With 122,465 subjects and 353,168 person-years of follow-up, our analysis includes the largest AF cohort to date addressing this issue, demonstrating that treatment

TABLE 2 Multivariate and Propensity-Matched Cox Regression Results

Model	Full Cohort (n = 122,465)	p Value	Propensity-Matched Cohort (n = 53,406)	p Value
Unadjusted	1.37 (1.33–1.40)	<0.001	–	–
Age, sex, race	1.40 (1.37–1.44)	<0.001	–	–
Full model*				
All patients	1.26 (1.23–1.29)	<0.001	1.21 (1.17–1.25)	<0.001
Adherence (MPR)-adjusted†	1.31 (1.27–1.36)	<0.001	1.18 (1.10–1.27)	<0.001
eGFR group, ml/min/1.73 m^2‡				
eGFR ≥90	1.37 (1.25–1.51)	<0.001	1.31 (1.17–1.46)	<0.001
eGFR 60–89	1.24 (1.19–1.29)	<0.001	1.22 (1.16–1.28)	<0.001
eGFR 45–59	1.26 (1.20–1.33)	<0.001	1.21 (1.14–1.29)	<0.001
eGFR 30–44	1.20 (1.13–1.29)	<0.001	1.14 (1.05–1.23)	0.001
eGFR 15–29	1.26 (1.13–1.41)	<0.001	1.21 (1.04–1.40)	0.01
eGFR <15	1.41 (1.04–1.92)	0.03	1.20 (0.79–1.83)	0.84
Dialysis	1.39 (0.996–1.93)	0.053	0.79 (0.53–1.18)	0.25

Values are hazard ratio (95% confidence interval). *For full cohort, full models were adjusted for age, sex, race, hypertension, stroke, HF, diabetes mellitus, $CHADS_2$ score, Charlson comorbidity score, beta-blockers, diuretic agents, antiplatelet agents, warfarin, statins, niacin/fibrates, ACE inhibitors/angiotensin receptor blockers, antiarrhythmic drug therapies, and eGFR group. †Full adherence (MPR)-adjusted model was created by adjusting for digoxin medication possession ratio (MPR) from date of first AF diagnosis to date of death or censoring, as a time-varying exposure. Also adjusted for age, sex, race, hypertension, stroke, HF, diabetes mellitus, $CHADS_2$ score, Charlson comorbidity score, digoxin, beta-blockers, diuretic agents, anti-platelet agents, warfarin, statins, niacin/fibrates, ACE inhibitors/angiotensin receptor blockers, antiarrhythmic drug therapies, and eGFR group. ‡p Values for interaction were not significant ($p > 0.10$) for eGFR as a potential effect modifier in either full or propensity-matched cohort.

Abbreviations as in Table 1.

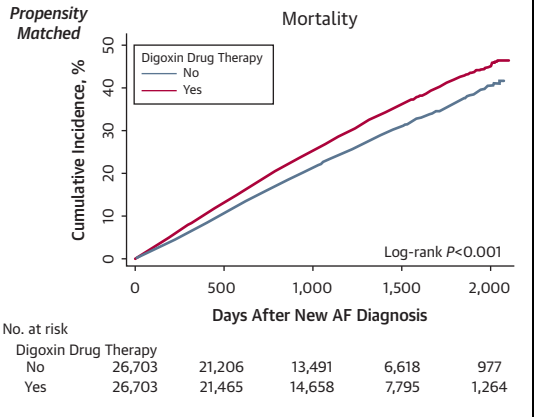


FIGURE 2 Cumulative Incidence of Death in the Propensity-Matched Cohort

The figure shows the cumulative incidence of death, comparing treated and untreated patients in the propensity matched cohort, with curves estimated using the Kaplan-Meier method. Differences in treated and untreated groups were assessed using the log-rank test. AF = atrial fibrillation/atrial flutter.

TABLE 3 Subgroup Analysis: Association of Digoxin With Mortality

	Full Cohort*		Propensity-Matched Cohort†	
	HR (95% CI)	p Value for Interaction	HR (95% CI)	p Value for Interaction
Male	1.26 (1.23–1.29)	NS	1.21 (1.17–1.25)	NS
Female	1.23 (0.98–1.55)	NS	1.31 (0.997–1.72)	NS
Age ≥65 yrs	1.24 (1.21–1.28)	NS	1.21 (1.17–1.26)	NS
Age <65 yrs	1.37 (1.27–1.48)	NS	1.27 (1.16–1.39)	NS
Previous diagnosis of HF	1.29 (1.23–1.36)	NS	1.28 (1.21–1.36)	NS
Previous diagnosis of MI‡	1.49 (1.34–1.67)	0.002	1.45 (1.26–1.66)	0.077
Treated with warfarin	1.27 (1.23–1.32)	NS	1.21 (1.16–1.26)	NS
Treated with beta-blocker	1.28 (1.23–1.32)	NS	1.24 (1.19–1.29)	NS
Treated with amiodarone	1.27 (1.17–1.38)	NS	1.26 (1.14–1.39)	NS

*Adjusted for age, sex, race, hypertension, stroke, HF, diabetes, $CHADS_2$ score, Charlson comorbidity score, beta-blockers, diuretic agents, antiplatelet agents, warfarin, statins, niacin/fibrates, ACE inhibitors/angiotensin receptor blockers, antiarrhythmic drug therapies, and eGFR. †Covariates considered for the propensity-matched analysis include: age, sex, race, Charlson comorbidity index, $CHADS_2$ 0 to 1, $CHADS_2$ 2 to 3, $CHADS_2$ 4 to 6, mean $CHADS_2$ score, HF, hypertension, diabetes, prior stroke/TIA, eGFR ≥90, eGFR 60 to 89, eGFR 45 to 59, eGFR 30 to 44, eGFR 15 to 29, eGFR <15, dialysis, diuretic agents, niacin or fibrates, statins, warfarin, all beta-blockers, antiplatelet agents, ACE inhibitors/angiotensin receptor blockers, and antiarrhythmic drug therapies. A relevant covariate was removed from the model when that variable defined the subgroup being analyzed. No p values for interaction were significant ($p > 0.10$) for potential effect modifiers in propensity-matched analyses. ‡p Value for interaction was significant ($p \leq 0.05$) for only 1 potential effect modifier: prior myocardial infarction ($p = 0.002$) in the full cohort.

CI = confidence interval; HR = hazard ratio; NS = not significant if $p > 0.10$ for interaction term; other abbreviations as in Table 1.

with digoxin is associated with increased risk of mortality. These observations were consistent across all subgroups and were independent of drug adherence, kidney dysfunction, HF, or concomitant therapy with beta-blockers or amiodarone. The risk may be increased in patients with prior MI. These findings challenge the current cardiovascular society guidelines, which give Class I and Class IIa recommendations for the use of digoxin as an adjunct to rate control monotherapy (2,3).

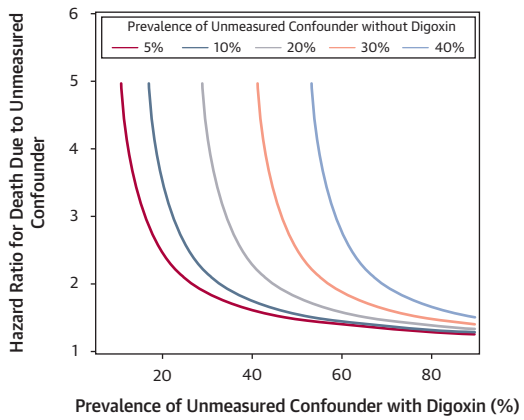


FIGURE 3 Effect of Unmeasured Confounding Factors

This sensitivity analysis shows how powerful an unmeasured confounder (or set of confounders) would have to be to explain the increased hazard of death associated with digoxin. The hypothetical prevalence of an unmeasured confounder in the treated group (x-axis) is graphed against the hypothetical prevalence in the untreated group (**colored curves** associated with 5%, 10%, 20%, 30%, and 40%, respectively). The y-axis represents the hypothetical hazard ratio of the unmeasured confounder required to fully explain the mortality difference observed between the treated and untreated groups for digoxin.

DIGOXIN THERAPY AND MORTALITY IN AF. Surprisingly, few studies have evaluated the safety of outpatient digoxin in AF (32). The Stockholm Cohort study of 2,824 patients with AF found that digoxin was not associated with mortality after adjustment or propensity matching, although unadjusted mortality was markedly higher in digoxin-treated patients (8). An AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) study secondary analysis demonstrated that digoxin exposure was associated with mortality (9). The point estimate was higher (HR: 1.41, 95% CI: 1.19 to 1.67) than in our study, which may be due to differences in patient populations, treatment options, or methods. The AFFIRM study predated contemporary treatment for HF, coronary disease, and stroke prevention. The AFFIRM study also used a propensity score as a covariate, which is less effective at balancing multiple covariates compared with propensity matching, particularly when match rates are high as in our cohort. Also, both of these studies were of patients with prevalent AF, which can introduce substantial survival or "immortal person-time" bias. Our study design, which is restricted to only patients with newly diagnosed AF, greatly minimizes such bias.

A more recent post-hoc analysis on the AFFIRM trial conducted by Gheorghiade et al. (11) attempted to address a few of these limitations with propensity matching, although still in a prevalent AF cohort. This AFFIRM study reanalysis found no association between digoxin exposure and mortality (HR: 1.06; 95% CI: 0.83 to 1.37; $p = 0.64$) after matching a total of 1,756 patients on propensity scores. However, patients from the AFFIRM trial were predominantly elderly, asymptomatic, or minimally symptomatic trial participants. In contradistinction, our data represent the total number of patients with new AF from the full denominator of the Veterans Affairs healthcare system. With 30 times as many propensity-matched patients, the present study also has greater statistical power.

The DIG (Digitalis Investigation Group) trial, which randomized patients with HF to digoxin, demonstrated no mortality difference but a decrease in HF hospitalizations compared with placebo (5). However, this trial excluded patients with AF and predated contemporary HF therapy, whereas background beta-blocker and angiotensin blocker use was

substantially higher in our study. A more recent observational analysis of 2,891 digoxin users in the Kaiser Permanente healthcare system with incident HF (not AF) did demonstrate an increased risk of death (33).

Finally, the subgroup interaction of digoxin in patients with prior MI is intriguing. However, it should be viewed as hypothesis-generating, particularly given the multiple subgroups evaluated.

ROLE OF UNIDENTIFIED CONFOUNDING. The observational nature of this study cannot preclude the presence of unidentified confounders. In particular, confounding by indication is the greatest concern, because unmeasured variables such as frailty, HF severity, and ejection fraction (which themselves are associated with death), could led to treatment selection with digoxin. Our sensitivity analysis (**Fig. 3**) evaluates the impact of unmeasured confounders. The results indicate that an unmeasured confounder, such as frailty, would require a fairly high hazard of death (>2.0 in most cases) and be at least twice as prevalent in the digoxin-treated patients.

However, it is well established that patients with frailty or severe HF have poorer drug adherence. We therefore did adjust for drug adherence, and results of the adherence-adjusted analyses were consistent with the overall results. A secondary data analysis from the SPORTIF (Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation) III and V studies, which also adjusted for blood pressure and left ventricular dysfunction, demonstrated a mortality HR of 1.53 for digoxin (34). Therefore, we believe that unmeasured confounding of sufficient severity to explain our findings is not likely.

STUDY LIMITATIONS. Our study is nonrandomized. The analysis cohort predominantly consists of male veterans, which limits generalizability of findings to women, although we did examine the mortality association with digoxin among women in subgroup analysis. We were unable to evaluate treatment dose on the basis of available data, although the mortality association was consistent across all strata of renal function and after adjustment for medication adherence.

Because AF is a progressive disease, the choice to include patients with new (incident) AF would be expected to minimize survival bias on the basis of duration of AF, but could also limit generalizability of our findings in prevalent AF cohorts. Additionally, survival bias could still occur if patients received the exposure or confounding therapies for other conditions before the index AF date.

We also could not measure HF severity, on the basis of symptom class, ejection fraction, or HF hospitalizations. Differences in HF severity could be a source of unidentified confounding, which we attempted to address through our sensitivity analysis. Although we specified adherence to digoxin as a time-varying covariate, there is a possibility that time-varying confounders, such as discontinuation of other cardiovascular medications, could influence survival.

We used all-cause mortality rather than cause-specific mortality, which could prevent a more meaningful determination of how drug exposure may have led to death. However, in 1 AFFIRM substudy, the magnitude of the HRs for digoxin was similar for all-cause, cardiovascular, and arrhythmic death (9). Furthermore, the recent propensity-matched AFFIRM substudy by Gheorghiade et al. (11) used all-cause mortality as the study endpoint, although there was no significant association with digoxin in their findings.

CONCLUSIONS

In this large, retrospective cohort of patients with newly diagnosed AF, treatment with digoxin was independently associated with mortality, regardless of age, sex, kidney function, heart failure status, concomitant therapies, or drug adherence.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: Digoxin is widely used to control the ventricular rate in patients with AF, but the evidence supporting safety and efficacy are limited.

COMPETENCY IN MEDICAL KNOWLEDGE 2: In patients with recently identified AF, treatment with digoxin was associated with an increased risk of death, independent of drug adherence, kidney function, cardiovascular comorbidities, or concomitant therapies.

COMPETENCY IN PATIENT CARE: Physicians should consider alternatives to digoxin in managing patients with AF.

TRANSLATIONAL OUTLOOK: Prospective studies are needed to confirm the findings of this observational report and explore the mechanisms responsible for the increased risk of mortality in patients with AF treated with digoxin.

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APPENDIX For a supplemental figure and tables, please see the online version of this article.