Digoxin and Risk of Death in Adults With Atrial Fibrillation
The ATRIA-CVRN Study

James V. Freeman, MD, MPH, MS; Kristi Reynolds, PhD; Margaret Fang, MD, MPH; Natalia Udaltsova, PhD; Anthony Steimle, MD, MPH; Niela K. Pomernacki, BA; Leila H. Borowsky, MPH; Teresa N. Harrison, SM; Daniel E. Singer, MD; Alan S. Go, MD

Background—Digoxin remains commonly used for rate control in atrial fibrillation, but limited data exist supporting this practice and some studies have shown an association with adverse outcomes. We examined the independent association between digoxin and risks of death and hospitalization in adults with incident atrial fibrillation and no heart failure.

Methods and Results—We performed a retrospective cohort study of 14787 age, sex, and high-dimensional propensity score-matched adults with incident atrial fibrillation and no previous heart failure or digoxin use in the AnTicoagulation and Risk factors In Atrial fibrillation-Cardiovascular Research Network (ATRIA-CVRN) study within Kaiser Permanente Northern and Southern California. We examined the independent association between newly initiated digoxin and the risks of death and hospitalization using extended Cox regression. During a median 1.17 (interquartile range, 0.49–1.97) years of follow-up among matched patients with atrial fibrillation, incident digoxin use was associated with higher rates of death (8.3 versus 4.9 per 100 person-years; \( P<0.001 \)) and hospitalization (60.1 versus 37.2 per 100 person-years; \( P<0.001 \)). Incident digoxin use was independently associated with a 71% higher risk of death (hazard ratio, 1.71; 95% confidence interval, 1.52–1.93) and a 63% higher risk of hospitalization (hazard ratio, 1.63; 95% confidence interval, 1.56–1.71). Results were consistent in subgroups of age and sex and when using intent-to-treat or on-treatment analytic approaches.

Conclusions—In adults with atrial fibrillation, digoxin use was independently associated with higher risks of death and hospitalization. Given other available rate control options, digoxin should be used with caution in the management of atrial fibrillation. (Circ Arrhythm Electrophysiol. 2015;8:49-58. DOI: 10.1161/CIRCEP.114.002292.)

Key Words: arrhythmia ■ atrial fibrillation ■ digoxin ■ morbidity ■ mortality

Digitalis has been used for more than a century for heart rate control in patients with atrial fibrillation (AF), and it remains commonly used for this indication worldwide. Current clinical practice guidelines for the management of atrial fibrillation recommend the use of digoxin alone for resting heart rate control in sedentary individuals, in combination with \( \beta \)-blockers for resting and exercise heart rate control, and in the setting of concurrent systolic heart failure. However, these guidelines are based on small, older clinical studies with limited follow-up of days to weeks that did not assess the long-term effects of digoxin on mortality or hospitalization. Although a randomized trial assessing the association between digoxin use and adverse outcomes such as death would be optimal, such a study is unlikely to be performed. Observational studies may be of particular utility for evaluating this association because the indication for digoxin use in AF is heart rate control, which has been shown to have no effect on adverse outcomes such as death in large randomized trials, thus minimizing the risk of confounding by indication. Recent observational studies and post hoc analyses from clinical trials have suggested that digoxin may be linked to excess mortality in atrial fibrillation, but these studies were limited by size and their ability to adjust for confounders and other studies have shown no effect of digoxin on the risk of death. Importantly, all previous studies evaluating the association between digoxin and mortality in patients with AF included high numbers of patients with concurrent heart failure, and the pharmacological risks and benefits may be different in these patients than in those with AF alone.
LONGITUDINAL EXPOSURE TO DIGOXIN

We implemented a new user design by excluding all patients with evidence of digoxin use ≤4 years before study entry to focus on outcomes associated with incident digoxin use and remove biases associated with including prevalent drug users.

We characterized use of digoxin in 2 ways (intent-to-treat and time-varying on-treatment exposure) based on estimated day supply information per dispensed prescription and observed refill patterns found in health plan pharmacy databases using previously validated methods. Briefly, for any 2 consecutive prescriptions, we examined the time between the projected end date of the first prescription and the date of the next filled prescription. Given that dose adjustment is not uncommon, we allowed a grace period of 30 days between dispensed prescriptions. Thus, if the time between the projected end date of the first prescription and the fill date of the next prescription was ≤30 days, we considered that individual to be continuously receiving digoxin therapy. If the refill interval was >30 days, then the individual was considered off digoxin therapy starting the day after the projected end date of the first prescription until the date of next filled prescription, if any. Because hospitalized patients receive their medications from the inpatient pharmacy and do not use their outpatient medication supply, we subtracted the number of hospital days from the subsequent refill interval if there was an interim hospitalization.

FOLLOW-UP AND OUTCOMES

Patients were followed through June 30, 2009 for the outcomes of all-cause death and hospitalization from any cause which was the latest date complete data were available at the time of analysis. Patients were censored at the time of health plan disenrollment or the end of follow-up. Death from any cause was identified from health plan databases (inpatient deaths, proxy report of outpatient deaths), annual California state death certificate files and Social Security Administration Death Master File quarterly updated data files. All-cause and heart failure-related hospitalizations were identified using comprehensive hospital discharge and billing claims databases; heart failure-related hospitalizations were based on primary discharge diagnoses of heart failure based on validated International Classification of Diseases, Ninth Revision codes as previously described.

AGE, SEX, AND HIGH-DIMENSIONAL PROPENSITY SCORE MATCHING

A high-dimensional propensity score for the initiation of digoxin was calculated for each person using logistic regression methods that included demographic characteristics and multidimensional patient characteristics. As opposed to standard propensity scoring which includes a limited group of preselected variables, the high-dimensional propensity score is generated automatically by an algorithm that scans through all available data in the Kaiser Permanente electronic medical record from the 3 dimensions of medication prescriptions, diagnoses, and procedures. The algorithm selects the most frequent 200 items from each of these 3 dimensions within a 5-year look-back period and after that selects the 300 best matched parameters out of the initial 600 items for use in the high-dimensional propensity score. This methodology has been shown to approximate point estimates of risk from randomized clinical trials substantially better than standard propensity scoring or regression methodologies.

Each digoxin user was matched to a maximum of 3 nondigoxin users (without replacement) based on age (±1 year), sex, and high-dimensional propensity score for the initiation of digoxin (caliper width of ±0.01) on the calendar date of the first digoxin prescription (model c statistic=0.68).

Data on age, sex, self-reported race/ethnicity, and socioeconomic status were obtained from health plan databases. We ascertained relevant medical history documented ≤5 years before cohort entry using previously validated approaches based on International Classification of Diseases, Ninth Revision diagnosis and procedure codes, current procedure terminology procedure codes, laboratory records, and pharmacy records. This included cardiovascular diseases (acute myocardial infarction, unstable angina, ischemic...
stroke, transient ischemic attack, intracranial hemorrhage, peripheral arterial disease, and valvular heart disease), previous ventricular arrhythmias (ventricular tachycardia or fibrillation), previous cardiac procedures (percutaneous coronary intervention or coronary artery bypass surgery), other cardiovascular risk factors (hypertension, diabetes mellitus, and dyslipidemia), and other coexisting medical illnesses (dementia, depression, thyroid disease, previous gastrointestinal bleed, other bleeding, cancer, lung disease, and liver disease; codes available on request). We ascertained body mass index and blood pressure ≤365 days before cohort entry from ambulatory visit information in health plan electronic medical records. We also characterized baseline kidney function using outpatient serum creatinine concentration values based on an IDMS-traceable assay and estimated glomerular filtration rate (mL/min per 1.73 m²) using the chronic kidney disease epidemiology collaboration equation.40

We characterized baseline exposure to other relevant cardiovascular medications using similar methods as described above for digoxin based on information from ambulatory pharmacy records for the following medications, such as warfarin, α-adrenergic receptor antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, β-blockers, aldosterone receptor antagonists, calcium channel blockers, nitrates, hydralazine, statins, other lipid lowering agents, antiplatelet agents, and diabetic medications.31,32

### Statistical Analysis

All analyses were performed using SAS statistical software, version 9.2 (Cary, NC). We compared the baseline characteristics for the overall cohort and the matched patients prescribed or not prescribed digoxin during follow-up using t test or Wilcoxon rank-sum test for continuous variables and the χ² test for categorical variables. Subsequent analyses were performed in the age, sex, and high-dimensional propensity score-matched cohort to minimize confounding.

We next calculated rates (per 100 person-years) with associated 95% confidence limits for death and hospitalization for those who received digoxin during follow-up compared with those who did not receive digoxin. We generated Kaplan–Meier survival curves for the outcomes of mortality and hospitalization, censoring patients at the time of death or loss to follow-up. We conducted extended Cox regression models to examine the independent association between digoxin use in the propensity score-matched cohort and the risk of adverse outcomes. We conducted additional analyses stratified by age and sex.

To assess whether changes in covariates in the follow-up period may confound the relationship between digoxin use and the outcomes of interest, we performed a secondary analysis with additional adjustment for time-updated covariates. In this secondary analysis, we performed extended Cox regression in the propensity score-matched cohort to examine the association of incident digoxin use and the risk of adverse outcomes with additional adjustment for time-updated comorbidities, including development of heart failure, targeted laboratory results, and longitudinal medication use (Table I in the Data Supplement).

Finally, because previous observational studies on this topic have shown discordant findings depending on whether they performed their analyses using an intent to treat or on-treatment analytic method,16,21 we performed a secondary analysis in which we examined digoxin use as a time-varying exposure within the propensity score-matched cohort. In this on-treatment analysis, the outcomes of death and hospitalization were only assigned to the digoxin use group if patients were classified as receiving the medication at the time of the event.
Table 1. Baseline Characteristics of Adults With Atrial Fibrillation Between January 2006 and June 2009 With No Known Heart Failure or Previous Digoxin Use, Overall and Stratified by New Digoxin Use During Follow-Up, in the Full Cohort and the Age, Sex, and High-Dimensional Propensity Score-Matched Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Full Digoxin Cohort</th>
<th>Age, Sex, and High-Dimensional Propensity Score-Matched Cohort (1:3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall (n=27,288)</td>
<td>Digoxin Users (n=4858)</td>
</tr>
<tr>
<td>Age, year, mean (SD)</td>
<td>70.7 (12.9)</td>
<td>71.9 (11.9)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>15,191 (55.7)</td>
<td>2,441 (50.2)</td>
</tr>
<tr>
<td>Women</td>
<td>12,097 (44.3)</td>
<td>2,417 (49.8)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>20,969 (76.8)</td>
<td>3,932 (80.9)</td>
</tr>
<tr>
<td>Black</td>
<td>1582 (5.8)</td>
<td>297 (6.1)</td>
</tr>
<tr>
<td>Native American</td>
<td>58 (0.2)</td>
<td>12 (0.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>2,043 (7.5)</td>
<td>257 (5.3)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>2,636 (9.7)</td>
<td>360 (7.4)</td>
</tr>
<tr>
<td>Hispanic ethnicity, n (%)</td>
<td>3,197 (11.7)</td>
<td>507 (10.4)</td>
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<tr>
<td>Socioeconomic status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low annual household income</td>
<td>3,514 (12.9)</td>
<td>722 (14.9)</td>
</tr>
<tr>
<td>Low educational attainment</td>
<td>5,778 (21.2)</td>
<td>1,110 (22.8)</td>
</tr>
<tr>
<td>Cardiovascular disease, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>999 (3.7)</td>
<td>125 (2.6)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>613 (2.2)</td>
<td>85 (1.7)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1,037 (3.8)</td>
<td>155 (3.2)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>728 (2.7)</td>
<td>116 (2.4)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>141 (0.5)</td>
<td>20 (0.4)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>949 (3.5)</td>
<td>160 (3.3)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>328 (1.2)</td>
<td>43 (0.9)</td>
</tr>
<tr>
<td>Ventricular arrhythmias, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>87 (0.3)</td>
<td>11 (0.2)</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>6 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Cardiovascular procedure history, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>Percutaneous coronary intervention</td>
<td>1,175 (4.3)</td>
<td>150 (3.1)</td>
</tr>
<tr>
<td>Coronary artery bypass surgery</td>
<td>825 (3.0)</td>
<td>81 (1.7)</td>
</tr>
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</table>

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Table 1. Continued

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Full Digoxin Cohort</th>
<th>Age, Sex, and High-Dimensional Propensity Score-Matched Cohort (1:3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall (n=27288)</td>
<td>Digoxin Users (n=4858) Nonusers (n=22430) P Value Overall (n=14787)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Digoxin Users (n=4231) Matched Nonusers (n=10556) P Value</td>
</tr>
</tbody>
</table>
| Other cardiovascular risk factors, n (%) | Hypertension 21163 (77.6) 3707 (76.3) 17456 (77.8) 0.02 11573 (78.3) 3260 (77.1) 8313 (78.8) 0.02 | 46
|                                     | Diabetes mellitus   6498 (23.8) 1116 (23.0) 5382 (24.0) 0.13 3416 (23.1) 974 (23.0) 2442 (23.1) 0.88 | 46
|                                     | Dyslipidemia 15112 (55.4) 2517 (51.8) 12595 (56.2) <0.001 8006 (54.1) 2249 (53.2) 5757 (54.5) 0.13 | 46
| Other coexisting medical illnesses, n (%) | Dementia 1470 (5.4) 248 (5.1) 1222 (5.4) 0.34 721 (4.9) 209 (4.9) 512 (4.9) 0.82 | 46
|                                     | Depression 4757 (17.4) 860 (17.7) 3897 (17.4) 0.58 2626 (17.8) 744 (17.6) 1882 (17.8) 0.73 | 46
|                                     | Thyroid disease 4196 (15.4) 765 (15.7) 3431 (15.3) 0.43 2368 (16.0) 671 (15.9) 1697 (16.1) 0.75 | 46
|                                     | Gastrointestinal bleeding 596 (2.2) 96 (2.0) 500 (2.2) 0.27 284 (1.9) 82 (1.9) 202 (1.9) 0.92 | 46
| Other bleeding                      95 (0.3) 25 (0.5) 70 (0.3) 0.03 55 (0.4) 24 (0.6) 31 (0.3) 0.01 | 46
| Cancer                              1761 (6.5) 371 (7.6) 1390 (6.2) <0.001 947 (6.4) 312 (7.4) 635 (6.0) 0.002 | 46
| Lung disease                        6162 (22.6) 1253 (25.8) 4909 (21.9) <0.001 3322 (22.5) 1036 (24.5) 2286 (21.7) <0.001 | 46
| Liver disease                       618 (2.3) 95 (2.0) 523 (2.3) 0.11 304 (2.1) 83 (2.0) 221 (2.1) 0.61 | 46
| Medications, n (%)                  | Warfarin 9363 (34.3) 1517 (31.2) 7846 (35.0) <0.001 4989 (33.7) 1420 (33.6) 3569 (33.8) 0.77 | 46
|                                     | α-adrenergic receptor antagonist 3821 (14.0) 615 (12.7) 3206 (14.3) 0.003 1941 (13.1) 555 (13.1) 1386 (13.1) 0.98 | 46
|                                     | Angiotensin-converting enzyme inhibitor 9873 (36.2) 1628 (33.5) 8245 (36.8) <0.001 5288 (35.8) 1442 (34.1) 3846 (36.4) 0.007 | 46
|                                     | Angiotensin receptor blocker 2465 (9.0) 402 (8.3) 2063 (9.2) 0.04 1313 (8.9) 364 (8.6) 949 (9.0) 0.45 | 46
|                                     | Diuretic 10399 (38.1) 1793 (36.9) 8606 (38.4) 0.06 5683 (38.4) 1576 (37.2) 4107 (38.9) 0.06 | 46
|                                     | β-Blocker 15926 (58.4) 2557 (52.6) 13369 (59.6) <0.001 8497 (57.5) 2351 (55.6) 6146 (58.2) 0.003 | 46
|                                     | Aldosterone receptor antagonist 345 (1.3) 58 (1.2) 287 (1.3) 0.63 186 (1.3) 49 (1.2) 137 (1.3) 0.49 | 46
|                                     | Calcium channel blocker 7920 (29.0) 1369 (28.2) 6551 (29.2) 0.15 4194 (28.4) 1224 (28.9) 2970 (28.1) 0.33 | 46
|                                     | Nitrates 2326 (8.5) 346 (7.1) 1980 (8.8) <0.001 1136 (7.7) 304 (7.2) 832 (7.9) 0.15 | 46
|                                     | Hydralazine 504 (1.8) 76 (1.6) 428 (1.9) 0.11 237 (1.6) 67 (1.6) 170 (1.6) 0.91 | 46
|                                     | Statin 12173 (44.6) 1960 (40.3) 10213 (45.5) <0.001 6385 (43.2) 1767 (41.8) 4618 (43.7) 0.03 | 46
|                                     | Other lipid lowering agent 1185 (4.3) 176 (3.6) 1009 (4.5) 0.007 619 (4.2) 164 (3.9) 455 (4.3) 0.23 | 46
|                                     | Antiplatelet agent 2018 (7.4) 283 (5.8) 1735 (7.7) <0.001 960 (6.5) 260 (6.1) 700 (6.6) 0.28 | 46
|                                     | Diabetes mellitus medications 4183 (15.3) 692 (14.2) 3491 (15.6) 0.02 2127 (14.4) 606 (14.3) 1521 (14.4) 0.89 | 46
|                                     | Baseline CHADS2 score, mean (SD) 1.56 (1.04) 1.55 (1.00) 1.56 (1.05) 0.59 1.56 (1.01) 1.56 (1.00) 1.56 (1.02) 0.89 | 46
|                                     | Body mass index, kg/m², n (%) <0.001 <0.001 | 46

(Continued)
Results

Baseline Characteristics
Between January 2006 and June 2009, we identified 27,288 adults who had incident atrial fibrillation and no previous digoxin use or a history of heart failure (Figure 1), of whom 4858 (17.8%) initiated digoxin during follow-up. The age, sex, and high-dimensional propensity score-matched cohort included 14,787 adults, of whom 4231 (28.6%) initiated digoxin during follow-up. Digoxin users were successfully matched to 3 nonusers in 65.4% of cases.

After age, sex, and high-dimensional propensity score matching, digoxin users and nonusers were similar in terms of characteristics at study entry (Table 1). However, digoxin users were slightly older, had lower household income, and had lower body mass index and blood pressure; digoxin users were also more likely to have a history of nongastrointestinal bleeding, cancer, and chronic lung disease. Nondigoxin users were more likely to have a history of acute myocardial infarction and coronary artery bypass surgery and they were more likely to be treated with β-blockers and statins.

Outcomes According to Digoxin Exposure
Median follow-up time in the propensity-matched cohort was 1.17 (interquartile range, 0.49–1.97) years. There were 1140 deaths (473 in digoxin users and 667 in nonusers of digoxin), during follow-up, with a significantly higher rate of death in digoxin users compared with nonusers (8.3 versus 4.9 per 100 person-years, respectively; P<0.001; Figure 2). Digoxin
use was associated with a 71% higher risk of death (hazard ratio [HR], 1.71; 95% confidence interval [CI], 1.52–1.93; Figure 3).

During follow-up, there were 8456 hospitalizations for any cause in the propensity-matched cohort (3411 in digoxin users versus 5045 in nonusers of digoxin). In the matched cohort, 2176 patients (632 digoxin users and 1544 nonusers of digoxin) were hospitalized and subsequently died during follow-up, and 11 patients (4 digoxin users and 7 nonusers of digoxin) died during hospitalization. There were 903 hospitalizations for heart failure in the propensity matched cohort (512 in digoxin users versus 391 in nonusers of digoxin). The rate of hospitalization was higher for patients who received digoxin compared with those who did not receive digoxin (60.1 versus 37.2 per 100 person-years, respectively; P<0.001; Figure 4).

Digoxin use was associated with a 63% higher risk of hospitalization (HR, 1.63; 95% CI, 1.56–1.71; Figure 5).

Outcomes According to Digoxin Use in Subgroups of Age and Sex

The association between incident digoxin use and the outcomes of death and hospitalization were consistent in subgroups of patient age, with 45% to 115% higher risks of death and hospitalization across all age strata (Figures 3 and 5). Similarly, in analyses stratified by sex, we observed 60% to 82% higher risks of death and hospitalization for both men and women (Figures 3 and 5).

Additional Adjustment for Time-Updated Covariates and On Treatment Analysis

We performed 2 secondary analyses using different analytic approaches to examine the consistency of our primary results. Results were consistent in analyses in which we additionally adjusted for potentially relevant time-updated comorbidities, including heart failure, targeted laboratory results, and medications. Digoxin use was associated with a 62% higher adjusted risk of death (adjusted HR, 1.62; 95% CI, 1.43–1.84) and a 45% higher adjusted risk of hospitalization for any cause (adjusted HR, 1.45; 95% CI, 1.39–1.52).

Similarly, results were consistent in analyses in which we treated digoxin use as a time-varying variable (on treatment analysis). Digoxin use was associated with a 40% higher risk of death (HR, 1.40; 95% CI, 1.23–1.6) and a 53% higher risk of hospitalization (HR, 1.53; 95% CI, 1.46–1.60).

Digoxin Prescription Dosages and Serum Digoxin Concentrations

Among digoxin users in the matched cohort, mean daily dose of digoxin was 0.164 mg. Mean daily dose of digoxin was not statistically different among those who died compared with those who did not die (0.162 mg daily versus 0.164 mg daily; P=0.30).

Among digoxin users in the matched cohort, serum digoxin concentration was never measured in 31%, measured once in 27%, measured twice in 17%, and 3 or more times in 25% during follow-up. Mean serum digoxin concentration was 0.964 ng/mL. Mean serum digoxin concentration was higher among those who died compared with those who did not die (1.151 versus 0.935; P<0.001).

Discussion

In a large, age, sex, and high-dimensional propensity score-matched cohort of adults with newly diagnosed atrial fibrillation and no known previous digoxin use or history of heart failure treated in the community, we found that incident

![Figure 2. Kaplan–Meier survival curves for the outcome of death from any cause in age, sex, and high-dimensional propensity score-matched adults with incident atrial fibrillation and no heart failure between 2006 and 2009 for digoxin users vs nonusers.](http://circep.ahajournals.org/)

![Figure 3. Risk of death from any cause in age, sex, and high-dimensional propensity score-matched adults with incident atrial fibrillation and no heart failure between 2006 and 2009 for digoxin users vs nonusers.](http://circep.ahajournals.org/)
digoxin use was independently associated with a 71% higher risk of death and a 63% higher risk of hospitalization. These results were consistent across strata of age and sex. Results were also consistent in secondary analyses in which we included additional adjustment for time-updated comorbidities and medications, and in secondary analyses in which we treated digoxin as a time-varying variable (on treatment analysis).

Digoxin remains commonly used for heart rate control in patients with AF. In a recent survey of AF, patients from 9 countries in Europe, it was prescribed in 19.4% of study subjects, and it was prescribed in 17.8% of incident AF in our cohort. Current clinical practice guidelines endorse digoxin use in patients with atrial fibrillation based primarily on small clinical studies designed to assess the short-term efficacy of heart rate control. However, these studies had limited follow-up of days to weeks, and did not evaluate long-term mortality or hospitalization. A large randomized trial specifically assessing the long-term safety of digoxin for heart rate control in patients with atrial fibrillation would be optimal for studying this question, but 1 has not been conducted and is unlikely to ever be performed. However, well-conducted observational studies may be of particular utility in evaluating the association between digoxin use in AF and adverse events because heart rate control has been shown in large randomized studies not to be associated with adverse outcomes, minimizing the risk of confounding by indication.

Our results support and substantially extend recent reports from smaller, more limited observational studies demonstrating incident digoxin use is independently associated with a higher risk of death and contradict the findings of 2 studies showing no association between digoxin and mortality. Notably, 2 post hoc studies of data from the AFFIRM trial showed conflicting results on this topic depending on the analytic strategy used, with 1 study showing an increased risk of mortality associated with digoxin using an on treatment analytic strategy and another study showing no association with mortality using a intent-to-treat analytic strategy. We showed a consistent and substantial increase in mortality and hospitalization risk using both the analytic methods. Importantly, our study is also the first to exclude patients with heart failure. All previous studies on this topic included substantial number of patients with comorbid heart failure, and the mechanisms of risk and benefit may be different than for these patients compared with those who have AF alone.

Although we were not able to assess the specific causes of death in our cohort, digoxin toxicity is well known to be a cause of arrhythmic death. Approximately 30% of the digoxin users in our study had a serum digoxin concentration measurement and an additional 27% only had it measured once, reflecting the fact that routine surveillance of digoxin levels is not commonly performed in community practice. Among digoxin users who did have serum digoxin concentration measured, levels were significantly higher among those who died compared with those who did not die, which may also be consistent with an arrhythmic cause for the increased mortality risk.

As an observational study of outcomes associated with a therapy used outside of a randomized trial, we cannot completely rule out residual confounding as an explanation for our findings. However, we implemented multiple design and analytic approaches to mitigate treatment selection bias. First, we studied contemporary patients with newly diagnosed atrial fibrillation and no known heart failure, and, therefore, we captured the full natural history of patients and prevented confounding by indication because of concomitant heart failure.

<table>
<thead>
<tr>
<th>Group</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cohort</td>
<td>1.63 (1.56-1.71)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.60 (1.45-1.76)</td>
</tr>
<tr>
<td>Women</td>
<td>1.66 (1.51-1.83)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>21-64 years</td>
<td>2.15 (1.80-2.56)</td>
</tr>
<tr>
<td>65-74 years</td>
<td>1.53 (1.34-1.73)</td>
</tr>
<tr>
<td>75-84 years</td>
<td>1.45 (1.31-1.62)</td>
</tr>
<tr>
<td>85+ years</td>
<td>1.68 (1.43-1.97)</td>
</tr>
</tbody>
</table>
Second, we used a new user design\textsuperscript{26} to focus on outcomes associated with newly initiated digoxin therapy to avoid biases associated with examining prevalent therapy and outcomes and captured longitudinal exposure to digoxin throughout follow-up. Third, we performed matching using age, sex, and the recently developed high-dimensional propensity score\textsuperscript{33} so that the digoxin users and nonusers we compared were similar with regard to potential confounders, including sociodemographic factors, comorbidity, laboratory results, and therapies. Results were also consistent in secondary analyses in which we included additional adjustment for time-updated comorbidities, including heart failure, laboratories, and medications, and in secondary analyses in which we treated digoxin as a time-varying exposure (on treatment analysis).

Our study was conducted within 2 large healthcare delivery systems in California, so the results may not be fully generalizable to all populations and practice settings, although our study included the largest and most diverse sample of adults with incident atrial fibrillation treated in clinical practice reported to date, which argues for greater generalizability. In addition, our results cannot be applied to those with concurrent heart failure and atrial fibrillation as we specifically excluded patients with known heart failure to mitigate confounding by indication.

Conclusions

We found that incident digoxin use was independently associated with higher risks of death and hospitalization in patients with atrial fibrillation and no known heart failure. These results were consistent across strata of age and sex and in secondary analyses using different analytic strategies. Given other available rate control options, digoxin should be used with caution in the management of atrial fibrillation.

Sources of Funding

This study was supported by grants 1RC2 HL101589 and U19 HL91179 from the National Heart, Lung, and Blood Institute; National Institutes of Health, United States and grant 0875162N for the American Heart Association Pharmaceutical Roundtable-SPina Cardiovascular Outcomes Research Center program.

Disclosures

None.

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Digoxin and Risk of Death in Adults With Atrial Fibrillation: The ATRIA-CVRN Study
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*Circ Arrhythm Electrophysiol.* 2015;8:49-58; originally published online November 20, 2014; doi: 10.1161/CIRCEP.114.002292

Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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Data Supplement (unedited) at:
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Supplemental Table 1. Covariates included in secondary analysis using multivariable extended Cox regression in the propensity score-matched cohort to examine the association of incident digoxin use and the risk of adverse outcomes.

- Age, gender, race, Hispanic ethnicity, low annual household income, low educational attainment, body mass index and time-updated information on coronary disease (acute myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass surgery), ischemic stroke, transient ischemic attack, intracranial hemorrhage, peripheral arterial disease, valvular heart disease, ventricular arrhythmias (ventricular fibrillation and tachycardia), diabetes mellitus, hypertension, dyslipidemia, dementia, depression, thyroid disease, gastrointestinal bleeding, other bleeding, systemic cancer, lung disease, liver disease, warfarin, alpha-adrenergic receptor antagonists, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, diuretics, beta-blockers, aldosterone receptor antagonists, calcium channel blockers, nitrates, hydralazine, statins, other lipid lowering therapy, antiplatelet agents, diabetic therapy, estimated glomerular filtration rate, systolic blood pressure, and heart failure during follow-up