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Increased mortality among patients taking digoxin—analysis from the AFFIRM study

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Aims Digoxin is frequently used for rate control of atrial fibrillation (AF). It has, however, been associated with increased mortality. It remains unclear whether digoxin itself is responsible for the increased mortality (toxic drug effect) or whether it is prescribed to sicker patients with inherently higher mortality due to comorbidities. The goal of our study was to determine the relationship between digoxin and mortality in patients with AF.

Methods and results The association between digoxin and mortality was assessed in patients enrolled in the AF Follow-Up Investigation of Rhythm Management (AFFIRM) trial using multivariate Cox proportional hazards models. Analyses were conducted in all patients and in subsets according to the presence or absence of heart failure (HF), as defined by a history of HF and/or an ejection fraction $<40\%$. Digoxin was associated with an increase in all-cause mortality [estimated hazard ratio (EHR) 1.41, 95% confidence interval (CI) 1.19–1.67, $P < 0.001$], cardiovascular mortality (EHR 1.35, 95% CI 1.06–1.71, $P = 0.016$), and arrhythmic mortality (EHR 1.61, 95% CI 1.12–2.30, $P = 0.009$). The all-cause mortality was increased with digoxin in patients without or with HF (EHR 1.37, 95% CI 1.05–1.79, $P = 0.019$ and EHR 1.41, 95% CI 1.09–1.84, $P = 0.010$, respectively). There was no significant digoxin–gender interaction for all-cause ($P = 0.70$) or cardiovascular ($P = 0.95$) mortality.

Conclusion Digoxin was associated with a significant increase in all-cause mortality in patients with AF after correcting for clinical characteristics and comorbidities, regardless of gender or of the presence or absence of HF. These findings call into question the widespread use of digoxin in patients with AF.

Keywords Arrhythmias • Atrial fibrillation • Digoxin • Congestive heart failure • Mortality

Introduction

Atrial fibrillation (AF) is by far the most common sustained cardiac arrhythmia in the general population. In addition to thromboprophylaxis, management of AF patients involves one of two strategies: (i) maintenance of sinus rhythm (SR), or the so-called 'rhythm-control' strategy, which frequently utilizes antiarrhythmic drugs (AADs); or (ii) a 'rate-control' strategy, which aims to avoid rapid ventricular rates during AF and frequently utilizes calcium-channel blockers, beta-blockers, and digoxin. Multiple studies have shown that patients with AF have an increased risk of morbidity and mortality when compared with patients in SR.[1–3] Based on this information, maintenance of SR has been a primary goal of many physicians. However, in the landmark Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial, a rhythm control strategy failed to improve survival compared with a rate control strategy.[4] This lack of benefit has been attributed to the toxicity of AADs as well as their poor efficacy in maintaining SR. Based on these results, many physicians now opt to rate control AF, especially among asymptomatic

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patients, due to the simplicity of the strategy, lower costs, and fewer side effects of rate-controlling medications.

Digoxin has been used worldwide for decades to achieve rate control in patients with AF. Its use in heart failure (HF) dates back centuries but remains controversial,[5] due to its narrow therapeutic index and a potential to contribute to life-threatening ventricular tachyarrhythmias and severe bradyarrhythmias.[6,7] Of particular concern is the fact that elevated serum levels of digoxin have been correlated with increased mortality in multiple patient populations.[7,8] Yet, several randomized prospective trials among patients with HF without AF have demonstrated clinical benefits. In the largest such trial (DIG study), digoxin had a neutral effect on mortality with an improvement in morbidity, but only in the setting of strict monitoring of serum drug levels.[5,9,10] In contrast, large observational studies have suggested that digoxin was an important predictor of all-cause and cardiovascular mortality.[11–15] It remains unclear whether such associations may be due to residual potential confounding effects as opposed to inherent drug toxicity.[11] We analysed the AFFIRM trial data to ascertain whether digoxin use predicted all-cause, cardiovascular, and arrhythmic cardiovascular mortality in all patients with AF, and in those with and without congestive heart failure (CHF)/ejection fraction (EF) <40%, after controlling for comorbidities potentially associated with mortality. We also explored potential gender-based interactions.

Methods

Study cohort and data acquisition

The AFFIRM trial design, baseline characteristics, and results have been published previously.[4] In brief, the study enrolled 4060 patients with AF considered at high risk for stroke. These patients were randomized to rate control vs. rhythm control over a 4-year period with a mean follow-up of 3.5 years. All patients provided informed consent to participate in the AFFIRM study, and all participating institutions received approval from their respective institutional review boards. Patients were seen for follow-up at 2 and 4 months after randomization and then every 4 months up to a maximum of 6 years. After approval from our institutional review board, a formal request was submitted through the Biologic Specimen and Data Repository Information Coordinating Center to obtain archived data on the patients enrolled in the AFFIRM study.

Statistical methods

Baseline variables in patients with and without digoxin therapy within 6 months of randomization were compared using Fisher's exact tests. Cardiovascular mortality was defined as death due to stroke, pulmonary emboli, aortic events, arrhythmias, HF, or cardiac surgery/interventions. Other deaths were considered non-cardiovascular. The cause of death and non-fatal endpoints were adjudicated by a committee blinded to the therapy received. After verifying proportionality assumptions, multivariate Cox proportional hazards models were used to assess the impact of digoxin as a time-dependent covariate on all-cause mortality, cardiovascular mortality, and arrhythmic cardiovascular mortality while controlling for multiple covariates including demographic characteristics, comorbidities, HF, and AF-related variables. Besides digoxin, permanency of AF (three follow-up visits with continuous AF and/or crossover from rhythm control to rate control), elevated heart rate (>100 b.p.m.), beta-blocker, ACE inhibitor, amiodarone, cumulative number of shock episodes (events with ≥1 cardioversions), New York Heart Association (NYHA) functional class, and Canadian Cardiovascular Society (CCS) angina status were modelled as time-dependent covariates; other variables were assessed at baseline. Analyses also controlled for propensity scores derived from a multivariate logistic regression model that used the covariates listed in the first column of *Table 1* to approximate the probability of being on digoxin within 6 months of randomization; Cochran–Mantel–Haenszel tests were used to verify appropriate balance from propensity scores. Variables considered in multivariate Cox proportional hazards models appear in the first column of *Table 2*. To gain greater insight into the influence of potential confounders on the relationship between digoxin and all-cause mortality, changes in the estimated hazard ratio (EHR) were examined stepwise in the multivariate Cox regression model.

Patients were also categorized according to whether or not they had CHF as defined by a left ventricular EF <40% and/or a history of CHF. Patients without a history of CHF but with missing EF data were classified as 'indeterminate'. To explore whether gender was an effect modifier of the relationships between digoxin and mortality outcomes, we also fit versions of the multivariate Cox proportional hazards models with a first-order interaction term between digoxin and gender. Analyses were repeated separately in patients with CHF, those without CHF, and in the indeterminate stratum. These stratified analyses allowed us to explore whether conclusions about the associations between digoxin and mortality outcomes (including interaction with gender) differed according to the CHF status.

We also performed three sensitivity analyses. Patients not on digoxin at baseline who received it later in the study may theoretically constitute a sicker population with inadequate rate control. To assess the potential for this additional bias, we first compared all-cause mortality in patients on digoxin at baseline vs. those not on digoxin at baseline. Second, we re-fit the Cox model using only data from patients who were: (a) on digoxin within 6 months preceding randomization and never off digoxin at any follow-up visit; or, (b) not on digoxin within the six months preceding randomization and never on digoxin at any follow-up visit. Thirdly, we re-fit the Cox model using only data for patients randomized to the rate control arm.

Finally, an analysis of the cause of death was conducted on the 666 patients who died over the course of the study, according to whether or not they received digoxin at their last follow-up visit. Comparisons were made using Fisher's exact tests. All *P*-values were two-sided, and a *P*-value of <0.05 was considered statistically significant. Version 9.3 of SAS software was used for data analyses.

Results

The AFFIRM trial randomized 4060 patients to rhythm control (2033 patients) vs. rate control (2027 patients). The study included 1594 females representing 39.3% of the study cohort. Overall, 2816 patients (69.4%) received digoxin within 6 months of randomization and/or during the study. In addition, 1647 patients (58.5%) and 1898 (67.4%) among the 2816 on digoxin received beta-blockers and ACE inhibitors at some point during the study, respectively, compared with the 718 patients (57.7%, $P = 0.65$) and 734 (59%, $P < 0.001$) not on digoxin (1244 patients). *Figure 1* summarizes the number of patients on digoxin vs. not on digoxin at baseline, through 8-month visit, last follow-up, and

Table 1 Covariates used to generate propensity scores in patients with and without digoxin therapy within 6 months of randomization

Covariate	Digoxin (n = 2153)	No digoxin (n = 1905)	P-value
History of coronary artery disease	837 (39%)	712 (37%)	0.33
History of angina pectoris	564 (26%)	481 (25%)	0.49
Prior myocardial infarction	392 (18%)	311 (16%)	0.11
History of hypertension	1486 (69%)	1390 (73%)	<0.001
History of cardiomyopathy	259 (12%)	82 (4%)	<0.0001
History of valvular heart disease	318 (15%)	186 (10%)	<0.0001
History of congenital heart disease	14 (<1%)	7 (<1%)	0.27
Symptomatic bradycardia/AV block	156 (7%)	127 (7%)	0.49
Prior stroke or TIA	272 (13%)	269 (14%)	0.16
History of peripheral vascular disease	163 (8%)	118 (6%)	0.09
History of hepatic or renal disease	130 (6%)	101 (5%)	0.34
History of pulmonary disease	370 (17%)	221 (12%)	<0.001
Permanent pacemaker	130 (6%)	120 (6%)	0.74
Prior interventional procedure	171 (8%)	183 (10%)	0.06
Oestrogen/progesterone within 6 months of randomization	224 (10%)	152 (8%)	<0.01
Lipid-lowering therapy within 6 months of randomization	434 (20%)	479 (25%)	<0.001
Symptoms during AF within 6 months of randomization	1969 (91%)	1635 (86%)	<0.0001
Cardioversion since qualifying episode of AF	900 (42%)	782 (41%)	0.63
Failure of antiarrhythmic drug prior to randomization	431 (20%)	281 (15%)	<0.0001
Hospitalization for qualifying arrhythmia	1021 (47%)	872 (46%)	0.29
Recurrent episodes of AF prior to randomization	682 (32%)	709 (37%)	<0.001
Amiodarone as initial therapy	399 (19%)	338 (18%)	0.54
Beta-blocker as initial therapy	552 (26%)	644 (34%)	<0.0001
Diltiazem as initial therapy	419 (19%)	364 (19%)	0.78
Sotalol as initial therapy	299 (14%)	314 (16%)	0.02
Verapamil as initial therapy	126 (6%)	119 (6%)	0.59
Class I drug as initial therapy	298 (14%)	226 (12%)	0.06

Hx, history; TIA, transient ischaemic attack; ACE, angiotensin converting enzyme; PND, paroxysmal nocturnal dyspnoea.
Atrial fibrillation symptoms included chest pain, diaphoresis, dizziness/light-headedness, dyspnoea, oedema, fast heart rate, fatigue, orthopnea, palpitations, panic, PND, syncope, and other.

death. Moreover, among the 2441 patients on digoxin at one or more follow-up visit (1389 rate control group; 1052 rhythm control), the median duration of therapy was 32 [interquartile range (IQR) 16, 46] months. Corresponding times for patients randomized to rate and rhythm control were 32 (IQR 16, 46) months and 28 (IQR 8, 44) months, respectively. *Figure 2* shows all-cause mortality for patients always vs. never on digoxin during the course of the study.

Heart failure, as defined by a history of CHF and/or EF <40%, was prevalent in 1076 (26.5%) patients. There were 811 patients (20.0%) with no history of CHF and missing EF data who were classified as having an indeterminate CHF status. A total of 636 patients (59.1%) with CHF had taken beta-blockers within 6 months of randomization and/or during the study. Over an average follow-up of 3.5 years (maximum 6 years), 666 patients died, 331 (49.7%) from a cardiovascular aetiology. Among the 666 patients who died, 375 (56.3%) were taking digoxin at their last follow-up visit.

All patients

The variables used to generate propensity scores are listed in *Table 1* according to whether or not patients received digoxin within 6 months of randomization. Significant differences in baseline comorbidities, history of AF, and medical therapy were observed. However, the propensity scores achieved reasonable balance, as reflected by the absence of significant associations between the variables of interest and digoxin in stratified Cochran–Mantel–Haenszel analyses.

Table 2 summarizes the results of multivariate Cox proportional hazards models for all-cause and cardiovascular mortality based on the full sample. Digoxin was associated with increased all-cause (EHR 1.41, 95% CI 1.19–1.67, $P < 0.001$) and cardiovascular mortality (EHR 1.35, 95% CI 1.06–1.71, $P = 0.016$) after controlling for clinical and demographic variables, as well as propensity scores. Similarly, digoxin was associated with an increase in arrhythmic deaths (EHR 1.61, 95% CI 1.12–2.30, $P = 0.009$); other significant predictors of arrhythmic mortality

Table 2 Multivariate Cox proportional hazards models for all-cause and cardiovascular mortality

Covariate	All-cause mortality		Cardiovascular mortality	
	EHR (95% CI)	*P*-value	EHR (95% CI)	*P*-value
Digoxin	1.41 (1.19–1.64)	<0.0001	1.34 (1.06–1.72)	0.01
Age ≥75 years	1.93 (1.64–2.26)	<0.0001	1.56 (1.24–1.96)	<0.001
Male gender	1.05 (0.88–1.24)	0.58	0.88 (0.69–1.11)	0.29
Hypertension	1.11 (0.92–1.34)	0.24	1.32 (1.01–1.75)	0.045
Diabetes	1.39 (1.16–1.66)	<0.001	1.50 (1.17–1.91)	<0.01
Cardiomyopathy	1.49 (1.11–1.99)	<0.01	1.95 (1.33–2.86)	<0.001
Valvular heart disease	1.22 (0.98–1.53)	0.06	1.26 (0.94–1.70)	0.11
Coronary artery disease	1.40 (1.13–1.73)	<0.01	1.34 (0.98–1.83)	0.06
Myocardial infarction	1.09 (0.88–1.35)	0.43	1.46 (1.08–1.96)	0.01
Stroke or TIA	1.54 (1.26–1.88)	<0.0001	2.03 (1.56–2.65)	<0.0001
Peripheral vascular disease	1.14 (0.89–1.47)	0.28	1.09 (0.77–1.53)	0.61
Hepatic or renal disease	1.50 (1.16–1.95)	<0.01	1.46 (1.02–2.10)	0.03
Pulmonary disease	1.59 (1.30–1.95)	<0.0001	1.20 (0.90–1.61)	0.20
Amiodarone	1.34 (1.11–1.63)	<0.01	1.21 (0.93–1.59)	0.15
Beta-blockers	1.01 (0.86–1.20)	0.87	1.04 (0.82–1.31)	0.77
ACE inhibitor	0.87 (0.73–1.03)	0.11	1.03 (0.81–1.32)	0.79
Coronary artery bypass graft	1.11 (0.88–1.38)	0.36	1.03 (0.76–1.39)	0.83
Interventional procedures	0.80 (0.61–1.05)	0.11	0.90 (0.62–1.30)	0.58
Heart rate (>100 b.p.m.)	2.92 (2.21–3.85)	<0.0001	2.31 (1.53–3.50)	<0.0001
CCS class I or higher	0.97 (0.77–1.23)	0.83	0.78 (0.56–1.08)	0.14
NYHA class II or higher	1.99 (1.66–2.37)	<0.0001	2.62 (2.04–3.37)	<0.0001
Indeterminate heart failure status (vs. no heart failure)	0.99 (0.78–1.25)	0.94	0.89 (0.61–1.29)	0.55
Heart failure (vs. no heart failure)	1.28 (1.04–1.57)	0.01	1.45 (1.085–1.96)	0.01
Cumulative number of shock episodes (with non-permanent AF)	0.96 (0.84–1.11)	0.63	0.95 (0.77–1.16)	0.63
Cumulative number of shock episodes (with permanent AF)	0.91 (0.77–1.08)	0.29	0.96 (0.76–1.22)	0.78
Transition to permanent AF (with no shock episodes)	1.08 (0.87–1.34)	0.45	1.09 (0.80–1.48)	0.58
Propensity score	0.88 (0.38–2.06)	0.77	1.20 (0.358–4.03)	0.76

EHR, estimated hazard ratio; TIA, transient ischaemic attack; ACE inhibitor, angiotensin converting enzyme inhibitor; NYHA, New York Heart Association functional class; CCS, Canadian Cardiovascular Society angina class.
Digoxin, permanency of AF (three follow-up visits with continuous AF and/or crossover from rhythm control to rate control), amiodarone, cumulative number of shock episodes (number of documented instances in which ≥1 cardioversions were received), NYHA, and CCS were time-dependent covariates; other covariates were evaluated at baseline. Heart failure was defined as the presence of CHF and/or qualitatively estimated EF <40%.

included history of stroke or transient ischaemic attack, NYHA functional class II or greater (time-dependent covariate), history of hypertension, and history of myocardial infarction. In re-fitted models that considered interactions between digoxin and gender, there was no significant interaction for all-cause ($P = 0.70$), cardiovascular ($P = 0.95$), or arrhythmic mortality ($P = 0.53$).

In a stepwise examination of the multivariate Cox regression model, the EHR for the association between digoxin and all-cause mortality ranged between 1.36 and 1.66 as the covariates were added, with 95% confidence intervals (CIs) that ranged from 1.16 to 1.94. The greatest change in the EHR followed addition of NYHA functional class, with a decrease from 1.66 (95% CI 1.42–1.94, $P < 0.001$) to 1.49 (95% CI 1.27–1.74, $P < 0.001$). Comparing the EHR with all covariates present to that with none present, 62.6% of digoxin over-mortality cannot be attributed to confounding from the covariates.

Analyses according to heart failure status

Of the 2173 patients without CHF, 905 (41.7%) were women and 259 (11.9%) died during the study. Digoxin was significantly associated with all-cause (EHR 1.37, 95% CI 1.05–1.79, $P = 0.019$) but not cardiovascular mortality (EHR 1.22, 95% CI 0.81–1.83, $P = 0.35$). There was a trend towards an increase in arrhythmic deaths (EHR 1.69, 95% CI 0.92–3.08, $P = 0.091$).

Of the 1076 patients with CHF, 386 (35.9%) were women and 305 (28.4%) died during follow-up. Digoxin was significantly associated with all-cause mortality (EHR 1.41, 95% CI 1.09–1.84, $P = 0.010$). There were also trends towards increased cardiovascular mortality (EHR 1.40, 95% CI 0.995–1.97, $P = 0.053$) and arrhythmic deaths (EHR 1.59, 95% CI 0.95–2.66, $P = 0.079$).

Of the 811 patients with an indeterminate CHF status, 303 (37.4%) were women and 102 (12.6%) died during follow-up. Digoxin was significantly associated with all-cause (EHR 1.64, 95% CI 1.07–2.52, $P = 0.023$) but not cardiovascular (EHR 1.67,

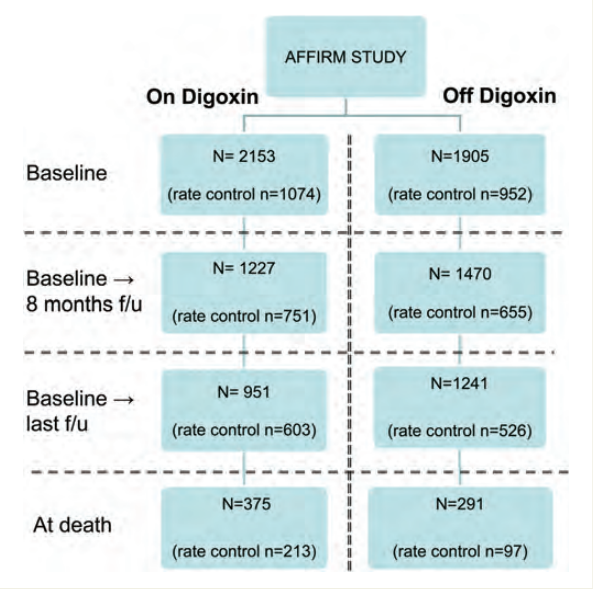

Figure 1 Number of patients on digoxin vs. not on digoxin at critical times of the study.

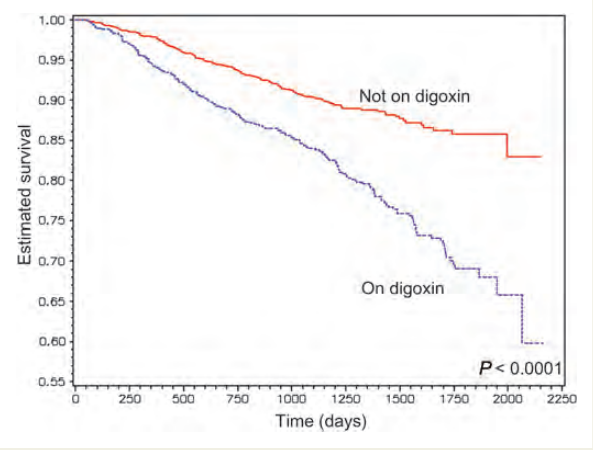

Figure 2 Kaplan–Meier curves for all-cause mortality based on digoxin use during the study. Shown are Kaplan–Meier curves for all-cause mortality in patients always or never on digoxin during the study. *P*-value for this comparison is <0.0001 by the likelihood ratio test.

95% CI 0.84–3.30, $P = 0.14$) or arrhythmic mortality (EHR 1.53, 95% CI 0.58–4.07, $P = 0.39$).

There were no significant digoxin–gender interactions for any subgroup analysis. Moreover, tests for digoxin–CHF interactions yielded *P*-values of 0.70, 0.71, and 0.96 for the endpoints of all-cause, cardiovascular, and arrhythmic mortality, respectively.

Sensitivity analyses

(i) Since only 44.2% of those on digoxin within the 6 months preceding randomization remained on digoxin throughout the study, replacing time-dependent digoxin with whether digoxin was used within the 6 months preceding randomization reduced the EHR to 1.02 (95% CI 0.86–1.20, $P = 0.83$). Even so, the Kaplan–Meier curves in *Figure 3* show that digoxin use within the six months preceding randomization is related to mortality in the absence of adjustments for other covariates.

(ii) Re-fitting the Cox model using only patients consistently on or consistently off digoxin yielded an EHR of 1.58 (95% CI 1.23–2.03, $P < 0.001$) for all-cause mortality.

(iii) Re-fitting the Cox model using only patients in the rate control arm, digoxin was associated with an EHR of 1.46 (95% CI 1.13–1.90, $P = 0.004$) for all-cause mortality.

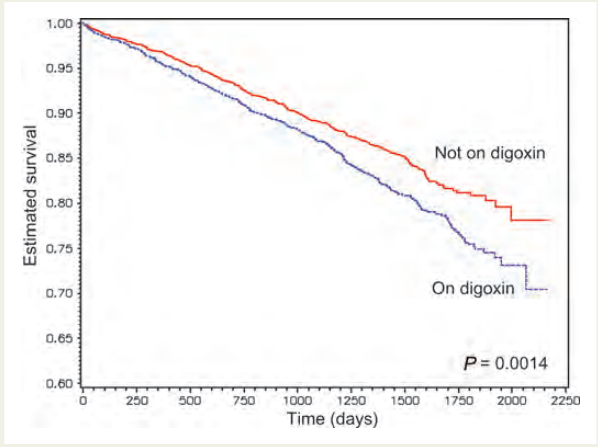

Figure 3 Kaplan–Meier curves for all-cause mortality based on digoxin use at baseline. Kaplan–Meier curves depict all-cause mortality in patients receiving or not receiving digoxin within the six months preceding randomization. *P*-value for this comparison is 0.0014 by the likelihood ratio test.

Causes of death by digoxin at last follow-up visit

Among the 666 patients who died during the study, 375 (56.3%) received digoxin and 291 (43.7%) had no digoxin at the last follow-up visit before death. When comparing those two groups, cardiac death with no evidence of ischaemia was a significantly more frequent cause of death among patients on digoxin at the last follow-up visit ($n = 139$, 37.1% vs. $n = 79$, 27.1%, $P = 0.007$). There were no statistical differences for the following causes of death: cancer; pulmonary; and non-cardiovascular.

Discussion

Our findings suggest that, in patients with AF, digoxin is associated with increased all-cause mortality after controlling for comorbidities and propensity scores, regardless of gender and the presence or absence of underlying HF. All-cause mortality was 41% higher in patients on digoxin. This effect was consistent across all HF strata.

Digoxin has survived as a mainstay of therapy for AF and CHF for decades despite controversies about its safety[16,17] and

continues to be utilized in the United States and worldwide. Digoxin use has ranged from 35 to 70% in recent AF studies[4,17–20] despite limited data addressing its safety for this indication. The AFFIRM study provided a unique opportunity to assess the safety of digoxin in a large AF cohort.

Patients with no congestive heart failure and ejection fraction ≥40%

In patients with AF and no HF, digoxin was associated with a 37% increase in mortality in an analysis that controlled for a host of comorbidities and propensity scores. This group represented more than half of all patients enrolled in AFFIRM. These findings are consistent with previously published results from the Registry of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA) study.[12] The RIKS-HIA study examined 1-year outcomes of patients with AF, CHF, or both on digoxin by comparing them to a matched group of patients not receiving digoxin. The 4426 patients with AF and no history of CHF taking digoxin had a significant increase in overall mortality (estimated relative risk 1.42, 95% CI 1.29–1.56) compared with 16 587 controls at discharge.

Patients without CHF or low EF lack the neurohormonal and inotropic derangements that may improve with digoxin, while remaining exposed to its potential deleterious effects such as proarrhythmia and bradycardia. In the AFFIRM trial, digoxin was utilized to meet the stringent rate control strategy requirement (resting heart rate <80 b.p.m. and exercise heart rate <110 b.p.m.), usually in combination with other atrioventricular (AV) nodal blockers such as beta-blockers or calcium-channel blockers. Indeed, digoxin was used as monotherapy for rate control in only 17% of patients.[21] In those patients, higher doses of digoxin with an increased risk for toxicity may have been used to achieve the stringent rate control goal, as high serum levels of digoxin were encouraged in the AFFIRM protocol (>1.0 ng/mL). It is currently thought that strict rate control at baseline is not superior to a more lenient strategy (resting heart rate <110 b.p.m.).[22–24] The major objectives of a rate control strategy are to minimize symptoms and avoid sustained rapid ventricular rates that can lead to rhythm-induced cardiomyopathies. Digoxin is known to slow heart rates and potentiate bradyarrhythmias[25] through its parasympathetic effect on the AV node, but has little effect on fast ventricular rates in the setting of enhanced sympathetic tone.[26] Therefore, digoxin is not the ideal choice to control rapid ventricular rates in most patients.

Patients with congestive heart failure and/or ejection fraction <40%

Digoxin may seem appealing for patients with AF and HF, in whom positive inotropic effects and improved neurohormonal responses are desired. Digoxin may also be beneficial during SR by reducing the heart rate as suggested in an analysis of the Dig trial.[27] However, in our analysis, digoxin was associated with a 41% increase in mortality for patients with HF. It may be hypothesized that potential benefits are offset by deleterious effects. For example, patients with CHF who experience AF may incur more frequent CHF exacerbations, frequent electrolyte fluctuations, and varying levels of acute kidney injury that increase susceptibility to digoxin toxicity.[28] Furthermore, a number of medications frequently prescribed to this patient population may directly interact with digoxin or impact digoxin levels indirectly via volume status changes, electrolyte imbalance, or drug elimination,[29] all of which can potentiate the risk of lethal tachy- and bradyarrhythmias (e.g. amiodarone, diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and calcium-channel blockers).

Although amiodarone may increase serum digoxin levels, in our analysis, digoxin's deleterious effect on mortality persisted after adjustment for amiodarone use. More recently, dronedarone has been associated with an increased mortality in the PALLAS study.[30] The increase in mortality is thought to be related to the interaction between dronedarone and digoxin.[31] The largest trial to examine the safety of digoxin in patients with HF, the DIG study, excluded patients with AF.[10] In that trial, patients were randomized to digoxin vs. placebo. Digoxin was found to have a neutral effect on the all-cause mortality (EHR 0.99; 95% CI 0.91–1.07; $P = 0.80$). However, it is important to note that real-world patients, including those in AFFIRM, are not routinely subject to the close follow-up and frequent monitoring of serum digoxin concentrations mandated in the DIG study. It is possible that such strict monitoring is required to ensure safety. Further analysis of the DIG trial data demonstrated that digoxin's beneficial effect applied only to patients in SR with low serum digoxin drug levels (<0.9 ng/mL).[7,32] Indeed, positive inotropic and neurohormonal effects are attained with low plasma drug concentrations.[6,20,32,33–38]. Patients with higher digoxin levels had worse outcomes, including 60% higher all-cause mortality ($P = 0.006$),[7,28] an increase in hospitalizations for suspected digoxin toxicity ($P < 0.001$), and an increase in arrhythmic mortality (15 vs. 13% in placebo, $P = 0.04$).[10] More recently, a positive association between serum digoxin concentrations and mortality was again demonstrated in patients with end-stage renal failure (EHR 1.28; 95% CI 1.25–1.31; $P < 0.001$).[8] Also, a higher proportion of patients in the AFFIRM trial were on beta-blockers (58.3%) compared with patients in the DIG and other trials.[5,9,10] While digoxin's positive neurohormonal effects in HF patients may be attenuated or lost when beta-blockers are concomitantly prescribed, the association between digoxin and mortality observed in our study was independent of beta-blocker use.

Death mechanism with digoxin

The mechanism by which digoxin increases total mortality in patients without HF remains speculative. Classic cardiac digoxin toxicity (i.e. lethal tachy- or bradyarrhythmias, drug interactions, narrow therapeutic window) may be implicated to a lesser degree in patients without HF, since cardiovascular mortality was not significantly increased in patients without HF. It is worthwhile noting that the accuracy of clinical classifications of death (in particular, of cardiovascular or arrhythmic death) is limited.[39] Moreover, subgroup analyses are inherently limited by smaller sample sizes. Although it is theoretically possible for digoxin to increase non-cardiac deaths, similar to the association between amiodarone and cancer deaths reported in a prior AFFIRM substudy,[40] our analysis of causes of death did not link digoxin to non-cardiovascular

causes. However, digoxin was associated with non-ischaemic cardiac causes.

Digoxin and gender

The greater increase in mortality with digoxin among women compared with men described in a *post hoc* analysis of the DIG study[41] is regarded as controversial. It was unclear whether this increase was due to higher serum drug concentrations or an unidentified gender-specific toxicity. In our study, we did not find a gender interaction with digoxin therapy. Both men and women experienced significantly increased overall mortality with digoxin use. Our findings are consistent with other recent analyses involving patients with AF.[10,13,14]

Study limitations

Our study is subject to the limitations inherent to *post hoc* analyses. The AFFIRM trial was designed to compare rhythm control to rate control and did not, therefore, randomize patients to digoxin therapy. The mortality excess with digoxin decreased from 66% without any covariates present to 41% with adjustments for covariates (including propensity scores). The association between digoxin and mortality may still be overestimated due to unknown and/or unmeasured potential confounders. However, given the large observed magnitude of effect and directionally consistent main and sensitivity analyses, invalidation of these results by residual confounding appears implausible.

While our results strongly suggest that mortality was increased by digoxin in the AFFIRM study, the pathophysiological mechanism remains to be elucidated. In keeping with standard clinical care, routine monitoring of digoxin levels, although encouraged, was not mandated nor recorded in the AFFIRM trial. We cannot, therefore, assess whether serum digoxin levels are predictive of mortality outcomes. No specific digoxin dosing recommendations were provided by the AFFIRM protocol and individual doses were not available. Measures of renal function (creatinine level, creatinine clearance) were not collected and, therefore, not available for analyses. Similarly, the exact duration of and compliance with digoxin therapy were not confirmed. However, our Cox proportional hazards models did account for the approximate duration of digoxin therapy by defining digoxin use as a time-dependent covariate based on whether the patient was on digoxin at each follow-up visit.

Finally, the threshold of $<40\%$ for defining a low EF was based on common clinical practice; whether a lower threshold (e.g. 30 or 35%) may yield similar mortality trends has not been explored.

Conclusion

Among patients with AF enrolled in the AFFIRM trial, digoxin was associated with increased all-cause mortality, cardiovascular mortality, and arrhythmic deaths in a propensity-adjusted analysis that controlled for multiple comorbidities. The increase in all-cause mortality was consistently observed in men and women and in patients with and without underlying HF. Our study underscores the importance of reassessing the role of digoxin in the contemporary management of AF in patients with or without HF.

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