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ORIGINAL INVESTIGATIONS

Digoxin and Mortality in Patients With Atrial Fibrillation

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ABSTRACT

BACKGROUND Digoxin is widely used in patients with atrial fibrillation (AF).

OBJECTIVES The goal of this paper was to explore whether digoxin use was independently associated with increased mortality in patients with AF and if the association was modified by heart failure and/or serum digoxin concentration.

METHODS The association between digoxin use and mortality was assessed in 17,897 patients by using a propensity score–adjusted analysis and in new digoxin users during the trial versus propensity score–matched control participants. The authors investigated the independent association between serum digoxin concentration and mortality after multivariable adjustment.

RESULTS At baseline, 5,824 (32.5%) patients were receiving digoxin. Baseline digoxin use was not associated with an increased risk of death (adjusted hazard ratio [HR]: 1.09; 95% confidence interval [CI]: 0.96 to 1.23; p = 0.19). However, patients with a serum digoxin concentration ≥1.2 ng/ml had a 56% increased hazard of mortality (adjusted HR: 1.56; 95% CI: 1.20 to 2.04) compared with those not on digoxin. When analyzed as a continuous variable, serum digoxin concentration was associated with a 19% higher adjusted hazard of death for each 0.5-ng/ml increase (p = 0.0010); these results were similar for patients with and without heart failure. Compared with propensity score–matched control participants, the risk of death (adjusted HR: 1.78; 95% CI: 1.37 to 2.31) and sudden death (adjusted HR: 2.14; 95% CI: 1.11 to 4.12) was significantly higher in new digoxin users.

CONCLUSIONS In patients with AF taking digoxin, the risk of death was independently related to serum digoxin concentration and was highest in patients with concentrations ≥1.2 ng/ml. Initiating digoxin was independently associated with higher mortality in patients with AF, regardless of heart failure. (J Am Coll Cardiol 2018;71:1063–74)

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CI = confidence interval

GDF = growth differentiation factor

HR = hazard ratio

LVEF = left ventricular ejection fraction

Digoxin, a well-established drug in cardiovascular medicine, is widely used in patients with atrial fibrillation (AF). Current guidelines (1,2) recommend digoxin for rate control in patients with AF, particularly those with concomitant heart failure. Digoxin has been evaluated in patients with heart failure and sinus rhythm (3), but no randomized controlled trial has assessed digoxin's long-term efficacy or safety in patients with AF. In an effort to address this gap, several observational analyses, including post hoc analyses from clinical trials, registries, and meta-analyses, have recently been published (4–20). These studies have provided conflicting results, possibly due to varying patient populations and analytical methods (21–27).

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Digoxin has a narrow therapeutic window, and its levels are markedly influenced by drug-drug interactions and comorbidities (28). A major limitation of all previous studies examining the safety of digoxin in patients with AF is the lack of serum digoxin concentration measurements necessary to define a possible dose-response relationship. A post hoc analysis of the DIG (Digitalis Investigation Group) trial in 1,171 patients with heart failure but not AF suggested that the serum digoxin concentration was directly related to mortality, with reduced mortality among patients with low digoxin levels (between 0.5 and 0.8 ng/ml) and increased mortality among patients with levels >1.1 ng/ml (29).

The present study explored the association between digoxin use, serum digoxin concentration, and mortality in patients with AF in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial (30,31). We analyzed whether this association was modified by the presence of heart failure, serum digoxin concentration, biomarkers, concomitant medications, or any other clinical or laboratory characteristics associated with digoxin use, serum digoxin concentration, and mortality. The efficacy and safety of apixaban versus warfarin were also assessed according to digoxin use.

METHODS

We performed a post hoc digoxin subgroup analysis of the ARISTOTLE trial, which compared apixaban with warfarin for the prevention of stroke or systemic embolism in patients with AF and at least 1 additional risk factor for stroke (30,31). The primary efficacy

were conducted at the Duke Clinical Research Institute and the Uppsala Clinical Research Center, and the authors had full access to all data. The Duke Clinical Research Institute coordinated the trial and managed the database. An academic steering committee designed the trial and was responsible for oversight of study conduct and reporting of all results, and takes responsibility for the accuracy and completeness of the data analyses. The authors are fully responsible for the study design, data collection, analysis and interpretation of the data, and writing of the manuscript; all authors agreed to submit the manuscript for publication. The sponsor played no role in the decision to submit the manuscript for publication. Dr. Lopes has received research grants from Bristol-Myers Squibb, GlaxoSmithKline, Medtronic, and Pfizer; and consulting fees/honoraria from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Medtronic, Merck & Co., Pfizer, and Portola. Dr. Rordorf has received speaking fees from Medtronic and St. Jude Medical. Dr. De Ferrari has received research grant support from Amgen; advisory board and speaking fees from Amgen, Merck, and Sigma-Tau; and steering committee support from Boston Scientific. Dr. Leonardi has received research grant support from AstraZeneca; and honoraria from The Medicines Company, Chiesi, Daiichi-Sankyo, and AstraZeneca. Dr. Lawrence was an employee of Bristol-Myers Squibb at the time of the trial. Dr. De Caterina has received research grants, consulting fees, and honoraria from Sanofi, Boehringer Ingelheim, Bayer, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, Novartis, and Merck. Dr. Vinereanu has received research grants from Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, Johnson & Johnson, and Bayer; and consulting/honoraria fees from Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, and Bayer. Dr. Hanna was an employee of Bristol-Myers Squibb at the time of the trial. Dr. Hohnloser has received consulting fees from Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Johnson & Johnson, Pfizer, Medtronic, and St. Jude Medical; and lecture fees from Boehringer Ingelheim, Bayer, Bristol-Myers Squibb, Pfizer, and Abbott. Dr. Alexander has received research grants from Bristol-Myers Squibb, Boehringer Ingelheim, CSL Behring, Sanofi, and Tenax Therapeutics; and consulting fees/honoraria from Cempra, CryoLife, CSL Behring, Pfizer, Portola Pharmaceuticals, and VasoPrep Surgical. Dr. Granger has received research grants from Armetheon, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Janssen Pharmaceuticals, Medtronic Foundation, Novartis Corporation, Pfizer, and The Medicines Company; and consulting fees/honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Daiichi-Sankyo, Eli Lilly, Gilead Sciences, Inc., GlaxoSmithKline, Hoffmann-La Roche, Janssen, Medtronic Inc., Novartis, Pfizer, The Medicines Company, and Verseon. Dr. Wallentin has received research grants from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline, Merck/Schering-Plough, Pfizer, and Roche Diagnostics; and consulting fees/honoraria from Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline, and Pfizer. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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outcome was stroke (ischemic or hemorrhagic) or systemic embolism. The primary safety outcome was major bleeding according to the International Society on Thrombosis and Haemostasis criteria. Clinical events, including cause of death, were adjudicated on the basis of prespecified criteria by a clinical events committee unaware of randomized treatment. All patients provided written informed consent, and approval by the appropriate ethics committees was obtained at all sites.

MORTALITY, DIGOXIN USE, AND HEART FAILURE. For this analysis, the primary endpoint was time to all-cause mortality; cardiovascular and non-cardiovascular mortality and sudden cardiac death were also analyzed, in which competing causes of death were handled by censoring (30).

All clinical outcomes were pre-specified in the statistical analysis plan. At each follow-up visit, the use of digoxin was recorded, with start and end dates of use. Patients were classified as taking or not taking digoxin at baseline if they were receiving or not receiving digoxin at the start of the study and as new users if they were not taking digoxin at baseline and started digoxin during the course of the study.

Heart failure was a subgroup of interest and was pre-specified in the statistical analysis plan. It was recorded in the case report form and defined as symptomatic congestive heart failure within 3 months or history of heart failure and/or a left ventricular ejection fraction (LVEF) ≤40% and/or moderate or severe left ventricular dysfunction if LVEF as a continuous variable was not available.

DIGOXIN AND OTHER BIOCHEMICAL ANALYSES. Digoxin concentrations were analyzed in serum samples obtained at baseline and stored frozen in aliquots until analysis in a central laboratory using an ARCHITECT ci8200 instrument (Abbott Core Laboratory, Abbott Park, Illinois). Reagents (1E06-21) and a TDM Multi-constituent Calibrator (5P04-01) for the latex-enhanced immunoturbidimetric method were also from Abbott. The analyses were performed at the Department of Clinical Chemistry, Uppsala University, Uppsala, Sweden, which is accredited according to SS-EN ISO/IEC 15189, including the interlaboratory external proficiency testing scheme from Equalis AB (Uppsala, Sweden). The levels of the prognostic biomarkers N-terminal pro-B-type natriuretic peptide, troponin I and T, and growth differentiation factor (GDF)-15 were measured in plasma samples by using the Roche or Abbott assays as previously published (32–35).

STATISTICAL ANALYSIS. Patients using and those not using digoxin, overall and within the heart failure groups, were compared by using the Fisher exact tests and the Wilcoxon rank sum test for categorical and continuous variables, respectively. Event rates per 100 patient-years of follow-up in patients taking/not taking digoxin at baseline were computed, and hazard ratios (HRs) with 95% confidence intervals (CIs) comparing event rates between groups were derived. Two different analyses were implemented: a prevalent user analysis and an incident (new) user analysis. Both analyses included mortality endpoints (all-cause, cardiovascular, noncardiovascular, and sudden cardiac death) and hospitalization for heart failure.

PREVALENT (BASELINE DIGOXIN USE) ANALYSIS. Patients taking and not taking digoxin were compared from the time of baseline by using a Cox regression model with overlap propensity score weighting (36). The propensity model was fit by logistic regression and included sociodemographic variables; medical history, including AF characteristics; concomitant medications; indicators of renal function (serum creatinine and estimated creatinine clearance); uric acid; and prognostic biomarkers (NT-pro brain natriuretic peptide, troponin I and T, and GDF-15) (Online Table 1). Randomized treatment was not associated with prevalent digoxin use and is unlikely to be a relevant confounder; it was therefore not included in the propensity model. Missing values were <1.7% for all variables excluding biomarkers in which missingness was ~18%, and were handled by single imputation using the fully conditional specification method (37). Covariate balance between groups (digoxin and no digoxin) was assessed by using standardized differences (Online Table 2). Serum digoxin concentrations in serum samples were available at baseline for 4,434 (76%) patients taking digoxin at baseline. The relationship between serum digoxin concentration and outcomes was evaluated via multivariable Cox regression.

To evaluate the treatment effect (apixaban vs. warfarin) on stroke/systemic embolism, all-cause mortality, and major bleeding according to the International Society on Thrombosis and Haemostasis criteria for patients taking and not taking digoxin at baseline, a Cox regression model was fitted including main effects for randomized treatment, digoxin use at baseline, and the interaction. HRs for apixaban versus warfarin with 95% CIs were derived in patients taking and not taking digoxin at baseline, and the p value for interaction was computed.

INCIDENT (NEW DIGOXIN USERS) ANALYSIS. To investigate the association between digoxin started during follow-up and outcomes, only patients not taking digoxin at baseline were considered

TABLE 1 Baseline Characteristics Stratified According to Heart Failure and Digoxin Use at Baseline

	Heart Failure			No Heart Failure			Overall	
	Digoxin (n = 3,003)	No Digoxin (n = 3,690)	p Value	Digoxin (n = 2,821)	No Digoxin (n = 8,383)	p Value	Digoxin (n = 5,824)	No Digoxin (n = 12,073)
Demographics								
Age, yrs	68 (60, 74)	69 (62, 75)	<0.0001	71 (64, 77)	71 (64, 76)	0.0103	69 (62, 76)	70 (63, 76)
Female	1,034 (34.4)	1,264 (34.3)	0.88	1,200 (42.5)	2,826 (33.7)	<0.0001	2,234 (38.4)	4,090 (33.9)
White race	2,411 (80.3)	3,196 (86.6)	<0.0001	2,253 (79.9)	6,950 (82.9)	0.0003	4,664 (80.1)	10,146 (84.0)
Hispanic or Latino	731 (24.3)	663 (18.0)	<0.0001	628 (22.3)	1,524 (18.2)	<0.0001	1,359 (23.3)	2,187 (18.1)
Current smoker	290 (9.7)	320 (8.7)	0.16	194 (6.9)	663 (7.9)	0.07	484 (8.3)	983 (8.1)
Medical history								
Previous stroke, TIA, or SE	495 (16.5)	690 (18.7)	0.0182	598 (21.2)	1,686 (20.1)	0.22	1,093 (18.8)	2,376 (19.7)
LVEF, %	42 (34, 55)	48 (38, 60)	<0.0001	60 (54, 65)	60 (55, 65)	0.0037	53 (40, 60)	58 (50, 65)
LA size, cm	4.8 (4.3, 5.4)	4.7 (4.2, 5.3)	0.0023	4.6 (4.1, 5.2)	4.5 (4.0, 5.0)	<0.0001	4.7 (4.2, 5.3)	4.6 (4.1, 5.1)
Diabetes	763 (25.4)	950 (25.7)	0.75	813 (28.8)	1,970 (23.5)	<0.0001	1,576 (27.1)	2,920 (24.2)
Hypertension	2,406 (80.1)	3,200 (86.7)	<0.0001	2,459 (87.2)	7,629 (91.0)	<0.0001	4,865 (83.5)	10,829 (89.7)
Coronary artery disease	1,236 (41.2)	1,778 (48.2)	<0.0001	676 (24.0)	2,273 (27.1)	.0010	1,912 (32.8)	4,051 (33.6)
Admitted with unstable angina	285 (9.5)	464 (12.6)	<0.0001	146 (5.2)	598 (7.1)	0.0003	431 (7.4)	1,062 (8.8)
Previous myocardial infarction	580 (19.3)	852 (23.1)	0.0002	243 (8.6)	879 (10.5)	0.0042	823 (14.1)	1,731 (14.3)
Previous cardiac surgery	1,111 (37.0)	1,768 (47.9)	<0.0001	1,192 (42.3)	4,099 (48.9)	<0.0001	2,303 (39.5)	5,867 (48.6)
Previous PCI	179 (6.0)	356 (9.6)	<0.0001	173 (6.1)	676 (8.1)	0.0008	352 (6.0)	1,032 (8.5)
NYHA functional class			<0.0001			<0.0001		
I	493 (16.4)	838 (22.7)		1,931 (68.6)	6,223 (74.4)		2,424 (41.7)	7,061 (58.6)
II	1,736 (57.8)	2,086 (56.5)		766 (27.2)	1,958 (23.4)		2,502 (43.0)	4,044 (33.5)
III	726 (24.2)	748 (20.3)		117 (4.2)	179 (2.1)		843 (14.5)	927 (7.7)
IV	47 (1.6)	18 (0.5)		1 (0.0)	4 (0.0)		48 (0.8)	22 (0.2)
At least moderate valvular disease	751 (25.0)	907 (24.6)	0.67	451 (16.0)	1,089 (13.0)	<0.0001	1,202 (20.6)	1,996 (16.5)
Sustained VT	41 (1.4)	58 (1.6)	0.49	13 (0.5)	58 (0.7)	0.18	54 (0.9)	116 (1.0)
VF/VT cardiac arrest	29 (1.0)	57 (1.5)	0.0365	15 (0.5)	43 (0.5)	0.90	44 (0.8)	100 (0.8)
Syncope	106 (3.5)	189 (5.1)	0.0016	134 (4.8)	422 (5.0)	0.55	240 (4.1)	611 (5.1)
Asthma	145 (4.8)	153 (4.2)	0.18	179 (6.4)	385 (4.6)	0.0002	324 (5.6)	538 (4.5)
Sleep apnea	122 (4.1)	203 (5.5)	0.0064	175 (6.2)	508 (6.1)	0.77	297 (5.1)	711 (5.9)
Thyroid disease	269 (9.0)	421 (11.4)	0.0010	342 (12.1)	992 (11.9)	0.70	611 (10.5)	1,413 (11.7)
Anemia	189 (6.3)	319 (8.7)	0.0003	179 (6.4)	547 (6.5)	0.74	368 (6.3)	866 (7.2)
Chronic renal disease	798 (26.6)	968 (26.2)	0.75	595 (21.1)	1,541 (18.4)	0.0015	1,393 (23.9)	2,509 (20.8)

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(n = 12,073). Each patient starting digoxin during follow-up was matched to 3 control participants. Risk-set matching (38) was implemented longitudinally, a method that obtains control participants for each digoxin initiation from among the risk-set of patients who remain alive and untreated at the time a patient starts digoxin treatment. Covariates, both baseline and time dependent, measured before matching are incorporated via a time-dependent propensity model for digoxin initiation, estimated by using Cox proportional hazards regression (39).

Sociodemographic and baseline characteristics were fixed covariates whereas concomitant medications, vital signs, laboratory values, and medical history were updated during follow-up (Online Table 3). Matching was performed within region, clinical setting where digoxin was initiated (during a heart failure hospitalization, during other hospitalization, or out of hospital), and heart failure status. Patients starting digoxin out of the hospital were also matched according to time from most recent hospitalization. Covariate balance between matched treated patients and control participants was assessed by using standardized differences (Online Table 4). New digoxin users and matched control participants were compared by using a Cox regression with robust sandwich estimate for the covariance matrix. A sensitivity analysis was conducted excluding pairs who were matched during a hospitalization, thus limiting the analysis to out-of-hospital digoxin initiation. In a preliminary analysis, we also evaluated the endpoint of mortality by using marginal structural models for time-varying treatments, and observed similar results. In our study, the

TABLE 1 Continued

	Heart Failure			No Heart Failure			Overall	
	Digoxin (n = 3,003)	No Digoxin (n = 3,690)	p Value	Digoxin (n = 2,821)	No Digoxin (n = 8,383)	p Value	Digoxin (n = 5,824)	No Digoxin (n = 12,073)
AF-related history								
Type of AF			<0.0001			<0.0001		
Paroxysmal	160 (5.3)	661 (17.9)		181 (6.4)	1,733 (20.7)		341 (5.9)	2,394 (19.8)
Permanent	2,843 (94.7)	3,027 (82.1)		2,640 (93.6)	6,649 (79.3)		5,483 (94.1)	9,676 (80.2)
Duration of AF			0.33			<0.0001		
<6 months	869 (29.0)	1,022 (27.9)		588 (20.9)	2,446 (29.2)		1,457 (25.1)	3,468 (28.8)
6 months to 2 yrs	611 (20.4)	725 (19.8)		495 (17.6)	1,619 (19.3)		1,106 (19.1)	2,344 (19.5)
>2 yrs	1,513 (50.6)	1,921 (52.4)		1,728 (61.5)	4,303 (51.4)		3,241 (55.8)	6,224 (51.7)
AF/flutter at enrollment	2,859 (95.4)	3,074 (83.6)	<0.0001	2,666 (94.6)	6,785 (81.3)	<0.0001	5,525 (95.0)	9,859 (82.0)
Paced rhythm at enrollment	158 (5.4)	282 (7.8)	<0.0001	125 (4.5)	526 (6.4)	0.0003	283 (4.9)	808 (6.8)
Duration of most recent episode ≥14 days	2,507 (83.8)	2,712 (74.0)	<0.0001	2,240 (80.0)	5,744 (69.5)	<0.0001	4,747 (81.9)	8,456 (70.9)
Treatment strategy: rate control	2,791 (93.0)	2,934 (79.7)	<0.0001	2,573 (91.4)	6,226 (74.4)	<0.0001	5,364 (92.2)	9,160 (76.0)
Previous cardioversion	336 (11.2)	597 (16.2)	<0.0001	515 (18.3)	1,615 (19.3)	0.24	851 (14.6)	2,212 (18.3)
Laboratory and vital signs								
Heart rate, beats/min	80 (69, 90)	75 (65, 86)	<0.0001	76 (67, 85)	74 (64, 84)	<0.0001	78 (68, 88)	74 (65, 84)
SBP, mm Hg	130 (118, 140)	130 (120, 140)	<0.0001	130 (120, 140)	130 (120, 141)	0.73	130 (120, 140)	130 (120, 140)
LBBB or RBBB on ECG	449 (38.0)	545 (36.6)	0.48	279 (29.4)	769 (27.3)	0.21	728 (34.1)	1,314 (30.5)
Creatinine, mg/dl	1.0 (0.9, 1.2)	1.1 (0.9, 1.3)	<0.0001	1.0 (0.8, 1.1)	1.0 (0.9, 1.2)	<0.0001	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)
Creatinine clearance, ml/min	74 (55, 97)	73 (56, 95)	0.37	72 (56, 94)	74 (58, 96)	0.0005	73 (55, 95)	74 (57, 95)
Creatinine clearance, ml/min			0.27			<0.0001		
≤50	560 (18.8)	671 (18.4)		526 (18.8)	1,275 (15.4)		1,086 (18.8)	1,946 (16.3)
>50 to ≤80	1,194 (40.1)	1,534 (42.1)		1,194 (42.7)	3,549 (42.9)		2,388 (41.4)	5,083 (42.6)
>80	1,223 (41.1)	1,442 (39.5)		1,075 (38.5)	3,458 (41.8)		2,298 (39.8)	4,900 (41.1)
NT-proBNP, ng/l	991 (565, 1,713)	802 (412, 1,494)	<0.0001	741 (413, 1,229)	590 (282, 1,028)	<0.0001	856 (474, 1,469)	647 (317, 1,146)
Troponin I, ng/l	8.2 (4.7, 16.0)	6.2 (3.6, 12.2)	<0.0001	5.7 (3.6, 10.1)	4.4 (2.8, 7.5)	<0.0001	7.0 (4.1, 13.1)	4.8 (3.0, 8.8)
Troponin T, ng/l	13.4 (9.1, 20.5)	11.8 (7.8, 18.3)	<0.0001	11.5 (8.0, 17.0)	9.8 (7.0, 14.4)	<0.0001	12.5 (8.5, 19.0)	10.3 (7.2, 15.5)
GDF-15, pg/ml	1,510 (1,049, 2,251)	1,452 (997, 2,231)	0.0133	1,430 (1,003, 2,076)	1,304 (948, 1,905)	<0.0001	1,473 (1,026, 2,180)	1,343 (960, 2,000)
Concomitant medications								
Aspirin	919 (30.6)	1,316 (35.7)	<0.0001	746 (26.4)	2,647 (31.6)	<0.0001	1,665 (28.6)	3,963 (32.8)
Clopidogrel/ticlopidine	48 (1.6)	89 (2.4)	0.0194	43 (1.5)	174 (2.1)	0.07	91 (1.6)	263 (2.2)
Previous VKA use >30 days	1,592 (53.0)	1,974 (53.5)	0.69	1,849 (65.5)	4,852 (57.9)	<0.0001	3,441 (59.1)	6,826 (56.5)
Sotalol	28 (0.9)	112 (3.0)	<0.0001	50 (1.8)	328 (3.9)	<0.0001	78 (1.3)	440 (3.6)
Amiodarone	305 (10.2)	637 (17.3)	<0.0001	158 (5.6)	950 (11.3)	<0.0001	463 (7.9)	1,587 (13.1)
Class I antiarrhythmic drugs	18 (0.6)	100 (2.7)	<0.0001	44 (1.6)	424 (5.1)	<0.0001	62 (1.1)	524 (4.3)
Diuretics	2281 (76.0)	2,429 (65.8)	<0.0001	1,360 (48.2)	3,630 (43.3)	<0.0001	3,641 (62.5)	6,059 (50.2)
Aldosterone antagonists	68 (2.3)	61 (1.7)	0.07	20 (0.7)	36 (0.4)	0.07	88 (1.5)	97 (0.8)
ACE inhibitors	1,827 (60.8)	2,248 (60.9)	0.95	1,224 (43.4)	3,584 (42.8)	0.56	3,051 (52.4)	5,832 (48.3)
Beta-blockers	2,032 (67.7)	2,695 (73.0)	<0.0001	1,554 (55.1)	5,194 (62.0)	<0.0001	3,586 (61.6)	7,889 (65.3)
Calcium-channel blockers	560 (18.6)	894 (24.2)	<0.0001	966 (34.2)	3,145 (37.5)	0.0018	1,526 (26.2)	4,039 (33.5)
Alpha-blockers	140 (4.7)	235 (6.4)	0.0025	200 (7.1)	778 (9.3)	0.0004	340 (5.8)	1,013 (8.4)
ARBs	583 (19.4)	808 (21.9)	0.0128	679 (24.1)	2,235 (26.7)	0.0066	1,262 (21.7)	3,043 (25.2)
Lipid-lowering medications	1,060 (35.3)	1,705 (46.2)	<0.0001	1,244 (44.1)	4,186 (49.9)	<0.0001	2,304 (39.6)	5,891 (48.8)

Values are median (25th, 75th percentiles) or n (%).

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; ECG = electrocardiograph; GDF = growth differentiation factor; LA = left atrial; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; RBBB = right bundle branch block; SBP = systolic blood pressure; SE = systemic embolism; TIA = transient ischemic attack; VF = ventricular fibrillation; VKA = vitamin K antagonist; VT = ventricular tachycardia.

TABLE 2 Event Rates According to HF and Digoxin Status at Baseline

	Digoxin Rate* (Events)	No Digoxin Rate* (Events)	Unadjusted HR (95% CI): Digoxin Versus No Digoxin	Adjusted HR (95% CI): Digoxin Versus No Digoxin	p Value
All-cause death					
Overall	4.81 (518)	3.19 (729)	1.51 (1.35–1.69)	1.09 (0.96–1.23)	0.19
No HF	3.35 (178)	2.43 (389)	1.38 (1.15–1.64)	1.16 (0.88–1.52)	0.30
HF	6.24 (340)	4.98 (340)	1.26 (1.08–1.46)	1.04 (0.83–1.30)	0.73
CV death					
Overall	2.61 (281)	1.58 (360)	1.65 (1.41–1.93)	1.11 (0.93–1.32)	0.24
No HF	1.41 (75)	1.13 (181)	1.24 (0.95–1.63)	1.07 (0.71–1.61)	0.76
HF	3.78 (206)	2.62 (179)	1.44 (1.18–1.76)	1.13 (0.84–1.54)	0.42
Sudden cardiac death					
Overall	1.08 (116)	0.59 (134)	1.83 (1.43–2.34)	1.27 (0.96–1.67)	0.09
No HF	0.64 (34)	0.41 (65)	1.57 (1.04–2.38)	1.51 (0.77–2.96)	0.23
HF	1.51 (82)	1.01 (69)	1.48 (1.07–2.04)	1.15 (0.72–1.86)	0.56
Non-CV death					
Overall	1.45 (156)	1.05 (239)	1.39 (1.13–1.70)	1.14 (0.92–1.42)	0.24
No HF	1.39 (74)	0.88 (140)	1.59 (1.20–2.11)	1.28 (0.82–1.99)	0.27
HF	1.50 (82)	1.45 (99)	1.04 (0.78–1.40)	1.01 (0.65–1.58)	0.95
HF hospitalization					
Overall	3.09 (323)	1.98 (444)	1.55 (1.34–1.79)	1.00 (0.85–1.16)	0.95
No HF	1.45 (76)	1.14 (180)	1.27 (0.97–1.66)	1.03 (0.68–1.56)	0.89
HF	4.75 (247)	4.03 (264)	1.17 (0.98–1.39)	0.98 (0.76–1.27)	0.89

Propensity score analysis: all variables listed in Table 1 were included in the propensity score model except for LA size and LBBB/RBBB at ECG due to a substantial percentage of missing values. *Rates per 100 patient-years of follow-up.

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; other abbreviations as given in Table 1.

risk-set matching approach was preferred for transparency and interpretability.

All analyses were performed by using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

POPULATION. A total of 17,897 patients (98% of the overall population) from ARISTOTLE (30,31) had information available on baseline digoxin use and heart failure status. Of those, 5,824 (32.5%) were taking digoxin at baseline, and 6,693 (37.4%) had concomitant heart failure. A total of 680 (11.7%) patients using digoxin at baseline stopped digoxin before the end of the trial. Median time to stopping was 184 days (25th, 75th percentiles: 50, 366 days). Table 1 summarizes the clinical differences between patients taking and not taking digoxin among those with and without heart failure.

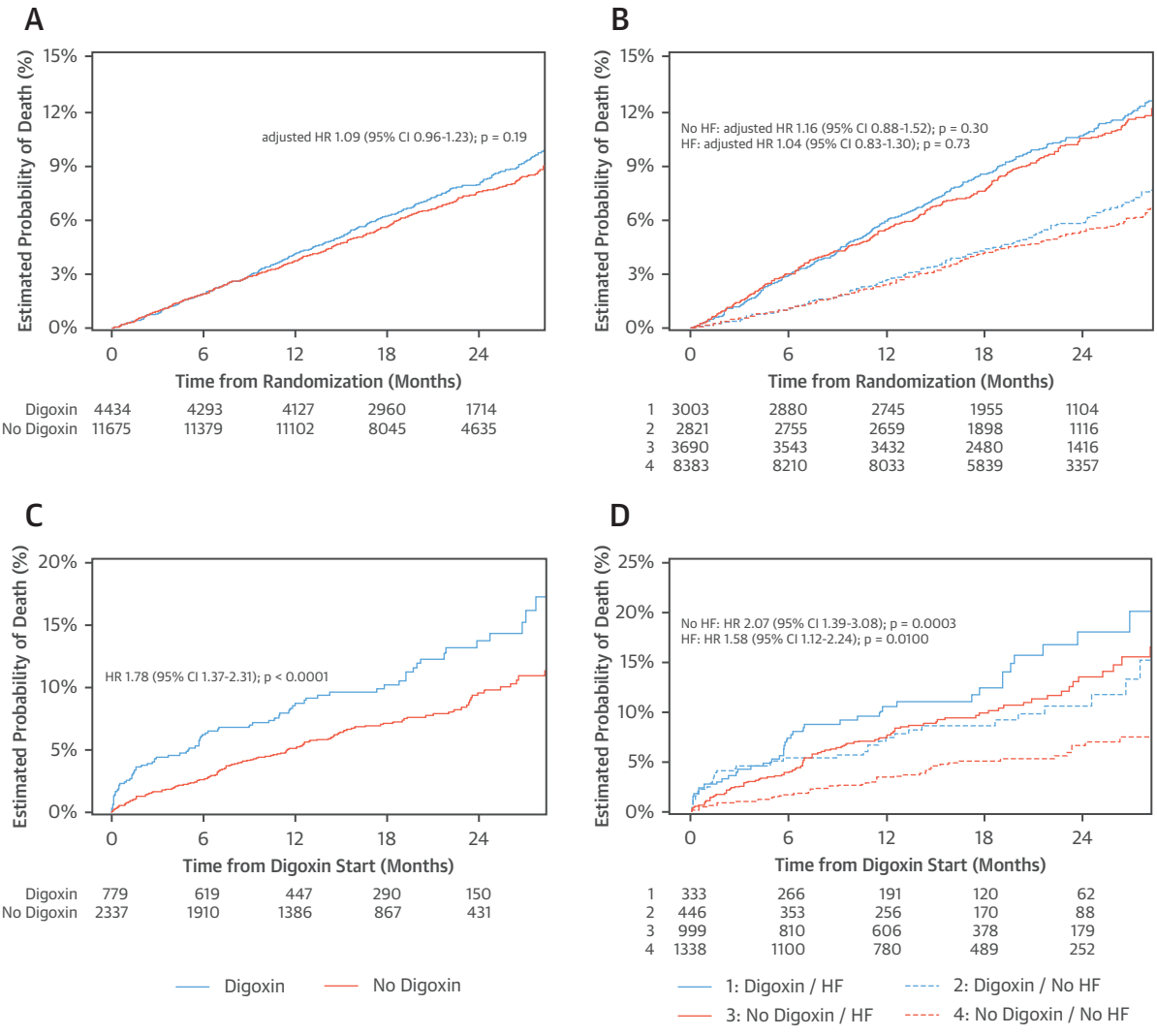
A total of 109 (0.6%) patients received an implantable cardioverter-defibrillator post-randomization: 32 (0.55%) in the digoxin-at-baseline group and 77 (0.64%) in the non-digoxin-at-baseline group. Forty-six (0.25%) patients received a cardiac resynchronization therapy defibrillator post-randomization: 18 (0.31%) in the digoxin-at-baseline group and 28 (0.23%) in the non-digoxin-at-baseline group. Among the 12,905 patients with LVEF data available, 1,146 (8.8%) had an LVEF <35%. In the remaining 5,296 patients with missing LVEF data, 1,716 had left ventricular dysfunction classification available, and 70 (4.1%) were classified as severe (defined as LVEF <30%).

BASELINE DIGOXIN USE AND OUTCOMES. Baseline digoxin use was not associated with higher all-cause mortality (4.81 vs. 3.19 events per 100 patient-years in patients on vs. off digoxin, respectively; adjusted HR: 1.09; 95% CI: 0.96 to 1.23; p = 0.19). Similar results were seen for patients with and without heart failure (Table 2). Rates of cardiovascular mortality (2.61 vs. 1.58 per 100 patient-years; adjusted HR: 1.11; 95% CI: 0.93 to 1.32; p = 0.2363), as well as sudden cardiac death (1.08 vs. 0.59 per 100 patient-years; HR: 1.27; 95% CI: 0.96 to 1.67; p = 0.0941), were numerically higher in patients using digoxin versus not using digoxin (Figures 1A and B).

SERUM DIGOXIN CONCENTRATIONS AND OUTCOMES. Serum digoxin concentrations at baseline were measured in 4,434 (76.1%) patients taking digoxin. Baseline characteristics of the patients with and without digoxin concentration data available were similar (Online Table 5). Median serum digoxin concentrations were significantly higher in patients who died compared with those who survived (median: 0.62 [25th, 75th percentiles: 0.39, 1.01] ng/ml vs. 0.55 [25th, 75th percentiles: 0.16, 0.86] ng/ml; p < 0.0001). For patients with digoxin levels <0.9 ng/ml (n = 3,373 [76% of patients for whom digoxin measurement was available]), there was no increased risk of death (adjusted HR: 1.00; 95% CI: 0.85 to 1.16; p = 0.96) compared with those not on digoxin. For patients with levels ≥0.9 and <1.2 ng/ml (n = 559 [12.6%]), there was a 16% nonsignificant increased risk of death (adjusted HR: 1.16; 95% CI: 0.87 to 1.55; p = 0.32) compared with those not on digoxin. For patients with digoxin levels ≥1.2 ng/ml (n = 499 [11.4%]), there was a significant 56% increased risk of death (adjusted HR: 1.56; 95% CI: 1.20 to 2.04; p = 0.0011) compared with those not on digoxin.

After adjustment for potential confounders, baseline serum digoxin concentration as a continuous variable exhibited a direct relationship with overall mortality (Central Illustration). Each 0.5-ng/ml increase in baseline serum digoxin concentration was associated with an increase in death in the overall population (adjusted HR: 1.19; 95% CI: 1.07 to 1.32; p = 0.0010), which was consistent in patients with heart failure (adjusted HR: 1.22; 95% CI: 1.08 to 1.38; p = 0.0018) and without heart failure (adjusted

FIGURE 1 **Relationship Between Baseline Digoxin Concentration and All-Cause Death**

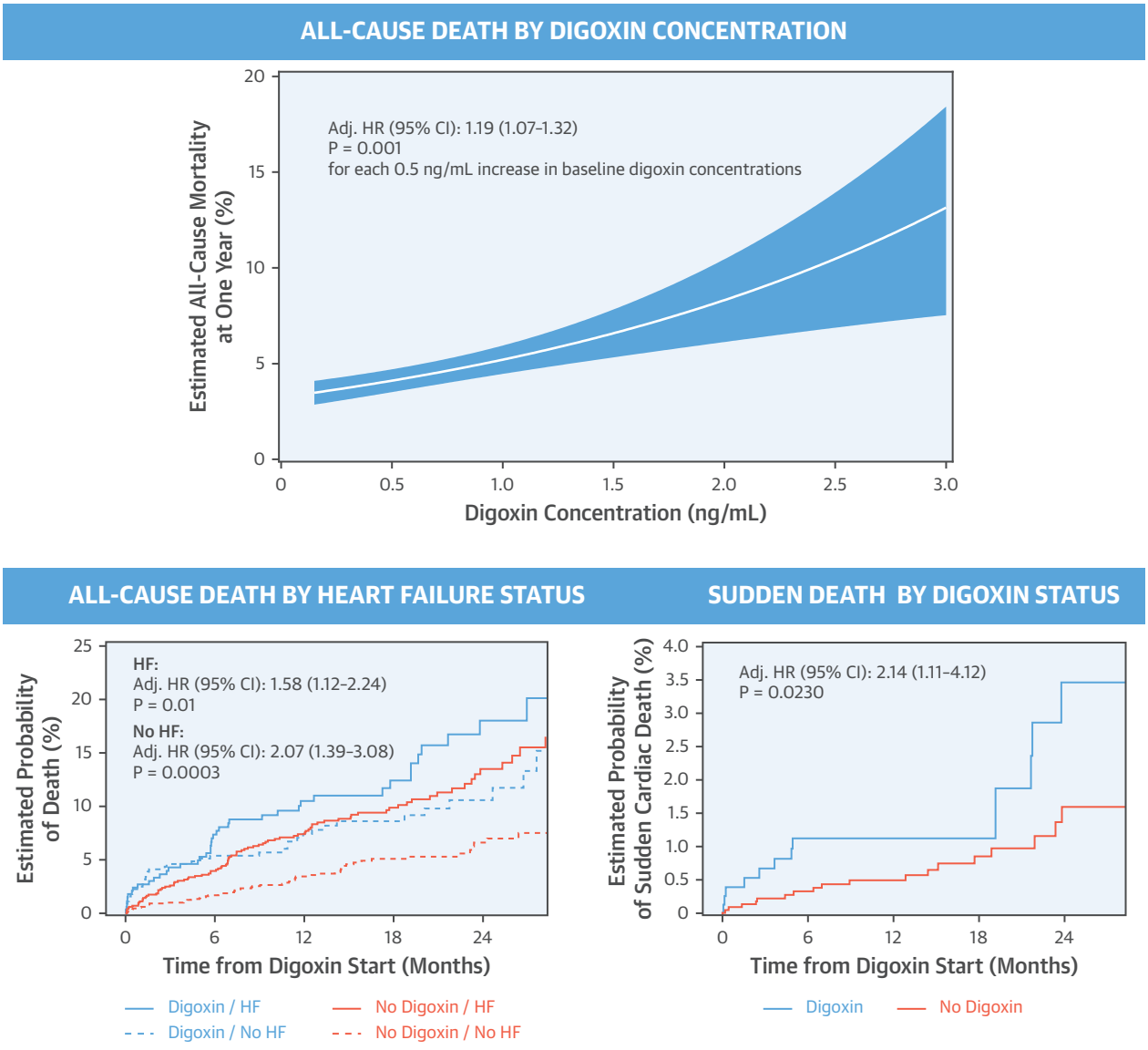


Kaplan-Meier curves for all-cause death in patients **(A)** using and not using digoxin at baseline; **(B)** using or not using digoxin at baseline with and without heart failure (HF); **(C)** starting digoxin or not among new starters; and **(D)** starting digoxin or not among new starters with and without HF. CI = confidence interval; HR = hazard ratio.

HR: 1.18; 95% CI: 0.97 to 1.45; p = 0.10). For each 0.1-ng/ml increase in baseline serum digoxin concentration, a 4% higher risk of overall mortality (adjusted HR: 1.04; 95% CI: 1.01 to 1.06) was recorded. Baseline serum digoxin concentrations were also significantly associated with a higher risk of cardiovascular death (adjusted HR: 1.24; 95% CI: 1.08 to 1.42; p = 0.0019 for each 0.5-ng/ml increase). A similar pattern was observed for sudden death (adjusted HR: 1.05; 95% CI: 0.83 to 1.34; p = 0.68 for each 0.5-ng/ml increase) (Online Table 6); these findings were similar in patients with heart failure (HR: 1.03; 95% CI: 0.76 to 1.40; p = 0.85, for each 0.5-ng/ml increase) and without heart failure (HR: 1.32; 95% CI: 0.81 to 2.14; p = 0.27, for each 0.5-ng/ml increase).

NEW DIGOXIN USERS. Of 12,703 patients not taking digoxin at baseline, 873 (6.9%) started digoxin during follow-up (new digoxin users). Of these, 786 patients were matched with 2,337 control participants (1:3). Five pairs were removed from the analysis due to the same control being matched to a case, resulting in 781 patients matched with 2,343 control participants (Online Table 4). When endpoint information was added, 2 additional pairs were removed, and the final

CENTRAL ILLUSTRATION **Digoxin and Mortality in Patients With Atrial Fibrillation**



Lopes, R.D. et al. J Am Coll Cardiol. 2018;71(10):1063–74.

In patients with atrial fibrillation taking digoxin, the risk of death is independently related to digoxin serum concentration. Initiating digoxin is independently associated with higher mortality and sudden death in patients with atrial fibrillation, regardless of heart failure. CI = confidence interval; HF = heart failure; HR = hazard ratio.

analysis included 779 patients and 2,337 control participants. Only 1 variable (chronic obstructive pulmonary disease) had standardized differences >10% (11.8%). Baseline characteristics in prevalent and incident cases are described in Online Table 7.

New digoxin users had significantly higher total mortality (adjusted HR: 1.78; 95% CI: 1.37 to 2.31; p < 0.0001) than matched control participants (**Table 3**). These results were similar for patients with heart failure (adjusted HR: 1.58; 95% CI: 1.12 to 2.24; p = 0.0100) and those without heart failure (adjusted HR: 2.07; 95% CI: 1.39 to 3.08; p = 0.0003). Among patients who started digoxin and died, the median time to death was 165 days (25th, 75th percentiles: 28, 363 days). Kaplan-Meier curves for all-cause death showed a significantly worse outcome in new digoxin users compared with matched control participants, both in the overall population and in patients with

and without heart failure at baseline (**Figures 1C and 1D**). In the sensitivity analysis, similar results were seen in the pairs matched on an outpatient setting only (Online Table 8). For all-cause death, the number needed to harm at 1 year was 34 (95% CI: 19 to 84) and at 2 years, it was 17 (95% CI: 9 to 41).

New digoxin use was associated with an increased risk of sudden cardiac death, with a 2-fold higher risk of events in new digoxin users compared with matched control participants (adjusted HR: 2.14; 95% CI: 1.11 to 4.12; p = 0.0230). Among patients who started digoxin and experienced sudden death, the median time to death was 148 days (25th, 75th percentiles: 48, 583 days). Survival curves for sudden death also confirmed a significantly worse outcome with an early separation of the curves in new digoxin users (**Central Illustration**) compared with those not taking digoxin. In the sensitivity analysis, results were similar in the pairs matched on an outpatient setting only (Online Table 8). For sudden cardiac death, the number needed to harm at 1 year was 180 (95% CI: 138 to 1,844) and at 2 years, it was 56 (95% CI: 43 to 568).

New digoxin users had significantly higher rates of hospitalization due to heart failure (adjusted HR: 1.69; 95% CI: 1.15 to 2.49; p = 0.0083) compared with matched control participants (**Table 3,** Online Figure 1). These results were similar for patients with heart failure (adjusted HR: 2.06; 95% CI: 1.30 to 3.27; p = 0.0022) but not for patients without heart failure (adjusted HR: 1.22; 95% CI: 0.61 to 2.47; p = 0.58) (Online Figure 2). Among patients who started digoxin and were hospitalized due to heart failure, the median time to hospitalization was 169 days (25th, 75th percentiles: 52, 326 days). For hospitalization due to heart failure, the number needed to harm at 1 year was 34 (95% CI: 16 to 159) and at 2 years, it was 23 (95% CI: 11 to 106).

APIXABAN VERSUS WARFARIN ACCORDING TO DIGOXIN USE AT BASELINE. The superiority of apixaban versus warfarin on overall mortality, stroke or systemic embolism, and major bleeding was preserved in digoxin users and nonusers (all p values for interaction >0.05) and consistent with the overall results of the trial (Online Table 9).

TABLE 3 Digoxin Use: New Users and Clinical Outcomes

	New Digoxin Users (n = 779) Rate* (Events)	Matched Control Participants† (n = 2,337) Rate* (Events)	HR (95% CI) Digoxin Versus No Digoxin	p Value
Death	8.13 (79)	5.11 (151)	1.78 (1.37–2.31)	<0.0001
CV death	3.70 (36)	2.30 (68)	1.60 (1.07–2.38)	0.0218
Sudden cardiac death	1.34 (13)	0.61 (18)	2.14 (1.11–4.12)	0.0230
Non-CV death	3.19 (31)	1.93 (57)	1.67 (1.12–2.49)	0.0121
HF hospitalization‡	4.22 (33)	2.52 (62)	1.69 (1.15–2.49)	0.0083

*Rate per 100 patient-years of follow-up. †Each patient starting digoxin was matched to 3 control participants within the same region, setting where digoxin was initiated (during an HF hospitalization, during other hospitalization, or sensitivity), and HF status. ‡HF hospitalization for digoxin/control participants out of hospital.
Abbreviations as in Table 2.

DISCUSSION

Our study showed that digoxin use at baseline was not independently associated with increased mortality in patients with AF at risk for stroke. However, in patients with AF currently taking digoxin, the risk of death was independently related to serum digoxin concentration and was highest in patients with concentrations ≥1.2 ng/ml (**Central Illustration**). There was an independent association between serum digoxin concentration and mortality, with a "dose-related effect" that is consistent with a plausible causal association between digoxin concentrations and risk of death. These observations were strengthened by the finding that, after using a robust risk-set matching approach based on a time-dependent propensity score, the risk of death was greatest early after initiation of digoxin in previous nonusers, particularly with respect to sudden cardiac death. Finally, contrary to what has been shown previously for patients with heart failure in sinus rhythm (3), we found that initiating digoxin in patients with AF was significantly associated with an increased risk of heart failure hospitalization, primarily among patients with previous heart failure. These findings indicate that digoxin should be used with caution and with monitoring of its serum concentration in patients with AF and preferably avoided if symptoms can be alleviated with other treatments.

Although digoxin's use has declined over the past 30 years (40), up to one-third of patients with AF worldwide are still treated with this agent (4,5,31). Recent observational studies have raised concern about a potential harmful effect of digoxin on survival in patients with AF (5-16). Other studies found no relationship between digoxin use and mortality after adjusting for baseline characteristics, showing that digoxin is more likely to be prescribed to elderly and more frail patients and therefore suggesting the presence of confounding factors in the association between digoxin and death (4,17-19). Selection bias, via conditioning on post-treatment survival, is likely present in prevalent digoxin comparisons. A new-user design such as the one used in the present study minimizes selection bias and is an important and novel contribution.

With respect to treated patients, it is not unexpected that incident users experienced more events than prevalent ones. Patients taking digoxin at

baseline may have already survived the potential harms of this medication or have already proven they can tolerate the medication (survival bias), otherwise they either would have died or the medication would have been stopped. This theory could help explain, at least in part, the lack of association between digoxin use and mortality in patients on stable digoxin treatment. Notably, the most recent 2016 guidelines for the management of AF still give a class I recommendation for digoxin, both in patients with reduced and preserved LVEF (2).

The elevated event rate in incident matched control participants deserves consideration. This observation can be attributed to measured differences in the cohorts. The new digoxin users reflect a combination of different patients: some high risk, and others recently hospitalized for AF, heart failure, and other reasons. We carefully matched on hospitalization history, recognizing the increased risk of events around the time of hospitalization. The sensitivity analysis, including only patients who initiated digoxin in an outpatient setting and their matched control participants, had lower event rates, which was similar to the prevalent population.

Several aspects of our observational analysis are consistent with a possible causal relationship between digoxin use and higher mortality. First, the estimated risk among new users was higher than among patients already using digoxin, as expected from a drug that potentially increases mortality. Second, the increase in sudden (presumably arrhythmic) death among new digoxin users is biologically plausible and somehow expected based on the mechanism of action of digoxin. Third, the early separation of the survival curves and the magnitude of increased risk among new digoxin users support the idea that digoxin might increase early mortality in this setting. Fourth, there was an independent and direct association between serum digoxin concentration and mortality, which is consistent with a dose-response relationship. A major limitation of most previous studies is that serum digoxin concentrations were not measured. The only exception is the DIG trial (3), performed >20 years ago in a limited population of 1,171 patients with heart failure who were in sinus rhythm (41).

Previous reports (11) showed significantly higher serum digoxin concentrations in patients who died compared with survivors. In the PALLAS (Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy) trial, serum digoxin concentrations were significantly higher in patients taking dronedarone versus placebo and concomitant digoxin, and dronedarone use significantly increased the risk of adverse events (42). In the present study, the evidence regarding the relationship between digoxin and mortality was strengthened by the continuous association, which was linear (no evidence of nonlinearity). This outcome indicates that increasing levels of digoxin concentration are related to increased risk of death. We presented a categorical version (subgroups) for comparability to previously published analyses of digoxin in the setting of heart failure (22) and not AF. This adjusted dose-effect finding underscores the gradual increase in the risk of death associated with the use of digoxin, particularly at levels ≥1.2 ng/ml.

STUDY LIMITATIONS. First and most importantly, this trial was an observational and not a randomized analysis; thus, we cannot exclude residual confounding despite extensive adjustment. For example, clinical deterioration not captured in the case report forms could have led to new digoxin use and worse outcomes. Moreover, small imbalances in our incidence analysis could be a concern. Given the smaller sample size of the incident cohort, the success in achieving balance was relatively reassuring, but small imbalances could still have affected borderline results. Although we measured serum digoxin concentration at baseline, digoxin levels were not captured during follow-up and/or for patients who started digoxin during the course of the trial. Serum digoxin concentrations were not measured in 100% of patients using digoxin at baseline, because not every patient participated in the ARISTOTLE biomarker substudy. Nonetheless, we reported data on the association between serum digoxin concentration and clinical outcome in >4,400 patients, which, to our knowledge, is the largest population ever studied with data on serum digoxin concentration within the controlled context of a clinical trial and the first time in patients with AF. Our definition of heart failure was broad. Further subgroups of heart failure, such as heart failure with reduced ejection fraction or preserved ejection fraction, were defined and used for adjustment purposes but were not explored as standalone subgroups due to small sample sizes and to avoid overfitting the statistical models. In addition, the present analysis includes a unique aspect, which is the adjustment for the currently available, very sensitive biochemical markers related to myocardial dysfunction and heart failure. N-terminal pro-B-type natriuretic peptide, high-sensitivity troponin T, high-sensitivity troponin I, and GDF-15 are powerful continuous descriptors of confounders and were available in almost all patients, and they were entered in the analyses of both chronic and new users. Although the definition of heart failure was broad and debatable, the correction of the results for

high-sensitivity markers of heart failure strongly suggests that our findings were consistent in patients with and without heart failure.

Despite these limitations, this study was an extensive and comprehensive exploration of the independent association between digoxin concentration and outcomes in the setting of AF. Therefore, given the lack of evidence of safety from randomized trials, the associations we describe may have a substantial impact on scientific guidelines and the treatment of patients with AF.

CONCLUSIONS

Our results indicate that in patients with AF currently taking digoxin, the risk of death was independently related to serum digoxin concentration, with a significantly higher risk in patients with concentrations ≥1.2 ng/ml. Initiating digoxin treatment in patients with AF was independently associated with higher mortality, regardless of heart failure status. Thus, in the absence of randomized trial data showing its efficacy and safety, digoxin should be used with caution and with monitoring of its serum concentration in patients with AF, and should preferably be avoided if symptoms can be alleviated with other treatments.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Initiation of digoxin in patients with AF was associated with higher mortality, regardless of heart failure status. In patients with AF already taking digoxin, it may be prudent to monitor serum concentration, targeting blood levels <1.2 ng/ml.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to assess the efficacy and safety of digoxin in patients with AF.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.