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Digoxin Use and Subsequent Clinical Outcomes in Patients With Atrial Fibrillation With or Without Heart Failure in the ENGAGE AF-TIMI 48 Trial

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Background—Digoxin is widely used in patients with atrial fibrillation despite the lack of randomized controlled trials. Observational studies report conflicting results regarding its association with mortality, perhaps because of residual confounding by the presence of heart failure (HF).

Methods and Results—In the ENGAGE AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48) trial, clinical outcomes of patients with atrial fibrillation with and without HF were examined by baseline digoxin use during a median follow-up of 2.8 years. HF was defined at baseline as prior or current clinical stage C or D HF. Of 21 105 patients enrolled, 6327 (30%) were treated with digoxin at baseline. Among patients without HF (n=8981), digoxin use (20%) was independently associated with sudden cardiac death (adjusted hazard ratio, 1.51; 95% CI, 1.10–2.08), with no significant interaction by age, sex, left ventricular ejection fraction, renal function, or concomitant medications ($P>0.05$ for each). Consistent results were observed using propensity matching (adjusted hazard ratio for sudden cardiac death, 1.90; 95% CI, 1.36–2.65). Among patients with HF (n=12 124), digoxin use (37%) was associated with an increase in all-cause death, cardiovascular death, sudden cardiac death, and death caused by HF/cardiogenic shock ($P<0.01$ for each), but not with noncardiovascular death, stroke/systemic embolism, or myocardial infarction.

Conclusions—In this observational analysis of patients with atrial fibrillation without investigator-reported HF, digoxin use was significantly associated with sudden cardiac death. While residual confounding cannot be excluded, the association between digoxin use and worse clinical outcomes highlights the need to examine digoxin use, particularly when prescribed to control heart rate in patients with atrial fibrillation in a randomized trial.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00781391. (*J Am Heart Assoc.* 2017;6:e006035. DOI: 10.1161/JAHA.117.006035.)

Key Words: atrial fibrillation • digoxin • heart failure • mortality • sudden cardiac death

Digoxin, a positive inotropic agent that blocks atrioventricular conduction, is widely used in patients with atrial fibrillation (AF), despite the lack of randomized clinical trials in this population.¹ In patients with AF and concomitant heart failure (HF), digoxin may be prescribed for both of these indications, while in patients without HF, it is used mainly as a rate-control therapy.^{2,3} The 2014 AF guidelines of the American Heart Association/American

College of Cardiology/Heart Rhythm Society recommend using digoxin to control resting heart rate in patients with reduced left ventricular ejection fraction (LVEF) (class I, level of evidence C), and also in combination with β -blockers or nondihydropyridine calcium channel blockers, regardless of HF status (class IIa, level of evidence B).^{4,5} The 2016 European Society of Cardiology AF guidelines recommend using digoxin in the long-term management of

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Accompanying Tables S1 through S3 are available at <http://jaha.ahajournals.org/content/6/7/e006035/DC1/embed/inline-supplementary-material-1.pdf>

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Clinical Perspective

What is New?

- In this observational analysis of patients with atrial fibrillation with or without heart failure (HF), digoxin use, after adjusting for multiple confounders, was associated with worse clinical outcomes. In patients with HF, it was associated with all-cause death, cardiovascular death, sudden cardiac death, HF death, and HF hospitalizations. In patients without HF, it was significantly associated with sudden cardiac death.
- While the results in patients with HF might be caused by residual confounding, the study highlights the need to examine digoxin use in patients with atrial fibrillation without HF in a randomized controlled trial.

What are the Clinical Implications?

- Given the availability of other rate-control agents, until the safety of digoxin in patients with atrial fibrillation without HF has been established, the use of the drug in this population should be undertaken with great care, if at all.

AF patients with LVEF above or below 40% (class I, level of evidence B).³

Conflicting data exist regarding adverse outcomes that are associated with digoxin use in patients with AF.^{6–16} While several retrospective studies and meta-analyses have demonstrated an association between digoxin use and all-cause mortality, cardiovascular death, and sudden cardiac death (SCD),^{6–13} other studies have not found a compelling association.^{14–16} These contradictory results can be attributed to the nature of observational studies and to digoxin prescription biases. It remains unclear whether the association between digoxin and worse clinical outcome is causal or may be the result of residual confounding, mainly dominated by the presence of HF.

Thus, we aimed to examine the association between digoxin use and clinical outcomes (fatal and nonfatal events) in a large contemporary cohort of patients with AF both with and without HF.

Methods

This study represents an analysis from the ENGAGE AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48) trial. The ENGAGE AF-TIMI 48 trial was a 3-group, randomized, double-blind, double-dummy multinational trial that compared 2 dosing regimens of the oral factor Xa inhibitor edoxaban with warfarin in 21 105 patients with AF (NCT00781391).¹⁷ A detailed description of the study population, study design, and results of the trial have been

published.^{17,18} In brief, eligible patients were 21 years and older with ECG evidence of AF within 12 months before randomization and had a CHADS₂ score ≥ 2 and planned anticoagulation. Key exclusion criteria were AF attributable to a reversible cause, presence of a mechanical valve or moderate-severe mitral stenosis, increased risk of bleeding, recent acute coronary syndrome or stroke within 30 days before randomization, severe renal insufficiency (creatinine clearance <30 mL/min), and life expectancy <12 months. Patients with any class of HF could be enrolled provided they were clinically stable at the time of randomization. The protocol and amendments were approved by the ethics committee at each participating center. All patients provided written informed consent.

Digoxin Use and HF Definition

Digoxin use was captured by the treating physician in the concomitant medication case report form at baseline before enrollment. HF was defined as the presence or history of clinical stage C or D HF according to the American College of Cardiology/American Heart Association criteria.¹⁹ This includes structural heart disease with prior or current symptoms of HF, such as shortness of breath, fatigue, and decreased exercise tolerance (stage C), or refractory HF requiring specialized interventions (stage D). Investigators classified HF at baseline as “systolic,” “diastolic,” or “both,” provided the New York Heart Association functional class, and when available, reported the most recent LVEF before randomization.

Clinical End Points

End points of this analysis were as defined in the trial protocol^{17,18} and examined during a median follow-up of 2.8 years. Deaths in the ENGAGE AF-TIMI 48 trial were adjudicated by an independent clinical end point committee without knowledge of randomized anticoagulant treatment assignment. Deaths were categorized as cardiovascular or noncardiovascular. Cardiovascular death included SCD, defined as an unexpected death that was either witnessed (occurring within 60 minutes from the onset of new symptoms, in the absence of a clear cause other than cardiovascular) or unwitnessed (within 24 hours of being observed alive, in the absence of preexisting progressive circulatory failure or other noncardiovascular causes of death), death caused by HF or cardiogenic shock, or other cardiovascular causes (eg, systemic embolic event, pulmonary embolism, atherosclerotic vascular disease excluding coronary, related to coronary revascularization, or other).^{17,18} Nonfatal events included stroke or systemic embolism, HF hospitalization, or myocardial infarction (MI).

Statistical Analysis

Baseline characteristics of patients by digoxin treatment and HF status were compared between groups using chi-square tests for categorical variables and Kruskal–Wallis tests for continuous variables. Three methods were used to examine the association between digoxin use and clinical outcomes. The first used the Cox proportional hazards model. Clinical outcomes were examined in the intention-to-treat population, including all events between randomization and the end of the study treatment period, whether occurring on or off study drug. Variables in the multivariable models were based on the baseline characteristics, with a $P < 0.1$ in the univariate model, omitting colinear variables and adding variables that were judged to be of clinical importance. All multivariable analyses were adjusted for the following baseline characteristics: age; sex; weight; region; race; creatinine; pattern of AF (persistent/permanent versus paroxysmal); hypertension; diabetes mellitus; prior stroke/transient ischemic attack; coronary artery disease; prior MI; peripheral arterial disease; smoking (current or past); increased risk of falling; LVEF; HF (when appropriate); mitral valve disease; aortic valve disease; prior electrical cardioversion; left ventricular hypertrophy on ECG; use of a vitamin K antagonist ≥ 60 consecutive days at any time before enrollment; lipid-lowering drugs; class I, class II (β -blockers), or class III antiarrhythmics; renin-angiotensin-aldosterone system inhibitors; randomization group; heart rate; chronic obstructive pulmonary disease; and diuretic use. Clinical outcomes were examined separately in patients with or without HF. Among patients with HF, clinical outcomes were further examined in patients with systolic HF, diastolic HF, or both.

The second method was propensity matching, which was performed on key baseline characteristics to balance digoxin use at baseline in patients with or without HF. Matching was performed using a 1:1 nearest neighbor approach without replacement with a caliper of 0.1 of the SD. In a sensitivity analysis of the propensity model, we explored a trimmed model eliminating patients with extreme propensity scores (< 5 th or > 95 th percentile) to reduce the potential impact of unmeasured confounders.

The third method utilized inverse probability treatment weighting (IPTW), which uses stabilized weights calculated with the inverse value of the propensity scores.

A sensitivity analysis using digoxin as a time-varying covariate examined the association between digoxin use during the trial and clinical outcomes in patients without HF. Digoxin use was reported at each study visit (every 3 months) and was regarded as a time-dependent variable using 2 methods. In the first method, if digoxin was not present at baseline but was started during follow-up, the patient was regarded as taking digoxin throughout the trial (digoxin “on”),

while in the second method, the patient was regarded as taking or not taking digoxin per the status of digoxin use every 3 months (digoxin “on/off”).

Results are presented as hazard ratios (HRs) and 95% CIs, with $P < 0.05$ considered significant. Propensity score matching was performed using R Studio. All other analyses were performed in SAS Enterprise Guide 7.1 (SAS Institute Inc).

Results

Overall Population

Of the 21 105 patients who were enrolled in the ENGAGE AF-TIMI 48 trial, 6327 patients (30.0%) were treated with digoxin at baseline. Compared with patients not treated with digoxin, patients taking digoxin were slightly younger, more often female, and were more likely to have persistent/permanent AF, HF at baseline, and lower LVEF ($P < 0.001$ for each; other baseline variables that differed between the 2 groups are shown in Table 1).^{20–22}

Digoxin use was associated with all-cause mortality (annual rate, 5.2% versus 3.6%; adjusted HR, 1.22 [95% CI, 1.12–1.34]), cardiovascular death, SCD, death caused by HF or cardiogenic shock, and HF hospitalizations (Table 2). No significant association was observed between digoxin use at baseline and noncardiovascular death, stroke or systemic embolism, or MI (Table 2). There was no effect of randomized treatment on the relationship between digoxin use and clinical outcomes (data not shown).

Patients With HF at Baseline

A total of 12 124 patients (57.4%) had HF reported at baseline. Of these, 4502 patients (37.1%) were treated with digoxin at baseline. Compared with patients not treated with digoxin, patients treated with digoxin were younger and more likely to have permanent AF, lower LVEF, worse New York Heart Association class, and higher heart rate and be treated with diuretics ($P < 0.001$ for each, Table S1).

In patients with HF, digoxin use was associated with an increase in all-cause mortality (adjusted HR, 1.27; 95% CI, 1.14–1.41), cardiovascular death (adjusted HR, 1.32; 95% CI, 1.16–1.49), SCD (adjusted HR, 1.45; 95% CI, 1.21–1.74), death caused by HF or cardiogenic shock (adjusted HR, 1.44; 95% CI, 1.13–1.83), and HF hospitalizations (adjusted HR, 1.21; 95% CI, 1.08–1.36) (Table 2). There was no significant association between digoxin use at baseline and noncardiovascular death, stroke or systemic embolism, or MI (Table 2). Consistent qualitatively similar results were demonstrated using propensity matching and IPTW for all end points except for

Table 1. Baseline Characteristics by Digoxin Use at Baseline

Characteristic, No. (%)	Digoxin n=6327 (30%)	No Digoxin n=14 778 (70%)	P Value	Total (N=21 105)
Age, median (IQR), y	71 (63–77)	72 (65–78)	<0.001	72 (64–78)
Female sex	2556 (40.4)	5484 (37.1)	<0.001	8040 (38.1)
Weight, mean (SD), kg	82.0 (20.6)	84.7 (20.0)	<0.001	83.9 (20.2)
Region*			<0.001	
North America	1154 (18.2)	3527 (23.9)		4681 (22.2)
Latin America	977 (15.4)	1684 (11.4)		2661 (12.6)
Western Europe	733 (11.6)	2503 (16.9)		3236 (15.3)
Eastern Europe	2315 (36.6)	4829 (32.7)		7144 (33.8)
Asia-Pacific and South Africa	1148 (18.1)	2235 (15.1)		3383 (16.0)
White race (n=21 104)	4892 (77.3)	12 175 (82.4)	<0.001	17 067 (80.9)
Type of atrial fibrillation (n=21 099)			<0.001	
Paroxysmal	713 (11.3)	4653 (31.5)		5366 (25.4)
Persistent	1424 (22.5)	3444 (23.3)		4868 (23.1)
Permanent	4189 (66.2)	6676 (45.2)		10 865 (51.5)
Qualifying risk factor				
Congestive heart failure	4502 (71.2)	7622 (51.6)	<0.001	12 124 (57.4)
Hypertension requiring treatment	5853 (92.5)	13 901 (94.1)	<0.001	19 754 (93.6)
Age ≥75 y	2279 (36.0)	6195 (41.9)	<0.001	8474 (40.2)
Diabetes mellitus	2329 (36.8)	5295 (35.8)	0.17	7624 (36.1)
Prior stroke or transient ischemic attack	1706 (27.0)	4267 (28.9)	0.005	5973 (28.3)
CHADS ₂ score [†]				
Mean (SD)	2.9 (1.0)	2.8 (1.0)	<0.001	2.8 (1.0)
4 to 6	1531 (24.2)	3237 (21.9)	<0.001	4768 (22.6)
CHA ₂ DS ₂ -VASc score [†]				
Mean (SD)	4.4 (1.4)	4.3 (1.4)	0.06	4.3 (1.4)
4 to 9	4471 (70.7)	10 448 (70.7)	0.96	14 919 (70.7)
HAS-BLED score [†]				
Mean (SD)	2.4 (0.9)	2.6 (1.0)	<0.001	2.5 (1.0)
≥3	2643 (41.8)	7159 (48.4)	<0.001	9802 (46.4)
Coronary artery disease (n=21 102)	2004 (31.7)	5019 (34.0)	0.001	7023 (33.3)
Prior myocardial infarction	704 (11.1)	1729 (11.7)	0.23	2433 (11.5)
Ejection fraction [‡]			<0.001	
<30%	398 (8.6)	384 (3.5)		782 (5.0)
30% to 39%	673 (14.6)	848 (7.7)		1521 (9.8)
40% to 49%	1058 (22.9)	1810 (16.5)		2868 (18.4)
≥50%	2488 (53.9)	7905 (72.2)		10 393 (66.8)
NYHA III or IV [§] (n=11 988)	1220 (27.4)	1415 (18.8)	<0.001	2635 (22.0)
Peripheral arterial disease (n=21 096)	211 (3.3)	630 (4.3)	0.002	841 (4.0)
Former/current smoker (n=21 098)	532 (8.4)	1020 (6.9)	<0.001	1552 (7.4)
COPD	626 (9.9)	1155 (7.8)	<0.001	1781 (8.4)
Mitral valve disease (n=20 983)	2276 (36.2)	4972 (33.8)	0.001	7248 (34.5)
Aortic valve disease (n=21 014)	907 (14.4)	2227 (15.1)	0.17	3134 (14.9)

Continued

Table 1. Continued

Characteristic, No. (%)	Digoxin n=6327 (30%)	No Digoxin n=14 778 (70%)	P Value	Total (N=21 105)
Prior electrical cardioversion for AF (n=21 104)	995 (15.7)	2796 (18.9)	<0.001	3791 (18.0)
Charlson comorbidity index, mean (SD)	2.9 (1.1)	2.8 (1.1)	<0.001	2.8 (1.1)
Heart rate, mean (SD), bpm (n=21 074)	77.1 (14.2)	73.0 (13.8)	<0.001	74.3 (14.0)
Hypertrophy per ECG (n=20 950)	1311 (20.8)	2126 (14.5)	<0.001	3437 (16.4)
Vitamin K antagonist experienced (n=21 104)	3918 (61.9)	8523 (57.7)	<0.001	12 441 (59.0)
Medication at randomization				
Aspirin (n=21 101)	1630 (25.8)	4550 (30.8)	<0.001	6180 (29.3)
Lipid-lowering	2558 (40.4)	7524 (50.9)	<0.001	10 082 (47.8)
Antiarrhythmics				
Class I	95 (1.5)	798 (5.4)	<0.001	893 (4.2)
Class II (β-blockers)	4119 (65.1)	9865 (66.8)	0.02	13 984 (66.3)
Class III	588 (9.3)	2546 (17.2)	<0.001	3134 (14.8)
Class IV	629 (9.9)	1276 (8.6)	0.002	1905 (9.0)
Diuretics	4445 (70.3)	8211 (55.6)	<0.001	12 656 (60.0)
RAAS inhibitor	4313 (68.2)	9593 (64.9)	<0.001	13 906 (65.9)
CrCl, median (IQR), mL/min	70.4 (53.5–93.0)	70.3 (53.9–91.4)	0.37	70.3 (53.8–91.9)
Dose reduction at randomization	1779 (28.1)	3577 (24.2)	<0.001	5356 (25.4)
Randomized treatment				
High-dose edoxaban	2078 (32.8)	4957 (33.5)	0.10	7035 (33.3)
Low-dose edoxaban	2073 (32.8)	4961 (33.6)		7034 (33.3)
Warfarin	2176 (34.4)	4860 (32.9)		7036 (33.3)

Data are expressed as number (percentage) unless otherwise indicated. bpm indicates beats per minute; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; IQR, interquartile range; RAAS, renin-angiotensin-aldosterone system.

*Percentages are for each region except for the Total column.

†CHADS₂ score—see reference²⁰; CHA₂DS₂-VASc score—see reference²¹; HAS-BLED score—see reference.²²

‡Ejection fraction was unknown for 5541 patients (digoxin, 1710 patients; no digoxin, 3831 patients).

§New York Heart Association (NYHA) functional class at baseline was reported only in patients with heart failure.

||Vitamin K antagonist experienced denotes ≥60 consecutive days of treatment with a vitamin K antagonist at any time before enrollment.

noncardiovascular death (matched HR, 1.21; 95% CI, 1.00–1.46) and MI (matched HR, 0.75; 95% CI, 0.59–0.95) (Table 3).

Among patients with systolic HF (n=5027), including 2875 patients with isolated systolic and 2152 patients with both systolic and diastolic HF, 34.3% were treated with digoxin at baseline. Among patients with isolated diastolic HF (n=4150), 41.3% were treated with digoxin at baseline. In patients with any systolic HF, digoxin use was associated with all-cause death, cardiovascular death, SCD, and death caused by HF or cardiogenic shock, with the latter being the strongest association (adjusted HR, 2.20; 95% CI, 1.48–3.29) (Table S2). In patients with isolated diastolic HF, a similar qualitative association between digoxin use and worse outcomes was observed, with the exception of death caused by HF or cardiogenic shock (adjusted HR, 1.17; 95% CI, 0.79–1.72 [*P* interaction by HF type=0.01]) (Table S2).

Patients Without HF at Baseline

A total of 8981 patients (42.6%) did not have HF at baseline. Of these, 1825 patients (20%) were treated with digoxin at baseline. Compared with patients not treated with digoxin, patients treated with digoxin were of similar age (median 75 years), were more likely to have permanent AF and higher heart rate, and were less likely to be treated with beta blockers (Table S1).

In patients without HF, digoxin use was significantly associated with SCD (adjusted HR, 1.51; 95% CI, 1.10–2.08 [*P*=0.01]) but not all-cause mortality, other causes of death, or nonfatal events (Table 2; Figure 1). Qualitatively similar results were demonstrated using IPTW (HR for SCD, 1.47; 95% CI, 1.02–2.10 [*P*=0.04]), propensity matching (HR for SCD, 1.90; 95% CI, 1.36–2.65 [*P*<0.001]) (Table 3), and a

Table 2. Clinical Outcomes by Digoxin Use and HF Status at Baseline

End Point, No. (%/y)	Total (N=21 105)			HF (n=12 124)			No HF (n=8981)		
	Digoxin (n=6327)	No Digoxin (n=14 778)	Adjusted HR* (95% CI)	Digoxin (n=4502)	No Digoxin (n=7622)	Adjusted HR* (95% CI)	Digoxin (n=1825)	No Digoxin (n=7156)	Adjusted HR* (95% CI)
All-cause death	899 (5.2)	1450 (3.6)	1.22 (1.12–1.34)	714 (5.9)	870 (4.2)	1.27 (1.14–1.41)	185 (3.6)	580 (2.9)	1.10 (0.92–1.31)
Cardiovascular death	673 (3.9)	995 (2.4)	1.27 (1.14–1.41)	555 (4.6)	633 (3.0)	1.32 (1.16–1.49)	118 (2.3)	362 (1.8)	1.13 (0.91–1.41)
SCD	333 (1.9)	416 (1.0)	1.49 (1.27–1.74)	273 (2.3)	273 (1.3)	1.45 (1.21–1.74)	60 (1.2)	143 (0.7)	1.51 (1.10–2.08)
HF/cardiogenic shock death	173 (1.0)	217 (0.5)	1.41 (1.14–1.76)	152 (1.3)	162 (0.8)	1.44 (1.13–1.83)	21 (0.4)	55 (0.3)	1.34 (0.77–2.33)
Noncardiovascular death	226 (1.3)	455 (1.1)	1.10 (0.92–1.31)	159 (1.3)	237 (1.1)	1.12 (0.90–1.40)	67 (1.3)	218 (1.1)	1.04 (0.77–1.40)
Stroke/SSE	317 (1.9)	699 (1.8)	1.00 (0.87–1.16)	218 (1.9)	348 (1.7)	0.99 (0.83–1.18)	99 (2.0)	351 (1.8)	1.06 (0.84–1.33)
HF hospitalizations	688 (4.3)	1073 (2.8)	1.22 (1.10–1.36)	608 (5.5)	786 (4.0)	1.21 (1.08–1.36)	80 (1.6)	287 (1.5)	1.11 (0.85–1.45)
MI	124 (0.7)	319 (0.8)	0.91 (0.73–1.14)	86 (0.7)	175 (0.9)	0.85 (0.64–1.13)	38 (0.8)	144 (0.7)	1.08 (0.74–1.58)

SCD indicates sudden cardiac death; SSE, stroke or systemic embolism.

*Hazard ratios (HRs) are adjusted for age; weight; sex; region; race; creatinine; atrial fibrillation type; heart failure (HF; for total HRs only); hypertension; diabetes mellitus; history of stroke or transient ischemic attack; history of coronary artery disease; prior myocardial infarction (MI); history of peripheral artery disease; smoking status; increased risk of falling; left ventricular ejection fraction; mitral valve disease; aortic valve disease; prior electrical cardioversion; left ventricular hypertrophy; previous use of vitamin K antagonists ≥ 60 days before randomization; lipid-lowering medications; class I, II, or III antiarrhythmics; renin-angiotensin-aldosterone inhibitors; randomized treatment group; heart rate; history of chronic obstructive pulmonary disease; and diuretic use at randomization.

trimmed propensity score (1.37; 95% CI, 0.96–1.95 [$P=0.08$]).

There was no significant heterogeneity in the association between digoxin use and SCD across subgroups including age, sex, region, weight, renal function, β -blocker use, and heart rate (Table 4). In addition, in patients without HF with LVEF $\geq 50\%$ (n=5525), digoxin use was associated with SCD

(adjusted HR, 1.58; 95% CI, 1.03–2.43) but not other causes of death including death caused by HF or cardiogenic shock (adjusted HR, 0.85; 95% CI, 0.35–2.06 [Figure 2]).

In a sensitivity analysis using digoxin as a time-variant covariate, digoxin use remained a significant predictor of SCD (HR, 5.53; 95% CI, 1.66–18.41 in the digoxin “on” analysis and HR, 4.45; 95% CI, 1.37–14.44 in the digoxin “on/off”

Table 3. Digoxin Use in Patients With or Without HF at Baseline Using Propensity Matching and Inverse Probability Weighting

End Point	HF		No HF	
	Propensity Matching* HR (95% CI)	Inverse Probability Weighting HR (95% CI)	Propensity Matching† HR (95% CI)	Inverse Probability Weighting HR (95% CI)
All-cause death	1.31 (1.19–1.43)	1.29 (1.15–1.44)	1.16 (0.98–1.36)	1.13 (0.92–1.38)
Cardiovascular death	1.34 (1.20–1.48)	1.33 (1.17–1.51)	1.22 (0.99–1.50)	1.11 (0.87–1.41)
SCD	1.58 (1.36–1.85)	1.46 (1.21–1.75)	1.90 (1.36–2.65)	1.47 (1.02–2.10)
HF/cardiogenic shock death	1.49 (1.21–1.84)	1.46 (1.14–1.86)	1.40 (0.78–2.50)	1.34 (0.75–2.38)
Noncardiovascular death	1.21 (1.00–1.46)	1.19 (0.93–1.51)	1.06 (0.81–1.38)	1.17 (0.82–1.65)
Stroke/SSE	0.87 (0.75–1.01)	1.00 (0.83–1.21)	0.84 (0.69–1.03)	0.97 (0.75–1.25)
HF hospitalizations	1.12 (1.02–1.24)	1.27 (1.12–1.43)	1.18 (0.91–1.51)	1.20 (0.89–1.63)
MI	0.75 (0.59–0.95)	0.95 (0.70–1.28)	0.83 (0.59–1.18)	1.08 (0.71–1.65)

HR indicates hazard ratio; MI, myocardial infarction; SCD, sudden cardiac death; SSE, stroke or systemic embolism.

*Included 4051 matched pairs based on age; sex; region; race; weight; atrial fibrillation type; hypertension; diabetes mellitus; history of stroke or transient ischemic attack; history of coronary artery disease; history of peripheral artery disease; increased risk of falling; left ventricular ejection fraction; prior electrical cardioversion; hypertrophy per ECG; previous use of vitamin K agonists for ≥ 60 days before randomization; lipid-lowering medications; class I, II, III, or IV antiarrhythmics; renin-angiotensin-aldosterone inhibitors; randomized treatment group; diuretic use; aspirin use; dose adjustment; serum creatinine; heart rate; Charlson comorbidity index; and heart failure (HF) type.

†Included 1817 matched pairs based on age; sex; region; race; weight; atrial fibrillation type; hypertension; diabetes mellitus; history of stroke or transient ischemic attack; history of coronary artery disease; history of peripheral artery disease; increased risk of falling; left ventricular ejection fraction; prior electrical cardioversion; hypertrophy per ECG; previous use of vitamin K agonists for ≥ 60 days before randomization; lipid-lowering medications; class I, II, III, or IV antiarrhythmics; renin-angiotensin-aldosterone inhibitors; randomized treatment group; diuretic use; aspirin use; dose adjustment; serum creatinine; heart rate; and Charlson comorbidity index.

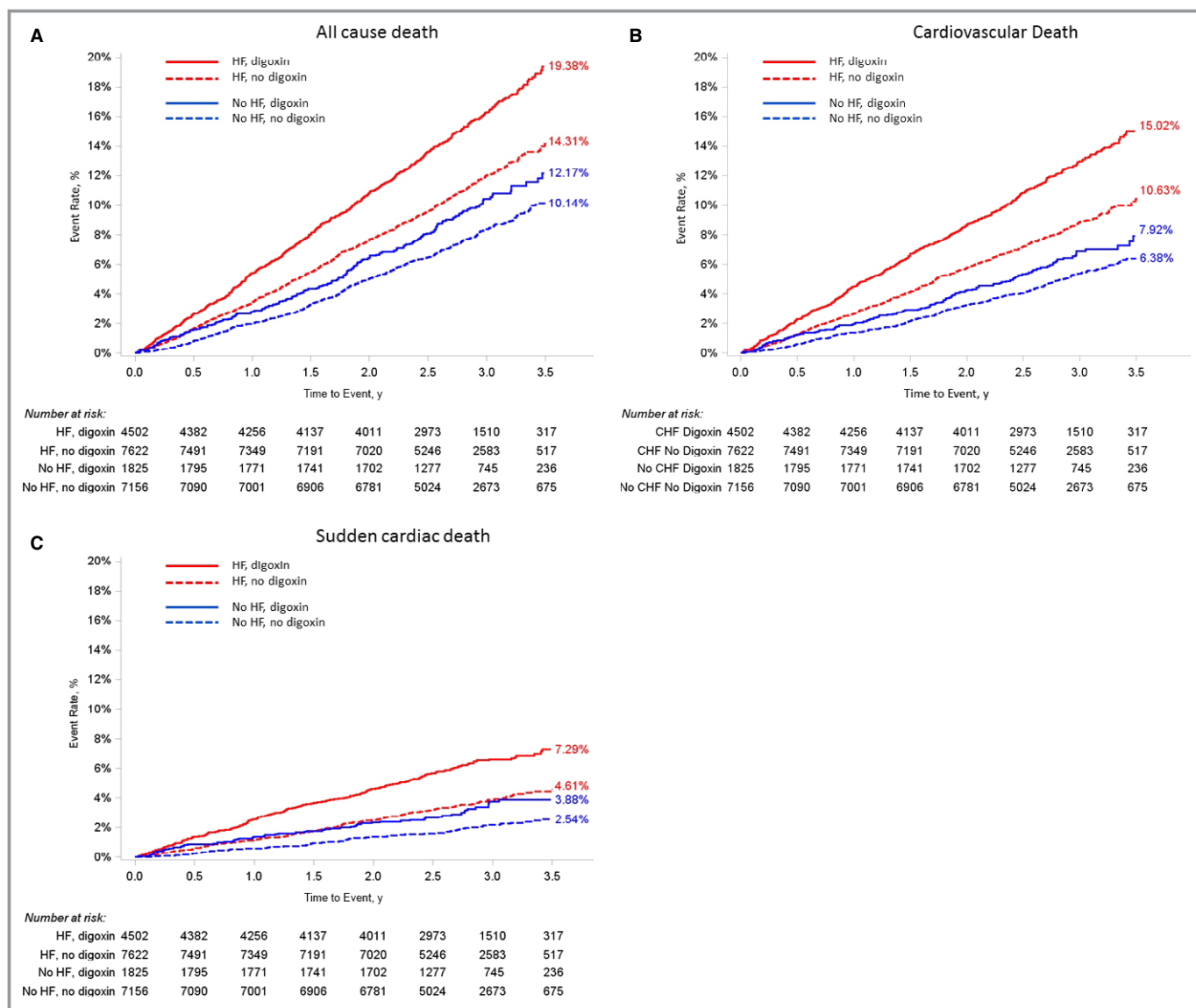


Figure 1. Kaplan–Meier curves of (A) all-cause death, (B) cardiovascular death, and (C) sudden cardiac death, by digoxin use at baseline and heart failure (HF) status. *P* interaction between digoxin use and HF status is 0.16 (A), 0.14 (B), and 0.75 (C). CHF indicates congestive heart failure.

analysis) (Table S3). Digoxin was not independently associated with all-cause death, all cardiovascular death (including both SCD and non-SCD), or noncardiovascular death in either analysis (Table S3).

Discussion

In the current analysis from a large international cohort of patients with AF, treatment with digoxin was common, with more than a third of the patients with concomitant HF and a fifth of the patients without HF taking the agent. In the trial as a whole, digoxin use was associated with increased all-cause mortality, cardiovascular death, SCD, death caused by HF or cardiogenic shock, and HF hospitalization. This association

was evident particularly among patients with HF. Importantly, in patients without HF, digoxin use was significantly associated with SCD. While the association between digoxin use and clinical outcomes may be a result of residual confounding by differences in comorbidities and treatment in patients with HF, it is less likely to be influenced by these factors in patients without HF.

Digoxin is widely used in patients with AF for several indications. While in patients with concomitant HF it is used both as a positive inotropic agent and as rate-control therapy, in patients with AF without HF it is prescribed primarily to achieve better rate control. As demonstrated in this study and others,^{1,9,14} in patients with HF, digoxin is prescribed to patients with more advanced HF, lower LVEF,

Table 4. SCD by Digoxin Use in Subgroups of Patients Without Heart Failure

Subgroup	Patients, No.	Digoxin SCD, No. (%/y)	No Digoxin SCD, No. (%/y)	Adjusted HR* (95% CI)	P Interaction
Age, y					0.36
<65	1665	7 (0.8)	24 (0.6)	1.11 (0.47–2.61)	
65–74	2657	17 (1.0)	27 (0.5)	2.21 (1.17–4.15)	
≥75	4659	36 (1.4)	92 (0.9)	1.39 (0.92–2.11)	
Sex					0.85
Male	5517	38 (1.3)	97 (0.8)	1.55 (1.04–2.29)	
Female	3464	22 (1.0)	46 (0.6)	1.46 (0.86–2.45)	
Race					0.98
White	7115	43 (1.1)	108 (0.7)	1.52 (1.05–2.21)	
Nonwhite	1865	17 (1.5)	35 (0.9)	1.51 (0.83–2.73)	
Region					0.33
North America	2814	17 (1.0)	36 (0.6)	1.73 (0.95–3.15)	
Latin America	975	10 (1.7)	37 (1.9)	0.77 (0.37–1.62)	
Western Europe	1808	11 (1.2)	29 (0.7)	1.72 (0.85–3.49)	
Eastern Europe	1719	9 (0.9)	19 (0.5)	1.83 (0.80–4.18)	
Asia-pacific and South Africa	1665	13 (1.3)	22 (0.6)	2.11 (1.06–4.20)	
Weight, kg					0.81
≤60	956	14 (1.9)	21 (1.1)	1.64 (0.83–3.25)	
>60	8025	46 (1.0)	122 (0.7)	1.50 (1.04–2.14)	
Type of AF					0.03
Paroxysmal	2928	2 (0.2)	44 (0.6)	0.21 (0.03–1.45)	
Persistent/permanent	6048	58 (1.3)	99 (0.8)	1.77 (1.25–2.50)	
LV ejection fraction					0.33
<50%	597	10 (2.5)	16 (1.3)	2.48 (1.06–5.81)	
≥50%	5525	31 (1.1)	82 (0.6)	1.55 (1.01–2.37)	
Charlson comorbidity index					0.45
≤Mean	5227	32 (1.1)	75 (0.6)	1.64 (1.07–2.52)	
>Mean	3754	28 (1.2)	68 (0.8)	1.30 (0.82–2.05)	
LV hypertrophy per ECG					0.55
Yes	737	9 (1.8)	22 (1.5)	1.23 (0.54–2.80)	
No	8164	50 (1.1)	118 (0.6)	1.61 (1.15–2.25)	
Heart rate at baseline, bpm					0.40
<80	6365	30 (0.9)	92 (0.6)	1.35 (0.89–2.05)	
≥80	2596	30 (1.7)	49 (0.9)	1.77 (1.09–2.88)	
β-Blockers at baseline					0.35
Yes	5313	36 (1.3)	87 (0.7)	1.72 (1.15–2.58)	
No	3668	24 (1.1)	56 (0.7)	1.26 (0.77–2.08)	
Diuretic use at baseline					0.38
Yes	3918	33 (1.3)	63 (0.7)	1.74 (1.12–2.71)	
No	5063	27 (1.0)	80 (0.7)	1.31 (0.83–2.07)	

Continued

Table 4. Continued

Subgroup	Patients, No.	Digoxin SCD, No. (%/y)	No Digoxin SCD, No. (%/y)	Adjusted HR* (95% CI)	P Interaction
CrCl, mL/min					0.96
≤60	3356	33 (1.7)	78 (1.1)	1.51 (0.98–2.33)	
>60	5625	27 (0.8)	65 (0.5)	1.48 (0.94–2.35)	
Randomized treatment					0.59
High-dose edoxaban	2938	20 (1.2)	45 (0.7)	1.70 (1.00–2.90)	
Low-dose edoxaban	3055	12 (0.7)	44 (0.6)	1.13 (0.59–2.17)	
Warfarin	2988	28 (1.6)	54 (0.8)	1.64 (1.02–2.64)	

AF indicates atrial fibrillation; bpm, beats per minute; CrCl, creatinine clearance; SCD, sudden cardiac death.

*Hazard ratios (HRs) are adjusted for age; weight; sex; region; race; creatinine; atrial fibrillation type; hypertension; diabetes mellitus; history of stroke or transient ischemic attack; history of coronary artery disease; prior myocardial infarction; history of peripheral artery disease; smoking status; increased risk of falling; left ventricular (LV) ejection fraction; mitral valve disease; aortic valve disease; prior electrical cardioversion; LV hypertrophy; previous use of vitamin K antagonists ≥60 days before randomization; lipid-lowering medications; class I, II, or III antiarrhythmics; renin-angiotensin-aldosterone inhibitors; randomized treatment group; heart rate; history of chronic obstructive pulmonary disease; and diuretic use at randomization.

worse New York Heart Association functional class, and greater burden of other comorbidities. As such, the association between digoxin use and clinical outcomes in patients with HF may be biased by residual confounding caused by the baseline medical condition and concomitant medications.¹⁵ Adjusting for multiple confounders, propensity matching, and IPTW may not fully account for this difference. Thus, our results in patients with HF should be interpreted with caution. In contrast, in patients without HF who are presumably treated with digoxin as a rate-control therapy, residual confounding may play a much smaller role. In these patients, the association between digoxin use and SCD,

which was also demonstrated in propensity matching and IPTW, was robust. Furthermore, given the possibility that among patients who were categorized as not having HF at baseline there were patients with undiagnosed HF, the association between digoxin use and clinical outcomes was also examined in a more homogenous group of patients without HF and LVEF ≥50%. In these patients, not only did the association between digoxin use and SCD remain significant, but the adjusted HRs were qualitatively similar. Furthermore, these results were strengthened by the lack of association between digoxin use and death caused by HF or cardiogenic shock (Figure 2).

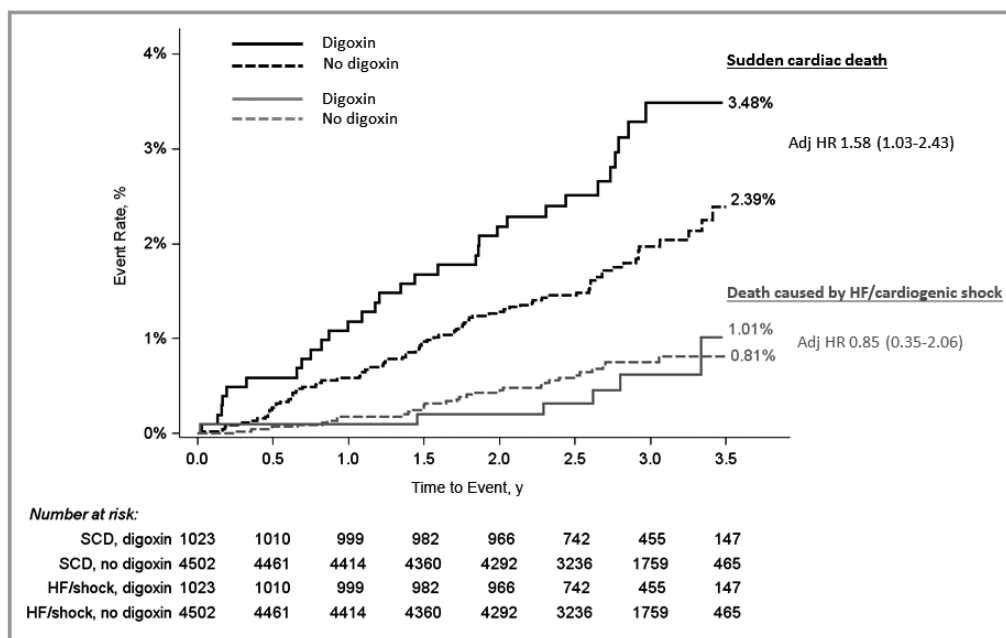


Figure 2. Kaplan–Meier curve of sudden cardiac death (SCD) and death caused by heart failure (HF) or cardiogenic shock, by digoxin use in patients without HF and left ventricular ejection fraction (LVEF) ≥50% (n=5525). Log-rank P value for SCD=0.02; log-rank P value for death caused by HF or cardiogenic shock=0.95. HR indicates hazard ratio.

SCD is the single most common cause of death among patients with AF, accounting for about a third of all deaths.^{23–26} In a recent analysis from the ENGAGE AF-TIMI 48 trial, the cause for SCD was unknown in most cases and an arrhythmia was documented in only a minority of SCD events (11.5%).²⁵ Digoxin is an important factor associated with SCD in this population.²⁵ The association between digoxin use and SCD in patients with AF appears to be more dominant in individuals without HF, yet the causality is not clear and seems complex. Digoxin has a narrow therapeutic range and is influenced by drug-to-drug interactions, serum electrolyte concentrations, and renal function.³ In patients with AF, the majority of whom are elderly with concomitant medically treated conditions, digoxin concentration may fluctuate. In this study, patients without HF who were treated with digoxin were elderly (more than half were ≥ 75 years) with a high burden of comorbidities including diabetes mellitus and reduced renal function. These characteristics may have predisposed them to abnormal digoxin concentration, yet our results did not show any heterogeneity for the risk of SCD by any of these factors, perhaps owing to low statistical power. Whether the concomitant use of β -blockers with digoxin in patients without HF has a protective effect against SCD is not known and it cannot be established from this observational study. In addition, whether digoxin's inotropic activity in patients without HF can be harmful deserves further research. Thus, revealing additional mechanisms of the association between digoxin use and SCD in patients with AF without HF is of interest.

This study has several clinical implications, mainly in patients with AF without HF, in whom randomized studies with digoxin are absent. In these patients, digoxin is usually not prescribed as a first-line therapy, but rather as an add-on treatment with another rate-control agent. Indeed, in our study, about 70% of the patients without HF treated with digoxin were also treated with β -blockers or nondihydropyridine calcium channel blockers. However, prescribing digoxin as a single rate-control agent in patients with AF without HF is not rare and may be the result of an adverse event, such as bradycardia experienced with the other rate-control therapies. Regardless of the reason for prescribing digoxin in patients with AF without HF, our study emphasizes the concern with the use of therapy, which is not supported by adequately sized randomized clinical trials. Consistent with prior data,^{1,27} our findings highlight the complex intersection between digoxin use, HF, and worse clinical outcomes, and raise a concern of a possible association between digoxin use and SCD. This study highlights the unmet need for examining digoxin use in patients with AF with, but particularly without, HF in a randomized trial.

Limitations

This study is an observational post hoc analysis of a randomized trial and should be considered hypothesis generating. Dose and drug concentrations of digoxin were not available during the study. Digoxin use was considered at baseline and data regarding its use during the trial were available only every 3 months in the study visit. Nevertheless, using digoxin as a time-variant covariate did not change the key results. In addition, both methods of analyzing a concomitant medication have their limitations.²⁸ Given the low rates of some end points, the multivariable models may be overspecified. Nevertheless, to be consistent, similar multivariate models were used throughout. With regard to SCD, several important factors were not available in this study including documentation of arrhythmia, family history of SCD, and genetic tests; however, all SCD events were adjudicated by an independent committee. The ENGAGE AF-TIMI 48 trial included patients with AF who were at moderate-high risk, and our results may not be generalized to low-risk patients with AF. Nevertheless, this study is based on the largest randomized controlled trial in patients with AF. Finally, the association between digoxin and worse clinical outcomes as demonstrated in the current analysis was not demonstrated in the only prospective trial with digoxin in patients with HF.²⁹ However, this trial was limited to patients in sinus rhythm, and no conclusions can be made with regards to patients with AF.

Conclusions

In this observational study in patients with AF, digoxin use was associated with worse clinical outcomes. In patients with HF, digoxin use was associated with all-cause death, cardiovascular death, SCD, HF death, and HF hospitalizations. In patients without HF, digoxin use was significantly associated with SCD. While the results in patients with HF might be caused by residual confounding, our results highlight the need to examine digoxin use in patients with AF without HF, in a randomized controlled trial. Given the availability of other rate-control agents, until the safety of digoxin in patients with AF without HF has been established, the use of the drug in this population should be undertaken with great care, if at all.

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics by baseline heart failure status and digoxin use.

Characteristic- n (%)	Heart failure (n=12124)				No heart failure (n=8981)			
	Digoxin n=4502 (37%)	No digoxin n=7622 (63%)	P value	Total	Digoxin n=1825 (20%)	No digoxin n=7156 (80%)	P value	Total
Age, years- median (IQR)	69 (61-76)	70 (63-76)	<0.001	70 (62-76)	75 (68-79)	75 (67-79)	0.36	75 (67-79)
Female sex	1758 (39.0)	2818 (37.0)	0.02	4576 (37.7)	798 (43.7)	2666 (37.3)	<0.001	3464 (38.6)
Weight, kg- mean (SD)	82.8 (20.7)	86.2 (20.2)	<0.001	84.9 (20.4)	80.1 (20.2)	83.1 (19.7)	<0.001	82.5 (19.8)
Region °			<0.001				0.04	
North America	586 (13.0)	1281 (16.8)		1867 (15.4)	568 (31.1)	2246 (31.4)		2814 (31.3)
Latin America	752 (16.7)	934 (12.3)		1686 (13.9)	225 (12.3)	750 (10.5)		975 (10.9)
Western Europe	402 (8.9)	1026 (13.5)		1428 (11.8)	331 (18.1)	1477 (20.6)		1808 (20.1)
Eastern Europe	1967 (43.7)	3458 (45.4)		5425 (44.7)	348 (19.1)	1371 (19.2)		1719 (19.1)
Asia-Pacific and SA	795 (17.7)	923 (12.1)		1718 (14.2)	353 (19.3)	1312 (18.3)		1665 (18.5)
White race (n=21104)	3481 (77.3)	6471 (84.9)	<0.001	9952 (82.1)	1411 (77.3)	5704 (79.7)	0.02	7115 (79.2)
Type of atrial fibrillation (n=21099)			<0.001				<0.001	
Paroxysmal	421 (9.4)	2017 (26.5)		2438 (20.1)	292 (16.0)	2636 (36.9)		2928 (32.6)
Persistent	1053 (23.4)	1853 (24.3)		2906 (24.0)	371 (20.3)	1591 (22.2)		1962 (21.9)
Permanent	3028 (67.3)	3751 (49.2)		6779 (55.9)	1161 (63.7)	2925 (40.9)		4086 (45.5)
Qualifying risk factor								
Hypertension requiring treatment	4169 (92.6)	7228 (94.8)	<0.001	11397 (94.0)	1684 (92.3)	6673 (93.3)	0.14	8357 (93.1)
Age ≥ 75 yr	1337 (29.7)	2478 (32.5)	0.001	3815 (31.5)	942 (51.6)	3717 (51.9)	0.80	4659 (51.9)
Diabetes mellitus	1439 (32.0)	2242 (29.4)	0.003	3681 (30.4)	890 (48.8)	3053 (42.7)	<0.001	3943 (43.9)
Prior stroke or TIA	999 (22.2)	1531 (20.1)	0.006	2530 (20.9)	707 (38.7)	2736 (38.2)	0.69	3443 (38.3)
CHADS ₂ score *								
Mean (SD)	3.0 (1.1)	3.0 (1.0)	0.84	3.0 (1.0)	2.7 (0.9)	2.6 (0.8)	0.03	2.7 (0.8)
4-6	1162 (25.8)	1963 (25.8)	0.95	3125 (25.8)	369 (20.2)	1274 (17.8)	0.02	1643 (18.3)

CHA ₂ DS ₂ -VASc score *								
Mean (SD)	4.4 (1.5)	4.5 (1.5)	0.005	4.5 (1.5)	4.2 (1.2)	4.1 (1.2)	0.001	4.2 (1.2)
4-9	3157 (70.1)	5524 (72.5)	0.006	8681 (71.6)	1314 (72.0)	4924 (68.8)	0.008	6238 (69.5)
HAS-BLED score *								
Mean (SD)	2.3 (0.9)	2.4 (1.0)	<0.001	2.4 (1.0)	2.6 (0.9)	2.7 (1.0)	<0.001	2.7 (1.0)
≥ 3	1749 (38.8)	3343 (43.9)	<0.001	5092 (42.0)	894 (49.0)	3816 (53.3)	<0.001	4710 (52.4)
Coronary artery disease (n=21102)	1600 (35.5)	3163 (41.5)	<0.001	4763 (39.3)	404 (22.1)	1856 (25.9)	<0.001	2260 (25.2)
Prior myocardial infarction	581 (12.9)	1143 (15.0)	0.002	1724 (14.2)	123 (6.7)	586 (8.2)	0.04	709 (7.9)
Ejection fraction †			<0.001				<0.001	
< 30%	388 (11.3)	362 (6.0)		750 (7.9)	10 (0.9)	22 (0.4)		32 (0.5)
30-39%	651 (18.9)	779 (13.0)		1430 (15.1)	22 (1.9)	69 (1.4)		91 (1.5)
40-49%	942 (27.3)	1452 (24.2)		2394 (25.4)	116 (9.9)	358 (7.2)		474 (7.7)
≥ 50%	1465 (42.5)	3403 (56.8)		4868 (51.6)	1023 (87.4)	4502 (90.9)		5525 (90.2)
NYHA III, IV ‡ (n=11988)	1220 (27.4)	1415 (18.8)	<0.001	2635 (22.0)	NA	NA		NA
Peripheral arterial disease (n=21096)	158 (3.5)	355 (4.7)	0.002	513 (4.2)	53 (2.9)	275 (3.8)	0.06	328 (3.7)
Former/current smoker (n=21098)	1722 (38.2)	3049 (40.0)	0.05	4771 (39.4)	753 (41.3)	3124 (43.7)	0.06	3877 (43.2)
COPD	475 (10.6)	725 (9.5)	0.06	1200 (9.9)	151 (8.3)	430 (6.0)	<0.001	581 (6.5)
Mitral valve disease (n=20983)	1755 (39.2)	2911 (38.4)	0.42	4666 (38.7)	521 (28.8)	2061 (29.0)	0.87	2582 (28.9)
Aortic valve disease (n=21014)	681 (15.2)	1248 (16.5)	0.06	1929 (16.0)	226 (12.5)	979 (13.7)	0.17	1205 (13.5)
Prior electrical cardioversion for AF (n=21104)	611 (13.6)	1505 (19.7)	<0.001	2116 (17.5)	384 (21.0)	1291 (18.0)	0.003	1675 (18.7)
Charlson comorbidity index, mean (SD)	3.1 (1.0)	3.1 (1.0)	0.46	3.1 (1.0)	2.5 (1.0)	2.4 (1.0)	0.001	2.4 (1.0)
Heart rate (BPM), mean (SD) (n=21074)	78.1 (14.2)	74.1 (14.0)	<0.001	75.6 (14.2)	74.5 (13.7)	71.9 (13.4)	<0.001	72.4 (13.5)
Hypertrophy per ECG (n=20950)	1124 (25.1)	1576 (20.8)	<0.001	2700 (22.4)	187 (10.3)	550 (7.8)	<0.001	737 (8.3)
Vitamin K antagonist experienced § (n=21104)	2583 (57.4)	4290 (56.3)	0.25	6873 (56.7)	1335 (73.2)	4233 (59.2)	<0.001	5568 (62.0)

Medication at randomization								
Aspirin (n=21101)	1216 (27.0)	2365 (31.0)	<0.001	3581 (29.5)	414 (22.7)	2185 (30.5)	<0.001	2599 (28.9)
Lipid lowering	1649 (36.6)	3584 (47.0)	<0.001	5233 (43.2)	909 (49.8)	3940 (55.1)	<0.001	4849 (54.0)
Antiarrhythmics								
Class I	53 (1.2)	343 (4.5)	<0.001	396 (3.3)	42 (2.3)	455 (6.4)	<0.001	497 (5.5)
Class II (beta-blockers)	3106 (69.0)	5565 (73.0)	<0.001	8671 (71.5)	1013 (55.5)	4300 (60.1)	<0.001	5313 (59.2)
Class III	458 (10.2)	1595 (20.9)	<0.001	2053 (16.9)	130 (7.1)	951 (13.3)	<0.001	1081 (12.0)
Class IV	336 (7.5)	488 (6.4)	0.02	824 (6.8)	293 (16.1)	788 (11.0)	<0.001	1081 (12.0)
Diuretics	3562 (79.1)	5176 (67.9)	<0.001	8738 (72.1)	883 (48.4)	3035 (42.4)	<0.001	3918 (43.6)
RAAS inhibitor	3290 (73.1)	5357 (70.3)	0.001	8647 (71.3)	1023 (56.1)	4236 (59.2)	0.02	5259 (58.6)
CrCl (ml/min), Median (IQR)	71.8 (54.5-95.3)	72.8 (55.1-94.4)	0.65	72.4 (54.8-94.6)	67.1 (51.7-87.9)	67.9 (53.0-87.7)	0.24	67.7 (52.8-87.7)
Dose reduction at randomization	1211 (26.9)	1705 (22.4)	<0.001	2916 (24.1)	568 (31.1)	1872 (26.2)	<0.001	2440 (27.2)
Randomized treatment			0.15				0.60	
High dose Edoxaban	1487 (33.0)	2610 (34.2)		4097 (33.8)	591 (32.4)	2347 (32.8)		2938 (32.7)
Low dose Edoxaban	1464 (32.5)	2515 (33.0)		3979 (32.8)	609 (33.4)	2446 (34.2)		3055 (34.0)
Warfarin	1551 (34.5)	2497 (32.8)		4048 (33.4)	625 (34.2)	2363 (33.0)		2988 (33.3)

Data shown are n (%) unless otherwise indicated

Abbreviations- BPM, beats per minute; CrCl, creatinine clearance; CV, cardiovascular; ECG, electrocardiogram; NYHA, New York heart association functional class; RAAS, renin angiotensin aldosterone system; SA, South Africa; SCD, sudden cardiac death; SD, standard deviation; TIA, transient ischemic attack.

* CHADS₂ score- see reference [27]; CHA₂DS₂-VASc score- see reference [28]; HAS-BLED score- see reference [29].

° Percentages are for each region except for the Total column.

† Ejection fraction was unknown for 5541 patients (heart failure- 2682 patients; no heart failure- 2859 patients).

‡ NYHA class at baseline was reported only in patients with HF.

§ Vitamin K antagonist experienced denotes ≥60 consecutive days of treatment with a vitamin K antagonist at any time prior to enrollment.

Table S2. Clinical outcomes by digoxin use and type of HF at baseline.

Endpoint- n (%/year)	Systolic heart failure (n=5027) *			Diastolic heart failure (n=4150)		
	Digoxin (n=1728)	No digoxin (n=3299)	Adj HR ‡ (95% CI)	Digoxin (n=1716)	No digoxin (n=2434)	Adj HR ‡ (95% CI)
All cause death	272 (5.9)	349 (3.9)	1.33 (1.12-1.58)	283 (6.2)	325 (4.9)	1.14 (0.96-1.35)
CV death	214 (4.6)	251 (2.8)	1.39 (1.13-1.69)	228 (5.0)	244 (3.7)	1.20 (0.99-1.45)
SCD	98 (2.1)	115 (1.3)	1.34 (0.99-1.81)	119 (2.6)	108 (1.6)	1.33 (1.00-1.76)
HF/cardiogenic shock death	69 (1.5)	53 (0.6)	2.20 (1.48-3.29)	61 (1.3)	68 (1.0)	1.17 (0.79-1.72)
Non-CV death	58 (1.3)	98 (1.1)	1.15 (0.81-1.64)	55 (1.2)	81 (1.2)	0.95 (0.64-1.40)
Stroke/ SSE	90 (2.0)	155 (1.8)	1.03 (0.77-1.36)	76 (1.7)	104 (1.6)	0.99 (0.73-1.35)
HF hospitalizations	228 (5.4)	328 (3.9)	1.17 (0.97-1.41)	284 (6.8)	300 (4.9)	1.37 (1.14-1.64)
MI	32 (0.7)	66 (0.8)	0.81 (0.51-1.29)	28 (0.6)	68 (1.1)	0.71 (0.43-1.18)

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; SCD, sudden cardiac death; SSE, stroke or systemic embolism.

Type of HF was unknown in 2634 patients.

*Systolic HF included patients with systolic HF (n=2875) and both systolic and diastolic HF (n=2152).

‡ Hazard ratios are adjusted for age, weight, sex, region, race, creatinine, atrial fibrillation type, hypertension, diabetes mellitus, history of stroke or transient ischemic attack, history of coronary artery disease, prior myocardial infarction, history of peripheral artery disease, smoking status, increased risk of falling, left ventricle ejection fraction, mitral valve disease, aortic valve disease, prior electrical cardioversion, left ventricular hypertrophy, previous use of vitamin K antagonists \geq 60 days prior to randomization, lipid lowering medications, class I, II, III antiarrhythmics, renin-angiotensin-aldosterone, randomized treatment group, heart rate, history of COPD, diuretic use at randomization.

Table S3. Hazard ratios (95% CIs) of digoxin use in patients without heart failure at baseline using digoxin as a time-variant covariate (digoxin "on", or digoxin "on/off" methods *).

Endpoint	Digoxin "on" * Adj HR (95% CI) ‡	Digoxin "on/off" * Adj HR (95% CI) ‡
All cause death	1.71 (0.95-3.07)	1.17 (0.60-2.27)
CV death	1.81 (0.85-3.85)	1.18 (0.49-2.81)
SCD	5.53 (1.66-18.41)	4.45 (1.37-14.44)
Non SCD	0.76 (0.24-2.36)	0.21 (0.03-1.64)
Non-CV death	1.68 (0.64-4.41)	1.18 (0.41-3.45)
Stroke/ SSE	1.36 (1.06-1.74)	0.96 (0.72-1.27)
HF hospitalizations	1.92 (1.51-2.44)	1.80 (1.40-2.32)
MI	1.55 (1.08-2.23)	1.34 (0.90-1.99)

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; SCD, sudden cardiac death; SSE, stroke or systemic embolism.

Data presented are for 8806 patients.

* Digoxin use was reported at each study visit (every 3 months) and was regarded as a time-dependent variable using 2 methods: In the first, if digoxin was started during follow-up, the patient was regarded as being on digoxin throughout the trial (digoxin "on"), while in the second, the patient was regarded as being on or off digoxin per the status of digoxin use every 3 months (digoxin "on/off").

‡ Hazard ratios are adjusted for age, weight, sex, region, race, creatinine, atrial fibrillation type, hypertension, diabetes mellitus, history of stroke or transient ischemic attack, history of coronary artery disease, prior myocardial infarction, history of peripheral artery disease, smoking status, increased risk of falling, left ventricle ejection fraction, mitral valve disease, aortic valve disease, prior electrical cardioversion, left ventricular hypertrophy, previous use of vitamin K antagonists \geq 60 days prior to randomization, lipid lowering medications, class I, II, III antiarrhythmics, renin-angiotensin-aldosterone, diuretic use, randomized treatment group, heart rate, chronic obstructive pulmonary disease.