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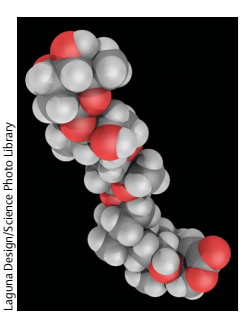
Digoxin use in atrial fibrillation: a critical reappraisal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Digoxin

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Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia, affecting more than 33·5 million individuals worldwide.[1] Despite pharmacological advances in the past two centuries, digoxin remains the oldest and one of the most common adjunctive treatments for rate control in AF. Although reports show a persistent decrease in overall digoxin prescription rates,[2] its use remains common in contemporary AF trials in nearly a third of participants.[3]

In *The Lancet*, Jeffrey Washam and colleagues[4] report the results of a retrospective analysis of 14 171 randomly assigned participants in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF). Baseline digoxin use was present in 5239 (37%) patients, and was associated with increased all-cause mortality (5·41% *vs* 4·30%; adjusted hazard ratio [HR] 1·17 [95% CI 1·04–1·32]), but not admissions to hospital, during a median follow-up of 707 days. Important between-group differences included a higher proportion of women (2221 [42%] *vs* 3384 [38%]); prevalence of diabetes (2254 [43%] *vs* 3393 [38%]) and chronic obstructive pulmonary disease (667 [13%] *vs* 814 [9%]); and history of heart failure (3841 [73%] *vs* 5010 [56%]) in patients on digoxin at baseline as compared with those not on digoxin. Strengths of this study include use of a large international contemporary clinical trial database and independent blinded event adjudication. Limitations include selection bias, with potential residual confounding of unmeasured factors likely to affect physician choice of digoxin prescription.

Washam and colleagues' study[4] does not represent the first time that use of digoxin has been questioned by post-hoc analyses in patients with AF, with conflicting results. In 122 465 patients in the Retrospective Evaluation and Assessment of Therapies in Atrial Fibrillation study with newly diagnosed AF,[5] digoxin was prescribed in 23% of patients, and this digoxin prescription was independently associated with increased mortality after multivariate adjustment (HR 1·26; 95% CI 1·23–1·29) and propensity matching (1·21; 1·17–1·25). By contrast, the Rate Control Efficacy in Permanent Atrial Fibrillation II trial[6] did not show an increase in mortality (0·97; 0·62–1·52) or cardiovascular-related admission to hospital (1·00; 0·69–1·45) with use of digoxin. Authors of two separate

retrospective analyses done in the Atrial Fibrillation Follow-up Investigation of Rhythm Management trial reported opposing results, with Whitbeck and colleagues[7] describing increased mortality, but Gheorghiade and colleagues[8] noting no difference in mortality with digoxin use. Importantly, digoxin was shown to be effective for rate control in the Atrial Fibrillation Follow-up Investigation of Rhythm Management trial[9] and in a randomised, double-blind study[10] when used alone or in combination with other drugs in heart failure.

The controversy surrounding digoxin use in AF is similar to that of two decades ago when authors of retrospective analyses raised concerns about increased mortality with digoxin use in patients with heart failure and sinus rhythm.[11] This debate laid the groundwork for the Digitalis Investigation Group (DIG) to do one of the largest randomised placebo-controlled studies, enrolling 6800 patients with heart failure and sinus rhythm.[12] Overall, digoxin use was safe, with similar rates of all-cause mortality (response rate 0·99; 95% CI 0·91–1·07) and death due to cardiovascular causes (1.01; 0·93–1·10). Furthermore, use of digoxin was associated with reduction in admission to hospital for worsening heart failure (0·72; 0·66–0·79). The ancillary trial,[13] which assessed 988 patients with heart failure and preserved ejection fraction, showed a similar safety profile for digoxin. The results of the DIG study prompted approval of digoxin by the US Food and Drug Administration in 1997 for heart failure and AF.

One plausible explanation for the conflicting results could be dose, in view of the narrow therapeutic window of digoxin. A key component of the DIG trial was a formula-based approach to digoxin dosage using age, sex, weight, and renal function, which achieved a mean plasma concentration of 0·8 ng/mL in follow-up, irrespective of absolute dose prescribed. In fact, a post-hoc analysis[14] of the DIG study showed reduction of all-cause mortality and admission to hospital when the serum digoxin concentration (SDC) was between 0·5 ng/mL and 0·9 ng/mL, and an increase in mortality when it was greater than 1·2 ng/mL. These findings prompted a modification in the reported therapeutic values in many laboratories in the USA for patients with heart failure and sinus rhythm, but did not extend to patients with AF in most institutions. Authors of a cross-sectional survey of laboratory directors in the USA in 2013 showed that 93% of respondents (56 of 60) reported an SDC of 2·0 ng/mL or greater as being within the normal range.[15] These data are further supported by the absence of a decrease in admissions for digoxin toxic effects, despite a fall in secular digoxin prescription rates.

The absence of standardisation of a therapeutic range for SDC in AF, leaving much room for provider-to-provider variability, is concerning and could lead to adverse outcomes. This might be compounded by common clinical practice to uptitrate digoxin to target ventricular rate control, and could result in use of high doses of digoxin in participants in AF trials.[16] Even the most recent iteration of the American College of Cardiology and American Heart Association AF Guideline[17] does not include either a dosing strategy or recommendations for plasma concentration monitoring when digoxin is used. The absence of tangible data on digoxin dose and serum concentration monitoring in many retrospective analyses, including that of ROCKET AF, limits mechanistic understanding of the attributable risk of digoxin.

What should change as a result of Washam and colleagues' retrospective analysis[4] of ROCKET-AF? Aside from reigniting an age-old controversy, no plausible reason or empirical evidence exists to discontinue use of digoxin in treatment of AF. Use of digoxin has clearly been shown to be safe in the DIG trial of almost 7000 patients with sinus rhythm and heart failure when dosing was based on a simple clinical formula. Little reason exists to suspect that the safety profile of digoxin should be different in patients with AF with and without heart failure when SDC is maintained at less than 1·0 ng/mL. The available data suggest a need to redefine how digoxin is used in patients with AF. We recommend that digoxin should continue to be used in patients with AF. However, dosing should be adjusted with a goal to maintain an SDC with an upper limit of 1·0 ng/mL and not to target ventricular rate.

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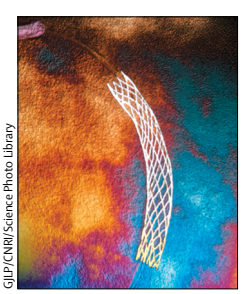
Prolonged antiplatelet therapy after drug-eluting stents



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After use of intracoronary drug-eluting stents, a regimen of two antiplatelet agents (ie, dual antiplatelet therapy [DAPT]) is necessary to prevent stent thrombosis, a complication associated with myocardial infarction and death. Conventional DAPT includes aspirin and a P2Y12 platelet receptor inhibitor such as clopidogrel, prasugrel, or ticagrelor.[1] The optimum duration of DAPT is the subject of much debate; prevention of stent thrombosis has to be balanced against the elevated risk of bleeding associated with two agents.

Because concerns were raised about the high risk of stent thrombosis associated with drug-eluting stents compared with bare-metal stents,[2,3] the default strategy has been to maintain DAPT for 12 months after drug-eluting stent implantation. However, recent observational data[4] suggested that the latest iterations of drug-eluting stents carried a lower risk of stent thrombosis over time and therefore did not need such prolonged DAPT. As a consequence, over the past few years, a series of randomised trials has been done to assess the clinical outcomes of short courses of DAPT versus long courses in patients receiving drug-eluting stents. Unfortunately, these trials were not powered to look at stent thrombosis as a primary endpoint; generally, the findings showed no difference in various combined clinical endpoints between short and long DAPT strategies, but with higher rates of bleeding in the long duration DAPT groups.[5]

As a result of these data, international guidelines have recently changed and recommend DAPT for 6 months in stable patients after implantation of a drug-eluting stent, or even less in those with an increased risk of bleeding.[6] But then the 12 or 30 months of Dual Antiplatelet Therapy after Drug-Eluting Stents (DAPT) trial was published, and knowledge about DAPT after drug-eluting stent implantation was turned on its head.[7] In this trial, patients who had already received 12 months DAPT after drug-eluting stent implantation were randomly assigned to a further 18 months of DAPT or to conventional therapy represented by aspirin alone. The trial showed significantly lower rates of both prespecified coprimary endpoints (ie, stent thrombosis, and major adverse cardiovascular and

Digoxin use in patients with atrial fibrillation and adverse cardiovascular outcomes: a retrospective analysis of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF)

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Summary

Background **Digoxin is a widely used drug for ventricular rate control in patients with atrial fibrillation (AF), despite a scarcity of randomised trial data. We studied the use and outcomes of digoxin in patients in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF).**

Methods **For this retrospective analysis, we included and classified patients from ROCKET AF on the basis of digoxin use at baseline and during the study. Patients in ROCKET AF were recruited from 45 countries and had AF and risk factors putting them at moderate-to-high risk of stroke, with or without heart failure. We used Cox proportional hazards regression models adjusted for baseline characteristics and drugs to investigate the association of digoxin with all-cause mortality, vascular death, and sudden death. ROCKET AF was registered with ClinicalTrials.gov, number NCT00403767.**

Findings **In 14 171 randomly assigned patients, digoxin was used at baseline in 5239 (37%). Patients given digoxin were more likely to be female (42% *vs* 38%) and have a history of heart failure (73% *vs* 56%), diabetes (43% *vs* 38%), and persistent AF (88% *vs* 77%; p<0·0001 for each comparison). After adjustment, digoxin was associated with increased all-cause mortality (5·41 *vs* 4·30 events per 100 patients-years; hazard ratio 1·17; 95% CI 1·04–1·32; p=0·0093), vascular death (3·55 *vs* 2·69 per 100 patient-years; 1·19; 1·03–1·39, p=0·0201), and sudden death (1·68 *vs* 1·12 events per 100 patient-years; 1·36; 1·08–1·70, p=0·0076).**

Interpretation **Digoxin treatment was associated with a significant increase in all-cause mortality, vascular death, and sudden death in patients with AF. This association was independent of other measured prognostic factors, and although residual confounding could account for these results, these data show the possibility of digoxin having these effects. A randomised trial of digoxin in treatment of AF patients with and without heart failure is needed.**

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, estimated to currently affect more than 30 million people worldwide.[1,2] It is associated with increased risk of stroke, heart failure, cognitive impairment, and death, and complicates management of other disorders.[3] A key treatment goal in AF is heart rate control, which can help to reduce symptoms and the risk of cardiomyopathy.[4] Rate control is often achieved with one or more drugs from several classes, including β blockers, non-dihydropyridine calcium channel antagonists, and digoxin. Present American Heart Association, American College of Cardiology, and Heart Rhythm Society treatment guidelines for management of AF[1] provide a class I recommendation (level of evidence C) for digoxin treatment as being effective for resting heart rate control in patients with heart failure and reduced left ventricular ejection fraction. A class IIa recommendation (level of evidence B) is made for use of digoxin in combination with either a β blocker or non-dihydropyridine calcium channel antagonist for patients with heart failure and preserved ejection fraction to control heart rate at rest and during exercise.[1] Present European Society of Cardiology guidelines for management of AF provide a class IIa recommendation (level of evidence C) for digoxin as a long-term rate control drug in patients with heart failure and left ventricular dysfunction, and in sedentary patients.[5]

Although digoxin has been assessed in a large randomised clinical trial of heart failure patients without AF,[6] randomised trials assessing the use of

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digoxin for AF are scarce. Additionally, observational studies designed to assess the effect of digoxin treatment on outcomes in patients with AF have produced inconsistent results.[7–11] Additional data from contemporary studies of patients with AF are therefore needed to inform clinical practice.

In this post-hoc analysis of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF),[12,13] we sought to assess cardiovascular outcomes associated with digoxin treatment in patients with AF, including those with and without heart failure.

Methods

Study design and participants

We undertook a retrospective analysis of data from ROCKET AF, a multicentre, randomised, double-blind, double-dummy, event-driven trial comparing fixed-dose rivaroxaban (20 mg once daily or 15 mg once daily in patients with creatinine clearance 30–49 mL/min) with adjusted-dose warfarin (target international normalised ratio 2·0–3·0) for prevention of all stroke (ischaemic or haemorrhagic) or systemic embolism, as described elsewhere.[12]

Patients with electrocardiographically documented paroxysmal, persistent, or permanent AF, and with risk factors placing them at moderate-to-high risk of stroke, were recruited at 1178 clinical sites and hospitals in 45 countries. Increased stroke risk was indicated by a history of stroke, transient ischaemic attack, or systemic embolism, or at least two of the following risk factors: heart failure or left ventricular ejection fraction 35% or lower; hypertension; age 75 years or older; or diabetes ($CHADS_2$ score ≥2). Complete inclusion and exclusion criteria have been published.[13]

Patients were randomly assigned with a central, 24 h, computerised, automated voice-response system to receive rivaroxaban (20 mg or 15 mg daily in patients with a creatinine clearance of 30–49 mL/min) or dose-adjusted warfarin (target international normalised ratio of 2·0–3·0). A double-blind design was chosen to minimise bias in cointerventions and reporting of clinical events. Institutional review boards at each site approved the protocol, and patients provided written informed consent.

Procedures

All randomly assigned patients were seen at 1, 2, and 4 weeks, and monthly thereafter, for the duration of the

	Overall (n=14 171)	Baseline digoxin (n=5239)	No baseline digoxin (n=8932)	p value
Age (years)	73 (65–78)	72 (64–78)	73 (66–78)	<0·0001
Women	5605 (40%)	2221 (42%)	3384 (38%)	<0·0001
Race				0·15
White	11 786 (83%)	4352 (83%)	7434 (83%)	..
Black	180 (1%)	60 (1%)	120 (1%)	..
Asian	1786 (13%)	652 (12%)	1134 (13%)	..
Other	419 (3%)	175 (3%)	244 (3%)	..
Hispanic or Latino	2331 (16%)	937 (18%)	1394 (16%)	0·0004
Region				<0·0001
West Europe	2096 (15%)	537 (10%)	1559 (17%)	..
Asia Pacific	2109 (15%)	785 (15%)	1324 (15%)	..
East Europe	5407 (38%)	2207 (42%)	3200 (36%)	..
Latin America	1878 (13%)	775 (15%)	1103 (12%)	..
North America	2681 (19%)	935 (18%)	1746 (20%)	..
Randomly allocated rivaroxaban	7081 (50%)	2605 (50%)	4476 (50%)	0·66
$CHADS_2$ score*	3 (3–4)	3 (3–4)	3 (3–4)	0·98
BMI (kg/m²)	14 162; 28·2 (25·1–32·0)	5235; 27·9 (24·7–31·9)	8927; 28·3 (25·3–32·0)	<0·0001
Heart rate (beats per min)	14 162; 76 (67–86)	5236; 78 (69–88)	8926; 75 (66–84)	<0·0001
Blood pressure (mm Hg)				
Systolic	14 159; 130 (120–140)	5236; 130 (120–140)	8923; 130 (120–140)	0·0223
Diastolic	14 159; 80 (70–85)	5236; 80 (70–85)	8923; 80 (70–86)	0·0033
Creatinine clearance (mL/min)†	14 157; 67 (52–87)	5235; 68 (52–88)	8922; 67 (52–86)	0·10
Type of AF				<0·0001
Persistent	11 485 (81%)	4609 (88%)	6876 (77%)	..
Paroxysmal	2490 (18%)	582 (11%)	1908 (21%)	..
Newly diagnosed or new onset	196 (1%)	48 (1%)	148 (2%)	..
Coexisting disorder				

(Table 1 continues on next page)

	Overall (n=14 171)	Baseline digoxin (n=5239)	No baseline digoxin (n=8932)	p value
(Continued from previous page)				
Stroke or TIA	7431 (52%)	2440 (47%)	4991 (56%)	<0·0001
Hypertension	12 824 (90%)	4763 (91%)	8061 (90%)	0·19
HF	8851/14 169 (62%)	3841/5238 (73%)	5010/8931 (56%)	<0·0001
Diabetes	5647 (40%)	2254 (43%)	3393 (38%)	<0·0001
COPD	1481/14 165 (10%)	667/5239 (13%)	814/8926 (9%)	<0·0001
Gastrointestinal bleed	496 (4%)	166 (3%)	330 (4%)	0·10
Liver disease	741 (5%)	305 (6%)	436 (5%)	0·0152
Vascular disease	3296 (23%)	1192 (23%)	2104 (24%)	0·27
Sleep apnoea	645/14 164 (5%)	217/5239 (4%)	428/8925 (5%)	0·07
Cigarette smoking	4760/14 167 (34%)	1761/5238 (34%)	2999/8929 (34%)	0·97
Alcohol consumption in past 12 months				0·0002
None	9158/14 169 (65%)	3505/5238 (67%)	5653/8931 (63%)	..
Light	4297/14 169 (30%)	1486/5238 (28%)	2811/8931 (31%)	..
Moderate	611/14 169 (4%)	214/5238 (4%)	397/8931 (4%)	..
Heavy	103/14 169 (1%)	33/5238 (1%)	70/8931 (1%)	..
Baseline drug				
Aspirin	4187 (30%)	1532 (29%)	2655 (30%)	0·54
VKA	172 (1%)	62 (1%)	110 (1%)	0·80
ACE inhibitor or ARB	9560 (67%)	3721 (71%)	5839 (65%)	<0·0001
Antiarrhythmic	1434 (10%)	302 (6%)	1132 (13%)	<0·0001
β blocker	9212 (65%)	3377 (64%)	5835 (65%)	0·30
Calcium channel blocker	3954 (28%)	1319 (25%)	2635 (30%)	<0·0001
Clopidogrel	241 (2%)	72 (1%)	169 (2%)	0·0214
Heparin	184 (1%)	54 (1%)	130 (1%)	0·0311
Statin	6092 (43%)	1942 (37%)	4150 (46%)	<0·0001

Denominators are given for variables which have missing data. Data are median (IQR), n (%), or n; median (IQR). $CHADS^2$=congestive heart failure, hypertension, age >75 years, diabetes, prior stroke or transient ischaemic attack. BMI=body-mass index. AF=atrial fibrillation. TIA=transient ischaemic attack. HF=heart failure. COPD=chronic obstructive pulmonary disease. VKA=vitamin K antagonist. ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. *The $CHADS_2$ score for risk of stroke ranges from 1 to 6, with the higher the score the higher the risk. †Creatinine clearance was calculated with the Cockcroft-Gault formula.

Table 1: **Baseline demographics and patient characteristics according to baseline digoxin use**

	Baseline digoxin	No baseline digoxin	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)	Unadjusted p value	Adjusted* p value
All-cause mortality	5·41 (522)	4·30 (692)	1·25 (1·12–1·40)	1·17 (1·04–1·32)	0·0001	0·0093
Vascular death	3·55 (343)	2·69 (433)	1·32 (1·15–1·52)	1·19 (1·03–1·39)	0·0001	0·0201
Sudden death	1·68 (162)	1·12 (181)	1·49 (1·21–1·85)	1·36 (1·08–1·70)	0·0002	0·0076
All-cause admission to hospital	14·83 (1234)	15·40 (2113)	0·97 (0·91–1·04)	1·02 (0·95–1·10)	0·41	0·64
Stroke or systemic embolism	2·11 (201)	2·37 (374)	0·90 (0·76–1·07)	0·92 (0·77–1·10)	0·22	0·34
Myocardial infarction	1·05 (101)	1·07 (171)	0·99 (0·77–1·26)	1·04 (0·80–1·34)	0·93	0·79

Data for baseline and no baseline digoxin are events per 100 patient-years (number of events). HR=hazard ratio. *Adjusted for age, sex, race, ethnic origin, region, body-mass index, systolic and diastolic blood pressure, heart rate, creatinine clearance, type of atrial fibrillation, stroke or transient ischaemic attack, heart failure, hypertension, diabetes, chronic obstructive pulmonary disease, gastrointestinal bleeding, liver disease, vascular disease, sleep apnoea, smoking, alcohol use, and baseline vitamin K antagonist, aspirin, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, antiarrhythmics, β blockers, calcium channel blockers, clopidogrel, heparin, and statins use.

Table 2: **Cox proportional hazards regression models for digoxin at baseline versus none**

study, for measurement of international normalised ratio and surveillance for primary endpoint events, transient ischaemic attack, myocardial infarction, medical or surgical procedures, adverse events, and vital status. A standardised questionnaire and examination were used to screen for stroke symptoms and potential clinical events during follow-up.

Use of digoxin was captured as a concomitant drug on the case report form during the study. Heart failure was identified by local site investigators and captured on the case report form. Heart failure was defined a priori as a history of clinical heart failure or a left ventricular ejection fraction less than 40%, and clinical stage was captured using the New York Heart Association (NYHA) Classification.

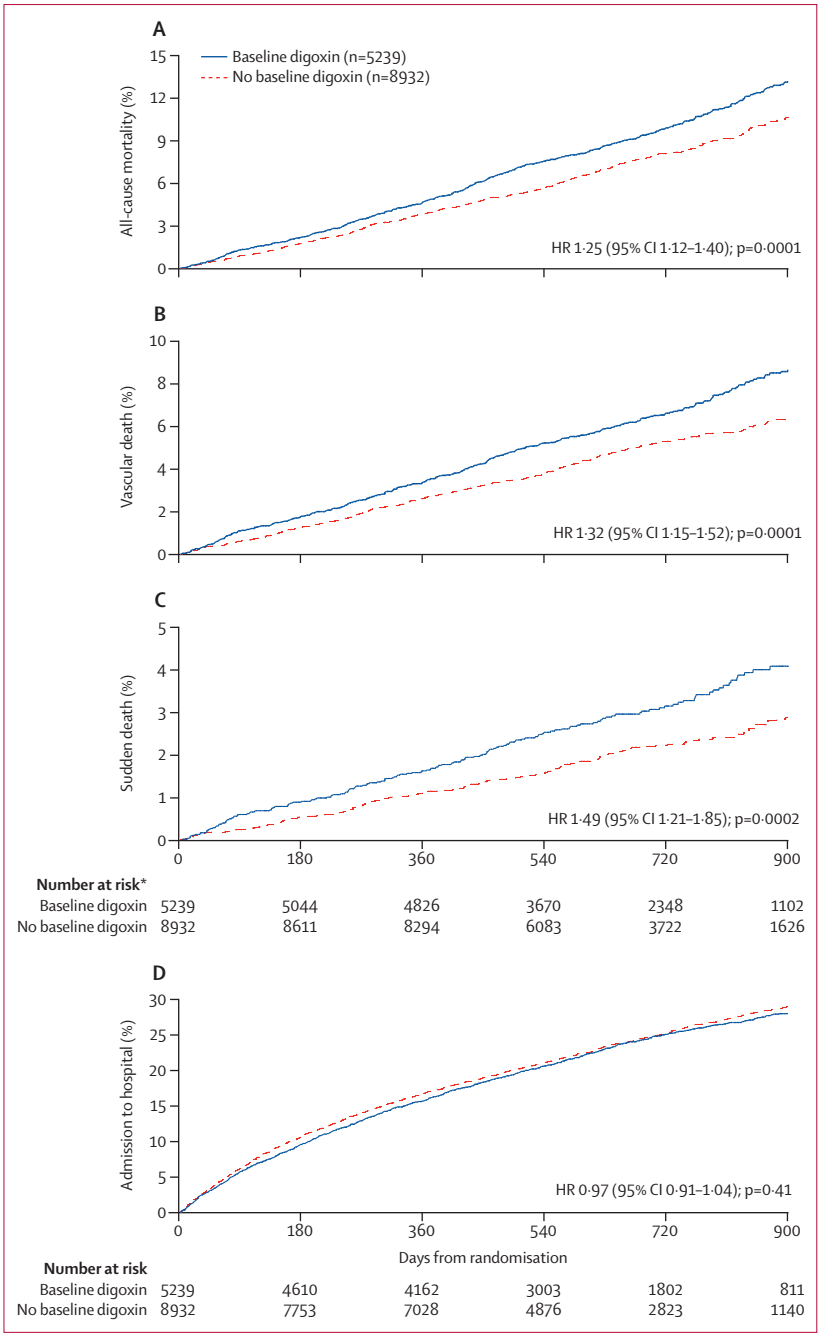

Figure: **Kaplan-Meier curves for (A) all-cause mortality, (B) vascular death, (C) sudden death, and (D) admission to hospital at baseline versus none**
*Applies to A–C.

Outcomes

An independent, masked, clinical endpoint committee applied the protocol definitions and adjudicated all suspected stroke and systemic embolism (the primary outcome of ROCKET AF), myocardial infarction, death, and bleeding events. Death events were also adjudicated for cause of death and subclassified into vascular death, including sudden death and non-cardiovascular death.

Statistical analyses

We summarised baseline patient characteristics with median (IQR) for continuous variables and number (percentage) for categorical variables. Patients who did and did not take digoxin at the time of randomisation were compared with Wilcoxon rank sum for continuous variables and χ^2 tests for categorical variables. A multivariable model for variables associated with baseline digoxin use was fitted with multiple logistic regression with backward elimination, with all variables in table 1 eligible for inclusion. We have presented event rates per 100 patient-years of follow-up (% per year) and total number of events for the endpoints of all-cause mortality, vascular death, sudden death, all-cause hospitalisation, stroke or systemic embolism, and myocardial infarction. We give rates separately for the time before and after digoxin was started. We used Cox proportional hazards regression models with digoxin as a time-dependent variable to test for an association between digoxin use and each clinical event. Digoxin use was time-updated at every visit (minimum of every 4 weeks). Digoxin use for less than 4 days in a week was disregarded as spurious data. Once digoxin was started, we deemed a patient to be on digoxin through the remainder of the follow-up. This convention was to reduce possible time-dependent confounding of digoxin use and the outcomes, and to allow the resulting analysis to be interpreted as intention to treat. Models were adjusted for all baseline patient characteristics shown in table 1. Models were repeated with inclusion of interactions of baseline heart failure, NYHA class, ejection fraction, randomised treatment assignment, and sex with time-dependent digoxin. We presented hazard ratios for digoxin versus no digoxin separately for patients in each of these subgroups. We examined the consistency of results using adjusted Cox proportional hazards regression models that included baseline rather than time-dependent digoxin, and using Cox proportional hazards models with inverse probability weighting for the propensity of the patient's digoxin treatment noted at baseline. We present Kaplan-Meier curves for each endpoint, separately for patients taking and not taking digoxin at baseline. p values less than 0·05 denote significance. We did all analyses with SAS version 9.2.

Role of the funding source

Janssen Research & Development and Bayer HealthCare AG funded ROCKET AF and supported this report through a grant to Duke University. All analyses were done at the Duke Clinical Research Institute and the authors had full access to all data. The Duke Clinical Research Institute coordinated the trial, managed the database, and did the secondary and post-hoc analyses for this report, independent of the funders. An international executive committee designed the trial and was responsible for oversight of study conduct and reporting of all results, and takes responsibility for

accuracy and completeness of data analyses. The funders of the study had no role in study design, data analysis, data interpretation, data collection, or writing of the report. All authors agreed to submit the manuscript for publication.

Results

In ROCKET AF, 5239 (37%) of 14171 patients were on digoxin at time of randomisation. Table 1 provides baseline characteristics of patients given digoxin versus those who were not. Patients with AF given digoxin were significantly more likely to be female, have a history of heart failure, have diabetes, and have persistent AF than those who were not (table 1). These patients also tended to have a higher baseline heart rate than those not given digoxin (table 1). Patient characteristics associated with baseline digoxin use with and without heart failure are presented in the appendix. Median duration of follow-up was 707 days (95% CI 519–885).

The overall rate of stroke or systemic embolism, the primary endpoint of ROCKET AF, was similar in patients given digoxin at baseline compared with those that were not (2·11 *vs* 2·37 events per 100 patient-years; adjusted hazard ratio [HR] 0·92; 95% CI 0·77–1·10; adjusted p=0·34; table 2). Adjusted rates of the primary safety endpoint (major and non-major clinically relevant bleeding) were similar between patients on baseline digoxin and those that were not (appendix).

Baseline digoxin use was associated with increased all-cause mortality (5·41 *vs* 4·30 events per 100 patient-years; adjusted HR 1·17 [95% CI 1·04–1·32]; adjusted p=0·0093), vascular death (3·55 *vs* 2·69; 1·19 [1·03–1·39]; p=0·0201), and sudden death (1·68 *vs* 1·12; 1·36 [1·08–1·70]; p=0·0076; table 2). Adjudicated causes of death are provided in the appendix. Baseline use of digoxin was not associated with increased all-cause admission to hospital (14·83 *vs* 15·40 events per 100 patients-years; adjusted HR 1·02 [95% CI 0·95–1·10]; p=0·64). The figure provides the Kaplan-Meier curves for all-cause mortality, vascular death, sudden death, and admission to hospital by baseline digoxin use.

We also did Cox proportional hazards regression models with inverse probability weighting for propensity for the patient's digoxin treatment at baseline, which showed consistently increased hazard for all-cause mortality (HR 1·14; 95% CI 1·01–1·29; p=0·0402) and sudden death (1·32; 1·06–1·66; p=0·0156). In this model, vascular death (HR 1·16; 95% CI 1·00–1·36; p=0·0502) and all-cause hospital admission (1·00; 0·93–1·08; p=0·94) were not significantly associated with digoxin use. With a multivariable model for predictors of baseline digoxin use, we identified several variables associated with its use, including heart failure and geographic region (appendix).

To understand digoxin use during the study, we developed a time-dependent Cox proportional hazards regression model. Digoxin use during the study was associated with increased all-cause mortality and vascular and sudden death (table 3). In these time-dependent analyses, we deemed patients to be on digoxin throughout follow-up once they had started digoxin. As a sensitivity check, we repeated this analysis considering all digoxin switches on and off, except if the switch had happened in the last 2 weeks before the event of interest or the end of follow-up. We used this convention to remove likely confounding between digoxin switches close to the event of interest and deterioration of patients' health that probably led to both the digoxin switch and the event. In these analyses, we noted similar results, although the magnitude of the effect was attenuated (all-cause mortality: HR 1·13 [95% CI 1·00–1·27]; vascular death: 1·14 [0·98–1·32]); sudden death: 1·24 [0·99–1·55]).

	Before digoxin	After digoxin*	Adjusted† HR (95% CI)	Adjusted† p value
All-cause mortality	4·15 (641)	5·56 (573)	1·22 (1·08–1·37)	0·0011
Vascular death	2·61 (403)	3·62 (373)	1·22 (1·05–1·42)	0·0076
Sudden death	1·13 (174)	1·64 (169)	1·29 (1·03–1·61)	0·0266
All-cause admission to hospital	15·31 (2038)	15·00 (1309)	1·04 (0·97–1·12)	0·30
Stroke or systemic embolism	2·33 (354)	2·18 (221)	0·96 (0·81–1·15)	0·66
Myocardial infarction	1·03 (158)	1·12 (114)	1·15 (0·89–1·48)	0·28

Data for before and after digoxin are events per 100 patient-years (number of events). HR=hazard ratio. *Patients event-free at digoxin start. †Baseline adjustment covariates: age, sex, race, ethnic origin, region, body-mass index, systolic blood pressure, diastolic blood pressure, type of atrial fibrillation, heart failure, hypertension, diabetes, stroke or transient ischaemic attack, chronic obstructive pulmonary disease, gastrointestinal bleed, liver disease, vascular disease, sleep apnoea, smoking, alcohol use, and aspirin, vitamin K antagonist, angiotensin-converting enzyme or angiotensin receptor blocker, β blocker, calcium channel blocker, clopidogrel, heparin, statin, and antiarrhythmic use, and creatinine clearance and heart rate.

Table 3: **Association between time-varying digoxin pharmacotherapy and all-cause mortality, cardiovascular death, sudden cardiac death, and admission to hospital endpoints using time-dependent Cox proportional hazards regression models**

We did not note a significant interaction between the increased risk associated with digoxin use and the randomised treatment of warfarin or rivaroxaban for all-cause mortality, vascular death, or sudden death (appendix). We noted no significant time-dependent interaction between the increased risk associated with digoxin use and the presence of heart failure for all-cause mortality, vascular death, and sudden death (table 4). Additionally, when we assessed heart failure status by either NYHA status or left ventricular ejection fraction (appendix), we noted no significant interaction with consistent hazard associated with digoxin use. We did, however, note a significant interaction between sex, digoxin use, and the outcome of all-cause mortality and vascular death, but not for sudden death or all-cause admission to hospital (table 5).

Discussion

The findings of this post-hoc analysis of ROCKET AF suggest that digoxin treatment is associated with an increase in the risk of all-cause mortality, vascular death, and sudden death in patients with AF. This increased risk was present after adjustment for baseline variables, adjustment with inverse probability weighting for

See Online for appendix

	Before digoxin		After digoxin in patients event-free at digoxin start		Adjusted HR (95% CI)*		Interaction p value
	No HF	HF	No HF	HF	No HF	HF*	
All-cause mortality	3·34 (235)	4·84 (406)	4·31 (125)	6·05 (448)	1·19 (0·95–1·48)	1·23 (1·07–1·41)	0·79
Vascular death	1·83 (129)	3·26 (274)	2·34 (68)	4·12 (305)	1·18 (0·88–1·59)	1·24 (1·05–1·47)	0·78
Sudden death	0·77 (54)	1·43 (120)	0·90 (26)	1·93 (143)	1·14 (0·71–1·82)	1·33 (1·04–1·71)	0·56
All-cause admission to hospital	14·85 (900)	15·69 (1138)	13·94 (344)	15·43 (965)	0·96 (0·85–1·09)	1·08 (0·99–1·18)	0·12

Data for before and after digoxin are events per 100 patient-years (number of events). HR=hazard ratio. HF=heart failure. *HRs for digoxin versus no digoxin.

Table 4: **Time-dependent HF–digoxin interactions**

	Before digoxin		After digoxin in patients event-free at digoxin start		Adjusted HR (95% CI)*		Interaction p value
	Men	Women	Men	Women	Men	Women	
All-cause mortality	4·38 (424)	3·76 (217)	6·39 (379)	4·43 (194)	1·34 (1·17–1·55)	1·01 (0·83–1·23)	0·0179
Vascular death	2·71 (262)	2·44 (141)	4·22 (250)	2·81 (123)	1·41 (1·17–1·68)	0·93 (0·73–1·20)	0·0076
Sudden death	1·29 (125)	0·85 (49)	2·07 (123)	1·05 (46)	1·42 (1·10–1·84)	0·99 (0·66–1·50)	0·13
All-cause admission to hospital	15·93 (1321)	14·29 (717)	15·75 (784)	14·02 (525)	1·04 (0·95–1·14)	1·04 (0·93–1·17)	0·96

Data for before and after digoxin are events per 100 patient-years (number of events). HR=hazard ratio. *HRs for digoxin versus no digoxin.

Table 5: **Time-dependent sex–digoxin interactions**

propensity for baseline digoxin use, and time-dependent adjustment for digoxin use during the study. Additionally, we noted no significant digoxin–heart failure interaction for all-cause mortality, vascular death, or sudden death. We noted a significant digoxin–sex interaction with the increased hazard associated with male patients with AF for all-cause mortality and vascular death. Taken together, these findings could have important implications for care of patients with AF (panel).

First and foremost, these results should be interpreted in the context of the limitations of the analysis. Although we have found a consistent hazard, this report is a post-hoc observational analysis in which digoxin treatment was not randomly assigned to patients. Despite the fact that we used different analytic techniques that showed consistent results, we cannot rule out the possibility of unmeasured variables that could have affected the results. As such, we report an association between digoxin use and increased all-cause mortality, vascular death, and sudden death, but causality versus residual confounding by potential unmeasured variables cannot be established. Of interest, we did not note a hazard with digoxin with respect to other adjudicated endpoints such as stroke, systemic embolism, or myocardial infarction, reducing the likelihood of significant unmeasured comorbidities. Nevertheless, scepticism might be warranted regarding the potential hazard with digoxin treatment in patients with AF.

However, for the clinical community, these findings should sound a note of caution with respect to digoxin use. With the absence of randomised trials in patients with AF receiving digoxin, this report represents the largest post-hoc analysis from a randomised controlled trial in this patient population. Even in light of the noted limitations, the possibility of a clinical benefit with digoxin treatment seems unlikely in patients with AF with or without HF. Furthermore, digoxin as monotherapy has been shown to be an ineffective rate-controlling drug in patients with ambulatory AF.[17] Yet digoxin continues to be frequently used in patients with AF. In ROCKET AF, a contemporary trial of stroke prevention in patients with AF, digoxin was prescribed in 37% of patients at baseline, and 41% of patients were exposed to digoxin during the trial. Similar rates of baseline digoxin use have been reported in other AF clinical trials[18,19] and in an analysis of patients enrolled in Medicare Part D (who have optional benefits for prescription drugs available to all people with Medicare),[20] which reported digoxin use in 30% of patients. Crude rates of digoxin use at baseline were greater than one of three patients enrolled in four of five geographical regions, with North America having disproportionately high use, supporting the fact that digoxin use for patients with AF is continuing and widespread. Moreover, in this analysis, only 65% of patients were on baseline β blockers and less than 30% were on calcium channel blockers, both of which can be deemed front-line drugs for rate control in AF.

Present guidelines recommend digoxin for rate control in patients with AF and heart failure.[1] Patients with heart failure were well represented in ROCKET AF, with 62·5% of patients reporting a baseline history of heart failure. This rate is by contrast with the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, which has also provided a post-hoc assessment of digoxin treatment in patients with AF—investigators of this trial reported baseline heart

failure in 23·1% of patients.[9,10,21] However, authors of a propensity-matched analysis of AFFIRM noted no mortality hazard with digoxin.[10] Additionally, although investigators of the Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate (RACE II) study[17] reported no increase in mortality or cardiovascular admission to hospital with use of digoxin, this study was limited by fewer than 300 patients and was probably underpowered to detect a possible digoxin hazard. In this analysis, a history of heart failure was significantly associated with baseline digoxin use (p<0·0001), and digoxin use was associated with significant increases in all-cause mortality, vascular death, and sudden death in those with heart failure.

The findings from this analysis are consistent with previous studies[7,9] that have associated digoxin treatment with an increase in mortality in patients with AF without heart failure. In the AFFIRM trial,[9] patients with AF and no heart failure had a 37% relative increase in risk of mortality. Similar results were noted from the Registry of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA) study, in which use of digoxin in patients admitted to the coronary care unit with AF and no history of heart failure was associated with a significant increase in 1 year mortality (adjusted relative risk 1·42; 95% CI 1·29–1·56). In this analysis, we did not note a significant heart failure–digoxin treatment interaction for all-cause mortality, vascular death, or sudden death. Additionally, this analysis has the strength of having independent masked adjudication of clinical events, specifically vascular and sudden death.

Some have suggested differing modes of death in patients with AF with and without heart failure, with sudden death occurring more frequently in patients with AF with heart failure than in those without.[22,23] In our analysis, although we noted sudden death to occur more frequently in patients with AF than in those without, we did not note any significant time-dependent interaction between the increased risk of sudden death with digoxin use and presence of heart failure. Mechanistically, the increased hazard seen with digoxin use in ROCKET AF is consistent with other clinical experience. Digoxin is a cardiac inotrope with important drug interactions, and dosing in elderly patients with changing renal function is difficult to manage. In the context of patients with AF receiving anticoagulation and antiarrhythmic treatment, the sudden death signal seen could be seen as mechanistically consistent.

Aside from a direct mechanistic effect of digoxin, the findings from this analysis could be the result of how the treatment was used. Because no specific recommendations for the use (dosing and monitoring) of digoxin were outlined in the trial, we cannot exclude the chance that the hazard associated with digoxin treatment could have been associated with how the drug was used. Findings from a large randomised trial of digoxin in patients with heart failure, the Digitalis Investigation Group (DIG) trial,[6] showed digoxin reduced admission to hospital, but did not reduce cardiovascular outcomes compared with placebo. The findings are limited by the exclusion of AF and requirement of sinus rhythm at baseline. Additionally, a post-hoc analysis[24] of the Digitalis Investigation Group trial associated high digoxin concentrations with increased mortality in male patients with heart failure and normal sinus rhythm. A limitation of this analysis is the absence of data for the daily dose and serum concentrations of digoxin, which were not collected in ROCKET AF. Thus, we were unable to analyse the effect of high digoxin doses and serum concentrations on outcomes, including sudden death. However, by including factors known to affect the pharmacokinetics of digoxin, such as renal function (ie, creatinine clearance) and bodyweight (ie, body-mass index), as covariates in the statistical models, we probably reduced the chance that the identified hazard with digoxin treatment was due solely to increased drug exposure. Nevertheless, this analysis shows overall outcomes of how digoxin is used in contemporary clinical practice.

In this post-hoc analysis of ROCKET AF, digoxin treatment was used frequently in patients with AF, and it was associated with an increased risk of all-cause mortality, vascular death, and sudden death. We noted this increased cardiovascular hazard in those with and without heart failure, without a significant treatment interaction. In view of the availability of other drugs for rate control in patients with AF, such as β blockers and non-dihydropyridine calcium channel antagonists, the findings of this study suggest digoxin treatment should not be deemed a first-line treatment and should be used with caution in patients with AF with or without heart failure. Further randomised studies aimed at understanding optimum rate

Panel: Research in context

Systematic review

We searched Medline from Jan 1, 1970 to July 31, 2014, with no language restrictions. We used the search terms "digoxin" and "atrial fibrillation" individually and in combination. We restricted search results to phase 3 clinical trials or systematic reviews. We did not use any formal scoring criteria to assess the quality of evidence. We did not identify any phase 3 randomised trials. We identified three recently published systematic reviews of atrial fibrillation (AF) treatment strategies; however, none of them included a meta-analysis of the effect of digoxin on mortality or cardiovascular events because of the small number of studies that assessed similar outcomes.[14–16]

Interpretation

This post-hoc analysis of the Rivaroxaban Versus Dose-Adjusted Warfarin for Stroke (ROCKET AF) trial provides the largest analysis so far of digoxin use and associated outcomes in patients with AF enrolled in a phase 3 clinical trial. In light of the absence of randomised controlled trials testing digoxin in patients with AF, and the inconsistency in results from published observational analyses, this analysis represents an important contribution to the existing literature. This analysis further shows the need for a randomised controlled trial to test digoxin treatment in patients with AF, including patients with and without heart failure.

control therapies, including the role of digoxin, in patients with AF are needed. The results of this analysis also suggest a need for reconsideration of present treatment recommendations for digoxin in patients with AF.

Contributors

JBW and MRP were responsible for conception and design of the work, contributed to collection and interpretation of data, and drafted the first version of the manuscript. JLH, GB, DES, KWM, GJH, SDB, CCN, KAAF, RMC, and JPP contributed to data collection, data revision, and the content and critical revision of the manuscript. YL and SRS did the statistical analyses and contributed to the content and critical revision of the manuscript.

Declaration of interests

JLH reports consulting fees from Bayer HealthCare AG, Boehringer Ingelheim, Daiichi Sankyo, Johnson & Johnson, Ortho-McNeil-Janssen Pharmaceuticals, Pfizer, Sanofi-Aventis, AstraZeneca, Biotronik, Boston Scientific, Janssen, and Medtronic. GB reports honoraria from Bayer HealthCare and Bristol-Myers Squibb and Pfizer, and consulting and advisory board fees from Bayer HealthCare, Bristol-Myers Squibb and Pfizer, and Sanofi-Aventis. DES reports consulting and advisory board fees from Bayer HealthCare, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Johnson & Johnson, Merck, and Pfizer, and research grants from Bristol-Myers Squibb and Johnson & Johnson. KWM reports consulting fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Forest, Johnson & Johnson, and WebMD. GJH reports honoraria for consulting and speaking at sponsored scientific symposia from Bayer and Medscape (theheart.org). SB is an employee of Bayer HealthCare AG. CCN is an employee of Janssen Research & Development. KAAF reports consulting fees and honoraria from Boehringer Ingelheim, Sanofi-Aventis, AstraZeneca, Johnson & Johnson and Bayer, and Janssen, and research grants from Eli Lilly. RMC reports research grants from Amylin, Bristol-Myers Squibb, Eli Lilly & Company, Janssen Research & Development, Merck, and Novartis; consulting fees from Amgen, Medscape (theheart.org), and Novartis; and has equity in N30 Pharma and Portola. JPP reports consulting fees and honoraria from Medtronic and Janssen Pharmaceuticals, and research grants from ARCA biopharma, GE Healthcare, Johnson & Johnson, ResMed, and Boston Scientific. MRP reports consulting fees and honoraria from Bayer Healthcare, Ortho-McNeil-Janssen, Medscape (theheart.org), and Ikaria, and research grants from Janssen, Maquet, AstraZeneca, the National Heart Lung and Blood Institute, and Genzyme. JBW, SRS, and YL declare no competing interests.

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