ARISTOTLE

ACC.17
66th Annual Scientific Session & Expo

Digoxin And Mortality in Patients With Atrial Fibrillation With and Without Heart Failure: Does Serum Digoxin Concentration Matter?

Renato D. Lopes, MD, PhD, FACC
on behalf of the ARISTOTLE Investigators

Duke Clinical Research Institute

UCR
Uppsala Clinical Research Center

Disclosures

- The ARISTOTLE trial was sponsored by Bristol-Myers Squibb and Pfizer.
- The present analysis was sponsored by the Duke Clinical Research Institute.
- The serum digoxin measurements were performed in blood samples stored in the Uppsala Biobank (UCR, Uppsala).

Background

- Digoxin is used in ≈ 30% of patients with atrial fibrillation (AF) worldwide, despite the lack of randomized clinical trials to assess its efficacy and safety in this setting.[1–3]
- Current AF guidelines recommend digoxin for rate control in patients with AF with and without heart failure (HF).[4,5]
- There are no specific recommendations about serum digoxin concentration monitoring in the AF guidelines.

[1]Allen LA, et al. J Am Coll Cardiol 2015;65:2691-8. [2]Washam JB, et al. Lancet 2015;385:2363-70. [3]Granger CB, et al. N Engl J Med 2011;365:981-92. [4]January CT, et al. Circulation 2014;130:2071-104. [5]Kirchof P, et al. Eur Heart J 2016;37:2893-962.

Research Context: ''A Controversial Topic''

European Heart Journal
doi:10.1093/eurheartj/ehv143

CLINICAL RESEARCH

Atrial fibrillation

Digoxin-associated mortality: a systematic review and meta-analysis of the literature

J Am Coll Cardiol. 2015 June 30; 65(25): 2691–2698. doi:10.1016/j.jacc.2015.04.045.

Digoxin use and subsequent outcomes among patients in a contemporary atrial fibrillation cohort

Larry A. Allen, MD, MHS*, Gregg C. Fonarow, MD†, DaJuanicia N. Simon, MS‡, Laine E. Thomas, PhD‡, Lucas N. Marzec, MD*, Sean D. Pokorney, MD, MBA‡, Bernard J. Gersh, MB

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)

Jeffrey B Washam, Susanna R Stevens, Yuliya Lokhnygina, Jonathan L Halperin, Günter Breithardt, Daniel E Singer, Kenneth W Mahaffey, Graeme J Hankey, Scott D Berkowitz, Christopher C Nessel, Keith A A Fox, Robert M Califf, Jonathan P Piccini, Manesh R Patel, for the ROCKET AF Steering Committee and Investigators

European Heart Journal (2013) **34**, 1481–1488

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

European Heart Journal (2013) **34**, 1489–1497

Lack of evidence of increased mortality among patients with atrial fibrillation taking digoxin: findings from *post hoc* propensity-matched analysis of the AFFIRM trial

European Heart Journal (2013) **34**, 1468–1470

Digoxin for patients with atrial fibrillation and heart failure: paradise lost or not?†

European Heart Journal (2013) **34**, 1465–1467

When 'digoxin use' is not the same as 'digoxin use': lessons from the AFFIRM trial

(*Circ Cardiovasc Qual Outcomes.* 2013;6:511-513.)

Editorial

Digitalis, Yesterday and Today, But Not Forever

Lionel H. Opie, MD, DSc

Atrial Fibrillation with at Least One Additional Risk Factor for Stroke

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Inclusion risk factors
- Age ≥ 75 years
- Prior stroke, TIA, or SE
- HF or LVEF ≤ 40%
- Diabetes mellitus
- Hypertension

Randomize
double blind, double dummy
(n = 18,201)

Exclusion
- Mechanical prosthetic valve
- Severe renal insufficiency
- Need for aspirin plus thienopyridine

Apixaban 5 mg oral twice daily (2.5 mg BID in selected patients)

Warfarin (target INR 2–3)

Warfarin/warfarin placebo adjusted by INR/sham INR based on encrypted point-of-care testing device

Primary outcome: stroke or systemic embolism

Biomarker substudy
(n=14,892)
- Blood samples at baseline
- Plasma aliquots stored at -70ºC

Lopes RD, et al. Am Heart J 2010;159:331–9.
Granger CB, et al. N Engl J Med 2011;365:981–92.

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Objectives

Using data from the ARISTOTLE trial, we aimed to:

- Explore the association between digoxin use and mortality
  - According to serum digoxin concentration
  - In patients with and without HF
- Assess the efficacy and safety of apixaban versus warfarin in patients taking and not taking digoxin.

Unique Features of Our Study

- Detailed serial assessment of concomitant medications, including digoxin.
- Two types of analyses: prevalence (baseline digoxin) and incidence (new digoxin users).
- Measurement of serum digoxin concentration at baseline.
- Comprehensive covariate adjustment, including for biomarker levels (NT-proBNP, troponin, GDF-15).

Digoxin Use at Baseline
(Prevalence analysis)

- Mortality in patients taking or not taking digoxin at baseline was compared using a Cox model with propensity weighting.
- The propensity model included sociodemographic characteristics, medical history, vital signs, AF characteristics, concomitant medications, labs, and biomarkers.
- The association between baseline digoxin concentration and mortality after multivariable adjustment was explored.

Digoxin Started During the Study
(Incidence analysis: “new digoxin users”)

- Risk-set matching was used to identify controls for each patient who started digoxin (3:1).
- Matches were based on a time-dependent propensity score including baseline and post-baseline covariates measured prior to the time of matching.
- Baseline covariates were updated during follow-up.
- Matching was performed within region, clinical setting, and HF status.

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Digoxin and Mortality

MAIN RESULTS

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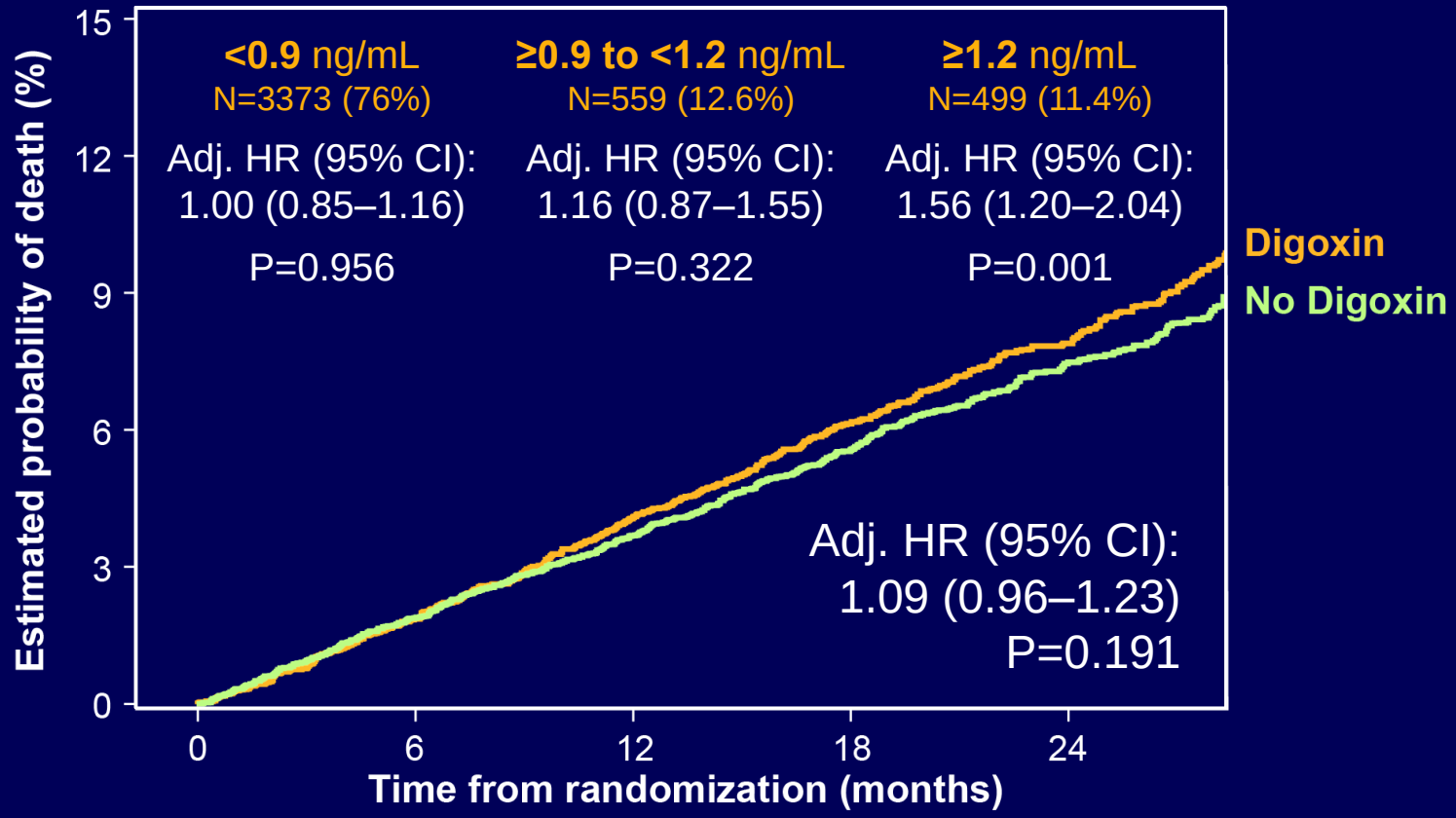
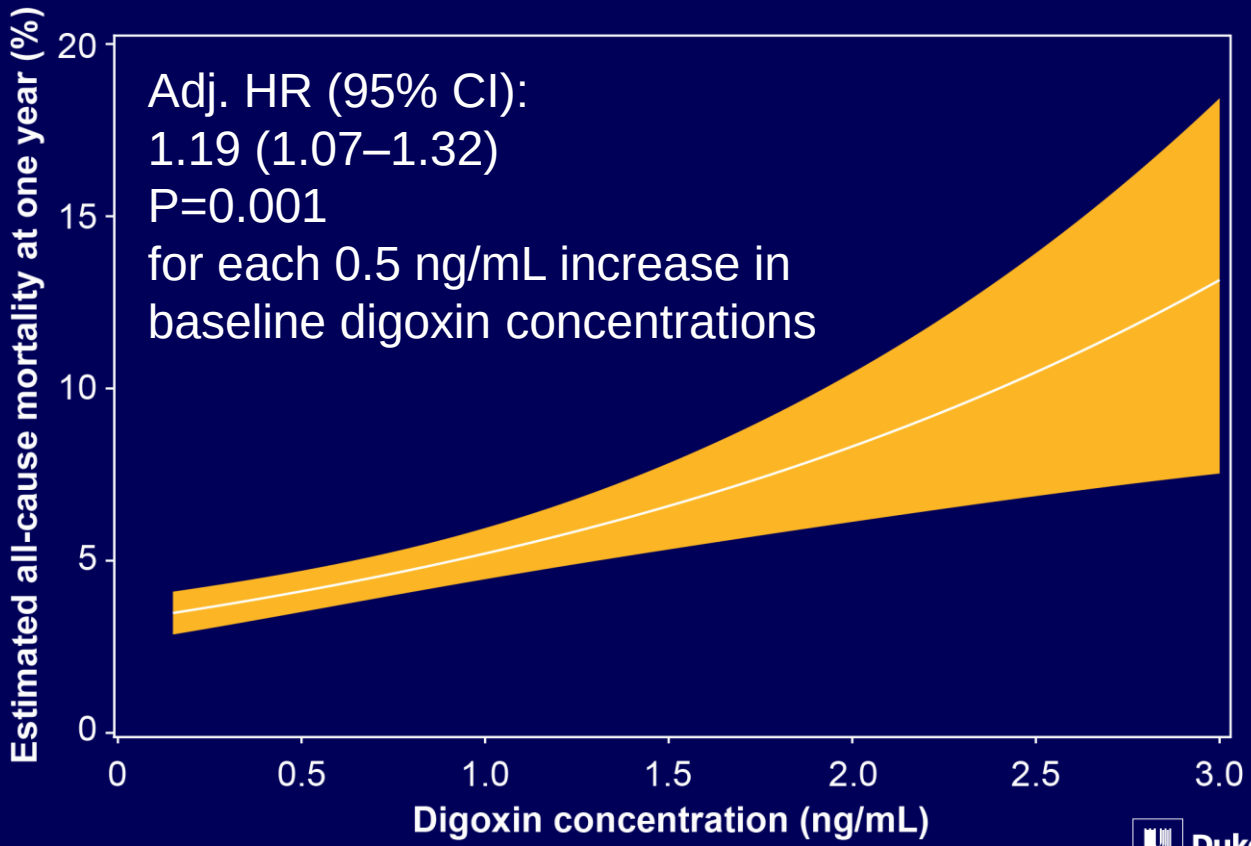
Baseline Serum Digoxin Concentration and Adjusted Mortality



Adjusted Mortality by Digoxin Concentration



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Characteristics of New Digoxin Users and Matched Controls

Characteristic		Digoxin (N=781)	Matched Control (N=2,343)
Age, median (25th, 75th), yrs		70 (63, 76)	70 (63, 76)
Female sex (%)		40.3	40.5
Prior stroke, TIA, or SE (%)		23.9	23.0
Heart failure/Left ventricular dysfunction (%)		42.9	42.9
LVEF, median (25th, 75th), %		55 (47, 64)	56 (45, 63)
NYHA class (%):	I	46.3	50.5
	II	42.1	39.4
	III	11.4	9.7
	IV	0.8	0.3
Type of AF (%):	Paroxysmal	15.9	14.5
	Persistent / Permanent	84.1	85.5

Biomarkers and Antiarrhythmic Medications in New Digoxin Users and Matched Controls

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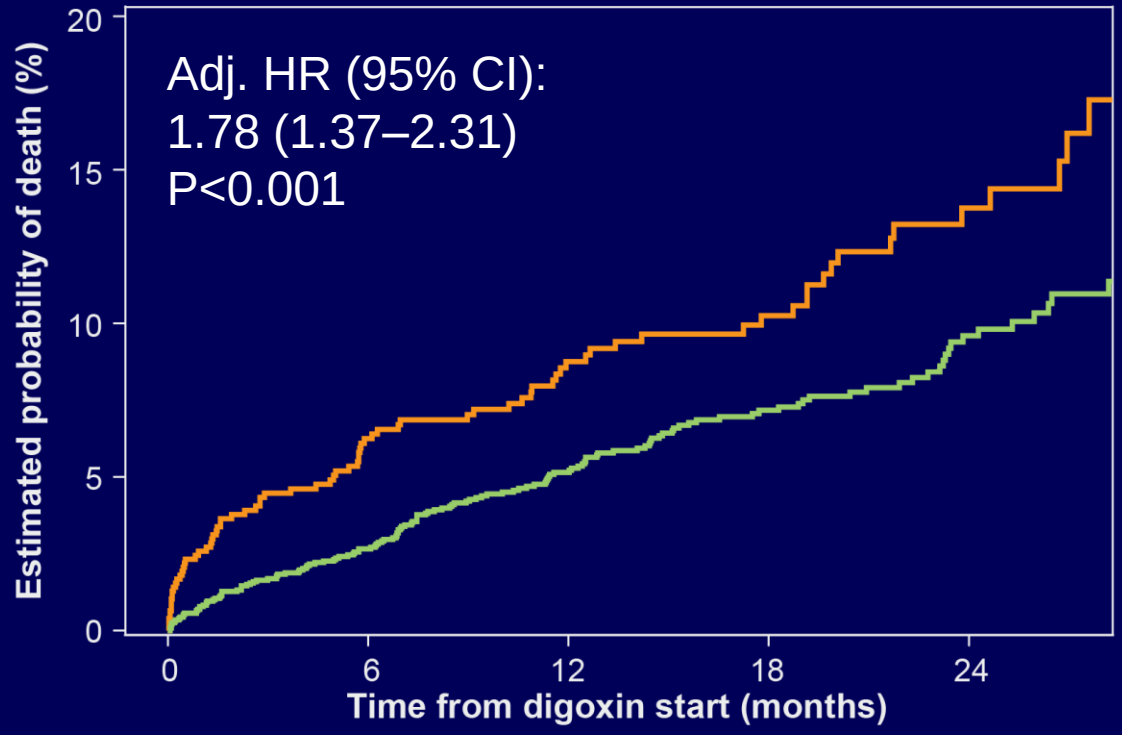
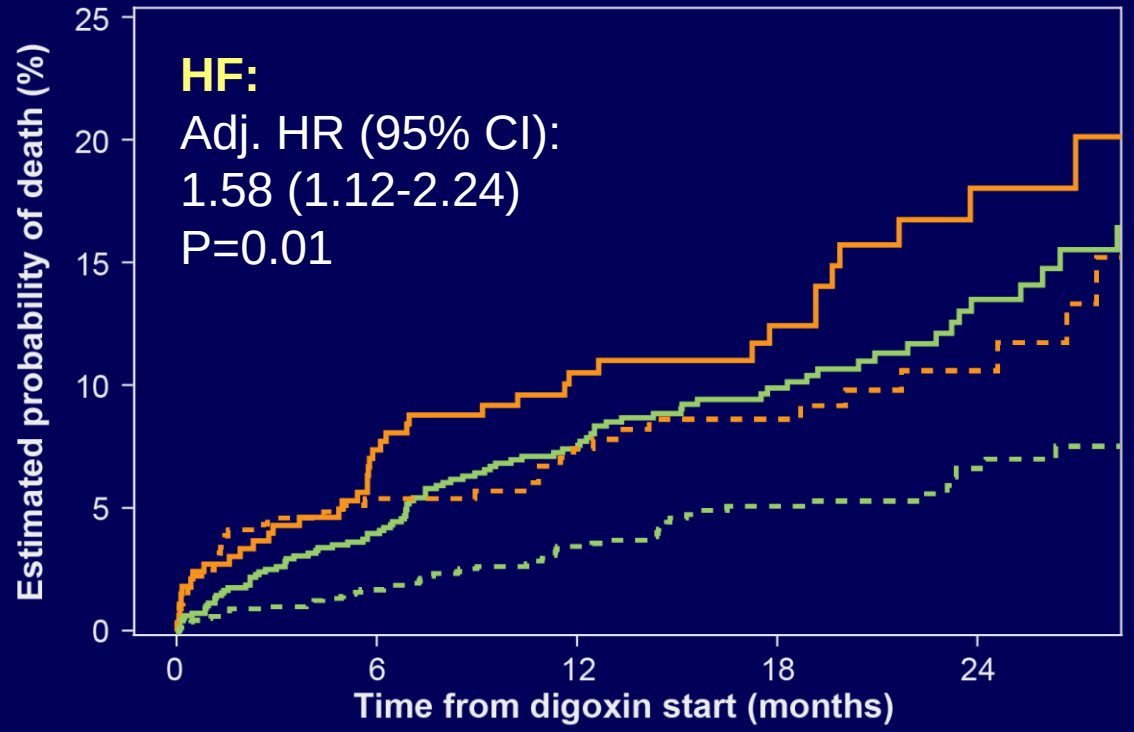
Characteristic	Digoxin (N=781)	Matched Control (N=2,343)
Creatinine clearance, median (25^{th}, 75^{th}), mL/min	69.8 (52.9, 90.4)	69.8 (52.7, 91.7)
NT-proBNP, median (25^{th}, 75^{th}), ng/L	838 (413, 1492)	834 (414, 1520)
Troponin I, median (25^{th}, 75^{th}), ng/L	5.4 (3.2, 10.4)	5.4 (3.1, 11.0)
Troponin T, median (25^{th}, 75^{th}), ng/L	10.8 (7.3, 16.4)	10.6 (7.3, 16.6)
GDF-15, median (25^{th}, 75^{th}), pg/mL	1466 (987, 2196)	1447 (981, 2138)
Class I antiarrhythmic drugs (%)	5.4	5.3
Beta blockers (%)	74.0	73.6
Sotalol (%)	3.6	3.5
Amiodarone (%)	13.6	13.8
Calcium channel blockers (%)	32.1	30.6

Adjusted Mortality in New Digoxin Users versus Matched Controls



New Digoxin Users	779	619	447	290	150
Matched Controls	2337	1910	1386	867	431

Adjusted Mortality in New Digoxin Users versus Matched Controls With and Without Heart Failure



New Digoxin Users / HF	333	266	191	120	62
New Digoxin Users / Non-HF	446	353	256	170	88
Matched Controls / HF	999	810	606	378	179
Matched Controls / Non-HF	1338	1100	780	489	252

New Digoxin Users / HF

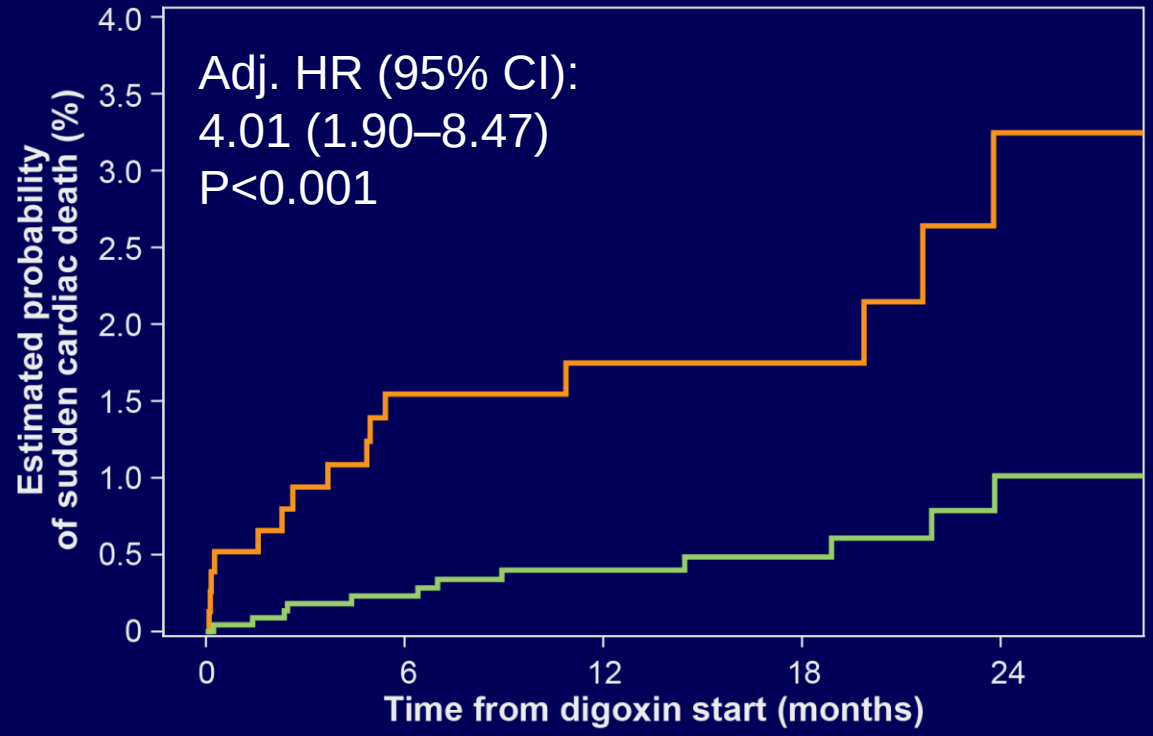
Matched Controls / HF

New Digoxin Users / Non-HF

Matched Controls / Non-HF

Non-HF:
Adj. HR (95% CI):
2.07 (1.39-3.08)
P=0.0003

Adjusted Sudden Death in New Digoxin Users versus Matched Controls



Apixaban versus Warfarin in Patients Using Digoxin and Not Using Digoxin at Baseline

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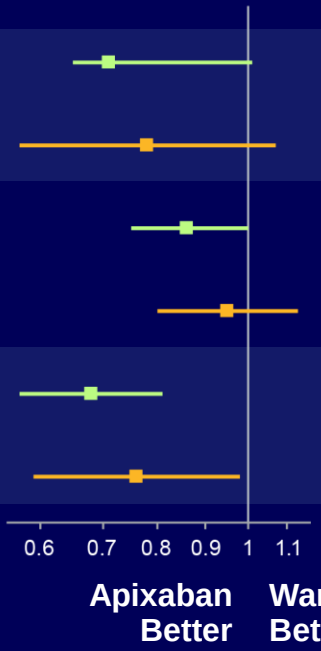
		Apixaban Rate[1] (Events)	Warfarin Rate[1] (Events)	HR (95% CI) Apixaban vs. Warfarin	Interaction p-value
Stroke/Systemic Embolism	No digoxin	1.25 (140)	1.54 (171)	0.71 (0.65-1.01)	0.87
	Digoxin	1.36 (72)	1.74 (91)	0.78 (0.57-1.07)	
All-cause Mortality *	No digoxin	2.96 (339)	3.43 (390)	0.86 (0.75-1.00)	0.42
	Digoxin	4.68 (253)	4.94 (265)	0.95 (0.80-1.13)	
Major Bleeding**	No digoxin	2.12 (216)	3.10 (310)	0.68 (0.57-0.81)	0.46
	Digoxin	2.21 (108)	2.88 (138)	0.76 (0.59-0.98)	



[1]Rate per 100 patient-years of follow-up.
* Apixaban (n=8963), Warfarin (n=8944).
**Apixaban (n=8934), Warfarin (n=8919).

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Conclusions

- In patients with AF currently taking digoxin, the risk of death is independently related to digoxin serum concentration and is highest in patients with concentrations ≥1.2 ng/mL.
- Initiating digoxin is independently associated with higher mortality in patients with AF, regardless of HF.
- The benefits of apixaban over warfarin are consistent in digoxin users and non-users.

Clinical Implication

- In the absence of randomized trial data showing its safety and efficacy, digoxin should not be prescribed for patients with AF, particularly if symptoms can be alleviated with other treatments.
- In patients with AF already taking digoxin, monitoring its serum concentration may be important, targeting blood levels <1.2 ng/mL.

THANKS TO ALL

ARISTOTLE Investigators and Patients

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Back-up Slides

Baseline Characteristics

Characteristic		Digoxin (N=5824)	No Digoxin (N=12,073)
Age, median (25th, 75th), yrs		69 (62, 76)	70 (63, 76)
Female sex		2234 (38.4)	4090 (33.9)
Current smoker		484 (8.3)	983 (8.1)
Prior stroke, TIA, or SE		1093 (18.8)	2376 (19.7)
LVEF, median (25th, 75th), %		53 (40, 60)	58 (50, 65)
NYHA class:	I	2424 (41.7)	7061 (58.6)
	II	2502 (43.0)	4044 (33.5)
	III	843 (14.5)	927 (7.7)
	IV	48 (0.8)	22 (0.2)
Type of AF:	Paroxysmal	341 (5.9)	2394 (19.8)
	Persistent / Permanent	5483 (94.1)	9676 (80.2)

Baseline Characteristics (continued)

Characteristic	Digoxin (N=5824)	No Digoxin (N=12,073)
Creatinine clearance, median (25th, 75th), mL/min	73.0 (55.0, 95.0)	74.0 (57.0, 95.0)
NT-proBNP, median (25th, 75th), ng/L	856 (474, 1469)	647 (317, 1146)
Troponin I, median (25th, 75th), ng/L	7.0 (4.1, 13.1)	4.8 (3.0, 8.8)
Troponin T, median (25th, 75th), ng/L	12.5 (8.5, 19.0)	10.3 (7.2, 15.5)
GDF-15, median (25th, 75th), pg/mL	1473 (1026, 2180)	1343 (960, 2000)
Class I antiarrhytmic drugs	62 (1.1)	524 (4.3)
Beta blockers	3586 (61.6)	7889 (65.3)
Sotalol	78 (1.3)	440 (3.6)
Amiodarone	463 (7.9)	1587 (13.1)
Calcium channel blockers	1526 (26.2)	4039 (33.5)

Clinical Setting of New Digoxin Users and Matched Controls

Setting where digoxin started:	Digoxin (N=781)	Matched Control (N=2,343)
During HF hospitalization (%)	6.0	6.0
During other hospitalization (%)	12.3	12.3
Out of hospital (%)	81.7	81.7

Discussion

Despite the observational nature of our analysis and potential for unmeasured confounding factors, the results appear to be consistent with a causal relationship between digoxin use and higher mortality.

- There was an independent association between baseline serum digoxin concentration and mortality.
- The estimated risk among new users was higher than among patients already using digoxin, which is consistent with a drug that increases early mortality.
- There was a marked and early increase in sudden death among new digoxin users with most of the deaths occurring in the first 6 months after digoxin initiation.