



PEUT ON ENCORE PRESCRIRE DES DIGITALIQUES AUX PATIENTS EN FIBRILLATION ATRIALE ?

J.Y. Le Heuzey
Hopital Georges Pompidou
Université René Descartes, Paris

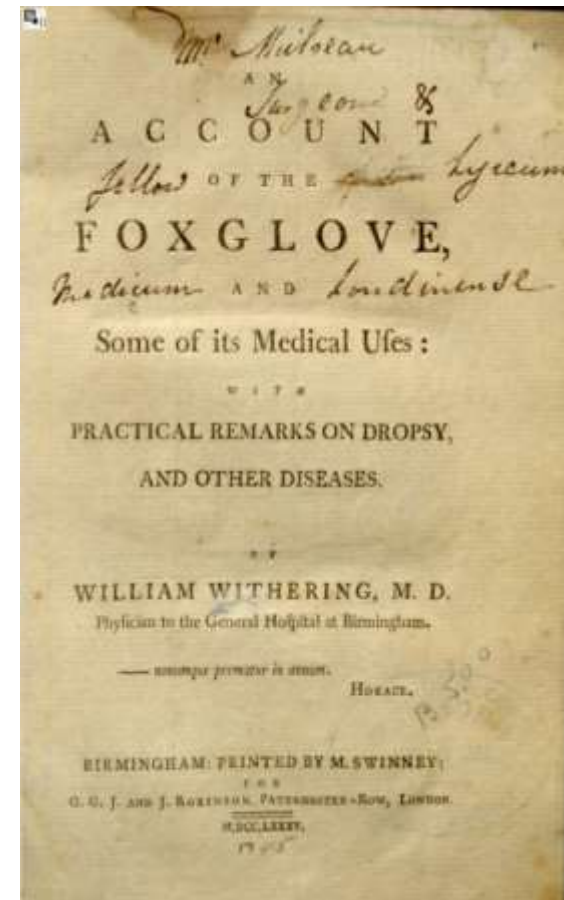
www.stcccv.org



Tabarka, 27 Octobre 2018

Disclosure

**Bayer, BMS / Pfizer, Boehringer Ingelheim, Daiichi-Sankyo,
Meda, Sanofi, Servier**



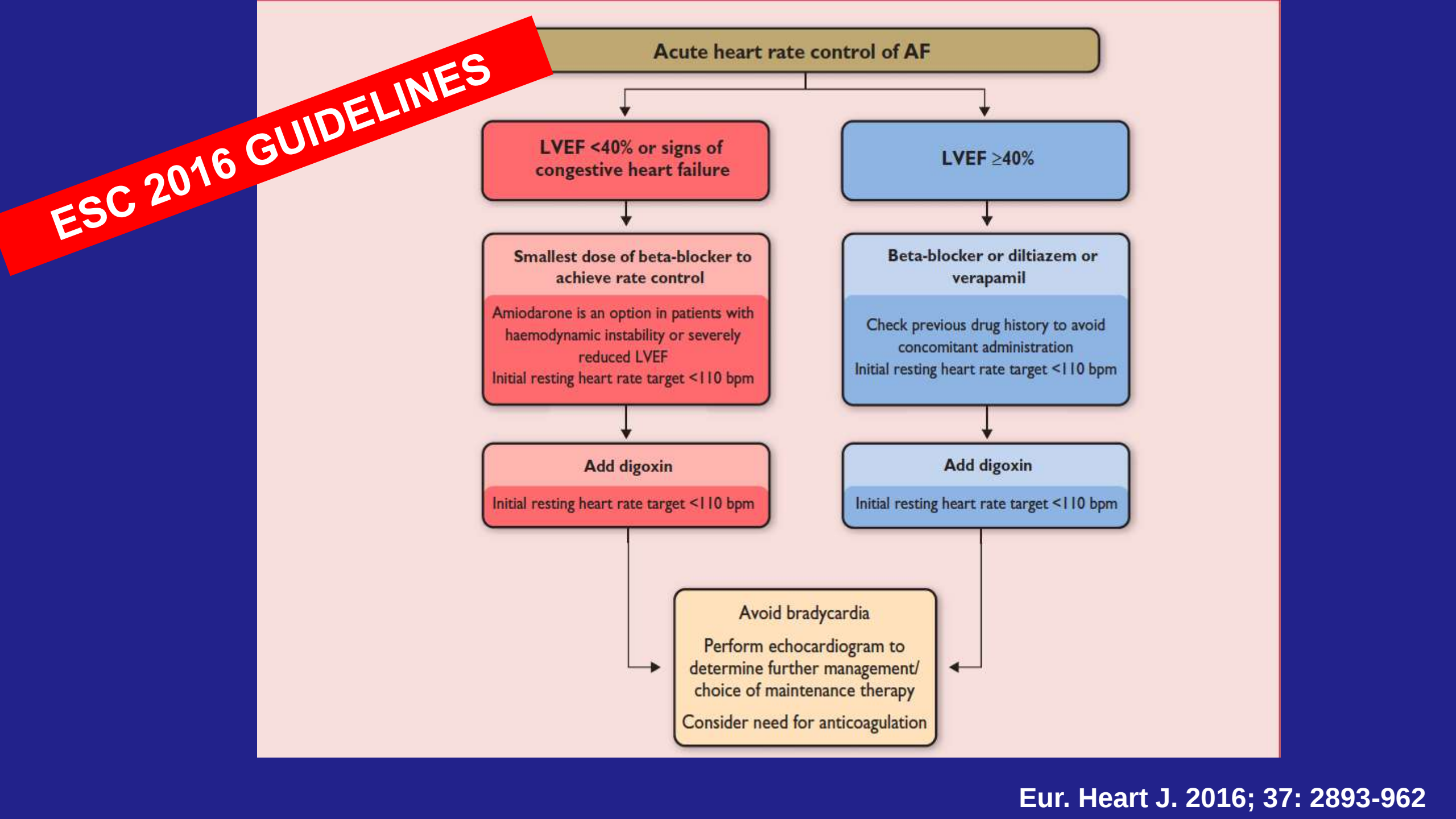
William Withering, 1785

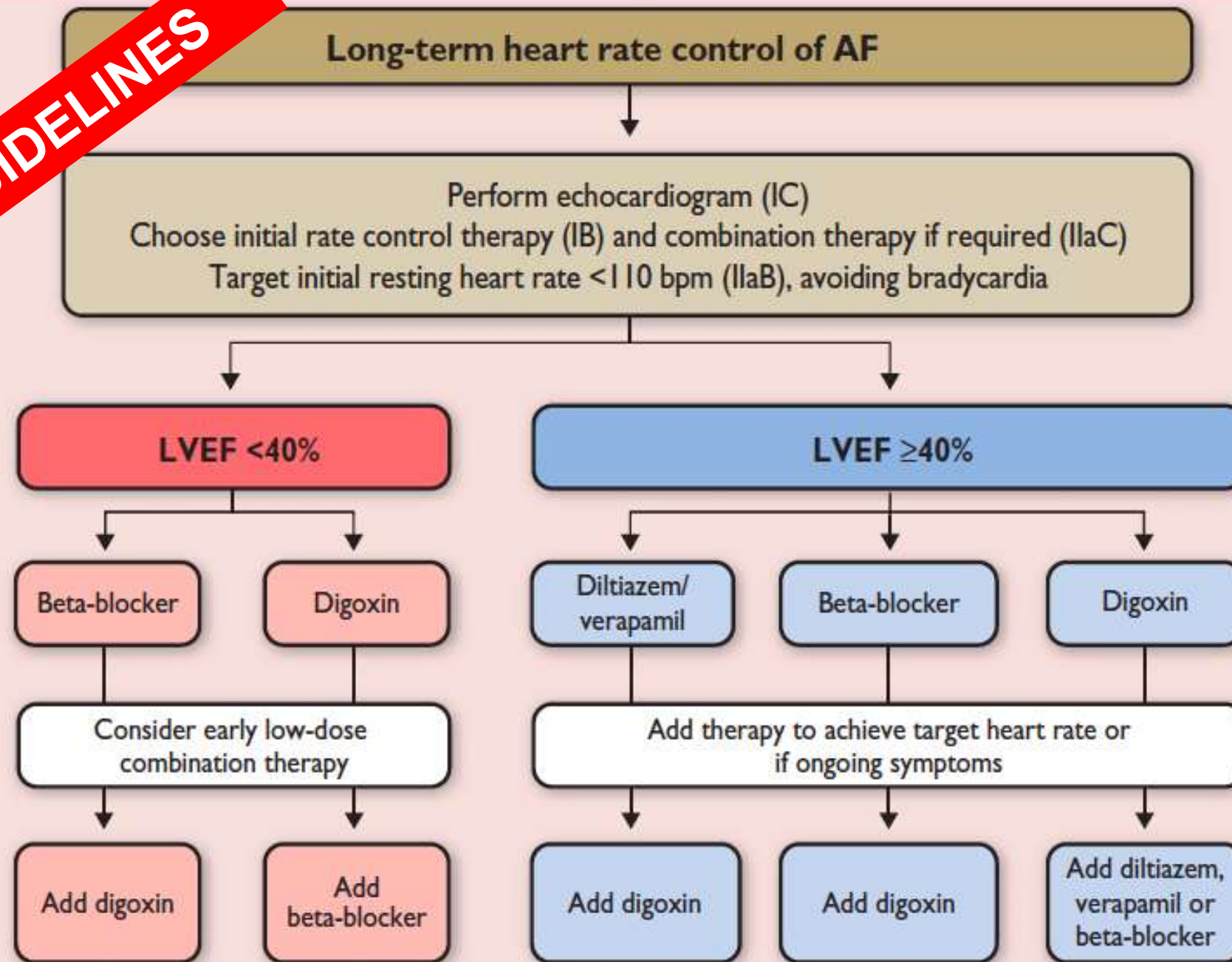
ACC/AHA/HRS 2014 AF Guidelines

- Digoxin is effective to control resting heart rate in patients with HFrEF. (class I, C)
- Digoxin plus beta-blocker (or plus a nondihydropyridine calcium channel antagonist in patients with HFpEF) is reasonable to control resting and exercise heart rate in pts with HF and AF. (class IIa, B)

ESC 2016 AF Guidelines

- Beta-blockers, digoxin, diltiazem, or verapamil are recommended to control heart rate in AF patients with LVEF $\geq 40\%$. (class I, B)
- Beta-blockers and/or digoxin are recommended to control heart rate in AF patients with LVEF $< 40\%$. (class I, B)





ESC 2016 GUIDELINES

Cardiac glycosides				
Digoxin	0.5 mg intravenous bolus (0.75–1.5 mg over 24 hours in divided doses).	0.0625–0.25 mg daily dose	Most common reported adverse symptoms are gastrointestinal upset, dizziness, blurred vision, headache and rash. In toxic states (serum levels >2 ng/mL), digoxin is proarrhythmic and can aggravate heart failure, particularly with co-existent hypokalaemia.	High plasma levels associated with increased risk of death. Check renal function before starting and adapt dose in patients with CKD. Contra-indicated in patients with accessory pathways, ventricular tachycardia and hypertrophic cardiomyopathy with outflow tract obstruction.
Digitoxin	0.4–0.6 mg intravenous bolus.	0.05–0.3 mg daily dose.		

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

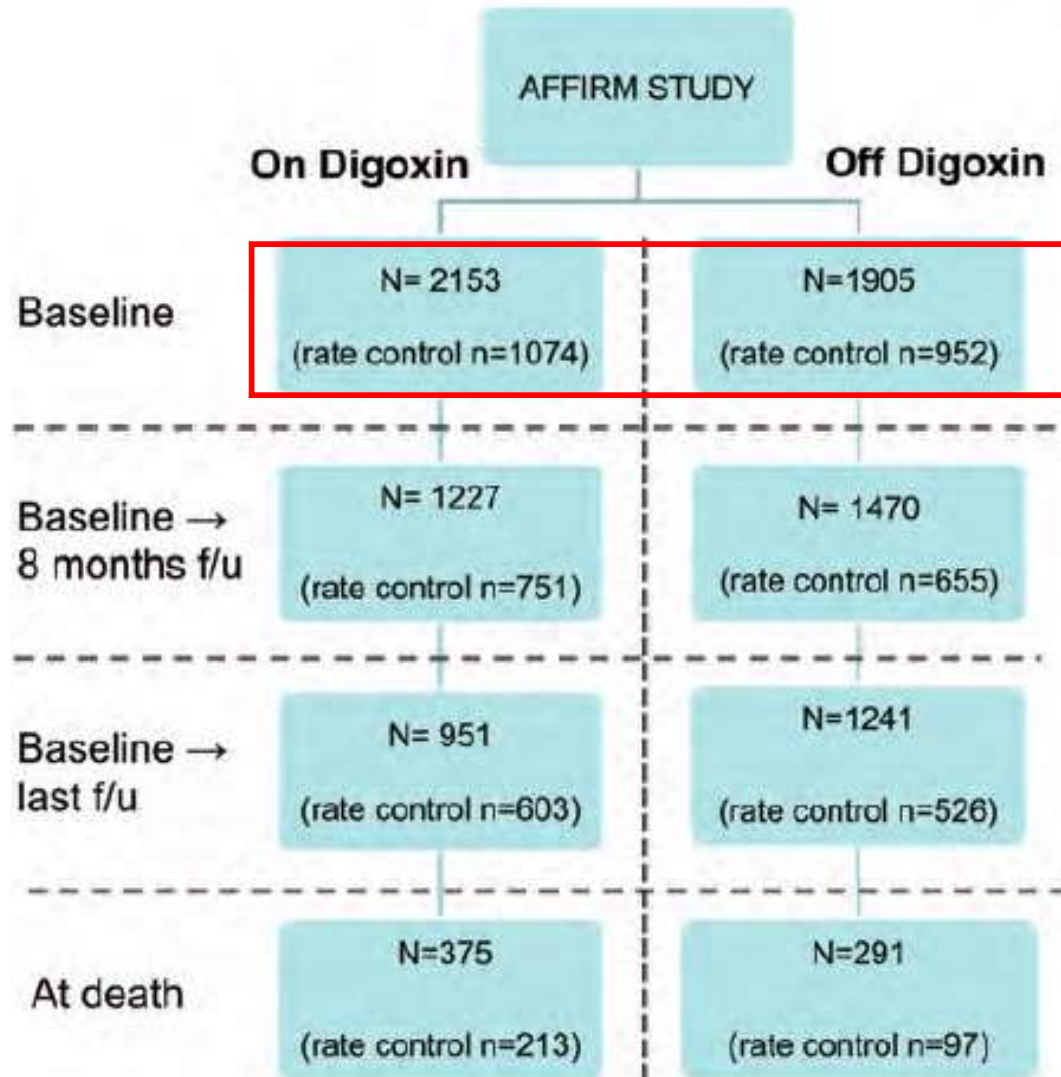
Matthew G. Whitbeck, Richard J. Charnigo, Paul Khairy, Khaled Ziada, Alison L. Bailey, Milagros M. Zegarra, Jignesh Shah, Gustavo Morales, Tracy Macaulay, Vincent L. Sorrell, Charles L. Campbell, John Gurley, Paul Anaya, Hafez Nasr, Rong Bai, Luigi Di Biase, David C. Booth, Guillaume Jondeau, Andrea Natale, Denis Roy, Susan Smyth, David J. Moliterno, and Claude S. Elayi*

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

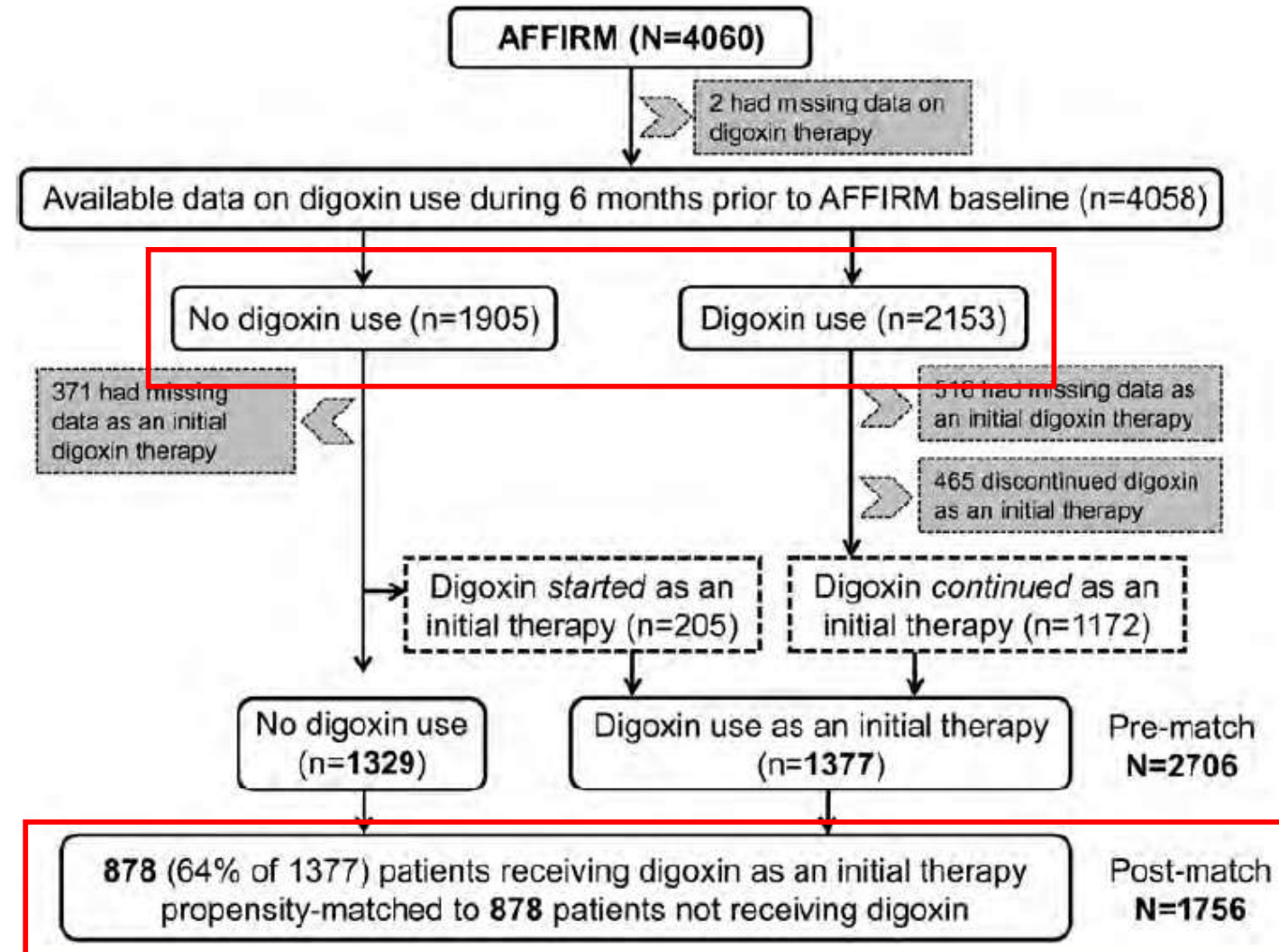
Mihai Gheorghiade¹, Gregg C. Fonarow², Dirk J. van Veldhuisen³, John G.F. Cleland⁴, Javed Butler⁵, Andrew E. Epstein⁶, Kanan Patel⁷, Inmaculada B. Aban⁷, Wilbert S. Aronow⁸, Stefan D. Anker⁹, and Ali Ahmed^{7,10*}

¹Northwestern University, Chicago, IL, USA; ²University of California, Los Angeles, CA, USA; ³University Medical Centre, Groningen, The Netherlands; ⁴Hull York Medical School, Kingston-Upon-Hull, UK; ⁵Emory University, Atlanta, GA, USA; ⁶University of Pennsylvania, Philadelphia, PA, USA; ⁷University of Alabama at Birmingham, 1720 2nd Avenue South, CH-19, Suite 219, Birmingham 35294-2041 AL, USA; ⁸New York Medical College, Valhalla, NY, USA; ⁹Center for Clinical and Basic Research, IRCCS San Raffaele, Rome, Italy; and ¹⁰Veterans Affairs Medical Center, Birmingham, AL, USA

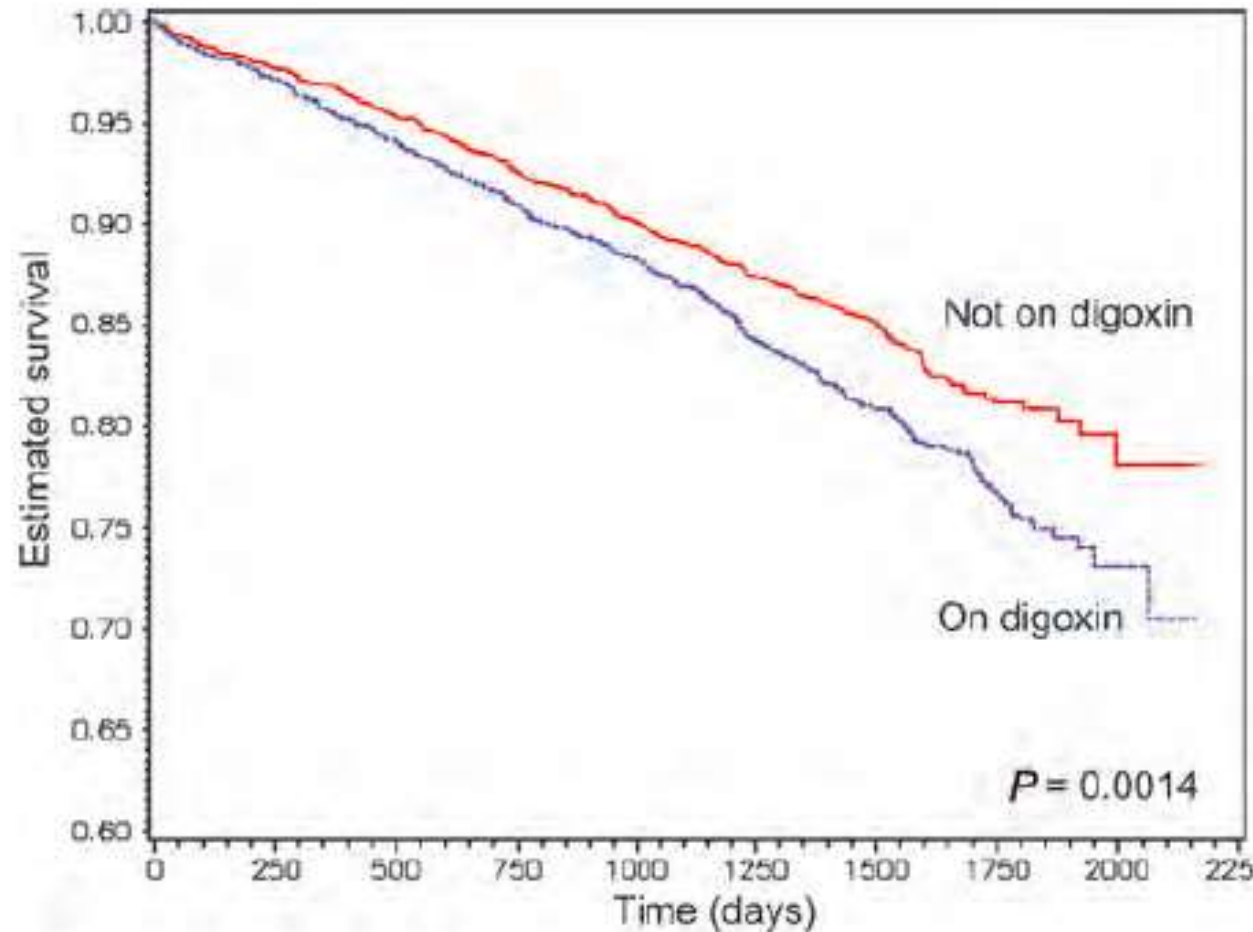
M.G. WHITBECK et al.



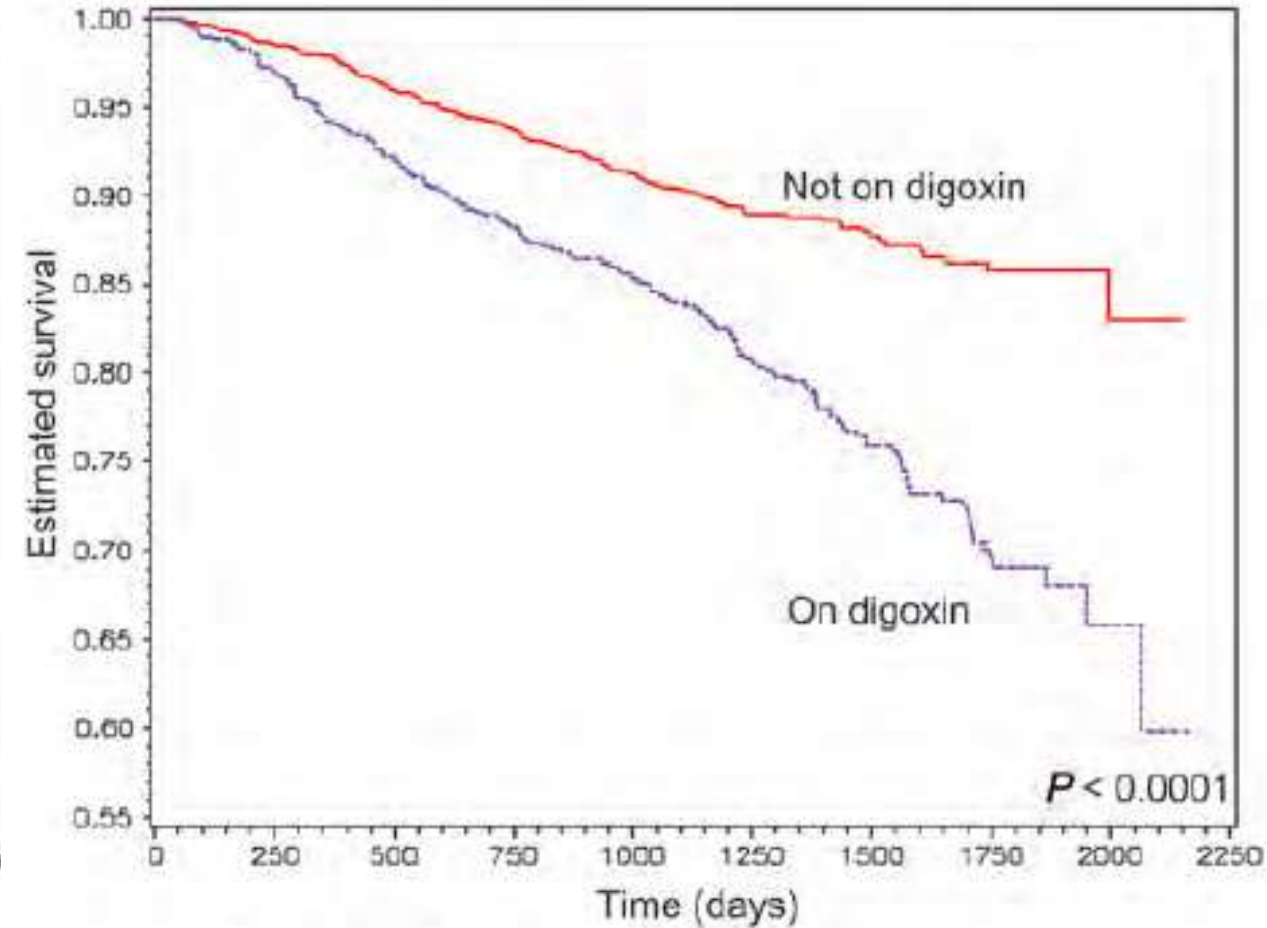
M. GHEORGHIADÉ et al.

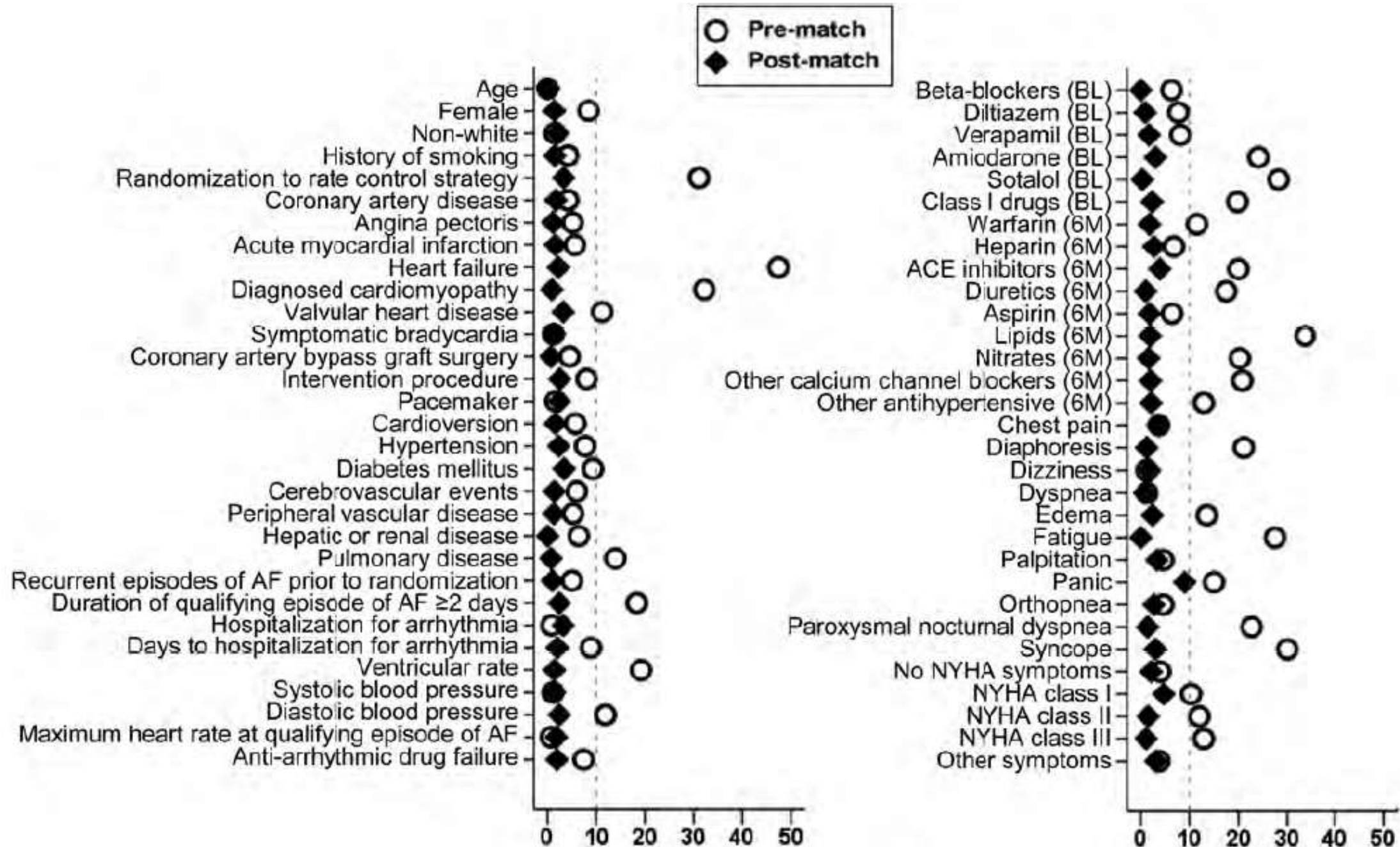


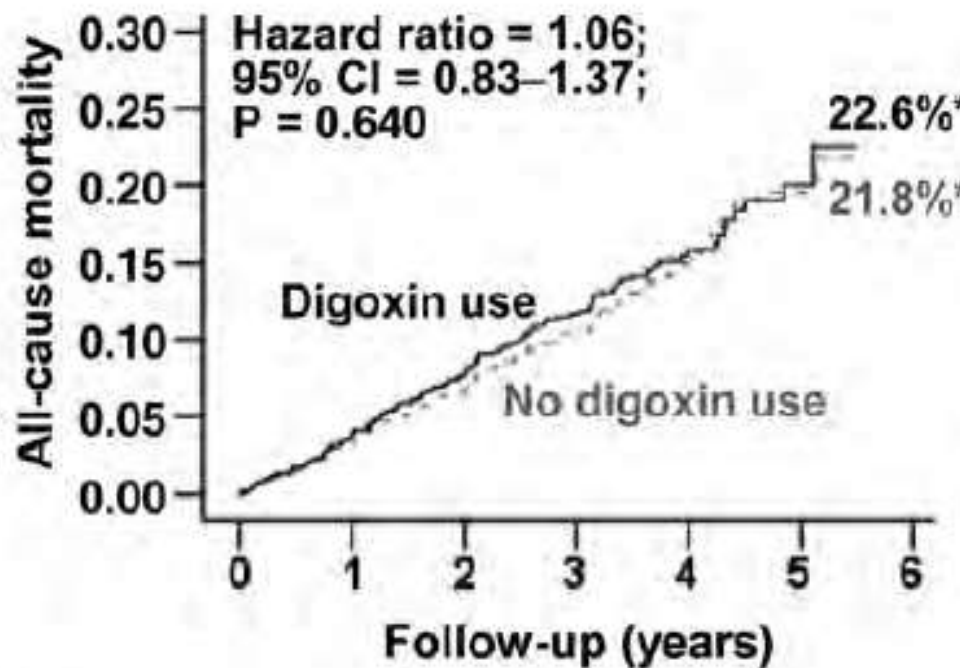
Digoxin use at baseline



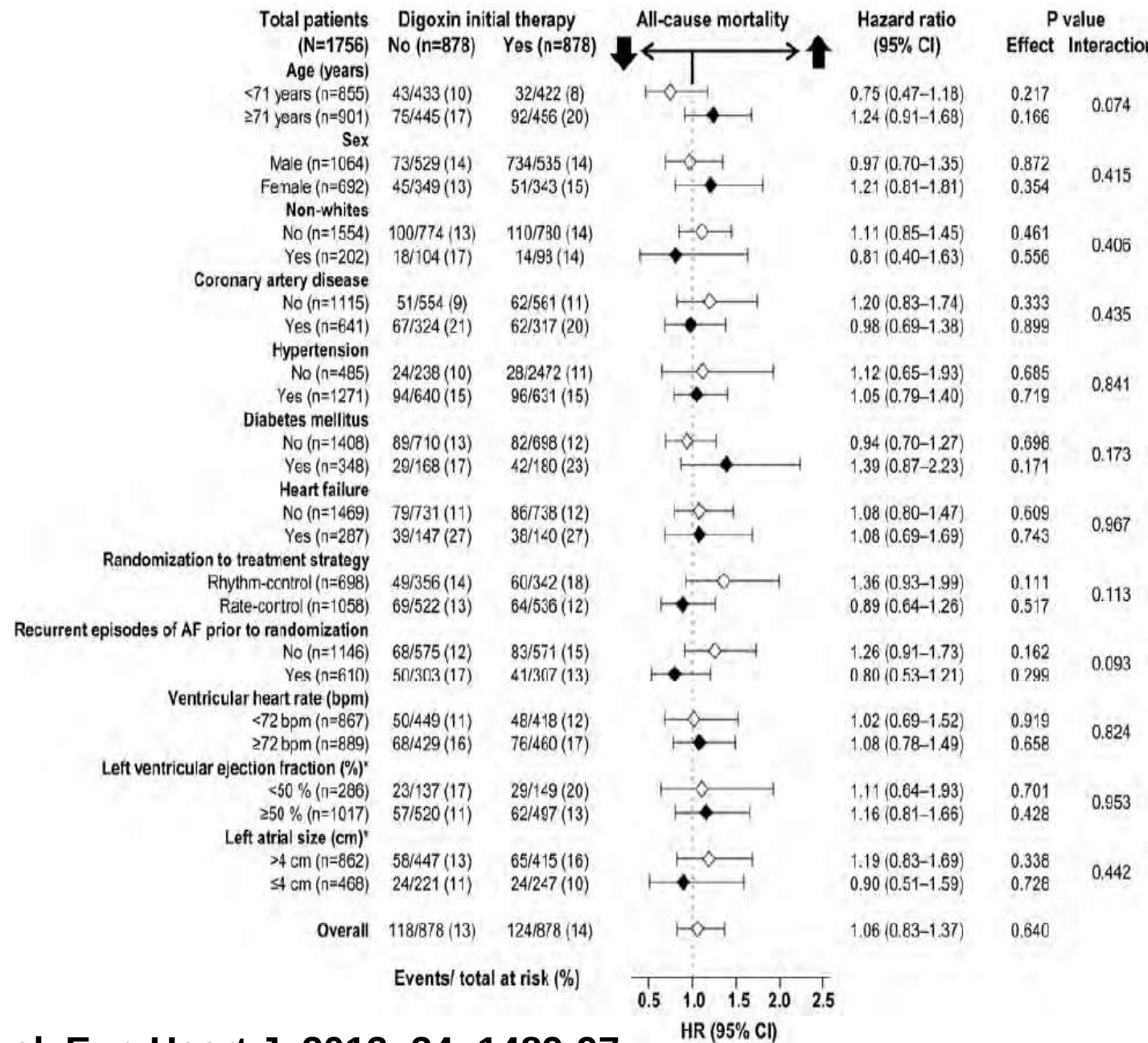
Digoxin use during the study







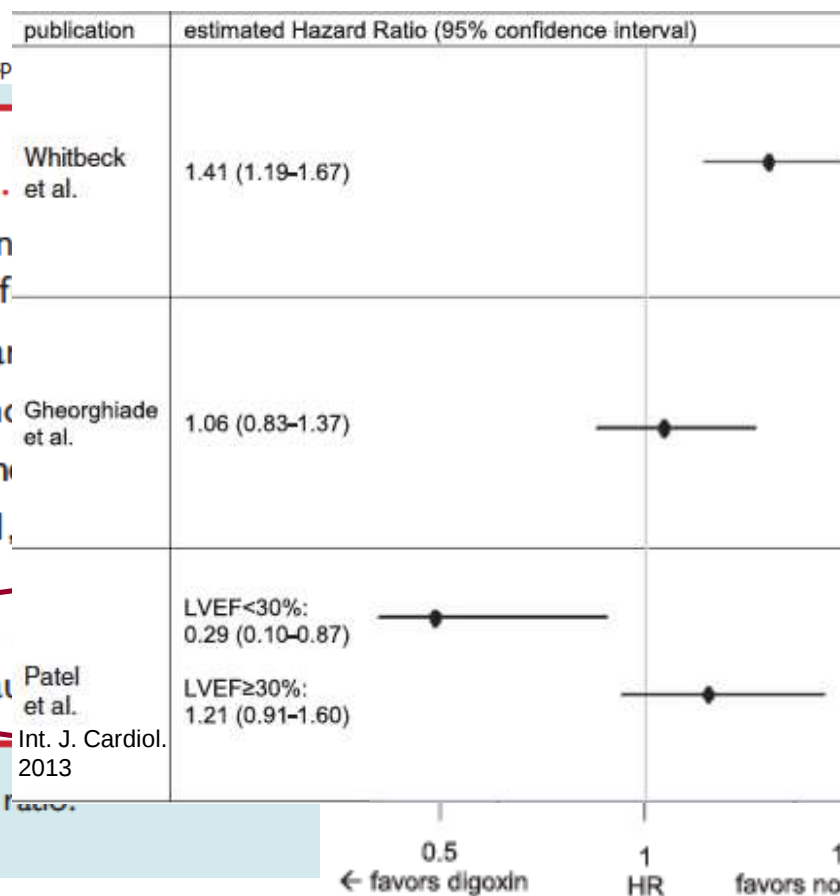
Number at risk						
No digoxin use	878	839	801	541	253	54
Digoxin use	878	835	781	534	240	48



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

Sabina A. Murphy*

TIMI Study Group, Brigham and Women's Hosp



Gheorghiade et al.

imized, observational analysis using
n randomized AFFIRM trial

aseline only

hort ($n = 1756$)

5% CI 0.83–1.37; $P = 0.640$

ce of increased mortality associated with
use as baseline initial therapy in patients with AF

Study design

Non-ran
data f

Time point digoxin used assessed

Time-var

Cohort

Full coh

Propensity method

Adjustm

Primary HR for digoxin and all-cause
mortality association

HR 1.41,

Main conclusion from authors

Digoxin
all-ca

AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio.

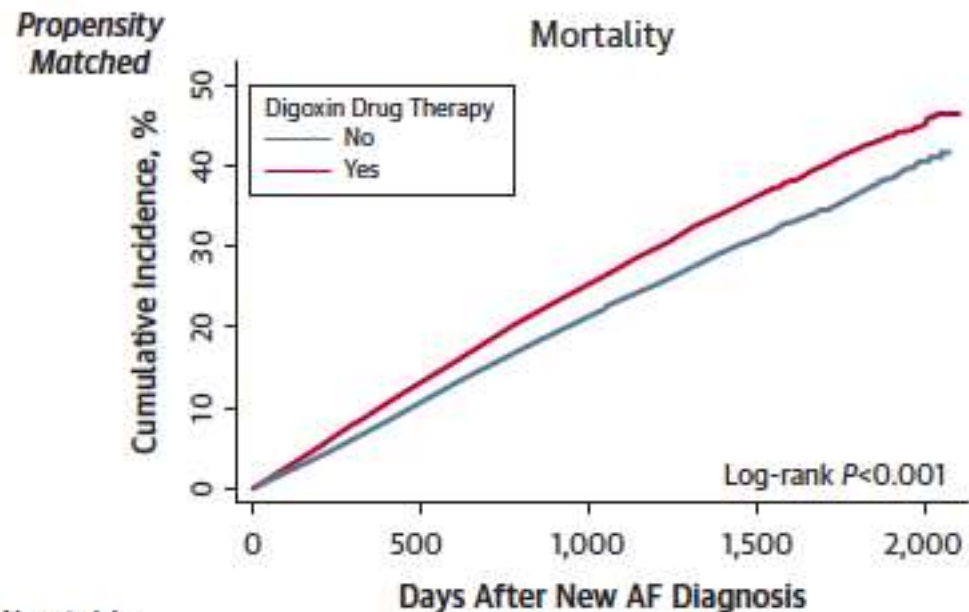
^aPropensity adjustment used for sensitivity analysis.

Increased Mortality Associated With Digoxin in Contemporary Patients With Atrial Fibrillation



Findings From the TREAT-AF Study

Mintu P. Turakhia, MD, MAS,^{*†} Pasquale Santangeli, MD,^{‡‡} Wolfgang C. Winkelmayr, MD, MPH, ScD,[§] Xiangyan Xu, MS,^{*} Aditya J. Ullal, BA,^{*} Claire T. Than, MPH,^{*} Susan Schmitt, PhD,^{*} Tyson H. Holmes, PhD,^{||} Susan M. Frayne, MD, MPH,^{*¶} Ciaran S. Phibbs, PhD,^{*#} Felix Yang, MD,^{**} Donald D. Hoang, BA,^{*} P. Michael Ho, MD, PhD,^{††‡‡} Paul A. Heidenreich, MD, MS[†]



In this large, retrospective cohort of patients with newly diagnosed AF, treatment with digoxin was independently associated with mortality, regardless of age, sex, kidney function, heart failure status, concomitant therapies, or drug adherence.

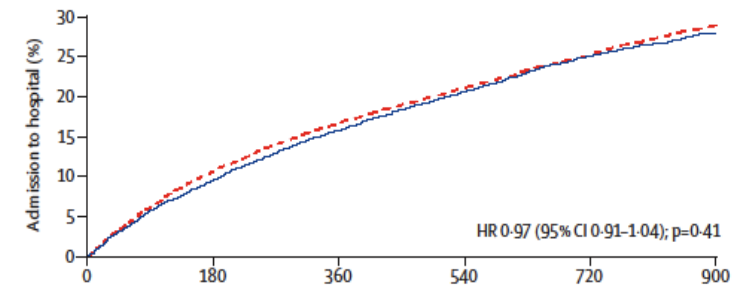
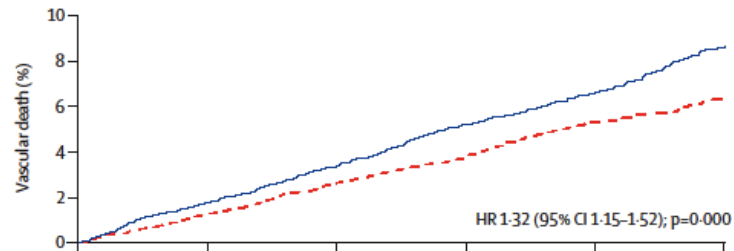
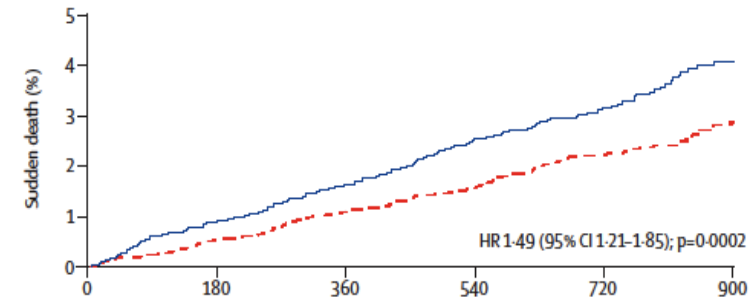
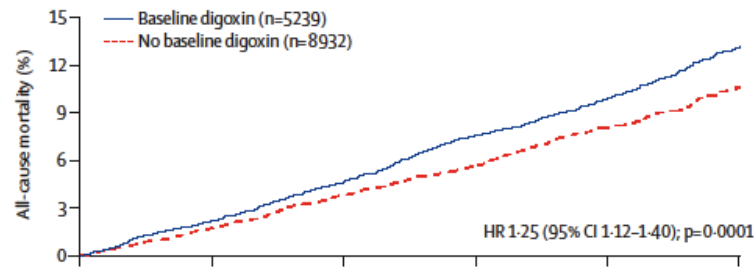
No. at risk					
Digoxin Drug Therapy					
No	26,703	21,206	13,491	6,618	977
Yes	26,703	21,465	14,658	7,795	1,264

J.Am Coll. Cardiol. 2014; 64: 660-8

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

Lancet 2015; 385: 2363 - 70



Digoxin Use and Subsequent Outcomes Among Patients in a Contemporary Atrial Fibrillation Cohort

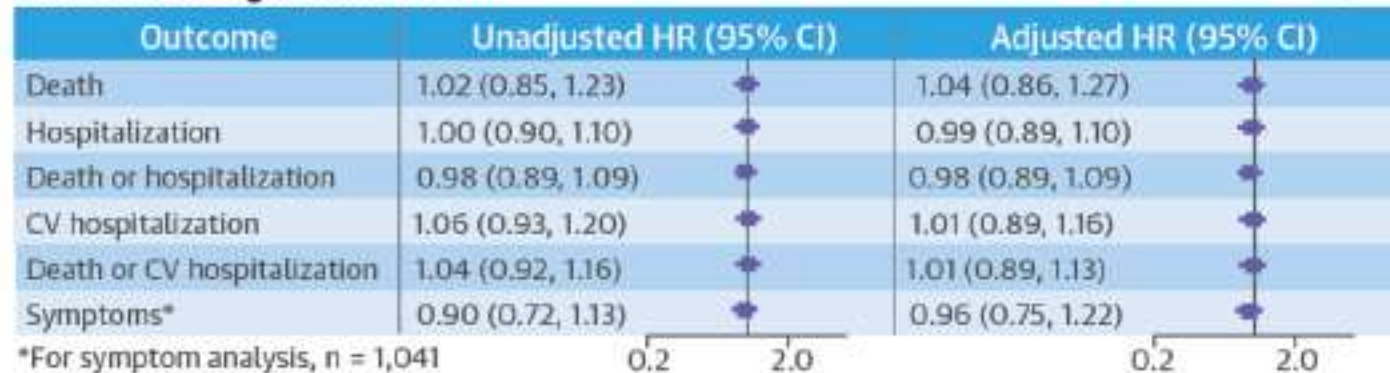


Larry A. Allen, MD, MHS,* Gregg C. Fonarow, MD,† DaJuanicia N. Simon, MS,‡ Laine E. Thomas, PhD,‡ Lucas N. Marzec, MD,* Sean D. Pokorney, MD, MBA,‡ Bernard J. Gersh, MB, ChB, DPHIL,§ Alan S. Go, MD,|| Elaine M. Hylek, MD, MPH,¶ Peter R. Kowey, MD,# Kenneth W. Mahaffey, MD,** Paul Chang, MD,†† Eric D. Peterson, MD, MPH,‡ Jonathan P. Piccini, MD, MHS,‡ for the ORBIT-AF Investigators

J. Am. Coll. Cardiol 2015; 65: 2691-8

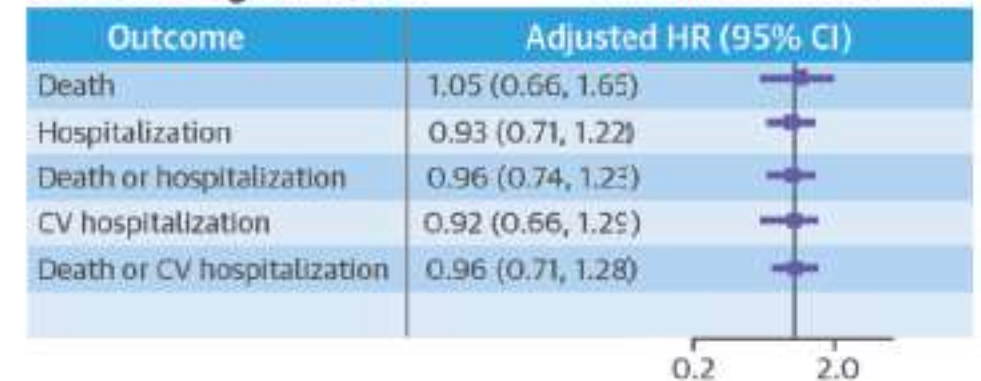
A. Prevalent Digoxin with HF

Number of Patients = 3,161



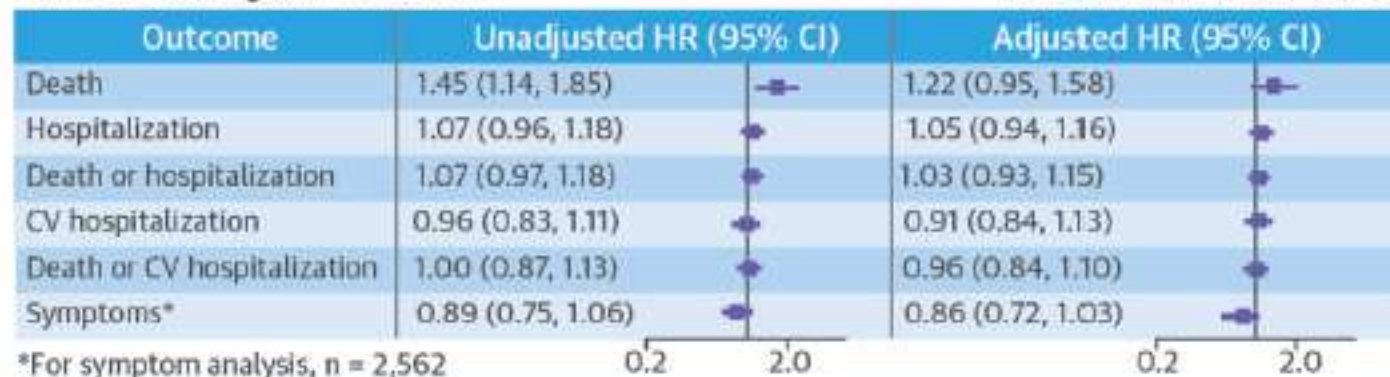
C. Incident Digoxin with HF

Number of Patients = 778



B. Prevalent Digoxin without HF

Number of Patients = 6,458



D. Incident Digoxin without HF

Number of Patients = 1,167



Digoxin
Fibrillation

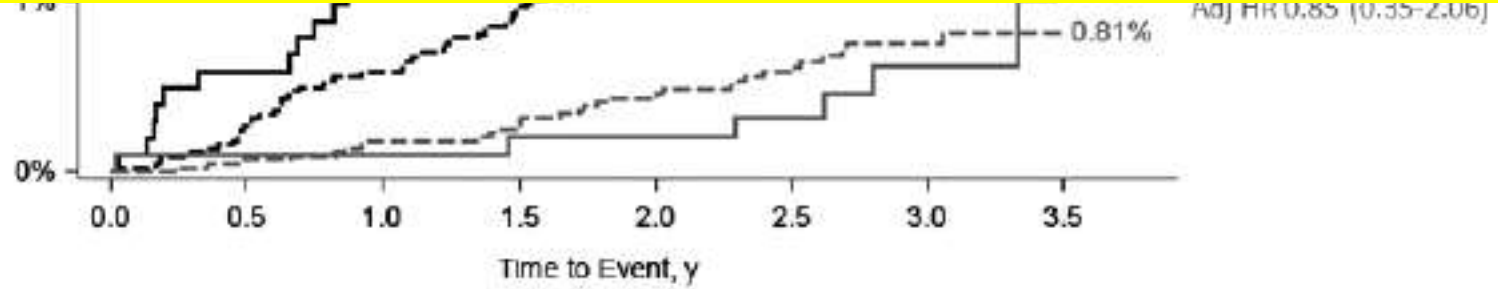
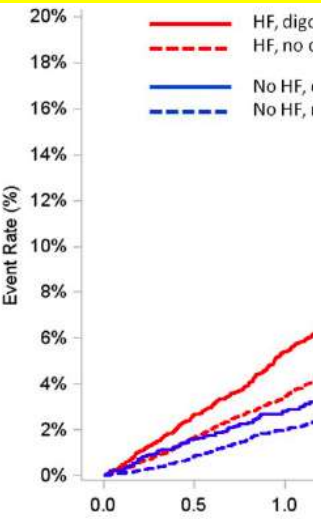
Alon Eisenberg
Christina L. Granger
Robert M. Gersh

trial
trial

MD;

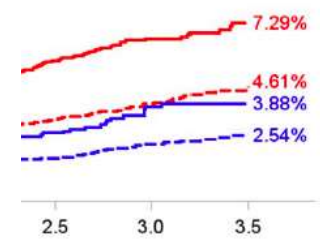


Other studies: Mulder 2014 (RACE II), Chao 2015, Fauchier 2015, Madelaire 2015 ...



Number at risk:

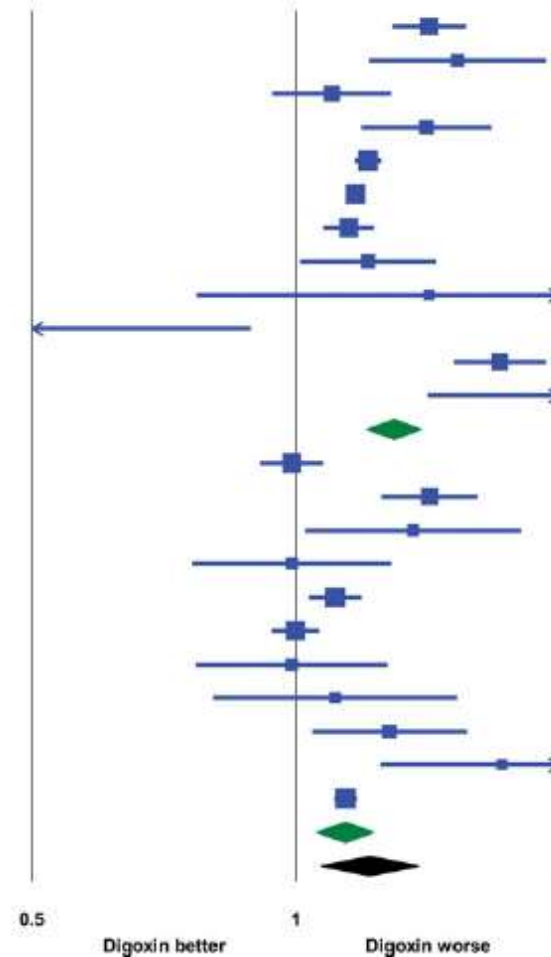
SCD, digoxin	1023	1010	999	982	966	742	455	147
SCD, no digoxin	4502	4461	4414	4360	4292	3236	1759	465
HF/shock, digoxin	1023	1010	999	982	966	742	455	147
HF/shock, no digoxin	4502	4461	4414	4360	4292	3236	1759	465



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

Mate Vamos, Julia W. Erath, and Stefan H. Hohnloser*

		Hazard ratio	95% CI	p-Value
Hallberg (RIKS-HIA), 2007 - AF	AF	1.42	1.29 1.56	0.00
Gjesdal (SPORTIF III, V), 2008	AF	1.53	1.21 1.93	0.00
Friberg (SCAF), 2009	AF	1.10	0.94 1.28	0.23
Whitlock (AFFIRM), 2012	AF	1.41	1.19 1.67	0.00
Turakhia (TREAT-AF), 2014	AF	1.21	1.17 1.25	0.00
Shah, 2014 - AF	AF	1.17	1.15 1.20	0.00
Garnst, 2014	AF	1.15	1.08 1.23	0.00
Chao, 2014	AF	1.21	1.01 1.44	0.04
Rodriguez-Manero (AFBAR), 2014	AF	1.42	0.77 2.61	0.26
Mulder (RACE II), 2014	AF	0.41	0.19 0.89	0.02
Freeman (ATRIA-CVRN), 2014	AF	1.71	1.52 1.93	0.00
Pastori, 2015	AF	2.22	1.42 3.48	0.00
Total	AF	1.29	1.21 1.39	<0.01
Garg (DIG), 1997	CHF	0.99	0.91 1.07	0.81
Domanski (SOLVD), 2005 - Men	CHF	1.42	1.26 1.61	0.00
Domanski (SOLVD), 2005 - Women	CHF	1.36	1.03 1.80	0.03
Ahmed (DIG Ancillary), 2006	CHF	0.99	0.76 1.28	0.94
Hallberg (RIKS-HIA), 2007 - CHF/SR	CHF	1.11	1.04 1.19	0.00
Hallberg (RIKS-HIA), 2007 - CHF/AF	CHF	1.00	0.94 1.06	1.00
Fauchier, 2008	CHF	0.99	0.77 1.27	0.94
Dhaliwal, 2008	CHF	1.11	0.81 1.53	0.52
Butler (Val-HeFT), 2010	CHF	1.28	1.05 1.57	0.02
Freeman, 2013	CHF	1.72	1.25 2.36	0.00
Shah, 2014 - CHF	CHF	1.14	1.11 1.17	0.00
Total	CHF	1.14	1.06 1.22	<0.01
Overall	AF, CHF	1.21	1.07 1.38	<0.01



Digoxin for atrial fibrillation and atrial flutter: A systematic review with meta-analysis and trial sequential analysis of randomised clinical trials

**Naqash J. Sethi^{1*}, Emil E. Nielsen¹, Sanam Safi¹, Joshua Feinberg¹,
Christian Gluud^{1,2}, Janus C. Jakobsen^{1,2,3}**

1 Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, **2** The Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, **3** Department of Cardiology, Holbæk Hospital, Holbæk, Denmark

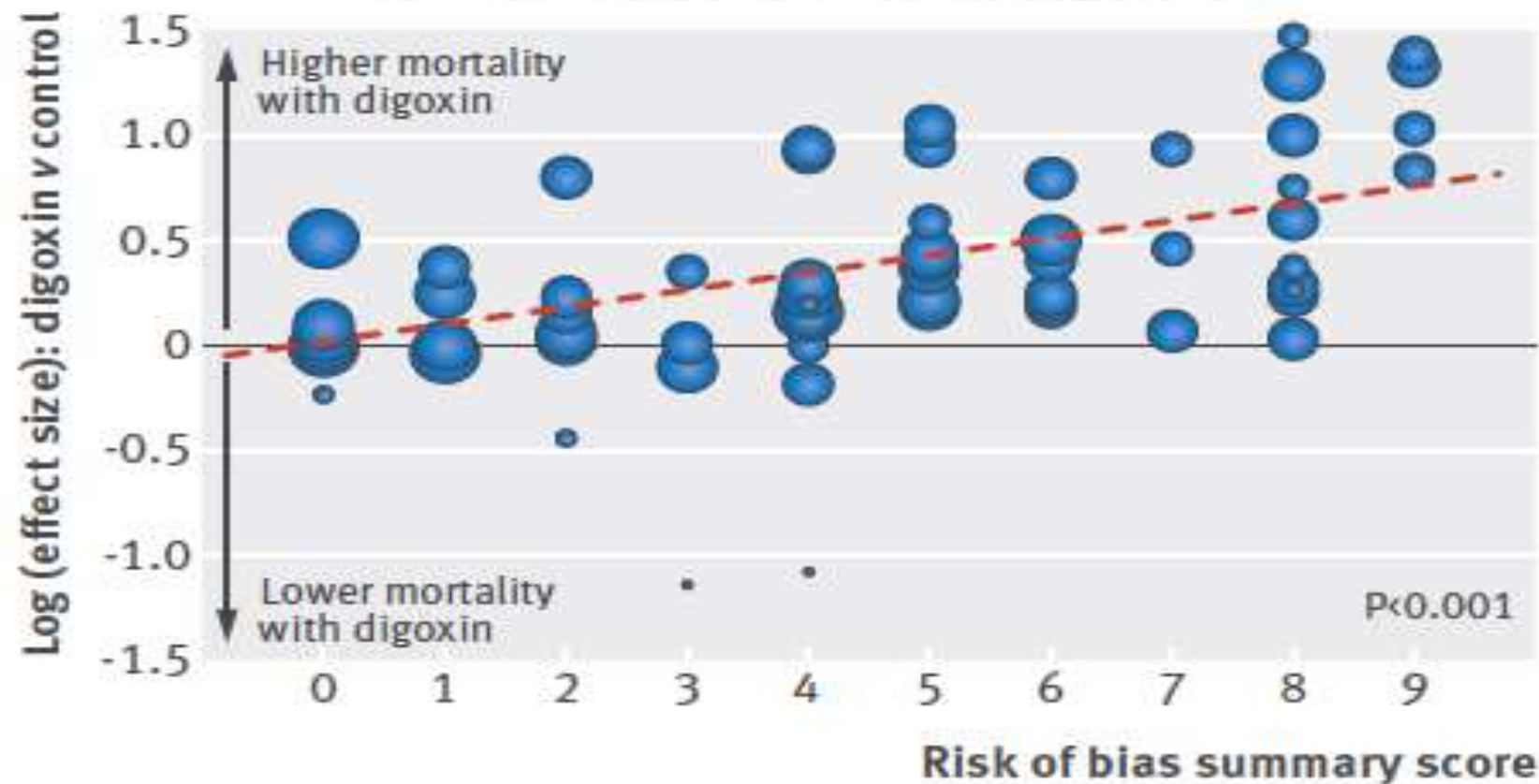
PLOS one 2018, 13(3): e193924

Our systematic review could neither confirm nor reject the findings from recent systematic reviews of observational studies showing that digoxin compared to no digoxin increased the risk of death.

Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data

Oliver J Ziff,^{1,2} Deirdre A Lane,^{1,3} Monica Samra,² Michael Griffith,⁴ Paulus Kirchhof,^{1,3} Gregory Y H Lip,^{1,3} Richard P Steeds,⁴ Jonathan Townend,^{1,4} Dipak Kotecha^{1,3,4,5}

BMJ 2105;351:h4451



Causes of Death and Influencing Factors in Patients With Atrial Fibrillation

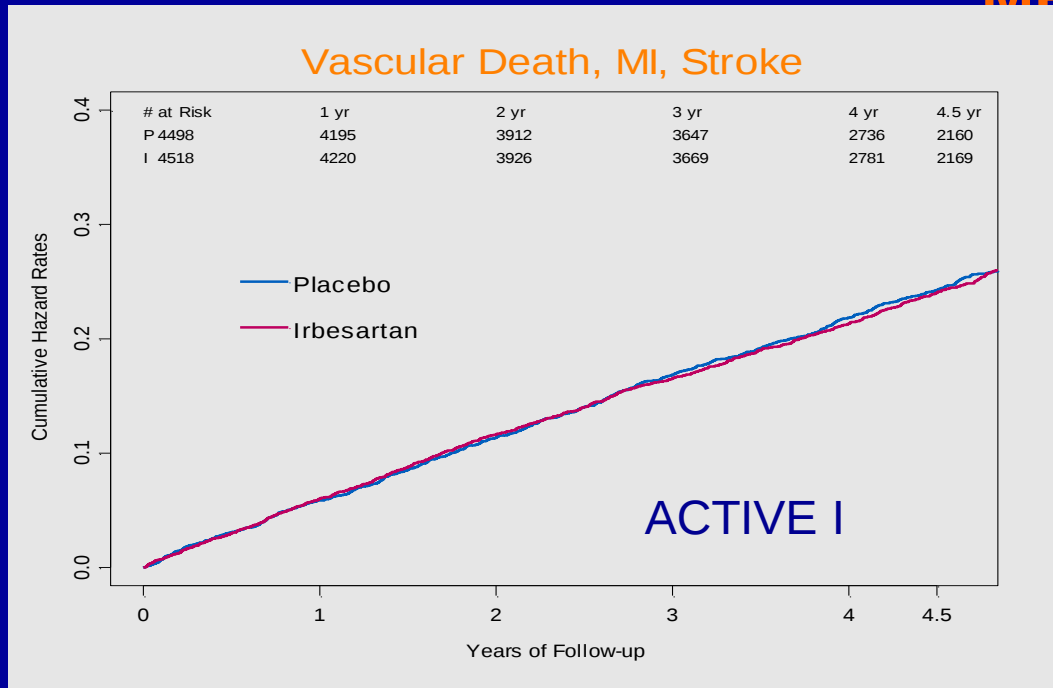
A Competing-Risk Analysis From the Randomized Evaluation of Long-Term Anticoagulant Therapy Study

Eloi Marijon, MD, PhD; Jean-Yves Le Heuzey, MD; Stuart Connolly, MD; Sean Yang, MSc; Janice Pogue, PhD; Martina Brueckmann, MD; John Eikelboom, MD; Ellison Themeles, BA; Michael Ezekowitz, MB, ChB, DPhil; Lars Wallentin, MD, PhD; Salim Yusuf, FRCPC, DPhil; for the RE-LY Investigators

Causes of death in the RE-LY® trial – descriptive data

	N	%
Causes of death in RE-LY®	Total	
Total	1371	100.00
Cardiovascular death	842	61.41
Cardiac	512	37.35
Sudden cardiac death	305	22.25
Progressive heart failure	207	15.10
Vascular	139	10.14
Stroke/peripheral embolism	96	7.00
Haemorrhage	39	2.84
Pulmonary embolism	4	0.29
Others/unknown	191	13.93
Noncardiovascular death	491	35.81
Undetermined death	38	2.77

PREVENTION OF ATRIAL FIBRILLATION WITH ANGIOTENSIN-RECEPTOR ENZYME INHIBITORS AND ANGIOTENSIN-RECEPTOR MODULATORS



ACTIVE I

Test for heterogeneity: chi-square=4.64 df=1 p=0.031

04 Post-Myocardial Infarction

TRACE	22 / 790	42 / 787
GISSI	665 / 8865	721 / 8846
Subtotal(95%CI)	687 / 9655	763 / 9633

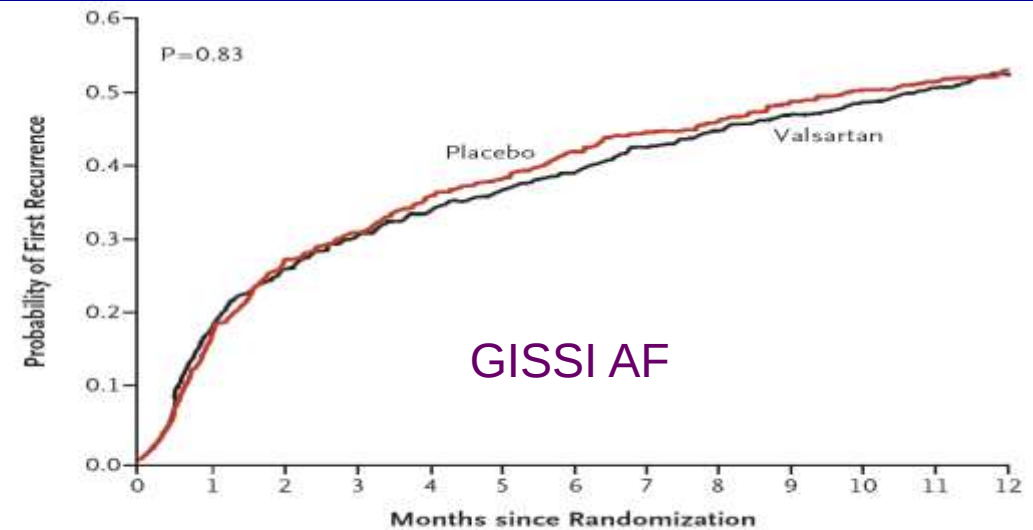
Test for heterogeneity chi-square=4.64 df=1 p=0.031

Test for overall effect z=-1.12 p=0.3

Total(95%CI) 1517 / 27089 2002 / 29220

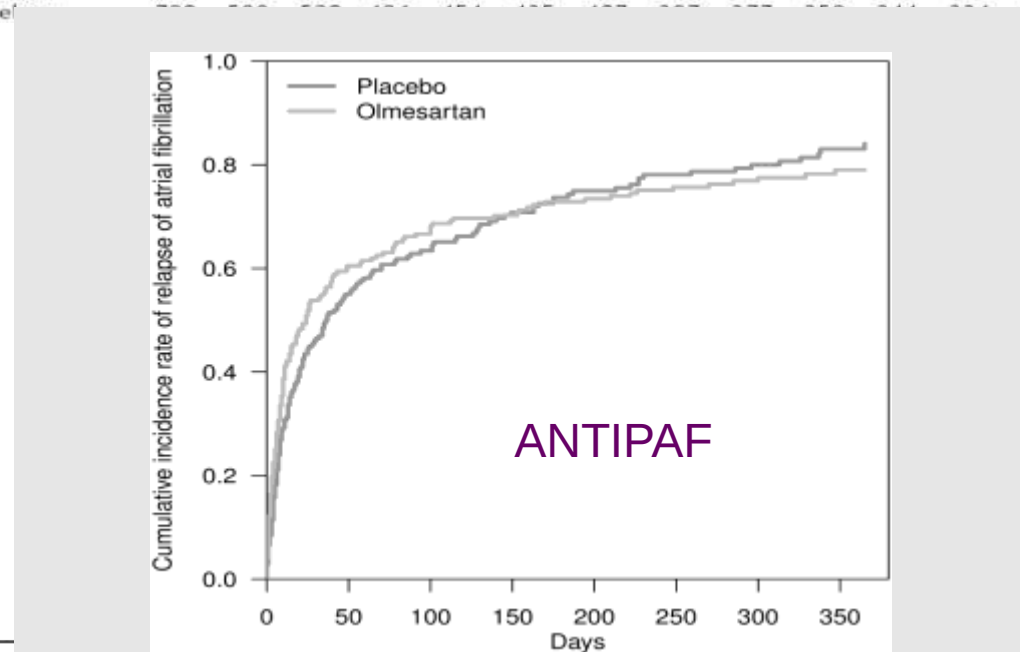
Test for heterogeneity chi-square=48.50 df=10 p<0.00001

Test for overall effect z=-3.74 p=0.0002



GISSI AF

No. at Risk	722	586	524	491	465	445	423	398	383	368	356	343	260
Valsartan													
Placebo													



ANTIPAF

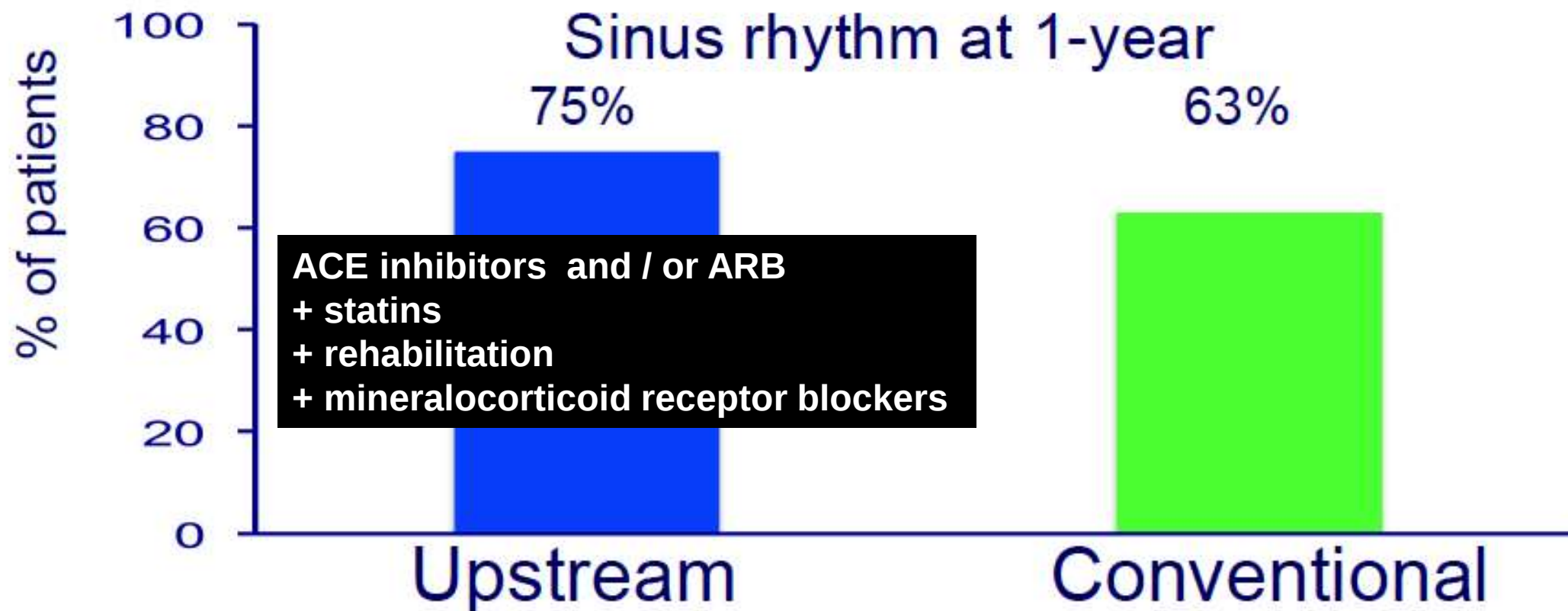
Favours treatment

Favours control





Primary endpoint



Odds ratio

1.765

Lower 95% confidence limit

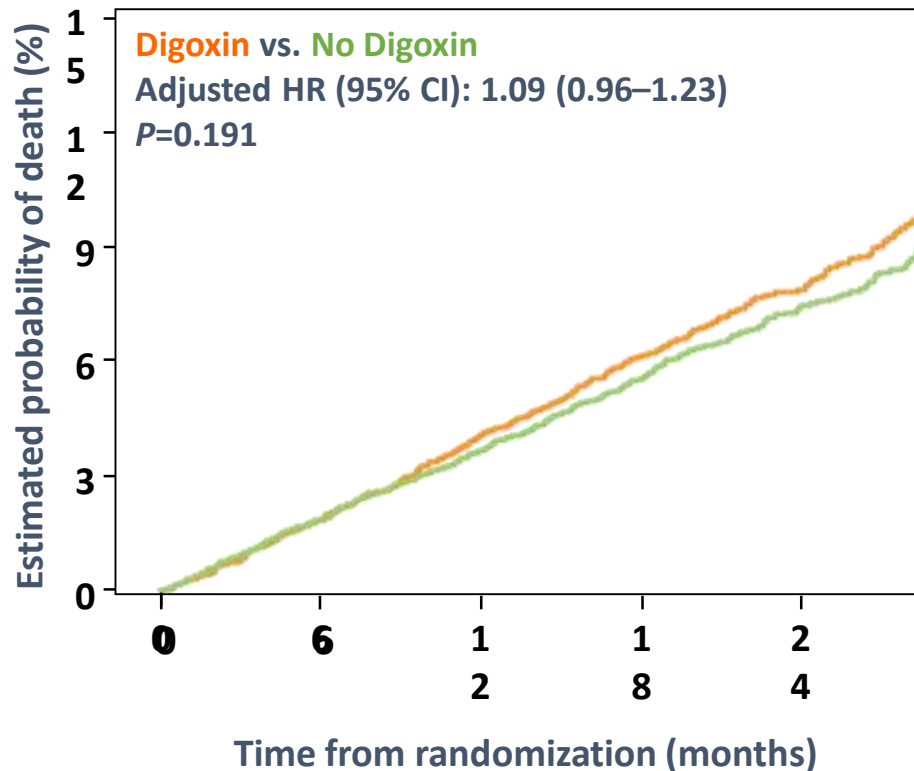
1.115

Superiority hypothesis is proven $p=0.021$

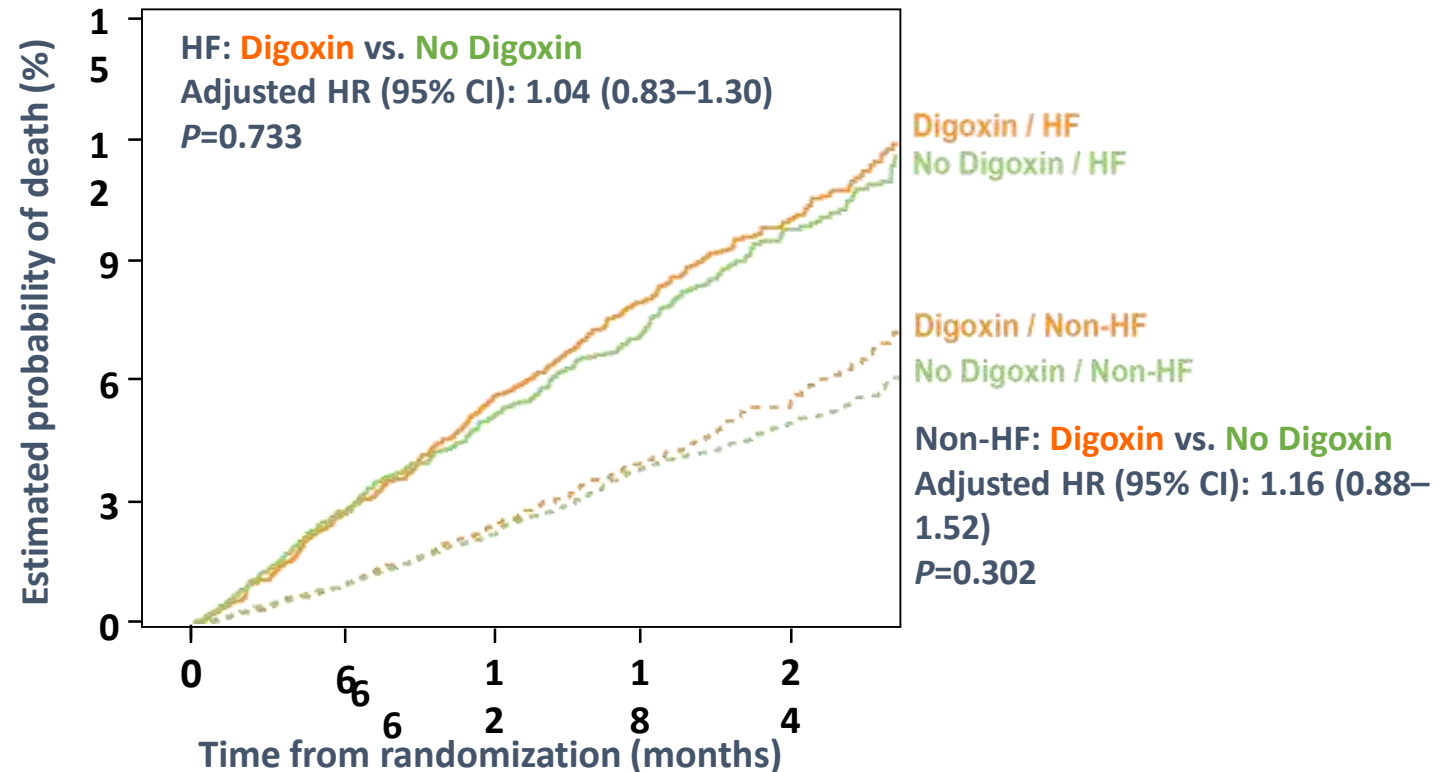
Digoxin and Mortality in Patients With Atrial Fibrillation With and Without Heart Failure (ARISTOTLE): Does Serum Digoxin Concentration Matter ?

Lopes R.D. et al., J. Am. Coll. Cardiol. 2018; 71: 1063-74

Adjusted All-cause Death in Patients Using Digoxin and Not Using Digoxin at Baseline



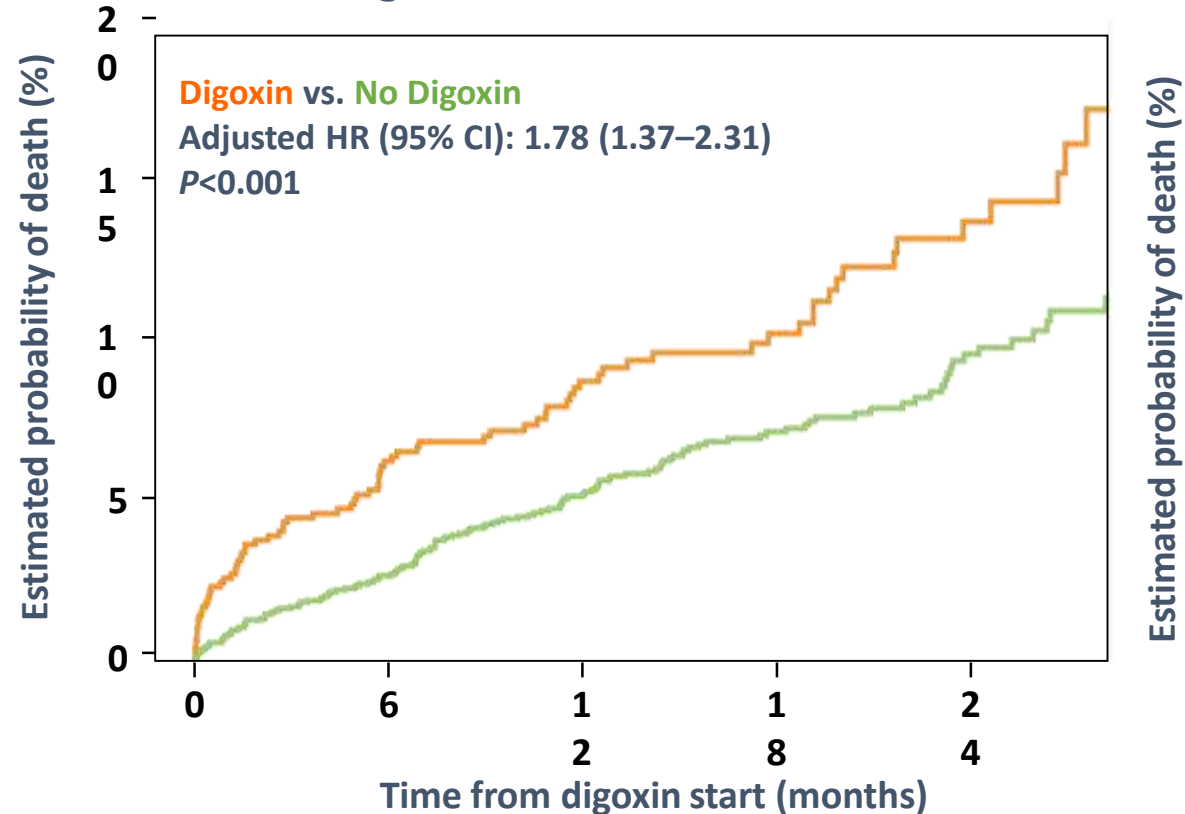
Adjusted All-cause Death in Patients Using or Not Digoxin at Baseline With and Without Heart Failure



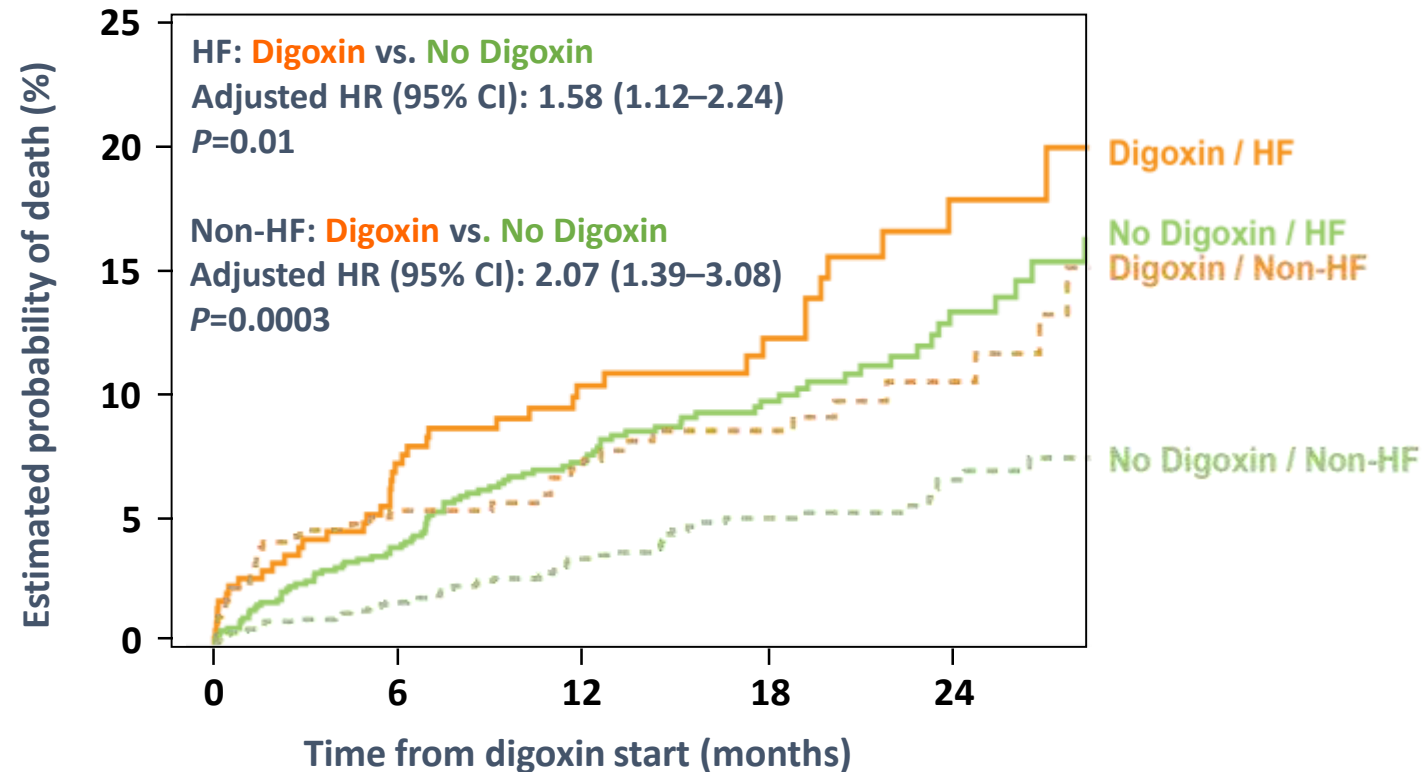
Digoxin and Mortality in Patients With Atrial Fibrillation With and Without Heart Failure (ARISTOTLE): Does Serum Digoxin Concentration Matter?

Lopes R.D. et al., J. Am. Coll. Cardiol. 2018; 71: 1063-74

Adjusted All-cause Death in New Users of Digoxin Versus Matched Controls

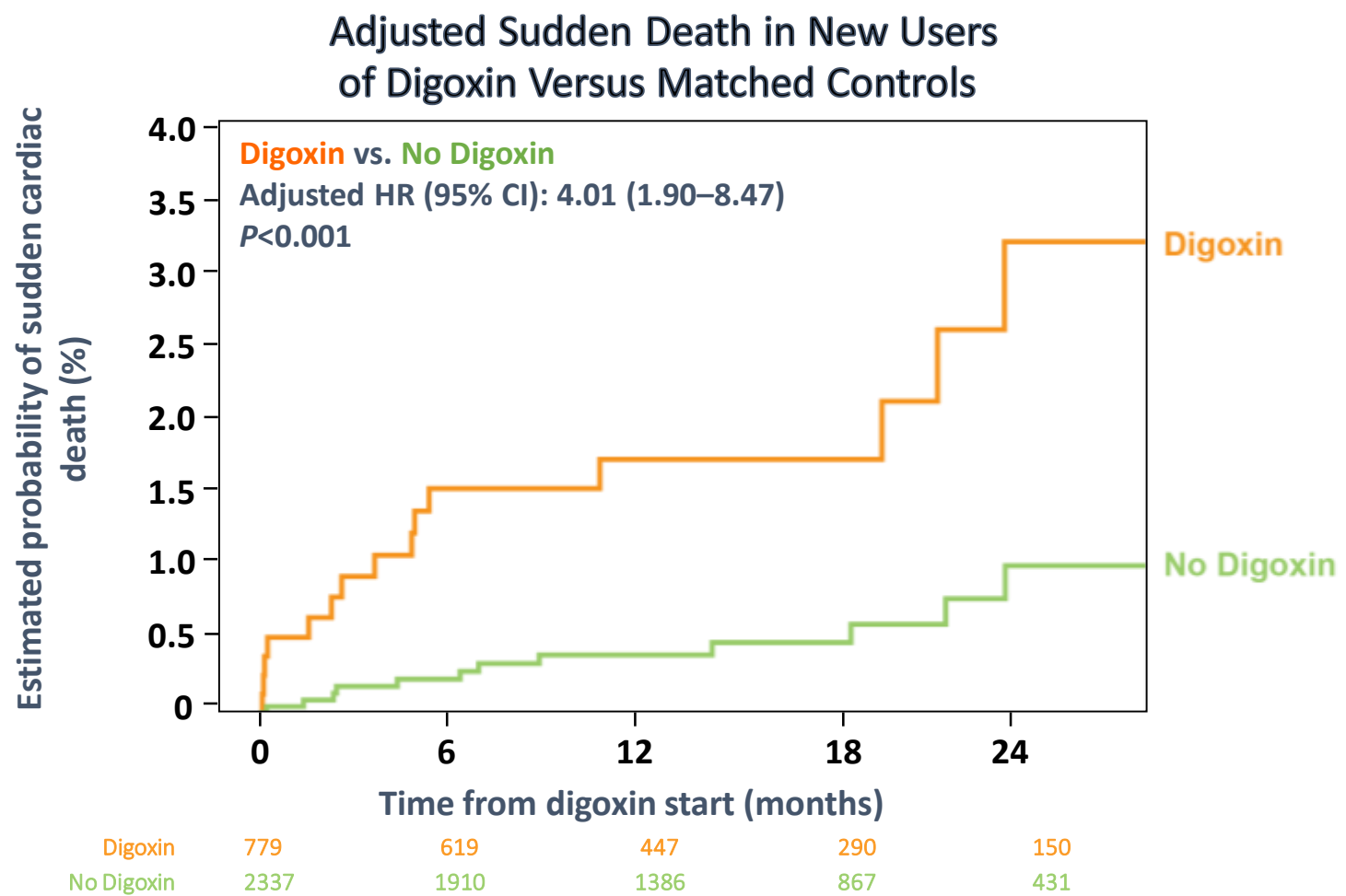


Adjusted All-cause Death in New Users of Digoxin Versus Matched Controls With and Without Heart Failure



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

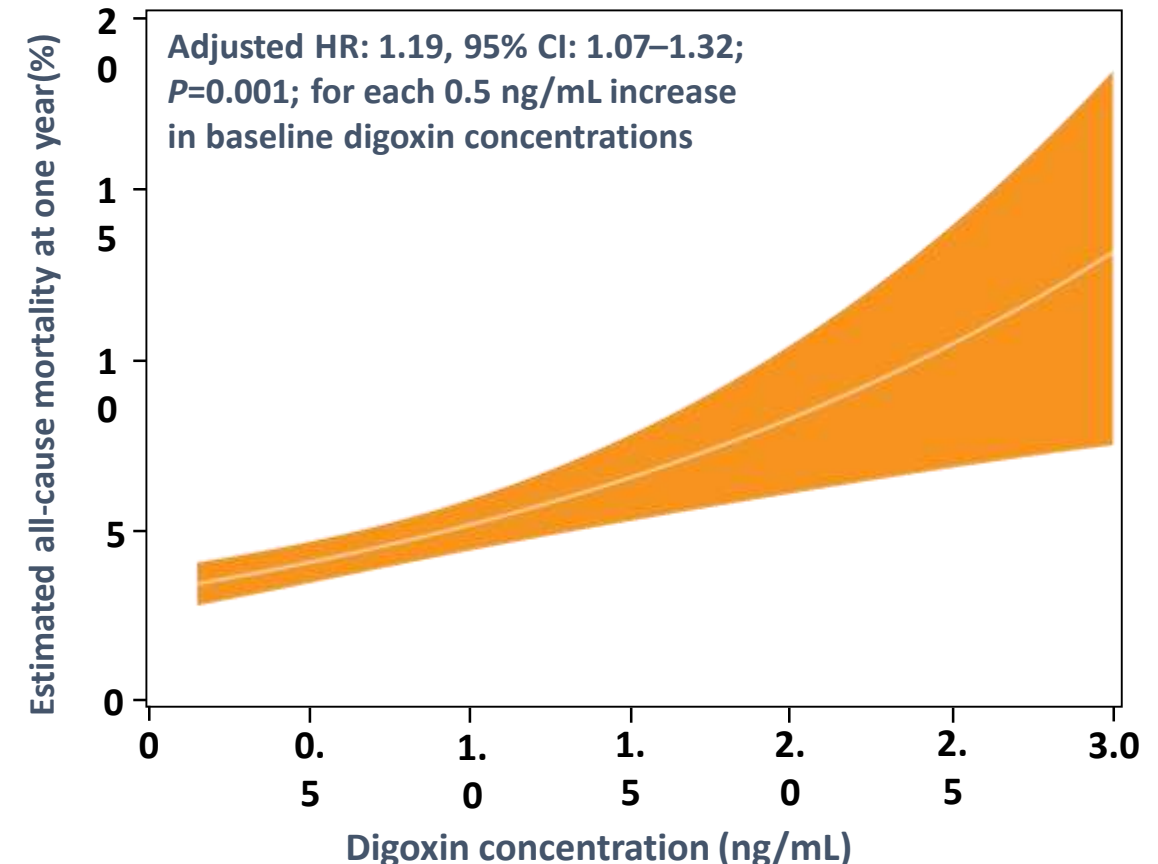
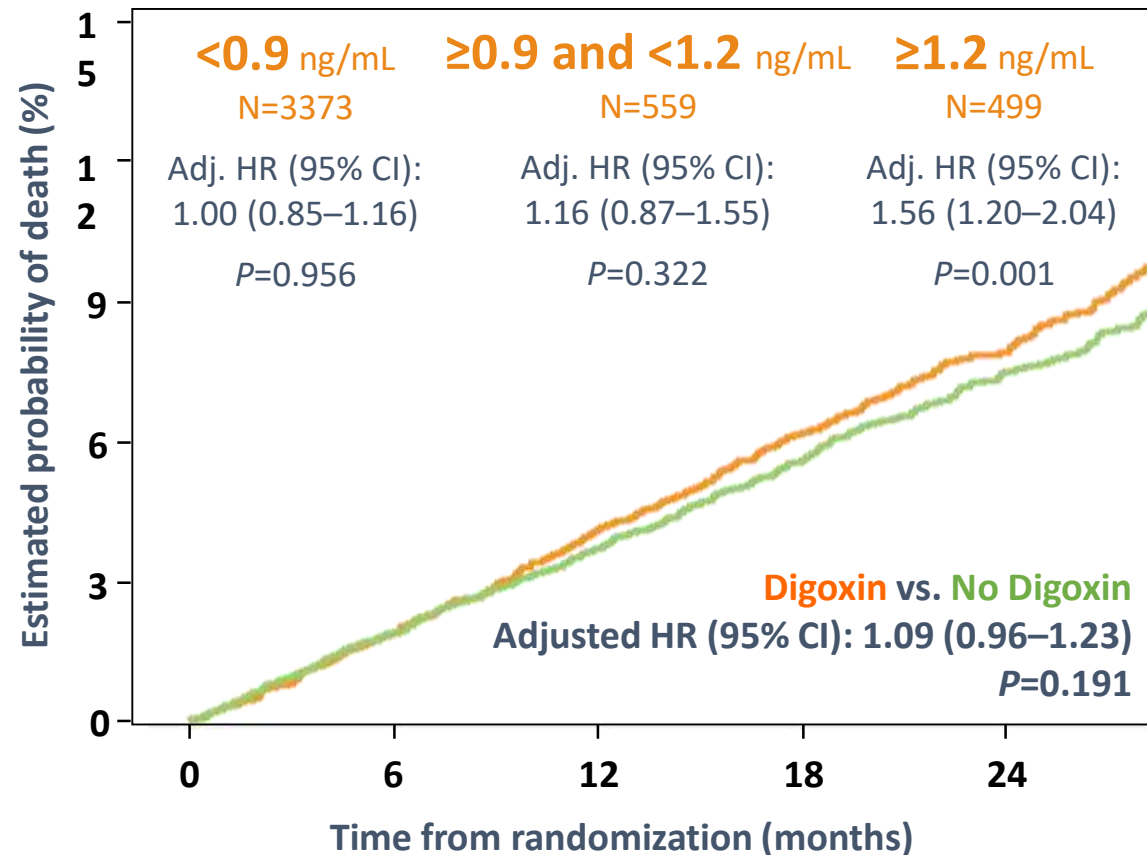
Lopes R.D. et al., J. Am. Coll. Cardiol. 2018; 71: 1063-74

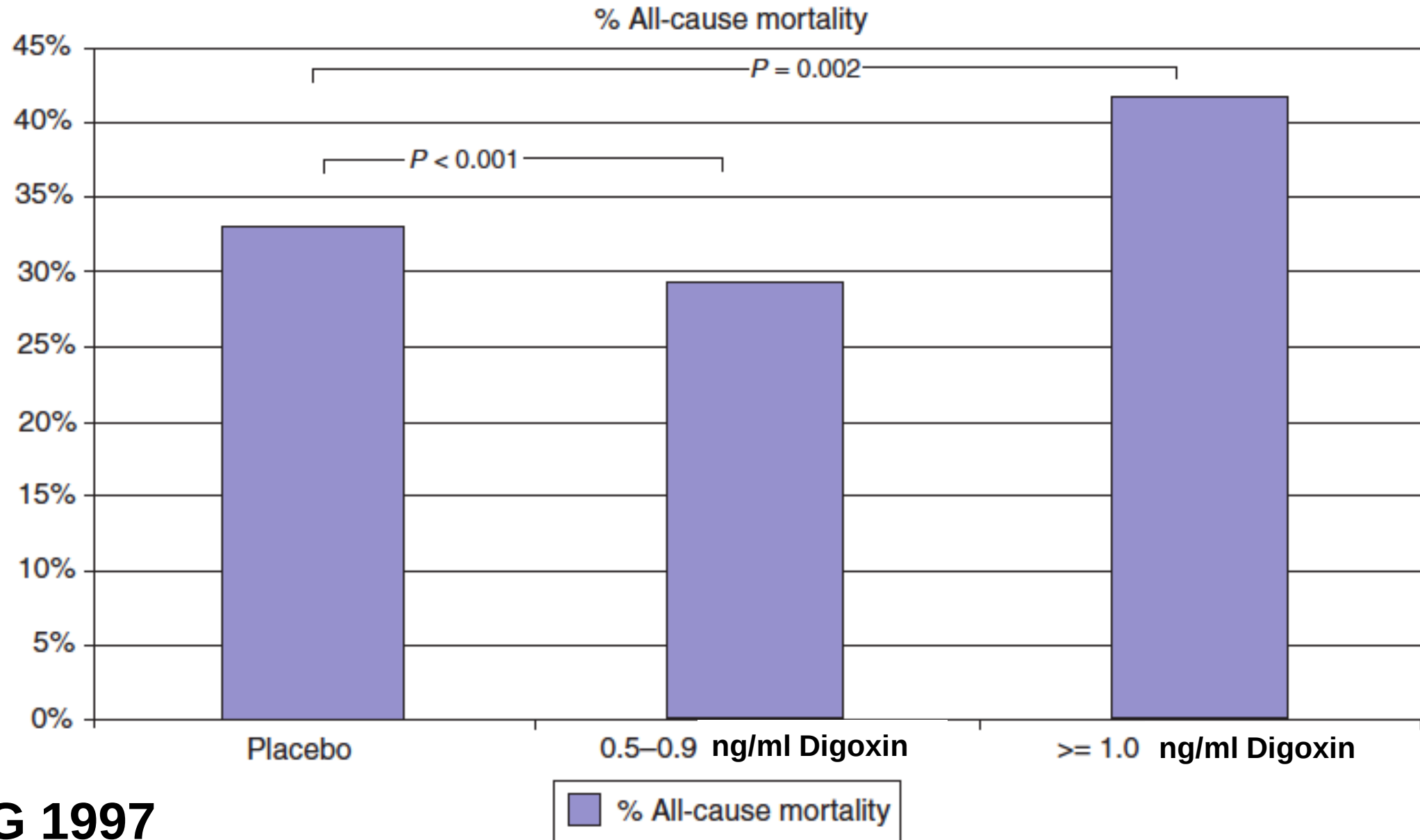


Digoxin and Mortality in Patients With Atrial Fibrillation With and Without Heart Failure (ARISTOTLE): Does Serum Digoxin Concentration Matter?

Lopes R.D. et al., J. Am. Coll. Cardiol. 2018; 71: 1063-74

Serum Digoxin Concentration and Mortality





DIG 1997

Adapted from Ahmed A. et al. Eur. Heart J. 2006; 27: 78-86

CONSIDERATIONS PRATIQUES

- La Digoxine a un **index thérapeutique étroit**
- Même si elle ne figure pas dans la classification de Vaughan-Williams, la Digoxine est un **antiarythmique** qui a, comme tous les médicaments antiarythmiques, un faible rapport bénéfice / risque
- La Digoxine peut induire des **effets proarythmiques** aussi bien à l'étage atrial que ventriculaire
- Cependant elle reste utile et sûre si elle est correctement prescrite, en évitant ses **contre indications** (arythmies ventriculaires, hypokaliémie, insuffisance rénale sévère) et sous stricte **surveillance**
- La mesure des **concentrations sériques** ne doit pas être systématique pour l'adaptation des doses (la toxicité dépend aussi de l'état myocardique et des co-médications) mais peut être très utile, particulièrement chez l'insuffisant rénal, pour contrôler la **sécurité**

Digoxin for patients and heart failure: pa

Dirk J. van Veldhuisen^{1*}, Isabelle C
and Mihai Gheorghiade³

EDITORIAL

Editorial

The New England Journal of Medicine

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VOLUME 336

FEBRUARY 20

NUMBER 8

THE EFFECT OF DIGOXIN ON MORTALITY AND MORBIDITY IN PATIENTS WITH
HEART FAILURE

THE DIGITALIS INVESTIGATION GROUP*

DIG : AF patients excluded

But Not Forever

013; 6: 511-13

What conclusions can be drawn from these two analyses? Given the non-randomized, observational design of both studies, the findings should be considered hypothesis generating. Even sophisticated statistical methods such as propensity analysis cannot replace randomization. When such observational studies are published, it is crucial for the reader to understand the cohorts and the how treatment groups are defined, because sometimes digoxin use is not the same as digoxin use.

Assumption versus evidence: the case of digoxin in atrial fibrillation and heart failure

Udo Bavendiek^{1*}, Lukas Aguirre Davila², Armin Koch², and Johann Bauersachs¹

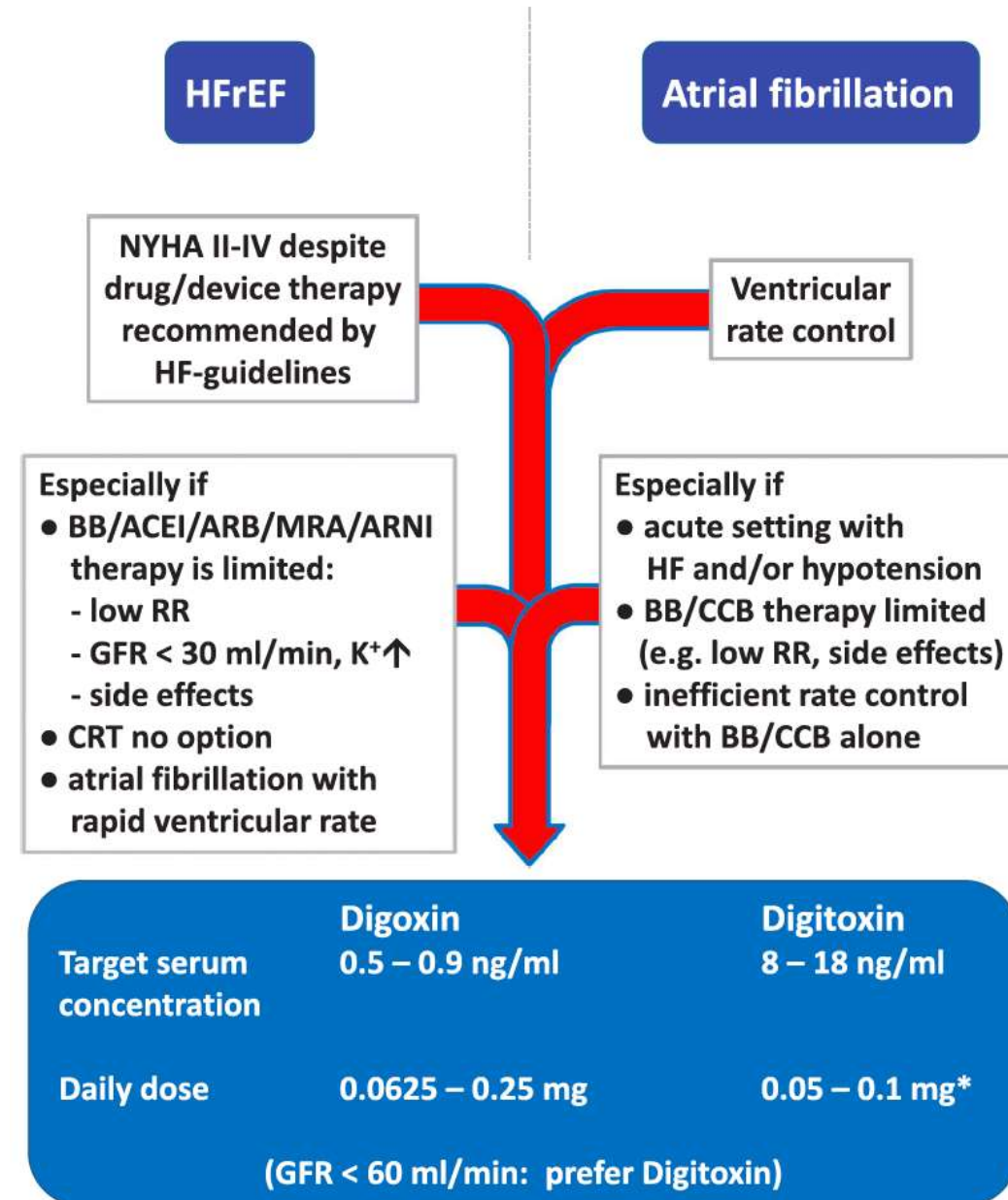
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Prospective clinical trials with cardiac glycosides initiated

RATE-AF (University of Birmingham/UK, funded by UK Dept. of Health) is powered to detect a difference in quality of life comparing digoxin to beta-blockers as initial rate control therapy in permanent AF. In addition, RATE-AF is a feasibility study to plan a future major randomized controlled event-driven clinical outcome trial (<https://clinicaltrials.gov/ct2/show/NCT02391337>, 24 November 2016).

DIGIT-HF (Hannover Medical School/Germany, funded by Federal Ministry of Education and Research [BMBF]), a prospective, randomized clinical outcome trial, investigates the hypothesis that digitoxin—at serum concentrations in the lower therapeutic range controlled for in all patients—reduces mortality and morbidity in patients with advanced chronic systolic HF (<https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-005326-38/DE>, 24 November 2016). DIGIT-HF has already been initiated with public funding from the German Federal Ministry for Research and Education and is currently recruiting patients and open for further centres interested to participate.

Recommendations for use of cardiac glycosides in clinical practice



CONCLUSIONS

- 1- La Digoxine est une **option thérapeutique** proposée dans les **recommandations** sur la fibrillation atriale
- 2- Les données de la littérature concernant sa **sécurité** restent **controversées** mais la majorité des publications montre une **augmentation de la mortalité** toutes causes
- 3- Toutes ces données proviennent d'**études retrospectives ou post hoc**
- 4- Un grand **essai prospectif randomisé** fait chez des patients ayant une fibrillation atriale avec ou sans insuffisance cardiaque est **nécessaire** pour clore définitivement le débat
- 5- Si la Digoxine est utilisée, la mesure des **concentrations sériques** est souhaitable chez les patients à risque pour identifier ceux ayant des concentrations supérieures à **1-1,2 ng/ml** qui sont menacés d'effets proarythmiques



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