Digoxin Reduces 30-Day All-Cause Hospital Admission in Ambulatory Older Patients with Chronic Heart Failure and Reduced Ejection Fraction

ACC Late Breaking Clinical Trial Session
March 11, 2013, San Francisco, CA

Ali Ahmed, Mihai Gheorghiade, Gregg Fonarow, Kanan Patel, Inmaculada Aban, Richard Allman, Jerome Fleg, Robert Bourge

University of Alabama at Birmingham
Veterans Affairs Medical Center
Birmingham, AL

Presenter Disclosure Information

Ali Ahmed, MD, MPH

Digoxin Reduces 30-Day All-Cause Hospital Admission in Ambulatory Older Patients with Chronic Heart Failure and Reduced Ejection Fraction

DISCLOSURE INFORMATION:

No relationships exist related to this presentation

Dr. Ahmed was supported in part by the National Institutes of Health through grants (R01-HL085561, R01-HL085561-S and R01-HL097047) from the National Heart, Lung, and Blood Institute (NHLBI)

Funding Disclosure Information

The Digitalis Investigation Group (DIG) trial was supported by the **NHLBI** and the **VA** Cooperative Studies Program

This article was prepared using a limited access dataset obtained from the **NHLBI** and does not necessarily reflect the opinions or views of the DIG Study or the NHLBI.

New Perspective on an Old Drug

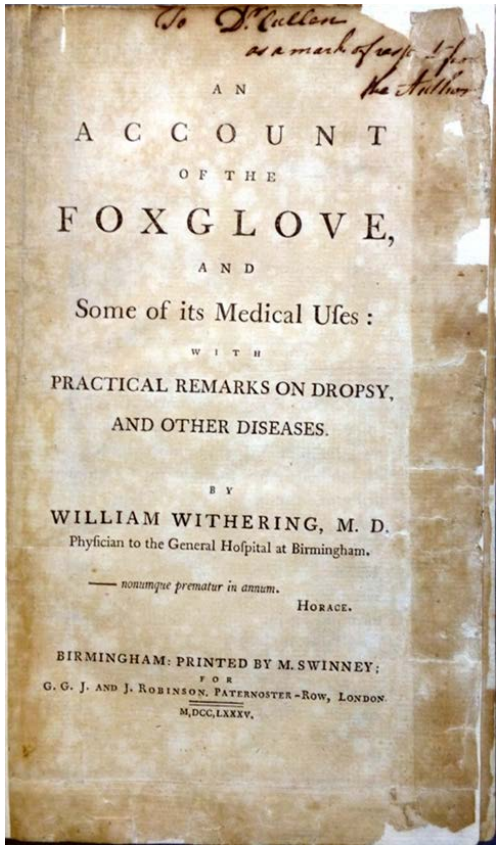
A Very Old Drug

Discovered Over 2 Centuries Ago

An Account of the Foxglove and Some of its Medical Uses

William Withering

1785



AN

ACCOUNT

OF THE

FOXGLOVE,

AND

Some of its Medical Uſes:

WITH

PRACTICAL REMARKS ON DROPSY,

AND OTHER DISEASES.

BY

WILLIAM WITHERING, M. D.

Phyſician to the General Hoſpital at Birmingham.

— nonumque prematur in annum.

HORACE.

BIRMINGHAM: PRINTED BY M. SWINNEY;

FOR

G. G. J. AND J. ROBINSON. PATERNOSTER-ROW, LONDON.

M,DCC,LXXXV.

Improves Heart Failure Symptoms (The RADIANCE Trial)

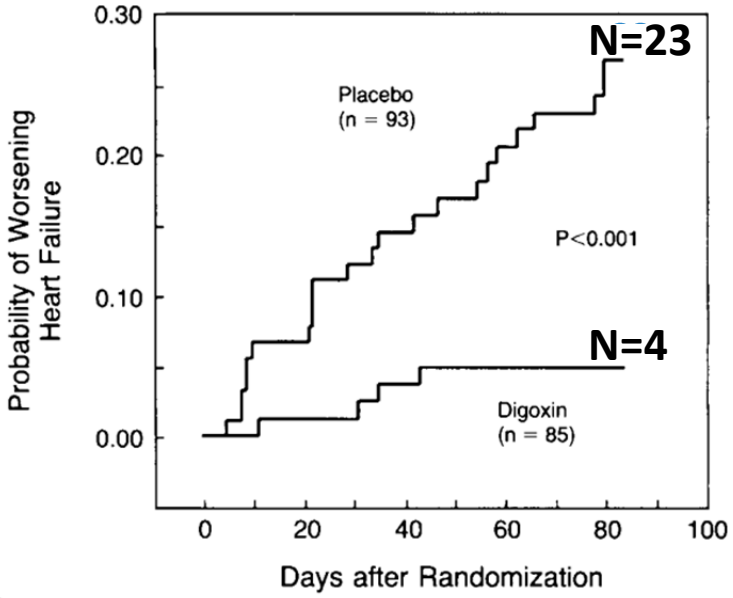


Figure 1. Kaplan–Meier Analysis of the Cumulative Probability of Worsening Heart Failure in the Patients Continuing to Receive Digoxin and Those Switched to Placebo.

Patients whose digoxin was **discontinued** (in the placebo group) had a **higher risk of worsening heart failure** (HR, 5.9; 95% CI = 2.1 to 17.2; P<0.001)

N Engl J Med 1993; 329:1-7

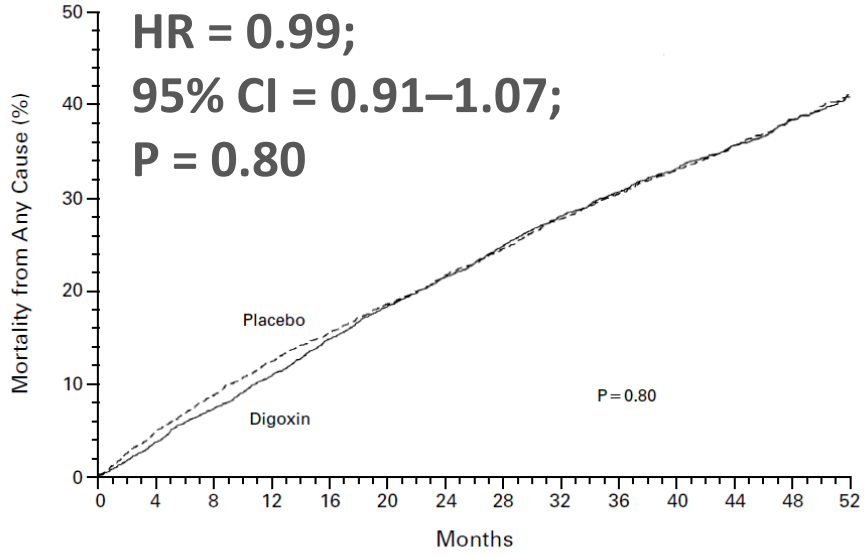
Reduces Risk of Hospital Admission (The DIG Trial)

	Placebo (n=3403)	Digoxin (n=3397)	Absolute Risk Difference	Hazard ratio (95% CI)	P value
Heart Failure	35%	27%	**–8%**	**0.72** (0.66–0.79)	<0.001
All-Cause	67%	64%	**–3%**	**0.92** (0.87–0.98)	0.006

Digoxin significantly **reduced** the risk of **hospitalization due to heart failure** by **28%** during 37 months of average follow-up, but its effect on **hospitalization due to all causes** was more modest (a **8%** reduction)

N Engl J Med. 1997; 336: 525-33

Does Not Increase Mortality (The DIG Trial)



No. of Patients at Risk

Placebo	3403	3239	3105	2976	2868	2758	2652	2551	2205	1881	1506	1168	734	339
Digoxin	3397	3269	3144	3019	2882	2759	2644	2531	2184	1840	1475	1156	737	335

Figure 1. Mortality in the Digoxin and Placebo Groups.
The number of patients at risk at each four-month interval is shown below the figure.

N Engl J Med. 1997; 336: 525-33

Approved by the FDA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 00N–1610]

RIN 0910–AC12

DMP

Display Date 11/22/00
Publication Date 11/24/00
Certifier LaJuana D. Caldwell

Digoxin Products for Oral Use; Revocation of Conditions for Marketing

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

In 1997, **FDA** approved digoxin for use in heart failure

Recommended by Guidelines

Digitalis can be beneficial in patients with current or prior symptoms of HF and reduced LVEF **to decrease hospitalizations for HF**

Recommendation Class: IIa
Level of Evidence: B

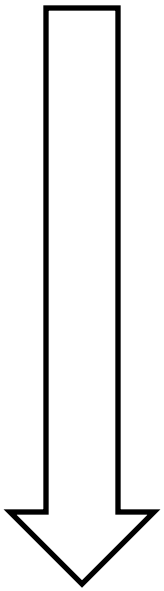
2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults

JACC. 2009 doi:10.1016/j.jacc.2008.11.013

However, Use Declined

- SOLVD (1991): **66%**
- US Carvedilol (1996): **90%**
- RALES (1999): **73%**

- CHARM-Alternative (2003): **45%**
- RAFT (2010): **35%**
- EMPHASIS (2011): **27%**



over the subsequent decades…in part due to lack of effect on death and downgrade in guideline recommendations

Yet, Heart Failure Remains the Leading Reason for Hospital Admission and Readmission

Condition at Index Discharge	30-Day All-Cause Readmission	Most Frequent Reason for Readmission
All Medical	21.0%	Heart Failure (8.6%)
Heart Failure	26.9%	Heart Failure (37.0%)
All Surgical	15.6%	Heart Failure (6.0%)

N Engl J Med 2009;360:1418-28

March 2010

The New Health Care Reform Act
Signed into Law

Requires CMS to **reduce payments** to hospitals with **excess readmissions**, effective **October 1, 2012**…

October 2012

Medicare imposed about **$300** million financial penalties against over **2,000** hospitals that had excessive readmission

Objective

- To examine the effect of digoxin on 30-day all-cause hospital admission in older, potentially Medicare-eligible, adults with heart failure and reduced ejection fraction in the main DIG trial

Digitalis Investigation Group (DIG)

- **Ambulatory chronic heart failure** (N=6800)
  - Ejection fraction **≤45%**
  - Normal sinus rhythm
  - From United States and Canada
  - Randomized to receive either digoxin or placebo
  - During **1991-1993**
  - Followed for an average of **3** years
  - >90% on **ACE inhibitors** and >80% on **diuretics**
- **3405** (50% of 6800) **were ≥65 years of age**

Baseline Characteristics (1)

Variables n (%) or mean (±SD)	Placebo (n=1712)	Digoxin (n=1693)	P value
Age (years)	72 (5)	72 (5)	0.974
Female	426 (25%)	415 (25%)	0.802
Non-whites	194 (11%)	180 (11%)	0.514
Body mass index (kg/m^2)	26.2 (4.7)	25.9 (4.5)	**0.040**
Heart rate (per minute)	78 (12)	78 (12)	0.445
Systolic BP (mm Hg)	128 (20)	128 (20)	0.643
Serum creatinine (mg/dL)	1.4 (0.4)	1.4 (0.4)	0.938
LVEF (%)	29 (9)	29 (9)	0.855
Cardiothoracic ratio	0.54 (0.08)	0.54 (0.07)	0.855
NYHA Class III-IV	602 (35%)	603 (36%)	0.599

Baseline Characteristics (2)

Variables n (%) or mean (±SD)	Placebo (n=1712)	Digoxin (n=1693)	P value
Heart failure duration (mos)	30 (37)	30 (38)	0.625
Prior myocardial infarction	1168 (68%)	1154 (68%)	0.969
Current angina pectoris	489 (29%)	465 (28%)	0.476
Hypertension	815 (48%)	784 (46%)	0.448
Diabetes mellitus	517 (30%)	488 (29%)	0.379
Chronic kidney disease	1038 (61%)	1045 (62%)	0.513
Dyspnea on exertion	1323 (77%)	1306 (77%)	0.924
Dyspnea at rest	386 (23%)	358 (21%)	0.323
4 or more symptoms/signs	1411 (82%)	1384 (82%)	0.525
Pulmonary edema by x-ray	266 (16%)	286 (17%)	0.283

Baseline Characteristics (3)

Variables n (%) or mean (±SD)	Placebo (n=1712)	Digoxin (n=1693)	P value
Dose of study medication			
0.125 mg/day	433 (25%)	426 (25%)	
0.25 mg/day	1197 (70%)	1209 (72%)	0.430
0.375 mg/day or higher	71 (5%)	48 (3%)	
Pre-trial digoxin use	739 (43%)	744 (44%)	0.646
ACE inhibitors	1605 (94%)	1591 (94%)	0.784
Diuretics	1405 (82%)	1374 (81%)	0.493
Nitroglycerines	788 (46%)	768 (45%)	0.697

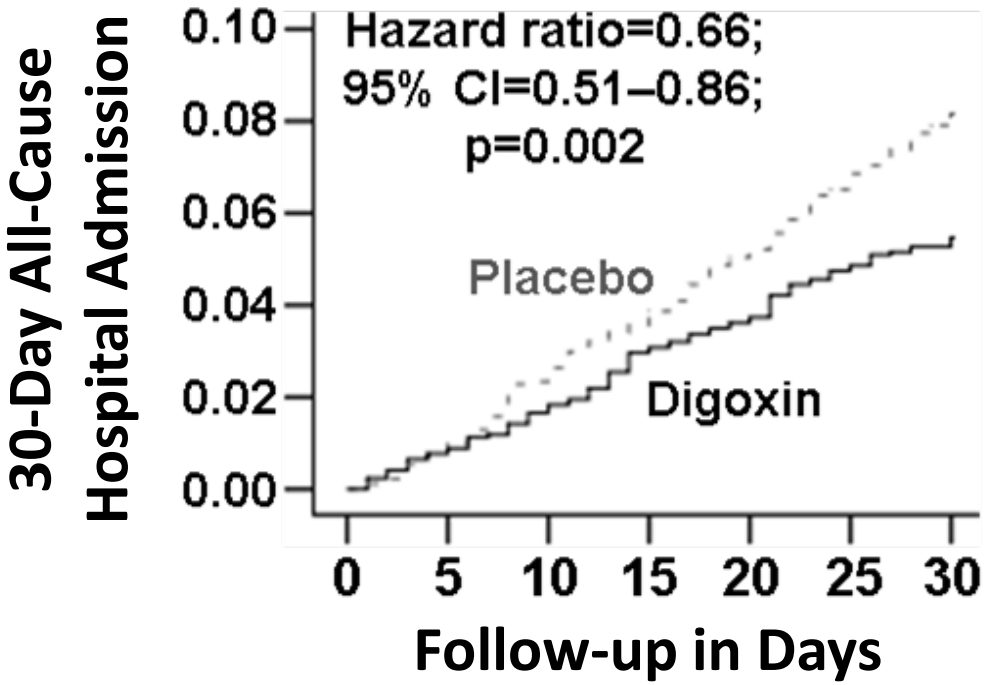
Overall, **ALL** baseline characteristics of patients assigned to digoxin and placebo were **balanced** *except* for a slightly lower BMI among those assigned to digoxin

30-Day Hospital Admission Due to All Causes

Placebo (n=1712)	Digoxin (n=1693)	Absolute Risk Difference	Hazard ratio (95% CI)	P value
8.1%	5.4%	**–2.7%**	**0.66** (0.51–0.86)	0.002

In the 30 days after randomization, in patients assigned to digoxin, the **absolute** risk and **relative** risk for all-cause hospital admission was reduced by an **2.7%** and **34%**, respectively

Kaplan-Meier Plot



Number at risk				
Placebo	1712	1666	1618	1566
Digoxin	1693	1659	1623	1592

60-Day and 90-Day All-Cause Hospital Admission

	Hazard ratio (95% CI)	P value
At 60 days	**0.76** (0.63–0.91)	0.003
At 90 days	**0.75** (0.63–0.88)	<0.001

The effect of digoxin on 30-day all-cause hospital admission **persisted** during 60 and 90 days after randomization, suggesting the **early benefit of digoxin was not at the cost of later harm**

30-Day Hospital Admission Due to Cardiovascular Causes

Placebo (n=1712)	Digoxin (n=1693)	Absolute Risk Difference	Hazard ratio (95% CI)	P value
6.5%	3.5%	**–3.0%**	**0.53** (0.38–0.72)	<0.001

In the 30 days after randomization, digoxin reduced the risk of hospital admission due to cardiovascular causes by 47%

30-Day Hospital Admission Due to Worsening Heart Failure

Placebo (n=1712)	Digoxin (n=1693)	Absolute Risk Difference	Hazard ratio (95% CI)	P value
4.2%	1.7%	**–2.5%**	**0.40** (0.26–0.62)	<0.001

In the 30 days after randomization, digoxin reduced the risk of hospital admission due worsening heart failure by 60%

30-Day Mortality

	Hazard ratio (95% CI)	P value
All-cause	0.55 (0.27-1.11)	0.096
Cardiovascular	0.64 (0.31-1.31)	0.222
Progressive heart failure	0.22 (0.05-1.04)	0.056

Although few deaths (n=**34**) occurred, they were numerically fewer in the digoxin group (**0.7%** vs. **1.3%** for placebo)…

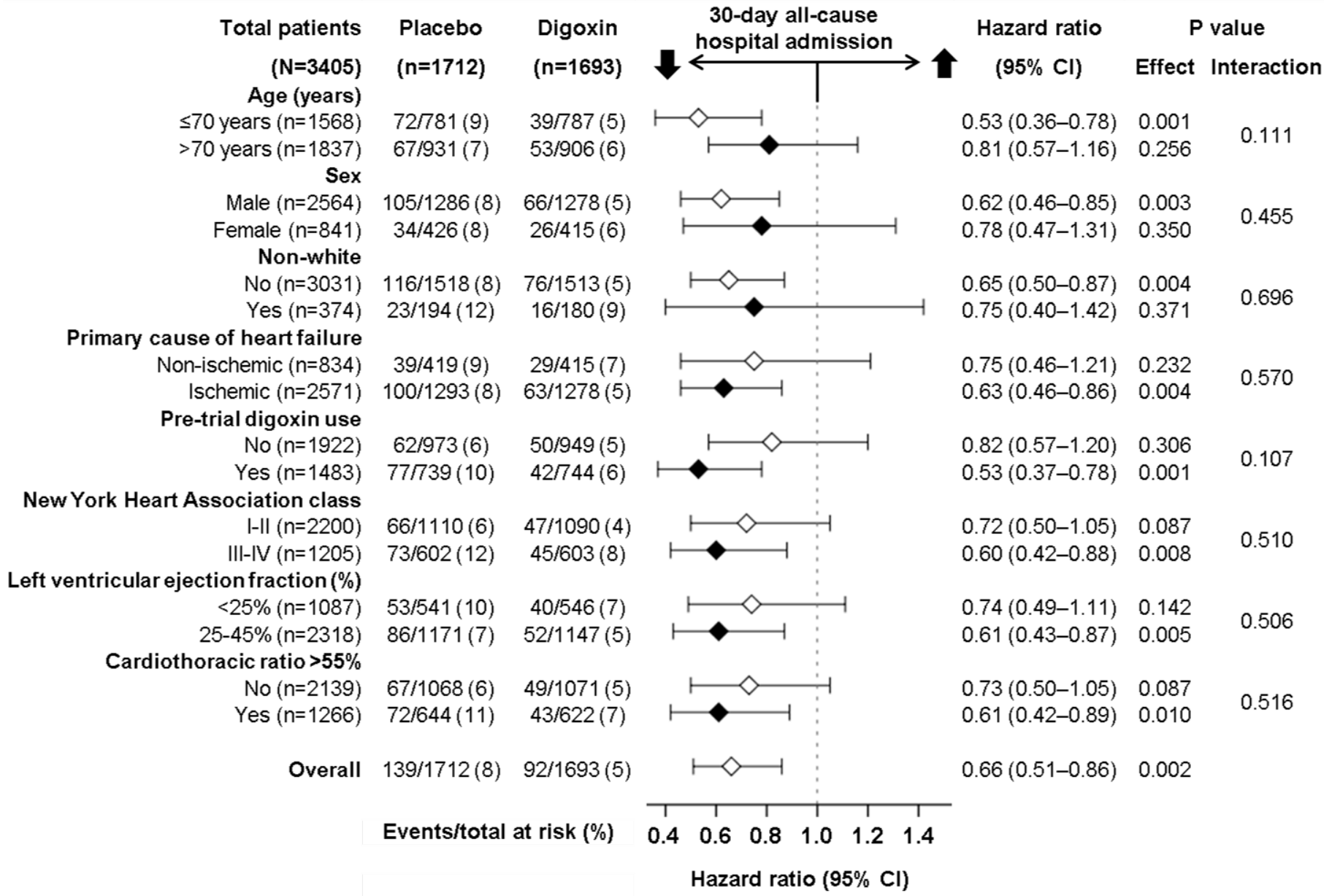
30-Day Combined Outcomes

Placebo (n=1712)	Digoxin (n=1693)	Absolute Risk Difference	Hazard ratio (95% CI)	P value
8.7%	6.0%	–2.7%	0.69 (0.53–0.88)	0.003

…consequently, the **composite outcome** of all-cause hospitalization or all-cause death at 30 days also was **reduced substantially** (by **31%**)

Only 4 patients were hospitalized because of suspected digoxin toxicity within 30 days of randomization, of whom 3 were from the digoxin group

Subgroup Analyses



Study Limitations

- Post hoc analysis of RCT
- Generalizability concerns
  - Ambulatory vs. post-discharge
  - Admission vs. re-admission
  - HFrEF vs. HFpEF
  - Not receiving beta-blockers
  - Not receiving aldosterone antagonists

Conclusions

- Digoxin reduced the risk of 30-day all-cause hospital *admission* in ambulatory older adults with chronic systolic heart failure receiving ACE inhibitors and diuretics
- If these findings can be replicated in contemporary older heart failure patients discharged from hospital after acute decompensation, digoxin may provide an inexpensive tool to reduce 30-day all-cause hospital *readmission*

Hopefully, as Predicted by a Wise Man over 2 Centuries Ago…

Dr. William Withering (1741-1799)

"After all, in spite of opinion, prejudice or error, ***Time*** **will fix the real value upon this discovery**, and determine whether I have imposed upon myself and others, or contributed to the benefit of science and mankind."

William Withering, 1785

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Digoxin Reduces 30-day All-cause Hospital Admission in Older Patients with Chronic Systolic Heart Failure

Robert C. Bourge, MD,[a] Jerome L. Fleg, MD,[b]
Gregg C. Fonarow, MD,[c] John G. F. Cleland, MD,[d]
John J. V. McMurray, MD,[e] Dirk J. van Veldhuisen, MD, PhD,[f]
Mihai Gheorghiade, MD,[g] Kanan Patel, MBBS, MPH,[a]
Inmaculada B. Aban, PhD,[a] Richard M. Allman, MD,[h,a]
Connie White-Williams, RN, PhD,[a] Michel White, MD,[i]
Gerasimos S. Filippatos, MD, PhD,[j] Stefan D. Anker, MD, PhD,[k]
Ali Ahmed, MD, MPH[a,h]

[a]University of Alabama at Birmingham, Birmingham; [b]National Heart, Lung, and Blood Institute, Bethesda, Md; [c]University of California, Los Angeles; [d]Hull York Medical School, Kingston-Upon-Hull, United Kingdom; [e]University of Glasgow, Glasgow, United Kingdom; [f]University Medical Centre, Groningen, The Netherlands; [g]Northwestern University, Chicago, Ill; [h]Veterans Affairs Medical Center, Birmingham, Ala; [i]Montreal Heart Institute, Montreal, Canada; [j]Attikon University Hospital, Athens, Greece; [k]Center for Clinical and Basic Research, IRCCS San Raffaele, Rome, Italy.

Advance Access Online Publication March 11, 2013 http://dx.doi.org/10.1016/j.amjmed.2013.02.001