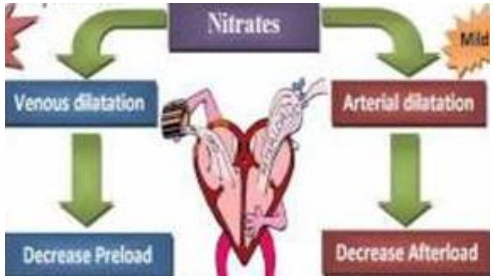
Θεραπευτικά διλήμματα στην καρδιακή ανεπάρκεια (πότε χρησιμοποιώ διγοξίνη και πότε νιτρώδη;)



Κρικίδης Δημήτριος MD, MSc

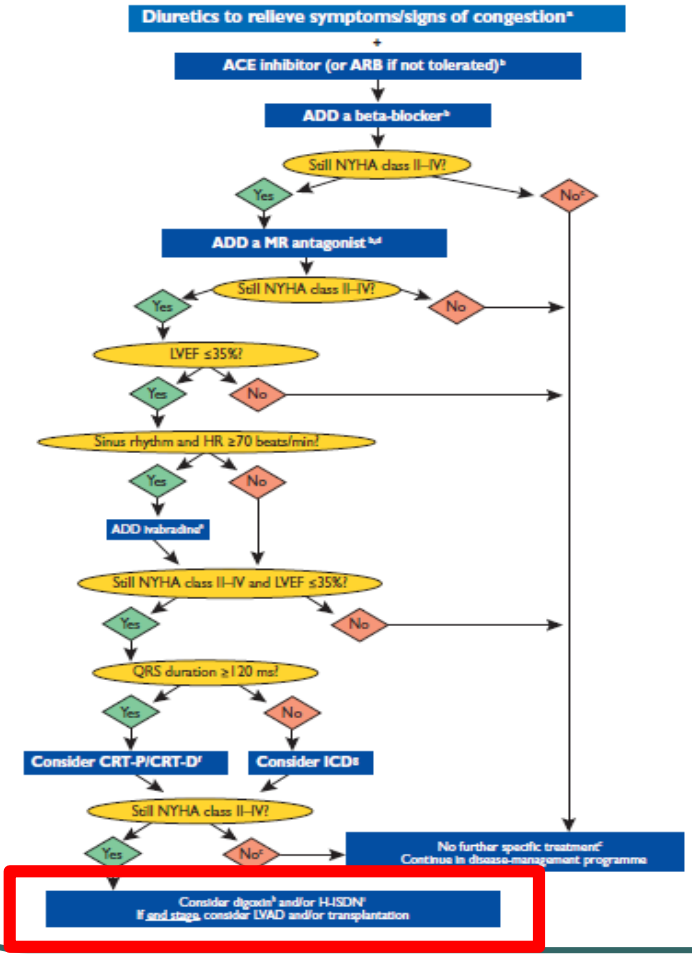
Καρδιολόγος

Επιστημονικός Συνεργάτης

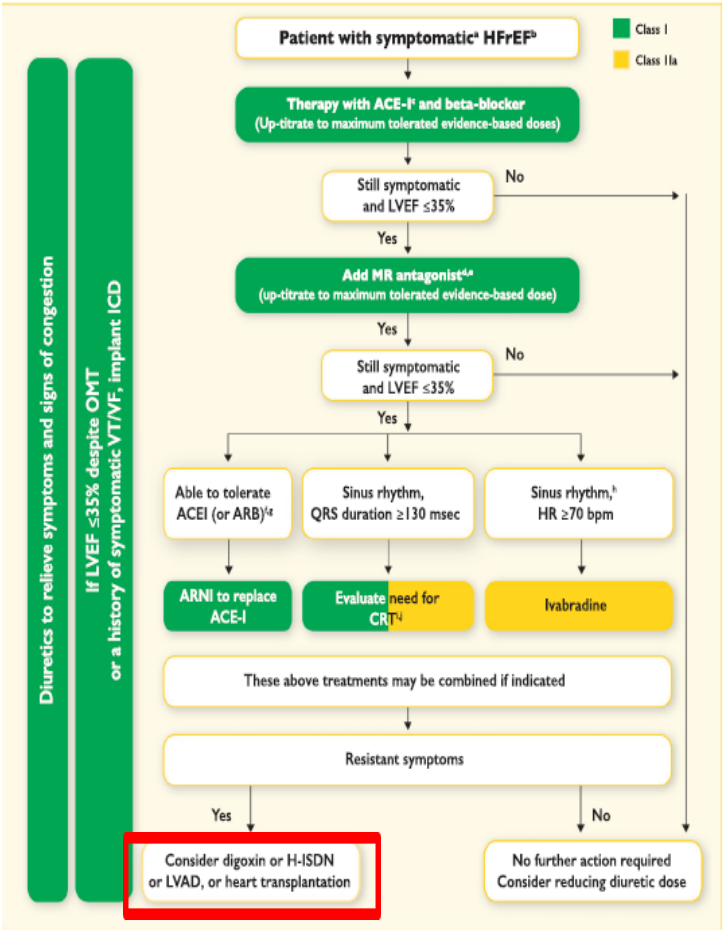
Ά Β Πανεπιστημιακής Καρδιολογικής Κλινικής Α.Π.Θ


DISCLOSURE

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

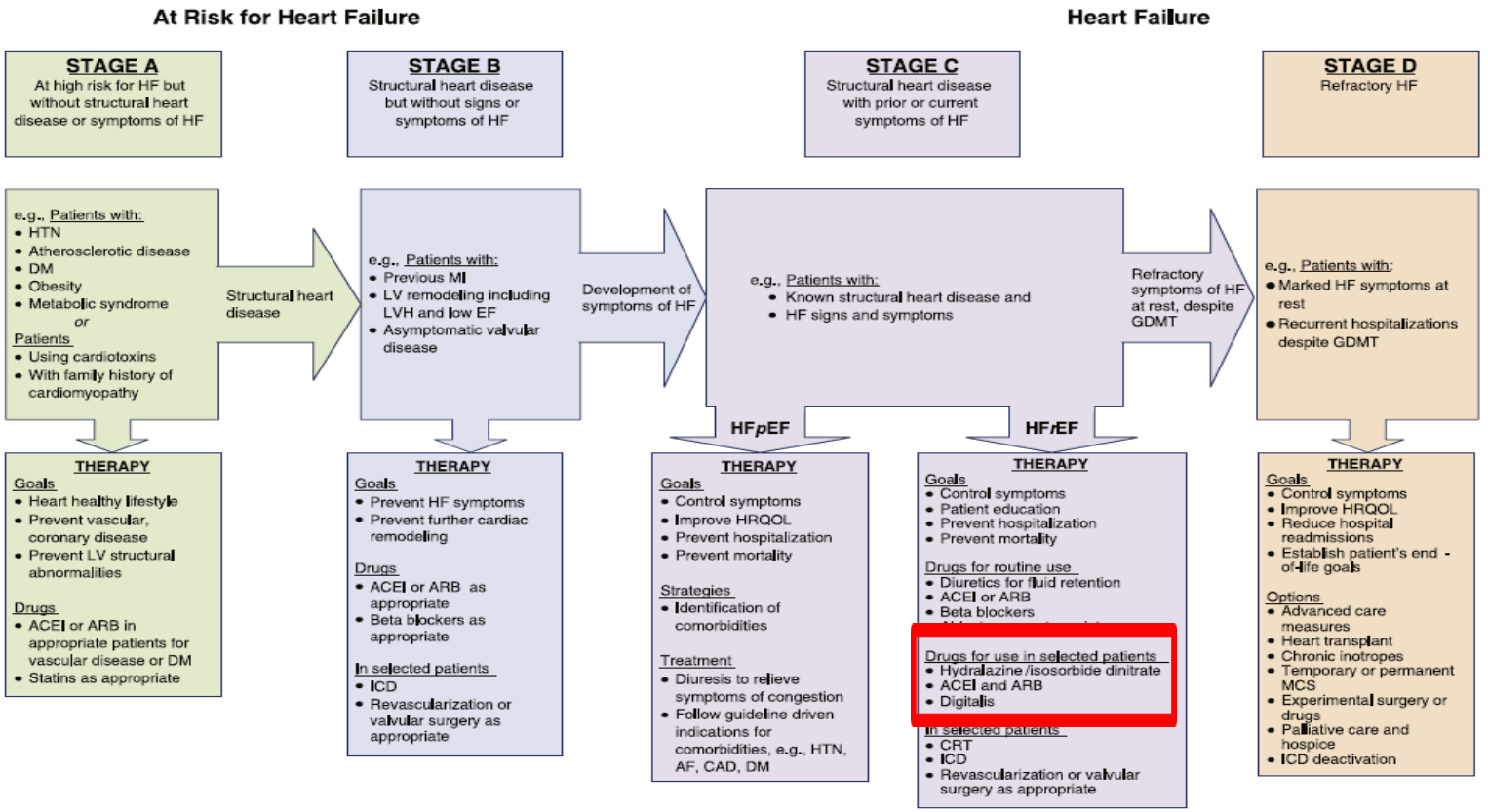


2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

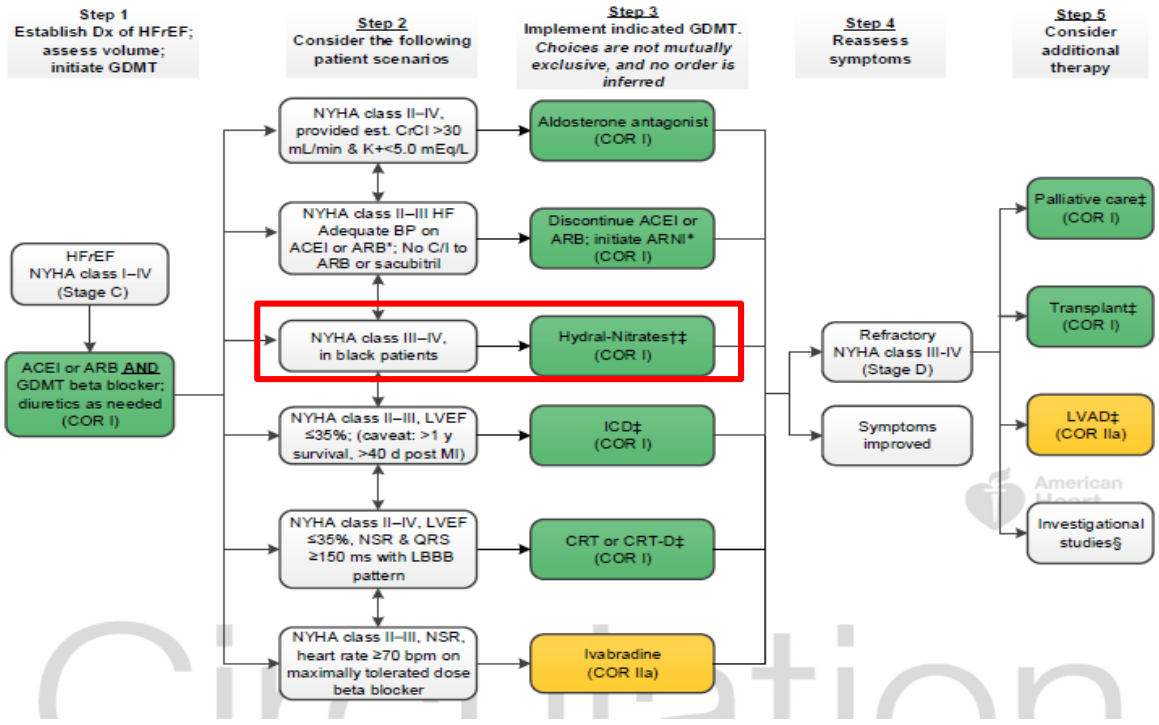


2013 ACCF/AHA Guideline for the Management of Heart Failure: Executive Summary

JACC Vol. 62, No. 16, 2013
October 15, 2013:1495–539



2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure



Resistant symptoms

digoxin or H-ISDN

Until the 1970s, treatment options for heart failure were limited to digitalis and diuretics

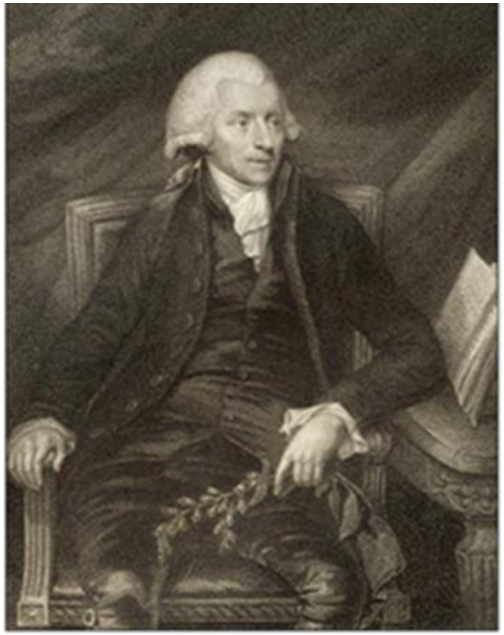
Digoxin

Digoxin is a purified cardiac glycoside extracted from the foxglove plant

Digoxin

William Withering

(1785)



…… as a treatment for swelling or edema.

……a slowing of the heart rate and of the heavy breathing

…..used improperly, foxglove can be deadly

J AM COLL CARDIOL
1983;1(2) 506–16

HISTORICAL NOTES

Digitalis Poisoning: Historical and Forensic Aspects

HOWARD B. BURCHELL, MD, FACC

Since the introduction of digitalis into therapy approximately 200 years ago, there have been continuing admonitions concerning its toxicity. Over 400 years ago, herbalists listed the plant as being poisonous. In fiction, the homicidal use of digitalis has appeared in the writings of Mary Webb, Dorothy Sayers and Agatha Christie.

Van Gogh's vision. Digitalis intoxication?

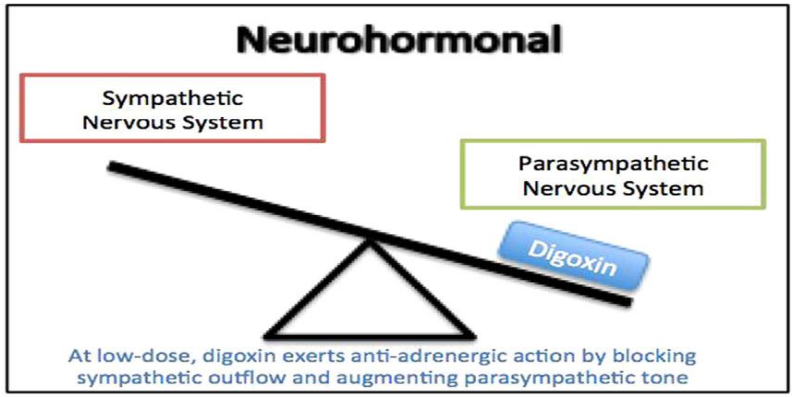
Lee TC.

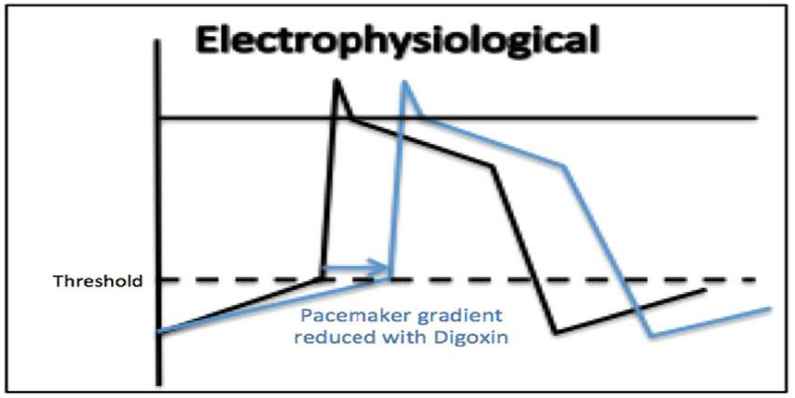
JAMA. 1981 Feb 20;245(7):727-9.

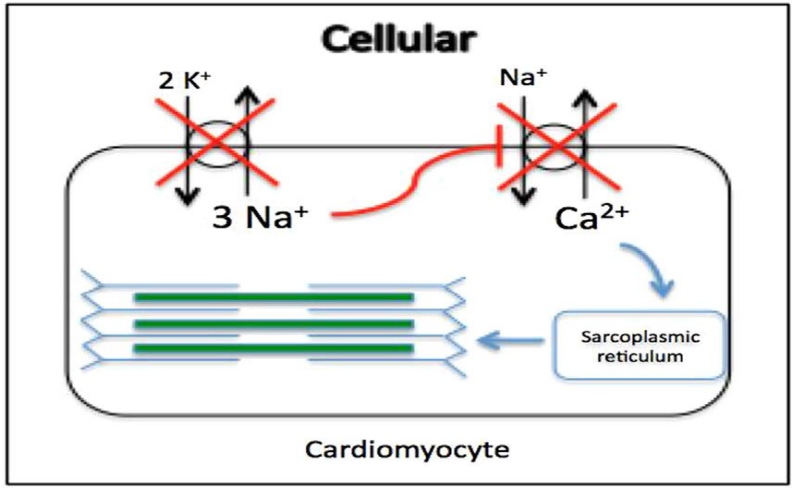
Abstract

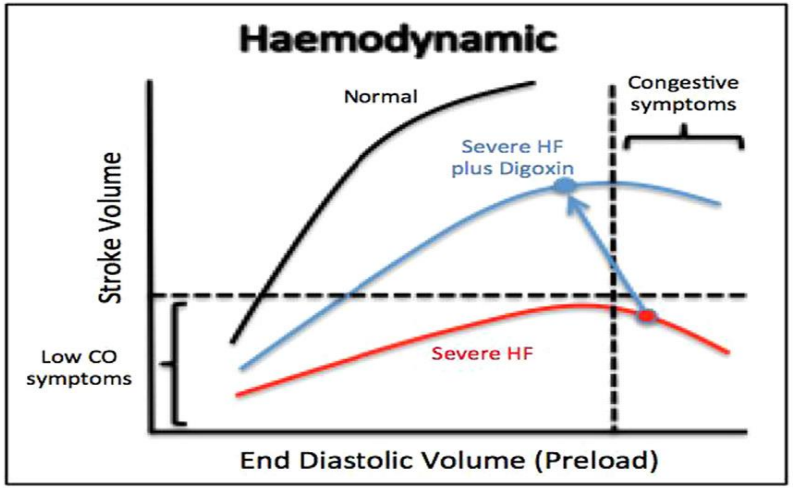
Vincent van Gogh, the Dutch postimpressionist painter, died in 1890. He was an uncommon man. Automutilation, depression, insanity, and suicide are part of his medical history. During the last few years of his life, his paintings were characterized by halos and the **color yellow**. Critics have ascribed these aberrations to innumerable causes, including chronic solar injury, glaucoma, and cataracts. **Van Gogh may have been under the influence of digitalis** intoxication and its side effects: xanthopsia and coronas. This hypothesis is based on his twice having painted his physician holding a foxglove plant; that this medicine wa
part of the 19th century in the treatment of ep
toxic effects of digitalis may have, in part, c
technique

Mechanism of action









Oliver J.Ziff et all.2016

Mechanism of action

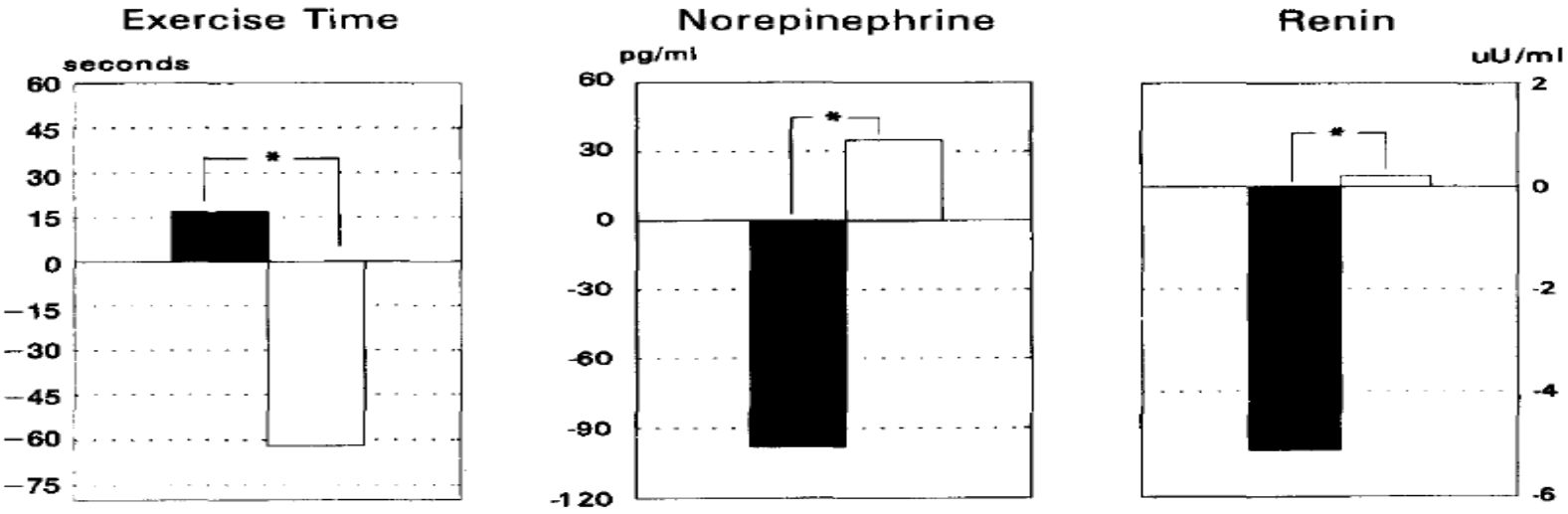
Table 2 Physiologic Effects of Digoxin Therapy

Hemodynamic	Neurohormonal	Electrophysiological
↑ LVEF	↑ Parasympathetic	SA node: slows sinus rate
↑ CO	↓ Sympathetic	AV node: prolongs conduction
↓ HR, ↔ BP	↓ RAAS	
↓ PCWP		

Value of Digoxin in Heart Failure and Sinus Rhythm: New Features of an Old Drug?

DIRK J. VAN VELDHUISEN, MD, PHD, FACC, PIETER A. DE GRAEFF, MD, PHD,
WILLEM J. REMME, MD, PHD, FACC, K. I. LIE, MD, PHD

Groningen, The Netherlands



JACC Vol. 22, No. 4
October 1993:955–62

Randomized Study Assessing the Effect of Digoxin Withdrawal in Patients With Mild to Moderate Chronic Congestive Heart Failure: Results of the PROVED Trial

BARRY F. URETSKY, MD, FACC, JAMES B. YOUNG, MD, FACC, F. EDEN SHAHIDI, MD, FACC, LARRY G. YELLEN, MD, MARIA C. HARRISON, BS, M. KING JOLLY, PharmD, ON BEHALF OF THE PROVED INVESTIGATIVE GROUP*

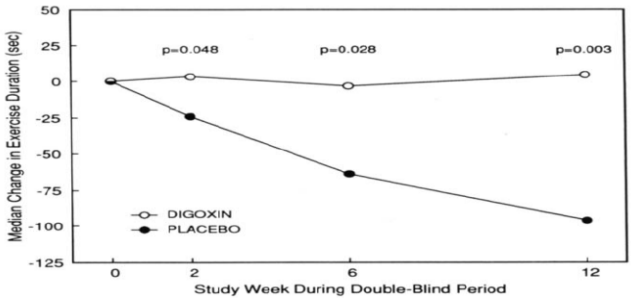


Table 2. Reasons for Withdrawal From the Trial

Reasons for Withdrawal	Placebo Group (n = 46) (no. [%])	Digoxin Group (n = 42) (no. [%])	p Value
Increase in drug therapy for worsening heart failure*	9 [20]	5 [12]	
Hospital admission for worsening heart failure	6 [13]	3 [7]	
Emergency room treatment for worsening heart failure	1 [2]	0 [0]	
Intercurrent/adverse events (includes death)	2 [4]	1 [2]	
Other†	3 [6]	1 [2]	
Total	21 [46]	10 [24]	0.032

PROVED Diuretic versus Diuretic + Digoxin

Conclusions. These data provide strong evidence of the clinical efficacy of digoxin in patients with normal sinus rhythm and mild to moderate chronic heart failure secondary to systolic dysfunction who are treated with diuretics.

The New England
Journal of Medicine

Volume 329 JULY 1, 1993 Number 1

WITHDRAWAL OF DIGOXIN FROM PATIENTS WITH CHRONIC HEART FAILURE TREATED WITH ANGIOTENSIN-CONVERTING–ENZYME INHIBITORS

MILTON PACKER, M.D., MIHAI GHEORGHIADE, M.D., JAMES B. YOUNG, M.D., PETER J. COSTANTINI, D.O., KIRKWOOD F. ADAMS, M.D., ROBERT J. CODY, M.D., L. KENT SMITH, M.D., LUCY VAN VOORHEES, M.D., LYNN A. GOURLEY, R.N., M.S., AND M. KING JOLLY, PHARM.D., FOR THE RADIANCE STUDY

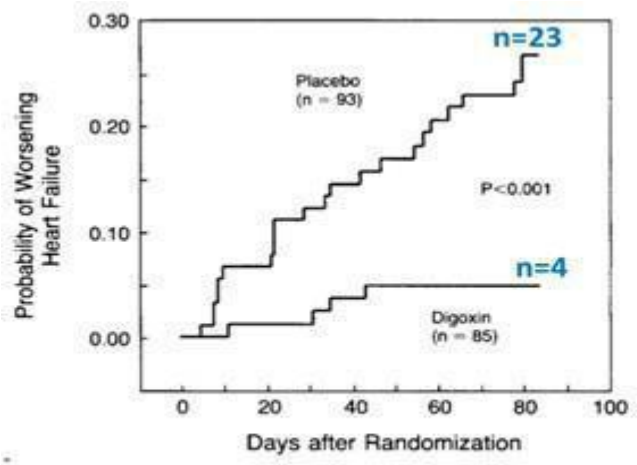


Figure 1. Kaplan–Meier Analysis of the Cumulative Probability of Worsening Heart Failure in the Patients Continuing to Receive Digoxin and Those Switched to Placebo.

RADIANCE ACEI + Diuretic versus
ACEI + Diuretic + Digoxin

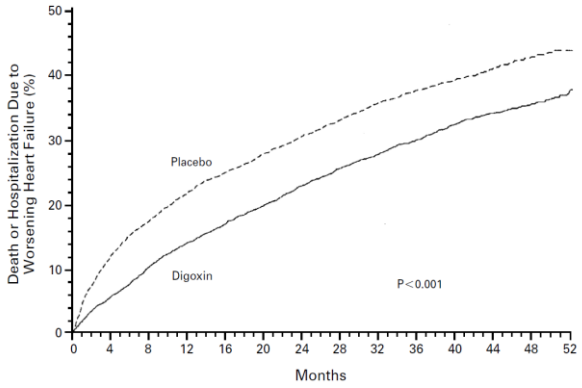
Conclusions. These findings indicate that the withdrawal of digoxin carries considerable risks for patients with chronic heart failure and impaired systolic function who have remained clinically stable while receiving digoxin and angiotensin-converting–enzyme inhibitors. (N Engl J Med 1993;329:1-7.)

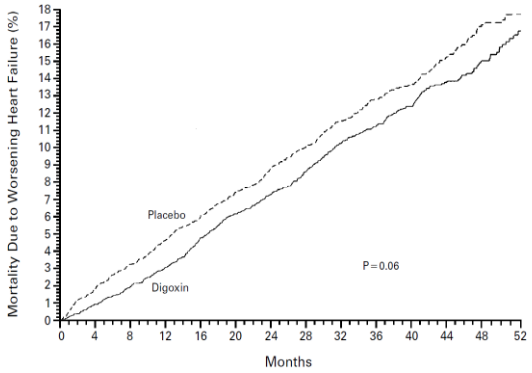
THE EFFECT OF DIGOXIN ON MORTALITY AND MORBIDITY IN PATIENTS WITH HEART FAILURE

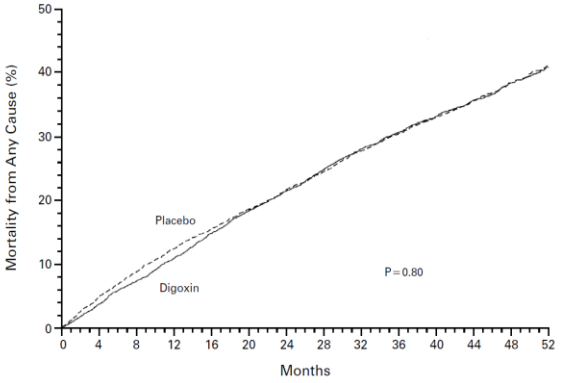
THE DIGITALIS INVESTIGATION GROUP* 1997

The DIG trial is currently the largest and most rigorous Assessment of digoxin in HFrEF patients with sinus rhythm

6800 participants with LVEF < 45%



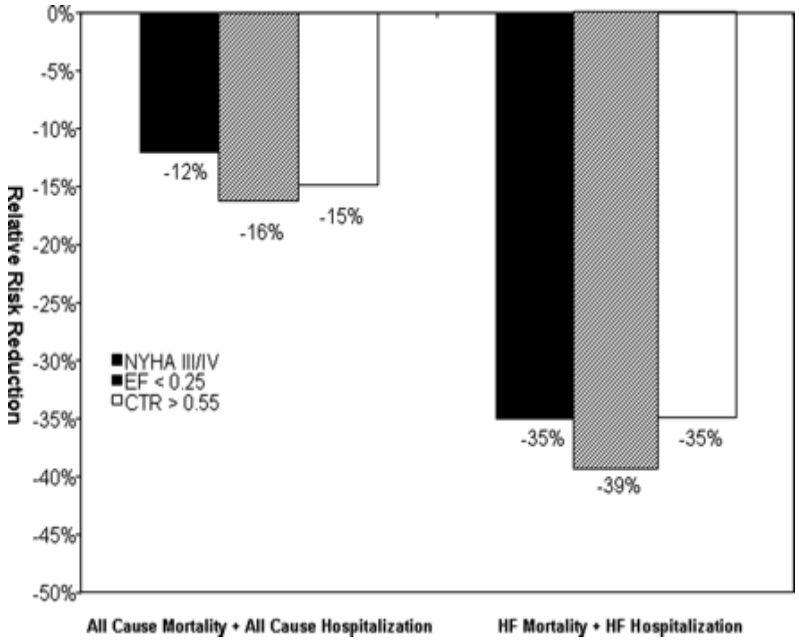


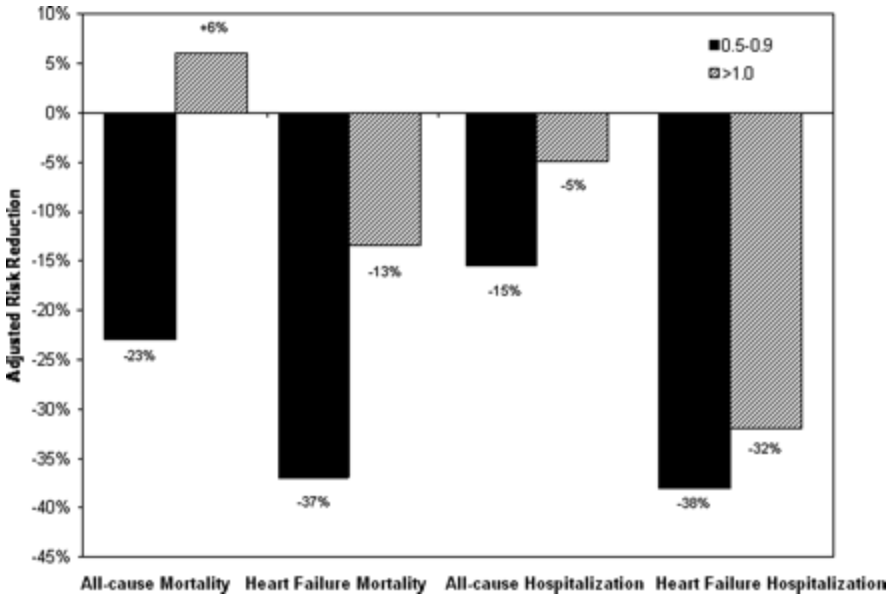


Conclusions Digoxin did not reduce overall mortality, but it reduced the rate of hospitalization both overall and for worsening heart failure. These find-

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

THE DIGITALIS INVESTIGATION GROUP*





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

Based on the review of NDA 20–405 for Lanoxin Tablets and with the recommendations of the advisory committee, FDA approved NDA 20–405 for the following indications:

Heart Failure: LANOXIN is indicated for the treatment of mild to moderate heart failure. LANOXIN increases left ventricular ejection fraction and improves heart failure symptoms as evidenced by exercise capacity and heart failure-related hospitalizations and emergency care, while having no effect on mortality. Where possible, LANOXIN should be used with a diuretic and an angiotensin-converting enzyme inhibitor, but an optimal order for starting these three drugs cannot be specified. [Glaxo Wellcome received 3 years of exclusivity for this indication.]

Digoxin Use in Major Heart Failure Trials

- SOLVD (1991): **66%**
- US Carvedilol (1996): **90%**
- **DIG (1997) >>>**
- COPERNICUS (2001): **65%**
- CHARM-Alternative (2003): **45%**
- RAFT (2010): **35%**
- EMPHASIS (2011): **27%**

However, the use of digoxin **declined** over the subsequent decades…

Digitalis for treatment of congestive heart failure in patients in sinus rhythm: a systematic review and meta-analysis

(William B. Hood Jr et all. 2004)

The literature indicates that the drug

has no effect on long-term mortality,

but

reduces the incidence of hospitalization,

and has a positive effect

on the clinical status of symptomatic patients.

Can Medications be Safely Withdrawn in Patients With Stable Chronic Heart Failure? Systematic Review and Meta-analysis

(Ingrid Hopper et all 2014)

Meta-analysis of 7 studies of digoxin withdrawal (2,987 participants)

showed

increased HF hospitalizations

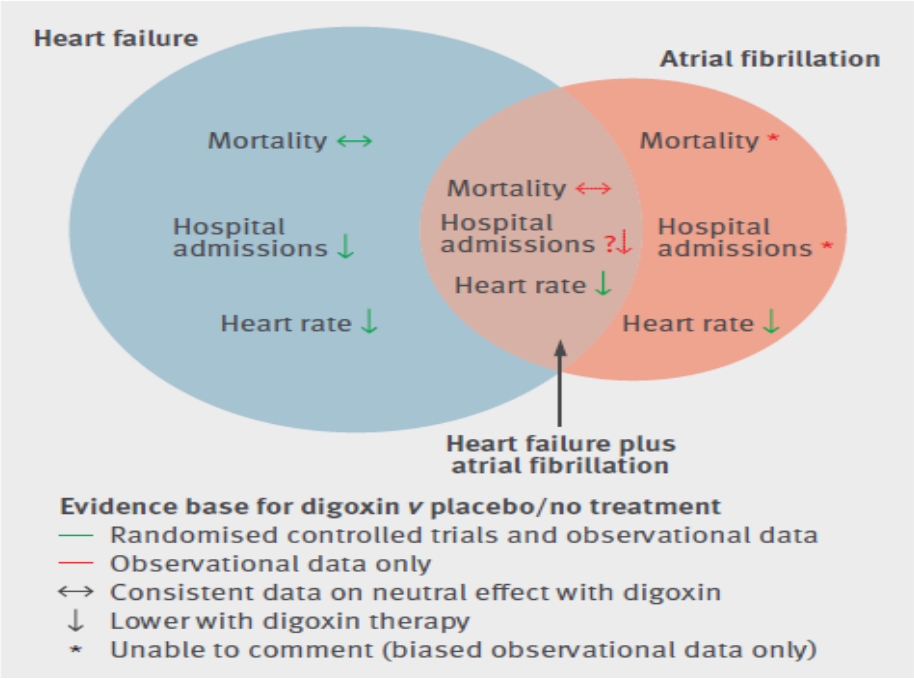
but

no impact on all-cause mortality

nor reduction in all-cause hospitalization

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]

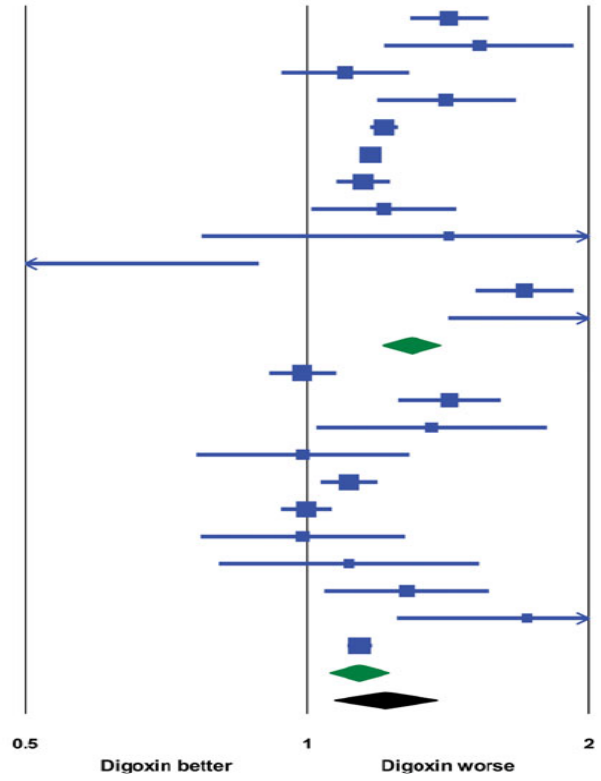


European Heart Journal (2015) **36**, 1831–1838
doi:10.1093/eurheartj/ehv143

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
Whitback (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
Gamst, 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**



Study	Patients	Digoxin dose (mg)	Statistics			
			Hazard ratio	95%	CI	p-Value
Garg (DIG), 1997	6800	0,244	0,99	0,91	1,07	0,81
Ahmed (DIG Ancillary), 2006	988	0,235	0,99	0,76	1,28	0,94
Freeman, 2013	2891	0,150	1,72	1,25	2,36	0,00
Mulder (RACE II), 2014	608	0,250	0,41	0,19	0,89	0,02
Freeman (ATRIA-CVRN), 2014	14787	0,164	1,71	1,52	1,93	0,00
Pastori, 2015	815	0,126	2,22	1,42	3,48	0,00
Total			**1,26**	**0,91**	**1,74**	**0,16**

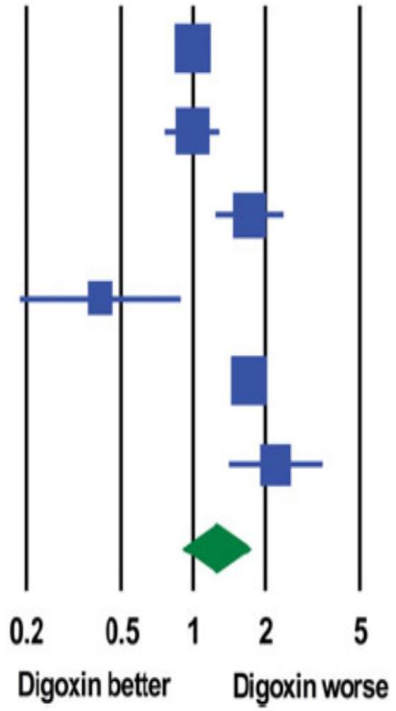
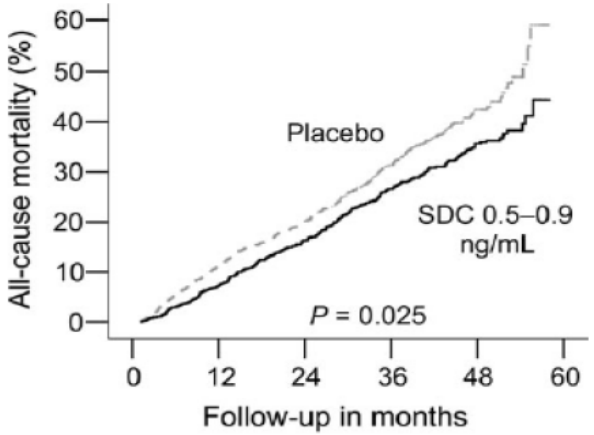
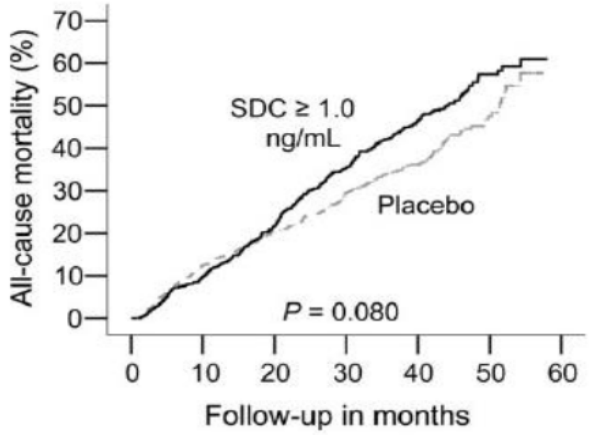


Figure 5 Sensitivity analysis of six studies which provided data on digoxin dosing.

Digoxin and reduction in mortality and hospitalization in heart failure: a comprehensive *post hoc* analysis of the DIG trial

Ali Ahmed[1*], Michael W. Rich[2], Thomas E. Love[3], Donald M. Lloyd-Jones[4], Inmaculada B. Aban[5], Wilson S. Colucci[6], Kirkwood F. Adams[7], and Mihai Gheorghiade[4]





HR = **0.81**;
95% CI = 0.67–0.97; P= **0.025**

HR = **1.19**;
95% CI = 0.98–1.45, P= **0.080**

Euro Heart J 2006; 27; 178–186

ELSEVIER

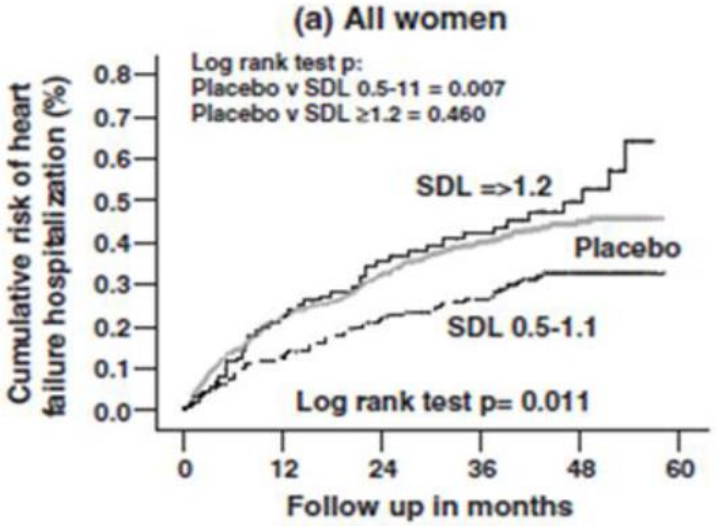
The European Journal of Heart Failure 8 (2006) 409 – 419

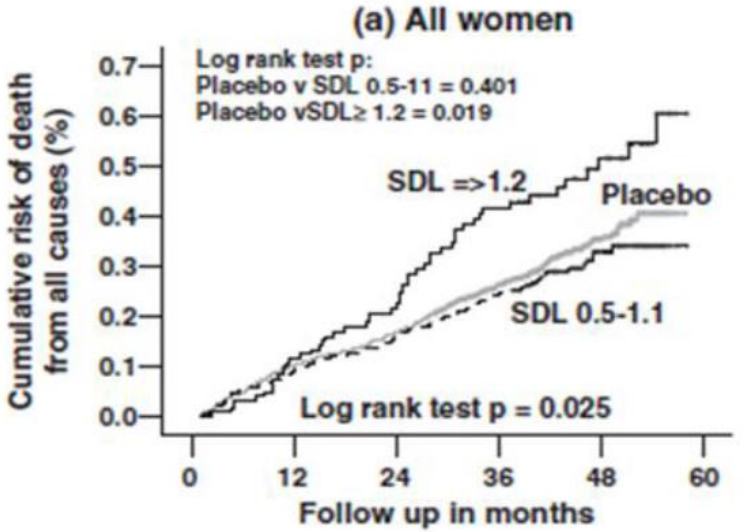
The European Journal of Heart Failure

www.elsevier.com/locate/heafai

Serum digoxin concentration and outcomes in women with heart failure: A bi-directional effect and a possible effect modification by ejection fraction

Ali Ahmed [a,b,d,e,*], Inmaculada B. Aban [c,e], Michael T. Weaver [a,e,f], Wilbert S. Aronow [g], Jerome L. Fleg [h]





The European Journal of Heart Failure 8 (2006) 409 – 419

Digoxin induced ventricular arrhythmia

Digoxin induced ventricular arrhythmia

Overdose of cardiac glycosides

induces,

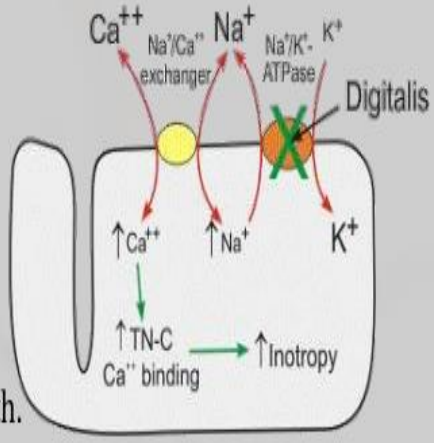
ventricular extra systoles,

ventricular tachycardia,

ventricular fibrillation and death.

Occurrence of these symptoms can be delayed by

anti-arrhythmic drugs



However, the same mechanism that explains the action of digoxin is probably also the one accountable for its toxicity.

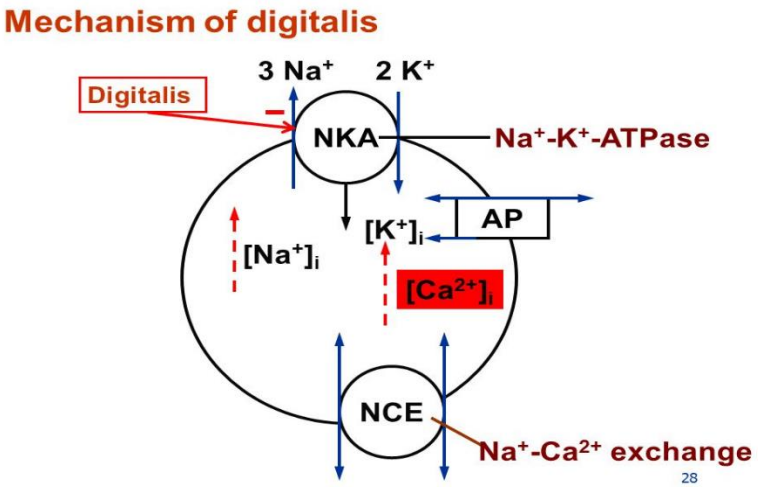
Progressively accumulating Ca ++ ions eventually exceed the storing capacity of the sarcoplasmic reticulum;this stimulates the forward mode of the Na + -Ca ++ exchanger and a transient inward depolarizing current arises.

This is believed to be the electrophysiological mechanism responsible for the generation of delayed after depolarizations, which in turn can induce polymorphic ventricular tachycardia due to triggered activity

Wasserstrom et.all .2005

Digitalis: new actions for an old drug

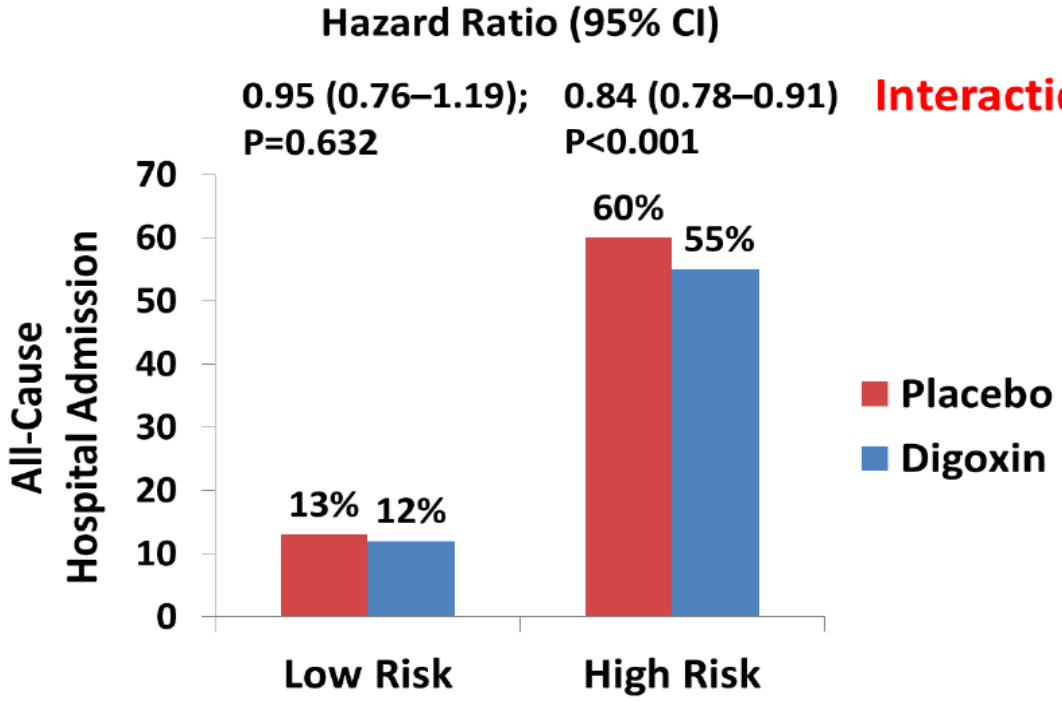
J. Andrew Wasserstrom[1,2,3] and Gary L. Aistrup[2] 2005



Wasserstrom, J. Andrew, and Gary L. Aistrup. Digitalis: new actions for an old drug. *Am J Physiol Heart Circ Physiol* 289: H1781–H1793, 2005; doi:10.1152/ajpheart.00707.2004.—The mechanisms by which digitalis causes its therapeutic and toxic actions have been studied for nearly a half century, revealing a great deal about cardiac cell regulation of intracellular ions via the Na-K-ATPase (NKA) and how it is altered by cardiac glycosides. However,

Effect of oral digoxin in high-risk heart failure patients: a pre-specified subgroup analysis of the DIG trial†

Mihai Gheorghiade[1], Kanan Patel[2], Gerasimos Filippatos[3], Stefan D. Anker[4], Dirk J. van Veldhuisen[5], John G.F. Cleland[6], Marco Metra[7], Inmaculada B. Aban[2], Stephen J. Greene[1], Kirkwood F. Adams[8], John J.V. McMurray[9], and Ali Ahmed[2,10]*

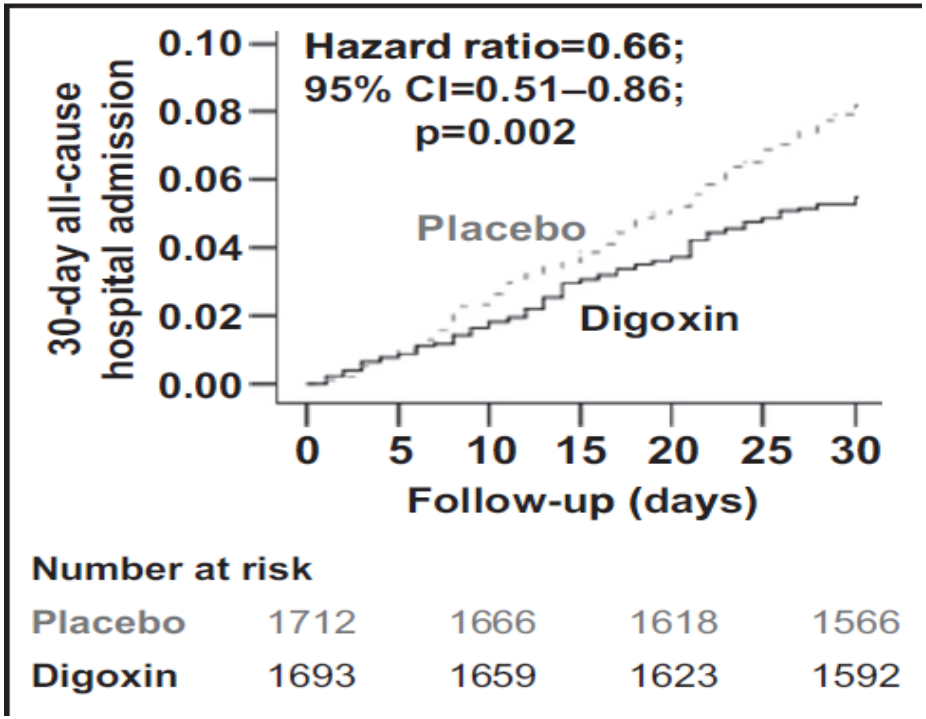


Digoxin was **more effective** in **high-risk patients** during the **first 2-years** of the trial…(*but **not** in low-risk patients*)…

European Journal of Heart Failure 2013; 15: 551–559

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]



Number at risk

Placebo	1712	1666	1618	1566
Digoxin	1693	1659	1623	1592

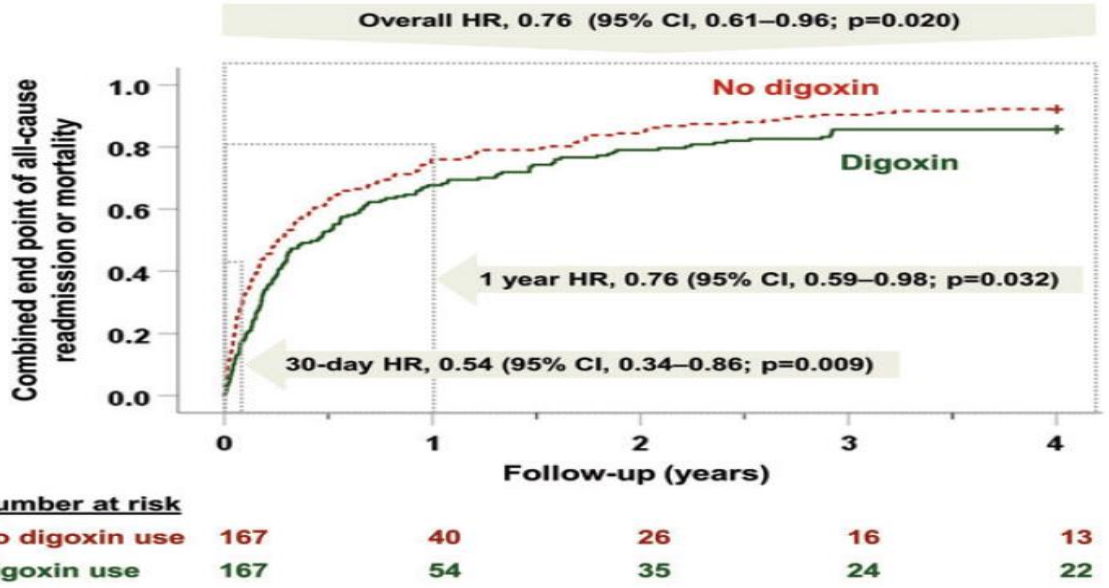
Received: 18 November 2017 | Revised: 29 December 2017 | Accepted: 3 January 2018
DOI: 10.1002/clc.22889

WILEY CLINICAL CARDIOLOGY

CLINICAL INVESTIGATIONS

Digoxin use and lower risk of 30-day all-cause readmission in older patients with heart failure and reduced ejection fraction receiving β-blockers

Phillip H. Lam[1,2] | Poonam Bhyan[1,2] | Cherinne Arundel[1,3] | Daniel J. Dooley[1,2] | Helen M. Sheriff[1,3] | Selma F. Mohammed[4] | Gregg C. Fonarow[5] | Charity J. Morgan[6] | Wilbert S. Aronow[7] | Richard M. Allman[8] | Finn Waagstein[9] | Ali Ahmed[1,3]

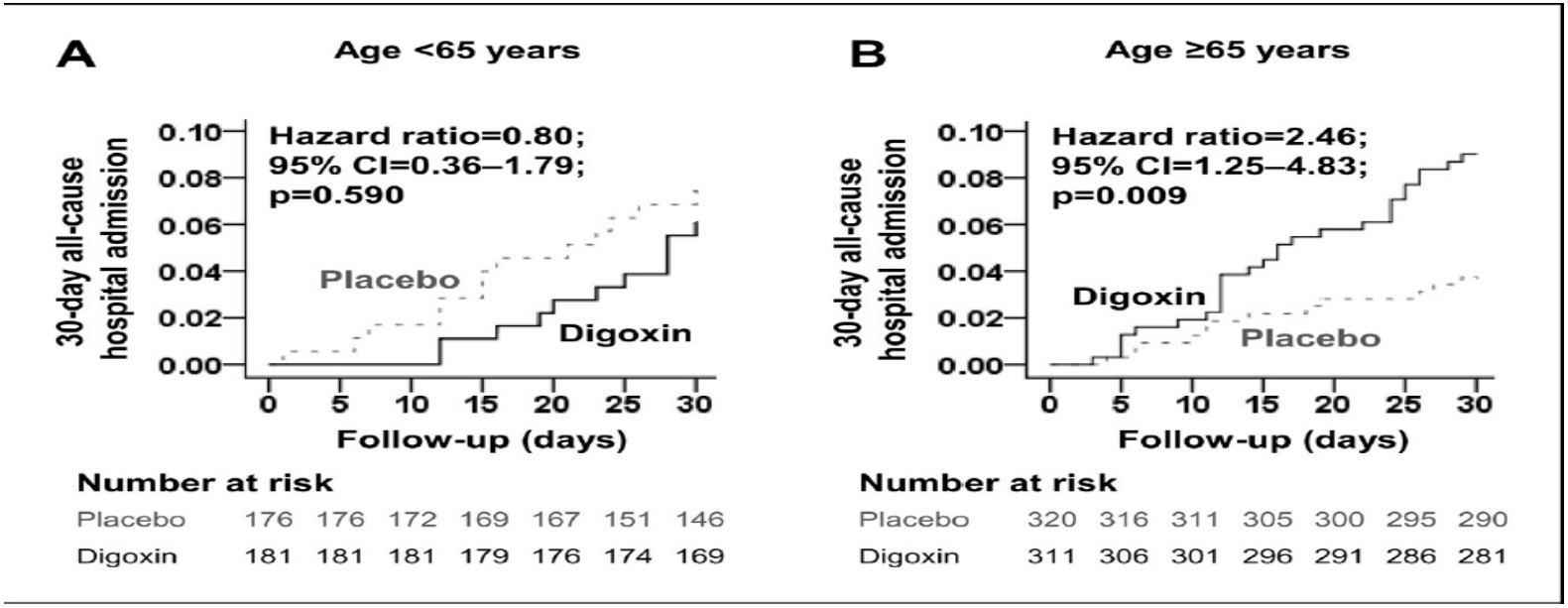


CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Digoxin and 30-day All-cause Hospital Admission in Older Patients with Chronic Diastolic Heart Failure

Taimoor Hashim, MD,[a,1] Shereen Elbaz, MBBCh, MPH,[a,1] Kanan Patel, MBBS, MPH,[a] Charity J. Morgan, PhD,[a] Gregg C. Fonarow, MD,[b] Jerome L. Fleg, MD,[c] Gerald McGwin, PhD,[a] Gary R. Cutter, PhD,[a] Richard M. Allman, MD,[a,d] Sumanth D. Prabhu, MD,[a,d] Michael R. Zile, MD,[e,f] Robert C. Bourge, MD,[a] Ali Ahmed, MD, MPH[a,d]



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?

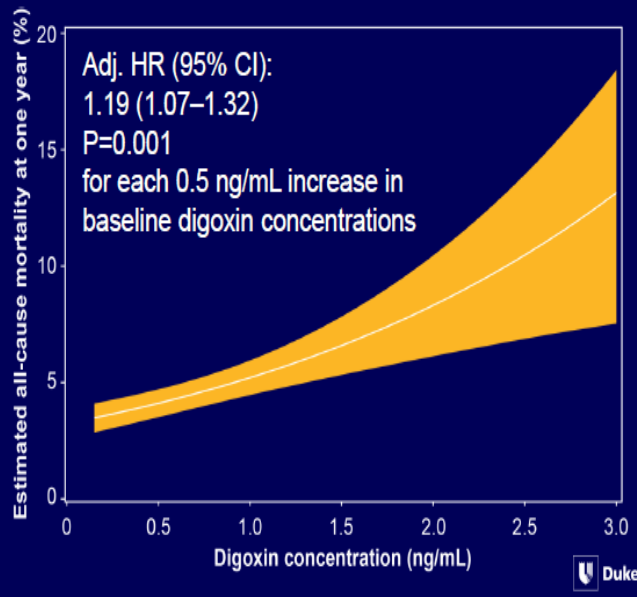
Renato D. Lopes, MD, PhD, FACC
on behalf of the ARISTOTLE Investigators

Duke Clinical Research Institute

UCR
Uppsala Clinical Research Center

Τα αποτελέσματα της ανάλυσης έδειξαν σημαντική αύξηση της θνητότητας στους ασθενείς που είναι σε αγωγή με διγοξίνη.

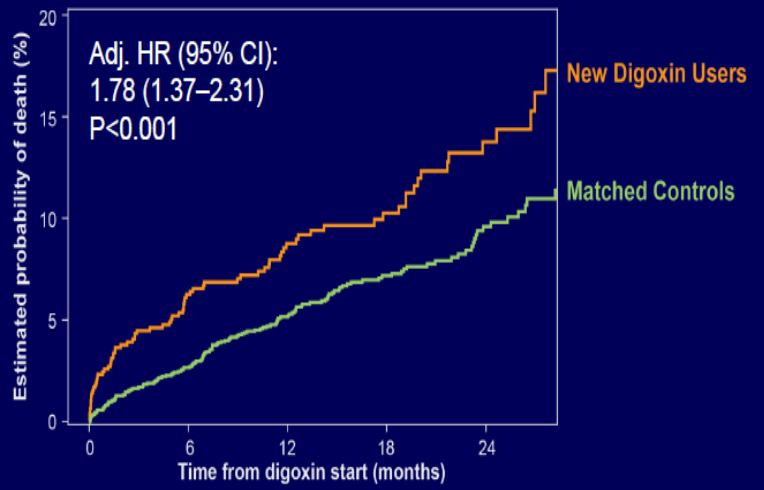
Adjusted Mortality by Digoxin Concentration



Duke Clinical Research Institute

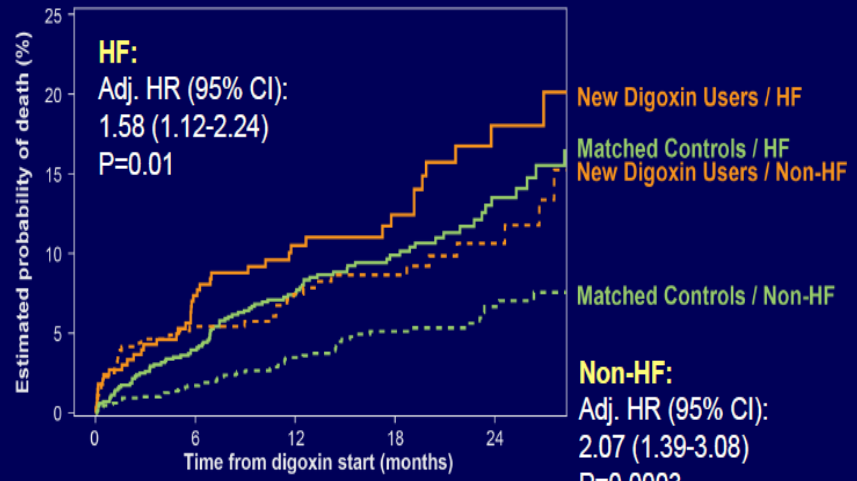
UCRO

Adjusted Mortality in New Digoxin Users versus Matched Controls



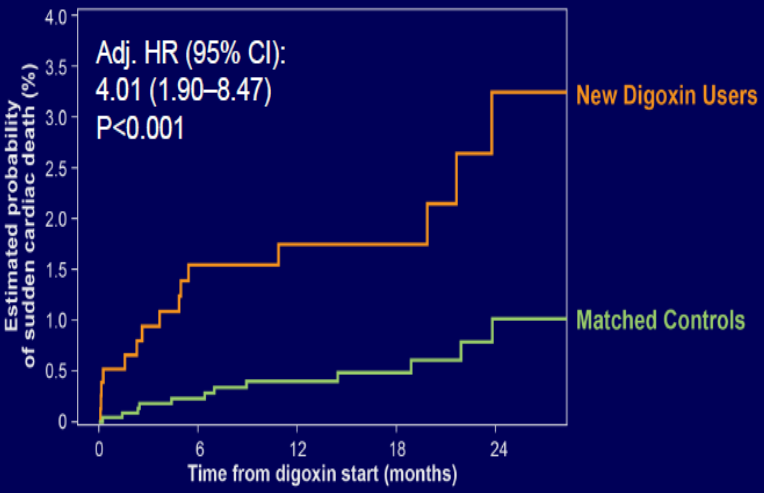
New Digoxin Users	779	619	447	290	150
Matched Controls	2337	1910	1386	867	431

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

Adjusted Sudden Death in New Digoxin Users versus Matched Controls



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

ARISTOTLE

Digoxin and Mortality

MAIN RESULTS

Παρατηρήθηκε αύξηση της θνητότητας κατά **19%** για **κάθε 0,5ng/ml** αύξηση της συγκέντρωσης διγοξίνης

Ασθενείς με επίπεδα διγοξίνης μεγαλύτερα από **1,2ng/ml** είχαν έως και **56%** αυξημένη θνητότητα.

Στους ασθενείς με καρδιακής ανεπάρκεια παρατηρήθηκε σημαντικότατη αύξηση κατά **58% της θνητότητας** σε αυτούς που τέθηκαν σε αγωγή με διγοξίνη κατά τη διάρκεια της μελέτης, σε σύγκριση με ασθενείς με καρδιακή ανεπάρκεια που δε λάμβαναν διγοξίνη.

Digoxin Use in Patients With AF

ROCKET-AF

Endpoint	Adjusted HR (95% CI)* No HF	HF	Interaction *P* Value
All-cause mortality	1.19 (0.95-1.48)	1.23 (1.07-1.41)	.79
Vascular death	1.18 (0.88-1.59)	1.24 (1.05-1.47)	.78
Sudden death	1.14 (0.71-1.82)	1.33 (1.04-1.71)	.56
All-cause hospitalization	0.96 (0.85-1.09)	1.08 (0.99-1.18)	.12

*HRs for digoxin vs no digoxin.

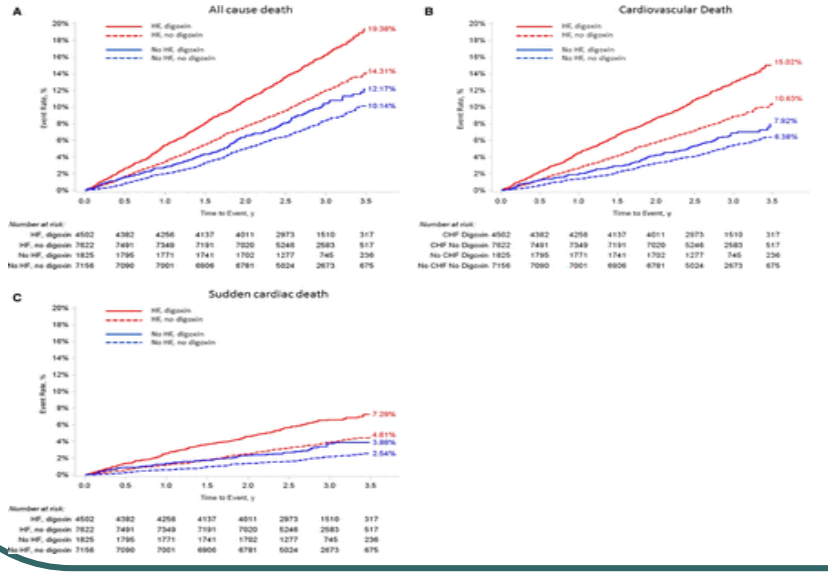
Washam JB, et al. *Lancet*. 2015;385:2363-2370.

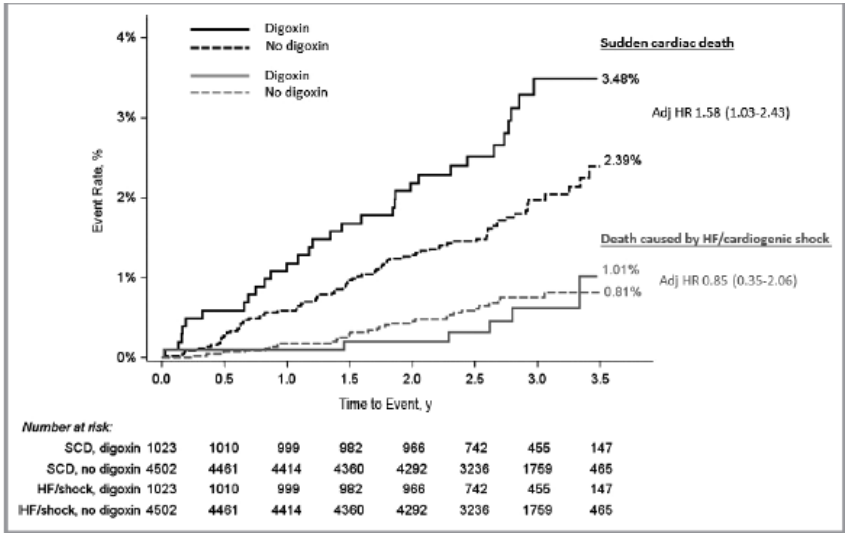
Digoxin Use and Subsequent Clinical Outcomes in Patients With Atrial Fibrillation With or Without Heart Failure in the ENGAGE AF-TIMI 48 Trial

Alon Eisen, MD; Christian T. Ruff, MD, MPH; Eugene Braunwald, MD; Rose A. Hamershock, MA; Basil S. Lewis, MD; Christian Hassager, MD; Tze-Fan Chao, MD; Jean Yves Le Heuzey, MD; Michele Mercuri, MD; Howard Rutman, MD; Elliott M. Antman, MD; Robert P. Giugliano, MD, SM

J Am Heart Assoc. 2017

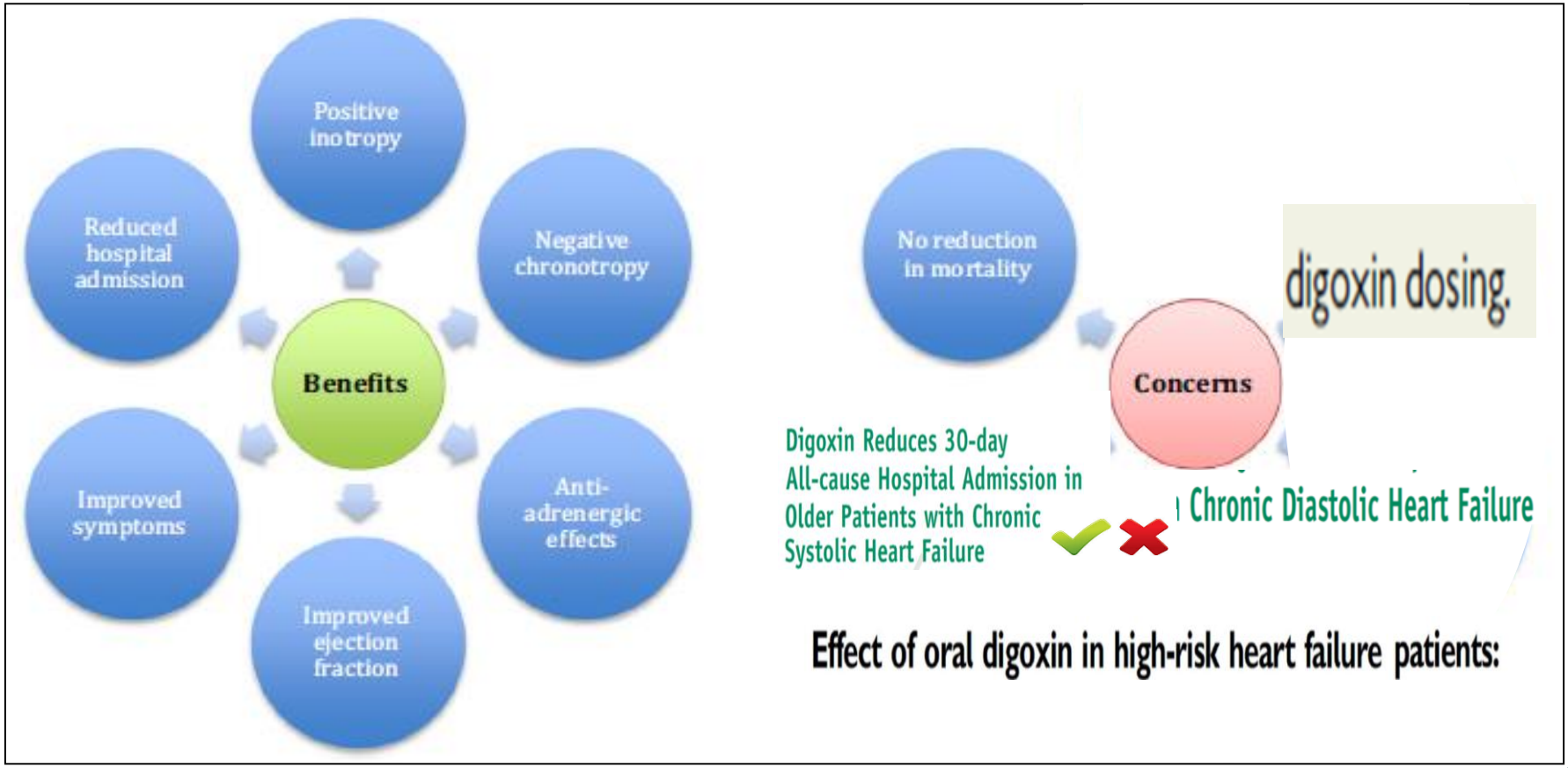
1.90; 95% CI, 1.36–2.65). Among patients with HF (n=12 124), digoxin use (37%) was associated with an increase in all-cause death, cardiovascular death, sudden cardiac death, and death caused by HF/cardiogenic shock ($P<0.01$ for each), but not with





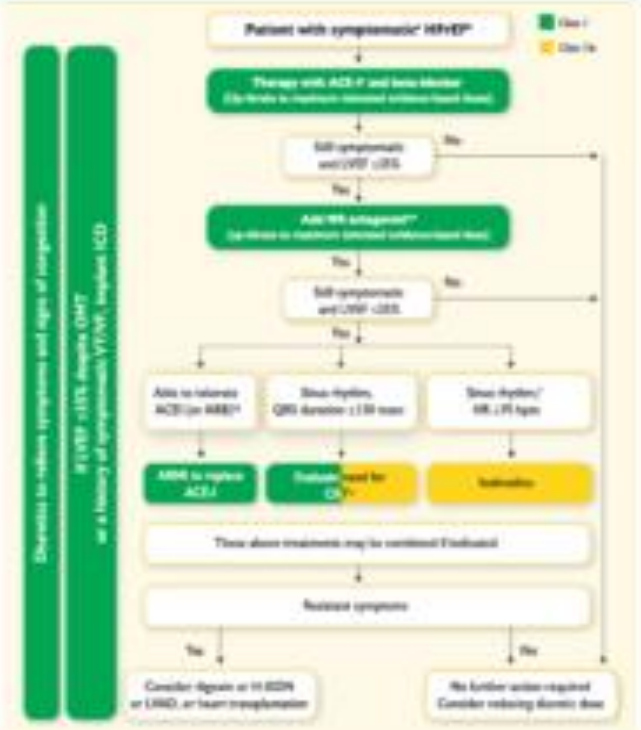
Digoxin: The good and the bad (2016)

Oliver J. Ziff, MBChB, BSc[a,b], and
Dipak Kotecha, MBChB, PhD, MRCP, FESC, FHEA[a,c,]*



ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure



2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

in selected patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction

Digoxin		
Digoxin may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE-I (or ARB), a beta-blocker and an MRA, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations).	IIb	B

Επισημαίνεται επίσης ότι τα επίπεδα διγοξίνης θα πρέπει να ελέγχονται και να παραμένουν εντός των ορίων **0.5-0.9ng/ml**.

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Atrial fibrillation

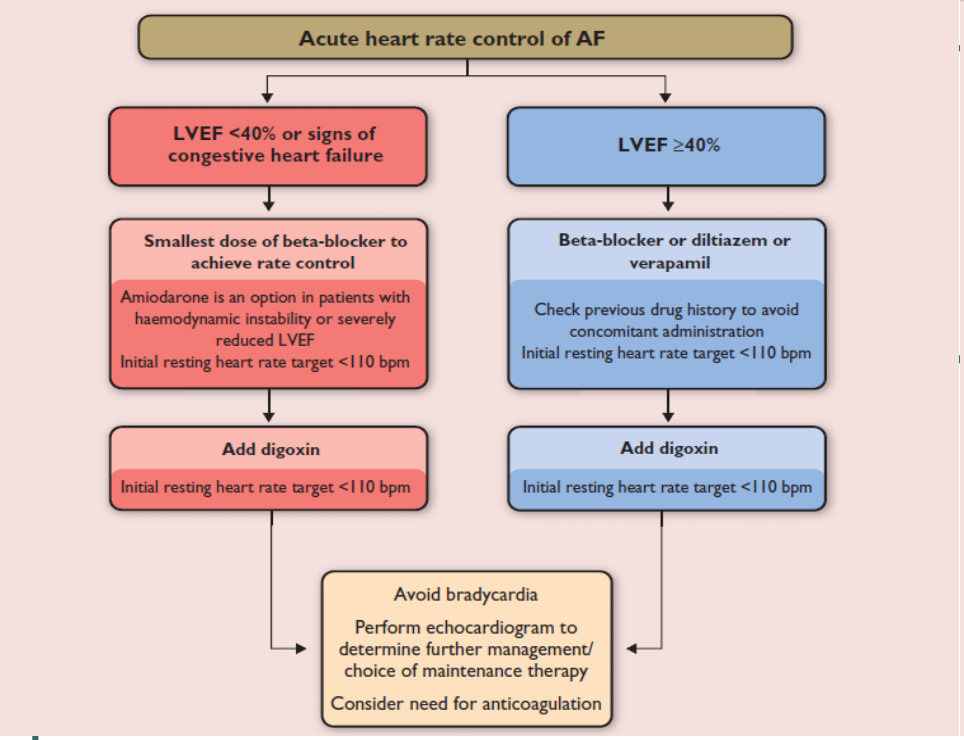
For patients in NYHA Class I–III, digoxin, should be considered when ventricular rate remains high[d] despite beta-blockers or when beta-blockers are not tolerated or contra-indicated.	IIa	B
For patients in NYHA Class IV, in addition to treatment for AHF, an intravenous bolus of amiodarone or, in digoxin-naïve patients, an intravenous bolus of digoxin should be considered to reduce the ventricular rate.	IIa	B

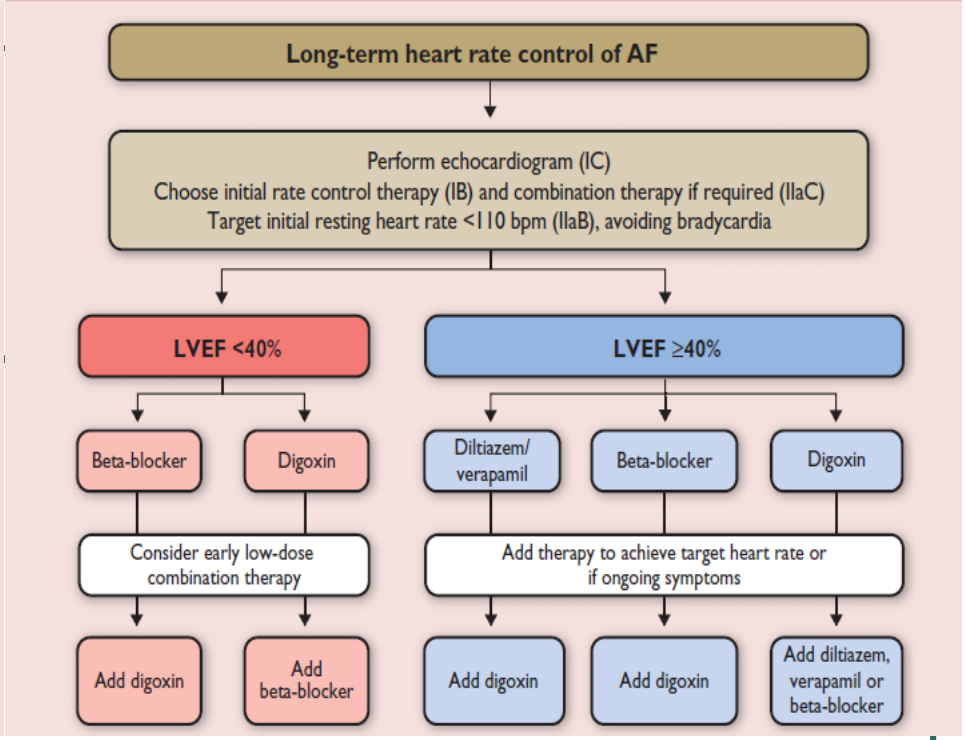
…..σε ασθενείς με **καρδιακή ανεπάρκεια και κολπική μαρμαρυγή**, όταν η συχνότητα **δεν** ελεγχεται παρά τη μέγιστη χορήγηση β-αναστολέων, ή όταν **αντενδείκνυται** η χορήγηση β-αναστολέων

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

Rate control therapy in atrial fibrillation

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.		





Beta-blockers and/or digoxin are recommended to control heart rate in AF patients with LVEF <40%.	I	B

2013 ACCF/AHA Guideline for the Management of Heart Failure: Executive Summary

Digoxin

Digoxin can be beneficial in patients with HF⁄EF

Digoxin in Heart Failure with a Reduced Ejection Fraction: A Risk Factor or a Risk Marker?

Dimitrios M. Konstantinou Haralambos Karvounis George Giannakoulas

First Cardiology Department, AHEPA University Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece

At least two factors can explain why clinicians seem reluctant to prescribe digoxin:

….from inotropic support to neurohormonal modulation

1) **There is a great deal of uncertainty regarding its clinical efficacy in modern HF patients**

2) **A series of reports on increased risks associated with long-term digoxin use, presumably due to its proarrhythmic properties, have cast doubt on its safety.**

Digoxin in Heart Failure with a Reduced Ejection Fraction: A Risk Factor or a Risk Marker?

Dimitrios M. Konstantinou Haralambos Karvounis George Giannakoulas

First Cardiology Department, AHEPA University Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece

Conclusions

Nevertheless, in our view, **cardiac glycosides should not be discarded from the HF** armamentarium. Digoxin probably **still plays a role in patients** with **severe HF with evidence of congestion who are unable to tolerate high doses of disease modifying agents due to borderline blood pressure/renal function.** Digoxin should be used with the aim of **reducing hospital readmissions**, while SDC and creatinine and potassium levels should be closely monitored to minimize the risk of toxicity.

Nitrate Therapy in Heart Failure

Why the combination of
Hy+ISDN
takes a back seat
in HFrEF therapy ?

.

JACC: Heart Failure
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ISSN 2213-1779/$36.00
http://dx.doi.org/10.1016/j.jchf.2013.03.003

STATE-OF-THE-ART PAPER

CME

Nitrate Therapy for Heart Failure

Benefits and Strategies to Overcome Tolerance

Benefits of Nitrate Therapy in Heart Failure

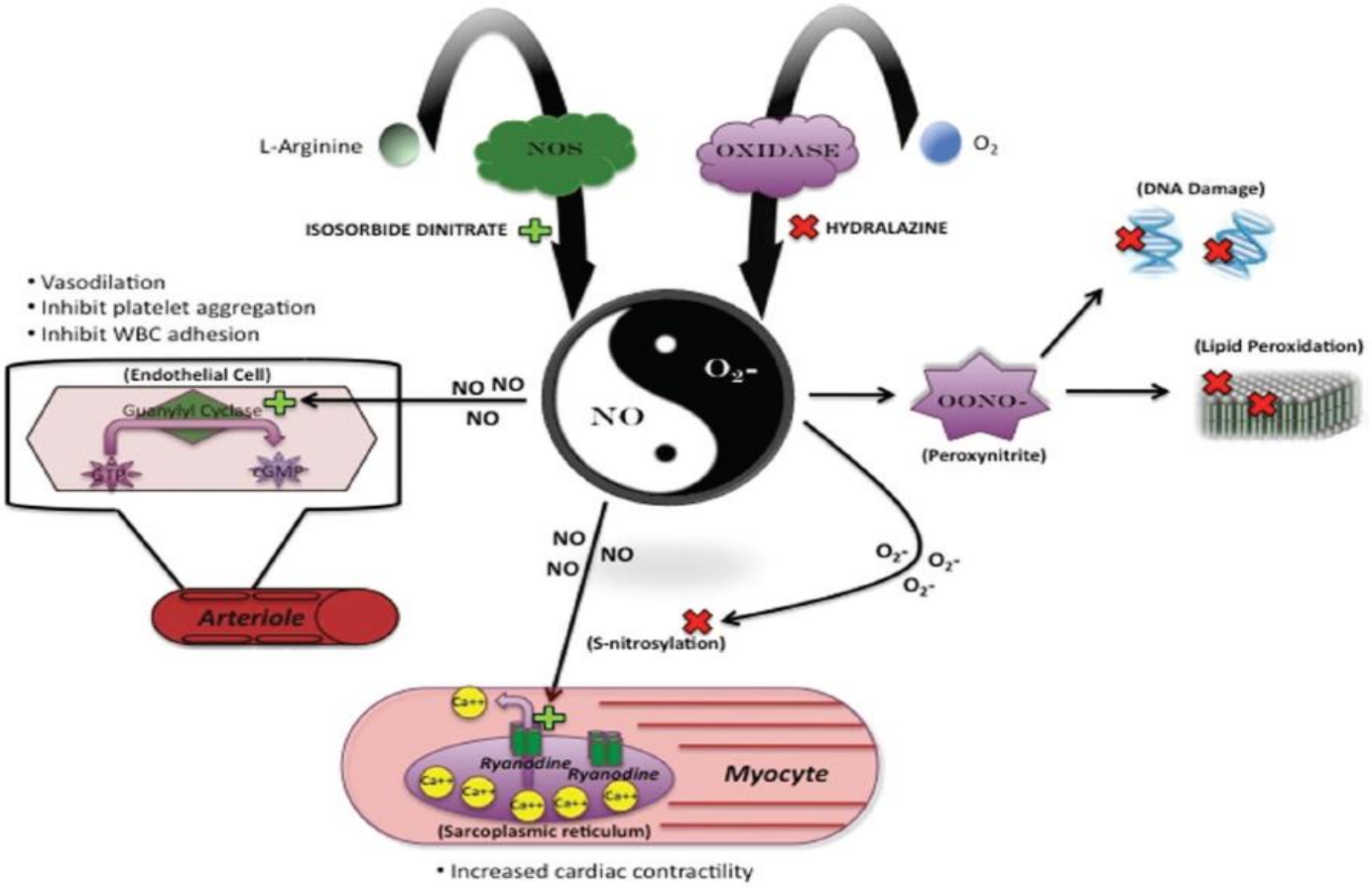
S-nitrosylation of effector proteins (8,13)
- Activates ryanodine receptors to improve myocardial contractility
- Regulates endothelial function
- Inhibits smooth muscle hyperplasia
- Regulates blood flow with changes in tissue oxygen tension matching flow to demand
- Protects myocytes by preventing oxidative dam
- Scavenges superoxide anions
- Regulates energy metabolism
- Protects cells from apoptosis

Guanylyl cyclase activation (8,17)
- Promotes venous and arterial smooth muscle re afterload
- Inhibits platelet aggregation by inhibiting platel endothelium
- Has anti-inflammatory effects by preventing leu endothelium
- Has antiapoptotic effects
- Has antiremodeling effects

Hemodynamic conditions (12,18,19)
- Decreased pulmonary capillary wedge pressure
- Decreased left ventricular end diastolic pressure
- Decreased pulmonary vascular resistance and right ventricular afterload
- Decreased systemic vascular resistance and left ventricular afterload
- Increased venous capacitance
- Decreased right atrial pressure
- Decreases myocardial oxygen demand

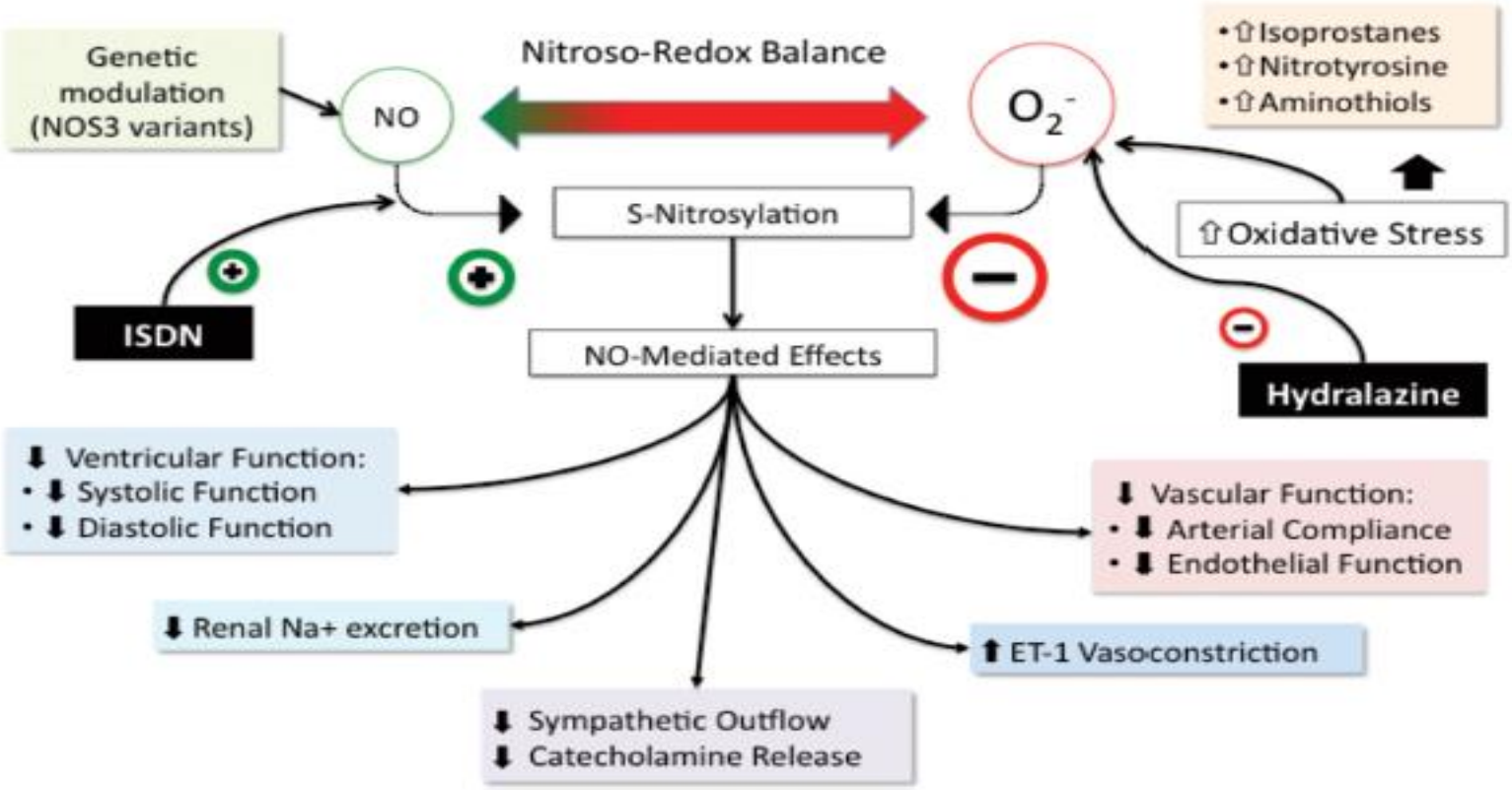
Hydralazine and Isosorbide Dinitrate in Heart Failure
Historical Perspective, Mechanisms, and Future Directions

Nitroso-Redox Balance and Heart Failure



Robert T. Cole. (*Circulation*. 2011

Nitroso-Redox Balance and Heart Failure

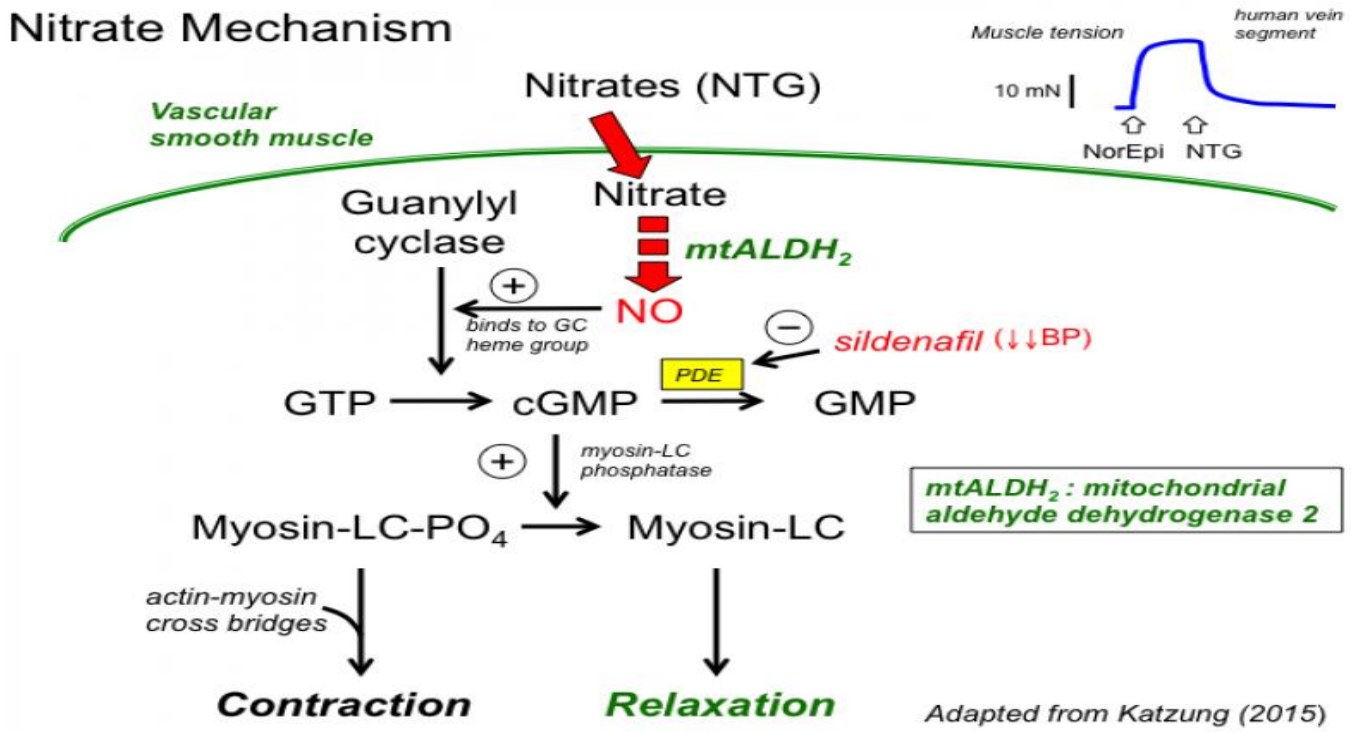


Robert T. Cole. (*Circulation*. 2011

Organic Nitrates in Heart Failure Revisited

Pentaerythritol Tetranitrate Induces Heme Oxygenase 1 to Protect the Myocardium

Philip Wenzel



Hypertension. 2015;66:933-934.

Nitrate Therapy in Heart Failure

In patients with heart failure, nitroprusside reduced

- **systemic vascular resistance by 50%,**
- **increased cardiac output by 56%,**
- **and reduced left ventricular filling pressure by 47%.**

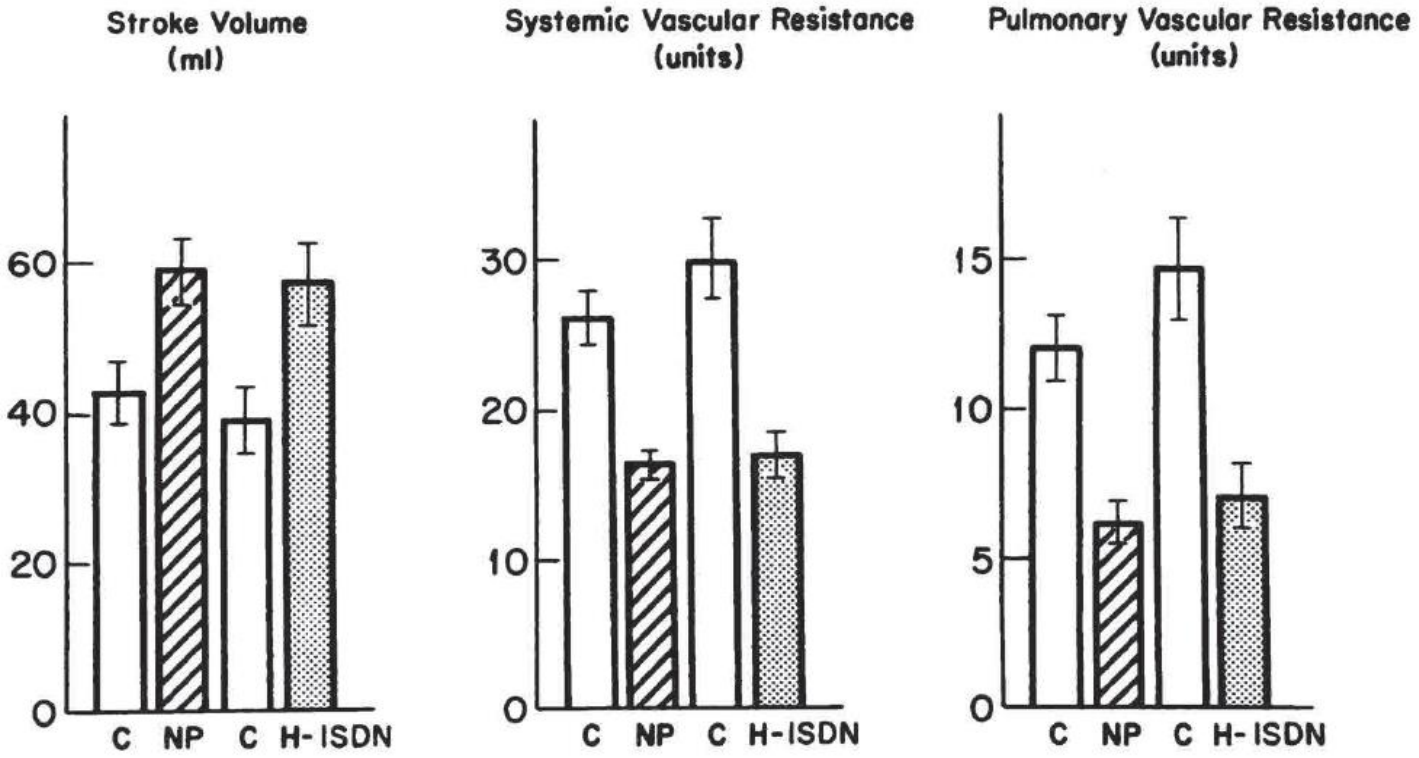
These hemodynamic benefits with nitroprusside led to studies with oral agents, including hydralazine, isosorbide dinitrate (ISDN)

Franciosa et all. Lancet. 1972
Guiha et all .N Engl J Med. 1974

Combined Oral Hydralazine-Nitrate Therapy in Left Ventricular Failure*

Hemodynamic Equivalency to Sodium Nitroprusside

Gordon L. Pierpont, M.D.; Jay N. Cohn, M.D.; and Joseph A. Franciosa, M.D.



… none was as effective as nitroprusside individually

CHEST, 73: 1, JANUARY, 1978

Cardiovascular Therapeutics

When Should We Use Nitrates in Congestive Heart Failure?

Enrico Vizzardi, Ivano Bonadei, Riccardo Rovetta, Antonio D'Aloia, Filippo Quinzani, Antonio Curnis & Livio Dei Cas

Section of Cardiovascular Diseases, Department of Experimental and Applied Medicine, University of Study of Brescia, Brescia, Italy

Table 4 Principal studies regarding use of organic nitrates in chronic heart failure

Study	Population	Treatment	Endpoint	Results
V-Heft I [29]	Patients with impaired cardiac function (average EF = 30%) and reduced exercise tolerance (n = 642)	Placebo (n = 263) versus 2.5 mg prazosin/daily (n = 183) versus 300–160 mg H-ISDN/daily (n = 186)	Cumulative mortality rate in 2.3 years of follow up	Similar in placebo and prazosin group. Risk reduction by 2 years: 34% H-ISDN versus Placebo ($P < 0.028$)
V-Heft II [30]	Patients with impaired cardiac function (average EF = 29%) and reduced exercise tolerance (n = 804)	Enalapril 20 mg/daily (n = 403) versus H-ISDN 300–160 mg/daily (n = 401)	Total mortality after 2 years Oxygen consumption (ml/Kg/min)	18% versus 25% ($P = 0.016$) Increased only by H-ISDN ($P < 0.05$)
A-Heft [31]	Black patients who had New York Heart Association class III or IV heart failure with average EF 30% (n = 1050)	H-ISDN 225–120 mg/daily (n = 518) versus placebo (n = 532)	Total mortality First hospitalization for heart failure	10.2% versus 6.2% ($P = 0.02$) 24.4% versus 16.4% ($P = 0.001$)
Mullens et al. [32]	Patient discharged with advance systolic congestive heart failure (NHYA III-IV; n = 239)	H-ISDN + ACE I/ARB (n = 142) versus ACEI/ARB (n = 97) titrated to hemodynamic response	All-cause mortality Cardiac transplant HF rehospitalization All-cause mortality + HF rehospitalization	34% versus 41% ($P = 0.04$) 22% versus 19% ($P = 0.5$) 59% versus 64% ($P = 0.4$) 70% versus 85% ($P = 0.03$)

The Vasodilator–Heart Failure Trials I

EFFECT OF VASODILATOR THERAPY ON MORTALITY IN CHRONIC CONGESTIVE HEART FAILURE

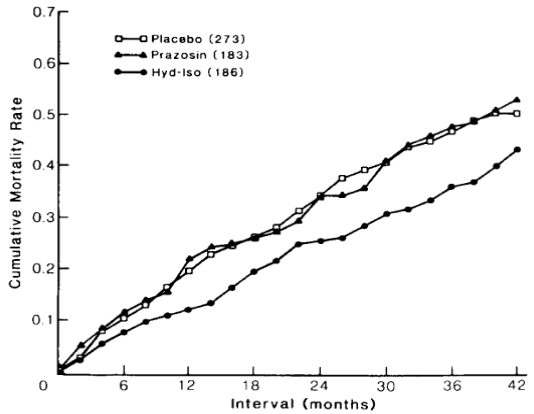


Figure 1. Cumulative Mortality from the Time of Randomization in the Three Treatment Groups.

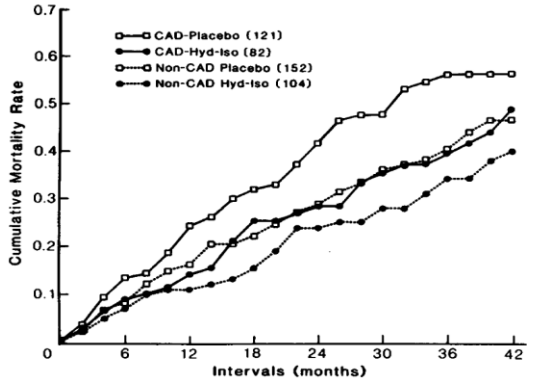


Figure 2. Cumulative Mortality among Patients with (n = 203) and without (n = 256) Coronary Artery Disease (CAD) Treated with Placebo or Hydralazine–Isosorbide Dinitrate (Hyd–Iso).

Table 4. Hemodynamic Response in the Three Treatment Groups.

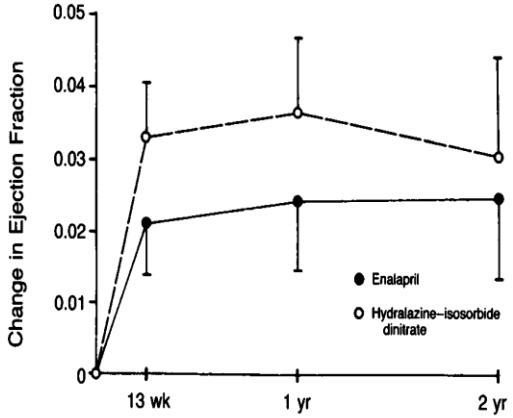
Hemodynamic Variable	Treatment Group*		
	Placebo	Prazosin	Hydralazine–Nitrate
Systolic blood pressure (mm Hg)			
Base line	118.9	119.2	119.6
Change at 8 wk	+0.2	−4.1†	+0.0
Change at 1 yr	−0.3	−4.6	+0.6
Diastolic blood pressure (mm Hg)			
Base line	76.1	75.7	75.0
Change at 8 wk	+0.6	−3.2§	−1.8‡
Change at 1 yr	−0.3	−2.7	−1.0
Ejection fraction (%)			
Base line	30.4	29.0	30.3
Change at 8 wk	+0.4	+0.7	+2.9§
Change at 1 yr	−0.1	+1.4	+4.2§

In summary, the V-HeFT I study demonstrated that the combination of Hy+ISDN can improve the survival of HFrEF patients significantly.

(N Engl J Med 1986; 314:1547-52.)

The Vasodilator–Heart Failure Trials II

A COMPARISON OF ENALAPRIL WITH HYDRALAZINE–ISOSORBIDE DINITRATE IN THE TREATMENT OF CHRONIC CONGESTIVE HEART FAILURE



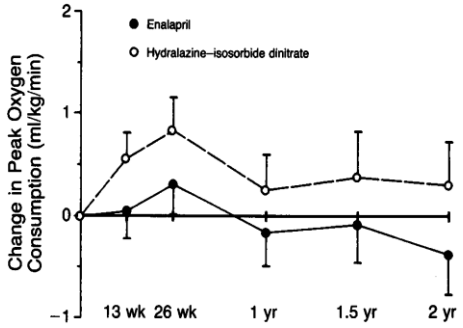
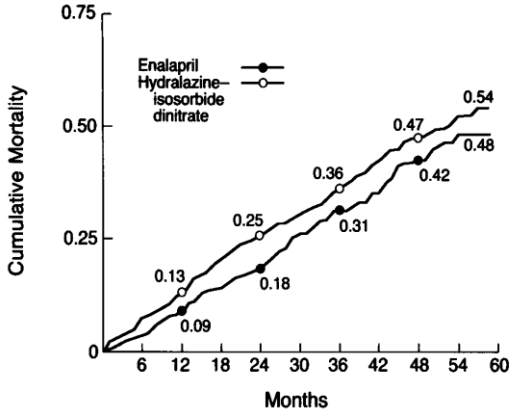


Figure 3. Mean Change from Base Line in Peak Oxygen Consumption over the First Two Years of the Study in Each Treatment Arm.

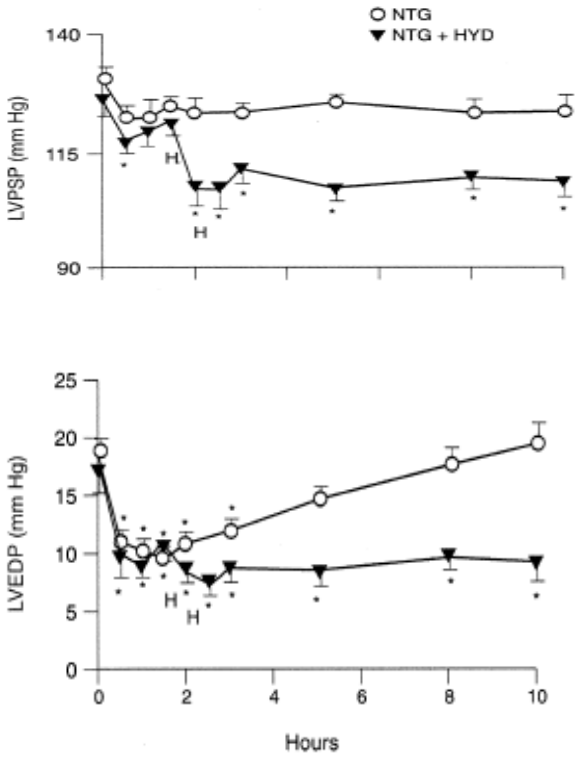


In summary, the V-HeFT II study showed that the combination of the direct-acting vasodilator Hy+ISDN is less favourable in terms of survival than the ACEi enalapril.

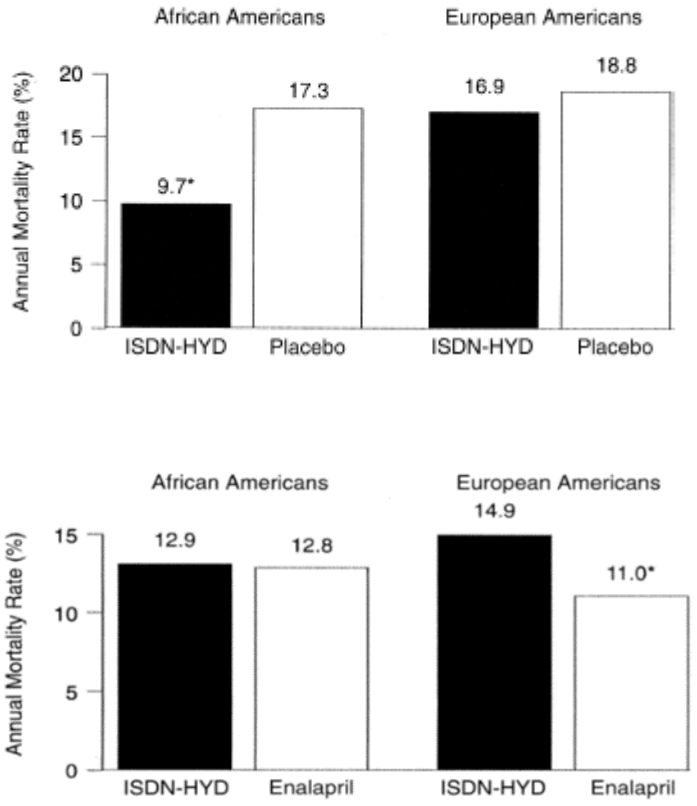
The arrhythmogenic side effects of the Hy+ISDN combination were primarily a consequence of the reflex increase in sympathetic activity due to the effect of arterial vasodilator hydralazine

Effects of Nitrates and Hydralazine in Heart Failure: Clinical Evidence Before the African American Heart Failure Trial

Uri Elkayam, MD,* and Fahed Bitar, MD



The American Journal of Cardiology (www.AJConline.org) Vol 96 (7B) October 10, 2005



African-American Heart Failure Trial

Combination of Isosorbide Dinitrate and Hydralazine in Blacks with Heart Failure

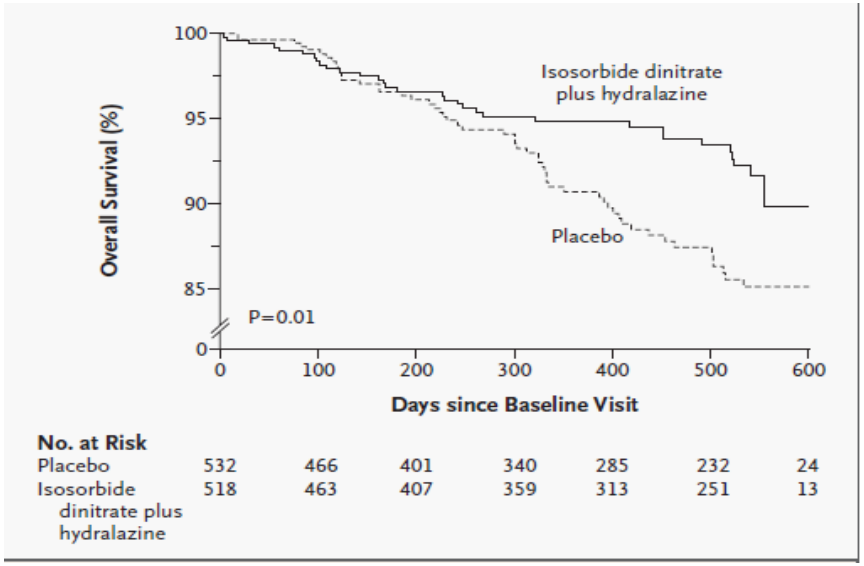


Table 3. End Points.*

End Point	Isosorbide Dinitrate plus Hydralazine (N=518)	Placebo (N=532)	P Value
Primary composite score†	−0.1±1.9	−0.5±2.0	0.01
Components of the primary composite score			
Death from any cause — no. (%)	32 (6.2)	54(10.2)	0.02
First hospitalization for heart failure — no. (%)	85 (16.4)	130 (24.4)	0.001
Change in quality-of-life score at 6 mo‡	−5.6±20.6	−2.7±21.2	0.02

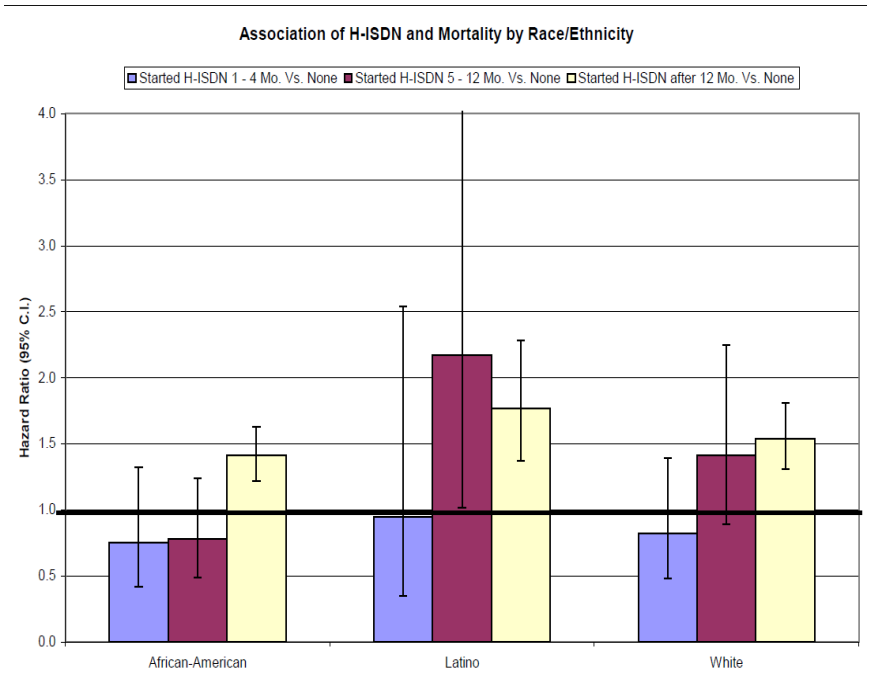
CONCLUSIONS

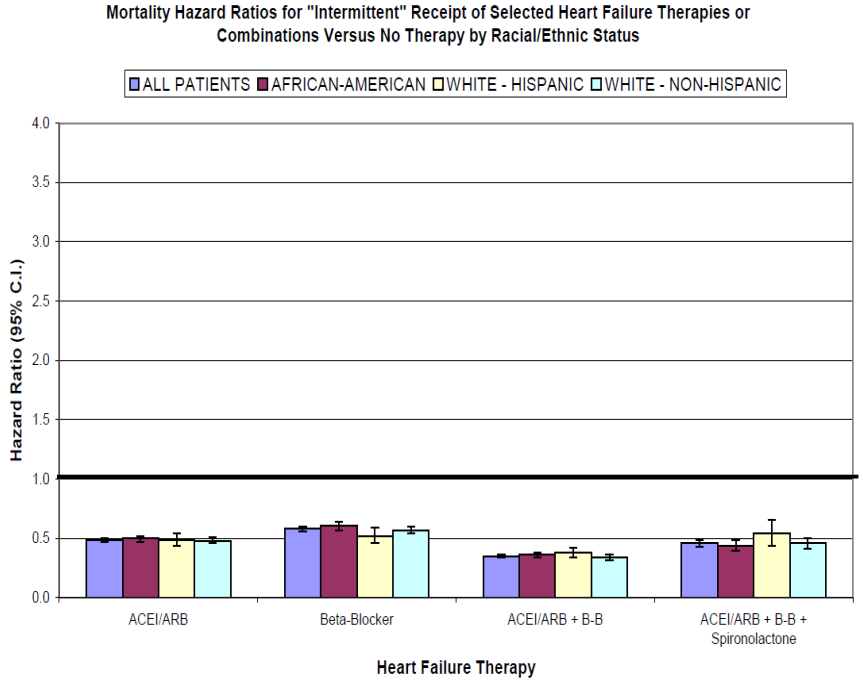
The addition of a fixed dose of isosorbide dinitrate plus hydralazine to standard therapy for heart failure including neurohormonal blockers is efficacious and increases survival among black patients with advanced heart failure.

Anne L. Taylor, 2004

Clinical Therapeutics/Volume 31, Number 3, 2009

Effectiveness of Hydralazine/Isosorbide Dinitrate in Racial/Ethnic Subgroups With Heart Failure





Clinical Effectiveness of Hydralazine–Isosorbide Dinitrate Therapy in Patients With Heart Failure and Reduced Ejection Fraction: Findings From the Get With The Guidelines-Heart Failure Registry

Prateeti Khazanie, MD, MPH; Li Liang, PhD; Lesley H. Curtis, PhD; Javed Butler, MD, MPH; Zubin J. Eapen, MD; Paul A. Heidenreich, MD; Deepak L. Bhatt, MD, MPH; Eric D. Peterson, MD, MPH; Clyde W. Yancy, MD; Gregg C. Fonarow, MD; Adrian F. Hernandez, MD, MHS

Table 2. Cumulative Incidence of Mortality and Readmission Within 3 Years

	Black Patients			Patients of Other Races		
	H-ISDN at Discharge, n (Rate)*			H-ISDN at Discharge, n (Rate)*		
Outcome	Yes (n=316)	No (n=1076)	*P* Value	Yes (n=595)	No (n=2676)	*P* Value
All-cause mortality	149 (53.9)	453 (51.9)	0.39	357 (68.9)	1585 (70.7)	0.13
All-cause readmission	241 (85.7)	779 (83.9)	0.53	459 (84.6)	1944 (81.2)	0.15
Cardiovascular readmission†	192 (68.9)	593 (65.2)	0.33	325 (60.8)	1401 (59.7)	0.26

H-ISDN indicates hydralazine–isosorbide dinitrate.

*Values are expressed as number of events (cumulative incidence per 100 patients at risk) unless otherwise indicated.

†Subcategorization of cardiovascular readmission refers to the first readmission.

Circ Heart Fail. 2016

Use of Hydralazine-Isosorbide Dinitrate Combination in African American and Other Race/Ethnic Group Patients With Heart Failure and Reduced Left Ventricular Ejection Fraction

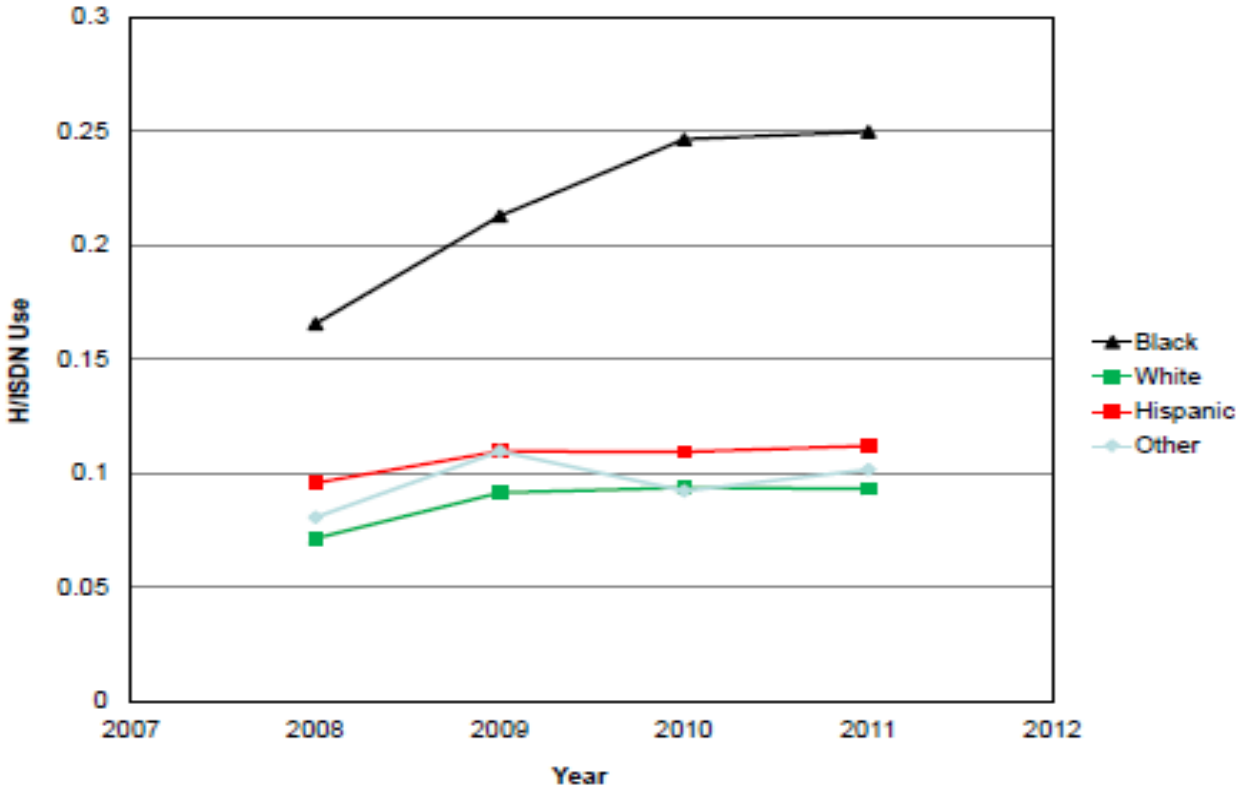


Figure 3. Trends in the use of hydralazine-isosorbide dinitrate (H-ISDN) at discharge in eligible patients from 2008 to 2012.

J Am Heart Assoc. 2013;

Am J Cardiol. 2009 April 15; 103(8): 1113–1119. doi:10.1016/j.amjcard.2008.12.028.

Usefulness of *Isosorbide Dinitrate* and *Hydralazine* as Add-on Therapy in Patients Discharged for Advanced Decompensated Heart Failure

Primary outcomes

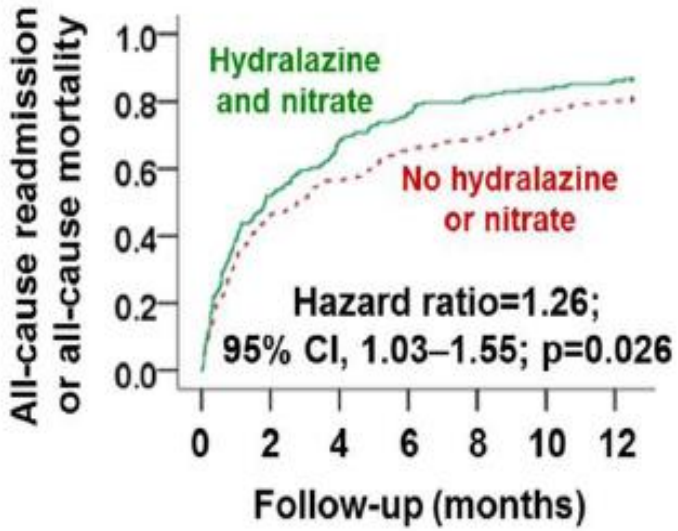
Primary Outcome	Control Group (n = 97)	I/H Group (n = 142)	p Value
All-cause mortality	41%	34%	0.04
Cardiac transplant	19%	22%	0.5
HF rehospitalization	64%	59%	0.4
All-cause mortality + HF rehospitalization	85%	70%	0.03

ACC.17

677
JACC March 21, 2017
Volume 69, Issue 11

Heart Failure and Cardiomyopathies

ADVERSE OUTCOMES WITH USE OF HYDRALAZINE AND NITRATE COMBINATION THERAPY IN HOSPITALIZED OLDER NON-BLACK PATIENTS WITH HEART FAILURE AND REDUCED EJECTION FRACTION (HFREF)



Conclusions: The use of hydralazine and nitrates together was associated with worse clinical outcomes among hospitalized non-black patients with HFrEF.

Hydralazine and nitrates alone or combined for the management of chronic heart failure: A systematic review

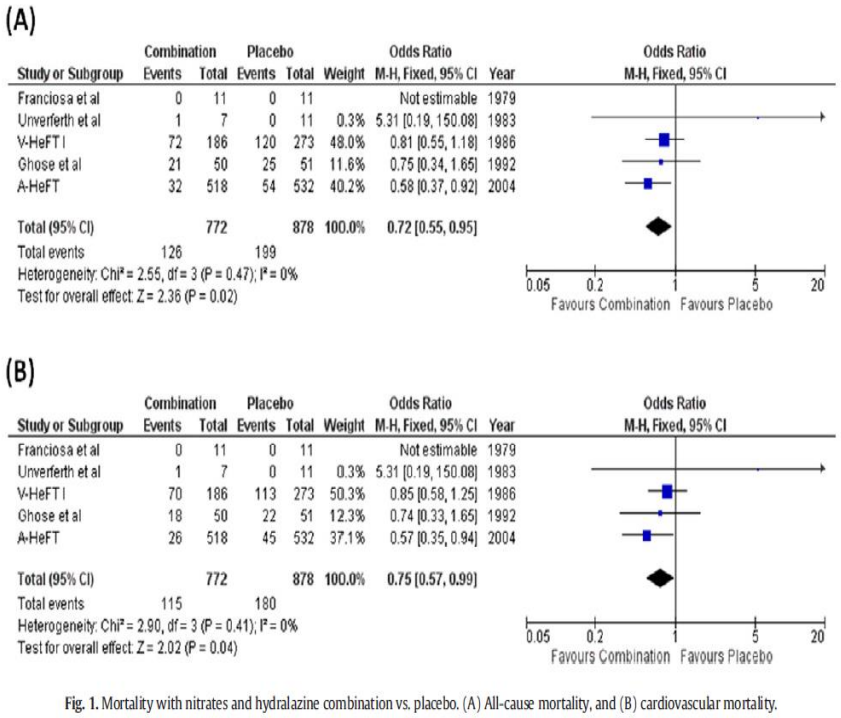
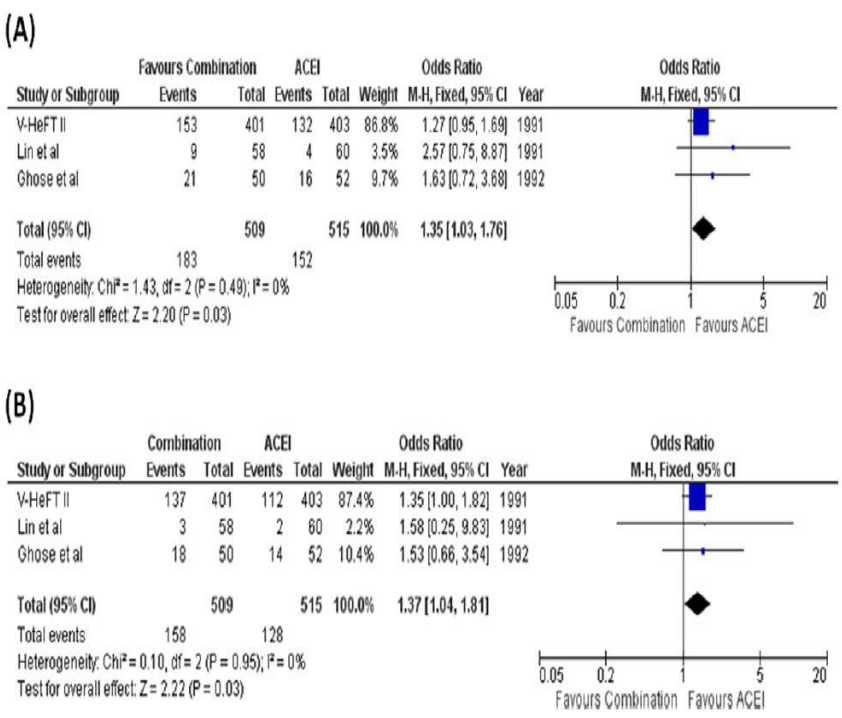
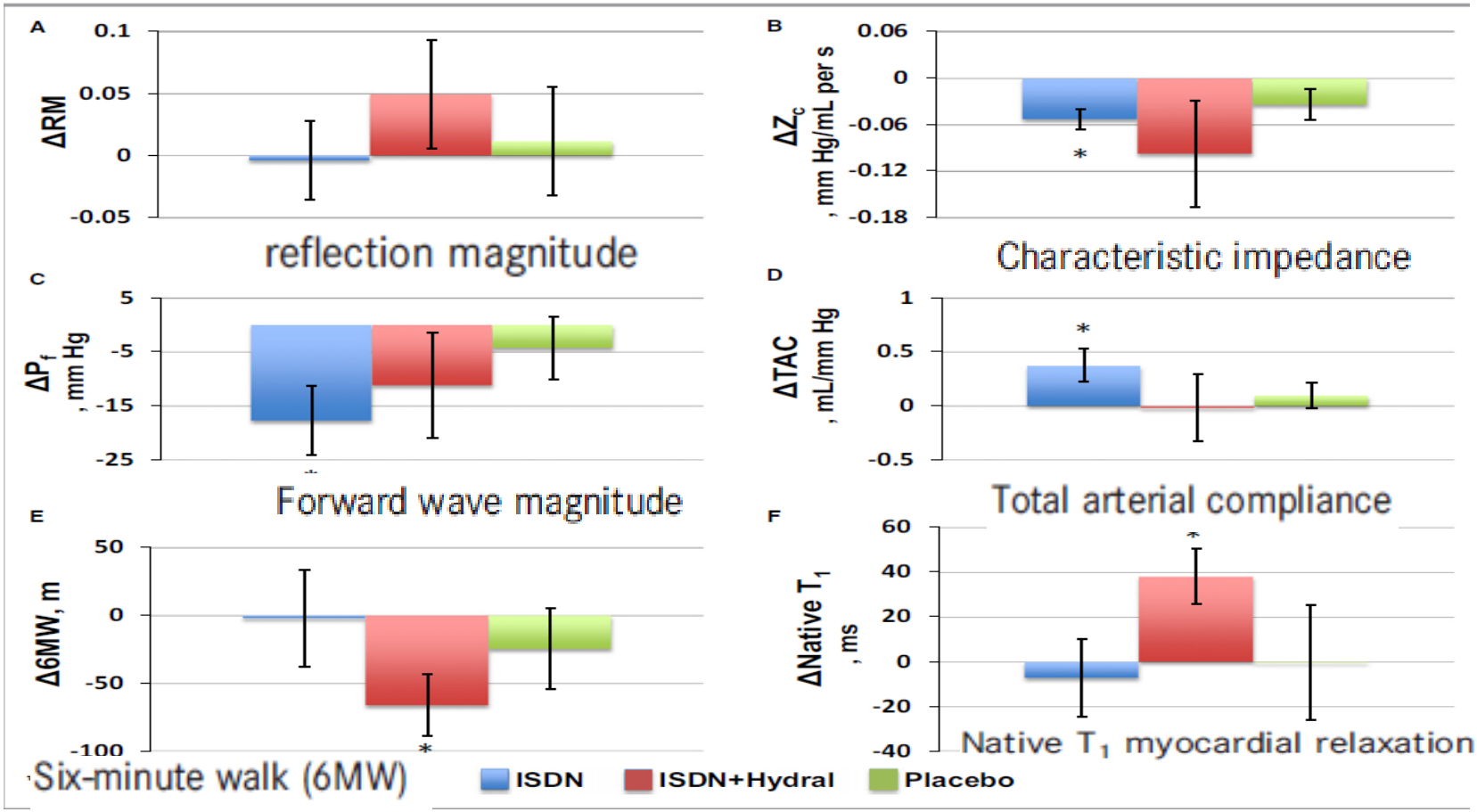


Fig. 1. Mortality with nitrates and hydralazine combination vs. placebo. (A) All-cause mortality, and (B) cardiovascular mortality.



Isosorbide Dinitrate, With or Without Hydralazine, Does Not Reduce Wave Reflections, Left Ventricular Hypertrophy, or Myocardial Fibrosis in Patients With Heart Failure With Preserved Ejection Fraction

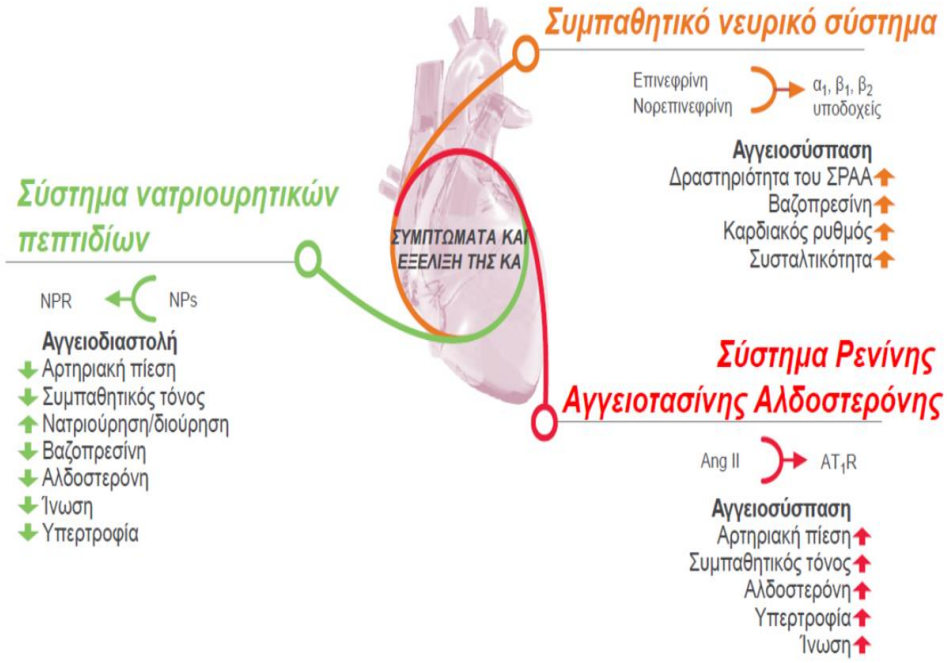


J Am Heart Assoc. 2017

The fact that the combination of Hy+ISDN takes a back seat in HFrEF therapy is partly due to changes in the concept of the pathophysiology of heart failure.

While in the **1950s and 1960s** the cardiorenal paradigm prevailed and heart failurewas predominantly treated with the use of digitalis and diuretics, the haemodynamic concept, which established the use of vasodilators, came to dominate in the **1970s and 1980s**.

From the**1990s** onwards, the treatment of heart failure based on the neurohumoral concept became prevalent, supplemented by highly effective neurohumoral antagonists



N. Nyolczas et al. 2017

Nitrate Therapy in Heart Failure

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Hydralazine and isosorbide dinitrate		
Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a beta-blocker and an MRA to reduce the risk of HF hospitalization and death.	IIa	B
Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE-I nor an ARB (or they are contra-indicated) to reduce the risk of death.	IIb	B

2013 ACCF/AHA Guideline for the Management of Heart Failure: Executive Summary

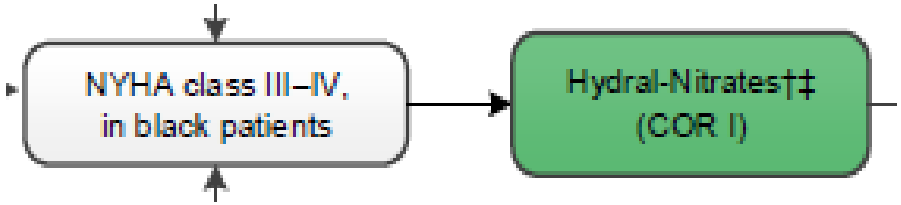
Hydralazine and isosorbide dinitrate

The combination of hydralazine and isosorbide dinitrate is recommended for African Americans with NYHA class III–IV HF*r*EF on GDMT

A combination of hydralazine and isosorbide dinitrate can be useful in patients with HF*r*EF who cannot be given ACE inhibitors or ARBs

I	A
IIa	B

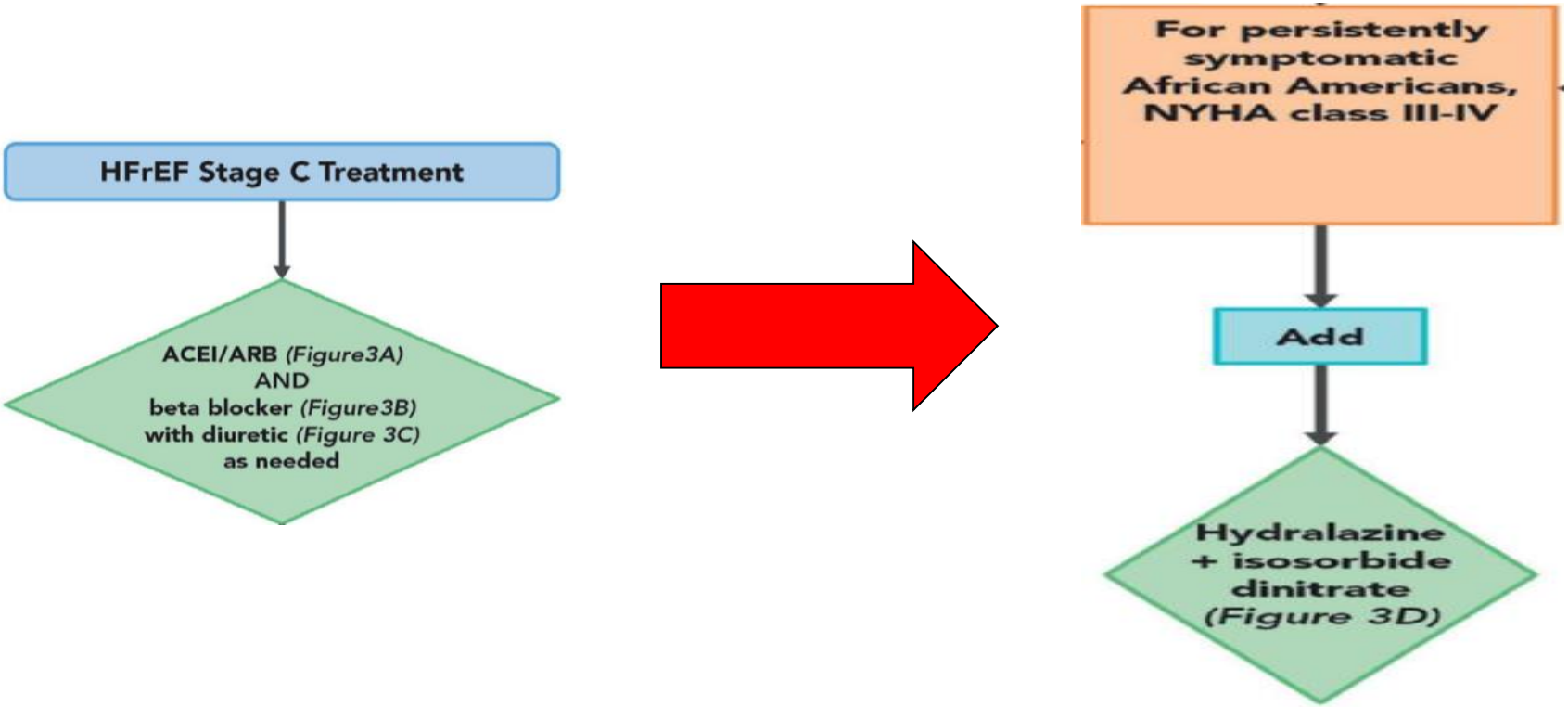
2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure



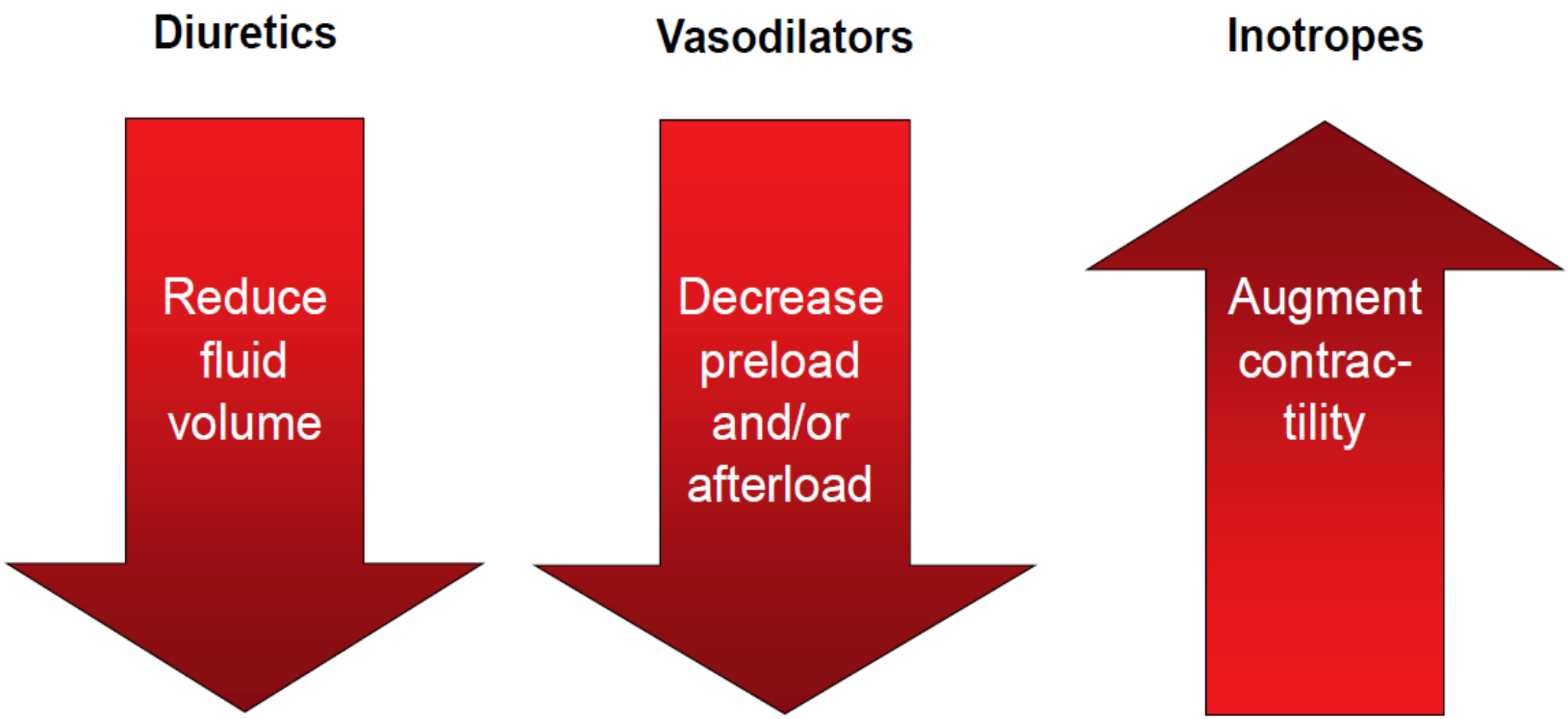
EXPERT CONSENSUS DECISION PATHWAY

2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction

A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways

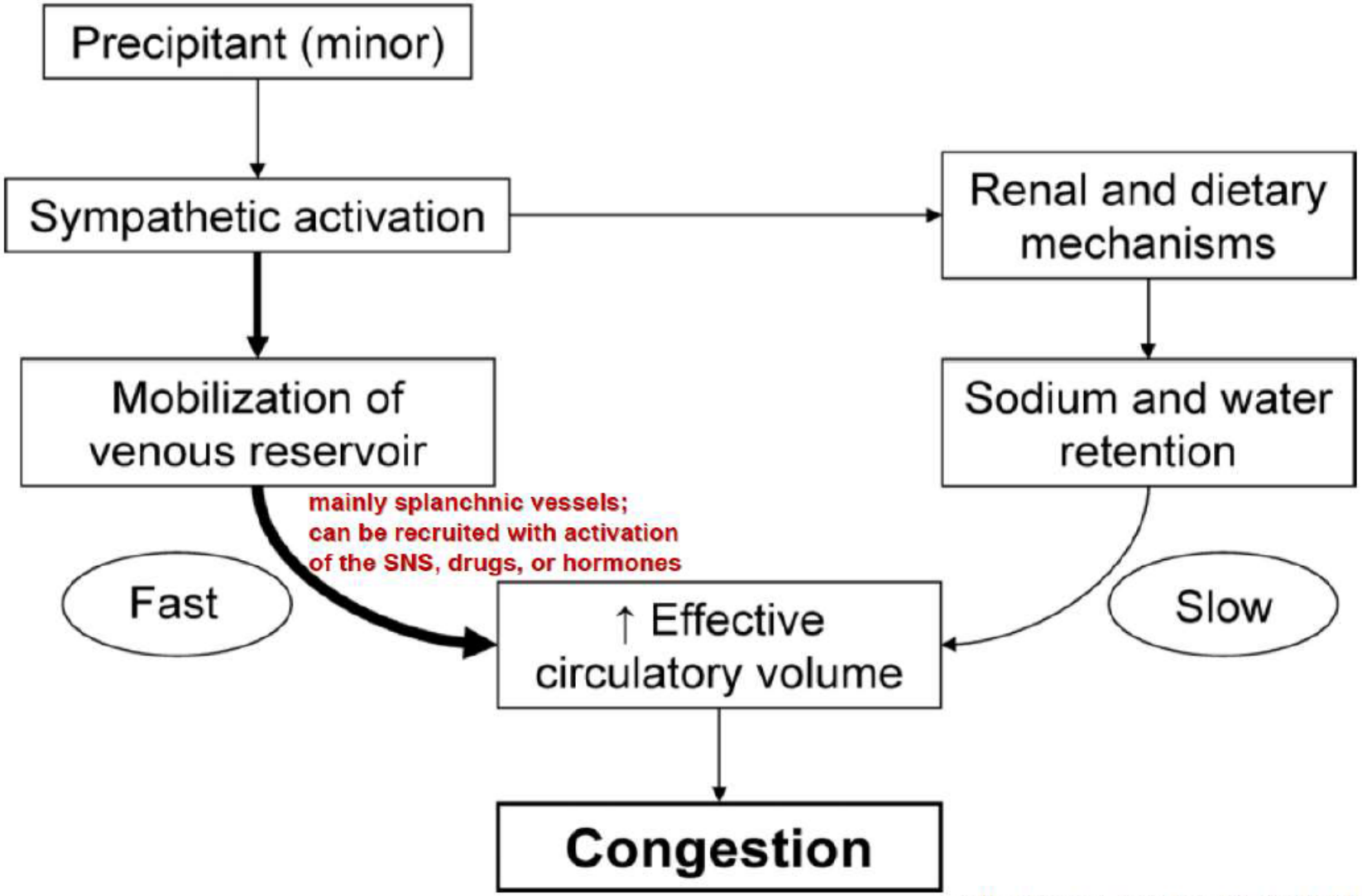


Conventional Treatment of Acute HF



Fonarow G. Rev Cardiovasc Med 2001

Fast and slow mechanisms of circulatory congestion



Fallick C et al. Circ Heart Fail. 2011;4:669-675

Acute heart failure:
recommendations and levels of evidence

Group	Medication	Class recommendation, level of evidence
Diuretics	Loop Diuretics	I, B
Vasodilators	Nitrates	IIa, B
	Sodium nitroprusside	IIb, B
Opiates	Morphine	IIa, C
Inotropics	Dopamine	IIb, C
	Dobutamine	IIa, C

McMurray et al. Eur Heart J 2012;33:1787-1846

Articles

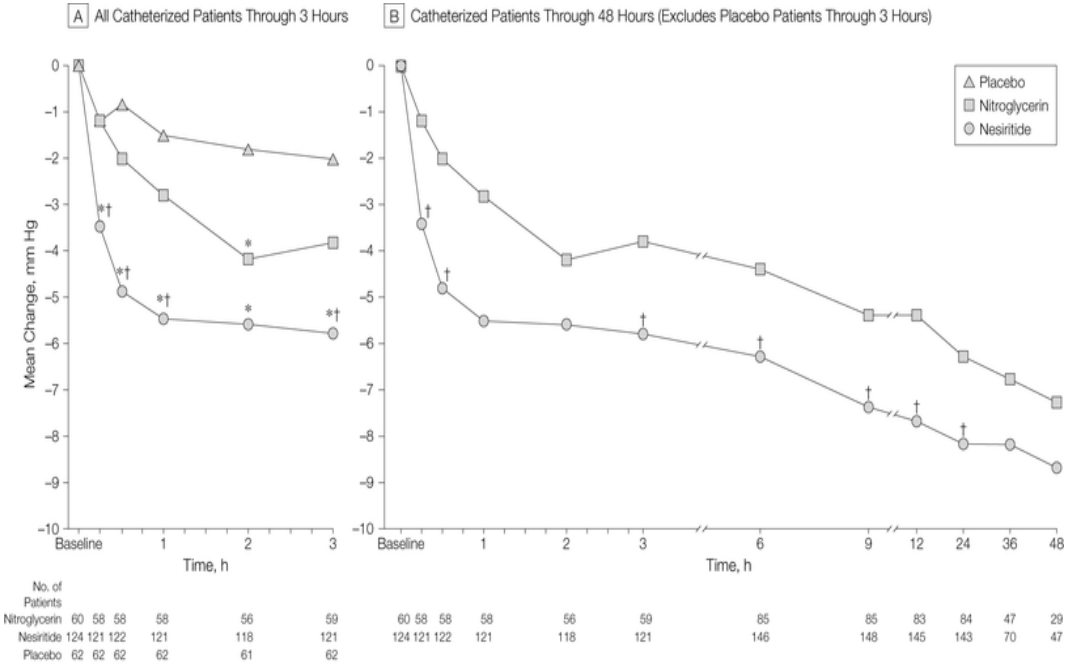
Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema

Gad Cotter, Einat Metzkor, Edo Kaluski, Zwi Faigenberg, Rami Miller, Avi Simovitz, Ori Shaham, Doron Marghitay, Maya Koren, Alex Blatt, Yaron Moshkovitz, Ronit Zaidenstein, Ahuva Golik

- High dose ISDN alone compared with low dose ISDN + furosemide did:
  - Not reduce mortality
  - Reduce the need for mechanical ventilation
  - Reduce the risk of myocardial infarction
  - Reduce the risk of any adverse event

Lancet 1998

Intravenous Nesiritide vs Nitroglycerin for Treatment of Decompensated Congestive Heart Failure
A Randomized Controlled Trial
Publication Committee for the VMAC Investigators



Conclusion

When added to standard care in patients hospitalized with acutely decompensated CHF, nesiritide improves hemodynamic function and some self-reported symptoms more effectively than intravenous nitroglycerin or placebo.

Effect of short-term infusion of sodium nitroprusside on mortality rate in acute myocardial infarction complicated by left ventricular failure: results of a Veterans Administration cooperative study.

Overall no effect on mortality; higher mortality when started early, lower mortality when started late

Conclusion of the authors: "Nitroprusside should probably not be used routinely in patients with high left ventricular filling pressures after acute myocardial infarction."

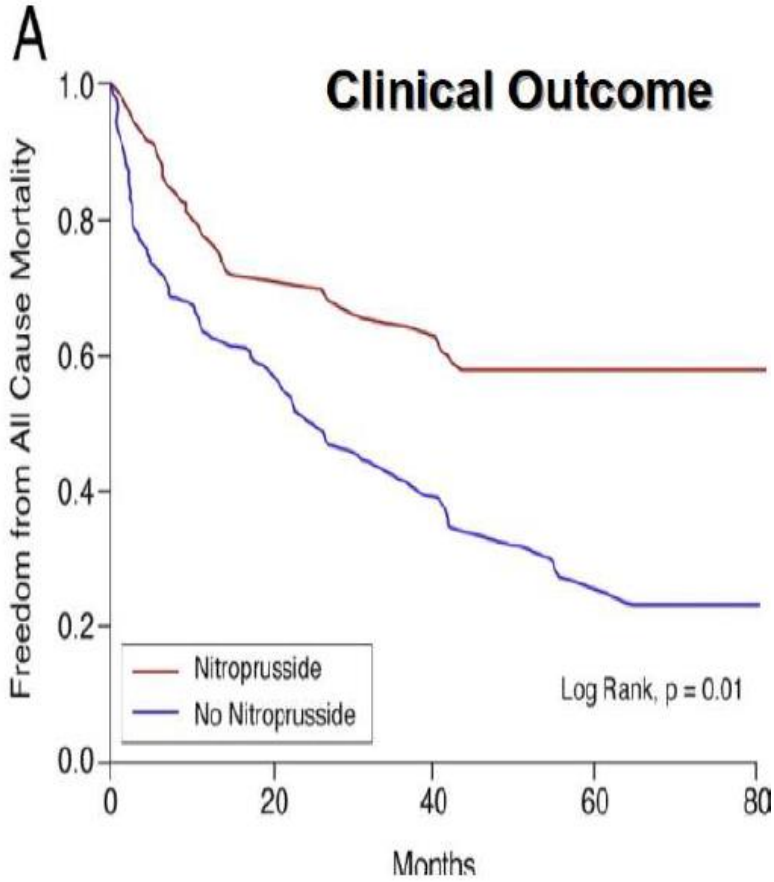
Vasodilators for Low-Output AHF

- 175 pts with AHF admitted to intensive care unit;
  78 treated with sodium nitroprusside (NYHA IV – 58%, SBP – 110 mmHg, Na – 137 mmol/L, PCWP – 29 mmHg, LVEF – 15%)

Haemodynamic Data

	Nitroprusside (n = 60)		
	Admission	Discharge	p Value
MAP (mmHg)	87 ± 12	74 ± 11	<0.001
Systolic PAP (mmHg)	65 ± 13	42 ± 12	<0.001
Diastolic PAP (mmHg)	33 ± 7	19 ± 6	<0.001
CI (L/min/m2)	1.6 ± 0.2	2.6 ± 0.5	<0.001

Clinical Outcome



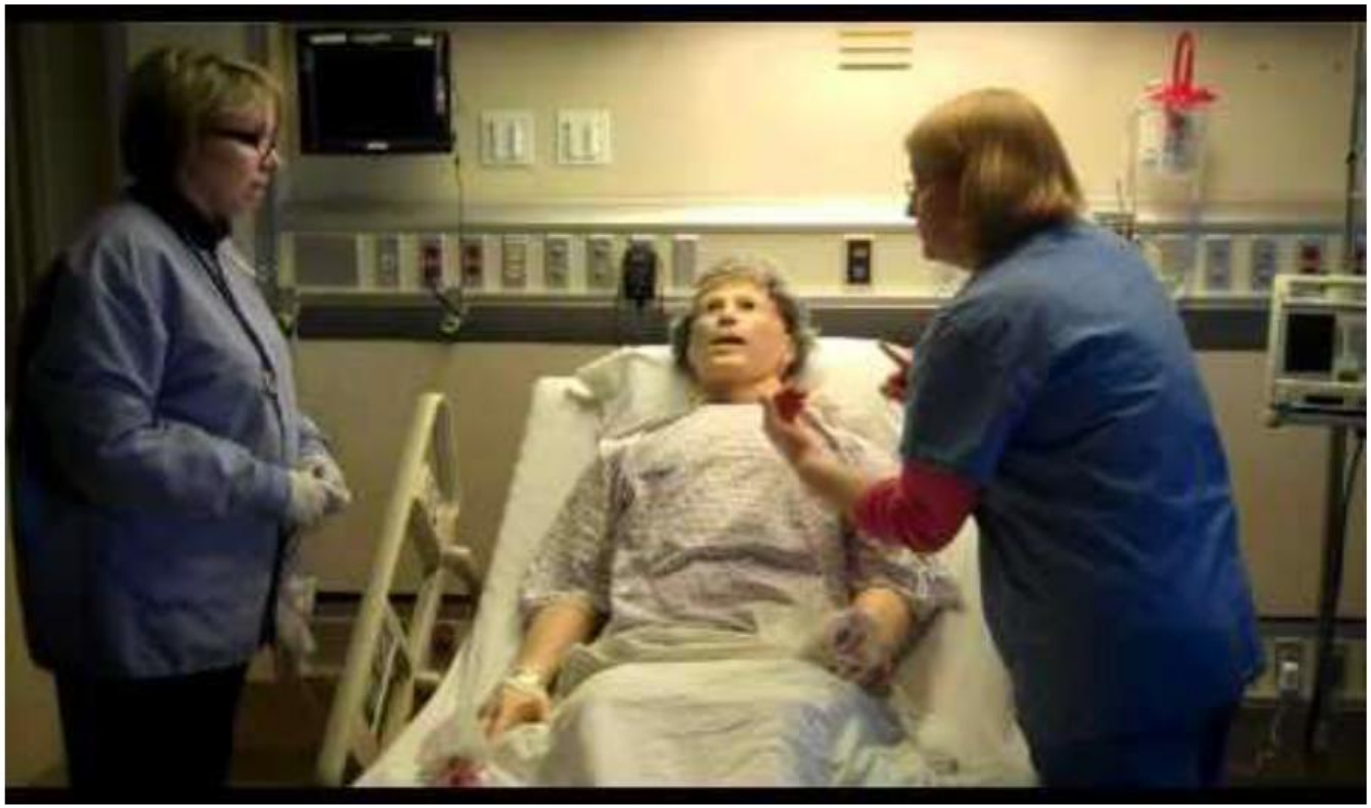
Mullens, W. et al. J Am Coll Cardiol 2008;52:200-207

in Acute Heart Failure

Vasodilators		
i.v. vasodilators should be considered for symptomatic relief in AHF with SBP >90 mmHg (and without symptomatic hypotension). Symptoms and blood pressure should be monitored frequently during administration of i.v. vasodilators.	IIa	B
In patients with hypertensive AHF, i.v. vasodilators should be considered as initial therapy to improve symptoms and reduce congestion.	IIa	B
An i.v. infusion of sodium nitroprusside may be considered in patients with pulmonary congestion/oedema and a systolic blood pressure >110 mmHg, who do not have severe mitral or aortic stenosis, to reduce pulmonary capillary wedge pressure and systemic vascular resistance. Caution is recommended in patients with acute myocardial infarction. Nitroprusside may also relieve dyspnoea and congestion. Symptoms and blood pressure should be monitored frequently during administration of i.v. nitroprusside.	IIb	B

Vasodilator	Dosing	Main side effects	Other
Nitroglycerine	Start with10–20 µg/min, increase up to 200 µg/min	Hypotension, headache	Tolerance on continuous use
Isosorbide dinitrate	Start with 1 mg/h, increase up to 10 mg/h	Hypotension, headache	Tolerance on continuous use
Nitroprusside	Start with 0.3 µg/kg/min and increase up to 5 µg/kg/min	Hypotension, isocyanate toxicity	Light sensitive
Nesiritide[a]	Bolus 2 µg/kg + infusion 0.01 µg/kg/min	Hypotension	

This Patient Is Hospitalized for Worsening Heart Failure. What Do You Do?



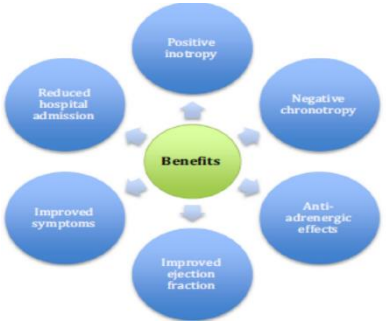
The best way to treat their "acute heart failure" is to prevent it by treating their underlying chronic heart failure


No digoxin
Digoxin
Heart Failure

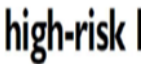
THE TAKE-HOME MESSAGE

Στην απόφασή μας..

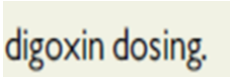
..να λάβουμε σοβαρά υπόψη τα οφέλη αλλά και τα πιθανόν αρνητικά της χορήγησης διγοξίνης



… και με φρόνηση να αποφασίζουμε εξατομικευμένα για τον εκάστοτε ασθενή.



…..συνιστάται ο συχνός έλεγχος των επιπέδων του φαρμάκου.



THE TAKE-HOME MESSAGE

….**μελέτες παρατήρησης**, κυρίως σε πληθυσμούς πολυκεντρικών μελετών,

για την αύξηση της θνητότητας

ύστερα από θεραπεία με διγοξίνη.

τυχαιοποιημένες μελέτες


Hy+ISDN.
No (Hy+ISDN.)
Heart Failure

THE TAKE-HOME MESSAGE

HY+ISDN therapy **improves** symptoms, quality of life, and exercise capacity, as well as reduces hospitalization and mortality.

In patients with HFrEF who **cannot receive** either an ACEi or an ARB due to **intolerance** or **contraindication**

In self-identified **African-American** patients with LVEF < 35% or with an LVEF <45% combined with a dilated left ventricle in NYHA class III-IV **despite optimal treatment** with ACEi or ARB, BB and MRA

Ευχαριστώ για την προσοχή σας