Role of Digoxin in Heart Failure and Atrial Fibrillation

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Professor of Medicine

Cedars-Sinai

@MKittlesonMD

Dr. John Mandrola: *ad homimen**

*I'm a huge fan!!

COMMENTARY

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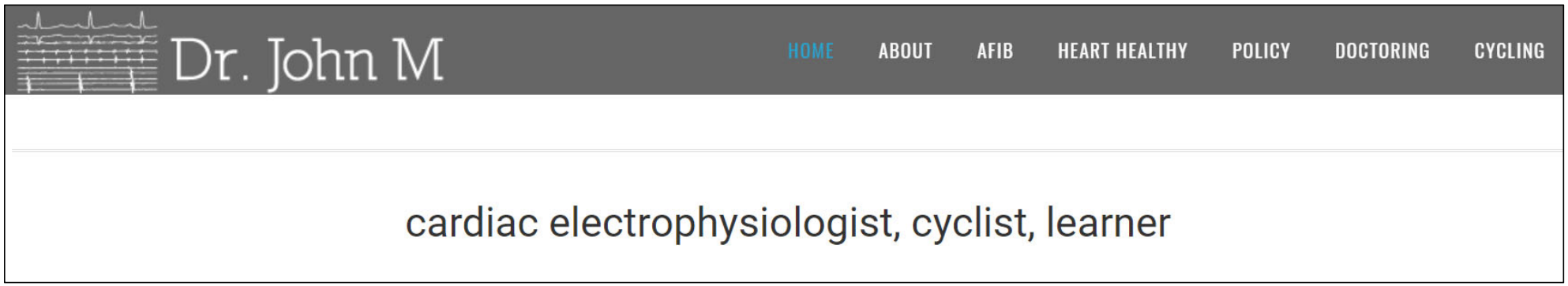
The Case for Being a Medical Conservative

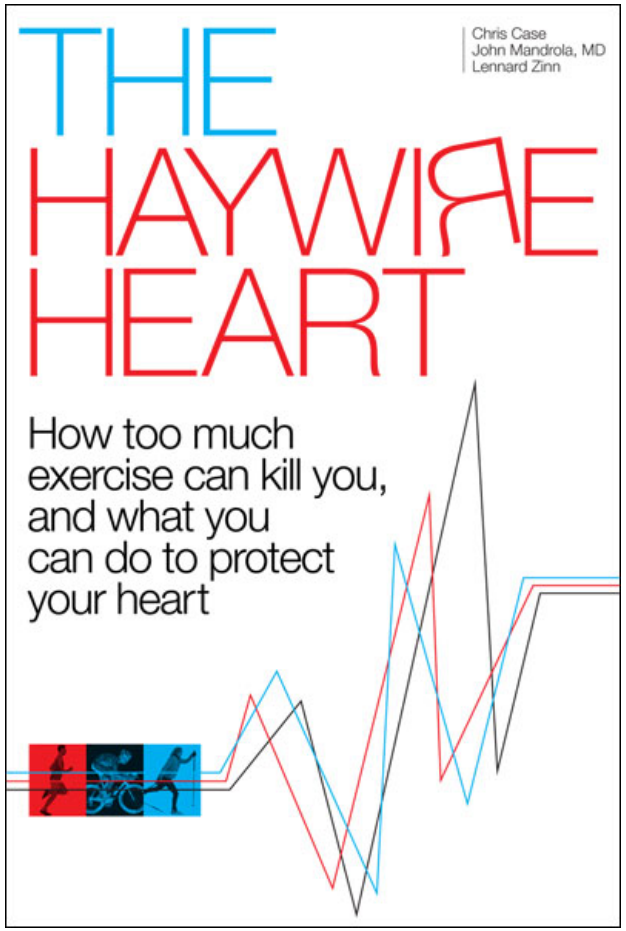
CrossMark

KEYWORDS: Bias; Critical appraisal; Evidence-based medicine; Medical decision-making

The Blog!


Dr. John M
HOME
ABOUT
AFIB
HEART HEALTHY
POLICY
DOCTORING
CYCLING
cardiac electrophysiologist, cyclist, learner

The Book!


THE
HAYWIRE
HEART
Chris Case
John Mandrola, MD
Lennard Zinn
How too much
exercise can kill you,
and what you
can do to protect
your heart

The Columns!

TRIALS AND FIBRILLATIONS WITH DR JOHN MANDROLA

MANDROLA ON MEDSCAPE

The Podcast!

The Twitter!

John Mandrola, MD
@drjohnm Follows you

Heart rhythm doc, writer/podcaster for @Medscape, learner, cyclist, r
#HPM doctor. #MedicalConservative. The more you see, the harder r

Louisville, KY drjohnm.org Born September 1 Joined

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Following

John Mandrola, MD @drjohnm · Apr 29

A mentor wisely advised me not to malign specific therapies.

The idea is that Rx A or B each have pros/cons.

He said what ought to be maligned was dumb usage of the therapy.

Better thread IMHO is most under-appreciated cardiac drug

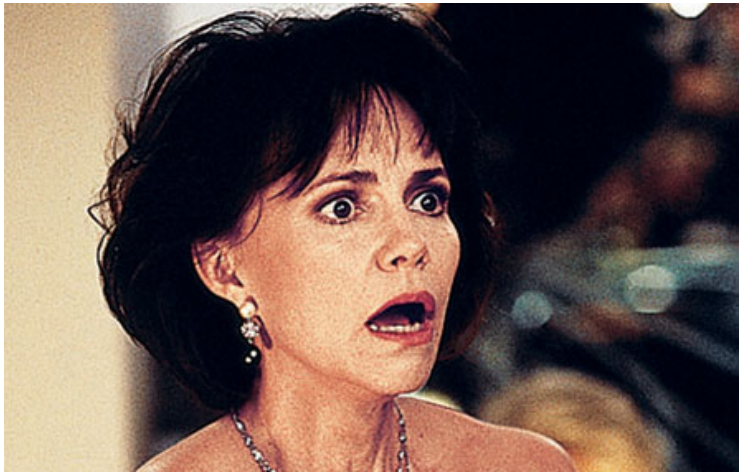
A: procainamide

Cc @MKIttlesonMD

John Mandrola, MD @drjohnm · Apr 29

Evidence to boot — ncbi.nlm.nih.gov/pmc/articles/P...

I need to debate you on digoxin



Foxglove for Dropsy

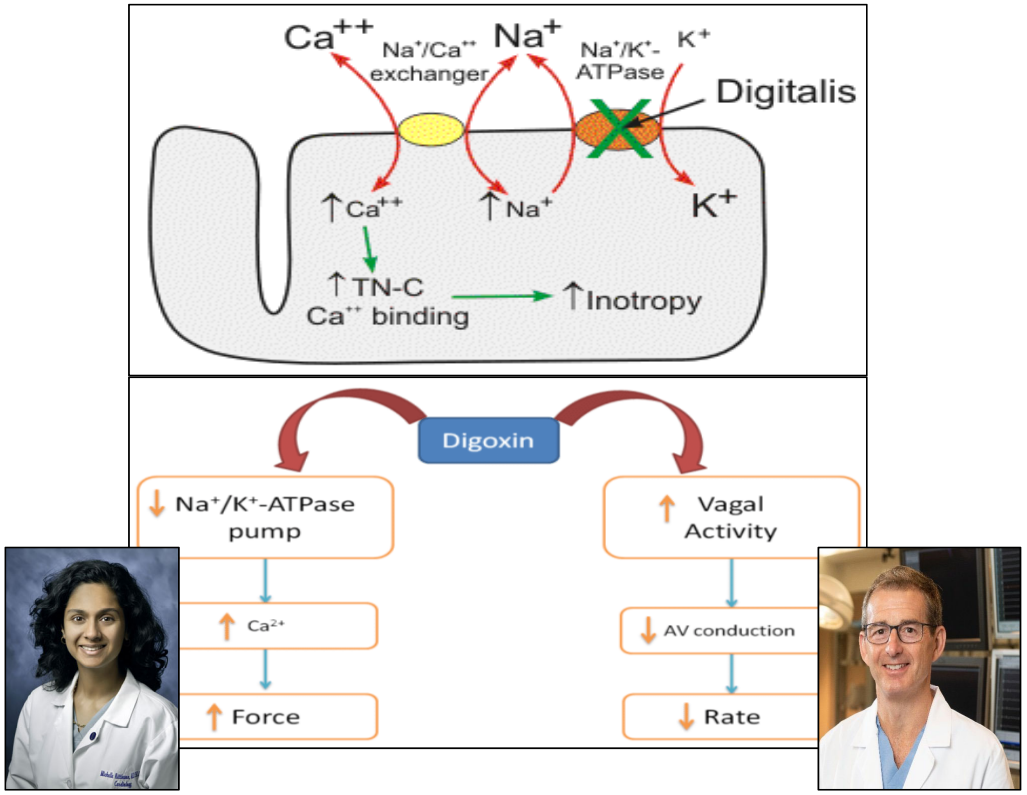
An Account of the Foxglove by British physician William Withering published 1785

Finger-like shape of flowers → *Digitalis*

"In the year 1775 my opinion was asked concerning a family receipt for the cure of the dropsy. . .it had long been kept a secret by an old woman in Shropshire. . .the active herb could be no other than the Foxglove."

"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."

Digoxin


Ca++
Na+/Ca++ exchanger
Na+
Na+/K+- ATPase
K+
Digitalis
↑Ca++
↑Na+
K+
↑TN-C Ca++ binding
↑Inotropy
Digoxin
↓Na+/K+-ATPase pump
↑Ca2+
↑Force
↑Vagal Activity
↓AV conduction
↓Rate

Digoxin in HF: The Early Years

Study name	Pts/design/ duration	Treatment	Results
Lee et al. *NEJM* 1982	25 HF pts w/o AF Blinded crossover	Digoxin vs placebo	56% had improvement in HF severity Responders: more chronic HF, greater LV dilation, S3
Guyatt et al. Am J Cardiol 1988	20 HF pts w/o AF Blinded crossover 7 w	Digoxin vs placebo	Digoxin: improved 6MWT and QOL Deterioration in patients when taking placebo
Cohn J et al. JAMA 1988	300 RCT		se time and NYHA class hosp, ED visits, increase in
Uretsky et al. PROVED trial J Am Coll Cardiol 1993	88 HF pts w/o AF 8w dig, 12w RCT on/off dig	Withdrawal vs continuation of digoxin	Withdrawal of digoxin: - decreased exercise time - more hosp, ED visits, increase in diuretics
Packer M et al. RADIANCE trial NEJM 1993	178 HF pts w/o AF NYHA II-III, EF ≤ 35% On ACEI/diuretics 12 weeks RCT	Withdrawal vs continuation of digoxin	Withdrawal of digoxin: - RR 5.9 for worsening HF - Decrease exercise tolerance and QOL

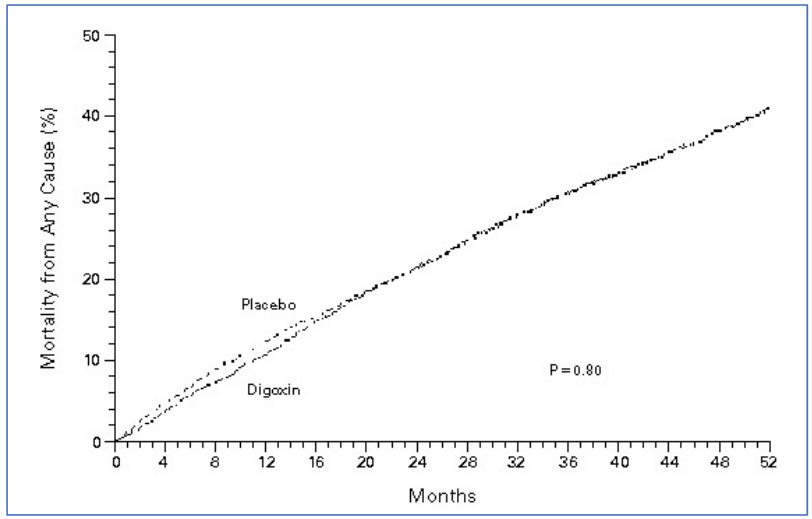
Lessons from the digoxin in early HF trials:

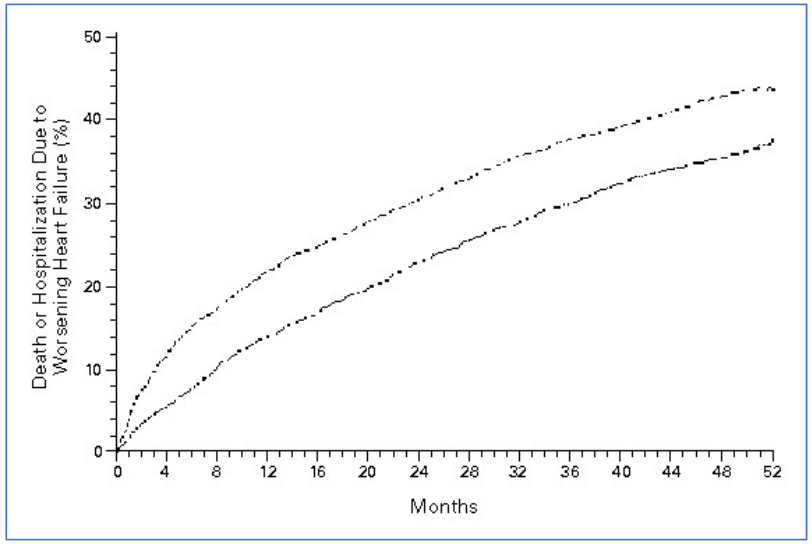
- HF patients feel better on digoxin than off it
- HF patients feel worse when digoxin is stopped

The DIG trial

6800 pts (~3400 with EF ≤ 45%)
Diuretics + ACEI
Digoxin vs placebo

No diff in mortality
↓ HF hosp: 27% vs 35%

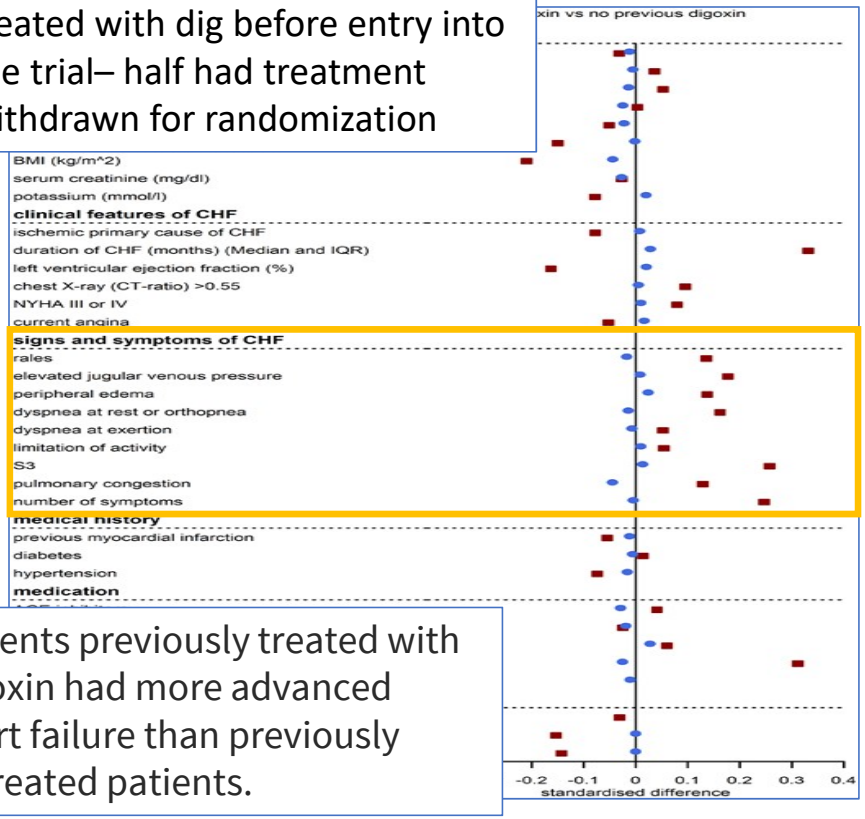




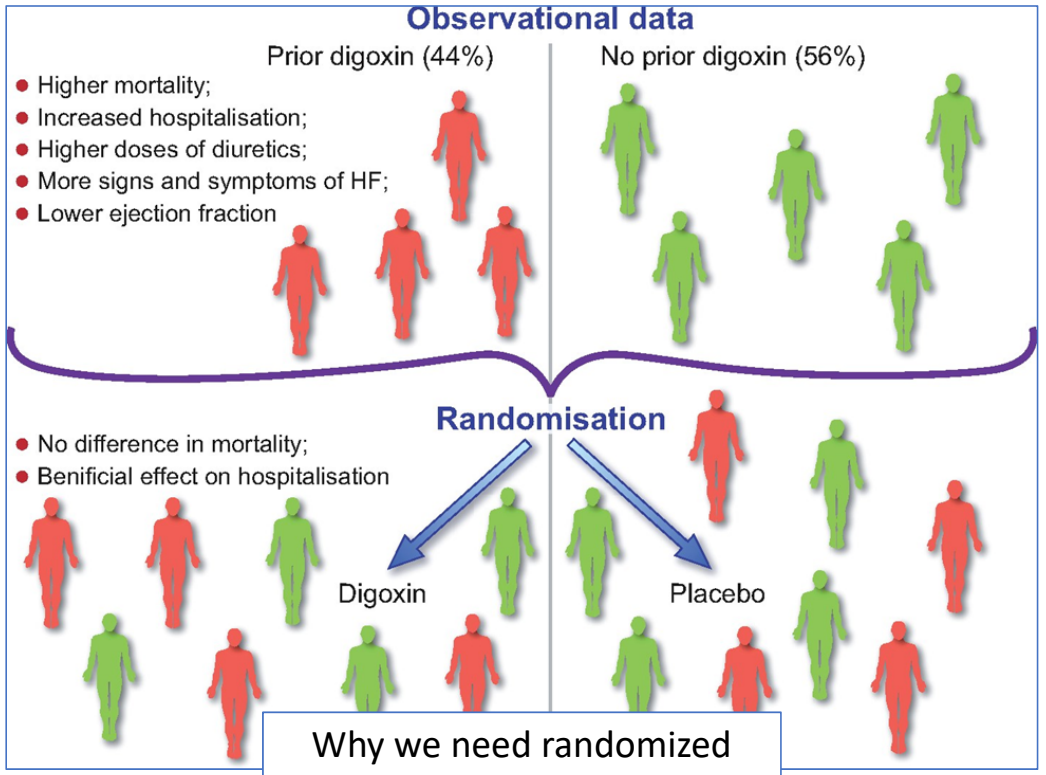
DIG group, NEJM 1997

Lesson #1: Observation (alone) is dangerous

44% of pts in the DIG trial were treated with dig before entry into the trial– half had treatment withdrawn for randomization



Patients previously treated with digoxin had more advanced heart failure than previously untreated patients.

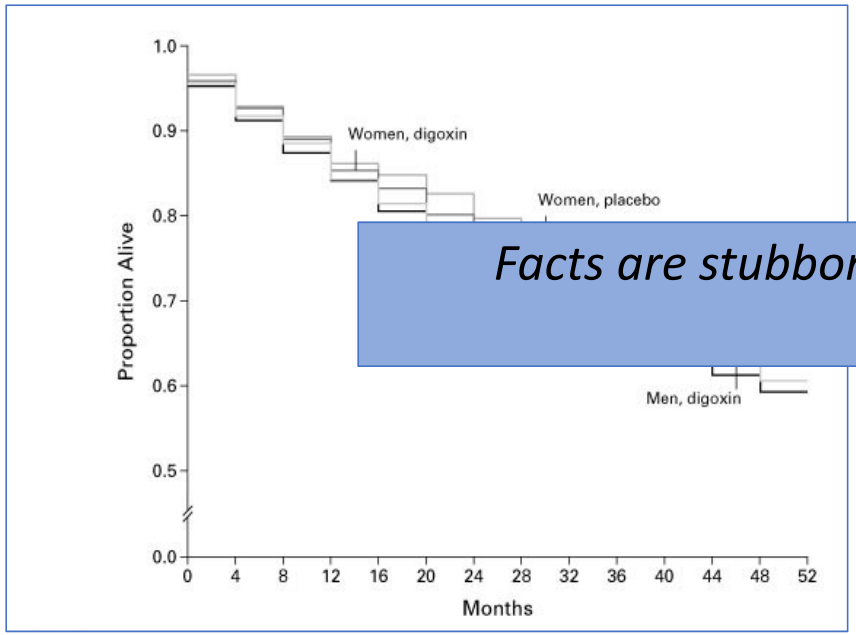


Why we need randomized controlled trials

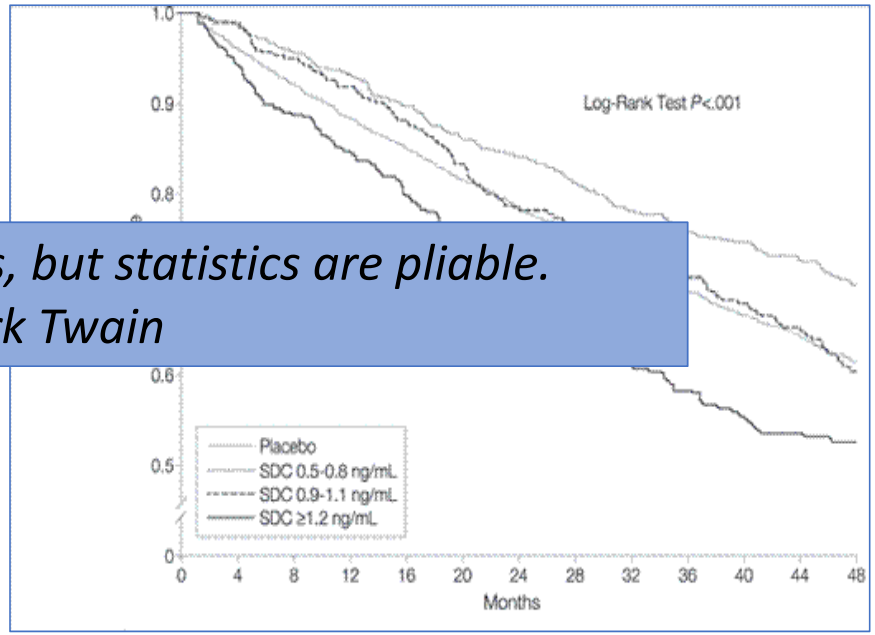
Aguirre Davila et al. Eur Heart J 2019.

Boorsma E et al. Eur Heart J 2019.

Lesson #2: Even RCTs aren't perfect



Facts are stubborn things, but statistics are pliable.
— Mark Twain



Men: no impact of dig on mortality
Women: increased mortality on dig

Low dig level → increased survival
High dig level → decreased survival

Rathore et al. NEJM 2002

Rathore et al. JAMA 2003

Lesson #3: We Need More RCT!

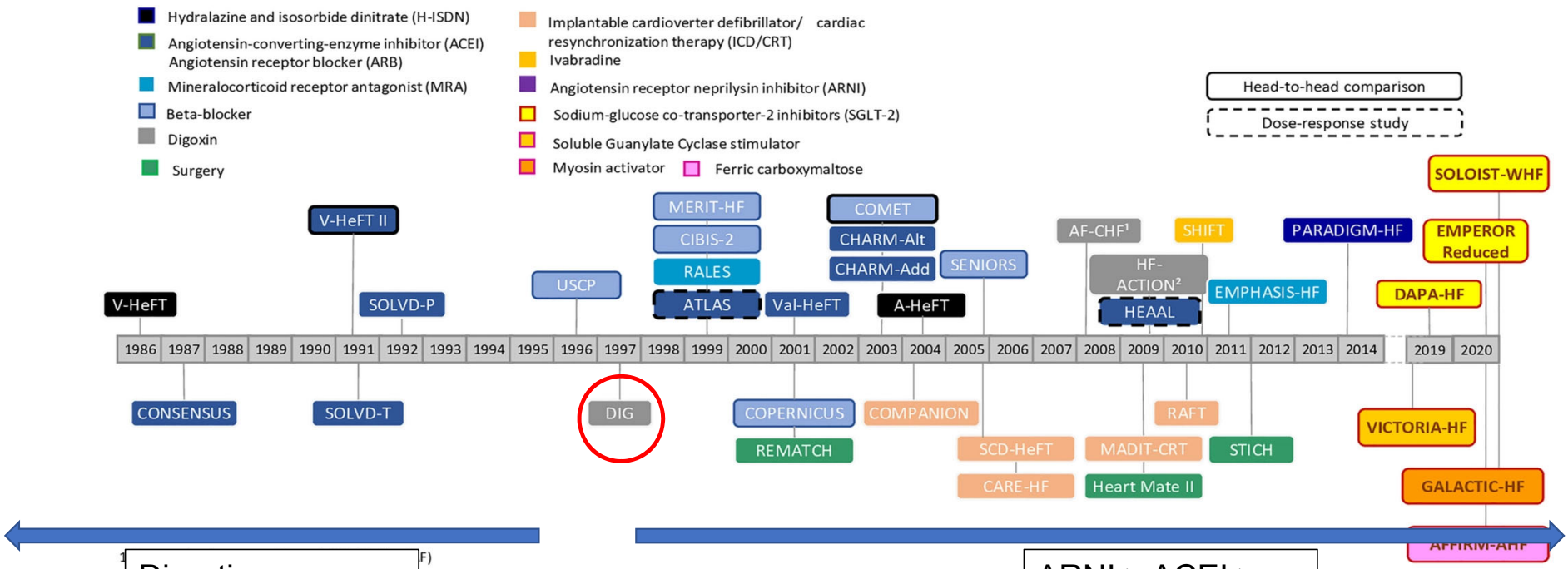
Digoxin Evaluation in Chronic Heart Failure: Investigational Study In Outpatients in the Netherlands (DECISION)

- 982 pts
- EF < 50%
- Digoxin 0.5-0.9 ng/mL
- Death + HF hospitalizations
- Study completion date: July 2025

DIGitoxin to Improve ouTcomes in patients with advanced chronic Heart Failure (DIGIT-HF)

- 2190 pts
- EF ≤ 40%
- Digitoxin 8- 18 ng/mL
- Death + HF hospitalization

1997 was a long time ago

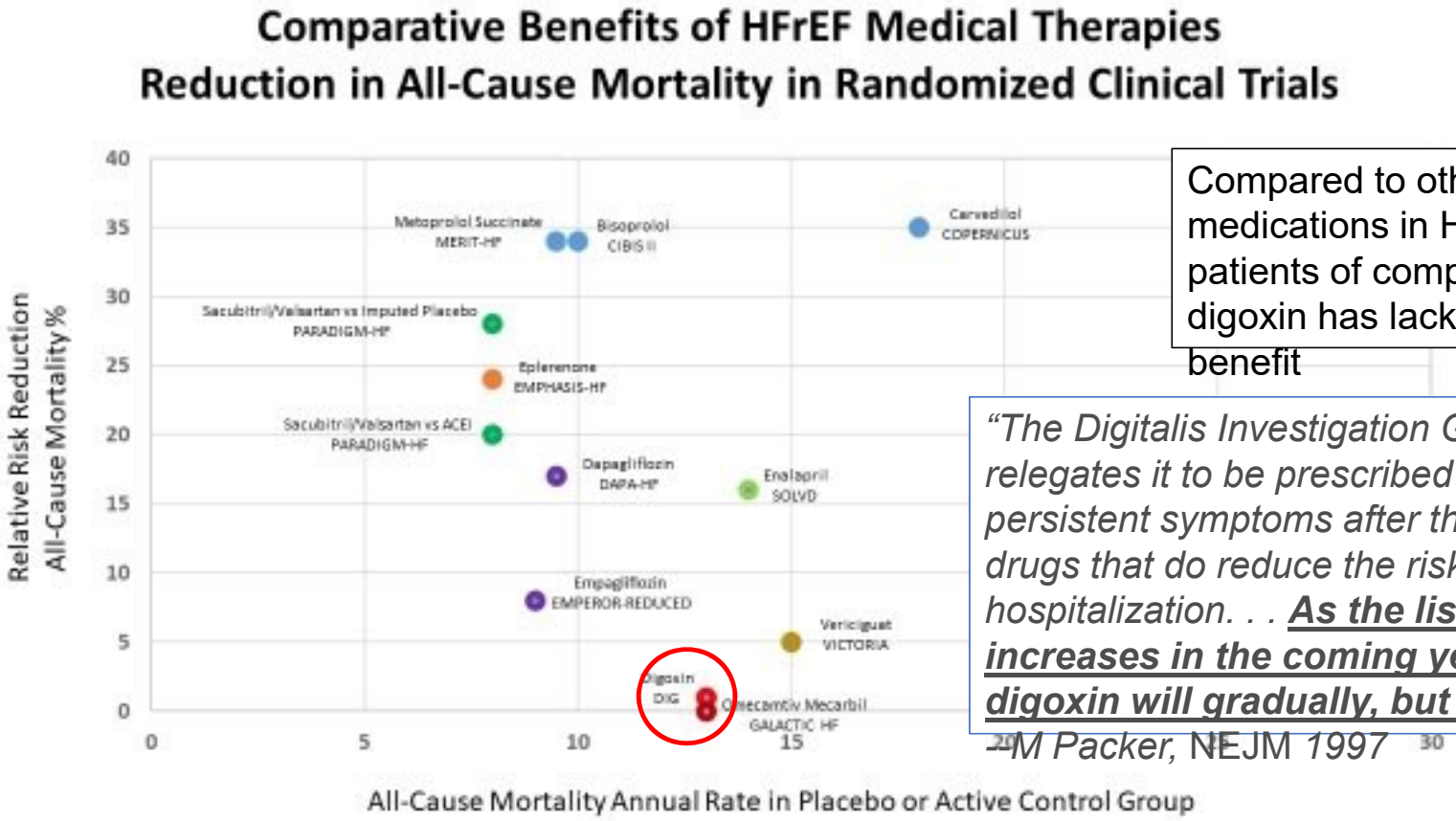


Diuretics
Isordil/hydralazine
ACE inhibitors
Digoxin

ARNI > ACEI > ARB
Evidence-based BB
MRA
SGLT2i

Tomasoni D et al. ESC Heart Failure 2020; 7: 3505-3530.

Digoxin is just. . . not that exciting.



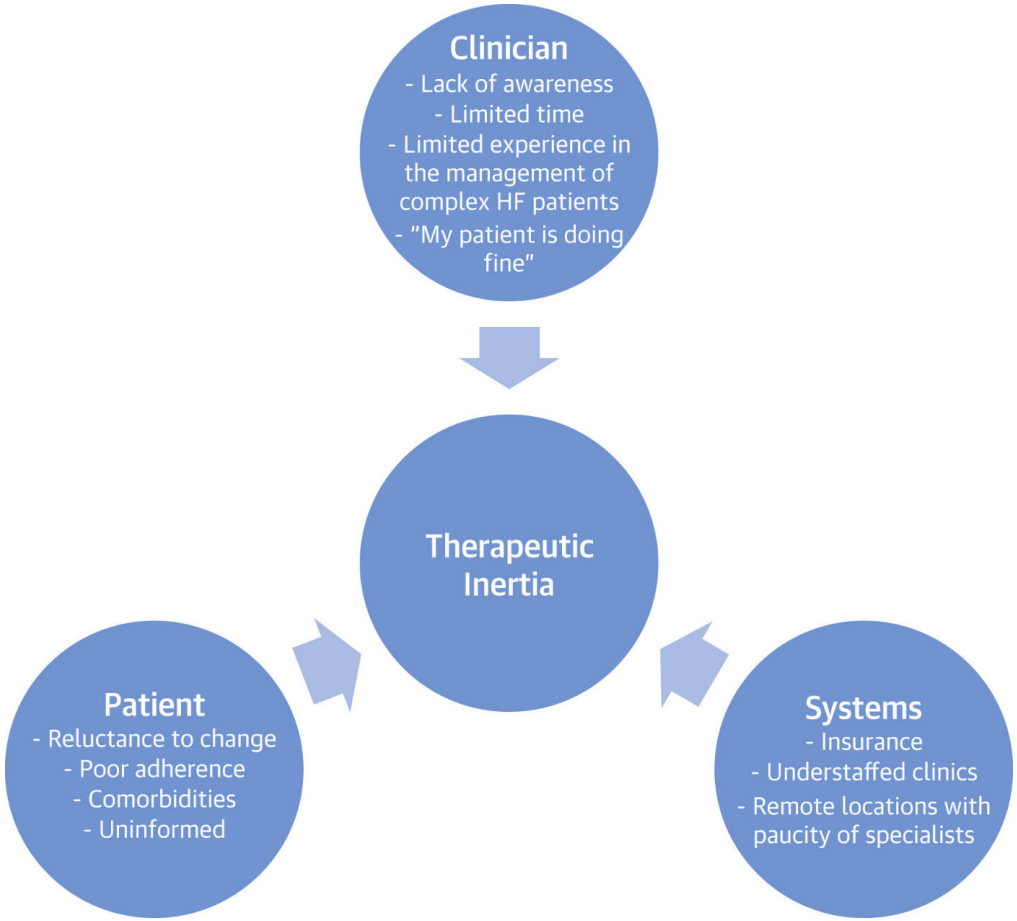
Compared to other medications in HFrEF patients of comparable risk, digoxin has lackluster benefit

"The Digitalis Investigation Group trial. . . effectively relegates it to be prescribed for the treatment of persistent symptoms after the administration of drugs that do reduce the risk of death and hospitalization. . . ***<u>As the list of such drugs increases in the coming years, the use of digoxin will gradually, but inevitably, diminish</u>.***"

–*M Packer,* NEJM *1997*

Courtesy of Gregg Fonarow MD

But how could a little digoxin hurt?



Jefferies JL et al. JACC 2018; 72: 367-369.

When it comes to HF. . .

- Quadruple therapy saves lives!
  - *"I agree that we have better first-line drugs . . .digoxin helps selected patients."*

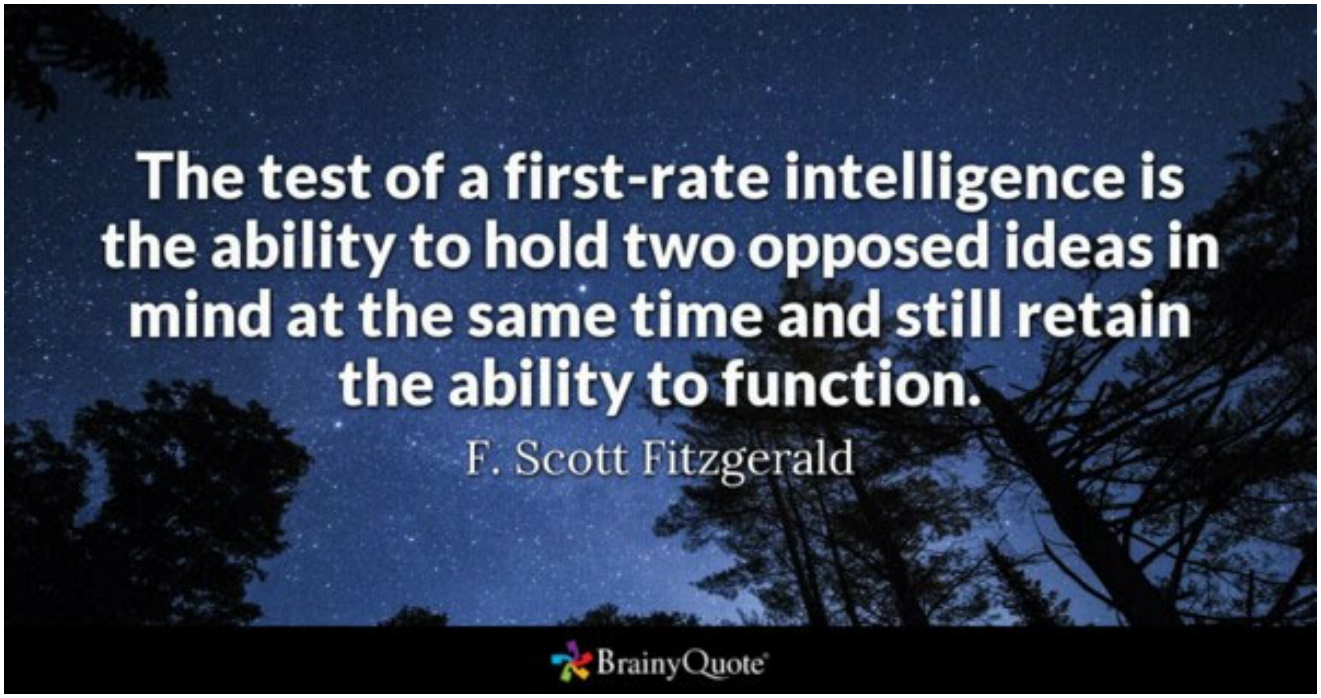
    -- John Mandrola Medscape 7/26/19

- Save digoxin for the electrophysiologists

LEARNING

RATIOS

^


The test of a first-rate intelligence is the ability to hold two opposed ideas in mind at the same time and still retain the ability to function.
F. Scott Fitzgerald
BrainyQuote

Digoxin in HF: The Early Years

Study name	No. pts/duration	Treatment	Results
Lee et al. *NEJM* 1982	25 HF pts w/o AF Blinded crossover	Digoxin vs placebo	Clincoradiographic score: 56% had improvement in HF severity Responders: more chronic HF, greater LV dilation, S3
Guyatt et al. Am J Cardiol 1988	20 HF pts w/o AF Blinded crossover 7 weeks on/off	Digoxin vs placebo	Digoxin improved 6MWT and QOL Deterioration occurred in patients only when taking placebo
Cohn J et al. JAMA 1988	300 HF pts RCT	Captopril vs digoxin	Captopril vs placebo: improved exercise time (mean increase, 82 s vs 35 s) and New York Heart Association class (41% vs 22%) Digoxin or captopril vs placebo: fewer hosp, ED visits, increase in diuretics
DiBianco et al. NEJM 1989	230 HF pts w/o AF 12 weeks RCT	Digoxin vs milrinone vs both vs placebo	Both increased exercise tolerance and reduced HF deterioration Milrinone increased ventricular arrhythmias
Uretsky et al. PROVED trial J Am Coll Cardiol 1993	88 HF pts w/o AF 8w dig, 12w RCT on/off dig	Withdrawal vs continuation of digoxin	Withdrawal of digoxin: decreased exercise time, more hosp, ED visits, increase in diuretics
Packer M et al. RADIANCE trial NEJM 1993	178 HF pts w/o AF NYHA II-III, EF ≤ 35% On ACEI/diuretics 12 weeks RCT	Withdrawal vs continuation of digoxin	Withdrawal of digoxin: - RR 5.9 for worsening HF - Decrease exercise tolerance and QOL

EDITORIAL

End of the Oldest Controversy in Medicine — Are We Ready to Conclude the Debate on Digitalis?

Milton Packer, M.D.

Article

February 20, 1997

15 References 30 Citing Articles Letters

CRITICAL APPRAISAL ❖ L'ÉVALUATION CRITIQUE

VOL 43: JULY • JUILLET 1997 ◆ *Canadian Family Physician*

Use of digoxin in heart failure

Should we bother?

John Frank, MD, CCFP, MSC Michael F. Evans, BA, MD, CCFP

Journal of Cardiac Failure Vol. 16 No. 1 2010

A Fond Farewell to the Foxglove? The Decline in the Use of Digitalis

ALLEN B. WEISSE, MD[1]

Sprinfield, New Jersey

JACC Vol. 26, No. 5
November 1, 1995:1376–98

ACC/AHA TASK FORCE REPORT

Guidelines for the Evaluation and Management of Heart Failure

Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Evaluation and Management of Heart Failure)

Pharmacologic Treatment of Left Ventricular Systolic Dysfunction

Class I

1. ACE inhibitors for all patients with significantly reduced left ventricular ejection fraction unless contraindicated
2. Hydralazine and isosorbide dinitrate in patients who cannot take ACE inhibitors
3. Digoxin in patients with heart failure due to systolic dysfunction not adequately responsive to ACE inhibitors and diuretic drugs
4. Digoxin in patients with atrial fibrillation and rapid ventricular rates

2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

7.3.2.7. Digoxin: Recommendation

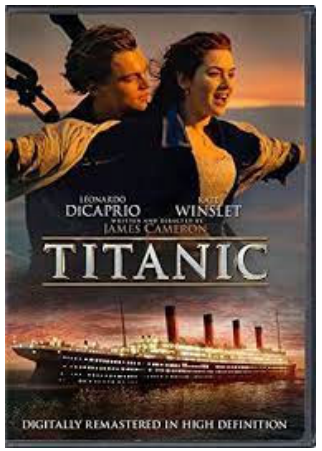
Class IIa

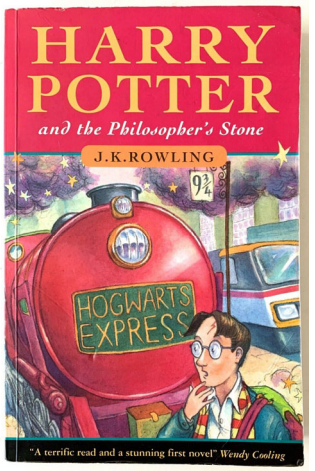
1. **Digoxin can be beneficial in patients with HF*r*EF, unless contraindicated, to decrease hospitalizations for HF.[484–491] *(Level of Evidence: B)***

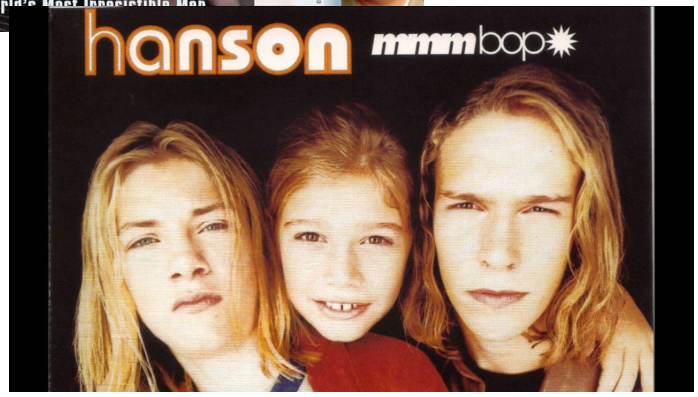
Several placebo-controlled trials have shown that treatment with digoxin for 1 to 3 months can improve symptoms, HRQOL, and exercise tolerance in patients with mild to moderate HF.[485–491] These benefits have been seen regardless of the underlying rhythm (normal sinus rhythm or AF), cause of HF (ischemic or nonischemic cardiomyopathy), or concomitant therapy (with or without ACE inhibitors). In a long-term trial that primarily enrolled patients with NYHA class II or III HF, treatment with digoxin for 2 to 5 years had no effect on mortality but modestly reduced the combined risk of death and hospitalization.[484]


The Boston Nanny: Killer—or Victim?
Convicted au pair Louise Woodward
People weekly
NOVEMBER 17, 1997
SPECIAL DOUBLE ISSUE
BRAD PITT
WILL SMITH
TOM CRUISE
HARRISON FORD
GEORGE CLOONEY
THE SEXIEST MAN ALIVE
1997 PLUS: 70 Pages of

1997


LEONARDO DICAPRIO
KATE WINSLET
JAMES CAMERON
TITANIC
DIGITALLY REMASTERED IN HIGH DEFINITION


HARRY POTTER
and the Philosopher's Stone
J.K.ROWLING
9¾
HOGWARTS EXPRESS
"A terrific read and a stunning first novel" Wendy Cooling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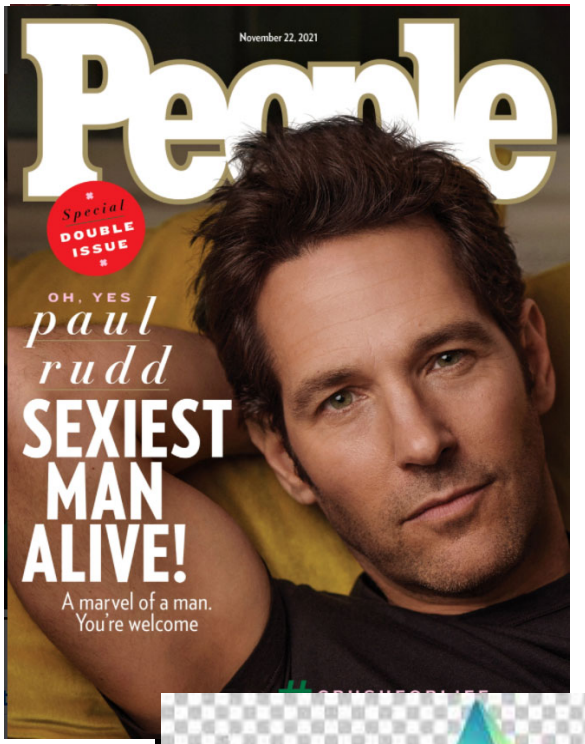
People
November 22, 2021
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rudd
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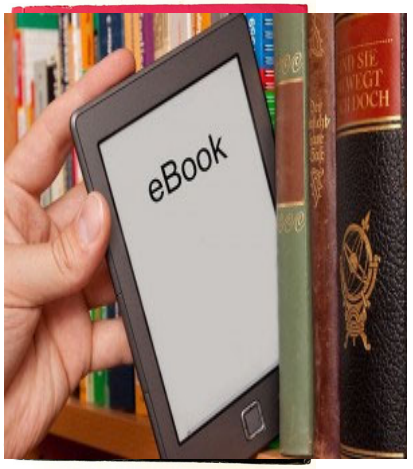
MAN
ALIVE!
A marvel of a man.
You're welcome


FRANCES McDORMAND
NOMADLAND
A FILM BY CHLOÉ ZHAO


eBook


2021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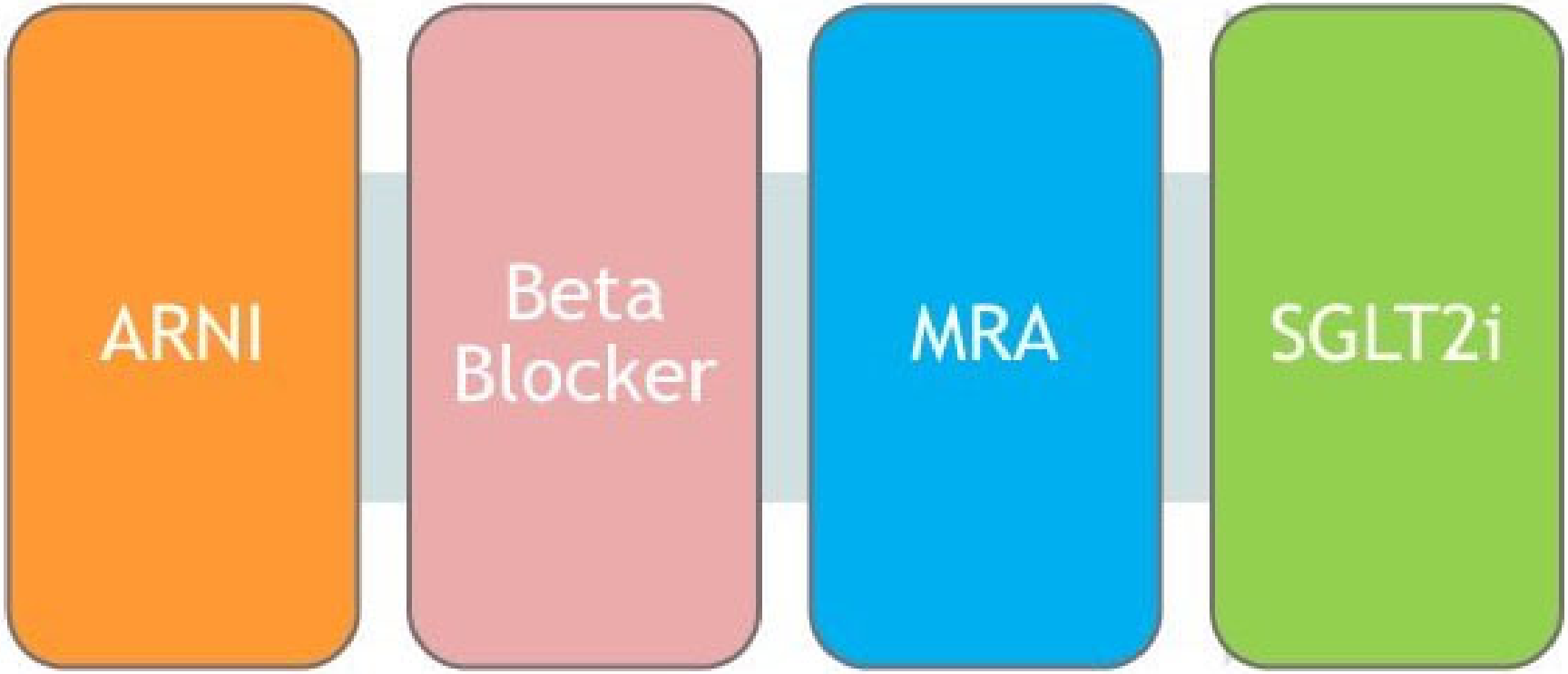
Google play
Spotify
amazon music
DEEZER


9:41

The Four Pillars are exciting!



Cumulative risk reduction in all-cause mortality if all four evidence-based medical therapies are used:
Relative risk reduction 72.9%, Absolute risk reduction: 25.5%, NNT = 3.9, over 24 months

Updated from Fonarow GC, et al. Am Heart J 2011;161:1024-1030 and Lancet 2008;372:1195-1196; Bassi NS et al JAMA Cardiol 2020, May 6, e200898

Courtesy of Gregg Fonarow MD