MEDICATIONS FOR THE FAILING HEART: WHAT'S NEW FOR THE PEDIATRIC PATIENT

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Children's Hospital of Philadelphia
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Children's Hospital of Philadelphia

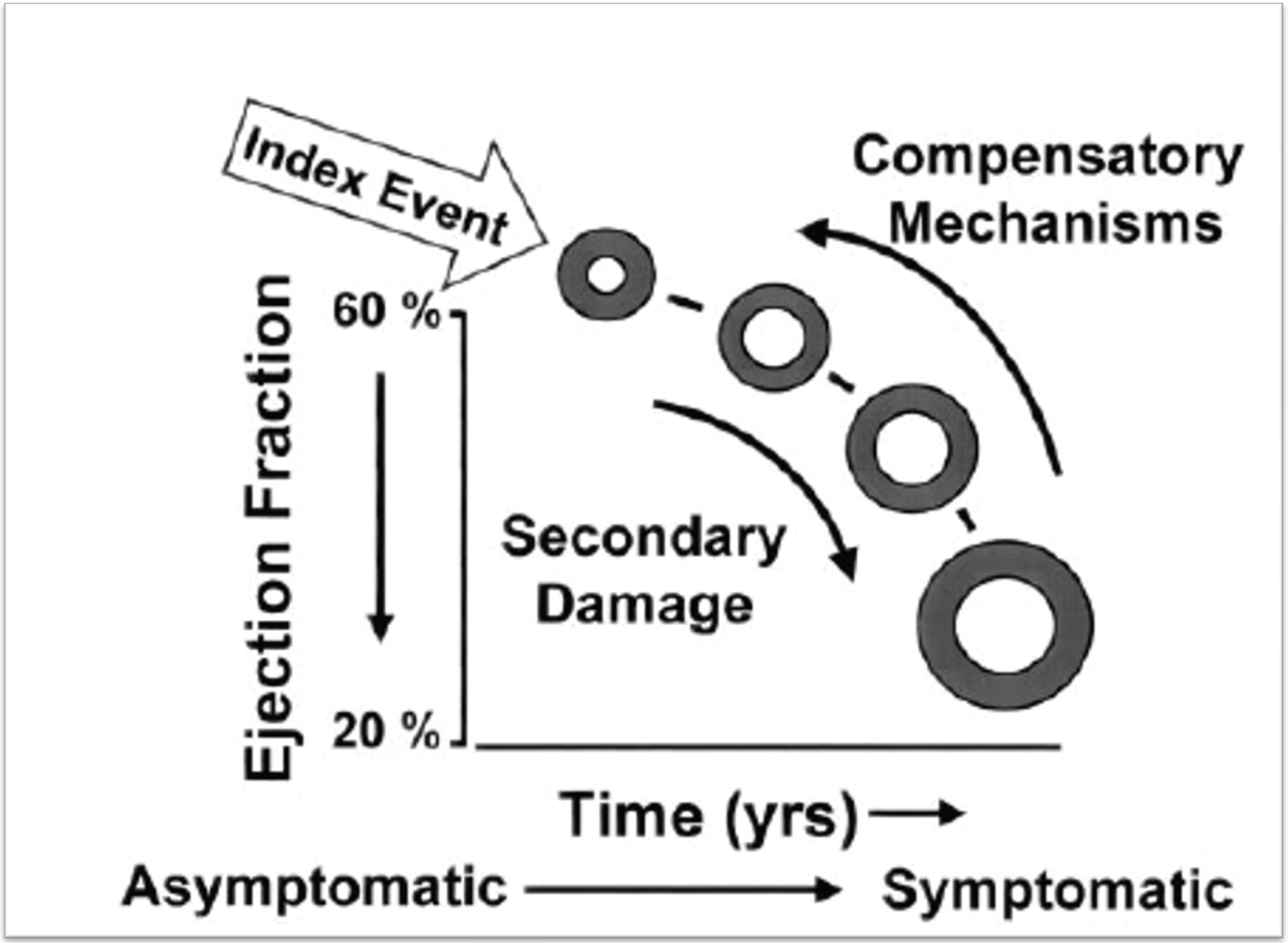
DISCLOSURES

- Paid Consultant Merck, Cytokinetics, Bayer, and Bristol Myers Squibb

OBJECTIVES

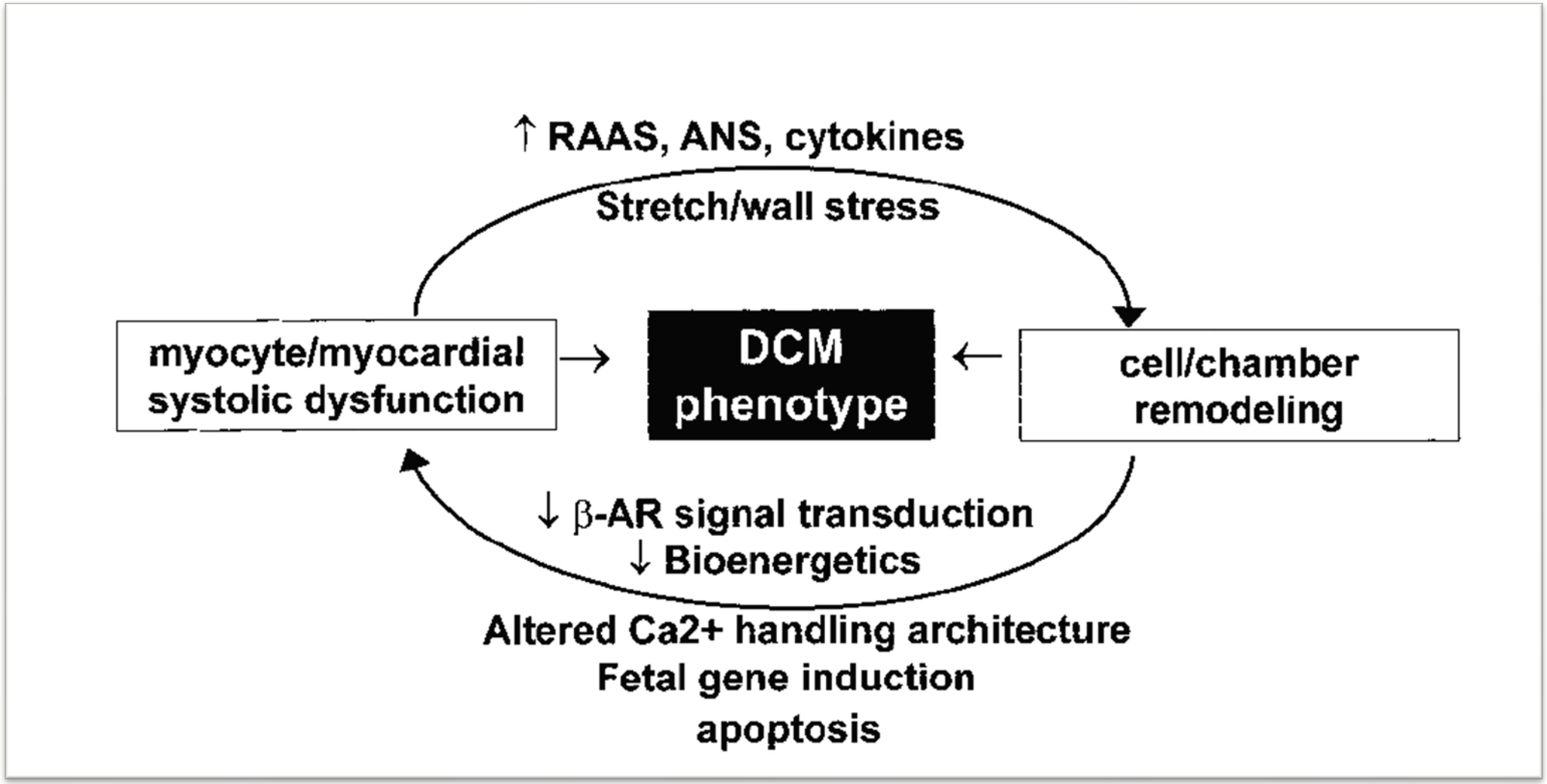
- Review medications historically used to treat heart failure in children

- Discuss exciting new therapies



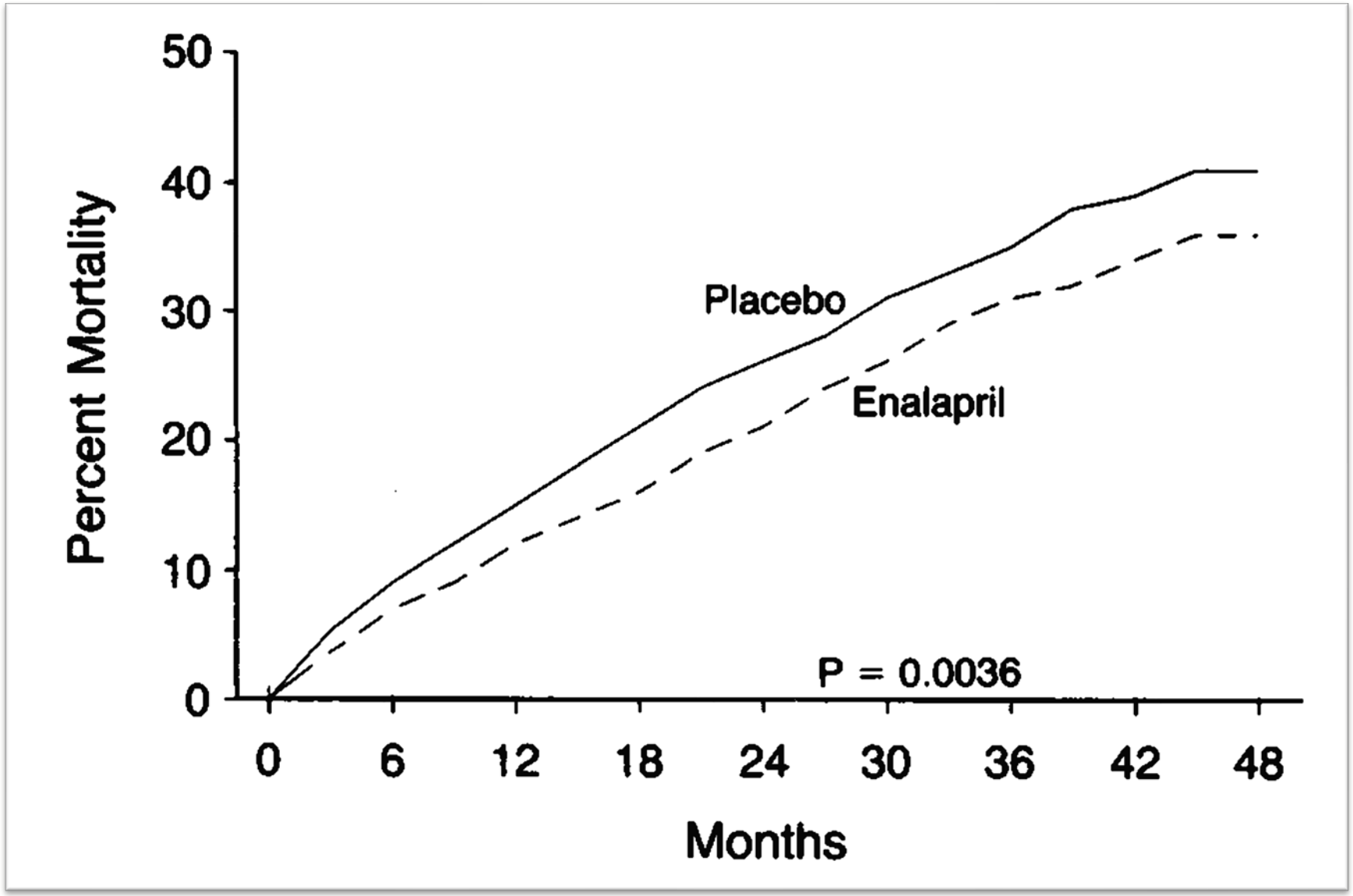
Mann DL. Circulation 2005

NEUROHORMONAL MODEL



Mann DL. Circulation 2005

ACE-INHIBITION



SOLVD Trial. NEJM 1991.

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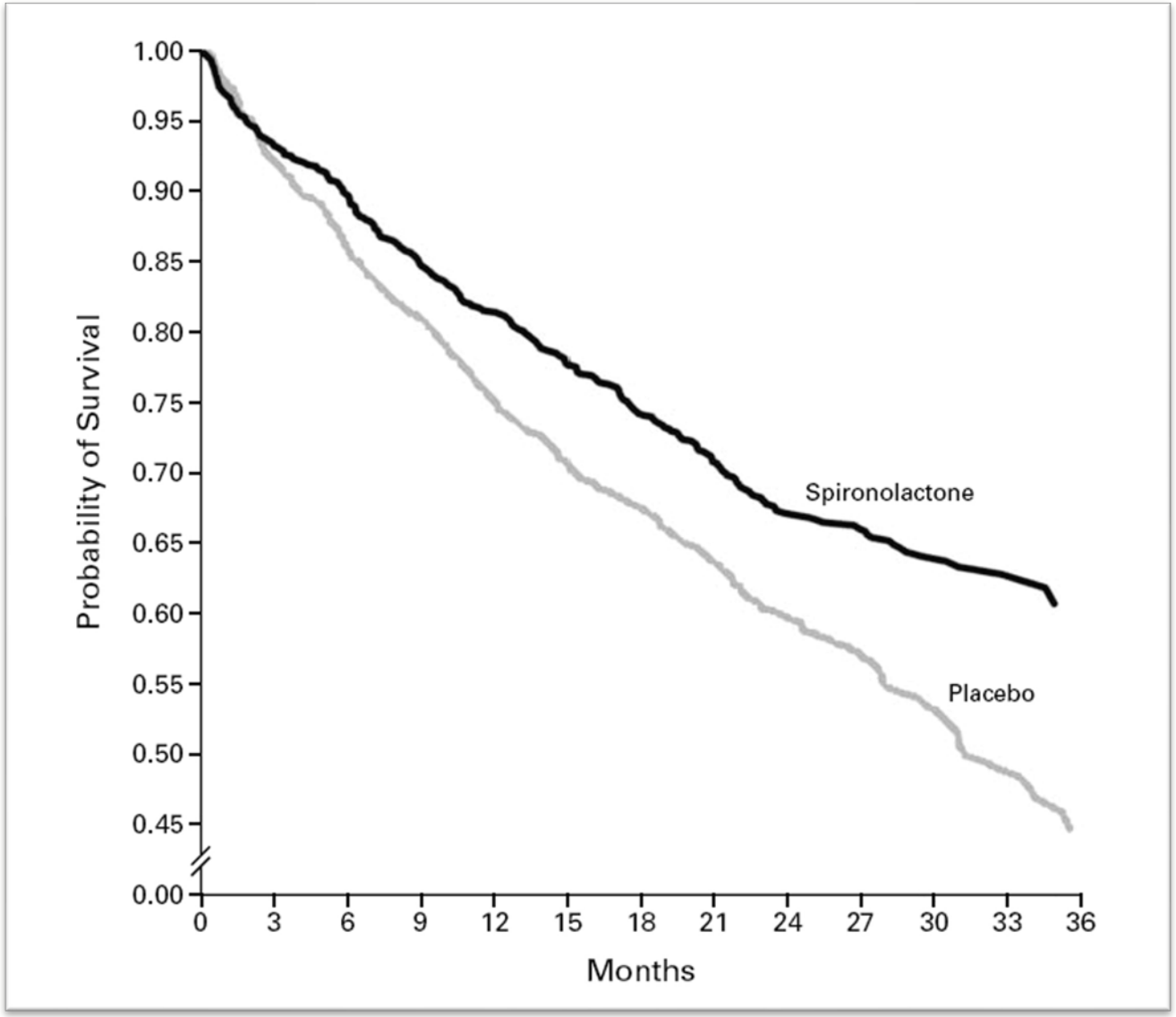
ALDOSTERONE ANTAGONISM



Pitt et al. NEJM 1999

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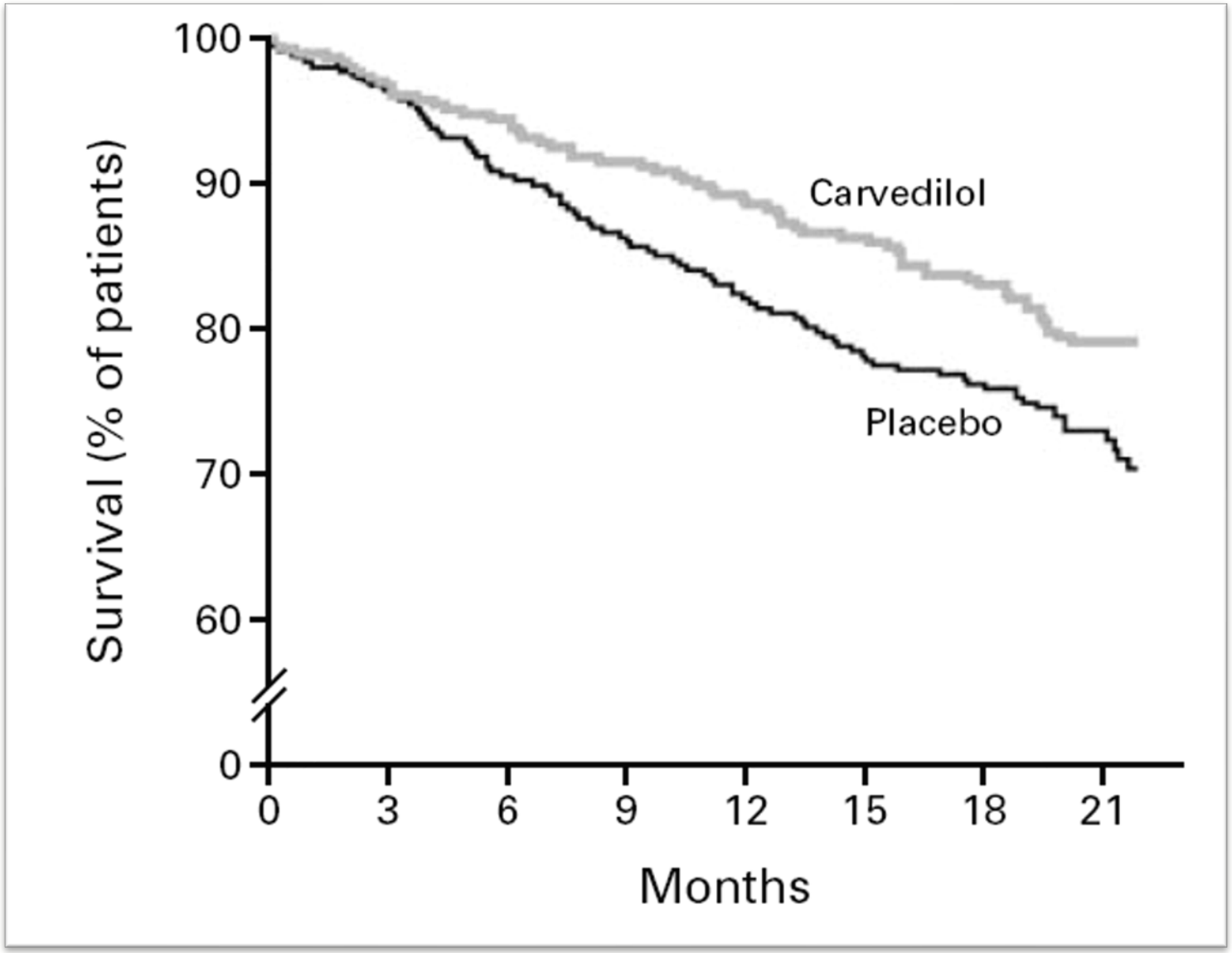
BETA-BLOCKERS



Packer et al. NEJM 2001

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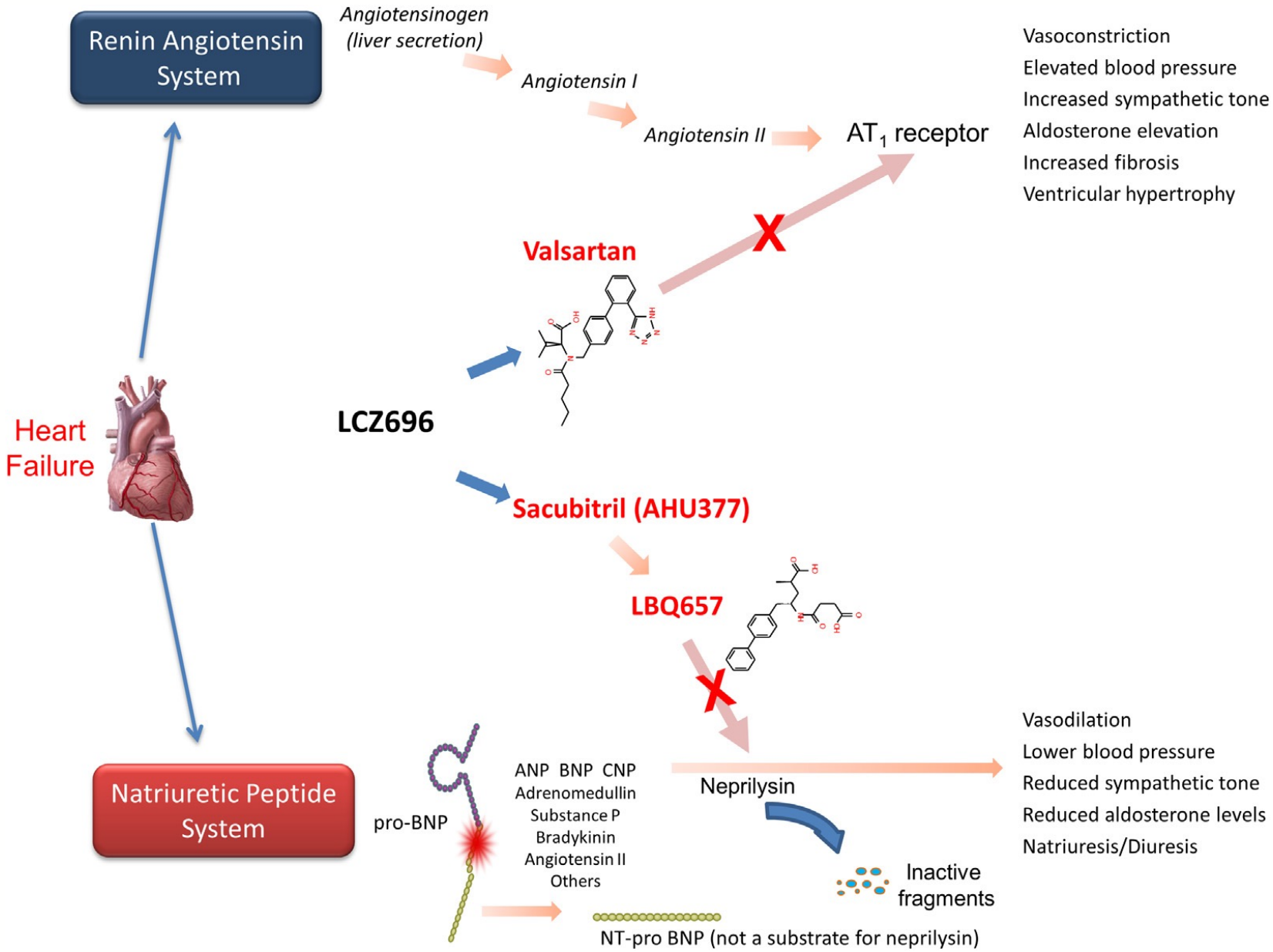

Vardeny O, et al. JACC HF 2014

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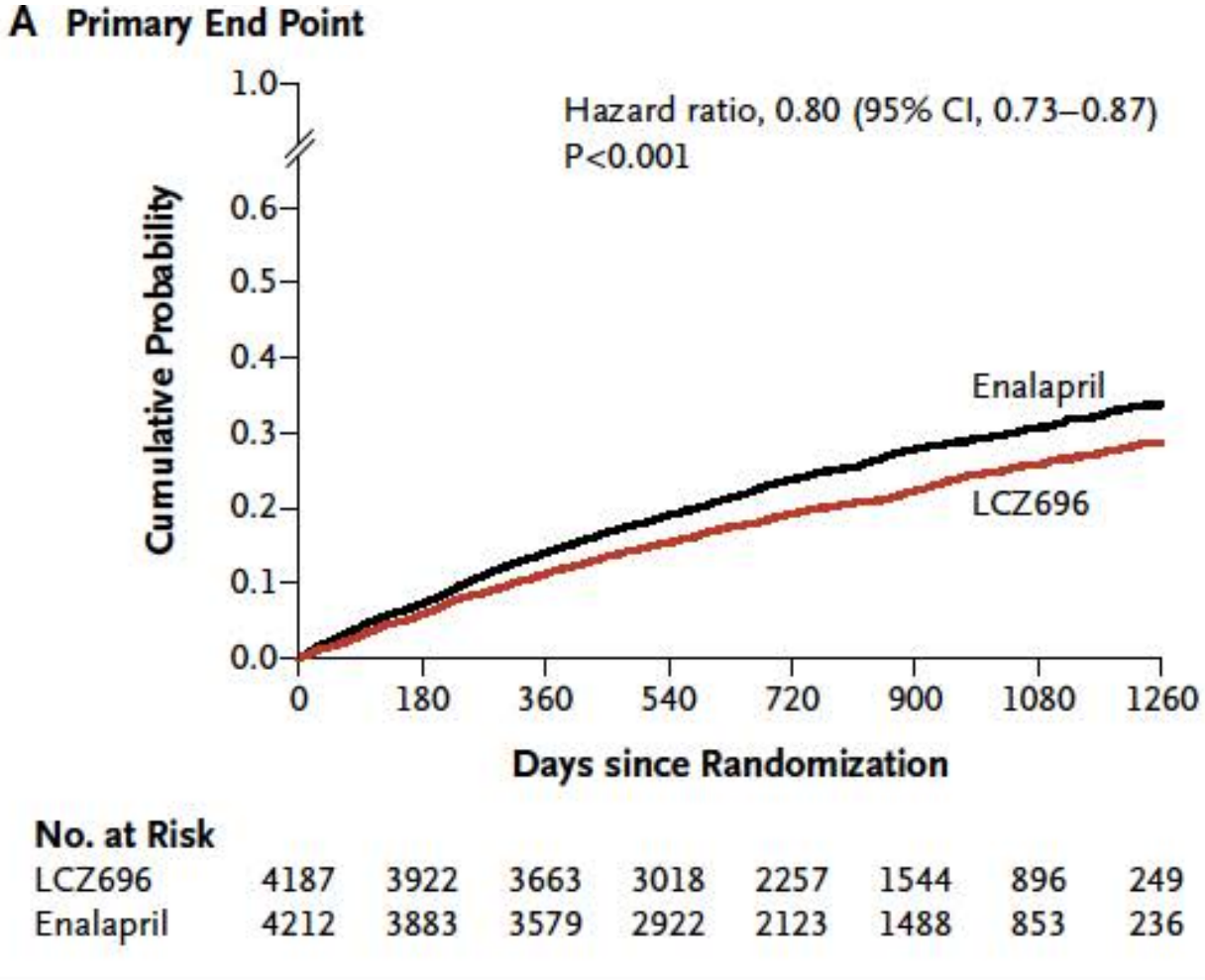
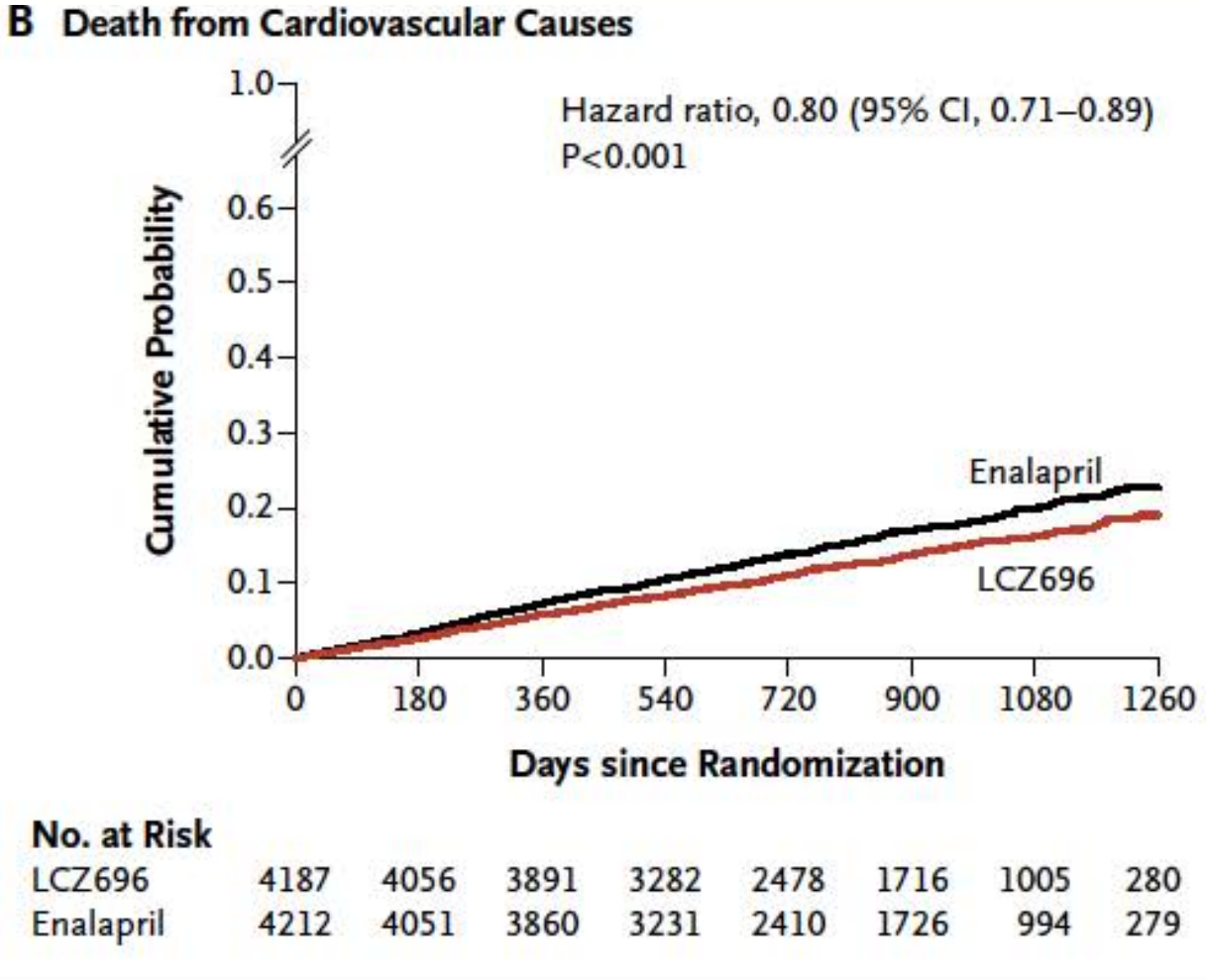
PARADIGM-HF TRIAL





McMurray JJV et al. NEJM 2014

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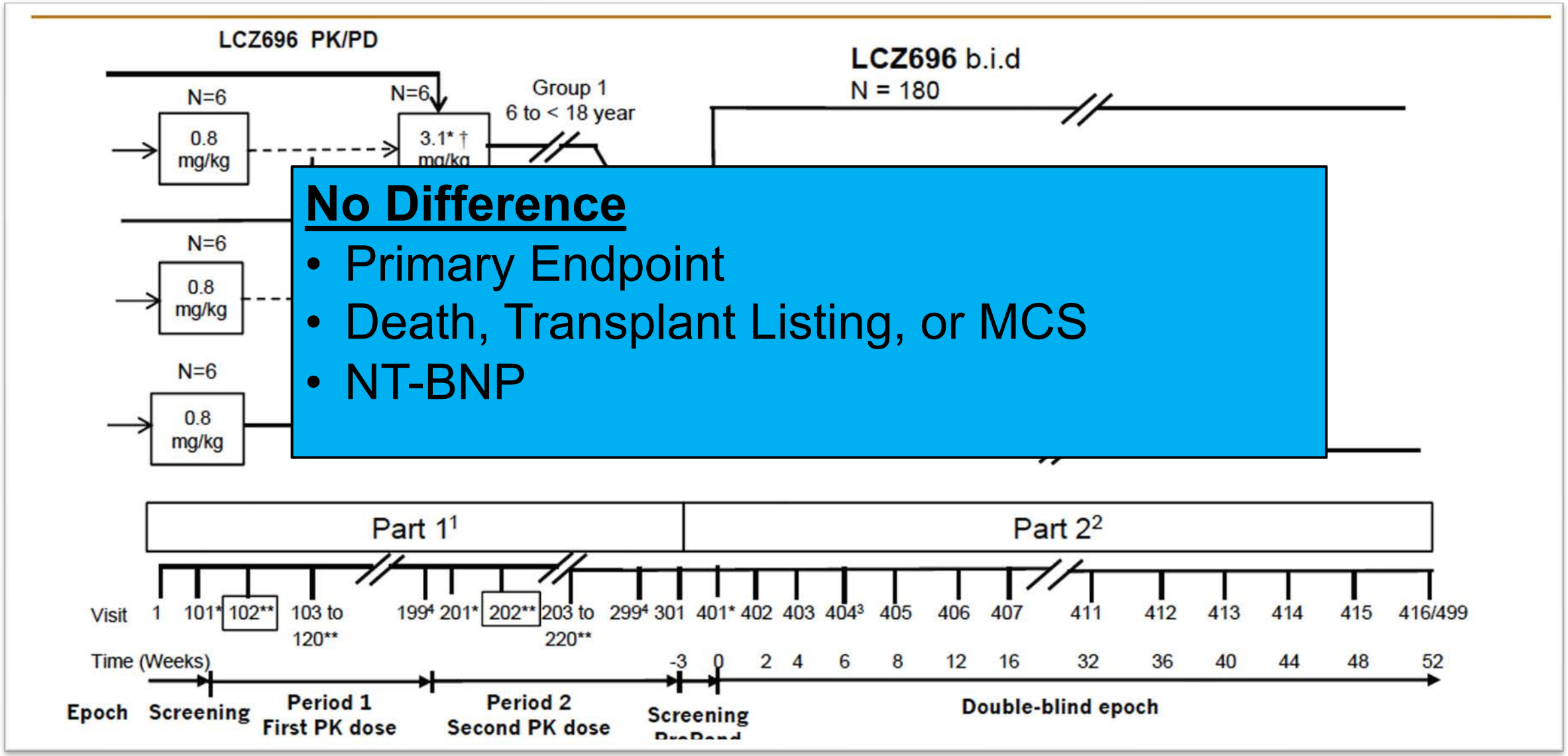
EVIDENCED BASED EFFECTIVE THERAPY FOR HEART FAILURE IN CHILDREN

- Randomized controlled trials
- Systematic reviews
- Cochrane database

PANAROMA-HF



Shaddy RE, et al. AHJ 2017
Shaddy RE, et al. ESC 2022

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Challenges and Opportunities in Pediatric Heart Failure and Transplantation

Update on Pharmacological Heart Failure Therapies in Children

Do Adult Medications Work in Children and if Not, Why Not?

Joseph W. Rossano, MD; Robert E. Shaddy, MD

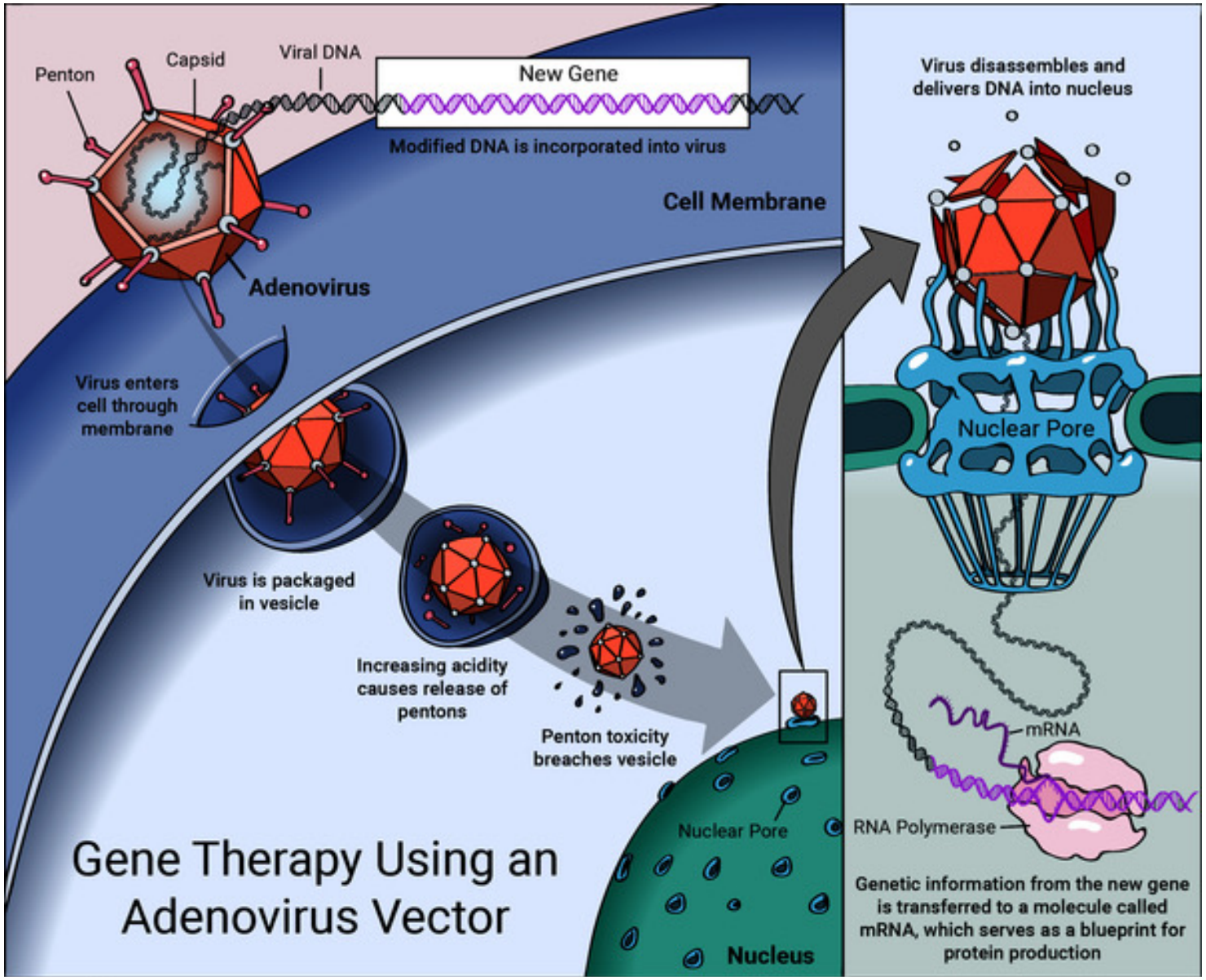
Rossano JW, Shaddy RE. Circulation 2014

POSSIBLE EXPLANATIONS

- Small sample; Type II errors
- Challenges with study design
- Diverse diseases
- Perhaps more patients would recover if not transplanted
- ***The therapies just don't work in pediatric patients***


The Future
NEXT EXIT

GENE THERAPY



Arabi F, et al. Biomedicine & Pharmacotherapy 2022

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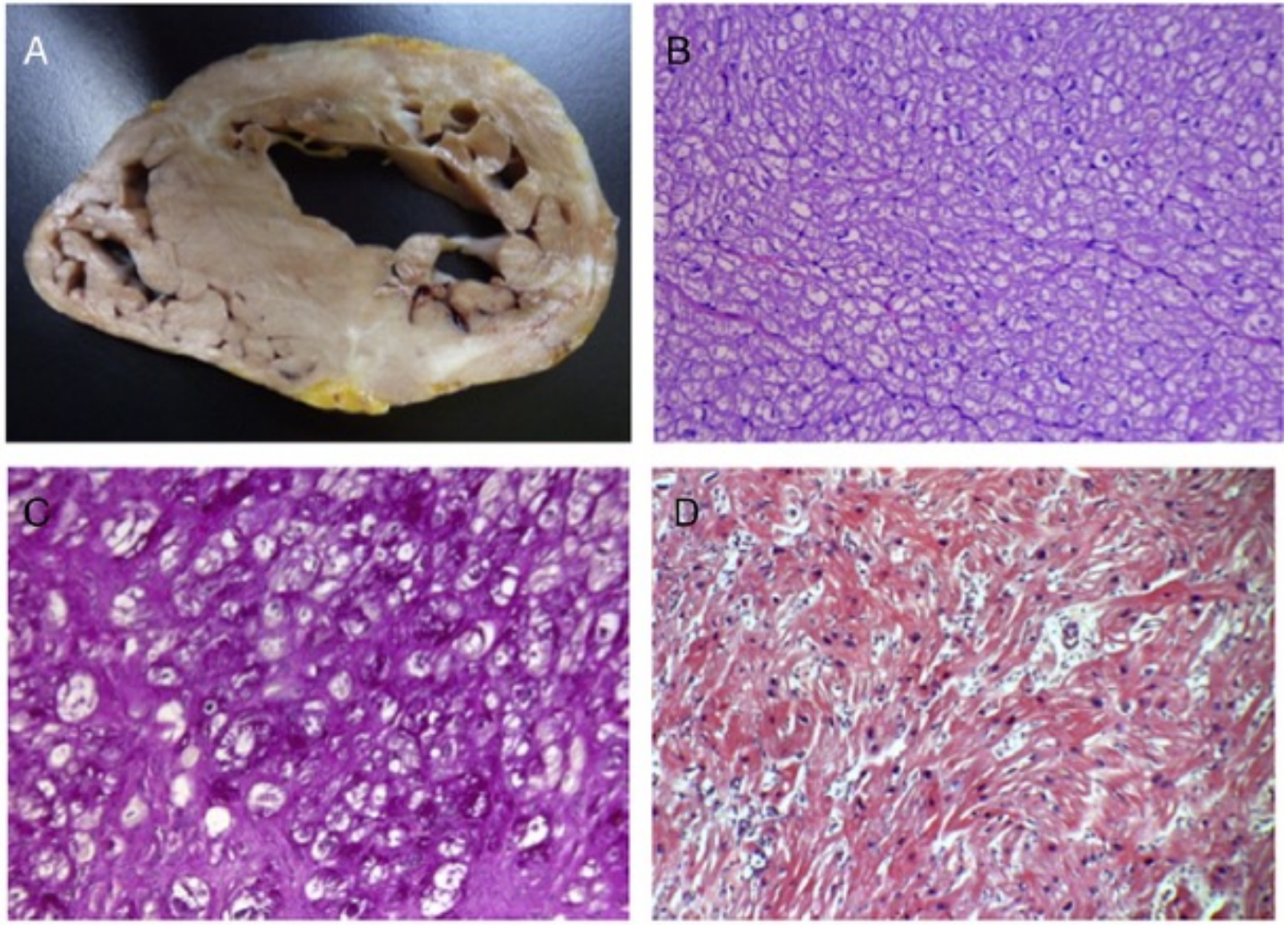
GENE THERAPY TRIAL FOR DANON DISEASE



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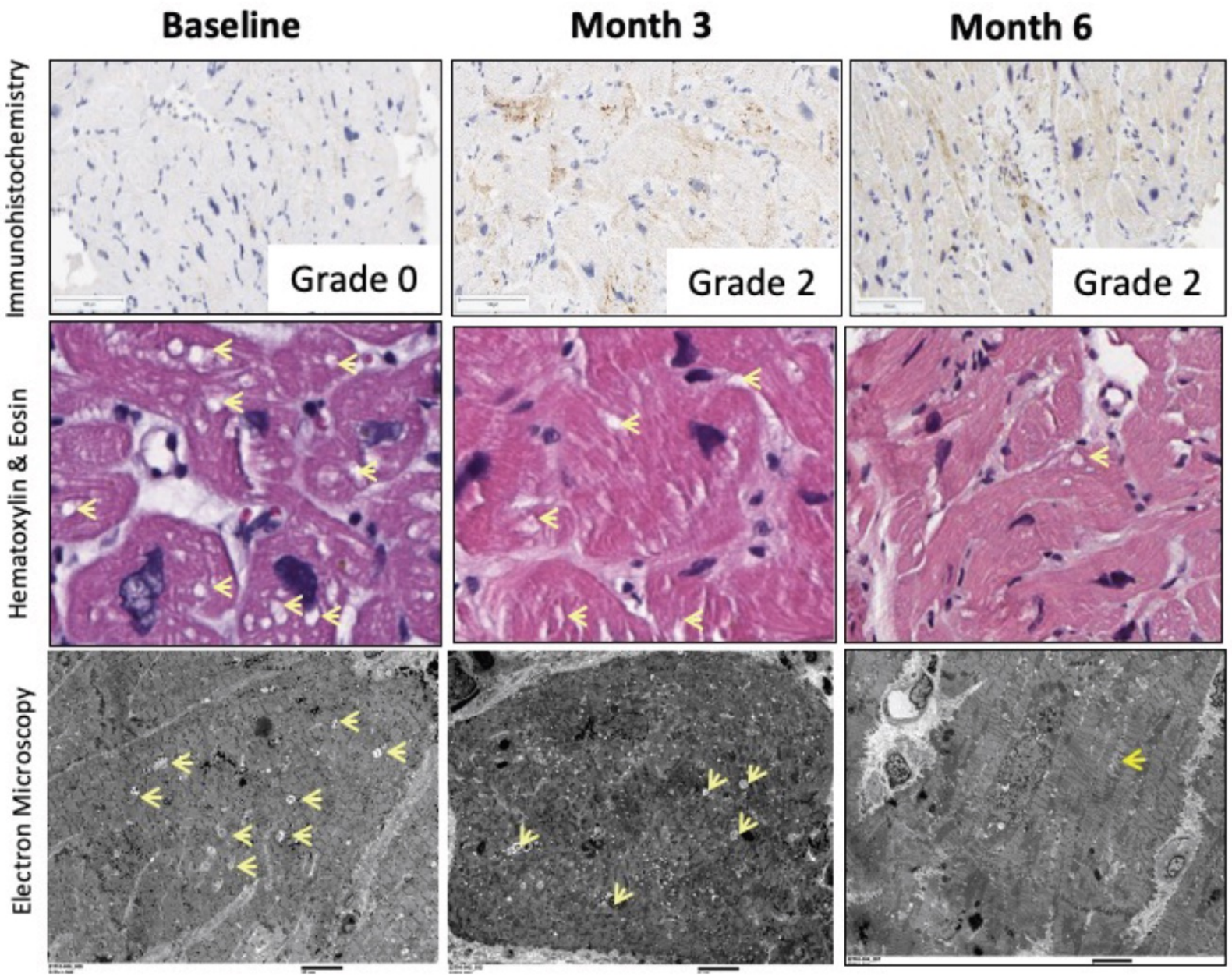

Rossano JW, et al. AHA 2022

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EARLY PEDIATRIC DATA ARE ENCOURAGING AND CONSISTENT WITH ADULT EFFICACY

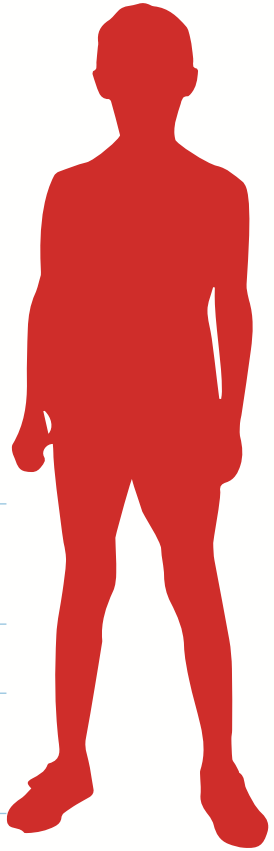
Patient ID: A501-008-1008

Baseline Characteristics

AGE AT INFUSION
12.3 years
ICD yes[1]
WPW yes

MAX LV WALL THICKNESS
41.9 mm, z-score +32
6MWT
438 meters

9 months



Variable	Baseline[2]	Most Recent Follow-up
LAMP2 protein[3] (%)	0.5	21[4]
Troponin-I (ng/mL)	1.89	0.28
BNP (pg/mL)	1837	406
KCCQ-overall score	50	93
NYHA Class	II	I

Patient ID: A501-008-1009

Baseline Characteristics

AGE AT INFUSION
11.7 years
ICD no
WPW no

MAX LV WALL THICKNESS
19.8 mm, z-score +12
6MWT
553 meters

6 months

Variable	Baseline[2]	Most Recent Follow-up
LAMP2 protein[3] (%)	2.6	35[4]
Troponin-I (ng/mL)	0.67	0.07
BNP (pg/mL)	297	113
KCCQ-overall score	52	81[5]
NYHA Class	II	I

[1] Recommended prior to enrollment; ICD implanted 3 months after RP-A501 infusion
[2] Baseline values for troponin-I and BNP are the mean values from all pre-dose visits
[3] All biopsies stained for LAMP2 were compared to normal controls. Data is quantitated in a blinded fashion from ~3-5 sections
[4] Most recent biopsy data available from 6 month visit for 1008 and 3 month visit for 1009
[5] Most recent KCCQ data available from 3 month visit for 1009

6MWT, 6-minute walk test; BNP, brain natriuretic peptide; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City cardiomyopathy questionnaire; LAMP2, lysosome-associated membrane protein 2; LV, left ventricle; NYHA, New York Heart Association; WPW, Wolff-Parkinson-White syndrome.

Rossano JW, et al. AHA 2022

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WHEN IT COMES TO LONGEVITY…..

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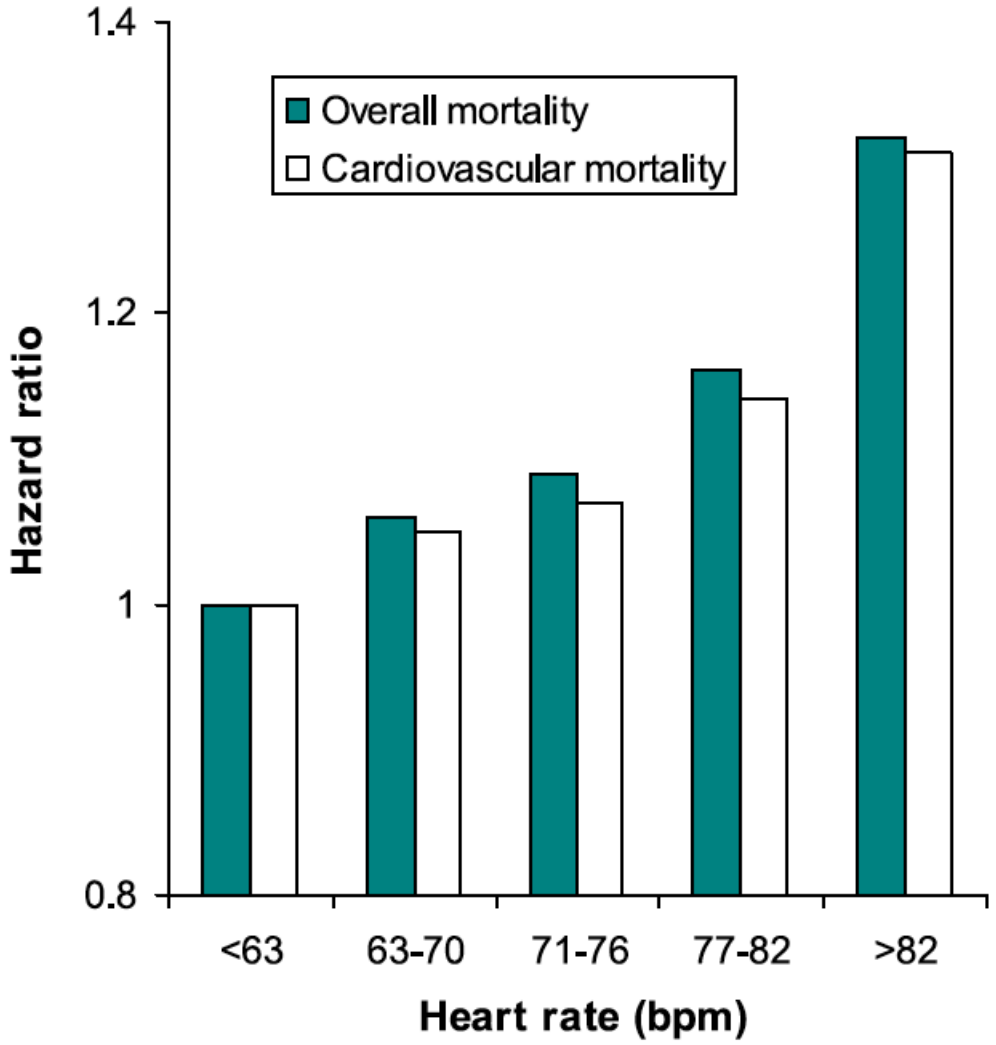
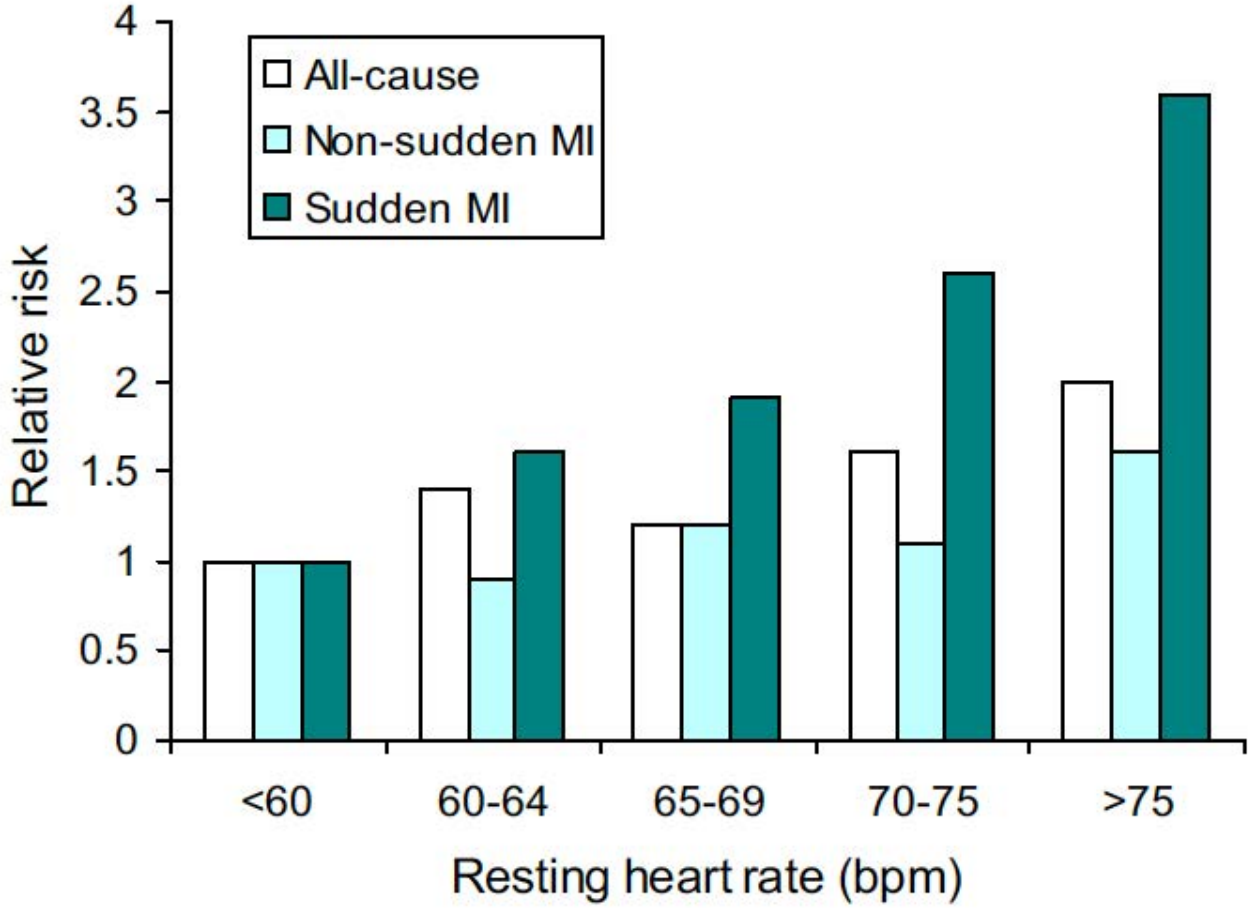


CAD Patients



Healthy Men

Fox K, et al. JACC 2007

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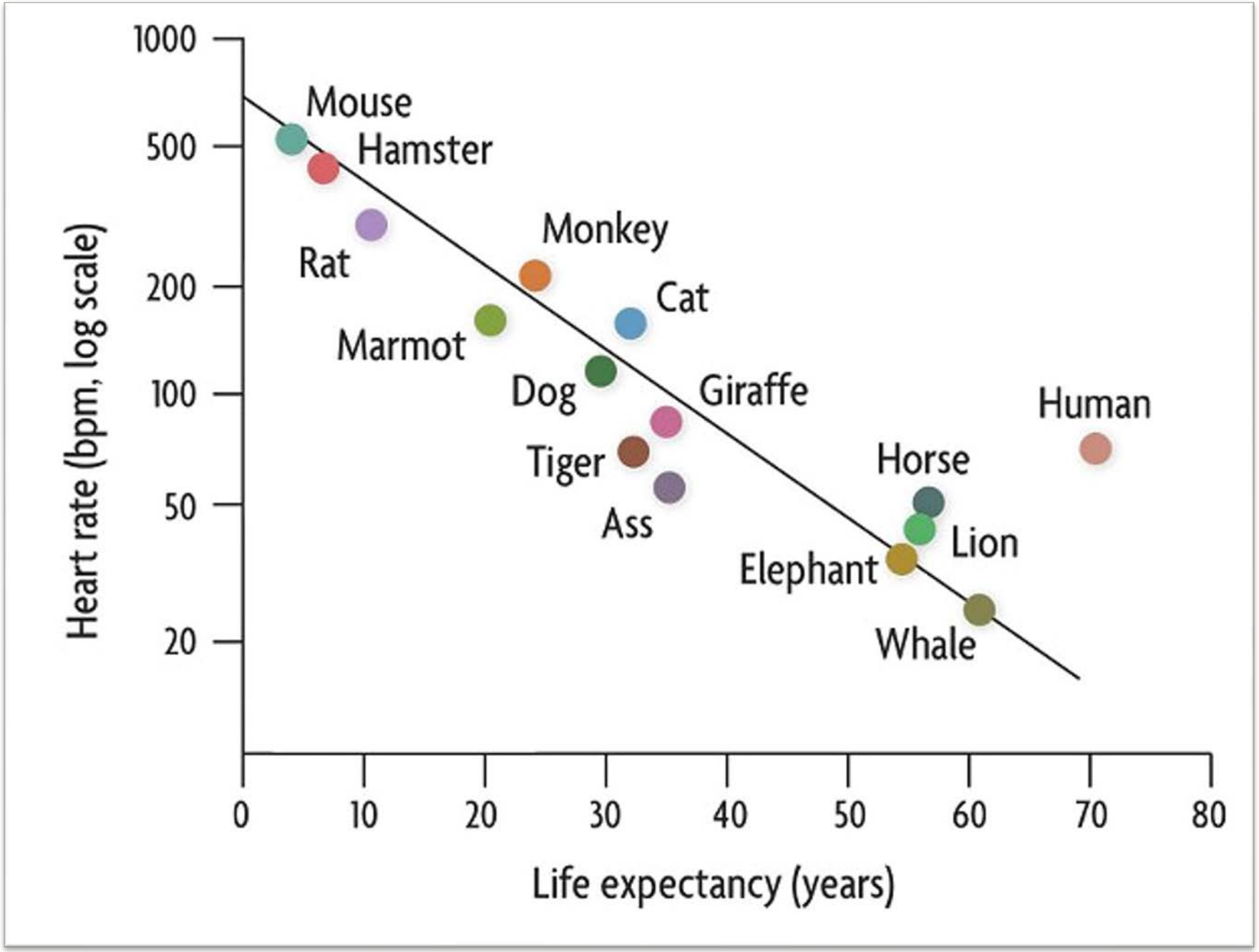

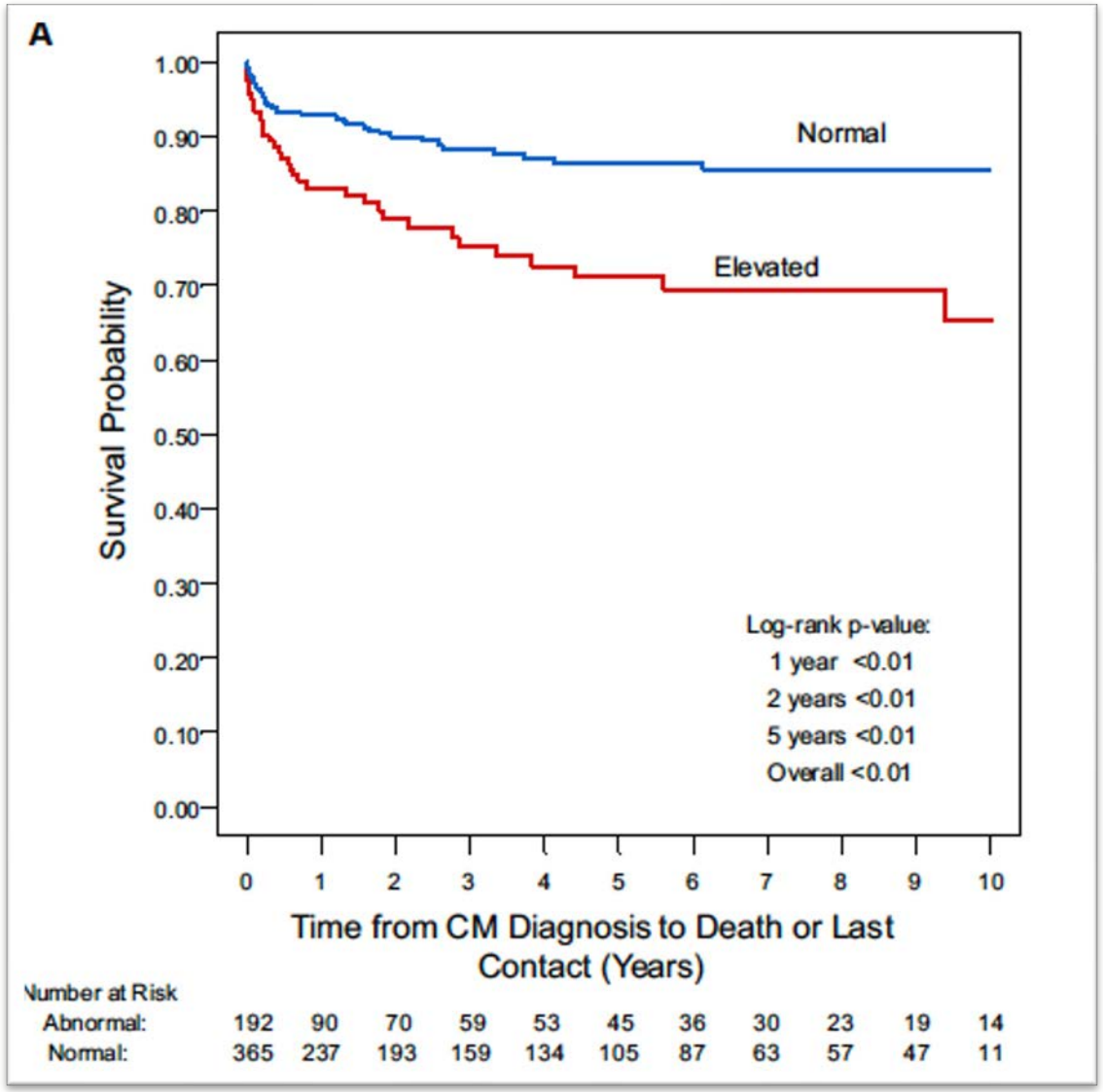

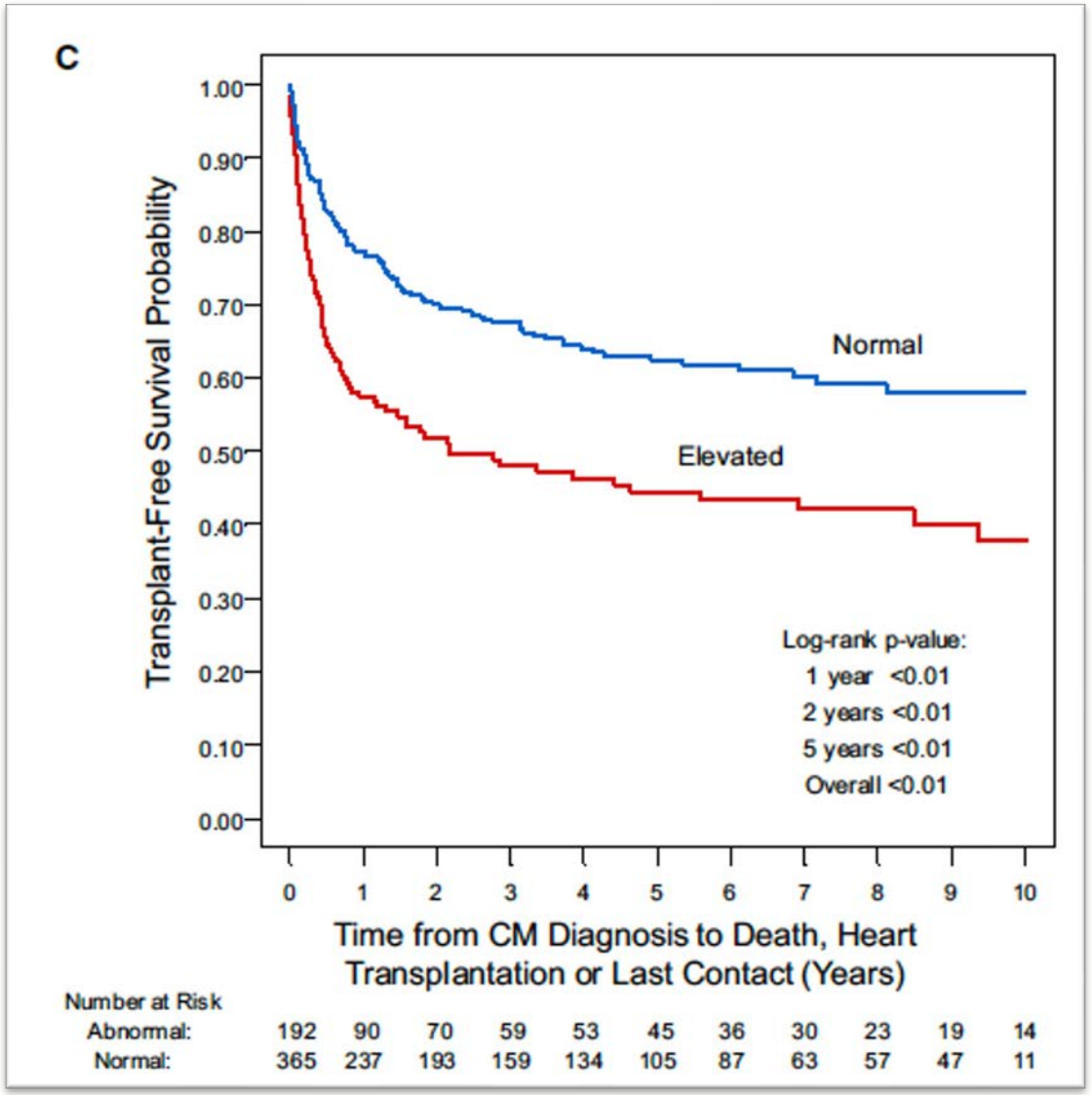

Rossano JW et al. JAHA 2020

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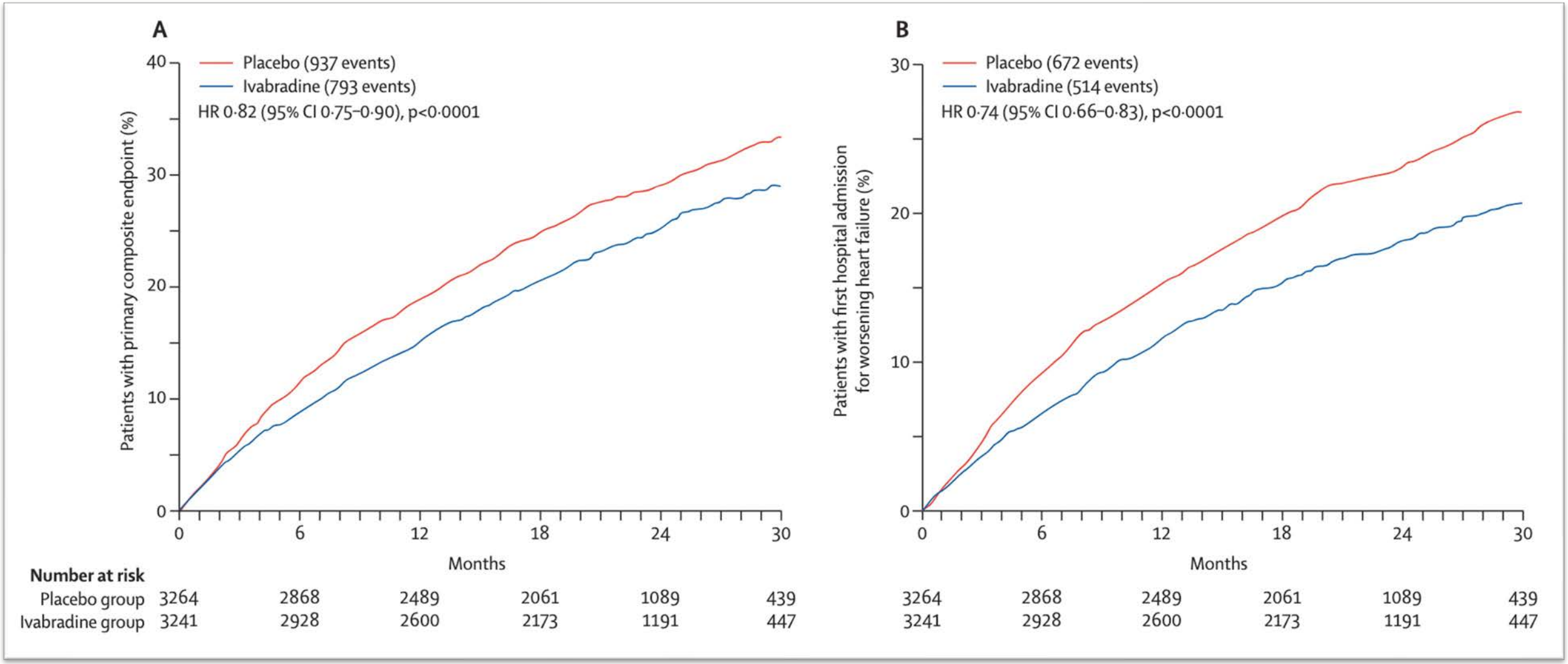
IVABRADINE

- Inhibitor of the I_f current in the sinoatrial node
- Elevated heart rates are associated with mortality in heart failure
- Decreases heart rate
  - No decrease in contraction

IVABRADINE



Swedberg K et al. Lancet 2010

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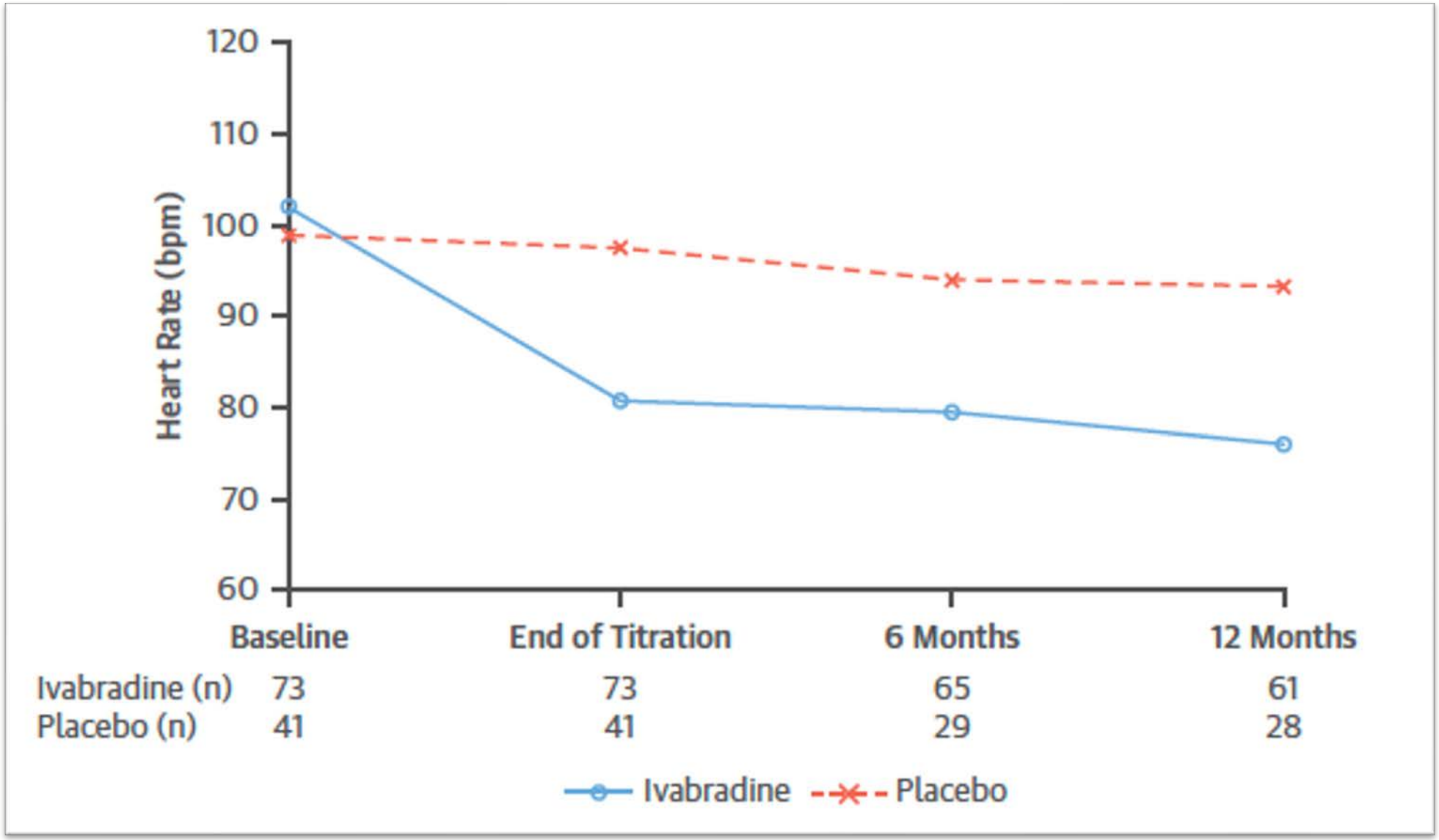
IVABRADINE IN PEDIATRIC DCM



Bonnet D, al. JACC 2017

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JUST MAKE THE HEART SQUEEZE HARDER…..

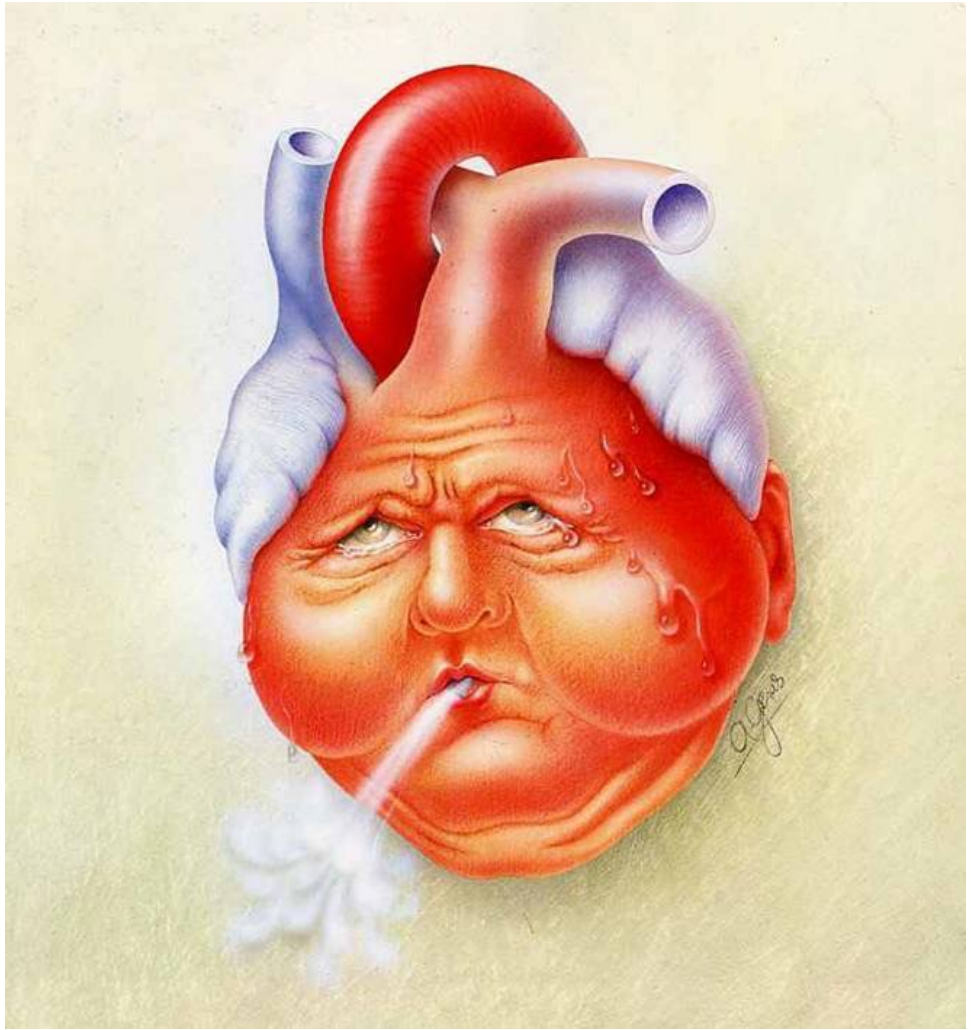
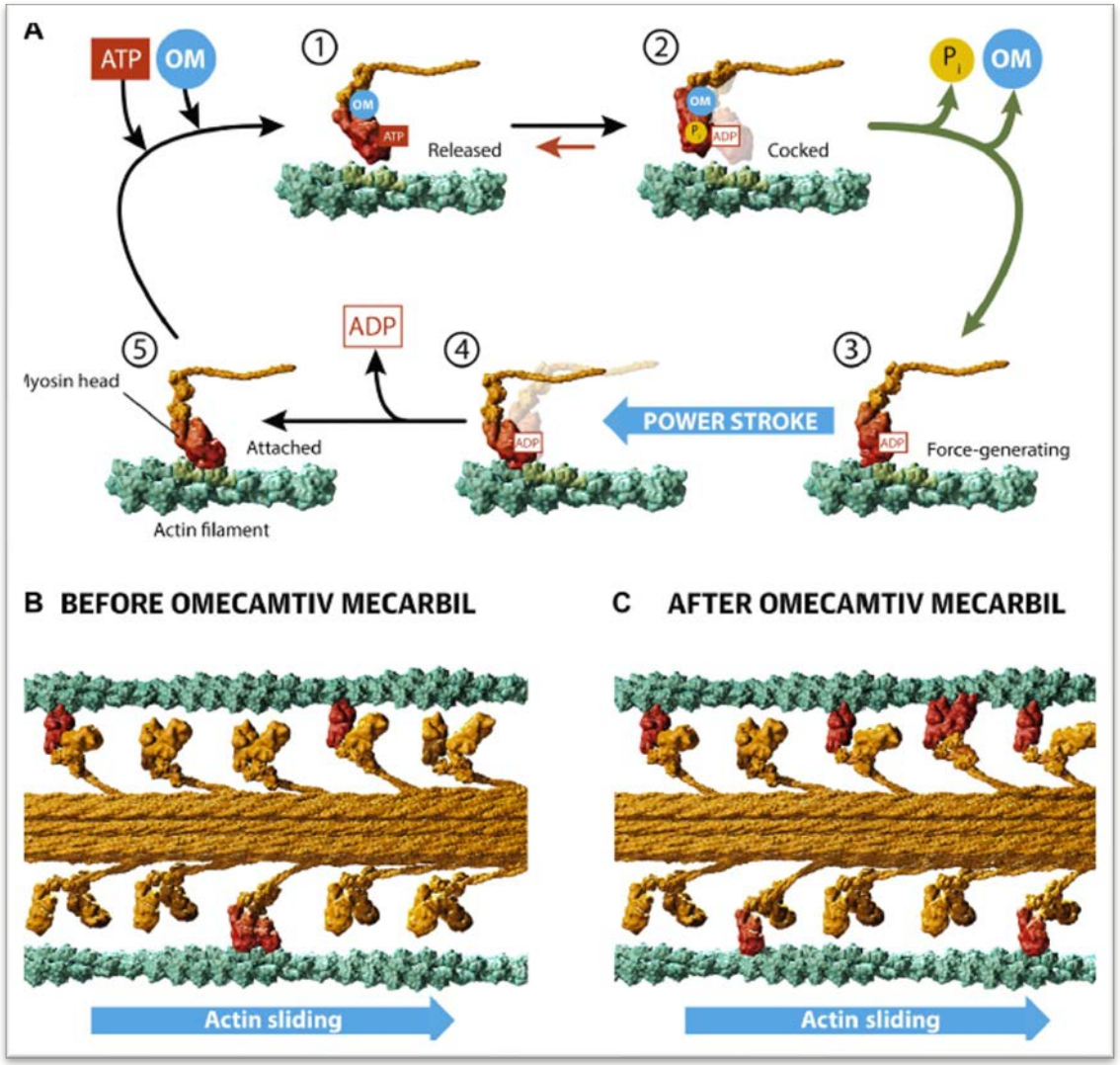


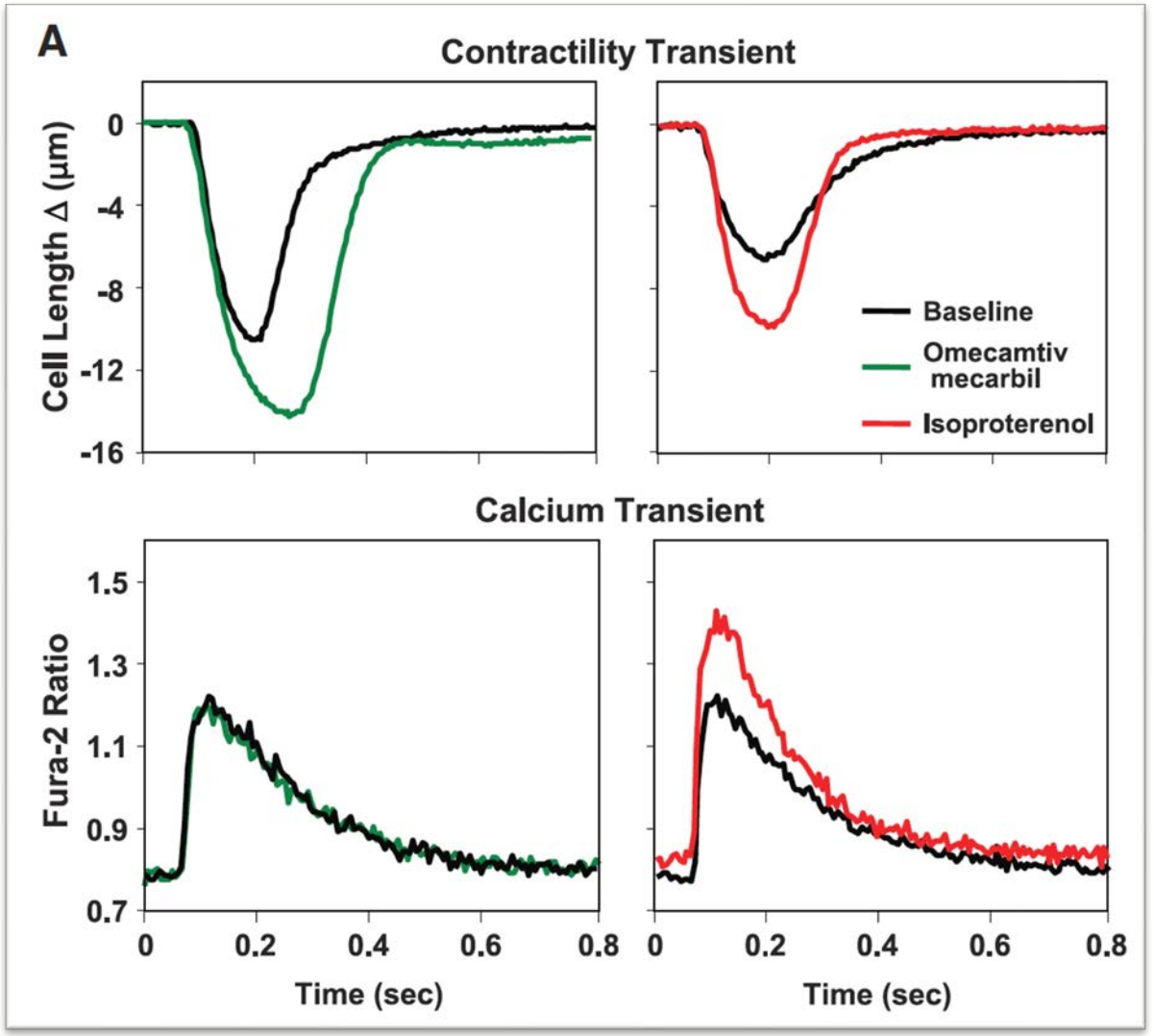
TABLE 1 Clinical Trials With Oral Calcitropic Drugs in Chronic Heart Failure

Clinical Trial (Ref. #)	Calcitrope	Year	N	Key Inclusion Criteria	Effects on Mortality
Xamoterol (Supplemental Ref. 1)	Xamoterol	1990	516	LVEF <35%, NYHA functional class III-IV	Xamoterol: 32 deaths/n = 352 (9.1%) Placebo: 6 deaths/n = 164 (3.7%) Within 100 days of randomization (p = 0.02)
PROMISE (Supplemental Ref. 2)	Milrinone	1991	1,088	LVEF ≤35%, NYHA functional class III-IV	Milrinone: 168 deaths/n = 561 (30%) Placebo: 127 deaths/n = 527 (24%) Log-rank test: 28% increase mortality; 95% CI: 1%-61%; p = 0.038
PROFILE (Supplemental Ref. 3)	Flosequinan	1993	2,345	LVEF ≤35%, NYHA functional class III-IV	Flosequinan: 255 deaths/n = 1,170 Placebo: 192 deaths/n = 1,175 HR: 1.39; 95% CI: 1.15-1.67; p = 0.0006
PICO (Supplemental Ref. 4)	Pimobendan	1996	317	LVEF ≤45%, NYHA functional class II-III	Pimobendan (2.5 mg): 13 deaths/n = 106; HR: 1.5; 95% CI: 0.9-2.5 Pimobendan (5.0 mg): 11 deaths/n = 103 HR: 1.2; 95% CI: 0.7-2.1 Placebo: 6 deaths/n = 108
PRIME II (Supplemental Ref. 5)	Ibopamine	1997	1,906	LVEF <35%, NYHA functional class III-IV	Ibopamine: 232 deaths/n = 953 (25%) Placebo: 193 deaths/n = 953 (20%) Relative risk: 1.26; 95% CI: 1.04-1.53; p = 0.017
VEST (Supplemental Ref. 6)	Vesnarinone	1998	3,833	LVEF ≤30, NYHA functional class III-IV	Vesnarinone (60 mg): 292 deaths/n = 1,275 (22.9%) p = 0.02 vs. placebo Vesnarinone (30 mg): 268 deaths/n = 1,275 (21.0%) p = 0.21 vs. placebo Placebo: 242 deaths/n = 1,283 (18.9%)
Enoximone Multicenter Trial (Supplemental Ref. 7)	Enoximone	1990	102	LVEF ≤40%, NYHA functional class II-III	Enoximone: 10 deaths/n = 50 Placebo: 3 deaths/n = 52 p < 0.05
EMOTE Trial (Supplemental Ref. 8)	Enoximone	2007	201	LVEF ≤25%, NYHA functional class IV, inotrope dependence	Enoximone: 38 deaths/n = 101 Placebo: 31 deaths/n = 100 p = 0.37
ESSENTIAL Trials Program (Supplemental Ref. 9)	Enoximone	2009	1,854	LVEF ≤35%, NYHA functional class III-IV (2 trials)	Enoximone: 196 deaths/n = 926 (21.2%) Placebo: 203 deaths/n = 928 (21.9%) HR: 0.97; 95% CI: 0.80-1.17; p = 0.73 (Note: No improvement in major clinical outcomes)

Teerlink JR, et al. JACC: Heart Failure. 2020

CARDIAC MYOSIN ACITIVATION





Malik F, et al. Science. 2011
Teerlink JR, et al. JACC: Heart Failure. 2020

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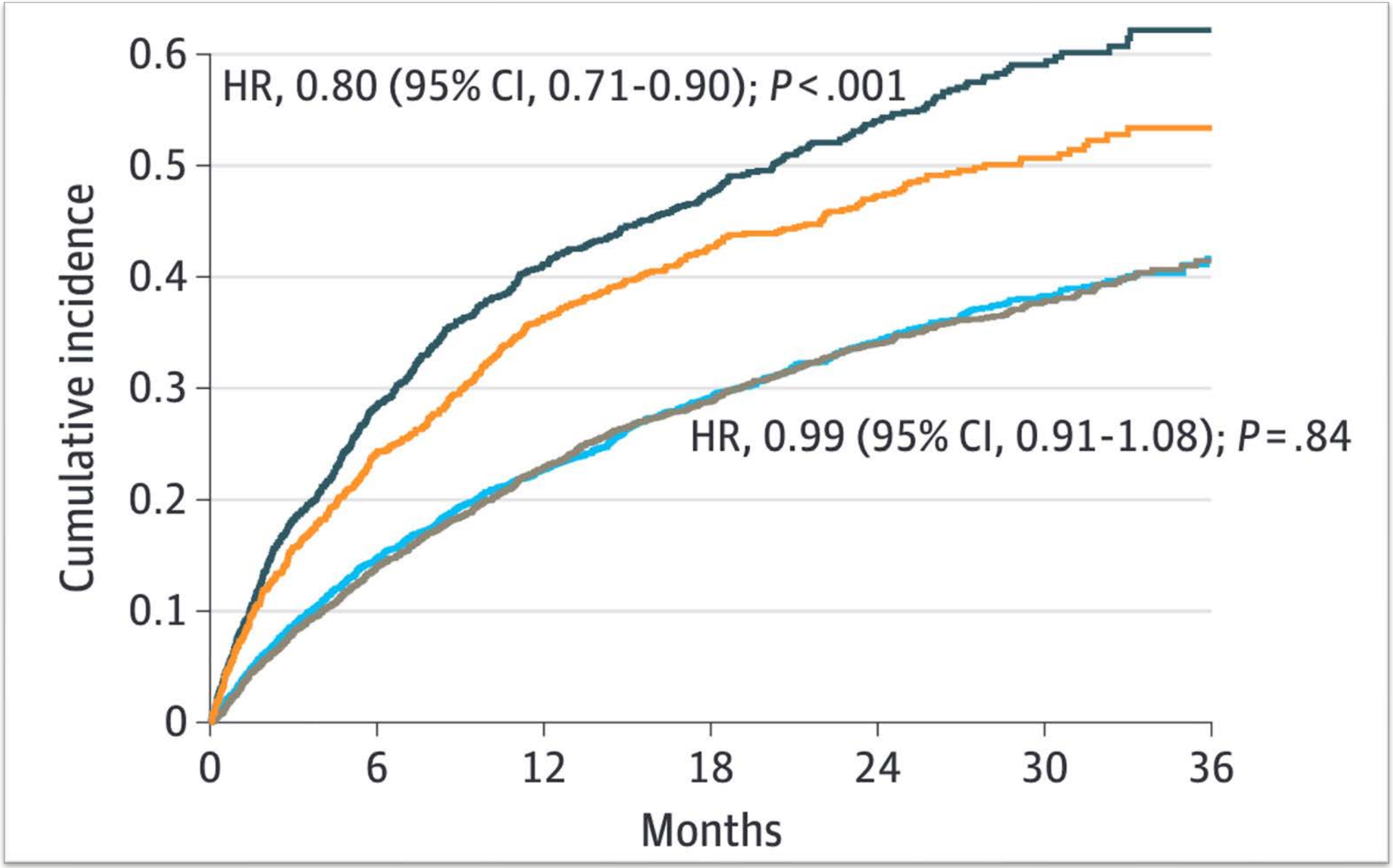

Felker GM, et al. JAMA Cardiology. 2022

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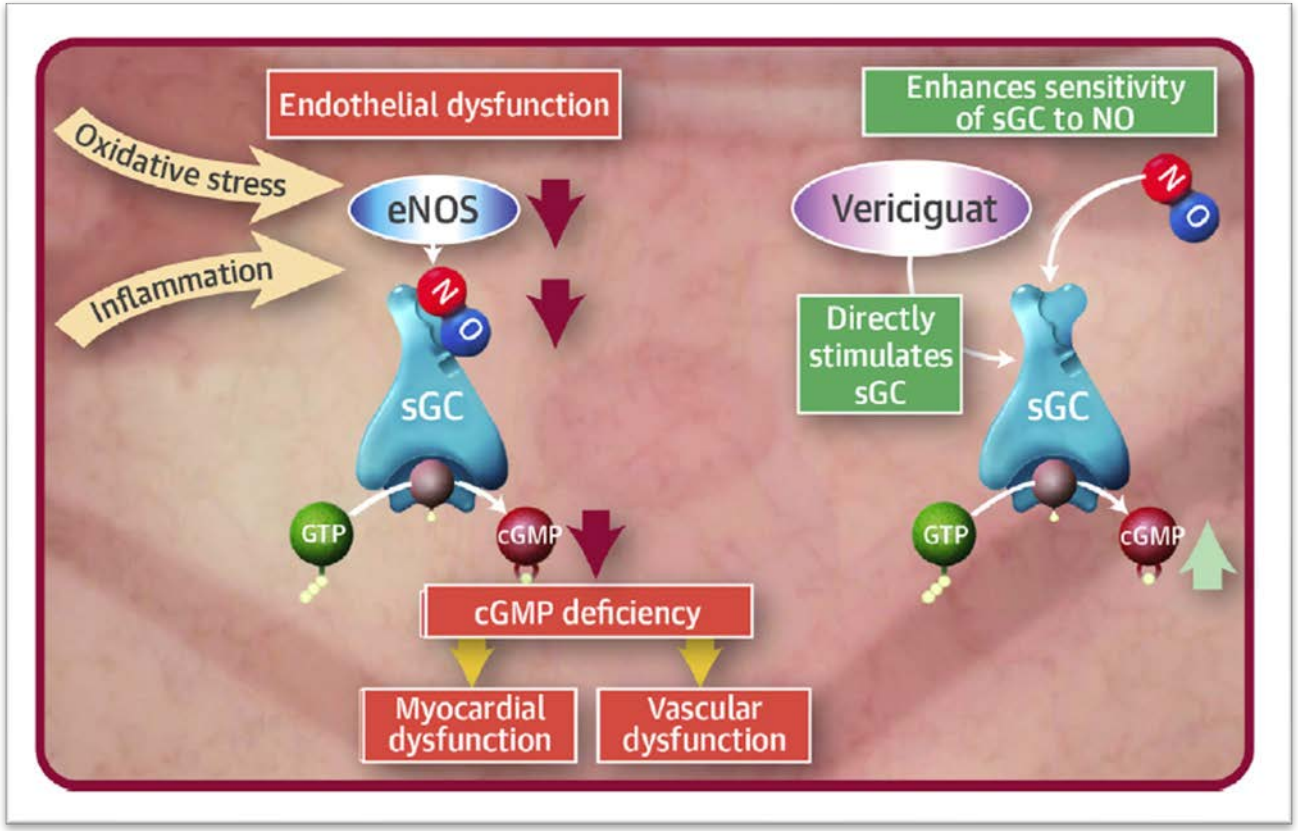
GUANYLATE CYCLASE STIMULATORS



- Endothelial dysfunction due to oxidative stress and inflammation leads to insufficient activation of sGC
- This leads to cGMP deficiency which is associated with myocardial dysfunction and impaired endothelial-dependent vasomotor regulation

Armstrong PW, et al. JACC Heart Failure 2018

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VICTORIA TRIAL

- Phase 3 trial
- 5,050 patients
  - NYHA II-IV
  - LVEF < 45%
  - Elevated natriuretic peptides
  - Placebo vs vericiguat (target dose 10 mg)
- Primary outcome
  - Death from cardiovascular cause
  - First hospitalization for heart failure

Armstrong PW, et al. NEJM 2020

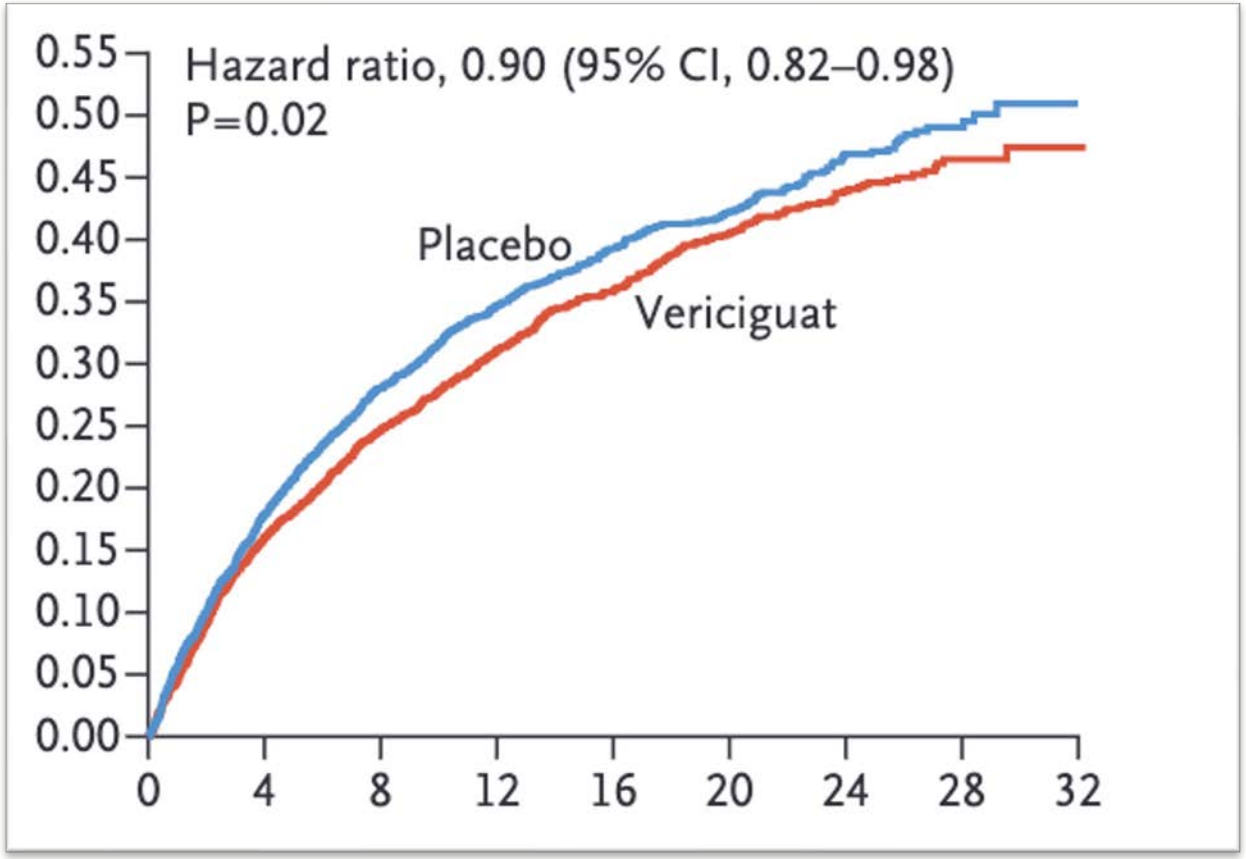
VICTORIA TRIAL

Primary and secondary outcomes:

Decreased death from cardiovascular causes or first heart failure admission (p=0.02)

Decreased total hospitalizations for heart failure (p=0.02)

Decreased death from all cause or first heart failure hospitalization (p=0.02)



Armstrong PW, et al. NEJM 2020

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VALOR

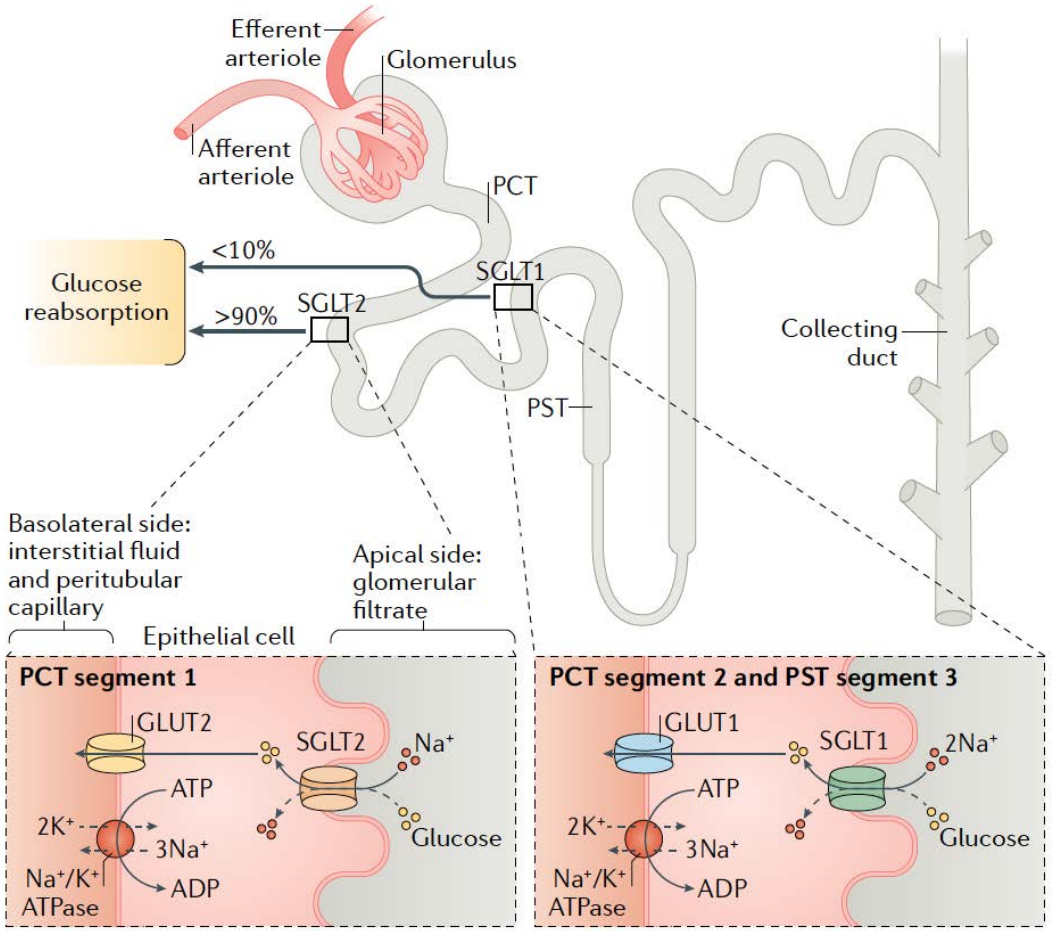
- Vericiguat in Pediatric Participants with Heart Failure due to Left Ventricular Systolic Dysfunction

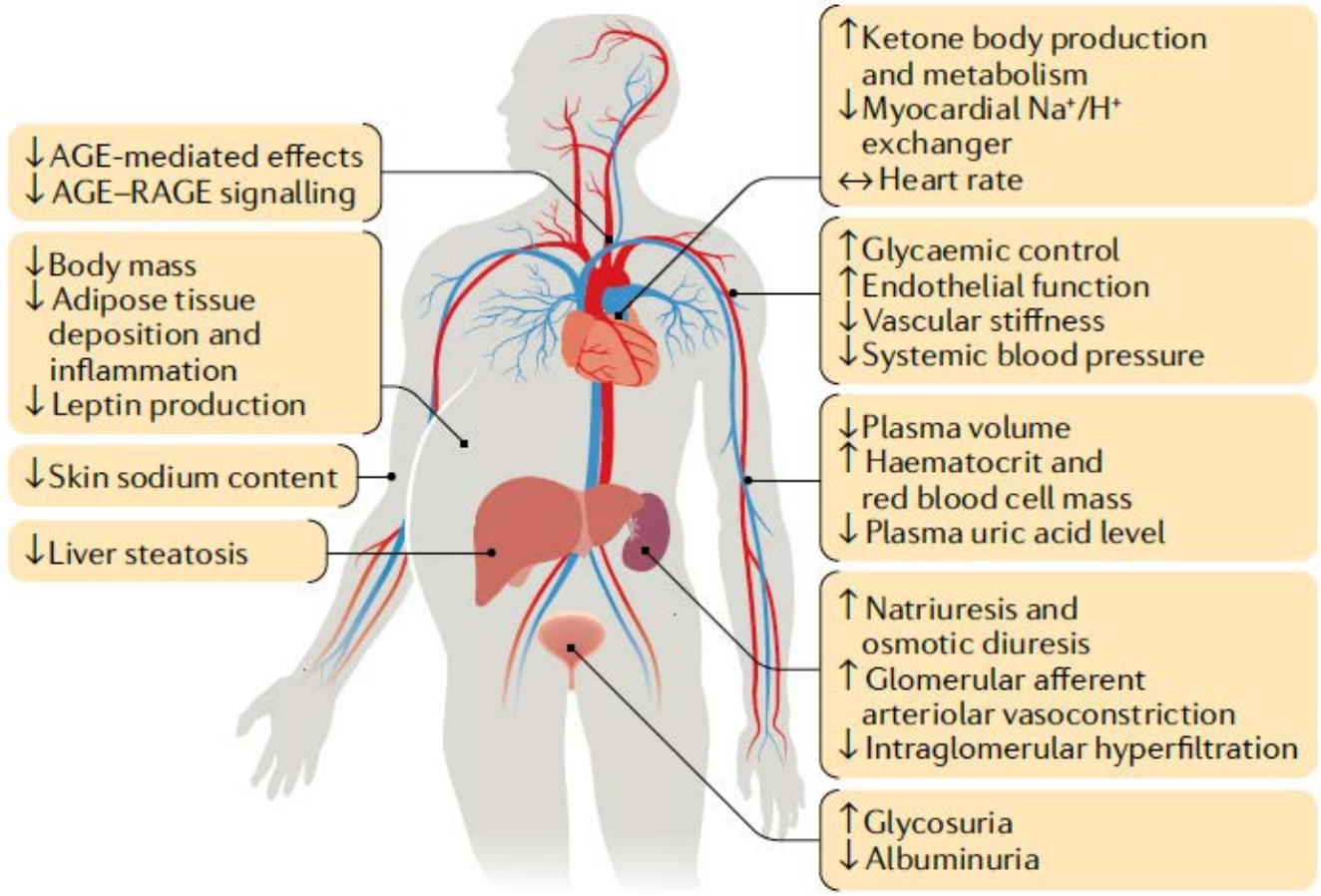
- Phase 2/3, Randomized, Placebo-Controlled, Double-blind, Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Vericiguat

VALOR STUDY POPULATION

- Chronic heart failure (NYHA / Ross II-IV)
- Biventricular physiology with systemic left ventricle
- LVEF < 45%
- NT-proBNP level 500 – 6,000 pg/ml within 30 days of randomization
- Primary endpoint: Change in NT-proBNP level at 16 weeks

SGLT2 INHIBITORS….????





Cowie MR, et al. Nature Reviews Cardiology 2020

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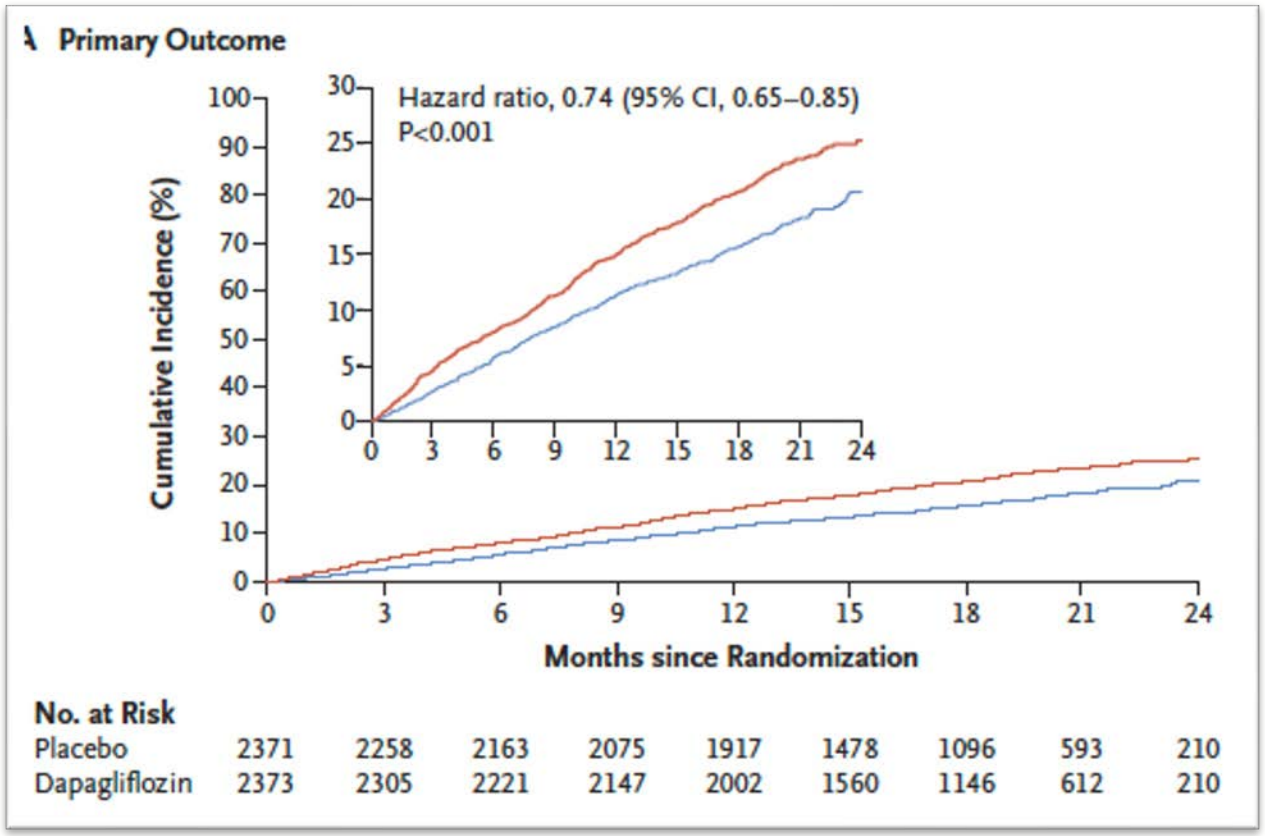
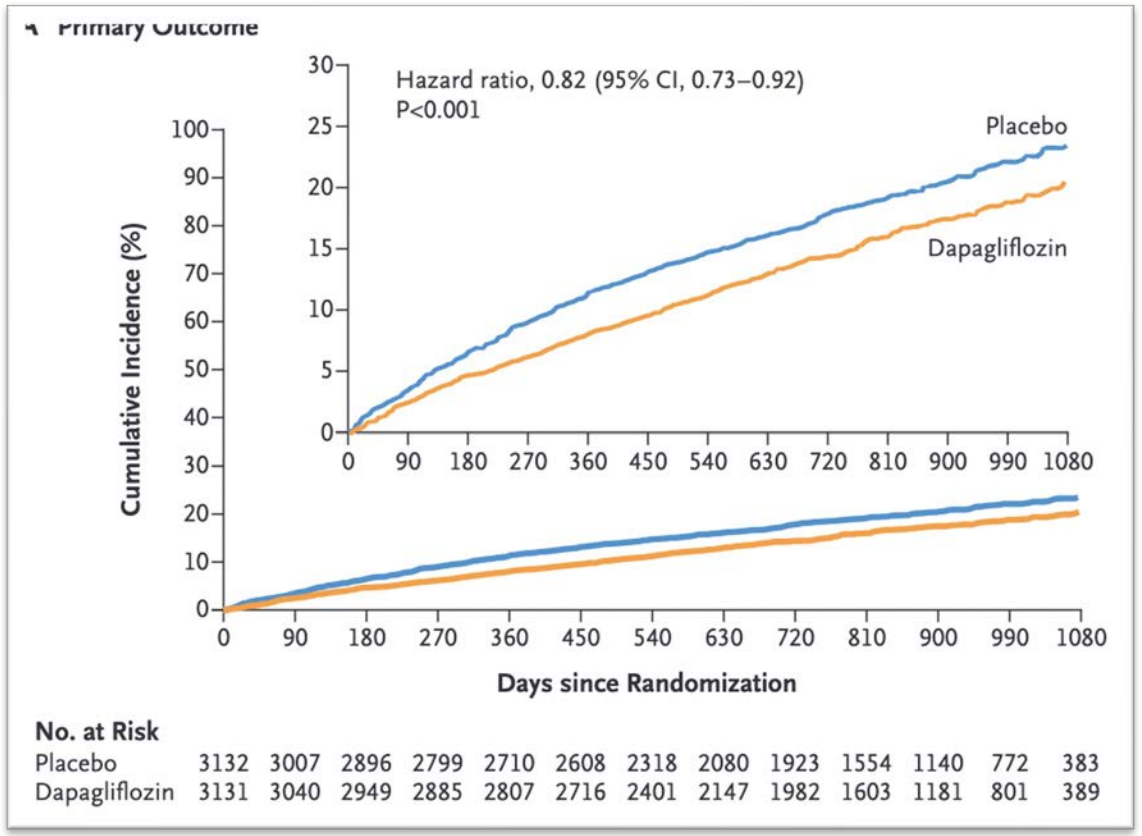
SGL2 INHIBITORS AND HEART FAILURE



Depressed Function



Preserved or Mildly Depressed Function

McMurray JJV, et al. NEJM 2019
Solomon SD, et al. NEJM 2022

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SUMMARY

- Heart failure is a common sequelae of cardiomyopathies and CHD
- Current ‘Gold Standard’ is not based on strong pediatric data
- New therapies expand and challenge old paradigms

CARDIOLOGY 2023

THANK YOU

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Perelman School of Medicine University of Pennsylvania

22CME0420/PPT/01-23

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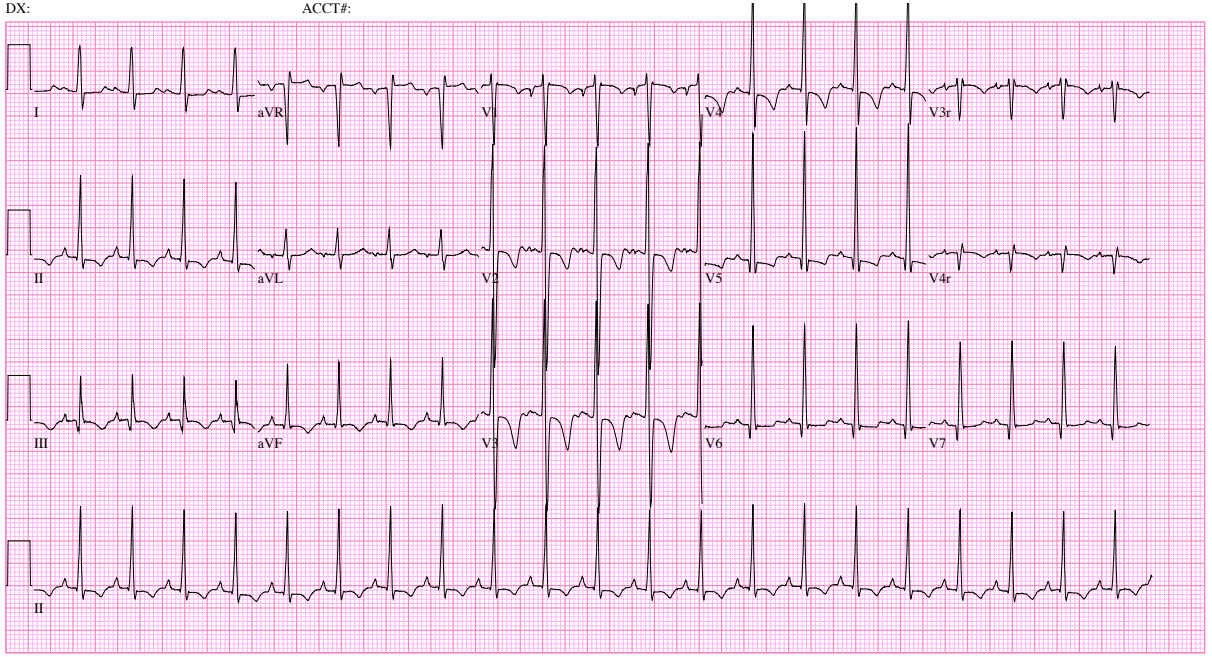
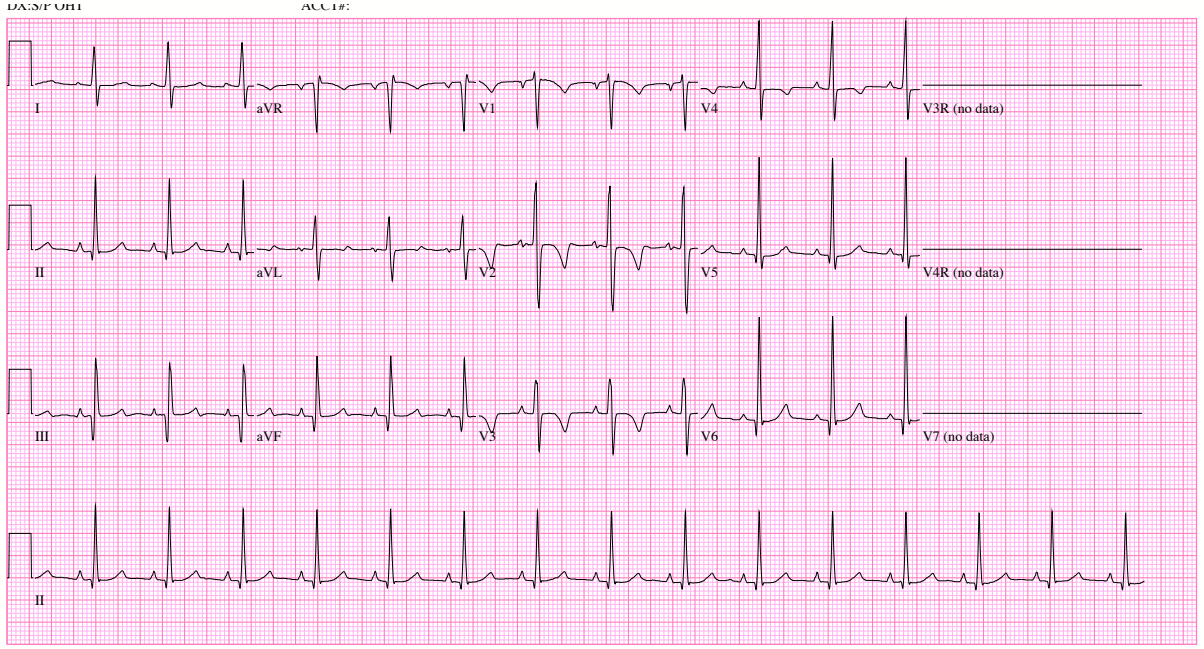


Pre ivabradine:
HR 130
T-wave inversions inferolateral leads

Post ivabradine:
HR 90
Improved T-waves



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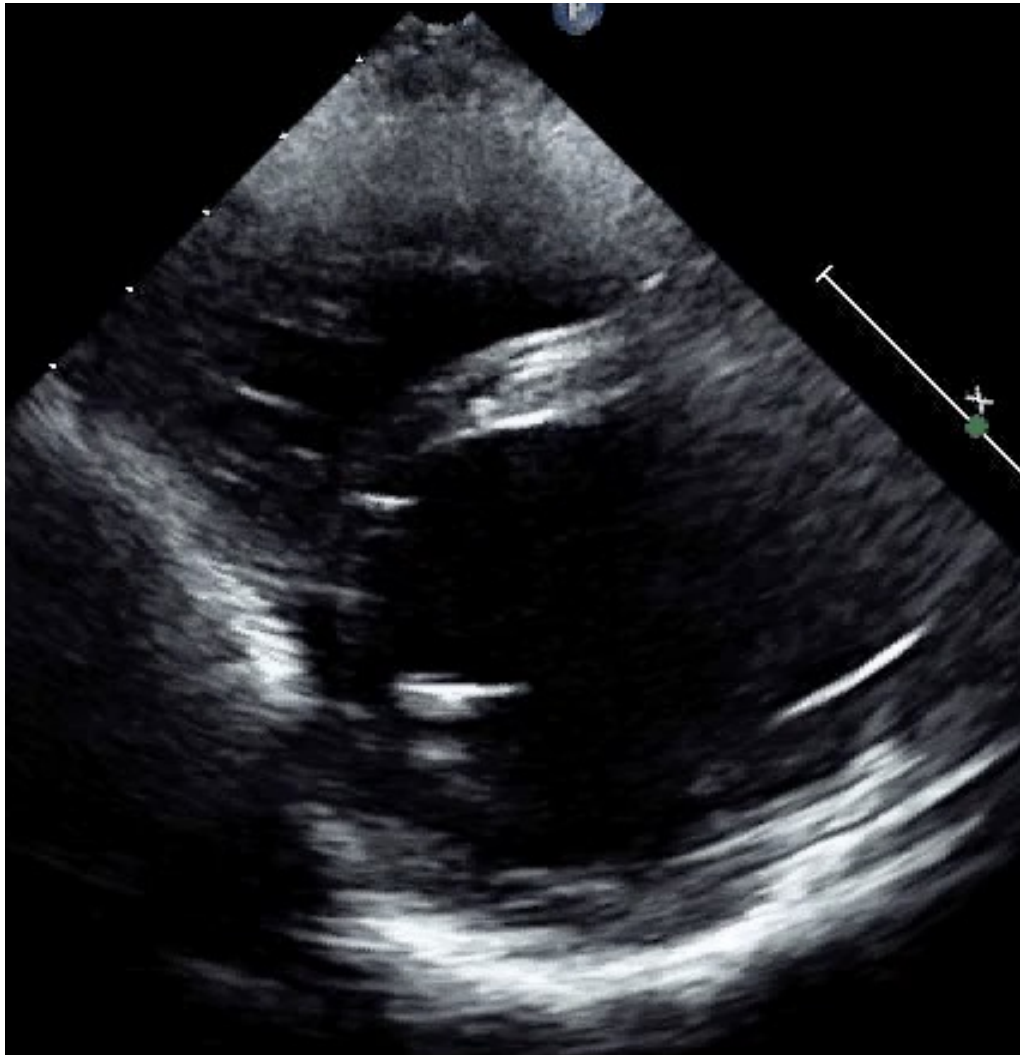
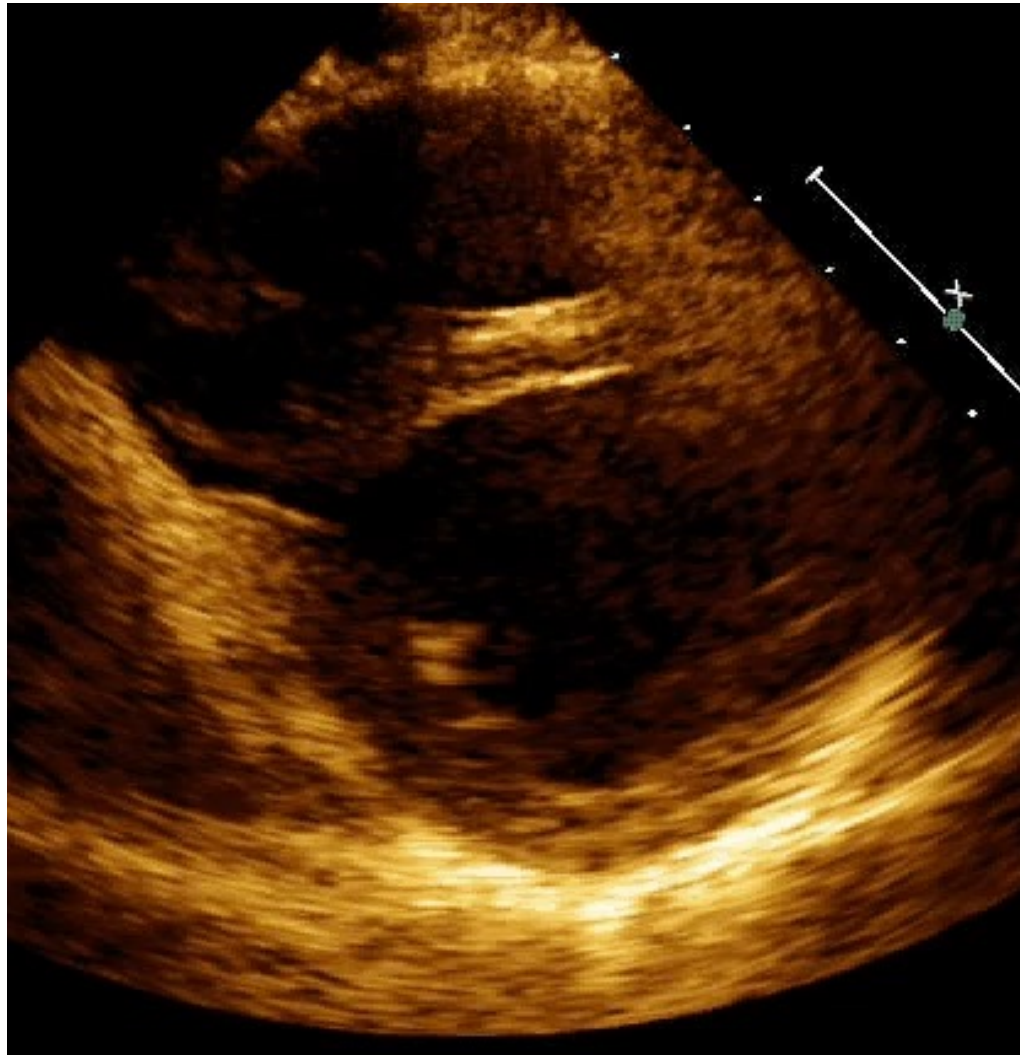
Pre Ivabradine
EF 46%



Post Ivabradine
EF 56%



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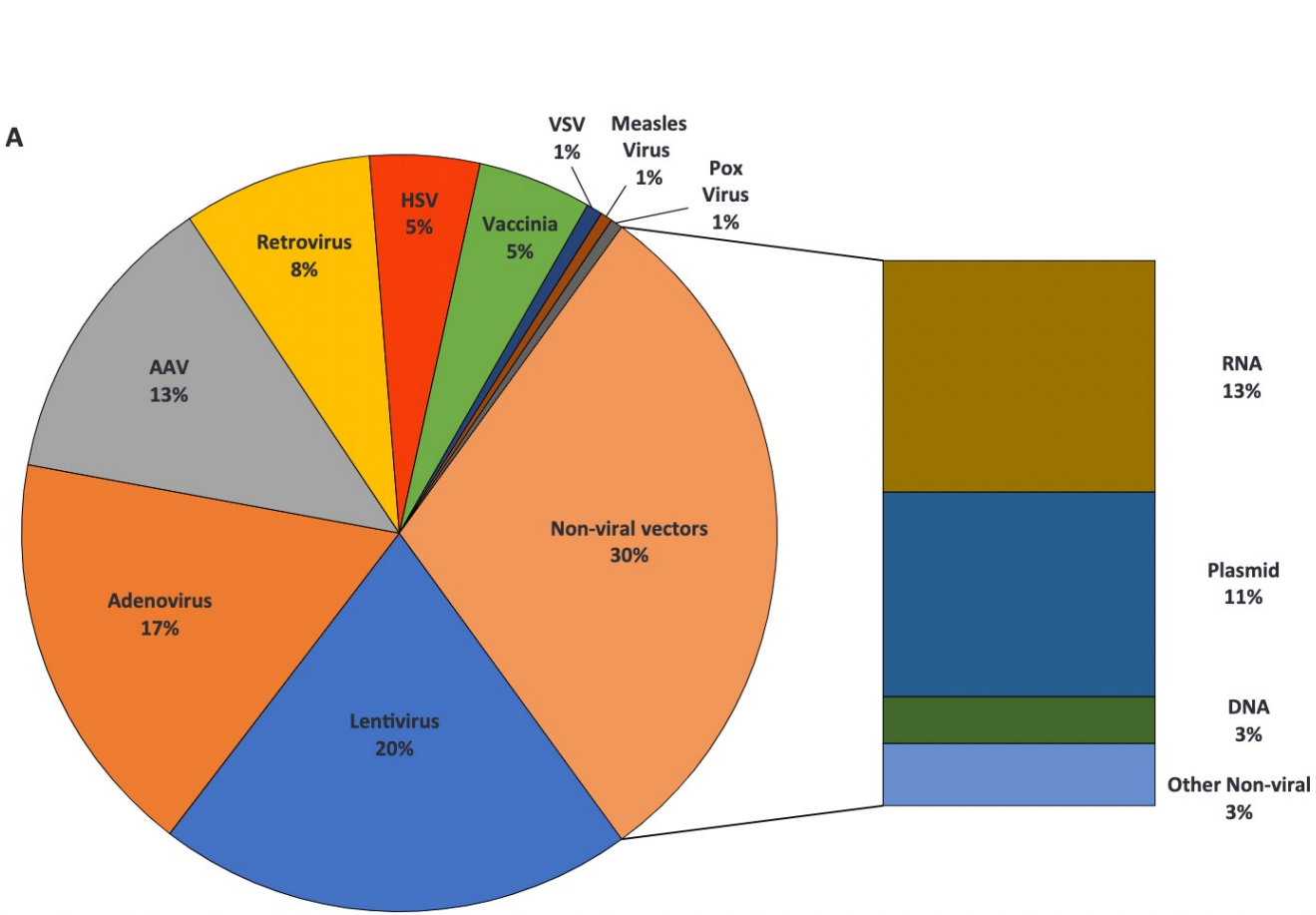

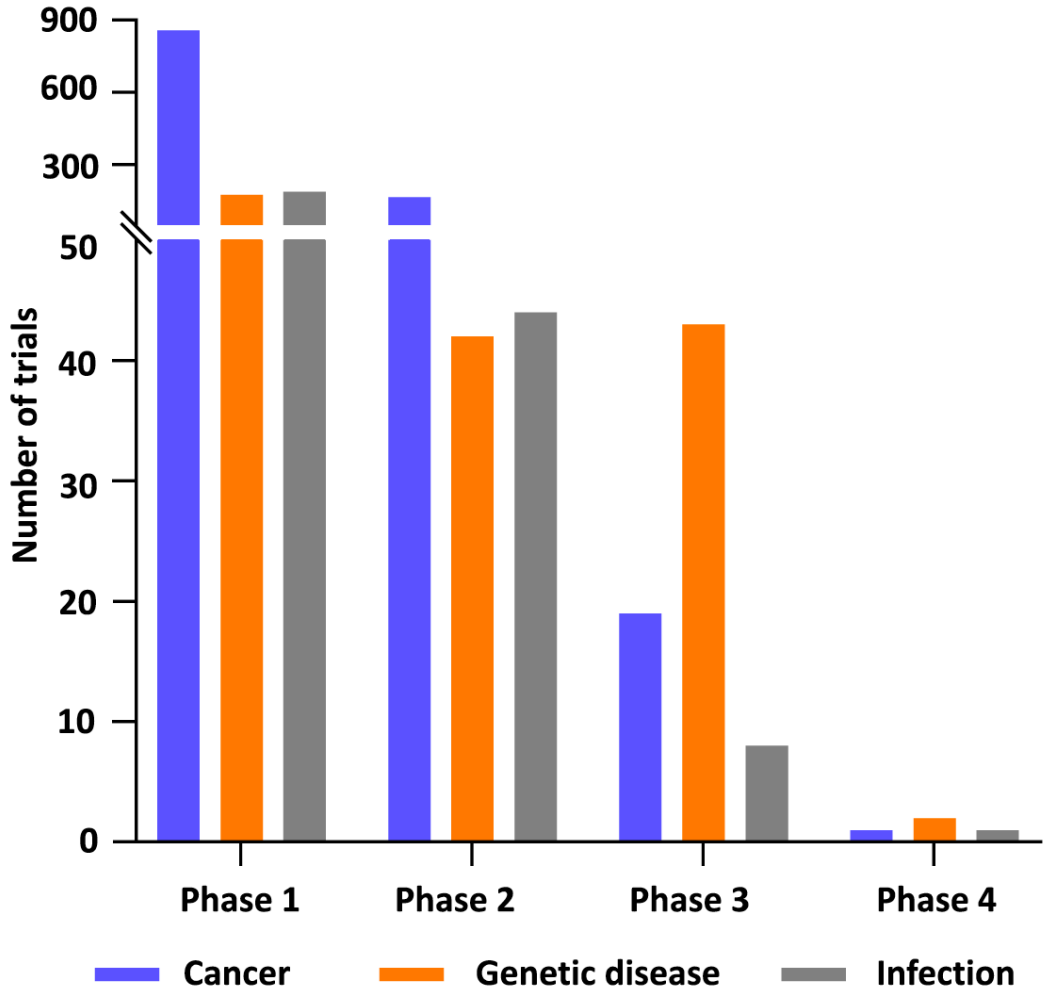

Arabi F, et al. Biomed and Pharm. 2022

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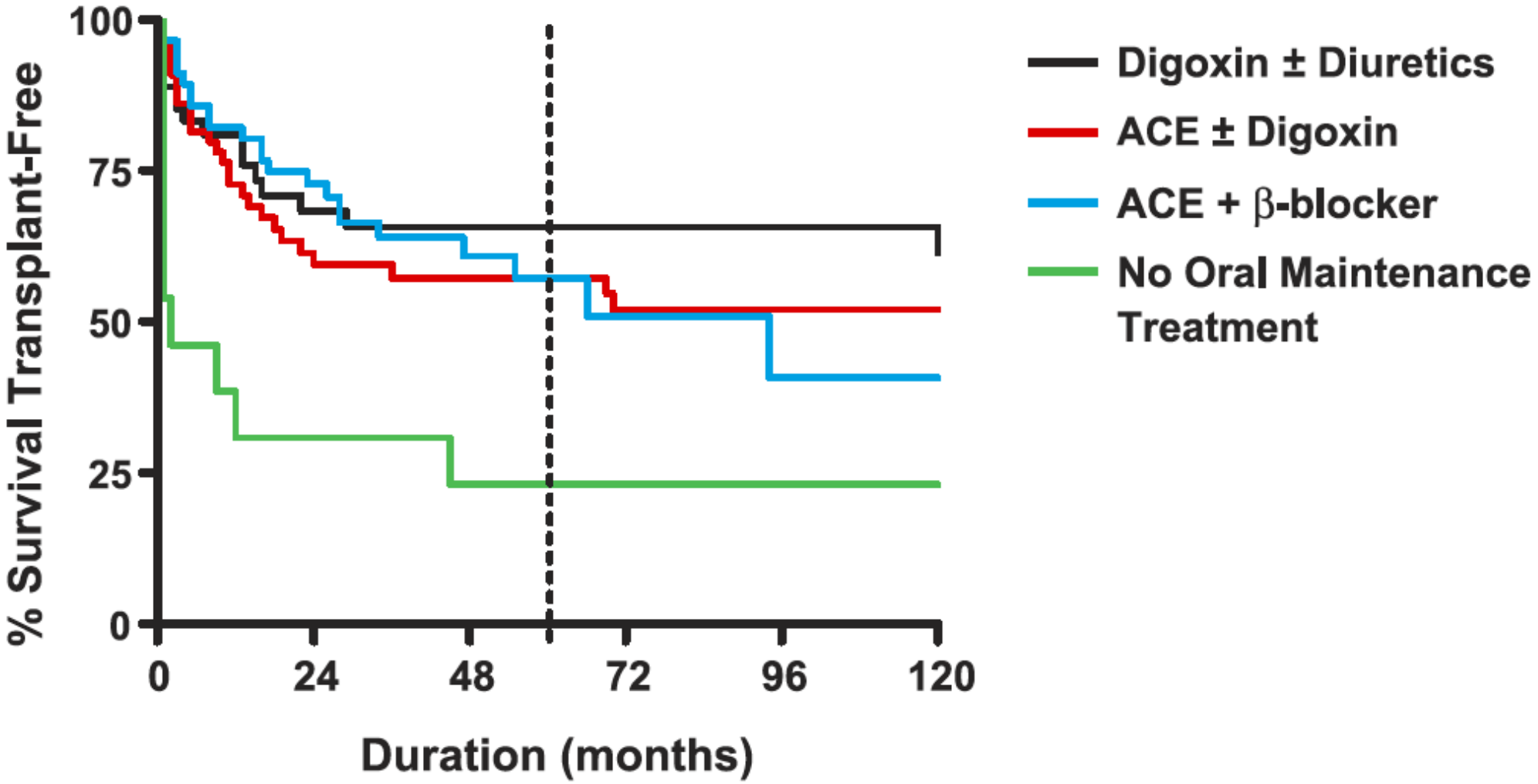
FAILURE OF MEDICAL THERAPY



Kantor PF, et al. JACC 2010

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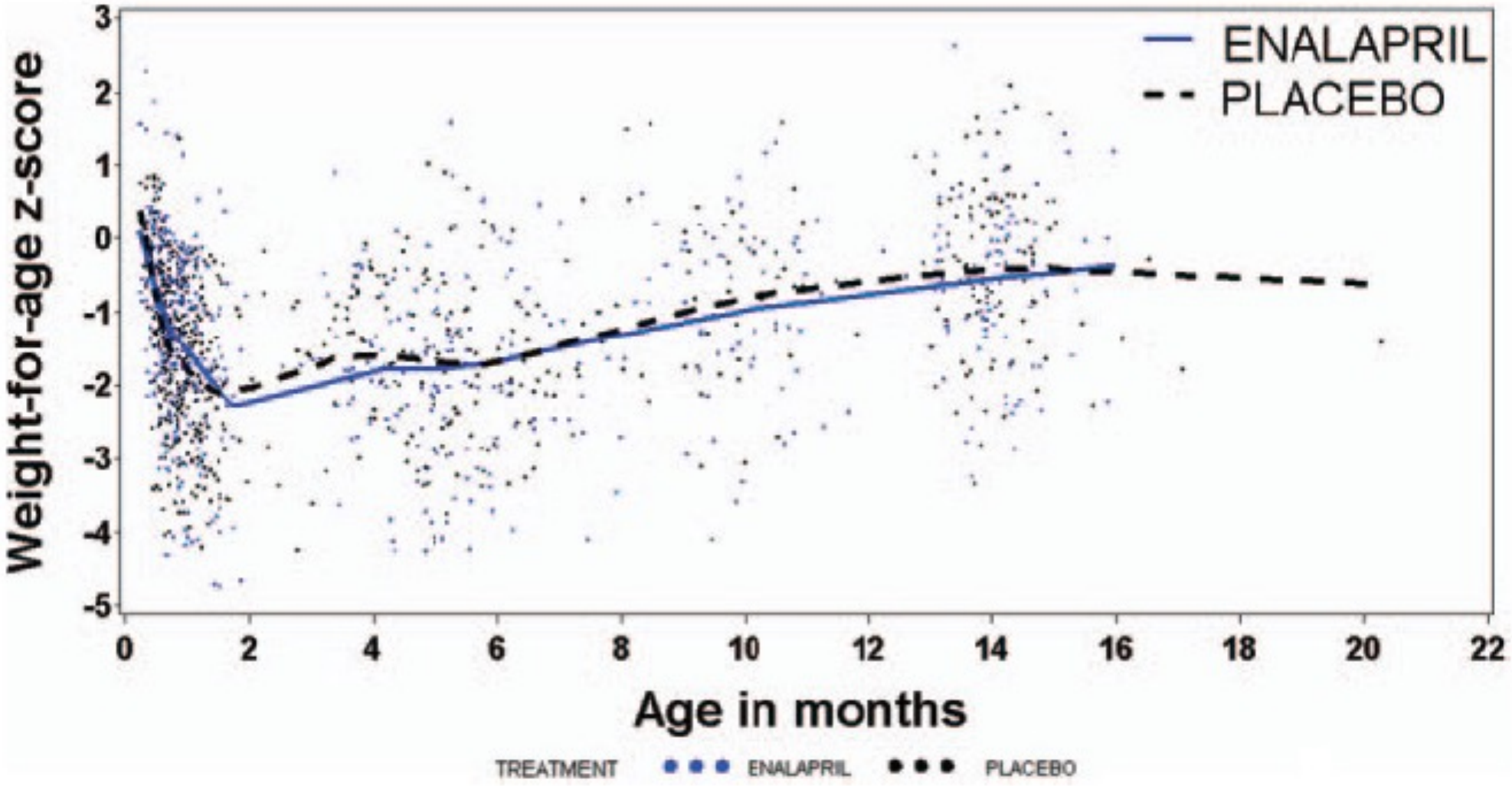
ACE-INHIBITORS



Hsu DT, et al. Circulation 2010

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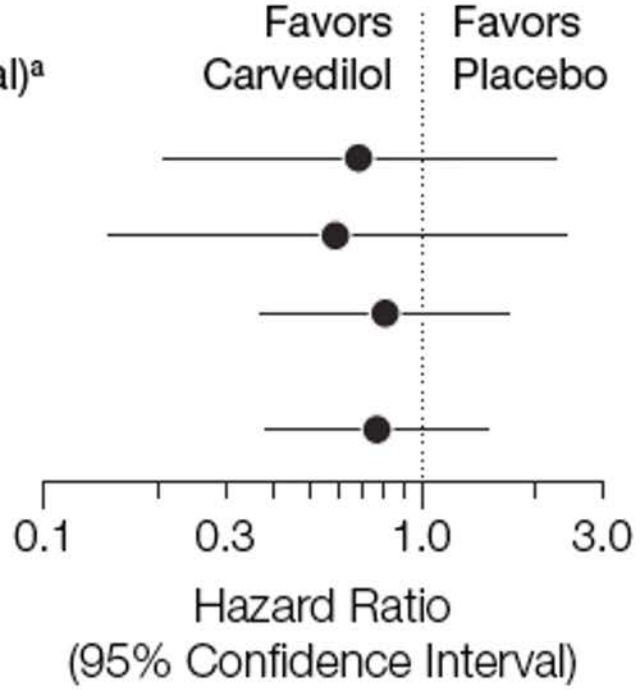
BETA-BLOCKERS IN PEDIATRIC HF

Figure 2. Number of Events and Hazard Ratios for Mortality and Hospitalization End Points

End Point	No. of Events: Carvedilol (n = 106)	No. of Events: Placebo (n = 55)	Hazard Ratio (95% Confidence Interval)[a]	*P* Value[a]
All-cause mortality	6	5	0.68 (0.21-2.25)	.55
Cardiovascular mortality	4	4	0.59 (0.15-2.4)	.44
All-cause mortality or heart failure hospitalization	17	12	0.8 (0.38-1.68)	.52
All-cause mortality or cardiovascular hospitalization	23	15	0.76 (0.39-1.48)	.39



Shaddy RE, et al. JAMA 2007

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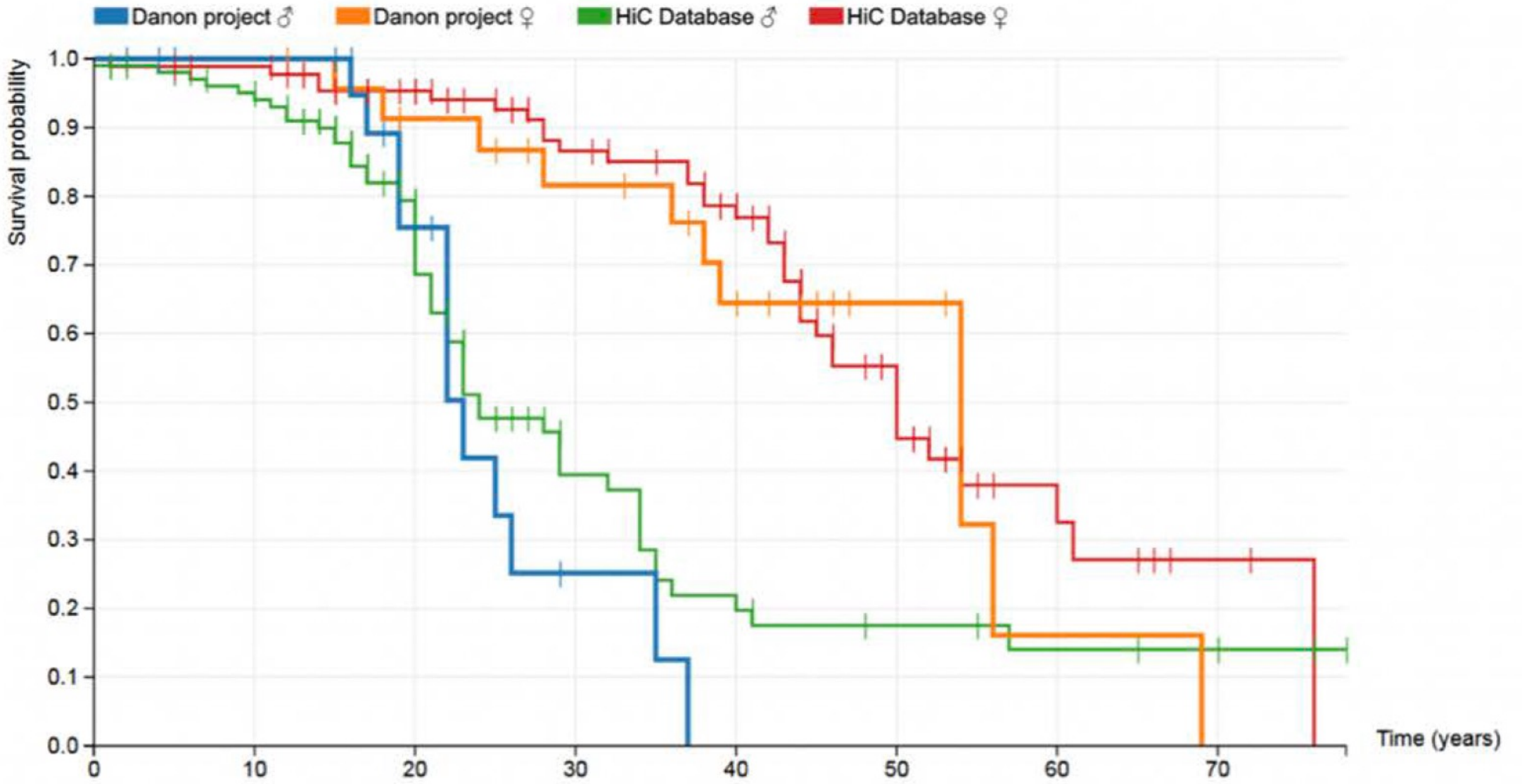

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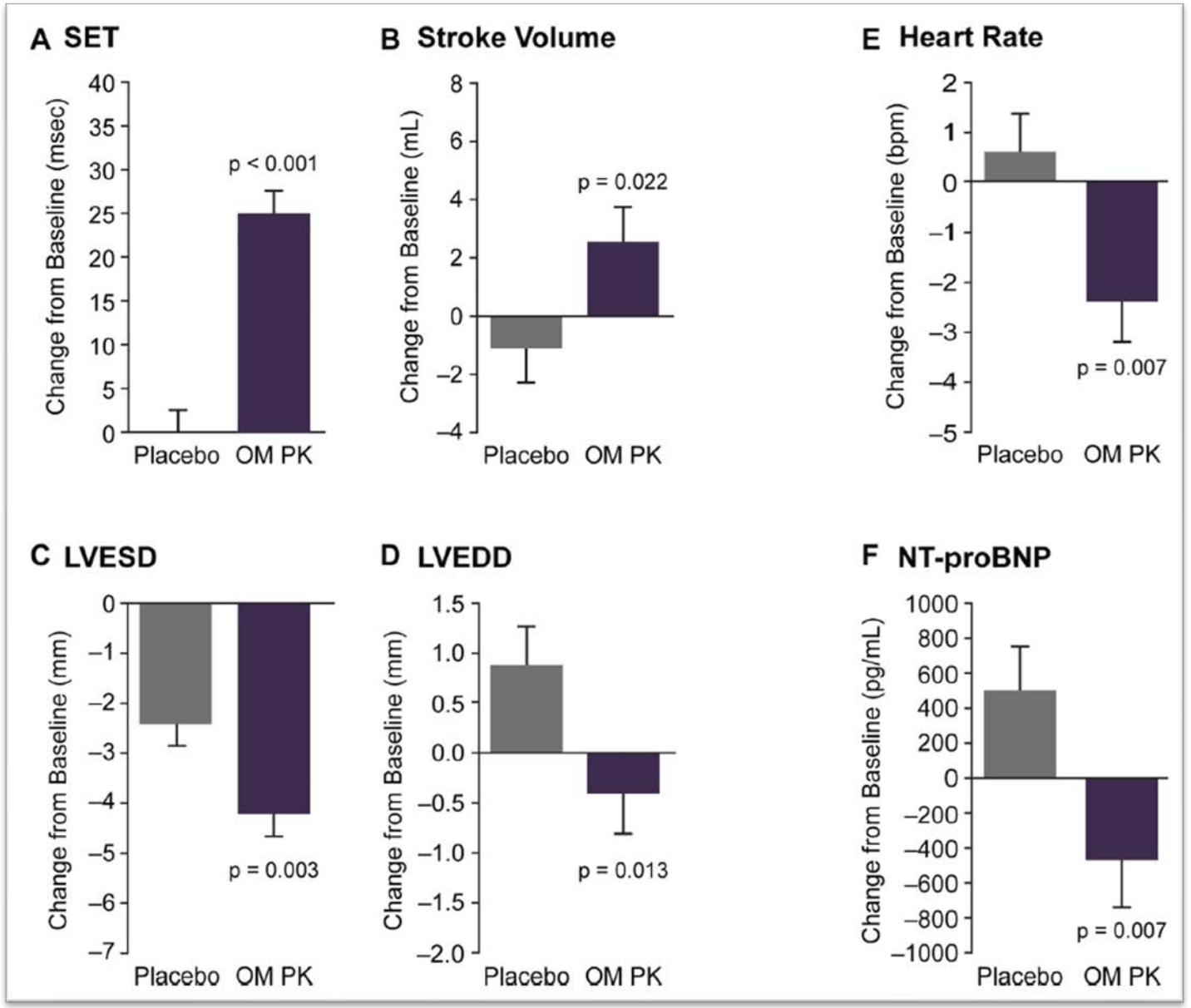
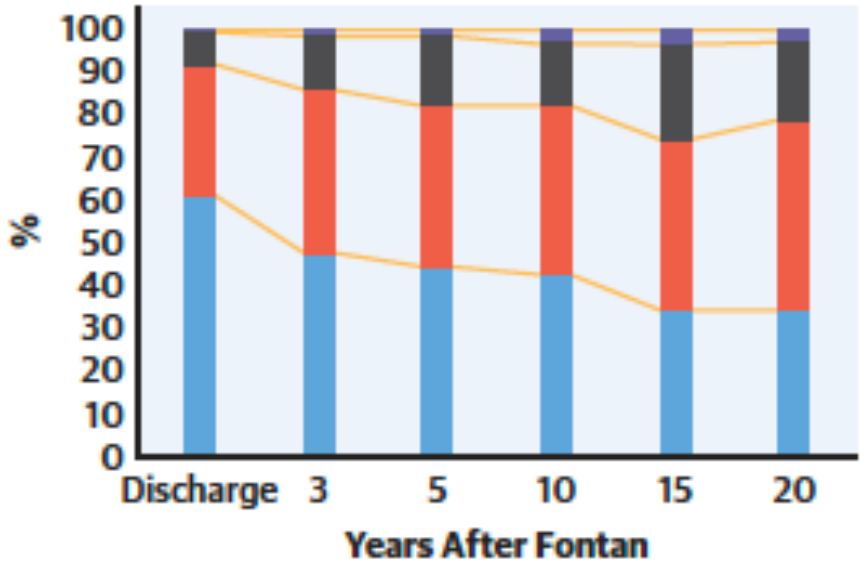
Lotan D, et al. Circulation: Genomic and Precision Med. 2020



Teerlink JR, et al. JACC: Heart Failure. 2020

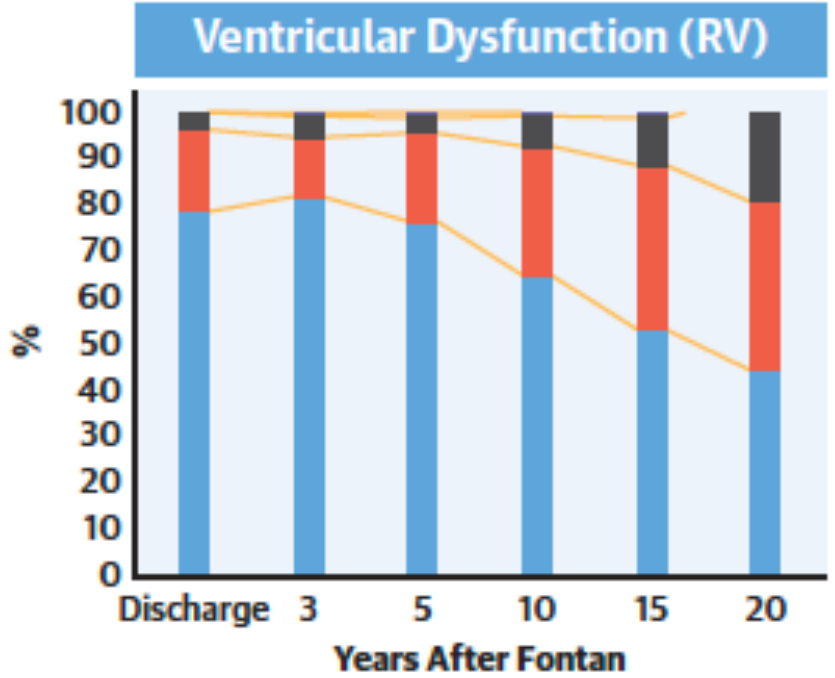
B



Number of Patients						
None	632	227	193	139	69	39
Mild	312	177	163	129	80	50
Moderate	76	60	69	46	44	20
Severe	3	5	6	10	6	3

% Incidence of AVVR ≥ Mod at Each Time Point							p Value
%	7	14	17	17	25	21	0.001

D



Number of Patients						
None	489	241	199	117	52	23
Mild	111	38	49	50	35	13
Moderate	22	13	8	11	9	10
Severe	0	2	3	2	2	0

% Incidence of Dysfunction ≥ Mod at Each Time Point							p Value
%	4	6	4	8	12	24	0.006

Moon J, et al. JACC. 2020

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