CORS at the SHORE

SGLT2 Inhibitors and New Devices and Medical Therapies for Heart Failure

June 23, 2023

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Disclosures

None Relevant for this Presentation.

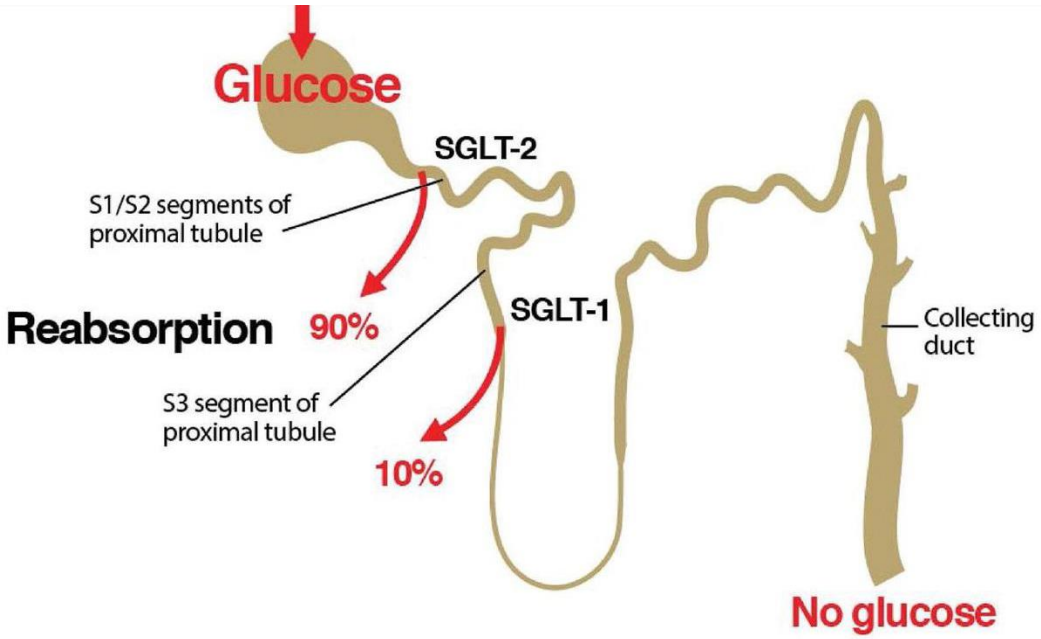
Chair Endpoint Committee, SIRONA, PROACTIVE. Sponsor: Endotronix

Chair Endpoint Committee CS01, CS03. Sponsor: Orchestra Biomed

SGLT2 INHIBITORS

Sodium-glucose co-transporter 2

- "Glucoretic"
  - –Inhibits glucose and sodium reabsorption in renal proximal tubule



- Effects
  - –HbA1c change: -0.54% (-0.67- -0.40), as much as -0.9%
  - –Weight change: 1.81 kg (-2.04- -1.57)
  - –Blood pressure reduction

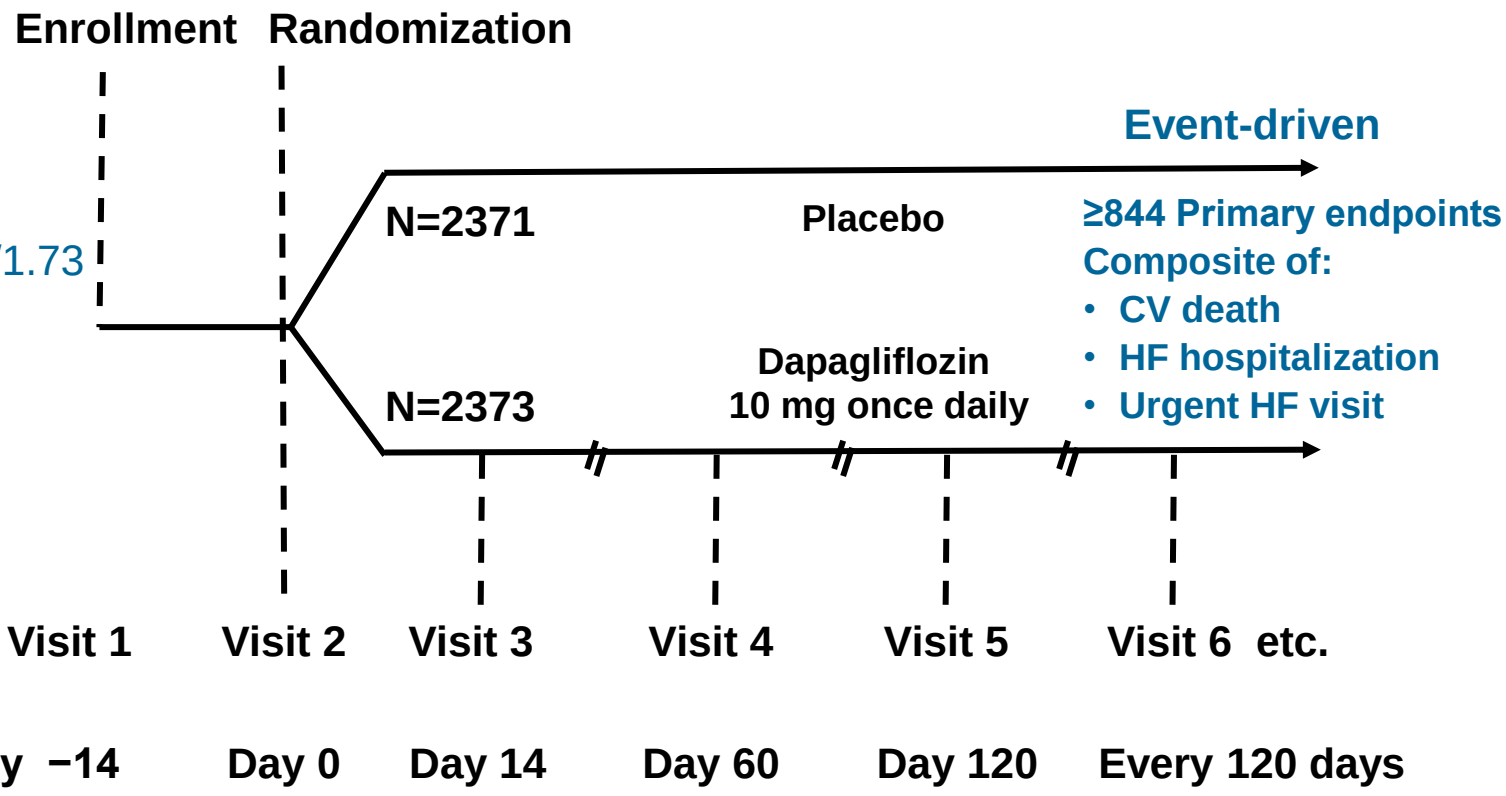
Approved in 2014 to reduce all CV events in type 2 diabetics. There was a marked reduction in heart failure in these patients

The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure Trial (DAPA-HF)

4,744 patients 20 countries

Inclusion:
- NYHA class II-IV
- LVEF ≤40%
- NT-proBNP ≥600 pg/ml*

Exclusion:
- eGFR <30 ml/min/1.73 m^2
- SBP <95 mmHg
- type 1 diabetes



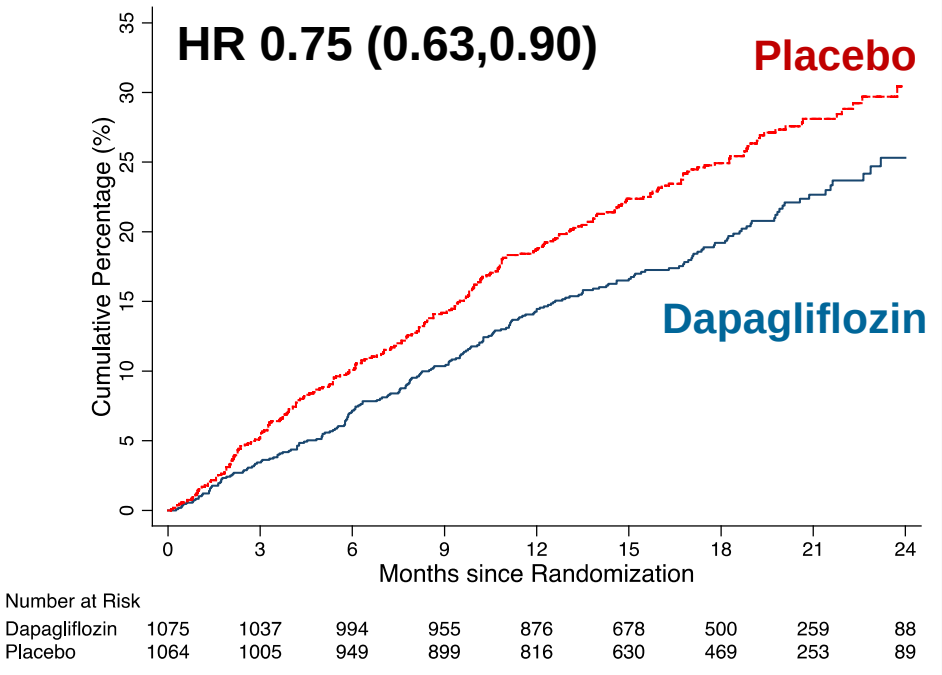
*≥400 pg/ml if HF hospitalization within ≤12 months; ≥900 pg/ml if atrial fibrillation/flutter

N Engl J Med 2019; 381:1995-2008

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF)

CV Death/HF hospitalization/Urgent HF visit

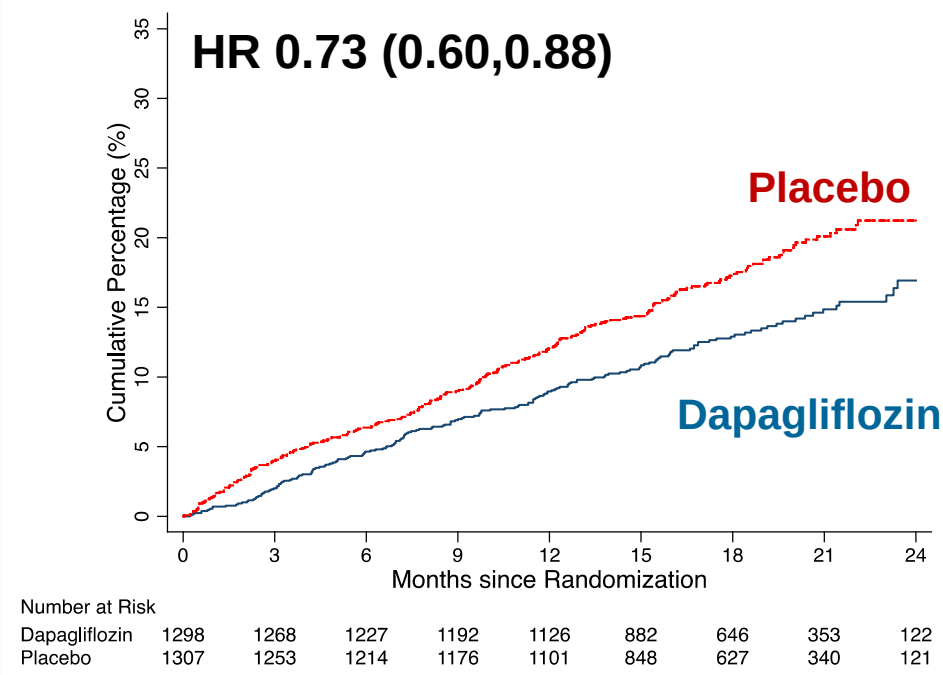
Diabetes



Number at Risk

Dapagliflozin	1075	1037	994	955	876	678	500	259	88
Placebo	1064	1005	949	899	816	630	469	253	89

No Diabetes



Number at Risk

Dapagliflozin	1298	1268	1227	1192	1126	882	646	353	122
Placebo	1307	1253	1214	1176	1101	848	627	340	121

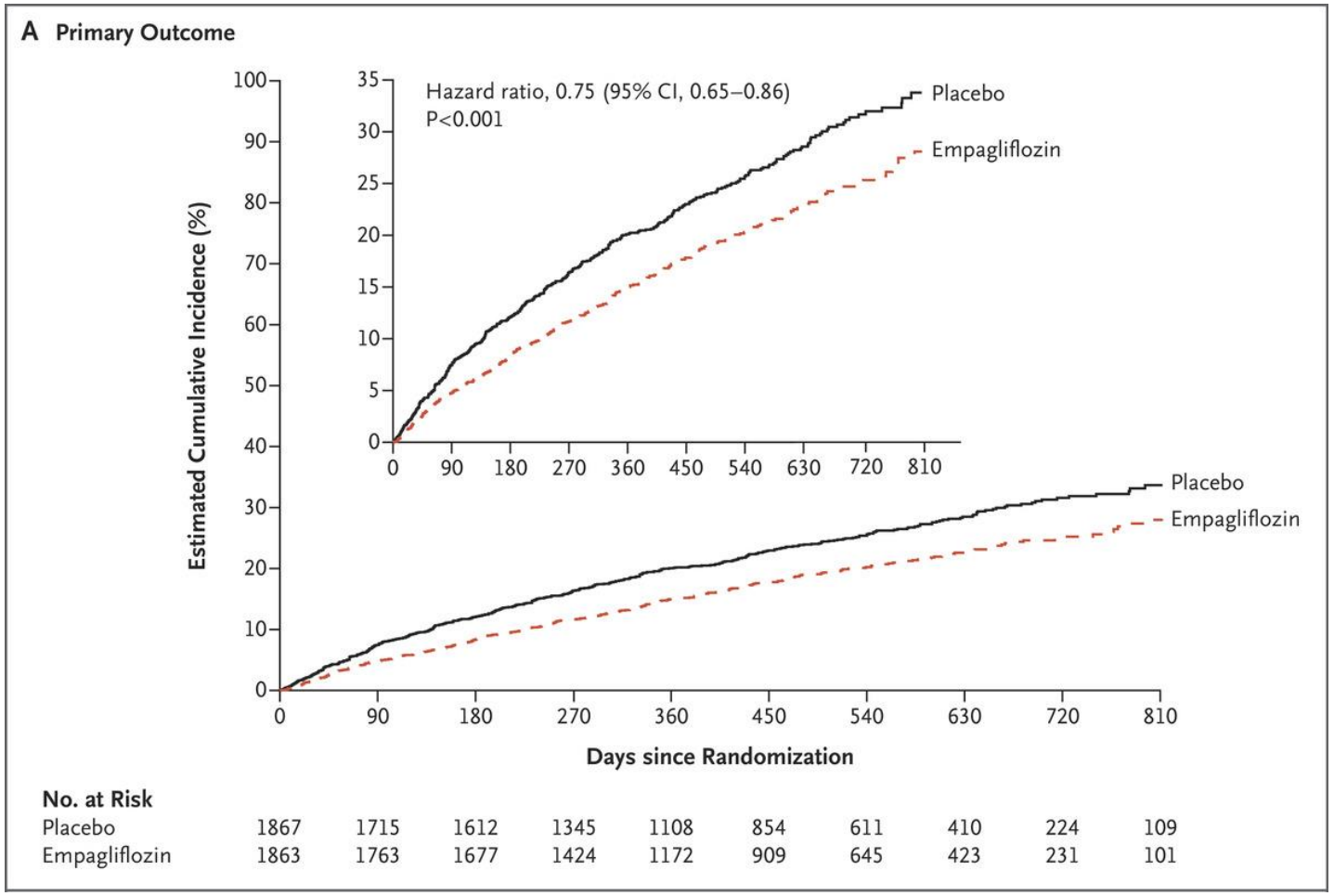
P interaction 0.80

Summary and Conclusions: DAPA-HF

- When added to standard therapy, dapagliflozin reduced the risk of worsening heart failure events and cardiovascular death, and improved symptoms, in patients with HFrEF, both ***with*** and ***without*** T2D
- May 5, 2020 the FDA approved Farxiga (dapagliflozin) oral tablets for adults with heart failure with reduced ejection fraction to reduce the risk of cardiovascular death and hospitalization for heart failure.
- With the approval, Farxiga is the first, sodium-glucose co-transporter 2 (SGLT2) inhibitors, to be approved to treat adults with NYHA class II-IV heart failure with reduced EF.

Cardiovascular and Renal Outcomes with Empagliflozin in HF (EMPEROR-Reduced)

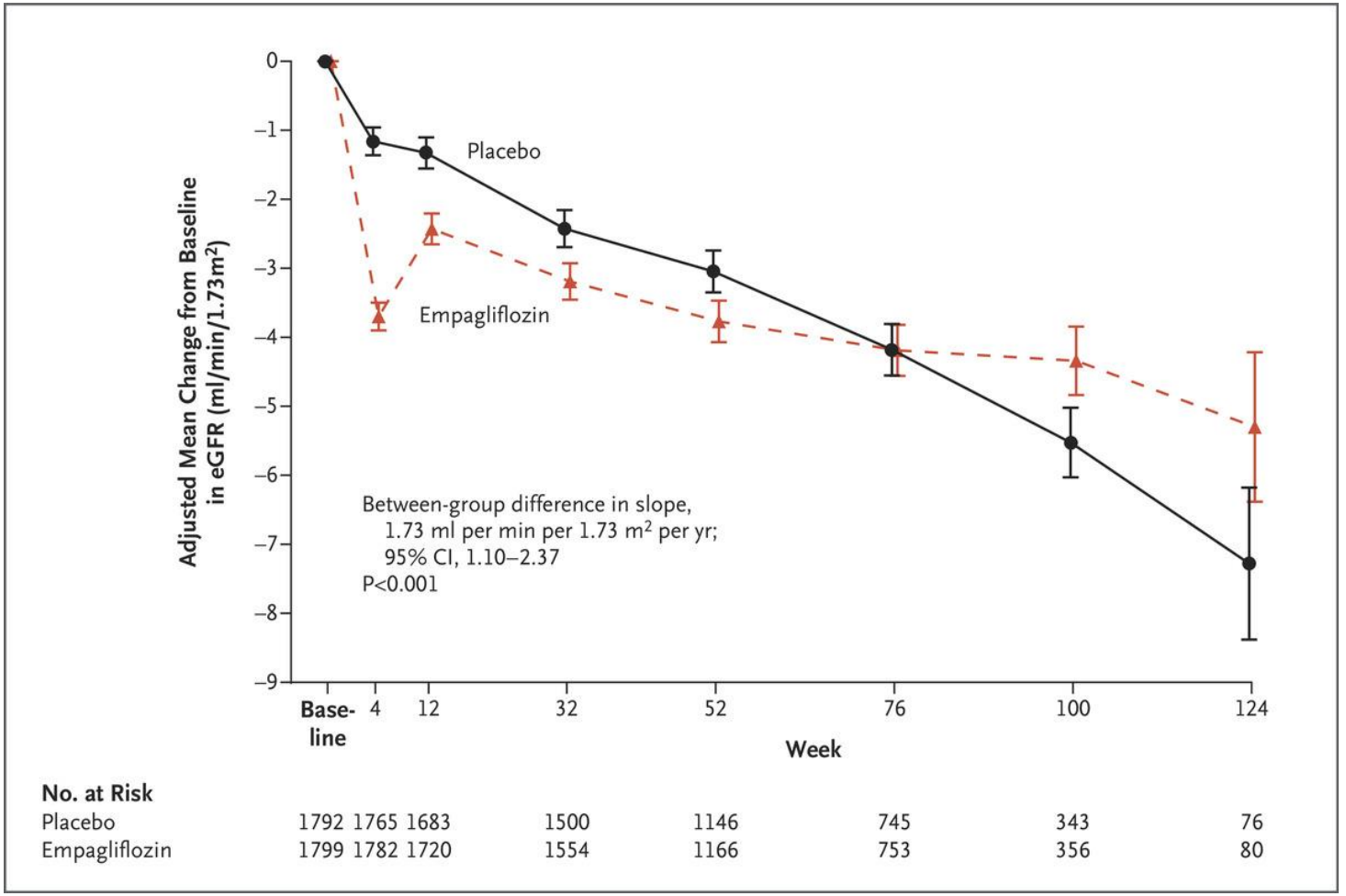
Composite of CV Death or Hospitalization for Worsening HF



M Packer et al. N Engl J Med 2020;383:1413-1424

Cardiovascular and Renal Outcomes with Empagliflozin in HF (EMPEROR-Reduced)

Changes in the Estimated Glomerular Filtration Rate.



M Packer et al. N Engl J Med 2020;383:1413-1424

FDA Approves Empagliflozin for HFrEF

- August 18, 2021 FDA approved empagliflozin (Jardiance) to reduce the risk of cardiovascular death plus hospitalization for HF in adults with HF with HFrEF.
- Empagliflozin can be initiated in adults with HFrEF with an eGFR as low as 20 mL/min/1.73 m^2.
- Approval based on results from the EMPEROR-Reduced phase III trial, which investigated the effect of adding Jardiance 10 mg versus placebo to standard of care in a broad range of 3,730 adults with and without type 2 diabetes who had heart failure (functional class II, III or IV) and a left ventricular ejection fraction of 40% or less.
- Empagliflozin significantly reduced the risk cardiovascular death or hospitalization for HF by 25% (5.3% absolute risk reduction, 0.75 HR).

Empagliflozin in Heart Failure with a Preserved Ejection Fraction (EMPEROR-Preserved)

- Multicenter, double-blind, randomized, placebo-controlled trial examined the effects of the SGLT2 inhibitor empagliflozin in patients HFpEF
- 5988 adults with NYHA class II–IV HF and an LVEF >40% were randomly assigned to receive empagliflozin, 10 mg qd or placebo, in addition to standard care.
- Primary outcome was a composite of CV death or HF hospitalization
- Median follow-up of 26.2 months

SD Anker et al. N Engl J Med 2021;385:1451-1461.

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Empagliflozin (N=2997)	Placebo (N=2991)
Age — yr	71.8±9.3	71.9±9.6
Female sex — no. (%)	1338 (44.6)	1338 (44.7)
Race — no. (%)†		
White	2286 (76.3)	2256 (75.4)
Black	133 (4.4)	125 (4.2)
Asian	413 (13.8)	411 (13.7)
Other or missing	165 (5.5)	199 (6.7)
Geographic region — no. (%)		
North America	360 (12.0)	359 (12.0)
Latin America	758 (25.3)	757 (25.3)
Europe	1346 (44.9)	1343 (44.9)
Asia	343 (11.4)	343 (11.5)
Other	190 (6.3)	189 (6.3)
NYHA functional classification — no. (%)		
Class I	3 (0.1)	1 (<0.1)
Class II	2432 (81.1)	2451 (81.9)
Class III	552 (18.4)	531 (17.8)
Class IV	10 (0.3)	8 (0.3)

SD Anker et al. N Engl J Med 2021;385:1451-1461.

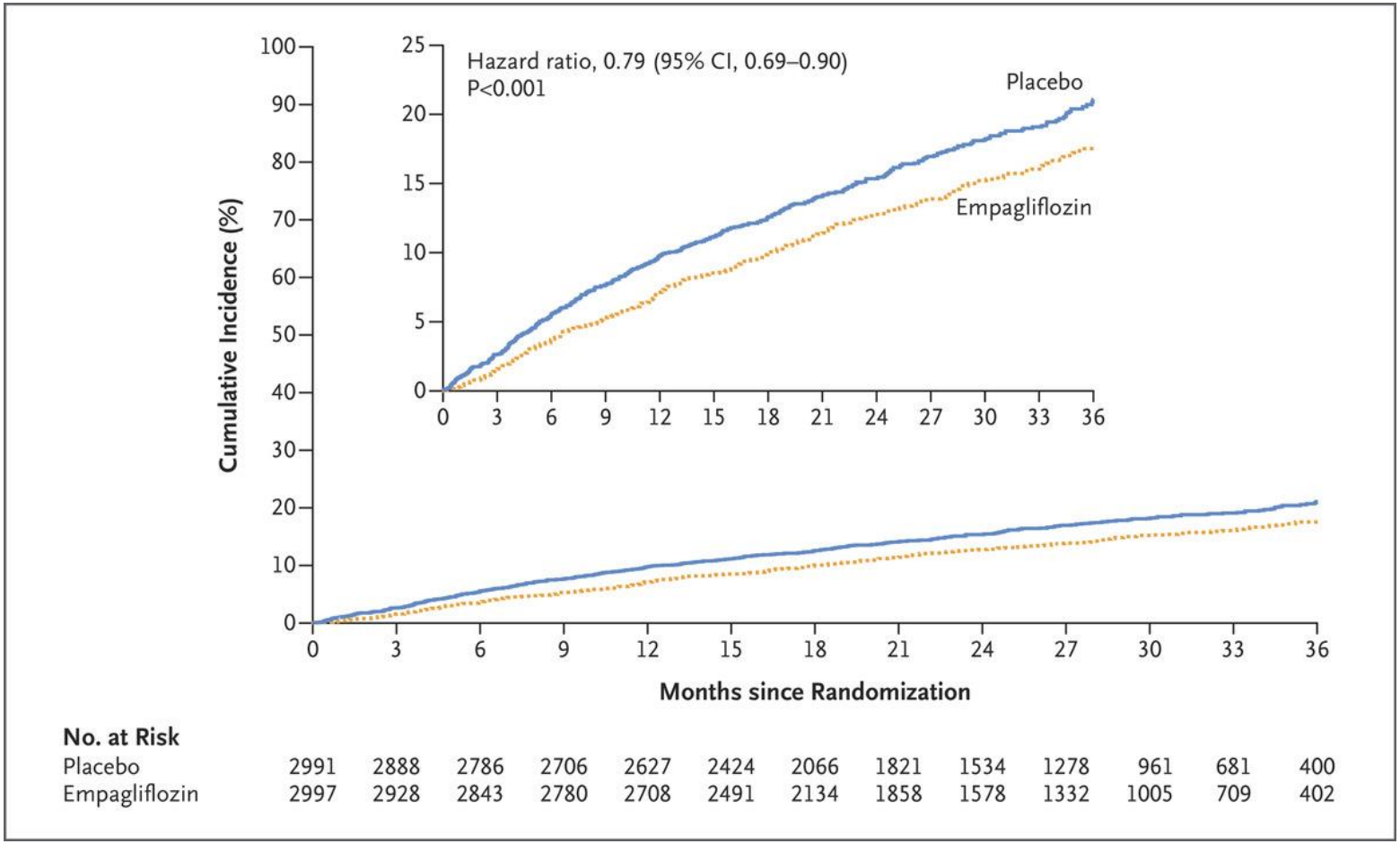
Empagliflozin in Heart Failure with a Preserved Ejection Fraction

Body-mass index‡	29.77±5.8	29.90±5.9
Heart rate — beats per minute	70.4±12.0	70.3±11.80
Systolic blood pressure — mm Hg	131.8±15.6	131.9±15.7
Left ventricular ejection fraction		
Mean left ventricular ejection fraction — %	54.3±8.8	54.3±8.8
Left ventricular ejection fraction >40% to <50% — no. (%)§	995 (33.2)	988 (33.0)
Left ventricular ejection fraction ≥50% to <60% — no. (%)	1028 (34.3)	1030 (34.4)
Left ventricular ejection fraction ≥60% — no. (%)	974 (32.5)	973 (32.5)
Median NT-proBNP (interquartile range) — pg/ml	994 (501–1740)	946 (498–1725)
Heart failure category — no. (%)		
Ischemic	1079 (36.0)	1038 (34.7)
Nonischemic	1917 (64.0)	1953 (65.3)
Cardiovascular history — no. (%)		
Hospitalization for heart failure during previous 12 mo	699 (23.3)	670 (22.4)
Atrial fibrillation	1543 (51.5)	1514 (50.6)
Diabetes mellitus	1466 (48.9)	1472 (49.2)
Hypertension	2721 (90.8)	2703 (90.4)
Mean eGFR — ml/min/1.73 m^2	60.6±19.8	60.6±19.9
eGFR <60 ml/min/1.73 m^2 — no./total no. (%)	1504/2997 (50.2)	1484/2989 (49.6)

SD Anker et al. N Engl J Med 2021;385:1451-1461.

Empagliflozin in Heart Failure with a Preserved Ejection Fraction (EMPEROR-Preserved)

Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure.



SD Anker et al. N Engl J Med 2021;385:1451-1461.

FDA Announcement February 24, 2022

- Today, the U.S. Food and Drug Administration approved Jardiance (empagliflozin) to reduce the risk of cardiovascular death and hospitalization for heart failure in adults.
- “Today’s approval will provide a treatment option for a wider range of patients with heart failure,” said Norman Stockbridge, M.D., Ph.D., Director of the Division of Cardiology and Nephrology in the FDA’s Center for Drug Evaluation and Research. “While Jardiance may not be effective in all patients with heart failure, this approval is a significant step forward for patients and our understanding of heart failure”.
- Empagliflozin is also approved to reduce the risk of death and hospitalization in patients with heart failure and low ejection fraction

DELIVER: Dapagliflozin in Heart Failure with Mildly Reduced and Preserved Ejection Fraction

Purpose:
To evaluate whether SGLT2 inhibitors (dapagliflozin) are effective in patients with heart failure and more than 40% left ventricular ejection fraction.

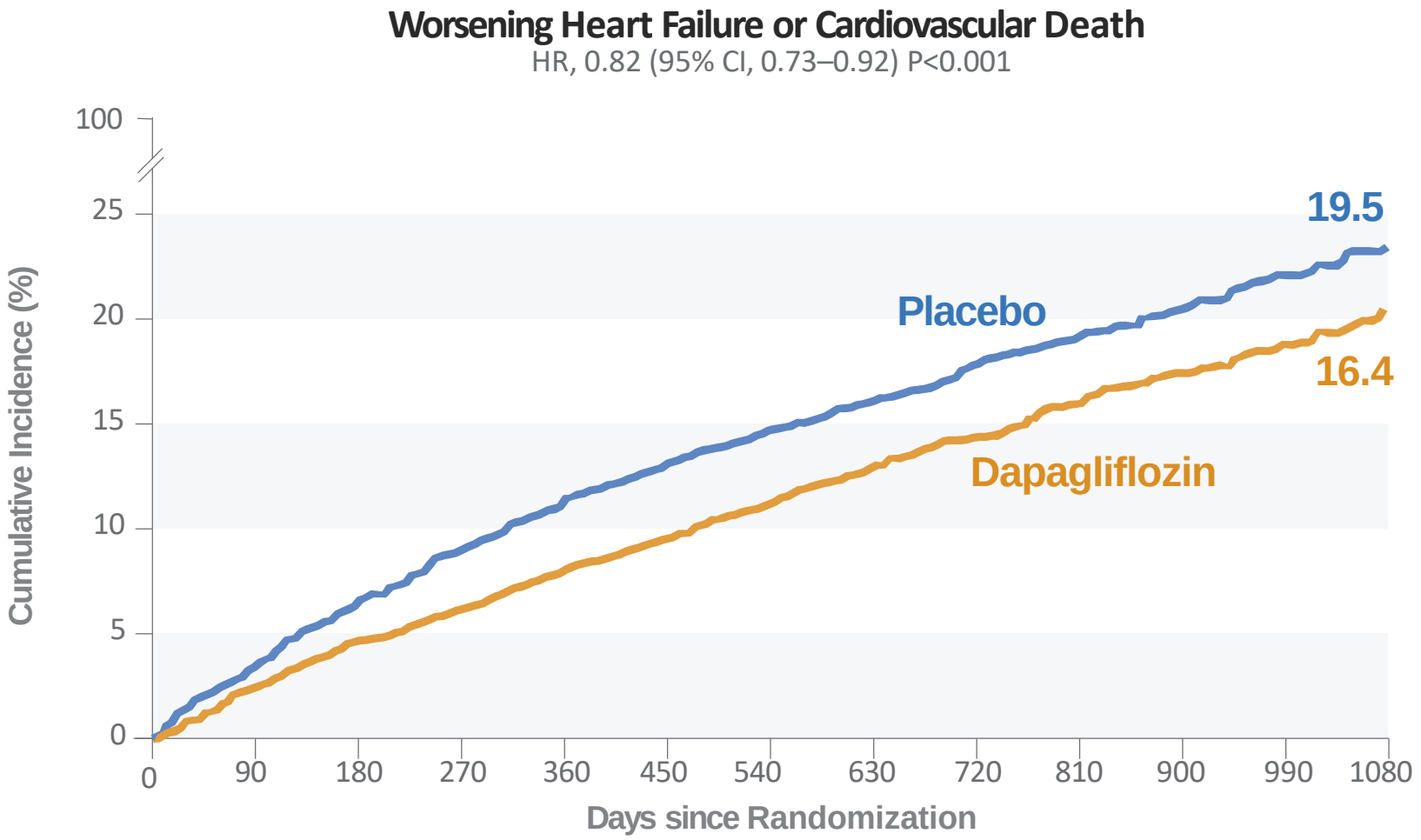
Trial Design: This was an international, multicenter, parallel-group, event-driven, randomized, double-blind, placebo-controlled study. N=6,263 patients with heart failure and a left ventricular ejection fraction of more than 40% were randomized in a 1:1 ratio to receive either dapagliflozin 10 mg or placebo.

Results	Dapagliflozin	Placebo	P-value
Primary Composite: # (%) Time to first occurrence of: CV death; Hosp. for HF; Urgent visit for HF (median of 2.3 years)	512 (16.4)	610 (19.5)	< 0.001
Total # of worsening HF events + Death	815	1057	< 0.001
Death from any cause:# (%)	497 (15.9)	526 (16.8)	NA
Change in total symptom score of KCCQ at 8 months	Win ratio, 1.11; 95% CI, 1.03-1.21; P=0.009		

Results: Among individuals with heart failure and a mildly reduced or preserved ejection fraction, dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death.

Presented by: Dr. Scott Solomon for the DELIVER Investigators

DELIVER: Dapagliflozin in Heart Failure with Mildly Reduced and Preserved Ejection Fraction



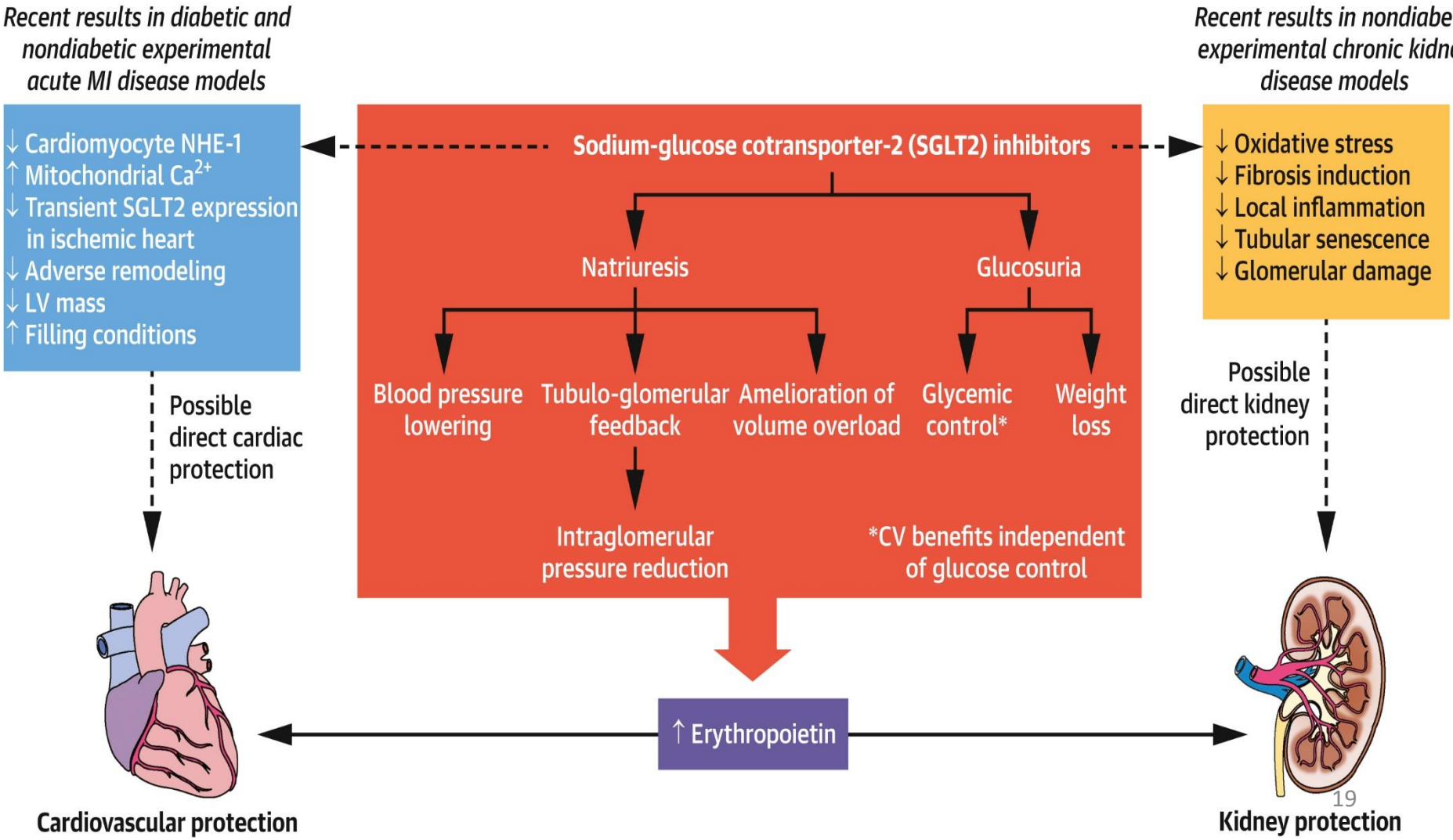
Solomon S, et al. N Engl J Med 2022; 387:1089-1098.

FDA Announcement May 9, 2023

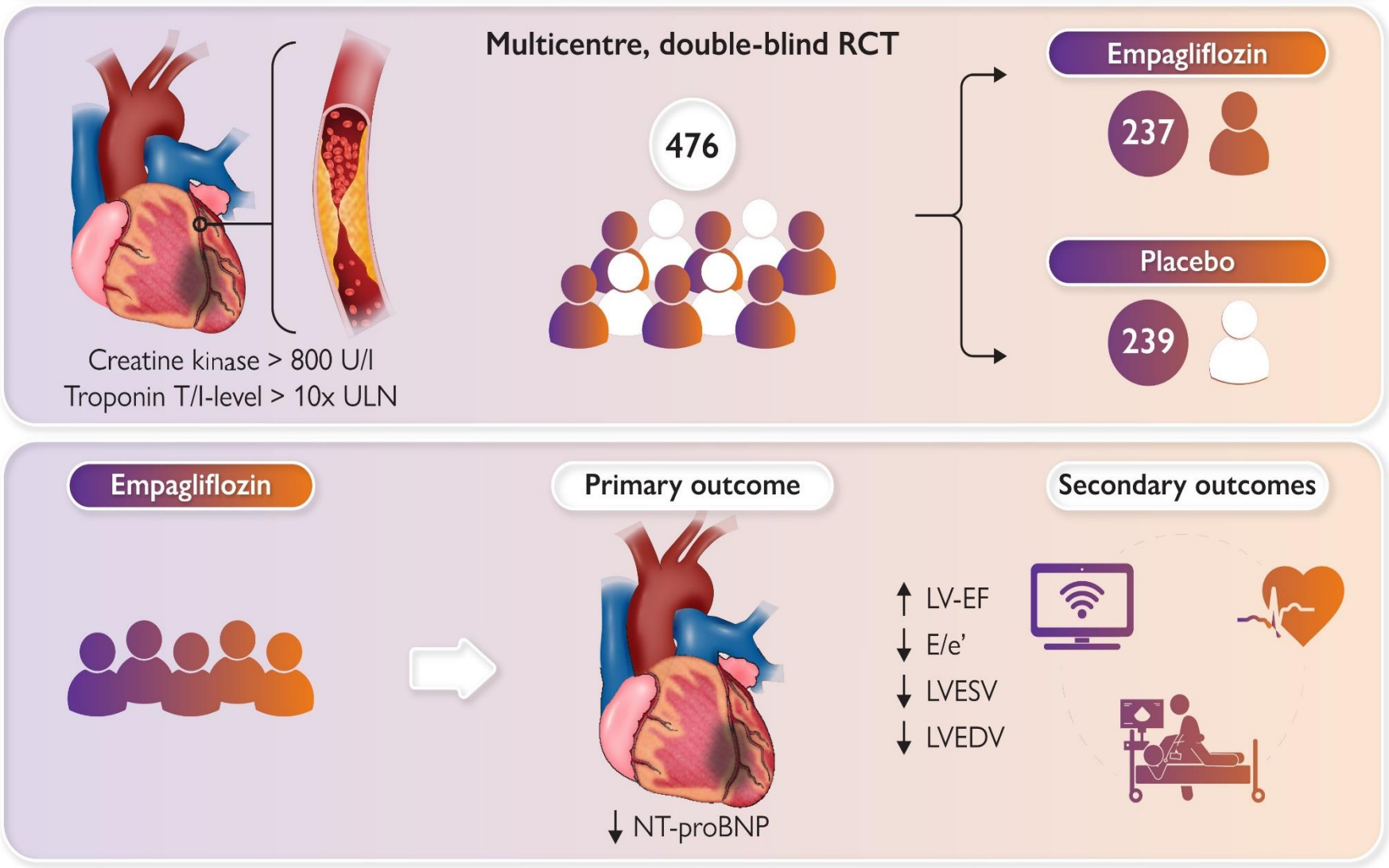
FARXIGA® (dapagliflozin) has been FDA approved to reduce the risk of CV death, hospitalization for HF and urgent HF visits. Approval was based on the positive results from the DELIVER Phase III trial which showed a significant reduction in the primary composite endpoint of CV death or hHF (including urgent HF visits) by 18% (HR 0.82; 95% CI: 0.73-0.92; p=0.0008) in patients with LVEF > 40%. Adverse Reactions in a pool of 12 placebo-controlled studies were female genital mycotic infections (8.4% vs 6.9% vs 1.5%), nasopharyngitis (6.6% vs 6.3% vs 6.2%), and UTI (5.7% vs 4.3% vs 3.7%).

DELIVER was an international, randomized, double-blind, parallel-group, placebo-controlled, event-driven Phase III trial designed to evaluate the efficacy of FARXIGA, compared with placebo, in the treatment of HF patients with LVEF > 40%, with or without T2D. FARXIGA, 10mg qd in addition to background therapy. DELIVER is the largest clinical trial to date in HF patients with LVEF above 40%, with 6,263 randomized patients..

Mechanistic Effect of SGLT2i in Animal Models of Myocardial Infarction

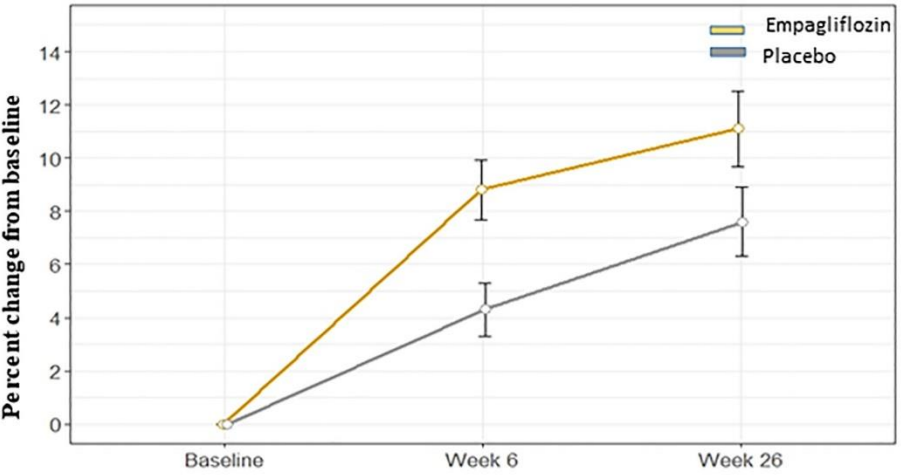


EMMY Trial: Empagliflozin Following Severe Myocardial Infarction



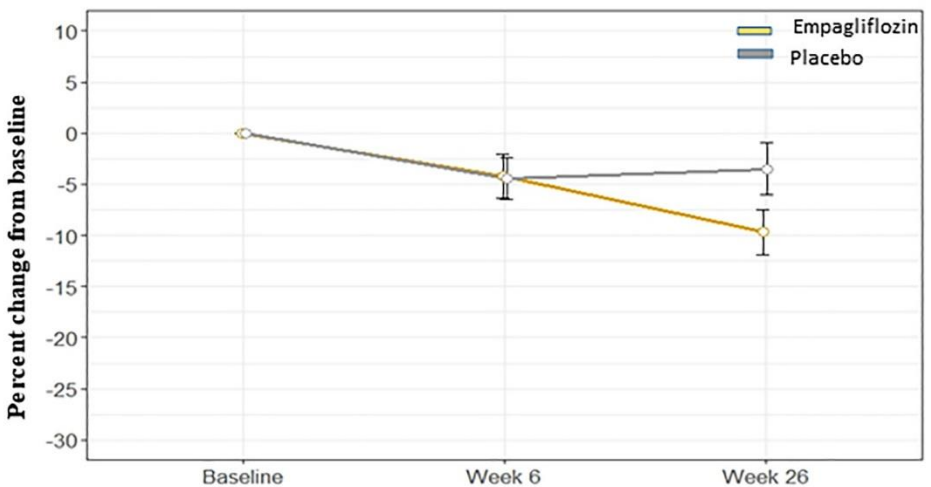
EMMY Trial: Emplagliflozin Following Severe Myocardial Infarction

A LVEF



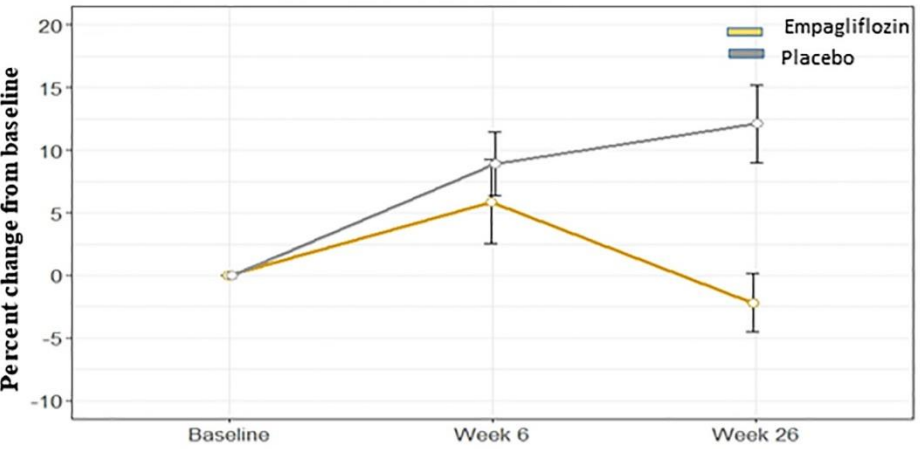
	Baseline	Week 6	Week 26
Placebo	0.0	4.3	7.6
EMpagliflozin	0.0	8.8	11.1

B E/e'



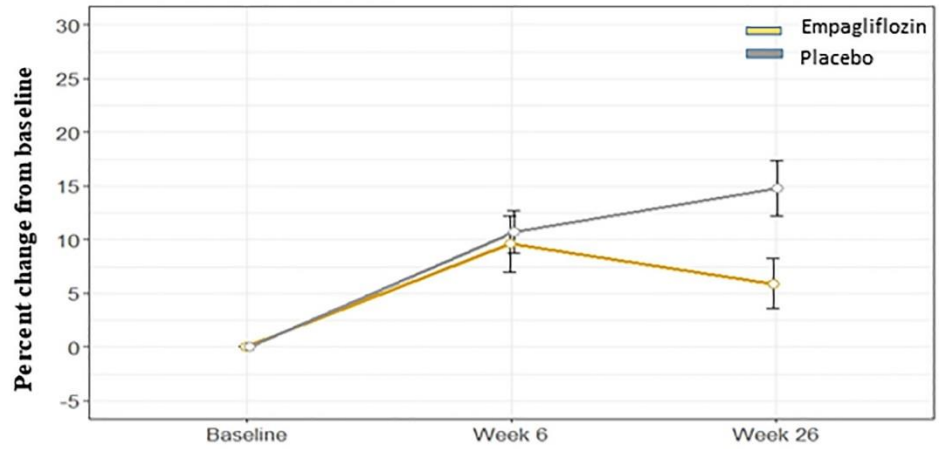
	Baseline	Week 6	Week 26
Placebo	0.0	-4.4	-3.5
EMpagliflozin	0.0	-4.2	-9.7

C LVESV



	Baseline	Week 6	Week 26
Placebo	0.0	8.9	12.1
EMpagliflozin	0.0	5.9	-2.2

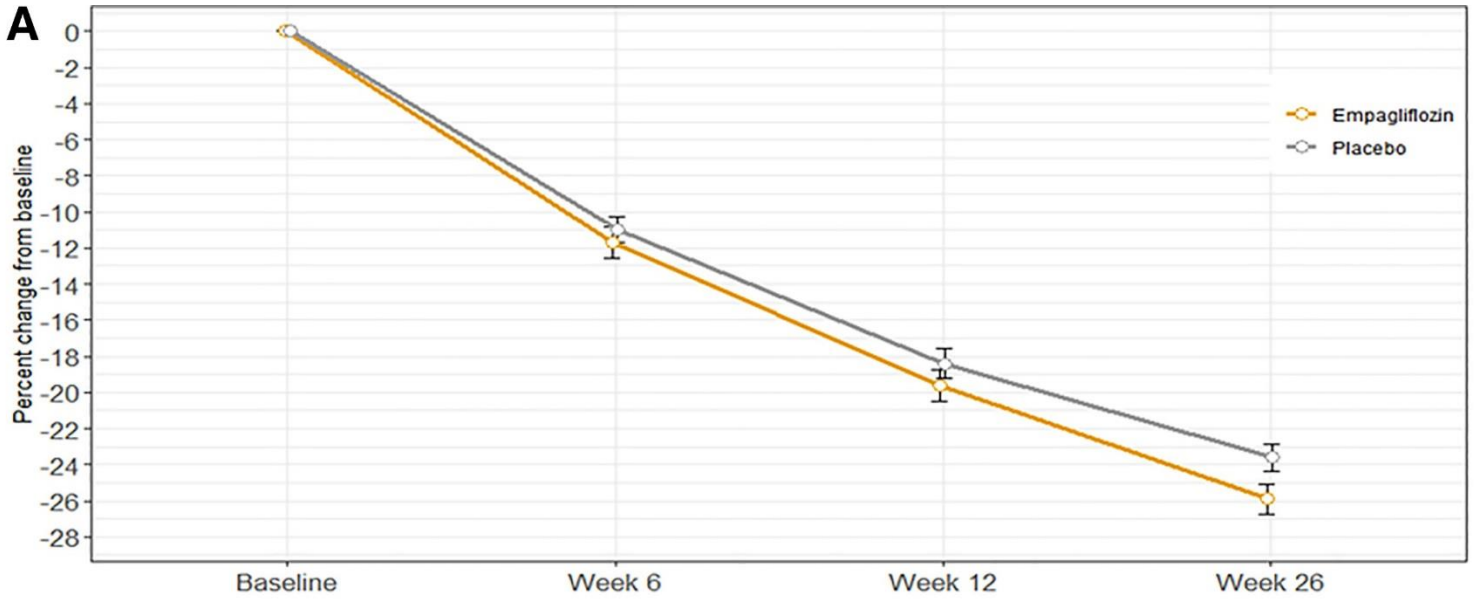
D LVEDV



	Baseline	Week 6	Week 26
Placebo	0.0	10.7	14.8
EMpagliflozin	0.0	9.6	5.9

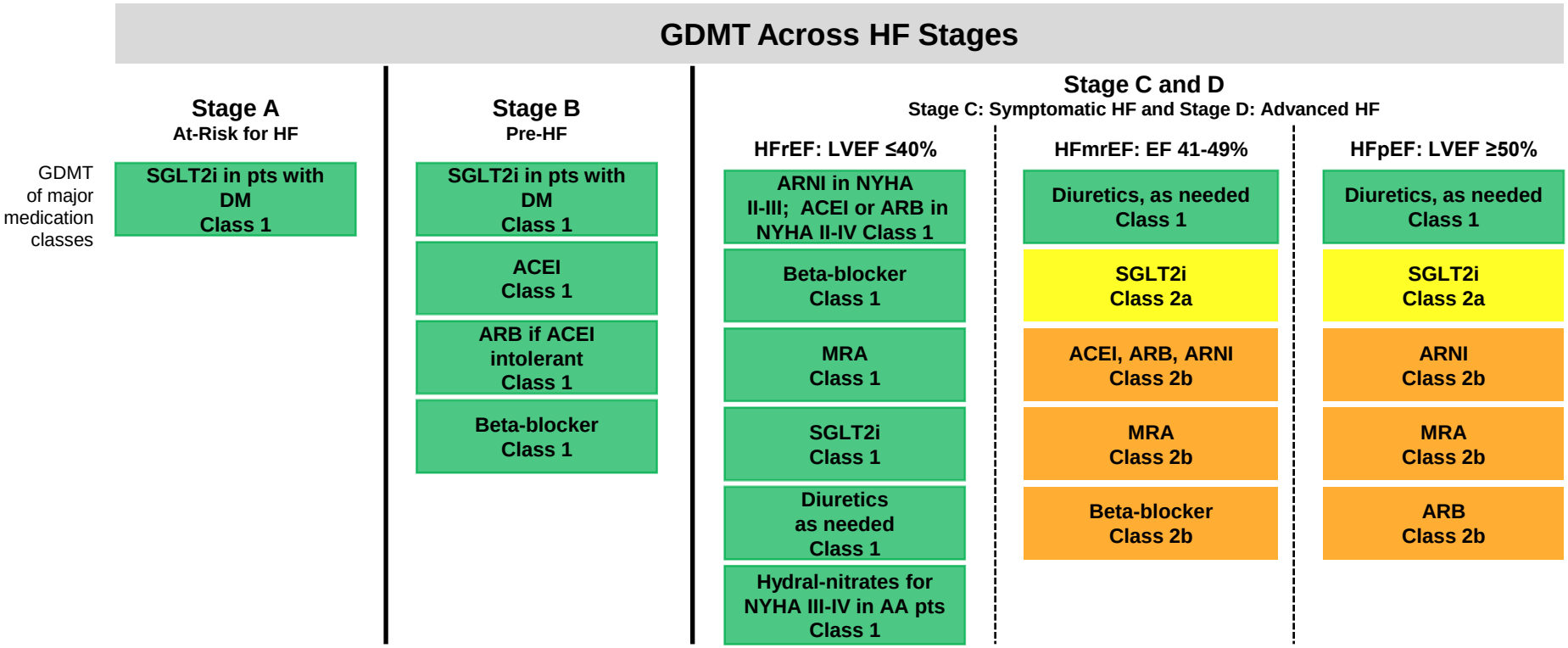
EMMY Trial: Emplagliflozin Following Severe Myocardial Infarction

Effect on NT-PROBNP



	Baseline	Week 6	Week 12	Week 26
Placebo	0.0	-11.0	-18.4	-23.6
Empagliflozin	0.0	-11.7	-19.6	-25.9

2022 AHA/ACC/HFSA HF Guidelines:



ACC = American College of Cardiology; ACEI = angiotensin-converting enzyme inhibitor; AHA = American Heart Association; ARB = angiotensin-receptor blocker; ARNI = angiotensin-receptor neprilysin inhibitor; DM = diabetes mellitus; GDMT = guideline-directed medical therapy; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HFSA = Heart Failure Society of America; Hydral-nitrates: hydralazine and isosorbide dinitrate; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

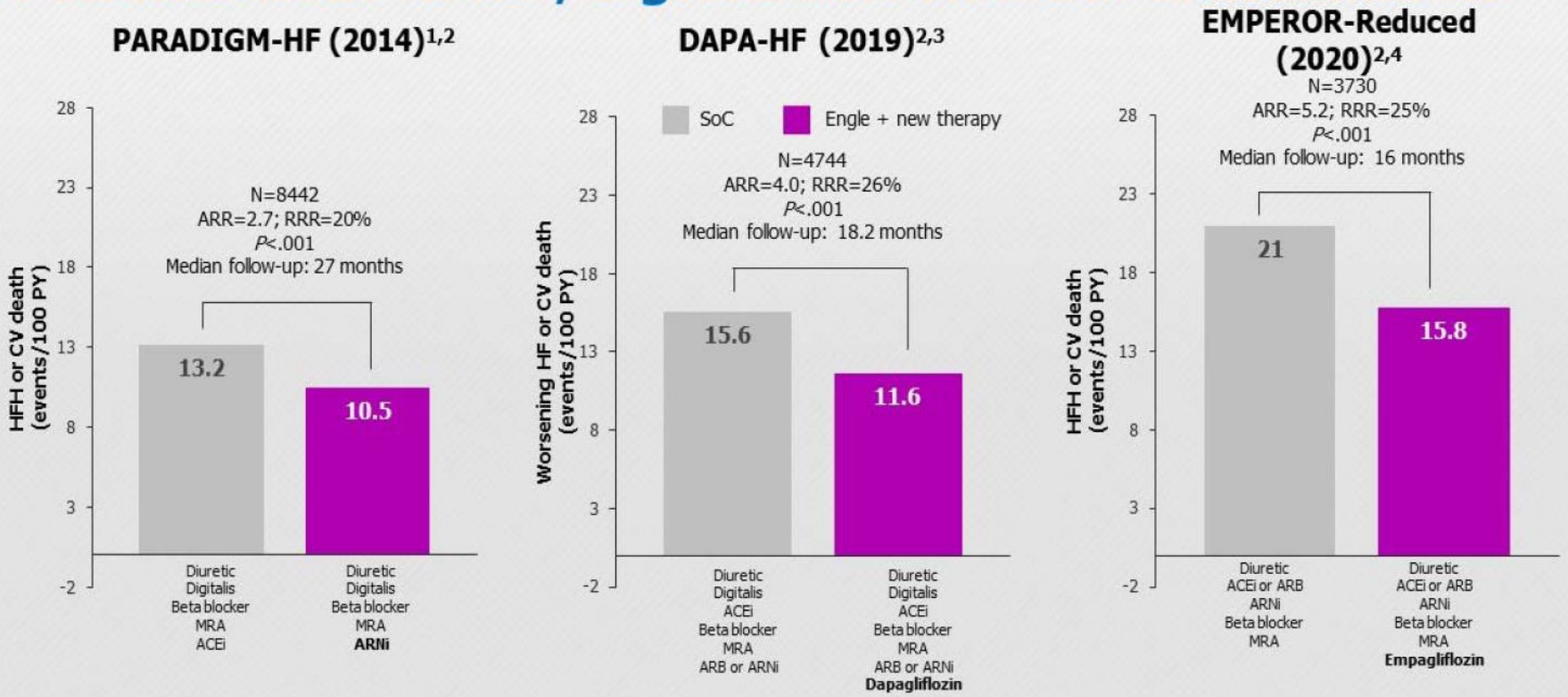
Heidenreich PA, et al. *Circulation*. 2022;145(18):e895-e1032.

Cors at the Shore 2023

However

Outcomes in Treatment Arms in Recent Trials

Despite Improved Outcomes With Contemporary Therapy in Patients With HFrEF, Significant Residual Risk Remains[1-4]



Major medical therapies listed. Each HF study was conducted independently, and no head-to-head HF studies have been completed that allow for direct comparisons.
ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor-neprilysin inhibitor; MRA = mineralocorticoid receptor antagonist; PY = patient-years; RRR = relative risk reduction; SoC = standard of care.

1. McMurray JJV *et al. N Engl J Med* 2014;371:993-1004; 2. Butler *J et al. Eur J Heart Fail* 2020;22:1991-1993; 3. McMurray JJV *et al. N Engl J Med* 2019;381:1995-2008; 4. Packer M *et al. N Engl J Med* 2020;383:1413-1424.

So, What's New

What's New

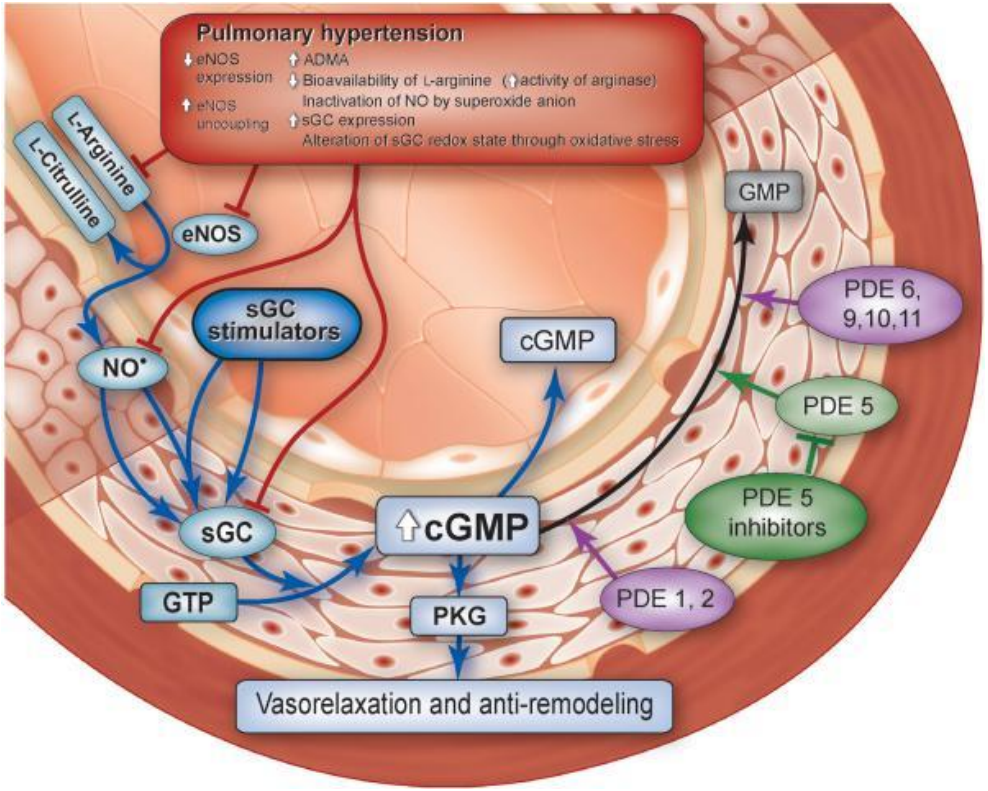
Medications:

- Soluble Guanylate Cyclase Stimulators
- Myotropes

Devices:

- Cardiac Contractility Modulation
- Autonomic Modulation

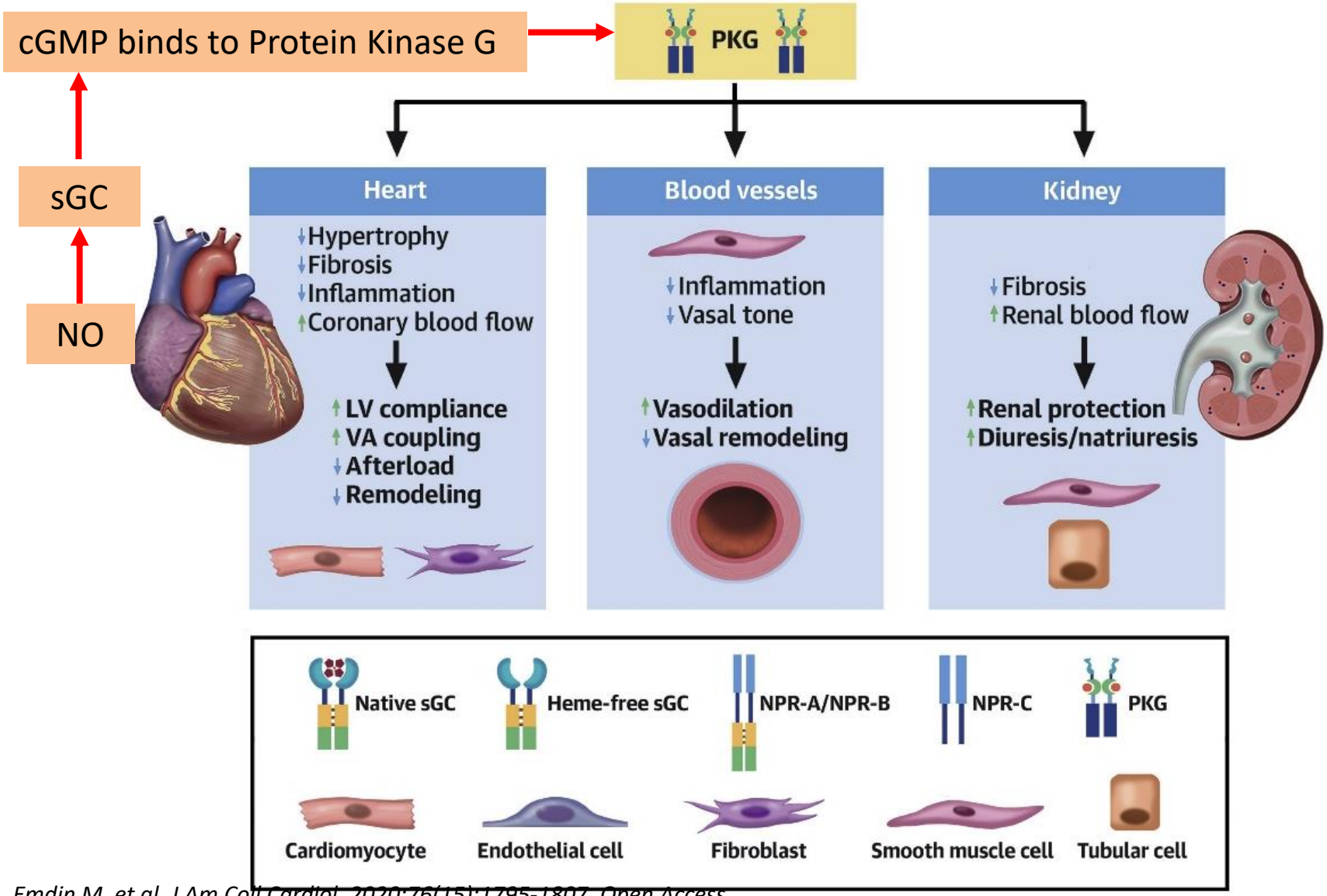
New Targets for the Treatment of HF
The NO/cGMP Signaling Pathway



- Nitric oxide (NO) is synthesized as the first messenger in endothelial cells and nerve endings via NO-synthases (eNOS, nNOS) from L-Arginine;
- NO binds to sGC in smooth muscle cells, myocytes and fibroblasts;
- When NO binds to sGC, it enhances synthesis of the 2nd messenger signaling molecule cGMP;
- cGMP activates PKG and plays important role in:
  - Regulating vascular tone
  - Proliferation
  - Fibrosis
  - Inflammation
- The signaling cascade is terminated by cGMP cleavage with phosphodiesterase (PDE5)

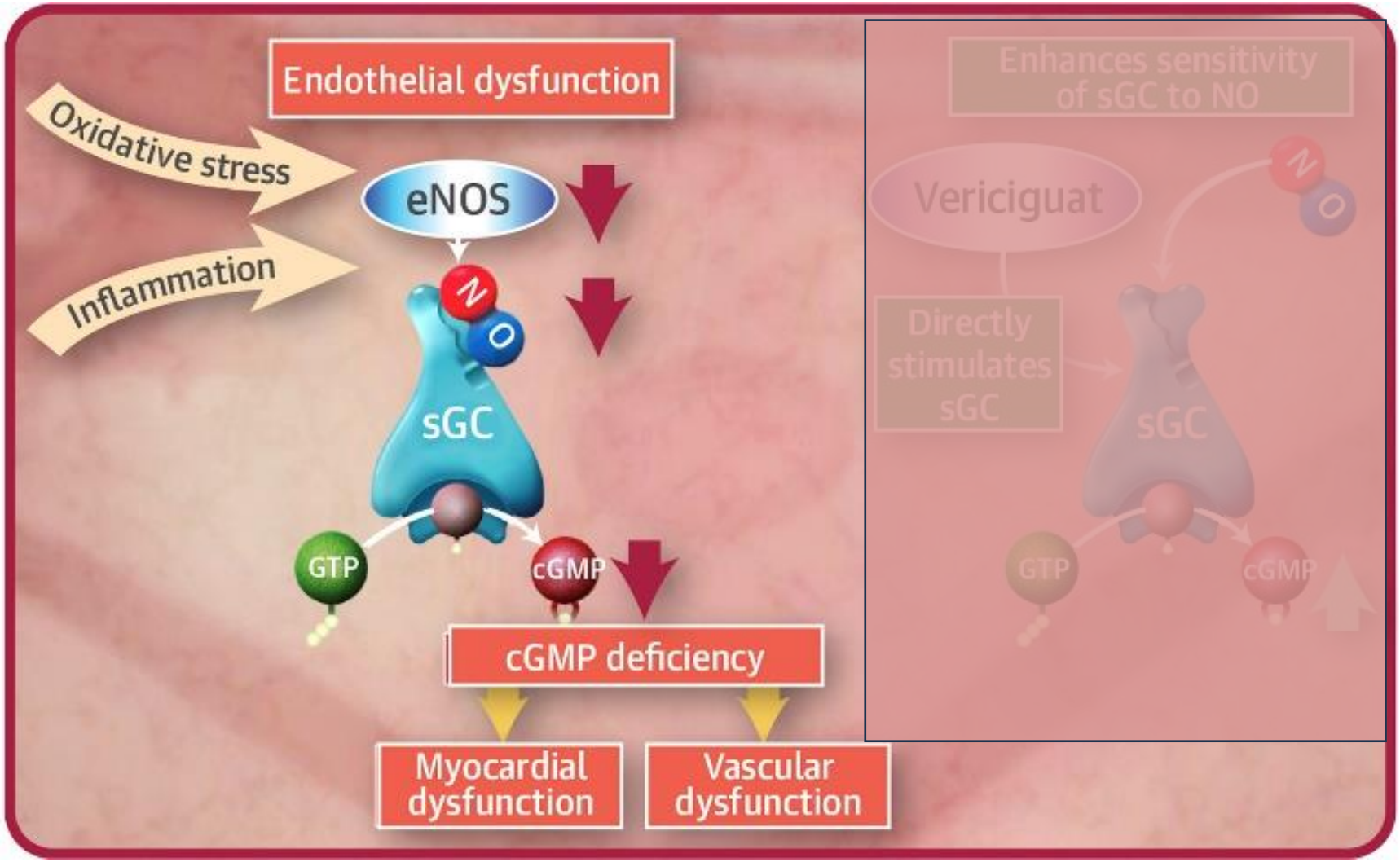
PKG = protein kinase G. Stasch JP, Hobbs AJ. Handb Exp Pharmacol. 2009:277-308.

New Targets for the Treatment of HF
The NO/cGMP Signaling Pathway



Emdin M, et al. J Am Coll Cardiol. 2020;76(15):1795-1807. Open Access.

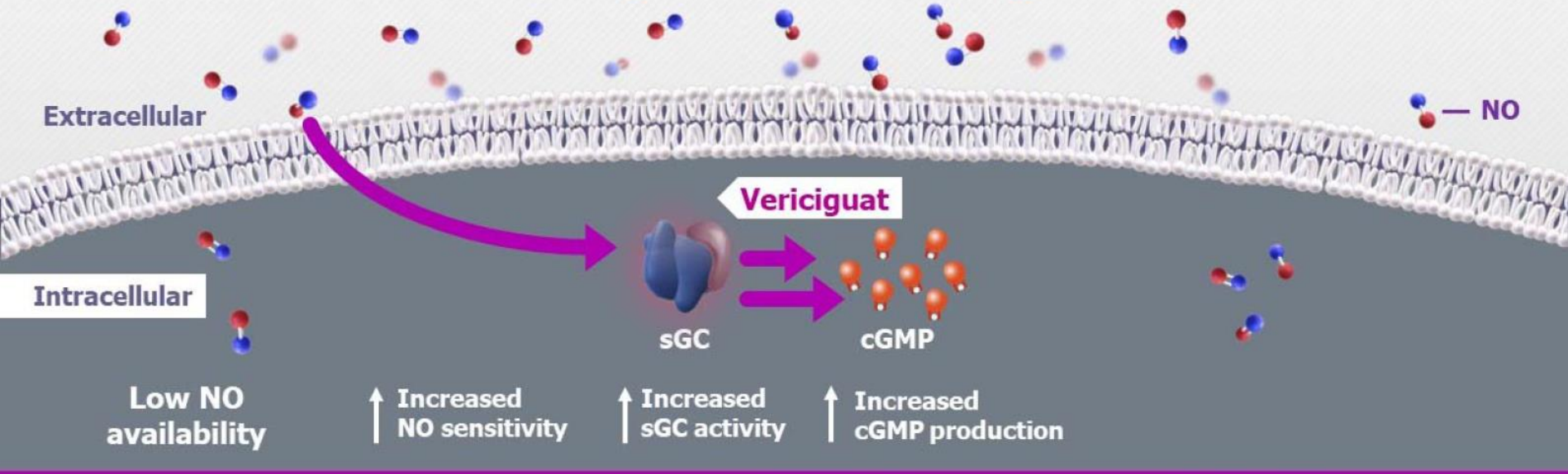
New Targets for the Treatment of HF
The NO/cGMP Signaling Pathway



eGFR= estimated glomerular filtration rate; NSR = normal sinus rhythm; OD = daily; SBP = systolic blood pressure.

Armstrong PW, et al. JACC Heart Fail. 2018;6(2):96-104; Armstrong PW, et al. N Engl J Med. 2020;382(20):1883-1893.

sGC Stimulation Targets an Untapped Pathway That May Lead to the Development and Progression of HF[1-8]



Heart
- ↓ Progressive myocardial stiffening
- ↓ Myocardial thickening
- ↓ Ventricular remodelling
- ↓ Fibrosis

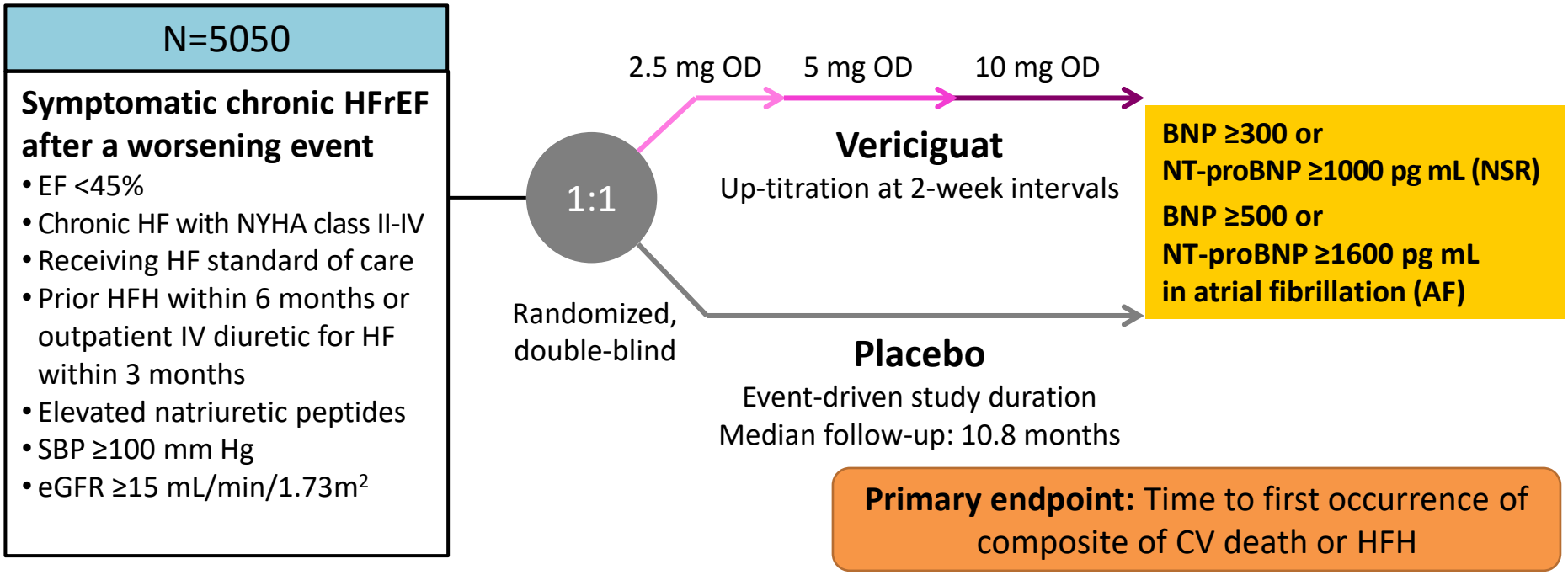
Vasculature
- ↓ Arterial constriction
- ↓ Vascular stiffness

Renal system
- ↓ Na+ and fluid retention
- ↑ Renal blood flow

1. Gheorghiade M, et al. *Heart Fail Rev.* 2013;18:123-134; 2. Mann DL, et al. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine.* 10th ed. Elsevier/Saunders; 2015; 3. Boerrigter G, et al. *Handb Exp Pharmacol.* 2009;191:485-506; 4. Breitenstein S, et al. *Handb Exp Pharmacol.* 2017;243:225-247; 5. Felker G & Mann D. *Heart Failure: A Companion to Braunwald's Heart Disease.* Elsevier; 2020; 6. Armstrong PW, et al. *JACC Heart Fail.* 2018;6:96-104; 7. Follmann M, et al. *J Med Chem.* 2017;60:5146-5161; 8. Mathar I, et al. *Circulation.* 2018;138:A15553. Slide courtesy of Dr. Butler.

Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction (VICTORIA)

Primary objective: To evaluate efficacy of vericiguat in comparison with placebo against background of contemporary HF therapies in increasing time to first occurrence of composite of CV death or HF hospitalization (HFH)

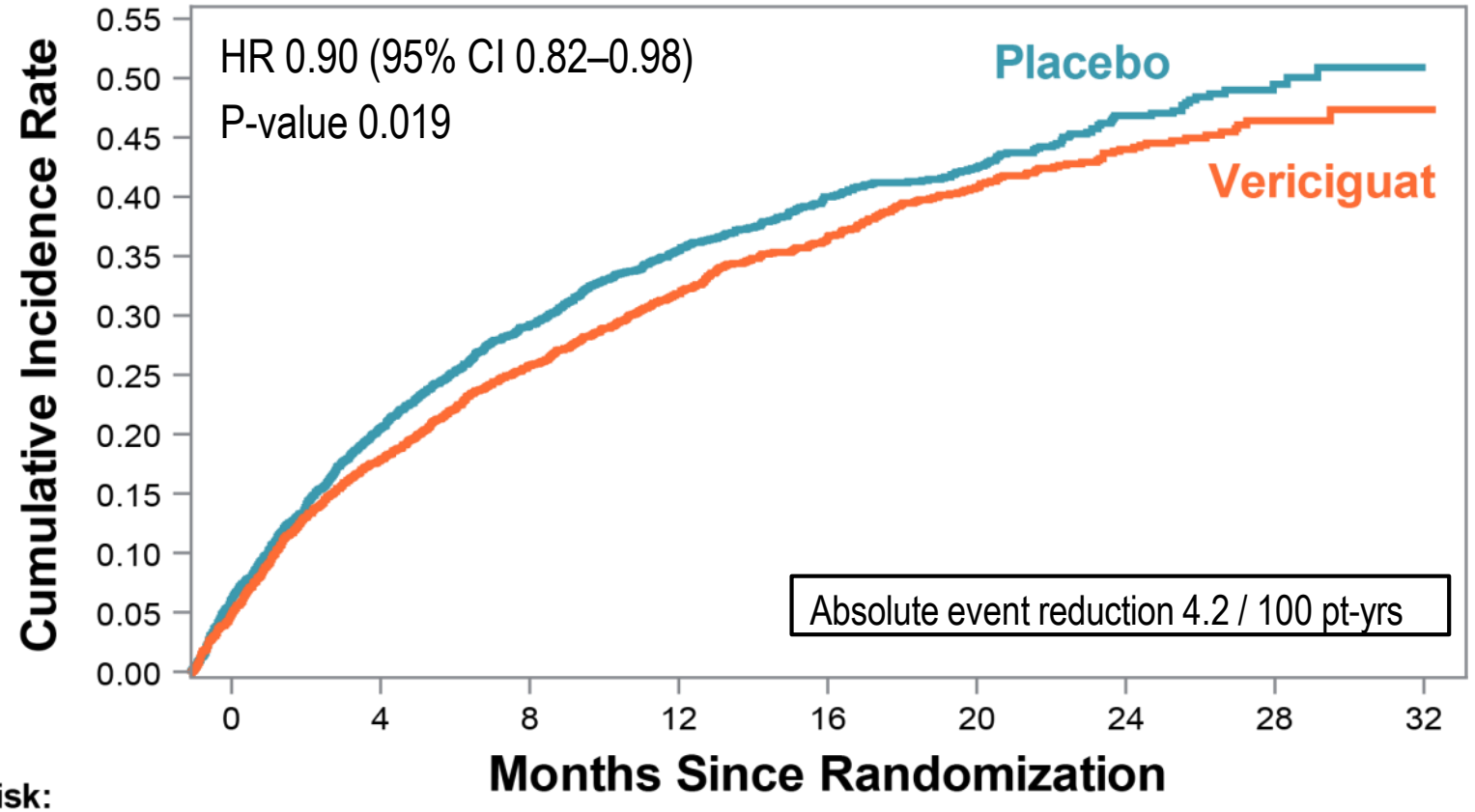


The FDA requested that the primary endpoint be evaluated with respect to baseline N-terminal pro-brain natriuretic peptide (NT-proBNP_ concentration by quartile)

eGFR= estimated glomerular filtration rate; NSR = normal sinus rhythm; OD = daily; SBP = systolic blood pressure.

Armstrong PW, et al. JACC Heart Fail. 2018;6(2):96-104; Armstrong PW, et al. N Engl J Med. 2020;382(20):1883-1893.

VICTORIA: Primary Composite Endpoint: CV Death or First HF Hospitalization



Number at Risk:									
Vericiguat	2526	2099	1621	1154	826	577	348	125	1
Placebo	2524	2053	1555	1097	772	559	324	110	0

Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction (VICTORIA)

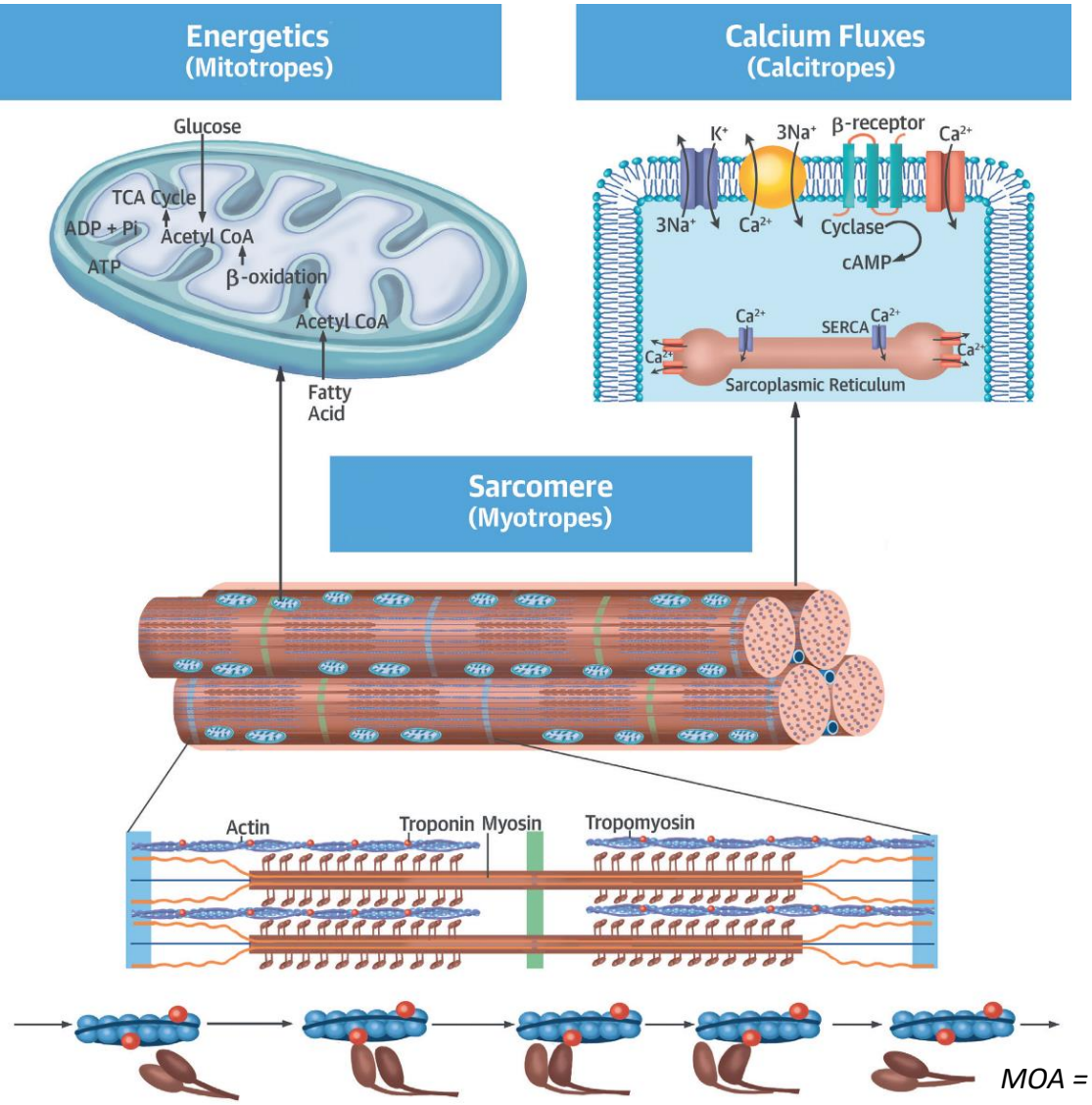
- January 20, 2021 FDA approved VERQUVO, a soluble guanylate cyclase (sGC) stimulator, to reduce the risk of cardiovascular death and heart failure hospitalization following a hospitalization for heart failure or need for outpatient intravenous (IV) diuretics in adults with symptomatic chronic heart failure and ejection fraction less than 45%.
- The approval of VERQUVO by the FDA, which is the first treatment for chronic heart failure approved specifically for patients following a hospitalization for heart failure or need for outpatient IV diuretics.
- More than half of this type of patient is rehospitalized within a month of discharge due to a worsening event and approximately one in five die within two years

Pharmacological Treatment for Stage C HFrEF: Soluble Guanylyl Cyclase Stimulators

Recommendation for Pharmacological Treatment for Stage C HFrEF Soluble Guanylyl Cyclase Stimulators		
COR	**LOE**	**Recommendation**
2b	**B-R**	In selected high-risk patients with HFrEF and recent worsening of HF already on GDMT, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death.

Improving Cardiac Performance:

Inotropes

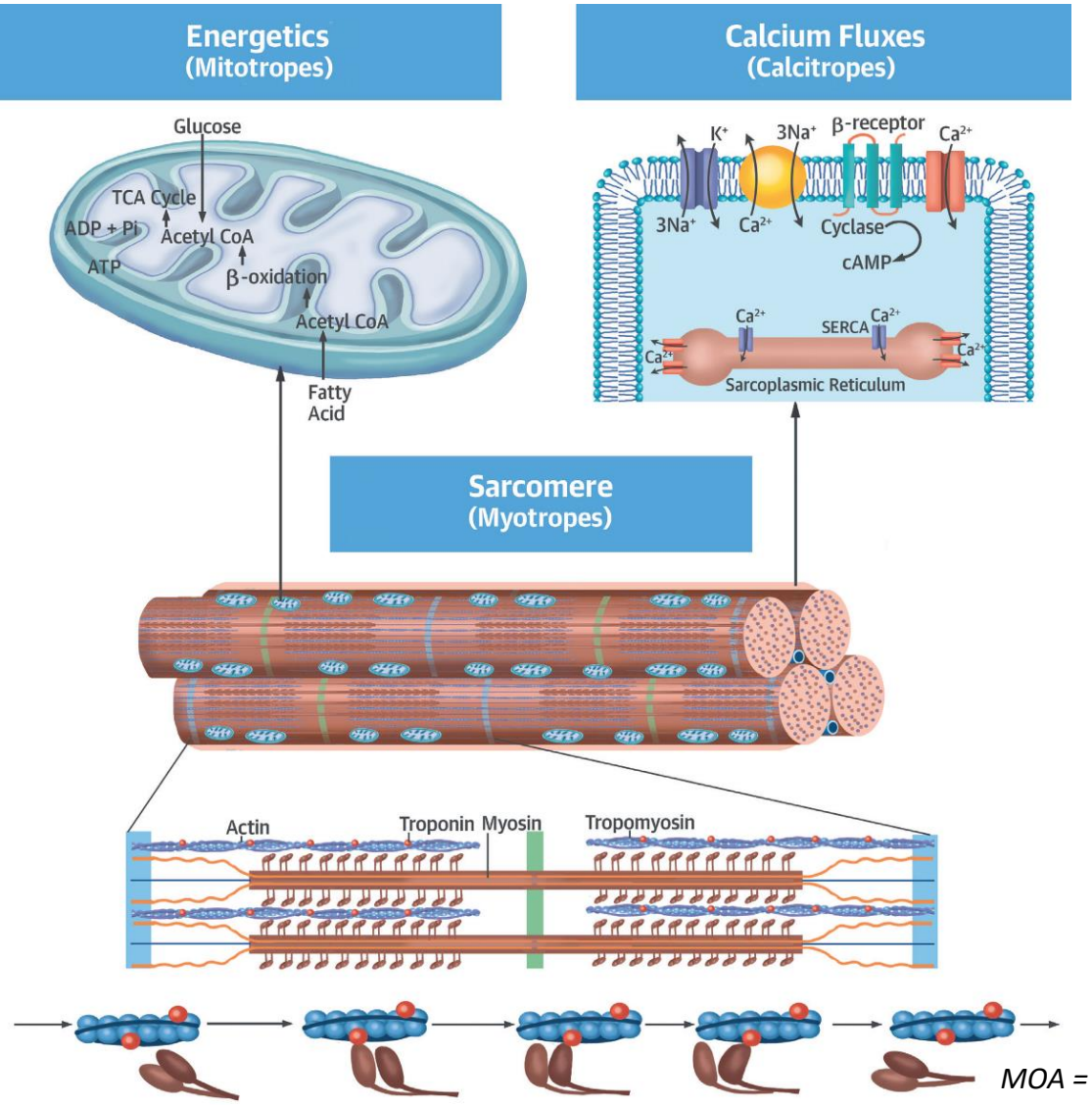


Therapies by Mechanism of Action:

- **Calcitropes** –alter intracellular calcium
- **Mitotropes**–influence energetics
- **Myotropes** –affect the molecular motor and scaffolding

MOA = mechanism of action. Psotka MA, et al. J Am Coll Cardiol. 2019;73(18):2345-2353. Open Access.

Improving Cardiac Performance: Calcitropes, Mitotropes, and Myotropes



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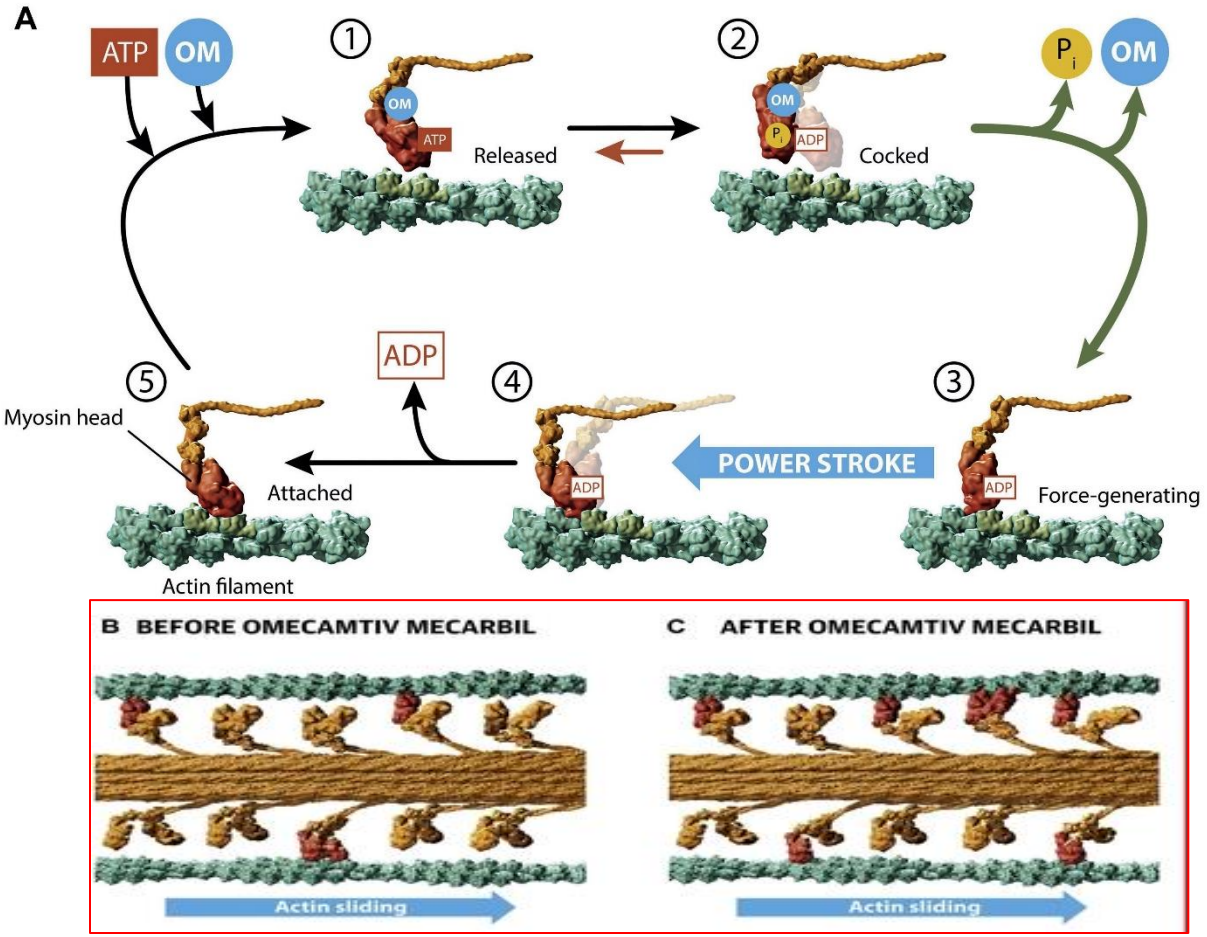
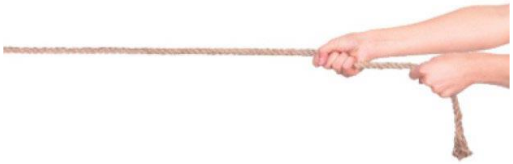
Novel Selective Cardiac Myosin Activator Omecamtiv Mecarbil (OM)

Omecamtiv mecarbil stabilizes Myosin increasing the entry rate of Myosin into the tightly-bound, force-producing state with Actin



Without omecamtiv mecarbil:



With omecamtiv mecarbil:

- More "hands" (myosin heads) to grasp the "rope" (actin filament) to produce more force

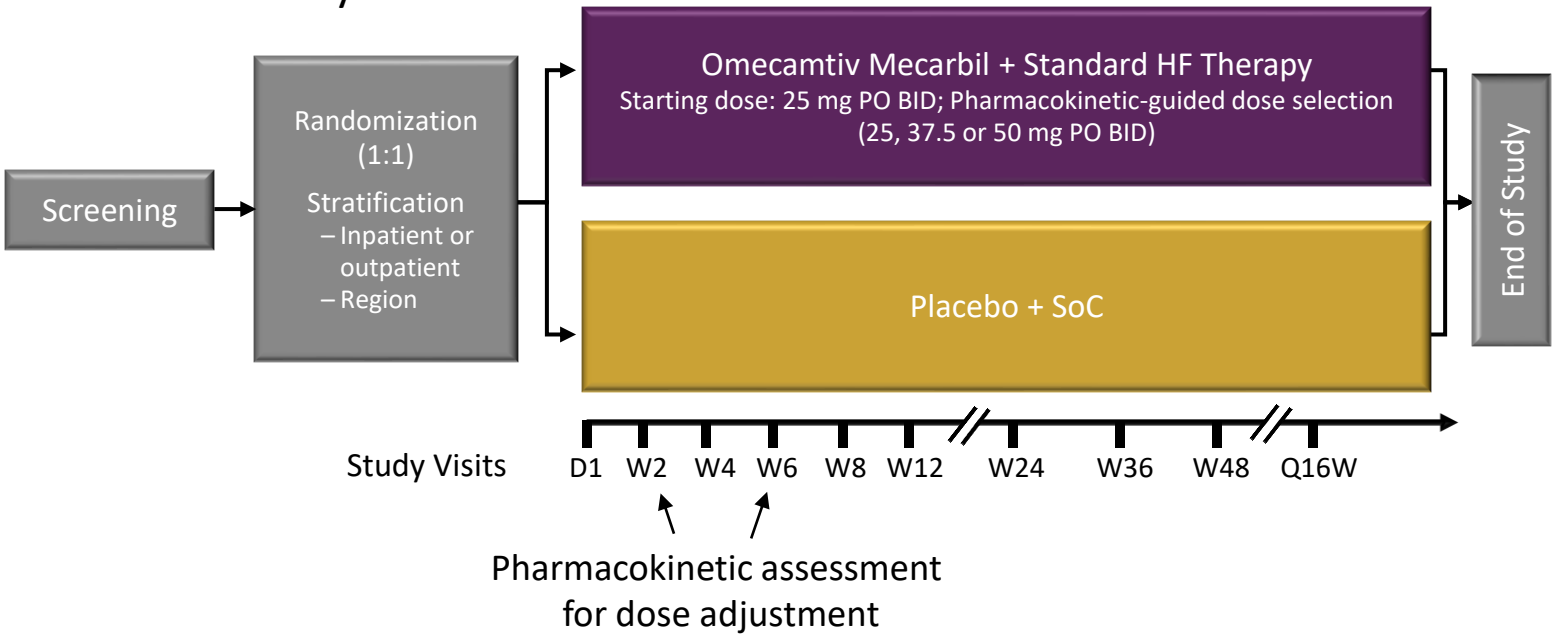
Malik FI, et al. Science.2011;331(6023):1439-1443; Shen YT, et al. Circ Heart Fail. 2010;3(4):522-527; Planelles-Herrero VJ, et al. Nat Commun. 2017;8(1):190; Teerlink JR, et al. JACC Heart Fail. 2020;8(4):329-340. Open Access.

Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure (GALACTIC-HF)

Hypothesis: Selectively improving cardiac function with the cardiac myosin activator, Omecamtiv Mecarbil, will improve clinical outcomes in HFrEF

Trial Design

Multicenter, international, randomized, double-blind, placebo-controlled, event-driven Phase 3 study



Teerlink JR, et al. *JACC Heart Fail* 2020;8:329–40.

Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure (GALACTIC-HF)

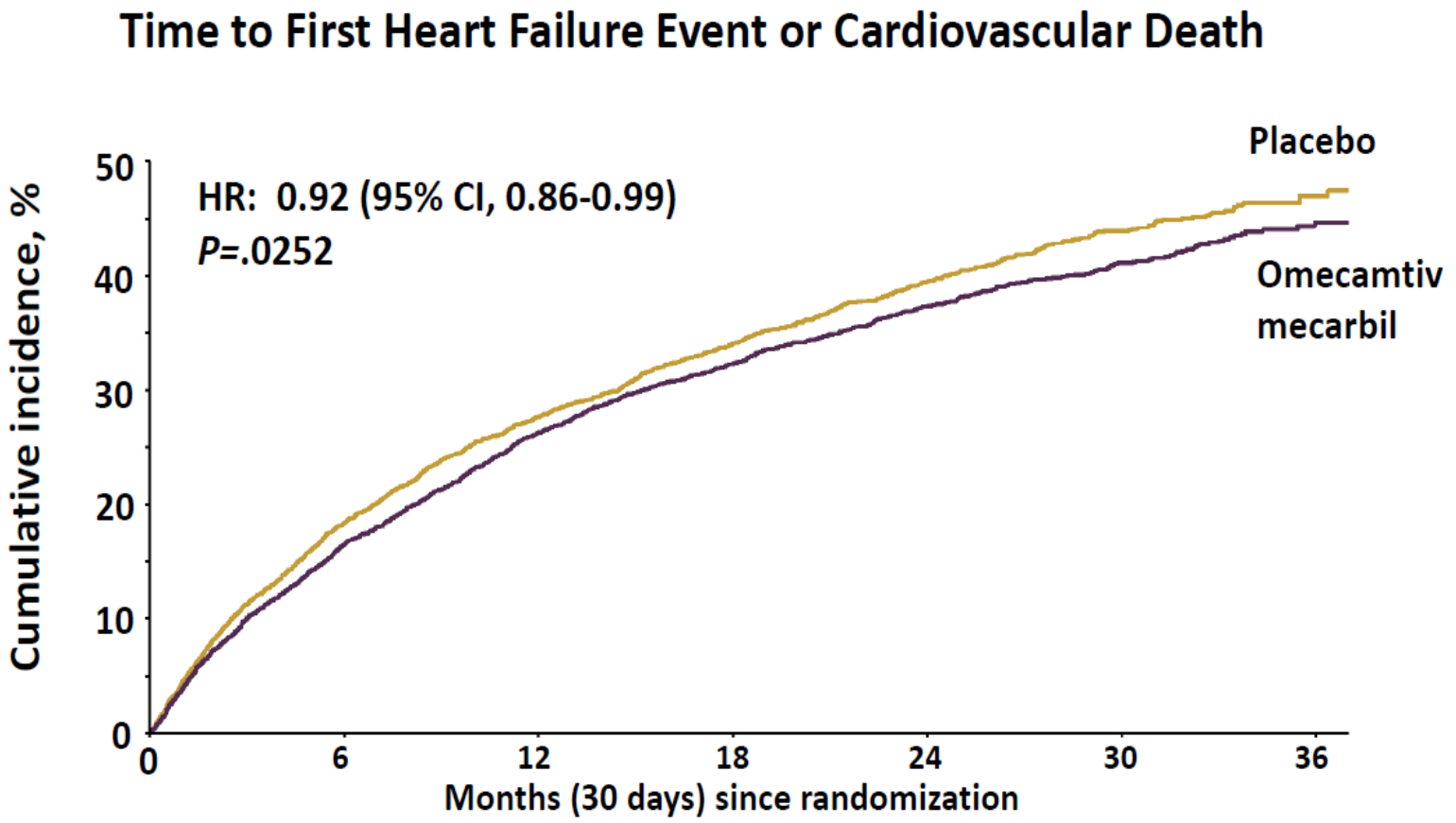
Baseline Characteristics

Characteristic	OM (N=4120)	Placebo (N=4112)
Demographics		
Age (years), median (Q1, Q3)	66 (58, 73)	66 (58, 73)
Sex, female, %	21	21
White/Asian/Black/other, %	78/9/7/7	78/9/7/7
Heart Failure History and Medical Conditions		
HF event prior to randomization (outpatients), median (months)	3.2	3.1
LVEF (%), mean (SD)	27 (6)	27 (6)
NYHA class, II/III/IV, %	53/44/3	53/44/3
Ischemic etiology, %	53	54
Atrial fib/flutter at screening, %	28	27
Type 2 diabetes, %	40	40

Characteristic	OM (N=4120)	Placebo (N=4112)
Vital signs and Laboratory Parameters		
SBP (mmHg), mean (SD)	116 (15)	117 (15)
Heart rate, mean (SD)	72 (12)	72 (12)
eGFR (mL/min/1.73m^2), median (Q1, Q3)	59 (44, 74)	59 (44, 74)
NT-proBNP (pg/mL), median (Q1, Q3)	1977 (980, 4061)	2025 (1000, 4105)
Cardiac TnI (ng/mL), median (Q3)	0.027 (0.052)	0.027 (0.052)
Medications and Cardiac Devices		
ACEI/ARB/ARNi , %	87	87
ARNi, %	20	19
BB, %	94	94
MRA, %	78	78
SGLT2i, %	2.5	2.8
CRT, %	14	14
ICD, %	32	31

Teerlink JR, et al. *Eur J Heart Fail* 2020:doi:10.1002/ejhf.2015.

Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure (GALACTIC-HF)



Patients at risk, n

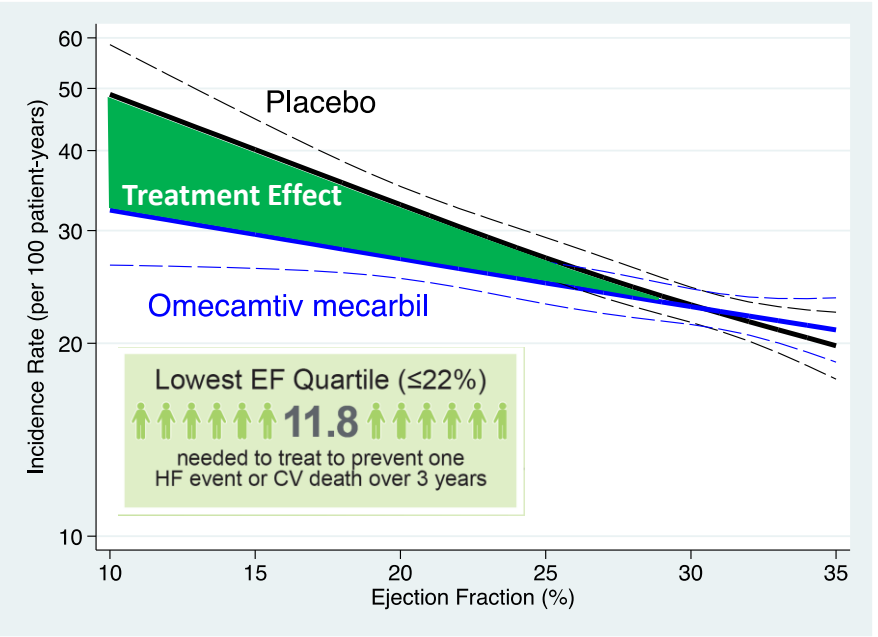
Placebo	4112	3310	2889	2102	1349	647	141
Omecamtiv mecarbil	4120	3391	2953	2158	1430	700	164

From Teerlink JR, et al. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. N Engl J Med.2020;384(2):105-116.

Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure (GALACTIC-HF)

Conclusions

- In patients with HFrEF, omecamtiv mecarbil reduced the 1° composite outcome (first HF event or CV death)
- The treatment effect of omecamtiv mecarbil increased with decreasing EF
- There was no difference in Serious Adverse, Ischemic or Arrhythmic Events compared to Placebo across the range of EF
- There was no adverse effect on blood pressure, heart rate, potassium homeostasis or renal function

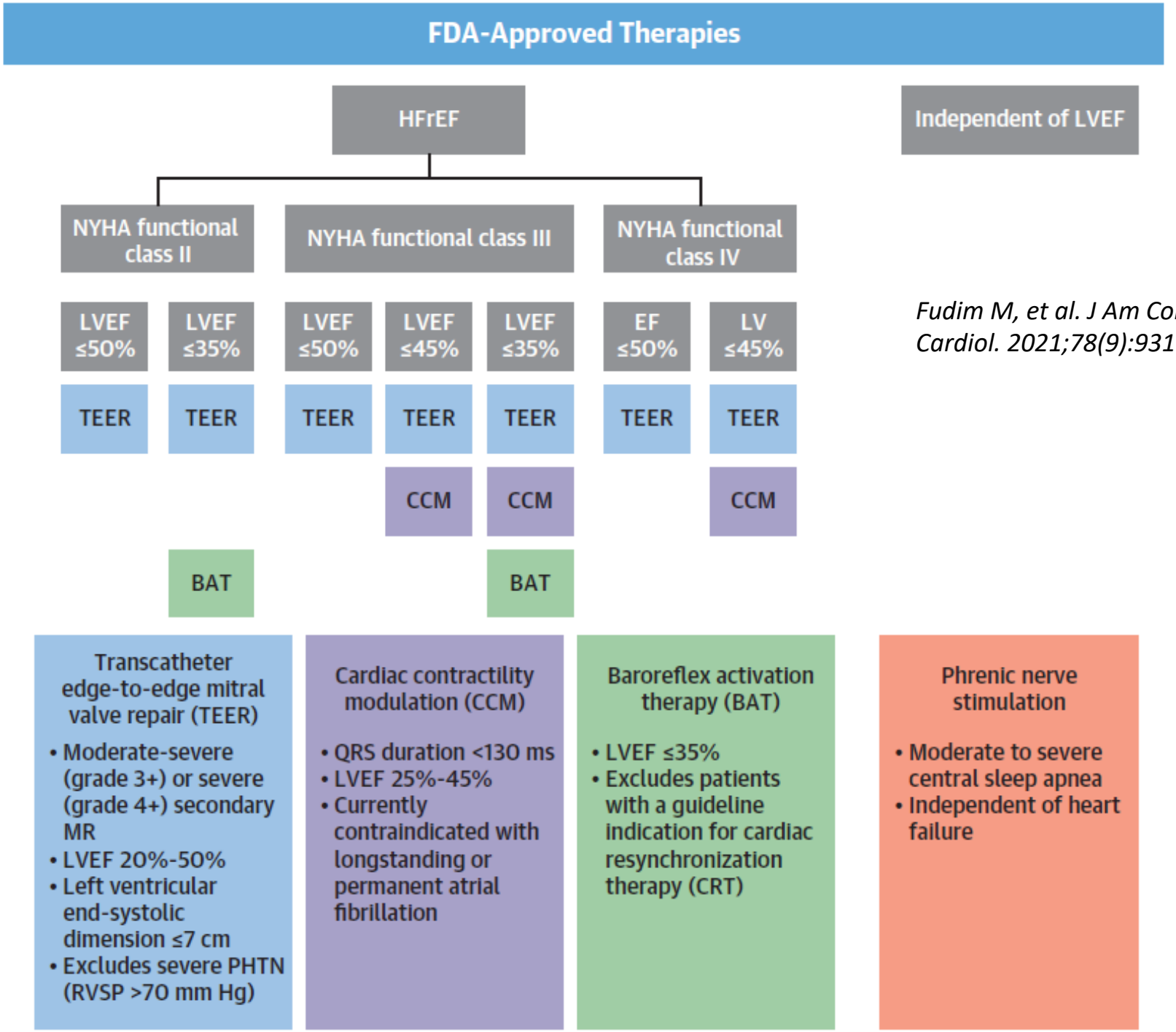


Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure (GALACTIC-HF)

FDA: February 28, 2023: Omecamtiv Mecarbil not approved

- FDA communicated that GALACTIC-HF is not sufficiently persuasive to establish substantial evidence of effectiveness for reducing the risk of heart failure events and cardiovascular death in adults with chronic heart failure with reduced ejection fraction, in lieu of evidence from at least two adequate and well-controlled clinical investigations.

- FDA stated that results from an additional clinical trial of omecamtiv mecarbil are required to establish substantial evidence of effectiveness for the treatment of HFrEF, with benefits that outweigh the risks.



Fudim M, et al. J Am Coll Cardiol. 2021;78(9):931-956.

Cardiac Contractility Modulation (CCM) for Chronic Heart Failure

Cardiac Contractility Modulation (CCM) for Heart Failure: OPTIMIZER® System

Programmer

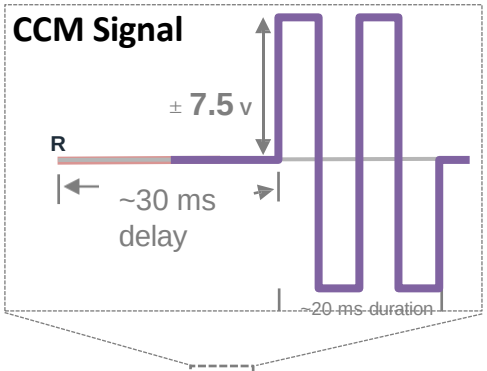
Implantable Pulse Generator (IPG)

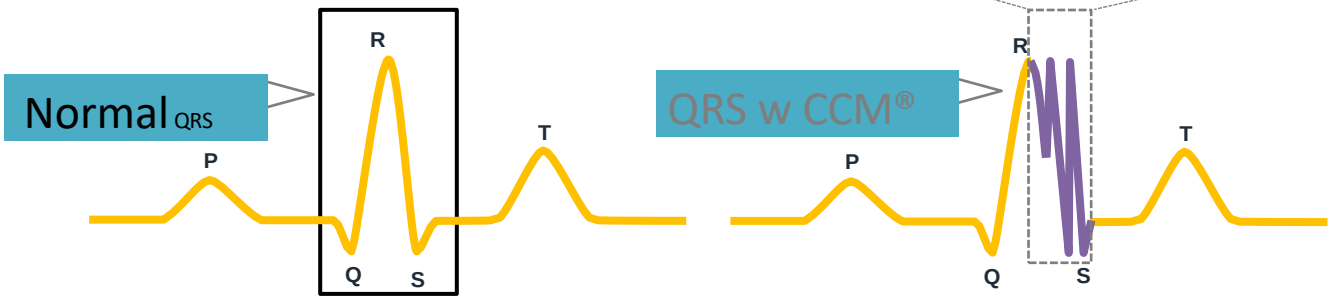
Mini Charger

Cardiac Contractility Modulation (CCM)
(Optimizer Smart System)

Therapy Delivery - Waveform

- Nonexcitatory - Applied during absolute refractory period (~ 30 ms delay)
- Biphasic
- Duration ~ 20 ms
- Amplitude ± 7.5 V
- Never on T wave



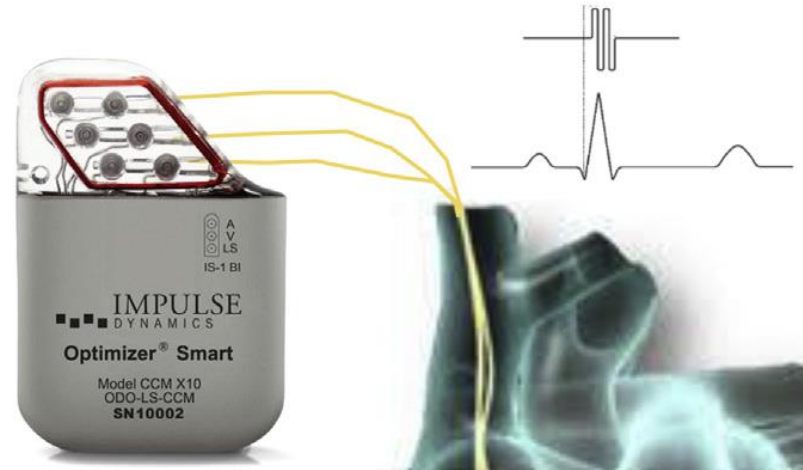


Cardiac Contractility Modulation (CCM)

Immediate Effects on Contractility

Increase in ventricular contractility with increased calcium uptake in the sarcoplasmic reticulum and downstream expression of genetic coding for improving myocardial inotropy

Cardiac Contractility Modulation



Rechargeable Implanted Pulse Generator

CCM Signal applied during absolute refractory period to the RV septum via standard pacing leads

Biological effects seen remotely over time

Biological effects seen rapidly in region of signal applications

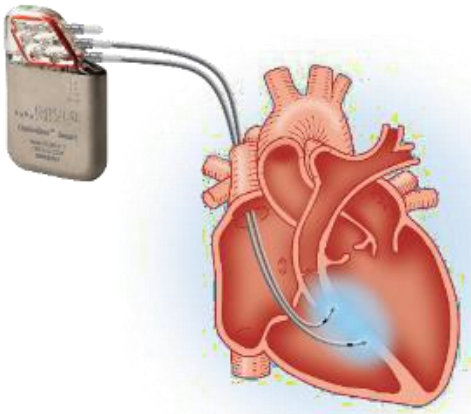
Improved peak VO2
MLWHFQ and NYHA;
Reduced HF Hospitalizations

Abraham W, et al. JACC Heart Fail. 2018 Oct;6(10):874-883.

Cardiac Contractility Modulation

Therapeutic Effects

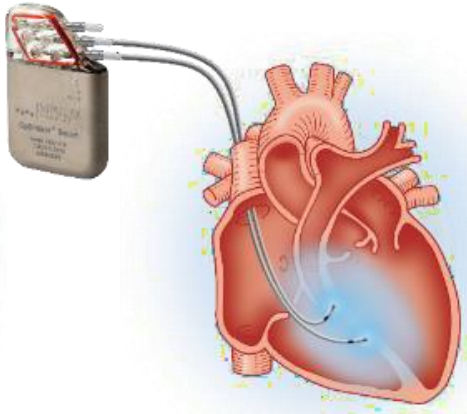
Rapid



Minutes to Hours$_{(1-3)}$

- Improved calcium cycling and contractile force

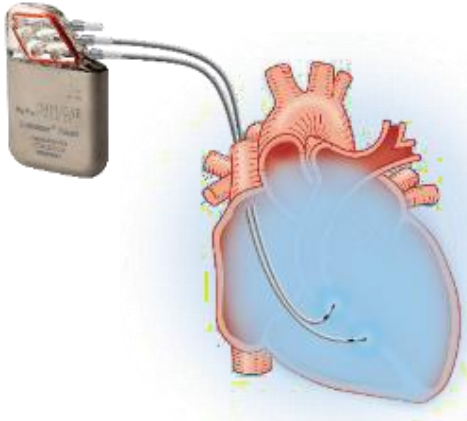
Intermediate



Hours to Weeks$_{(1-3)}$

- Shift of gene program from heart failure to normal

Long-Term

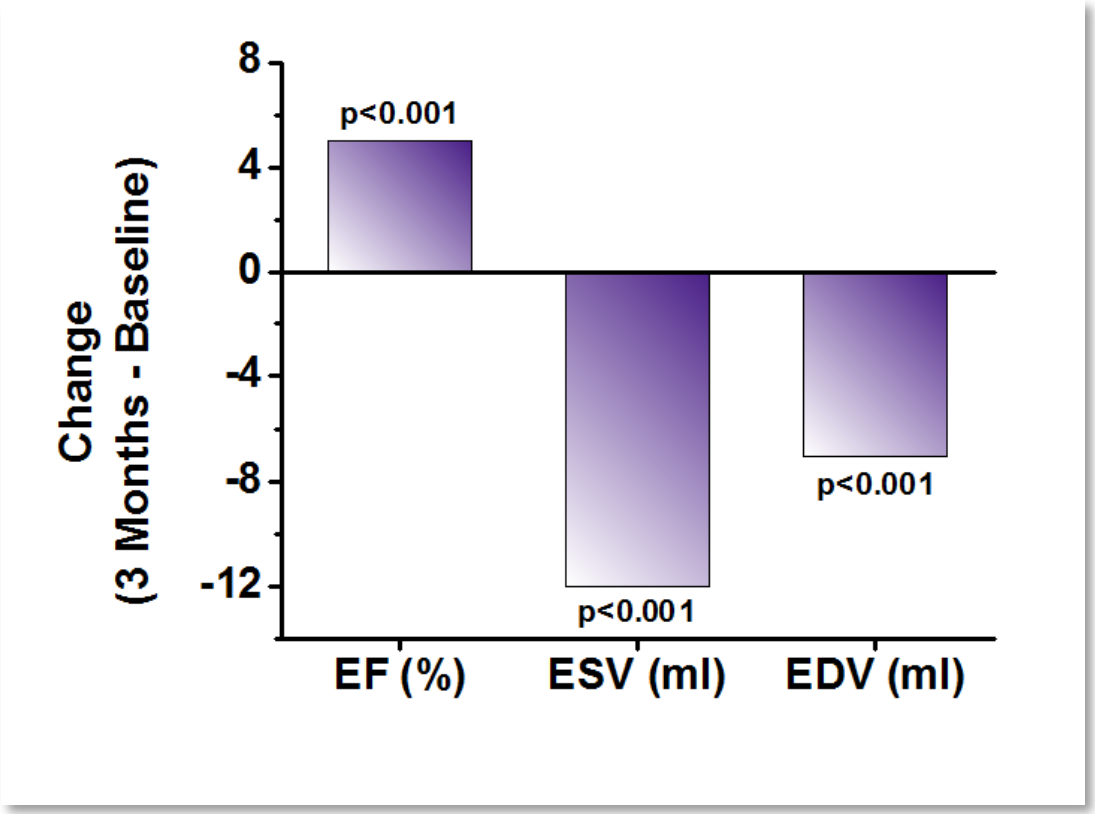


Weeks to Months$_{(\sim 4)}$

- Beneficial effect on global ventricular properties and reverse remodeling

Cardiac Contractility Modulation

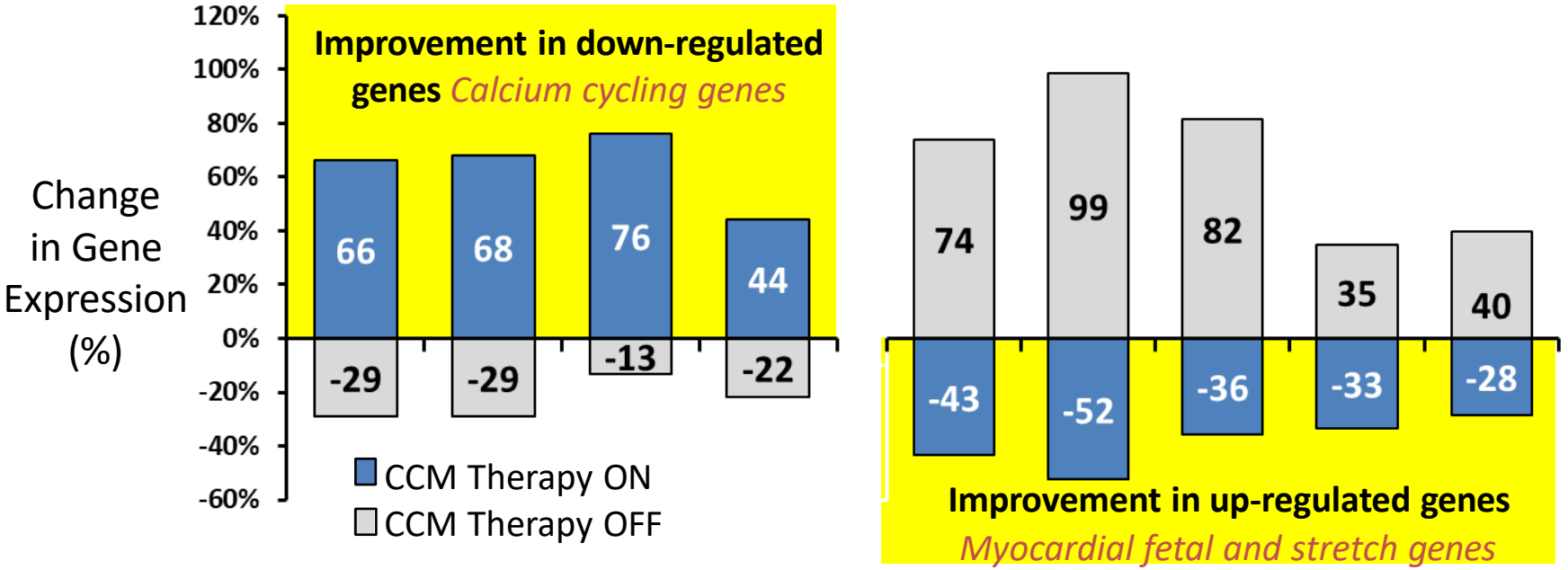
Improved Regional Cardiac Function Induces Global Improvement & Reverse Remodeling in Humans



Source - Yu, et al., Impact of cardiac contractility modulation on left ventricular global and regional function and remodeling. JACC Cardiovasc Imaging. 2009 Dec;2(12):1341-9. doi: 10.1016/j.jcmg.2009.07.011.

Cardiac Contractility Modulation

Modifies Multiple Gene Programs Implicated in Heart Failure

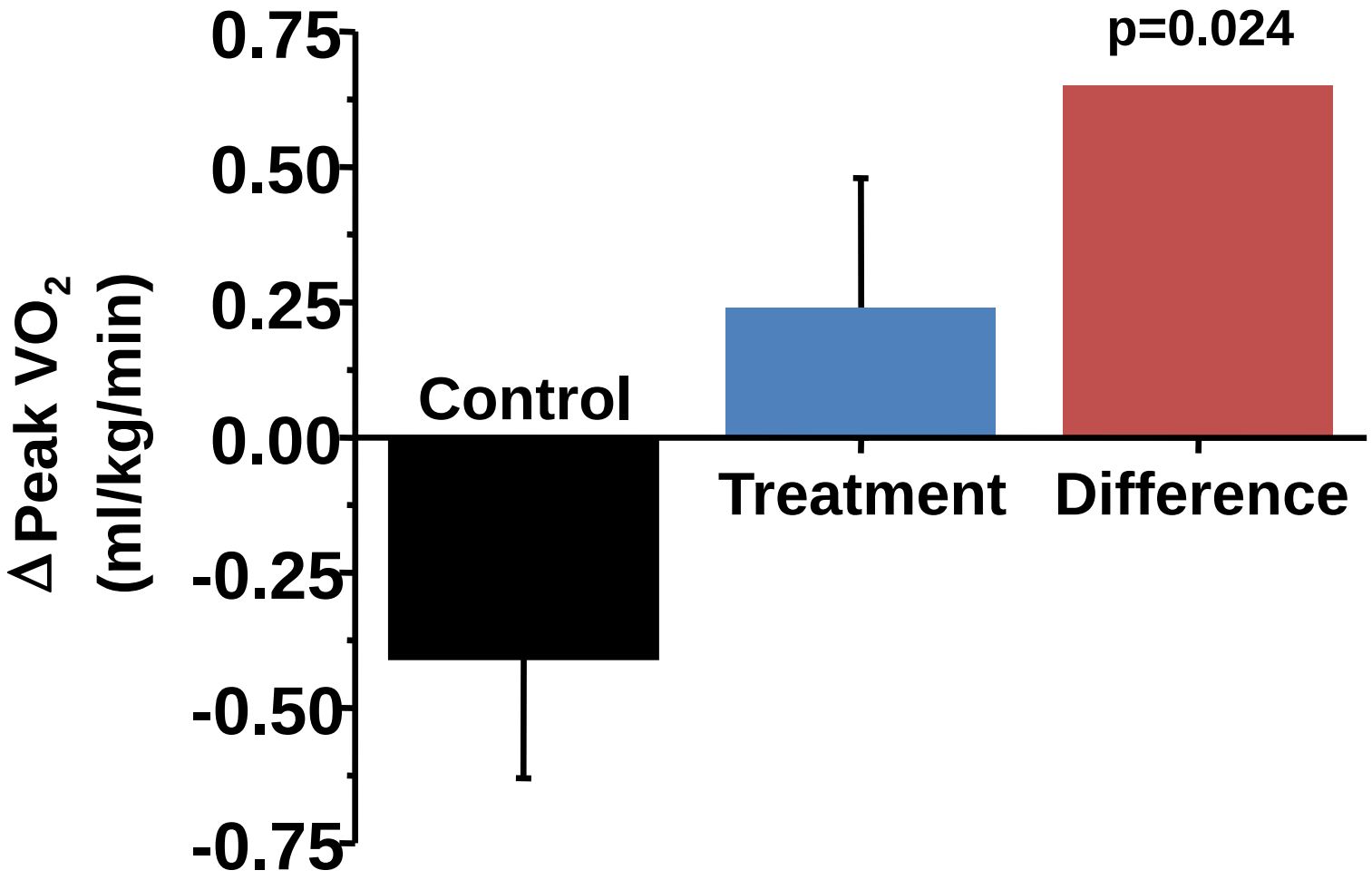


SERCA 2A	a-MHC	PLB	RyR2	ANP	BNP	NCX	P38 MAPK	P21 RAS
p=0.005	p<0.001	p=0.002	p<0.001	p=0.001	p=0.0003	p=0.030	p=0.005	p=0.044

Adapted from Butter, JACC 2008 FIX-HF-4 (N=11 patients); Group 1: Therapy On > Off (n=7); Group 2: Therapy Off to On (n=4)

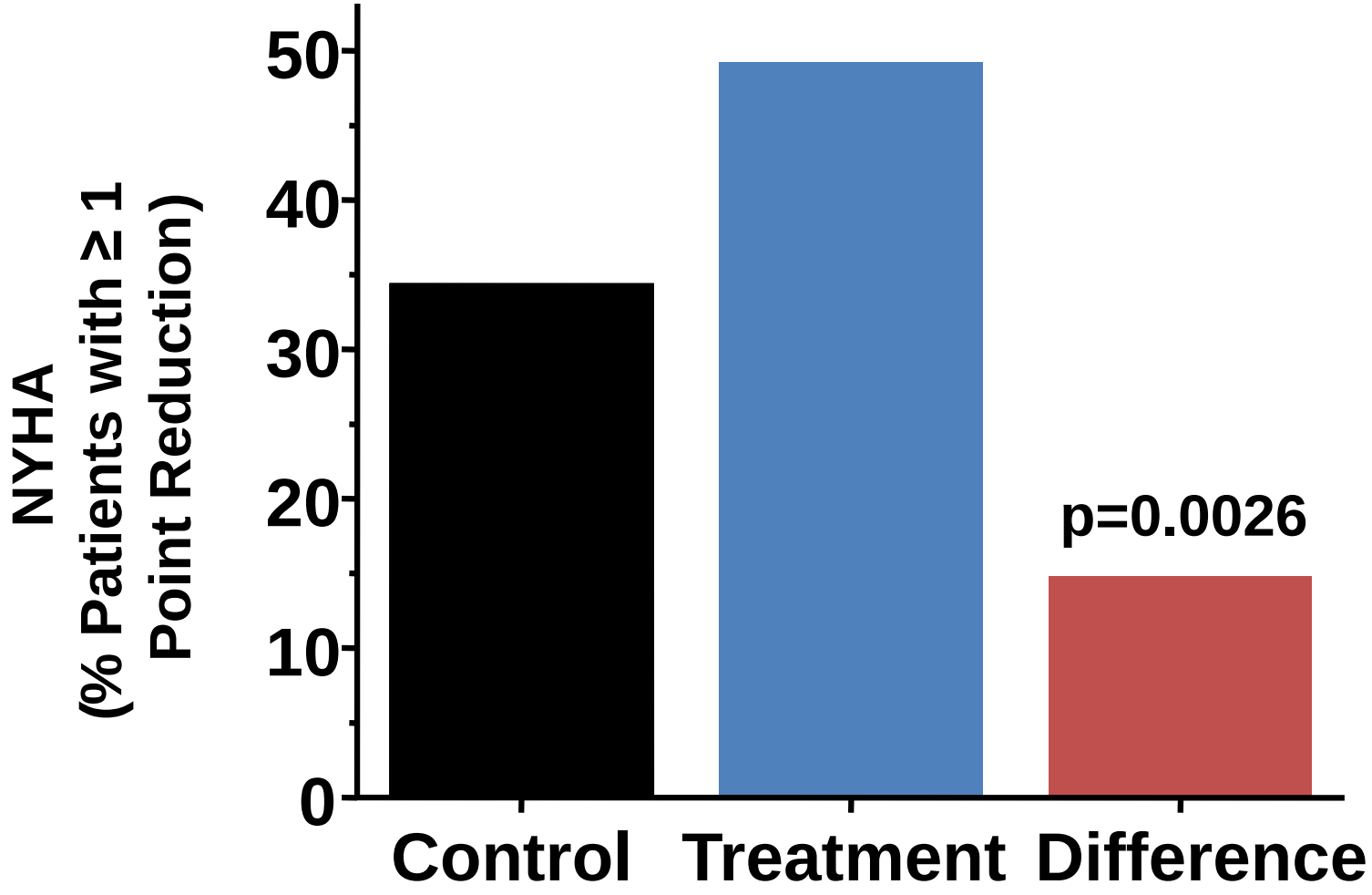
FIX-HF-5:Secondary Efficacy Endpoint

Peak VO_2 Comparison of Mean Change



FIX-HF-5: Other Efficacy Endpoint

Change in NYHA Functional Class



Cardiac Contractility Modulation

Indications

The OPTIMIZER Smart System which delivers Cardiac Contractility Modulation therapy is indicated and FDA approved to:

1. Improve functional status (Peak Vo2)
2. Improve 6-minute hall walk distance, and
3. Improve quality of life for:

NYHA Class III heart failure patients who:

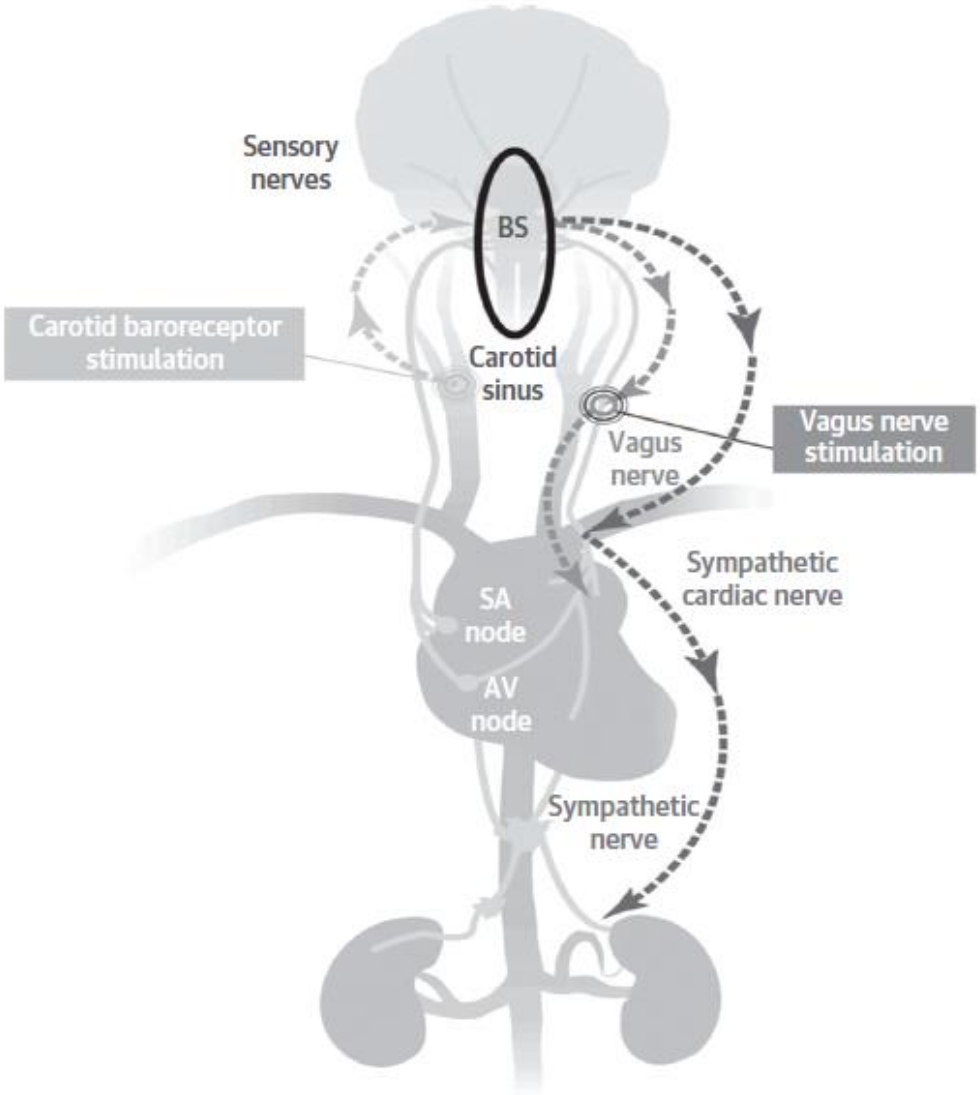
A. Remain symptomatic despite guideline directed medical therapy
B. Are not indicated for Cardiac Resynchronization Therapy, and
C. Have a left ventricular ejection fraction ranging from 25% to 45%.

To date no benefits in clinical trials for death or hospitalizations have been observed

Autonomic Modulation for Chronic Heart Failure

Autonomic Modulation
Baroreflex Activation Therapy

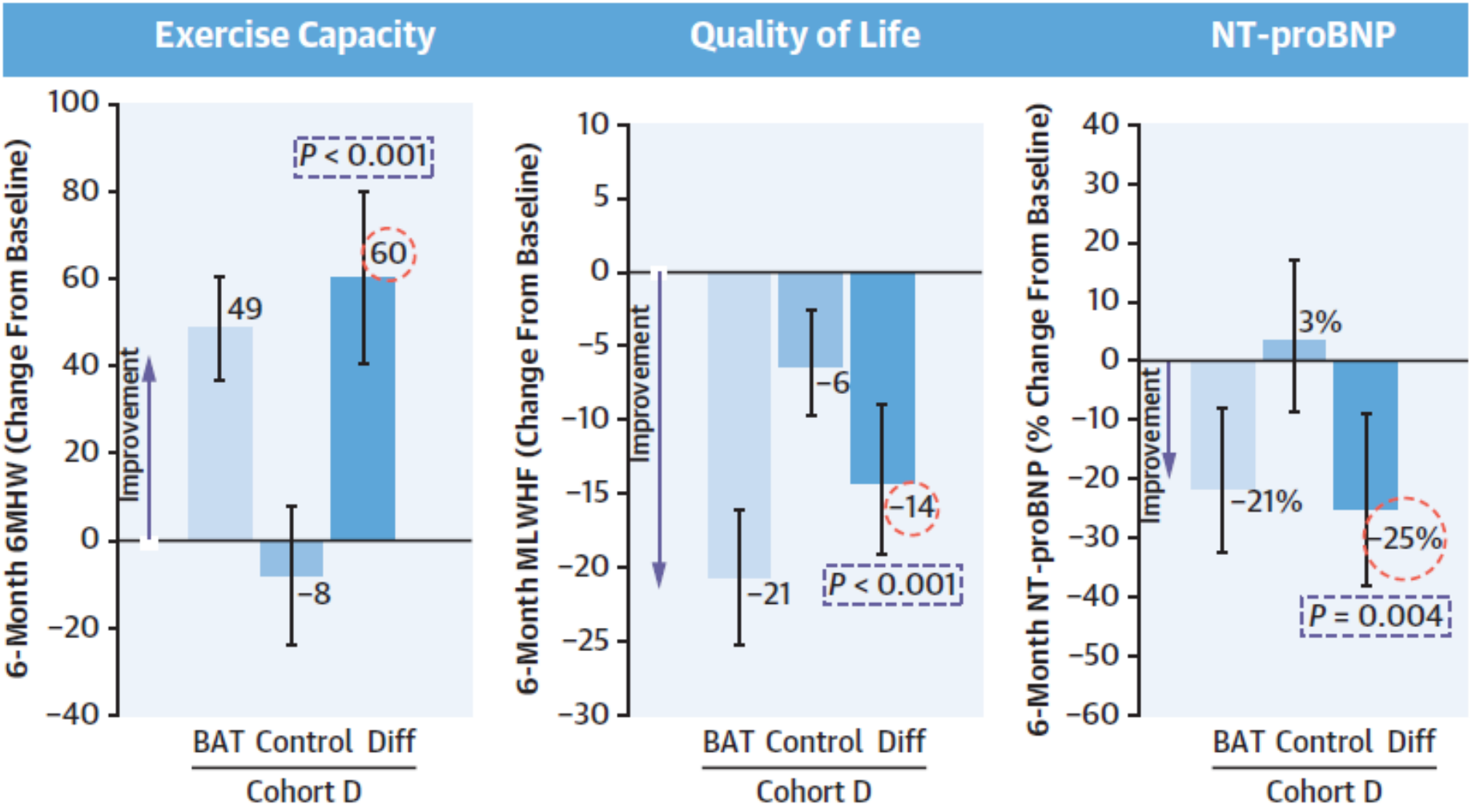
Baroreflex activation therapy (BAT) stimulates the carotid baroreceptor by electrical impulses from an implanted pulse generator (in the pectoral region) resulting in a centrally mediated decrease in sympathetic activity and an increase in the parasympathetic outflow.



Fudim M, et al. J Am Coll Cardiol. 2021;78(9):931-956.

Autonomic Modulation: Baroreflex Activation Therapy: BAROSTIM

HOPE4HF - 146 patients; BeAT-HF- 408 patients



Fudim M, et al. J Am Coll Cardiol. 2021;78(9):931-956.

Autonomic Modulation: BAROSTIM

FDA Approval

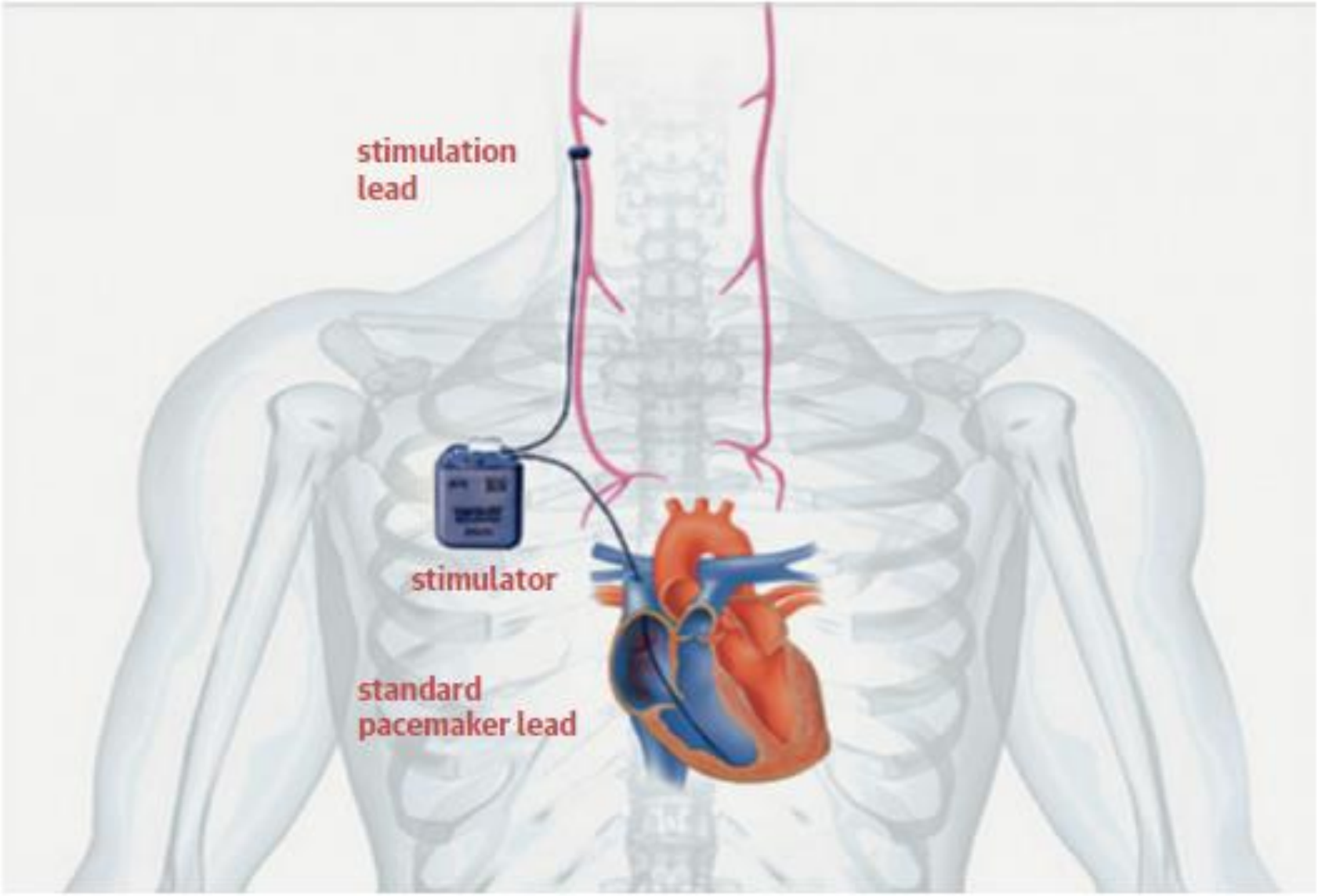
The BAROSTIM NEO System is indicated for the improvement of symptoms of heart failure:

- Quality of life
- Six-minute hall walk and
- Functional status for:
- Patients who remain symptomatic despite treatment with guideline-directed medical therapy and are;

  NYHA Class III or Class II (who had a recent history of Class III),
  Have a left ventricular ejection fraction <= 35%,
  NT-proBNP < 1600 pg/ml and
  Excluding patients indicated for Cardiac Resynchronization Therapy (CRT)

To date no benefits in clinical trials for death or hospitalizations have been observed

Autonomic Modulation: Vagus Nerve Stimulation – ANTHEM-HF



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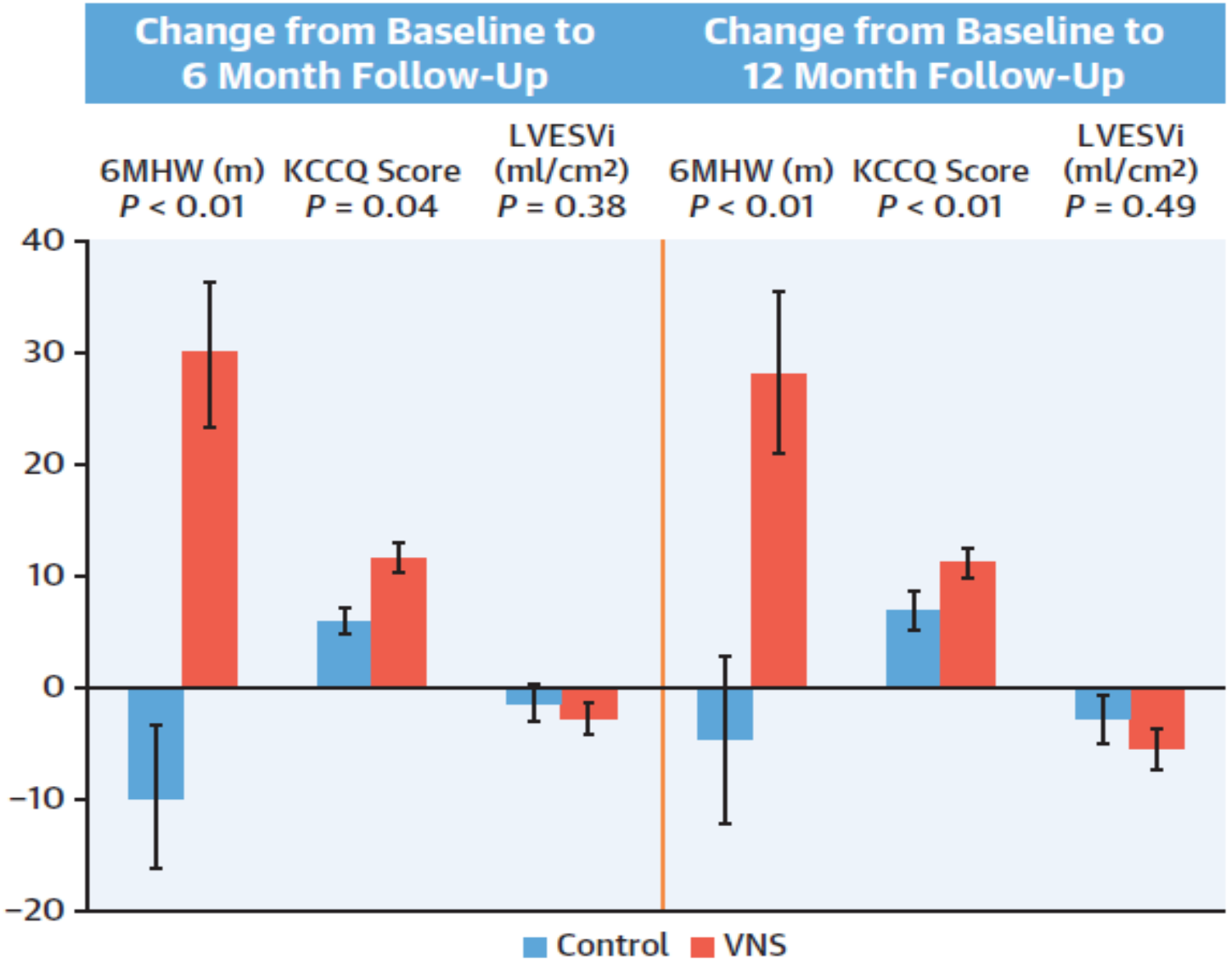
Autonomic Modulation
Vagus Nerve Stimulation – ANTHEM-HF



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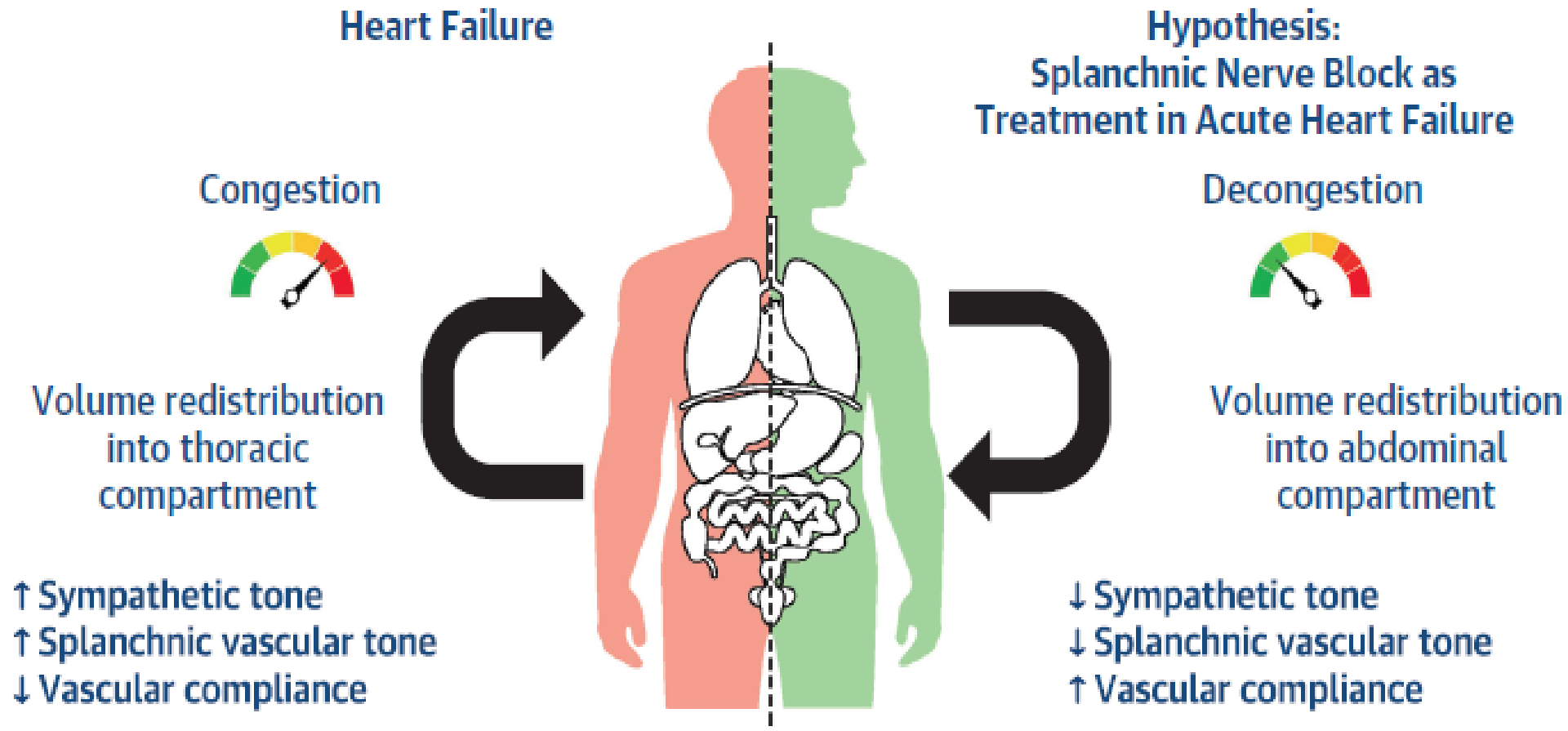
Autonomic Modulation: Splanchnic



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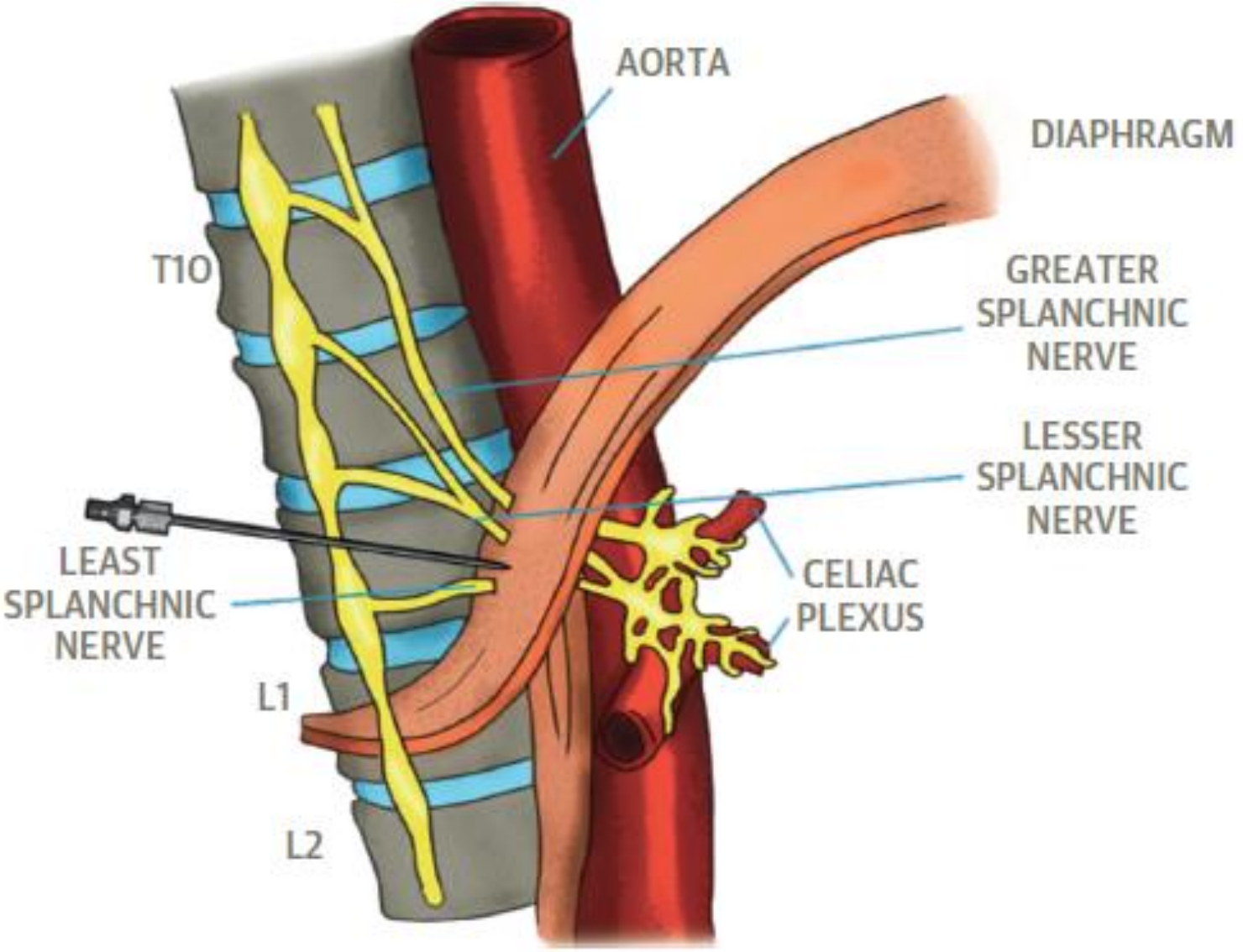
Autonomic Modulation: Splanchnic



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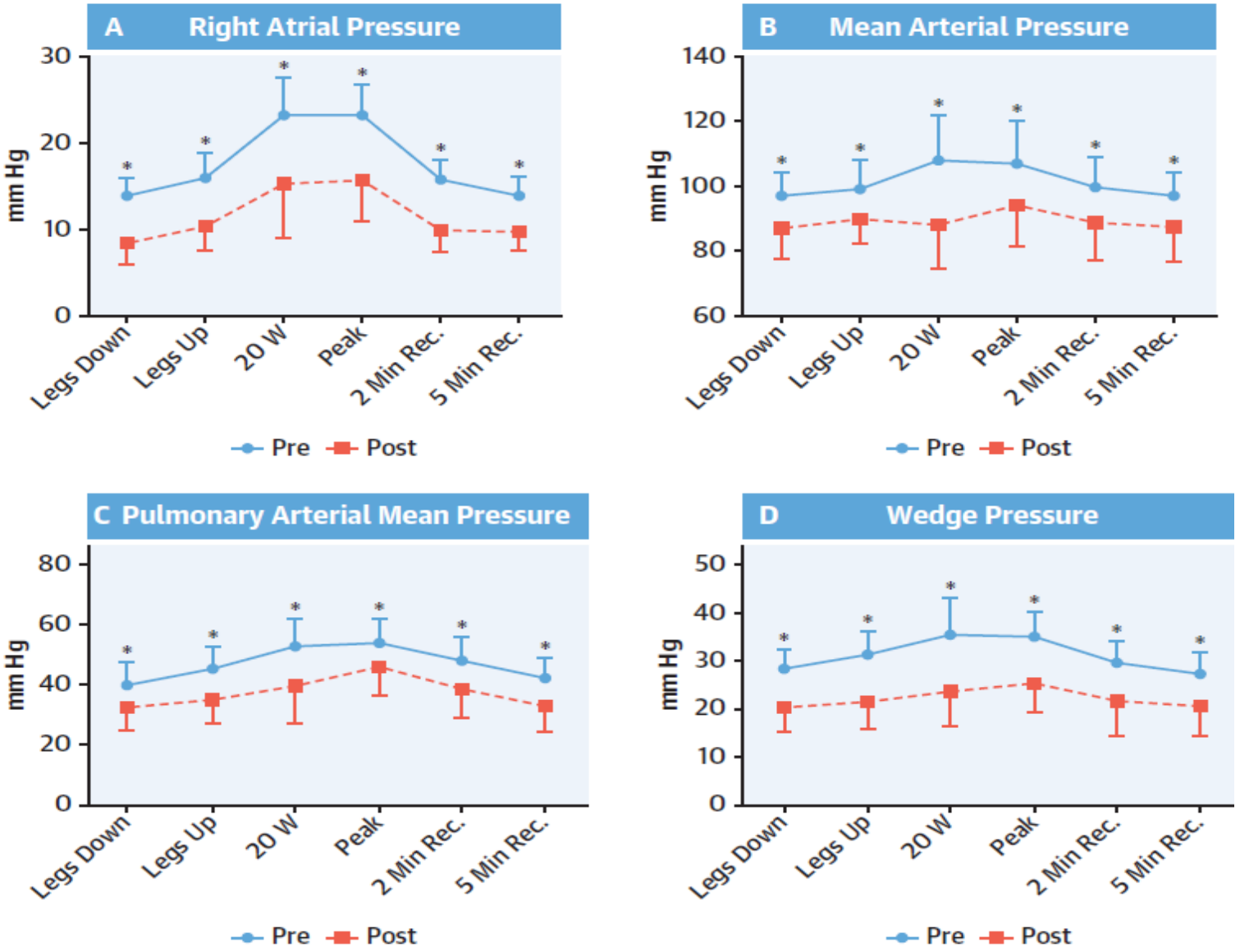
Splanchnic Nerve Blockade



Fudim M, et al. J Am Coll Cardiol. 2021;78(9):931-956.

New Medical and Device Therapies for HF

Medications:

- Soluble Guanylate Cyclase Stimulators: Vericiguat
- Myotropes: Omecamtiv Mecarbil

Devices:

- Cardiac Contractility Modulation
- Autonomic Modulation: Carotid; Vagus; Splanchnic