Congestive Heart Failure: What's Old and New

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Advanced Heart Failure and Transplant Cardiology

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Disclosures

- None related to current topic

Congestive Heart Failure: What's Old and New

Objectives

- Identify established guideline medical therapy in systolic heart failure
- Describe novel therapies in both systolic and diastolic heart failure
- Discuss the role of defibrillators and remote hemodynamic monitoring in the management of heart failure
- Discuss the benefits and outcomes of advanced heart failure therapies

Why it matters

- HF hospitalizations in the US decreased until 2012
- From 2013 to 2017, there was a 26% increase in HF hospitalizations
  - 1.2 million hospitalizations among 924,000 patients in 2017
- Mortality also increasing
  - 275,000 deaths in 2009
  - 310,000 deaths in 2014
- Data from 2000 to 2010 showed 5-year mortality after diagnosis of approximately 50%

Ni H, Xu J. *Recent trends in heart failure-related mortality: United States, 2000-2014*. NCHS Data Brief; 2015:1–8
Agarwal MA, Fonarow GC, Ziaeian B. National trends in heart failure hospitalizations and readmissions from 2010 to 2017.**JAMA Cardiol**. 2021; 6:952–956.
Gerber Y, Weston SA, Redfield MM, et al. A contemporary appraisal of the heart failure epidemic in olmsted county, minnesota, 2000 to 2010. *JAMA Intern Med*. 2015;175(6):996.

Why it matters

- Economic burden is considerable
- Total costs of HF in 2012 was estimated to be $30.7 billion dollars
- By end of 2030, cost is predicted to reach $69.8 billion dollars
- Driven by:
  - Aging population
  - Increase risk factors
    - Obesity
    - HTN
    - DM
    - CAD

Benjamin E, Muntner P, Alonso A, et al; Heart disease and stroke statistics – 2019 update: a report from the American Heart Association. *Circulation*. 2019;139(10):e56-e528. doi: 10.1161/CIR.0000000000000659
Albert N, Swindle J, Buysman E, Chang C. Lower hospitalization and healthcare costs with sacubitril/valsartan versus angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker in a retrospective analysis of patients with heart failure. *J Am Heart Assoc*. 2019;8(9):e011089. doi: 10.1161/JAHA.118.011089

Definitions

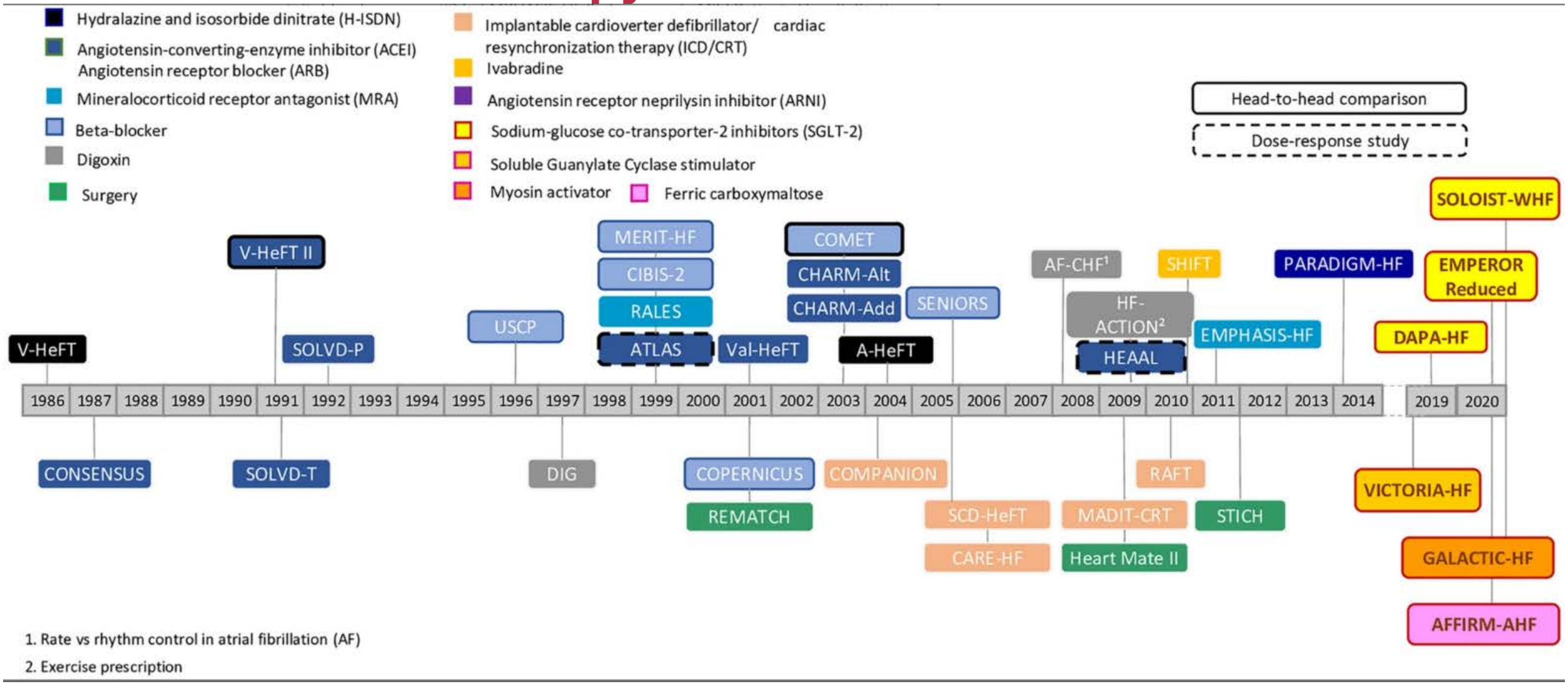
NYHA grading		MET*
Class I	No limitations. Ordinary physical activity does not cause undue fatigue, dyspnoea or palpitations (asymptomatic LV dysfunction).	>7
Class II	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnoea or angina pectoris (mild CHF).	5
Class III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms (moderate CHF).	2–3
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of CHF present at rest (severe CHF).	1.6

*MET (metabolic equivalent) is defined as the resting VO_2 for a 40-year-old 70kg man.[1] MET = 3.5mL O_2/min/kg body weight.

Reproduced from: National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (Chronic Heart Failure Guidelines Expert Writing Panel). Guidelines for the prevention, detection and management of chronic heart failure in Australia. *Updated October 2011*

Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 aha/acc/hfsa guideline for the management of heart failure: a report of the american college of cardiology/american heart association joint committee on clinical practice guidelines. *Circulation*. 2022;145(18).

Heart Failure Therapy Trials



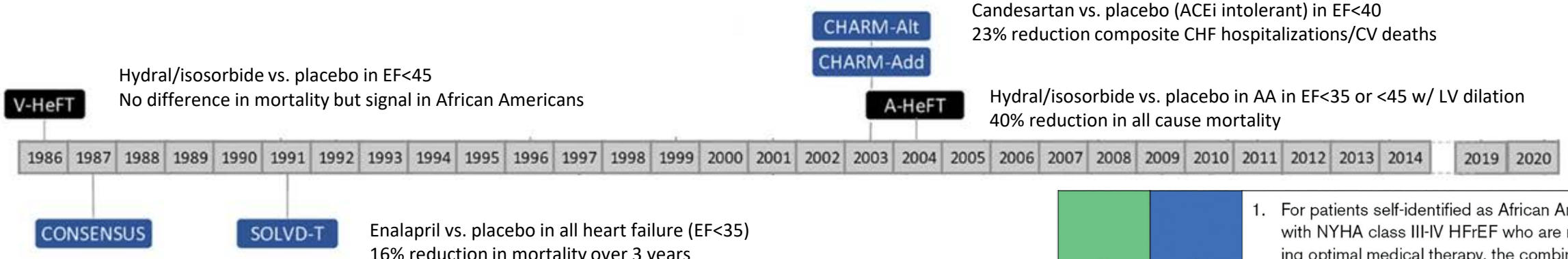
Tomasoni D, Adamo M, Anker MS, Haehling S, Coats AJS, Metra M. Heart failure in the last year: progress and perspective. ESC Heart Failure. 2020;7(6):3505-3530.

Classic Medical Therapy

ACEi/ARB and hydralazine/isosorbide dinitrate

- Hydralazine and isosorbide dinitrate (H-ISDN)
- Angiotensin-converting-enzyme inhibitor (ACEI) Angiotensin receptor blocker (ARB)
- Mineralocorticoid receptor antagonist (MRA)
- Beta-blocker
- Digoxin
- Surgery
- Implantable cardioverter defibrillator/ cardiac resynchronization therapy (ICD/CRT)
- Ivabradine
- Angiotensin receptor neprilysin inhibitor (ARNI)
- Sodium-glucose co-transporter-2 inhibitors (SGLT-2)
- Soluble Guanylate Cyclase stimulator
- Myosin activator
- Ferric carboxymaltose

1	A	1. In patients with LVEF ≤40%, ACEi should be used to prevent symptomatic HF and reduce mortality.[1–4]



Candesartan vs. placebo (ACEi intolerant) in EF<40
23% reduction composite CHF hospitalizations/CV deaths

Hydral/isosorbide vs. placebo in EF<45
No difference in mortality but signal in African Americans

Hydral/isosorbide vs. placebo in AA in EF<35 or <45 w/ LV dilation
40% reduction in all cause mortality

Enalapril vs. placebo in all heart failure (EF<35)
16% reduction in mortality over 3 years

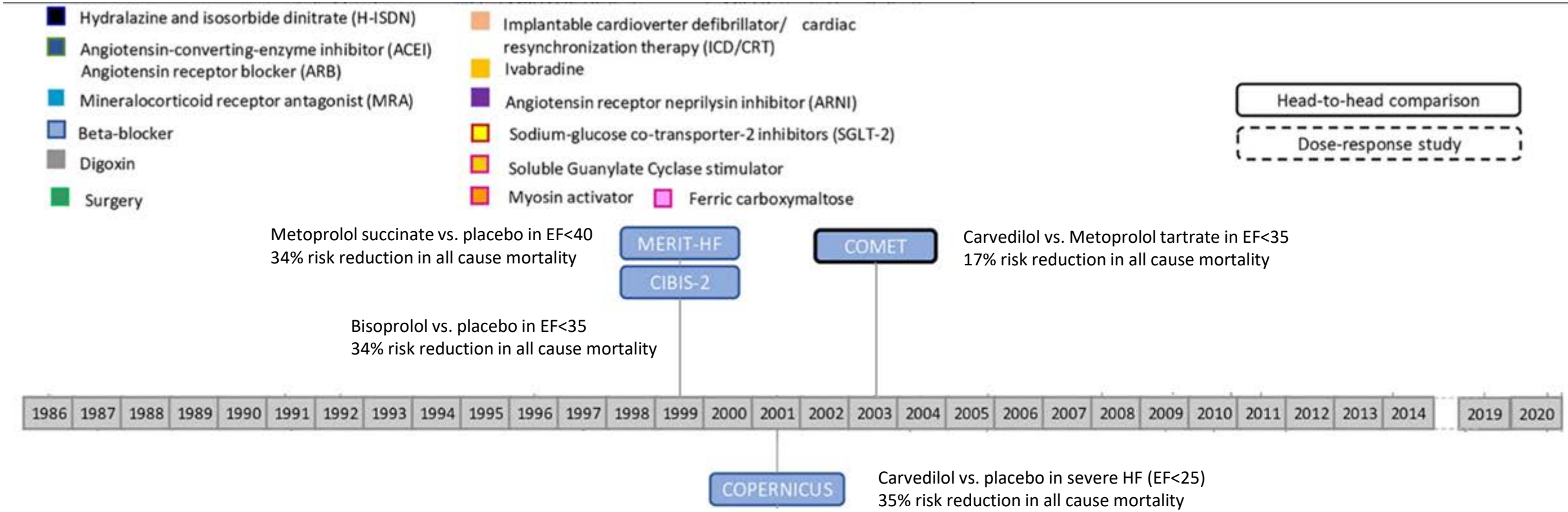
Enalapril vs. placebo in NYHA IV
40% reduction in mortality at 6 months

1	A	1. For patients self-identified as African American with NYHA class III-IV HFrEF who are receiving optimal medical therapy, the combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality.[1,2]
2b	C-LD	3. In patients with current or previous symptomatic HFrEF who cannot be given first-line agents, such as ARNi, ACEi, or ARB, because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate might be considered to reduce morbidity and mortality.[4,5]

Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 aha/acc/hfsa guideline for the management of heart failure: a report of the american college of cardiology/american heart association joint committee on clinical practice guidelines. *Circulation*. 2022;145(18).

Classic Medical Therapy

Beta Blockers

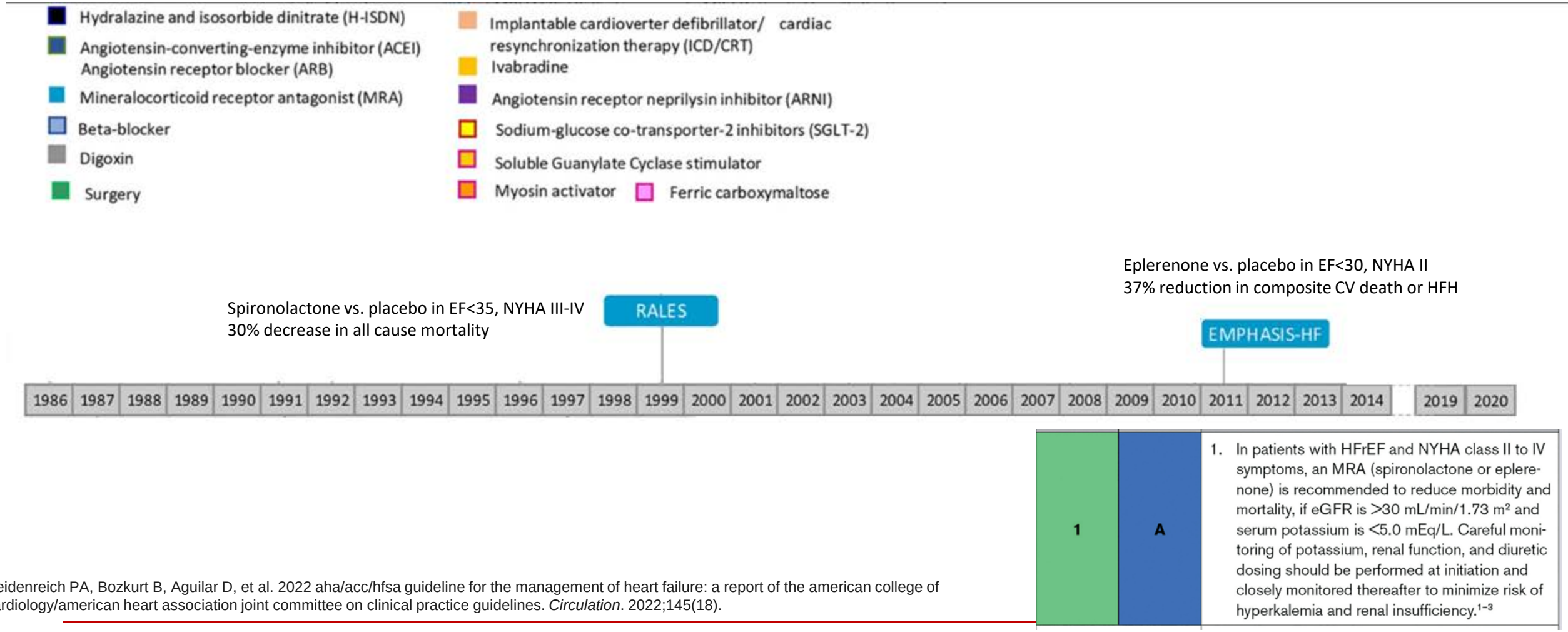


1	C-LD	6. In patients with LVEF ≤40%, beta blockers should be used to prevent symptomatic HF.[12,13]

Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 aha/acc/hfsa guideline for the management of heart failure: a report of the american college of cardiology/american heart association joint committee on clinical practice guidelines. *Circulation*. 2022;145(18).

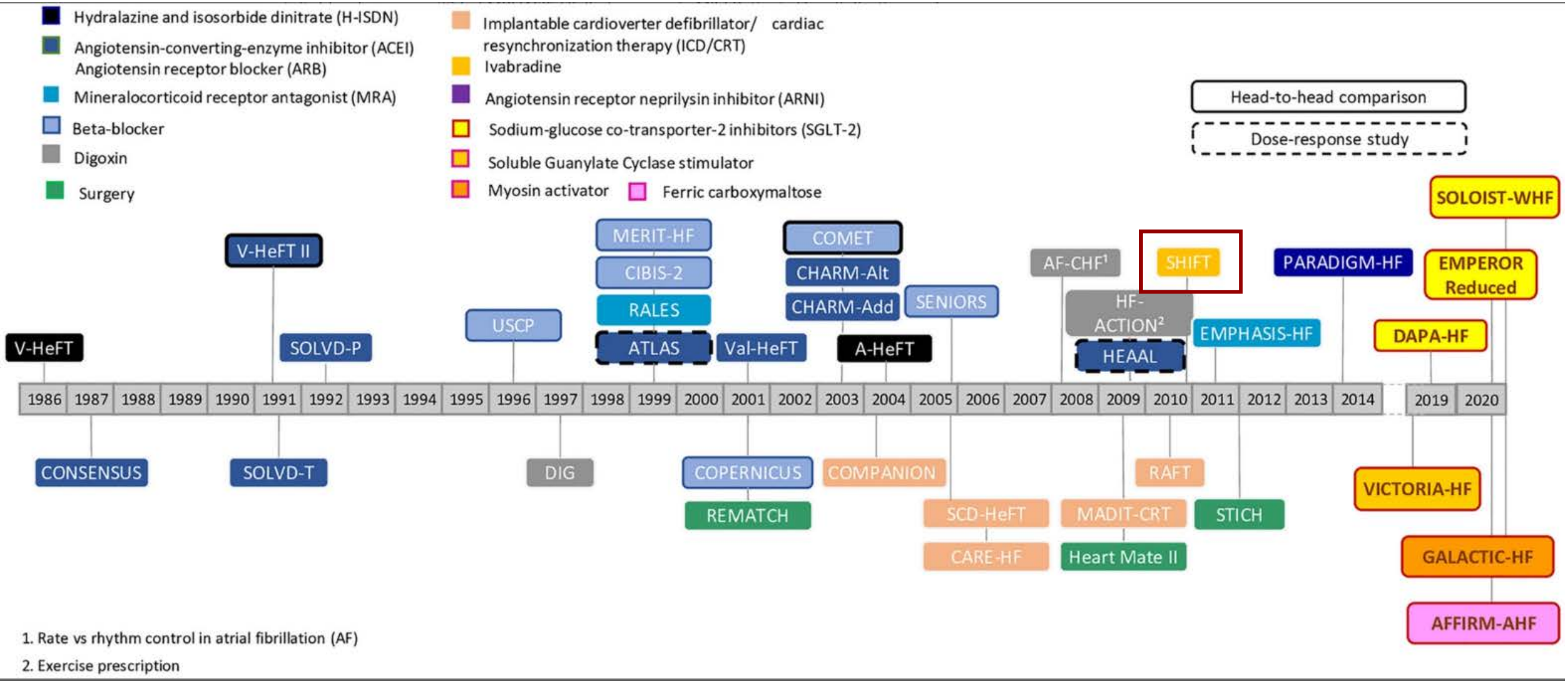
Classic Medical Therapy

Mineralocorticoid Receptor Antagonists



Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 aha/acc/hfsa guideline for the management of heart failure: a report of the american college of cardiology/american heart association joint committee on clinical practice guidelines. *Circulation*. 2022;145(18).

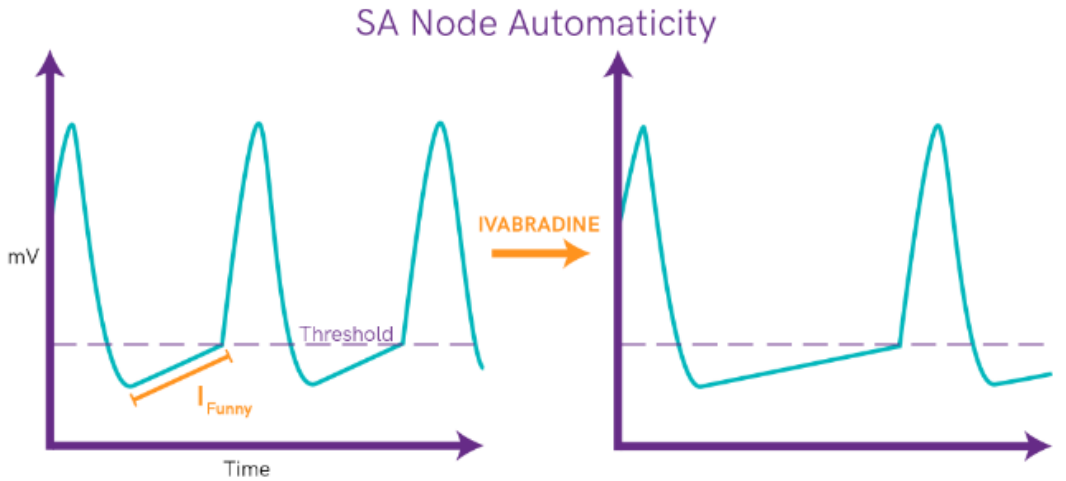
Ivabradine



1. Rate vs rhythm control in atrial fibrillation (AF)
2. Exercise prescription

Ivabradine

- Inhibits “funny current (I_f)” in the sinoatrial node
- Decreased chronotropy
- Does not decrease myocardial inotropy unlike beta blockers
- Can reducing heart rate improve outcomes in heart failure patients?



Swedbug K, Komajda M, Bohm M, et al. The Lancet. 2010; 376(9744): 875-885

Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

*Karl Swedberg, Michel Komajda, Michael Böhm, Jeffrey S Borer, Ian Ford, Ariane Dubost-Brama, Guy Lerebours, Luigi Tavazzi, on behalf of the SHIFT Investigators**

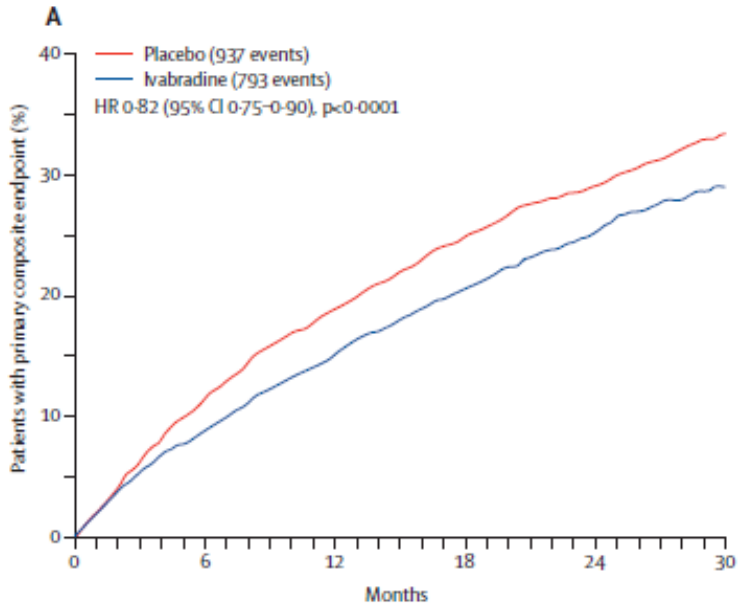
Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (Shift): a randomised placebo-controlled study. *Lancet*. 2010;376(9744):875-885.

SHIFT Trial

- Major inclusion criteria:
  - LVEF < 35%
  - Sinus rhythm, HR > 70 bpm
  - On maximally tolerated GDMT (ACE/ARB, BB and MRA)
- Randomized to either ivabradine or placebo
- Primary endpoint: composite cardiovascular death or HF hospitalization
- Enrolled 6558 patients between 2006 and 2010

SHIFT Trial

- 18% reduction in primary endpoint in ivabradine group (HR 0.82, p <0.0001)
  - Driven by decrease in heart failure hospitalization (HR 0.74, p<0.0001)
  - No difference in all cause mortality (p = 0.092)



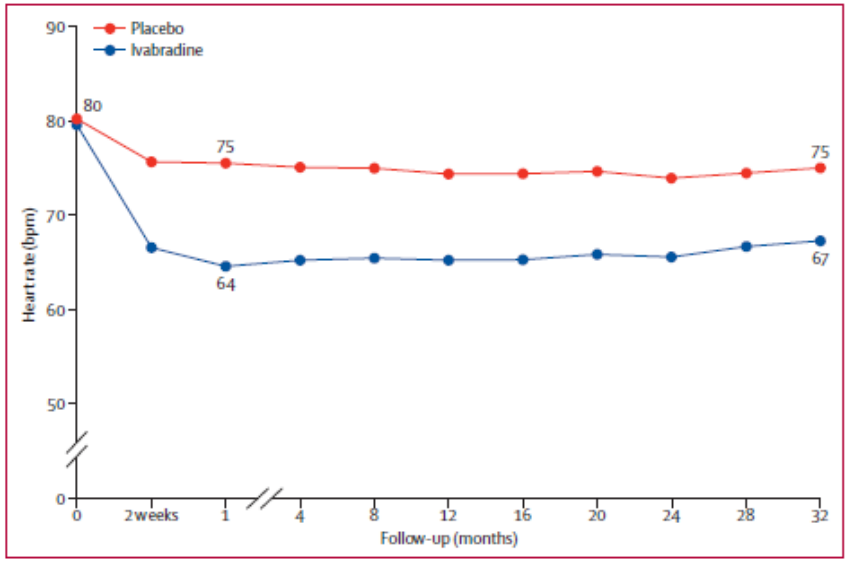
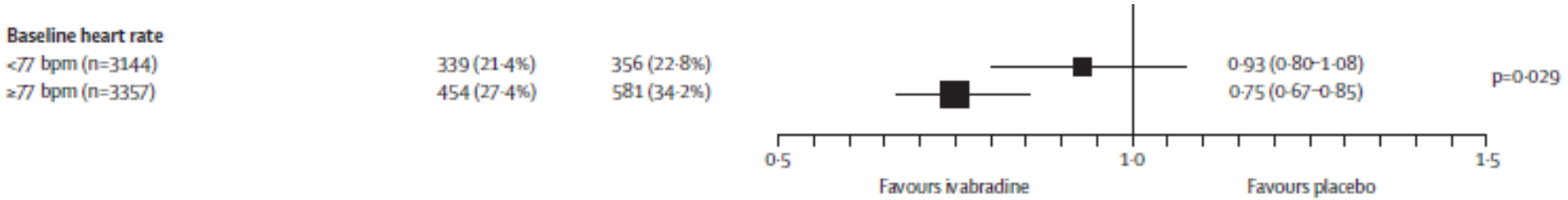


Figure 2: Mean heart rate during the study in the total study population, by allocation groups

SHIFT Trial

- Benefit seen in those with baseline HR > 77



SHIFT Trial

GDMT	Ivabradine N=3241	Placebo N=3264
β-blocker, %*	89	90
At least ½ target dose	55	56
At target dose	26	26
ACEi / ARB, %	93	92
Diuretics, %	84	83
Aldosterone antagonists, %	61	59

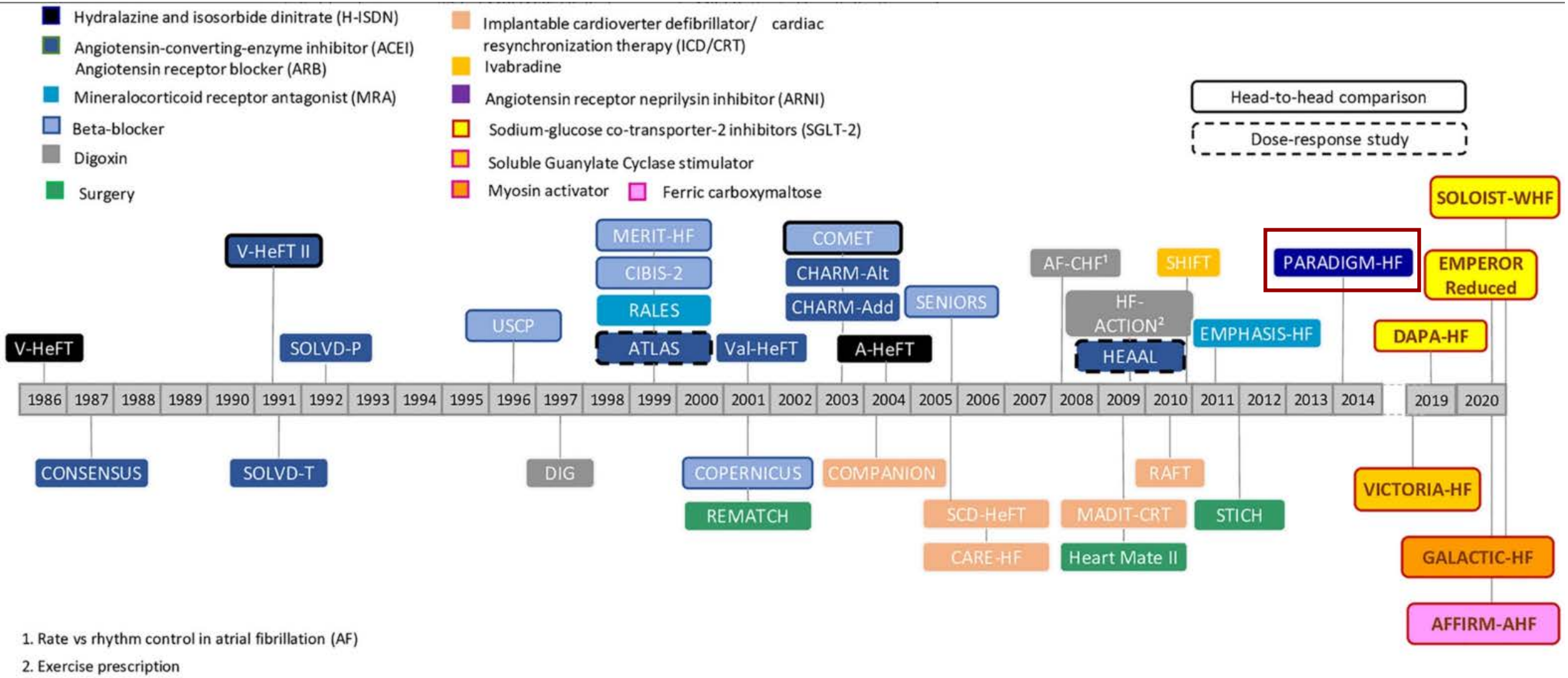
*Most common reasons for not reaching target dose: Hypotension (44%), fatigue (32%), dyspnea (14%), and dizziness (13%).

Ivabradine

- Approved by FDA in 2015 for use in heart failure
- Indicated for those with:
  - LVEF < 35%
  - Sinus rhythm, resting HR > 70 bpm
  - On max tolerated beta blocker
- **Not meant to be a substitute for beta blocker**
- **Not indicated for HFpEF patients**

COR	LOE	Recommendation
2a	B-R	1. For patients with symptomatic (NYHA class II to III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDMT, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of ≥70 bpm at rest, ivabradine can be beneficial to reduce HF hospitalizations and cardiovascular death.[1,2]

Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 aha/acc/hfsa guideline for the management of heart failure: a report of the american college of cardiology/american heart association joint committee on clinical practice guidelines. *Circulation*. 2022;145(18).



1. Rate vs rhythm control in atrial fibrillation (AF)
2. Exercise prescription

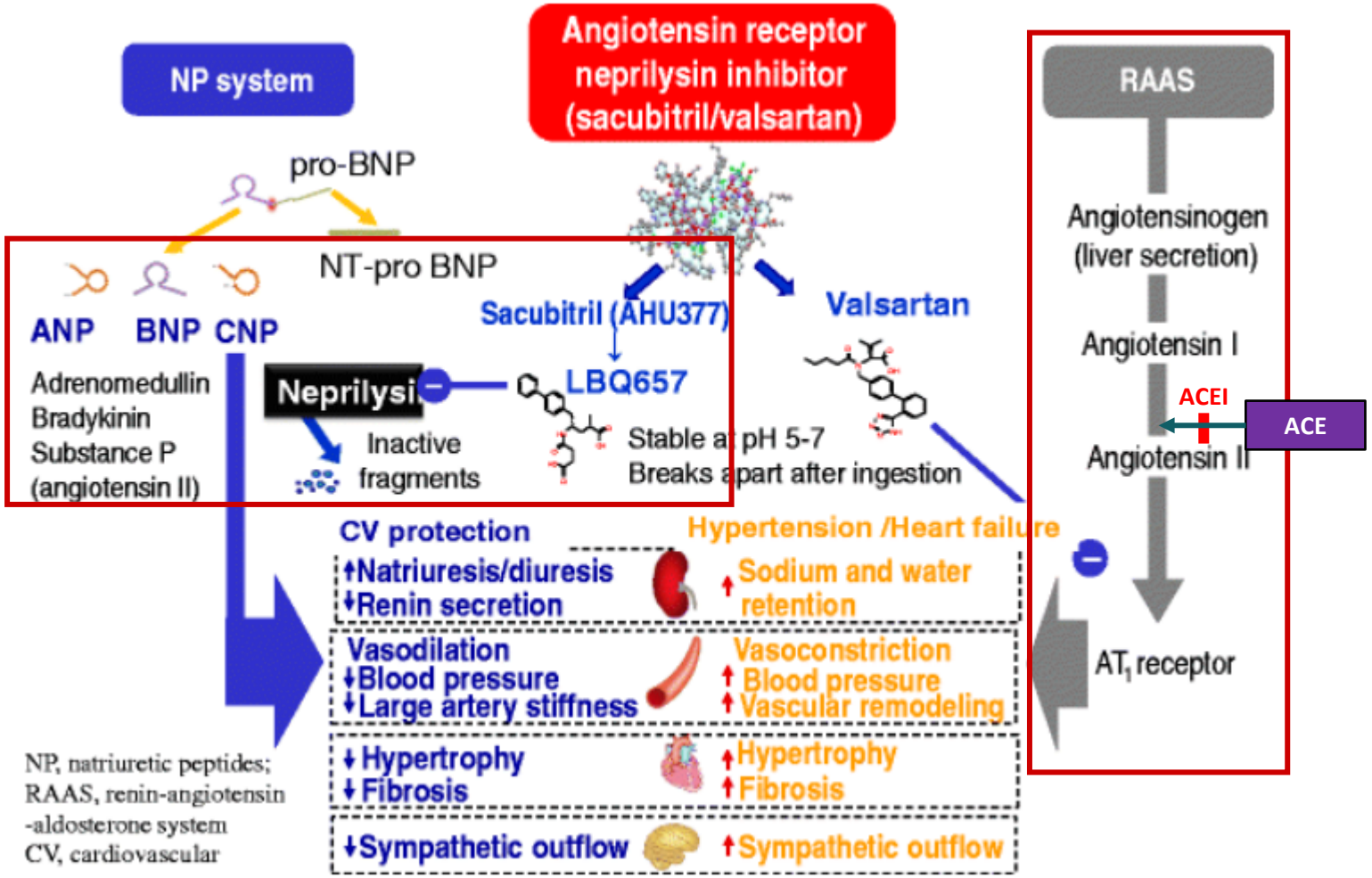
Angiotensin-Neprilysin Inhibitors (ARNI)

- Two drugs:
  - Sacubitril: neprilysin inhibitor
  - Valsartan: angiotensin receptor blocker

https://www.managedhealthcareexecutive.com/view/entresto-gets-broader-indication-from-the-fda

Sacubitril-Valsartan

Mechanism of Action



Kario K. The sacubitril/valsartan, a first-in-class, angiotensin receptor neprilysin inhibitor (Arni): potential uses in hypertension, heart failure, and beyond. *Curr Cardiol Rep*. 2018;20(1):5.

PARADIGM-HF

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

- Multicenter, prospective, randomized trial
- Enrolled 8,399 patients between 2009 and 2012
  - Randomized to ARNi (equivalent to valsartan 160 mg bid) vs. Enalapril (10 mg bid)
- Primary outcome: composite CV mortality or first HF hospitalization

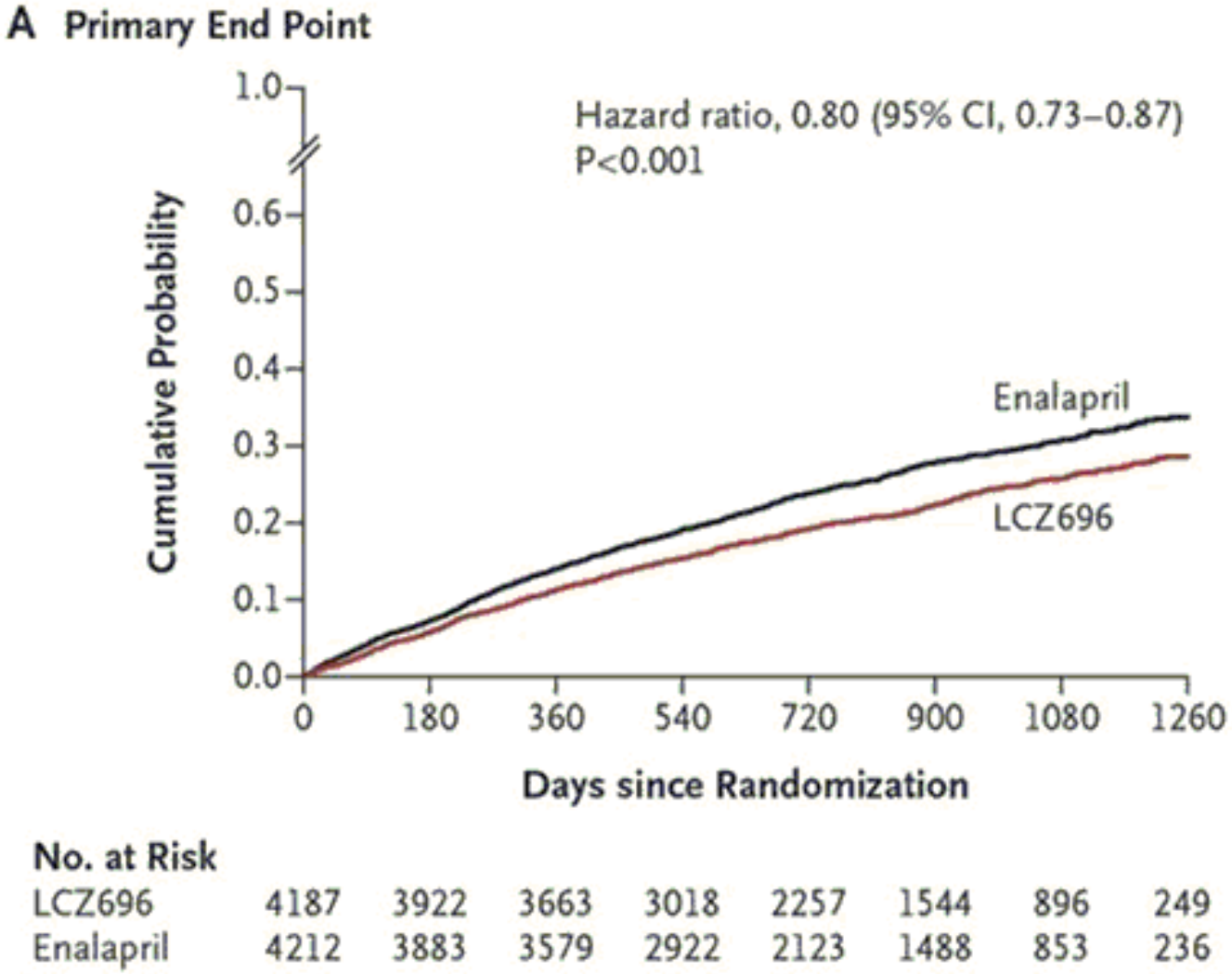
McMurray JJV, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993-1004.

PARADIGM-HF

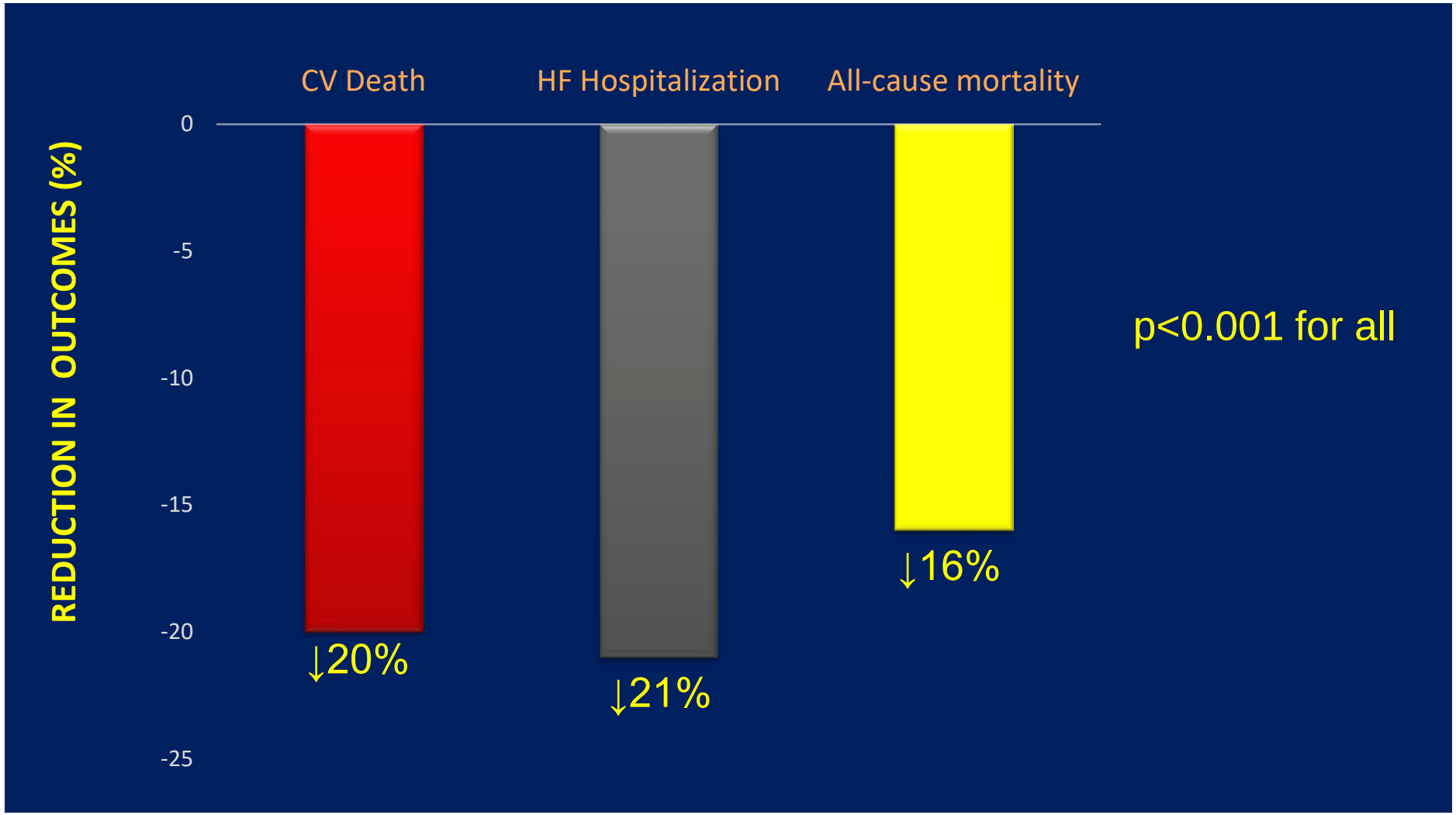
- Inclusion criteria
  - NYHA II-IV
  - LVEF < 40%
  - On stable dose of ACEi or ARB
  - On stable dose of beta blocker
- Exclusion criteria
  - Hypotension
  - eGFR < 30 mL/min/1.73 m2
  - Hyperkalemia (K > 5.2 at screening or > 5.4 at randomization)
  - History of angioedema
  - Intolerant to ACEi or ARB

PARADIGM-HF

- Met primary endpoint
  - HR 0.8, p<0.001
  - 20% reduction in endpoint
  - NNT=21



PARADIGM-HF



PARADIGM-HF

Adverse Events

Table 3. Adverse Events during Randomized Treatment.*

Event	LCZ696 (N=4187)	Enalapril (N=4212)	P Value
	no. (%)		
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with systolic blood pressure <90 mm Hg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dl	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dl	63 (1.5)	83 (2.0)	0.10
Elevated serum potassium			
>5.5 mmol/liter	674 (16.1)	727 (17.3)	0.15
>6.0 mmol/liter	181 (4.3)	236 (5.6)	0.007
Cough	474 (11.3)	601 (14.3)	<0.001
Angioedema†			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19
Use of catecholamines or glucocorticoids without hospitalization	6 (0.1)	4 (0.1)	0.52
Hospitalization without airway compromise	3 (0.1)	1 (<0.1)	0.31
Airway compromise	0	0	—

ARNi

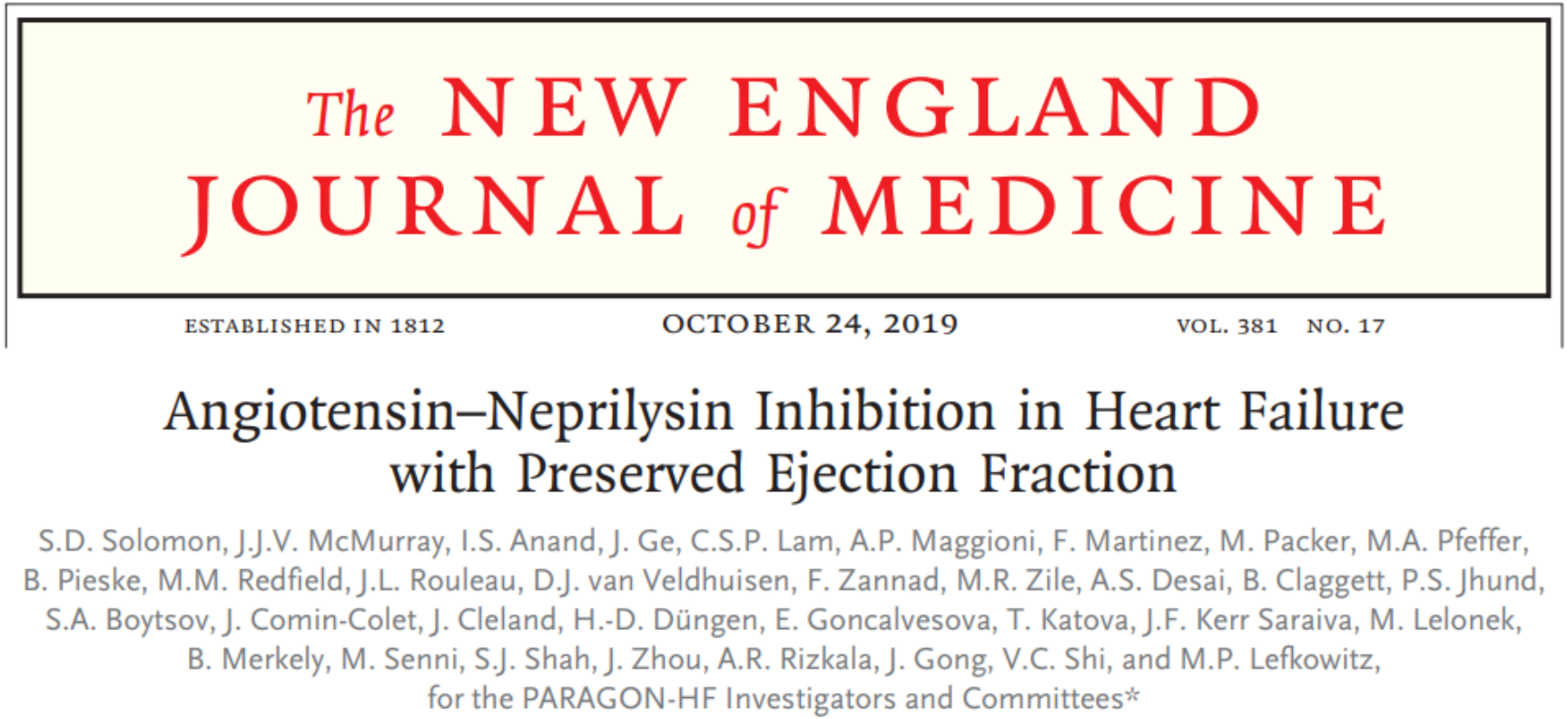
- Contraindications
  - Any history of angioedema
  - Within 36 hours of last dose of ACEi
  - Pregnancy

COR	LOE	Recommendations
1	A	1. In patients with HFrEF and NYHA class II to III symptoms, the use of ARNi is recommended to reduce morbidity and mortality.[1–5]
1	A	2. In patients with previous or current symptoms of chronic HFrEF, the use of ACEi is beneficial to reduce morbidity and mortality when the use of ARNi is not feasible.[6–13]
1	A	3. In patients with previous or current symptoms of chronic HFrEF who are intolerant to ACEi because of cough or angioedema and when the use of ARNi is not feasible, the use of ARB is recommended to reduce morbidity and mortality.[14–18]
Value Statement: High Value (A)		4. In patients with previous or current symptoms of chronic HFrEF, in whom ARNi is not feasible, treatment with an ACEi or ARB provides high economic value.[19–25]
1	B-R	5. In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEi or ARB, replacement by an ARNi is recommended to further reduce morbidity and mortality.[1–5]
Value Statement: High Value (A)		6. In patients with chronic symptomatic HFrEF, treatment with an ARNi instead of an ACEi provides high economic value.[26–29]

Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 aha/acc/hfsa guideline for the management of heart failure: a report of the american college of cardiology/american heart association joint committee on clinical practice guidelines. *Circulation*. 2022;145(18).

PARAGON-HF

- What is the utility in using ARNi in HFpEF patients?



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 24, 2019 VOL. 381 NO. 17

Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, I.S. Anand, J. Ge, C.S.P. Lam, A.P. Maggioni, F. Martinez, M. Packer, M.A. Pfeffer, B. Pieske, M.M. Redfield, J.L. Rouleau, D.J. van Veldhuisen, F. Zannad, M.R. Zile, A.S. Desai, B. Claggett, P.S. Jhund, S.A. Boytsov, J. Comin-Colet, J. Cleland, H.-D. Düngen, E. Goncalvesova, T. Katova, J.F. Kerr Saraiva, M. Lelonek, B. Merkely, M. Senni, S.J. Shah, J. Zhou, A.R. Rizkala, J. Gong, V.C. Shi, and M.P. Lefkowitz, for the PARAGON-HF Investigators and Committees*

Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381(17):1609-1620.

PARAGON-HF

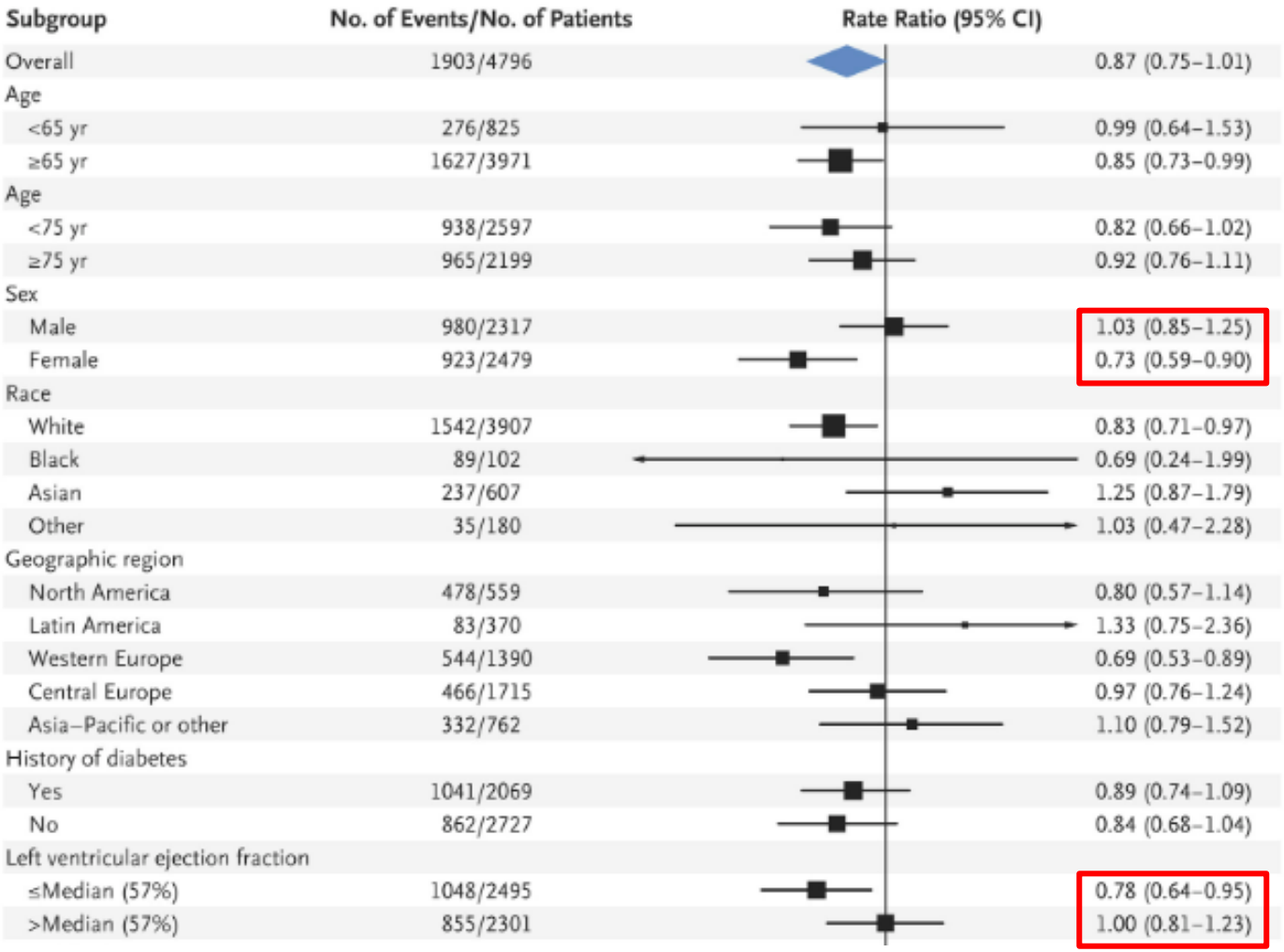
- 4,822 patients randomized to ARNi versus valsartan
- Inclusion criteria
  - LVEF > 45%
  - NYHA II-IV symptoms
  - NT-proBNP > 300 pg/mL (> 900 pg/mL if A-Fib)
- Primary outcome: Composite of total heart failure hospitalizations and CV death

PARAGON-HF

Outcome	Sacubitril–Valsartan (N = 2407)	Valsartan (N = 2389)	Ratio or Difference (95% CI)
Primary composite outcome and components			
Total hospitalizations for heart failure and death from cardiovascular causes†			RR, 0.87 (0.75–1.01)
Total no. of events	894	1009	
Rate per 100 patient-yr	12.8	14.6	
Total no. of hospitalizations for heart failure	690	797	RR, 0.85 (0.72–1.00)
Death from cardiovascular causes — no. (%)	204 (8.5)	212 (8.9)	HR, 0.95 (0.79–1.16)

P=0.06

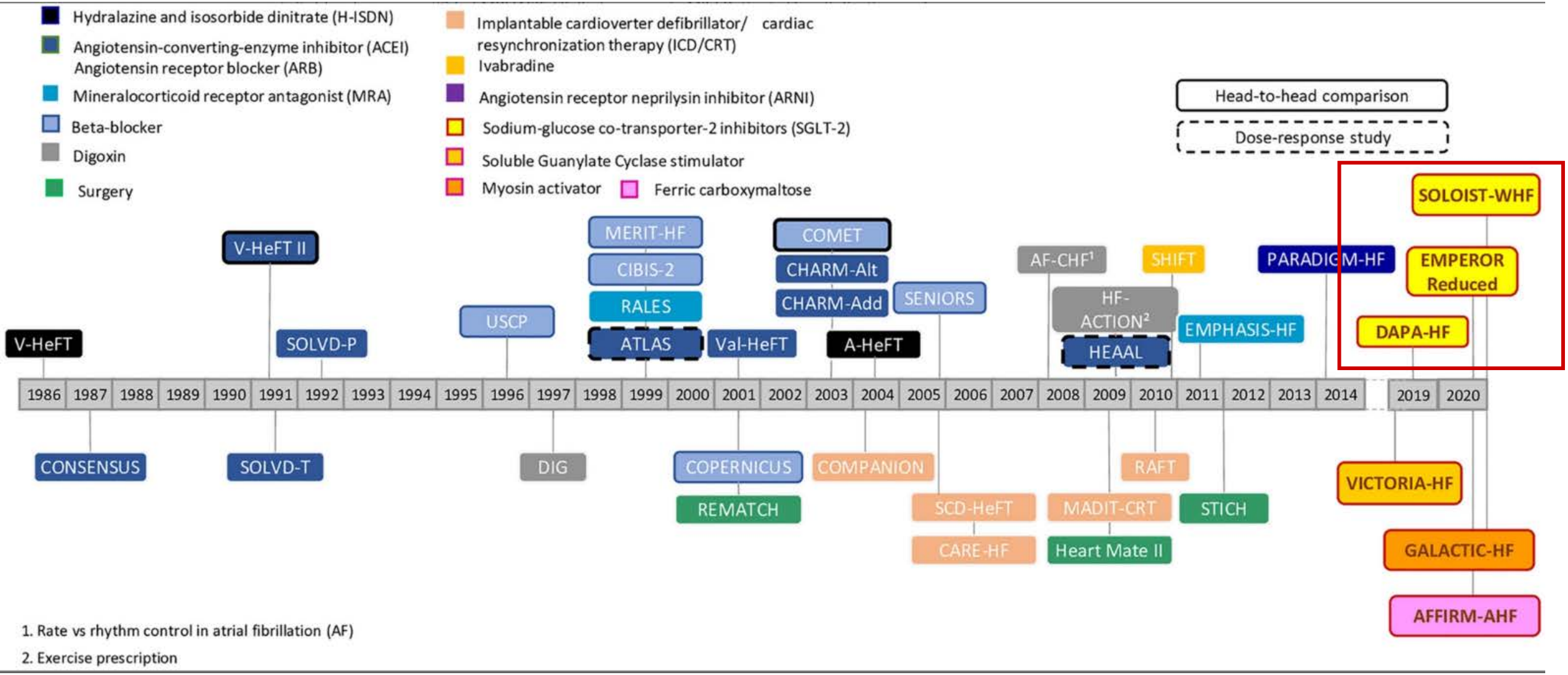
PARAGON-HF



Subgroup	No. of Events/No. of Patients	Rate Ratio (95% CI)
Overall	1903/4796	0.87 (0.75–1.01)
Age		
<65 yr	276/825	0.99 (0.64–1.53)
≥65 yr	1627/3971	0.85 (0.73–0.99)
Age		
<75 yr	938/2597	0.82 (0.66–1.02)
≥75 yr	965/2199	0.92 (0.76–1.11)
Sex		
Male	980/2317	1.03 (0.85–1.25)
Female	923/2479	0.73 (0.59–0.90)
Race		
White	1542/3907	0.83 (0.71–0.97)
Black	89/102	0.69 (0.24–1.99)
Asian	237/607	1.25 (0.87–1.79)
Other	35/180	1.03 (0.47–2.28)
Geographic region		
North America	478/559	0.80 (0.57–1.14)
Latin America	83/370	1.33 (0.75–2.36)
Western Europe	544/1390	0.69 (0.53–0.89)
Central Europe	466/1715	0.97 (0.76–1.24)
Asia–Pacific or other	332/762	1.10 (0.79–1.52)
History of diabetes		
Yes	1041/2069	0.89 (0.74–1.09)
No	862/2727	0.84 (0.68–1.04)
Left ventricular ejection fraction		
≤Median (57%)	1048/2495	0.78 (0.64–0.95)
>Median (57%)	855/2301	1.00 (0.81–1.23)

2b	B-R	6. In selected patients with HFpEF, ARNi may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[10,11]

SGLT-2 Inhibitors

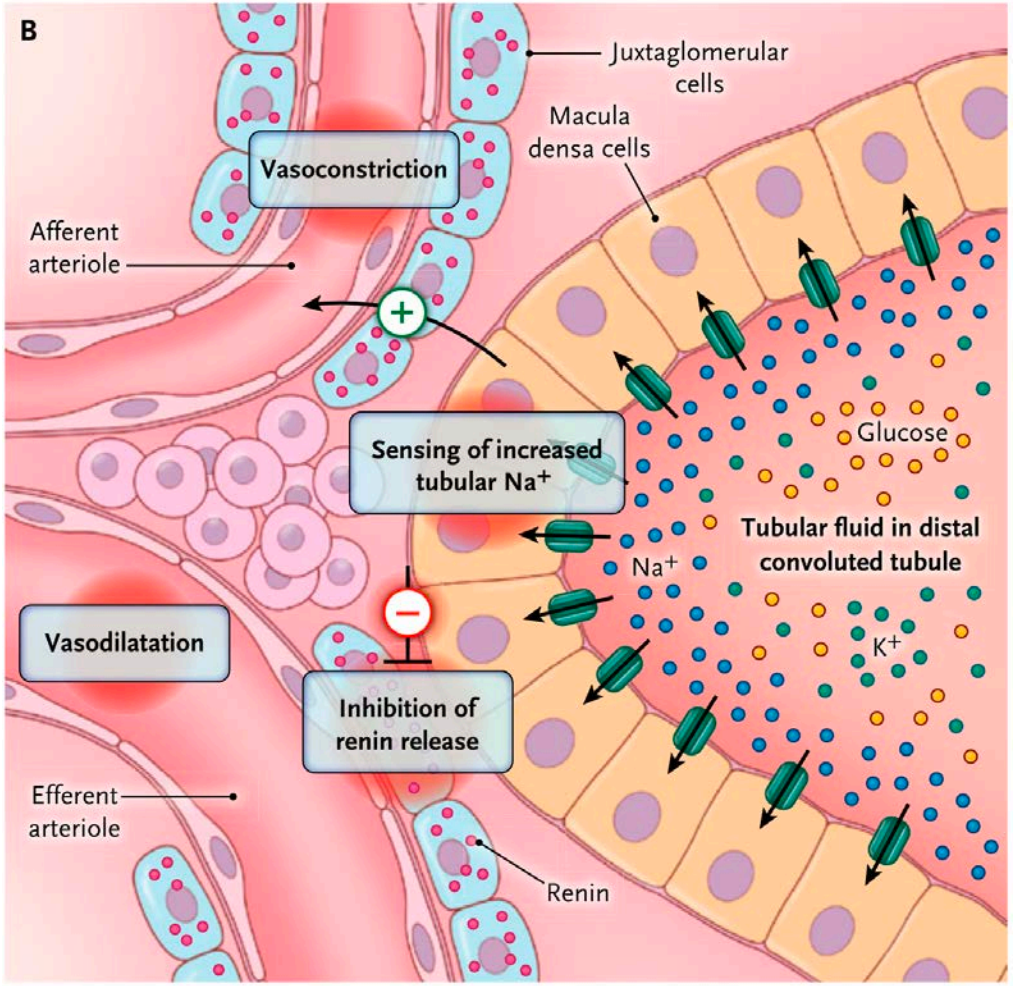


1. Rate vs rhythm control in atrial fibrillation (AF)
2. Exercise prescription

SGLT-2 Inhibitors

Mechanisms of action: Glomerular

- Inhibits SGLT-2
  - Increase glucose and Na in urine
- Macula densa senses increased Na in the DCT
  - Afferent vasoconstriction via tubuloglomerular feedback
  - Macula densa inhibits renin release from juxtaglomerular cells causing efferent vasodilation
- Afferent vasoconstriction + efferent vasodilation leads to acute decrease in eGFR

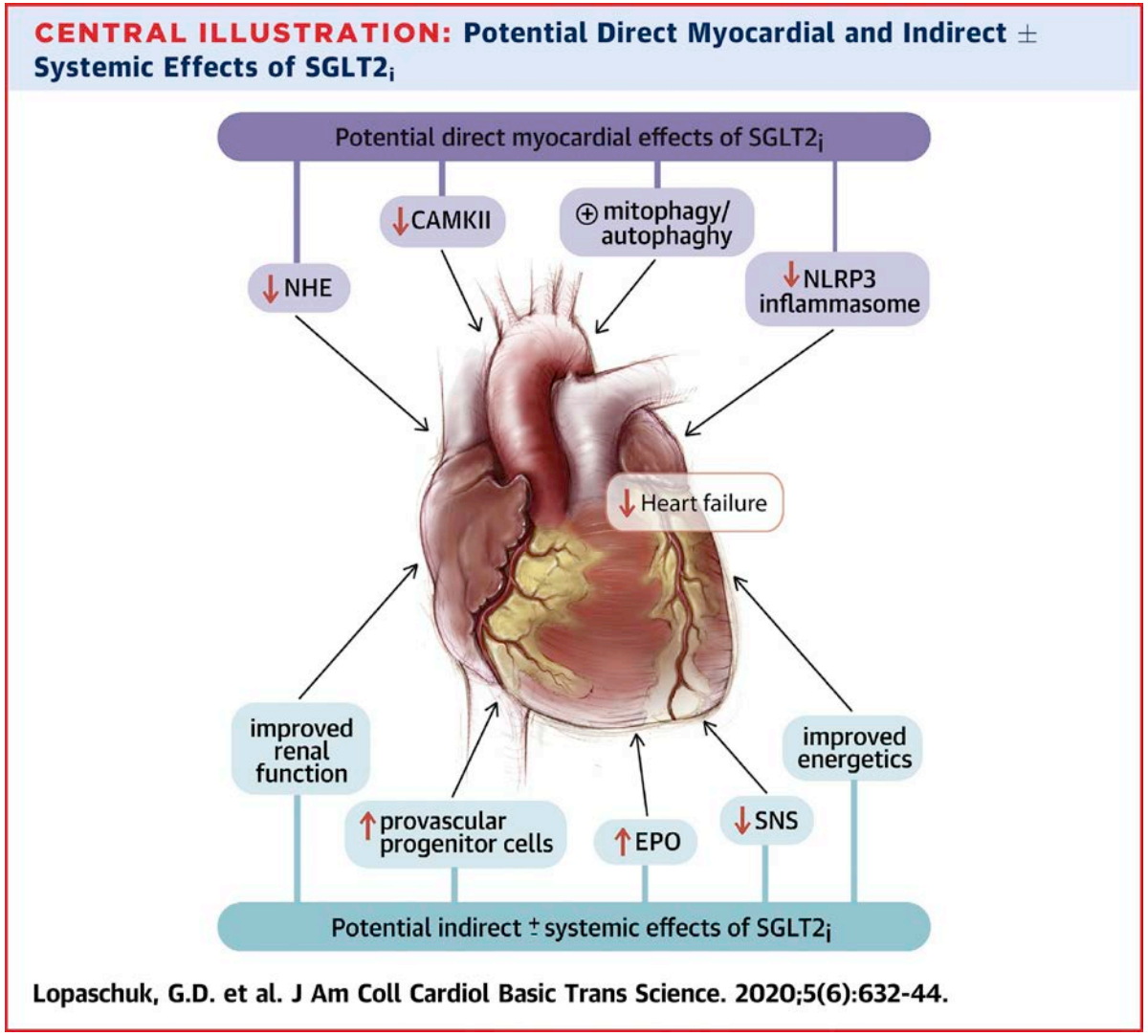


Braunwald E. Gliflozins in the management of cardiovascular disease. Longo DL, ed. *N Engl J Med*. 2022;386(21):2024-2034.

SGLT-2 Inhibitors

Mechanisms of action: Cardiac

- Unclear mechanism
- Many proposed mechanism
- Increase in erythropoietin seems to be important
  - Increase in Hgb independent of volume depletion/hemoconcentration



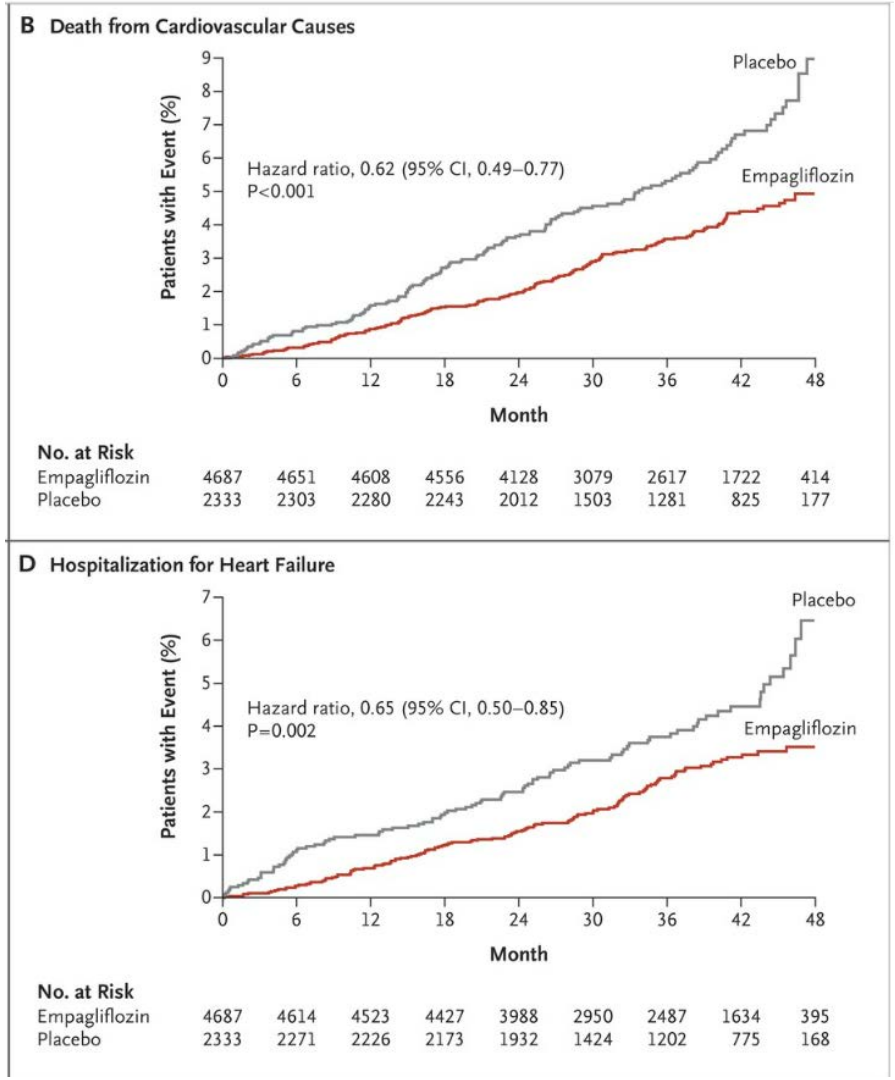
Empagliflozin Cardiovascular Outcomes

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators



Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128.

DAPA-HF

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

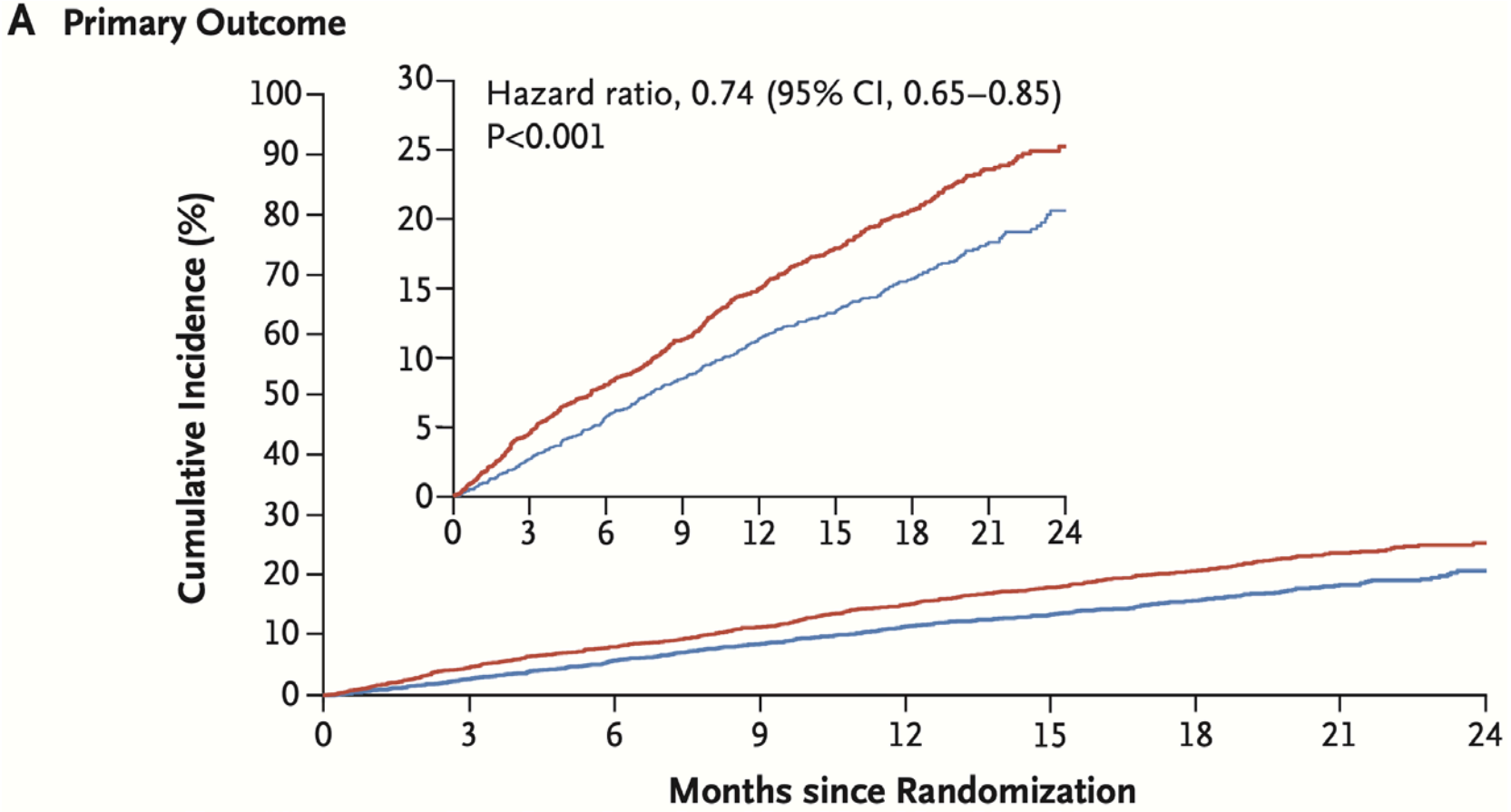
J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381(21):1995-2008.

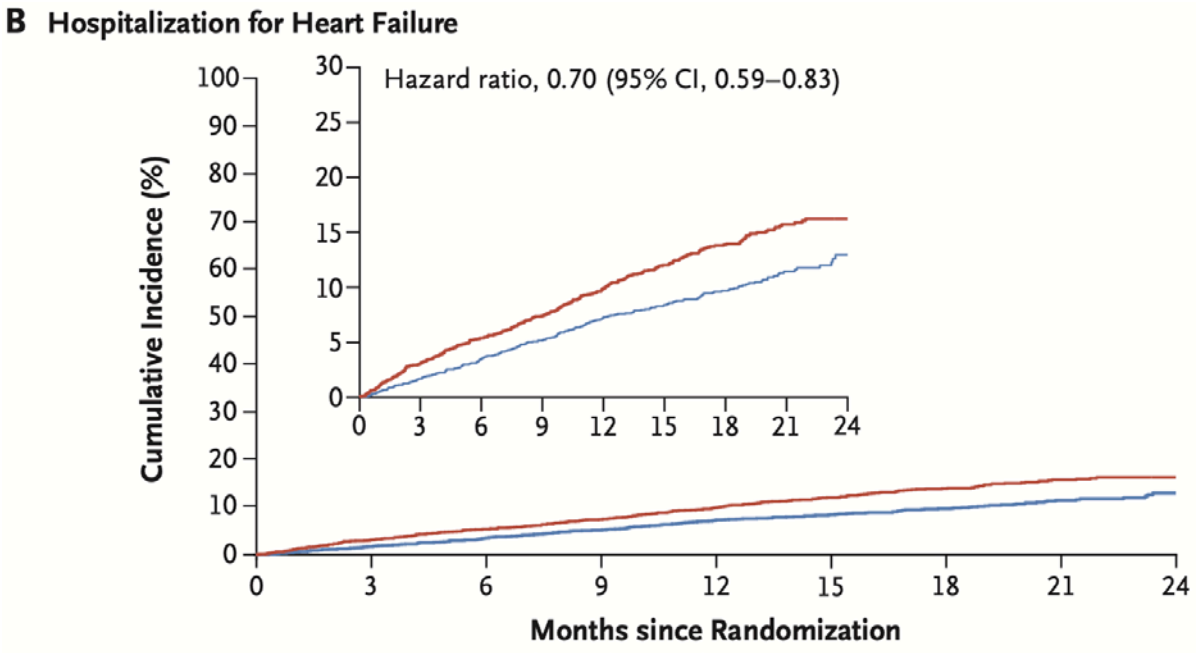
DAPA-HF

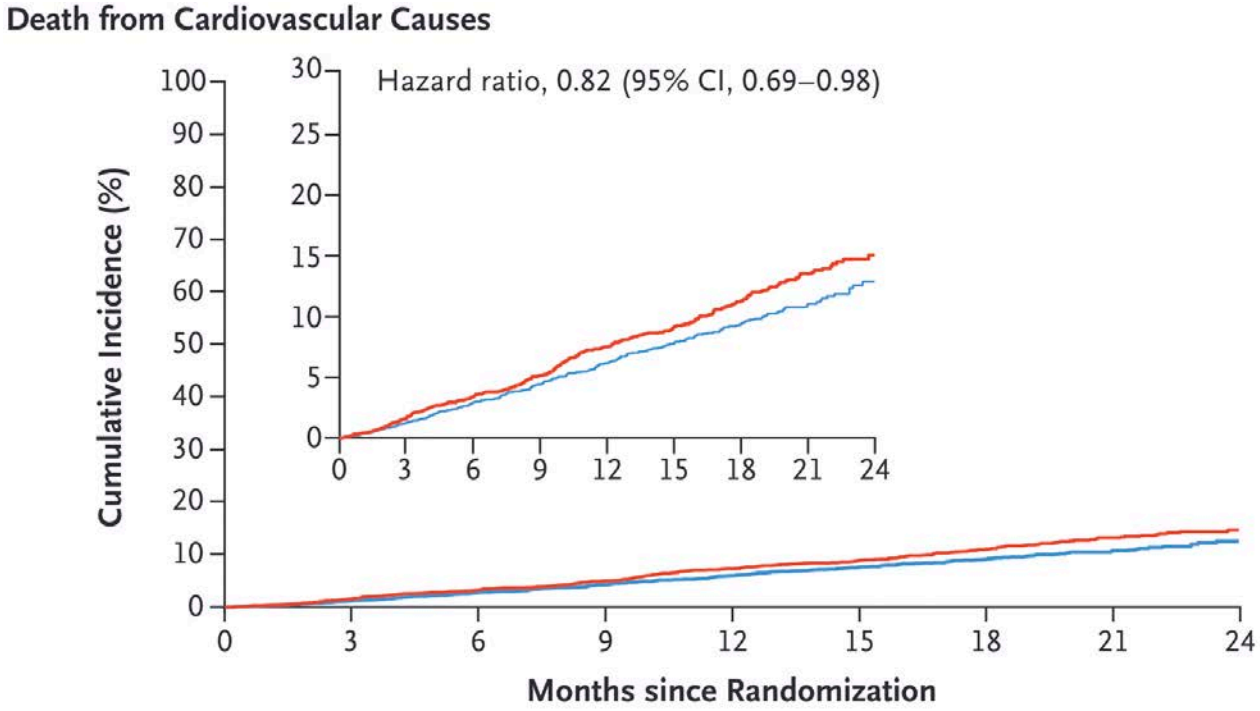
- Inclusion criteria
  - LVEF < 40%
  - NYHA class II-IV
  - Diabetes NOT an inclusion criteria
- Exclusion criteria
  - SBP ≤ 95 mmHg
  - eGFR ≤ 30 mL/min
  - DM type I
- Randomized to dapagliflozin vs. placebo
- Primary outcome: Composite CV death or worsening HF
  - Worsening HF: heart failure hospitalization or urgent care visit needing IV diuretics

DAPA-HF

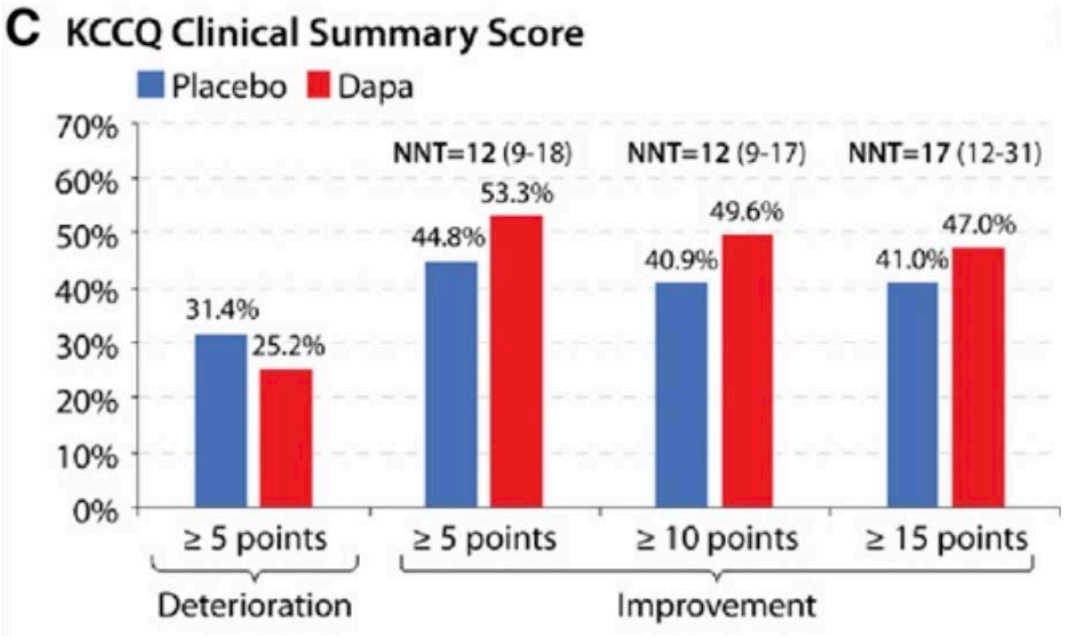


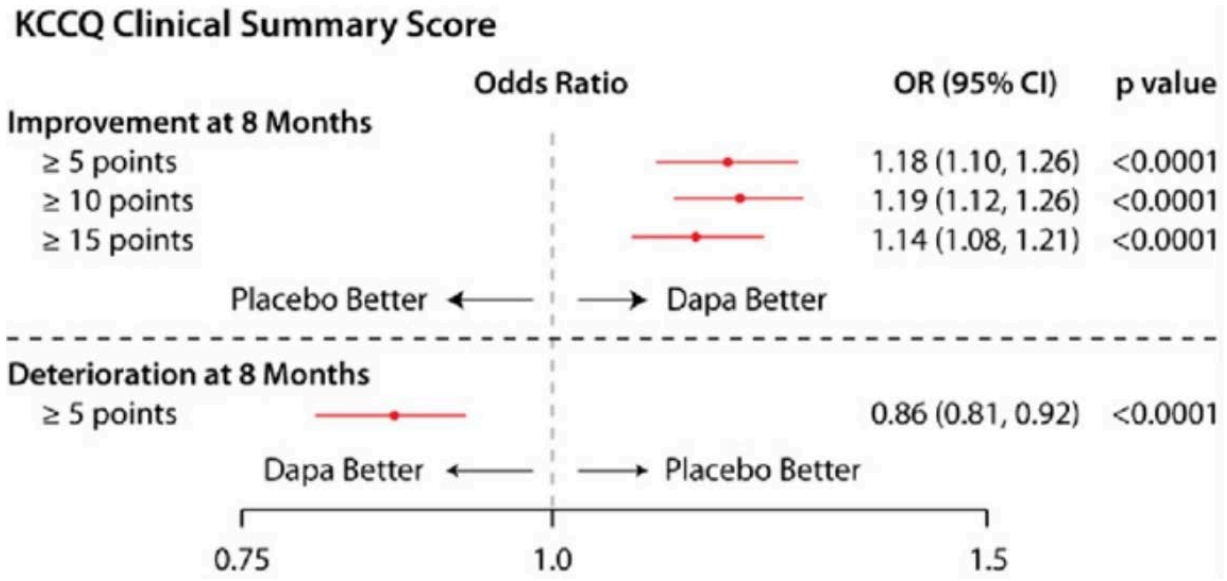
DAPA-HF





DAPA-HF KCCQ Score





EMPEROR-Reduced

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 8, 2020 VOL. 383 NO. 15

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

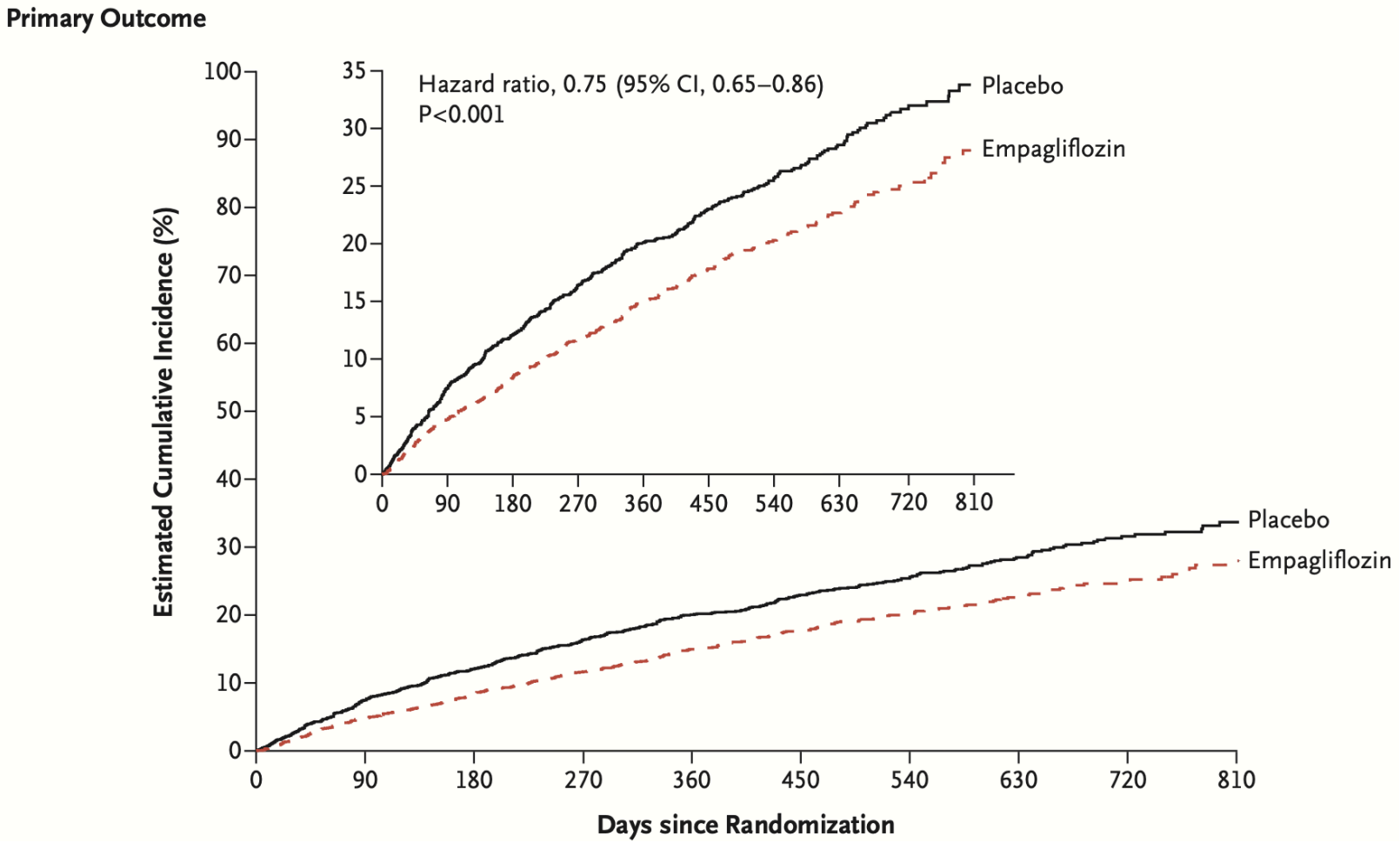
M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.R. Gonzalez Juanatey, S. Kaul, H.-P. Brunner-La Rocca, B. Merkely, S.J. Nicholls, S. Perrone, I. Pina, P. Ponikowski, N. Sattar, M. Senni, M.-F. Seronde, J. Spinar, I. Squire, S. Taddei, C. Wanner, and F. Zannad, for the EMPEROR-Reduced Trial Investigators*

Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383(15):1413-1424.

EMPEROR-Reduced

- Inclusion Criteria:
  - EF ≤ 40%
  - If LVEF 30-40%, then required HFH < 12 mo, or high NT-proBNP (≥ 1000 pg/mL if EF 31-35% or ≥ 2500 pg/mL if EF 36-40%)
  - If LVEF ≤ 30 %, NT-proBNP ≥ 600 pg/mL
- Primary outcomes: composite CV death or first HF hospitalization

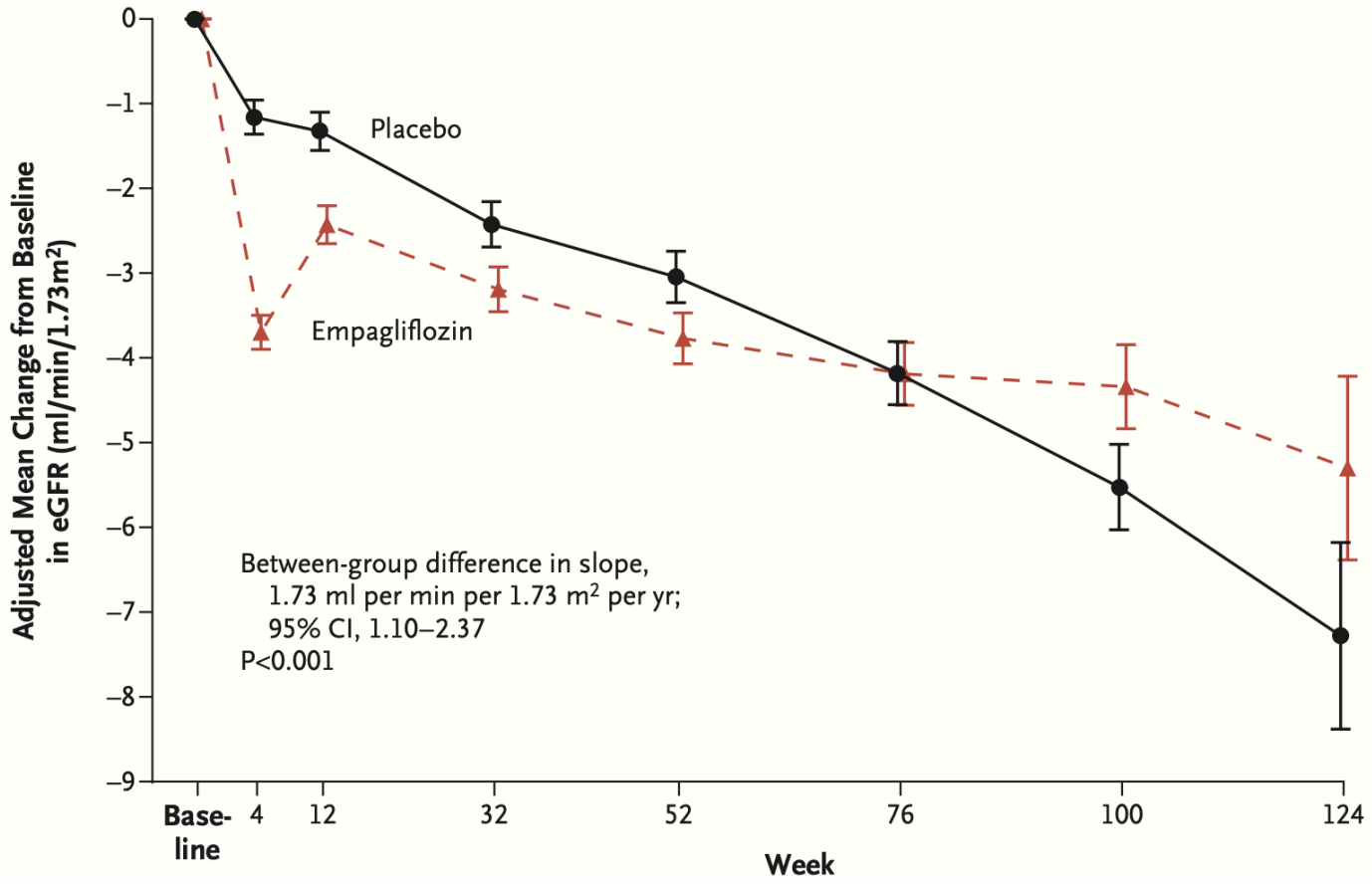
EMPEROR-Reduced



Primary composite outcome — no. (%)	361 (19.4)	15.8	462 (24.7)	21.0	0.75 (0.65 to 0.86)	<0.001
Hospitalization for heart failure	246 (13.2)	10.7	342 (18.3)	15.5	0.69 (0.59 to 0.81)	
Cardiovascular death	187 (10.0)	7.6	202 (10.8)	8.1	0.92 (0.75 to 1.12)	

EMPEROR-Reduced

Secondary Outcomes



EMPEROR-Preserved

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 14, 2021 VOL. 385 NO. 16

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

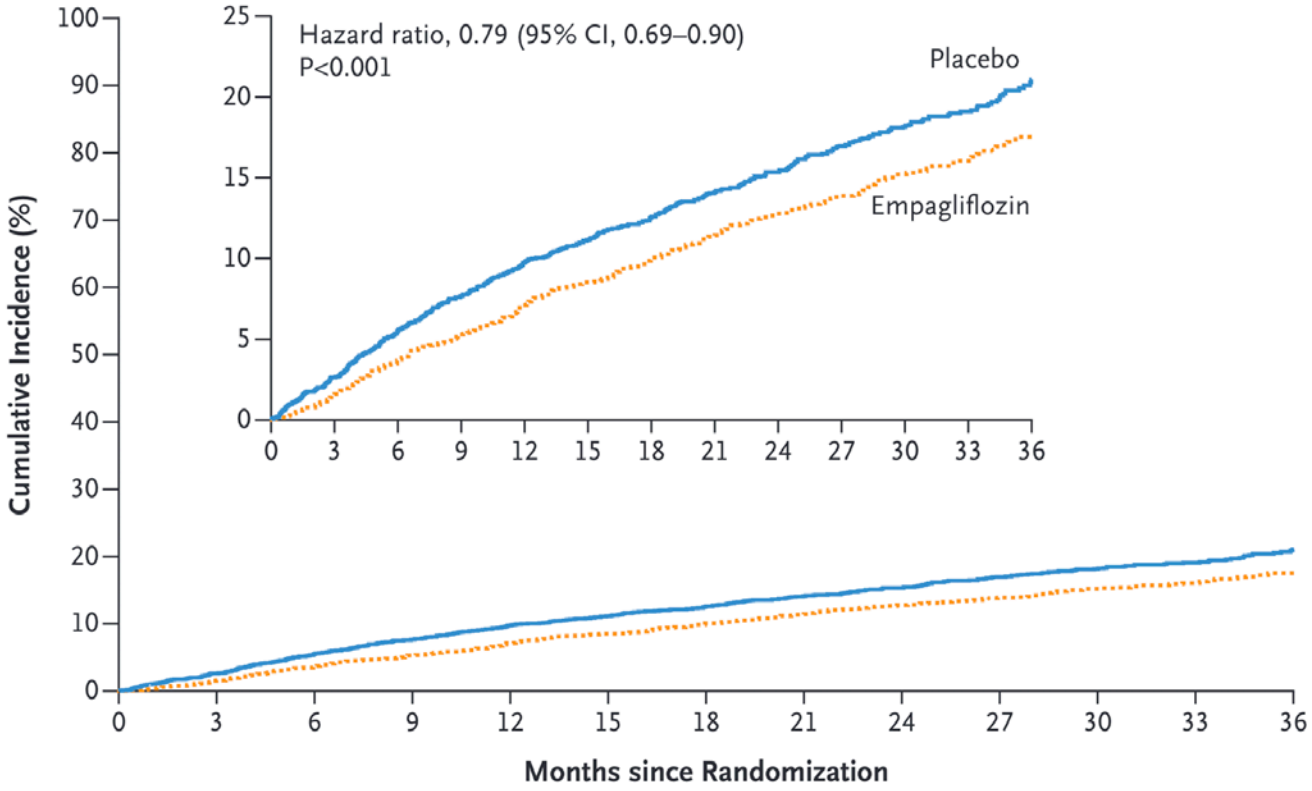
S.D. Anker, J. Butler, G. Filippatos, J.P. Ferreira, E. Bocchi, M. Böhm, H.-P. Brunner–La Rocca, D.-J. Choi, V. Chopra, E. Chuquiure-Valenzuela, N. Giannetti, J.E. Gomez-Mesa, S. Janssens, J.L. Januzzi, J.R. Gonzalez-Juanatey, B. Merkely, S.J. Nicholls, S.V. Perrone, I.L. Piña, P. Ponikowski, M. Senni, D. Sim, J. Spinar, I. Squire, S. Taddei, H. Tsutsui, S. Verma, D. Vinereanu, J. Zhang, P. Carson, C.S.P. Lam, N. Marx, C. Zeller, N. Sattar, W. Jamal, S. Schnaidt, J.M. Schnee, M. Brueckmann, S.J. Pocock, F. Zannad, and M. Packer, for the EMPEROR-Preserved Trial Investigators*

Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385(16):1451-1461.

EMPEROR-Preserved

- Major Inclusion Criteria:
  - EF > 40%
  - NYHA II-IV
  - NT-proBNP > 300 pg/mL (> 900 pg/mL if A-Fib)
- Randomized to empagliflozin vs placebo
- Primary outcome: composite CV death or first HF hospitalization

EMPEROR-Preserved



Variable	Empagliflozin (N=2997)	events per 100 patient-yr	Placebo (N=2991)	events per 100 patient-yr	Hazard Ratio or Difference (95% CI)	P Value
Primary composite outcome — no. (%)	415 (13.8)	6.9	511 (17.1)	8.7	0.79 (0.69–0.90)	<0.001
Hospitalization for heart failure	259 (8.6)	4.3	352 (11.8)	6.0	0.71 (0.60–0.83)	
Cardiovascular death	219 (7.3)	3.4	244 (8.2)	3.8	0.91 (0.76–1.09)	

EMPEROR-Preserved

Subgroup

Subgroup	Empagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
Overall	415/2997	511/2991	0.79 (0.69–0.90)
Diabetes at baseline			
Yes	239/1466	291/1472	0.79 (0.67–0.94)
No	176/1531	220/1519	0.78 (0.64–0.95)
LVEF at baseline			
<50%	145/995	193/988	0.71 (0.57–0.88)
≥50% to <60%	138/1028	173/1030	0.80 (0.64–0.99)
≥60%	132/974	145/973	0.87 (0.69–1.10)

DELIVER

ORIGINAL ARTICLE

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

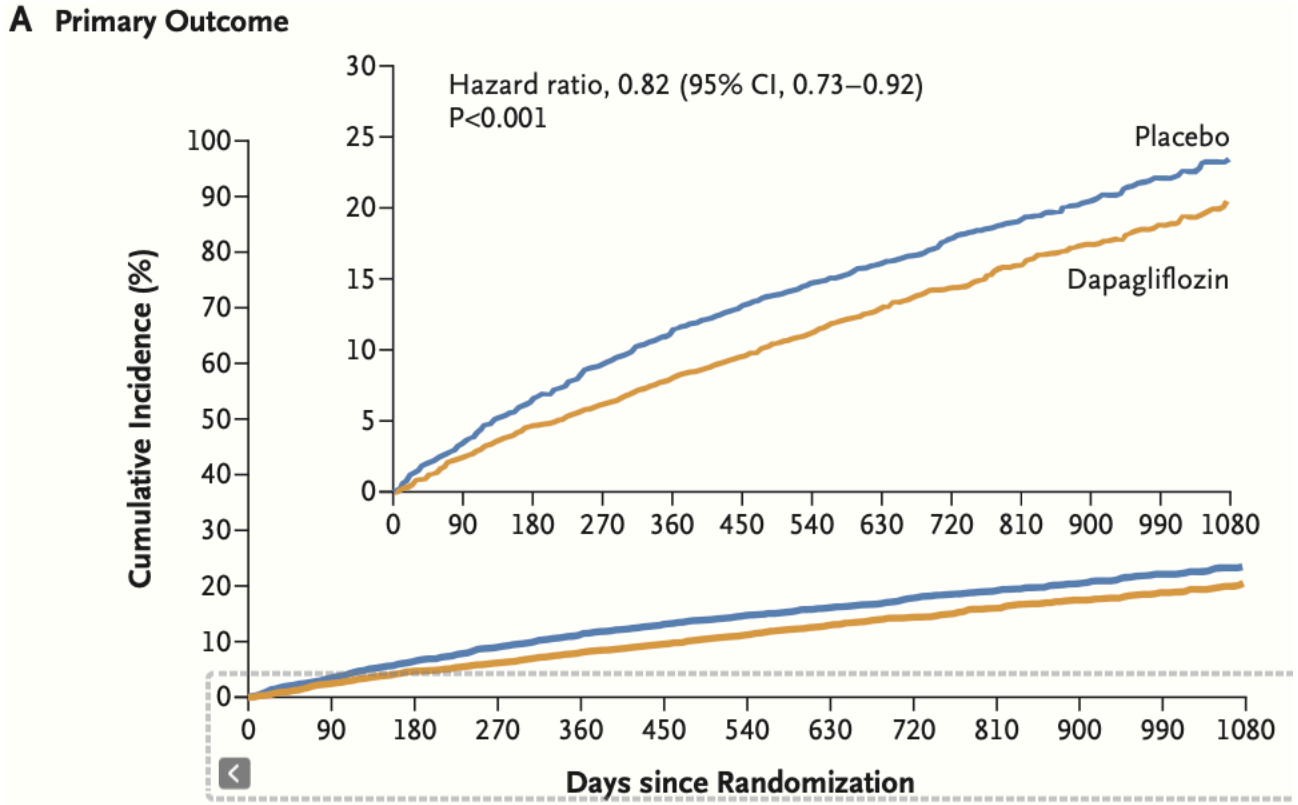
S.D. Solomon, J.J.V. McMurray, B. Claggett, R.A. de Boer, D. DeMets, A.F. Hernandez, S.E. Inzucchi, M.N. Kosiborod, C.S.P. Lam, F. Martinez, S.J. Shah, A.S. Desai, P.S. Jhund, J. Belohlavek, C.-E. Chiang, C.J.W. Borleffs, J. Comin-Colet, D. Dobreanu, J. Drozdz, J.C. Fang, M.A. Alcocer-Gamba, W. Al Habeeb, Y. Han, J.W. Cabrera Honorio, S.P. Janssens, T. Katova, M. Kitakaze, B. Merkely, E. O'Meara, J.F.K. Saraiva, S.N. Tereshchenko, J. Thierer, M. Vaduganathan, O. Vardeny, S. Verma, V.N. Pham, U. Wilderäng, N. Zaozerska, E. Bachus, D. Lindholm, M. Petersson, and A.M. Langkilde, for the DELIVER Trial Committees and Investigators*

Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. 2022;387(12):1089-1098.

DELIVER

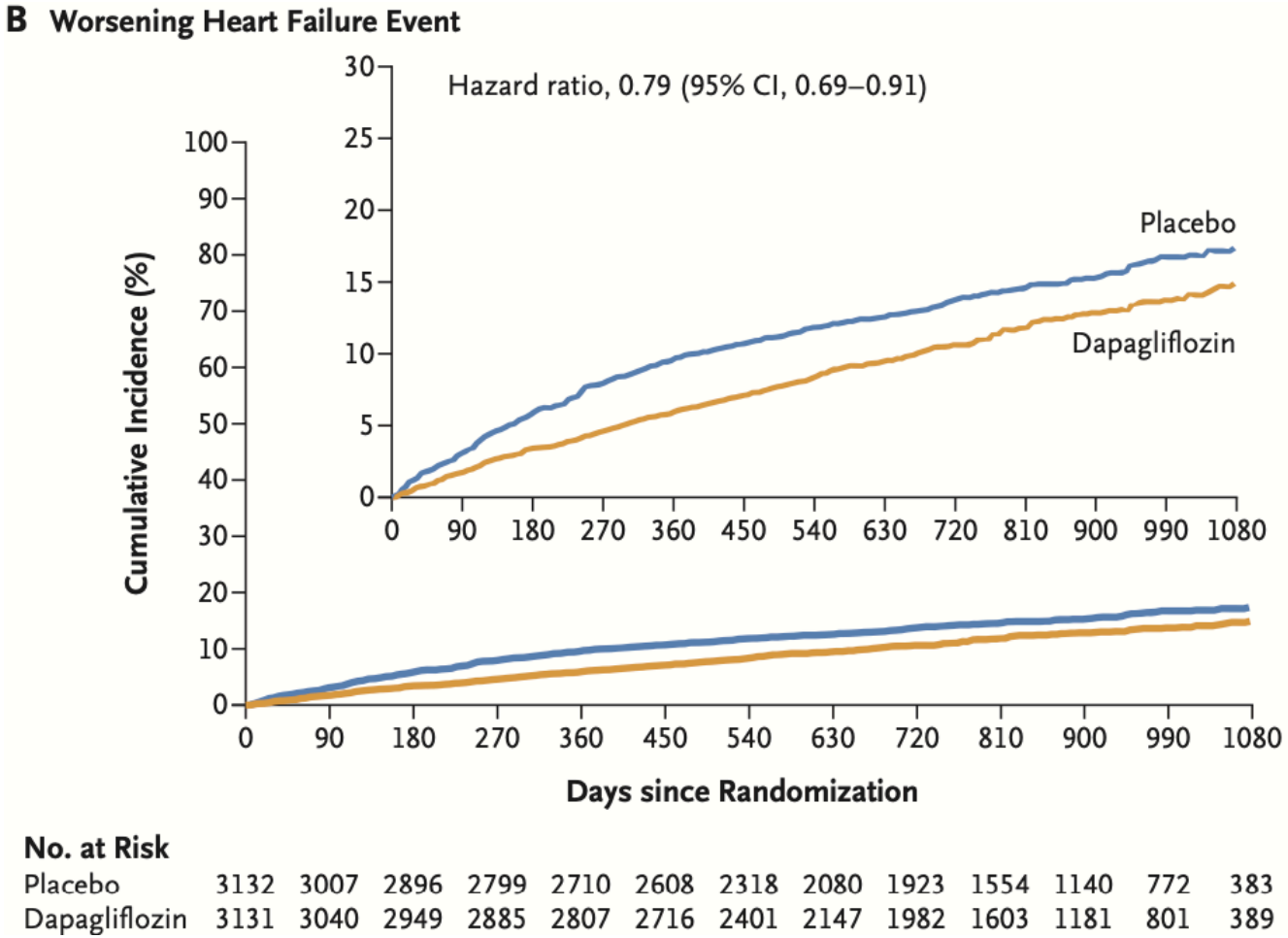
- Major Inclusion Criteria:
  - EF > 40%
  - Structural heart disease (enlargement of LA or LV hypertrophy)
  - NT-proBNP > 300 pg/mL (> 600 pg/mL if A-Fib)
- Primary outcome: Time to event
  - CV death
  - Worsening HF (unplanned hospitalization or urgent visit for HF)

DELIVER



DELIVER

- Driven by decreased hospitalizations
- No difference in CV death
  - HR 0.88 (0.74-1.05)



Primary composite outcome — no. (%)	512 (16.4)	7.8	610 (19.5)	9.6	0.82 (0.73–0.92)	<0.001
Hospitalization for heart failure or an urgent visit for heart failure	368 (11.8)	5.6	455 (14.5)	7.2	0.79 (0.69–0.91)	NA
Hospitalization for heart failure	329 (10.5)	5.0	418 (13.3)	6.5	0.77 (0.67–0.89)	NA
Urgent visit for heart failure	60 (1.9)	0.9	78 (2.5)	1.1	0.76 (0.55–1.07)	NA
Cardiovascular death†	231 (7.4)	3.3	261 (8.3)	3.8	0.88 (0.74–1.05)	NA

DELIVER

- Benefit seen in patients with higher LVEF

Subgroup	Dapagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
LVEF at enrollment			
≤49%	207/1067	229/1049	0.87 (0.72–1.04)
50–59%	174/1133	211/1123	0.79 (0.65–0.97)
≥60%	131/931	170/960	0.78 (0.62–0.98)

SGLT-2 inhibitors

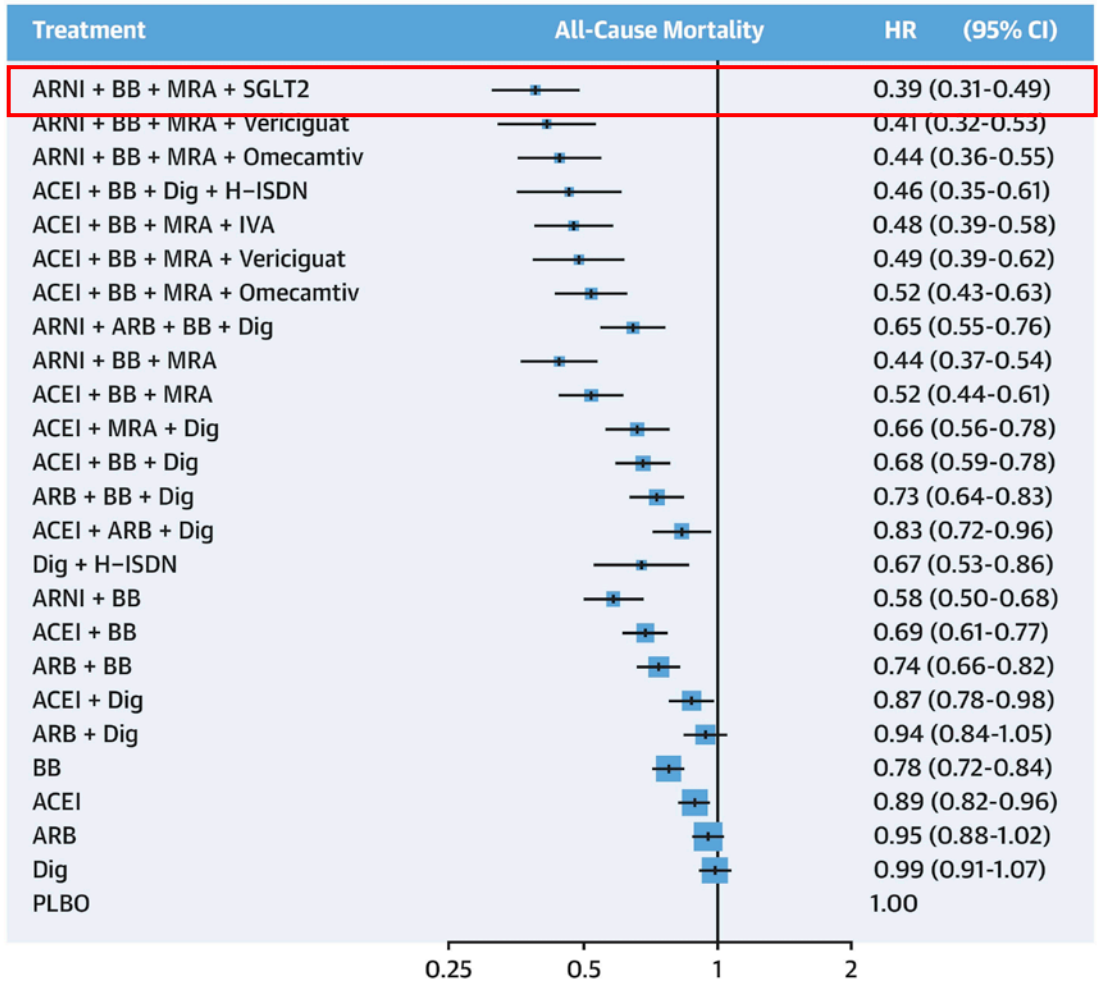
Guidelines

- 1A in symptomatic chronic HFrEF (EF<40%)
- 2A in symptomatic HF with HFpEF (EF>50%)
- 2A in symptomatic HF with HFmrEF (EF 41-49%)

Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 aha/acc/hfsa guideline for the management of heart failure: a report of the american college of cardiology/american heart association joint committee on clinical practice guidelines. *Circulation*. 2022;145(18).

CENTRAL ILLUSTRATION: Relative Risk Reduction of Different Pharmacological Treatment Combinations for Heart Failure

A

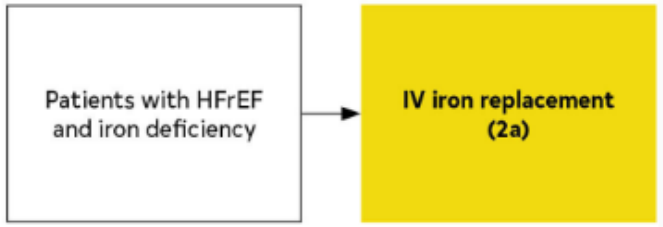


Tromp, J. et al. J Am Coll Cardiol HF. 2022;10(2):73-84.

Iron deficiency anemia

AFFIRM-AHF

- Enrolled HFH patients and iron deficiency from 2017 to 2019
  - EF<50%
  - Iron deficient: Ferritin <100 µg/L, or 100–299 µg/L with transferrin saturation <20%
- Randomized to IV ferric carboxymaltose vs. placebo
- Enrolled 1132 patients
- Primary outcome: composite total HFH and CV death
  - 370 events in treatment arm, 451 events in placebo arm (RR 0.8, p=0.05)
  - Driven by total HFH: 217 vs. 294 (RR 0.74, p = 0.013)



Ponikowski P, Kirwan BA, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *The Lancet*. 2020;396(10266):1895-1904.
Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 aha/acc/hfsa guideline for the management of heart failure: a report of the american college of cardiology/american heart association joint committee on clinical practice guidelines. *Circulation*. 2022;145(18).

Vericiguat

- An oral soluble guanylyl cyclase stimulator
  - Increases cyclic GMP levels leading to decreased inflammation, fibrosis and vasodilation
- The VICTORIA trial studied vericiguat in HFrEF (LVEF < 45%)
  - High risk cohort: Recent HFH or IV diuretic as an outpatient
  - Outcomes:
    - Positive for primary outcome: composite CV death and HFH, driven by HFH (HR 0.9, P = 0.02)
    - 3% ARR in primary outcome was considered underwhelming in a high-risk cohort

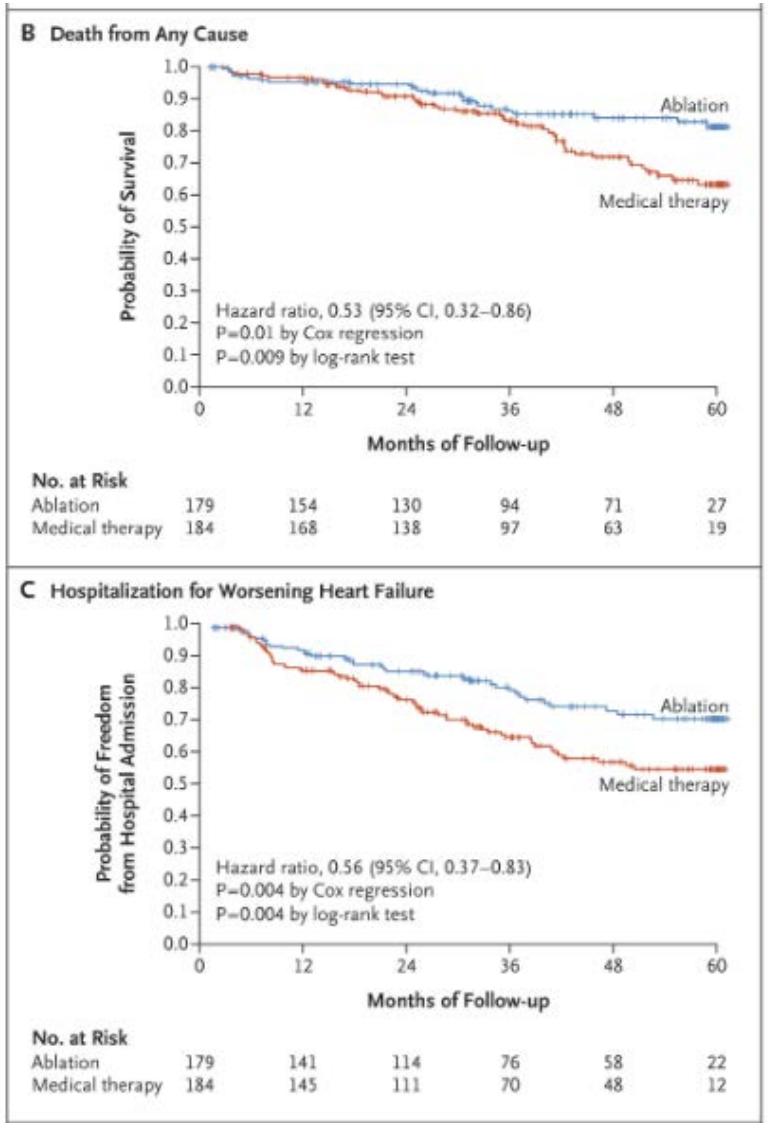
COR	LOE	Recommendation
2b	B-R	1. In selected high-risk patients with HFrEF and recent worsening of HF already on GDMT, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death.[1]

Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2020;382(20):1883-1893.
Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 aha/acc/hfsa guideline for the management of heart failure: a report of the american college of cardiology/american heart association joint committee on clinical practice guidelines. *Circulation*. 2022;145(18).

Atrial Fibrillation Ablation

CASTLE-AF

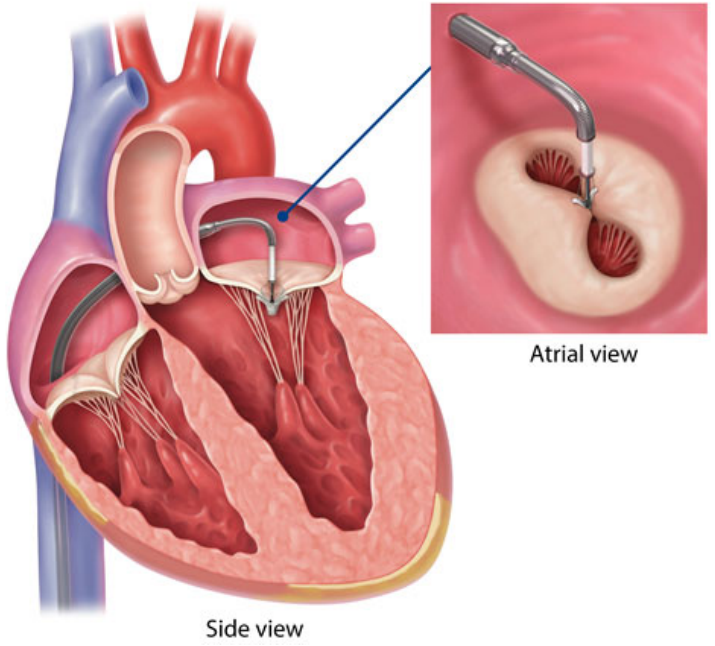
- Randomized symptomatic paroxysmal/permanent AF with EF<35
  - Catheter ablation vs. medical therapy (rate or rhythm control)
- Primary outcome: composite death or HFH
- Enrolled 363 patients from 2008 to 2016
- Less total events in treatment arm (HR 0.62, p=0.007)
  - Less HFH and less deaths



Marrouche NF, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med*. 2018;378(5):417-427.
Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 aha/acc/hfsa guideline for the management of heart failure: a report of the american college of cardiology/american heart association joint committee on clinical practice guidelines. *Circulation*. 2022;145(18).

Mitral Regurgitation

- Primary mitral regurgitation
  - Due to structural deformity or damage to the leaflets, chordae and/or papillary muscles
  - Fix surgically when needed
- Secondary mitral regurgitation (aka functional)
  - No structural problem with valve
  - Due to LV wall motion abnormalities or dilation
    - Leads to mitral annular dilation or displacement of papillary muscle causing regurgitation
  - Until recently, unclear if beneficial to fix
  - A transcatheter repair has recently been developed



Dal-Bianco JP, Beaudoin J, Handschumacher MD, Levine RA. Basic mechanisms of mitral regurgitation. Can J Cardiol. 2014 Sep;30(9):971-81
Asgar AW, Mack MJ, Stone GW. Secondary mitral regurgitation in heart failure: pathophysiology, prognosis, and therapeutic considerations. J Am Coll Cardiol 2015;65:1231-1248.
https://www.baptistjax.com/services/heart-vascular-care/structural-heart-program/mitraclip

MITRA-FR

- Patients with severe secondary MR randomized to transcatheter repair (n = 152) versus medical therapy (n = 152)
- Inclusion criteria
  - LVEF 15% to 40%
  - NYHA II-IV
- Primary outcome: composite death or unplanned heart failure hospitalization at 12 months

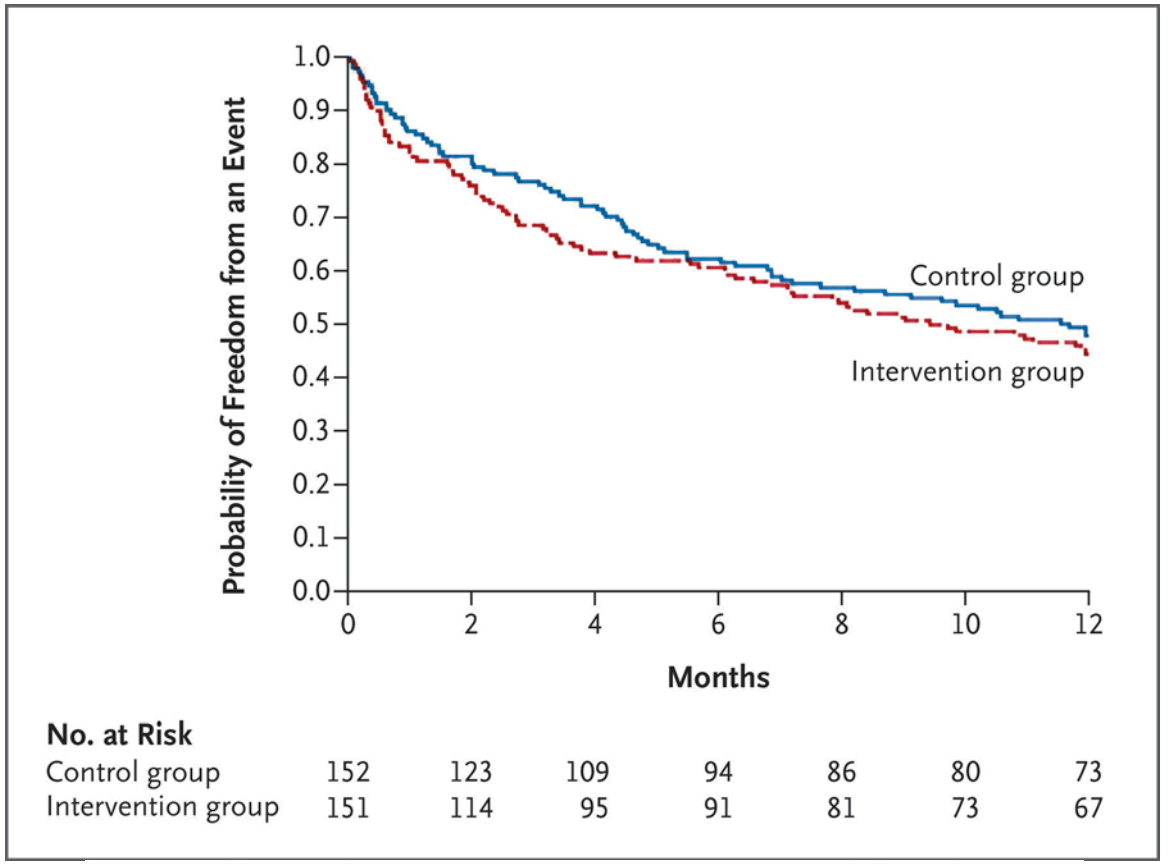


Table 3. Primary Outcome and Secondary Efficacy Outcomes at 12 Months (Intention-to-Treat Population).

Outcome	Intervention Group (N=152)	Control Group (N=152)	Hazard Ratio or Odds Ratio (95% CI)*	P Value†
Composite primary outcome: death from any cause or unplanned hospitalization for heart failure at 12 months — no. (%)	83 (54.6)	78 (51.3)	1.16 (0.73–1.84)	0.53
Secondary outcomes‡				
Death from any cause	37 (24.3)	34 (22.4)	1.11 (0.69–1.77)	
Cardiovascular death	33 (21.7)	31 (20.4)	1.09 (0.67–1.78)	
Unplanned hospitalization for heart failure	74 (48.7)	72 (47.4)	1.13 (0.81–1.56)	
Major adverse cardiovascular events§	86 (56.6)	78 (51.3)	1.22 (0.89–1.66)	

Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med*. 2018;379(24):2297-2306.

COAPT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Transcatheter Mitral-Valve Repair in Patients with Heart Failure

G.W. Stone, J.A. Lindenfeld, W.T. Abraham, S. Kar, D.S. Lim, J.M. Mishell, B. Whisenant, P.A. Grayburn, M. Rinaldi, S.R. Kapadia, V. Rajagopal, I.J. Sarembock, A. Brieke, S.O. Marx, D.J. Cohen, N.J. Weissman, and M.J. Mack, for the COAPT Investigators*

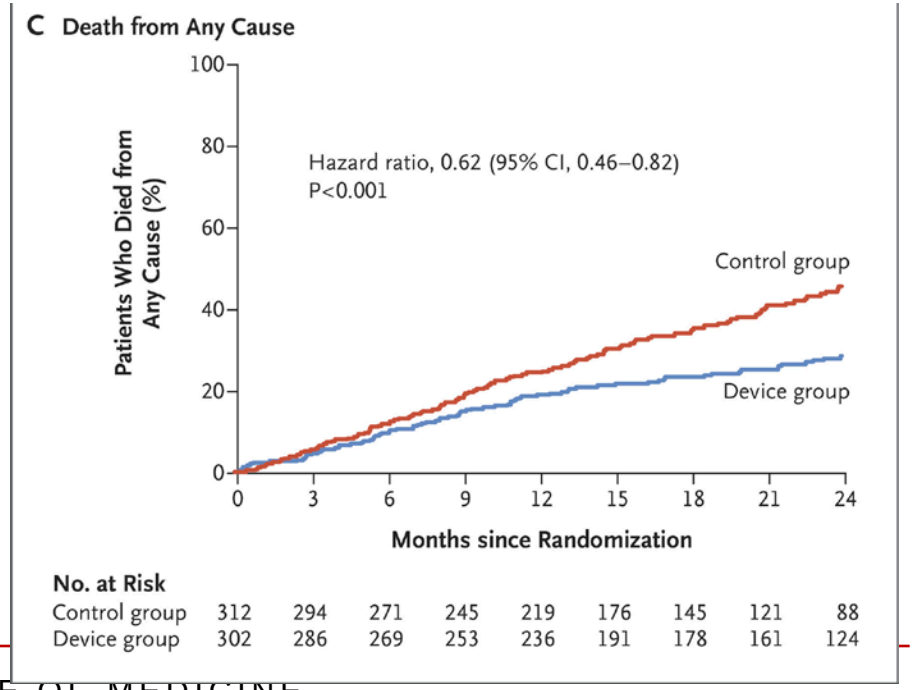
Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379(24):2307-2318.

COAPT

- Patients with moderate-severe to severe secondary MR randomized to transcatheter repair (n = 302) vs. medical therapy (n = 312)
- Primary outcome: heart failure hospitalizations
- Inclusion criteria:
  - NYHA class II or greater
  - LVEF ≥ 20% and ≤ 50%
  - LVIDs ≤ 70mm
  - At least one hospitalization for heart failure in last year OR corrected BNP ≥ 300 pg/mL or corrected NTproBNP ≥ 1500 pg/mL
  - Optimization of GDMT by a heart failure specialist
  - PASP < 70 mmHg

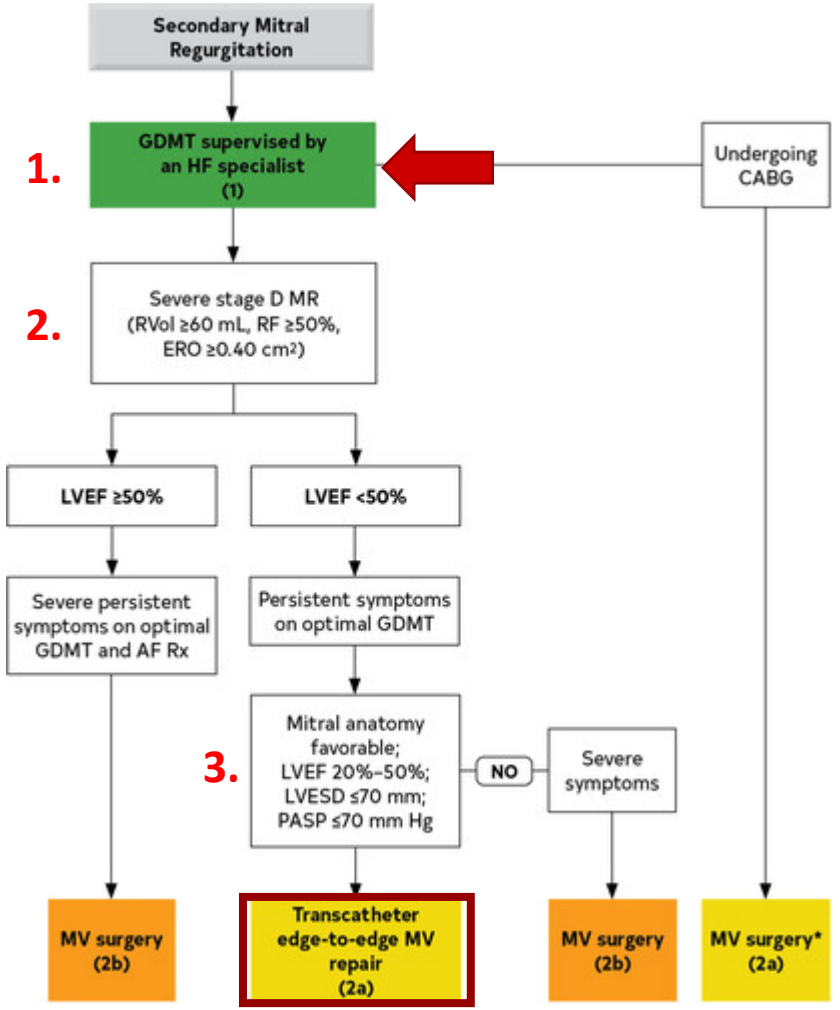
COAPT

- Intervention group:
  - Less HFH
  - Less all cause deaths
  - Increased KCCQ scores
    - Control group scores worsened
  - Less LV dilation at 12 months



Study differences

- COAPT had more severe mitral regurgitation
  - Mean EROA of 41 mm2 versus 31 mm2
- COAPT had less dilated ventricles
  - Mean LVEDV index of 101 mL/m2 versus 134 mL/m2
- COAPT required heart failure specialists to ensure patients were on optimal GDMT



Primary Prevention Defibrillators

Recommendations for Primary Prevention of SCD in Patients With Ischemic Heart Disease

References that support the recommendations are summarized in Online Data Supplement 21.

COR	LOE	Recommendations
I	A	1. In patients with LVEF of 35% or less that is due to ischemic heart disease who are at least 40 days' post-MI and at least 90 days postrevascularization, and with NYHA class II or III HF despite GDMT, an ICD is recommended if meaningful survival of greater than 1 year is expected.[S6.1.2-1,S6.1.2-2]
I	A	2. In patients with LVEF of 30% or less that is due to ischemic heart disease who are at least 40 days' post-MI and at least 90 days postrevascularization, and with NYHA class I HF despite GDMT, an ICD is recommended if meaningful survival of greater than 1 year is expected.[S6.1.2-2,S6.1.2-3]

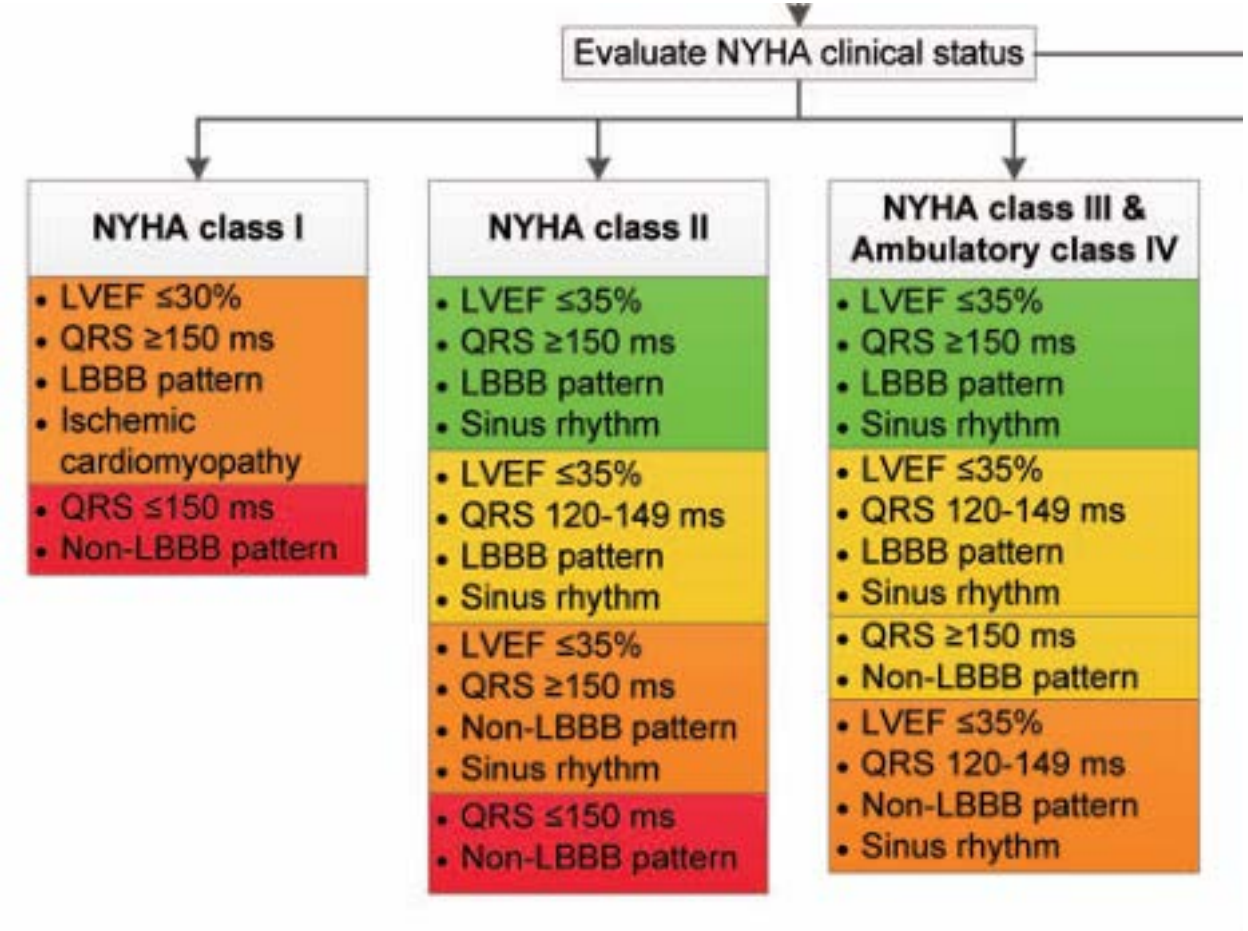
Recommendations for Primary Prevention of SCD in Patients With NICM

References that support the recommendations are summarized in Online Data Supplement 27 and 28.

COR	LOE	Recommendations
I	A	1. In patients with NICM, HF with NYHA class II–III symptoms and an LVEF of 35% or less, despite GDMT, an ICD is recommended if meaningful survival of greater than 1 year is expected.[S6.2.2-1–S6.2.2-6]
IIa	B-NR	2. In patients with NICM due to a *Lamin A/C* mutation who have 2 or more risk factors (NSVT, LVEF <45%, nonmissense mutation, and male sex), an ICD can be beneficial if meaningful survival of greater than 1 year is expected.[S6.2.2-7–S6.2.2-10]
IIb	B-R	3. In patients with NICM, HF with NYHA class I symptoms and an LVEF of 35% or less, despite GDMT, an ICD may be considered if meaningful survival of greater than 1 year is expected.[S6.2.2-5]
III: No Benefit	C-EO	4. In patients with medication-refractory NYHA class IV HF who are not also candidates for cardiac transplantation, an LVAD, or a CRT defibrillator that incorporates both pacing and defibrillation capabilities, an ICD should not be implanted.

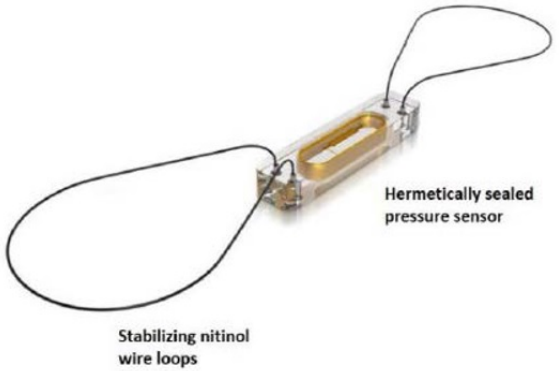
Cardiac Resynchronization Therapy (CRT)

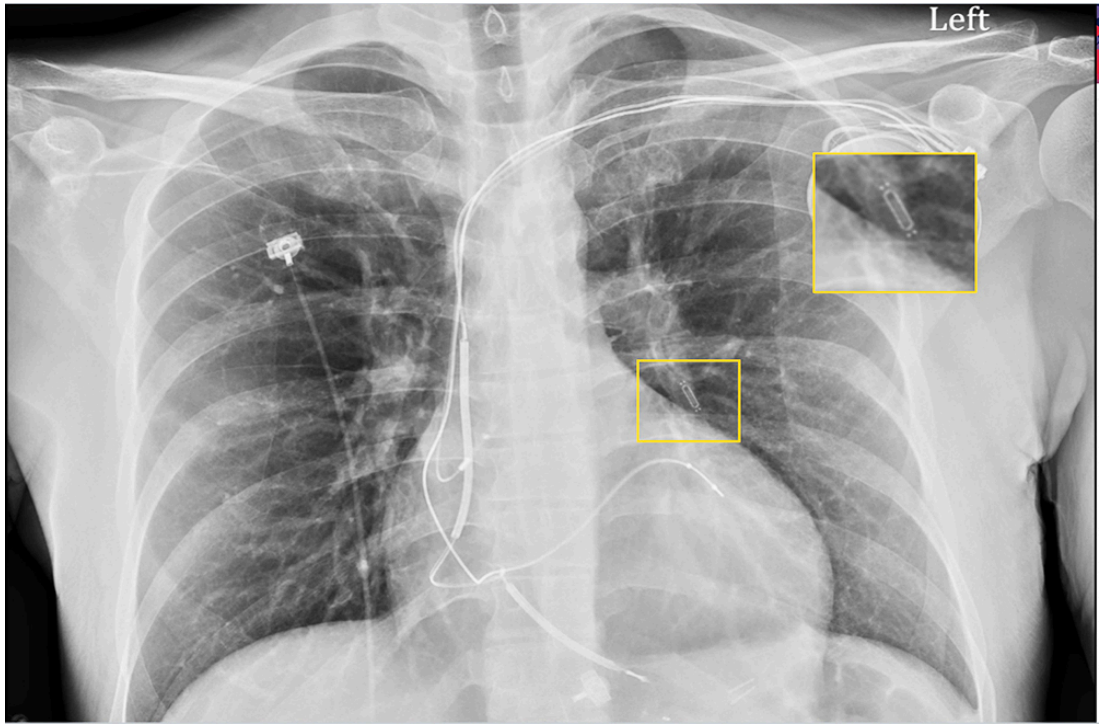
- LBBB and NYHA II-IV
  - Do it
- LBBB and NYHA I and EF < 30%
  - Consider it if QRS > 150 ms
- RBBB and NYHA III-IV
  - Do it if QRS > 150 ms
  - Consider it if QRS between 120-149 ms
- RBBB and NYHA II
  - Consider it if QRS >150
  - **Do not do it if QRS < 150**
- RBBB and NYHA I
  - **Do not do it**



CardioMEMS

- Device implanted into pulmonary artery percutaneously
- Wirelessly monitors pulmonary artery pressures
  - Patient lays on a “pillow” to take daily measurements
- Use pulmonary artery diastolic pressure as surrogate for left atrial pressure
  - Detect volume overload before weights increase





https://www.fda.gov/medical-devices/recently-approved-devices/cardiomems-hf-system-p100045s056
https://www.holy-cross.com/find-a-service-or-specialty/heart-and-vascular-care/treatments-and-procedures/cardiomems-technology
https://www.pennmedicine.org/for-health-care-professionals/for-physicians/physician-education-and-resources/clinical-briefings/2020/october/cardiomems-clinical-briefing

CHAMPION Trial

Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial

Lancet 2011; 377: 658–66
Published Online
February 10, 2011
DOI:10.1016/S0140-6736(11)60101-3

*William T Abraham, Philip B Adamson, Robert C Bourge, Mark F Aaron, Maria Rosa Costanzo, Lynne W Stevenson, Warren Strickland, Suresh Neelagaru, Nirav Raval, Steven Krueger, Stanislav Weiner, David Shavelle, Bradley Jeffries, Jay S Yadav, for the CHAMPION Trial Study Group**

Abraham WT, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet*. 2011;377(9766):658-666.

CHAMPION Trial

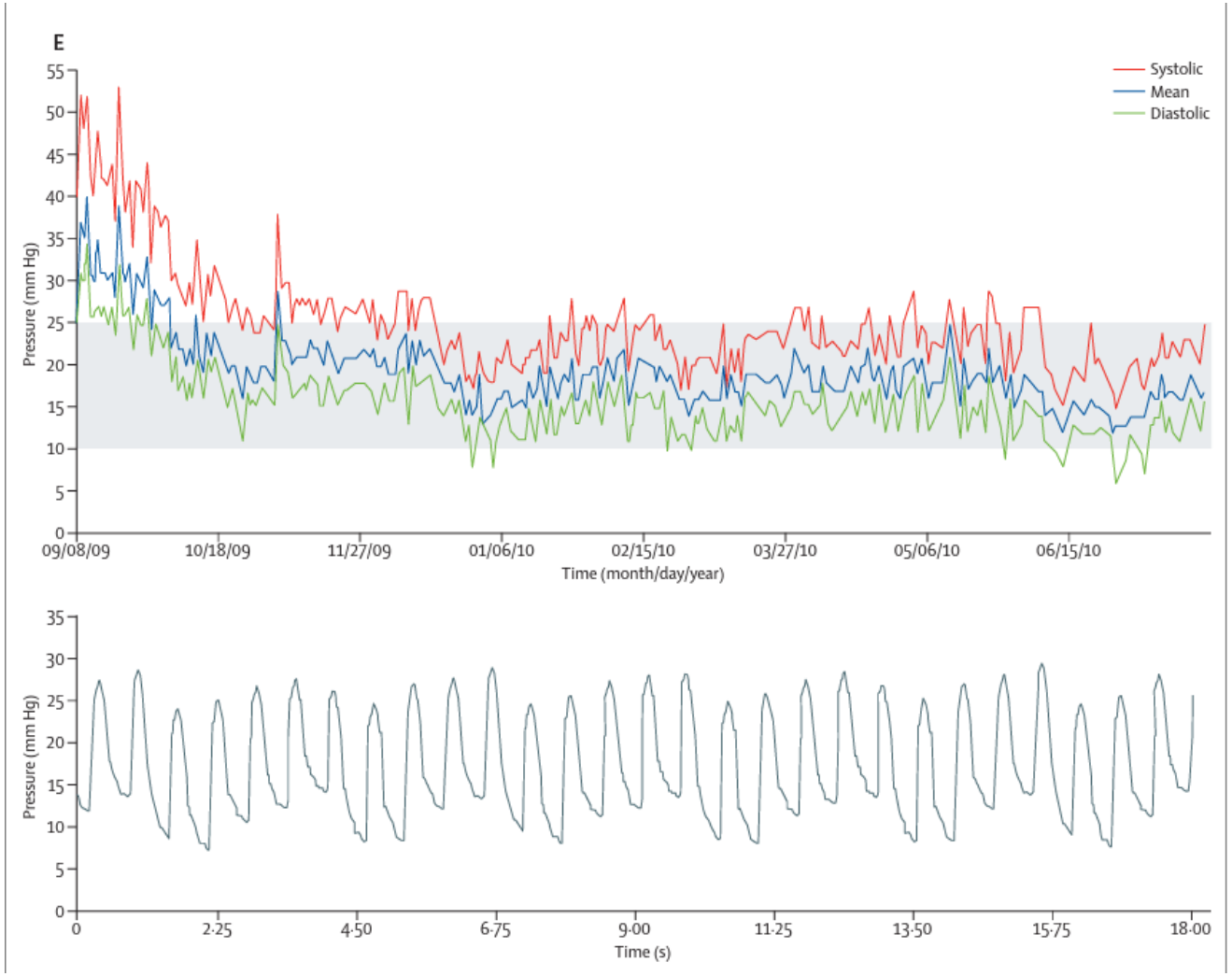
- Prospective, single blinded trial
- All patients had CardioMEMS devices implanted
  - Half were randomized to treatment group (physicians had access to data) or standard therapy (data was blocked)
- Inclusion criteria
  - NYHA class III patients
  - HF hospitalization within past 12 months
  - Optimal guideline directed medical therapy
  - No LVEF cutoff

CHAMPION Trial

- 270 patients in treatment arm
  - Pressure data reviewed at least once a week
- 280 patients in standard therapy arm
- Primary endpoint: rate of heart failure related hospitalizations within 6 months of implantation

CHAMPION Trial

- Data includes trends in pressures and individual PA pressure waveforms



CHAMPION Trial

- At 6 months:
  - 84 total HFH in treatment group
  - 120 total HFH in control group
  - P = 0.0002, NNT 8
- At entire follow up
  - 158 HFH in treatment group
  - 254 HFH in control group
  - P < 0.0001, NNT 4

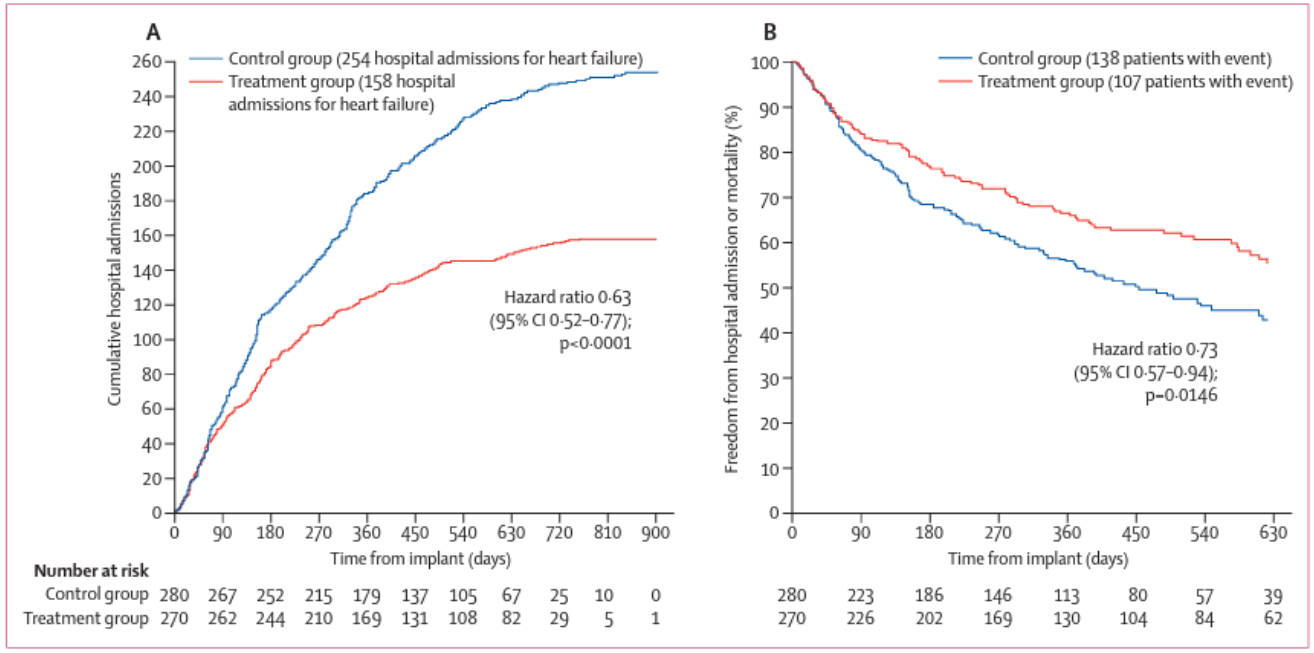


Figure 3: **Cumulative heart-failure-related hospitalisations during entire period of randomised single-blind follow-up (A), and freedom from first heart-failure-related hospitalisation or mortality during the entire period of randomised follow-up (B)**

CHAMPION Trial

- Treatment group had shorter hospitalizations
  - 2.2 days versus 3.8 days, P = 0.02
- Treatment group had greater number of changes to heart failure drugs
  - 2468, mean 9.1 per patient versus 1061, mean 3.8 per patient, P < 0.0001
- Benefit seen in both HFrEF and HFpEF patients
- 15 serious adverse events during 575 implant attempts (2.6%)

CardioMEMS

May 27, 2014

FDA Approves the CardioMEMS HF System for Remote Monitoring of Pulmonary Artery Pressure

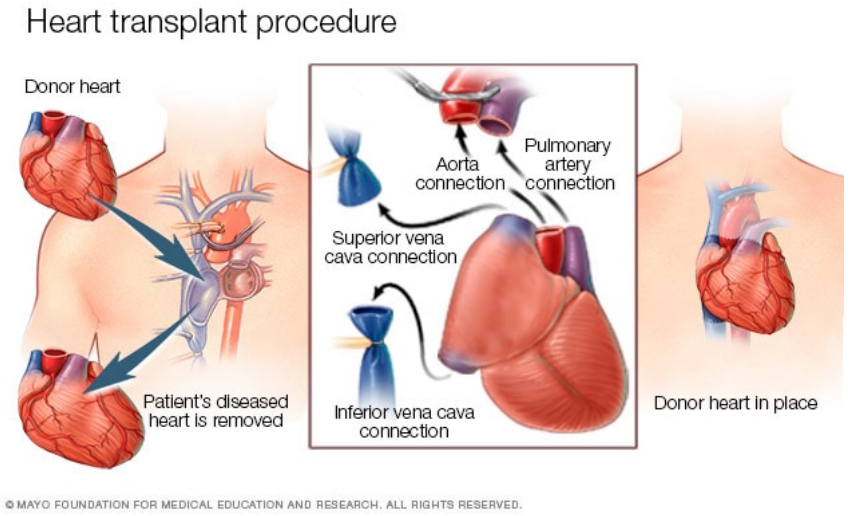
News | February 22, 2022

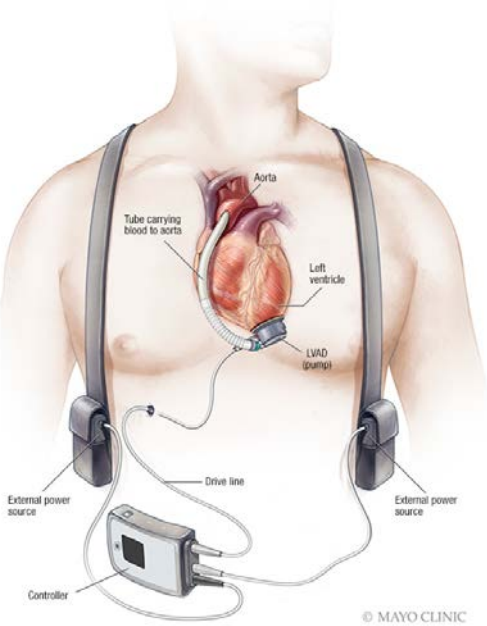
FDA approves Abbott's CardioMEMS HF System for earlier-stage heart failure

The new indication includes patients with Class II heart failure and high biomarker levels of natriuretic peptides.

Advanced Therapies

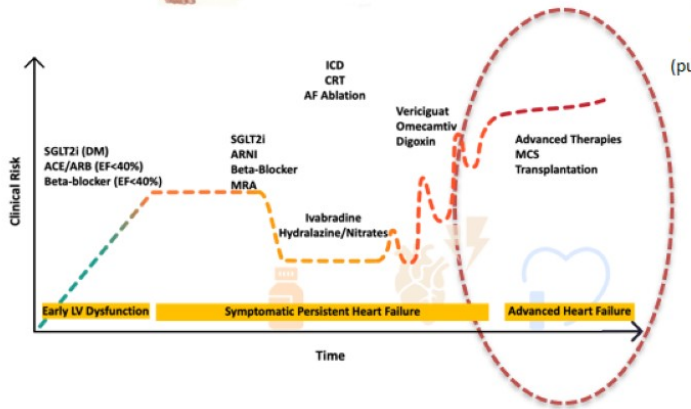
- 3,817 heart transplants performed in 2021
- From June 2006 to Dec 2017, 20,130 LVADs were implanted





https://www.mayoclinic.org/tests-procedures/heart-transplant/about/pac-20384750

LVAD Therapy



HeartMate XVE
(pulsatile, large pump)

HeartMate II
(Axial-flow pump)

HeartMate 3
(Centrifugal-flow Pump)

Pulsatile Pump

Continuous Flow Pumps

2000

2019

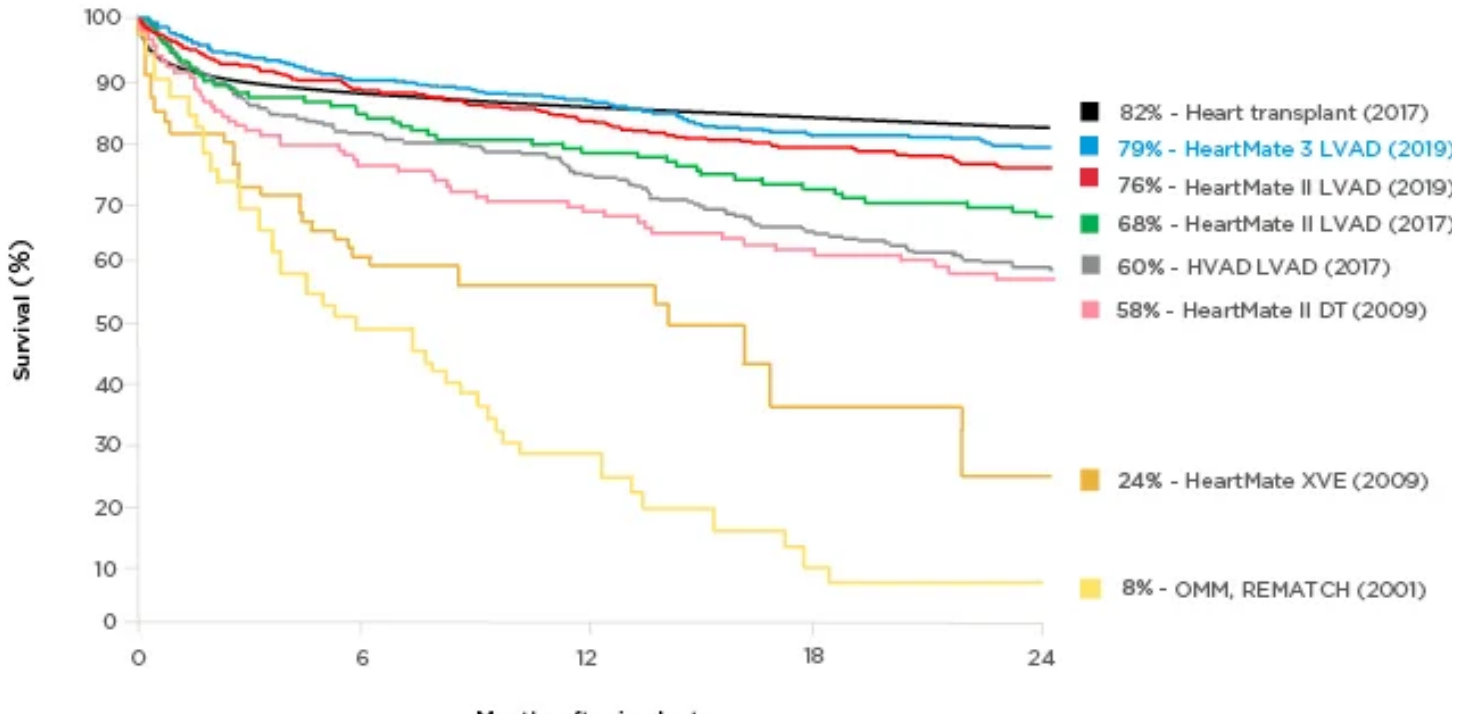
- Smaller pumps
- Intrathoracic implantation
- Reduced complications
- Durable
- Ushered in “Destination Therapy”

MOMENTUM 3

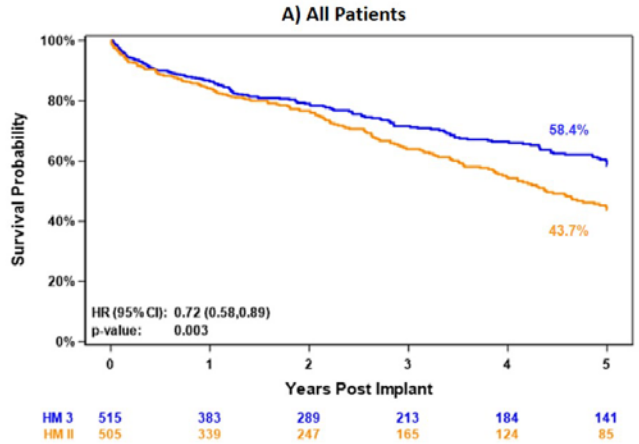
Mehra MR, Goldstein DJ, Cleveland JC, et al. Five-year outcomes in patients with fully magnetically levitated vs axial-flow left ventricular assist devices in the momentum 3 randomized trial. *JAMA*. Published online September 8, 2022.

LVAD Therapy

- Long term survival has steadily improved with newer LVADs
- 2 year survival for HM3 is 79%
  - OMT is 8% (based on 2001 data, 72% on inotropes)
- 5 year survival for HM3 is 58.4%
  - Significantly better than HM2 (43.7%, p = 0.003)



Overall Survival



Hazard ratio presented for HM3 vs HMII and p-value from Cox regression. CI, confidence intervals; HM3, HeartMate 3; HMII, HeartMate II; HR, hazard ratio

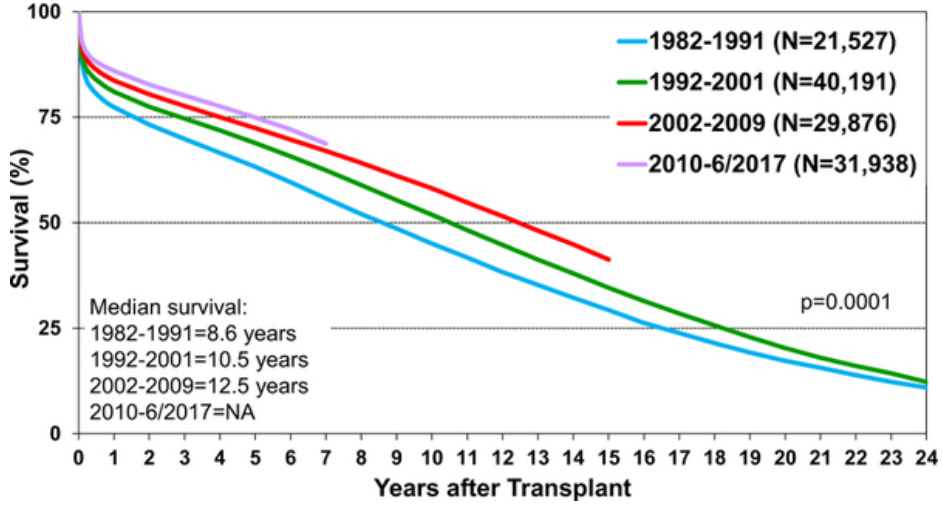
https://www.emjreviews.com/cardiology/symposium/surrounding-advanced-heart-failure-the-role-of-the-latest-left-ventricular-assist-devices/

Mehra MR, Goldstein DJ, Cleveland JC, et al. Five-year outcomes in patients with fully magnetically levitated vs axial-flow left ventricular assist devices in the momentum 3 randomized trial. *JAMA*. Published online September 8, 2022.

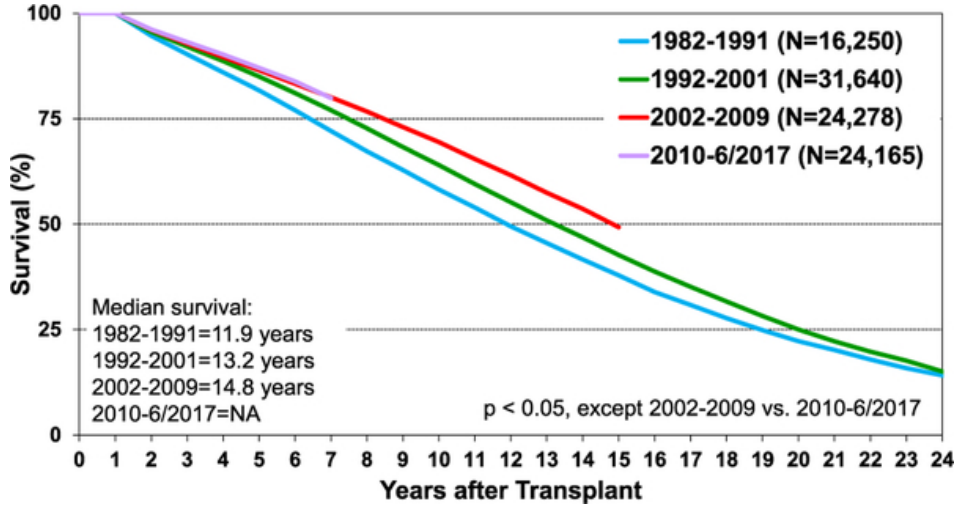
Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med*. 2001;345(20):1435-1443.

Heart Transplant

- Over 108,000 heart transplants performed between 1992 and 2018 worldwide
- Survival has improved with more contemporary immunosuppression
- Median survival (transplanted 2002-2009)
  - 12.5 years
  - 14.8 years if survive first year
- Perspective
  - 5 year survival for HF: 50%
  - 2 year survival for advanced HF: 8%
  - 5 year survival with HMIII: 60%
  - 5 year survival with transplant: 75%



Kaplan-Meier survival by era (adult heart transplants: January 1982–June 2017). NA, not available.



Kaplan-Meier survival by era, conditional on survival to 1 year after transplant (adult heart transplants: January 1982–June 2017). NA, not available.

Khush KK, Cherikh WS, Chambers DC, et al. The international thoracic organ transplant registry of the international society for heart and lung transplantation: thirty-sixth adult heart transplantation report - 2019; focus theme: donor and recipient size match. *J Heart Lung Transplant*. 2019;38(10):1056-1066.

Heart Transplant

- Important contraindications to transplantation
  - Systemic illness with life expectancy < 2 years
  - Active or recent malignancy within 5 years
  - Irreversible renal or hepatic dysfunction
  - Severe COPD
  - Fixed pulmonary hypertension
  - Severe PAD
  - Severe DM with end stage organ damage
  - Drug, tobacco or alcohol abuse within 6 months
  - Active mental illness or psychosocial instability
  - Age/BMI (center dependent)

When to Refer to Advanced Heart Failure Program

Remember acronym to assist in decision making for referral to advanced heart failure specialist:

I-NEED-HELP (also see *Table 6*)

I: IV inotropes

N: NYHA IIIB/IV or persistently elevated natriuretic peptides

E: End-organ dysfunction

E: Ejection fraction ≤35%

D: Defibrillator shocks

H: Hospitalizations >1

E: Edema despite escalating diuretics

L: Low blood pressure, high heart rate

P: Prognostic medication – progressive intolerance or down-titration of GDMT

Summary of Novel Therapies

- HFrEF
  - ARNi
  - SGLT-2 inhibitors (regardless of DM status)
  - Transcatheter repair for severe MR
  - CardioMEMS
  - Consider defibrillators and CRT in select patients
  - IV iron if iron deficient
  - Atrial fibrillation ablation if symptomatic
  - Consider ivabradine and vericiguat
  - Advanced therapies
- HFpEF
  - SGLT-2 inhibitors (regardless of DM status)
  - CardioMEMS
  - Consider ARNi and spironolactone

Our team is available at any time for questions or referrals

Thank you!

Vaiibhav Patel

vaiibhav.patel@osumc.edu

Table 15. Benefits of Evidence-Based Therapies for Patients With HFrEF[3–6,8,10–14,23,31–42]

Evidence-Based Therapy	Relative Risk Reduction in All-Cause Mortality in Pivotal RCTs, %	NNT to Prevent All-Cause Mortality Over Time*	NNT for All-Cause Mortality (Standardized to 12 mo)	NNT for All- Cause Mortality (Standardized to 36 mo)
ACEi or ARB	17	22 over 42 mo	77	26
ARNi†	16	36 over 27 mo	80	27
Beta blocker	34	28 over 12 mo	28	9
Mineralocorticoid receptor antagonist	30	9 over 24 mo	18	6
SGLT2i	17	43 over 18 mo	63	22
Hydralazine or nitrate‡	43	25 over 10 mo	21	7
CRT	36	12 over 24 mo	24	8
ICD	23	14 over 60 mo	70	23

DAPA-HF

- Key Baseline Characteristics
  - 23% Female sex
  - 70% White, 23% Asian, 5% Black
  - 67% NYHA II, 32% NYHA III
  - Median NT-proBNP 1450 pg/mL
  - Median LVEF of approximately 31%
  - 42% with DM2

Heart failure medication — no. (%)	
Diuretic	2216 (93.4)
ACE inhibitor	1332 (56.1)
ARB	675 (28.4)
Sacubitril–valsartan	250 (10.5)
Beta-blocker	2278 (96.0)
Mineralocorticoid receptor antagonist	1696 (71.5)
Digitalis	445 (18.8)

EMPEROR-Reduced

- Key Baseline Characteristics
  - 24% Female sex
  - 70% White, 18% Asian, 7% Black
  - 75% NYHA II, 25% NYHA III
  - Median NT-proBNP 1900 pg/mL
  - 50% with DMT2
  - Mean LVEF of approximately 27%

Characteristic	Empagliflozin (N = 1863)	Placebo (N = 1867)
Heart failure medication — no. (%)		
Renin–angiotensin inhibitor§		
Without neprilysin inhibitor	1314 (70.5)	1286 (68.9)
With neprilysin inhibitor	340 (18.3)	387 (20.7)
Mineralocorticoid receptor antagonist	1306 (70.1)	1355 (72.6)
Beta-blocker	1765 (94.7)	1768 (94.7)

EMPEROR-Preserved

- Key Baseline Characteristics
  - 45% Female sex
  - 76% White, 14% Asian, 4% Black
  - 82% NYHA II, 18% NYHA III
  - Median NT-proBNP 950 pg/mL
  - 49% with DMT2

Left ventricular ejection fraction	
Mean left ventricular ejection fraction — %	54.3±8.8
Left ventricular ejection fraction >40% to <50% — no. (%)§	995 (33.2)
Left ventricular ejection fraction ≥50% to <60% — no. (%)	1028 (34.3)
Left ventricular ejection fraction ≥60% — no. (%)	974 (32.5)

DELIVER

- Key Baseline Characteristics
  - 44% Female sex
  - 71% White, 21% Asian, 3% Black
  - 75% NYHA II, 24% NYHA III
  - 45% with DMT2
  - Median NT-proBNP 1011 pg/Ml

CHAMPION Trial

- Key baseline characteristics
  - Mean age of 62
  - Male sex: 73%
  - Caucasian: 73%
  - Mean BMI of 31
  - Average GFR of 61 mL/min per 1.73 m2

GUIDE-HF

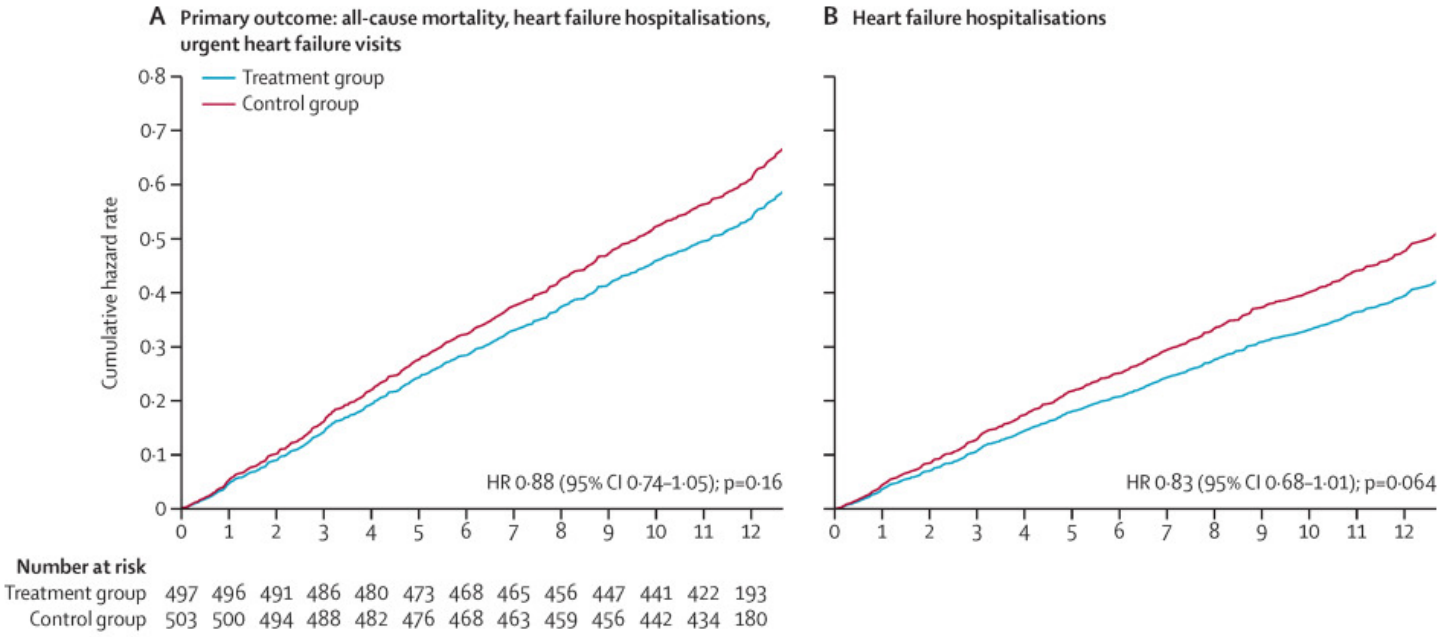
- Beneficial in NYHA class III patients, what about II, IV?
- GUIDE-HF randomized 1000 patients to treatment/control after CardioMEMs implantation
  - NYHA class II-IV
  - All ejection fractions
  - Hospitalization within 12 months or elevated BNP (≥250 pg/mL) or NT-proBNP (≥1000 pg/mL) within 30 days of consent
- Primary endpoint: composite all cause mortality and total heart failure events (hospitalizations, urgent care visits) at 12 months

New York Heart Association functional class			
	II	146 (29%)	150 (30%)
	III	322 (65%)	328 (65%)
	IV	29 (6%)	25 (5%)

Lindenfeld J, Zile MR, Desai AS, et al. Haemodynamic-guided management of heart failure (Guide-hf): a randomised controlled trial. *Lancet*. 2021;398(10304):991-1001.

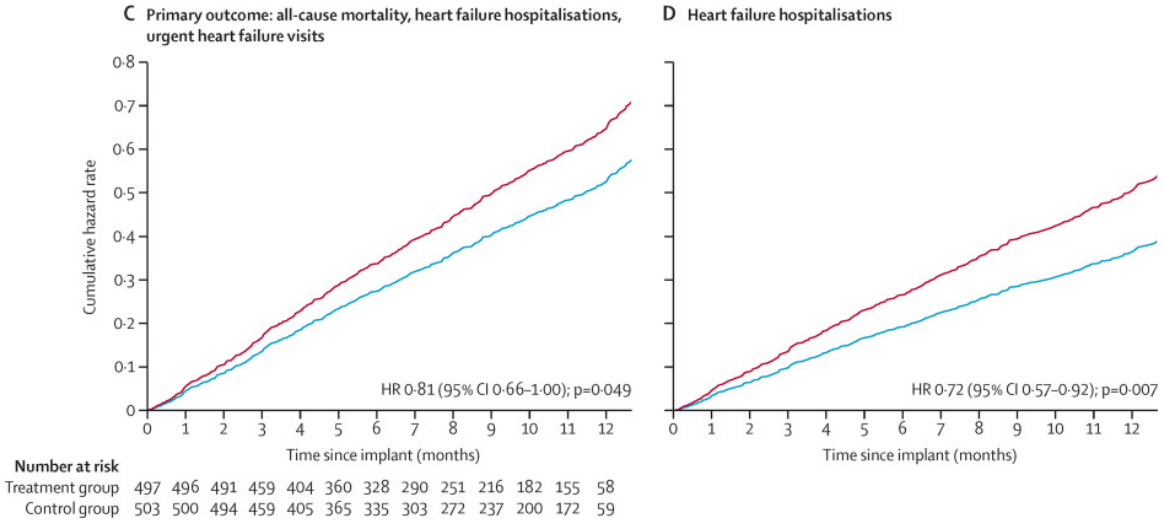
GUIDE-HF

- Overall negative study
  - HR 0.88, P = 0.16
- Trend towards benefit with treatment



GUIDE-HF

- COVID pandemic occurred during follow up period
- During COVID, HFH decreased across the board
- Sensitivity analysis showed an effect of COVID on primary endpoint
- Analysis of all endpoints prior to national emergency declaration performed
- Significant difference seen between groups



Omecamtiv mecarbil

- An oral selective myosin activator
- The GALACTIC-HF trial studied omecamtiv mecarbil in HFrEF (LVEF ≤35%)
  - Outcomes:
    - Positive for primary outcome: composite CV death and HFH, driven by HFH (2% ARR)
    - Subgroups suggest improved outcomes if LVEF < 28% and SBP < 100 mmHg
- In COSMIC-HF, OM improved KCCQ
- No comment in recent guidelines update

Teerlink JR, Diaz R, Felker GM, et al. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. *N Engl J Med*. 2021;384(2):105-116.
Felker GM, Solomon SD, McMurray JJV, et al. Effects of omecamtiv mecarbil on symptoms and health-related quality of life in patients with chronic heart failure: results from the cosmic-hf study. *Circ: Heart Failure*. 2020;13(12):e007814.

COAPT

- Key Baseline Characteristics
  - Median age of around 72, 64% men
  - 61% ischemic
  - 39% NYHA II, 52% NYHA III, 8% NYHA IV
  - Mean LVEF: 31%
  - Mean LV end diastolic dimension: 6.2 cm

PARADIGM-HF

Baseline characteristics

- Median Age: 64.8 years old
- Baseline creatinine:
  - 1.12 in enalapril arm, 1.13 in ARNi arm
- Baseline LVEF:
  - 29.4% in enalapril arm, 29.6% in ARNi arm
- 90% of patients were either NYHA class II or III

Table 1. (Continued.)

Characteristic	LCZ696 (N=4187)	Enalapril (N=4212)
Treatments at randomization — no. (%)		
Diuretic	3363 (80.3)	3375 (80.1)
Digitalis	1223 (29.2)	1316 (31.2)
Beta-blocker	3899 (93.1)	3912 (92.9)
Mineralocorticoid antagonist	2271 (54.2)	2400 (57.0)
Implantable cardioverter–defibrillator	623 (14.9)	620 (14.7)
Cardiac resynchronization therapy	292 (7.0)	282 (6.7)