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Foundations of Cardiometabolic Health Certification Course

Certified Cardiometabolic Health Professional (CCHP)

Heart Failure Treatment in the Era of Multiple Therapies: A Potpourri

Ileana L. Piña, MD, MPH, FAHA, FACC, FHFSA
Professor Medicine, Thomas Jefferson University
Clinical Professor of Medicine
Central Michigan University
Adjunct Professor of Epi/Biostats, Case Western Reserve University
Senior Staff Fellow for FDA, CDRH, Medical Officer

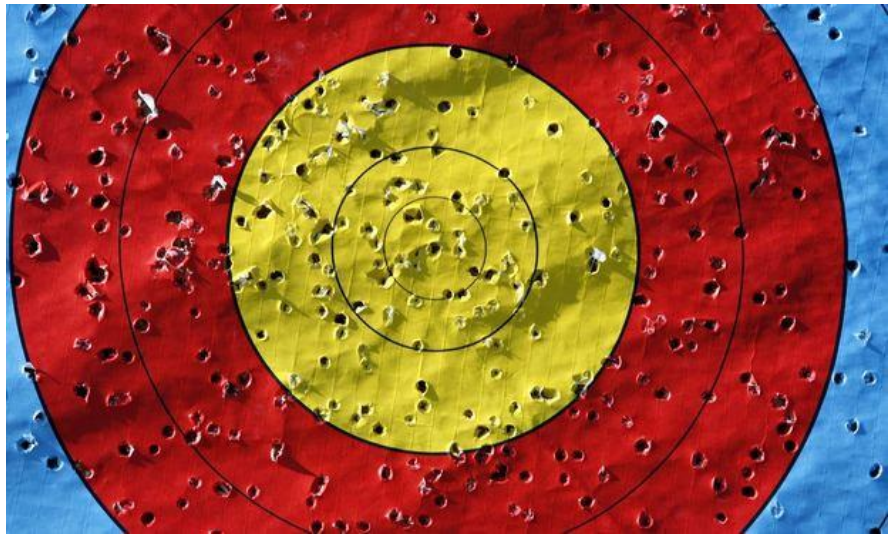
The Landscape of Heart Failure

- Complex
- Hospitalizations are frequent
- Costs are high
- CMS rule penalties
- Patients are becoming more challenging
- Team effort

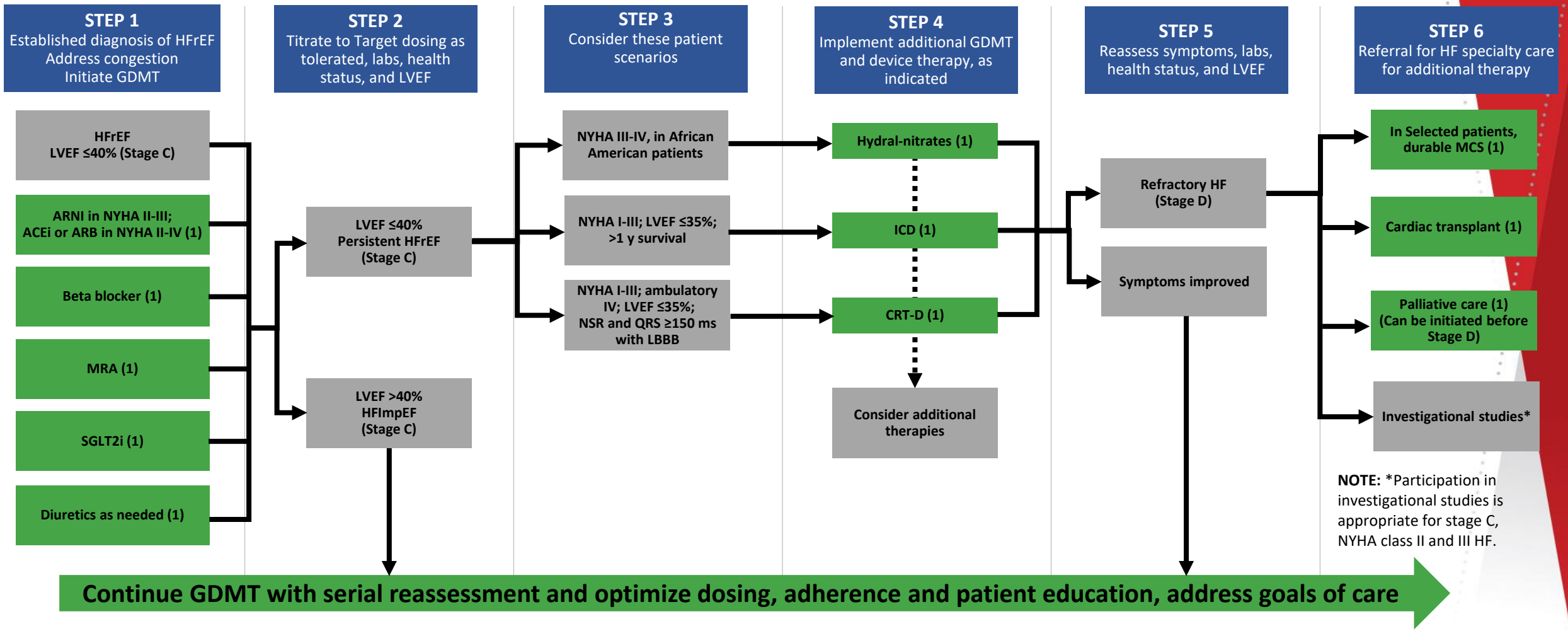
CMS, Centers for Medicare & Medicaid Services.

Where Have Our Old Targets Been?

- Sympathetic nervous system
- Angiotensin-converting enzyme
- Aldosterone
- Angiotensin II receptor blocker
- Vasopressin
- Endothelin
- Sodium and water retention
- Loss of contractility



Treatment of HFrEF Stages C and D

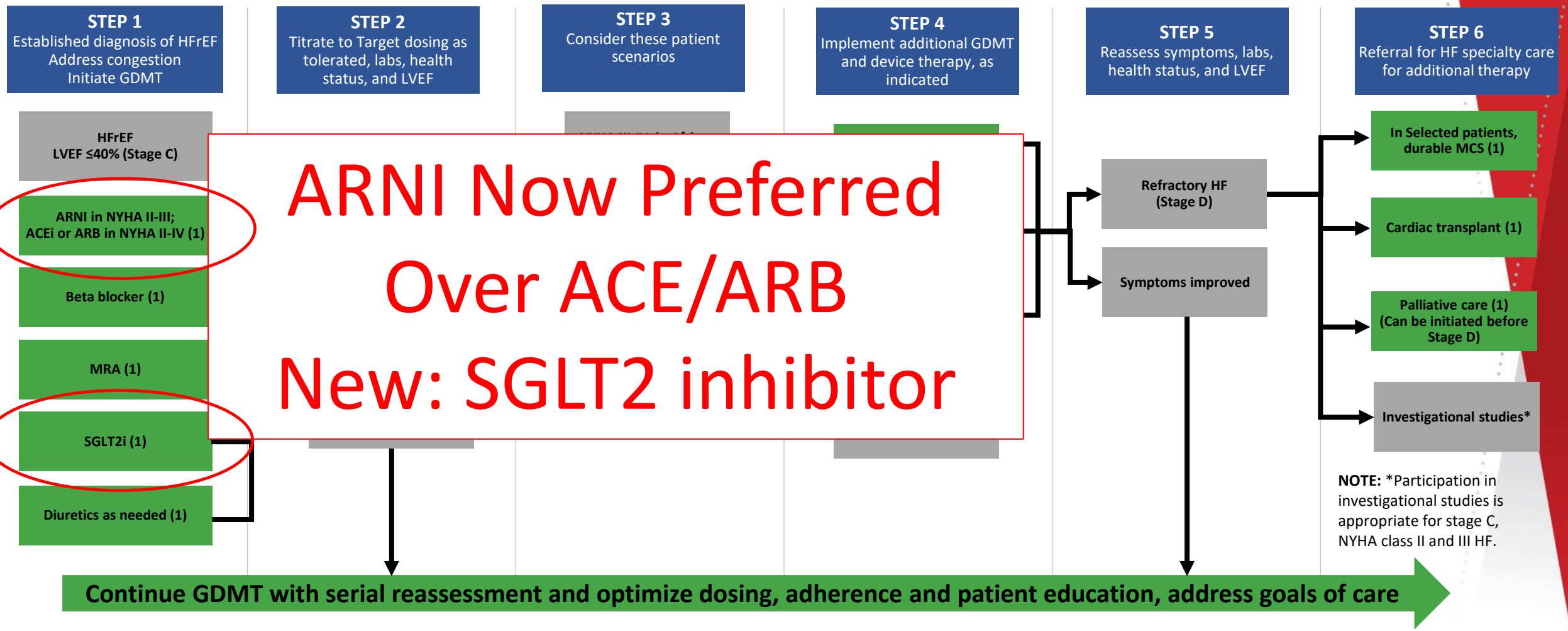


Abbreviations: ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; hydral-nitrates, hydralazine and isosorbide dinitrate; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; NSR, normal sinus rhythm; NYHA, New York Heart Association; SCD, sudden cardiac death; and SGLT2i, sodium-glucose cotransporter 2 inhibitor.

American Heart Association.

Heidenreich, P. A. et al. (2022). 2022 AHA/ACC/HFSA Guideline for Heart Failure. *Circulation*.

Treatment of HFrEF Stages C and D

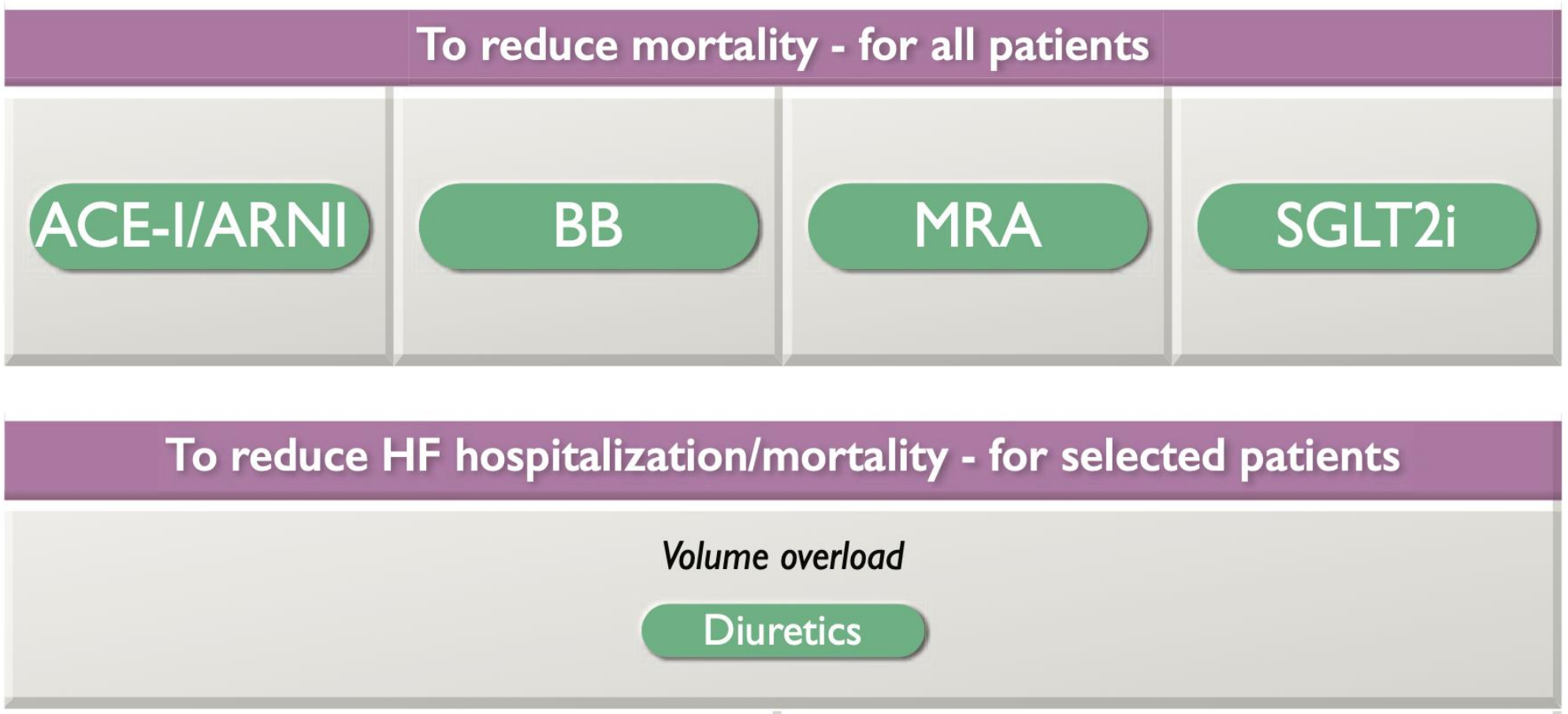


Abbreviations: ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; hydral-nitrates, hydralazine and isosorbide dinitrate; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; NSR, normal sinus rhythm; NYHA, New York Heart Association; SCD, sudden cardiac death; and SGLT2i, sodium-glucose cotransporter 2 inhibitor.

American Heart Association.

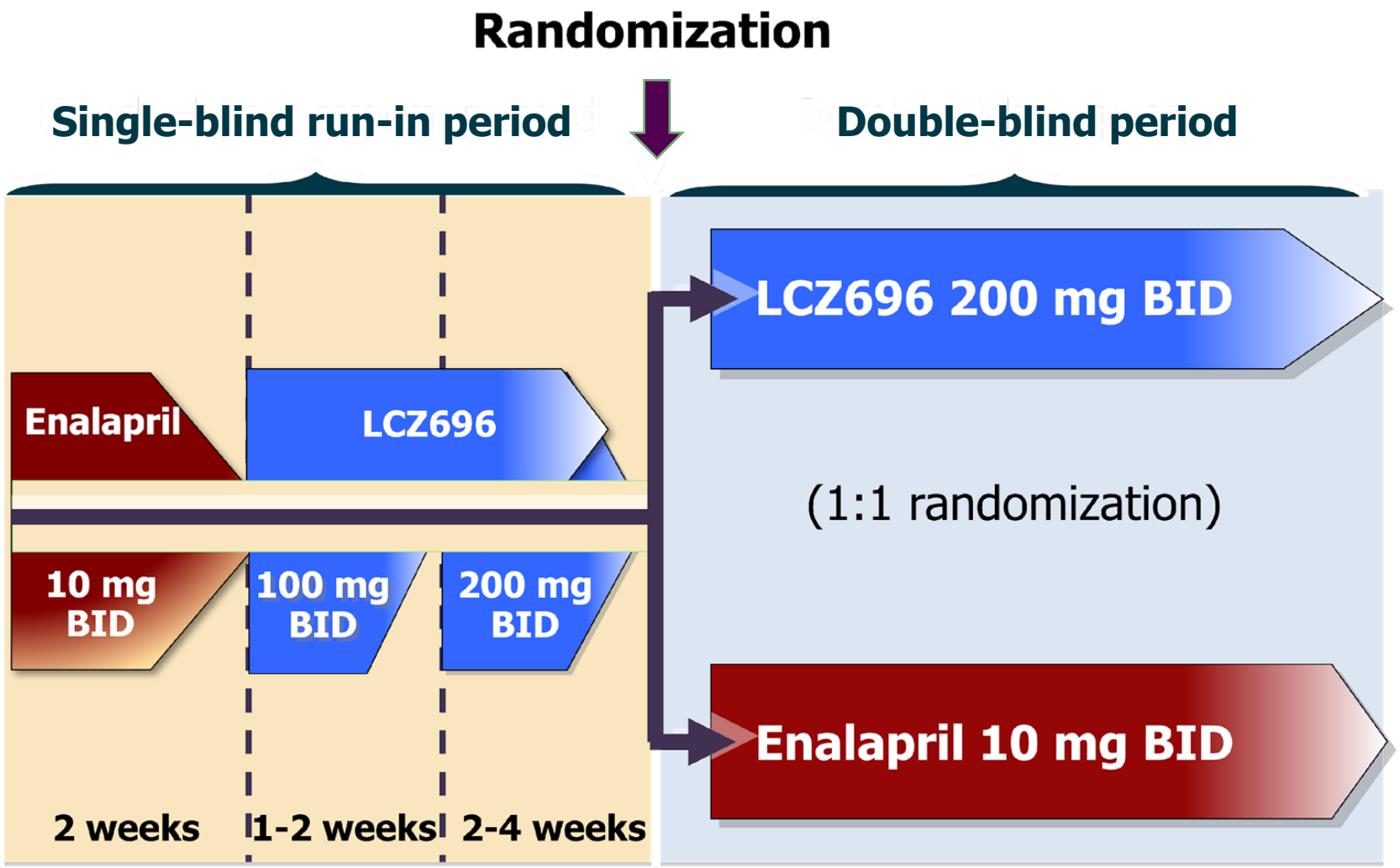
Heidenreich, P. A. et al. (2022). 2022 AHA/ACC/HFSA Guideline for Heart Failure. *Circulation*.

4 “Pillars” of Foundational Therapy for Optimal Management of HFrEF



McDonagh et al EHJ 2021

PARADIGM-HF: Study Design



McMurray JJV, et al, for the PARADIGM-HF Investigators and Committees. N Engl J Med. 2013;371(11):993-1004.

PARADIGM-HF: Baseline Characteristics

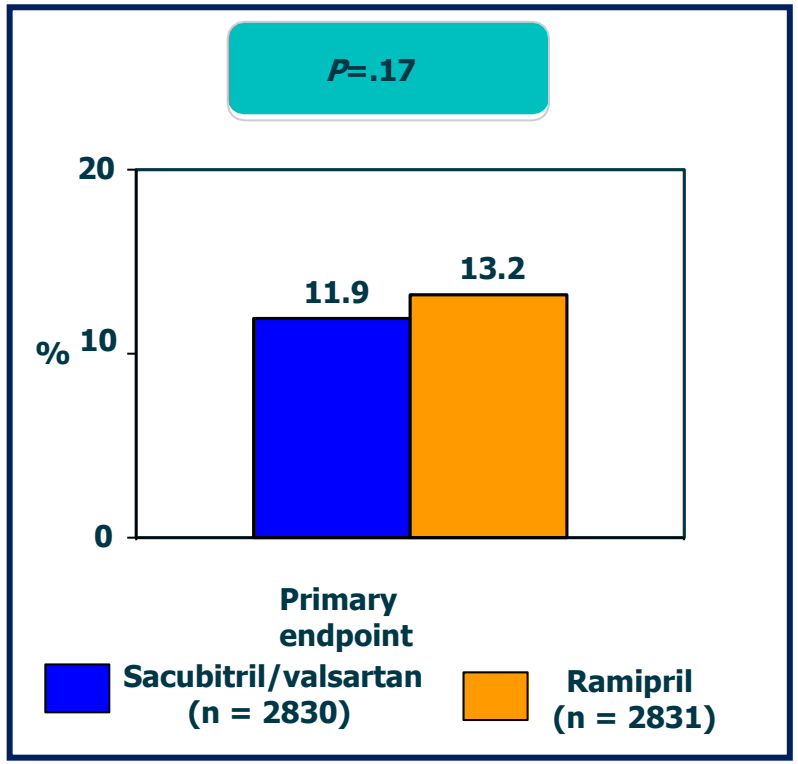
	LCZ696 (n=4187)	Enalapril (n=4212)
Age (years)	63.8 ± 11.5	63.8 ± 11.3
Women (%)	21.0%	22.6%
Ischemic cardiomyopathy (%)	59.9%	60.1%
LV ejection fraction (%)	29.6 ± 6.1	29.4 ± 6.3
NYHA functional class II / III (%)	71.6% / 23.1%	69.4% / 24.9%
Systolic blood pressure (mm Hg)	122 ± 15	121 ± 15
Heart rate (beats/min)	72 ± 12	73 ± 12
N-terminal pro-BNP (pg/mL)	1631 (885-3154)	1594 (886-3305)
B-type natriuretic peptide (pg/mL)	255 (155-474)	251 (153-465)
History of diabetes	35%	35%
Digitalis	29.3%	31.2%
Beta-adrenergic blockers	93.1%	92.9%
Mineralocorticoid antagonists	54.2%	57.0%
ICD and/or CRT	16.5%	16.3%

McMurray JJV, et al, for the PARADIGM-HF Investigators and Committees. N Engl J Med. 2013;371(11):993-1004.

PARADISE-MI

#ACC21

Trial Description: Patients with acute myocardial infarction (AMI) presentation and newly diagnosed LVEF ≤40% were randomized in a 1:1 fashion to either sacubitril/valsartan (target dose 97/103 mg BID) or ramipril (target dose 5 mg BID). Patients were followed for a median of 23 months.



RESULTS

- Primary endpoint of CV death, first HF hospitalization, or outpatient HF event for sacubitril/valsartan versus ramipril: 11.9% vs 13.2% (*P*=.17)
- CV death: 5.9% vs 6.7% *(P*=.20)
- HF hospitalization: 6% vs 6.9% *(P*= .17)
- All-cause mortality: 7.5% vs 8.5% *(P*= .16)
- Total HF hospitalization, outpatient HF events, and CV mortality: 8.4 vs 10.1/100 patient-years *(P*= .02)

CONCLUSIONS

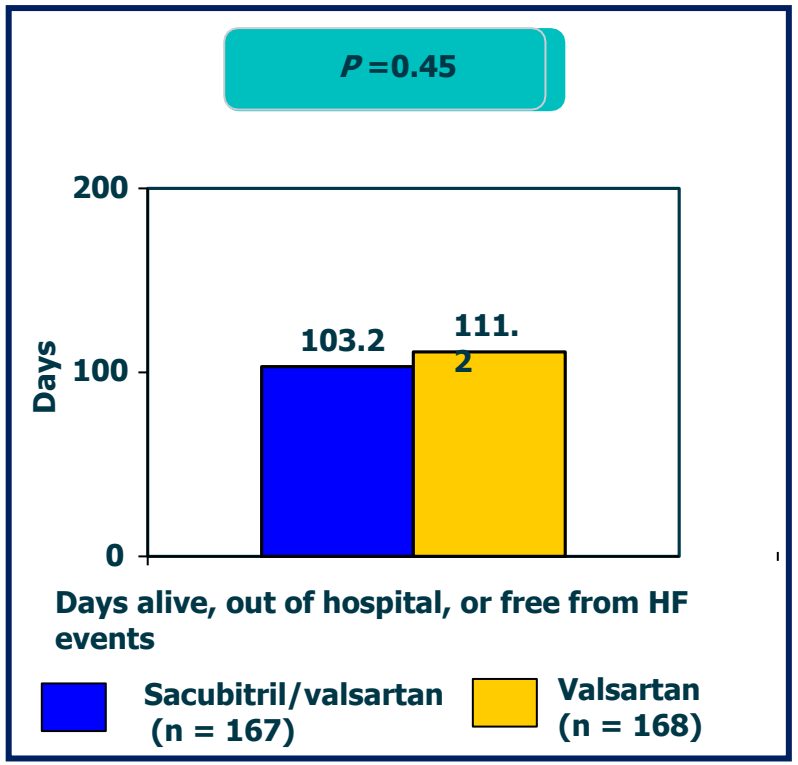
- Combination sacubitril/valsartan did not reduce the primary endpoint in a contemporary enriched AMI population versus ramipril
- Rates were numerically lower in the sacubitril/valsartan arm, and composite endpoint including all HF events showed benefit with sacubitril/valsartan

Presented by Dr. Marc Pfeffer at ACC.21
Developed by Dr. Neil Keshvani in collaboration with the ACC.org Editorial Board

LIFE

#ACC21

Trial Description: Patients with advanced HFrEF were randomized in a 1:1 fashion to either sacubitril/valsartan or valsartan. Patients were followed for 24 weeks.



RESULTS

- Primary endpoint, area under the curve for the proportional change in the ratio of NT-proBNP to baseline, for sacubitril/valsartan versus valsartan: *P*=.45
- Days alive, out of hospital, or free from HF events: 103.2 vs 111.2 days (*P*=.45)
- CV death or hospitalization for HF: HR 1.32, 95% CI 0.86-2.03 (*P*=.20)
- Hypotension: 17% vs 12% (*P*=.16); hyperkalemia: 17% vs 9% (*P*=.035)

CONCLUSIONS

- Sacubitril/valsartan did not reduce NT-proBNP or clinical outcomes among patients with advanced HFrEF and comorbidities
- Hyperkalemia was higher with sacubitril/valsartan

Presented by Dr. Douglas L. Mann at ACC.21

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Heart Failure: Challenges with GDMT Optimization

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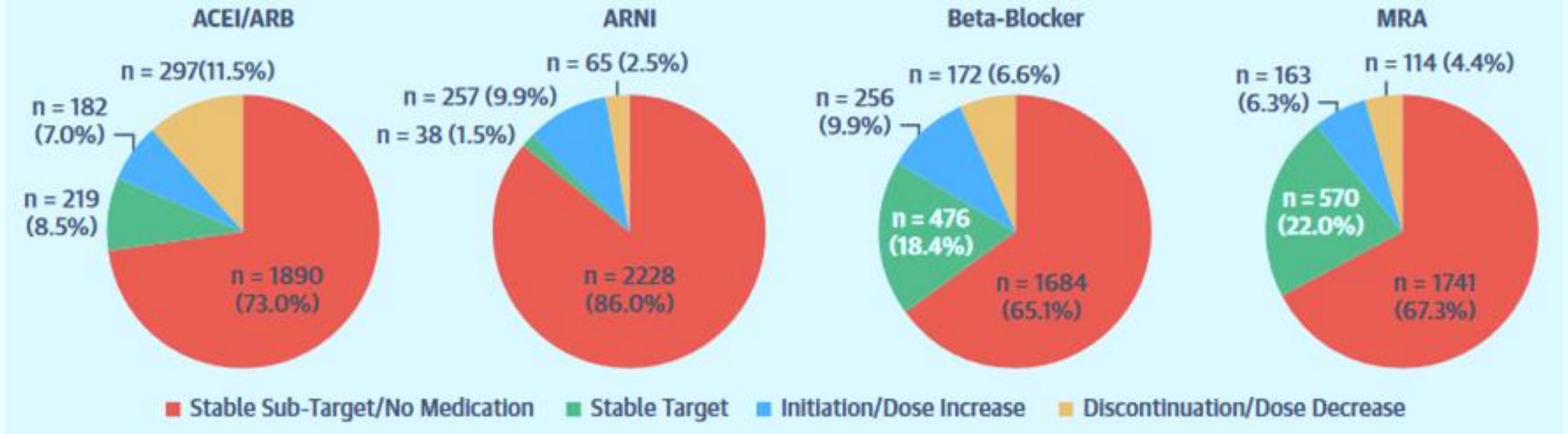
Adjunct Professor of Epi/Biostats, Case Western Reserve University
Senior Staff Fellow for FDA, CDRH, Medical Officer

However, ~80% of Patients With Chronic HF Are Either not on Target Dose, or RAASi Therapy Has Been Down Titrated or Discontinued

The CHAMP-HF registry of 2588 US outpatients with chronic HFrEF receiving ≥1 oral medication
At baseline 658 (25%), 525 (20%), 287 (11%), and 45 (2%) pts were receiving target doses of MRA, Beta-Blocker, ACEI/ARB, and ARNi therapy, respectively

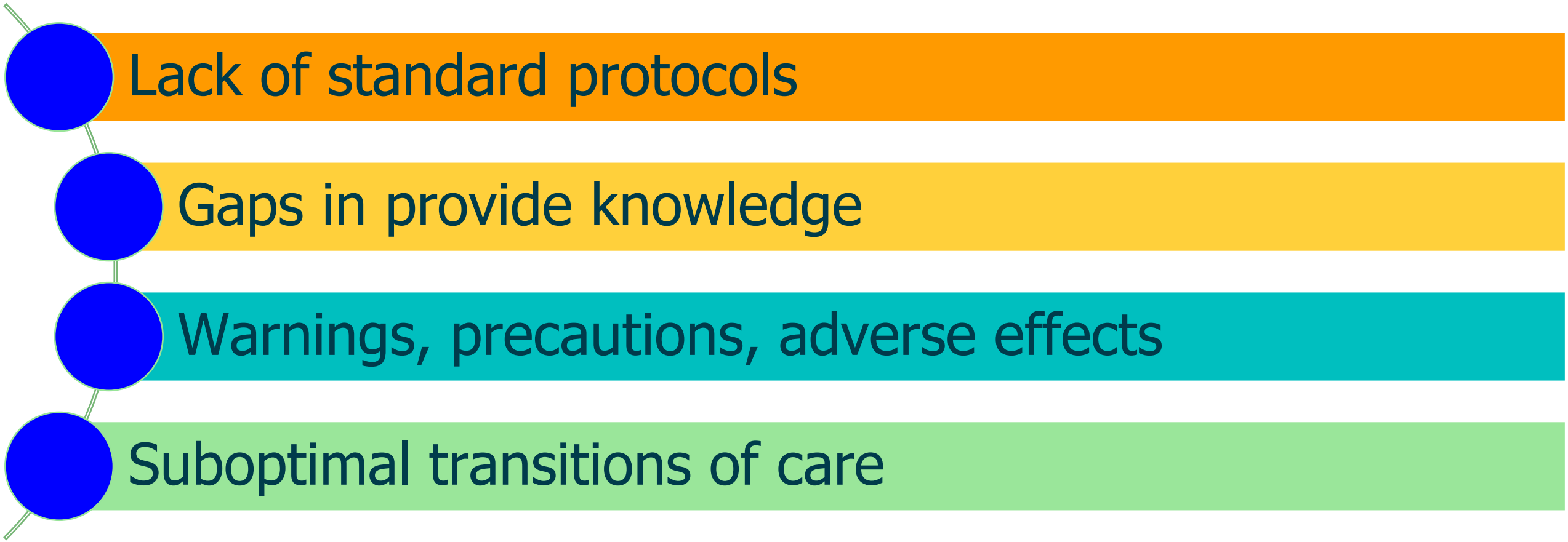
Dose of Medication at 12-Month Follow-up Compared With Baseline



ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; RAASi, renin–angiotensin–aldosterone system inhibitor

Greene SJ, et al. J Am Coll Cardiol. 2019;73(19):2365-2383. Open Access.

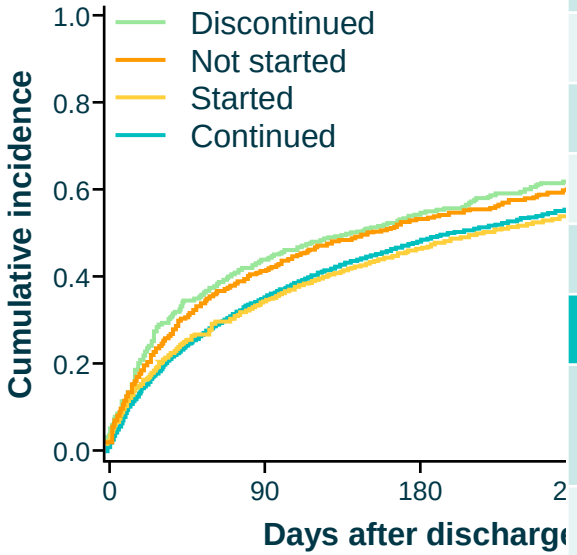
Barriers to Prescribing GDMT



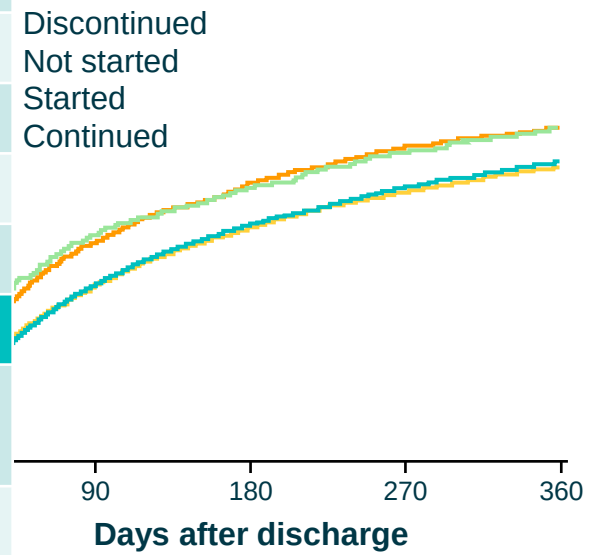
GDMT, guideline-directed medical therapy.

Withdrawal of ACEi/ARB During Heart Failure Hospitalization Is Associated With Higher Rates of Post-discharge Re-admission and Mortality

Incidence rates of 1-year re-admission, 1-year mortality and 1-year composite endpoint (mortality or re-admission), stratified by ACEi/ARB use



ACEi contraindication	N=6753	
Hypotension / risk for cardiogenic shock	588	8.71%
Azotaemia	1589	23.53%
Other	4023	59.57%
Patient reason	796	11.79%
System reason	58	0.86%
ARB contraindication	**N=6739**	
Hypotension / risk for cardiogenic shock	587	8.71%
Azotaemia	1610	23.89%
Other	3983	59.10%
Patient reason	765	11.35%
System reason	56	0.83%



Gilstrap LG, et al. J Am Heart Assoc. 2017;6:e004675. Open Access.

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New Targets & Trials In HF: An Overview

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Clinical Professor of Medicine
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Adjunct Professor of Epi/Biostats, Case Western Reserve University
Senior Staff Fellow for FDA, CDRH, Medical Officer

New Targets / Trials

(looking at the syndrome from different angles)

New vasodilators /GMPc modulators

Synthetic natriuretic peptides

Sinus node inhibition for heart rate reduction

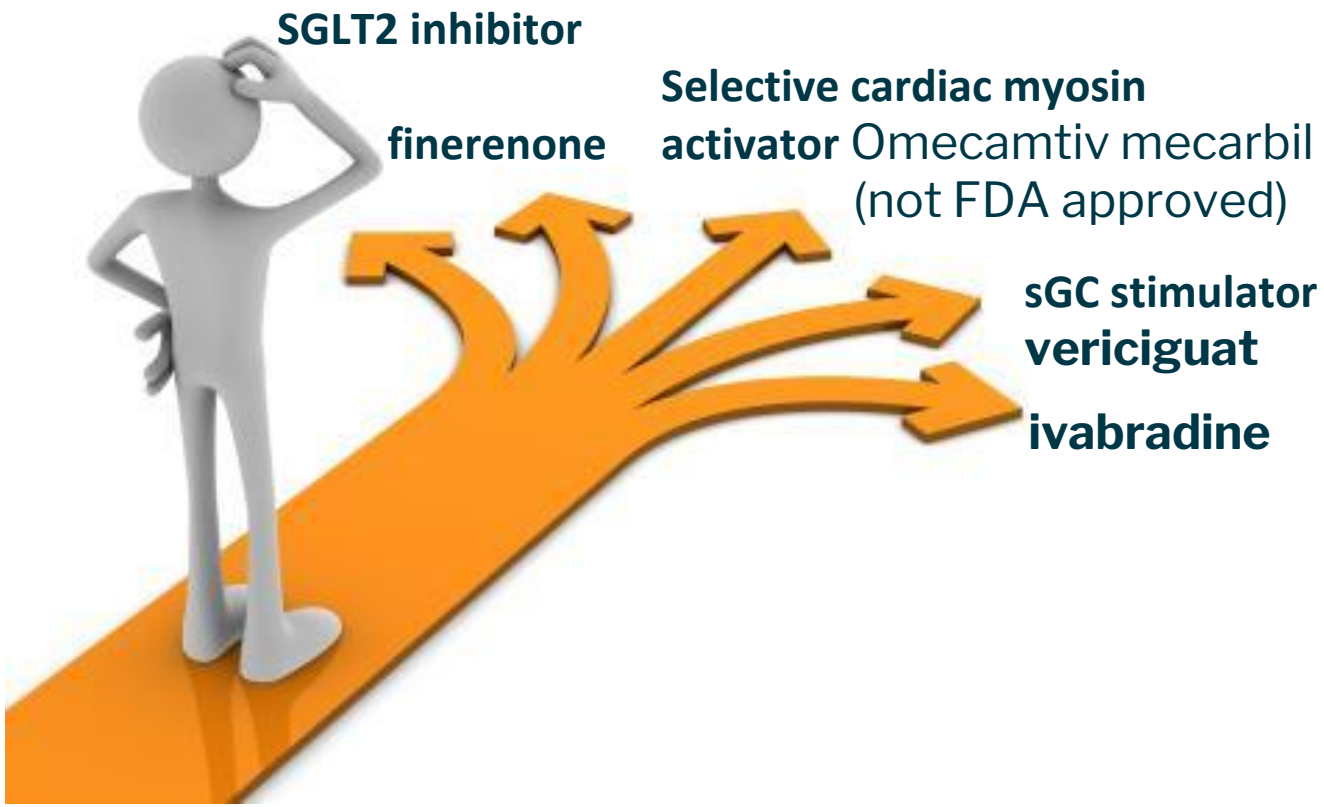
NEP inhibitors (+ ARB) (ARNI)

Binders of actin-myosin

Novel nonsteroidal MRAs

Refinement of therapy, biomarkers, remodelling

A Plethora of Choices…



Therapies With Effects on B-Type Natriuretic Peptide Levels

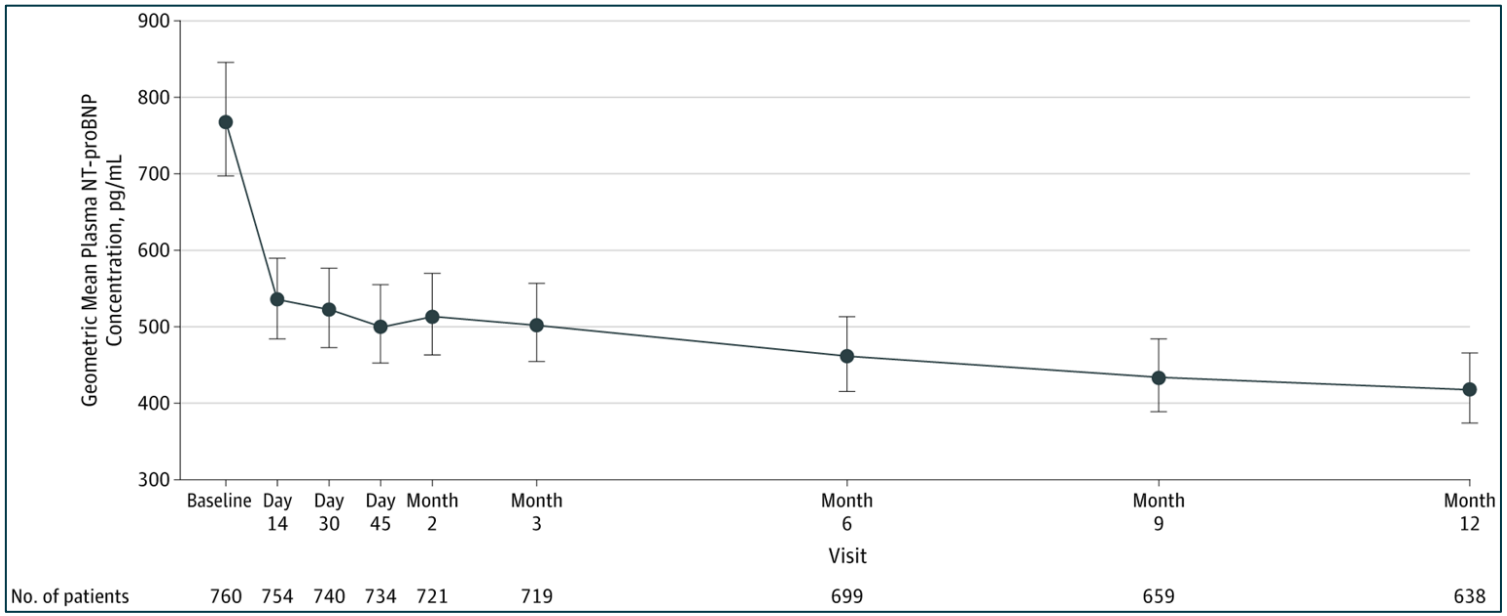
Therapy	Effect on BNP/NT-proBNP
Diuresis	↓
ACEi/ARB	↓
β blockers	↓
Aldosterone antagonists	↓
Biventricular pacing	↓
Exercise	↓
Rate control of atrial fibrillation	↓
Natriuretic peptide infusions	↓
Serelaxin	↓
Valsartan/sacubitril	↓ NT-proBNP, ↑ BNP
Neuregulin	↑

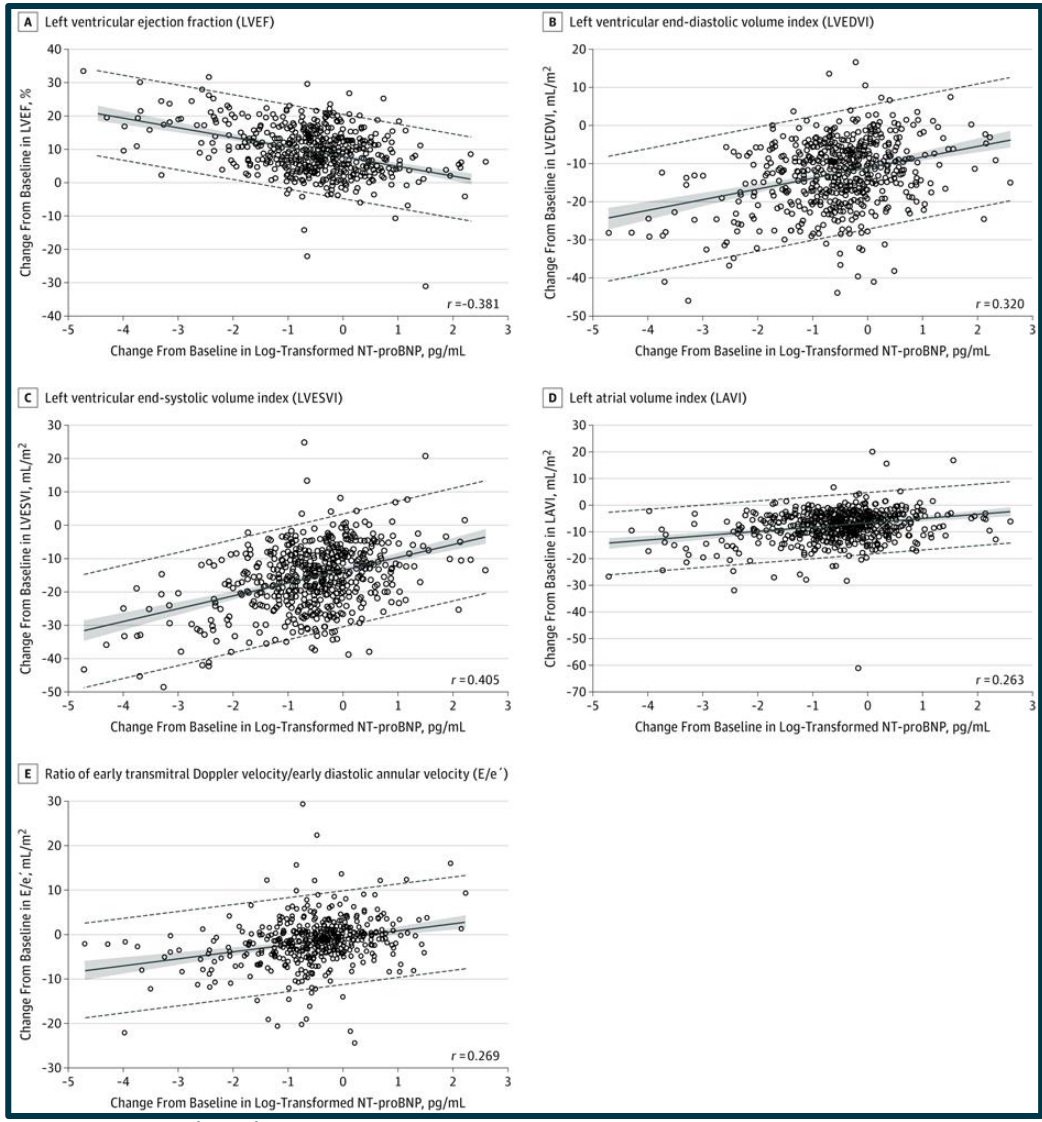
Courtesy of James L. Januzzi, MD

JAMA | Original Investigation

Association of Change in N-Terminal Pro–B-Type Natriuretic Peptide Following Initiation of Sacubitril-Valsartan Treatment With Cardiac Structure and Function in Patients With Heart Failure With Reduced Ejection Fraction

James L. Januzzi Jr, MD; Margaret F. Prescott, PhD; Javed Butler, MD, MPH, MBA; G. Michael Felker, MD, MHS; Alan S. Maisel, MD; Kevin McCague, MA; Alexander Camacho, PhD; Ileana L. Piña, MD, MPH; Ricardo A. Rocha, MD; Amil M. Shah, MD, MPH; Kristin M. Williamson, PharmD; Scott D. Solomon, MD; for the PROVE-HF Investigators





Concentrations of N-Terminal Pro–B-Type Natriuretic Peptide (NT-proBNP) Across Study VisitsReduction in NT-proBNP was evident by the first follow-up visit and was sustained throughout the 12 months. Concentrations of NT-proBNP were included if collected 6 or more hours from the first dose of sacubitril-valsartan. Distributions of NT-proBNP at each time point can be found in eTable 2 and eFigure 3 in Supplement 3.

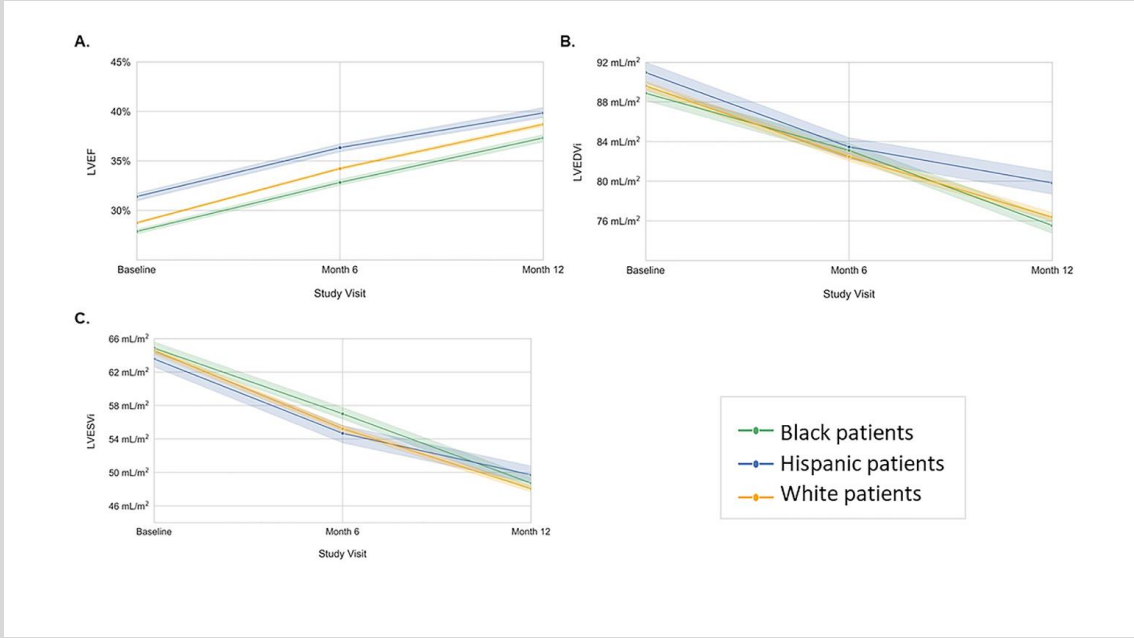
Januzzi JL Jr, et al. *JAMA.* 2019;322(11):1085-1095. Open Access.

Circulation: Heart Failure

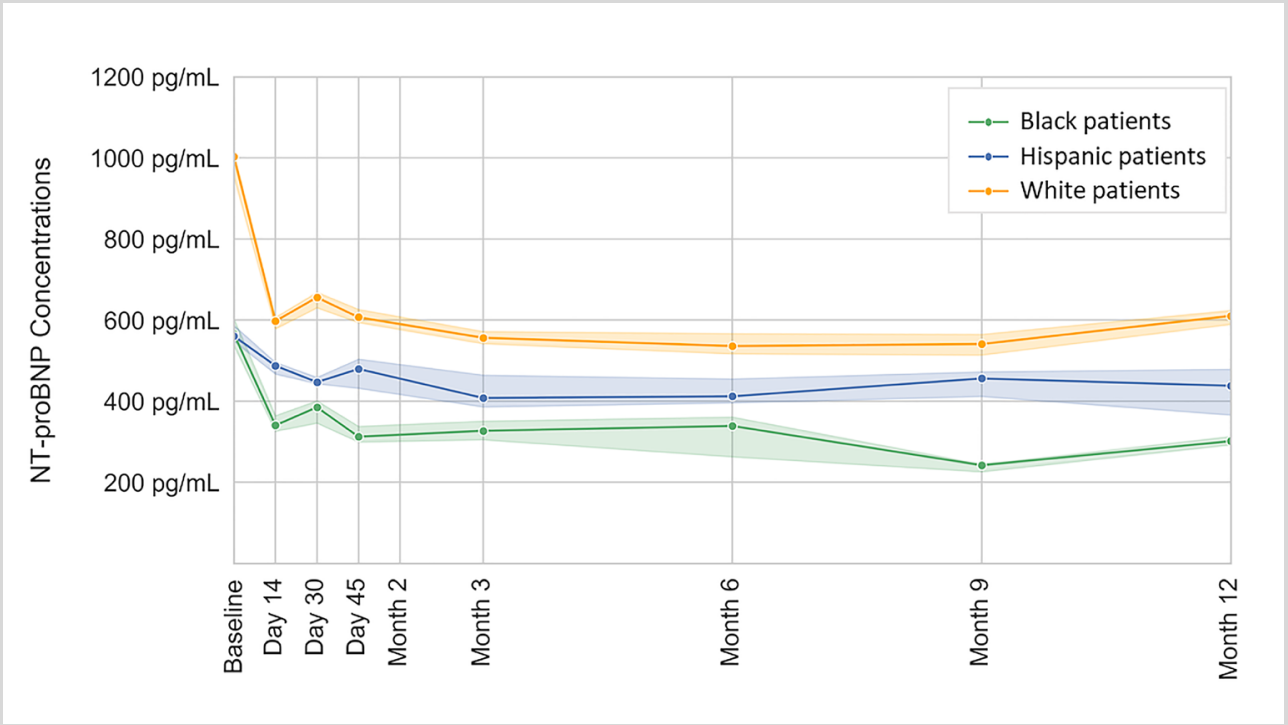
ORIGINAL ARTICLE

Racial and Ethnic Differences in Biomarkers, Health Status, and Cardiac Remodeling in Patients With Heart Failure With Reduced Ejection Fraction Treated With Sacubitril/Valsartan

Nasrien E. Ibrahim, MD; Ileana L. Piña, MD, MPH; Alexander Camacho, PhD; Devavrat Bapat, MS; G. Michael Felker, MD, MHS; Alan S. Maisel, MD; Javed Butler, MD, MPH, MBA; Margaret F. Prescott, PhD; Cheryl A. Abbas, PharmD; Scott D. Solomon, MD; James L. Januzzi, Jr, MD; on behalf of the Prospective Study of Biomarkers, Symptom Improvement and Ventricular Remodeling During Entresto Therapy for Heart Failure (PROVE-HF) Study Investigators



Consistent across race/ethnicity



Ibrahim NE, et al. *Circ Heart Fail.* 2020;13(11):e007829. Open Access.

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Cardiac Myosin Activators in HFrEF

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Clinical Professor of Medicine
Central Michigan University
Adjunct Professor of Epi/Biostats, Case Western Reserve University
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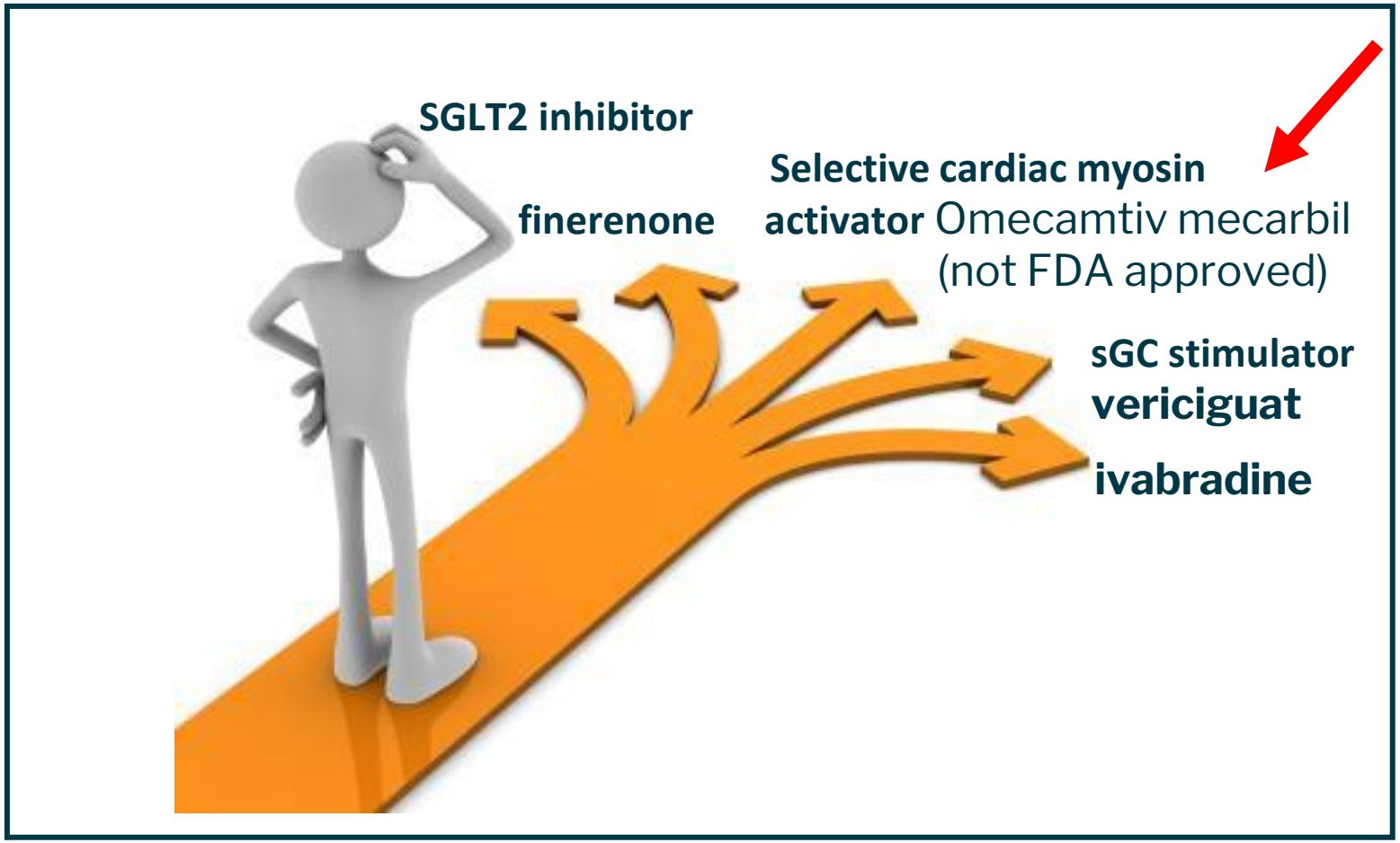
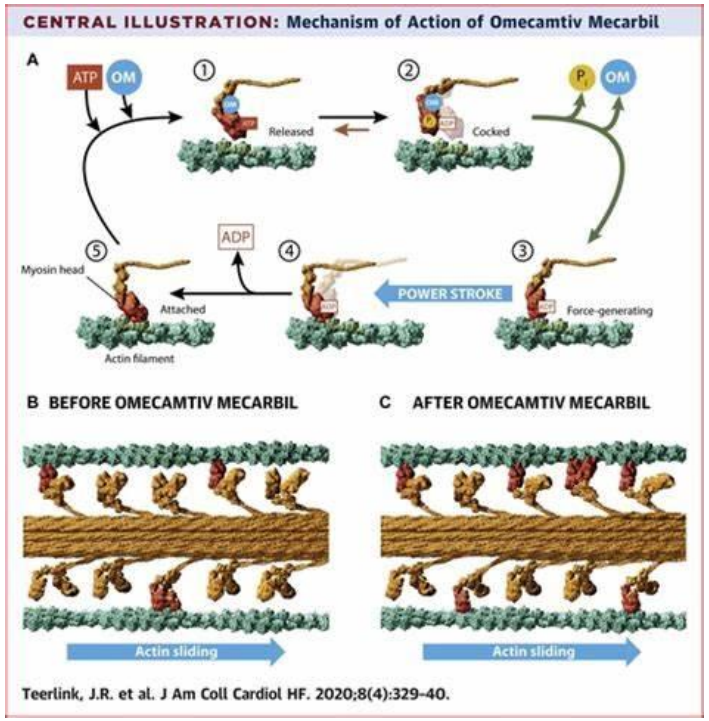
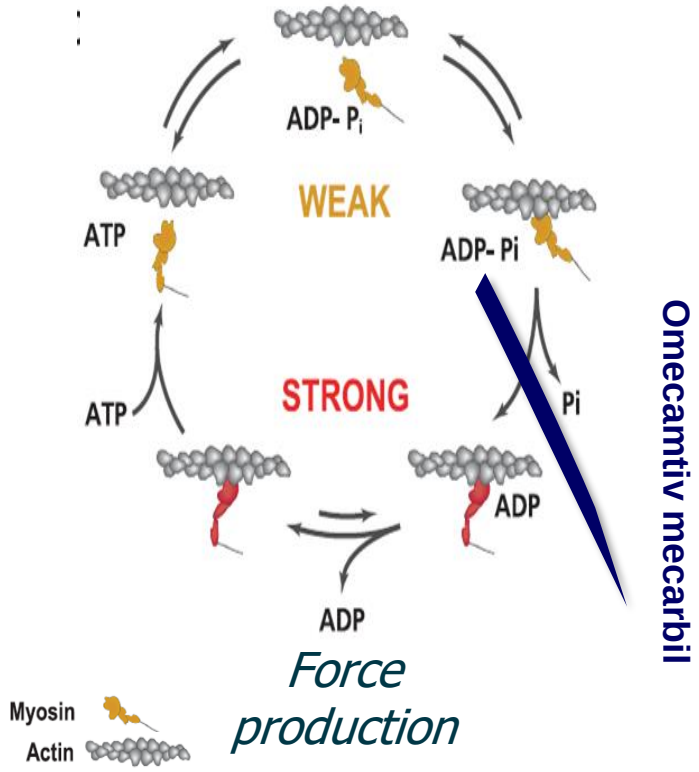
A Plethora of Choices…



ATOMIC-AHF: Omecamtiv Mecarbil (OM) Is a Novel Selective Cardiac Myosin Activator



Mechanochemical Cycle of Myosin



Omecamtiv mecarbil increases the entry rate of myosin into the tightly bound, force-producing state with actin

"More hands pulling on the rope"

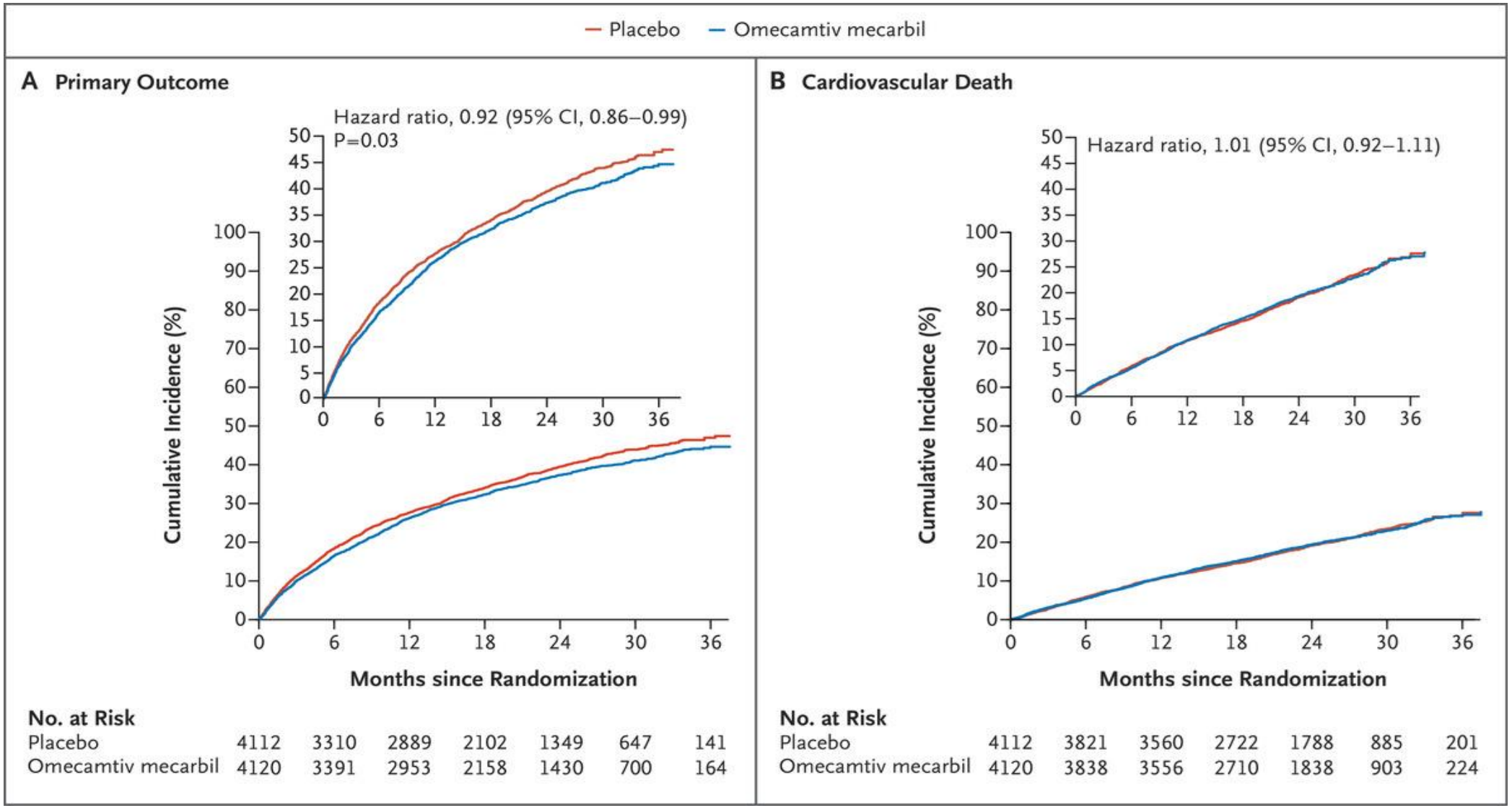
- Increases duration of systole
- Increases stroke volume
- No increase in myocyte calcium
- No change in dP/dt_{max}
- No increase in MVO_2

dP/dt_{max}, peak positive derivatives of LV pressure; MVO_2, myocardial oxygen consumption.

Malik FI, et al. *Science.* 2011;331(6023):1439-1443.

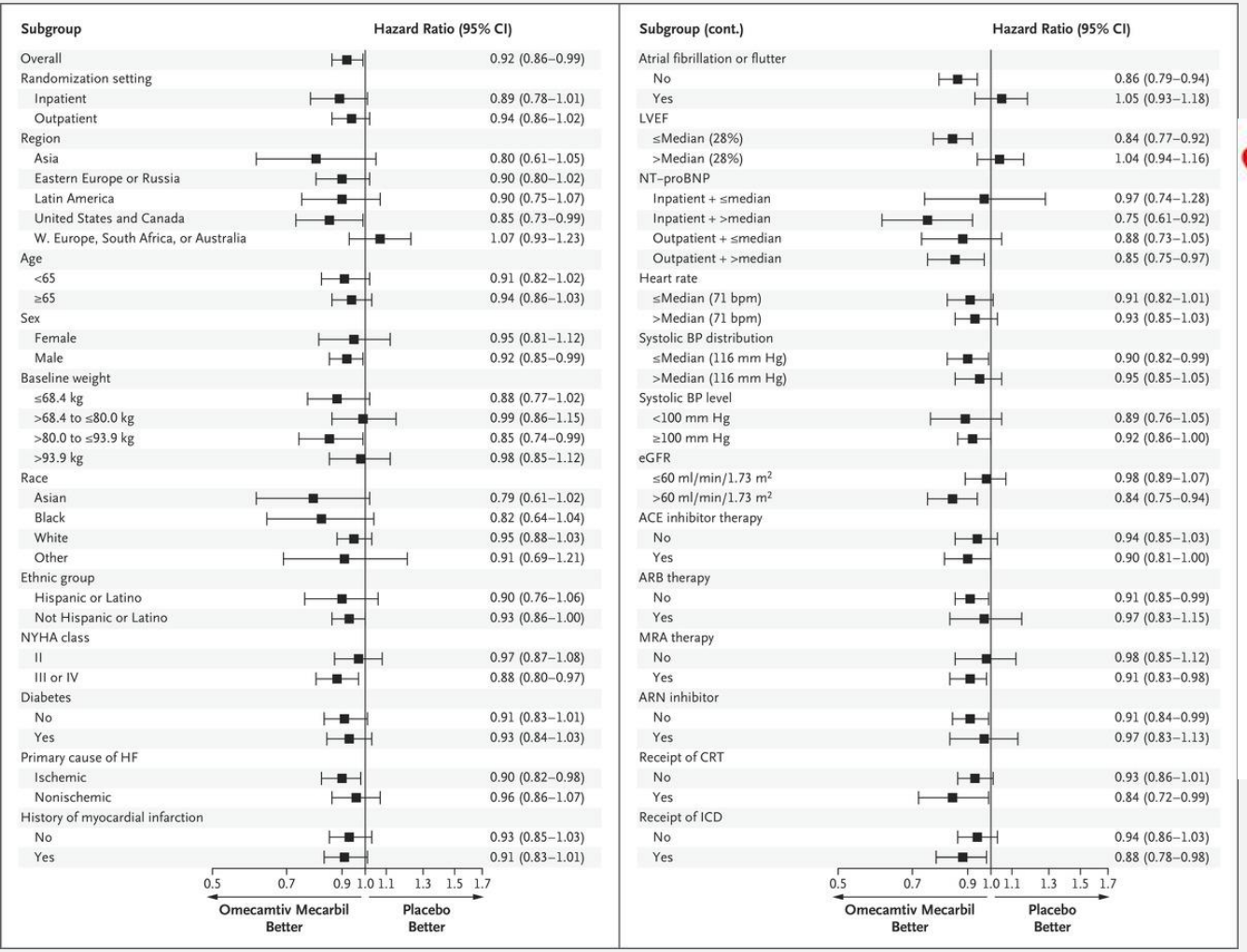
Teerlink JR, et al. *J Am Coll Cardiol.* 2016;67(12):1444-1455. Open Access.

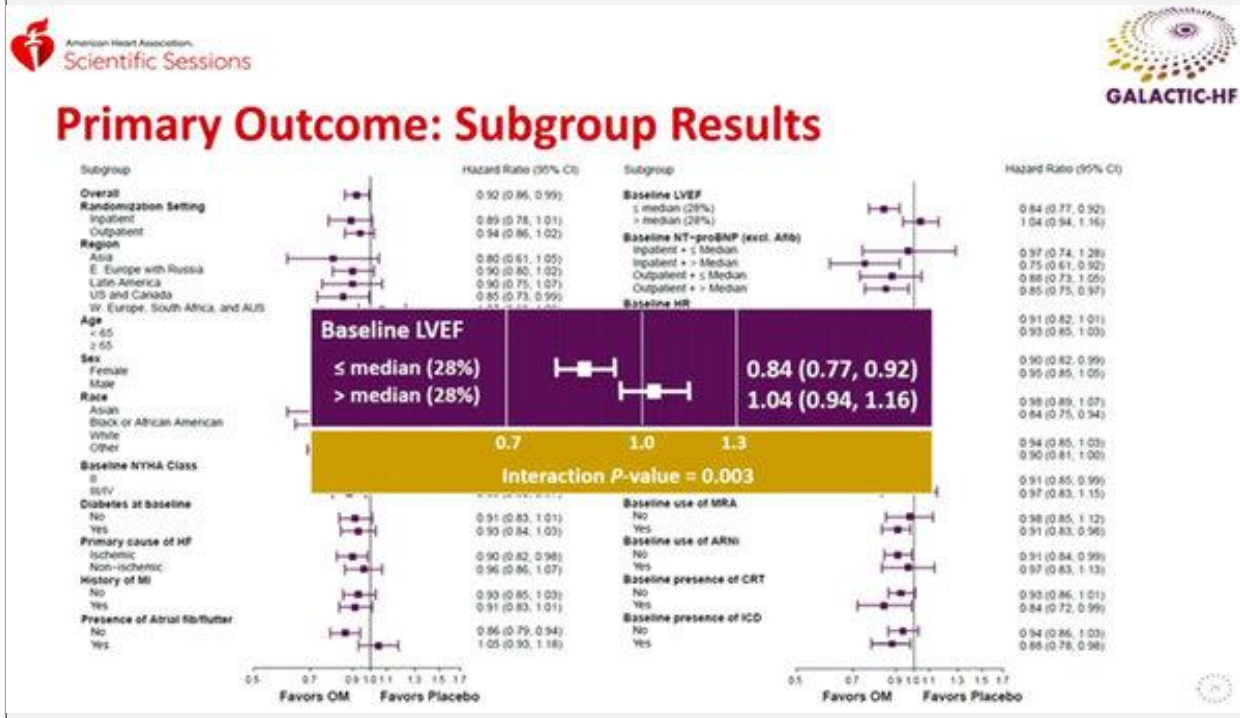
Primary Composite Outcome: HF Event or CV Death



Teerlink JR, et al. *N Engl J Med.* 2021;384(2):105-116.

Primary Composite Outcome, According to Prespecified Subgroup





Teerlink JR, et al. *N Engl J Med.* 2021;384(2):105-116.

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sGC Stimulators in HFrEF

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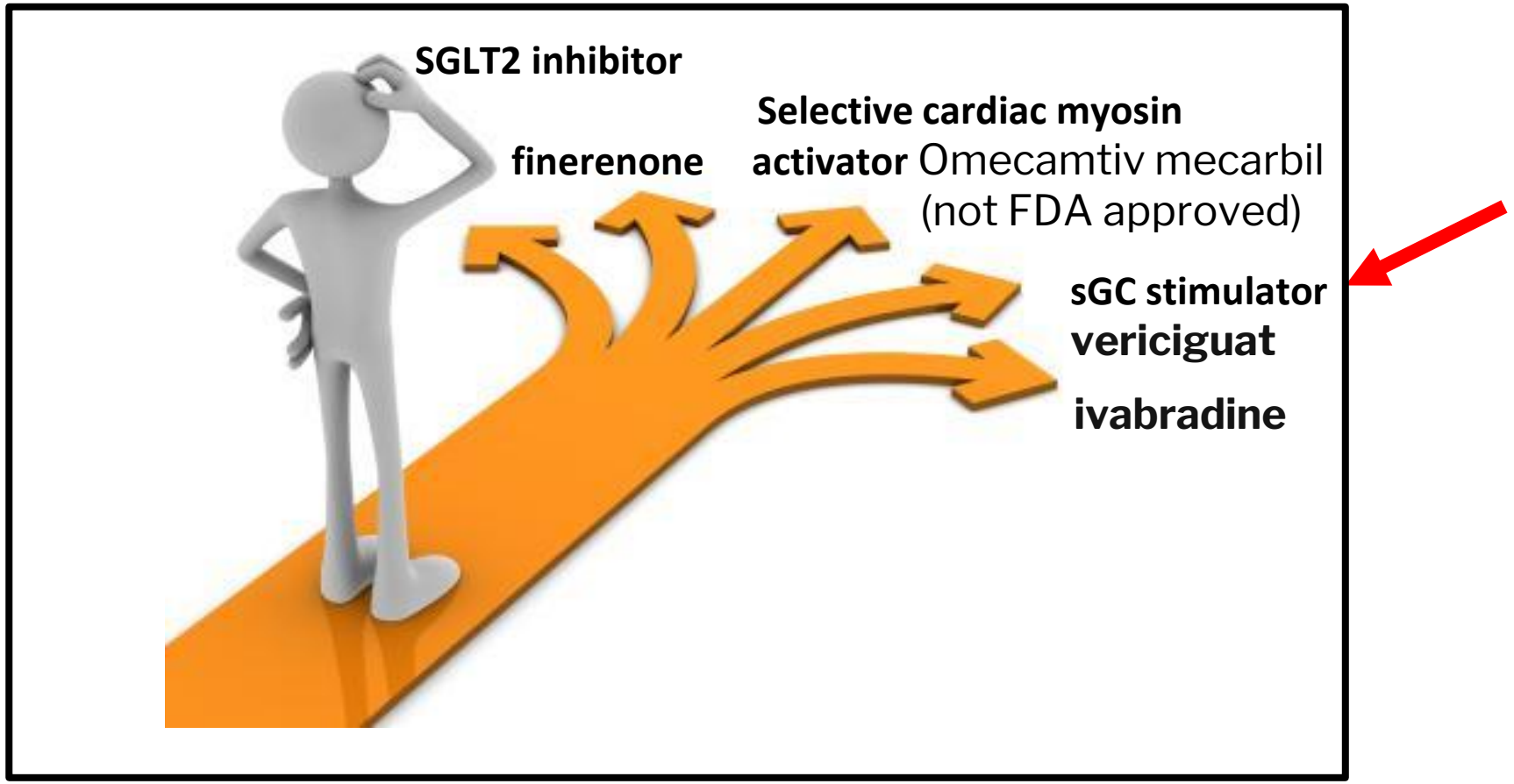
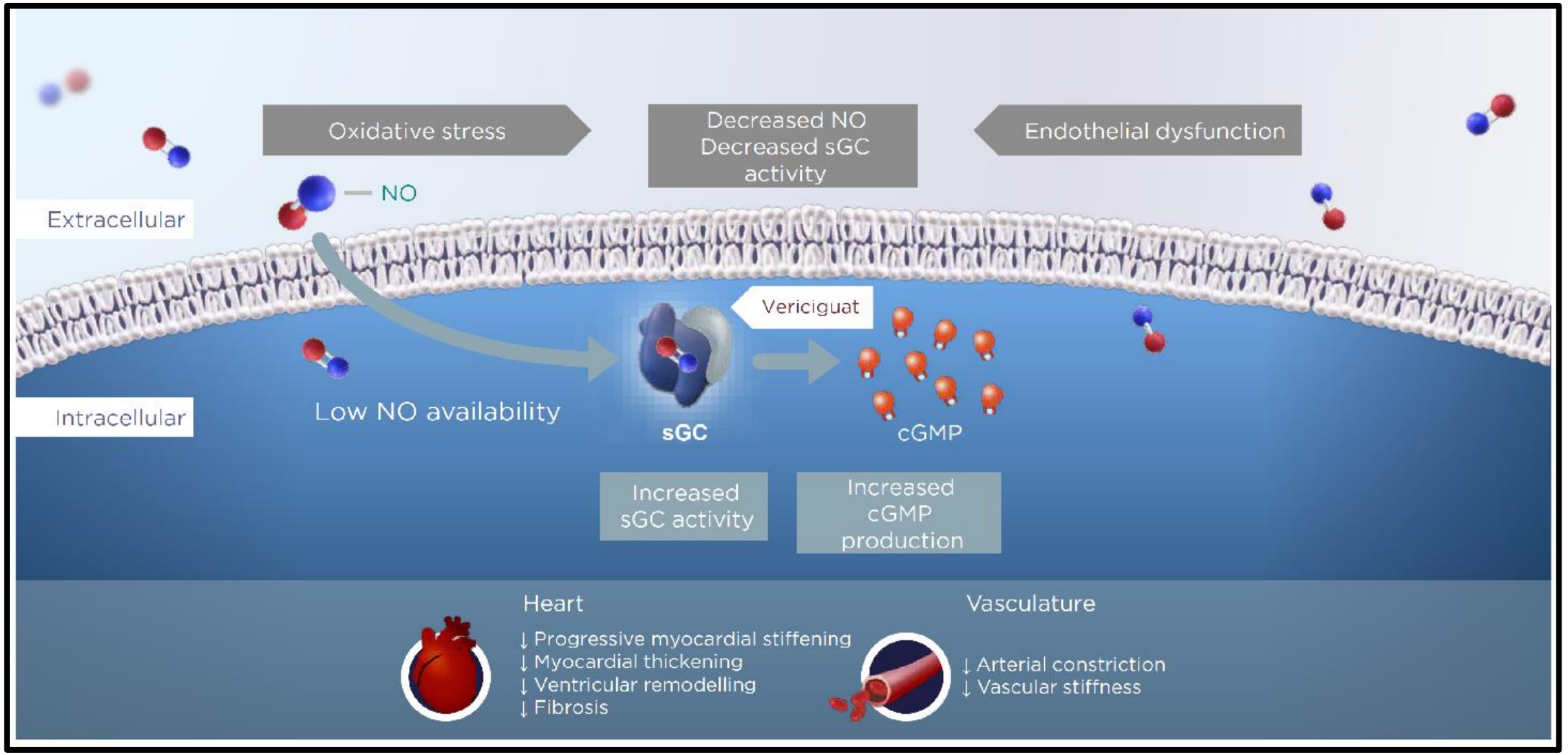
A plethora of choices…

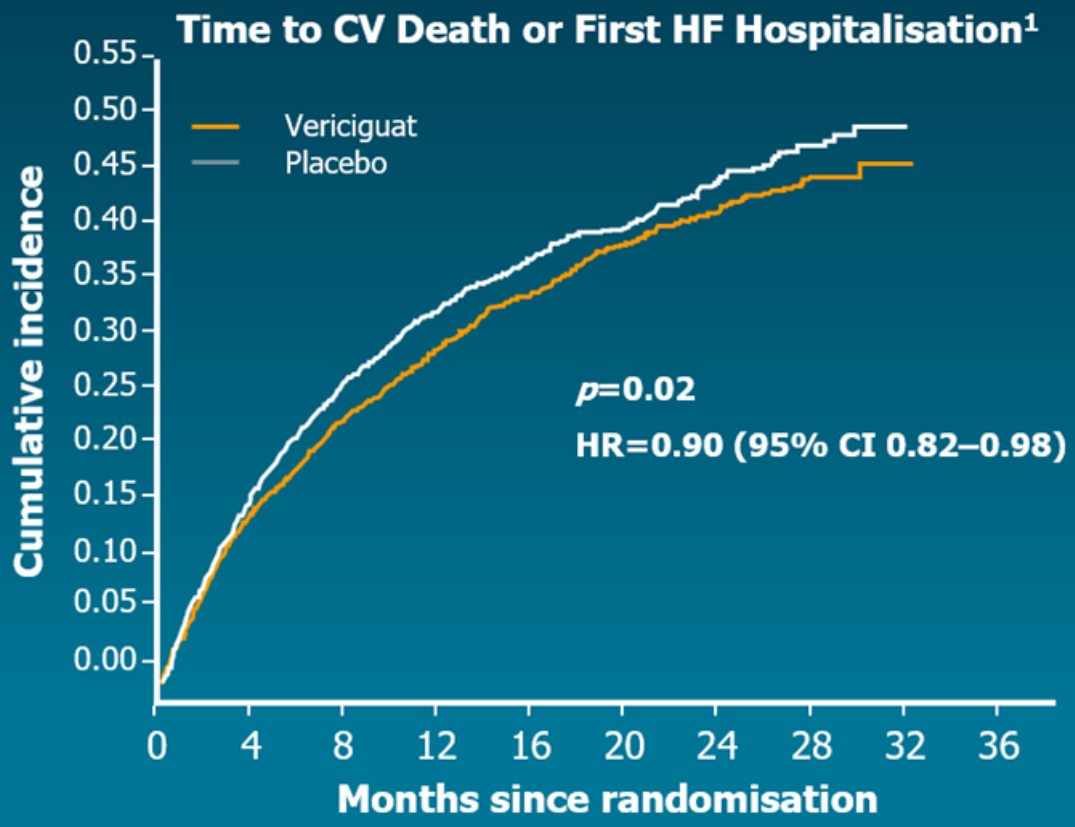


Vericiguat Increases sGC Activity to Improve Myocardial and Vascular Function



Heart Fail Rev 2013;18:123-124; Braunwald's Heart Disease 2015; Handb Exp Pharmacol. 2017;243:225-247; Heart Failure: A Companion to Braunwald's Heart Disease 2020; EMJ Cardiol. 2020;8[1]:26-33

Results From the VICTORIA Trial: Primary Endpoint and Components



Primary endpoint[2]		
Annualised event rates	**Guideline-directed therapies**	**Vericiguat**
Primary endpoint*	37.8	33.6
ARR	4.2	

Components of the primary endpoint[2]		
Annualised event rates	**Guideline-directed therapies**	**Vericiguat**
CV death	13.9	12.9
ARR	1.0	
First HFH	29.1	25.9
ARR	3.2	

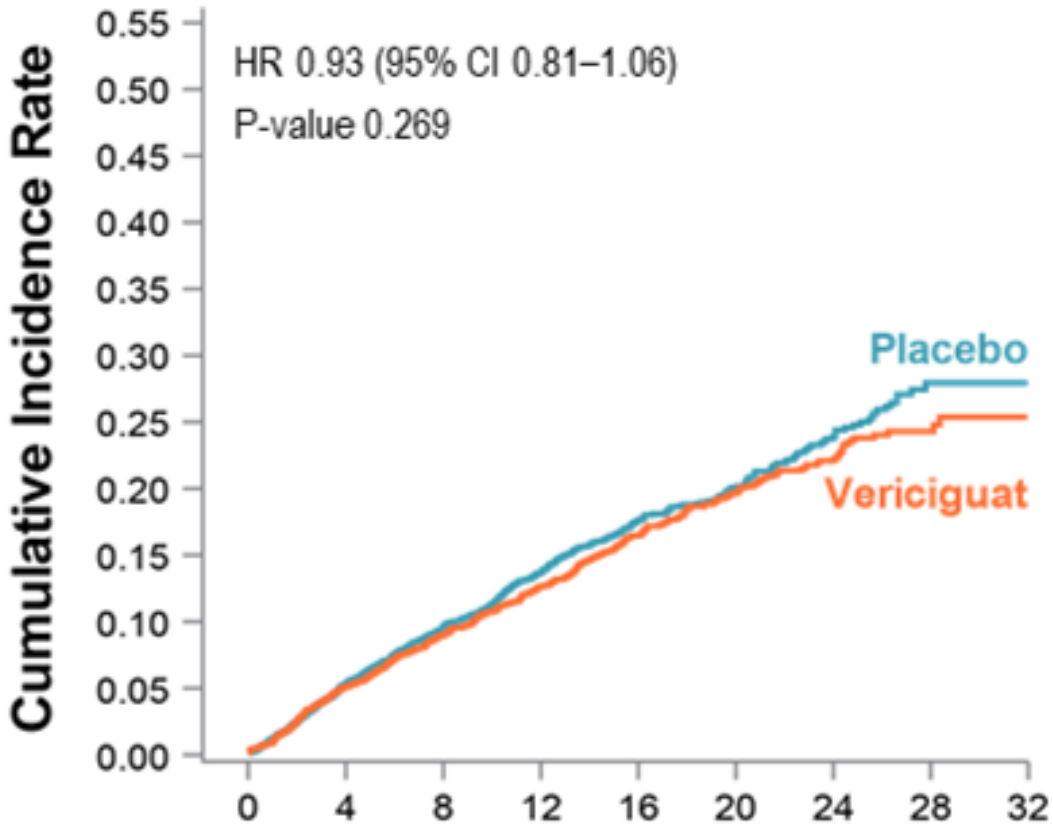
Annual NNT for the composite endpoint of CV death or first HFH = 24#

*The primary endpoint was a composite of death from CV causes or first HFH; #annual NNT: 100/4.2 = 24

ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HF, heart failure; HFH, heart failure hospitalisation; HR, hazard ratio; NNT, number needed to treat

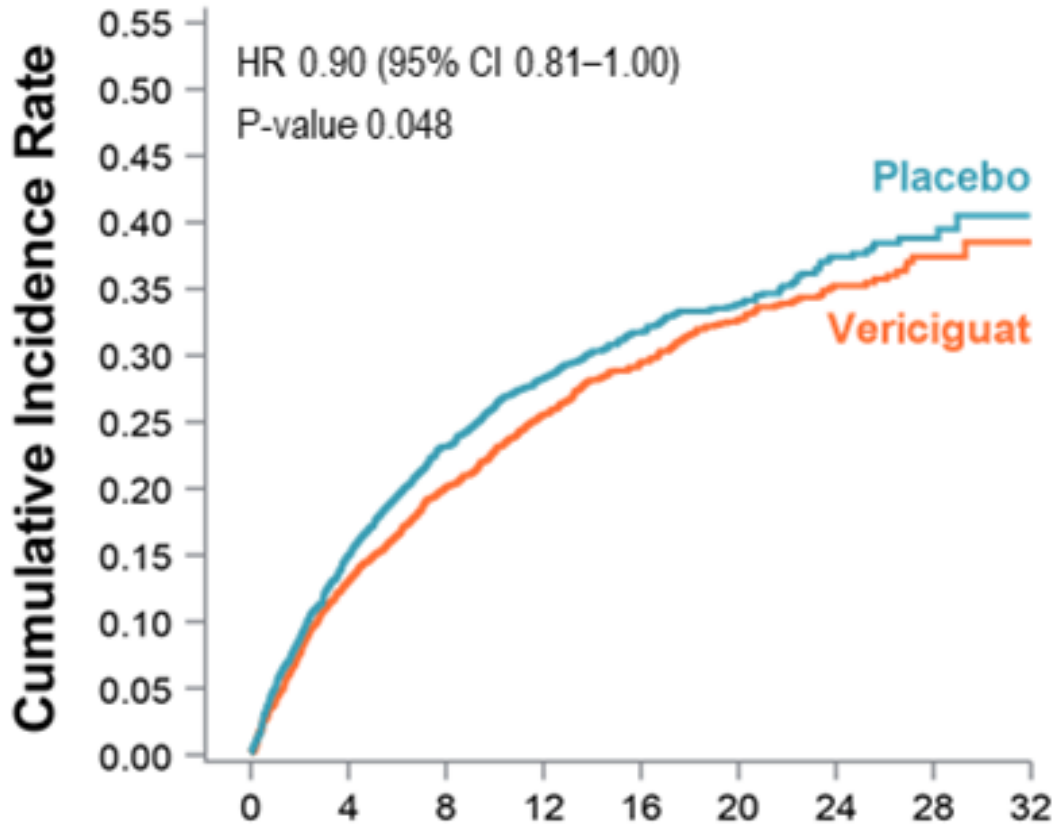
1. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893; 2. Butler J et al. *Circulation*. 2020; doi: 10.1161/CIRCULATIONAHA.120.047086 Courtesy of Dr Javed Butler.

Cardiovascular Death



Number at Risk:									
Vericiguat	2526	2376	1968	1468	1070	779	487	185	1
Placebo	2524	2370	1951	1439	1045	768	471	157	0

First HF Hospitalization

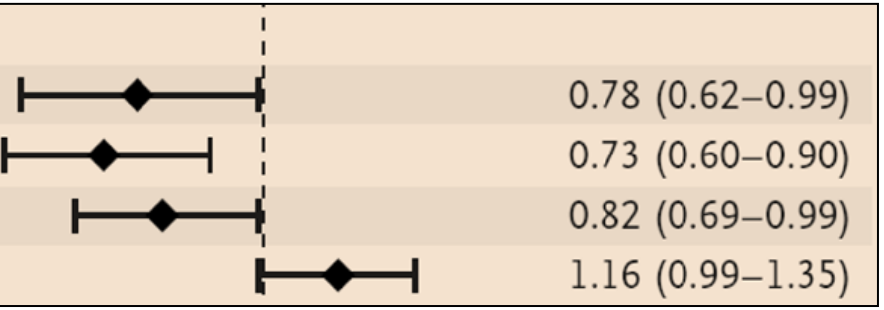


Number at Risk:									
Vericiguat	2526	2098	1620	1153	825	577	348	125	1
Placebo	2524	2052	1554	1096	771	558	323	110	0

1. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893; 2. Butler J et al. *Circulation*. 2020; doi: 10.1161/CIRCULATIONAHA.120.047086

Baseline NP Level And Effect Of Vericiguat In VICTORIA

Subgroup	Vericiguat	Placebo	Hazard Ratio (95% CI)
	no. of events		
NT-proBNP level			
Quartile 1 (≤1556.0 pg/ml)	128	161	0.78 (0.62–0.99)
Quartile 2 (>1556.0 to ≤2816.0 pg/ml)	165	201	0.73 (0.60–0.90)
Quartile 3 (>2816.0 to ≤5314.0 pg/ml)	213	257	0.82 (0.69–0.99)
Quartile 4 (>5314.0 pg/ml)	355	302	1.16 (0.99–1.35)



~ 1250 pts per group

1. Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893.
Courtesy of Dr Javed Butler.

Annualized event rate in recent HFrEF Trials

(events per 100 patient-years at risk)
High event rate in VICTORIA

	PARADIGM-HF		DAPA-HF		EMPEROR-Reduced		GALACTIC-HF		VICTORIA	
	Comparator	Sacubitril/ Valsartan	Comparator	Dapagliflozin	Comparator	Empagliflozin	Comparator	Omecamtiv Mecarbil	Comparator	Vericiguat
Primary endpoint	13.2	10.5	15.6	11.6	21.0	15.8	26.3	24.2	37.8	33.6
Absolute rate reduction	2.7		4.0		5.2		2.1		4.2	
CV death	7.5	6.0	7.9	6.5	8.1	7.6	10.8	10.9	13.9	12.9
Absolute rate reduction	1.5		1.4		0.6		-0.1		1.0	
First HF hospitalisation	NR	NR	9.8	6.9	15.5	10.7	19.1	18.0	29.1	25.9
Absolute rate reduction	1.6		2.9		4.8		1.1		3.2	

Courtesy of Dr Javed Butler

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SGLT-2 Inhibitors in HFrEF

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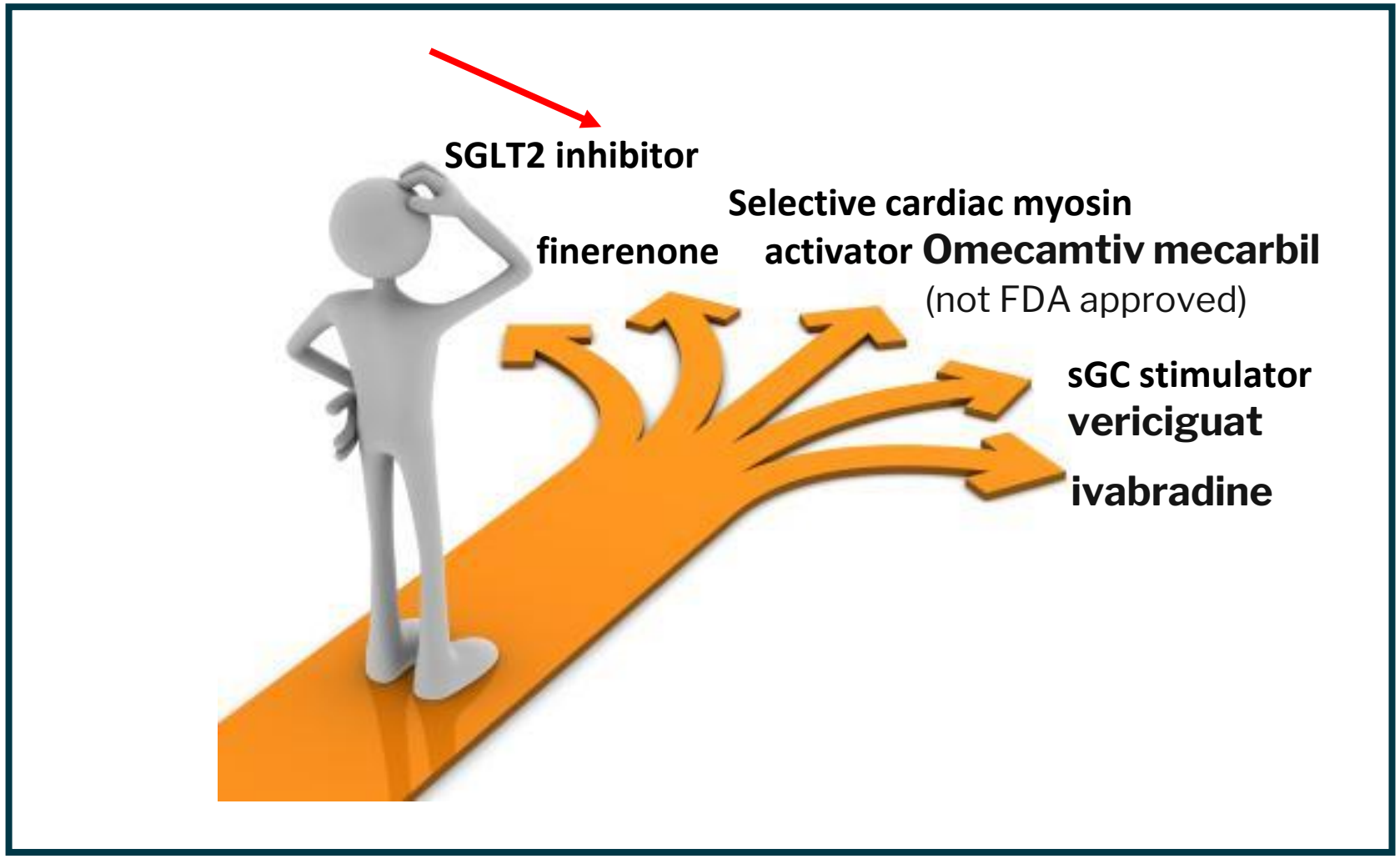
Professor Medicine, Thomas Jefferson University
Clinical Professor of Medicine
Central Michigan University
Adjunct Professor of Epi/Biostats, Case Western Reserve University
Senior Staff Fellow for FDA, CDRH, Medical Officer

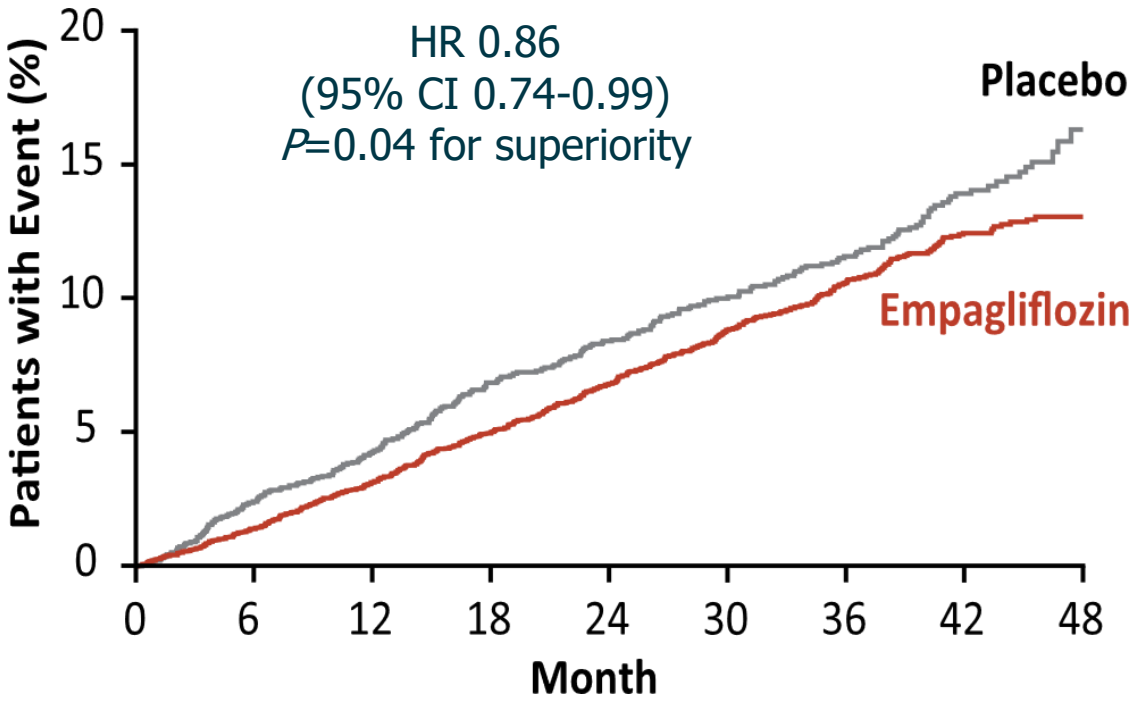
A Plethora of Choices…



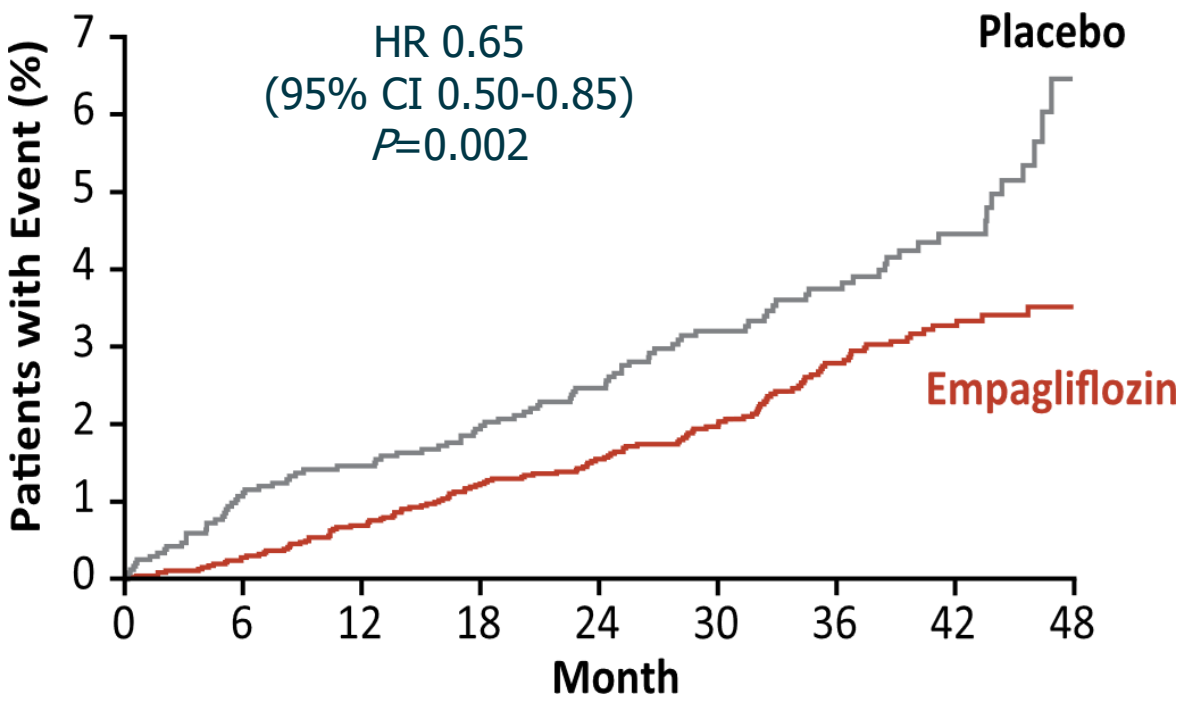
EMPA-REG OUTCOME

7020 Patients With T2DM + High CV Risk

CV Death, MI, Stroke



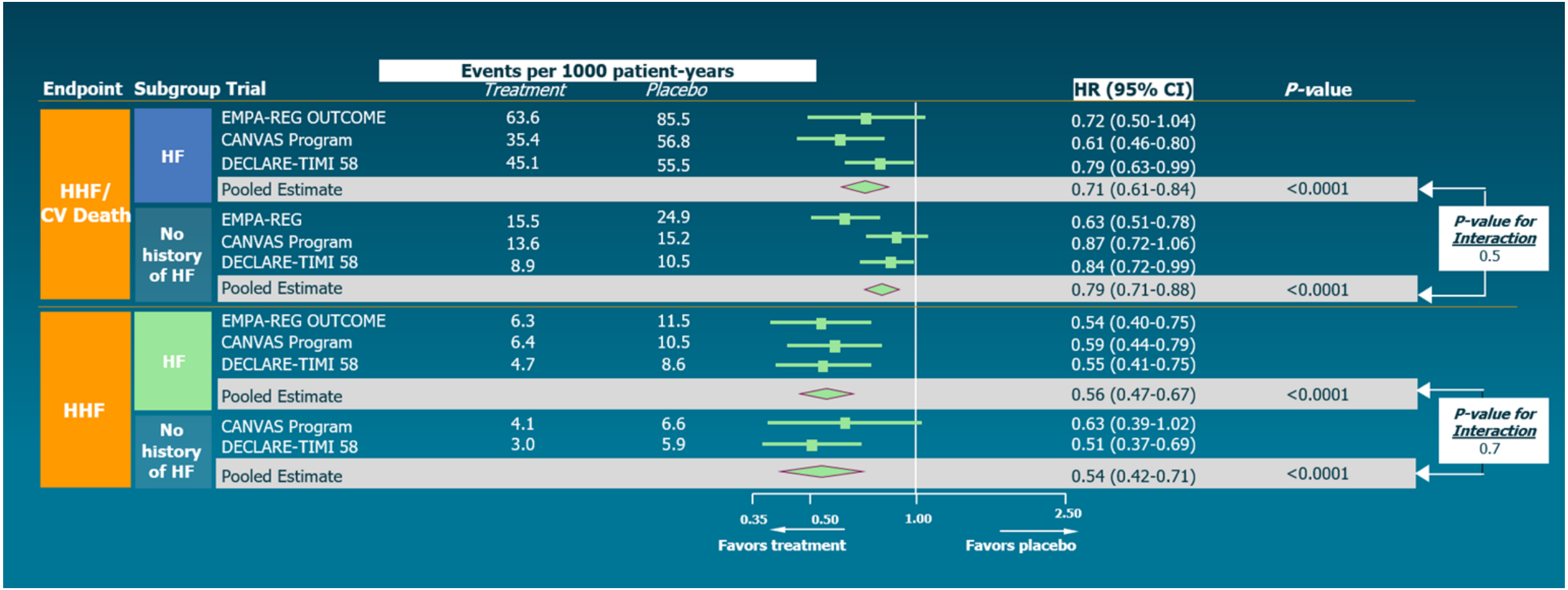
Hospitalization for HF (HHF)



MI, myocardial infarction.

Zinman B, et al. *N Engl J Med*. 2015;373(22):2117-2128.

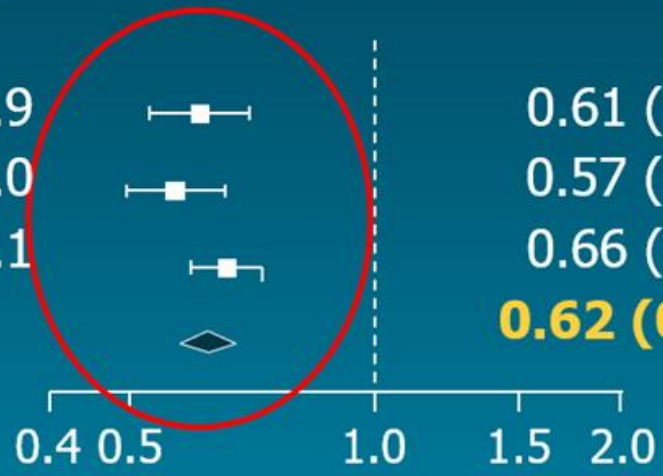
Meta-analysis of SGLT2 Inhibitor CVOTs Evaluating CV Benefit in Patients With and Without HF



Zelniker TA, et al. *Lancet*. 2019;393(10166):31-39.

Meta-analysis of SGLT2i Trials on Renal Endpoint Stratified by Drug Class

Trials	Patients	Events	Treatment n/N	Placebo n/N	Weights	Hazard Ratio HR (95% CI)
EMPA-REG Outcome	6185	913	525/4124	388/2061	24.9	0.61 (0.53 - 0.70)
CANVAS Program	10142	847	NA	NA	25.0	0.57 (0.50 - 0.66)
DECLARE-TIMI 58	1675	1675	678/8582	997/8578	50.1	0.66 (0.60 - 0.73)
Fixed Effects for SGLT2i (*P*<.001)						**0.62 (0.58 - 0.67)**

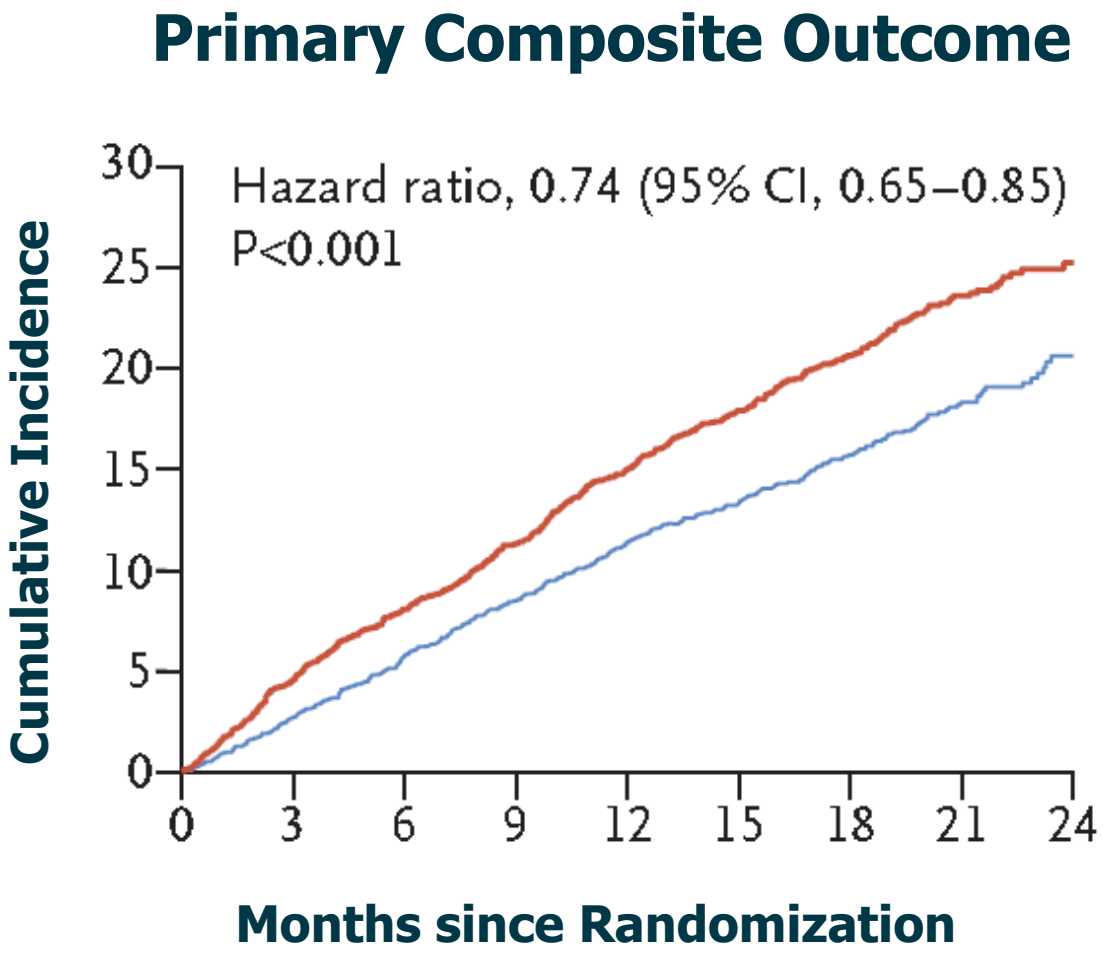


Zelniker TA, et al. Circulation. 2019;139(17):2022-2031.

DAPA-HF: Primary Outcome

Median follow-up: **18.2 months**

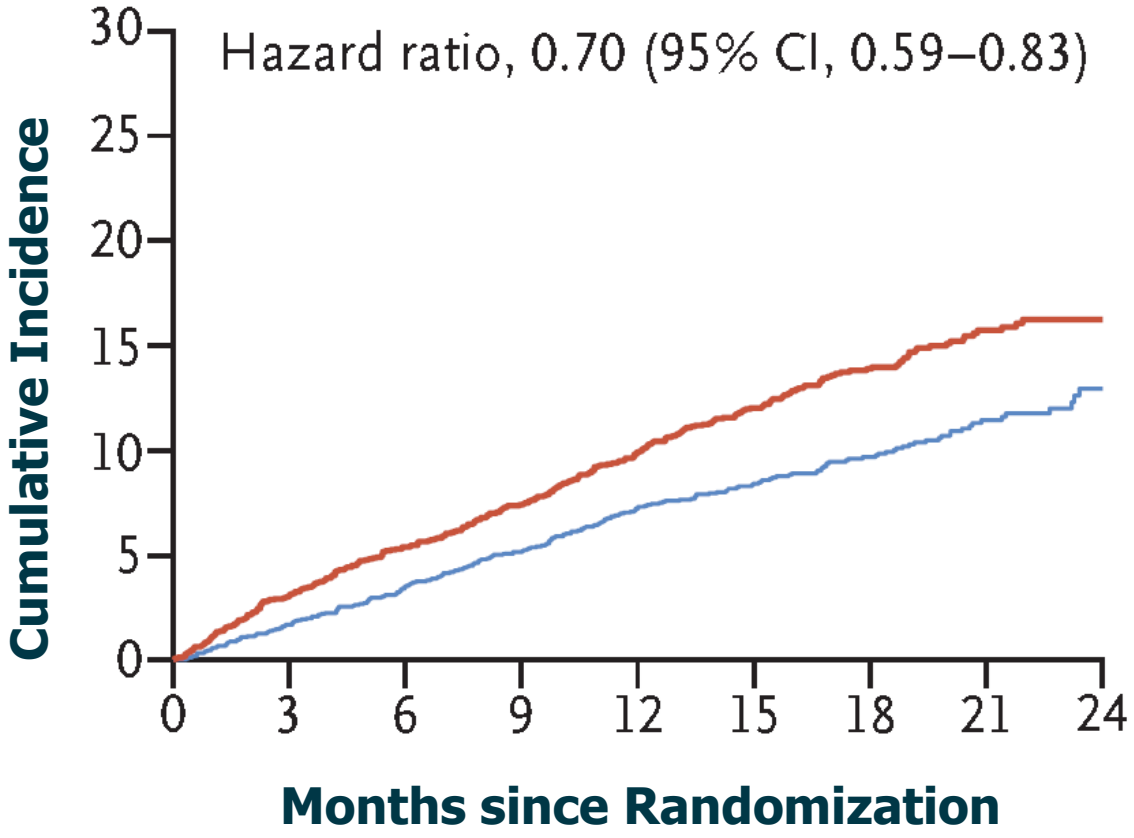
	HR or RR or Difference (95% CI)
Primary Composite Outcome	**0.74 (0.65 to 0.85) *P*<0.001**
Hospitalization or an urgent HF visit	0.70 (0.59 to 0.83)
HHF	0.70 (0.59 to 0.83)
Urgent HF visit	0.43 (0.20 to 0.90)
CV death	0.82 (0.69 to 0.98)



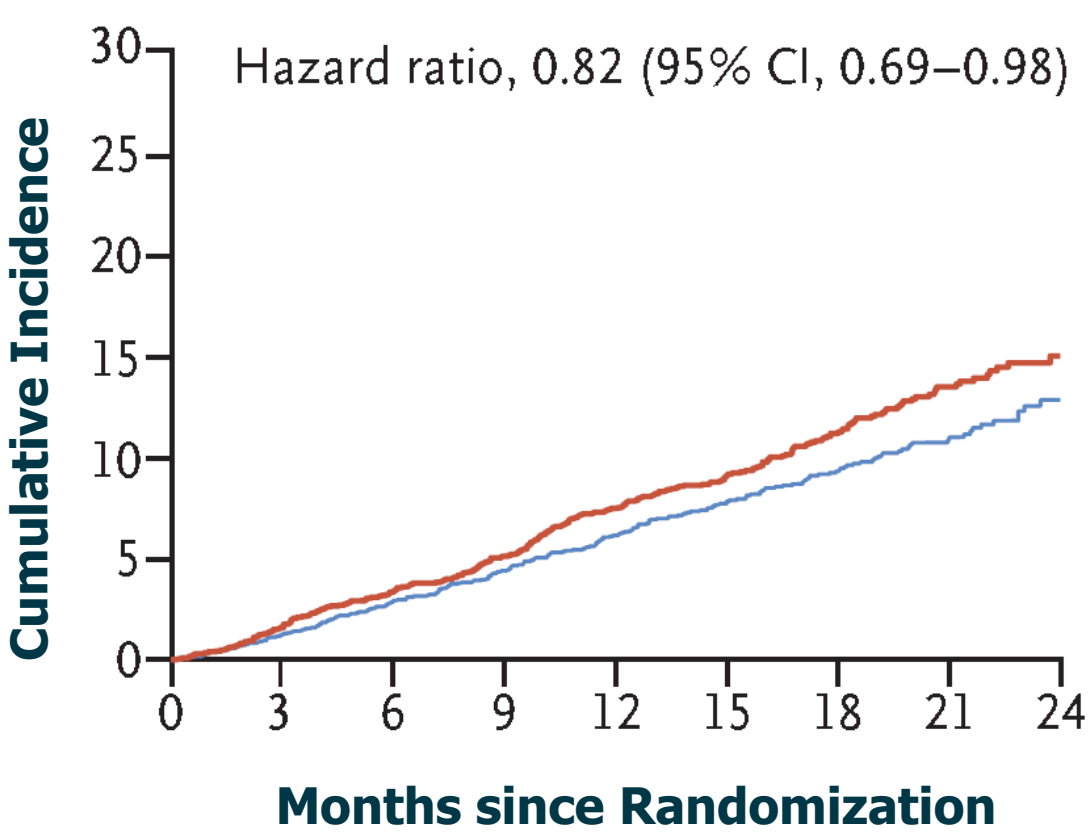
McMurray JJV, et al. *N Engl J Med.* 2019;381(21):1995-2008.

DAPA-HF: Components of Primary Outcome

HHF

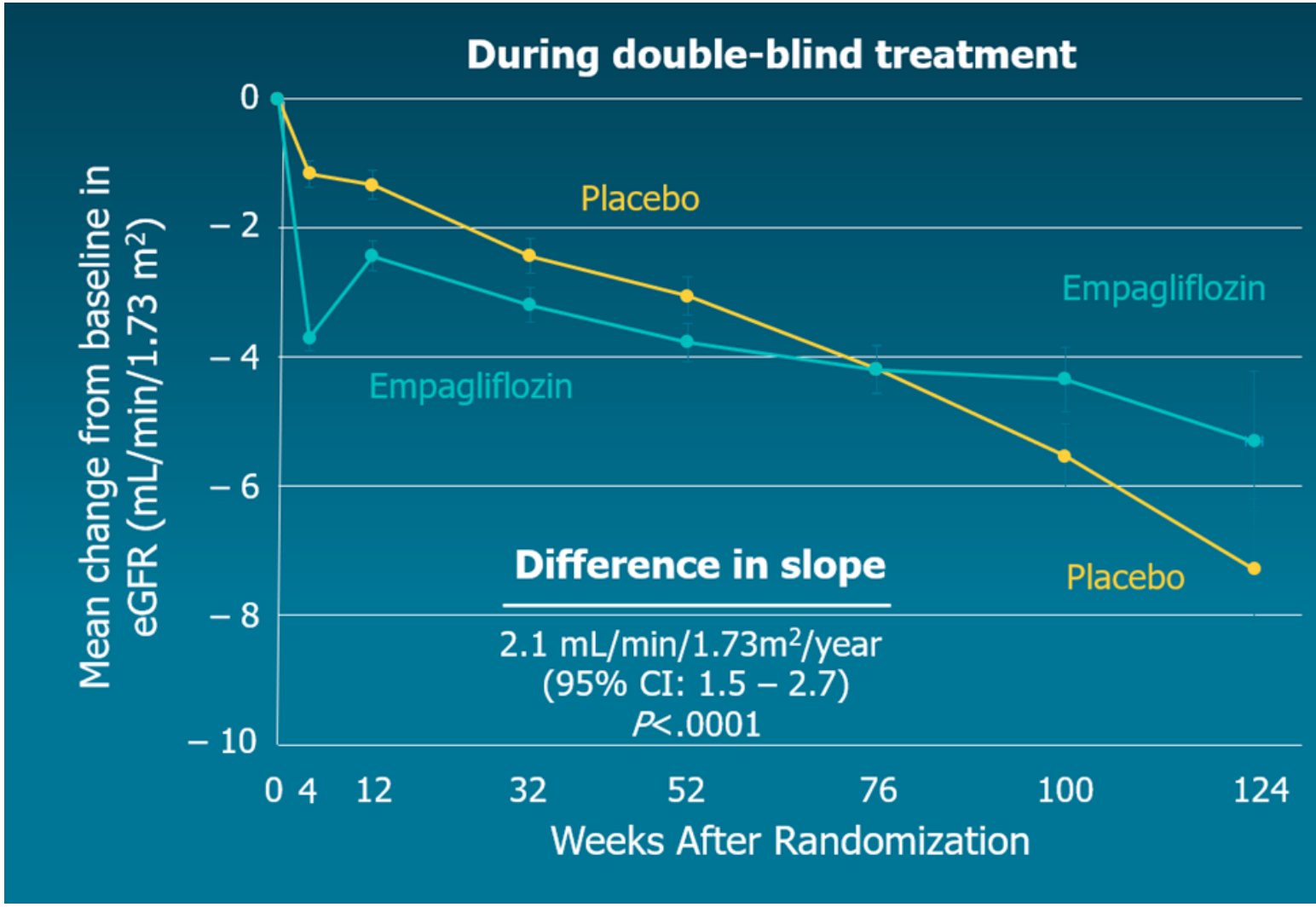


CV Death



McMurray JJV, et al. N Engl J Med. 2019;381(21):1995-2008.

Emperor-Reduced: Slope of Decline in Glomerular Filtration Rate — Hierarchical Endpoint #3



In 966 patients, eGFR was reassessed at the end of the trial 23-42 days after the withdrawal of double-blind therapy, thus allowing unconfounded assessment of the effects of treatment. Over 16 months, eGFR deteriorated by:

– 4.2 ml/min/1.73 m² on placebo

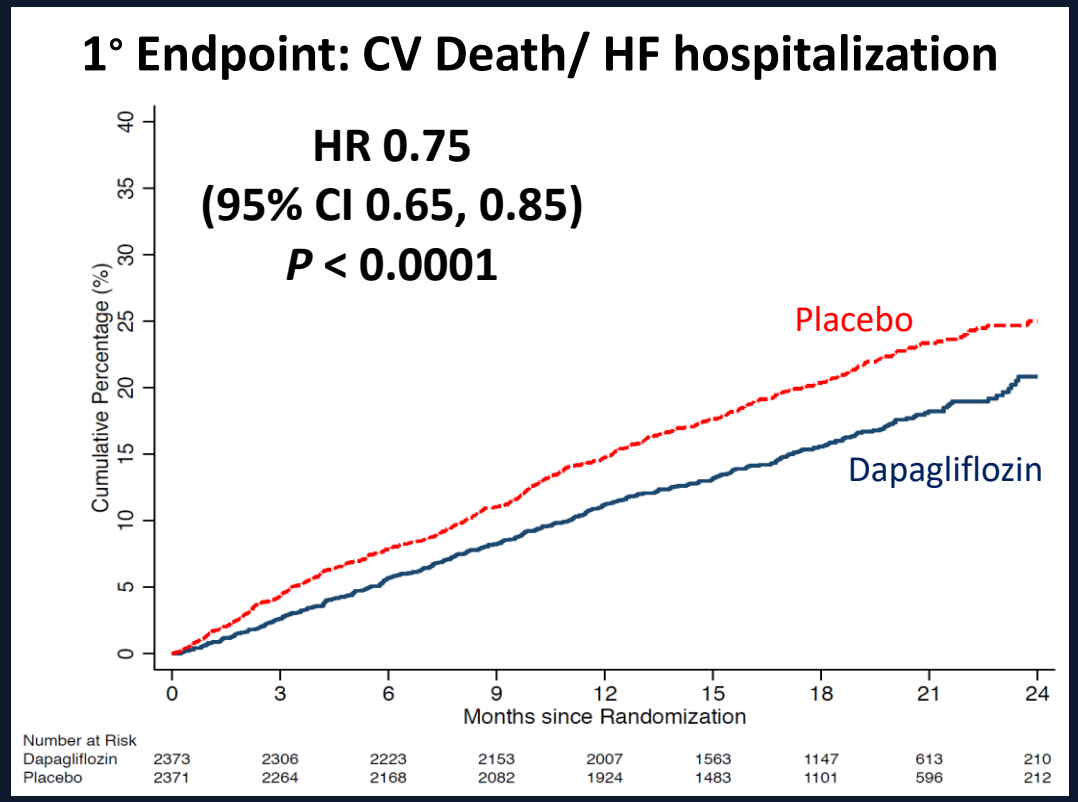
– 0.9 m/min/1.73 m² on empagliflozin

***P*<.0001**

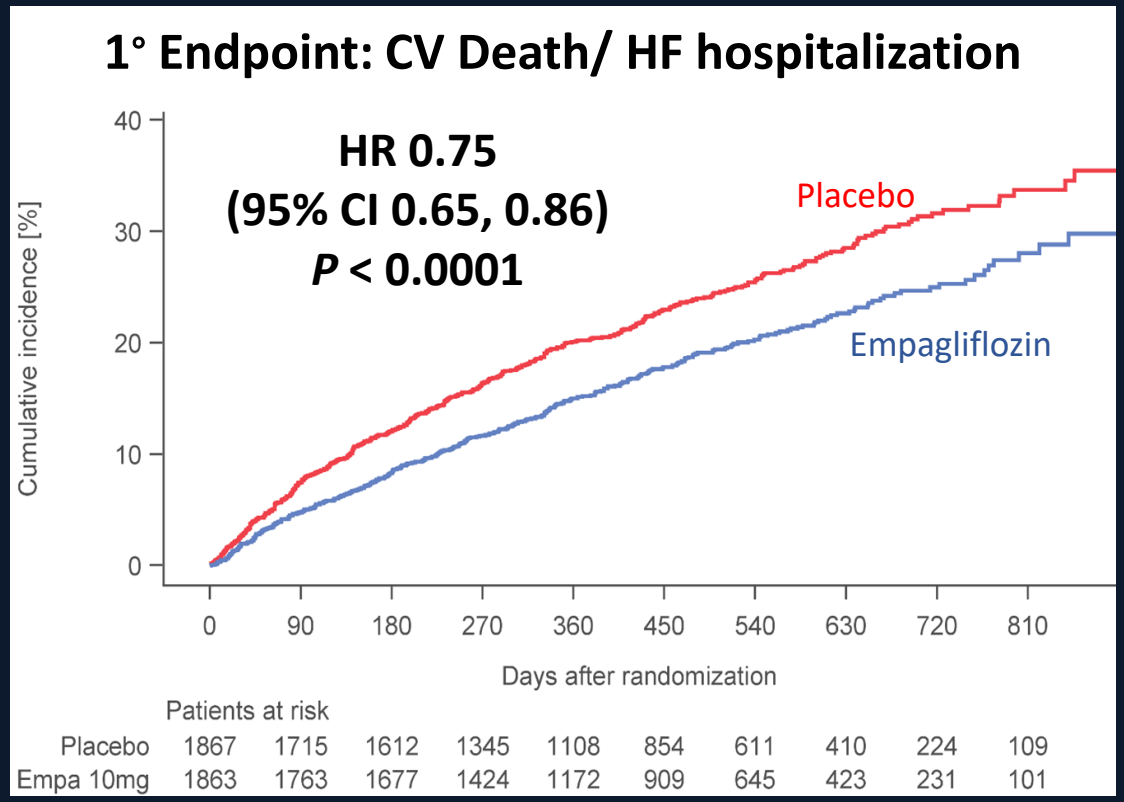
Zannad F, et al. Circulation. 2021;143(4):310-321. Open Access.

SGLT2 inhibitors in patients with chronic HFrEF Consistency of findings.

DAPA-HF



EMPEROR-Reduced

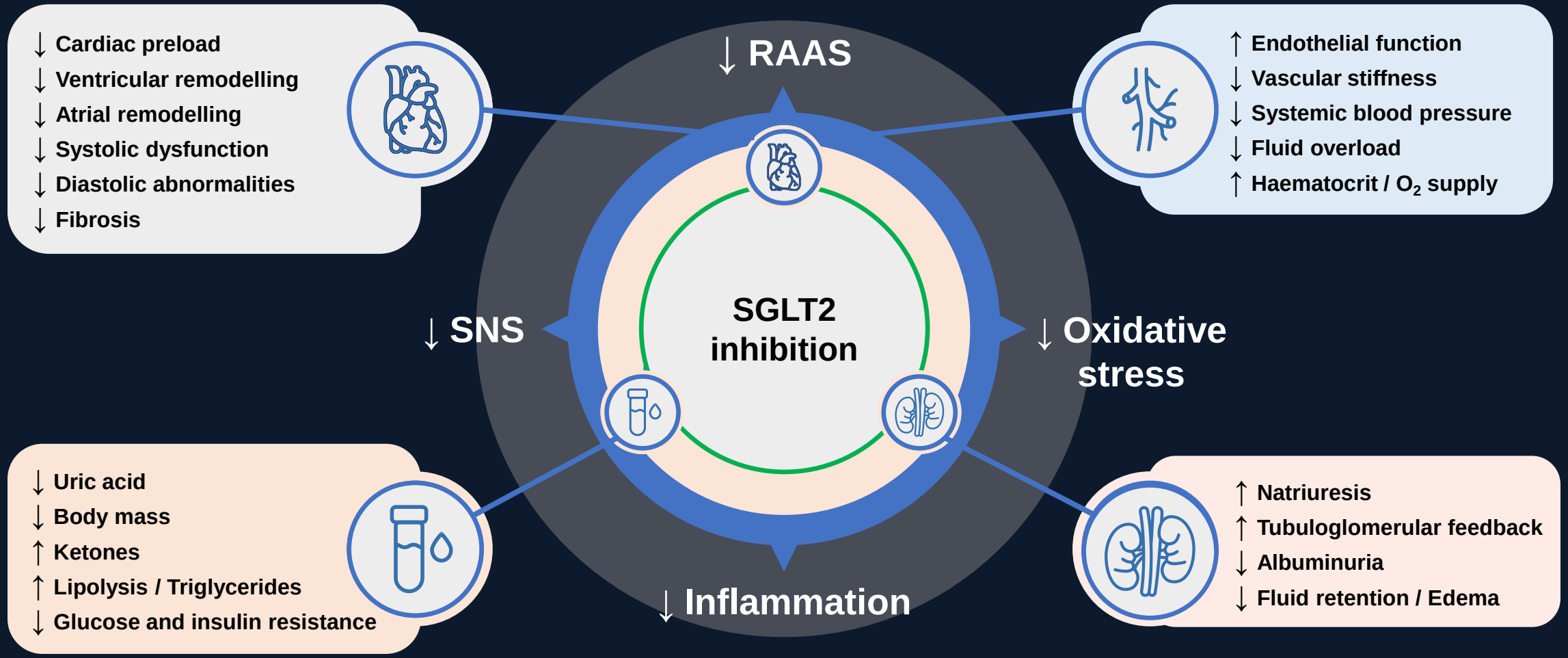


Outcome similar with or without comorbid diabetes

McMurray N Engl J Med. 2019;318:1995-2008

Packer M et al N Engl J Med. 2020 Aug 29.

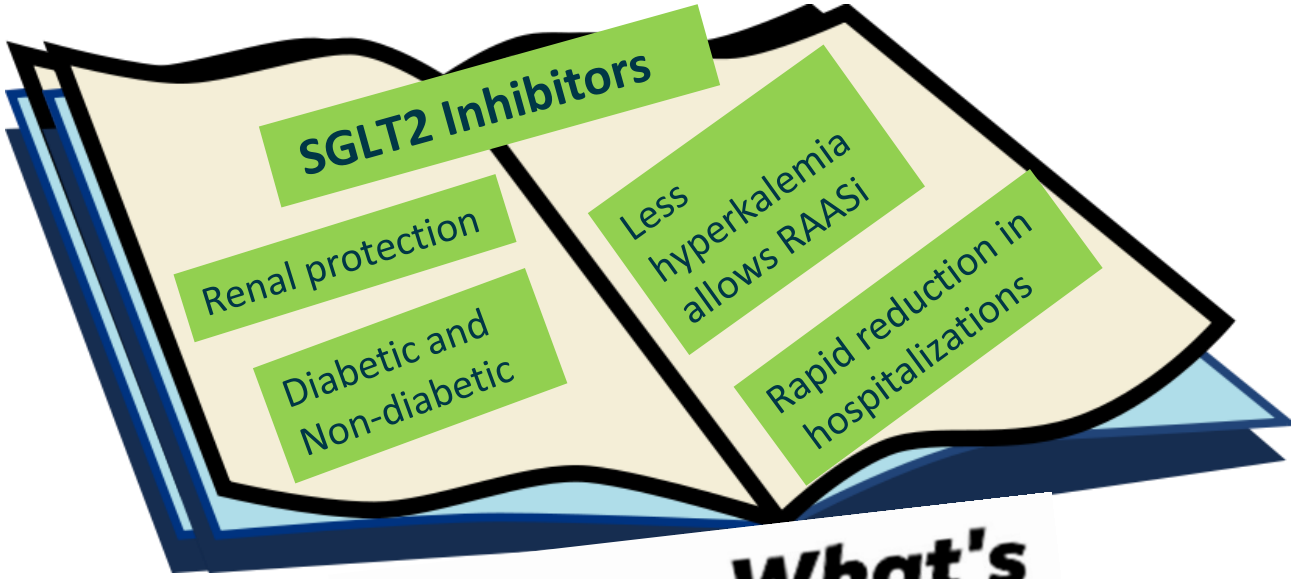
Direct and Indirect Actions of SGLT2 Inhibitors[1–5]



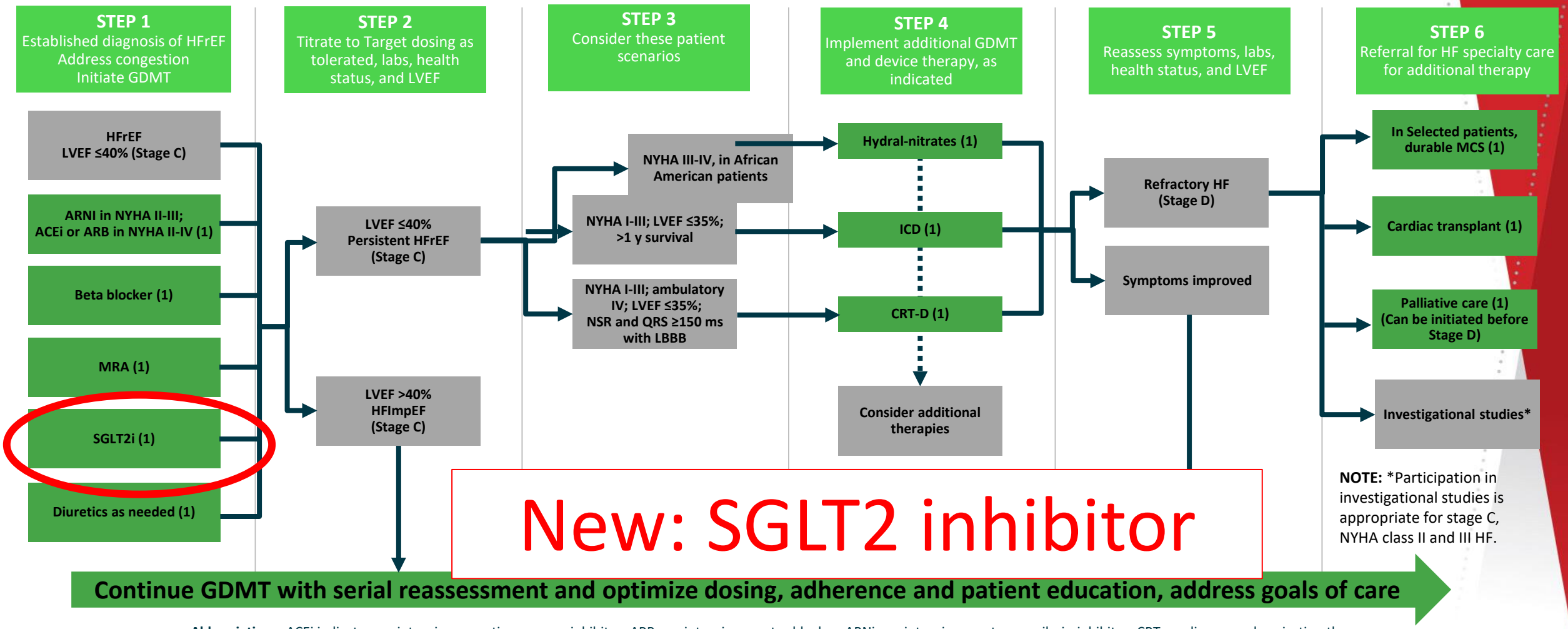
ATP, adenosine triphosphate; CRM, cardiovascular, renal and metabolic; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

1. Givens RC, Schulze PC. Molecular changes in heart failure. In: Eisen H, ed. Heart Failure: A Comprehensive Guide to Pathophysiology and Clinical Care. London: Springer Verlag; 2017:1–26. 2. Ronco C et al., *J Am Coll Cardiol*. 2008;52:1527. 3. Santos-Ferreira D, et al. *Cardiology*. 2020;145:311–20. 4. Cowie M, Fisher M. *Nat Rev Cardiol*. 2020;17:761–72. 5. Scheen AJ. *Nat Rev Endocrinol*. 2020;16:556–77.

The Story Is Unfolding: SGLT2 Inhibitors



Treatment of HFrEF Stages C and D

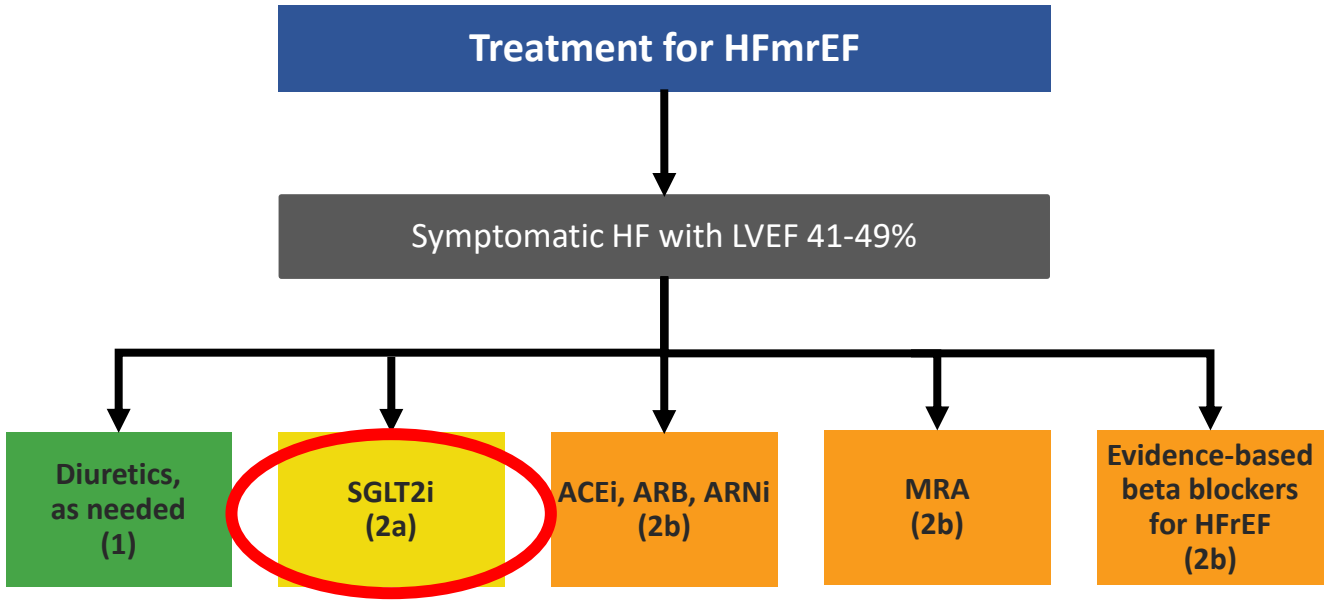


Abbreviations: ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; hydral-nitrates, hydralazine and isosorbide dinitrate; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; NSR, normal sinus rhythm; NYHA, New York Heart Association; SCD, sudden cardiac death; and SGLT2i, sodium-glucose cotransporter 2 inhibitor.

Heidenreich, P. A. et al. (2022). 2022 AHA/ACC/HFSA Guideline for Heart Failure. *Circulation*.

American Heart Association.

Recommendations for Patients with Mildly Reduced LVEF



Patients With HFimpEF

COR	RECOMMENDATIONS
1	1. In patients with HFimpEF after treatment, GDMT should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic. (1)

Abbreviations: ARB indicates angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LV, left ventricle; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; and SGLT2i, sodium-glucose cotransporter-2 inhibitor.

Heidenreich, P. A. et al. (2022). 2022 AHA/ACC/HFSA Guideline for Heart Failure. *Circulation*.

American Heart Association.

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Heart Failure with Preserved Ejection Fraction (HFpEF): Challenges and Treatment Advances

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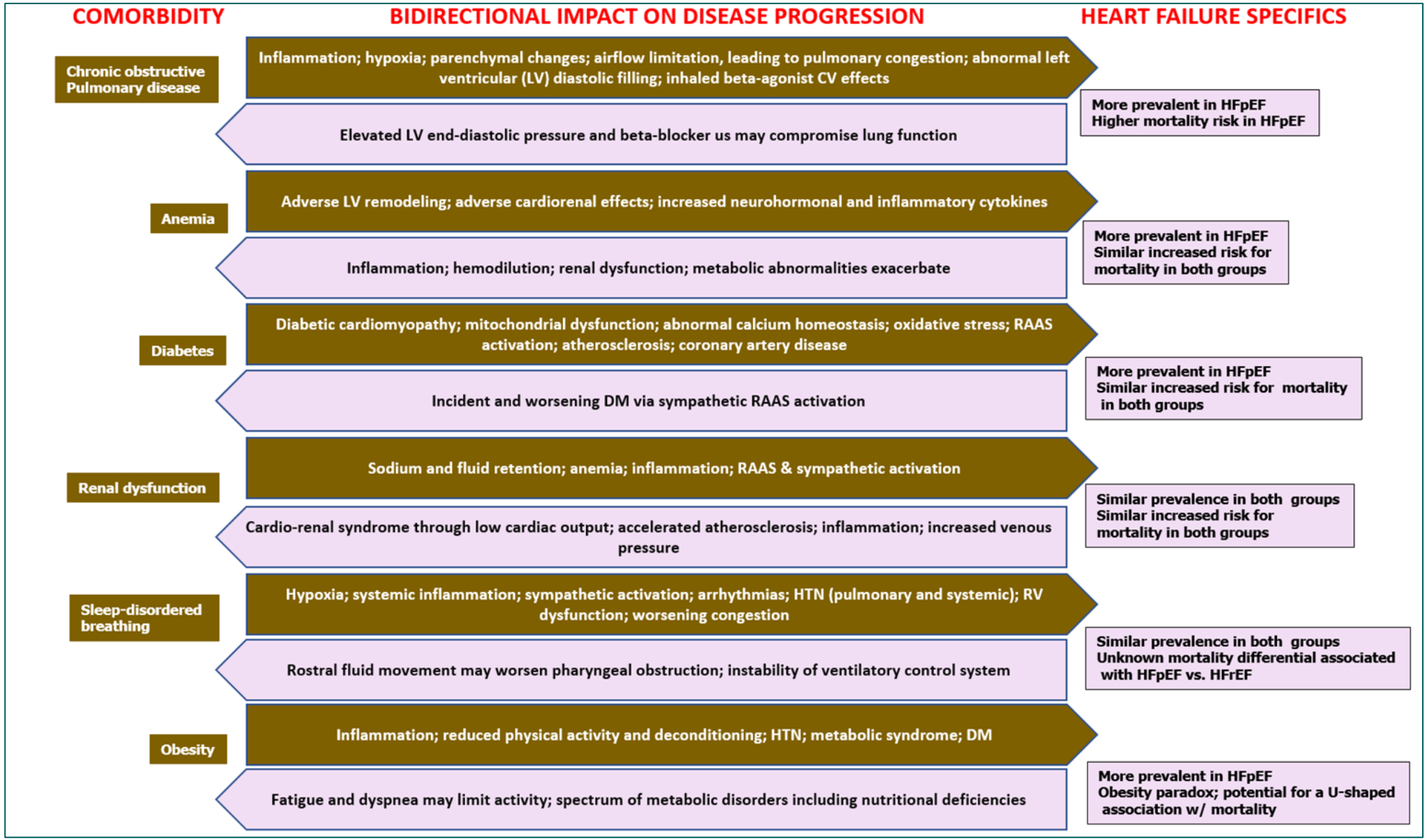
Professor Medicine, Thomas Jefferson University
Clinical Professor of Medicine
Central Michigan University
Adjunct Professor of Epi/Biostats, Case Western Reserve University
Senior Staff Fellow for FDA, CDRH, Medical Officer

HFpEF: The Real Unmet Need

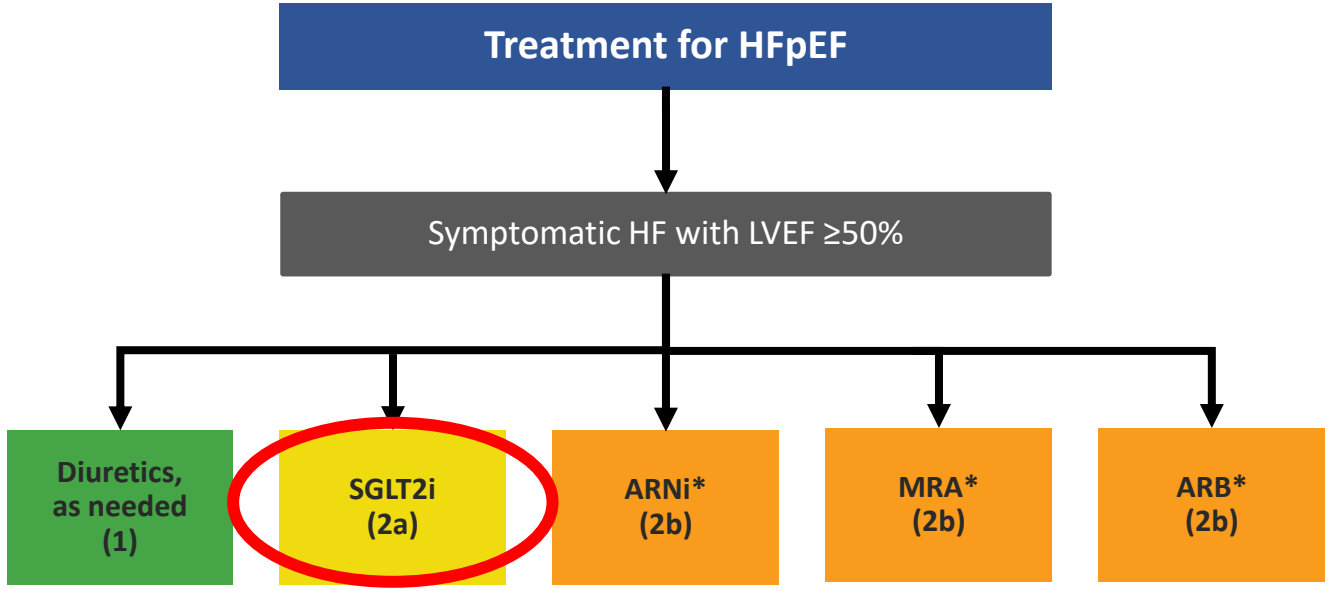
- LV diastolic dysfunction is defined as impaired LV filling at normal left atrial pressure
- Most rapidly growing type of HF
- More common in elderly patients, women
- Responsible for up to >40% of HF in adults
- Many patients have both LV systolic and diastolic dysfunction
- Definitions continue to evolve

Seeing HFpEF Through Comorbidities



Mentz R, et al. *J Cardiac Fail.* 2016;22(7):545-547.

Recommendations for Patients with Preserved LVEF



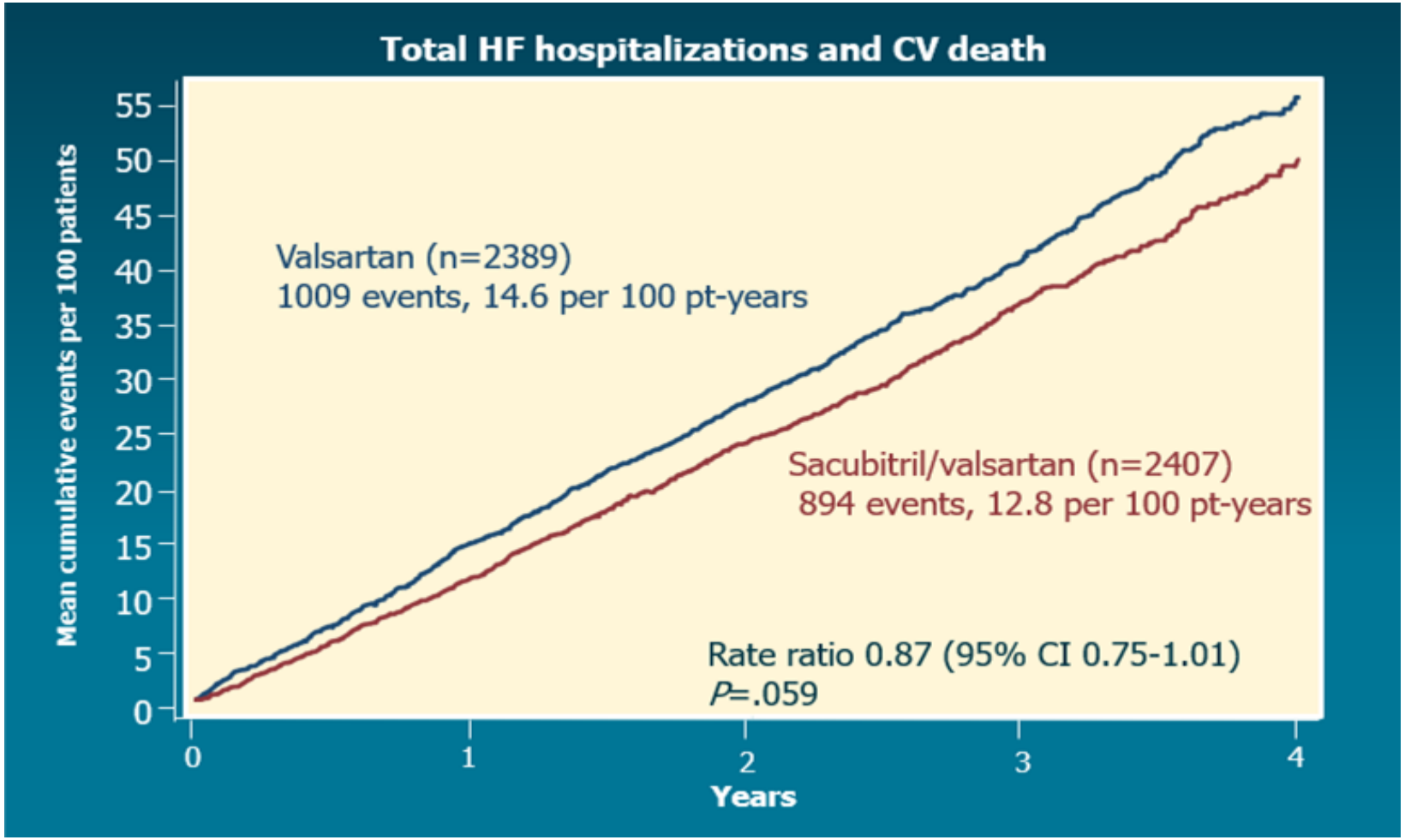
NOTE: *Greater benefit in patients with LVEF closer to 50%

Abbreviations: ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; HFimpEF, heart failure with improved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; and SGLT2i, sodium- glucose cotransporter 2 inhibitor.

Heidenreich, P. A. et al. (2022). 2022 AHA/ACC/HFSA Guideline for Heart Failure. *Circulation*.

PARAGON-HF Primary Results

Recurrent event analysis of total HF hospitalizations and CV death*

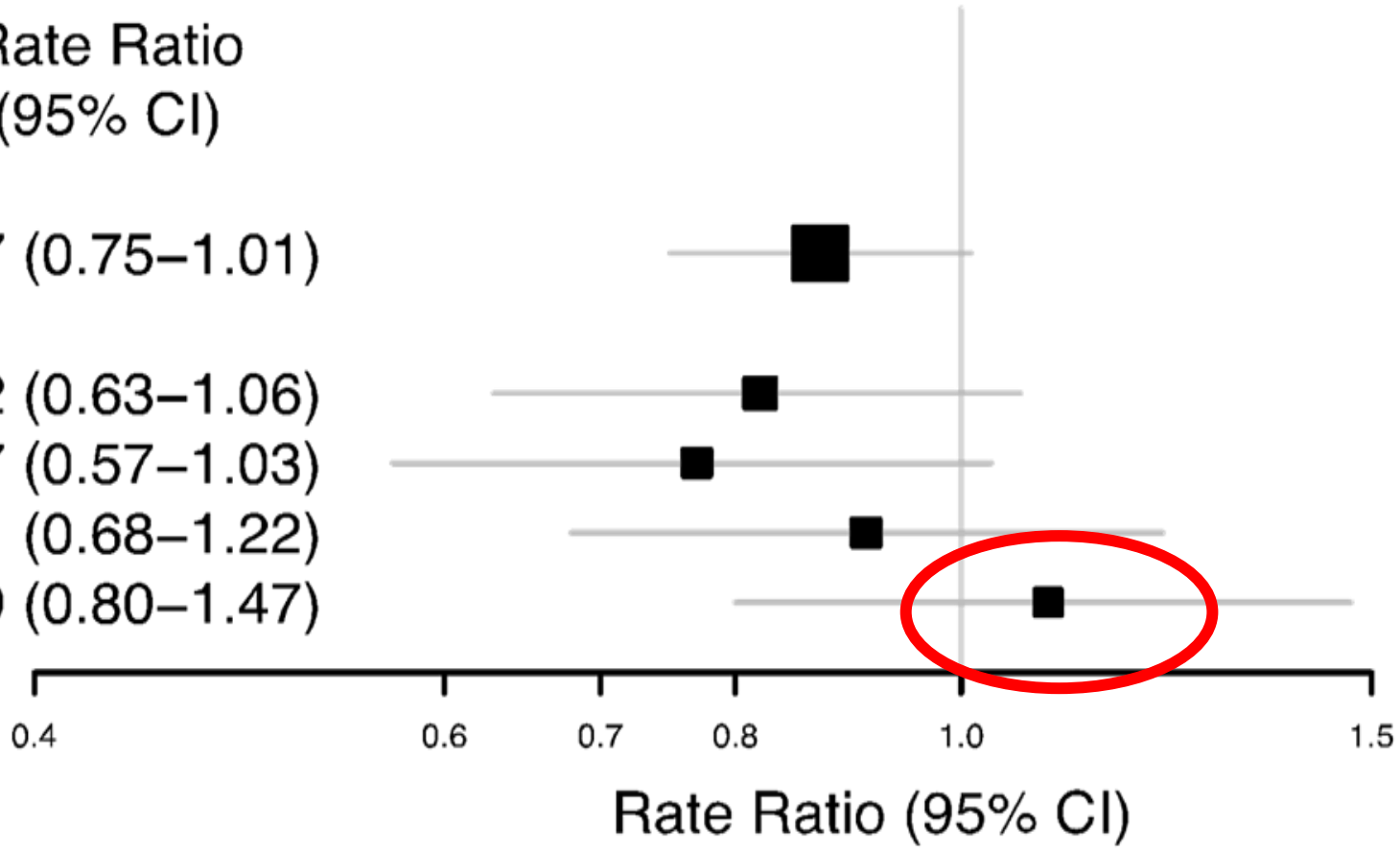


McMurray J, et al. PARAGON-HF presented at: ESC Congress; September 1, 2019. Paris, France.

Treatment Effect By Ejection Fraction Quartiles

Primary Composite Total HF Hospitalizations and CV Death

Subgroup	No. of Events/Patients	Rate Ratio (95% CI)
Overall	1903/4796	0.87 (0.75–1.01)
EF		
<=50	512/1208	0.82 (0.63–1.06)
>50–57	536/1287	0.77 (0.57–1.03)
>57–63	467/1202	0.91 (0.68–1.22)
>63	388/1099	1.09 (0.80–1.47)



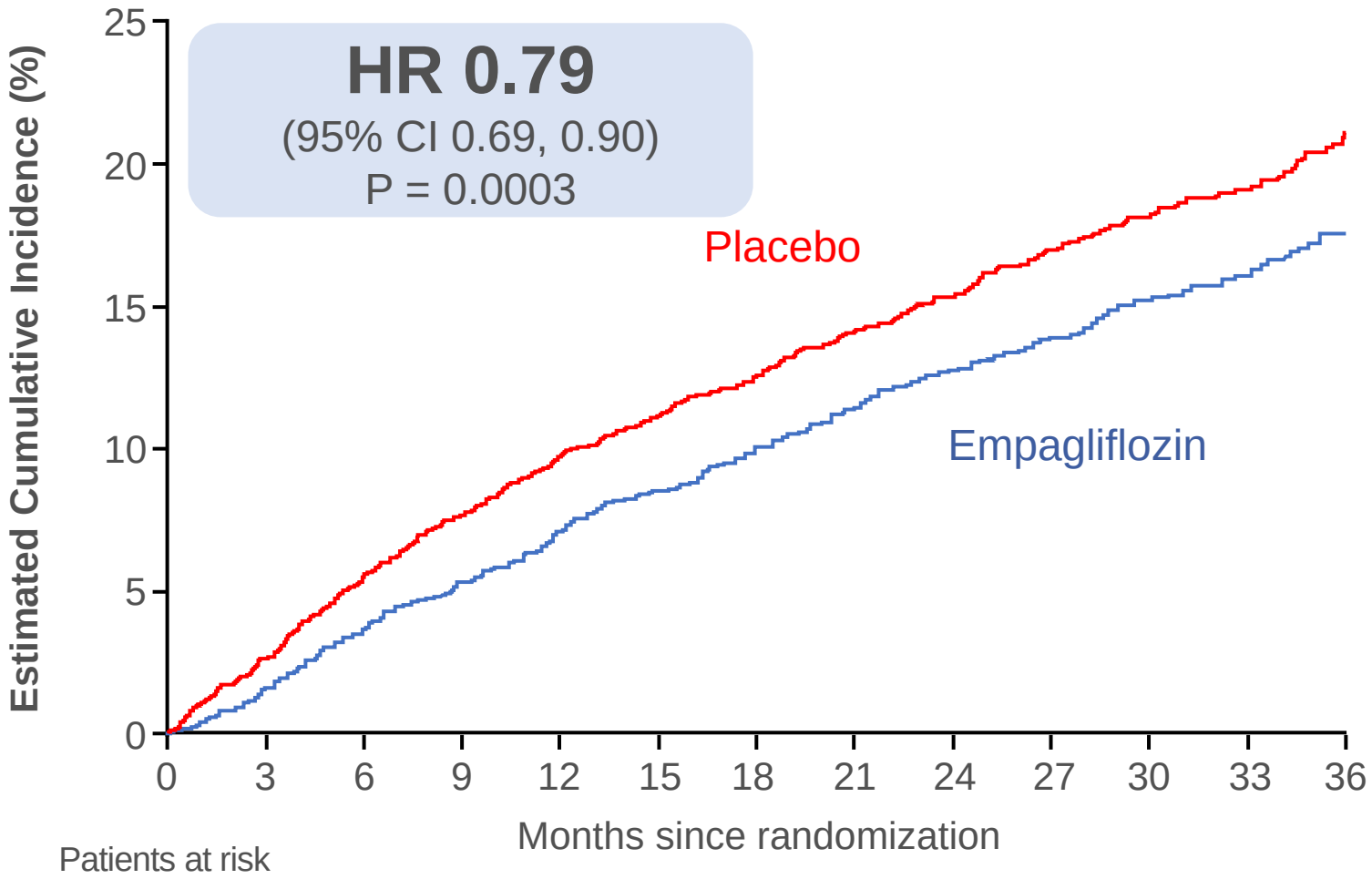
Are we re-defining the HFpEF EF cutoff?
Is HFmrEF really milder level HFrEF?

EMPEROR PRESERVED

Demographics and baseline characteristics

	Empagliflozin (n=2997)	Placebo (n=2991)
Age (yr)	71.8 ± 9.3	71.9 ± 9.6
Women (%)	1338 (45)	1338 (45)
Diabetes mellitus (%)	1466 (49)	1472 (49)
Ischaemic HF (%)	1079 (36)	1038 (35)
NYHA functional class II (%)	2432 (81)	2451 (82)
LV ejection fraction (%)	54.3 ± 8.8	54.3 ± 8.8
NT-proBNP (median, IQR), pg/mL	994 (501, 1740)	946 (498, 1725)
Atrial fibrillation	1543 (52)	1514 (51)
Glomerular filtration rate (mL/min/1.73 m^2)	60.6 ± 19.8 (50% <60)	60.6 ±19.9 (50% <60)
Co-medications of interest		
RAASi ± ARNI	2428 (81)	2404 (80)
MRA	1119 (37)	1125 (38)
Beta blocker	2598 (87)	2569 (86)
Statins	2042 (68)	2089 (70)

EMPEROR-Preserved: Empagliflozin in Chronic HFpEF



Population: 5988 patients with structural heart disease or HFH within 12 months of screening, T2DM & non-T2DM, chronic HF (NYHA class II–IV), eGFR≥20

Aim: to evaluate efficacy and safety of empagliflozin versus placebo, on top of standard of care, in **patients with HFpEF** with or without diabetes

Primary endpoint: **Time to first event of adjudicated CV death or HF hospitalization**

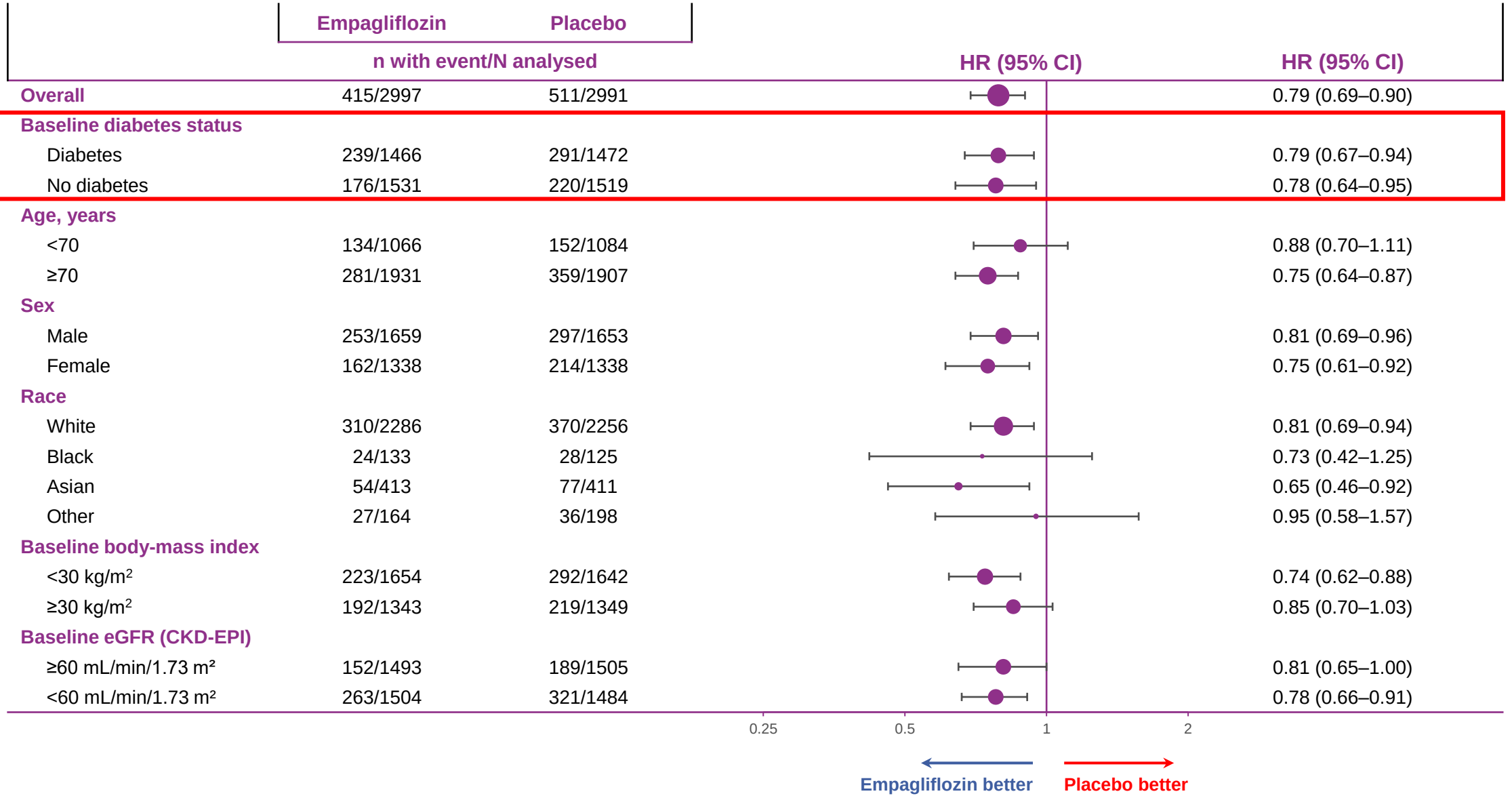
Anker et al. *N Engl J Med*. 2021;385:1451-61

Primary endpoint: individual components

	Empagliflozin (n=2997)		Placebo (n=2991)		Hazard ratio (95% CI)	P value
	Number of events (%)	Events/100 patient-yrs	Number of events (%)	Events/100 patient-yrs		
Primary composite outcome	415 (13.8%)	6.9	511 (17.1%)	8.7	0.79 (0.69 – 0.90)	0.0003
First 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)	

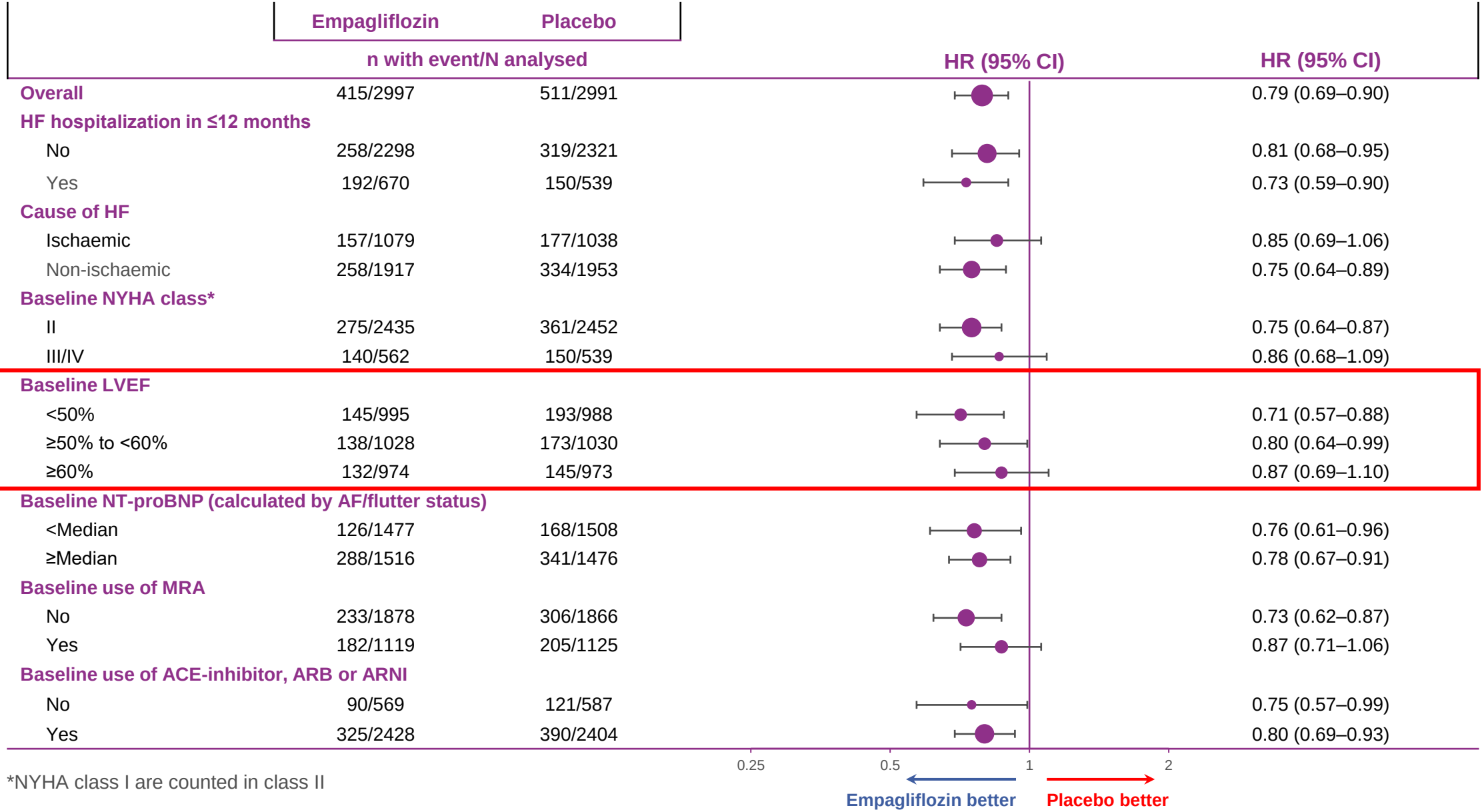
Anker, Stefan D., et al. *England Journal of Medicine* 385.16 (2021): 1451-1461.

Primary endpoint: Subgroup analysis (1 of 2)



Anker, Stefan D., et al. *England Journal of Medicine* 385.16 (2021): 1451-1461.

Primary endpoint: Subgroup analysis (2 of 2)



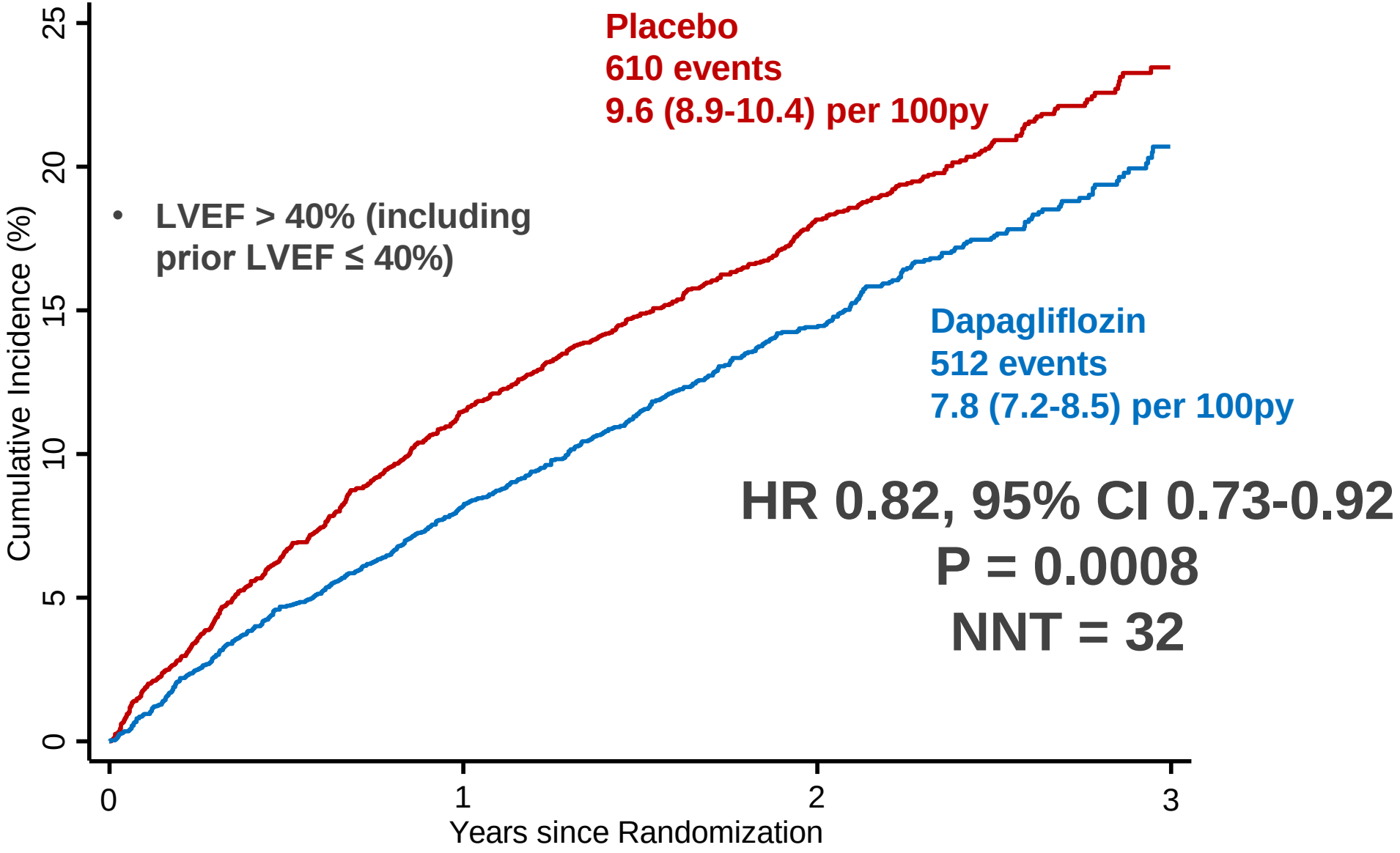
	Empagliflozin n with event/N analysed	Placebo n with event/N analysed	HR (95% CI)	HR (95% CI)
Overall	415/2997	511/2991		0.79 (0.69–0.90)
HF hospitalization in ≤12 months				
No	258/2298	319/2321		0.81 (0.68–0.95)
Yes	192/670	150/539		0.73 (0.59–0.90)
Cause of HF				
Ischaemic	157/1079	177/1038		0.85 (0.69–1.06)
Non-ischaemic	258/1917	334/1953		0.75 (0.64–0.89)
Baseline NYHA class*				
II	275/2435	361/2452		0.75 (0.64–0.87)
III/IV	140/562	150/539		0.86 (0.68–1.09)
Baseline LVEF				
<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)
Baseline NT-proBNP (calculated by AF/flutter status)				
<Median	126/1477	168/1508		0.76 (0.61–0.96)
≥Median	288/1516	341/1476		0.78 (0.67–0.91)
Baseline use of MRA				
No	233/1878	306/1866		0.73 (0.62–0.87)
Yes	182/1119	205/1125		0.87 (0.71–1.06)
Baseline use of ACE-inhibitor, ARB or ARNI				
No	90/569	121/587		0.75 (0.57–0.99)
Yes	325/2428	390/2404		0.80 (0.69–0.93)

*NYHA class I are counted in class II

Anker, Stefan D., et al. *England Journal of Medicine* 385.16 (2021): 1451-1461.

Primary Endpoint: CV Death or Worsening HF

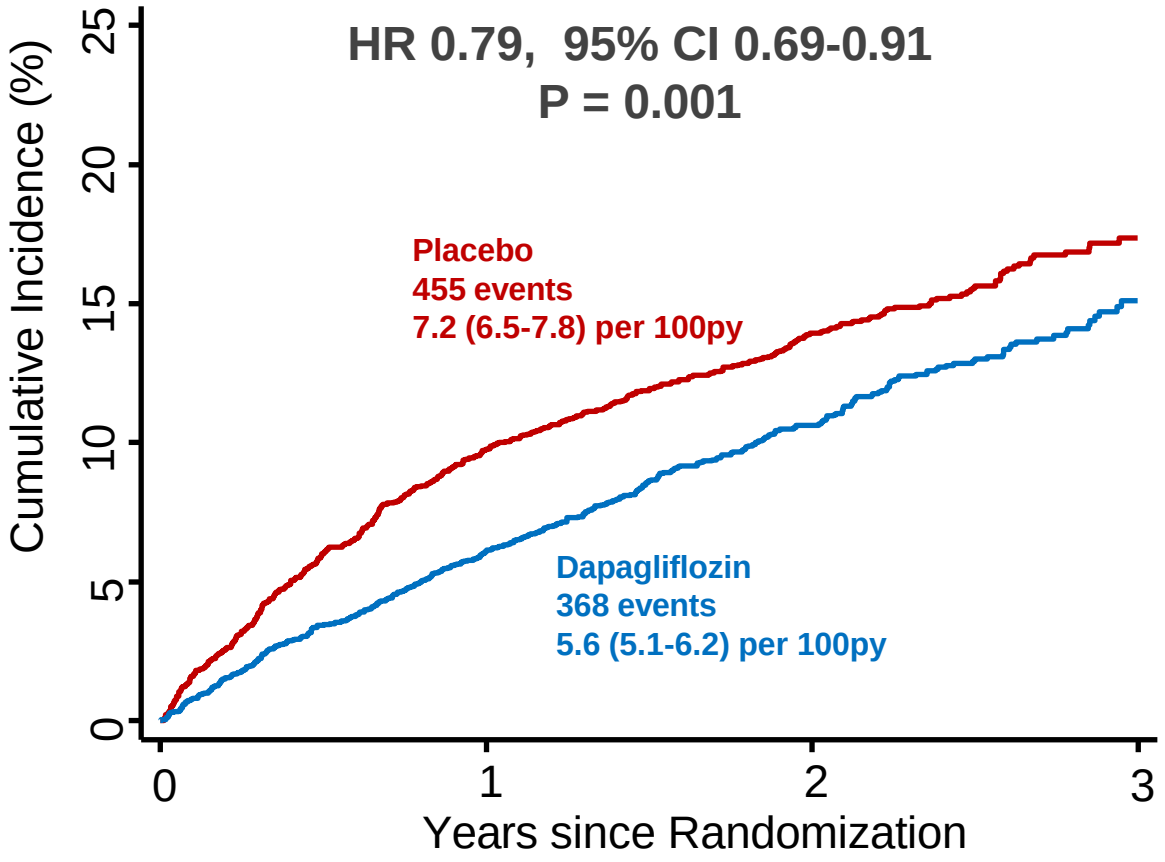
Full Population



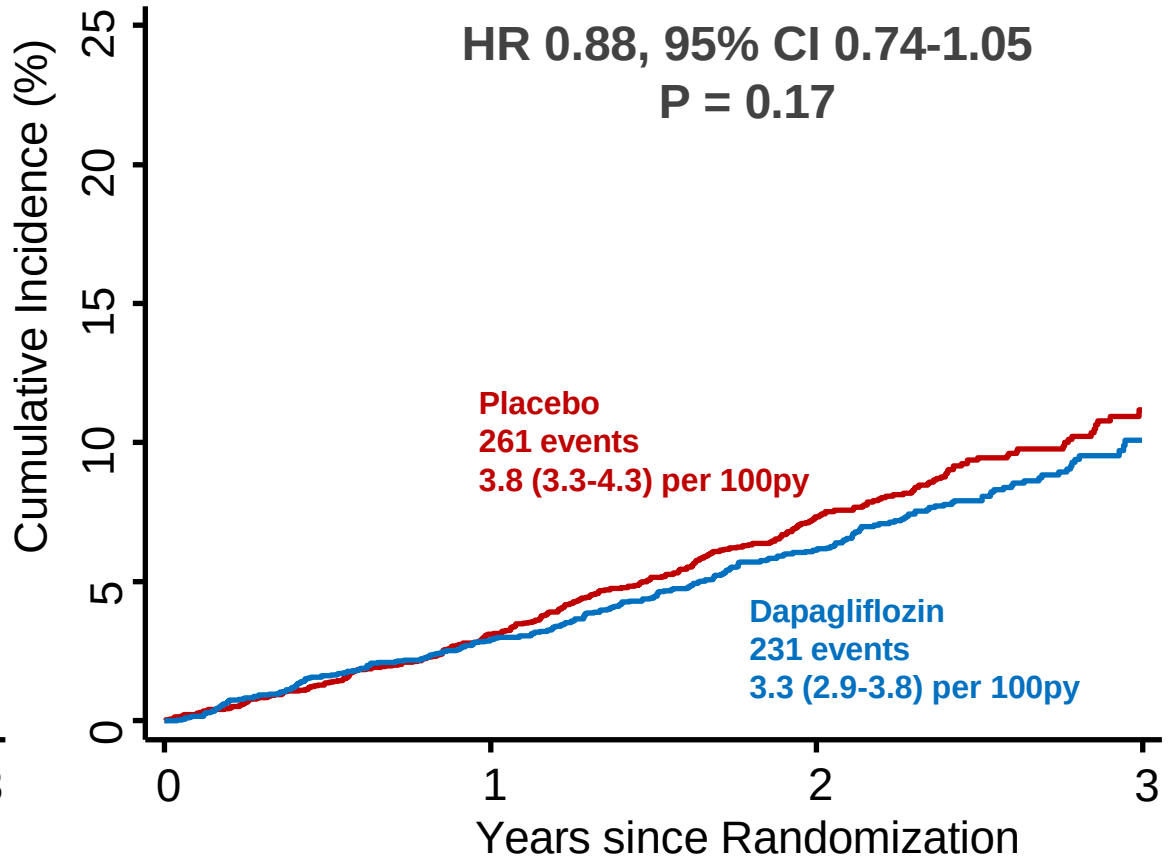
Components of Primary Endpoint

Full Population

Worsening Heart Failure (HF Hospitalization + Urgent HF Visit)



Cardiovascular Death



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Treatment of HF: Summary and Concluding Remarks

Ileana L. Piña, MD, MPH, FAHA, FACC, FHFSA
Professor Medicine, Thomas Jefferson University
Clinical Professor of Medicine
Central Michigan University
Adjunct Professor of Epi/Biostats, Case Western Reserve University
Senior Staff Fellow for FDA, CDRH, Medical Officer

2023 Classifications of HF According to Ejection Fraction (EF)

Normal:

- LVEF >55%

HF with reduced EF (HFrEF):

- HF with LVEF ≤40%

HF with mildly reduced EF (HFmrEF):

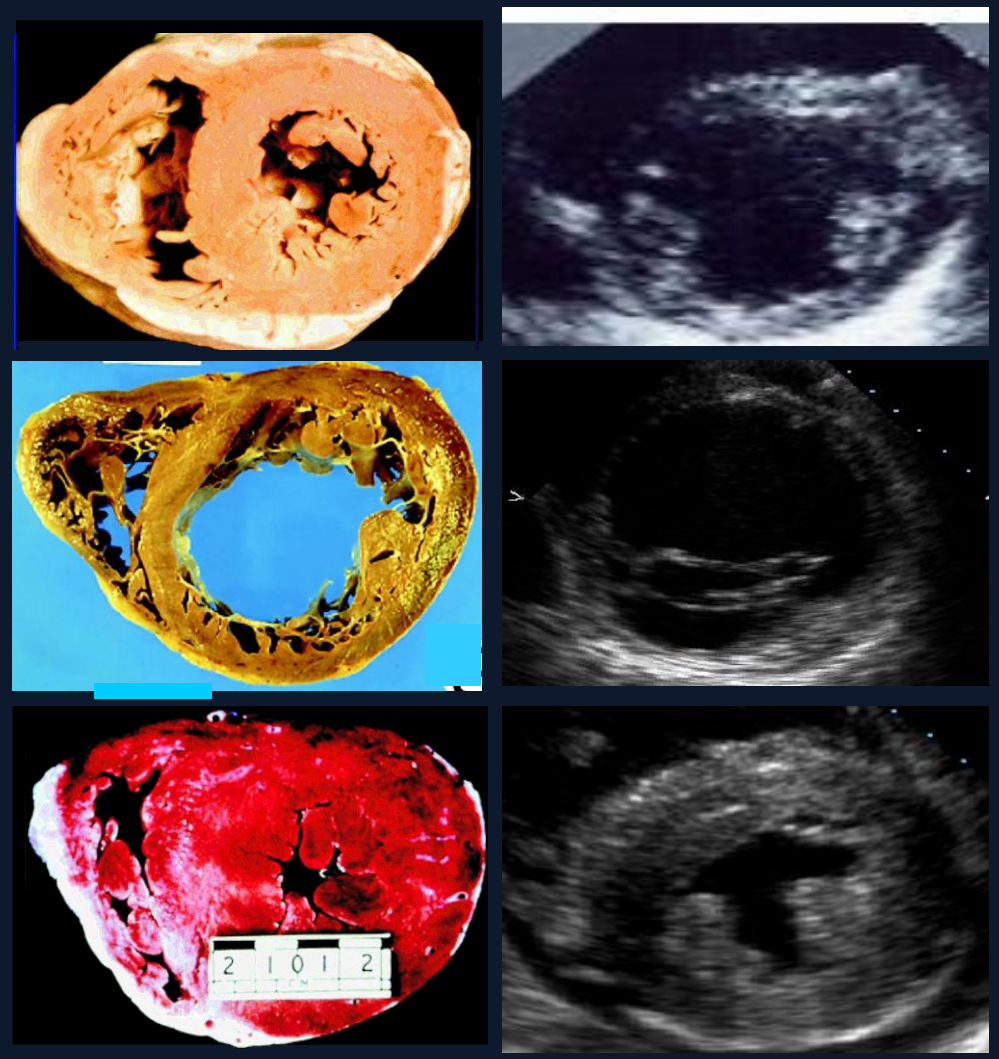
- HF with LVEF 41–49%

HF with preserved EF (HFpEF):

- HF with LVEF ≥50%

HF with improved EF (HFimpEF):

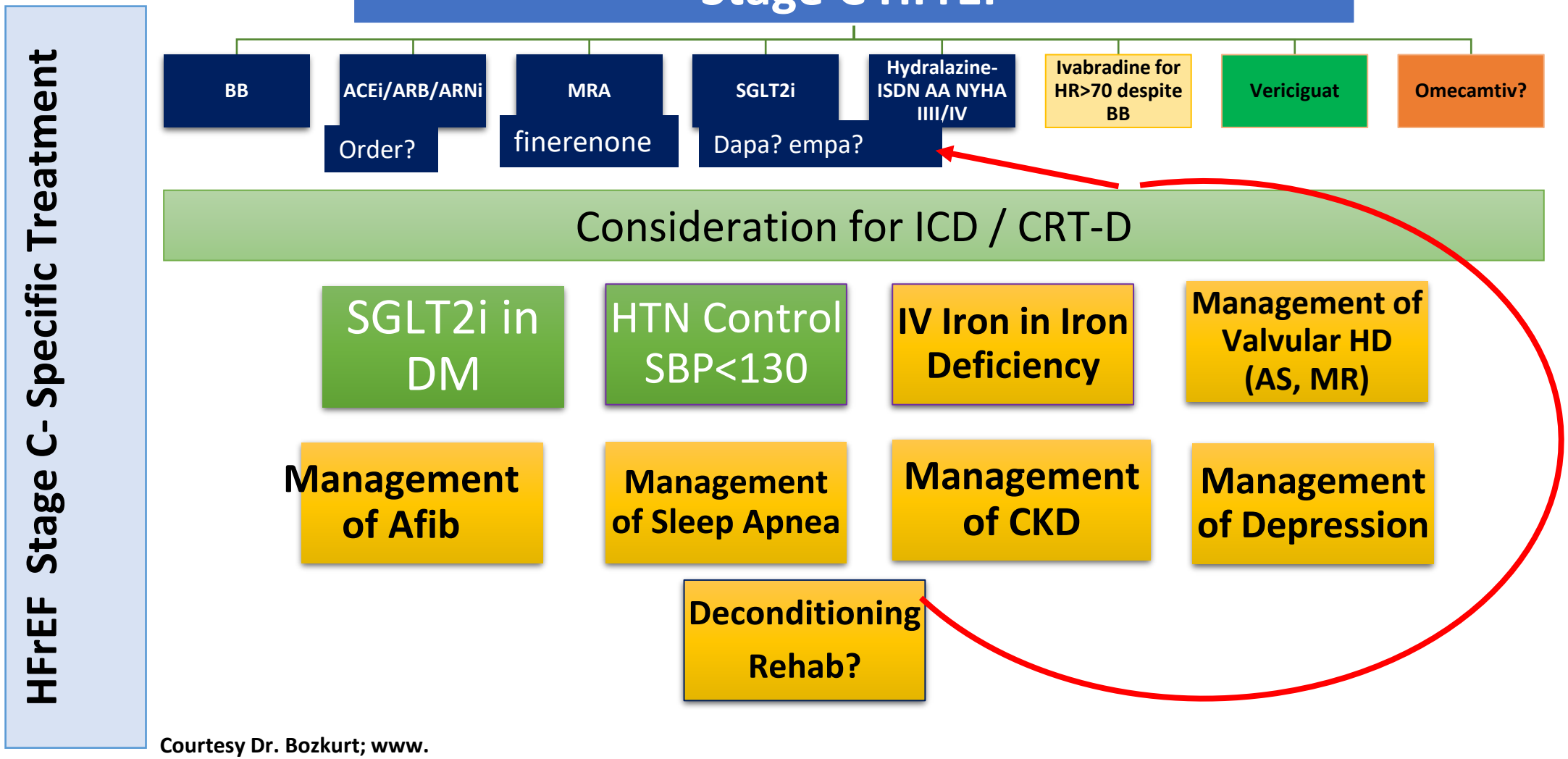
- HF with a baseline LVEF ≤40%, a ≥10 point increase from baseline LVEF, and a second measurement of LVEF >40%



Bozkurt et al. *J Card Fail.* 2021

Image Source: Jessup M, Brozena SA. *N Engl J Med.* 2003;348:2007-2018*:*

Specific Treatment of Comorbidities: Is it time for "precision"? Do not forget Cardiac Rehabilitation for the HF patient.



Courtesy Dr. Bozkurt; www.Globalcvctforum.com

What Is Precision Medicine? When Is the Right Time?

- Personalized approach to improving health and treating disease
- Approach to disease prevention and treatment strategies that takes into account individual variability in genes, comorbidities, environment, lifestyle, access, and affordability – not "cookbook" medicine
- Patient engagement-partners
- Use of electronic health records
- Availability of mobile health technologies
- Tools for analyzing large datasets
- Ability to identify key genetic mechanisms

www.whitehouse.gov/precision-medicine
Collins FS, et al. N Engl J Med. 2015;372(9):793-795.

What Does the Future Hold?

- HFrEF-----SGLT2, mechanisms
- How to start the pillars of HF care? Strategies?
- An “a-ha” moment for renal physiology in HFrEF
- HFpEF—strategies, phenotyping, Empa HFpEF and DELIVER positive. More agents in studies.
- Mechanisms of kidney protection: Importance of kidney protection
- Acute heart failure—treated as a “blip” in the patient journey

Summary and Looking Ahead

- New era of discovery in HF
- New targets
- New agents without mortality reduction
- New mechanisms, different perspective
- Taking lessons from failed trials
- Reordering entry criteria, reordering therapy
- Earlier intervention
- Better refine patient population, e.g., biomarkers
- Mechanisms of kidney protection: Importance of kidney protection
- Transition from acute to chronic
- We have much work to do!