What is the minimal optimal therapy in heart failure with non-reduced ejection fraction (HFnrEF)?

Gordon Moe, MD, FRCP(C), FACC, FAHA, FHFSA

ST. MICHAEL'S
UNITY HEALTH TORONTO

Presenter Disclosure

Dr. Gordon Moe

What is the minimal optimal therapy in HFnrEF

Relationships with financial sponsors:

- **Grants/Research Support:** Bayer
- **Speakers Bureau/Honoraria:** Bayer, CHRC
- **Consulting Fees:** AstraZeneca, Bayer, Ortho Nordisk
- **Patents:** N/A
- **Other:** N/A

Objectives

- Define heart failure (HF) and HF with non-reduced ejection fraction (HFnrEF)
- Review late-breaking clinical trials underlying the term HFnrEF
- Critically review the 2025 Canadian Cardiovascular Society HF guideline update

The Old! Conventional Phenotype According to LVEF

LVEF < 40%	*HFrEF*
LVEF = 41-50%	*HFmrEF*
LVEF > 50%	*HFpEF*
Baseline LVEF ≤40%; ↑≥10 % points to >40% on 2nd measurement	*HFimpEF*

Canadian Journal of Cardiology 41 (2025) 1857–1874

Guidelines

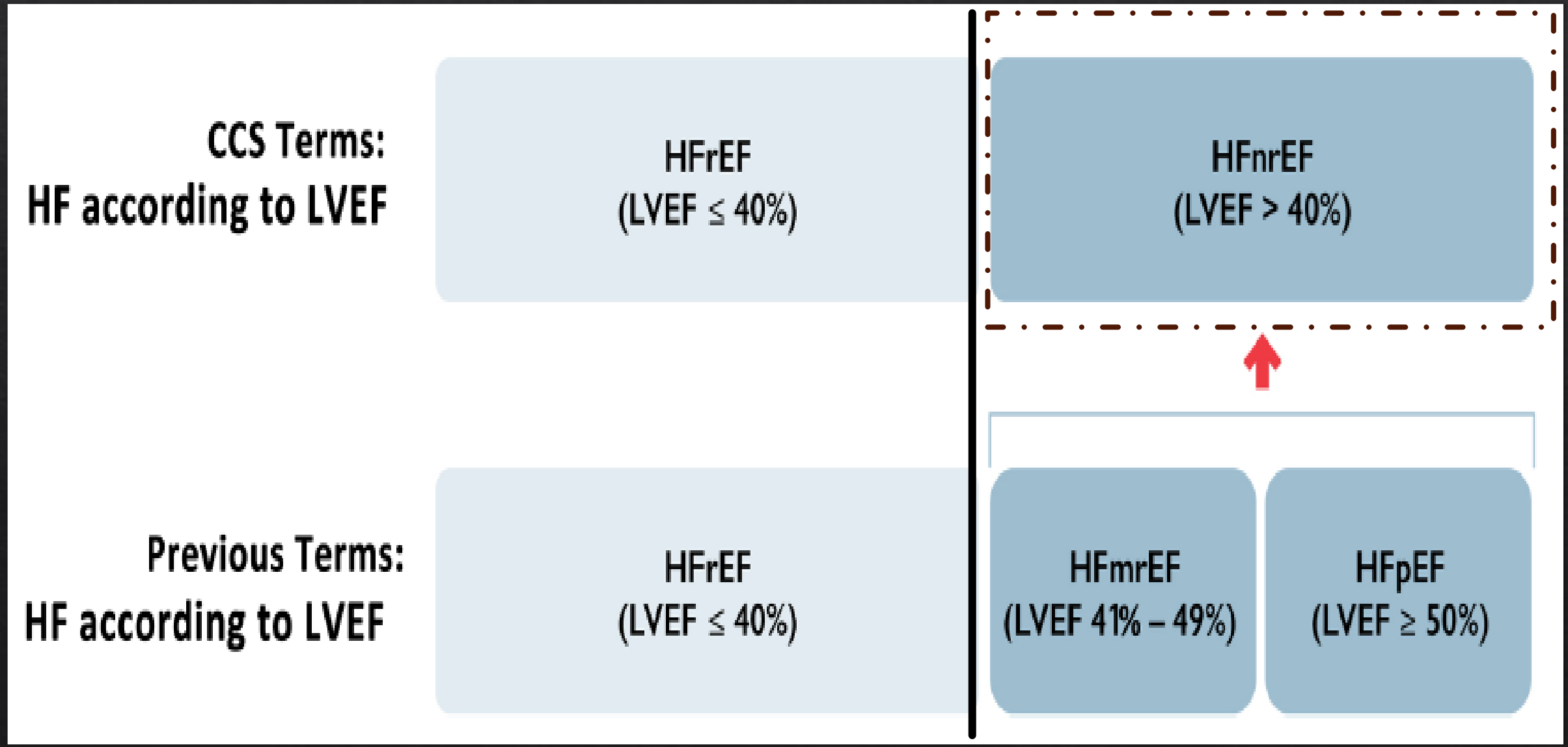
Canadian Cardiovascular Society/Canadian Heart Failure Society 2025 Guideline Update for Pharmacologic Management of Heart Failure With Nonreduced Ejection Fraction (LVEF > 40%)

Primary Panel: Sean Virani, MD, (Co-chair),[a] Shelley Zieroth, MD, (Co-chair),[b] Natasha Aleksova, MD,[c] Kim Anderson, MD, MSc,[d] Brian Clarke, MD,[a] Anique Ducharme, MD,[c] Justin A. Ezekowitz, MBBCh,[f] Farid Foroutan, HBSc, PhD,[g] Nadia Giannetti, MD,[h] Rahul Jain, MD,[i] Douglas Lee, MD, PhD,[c] Serge Lepage, MD,[j] Kristin Lyons, MDCM,[k] Michael McDonald, MD,[c] Caroline McGuinty, MD,[l] Lisa Mielniczuk, MD,[l,m] Eileen O'Meara, MD,[c] Stephanie Poon, MD,[i] Kyla Siatecki, MN, NP,[b] Elizabeth Swiggum, MD,[n] Mustafa Toma, MD,[a] Ricky D. Turgeon, PharmD,[o]

Review Panel: Marc Bains,[p] Margot K. Davis, MD, SM,[a] Sabe De, MD,[q] Nowell Fine, MD, SM,[k] Jodi Heshka, MD,[r] Sabina Keen, MD,[s] Alexandra King, MD,[t] Andrea Lavoie, MD,[u] Susanna Mak, MD, PhD,[v] Lynn McCleary, RD, PhD,[w] Oussama Outbih, MD,[x] Rodolfo Pike, RN, BN, MN, NP,[y] Abhinav Sharma, MD, PhD,[h] Harriette G.C. Van Spall, MD, MPH,[z,aa] and Amelia Ming Ching Yip, MD[ab]

Canadian Journal of Cardiology 41 (2025) 1857-1874

The New! Canadian Cardiovascular Society (CCS)/Canadian Heart Failure Society (CHFS) nomenclature for HF stratified according to LVEF



Objectives

- Define heart failure with non-reduced ejection fraction (HFnrEF)
- Review late-breaking clinical trials underlying the defining of HFnrEF
- Critically review 2025 Canadian Cardiovascular Society heart failure guideline update

Case

- 73-year-old male
- Hypertension, type II diabetes
- CAD, PCI 5 years ago
- Dyspnea and ankle edema for 2 months

- Distended neck vein, lung crackles, bilateral ankle edema
- BP 158/89 mmHg, pulse 86 bpm, irregular rhythm

Case (continued)

- CXR: congested
- Echo: LVH, LVEF 46% mild MR and TR

- Na 138, K 5.1, creatinine 101, eGFR 63, NT-proBNP 5423

What is the minimal optimal therapy?

1st positive outcome trial in patients with HF with LVEF ≥40%

The NEW ENGLAND JOURNAL of MEDICINE

N=5988, LVEF >40%

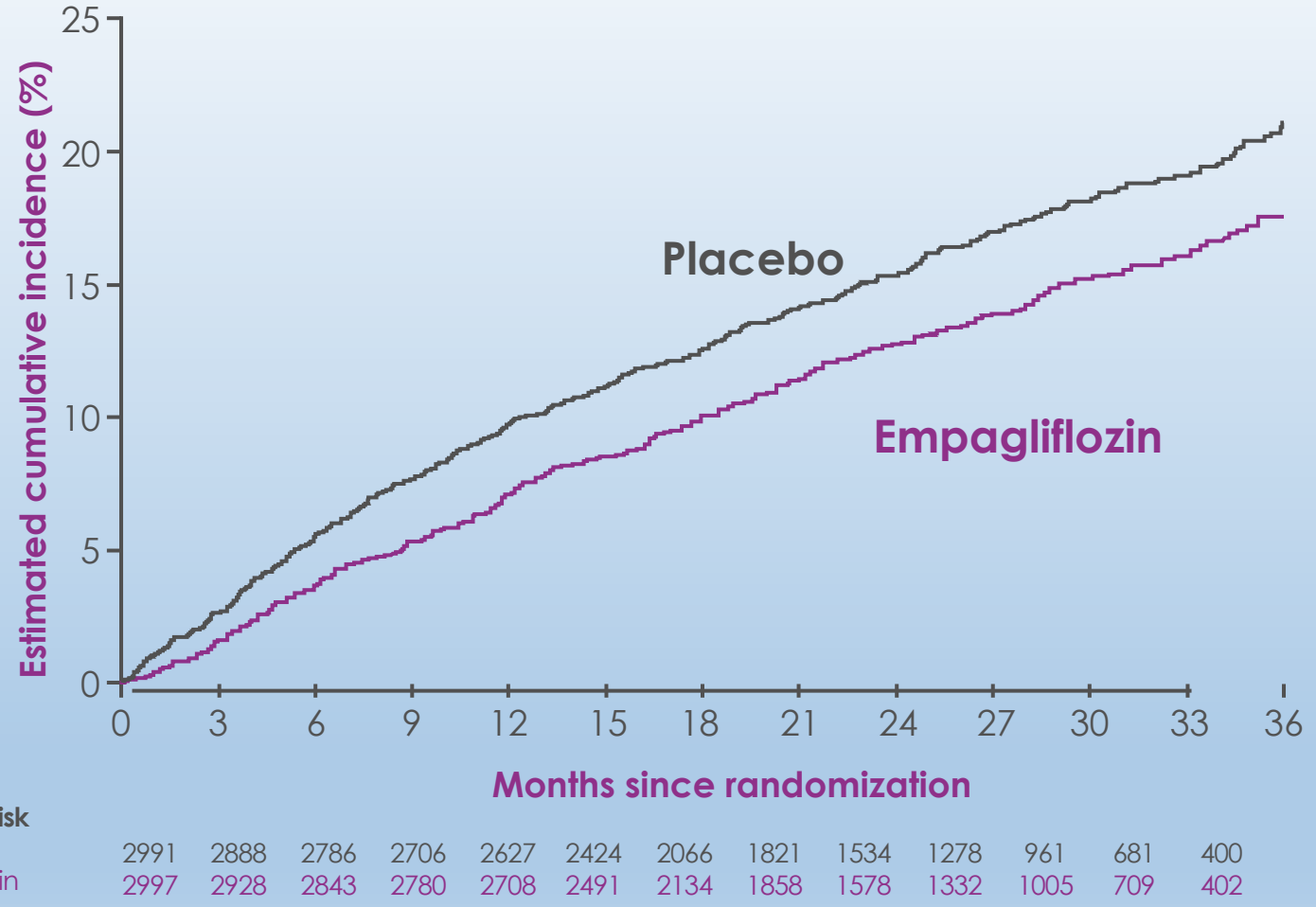
ORIGINAL ARTICLE

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 et al. N Engl J Med 2021, Aug 27

EMPEROR-Preserved Primary Endpoint: CV death or Hospitalization



Patients at risk													
Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

RRR 21%

ARR 3.3%

NNT*=31

Hazard Ratio: 0.79
(95% CI: 0.69, 0.90)
p<0.001

Empagliflozin:
415 (14%) patients with event
Rate: 6.9/100 patient-years
Placebo:
511 (17%) patients with event
Rate: 8.7/100 patient-years

*During a median trial period of 26 months.
ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; NNT, number needed to treat; RRR, relative risk reduction.
Anker S et al. N Engl J Med. 2021. DOI:10.1056/NEJMoa2107038

2nd trial: $SGLT_2$ inhibitor in Chronic and Acute HF with LVEF>40%

The NEW ENGLAND JOURNAL of MEDICINE

N=6263 LVEF >40%

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*

ABSTRACT

DELIVER: largest and broadest trial to date in patients with HF and EF>40%[1]

DELIVER[1,2]

N=6263

- **LVEF >40%** and evidence of structural heart disease
- Elevated NT-proBNP
- **Ambulatory or hospitalized**
- eGFR ≥25 mL/min/1.73 m²

1:1 randomization

- **DAPA 10 mg**
- **Placebo**

Median follow-up: 2.3 years

Primary endpoint[2]

Composite of CV death or worsening HF (hHF or an urgent HF visit):

- **Full patient population**
- **Patients with LVEF <60%**

Secondary endpoints[2]

- **Total # of hHF (first and recurrent) and CV death**
- **Change in KCCQ-TSS to 32 weeks**
- **CV death**
- **All-cause mortality**

Baseline characteristics[1,2]

1011 pg/mL
Median NT-proBNP

54%
Average LVEF

55%
Without T2D

50%
With an eGFR <60 mL/min/1.73 m²

10%
Hospitalized or recently discharged

~18%
With prior LVEF ≤40%

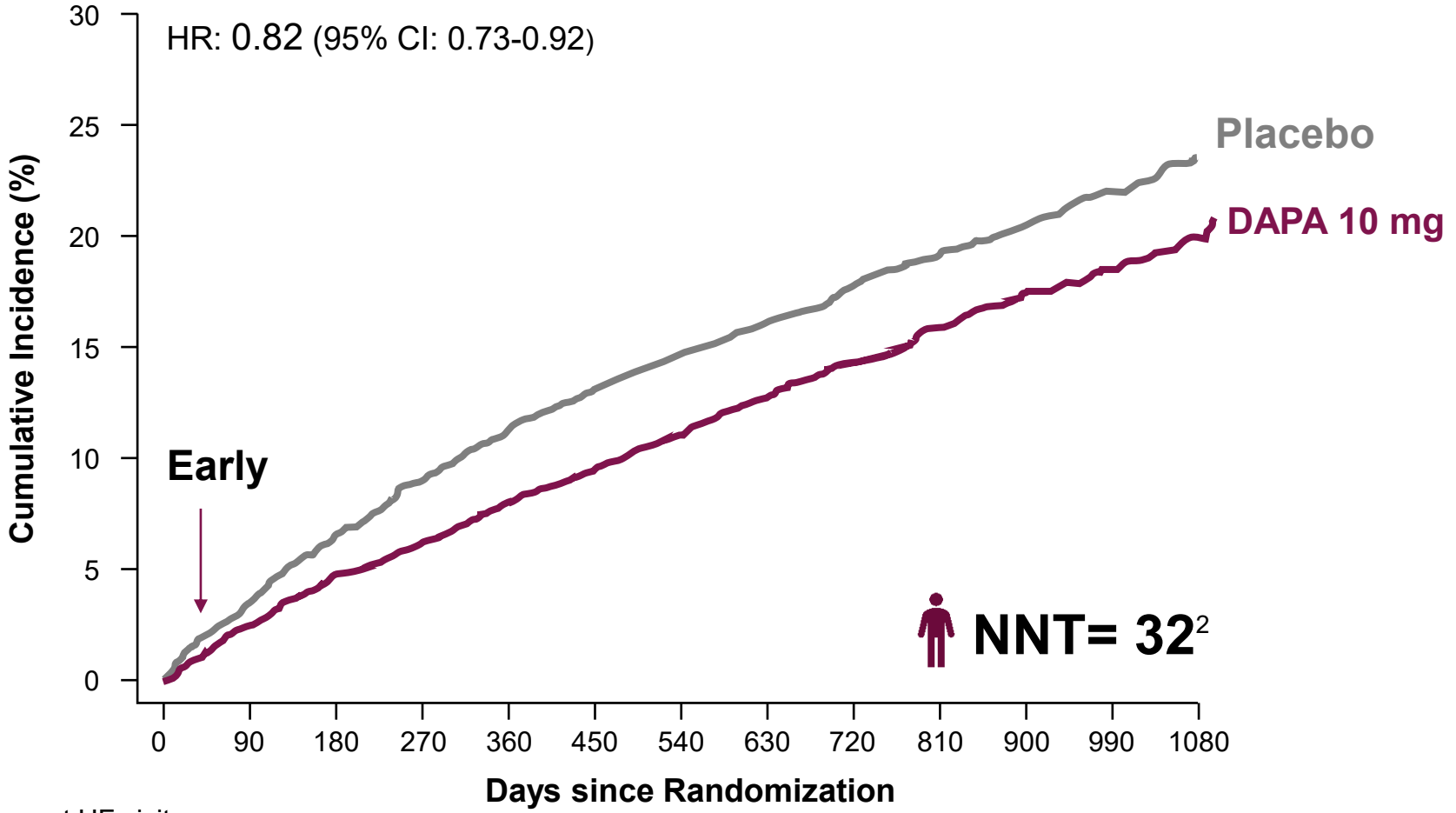
1. Solomon SD et al. *JACC Heart Fail*. 2022;10(3):184-197; 2. Solomon SD et al. Article and supplementary appendix online ahead of print. *N Engl J Med*. 2022.

DELIVER Primary Endpoint: Risk of CV death or worsening HF in patients

DELIVER

Primary Endpoint

Composite of CV Death or Worsening HF[a]



18 % RRR

3.1% ARR
p=0.0008[2]

[a] HF hospitalization an urgent HF visit.

1. Solomon SD et al. Online ahead of print. *N Engl J Med*. 2022; 2. Solomon SD. Presented at: ESC Congress; August 26-29, 2022; Barcelona, Spain.

3rd trial: Non-steroidal MRA in HFnrEF (LVEF>40%)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 24, 2024 VOL. 391 NO. 16

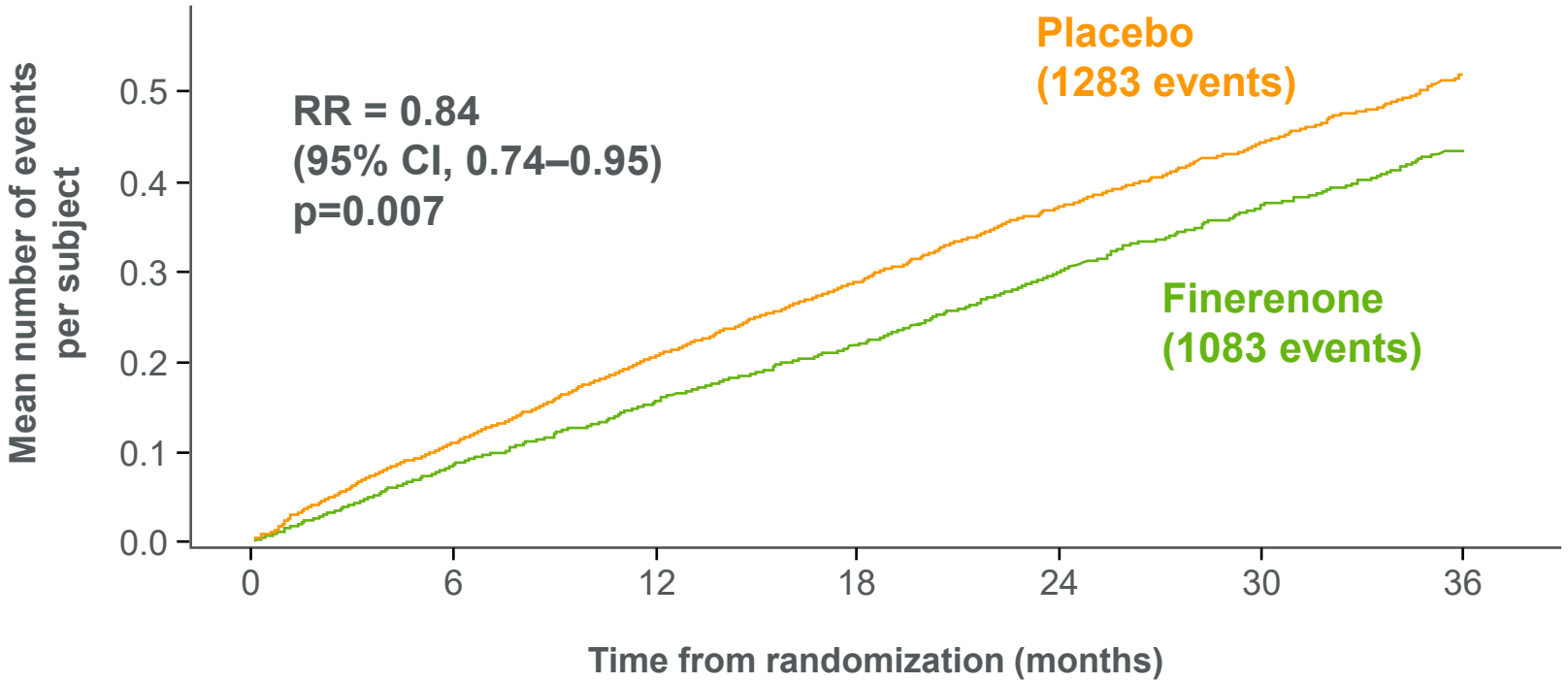
Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, M. Vaduganathan, B. Claggett, P.S. Jhund, A.S. Desai, A.D. Henderson, C.S.P. Lam, B. Pitt, M. Senni, S.J. Shah, A.A. Voors, F. Zannad, I.Z. Abidin, M.A. Alcocer-Gamba, J.J. Atherton, J. Bauersachs, M. Chang-Sheng, C.-E. Chiang, O. Chioncel, V. Chopra, J. Comin-Colet, G. Filippatos, C. Fonseca, G. Gajos, S. Goland, E. Goncalvesova, S. Kang, T. Katova, M.N. Kosiborod, G. Latkovskis, A.P.-W. Lee, G.C.M. Linssen, G. Llamas-Esperón, V. Mareev, F.A. Martinez, V. Melenovský, B. Merkely, S. Nodari, M.C. Petrie, C.I. Saldarriaga, J.F.K. Saraiva, N. Sato, M. Schou, K. Sharma, R. Troughton, J.A. Udell, H. Ukkonen, O. Vardeny, S. Verma, D. von Lewinski, L. Voronkov, M.B. Yilmaz, S. Zieroth, J. Lay-Flurrie, I. van Gameren, F. Amarante, P. Kolkhof, and P. Viswanathan, for the FINEARTS-HF Committees and Investigators*

N Engl J Med 2024;391:1475-85

FINEART-HF Primary Outcome

Primary endpoint: Number of CV deaths and total HF events[1]



Differences in treatment effect on the composite CV outcome were observed early and remained consistent throughout

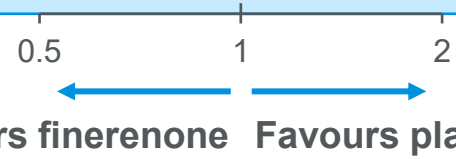
ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HF, heart failure; PY, patient year; RR, rate ratio.

Solomin SD et al N Engl J Med 2024;391:1475-85. DOI: 10.1056/NEJMoa24071071..

FINEARTS-HF
Reduction in the composite CV outcome driven by a reduction in HF events

Primary endpoint: Components of composite CV outcome

Outcome	Finerenone (N=3003) n	Placebo (N=2998) n	Ratio or difference (95% CI)	p-value
Composite CV outcome	**1083**	**1283**	**RR=0.84 (0.74–0.95)**	**0.007**
Total (first and recurrent) HF events*	**842**	**1024**	**RR=0.82 (0.71–0.94)**	**0.006**
CV death	242	260	HR=0.93 (0.78–1.11)	NR



*One patient in each group was reported as having a HF event on the same day as a CV death and was counted as only one composite event in the primary analysis.
CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; NR, not reported; RR, rate ratio.
Solomin SD e t al. N Engl J Med 2024;391:1475-85.DOI: 10.1056/NEJMoa2407107

4th trial: ARNI in Chronic HFpEF: The PARAGON Trial

The NEW ENGLAND JOURNAL of MEDICINE

N=4822 LVEF >45%

ORIGINAL ARTICLE

Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

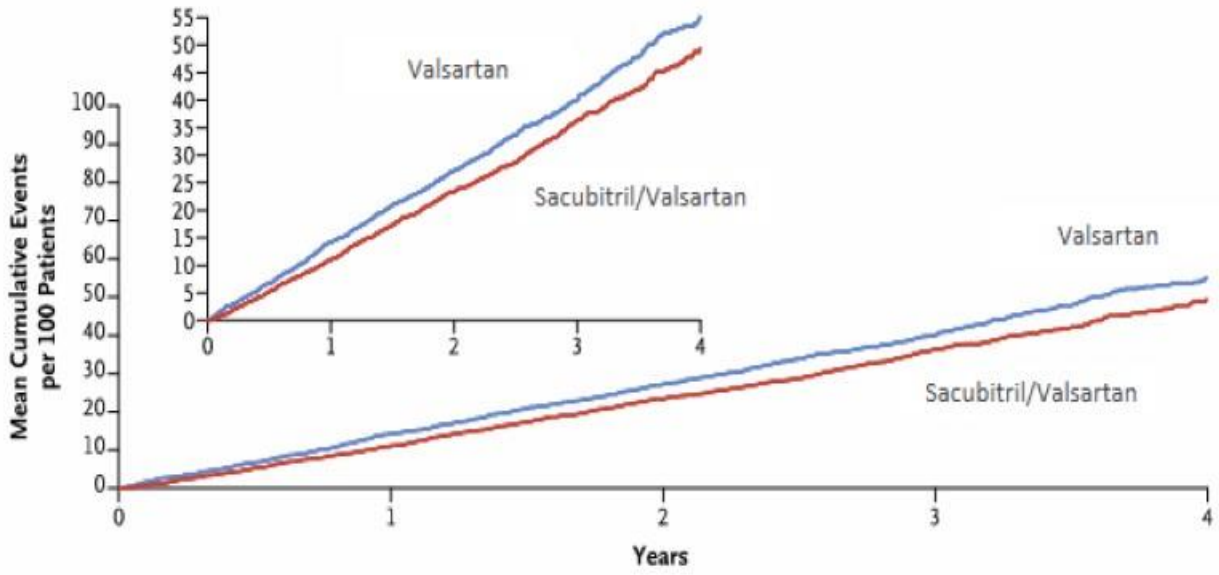
S.D. Solomon, J.J.V. McMurray, I.S. Anand, J. Ge, C.S.P. Lam, A.P. Maggioni, F. Martinez, M. Packer, M.A. Pfeffer, B. Pieske, M.M. Redfield, J.L. Rouleau, D.J. van Veldhuisen, F. Zannad, M.R. Zile, A.S. Desai, B. Claggett, P.S. Jhund, S.A. Boytsov, J. Comin-Colet, J. Cleland, H.-D. Düngen, E. Goncalvesova, 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, et al. N Engl J Med 2019;381:1609-20

ARNI in Patients With HFpEF: *Data from PARAGON-HF*

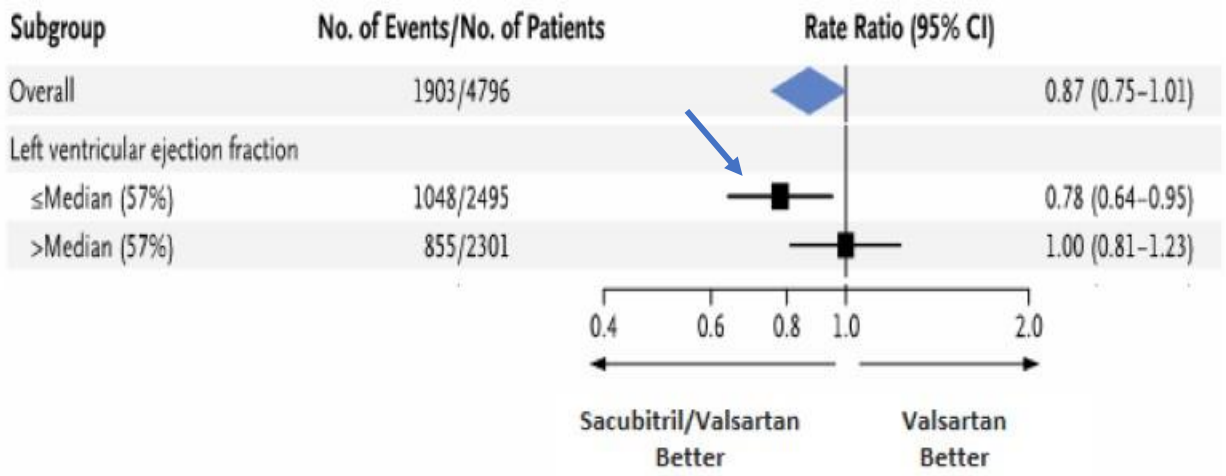
LVEF >45%

Primary Endpoint: Composite of CV Death/HHF



RR: 0.87 (95% CI: 0.75, 1.01); *P* = .06

Primary Endpoint Prespecified Subgroup: LVEF



Solomon SD, et al. N Engl J Med 2019;381:1609-20

6th trial: GLP-1 Receptor Agonist in HFpEF and Obesity
The STEP-HFpEF trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

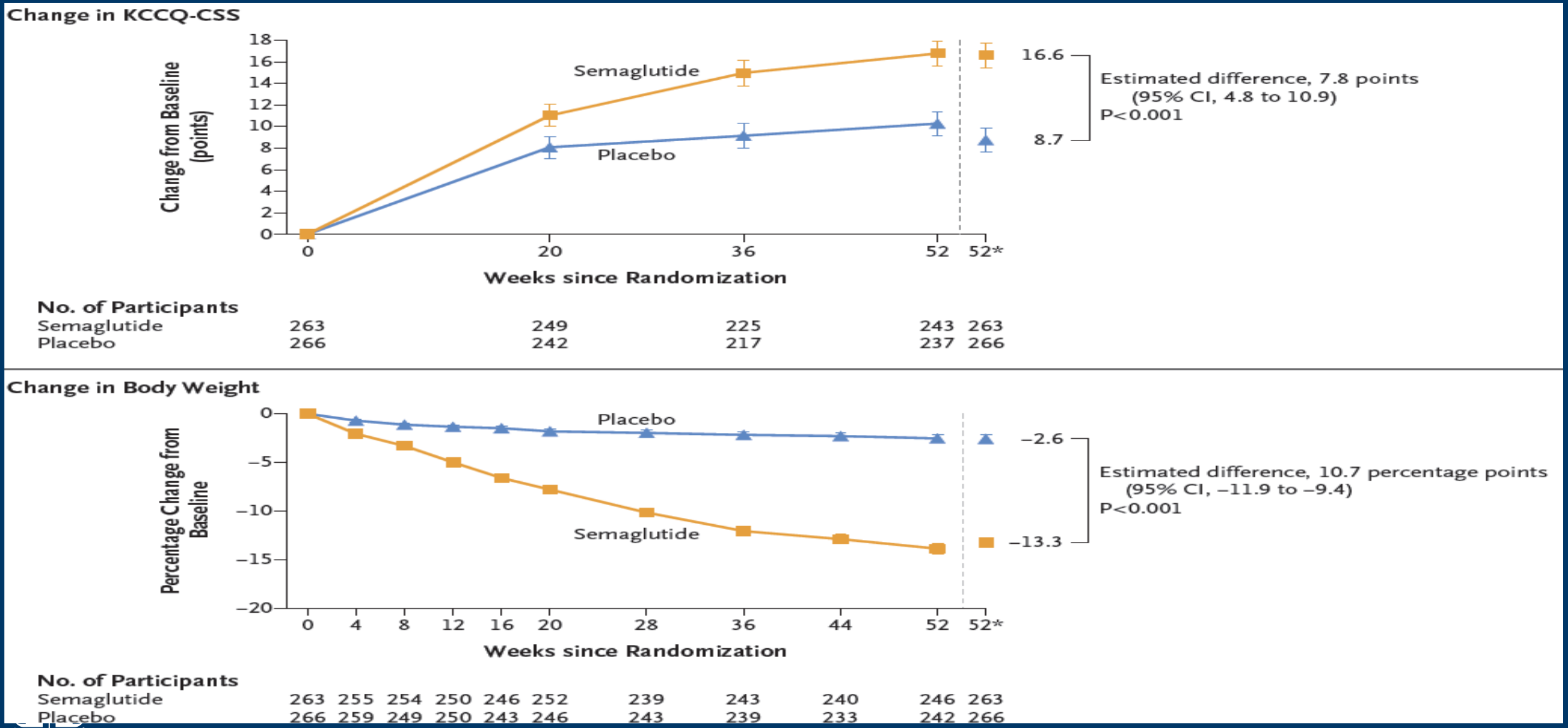
Semaglutide* in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

M.N. Kosiborod, S.Z. Abildstrøm, B.A. Borlaug, J. Butler, S. Rasmussen, M. Davies, G.K. Hovingh, D.W. Kitzman, M.L. Lindegaard, D.V. Møller, S.J. Shah, M.B. Treppendahl, S. Verma, W. Abhayaratna, F.Z. Ahmed, V. Chopra, J. Ezekowitz, M. Fu, H. Ito, M. Lelonek, V. Melenovsky, B. Merkely, J. Núñez, E. Perna, M. Schou, M. Senni, K. Sharma, P. Van der Meer, D. von Lewinski, D. Wolf, and M.C Petrie, for the STEP-HFpEF Trial Committees and Investigators*

** Not yet approved for HF*

N Engl J Med 2023;389:1069-1084, DOI:10.1056/NEJMoa2306963

STEP-HFpEF trial: Dual Primary Endpoints

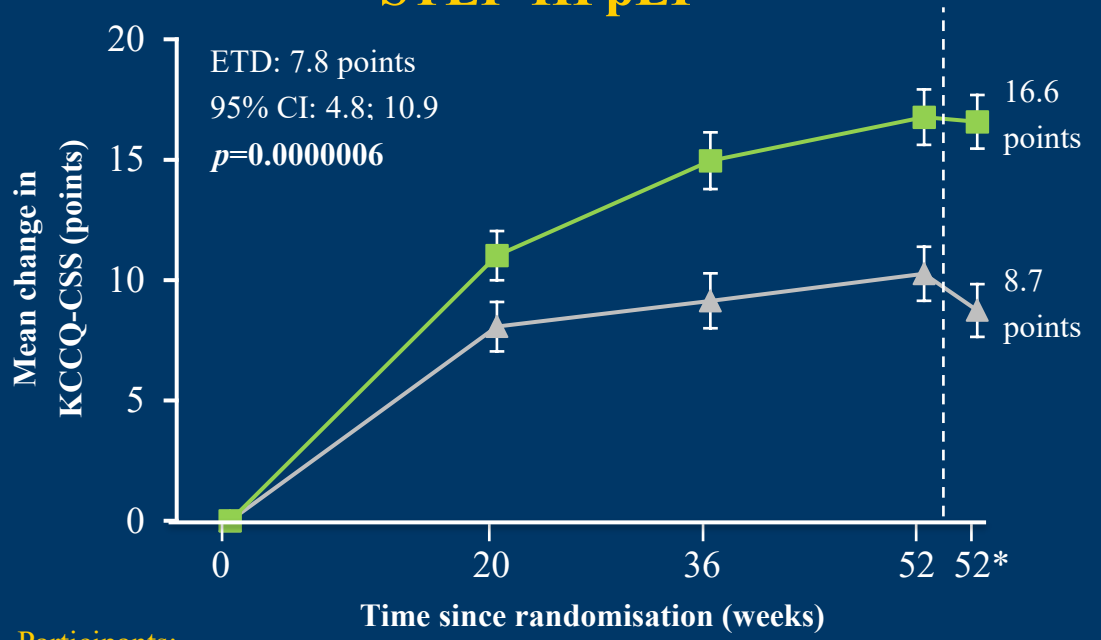


N Engl J Med 2023;389:1069-1084 DOI: 10.1056/NEJMoa2306963

Change from baseline to week 52 in KCCQ-CSS

2nd dual primary endpoint in 2 trials: patients with or without diabetes

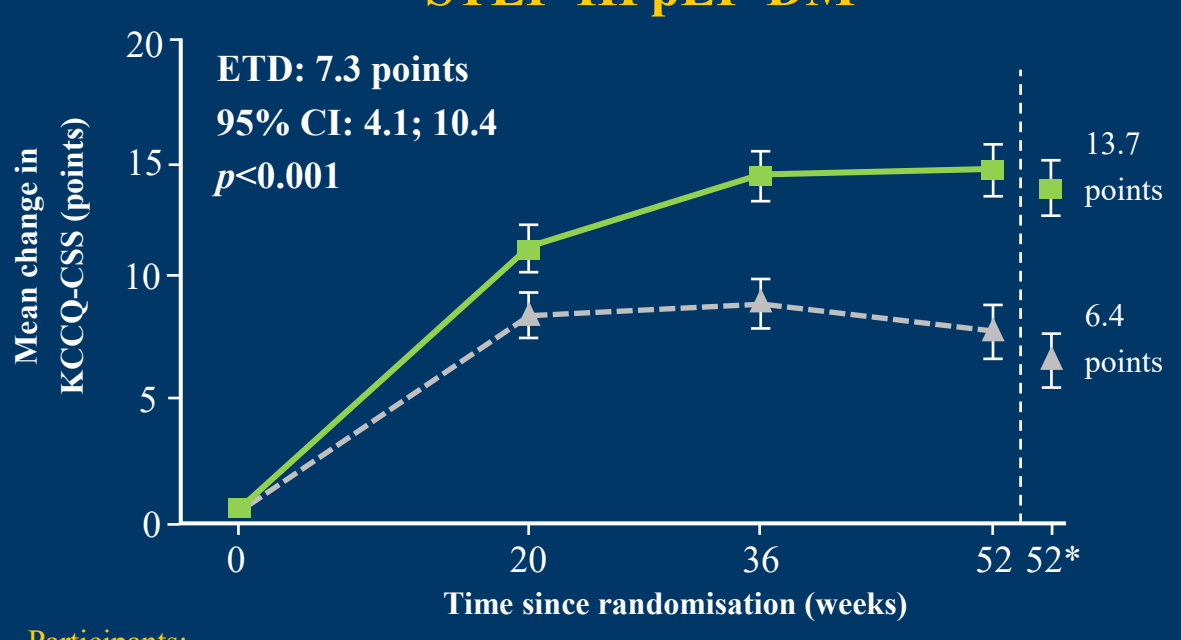
STEP-HFpEF[1]



Participants:					
Sema 2.4 mg	263	249	225	243	263
Placebo	266	242	217	237	266

Overall mean baseline KCCQ-CSS (points) 56.7

STEP-HFpEF-DM[2]



Participants:					
Sema 2.4 mg	310	289	274	281	310
Placebo	306	284	270	272	306

Overall median baseline KCCQ-CSS (points) 59.4

Semaglutide 2.4 mg
Placebo

Data are for the treatment policy estimand; *Data are estimated mean changes from baseline to Week 52 for the treatment policy estimand using ANCOVA and an imputation approach for missing data
ANCOVA, analysis of covariance; CI, confidence interval; DM, diabetes mellitus; ETD, estimated treatment difference; HFpEF, heart failure with preserved ejection fraction;
KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; sema, semaglutide

1. Kosiborod MN et al. *N Engl J Med* 2023;389:1069–1084; 2. Kosiborod MN et al. *N Engl J Med* 2024

6th trial: Glucose-dependent Insulinotropic Polypeptide (GIP-RA)/Glucagon-Like Peptide-1 receptors agonist (GLP-1 RA) in HFpEF and obesity (EF≥50%, BMI ≥30)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 30, 2025 VOL. 392 NO. 5

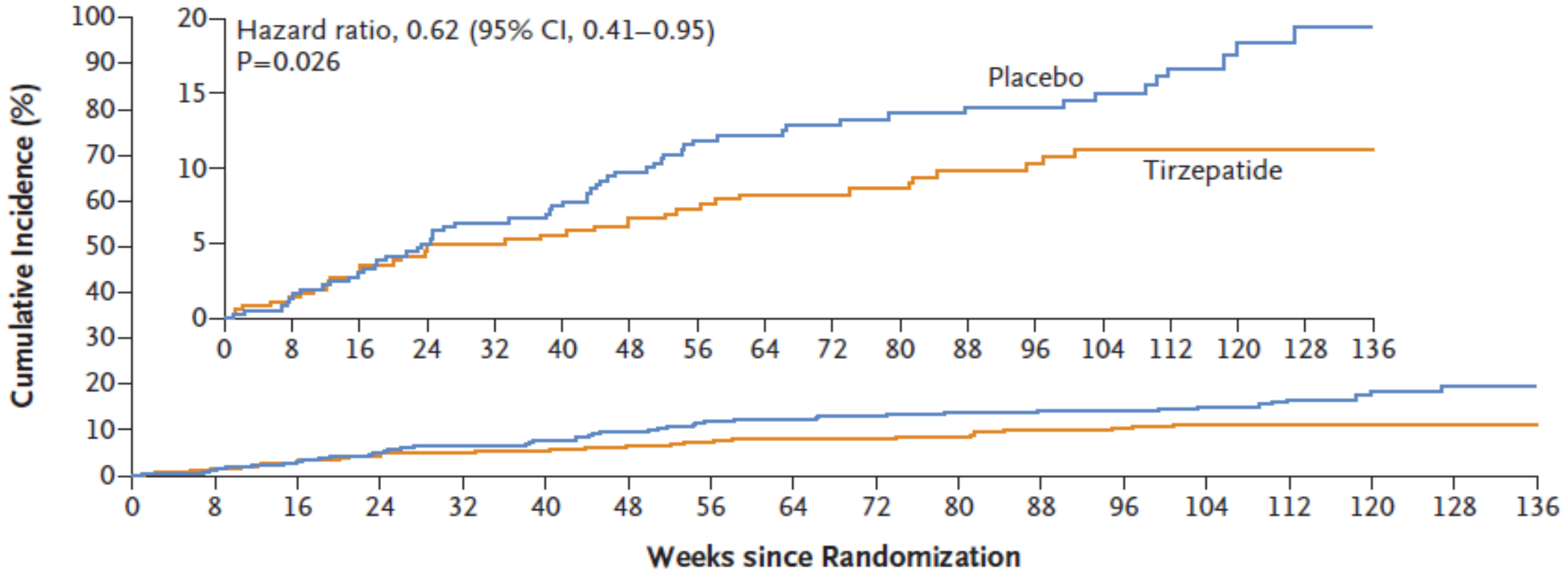
N=731 LVEF >50% BMI >30

Tirzepatide* for Heart Failure with Preserved Ejection Fraction and Obesity

Milton Packer, M.D., Michael R. Zile, M.D., Christopher M. Kramer, M.D., Seth J. Baum, M.D., Sheldon E. Litwin, M.D., Venu Menon, M.D., Junbo Ge, M.D., Govinda J. Weerakkody, Ph.D., Yang Ou, Ph.D., Mathijs C. Bunck, M.D., Karla C. Hurt, B.S.N., Masahiro Murakami, M.D., and Barry A. Borlaug, M.D., for the SUMMIT Trial Study Group*

** Not yet approved for HF*

SUMMIT Trial Primary Endpoint



No. at Risk																		
Placebo	367	361	349	339	332	328	318	268	259	240	219	215	195	165	145	94	73	45
Tirzepatide	364	359	349	344	340	338	333	284	275	251	228	220	196	167	146	105	82	46

Packer M, et al. N Engl J Med 392;5:427-37

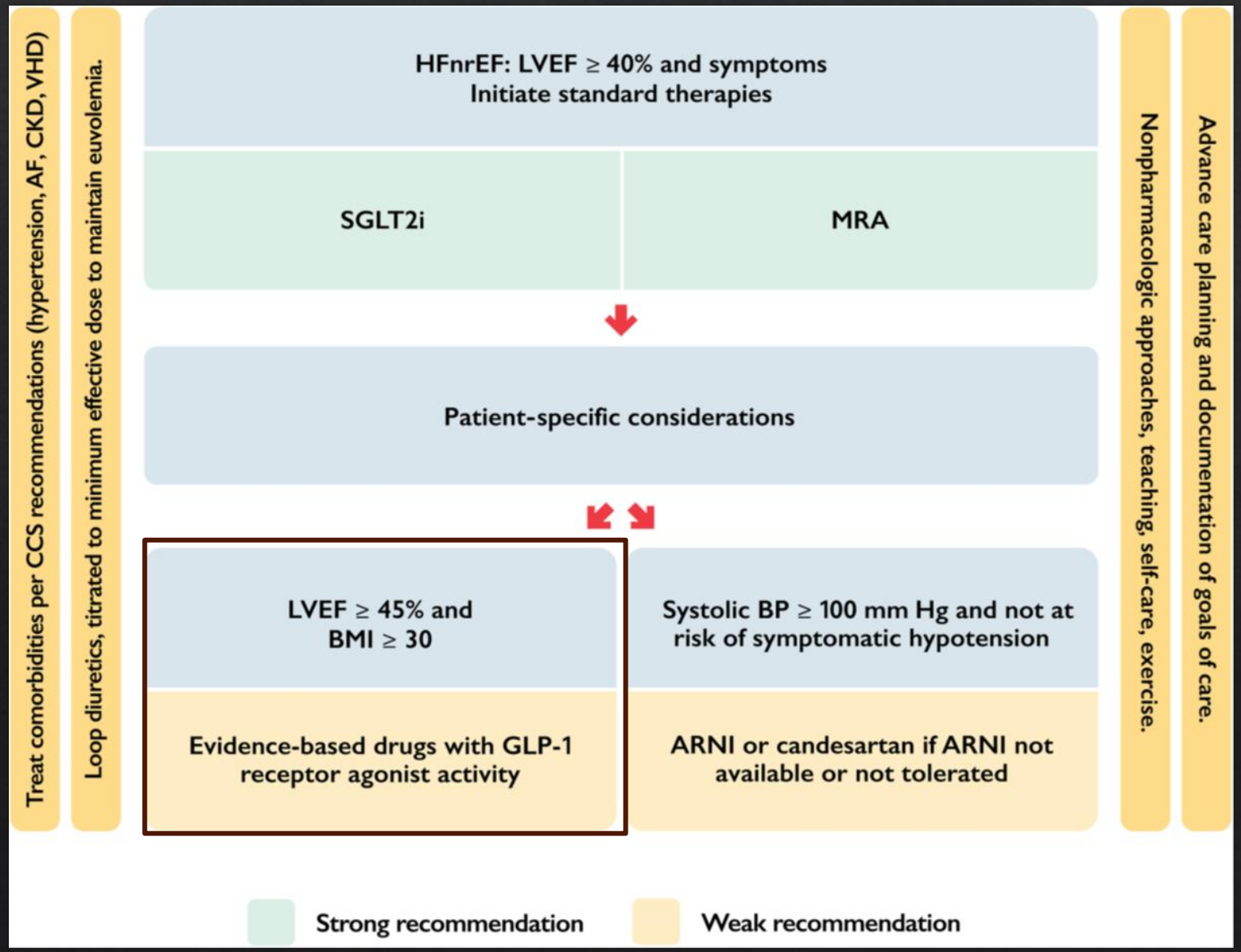
To date:
Unanswered questions re GIP-1 RA in HF

- GLP-1 RA effective in **non-obese** patients with heart failure?
- GLP-1 RA effective in patients with **heart failure and reduced ejection fraction**?

Objectives

- Define heart failure with non-reduced ejection fraction (HFnrEF)
- Review clinical trials underlying HFnrEF
- Critically review 2025 Canadian Cardiovascular Society heart failure guideline update

Simplified evidence-based treatment approach for reducing HF hospitalization in people with HF with non-reduced EF (HFnrEF)



- Only evidence-based medications should be used for the treatment of HF. The literature currently does not support a specific sequence to initiating therapy within a given treatment tier.
- The order of prescribing should be individualized on basis of patient characteristics and through a shared decision-making approach

International Use of the Term “HFnrEF”

Use of the term

- Canadian Cardiovasc Society 2025 update
- Japanese Circulation Society (JCS)/Japanese Heart Failure Society (JHFS) 2025 Guidelines (referred to CCS guideline)
- Turkish Society of Cardiology 2022 consensus

Not use

- Am Heart Association
- Am College of Cardiology
- European Society of Cardiology
- Heart Failure Society of America

What is the limitation of CCS 2025 Guideline

Where is HFimpEF??

(Patients with previous LVEF <40%)

DELIVER: Analysis of Patients with HF with improved EF

Article

https://doi.org/10.1038/s41591-022-02102-9

Dapagliflozin in heart failure with improved ejection fraction: a prespecified analysis of the DELIVER trial

Received: 5 September 2022

Accepted: 21 October 2022

Published online: 15 December 2022

Check for updates

A list of authors and their affiliations appears at the end of the paper

With modern treatments for heart failure with reduced ejection fraction (EF), indicative of impaired cardiac systolic function, patients may exhibit an increase in EF. Limited data are available regarding the clinical management of this growing population, categorized as heart failure with improved EF (HFimpEF), which has a high event rate and has been excluded from virtually all prior heart failure outcomes trials. In a prespecified analysis of the DELIVER trial (NCT03619213), of a total of 6,263 participants with symptomatic heart failure and a left ventricular EF >40%, 1,151 (18%) had HFimpEF, defined as patients whose EF improved from ≤40% to >40%. Participants were randomized to 10 mg dapagliflozin or placebo daily and the primary outcome of the trial was a composite of cardiovascular death or worsening heart failure (heart failure hospitalization or an urgent heart failure visit). Participants with HFimpEF had similar event rates to those with an EF consistently >40%. In participants with HFimpEF, dapagliflozin reduced the primary composite outcome (hazard ratio (HR) = 0.74, 95% confidence interval (CI) = 0.56–0.97), first worsening heart failure events (HR = 0.84, 95% CI = 0.61–1.14), cardiovascular death (HR = 0.62, 95% CI = 0.41–0.96) and total worsening heart failure events (rate ratio = 0.68, 95% CI = 0.50–0.94) to a similar extent as for individuals with an EF consistently >40%. These data suggest that patients with HFimpEF who are symptomatic may benefit from the addition of a sodium/glucose cotransporter 2 inhibitor to previously instituted guideline-directed medical therapy to further reduce morbidity and mortality.

18% (1151) of patients in the DELIVER trial

Nature Medicine | Volume 28 | December 2022 | 2504–2511

DELIVER trial: Subgroup of patients with HFimpEF

Nature Medicine | Volume 28 | December 2022 | 2504–2511

Finerenone in patients with HFimpEF

JAMA Cardiology | Brief Report

N=6001

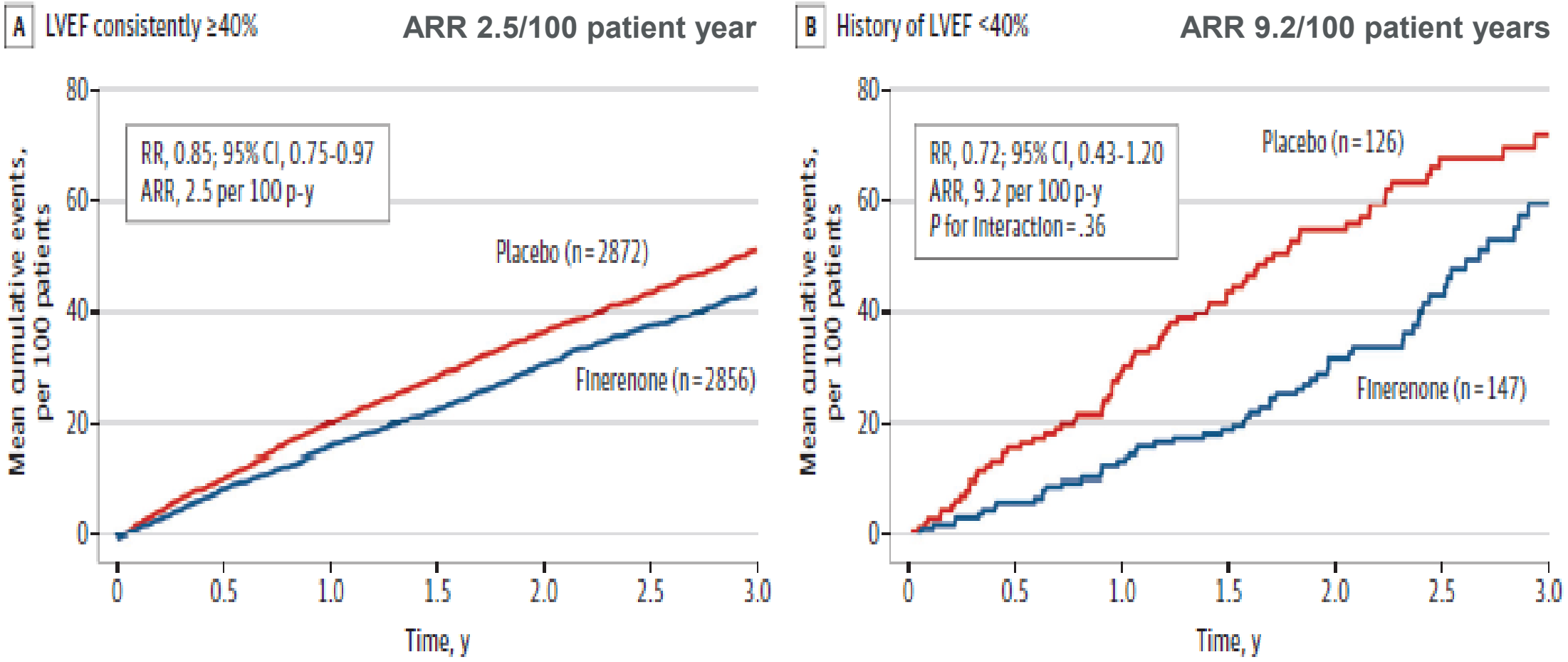
Finerenone in Heart Failure With Improved Ejection Fraction
The FINEARTS-HF Randomized Clinical Trial

Maria A. Pabon, MD; Orly Vardeny, PharmD, MS; Muthiah Vaduganathan, MD, MPH; Akshay S. Desai, MD, MPH; Brian L. Claggett, PhD; Ian J. Kulac, MS; Pardeep S. Jhund, MBChB, MSc, PhD; Carolyn S. P. Lam, MBBS, PhD; Michele Senni, MD; Sanjiv J. Shah, MD; Adriaan A. Voors, MD, PhD; Faiez Zannad, MD, PhD; Bertram Pitt, MD; Clara I. Saldarriaga, MD; Mark C. Petrie, MD; Béla Merkely, MD, PhD; Maria Borentain, MD; Katharina Mueller, MSc; Prabhakar Viswanathan, MBBS, PhD; Flaviana Amarante, MD; Alanna Morris, MD, MSc; John J. V. McMurray, MD; Scott D. Solomon, MD

JAMA Cardiol. 2025;10(7):740-745. doi:10.1001/jamacardio.2025.1101

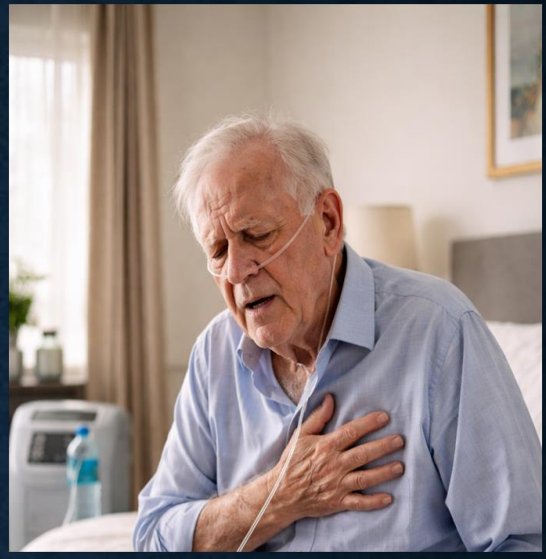
FINEARTS-HF

Finerenone in HF with consistent LVEF >40% and history of LVEF <40% (HFimpEF)



LVEF indicates left ventricular ejection fraction; RR, risk reduction; ARR, absolute risk reduction.

JAMA Cardiol. 2025;10(7):740-745. doi:10.1001/jamacardio.2025.1101



Minimal optimal therapy

- Treat co-morbid conditions
- Diuretics
- $SGLT_2$ inhibitor (empagliflozin or dapagliflozin)
  non-steroidal MRA (finerenone)

If still symptomatic

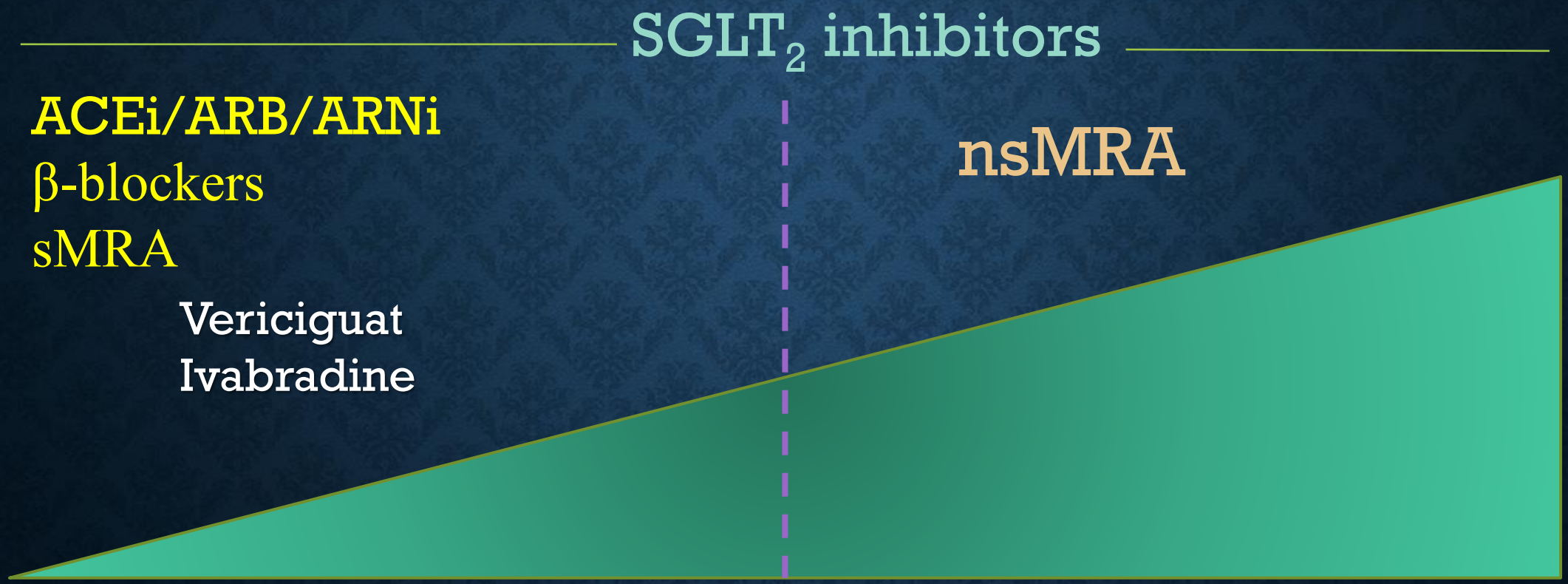
- ARNi (sacubitril valsartan)

If still symptomatic and obese

- GLP-1 RA (semaglutide)*

** Not yet approved*

GDMT for Heart Failure: all LVEF



sMRA and nsMRA, steroidal and non-steroidal MRA respectively

Conclusions

What is the minimal optimal therapy in heart failure with non-reduced ejection fraction (HFnrEF) (LVEF >40%)?

Heart failure with non-reduced ejection fraction (HFnrEF)

- The term originates from CCS 2025 guideline
- Attempted to simplify the phenotypic classification according to LVEF
- Based on landmark trials of $SGLT_2$ inhibitors and non-steroidal MRA, ARNi and GLP-1 RA
- There remains important limitations and omissions in the CCS 2025 guideline