DGK CARDIO UPDATE 2024

16. und 17. Februar
23. und 24. Februar

Herzinsuffizienz

Michael Böhm, Homburg

Interessenkonflikte

- Deutsche Forschungsgemeinschaft
- Federal State of the Saarland (Ministery of Science and Economy
- BMBF
- European Union

1. Study Support:	Abbott, Amgen, Astra Zeneca, Bayer AG, Boehringer Ingelheim, Medtronic, Novartis, Pfizer, Sanofi-Aventis, Servier
2. Advisory Boards:	Abbott, Astra Zeneca, Bayer AG, Boehringer Ingelheim, Cordis, COSMOS,Cytokinetics, Daiichi-Sankyo, Medtronic, MSD, Novartis, Pfizer, Sanofi-Aventis, Servier, Vifor
3. Speaker:	Astra Zeneca, Bayer, Boehringer Ingelheim, Berlin-Chemie, COSMOS, Daiichi-Sankyo, Edwards, Medtronic, Novartis, Pfizer, ReCor, Sanofi-Aventis, Servier, Vifor

Herzinsuffizienz

- **Guidelines**
- **Notwendigkeit der Aktualisierung**
  - **Definitionen**
  - **Neue HFpEF und HFmrEF Empfehlungen**
  - **Prävention**
  - **Komorbidität Eisenmangel**
  - **Wie initiieren**
- **Adipositas und HFpEF**
- **GLP1 Agonisten**

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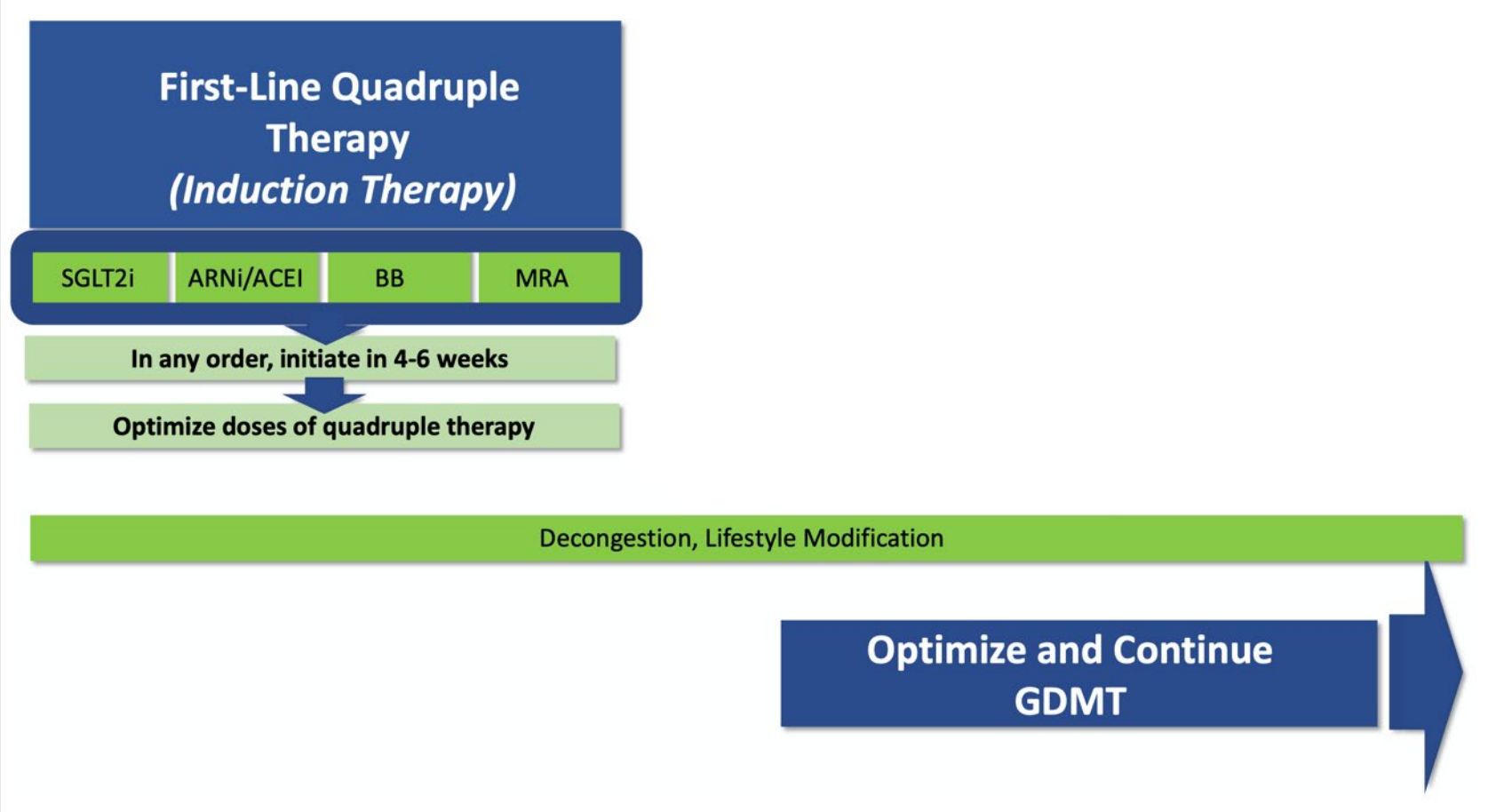
State of the Art - Herzinsuffizienz

Bozkurt et al, JACC Heart Fail 10 (2022): 992-995



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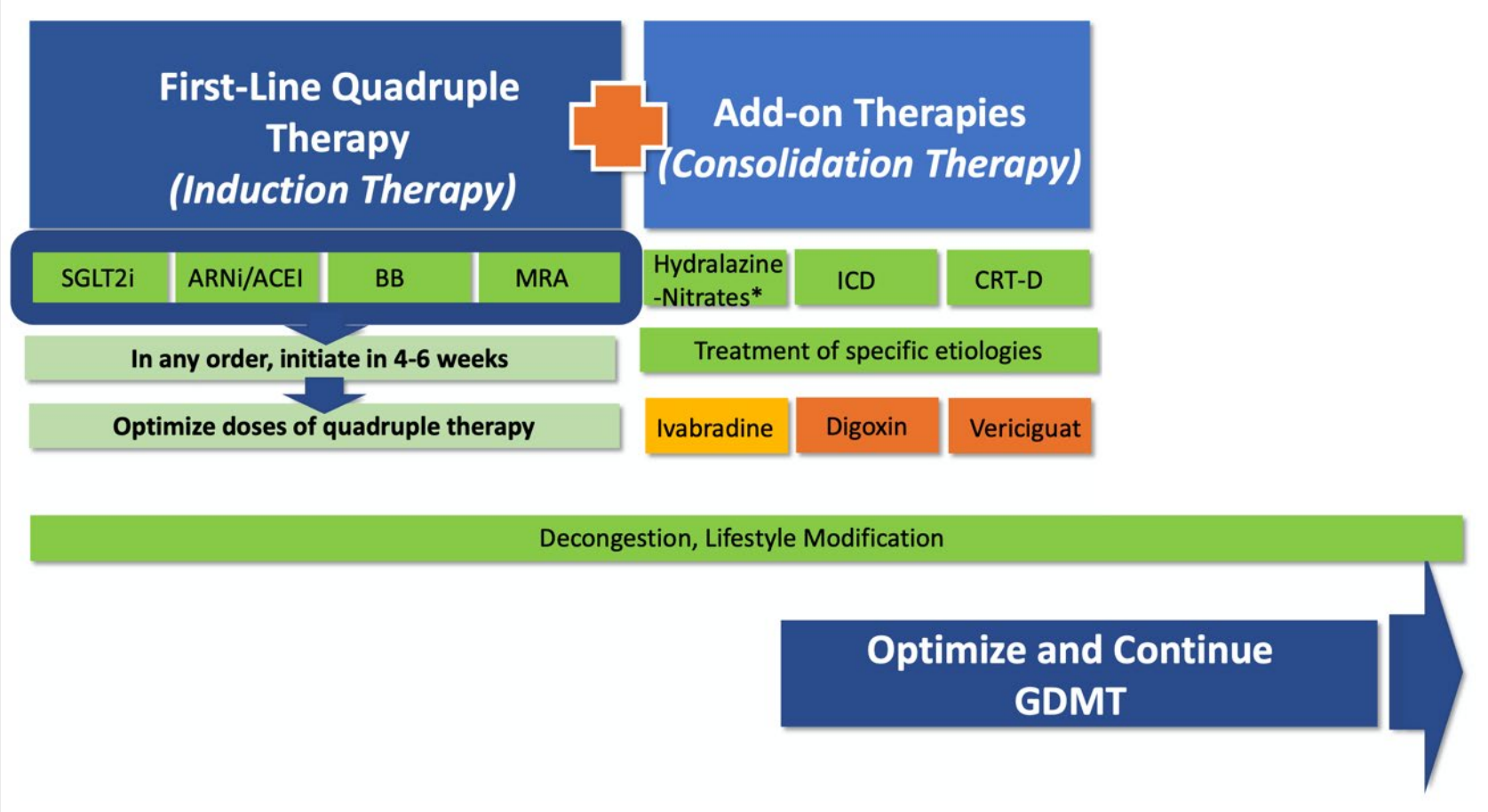

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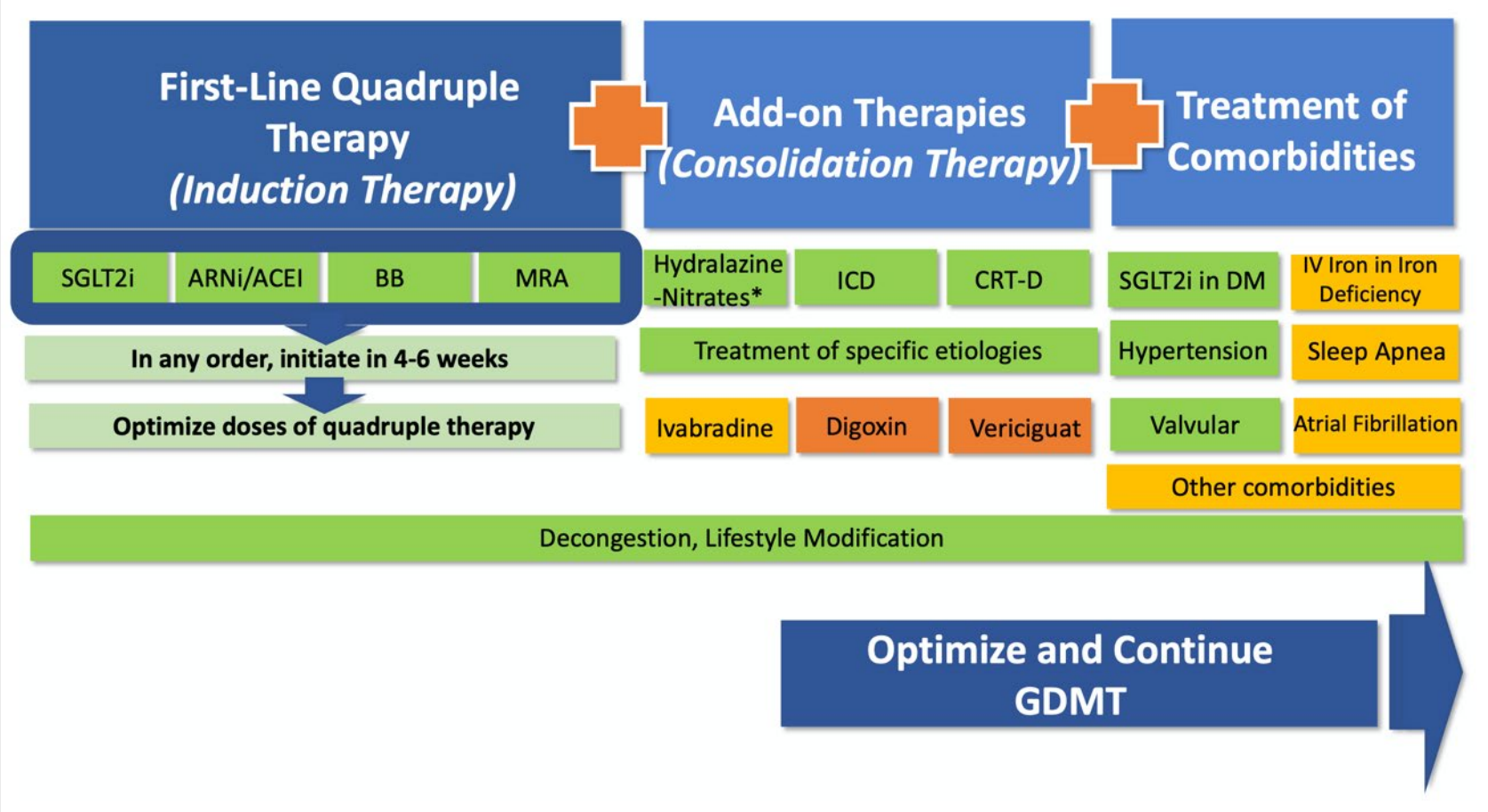

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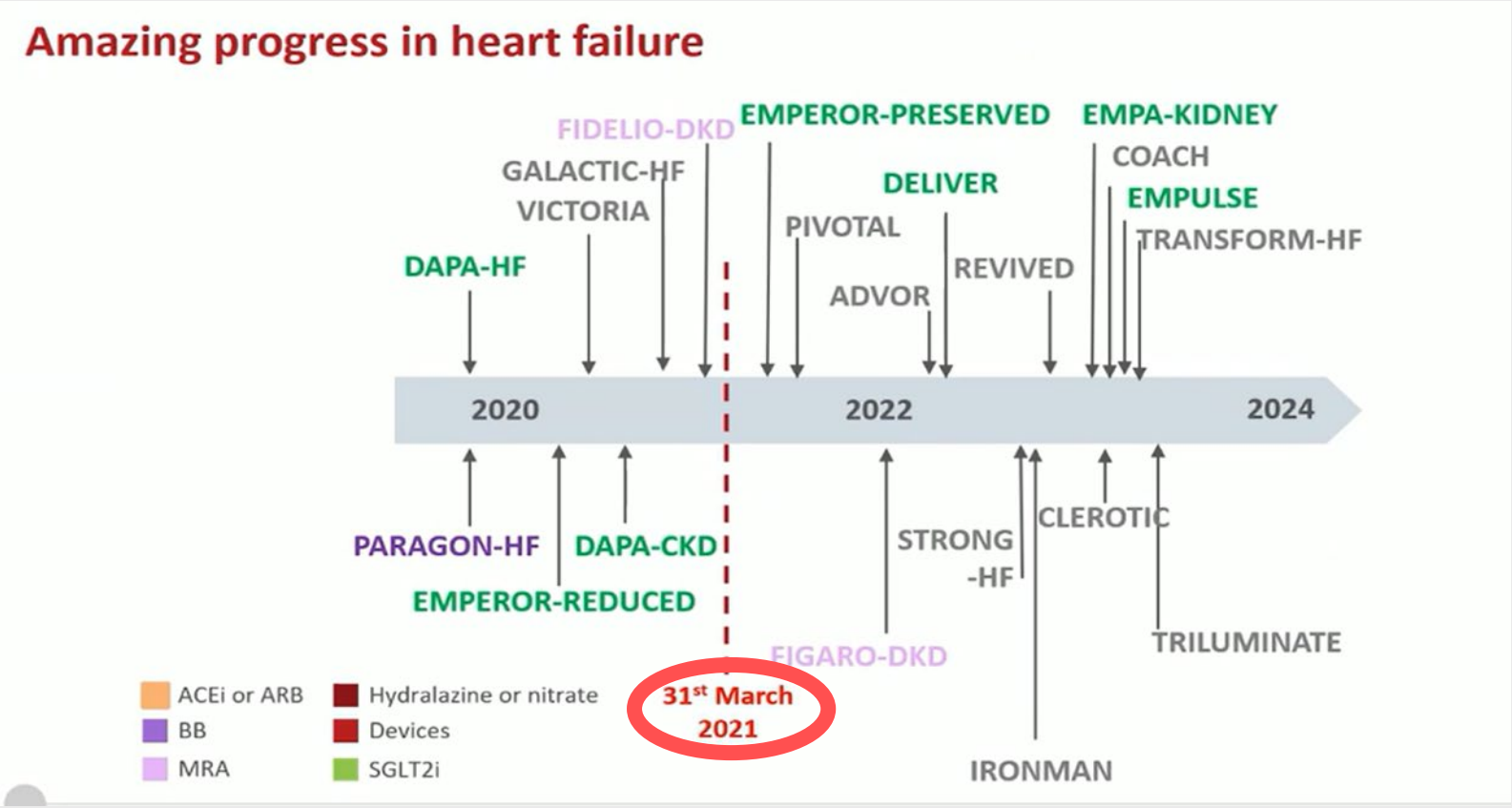
Die Aktualisierung der ESC 2021 Herzinsuffizienzleitlinien 2023

Intention

- **Implementierung neuer Studien censored zum 31.3. 2023**
- **Berücksichitgung nur der Primären Endpunkte**
- **Ausschluß, wenn Empfehlung im Widerspruch zu anderen ESC Leitlinien**
- **Aufnahme nur, wenn Annahme mit 75 % Mehrheit in geheimer Abstimmung**

2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure



2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

McDonagh et al, Eur Heart J 44 (2023): 3627-3639

Authors/Task Force Members: Theresa A. McDonagh *†, (Chairperson) (United Kingdom), Marco Metra *†, (Chairperson) (Italy), Marianna Adamo ‡, (Task Force Co-ordinator) (Italy), Roy S. Gardner ‡, (Task Force Co-ordinator) (United Kingdom), Andreas Baumbach (United Kingdom), Michael Böhm (Germany), Haran Burri (Switzerland), Javed Butler (United States of America), Jelena Čelutkienė (Lithuania), Ovidiu Chioncel (Romania), John G.F. Cleland (United Kingdom), Maria Generosa Crespo-Leiro (Spain), Dimitrios Farmakis (Greece), Martine Gilard (France), Stephane Heymans (Netherlands), Arno W. Hoes (Netherlands), Tiny Jaarsma (Sweden), Ewa A. Jankowska (Poland), Mitja Lainscak (Slovenia), Carolyn S.P. Lam (Singapore), Alexander R. Lyon (United Kingdom), John J.V. McMurray (United Kingdom), Alexandre Mebazaa (France), Richard Mindham (United Kingdom), Claudio Muneretto (Italy), Massimo Francesco Piepoli (Italy), Susanna Price (United Kingdom), Giuseppe M. C. Rosano (United Kingdom), Frank Ruschitzka (Switzerland), Anne Kathrine Skibelund (Denmark), and ESC Scientific Document Group

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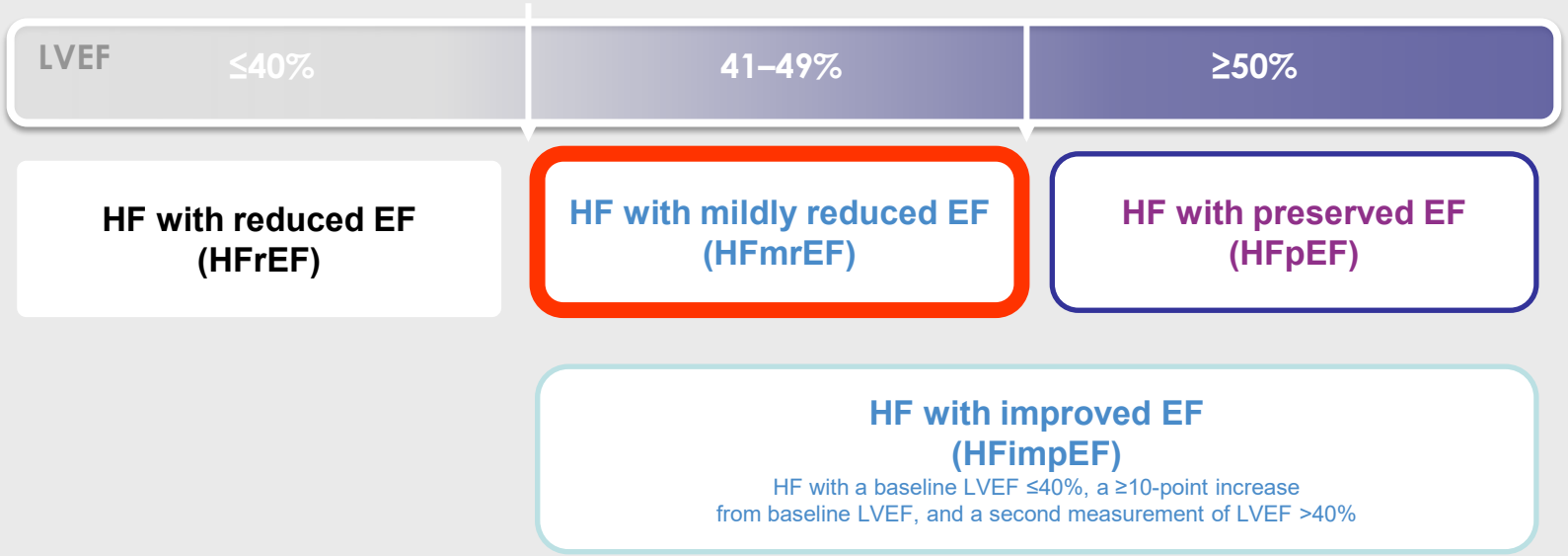
Universal definition and classification of heart failure

Bozkurt et al, Eur J Heart Fail 23 (2021): 352-380

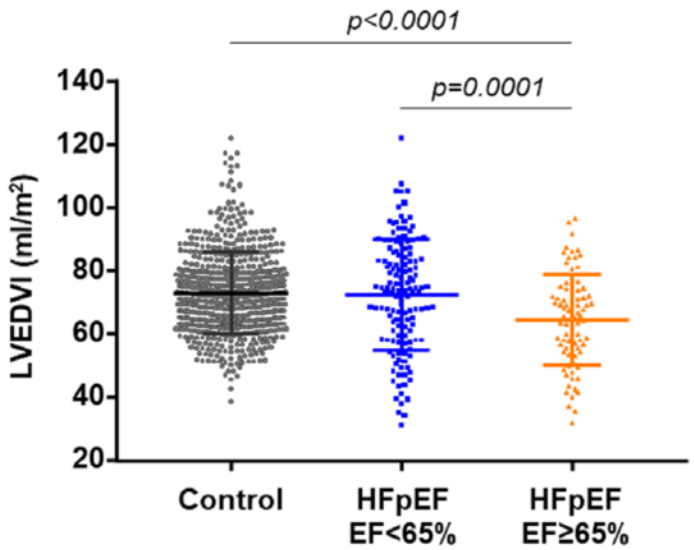
Biykem Bozkurt* (Chair) (USA), Andrew J.S. Coats (Co-Chair) (UK and Australia), Hiroyuki Tsutsui (Co-Chair) (Japan), Ca Magdy Abdelhamid (Egypt), Stamatis Adamopoulos (Greece), Nancy Albert (USA), Stefan D. Anker (Germany), John Atherton (Australia), Michael Böhm (Germany), Javed Butler (USA), Mark H. Drazner (USA), G. Michael Felker (USA), Gerasimos Filippatos (Greece), Mona Fiuzat (USA), Gregg C. Fonarow (USA), Juan-Esteban Gomez-Mesa (Colombia), Paul Heidenreich (USA), Teruhiko Imamura (Japan), Ewa A. Jankowska (Poland), James Januzzi (USA), Prateeti Khazanie (USA), Koichiro Kinugawa (Japan), Carolyn S.P. Lam (Singapore), Yuya Matsue (Japan), Marco Metra (Italy), Tomohito Ohtani (Japan), Massimo Francesco Piepoli (Italy), Piotr Ponikowski (Poland), Giuseppe M.C. Rosano (Italy), Yasushi Sakata (Japan), Petar Seferović (Serbia), Randall C. Starling (USA), John R. Teerlink (USA), Orly Vardeny (USA), Kazuhiro Yamamoto (Japan), Clyde Yancy (USA), Jian Zhang (China), Shelley Zieroth (Canada)



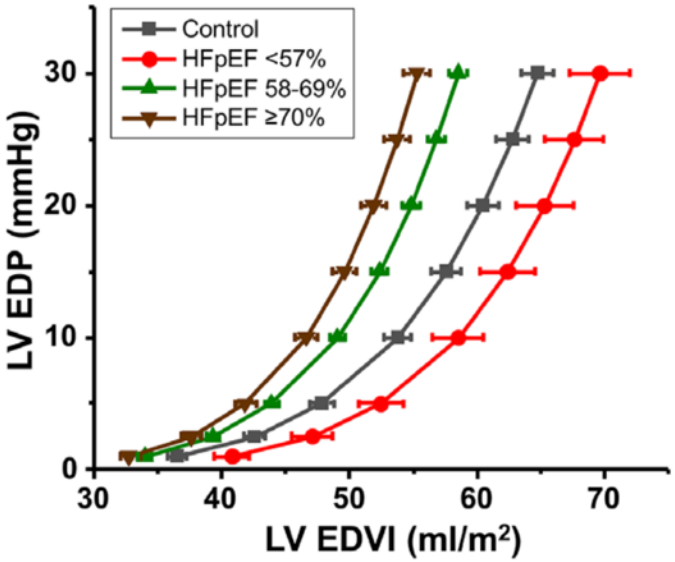
Ventricular stiffening and chamber contracture in heart failure with higher ejection fraction

Popovic et al, Eur J Heart Fail (2023): [doi:10.1002/ejhf.2843]

Left Ventricular Chamber Contracture and Stiffening in HFpEF with Higher Ejection Fraction



Smaller left ventricular (LV) end diastolic volume index (LVEDVI) in patients with HFpEF and higher EF compared to HFpEF with lower EF as well as healthy controls

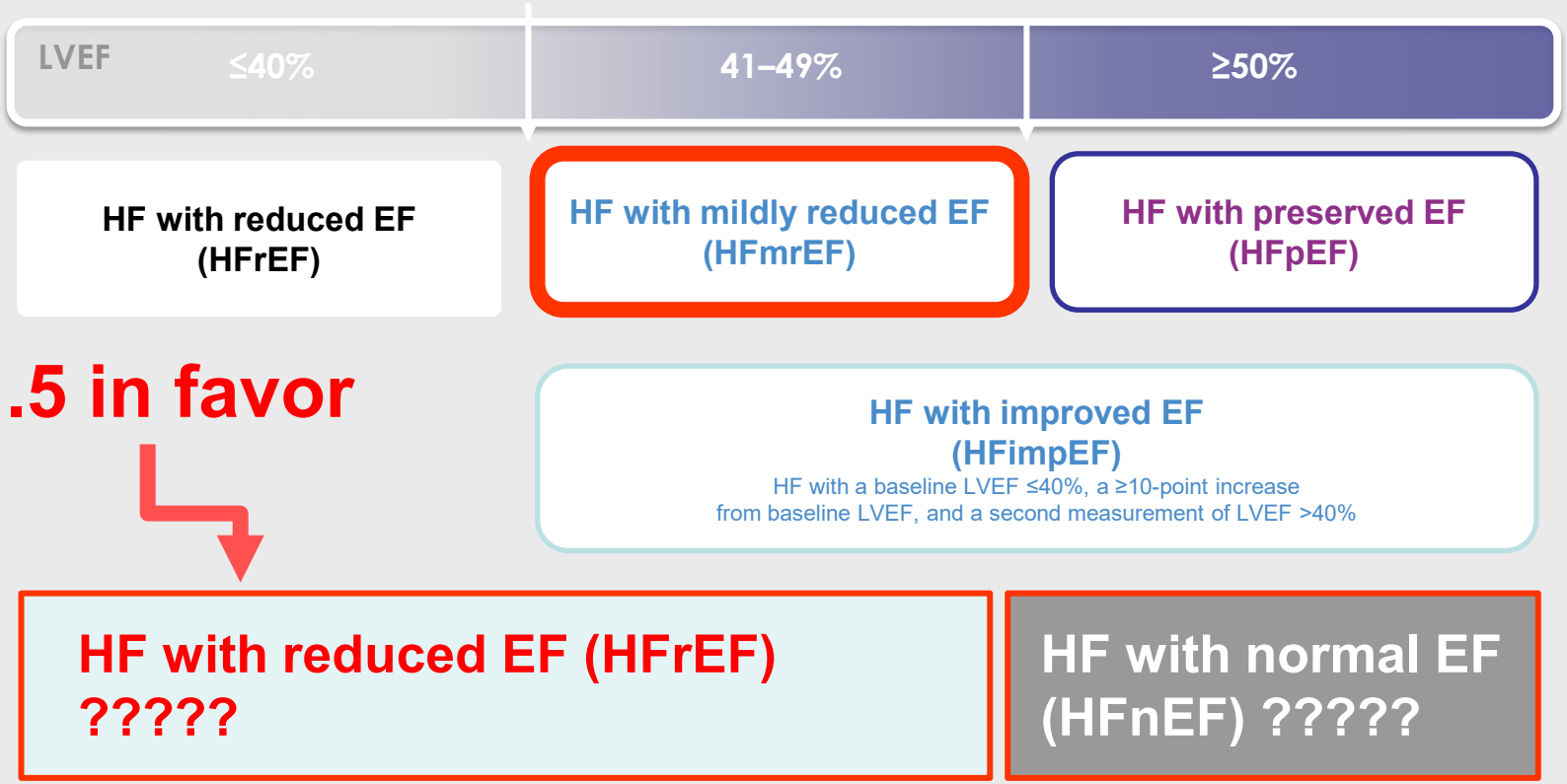


Leftward and upward shift in the LV end diastolic pressure volume relationship with higher EF in HFpEF indicating ↑LV diastolic stiffness and ↓LV capacitance

- ✓ *May explain attenuated response to neurohormonal antagonists in HFpEF with higher EF*
- ✓ *Potential Role for Novel Therapies to ↑Eccentric LV Remodeling & ↓Stiffness in HFpEF with higher EF*

Universal definition and classification of heart failure

Bozkurt et al, Eur J Heart Fail 23 (2021): 352-380



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2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

McDonagh et al, Eur Heart J 42 (2021): 3599-3726

HFpEF

Recommendations for the treatment of patients with heart failure with preserved ejection fraction

Recommendations	Class[a]	Level[b]
Screening for, and treatment of, aetiologies, and cardiovascular and non-cardiovascular comorbidities is recommended in patients with HFpEF (see relevant sections of this document).	I	C
Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs.[137]	I	C

HFpEF = heart failure with preserved ejection fraction.
[a]Class of recommendation.
[b]Level of evidence.

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

McDonagh et al, Eur Heart J 44 (2023): 3627-3639

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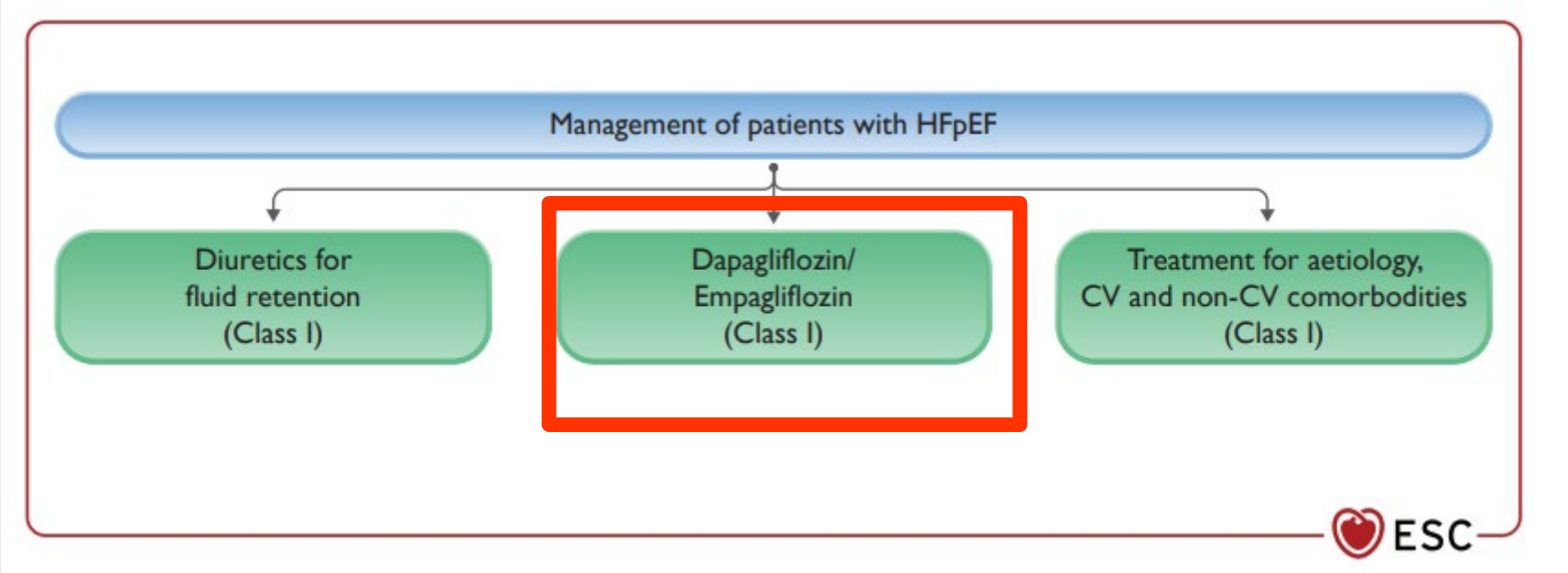


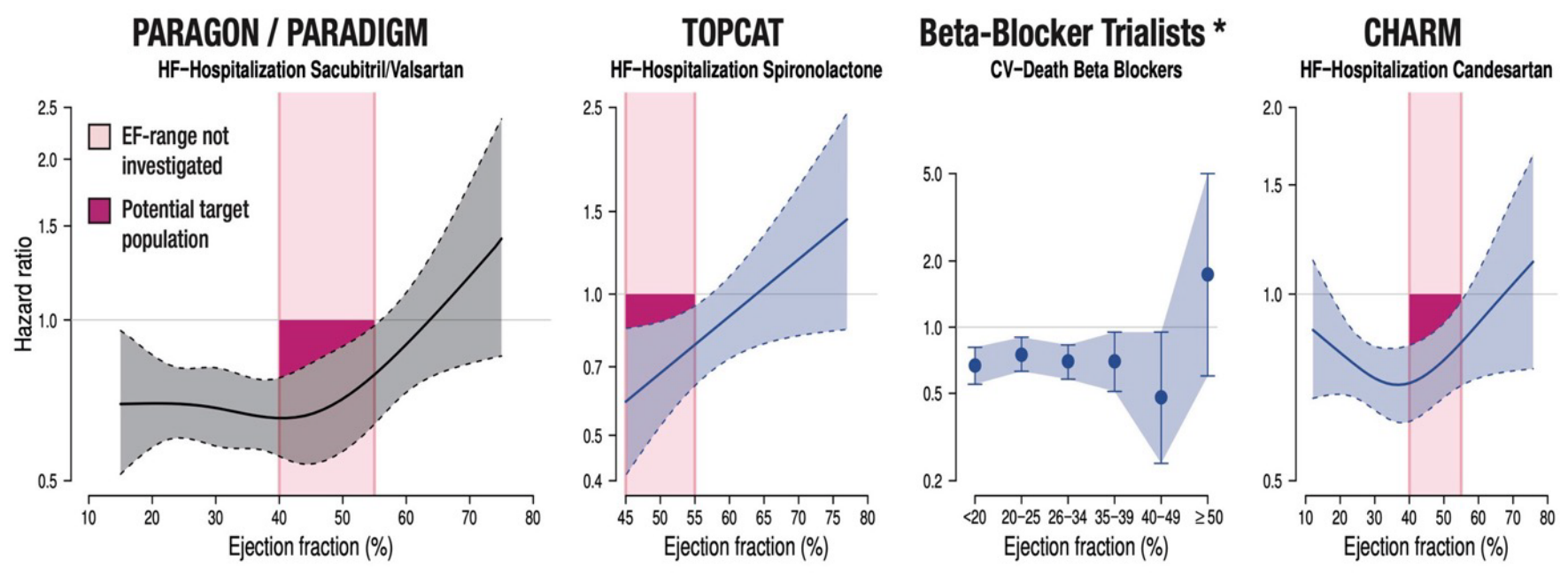
Heart failure guidelines 2021: pharmacological treatment
Pharmacological treatments in patients with (NYHA class II-IV) HF with mildly reduced ejection fraction

Metra et al, Heart Failure Guidelines 2021, ESC-HF 2021

Recommendations	Class of recommendation	Level of evidence
Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs.	I	C
An ACEi may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb	C
An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb	C
A beta-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb	C
A MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb	C
Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb	C

Ejection fraction in heart failure revisited. where does the evidence start?

Metra et al, Heart Failure Guidelines 2021, ESC-HF 2021



2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

McDonagh et al, Eur Heart J 44 (2023): 3627-3639

Recommendation Table 1 — Recommendation for the treatment of patients with symptomatic heart failure with mildly reduced ejection fraction

Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of HF hospitalization or CV death.[c] [6,8]	I	A

Recommendation Table 2 — Recommendation for the treatment of patients with symptomatic heart failure with preserved ejection fraction

Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFpEF to reduce the risk of HF hospitalization or CV death.[c] [6,8]	I	A

New treatment in HFmrEF and HFpEF

Solomon et al, N Engl J Med 387 (2022): 1089-1098. ; Anker et al, N Eng J Med 385 (2021): 1451-1461

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.*

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*

New treatment in HFmrEF and HFpEF

Anker et al, N Eng J Med 385 (2021): 1451-1461 ; Solomon et al, N Engl J Med 387 (2022): 1089-1098

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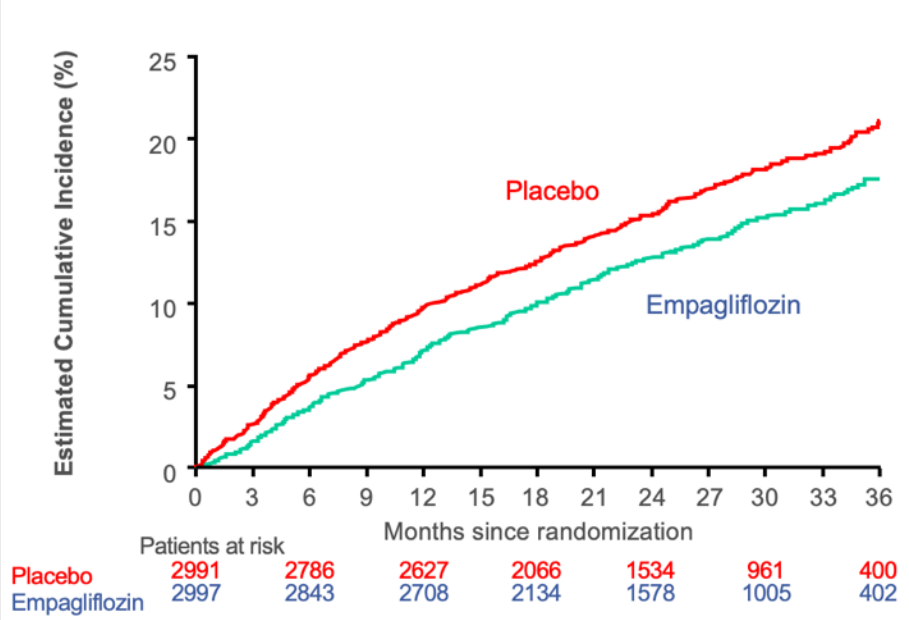
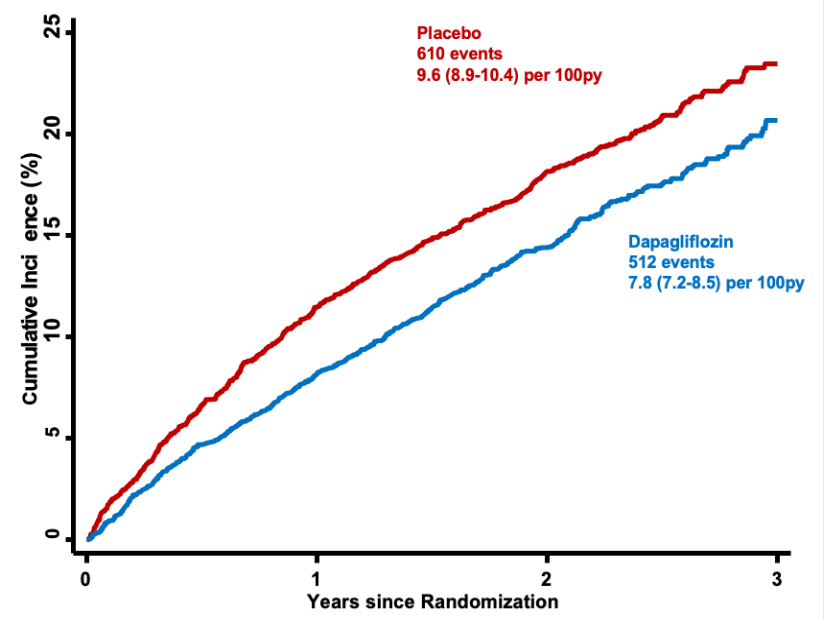
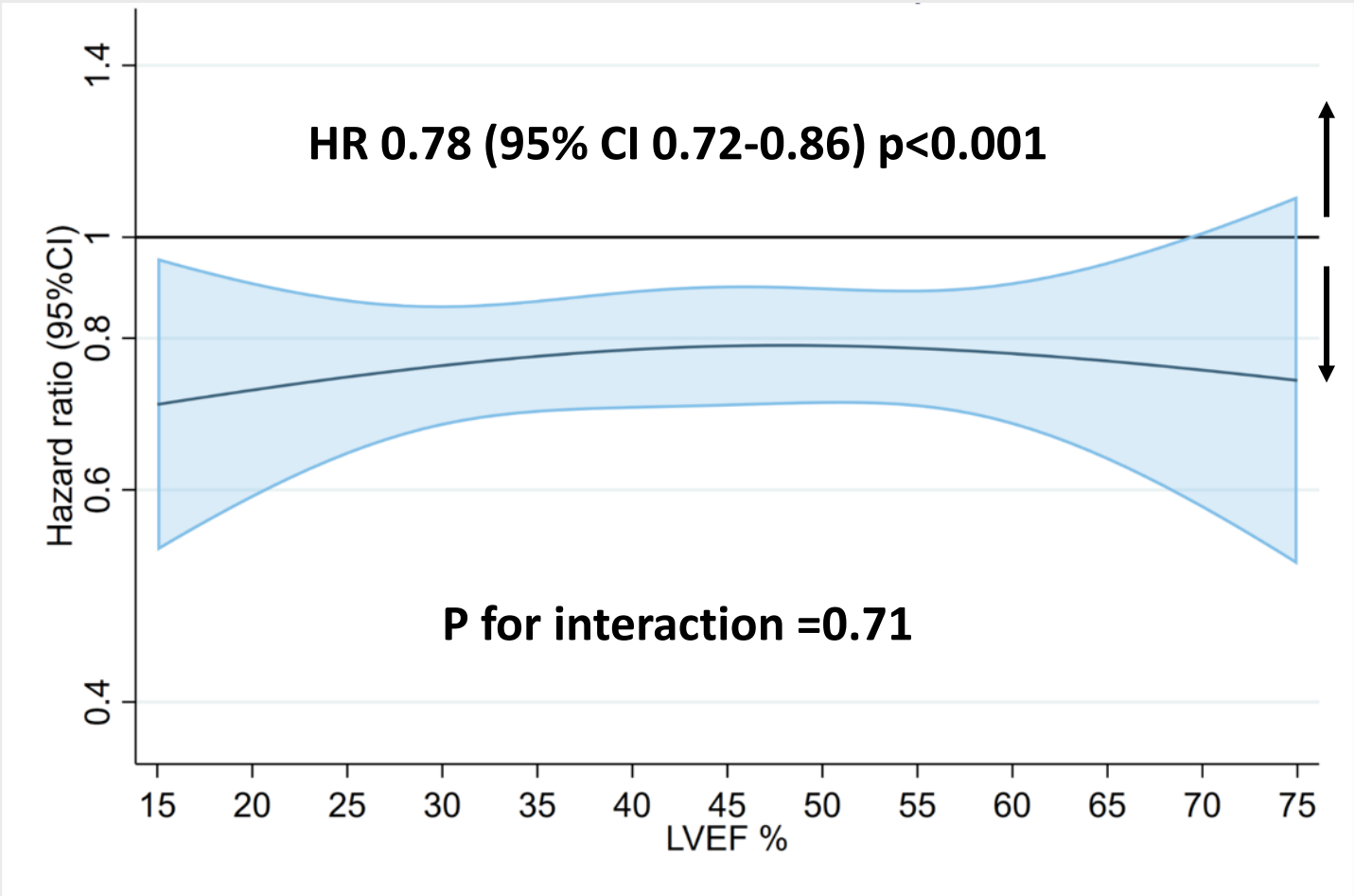




DAPA-HF & DELIVER: CV death/HF hospitalisation

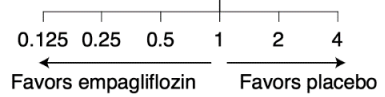
Jundh et al, Nature Med 28 (2022): 1956-1964



Efficacy of empagliflozin in heart failure with preserved versus mid-range ejection fraction: a pre-specified analysis of EMPEROR-Preserved

Anker et al, Nature Med 28 (2022): 2512-2520

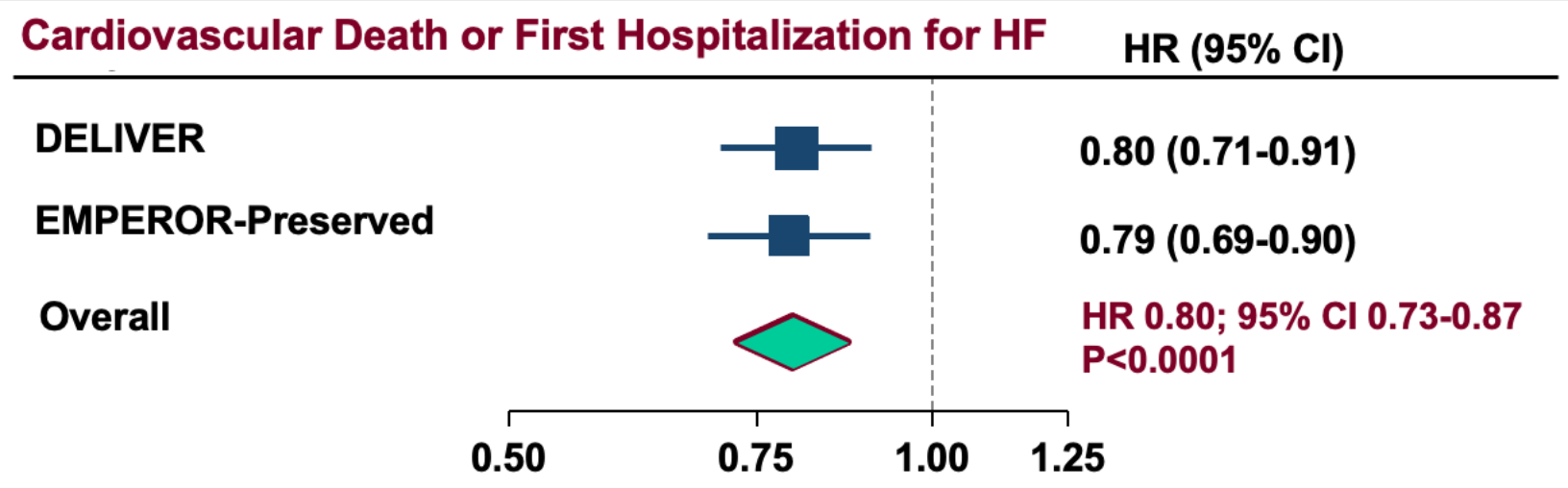
	no. of events/no. of patients (events/100 patient-years)			*P* value for trend
	Empagliflozin	Placebo	HR (95% CI)	
Time to first event of adjudicated CV death or HHF				
LVEF ≥50 to <55%	76/504 (7.5)	97/545 (9.0)	0.86 (0.64–1.17)	
LVEF ≥55 to <60%	62/524 (5.9)	76/485 (7.9)	0.74 (0.53–1.04)	
LVEF ≥60 to <65%	72/546 (6.5)	85/536 (8.0)	0.80 (0.58–1.10)	0.91
LVEF ≥65 to <70%	41/263 (8.1)	32/283 (5.8)	1.34 (0.84–2.12)	
LVEF ≥70%	19/165 (5.6)	28/154 (9.4)	0.57 (0.32–1.02)	
Time to first event of adjudicated HHF				
LVEF ≥50 to <55%	44/504 (4.3)	63/545 (5.8)	0.78 (0.53–1.15)	
LVEF ≥55 to <60%	43/524 (4.1)	59/485 (6.1)	0.64 (0.43–0.95)	
LVEF ≥60 to <65%	47/546 (4.3)	59/536 (5.6)	0.75 (0.51–1.09)	0.51
LVEF ≥65 to <70%	33/263 (6.5)	22/283 (4.0)	1.55 (0.90–2.65)	
LVEF ≥70%	15/165 (4.4)	23/154 (7.8)	0.55 (0.29–1.06)	
Total HHF				
LVEF ≥50 to <55%	58/504	91/545	0.70 (0.45–1.09)	
LVEF ≥55 to <60%	71/524	91/485	0.62 (0.40–0.96)	
LVEF ≥60 to <65%	69/546	70/536	1.04 (0.67–1.63)	0.29
LVEF ≥65 to <70%	64/263	37/283	1.81 (1.02–3.21)	
LVEF ≥70%	23/165	43/154	0.41 (0.20–0.86)	

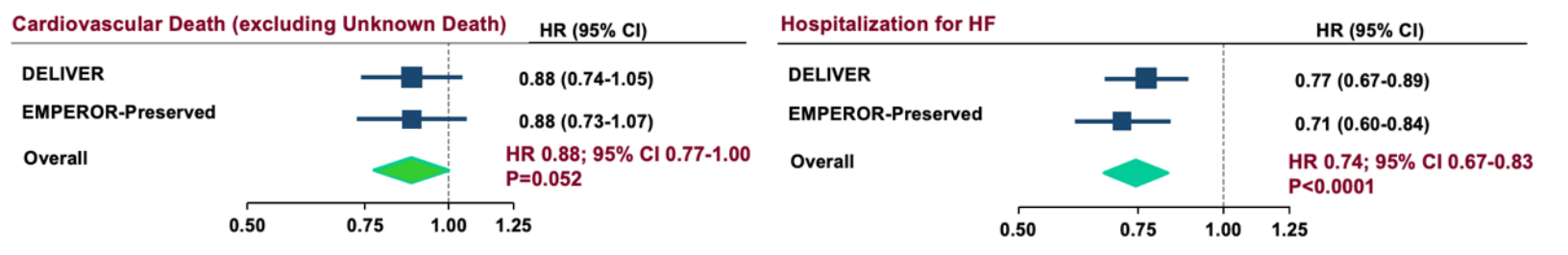


SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials

Vaduganathan et al, Lancet 400 (2022): 757-767

$P_{heterogeneity}$ >0.40 for all endpoints





DELIVER and EMPEROR-Preserved Meta-Analysis:

↓ 20% (13-27%) Relative Risk Reduction of Primary Endpoint with Consistent Reductions in Both Components

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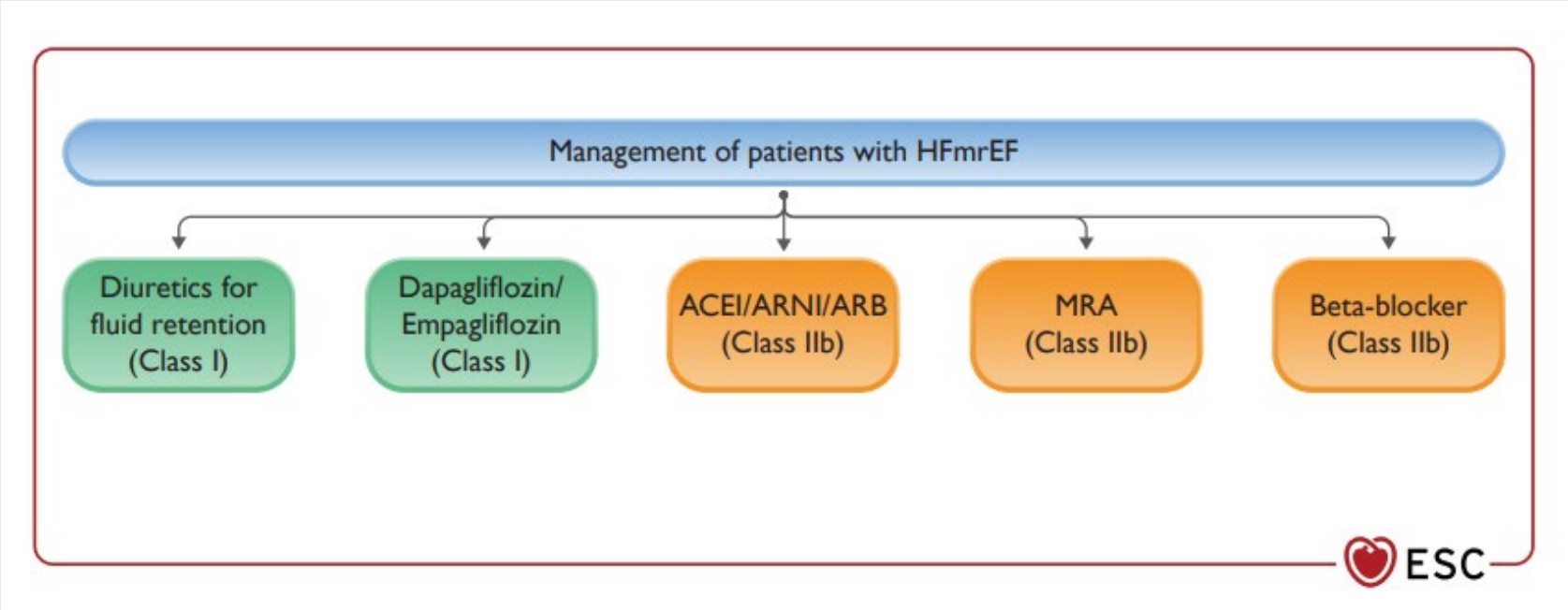
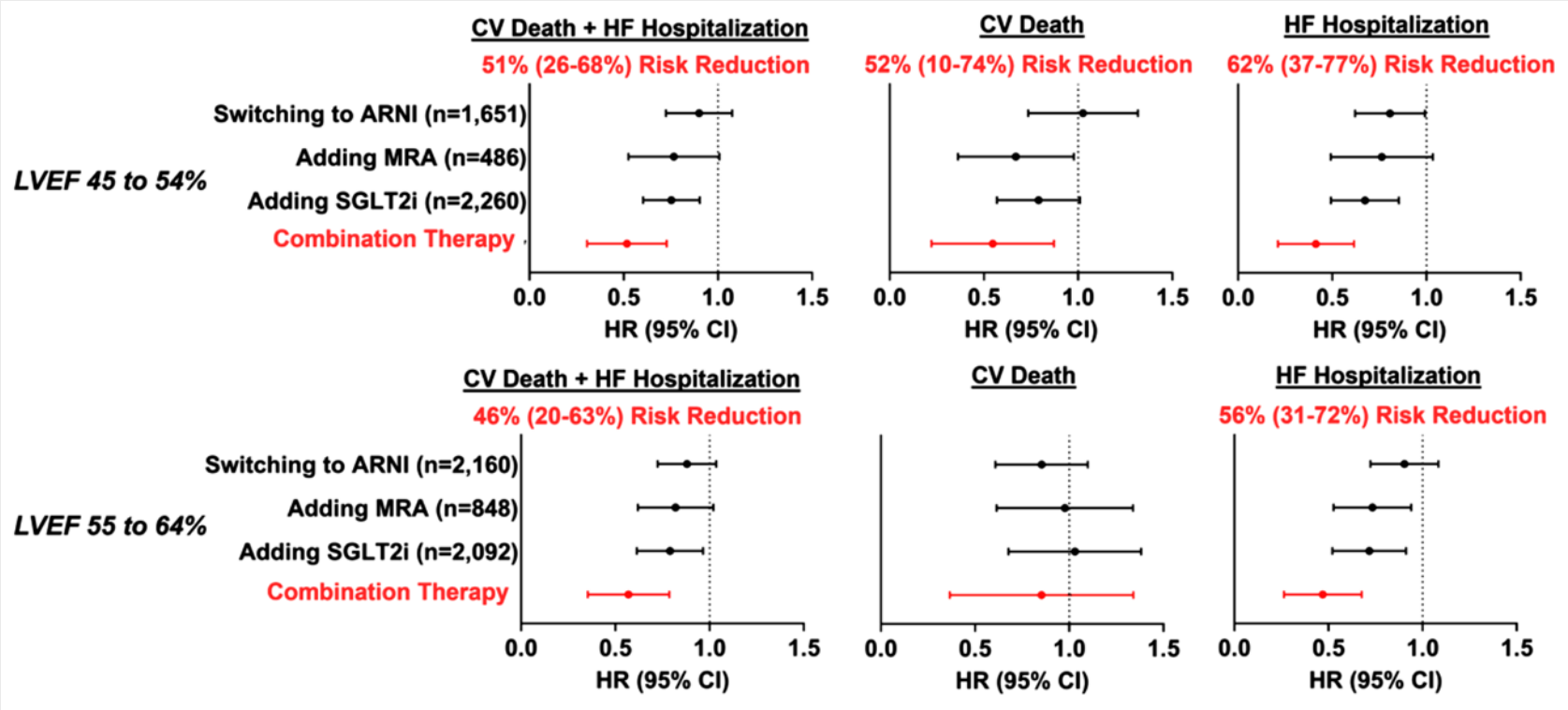
McDonagh et al, Eur Heart J 44 (2023): 3627-3639



Estimating the Benefits of Combination Medical Therapy in Heart Failure With Mildly Reduced and Preserved Ejection Fraction

Vaduganathan et al, Circulation 145 (2022): 1741-1743



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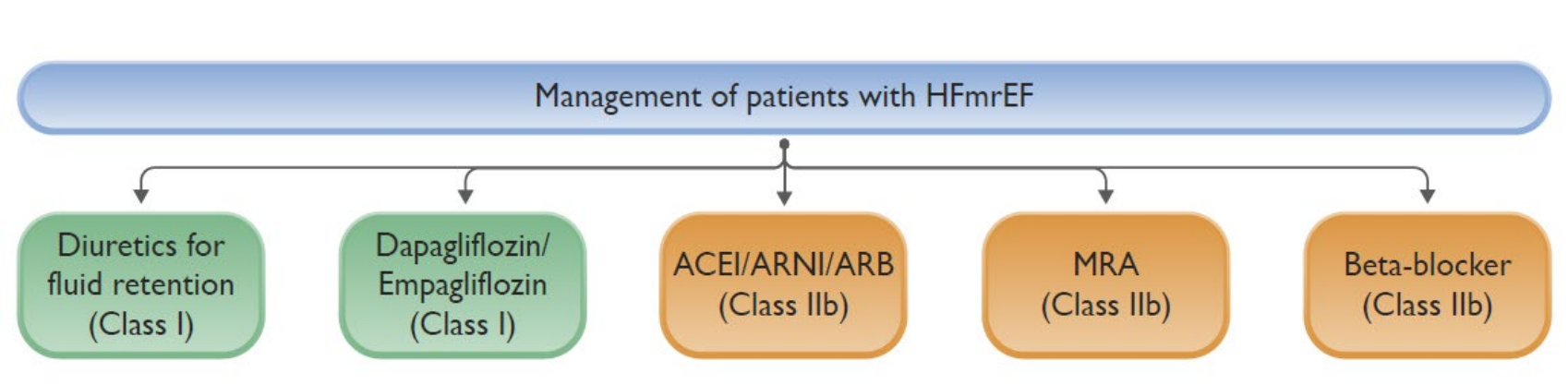
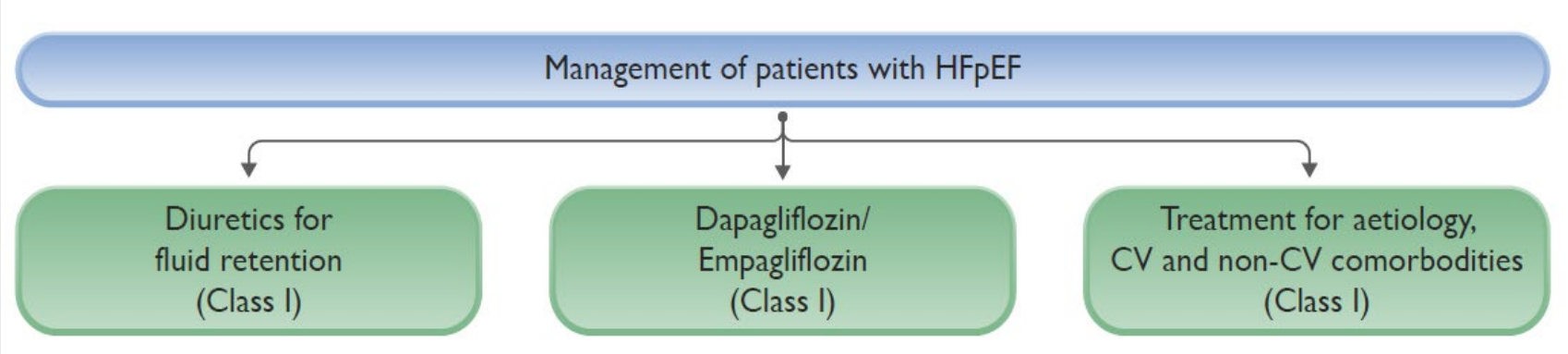
McDonagh et al, Eur Heart J 44 (2023): 3627-3639

HFmrEF



HFpEF



Herzinsuffizienz

- Guidelines
- Notwendigkeit der Aktualisierung
  - Definitionen
  - Neue HFpEF unf HFmrEF Empfehlungen
  - Prävention
  - Komorbidität Eisenmangel
  - Wie initiieren
- Adipositas und HFpEF
- GLP1 Agonisten

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

McDonagh et al, Eur Heart J 42 (2021): 3599-3726

Diabetes and prevention

Recommendations for the primary prevention of heart failure in patients with risk factors for its development

Recommendations	Class[a]	Level[b]
Treatment of hypertension is recommended to prevent or delay the onset of HF, and to prevent HF hospitalizations.[287–290]	I	A
Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations.[291,292]	I	A
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalizations.[293–297]	I	A
Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF.[298–302]	I	C

CV = cardiovascular; HF = heart failure; SGLT2 = sodium-glucose co-transporter 2.
[a]Class of recommendation.
[b]Level of evidence.

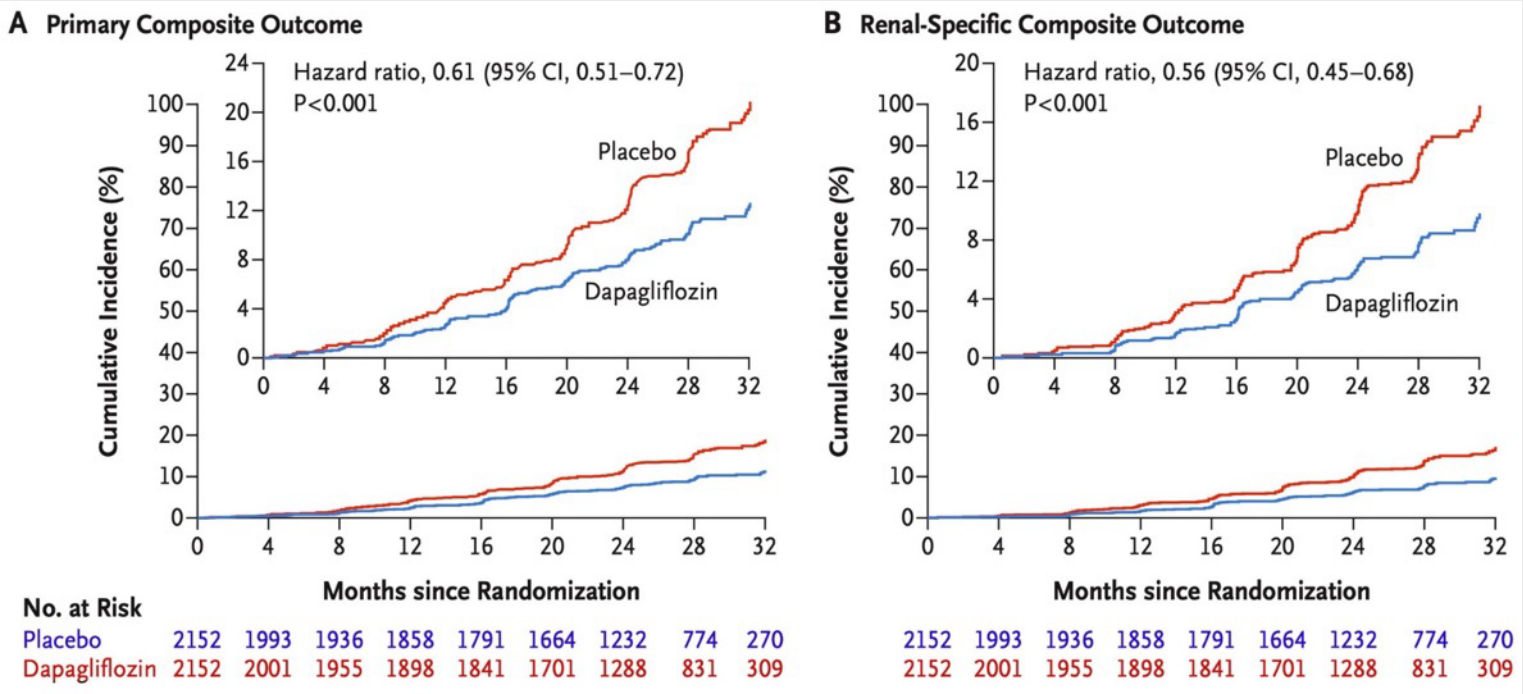
2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

McDonagh et al, Eur Heart J 44 (2023): 3627-3639

Recommendations	Class[a]	Level[b]
In patients with T2DM and CKD,[c] SGLT2 inhibitors are recommended to reduce the risk of HF hospitalization or CV death.[35]	I	A
In patients with T2DM and CKD,[c] finerenone is recommended to reduce the risk of HF hospitalization.[10,11,34,40]	I	A

Dapagliflozin in Patients with Chronic Kidney Disease

Heerspink et al, N Engl J Med 383 (2020): 1436-1446



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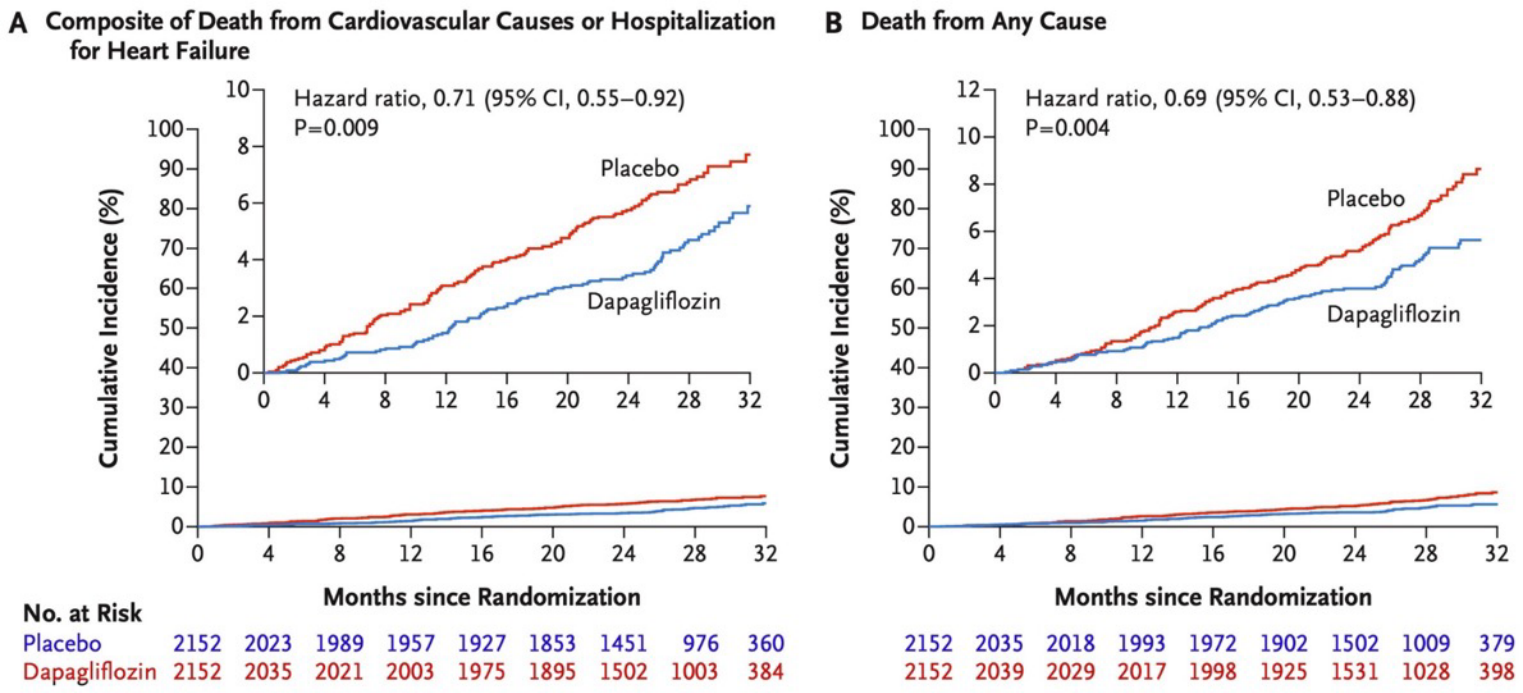
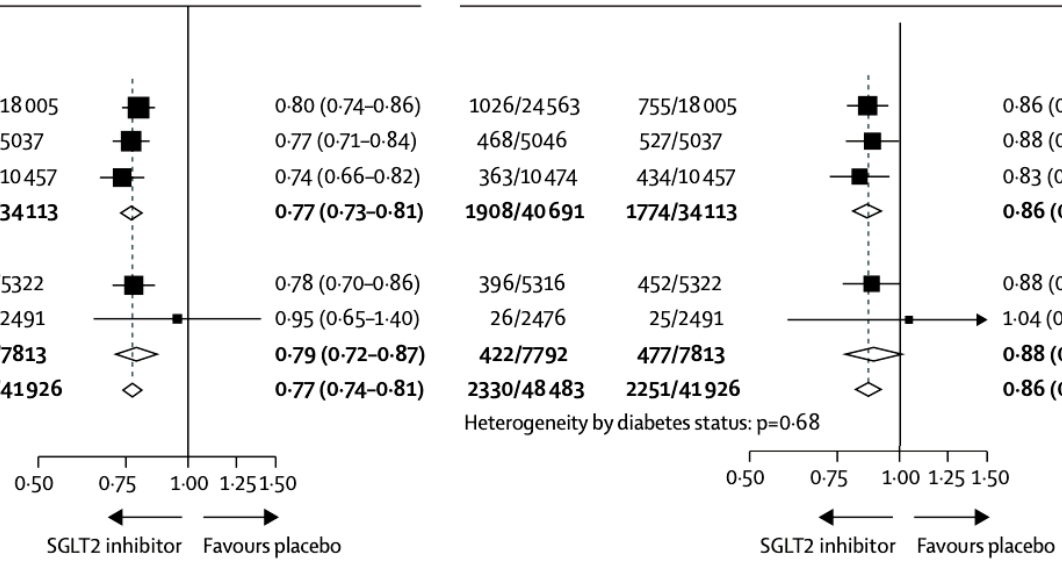


Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials

Nuffield Department of Population Health Renal Studies Group, Lancet 400 (2022): 1788-1801

	Cardiovascular death or hospitalisation for heart failure*				Cardiovascular death		
	Mean baseline eGFR, mL/min per 1·73m²	Events/participants		RR (95% CI)	Events/participants		RR (95% CI)
		SGLT2 inhibitor	Placebo		SGLT2 inhibitor	Placebo	
Diabetes							
High atherosclerotic cardiovascular risk trials	80	1490/24 563	1232/18 005	0·80 (0·74–0·86)	1026/24 563	755/18 005	0·86 (0·78–0·95)
Stable heart failure trials†	61	923/5046	1154/5037	0·77 (0·71–0·84)	468/5046	527/5037	0·88 (0·78–0·99)
Chronic kidney disease trials	45	643/10 474	847/10 457	0·74 (0·66–0·82)	363/10 474	434/10 457	0·83 (0·72–0·95)
Subtotal: diabetes	**67**	**3056/40 691**	**3233/34 113**	**0·77 (0·73–0·81)**	**1908/40 691**	**1774/34 113**	**0·86 (0·80–0·92)**
No diabetes							
Stable heart failure trials†	64	710/5316	890/5322	0·78 (0·70–0·86)	396/5316	452/5322	0·88 (0·77–1·00)
Chronic kidney disease trials	40	50/2476	53/2491	0·95 (0·65–1·40)	26/2476	25/2491	1·04 (0·59–1·83)
Subtotal: no diabetes	**56**	**760/7792**	**943/7813**	**0·79 (0·72–0·87)**	**422/7792**	**477/7813**	**0·88 (0·78–1·01)**
Total: overall	**65**	**3816/48 483**	**4176/41 926**	**0·77 (0·74–0·81)**	**2330/48 483**	**2251/41 926**	**0·86 (0·81–0·92)**
Heterogeneity by diabetes status: p=0·67					Heterogeneity by diabetes status: p=0·68		



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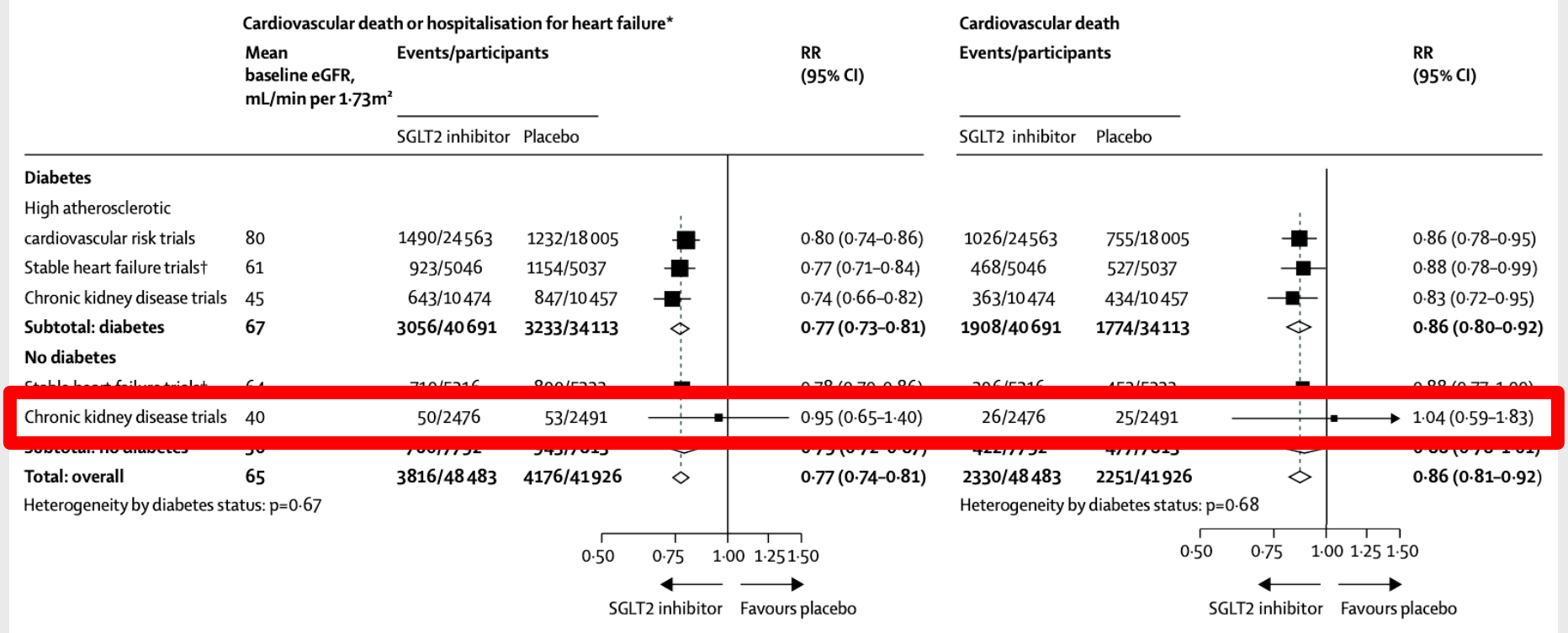

	Mean baseline eGFR, mL/min per 1·73m²	Cardiovascular death or hospitalisation for heart failure* Events/participants: SGLT2 inhibitor	Placebo	RR (95% CI)	Cardiovascular death Events/participants: SGLT2 inhibitor	Placebo	RR (95% CI)
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McDonagh et al, Eur Heart J 44 (2023): 3627-3639

Recommendations	Class[a]	Level[b]
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Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis

Agarwal et al, Eur Heart J 43 (2022): 474-484

Pooled analysis study details

Study name	FIDELIO-DKD[7]	FIGARO-DKD[10]
Publication year	2020	2021
Study design	Phase III, randomized, double-blind, placebo-controlled, multicentre clinical trial	Phase III, randomized, double-blind, placebo-controlled, multicentre clinical trial
Sample size[a]	5734	7437
Inclusion criteria	• Age ≥18 years • T2D and CKD defined as UACR 30–<300 mg/g, eGFR 25–<60 mL/min/1.73 m^2, and diabetic retinopathy, *or* UACR 300–5000 mg/g and eGFR 25–<75 mL/min/1.73 m^2 • Maximum tolerated dose of an RAS inhibitor • Serum potassium ≤4.8 mmol/L	• Age ≥18 years • T2D and CKD defined as UACR 30–<300 mg/g and eGFR 25–90 mL/min/1.73 m^2, *or* UACR 300–5000 mg/g and eGFR ≥60 mL/min/1.73 m^2 • Maximum tolerated dose of an RAS inhibitor • Serum potassium ≤4.8 mmol/L

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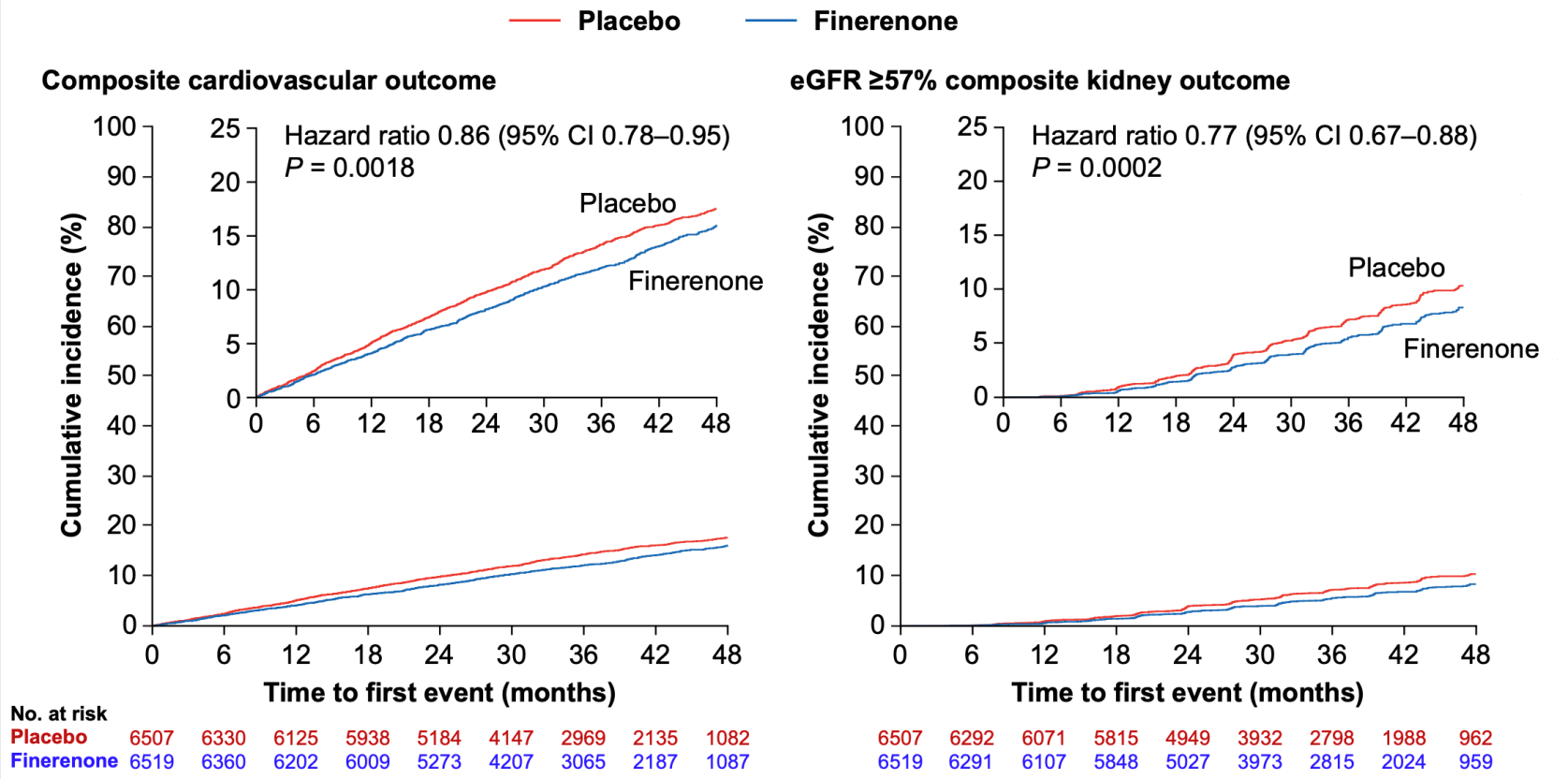

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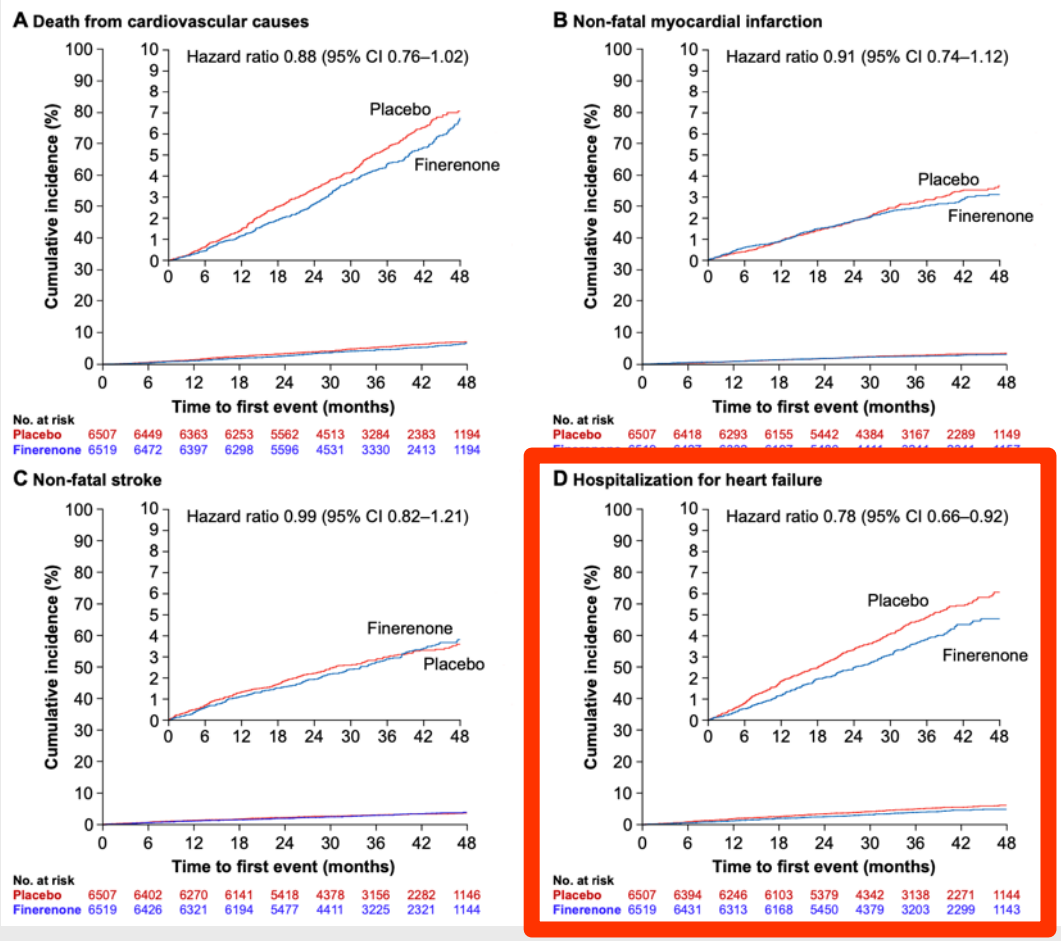

MOONRAKER will generate further data for finerenone across clinical settings in more than 15,000 patients

https://clinicaltrials.gov/ct2/show/NCT04435626 [accessed 18 August 2023] ; https://clinicaltrials.gov/ct2/show/NCT06008197 [accessed 24 August 2023]

FINEARTS-HF[1]

Efficacy and safety profile of finerenone in patients with symptomatic HF vs placebo (N=6016)

Population: Patients with HF (NYHA class II–IV) and LVEF ≥40%)

Primary outcome: Total number of CV deaths and HF events

REDEFINE-HF[2]

Efficacy and safety profile of finerenone when initiated early in patients hospitalised with HF vs placebo (N=5200)

Population: Patients hospitalised due to HF with LVEF ≥40%

Primary outcome: Total number of CV deaths and HF events

CONFIRMATION-HF[3]

Efficacy and safety profile of early combination Rx in patients with HF independent of LVEF (finerenone + SGLT-2i vs usual care; N=1500)

Population*: Patients hospitalised due to HF independent of LVEF

Primary outcome: All-cause mortality, total HF events, time to first HF events and KCCQ-TSS (win ratio)

FINALITY-HF[3]

Efficacy and safety profile of finerenone in patients with symptomatic HFrEF intolerant of or not eligible for sMRA (vs placebo; N=2600)

Population#: Patients with HFrEF, enriched with those hospitalised due to HF

Primary outcome: Time to first CV death or HF event

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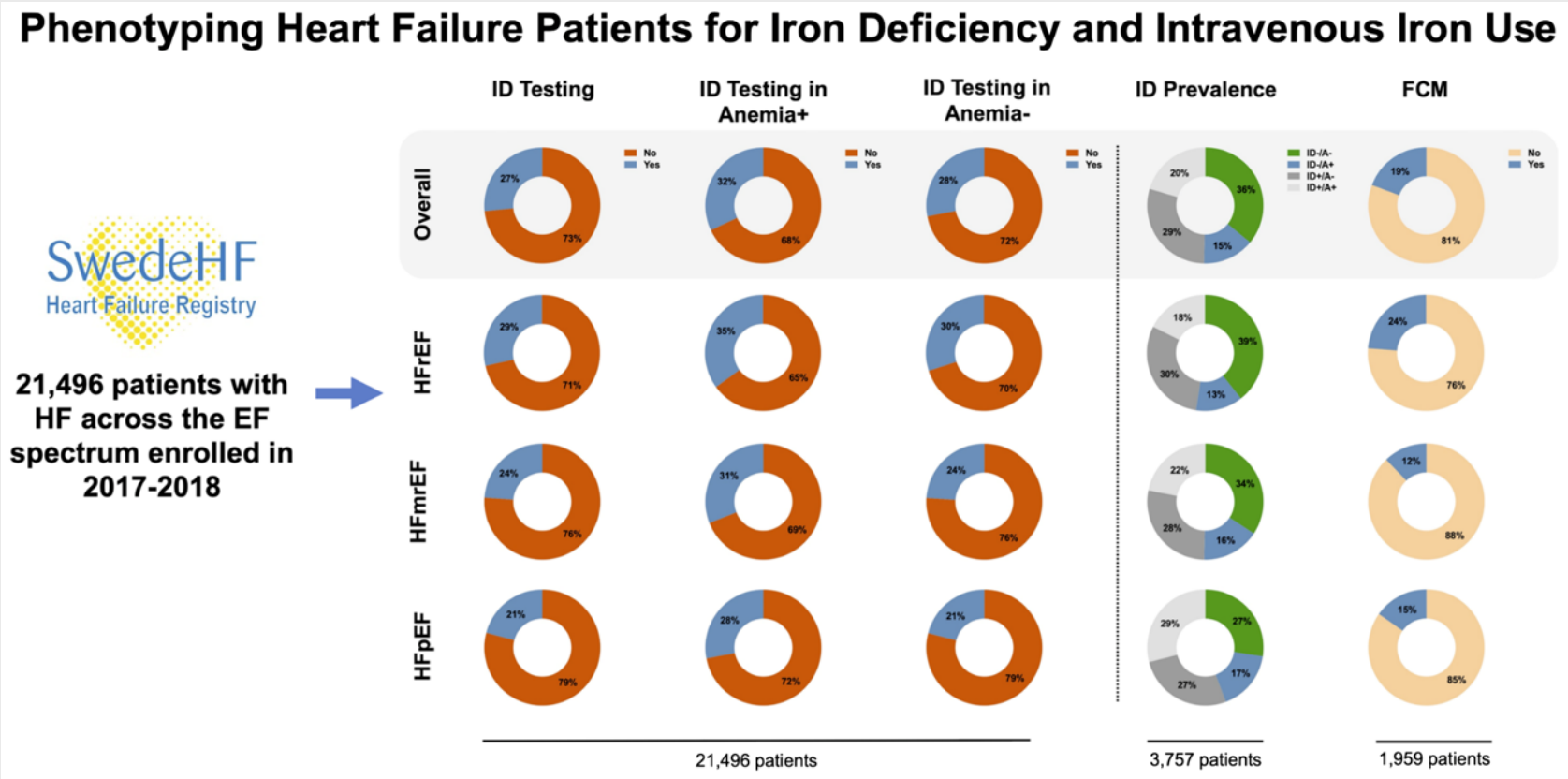
Phenotyping heart failure patients for iron deficiency and use of intravenous iron therapy: data from the Swedish Heart Failure Registry

Becher et al, Eur J Heart Fail 23 (2021): 1844-1854



Problems of substitution with oral iron

Bozkurt et al, JACC Heart Fail 10 (2022): 992-995

Therapeutischer Bereich	ΔHb (g/dl)	Serum-Ferritin (ng/ml)	Eisenbedarf* (mg)	Orale Therapiedauer**
Prädialyse Mann, 80 kg	1	110	700	3 Monate
Morbus Crohn Frau, 60 kg	2	5	800	3 Monate
Tumoranämie Frau, 70 kg	3	50	1.000	4 Monate
Herzinsuffizienz Mann, 95 kg	3	10	1.200	5 Monate
Postpartum Frau, 65 kg	4	15	1.100	4 ½ Monate

* Berechnung nach Ganzoni

** bei optimaler Resorption (8 mg Eisen pro Tag) und 100%iger Compliance

Risiko eines funktionellen Eisenmangels → verminderte Eisen-Resorption

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Risiko eines funktionellen Eisenmangels → verminderte Eisen-Resorption

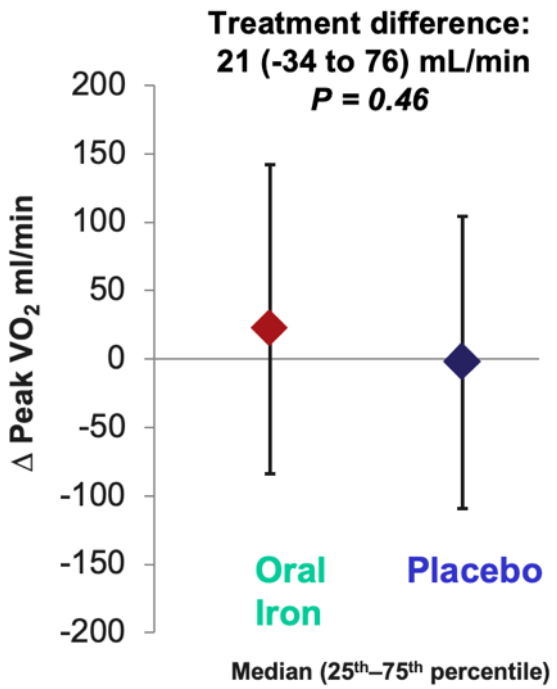
Calculation!

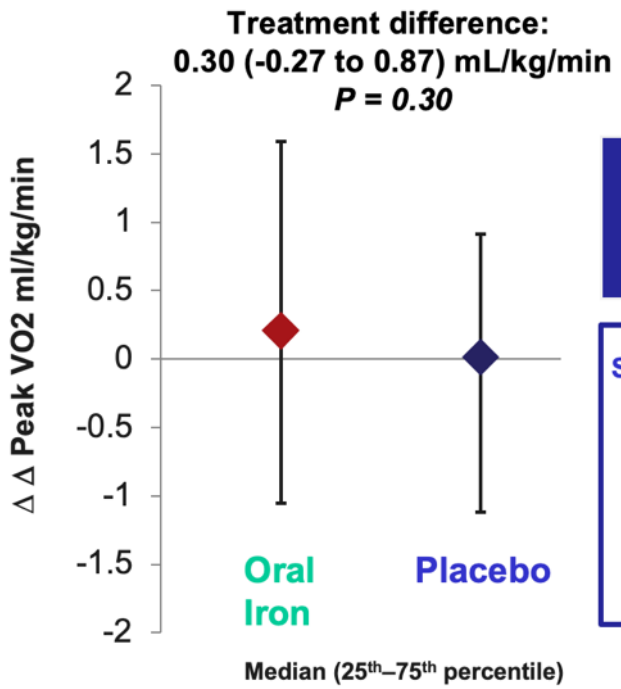
- 100 g pig liver contains . 22 mg Eisen
- Daily absobtion cc. 2 mg

1.500 mg Eisen = 75 kg pig liver
1.500 mg Eisen = 495 kg

IRON-OUT: oral iron (iron polysaccharide) did not improve exercise capacity in patients with HFrEF + ID

Lewis et al, JAMA 317 (2017): 1958–1966





There is limited evidence supporting the use of oral iron for treatment of iron deficiency in HFrEF

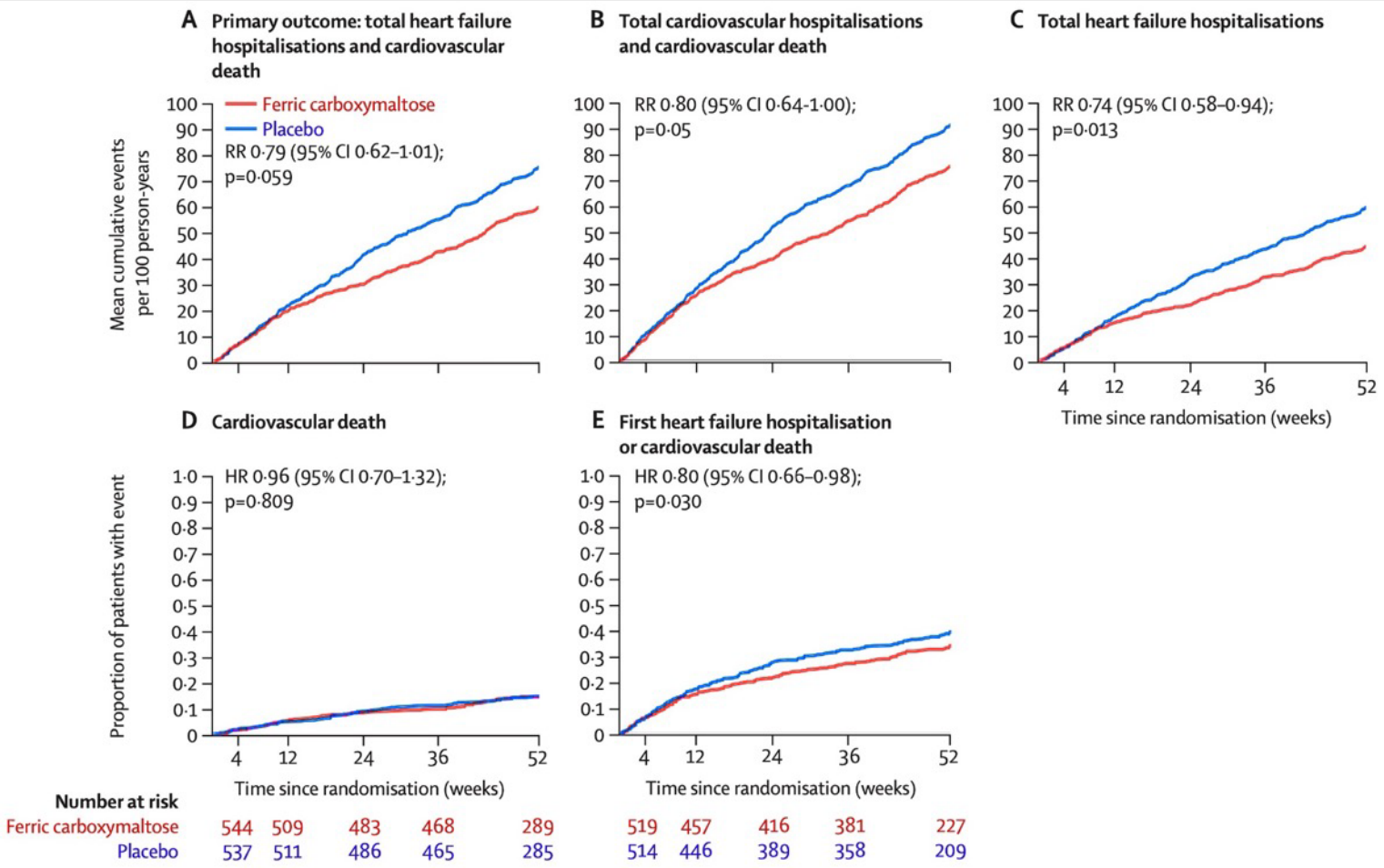
Secondary end points (all neutral, p≥0.19)

- Δ 6 MW distance at 16 weeks, meters
- Δ Mean response time, seconds
- Δ Ventilatory efficiency (VE/VCO_2 slope)
- Δ NT-BNP level, pg/ml
- Δ KCCQ score at 16 weeks

HFrEF, heart failure with reduced ejection fraction; ID, iron deficiency; KCCQ, Kansas City Cardiomyopathy Questionnaire; MW, minute walk; NT-BNP, N-terminal pro B-type natriuretic peptide

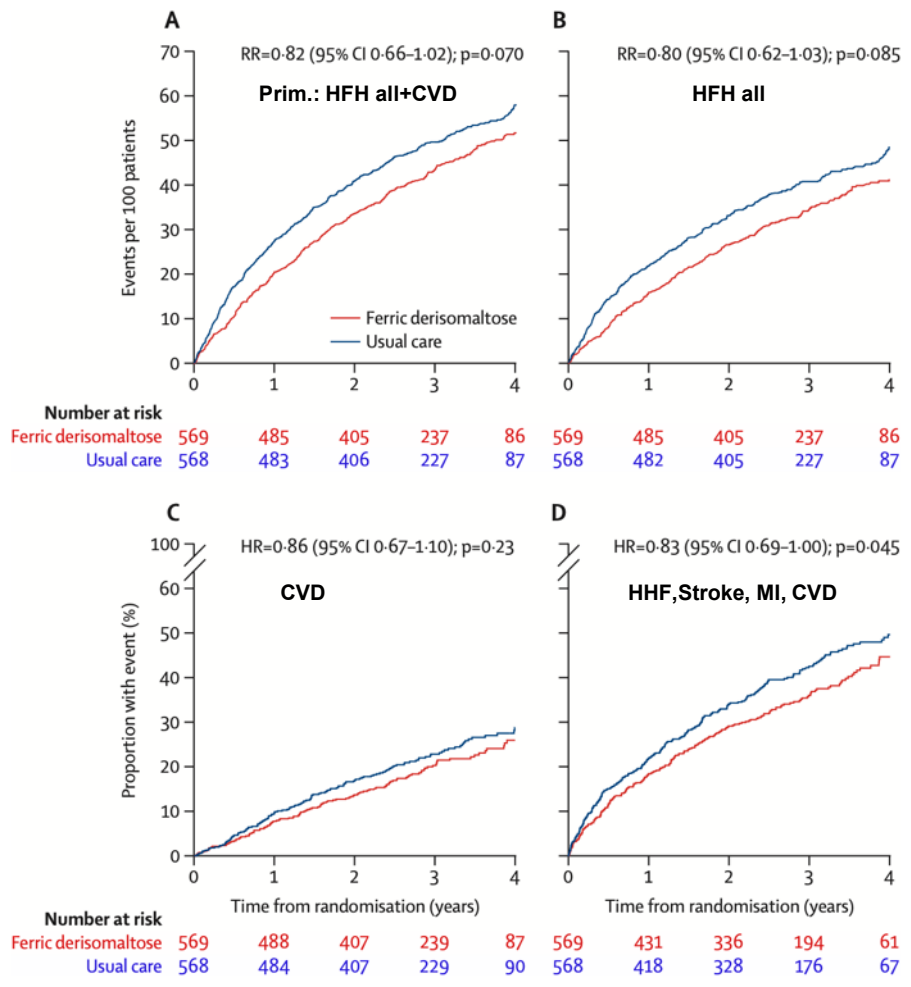
Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial

Ponikowski et al, Lancet 396 (2020): 1895-1904



Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial

Kalra et al, Lancet 400 (2022): 2199-2209



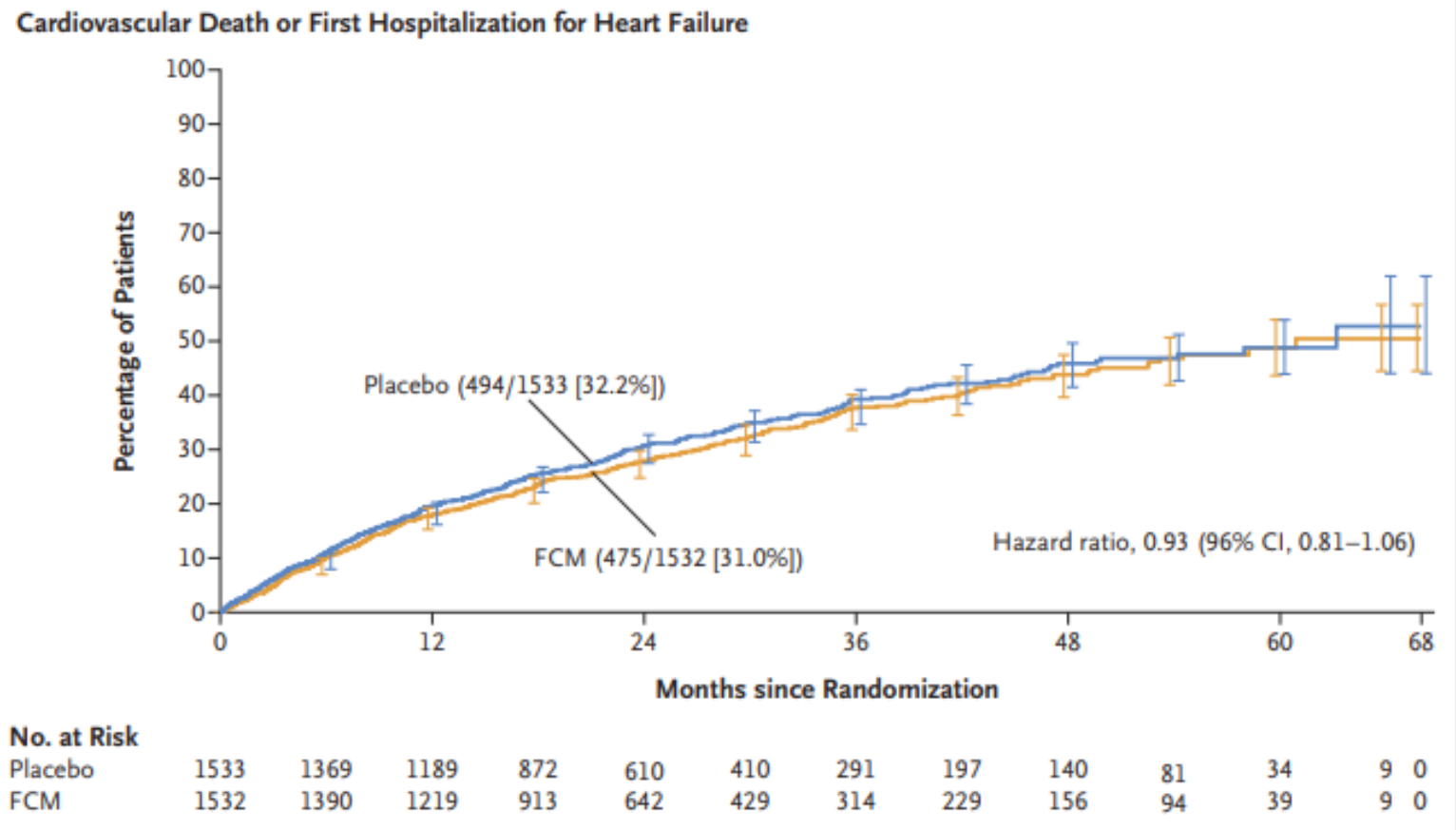
2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

McDonagh et al, Eur Heart J 44 (2023): 3627-3639

Recommendations	Class[a]	Level[b]
Intravenous iron supplementation is recommended in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to alleviate HF symptoms and improve quality of life.[c] [12,41,47–49]	I	A
Intravenous iron supplementation with ferric carboxymaltose or ferric derisomaltose should be considered in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to reduce the risk of HF hospitalization.[c] [12,41,43–46]	IIa	A

Ferric Carboxymaltose in Heart Failure with Iron Deficiency

Mentz et al, N Engl J Med 389 (2023): 975-986



Ferric Carboxymaltose in Heart Failure with Iron Deficiency

Mentz et al, N Engl J Med 389 (2023): 975-986

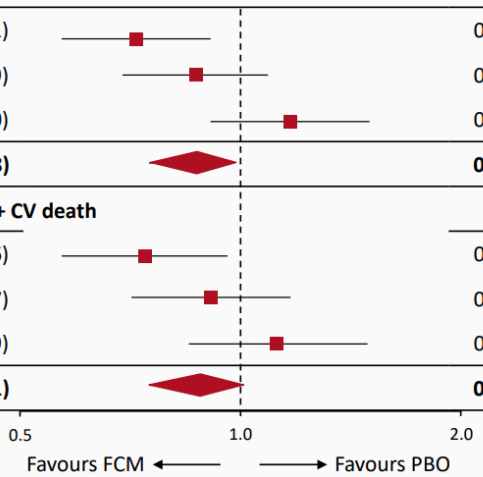
Laboratory values		
Hemoglobin level		
Mean — g/dl	12.6±1.4	12.5±1.4
No. of patients with data	1515	1521
Serum ferritin level		
Mean — μg/liter	56.0±47.3	57.3±51.4
No. of patients with data	1517	1526
Transferrin saturation		
Mean — %	23.9±11.2	23.0±10.3
No. of patients with data	1515	1517

Impact of ferric carboxymaltose (FCM) on heart failure-related clinical outcomes in patients with heart failure and iron deficiency

Ponikowski, Hotline presentation, ESC Amsterdam (2023)

Impact of TSAT Level on Treatment Effect

		FCM N=2237 %	PBO N=2233 %	Rate ratio (95% CI)	*P*-value	*P*-int
Total CV hospitalisations + CV death						
TSAT, %	<15	32.7	41.9	0.72 (0.57–0.91)	0.006	
	≥15 and <24	29.2	30.9	0.87 (0.69–1.09)	0.223	0.019
	≥24	21.6	18.5	1.17 (0.91–1.50)	0.213	
Overall		**27.6**	**30.5**	**0.86 (0.75–0.98)**	**0.029**	
Total HF hospitalisations + CV death						
TSAT, %	<15	27.4	36.0	0.74 (0.57–0.96)	0.021	
	≥15 and <24	24.1	25.9	0.91 (0.71–1.17)	0.468	0.095
	≥24	16.6	13.6	1.12 (0.85–1.49)	0.412	
Overall		**22.5**	**25.2**	**0.87 (0.75–1.01)**	**0.076**	



CV=cardiovascular; FCM=ferric carboxymaltose; HF=heart failure; PBO=placebo; TSAT=transferrin saturation.

TSAT, %	<20	380/1140 (33.3)	456/1183 (38.5)	0.80 (0.67–0.95)	0.012	0.100
	≥20	232/1079 (21.5)	215/1032 (20.8)	1.00 (0.81–1.23)	0.989	
TSAT, %	<15	222/678 (32.7)	292/697 (41.9)	0.72 (0.57–0.91)	0.006	
	≥15 and <24	216/739 (29.2)	244/790 (30.9)	0.87 (0.69–1.09)	0.223	0.019
	≥24	173/802 (21.6)	135/728 (18.5)	1.17 (0.91–1.50)	0.213	

Study Drug Dosing and Iron Indices

Menz, Hotline presentation, ESC Amsterdam (2023)

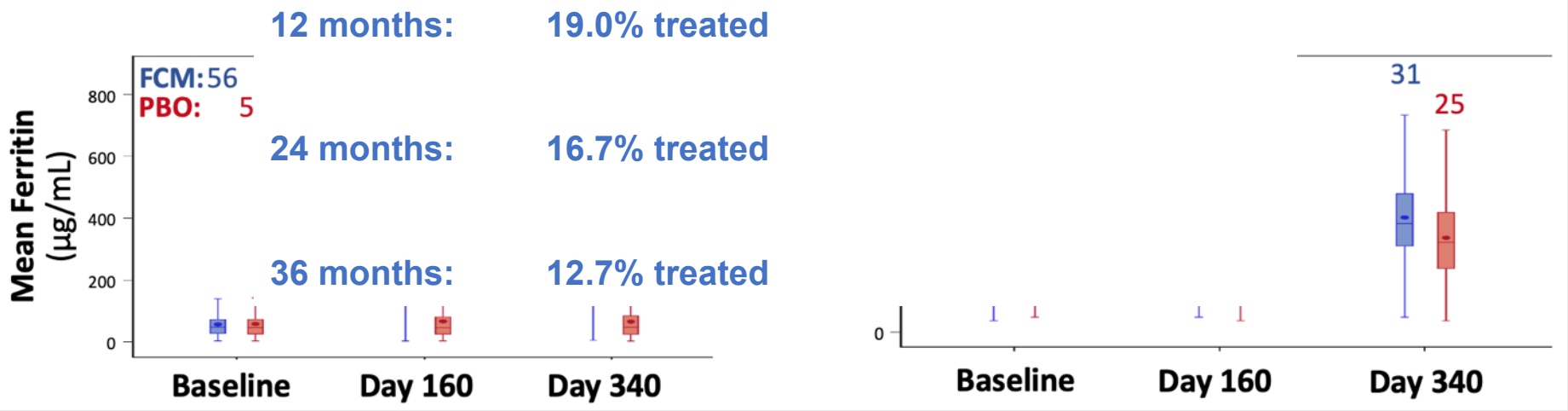
Measure	FCM	Placebo
Number of injection		6 (4, 10)
Cumulative dose of		N/A
Day 180 — received		N/A
IV iron outside proto		104 (7%)

6 months: 16.1% treated
(224 treated [i.e. not on placebo and not missing the vist] as per Table S3
and 1390 at risk in the FCM group as per Figure 2B)

12 months: 19.0% treated

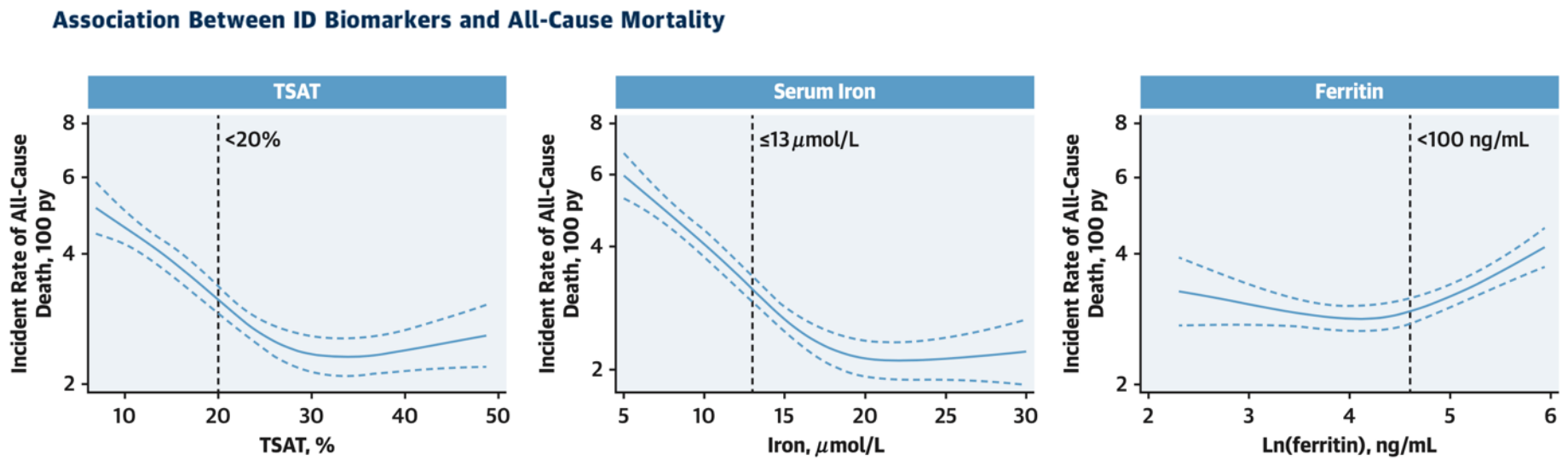
24 months: 16.7% treated

36 months: 12.7% treated



Criteria for Iron Deficiency in Patients With Heart Failure

Masini et al, J Am Coll Cardiol 79 (2022): 341-351



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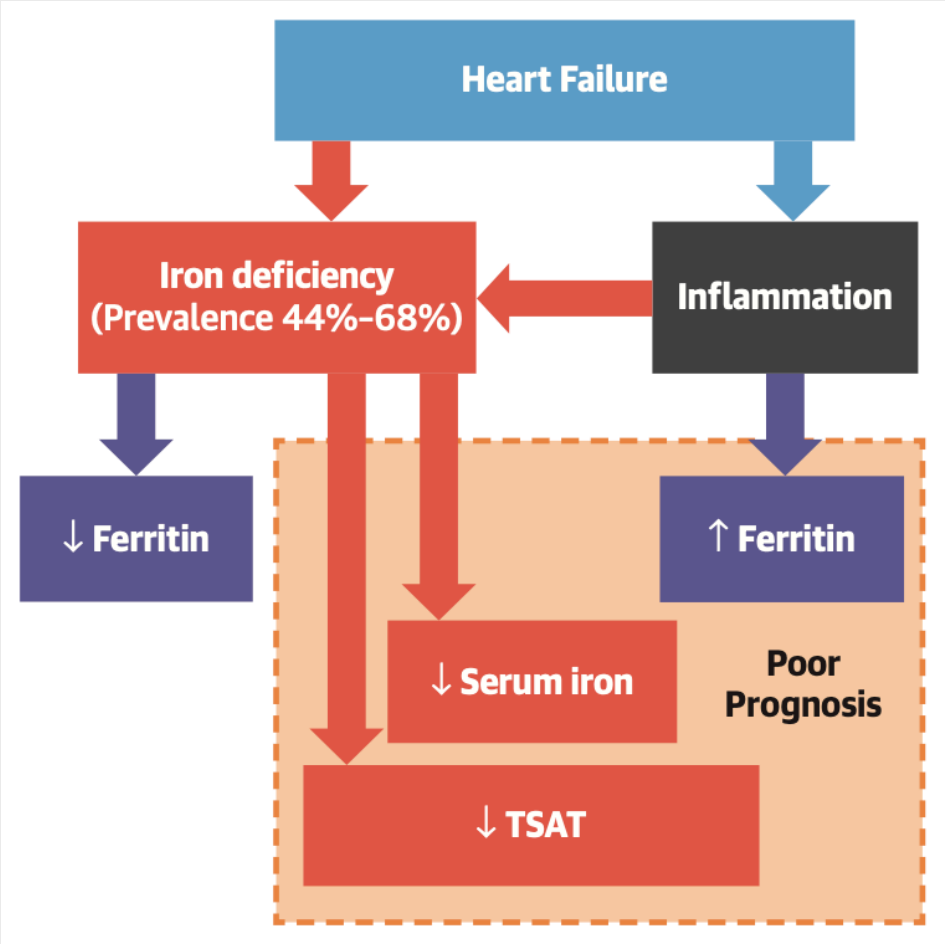

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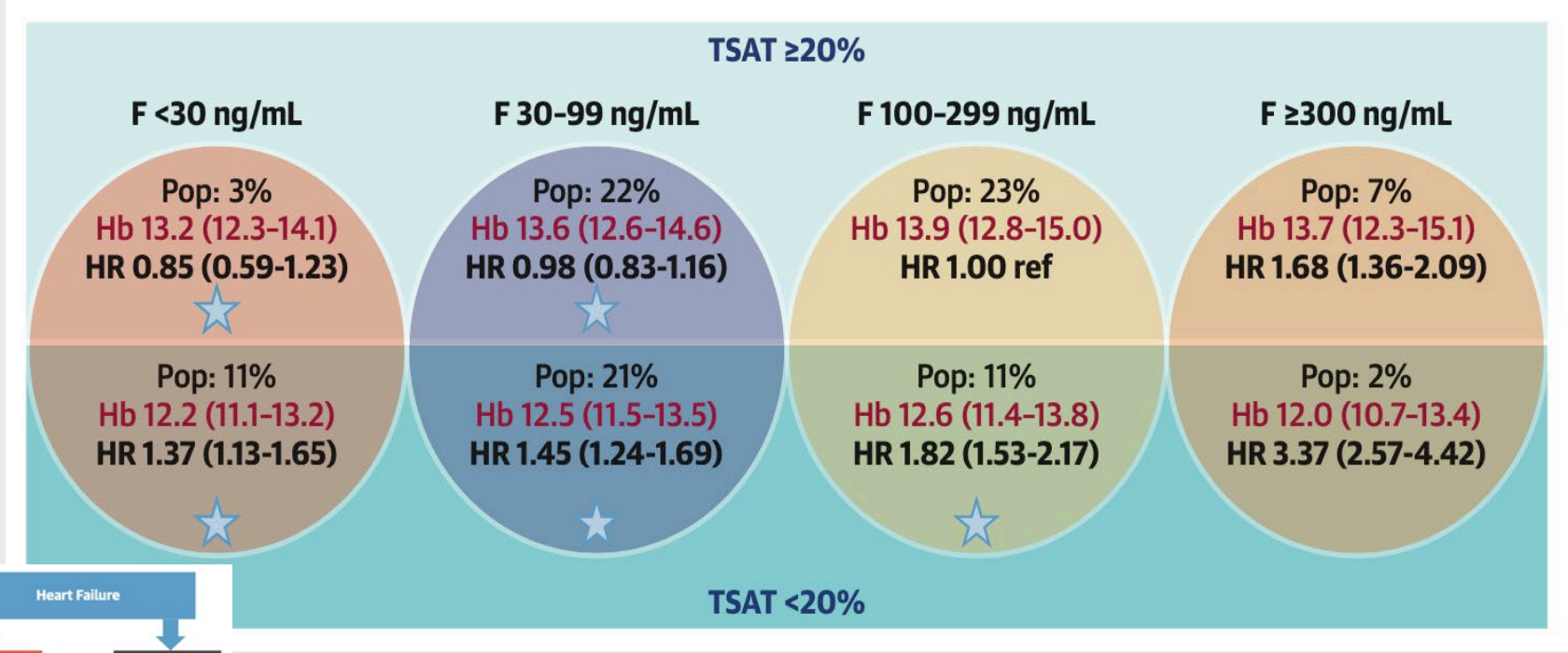

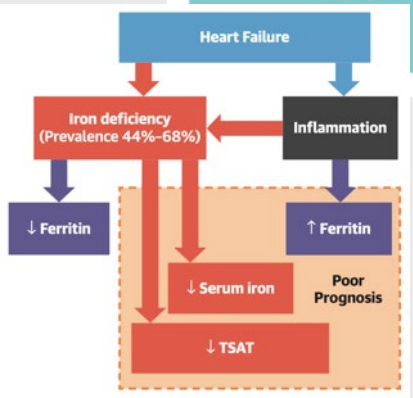

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2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

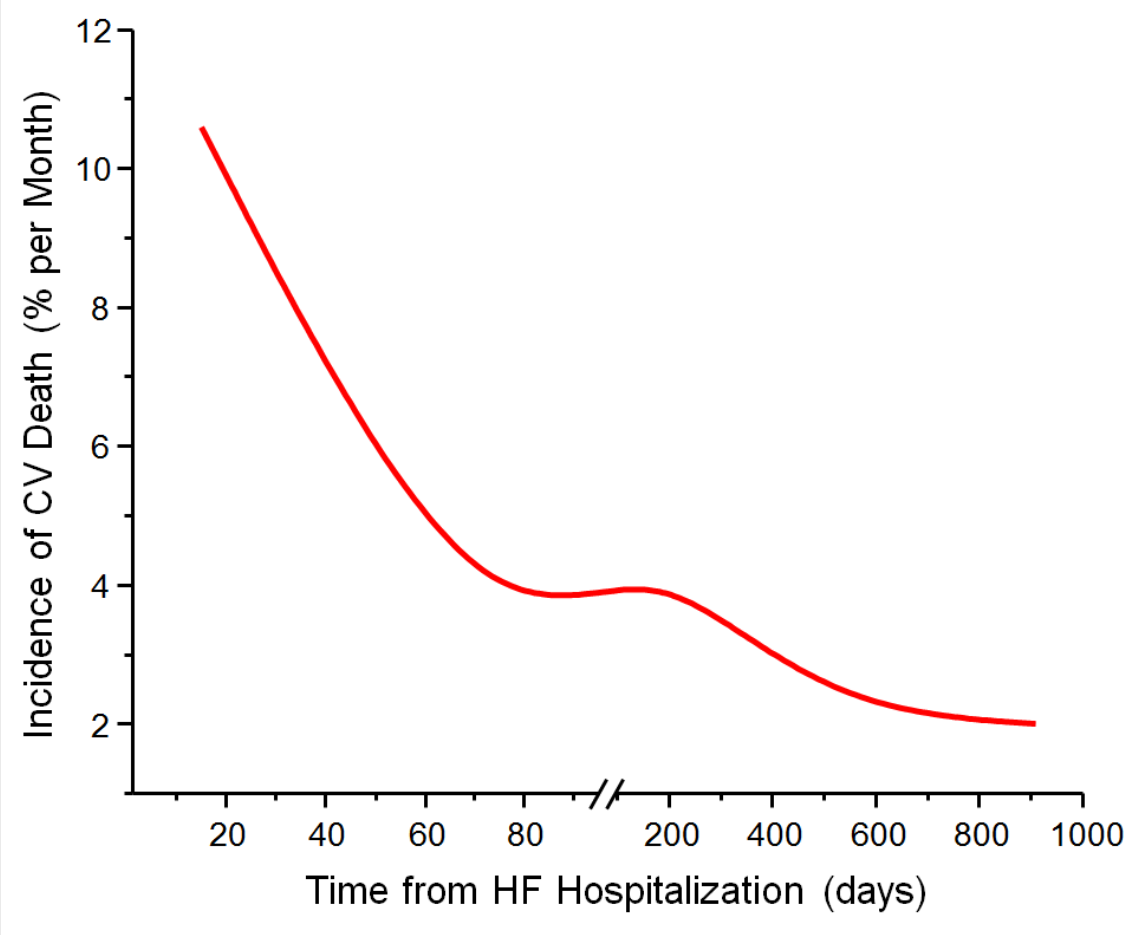
McDonagh et al, Eur Heart J 44 (2023): 3627-3639

New recommendations

Recommendations for management of patients after HF hospitalization	
It is recommended that patients hospitalized for HF be carefully evaluated to exclude persistent signs of congestion before discharge and to optimize oral treatment.	I
It is recommended that evidence-based oral medical treatment be administered before discharge.	I
An early follow-up visit is recommended at 1–2 weeks after discharge to assess signs of congestion, drug tolerance, and start and/or uptitrate evidence-based therapy.	I

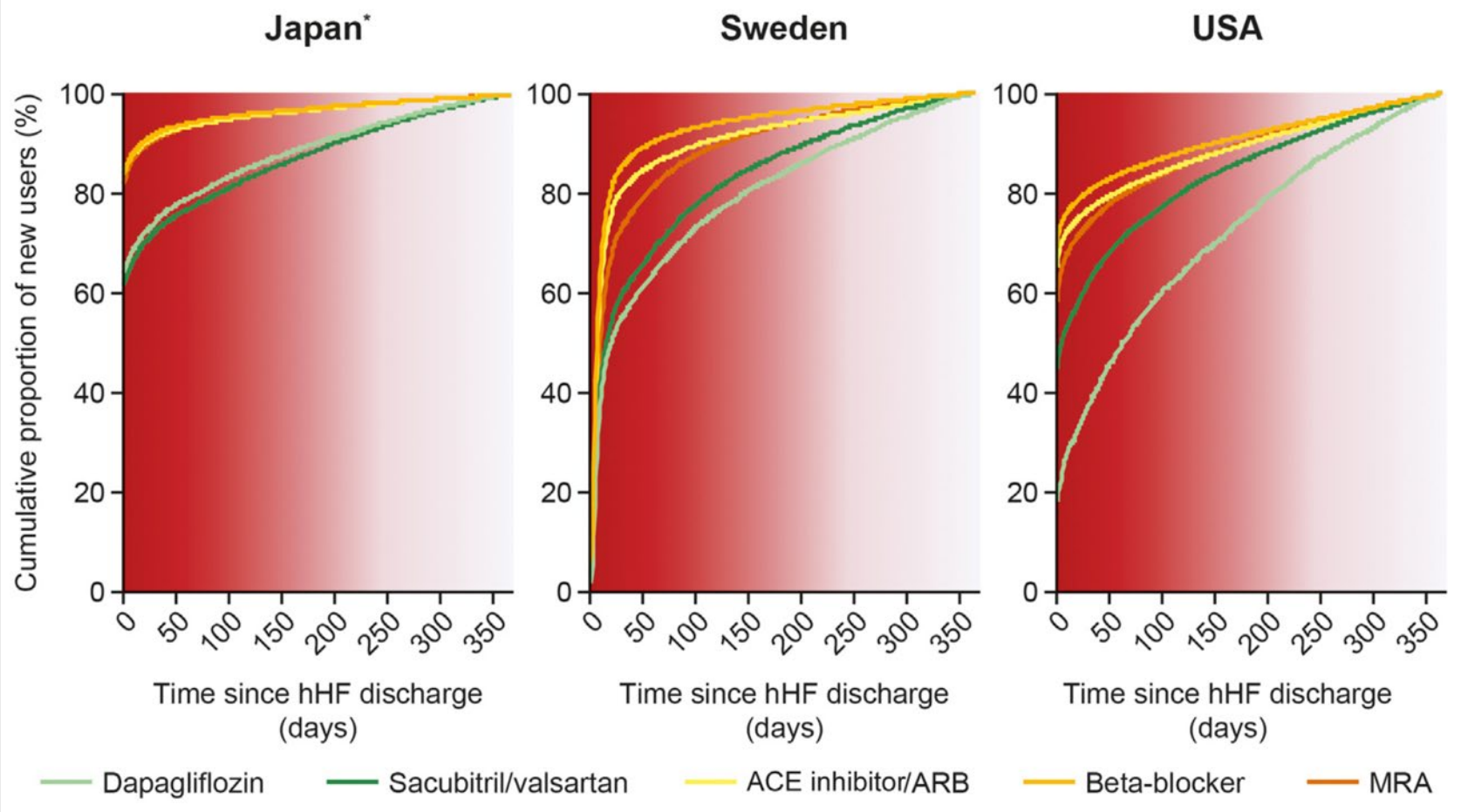
Incidence of Death Following a HF Hospitalization is Highest in First 90 Days

Solomon et al, Circulation 112 (2005): 3738-3744



Heart Failure Drug Treatment-Inertia, Titration, and Discontinuation

Savarese et al, JACC Heart Fail 11 (2022): 1-14



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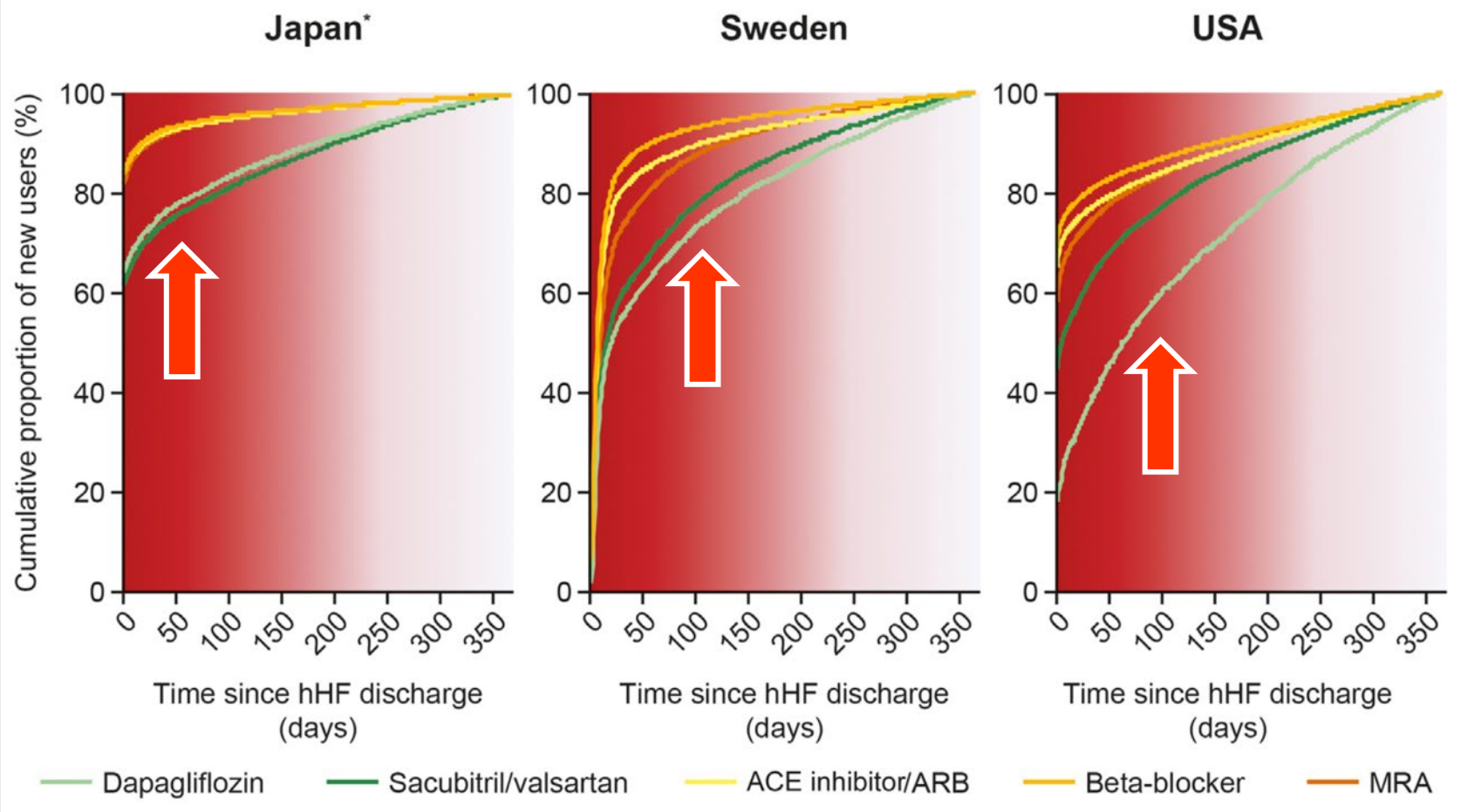
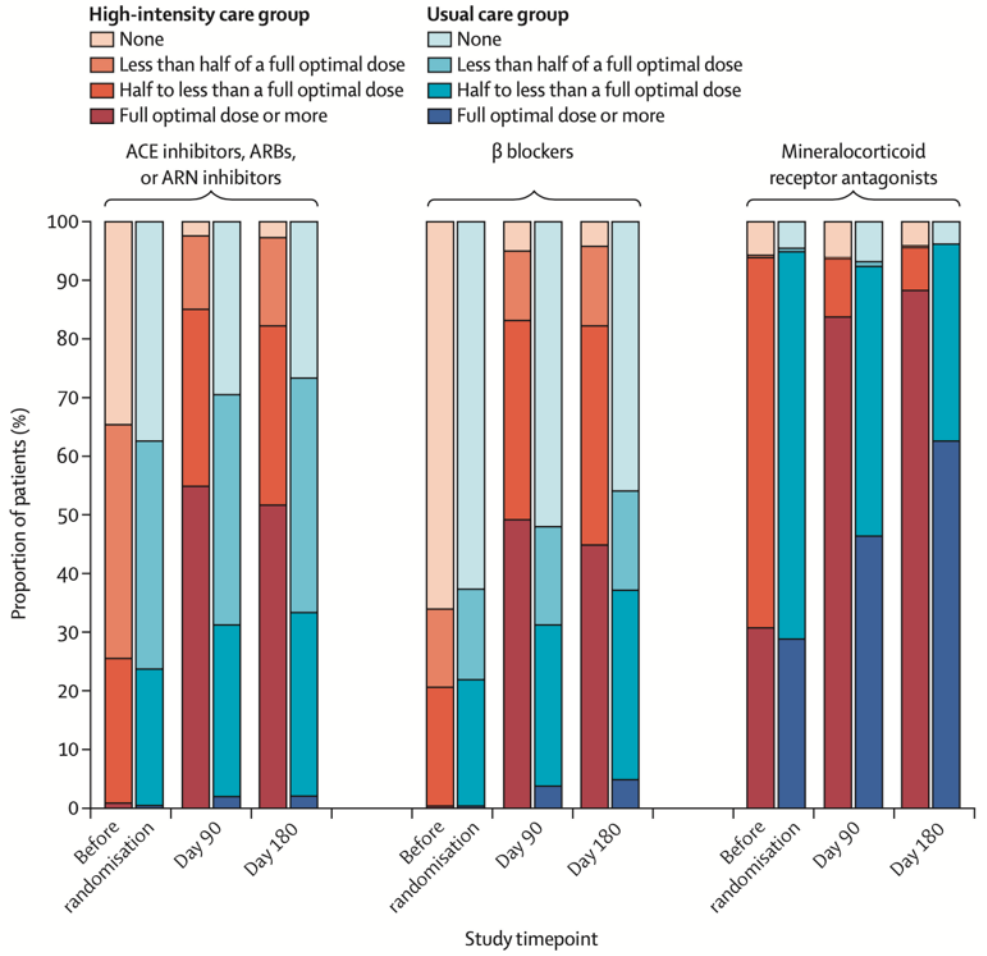


Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial

Mebazaa et al, Lancet 400 (2022): 1938-1952



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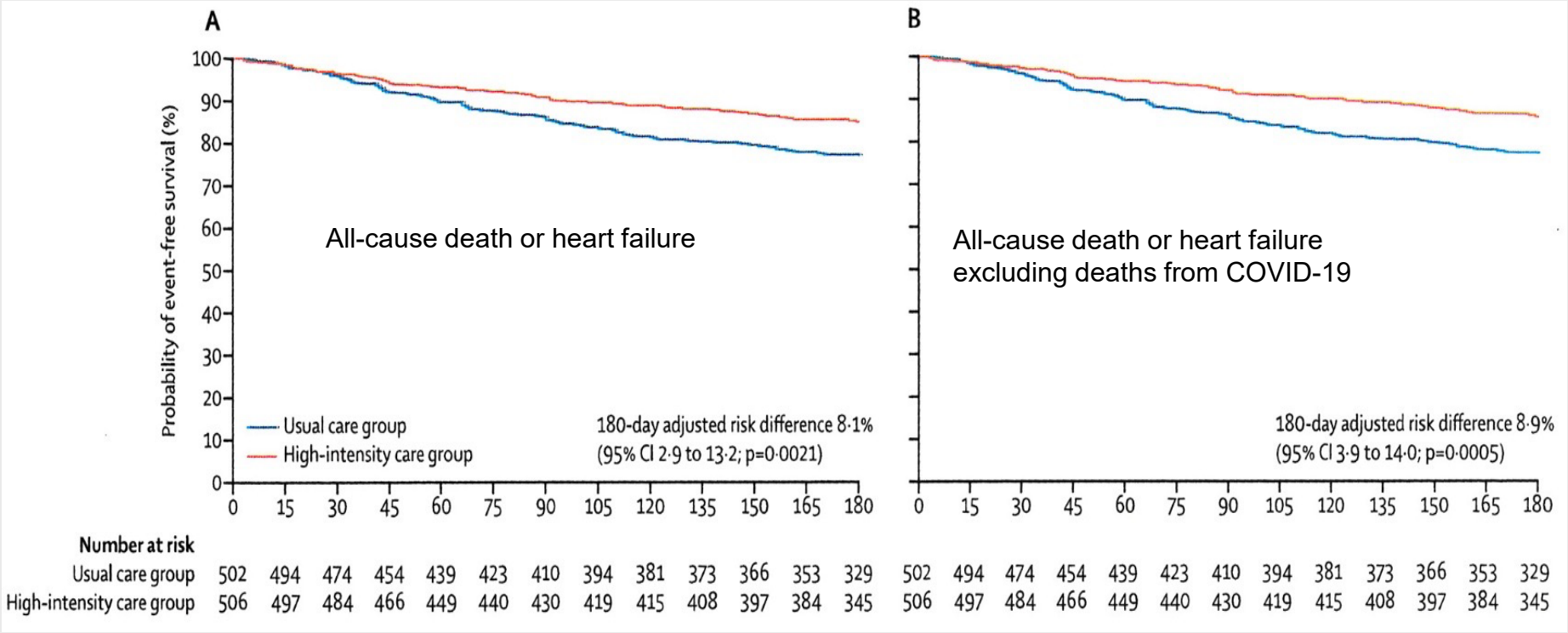
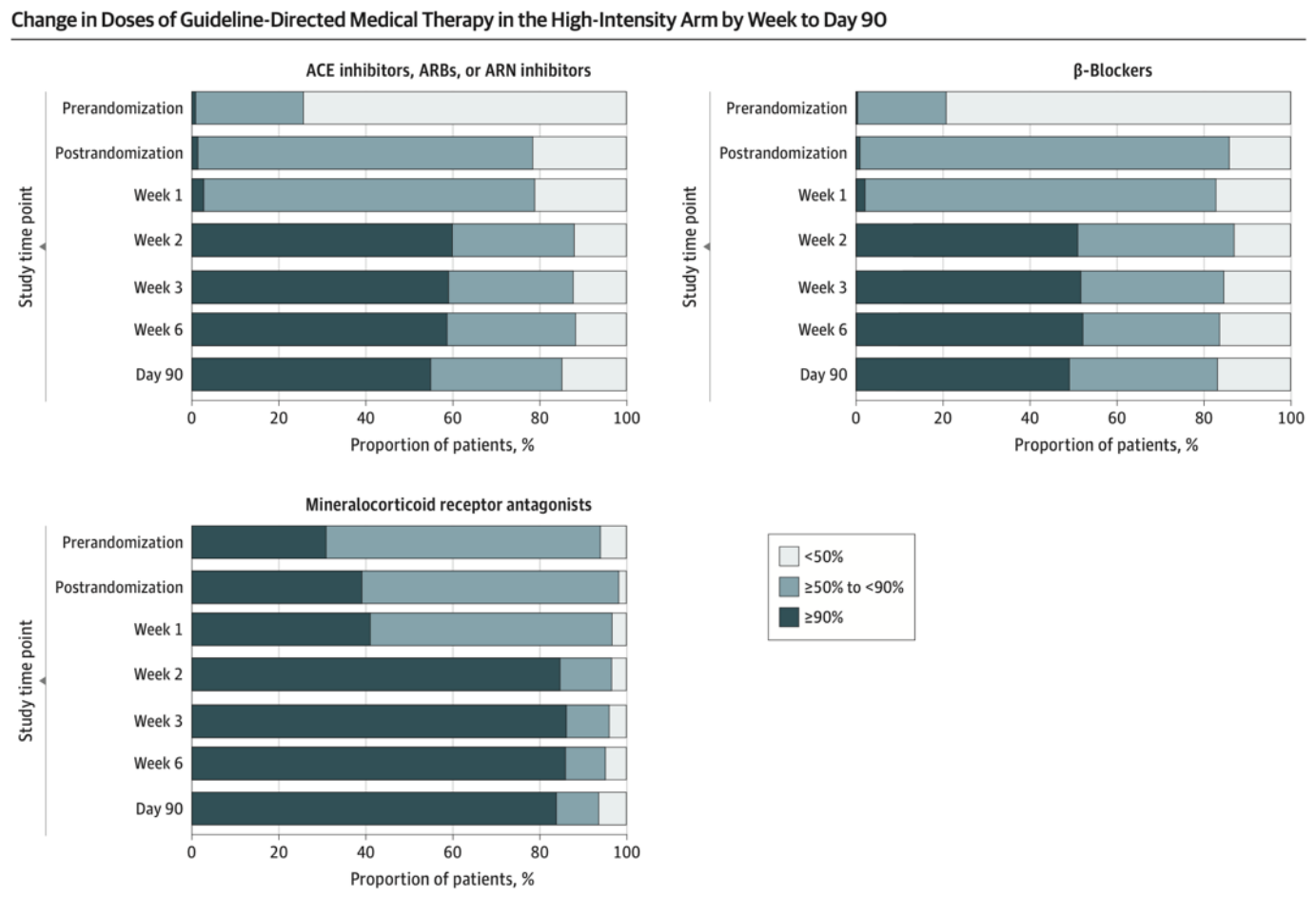


Optimization of Evidence-Based Heart Failure Medications After an Acute Heart Failure Admission

A Secondary Analysis of the STRONG-HF Randomized Clinical Trial

Cotter et al, JAMA Cardiol (2023): [doi:10.1001/jamacardio.2023.4553]



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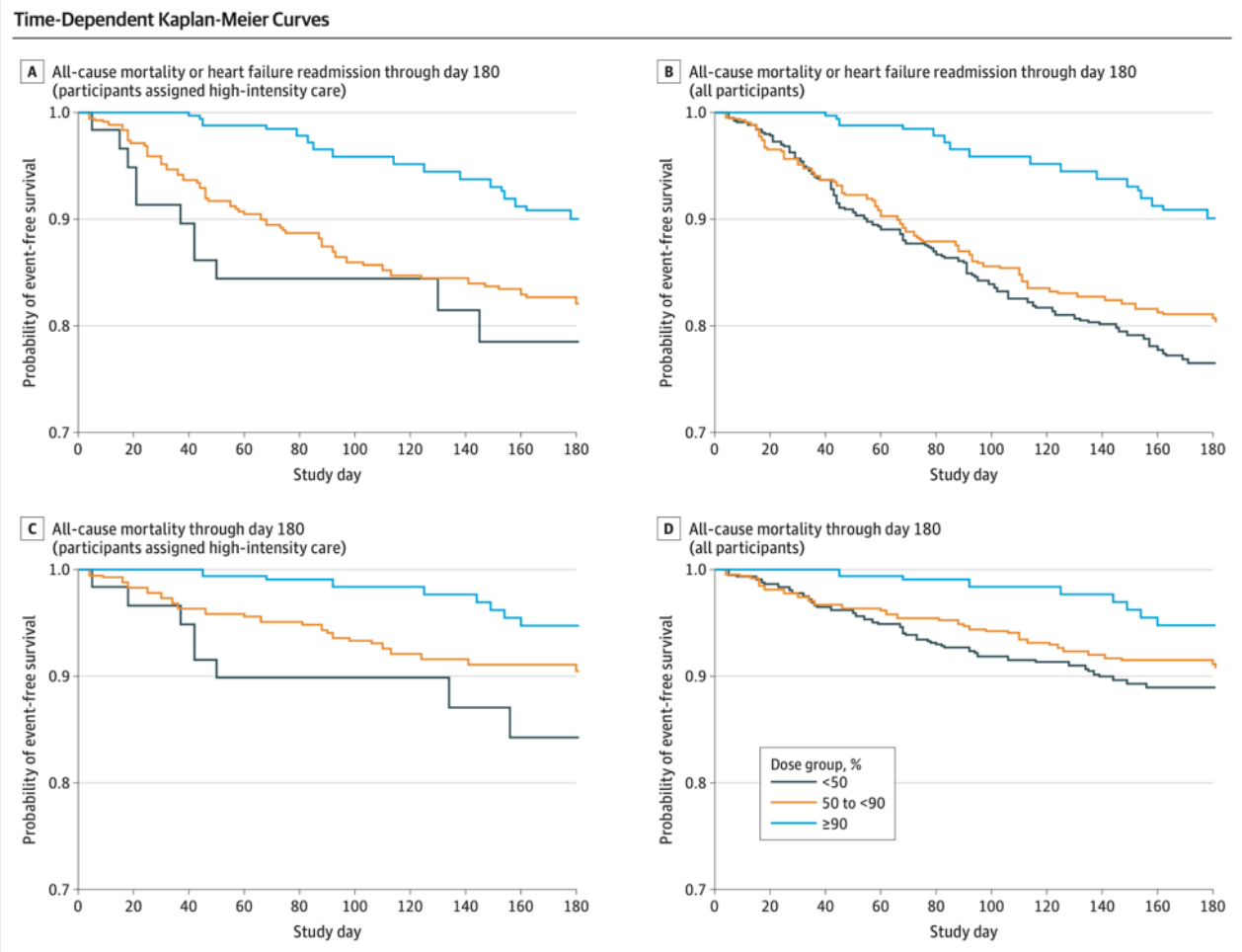
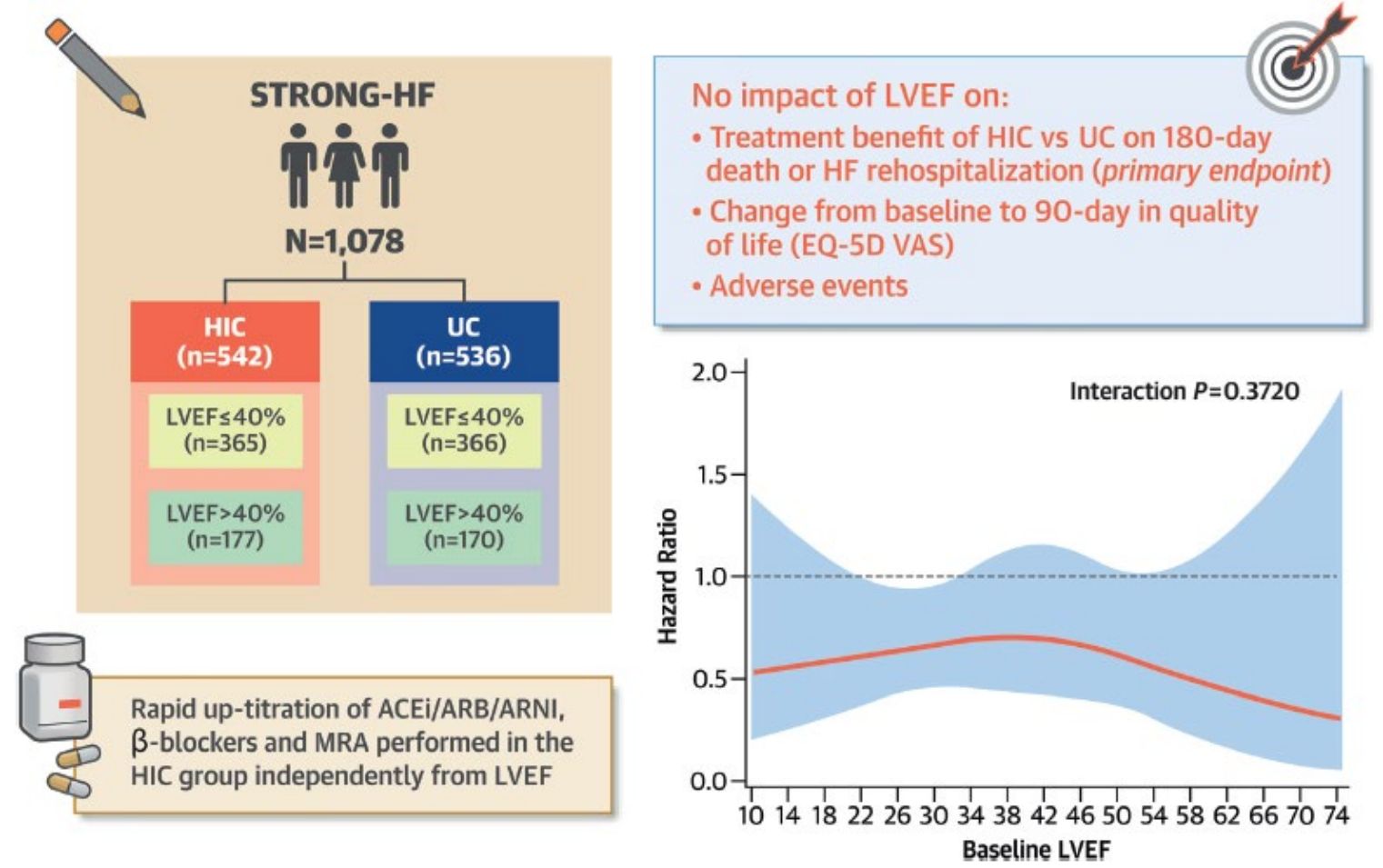


LV Ejektionsfraktion und Hochtitration der Leitlinien-gerechten Herzinsuffizienz-Therapie in STRONG-HF

Pagnesi et al, J Am Coll Cardiol 81 (2023): 2131-2144



2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

McDonagh et al, Eur Heart J 44 (2023): 3627-3639

Recommendation Table 3 — Recommendation for pre-discharge and early post-discharge follow-up of patients hospitalized for acute heart failure

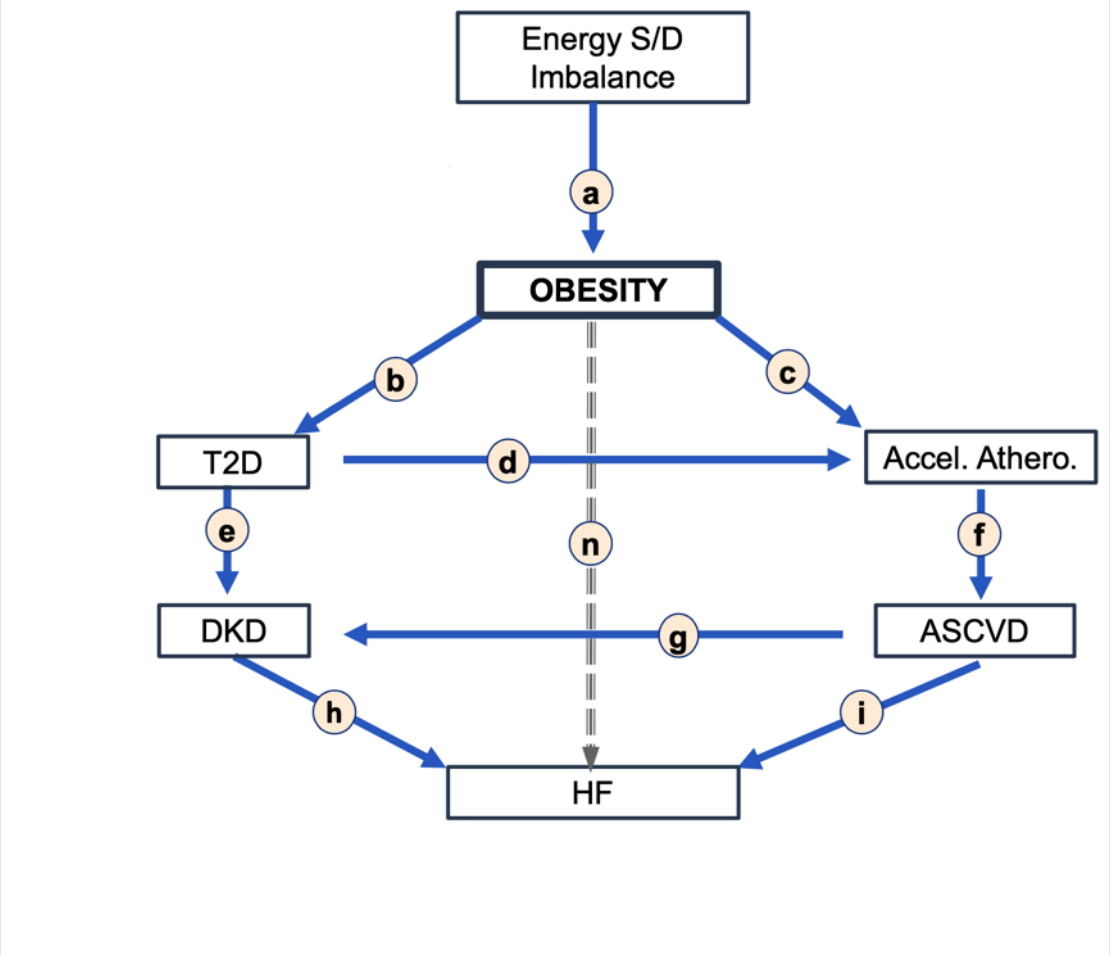
Recommendation	Class[a]	Level[b]
An intensive strategy of initiation and rapid up-titration of evidence-based treatment before discharge and during frequent and careful follow-up visits in the first 6 weeks following a HF hospitalization is recommended to reduce the risk of HF rehospitalization or death.[c,d,e] [16]	I	B

Herzinsuffizienz

- Guidelines
- Notwendigkeit der Aktualisierung
  - Definitionen
  - Neue HFpEF unf HFmrEF Empfehlungen
  - Prävention
  - Komorbidität Eisenmangel
  - Wie initiieren
- **Adipositas und HFpEF**
- GLP1 Agonisten

Diabetocardiology: a new subspecialty?

Braunwald, Eur Heart J 44 (2023): 4214-4216



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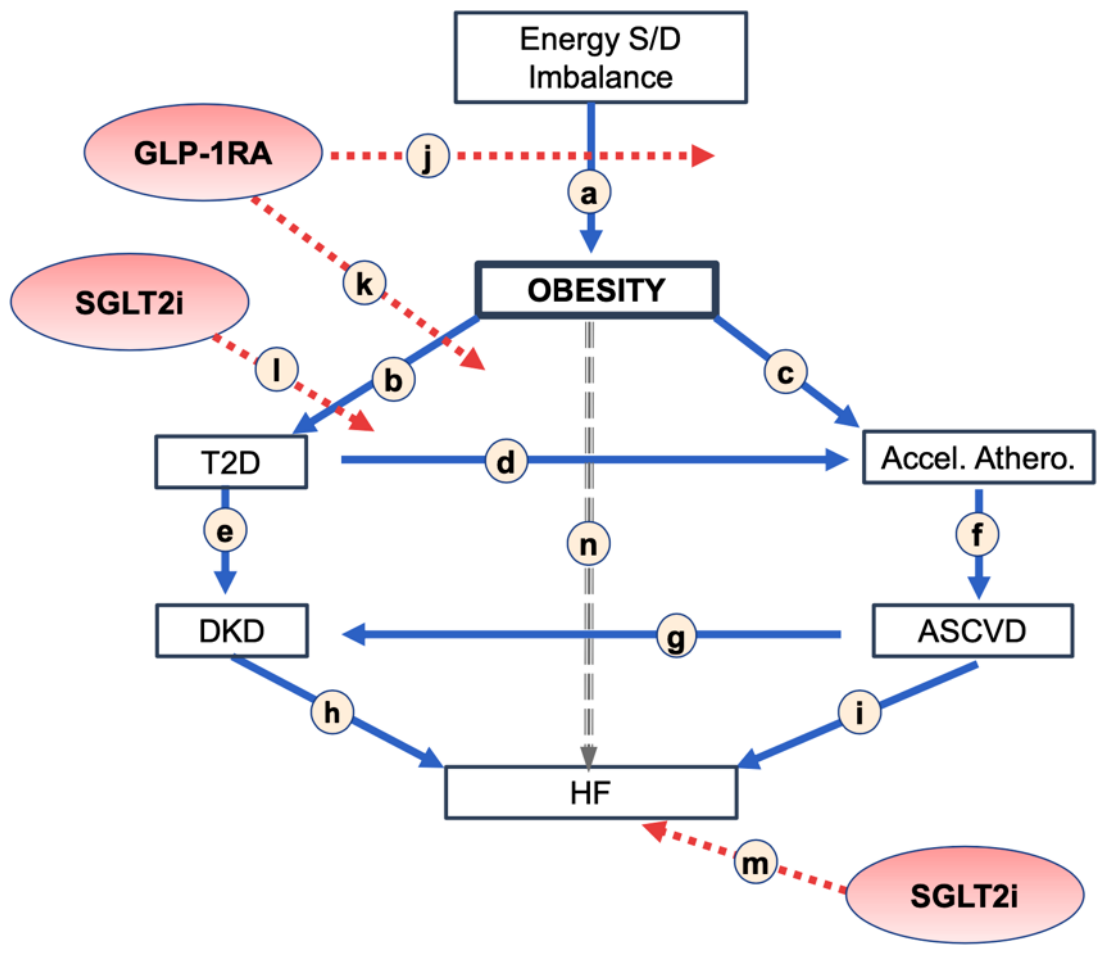
Braunwald, Eur Heart J 44 (2023): 4214-4216



Bariatric Surgery and Cardiovascular Outcomes in Patients With Obesity and Cardiovascular Disease:
A Population-Based Retrospective Cohort Study

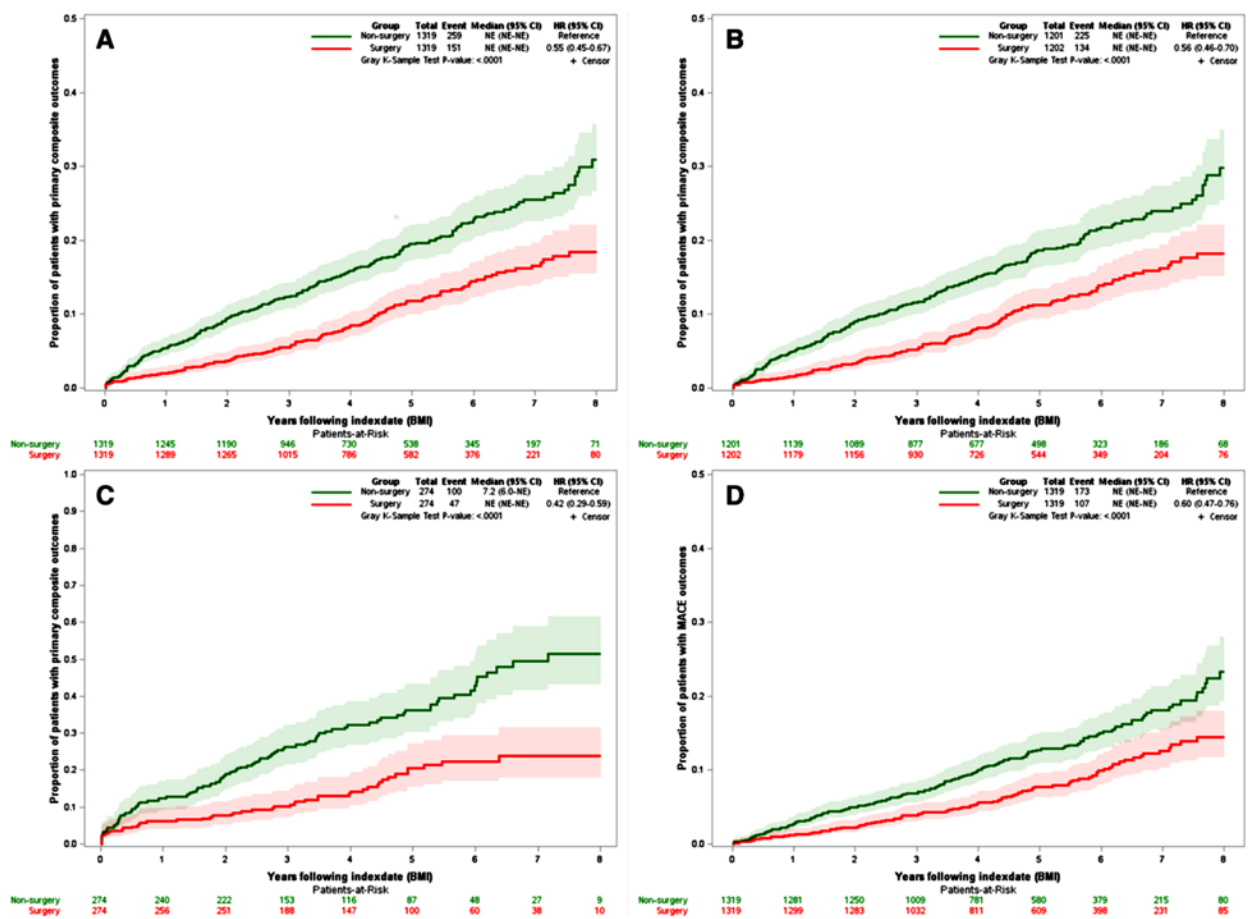
Doumouras et al, Circulation 143 (2023): 1468-1480

Overall cohort for primary outcome

Ischemic heart disease patients for primary outcome

Heart failure patients for primary outcome

Overall cohort for secondary outcome



Bariatric Surgery and Cardiovascular Outcomes in Patients With Obesity and Cardiovascular Disease:
A Population-Based Retrospective Cohort Study

Doumouras et al, Circulation 143 (2023): 1468-1480

Association Between Bariatric Surgery and Cause-Specific Mortality

Variable	Total cohort		Ischemic heart disease		Heart failure	
	Adjusted hazard ratio* (95% CI)	*P* value	Adjusted hazard ratio* (95% CI)	*P* value	Adjusted hazard ratio* (95% CI)	*P* value
All-cause mortality	0.50 (0.34–0.74)	<0.001	0.44 (0.28–0.68)	<0.001	0.43 (0.24–0.78)	0.006
Cardiovascular mortality	0.35 (0.15–0.80)	0.01	0.30 (0.11–0.79)	0.02	0.31 (0.10–0.94)	0.04
Other mortality	0.56 (0.36–0.88)	0.01	0.50 (0.30–0.81)	0.01	0.50 (0.25–1.02)	0.06
Coronary artery events	0.67 (0.49–0.92)	0.01	0.64 (0.46–0.89)	0.008	0.66 (0.34–1.28)	0.22
Myocardial infarction	0.63 (0.42–0.96)	0.03	0.63 (0.41–0.96)	0.03	0.39 (0.15–1.02)	0.05
Stent/coronary artery bypass grafting	0.70 (0.51–0.96)	0.03	0.66 (0.47–0.91)	0.01	0.69 (0.35–1.34)	0.27
Cerebrovascular events	0.98 (0.58–1.66)	0.93	0.96 (0.55–1.69)	0.89	0.48 (0.16–1.46)	0.20
Heart failure hospitalization	0.37 (0.25–0.54)	<0.001	0.38 (0.25–0.58)	<0.001	0.33 (0.20–0.53)	<0.001

*Adjusted for age, body mass index, sex, immigrant status, income, rurality, diabetes status, overall cardiac history, stroke, chronic obstructive pulmonary disease, hypertension, sleep apnea, renal disease, smoking status, previous malignancy, substance abuse, self-harm, mood disorder, cancer screening (colon, breast, cervical), and health care use in the previous year (family physician, hospital inpatient, emergency room visit, specialist visit).

Herzinsuffizienz

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  - Prävention
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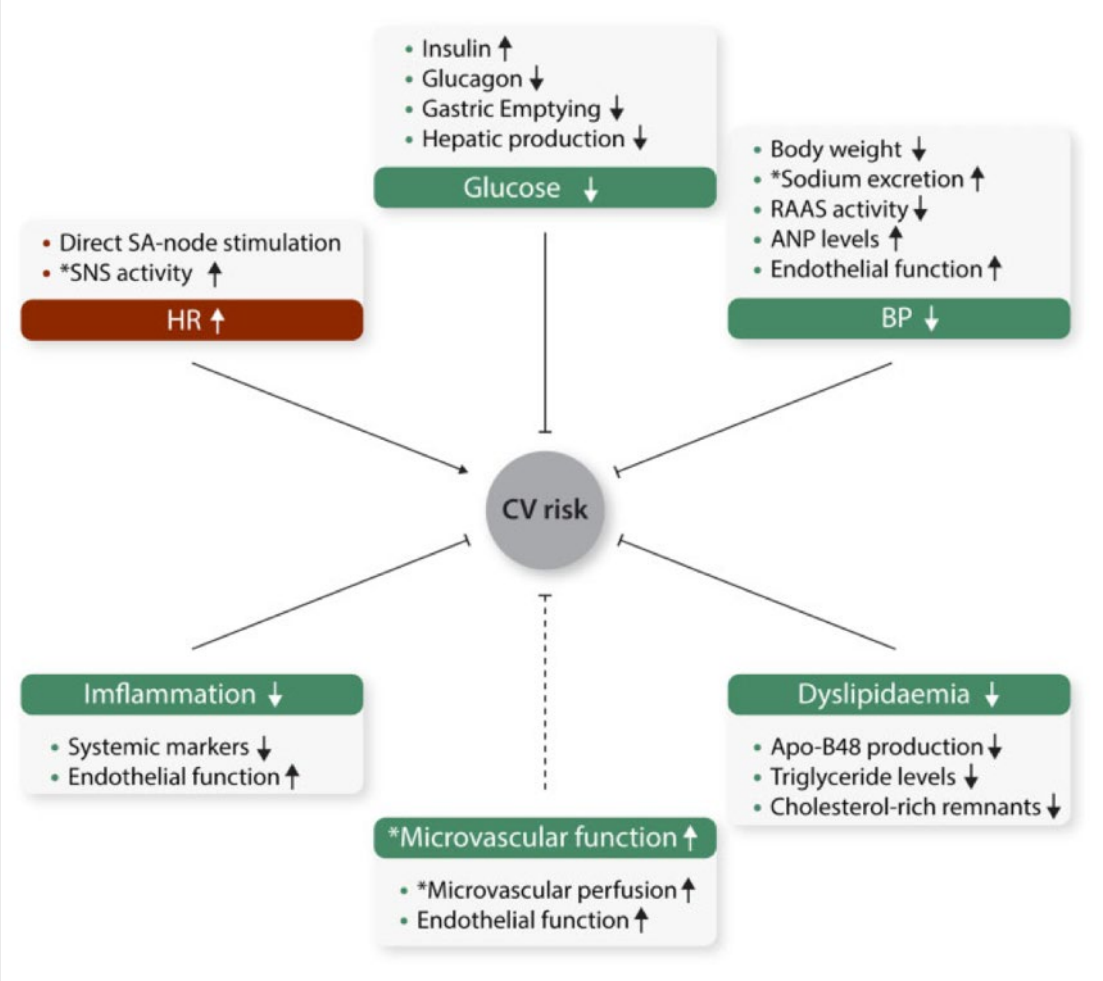
  - Wie initiieren
- Adipositas und HFpEF
- **GLP1 Agonisten**

Cardiovascular effects of glucagon-like peptide 1 receptor agonists: from mechanistic studies in humans to clinical outcomes

Heuvelman et al, Cardiovasc Res 116 (2019): 916-930

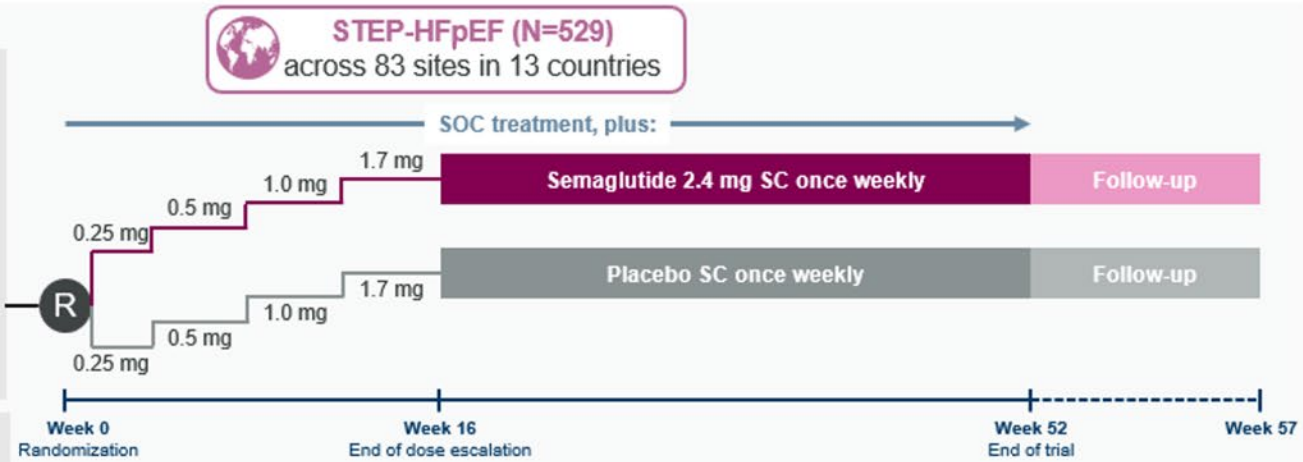


STEP-HFpEF - Study design

Kosiborod et al, JACC Heart Fail 11 (2023): 1000-1010 ; Kosiborod et al, N Engl J Med 389 (2023): 1069-1084 ; Kosiborod, Hotline presentation, ESC (2023)

Key inclusion criteria
- **Adults, ≥18 years, BMI ≥30 kg/m²**
- LVEF ≥45%, NYHA functional class II-IV, KCCQ-CSS <90 points, 6 MWD ≥100 m, and ≥1 of the following:
  - Elevated filling pressures
  - Elevated natriuretic peptide levels + structural echo abnormalities
  - HF hospitalization (previous 12 months) + ongoing requirement for diuretics and/or structural echo abnormalities

Key exclusion criteria
- Prior/planned bariatric surgery
- Recent self-reported change in body weight >5 kg (11 lbs)
- Recent (last ≤30 days) adverse CV event or HHF
- SBP of >160 mmHg at screening
- if they had HbA_{1c} ≥6.5%

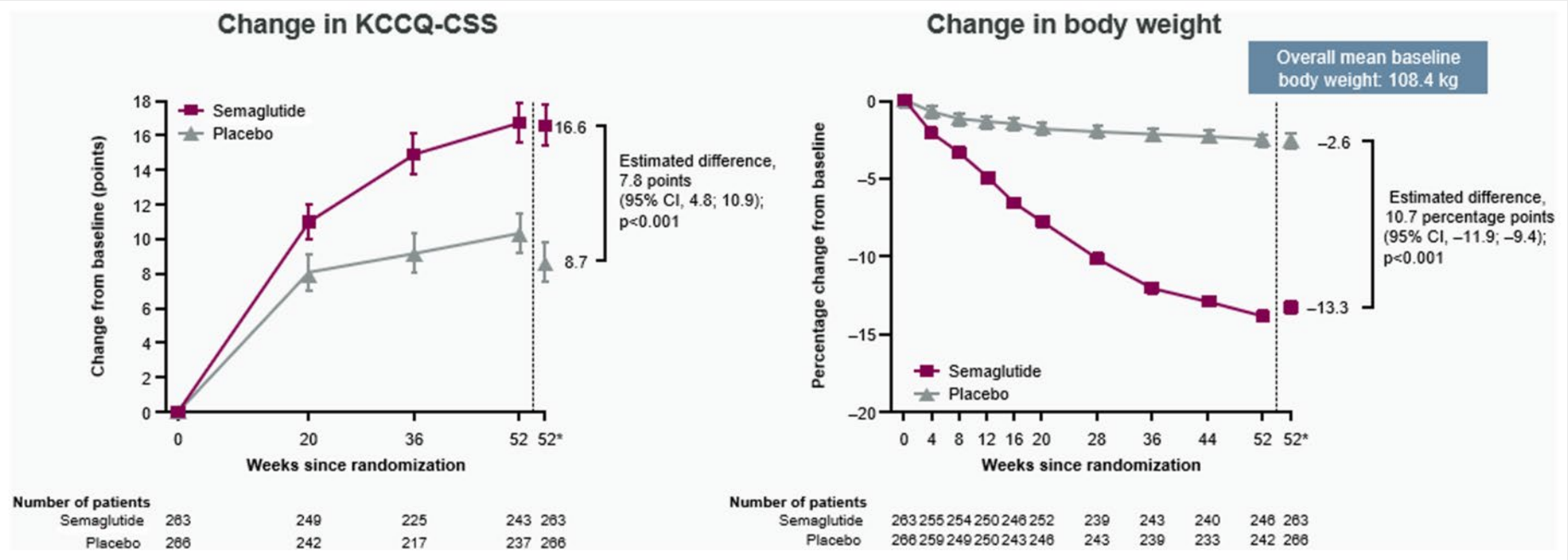


Dual primary endpoints
- Change in KCCQ-CSS from baseline to week 52
- Change in body weight from baseline to week 52

Confirmatory secondary endpoints
- Change in 6MWD and change in CRP from baseline to week 52
- Hierarchical composite endpoint comprising:
  - Time to all-cause death
  - Number of HF events requiring hospitalization or urgent HF visit
  - Time to first HF event requiring hospitalization or urgent HF visit
  - Differences of at least 15, 10 and 5 points in KCCQ-CSS change between baseline and week 52
  - Difference of at least 30 meters in 6MWD change between baseline and week 52

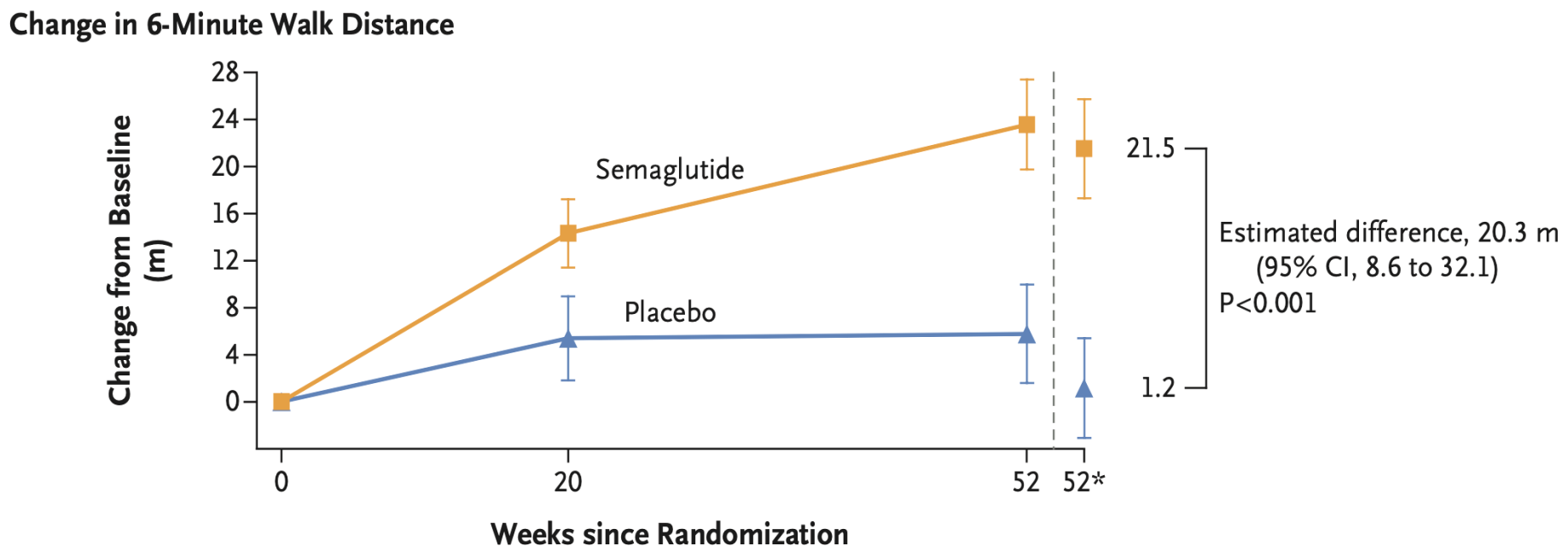
STEP-HFpEF - Co-primary endpoint results

Kosiborod et al, JACC Heart Fail 11 (2023): 1000-1010 ; Kosiborod et al, N Engl J Med 389 (2023): 1069-1084 ; Kosiborod, Hotline presentation, ESC (2023)



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

Kosiborod et al, N Engl J Med 389 (2023): 1069-1084



No. of Participants

Semaglutide	263	245	240	263
Placebo	266	232	225	266

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

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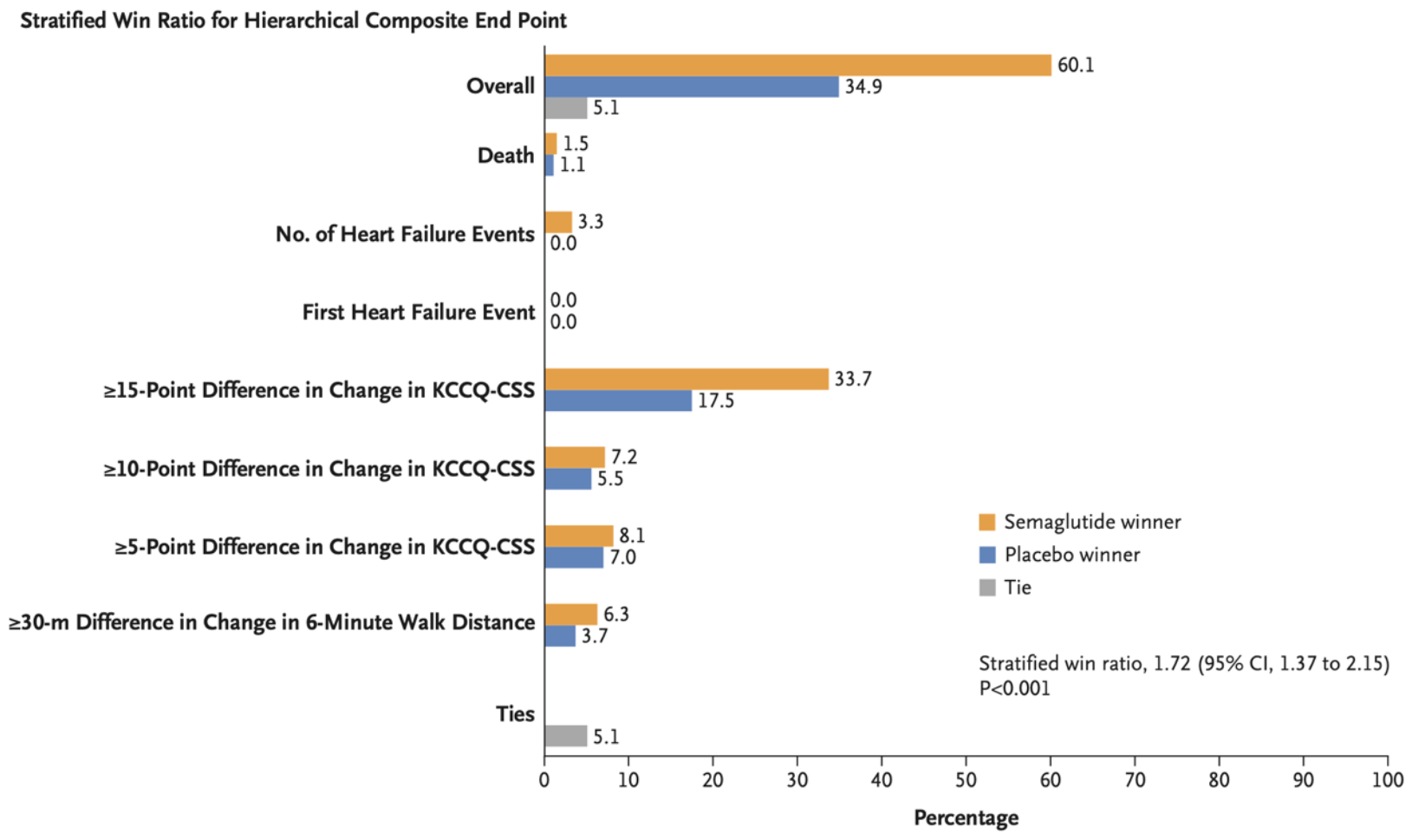


Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

Kosiborod et al, N Engl J Med 389 (2023): 1069-1084

Efficacy End Points.*

End Point	Semaglutide (N=263)	Placebo (N=266)	Estimated Difference or Ratio (95% CI)	P Value
Dual primary end points				
Change in KCCQ-CSS from baseline to week 52 — points	16.6	8.7	7.8 (4.8 to 10.9)†	<0.001
Percentage change in body weight from baseline to week 52	–13.3	–2.6	–10.7 (–11.9 to –9.4)†	<0.001
Confirmatory secondary end points				
Change from baseline to week 52 in 6-minute walk distance — m	21.5	1.2	20.3 (8.6 to 32.1)†	<0.001
Change from baseline to week 52 in CRP level — %	–43.5	–7.3	0.61 (0.51 to 0.72) ‡§	<0.001
Hierarchical composite end point — crude percentage of wins¶	60.1	34.9	1.72 (1.37 to 2.15)‖	<0.001

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

Kosiborod et al, N Engl J Med 389 (2023): 1069-1084

Efficacy End Points.*

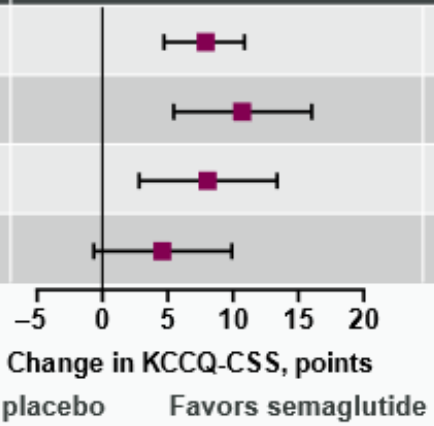
End Point	Semaglutide (N=263)	Placebo (N=266)	Estimated Difference or Ratio (95% CI)	P Value
Exploratory end points assessed in the overall population				
Percentage reduction from baseline to week 52 in NT-proBNP level	–20.9	–5.3	0.84 (0.71 to 0.98)‡§§	—
≥15-point improvement in KCCQ-CSS at week 52 — no. of participants (%)	123 (50.6)	85 (35.9)	2.2 (1.5 to 3.2)‖	—
Adjudicated heart failure event (hospitalization or urgent visit for heart failure), time-to-event analysis — no. of events	1	12	0.08 (0.00 to 0.42)¶¶	—

STEP-HFpEF
KCCQ subanalysis Dual primary endpoint

Kosiborod et al, JACC Heart Fail 11 (2023): 1000-1010 ; Kosiborod et al, N Engl J Med 389 (2023): 1069-1084 ; Kosiborod, Hotline presentation, ESC (2023)

Change in KCCQ-CSS from baseline to week 52 by KCCQ-CSS tertiles

Population	Semaglutide 2.4 mg		Placebo		ETD (95% CI)	Interaction p -value
	n	Change from baseline to week 52	n	Change from baseline to week 52		
Overall	243	16.6	237	8.7	7.8 (4.8; 10.9)	
Tertile 1 (≤48.4)	76	17.7	86	7.0	10.7 (5.4; 16.1)	
Tertile 2 (>48.4; ≤66.7)	80	17.2	76	9.2	8.1 (2.7; 13.4)	**0.276**
Tertile 3 (>66.7)	87	14.8	75	10.2	4.6 (–0.6; 9.9)	

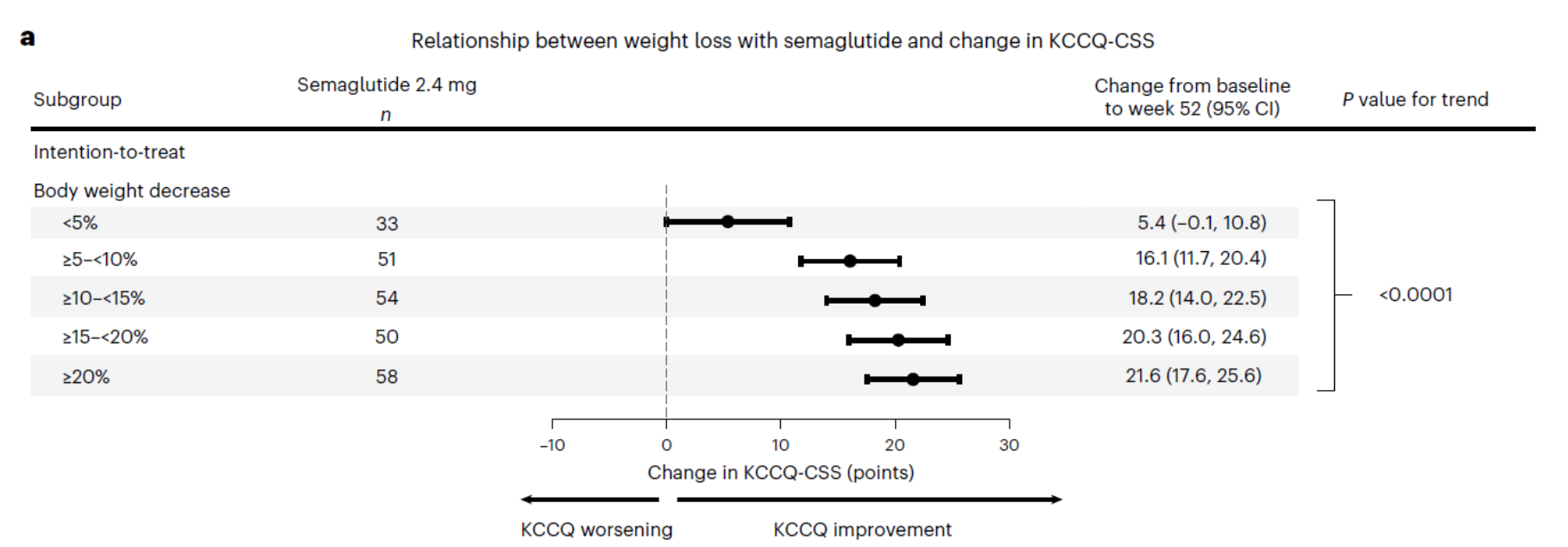


Data are from the in-trial period for the full analysis set; n are the number of participants with an observation at week 52; week 52 responses were analyzed using an ANCOVA model with randomized treatment, subgroup, and treatment by subgroup interaction as factors and baseline KCCQ-CSS as covariate; Missing observations due to reasons other than CV death or previous heart failure events (of non-retrieved) were multiple (x1000) imputed from retrieved participants of the same randomized treatment arm; missing observations due to CV death or previous heart failure events were imputed using a composite strategy with the least favorable value determined during the trial; p-value for the linear trend of the KCCQ tertiles was 0.113.
ANCOVA, analysis of covariance; CSS, Clinical Summary Score; ETD, estimated treatment difference.

STEP-HFpEF

Relationship between weight loss with semaglutide and change in KCCQ-CSS

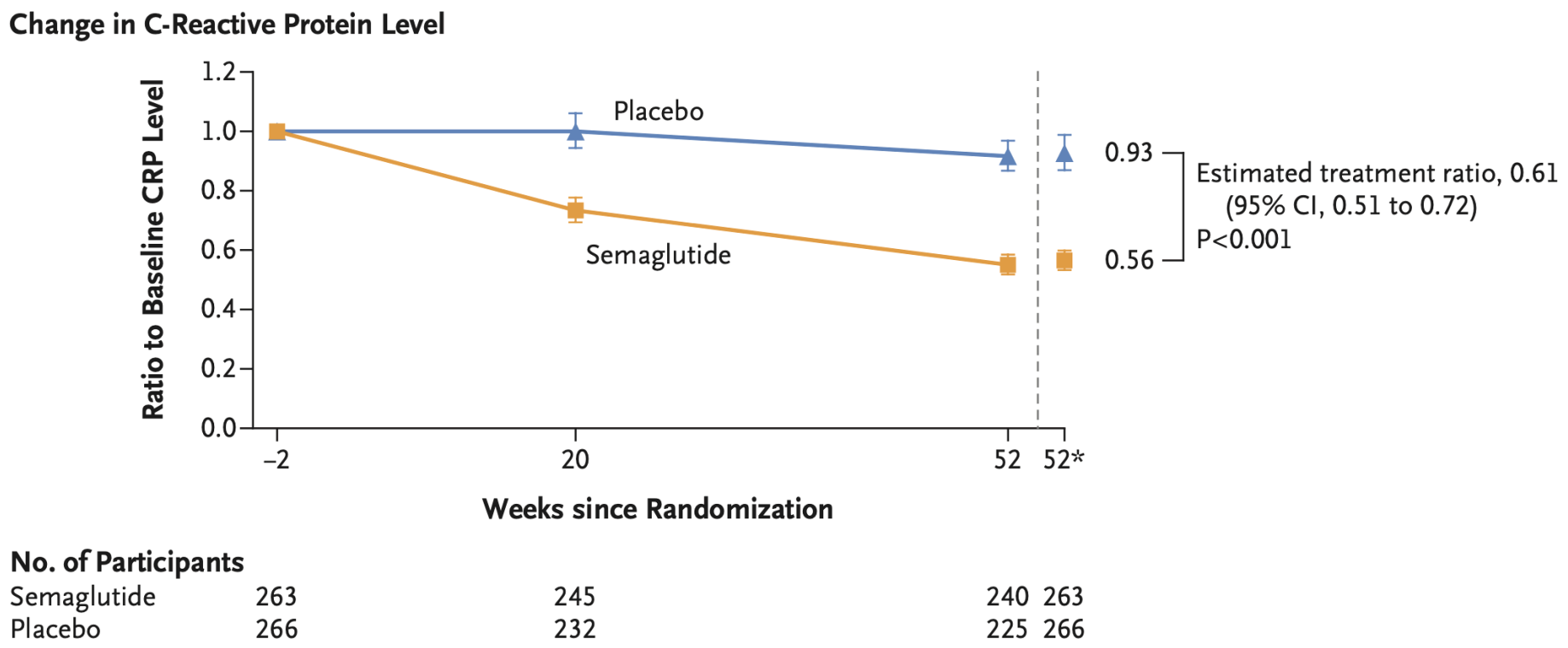
Borlaug et al, Nat Med 29 (2023): 2358-2365



Bei Patienten mit HFpEF und Adipositas führt die Therapie mit Semaglutid (2,4mg/Woche) zu einer deutlicheren Reduktion des Körpergewichts, der Symptomlast und zu einer Verbesserung der körperlichen Aktivität

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

Kosiborod et al, N Engl J Med 389 (2023): 1069-1084



Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes SELECT – Secondary Prevention

Lincoff et al, N Engl J Med 389 (2023): 2221-2232

Characteristic	(N=8803)	(N=8801)
Age — yr	61.6±8.9	61.6±8.8
Male sex — no. (%)	6355 (72.2)	6377 (72.5)
Race or ethnic group — no. (%)†		
White	7387 (83.9)	7404 (84.1)
Asian	720 (8.2)	727 (8.3)
Black	348 (4.0)	323 (3.7)
Other	253 (2.9)	273 (3.1)
Hispanic or Latino	914 (10.4)	908 (10.3)
Body weight — kg	96.5±17.5	96.8±17.8
BMI‡	33.3±5.0	33.4±5.0
Waist circumference — cm	111.3±13.1	111.4±13.1
Glycated hemoglobin level — %	5.78±0.34	5.78±0.33
Distribution — no. (%)		
<5.7%	2925 (33.2)	2980 (33.9)
≥5.7%	5877 (66.8)	5819 (66.1)
Median high-sensitivity CRP level (IQR) — mg/liter	1.87 (0.89–4.18)	1.80 (0.86–4.06)

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes SELECT – Secondary Prevention

Lincoff et al, N Engl J Med 389 (2023): 2221-2232

Cardiovascular inclusion criteria — no. (%)		
Myocardial infarction only	5962 (67.7)	5944 (67.5)
Stroke only	1578 (17.9)	1556 (17.7)
Peripheral arterial disease only	376 (4.3)	401 (4.6)
Two or more inclusion criteria	718 (8.2)	719 (8.2)
Other§	169 (1.9)	181 (2.1)
eGFR — ml/min/1.73 m^2	82.4±17.5	82.5±17.3
Median lipid level (IQR) — mg/dl		
Total cholesterol	153 (131–182)	153 (131–183)
HDL cholesterol	44 (37–52)	44 (37–52)
LDL cholesterol	78 (61–102)	78 (61–102)
Triglycerides	134 (99–188)	135 (100–190)
Systolic blood pressure — mm Hg	131.0±15.6	130.9±15.3
Diastolic blood pressure — mm Hg	79.4±10.0	79.2±9.9
Pulse — beats/min	68.9±10.6	68.6±10.7

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes SELECT – Secondary Prevention

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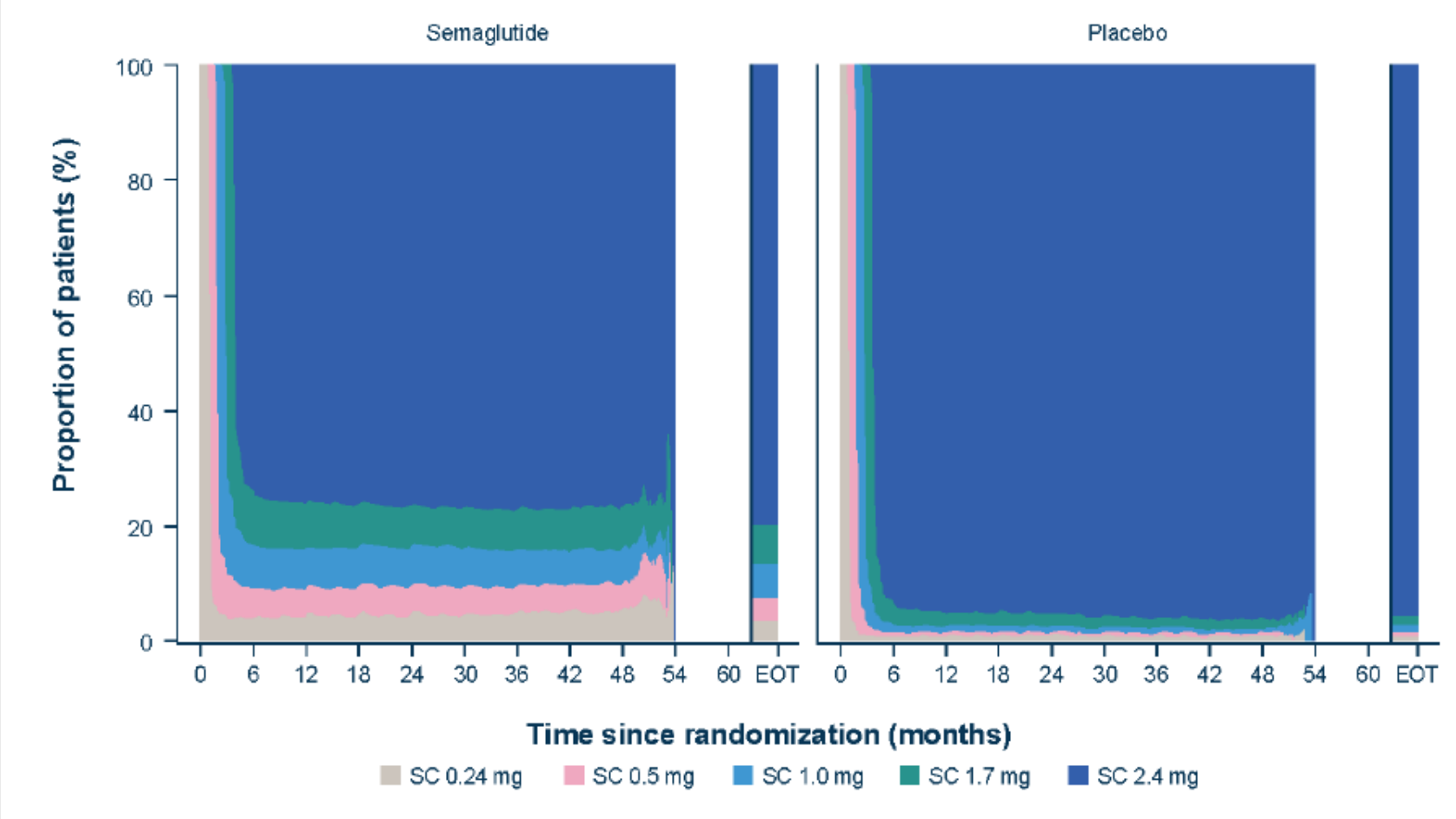

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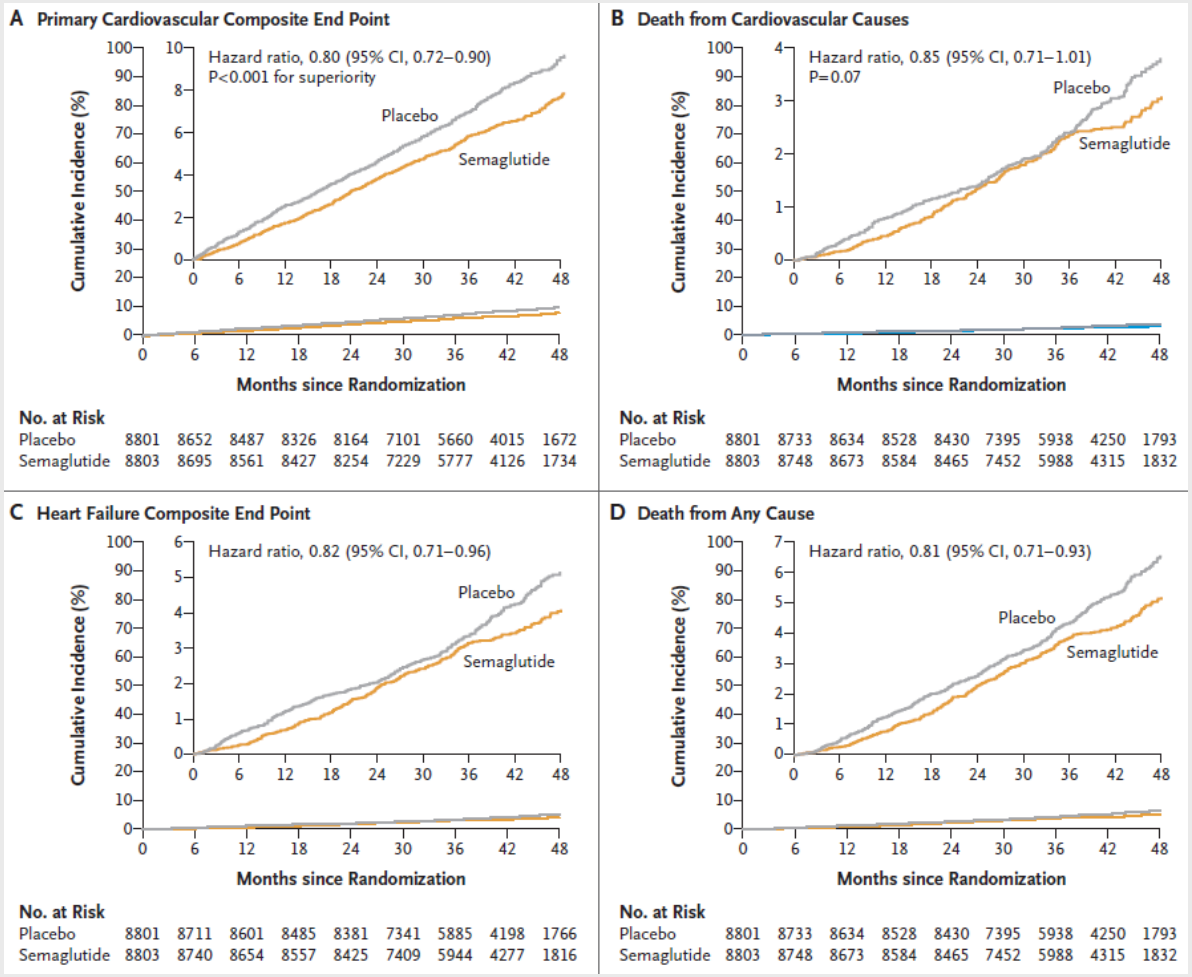

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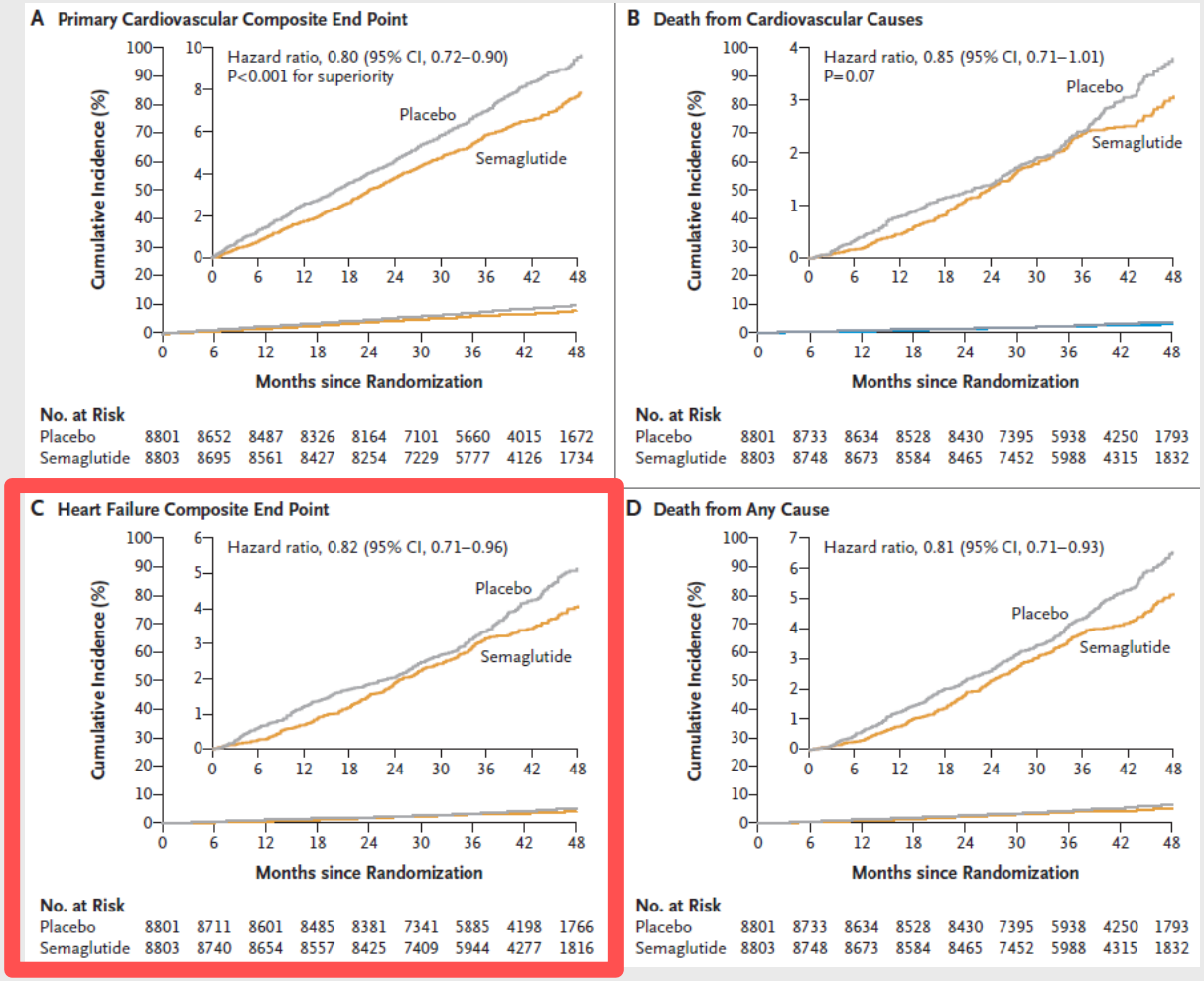

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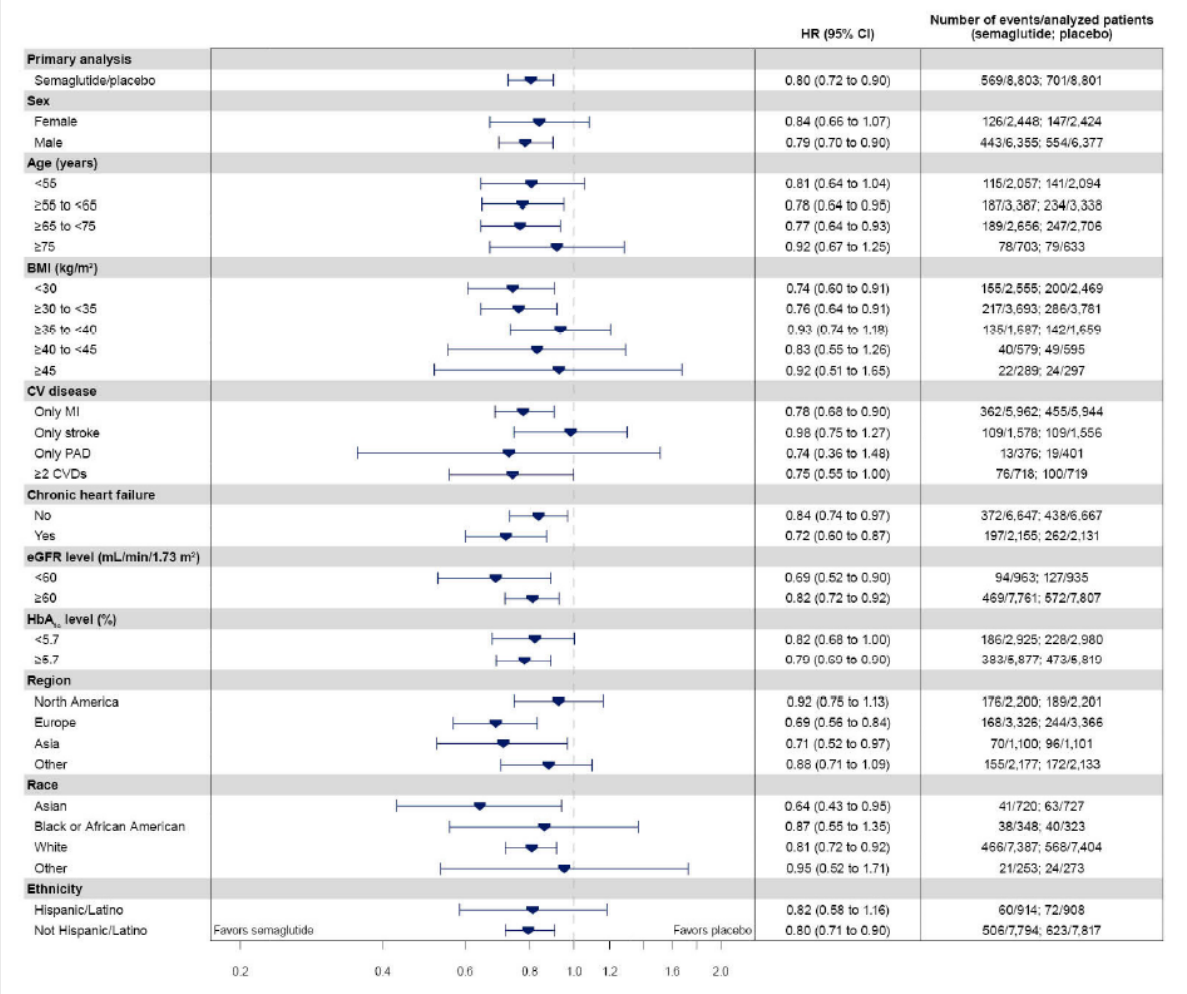

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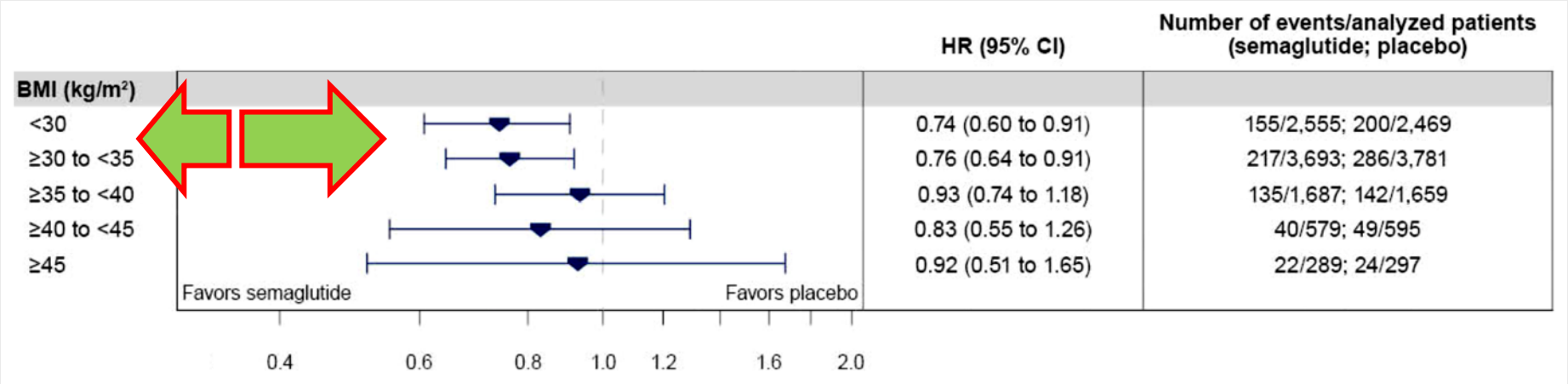

State of the Art - Herzinsuffizienz

- **Behandlung HFmrEF und HFpEF mit SGLT2i nun Class I**
- **Prävention der HF DM and CKD bei DM mit SGLT2i und Finerenon**
- **Empfehlungen zum Behandlungsbeginn in der Klinik und der intensiven Nachsorge Class IB**
- **Eisenmangel immer diagnostizieren (IA), auch therapieren**
- **Reduktion der Hospitalisierung IIaA**
- **GLP Agonisten HF Therapie und HI Prävention?**

Literatur 1/2

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

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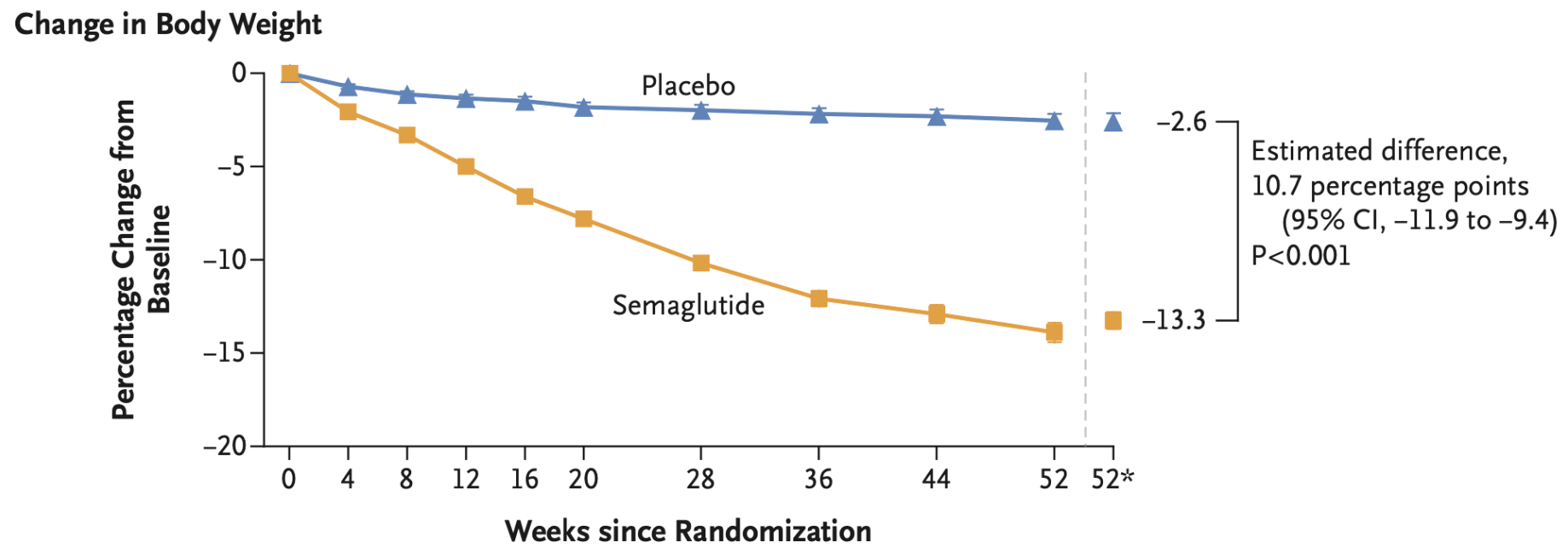
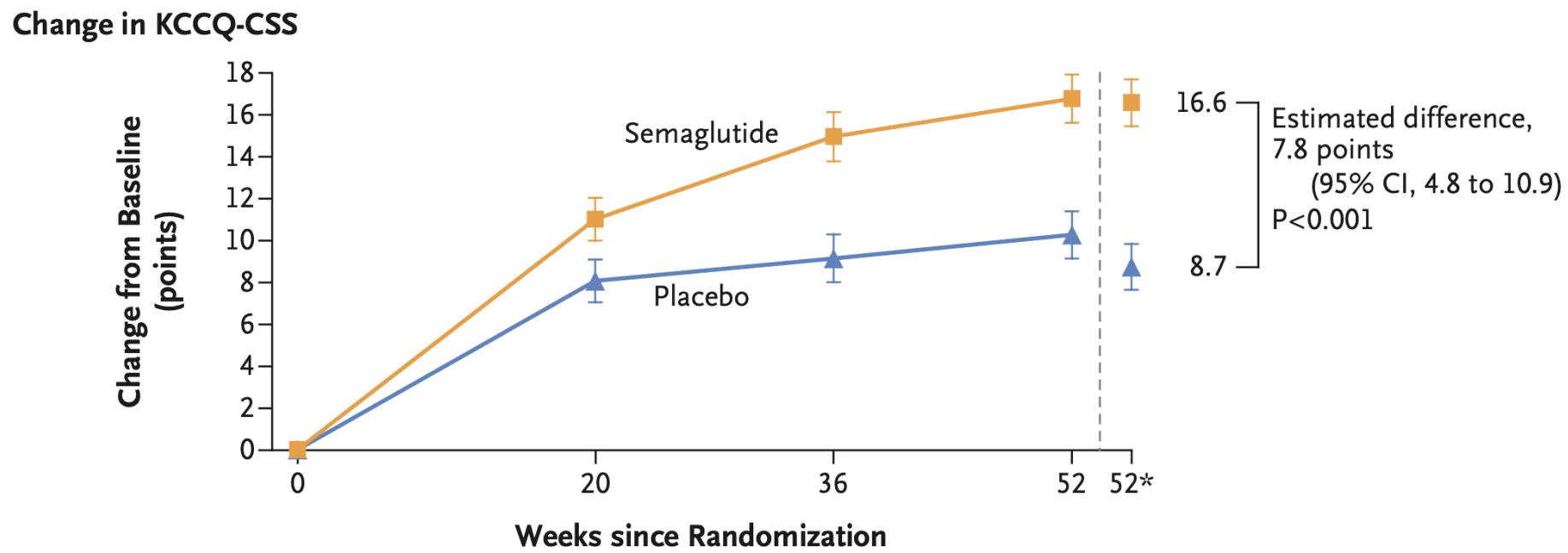


No. of Participants

Semaglutide	263	255	254	250	246	252	239	243	240	246	263
Placebo	266	259	249	250	243	246	243	239	233	242	266

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

Kosiborod et al, N Engl J Med 389 (2023): 1069-1084

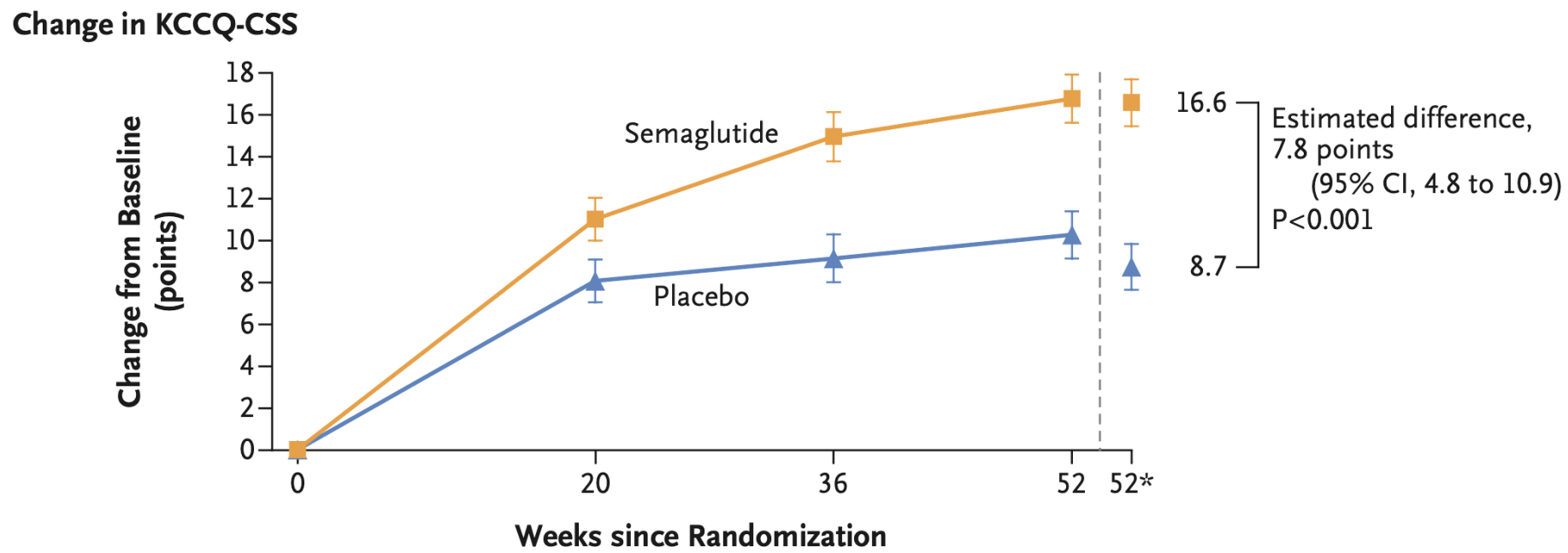


No. of Participants

Semaglutide	263	249	225	243	263
Placebo	266	242	217	237	266

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

Kosiborod et al, N Engl J Med 389 (2023): 1069-1084



No. of Participants

Semaglutide	263	249	225	243	263
Placebo	266	242	217	237	266