



UNIVERSITÄTS
KLINIKUM
HEIDELBERG



HERZ ZENTRUM
Universitätsklinikum Heidelberg

48. Nephrologisches Seminar

Aktuelle Therapie der Herzinsuffizienz

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ESC

European Society
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ESC GUIDELINES

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





Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

With the special contribution of the Heart Failure Association (HFA) of the ESC

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

Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

With the special contribution of the Heart Failure Association (HFA) of the ESC

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2023 “Focused update” der 2021 ESC Leitlinien zur Herzinsuffizienz

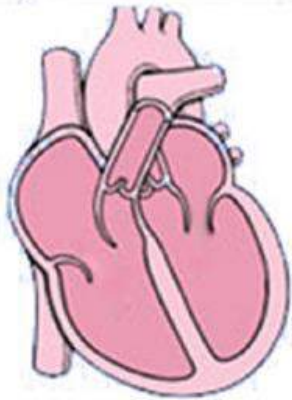
- Since the publication of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure there have been several randomized controlled trials that should change patient management ahead of the next scheduled full guideline
- The task force considered major RCTs and meta-analyses published **between 31st March 2021 and 31st March 2023**
- New recommendations are additive to, and changed recommendations substitute, those of the 2021 Guideline

Updated the following sections:

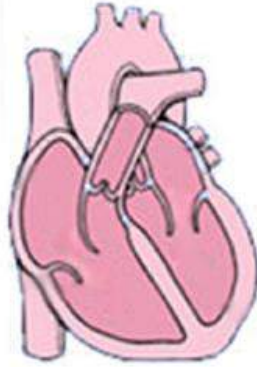
- Chronic HF
 - HF with mildly reduced ejection fraction (HFmrEF)
 - HF with preserved ejection fraction (HFpEF)
- Acute HF
- Comorbidities and prevention of HF

ADVOR
 CLOROTIC
 COACH
 DAPA-CKD
 DELIVER
 EMPA-KIDNEY
 EMPEROR-Preserved
 EMPULSE
 FIDELIO-DKD
 FIGARO-DKD
 IRONMAN
 PIVOTAL
 REVIVED-BCIS2
 STRONG-HF
 TRANSFORM-HF
 TRILUMINATE Pivotal

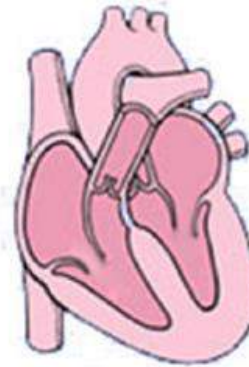
Medikamentöse Therapie der Herzinsuffizienz



HFrEF
(LVEF < 40%)



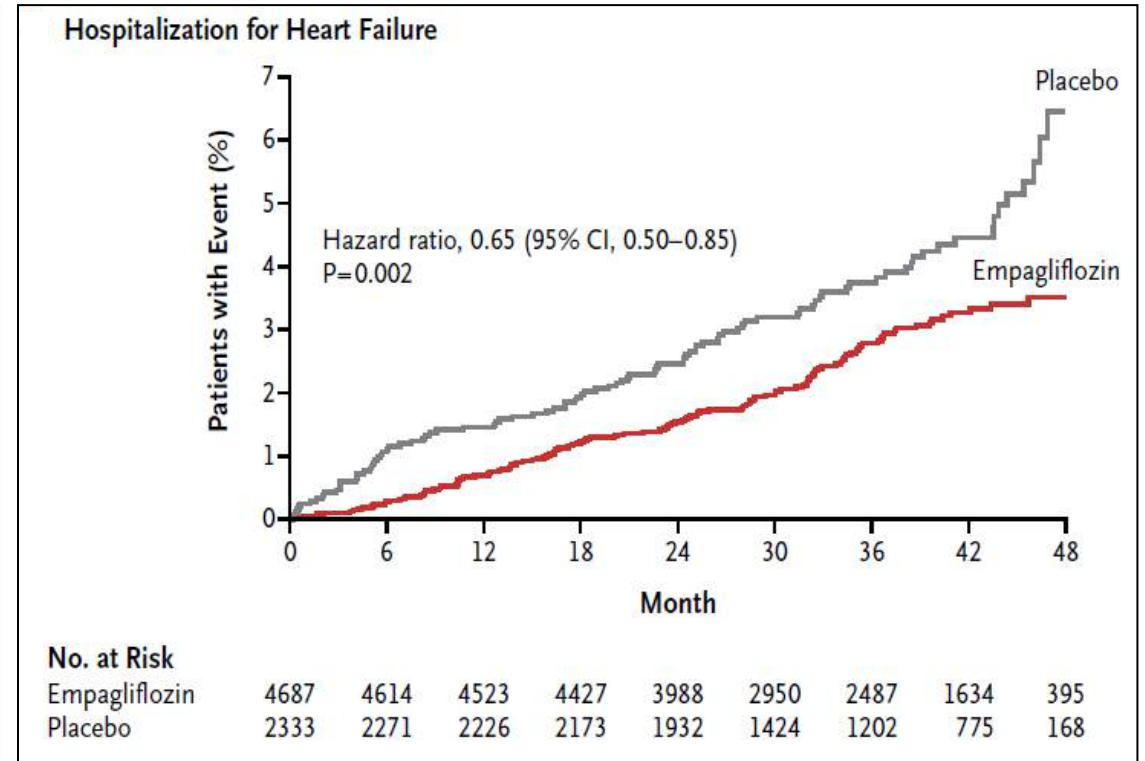
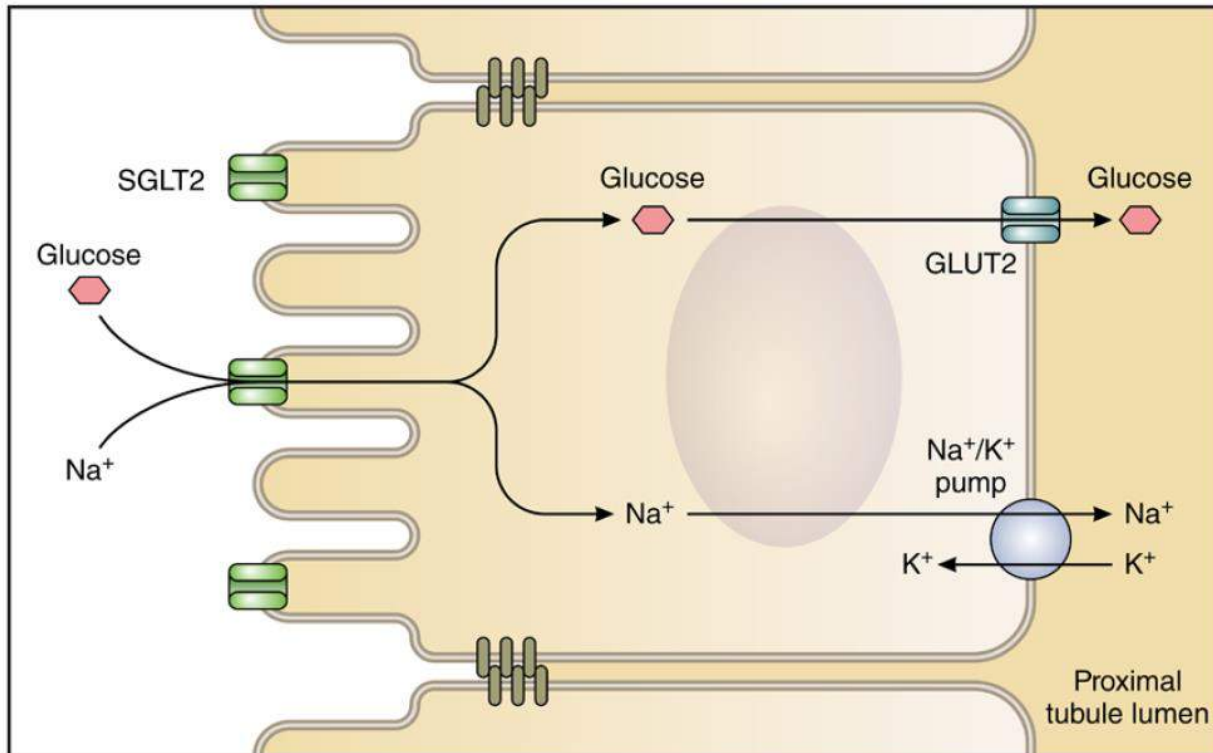
HFmrEF
(LVEF 40-49%)



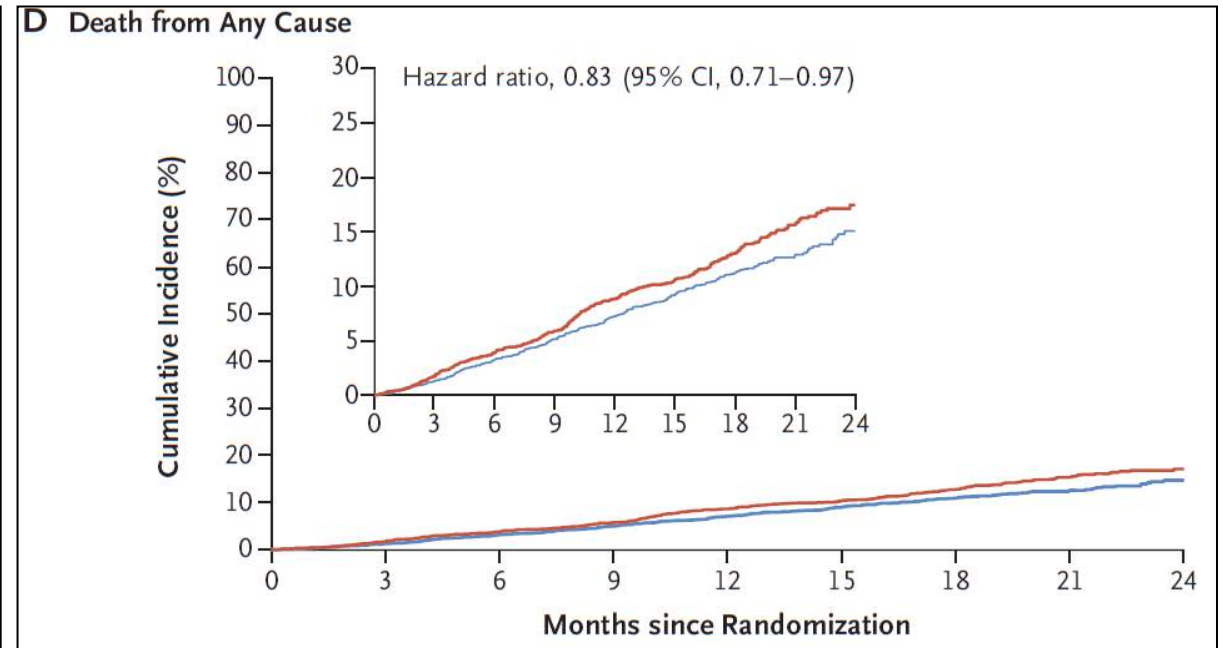
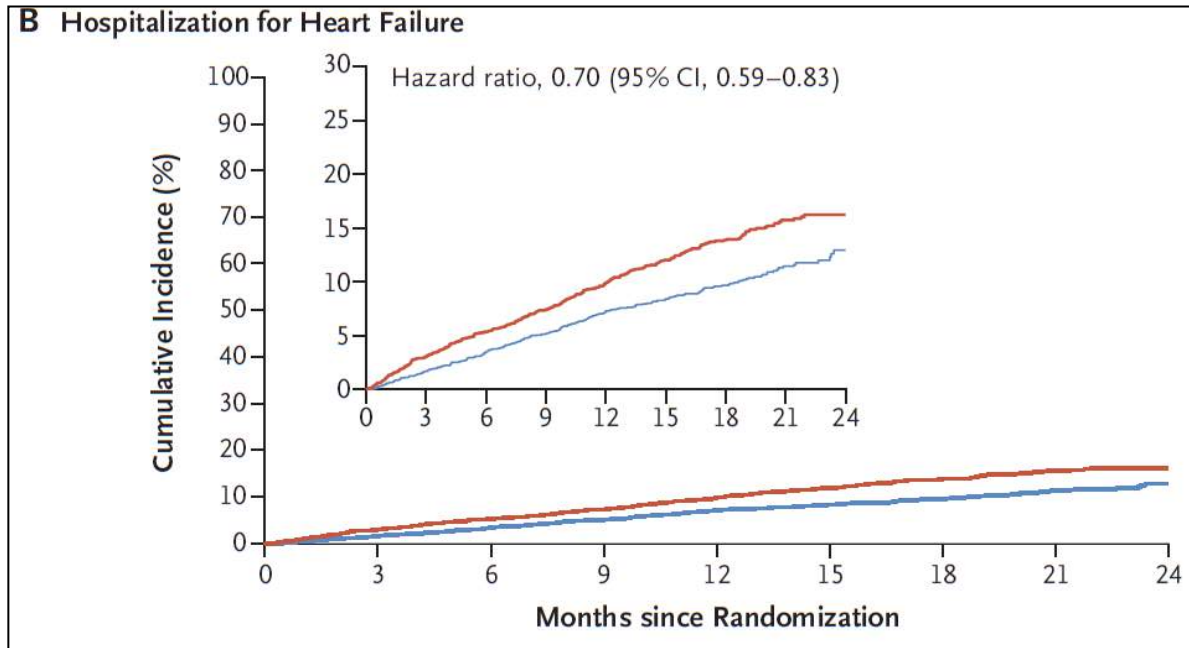
HFpEF
(LVEF ≥ 50%)

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs ^a	Symptoms ± Signs ^a	Symptoms ± Signs ^a
	2	LVEF ≤ 40%	LVEF 41 – 49% ^b	LVEF ≥ 50%
	3	—	—	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides ^c

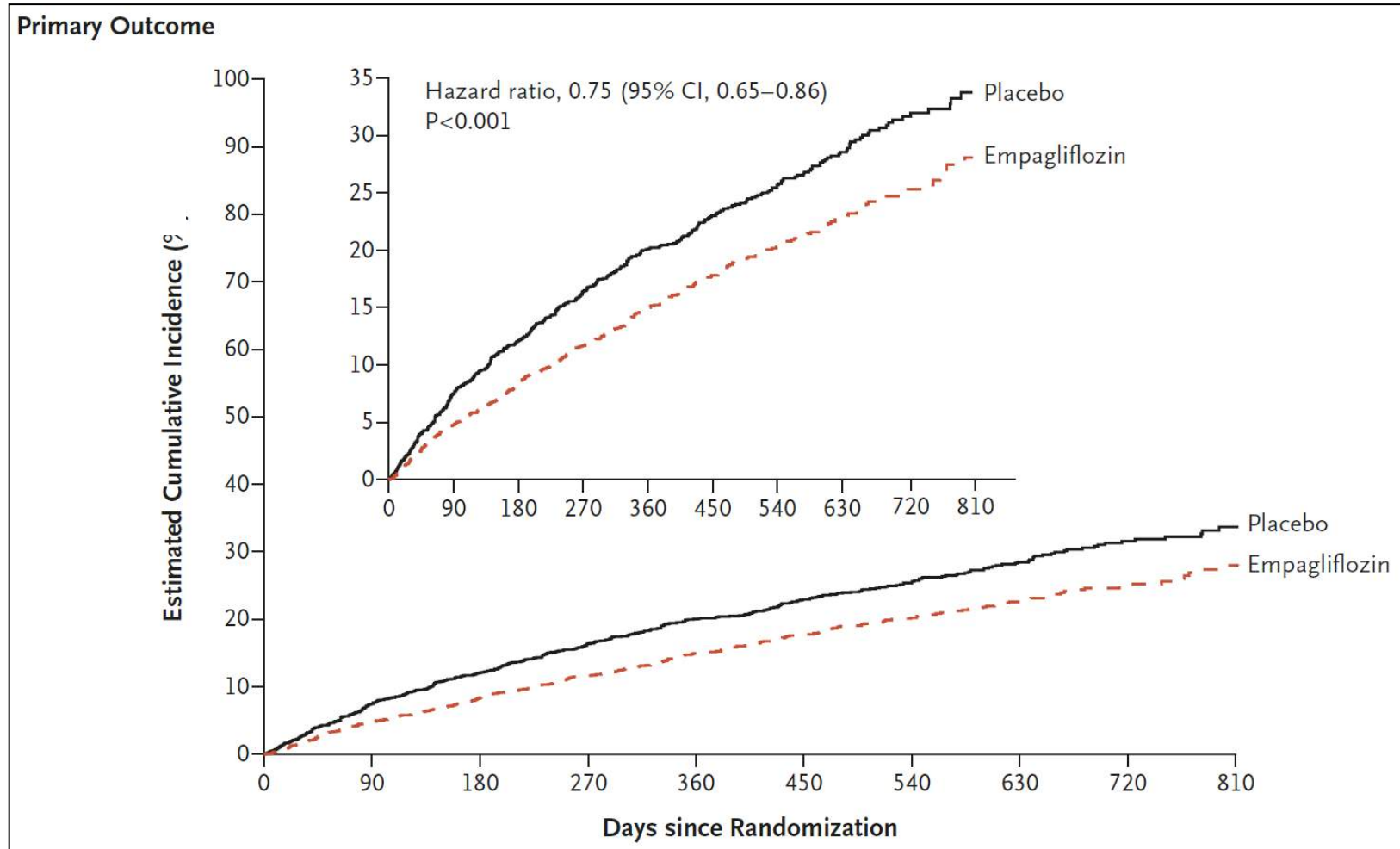
SGLT2-Hemmer und Herzinsuffizienz



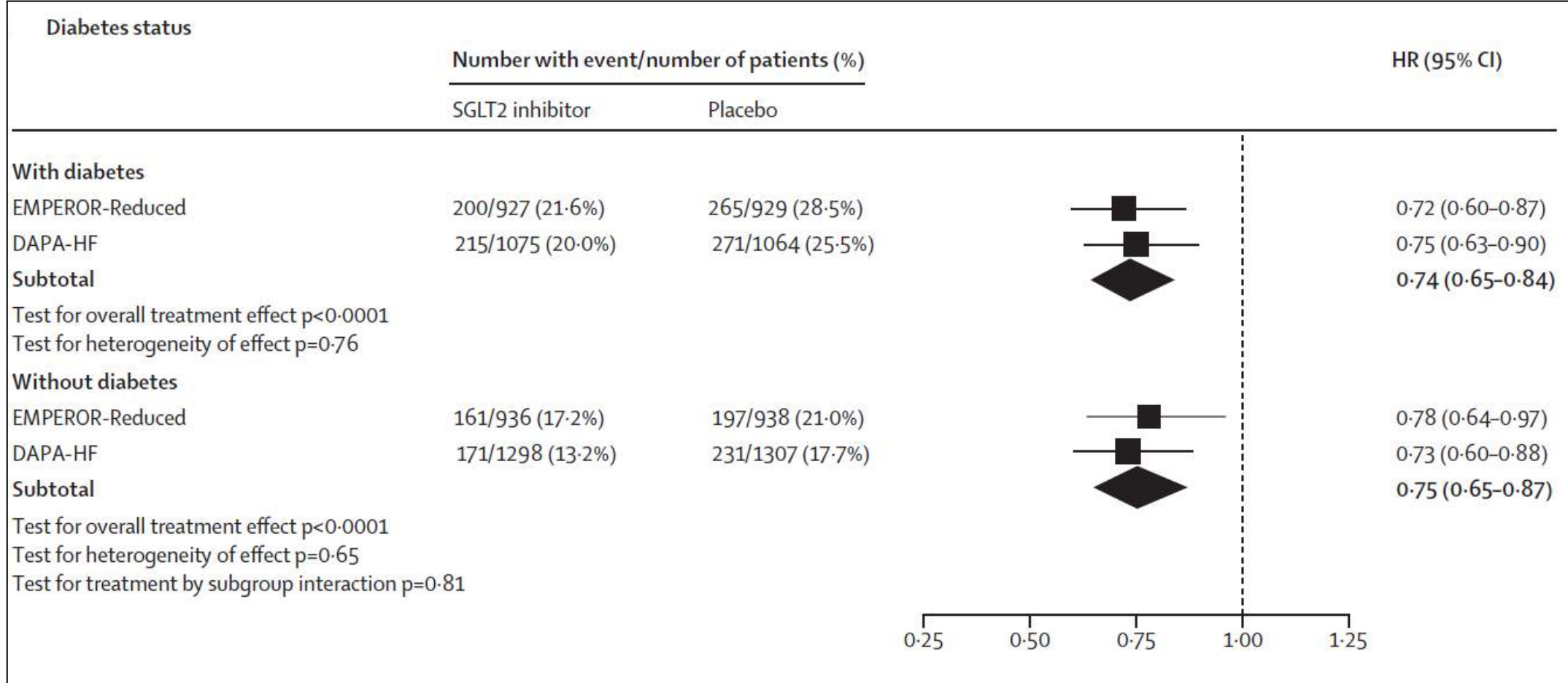
DAPA-HF: Dapagliflozin bei Herzinsuffizienz (HFrEF)



EMPEROR-Reduced: Empagliflozin bei Herzinsuffizienz (HFrEF)



Meta-Analyse SGLT2 Hemmer bei Herzinsuffizienz (HFrEF): Diabetes ja/nein



Therapie der Herzinsuffizienz (HFrEF): Basistherapie zur Mortalitätsreduktion

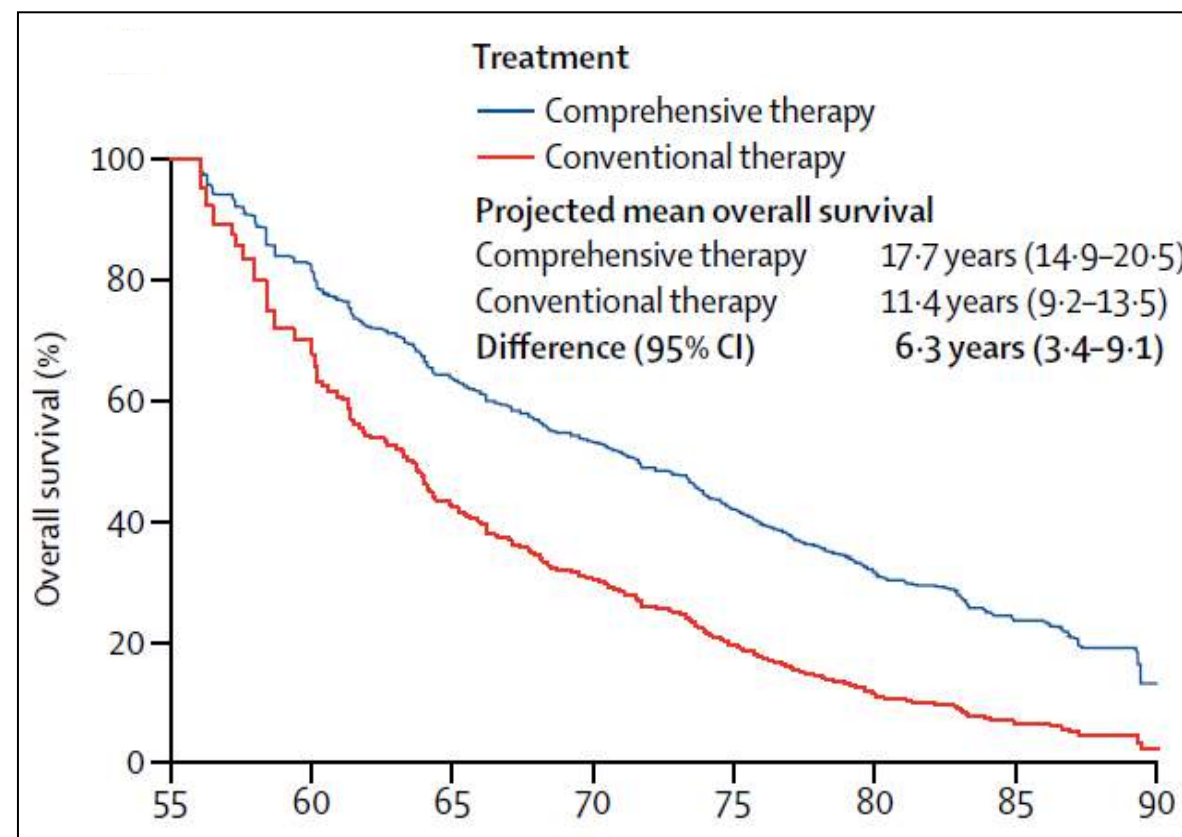


Pharmacological treatments indicated in patients with (NYHA class II–IV) heart failure with reduced ejection fraction (LVEF ≤40%)

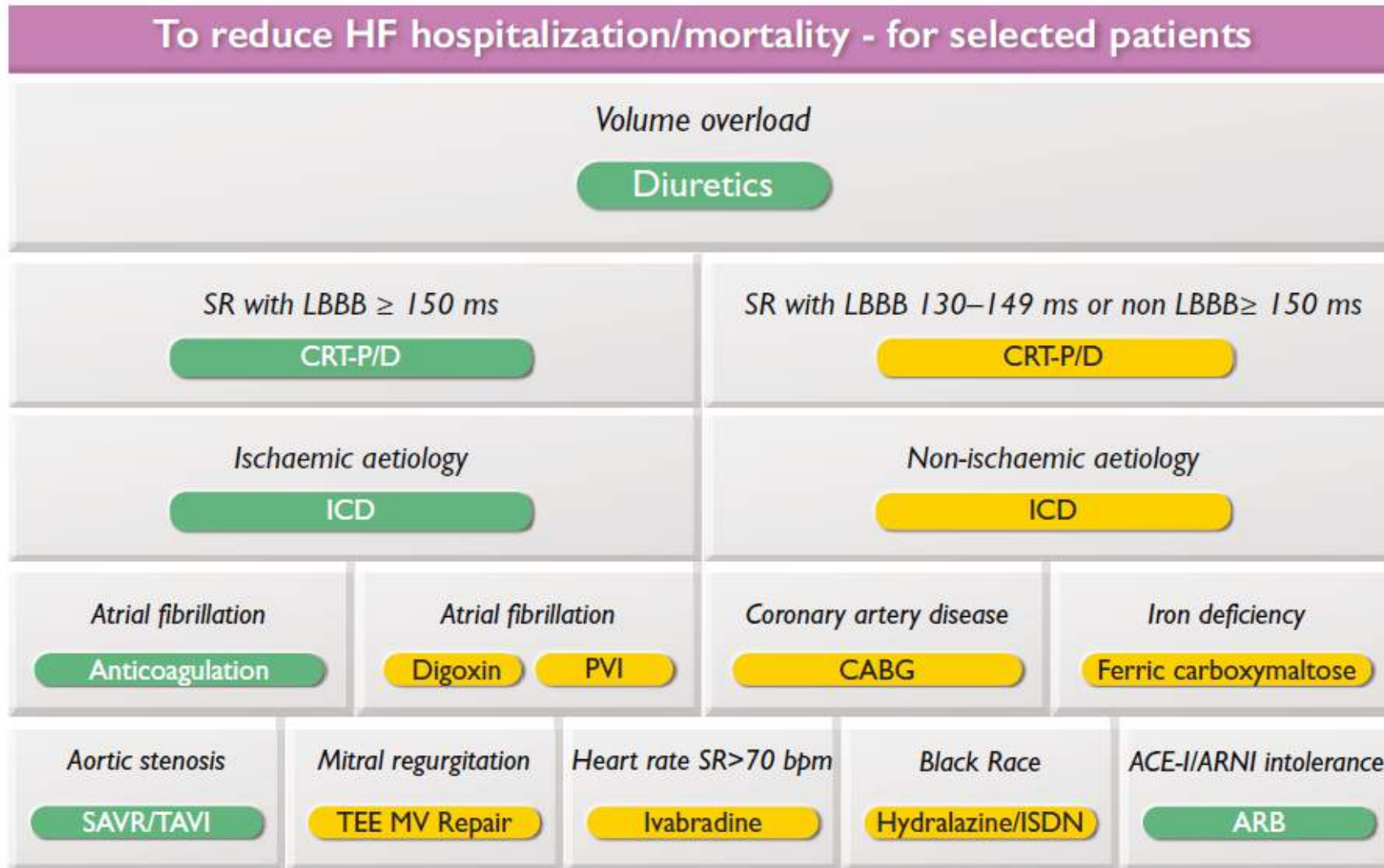
Recommendations	Class ^a	Level ^b
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. ^{110–113}	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death. ^{114–120}	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. ^{121,122}	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. ^{108,109}	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death. ¹⁰⁵	I	B

„Moderne“ Therapie vs. Standard (ACEi und BB) bei HFrEF

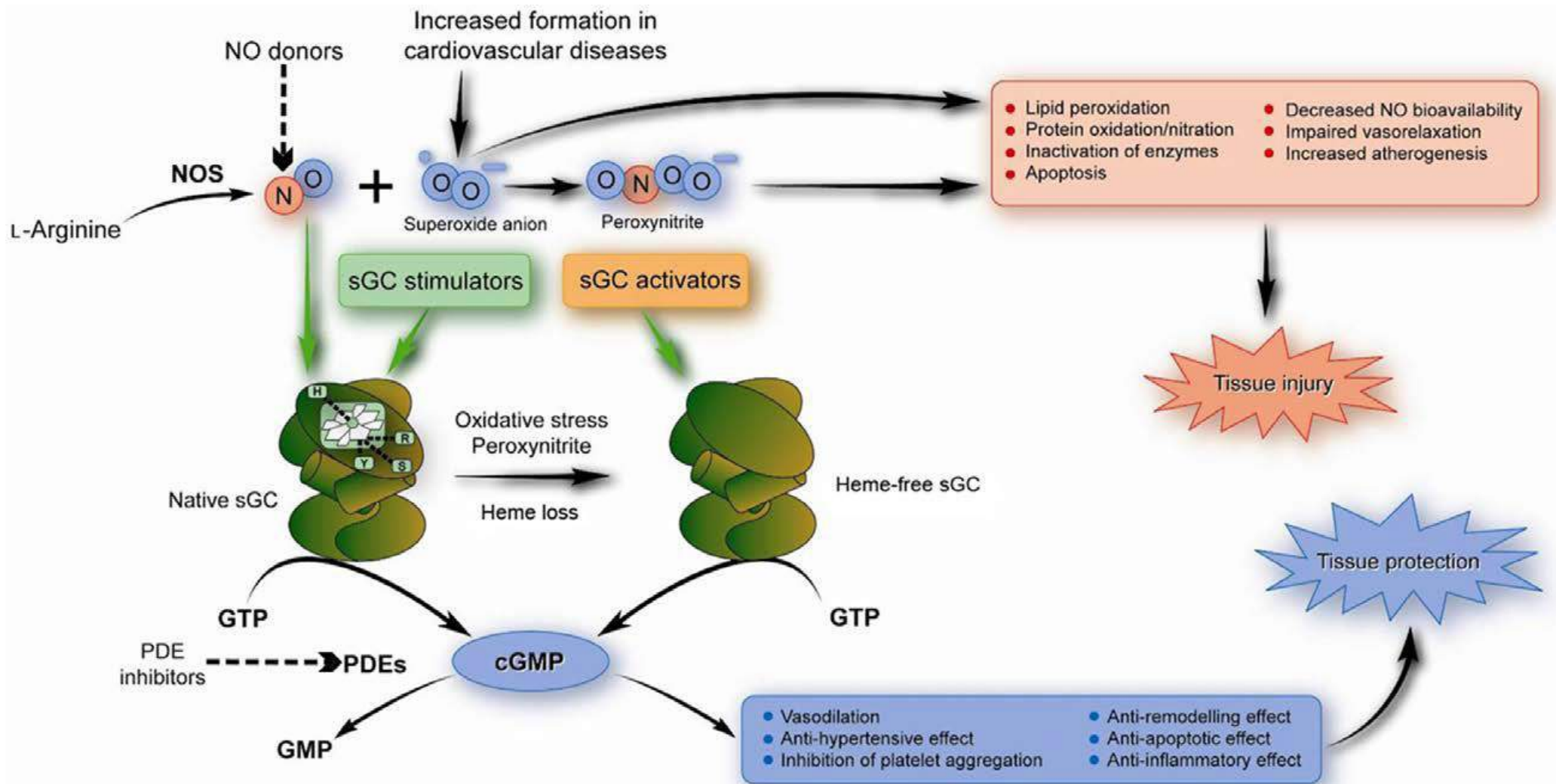
	EMPHASIS-HF ⁶ (n=2737)	PARADIGM-HF ⁹ (n=8399)	DAPA-HF ⁸ (n=4744)
Comparison	Eplerenone vs placebo	Sacubitril-valsartan vs enalapril	Dapagliflozin vs placebo
Enrolment period	2006–10	2009–12	2017–18
Median follow-up, months	21 (10–33)	27 (19–36)	18 (13–21)
Age, years	69 (8)	64 (11)	66 (11)
Sex			
Men	2127 (78%)	6567 (78%)	3635 (77%)
Women	610 (22%)	1832 (22%)	1109 (23%)
Systolic blood pressure, mm Hg	124 (17)	121 (15)	122 (16)
Heart rate, beats per min	72 (13)	72 (12)	72 (12)
Left ventricular ejection fraction, %	26 (5)	30 (6)	31 (7)
New York Heart Association class			
1	0	389 (5%)	0
2	2737 (100%)	5919 (70%)	3203 (68%)
3	0	2018 (24%)	1498 (32%)
4	0	60 (1%)	43 (1%)
Atrial fibrillation	844 (31%)	3091 (37%)	1818 (38%)
Diabetes	859 (31%)	2907 (35%)	1983 (42%)
Previous hospital admission for heart failure	1440 (53%)	5274 (63%)	2251 (47%)



Therapie der Herzinsuffizienz (HFrEF): Individualisierte Therapie



sGC-Stimulation bei Herzinsuffizienz ?



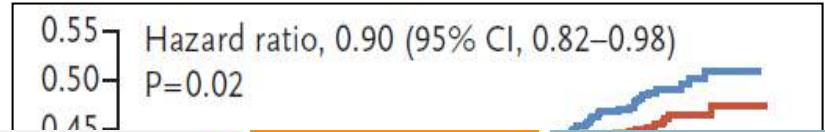
VICTORIA: sGC-Aktivator Vericiguat bei HFrEF

N=5050
 Patienten mit sich verschlechterter Herzinsuffizienz

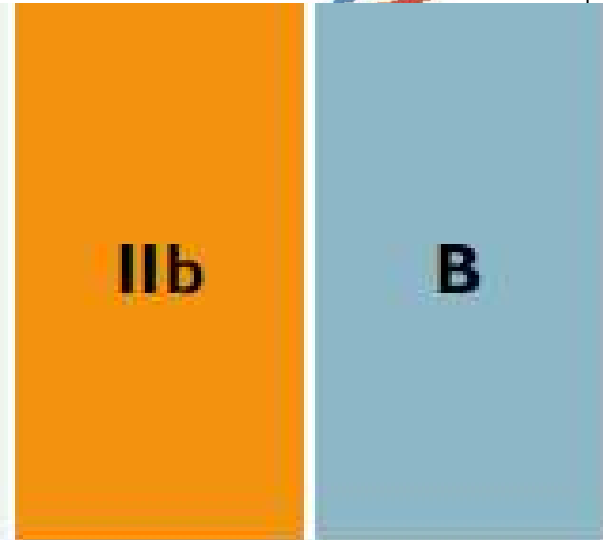
- EF <45%
- NYHA II-IV
- Vorheriger Krankenhausaufenthalt wegen HF
- Gabe i.v. Diuretika
- Erhöhter NT-proBNP
- SBP ≥100 mmHg
- eGFR ≥15 ml/min/1,73 m²

Primärer Endpunkt: bestehend aus KV-Tod oder Krankenhausaufenthalt wegen HF

Sekundäre Endpunkte:

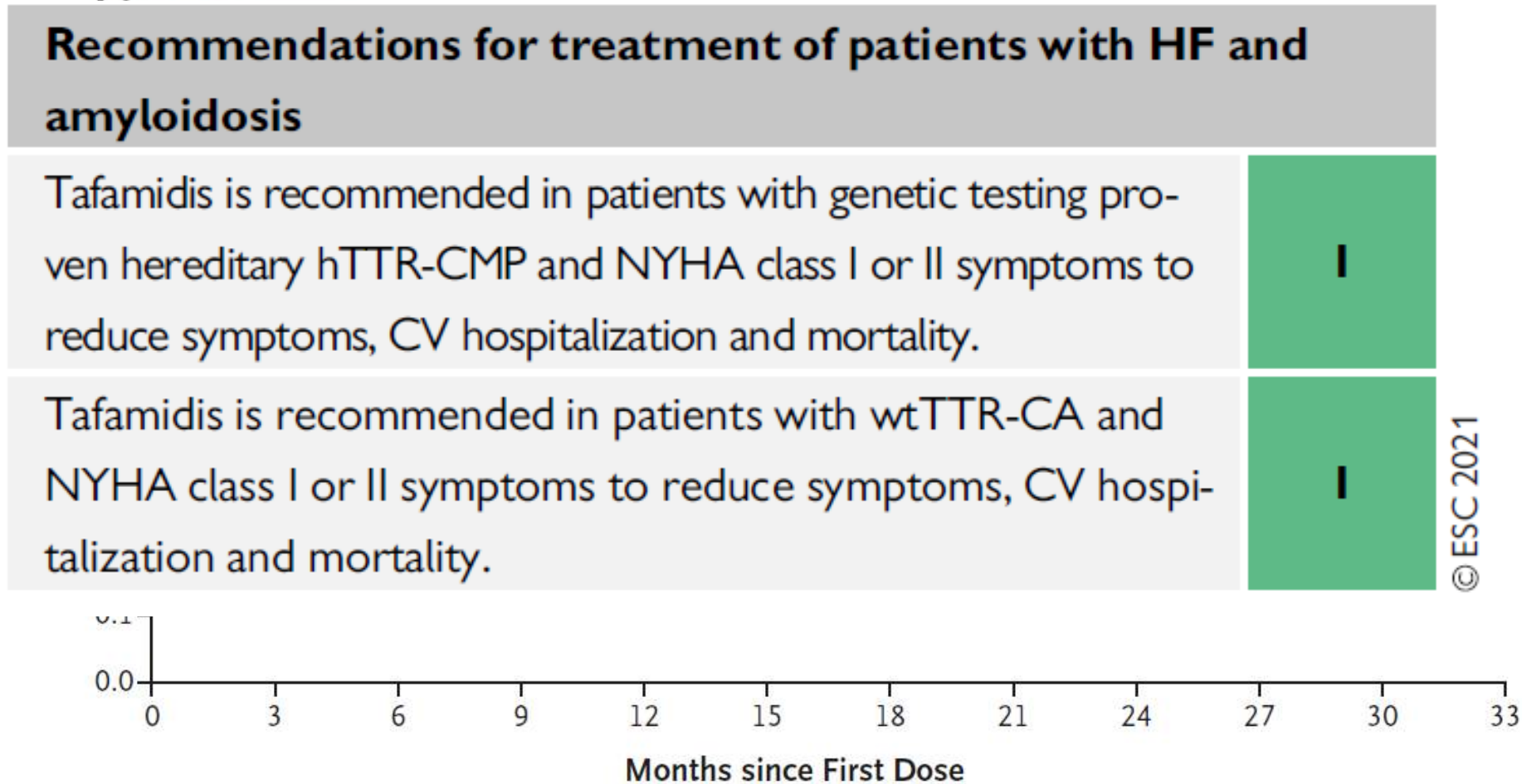


Vericiguat may be considered in patients in NYHA class II–IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization.¹⁴¹



Tafamidis bei Herzinsuffizienz durch ATTR-Amyloidose: ATTR-ACT

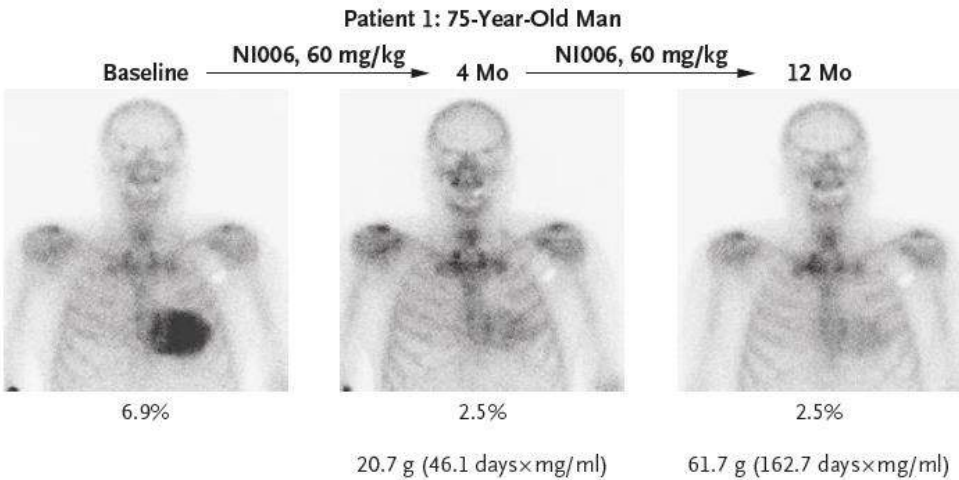
Analysis of All-Cause Mortality



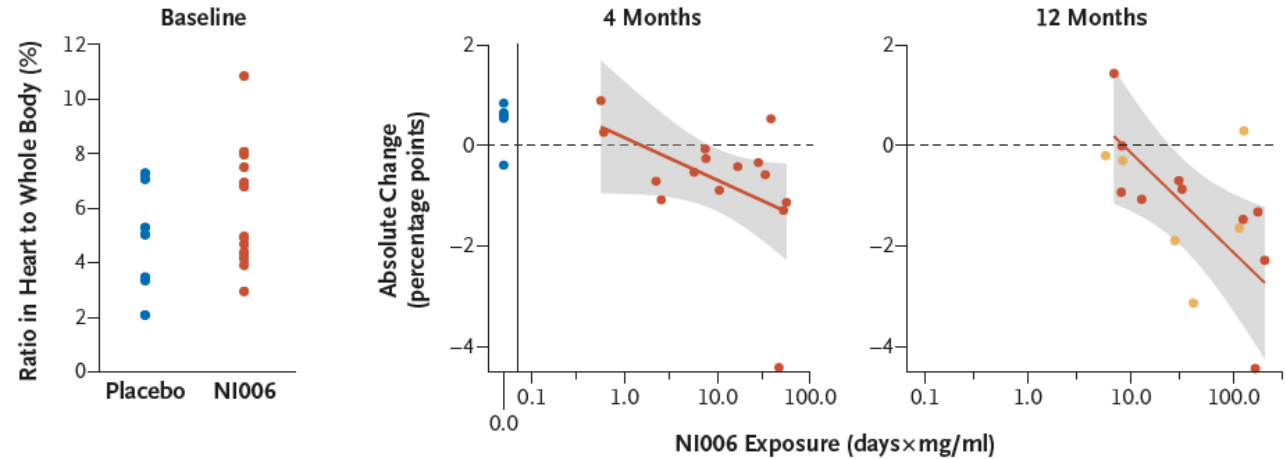
Kardiale ATTR-Amyloidose: Reversibel durch Antikörper-Therapie ?

Phase 1 Trial of Antibody NI006 for Depletion of Cardiac Transthyretin Amyloid

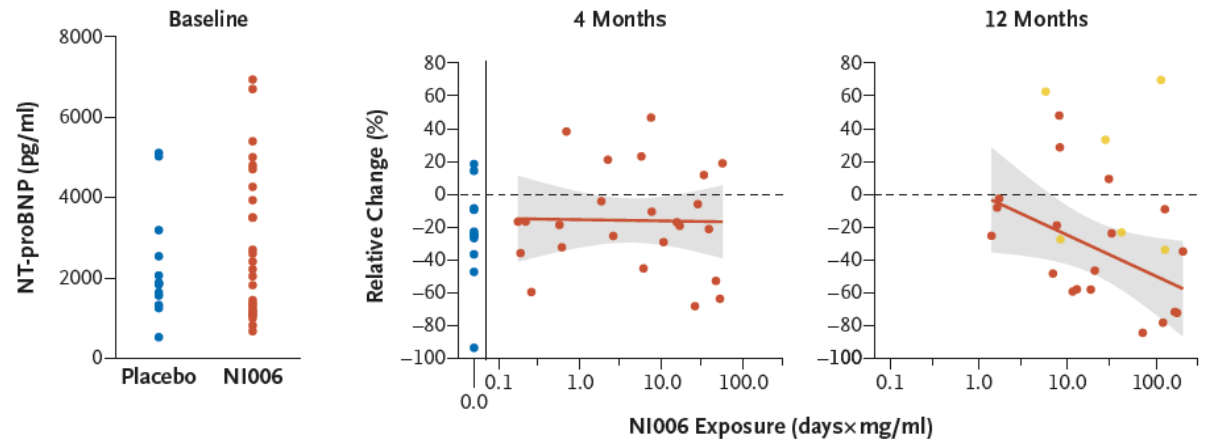
Pablo Garcia-Pavia, M.D., Ph.D., Fabian aus dem Siepen, M.D.,
Erwan Donal, M.D., Ph.D., Olivier Lairez, M.D., Peter van der Meer, M.D., Ph.D.,
Arnt V. Kristen, M.D., Michele F. Mercuri, M.D., Ph.D., Aubin Michalon, Ph.D.,
Robert J.A. Frost, M.D., Ph.D., Jan Grimm, Ph.D., Roger M. Nitsch, M.D.,
Christoph Hock, M.D., Peter C. Kahr, M.D., and Thibaud Damy, M.D., Ph.D.



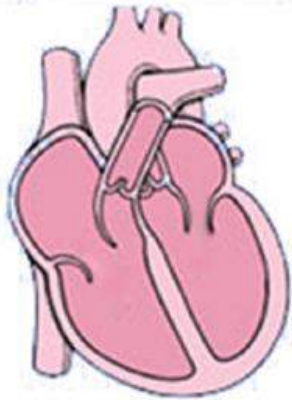
Cardiac Tracer Uptake on Scintigraphy



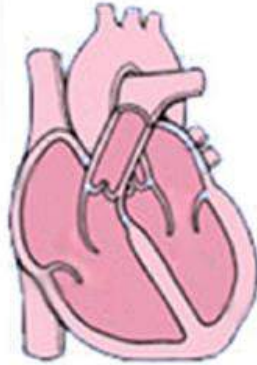
NT-proBNP Level



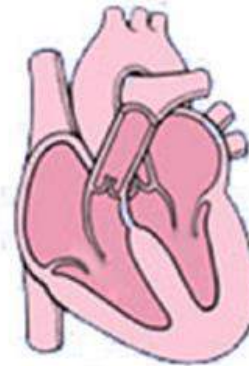
Medikamentöse Therapie der Herzinsuffizienz



HFrEF
(LVEF < 40%)



HFmrEF
(LVEF 40-49%)



HFpEF
(LVEF ≥ 50%)

Type of HF	HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs ^a	Symptoms ± Signs ^a
	2	LVEF ≤ 40%	LVEF ≥ 50%
	3	—	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides ^c

Empagliflozin bei HFmrEF/HFpEF ?

- EMPEROR-Preserved -

EMPEROR-Preserved

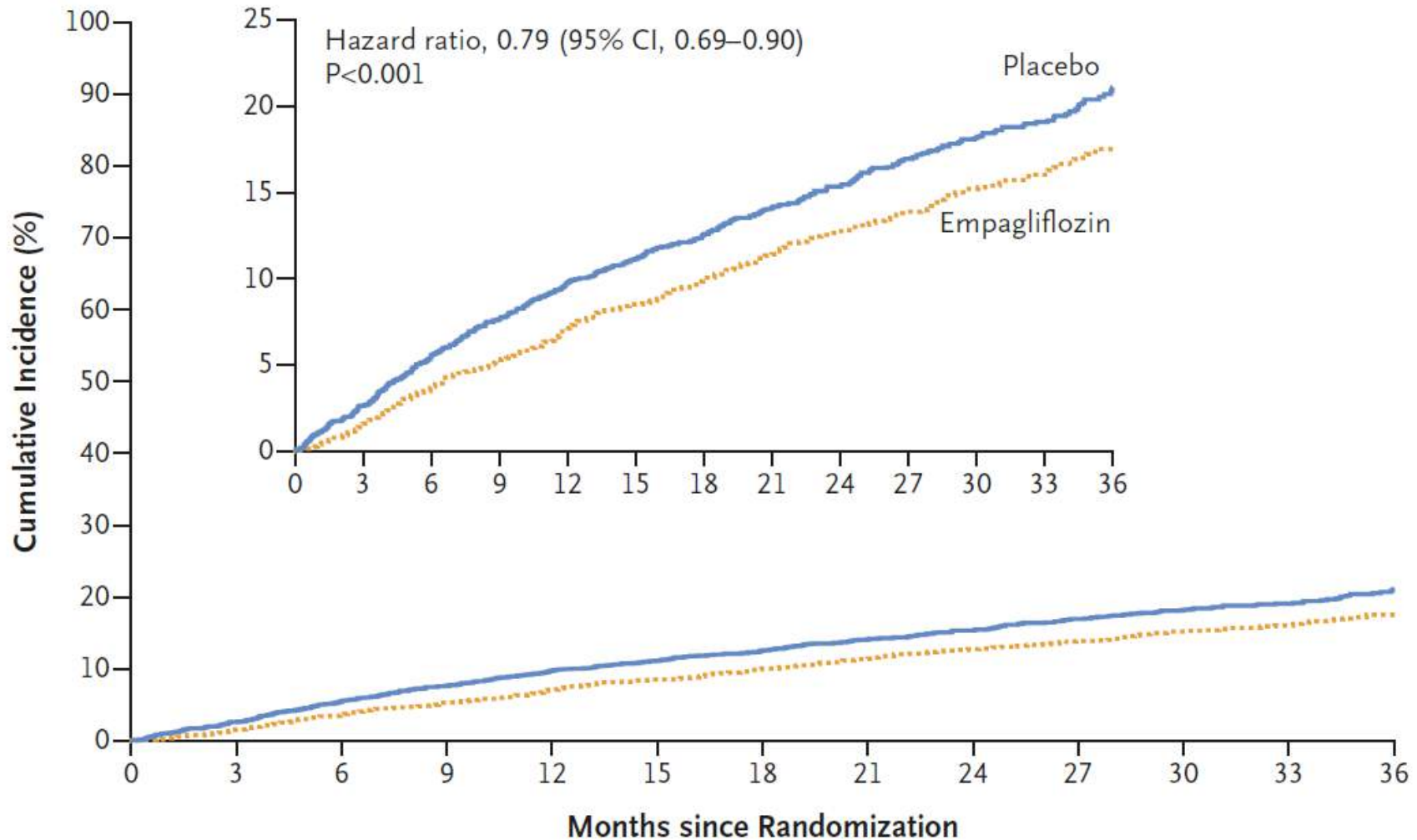
Phase III randomised double-blind placebo-controlled event driven trial

Key Inclusion Criteria: T2D and non-T2D, aged ≥ 18 years, chronic HF (NYHA class II–IV) with LVEF $> 40\%$, elevated NT-proBNP concentrations and structural heart changes or documented HHF within 12 months.

Key Exclusion Criteria: Symptomatic hypotension and eGFR < 20 mL/min/1.73m².



EMPEROR-PRESERVED: sGLT2-Hemmer bei HFpEF

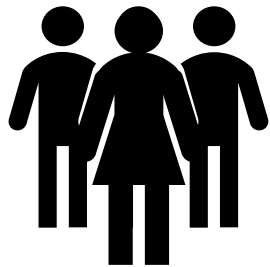


DELIVER Studie

Eligibility Criteria

- Age \geq 40 years
- NYHA class II-IV
- LVEF $>$ 40% (including prior LVEF \leq 40%)
- Structural Heart Disease (LVH or LA Enlargement)
- Elevated Natriuretic Peptides ($>$ 300 pg/ml or 600 pg/ml in AFF)
- Either Ambulatory or Hospitalized for Heart Failure

Double-blind
Treatment period

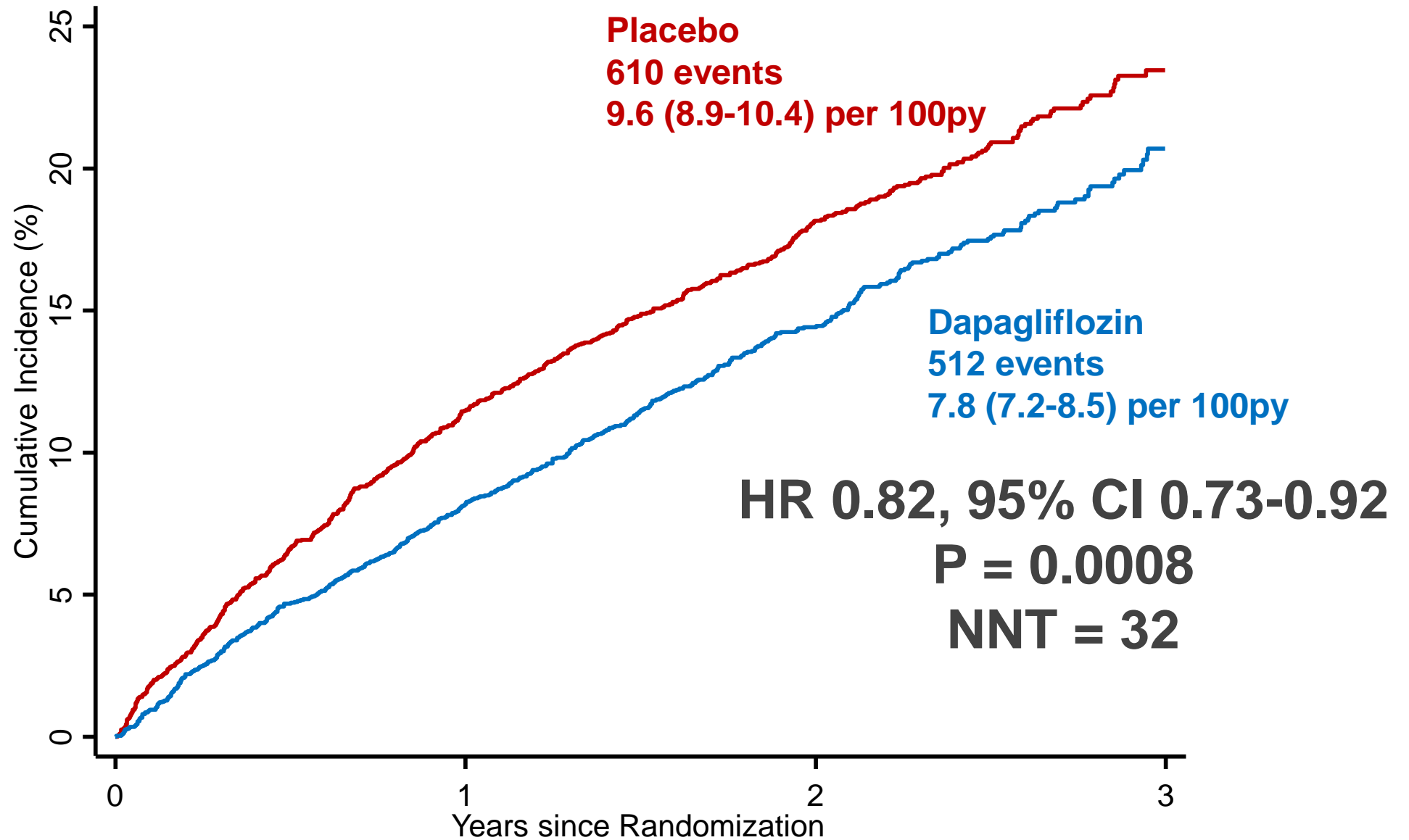


Dapagliflozin 10mg once daily

Event Driven (1117 estimated events)

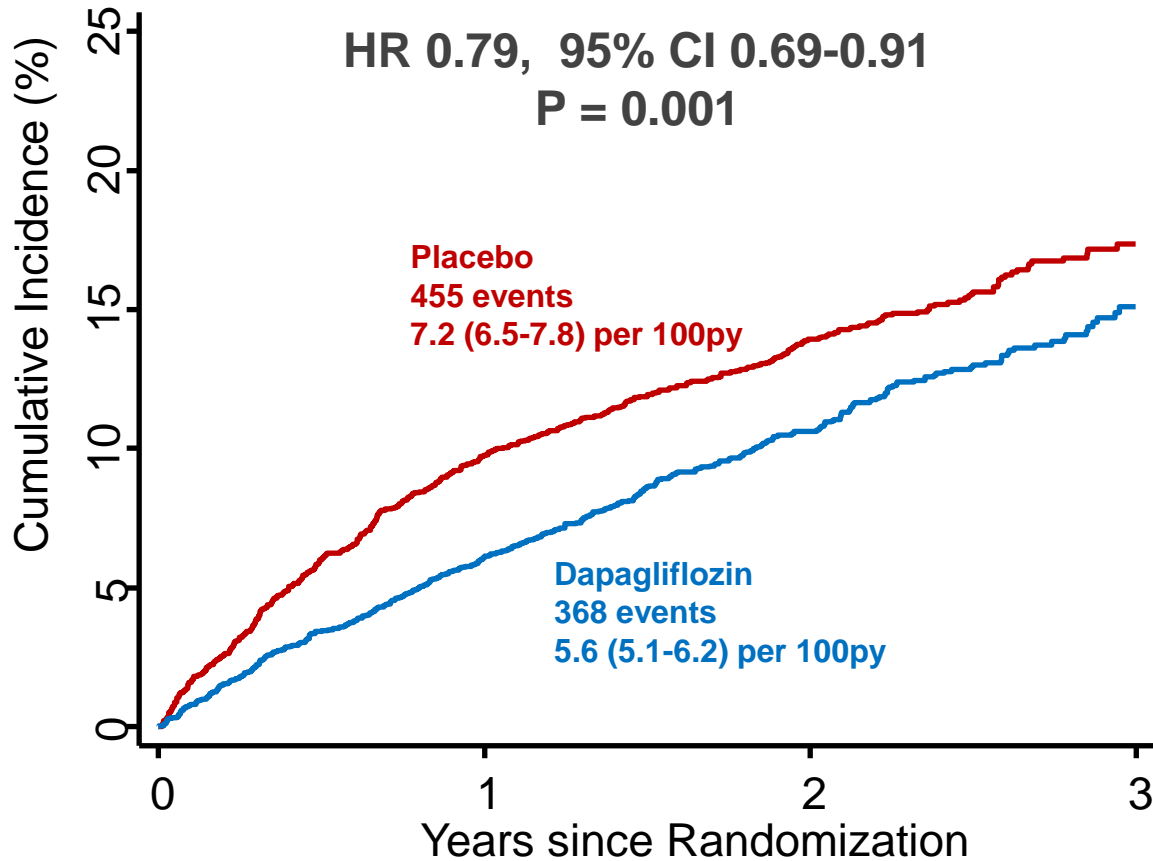
Placebo

Primärer Endpunkt: CV Death/Worsening HF

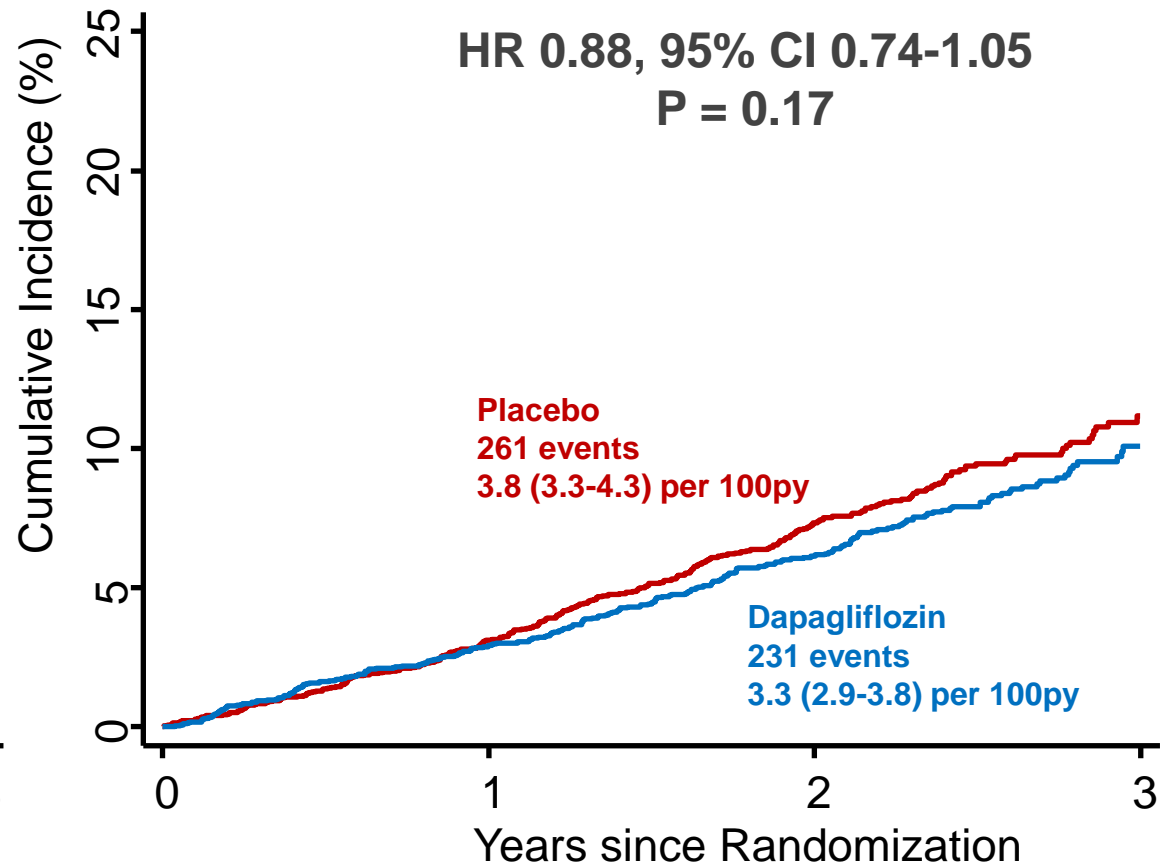


DELIVER: Komponenten des primären Endpunktes

Worsening Heart Failure (HF Hospitalization + Urgent HF Visit)



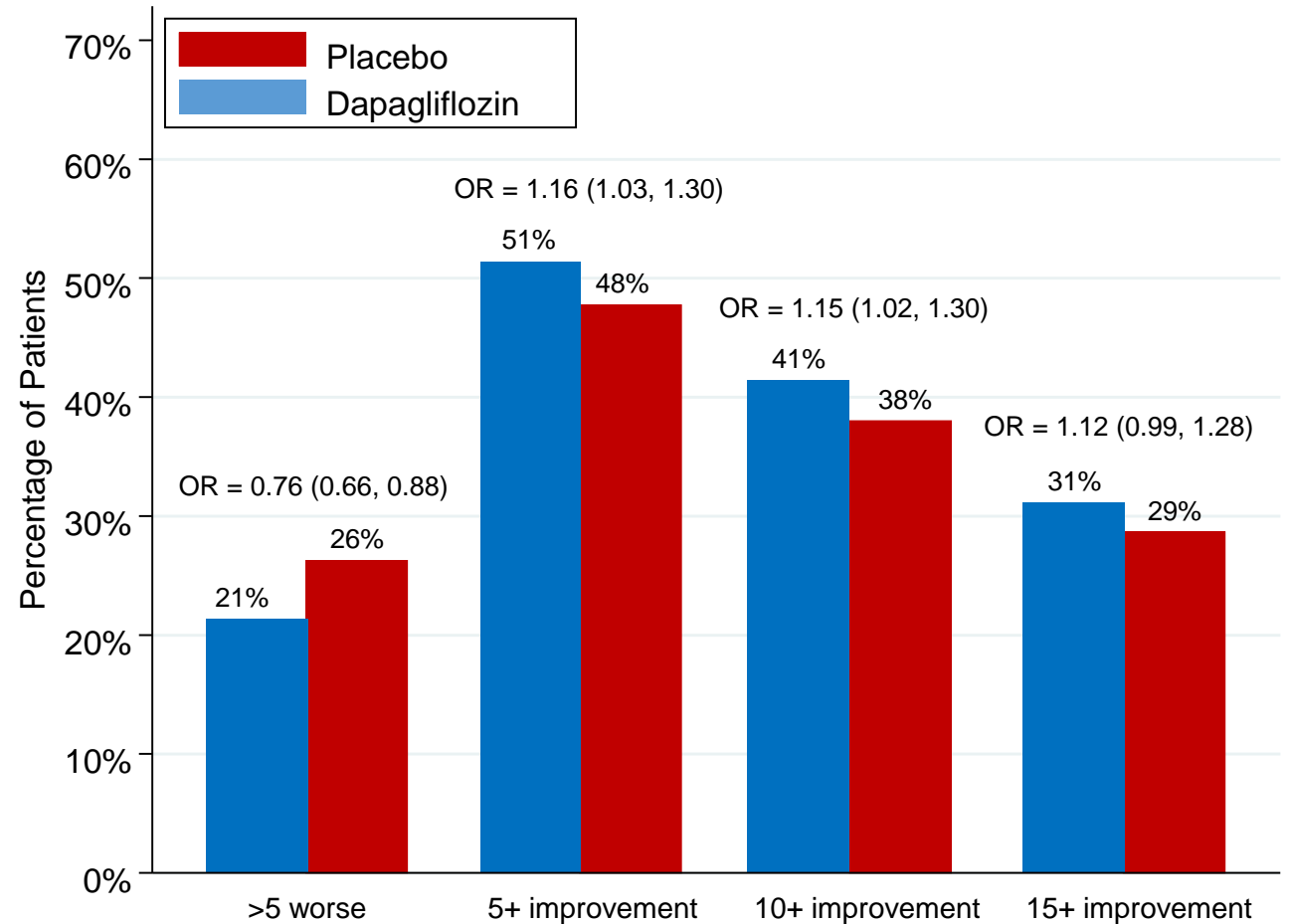
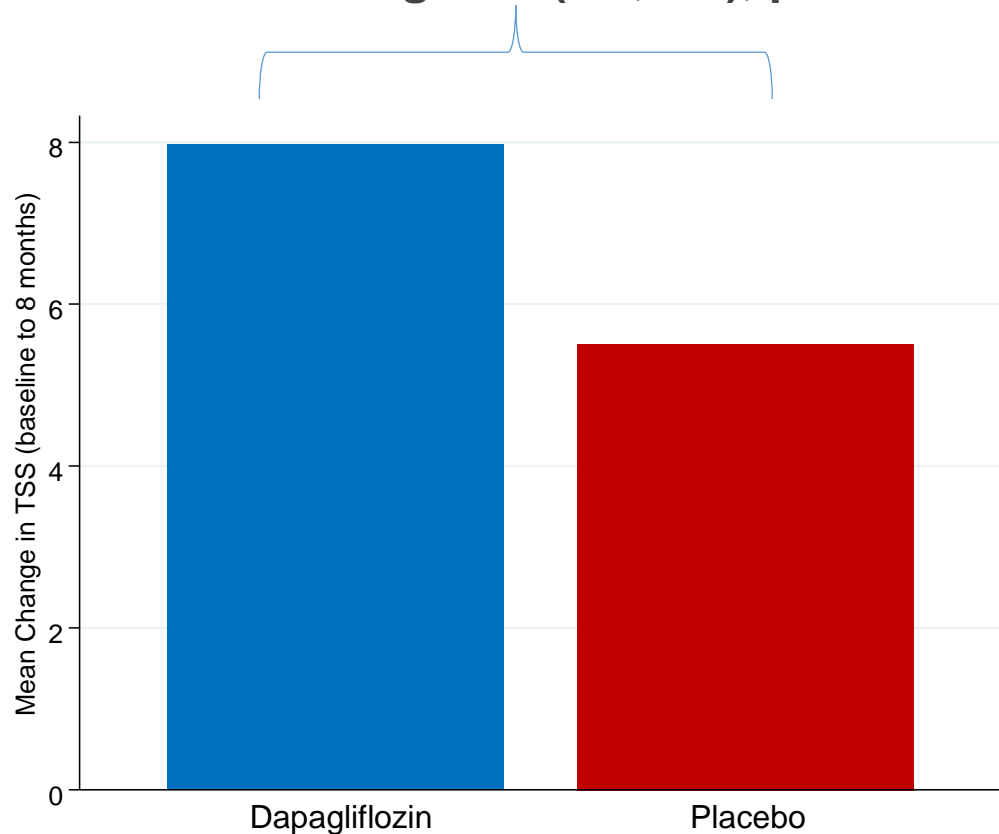
Cardiovascular Death



Klinische Verbesserung: KCCQ Total Symptom Score

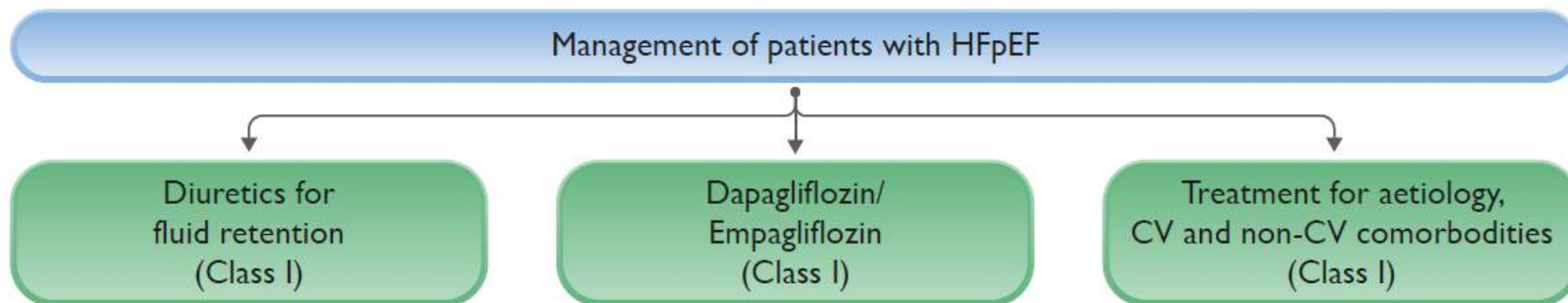
Win Ratio* 1.11 (1.03, 1.21), p = 0.009

Mean Change 2.4 (1.5, 3.4), p < 0.001



*Primary Analysis Method in patients who reached 8 months prior to COVID-19 Pandemic

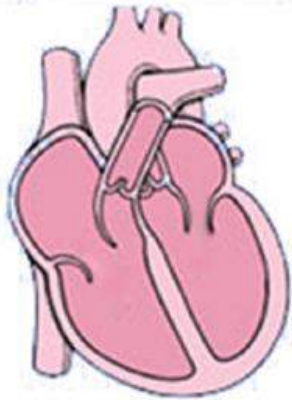
ESC Leitlinien 2023: Therapie der Herzinsuffizienz (HFpEF)



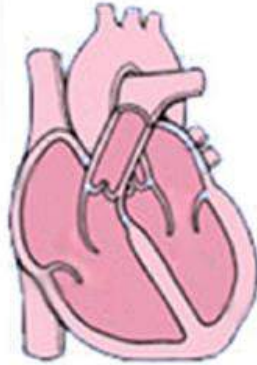
Recommendation	Class ^a	Level ^b
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFpEF to reduce the risk of HF hospitalization or CV death. ^{c 6,8}	I	A

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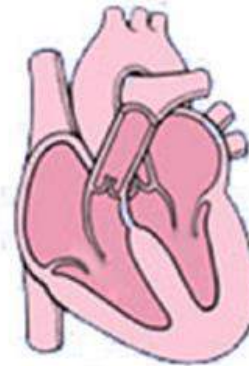
Medikamentöse Therapie der Herzinsuffizienz



HFrEF
(LVEF < 40%)



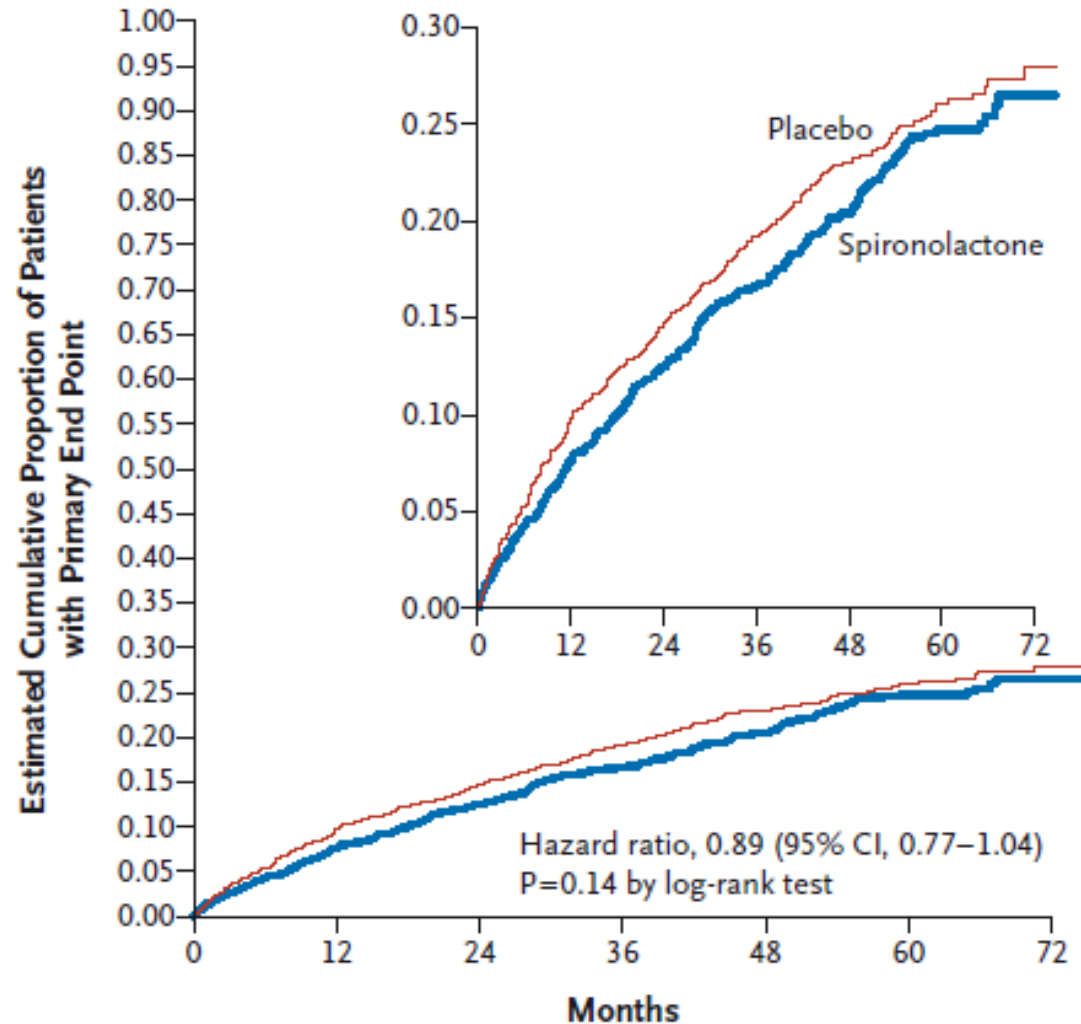
HFmrEF
(LVEF 40-49%)



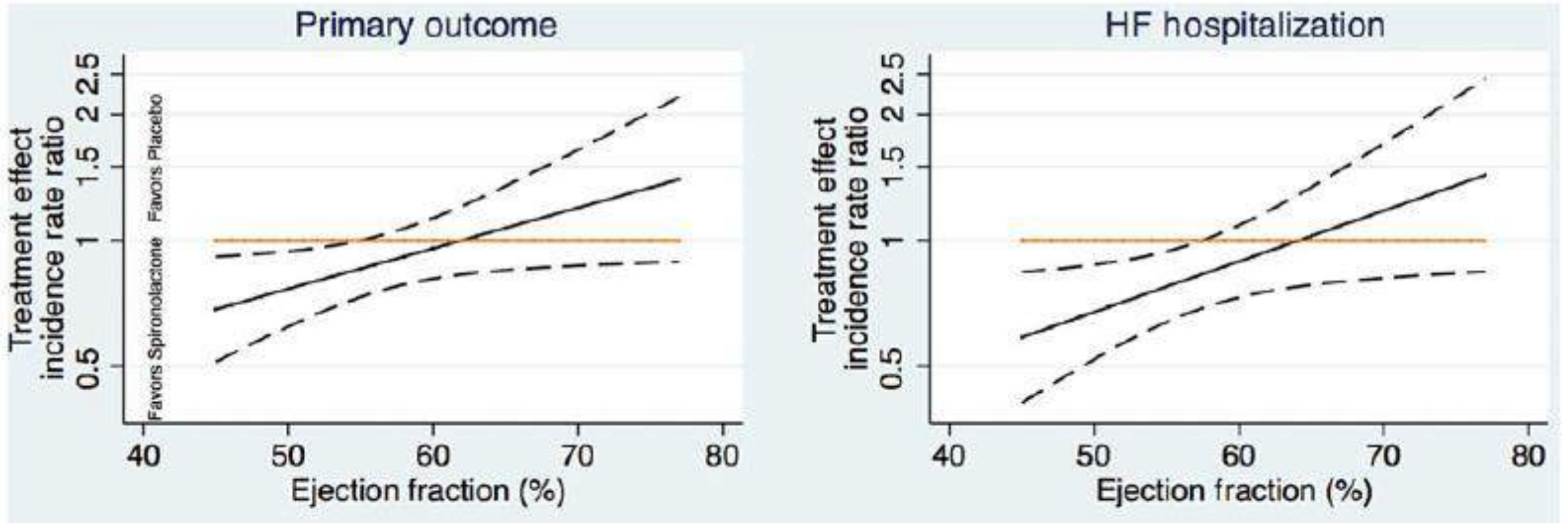
HFpEF
(LVEF ≥ 50%)

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs ^a	Symptoms ± Signs ^a	Symptoms ± Signs ^a
	2	LVEF ≤ 40%	LVEF 41 – 49% ^b	LVEF ≥ 50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides ^c

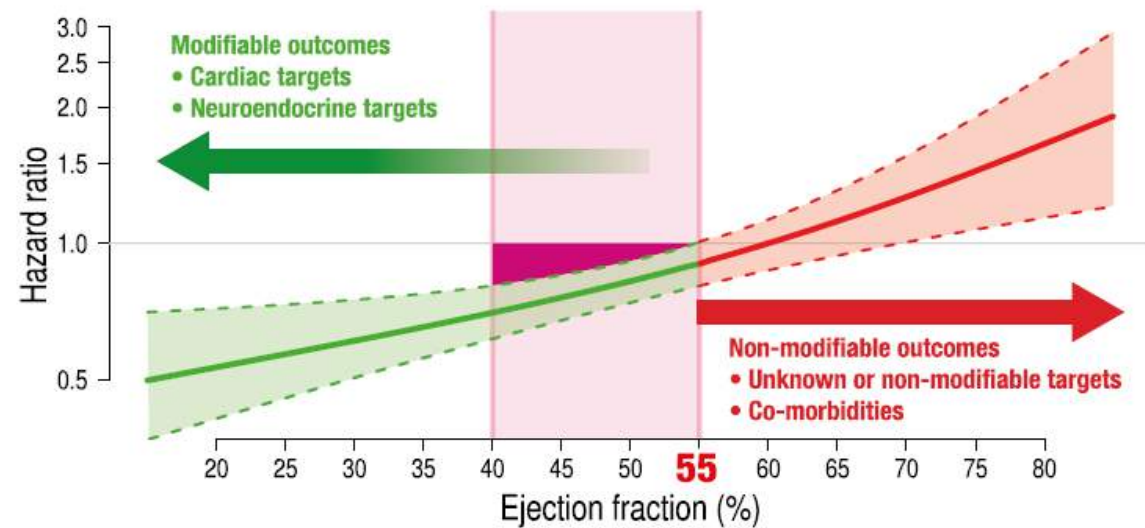
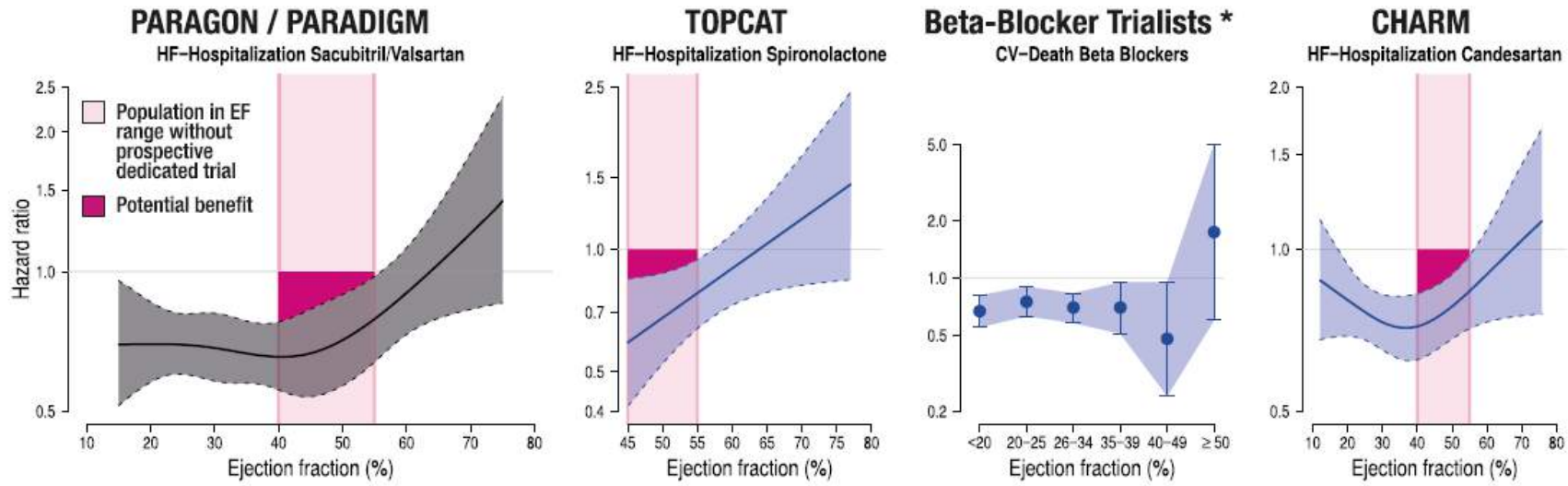
TOPCAT: Aldosteronantagonisten bei „diastolischer“ Herzinsuffizienz



TOPCAT: Outcome abhängig von der EF



Therapie der Herzinsuffizienz: HFmrEF

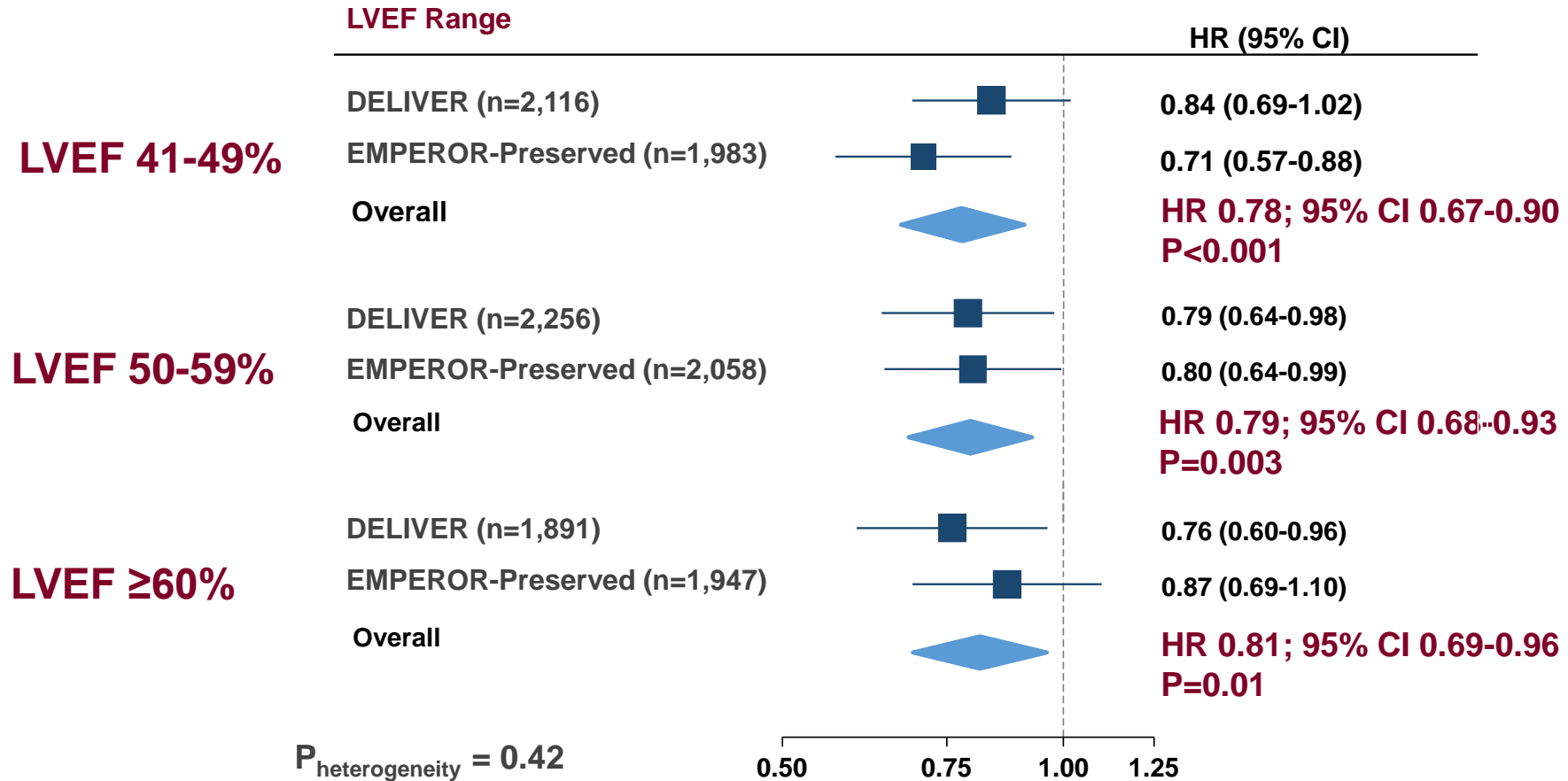


ESC Leitlinien 2021: Therapie der „milden“ systolischen Herzinsuffizienz (HFmrEF)

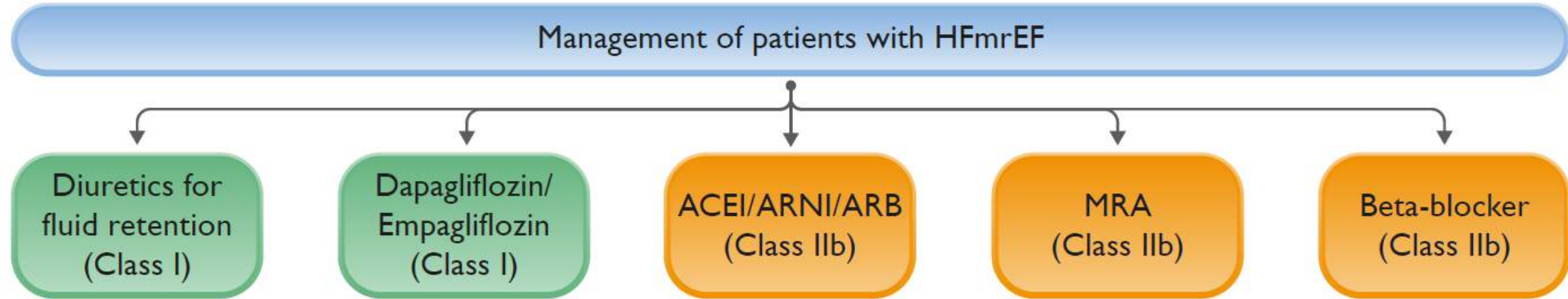
Recommendations	Class ^a	Level ^b
Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs. ¹³⁷	I	C
An ACE-I may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. ¹¹	IIb	C
An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. ²⁴⁵	IIb	C
A beta-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. ^{12,119}	IIb	C
An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. ²⁴⁶	IIb	C
Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. ^{13,247}	IIb	C

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DELIVER und EMPEROR-Preserved: Meta-Analyse nach EF



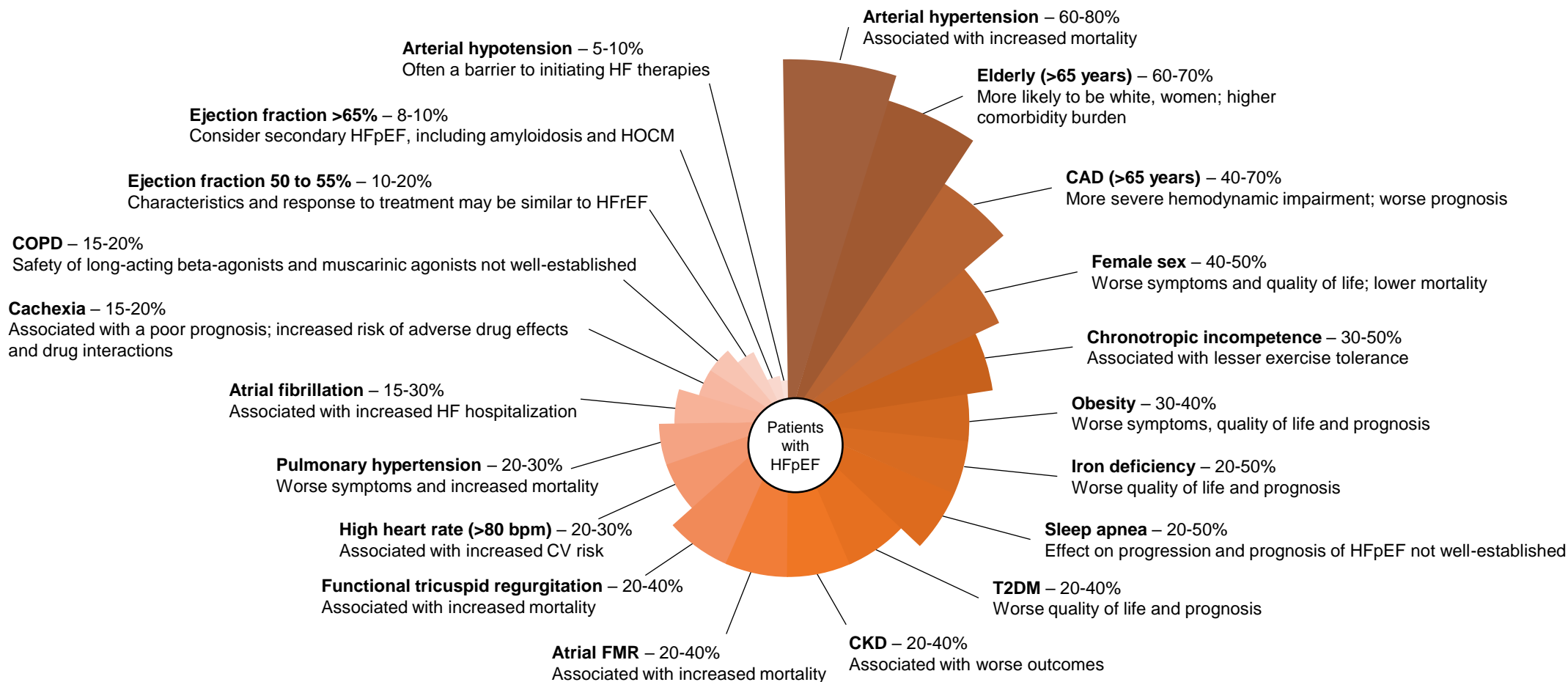
ESC Leitlinien 2023: Therapie der Herzinsuffizienz (HFmrEF)



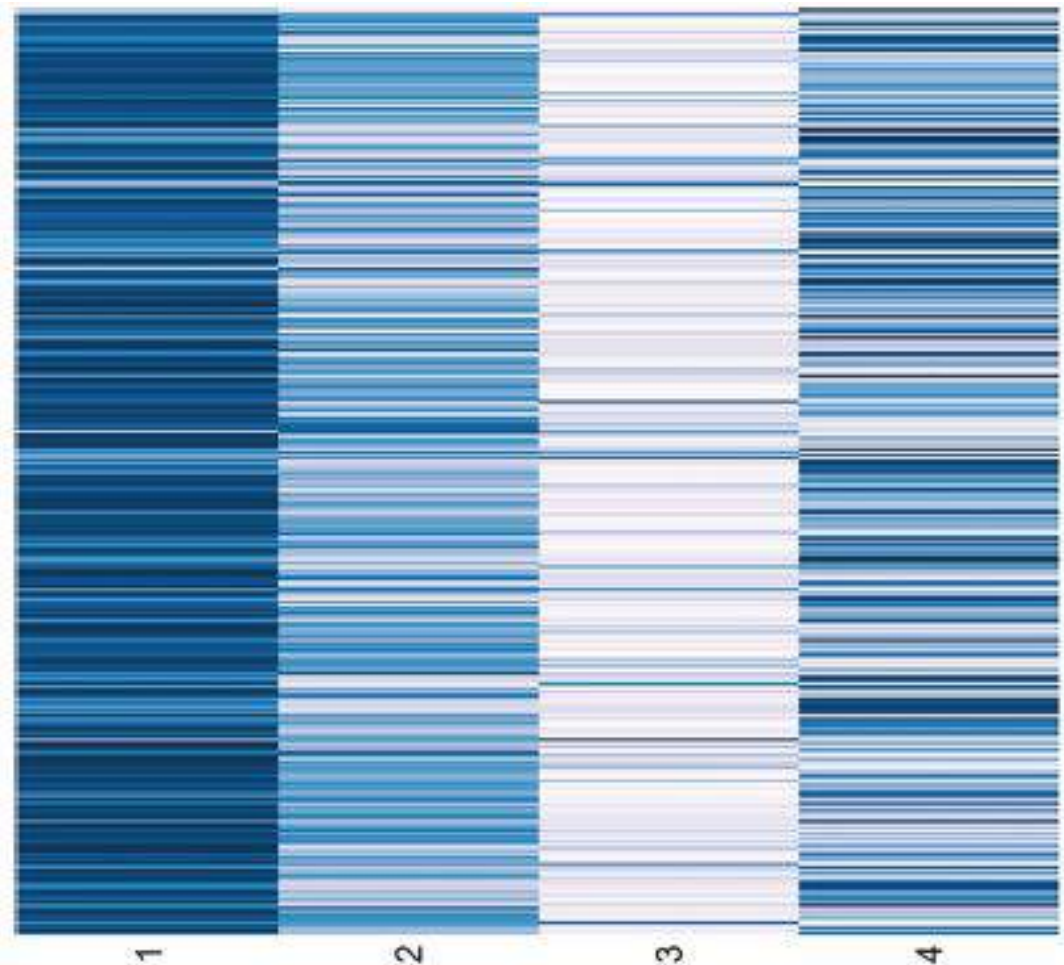
Recommendation	Class ^a	Level ^b
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of HF hospitalization or CV death. ^{c 6,8}	I	A

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Herzinsuffizienz: Komorbiditäten

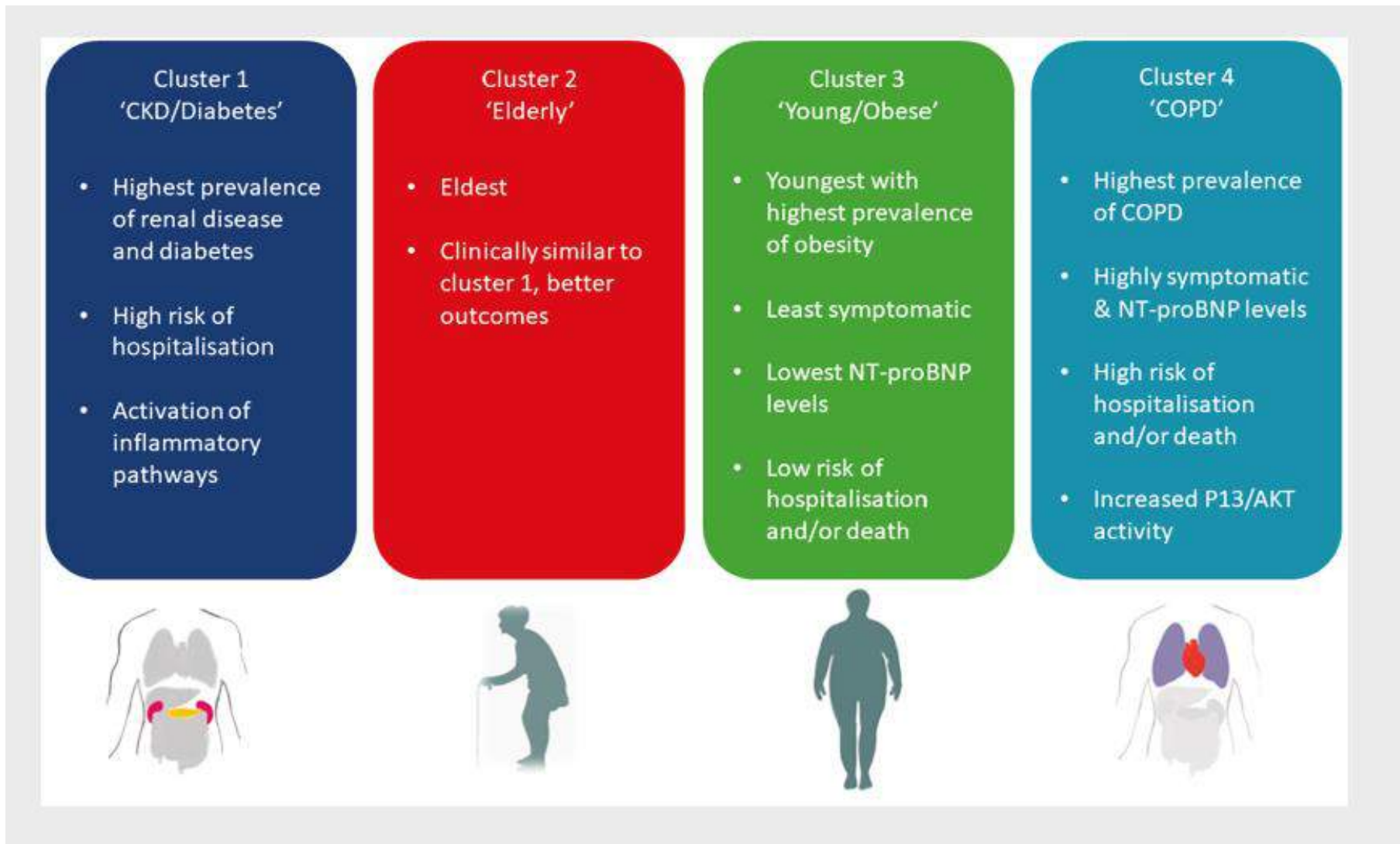


Subgruppen von HFpEF: Vorhersage durch maschinelles Lernen

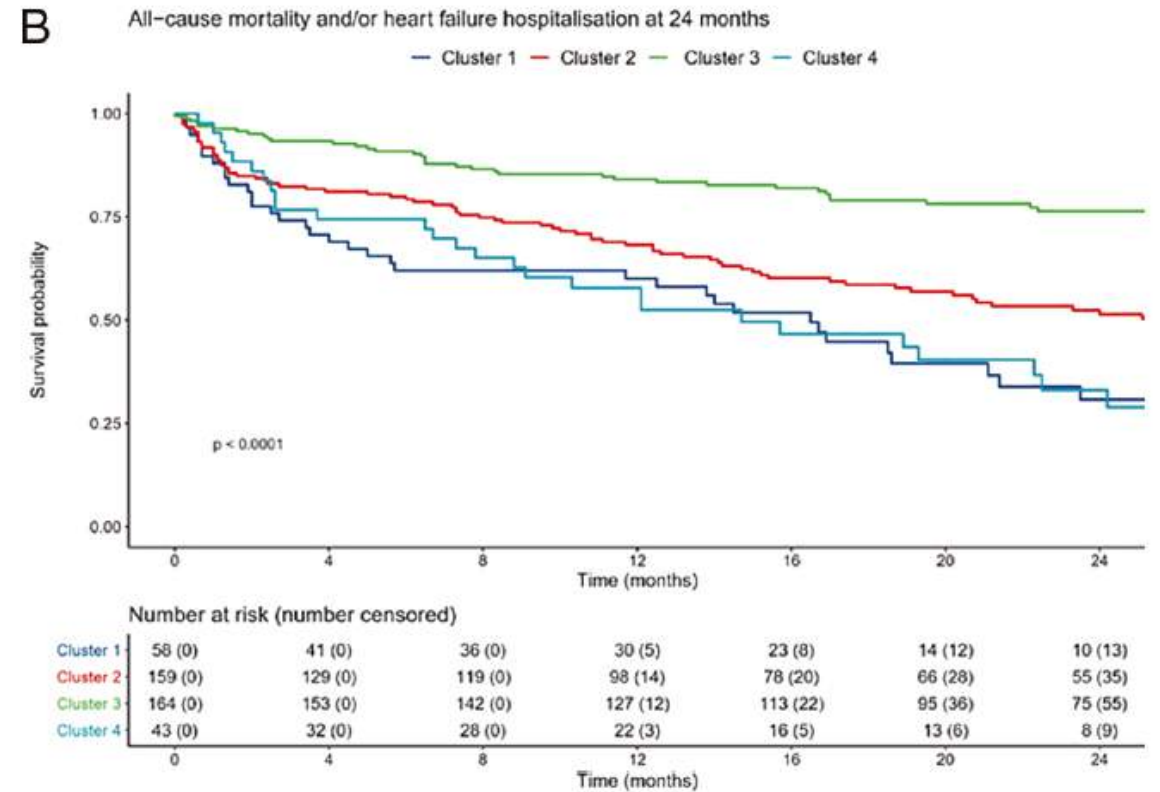
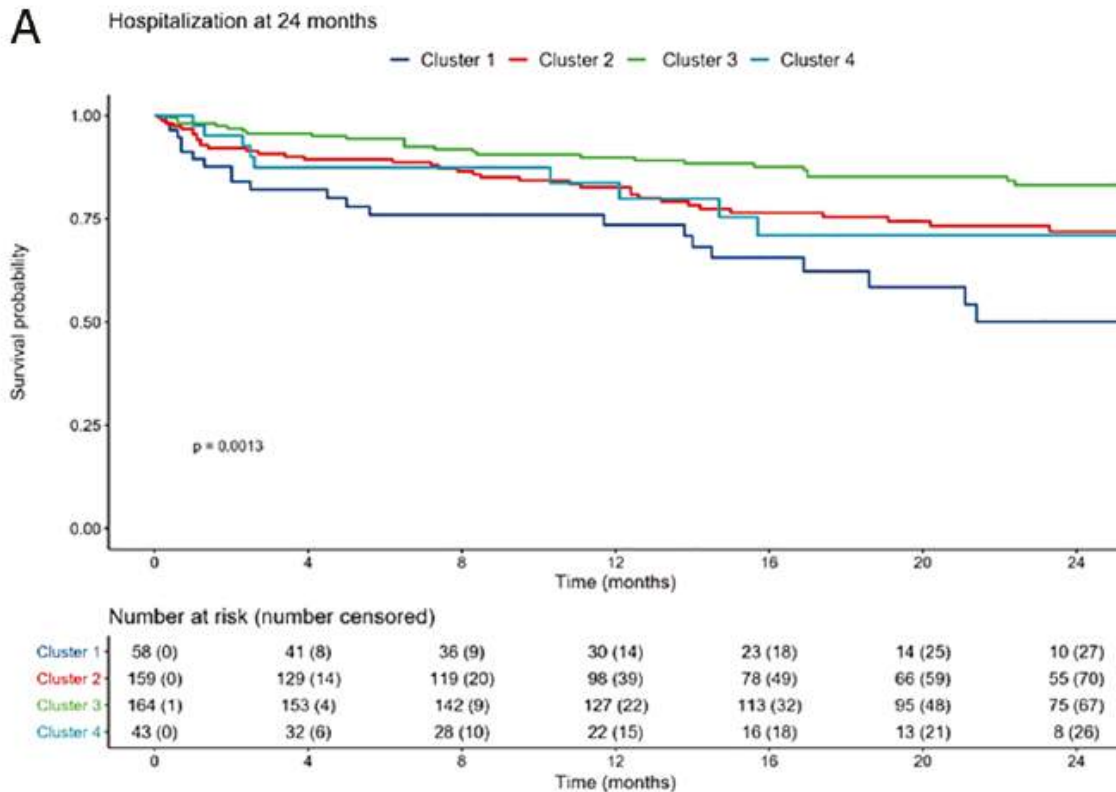


	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P-value
n	58	159	164	43	
Demographics					
Age (years)	79.0 [73.0–82.0]	80.0 [72.5–86.5]	74.0 [66.8–81.0]	79.0 [71.5–83.0]	<0.001
Male sex	35 (60.3%)	84 (52.8%)	93 (56.7%)	26 (60.5%)	0.689
BMI (kg/m ²)	29.1 [24.8–33.2]	28.4 [24.2–34.2]	30.4 [25.4–34.7]	29.4 [25.4–33.4]	0.408
BSA (m ²)	1.97 [1.80–2.11]	1.85 [1.68–2.01]	2.02 [1.79–2.21]	2.01 [1.79–2.13]	0.032
Ischaemic aetiology	31 (54.4%)	99 (65.1%)	101 (66.4%)	31 (72.1%)	0.272
Cardiomyopathy	4 (7.02%)	4 (2.63%)	3 (1.97%)	1 (2.33%)	0.293
NYHA class					<0.001
I	0 (0.0%)	0 (0.0%)	4 (2.44%)	0 (0.0%)	
II	15 (25.9%)	37 (23.3%)	72 (43.9%)	8 (18.6%)	
III	32 (55.2%)	83 (52.2%)	65 (39.6%)	24 (55.8%)	
IV	11 (19.0%)	39 (24.5%)	23 (14.0%)	11 (25.6%)	
Medical history					
Anaemia	27 (46.6%)	72 (45.9%)	50 (30.9%)	22 (51.2%)	0.012
Atrial fibrillation	31 (54.4%)	74 (46.5%)	67 (41.1%)	24 (55.8%)	0.185
Diabetes	31 (53.4%)	53 (33.3%)	57 (35.2%)	15 (35.7%)	0.048
COPD	11 (19.0%)	44 (27.7%)	36 (22.1%)	18 (41.9%)	0.034
CKD	42 (73.7%)	107 (67.7%)	34 (21.5%)	23 (53.5%)	<0.001
Hypertension	42 (72.4%)	115 (72.3%)	102 (62.2%)	31 (72.1%)	0.190
Malignancy	6 (10.5%)	5 (3.14%)	6 (3.66%)	2 (4.65%)	0.141
Obesity	25 (43.9%)	69 (43.7%)	86 (53.8%)	19 (44.2%)	0.270
Stroke	13 (22.4%)	31 (19.5%)	30 (18.4%)	9 (21.4%)	0.913
Past/current smokers	25 (43.9%)	72 (45.9%)	69 (42.3%)	28 (65.1%)	0.063
Signs and symptoms					
Extent of peripheral oedema					0.121
Not present	7 (13.0%)	46 (31.7%)	54 (37.0%)	9 (22.5%)	
Ankle	22 (40.7%)	52 (35.9%)	42 (28.8%)	15 (37.5%)	
Below knee	18 (33.3%)	34 (23.4%)	40 (27.4%)	12 (30.0%)	
Above knee	7 (13.0%)	13 (8.97%)	10 (6.85%)	4 (10.0%)	
JVP elevated (%)	24 (49.0%)	41 (29.1%)	45 (34.1%)	9 (25.7%)	0.035
Pulmonary congestion with rales	36 (64.3%)	75 (48.4%)	70 (45.2%)	32 (74.4%)	0.001
Laboratory					
Haemoglobin (g/dL)	12.2 [11.2–13.5]	12.5 [10.9–13.5]	13.3 [12.3–14.4]	12.5 [10.8–13.8]	<0.001
Leucocytes (10 ⁹ /L)	7.45 [5.55–10.0]	7.55 [5.93–9.00]	7.25 [5.90–8.80]	9.90 [7.50–12.8]	<0.001
Creatinine (μmol/L)	126 [96.0–148]	112 [88.0–142]	81.5 [66.8–94.2]	96.0 [79.0–121]	<0.001
Urea (mmol/L)	11.1 [7.90–15.3]	9.80 [7.93–13.5]	6.60 [5.47–8.43]	10.2 [7.90–13.9]	<0.001
eGFR (mL/min/1.73 m ²)	46.0 [36.0–59.5]	51.0 [38.0–60.0]	60.0 [60.0–60.0]	58.0 [48.0–60.0]	<0.001
Gamma-GT (U/L)	61.0 [39.5–138]	44.0 [27.0–80.0]	35.0 [25.0–62.0]	47.0 [32.0–94.8]	0.001
Glucose (mmol/L)	7.90 [5.60–10.6]	6.60 [5.60–9.10]	6.05 [5.10–8.40]	7.80 [6.00–10.2]	0.002
Iron (μmol/L)	8.00 [6.00–12.0]	9.00 [6.00–13.0]	13.0 [8.00–16.0]	8.00 [4.25–11.8]	<0.001
Ferritin (ng/mL)	154 [58.0–270]	93.0 [43.0–209]	94.5 [35.5–202]	98.0 [52.0–262]	0.162
NT-proBNP (pg/L)	1720 [544–4831]	1304 [526–2938]	591 [234–1621]	2175 [898–4542]	<0.001
GDF-15 (pg/mL)	5877 [3412–8555]	3510 [2507–5228]	2174 [1532–2982]	3777 [2815–5970]	<0.001
Troponin T (ng/L)	45.0 [26.9–79.6]	32.6 [18.9–63.1]	19.0 [12.4–31.3]	46.2 [30.4–271]	<0.001

Subphänotypen von HFpEF

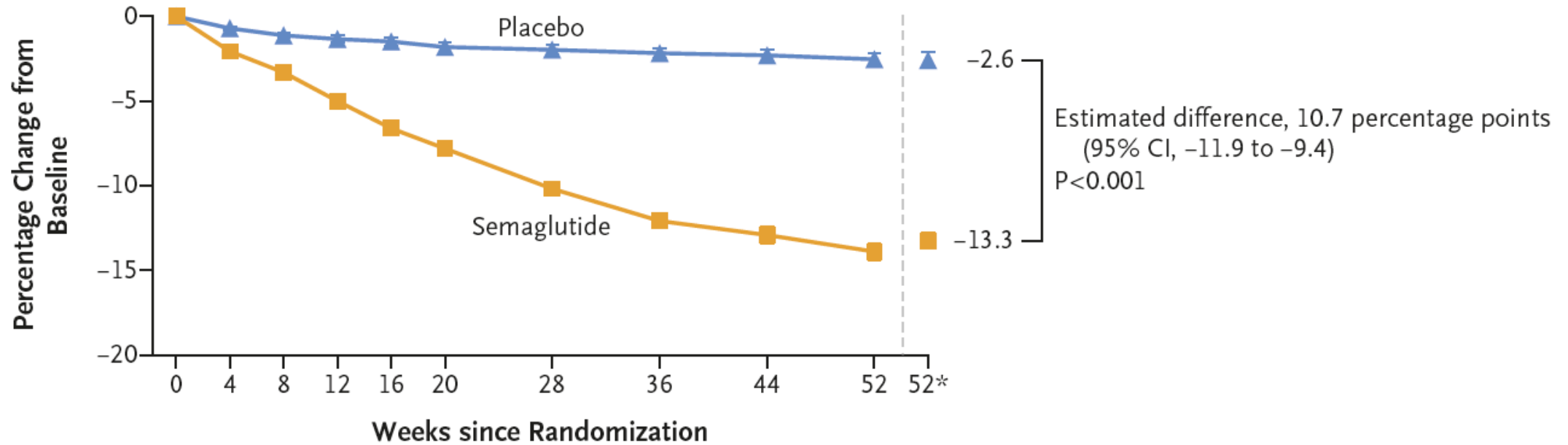


Subgruppen von HFpEF: Vorhersage durch maschinelles Lernen



STEP-HFpEF: Semaglutid bei Adipositas und Herzinsuffizienz (HFpEF) ?

Change in Body Weight

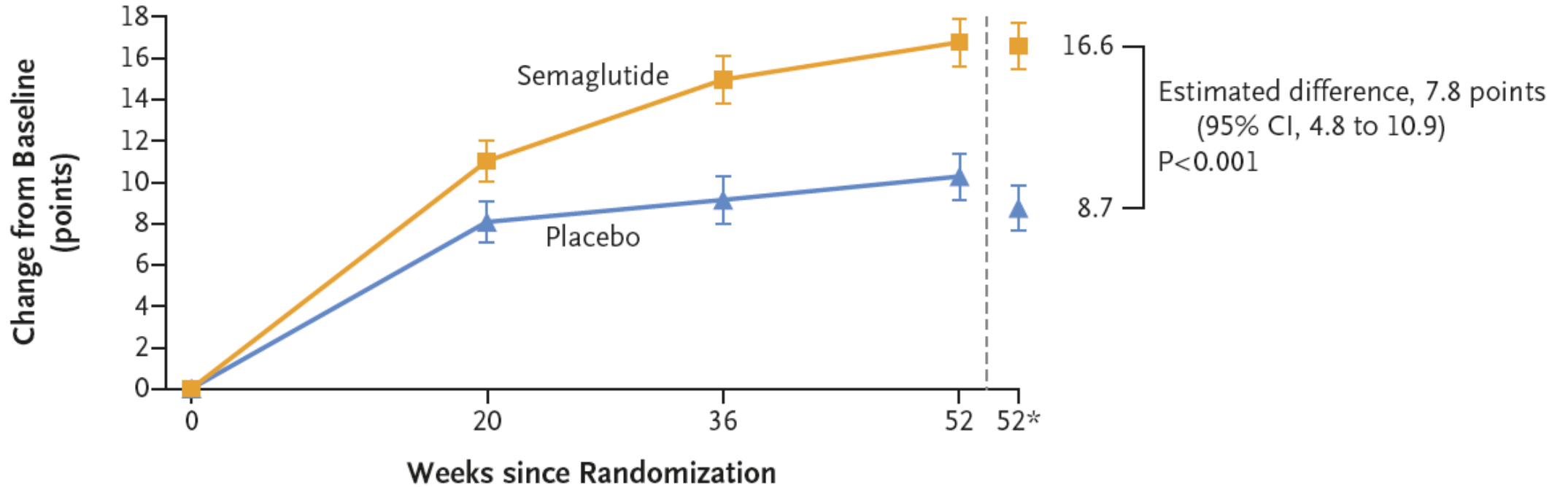


No. of Participants

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

STED-HFpEF: Semaglutid bei Adipositas und Herzinsuffizienz (HFpEF) ?

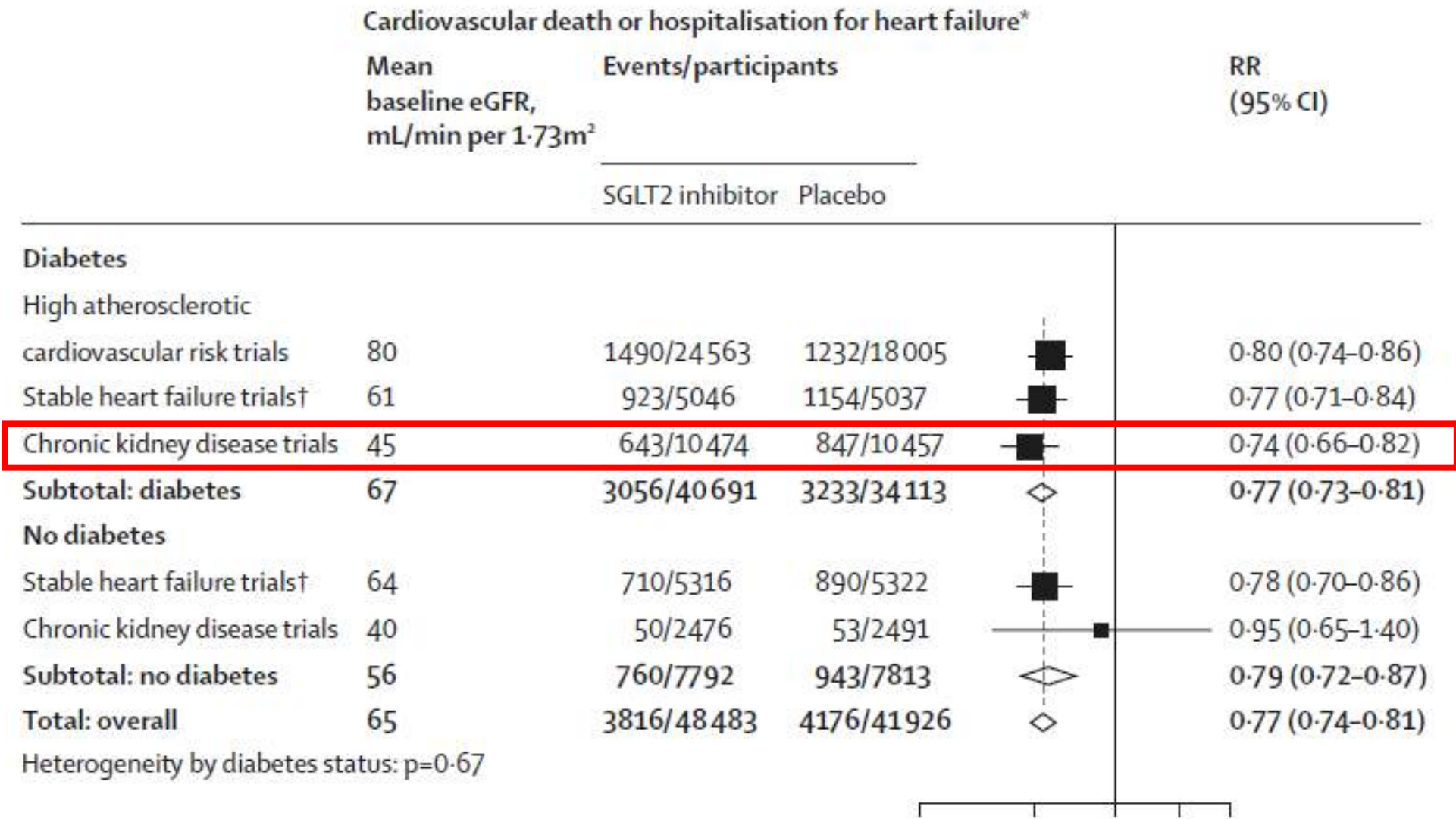
Change in KCCQ-CSS



No. of Participants

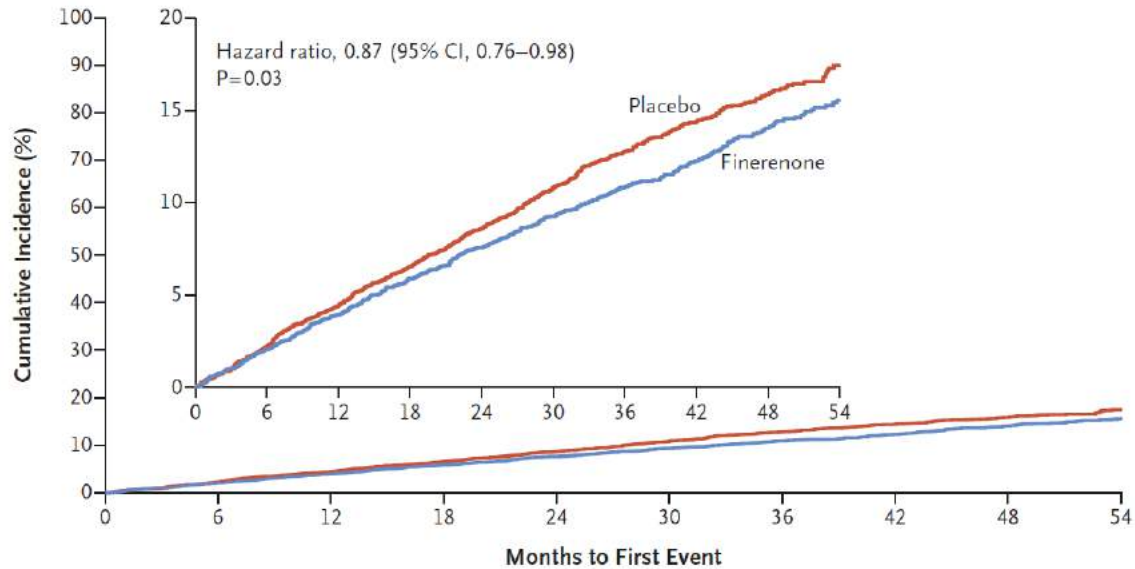
Semaglutide	263	249	225	243	263
Placebo	266	242	217	237	266

sGLT2-Hemmer bei Niereninsuffizienz



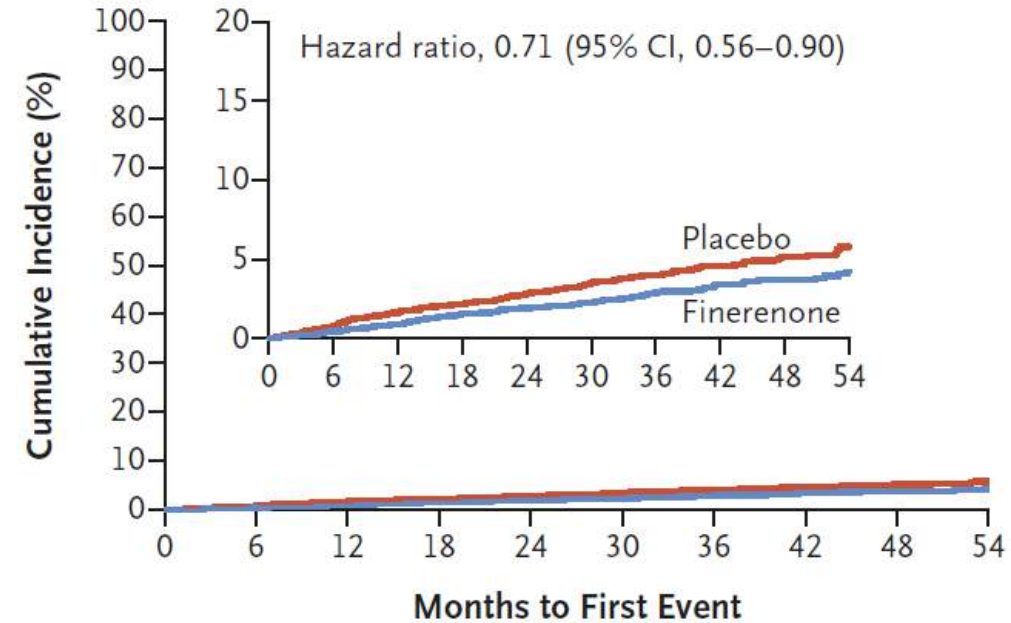
FIGARO-DKD: Finerenon bei diabetischer Nephropathie

Primary Composite Outcome



No. at Risk	0	6	12	18	24	30	36	42	48	54
Placebo	3666	3577	3479	3389	3267	2730	2125	1657	1076	585
Finerenone	3686	3600	3517	3427	3320	2781	2184	1712	1093	598

Hospitalization for Heart Failure



ESC Leitlinien Herzinsuffizienz 2023: Diabetes mellitus und chronische Niereninsuffizienz

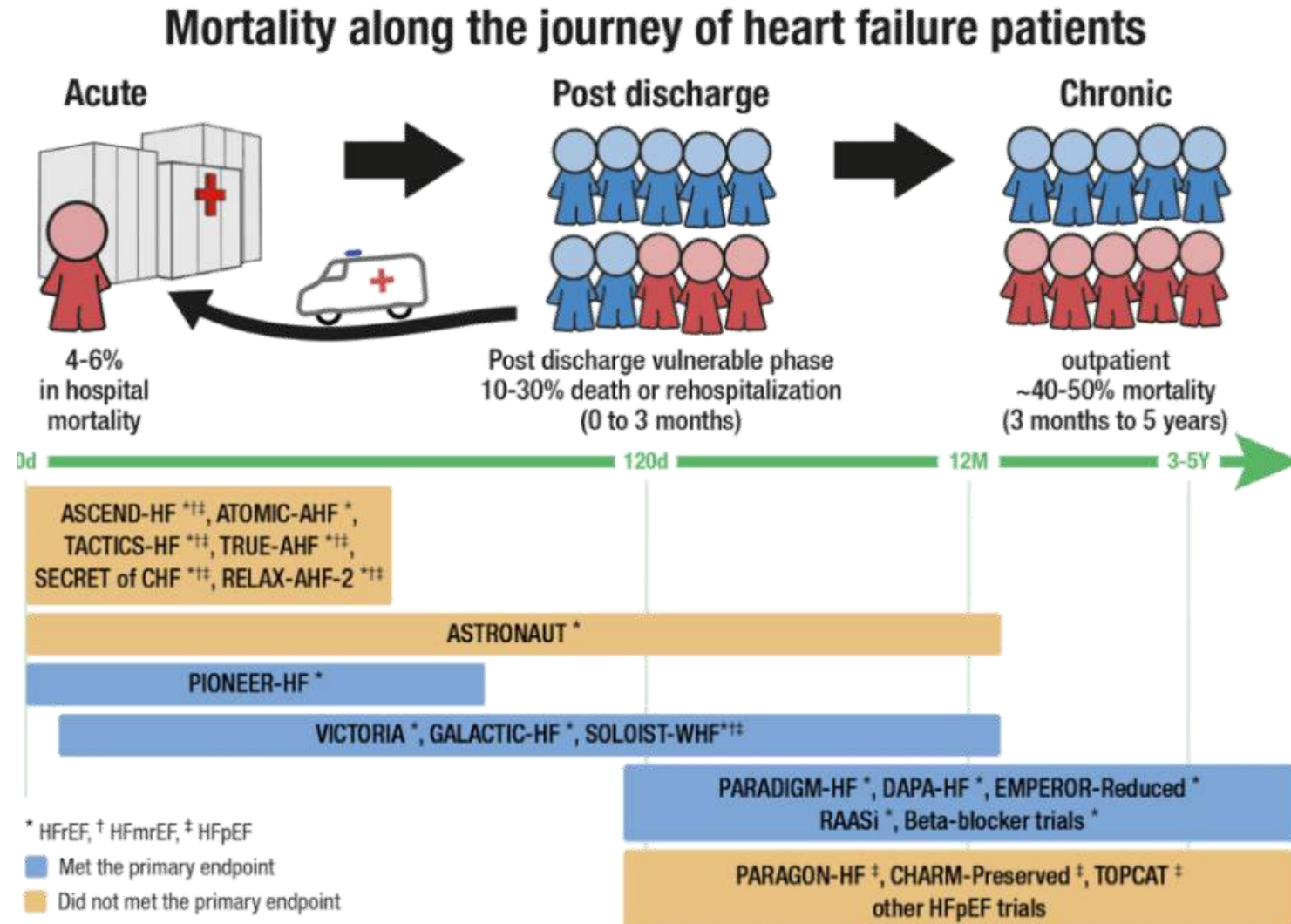
Recommendations	Class ^a	Level ^b
In patients with T2DM and CKD, ^c SGLT2 inhibitors (dapagliflozin or empagliflozin) are recommended to reduce the risk of HF hospitalization or CV death. ^{5,7,35}	I	A
In patients with T2DM and CKD, ^c finerenone is recommended to reduce the risk of HF hospitalization. ^{10,11,34,40}	I	A

ESC Leitlinien 2023: Herzinsuffizienz-Managementstrategien

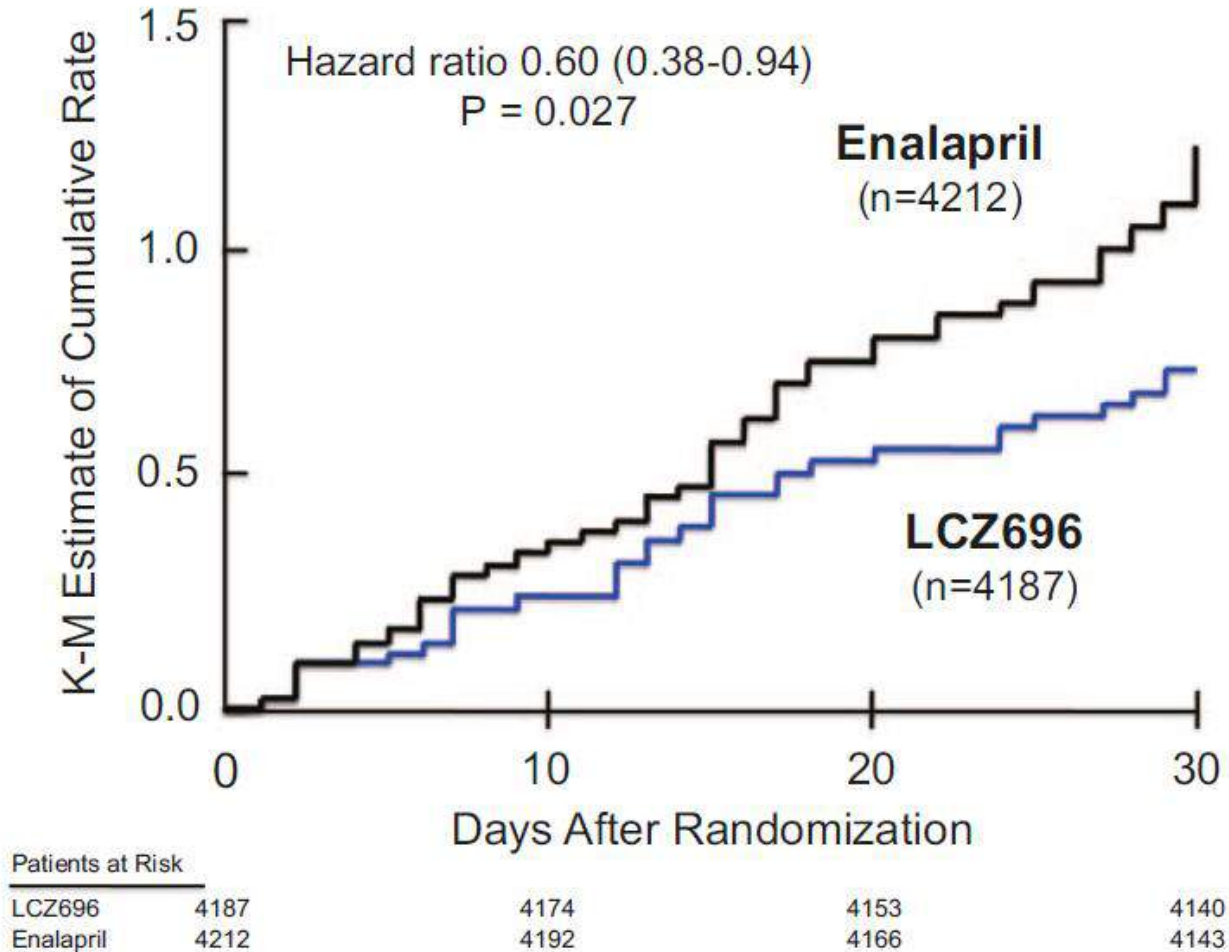
Recommendation	Class ^a	Level ^b
<p>An intensive strategy of initiation and rapid up-titration of evidence-based treatment before discharge and during frequent and careful follow-up visits in the first 6 weeks following a HF hospitalization is recommended to reduce the risk of HF rehospitalization or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

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„Time is prognosis“: Frühe vulnerable Phase

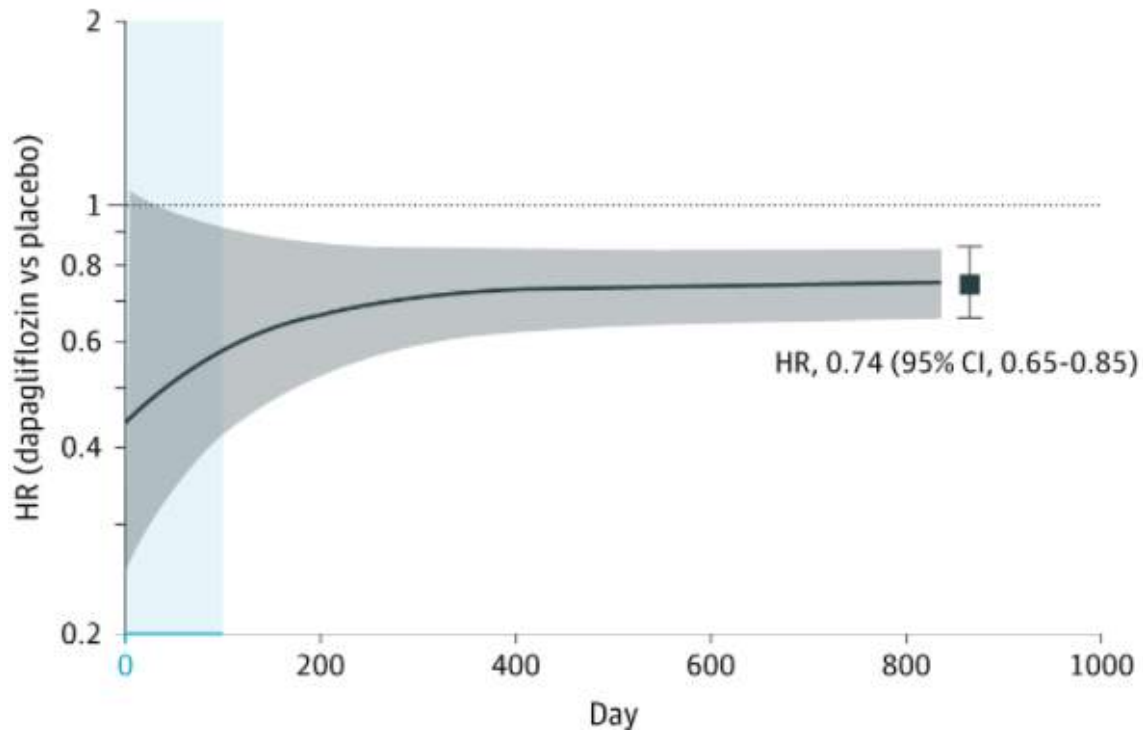


PARADIGM-HF: Früher Nutzen von Sacubitril/Valsartan

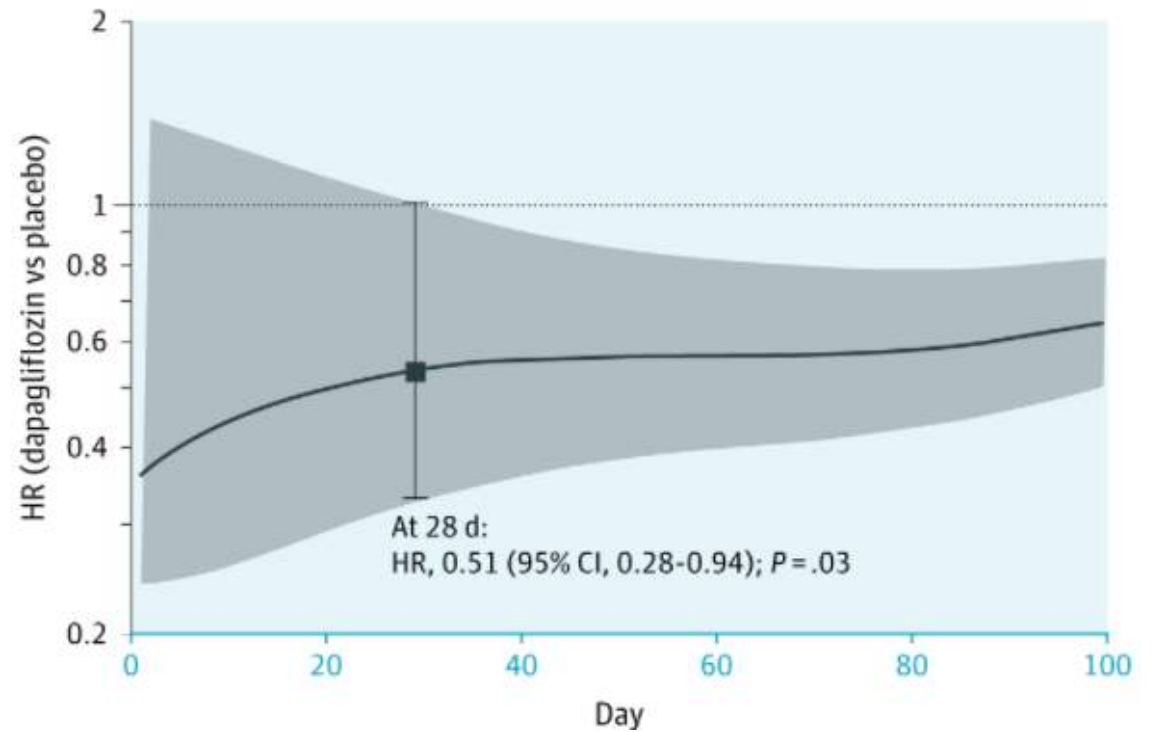


Früher Nutzen einer Therapie mit SGLT2-Hemmern

A Worsening heart failure or cardiovascular death



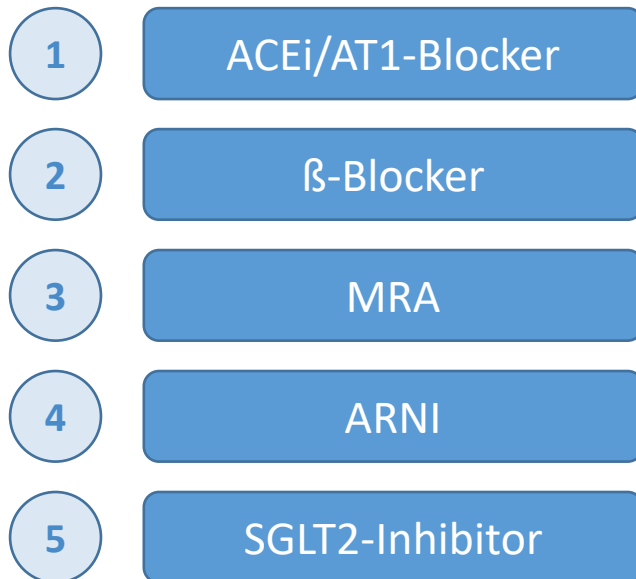
B Worsening heart failure or cardiovascular death, first 100 d



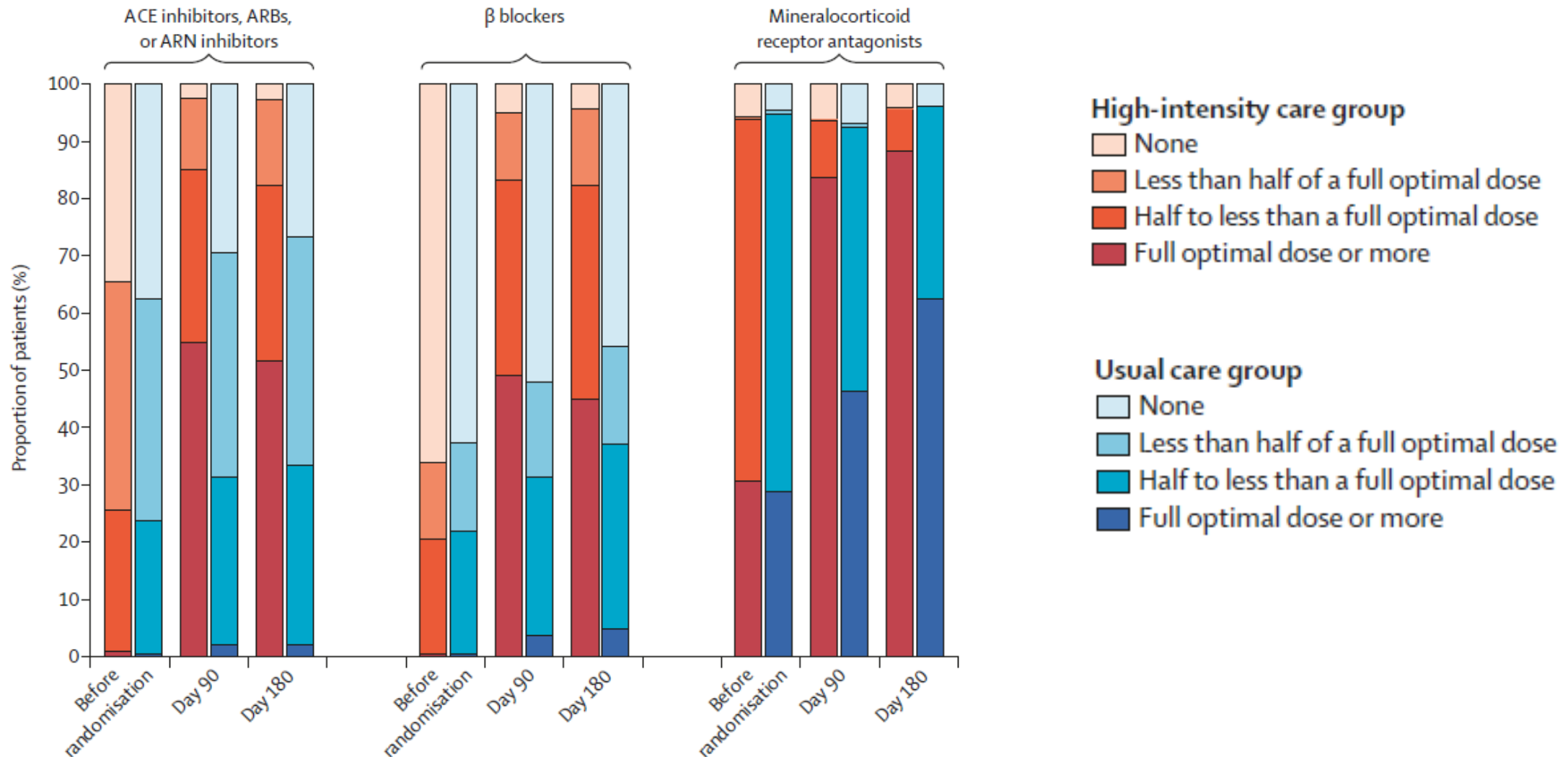
Therapieinitiierung oraler Herzinsuffizienz-Medikationen (HFrEF)

Herkömmliches Therapieschema

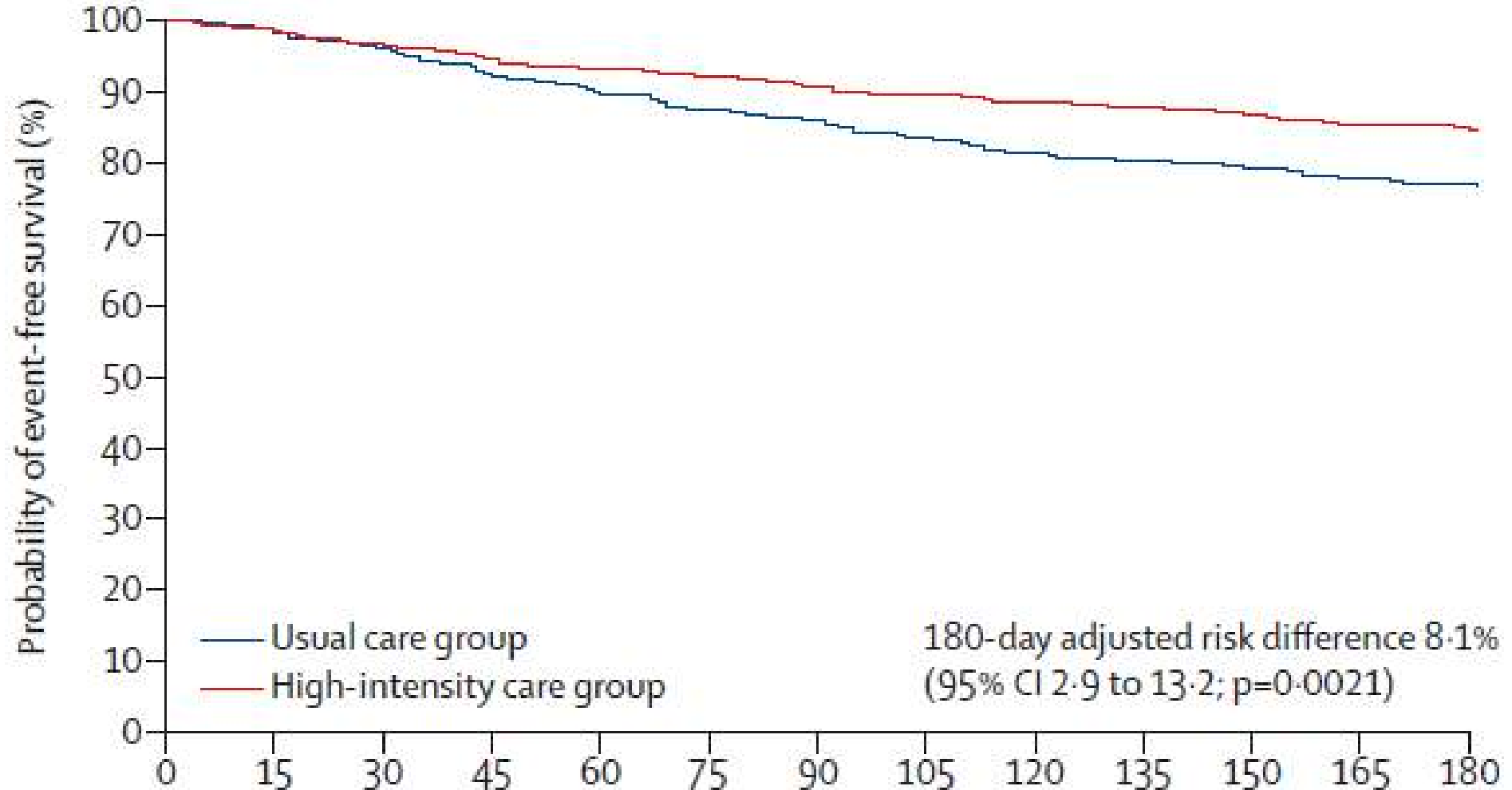
- Titration bei zur Zieldosis bei jedem Schritt
- Übliche Zeitdauer > 6 Monate



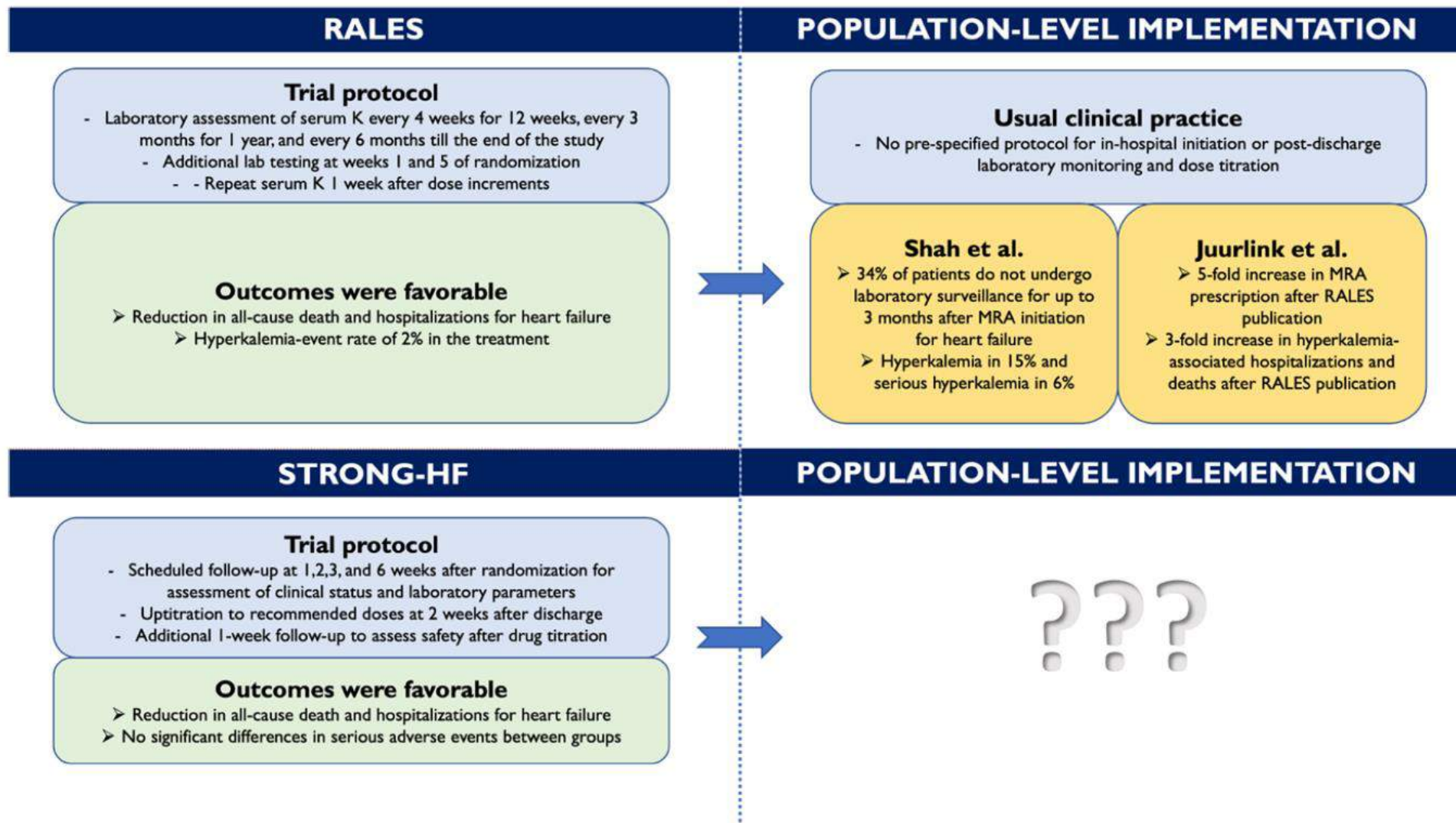
STRONG-HF: Rasche Auftritation der Medikation nach akuter Dekompensation ?



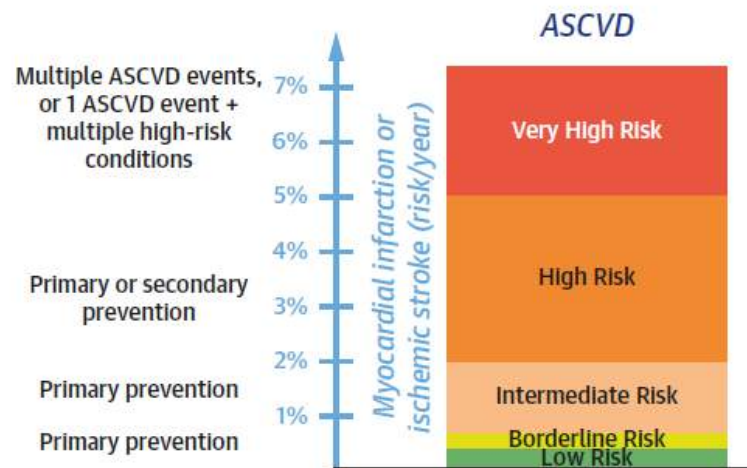
STRONG-HF: Rasche Auftritation der Medikation nach akuter Dekompensation



STRONG-HF: Umsetzung in die Praxis ?



„Worsening heart failure“: Eine neue Entität?



„Worsening heart failure“ als eigene Entität ?



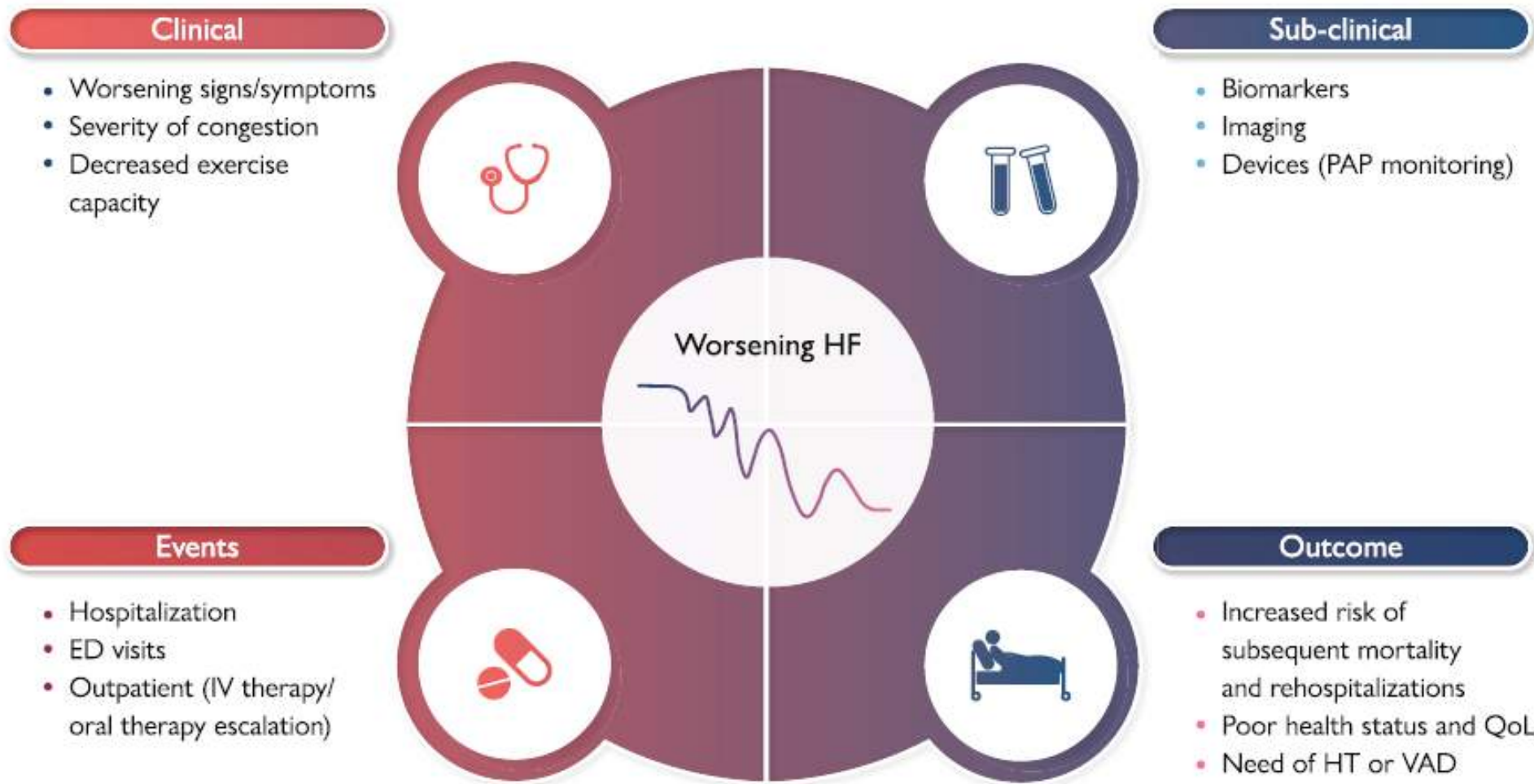
European Journal of Heart Failure (2023) 25, 776–791
doi:10.1002/ejhf.2874

CONSENSUS STATEMENT

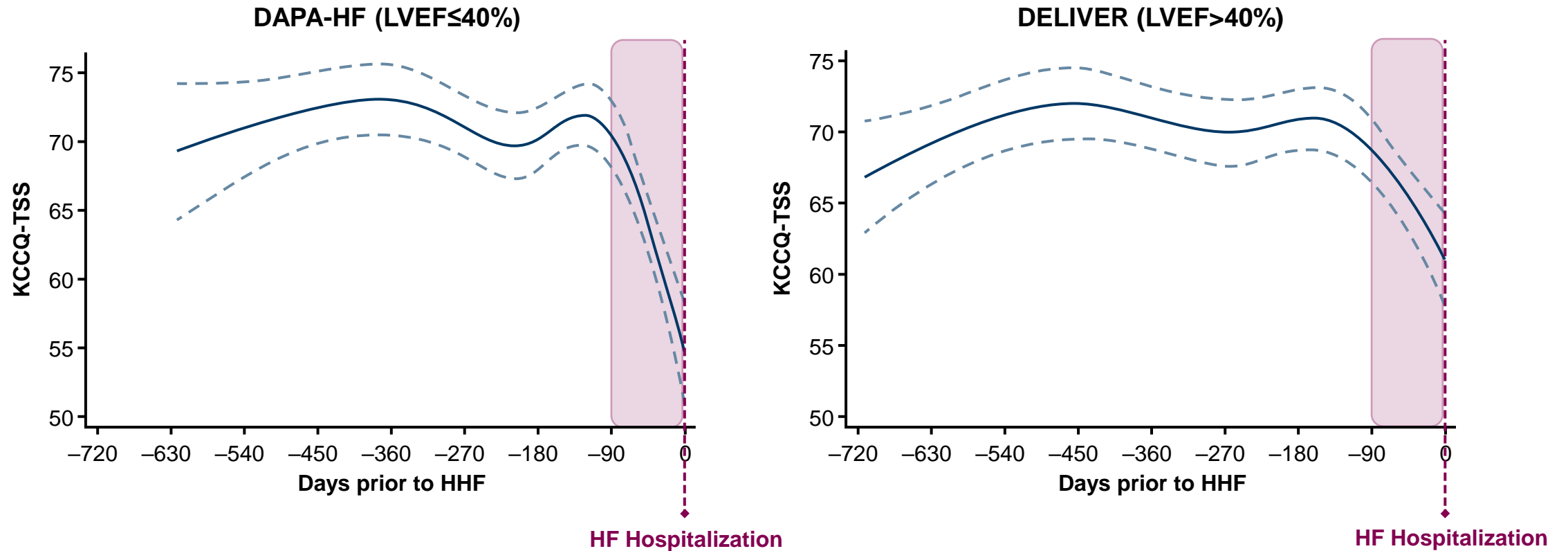
Worsening of chronic heart failure: definition, epidemiology, management and prevention. A clinical consensus statement by the Heart Failure Association of the European Society of Cardiology

Marco Metra^{1#}, Daniela Tomasoni^{1#}, Marianna Adamo^{1*}, Antoni Bayes-Genis², Gerasimos Filippatos³, Magdy Abdelhamid⁴, Stamatis Adamopoulos⁵,

„Worsening heart failure“: Manifestation

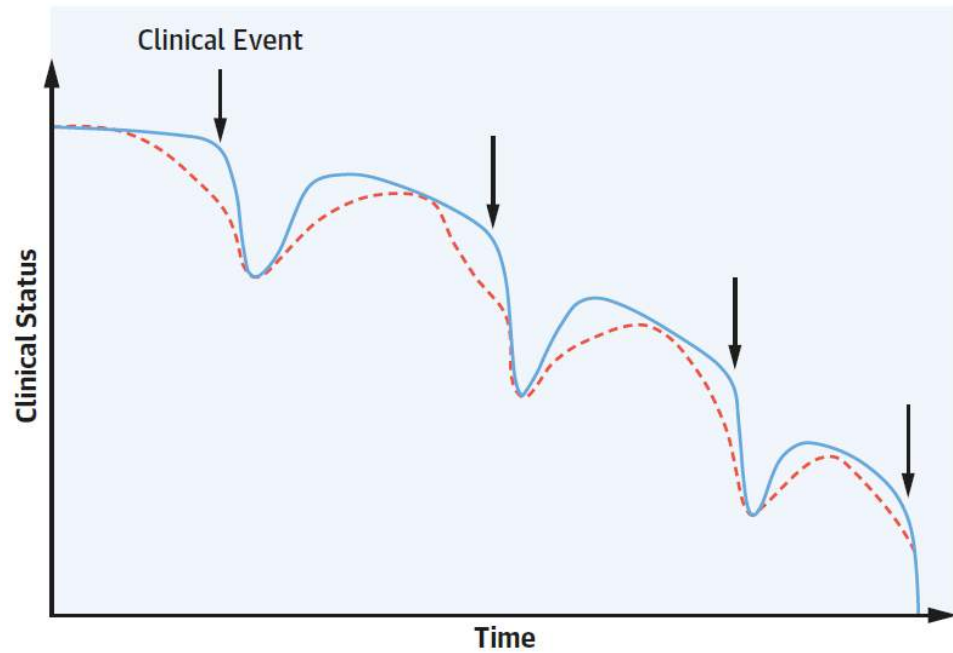


DAPA-HF & DELIVER gepooled – Lebensqualität vor Hospitalisation wg. Herzinsuffizienz



Declines in KCCQ precede HF hospitalization

„Worsening heart failure“: Therapie-Intensivierung



Treatment

In-hospital
Emergency department
Outpatient

Treatment of congestion

Intensification of diuretic therapy

- Switch to intravenous loop diuretic
- Escalate oral dose of loop diuretic
- Switch to subcutaneous loop diuretic?
- Add acetazolamide
- Add thiazide-like diuretics?
- Other options (i.e. ultrafiltration)

Treatment of hypoperfusion

Intravenous inotropic therapy

- Single administration/ intermittent oral agents
- Digitalis glycosides
- New agents? ^a

Prevention

Start early, possibly before discharge ^b
Combine drugs as their effects are additive
Administer simultaneously or in rapid sequence

Neurohormonal antagonists and modulators

In patients with HFrEF

- ARNI
- Beta-blockers
- MRA

SGLT2i

In all patients

- Dapagliflozin or Empagliflozin

Intravenous iron supplementation

In patients with ID and LVEF <50%

sGC stimulators

In patients with LVEF <45%

Zusammenfassung Therapie der Herzinsuffizienz 2024

- **Basistherapie HFrEF/HFmrEF „4er-Kombi“:**
 - ARNI/ACEI
 - β -Blocker
 - Aldosteronantagonist (MRA)
 - sGLT2-Hemmer
- **Basistherapie HFpEF:**
 - sGLT2-Hemmer
 - Diuretika
- **Individuelle Ergänzung/Eskalation:**
 - Vericiguat, Ivabradin, Eisen, GLP1-Analoga,...
 - Device-/Klappentherapie/LVAD/Herztransplantation
- **Strategien der Therapie-Initiierung/-eskalation:**
 - Möglichst rasche Einleitung der Therapie (ggf. parallel), zügige Titration