CMP und Therapieoptionen

Aktuelle Therapiestrategien bei der Herzinsuffizienz

- IKIM 2024 -

Noemi Pavo

Universitätsklinik für Innere Medizin II / Abteilung für Kardiologie

Herzinsuffizienz
Klinische Relevanz

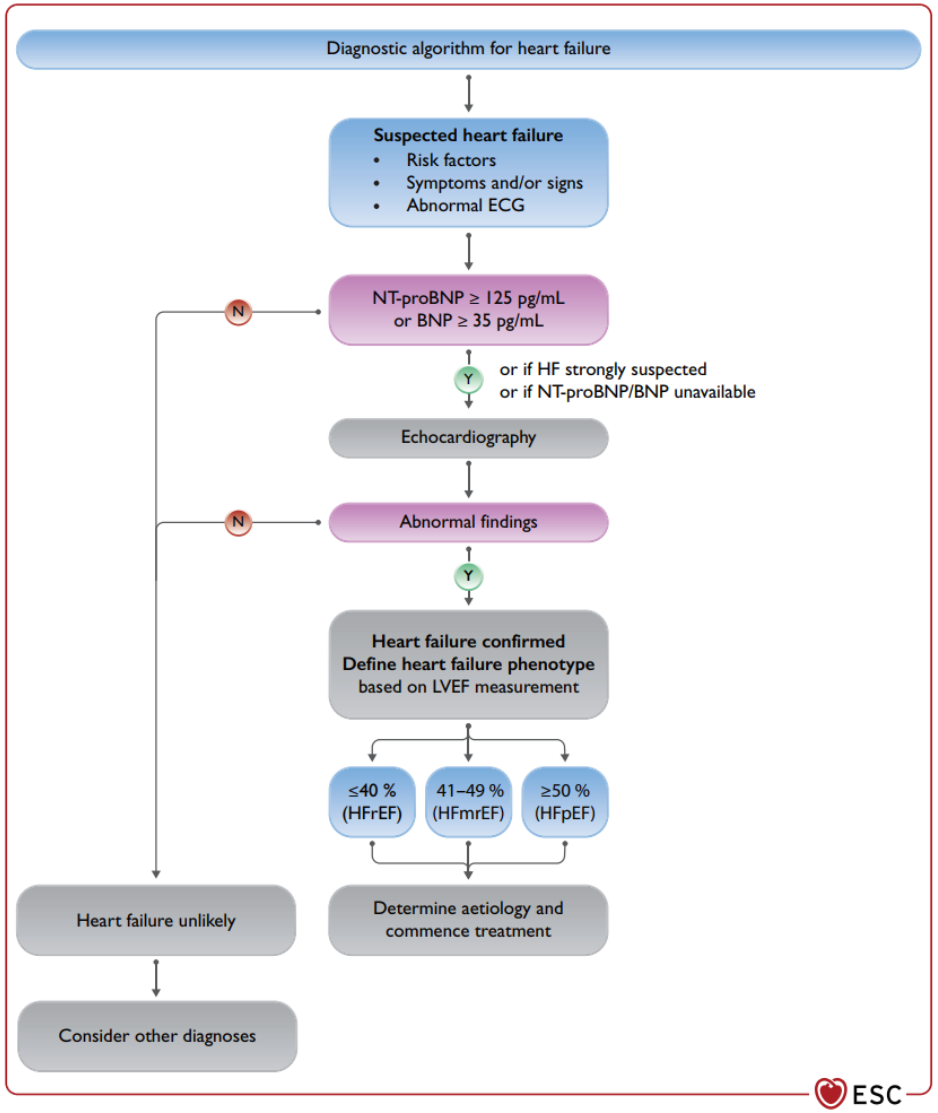
HF is a clinical syndrome with different etiologies and pathophysiology rather than a specific disease.

Definition und Diagnosealgorhithmus

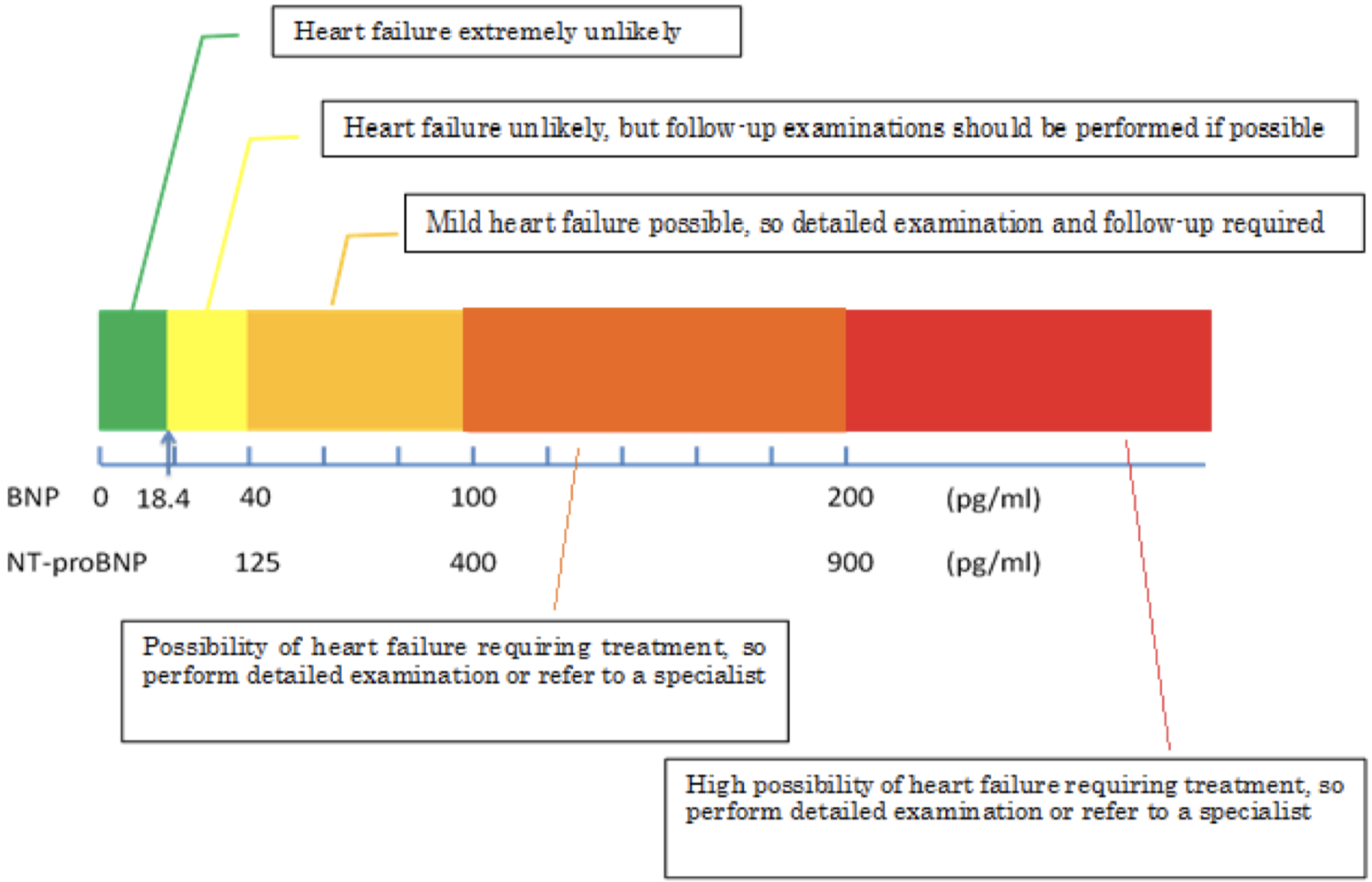
3.1 Definition of heart failure

Heart failure is not a single pathological diagnosis, but a clinical syndrome consisting of cardinal symptoms (e.g. breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema). It is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise.

Identification of the aetiology of the underlying cardiac dysfunction is mandatory in the diagnosis of HF as the specific pathology can determine subsequent treatment. Most commonly, HF is due to myocardial dysfunction: either systolic, diastolic, or both. However, pathology of the valves, pericardium, and endocardium, and abnormalities of heart rhythm and conduction can also cause or contribute to HF.



BNP / NTproBNP – Biomarker für Herzinsuffizienz



- **Stabile Herzinsuffizienz**
  - NT-proBNP <125pg/ml
  - BNP <35pg/ml
- **Akute Herzinsuffizienz**
  - NT-proBNP <300pg/ml
  - BNP <100pg/ml

From the Japanese Heart Failure Society.

Einteilung der Herzinsuffizienz

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]

HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricle; LVEF = left ventricular ejection fraction.

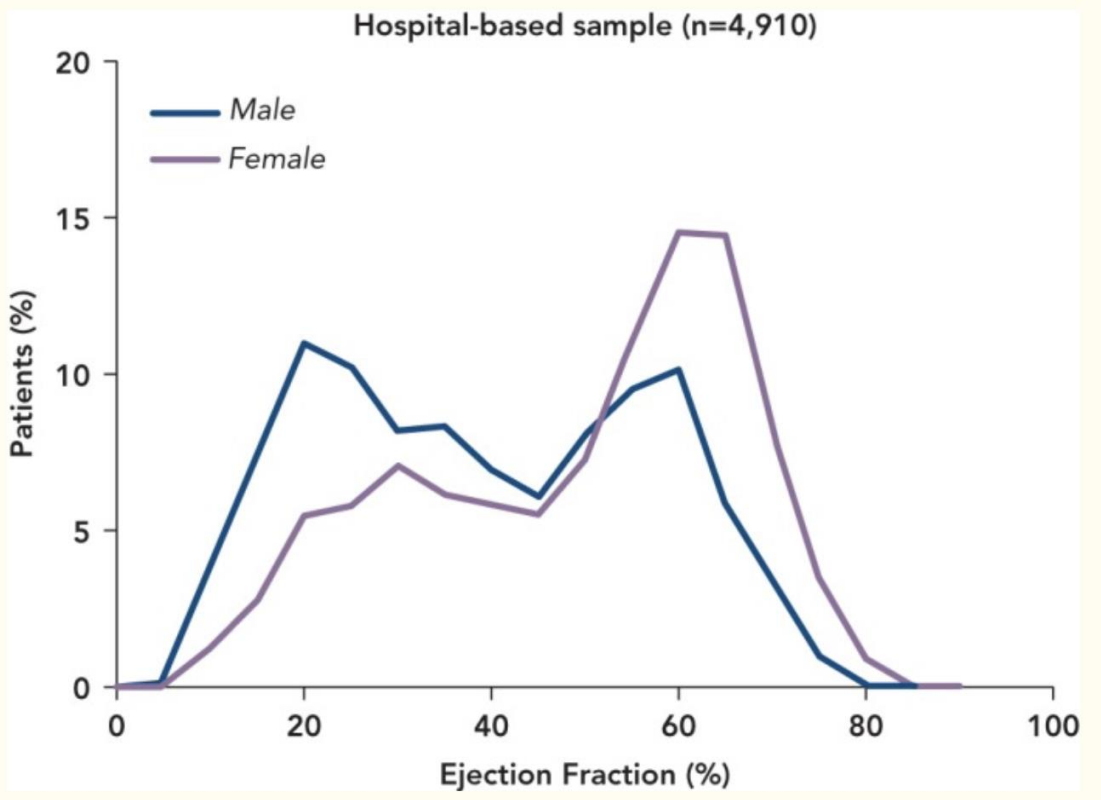
[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in optimally treated patients.

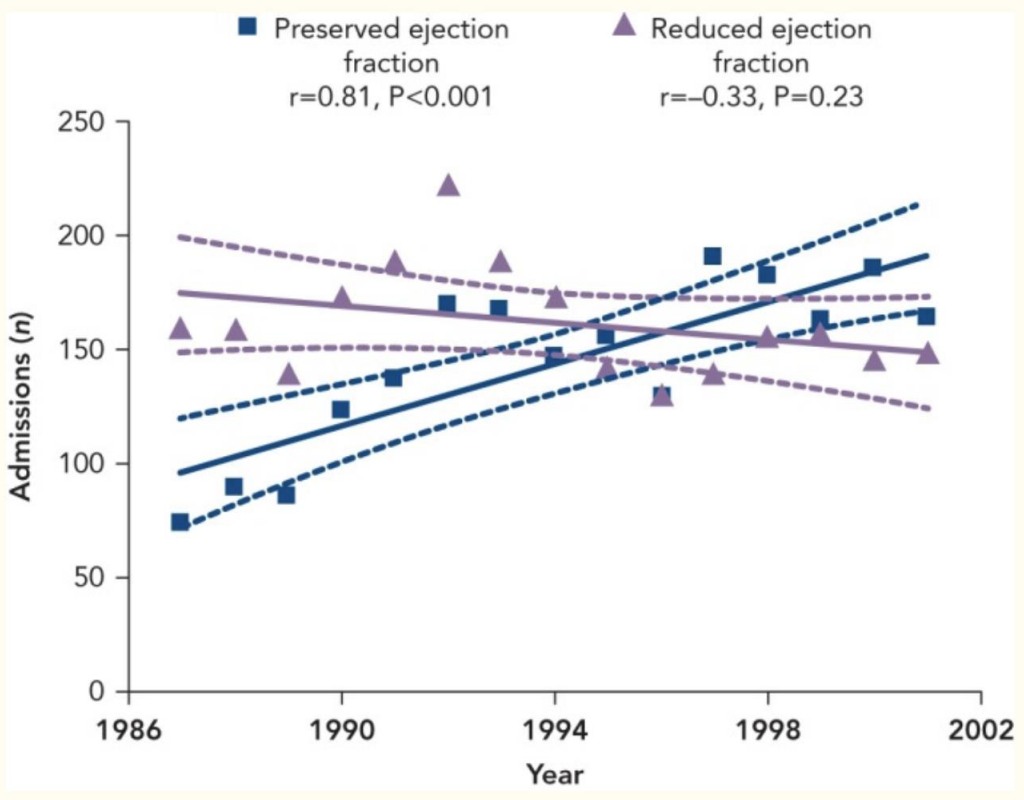
[b]For the diagnosis of HFmrEF, the presence of other evidence of structural heart disease (e.g. increased left atrial size, LV hypertrophy or echocardiographic measures of impaired LV filling) makes the diagnosis more likely.

[c]For the diagnosis of HFpEF, the greater the number of abnormalities present, the higher the likelihood of HFpEF.

Die Herzinsuffizienzstudien befolgen die Einteilung in HFrEF, HFmrEF und HFpEF, also ist die Einteilung des Patienten in diese LVEF Kategorien wichtig um die passende evidenz-basierte Therapie einleiten zu können.

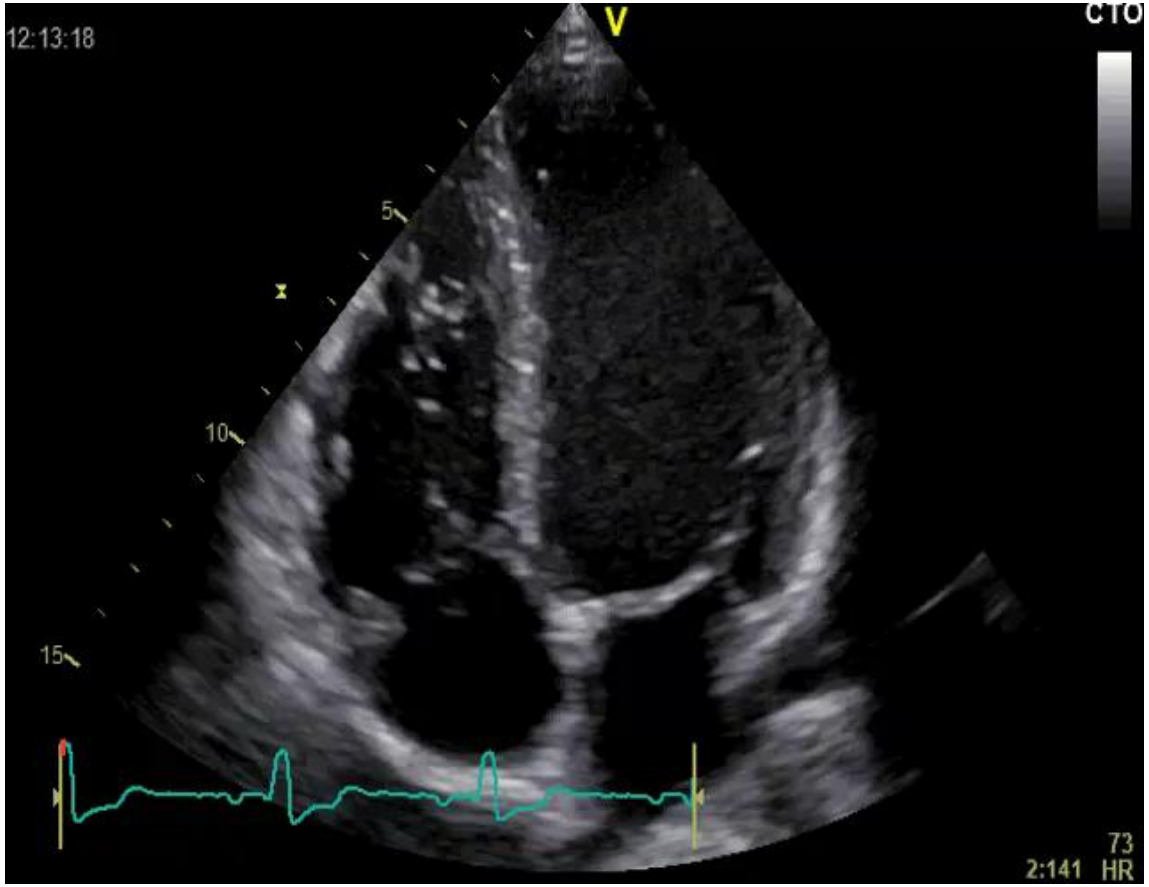
„Bimodale Verteilung“ der LVEF

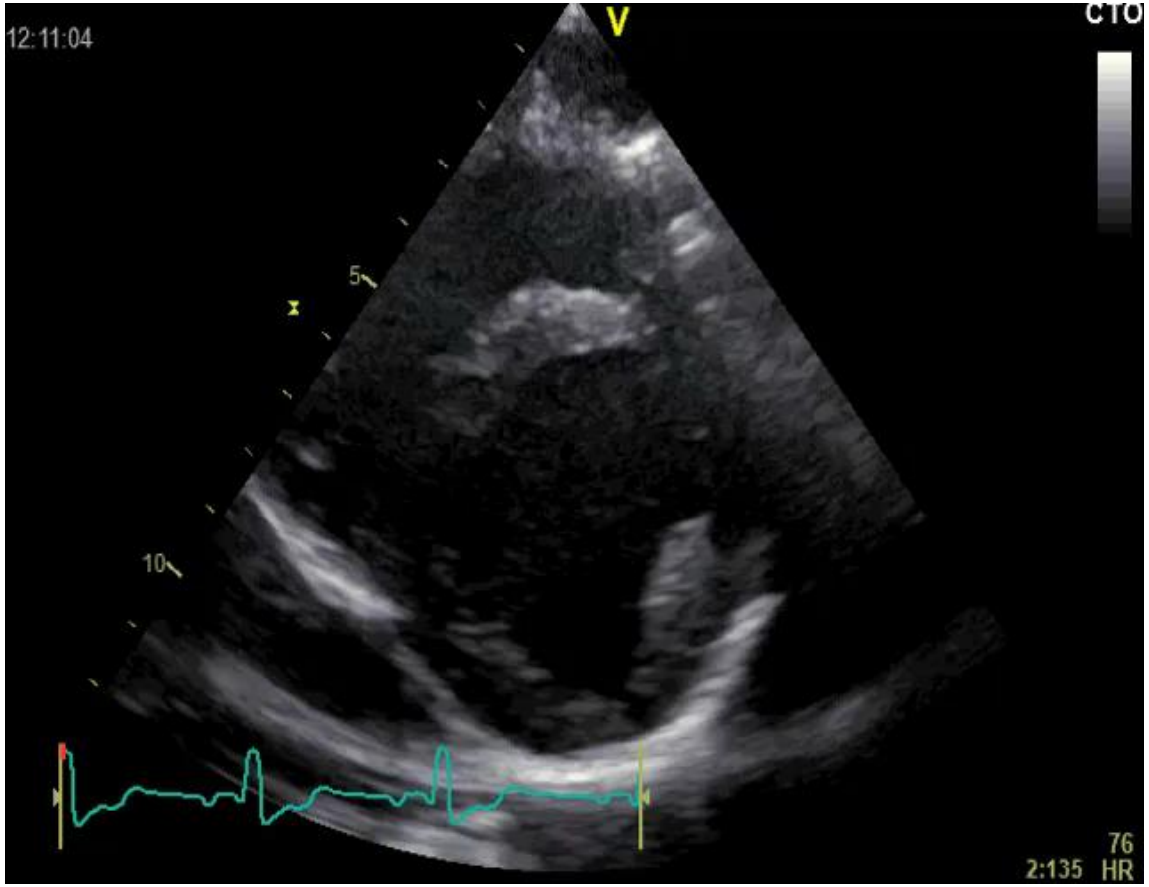




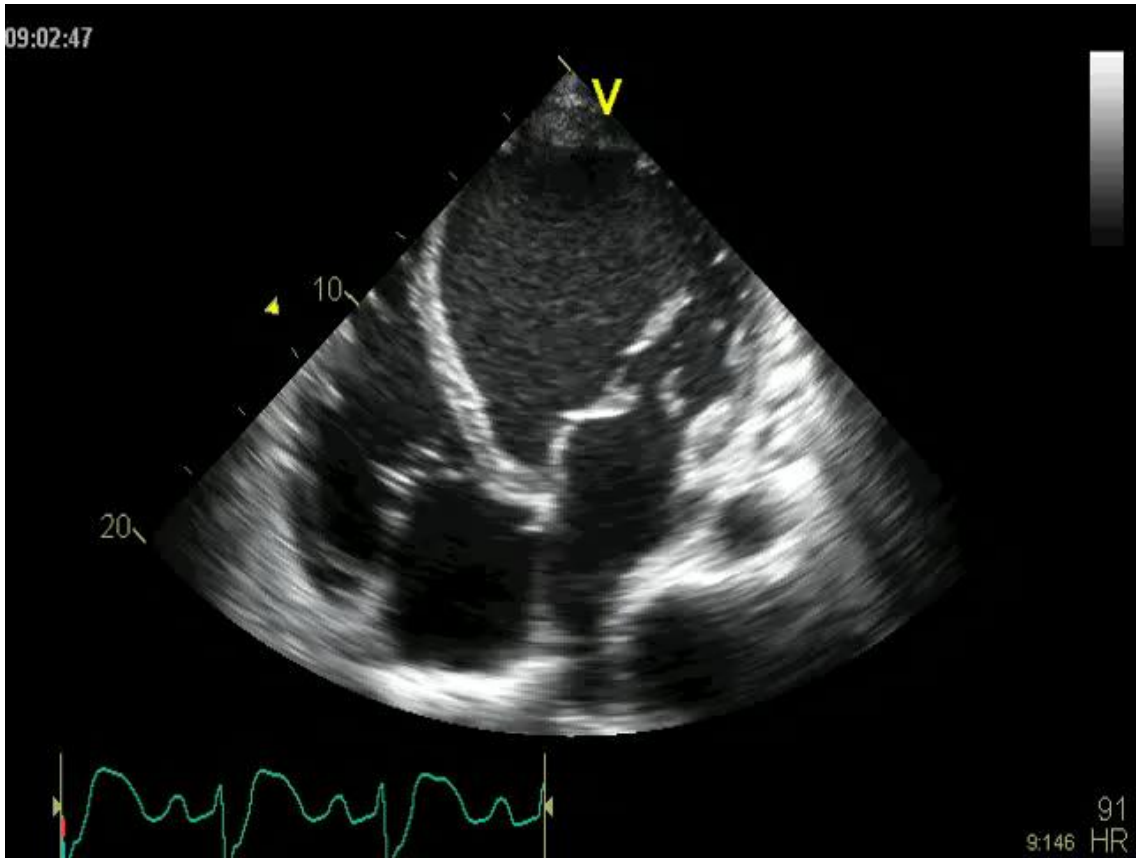
Savarese et al., Card Fail Rev, 2017

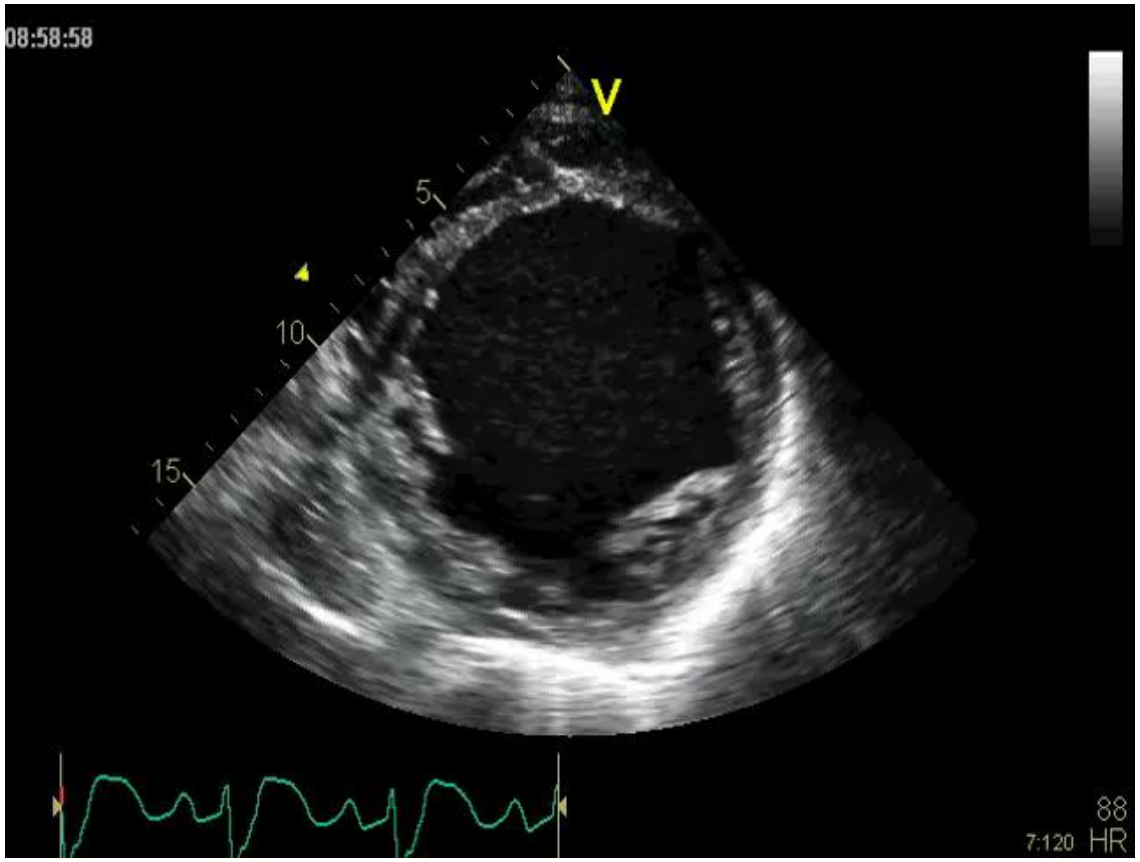
Echo - Gesundes Herz



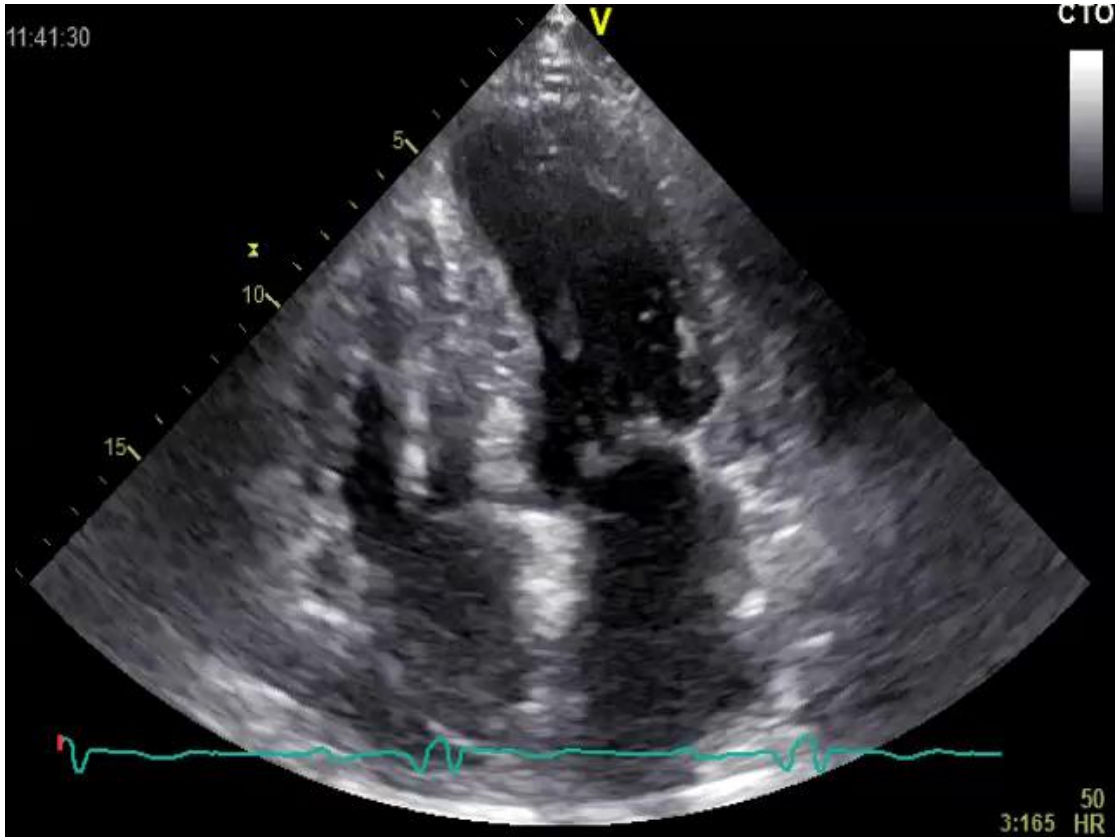


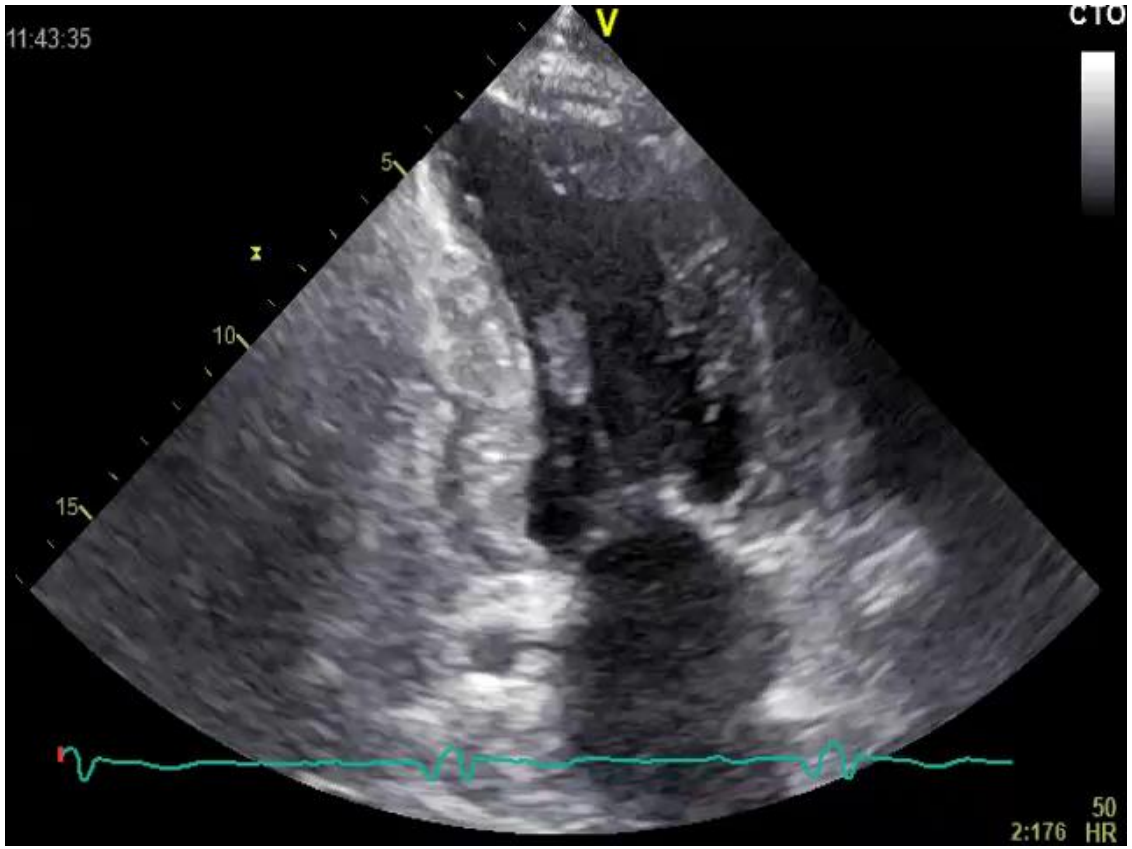
Echo – HFrEF bei dilatativer CMP





Echo – HFpEF bei Amyloidose





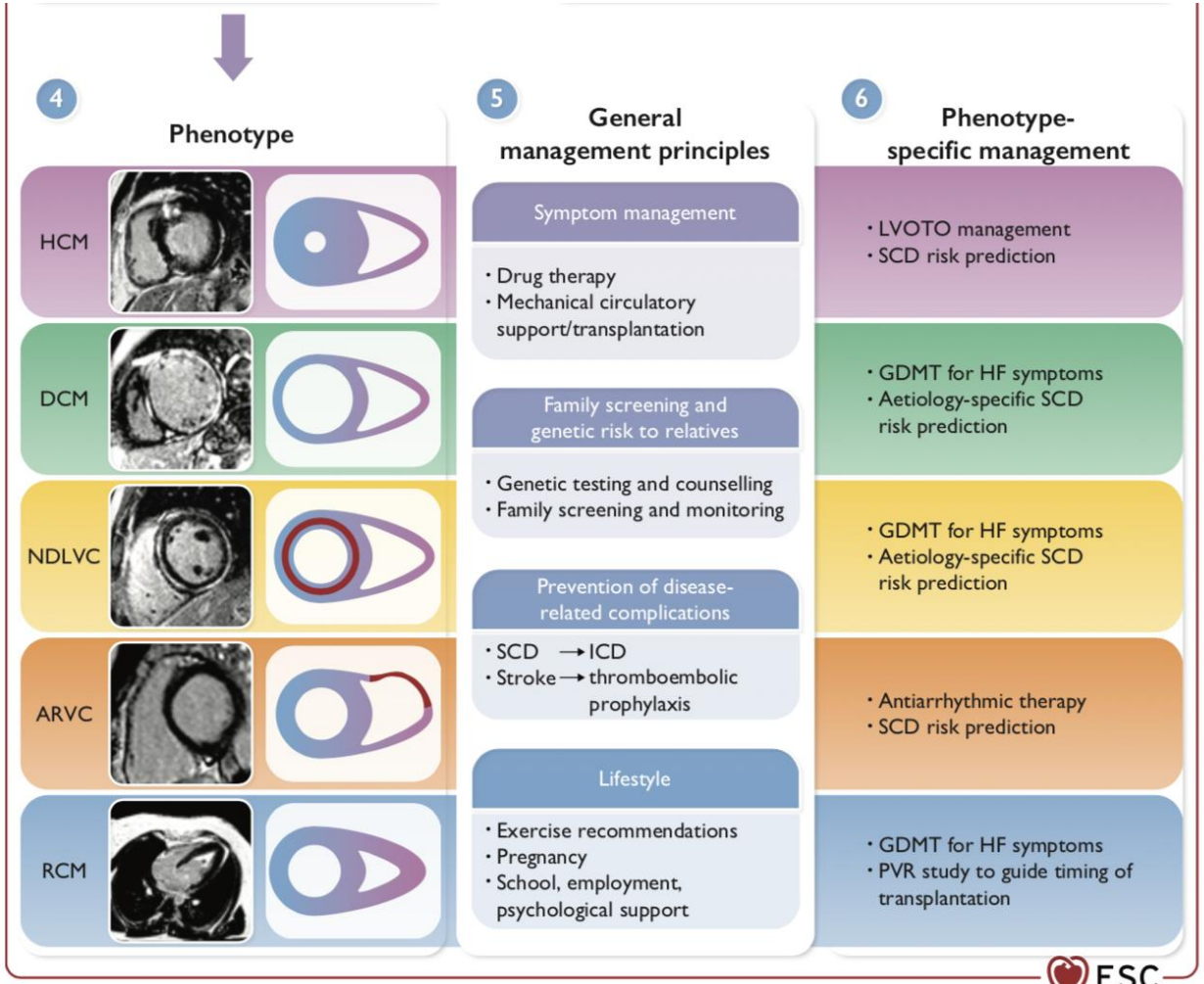
Die neuen ESC 2023 CMP guidelines: Phänotyp-basiertes diagnostisches work-up

neuer Phänotyp: NDLVC

Central illustration

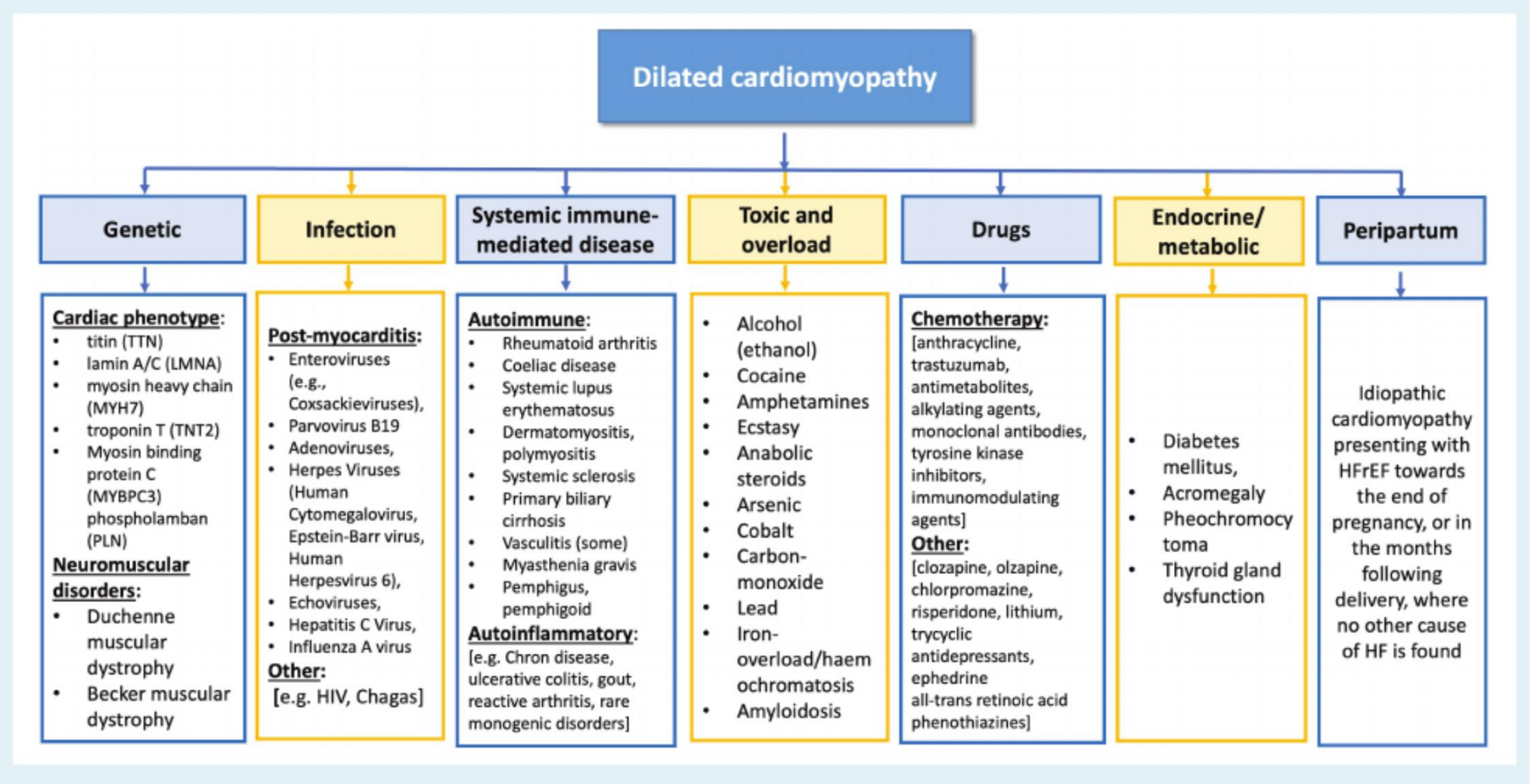
Key aspects in the evaluation and management of CMPs

The **patient pathway**, from presentation (**clinical scenario**) to the morphological and functional characterization (the **phenotype**) **using a multiparametric approach** that include additional variants such as pedigree analysis, genetic test, extracardiac involvement, laboratory markers, **to arrive at an aetiological diagnosis.**



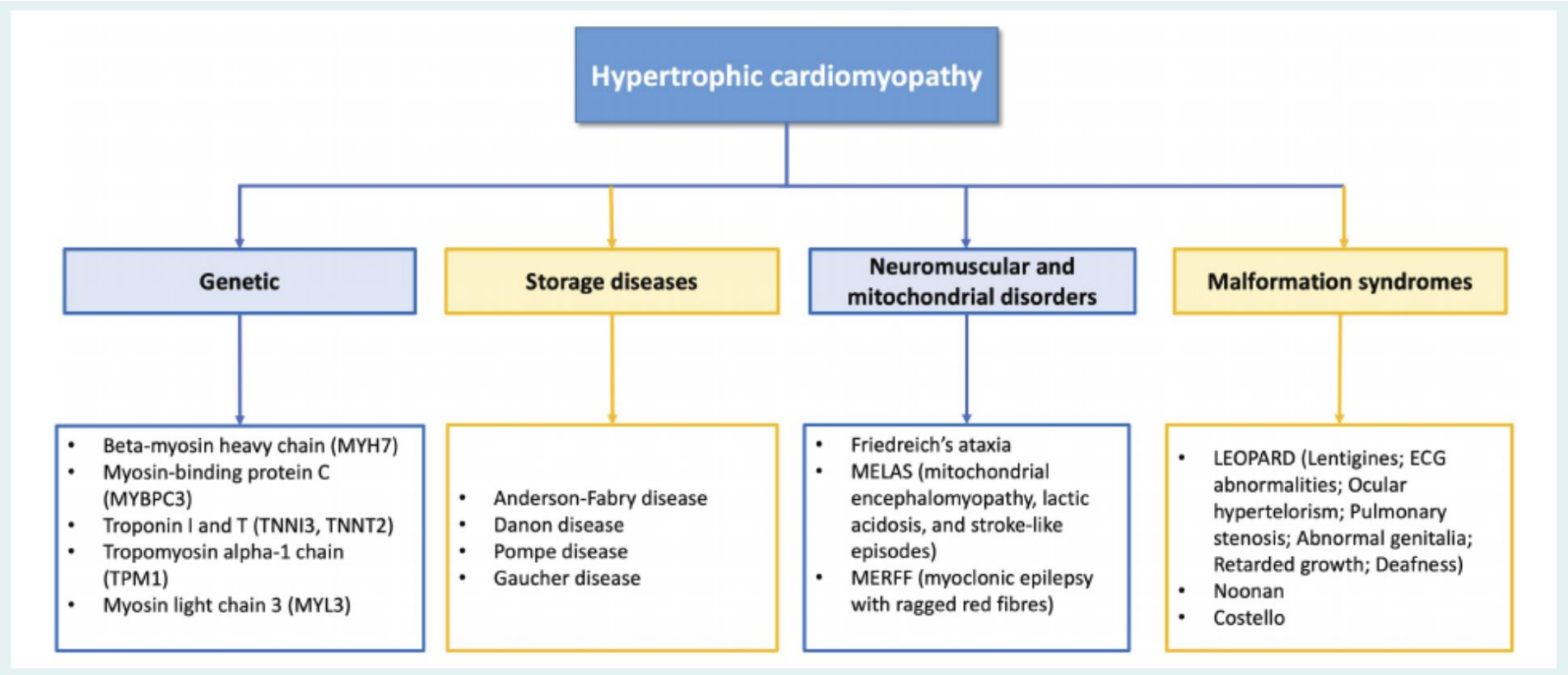
Arbelo et al, *EHJ*, 2023.

Ursachen der dilatativen CMP



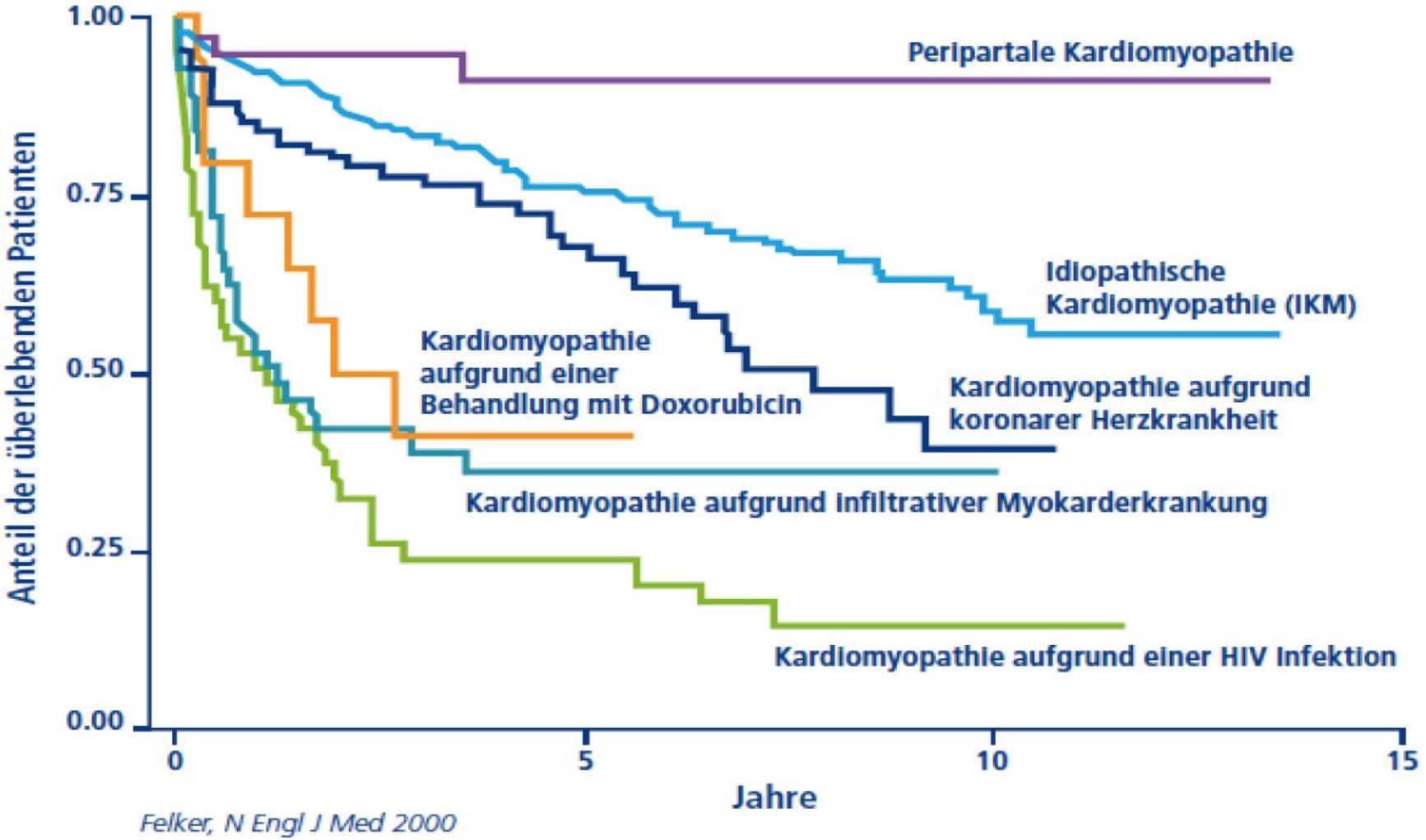
Seferovic et al, *EJHF*, 2019.

Ursachen der hypertrophen CMP



Seferovic et al, *EJHF*, 2019.

Je nach Ursache ganz andere Prognose



Felker, N Engl J Med 2000

Einige Ätiologien brauchen eine spezifische Therapie

Etiology for DCM	Specific Treatment
Alcoholic	Abstinence
Cocaine, illicit drugs	Abstinence
Collagen vascular disease	
SLE, RA, sarcoidosis	Steroids, cytotoxic or immunomodulating agents
Scleroderma	Steroids, Ca channel blockers for Raynaud
Kawasaki disease	IV Immunoglobulin
Viral myocarditis	Prednisone and immunosuppressant therapy or transplant for fulminant course
Chagas disease	Benznidazole, nifurtimox
HIV/AIDS	Highly active retroviral therapy, increase CD4 count
Nutritional deficiency	
Thiamine, selenium, or carnitine deficiency)	Replacement

Etiology for DCM	Specific Treatment
Hyperthyroidism/hypothyroidism	Achieve euthyroid state
Uremia	Dialysis
Pheochromocytoma	Removal of tumor
Tachycardia induced	Ablation, maintenance of sinus rhythm
Stress-induced cardiomyopathy	Management of psychosocial stress
Peripartum cardiomyopathy	Multidisciplinary high-risk pregnancy management, avoid subsequent pregnancy if LV function does not normalize
Chemotherapy-induced cardiomyopathy	Reduce dose or discontinue, avoid cardiotoxic other chemotherapy combinations and XRT, initiate early standard treatment for heart failure
Genetic	Genetic counseling, prenatal diagnosis, new experimental treatment modalities with gene editing, RNA silencing or RNA interference

AIDS, Acquired immunodeficiency syndrome; *DCM*, dilated cardiomyopathy; *HIV*, human immunodeficiency virus; *IV,* intravenous; *LV*, left ventricle; *RA,* rheumatoid arthritis; *SLE*, systemic lupus erythematosus; *XRT,* radiation therapy.

Ziel der Herzinsuffizienztherapie

5.2.1 Goals of pharmacotherapy for patients with heart failure with reduced ejection fraction

Pharmacotherapy is the cornerstone of treatment for HFrEF and should be implemented before considering device therapy, and alongside non-pharmacological interventions.

There are three major goals of treatment for patients with HFrEF: (i) reduction in mortality, (ii) prevention of recurrent hospitalizations due to worsening HF, and (iii) improvement in clinical status, functional capacity, and QOL.[100–102]

The key evidence supporting the recommendations in this section for patients with symptomatic HFrEF is given in *Supplementary Table 1*.

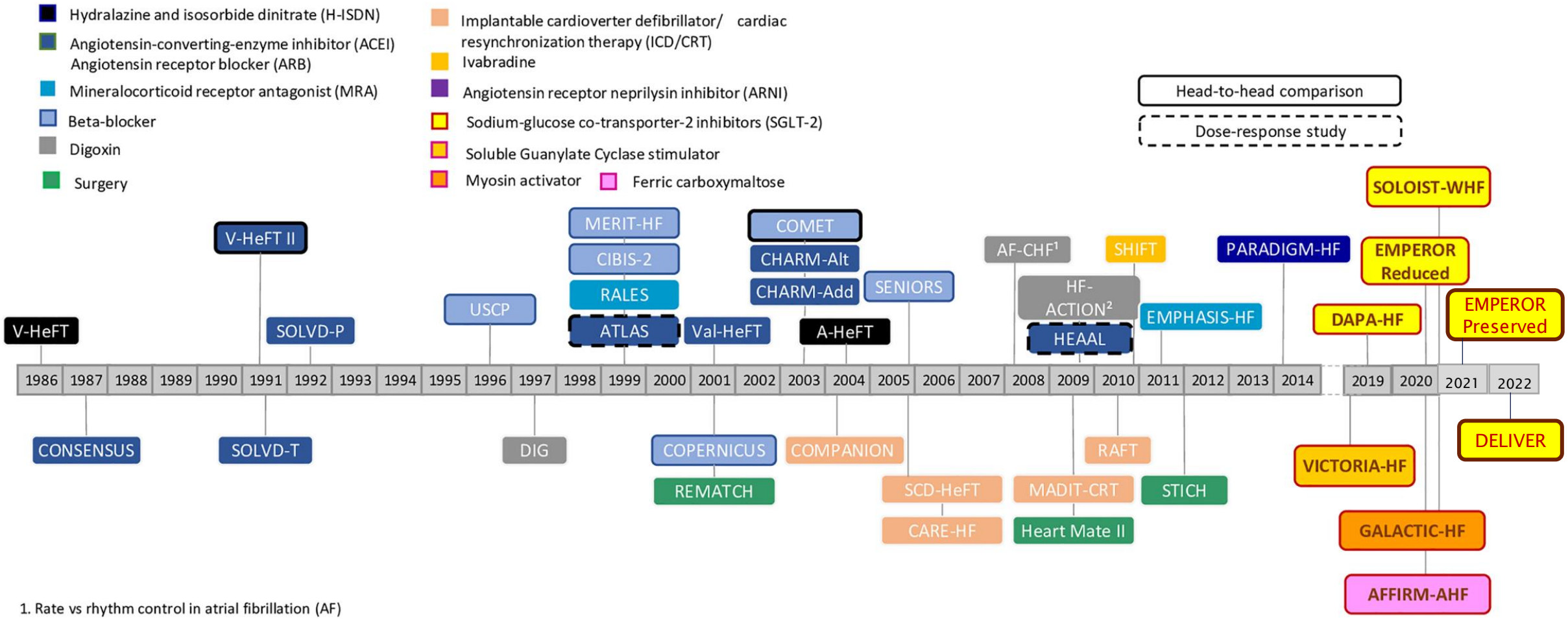
Figure 2 depicts the algorithm for the treatment strategy, including drugs and devices in patients with HFrEF, for Class I indications for the reduction of mortality (either all-cause or CV). The recommendations for each treatment are summarized below.

i) Reduktion der Mortalität

ii) Prävention der Hospitalisierung aufgrund Verschlechterung der Herzinsuffizienz

iii) Verbesserung des klinischen Status und der Leistungsfähigkeit

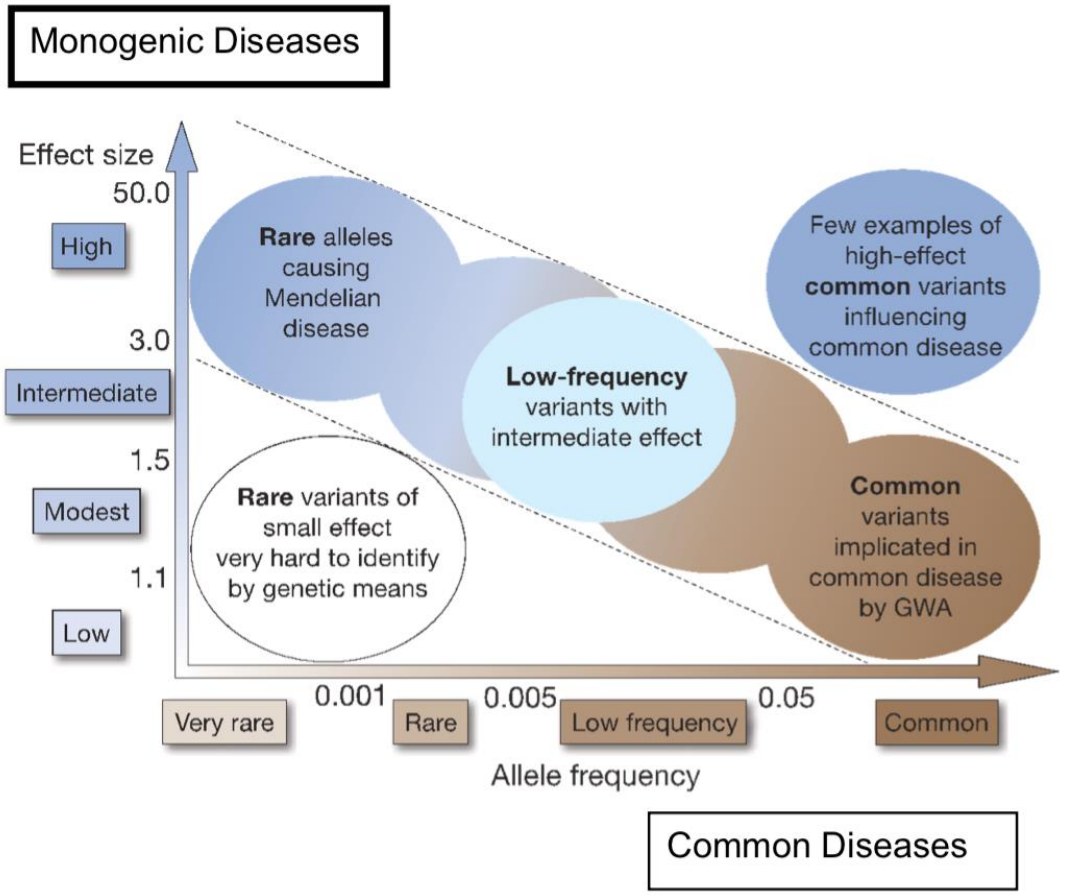
Meilensteine



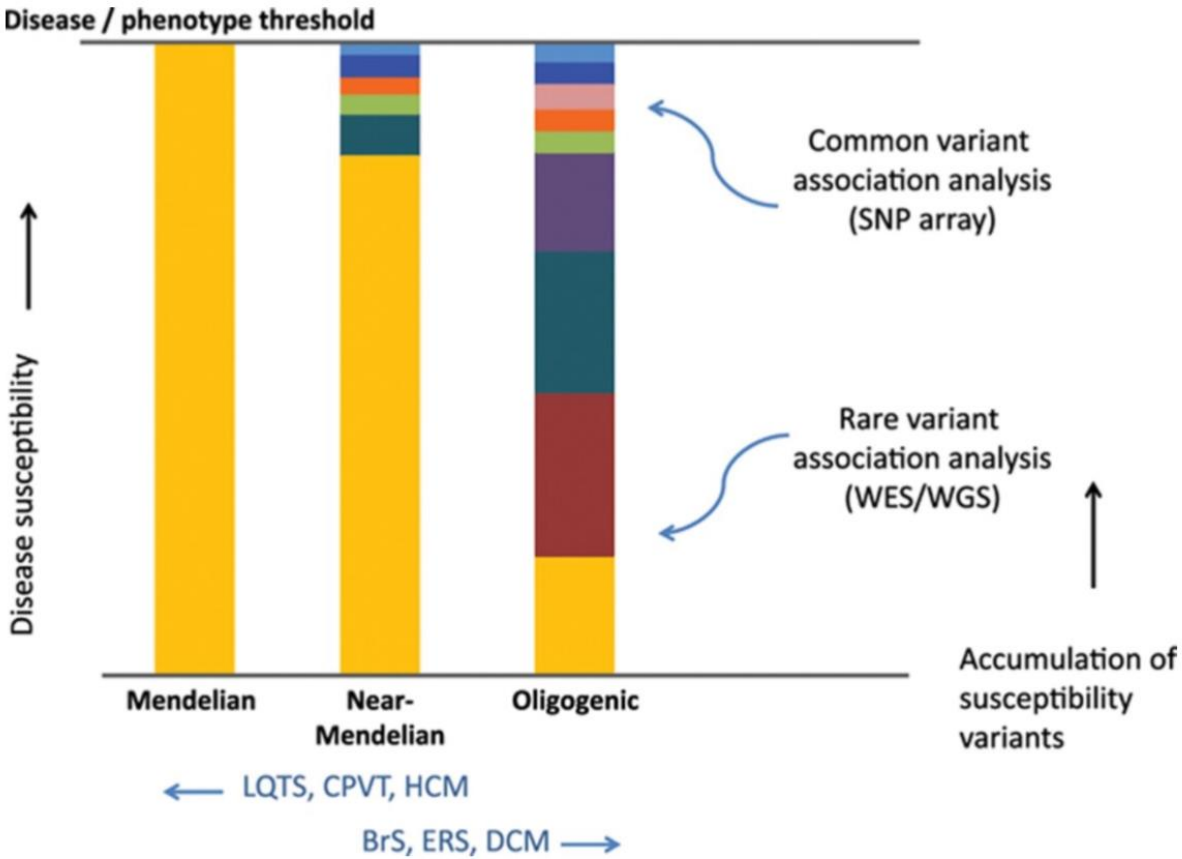
1. Rate vs rhythm control in atrial fibrillation (AF)
2. Exercise prescription

Genetisches Testen

Genetic architecture of „rare“ inherited cardiac conditions



Manolio et al, *Nature*, 2009.



Bezzina et al, *Crc Res*, 2015.

Table 1 | Genes associated with nonsyndromic familial dilated cardiomyopathy

Gene	Protein	Function	Estimated contribution to total number of patients	Allelic disorders
Sarcomere				
ACTC1[62,63]	α-Cardiac actin	Muscle contraction	<1%	Hypertrophic cardiomyopathy
ACTN2[64]	α-Actinin-2	Anchor for myofibrillar actin	1%	NA
ANKRD1[65]	Ankyrin repeat domain-containing protein 1	Localized to myopalladin/titin complex	NA	NA
CSRP3[66,67]	Cysteine and glycine-rich protein 3 (cardiac LIM protein)	Z-disc protein; stretch sensor	<1%	NA
MYBPC3[68,69]	Cardiac-type myosin-binding protein C	Muscle contraction	2%	Hypertrophic cardiomyopathy
MYH6[69,70]	Myosin-6 (α-myosin heavy chain)	Muscle contraction	4%	NA
MYH7[66,68,71,72]	Myosin-7 (β-myosin heavy chain)	Muscle contraction	4%	Laing distal myopathy, hypertrophic cardiomyopathy
MYPN[73]	Myopalladin	Z-disc protein	3–4%	NA
TCAP[66,74]	Telethonin (titin cap protein)	Z-disc protein; sarcomere assembly	1%	LGMD2G
TNNC1[75,76]	Cardiac muscle troponin C	Muscle contraction	<1%	NA
TNNI3[75,77,78]	Cardiac muscle troponin I	Muscle contraction	<1%	NA
TNNT2[66,71,72,79,80]	Cardiac muscle troponin T	Muscle contraction	3%	Hypertrophic cardiomyopathy
TPM1[75,81,82]	α -Tropomyosin	Muscle contraction	<1%	Hypertrophic cardiomyopathy
TTN[36–38,83]	Titin	Extensible scaffold	25%	Udd distal myopathy, hypertrophic cardiomyopathy
Cytoskeleton				
DES[84,85]	Desmin	Transduces contractile forces	<1%	Desminopathy, myofibrillar myopathy
DMD[86,87]	Dystrophin	Transduces contractile forces	NA	Dystrophinopathies (Duchenne muscular dystrophy, Becker muscular dystrophy)
ILK[88]	Integrin-linked protein kinase	Intracellular serine–theonine kinase; interacts with integrins	<1%	NA
LAMA4[88]	Laminin subunit α_4	Extracellular matrix protein	1%	NA
LDB3[67,89]	LIM domain-binding protein 3 (protein cypher, ZASP)	Cytoskeletal assembly; clustering of membrane proteins	1%	NA
PDLIM3[90]	PDZ and LIM domain protein 3	Cytoskeletal protein	<1%	NA
SGCD[91–93]	δ-Sarcoglycan	Transduces contractile forces	<1%	δ-Sarcoglycanopathy (LGMD2F)
VCL[72,94]	Vinculin	Sarcomere structure; intercalated discs	1%	NA
Nuclear envelope				
LMNA[43,95–106]	Lamin-A/C	Stability of inner nuclear membrane; regulation of gene expression	6%	Partial lipodystrophy, Charcot–Marie–Tooth disease type 2B1, Emery–Dreifuss muscular dystrophy, Hutchinson–Gilford progeria syndrome, LGMD1B
TMPO[107]	Thymopoietin	Lamin-associated nuclear protein	1%	NA
γ-Secretase activity				
PSEN1[108]	Presenilin-1	Transmembrane protein, γ-secretase activity	<1%	Alzheimer disease
PSEN2[108]	Presinillin-2	Transmembrane protein, γ-secretase activity	<1%	Alzheimer disease
Ion channel				
ABCC9[82]	ATP-binding cassette subfamily C member 9 (sulfonylurea receptor 2)	$K_{ir}6.2$ regulatory subunit; inwardly rectifying cardiac K_{ATP} channel	<1%	NA
SCN5A[66,109,110]	Sodium channel protein type 5 subunit α	Controls Na^+ flux	2–3%	Long QT syndrome
Mitochondrial				
TAZ (G4.5)[111,112]	Tafazzin	NA	NA	Barth syndrome, endocardial fibroelastosis type 2, familial isolated noncompaction of the left ventricular myocardium
Spliceosomal				
RBM20[113,114]	RNA-binding protein 20	Spliceosome protein; regulates splicing of several cardiac genes	2%	NA
Sarcoplasmic reticulum				
PLN[72,115–118]	Phospholamban	Sarcoplasmic reticulum Ca^{2+} regulator; inhibits SERCA2a pump	<1%	NA
Desmosomal				
DSC2[119]	Desmocollin-2	Component of desmosomal junction	NA	Arrhythmogenic right ventricular cardiomyopathy
DSG2[119]	Desmoglein-2	Component of desmosomal junction	NA	Arrhythmogenic right ventricular cardiomyopathy
DSP[119]	Desmoplakin	Component of desmosomal junction	NA	Arrhythmogenic right ventricular cardiomyopathy
Other				
BAG3[120,121]	BAG family molecular chaperone regulator 3	Inhibits apoptosis	NA	Myofibrillar myopathy
CRYAB[122]	α-Crystalin B chain	Cytoskeletal protein	<1%	NA
EYA4[123]	Eyes absent homolog 4	Transcriptional coactivator	NA	NA

Abbreviations: LGMD, limb girdle muscular dystrophy; NA, not applicable or not available; SERCA2a, sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2a.

Hershberger et al, *Nat rev cardiol*, 2013.

Genes and dilated cardiomyopathy – allelic heterogenity
disease-causing mutations are scattered across one gene

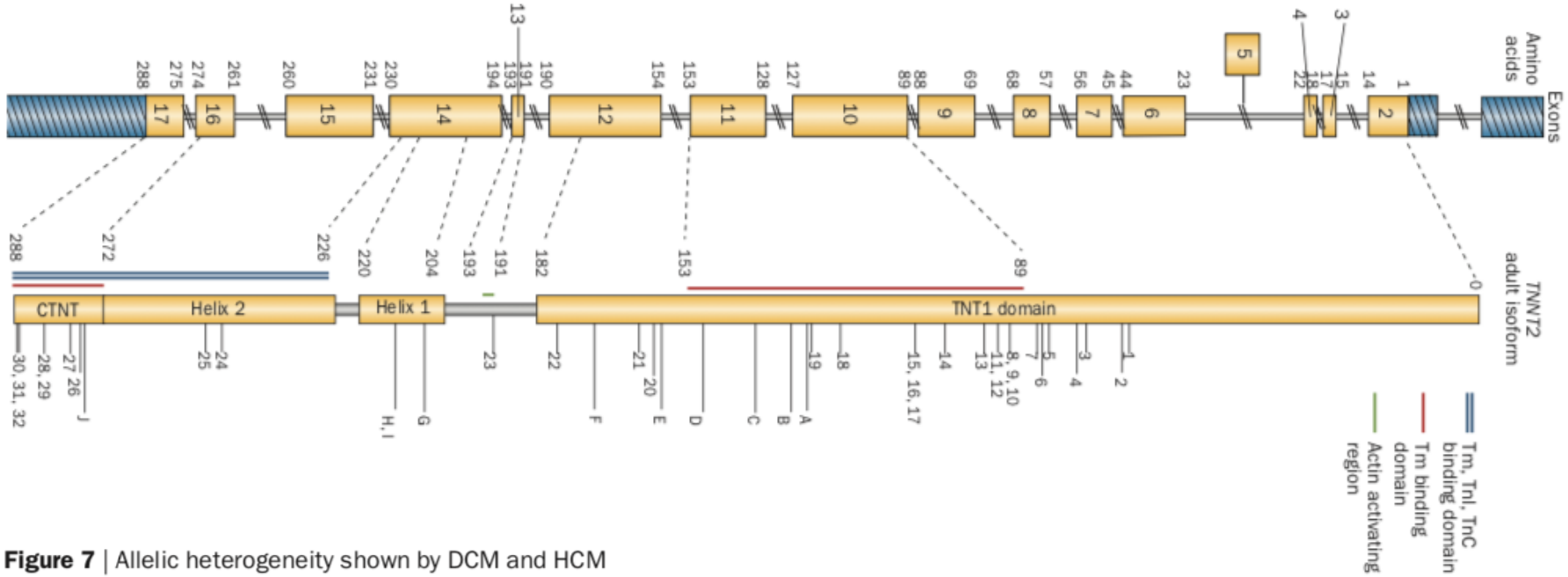
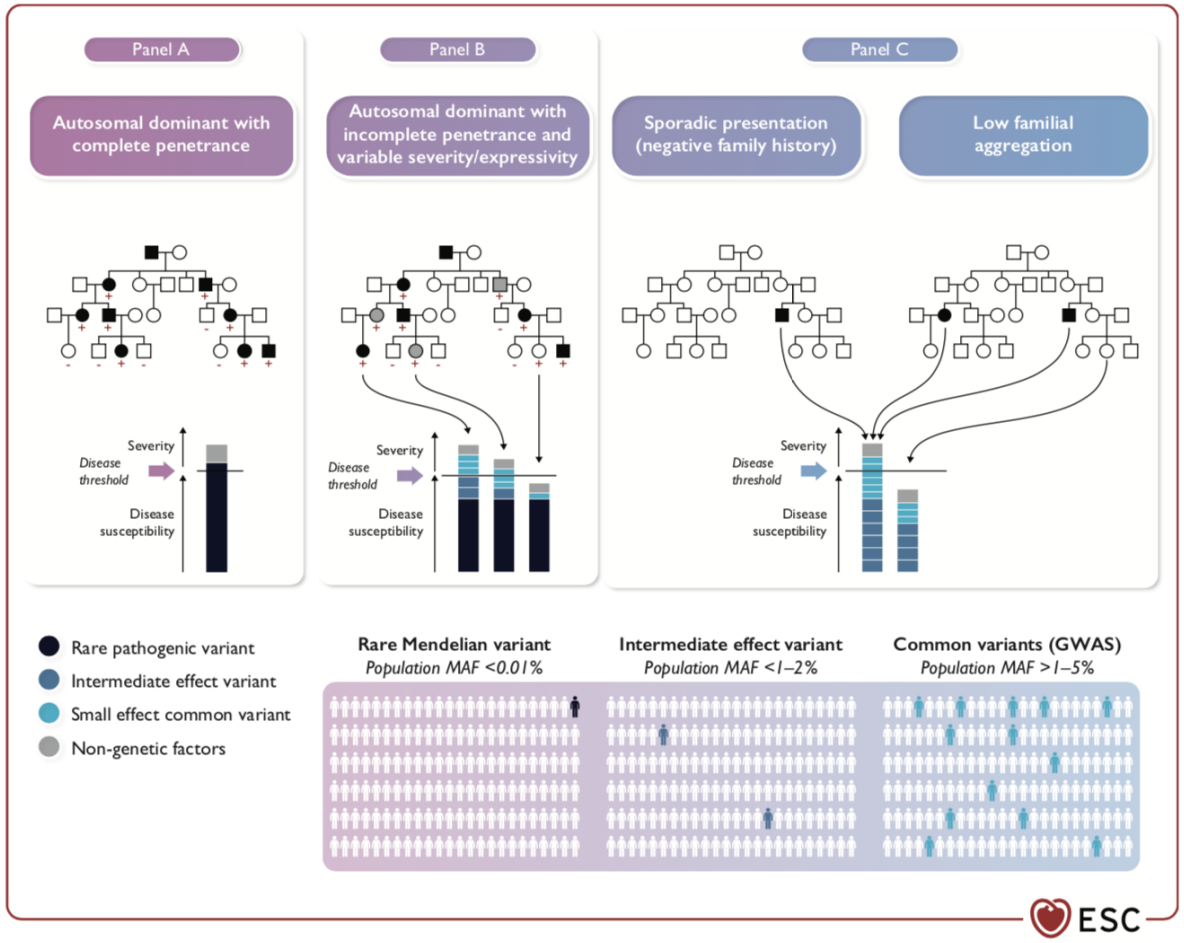


Figure 7 | Allelic heterogeneity shown by DCM and HCM mutations in *TNNT2*, which encodes cardiac troponin T.[130] *TNNT2* and its adult protein isoform, cardiac troponin T, are shown, encoded by exons 2–17 encompassing 288 amino acids. DCM mutations are shown by letters (A–J), and HCM mutations are shown by numbers (1–32). The binding regions for other key sarcomeric proteins are illustrated.

* Complicated the prediction of the phenotype
* Same phenotype by different mutations
* DCM or HCM by the same mutation

Burke et al, *JACC*, 2016.

Die neuen ESC 2023 CMP guidelines: Genetisches Testen



Gene	Cardiomyopathy phenotype					Associated phenotype
	HCM	DCM	NDLVC	ARVC	RCM	
ABCC9	[a]	○				[a] Cantu syndrome
ACTA1	○					
ACTC1	●	◐	◐	○	◐	
ACTN2[b]	◐	◐	◐			
ALPK3	●					
ANKRD1	○	○				
BAG3	[a]	●●			◐	[a] Myofibrillar myopathy
CACNA1C	[c]					[c] Timothy syndrome
CACNB2	○					
CALR3	○					
CASQ2	○					
CAV3	[a]					[a] Caveolinopathy
CDH2				○		
COX15	[a]					[a] Leigh syndrome
CRYAB	[a]					[a] Alpha-B crystallinopathy
CSRP3	◐	○				
CTF1		○				

Arbelo et al, *EHJ*, 2023.

Die neuen ESC 2023 CMP guidelines: Genetisches Testen

Recommendations	Class[a]	Level[b]
Genetic counselling		
Genetic counselling, provided by an appropriately trained healthcare professional and including genetic education to inform decision-making and psychosocial support, is recommended for families with an inherited or suspected inherited cardiomyopathy, regardless of whether genetic testing is being considered.[204,206,208,209,221–224]	I	B
It is recommended that genetic testing for cardiomyopathy is performed with access to a multidisciplinary team, including those with expertise in genetic testing methodology, sequence variant interpretation, and clinical application of genetic testing, typically in a specialized cardiomyopathy service or in a network model with access to equivalent expertise.[222,224–226]	I	B
Pre- and post-test genetic counselling is recommended in all individuals undergoing genetic testing for cardiomyopathy.[204,208,227–236]	I	B
If pre-natal diagnostic testing is to be pursued by the family, it is recommended that this is performed early in pregnancy, to allow decisions regarding continuation or co-ordination of pregnancy to be made.	I	C
A discussion about reproductive genetic testing options with an appropriately trained healthcare professional should be considered for all families with a genetic diagnosis.	IIa	C
Index patients		
Genetic testing is recommended in patients fulfilling diagnostic criteria for cardiomyopathy in cases where it enables diagnosis, prognostication, therapeutic stratification, or reproductive management of the patient, or where it enables cascade genetic evaluation of their relatives who would otherwise be enrolled into long-term surveillance.[227–231,237,238]	I	B
Genetic testing is recommended for a deceased individual identified to have cardiomyopathy at *post-mortem* if a genetic diagnosis would facilitate management of surviving relatives.[239–243]	I	C
Genetic testing may be considered in patients fulfilling diagnostic criteria for cardiomyopathy when it will have a net benefit to the patient, considering the psychological impact and preference, even if it does not enable diagnosis, prognostication, or therapeutic stratification, or cascade genetic screening of their relatives.	IIb	C
Genetic testing in patients with a borderline phenotype not fulfilling diagnostic criteria for a cardiomyopathy may be considered only after detailed assessment by specialist teams.	IIb	C
Family members		
It is recommended that cascade genetic testing, with pre- and post-test counselling, is offered to adult at-risk relatives if a confident genetic diagnosis (i.e. a P/LP variant) has been established in an individual with cardiomyopathy in the family (starting with first-degree relatives if available, and cascading out sequentially).[204,227–232]	I	B
Cascade genetic testing with pre- and post-test counselling should be considered in paediatric at-risk relatives if a confident genetic diagnosis (i.e. a P/LP variant) has been established in an individual with cardiomyopathy in the family (starting with first-degree relatives, if available, and cascading out sequentially), considering the underlying cardiomyopathy, expected age of onset, presentation in the family, and clinical/legal consequences.[233–236,244]	IIa	B
Testing for the presence of a familial variant of unknown significance, typically in parents and/or affected relatives, to determine if the variant segregates with the cardiomyopathy phenotype should be considered if this might allow the variant to be interpreted with confidence.	IIa	C
Diagnostic genetic testing is not recommended in a phenotype-negative relative of a patient with cardiomyopathy in the absence of a confident genetic diagnosis (i.e. a P/LP variant) in the family.	III	C

Arbelo et al, *EHJ*, 2023.

Herzinsuffizienz

Pharmakologische Therapiestrategien – die 4 Säulen

Die vier Säulen der pharmakologischen Therapie

HFrEF

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

ACE-I = angiotensin-converting enzyme inhibitor; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.

[a]Class of recommendation.

[b]Level of evidence.

HFmrEF und HFpEF

HFmrEF

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

HFmrEF scheint mehr zur HFrEF als zur HFpEF zu gehören. Die 4 Säulen der HFrEF Therapie erhalten aufgrund der meist retrospektiver Analysen der HFmrEF Subgruppen eine IIb C Empfehlung.

HFpEF

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

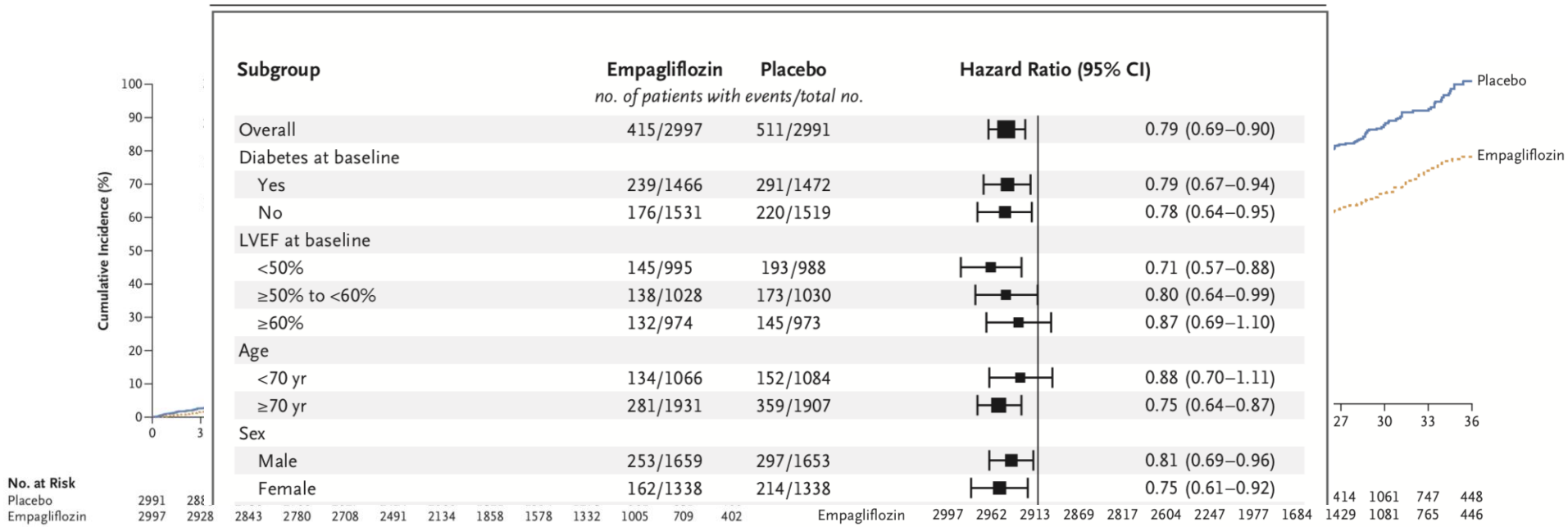
Reducing body weight in obese patients and increasing exercise may further improve symptoms and exercise capacity and should therefore be considered in appropriate patients.

Obwohl Erfolge für einzelne spezifische Formen der HFpEF erzielt wurden, konnte bis 2021 keine Therapie die Mortalität oder Morbidität in der HFpEF überzeugend reduzieren.

EMPEROR-Preserved

Whether SGLT2 inhibitors are effective in patients with a higher left ventricular ejection fraction remains less certain.

5988 patients, LVEF >40%
NT-proBNP 300pg/ml (SR) / 900pg/ml (VHF)
Empagliflozin vs placebo



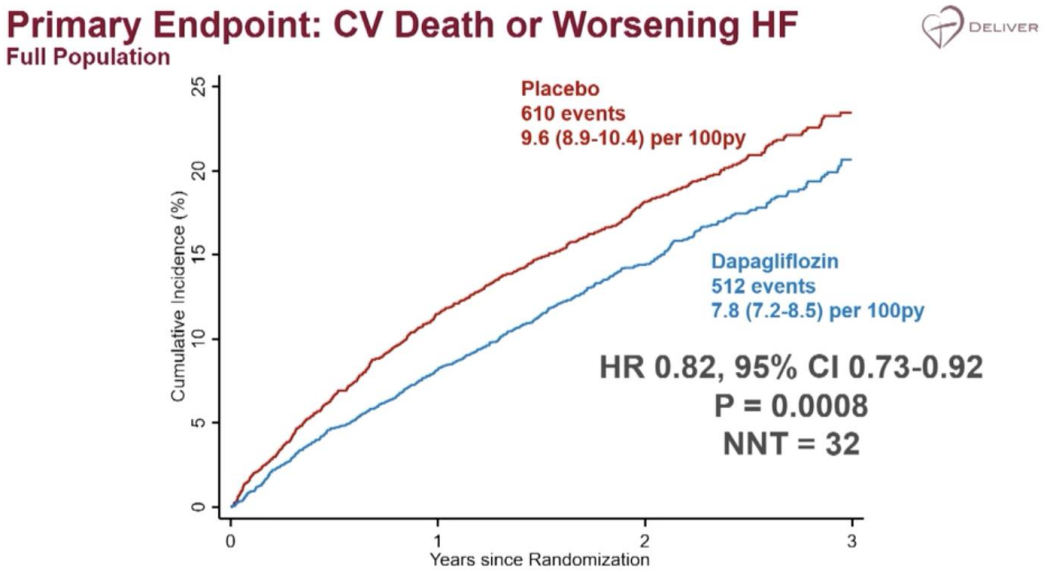
Anker et al, *NEJM*, 2021.

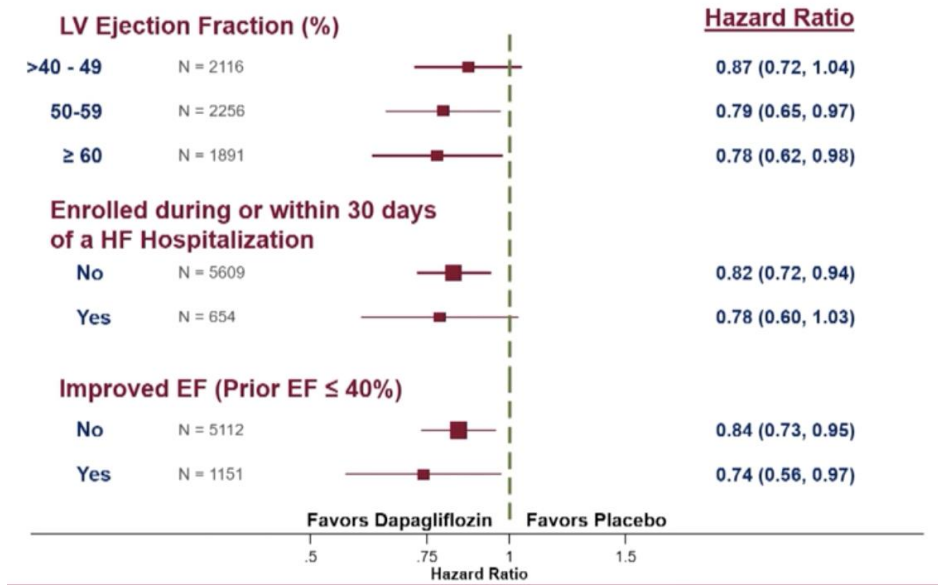
Empagliflozin reduced the combined risk of CV death or HHF in patients with HFpEF, regardless of the presence or absence of diabetes.

DELIVER

Whether SGLT2 inhibitors are effective in patients with a higher left ventricular ejection fraction remains less certain.

6263 patiients, LVEF >40%
Structural heart disease (LVH or LA enlargement)
NT-proBNP 300pg/ml (SR) / 600pg/ml (VHF)
Dapagliflozin vs placebo



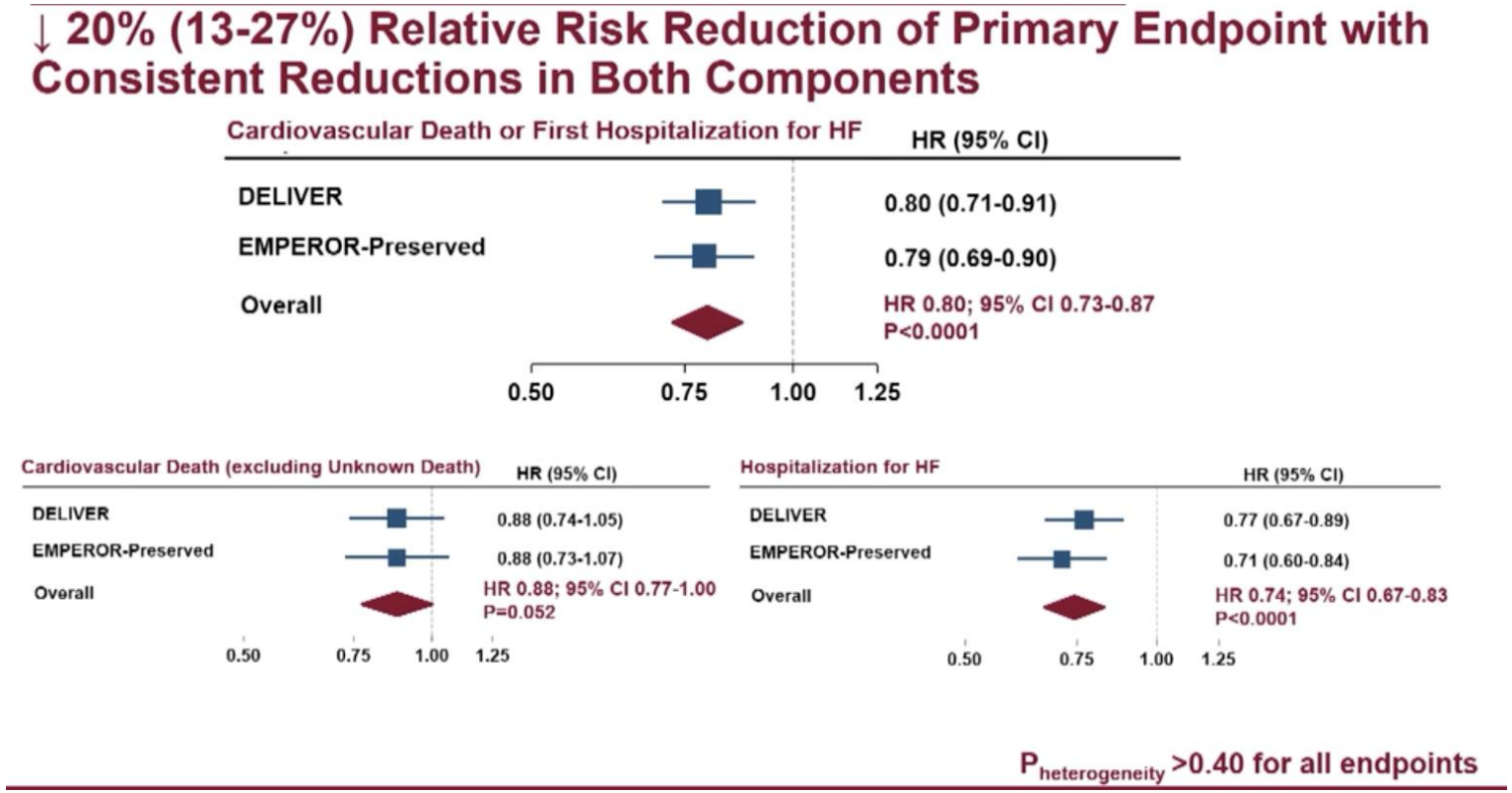


Solomon et al, *NEJM*, 2022.

Supports the use of SGLT2i as foundational therapy in patients with regardless of care setting and LVEF.

DELIVER – EMPEROR-Preserved

What is the treatment effect of SGLT2i in LVEF>40%?



Vaduganathan et al, clinical trial results.

20% RR reduction on primary endpoint consistent in both components.

SGLT2i auch für HFmrEF und HFpEF nun I A

2023 ESC Guideline Update

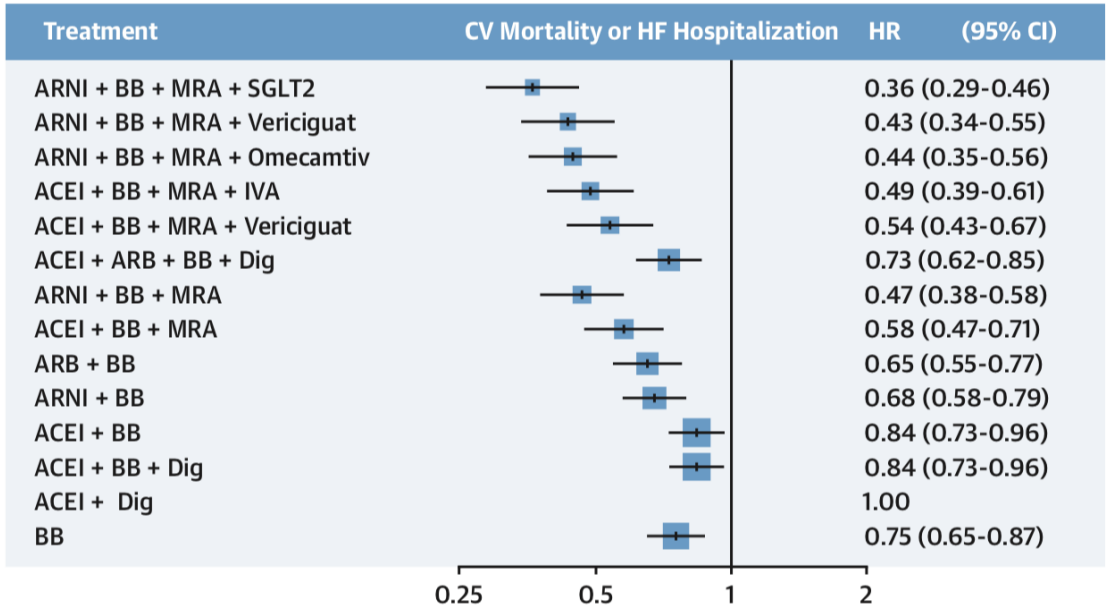
Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of HF hospitalization or CV death.[c] [6,8]	I	A

Recommendation	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

Aufgrund EMPEROR-Preserved und DELIVER erhalten SGLT2i für HFmrEF und HFpEF eine Klasse I A Empfehlung.

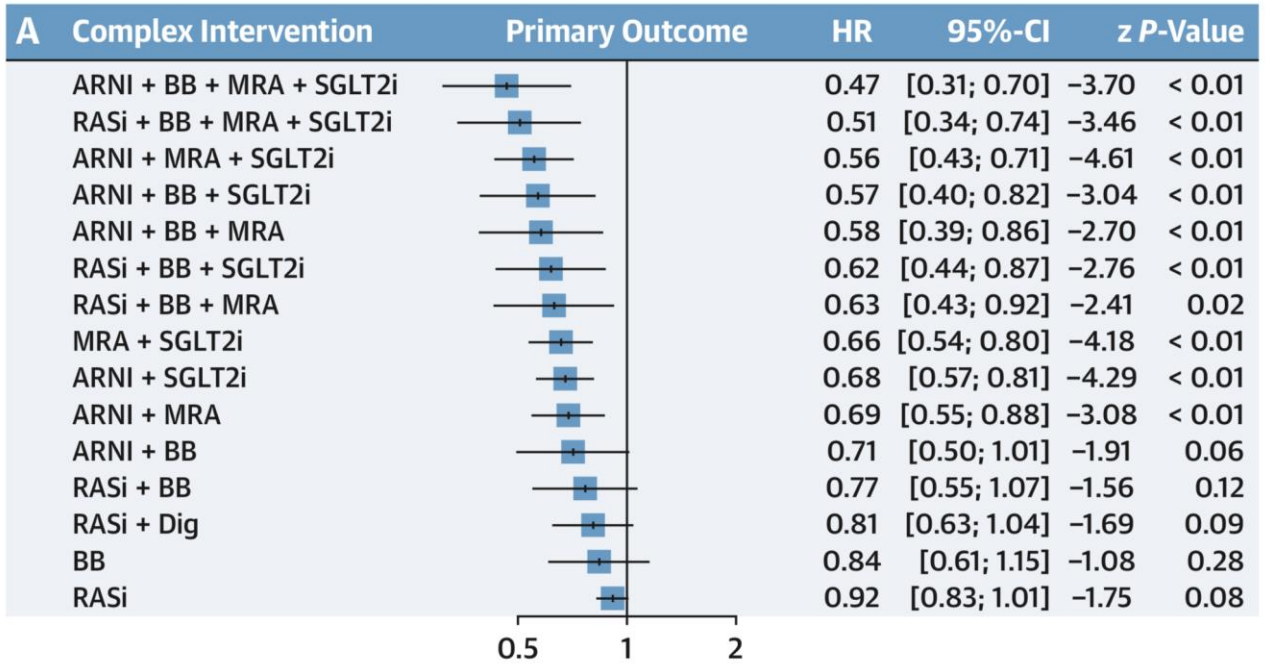
Reduktion der Mortalität/HHF mit der Kombination von HF Medikamenten

HFrEF



Tromp et al, *JACC HF*, 2022.

HFmrEF + HFpEF

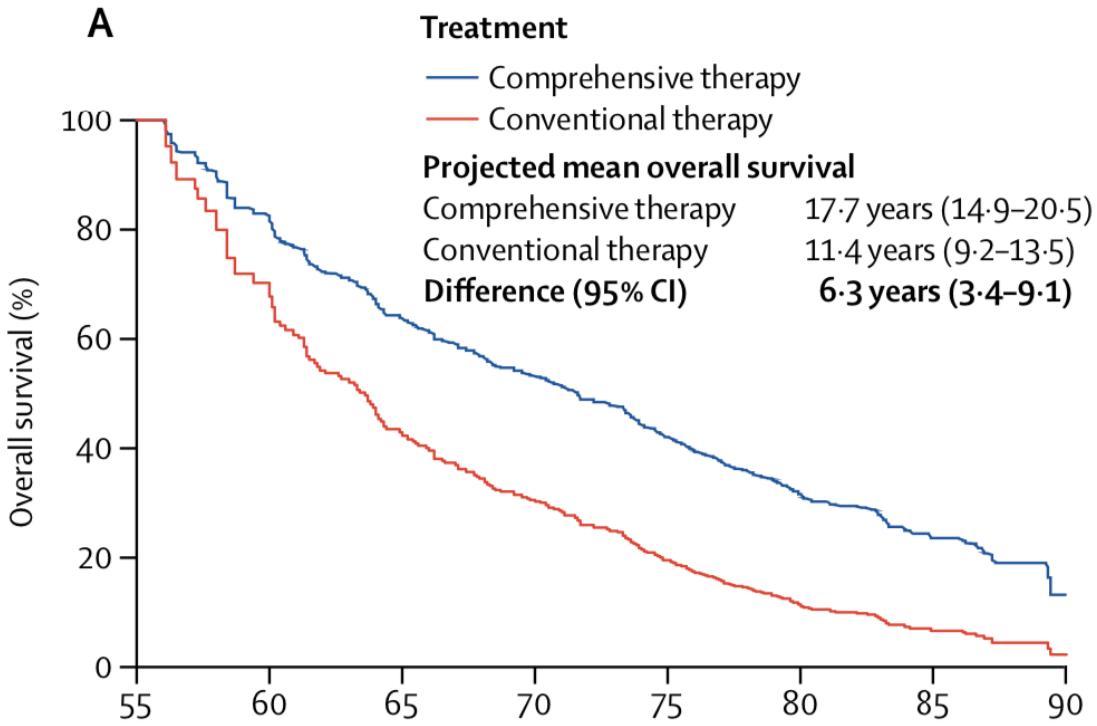


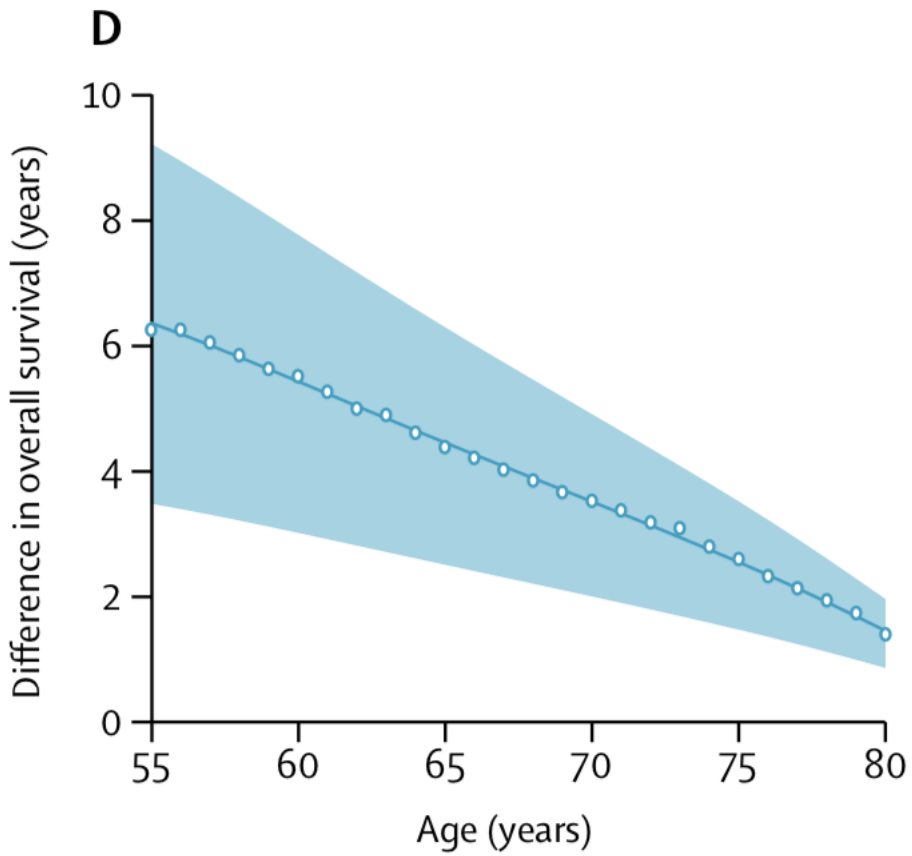
Zafeiropoulos et al, *JACC HF*, 2023.

GDMT verlängert das Überleben und verlangsamt die Progression

EMPHASIS-HF, PARADIGM-HF, DAPA-HF
N=15880, control group: control arm of EMPHASIS-HF

start at age of 55 years

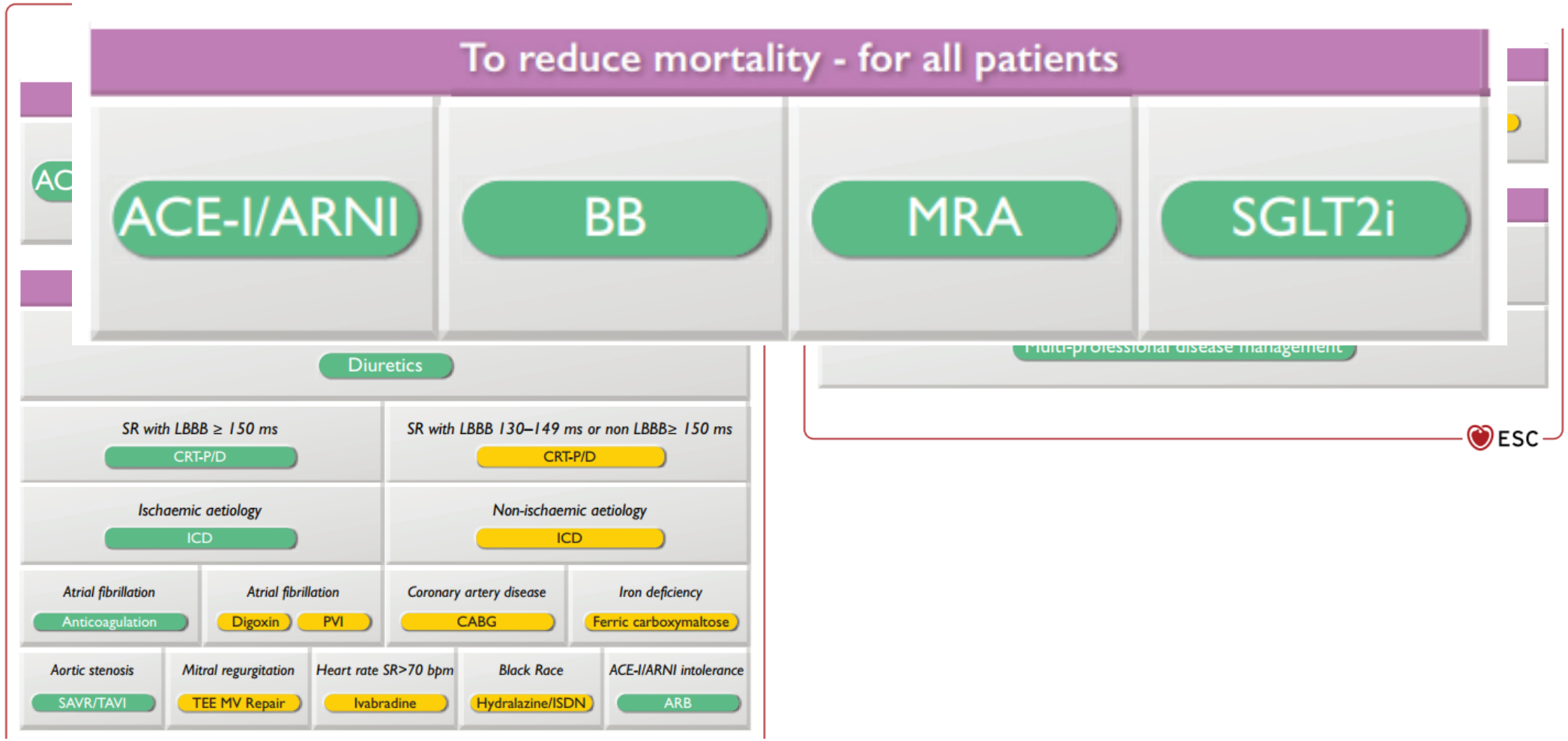




Vaduganathan et al, *Lancet*, 2020.

Therapie-Implementierung

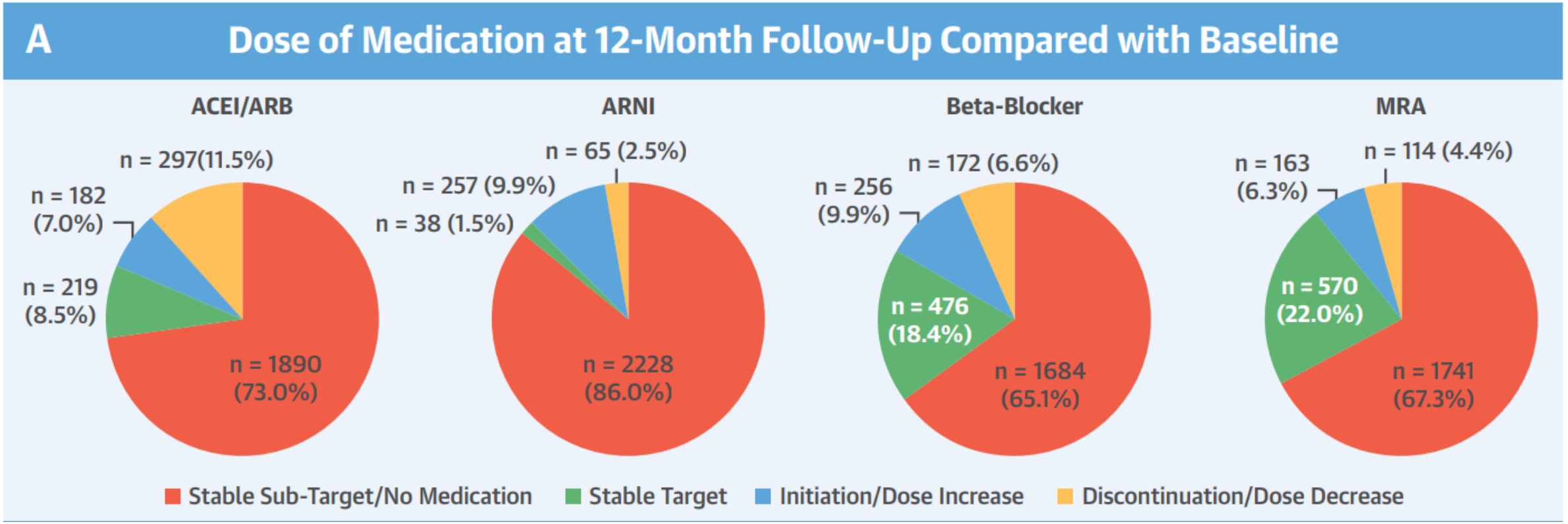
Die 4 Säulen und weitere Therapien nach klinischem Profil



Die 4 Säulen der HF Therapie sind bezüglich des Zeitpunktes für Therapiebeginn in den Guidelines 2021 nicht mehr sequentiell sondern gleichgestellt.

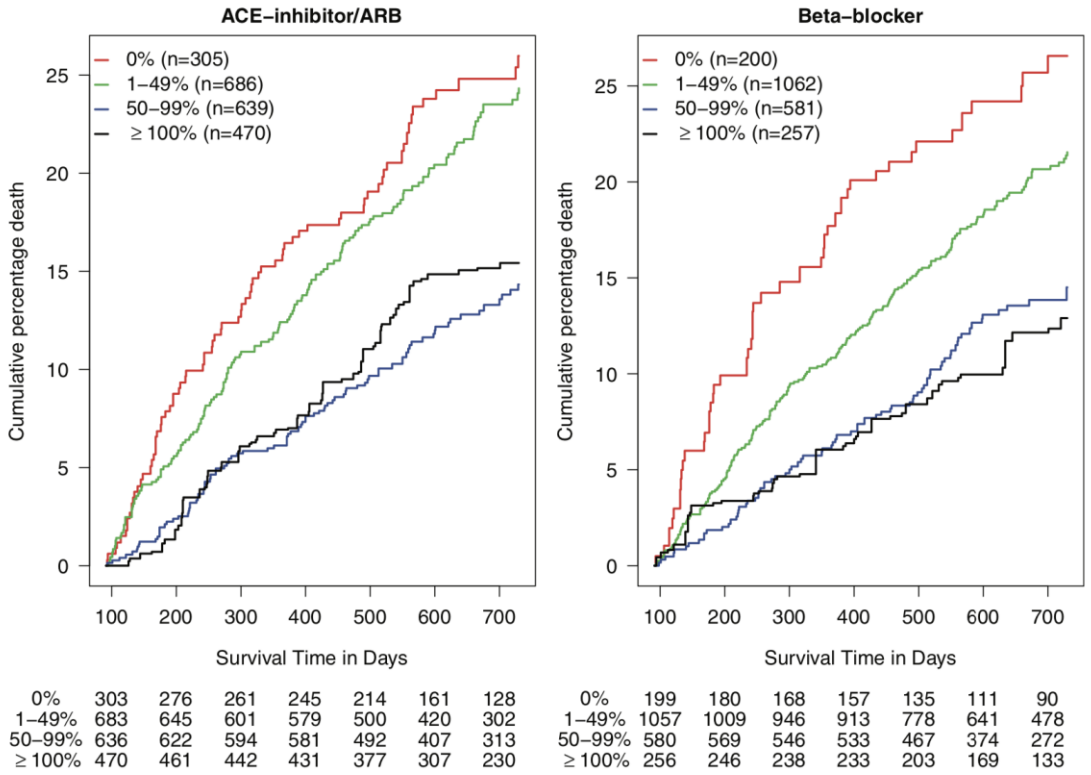
Nur <10% der Patienten haben die optimale Zieldosis

2588 HFrEF outpatients from the CHAMP-HF registry (US)



Greene et al, *JACC*, 2019.

Auftitration auf Zieldosis oder individuell maximal tolerierte Dosis

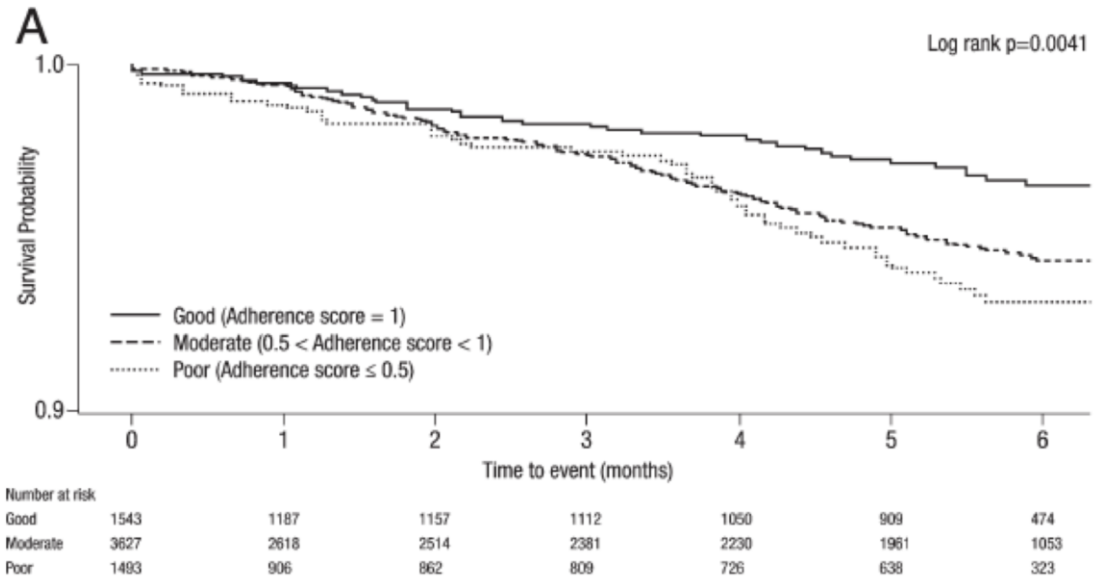


0%	303	276	261	245	214	161	128
1–49%	683	645	601	579	500	420	302
50–99%	636	622	594	581	492	407	313
≥ 100%	470	461	442	431	377	307	230

0%	199	180	168	157	135	111	90
1–49%	1057	1009	946	913	778	641	478
50–99%	580	569	546	533	467	374	272
≥ 100%	256	246	238	233	203	169	133

Ouwerkerk et al, *EHJ*, 2017.

Guideline adherence und Sterberate

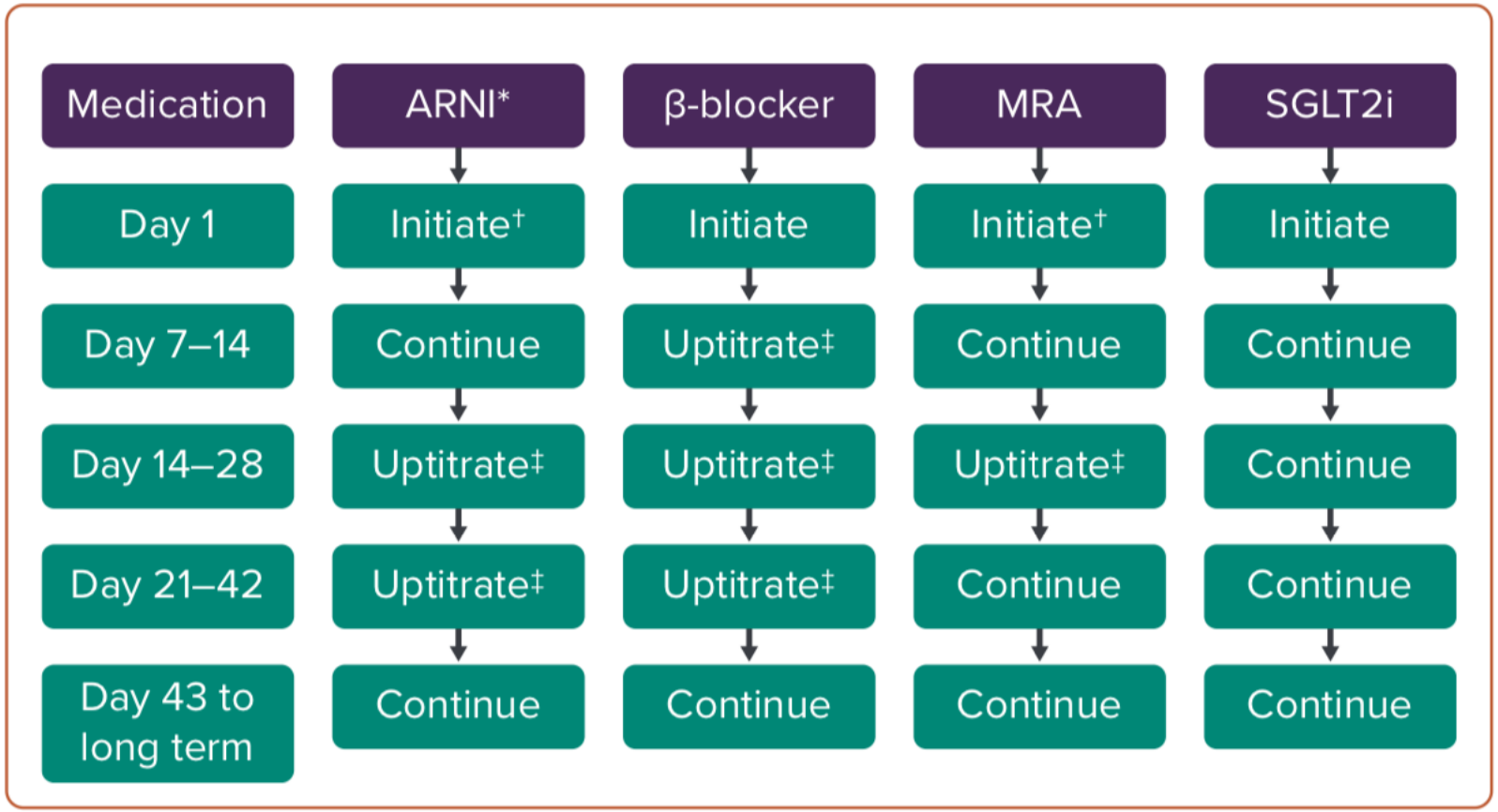


Number at risk							
Good	1543	1187	1157	1112	1050	909	474
Moderate	3627	2618	2514	2381	2230	1961	1053
Poor	1493	906	862	809	726	638	323

Komajda et al, *EHJ*, 2017.

Mögliche Therapieinitiierung

Simultaneous rapid sequence initiation of GDMT

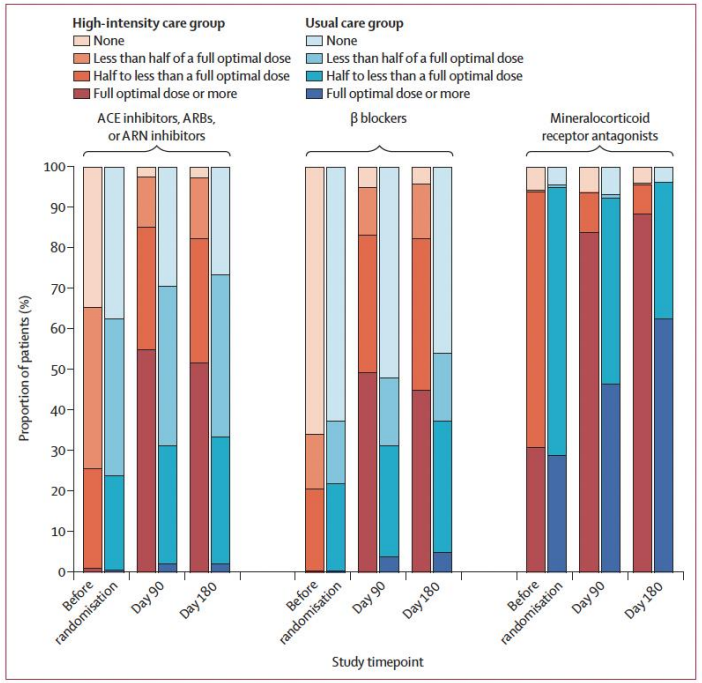


Brownell et al, *Card Reviews*, 2021.

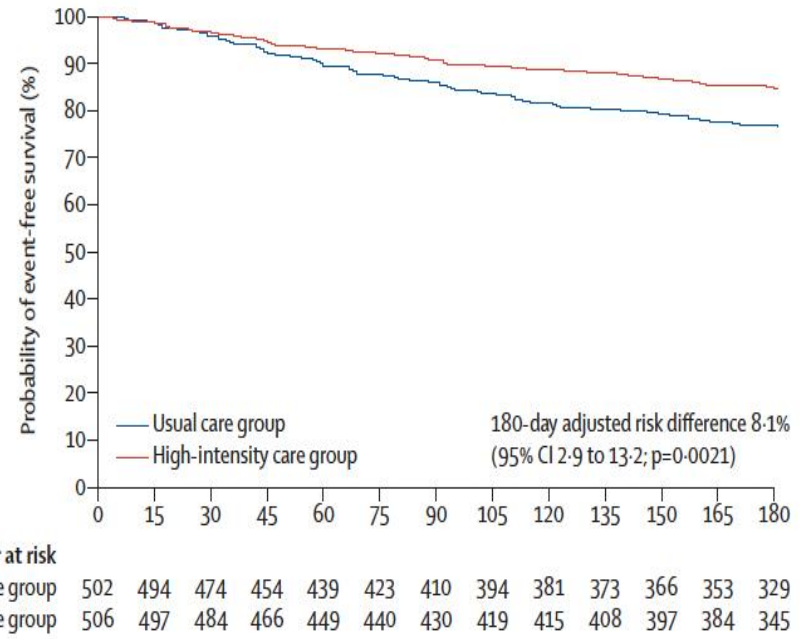
STRONG-HF

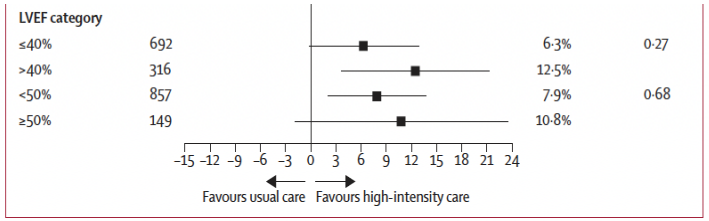
Is rapid uptitration of GDMT before discharge from acute HF hospitalization safe and effective?

1078 patients acute HF, all LVEF
High-intensity care (forecd uptitration vs usual care



All-cause death and HHF





	High-intensity care group (n=542)	Usual care group (n=536)	Adjusted treatment effect (95% CI)	Adjusted risk ratio (95% CI)	p value
Primary endpoint					
All-cause death or heart failure readmission by day 180*	74/506 (15·2%)	109/502 (23·3%)	8·1 (2·9 to 13·2)	0·66 (0·50 to 0·86)	0·0021
Secondary endpoints					
Change from baseline to day 90 in EQ-5D VAS†	10·72 (0·88)	7·22 (0·90)	3·49 (1·74 to 5·24)	NA	<0·0001
All-cause death by day 180*	39/506 (8·5%)	48/502 (10·0%)	1·6 (-2·3 to 5·4)	0·84 (0·56 to 1·26)	0·42
All-cause death or heart failure readmission by day 90*	55 (10·4%)	72 (13·8%)	3·4 (-0·4 to 7·3)	0·73 (0·53 to 1·02)	0·081

Mebazaa et al, *Lancet*, 2022.

Rapid uptitration was associated with reduced all-cause death and HF hospitalizations driven by HF hospitalizations. Also it reduced symptoms and improved quality of life.

Update on the 2021 HF guidelines – management

2023 ESC Guideline Update

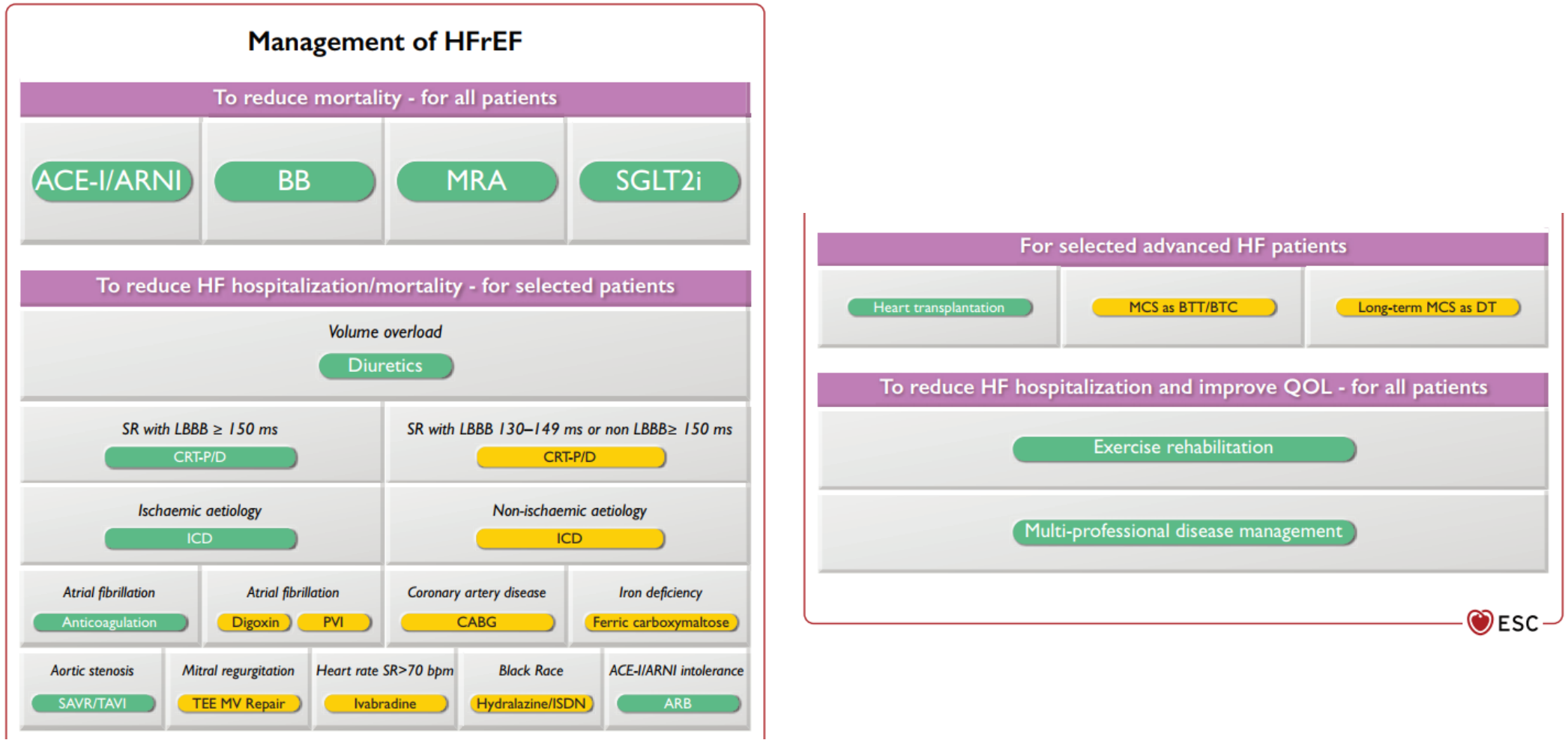
Recommendation	Class[a]	Level[b]
An intensive strategy of initiation and rapid up-titration of evidence-based treatment before discharge and during frequent and careful follow-up visits in the first 6 weeks following a HF hospitalization is recommended to reduce the risk of HF rehospitalization or death.[c,d,e]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

McDonagh et al, *EHJ*, 2023.

Herzinsuffizienz

Therapiestrategien – über die 4 Säulen hinaus

Weitere Therapien nach klinischem Profil



Neue pharmakologische Mechanismen

Zusätzliche Pharmakotherapie 1

Recommendations	Class[a]	Level[b]
Loop diuretics		
Diuretics are recommended in patients with HFrEF with signs and/or symptoms of congestion to alleviate HF symptoms, improve exercise capacity, and reduce HF hospitalizations.[137]	I	C
ARB		
An ARB[c] is recommended to reduce the risk of HF hospitalization and CV death in symptomatic patients unable to tolerate an ACE-I or ARNI (patients should also receive a beta-blocker and an MRA).[138]	I	B
I_f channel inhibitor		
Ivabradine should be considered in symptomatic patients with LVEF ≤35%, in SR and a resting heart rate ≥70 b.p.m. despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I/(or ARNI), and an MRA, to reduce the risk of HF hospitalization and CV death.[139]	IIa	B
Ivabradine should be considered in symptomatic patients with LVEF ≤35%, in SR and a resting heart rate ≥70 b.p.m. who are unable to tolerate or have contraindications for a beta-blocker to reduce the risk of HF hospitalization and CV death. Patients should also receive an ACE-I (or ARNI) and an MRA.[140]	IIa	C

Zusätzliche Pharmakotherapie 2

5.4.6 Recently reported advances from trials in heart failure with reduced ejection fraction

Soluble guanylate cyclase receptor stimulator

The VICTORIA study assessed the efficacy and safety of the oral soluble guanylate cyclase receptor stimulator, vericiguat, in patients with a reduced EF and recently decompensated CHF. The incidence of the primary endpoint of death from CV causes or hospitalization for HF was lower among those who received vericiguat than among those who received placebo.[141] There was no reduction in either all-cause or CV mortality. Thus, vericiguat may be considered, in addition to standard therapy for HFrEF, to reduce the risk of CV mortality and hospitalizations for HF.

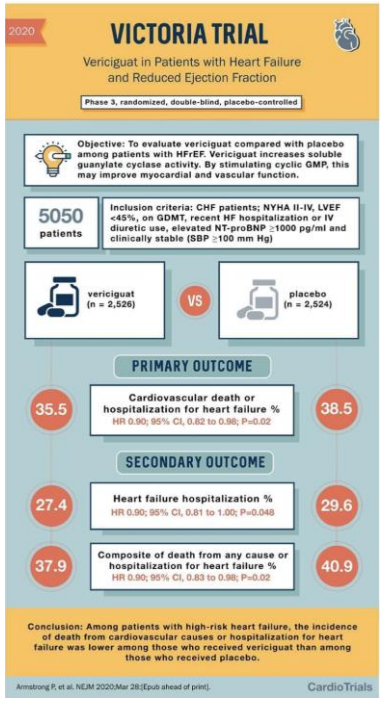
Cardiac myosin activator

The GALACTIC-HF study assessed the efficacy and safety of the cardiac myosin activator, omecamtiv mecarbil, in HFrEF patients, enrolling patients in both the inpatient and outpatient settings. The primary endpoint of a first HF event or CV death was reduced by 8%. There was no significant reduction in CV mortality. Currently, this drug is not licensed for use in HF. However, in the future it may be able to be considered, in addition to standard therapy for HFrEF to reduce the risk of CV mortality and hospitalization for HF.[159]

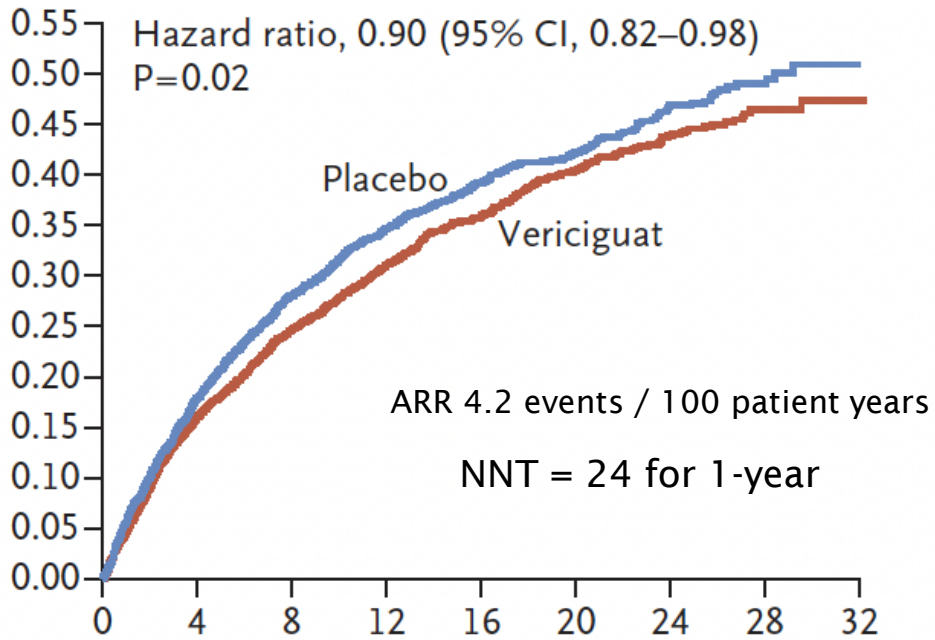
Neuer Wirkmechanismus mit Vericiguat - VICTORIA

What is the effect of vericiguat, a novel oral soluble guanylate cyclase stimulator, on outcome in high-risk HFrEF?

5050 patients, HF LVEF<45%, recent HHF or iv diuretics
vericiguat vs placebo, 2.5mg -> 5mg -> 10mg



CV death or first hospitalization for heart failure



Soluble guanylate cyclase receptor stimulator		
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]	IIb	B

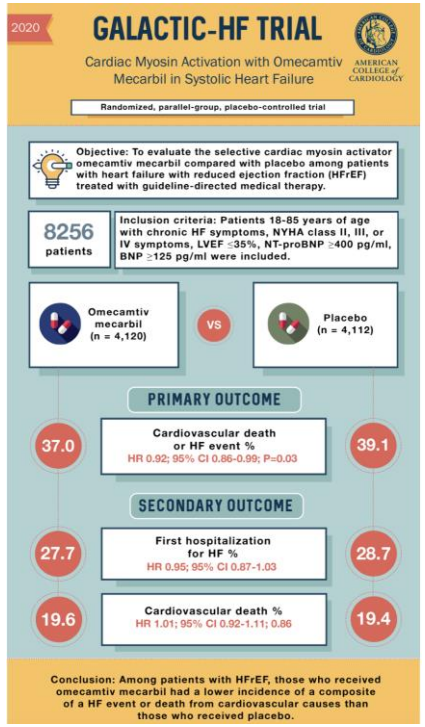
Armstrong et al, *NEJM*, 2020.

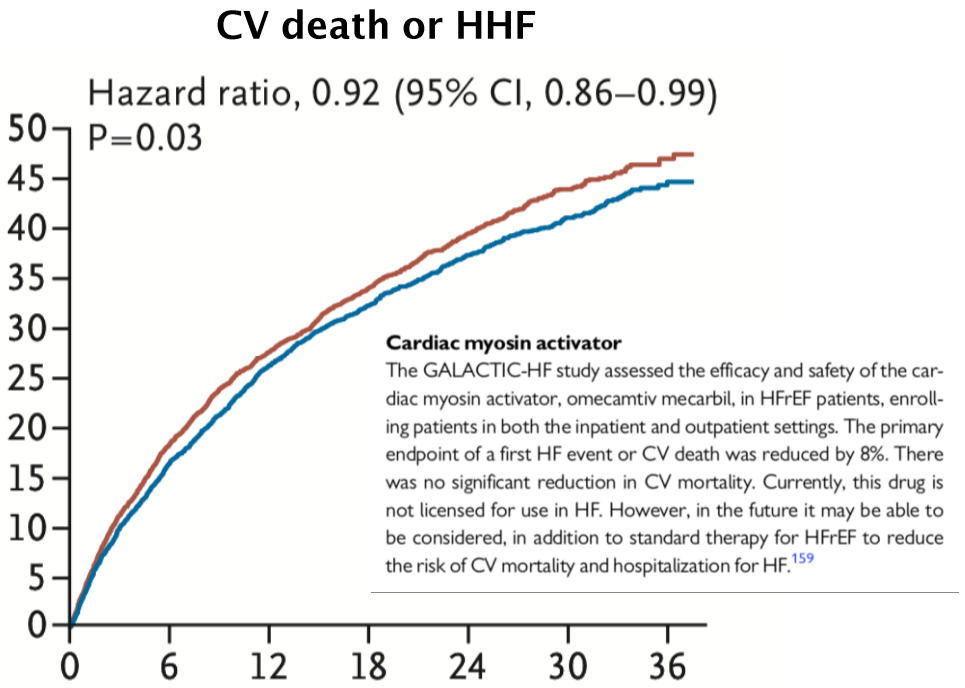
The incidence of CV death or HHF was lower among those who received vericiguat than among those who received placebo. Vericiguat received a IIb B recommendation in the 2021 guidelines for paatients with worsening HF.

Neuer Wirkmechanismus mit Omecamtiv mecarbil? – GALACTIC-HF

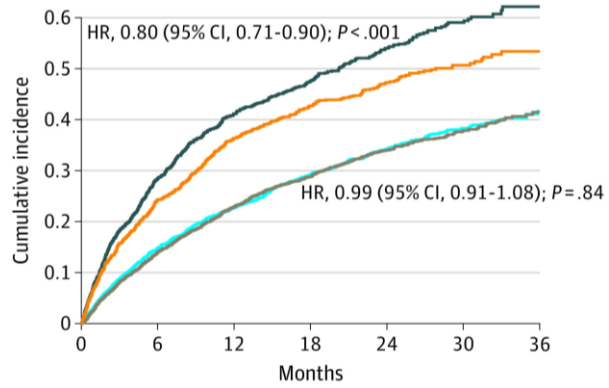
What is the effect of omecamtiv mecarbil, a selective cardiac myosin activator, on outcome in HFrEF?

8256 patients, HF LVEF<35%, NTproBNP>400pg/ml
Omecamtiv mecarbil vs placebo





The effect is even more pronounced in severe HF.



No. at risk							
No severe HF with placebo	2960	2492	2228	1602	1003	479	97
Severe HF with placebo	1152	808	650	464	290	119	13
No severe HF with OM	3014	2565	2271	1651	1051	516	96
Severe HF with OM	1106	814	671	480	320	137	31

Teerlink et al, *NEJM*, 2021. Felker et al, *JAMA Cardiol*, 2022.

The incidence of a composite of a heart-failure event or CV death was lower with omecamtiv mecarbil than with placebo.

Herzinsuffizienzmedikamente nach GFR

Drug	Evidence across GFR strata according to baseline eGFR enrolment criteria	Acute drop GFR	Impact on GFR slope in HF trial	CKD treatment interaction	Treatment effect with CKD
	ESKD 15–30 30–60 >60				
ACE-I/ARB	Moderate evidence if dialysis, weak evidence if not on dialysis	Yes	No (beneficial effect of around 1–2 ml/min/1.73 m^2 per year in CKD trials)	No	Relative benefit: ~ Absolute benefit: ↑
Beta-blockers		No	No	Yes (potentially but some conflicting results)	Relative benefit: ~ Absolute benefit: ↑
MRA		Yes	No	No	Relative benefit: ~ Absolute benefit: ↑
ARNI		Yes	Yes (around 0.5 ml/min/1.73 m^2 per year)	No	Relative benefit: ~ Absolute benefit: ↑
SGLT2-i	>20	Yes	Yes (around 1–2 ml/min/1.73 m^2 per year)	No	Relative benefit: ~ Absolute benefit: ↑
Ivabradine		No	No	No	Relative benefit: ~ Absolute benefit: ↑
Vericiguat		No	No	No	Relative benefit: ~ Absolute benefit: ↑
Omecamtiv mecarbil		No	No	No	Relative benefit: ~ Absolute benefit: ↑

A decrease in eGFR over time does not automatically mean RAASi/SGLT2-i need to be downtitrated or discontinued

Vericiguat und Omecamtiv mecarbil sind bis zu einer GFR von 15ml/kg/min getestet und sicher und stellen damit eine Option für u.a. Patienten mit fortgeschrittener Herzinsuffizienz und renaler Dysfunktion dar.

Mullens et al, *EJHF*, 2022.

Nierenfunktion und GDMT in der Herzinsuffizienz

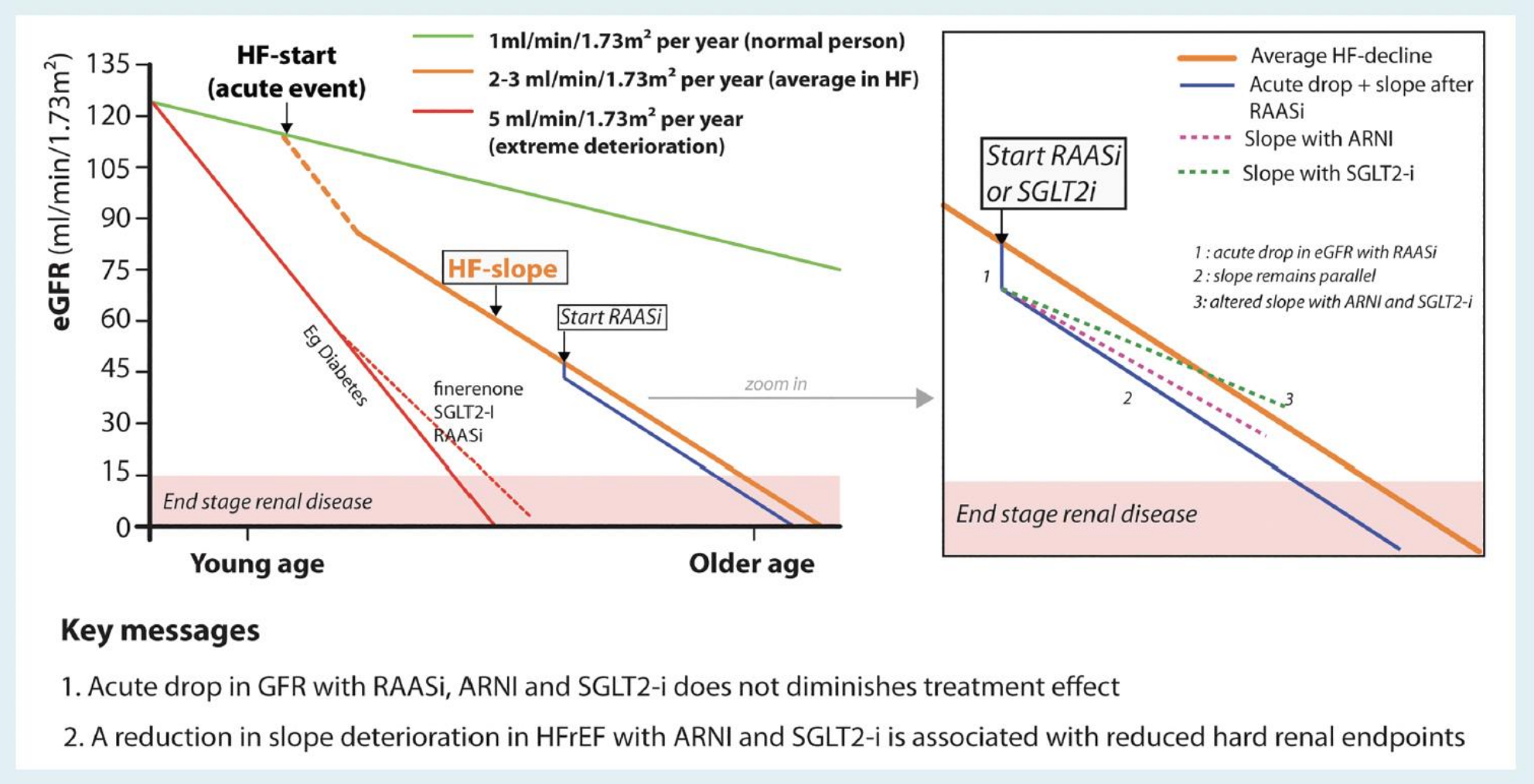
HI Studien und Ausschluss von Patienten mit niedriger GFR

Trial	Comparison	CKD Exclusion Criteria	Proportion with CKD (eGFR <60)
β-blockers			
MERIT HF[15]	Metoprolol versus placebo	There were no exclusions relating to renal function or baseline serum creatinine	1,469 (37.0%)
CIBIS II[18]	Bisoprolol versus placebo	Serum creatinine >300 µmol/l	1,119 (42.1%)
Angiotensin-converting enzyme inhibitor			
SAVE[21]	Captopril versus placebo	Serum creatinine >220 µmol/l	719 (32.9%)
SOLVD[23]	Enalapril versus placebo	Serum creatinine >250 µmol/l	1,036 (41.0%)
CONSENSUS[22]	Enalapril versus placebo	Serum creatinine >300 µmol/l	-
Angiotensin II receptor blocker			
CHARM[24]	Candesartan versus placebo	Serum creatinine 265 µmol/l	-
Val-HEFT[25]	Valsartan versus placebo	Serum creatinine >177 µmol/l	-
Mineralocorticoid receptor antagonist			
RALES[28]	Spironolactone versus placebo	Serum creatinine >250 µmol/l	866 (52.0%)
EMPHASIS[30]	Eplerenone versus placebo	eGFR <30 ml/min	912 (33.3%)
EPHESUS[29]	Eplerenone versus placebo in patients after MI	Serum creatinine >220 µmol/l	295 (40%)
Sodium–glucose co-transporter 2 Inhibitors			
DAPA-HF[36]	Dapagliflozin versus placebo	eGFR <30 ml/min	1,926 (41.0%)
EMPEROR-Reduced[35]	Empagliflozin versus placebo	eGFR <20 ml/min	1,978 (53.0%)
Angiotensin receptor and neprilysin inhibitor			
PARADIGM-HF[37]	Sacubitril/valsartan versus enalapril	eGFR <30 ml/min	-
Ivabradine			
SHIFT-HF[42]	Ivabradine versus placebo	Serum creatinine >220 µmol/l	-
Soluble guanylate cyclase stimulators			
VICTORIA[52]	Vericiguat versus placebo	eGFR <15 ml/min or receiving renal replacement therapy	-
IV iron			
FAIR-HF[46]	IV ferric carboxymaltose versus placebo	Excluded patients on renal replacement therapy	-
CONFIRM-HF[47]	IV ferric carboxymaltose versus placebo	Excluded patients on renal replacement therapy	-
EFFECT-HF[48]	IV ferric carboxymaltose versus placebo	Excluded patients on renal replacement therapy	-
AFFIRM-HF[45]	IV ferric carboxymaltose versus placebo	Excluded patients on renal replacement therapy	580 (51.0%)

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HF = heart failure.

Ryan et al, *ECR*, 2019.

Nierenfunktionsverlauf in HF und der Effekt der HF-Therapie

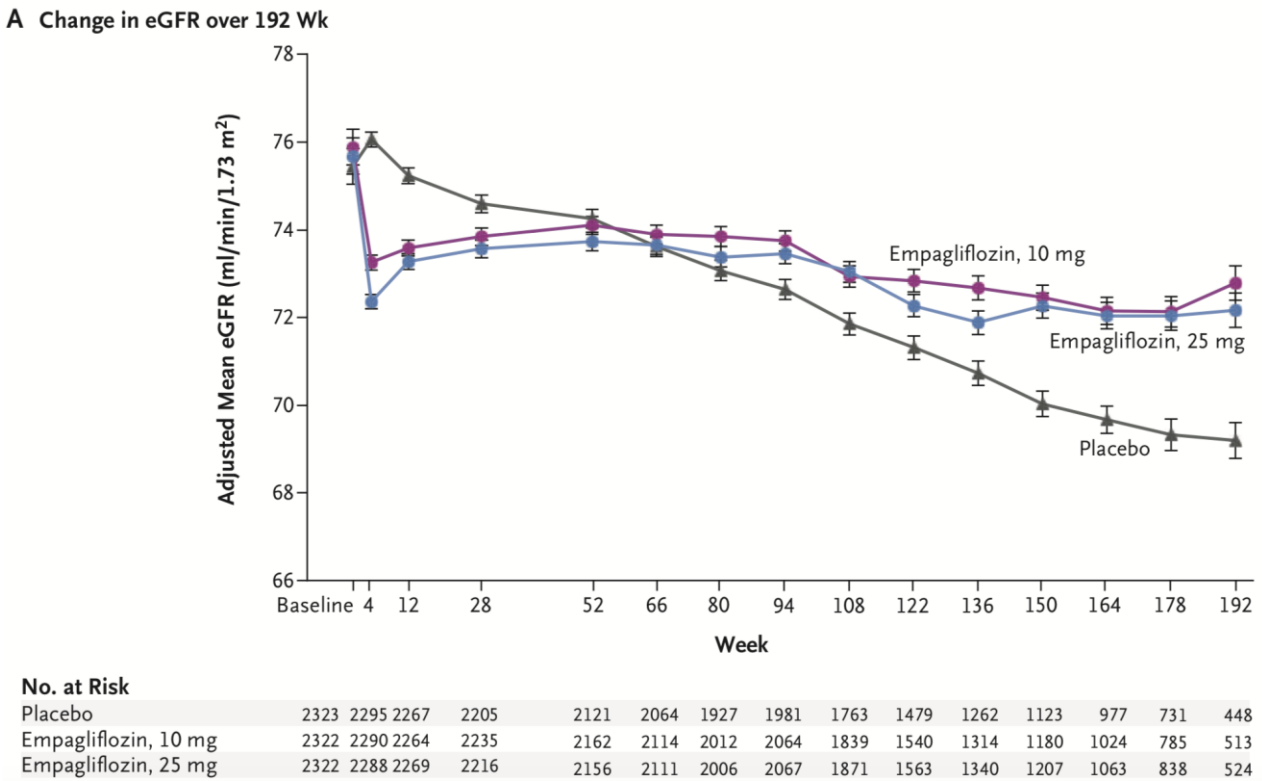


Key messages

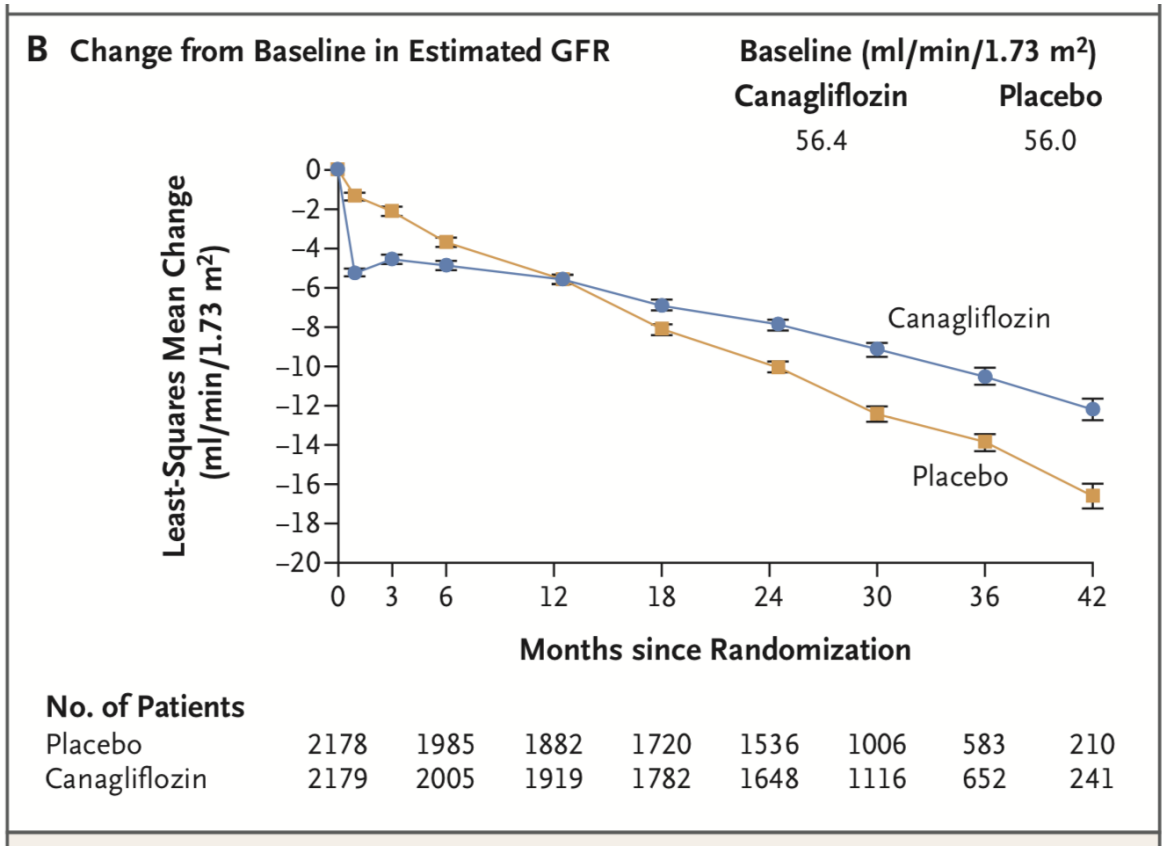
1. Acute drop in GFR with RAASi, ARNI and SGLT2-i does not diminishes treatment effect
2. A reduction in slope deterioration in HFrEF with ARNI and SGLT2-i is associated with reduced hard renal endpoints

Mullens et al, *EJHF*, 2022.

Effekt der SGLT2i auf die Nierenfunktion in HF – initial physiologischer GFR Abfall

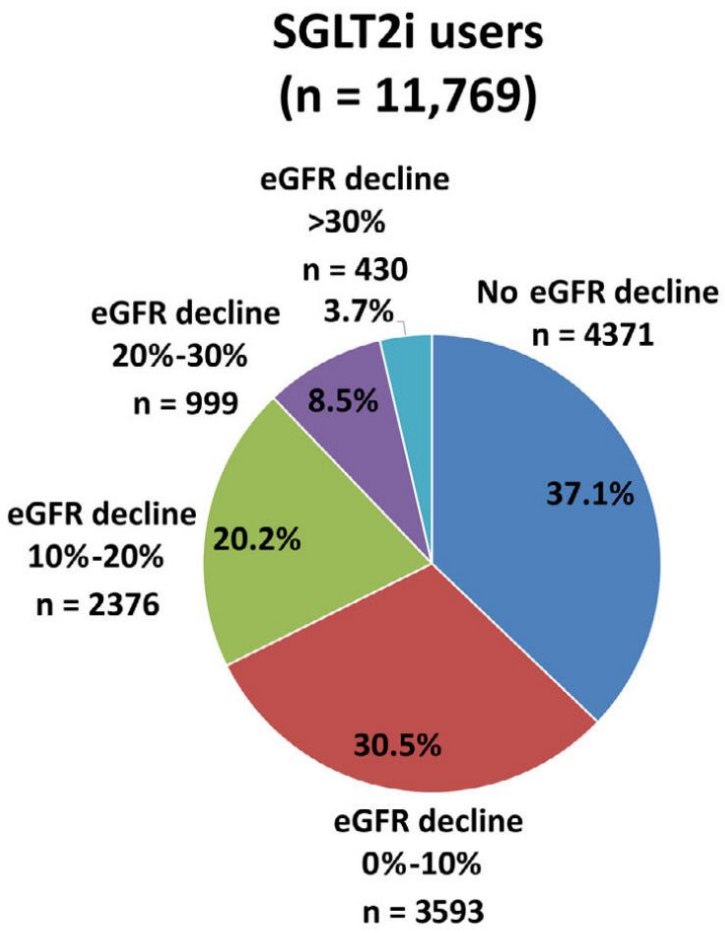


Wanner et al, *NEJM*, 2016.

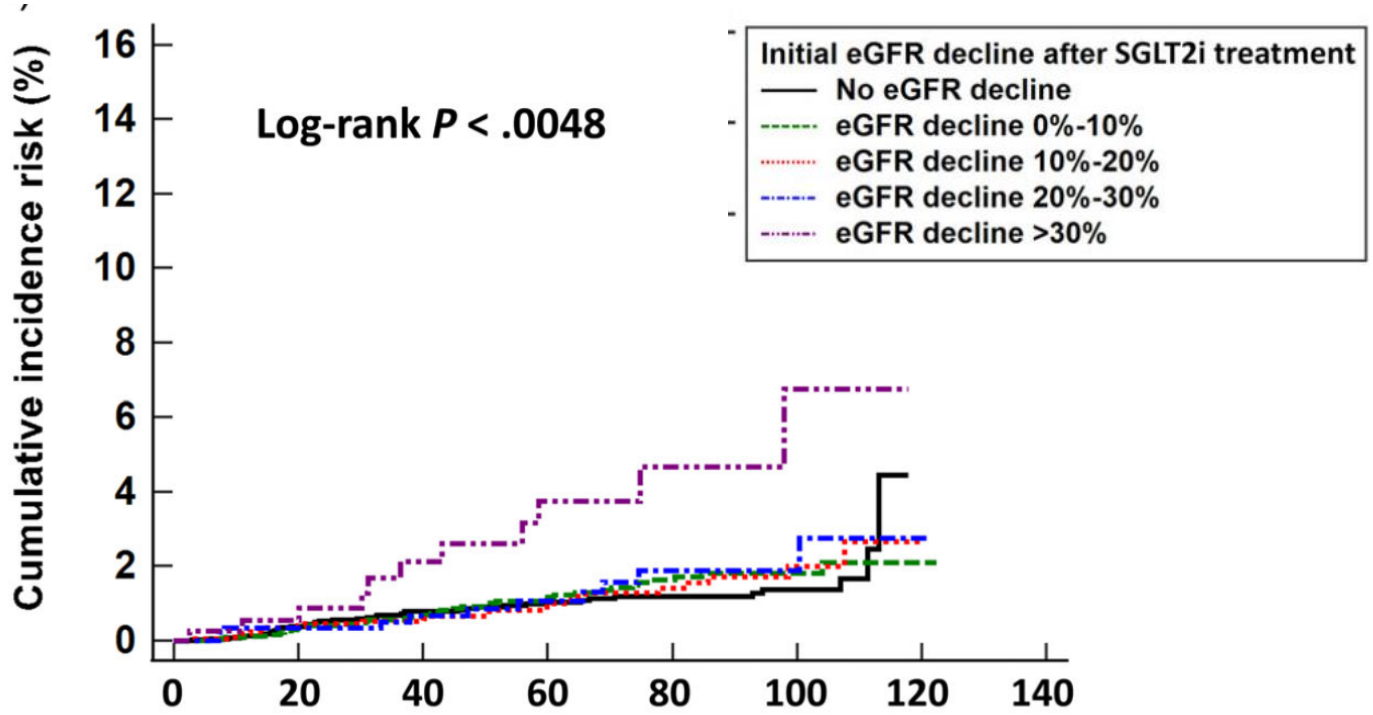


Perkovic et al., *NEJM*, 2019.

Initialer GFR-Abfall und Outcome

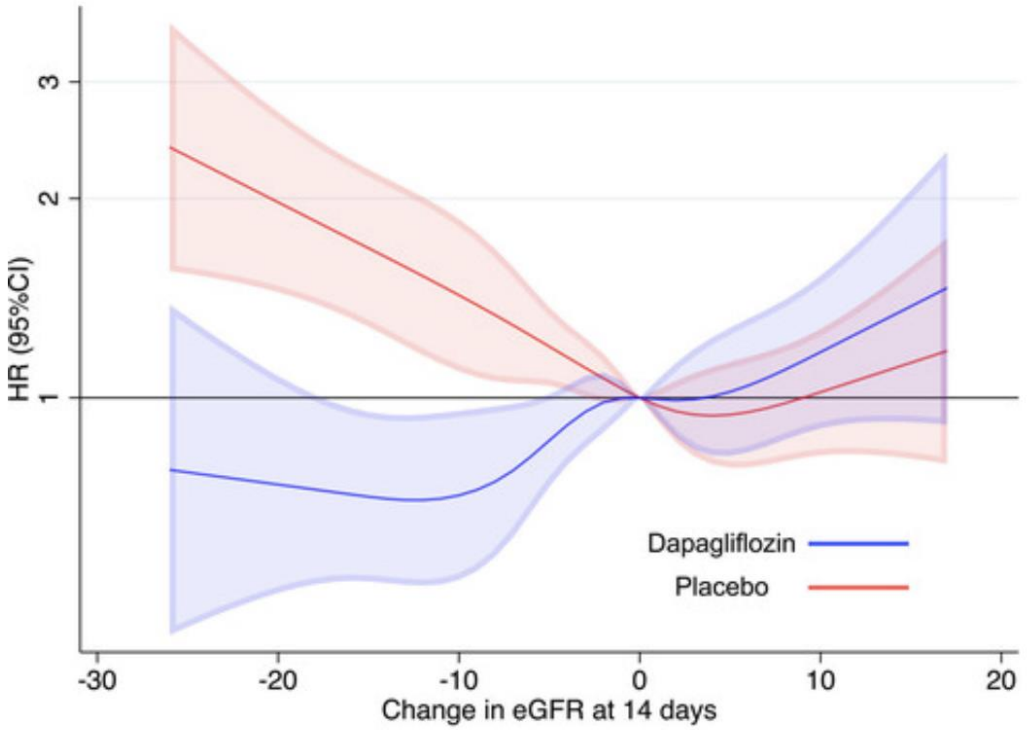


MACE / HF

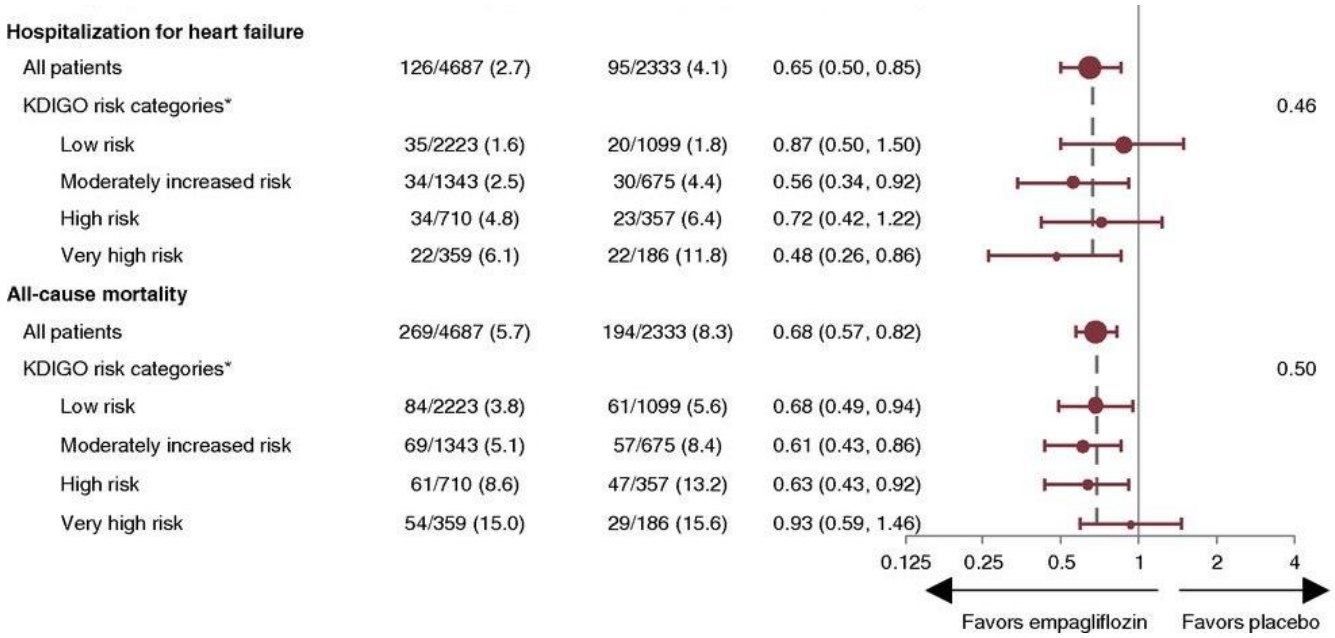


Chan et al, *Diabetes Obes Meab*, 2021.

Kardialer Benefit der SGLT2i unabhängig von eGFR dip oder der eGFR Kategorie



Adamson et al, *Circ*, 2022.

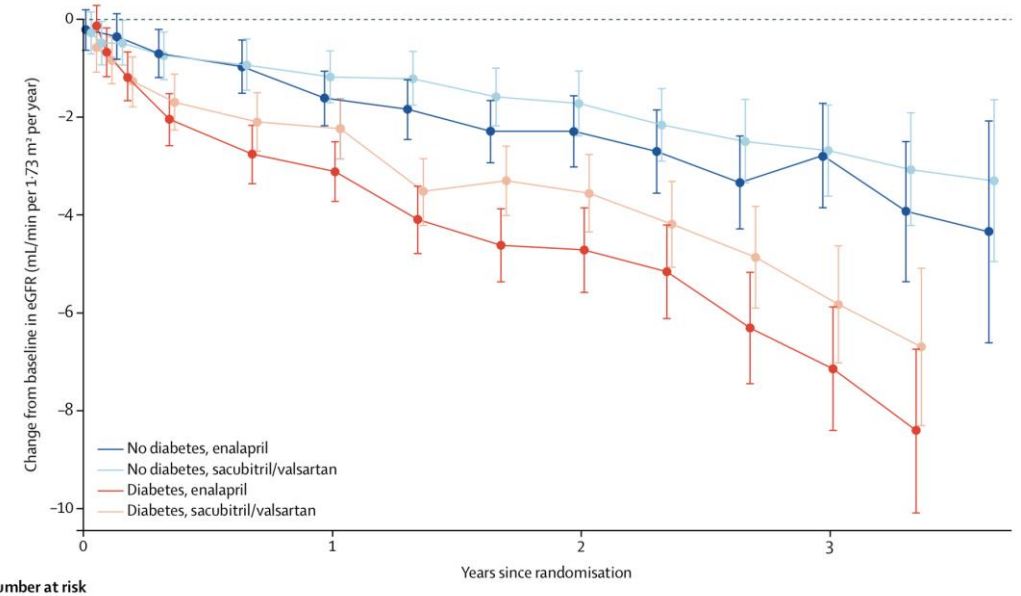


Adeera et al, *CiASN*, 2020.

Kardialer Benefit der SGLT2i ist unabhängig vom eGFR dip bis zu -30% oder GFR Kategorie erhalten.

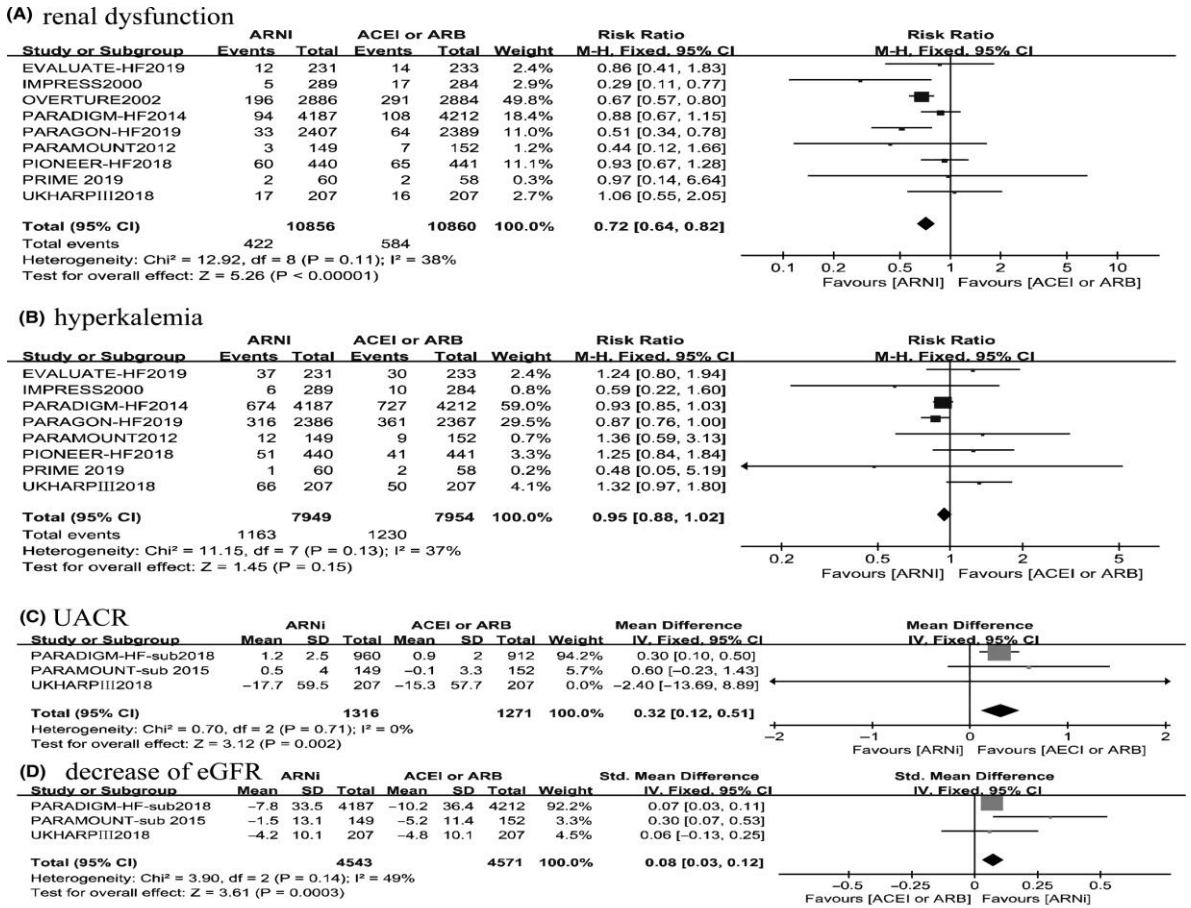
Effekt der ACEi/ARNi auf die Nierenfunktion in HF

PARADIGM-HF



Number at risk			
No diabetes, sacubitril/valsartan	1969	1425	672
No diabetes, enalapril	1937	1344	667
Diabetes, sacubitril/valsartan	1566	1101	504
Diabetes, enalapril	1557	1086	502

Packer et al, *Lancet Diabet Endocrinol*, 2018.



Feng et al, *J Clin Pharm Ther*, 2020.

HF Benefit über verschiedene GFR Strata - ARNi

PARADIGM-HF

Subgroup	LCZ696	Enalapril	Primary End Point: Hazard Ratio (95% CI)	Primary End Point: P value for interaction	Death from Cardiovascular Causes: Hazard ratio (95% CI)	Death from Cardiovascular Causes: P value for interaction
	no.					
Estimated GFR				0.91		0.73
<60 ml/min/1.73 m²	1541	1520				
≥60 ml/min/1.73 m²	2646	2692				

PARAGON

Subgroup	No. of Events/No. of Patients	Rate Ratio (95% CI)
Baseline estimated GFR		
<60 ml/min/1.73 m²	1115/2341	0.79 (0.66–0.95)
≥60 ml/min/1.73 m²	787/2454	1.01 (0.80–1.27)

Es besteht keine Interaktion zwischen den untersuchten GFR-Kategorien und der Wirkung der ARNi in der HFrEF.

Effekt der MRA auf die Nierenfunktion in HF

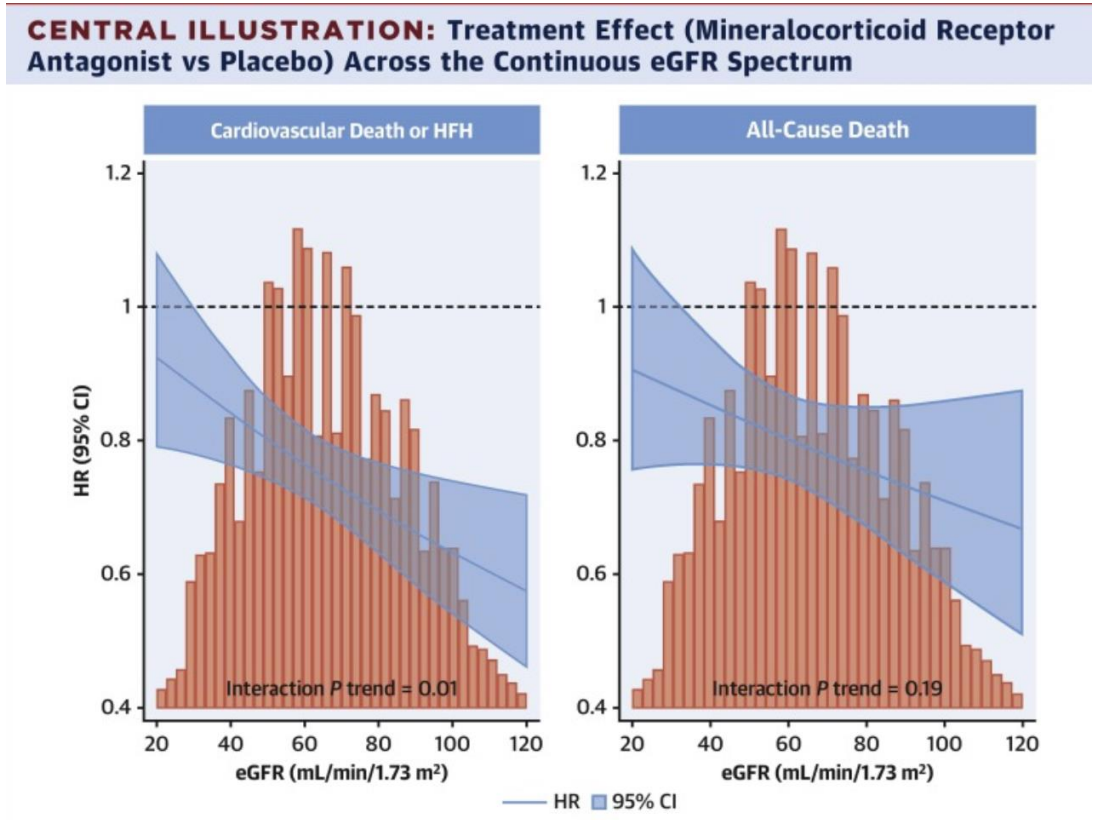
TABLE 3 Adverse Events According to eGFR Categories

Outcome/eGFR Category[a]	Event-Rate[b] Placebo n/N (%)	Event-Rate[b] MRA n/N (%)	OR (95% CI)	Interaction *P* for Trend[c]	Study Heterogeneity[d]
Hyperkalemia				0.002	0.65
>90	52/803 (6.5)	85/865 (9.8)	1.57 (1.13-2.19)		
61-90	226/2,788 (8.1)	311/2,759 (11.3)	1.44 (0.88-2.35)		
46-60	167/1,600 (10.4)	295/1,580 (18.7)	1.97 (1.32-2.94)		
31-45	100/903 (11.1)	225/889 (25.3)	2.72 (2.02-3.67)		
≤30	27/157 (17.2)	49/162 (30.2)	2.09 (1.38-3.15)		
Worsening kidney function				0.39	0.25
>90	207/772 (26.8)	262/843 (31.1)	1.23 (0.99-1.53)		
61-90	588/2,688 (21.9)	738/2,668 (27.7)	1.37 (1.15-1.62)		
46-60	309/1,533 (20.2)	410/1,515 (27.1)	1.47 (1.28-1.68)		
31-45	180/853 (21.1)	248/851 (29.1)	1.54 (1.21-1.95)		
≤30	21/147 (14.3)	39/153 (25.5)	2.05 (1.24-3.41)		

Ferreira et al, *JACC HF*, 2022.

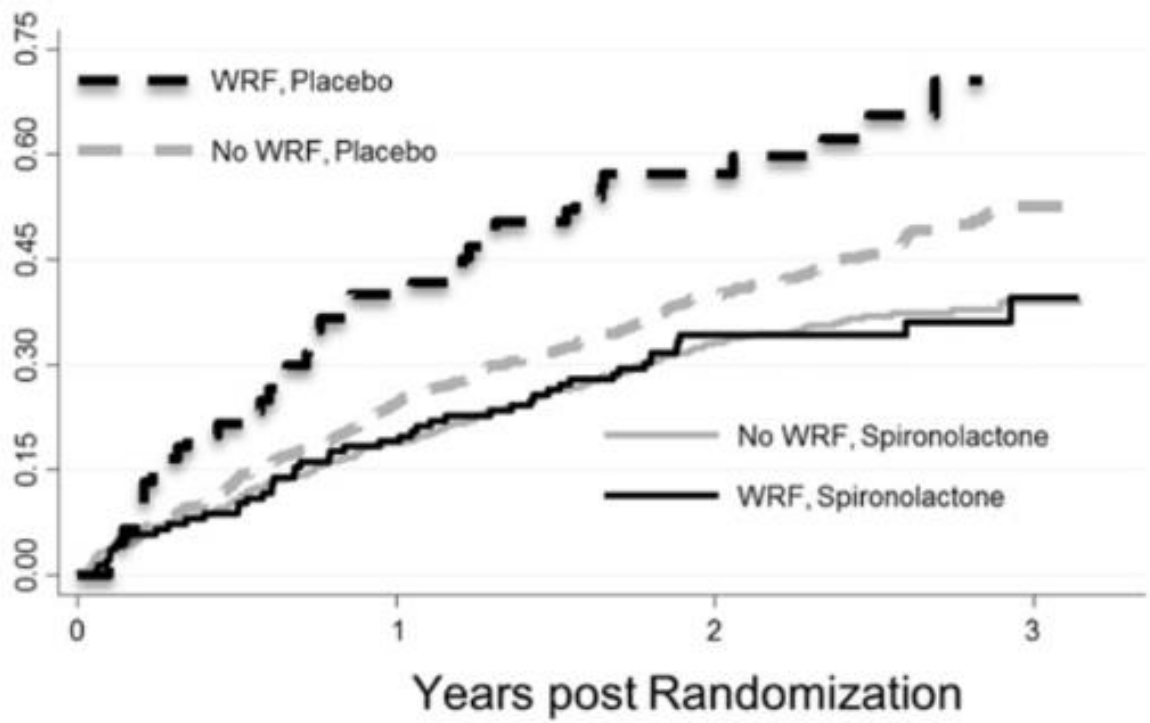
HF Benefit über das gesamte Spektrum der GFR - MRA

Meta-analysis



Ferreira et al, *JACC HF*, 2022.

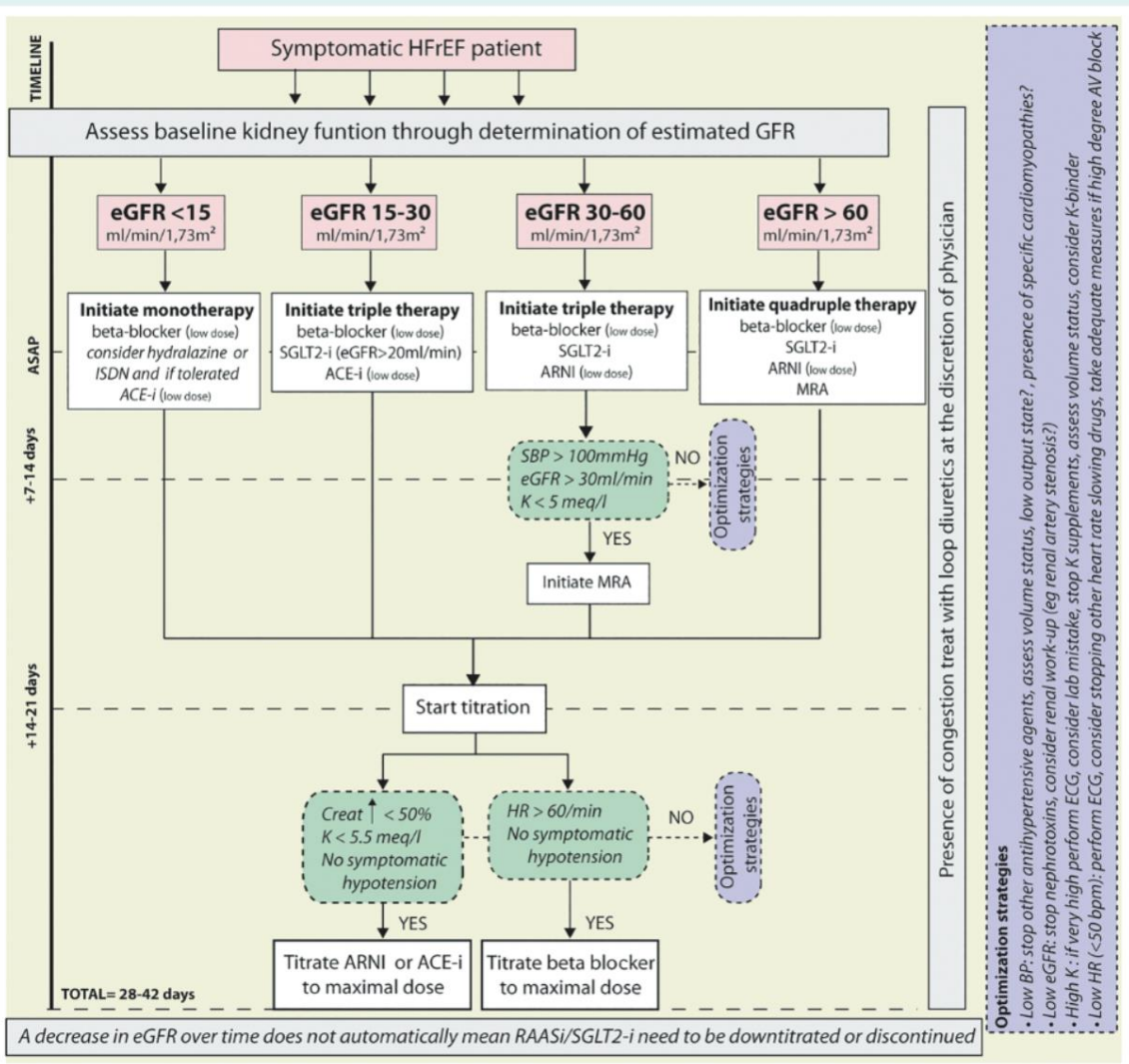
RALES



Vardeny et al, *JACC*, 2012.

Der Benefit der MRA bezüglich CV Endpunkte und Mortalität ist über das gesamte Spektrum der GFR erhalten, auch unabhängig von einer eventuell auftretenden Verschlechterung der Nierenfunktion.

Strategie in (UN)Abhängigkeit der Baseline GFR?



Mullens et al, *EJHF*, 2022.

Strategie bei Veränderungen der GFR?

Patient established on RAAS blocker presenting unwell with AKI/WRF

Primary presenting problem

	Recommendations for RAAS inhibitors	
Change in renal function compared with baseline	**HFpEF (assuming no other prognostic indication).**	**HFREF.**
Increase in serum creatinine by <30%	Consider stop ACEI/ARB/ARNI Review MRA according to fluid status.	Continue unless symptomatic hypotension.
Increase in serum creatinine 30%–50%	Stop RAAS inhibitor.	Consider reducing dose or temporary withdrawal.*
Increase in serum creatinine >50%	Stop RAAS inhibitor.	Temporarily stop RAAS inhibitor.*
Severe renal dysfunction, for example, eGFR <20	Stop RAAS inhibitor.	Stop RAAS inhibitor if symptomatic uraemia irrespective of baseline function.

*Reinitiate and/or retitrate when renal function improved in patients with HFrEF.

HFrEF

Consider reducing or withholding RAAS blocker only if:

- symptomatic hypotension
- moderate-severe hyperkalaemia
- or progressive WRF*

HFpEF

- Stop ACEi/ARB – no prognostic benefit
- MRA may offer symptomatic benefit

hyperkalaemia or progressive WRF*

Clark et al, *Heart*, 2019.

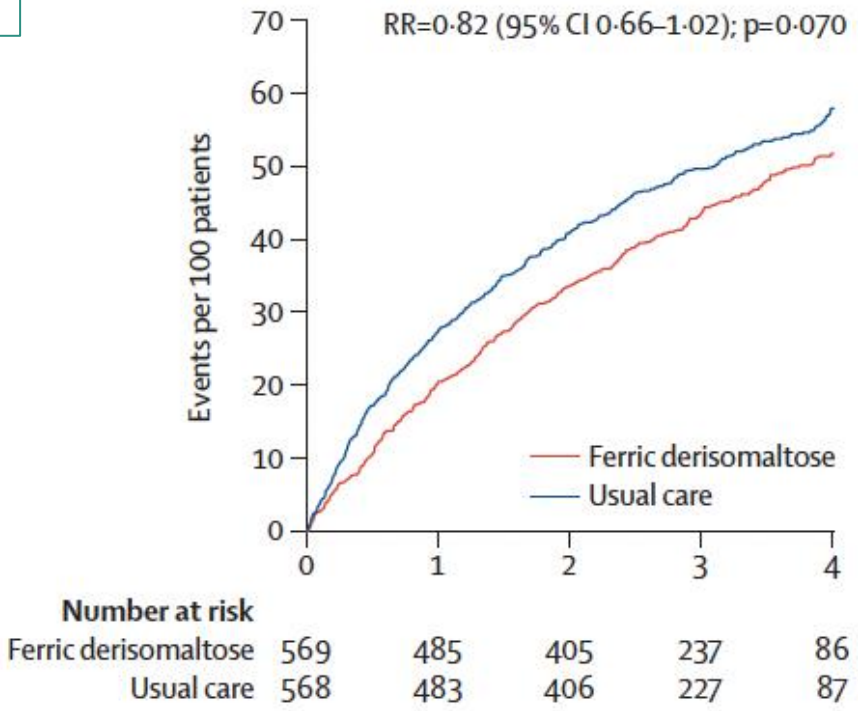
Iv Eisen und Finerenone

Behandlung des Eisenmangels – IRONMAN

Longer-term effects of intravenous ferric derisomaltose on cardiovascular events in patients with heart failure?

1869 patients LVEF <45%,
iv ferric desiromaltose vs placebo

CV death and HHF



COVID-19 analysis

	Ferric derisomaltose group (n=527)	Usual care group (n=536)	Estimated treatment effect (95% CI)	p value
Primary endpoint				
Cardiovascular death and hospital admission for heart failure, number of events (rate per 100 patient-years)	210 (22·3)	280 (29·3)	0·76 (0·58–1·00)*	0·047
Secondary endpoints				
Hospital admissions for heart failure, number of events (rate per 100 patient-years)	163 (17·3)	218 (22·8)	0·76 (0·56–1·03)*	0·077
Cardiovascular hospital admission, n (%)	177 (34%)	205 (38%)	0·86 (0·70–1·05)†	0·14
Cardiovascular death or hospital admission for heart failure, n (%)	127 (24%)	160 (30%)	0·80 (0·63–1·01)†	0·055
Cardiovascular death, n (%)	67 (13%)	86 (16%)	0·79 (0·57–1·09)†	0·15
Cardiovascular death or hospital admission for stroke, myocardial infarction, or heart failure, n (%)	137 (26%)	175 (33%)	0·78 (0·62–0·98)†	0·030
All-cause mortality, n (%)	103 (20%)	115 (21%)	0·91 (0·70–1·19)†	0·48
All-cause hospital admission, n (%)	260 (49%)	288 (54%)	89 (0·75–1·05)†	0·18
All-cause mortality or all-cause unplanned hospital admission, n (%)	271 (51%)	303 (57%)	0·89 (0·75 to 1·04)†	0·15

All comparisons are of the ferric derisomaltose group with the usual care group. *Rate ratio (estimated using the method of Lin and colleagues[32]). †Hazard ratio (estimated from Cox proportional hazards models).

Kalra et al, *Lancet*, 2022.

Intravenous ferric derisomaltose administration was associated with a lower risk of hospital admissions for heart failure and cardiovascular death.

Update on the 2021 HF guidelines

2023 ESC Guideline Update

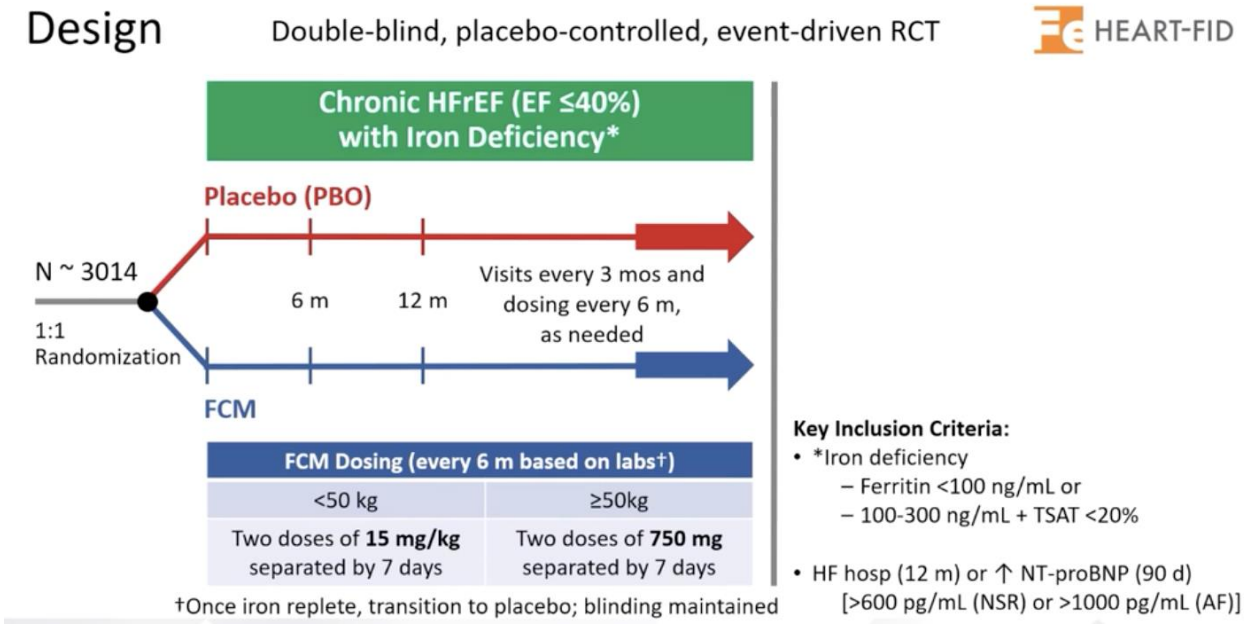
Recommendations	Class[a]	Level[b]
Intravenous iron supplementation is recommended in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to alleviate HF symptoms and improve quality of life.[c] 12,41,47–49	I	A
Intravenous iron supplementation with ferric carboxymaltose or ferric derisomaltose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

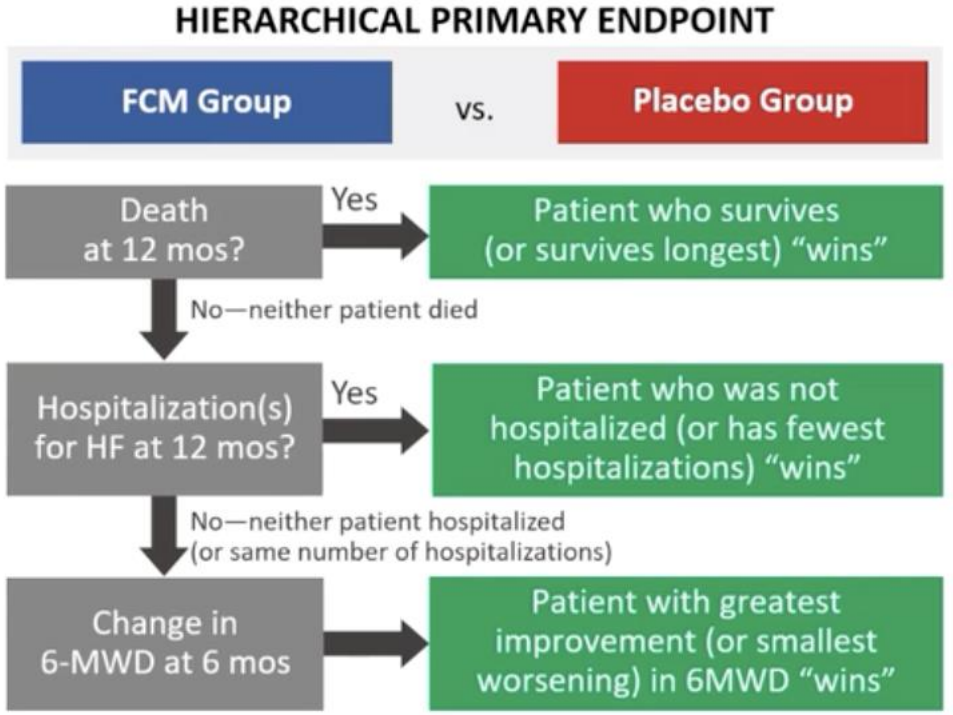
McDonagh et al, *EHJ*, 2023.

Behandlung des Eisenmangels – HEART-FID

Can FCM reduce hard endpoints in stable HFrEF and ID?

3065 patients LVEF <40% and ID, 1:1 FCM vs placebo

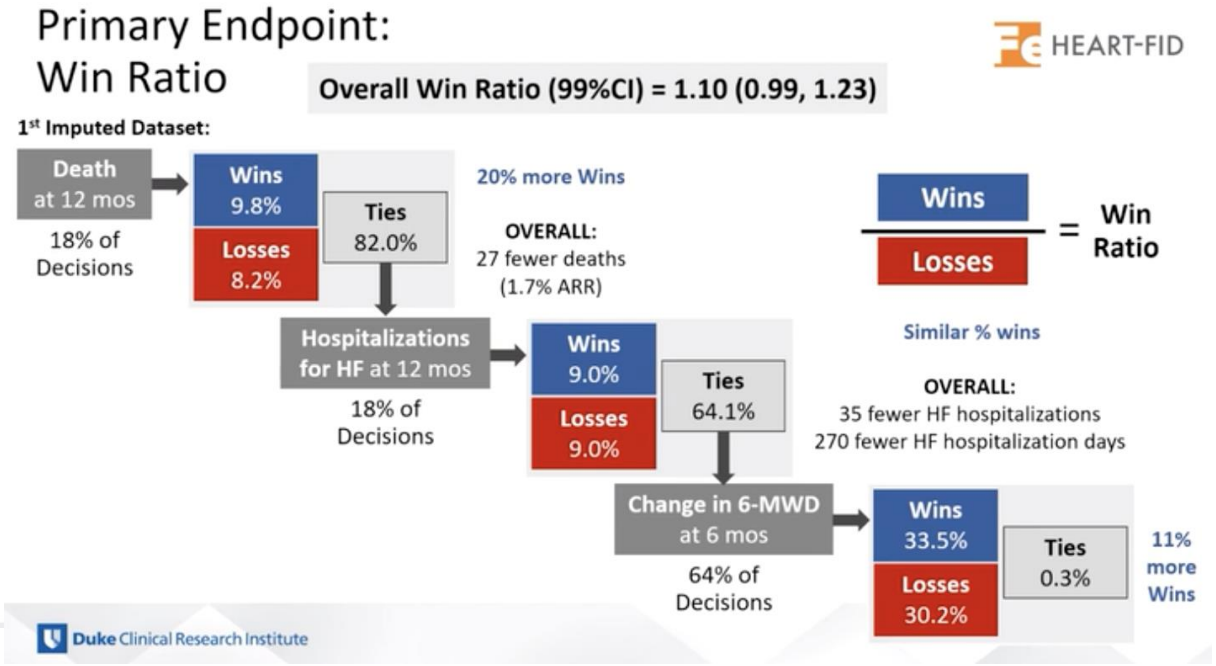


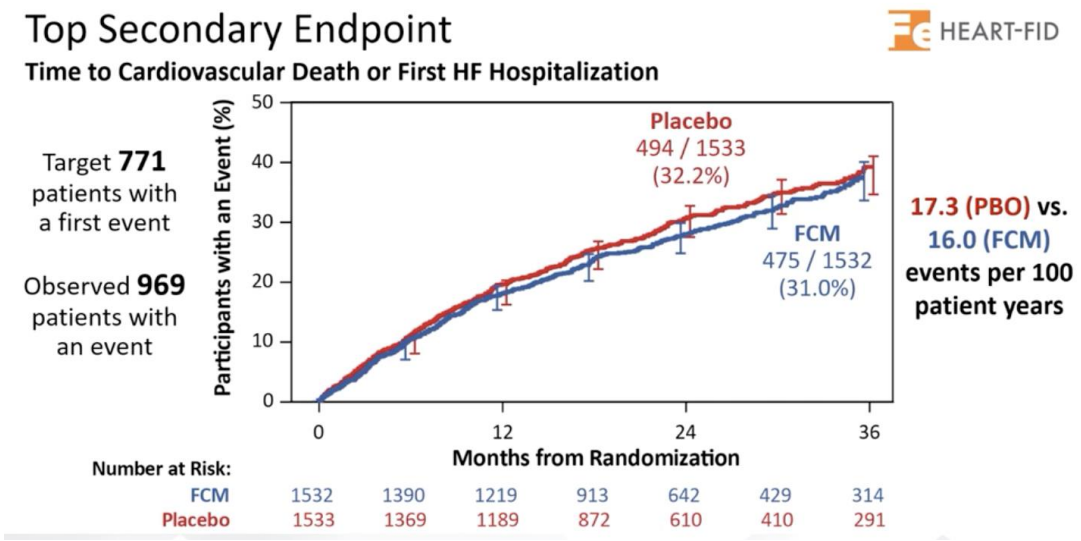


Mentz et al, *ESC congress* 2023.

Behandlung des Eisenmangels – HEART-FID

Can FCM reduce hard endpoints in stable HFrEF and ID?

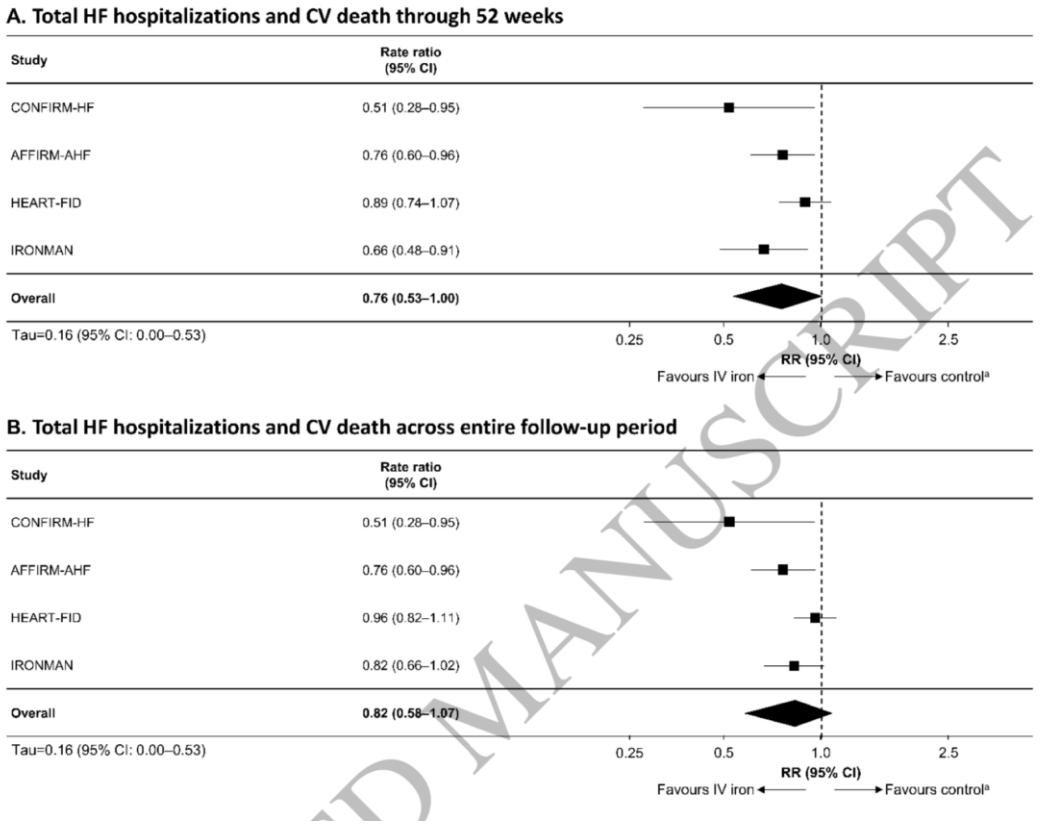




Mentz et al, *ESC congress* 2023.

The totality of evidence of FCM in HF and ID show overall safety and clinical benefits.

Behandlung des Eisenmangels nach HEART-FID?



Ponikowski at al, *EHJ*, 2023.

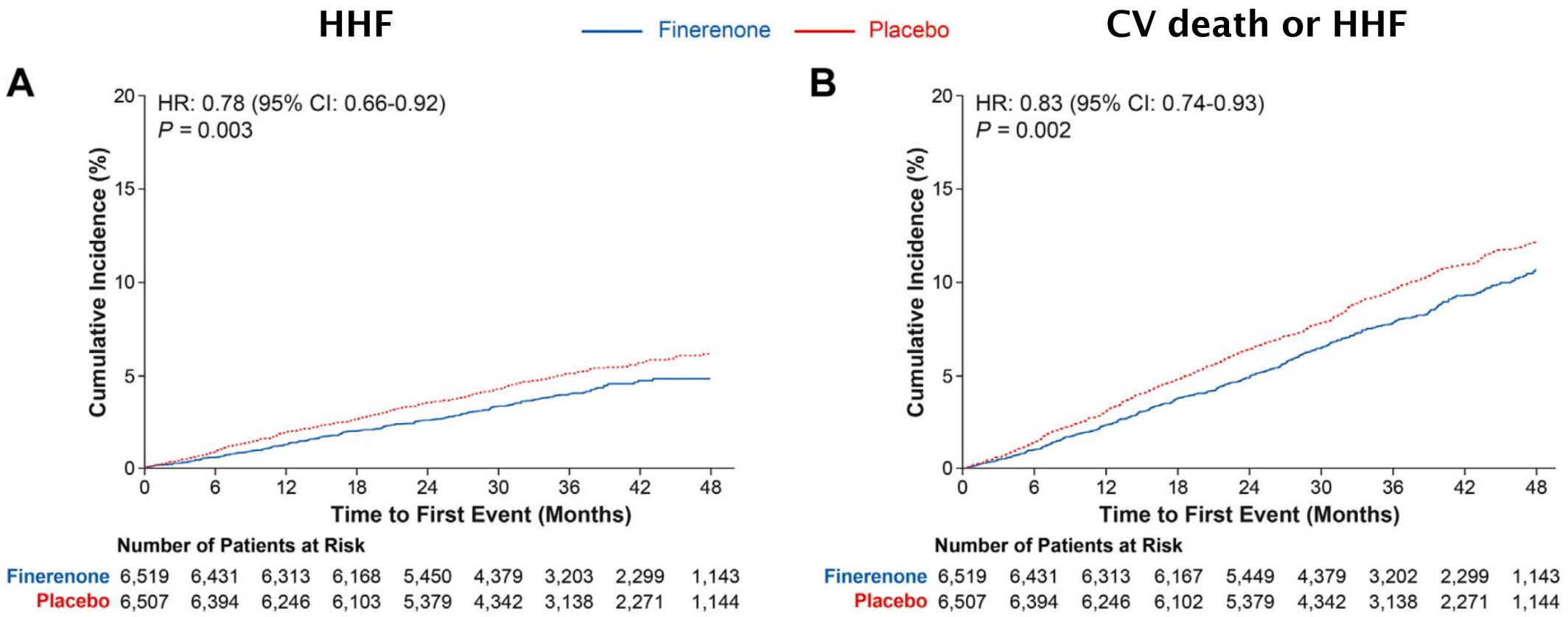
Apples to Apples Comparison of Contemporary Heart Failure Trials

IV Iron trials modest in comparison to trials that have informed GDMT

	Trial	Number of Patients	CV Death or HF Hospitalization: Number of Events	CV Death or HF Hospitalization: HR (95% CI)	CV Death: Number of Events	CV Death: HR (95% CI)
	HEARTFID	1532 v. 1533	475 v. 494	0.93 (0.81- 1.06)	251 v. 275	0.86 (0.72- 1.03)
	AFFIRM-HF	558 v. 550	181 v. 209	0.80 (0.66- 0.98)	77 v. 78	0.96 (0.70- 1.32)
	IRONMAN	569 v. 568	198 v. 231	0.84 (0.70- 1.02)	119 v. 138	0.86 (0.67- 1.10)
GDMT	EMPHASIS-HF	1364 v. 1373	249 v. 356	0.63 (0.54–0.74)	147 v. 185	0.76 (0.61/0.94)
GDMT	DAPA-HF	2373 v. 2371	382 v. 495	0.75 (0.65- 0.85)	227 v. 273	0.82 (0.69- 0.98)
GDMT	PARADIGM-HF	4187 v. 4212	914 v. 1117	0.80 (0.73–0.87)	558 v. 693	0.80 (0.71–0.89)
	VICTORIA	2526 v. 2524	897 v. 972	0.90 (0.82– 0.98)	414 v. 441	0.93 (0.81– 1.06)

Solomon, *ESC congress* 2023.

Finerenone in der Herzinsuffizienz - **FIDELITY**



Filippatos, *JACC HF*, 2021.

Update on the 2021 HF guidelines

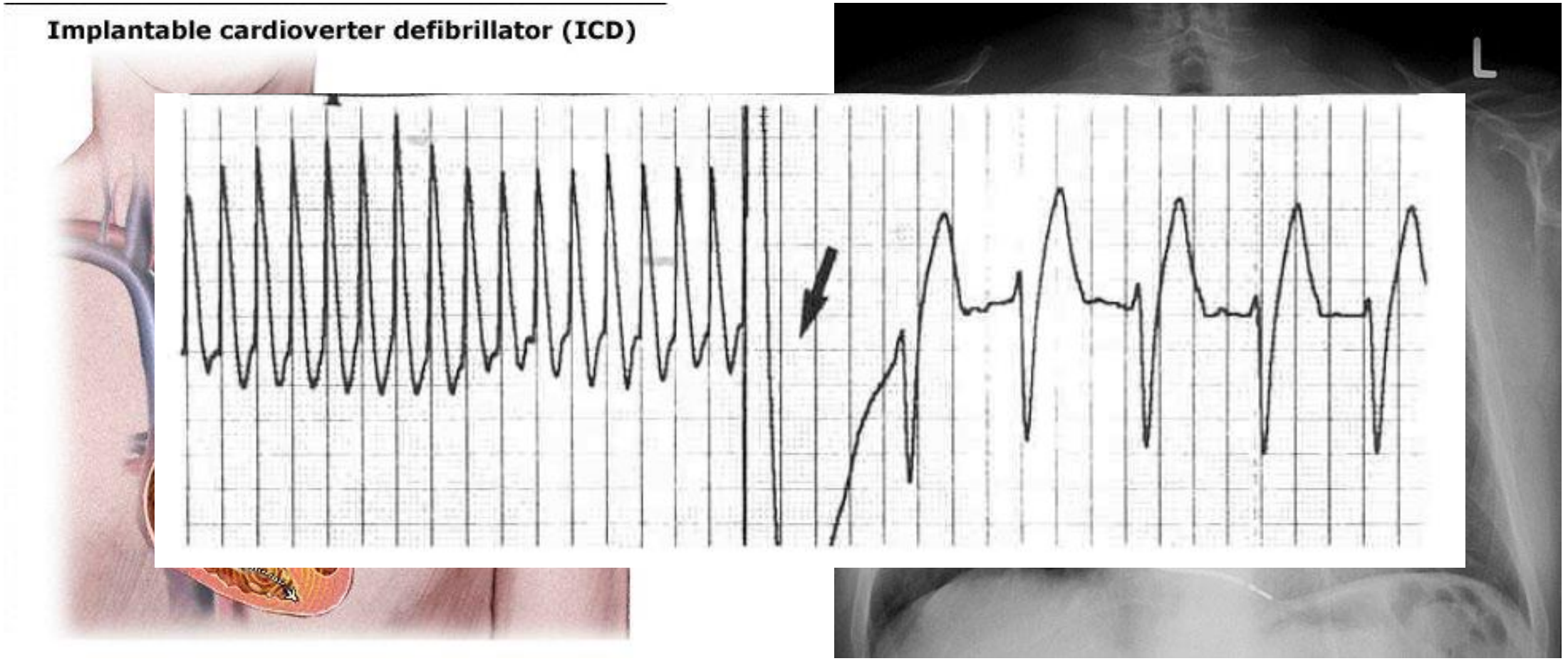
2023 ESC Guideline Update

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

McDonagh et al, *EHJ*, 2023.

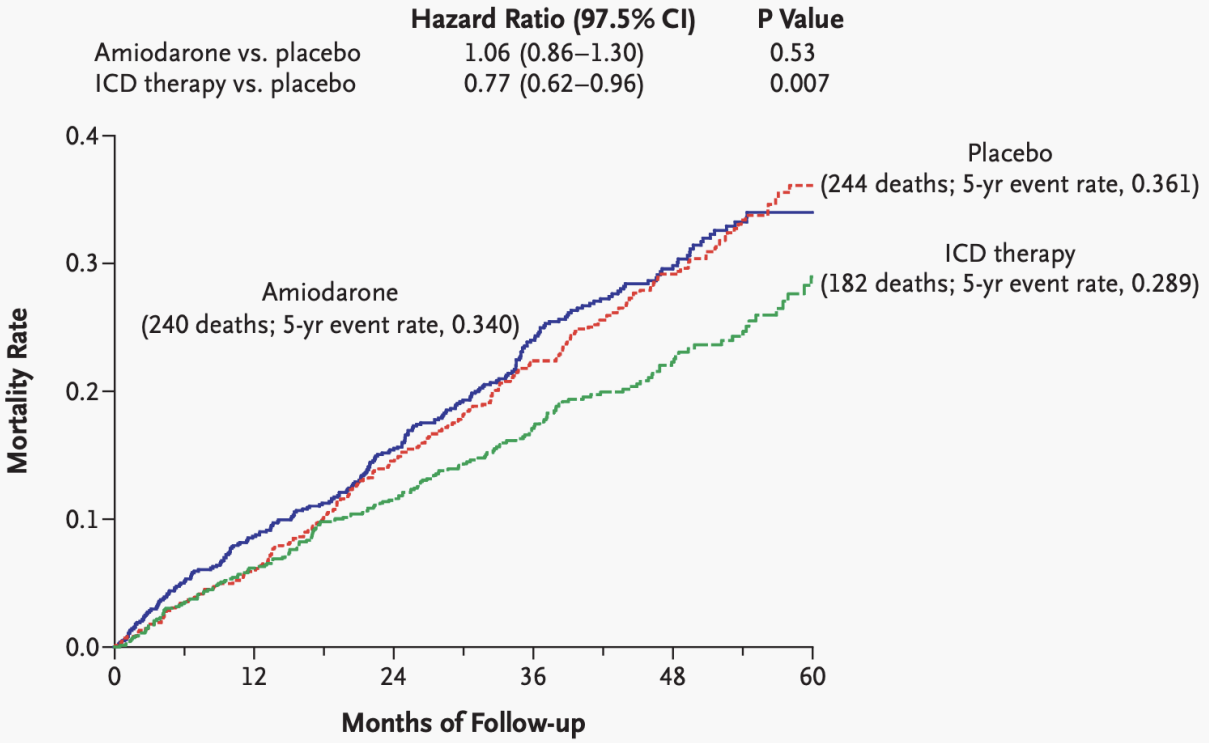
Devices

ICD



ICD

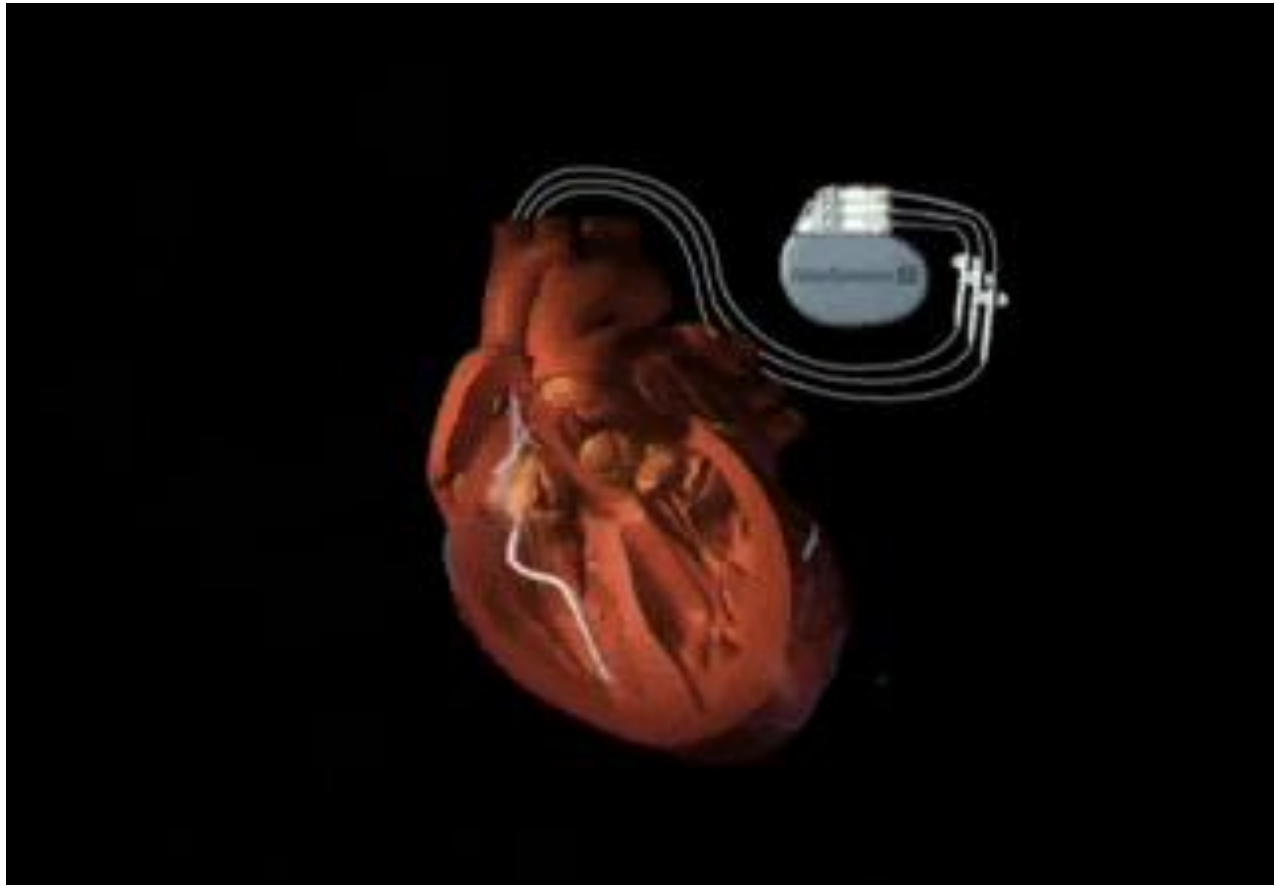
SCD-HeFT

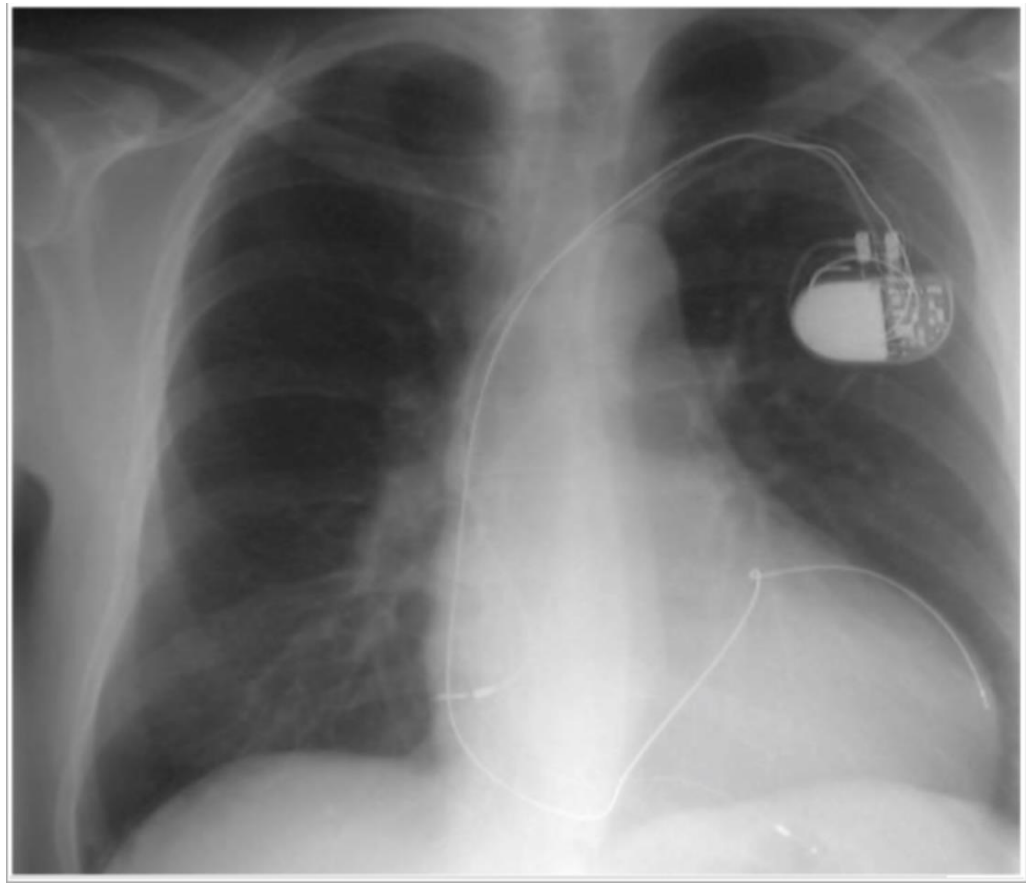


Primary prevention		
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II–III) of an ischaemic aetiology (unless they have had a MI in the prior 40 days—see below), and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status.[161,165]	I	A
An ICD should be considered to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II–III) of a non-ischaemic aetiology, and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status.[161,166,167]	IIa	A

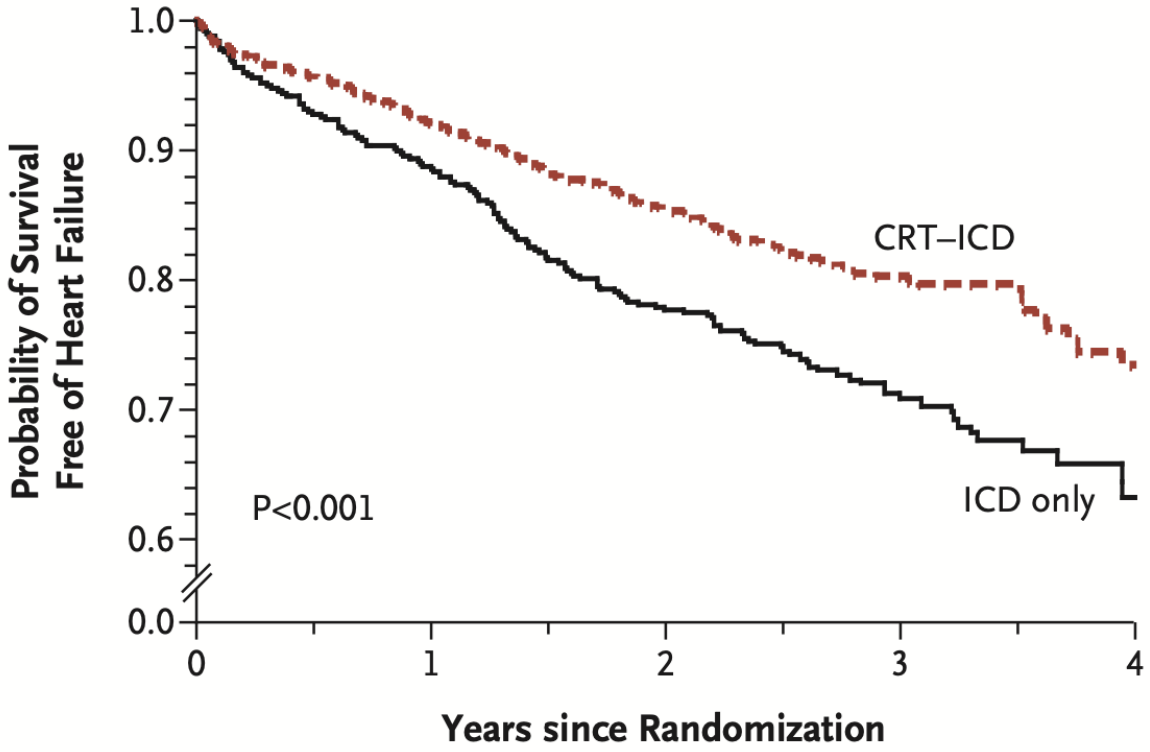
Bardy et al, *NEJM*, 2005.

CRT





CRT



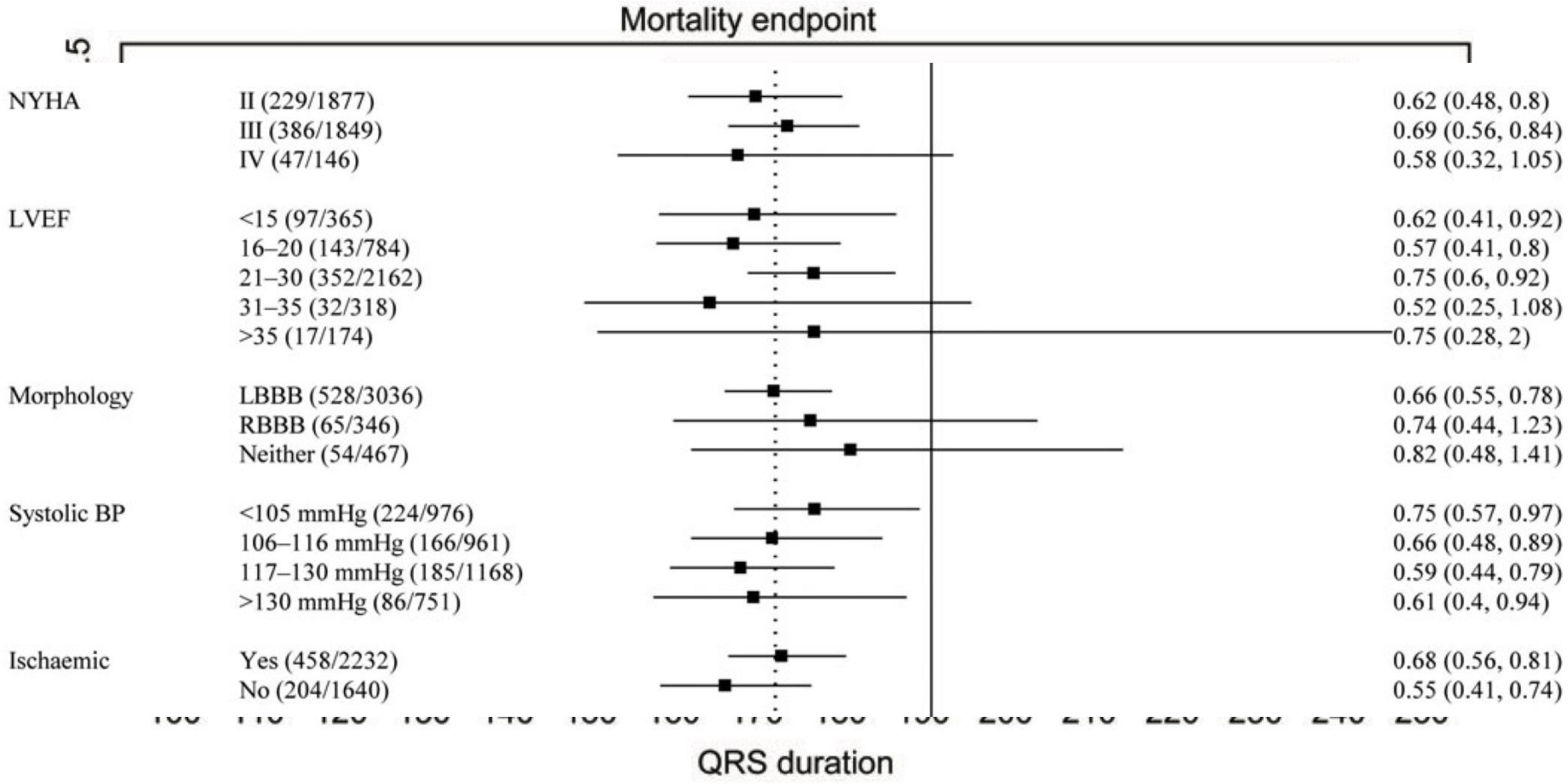
No. at Risk (Probability of Survival)

ICD only	731	621 (0.89)	379 (0.78)	173 (0.71)	43 (0.63)
CRT–ICD	1089	985 (0.92)	651 (0.86)	279 (0.80)	58 (0.73)

Moss et al, *NEJM*, 2009.

Recommendations	Class[a]	Level[b]
CRT is recommended for symptomatic patients with HF in SR with a QRS duration ≥150 ms and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.[205–215]	I	A
CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class or QRS width who have an indication for ventricular pacing for high degree AV block in order to reduce morbidity. This includes patients with AF.[216–219]	I	A
CRT should be considered for symptomatic patients with HF in SR with a QRS duration ≥150 ms and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.[205–215]	IIa	B
CRT should be considered for symptomatic patients with HF in SR with a QRS duration of 130–149 ms and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.[211,220]	IIa	B

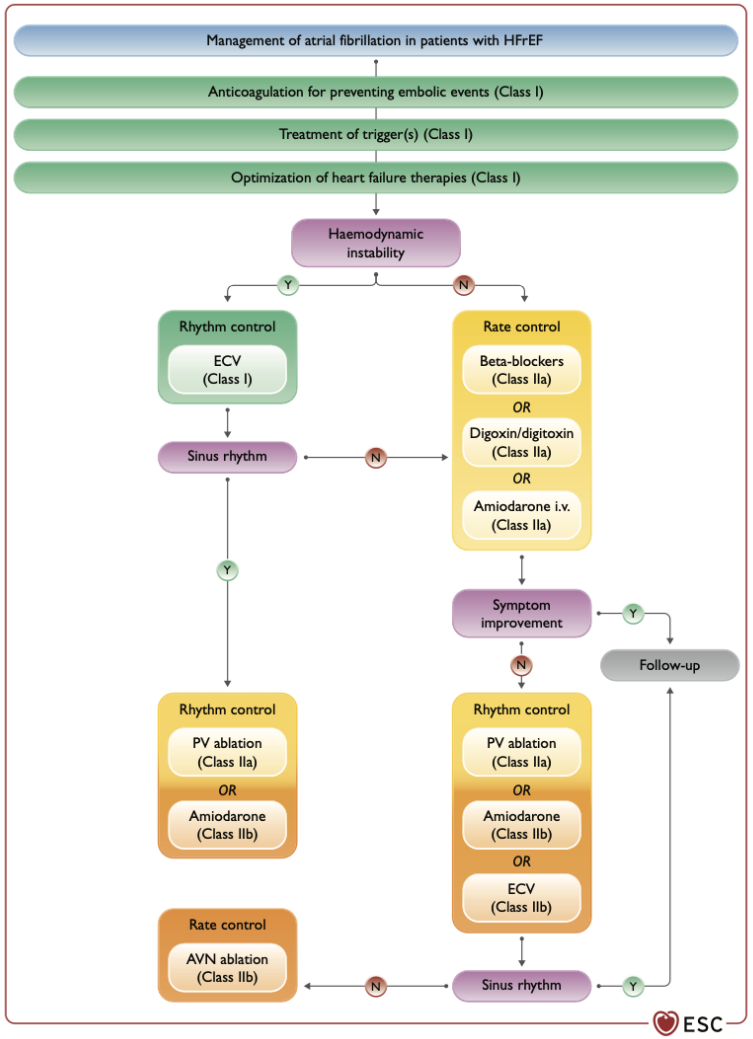
CRT



Cleland et al, *EHJ*, 2013.

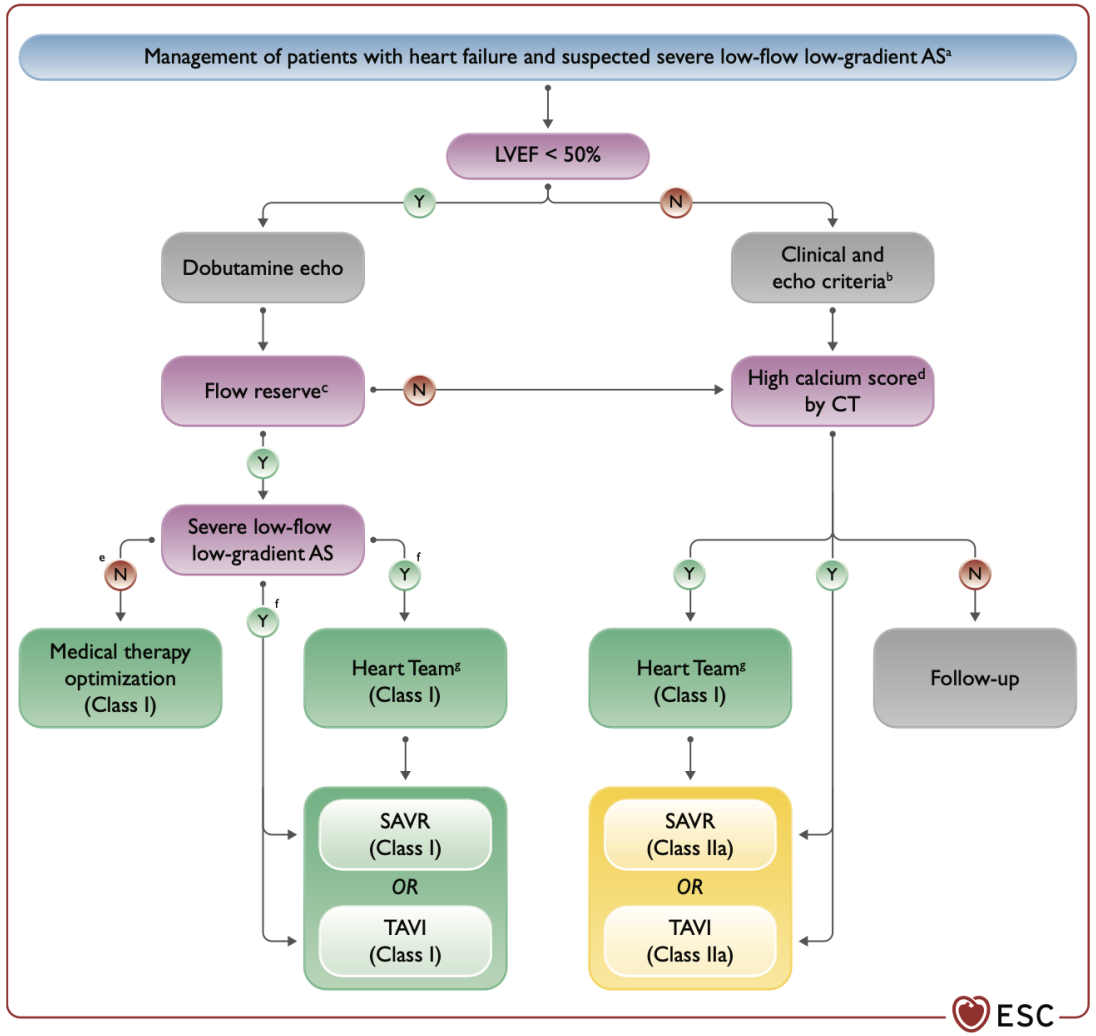
Kardiale Komorbiditäten

Atrial fibrillation



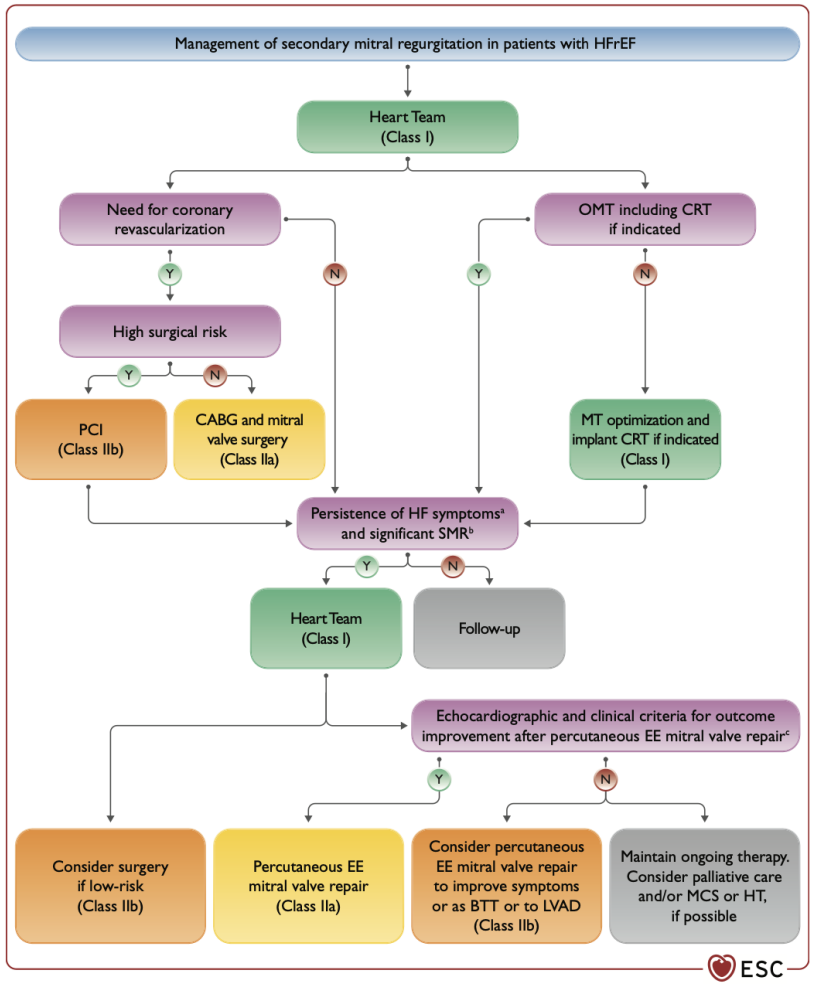
Rate control		
Beta-blockers should be considered for short- and long-term rate control in patients with HF and AF.[535]	**IIa**	**B**
Digoxin should be considered when the ventricular rate remains high, despite beta-blockers, or when beta-blockers are contraindicated or not tolerated.[536]	**IIa**	**C**
Cardioversion		
Urgent ECV is recommended in the setting of acute worsening of HF in patients presenting with rapid ventricular rates and haemodynamic instability.	**I**	**C**
Cardioversion may be considered in patients in whom there is an association between AF and worsening of HF symptoms despite optimal medical treatment.[7,541]	**IIb**	**B**

Aortic stenosis



Aortic stenosis		
Aortic valve intervention, TAVI or SAVR, is recommended in patients with HF and severe high-gradient aortic stenosis to reduce mortality and improve symptoms.[594]	I	B
It is recommended that the choice between TAVI and SAVR be made by the Heart Team, according to individual patient preference and features including age, surgical risk, clinical, anatomical and procedural aspects, weighing the risks and benefits of each approach.[592]	I	C

Secondary mitral regurgitation



Secondary mitral regurgitation		
Percutaneous edge-to-edge mitral valve repair should be considered in carefully selected patients with secondary mitral regurgitation, not eligible for surgery and not needing coronary revascularization, who are symptomatic[c] despite OMT and who fulfil criteria[d] for achieving a reduction in HF hospitalizations.[612]	IIa	B
In patients with HF, severe secondary mitral regurgitation and CAD who need revascularization, CABG and mitral valve surgery should be considered.	IIa	C
Percutaneous edge-to-edge mitral valve repair may be considered to improve symptoms in carefully selected patients with secondary mitral regurgitation, not eligible for surgery and not needing coronary revascularization, highly symptomatic despite OMT and who do not fulfil criteria for reducing HF hospitalization.[617]	IIb	C

Herzinsuffizienz

Verlauf

Verlauf der Erkrankung

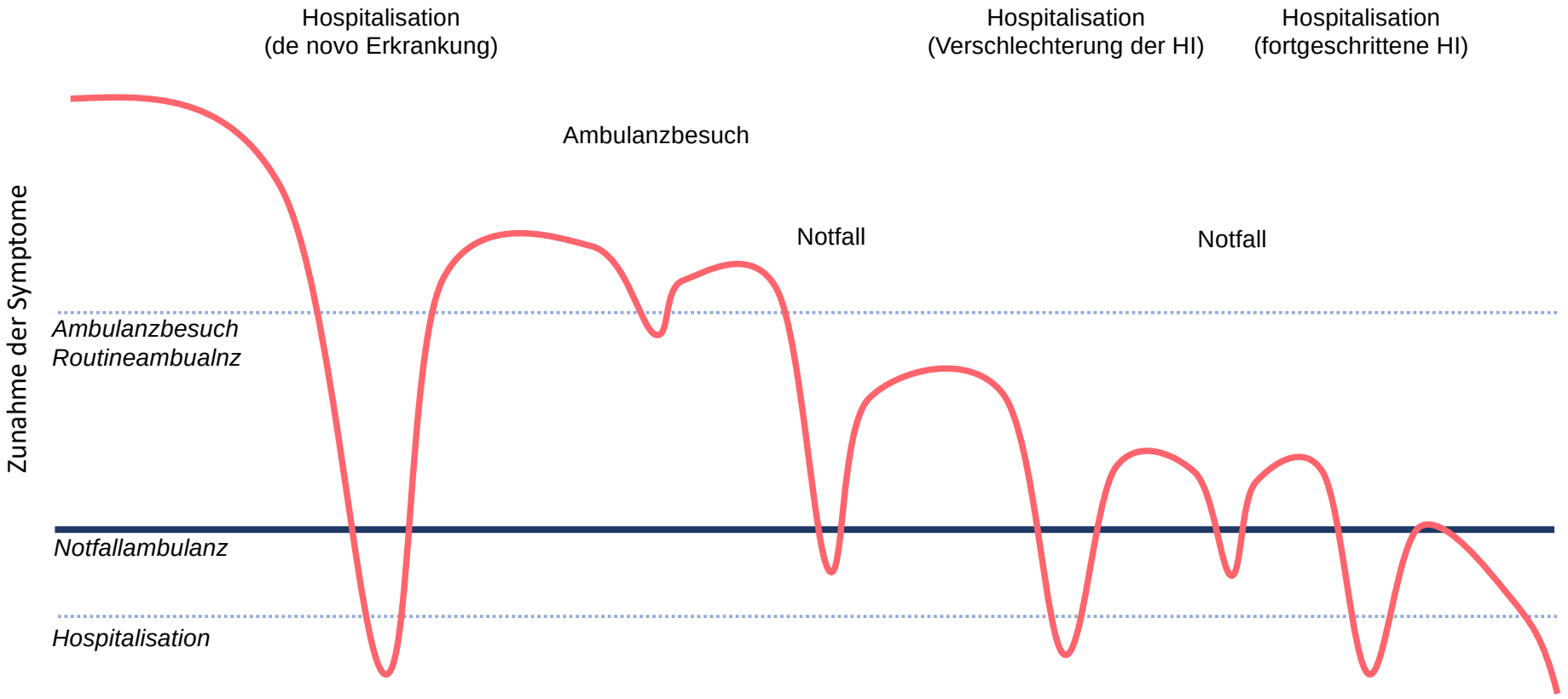
Herzinsuffizienz
myokardiale Dysfunktion

↓

Flüssigkeitsretention
Hypoperfusion

↓

Zeichen und Symptome



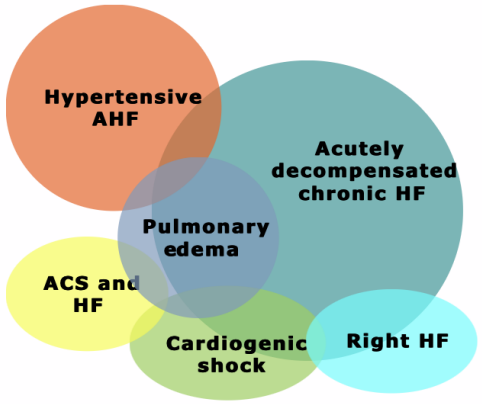
Akute Herzinsuffizenz – oft eine Verschlechterung der vorbekannten HI

ESC-HF Long Term Registry (ESC-HF-LT) 6629 AHF patients

- >50% incidence for ↑SBP[1]
- Mainly pulmonary rather than systemic congestion[1]
- Many patients have preserved ejection fraction[1]

- <3% incidence[1]
- Clinical characteristics: severe dyspnea, tachypnea, tachycardia and hypoxemia, which may require immediate airway intervention[1]

- Unknown incidence[1]
- Many patients have signs and symptoms of ACS that resolve after initial therapy or resolution of ischemia[1]
- Acute HF frequently precipitated by or associated with an arrhythmia[2]

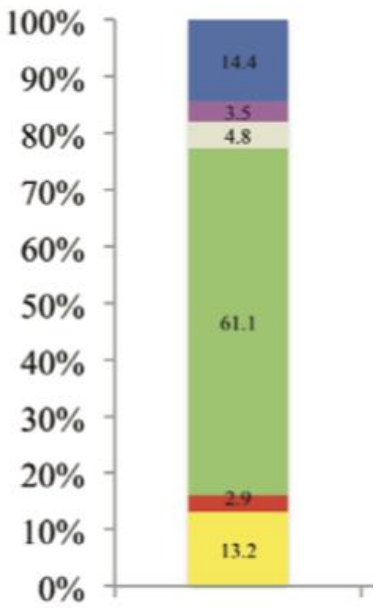


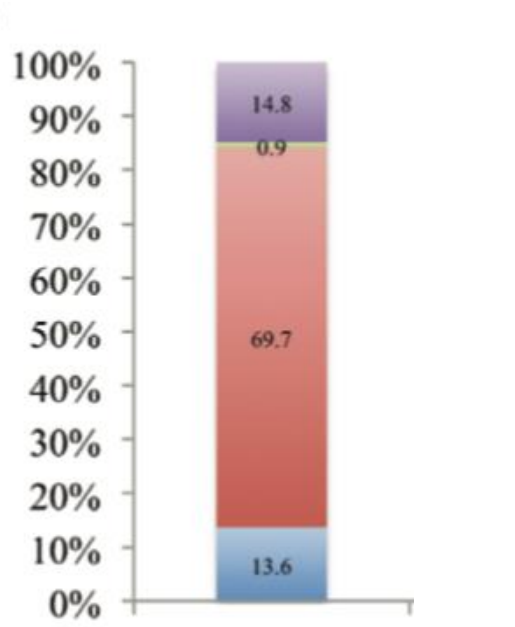
- 70% incidence[1]
- Usually a history of progressive worsening of chronic HF on treatment and evidence of systemic and pulmonary congestion[2]

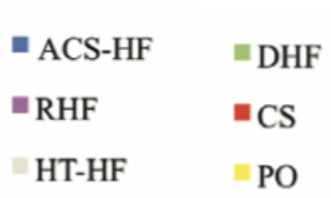
- Unknown incidence[1]
- Low output syndrome in the absence of pulmonary congestion, increased JVP and low LV filling pressures[2]

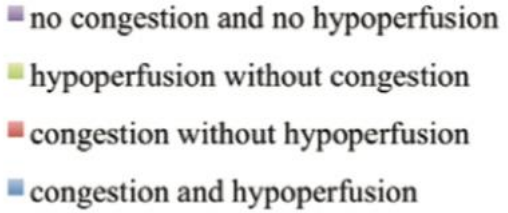
- <1% incidence[1]
- Primarily complicating acute MI, fulminant myocarditis[1]
- Tissue hypoperfusion after adequate correction of preload and major arrhythmia[2]

ACS=acute coronary syndrome; AHF=acute HF; HF=heart failure; JVP=jugular venous pressure; LV=left ventricular; MI=myocardial infarction; SBP=systolic blood pressure
1. Gheorghiade et al. Circulation 2005;112:3958–68; 2. Dickstein et al. Eur Heart J 2008;29:2388–442









Chioncel et al, *EJHF*, 2017.

60% der Patienten mit akuter HI haben eine Verschlechterung der chronischen HI, die meisten Patienten präsentieren sich mit Flüssigkeitsretention bei normaler Perfusion.

Entlassungsmanagement – AG Herzinsuffizienz

ÖKG
Österreichische Kardiologische Gesellschaft

Arbeitsgruppe Herzinsuffizienz
der Österreichischen Kardiologischen Gesellschaft

CHECKLISTE ENTLASSUNG

Herzinsuffizienz nach akuter Dekompensation: Die Checkliste

Die AG Herzinsuffizienz der ÖKG hat diese Checkliste mit dem Ziel entwickelt, die Versorgung von Herzinsuffizienz (HI) PatientInnen nach einer akuten Dekompensation in Österreich zu verbessern. Prinzipiell bestehen bei einer Entlassung zwei problematische Komponenten: Erstens besteht ein hoher Bettendruck, sodass rasche Entlassungen gewünscht sind. Somit kann oft der eine oder andere wesentliche Punkt übersehen bzw. nicht abgearbeitet werden. Solche vorzeitigen Entlassungen führen zu einer raschen Rehospitalisation. Diesem versucht die Arbeitsgruppe für Herzinsuffizienz mit einer Checkliste entgegenzuarbeiten. Hier kann sehr klar entschieden werden, was noch im stationären Bereich getan werden muss oder was für die Entlassung zu planen und an Information weiterzugeben ist.
Zweitens besteht bei der Entlassung eine relevante Schnittstellenproblematik. Essentielle Informationen gehen verloren; Informationen welche jedoch für den niedergelassenen Bereich notwendig sind um den/die PatientIn konsequent weiter zu betreuen. Unter Punkt 10 findet sich eine Checkliste zum Thema Entlassungsbrief.
Konkret wurden Ziele für HI-PatientInnen mit akuter Dekompensation definiert und empfohlen. Durch Berücksichtigung der Empfehlungen wird der/die PatientIn einerseits im Krankenhaus optimal betreut und andererseits ideal für die Entlassung in den niedergelassenen Bereich vorbereitet.

Therapieziele HFrEF:

1. Ist die Euvolämie bestmöglich behandelt (systemisch/lokal)?

Stauung im Lungenröntgen	☐ *ja*	☐ *nein*
Periphere Ödeme	☐ *ja*	☐ *nein*
Zielgewicht erreicht	☐ *ja*	☐ *nein*

2. Wurden auslösende Ursachen behoben? ☐ *ja* ☐ *nein*

3. Haben sich ausgelenkte Laborparamter wieder signifikant gebessert?

Niere	☐ *ja*	☐ *nein*	NT-proBNP/BNP	☐ *ja*	☐ *nein*
Leber	☐ *ja*	☐ *nein*	Troponin	☐ *ja*	☐ *nein*
Infektzeichen	☐ *ja*	☐ *nein*			

4. Sind bzgl EKG/ECHO alle Optimierungsmöglichkeiten ausgeschöpft

QRS <130 ms	☐ *ja*	☐ *nein*	HF <75 bpm	☐ *ja*	☐ *nein*
SR	☐ *ja*	☐ *nein*	EF >35 %	☐ *ja*	☐ *nein*

5. Ist die orale HI-Therapie(-dosis) entsprechend dem Therapiealgorithmus optimiert?

RAS-Blockade (ACE/ARB/ARNI)	☐ ja	☐ nein
BB	☐ ja	☐ nein
MRA	☐ ja	☐ nein
Ivabradin	☐ ja	☐ nein
Optimale Langzeit-Diuretikadosierung	☐ ja	☐ nein

6. Wurde die sonstige Begleitmedikation optimiert? ☐ *ja* ☐ *nein*

SGLT2-Inhibitor bei Diabetes	☐ *ja*	☐ *nein*
nichtsteroidale Antiphlogistika abgesetzt	☐ *ja*	☐ *nein*

7. Wurde der/die PatientIn geschult, bzw. mündlich und schriftlich über seine Verhaltensmaßnahmen aufgeklärt? ☐ *ja* ☐ *nein*

Entlassungsmanagement – AG Herzinsuffizienz

ÖKG
Österreichische
Kardiologische
Gesellschaft

Weiteres PatientInnenmanagement:

8. Wurde eine Folgebetreuung organisiert? ☐ *ja* ☐ *nein*

9. Enthält der Arztbrief alle relevanten Informationen bzgl. der weiteren HI-Betreuung (siehe Checkliste Entlassungsbrief)? ☐ *ja* ☐ *nein*

Entlassungsbrief:

10. Checkliste zum Entlassungsbrief:

(a) Dokumentation und Diskussion der auslösenden Ursache

(b) Dokumentation relevanter Laborbefunde bei Aufnahme und Entlassung

Niere	☐ *ja*	☐ *nein*	NT-proBNP/BNP	☐ *ja*	☐ *nein*
Leber	☐ *ja*	☐ *nein*	Troponin	☐ *ja*	☐ *nein*
Infektzeichen	☐ *ja*	☐ *nein*			

(c) Dokumentation therapierelevanter Parameter des Status/EKG/Echo

QRS	☐ *ja*	☐ *nein*	Vitien	☐ *ja*	☐ *nein*
HF	☐ *ja*	☐ *nein*	Gewicht	☐ *ja*	☐ *nein*
Rhythmus	☐ *ja*	☐ *nein*	Blutdruck	☐ *ja*	☐ *nein*
LVEF u. RVEF	☐ *ja*	☐ *nein*			

(d) Dokumentation der HI-Therapie bei Entlassung ☐ *ja* ☐ *nein*

(e) Empfehlung der weiteren Vorgehensweise

Wurden nicht erreichte Therapieziele diskutiert (Entlassungsmanagment Punkt 1–7) ☐ *ja* ☐ *nein*

Angabe der Therapieziele HFrEF zur Optimierung der HI-Therapie ☐ *ja* ☐ *nein*

Geplante/empfohlene Interventionen ☐ *ja* ☐ *nein*

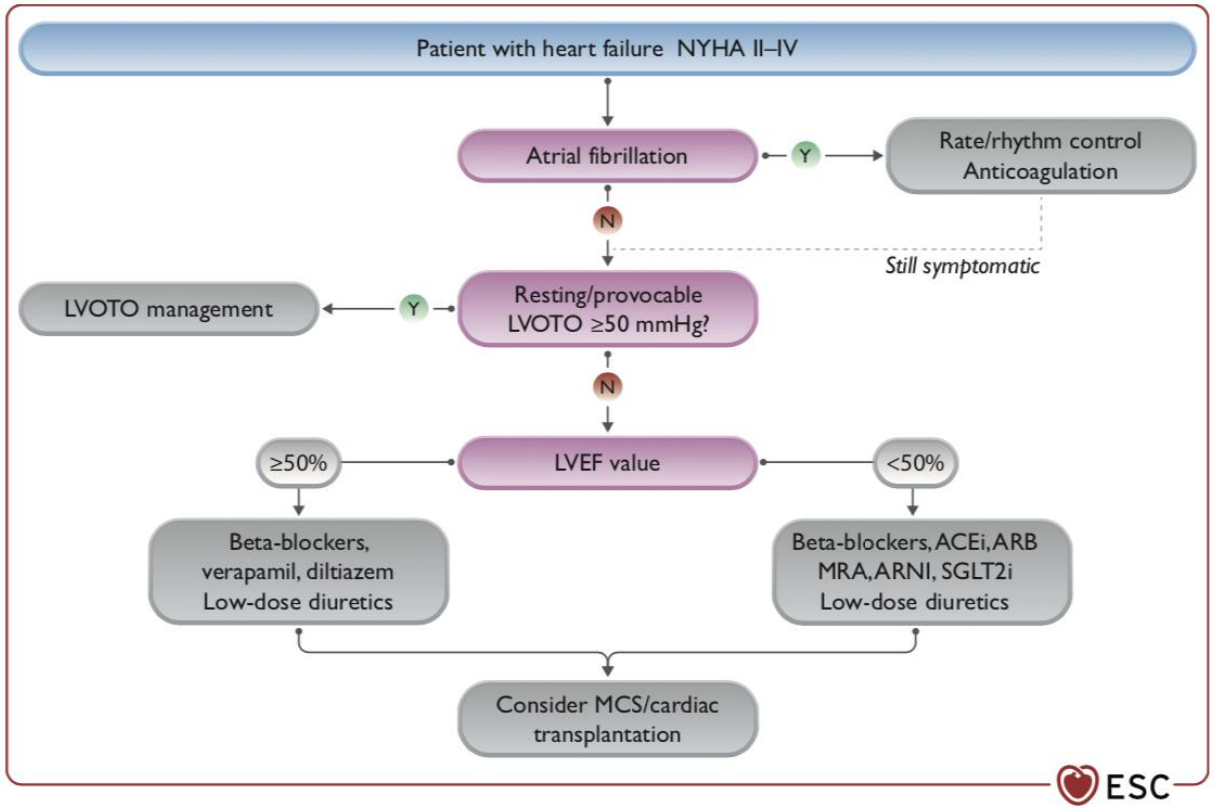
Betreuungsintensität (Allgemeinmediziner/ Kardiologie/HI-Ambulanz/DMP-Programm) ☐ *ja* ☐ *nein*

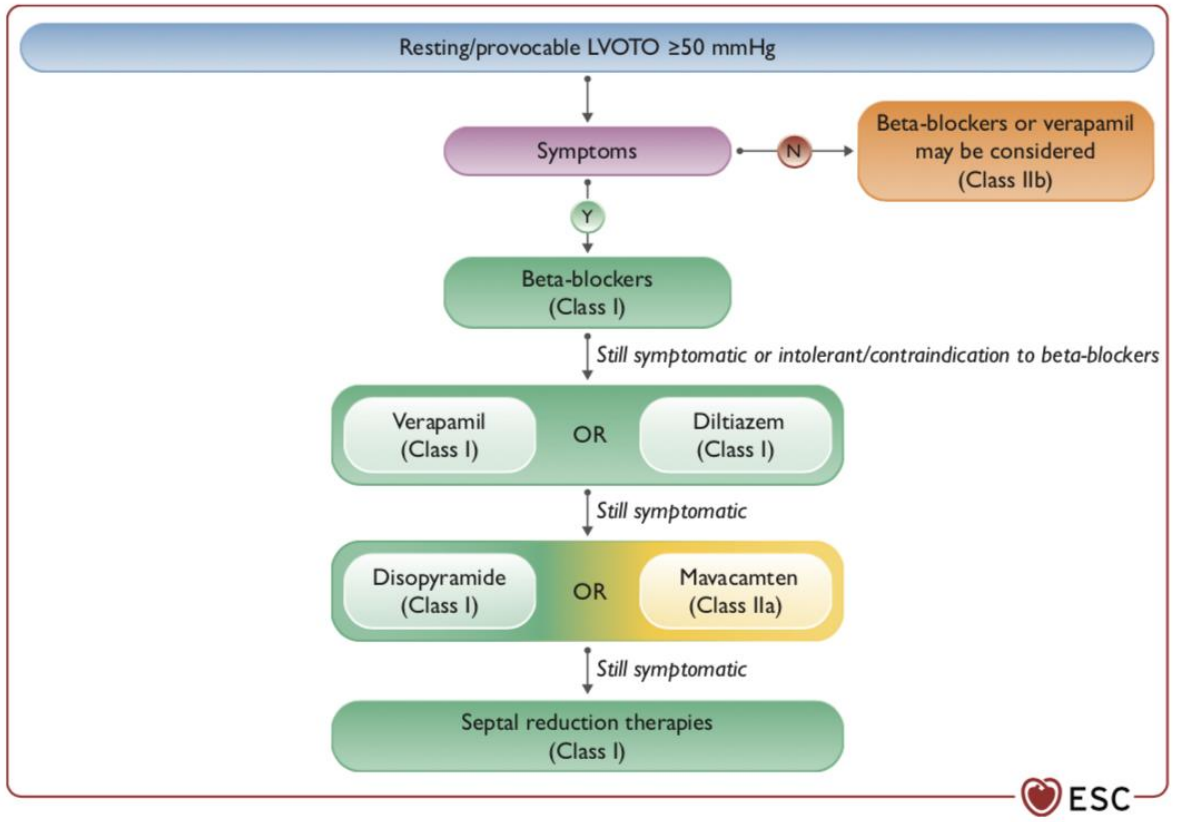
(f) Dokumentation von Folgeterminen ☐ *ja* ☐ *nein*

Herzinsuffizienz

Spezifische Therapien

HCM





Arbelo et al, *EHJ*, 2023.

Kardiale Amyloidose

ESC European Society of Cardiology
European Heart Journal (2021) 42, 1554–1568
doi:10.1093/eurheartj/ehab072
SPECIAL ARTICLE
Heart failure and cardiomyopathies

Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases

Cardiac amyloidosis
ESC Myocardial WG position paper

SUSPECT

Screen if

Left ventricle wall thickness ≥ 12 mm
&
≥ 1 Red Flag or Clinical Scenario

Left Ventricular Wall Thickness ≥ 12 mm + ≥1 of:
- Heart failure in ≥ 65 years
- Aortic stenosis in ≥ 65 years
- Hypotension or normotensive if previously hypertensive
- Sensory involvement, autonomic dysfunction
- Peripheral polyneuropathy
- Proteinuria
- Skin bruising
- Bilateral carpal tunnel syndrome
- Ruptured biceps tendon
- Subendocardial/transmural LGE or increased ECV
- Reduced longitudinal strain with apical sparing
- Decreased QRS voltage to mass ratio
- Pseudo Q waves on ECG
- AV conduction disease
- Possible family history

DIAGNOSIS

Diagnostic criteria

Invasive (all types)	Non-Invasive (only for ATTR)
Cardiac Biopsy positive for amyloid or Extracardiac Biopsy positive for amyloid + Echocardiographic/CMR criteria	Grade 2 or 3 cardiac uptake at diphosponate Scintigraphy + Negative serum free light chains & negative serum and urine immunofixation (SPIE & UPIE) + Echocardiographic/CMR criteria

Diagnostic algorithm

^{99m}Tc-DPD/PYP/HMDP Scintigraphy with SPECT & Haematologic tests (serum free-light chain quantification & serum and urine immunofixation)

Diagnosis made or proceed to **CMR and/or biopsy** according to results

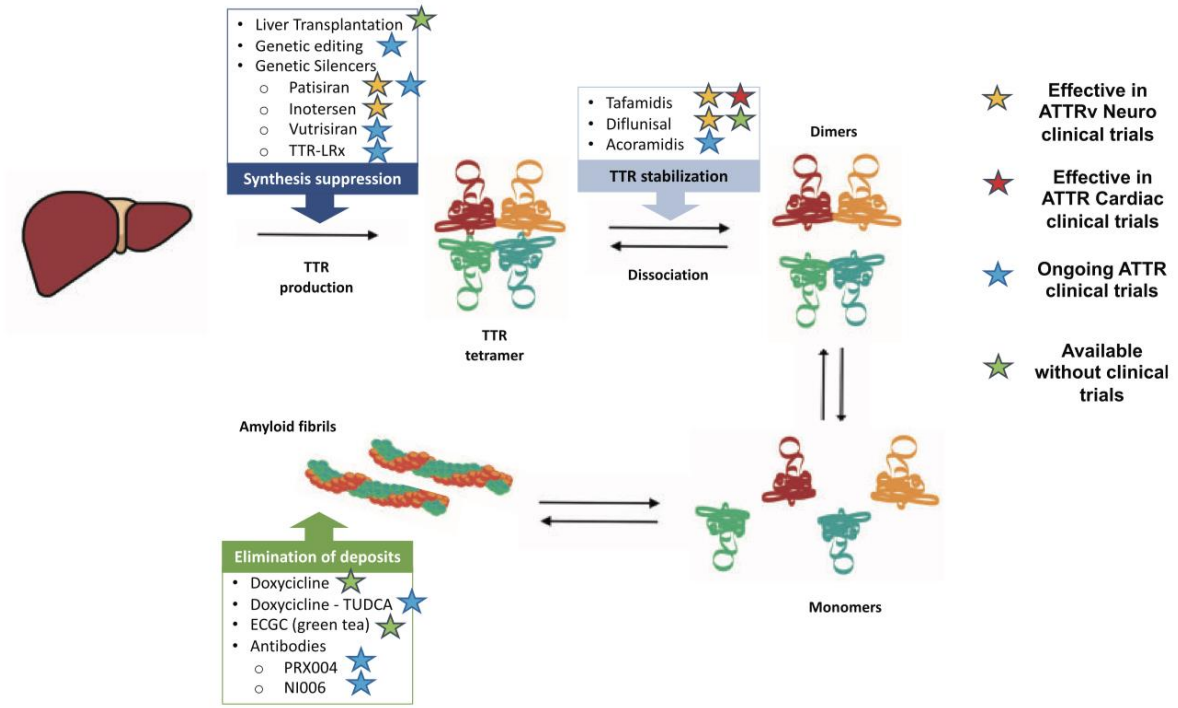
TREATMENT

Cardiac complications and comorbidities

- Heart Failure
- Thromboembolism
- Atrial fibrillation
- Conduction disorders
- Ventricular arrhythmias
- Aortic stenosis

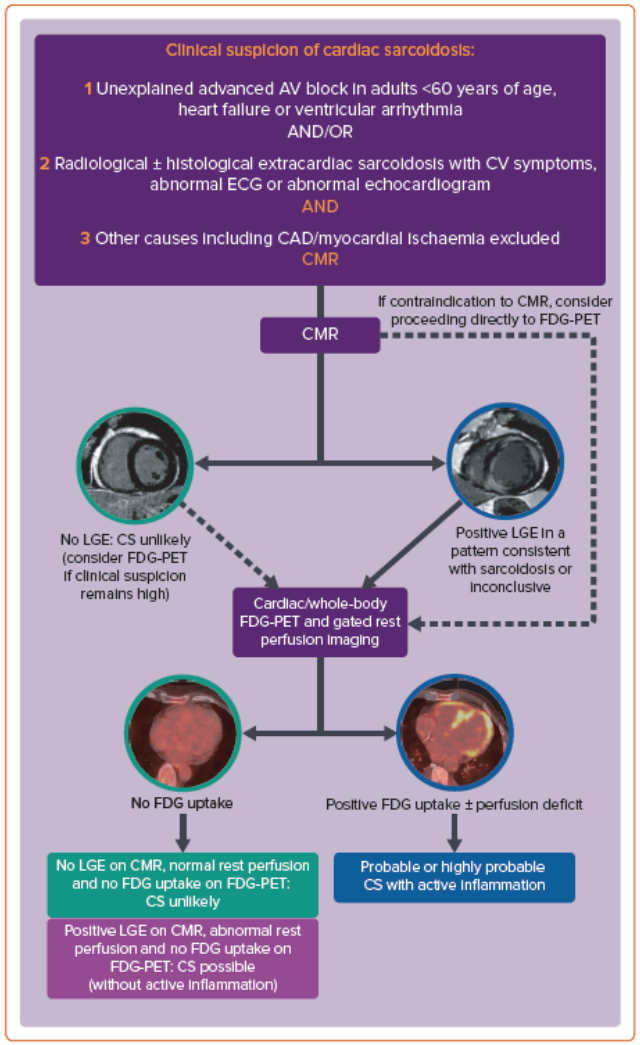
Disease modifying treatment

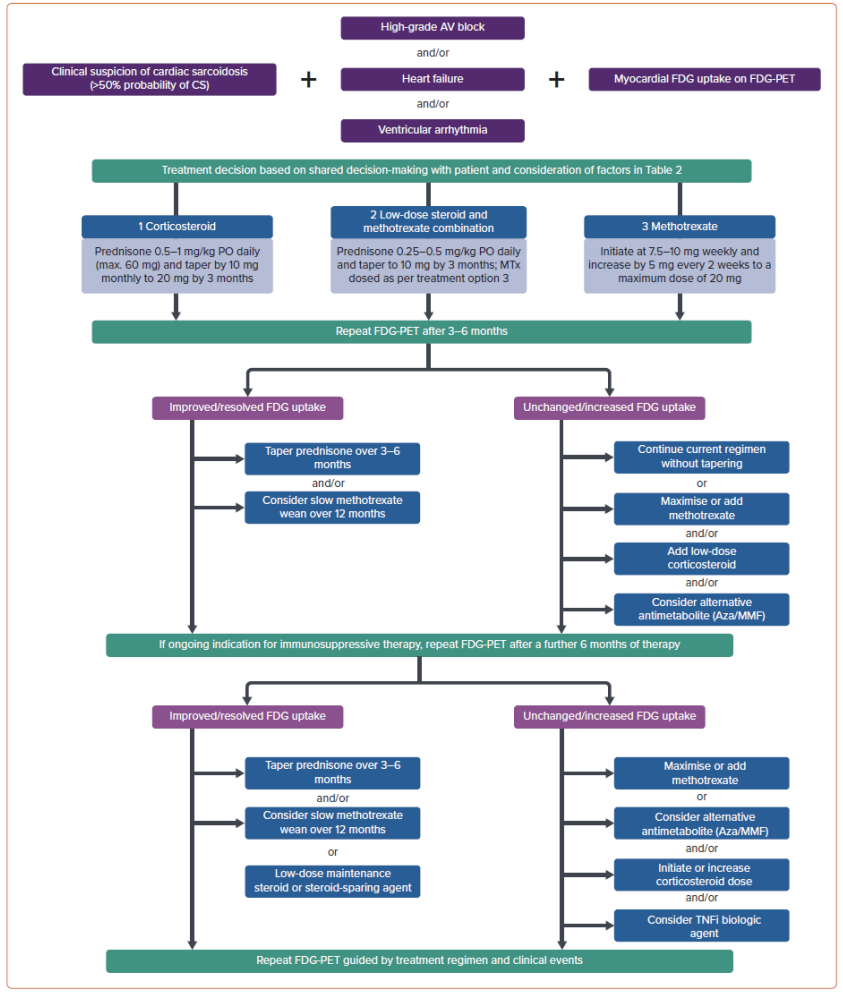
- **ATTR**: genetic silencers, stabilizers and removers.
- **AL**: chemotherapy and ASCT.
- **AA**: anti-inflammatory, anti-infective and immunosuppressive drugs.

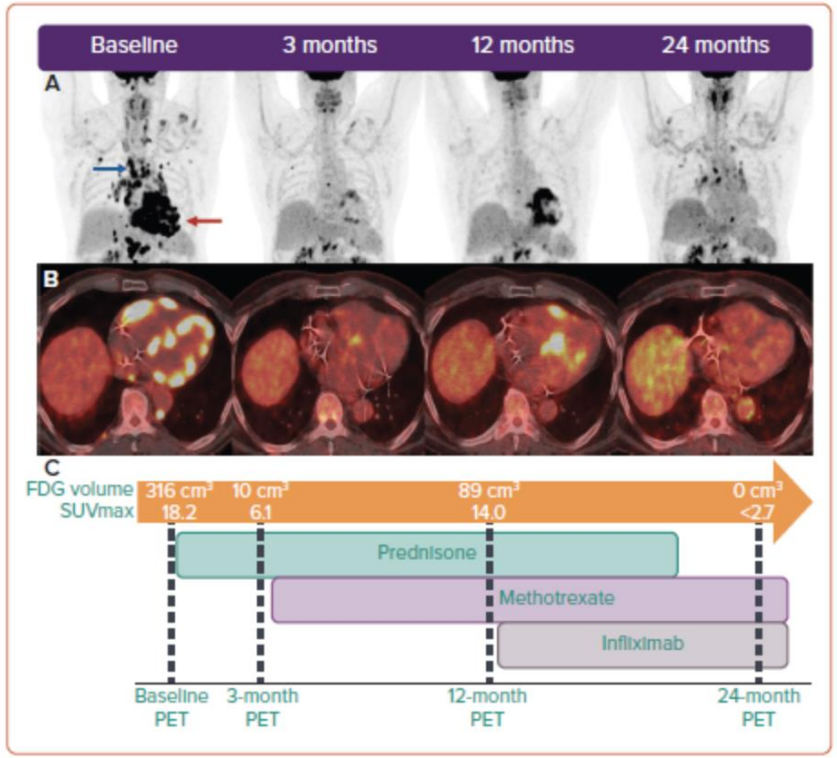


Gacia-Pavia et al, *EHJ*, 2021.

Kardiale Sarkoidose



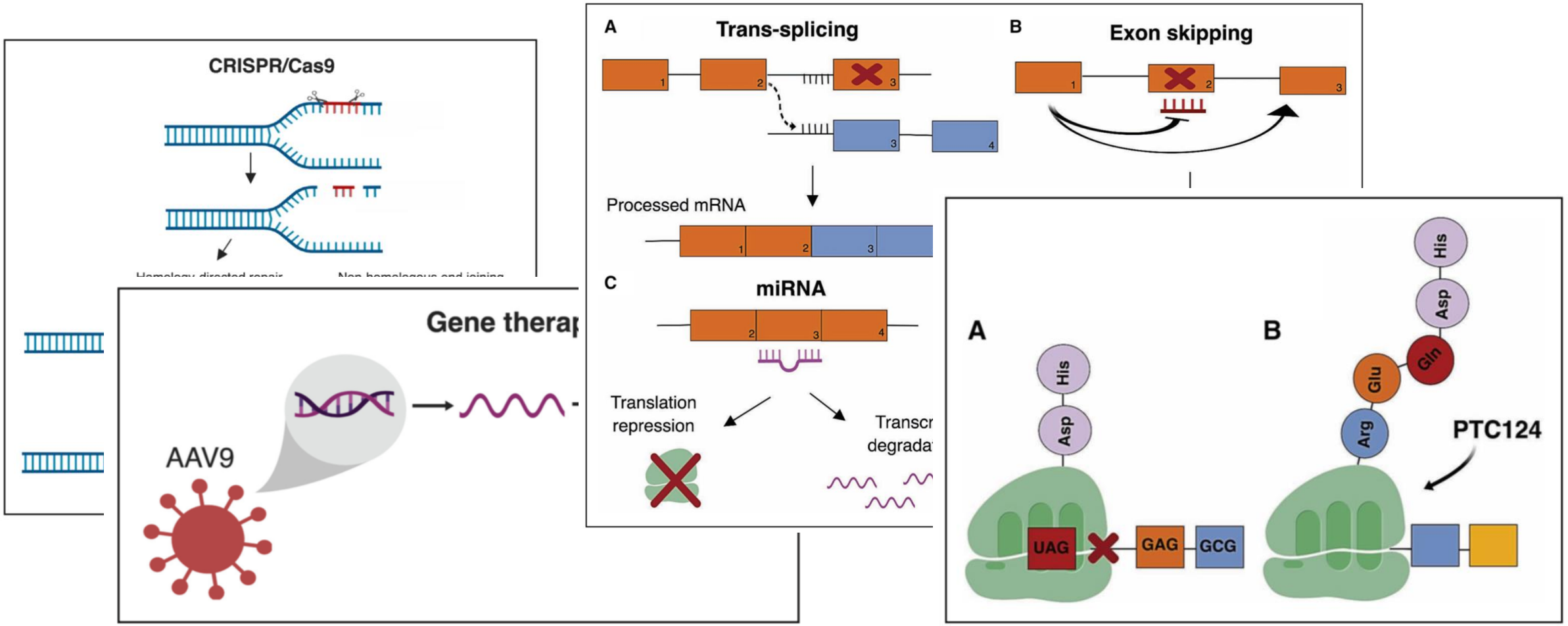




AV = atrioventricular; CAD = coronary artery disease; CMR = cardiac MRI; CS = cardiac sarcoidosis; CV = cardiovascular; FDG = fluorodeoxyglucose; LGE = late gadolinium enhancement.

Giblin et al, *Card Fail Rev*, 2021.

Therapiestrategien der genetischen CMPs – Zukunft?



Repetti et al, *Circ Res*, 2019.

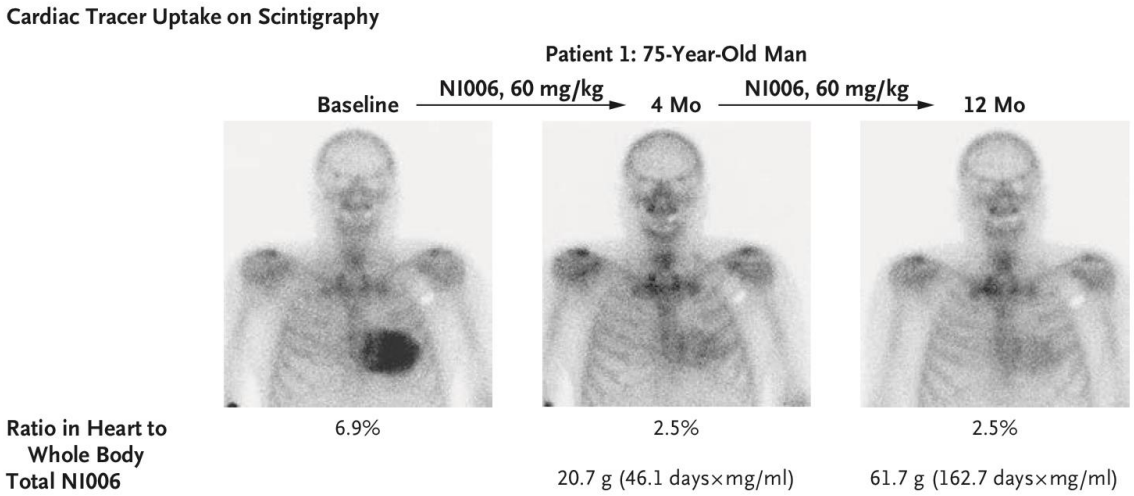
Herzinsuffizienz

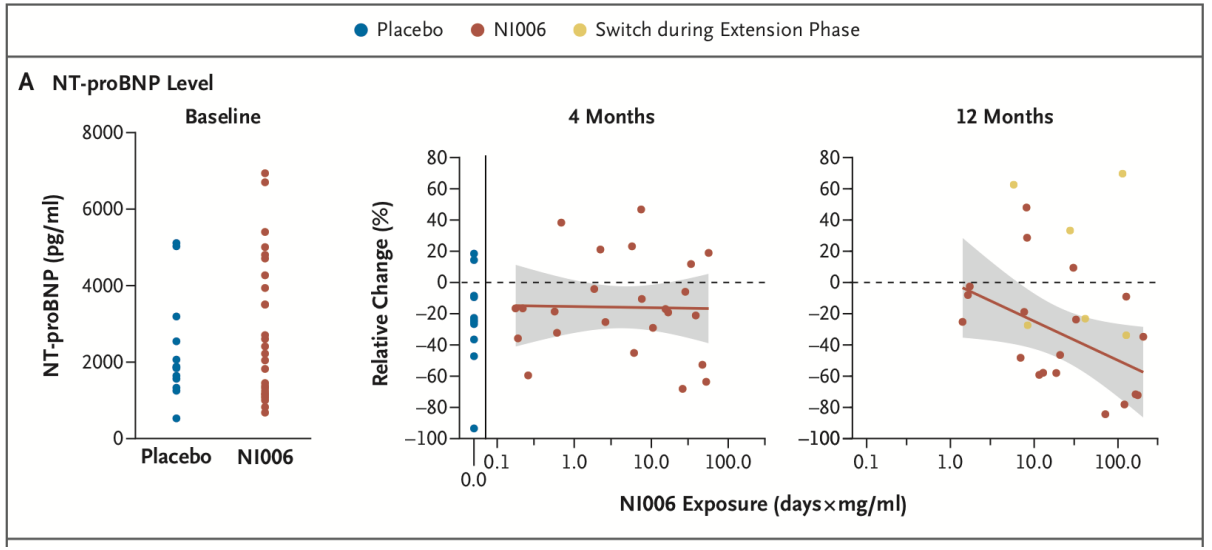
Neue Ansätze – neue Studien

Antibody NI006 – phase 1 trial

Is NI006, a recombinant human anti-ATTR antibody, safe for depletion of amyloid deposits in ATTR-CM?

40 patients wt ATTR CMP
Iv NI006/placebo for 4 months





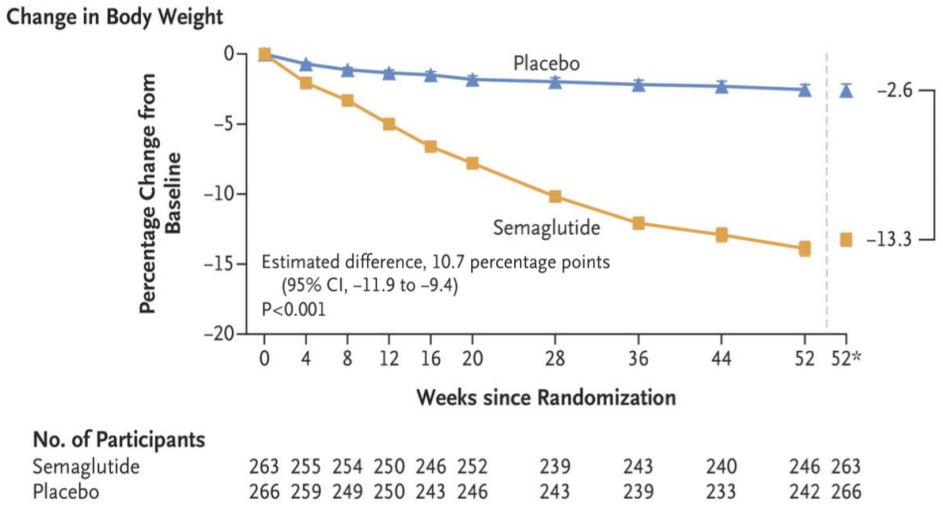
Garcia-Pavia et al, *NEJM*, 2023.

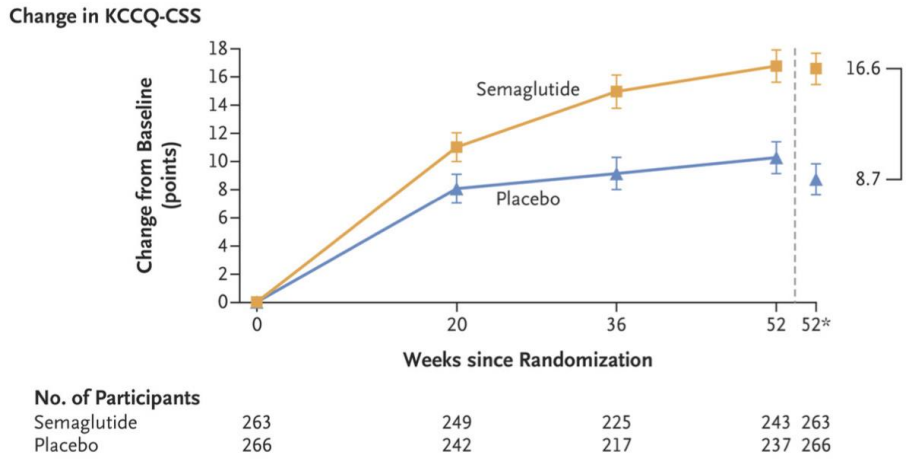
The use of NI006 was associated with no apparent drug-related serious adverse events.

STEP-HFpEF

Can semaglutide safely reduce weight and enhance exercise capacity in obesity-related HFpEF?

529 patients LVEF <40% BMI >30kg/m2, no T2DM,
1:1 2.4mg semaglutide sc once weekly vs placebo for 52 weeks
PEP: change in body weight, change in KCCQ





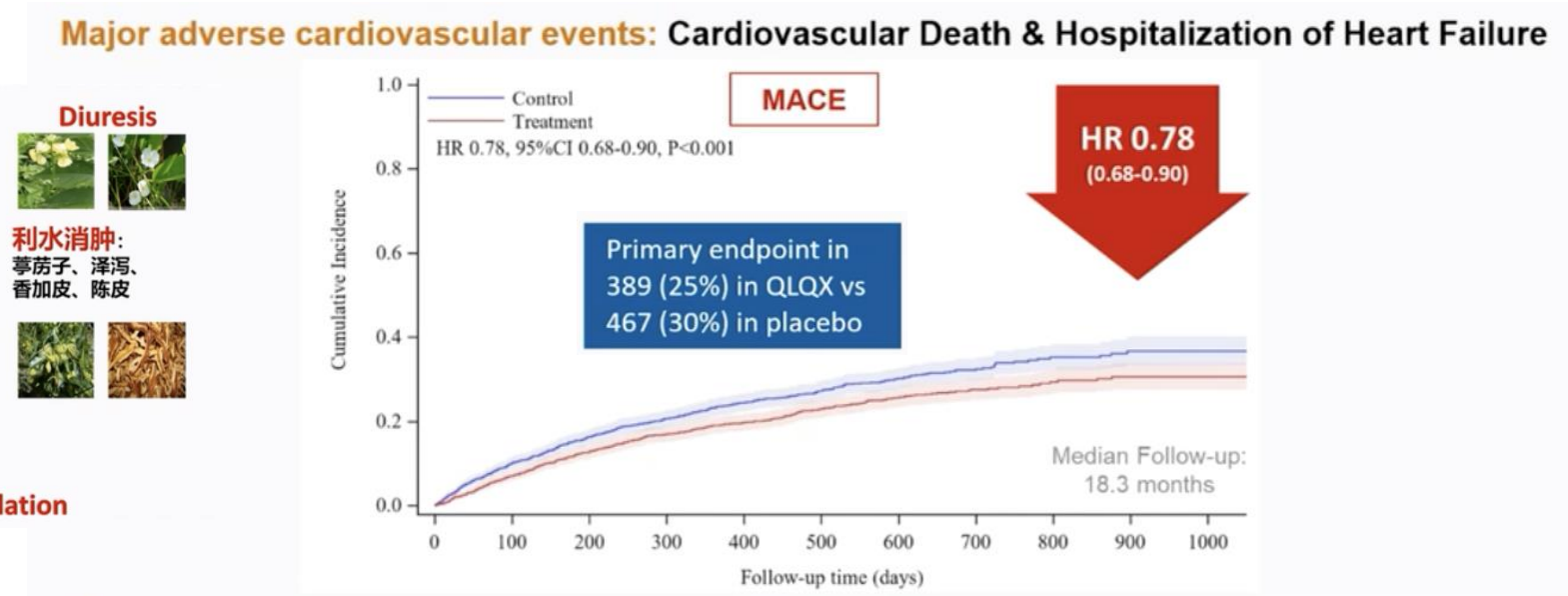
Kosiborod et al, *NEJM*, 2023.

In patients with HFpEF and obesity 2.4mg semaglutide was safe (also more GI side effects) and led to greater weight loss and a higher reduction in symptoms and physical limitation than placebo.

QUEST

Is Qili Qiangxin able to reduce the hard combined endpoint CV-death and HHF in HFrEF?

3080 patients LVEF <40%,
NT-proBNP >450pg/ml,
QL vs placebo

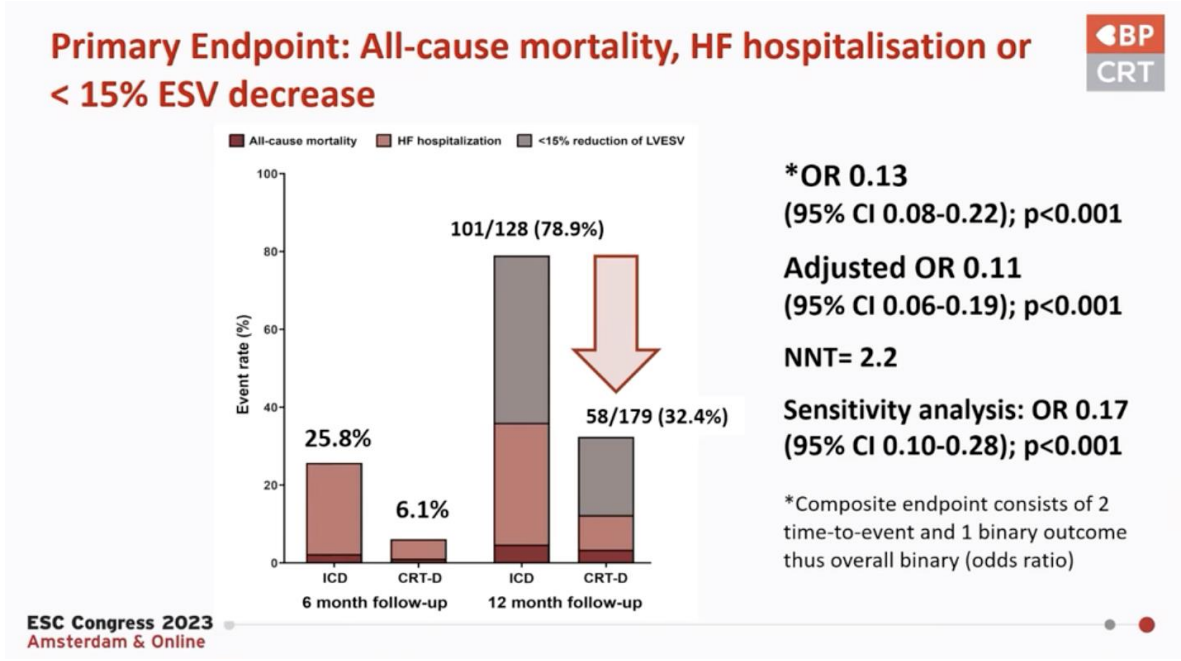


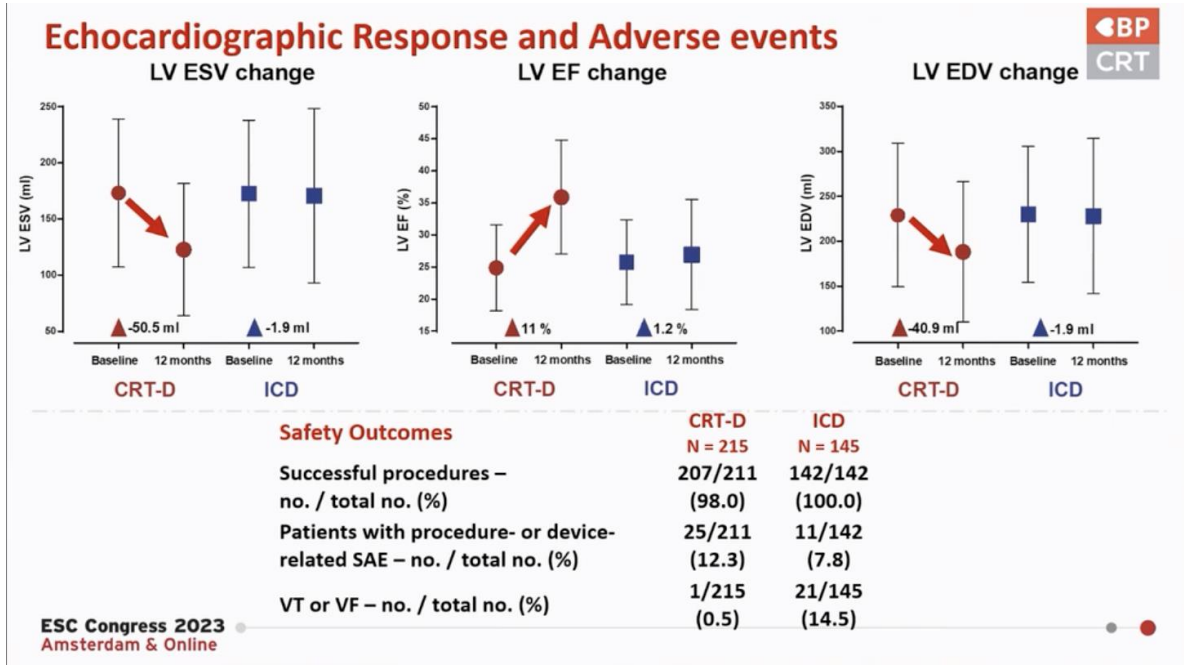
Li et al, *ESC congress* 2023.

Qili Qianxin caapsules reduce CV death and HHF significantly while being safe. The effect seemed attenuated in patients with GDMT, suggesting shared mechanisms? Limitations: the susbatnce is a compound, the active component(s) are unknown.

Budapest CRT

Can a CRT upgrade in HFrEF with PM/ICD and significant RV-pacing effectively reduce mortality, HHF and adverse remodeling?





Merkely et al, *ESC congress* 2023.

In the investigated patient population CRT upgrade ist effective in reducing HHF and LV reverse remodeling. Patients with HFrEF aand PM/ICD should be closely monitored for RV pacing rate and referred for a CRT upgrade when eligible.

CASTLE HTx

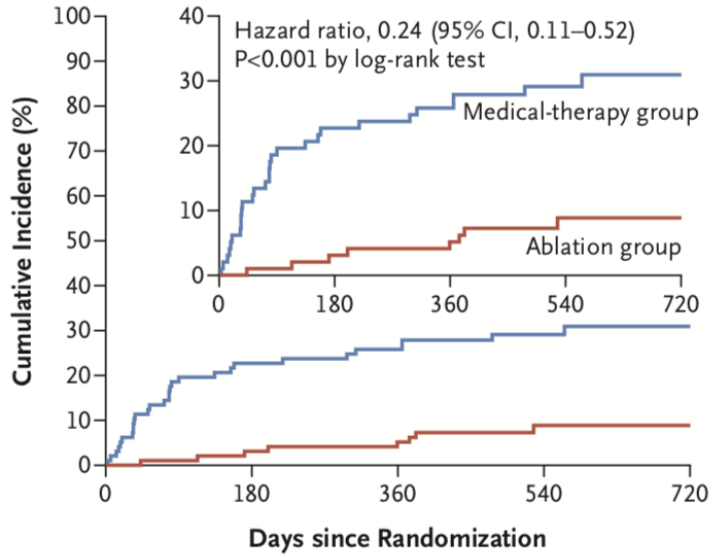
What is the role of catheter ablation in patients with symptomatic atrial fibrillation and end- stage heart failure?

Single center, open label
194 patients, symptomatic Afib, end stage HF
ablation + GDMT vs GDMT

Table 2. Primary and Secondary End Points.

End Point	Ablation Group (N=97)	Medical-Therapy Group (N=97)	Hazard Ratio (95% CI)*	P Value†
	no. (%)			
Primary end point‡	8 (8)	29 (30)	0.24 (0.11 to 0.52)	<0.001
Secondary end points				
Death from any cause	6 (6)	19 (20)	0.29 (0.12 to 0.72)	
Cardiovascular	5 (5)	18 (19)	0.25 (0.09 to 0.68)	
Cerebrovascular	0	1 (1)		
Cancer	1 (1)	0		
Death after nonfatal primary end point	0	5 (5)		
Implantation of left ventricular assist device	1 (1)	10 (10)	0.09 (0.01 to 0.70)	
Urgent heart transplantation	1 (1)	6 (6)	0.15 (0.02 to 1.25)	

all-cause death, LVAD or HTx



No. at Risk

Medical-therapy group	97	75	72	41	12
Ablation group	97	94	88	50	20

Sohns et al, *NEJM,* 2023.

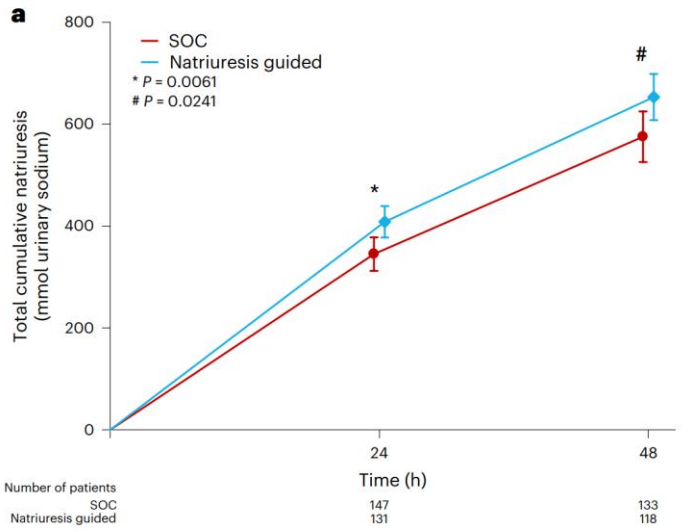
The combination of catheter ablation and guideline-directed medical therapy was associated with a lower likelihood of a composite of death from any cause, implantation of a LVAD, or urgent HTx.

PUSH-AHF

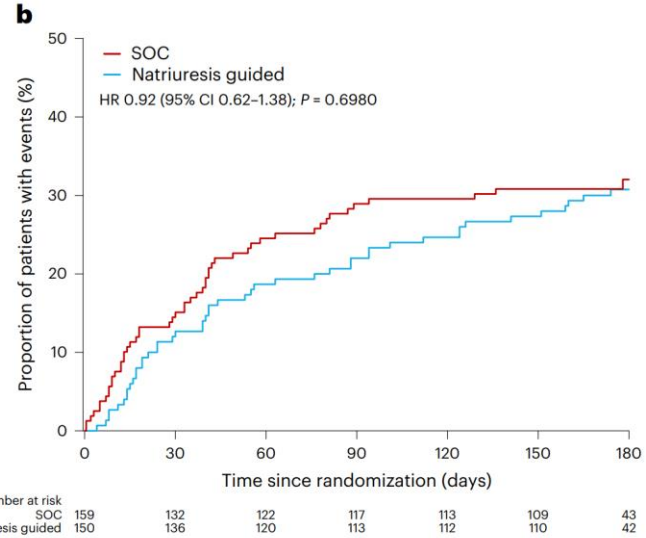
Can natriuresis-guided diuretic therapy in patients with AHF improve natriuresis and clinical outcomes?

open label
310 patients with AHF requiring diuretic therapy
Natriuresis guided therapy vs standard of care
Dual PEP: 24h urinary Na excretion, mortality/HHF at 180days

natriuresis



all-cause death or HHF



Ter Maaaten et al, *Nat Med,* 2023.

Higher natriuresis can be achieved by the natriuresis guided therapy, while no difference was observed in hard endpoints. Natriuresis-guided therapy could be a first step towards personalized treatment of AHF.

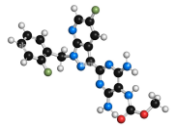
Take home study news in HF

„fantastic four“ der HFrEF
die jeder Patient bekommen sollte (I A)
ACEi/ARNi, BB, MRA, SGLT2i

Es existiert eine große Therapielücke (therapy inertia) in der Implementation der GDMT.
4 drugs in 4 weeks für die HFrEF!

Die **SGLT2i dapagliflozin und empagliflozin** sollten unabhängig der LVEF für alle Patienten verschrieben werden (I A)

HEART-FID: **Eisen überzeugt nicht** bei der Reduktion von harten Endpunkten in der HFrEF



Vericiguat sollte bei high-risk Patienten und GDMT erwogen werden (IIb B)

bei unklarer CMP **Suche nach der Ätiologie** unerlässlich


MEDIZINISCHER UNIVERSITÄTSCAMPUS
MEDIZINISCHE UNIVERSITÄT WIEN
Allgemeines Krankenhaus der Stadt Wien

Akute Herzinsuffizienz

Verlauf der Erkrankung

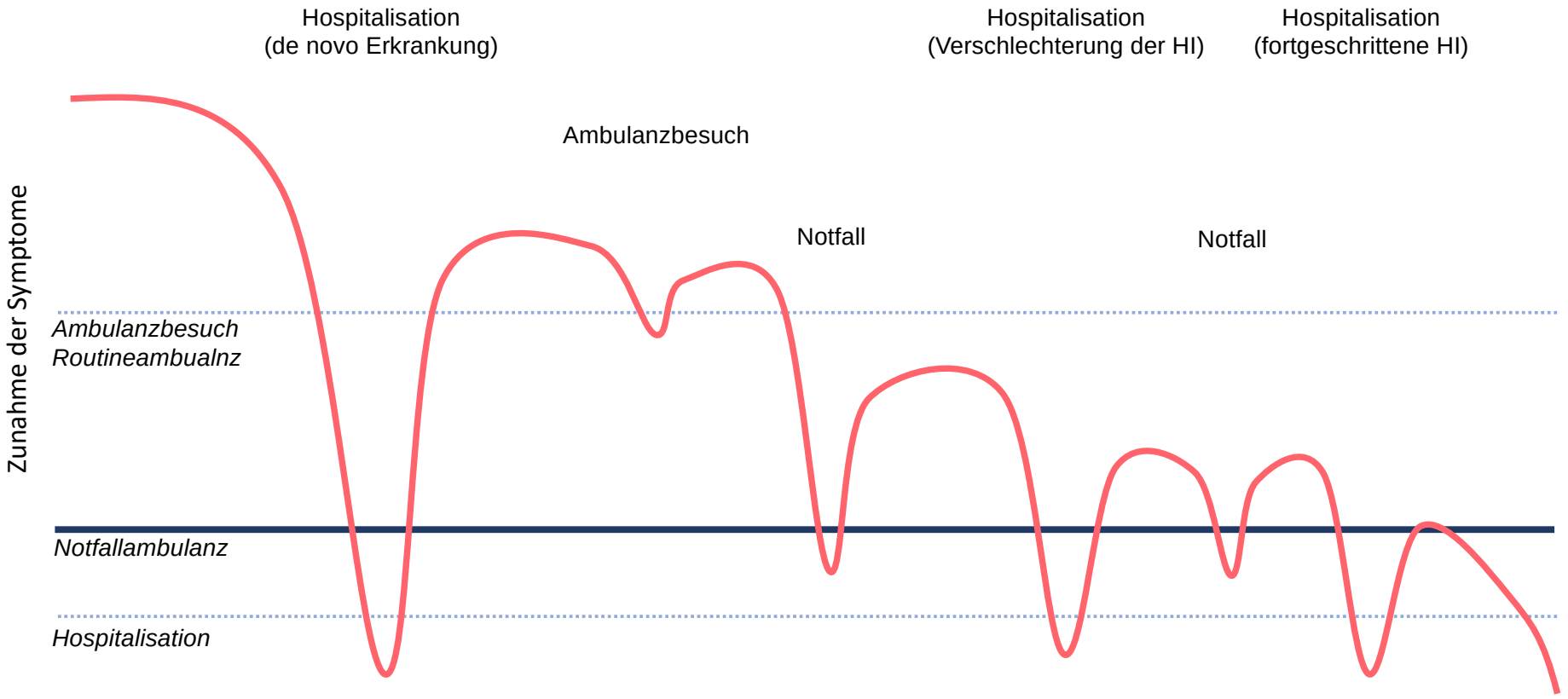
Herzinsuffizienz
myokardiale Dysfunktion

↓

Flüssigkeitsretention
Hypoperfusion

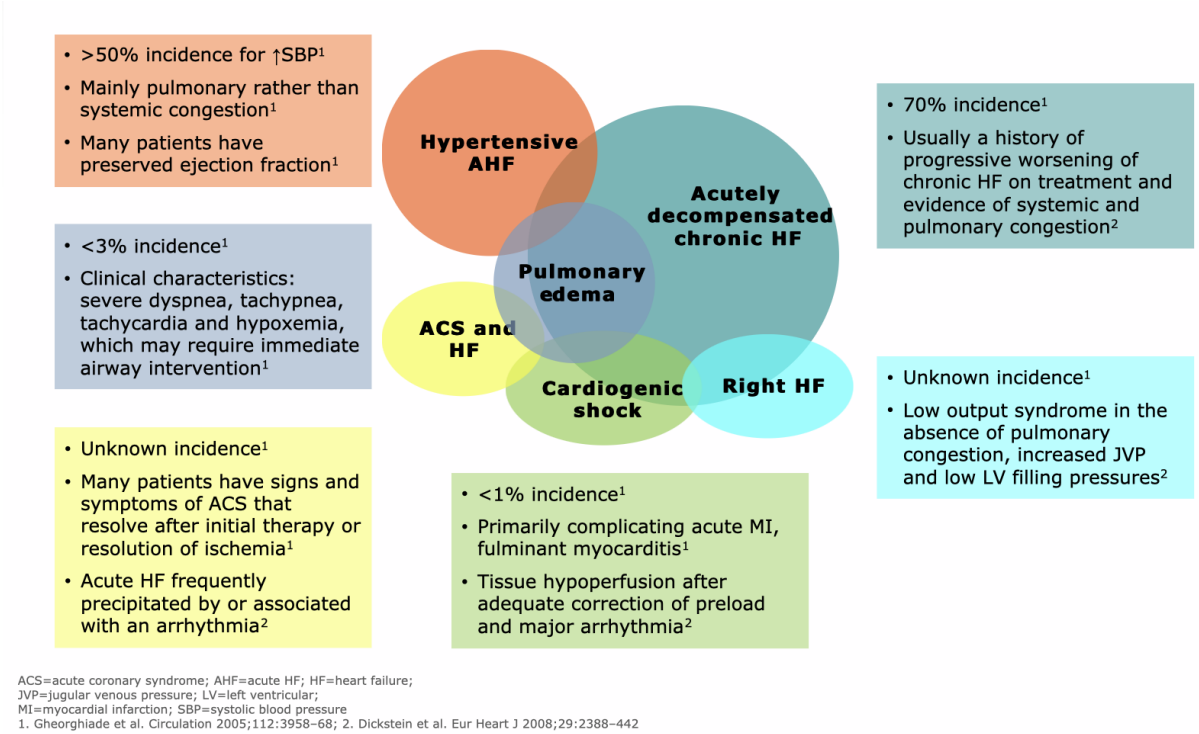
↓

Zeichen und Symptome



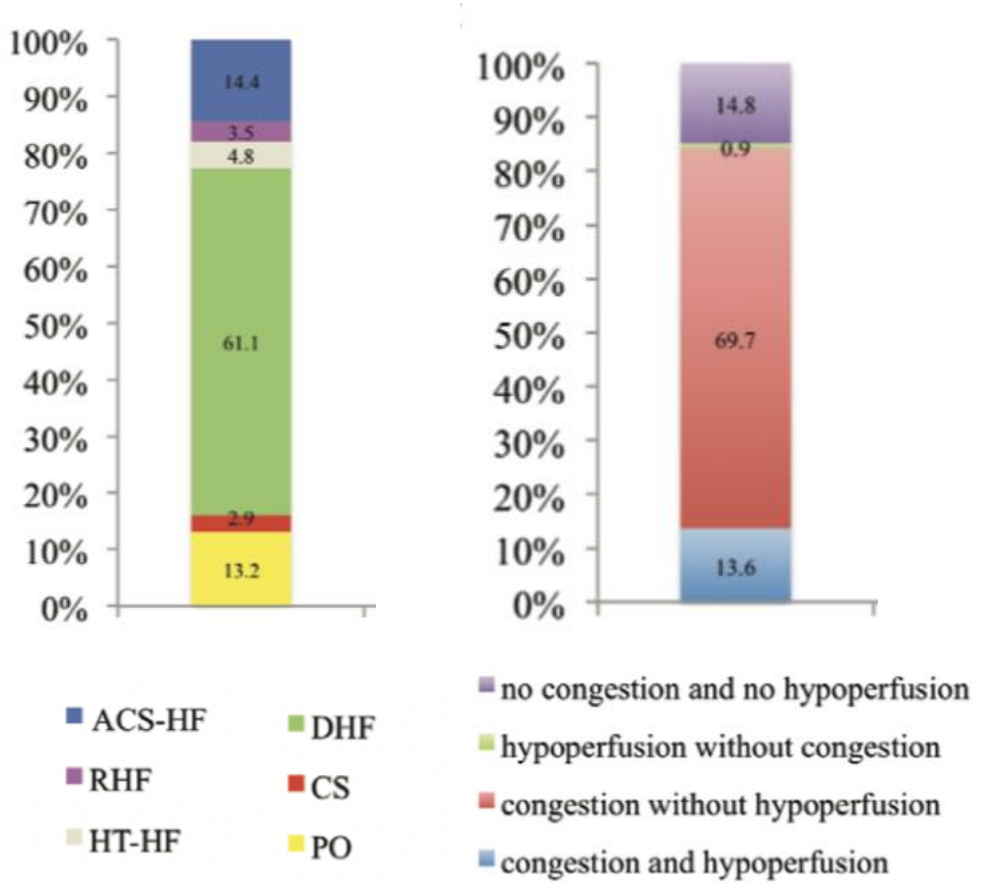
Akute Herzinsuffizenz – oft eine Verschlechterung der vorbekannten HI

ESC-HF Long Term Registry (ESC-HF-LT) 6629 AHF patients



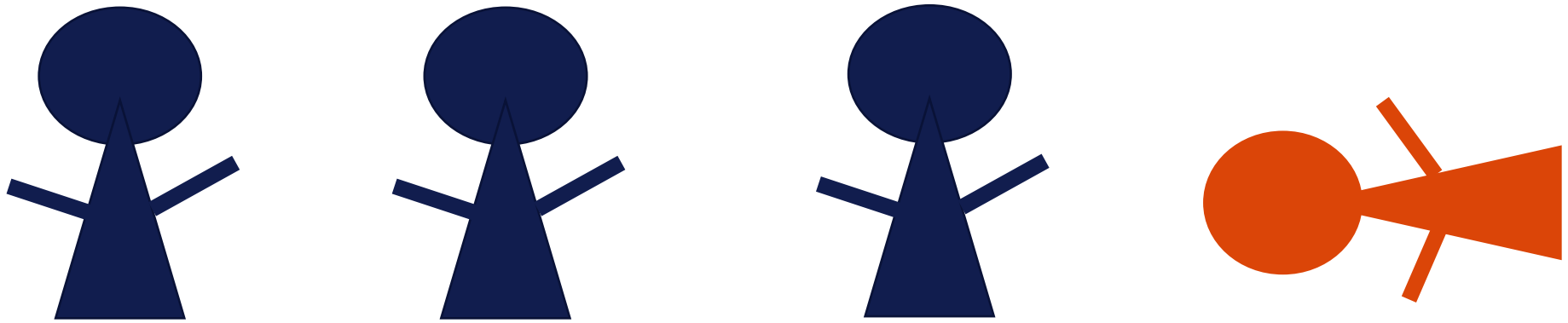
ACS=acute coronary syndrome; AHF=acute HF; HF=heart failure; JVP=jugular venous pressure; LV=left ventricular; MI=myocardial infarction; SBP=systolic blood pressure
1. Gheorghiade et al. Circulation 2005;112:3958–68; 2. Dickstein et al. Eur Heart J 2008;29:2388–442

Chioncel et al, *EJHF*, 2017.



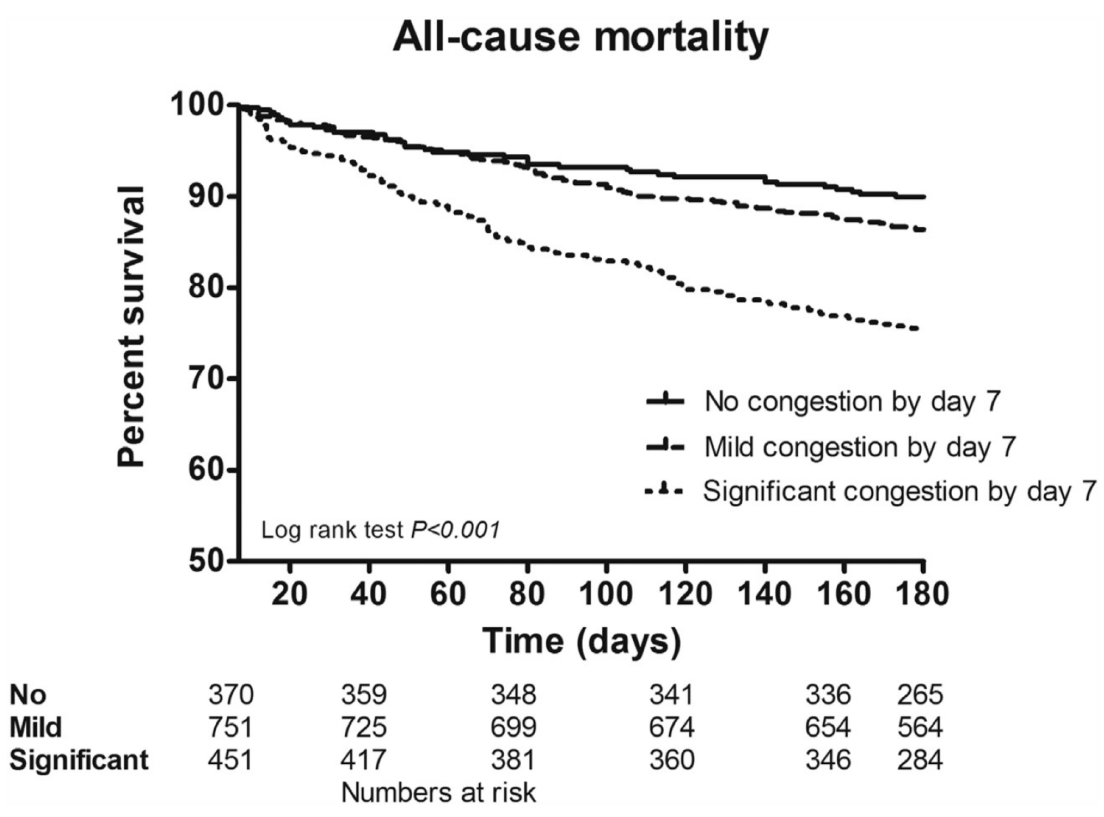
60% der Patienten mit akuter HI haben eine Verschlechterung der chronischen HI, die meisten Patienten präsentieren sich mit Flüssigkeitsretention bei normaler Perfusion.

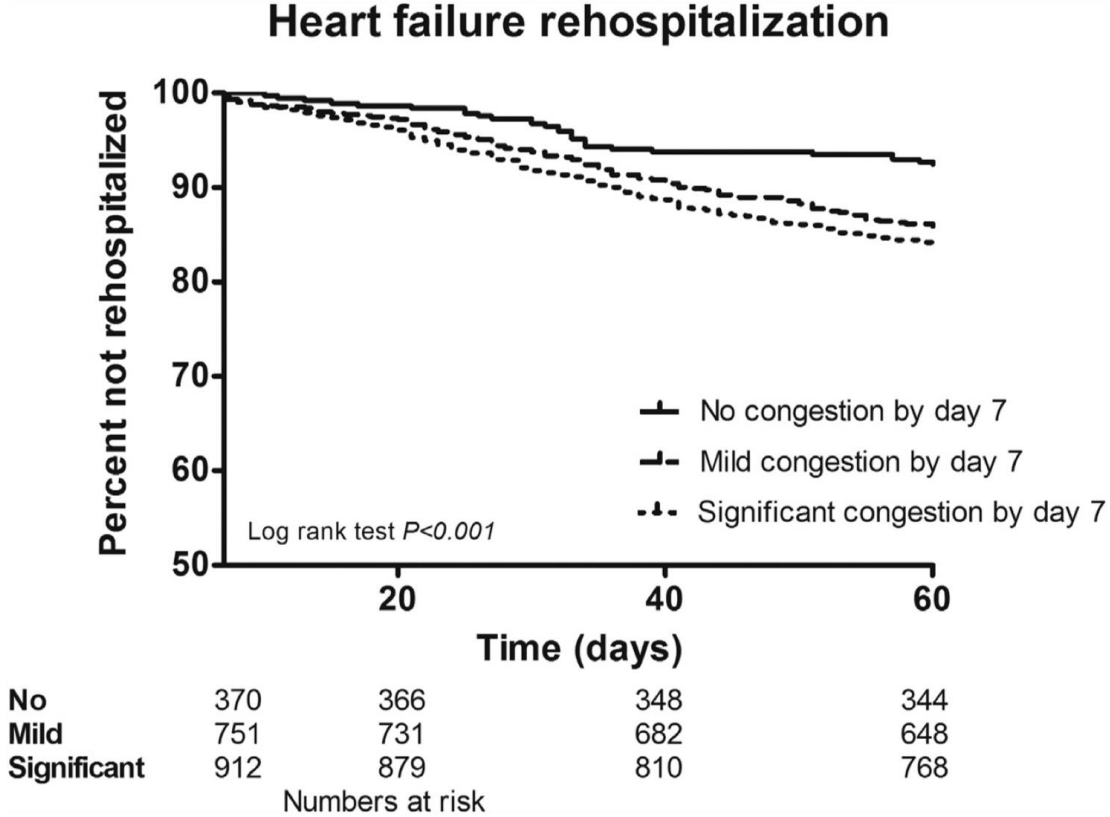
Akute Herzinsuffizenz – hohe Mortalität



Hohe 1-Jahres Mortalität

Akute Herzinsuffizenz – Bedeutung der Rekompensation





Rubio-Gracia et al, *Int J Cardiol*, 2018.

Rekompensation ist eines der Hauptziele vor Entlassung.

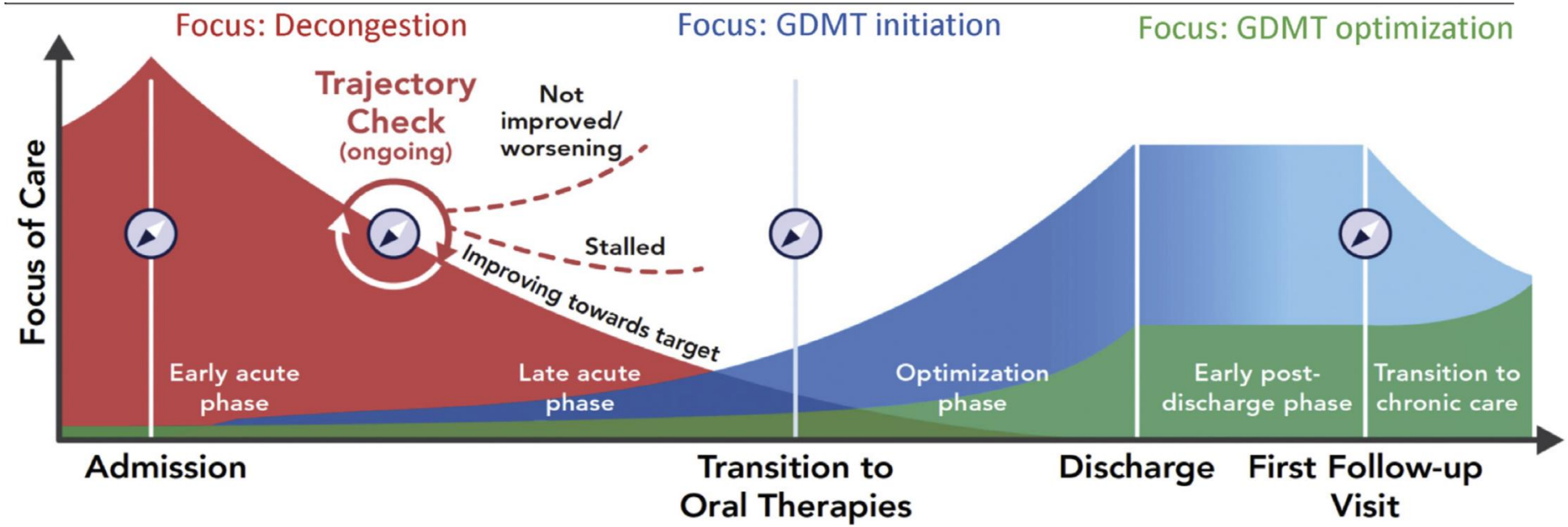
ARNi und SGLT2i Studien in der akuten und stabilen Phase

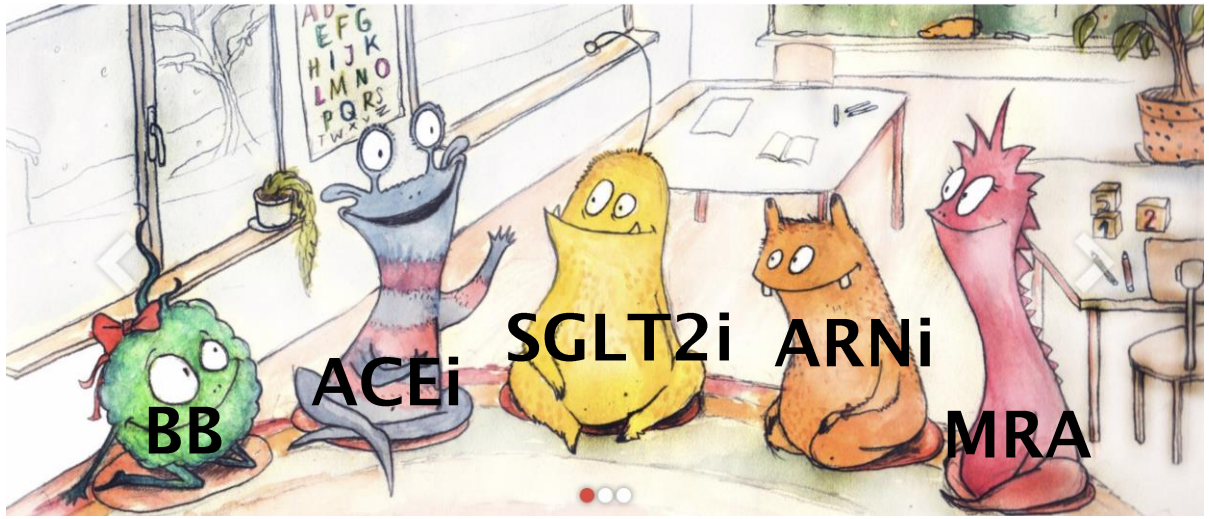
DICTATE-AHF
EMPA-RESPONSE

DAPA ACT HF TIMI 68
EMPULSE
TRANSITION, PIONEER

SOLOIST-WHF

DAPA-HF / DELIVER
EMPEROR-Reduced / EMPEROR-Preserved
PARADIGM / PARAGON





NT-proBNP

Diagnose der HFpEF

HFpEF
Symptoms ± Signs[a]
LVEF ≥50%
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]

8.3 The diagnosis of heart failure with preserved ejection fraction

The diagnosis of HFpEF remains challenging. Several diagnostic criteria have been proposed by societies and in clinical trials.[260] These criteria vary widely in their sensitivities and specificities for diagnosing HFpEF. More recently, two score-based algorithms (H_2FPEF and HFA-PEFF) have been proposed to aid the diagnosis.[259,261] While the generalizability of the scores has been tested in various trial and observational cohorts, their diagnostic performance has varied.[262–269]

* Guidelines acknowledge difficulties in nomenclature and lack of consensus on optimal LVEF cut-off
* Variability in LVEF and imaging modalities, what is HFnEF?, HFpEF kept at a cut-off of 50%
* LVEF cut-offs in definitions are arbitrary
* HF with a very high LVEF (60-65%) should prompt serach for a pathology

Strukturelle und funktionelle Veränderungen kompatibel mit der Diagnose HFpEF

Parameter[a]	Threshold	Comments
LV mass index **Relative wall thickness**	≥**95** g/m^2 (Female), ≥**115** g/m^2 (Male) >**0.42**	Although the presence of concentric LV remodelling or hypertrophy is supportive, the absence of LV hypertrophy does not exclude the diagnosis of HFpEF
LA volume index[a]	>**34** mL/m^2 (SR)	In the absence of AF or valve disease, LA enlargement reflects chronically elevated LV filling pressure (in the presence of AF, the threshold is >40 mL/m^2)
E/e' ratio at rest[a]	>**9**	Sensitivity 78%, specificity 59% for the presence of HFpEF by invasive exercise testing, although reported accuracy has varied. A higher cut-off of 13 had lower sensitivity (46%) but higher specificity (86%).[71,259,274]
NT-proBNP **BNP**	>**125** (SR) or >**365** (AF) pg/mL >**35** (SR) or >**105** (AF) pg/mL	Up to 20% of patients with invasively proven HFpEF have NPs below diagnostic thresholds, particularly in the presence of obesity
PA systolic pressure **TR velocity at rest[a]**	>**35** mmHg >**2.8** m/s	Sensitivity 54%, specificity 85% for the presence of HFpEF by invasive exercise testing[259,261]

Diagnose der HFpEF – einfach oder kompliziert?

ESC 2016 Heart Failure Guidelines

European Journal of Heart Failure (2016) 18, 891–975
doi:10.1002/ejhf.592

ESC GUIDELINES

2016 ESC Guidelines for the treatment of acute and chro

The Task Force for the diagnosis and tr
heart failure of the European Society of

Table 3.1 Definition of heart failur
(HFrEF)

Type of HF		HFrEF
CRITERIA	1	Symptoms ± Signs*
	2	LVEF <40%
	3	–

How diagnose HFpEF ? – HFA-PEFF diagnostic algorithm and score

ESC European Society of Cardiology

FASTTRACK CLINICAL RESEARCH
Heart failure/cardiomyopathy

How to diagnose heart failure with preserved ejection fraction: the HFA–PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC)

Burkert Pieske[1,2,3,4*], Carsten Tschöpe[1,2,5], Rudolf A. de Boer[6], Alan G. Fraser[7],

Step E: Echo and N
functional, morph

	Functional	Morphologic
Major	septal e' < 7 cm/s or lateral e' < 10 cm/s or Average E/e' ≥ 15 or TR velocity > 2.8 m/s (PASP > 35 mmHg)	LAVI > 34 ml/m² or LVMI > 149/122 g/m and RWT > 0,42 #
Minor	Average E/e' 9 -14 or GLS < 16 %	LAVI 29-34 ml/m² or LVMI > 115/95 g/m² or RWT > 0,42 or LV wall thickness ≥
Major Criteria: 2 points		≥ 5 points: HFpEF
Minor Criteria: 1 point		2-4 points: Diastoli

Figure 3 Step 2 (E): Echocardiographic and natriuretic peptide
tic workup).

Pieske B, et al. Eur J Heart Fail. 2020 Mar;22(3):391-412.

How to diagnose HFpEF? – H_2FPEF score

Circulation

ORIGINAL RESEARCH ARTICLE

A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction

Editorial, see p 871

Yogesh N.V. Reddy, MD
Rickey E. Carter, PhD
Masaru Obokata, MD, PhD
Margaret M. Redfield, MD
Barry A. Borlaug, MD

BACKGROUND: Diagnosis of heart failure with preserved ejection fraction (HFpEF) is challenging in euvolemic patients with dyspnea, and no evidence-based criteria are available. We sought to develop and then

	Clinical Variable	Values	Points
H_2	Heavy	Body mass index > 30 kg/m²	2
	Hypertensive	2 or more antihypertensive medicines	1
F	Atrial Fibrillation	Paroxysmal or Persistent	3
P	Pulmonary Hypertension	Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure > 35 mmHg	1
E	Elder	Age > 60 years	1
F	Filling Pressure	Doppler Echocardiographic E/e' > 9	1
	H_2FPEF score		Sum (0-9)

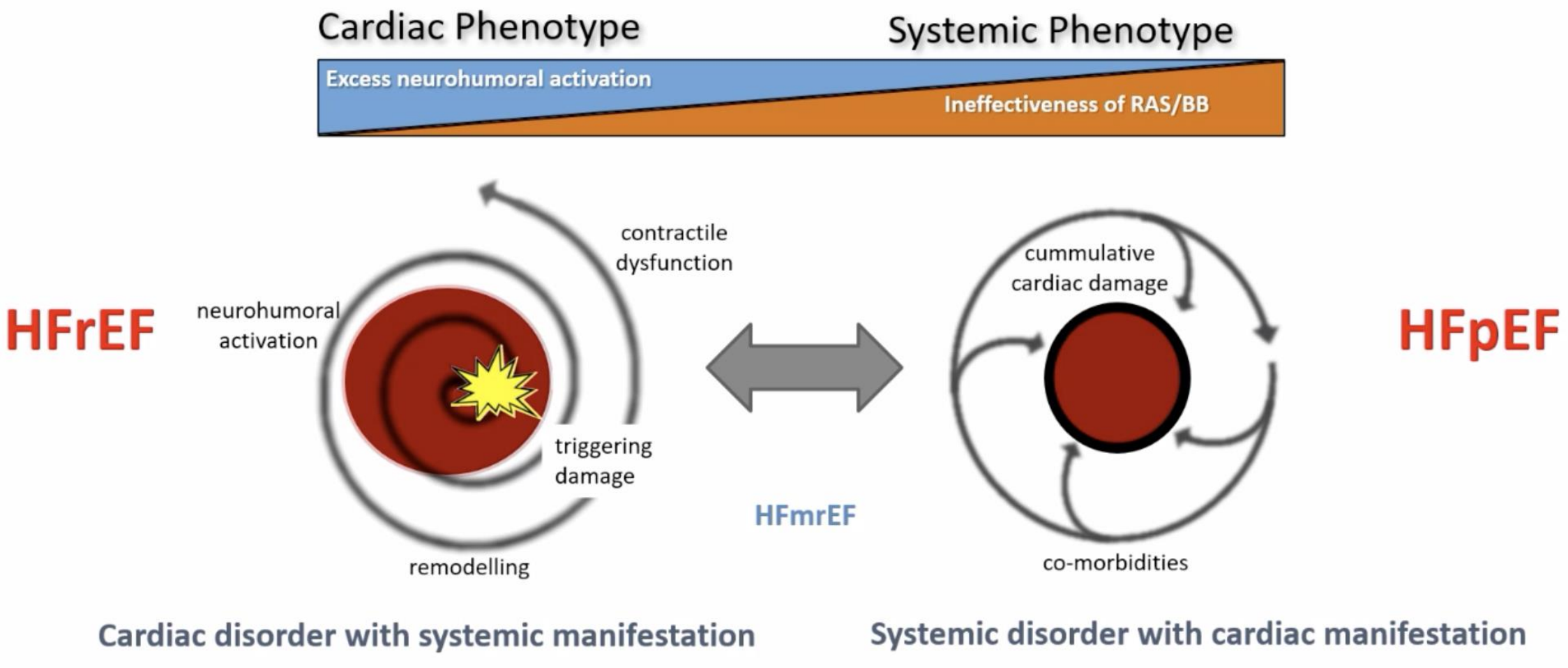
Total Points 0 1 2 3 4 5 6 7 8 9

Probability of HFpEF 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 0.95

Figure 1. **Description of the H_2 FPEF score.** Description of the H_2FPEF score and point allocations for each clinical characteristic (top), with associated probability of having heart failure with preserved ejection fraction (HFpEF) based on the total score as estimated from the model (bottom).

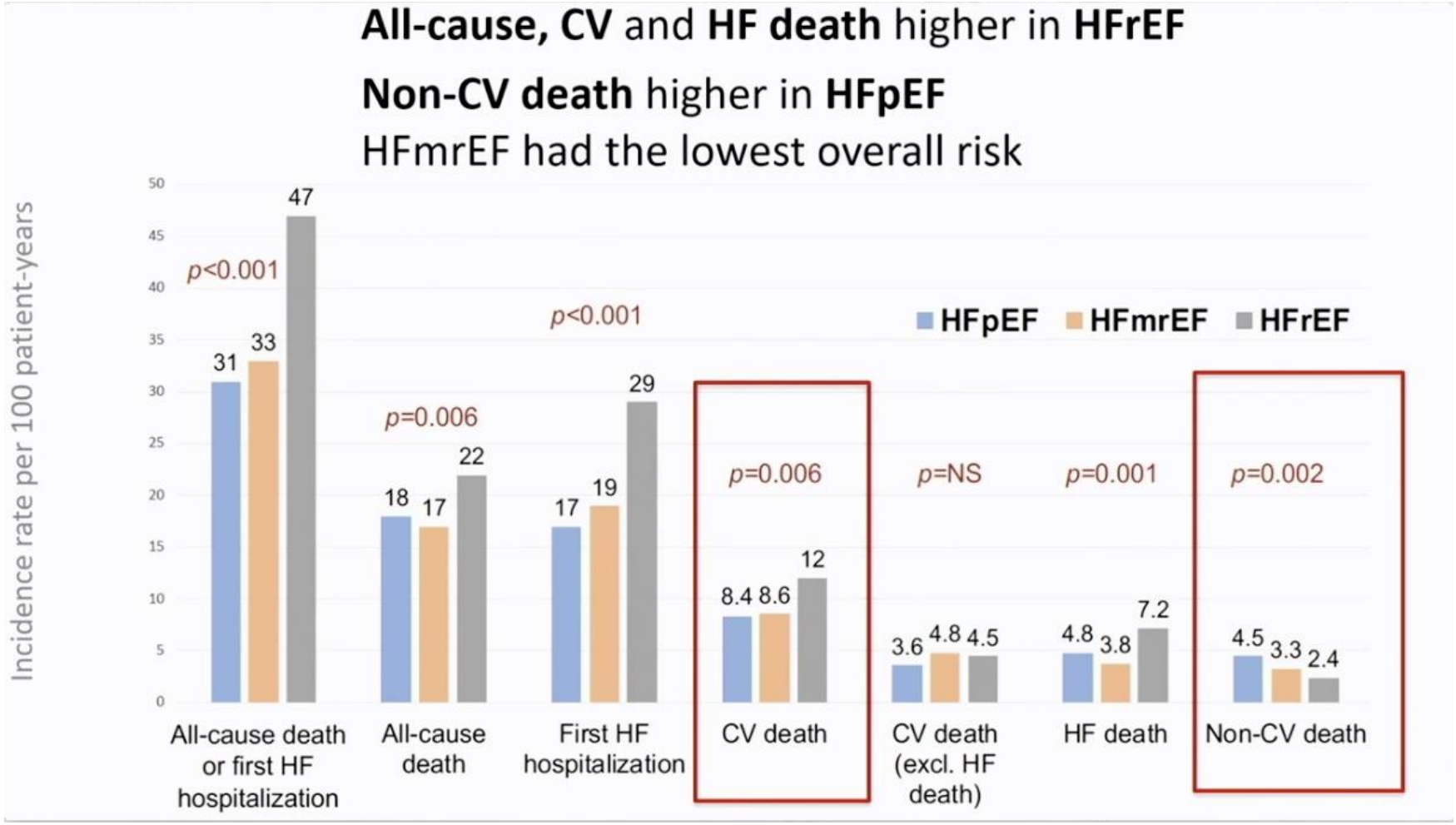
Reddy YNV, et al. Circulation. 2018 Aug 28;138(9):861-870.

Pathomechanistische Trigger der HFrEF vs HFpEF



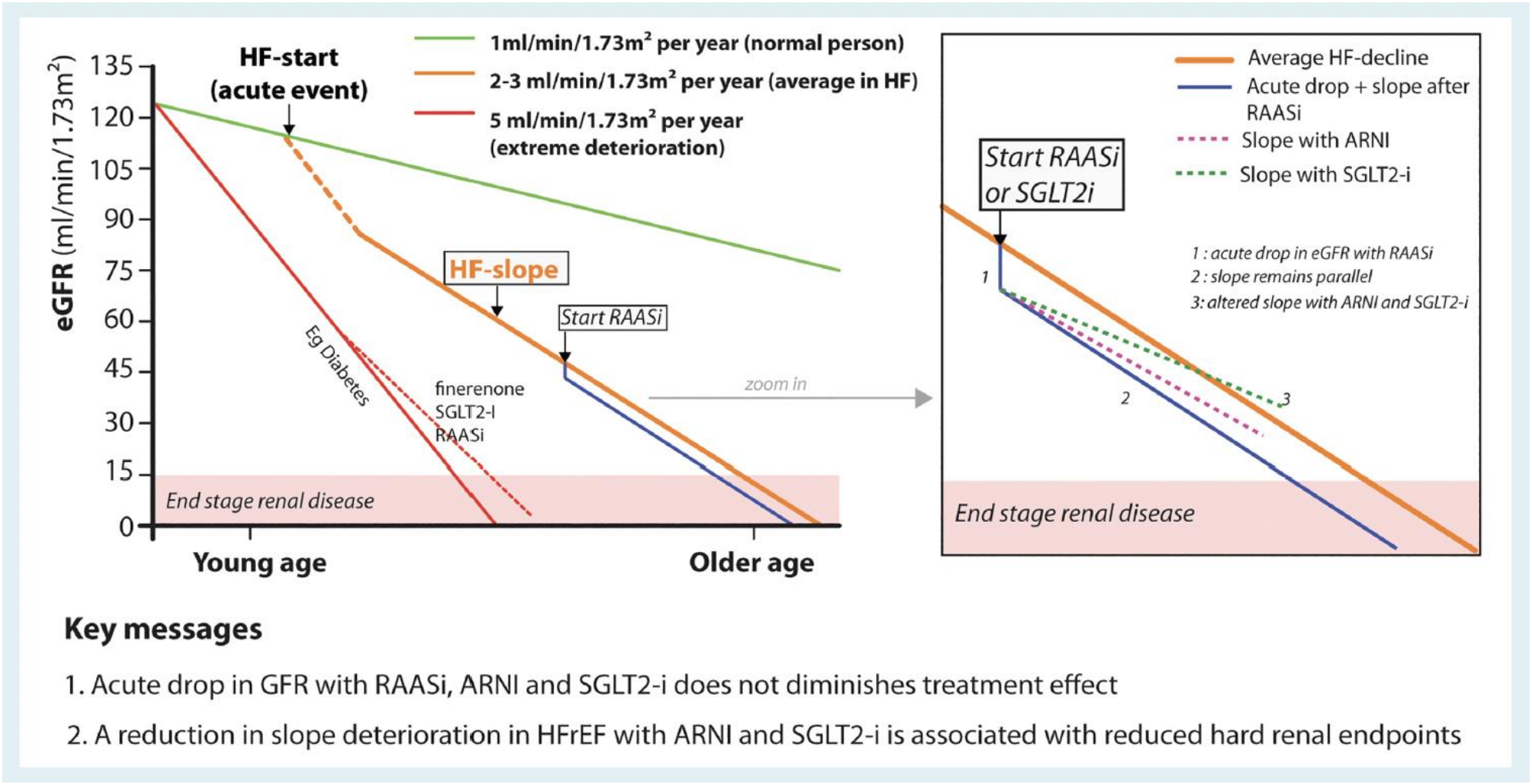
Pieske et al., *DFG application*, 2019.

Todeesursachen der HF aus dem ESC-HF long-term registry



Herzinsuffizienz / CMPs
Behandlung nach Ätiologie

Nephroprotektion durch SGLT2i und ARNi

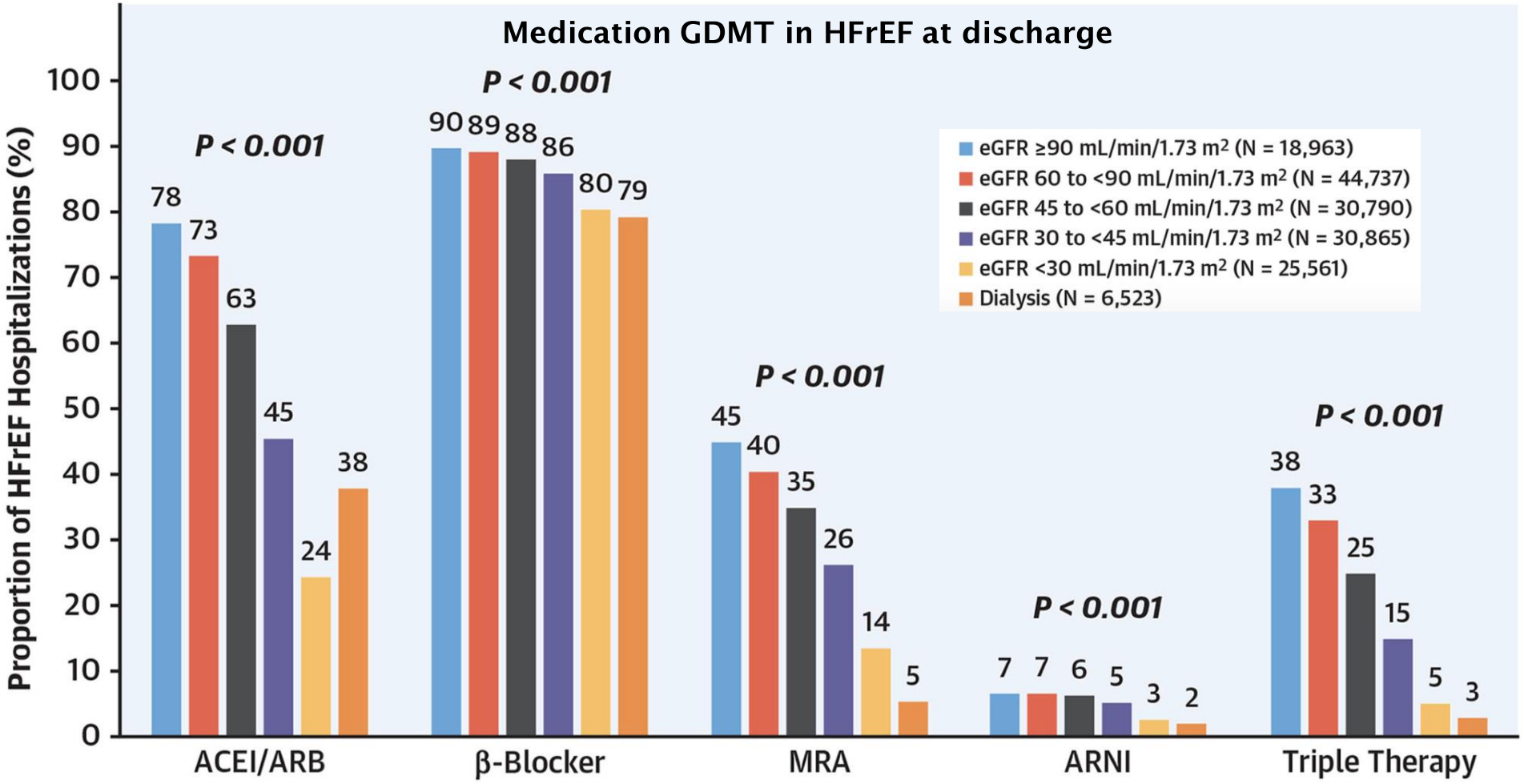


Key messages

1. Acute drop in GFR with RAASi, ARNI and SGLT2-i does not diminishes treatment effect
2. A reduction in slope deterioration in HFrEF with ARNI and SGLT2-i is associated with reduced hard renal endpoints

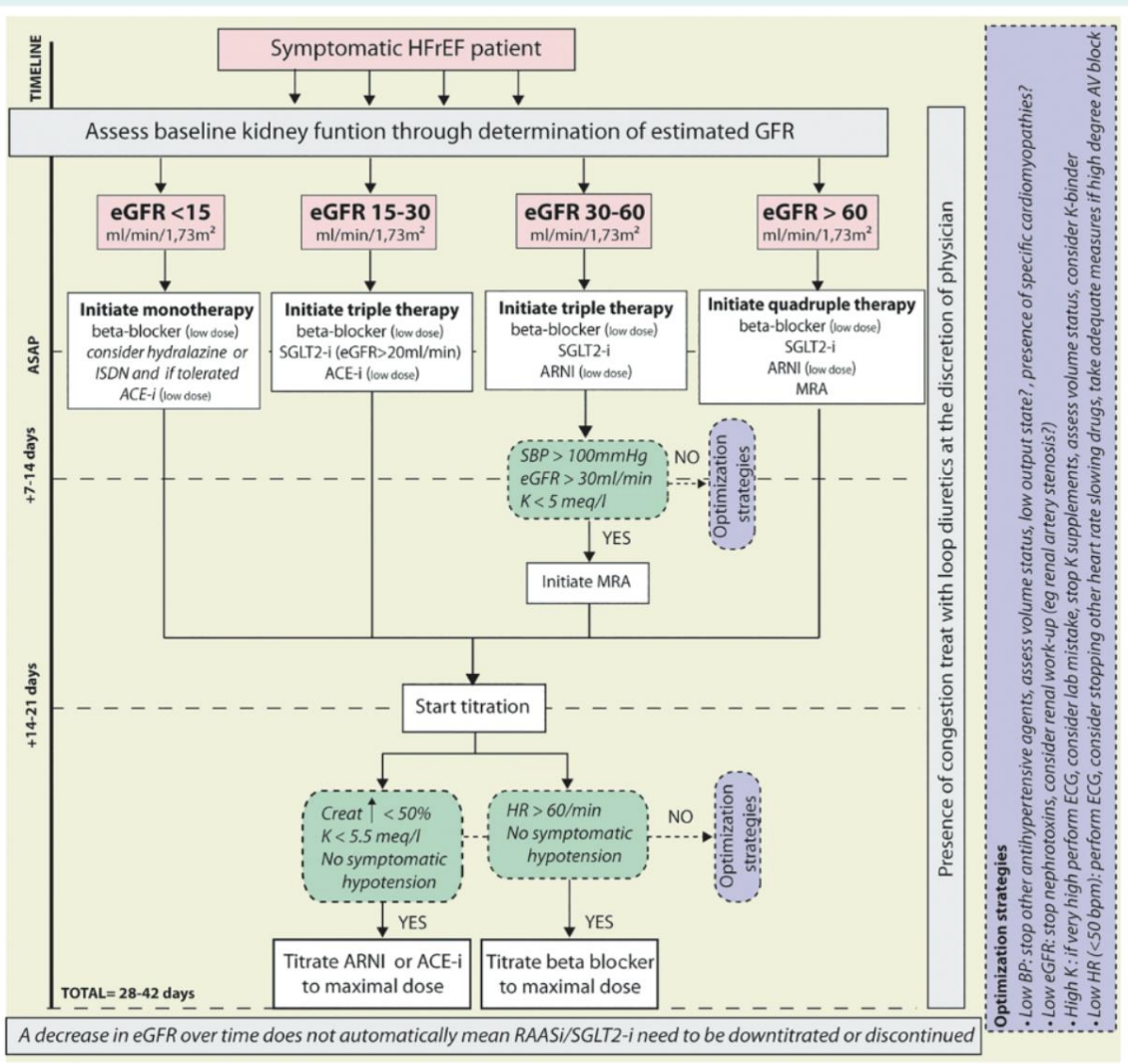
Mullens et al, *EJHF*, 2022.

CKD limitiert GDMT



Patel et al, *JACC*, 2021.

Strategie in (UN)Abhängigkeit der Baseline GFR?



Mullens et al, *EJHF*, 2022.

Strategie bei Veränderungen der GFR?

Patient established on RAAS blocker presenting unwell with AKI/WRF

Primary presenting problem

	Recommendations for RAAS inhibitors	
Change in renal function compared with baseline	**HFpEF (assuming no other prognostic indication).**	**HFREF.**
Increase in serum creatinine by <30%	Consider stop ACEI/ARB/ARNI Review MRA according to fluid status.	Continue unless symptomatic hypotension.
Increase in serum creatinine 30%–50%	Stop RAAS inhibitor.	Consider reducing dose or temporary withdrawal.*
Increase in serum creatinine >50%	Stop RAAS inhibitor.	Temporarily stop RAAS inhibitor.*
Severe renal dysfunction, for example, eGFR <20	Stop RAAS inhibitor.	Stop RAAS inhibitor if symptomatic uraemia irrespective of baseline function.

*Reinitiate and/or retitrate when renal function improved in patients with HFrEF.

HFrEF

Consider reducing or withholding RAAS blocker only if:

- symptomatic hypotension
- moderate-severe hyperkalaemia
- or progressive WRF*

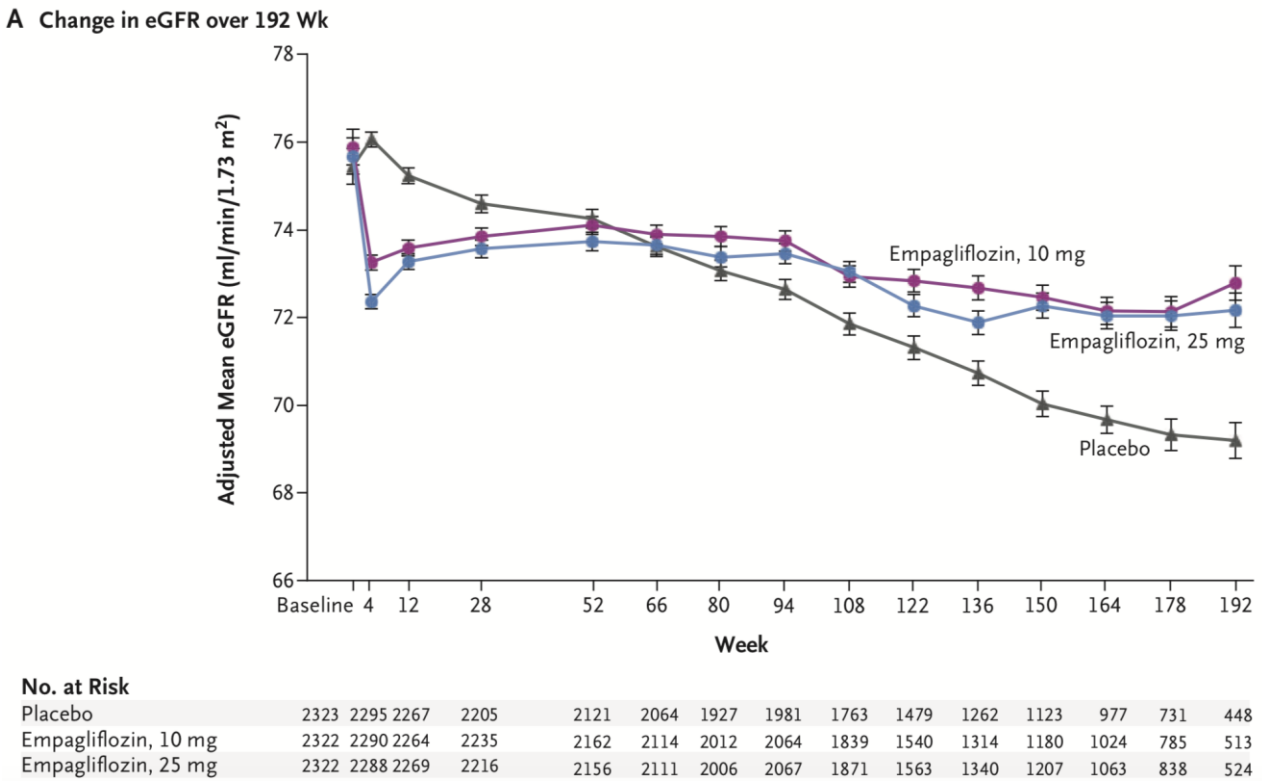
HFpEF

- Stop ACEi/ARB – no prognostic benefit
- MRA may offer symptomatic benefit

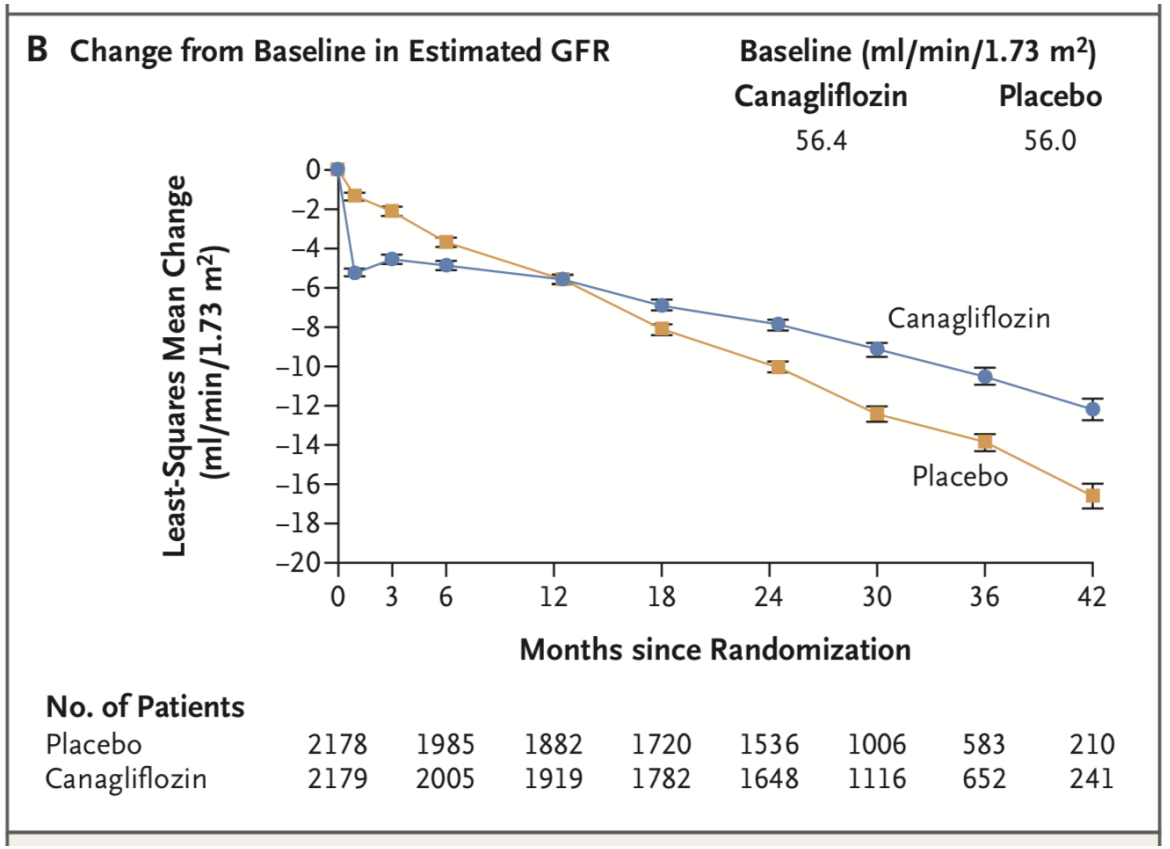
hyperkalaemia or progressive WRF*

Clark et al, *Heart*, 2019.

Effekt der SGLT2i auf die Nierenfunktion in HF – initial physiologischer GFR Abfall

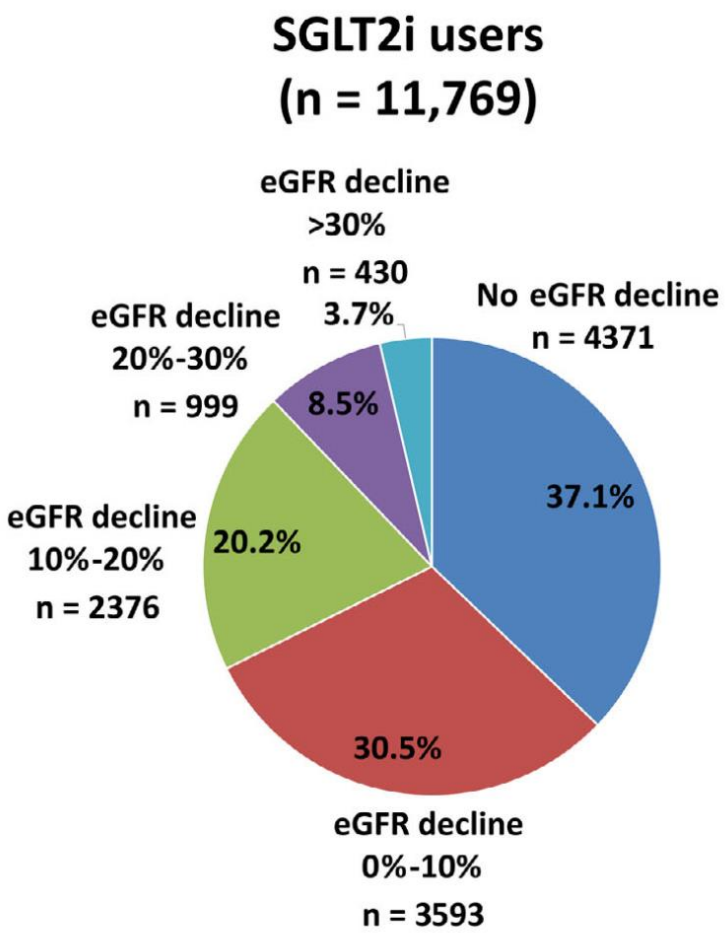


Wanner et al, *NEJM*, 2016.

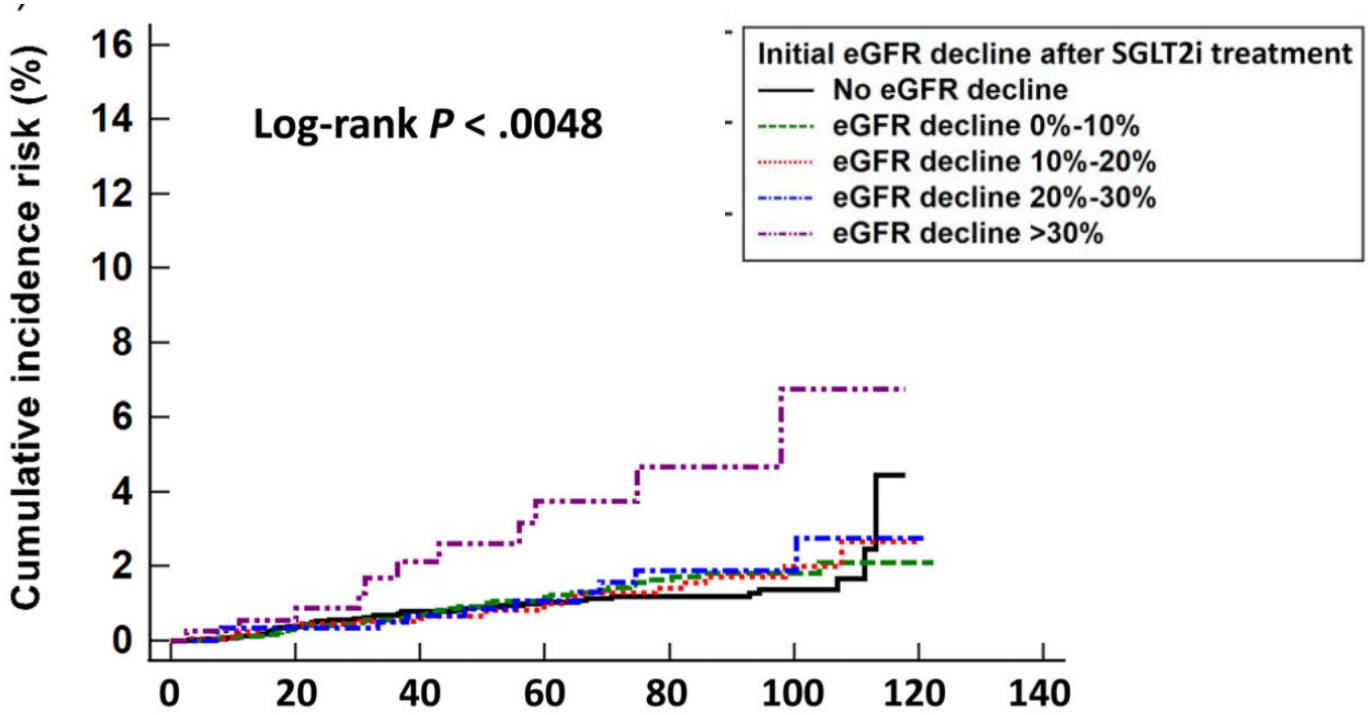


Perkovic et al., *NEJM*, 2019.

Initialer GFR-Abfall und Outcome

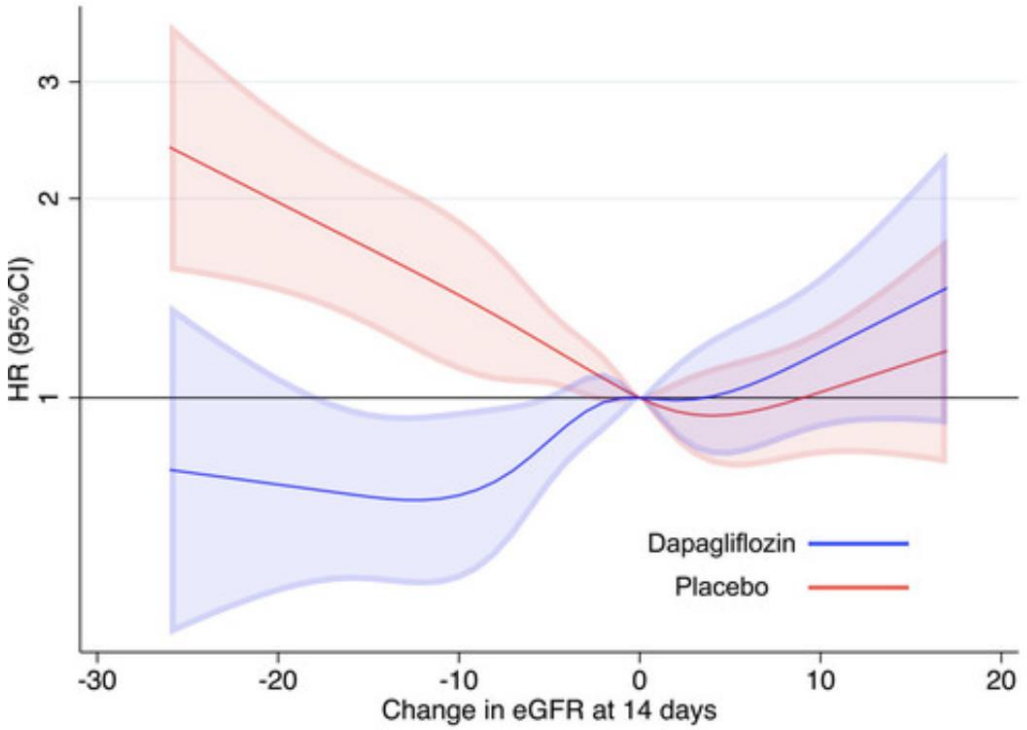


MACE / HF

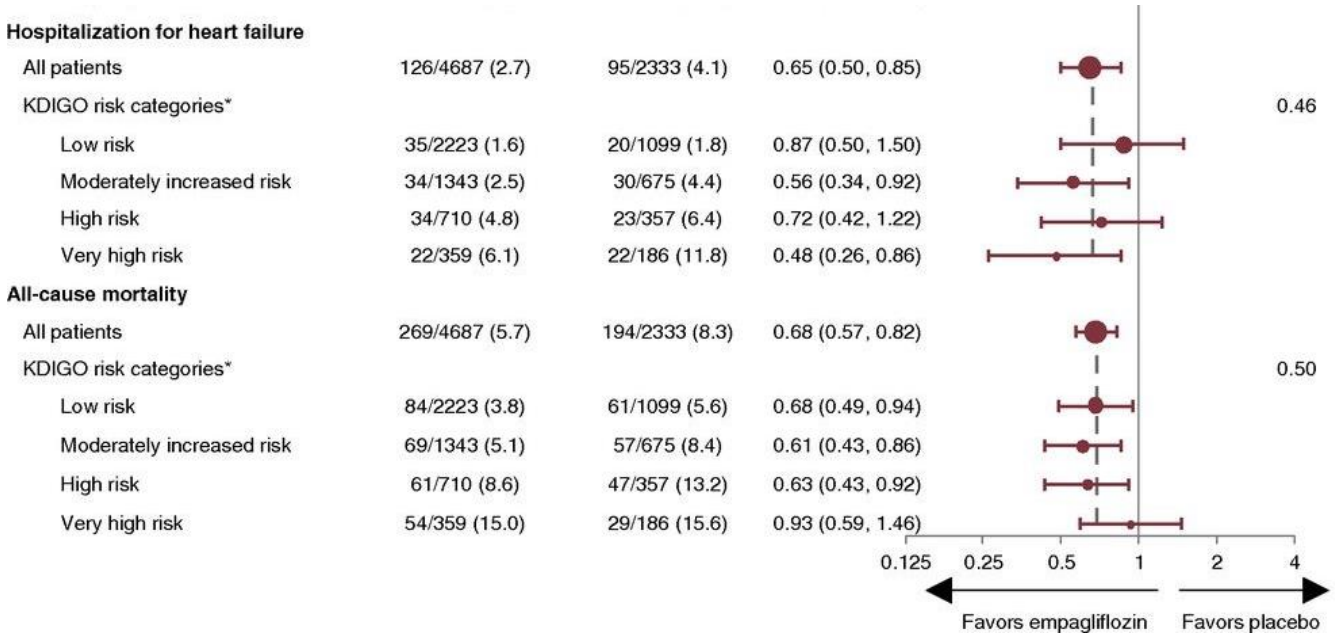


Chan et al, *Diabetes Obes Meab*, 2021.

Kardialer Benefit der SGLT2i unabhängig von eGFR dip oder der eGFR Kategorie



Adamson et al, *Circ*, 2022.

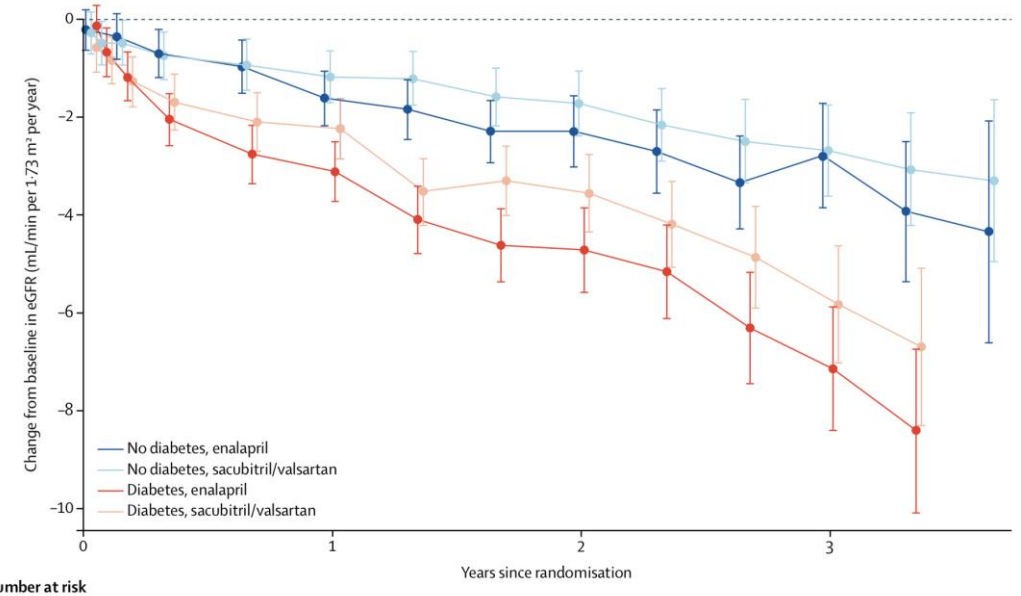


Adeera et al, *CiASN*, 2020.

Kardialer Benefit der SGLT2i ist unabhängig vom eGFR dip bis zu -30% oder GFR Kategorie erhalten.

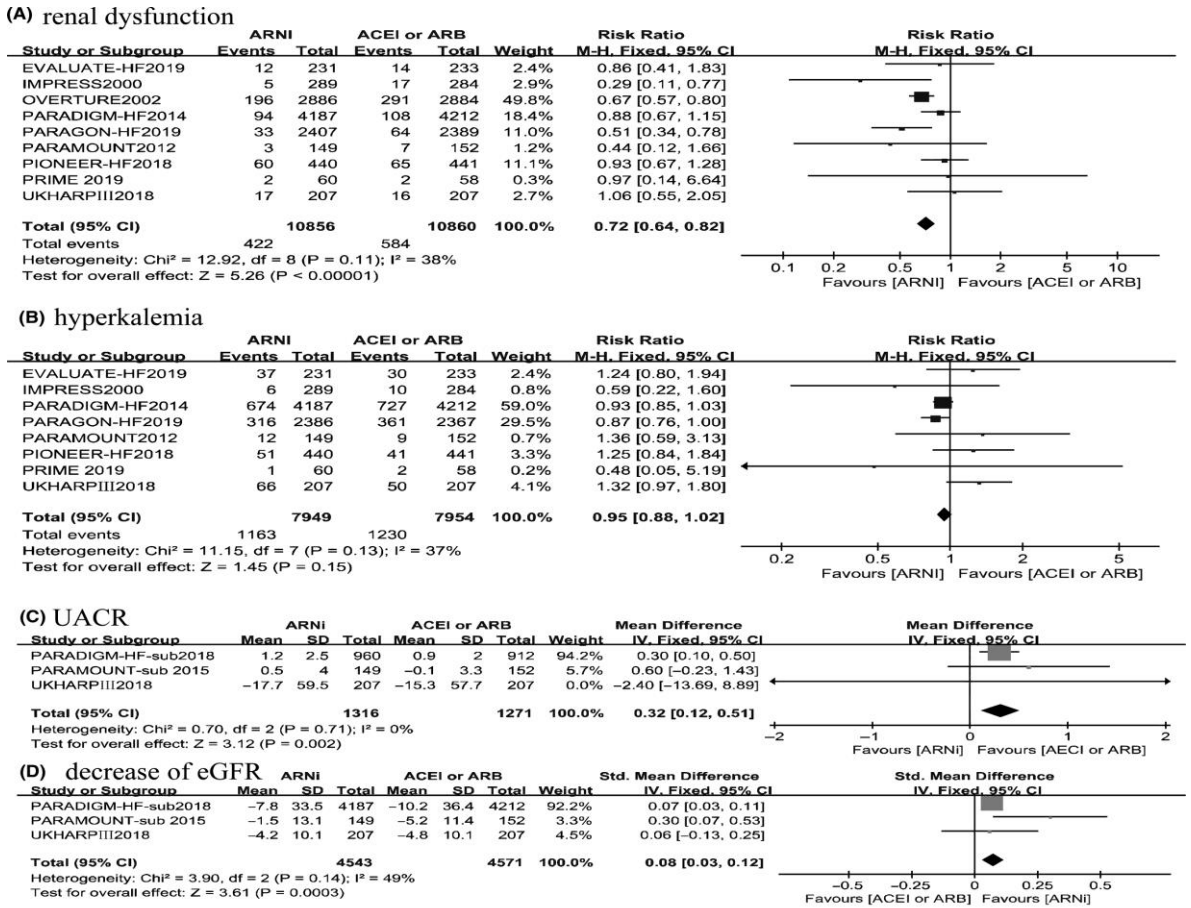
Effekt der ACEi/ARNi auf die Nierenfunktion in HF

PARADIGM-HF



Number at risk			
No diabetes, sacubitril/valsartan	1969	1425	672
No diabetes, enalapril	1937	1344	667
Diabetes, sacubitril/valsartan	1566	1101	504
Diabetes, enalapril	1557	1086	502

Packer et al, *Lancet Diabet Endocrinol*, 2018.



Feng et al, *J Clin Pharm Ther*, 2020.

HF Benefit über verschiedene GFR Strata - ARNi

PARADIGM-HF

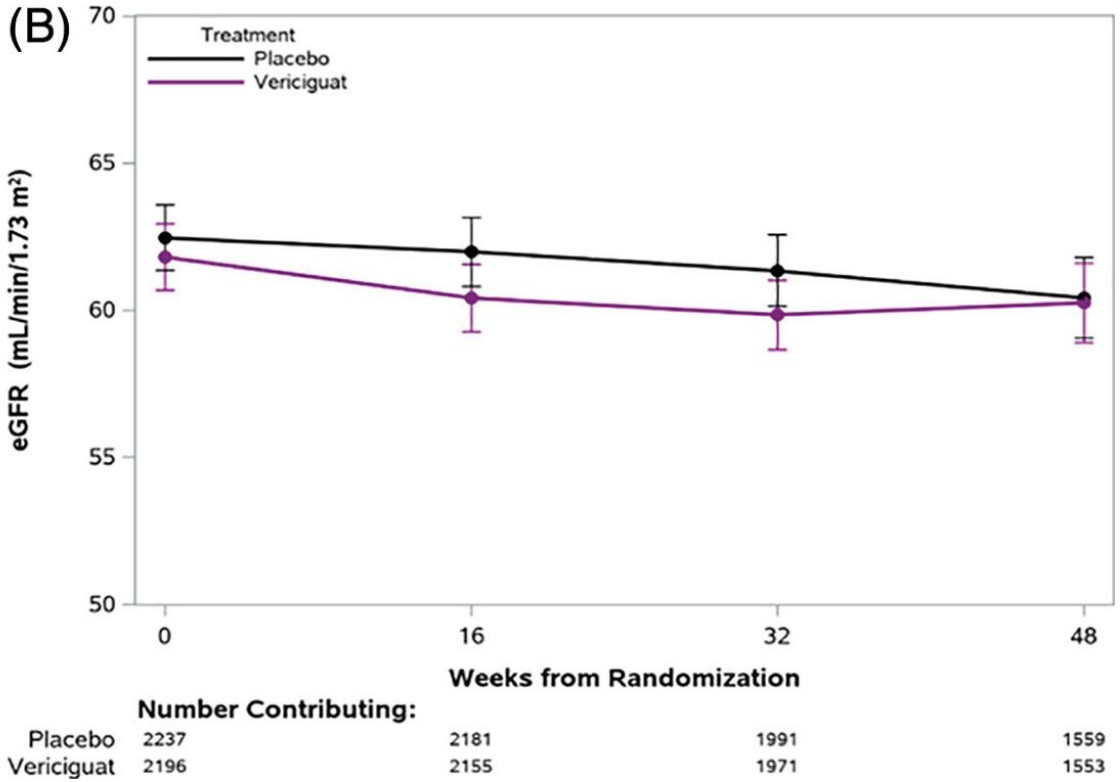
Subgroup	LCZ696	Enalapril	Primary End Point: Hazard Ratio (95% CI)	Primary End Point: P value for interaction	Death from Cardiovascular Causes: Hazard ratio (95% CI)	Death from Cardiovascular Causes: P value for interaction
	no.					
Estimated GFR				0.91		0.73
<60 ml/min/1.73 m²	1541	1520				
≥60 ml/min/1.73 m²	2646	2692				

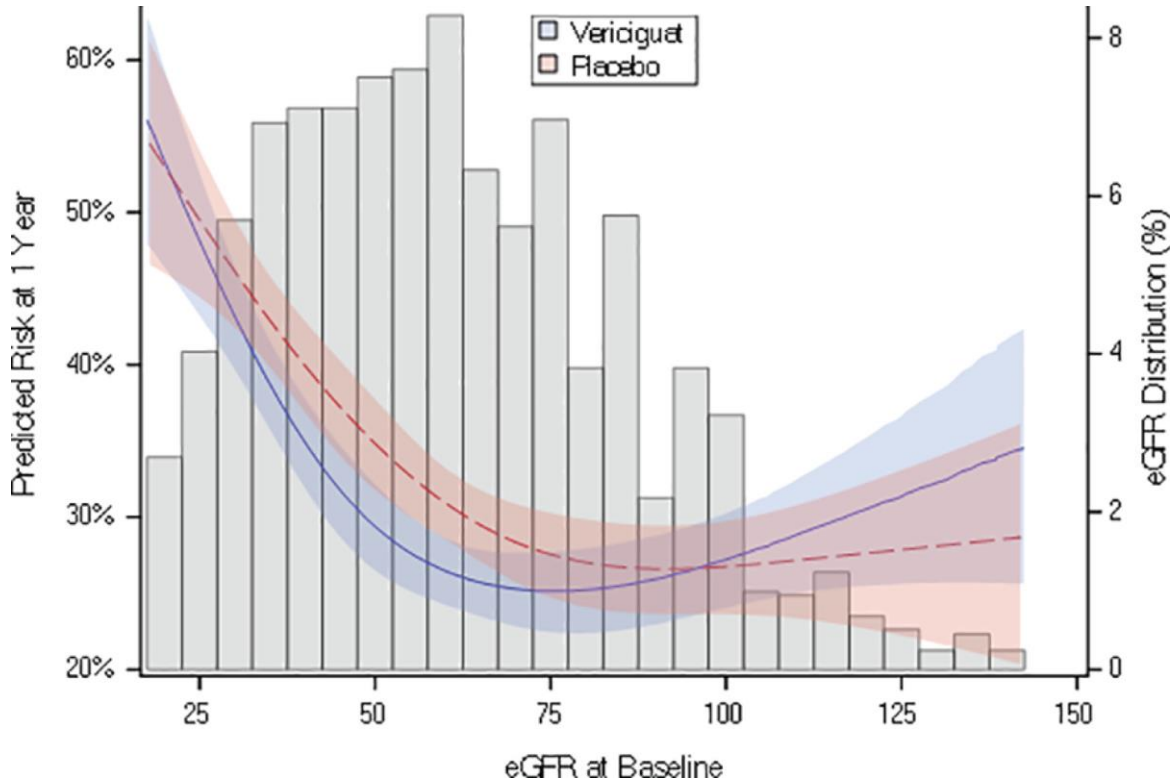
PARAGON

Subgroup	No. of Events/No. of Patients	Rate Ratio (95% CI)
Baseline estimated GFR		
<60 ml/min/1.73 m²	1115/2341	0.79 (0.66–0.95)
≥60 ml/min/1.73 m²	787/2454	1.01 (0.80–1.27)

Es besteht keine Interaktion zwischen den untersuchten GFR-Kategorien und der Wirkung der ARNi in der HFrEF.

Vericiguat

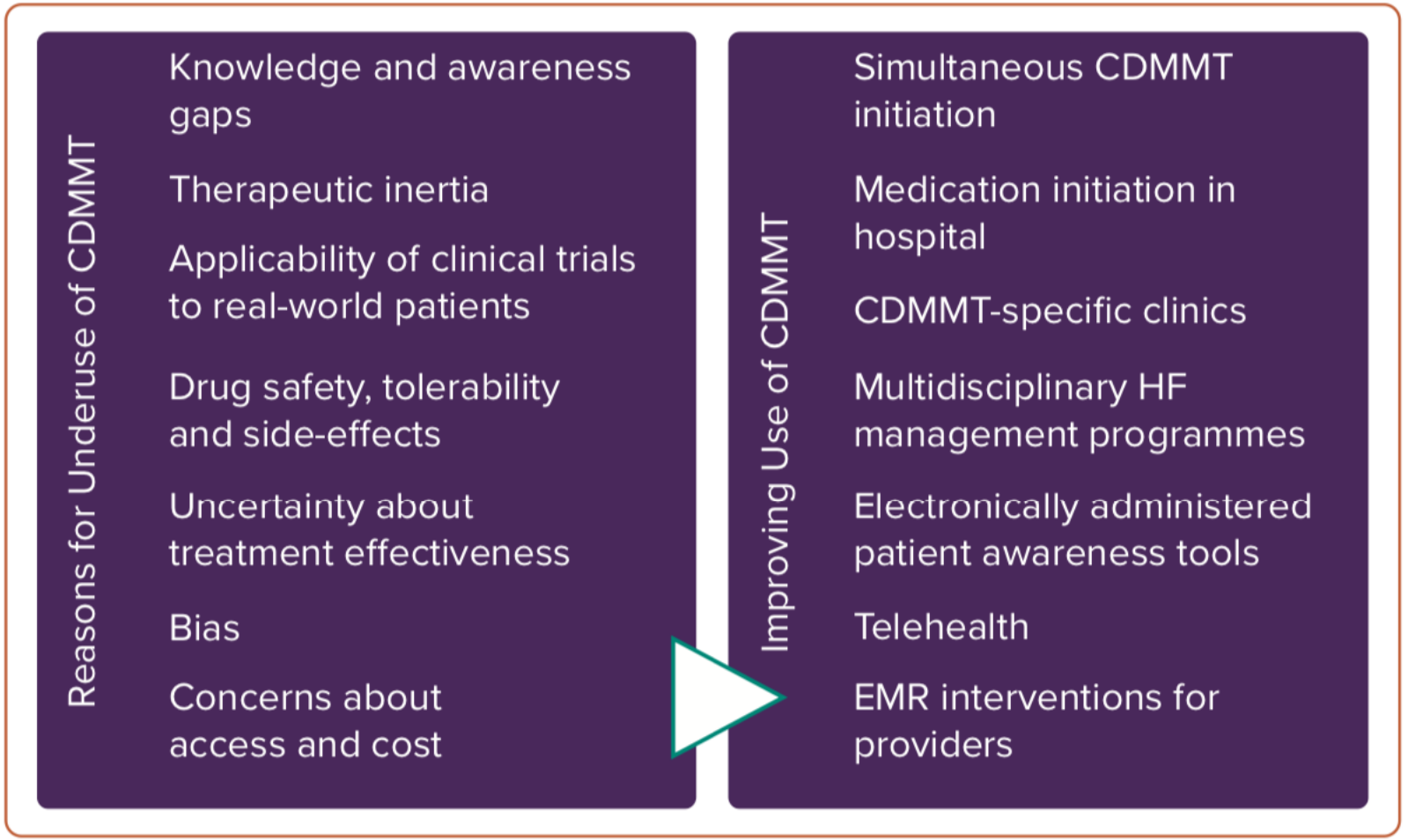




Die Nierenfunktionsverläufe sind ähnlich mit Vericiguat wie Placebo, während der Benefit von Vericiguat im gesamten Spektrum der GFR erhalten scheint.

Voors et al, *EJHF*, 2021.

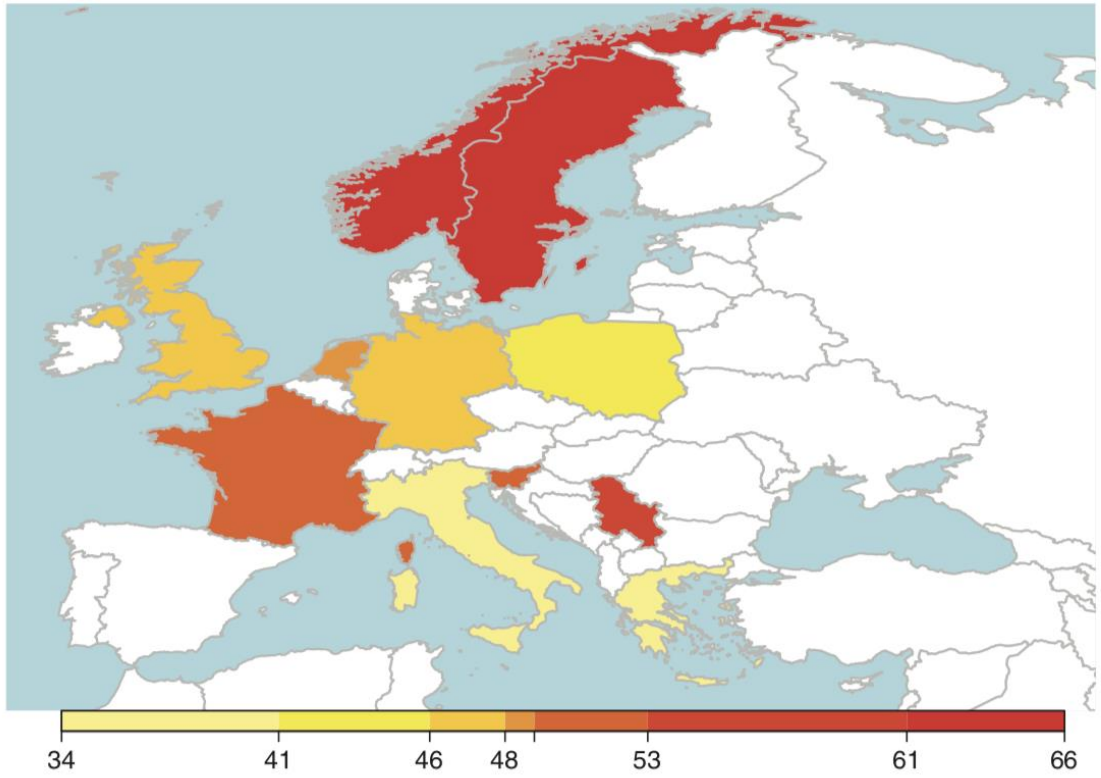
Gründe für Unterversorgung mit GDMT und mögliche Verbesserungen



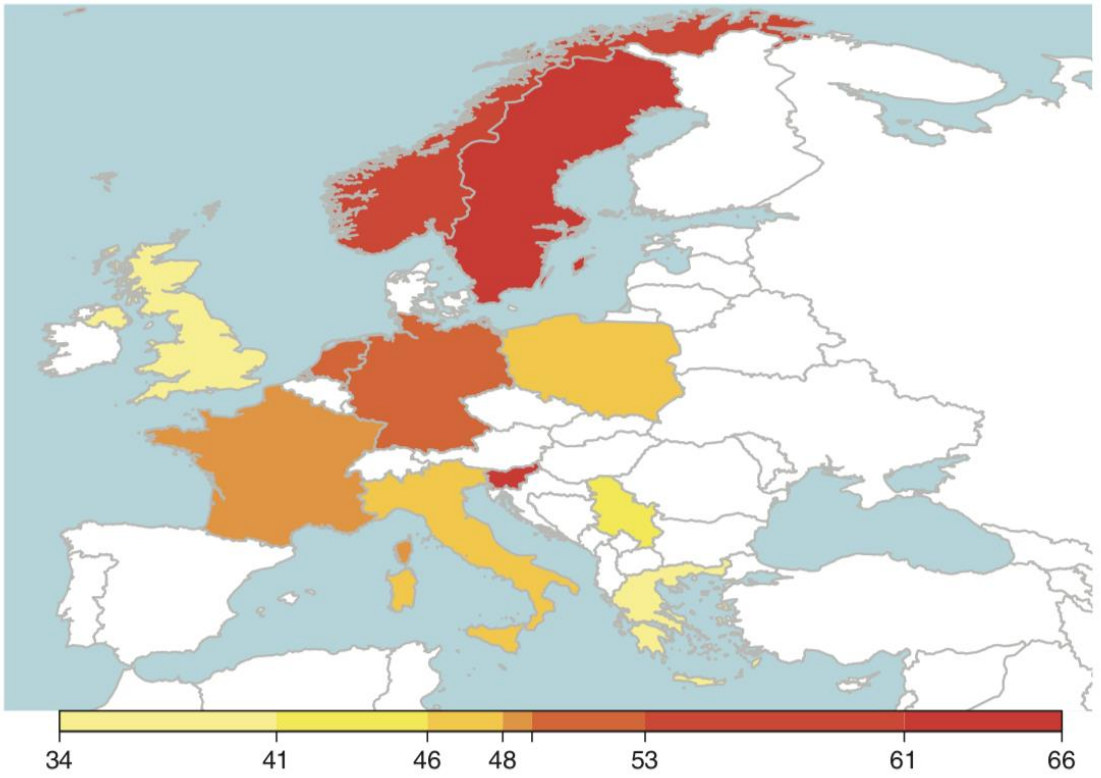
Brownell et al, *Card Reviews*, 2021.

Große Lücken in der Implementierung der lebensverlängernden Therapien

ACEi /ARB



BB

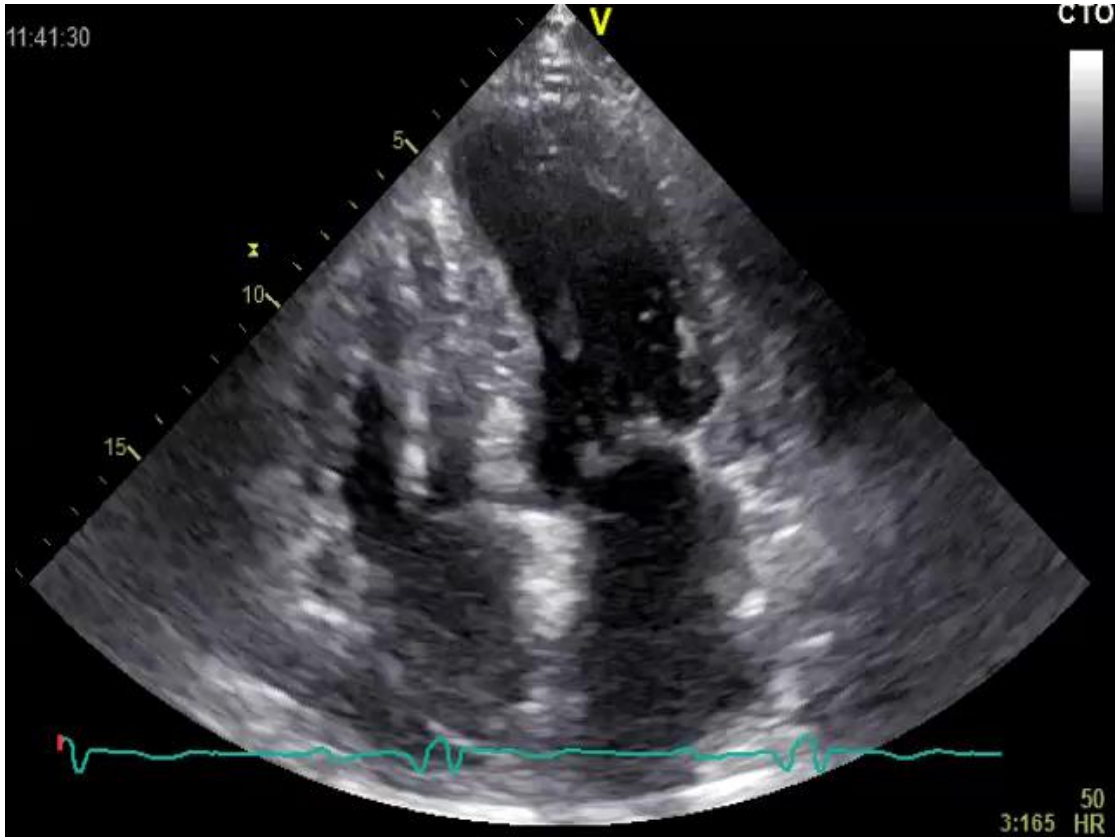


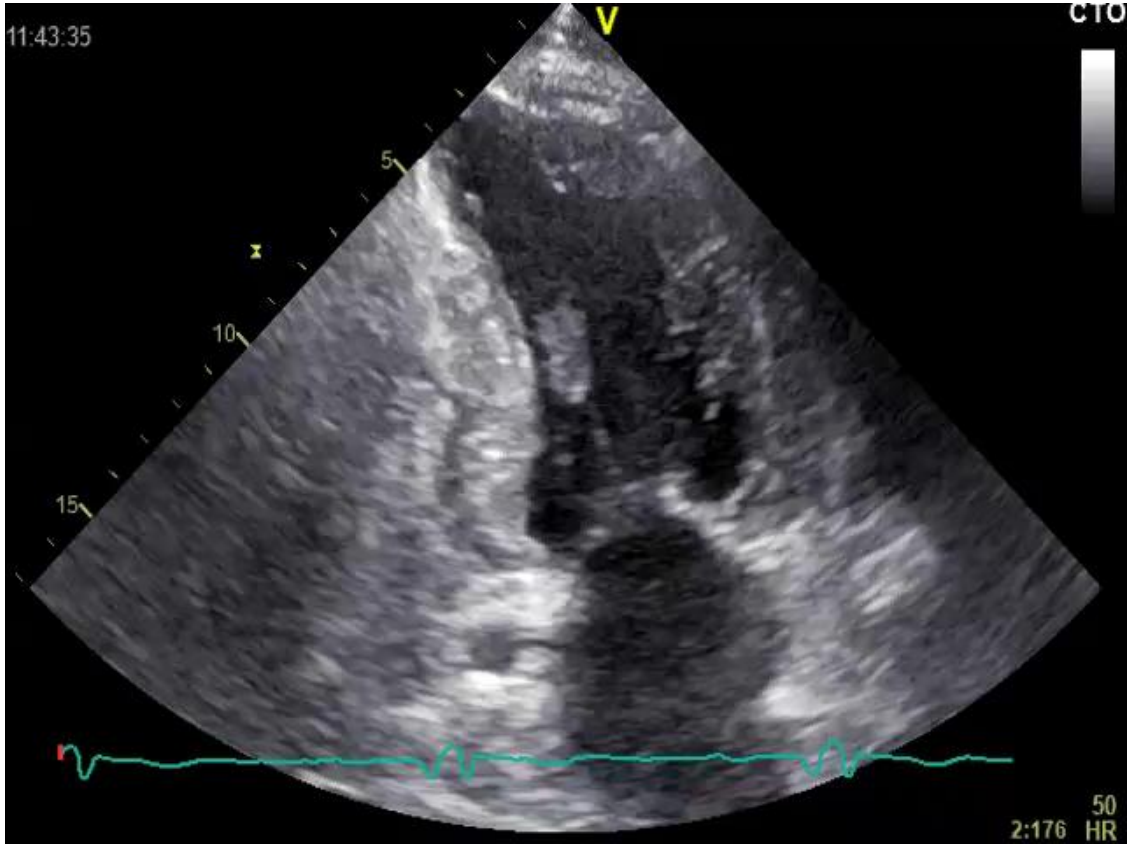
Ouwerkerk et al, *EHJ*, 2017.

Individuelle Auftitration nach klinischem Profil?

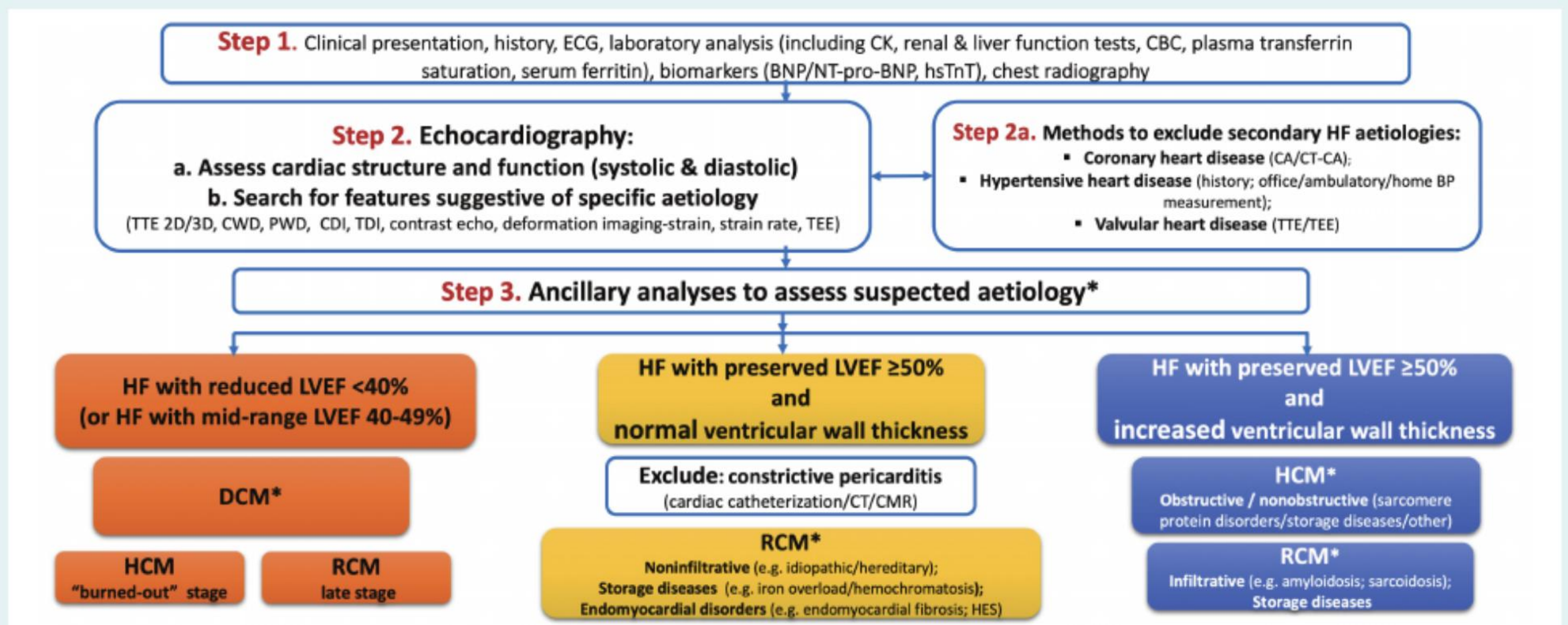
Rosano et al, *EJHF*, 2021.

Echo – HFpEF bei Amyloidose



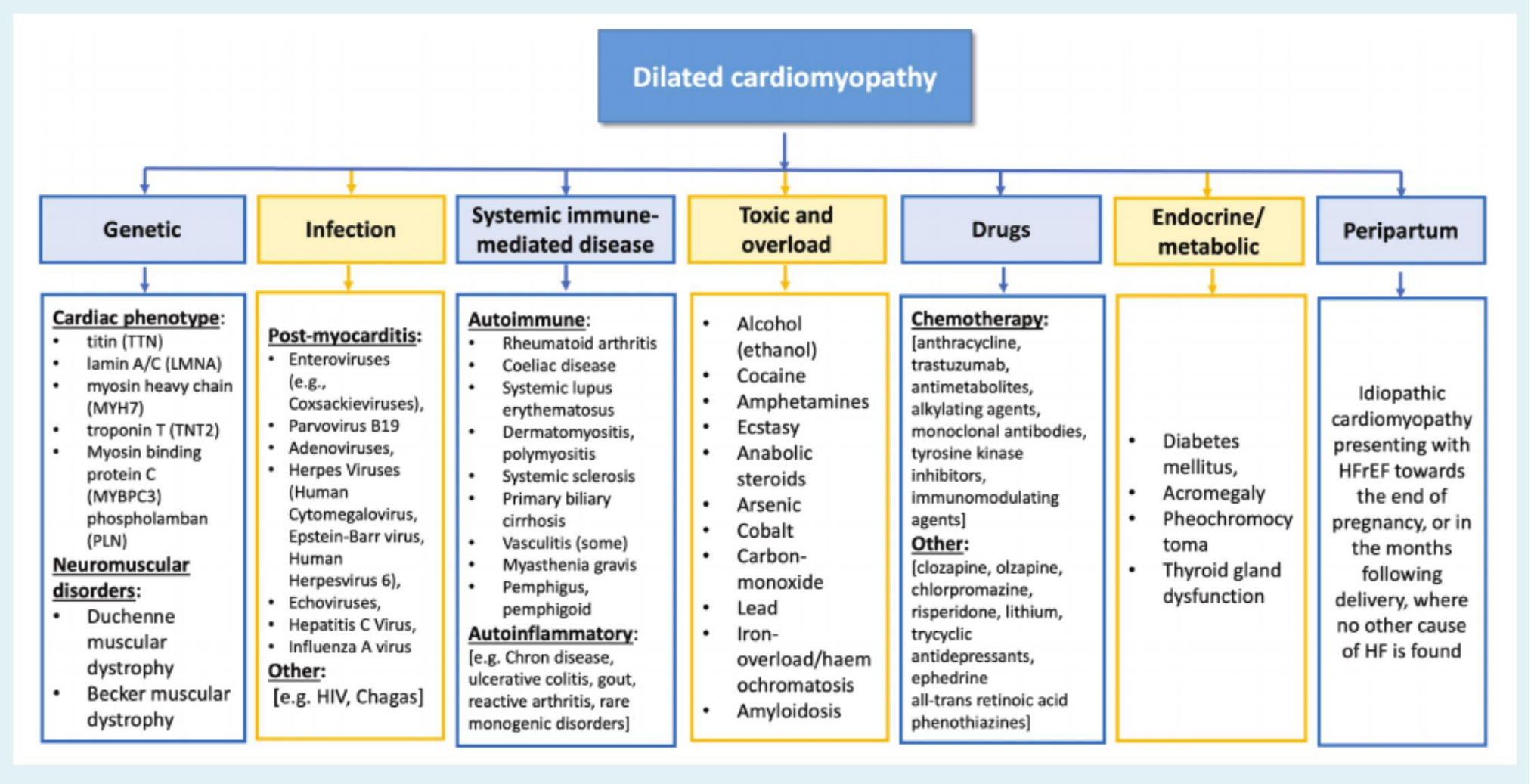


Diverse Phänotypen



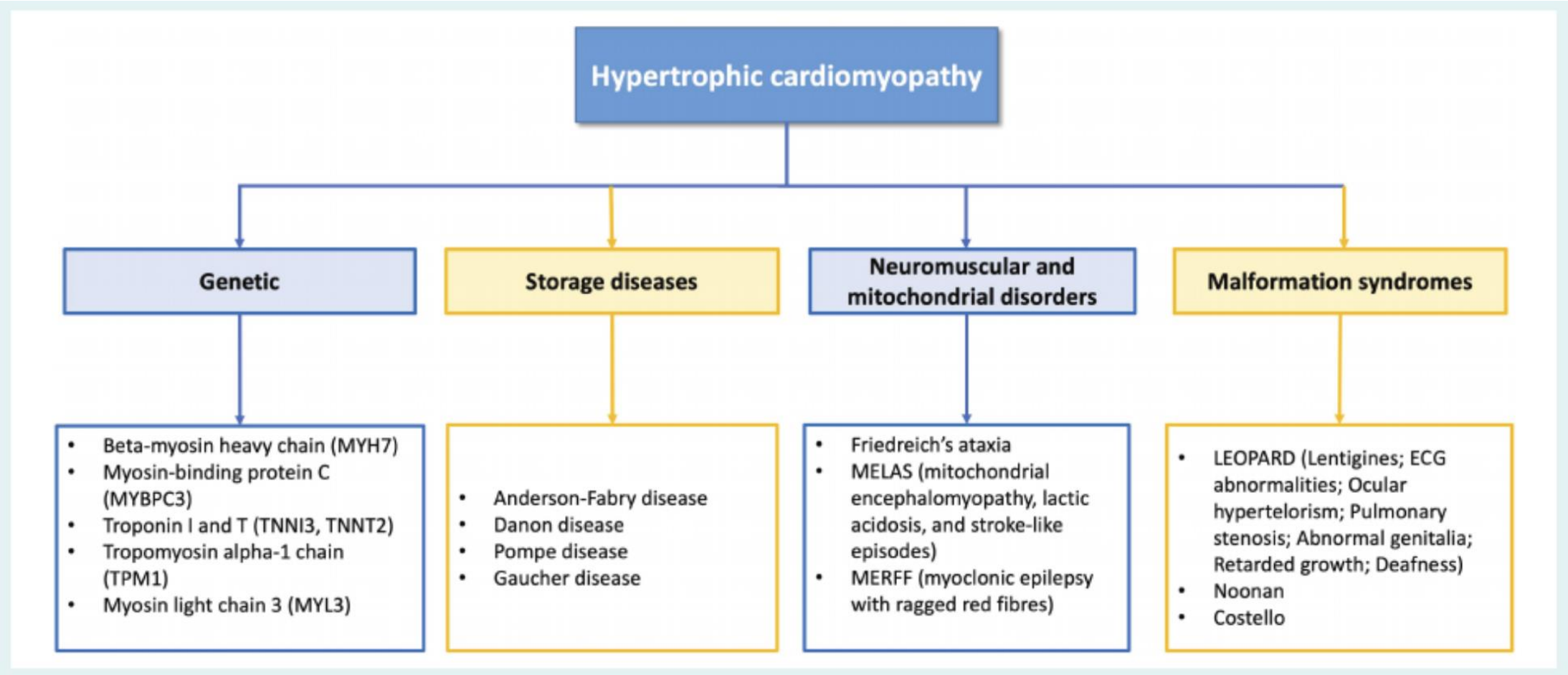
Seferovic et al, *EJHF*, 2019.

Ursachen der dilatativen CMP



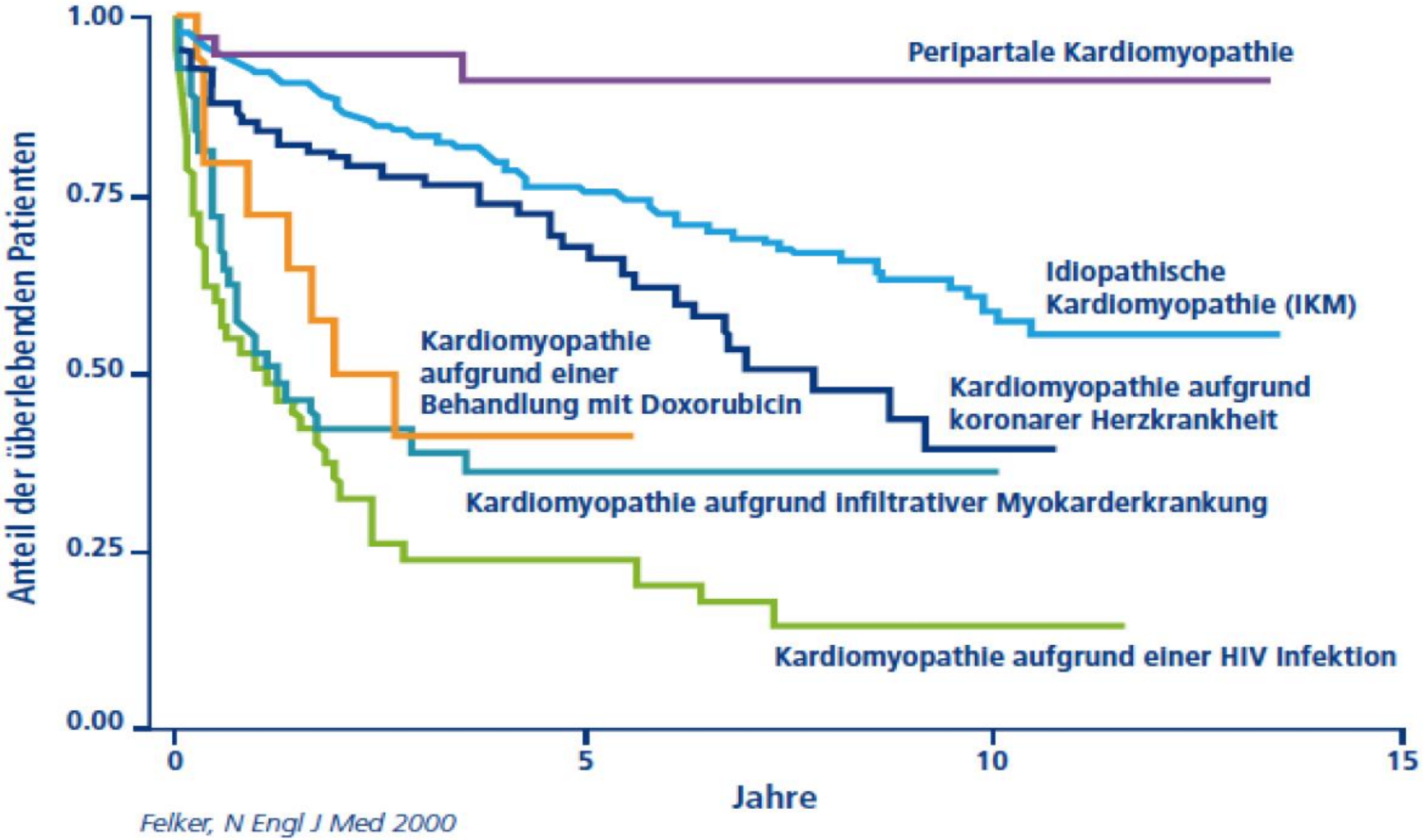
Seferovic et al, *EJHF*, 2019.

Ursachen der hypertrophen CMP



Seferovic et al, *EJHF*, 2019.

Je nach Ursache ganz andere Prognose



Felker, N Engl J Med 2000

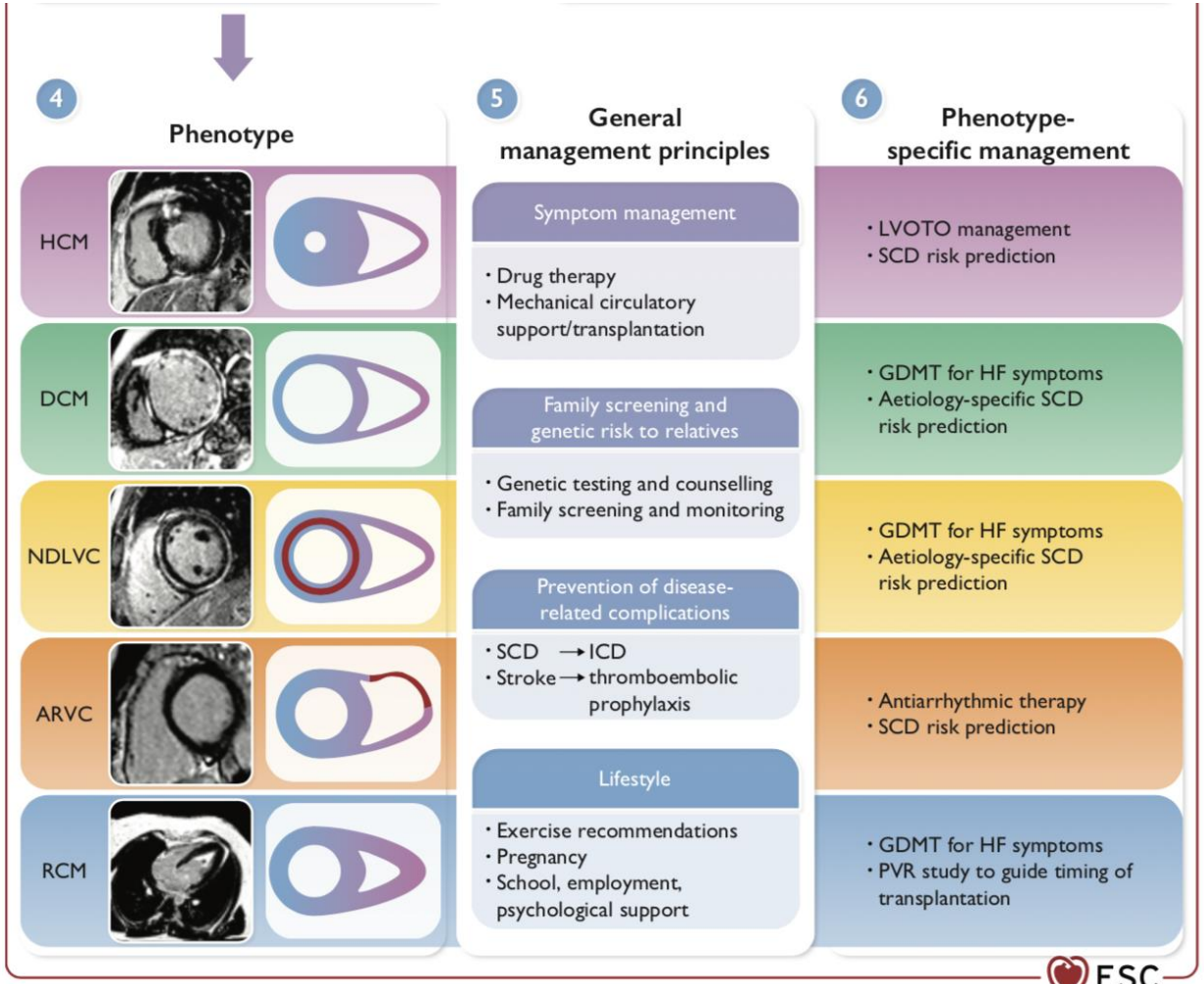
Die neuen ESC 2023 CMP guidelines: Phänotyp-basiertes diagnostisches work-up

neuer Phänotyp: NDLVC

Central illustration

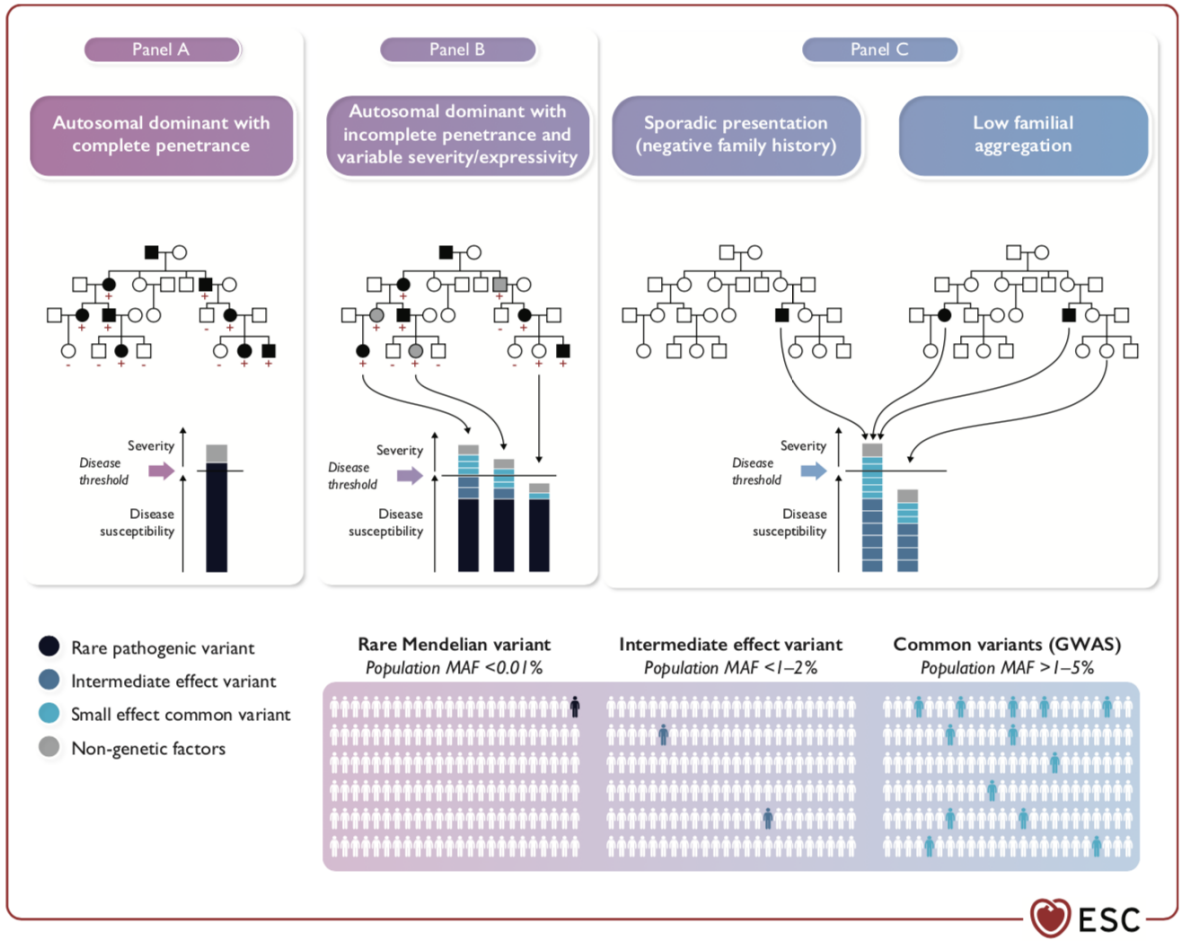
Key aspects in the evaluation and management of CMPs

The **patient pathway**, from presentation (**clinical scenario**) to the morphological and functional characterization (the **phenotype**) **using a multiparametric approach** that include additional variants such as pedigree analysis, genetic test, extracardiac involvement, laboratory markers, **to arrive at an aetiological diagnosis.**



Arbelo et al, *EHJ*, 2023.

Die neuen ESC 2023 CMP guidelines: Genetisches Testen



Gene	Cardiomyopathy phenotype					Associated phenotype
	HCM	DCM	NDLVC	ARVC	RCM	
ABCC9	● [a]	○				[a] Cantu syndrome
ACTA1	○					
ACTC1	●	◐	◐	○	◐	
ACTN2 [b]	◐	◐	◐			
ALPK3	●					
ANKRD1	○	○				
BAG3	● [a]	● ●			◐	[a] Myofibrillar myopathy
CACNA1C	● [c]					[c] Timothy syndrome
CACNB2	○					
CALR3	○					
CASQ2	○					
CAV3	● [a]					[a] Caveolinopathy
CDH2				○		
COX15	● [a]					[a] Leigh syndrome
CRYAB	● [a]					[a] Alpha-B crystallinopathy
CSRP3	◐	○				
CTF1		○				

Arbelo et al, *EHJ*, 2023.

Die neuen ESC 2023 CMP guidelines: Genetisches Testen

Recommendations	Class[a]	Level[b]
Genetic counselling		
Genetic counselling, provided by an appropriately trained healthcare professional and including genetic education to inform decision-making and psychosocial support, is recommended for families with an inherited or suspected inherited cardiomyopathy, regardless of whether genetic testing is being considered.[204,206,208,209,221–224]	I	B
It is recommended that genetic testing for cardiomyopathy is performed with access to a multidisciplinary team, including those with expertise in genetic testing methodology, sequence variant interpretation, and clinical application of genetic testing, typically in a specialized cardiomyopathy service or in a network model with access to equivalent expertise.[222,224–226]	I	B
Pre- and post-test genetic counselling is recommended in all individuals undergoing genetic testing for cardiomyopathy.[204,208,227–236]	I	B
If pre-natal diagnostic testing is to be pursued by the family, it is recommended that this is performed early in pregnancy, to allow decisions regarding continuation or co-ordination of pregnancy to be made.	I	C
A discussion about reproductive genetic testing options with an appropriately trained healthcare professional should be considered for all families with a genetic diagnosis.	IIa	C
Index patients		
Genetic testing is recommended in patients fulfilling diagnostic criteria for cardiomyopathy in cases where it enables diagnosis, prognostication, therapeutic stratification, or reproductive management of the patient, or where it enables cascade genetic evaluation of their relatives who would otherwise be enrolled into long-term surveillance.[227–231,237,238]	I	B
Genetic testing is recommended for a deceased individual identified to have cardiomyopathy at *post-mortem* if a genetic diagnosis would facilitate management of surviving relatives.[239–243]	I	C
Genetic testing may be considered in patients fulfilling diagnostic criteria for cardiomyopathy when it will have a net benefit to the patient, considering the psychological impact and preference, even if it does not enable diagnosis, prognostication, or therapeutic stratification, or cascade genetic screening of their relatives.	IIb	C
Genetic testing in patients with a borderline phenotype not fulfilling diagnostic criteria for a cardiomyopathy may be considered only after detailed assessment by specialist teams.	IIb	C
Family members		
It is recommended that cascade genetic testing, with pre- and post-test counselling, is offered to adult at-risk relatives if a confident genetic diagnosis (i.e. a P/LP variant) has been established in an individual with cardiomyopathy in the family (starting with first-degree relatives if available, and cascading out sequentially).[204,227–232]	I	B
Cascade genetic testing with pre- and post-test counselling should be considered in paediatric at-risk relatives if a confident genetic diagnosis (i.e. a P/LP variant) has been established in an individual with cardiomyopathy in the family (starting with first-degree relatives, if available, and cascading out sequentially), considering the underlying cardiomyopathy, expected age of onset, presentation in the family, and clinical/legal consequences.[233–236,244]	IIa	B
Testing for the presence of a familial variant of unknown significance, typically in parents and/or affected relatives, to determine if the variant segregates with the cardiomyopathy phenotype should be considered if this might allow the variant to be interpreted with confidence.	IIa	C
Diagnostic genetic testing is not recommended in a phenotype-negative relative of a patient with cardiomyopathy in the absence of a confident genetic diagnosis (i.e. a P/LP variant) in the family.	III	C

Arbelo et al, *EHJ*, 2023.

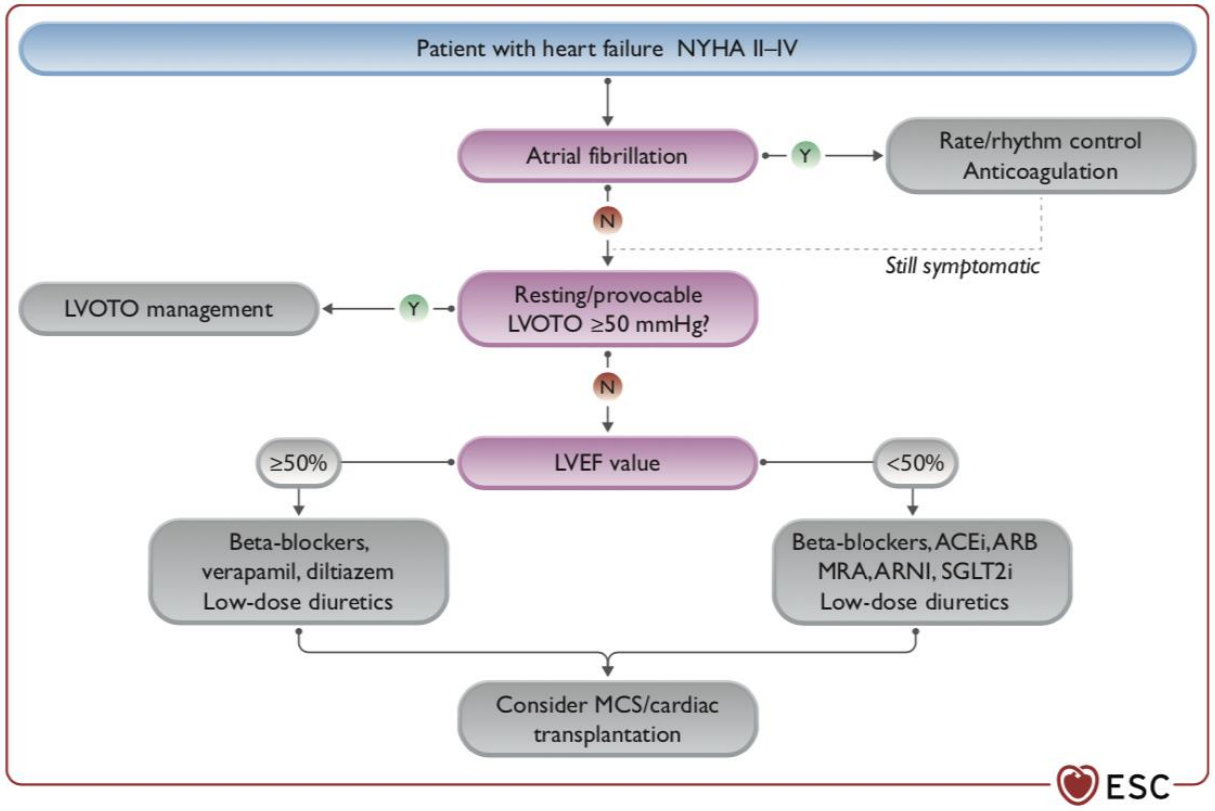
Einige Ätiologien brauchen eine spezifische Therapie

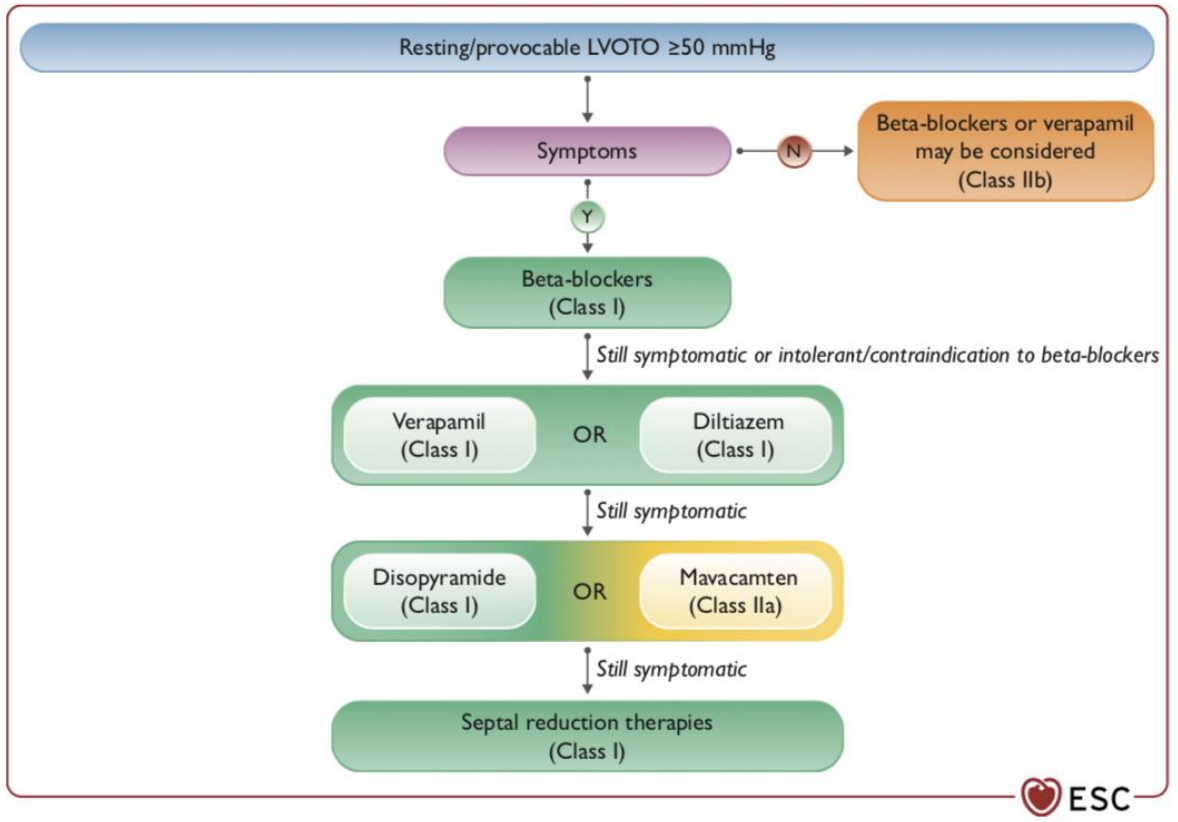
Etiology for DCM	Specific Treatment
Alcoholic	Abstinence
Cocaine, illicit drugs	Abstinence
Collagen vascular disease	
SLE, RA, sarcoidosis	Steroids, cytotoxic or immunomodulating agents
Scleroderma	Steroids, Ca channel blockers for Raynaud
Kawasaki disease	IV Immunoglobulin
Viral myocarditis	Prednisone and immunosuppressant therapy or transplant for fulminant course
Chagas disease	Benznidazole, nifurtimox
HIV/AIDS	Highly active retroviral therapy, increase CD4 count
Nutritional deficiency	
Thiamine, selenium, or carnitine deficiency)	Replacement

Etiology for DCM	Specific Treatment
Hyperthyroidism/hypothyroidism	Achieve euthyroid state
Uremia	Dialysis
Pheochromocytoma	Removal of tumor
Tachycardia induced	Ablation, maintenance of sinus rhythm
Stress-induced cardiomyopathy	Management of psychosocial stress
Peripartum cardiomyopathy	Multidisciplinary high-risk pregnancy management, avoid subsequent pregnancy if LV function does not normalize
Chemotherapy-induced cardiomyopathy	Reduce dose or discontinue, avoid cardiotoxic other chemotherapy combinations and XRT, initiate early standard treatment for heart failure
Genetic	Genetic counseling, prenatal diagnosis, new experimental treatment modalities with gene editing, RNA silencing or RNA interference

AIDS, Acquired immunodeficiency syndrome; *DCM*, dilated cardiomyopathy; *HIV*, human immunodeficiency virus; *IV,* intravenous; *LV*, left ventricle; *RA,* rheumatoid arthritis; *SLE*, systemic lupus erythematosus; *XRT,* radiation therapy.

HCM





Arbelo et al, *EHJ*, 2023.

Kardiale Amyloidose

ESC European Society of Cardiology
European Heart Journal (2021) 42, 1554–1568
doi:10.1093/eurheartj/ehab072
SPECIAL ARTICLE
Heart failure and cardiomyopathies

Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases

Cardiac amyloidosis
ESC Myocardial WG position paper

SUSPECT

Screen if

Left ventricle wall thickness ≥ 12 mm
&
≥ 1 Red Flag or Clinical Scenario

Left Ventricular Wall Thickness ≥ 12 mm + ≥1 of:
- Heart failure in ≥ 65 years
- Aortic stenosis in ≥ 65 years
- Hypotension or normotensive if previously hypertensive
- Sensory involvement, autonomic dysfunction
- Peripheral polyneuropathy
- Proteinuria
- Skin bruising
- Bilateral carpal tunnel syndrome
- Ruptured biceps tendon
- Subendocardial/transmural LGE or increased ECV
- Reduced longitudinal strain with apical sparing
- Decreased QRS voltage to mass ratio
- Pseudo Q waves on ECG
- AV conduction disease
- Possible family history

DIAGNOSIS

Diagnostic criteria

Invasive (all types)	Non-Invasive (only for ATTR)
Cardiac Biopsy positive for amyloid or Extracardiac Biopsy positive for amyloid + Echocardiographic/CMR criteria	Grade 2 or 3 cardiac uptake at diphosponate Scintigraphy + Negative serum free light chains & negative serum and urine immunofixation (SPIE & UPIE) + Echocardiographic/CMR criteria

Diagnostic algorithm

^{99m}Tc-DPD/PYP/HMDP Scintigraphy with SPECT & Haematologic tests (serum free-light chain quantification & serum and urine immunofixation)

Diagnosis made or proceed to **CMR and/or biopsy** according to results

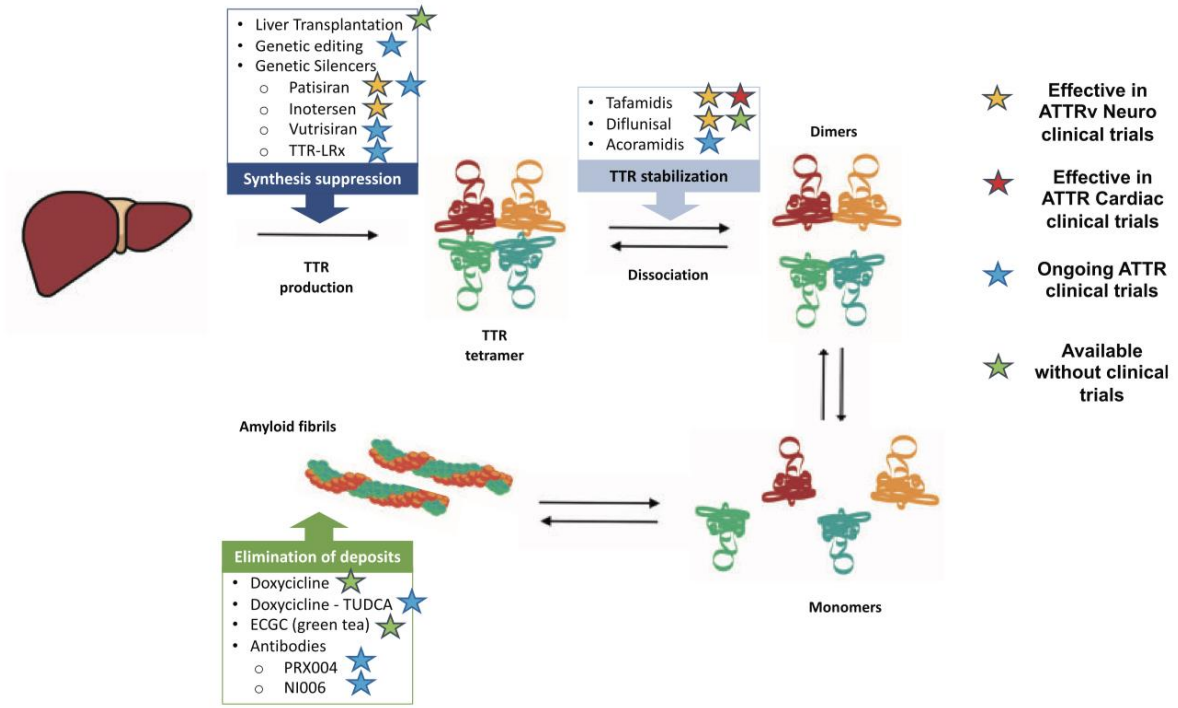
TREATMENT

Cardiac complications and comorbidities

- Heart Failure
- Thromboembolism
- Atrial fibrillation
- Conduction disorders
- Ventricular arrhythmias
- Aortic stenosis

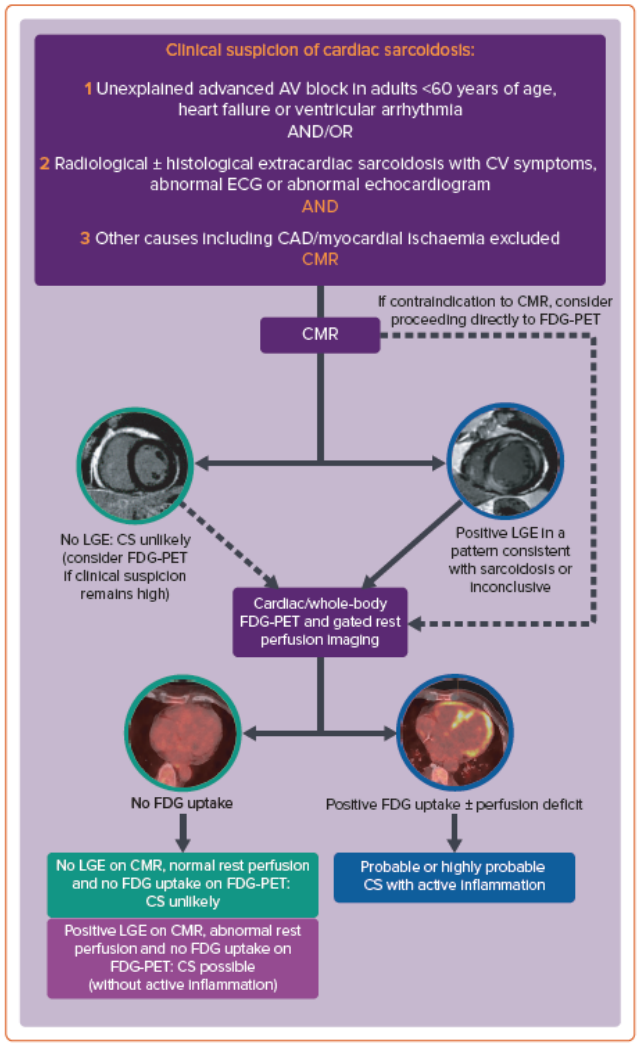
Disease modifying treatment

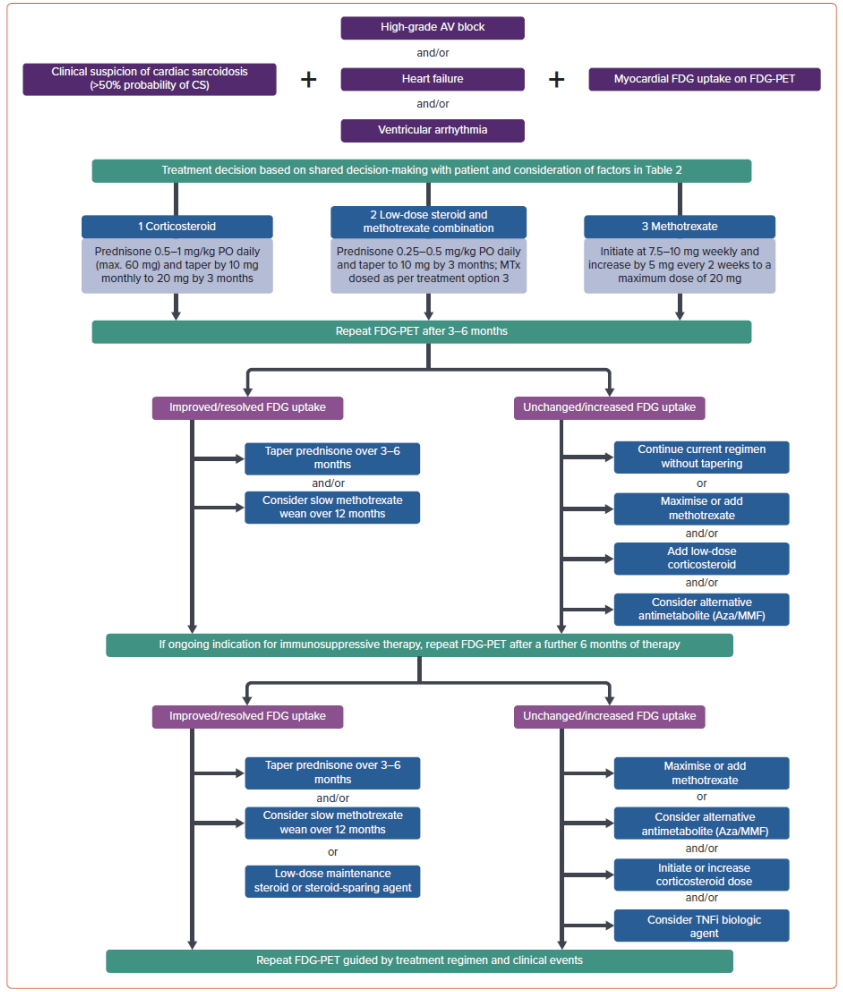
- **ATTR**: genetic silencers, stabilizers and removers.
- **AL**: chemotherapy and ASCT.
- **AA**: anti-inflammatory, anti-infective and immunosuppressive drugs.

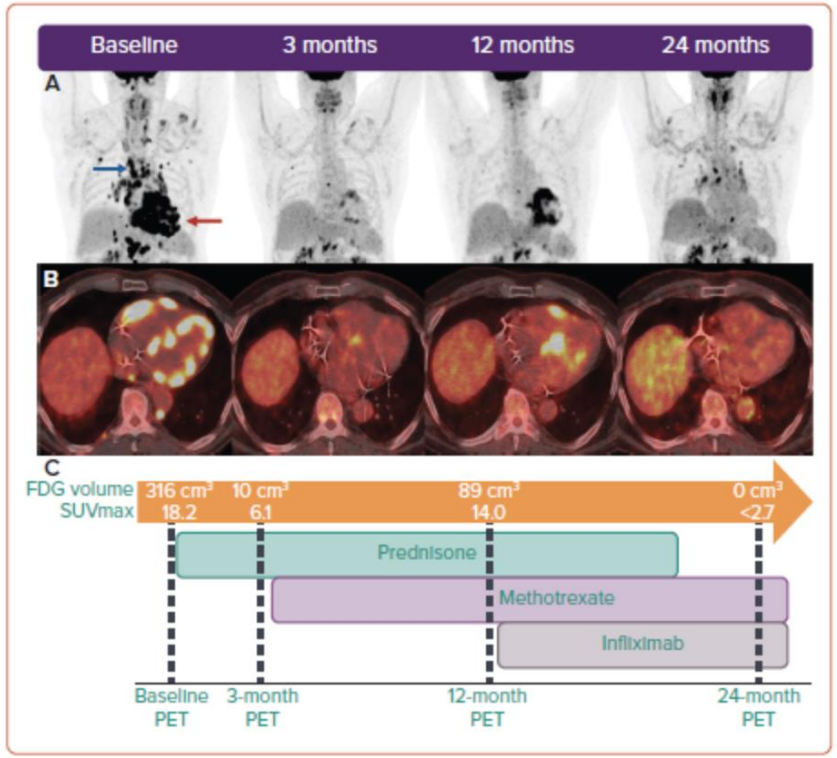


Gacia-Pavia et al, *EHJ*, 2021.

Kardiale Sarkoidose



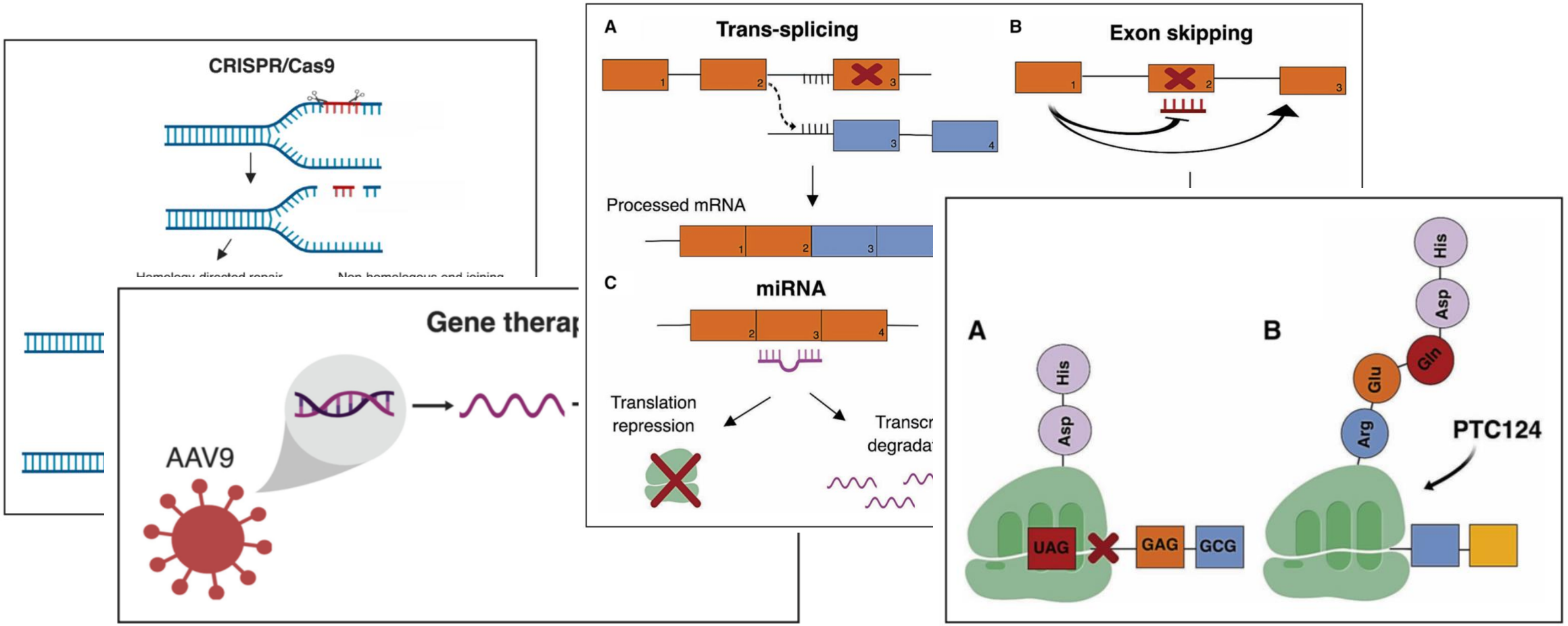




AV = atrioventricular; CAD = coronary artery disease; CMR = cardiac MRI; CS = cardiac sarcoidosis; CV = cardiovascular; FDG = fluorodeoxyglucose; LGE = late gadolinium enhancement.

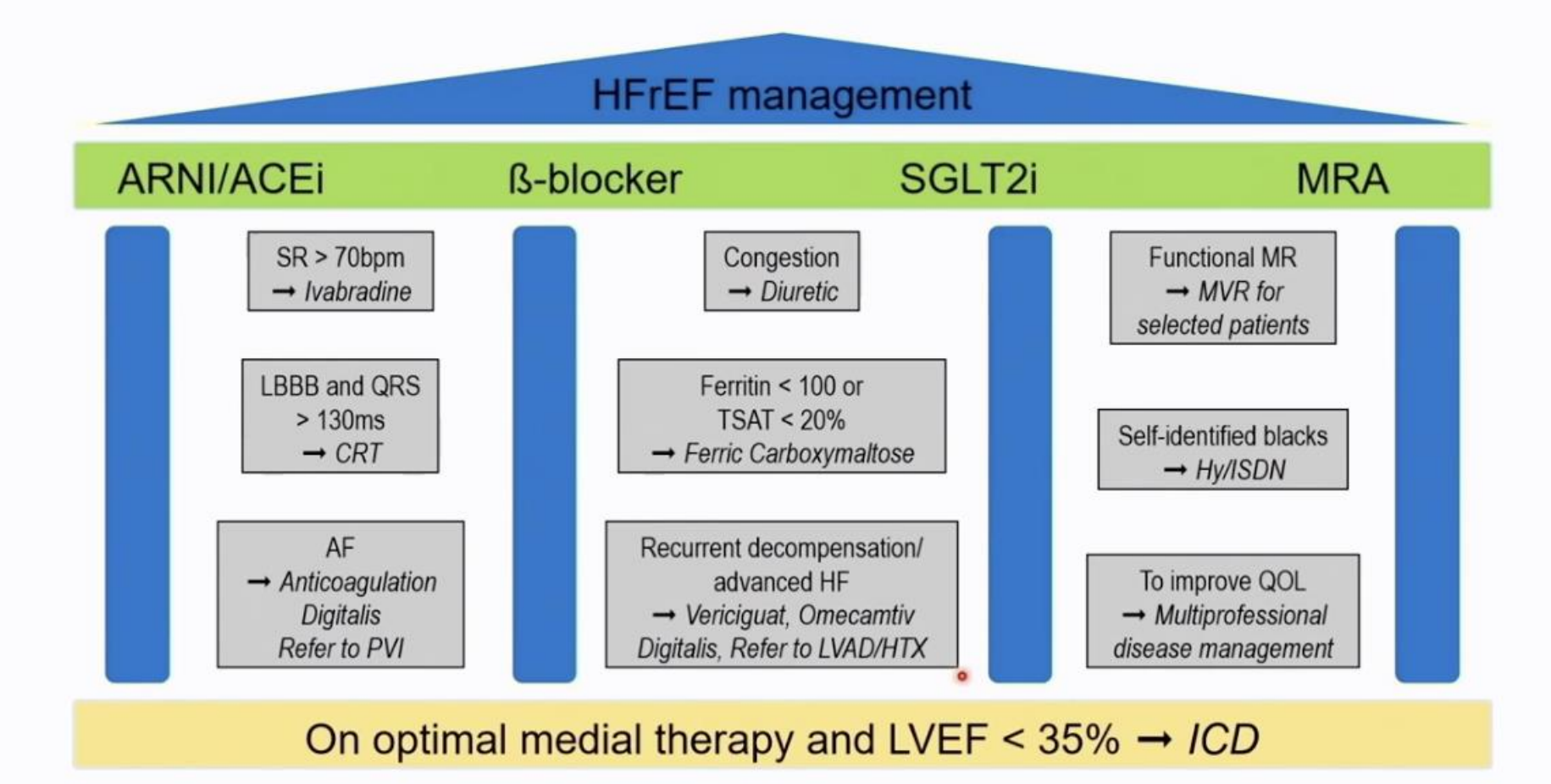
Giblin et al, *Card Fail Rev*, 2021.

Therapiestrategien der genetischen CMPs – Zukunft?



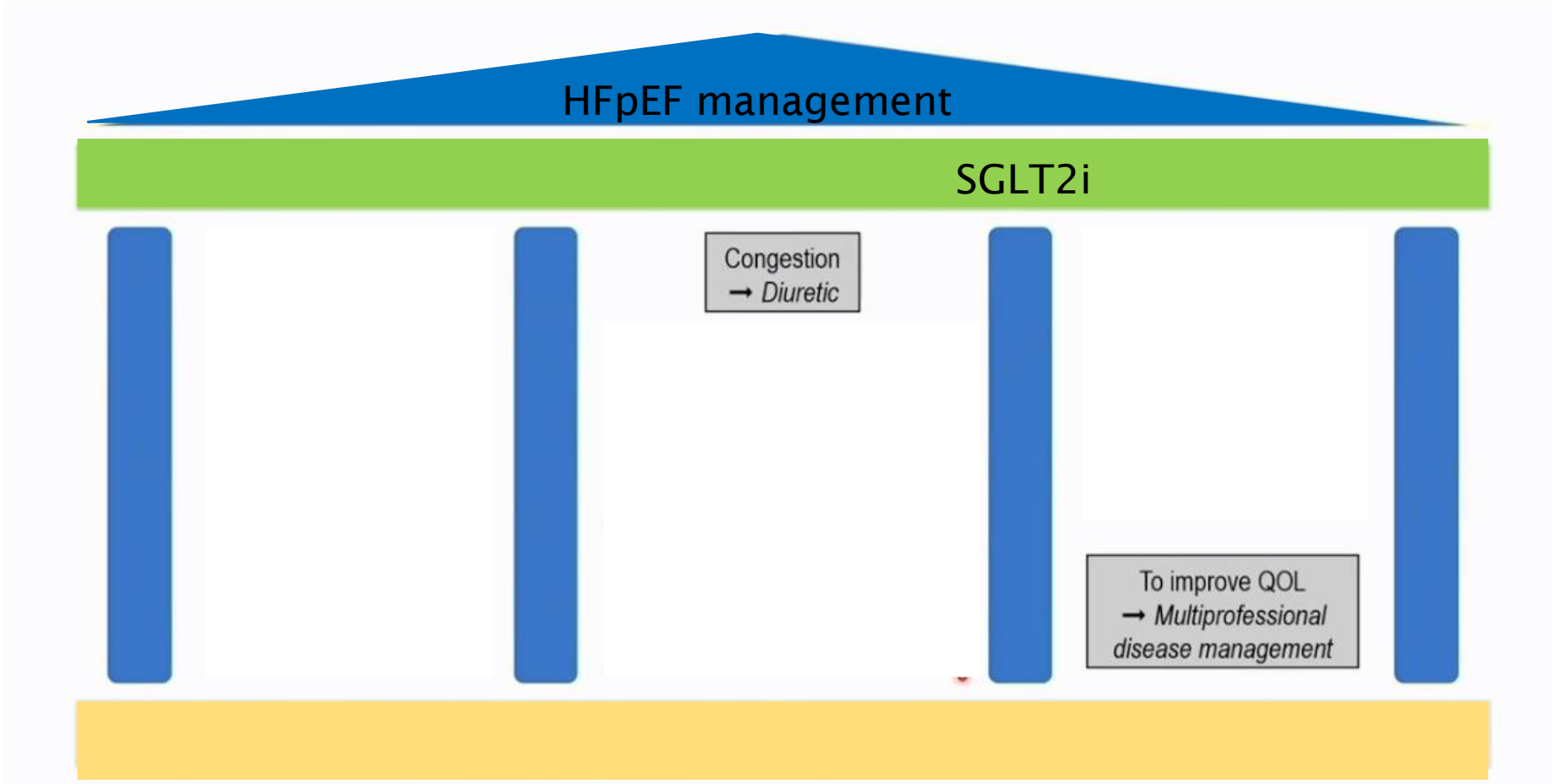
Repetti et al, *Circ Res*, 2019.

HFrEF management

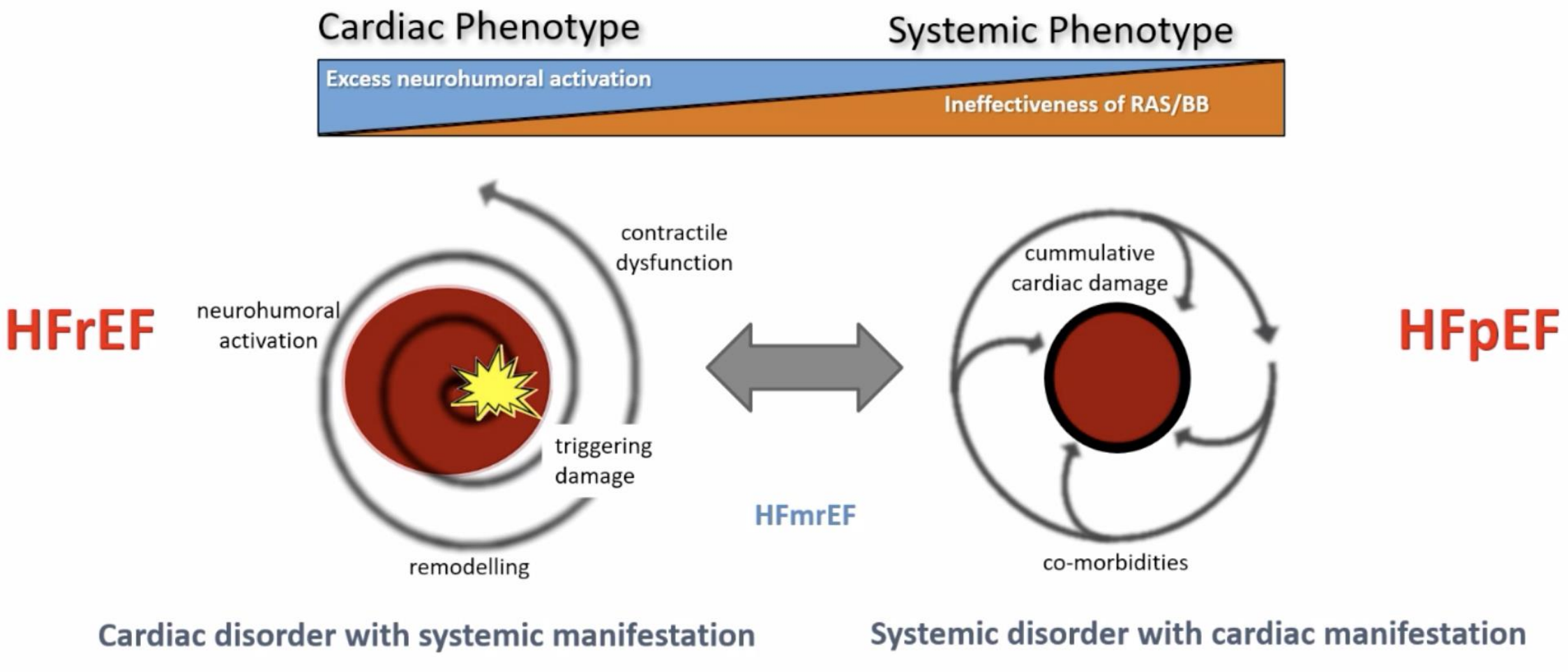


Abdin and Böhm et al, *unpublished*, 2021.

HFpEF management



Pathomechanistische Trigger der HFrEF vs HFpEF



Pieske et al., *DFG application*, 2019.

Todeesursachen der HF aus dem ESC-HF long-term registry