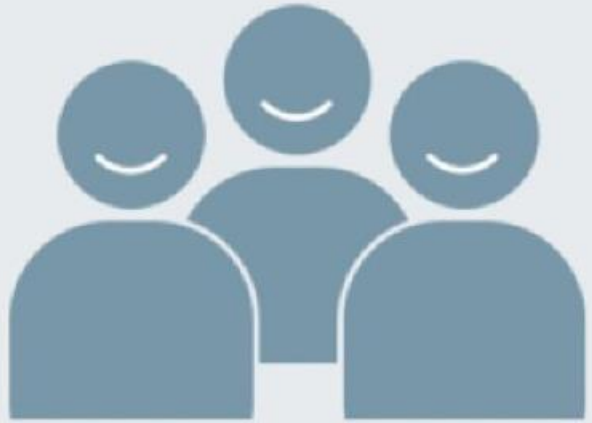
4th IHEF CARD
The 4th Indonesian
Symposium on Heart Failure and
Cardiometabolic Disease

Tailored Therapeutic Approaches for HF : Which Treatments are Appropriate, At What Time and For Which Patients ?

Paskariatne Probo Dewi

Goals of HF care

Increase Survival	Reduce Hospitalization	Make Patients Feel Better
		
Reduce mortality by reducing sudden cardiac death and death from progressive HF	Rehospitalizations incur a bad prognosis, is costly, and distressing for patients and families	Improve symptoms/quality of life; slow rate of deterioration

McDonagh TA, et al. Eur Heart J. 2021; 42:3599-3726

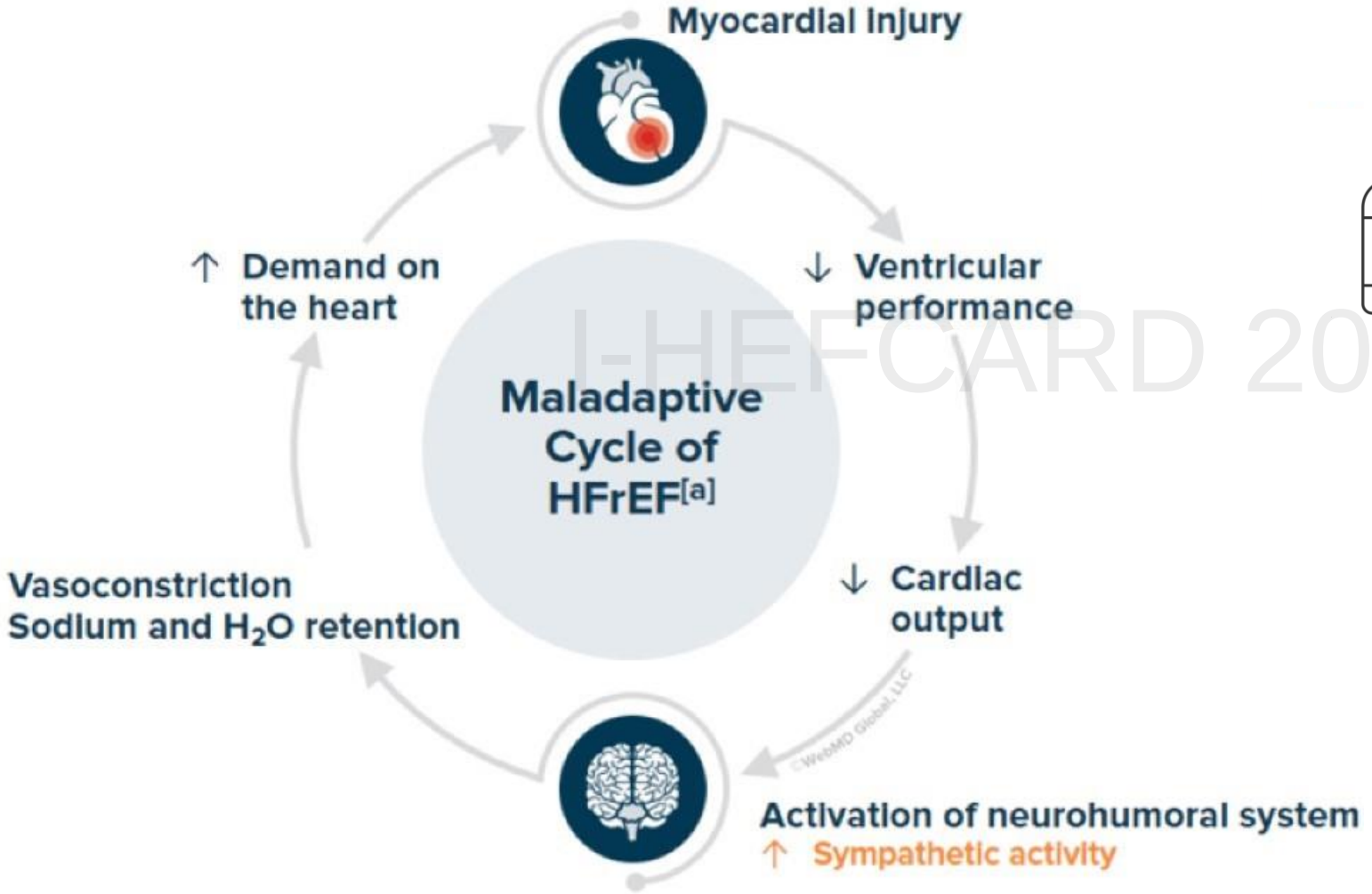
Tailored Therapeutic Approaches for HF

Which treatments

At what time

For which patients

Neurohormonal activation in HFrEF



Neurohormonal modulation is the cornerstone of HFrEF treatment

- RAAS inhibitor
- Beta-blocker
- MRA
- SGLT2 inhibitor

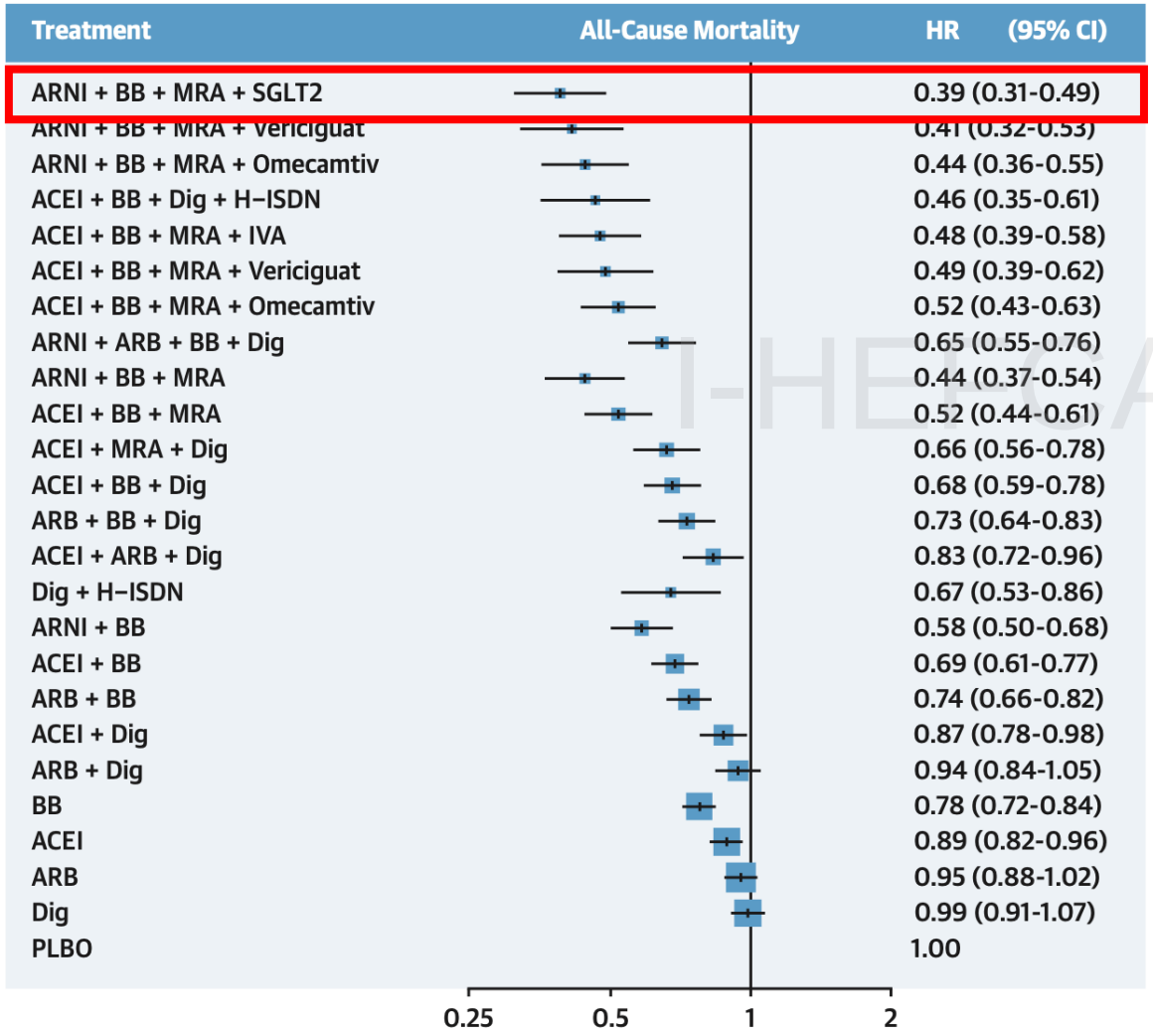
Booth LC et al. 2015;6:270; McDonagh TA, et al. Eur Heart J. 2021; 42:3599-3726

Rekomendasi	COR	LOE
ACE-I direkomendasikan untuk semua pasien gagal jantung HfrEF untuk mengurangi rawat ulang akibat perburukan gagal jantung, dan meningkatkan angka kesintasan pasien.	I	A
Penyekat-β direkomendasikan untuk semua pasien gagal jantung HfrEF yang stabil untuk mengurangi perawatan rumah sakit karena perburukan gagal jantung, dan menurunkan mortalitas	I	A
MRA direkomendasikan untuk semua pasien gagal jantung HfrEF untuk mengurangi perawatan rumah sakit karena perburukan gagal jantung, dan meningkatkan angka kesintasan pasien.	I	A
ARNI direkomendasikan sebagai terapi subsitusi pasien HFrEF yang telah mendapatkan ACE-I atau ARB untuk menurunkan angka perawatan berulang karena gagal jantung dan mortalitas	I	B
Dapagliflozin atau Empagliflozin direkomendasikan untuk semua pasien gagal jantung HfrEF untuk menurunkan angka rawat ulang akibat perburukan gagal jantung dan mortalitas	I	A
ARB direkomendasikan sebagai terapi subsitusi pasien HFrEF dengan tanda dan gejala gagal jantung yang intoleran terhadap ACE-I maupun ARNI untuk menurunkan angka rawat ulang akibat perburukan gagal jantung dan mortalitas	I	B
Diuretik loop direkomendasikan pada HFrEF untuk menghilangkan kongesti	I	C

Greatest benefit with 4 pillars HF therapy

CENTRAL ILLUSTRATION Relative Risk Reduction of Different Pharmacological Treatment Combinations for Heart Failure

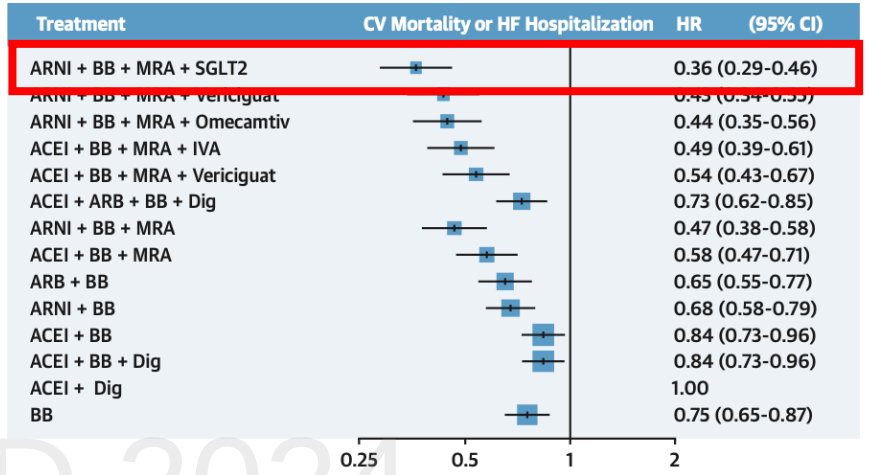
A



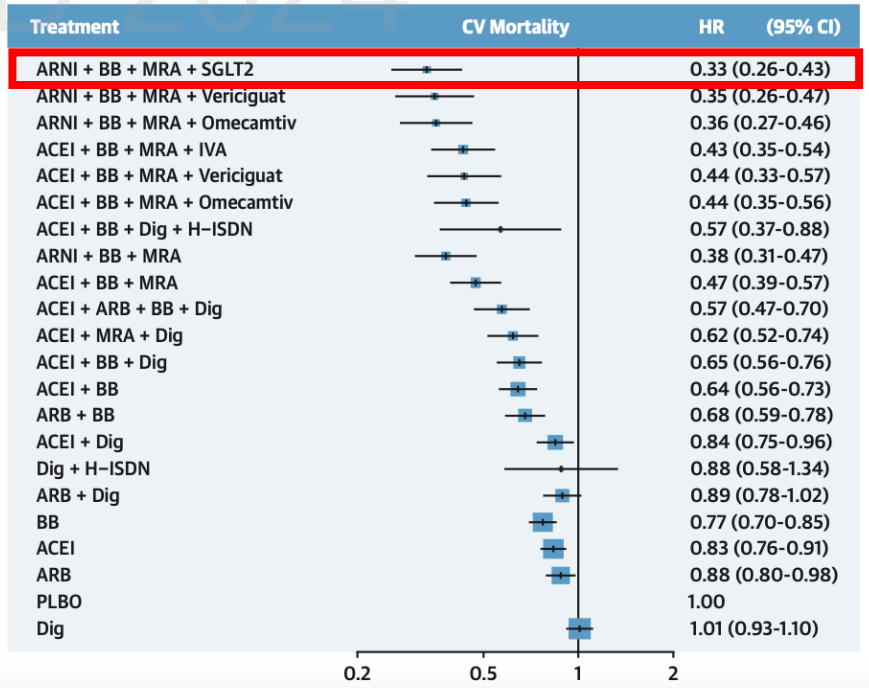
Tromp, J. et al. J Am Coll Cardiol HF. 2022;10(2):73-84.

CENTRAL ILLUSTRATION Continued

B



C



Tailored Therapeutic Approaches for HF

Which treatments

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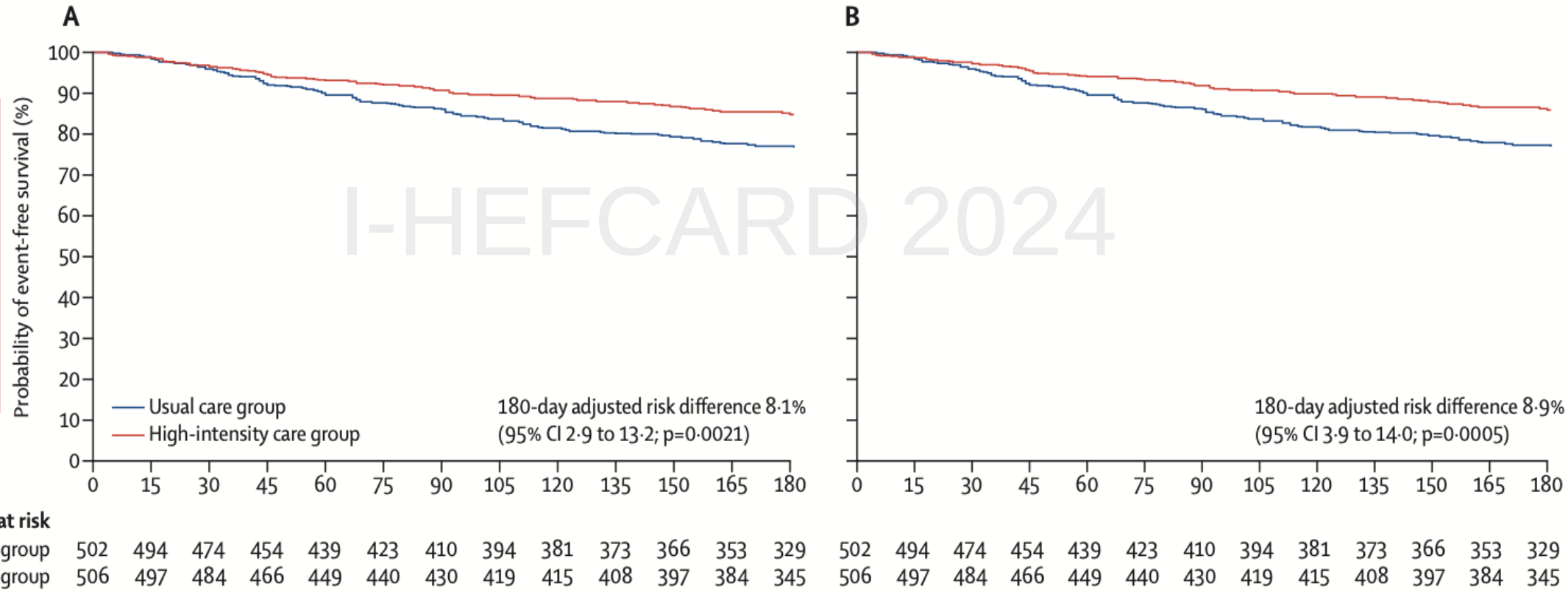
Early initiation of HFrEF medication

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

McDonagh TA, et al. Eur Heart J. 2021; 42:3599-3726

Rapid Optimizing HF treatment in inpatient setting STRONG HF study

All HF medications initiate and optimize during hospitalization at least up to 50% from max recommended dose



OMT in 2 weeks after hospital discharged and close follow up

Mebazaa A, et al. Lancet.2022;400:1938-1952

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

Recommendation	Class[a]	Level[b]
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]		

In-hospital initiation and speed matter

McDonagh TA, et al. Eur Heart J. 2023; 00:1-13

Not eligible for certain group of pts

- Age < 18 or > 85 y.o
- Significant comorbidities
- Primary liver disease considered to be life threatening
- Renal disease or eGFR < 30 mL/min/1.73m2
- Intolerance to high dose BB, RAS blockers
- ACS in 3 mo
- Advanced HF
- Psychiatry or neurological disorder

Mebazaa A, et al. Lancet.2022;400:1938-1952

Simultaneous or rapid sequence initiation of quadruple medical therapy for HF

Early relative risk reduction			Initiation and optimization of medication dosing				
Outcomes	Change, %	CDMMT	Day 1	Days 7-14	Days 14-28	Days 21-42	After day 42
CV death or HF hospitalization	-42	ARNI	Initiate at low dose	Continue	Titrate, as tolerated	Titrate, as tolerated	Maintenance or additional titration of the 4 foundational therapies
Death	-25	β-Blocker	Initiate at low dose	Titrate, as tolerated	Titrate, as tolerated	Titrate, as tolerated	Consideration of EP device therapies or transcatheter mitral valve repair
CV death or HF hospitalization	-37	MRA	Initiate at low dose	Continue	Titrate, as tolerated	Continue	Consideration of add-on medications or advanced therapies, if refractory
Death, HF hospitalization,or emergency/ urgent visit for worsening HF	-58	SGLT2i	Initiate	Continue	Continue	Continue	Manage comorbidities

- Ensure All 4 drugs are started
- Minimize the possibility of clinical inertia

Tolerability :

- 2 of 4 can affect BP
- Difficult to sort out an AE

Patient profiling in HFrEF for tailoring medical therapy

- More tolerable
- Applicable in clinical practice

Greene SJ, et al.JAMA.2021; Rosano GMC et al. Eur J Heart Fail. 2021;23(6):872-881

Tailored Therapeutic Approaches for HF

Which treatments

At what time

For which patients

ESC European Society of Cardiology
European Journal of Heart Failure (2021)
doi:10.1002/ejhf.2206
POSITION PAPER

Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology

"A personalized approach, adjusting guideline-directed medical therapy to patient profile, may allow to achieve a better and more comprehensive therapy for each individual patient than the more traditional, forced titration of each drug class before initiating treatment with the next."

Rosano GMC et al. Eur J Heart Fail. 2021;23(6):872-881

Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology

- **Profile 1:** Patients with low BP and high HR (SBP <90 mmHg; HR >70 bpm)
- **Profile 2**: Patients with low BP and low HR (SBP <90 mmHg; HR <60 bpm)
- **Profile 3**: Patients with normal BP and low HR
- **Profile 4**: Patients with normal BP and high HR
- **Profile 5**: Patients with AF and normal BP
- **Profile 6**: Patients with AF and low BP
- **Profile 7**: Patients with CKD
- **Profile 8**: Pre-discharge patient
- **Profile 9**: Patient with hypertension despite GDMT

Black—drugs that should be given to patients;

Red—drugs that should be reduced or discontinued

Blue—drugs that should be added.

Rosano GMC et al. Eur J Heart Fail. 2021;23(6):872-881

2021 ESC Consensus on HF patient profiling for tailoring medical therapy
Achieving better and more comprehensive therapy for each individual patient

Patient profile	Drugs to be given	Drugs to be downtitrated or suspended	Drugs to be added
Patient with ↓ BP and ↑ HR	SGLT2i, MRA	BB, ACEi/ARB/ARNI, diuretic	Ivabradine
Patient with ↓ BP and ↓ HR	SGLT2i, MRA	BB, ACEi/ARB/ARNI, diuretic	
Patient with normal BP and ↓ HR	SGLT2i, ACEi/ARB/ARNI, MRA, diuretic	BB	Vericiguat
Patient with normal BP and ↑ HR	SGLT2i, ACEi/ARB/ARNI, BB, MRA, diuretic		Ivabradine
Patient with AF and normal BP	SGLT2i, ACEi/ARB/ARNI, BB, MRA, diuretic		Anticoagulant, digoxin
Patient with AF and ↓ BP	SGLT2i, ACEi/ARB/ARNI, MRA	BB, diuretic	Anticoagulant
Patient with CKD and/or ↑ K^+	SGLT2i, BB, diuretic	ACEi/ARB/ARNI, MRA (based on eGFR, ↑ K^+)	Vericiguat, Hydralazine / isosorbide dinitrate (CKD), potassium binder (↑ K^+)
Pre-discharge patient	SGLT2i, MRA, ACEi (SPB >90), ARNI (SPB >100), BB	BB (residual congestion), ARNI (SPB <100), ACEi (SPB <90)	Omecamtiv mecarbil, vericiguat (in selected patients)
Patient with HT despite GDMT	SGLT2i, ACEi/ARB/ARNI, BB, MRA, diuretic		Vericiguat, hydralazine / isosorbide dinitrate

Pasien dengan FEVKi ≤40%

Obat utama, lakukan inisiasi dan titrasi hingga dosis optimal/toleransi

- Penghambat SRAA (urutan sesuai prioritas)*
  1. ACE-I
  2. ARNI
  3. ARB
- Penyekat reseptor beta
- Antagonis aldosteron
- Penghambat SGLT2**
- Diuretik loop (bila ada tanda dan gejala kongesti)

Obat/alat tambahan digunakan sesuai indikasi komorbiditas

- Irama sinus & laju jantung > 70 per menit: ivabradine
- Fibrilasi atrium: antikoagulan
- Defisiensi besi: *ferric carboxymaltose*
- Etiologi iskemik: revaskularisasi
- Penyakit jantung katup: perbaikan/penggantian katup
- Lebar kompleks QRS > 120ms: terapi resinkronisasi jantung
- Menurunkan kejadian henti jantung mendadak: defibrillator intrakardiak

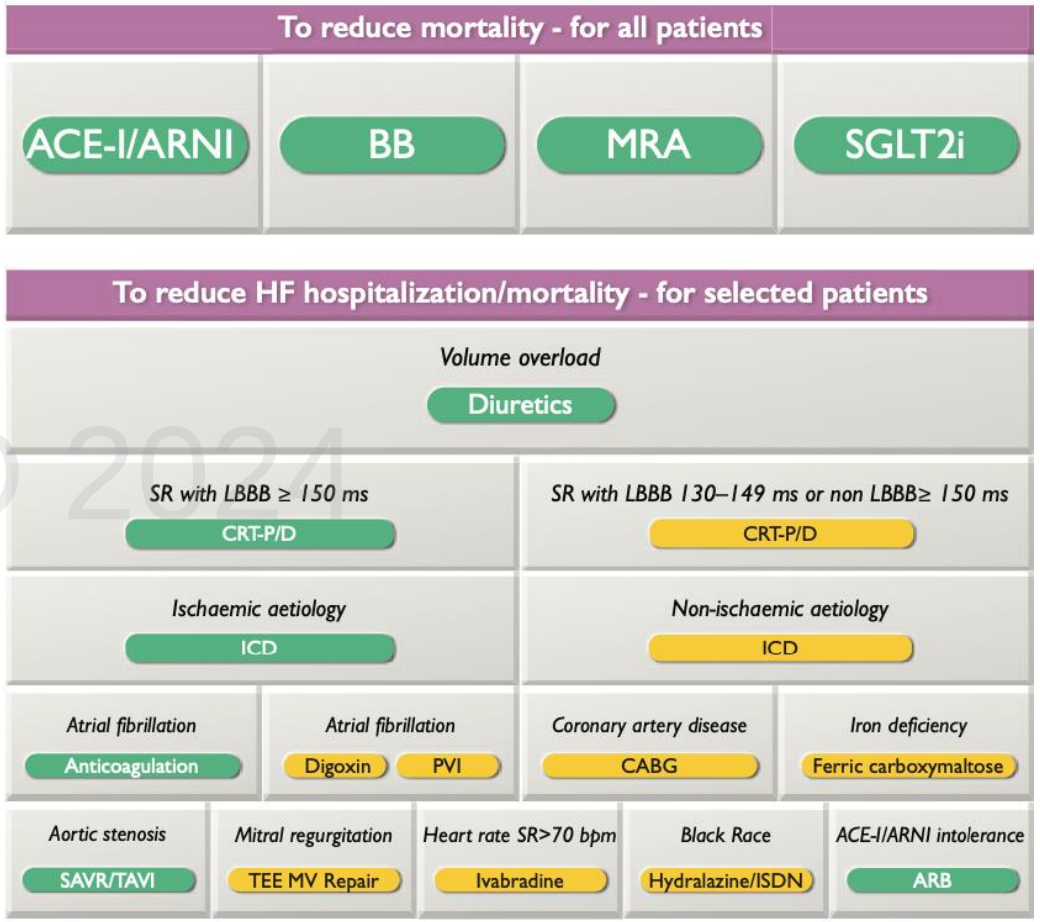
- Rehabillitasi Jantung
- Penanganan tim multidisiplin untuk kontrol faktor risiko dan komorbiditas

Evaluasi klinis (tanda dan gejala kongestif) & ekokardiografi (dalam 6 bulan)[a]

Tidak terdapat perbaikan klinis/perburukan gagal jantung:
- Optimalisasi diuretik (penambahan dosis atau penggantian menjadi sediaan injeksi)
- Optimalisasi dosis obat gagal jantung
- Evaluasi dan kontrol faktor risiko serta komorbiditas
- Vericiguat**

Perbaikan klinis & fraksi ejeksi:
- Terapi dilanjutkan

*Pilih salah satu, sesuai prioritas ketersediaan
**Apabila tersedia
[a]Ekokardiografi evaluasi dilakukan dalam 6 bulan paska inisiasi pada pasien yang stabil secara klinis untuk mengevaluasi perbaikan klinis, evaluasi ekokardiografi selanjutnya dilakukan sesuai dengan kondisi klinis pasien



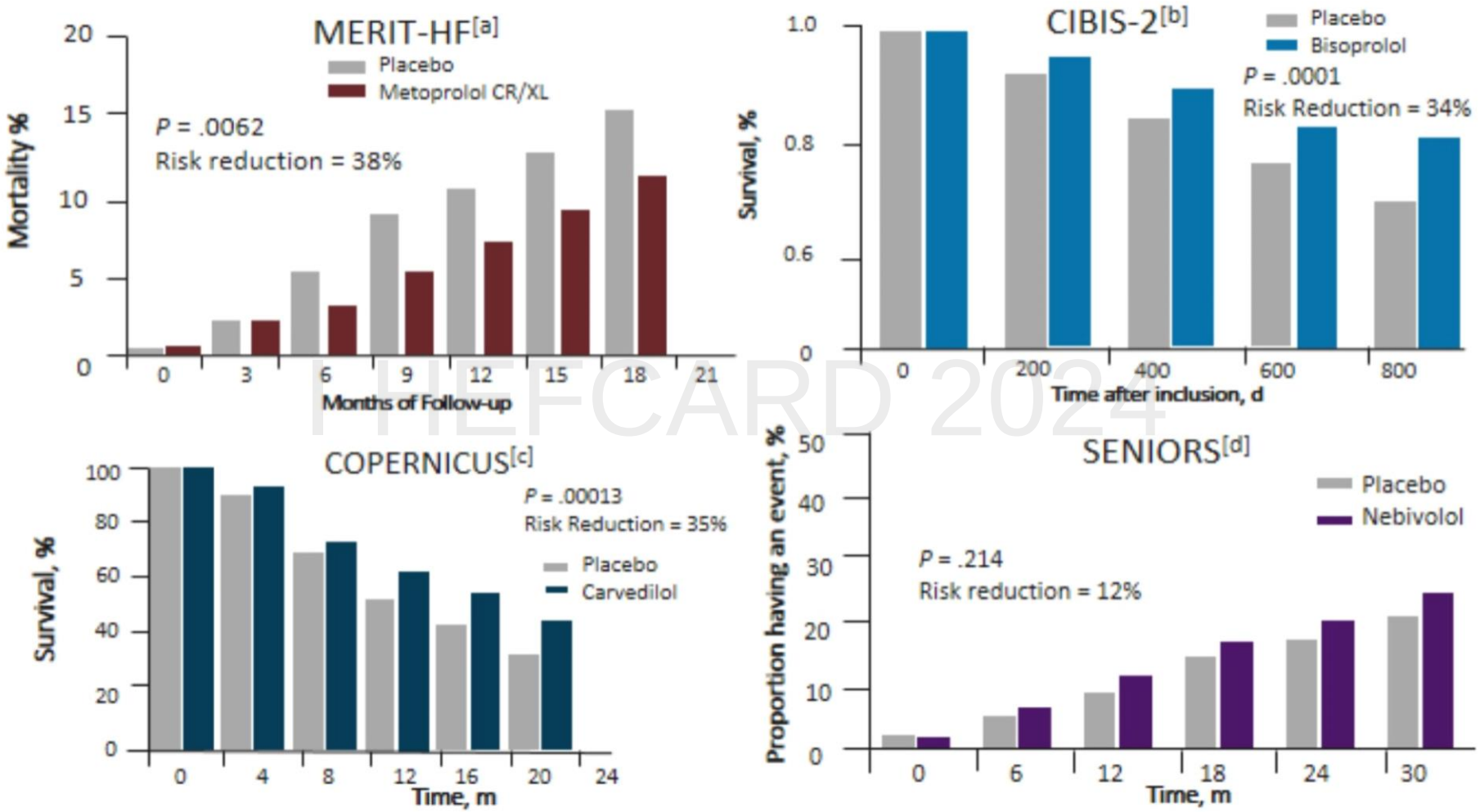
Challenge during HF treatment optimization

Comorbidity	GDMT	Precaution
Coronary artery disease and angina	✓	
Diabetes	✓	
Lung disease		Asthma is a relative contraindication to beta-blocker; starting with low doses of cardio-selective beta-blocker may allow its use
Depression	✓	
Erectile dysfunction	✓	
Iron deficiency/anaemia	✓	
Kidney dysfunction		ACEi, ARB, ARNI, MRA may have some limitations (see text)
Cachexia		ACEi, ARB, ARNI should be up-titrated carefully because of orthostatic hypotension

	QUALIFY [20]	ESC HF Long-term Registry [22]	TSOC-HFrEF [24]
ACEi/ARB	Worsening renal function Hypotension Cough	Worsening renal function Hypotension	Worsening renal function Older age
BB	Worsening of asthma and COPD Hypotension Bradycardia Fatigue	 Hypotension Bronchospasm	Worsening of asthma and COPD Older age
MRA	Hyperkalemia Renal dysfunction	Hyperkalemia Renal dysfunction	 Renal dysfunction Older age

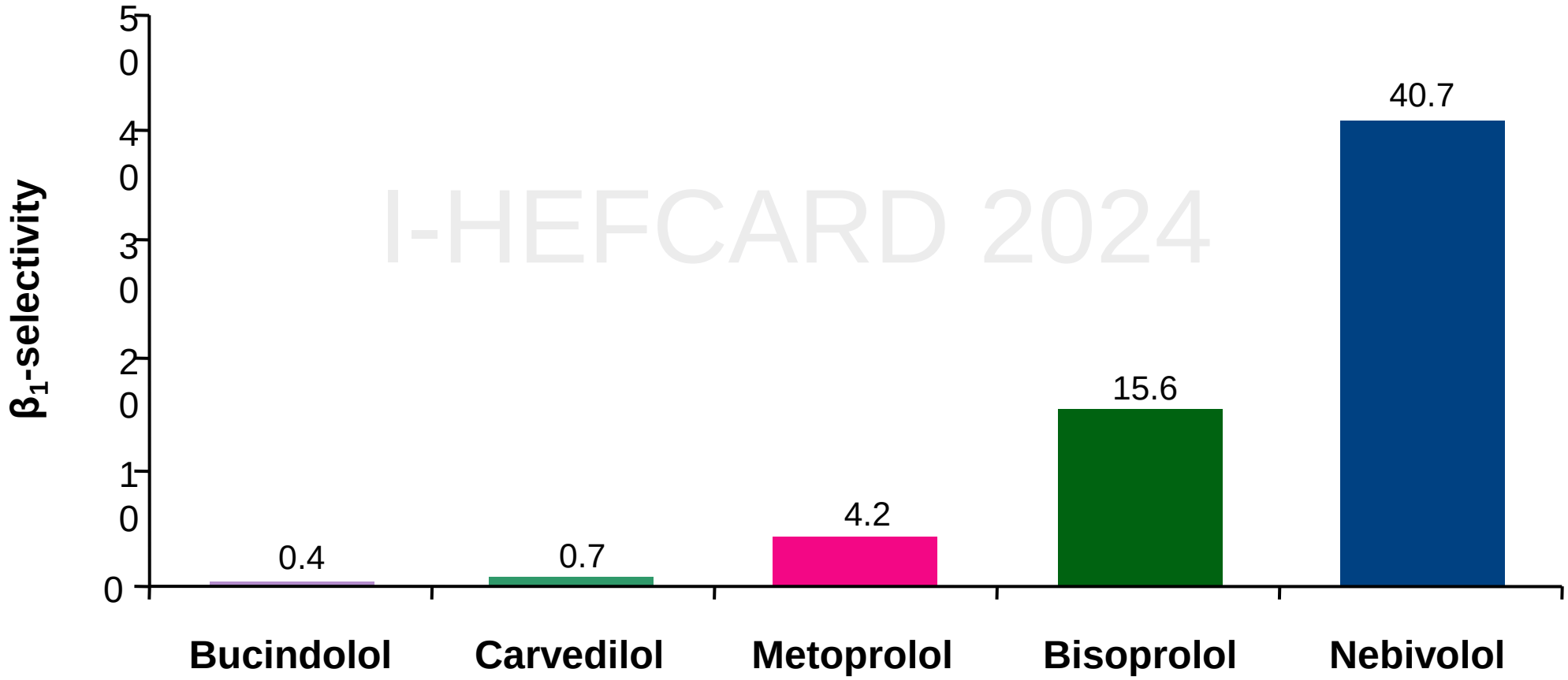
Rosano GMC et al. Eur J Heart Fail. 2021;23(6):872-881; Verhestraeten C, et al. Heart Failure Rev.2021

Beta blockers reduce all-cause mortality and hospitalizations in HFrEF



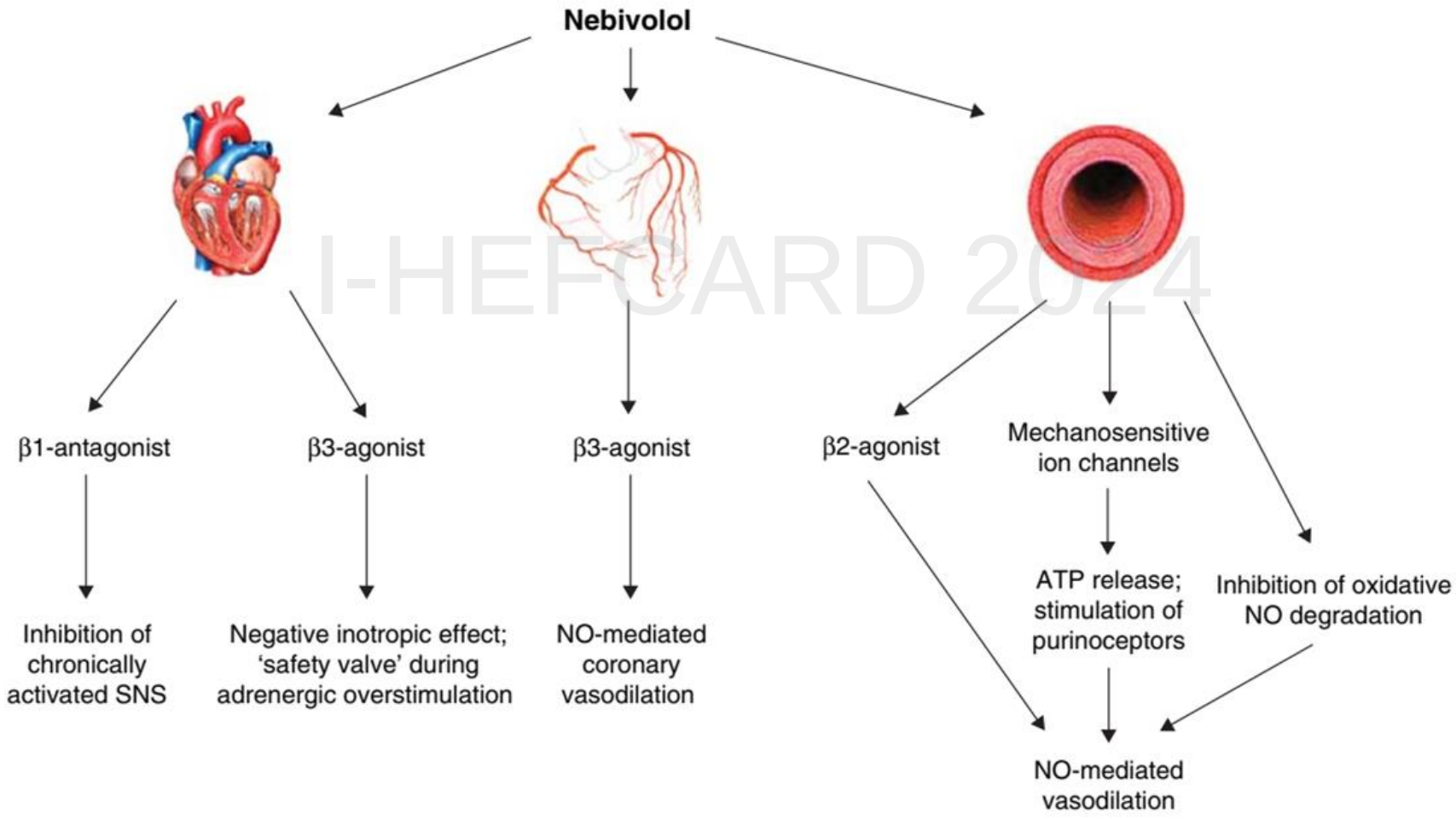
a. MERIT-HF Study Group. *Lancet*. 1999;353:2001-2007; b. CIBIS II Investigators. *Lancet*. 1999;353:9-13;
c. Packer M, et al. *Circulation*. 2002;106:2194-2199; d. Flather MD,et al. *Eur Heart J*. 2005;26:215-225.

Nebivolol: higher β1 selectivity compare to other beta-blockers



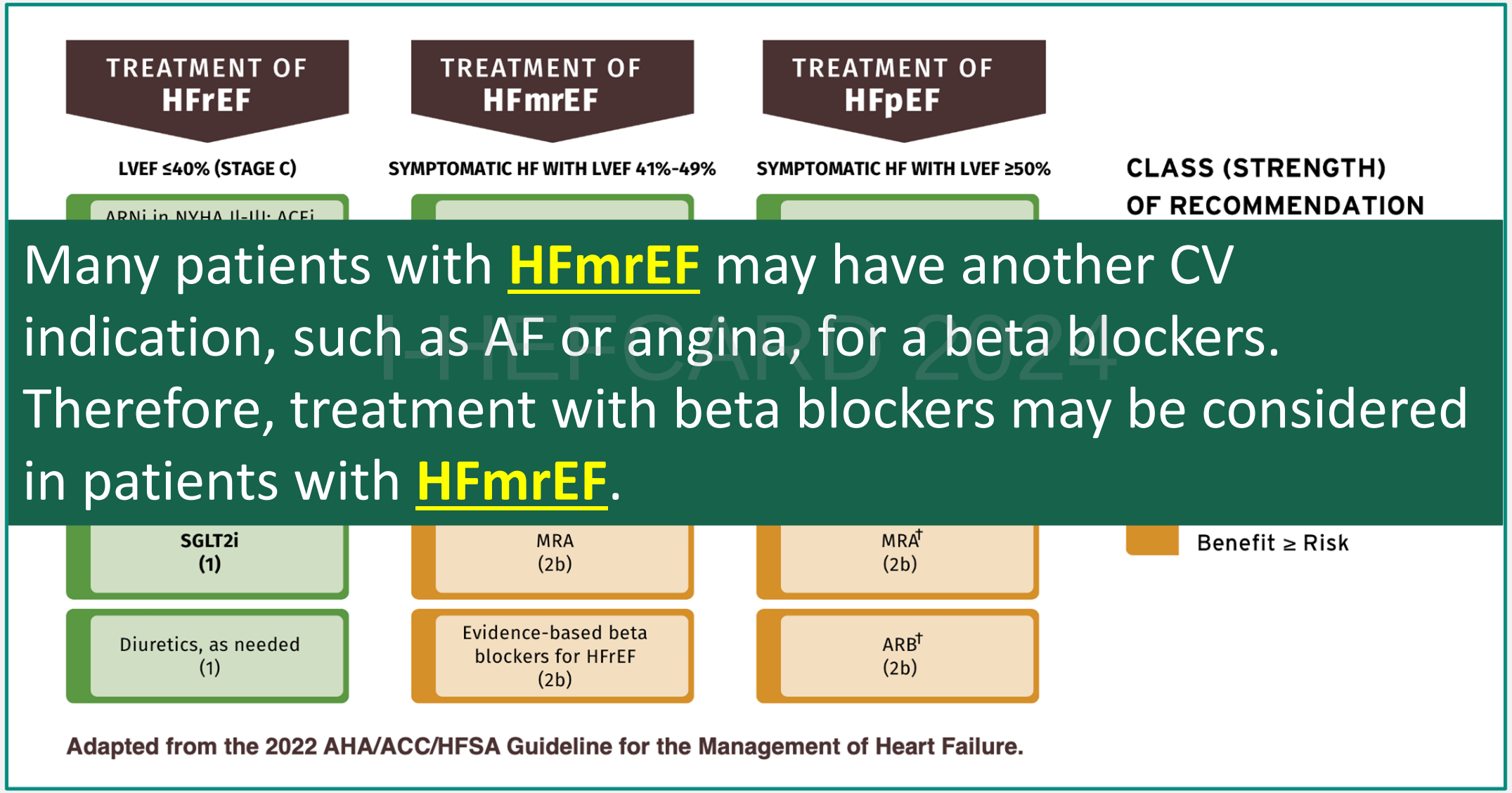
Brixius K, et al. British Journal of Pharmacology (2001) 133, 1330 – 1338

The effects of nebivolol in cardiovascular system, direct action in myocardial tissue, coronary and peripheral vessels



Lipsic E & van Veldhuisen DJ. Expert Opinion on Pharmacotherapy. 2010, 11:6, 983-992

Beta blockers in HFmrEF and HFpEF?



Many patients with **HFmrEF** may have another CV indication, such as AF or angina, for a beta blockers. Therefore, treatment with beta blockers may be considered in patients with **HFmrEF**.

Age of Patients in Major Trials of Previous β-Blocker

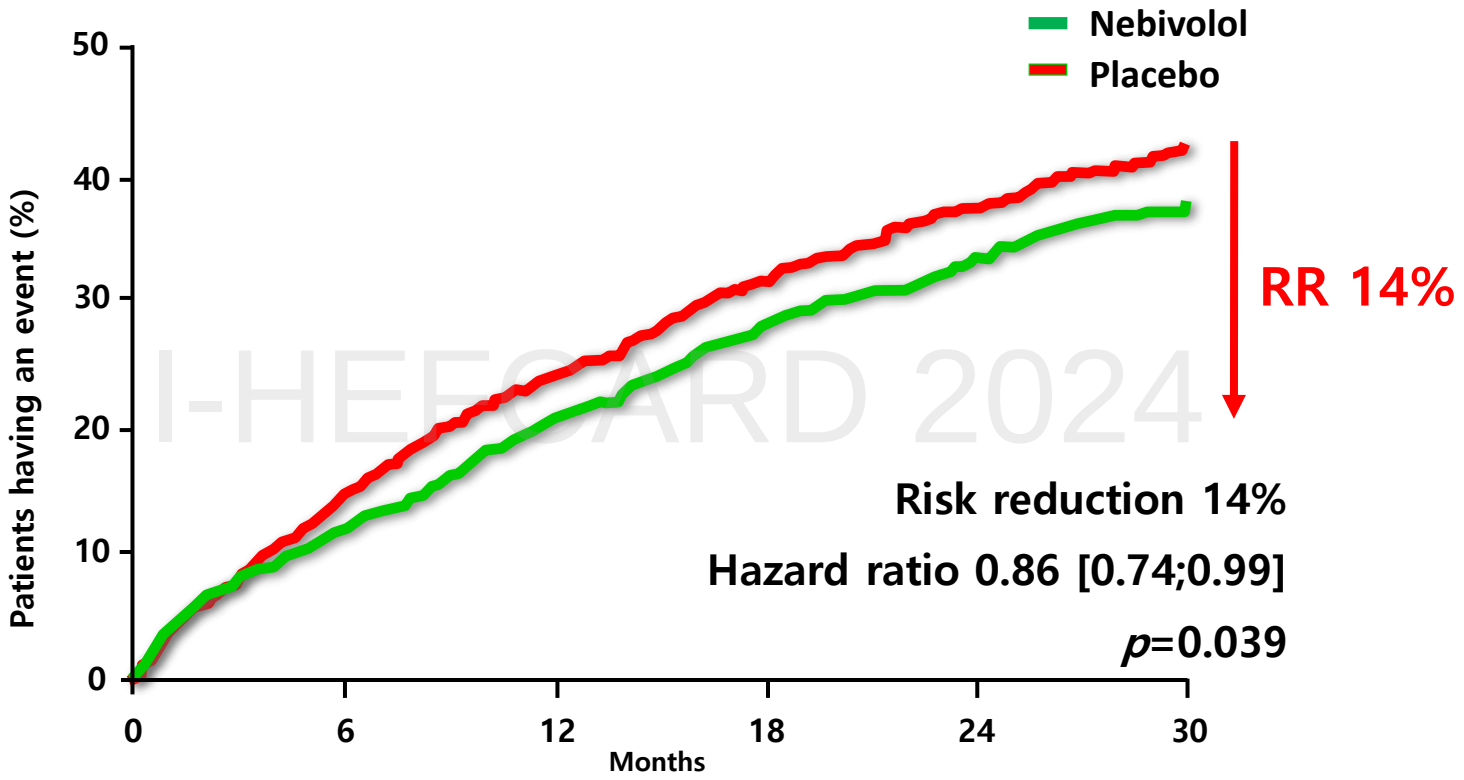
Table 3. Major trials of β-blockers in heart failure.

Year	Trial	Patients (n)	Drug	Comparator	Age (years)	Outcome	Ref.
1994	CIBIS-I	641	Bisoprolol	Placebo	60	Not superior mortality; improved function	[56]
1996	US-Carvedilol	1094	Carvedilol	Placebo	58	↓ mortality; ↓ risk of hospitalization for CV causes	[57]
1997	ANZ-Carvedilol	415	Carvedilol	Placebo	63	↓ mortality; ↓ risk of hospitalization for CV causes	[58]
1999	CIBIS-II	2647	Bisoprolol	Placebo	61	↓ mortality in patients with stable HF	[59]
2000	MERIT-HF	3991	Metoprolol	Placebo	63.8	↓ mortality; ↓ risk of hospitalization for CV causes	[60]
2001	Cumulative Survival	2889	Carvedilol	Placebo	63	↓ mortality; ↓ risk of hospitalization for CV causes	[61]
2001	BEST	2708	Bucindolol	Placebo	60	Lower death rate from CV causes; improved LVEF	[62]
2002	COPERNICUS	2289	Carvedilol	Placebo	NA	↓ less serious adverse events	[63]
2003	COMET	1511	Carvedilol	Metoprolol	62	↓ mortality	[64]
2005	SENIORS	2128	Nebivolol	Placebo	76	↓ mortality; ↓ risk of hospitalization for CV causes	[65]
2006	SENIORS	112	Nebivolol	Placebo	76	↓ ventricular size; improves EF	[66]
2008	CIBIS-III	1010	Bisoprolol	Enalapril	72.4	Not superior mortality; ↑ worsening of HF with bisoprolol	[67]

↓: Decrease in; ↑: Increase in; BEST: Beta-blocker Evaluation of Survival Trial; CIBIS: Cardiac Insufficiency Bisoprolol Study; COMET: Carvedilol or Metoprolol European Trial; COPERNICUS: Carvedilol Prospective Randomized Cumulative Survival; CV: Cardiovascular; HF: Heart failure; LVEF: Left ventricular ejection fraction; MERIT-HF: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; NA: Not available; SENIORS: Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors With Heart Failure.

Bodh I Jugdutt. Expert Rev. Cardiovasc. Ther. 8(5), 695–715 (2010)

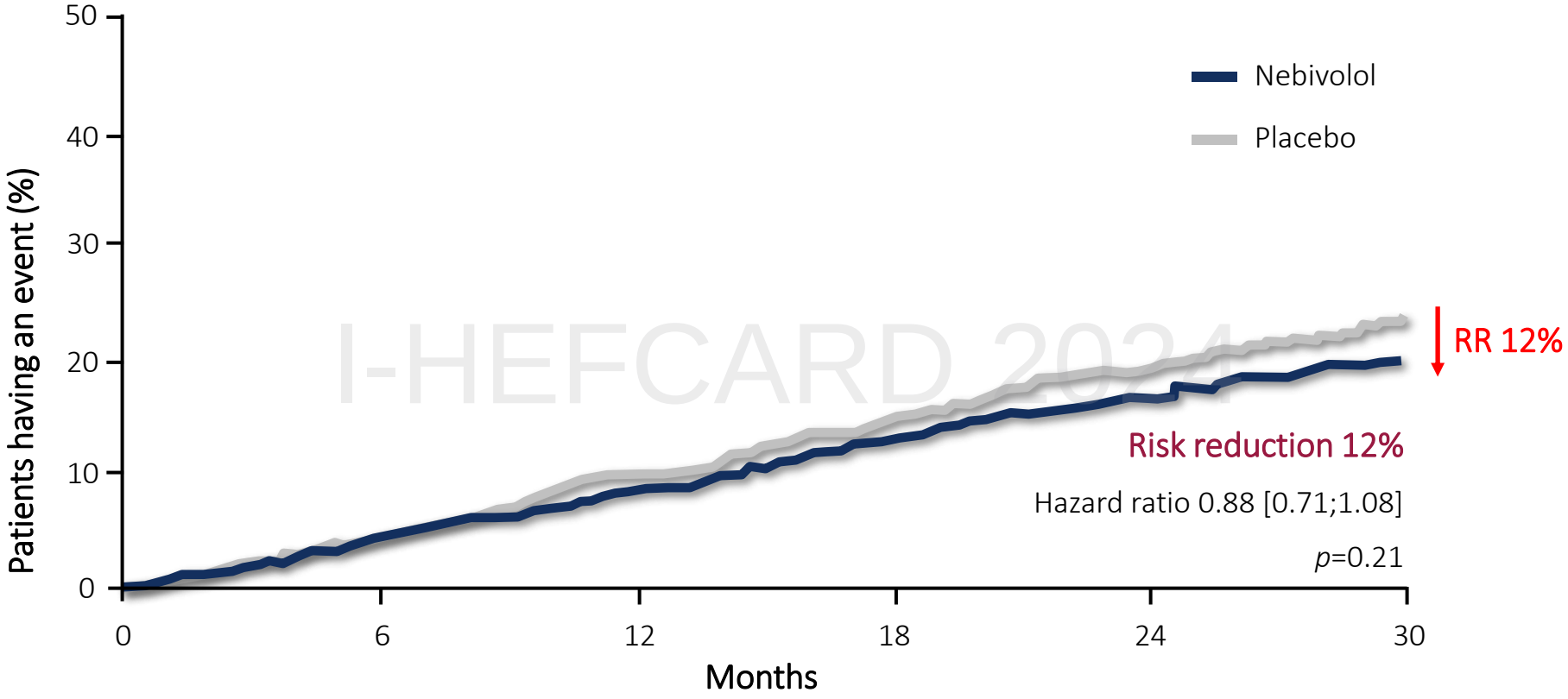
The SENIORS trial – primary endpoint results (combine endpoint of all-cause mortality or cardiovascular hospital admission)



N. of events:
nebivolol 332 (31.1%); placebo 375 (35.3%)

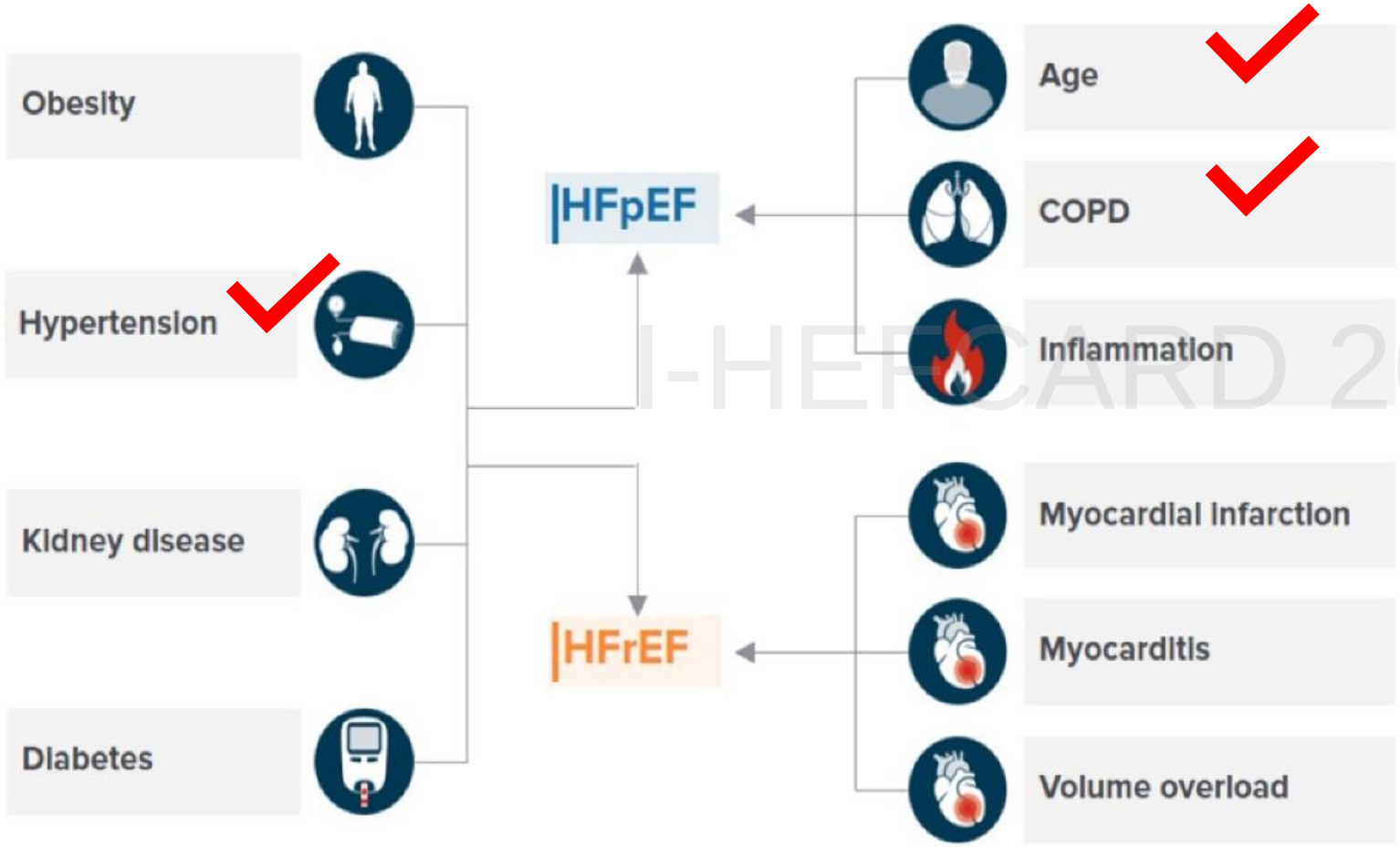
Flather MD, et al. Eur Heart J 2005;26:215-25

The SENIORS trial – secondary endpoint results all-cause mortality



N. of events:
nebivolol 169 (15.8%); placebo 192 (18.1%)

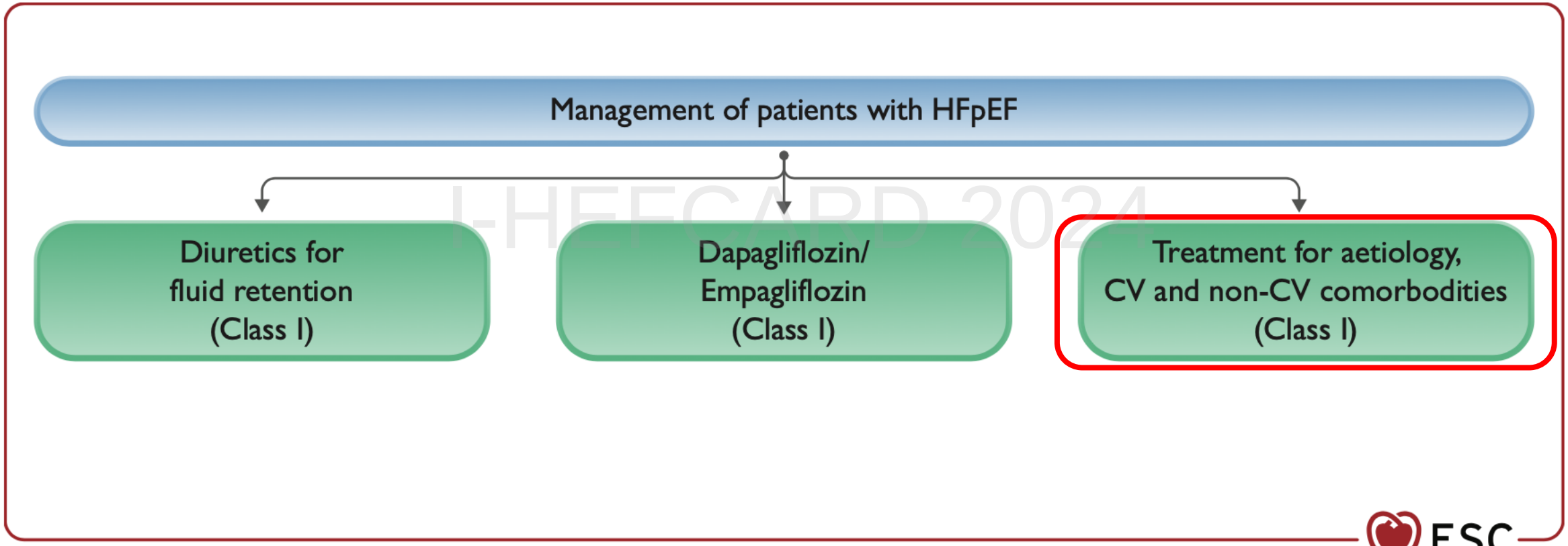
Risk factors and comorbidities : HFrEF vs HFpEF



- HFpEF : older, predominance of women, higher prevalence of non-cardiac comorbidities
- The incidence of hospitalization for comorbidity-related illness in HFpEF > HFrEF

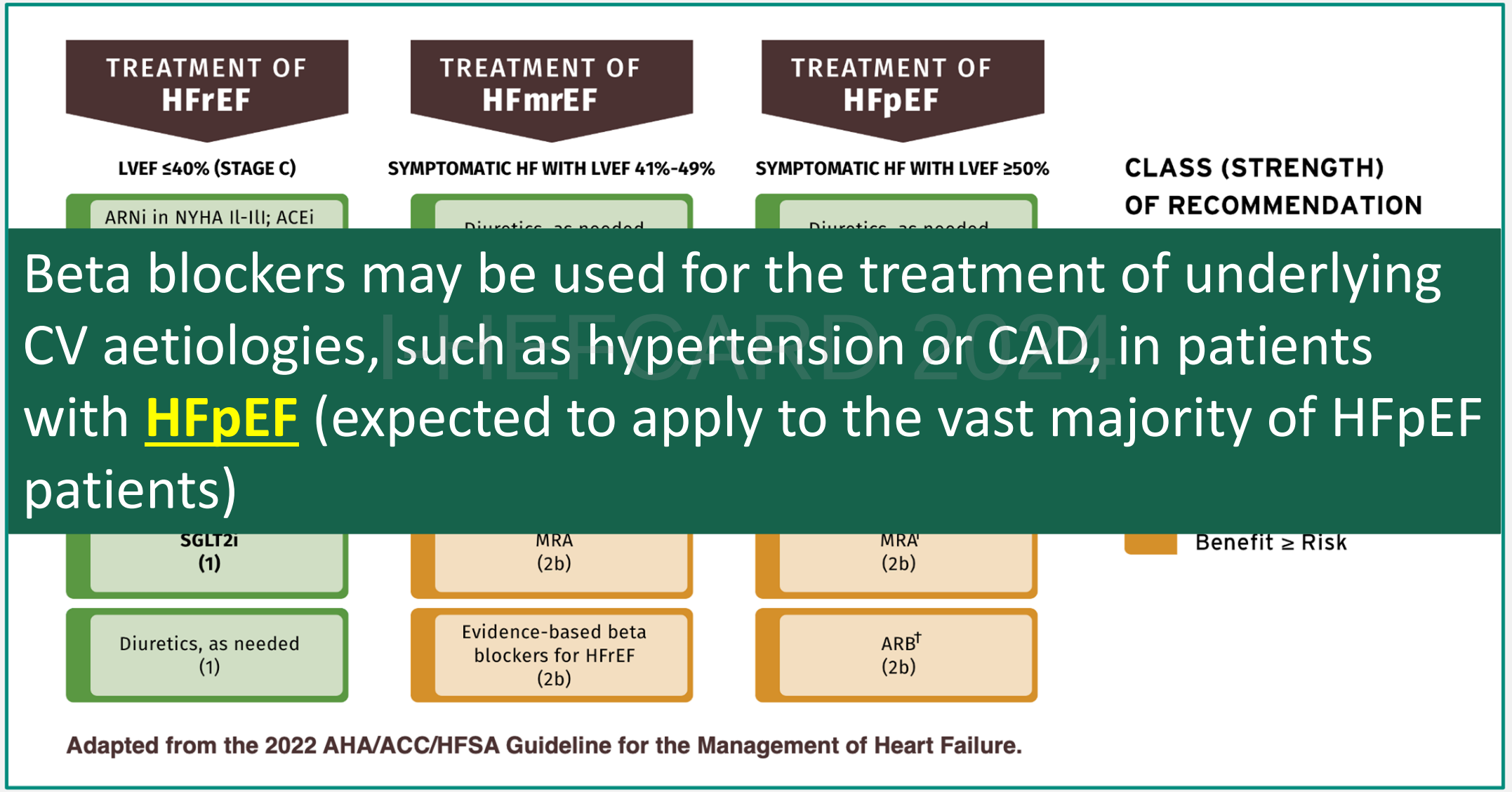
Simmonds SJ et al. Cells. 2020;9:242

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



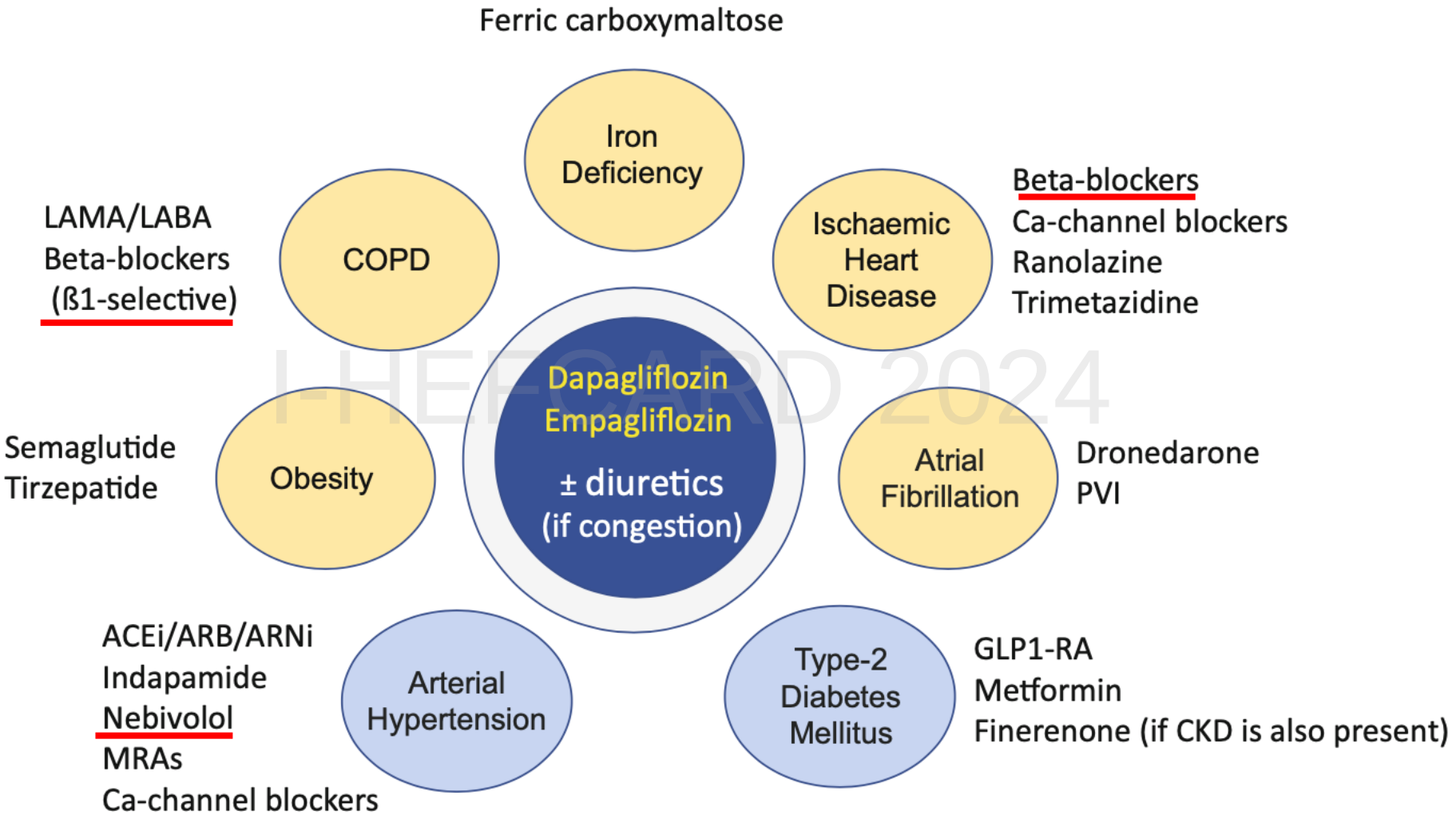
McDonagh TA, et al European Heart Journal (2023) **00**, 1–13

Beta blockers in HFmrEF and HFpEF?



Beta blockers may be used for the treatment of underlying CV aetiologies, such as hypertension or CAD, in patients with **HFpEF** (expected to apply to the vast majority of HFpEF patients)

Patient profiling in HFpEF and consequent therapeutic considerations



Anker SD et al. European Journal of Heart Failure (2023) 25, 936–955

Take home messages

- The simultaneous initiation of class IA medications is warranted at any encounter with HF patients and their up-titration should be implemented according to patient phenotypes
  - Priority is for foundational therapies
  - Take advantage of in-hospital initiation
  - Speed matters, but start any way you think is appropriate
- Clinical profiling
  - to achieve a more comprehensive medical therapy in HFrEF
  - to adjust treatment for specific HFpEF phenotypes
  - to better select patients for devices and interventions
- Nebivolol has higher β1-selectivity, NO-mediated vasodilating properties, and has been shown to significantly reduce death or hospitalization in elderly HF patients

Thank you

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