The 4th Indonesian Symposium on Heart Failure and Cardiometabolic Diseas

Initiating and optimizing beta-blocker to improve outcomes in HFrEF
- Are all beta-blockers the same?

Yogi P. Rachmawan
Indonesia Heart Failure and Cardiometabolic Disease Working Group

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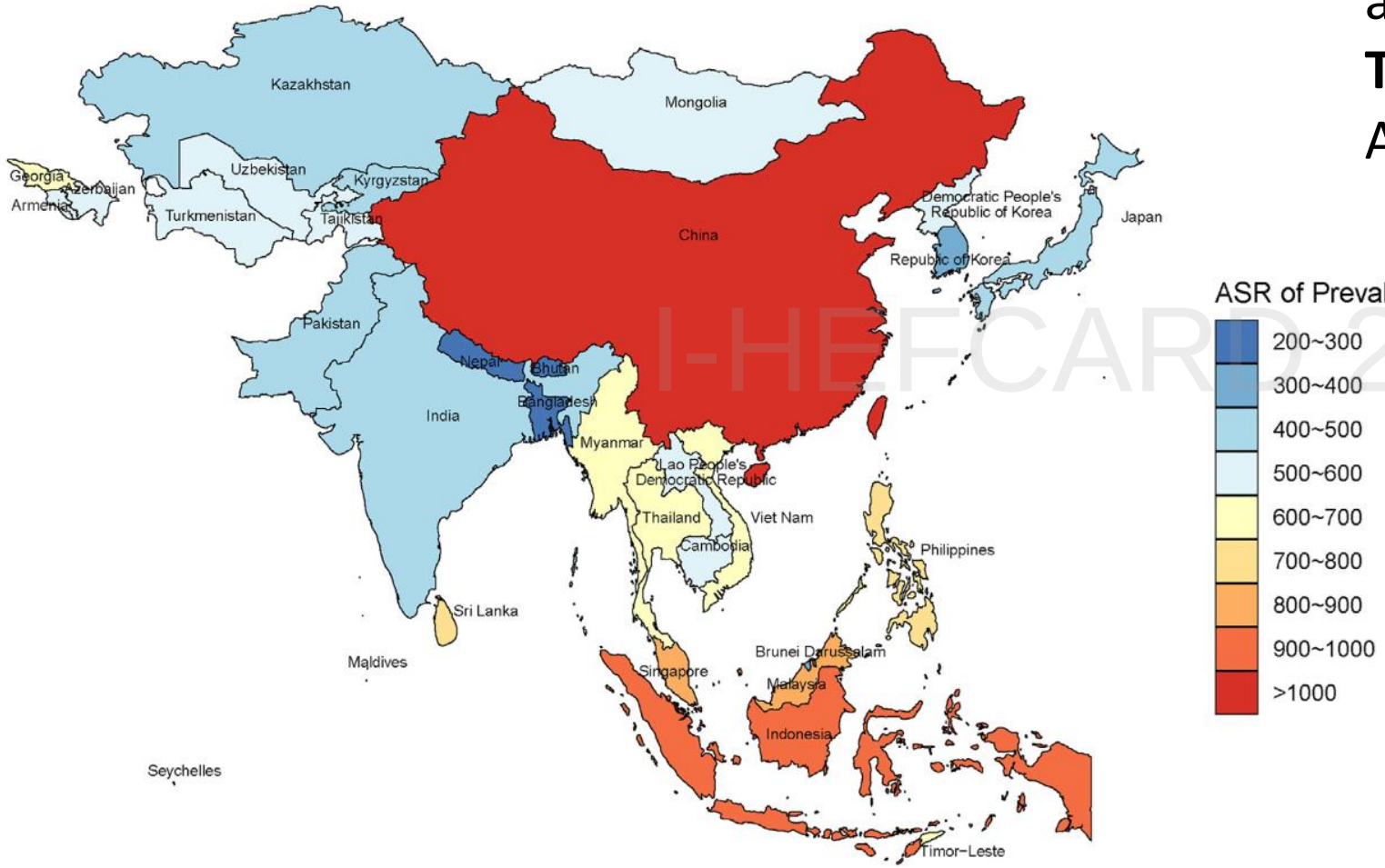
Outline

- Heart Failure in Indonesia
- Prescribing Pattern GDMT in Indonesia
- Beta Blockers Studies
- Initiation and Uptitration
- Conclusions

Age-Standardized Prevalence Rate of Heart Failure in Asia



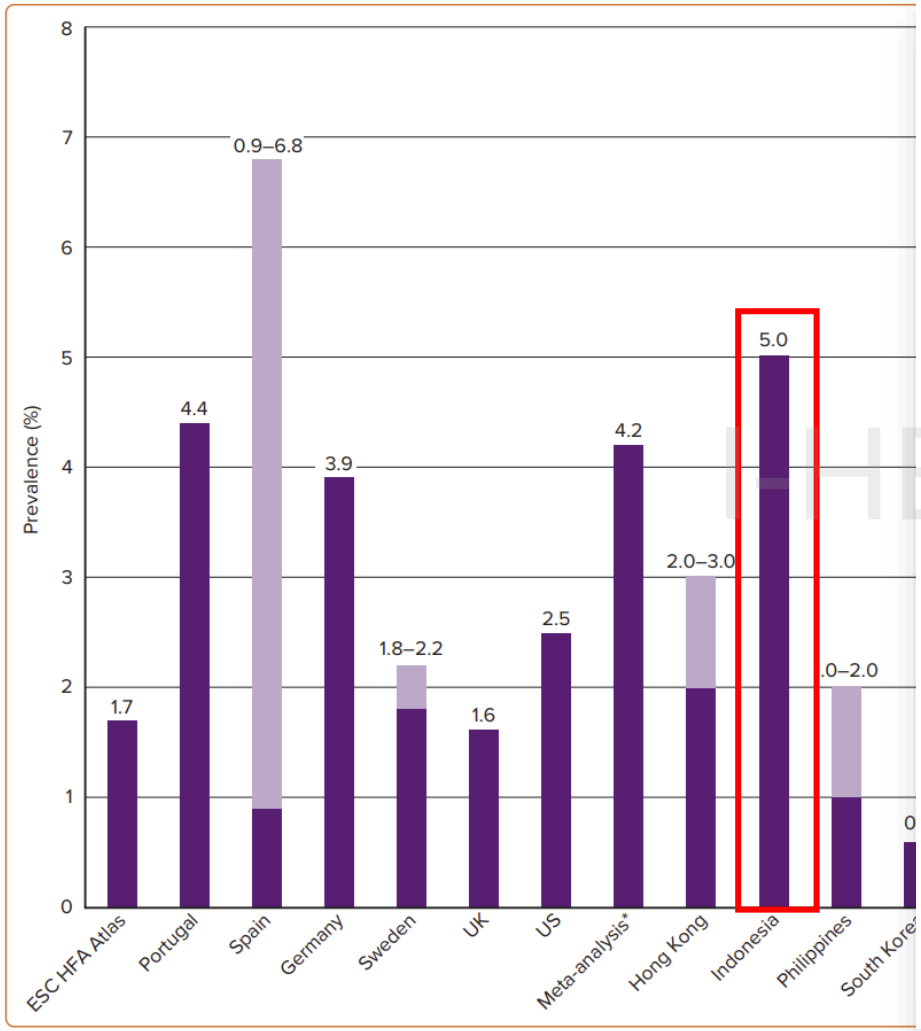
China (1,032.84), **Indonesia (900.90)**, and Malaysia (809.47) are:
The 3 highest nations in terms of ASR for prevalence of HF

Indonesia:
ASR 1990: 835.45
ASR 2019: 900.90

7.83%

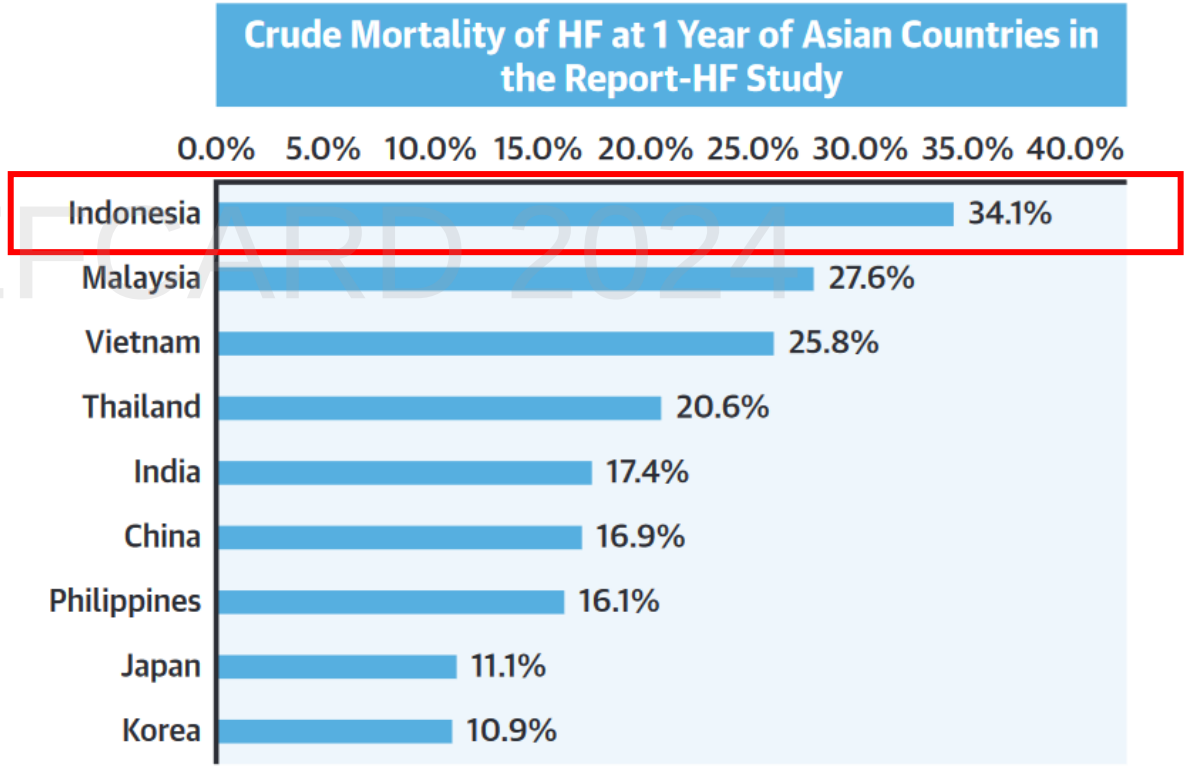
Feng J, et al. JACC: Asia. 2024;4(4):249–264.

Prevalence of Heart Failure Worldwide



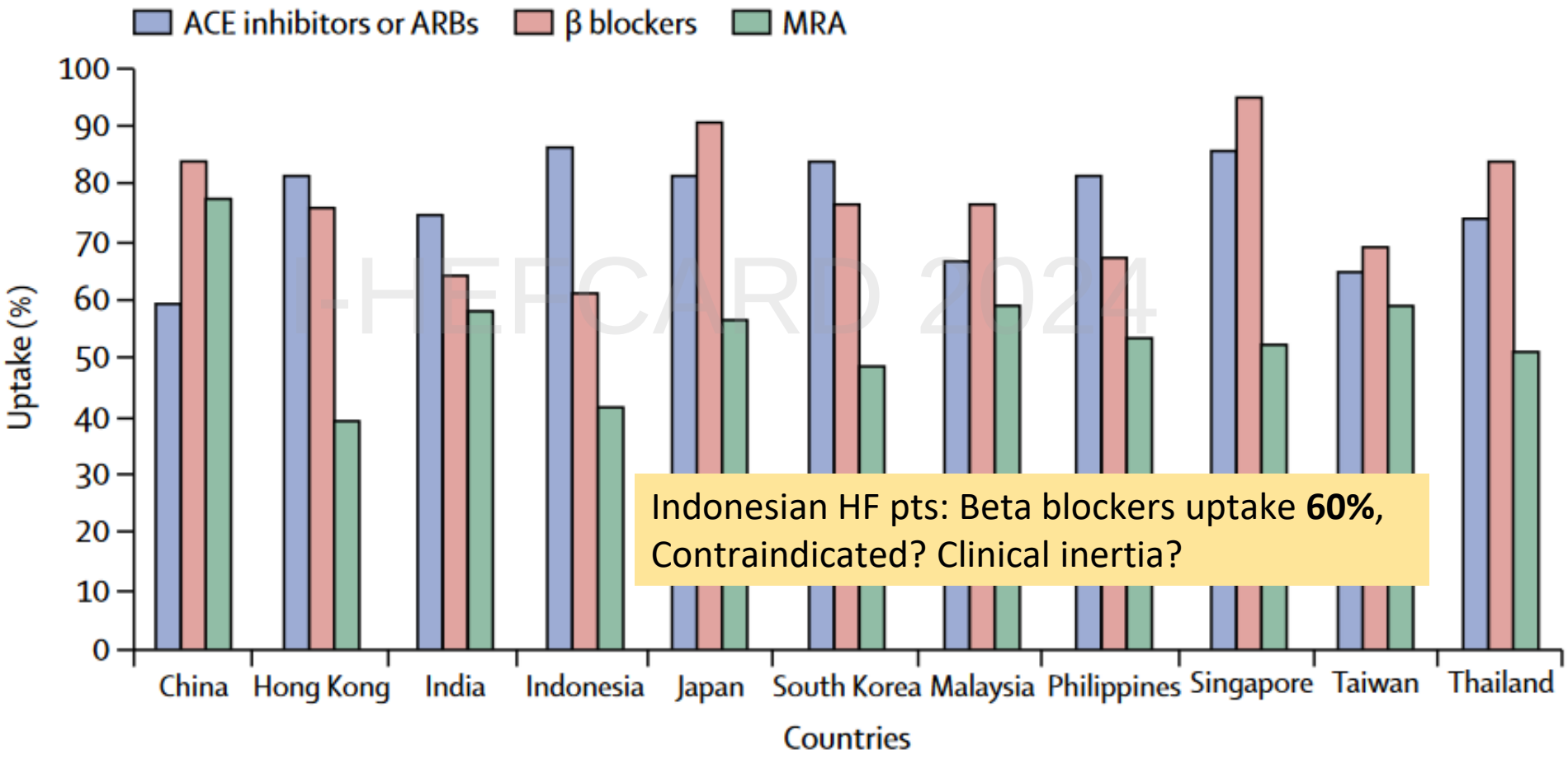
*Meta-analysis of studies from developed countries using echocardiographic case validation. ESC = European Society of Cardiology; HFA = Heart Failure Association.

The 1-Year Mortality of Asian HF Patients Is Still High, Especially in Southeast and South Asia: CV Death is the Primary Cause of Death for HF



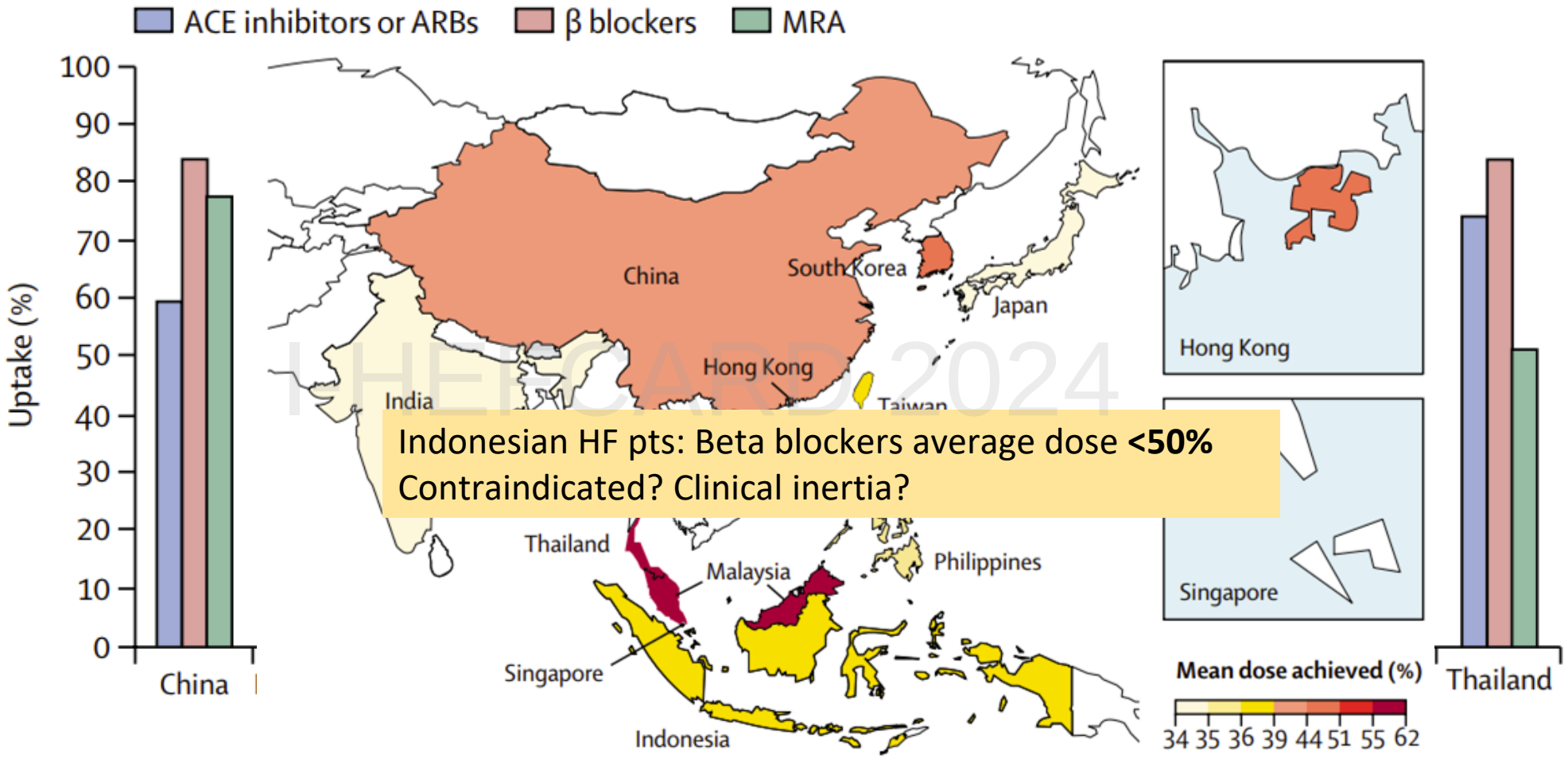
Shahim et al. Cardiac Failure Review 2023;9:e11
Feng J, et al. JACC: Asia. 2024;4(4):249–264.

Regional variation in uptake of GDMT



Indonesian HF pts: Beta blockers uptake **60%**, Contraindicated? Clinical inertia?

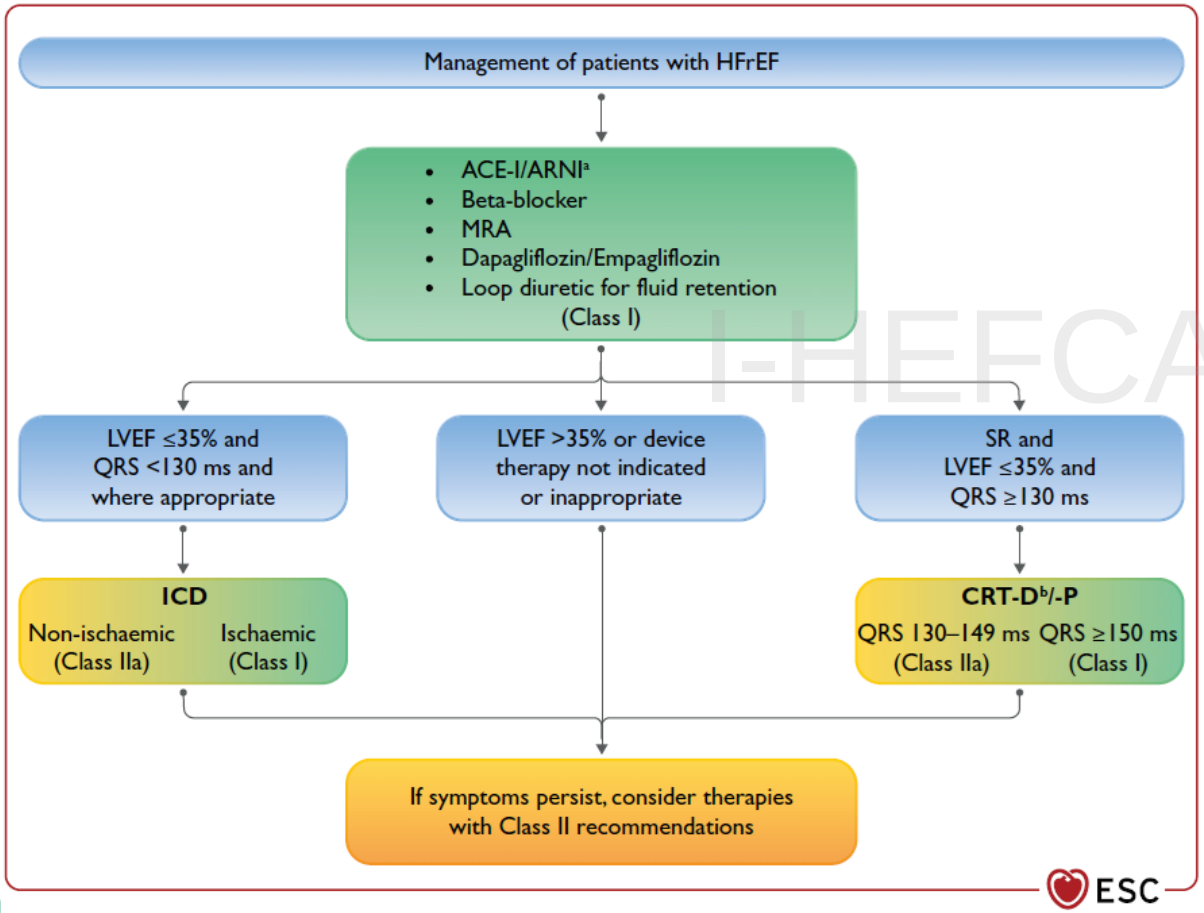
Teng, Tiew-Hwa K et al. The Lancet Global Health. 2018: e1008 - e1018

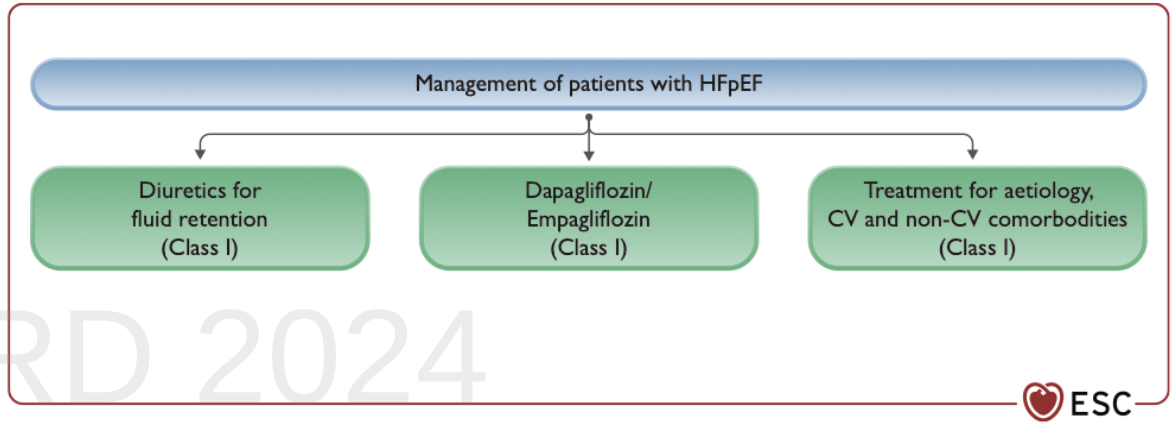


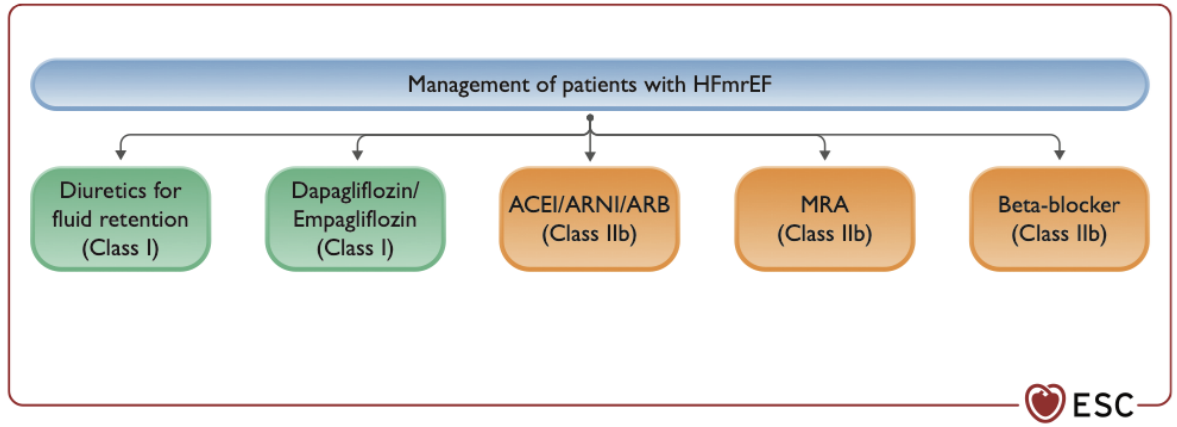
Indonesian HF pts: Beta blockers average dose **<50%**
Contraindicated? Clinical inertia?

Teng, Tiew-Hwa K et al. The Lancet Global Health. 2018: e1008 - e1018

ESC 2021 and 2023 Focused Update Heart Failure Guidelines



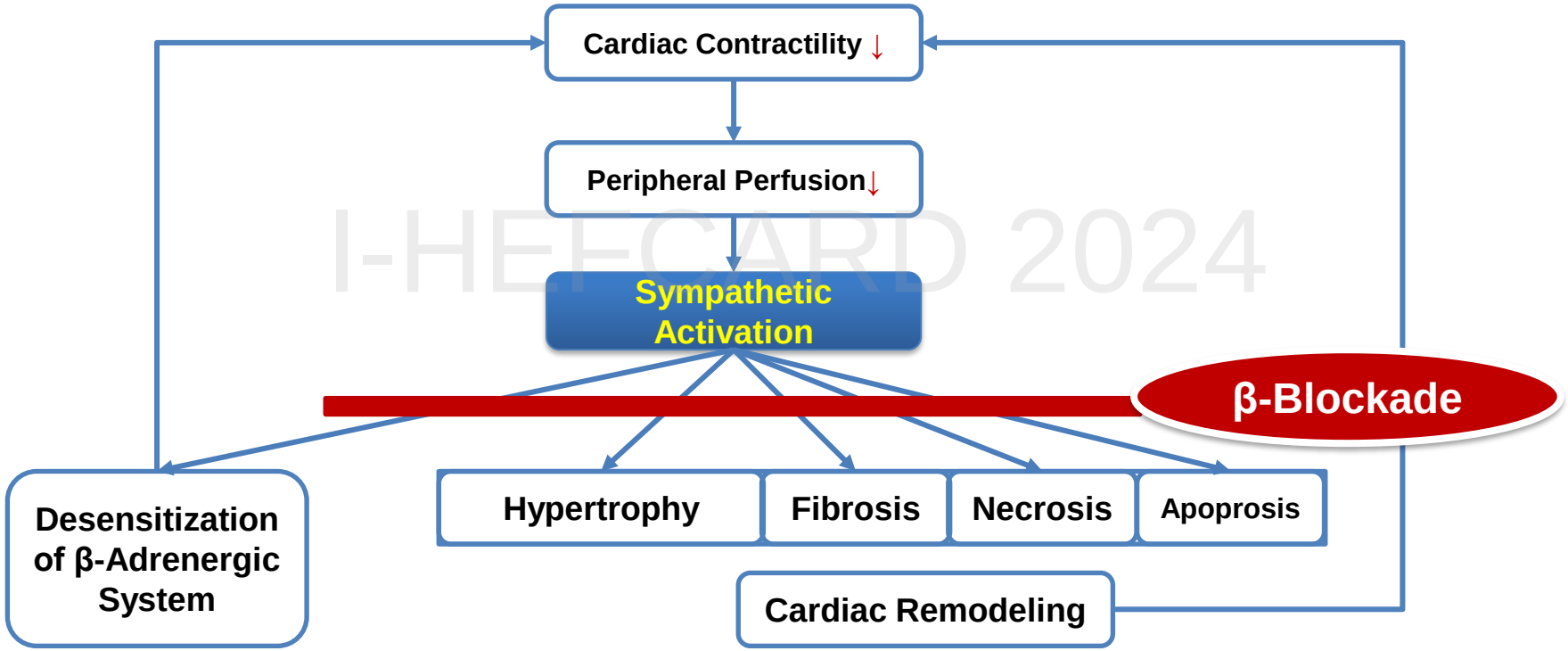




McDonagh TA, et al. European Heart Journal (2023) 00, 1–13

Beta-Blockers Intervene Progressive Deterioration of Cardiac Function by Inhibiting Sympathetic Overactivation

Vicious cycle of sympathetic activation in chronic heart failure
(The goal of pharmacologic intervention by β blockade is to inhibit progressive deterioration of cardiac function)



The compensatory activation of the sympathetic nervous system initiates a vicious cycle with progressive deterioration of cardiac function and heart failure as the final result. Thus, therapeutic intervention of this vicious cycle by inhibiting the effects of sympathetic activation by the application of a β blocker

Maack C, et al. Congest Heart Fail. 2003;9(5):263-70.

Beta Blockers – Landmarks Study

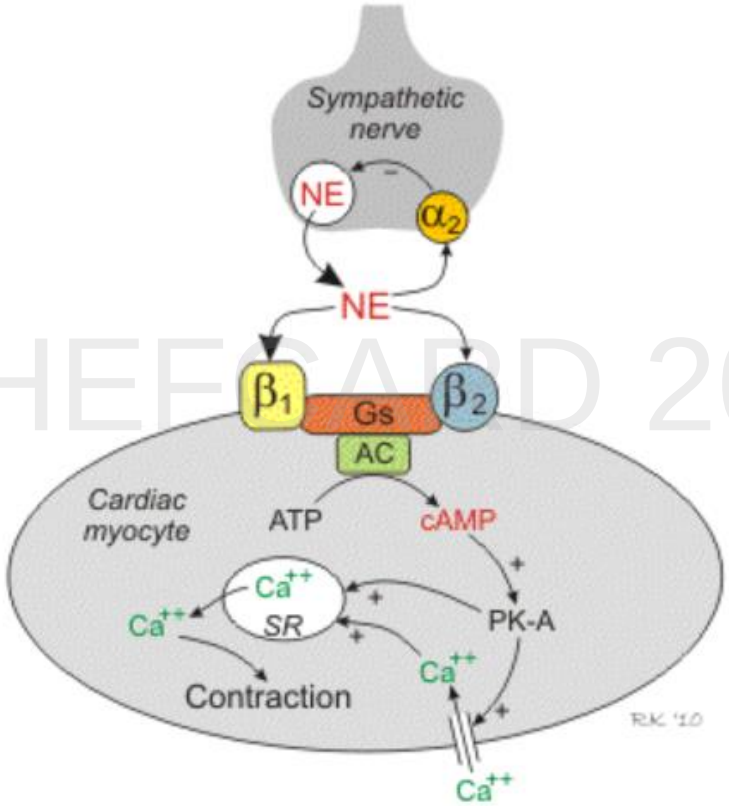
Classification of ß-blockers

Non-Selective

those producing a competitive blockade of both b1- and b2-adrenergic receptors

Non-selective

- **Pindolol**
- **Propanolol**
- **Sotalol**
- **Timolol**



Abbreviations: NE, norepinephrine; Gs, G-stimulatory protein; AC, adenylyl cyclase; PK-A, cAMP-dependent protein kinase; SR, sarcoplasmic reticulum

Selective

those with much higher affinity for the b1 than for the b2 receptors

Selective Beta 1-adrenergic antagonists

- **Atenolol**
- **Bisoprolol**
- **Metoprolol**
- **Nebivolol**

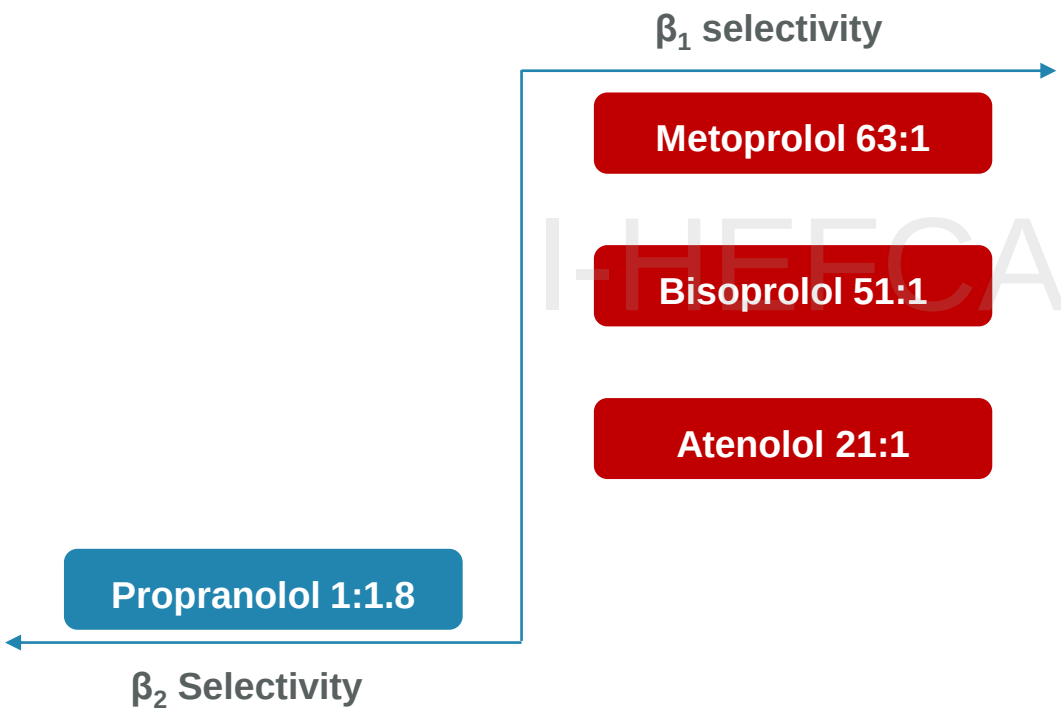
Alpha 1- and ß-adrenergic antagonists

- **Carvedilol**
- **Labetalol**

Sendon JL et al. European Heart Journal. 2004. 25, 1341–1362

Picutre adapted from https://www.cvpharmacology.com/cardioinhibitory/beta-blockers

The β1-Receptor Selectivity: Metoprolol Has a High Degree



- **Metoprolol** has a **higher** β1 selectivity[1,2] in selective β1-blockers
- Metoprolol, a high selective β-blocker, **has little effect on glucose and lipid metabolism and airway**[3]

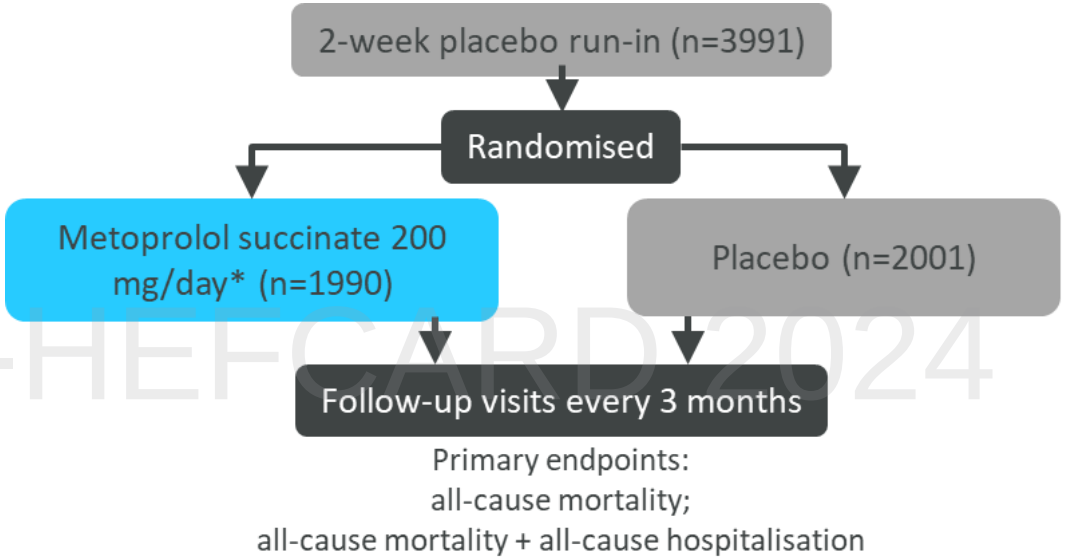
1. Hoffmann C et al. Arch Pharmacol. 2004;369:151-159.
2. Smith C et al. Cardiovascular Durgs and Therapy 1999;13:123-126
3. 2009 Expert consensus on beta adrenergic receptor blocker in cardiovascular diseases

Beta Blockers Major Clinical Trials in HFrEF[1]

Trial	Drug	Major Inclusion Criteria	Mean follow-up (years)	Impact of treatment on primary endpoint	Other results
COPERNICUS[2]	**Carvedilol** (n=1156) vs placebo (n=1133)	LVEF < 25%, NYHA IV	0.9	**All-cause mortality** reduced by 35% (11% vs 17%) (p<0.001)	Reduction in combined all-cause mortality and any hospitalization rate by 24% (p<0.001)
CIBIS-II[3]	**Bisoprolol** (n=1327) vs placebo (n=1320)	LVEF ≤ 35%, NYHA III-IV	1.3	**All-cause mortality** reduced by 34% (12% vs 17%) (p<0.001)	Reduction in combined CV mortality or CV hospitalization rate by 21% (p<0.001)
MERIT-HF[4]	**Metoprolol CR/XL** (n=1991) vs placebo (n=2001)	LVEF ≤ 40%, NYHA II-IV	1.0	**All-cause mortality** reduced by 34% (7% vs 11%) (p<0.001)	Reduction in the risk of **CV death** by 38% (p<0.001), **sudden death** by 41% (p<0.001) and **death from aggravated HF** by 49% (p=0.002)
SENIORS[5]	**Nebivolol** (n=1067) vs. placebo (n=1061)	Age ≥70y, HF confirmed as hospitalization in recent 12 months and/or LVEF≤35% in recent 6 months	1.8	Combined all-cause mortality and CV hospitalization rate reduced by 14% (31% vs 35%, p=0.04)	-

1. McDonagh TA, et al. Eur Heart J. 2021;42(36):3599-726
2. Packer M, et al. N Engl J Med. 2001;344:1651-58
3. CIBIS-II Investigators and Committees. Lancet. 1999;353:9-13
4. MERIT-HF Study Group. Lancet. 1999; 353:2001-7
5. Flather MD, et al. Eur Heart J. 2005;26:215-225

MERIT-HF Trial Design

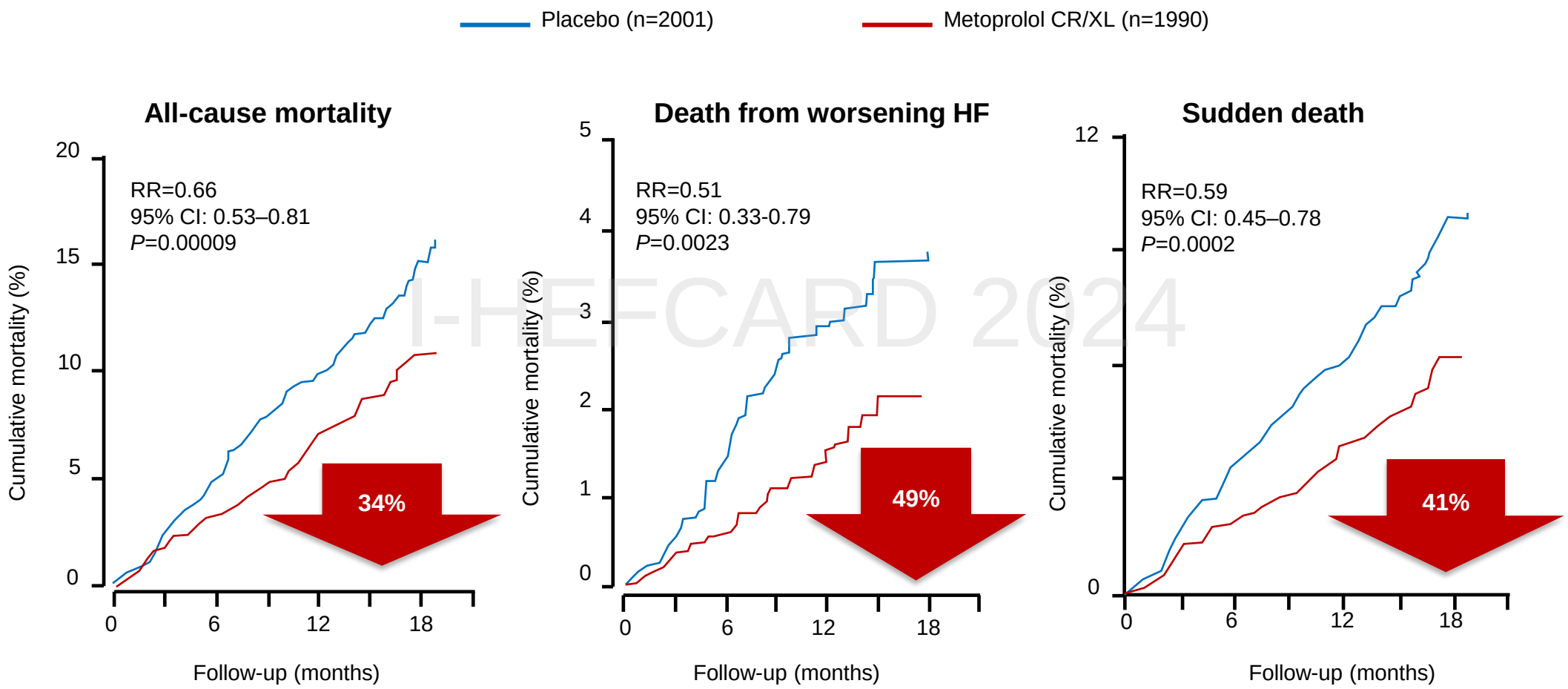


*Initial dose of 12.5 or 25 mg/day, increased gradually every 2 weeks to maximum dose of 200 mg/day

The intended duration of the trial was 3 years but it was stopped early at the request of the Independent Safety Monitoring Committee due to a significant reduction in all-cause mortality in the Metoprolol Succinate treatment arm (based on pre-defined criteria). Mean follow-up time was 1 year at which time 3980 patient-years had been accumulated.

MERIF-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HFLancet 1999;353:2001-2007

MERIT-HF: Metoprolol Succinate (CR/XL) Significantly Reduced All-Cause Mortality, Death from Worsening HF and Sudden Death

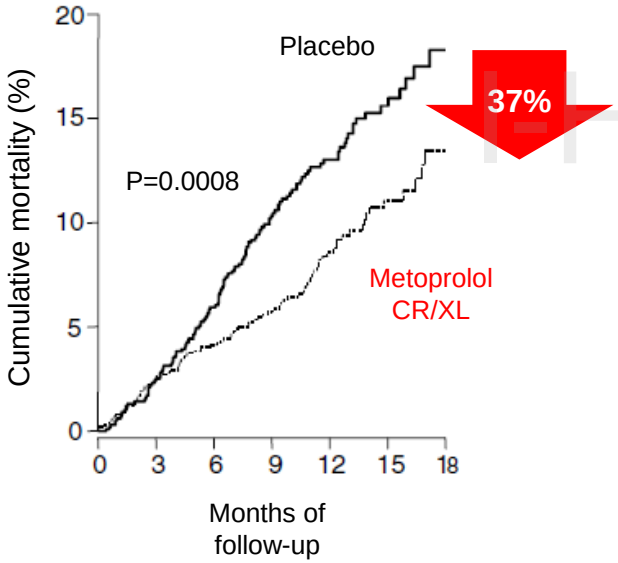


MERIF-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HFLancet 1999;353:2001-2007

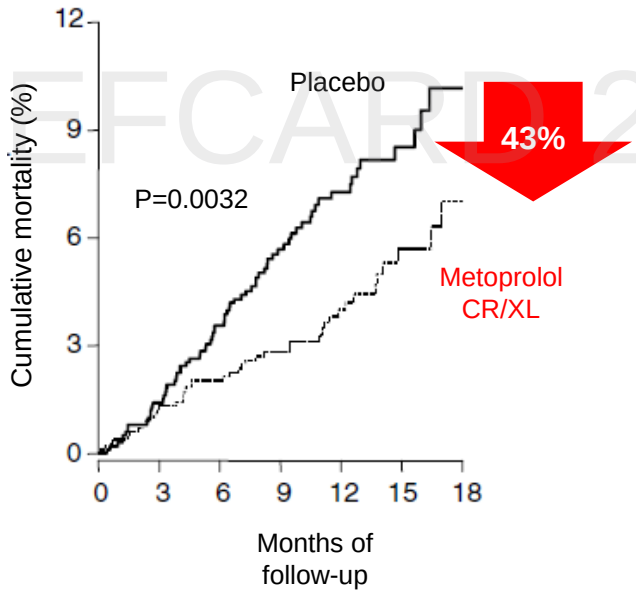
Analysis of the Elderly Subgroup in MERIT-HF Study

Metoprolol Succinate Reduced All-Cause Mortality, Sudden Death, and Death Due to Worsening HF in Elderly Patients (≥ 65 Years of Age) with HFrEF

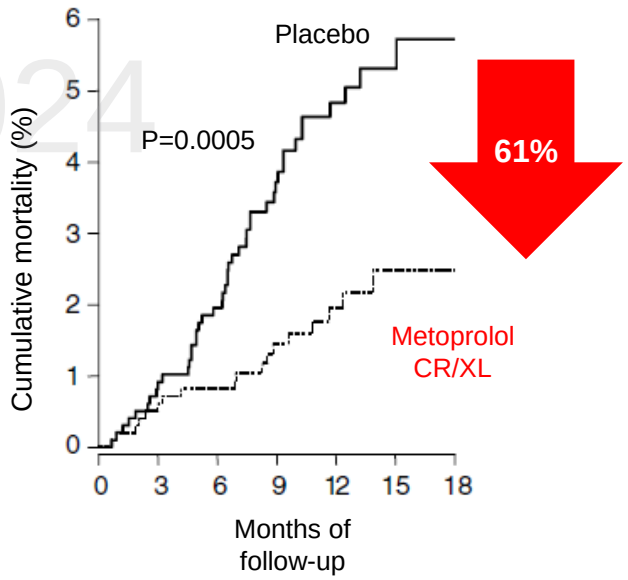
All-cause mortality



Sudden death



Death from worsening HF



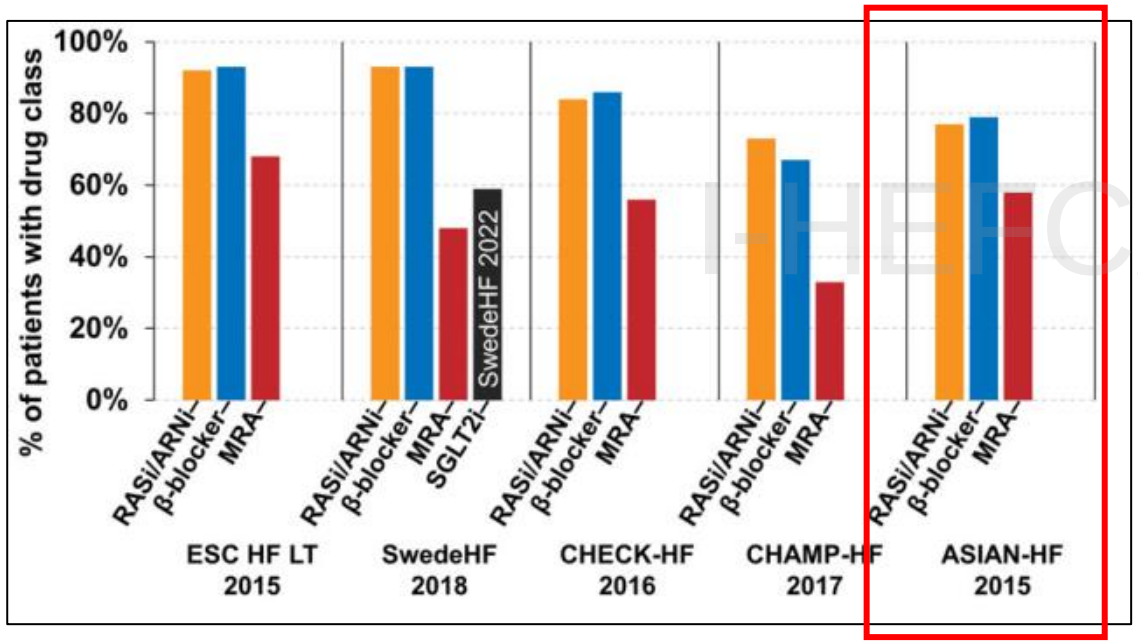
Analysis of the elderly subgroup in MERIT-HF Study: subjects to be analyzed were 1,982 patients aged ≥ 65 years with CHF who have NYHA class II–IV and EF ≤ 0.40 at the time of randomization in MERIT-HF study. Among them, 992 patients received placebo and 990 patients received metoprolol-controlled release/extended-release tablets (CR/XL). The Cox proportional hazards model was used to calculate hazard ratios (HR) and 95% confidence intervals (CI). This analysis was to study the efficacy and tolerability of BBs in elderly patients with HF in the MERIT-HF Study

Deedwania PC, et al. Eur Heart J. 2004;25(15):1300-9

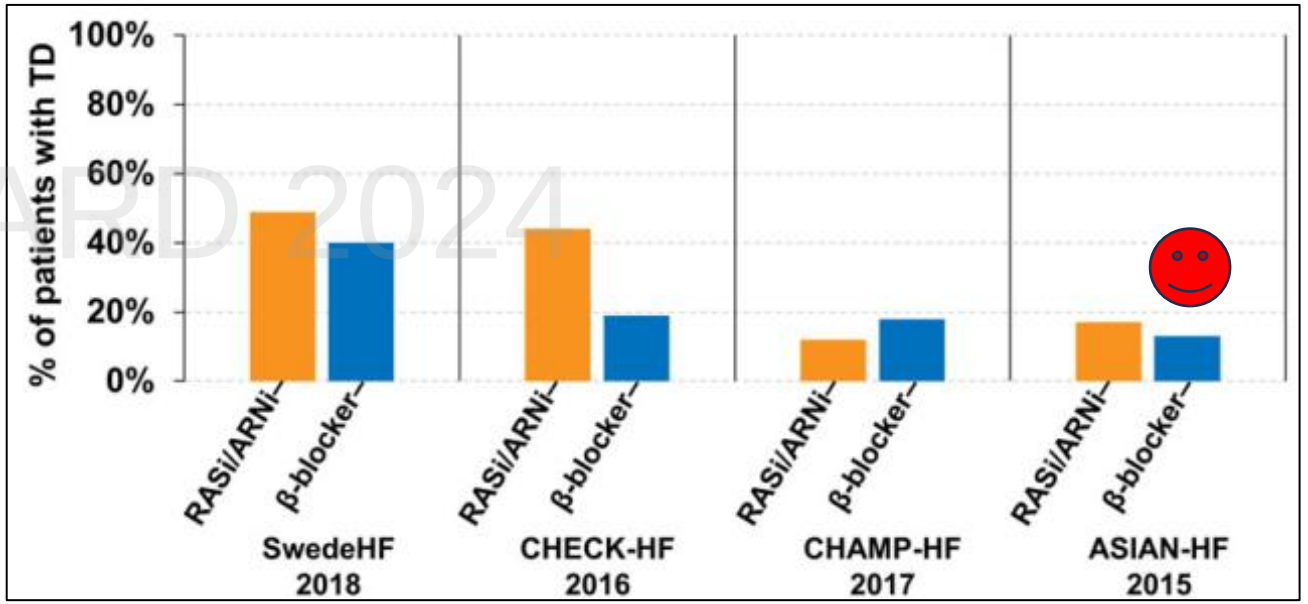
Initiation and Uptitration of Beta Blockers

Status of guideline-directed medical therapy (GDMT) implementation in major national and multi-national registries

Use of HFrEF GDMT drug classes



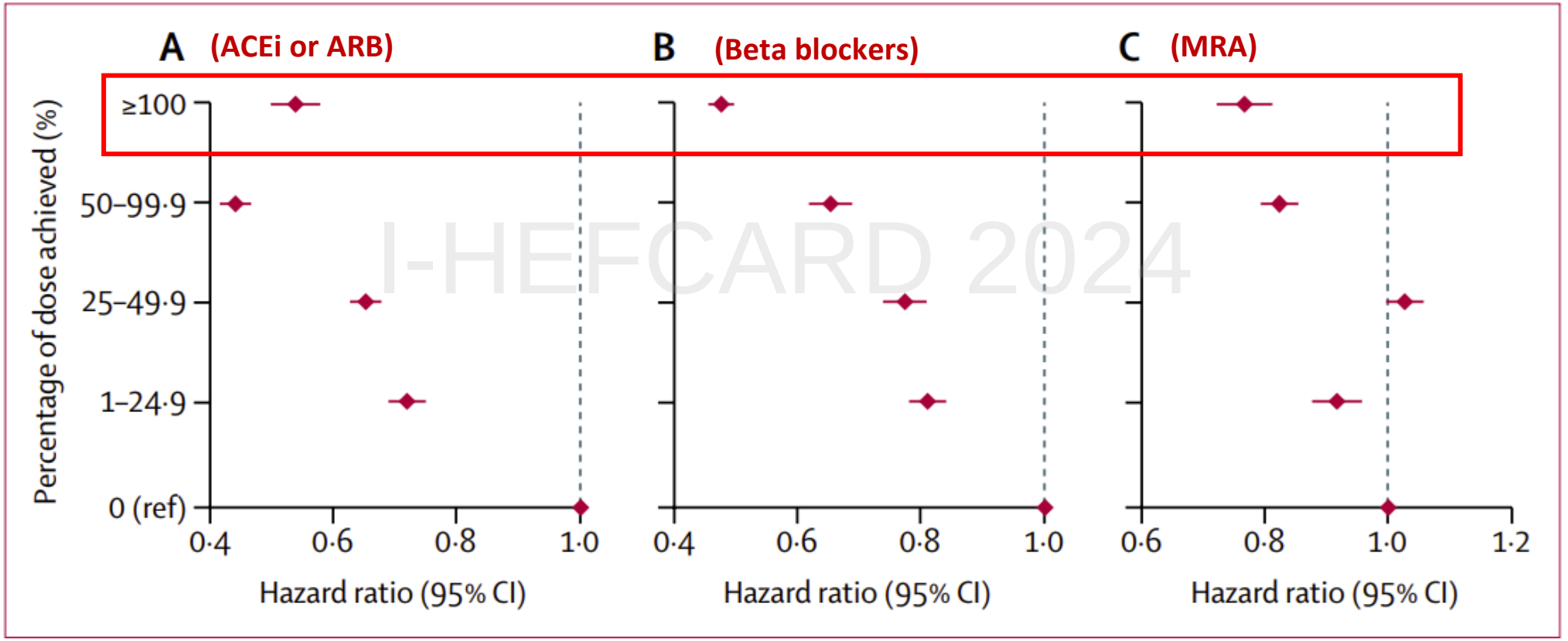
Target dose (TD) achievement



G. Savarese *et al*. European Journal of Heart Failure. 2024

Why dose is important?

Association of doses achieved with 1-year composite outcome of all-cause deaths or hospitalization for heart failure



Teng, Tiew-Hwa K et al. The Lancet Global Health. 2018: e1008 - e1018

What is optimal treatment for HFrEF?

ESC European Society of Cardiology
European Journal of Heart Failure (2020) 22, 2175–2186
doi:10.1002/ejhf.2018
POSITION PAPER

Standardized definitions for evaluation of heart failure therapies: scientific expert panel from the Heart Failure Collaboratory and Academic Research Consortium

SCORING

- Beta blocker
  - None : 0
  - <50% max dose : 1
  - ≥50% max dose : 2
- ACE-I or ARB
  - None : 0
  - <50% max dose : 1
  - ≥50% max dose : 2
- Sacubitril/valsartan
  - None : 0
  - Any dose : 2
- MRA
  - None : 0
  - Any dose : 1
- Hydralazine and ISDN
  - None : 0
  - Any dose : 1

OPTIMAL MEDICAL THERAPY SCORE

- Sub-optimal
  - Score < 3, or
  - No HF specific beta blocker or no ACE-I, ARB, or ARNI, without documented intolerance to these agents
- Acceptable
  - Score 3-4 if
  - Treated with HF specific beta blocker and ACE-I, ARB, or ARNI, unless pts has documented intolerance to these agents
- Optimal
  - Score > 5 if
  - Treated with HF specific beta blocker and ACE-I, ARB, or ARNI, unless pts has documented intolerance to these agents

Abraham WT, et al. Eur J Heart Fail. 2020;22(12):2175–86.

Blood pressure (BP) – including orthostatic BP (postural drop):[11,13] Review 1–2 weeks after each medicine initiation / each medicine dose increase[1,7]

ADVERSE EFFECTS	ACTIONS[a]		
	ACEI / ARB / ARNI	HEART FAILURE BETA BLOCKER	MRA
Asymptomatic hypotension[7,11]	Continue therapy	Continue therapy	Continue therapy
Symptomatic hypotension eg dizziness, light-headedness and/or confusion[1,7,11]	1. Assess volume status, consider reducing or stopping diuretic if there are no signs or symptoms of congestion 2. Review other medicines that can reduce blood pressure (eg calcium channel blockers, nitrates, diuretics) 3. If still symptomatic: a. temporarily decrease dose of either ACEI/ARB, ARNI or heart failure beta blocker b. review patient within 1 week and if still symptomatic continue dose reduction (or cease) and seek specialist advice		Continue therapy Only consider decreasing dose if, after implementing actions for ACEI/ARB/ARNI and/ or heart failure beta blocker to address symptomatic hypotension, the patient is still symptomatic.
Severe symptomatic hypotension / cardiogenic shock eg cold and sweaty skin, dyspnoea, blue skin tone or weak and rapid pulse[1,11,12]	Immediate referral to an emergency department		

[a] Diuretic dose may be reduced at any time if euvolaemic (unless this has previously exacerbated symptoms)

Largely based on the Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018

Heart rate: Review 1–2 weeks after each medicine initiation / each medicine dose increase[1,7]

ADVERSE EFFECTS	ACTIONS[a]		
	HEART FAILURE BETA BLOCKER	ACEI / ARB / ARNI	MRA
Asymptomatic bradycardia (50–60 bpm)[1,14,15]	Continue therapy	Continue therapy	Continue therapy
Symptomatic bradycardia (< 50 bpm) eg marked fatigue, dizziness light-headedness[1,11,14]	1. Arrange ECG to document rhythm 2. Review need for other medicines that can lower heart rate (eg digoxin, amiodarone) 3. If above not successful, may need to decrease dose and seek specialist advice	Continue therapy	Continue therapy

[a] Diuretic dose may be reduced at any time if euvolaemic (unless this has previously exacerbated symptoms)

Largely based on the Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018

Renal function: Review 1–2 weeks after each medicine initiation / each medicine dose increase[1,7]

RESULTS / ADVERSE EFFECTS	ACTIONS[a]		
	MRA	ACEI / ARB / ARNI	HEART FAILURE BETA BLOCKER
eGFR decrease ≤ 30%[7]	Continue therapy	Continue therapy	Continue therapy
eGFR decrease > 30%[1,7,11]	1. Assess volume status 2. Review need for other medicines that impact on renal function (eg NSAIDs, diuretics) 3. If above not successful:		Continue therapy
	• for MRA; decrease dose	• for ACEI/ARB/ARNI; may need to: a. decrease (or stop) dose b. seek specialist advice	
Hyperkalaemia Serum K+ (potassium) > 5.5 mmol/L[1,7]	1. Assess volume status 2. Review need for other medicines that impact on serum K+ (eg potassium supplements) 3. If above not successful:		Continue therapy
	• for MRA; decrease dose	• for ACEI/ARB/ARNI; may need to: a. decrease (or stop) dose b. seek specialist advice	
Hyperkalaemia serum K+ (potassium) > 6.0 mmol/L[1,7]	• for MRA, stop and seek specialist advice	• for ACEI/ARB/ARNI follow above steps 1, 2, 3	
Creatinine increase ≤ 30%[1]	Continue therapy	Continue therapy	Continue therapy

[a] Diuretic dose may be reduced at any time if euvolaemic (unless this has previously exacerbated symptoms)

Largely based on the Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018

Volume status: Review 1–2 weeks after each medicine initiation / each medicine dose increase[1,14]

ADVERSE EFFECTS	ACTIONS			
	DIURETIC	HEART FAILURE BETA BLOCKER	ACEI / ARB / ARNI	MRA
Congestion (fluid overload, wet) Signs and symptoms include: dyspnoea, peripheral/sacral oedema, increased jugular venous pressure, weight gain; ≥ 2 kg over 2 days[1,16,17]	If not on a diuretic; start at low dose (eg furosemide 20–40 mg daily) and adjust according to clinical response If on a diuretic; increase dose by 50%–100% with goal of reducing weight by 0.5–1 kg a day If weight continues to increase, seek specialist advice	If increasing congestion, consider: **a.** decreasing dose, or **b.** temporarily stopping if recently started	Continue therapy	Continue therapy
Dehydration (over-diuresis, dry) Signs and symptoms include: weight loss; ≥ 2 kg over 2 days, dizziness, thirst, fatigue, reduced urine output, increased urine concentration, orthostatic BP (postural drop)[1,16,17]	If on a diuretic; decrease dose (eg furosemide, reduce by 40 mg) until weight returns to baseline If weight continues to decrease, seek specialist advice	Continue therapy Closely monitor symptoms Review renal function	Continue therapy Closely monitor symptoms Review renal function	Continue therapy Closely monitor symptoms Review renal function

Largely based on the Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018

Guidance for managing miscellaneous adverse effects

CLINICAL INDICATOR	ADVERSE EFFECTS	ACTIONS		
		ACEI / ARB / ARNI	HEART FAILURE BETA BLOCKER	MRA
Respiratory As part of clinical review after medicine initiation and each dose up-titration	**Cough** dry, non-productive, interfering with quality of life[1]	May change ACEI to ARB	Continue therapy	Continue therapy
Allergic reactions As part of clinical review at each dose increase	**Angioedema**[1]	Manage the angioedema, stop ACEI , ARB or ARNI and seek specialist advice	Continue therapy	Continue therapy

Largely based on the Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018

Take home messages

- **Sympathetic Activation** Closely Related to the Development and **Progression of HF**
- **Beta-Blockers** Intervene Progressive Deterioration of Cardiac Function by **Inhibiting Sympathetic Overactivation**, So As to Treat Heart Failure
- In patients with HFrEF, with current or previous symptoms (stage C), **beta blockers (Metoprolol Succinate)** is recommended to **reduce mortality and hospitalizations**
- **Metoprolol succinate** in MERIT-HF trial **reduced all-cause mortality**, **death from worsening HF**, and **sudden death** in heart failure with reduced ejection fraction (LVEF < 40%) NYHA class II-IV
- Close monitoring on beta blockers **initiation and optimization is important**, but **clinical innersia** will make HFrEF patients fall into a **worse condition** and the target of reducing mortality according to the landmark study will not be achieved