5th IHEF CARD
The 5th Indonesian Symposium on Heart Failure and Cardiometabolic Disease

in conjunction with :
WHFS25
World Heart Failure Society Congress 2025

Beta Blocker Unlashed :

Why Target Dosing is The Key to Transforming Chronic Heart Failure Outcome

Wahyu Aditya, MD

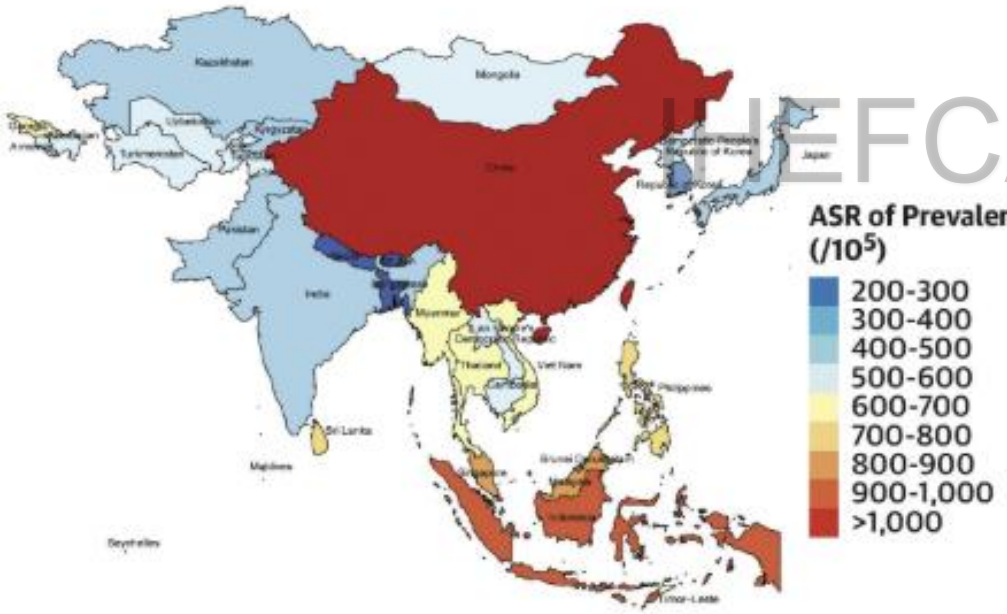
OUTLINES

1. Why beta blocker is important for HF?
2. What's the target dose of beta blocker and target heart rate in HF?
3. Which HF patients are eligible/not eligible for beta blockers?
4. Atrial Fibrillation in HF

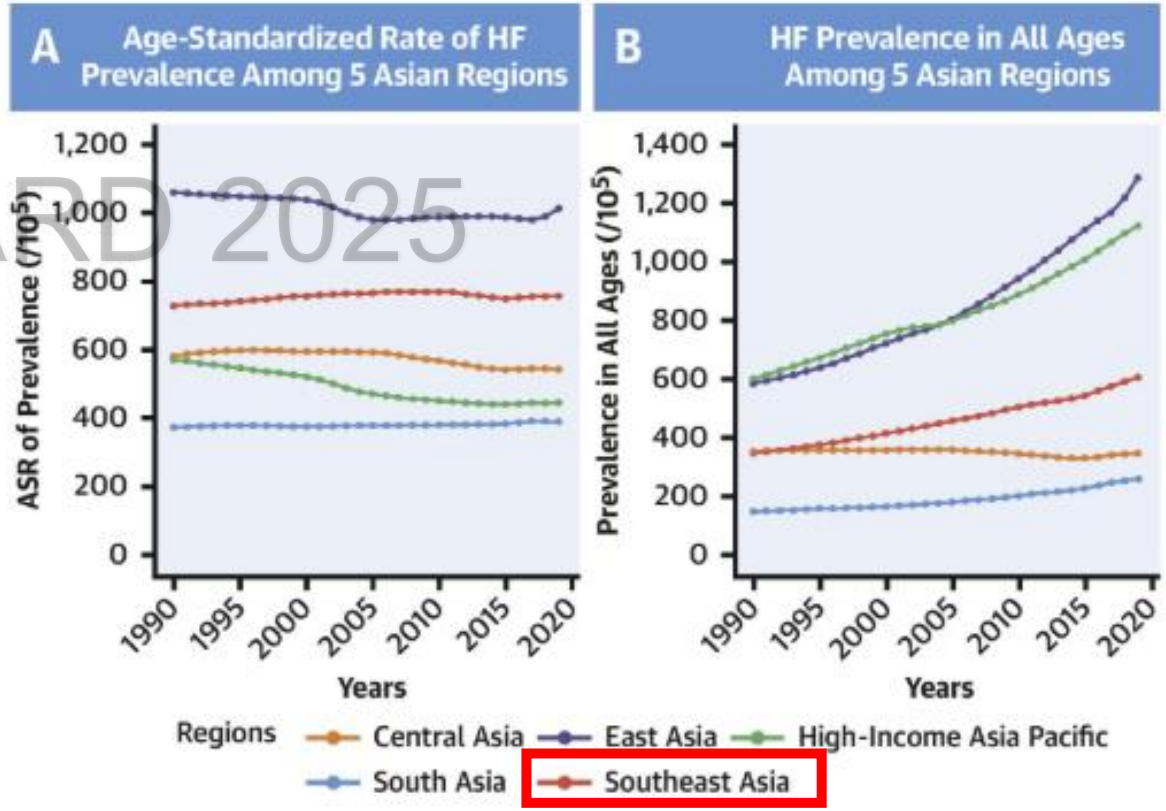
1. Why beta blocker is important for HF?

Epidemiology and Burden of Heart Failure in Asia

The Prevalence of HF in Asia is High: China, Indonesia, and Malaysia Are the 3 Highest Nations in Terms of Age-Standardized Prevalence



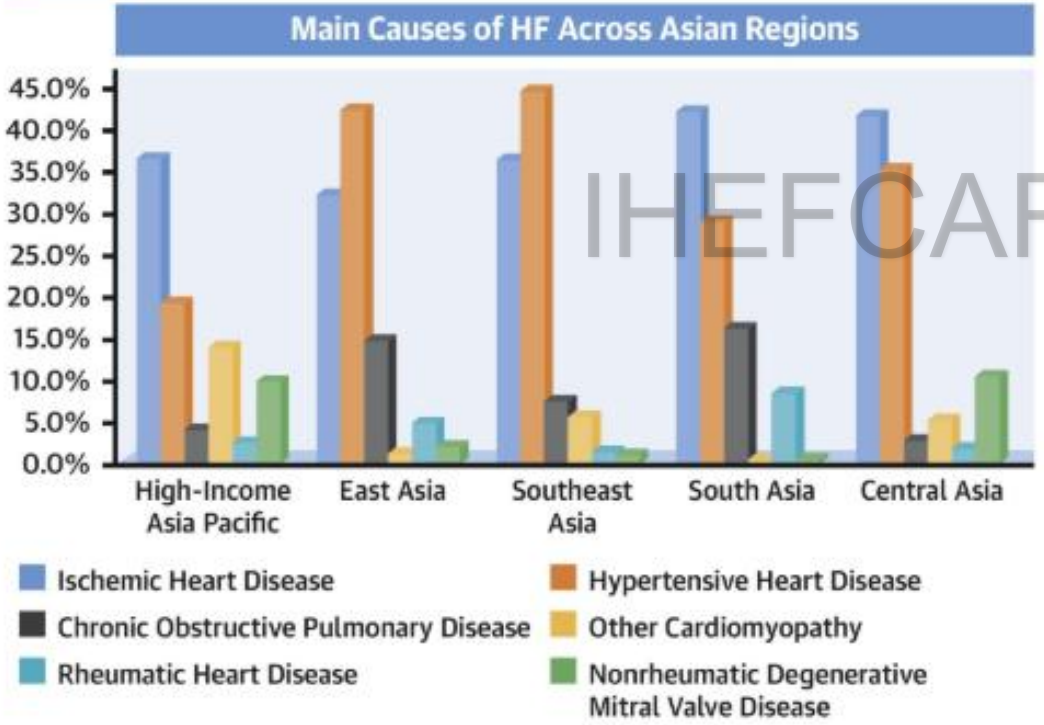
The Absolute Numbers of HF Prevalence Increased in Asia: The Age-Standardized Prevalence of HF Were Only Increased in Southeast Asia and South Asia



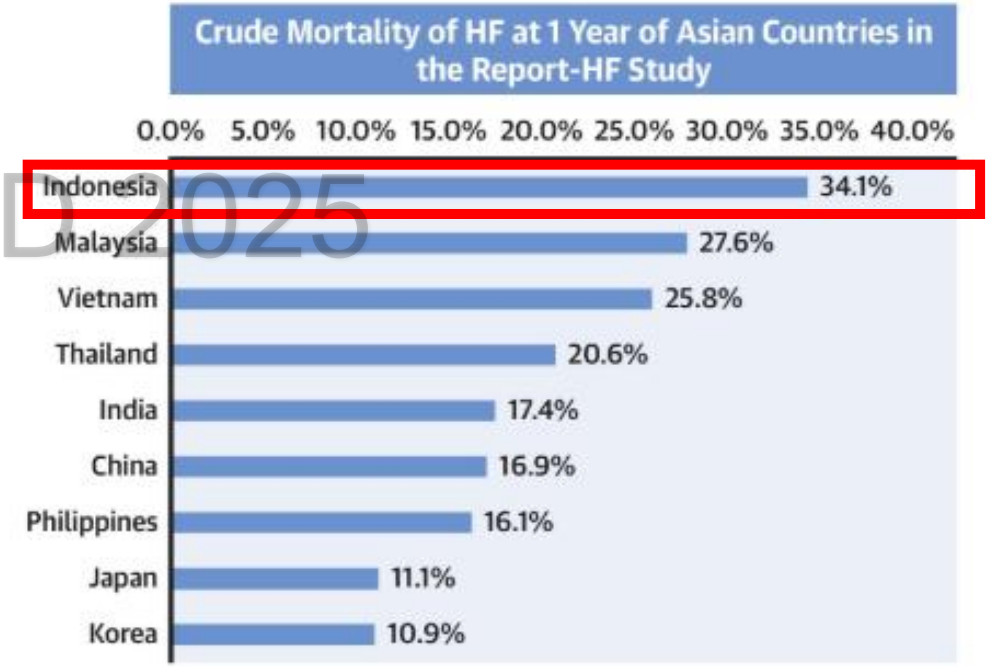
Feng J, et al. JACC: Asia. 2024;4(4):249-264.

Epidemiology and Burden of Heart Failure in Asia

The Leading Causes of HF Worldwide and in Asia Are Ischemic Heart Disease and Hypertensive Heart Disease



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



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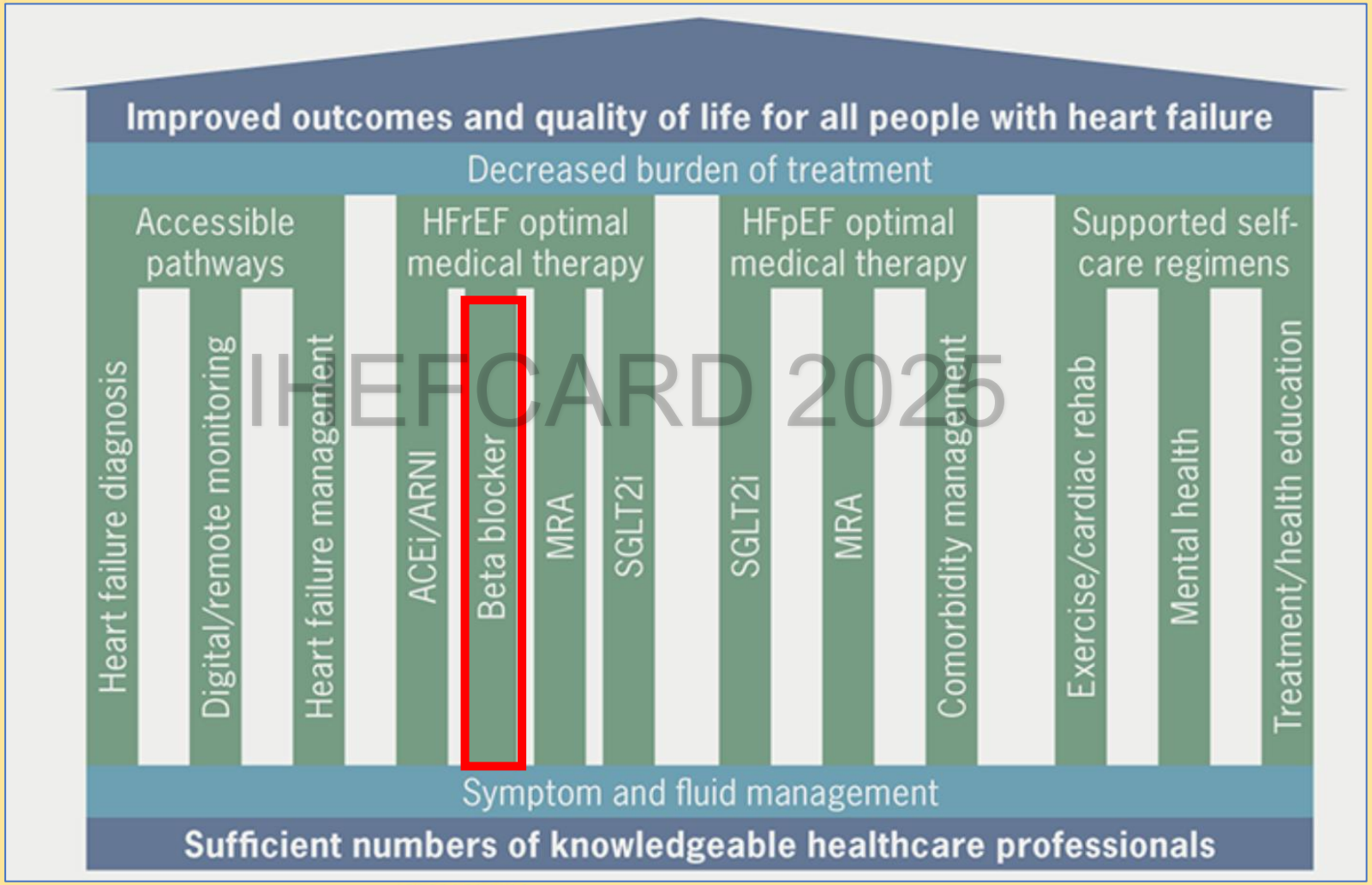
Patient-centered Pillars of Care For All Types of Heart Failure



Br J Cardiol 2024;31:7–8

RAASi Treatment Benefits in Patients with HFrEF are Demonstrated Across Numerous Landmarks Studies

ACEis
CONSENSUS (N=253)[1]
SOLVD-Treatment (N=2,569)[1,2]

- **40%** reduction in all-cause mortality vs placebo at 6 months (*P*=0.002)[1]
- **31%** reduction in all-cause mortality vs placebo at 12 months (*P*=0.001)[1]
- **16%** reduction in all-cause mortality vs placebo (*P*=0.0036)[2]

ARBs
CHARM-Added (N=2,548)[1,3]
CHARM-Alternative (N=2,028)[1,4]

- **15%** reduction in combined CV mortality or HF hospitalisation rate vs placebo (*P*=0.01)[3]
- **23%** reduction in combined CV mortality or HF hospitalisation rate vs placebo (*P*=0.0004)[4]

MRAs
RALES (N=1,663)[1,5]
EMPHASIS-HF (N=2,737)[1,6]

- **30%** reduction in all-cause mortality vs placebo (*P*<0.001)[5]
- **35%** reduction in cardiac hospitalisation rate vs placebo (*P*<0.001)[5]
- **37%** reduction in combined CV mortality or HF hospitalisation rate vs placebo (*P*<0.001)[6]
- **24%** reduction in all-cause mortality (*P*=0.008) and CV mortality (*P*=0.01) vs placebo[6]

ARNis
PARADIGM-HF (N=8,399)[1,7]

- **20%** reduction in risk of death from CV causes or a first HF hospitalisation vs enalapril (*P*<0.001)[7]
- **16%** reduction in risk of all-cause mortality vs enalapril (*P*<0.001)[7]
- **20%** reduction in CV mortality vs enalapril (*P*<0.001)[7]
- **21%** reduction in HF hospitalisation vs enalapril (*P*<0.001)[7]

1. McDonagh TA, et al. Eur Heart J 2021;ehab368. doi: 10.1093/eurheartj/ehab368; 2. The SOLVD investigators. N Engl J Med 1991;325:293–302; 3. McMurray JV, et al. Lancet 2003;362:767–71; 2003; 4. Granger CB, et al. Lancet 2003;362:772–6; 5. Pitt B, et al. N Engl J Med 1999;341:709–17; 6. Zannad F, et al. N Engl J Med 2011;364:11–21;
7. McMurray JJ, et al. N Engl J Med 2014;371:993–1004.

Mechanisms of benefit of beta-blockers in heart failure[1-4]

Benefits of beta-blockers in CHF are mediated via blockade of beta$_1$ receptors[1-3]

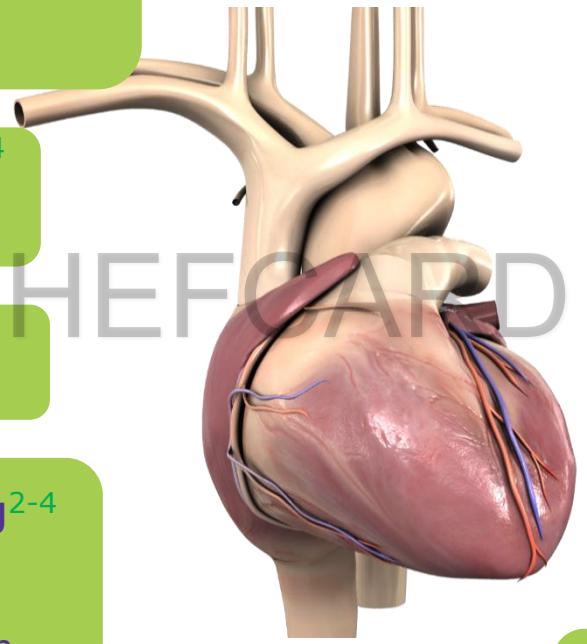
Reduction of sympathetic tone[3,4]
⇧ Increase in vagal tone
⇧ Improved autonomic balance/heart rate variability
⇩ Reduced sudden death

Antiarrhythmic activity[1-4]
⇩Reduced sudden death

Up-regulation of cardiac β_1-receptors[1-4]

Modification of remodelling[2-4]
⇨ Reverse remodeling
⇩ Reduced LV volumes
⇧ Increased LV ejection fraction

Antagonism of stimulatory β_1-receptor autoantibodies[2-4]



Heart rate reduction[1-4]
⇩ Reduced cardiac work and oxygen requirement
⇩ Prolonged diastolic coronary filling time

Inhibition of the renin-angiotensin system[1-4]
⇩ Reduced renin release

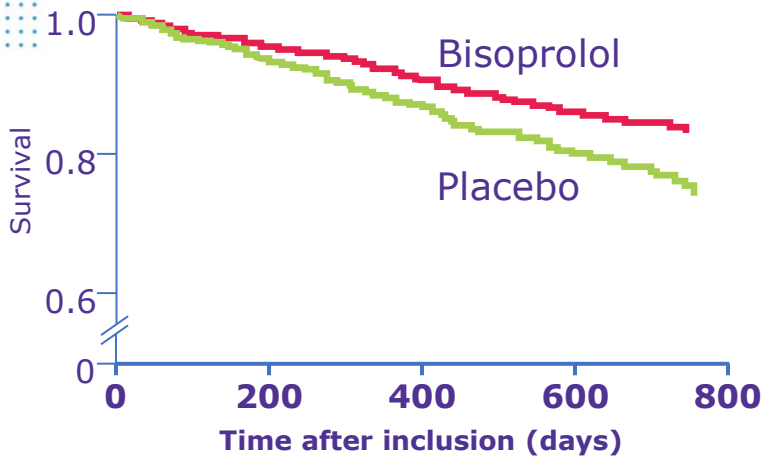
Inhibition of catecholamine-induced necrosis/apoptosis/inflammation (reduced cytokines)[2-4]

Restoration of Ca^{2+} release/cardiac ryanodine receptor function[2]
⇩ Probably linked to reduced sudden death risk

1. Cruickshank JM. Are we misunderstanding beta-blockers? Int J Cardiol 2007;120:10-27
2. Cruickshank JM. The modern role of beta-blockers in cardiovascular medicine. People's Medical Publishing House - Shelton, CT, USA; 2011
3. Waagstein F. Beta-blockers in congestive heart failure: the evolution of a new treatment concept – mechanisms of action and clinical implications. J Clin Basic Cardiol 2002;5:215–23
4. Silke B. Beta-blockade in CHF: pathophysiological considerations. Eur Heart J Suppls 2006;8(Suppl C):C13-C18

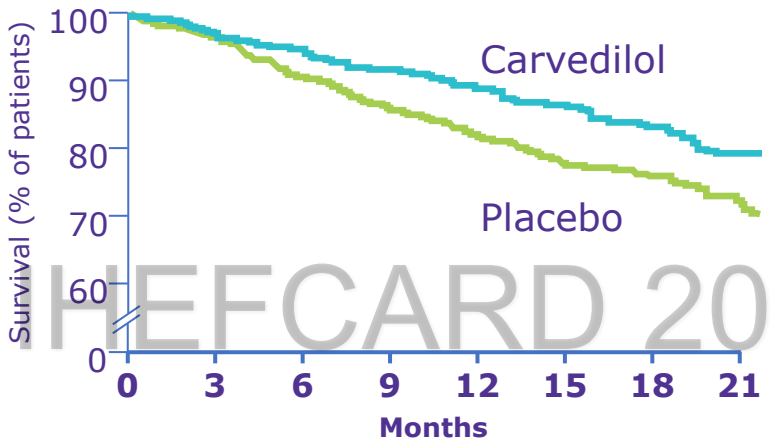
Effect of beta-blockers on all-cause mortality/survival in key heart failure trials[1-4]

CIBIS II[1]



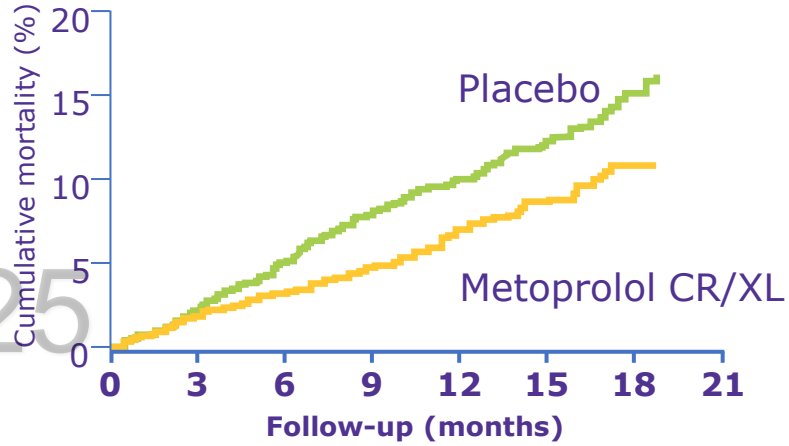
p<0.0001
Risk reduction = 34%
Sudden death : ⇩ 44%

COPERNICUS[2,3]



p=0.0014
Risk reduction = 35%
Sudden death: ⇩ 36%

MERIT-HF[4]

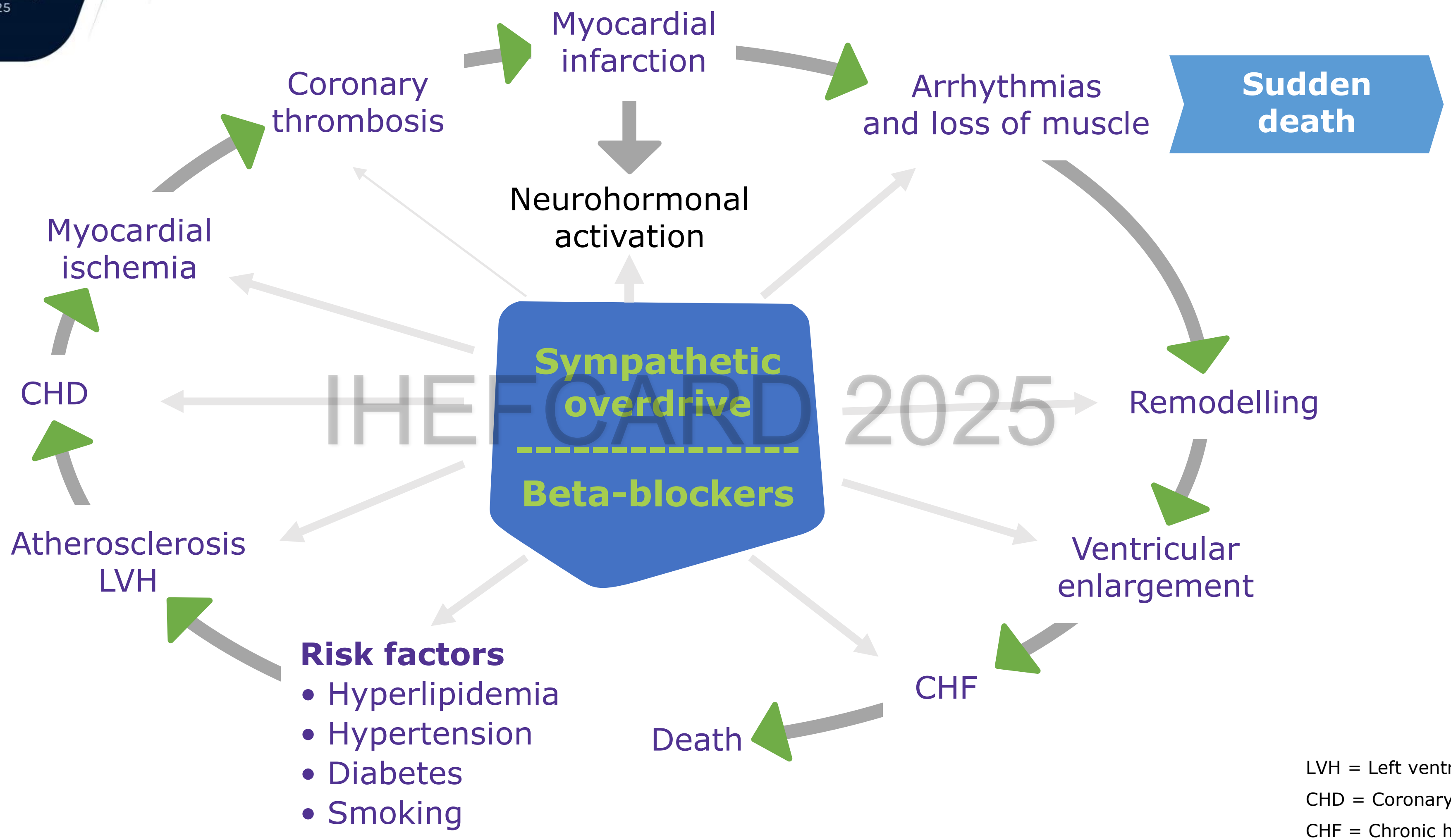


p=0.0062
Risk reduction = 34%
Sudden death : ⇩ 41%

Graphs adapted from references 1,2,4

1. CIBIS II Investigators and Committees. The cardiac insufficiency bisoprolol study II (CIBIS II). Lancet 1999;353:9–13
2. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344(22):1651–58
3. Packer M, Fowler MB, Roecker EB, et al., for the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study group. Effect of carvedilol on the mortality of patients with severe chronic heart failure. Results from the COPERNICUS study. Circulation 2002;106:2194-99
4. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001–9

Sympathetic overdrive contributes to every stage of the cardiovascular continuum[2]



LVH = Left ventricular hypertrophy
CHD = Coronary heart disease
CHF = Chronic heart failure

Beta-blockers can intervene at many points in the cardiovascular continuum[1]

1. Willenheimer R, Erdmann E. Beta-blockade across the cardiovascular continuum – when and where to use? Eur Heart J Suppls 2009;11(Suppl A):A1–2
2. Grassi G, Seravalle G, Mancia G. Sympathetic activation in cardiovascular disease: evidence, clinical impact and therapeutic implications. Review. Eur J Clin Invest 2015

Beta-blockers effectively reduce sudden cardiac death in CHF studies[1]

Study	Drug	Placebo [%]	Verum [%]	ARR [%]	RRR [%]
CIBIS II[6]	Bisoprolol	6.3	3.6	2.7	**44**
CIBIS I + II[7]	Bisoprolol	6.1	3.8	2.3	**37**
MERIT-HF[4]	Metoprolol	6.6	4.0	2.6	**41**
COPERNICUS[8]	Carvedilol	**6.1**	3.9	2.2	**36**
CAPRICORN[9]	Carvedilol	**7.0**	5.2	1.8	**26**
BEST[10]	Bucindolol	15.0	13.4	1.6	**12**
SENIORS[11]	Nebivolol	6.6	4.1	2.5	**38**

BBs reduce sudden cardiac death by 30-50% in patients with hypertension, HF, and CHD.
Sudden death is the most common cause of death in patients with HF.
BBs reduce this risk by up to 45%, which is greater than any other class of antihypertensive or antiarrhythmic agents.[1]

ARR = absolute risk reduction
RRR = relative risk reduction

1. Egan BM, Basile J, Chilton RJ, et al. Cardioprotection: the role of β-blocker therapy. J Clin Hypertens 2005;7:409-16

2. What's the target dose of beta blocker and target heart rate in HF?

Evidence-based doses of disease-modifying drugs in key randomized trials in patients with heart failure with reduced ejection fraction (2)

	Starting dose	Target dose
Beta-blockers		
Bisoprolol	1.25 mg *o.d.*	10 mg *o.d.*
Carvedilol	3.125 mg *b.i.d.*	25 mg *b.i.d.*[e]
Metoprolol succinate (CR/XL)	12.5–25 mg *o.d.*	200 mg *o.d.*
Nebivolol[d]	1.25 mg *o.d.*	10 mg *o.d.*

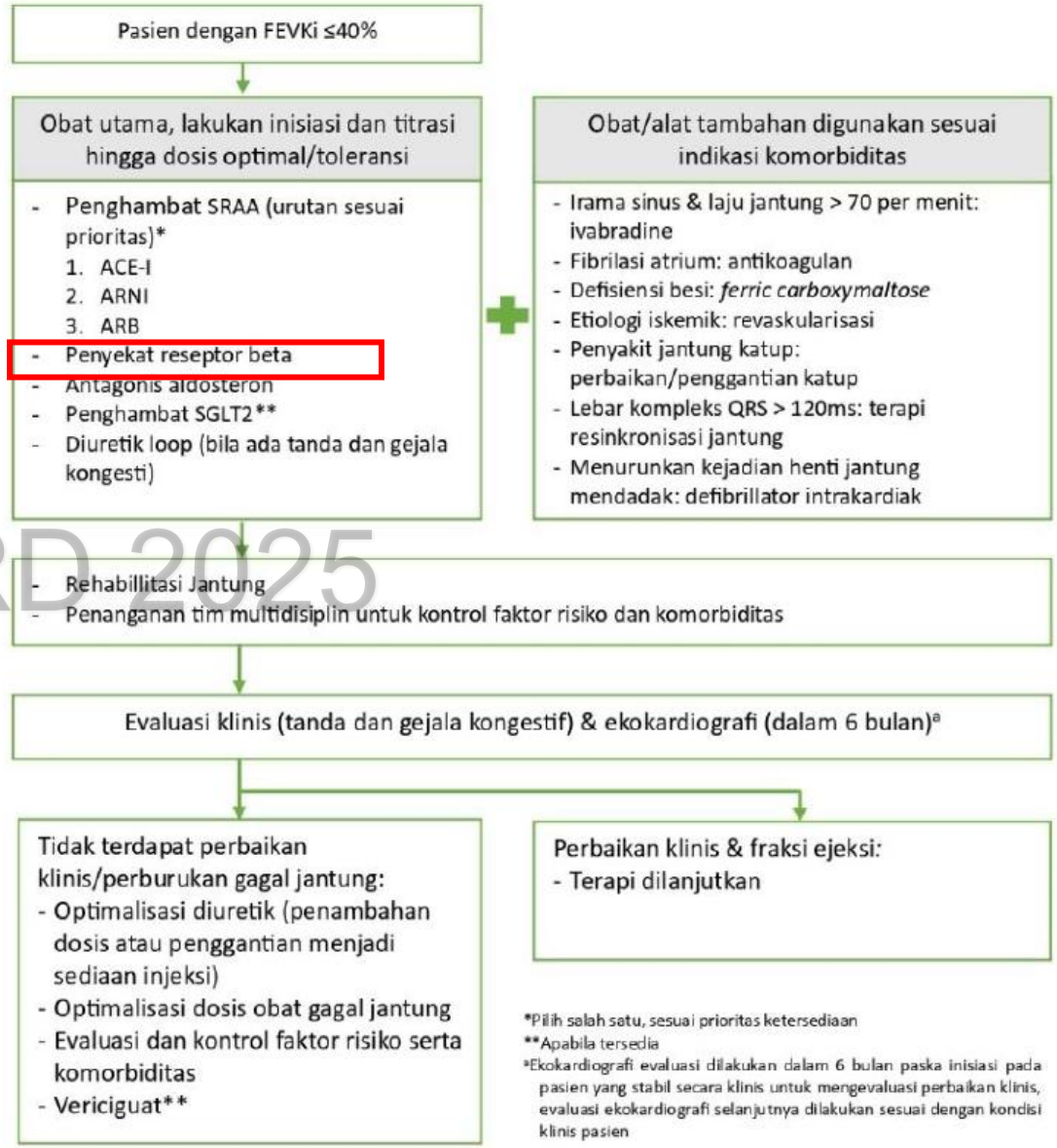
b.i.d. = bis in die (twice daily); CR = controlled release; MRA = mineralocorticoid receptor antagonist; o.d. = omne in die (once daily); XL = extended release.
[d]Indicates a treatment not shown to reduce CV or all-cause mortality in patients with heart failure (or shown to be non-inferior to a treatment that does).
[e]A maximum dose of 50 mg twice daily can be administered to patients weighing over 85 kg.
[f]Spironolactone has an optional starting dose of 12.5 mg in patients where renal status or hyperkalaemia warrant caution.

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

2023 PERKI Guideline for HF

Tabel 4. 2 Rekomendasi tatalaksana farmakologis HFrEF

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
Ivabradine direkomendasikan pada HFrEF dengan tanda dan gejala gagal jantung, irama sinus dan laju jantung istirahat $\geq$70 kali per menit walaupun telah mendapat BB dosis maksimal (dosis yang dapat ditoleransi pasien), ACE-I dan MRA untuk menurunkan angka rawat ulang akibat perburukan gagal jantung dan mortalitas kardiovaskular	IIa	B
Ivabradine direkomendasikan pada HFrEF dengan tanda dan gejala gagal jantung, irama sinus dan laju jantung istirahat $\geq$70 kali per menit yang tidak dapat mentolerir atau kontraindikasi BB untuk menurunkan angka rawat ulang akibat perburukan gagal jantung dan mortalitas kardiovaskular. Pasien juga telah mendapatkan ACE-I dan MRA.	IIa	C



Gambar 4. 1 Algoritma tatalaksana HFrEF

2023 PERKI Guideline for HF: Dosage Uptitration

obat lain yang digunakan.[60] Data terbaru menunjukkan dalam penurunan mortalitas adalah kecepatan uptitrasi GDMT.[73] Inisiasi lebih dini dari terapi gagal jantung setelah diagnosis atau setelah proses eksaserbasi akut direkomendasikan untuk memperbaiki prognosis. Pada studi STRONG-HF, 900 pasien gagal jantung yang dirawat dibagi menjadi 2 kelompok yaitu yang mendapat *usual care* atau *high intensity care*. Pada kelompok *high intensity care,* terapi GDMT diuptitrasi secara cepat untuk mencapai dosis optimal dalam 2 minggu setelah rawat jalan dan pendekatan ini terbukti aman dan memungkinkan, serta menurunkan risiko *all cause death* atau perawatan karena gagal jantung dalam 180 hari.[49]

Relationship of HR change to survival in BB trials of CHF patients[1]

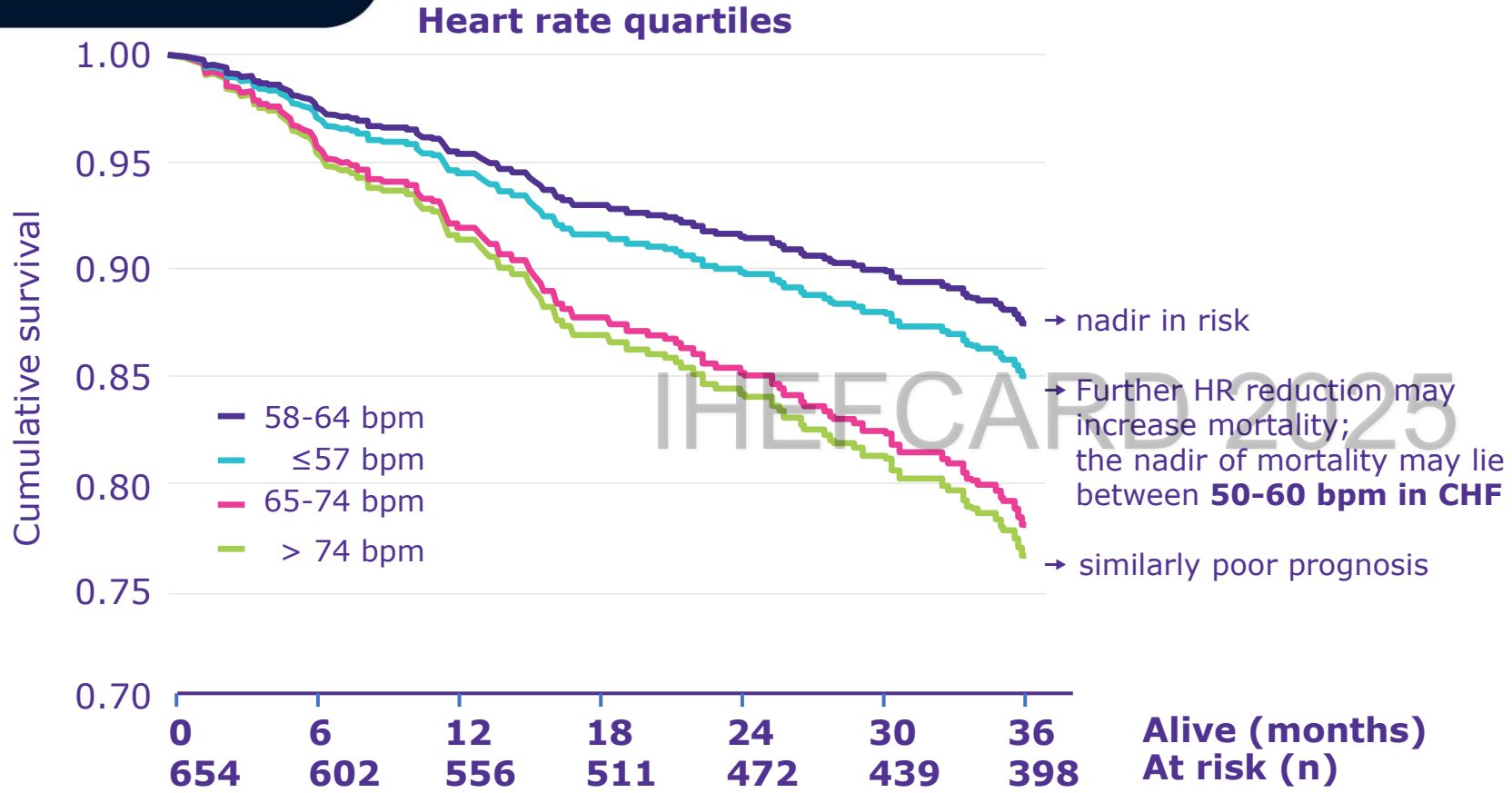
For every 5 beat/min reduction in mean HR, the risk ratio for death decreases by 18%[1]

Results of 13 Univariable Meta-regressions Evaluating the Effect of Individual Covariates on Death Benefits of Beta-Blockers in Heart Failure				
Potential Modifier	Trials, *n*	Patients, *n*	Ratio of Relative Risk (95% CI)	*P* Value
Percentage of men	21	18 733	0.93 (0.79-1.10) per 10% increment	0.38
Mean age	21	18 733	1.04 (0.86-1.24) per decade	0.69
Percentage with an ischemic cause	21	18 733	0.99 (0.86-1.14) per 20% increment	0.88
Mean baseline LVEF	20	18 392	1.04 (0.92-1.18) per 5% increment	0.54
Percentage NYHA class III or IV symptoms	21	18 733	1.00 (0.96-1.05) per 10% increment	0.84
Percentage with atrial fibrillation	8	8 915	1.00 (0.91-1.09) per 5% increment	0.95
Percentage with digoxin use	19	18 336	1.01 (0.96-1.06) per 10% increment	0.64
Baseline heart rate	19	17 981	1.07 (0.88-1.32) per 5 beats/min	0.47
Heart rate reduction*	17	17 831	0.82 (0.71-0.94) per 5 beats/min	0.006
β-Blocker dose	17	17 660	1.02 (0.93-1.10) per increment	0.69
Mean baseline SBP	17	17 516	1.00 (0.73-1.35) per 20 mm Hg	0.99
Mean SBP reduction	10	5 462	1.02 (0.87-1.20) per 2 mm Hg	0.78
Agent	21	18 773	-	-

* For every 5-beat/min reduction in mean heart rate, the risk ratio for death decreases by 18% (relative risk ratio, 0.82 [95% CI, 0.71 to 0.94]). Therefore, starting with the pooled risk ratio of 0.76 for death and the median heart rate reduction of 12 beats/min, it would be reasonable to expect that a mean heart rate reduction of 17 beats/min would confer a relative risk for death of approximately 0.62.

1. McAlister FA, MD, Wiebe N, Ezekowitz JA, et al. Meta-analysis: β-blocker dose, heart rate reduction, and death in patients with heart failure. Ann Intern Med 2009;150:784-794

Beta-blocker use and resting heart rate achieved are both independently associated with mortality in CHF[1]



→ nadir in risk

→ Further HR reduction may increase mortality; the nadir of mortality may lie between **50-60 bpm in CHF**

→ similarly poor prognosis

A resting **HR <50bpm** may be associated with an **adverse outcome.**

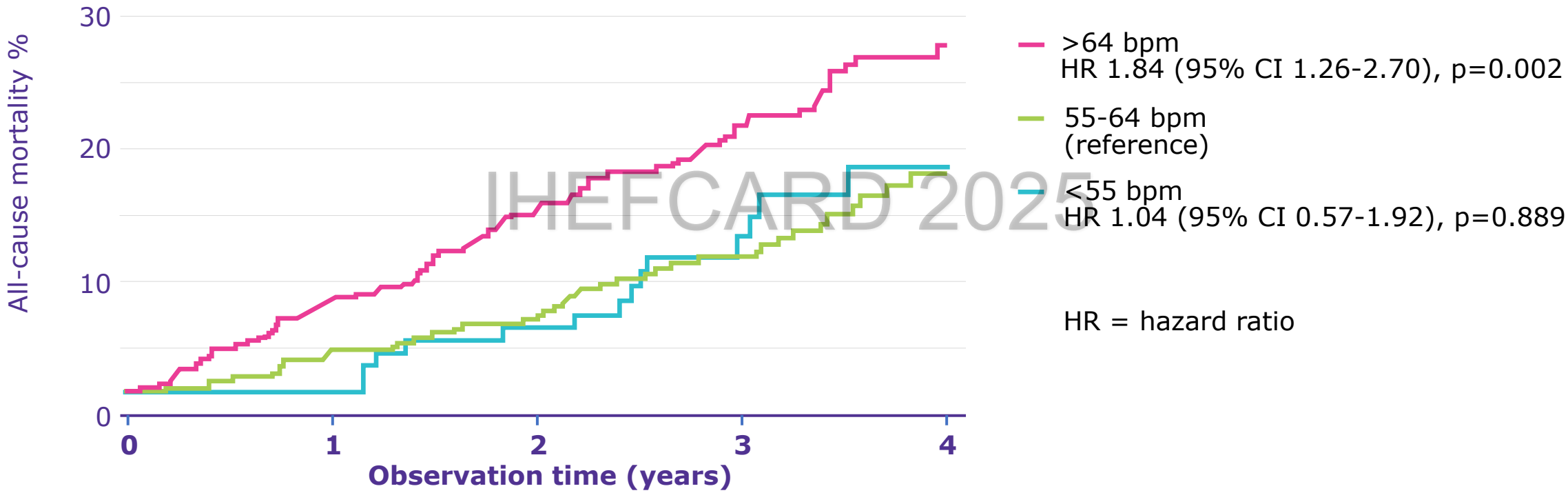
654 CHF patients referred to a community heart failure clinic in UK; mean age: 70 years
537 patients (82%) were treated with a beta-blocker at visit 2 (after 4 months of follow-up; maximum follow-up after visit 2 was 36 months, during which time 142 (22%) patients died)

1. Cullington D, Goode KM, Clark AL, Cleland JGF. Heart rate achieved or beta-blocker dose in patients with chronic heart failure: which is the better target? Eur J Heart Fail 2012;14:737-47"

Heart rate range 55-64 bpm showed lowest mortality and treatment-related adverse events[1]

A heart rate between 55 and 65 bpm could be considered a pragmatic treatment goal in elderly CHF patients[1]

Subgroups by heart rate at the end of up-titration

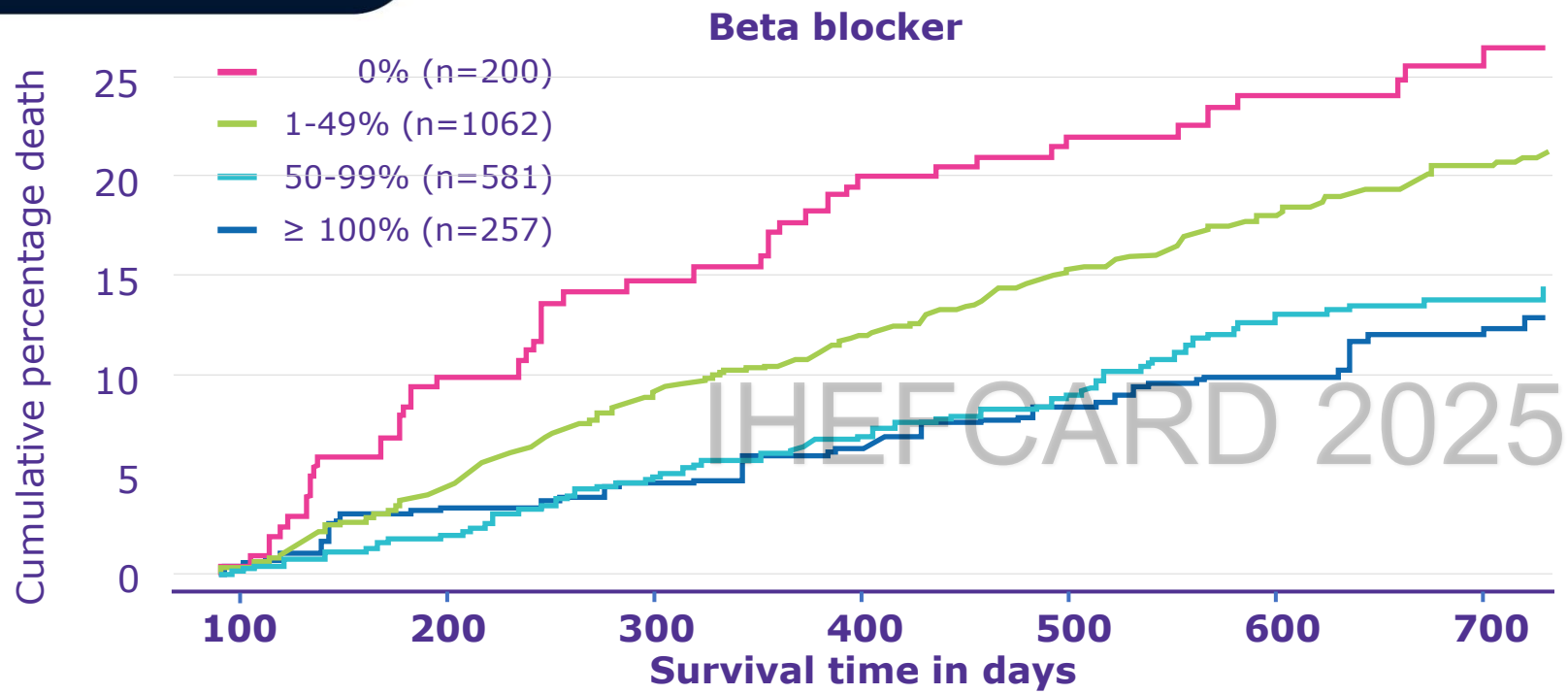


- Heart rates **<55 bpm** after up-titration were **no more beneficial** in regard to survival than heart rates in the range of 55–64 bpm (HR 1.09, CI 0.58–2.07, *p*=0.787).[1]
- Heart rate **<55 bpm** following up-titration was associated with the **highest rate of adverse events** (OR 2.58, 95% CI 1.53–4.48, *p*<0.001).[1]

1. Düngen HD, Musial-Bright L, Inkrot S, et al. Heart rate following short-term beta-blocker titration predicts all-cause mortality in elderly chronic heart failure patients: insights from the CIBIS-ELD trial. Eur J Heart Fail 2014;16:907-14

Reaching <50% of the recommended beta-blocker dose was associated with increased risk of death and/or heart failure hospitalization compared with patients reaching ≥100%[1]

Data from the BIOSTAT-CHF project[1]



Patients treated with at least 50% of recommended BB target dose had a better survival (clinical outcome)

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

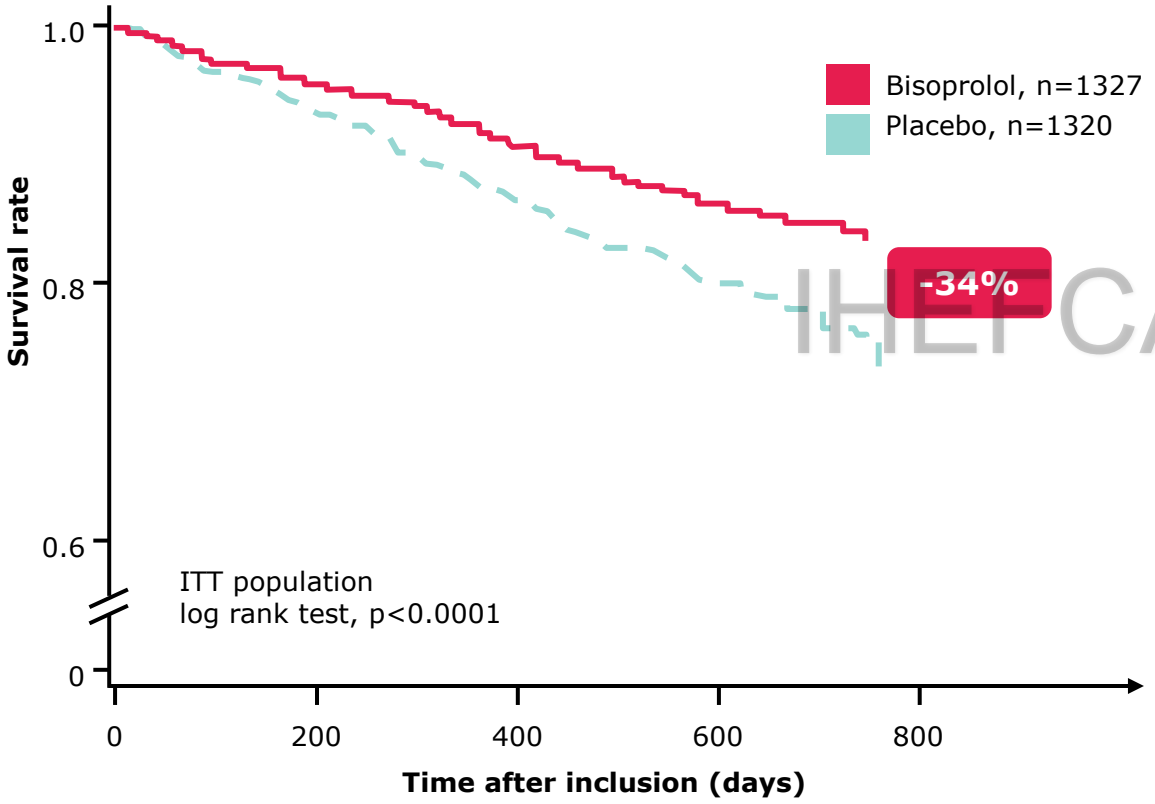
Adjusted mortality rate for patients receiving 0%, 1-49%, 50-99% or ≥100% of the recommended beta-blocker dose, together with the risk set sizes at each time point.

Graph adapted from reference 1

1. Ouwerkerk W, Voors AA, Anker SD, et al. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study. Eur Heart J 2017;00:1-10; doi:10.109/eurheartj/ehx026

CIBIS II: Significant Mortality Benefit of Bisoprolol in Ambulatory Patients with Stable Heart Failure with Reduced Ejection Fraction

Reduction of all-cause mortality



Significantly lower all-cause mortality (primary outcome) in bisoprolol group **HR 0.66 [95% CI 0.54–0.81],** p<0.0001 vs placebo

Independent of the severity or cause of heart failure treatment effects

Double-blind placebo-controlled randomized trial, 2647 ambulatory patients with heart failure with reduced ejection fraction (HFrEF), 96% of patients on ACEi and 99% on diuretics at baseline, treatment with bisoprolol up to 10 mg or placebo additional to standard care

CI, confidence interval, **HR**, hazard ratio **ITT**, intent to treat

Adapted from The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomized trial. *Lancet.* 1999 Jan 2;353(9146):9-13. PMID: 10023943.

Lower Risk of All-cause Mortality, Cardiovascular Deaths, All-cause Hospitalizations and Cardiovascular Hospitalizations in the High And Moderate Doses of Bisoprolol Compared to Low Dose

Risks of the outcome events in bisoprolol dose groups, after adjustment for baseline differences and patient treatment withdrawal during follow-up

Event	Low dose (1.25, 2.50 or 3.75 mg/day)	Moderate dose (5.0 or 7.50 mg/day)	High dose (10.0 mg/day)
All-cause mortality	1	0.49 (0.32-0.75)	0.30 (0.19-0.46)
All CV causes of death	1	0.44 (0.27-0.71)	0.26 (0.16-0.43)
Pump failure death	1	0.20 (0.07-0.59)	0.16 (0.06-0.43)
Sudden death	1	0.74 (0.35-1.55)	0.45 (0.21-0.95)
Other CV causes death	1	0.28 (0.09-0.84)	0.17 (0.06-0.50)
All-cause hospitalizations	1	0.62 (0.48-0.79)	0.38 (0.30-0.48)
All CV cause hospitalizations	1	0.63 (0.48-0.84)	0.33 (0.25-0.44)

Increase in mortality risk in patients with bisoprolol withdrawal: 1.79, [95% CI:1.14–2.82], p=0.01, 1.95, [95% CI=0.74–5.16], p=0.18 and 10.17 [95% CI:3.85–26.86], p<0.0001 in LD, MD and HD bisoprolol groups, respectively.

"All efforts should be made to maintain bisoprolol therapy based on the individual patient's tolerability and decrease the dose, if necessary, in case of intolerance…"

Adapted from Simon T. et al. Bisoprolol dose–response relationship in patients with congestive heart failure: a subgroup analysis in the cardiac insufficiency bisoprolol study (CIBIS II). *European Heart Journal* (2003) 24, 552–559

Bisoprolol has a balanced clearance

Bisoprolol has a 'balanced' clearance[1-3]

- 50% renal elimination of unchanged drug
- 50% hepatic metabolism to inactive metabolites – also renally excreted

Metabolism

- Only by oxidation – no subsequent conjugation[4,5]
- Primarily by **CYP3A4** (~95%)[4]
- Only minor contribution of **CYP2D6**[4] (→ metabolism not dependent on CYP2D6 gene polymorphism, formerly debrisoquine-sparteine polymorphism[2])

➔ No dose adjustment necessary in mild to moderate liver or kidney impairment[6]
➔ Daily dose to be limited to 10 mg in severe liver or kidney impairment[6]
➔ The maximum recommended dose in CHF is 10 mg once daily.[6]

1. Leopold G, Pabst J, Ungethüm W, Bühring K-U. Basic pharmacokinetics of bisoprolol, a new highly beta1-selective adrenoceptor antagonist. J Clin Pharmacol. 1986;26:616-21.
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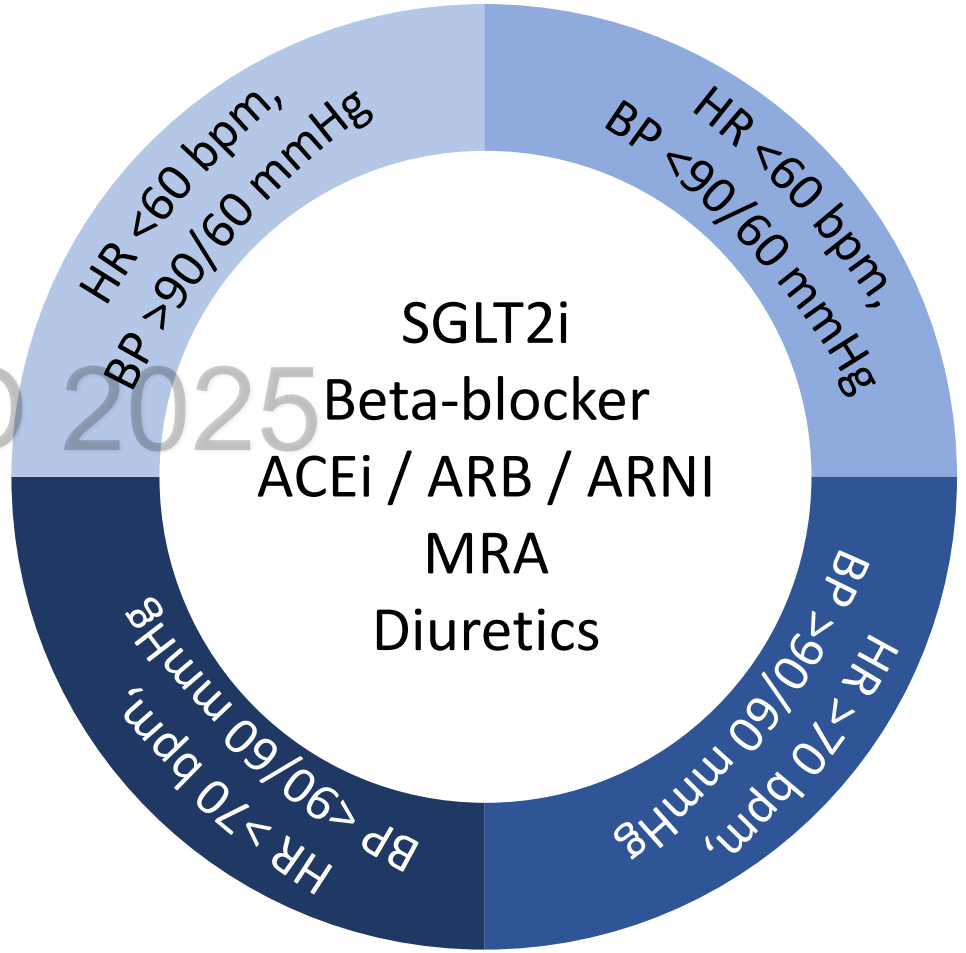
6. Concor® / Concor® COR Product information (abbreviated prescribing information), Merck KGaA, Darmstadt, Germany; July 2017.

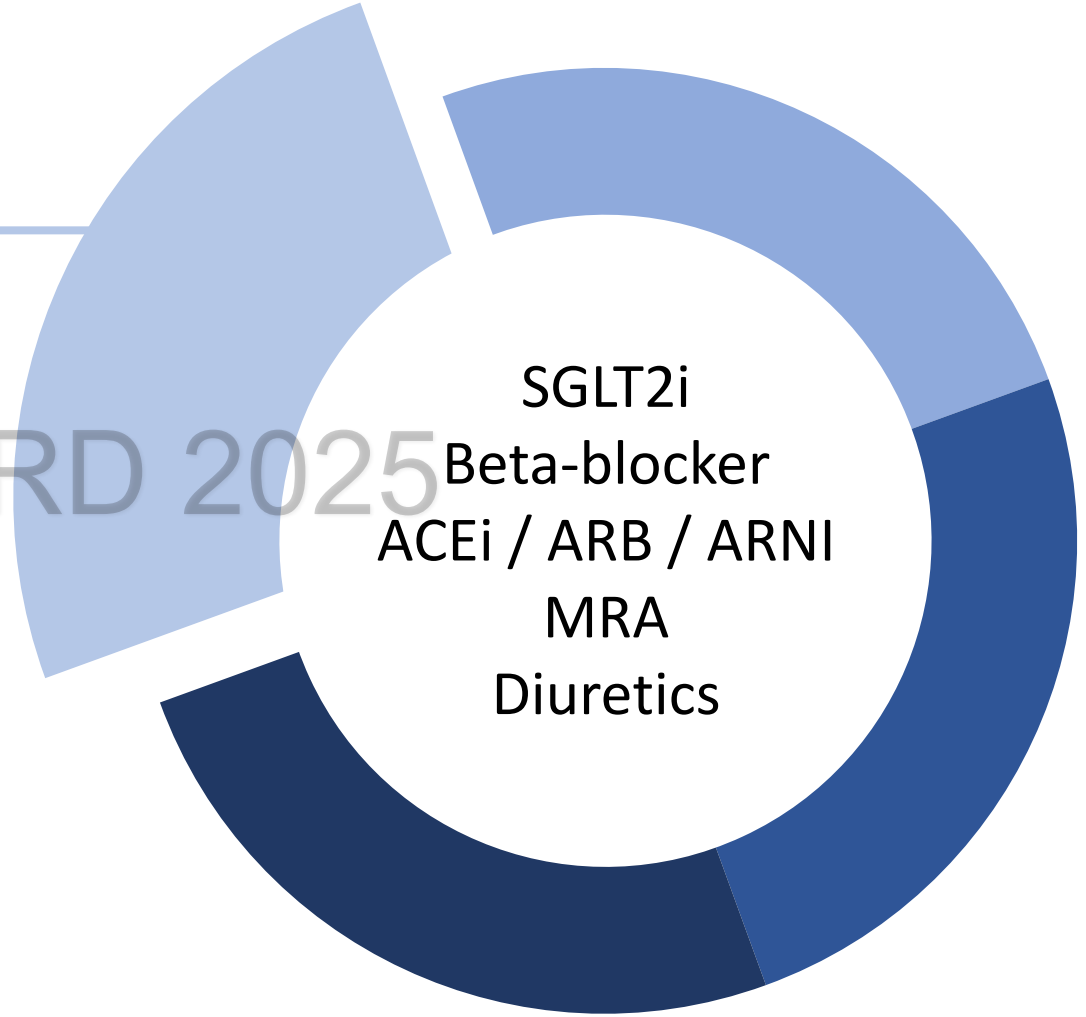
3. Which HF patients are eligible/not eligible for beta blockers?

Tailoring of medical therapy according to clinical profiles



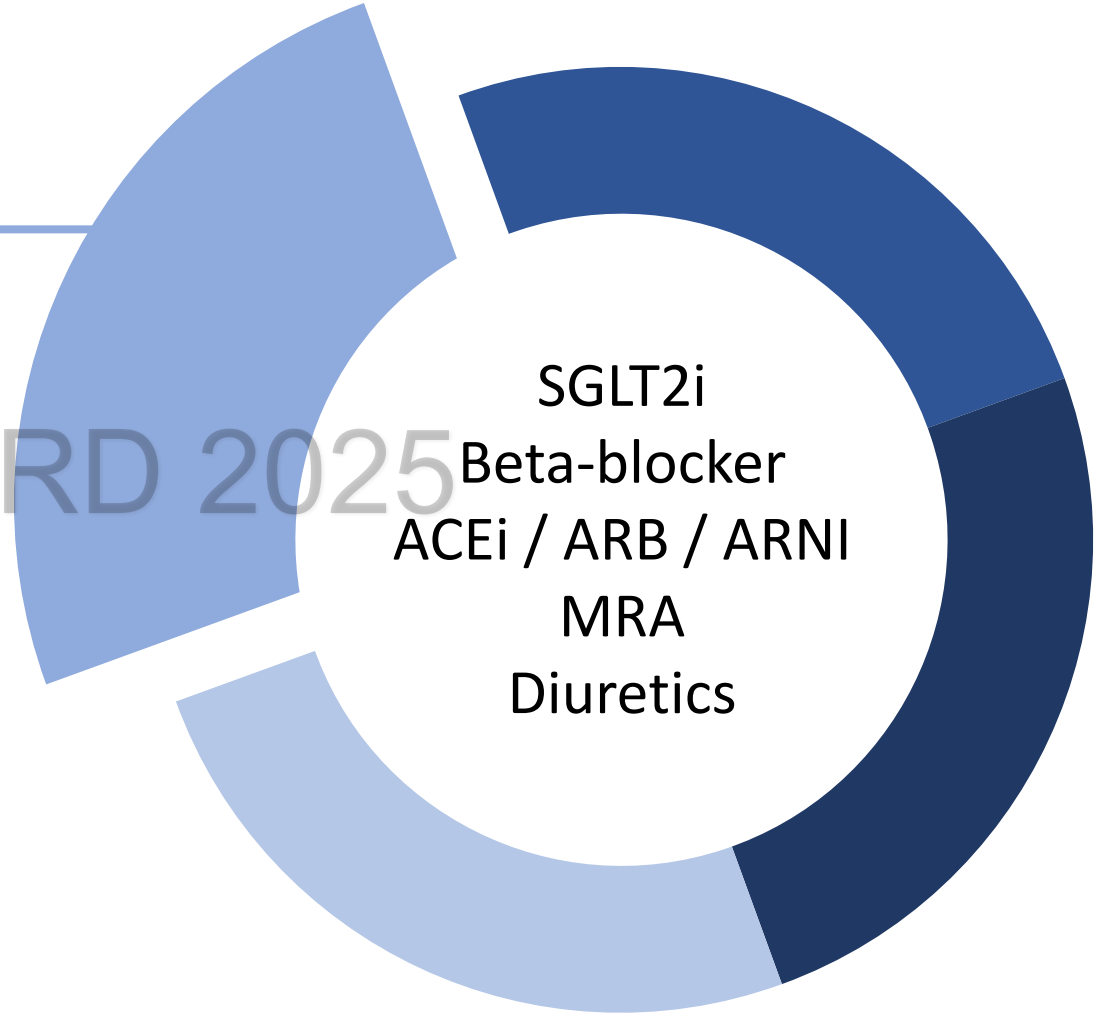
HR <60 bpm, BP >90/60 mmHg

SGLT2i
↓**Beta-blocker**
ACEi / ARB / ARNI
MRA
Diuretics
Vericiguat



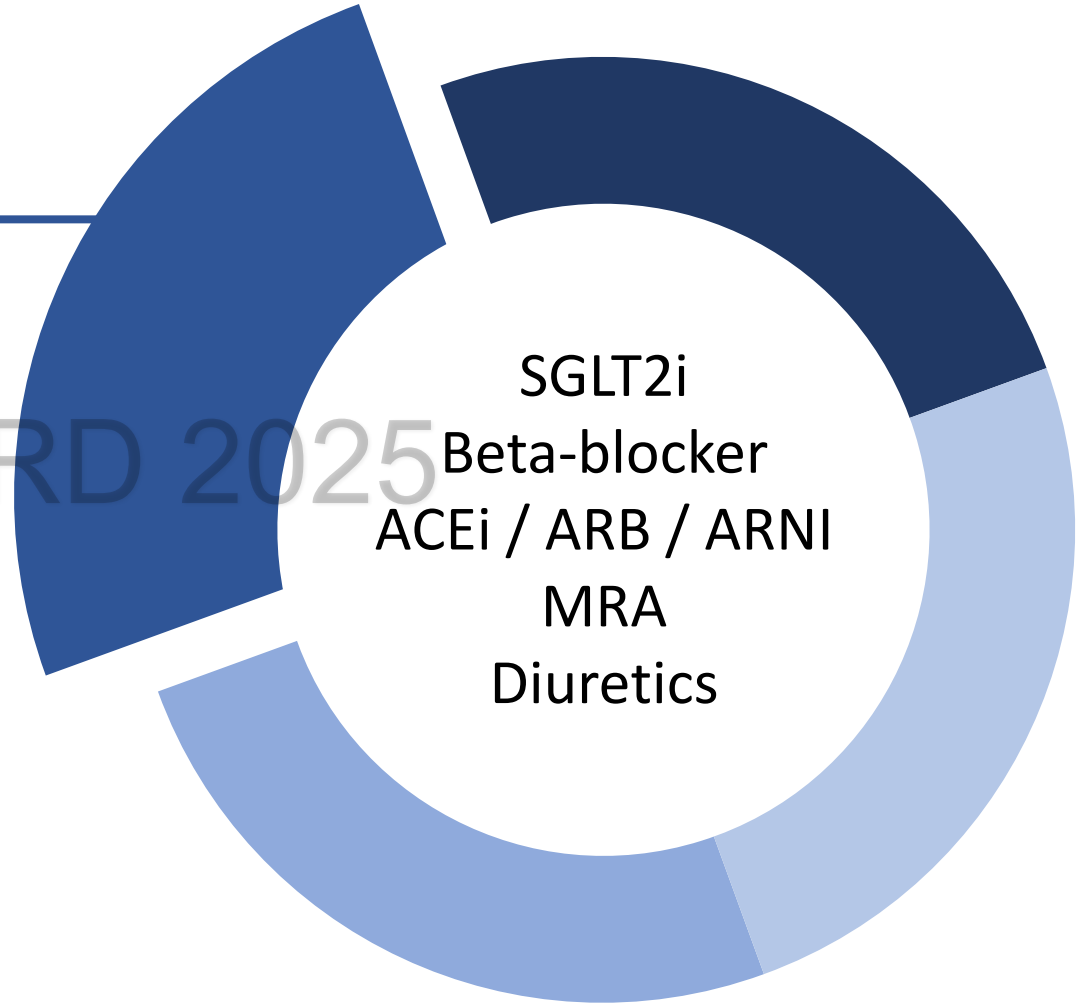
HR <60 bpm, BP <90/60 mmHg

SGLT2i
MRA
↓Beta-blocker
↓ ACEi / ARB / ARNI
↓ Diuretics



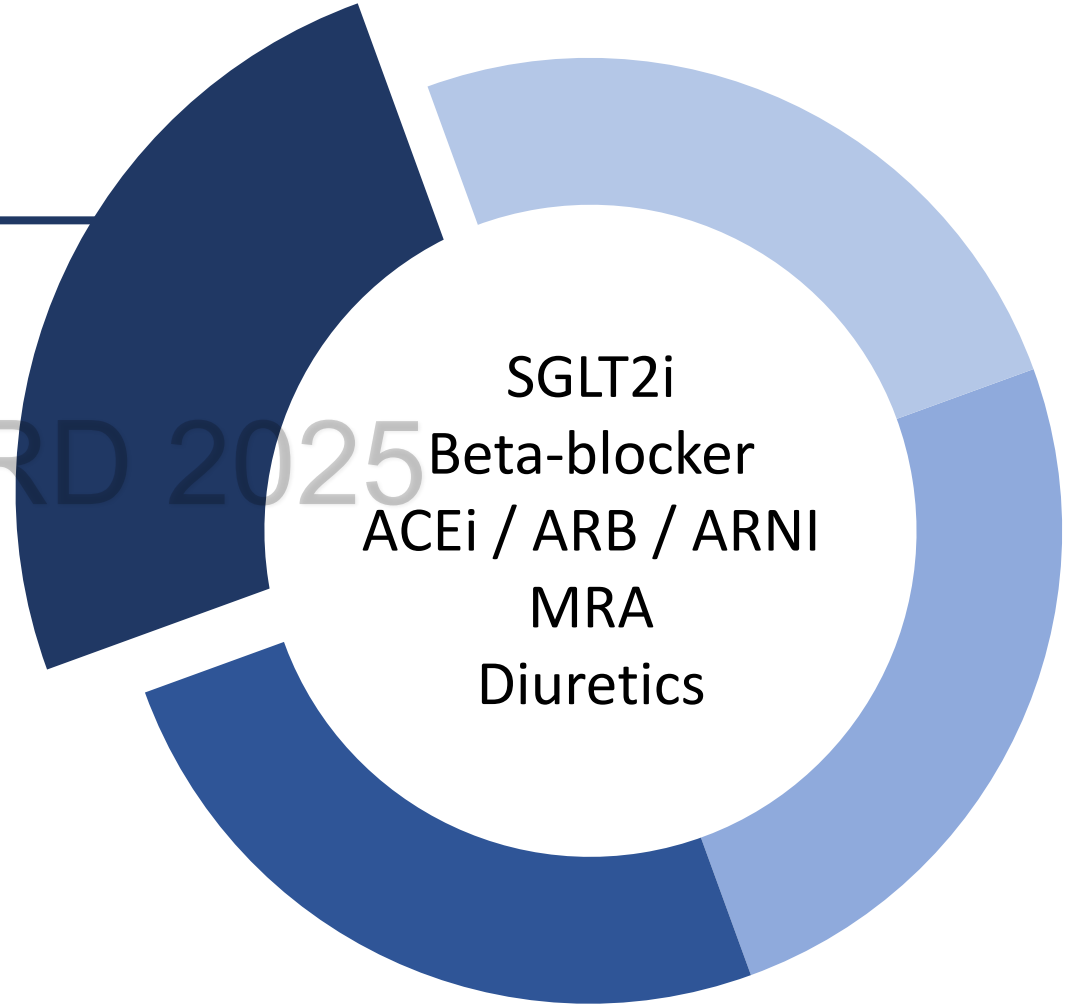
HR >70 bpm, BP >90/60 mmHg

SGLT2i
Beta-blocker
ACEi / ARB / ARNI
MRA
Diuretics
Ivabradine



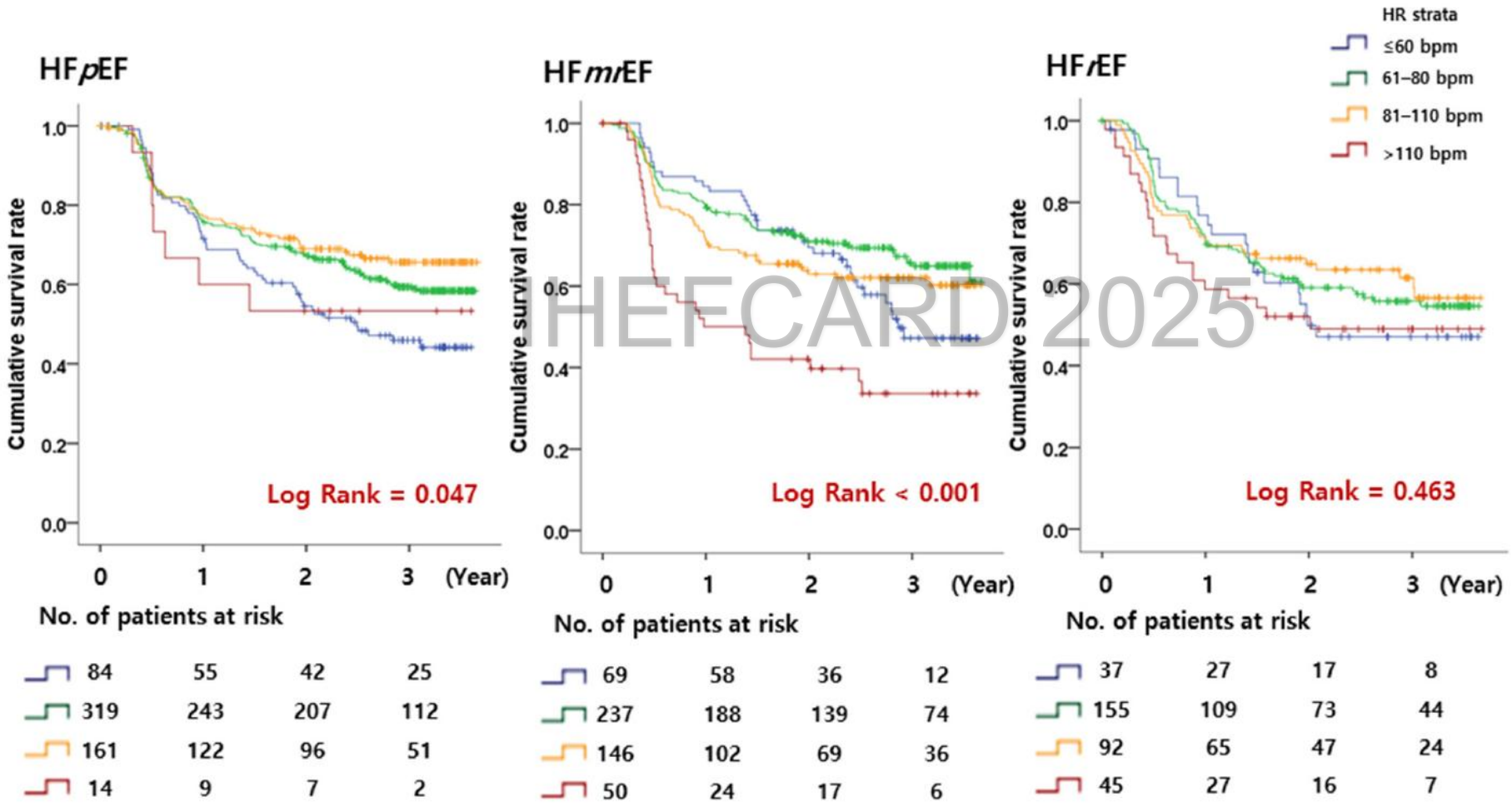
HR >70 bpm, BP <90/60 mmHg

SGLT2i
MRA
Ivabradine
↓Beta-blocker
↓ ACEi / ARB / ARNI
↓ Diuretics



3. Atrial Fibrillation in HF

Clinical Implications of Heart Rate Control in Heart Failure With Atrial Fibrillation: Multi-Center Prospective Observation Registry (CODE-AF Registry)



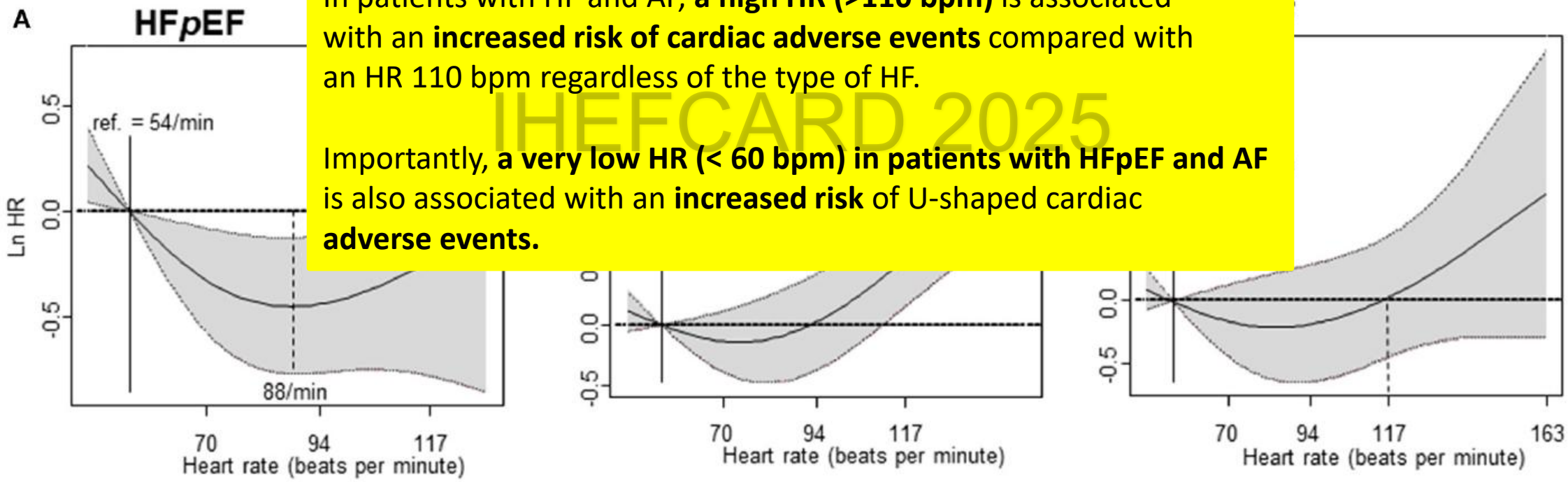
doi: 10.3389/fcvm.2022.787869

Clinical Implications of Heart Rate Control in Heart Failure With Atrial Fibrillation: Multi-Center Prospective Observation Registry (CODE-AF Registry)

CONCLUSION

In patients with HF and AF, **a high HR (>110 bpm)** is associated with an **increased risk of cardiac adverse events** compared with an HR 110 bpm regardless of the type of HF.

Importantly, **a very low HR (< 60 bpm) in patients with HFpEF and AF** is also associated with an **increased risk** of U-shaped cardiac **adverse events.**



Cox regression analysis – penalized spline.

doi: 10.3389/fcvm.2022.787869

Summary

- The Increase of heart rate as one marker of sympathetic overdrive stimulates the progression of heart failure and contributes to the mortality and morbidity (hospitalizations) in CHF.
- Heart rate is considered a therapeutic target in heart failure.
- BBs have been shown to reduce all-cause mortality in CHF by 34-35% in three landmark trials, with recommended target dose.
- BBs effectively lower heart rate in CHF, and several analyses have shown that the change in heart rate is more important for survival in CHF than the BB dose.
- Low mortality risk : at resting heart rates of 55-65 bpm in sinus rhythm and 60-100 bpm in AF
- On the other hand, patients treated with at least 50% of recommended BB target dose had a better survival.