The 6th Indonesian Symposium on Heart Failure and Cardiometabolic Disease

Heart Rate Matters More than We Think: a Neglected Risk Factor in HF Patients

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Disclaimer

- This presentation supported by PT Merck Indonesia

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Outline

- Global burden of heart failure
- Heart rate and mortality
- BBs as important part of GDMT
- GDMT and GRTD

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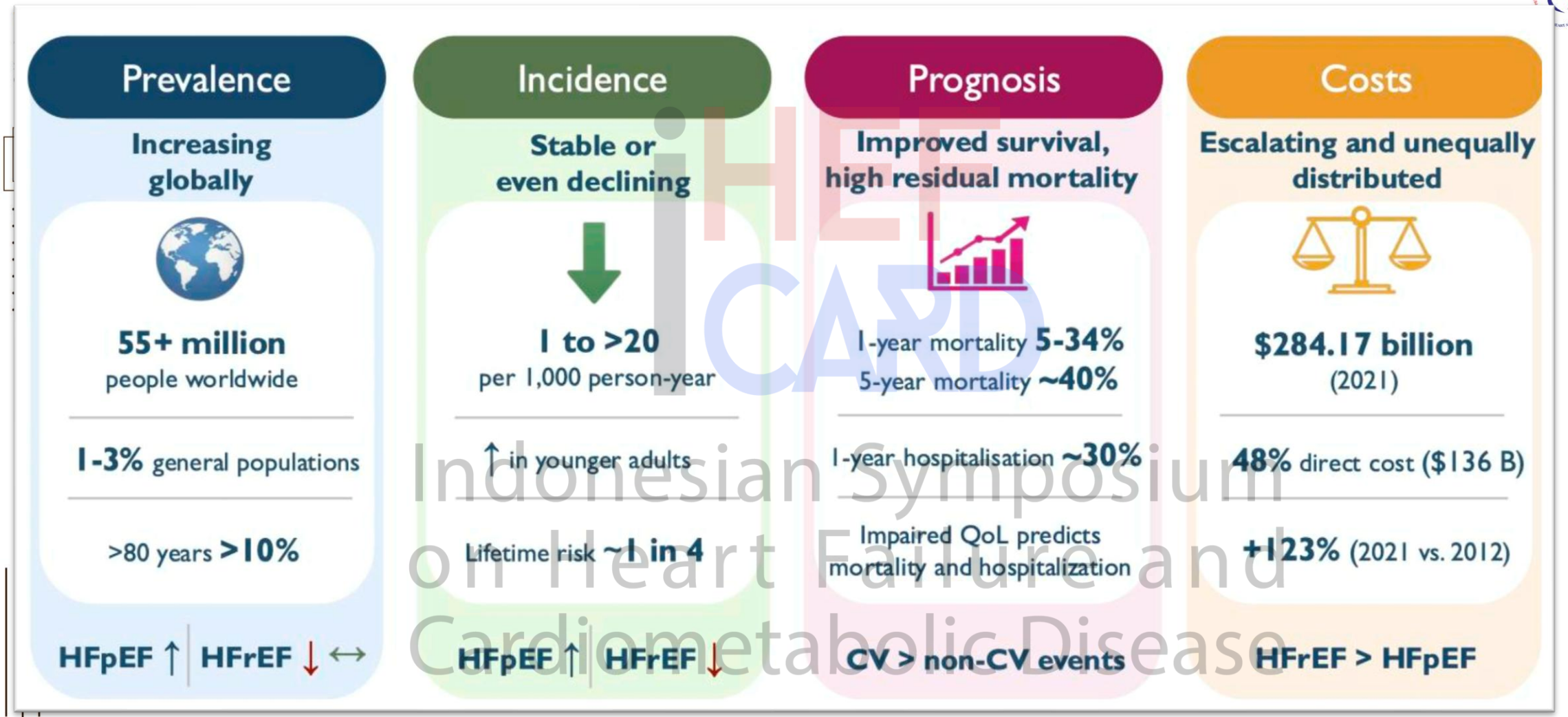
Global Burden of Heart Failure



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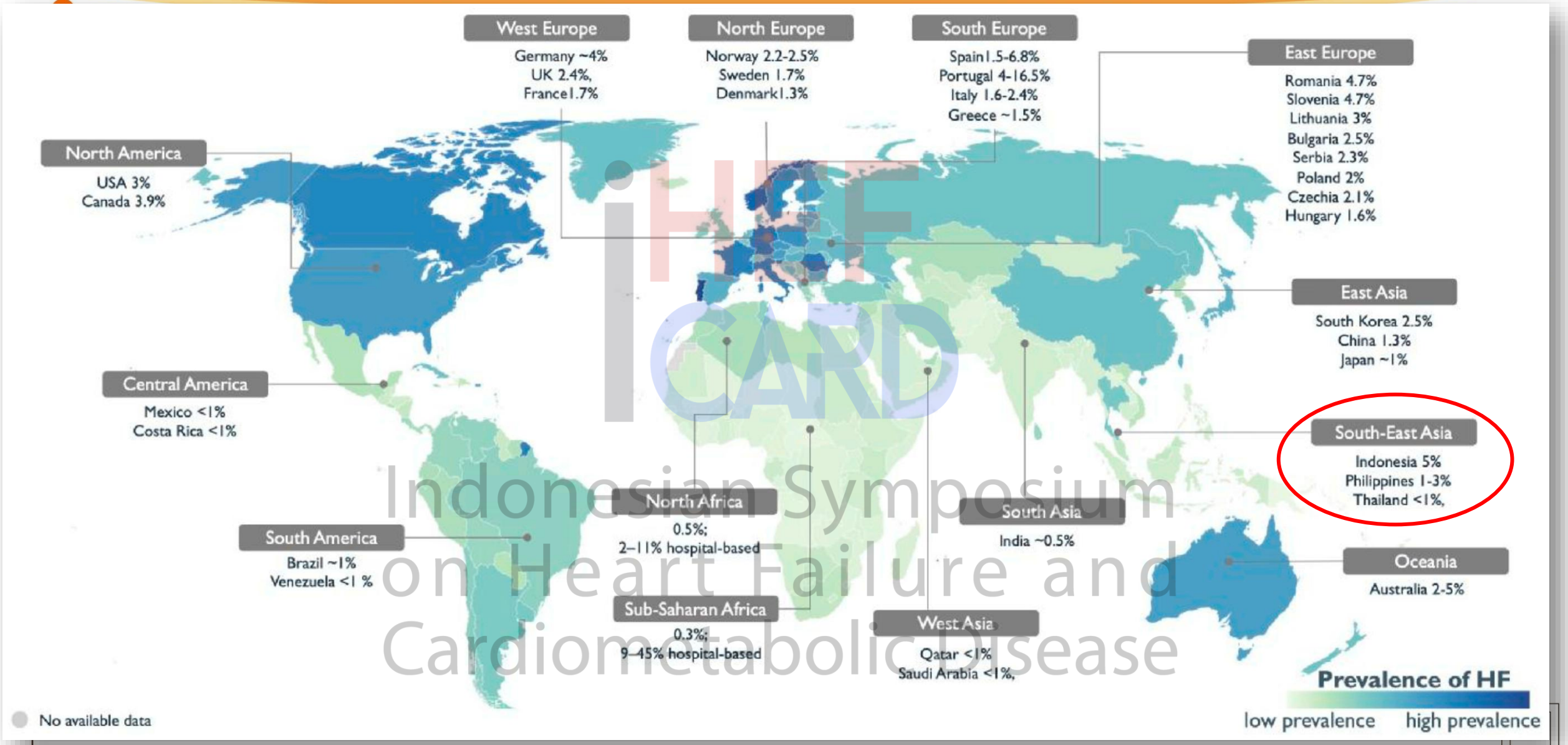
Valente et al. *European Journal of Heart Failure.* 2026; xuag: 121



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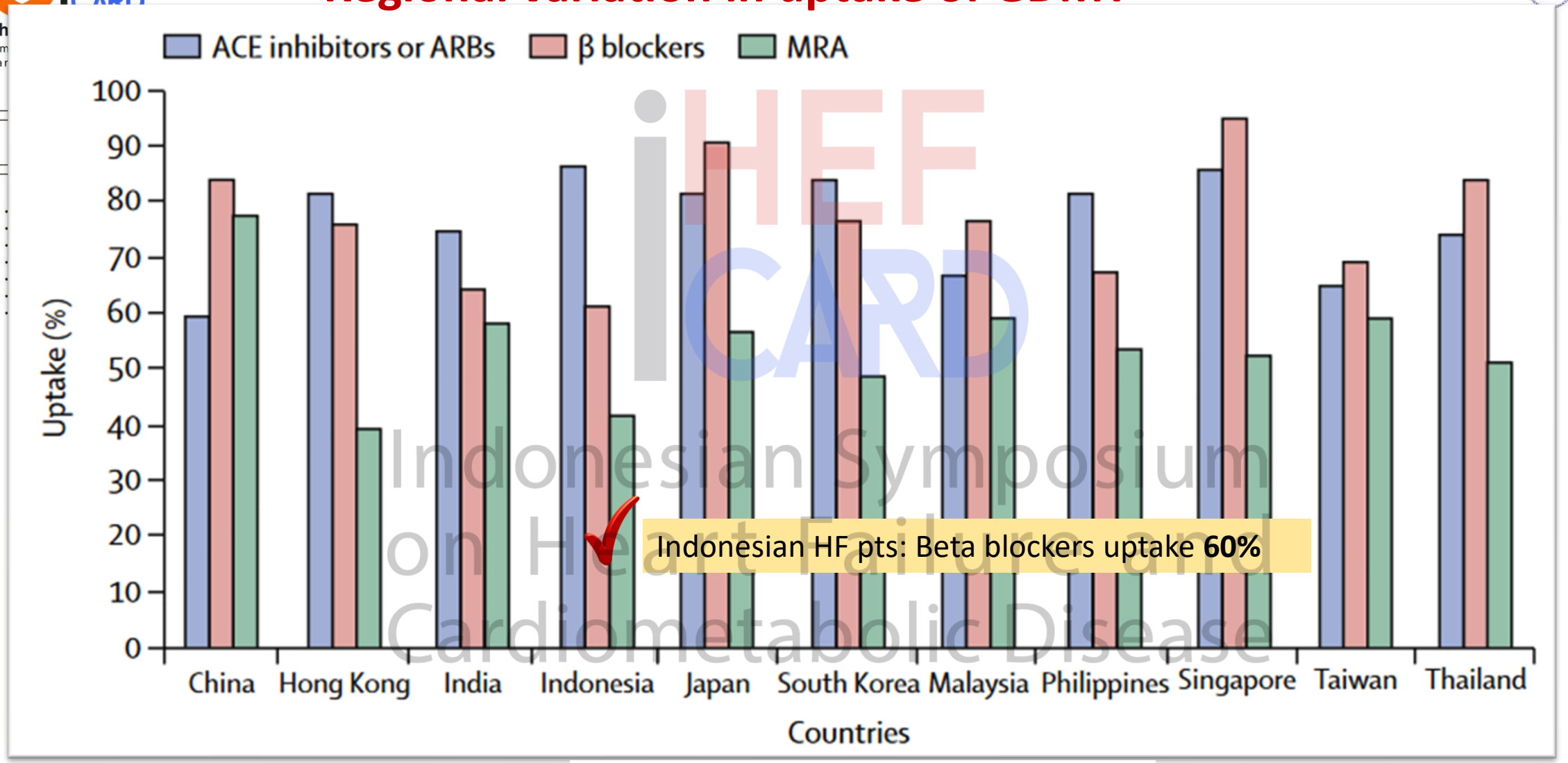
Valente et al. *European Journal of Heart Failure.* 2026; xuag: 121

Regional variation in uptake of GDMT



Indonesian HF pts: Beta blockers uptake **60%**

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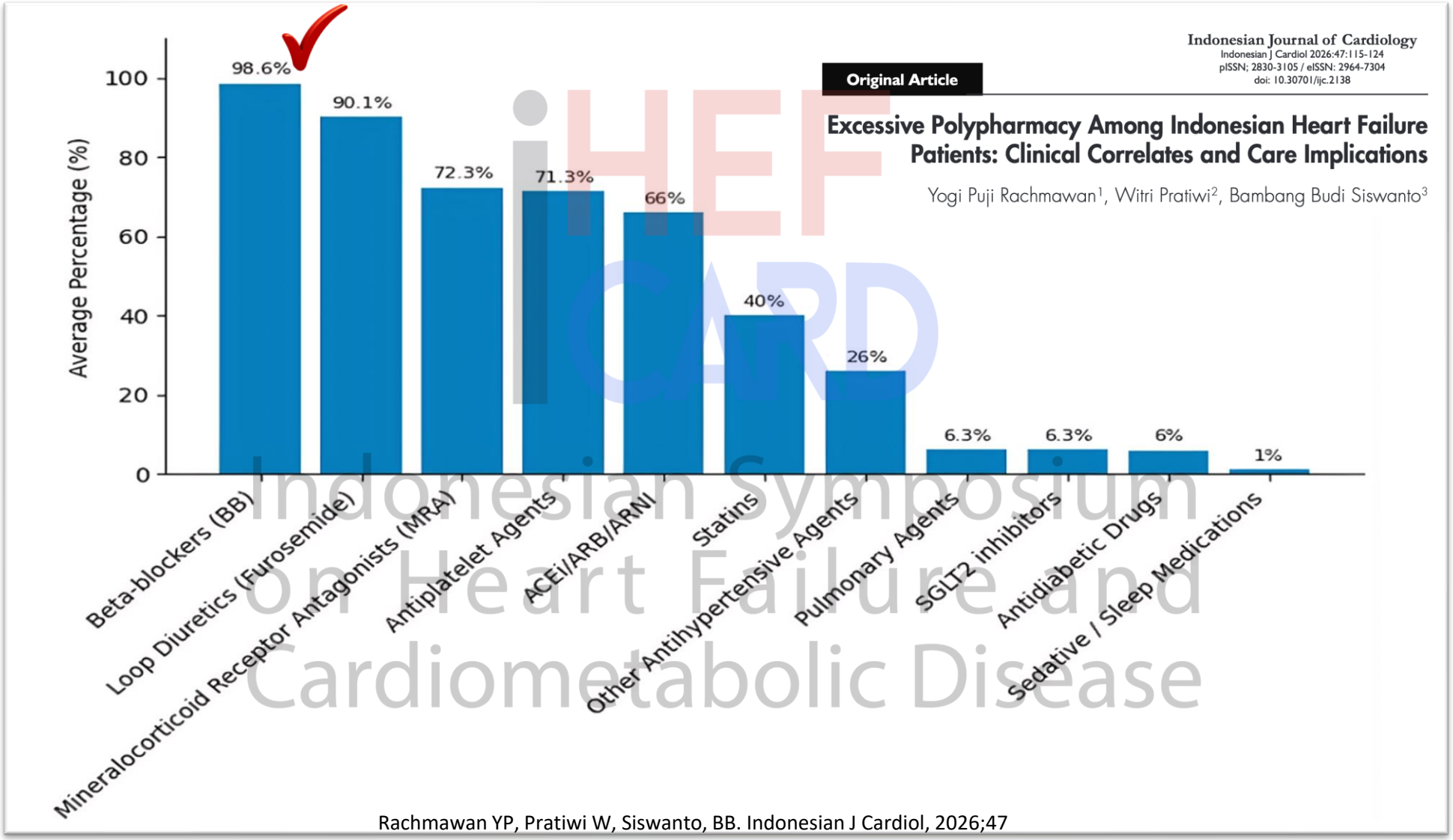
Teng, Tiew-Hwa K et al. The Lancet Global Health. 2018: e1008 - e1018

Proportion of prescribed medication classes among HF patients



Indonesian Journal of Cardiology
Indonesian J Cardiol 2026:47:115-124
pISSN: 2830-3105 / eISSN: 2964-7304
doi: 10.30701/ijc.2138

Original Article

Excessive Polypharmacy Among Indonesian Heart Failure Patients: Clinical Correlates and Care Implications

Yogi Puji Rachmawan[1], Witri Pratiwi[2], Bambang Budi Siswanto[3]

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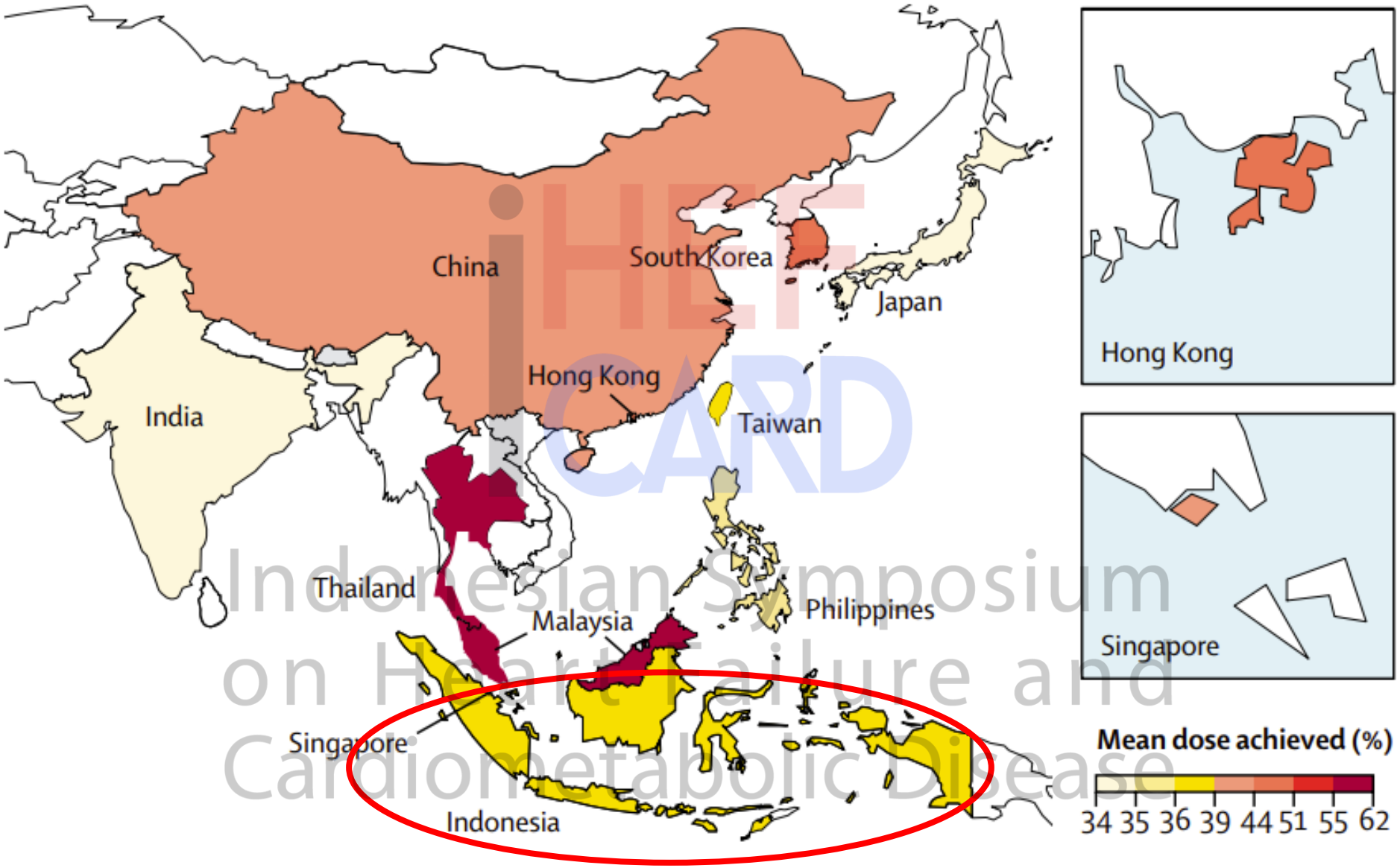
Rachmawan YP, Pratiwi W, Siswanto, BB. Indonesian J Cardiol, 2026;47



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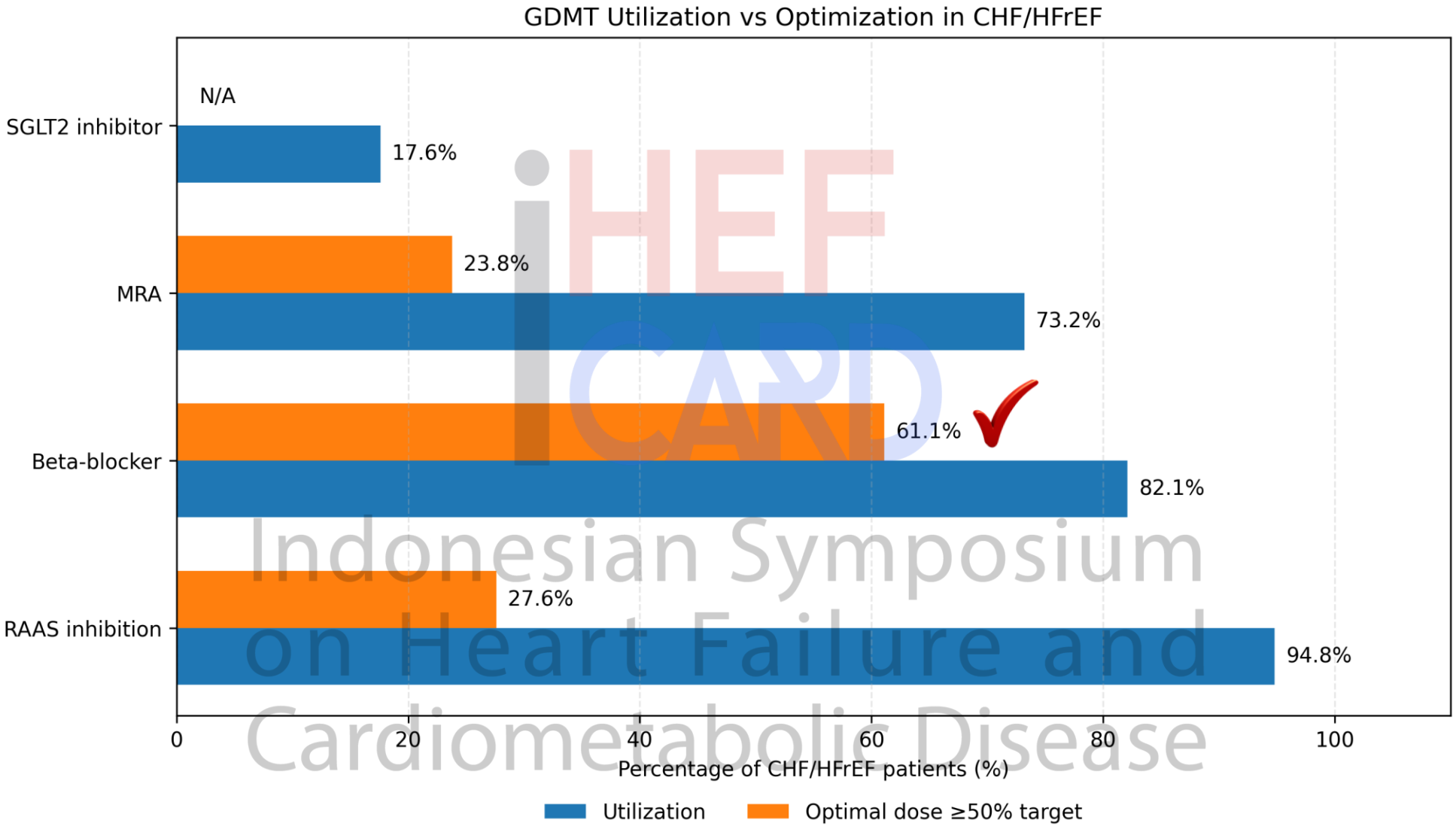
Teng, Tiew-Hwa K et al. The Lancet Global Health. 2018: e1008 - e1018



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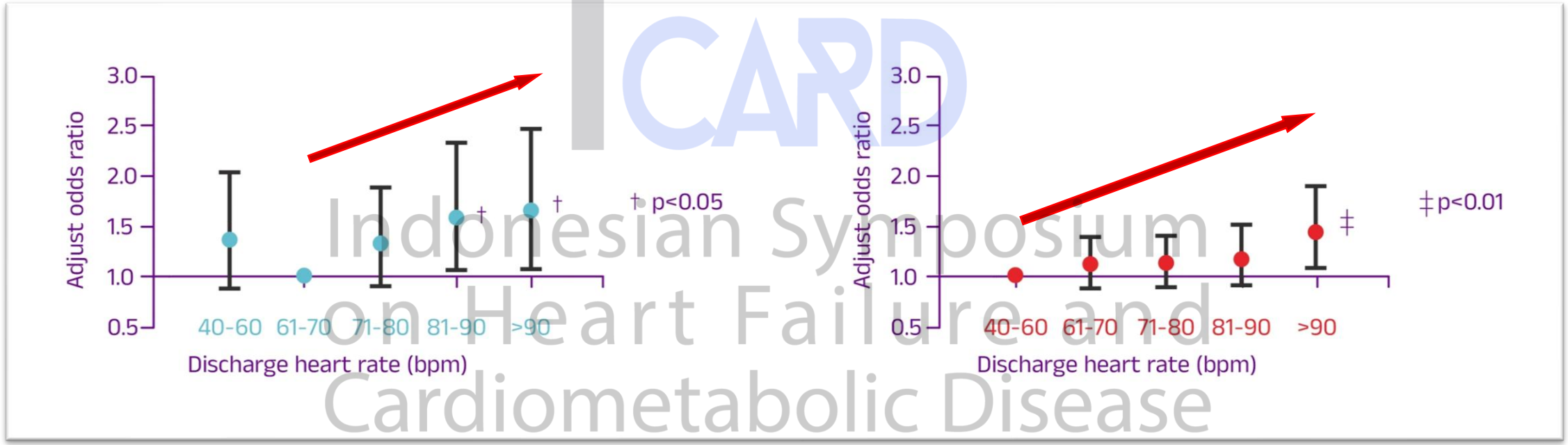
Data from I-TREAT HF Registry. Unpublished

Higher discharge HR was associated with a greater risk of all-cause mortality, cardiovascular death, and hospitalizations for HF

Higher discharge heart rates were associated with greater risk of mortality at 30 days and at 1 year.[1]



Association of discharge heart rate with 30-day cardiovascular death

Association of discharge heart rate with 1-year cardiovascular death

Habal MV et al. Circ Heart Fail 2014;7:12-20

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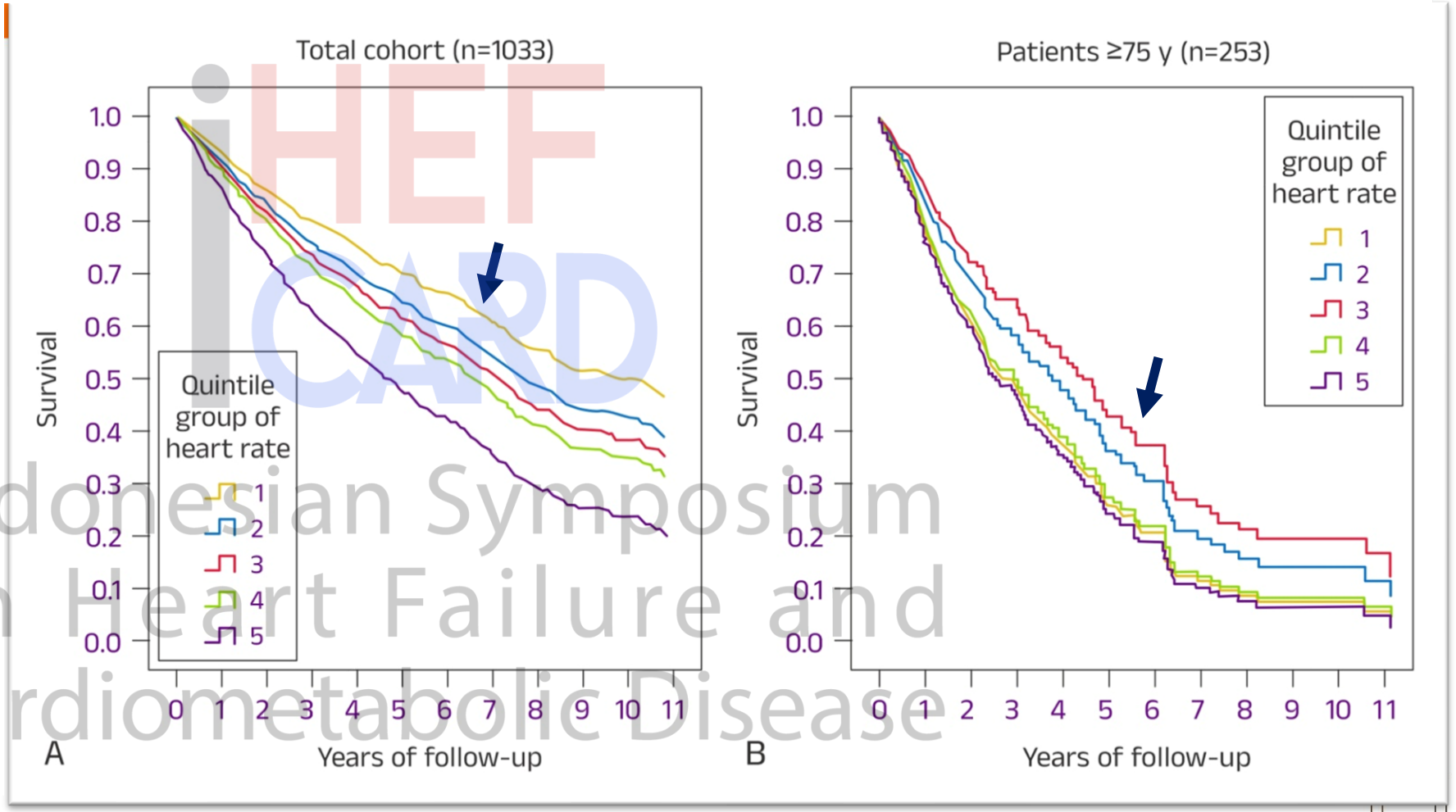
Survival curves according to heart rate quintiles

Heart rate quintiles:

1. less than 60 beats/min
2. 60 to 67 beats/min
3. 68 to 73 beats/min
4. 74 to 82 beats/min
5. 83 beats/min or higher

Patients aged 75 yo or older have the best outcomes with target **HR of 68 beats/min**; however,

Younger patients may benefit from lower heart rates, even **below 55 beats/min.**



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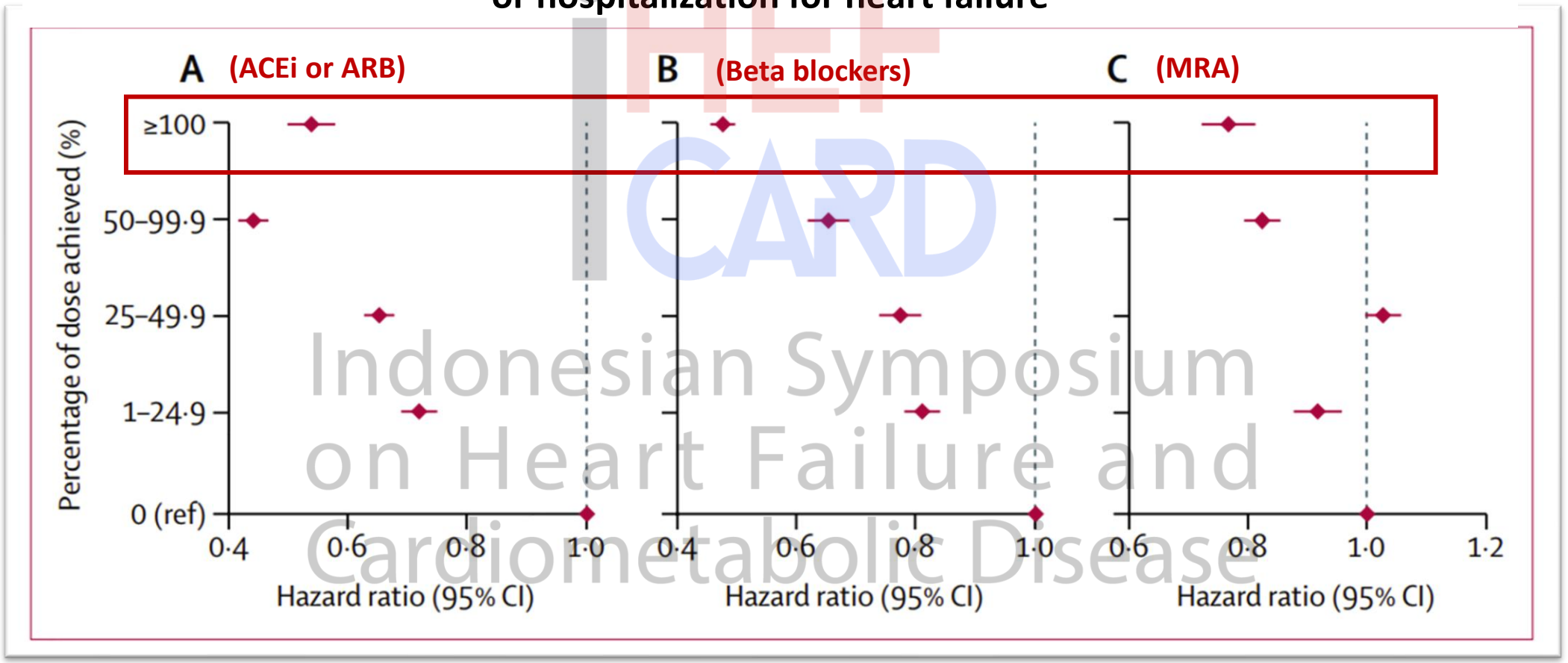
Mayo Clin Proc. 2015;90(6):765-772

Why dose is important?

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



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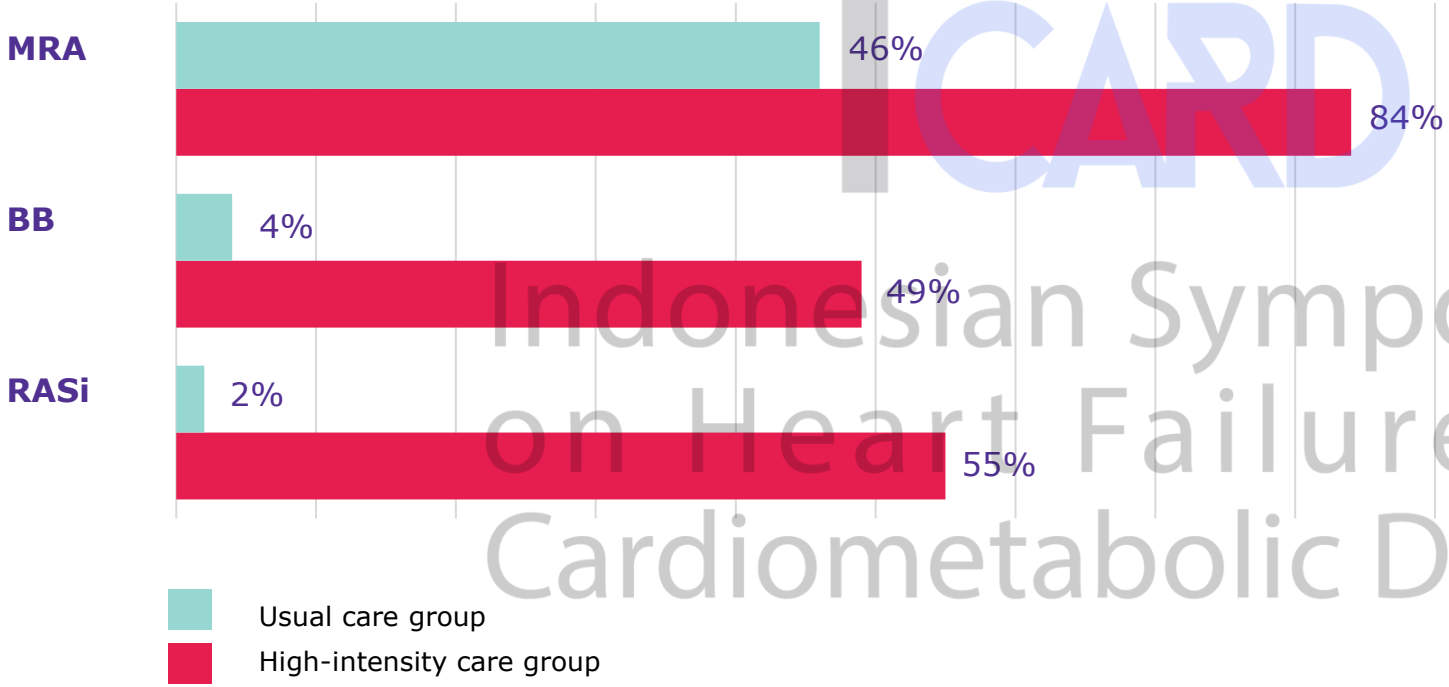
Teng, Tiew-Hwa K et al. The Lancet Global Health. 2018: e1008 - e1018

STRONG-HF Trial:

Up-titration of Guideline-Directed Medication to a Full-Dose was Achieved in 49-84% of patients in a High-Intensity Group Compared to 2-46% in a Usual Care Group

Percent of patients on full-dose guideline-directed drug treatment by day 90



Multinational, open-label, randomised, parallel-group trial (STRONG-HF), patients aged 18–85 years admitted to hospital with acute heart failure, not treated with full doses of guideline-directed drug treatment.

High-intensity care group - up-titration of treatments to 100% of recommended doses within 2 weeks of discharge and four scheduled outpatient visits over the 2 months after discharge, **usual care group** followed usual local practice.

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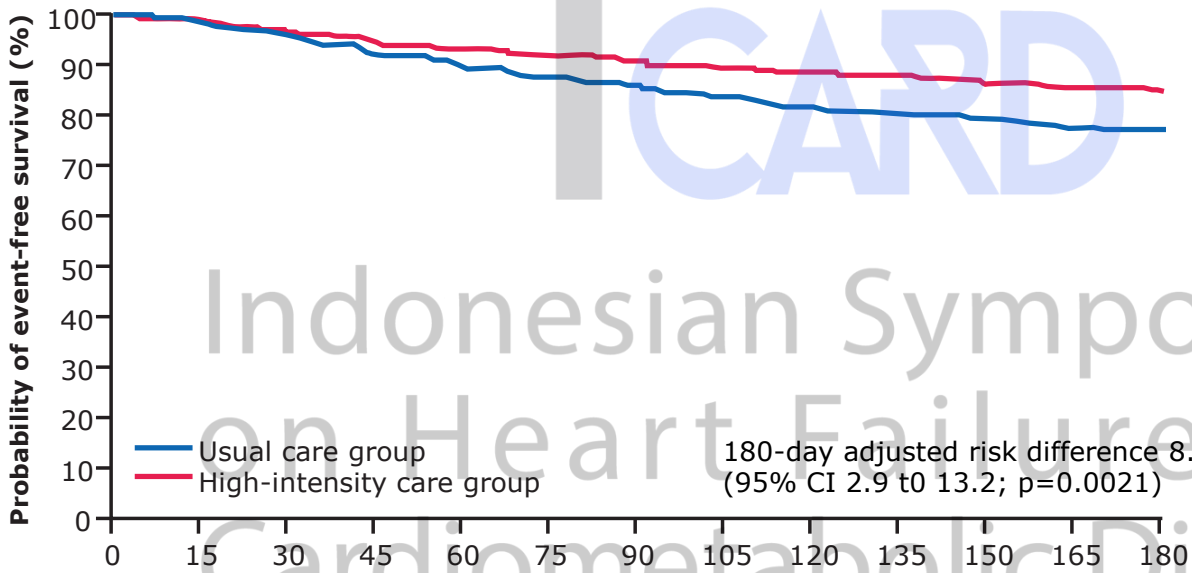
Adapted from Mebazaa A. et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. Lancet. 2022 Dec 3;400(10367):1938-1952.

STRONG-HF Trial:

Rapid Up-titration of Guideline-Directed Medication and Close Follow-up after an Acute Heart Failure Admission Reduced the Risk Of 180-day All-cause Death or Heart Failure Readmission Compared with Usual Care

Cumulative 180-day event-free (readmission to hospital due to heart failure or all-cause death) survival



-34%

Number at risk

Usual care group	502	494	474	454	439	423	410	394	381	373	366	353	329
High-intensity care group	506	497	484	466	449	440	430	419	415	408	397	384	345

Multinational, open-label, randomised, parallel-group trial (STRONG-HF), patients aged 18–85 years admitted to hospital with acute heart failure, not treated with full doses of guideline-directed drug treatment.

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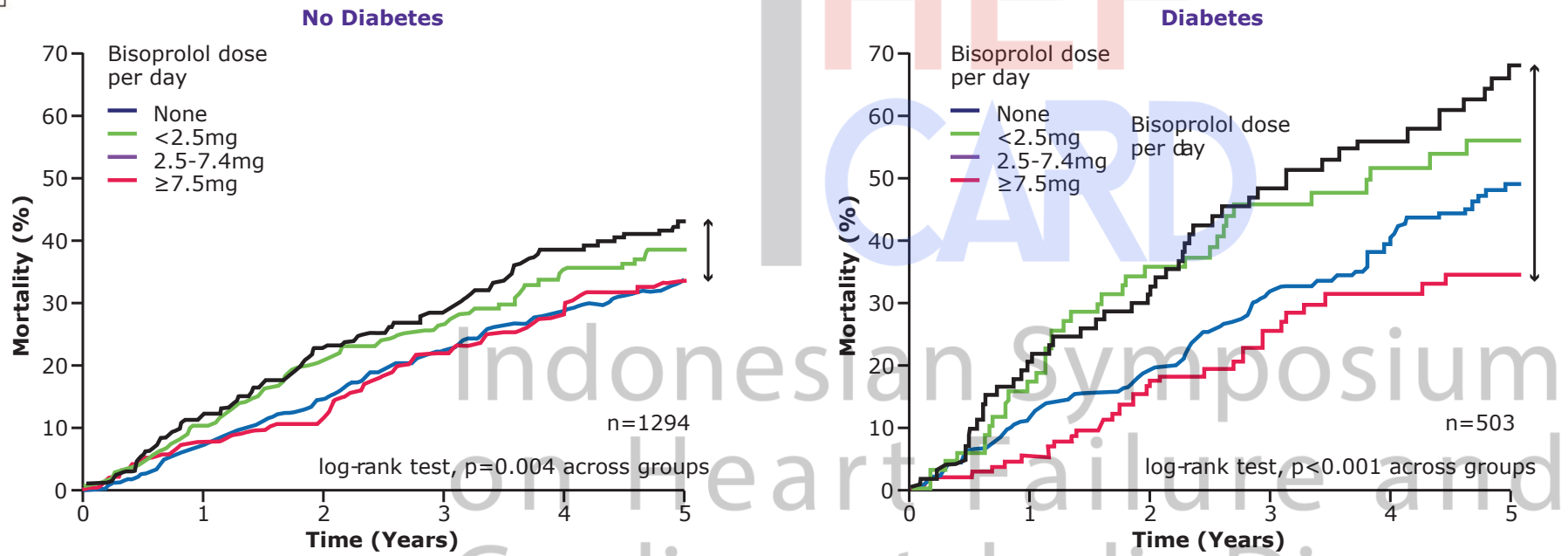
Increasing Beta-blocker Dose was Associated with Lower Mortality in Patients with HFrEF, with a Greater Prognostic Advantage in Diabetes

5-year all-cause mortality according to the dose of β-blocker in patients with and without diabetes



A prospective cohort study,1797 patients with CHF recruited between 2006 and 2014, with mean follow-up of 4 years, 28% of patients with diabetes, β-Blocker dose was expressed as the equivalent dose of bisoprolol (mg/day) as **83.8% received bisoprolol**, 10.8% received carvedilol, and 5.4% other beta-blockers (predominantly metoprolol or nebivolol). Cox regression analysis to examine the interaction between diabetes and drug dose on all-cause mortality.

Most pronounced association between higher beta-blocker dose and reduced mortality was in patients with diabetes and severe heart failure (LVEF<32%)

Bisoprolol must be used with special caution in diabetes mellitus with extremely fluctuating blood glucose levels; symptoms of hypoglycaemia (e.g., tachycardia, palpitations or sweating) may be masked.
For complete contraindications, warnings and precautions for use please refer to the locally approved Summary of Product Characteristics for your Country or the abbreviated prescribing information.

Adapted from Klaus K, et al. Mortality Reduction Associated With β-Adrenoceptor Inhibition in Chronic Heart Failure Is Greater in Patients With Diabetes. Diabetes Care 2018, 41 (1) 136-142.

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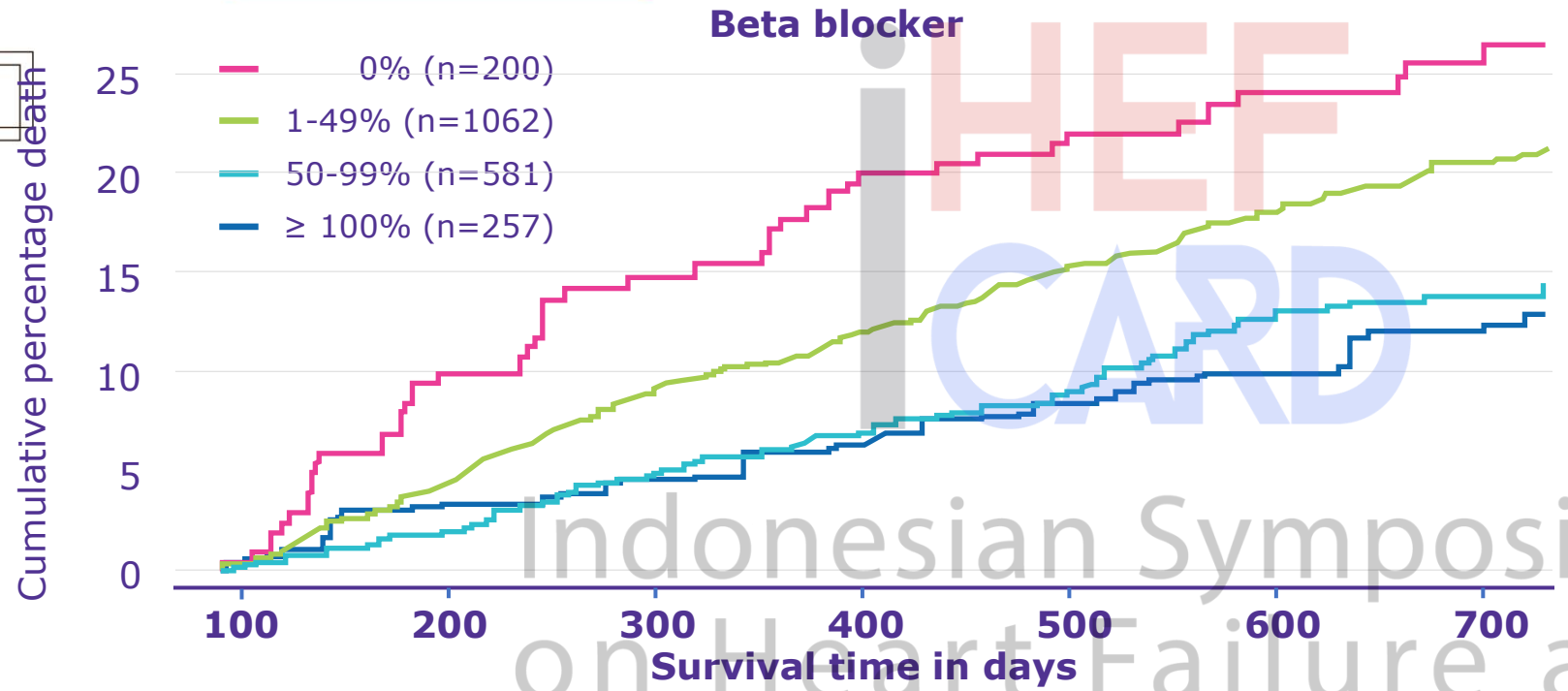
Reaching <50% of the recommended beta-blocker dose was associated with increased risk of death and/or heart failure hospitalization compared with patients reaching ≥100%[1]

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

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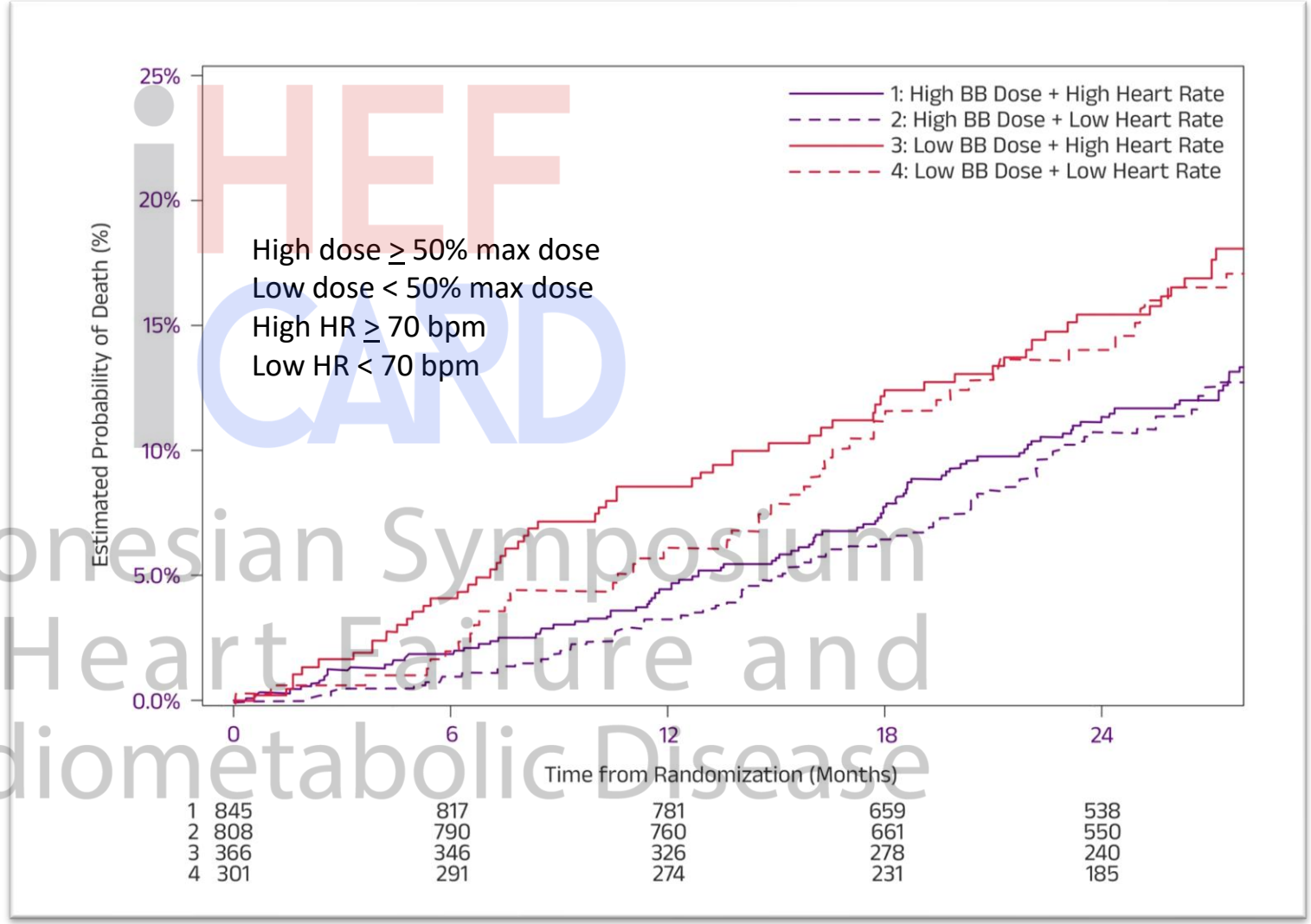
Estimated risk of death or hospitalization by discrete groups

HF-ACTION Trial

Higher BB dose remained significantly associated with improved outcomes **regardless of high or low HR**



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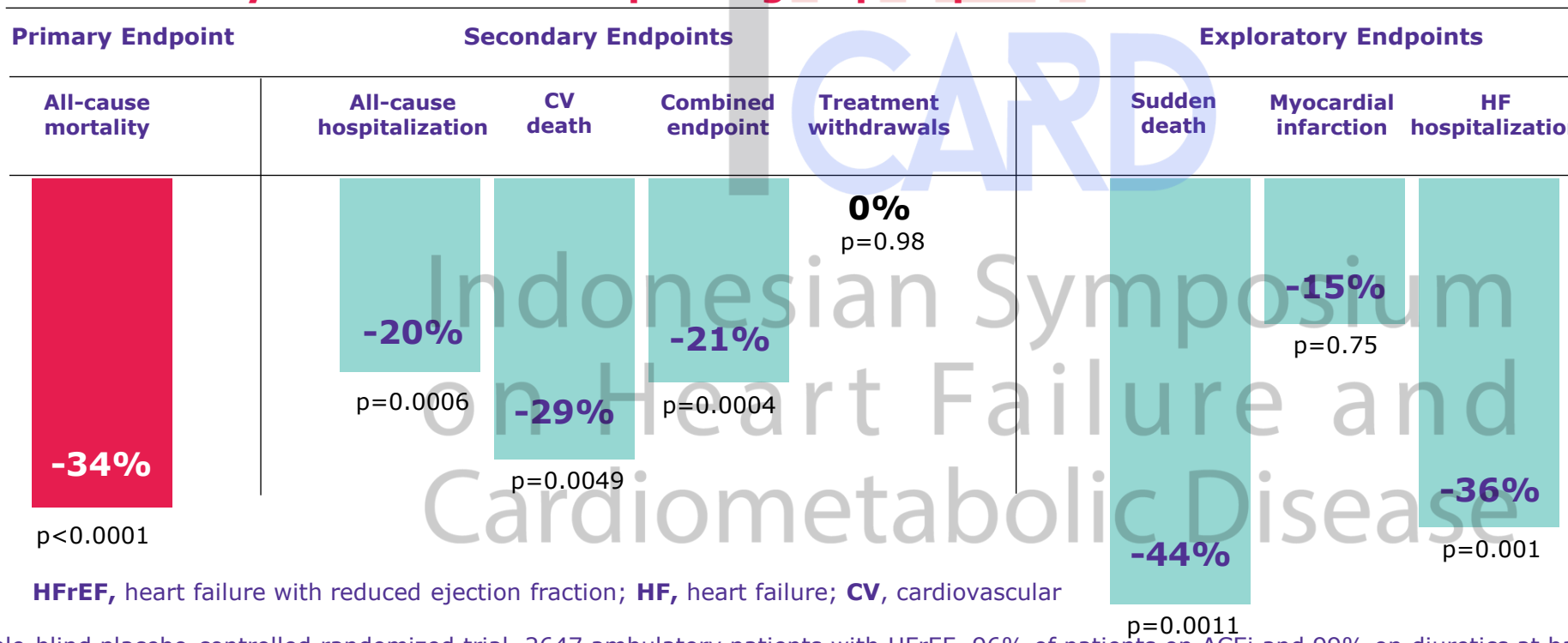
Fiuzat M eta l. J Am Coll Cardiol HF 2016;4:109–15

Why Bisoprolol May Be Recommended in Newly Diagnosed HFrEF?

Bisoprolol Given in Addition To Standard Therapy Significantly Reduced All-cause and CV Mortality, All-cause and CV Hospitalizations, and Sudden Death in Stable HFrEF Patients and was Well Tolerated

CIBIS II key outcomes in bisoprolol group vs placebo



54% of patients were treated with bisoprolol 7,5 or 10 mg

HFrEF, heart failure with reduced ejection fraction; **HF,** heart failure; **CV**, cardiovascular

Double-blind placebo-controlled randomized trial, 2647 ambulatory patients with 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

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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

High dose of Bisoprolol (10 mg/day) offered **70%** all cause mortality risk reduction benefit comparing to low dose (1.25 – 3.75 mg/day)

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

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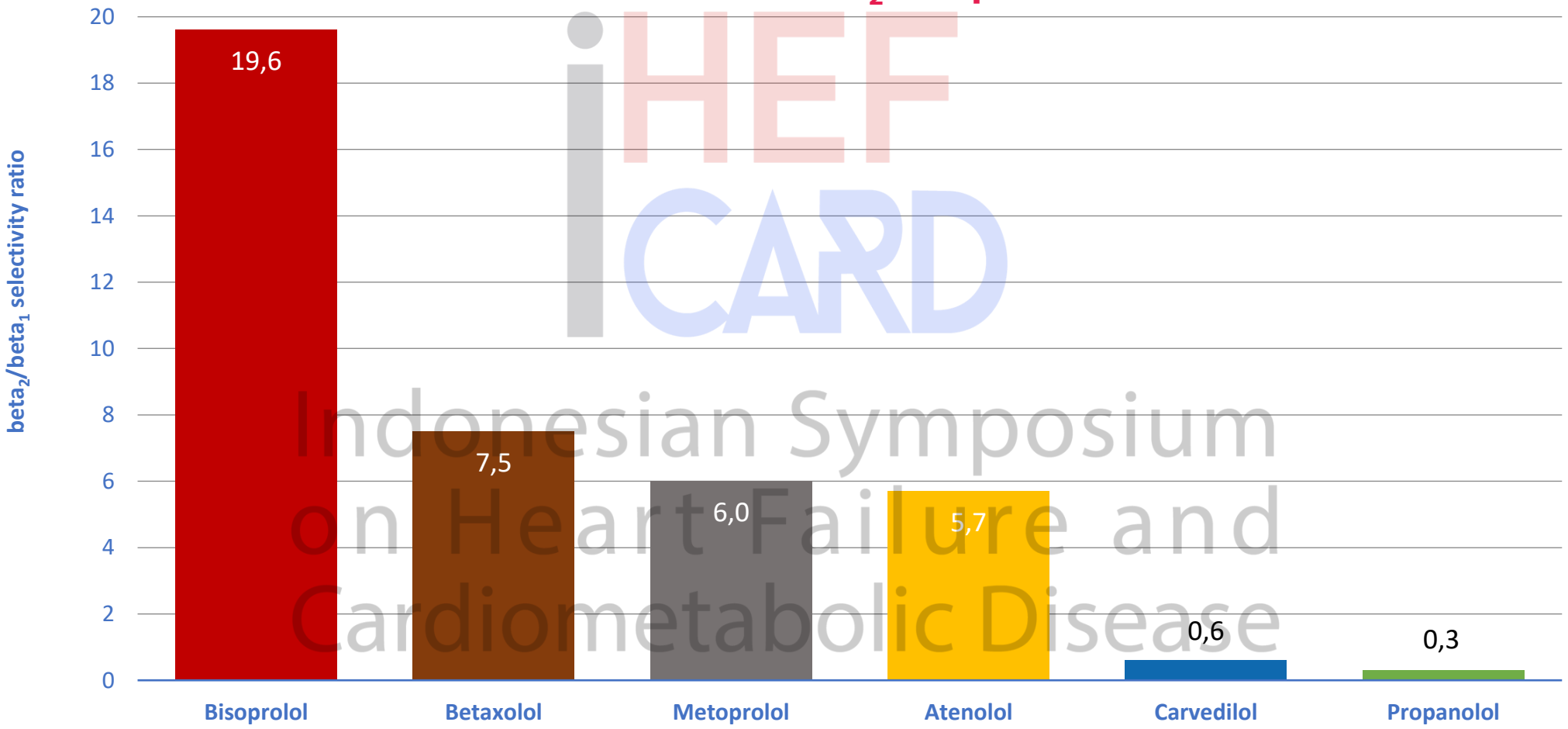
Bisoprolol:
Beta2/beta1 selectivity ratio at human beta-receptors in vitro1,2

Bisoprolol has a 19.6-fold higher affinity for the $beta_1$ receptor than for the $beta_2$ receptor[1]



Graph adapted from reference 2

1. Smith C, Teitler M. Beta-blocker selectivity at cloned human beta1- and beta2-adrenergic receptors. Cardiovasc Drugs Ther. 1999;13:123–6.
2. Cruickshank JM. Essential Hypertension. Shelton, CT: People's Medical Publishing House-USA;2013, Fig. 8-28

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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.*

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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.

©ESC

Theresa A McDonagh, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal (2021) 42, 3599 - 3726

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.

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2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Recommendations	Class [a]	Level [b]
When pauses >3 seconds are identified on the ECG, or if the bradycardia is symptomatic and the resting ventricular rate is <50 bpm in sinus rhythm or <60 bpm in AF, it should be considered whether there is need for any rate limiting medications prescribed; for patients in sinus rhythm beta-blockers should be reduced in dose or withdrawn only as a last resort.	IIa	C

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Ponikowski P, et al. Eur Heart J 2016;37:2129-2200

Take home messages

- **Heart rate matters more than we think**
  Higher heart rate is consistently associated with worse clinical outcomes in heart failure.
- **GDMT alone is not enough—dose optimization matters**
  Achieving higher doses of guideline-directed therapy is associated with better survival and fewer hospitalizations.
- **Rapid up-titration with close follow-up improves outcomes**
  Early optimization after discharge reduces rehospitalization and mortality.
- **Reaching at least 50% of target beta-blocker dose should be prioritized**
  Patients receiving lower doses have substantially worse outcomes.
- **Optimize early, optimize aggressively, optimize continuously**
  Improving heart rate control and GDMT optimization should become a routine part of HFrEF care.

Matur Nuwun

Thank You..

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