The 3rd Indonesian Symposium on Heart Failure and Cardiometabolic Disease 2023

# Beta Blocker Dose vs Target Heart Rate in Heart Failure: which one is the better goal?

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# Disclosure

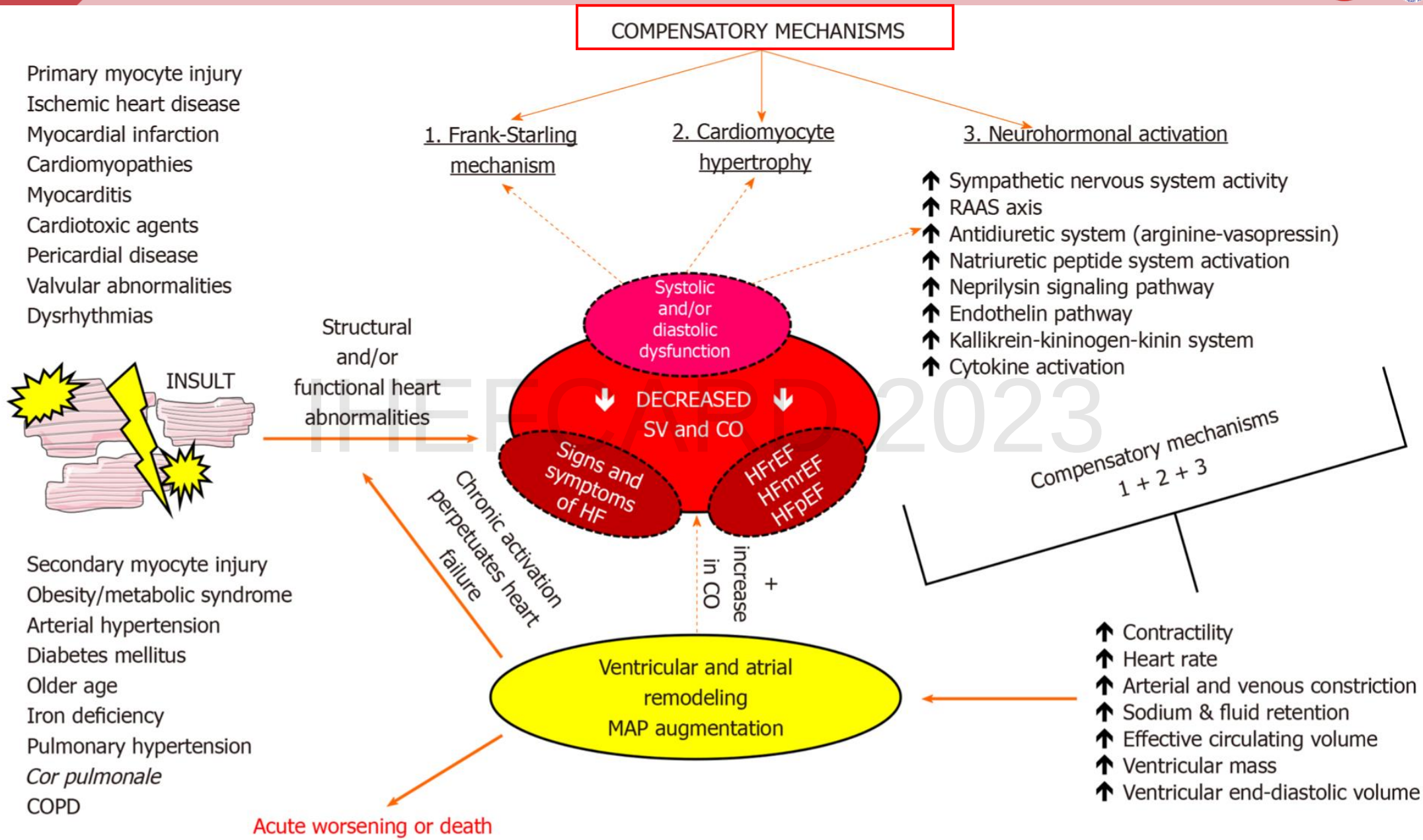
MERCK

# Introduction

- β-Blockers are one of the cornerstones in the treatment of heart failure (HF) with reduced ejection fraction (HFrEF) patients.
- Trials with β-blockers have documented consistent effects on reducing morbidity and mortality in HFrEF patients.
- Recent data have shown that HR is an important modifiable risk factor in improves outcomes in chronic HF patients.
- It has also been shown that titration of doses of BBs reduce mortality in heart failure patients
- Conflicting evidence exists on whether clinicians should target β-blocker dose, HR reduction, or both, in chronic HF



Eriksen-Volnes T, Westheim A, Gullestad L, Slind EK, Grundtvig M. β-Blocker Doses and Heart Rate in Patients with Heart Failure: Results from the National Norwegian Heart Failure Registry. Biomed Hub. 2020 Feb 21;5(1):9-18.
Fiuzat et al. Heart Rate vs. Beta-Blocker Dose and Outcomes From the HF-ACTION Trial. JACC Heart Failure 2016








Borovac et al. World J Cardiol. 2020;12(8):373-408

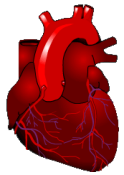
# Sympathetic overdrive plays a key role in the pathophysiology of cardiovascular disease

**⇧ Sympathetic nervous activity**

**Neural release of norepinephrine**



**$Beta_1$ receptor stimulation**



- ⇧ Heart rate
- ⇩ Heart rate variability
- ⇧ Contractility

**Mechanical/ vascular damage**

- Pulsatile stress on vascular system
- Augment atherosclerosis
- Plaque rupture
- Risk of cardiac ischemia

**$Beta_1$ receptor stimulation**

- ⇧ Renin release
- ⇧ Angiotensin
- ⇧ Blood pressure
- ⇧ Left ventricular hypertrophy
- ⇧ Heart failure

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

# Principles and Pathophysiologic Targets of HFrEF Pharmacotherapy

## 5 PATHWAYS

Modulation of five pathways shown to improve outcomes in the general HFrEF population

**Angiotensin 2**

**Norepinephrine**

**Aldosterone**

**Neprilysin**

**SGLT**

## 4 DRUGS

**ARNI**

*May start with ACEi/ARB or ARNI in de novo. May use ACEi/ARB if cost or availability concerns.*

**Beta-blockers**

*Carvedilol, bisoprolol, metoprolol succinate*

**MRAs**

**SGLT2i**

*Dapagliflozin, Empagliflozin*

## 3 OTHERS

Three additional pathways shown to improve outcomes in specific populations:

**Ivabradine**

*NSR HR≥70 bpm*

**Hydralazine/nitrate**

*Self identified blacks*

**Vericiguat**

*Worsening HF*



Tolerability, availability, costs, patient preference, and other consideration may impact choices, doses, and sequences of therapies – but pharmaco-pathophysiologic rationale suggests that **all attempts should be made to modulate all five pathways**.

Carolyn SP Lam, Javed Butler. Circulation 2020;142:1129-1131

# HF Guideline CCS 2021

## Management of HFrEF

**To reduce mortality - for all patients**

ACE-I/ARNI | BB | MRA | SGLT2i

**To reduce HF hospitalization/mortality - for selected patients**

*Volume overload*
- Diuretics

| | |
|---|---|
| *SR with LBBB ≥ 150 ms* — CRT-P/D | *SR with LBBB 130–149 ms or non LBBB≥ 150 ms* — CRT-P/D |
| *Ischaemic aetiology* — ICD | *Non-ischaemic aetiology* — ICD |
| *Atrial fibrillation* — Anticoagulation | *Atrial fibrillation* — Digoxin, PVI |
| *Coronary artery disease* — CABG | *Iron deficiency* — Ferric carboxymaltose |
| *Aortic stenosis* — SAVR/TAVI | *Mitral regurgitation* — TEE MV Repair |
| *Heart rate SR>70 bpm* — Ivabradine | *Black Race* — Hydralazine/ISDN |
| *ACE-I/ARNI intolerance* — ARB | |

**For selected advanced HF patients**

Heart transplantation | MCS as BTT/BTC | Long-term MCS as DT

**To reduce HF hospitalization and improve QOL - for all patients**

Exercise rehabilitation

Multi-professional disease management

ESC

TREAT COMORBIDITIES PER CCS HF RECOMMENDATIONS (INCL. AF, FUNCTIONAL MR, IRON DEF, CKD, DM)

DIURETICS TO RELIEVE CONGESTION (TITRATED TO MINIMUM EFFECTIVE DOSE TO MAINTAIN EUVOLEMIA)

**HFrEF: LVEF ≤ 40% AND SYMPTOMS**

**Initiate Standard Therapies**

| ARNI or ACEi/ARB then substitute ARNI | BETA BLOCKER | MRA | SGLT2 INHIBITOR |
|---|---|---|---|

**Assess Clinical Factors for Additional Interventions**

| HR >70 bpm and sinus rhythm | Recent HF hospitalization | Black patients on optimal GDMT, or patients unable to tolerate ARNI/ACEi/ARB | Suboptimal rate control for AF, or persistent symptoms despite optimized GDMT |
|---|---|---|---|
| • Consider ivabradine* | • Consider vericiguat ** | • Consider combination hydralazine-nitrates | • Consider digoxin |

*Initiate standard therapies as soon as possible and titrate every 2-4 weeks to target or maximally tolerated dose over 3-6 months*

**Reassess LVEF, Symptoms, Clinical Risk**

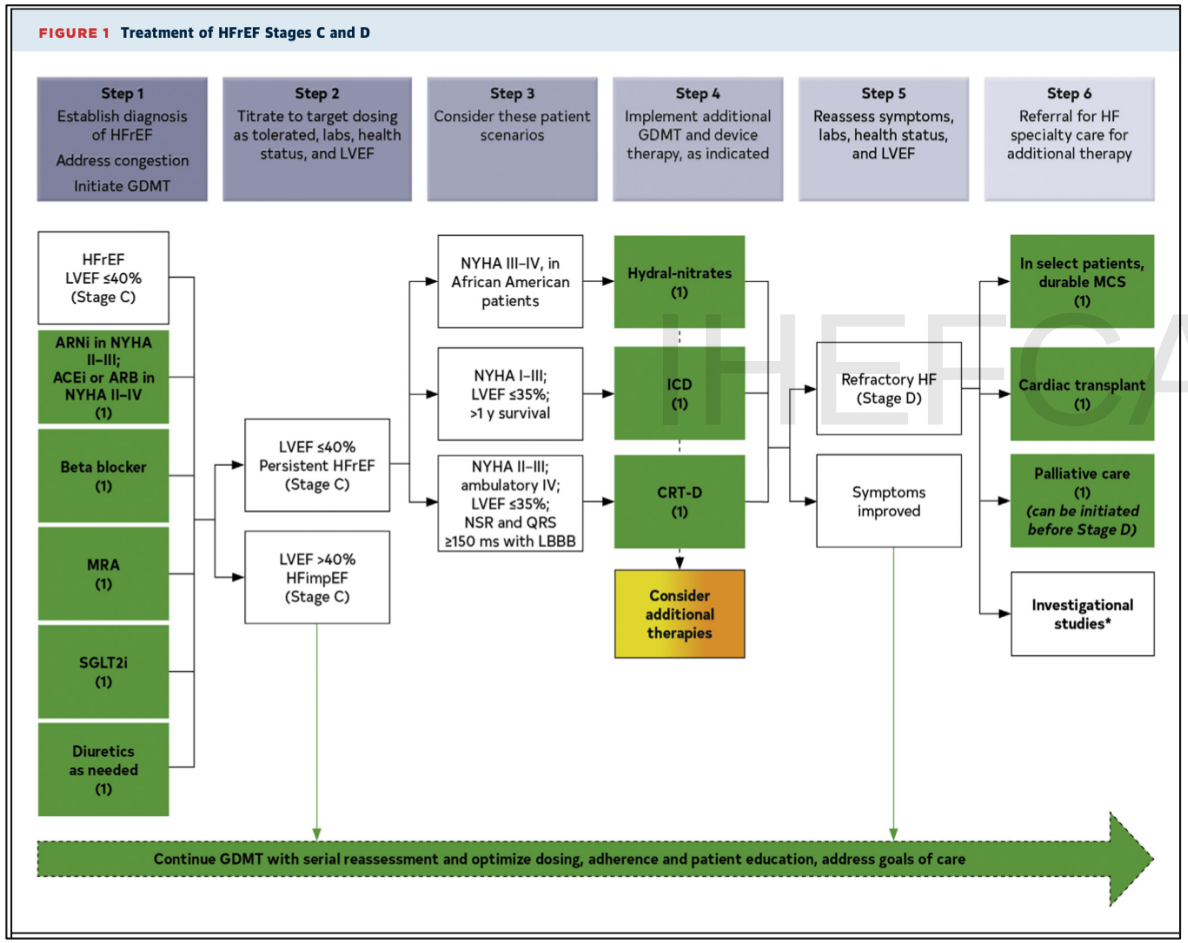
| NYHA III/IV, Advanced HF or High-Risk Markers | LVEF ≤ 35% and NYHA I-IV (ambulatory) | LVEF > 35%, NYHA I, and Low Risk |
|---|---|---|
| CONSIDER<br>• Referral for advanced HF therapy (mechanical circulatory support/transplant)<br>• Referral for supportive/palliative care | Refer to CCS CRT/ICD recommendations | Continue present management, reassess as needed |

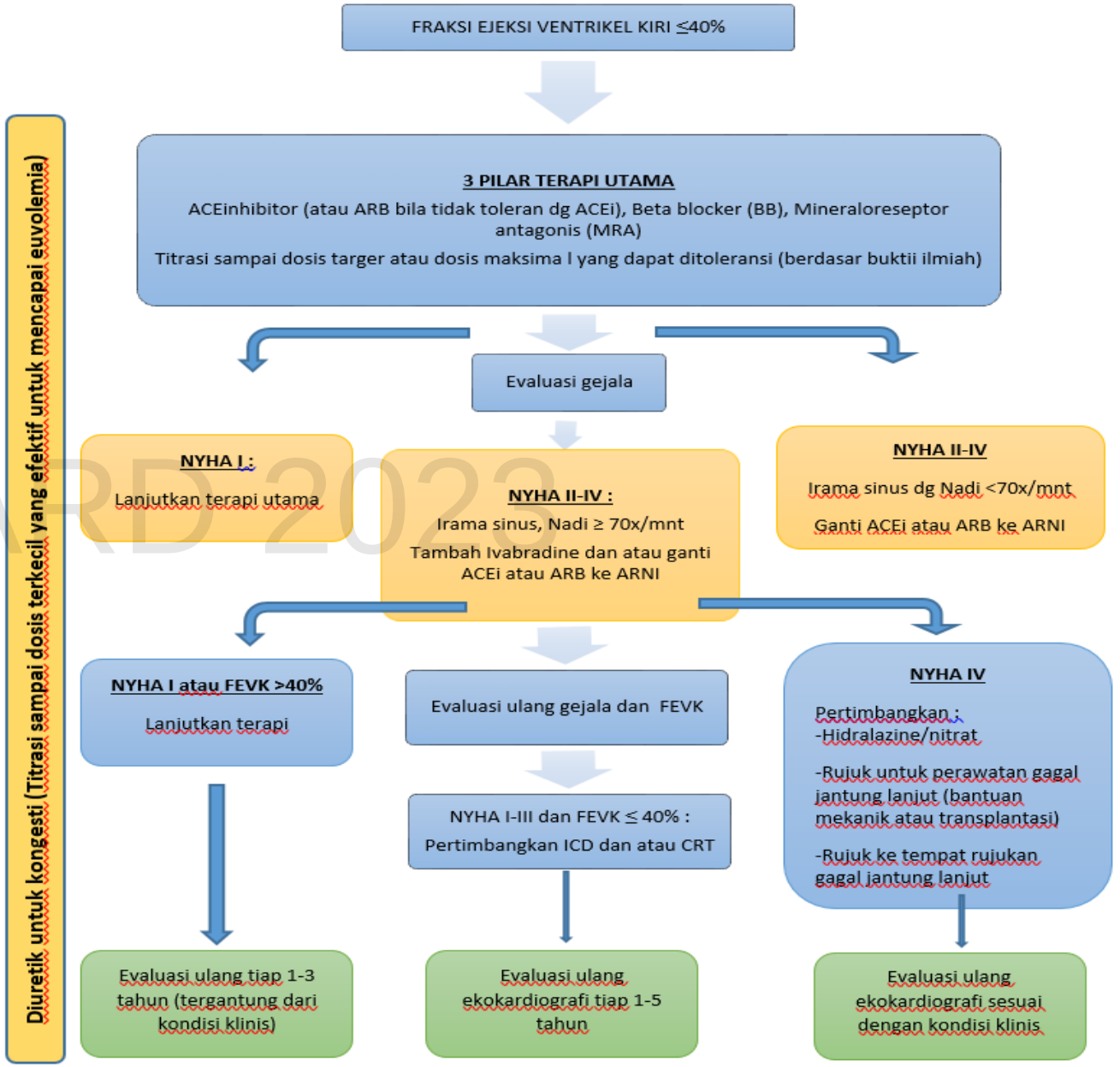
NON-PHARMACOLOGIC THERAPIES (EDUCATION, SELF-CARE, EXERCISE)

ADVANCE CARE PLANNING AND DOCUMENTATION OF GOALS OF CARE

| 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.* |

# HF Guideline ACC 2022



# Benefit of β-blockers in Heart Failure

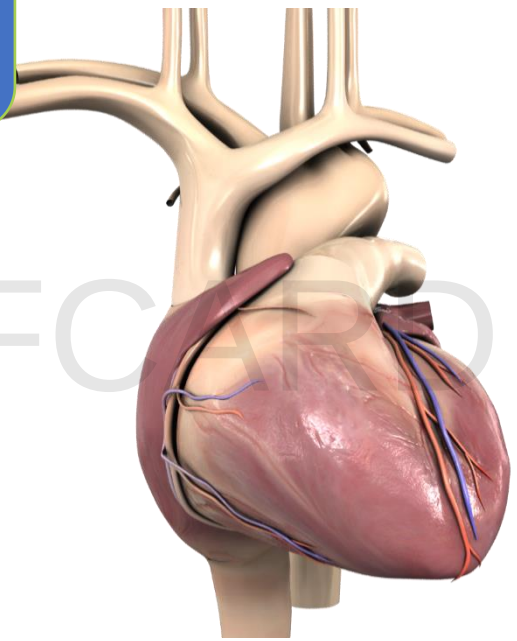
**Reduction of sympathetic tone**[3,4]
⇧ Increase in vagal tone
⇧ Improved autonomic balance/heart rate variability
⇩ Reduced sudden death

**Antiarrhythmic activity**[1-4]
⇩Reduced sudden death

**Up-regulation of cardiac $\beta_1$-receptors**[1-4]

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

**Antagonism of stimulatory $\beta_1$-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

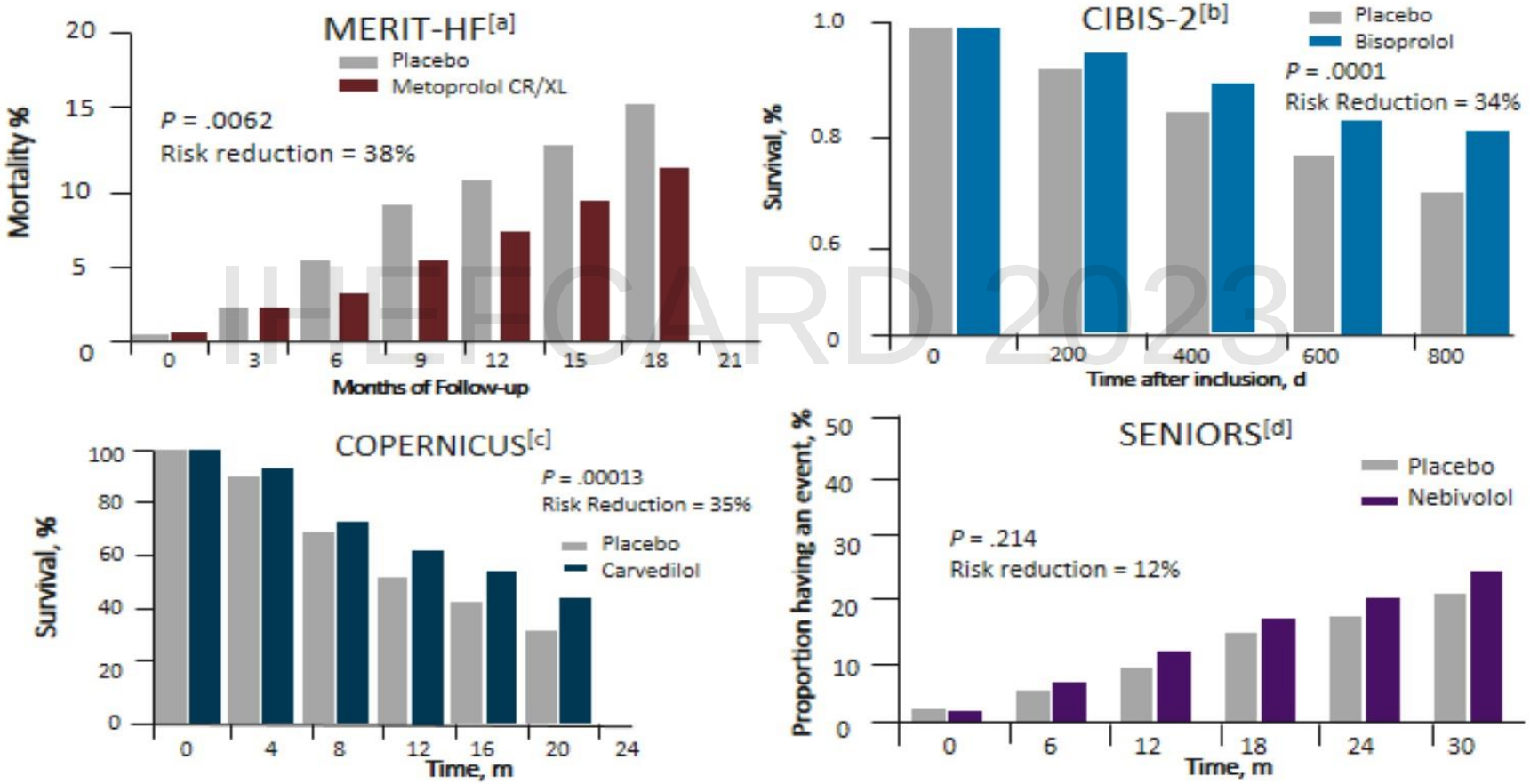
**Inhibition of catecholamine-induced necrosis/apoptosis/ inflammation** (reduced cytokines)[2-4]

**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

# Beta Blockers Reduce All-Cause Mortality and Hospitalization 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.

**TABLE 1** Characteristics of Major β-Blocker Trials in HF

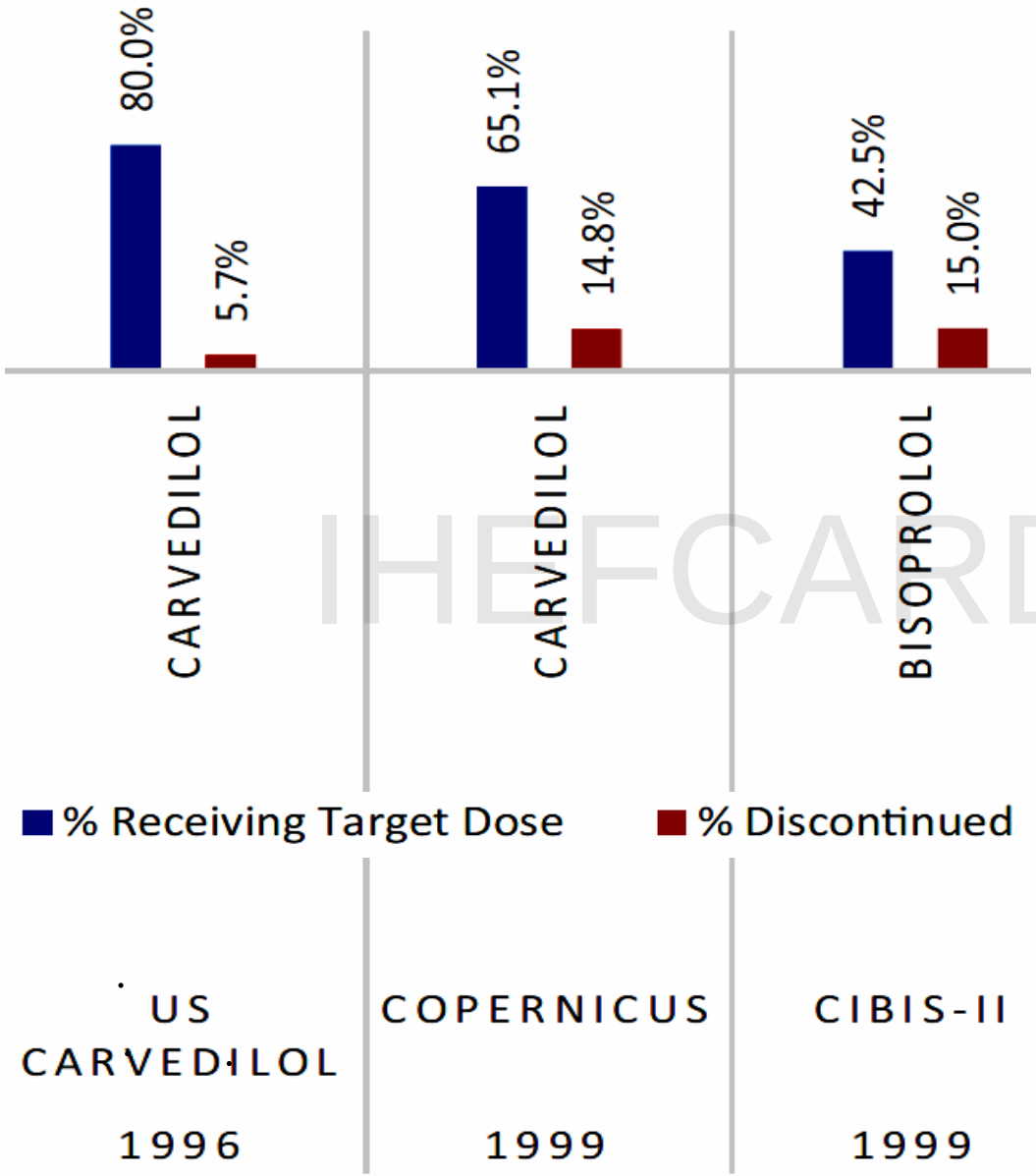
| | Study | | | | | |
|---|---|---|---|---|---|---|
| | **USCS (N = 1,094)** | **MERIT-HF (N = 3,991)** | **CIBIS-II (N = 2,647)** | **COPERNICUS (N = 2,289)** | **BEST (N = 2,708)** | **SENIORS (N = 2,128)** |
| β-blocker | Carvedilol | Metoprolol Succinate | Bisoprolol | Carvedilol | Bucindolol | Nebivolol |
| Mean age, yrs | 58 | 64 | 61 | 64 | 60 | 76 |
| Starting dose, mg | 6.25 b.i.d. | 12.5 q.d. | 1.25 q.d. | 3.125 b.i.d. | 3.0 b.i.d. | 1.25 q.d. |
| Target dose, mg | 25-50 b.i.d. | 200 q.d. | 10 q.d. | 25 b.i.d. | 50-100 b.i.d. | 10 q.d. |
| Mean daily dose achieved, mg | 45.0 | 159.0 | 7.5 | 37.0 | 152.0 | 7.7 |
| Baseline heart rate, beats/min* | 84 ± 12 | 83 ± 10 | 80 ± 15 | 83 ± 13 | 82 ± 13 | 79 ± 14 |
| Heart rate reduction, beats/min | 12.6 | −14.0 | −9.8 | NR | −9.4 | −10.3 |
| Baseline SBP, mm Hg* | 116 ± 17 | 130 ± 17 | 129 ± 19 | 123 ± 19 | 117 ± 18 | 139 ± 20 |
| Titration period, weeks | 2-10 | 1-8 | 1-15 | 1-8 | 1-9 | 1-16 |
| % Relative effect on all-cause mortality | ↓ 65 | ↓ 34 | ↓ 34 | ↓ 35 | ↓ 10 | ↓ 12 |
| p value | <0.001 | <0.001 | <0.001 | <0.001 | 0.13 | 0.21 |

*Values are mean ± SD.

↓ = reduced; BEST = Beta-Blocker Evaluation of Survival Trial; b.i.d. = twice a day; CIBIS-II = Cardiac Insufficiency Bisoprolol Study II; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; HF = heart failure; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; q.d. = daily; SBP = systolic blood pressure; SENIORS = Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure; USCS = U.S. Carvedilol HF Study.



Bhatt et al. J Am Coll Cardiol 2017;69:2542–50

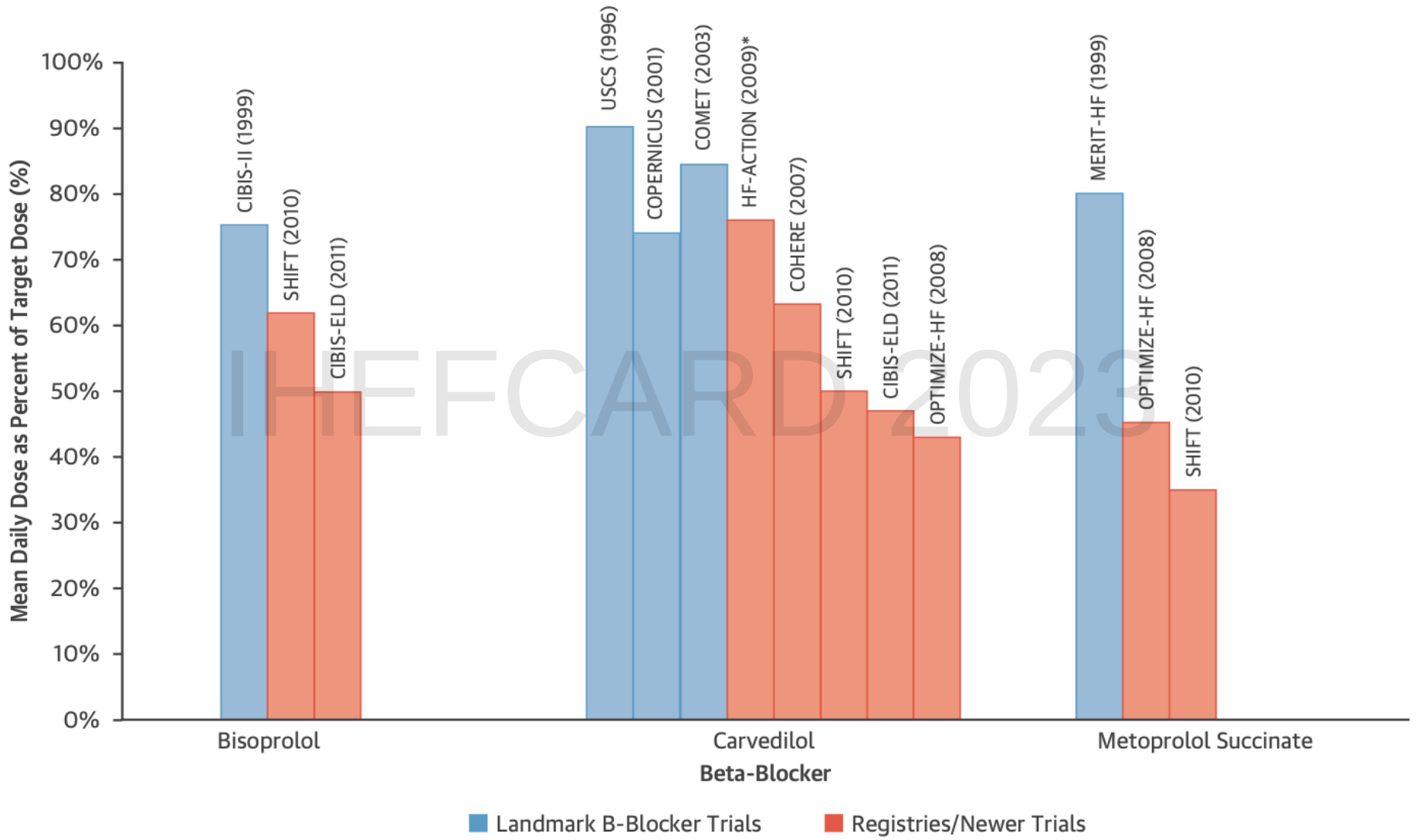



# Achievement of Target Dose in Clinical Trials



Bozkurt B. JACC: Heart Failure 2019;7:359-62

**FIGURE 1** Percentage of Target β-Blocker Dose Achieved in Major Clinical Trials and Registries

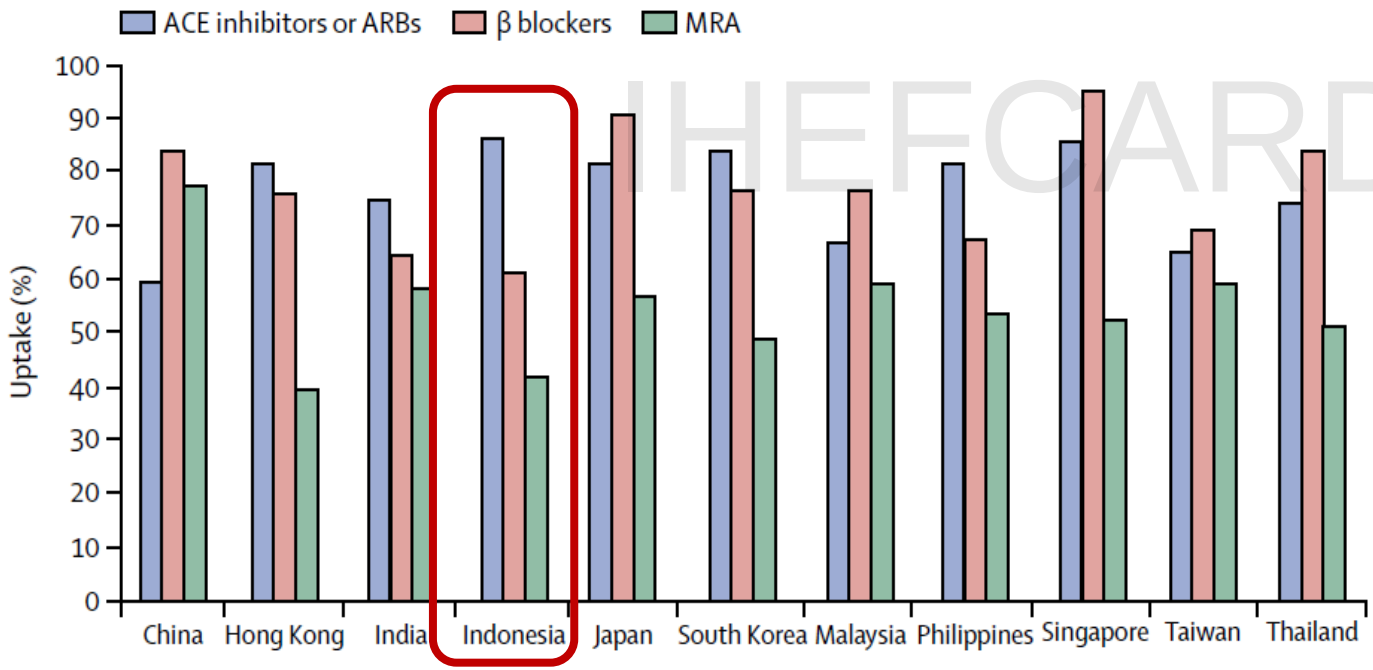





Bhatt et al. J Am Coll Cardiol 2017;69:2542–50

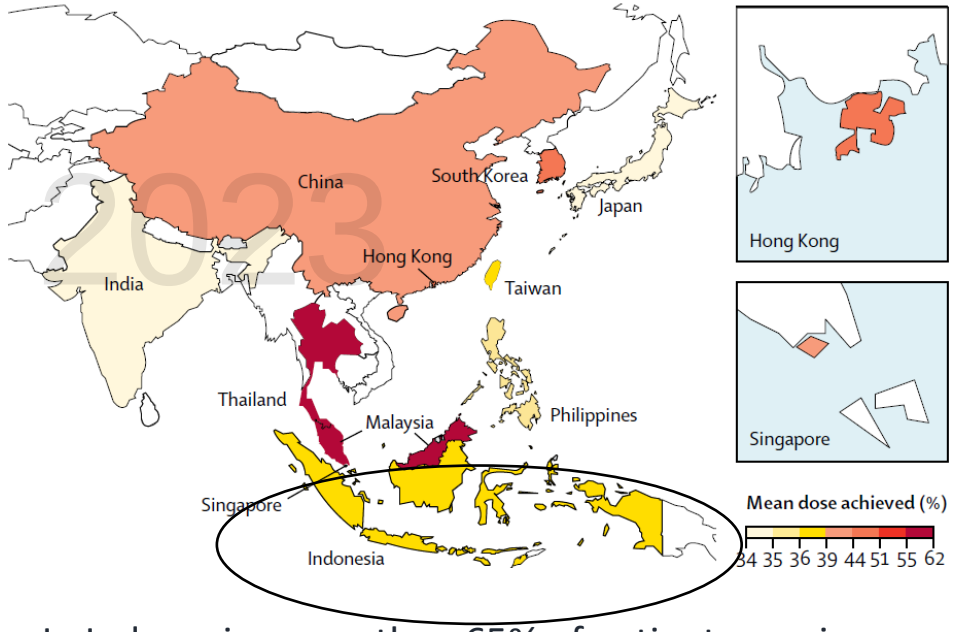
# Under-utilization of Medical Therapy in Indonesia

- Overall uptake 79% but only 13% achieved guideline-recommended doses
- Median dosage fraction 0.25 (IQR 0.13-0.5)
- Lowest in India; highest in Malaysia & Thailand
- Highest uptake (91%) but lowest mean doses in Japan






**BBs Mean Dose Achieved in Indonesia**



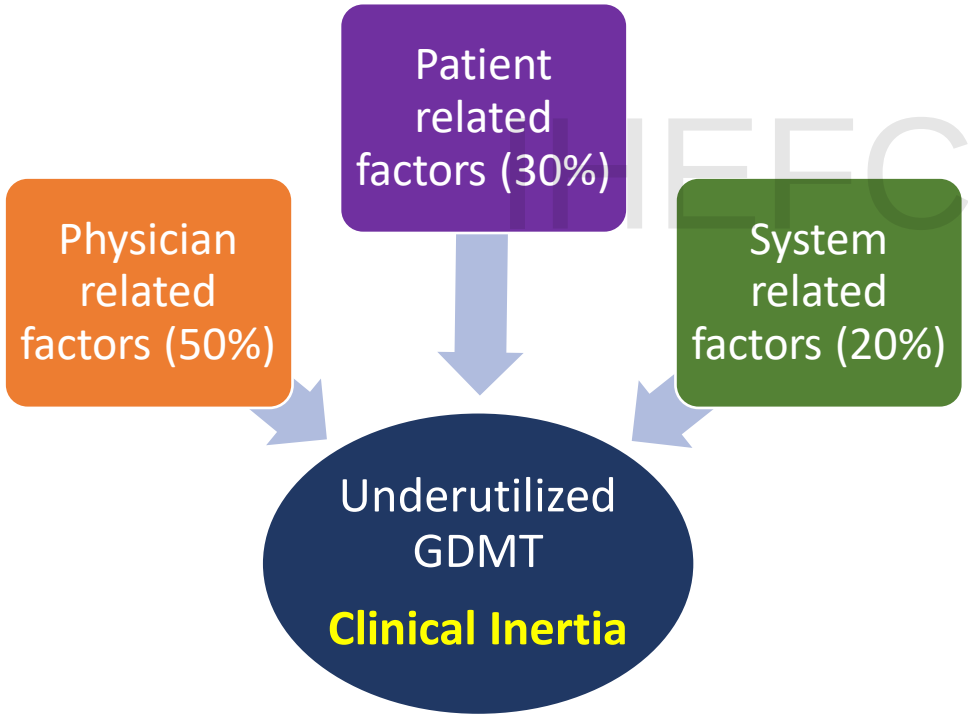

In Indonesia, more than 65% of patients receive <50% of BBs target dose

Tiew-Hwa K.T, et al. Glob Health. 2018 (Asian HF Registry)

Heart Failure Reviews (2021) 26:1359–1370
https://doi.org/10.1007/s10741-020-09979-z

# Clinical inertia in the treatment of heart failure: a major issue to tackle

Caroline Verhestraeten[1] · Ward A. Heggermont[2,3] · Michael Maris[1]






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

JACC: HEART FAILURE VOL. 4, NO. 2, 2016
ISSN 2213-1779
http://dx.doi.org/10.1016/j.jchf.2015.09.002



# Heart Rate or Beta-Blocker Dose? Association With Outcomes in Ambulatory Heart Failure Patients With Systolic Dysfunction

## Results From the HF-ACTION Trial

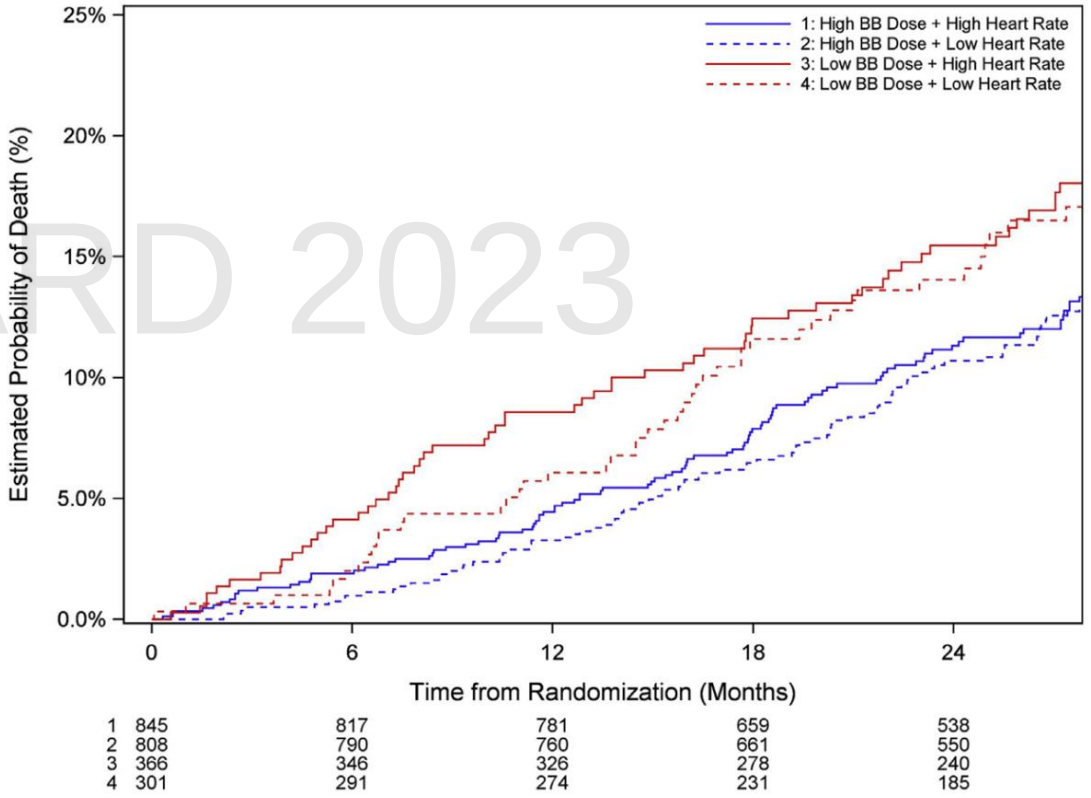
Mona Fiuzat, PharmD,[a] Daniel Wojdyla, MS,[a] Ileana Pina, MD,[b] Kirkwood Adams, MD,[c] David Whellan, MD,[d] Christopher M. O'Connor, MD[a,e]



**Conclusions:**

There were more associated improvements in outcomes with **higher BB dose** than with **reduced HR** in this well-treated HF cohort with systolic dysfunction, which suggests that **titration of BB doses may confer a greater benefit** than reduction of HR in such patients

**FIGURE 1** All-Cause Death or Hospitalization by BB Dose (High/Low) and HR (High/Low) at Baseline




Estimated risk of death or hospitalization by discrete groups (high BB dose/high HR; high BB dose/low HR; low BB dose/high HR; low BB dose/low HR). BB = beta-blocker; HR = heart rate.

# All-cause death or hospitalization by beta blocker dose and heart rate at baseline

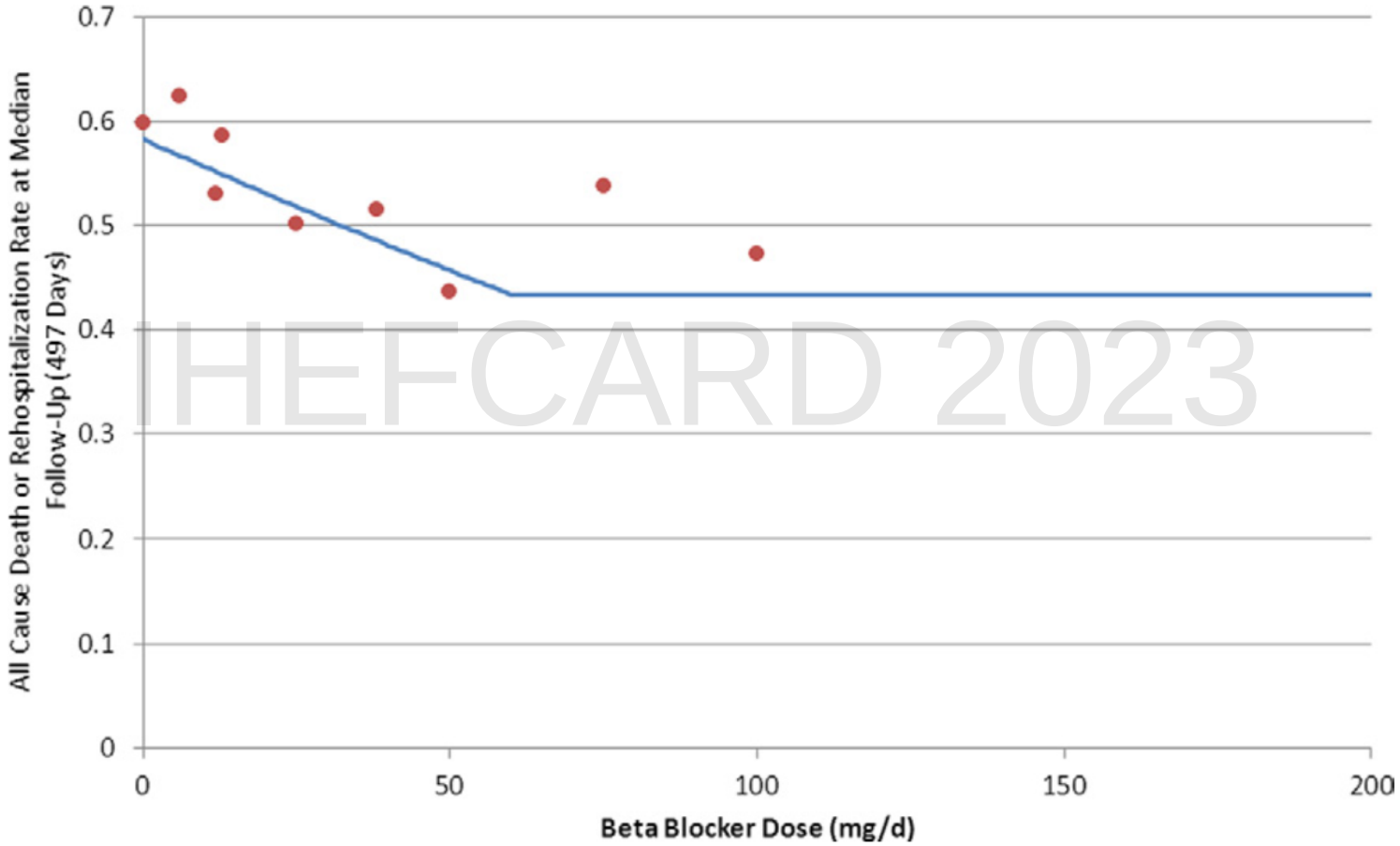
| | Unadjusted | | | Adjusted*† | | |
|---|---|---|---|---|---|---|
| | Chi-Square | p Value | HR (95% CI) | Chi-Square | p Value | HR (95% CI) |
| All-cause death or all-cause rehospitalization | | | | | | |
| Beta-blocker effect (high vs. low dose)‡ | 21.8 | <.0001 | 0.77 (0.7-0.86) | 4.7 | 0.03 | 0.87 (0.77-0.99) |
| Heart rate effect (heart rate ≥70 vs. <70 beats/min) | 6.4 | 0.01 | 1.14 (1.03-1.26)§ | 2.9 | 0.09 | 1.11 (0.98-1.24)§ |
| Beta-blocker by heart rate | 3.5 | 0.06 | | 1.8 | 0.19 | |



† adjustment by sex, body mass index, loop diuretic agents, Canadian Cardiovascular Society angina class, creatinine, exercise duration, ventricular conduction, and left ventricular ejection fraction.

Fiuzat et al. Heart Rate vs. Beta-Blocker Dose and Outcomes From the HF-ACTION Trial. JACC Heart Failure 2016

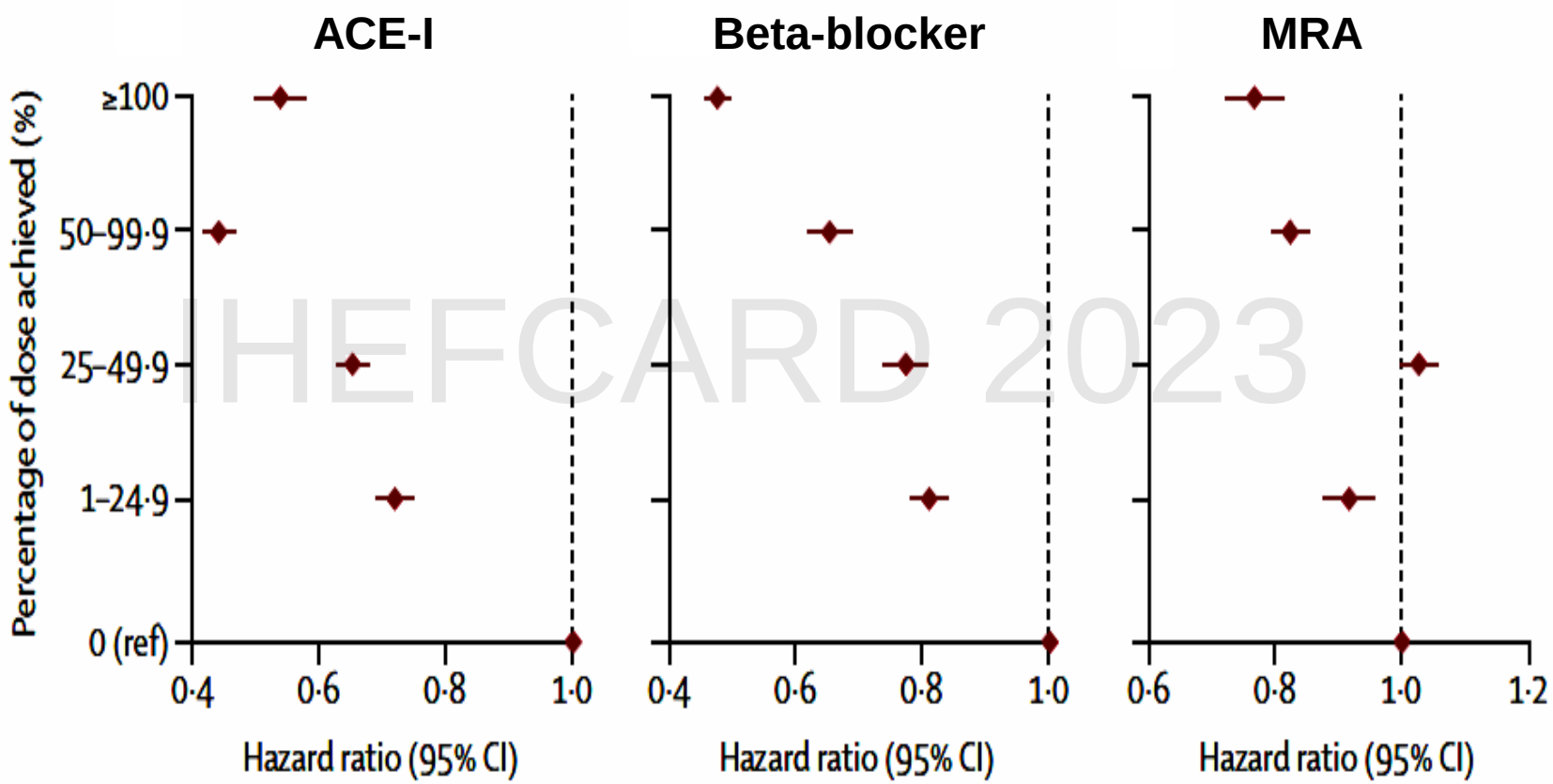
# All-Cause Death or Hospitalization by Beta-Blocker (Carvedilol) Dose at Baseline






Fiuzat M, et al. J Am Coll Cardiol 2012;60:208–15

# Association of doses achieved with 1-year composite outcome of all-cause deaths or hospitalization for heart failure in ASIAN-HF Registry

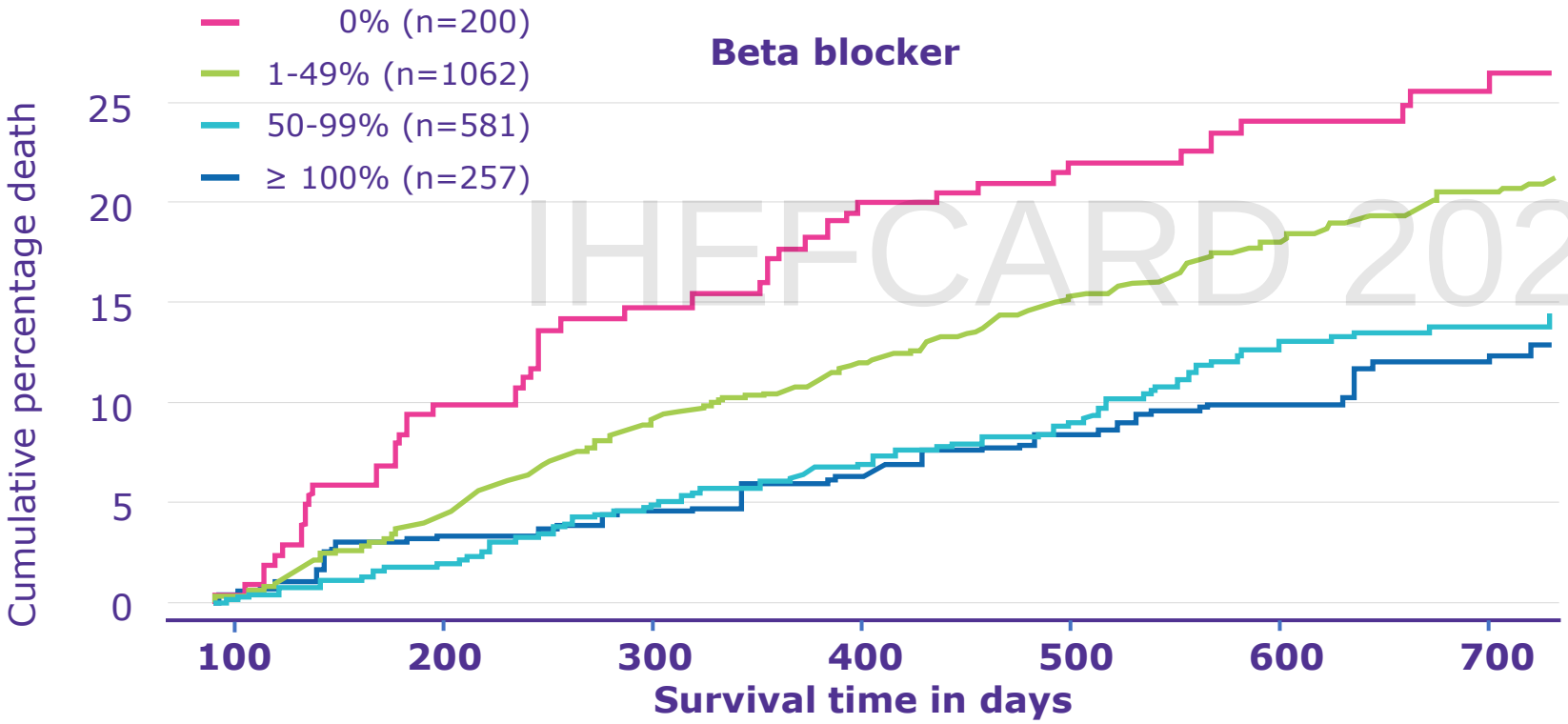





Teng TK, et al. Lancet Glob Health. 2018;6:e1008–e1018

# BIOSTAT-CHF project

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]





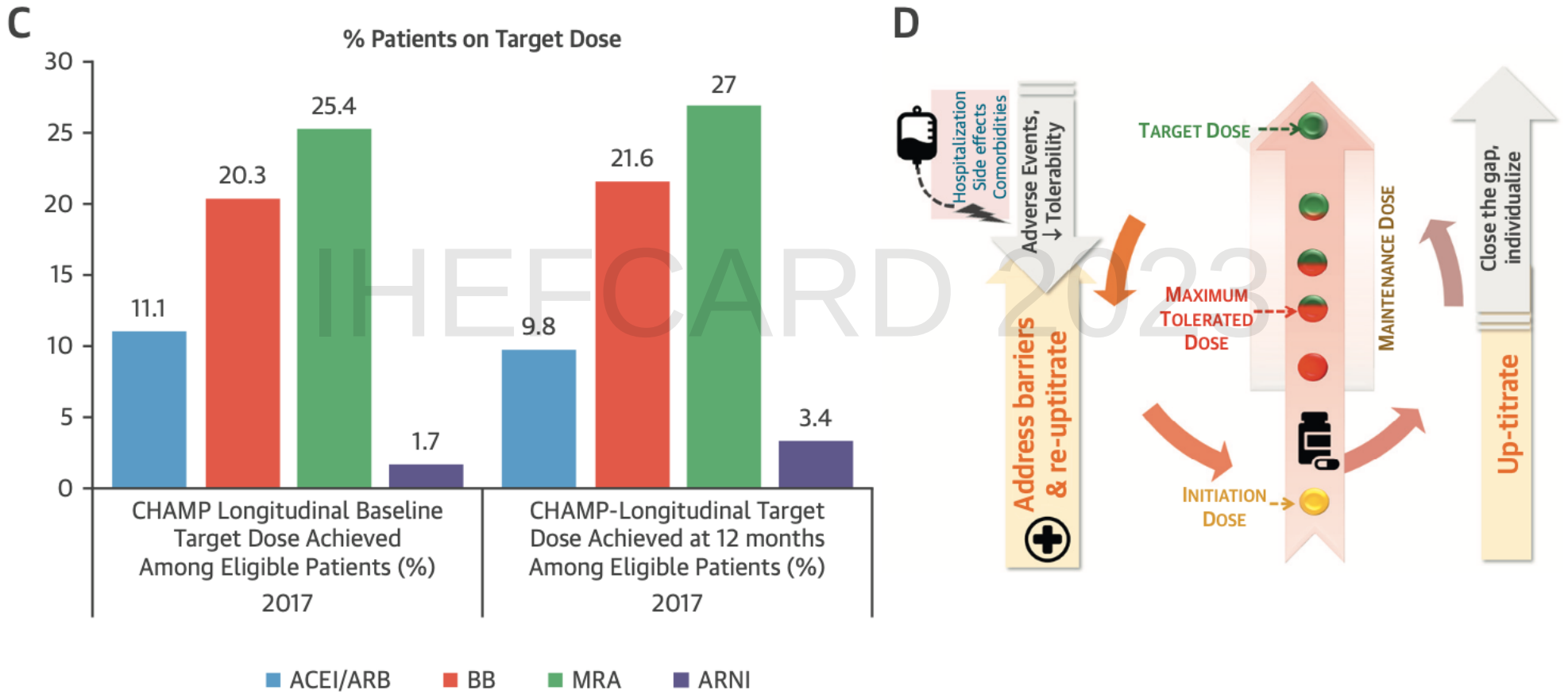

Patients treated with at least 50% of recommended BB target dose had a better survival (clinical outcome)

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

**FIGURE 1 Continued**






Bozkurt B. JACC: Heart Failure 2019;7:359-62

# Achieving 'Maximally Tolerated Dose' of Beta-blockers

## Treat modifiable causes of worsening symptoms before reducing the dose of beta-blocker

| |
|---|
| **Worsening symptoms or signs** (e.g. increasing dyspnoea, fatigue, oedema, weight gain): |
| Increased congestion: add diuretic dose, if does **not work**, halve dose of beta-blocker |
| Marked fatigue: halve dose of beta-blocker (rarely necessary) |
| Serious deterioration, halve dose of beta-blocker or stop treatment (rarely necessary) |
| **Low heart rate**: |
| If sinus rhythm <50 bpm or AF <60 bpm and worsening symptoms, halve dose of beta-blocker, or, if severe deterioration, stop beta-blocker (rarely necessary) |
| **Symptomatic hypotension**: |
| Reconsider need for nitrates, calcium-channel blockers, and other vasodilators and reduce/stop, if possible |
| If no signs or symptoms of congestion, consider reducing diuretic dose |

# Take-home messages

- The activation of neurohormonal systems (sympathetic nervous system, renin-angiotensin system) and compensatory mechanisms play the principal role in the pathophysiology of heart failure.
- The mechanism of β-Blockers benefits are multiple and complex, **not only by reducing HR** but also by delaying or reversing cardiac remodelling, increasing antiarrhythmic effects, and reducing the progression of atherosclerotic and free-radical mediated cell damage process
- Titration of β-Blockers doses → **greater benefit** for HFrEF patients, and supports the current clinical guideline recommendations that β-Blockers therapy should be titrated to **moderate to high doses**
- The goal of β-blockers in HF is not to achieve a slow HR; **the goal is to save lives**


Thank you