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

Beta-adrenoreceptor Antagonist Roles in Early Stage of Heart Failure

Lia Valentina, MD, FIHA

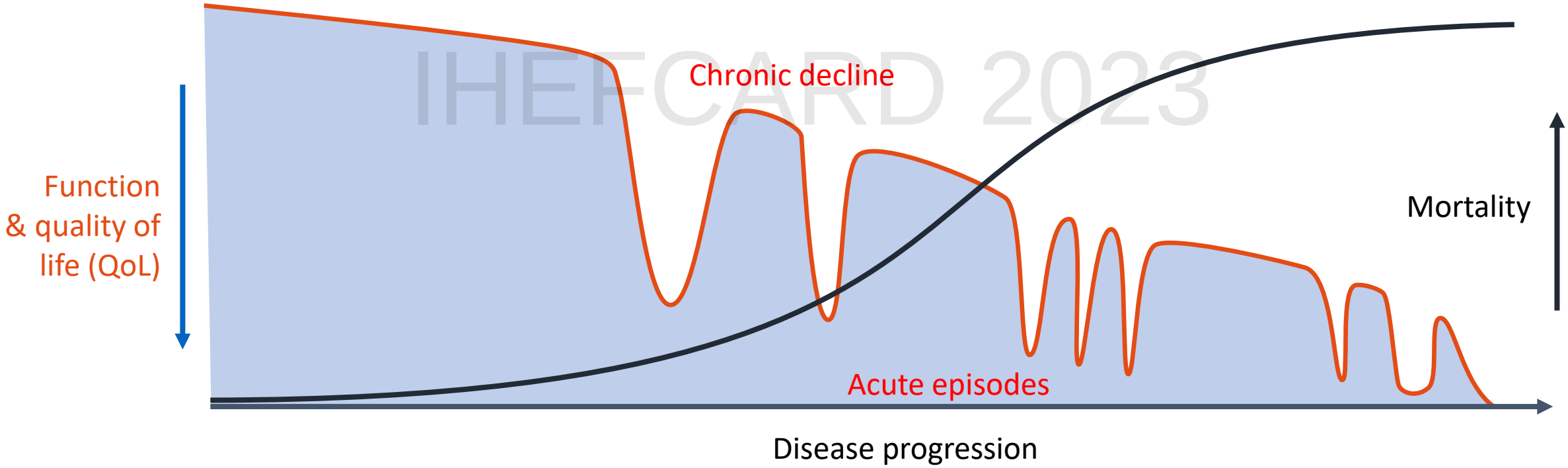
Klinik Gagal Jantung RS Prima Pekanbaru

Disclaimer :

- This session in sponsored by Darya Varia (Carvilol)

HF : A progressive condition with high mortality

- Increasing frequency of acute events with disease progression leads to high rates of hospitalization and increased risk of mortality
- With each acute event, myocardial injury may contribute to progressive LV dysfunction



LV: left ventricular

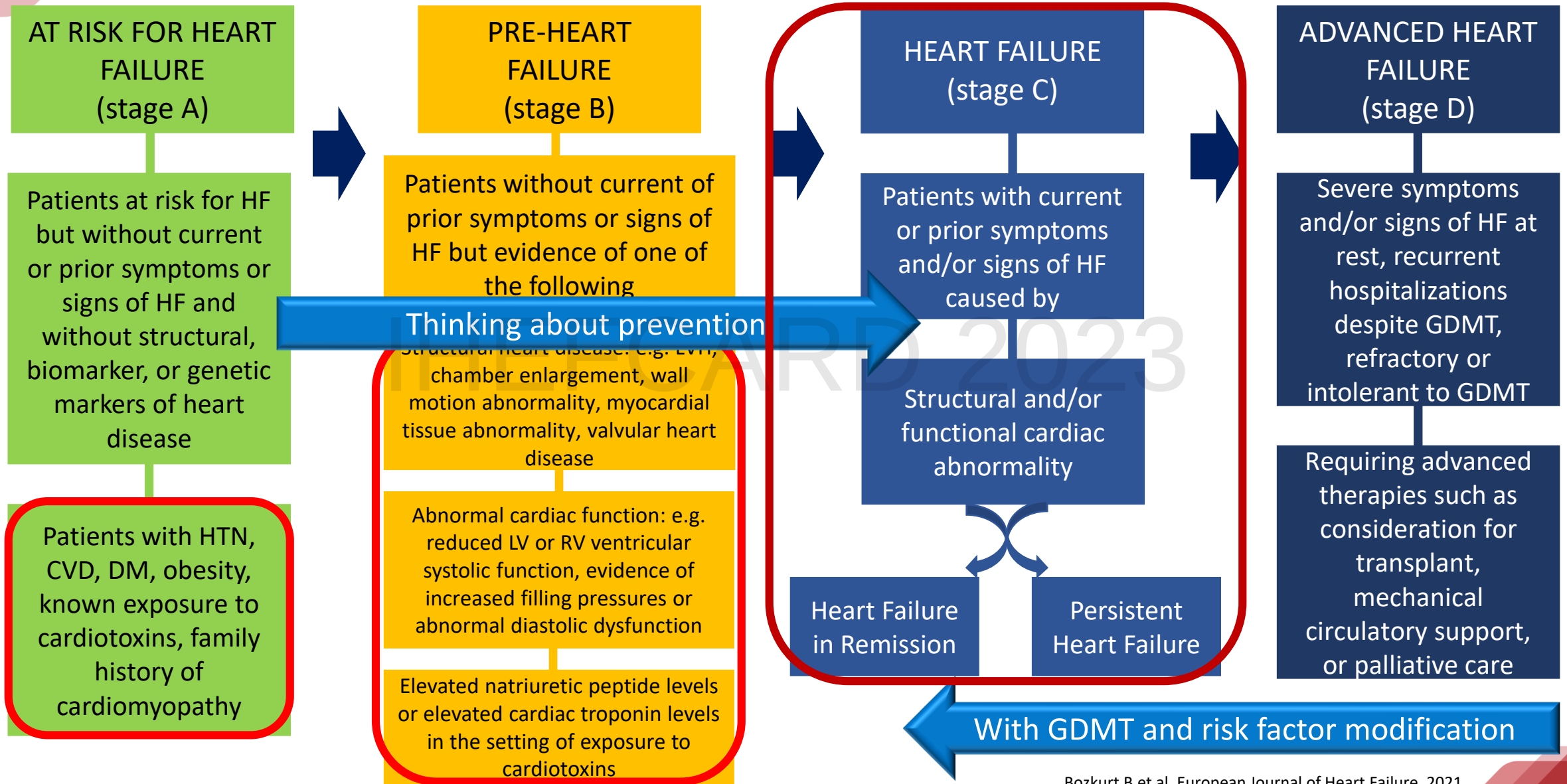
Gheorghiade et al. Am J Cardiol 2005;96:11G–17G; Gheorghiade & Pang. J Am Coll Cardiol 2009;53:557–73

Goals of treatment

1. Prognosis	Menurunkan mortalitas
2. Morbiditas	Meringankan gejala dan tanda Memperbaiki kualitas hidup Menghilangkan edema dan retensi cairan Meningkatkan kapasitas aktivitas fisik Mengurangi kelelahan dan sesak nafas Mengurangi kebutuhan rawat inap Menyediakan perawatan akhir hayat
3. Pencegahan	Timbulnya kerusakan miokard Perburukan kerusakan miokard Remodeling miokard Timbul kembali gejala dan akumulasi cairan Rawat inap

Universal definition & classification of heart failures

a report of the America Heart Failure Society



2023_Ryn

Bozkurt B et al. European Journal of Heart Failure. 2021.

Steps That Should Be Addressed at the Current Site of Care for All Patients With HF

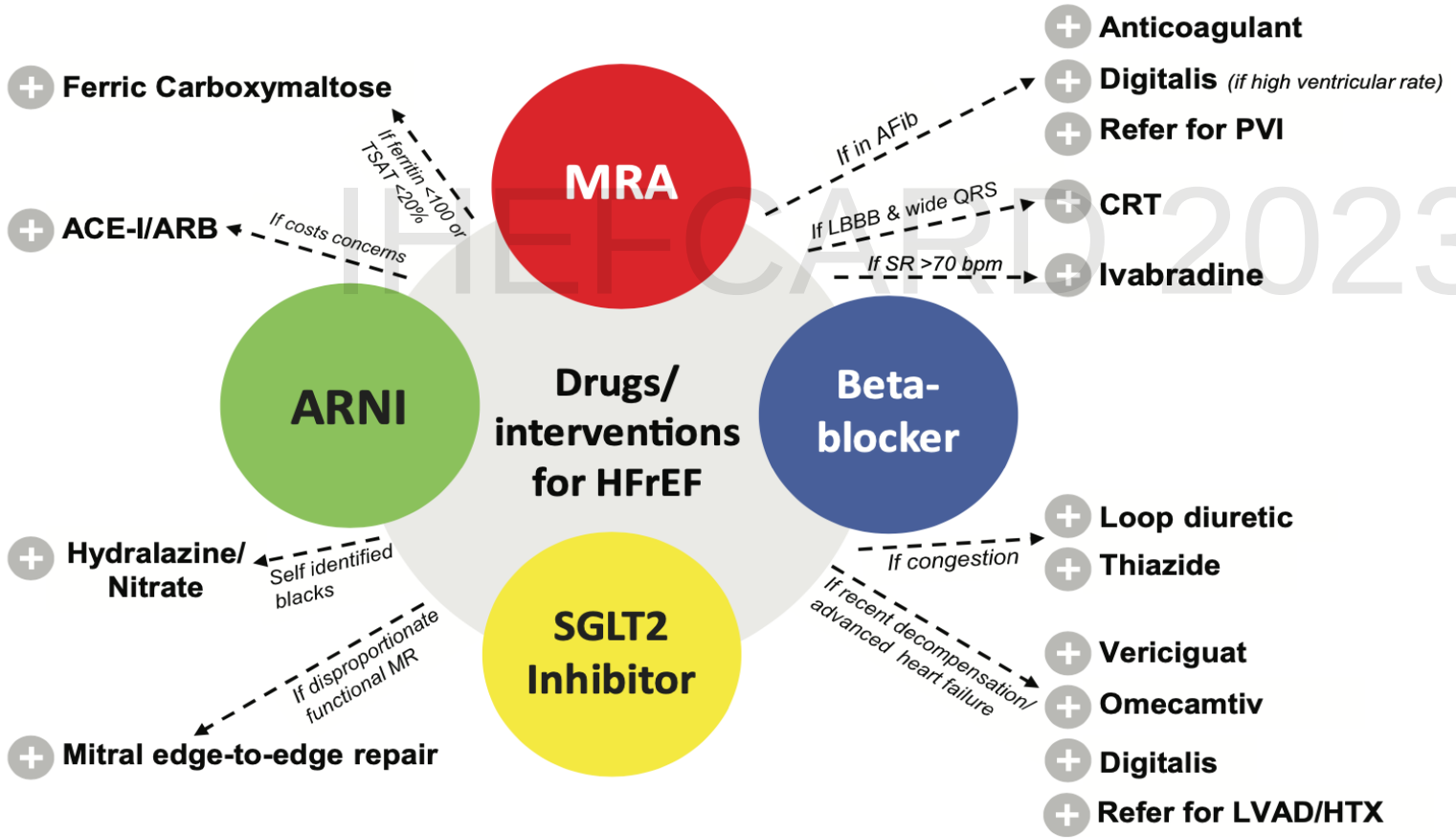
Evaluate and treat any reversible pathogeneses
Unrevascularized CAD Untreated arrhytmias Treatable causes (eg, thyroid disease)
Attempt to initiate and optimize GDMT
Optimize device therapy (CRT for patients with LBBB, QRS>120 ms)
Provide appropriate management of noncardiac comorbid conditions
Optimization of diabetes care with reduction of hemoglobin A1c as appropriate Encourage physical activity or cardiac rehabilitation Encourage weight loss for patients with class II obesity or greater; consultation with an obesity medicine specialist is encouraged when available
Educate patient about factors that may worsen their HF symptoms and delay their candidacy for LVAD or HT on referral and, if present, help them rectify
Nonadherence with medical appointments Stopping or frequently missing medications without first discussing with their health care professional Ongoing use/abuse of illicit substances or alcohol
Ensure that the patient has an adequate support system to allow adherence to the recommended medical regimen and lifestyle

Morris et al. Circulation. 2021;144:e238–e250.

2022_Ryn

ESC European Society of Cardiology
European Heart Journal (2021) **42**, 681–683
doi:10.1093/eurheartj/ehaa1012

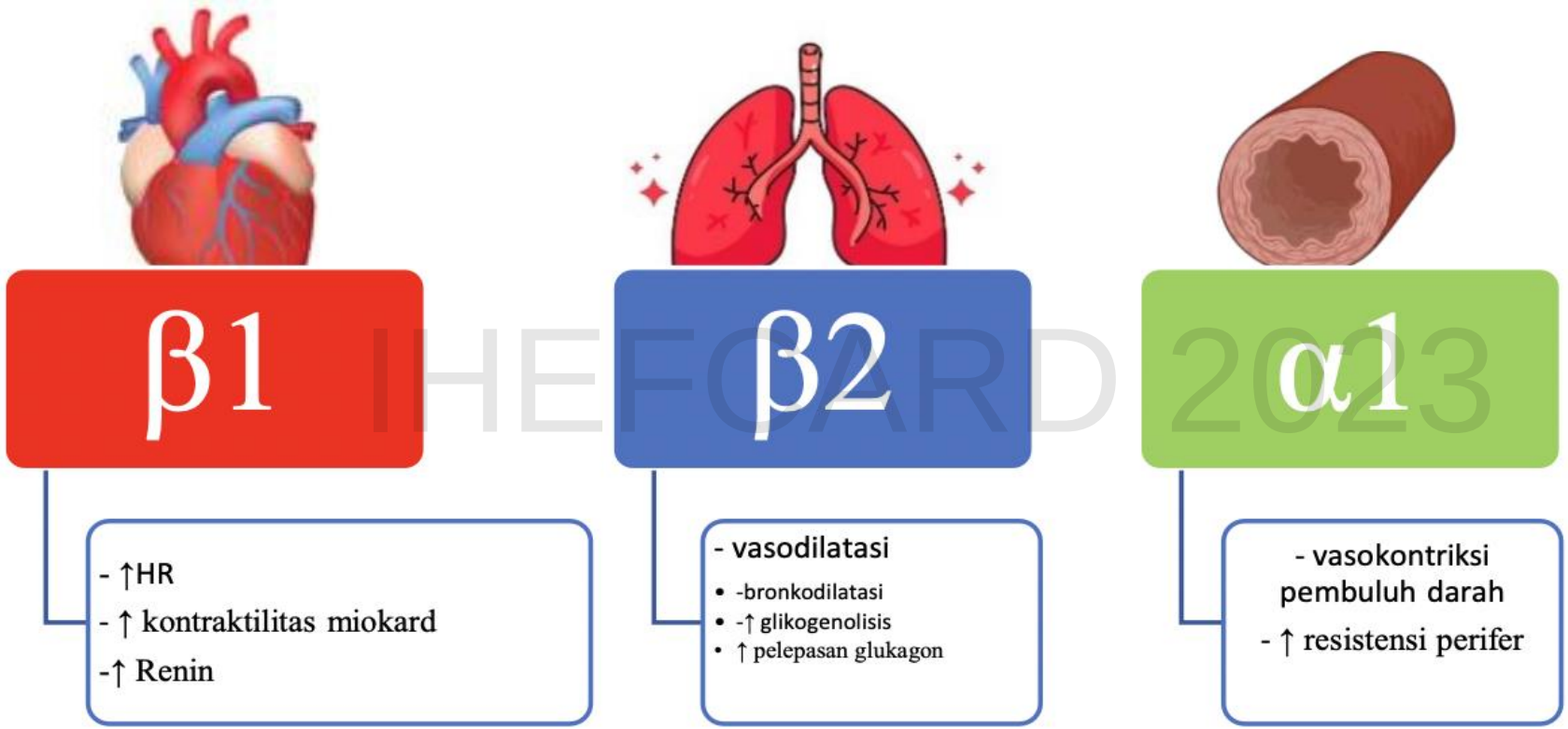
Heart failure drug treatment: the fantastic four



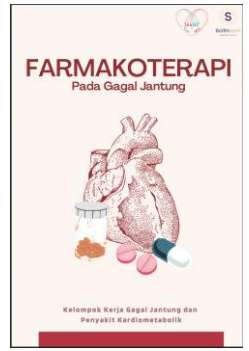
✓ Initiate
✓ Optimize
✓ Re-assess

Beta Blockers : what, why, how ?

Human Adrenergic Receptors



Gambar 5. 2 Subtipe reseptor adrenergi. Efek fisiologis dari ikatan katekolamin pada reseptor spesifik[1,2]



DON'T MISS IT TOMORROW !!

FIRST GENERATION OF BETA BLOCKER

NOT SPESIFIC to block Beta 1 receptor
→ Beta 2 receptor (respiratory level)

SECOND GENERATION OF BETA BLOCKER

SPESIFIC to block Beta 1 receptor
increase vascular resistance

THIRD GENERATION OF BETA BLOCKER

(+) peripheral vasodilatation and alpha-blocking activity
CARVEDILOL
NEBIVOLOL

β-blocker clinical trials in heart failure

Table 2. Summary of randomized control clinical trials in heart failure with reduced ejection fraction. LVEF: left ventricular ejection fraction, NYHA: New York Health Association.

Trial	Year	Type of β-Blockers	n° of Patients	Inclusion Criteria	Effects on Mortality
CIBIS	1994	Bisoprolol	641	LVEF < 40%, NYHA class III-V	No significant difference in mortality between the two groups
MERIT HF	1999	Metoprolol	3991	LVEF < 40%, NYHA class II-IV	34% relative risk reduction in all-cause mortality
CIBIS II	1999	Bisoprolol	2647	LVEF < 35%, NYHA class III-IV	34% relative risk reduction in all-cause mortality
CAPRICORN	2001	Carvedilol	1959	Previous AMI and LVEF < 40%	23% relative risk reduction in all-cause mortality
COPERNICUS	2001	Carvedilol	2289	LVEF < 25% and NYHA class III-IV	31% relative risk reduction in all-cause mortality
COMET	2003	Metoprolol vs Carvedilolo	2309	LVEF < 35% and NYHA class II-IV	17% relative risk reduction in all-cause mortality in carvedilol group
SENIORS	2005	Nebivolol	2128	LVEF < 35%, NYHA class II-IV, age > 7o years	No significant difference in mortality between the two groups

Pharmacological treatments indicated in patients with (NYHA class II–IV) heart failure with reduced ejection fraction (LVEF ≤40%)

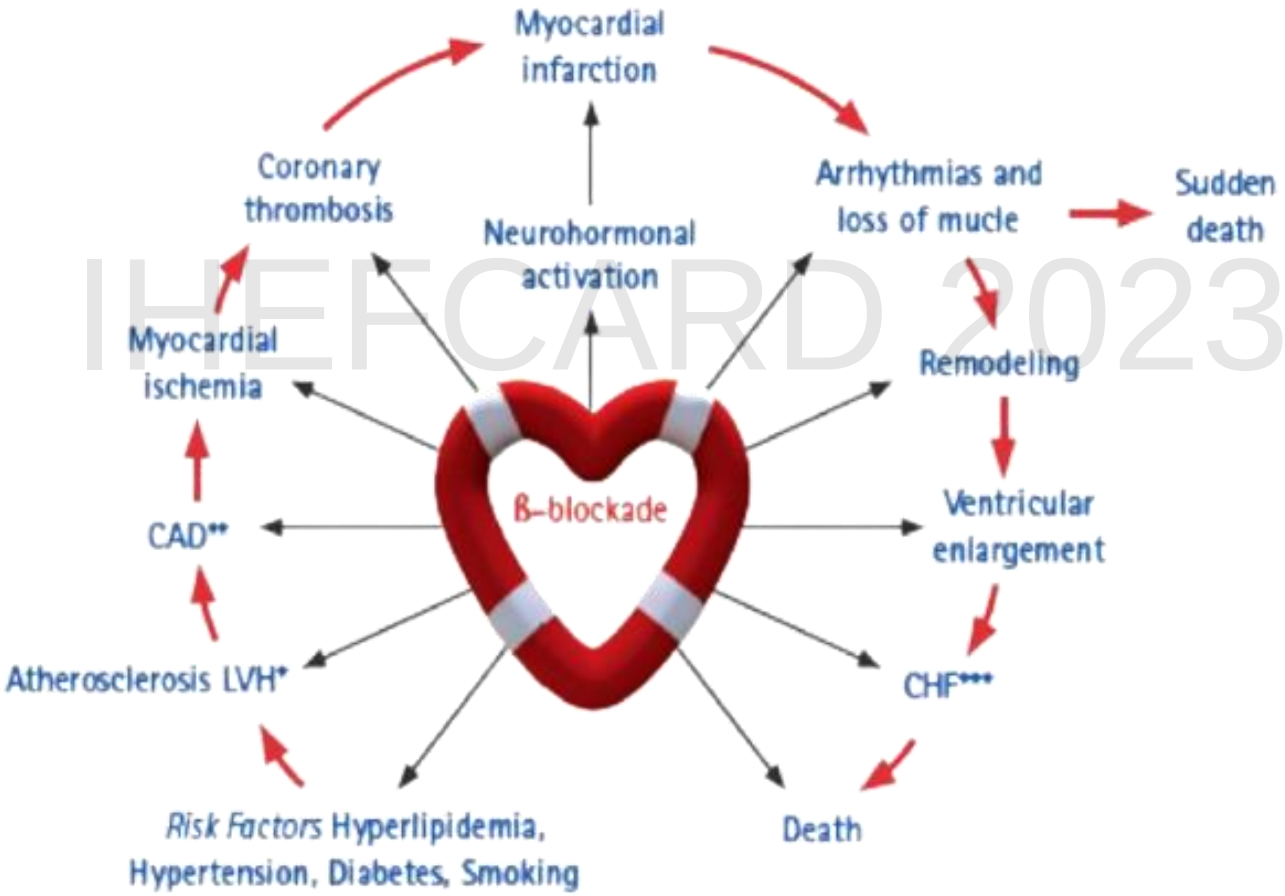
Recommendations	Class[a]	Level[b]
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[110–113]	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.[114–120]	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[121,122]	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109]	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.[105]	I	B

ACE-I = angiotensin-converting enzyme inhibitor; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.

[a]Class of recommendation.

[b]Level of evidence.

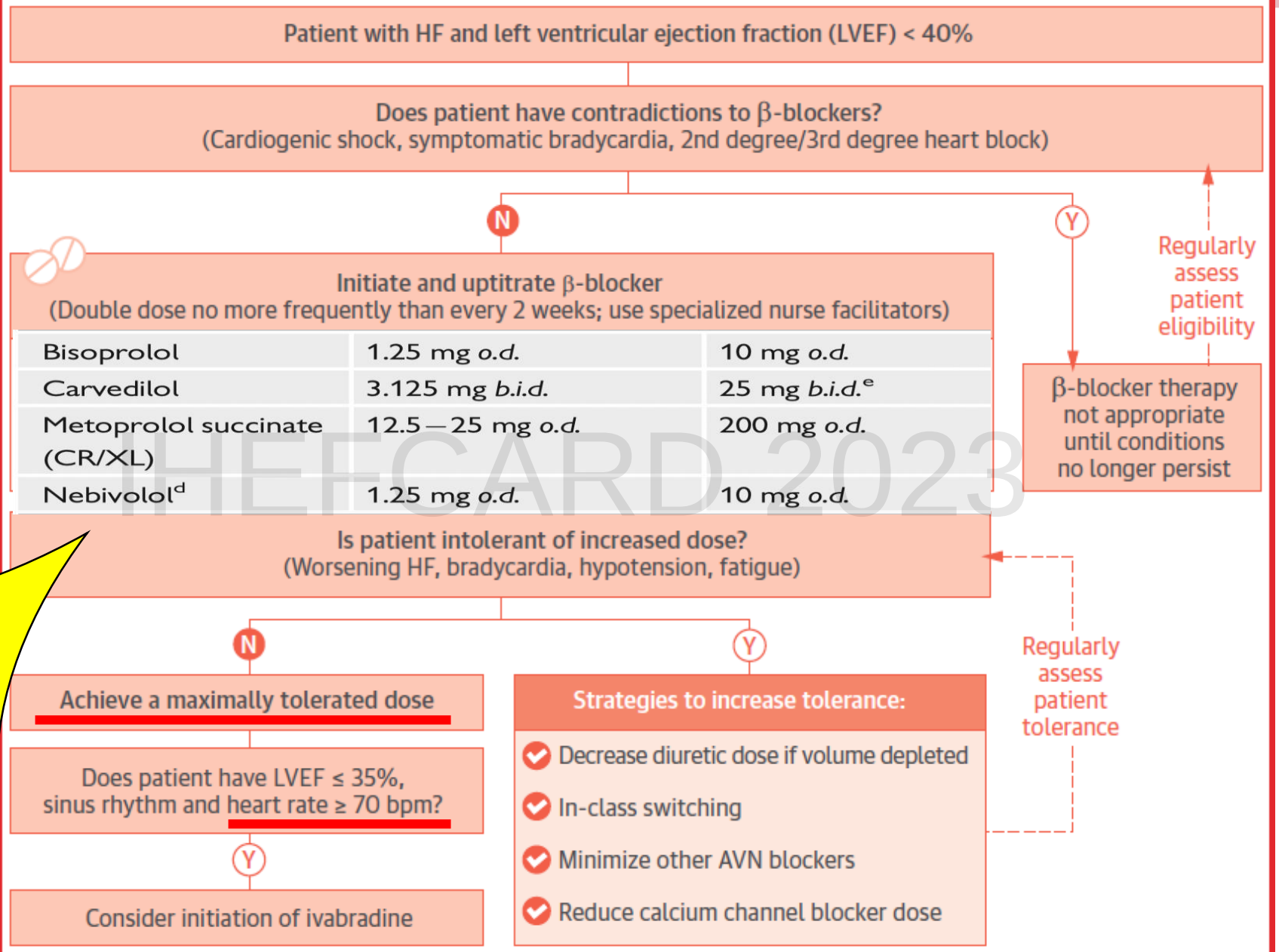
Beta-Blockers can intervene at many points in the Cardiovascular Continuum



2022_Ryn

Willenheimer R, Erdmann E. Eur Heart J Suppls. 2009;11 9Suppl A): A1-2.

CENTRAL ILLUSTRATION Clinical Algorithm for Up-Titration of β-Blockers



Start Low
Go Slow

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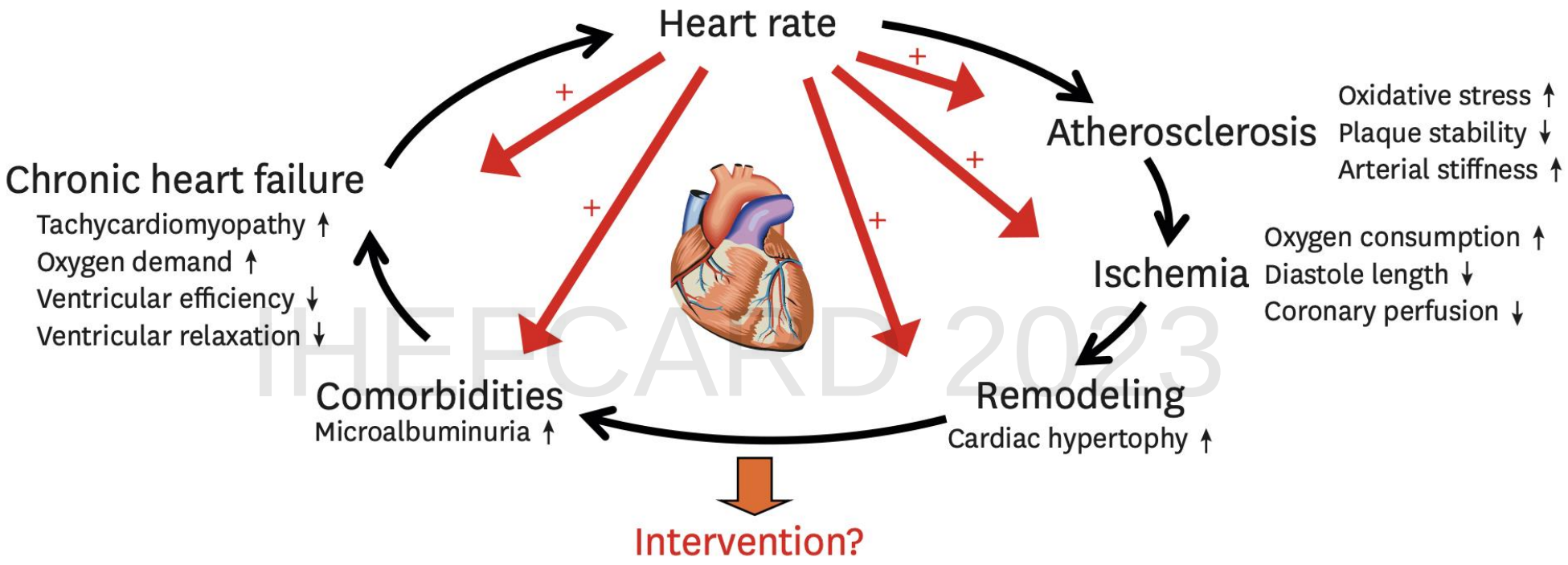
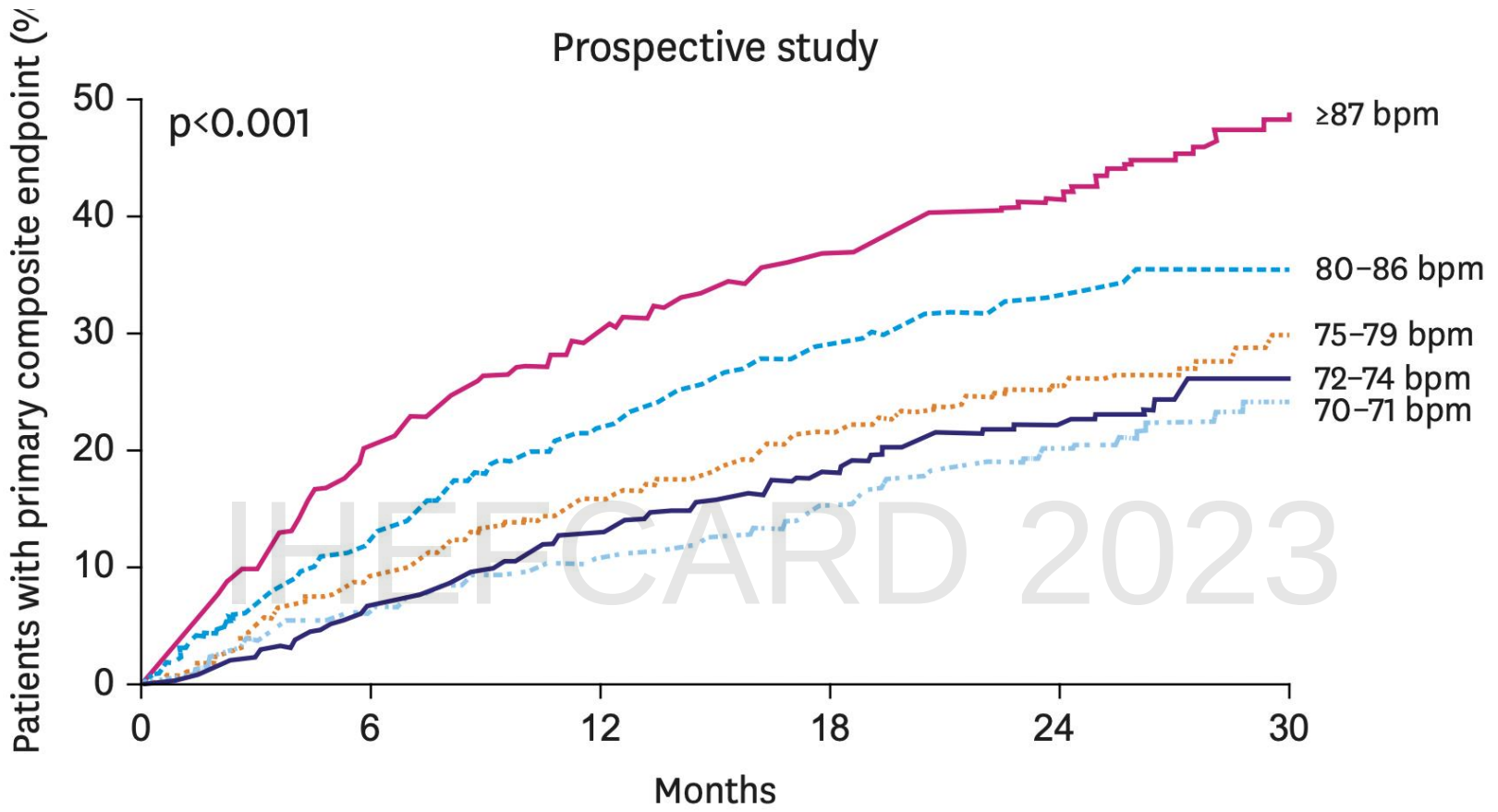
Lowering HR in Heart Failure : Why so important and How Low can we go ?

Heart rate: risk factor or marker?



Reducing HR in HF is a must !!



Primary composite endpoint: risk increases by 2.9% per 1 bpm increase, and by 15.6% per 5 bpm increase

Figure 2. Kaplan Meier cumulative event curves for the primary composite endpoint (cardiovascular death or heart failure hospitalization) according to patient groups defined by quintiles of heart rate at 28 days on placebo. Log rank p values show the difference between the groups. Modified according to 7.

Which BB is better ?

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

	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.*

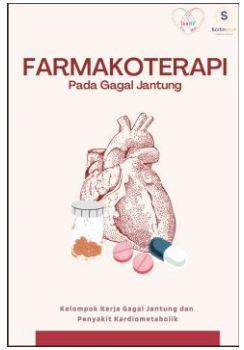
b.i.d. = bis in die (twice daily); CR = controlled release; MRA = mineralocorticoid receptor antagonist; o.d. = omne in die (once daily); XL = extended release.
[d]Indicates a treatment not shown to reduce CV or all-cause mortality in patients with heart failure (or shown to be non-inferior to a treatment 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.

www.escardio.org/guidelines

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

Tabel 5. 1 Pilihan jenis penyekat beta pada gagal jantung[2]

Pilihan penyekat β	Indikasi	Dosis dan sediaan
Esmolol	Hipertensi + iskemia + takikardia	50-250 μ/kg/min (drip iv)
Labetolol	Hipertensi , angina Hipertensi emergensi	3x300-600 mg (oral) 2-300 mg/menit (drip iv)
Propanolol	Angina, hipertensi	2x80-160 mg (oral)
Sotalol	Ventrikular aritmia Atrial fibrilasi	2x 80-240 mg (oral) 1x80-320 mg (oral)
Carvedilol	Gagal jantung	Dosis awal 2 x 3.125 mg (oral) Dosis target 2 x 25 mg (oral)
Acebutolol	Premature ventricular contraction (PVC)	2x400-1200 mg (oral)
Atenolol	Angina	1x50-200 mg (oral)
Bisoprolol	Gagal jantung	Dosis awal 1x1.25 mg (oral) Dosis target 1x10 mg (oral)
Metoprolol	Gagal jantung	Dosis awal 2x12.5 mg (oral) Dosis target 2x200 mg (oral)
Nebivolol	Gagal jantung	Dosis awal 1x1.25 mg Dosis target 1x5 mg



DON'T MISS IT TOMORROW !!

Choice of ß-blockers according to clinical scenario

Clinical Scenario	β-Blockers
Hypertension	Carvedilol, nebivolol
Asthma and Chronic Obstructive Pulmonary Disease	Bisoprolol, nebivolol
Diabetes mellitus	Carvedilol, bisoprolol
Atrial fibrillation	Metoprolol, bisoprolol
Peripheral Artery Disease	Carvedilol, nebivolol
Hypercholesterolemia	Carvedilol
Hyperthyroidism	Metoprolol

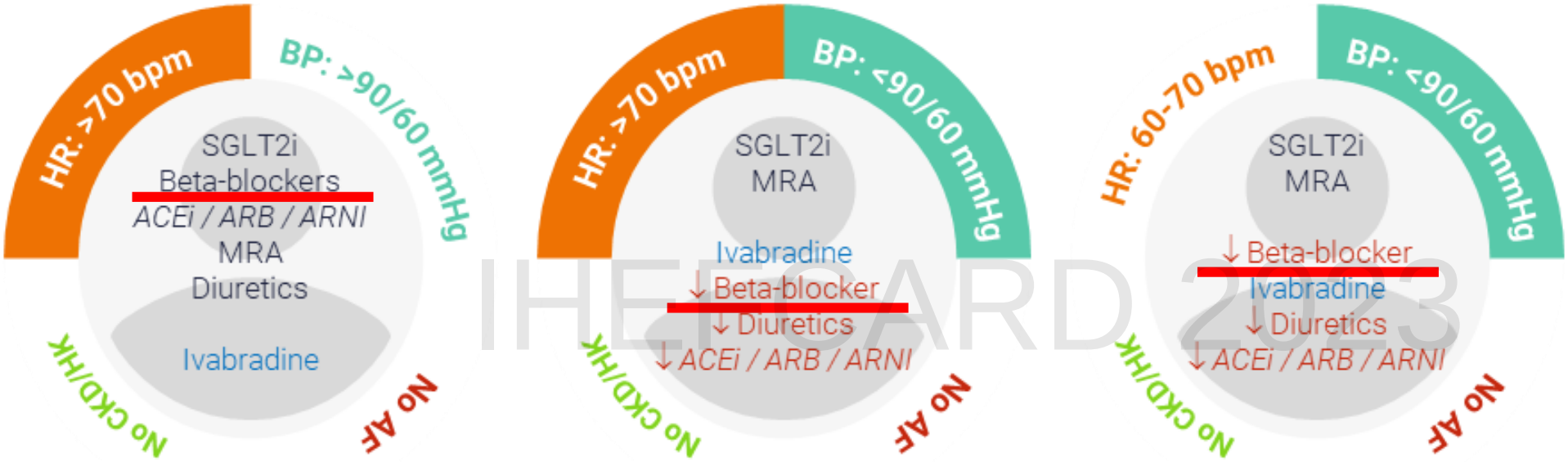
Masarone, D. et al. J. Cardiovasc. Dev. Dis. 2021,8, 101.

Common problems in daily practice

In clinical practice, the main factors that may limit the uptitration of β-blockers are:

- Peripheral congestion
- Hypotension
- Symptomatic bradycardia

Patient profiling in HFrEF for tailoring medical therapy (1)



Black—drugs that should be given to patients;

Red—drugs that should be reduced or discontinued

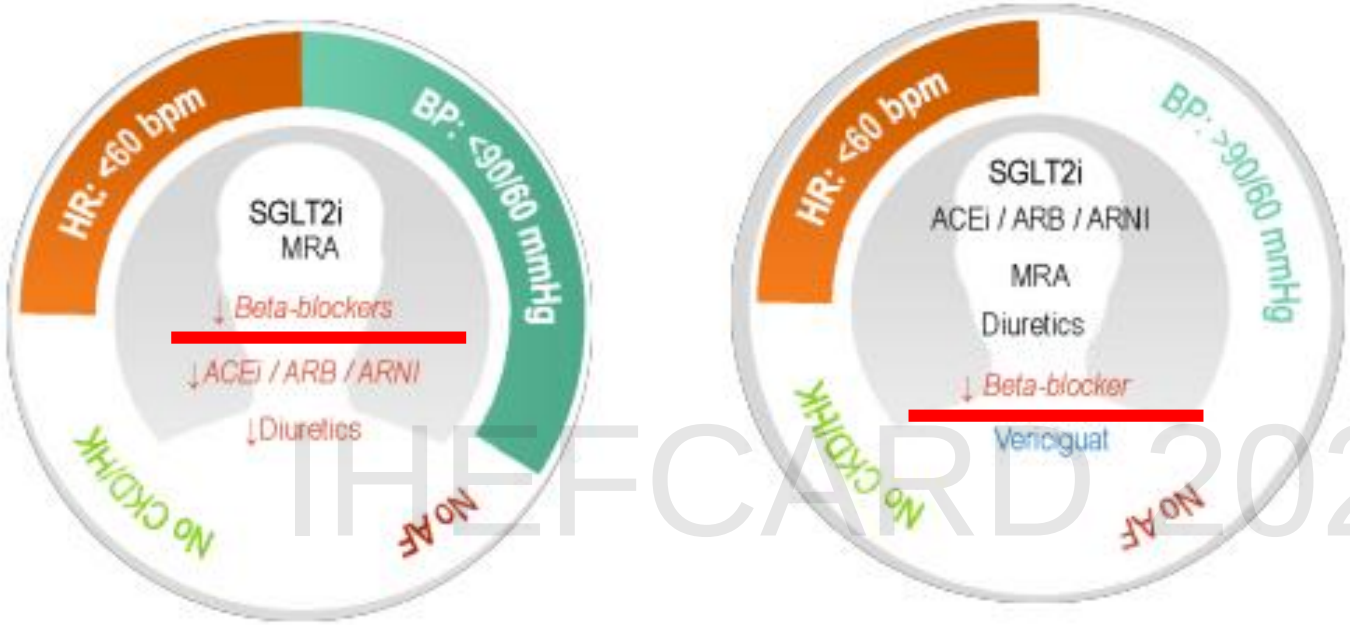
Blue—drugs that should be added.

Strategy in patients with elevated heart rate

Lower heart rate is associated with improved survival in HFrEF and sinus rhythm, and the most favorable outcome is observed with a heart rate around 60 bpm

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

Patient profiling in HFrEF for tailoring medical therapy (2)



Black—drugs that should be given to patients;

Red—drugs that should be reduced or discontinued

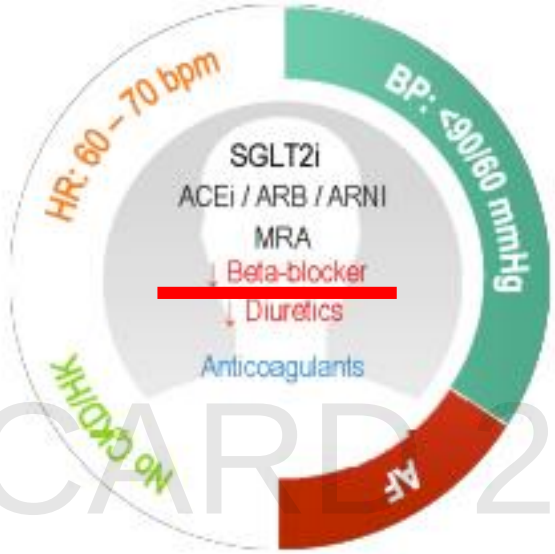
Blue—drugs that should be added.

Strategy in patients with lower HR

- Reduction of BB may be necessary if the patient has a heart rate <50bpm, or symptomatic bradycardia.
- Drugs with a negative chronotropic effect should be carefully reconsidered and if possible discontinued, such as non-dihydropyridine calcium channel blockers (diltiazem and verapamil), digoxin, or antiarrhythmic drugs.

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

Patient profiling in HFrEF for tailoring medical therapy (3)



Black—drugs that should be given to patients;

Red—drugs that should be reduced or discontinued

Blue—drugs that should be added.

Strategy in patients with AF

- The optimal resting ventricular rate in HF patients with AF remains to be clearly determined but may be between 60–80bpm.

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

Patient profiling in HFrEF for tailoring medical therapy (4)

Black—drugs that should be given to patients;

Red—drugs that should be reduced or discontinued

Blue—drugs that should be added.

Strategy in patients with CKD

- BBs can be safely given to patients down to an eGFR of 30 mL/min/1.73 m2 , with a clear benefit in mortality.

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

Pharmacological and Pharmakokinetics Properties among β-Blockers

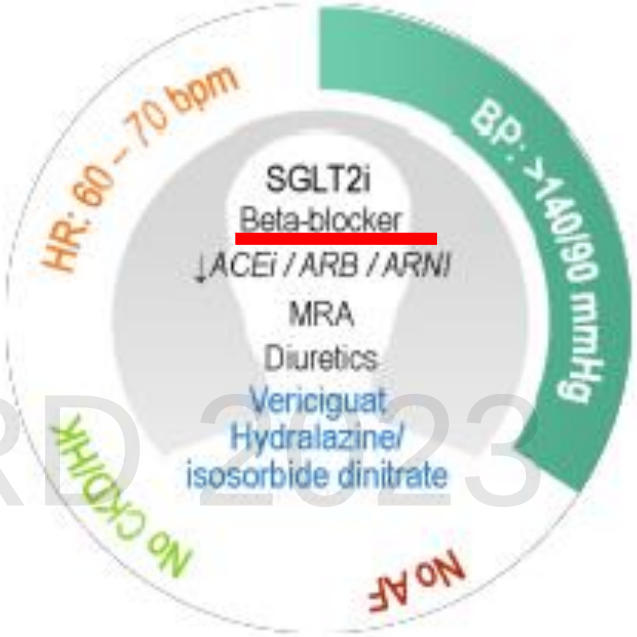
β-Blocker	β-Receptor Activity	Membrane Stabilizing Activity	Intrinsic Sympathomimetic Activity	Lipid Solubility	Elimination Half-life	Route of Elimination	Approximate Oral Bioavailability
Propranolol[a]	No	Yes	No	High	3.5-6 Hours	Hepatic	30%
Atenolol[b]	β_1	No	No	Low	6-7 Hours	Renal	40%
Bisoprolol	β_1	No	No	Low	9-12 Hours	Renal	80%
Carvedilol[c]	No	No	No	Moderate	7-10 Hours	Hepatic	25%-35%
Metoprolol	β_1	At high levels	No	Moderate	Tartrate: 3-4 hours; succinate: 3-7 hours	Hepatic	50%
Nebivolol[d]	β_1	No	No	Low	12 Hours	Hepatic	12%-96%

[a]Prototype β-blocker, for reference.
[b]Antihypertensive effect not related to serum concentration. Once-daily dosing recommended in prescribing information.
[c]Carvedilol has α1-adrenergic blocking activity and antioxidant properties.
[d]Nebivolol has vasodilating activity related to potentiation of nitric oxide; elimination half-life is 19 hours in poor metabolizers.

Toni L et.al. β-Blockers: A Review of Their Pharmacological and Physiological Diversity. Annals of Pharmacotherapy 1 –11

Patient profiling in HFrEF for tailoring medical therapy

- In patients with a hypertensive profile, it is important to ensure the patient is not taking any medication that may increase blood pressure (i.e. non-steroidal anti-inflammatory drugs, corticoids, or bronchodilators).



Black—drugs that should be given to patients;

Red—drugs that should be reduced or discontinued

Blue—drugs that should be added.

Strategy in patients with hypertension

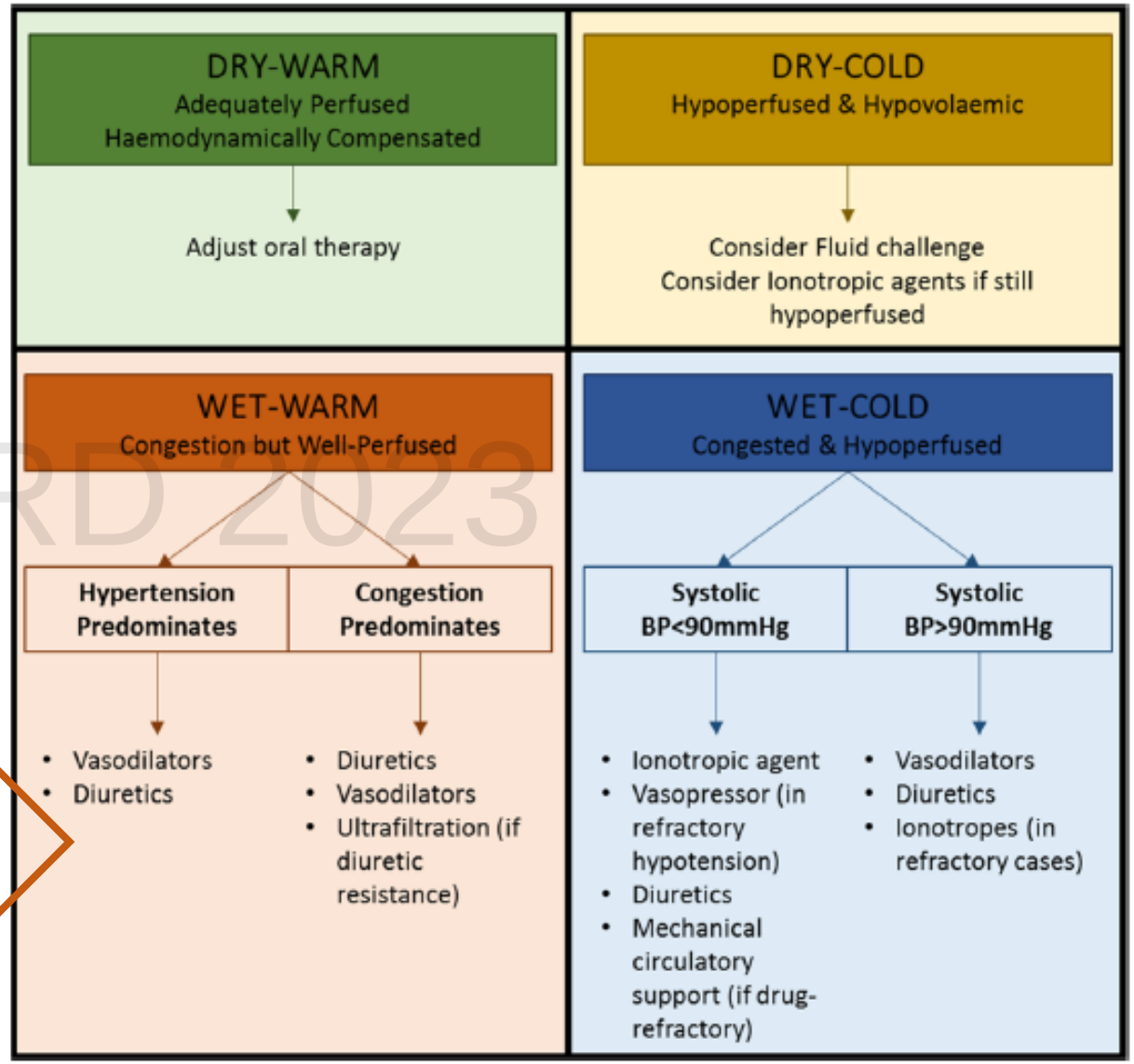
Rosano GMC et al. *Eur J Heart Fail*. 2021;23(6):872-881.

BBs in Acute Heart Failure : Should we discontinued ?

Acute Heart Failure

Acute Heart Failure (AHF) also known as **acute decompensated heart failure or cardiac failure**, is not a single disease entity, but rather a **syndrome of the worsening of signs and symptoms reflecting an inability of the heart to pump blood at a rate commensurate to the needs of the body at normal filling pressure**

95% of Patients presenting with AHF to the **hospital** have **clinical features of congestion (WET)**



Sameer Karmani., et al. 2017. *Acute Heart Failure: Definition, Classification, and Epidemology*. Curr Heart Fail Rep, DOI 10.1007/s11897-017-0351-y

European Heart Journal (2009) **30**, 2186–2192
doi:10.1093/eurheartj/ehp323

FASTTRACK
ESC CLINICAL TRIAL UPDATE

B-CONVINCED: Beta-blocker CONtinuation Vs. INterruption in patients with Congestive heart failure hospitalizED for a decompensation episode

Guillaume Jondeau[1]*, Yannick Neuder[2], Jean-Christophe Eicher[3], Patrick Jourdain[4], Elodie Fauveau[5], Michel Galinier[6], Arnaud Jegou[7], Fabrice Bauer[8], Jean Noel Trochu[9], Anissa Bouzamondo[10], Marie-Laure Tanguy[10], and Philippe Lechat[10] for the B-CONVINCED Investigators

Aims Whether or not beta-blocker therapy should be stopped during acutely decompensated heart failure (ADHF) is unsure.

Methods and results In a randomized, controlled, open labelled, non-inferiority trial, we compared beta-blockade continuation vs. discontinuation during ADHF in patients with LVEF below 40% previously receiving stable beta-blocker therapy. 169 patients were included, among which 147 were evaluable. Mean age was 72 ± 12 years, 65% were males. After 3 days, 92.8% of patients pursuing beta-blockade improved for both dyspnoea and general well-being according to a physician blinded for therapy vs. 92.3% of patients stopping beta-blocker. This was the main endpoint and the upper limit for unilateral 95% CI (6.6%) is lower that of the predefined upper limit (12.5%), indicating non-inferiority. Similar findings were obtained at 8 days and when evaluation was made by the patient. Plasma BNP at Day 3, length of hospital stay, re-hospitalization rate, and death rate after 3 months were also similar. Beta-blocker therapy at 3 months was given to 90% of patients vs. 76% ($P < 0.05$).

Conclusion In conclusion, during ADHF, continuation of beta-blocker therapy is not associated with delayed or lesser improvement, but with a higher rate of chronic prescription of beta-blocker therapy after 3 months, the benefit of which is well established.

Table 3 Clinical events

	Keep BB, $n = 69$	Stop BB, $n = 78$	*P*-value
During hospitalization			
Durations (days)	11.5 ± 8.3	10.4 ± 9.7	0.2
Median, range	9 (1–50)	8 (1–62)	
Deaths (n)	1 (HF)	2 (HF)	
Dobutamine (*n*)	3	1	
After 3 months			
Deaths, *n* (%)	6 (9)	6 (8)	0.83
Rehospit, *n* (%)	27 (40)	36 (47)	0.43
For HF	15 (22)	24 (32)	0.19
For arrhythmia	2 (3)	3 (4)	1
Receiving BB, *n* (%)	61 (90)	58 (76)	0.04

Rehospit, rehospitalization; HF, heart failure; BB, beta-blocker.

BMJ Open

Non-withdrawal of beta blockers in acute decompensa novo heart failure fraction in a prosp study of patients in the Middle Eas

Table 2 Effect of non-withdrawal of beta blockers in acute dec admission and a LVEF <40%

	All patients with acute decompensated heart failure, LVEF<40% and on beta-treatmen admission n=1018			
Inhospital outcome				
Death	52/1018 (5.1)			
Length of stay (days)	9.9±15.0			
3-Month follow-up				
Death	86/946 (9.1)			
Rehospitalisation for HF	219/859 (25.5)	204/818 (24.9)	15/41 (36.6%)	0.09
Length of stay (days)	8.1±7.6	8.1±7.8	7.7±4.3	0.86
12-Month follow-up				
Death	139/880 (15.8)	128/835 (15.3)	11/45 (24.4%)	0.10
Rehospitalisation for HF	333/741 (44.9)	316/707 (44.7)	17/34 (50.0%)	0.54
Length of stay (days)	9.6±12.0	9.6±12.1	10.9±11.1	0.73

The frequencies and percentages for death, rehospitalisation for HF and length of hospital stay. Death rates were cumulative. All values are given as n (%) or mean±SD.
HF, heart failure; LVEF, left ventricular ejection fraction.

Table 4 Effect of non-withdrawal of beta blockers in acute decompensated de novo heart failure with beta blocker therapy on admission and an LVEF <40%

	All patients with de novo heart failure, LVEF<40% and on beta blockers treatment on admission n=260	Beta blockers maintained during hospitalisation n=224 (86.2%)	Beta blockers withdrawn during hospitalisation n=36 (13.8%)	p Value
Inhospital outcome				
Death	22/260 (8.5)	5/224 (2.2)	17/36 (47.2)	<0.001
Length of stay (days)	9.7±16.1	9.6±16.6	10.1±12.1	0.86
3-Month follow-up				
Death	9/232 (3.9)	7/214 (3.3)	2/18 (11.1)	0.14
Rehospitalisation for HF	39/223 (17.5)	38/207 (18.4)	1/16 (6.3)	0.31
Length of stay (days)	8.8±9.8	8.8±9.9	8.0±NE	NE
1-year follow-up				
Death	15/221 (6.8)	13/206 (6.3)	2/15 (13.3)	0.27
Rehospitalisation for HF	61/206 (29.6)	73/193 (37.8)	3/13 (23.1)	0.38
Length of stay (days)	7.9±7.5	8.2±7.6	2.7±2.1	0.21

The frequencies and percentages for death, rehospitalisation for HF and length of hospital stay. Death rates were cumulative. All values are given as n (%) or mean ±SD.
HF, heart failure; LVEF, left ventricular ejection fraction; NE, not estimable.

Conclusion :
Non-withdrawal of beta blocker therapy during acute heart failure **REDUCES** intrahospital **MORTALITY** risk in patients with acute decompensated chronic and de novo heart failure.

Table 3. Management of chronic heart failure therapies during hospitalization.

Medication	Transition in Hospital	Monitoring
Diuretics	Continue or augment (if indicated), unless signs/symptoms of dehydration	Daily weight (standing) Strict intake and output Vital signs (BP, HR, RR, O_2 saturation) including orthostatic BP, HR BUN, serum creatinine Serum potassium and magnesium
Beta blockers	Continue unless decompensation due to recent addition or dose increase (in which case reduce dose). Discontinue if significant hypotension, bradycardia, or overt cardiogenic shock.	BP and HR including orthostatic BP, HR
ACE inhibitors and ARBs	Continue, unless hypotension or acutely worsening renal function	BP and HR including orthostatic BP, HR Strict intake and output BUN, serum creatinine Serum potassium
MRAs	Continue unless $K^+ > 5.5$ or CrCl < 30 mL/min	BP and HR including orthostatic BP, HR Strict intake and output BUN, serum creatinine Serum potassium
Digoxin	Continue unless acutely worsening renal function, significant bradycardia (HR < 45 bpm), or signs/symptoms of toxicity Note: half-life =36 hrs if normal renal function (minimum of 5-7 days to reach steady state post initiation or dose change)	HR Serum creatinine Serum potassium, magnesium, and calcium Serum digoxin concentration (at least 6 hrs post dose) if not recently obtained, change in renal function, or addition/removal of interacting medication
Hydralazine/ Isosorbide dinitrate	Continue unless significant hypotension	BP and HR including orthostatic BP, HR

ACE = angiotensin converting enzyme, ARBs = angiotensin receptor blockers, BP = blood pressure, BUN = blood urea nitrogen, CrCl = creatine clearance, HR = heart rate, K^+ = potassium, MRAs = mineralocorticoid receptor antagonists, O_2 = oxygen, RR = respiratory rate.

J Teerling et al, Current Cardiology Review 2015

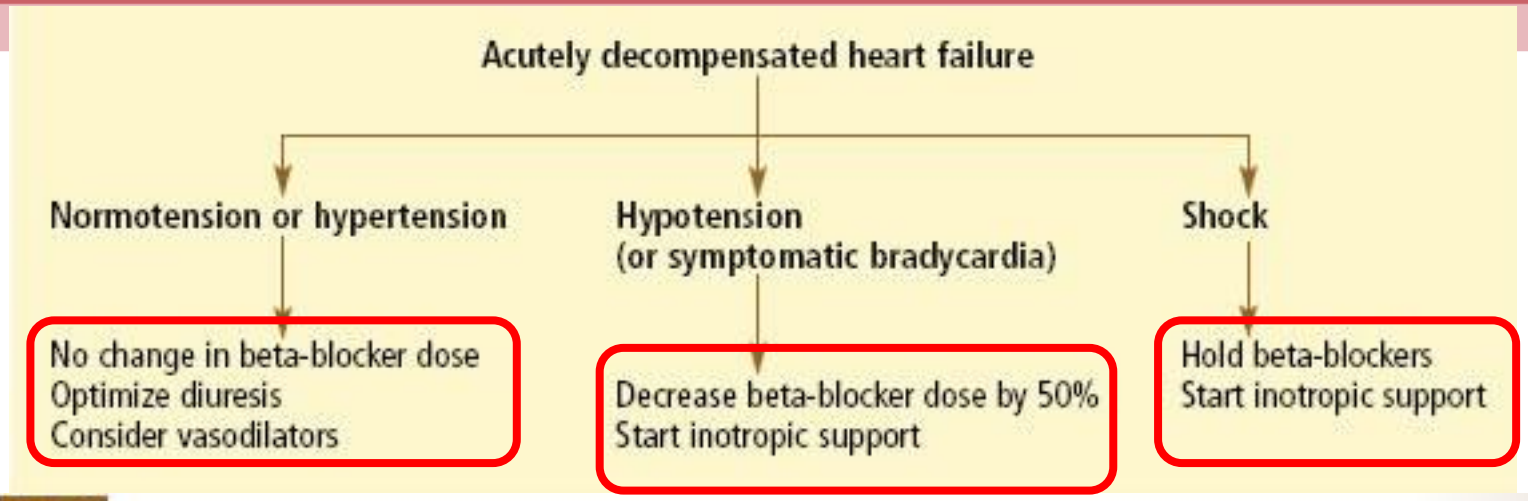
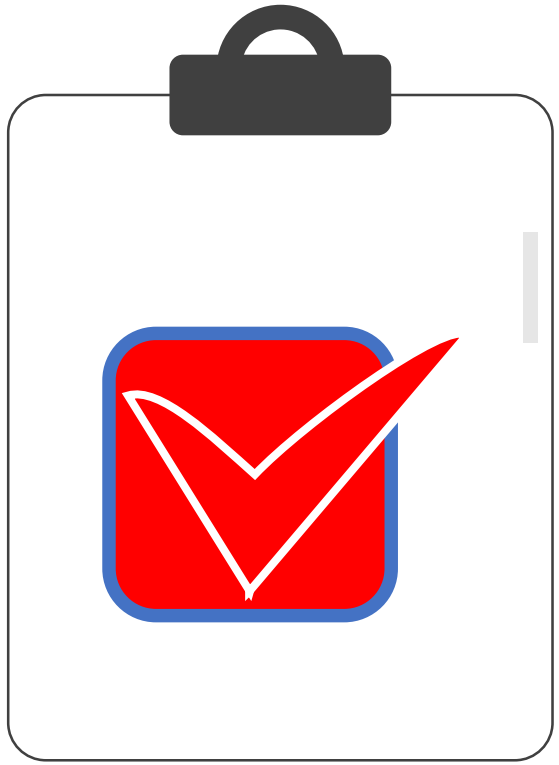


TABLE 1

Managing medications on the basis of congestion and perfusion status

PERFUSION AND VOLUME STATUS	BETA-BLOCKER DOSE	DIURETIC DOSE	INOTROPIC MEDICATION
"Wet and warm" (congested, well perfused)	Don't change	Increase	Usually not required
"Wet and cold" (congested, poorly perfused)	Hold or significantly reduce dose	Increase or don't change	Usually required
"Dry and warm" (euvolemic or hypovolemic, well perfused)	Don't change	Don't change	Usually not required
"Dry and cold" (euvolemic or hypovolemic, poorly perfused)	Hold or significantly reduce dose	Hold or significantly reduce dose	Usually required

Take Home Messages



01 **Early diagnosis** and treatment in HF will lead to **better** outcome.

02 Beta blockers improve survival and reduce hospitalization for HF patients.

03 Beta blockers for HF: **Choose the best, start low and go slow.**

04 **Carvedilol** clinically proven for heart failure and reduce cardiovascular mortality.

Thank you