The 4th Indonesian Symposium on Heart Failure and Cardiometabolic Disease

Metabolic Effect Of Heart Failure Drug

focus on Beta Blocker

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Heart Failure and cardiometabolic working group Indonesian Heart Association

Introduction

- Metabolic impairment is an intrinsic component of heart failure (HF) pathophysiology.
- Specifically, HF-associated metabolic dysfunction includes alterations in substrate utilization, insulin resistance, defects in energy production, and imbalanced anabolic-catabolic
- Metabolic abnormalities → significant morbidity and mortality in patients with HF → detection and therapeutic management remains challenging.
- During HF, the myocardium is undoubtedly in a state of dyssynchrony with regard to energy demand and ATP generation. Compensatory mechanisms attempt to regain synchrony through decreasing workload and increasing metabolism

Wyn G Huntere et al. Metabolic Dysfunction in Heart Failure: Diagnostic, Prognostic, and Pathophysiologic Insights From Metabolomic Profiling .Cur Heart Failure Resp.2016

CENTRAL ILLUSTRATION: Projected Future of Cardiovascular Risk Factors and Cardiovascular Diseases by 2060

Projections of Future Cardiovascular Risk Factors and Cardiovascular Disease in the United States From 2025 to 2060

Cardiovascular Risk Factors	*Cardiovascular Diseases*
Diabetes: ↑ of 39.3% to 55 million persons	Ischemic heart disease: ↑ of 30.7% to 29 million persons
Hypertension: ↑ of 27.1% to 162 million persons	Heart failure: ↑ of 33.4% to 13 million persons
Dyslipidemia: ↑ of 27.6% to 126 million persons	Myocardial infarction: ↑ of 16.9% to 16 million persons
Obesity: ↑ of 18.3% to 126 million persons	Stroke: ↑ of 33.8% to 15 million persons

Key points

- Projections for future cardiovascular risk factors and cardiovascular disease were based on NHANES data combined with 2020 U.S. Census projections for future population distributions
- Although steep rise in cardiovascular risk factors and cardiovascular diseases are expected in upcoming years, differences between women and men will largely remain stable over time
- Disproportionate increase in cardiovascular risk factors and cardiovascular disease are projected to impact racial and ethnic minority populations
- The results from this study have important implications for motivating policy decisions regarding equitable delivery of quality health care to all Americans

Mohebi R, et al. J Am Coll Cardiol. 2022;80(6):565-578.

HEART FAILURE IN INDONESIA

Indonesia Heart Failure Working Group 2021

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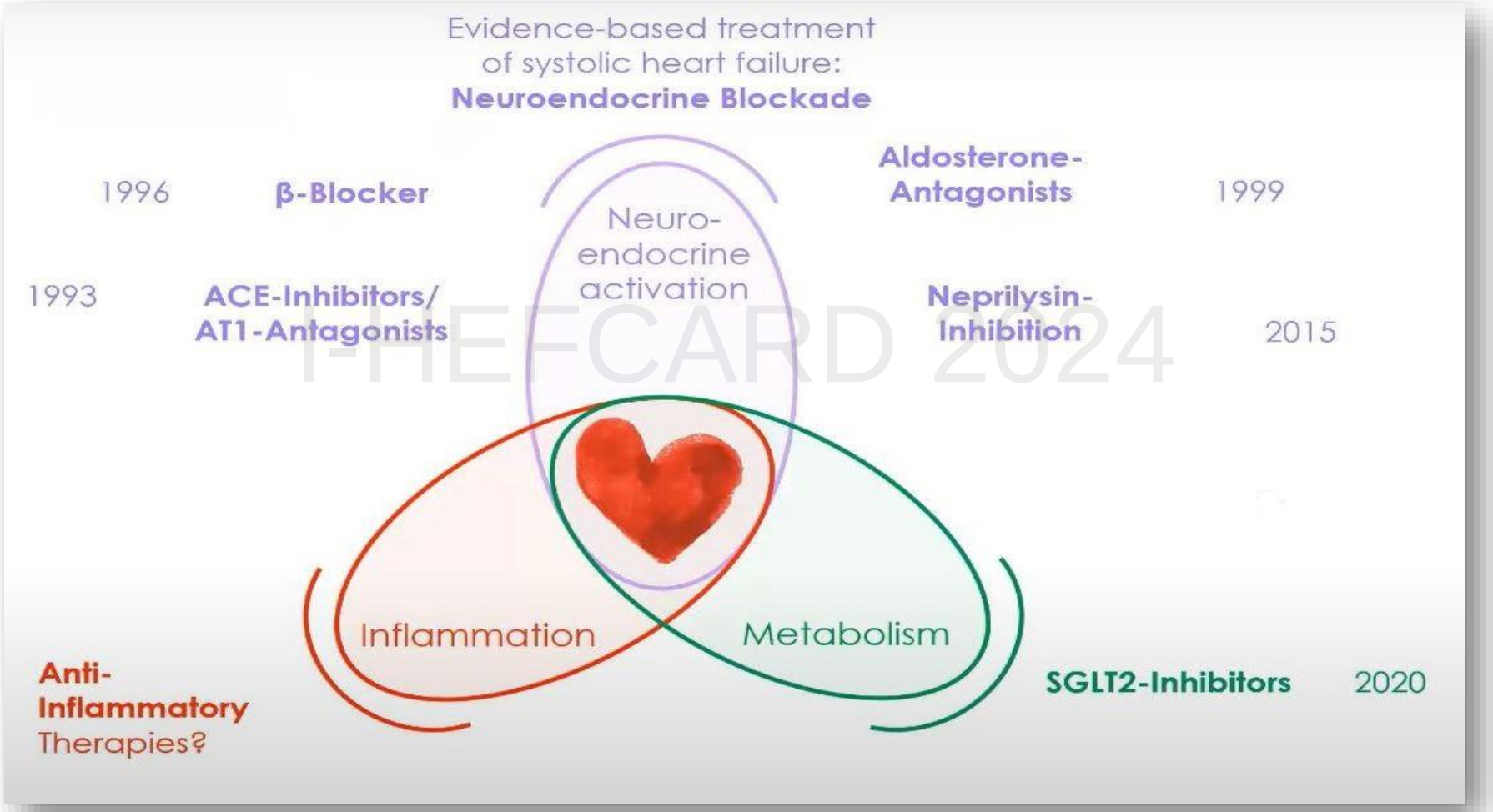
Hypothetical Model for the Metabolic Origins of Heart Failure

- To maintain adequate energy production in the face of dynamic changes in substrate availability and physiologic stresses, the myocardium is able to oxidize a variety of carbon fuels such as fatty acids, glucose, lactate, ketones, and amino acids
- Despite its "omnivorous" diet, the myocardium does not utilize all substrates for energy production in equal proportions.
- Under resting conditions, the healthy myocardium utilizes fatty acids as the predominant fuel source; β-oxidation generates 60–90 % of the total ATP production .
- The second major fuel source in the healthy resting state → pyruvate; it is derived in nearly equal amounts from glycolysis and lactate oxidation and generates 10–40 % of N myocardial ATP .
- Supplementary contributions are made from amino acid and ketone oxidation

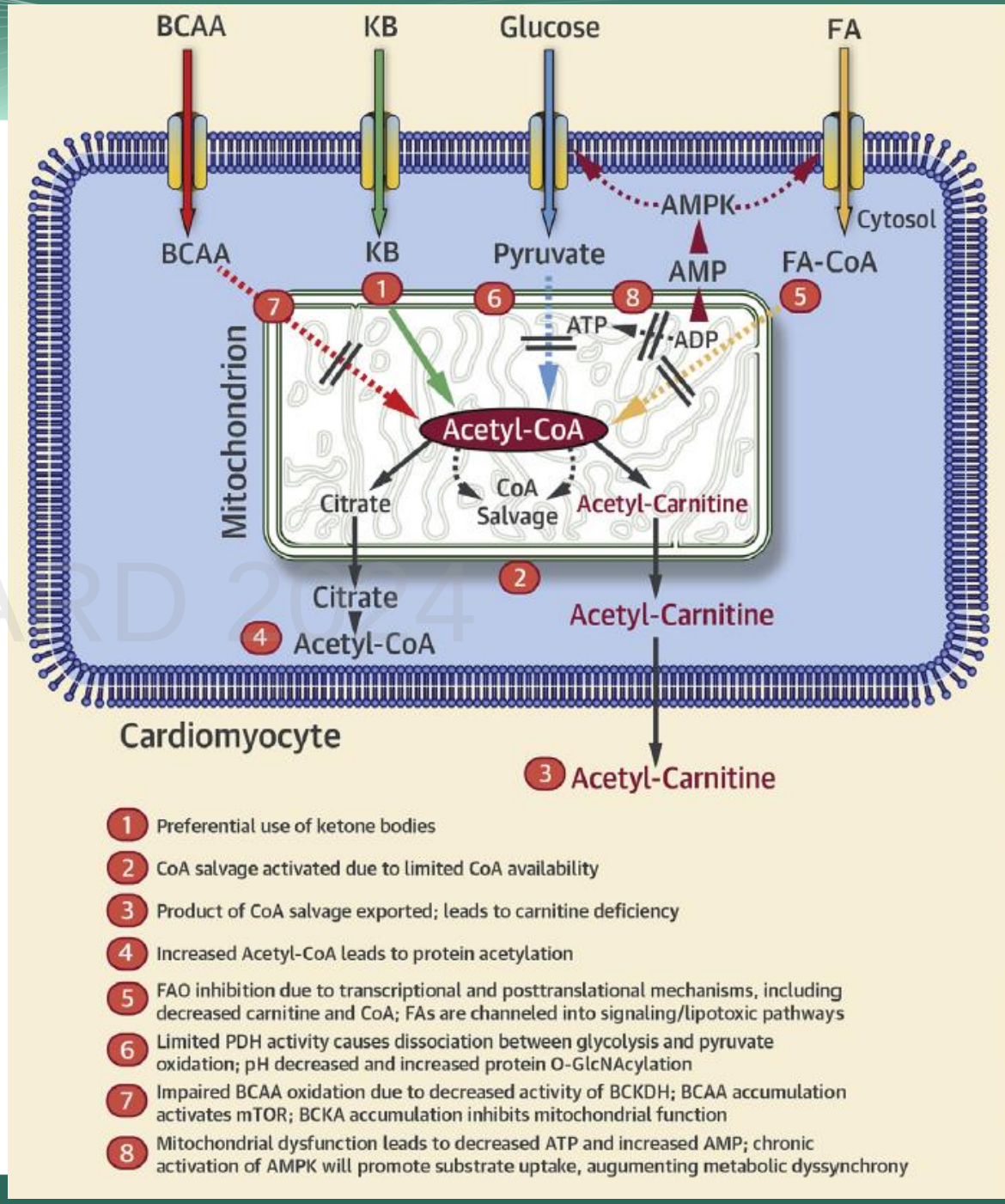
COMORBIDITIES AFFECT THE HEART & VICE VERSA



Hypothetical Model for the Metabolic Origins of Heart Failure

- The failing heart is oversupplied with macronutrients , leading to an imbalance in fuel availability and use and subsequent accumulation of key metabolic intermediates that worsen contractile function of the heart.
- The strategies that need to designed to regain synchrony among energy demand, substrate availability, and substrate use would be beneficial during HF.
- ß-blocker will work on reduction of workload, which in turn would help regain synchrony due to attenuation of energy demand. In addition, b-blockers help regain synchrony further through inhibition of lipolysis, thus decreasing substrate supply (FAs, and likely ketone bodies).

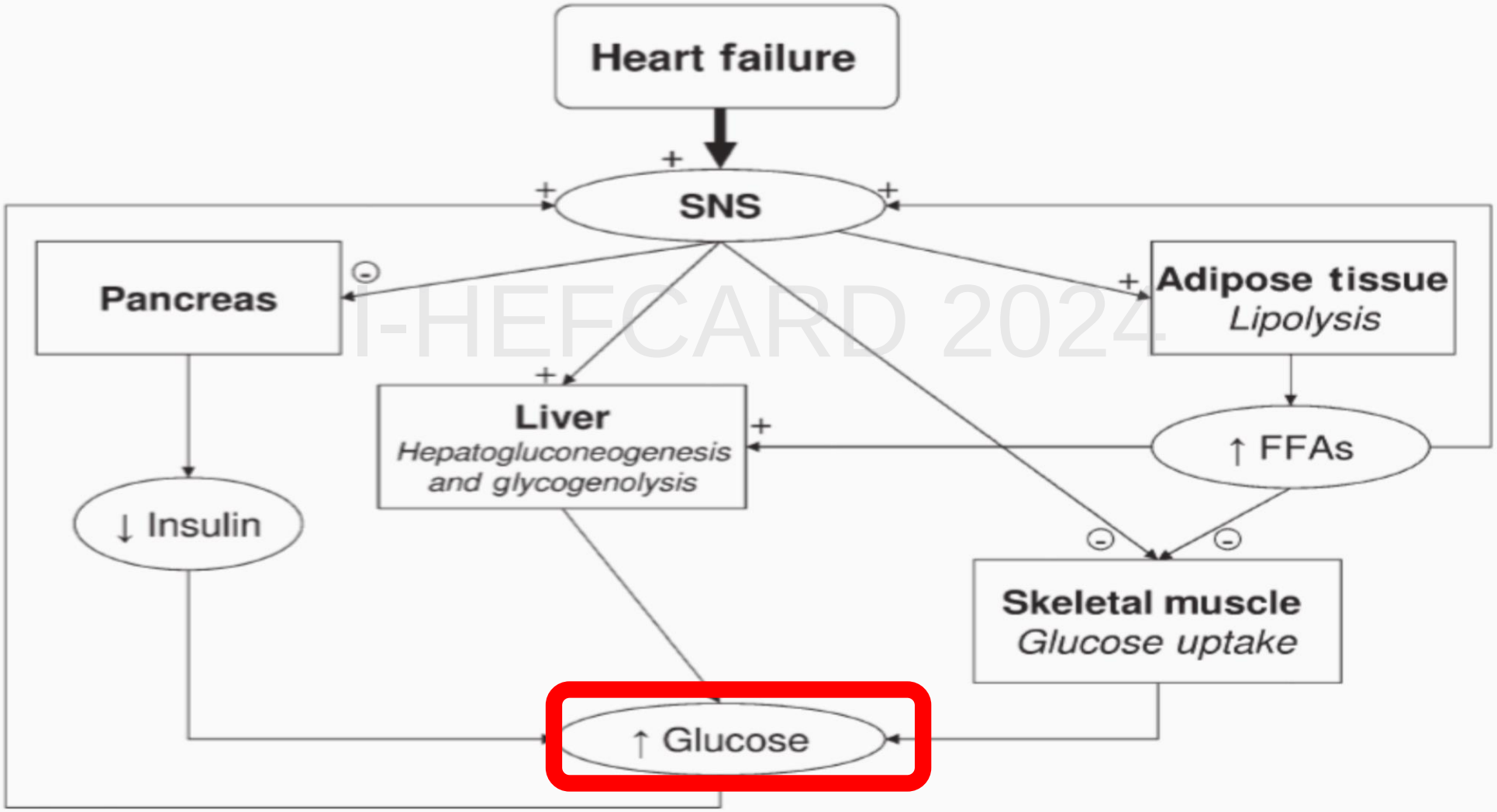
Wende, A.R. et al. J Am Coll Cardiol Basic Trans Science. 2017;2(3):297–310.



Diabetes dan Heart Failure

- Diabetes is an important risk factor for HF → Observational studies have consistently → a two- to four-fold increased risk of HF in individuals with diabetes compared with those without diabetes
- CV mortality, including death caused by worsening HF, is also 50–90% higher in patients with HF and diabetes compared with HF patients without diabetes, regardless of HF phenotype.
- Traditionally recognized as the hallmark metabolic lesion of type II diabetes mellitus, insulin resistance (IR) → identified as a key metabolic derangement in HF (Present in up to 61 % of nondiabetic HF patients)
- Given the high prevalence of IR in HF and its well-described associations with adverse outcomes, interest in IR as a potential therapeutic target and phenotypic divisor in HF has increased in recent years

Heart Failure causes Insulin Resistance



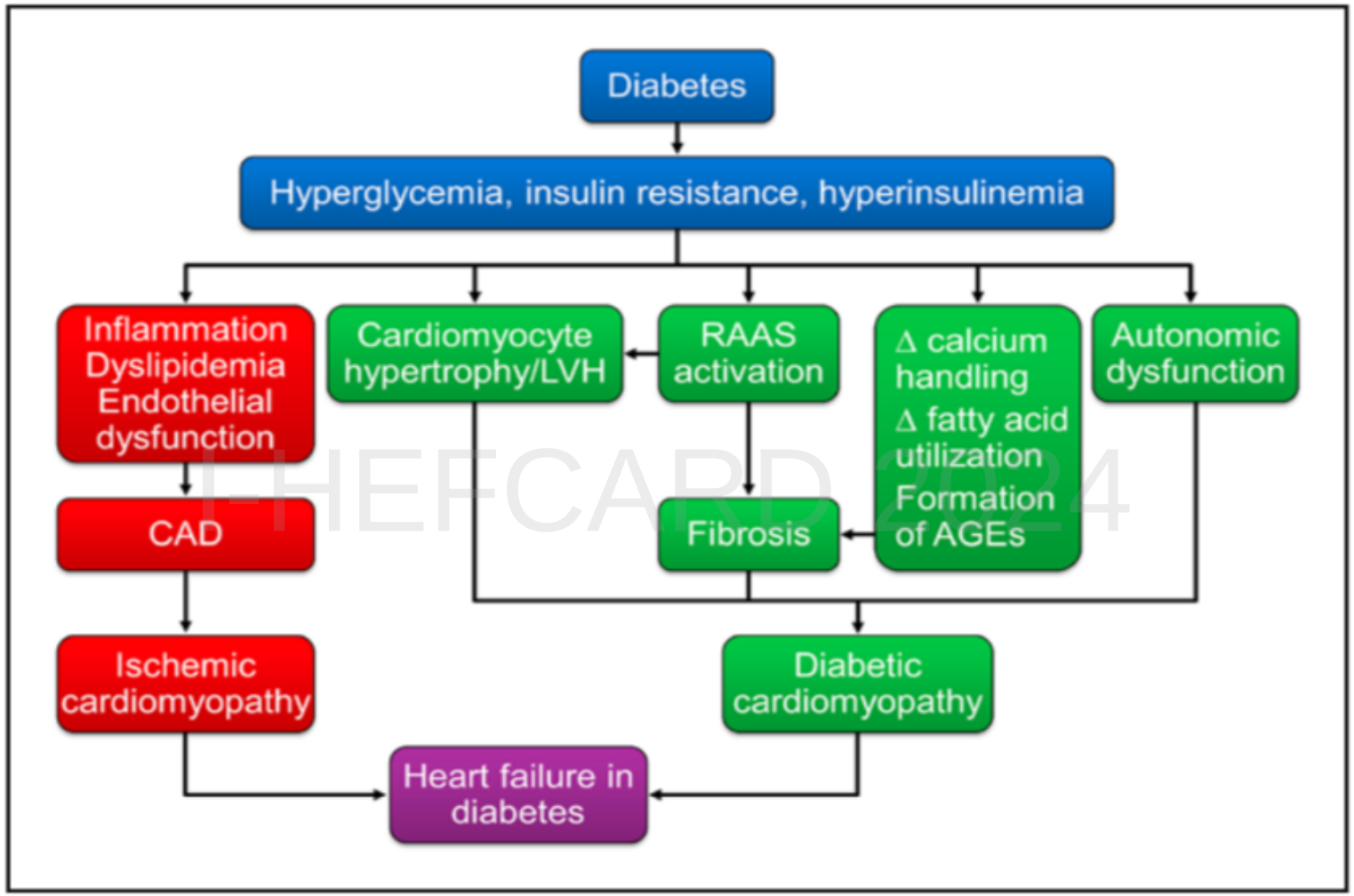


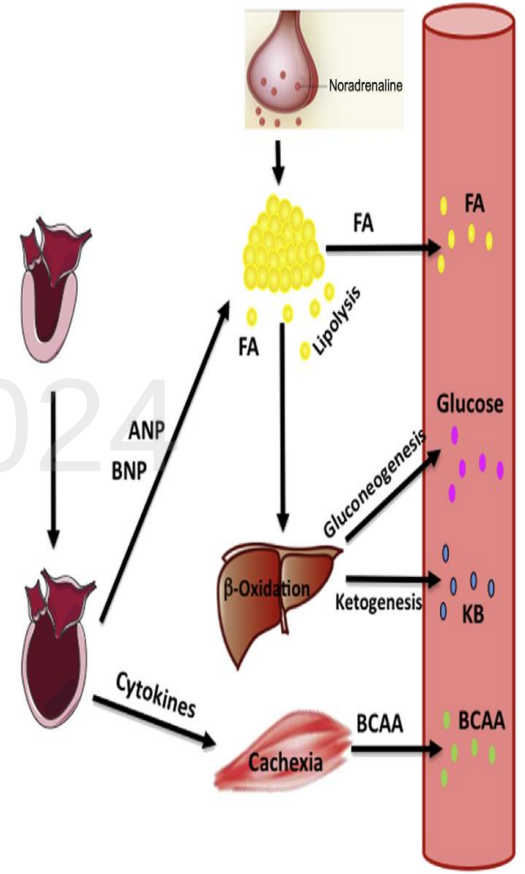
Figure 1. Pathophysiology of heart failure in diabetes mellitus.

AHA Scientific statement. Type 2 Diabetes Mellitus and Heart Failure. A Scientific statement from American Heart Association and Heart Failure society of America. Circulation 2019

Fatty Acid Oxydation (FAO)

- Cardiac FAO deficits could potentially precipitate contractile dysfunction through energy impairment and/or diversion of excess FAs into signaling and/or “lipotoxic” pathways.
- Decrease in FAO rates could reduce ATP availability for contraction (if below the capacity of alternative compensating pathways) concomitant with increased diversion of FA species into signaling/lipotoxic path ways, →impairment of contractility.

FIGURE 4 Increased Circulating Levels of Various Substrates During Heart Failure



ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; FA = fatty acid; FAO = fatty acid oxidation; GLOX = glucose oxidation; KB = ketone body; other abbreviation as in Figure 2.

Tailoring of Medical Therapy According to Clinical Profiles

Giuseppe et al. European Journal of Heart Failure. 2021;23:872–881.

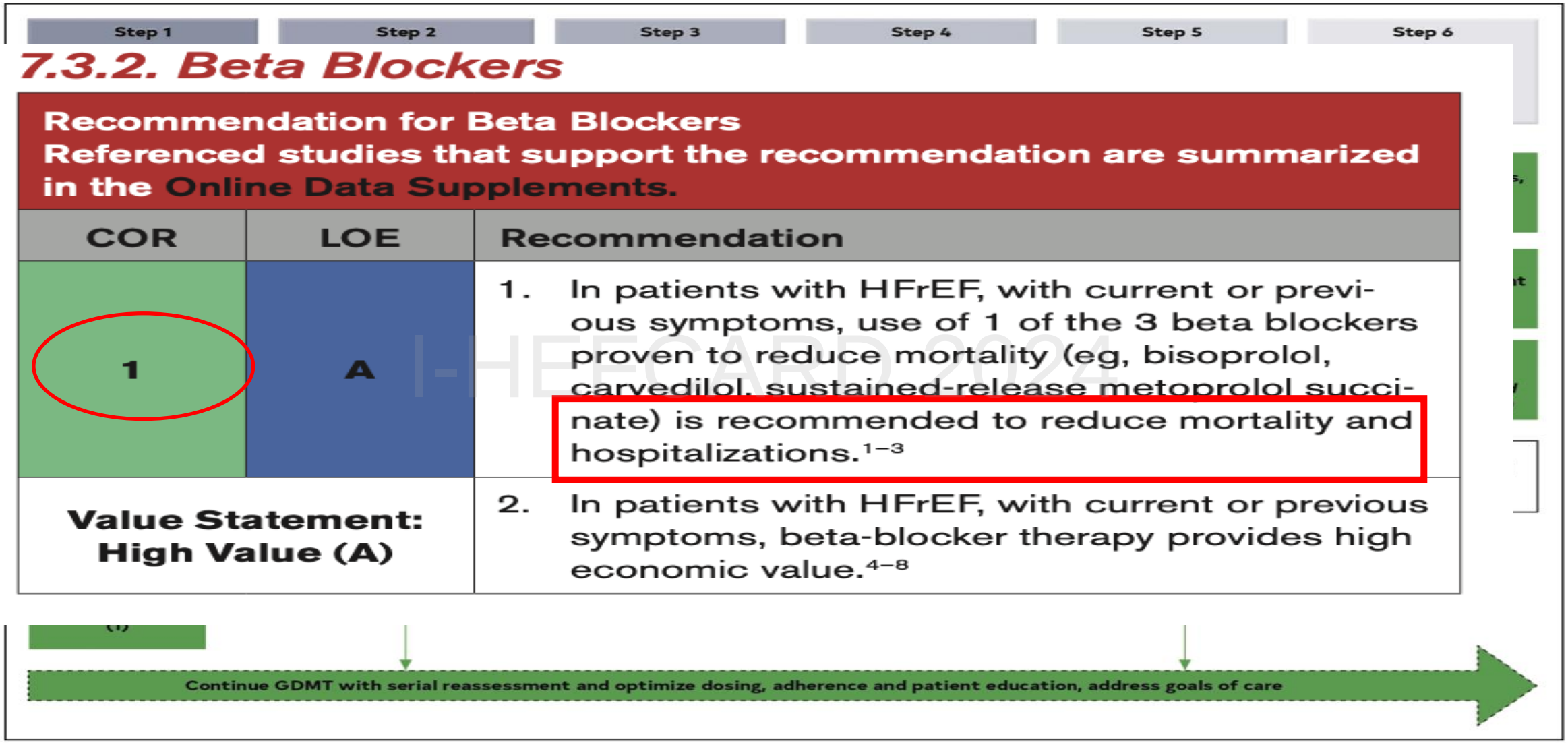


Figure 6. Treatment of HFrEF Stages C and D.

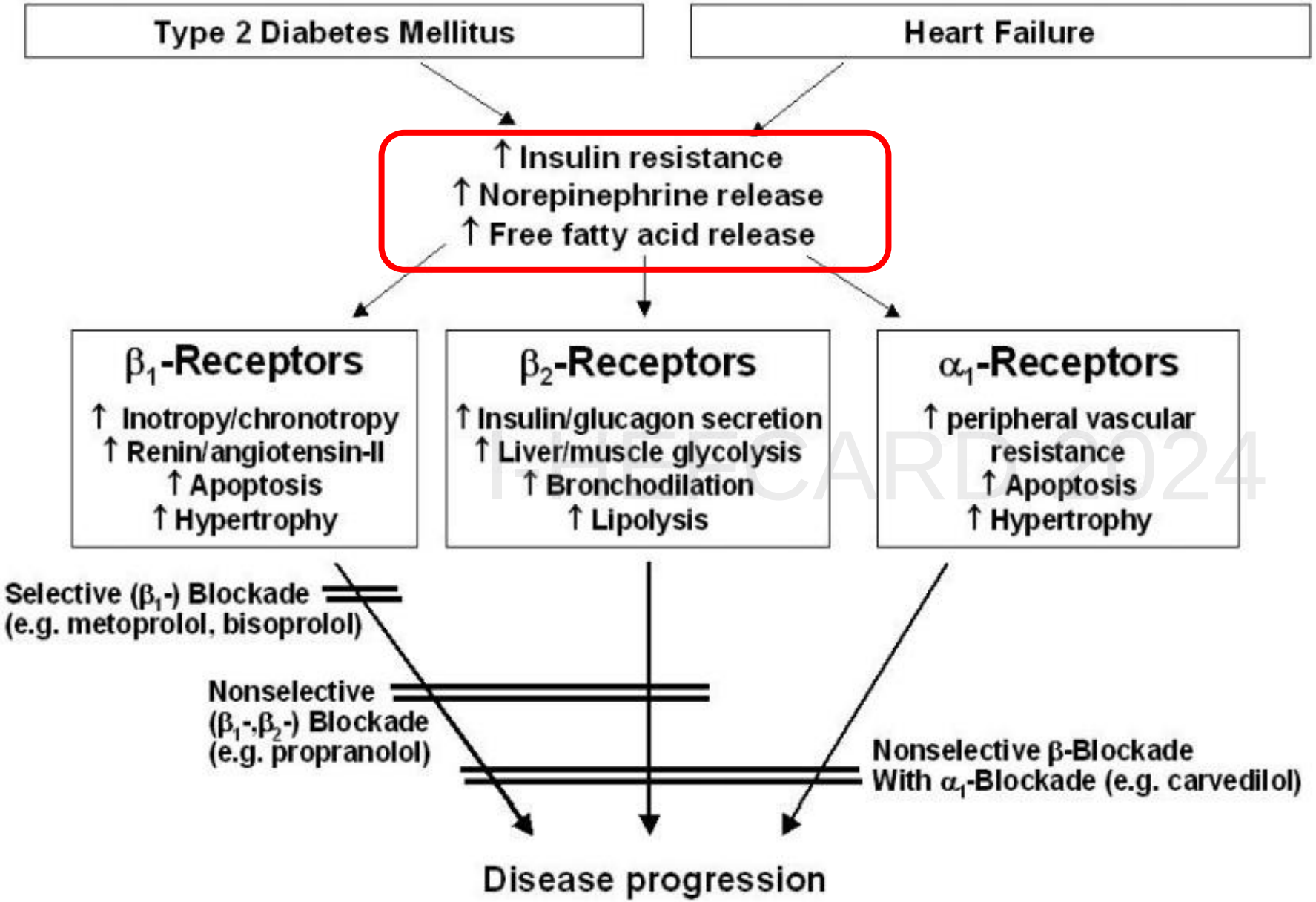
AHA. Heart Failure Guidelines 2022

Metabolic Effects of β-Blockers

- β-adrenoceptor antagonists (β-blockers) have effects on metabolism via their mechanism as blockers of adrenergic stimulation
- Most interest in the **metabolic effects of β-blockers** is caused by their effect on glucose metabolism
- Strict metabolic control and management of cardiovascular risk factors in patients with diabetes mellitus has proven to be of **great importance** in the improvement of prognosis
- The use of β-blockers in patients with diabetes mellitus has been **controversial** because of fear of deterioration of metabolic control of glucose and lipids and blunting of the symptoms of hypoglycemia
- Currently, it appears that there is a **beneficial metabolic effect** with the third-generation β-blocker **Carvedilol**

2021_Ryn

Kveiborg, B., Christiansen, B., Major-Petersen, A. *et al.* Metabolic Effects of β-Adrenoceptor Antagonists with Special Emphasis on Carvedilol. *Am J Cardiovasc Drugs* **6,** 209–217 (2006).



Potential Beneficial Effects of Anti-Adrenergic Blockers in Diabetic Patients with Heart Failure

Wilson tang et al.Vascular Health and Risk Management 2007:3(5) 639-645.

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Pharmacological comparisons between carvedilol versus atenolol and metoprolol

Table 1 Atenolol and metoprolol versus carvedilol

Outcome	Carvedilol	Atenolol	Metoprolol
Worsens lipids	No	Yes	Yes
Worsens glycaemic control	No	Yes	Yes
Mainly lowers BP through reductions in vasodilation versus cardiac output	Yes	No	No
Higher risk of microalbuminuria	No	No direct comparison	Yes
Increases weight	No	No direct comparison	Yes
Lower risk of mortality in patients with systolic HF and AMI	Yes	No	No

AMI, acute myocardial infarction; BP, blood pressure; HF, heart failure.

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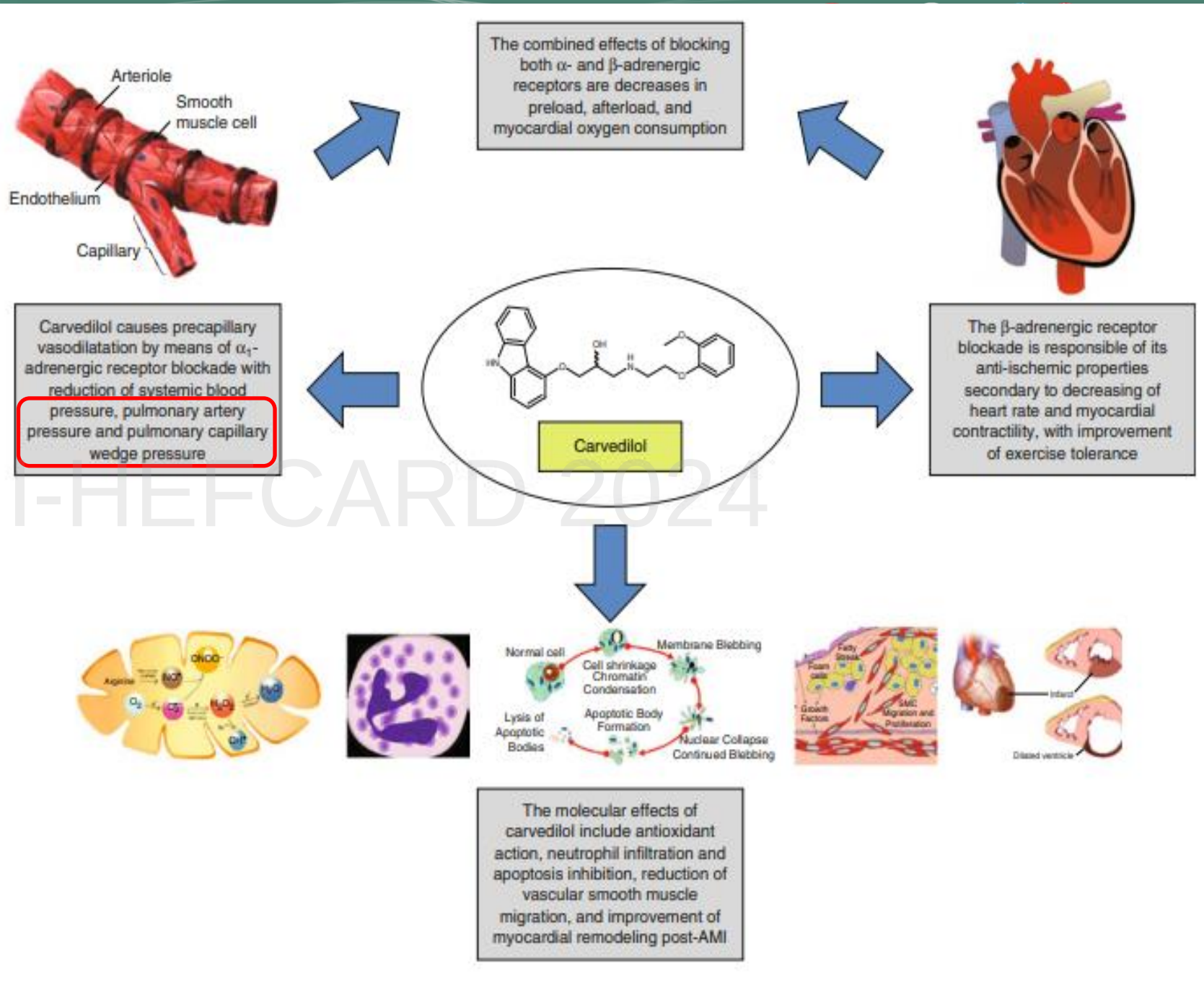
DiNicolantonio JJ, Fares H, Niazi AK, et al. Open Heart 2015;2:e000230. doi:10.1136/openhrt-2014-000230

MoA of Carvedilol in Managing HF



Scarabelli, et al. Am J Cardiovasc Drugs 2012; 12 (6)

Consensus recommendations for management of patients with type 2 diabetes mellitus and cardiovascular diseases

Alaaeldin Bashier[1*], Azza Bin Hussain[1], Elamin Abdelgadir[1], Fatheya Alawadi[1], Hani Sabbour[2] and Robert Chilton[3]

The beta-blockers in patients with T2DM and HF, in large randomized clinical trials, demonstrated **significant improvements in morbidity and mortality** that were comparable in patients without T2DM. Furthermore, a meta-analysis of several beta-blocker trials demonstrated to reduce all-cause mortality in patients with T2DM. Also, **the treatment benefits of beta-blockers in T2DM patients far outweigh the theoretical risks related to hypoglycaemia, slight changes in HbA1c along with serum lipids.** These benefits, therefore, strongly support beta-blocker treatment in patients with concurrent T2DM and HF

Bashier et al. Diabetol Metab Syndr (2019) 11:80 https://doi.org/10.1186/s13098-019-0476-0

Effects of β-blockers on all-cause mortality in patients with type 2 diabetes and coronary heart disease

Tetsuro Tsujimoto MD, PhD[1] | Takehiro Sugiyama MD, MSHS, PhD[2,3] | Hiroshi Kajio MD, PhD[1]

Cox proportional hazards analysis to assess the effects of β-blockers on all-cause

- **All-cause mortality in patients with MI/HFrEF was significantly lower in those receiving β-blockers** than in those not receiving β-blockers, whereas that in patients without MI/HFrEF did not

Conclusions:

In patients with diabetes and CHD, the use of β-blockers was effective in reducing all-cause mortality in those with MI/HFrEF but not in those without MI/HFrEF.

- The risk of major cardiovascular events in patients without MI/HFrEF was not significantly different between those on and those not on β-blocker treatment.

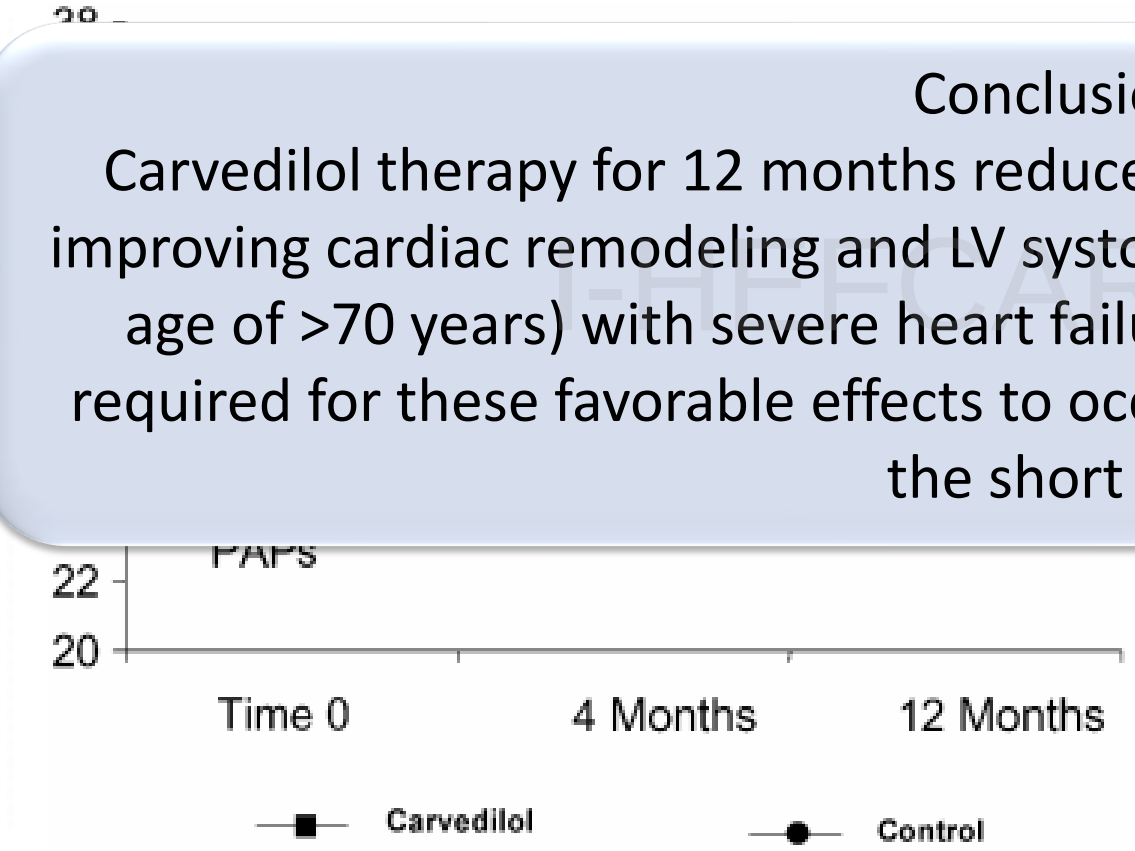
Tsujimoto et al. Diabetes Obes Metab. 2017;19:800–808

Effects of carvedilol on left ventricular remodeling and systolic function in elderly patients with heart failure

A. Palazzuoli*, F. Bruni, L. Puccetti, M. Pastorelli, P. Angori, A.L. Pasqui, A. Auteri

Conclusions:

Carvedilol therapy for 12 months reduced LV diameters and volumes. Thus, improving cardiac remodeling and LV systolic function in elderly patients (mean age of >70 years) with severe heart failure. Several months of therapy are required for these favorable effects to occur, as these changes do not occur in the short term



A Pallazuoli, et al. The European Journal of Heart Failure 4 (2002) 765–770

β-blocker clinical trials in

Trial (year)	Patients (n)	Results
COMET (2003)	3029	17% reduction in mortality compared with metoprolol tartrate.
COPERNICUS (2001)	2289	✓ 27% reduction in combined end point (risk of death or hospitalization due to a cardiovascular reason
Research Collaborative Group (1997)		✓ 5.3% increase LVEF and significant reductions in end-diastolic and end-systolic dimension by 1.7 mm and 3.2 mm, respectively for carvedilol compared with placebo.
US Carvedilol HF Study Group (1996)	1094	65% reduction in all cause mortality compared with placebo

Carvedilol :

The β-blocker that reduce mortality and hospital admission in heart failure as shown in the Comet, Copernicus, ANZ group and US Carvedilol clinical studies.

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Dinicolantonio, et al. Expert Rev. Cardiovasc. Ther. 10(1), 13–25 (2012)

Take Home Messages

01

Heart failure is the cardiovascular epidemic of the 21st century.

02

Comorbidities are both cause and effect of HF & aggravate the prognosis of HF and must therefore be treated .

03

The usage of Beta blocker would help regain metabolic synchrony in HF.

04

Carvedilol appears to have beneficial metabolic effects.

05

Carvedilol clinically proven for heart failure and reduce cardiovascular mortality.

06

Beta blockers: Choose the best, start low and go slow.

THANK YOU

Results: There were 1020 patients on carvedilol, 886 on selective beta blockers, and 10,216 on no beta blocker at admission. After controlling for other variables, the odds of $Hypo_{1day,}$ $Hypo_{T}$ and $Hypo_{severe}$ were higher for carvedilol and selective beta blocker recipients than non-recipients, but only in basal insulin nonusers. The odds of $Hypo_{1day}$ (odds ratio [OR] 1.99, 95% confidence interval [CI] 1.28, 3.09, $p=0.0002$) and $Hypo_{T}$ (OR 1.38, 95% CI 1.02, 1.86, $p=0.03$) but not $Hypo_{severe}$ (OR 1.90, 95% CI 0.90, 4.02, $p=0.09$) were greater for selective beta blocker vs. carvedilol recipients in basal insulin nonusers. $Hypo_{1day}$, $Hypo_{T}$, and $Hypo_{severe}$ were all associated with increased mortality in adjusted models among non-beta blocker and selective beta blocker recipients, but not among carvedilol recipients.

Conclusions: Beta blocker use is associated with increased odds of hypoglycemia among hospitalized patients not requiring basal insulin, and odds are greater for selective beta blockers than for carvedilol. The odds of hypoglycemia-associated mortality are increased with selective beta blocker use or nonusers but not in carvedilol users, warranting further study.

Keywords: Hypoglycemia, Beta blocker, Diabetes mellitus, Hospitalized patients, Mortality

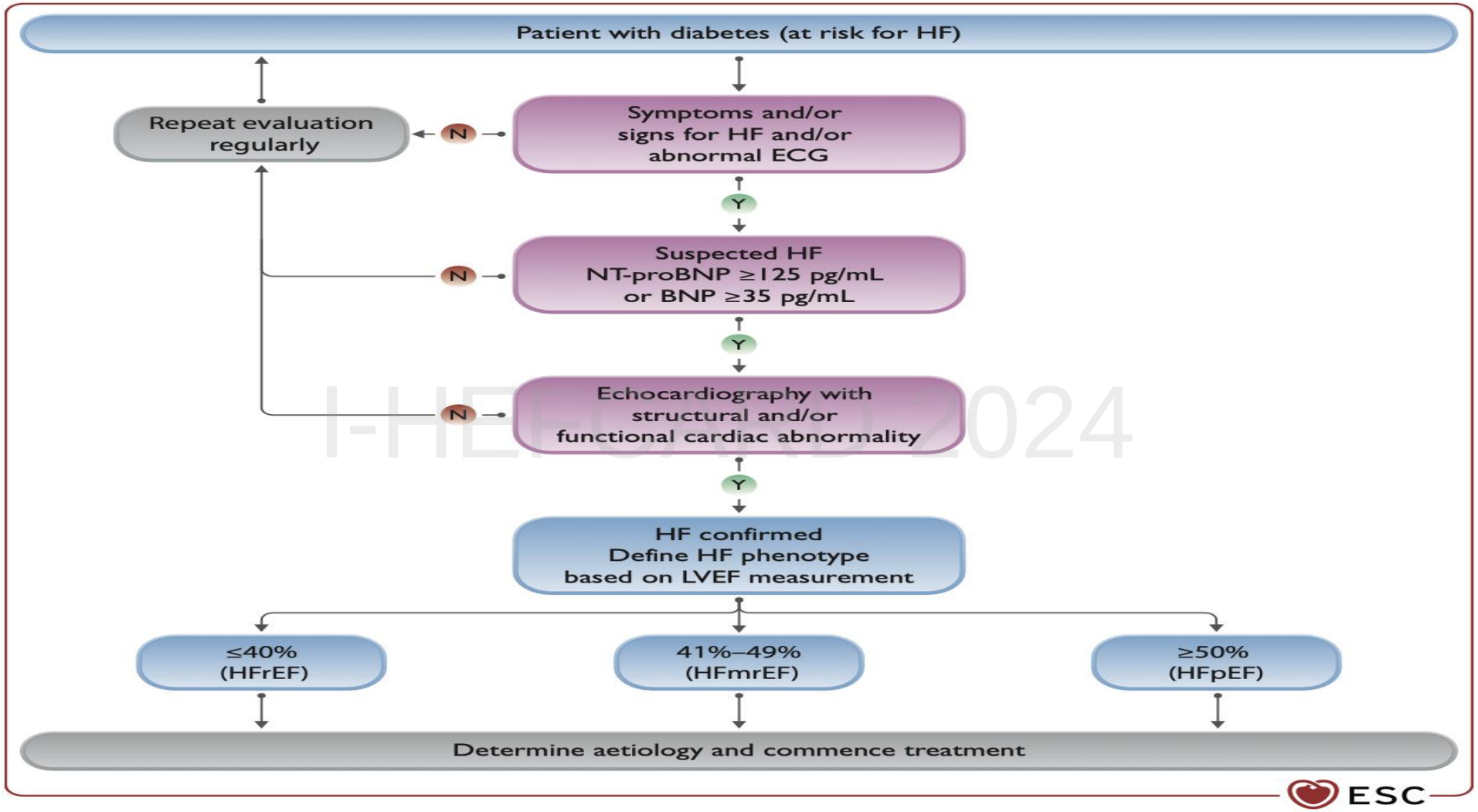
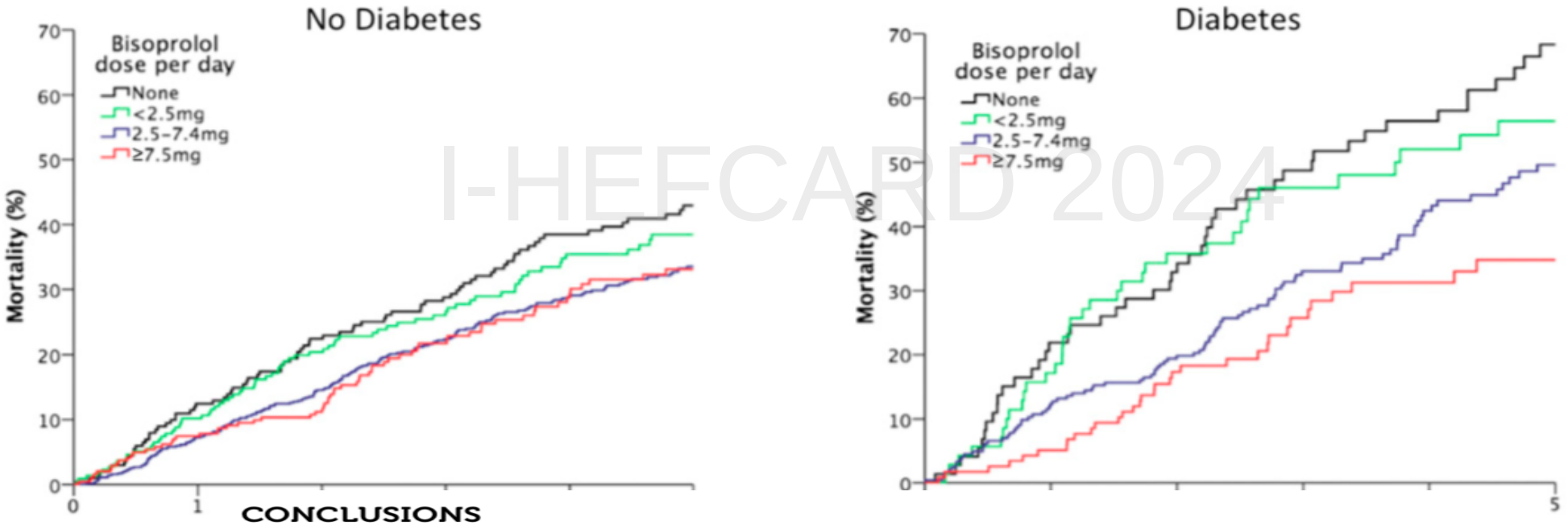


Figure 14 Diagnostic algorithm for heart failure in patients with diabetes. BNP, B-type natriuretic peptide; ECG, electrocardiogram; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Mortality Reduction Associated With β-Adrenoceptor Inhibition in Chronic Heart Failure Is Greater in Patients With Diabetes

Klaus K. Witte,[1] Michael Drozd,[1] Andrew M.N. Walker,[1] Peysh A. Patel,[1] Jessica C. Kearney,[1] Sally Chapman,[1] Robert J. Sapsford,[2] John Gierula,[1] Maria F. Paton,[1] Judith Lowry,[1] Mark T. Kearney,[1] and Richard M. Cubbon[1]

Diabetes Care 2018;41:136–142 | https://doi.org/10.2337/dc17-1406



CONCLUSIONS

Increasing β-blocker dose is associated with a greater prognostic advantage in CHF patients with diabetes than in CHF patients without diabetes.

Hyperthyroidism and Heart Failure

- HF represents the initial clinical presentation in about 6% of patients with hyperthyroidism, with h
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It is important to assess other precipitants that may exacerbate existing CV disease → Thyroid Dysfunction

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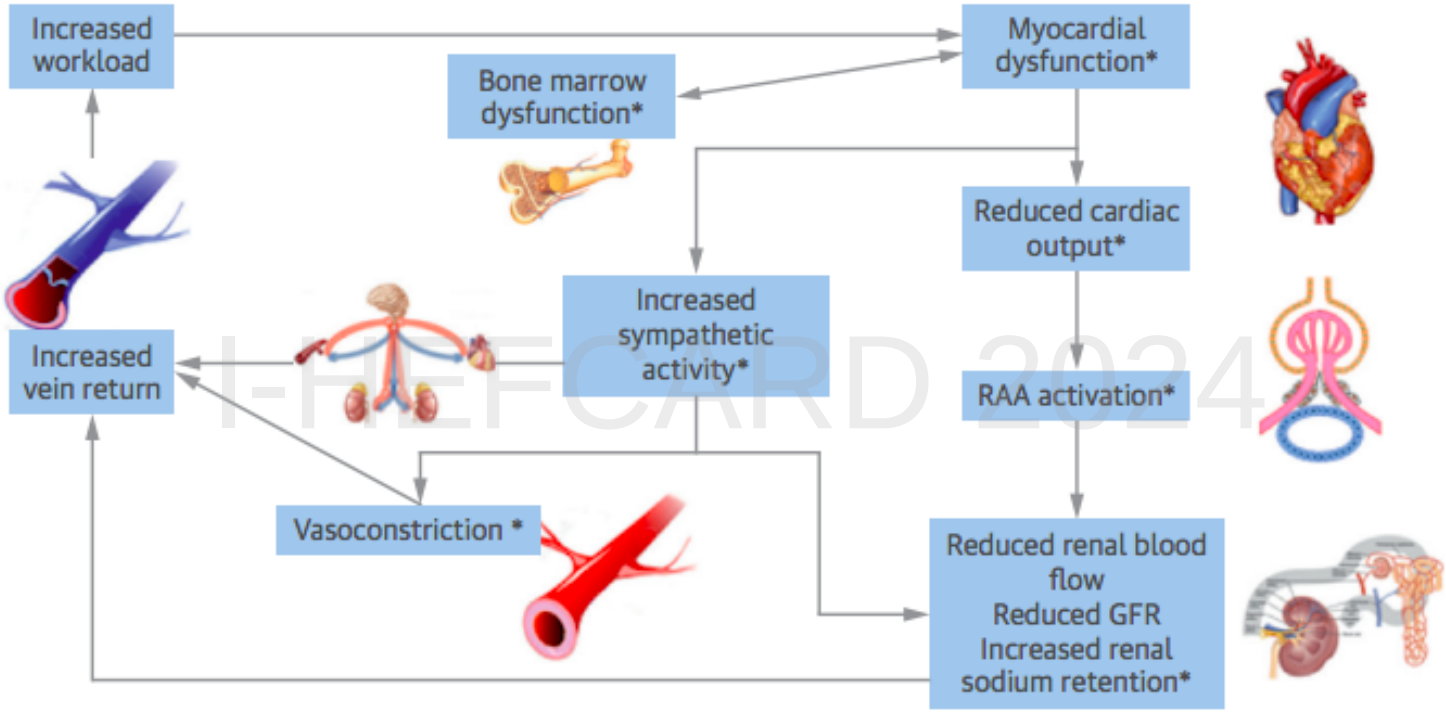
Khan R, Sikanderkhel S, Gui J, Adeniyi AR, et al. Thyroid and Cardiovascular Disease: A Focused Review on the Impact of Hyperthyroidism in Heart Failure. *Cardiol Res*. 2020;11(2):68-75
Razvi S, Jabbar A, et al. Thyroid Hormones and Cardiovascular Function and Diseases. J Am Coll Cardiol. 2018 Apr 24;71(16):1781-1796

The Role of Thyroid Hormones in the Pathophysiology of Heart Failure



Low thyroid function reduces cardiac function and induces morphological, molecular, and structural changes of the myocardium. Low thyroid function also increases peripheral vascular resistance, plasma noradrenaline concentrations, and plasma renin activity, and reduces erythropoietin. *Critical points where low thyroid state (function) may contribute to the progression and worsening of heart failure.
GFR = glomerular filtration rate; HF = heart failure; RAA = renin-angiotensin-aldosterone axis; TH = thyroid hormones.

Razvi S, Jabbar A, et al. Thyroid Hormones and Cardiovascular Function and Diseases. J Am Coll Cardiol. 2018 Apr 24;71(16):1781-1796

assigned to receive either carvedilol (*n* = 15) or metoprolol (*n* = 15). Thyroid-stimulating hormone (TSH), free T3, free T4, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride, and total cholesterol levels were measured before and following 3 months of treatment. *Results.* Systolic and diastolic blood pressure, heart rate, TSH, and free T4 improved significantly in both treatment groups. There were no statistically significant changes in the lipid parameters in either of the two treatment groups; however, triglyceride levels slightly decreased with carvedilol treatment. There were also no differences between the two groups in terms of the typical symptoms of hyperthyroidism. *Conclusion.* Carvedilol might be a preferred agent to treat hyperthyroid patients who have hypertension and dyslipidemia. This is likely due to the possible beneficial effect of carvedilol on lipid parameters, especially on triglyceride levels.

Hyperthyroidism | Dyslipidemia | Hypertension | Triglyceride | Carvedilol | Metoprolol

Introduction

HEART FAILURE MANAGEMENT

1. Improve survival
2. Improve symptoms
3. Increase functional status
4. Improve patient's compliance

Co-morbidities

- IMPROVE QoL
- DECREASE Frequency of hospitalization, length of stay & visits to ED
- DECREASE overall medical costs