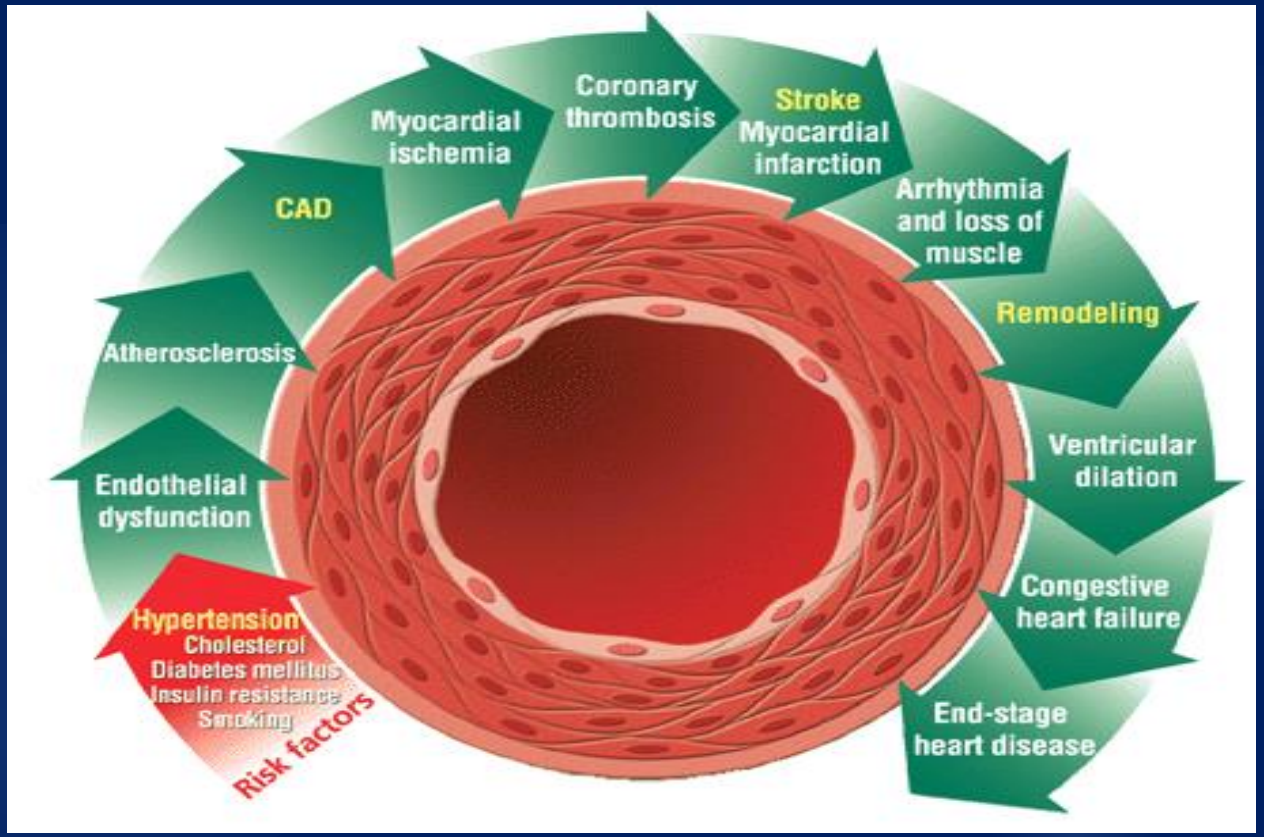
Advanced Heart Failure : Role of Beta Blockers

Workshop on Heart Failure 20 Mei 2017

Cardiovascular Disease Continuum

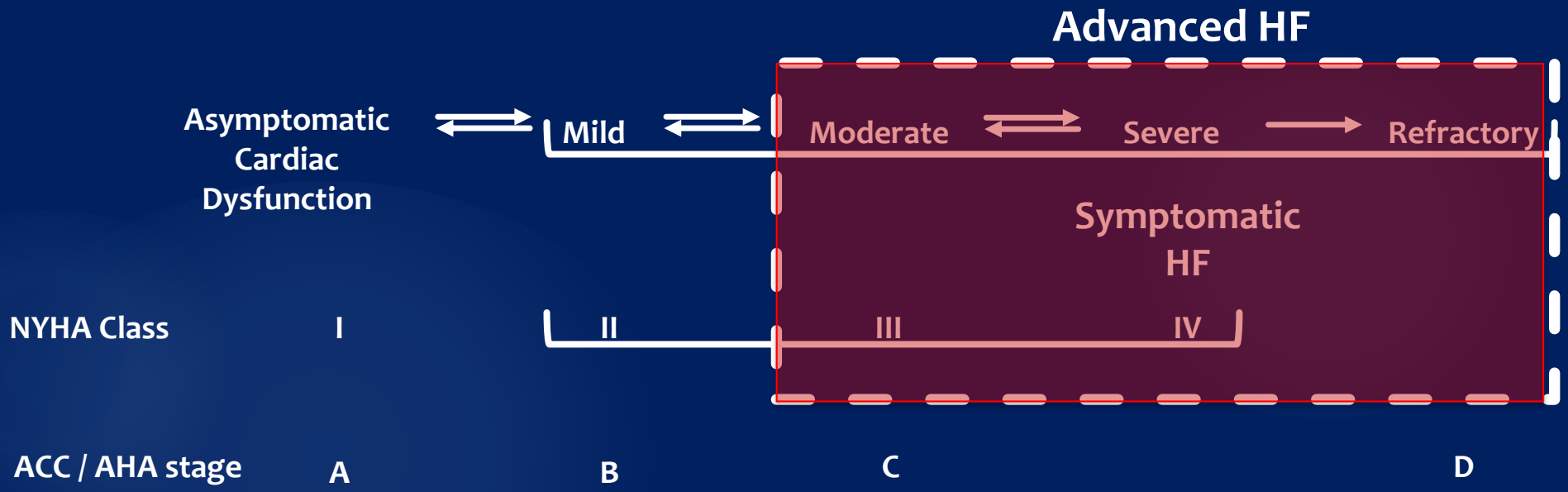


HF Classification

Type of HF		HFrEF	HFmrEF	HFpEF
Criteria	1	Symptoms ± signs	Symptoms ± signs	Symptoms ± signs
	2	LVEF < 40 %	LVEF 40 - 49 %	LVEF ≥ 50 %
	3	-	1. Elevated levels of natriuretic peptides 2. At least one additional criterion : • Relevant structural heart disease (LVH and / or LAE) • Diastolic dysfunction	1. Elevated levels of natriuretic peptides 2. At least one additional criterion : • Relevant structural heart disease (LVH and / or LAE) • Diastolic dysfunction

ESC guidelines on AHF and CHF 2016

Advanced ~ Other Classification of HF



Metra et al, European Journal of Heart Failure 9 (2007) 684–694

Advanced heart failure : definition

1. Severe symptoms of HF with dyspnoea and/or fatigue at rest or with minimal exertion (NYHA functional class III or IV)
2. Episodes of fluid retention (pulmonary and/or systemic congestion, peripheral oedema) and/or of reduced cardiac output at rest (peripheral hypoperfusion)
3. Objective evidence of severe cardiac dysfunction, shown by at least one of the following:
   - A low LVEF (<30%),
   - A severe abnormality of cardiac function on Doppler echocardiography with a pseudonormal or restrictive mitral inflow pattern
   - High LV filling pressures (mean PCWP>16 mm Hg, and/or mean RAP>12 mm Hg by pulmonary artery catheterisation)
   - High BNP or NT-ProBNP plasma levels, in the absence of non-cardiac causes.

Metra et al. EHJ 2007; 9 : 684-694

Advanced heart failure : definition

4. Severe impairment of functional capacity shown by one of the following:
   - Inability to exercise,
   - 6-MWT distance<300 m, or less in females and/or patients aged ≥75 years
   - peak VO2 <12 to 14 ml/kg/min
5. History of ≥1 HF hospitalisation in the past 6 months
6. Presence of all the previous features despite "attempts to optimise" therapy including diuretics, inhibitors of the renin–angiotensin–aldosterone system, and beta-blockers, unless these are poorly tolerated or contraindicated, and CRT, when indicated.

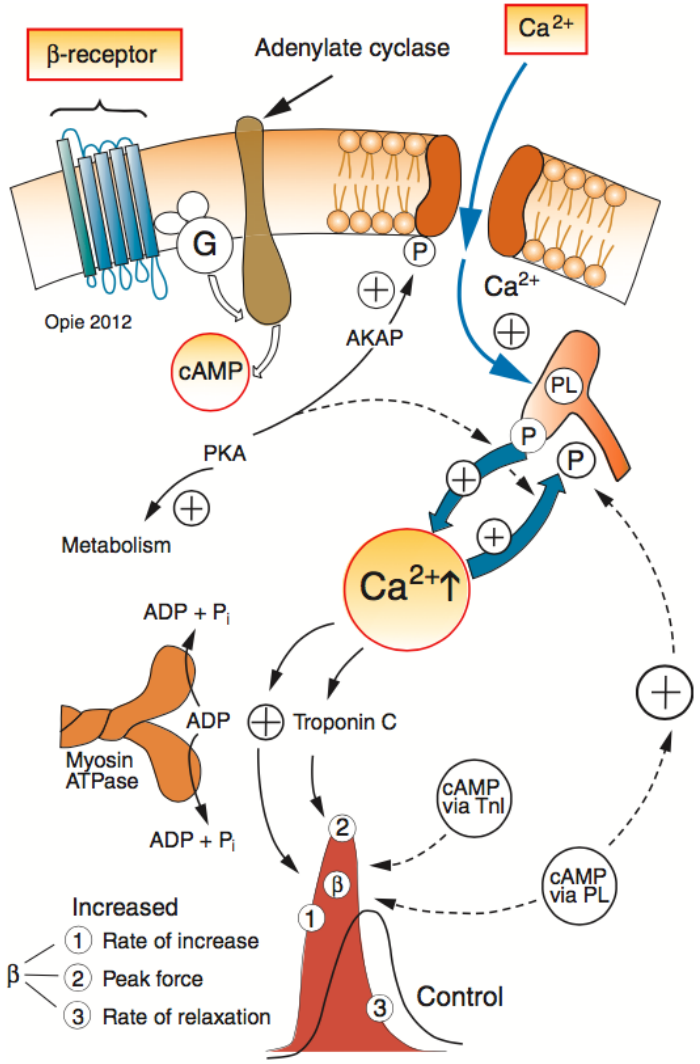
Metra et al. EHJ 2007; 9 : 684-694

Mechanism of action

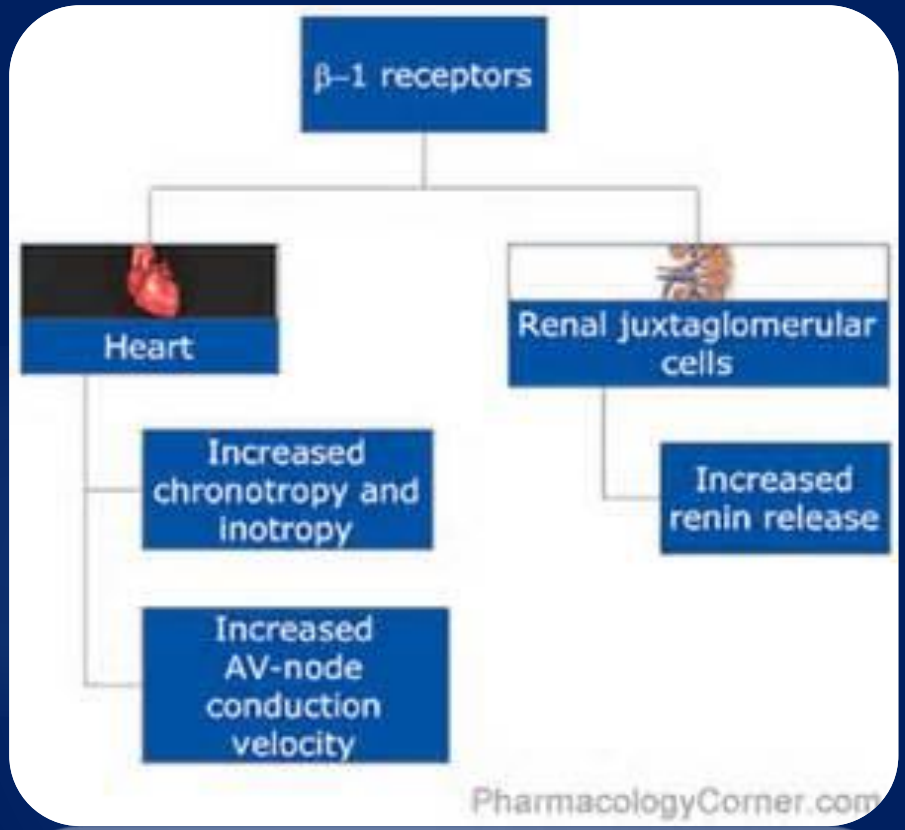
Beta-receptors

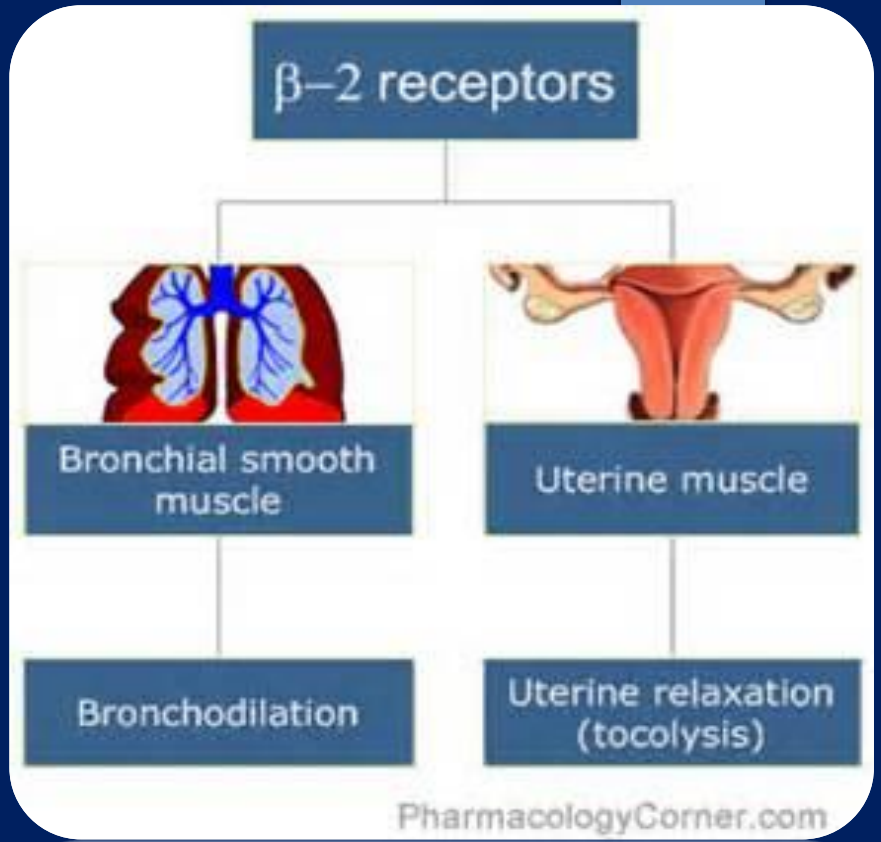
… are on the surface of cells innervated by the sympathetic nervous system

… mediate certain physiological responses to adrenaline



ESC Expert Consensus on Betablocker, 2004
Opie, Drugs for the heart

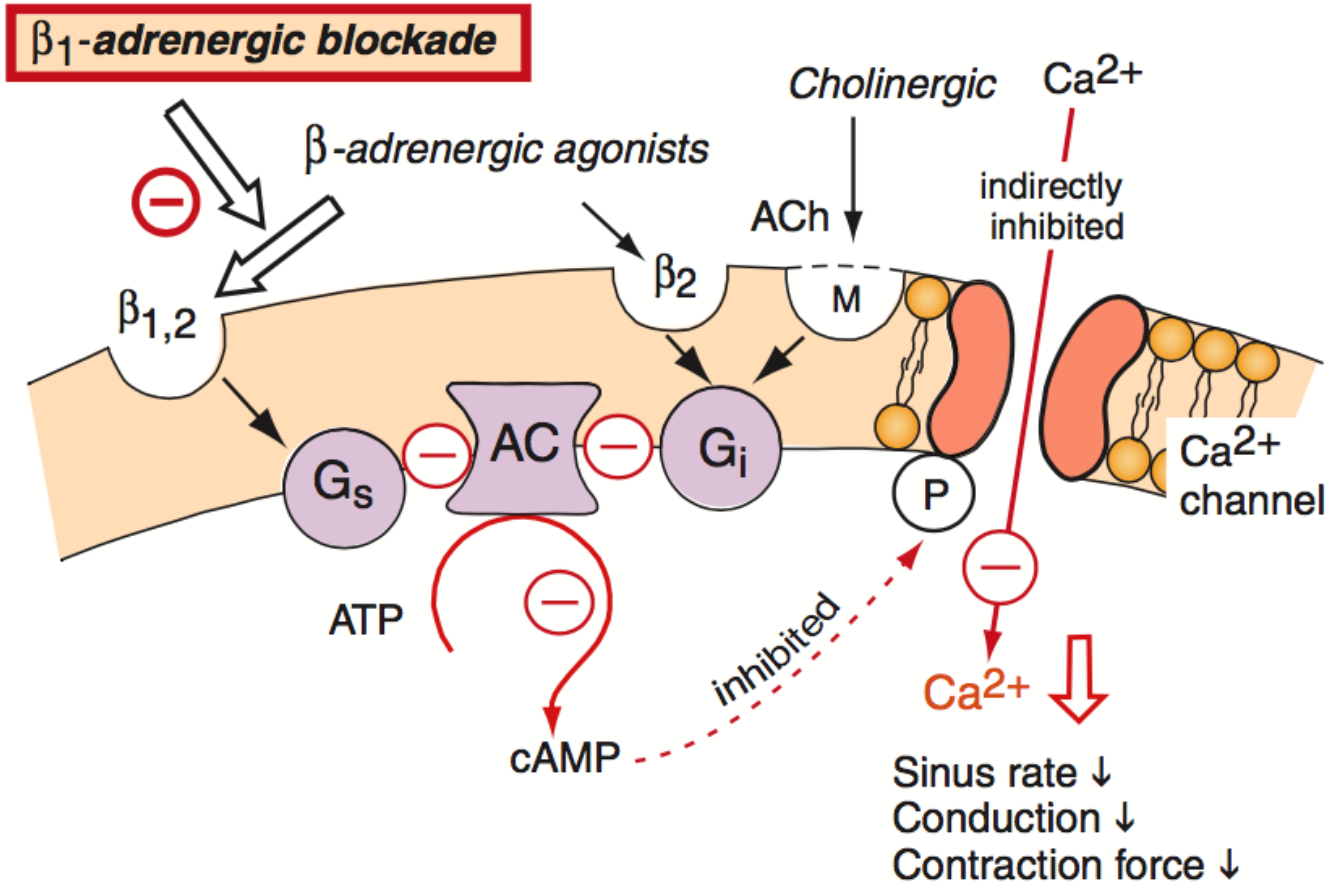




ESC Expert Consensus on Betablocker, 2004

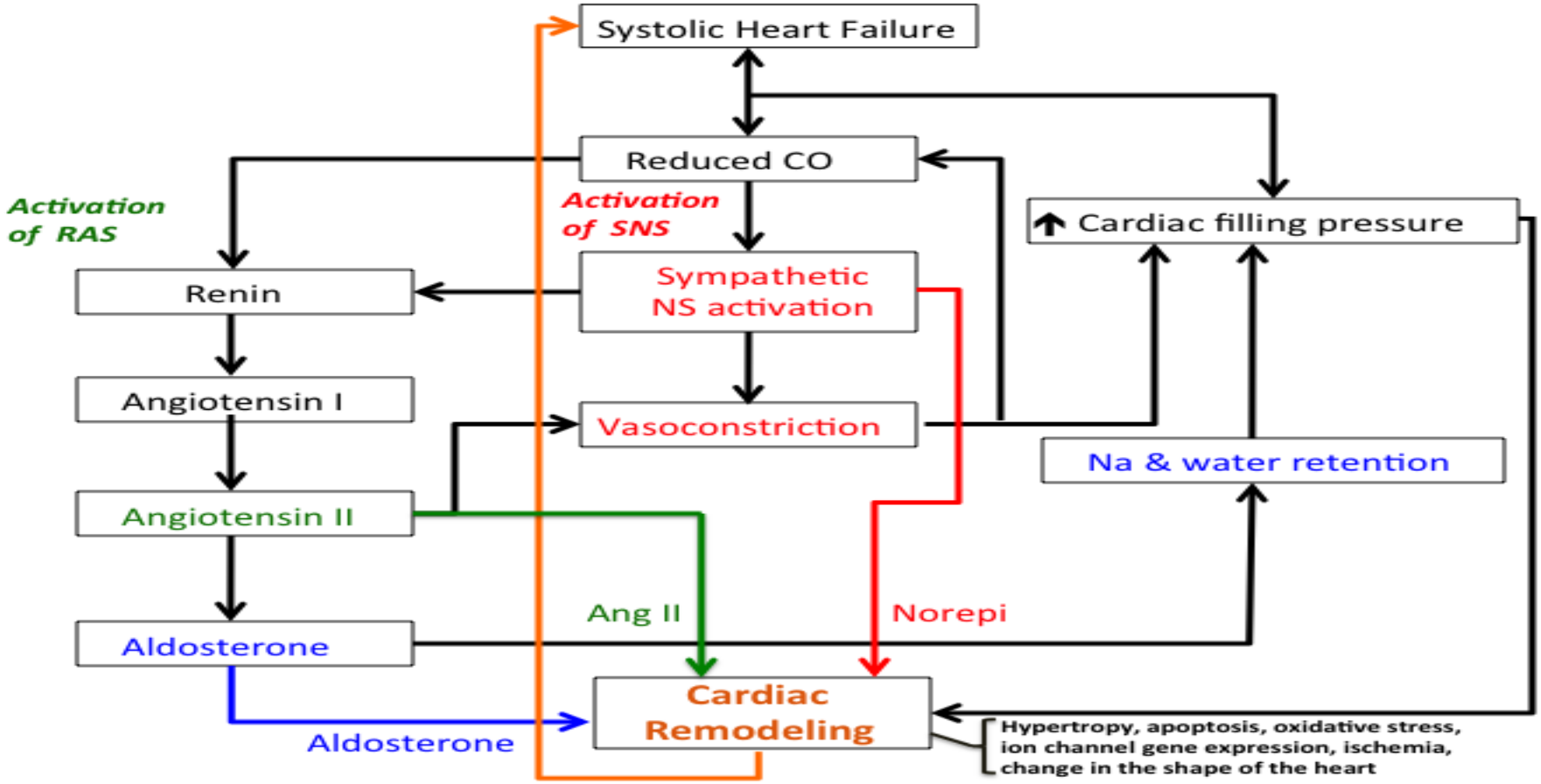
BETA-RECEPTOR BLOCKADE

Opie 2012



Rationale for BB therapy in HF

Pathophysiology



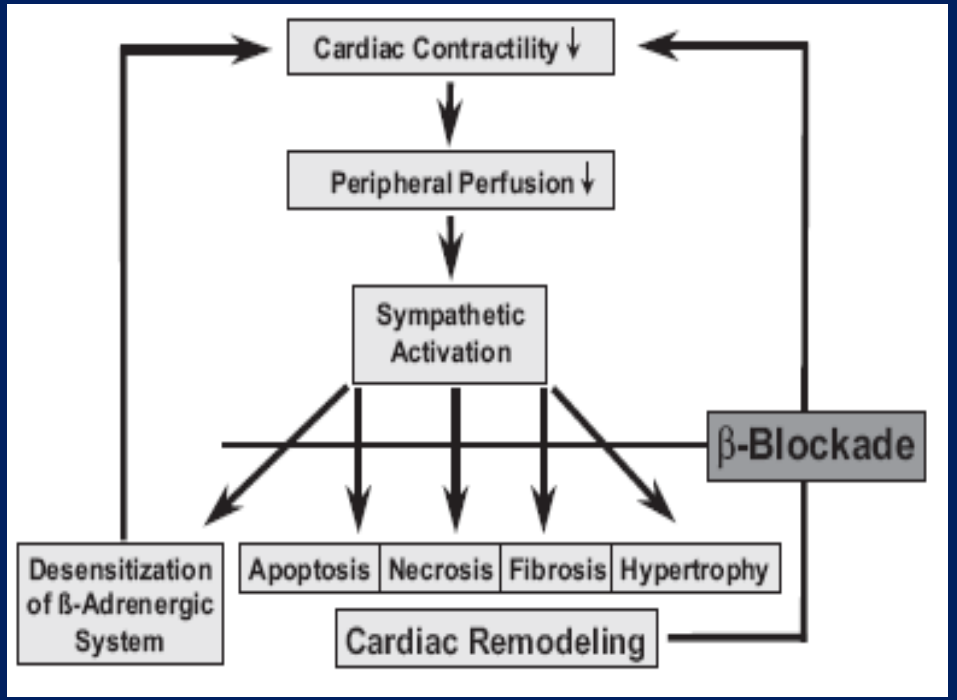
β-blockade in heart failure

- Upregulation of β-receptors and improved β adrenergic signaling
- ↑coronary blood flow and decreased myocardial oxygen demand
- Protection from catecholamine myocyte toxicity.
- Antiarrhythmic effect
- Inhibition of RAAS.
- Improved ventricular contractility
- Inhibition of norepinephrine-mediated muscular hypertrophy
- Prevention of norepinephrine-mediated apoptosis
- Decreased central sympathetic outflow
- Increased myocardial catecholamine stores

Adhikari CM. Nepalese Heart Journal 2013;10(1):38-45.

How well do β-blockers work in HF ?

- ± 34 % reduction in mortality
- Suggested mechanisms also include reduce remodeling
- β-Blockers may be beneficial through resensitization of the down-regulated receptor, improving myocardial contractility.
- Acts primarily by inhibiting the sympathetic nervous system.
- Increases beta receptor sensitivity (up regulation).
- Anti-arrhythmic properties.
- Anti-oxidant properties



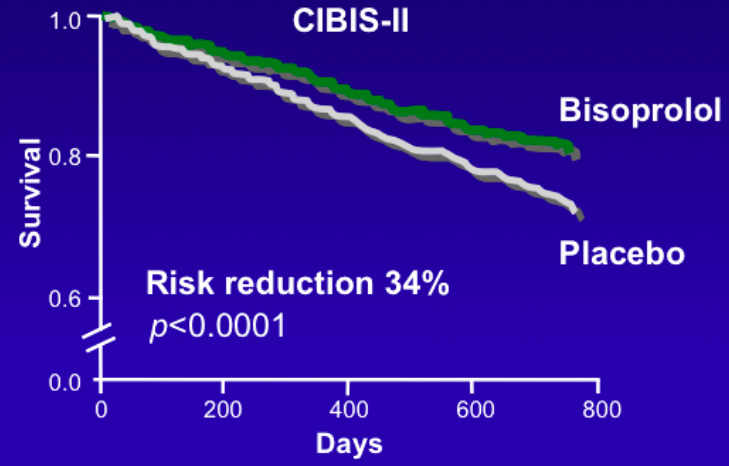
Kumar S, 2009. CHF – Le Jacq Comm, 2003

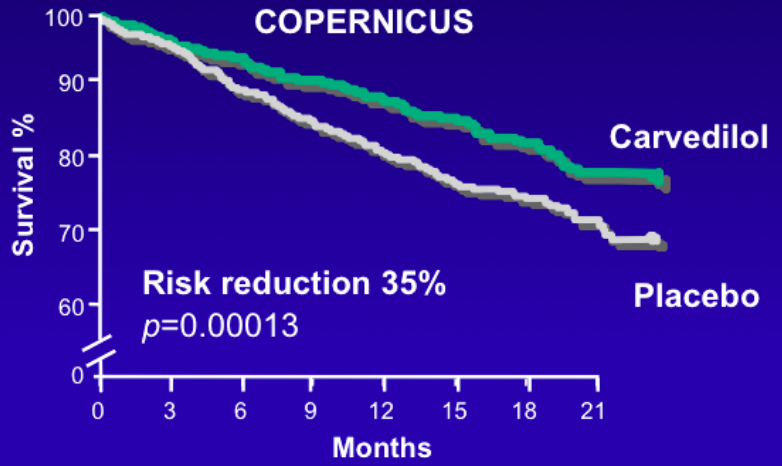
Trials with significant positive results

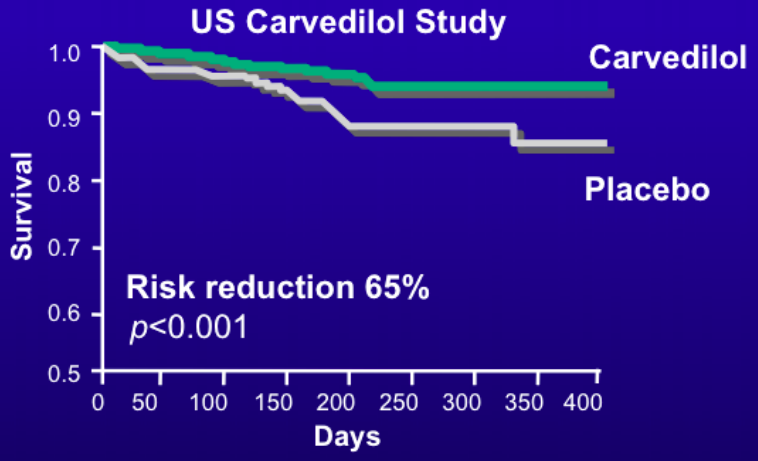
- CIBIS II - bisoprolol
- US Carvedilol - carvedilol
- COPERNICUS - carvedilol
- MERIT-HF - metoprolol
- CAPRICORN - carvedilol (*post-AMI*)
- COMET - carvedilol/metoprolol
- SENIORS - nebivolol

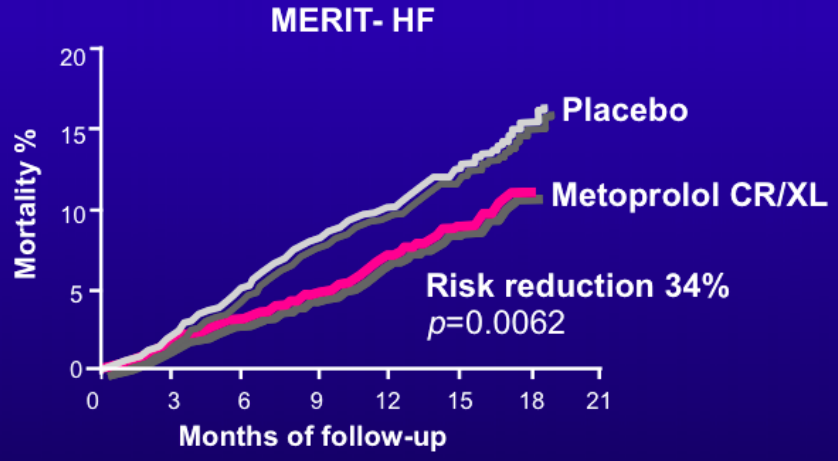
Flather MD, et al. Eur Heart J 2005; 26:215-25; Cibis II Investigators. Lancet 1999; 335:9-13; Packer N, et al. N Eng J Med 1996; 334:1349-55; Packer N, et al. N Eng J Med 2001; 344(22): 1651-8; MERIT-HF. Study group. Lancet 1999; 353:2001-7; Mc Murray J, et al. J Am Coll Cardiol 2005; 45(4):525-30; Poole-Wilson PA, et al. Lancet 2003; 362 (9377): 7-13.

Evidence On the Use of Beta Blockers in CHF









β-Blocker History

First Generation

Nonselective

Propranolol

Timolol

↓

Second Generation

Selective

Atenolol

Metoprolol

Bisoprolol

↓

Third Generation

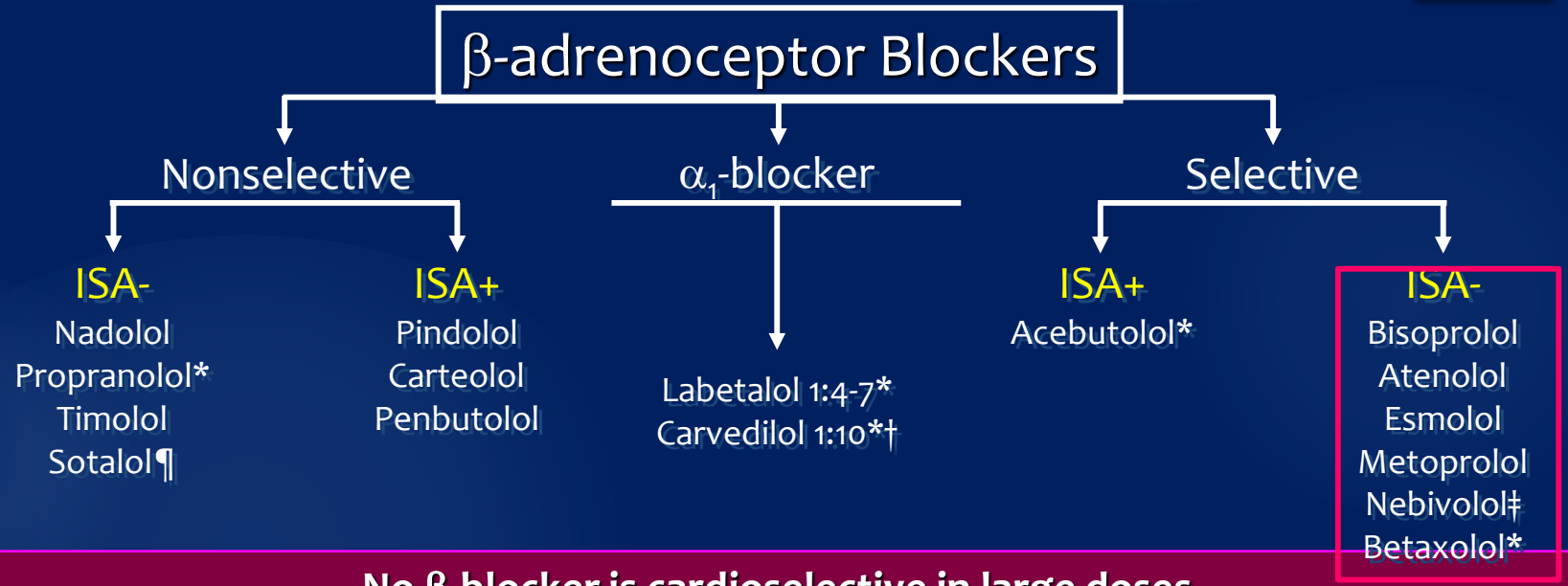
Vasodilatory

Labetalol

Carvedilol

Nebivolol

Characteristics



No β-blocker is cardioselective in large doses
β_2-blockade is needed for tremor and migraines
β_1-blockers are better for bronchospasm & insulin-requiring diabetes

* Membrane Stabilizing Activity
† Antioxidant
‡ Nitric oxide-mediated vasodilation
¶ Class III antiarrhythmic

Modified from Kaplan NM. *Clinical Hypertension* (8ed). 2002;262.

What do the guidelines said

European Heart Journal
doi:10.1093/eurheartj/ehw128

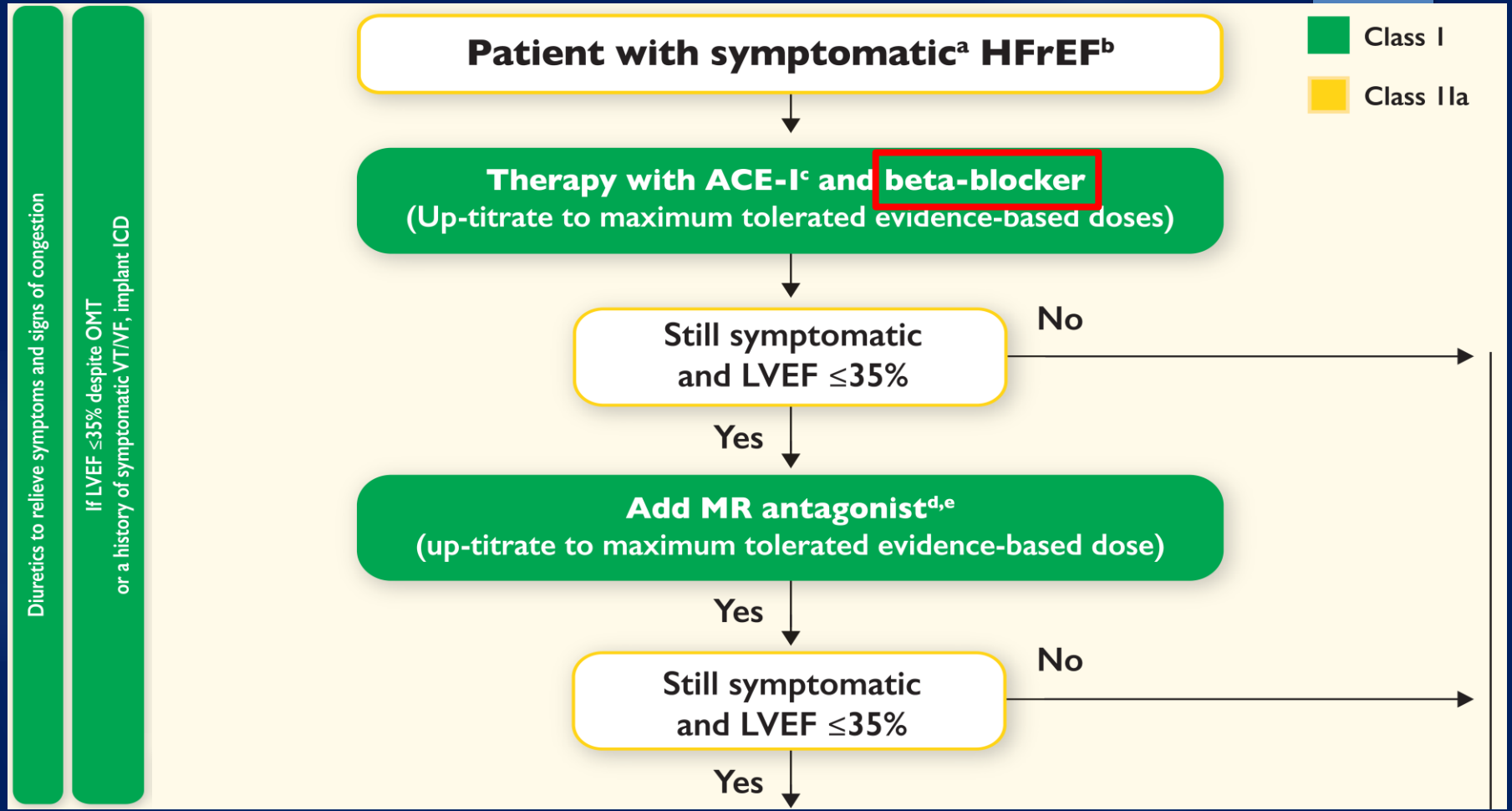
ESC GUIDELINES

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

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: Piotr Ponikowski* (Chairperson) (Poland), Adriaan A. Voors* (Co-Chairperson) (The Netherlands), Stefan D. Anker (Germany), Héctor Bueno (Spain), John G. F. Cleland (UK), Andrew J. S. Coats (UK), Volkmar Falk (Germany), José Ramón González-Juanatey (Spain), Veli-Pekka Harjola (Finland), Ewa A. Jankowska (Poland), Mariell Jessup (USA), Cecilia Linde (Sweden), Petros Nihoyannopoulos (UK), John T. Parissis (Greece), Burkert Pieske (Germany), Jillian P. Riley (UK), Giuseppe M. C. Rosano (UK/Italy), Luis M. Ruilope (Spain), Frank Ruschitzka (Switzerland), Frans H. Rutten (The Netherlands), Peter van der Meer (The Netherlands)



ESC guidelines on CHF and AHF 2016

Pharmacological treatments in symptomatic (NYHA fc II-IV) HFrEF

An ACE-I[d] is recommended, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
A beta-blocker is recommended, in addition an ACE-I[d], for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.	I	A
An MRA is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE-I[d] and a beta-blocker, to reduce the risk of HF hospitalization and death.	I	A

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

ESC guidelines on CHF and AHF 2016

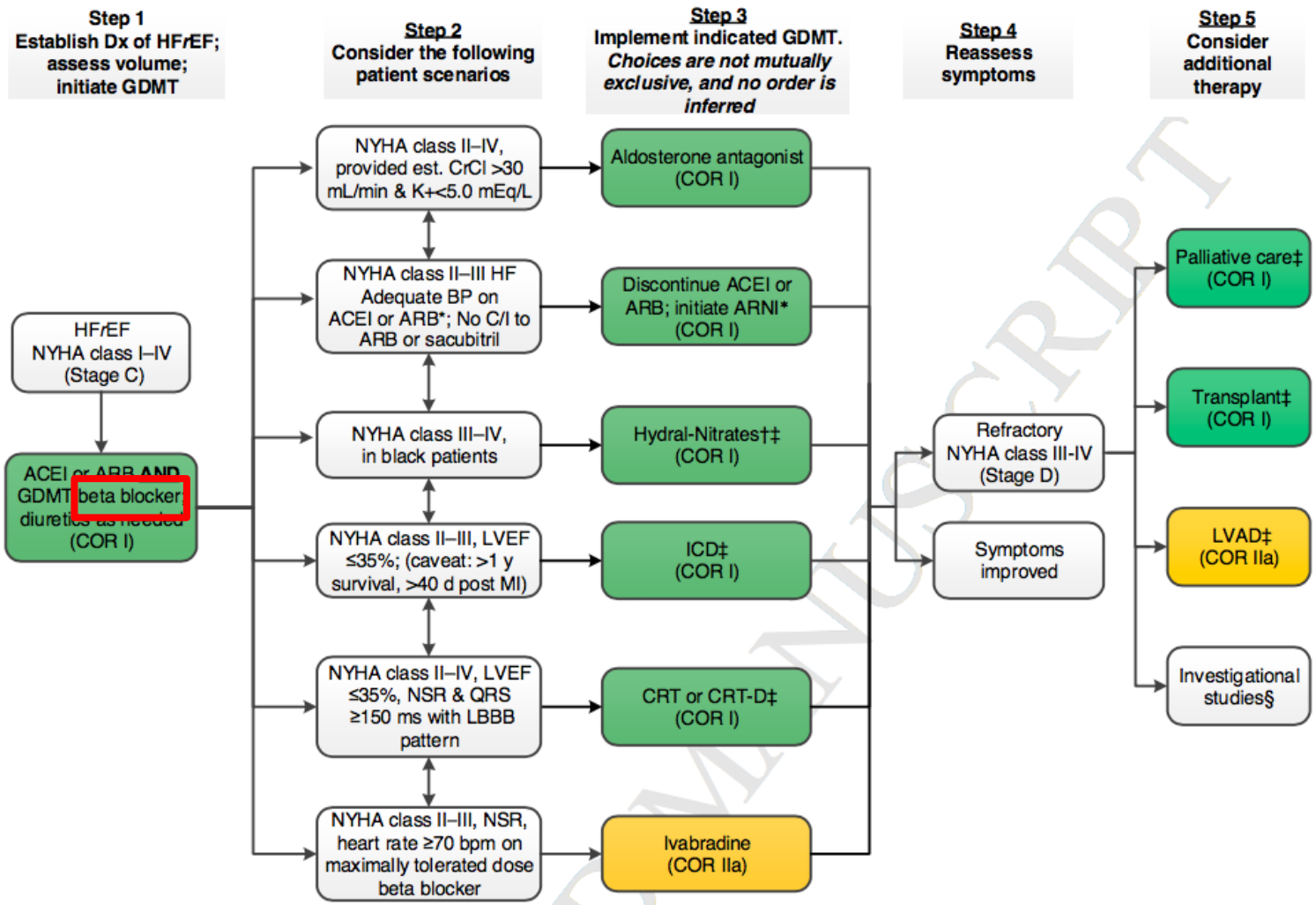
2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

Developed in Collaboration with the American Academy of Family Physicians, American College of Chest Physicians, and International Society for Heart and Lung Transplantation

WRITING GROUP MEMBERS*

Clyde W. Yancy, MD, MSc, MACC, FAHA, FHFSA, *Chair*
Mariell Jessup, MD, FACC, FAHA, *Vice Chair*
Biykem Bozkurt, MD, PhD, FACC, FAHA*†
Javed Butler, MD, MBA, MPH, FACC, FAHA*‡
Donald E. Casey, Jr, MD, MPH, MBA, FACC§
Monica M. Colvin, MD, FAHA‖
Mark H. Drazner, MD, MSc, FACC, FAHA, FHFSA‡
Gerasimos S. Filippatos, MD*
Gregg C. Fonarow, MD, FACC, FAHA, FHFSA*‡
Michael M. Givertz, MD, FACC, FHFSA*¶
Steven M. Hollenberg, MD, FACC#
JoAnn Lindenfeld, MD, FACC, FAHA, FHFSA*¶
Frederick A. Masoudi, MD, MSPH, FACC**
Patrick E. McBride, MD, MPH, FACC††
Pamela N. Peterson, MD, FACC, FAHA‡
Lynne Warner Stevenson, MD, FACC*‡
Cheryl Westlake, PhD, RN, ACNS-BC, FAHA, FHFSA¶


Step 1
Establish Dx of HFrEF; assess volume; initiate GDMT
Step 2
Consider the following patient scenarios
Step 3
Implement indicated GDMT. Choices are not mutually exclusive, and no order is inferred
Step 4
Reassess symptoms
Step 5
Consider additional therapy
HFrEF
NYHA class I–IV
(Stage C)
ACEI or ARB AND
GDMT beta blocker;
diuretics as needed
(COR I)
NYHA class II–IV, provided est. CrCl >30 mL/min & K+<5.0 mEq/L
NYHA class II–III HF Adequate BP on ACEI or ARB*; No C/I to ARB or sacubitril
NYHA class III–IV, in black patients
NYHA class II–III, LVEF ≤35%; (caveat: >1 y survival, >40 d post MI)
NYHA class II–IV, LVEF ≤35%, NSR & QRS ≥150 ms with LBBB pattern
NYHA class II–III, NSR, heart rate ≥70 bpm on maximally tolerated dose beta blocker
Aldosterone antagonist (COR I)
Discontinue ACEI or ARB; initiate ARNI* (COR I)
Hydral-Nitrates†‡ (COR I)
ICD‡ (COR I)
CRT or CRT-D‡ (COR I)
Ivabradine (COR IIa)
Refractory NYHA class III-IV (Stage D)
Symptoms improved
Palliative care‡ (COR I)
Transplant‡ (COR I)
LVAD‡ (COR IIa)
Investigational studies§

Drugs Commonly Used for HF*r*EF (Stage C HF)

Drug	Initial Daily Dose(s)	Maximum Doses(s)	Mean Doses Achieved in Clinical Trials
Beta Blockers			
Bisoprolol	1.25 mg once	10 mg once	8.6 mg/d (118)
Carvedilol	3.125 mg twice	50 mg twice	37 mg/d (446)
Carvedilol CR	10 mg once	80 mg once	---------
Metoprolol succinate extended release (metoprolol CR/XL)	12.5 to 25 mg once	200 mg once	159 mg/d (447)

Practical guidance for using BB in HFrEF

Who should receive BB?

- First-line treatment, along with an ACE-I, in patients with stabilized HF; start **as early as possible** in the course of disease.
- Patients with severe HF also benefit from BB but treatment should be started under the care of a specialist

ESC guidelines AHF and CHF web addenda. 2016

Contra-indications

- Second- or third-degree AV block (in the absence of a permanent pacemaker).
- Critical limb ischaemia.
- Asthma (relative contra-indication): if cardio-selective beta-blockers are indicated, asthma is not necessarily an *absolute* contra-indication
- Known allergic reaction/other adverse reaction (drug specific)
- COPD is not a contra-indication.

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How to use ?

- Start with a low dose in a stable condition
- Double the dose at not less than 2-week intervals (slower up-titration may be needed in some patients).
- Aim for target dose, or the highest tolerated dose (remember: some beta-blocker is better than no beta-blocker).
- Monitor heart rate, blood pressure, and clinical status (symptoms, signs–especially signs of congestion, body weight).

ESC guidelines AHF and CHF web addenda. 2016

Problem solving

Worsening symptoms or signs (e.g. increasing dyspnoea, fatigue, oedema, weight gain):

- If increasing congestion, increase dose of diuretic or halve dose of beta-blocker (if increasing diuretic dose does not work).
- If marked fatigue (or bradycardia), halve dose of beta blocker (rarely necessary); review patient in 1–2 weeks
- If serious deterioration, halve dose of beta-blocker or stop this treatment (rarely necessary)

Low heart rate:

- If <50 bpm and worsening symptoms, halve dose of beta-blocker, or, if severe deterioration, stop beta-blocker (rarely necessary).
- Review need for other heart rate-slowing drugs (e.g. digoxin, amiodarone, diltiazem, or verapamil).
- Arrange electrocardiogram to exclude heart block.

ESC guidelines AHF and CHF web addenda. 2016

Table 2. Recent HF Guidelines on Beta-Blockers in Acute Decompensation

	ESC (2012)[10]	ACCF/AHA (2013)[40]	NICE (2014)[34]
Continuation during AHF hospitalization	May be continued in many patients during an episode of decompensation, although dose reduction may be necessary	Continue in the absence of hemodynamic instability or contraindications	Continue unless patient has heart rate <50 beats/min, second- or third-degree atrioventricular block, or shock
Temporary discontinuation during AHF	Advised in patients with shock or severe hypoperfusion	Should be considered only in patients hospitalized after recent initiation or increase in β-blocker therapy or with marked volume overload or marginal/low cardiac output	No recommendation
Initiation after de novo AHF	Should be started as soon as possible before discharge	Start or restart during hospital admission	Start or restart during hospital admission
Timing of initiation/ restarting	After stabilization, blood pressure and heart rate permitting	After optimization of volume status and successful discontinuation of i.v. diuretics, vasodilators, and inotropic agents	Once patient condition has stabilized, eg, when i.v. diuretics are no longer needed
Cautious observation after initiation	The dose should be up-titrated as far as possible before discharge, and a plan made to complete dose up-titration after discharge	Should be initiated at a low dose and only in stable patients Caution should be used when initiating in patients who required inotropes during hospital course	Ensure that the patient's condition is stable for typically 48 h after starting or restarting and before discharge from hospital

Lee HY, Baek SH. Circ J 2016; 80: 565-571

Problem solving

Asymptomatic low blood pressure:

- Does not usually require any change in therapy.

Symptomatic hypotension:

- If dizziness, light headedness, or confusion and a low blood pressure, 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.

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Summary : tips for doctors

- Guidelines emphasized the importance of Beta Blocker on therapeutic regiment of CHF (Class IA)
- Do not with-hold from patients with comorbidities (COPD, DM, PAD)
- Avoid in total AV block, severe poorly controlled asthma, and critical limb ischaemia
- Use drug licensed for HF : bisoprolol, carvedilol, metoprolol, nebivolol
- Start with small dose, titrate slowly every 2 weeks
- Aim to achieve recommended target dose, but accept the maximum tolerated dose
- Check standing and sitting BP and heart rate, bradycardia in the absence of symptoms does not require dose reduction
- Try not to stop the β-blocker if the HF deteriorates, try to adjust other drugs to regain control of symptoms and fluid balance

Thank you