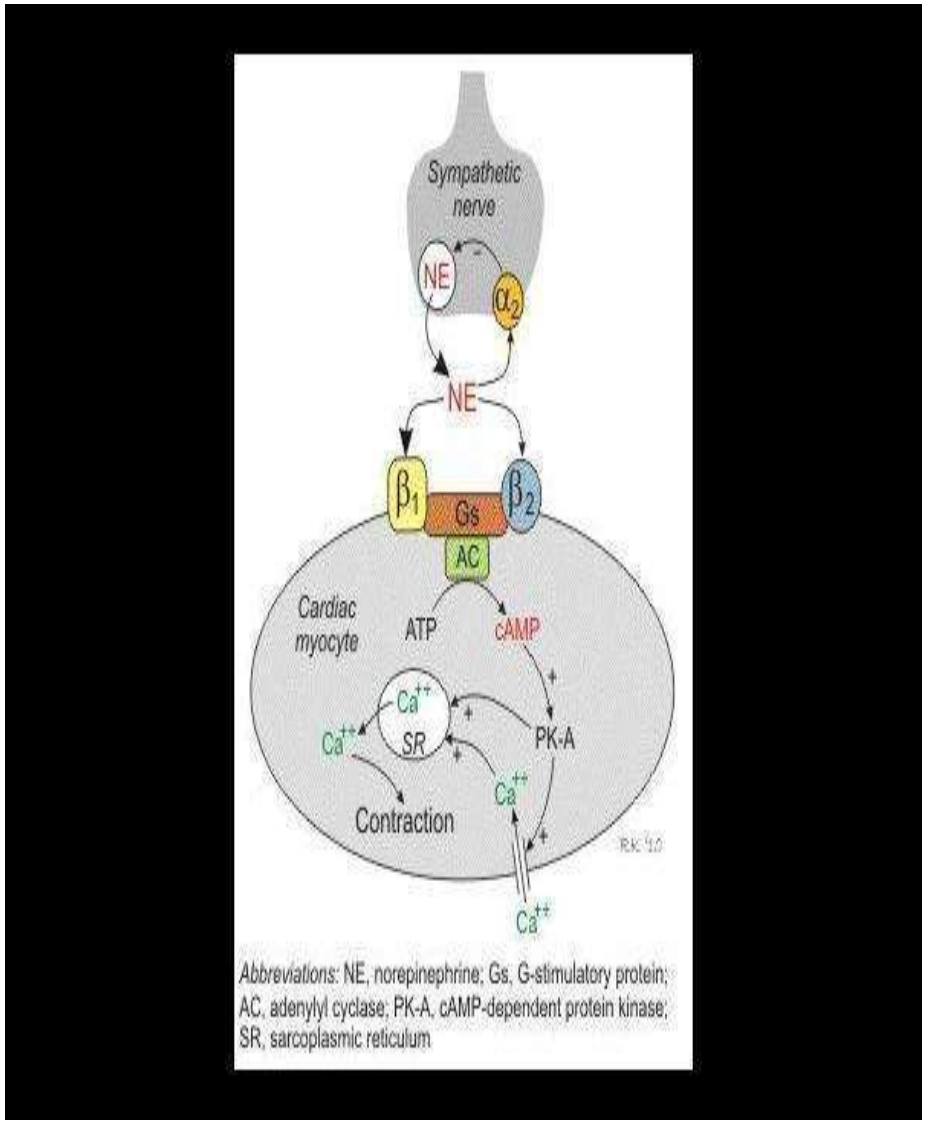
# Heart Failure Management :

## Which Betablocker, When to start and how to start

# Mode of Action

- Beta-receptors
- …are on the surface of cells innervated by the sympathetic nervous system
- …mediate certain physiological responses to adrenaline



# Mode of Action

β–1 receptors

Heart

- Increased chronotropy and inotropy
- Increased AV-node conduction velocity

Renal juxtaglomerular cells

- Increased renin release

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β–2 receptors

Bronchial smooth muscle

- Bronchodilation

Uterine muscle

- Uterine relaxation (tocolysis)

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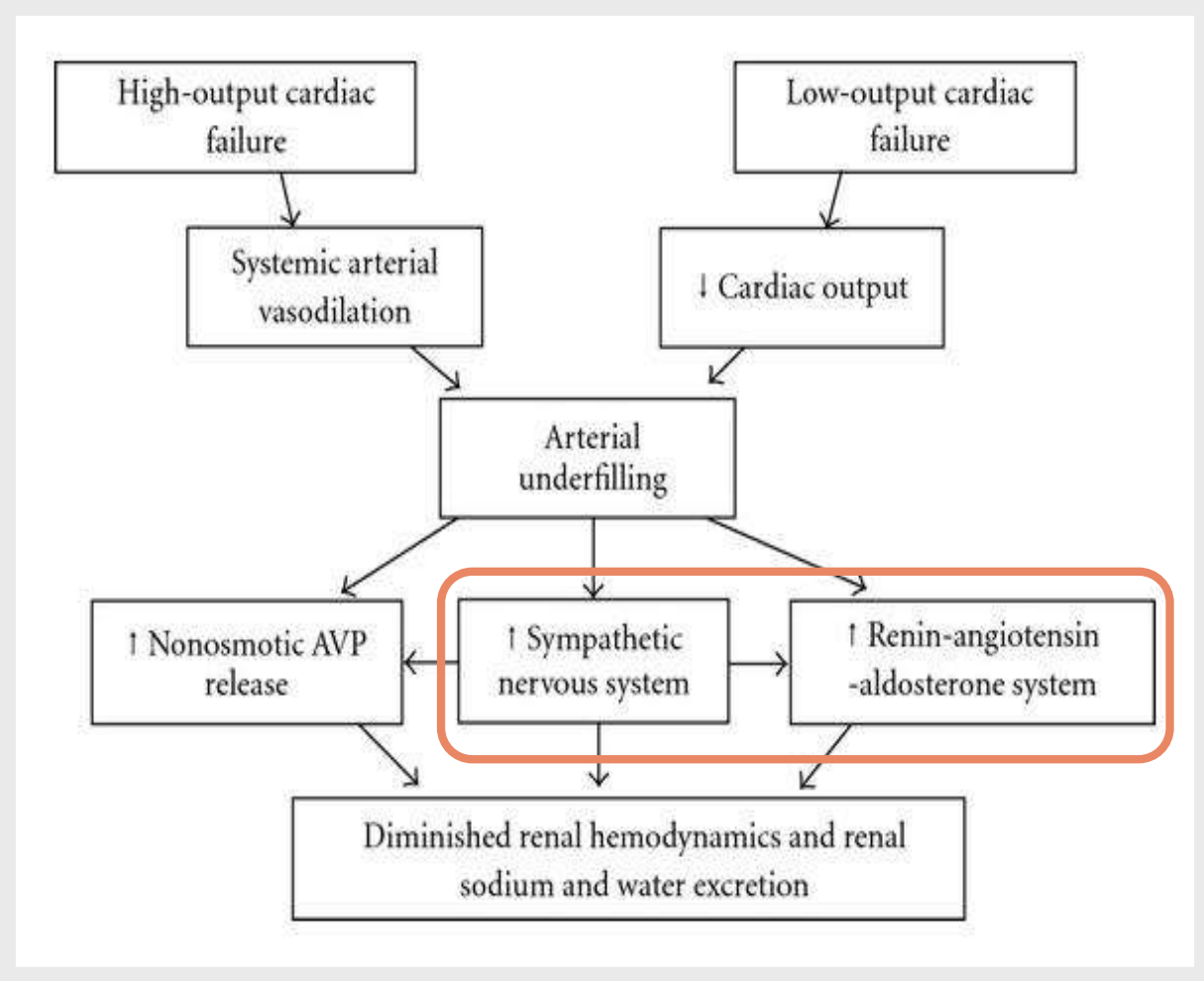
# Effects of β-blockers

| Tissue | Receptor | Effect |
|---|---|---|
| Heart | | |
| SA node | $\beta_1$, $\beta_2$ | Increase in heart rate |
| AV node | $\beta_1$, $\beta_2$ | Increase in conduction velocity |
| Atria | $\beta_1$, $\beta_2$ | Increase in contractility |
| Ventricles | $\beta_1$, $\beta_2$ | Increase in contractility, conduction velocity and automaticity of idioventricular pacemakers |
| Arteries | $\beta_2$ | Vasodilation |
| Veins | $\beta_2$ | Vasodilation |
| Skeletal muscle | $\beta_2$ | Vasodilation, increased contractility<br>Glycogenolysis, $K^+$ uptake |
| Liver | $\beta_2$ | Glycogenolysis and gluconeogenesis |
| Pancreas (β cells) | $\beta_2$ | Insulin and glucagon secretion |
| Fat cells | $\beta_1$ | Lipolysis |
| Bronchi | $\beta_2$ | Bronchodilation |
| Kidney | $\beta_1$ | Renin release |
| Gallbladder and ducts | $\beta_2$ | Relaxation |
| Urinary bladder detrusor | $\beta_2$ | Relaxation |
| Uterus | $\beta_2$ | Relaxation |
| Gastrointestinal | $\beta_2$ | Relaxation |
| Nerve terminals | $\beta_2$ | Promotes noradrenaline release |
| Parathyroid glands | $\beta_1$, $\beta_2$ | Parathormone secretion |
| Thyroid gland | $\beta_2$ | T4 → T3 conversion |

SA: Sino-Atrial; AV: Auriculo-Ventricular.

# Heart Failure

- Characterized by neurohormonal activation (RAA system and SNS)
- Reducing this activation with ACEi/ ARBs and Betablockers have been the mainstay of the management for so many years  GUIDELINES
- Recommended and licensed β-blockers for HF : bisoprolol, carvedilol, metoprolol and nebivolol



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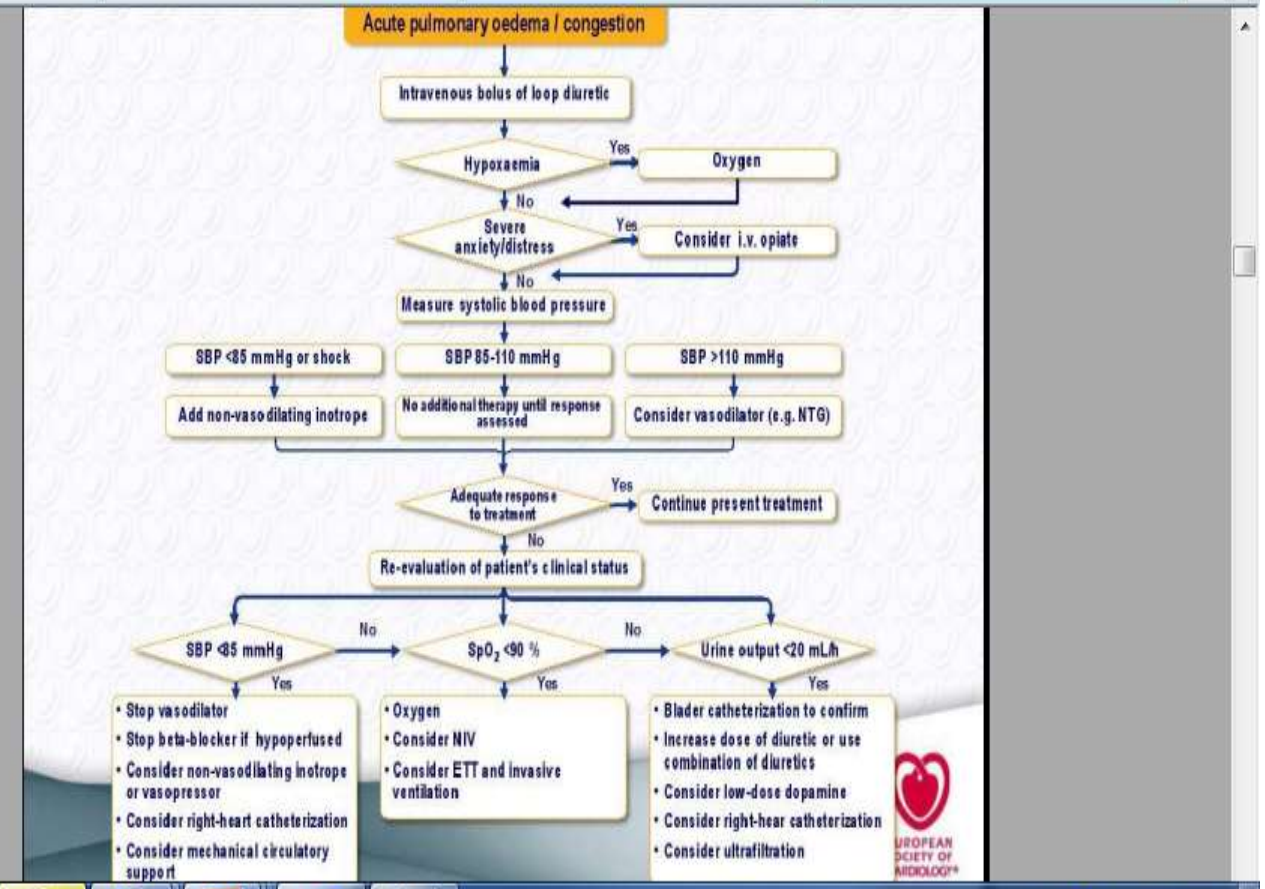


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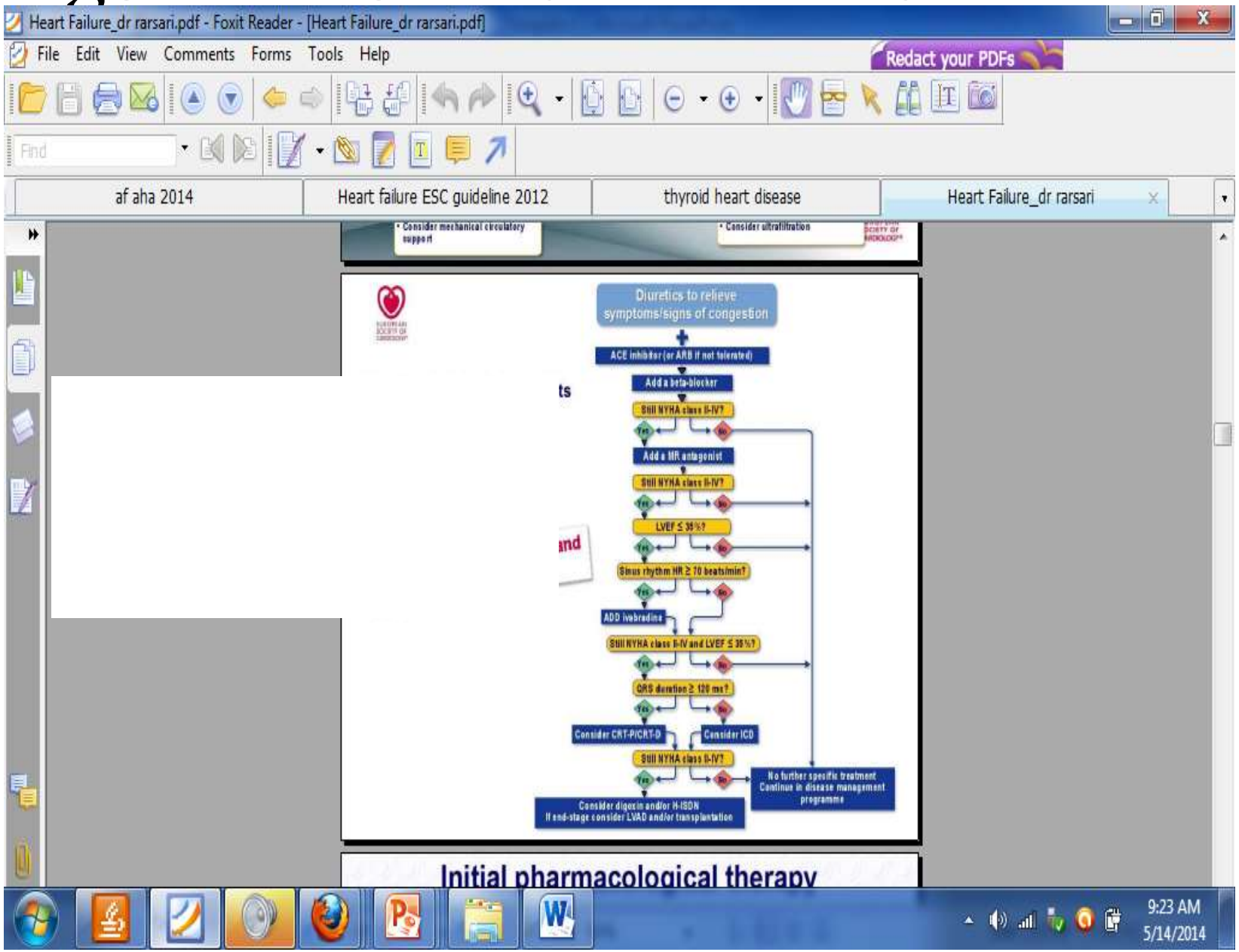
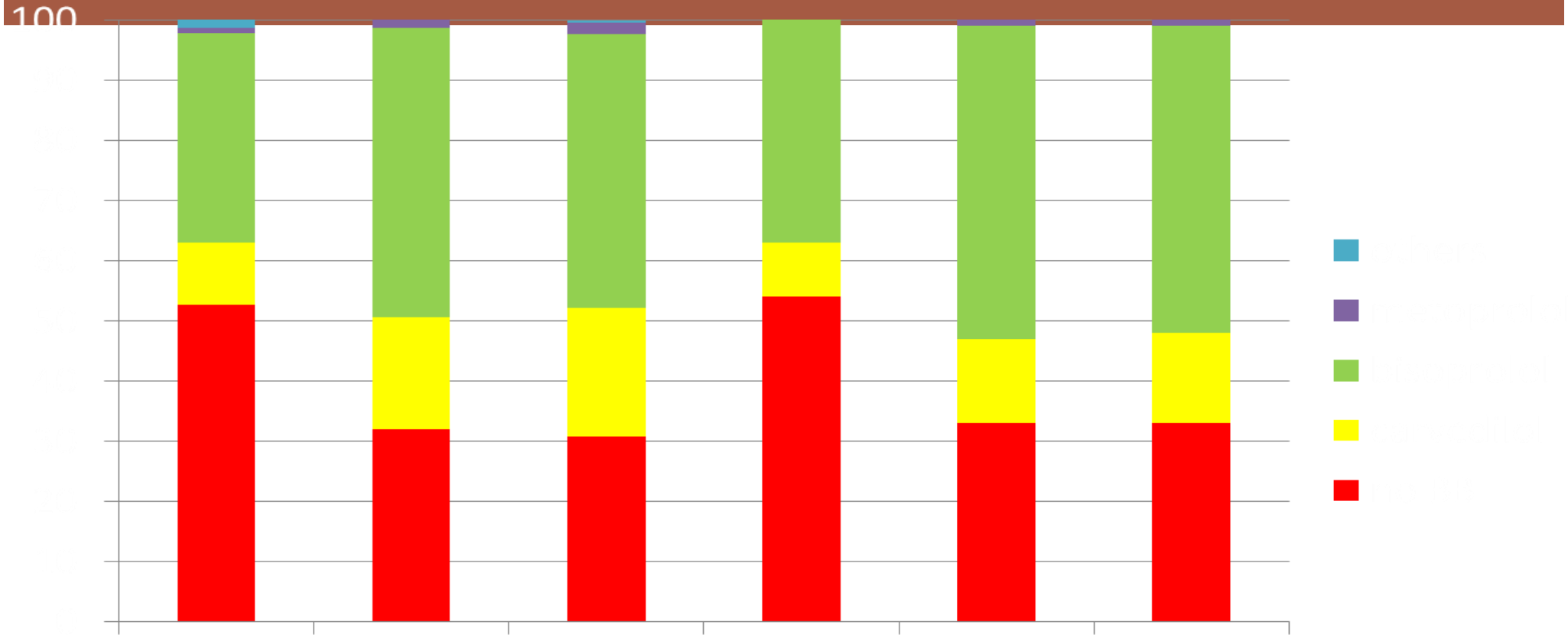
# Algorithm on Heart Failure

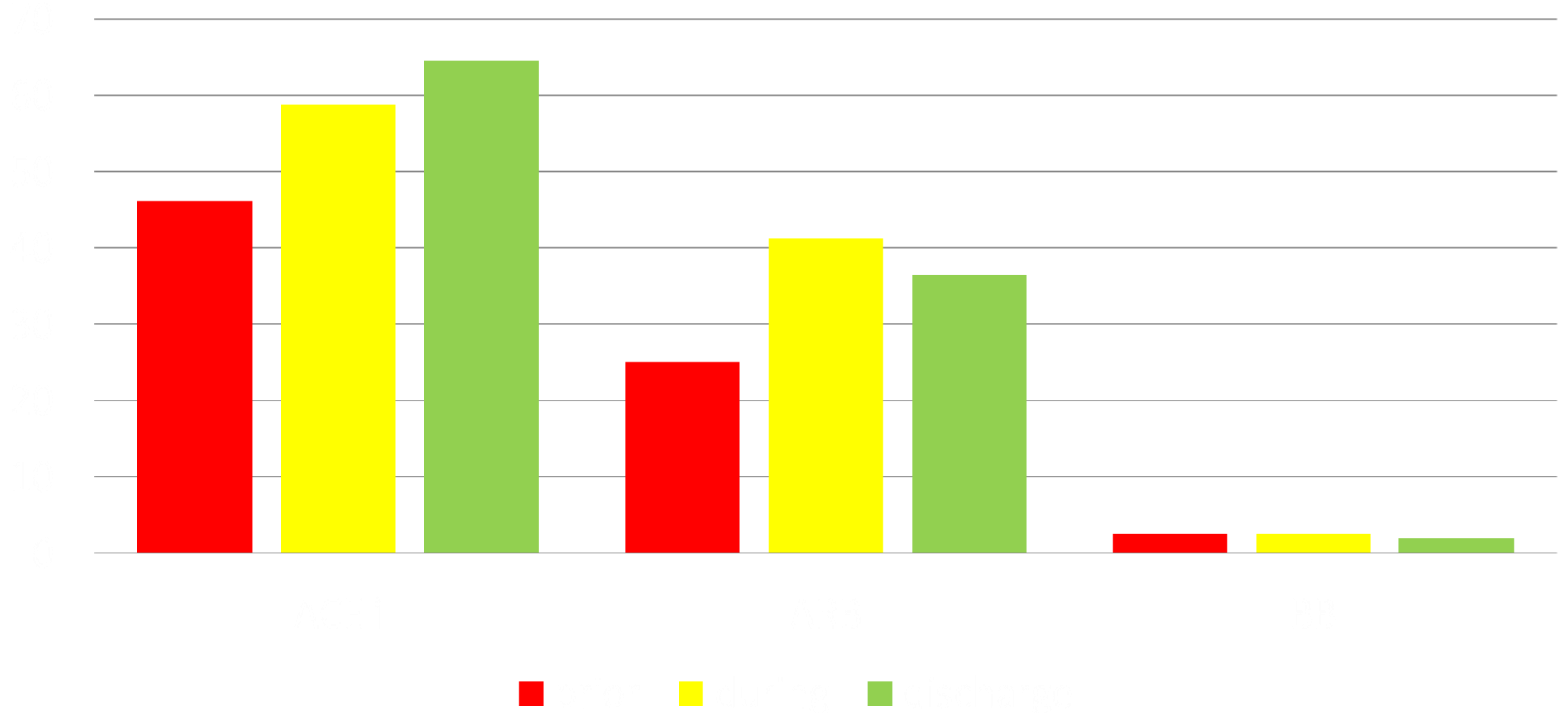


# Use in HF patients ?



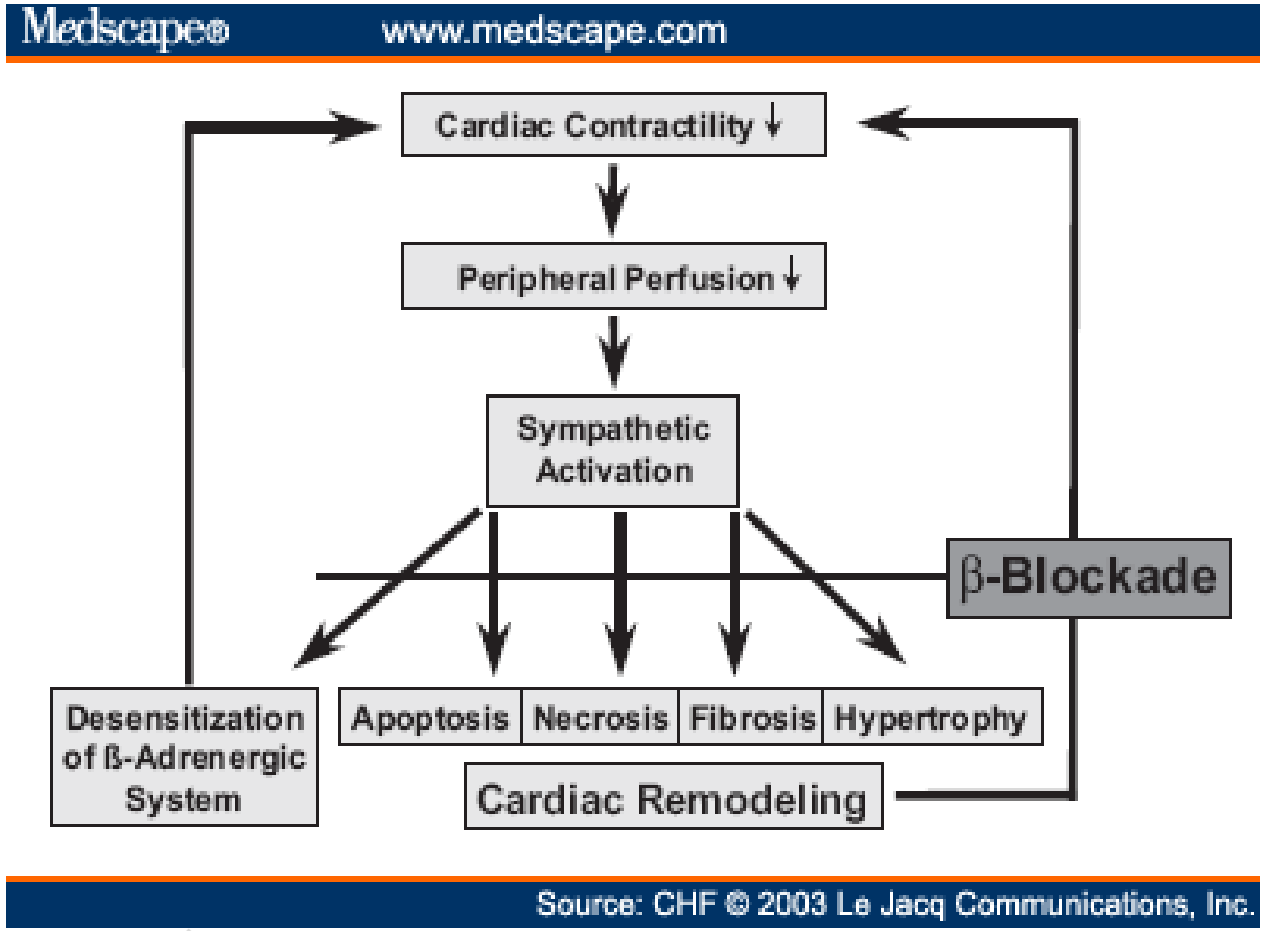
# Are we on target dose ?

## Heart Failure Registry 2011



# 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



# How safe are β-blockers ?

- Possible side effects :
  - Bronchospasm
  - Cold peripheries
  - Hypotension
  - Bradycardia
  - ADHF
  - Deterioration in blood glucose control

- Withhold :
  - Asthma or COPD
  - ~~Elderly~~
  - PAD patients
  - Severe LV dysfunction
  - DM

# Advanced /chronic heart failure with decompensation

- In those with EF < 30 % □ biventricular HF
- In patients who develop acutely decompensated HF while on chronic beta-blocker therapy, the dose of these agents may be reduced, or they may be temporarily withdrawn, but treatment should be restarted as soon as clinical conditions stabilize*
- Continuation of beta-blocker treatment during an episode of decompensation has been shown in an RCT to be safe **although** dose reduction may be necessary**
- Temporary discontinuation is advised in shocked or severely hypoperfused patients**

# Expert consensus document on β-adrenergic receptor blockers

## The Task Force on Beta-Blockers of the European Society of Cardiology

**Table 8** Use of β-blockers in chronic heart failure: guidelines

| Setting/indication | Class | Level |
|---|---|---|
| All stable patients, with symptomatic heart failure and reduced LVEF, functional class II–IV (to prolong survival) | I | A |
| LVSD without symptoms after AMI | I | A |
| LVSD without symptoms, no previous MI | I | B |
| Chronic HF with preserved systolic function (to reduce heart rate) | IIa | C |
| Acute, compensated heart failure after AMI | IIa | B |
| Patient stable after acutely decompensated chronic heart failure | I | A |

AMI: Acute Myocardial Infarction; LVEF: Left Ventricular Ejection Fraction; LVSD: Left Ventricular Systolic Dysfunction.

# Elderly

- Under presented in many clinical trials
- Deedwania et al (2004) : subgroup analysis of 1982 patients over 65 years  reduction of one-year-all cause mortality  comparable to those in younger patients
- Flather et al (2005) : an RCT of 2128 patients over 70 years  reduction in composite endpoints

**OLDER PATIENTS WITH HEART FAILURE WITH IMPAIRED SYSTOLIC FUNCTION HAVE SIMILAR OUTCOMES WITH β-BLOCKERS AS YOUNGER PATIENTS**

# Asthma and COPD

- Considered as the major contraindication
- Salpeter SR et al (2002) : … at least, in the short term, no deterioration of lung fuction occurs when cardioselective β-blockers are used in mild to moderate asthma
- Salpeter SR et al (2005) : cardioselective β-blockers given to patients with COPD, including those with reversible and irreversible airways disease, found no change in forced expiratory volume, breathlessness or effect of bronchodilators
- Krum H et al (2000) : tolerability of carvedilol in heart failure was similar in patients with and without COPD

# Peripheral vascular disease

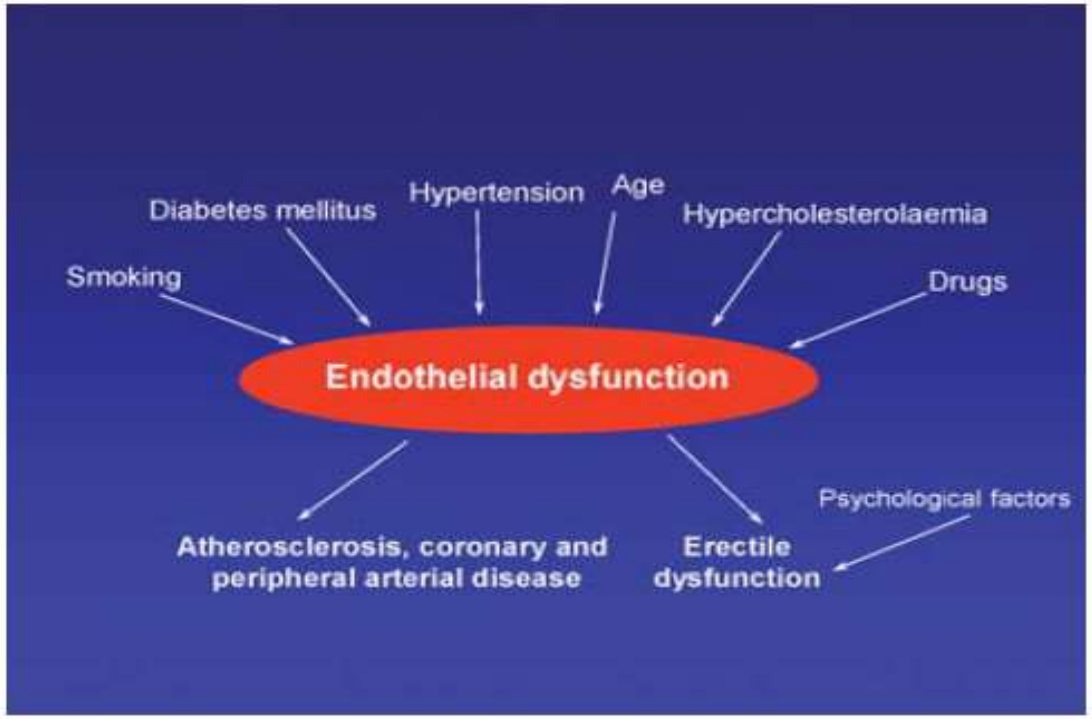
- Theory : β-blocker  decrease in CO and BP, impaired muscle vasodilatation  worsening symptoms of PAD
- Radack et al (1991) : meta analysis 11 RCTs  β-blockers in stable mild to moderate claudication showed no significant effect on pain-free walking distance
- Krum et al (2000) : good tolerability of β-blockers in patients with PAD and HF
- In critical limb ischaemia  contraindication

# Diabetes mellitus

- Theory : β-blockers □ inhibit glycogenolysis □ mask the symptoms of hypoglycemia
- No randomize trials focusing on patients DM and HF
- Erdmann et al (2001)
- Shibata et al (2001)
- Poole-Wilson et al (2003)

similar tolerability and benefits

# Erectile Dysfunction




| Drug class | Age-adjusted relative risk of ED |
|---|---|
| Angiotensin II antagonists | 2.4 |
| Non-selective beta-blockers | 2.0 |
| Calcium antagonists | 1.8 |
| Diuretics | 1.4 |
| ACE-inhibitors | 1.2 |
| Selective beta-blockers | 1.0 |
| Statins | 0.9 |
| Organic nitrates | 0.8 |

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      - Fourth level

# How do β-blockers compare with other drugs ?

- ACEi and ARBs  not an alternative :
  - additive effect on mortality and morbidity
  - B-blockers is an add-on therapy
- Spironolactone and Ivabradine  as add-on therapies

# Practical Guidance in HF

Betablockers : Bisoprolol, carvedilol, metoprolol, nebivolol

Who should receive β-blockers ?

- All patients with chronic, stable HF
- Without contraindication (symptomatic hypotension, severe asthma)

When to start ?

- No physical evidence of fluid retention
- Start ACEi first (if not contraindicated)
- In stable hospitalized patients (if possible)
- NYHA class IV or severe CHF patients should be referred for specialist advice
- Review treatment, avoid verapamil, diltiazem, antiarrhythmics, NSAID

# Practical Guidance in HF

## Monitor

- Evidence of HF, fluid retention, hypotension and bradycardia
- Instruct patients to weigh themselves daily

## Dose

- Start low – go slow
- Aim for target dose, if not tolerated  the highest dose tolerated

| | Start (mg) | Target (mg) |
|---|---|---|
| **Bisoprolol** | **1.25 once daily** | **10 once daily** |
| **Carvedilol** | **3.125 twice daily** | **25 – 5- twice daily** |

# Problem solving

- Reduce/ discontinue only if other actions were ineffective to control symptoms
- Always consider the re-introduction and/or uptitration when stable
- Seek specialist advice if in doubt

**Symptomatic hypotension**

- Reconsider needs of other hypotensive agents : nitrates, CCB or other vasodilators
- If no signs/ symptoms of congestion, consider reducing diuretics dose

**Severe decompensated HF, pulmonary edema, shock**

- Admit patient to the hospital
- Discontinue, if inotropic is needed

# Problem solving

## Worsening symptoms/ signs of HF

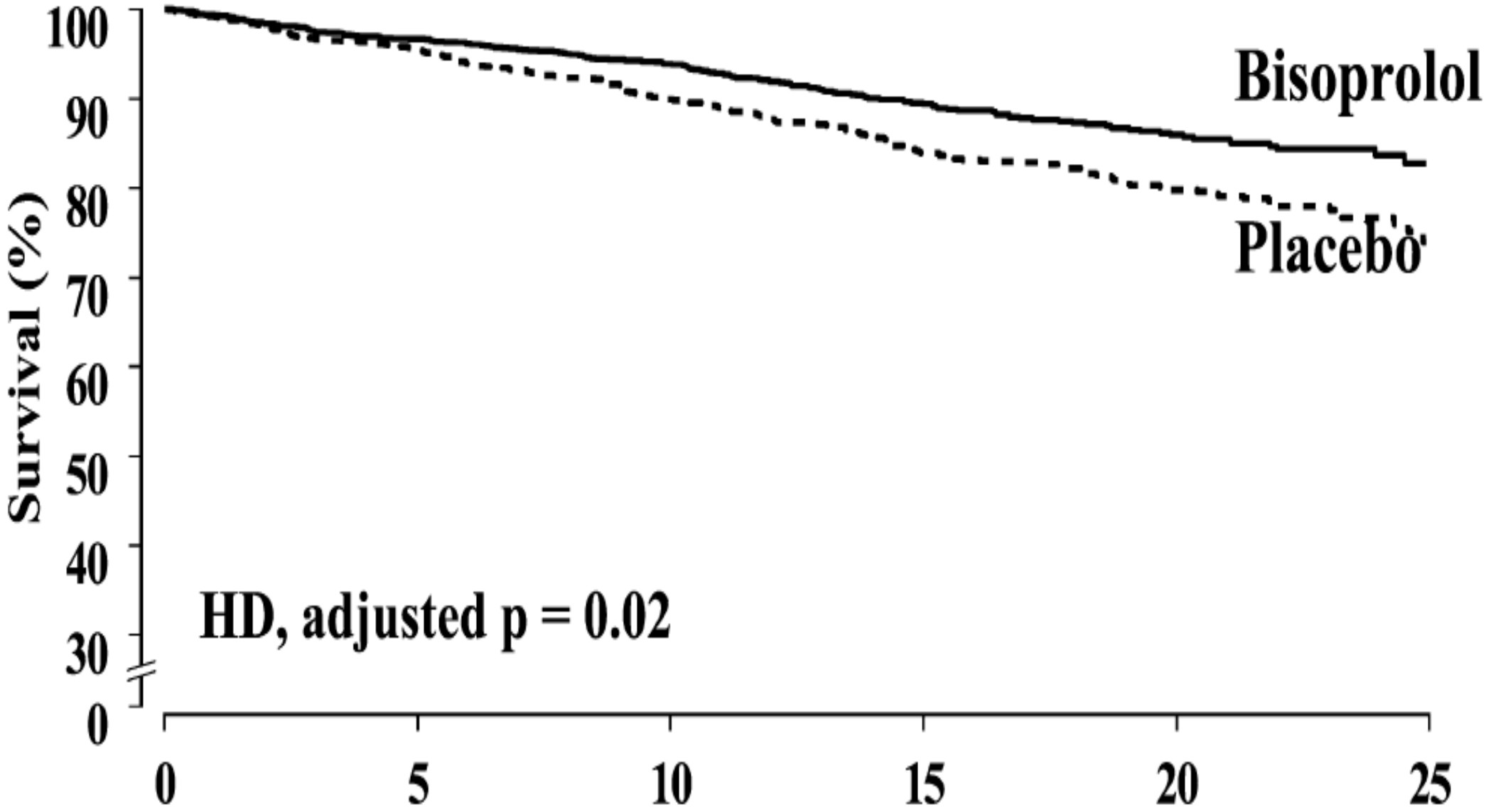
- No need to discontinue  double dose of diuretic and or ACEi
- Temporarily reduce the dose if increasing diuretics dose does not work
- If serious deterioration  half dose
- Discontinuation (rarely necessary)
- Review patients in 1 – 2 weeks, if not improved seek specialist advice

## Bradycardia (symptomatic)

- ECG to exclude heart block
- Consider pacemaker support if severe bradycardia, AV block or SSS early after starting
- Review : need, reduction or discontinuing other heart rate slowing drugs e.g digoxin, amiodarone, diltiazem
- Reduce dose ( discontinuation rarely necessary)

# Conclusion ~ Tips for doctors

- Always consider adding β-blocker to standard treatment for HF with impaired systolic function, regardless of severity
- 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
- In patients who also have asthma or COPD, monitor symptoms and peak expiratory flow rates closely


Survival (%)
100
90
80
70
60
50
40
30
0
Bisoprolol
Placebo
HD, adjusted p = 0.02
0
5
10
15
20
25

# Thank you