

## Beta Blockers in HF

- Corner stone of Rx for chronic HFREF, along with ACEI or ARB, aldosterone blocker and CRT/D.

### Pathophysiology

- Chronic elevation of catecholamine results in
  - ↑ ventricular contraction, ↑ vascular resistance, ↑ HR
  - ↑ myocardial O<sub>2</sub> demand
  - ↑ myocardial apoptosis, fibrosis, ischemia, ↑ oxidative stress, ↑ cytokines (eg. TNF-α, IL-1 β, IL-6)
  - ↓ β-adrenergic receptor density
- Failing heart is less response to sympathetic activation and causing adverse remodeling, dilate and less contractile heart

### RCT of beta blocker in chronic HFREF (JAMA 2002;287:883)

Study	Medication N	Inclusion (EF, NYHA)	Background Rx	Dose (starting, target, mean)	All-cause death F/U time	Note
MERIT-HF Lancet 1999	Metoprolol CR/XL N=3991	≤40% II-IV	90% diuretics 90% ACEI 63% digoxin	12.5 daily 200 daily 160 daily	7.3 vs 10.8 (RRR = 35%) 1 yr	↓ SCD ↓ pump failure
CIBIS II Lancet 1999	Bisoprolol N=2446	≤35% III-IV	99% diuretics 96% ACEI 50% digoxin	1.25 daily 10 daily 6.5 daily	12% vs 17% (RRR = 34%) 1.3 yr	↓ SCD ↓ HF hosp
US carvedilol NEJM 1996	Carvedilol N=1094	≤35% II-IV	95% diuretics 90% ACEI 90% digoxin	12.5 bid 25-50 bid 45mg/d	3% vs 8% (RRR = 65%) 6 mo	↓ SCD ↓ HF hosp Unusual starting dose
COPERNICUS Circ 2002	Carvedilol N=2289	≤ 25% IIIb-IV	95% diuretics 97% ACEI 66% digoxin 20% spironolactone	3.125 bid 25 bid 37 mg/d	11% vs 19% (RRR = 35%) 10 mo	pt with severe HF

- Note:
- All studies include both ischemic and non-ischemic causes of HF.
  - Each of these studies is stopped early because of proven benefit.
  - Other notable RCTs of BB in HF: MDC (1993), CIBIS I (1994), BEST (2001), SENIORS (2005)

### Benefit of Beta blocker in chronic HFREF

- ↑ Ventricular function (CO, EF) → ↓ Mortality, ↓ HF hospitality, ↓ SCD, ↑ exercise capacity
- Overall ~ 30% RRR in mortality, ~ 40% RRR in hospitalization
- NNT =26 to avoid 1 death and 1 hospitalization

### Contraindication (JAMA2002;288:351-57)

- Evidence of fluid retention
- Bradycardia (HR < 55-60), AV block (2<sup>nd</sup>, 3<sup>rd</sup> degree)
- Ongoing hypotension with hypoperfusion
- Asthma/reactive airways (only active wheezing)
- PAD with resting limb ischemia
- S/E: depression (?), fatigue (1.8%), erectile dysfunction (0.5%), metabolic (Facilitation of hypoglycemia, weight gain, hyper K, lipid (10% ↓HDL, 30% ↑TG))

### Using Beta blocker for chronic HFREF

- Use one of the BBs proven to reduce mortality: Bisoprolol, carvedilol and metoprolol succinate. Nebivolol is recommended in ESC but not ACC. Lower benefit? (SENIOR lancet 2005).
  - No head to head RCT comparing between guideline proven BBs.
  - Carvedilol decreased CV death comparing to metoprolol tartate. (COMET Lancet2003)

- Start only when patient is euvolemic.
- Since all RCTs of BB in HF were in patients with ACEI, consider started ACEI before or at the same time as beta blockers.
  - BB may be started prior to ACEI without significant different. (CIBIS III Circ2005)
- Start low / Go slow: Small initial dose then up titrating q 1-4 weeks.
- Up titrate to a highest tolerable dose. Higher dose, higher benefits.
  - Benefit is highly dependent on degree of beta-blockage (HR reduction, HR achieve) (Circ1996;94:2807, JACC2002;40:491).
- Inpatient with acute HF who is on stable chronic dose of BB, do not stop BB. May decrease to half dose or stop in patient with shock or low perfusion. (JACC 2008;52:190).

### Beta blockers in a specific population with HF

- Same benefit in ischemic vs nonischemic, women vs men, black, DM, elderly, CKD, NYHA I-IV.
- HF c AF: May not ↓ mortality or hospitalization (meta-analysis Lancet. 2014)
- HFpEF: Limited evidence but may improve outcome e.g. nebivolol (meta-analysis, SENIOR).
- Pre-ChemoRx: Carvedilol plus enalapril prophylaxis before chemoRx (OVERCOME JACC 2013).
- May consider discontinue in patient with palliative care.

### Beta blocker property (Adapt from Foye's Principles of Med Chem)

	Drug	β-1 selective	α block	Lipophilicity	Elimination	Note
<b>1st gen BB Non-selective</b>	Propranolol	no	no	high	L	MSA
	Nadolol *	no	no	low	K	Long acting
	Sotalol *	no	no	mod	L > K	Class III antiarrhythmia
	Timolol	no	no	mod	L > K	glaucoma
	Pindolol	no	no	mod	L > K	ISA, MSA
<b>2nd gen BB β1-selective</b>	Atenolol	yes	no	low	K	
	Bisoprolol	yes	no	mod	L & K	
	Metoprolol	yes	no	mod	L	
	Esmolol	yes	no	low	K	IV ultrashort acting
	Acebutolol *	yes	no	low	L > K	ISA, MSA
<b>3rd gen BB Vasodilation property</b>	Carvedilol	no	yes	high	L	metabolic effect, antioxidant, MSA
	Nebivolol	yes	no	high	L	Vasodilator via B3 agonist (NO release)
	Labetalol	no	yes	mod	L	ISA

**Note:** \* not available in Thailand. ISA: intrinsic sympathomimetic activity; MSA: membrane stabilizing activity; L: liver; K: kidney.

#### • Adrenergic receptor agonist

	Cardiovascular	Others
β1	♥ Chronotropic (↑ contractility) ♥ Inotropic (↑ HR)	
β2	Vasodilatation	Bronchodilatation, ↑ glucose, Smooth muscle relaxation
α1	Vasoconstriction	Dilate pupil (mydriasis), erects hair, GI tract contraction, bladder contraction
α2	Vasoconstriction	Post synaptic adrenoreceptors. platelet aggregation

- Other indications of BB may include AMI, CAD, anti-angina, HCM, VT, AFib/Aflutter (rate control), LQTS, CPVT, HTN, aortic dissection, cirrhosis, hyperthyroid, pheochromocytoma, migraine, anxiety, alcohol withdraw, glaucoma, etc.