Key Pharmacological Aspects & Pleiotropic Effects of Anti-hypertensive

β-blockers

Asst. Prof. Surakit Nathisuwan, PharmD, BCPS
Clinical Pharmacy Division, Department of Pharmacy
Faculty of Pharmacy, Mahidol University

Overview

- Introduction
- Role of sympathetic nervous system in CVD pathogenesis
- Review on β-adrenergic blockers
  - Clinical pharmacology
  - Clinical use
  - Recent controversy
- Summary

Role of the SNS in Heart Failure

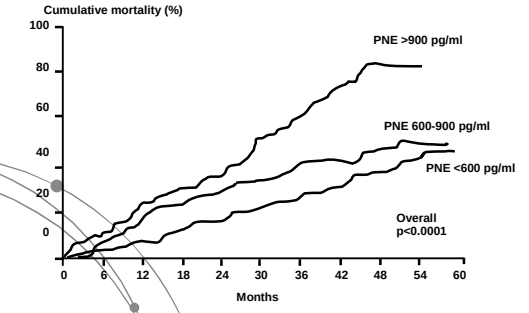
Norepinephrine

α-adrenoreceptor | ß-adrenoreceptor

Myocardial remodelling
Myocyte hypertrophy
Abnormal contractile function
Myocyte apoptosis

Myocardial failure

Relationship between Plasma Norepinephrine and Mortality



(Francis et al from V-HeFT II Circulation 1993; 87: V140-48)

Evolution of β-blockers*

1st Generation	2nd Generation
Nonselective	*ß-1 Selective*
Propranolol	Metoprolol
Pindolol	Bisoprolol
Timolol	Atenolol

3rd Generation

Vasodilatory effects
Carvedilol
Nebivolol

* only agents that are available in Thailand

Consideration for β-blockers Therapy

Receptor selectivity
Intrinsic sympathomimetic activity
Lipo/hydrophillicity

P'kinetics
Hemodynamic effects
Vasodilatory properties

Which One?

ß-blockers

Side Effects | Metabolic Profile | Outcomes Trials

Characteristics of β-blockers

β-adrenoceptor Blockers

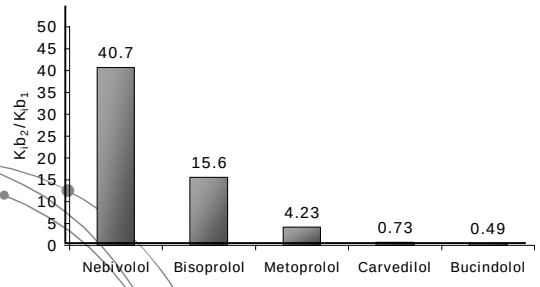
Nonselective			α_1-blocker	Selective	
ISA-	ISA+			ISA+	ISA-
Nadolol	Pindolol		Labetalol 1:4-7*	Acebutolol*	Atenolol
Propranolol*	Carteolol		Carvedilol 1:10*†		Esmolol
Timolol	Penbutolol				Metoprolol
Sotalol¶					Nebivolol‡
					Bisoprolol
					Betaxolol*

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

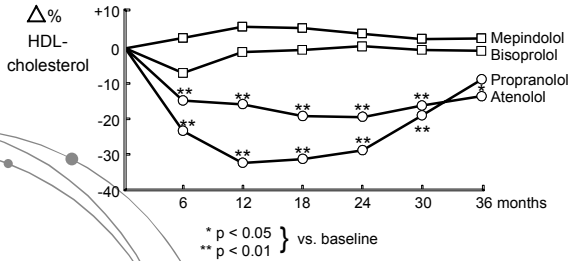
Modified from Kaplan NM. *Clinical Hypertension* (8ed). 2002;262.

β_1-Selectivity of Various β-blockers



Brixius K, et al. *Br J Pharmacol* 2001;133:1330-1338.

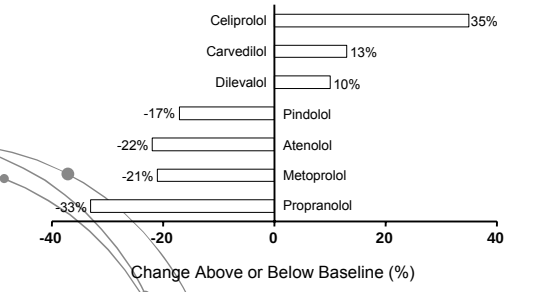
Effects of Various β-blockers on HDL-C



* p < 0.05
** p < 0.01
} vs. baseline

Fogarl et al 1980

Effect of β-blockers on Insulin Sensitivity in Hypertensive Patients

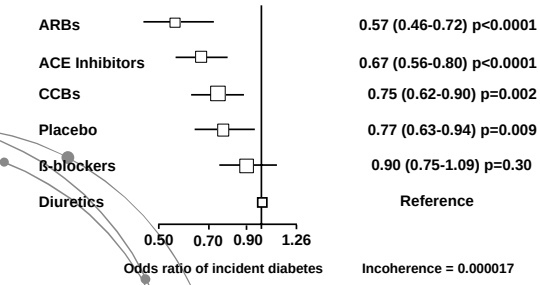


Jacob S et al. *Am J Hypertens.* 1998;11:1258-1265.

Metabolic ADRs

- ↓ insulin sensitivity, ↑ blood sugar, ↑ TG & VLDL, ↓ HDL are associated with β_2-blockade
- Ranking of severity
  - Highest: propranolol, timolol (non-selective)
  - Moderate: metoprolol, atenolol (partial selective)
  - Low or neutral:
    - Bisoprolol (highly selective)
    - Carvedilol (alpha-blocking)
    - Nebivolol (highly selective, β_2-ISA?)

Incident Diabetes in Clinical Trials of Antihypertensive Drugs
A Network Meta-analysis

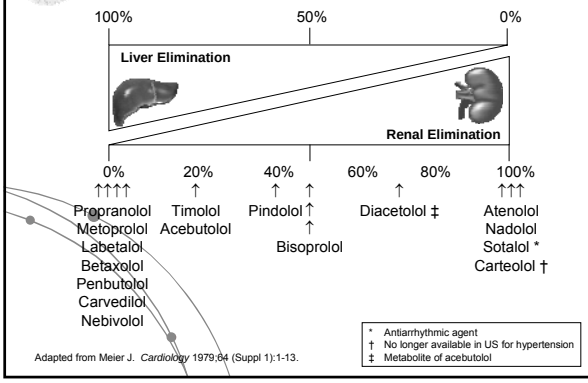


Elliott WJ, Meyer PM. *Lancet.* 2007;369:201–207.

Lipophilic (vs Hydrophilic) β-blockers

- Extensively metabolized in the gut wall and liver (first pass effect) → ↓ oral bioavailability (10–30%)
- Accumulate when reduced hepatic blood flow:
  - Elderly, heart failure, liver cirrhosis
- Easily cross BBB, ↑ incidence of CNS ADR (sedation)
- Also crosses placenta → fetal bradycardia
  - Comparative lipid solubility
    - High: propranolol, metoprolol, pindolol, timolol
    - Moderate: bisoprolol, carvedilol
    - Low: atenolol

Route of Elimination



Adapted from Meier J. *Cardiology* 1979;64 (Suppl 1):1-13.

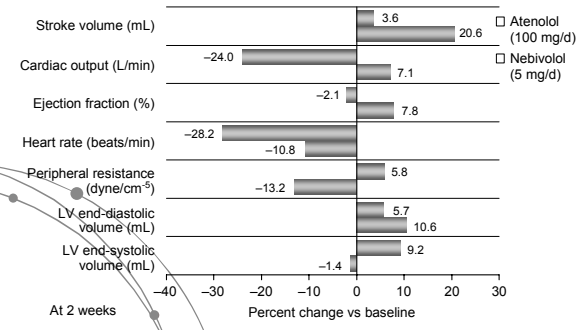
Metabolism of Beta-Blockers

	Elimination	Major	Minor
Propranolol	Liver	2D6	2C19, 1A2, P-glycoprotein
Atenolol	50/50	-	-
Bisoprolol	50/50	-	2D6, 3A4
Metoprolol	Liver	2D6	-
Carvedilol	Liver	2D6, 2C9	3A4,2C19,1A2,2E1
Nebivolol	Liver	2D6, UGT	-

β-blockers: Peripheral Vasodilating Activity

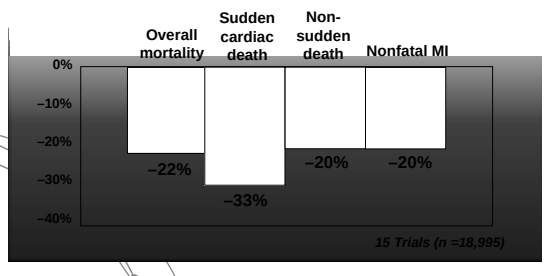
- Carvedilol, labetalol
  - α_1-blockade
  - Nitric oxide release ?
- Nebivolol
  - Nitric oxide release
  - β_3-agonist ?
- Bucindolol (not marketed because of BEST)
  - ? cGMP-dependent mechanism

Differing Effects of β-blockers on Hemodynamics in Hypertensive Patients



Kamp O et al. *Am J Cardiol.* 2003;92(3):344-348.

Risk Reduction With β-blockers in Post-MI Patients



Hanes DS et al. *J Clin Hypertens (Greenwich).* 2001;3(4):236-243.

β-blockers in 2nd Prevention of CHD

Phase of Treatment	Total # Patients	RR (95% CI)
Acute treatment	28,970	0.87 (0.77-0.98)
2nd prevention	24,298	0.77 (0.70-0.84)
Overall	53,268	0.81 (0.75-0.87)

0.5 1.0 2.0

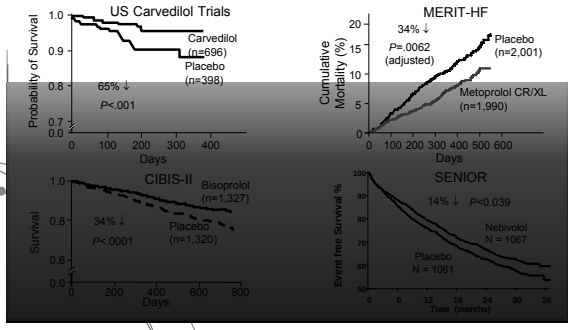
RR of death

β-blocker better | Placebo better

CI=Confidence interval, RR=Relative risk

Antman E, Braunwald E. Acute Myocardial Infarction. In: Braunwald E, Zipes DP, Libby P, eds. Heart Disease: A textbook of Cardiovascular Medicine, 6th ed., Philadelphia, PA: W.B. Sanders, 2001, 1168.

Addition of β-Blockers to ACEIs Reduces Mortality in Heart Failure



Packer M et al. *N Engl J Med.* 1996;334:1349-1355. MERIT-HF Study Group. *Lancet.* 1999;253:2001-2007. CIBIS-II Investigators. *Lancet.* 1999;353:9-13. Packer M et al. *N Engl J Med.* 2001;344:1651-1658.

Review

Are β-Blockers Efficacious as First-line Therapy for Hypertension in the Elderly?

A Systematic Review

Franz H. Messerli, MD; Ehud Grossman, MD; Uri Goldbourt, PhD

Atenolol in hypertension: is it a wise choice?

Lancet 2004; 364: 1684–89

Bo Carlberg, Ola Samuelsson, Lars Hjalmar Lindholm

Summary

Background Atenolol is one of the most widely used β blockers clinically, and has often been used as a reference drug in randomised controlled trials of hypertension. However, questions have been raised about atenolol as the best reference drug for comparisons with other antihypertensives. Thus, our aim was to systematically review the effect of atenolol on cardiovascular morbidity and mortality in hypertensive patients.

Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis

Lars Hjalmar Lindholm, Bo Carlberg, Ola Samuelsson

Summary

Background: β blockers have been used widely in the treatment of hypertension and are recommended as first-line drugs in hypertension guidelines. However, a preliminary analysis has shown that atenolol is not very effective in hypertension. We aim to substantially enlarge the data on atenolol and analyse the effect of different β blockers.

Lancet 2005; 366: 1545–53

Published online October 18, 2005

β-Blockers vs. Other Anti-HTN Drugs: Composite Outcome*

Study Population	β-Blockers n/N	Other Drugs n/N	RR (95% CI)
Participants <60 yrs	745/15136	770/15276	0.97 (0.88-1.07)
Participants ≥60 yrs	3588/39010	3817/40765	1.06 (1.01-1.10)

Khan N, et al. *CMAJ.* 2006;174:1737-1742

*Death, stroke or MI

Follow-up 2006 Meta-Analysis: Atenolol vs Other Treatments

	2006 Meta-analysis
End Point	Summary OR (95% CI)
Death	1.10 (1.03-1.16) *P*=0.003
CV Death	1.13 (1.04-1.22) (*P*=0.005)
MI	1.05 (0.97-1.14) *P*=0.19
Stroke	1.26 (1.15-1.38) *P*=0.0000006

Elliott WJ. *JACC.* 2006;47 (Suppl):361A.

Beta-blockers for hypertension (Review)

Wiysonge CSU, Bradley HA, Mayosi BM, Maroney RE, Mbewu A, Opie L, Volmink J

THE COCHRANE COLLABORATION

The available evidence does not support the use of beta-blockers as first-line drugs in the treatment of hypertension.

WILEY Publishers Since 1807

Wiysonge C, et al. Cochrane Database of Systematic Reviews, Issue 2, 2009

2006 UK NICE Guidelines for the Treatment of Newly Diagnosed Hypertension

	<55 years	≥55 years or blacks at any age
Step 1	ACEI (or ARB*)	CCB or thiazide-type diuretic
Step 2	ACEI (or ARB*) + CCB *or* ACEI (or ARB*) + thiazide diuretic	
Step 3	ACEI (or ARB*) + CCB + diuretic	
Step 4	Add further diuretic therapy, α-blocker, or β-blocker. Consider seeking specialist advice	

*If ACE inhibitor (ACEI) not tolerated

http://www.nice.org.uk/download.aspx?o=CG034fullguideline.

Key Issues in β-blockers Controversy in HTN

- Fact:
  - Based on outcome data, β-blocker is the least supported class (compared to other classes)
- Controversy:
  - What is(are) the reason(s) for inferior outcome?
    - •Problems within itself (drug, dosing, etc.)?
    - •Advantages of other agents?
  - Is this a class effect of β-blocker ?
  - Can we mitigate/abolish that effects?

Problem with Atenolol Dosing ? Should it be dose twice daily ?

	Dose	T1/2	Trough/Peak Ratio
Propranolol	40-160 mg BID	1-6	
Atenolol	25 -100 mg OD	6-9	⇨ 31%
Bisoprolol	2.5-10 mg OD	9-12	⇨ 78%
Metoprolol	50-100 mg BID	3-7	
Carvedilol	12.5-25 mg BID	7-10	

Anglo-Scandinavian ascot Cardiac Outcomes Trial

A randomized controlled trial of the prevention of CHD and other vascular events by BP and cholesterol lowering in a factorial study design

B.Dahlof (Co-chair), P.Sever (Co-chair), N. Poulter (Secretary)
H. Wedel (Statistician), G. Beevers, M. Caulfield, R. Collins
S. Kjeldsen, A. Kristinsson, J. Mehlsen, G. McInnes, M. Nieminen
E. O'Brien, J. Östergren, on behalf of the ASCOT Investigators

Treatment Algorithm to BP targets < 140/90 mm Hg or < 130/80 mm Hg in Patients with Diabetes

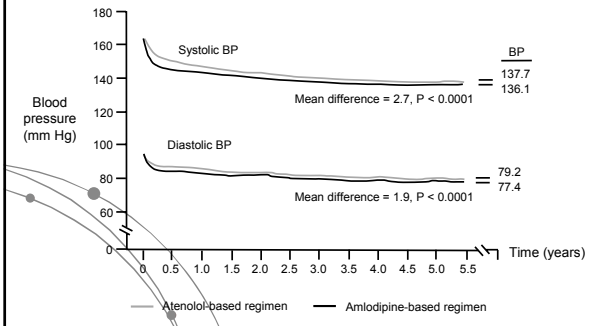
Amlodipine 5-10 mg → add → Perindopril 4-8 mg

Atenolol 50-100 mg → add → Bendroflumethiazide-K 1.25-2.5 mg

add → Doxazosin GITS 4-8 mg

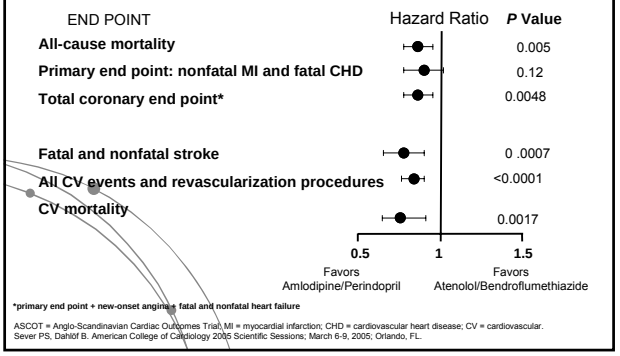
add → Additional drugs, eg, moxonidine/spironolactone

ASCOT-BPLA: Reductions in BP over time



Dahlöf B et al; ASCOT Investigators. *Lancet*. 2005;366:895-906.

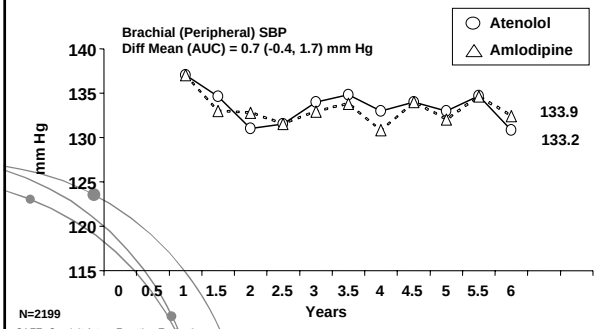
ASCOT: Primary/Secondary End Points
Amlodipine/Perindopril vs Atenolol/Bendroflumethiazide



*primary end point + new-onset angina + fatal and nonfatal heart failure

ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; MI = myocardial infarction; CHD = cardiovascular heart disease; CV = cardiovascular.
Sever PS, Dahlöf B. American College of Cardiology 2005 Scientific Sessions; March 6-9, 2005; Orlando, FL.

CAFÉ (ASCOT SubStudy): Differences in *Brachial vs Aortic SBP*



CAFE, Conduit Artery Function Evaluation;
AUC, area under the curve; SBP, systolic blood pressure.

Williams B et al. *Circulation.* 2006;113(9):1213-1225.

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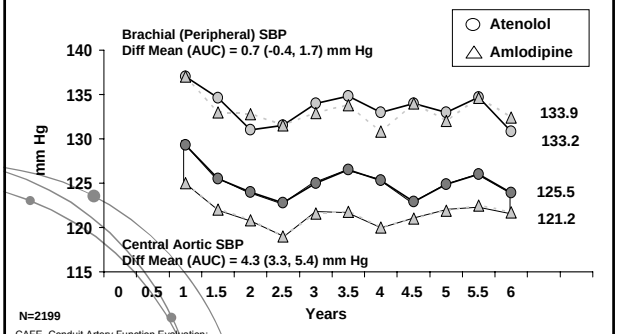
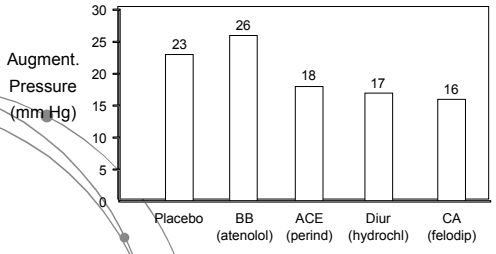


CAFE, Conduit Artery Function Evaluation;
AUC, area under the curve; SBP, systolic blood pressure.

Williams B et al. *Circulation.* 2006;113(9):1213-1225.

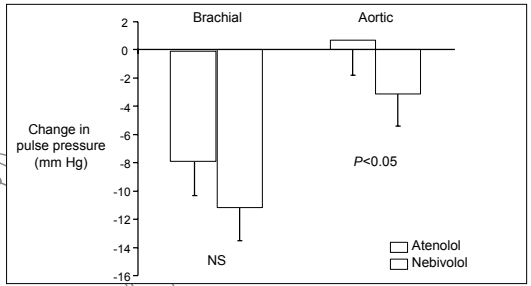
Effect of Various Antihypertensive Agents on Central Aortic Pressure

A double blinded, randomized, cross-over study (1 month/each agent)
Subject: 32 elderly HTN, mean age 77 yr, mean BP: $^{167}/_{87}$ mmHg; PP = 80 mm Hg)



Morgan T, et al Am J Hypertens 2004;17:118–23.

Effects of a Vasodilating vs a Non-vasodilating β-blockers on Central Aortic Pressure in HTN Patients



N=16: 5 weeks of crossover treatment with atenolol & nebivolol

Dhakam Z et al. *J Hypertens.* 2008;26:351-356.

Questions Needing Answers

- For uncomplicated HTN, should β-blockers remain first line?
  - Watch out for JNC 8 (2010)
- Would this finding translate to all β-blockers other than atenolol?
- Is it only BP or might it really be "Beyond Blood Pressure"?
- Where and how should we measure blood pressure?

Summary

- Irrefutable role of β-blockers
  - Heart failure
  - Post-myocardial infarction
- For uncomplicated HTN
  - β-blocker is least supported by data
    - Most trials were done with atenolol
    - What about others?
  - Mechanism for inferiority
    - Less effective for ↓ central pressure ?
- One thing for sure: let's get to goal!!