# Beta Blockers in Hypertension

Arieska Ann Soenarta
National Cardiovascular Center – Harapan Kita Jakarta

Workshop 2011 Regional Cardiology Symposium
Seoul, March 2011

# Case Study

- Male Patient, age 45 :
  - Stressfull Job
  - Palpitation on and off
  - Heavy Smoker
  - Sedentary habits
  - Drinks a lot of coffee
  - Family History : CAD, Hypertension, Stroke

# Case Study

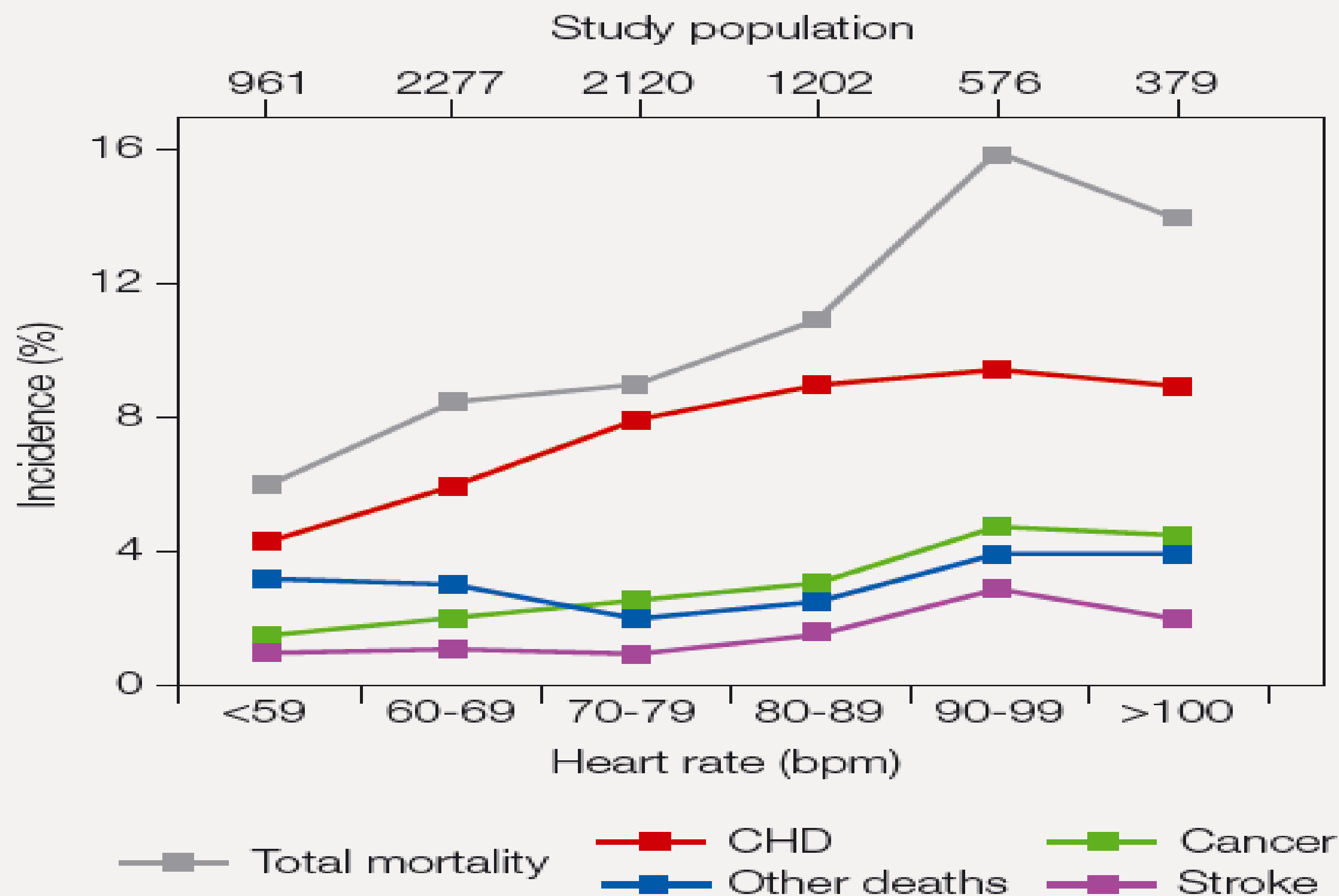
- Physical Examination Findings :
  - Looks stressfull
  - BP 170/100
  - Resting Pulse Rate 84 – 94 bpm
  - ECG normal
  - Chest X-ray normal
  - Lab findings : FBS : 125 mg/dl, Creatinin normal, Ureum normal, LDL 140 mg/dl, HDL 30 mg/dl , TG 250 mg/dl.

# Question 1

This patient's belongs to the high sympathetic activity type. The risk of dying from all cause including CVD increases :

1. True
2. False

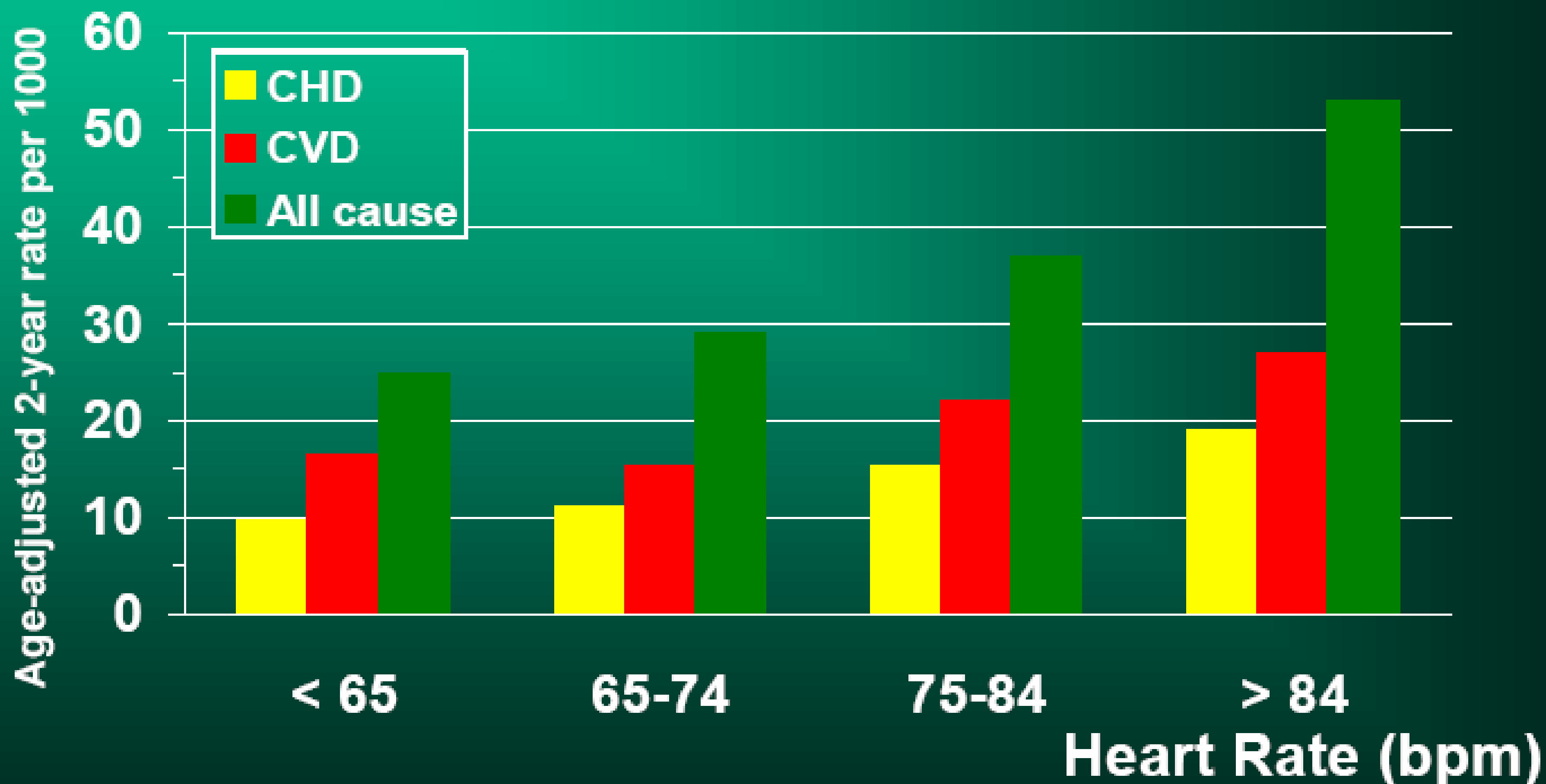
# All Cause and Cause Specific Mortality and Heart Rate in General Population




Modified from Wilhelmsem I. et al EHJ 1996;7 : 279-288

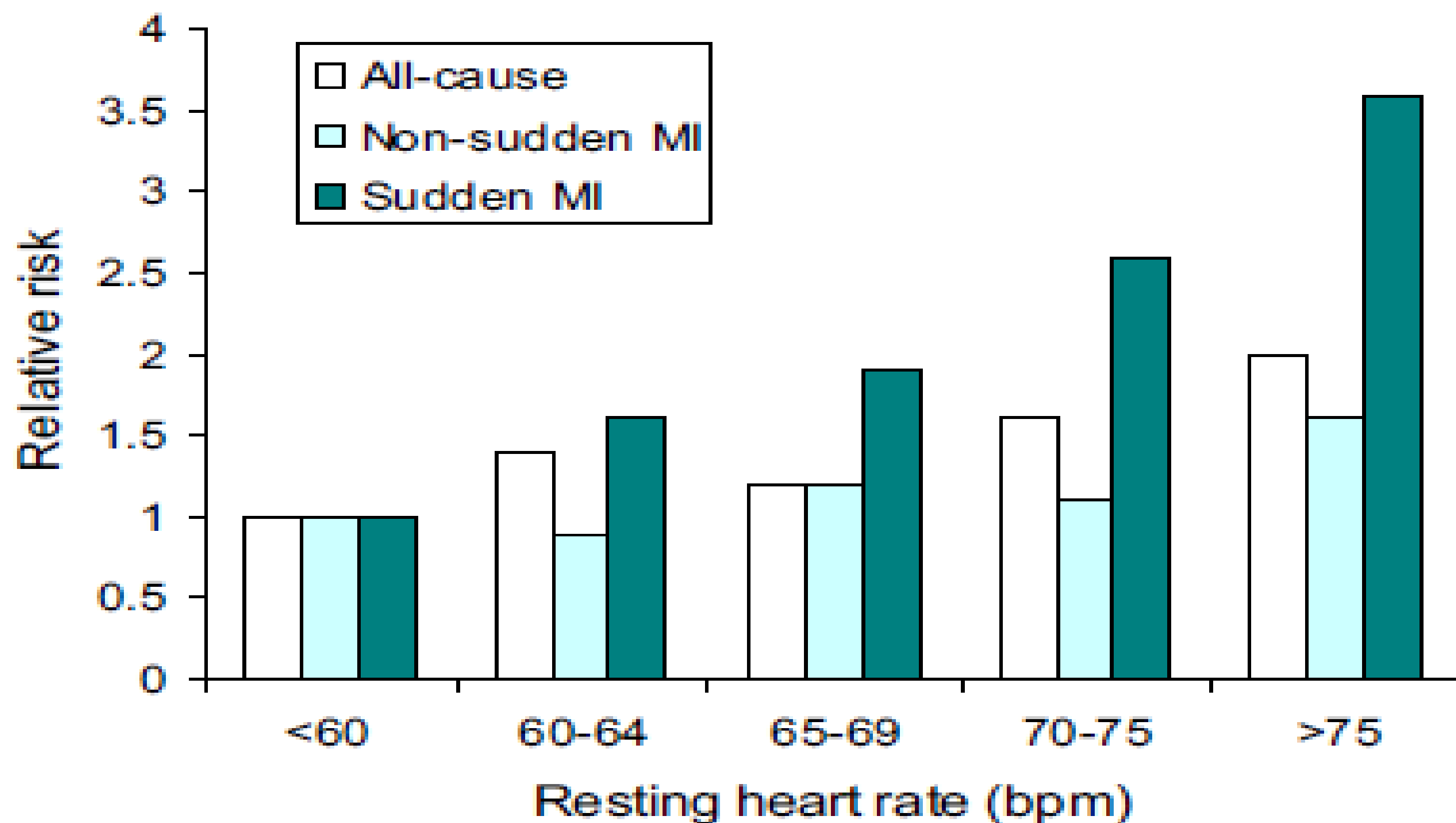
# ASSOCIATION OF HEART RATE WITH MORTALITY RATE AMONG MEN WITH HYPERTENSION

## (The Framingham Study)




Gillman et al., Am Heart J 1993; 125: 1148

# Heart Rate and Mortality in Healthy Men




JACC 2007 : 50(9) ; 1823-30

# Question 2

This is a high risk hyperkinetic HT patient prone to develop CVD. Do you agree to give beta blockers  as the first antihypertensive agent?

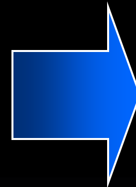
1. Yes
2. No

- 2007 Guidelines for the Management of Hypertension
- 2007 InaSH CONSENSUS ARTERIAL HYPERTENSION MANAGEMENT

# Choice of antihypertensive drugs

*Box 10 Position statement: Choice of antihypertensive drugs*

- The main benefits of antihypertensive therapy are due to lowering of BP *per se*.
- Five major classes of antihypertensive agents – thiazide diuretics, calcium antagonists, ACE inhibitors, angiotensin receptor antagonists and β-blockers – are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination. β-blockers, especially in combination with a thiazide diuretic, should not be used in patients with the metabolic syndrome or at high risk of incident diabetes.
- Because in many patients more than one drug is needed, emphasis on identification of the first class of drugs to be used is often futile. Nevertheless, there are many conditions for which there is evidence in favour of some drugs versus others either as initial treatment or as part of a combination.
- The choice of a specific drug or a drug combination, and the avoidance of others, should take into account the following:
  1. The previous favourable or unfavourable experience of the individual patient with a given class of compounds.
  2. The effect of drugs on cardiovascular risk factors in relation to the cardiovascular risk profile of the individual patient.
  3. The presence of subclinical organ damage, clinical cardiovascular disease, renal disease or diabetes which may be more favourably treated by some drugs than others (Box 11 and *Table 6*).
  4. The presence of other disorders that may limit the use of particular classes of antihypertensive drugs (*Table 7*).
  5. The possibilities of interactions with drugs used for other conditions.
  6. The cost of drugs, either to the individual patient or to the health provider, but cost considerations should never predominate over efficacy, tolerability, and protection of the individual patient.
- Continuing attention should be given to side effects of drugs, because they are the most important cause of non-compliance. Drugs are not equal in terms of adverse effects, particularly in individual patients.
- The BP lowering effect should last 24 hours. This can be checked by office or home BP measurements at trough or by ambulatory BP monitoring.
- Drugs which exert their antihypertensive effect over 24 hours with a once-a-day administration should be preferred because a simple treatment schedule favours compliance.



- five important drug classes noted: diuretics, ACE-I, CCBs, ARBs, Beta-blockers
- No particular class recommended
- Set of drugs also include beta-blockers
  - to be used in many patients
  - but not in patients with metabolic syndrome or a high risk for incident diabetes

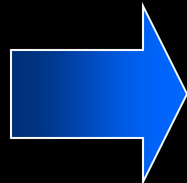
- 2007 Guidelines for the Management of Hypertension
- 2007 InaSH CONSENSUS ARTERIAL HYPERTENSION MANAGEMENT

# Which drug to prefer?

*Box 11 Position statement: Antihypertensive treatment: Preferred drugs*

| | |
|---|---|
| **Subclinical organ damage** | |
| LVH | ACEI, CA, ARB |
| Asympt. atherosclerosis | CA, ACEI |
| Microalbuminuria | ACEI, ARB |
| Renal dysfunction | ACEI, ARB |
| **Clinical event** | |
| Previous stroke | any BP lowering agent |
| Previous MI | BB, ACEI, ARB |
| Angina pectoris | BB, CA |
| Heart failure | diuretics, BB, ACEI, ARB, antialdosterone agents |
| Atrial fibrillation | |
| Recurrent | ARB, ACEI |
| Permanent | BB, non-dihydropiridine CA |
| ESRD/proteinuria | ACEI, ARB, loop diuretics |
| Peripheral artery disease | CA |
| **Condition** | |
| ISH (elderly) | diuretics, CA |
| Metabolic syndrome | ACEI, ARB, CA |
| Diabetes mellitus | ACEI, ARB |
| Pregnancy | CA, methyldopa, BB |
| Blacks | diuretics, CA |

Abbreviations: LVH: left ventricular hypertrophy; ISH: isolated systolic hypertension; ESRD: renal failure; ACEI: ACE inhibitors; ARB: angiotensin receptor antagonists; CA: calcium antagonists; BB: β-blockers



- Selecting the right drug for each individual patients is dependent on the co-morbidities
- Beta-blocker
  - ⇨ preferred in patients with angina pectoris, heart failure, recent MI, important hypertension related complications
  - ⇨ not preferred in hypertensives with multiple metabolic risk factors

# Compelling Indications for Individual Drug Classes (1)

| Compelling Indication | Initial Therapy Options | Clinical Trial Basis |
|---|---|---|
| **Heart failure** | **THIAZ, BB, ACEI, ARB, ALDO ANT** | **ACC/AHA Heart Failure Guideline, MERIT-HF, COPERNICUS, CIBIS, SOLVD, AIRE, TRACE, ValHEFT, RALES** |
| **Postmyocardial infarction** | **BB, ACEI, ALDO ANT** | **ACC/AHA Post-MI Guideline, BHAT, SAVE, Capricorn, EPHESUS** |
| **High CAD risk** | **THIAZ, BB, ACE, CCB** | **ALLHAT, HOPE, ANBP2, LIFE, CONVINCE** |

*2007 ESH/ESC Guidelines*

# Compelling Indications for Individual Drug Classes (2)

| Compelling Indication | Initial Therapy Options | Clinical Trial Basis |
| --- | --- | --- |
| **Diabetes** | **THIAZ, BB, ACE, ARB, CCB** | **NKF-ADA Guideline, UKPDS, ALLHAT** |
| **Chronic kidney disease** | **ACEI, ARB** | **NKF Guideline, Captopril Trial, RENAAL, IDNT, REIN, AASK** |
| **Recurrent stroke prevention** | **THIAZ, ACEI** | **PROGRESS** |

*2007 ESH/ESC Guidelines*

# 2007 ESH/ESC Guidelines for the management of hypertension

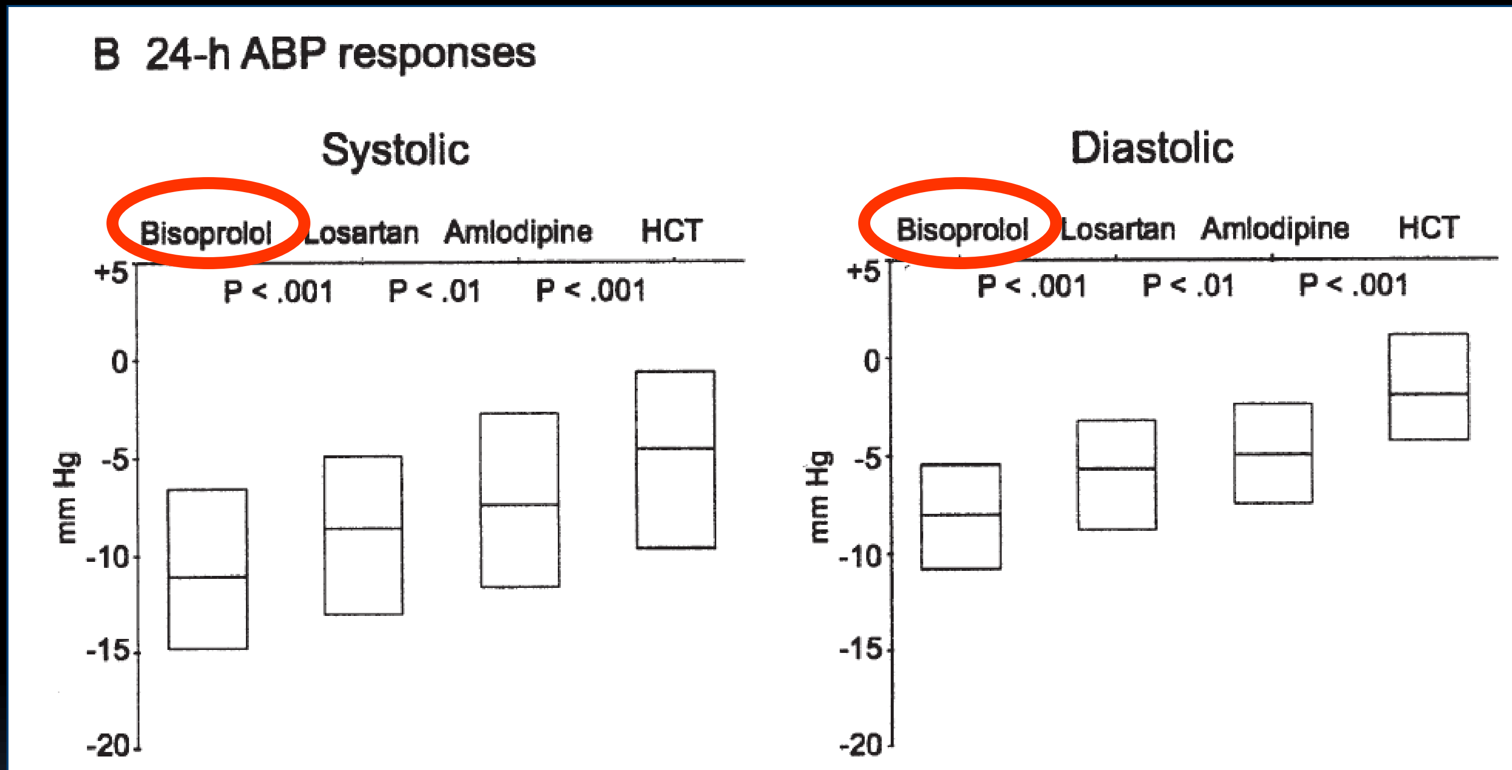
1. The guidelines, concerning beta-blockers, are less severe than the NICE/BHS guidelines
2. All 5 major antihypertensive agents (incl. BBs) are suitable for the initiation of therapy (even in the elderly!)
3. Warns against beta-blockers (particularly in combination with a diuretic) in patients with the metabolic syndrome or at high risk of developing diabetes
4. In diabetics, agents that block the renin-angiotensin system are favoured (reno-protective)
5. Recommends initiating therapy in patients with moderate/severe hypertension with a once daily fixed, low-dose combination

# Question 3

Beta Blockers are less effective in lowering high blood pressure.

1. True
2. False

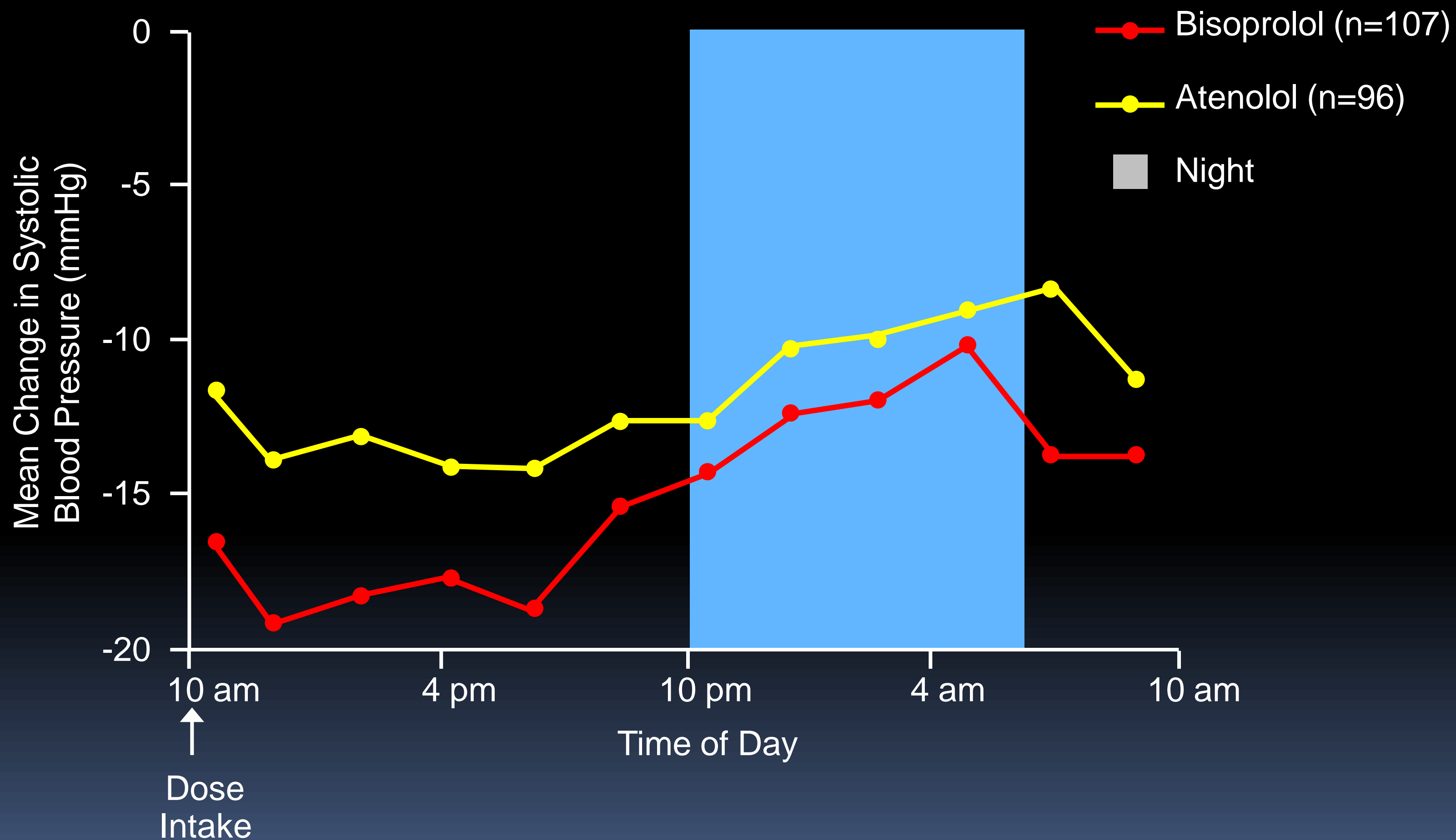
# Bisoprolol vs other antihypertensive agents (the GENRES study)




Hiltunen TP et al. Am J Hypertens 2007;20:311-8
Prospective, randomized double-blind, cross-over, placebo-controlled study in 208 moderately hypertensive men (aged 35 to 60 years: amlodipine 5 mg, bisoprolol 5 mg, HCTZ 25 mg, losartan 50 mg.

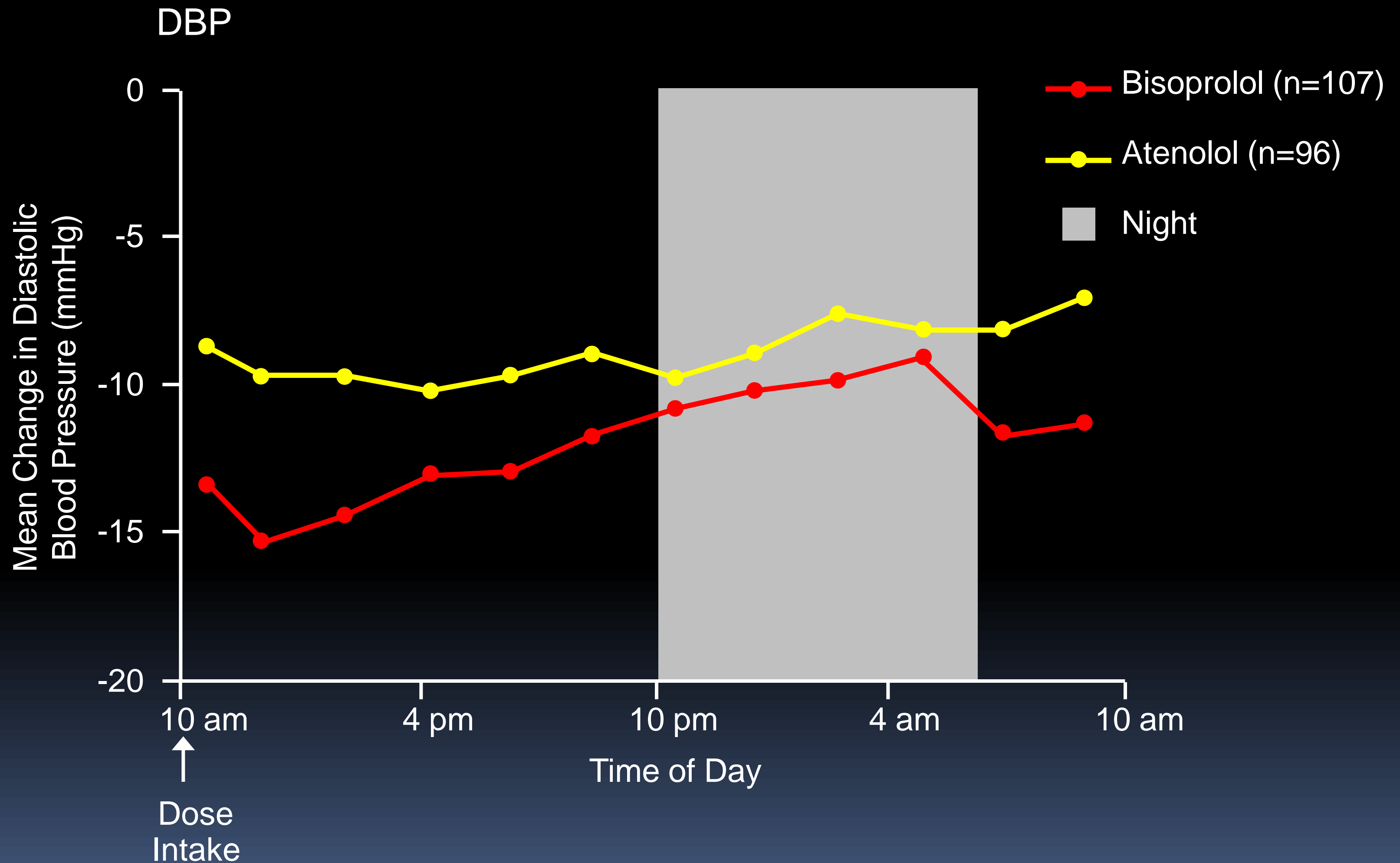
→ **Bisoprolol showed the best antihypertensive effect.**

# Bisoprolol vs atenolol in the treatment of hypertension
# Effect on systolic blood pressure




Neutel JM et al. *Am J Med* 1993;94:181–187

# Bisoprolol vs atenolol in the treatment of hypertension
# Effect on diastolic blood pressure




Neutel JM et al. *Am J Med* 1993;94:181–187

# Question 4

- All Beta Blockers are the same?
  1. Agree
  2. Not Agree

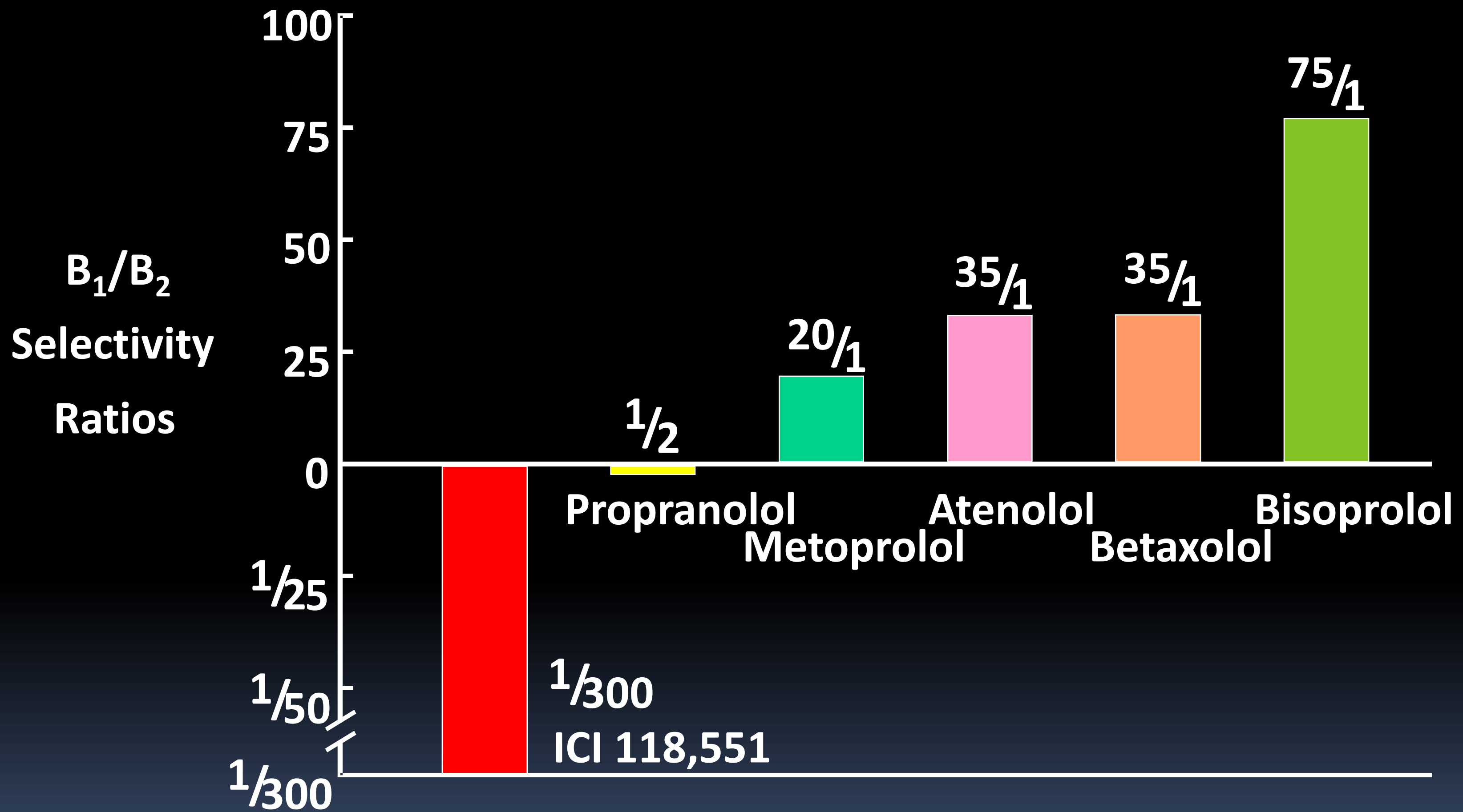
# BETA BLOCKER : THE CONTROVERSIES

Which beta blocker ?

# The -Blocking agents differ

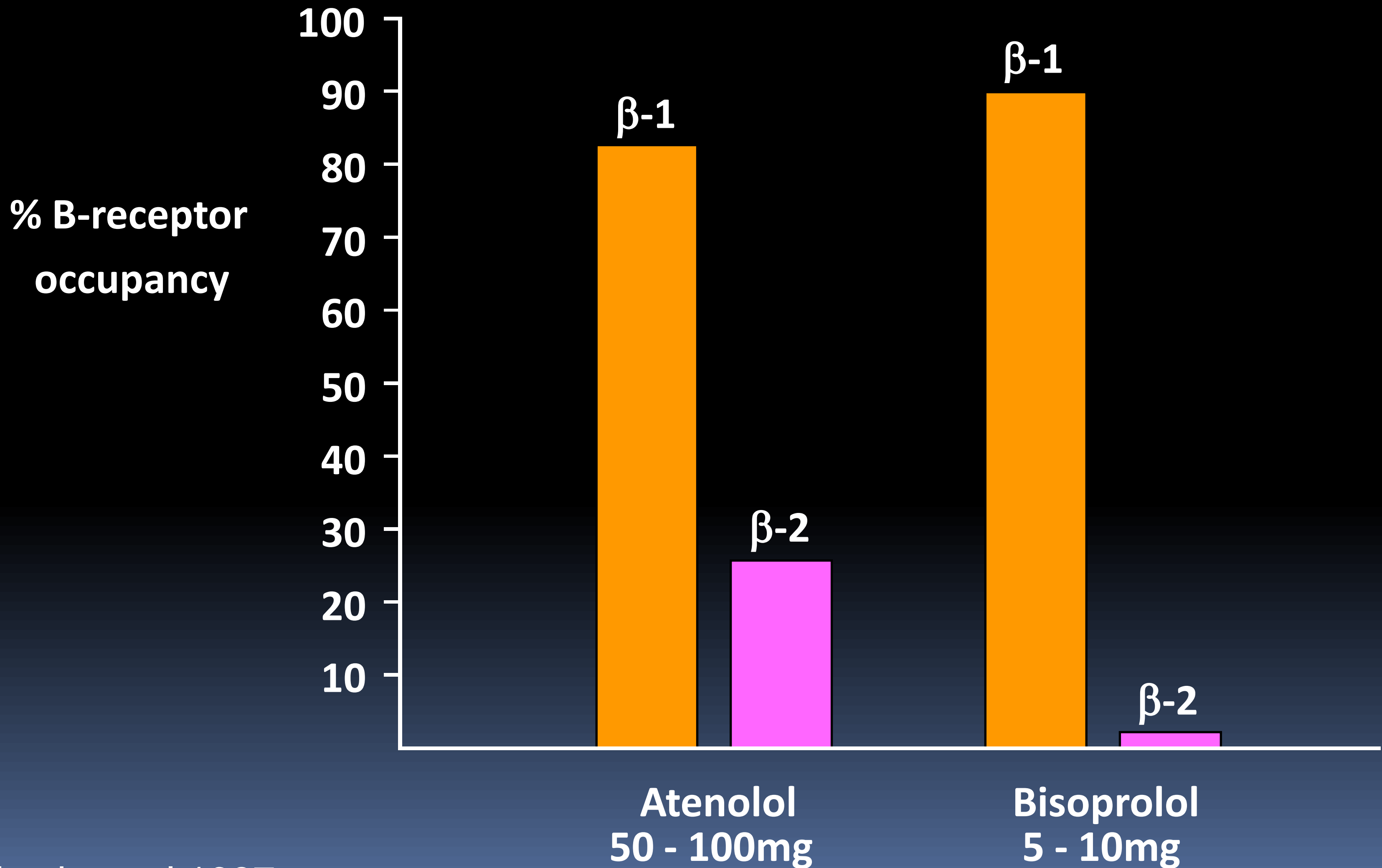
1. Relative ***selectivity*** in blocking $b_1$- versus $b_2$-receptors
2. ***Lipid solubility***
3. Degree of ***intrinsic sympathomimetic activity*** (ISA).

# Beta$_1$ and Beta$_2$ Selectivity Ratios




*Wellstein et al Europ Heart J 1987*

# Atenolol (compared to bisoprolol) is only moderately β-1 selective




Wellstein et.al 1987

# β- BLOCKERS - LIPID SOLUBLE

**Propanolol (Inderal) / Metoprolol (Lopressor)**

- **Cross blood brain barrier**
- **More Central Nervous System effects.**
- **Inactivated more rapidly by the liver**
  **∴ Shorter duration of action**

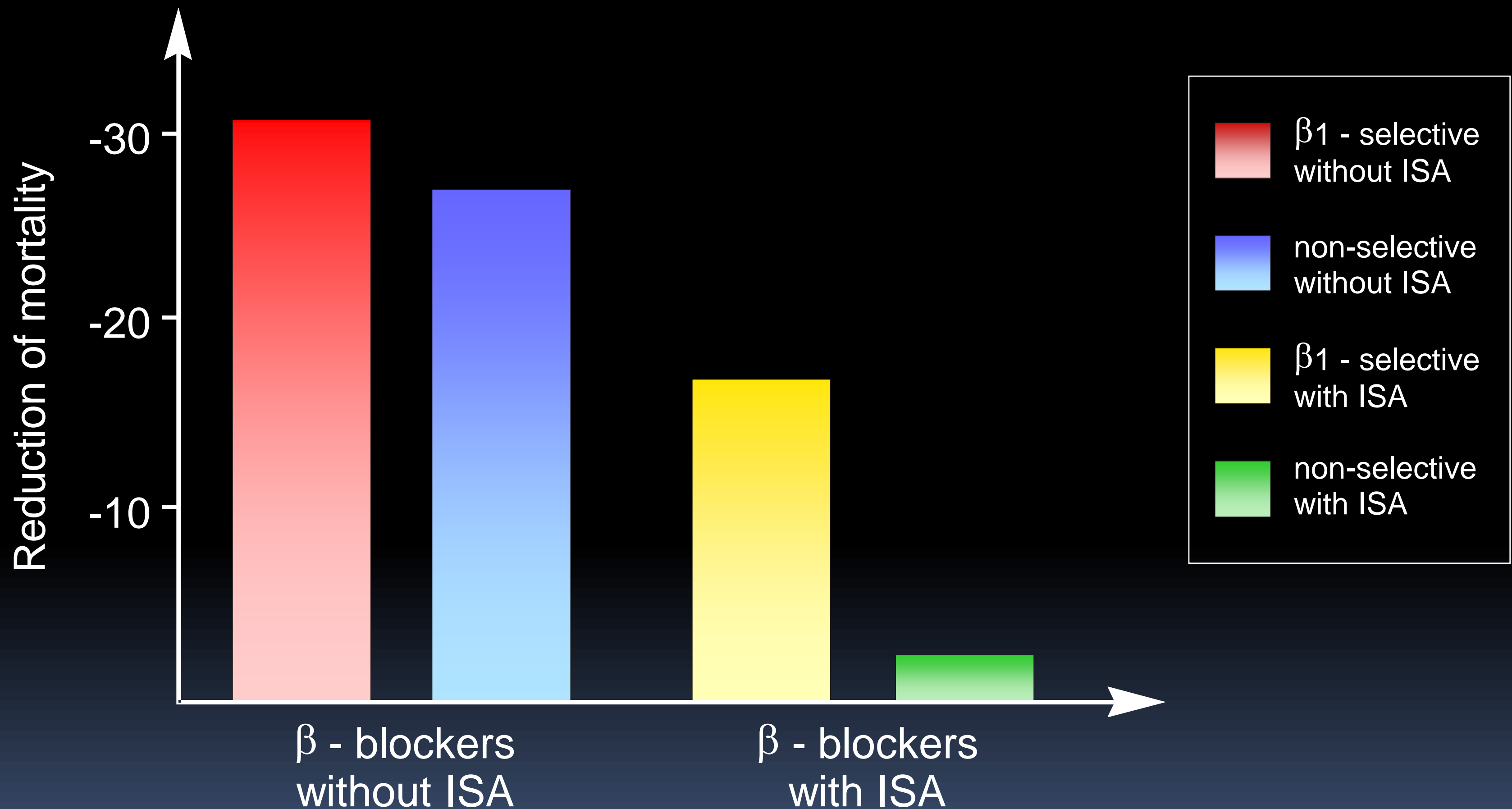
# ISA

- ISA
  compounds with intrinsic sympathomimetic activity (ISA) - so-called because they may cause an ***activation of the sympathetic nervous system***, ie, the adrenergic response
- Without ISA

  -results of the postmyocardial infarction (MI) survival trials, where beta-blockers without ISA reduced morbidity and mortality

  -pulse rate is < 60 bpm, however, the use of a beta-blocker with ISA might be indicated.

# Secondary prevention of myocardial infarction with different types of β - blockers




*Yusuf S et al. Progress Cardiovasc. Diseases 1985; 5: 335-371*

# Beta-blockers (BB) and heart failure – Intrinsic Sympathomimetic Activity (ISA) impairs efficacy

| Beta-blockers with ISA | | Beta-blockers without ISA | |
|---|---|---|---|
| **Type of BB** | **Comment** | **Type of BB** | **Comment** |
| Xamoterol (43% beta-1 ISA) | Actually increased mortality by 250% in moderate/severe heart failure v placebo | Carvedilol – 3 studies | All 3 BBs decrease mortality by about 35% v placebo |
| Bucindolol (25% ISA; also a powerful sympatholytic - ? via dense beta-2 blockade)-BEST study | A non-significant 10% reduction in mortality (worse if LV dysfunction severe) v placebo | Bisoprolol -CIBIS 2 | |
| Nebivolol (contains both beta-2 and beta-3 ISA)-SENIORS study | A non-significant 12% reduction in mortality in elderly patients v placebo | Metoprolol (succinate) - MERIT study | |

# Pharmacologic Properties of Some Beta-Blockers

| Drug | Trade Name | $Beta_1$ Selectivity | Intrinsic Sympathomimetic Activity | Alpha-Blockage | Lipid Solubility | Usual Daily Dose (Frequency) |
|---|---|---|---|---|---|---|
| Acebutolol | Sectral | + | + | - | ++ | 200-800 mg |
| Atenolol | Tenormin | ++ | - | - | - | 25-100 mg |
| Bisoprolol | Concor | ++++ | 0 | - | ++ | 2.5-10 mg |
| Carvedilol | Dilbloc | - | 0 | + | ++ | 12.5-50 mg |
| Metoprolol | Lopressor, Seloken | ++ | - | - | +++ | 50-200 mg |
| Nadolol | Corgard | - | - | - | - | 40-320 mg |
| Pindolol | Visken | - | +++ | - | ++ | 10-60 mg |
| Propranolol | Inderal LA | - | - | - | +++ | 40-480 mg |

# Question 5

- Would you still give a beta blocker in this patient with an elevated fasting blood sugar and dyslipidemia?
  1. Yes, but I will choose a BB with less metabolic effects like bisoprolol
  2. No

# New onset diabetes in the LIFE and the ASCOT trials

- LIFE

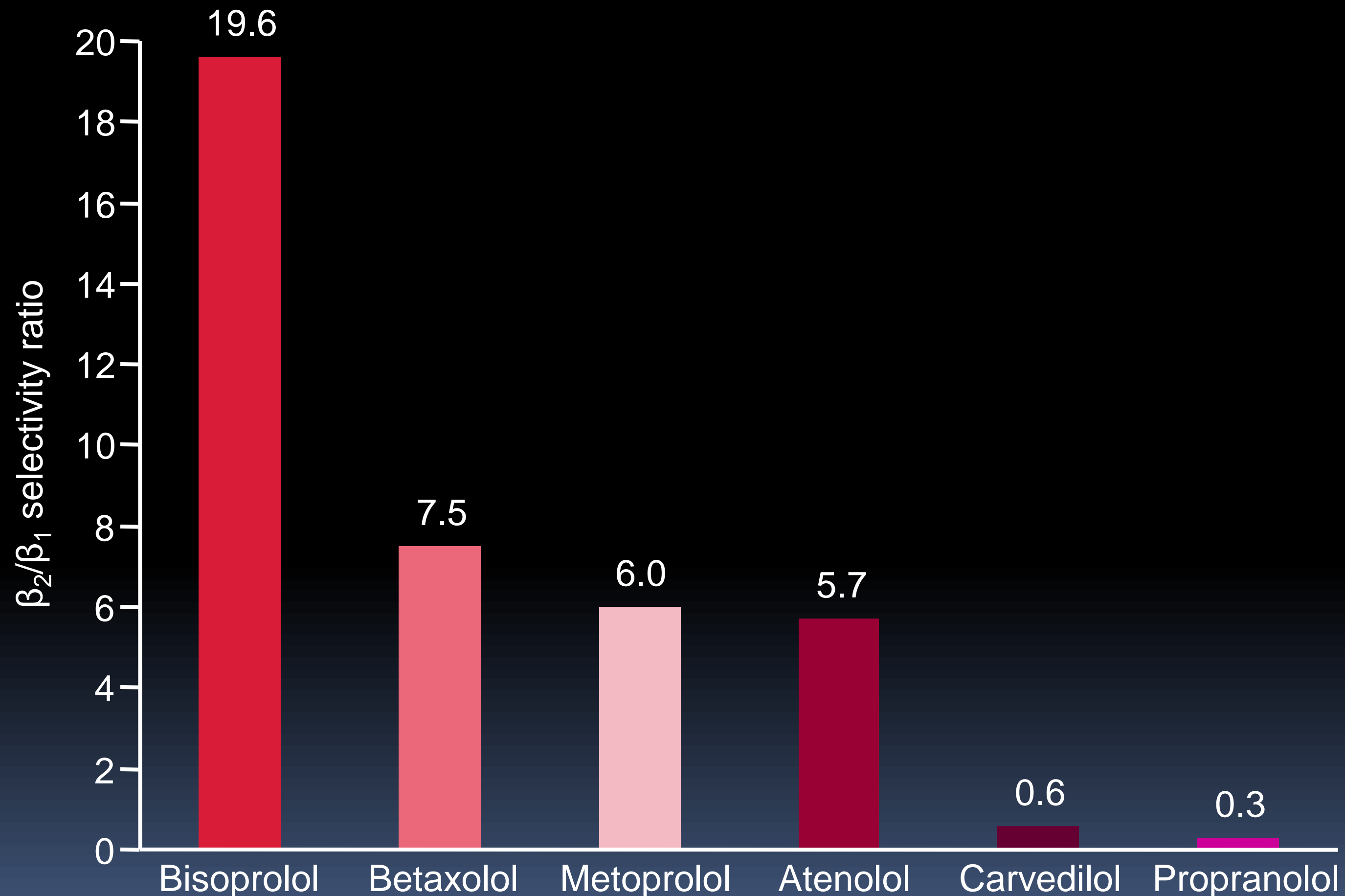
| LOSARTAN | ATENOLOL | Hazard ratio | P value |
|---|---|---|---|
| 6% | 8% | 0,75 (0,63-0,88) | 0,001 |

- ASCOT

| AMLODIPINE | ATENOLOL | Hazard ratio | P value |
|---|---|---|---|
| 6% | 8% | 0,70 (0,63-0,78) | < 0,001 |

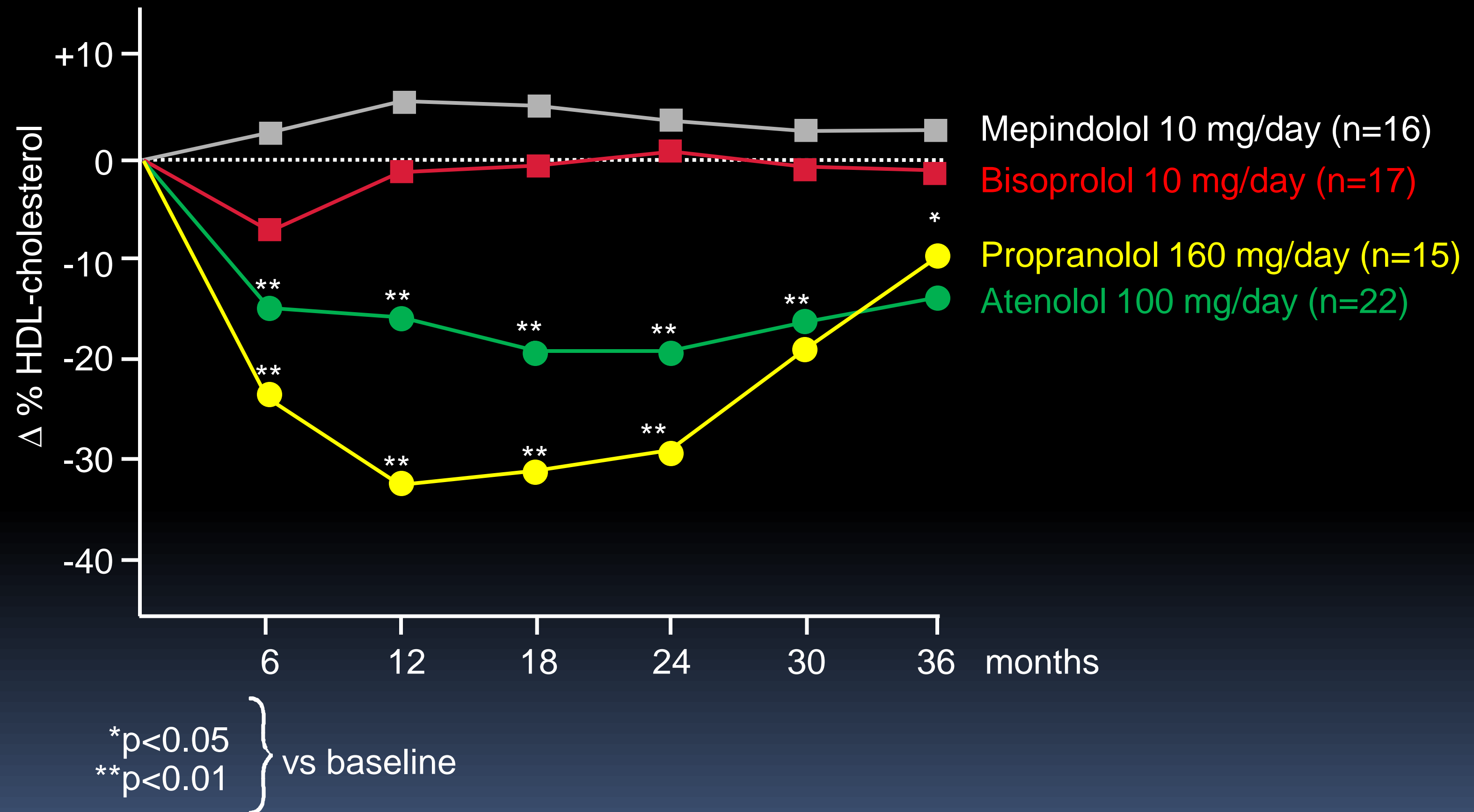
- Lancet 2002;359:995-1003
- Lancet 2005;366:895-906

# Bisoprolol: $\beta_2/\beta_1$ selectivity ratio at human $\beta$-receptors *in vitro*



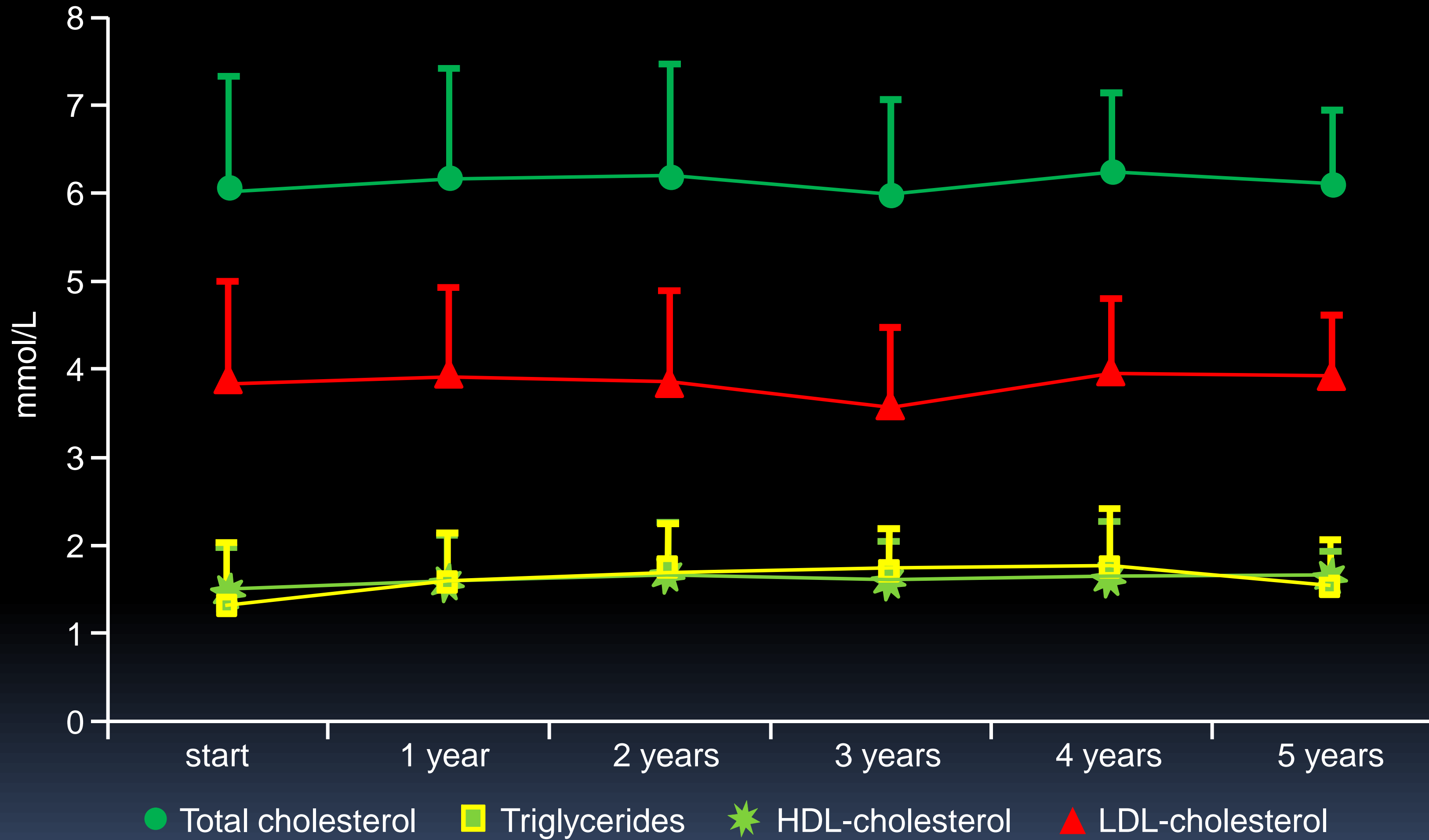

Smith C,Teitler M. *Cardiovasc Drugs Ther* 1999;13:123–126

# Effect of different betablockers on HDL-cholesterol



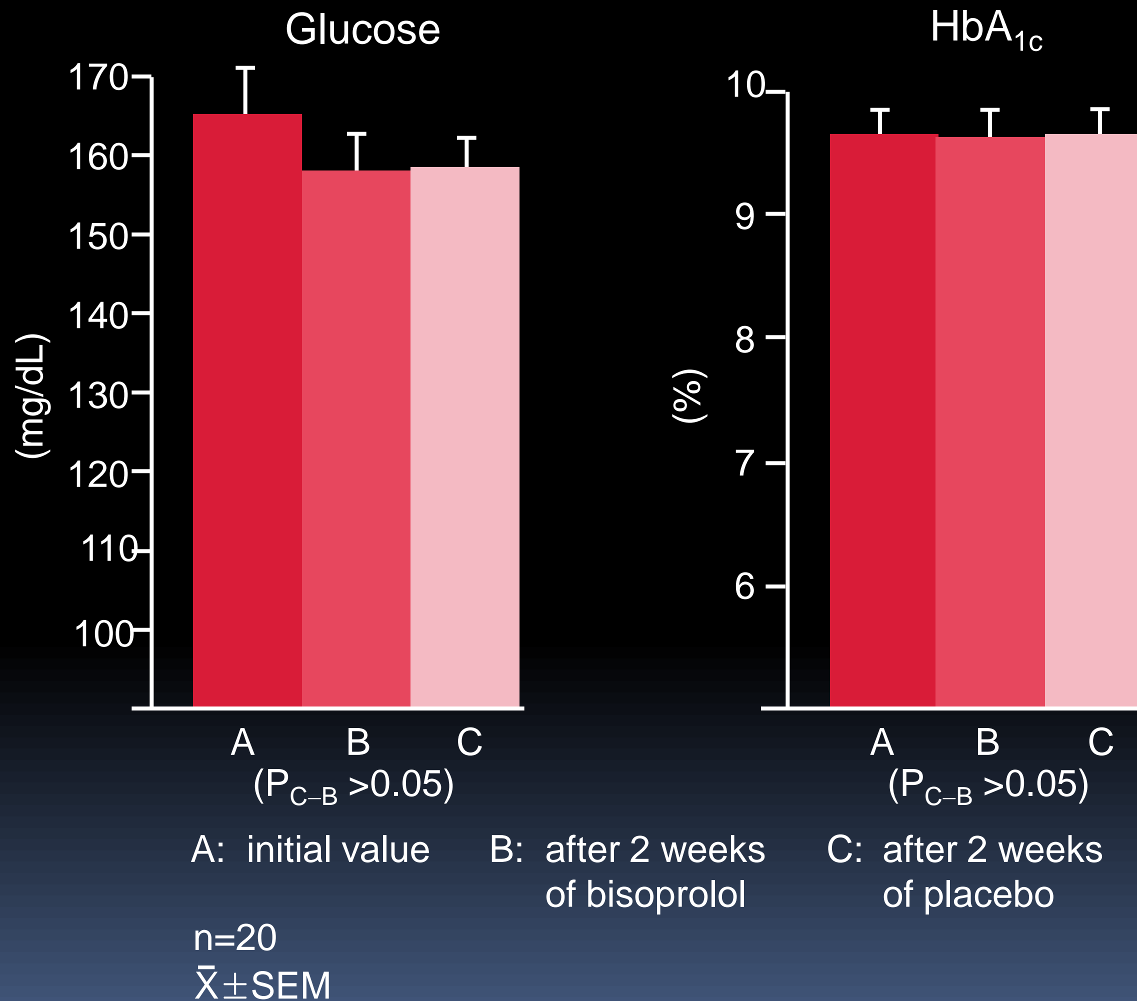

Fogari R et al. *J Cardiovasc Pharmacol* 1990;16 (Suppl 5):S76–80

# Effect bisoprolol on lipid parameters




Frithz G. *Cardiovasc Drugs Ther* 1993;7(suppl 2):424 (abstract 149)

# Effect of bisoprolol on glucose metabolism in type 2 diabetic patients




Janka HU et al. *J Cardiovasc Pharmacol* 1986;8(Suppl. 11):96–99

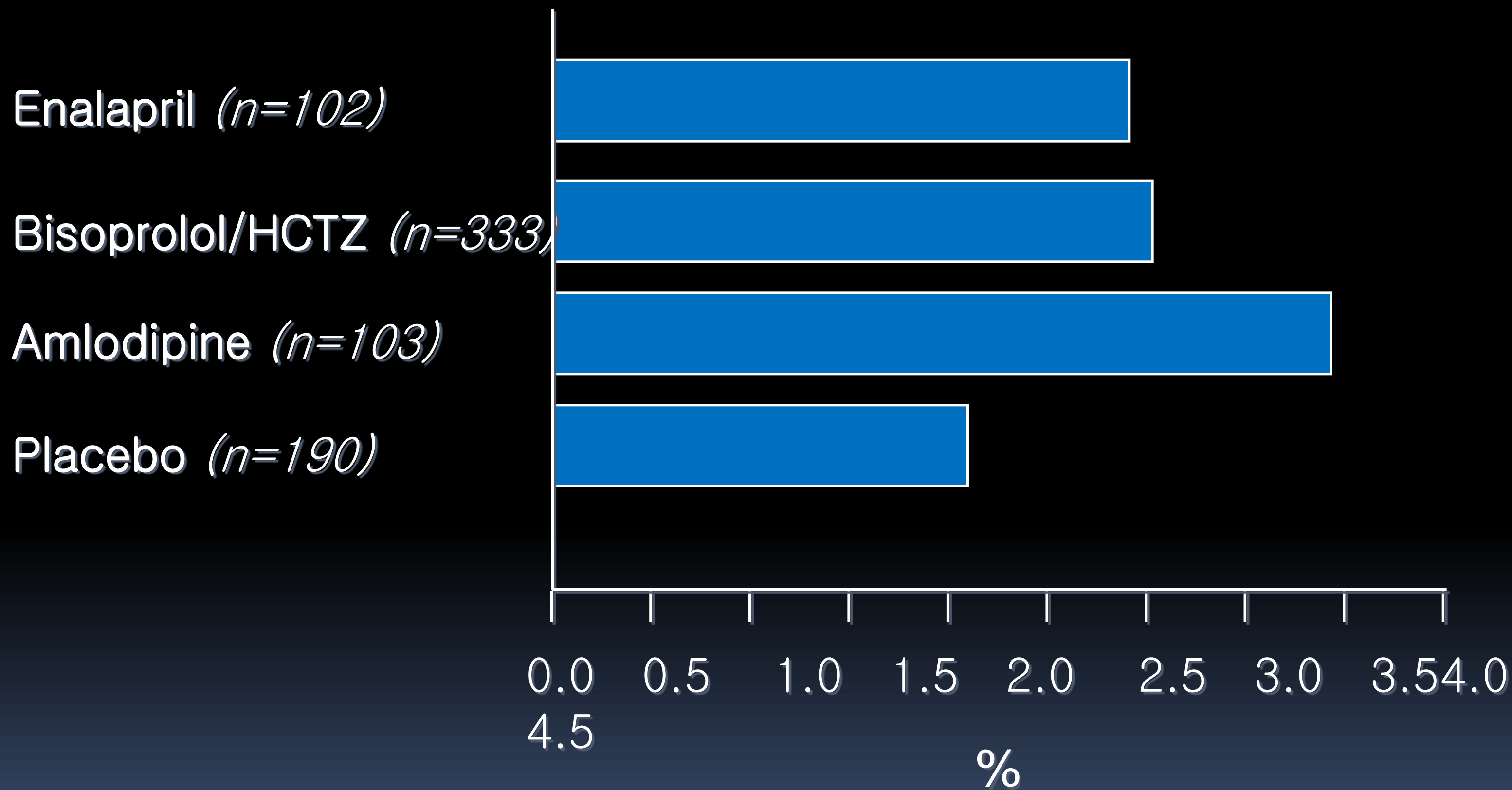
# Question 6

- Regarding sexual function, with beta blocker will you choose among the available beta blockers agents :
    1. Carvedilol
    2. Propanolol
    3. Atenolol
    4. Bisoprolol

# Effect of different betablockers on sexual function (vs placebo)

| Beta-blocker | Sexual dysfunction – % increase vs placebo | Reference |
|---|---|---|
| Carvedilol | 13.5 | Fogari R et al 2001 |
| Propranolol | 5.0 | MRC-Mild Hypert 1985 |
| Atenolol | 3.0 | Silvestri A et al 2003 |
| Bisoprolol | 0.0 | Broekman CP et al 1992 |

# Self-reported erectile dysfunction in prospective, randomized trials



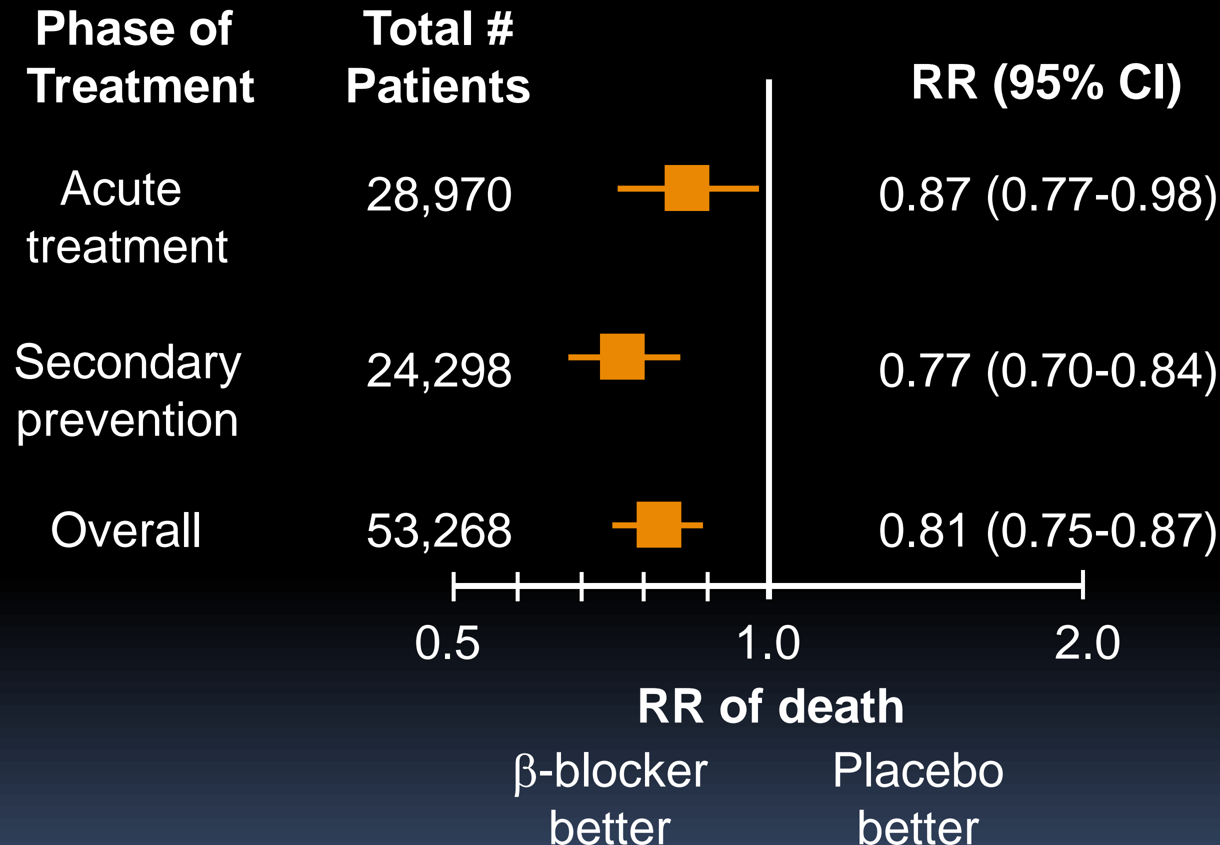

*Prisant et al, J Clin Hypertens, 1999*

# Question 7

- Conditions favouring  beta blockers vs other hypertensives agents :
    1. Angina Pectoris
    2. Post Myocardial Infarction
    3. Heart Failure
    4. Tachy Arrhytmia
    5. Glaucoma
    6. Pregnancy
    7. All of the above

# The role of betablockers in the treatment of MI

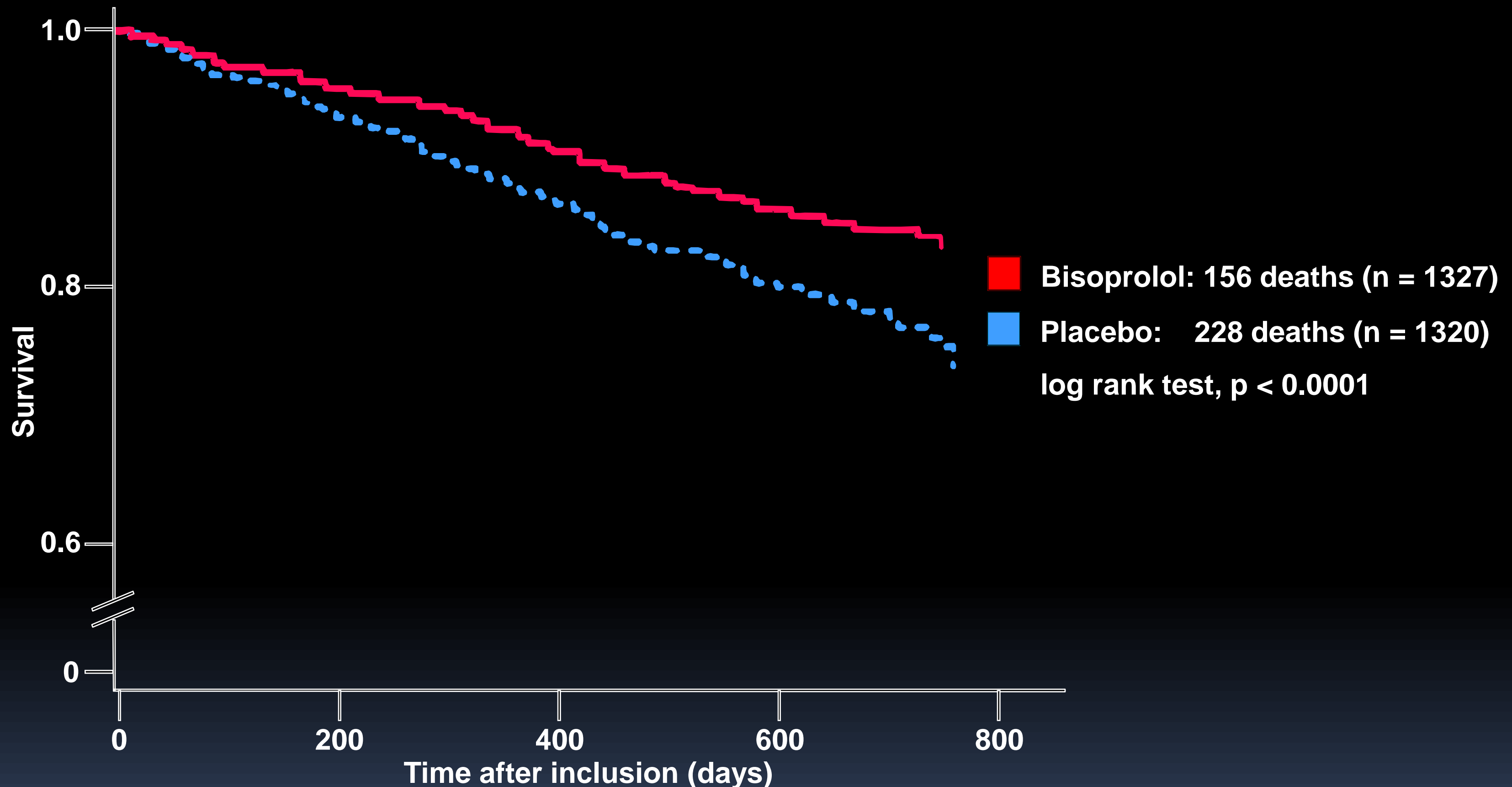
## Summary of Secondary Prevention Trials of β-blocker Therapy




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.

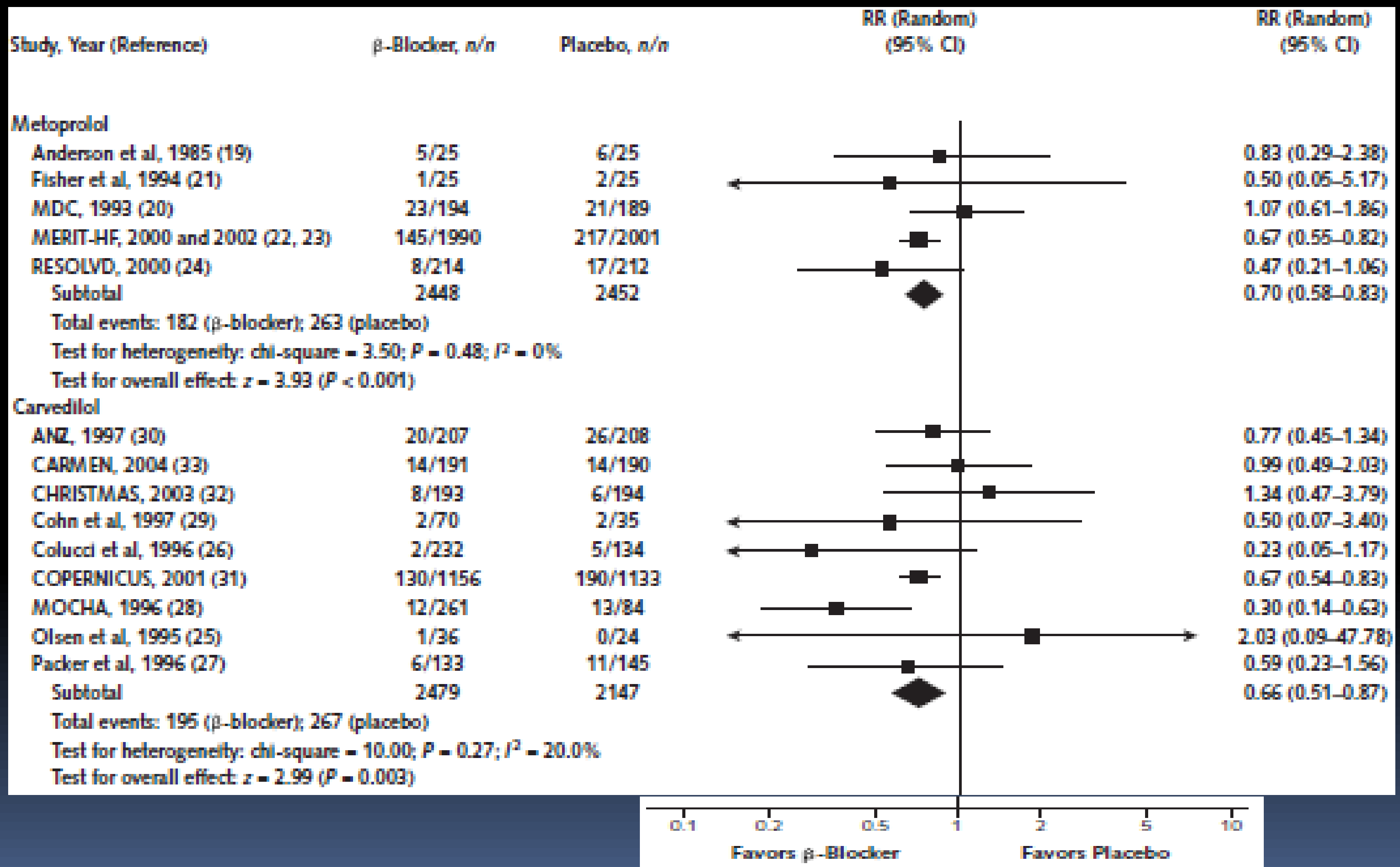
# CIBIS II
# (Cardiac Insufficiency Bisoprolol Study II)




➔ 34% reduction in all-cause mortality with bisoprolol

*(Lancet 1999;353:9-13)*

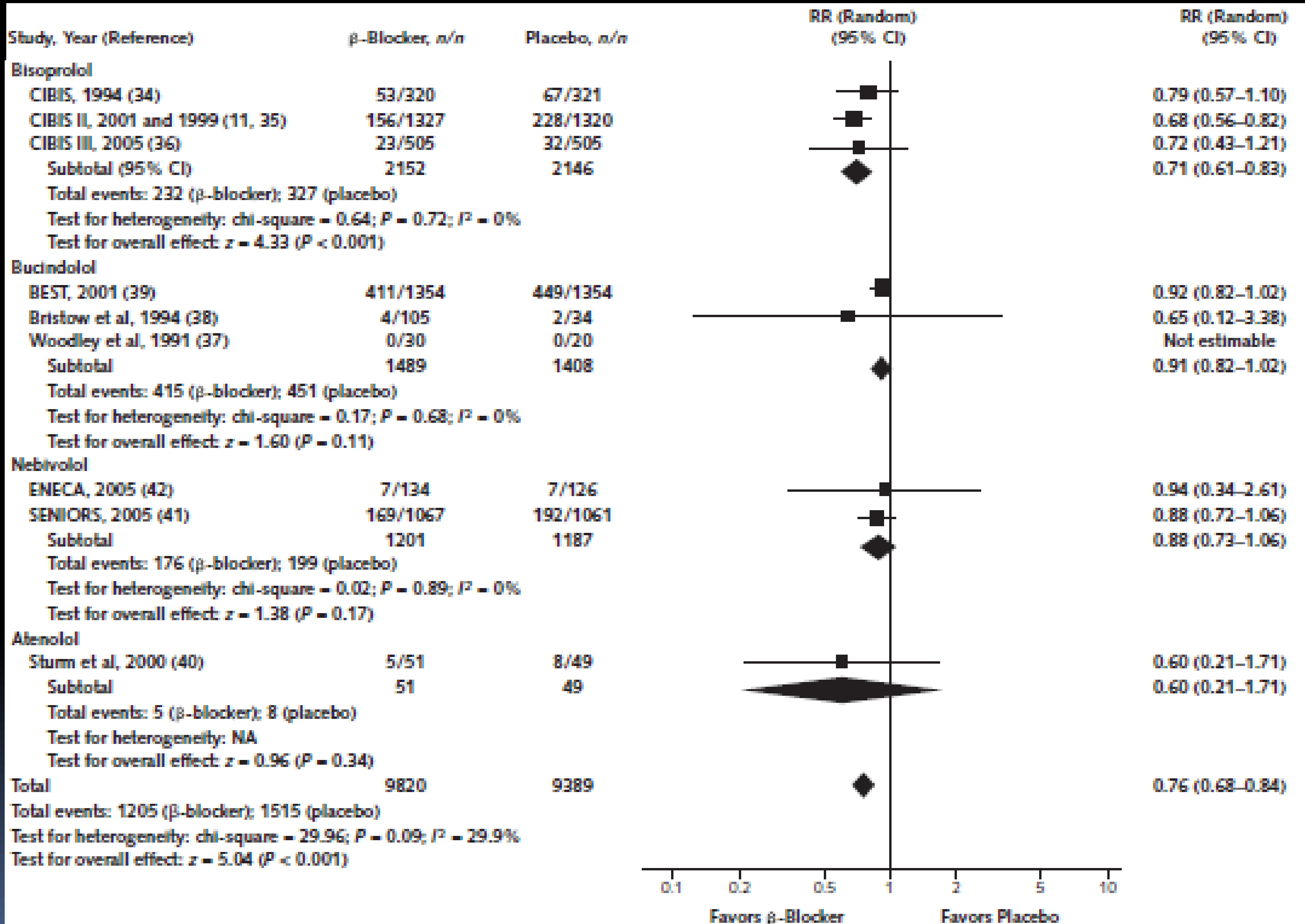
# Mortality Rate in BB Trials with HF Patients (1)




| Study, Year (Reference) | β-Blocker, n/n | Placebo, n/n | RR (Random) (95% CI) |
|---|---|---|---|
| **Metoprolol** | | | |
| Anderson et al, 1985 (19) | 5/25 | 6/25 | 0.83 (0.29–2.38) |
| Fisher et al, 1994 (21) | 1/25 | 2/25 | 0.50 (0.05–5.17) |
| MDC, 1993 (20) | 23/194 | 21/189 | 1.07 (0.61–1.86) |
| MERIT-HF, 2000 and 2002 (22, 23) | 145/1990 | 217/2001 | 0.67 (0.55–0.82) |
| RESOLVD, 2000 (24) | 8/214 | 17/212 | 0.47 (0.21–1.06) |
| Subtotal | 2448 | 2452 | 0.70 (0.58–0.83) |
| Total events: 182 (β-blocker); 263 (placebo) | | | |
| Test for heterogeneity: chi-square = 3.50; $P = 0.48$; $I^2 = 0\%$ | | | |
| Test for overall effect: $z = 3.93$ ($P < 0.001$) | | | |
| **Carvedilol** | | | |
| ANZ, 1997 (30) | 20/207 | 26/208 | 0.77 (0.45–1.34) |
| CARMEN, 2004 (33) | 14/191 | 14/190 | 0.99 (0.49–2.03) |
| CHRISTMAS, 2003 (32) | 8/193 | 6/194 | 1.34 (0.47–3.79) |
| Cohn et al, 1997 (29) | 2/70 | 2/35 | 0.50 (0.07–3.40) |
| Colucci et al, 1996 (26) | 2/232 | 5/134 | 0.23 (0.05–1.17) |
| COPERNICUS, 2001 (31) | 130/1156 | 190/1133 | 0.67 (0.54–0.83) |
| MOCHA, 1996 (28) | 12/261 | 13/84 | 0.30 (0.14–0.63) |
| Olsen et al, 1995 (25) | 1/36 | 0/24 | 2.03 (0.09–47.78) |
| Packer et al, 1996 (27) | 6/133 | 11/145 | 0.59 (0.23–1.56) |
| Subtotal | 2479 | 2147 | 0.66 (0.51–0.87) |
| Total events: 195 (β-blocker); 267 (placebo) | | | |
| Test for heterogeneity: chi-square = 10.00; $P = 0.27$; $I^2 = 20.0\%$ | | | |
| Test for overall effect: $z = 2.99$ ($P = 0.003$) | | | |

Mac Alliter . Ann Intern Med 2009 ; 150 : 784-794

# Mortality Rate in BB Trials with HF Patients (2)




Mac Alliter . Ann Intern Med 2009 ; 150 : 784-794

# Compelling Indications for Individual Drug Classes (1)

| Compelling Indication | Initial Therapy Options | Clinical Trial Basis |
| --- | --- | --- |
| **Heart failure** | **THIAZ, BB, ACEI, ARB, ALDO ANT** | **ACC/AHA Heart Failure Guideline, MERIT-HF, COPERNICUS, CIBIS, SOLVD, AIRE, TRACE, ValHEFT, RALES** |
| **Postmyocardial infarction** | **BB, ACEI, ALDO ANT** | **ACC/AHA Post-MI Guideline, BHAT, SAVE, Capricorn, EPHESUS** |
| **High CAD risk** | **THIAZ, BB, ACE, CCB** | **ALLHAT, HOPE, ANBP2, LIFE, CONVINCE** |

*2007 ESH/ESC Guidelines*

# Compelling Indications for Individual Drug Classes (2)

| Compelling Indication | Initial Therapy Options | Clinical Trial Basis |
|---|---|---|
| **Diabetes** | **THIAZ, BB, ACE, ARB, CCB** | **NKF-ADA Guideline, UKPDS, ALLHAT** |
| **Chronic kidney disease** | **ACEI, ARB** | **NKF Guideline, Captopril Trial, RENAAL, IDNT, REIN, AASK** |
| **Recurrent stroke prevention** | **THIAZ, ACEI** | **PROGRESS** |

*2007 ESH/ESC Guidelines*

Thank You