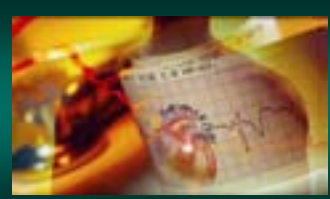


# Primary Care Summit In Cardiovascular Medicine

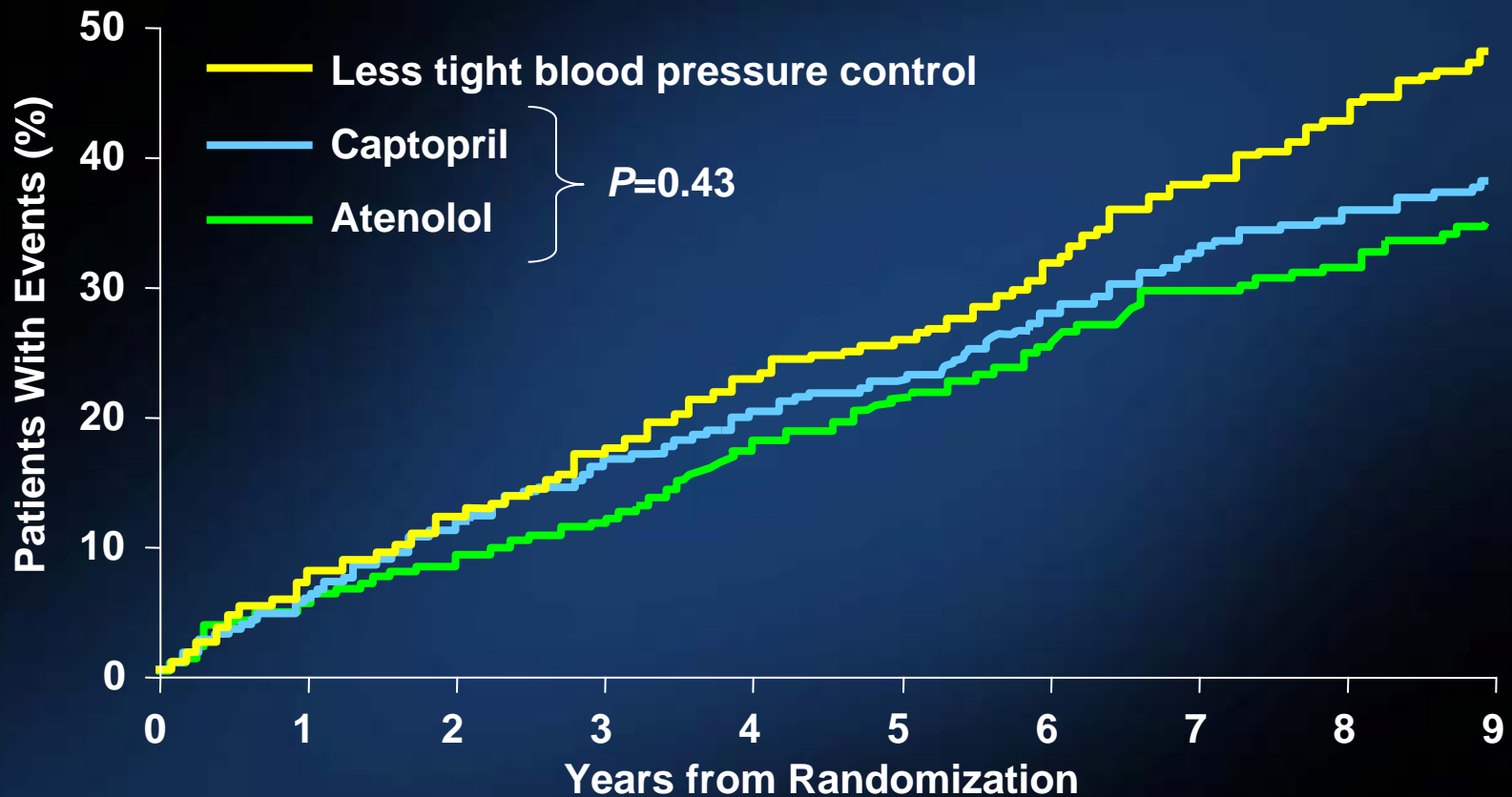
## The Role of $\beta_1$ Cardioselective Beta Blockers for Management of Hypertension and Related Cardiovascular Conditions

Elijah Saunders, M.D., FACC, FACP, FAHA  
Professor (Cardiology)  
Head, Section of Hypertension  
University of MD. School of Medicine



# Patients With Hypertension and Type 2 Diabetes

# Kaplan-Meier: Proportion of Patients with Any Diabetes-Related Endpoint



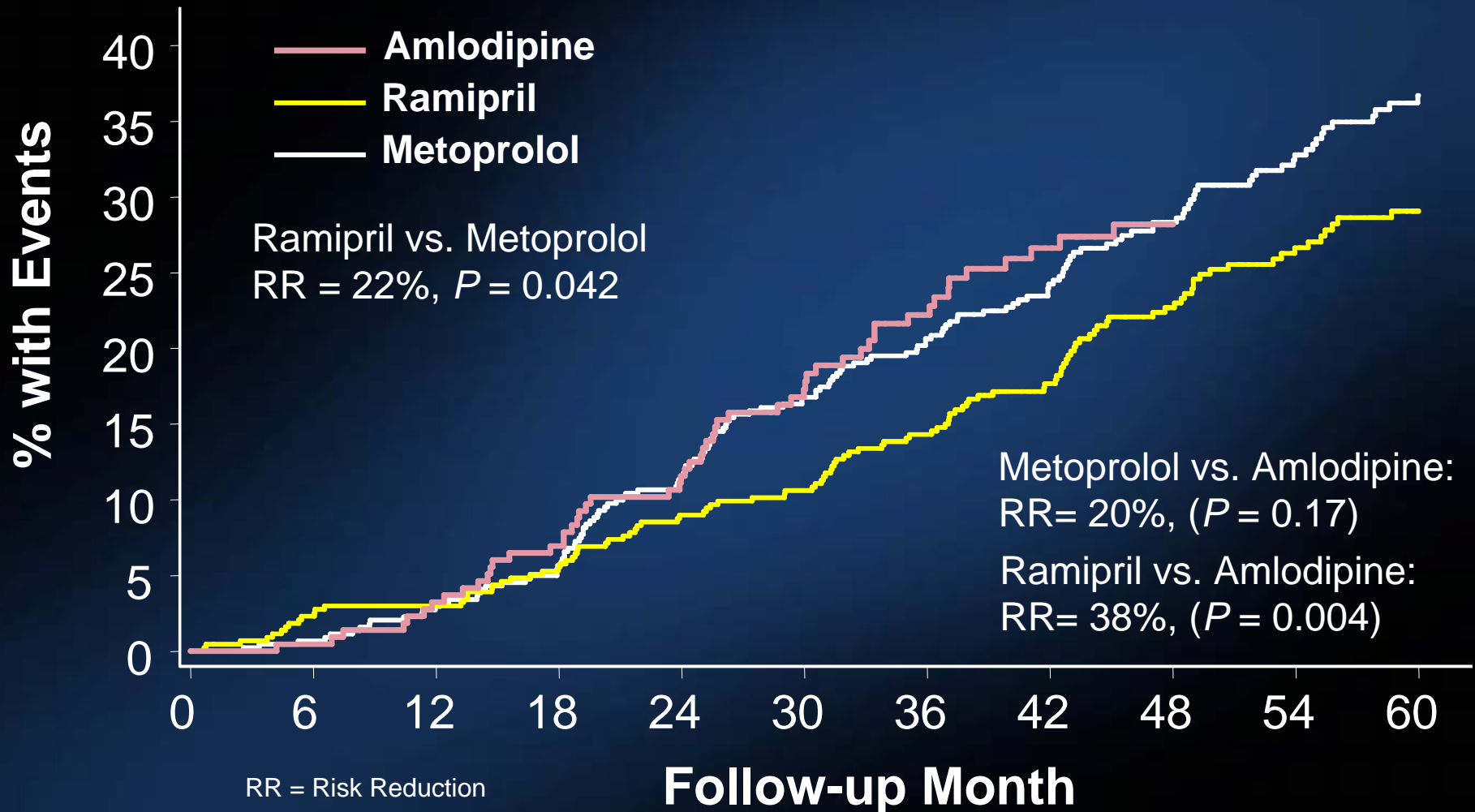
No. of patients at risk:

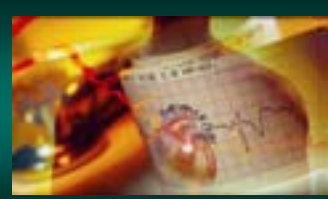
Captopril	400	327	257	124
Atenolol	358	314	237	112



# Patients With Hypertension and Renal Disease

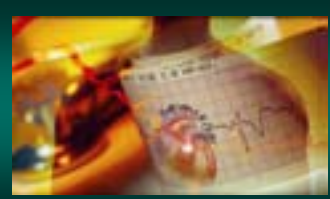
# Main Clinical Composite Outcome: Declining GFR Event, ESRD, or Death





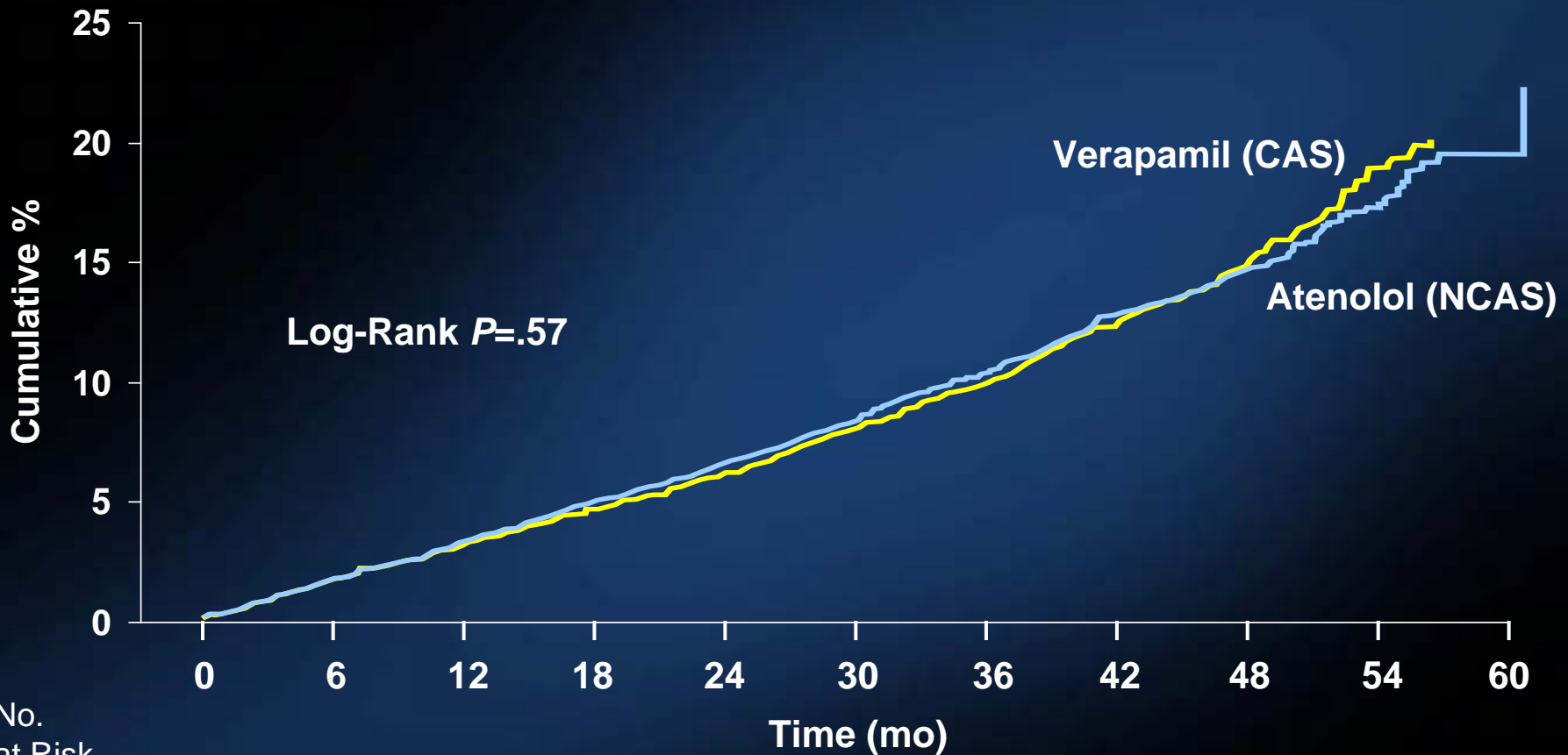
# AASK: Conclusions

- ▶ **Reducing BP to levels below current guidelines for CV risk reduction did not prevent progression of hypertensive nephrosclerosis in a cohort of African-Americans**
- ▶ **ACE inhibitors should be considered first-line therapy over  $\beta$ -blockers and calcium-channel blockers in this patient population; however, these type patients typically need between 3 and 4 drugs to effect blood pressure control.**



# Patients With Hypertension and CAD

# Primary Outcome by Treatment Strategy



No.  
at Risk

CAS	11267	10921	10716	10512	10008	6612	3738	1568	974	393	35
NCAS	11309	10991	10785	10536	10048	6604	3706	1563	960	390	33

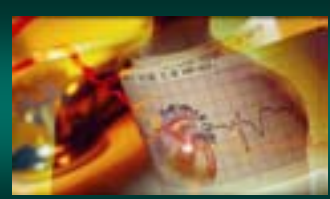


# Patients With Hypertension and Left Ventricular Hypertrophy



# LIFE: Conclusions

- ▶ **Losartan reduced the combined risk of CV morbidity and mortality compared to atenolol**
  - CV death, stroke or MI (-13%)
  - Strokes (-25%)
- ▶ **Losartan reduced the rate of new-onset diabetes (-13%)**
- ▶ **Among subjects with diabetes, losartan reduced CV morbidity and mortality**



# Post-MI Patients

# β-Blocker Trials in Post-MI Populations: Overview

	N	Active Drug	Average Follow-up (mo)	Mortality Active vs Placebo	% Relative Decrease
BHAT	3837	Propranolol 60 – 80 mg TID	25	7.2% vs 9.8%	26% (P<.005)
Gutenberg Metoprolol Trial	1395	Metoprolol 100 mg Q12h	3	5.7% vs 8.9%	36% (P<.03)
Norwegian Propranolol Study	560	Propranolol 40 mg QID	12	9.0% vs 13.1%	31% (P=.11)
Norwegian Timolol Trial	1884	Timolol 10 BID	33	10.6% vs 17.5%	39.4% (P=.0005)
APSI	607	Acebutolol 200 mg BID	10	5.7% vs 11.0%	48% (P=.019)
CAPRICORN	1959	Carvedilol 25 mg BID	16	12% vs 15%	23% (P=.031)

BHAT. *JAMA*. 1982;247:1707-1714.

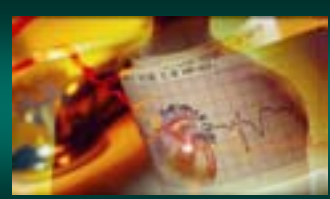
Boissel J-P, et al. *Am J Cardiol*.

Hjalmarson A, et al. *Circulation*. 1983;67(6 pt 2):I26-I32.

Hansteen V, et al. *Circulation*. 1983;67(6 pt 2):I57-I60. 1990;66(9):24C-31C.

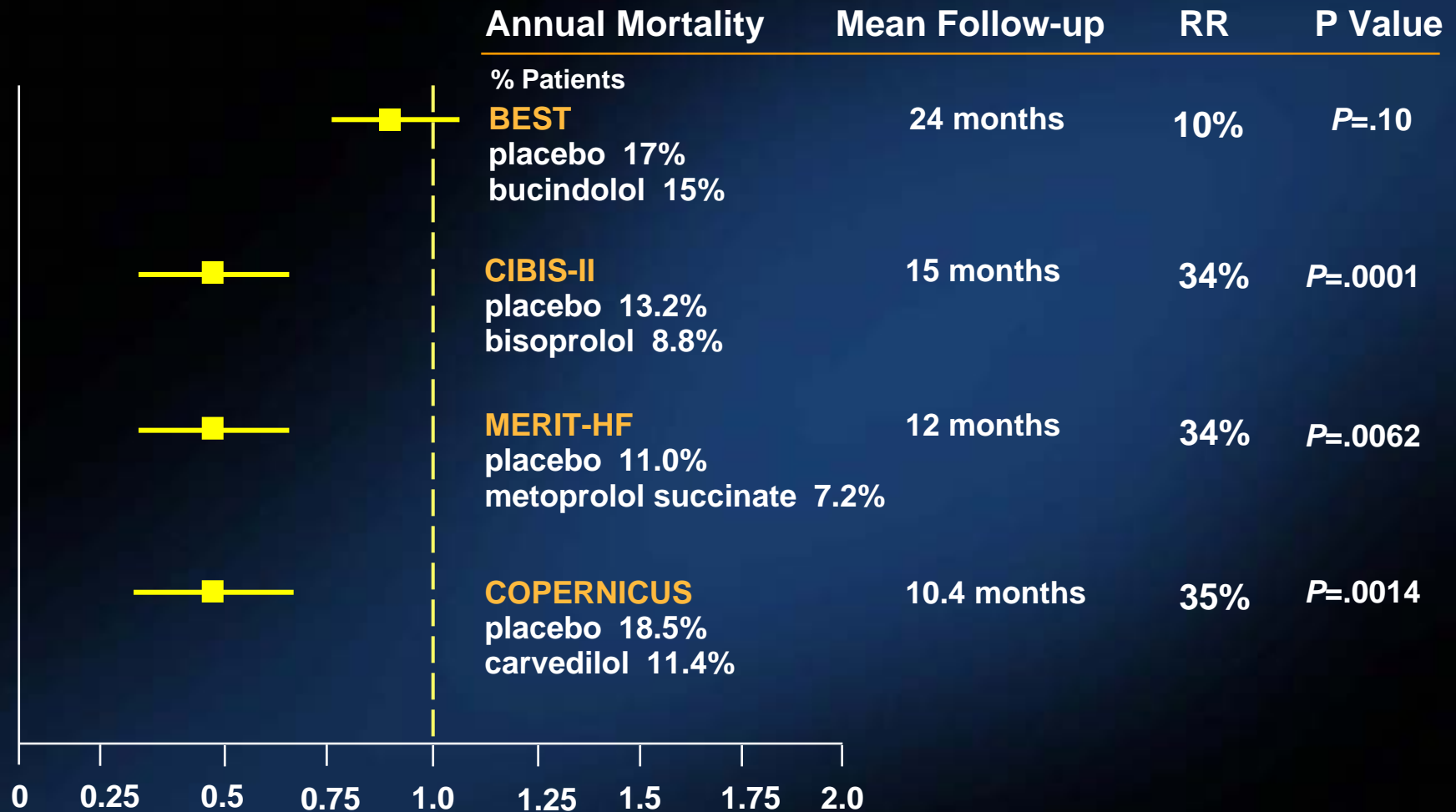
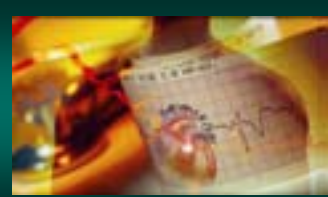
CAPRICORN Investigators. *Lancet*. 2001;357:1385-1390.

Norwegian Multicenter Study Group. *N Engl J Med*. 1981;304:801-807.



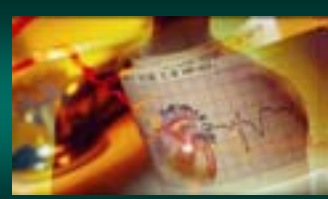
# Heart Failure Patients

# β-Blocker Trials in Heart Failure: Overview



Relative Risk and 95% Confidence Intervals

*Lancet.* 1999;353:2001-2007; CIBIS II Investigator and Committees. *Lancet.* 1999;353:9-13; Packer M et al. *N Engl J Med.* 2001;344:1651-1658; Beta-blockers Evaluation Survival Trial Investigators. *N Engl J Med.* 2001;344:1659-1667.



# Effectiveness of $\beta$ -blockers in Preventing CV Events: Evidence from Recent Meta-Analyses

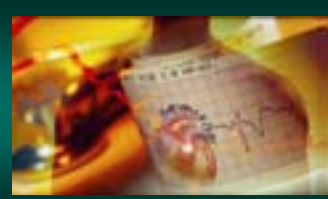


# 2004 Meta-Analysis of Outcomes: Atenolol vs. Other Antihypertensive Treatments

- ▶ **Analysis of 5 studies: Atenolol versus other antihypertensive therapy**
- ▶ **17,671 patients included, with a mean follow-up of 4.6 years**
- ▶ **No differences in BP lowering**

	Risk Reduction (95% CI)
All-Cause Mortality	1.13 (1.02–1.25)
CV Mortality	1.16 (1.00–1.34)
Myocardial Infarction	1.04 (.89–1.20)
Stroke	1.30 (1.12–1.50)

Trials included in meta-analysis: MRC Old (Medical Research Council Trial of Treatment of Hypertension in Older Adults); UKPDS (United Kingdom Prospective Diabetes Study); ELSA (European Lacidipine Study of Atherosclerosis); HAPPHY (The Heart Attack Primary Prevention in Hypertension Trial); LIFE (The Losartan Intervention for Endpoint Reduction Study).



# Meta-Analyses of Atenolol vs. Other Antihypertensive Agents: Summary

**When data from CONVINCe, INVEST and ASCOT are added to 2004 analysis:**

- ▶ Atenolol still has significantly higher risk for all-cause mortality and stroke than other antihypertensive therapy
- ▶ Based on these findings, previous advisory comments about the use of atenolol as initial therapy for hypertension still appear to be warranted



# $\beta$ -blockers vs. Other Antihypertensive Treatments: Outcomes

Endpoint	$\beta$ -blocker n/N	Other Drug n/N	RR (95% CI)
Stroke	1650/51963	1594/53882	1.16 (1.31-3.95)
Myocardial Infarction	1935/51963	2042/53882	1.02 (0.93-1.12)
Mortality for All Causes	3525/52016	3766/53935	1.03 (0.99-1.08)



# Atenolol vs. Other Antihypertensive Treatments: Outcomes

Endpoint	$\beta$ -blocker n/N	Other Drug n/N	RR (95% CI)
Stroke	1019/28132	810/28169	1.26 (1.15-1.38)
Myocardial Infarction	1216/28132	1167/28169	1.05 (0.91-1.21)
Mortality for All Causes	2387/28132	2216/28169	1.08 (1.02-1.14)



# Effectiveness of $\beta$ -blockers in Reducing CV Events in the Elderly: Recent Meta-Analyses



# Khan Meta-Analysis: Overview

- ▶ **Design:** Meta-analysis comparing the efficacy of  $\beta$ -blockers in different age groups
  - N=145,811 subjects
- ▶ **Trials:** 21 randomized trials evaluating efficacy of  $\beta$ -blockers as first-line therapy in preventing CV outcomes
  - Trials enrolling older pts (mean age  $\geq 60$  yrs) separated from those enrolling younger pts (mean age  $< 60$  yrs)
- ▶ **Primary outcomes:**
  - Composite of stroke, MI and death



# Beta-Blockers vs. Other Antihypertensive Drugs: Composite Outcome\*

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

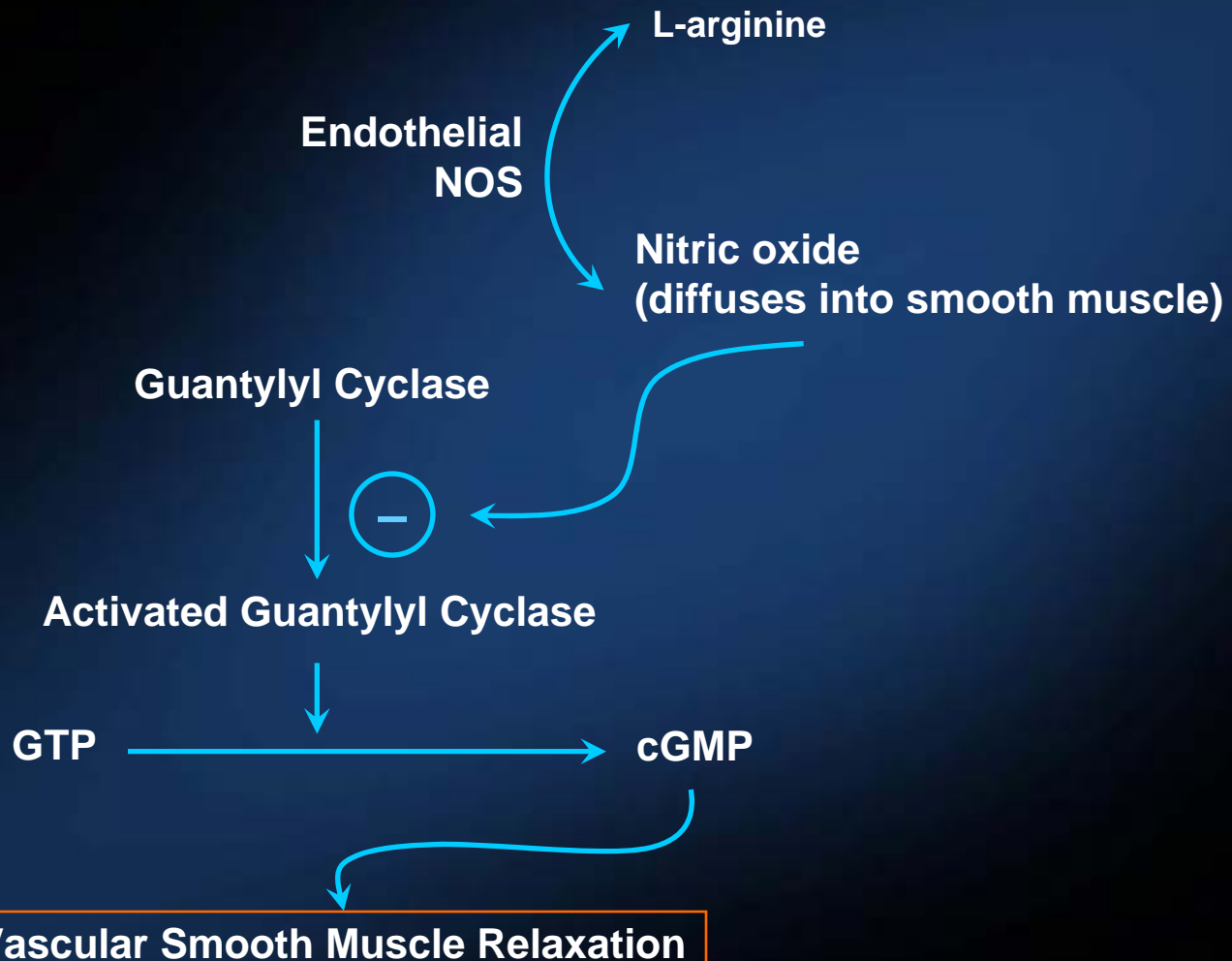
\*Death, stroke or MI



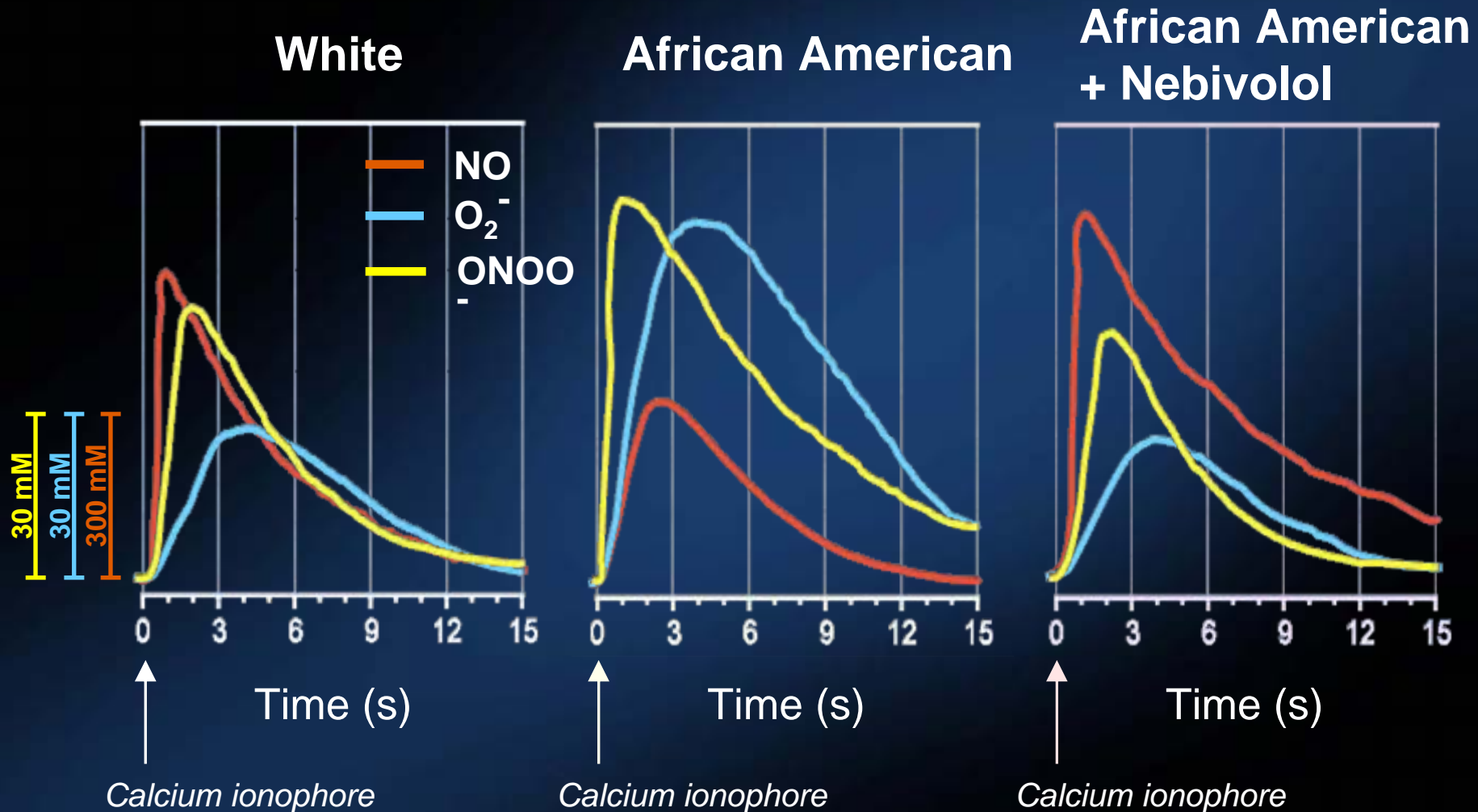
# Nebivolol: Potential Benefits of Nitric Oxide Potentiation

- ▶ **Endothelial dysfunction is:**
  - A key marker of atherosclerosis
  - Characterized by reduced nitric oxide bioactivity
- ▶ **Nebivolol has been shown to enhance nitric oxide bioactivity and improve endothelial function**
- ▶ **This effect may explain the cardioprotective benefits of the vasodilating  $\beta$ -blocker nebivolol**

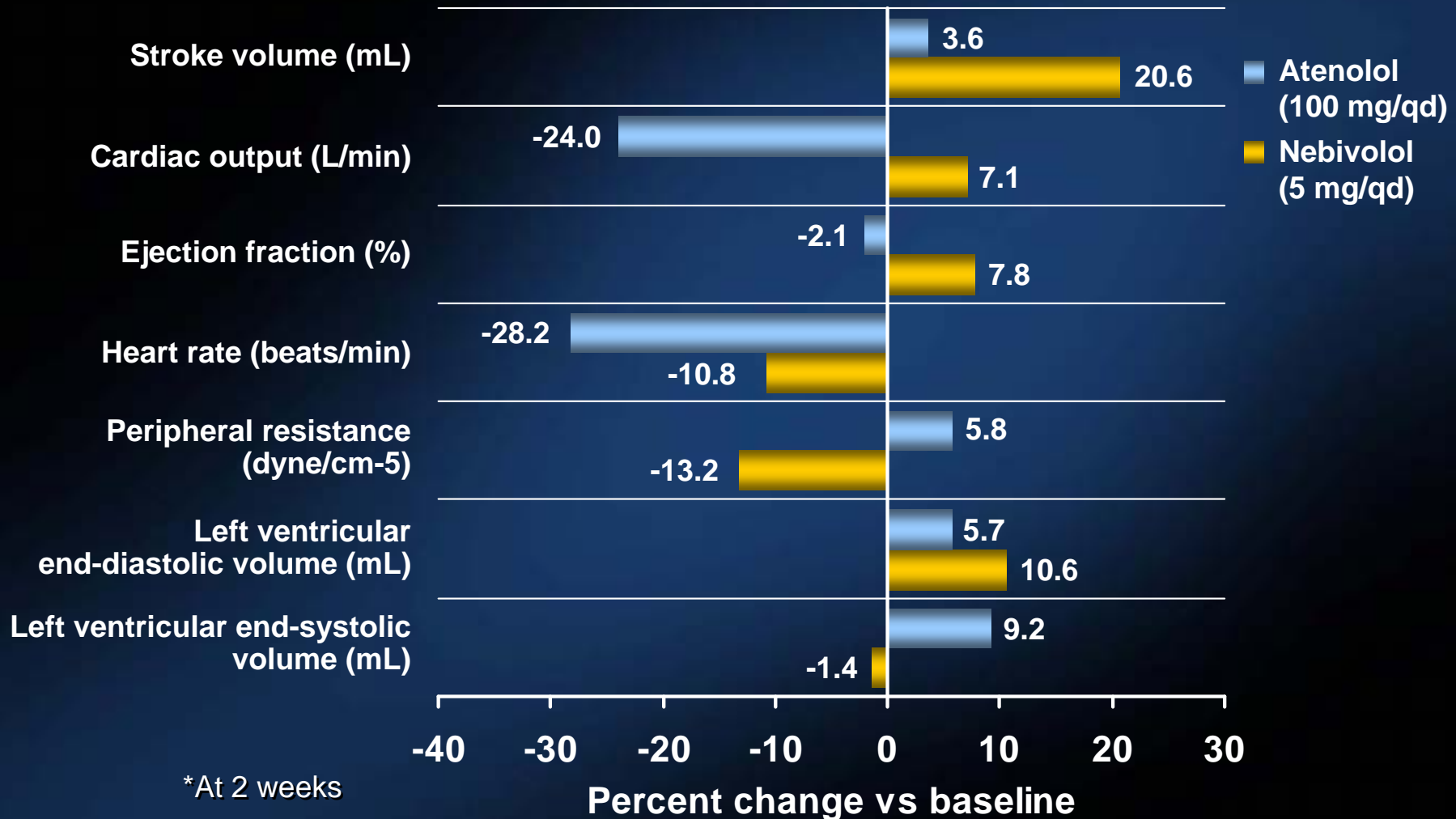
# Vascular Relaxation via the L-arginine–Nitric-Oxide Pathway

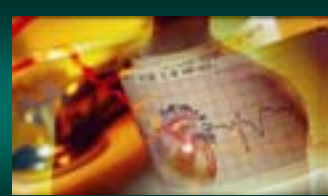


# Release of Nitric Oxide from Human Endothelium: White and African Americans



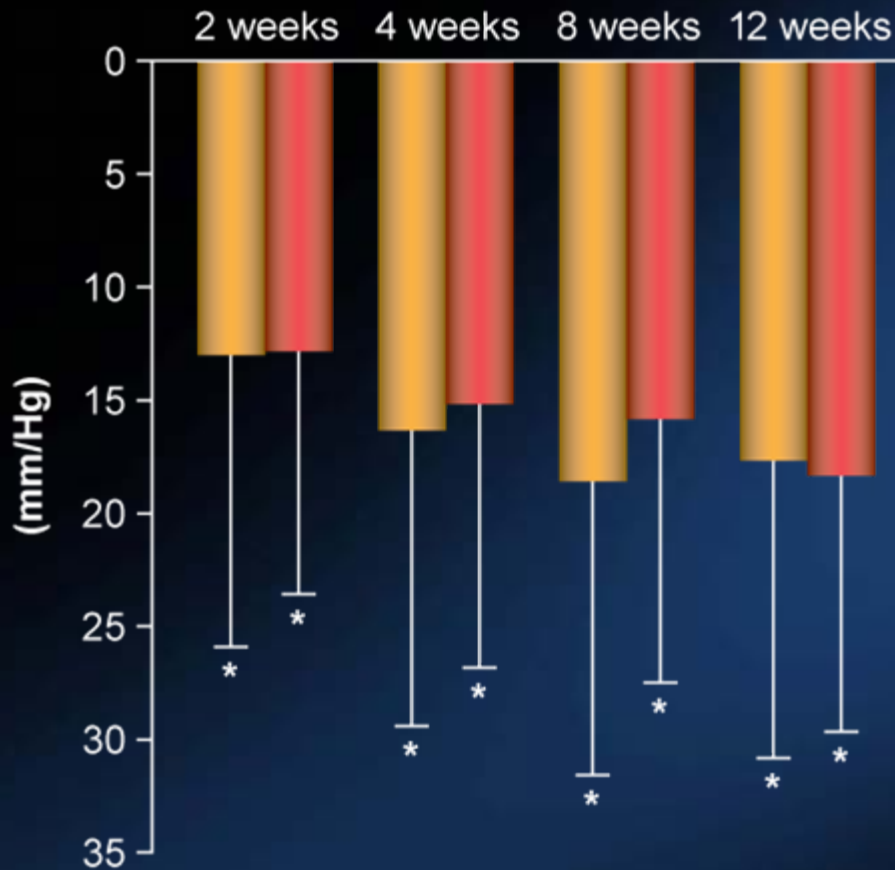
# Hemodynamic Effects of Nebivolol and Atenolol in Patients with Hypertension\*



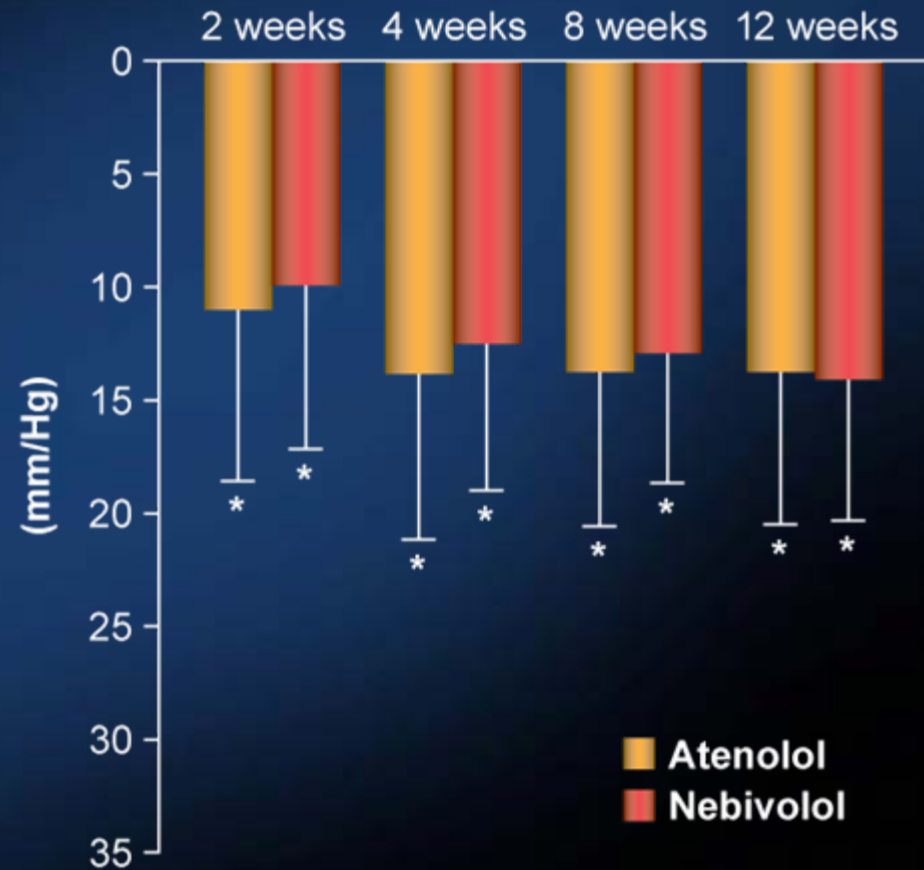


# Changes in Systolic and Diastolic Blood Pressure Measured in Sitting Position

## Systolic Blood Pressure



## Diastolic Blood Pressure



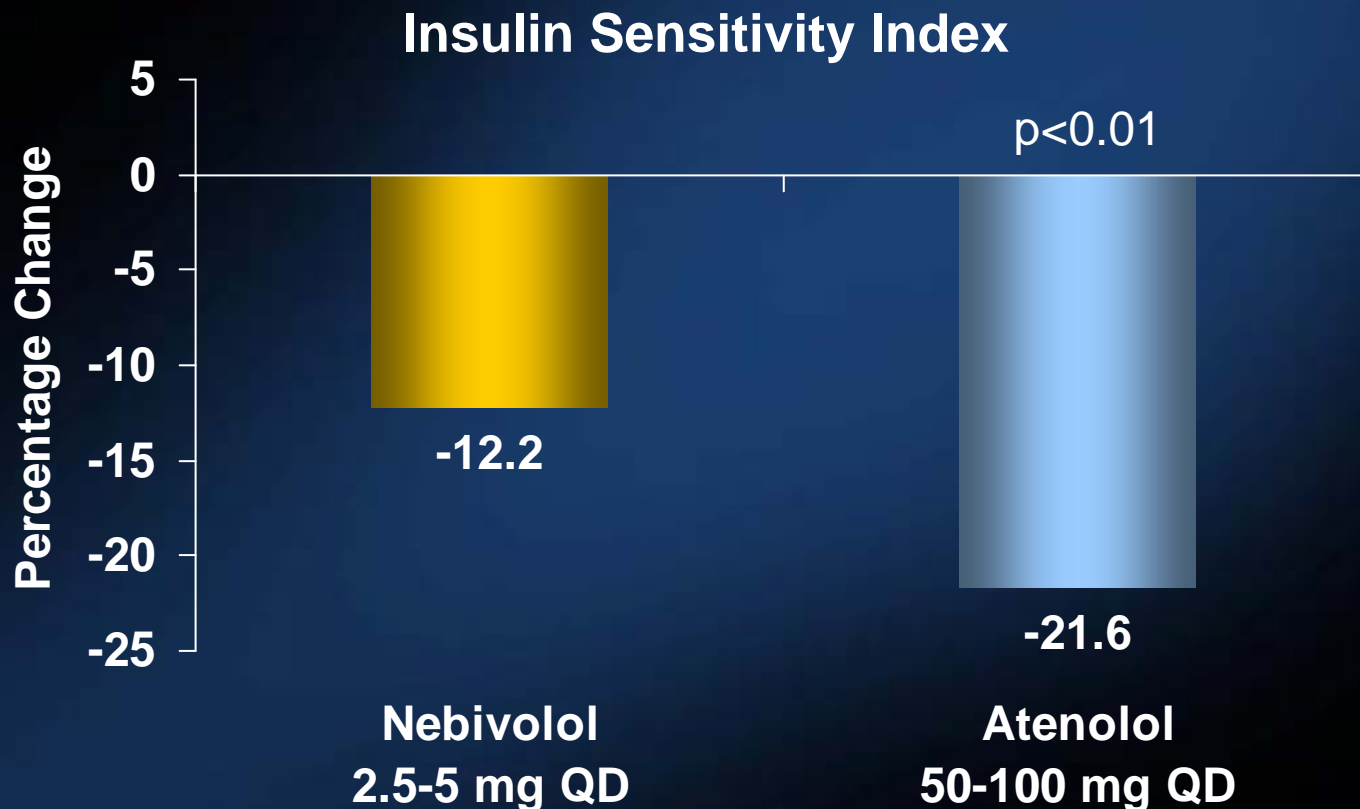
■ Atenolol  
■ Nebivolol

Efficacy and Tolerability Profile of Nebivolol vs Atenolol in Mild-to-moderate Essential Hypertension: Results of a Double-blind Randomized Multicentre Trial. Guido Grassi et al. *Blood Pressure*. 2003;12(Suppl 2):35–40

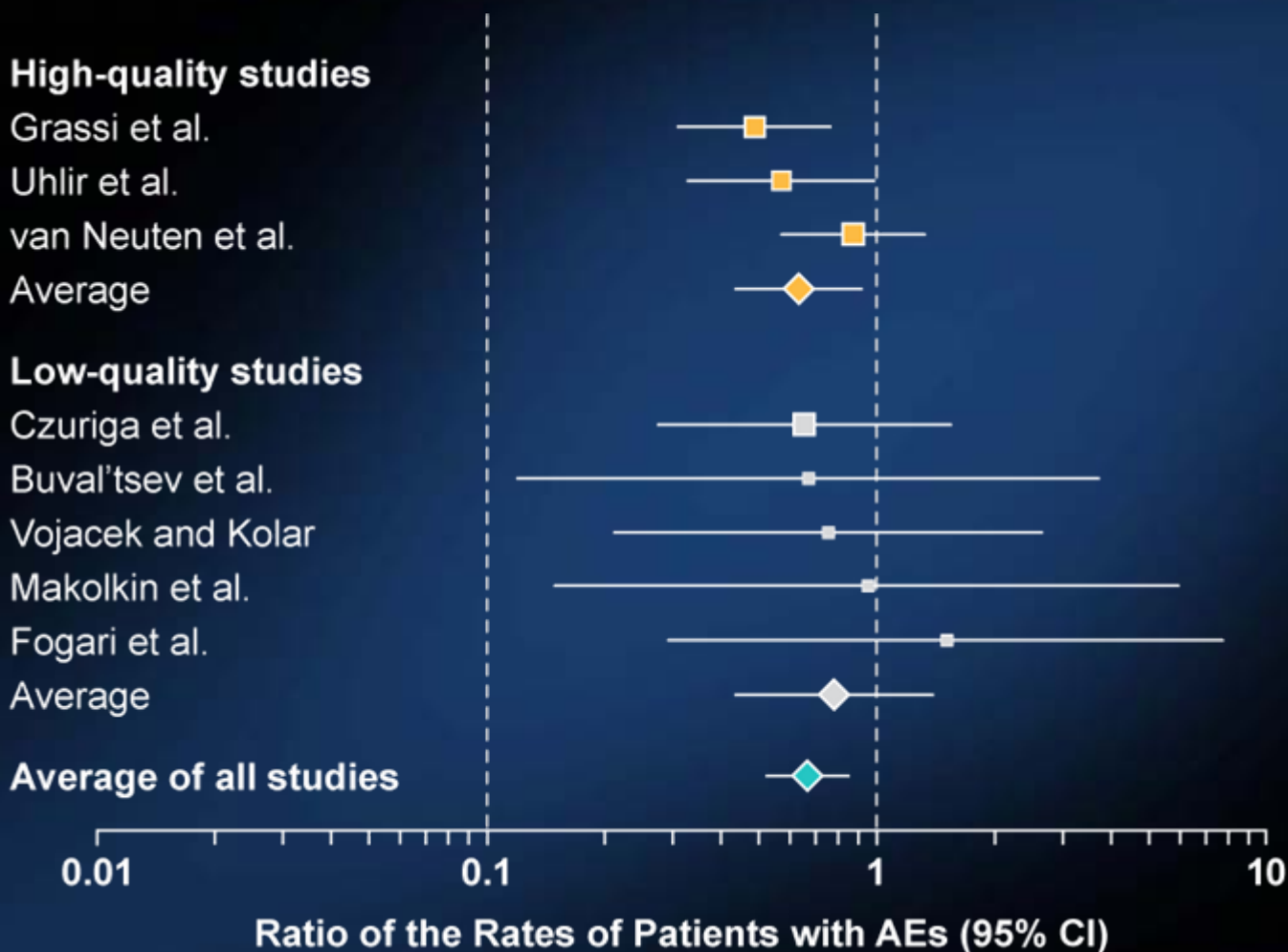


# Insulin Resistance: Effect of Nebivolol vs. Atenolol

36-week Randomized, Double-blind Crossover Design  
n = 25



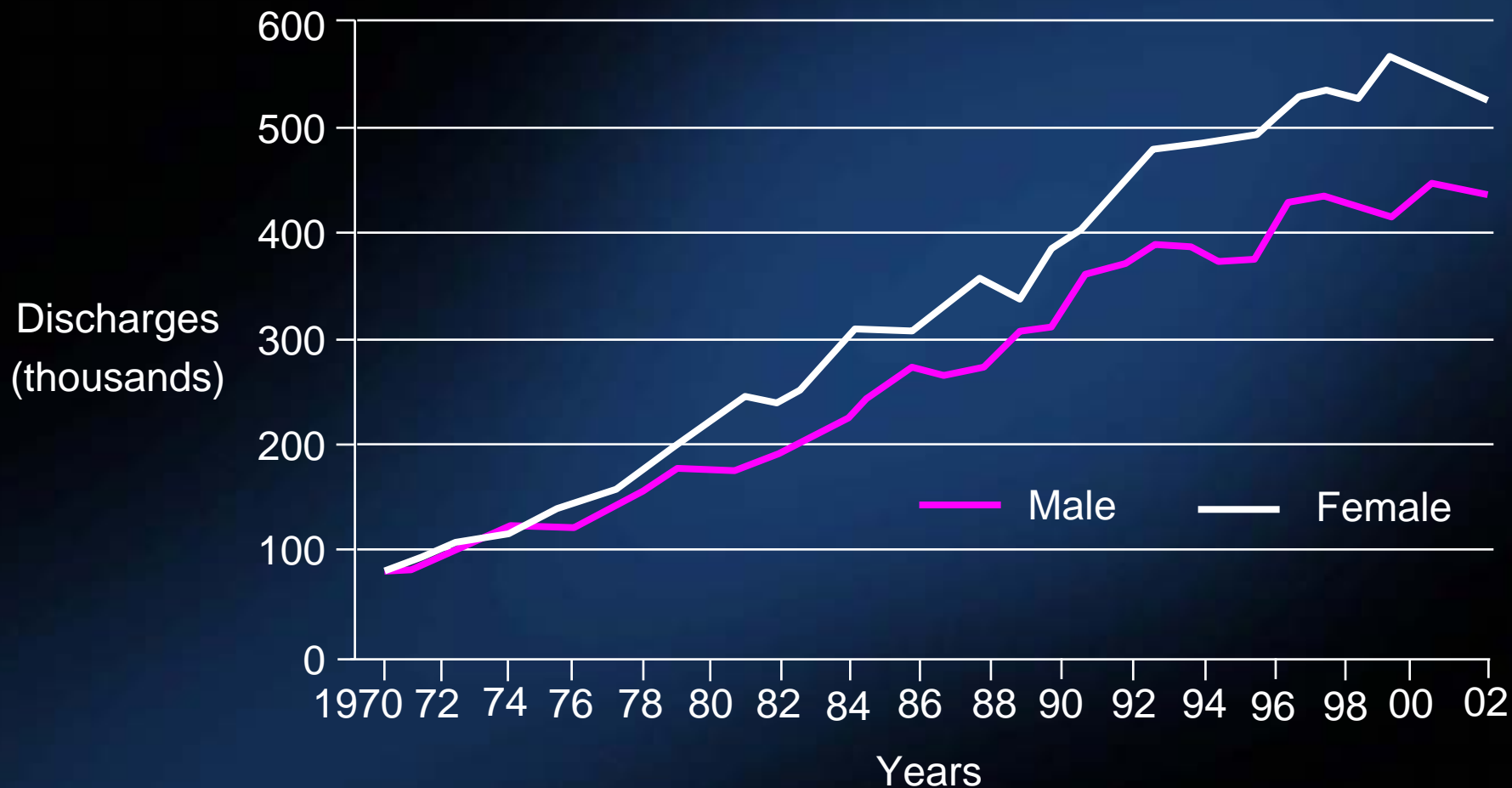
# Ratio of the Rates of Patients with AEs in Randomized Clinical Trials of Nebivolol vs Other Cardiovascular $\beta$ -Blockers in the Treatment of Hypertension





# Hospital Discharges\* for Chronic Heart Failure by Sex

**United States: 1970-2002**



\*Hospital discharges include people both living and dead

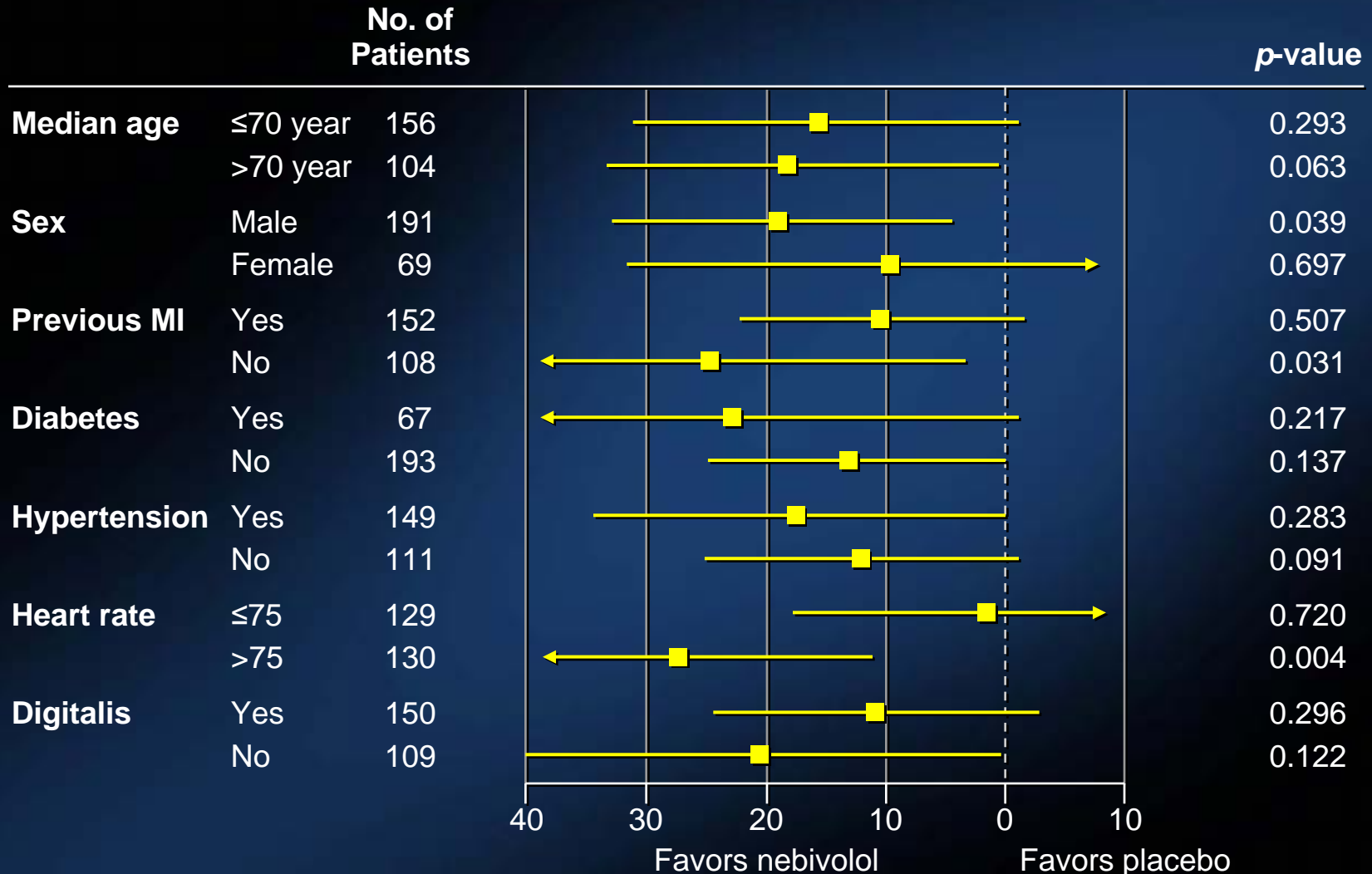
American Heart Association. *Heart Disease and Stroke Statistics — 2005 Update*



# ENECA STUDY-Aim

- ▶ **To examine the effects of the beta<sub>1</sub>-selective beta-blocker nebivolol, administered as add-on therapy, on left ventricular function in 260 elderly patients (>65 years) with chronic heart failure (CHF).**

# Relative Change in LVEF (%)



Effects of nebivolol on left ventricular function in elderly patients with chronic heart failure: results of the ENECA study. Istvan Edes, Zbigniew Gasior, Krystian Wita. *The European Journal of Heart Failure*. 2005;7:631–639.



# SENIORS: Inclusion Criteria

- ▶ **Age  $\geq 70$  years**
  
- ▶ **A clinical diagnosis of chronic HF and either**
  - a) **documented LVEF  $\leq 35\%$  within previous 6 months**
  - or**
  - b) **hospital admission within previous year for HF**
  
- ▶ **Written consent prior to enrollment into the study**

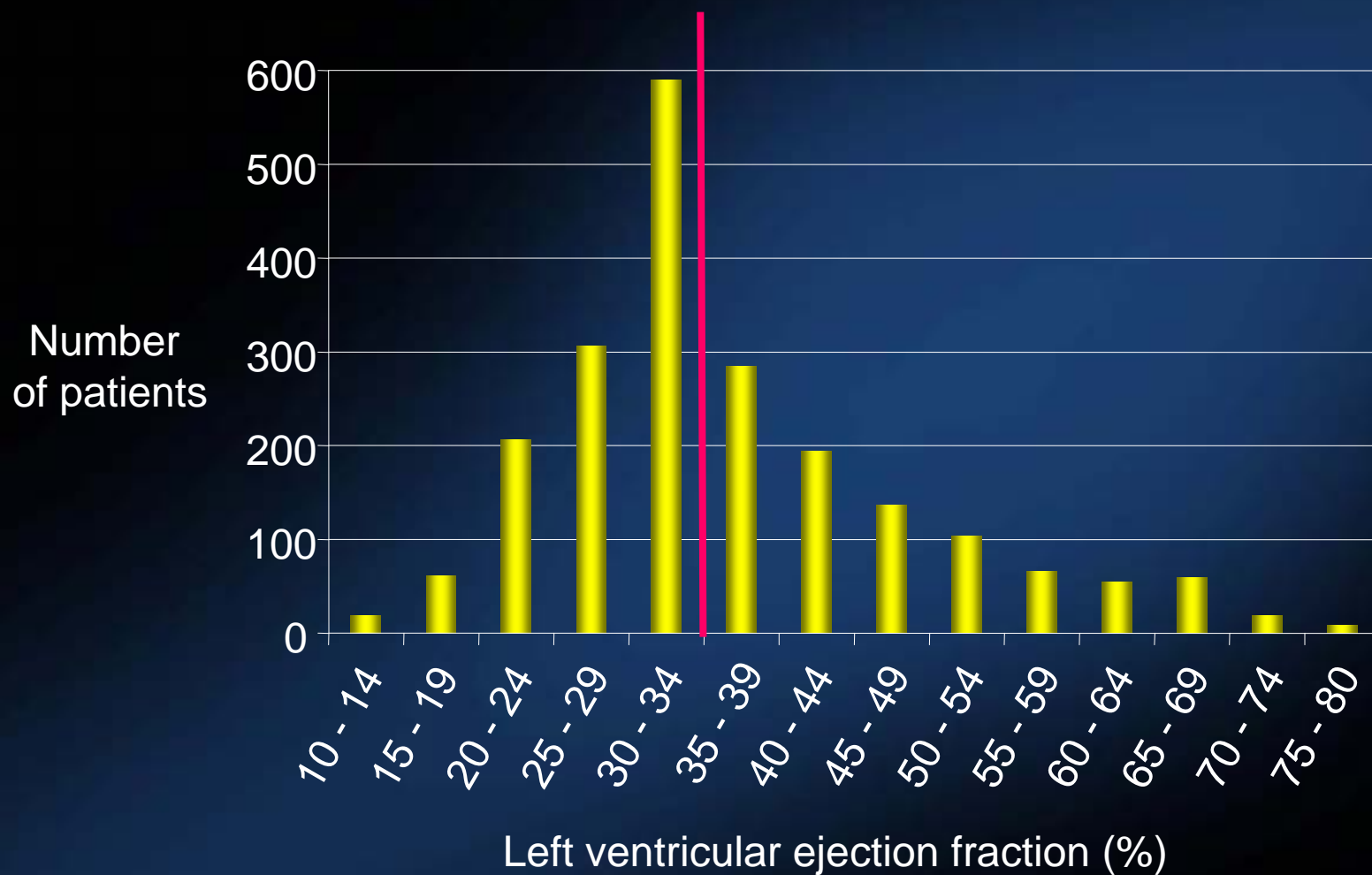


# SENIORS: Baseline Characteristics

	Nebivolol (n=1067)	Placebo (n=1061)
<b>Mean age (years)</b>	76.1	76.1
<b>Male, n (%)</b>	657 (61.6)	686 (64.7)
<b>LVEF <math>\leq</math>35%, n (%)</b>	683 (64.3)	686 (64.8)
<b>Mean LVEF (%)</b>	36.0 (13)	36.0 (12)
<b>NYHA Class, n (%)</b>		
I	32 (3.0)	29 (2.7)
II	603 (56.5)	597 (56.3)
III	413 (38.7)	411 (38.7)
IV	19 (1.8)	24 (2.3)
<b>SiBP (mm Hg)</b>	138.6/80.5	139.5/80.6

NYHA, New York Heart Association; SiBP, sitting blood pressure.

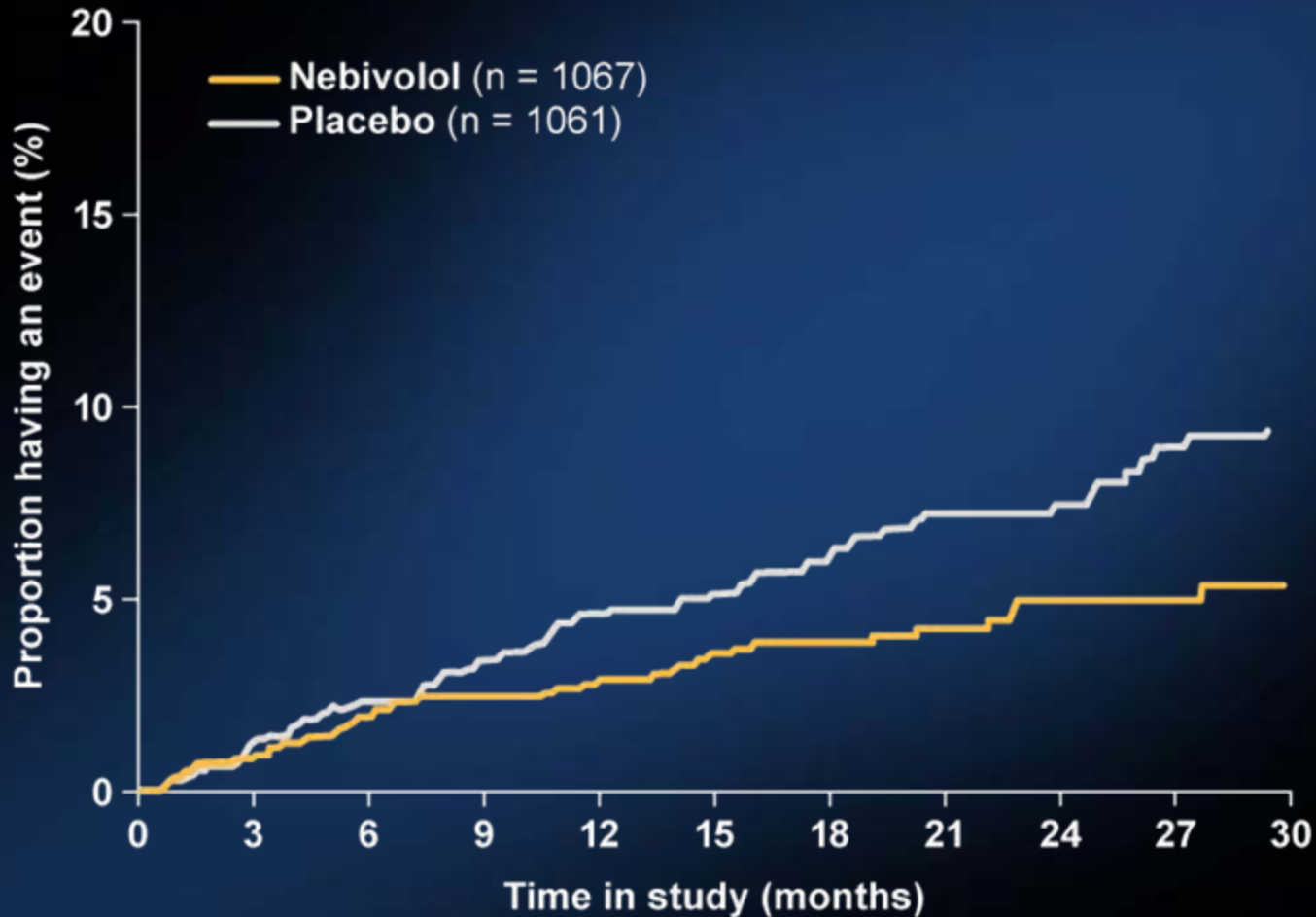
# SENIORS: Distribution of LVEF



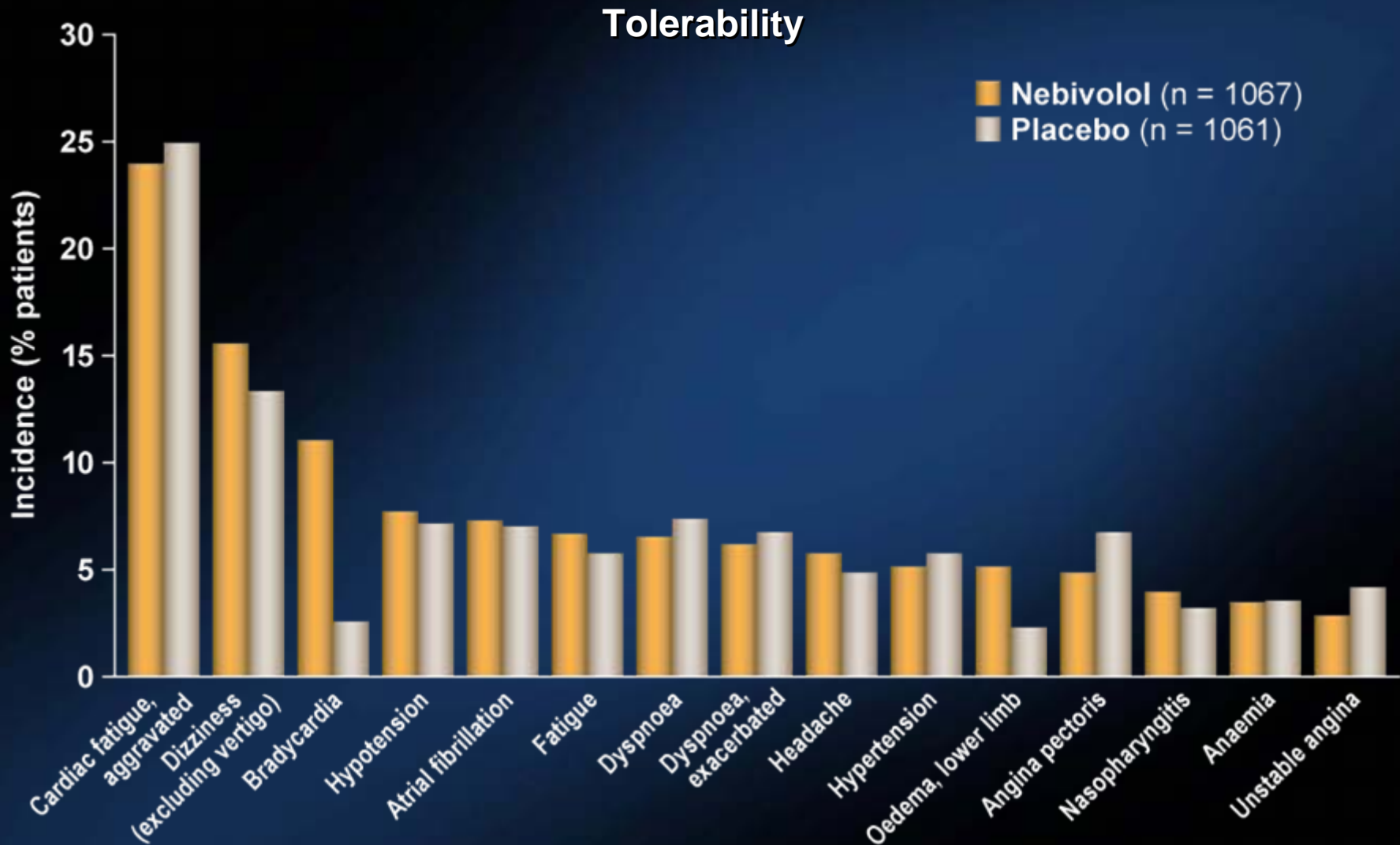
# Effect of Nebivolol on Time to Sudden Cardiac Death in SENIORS



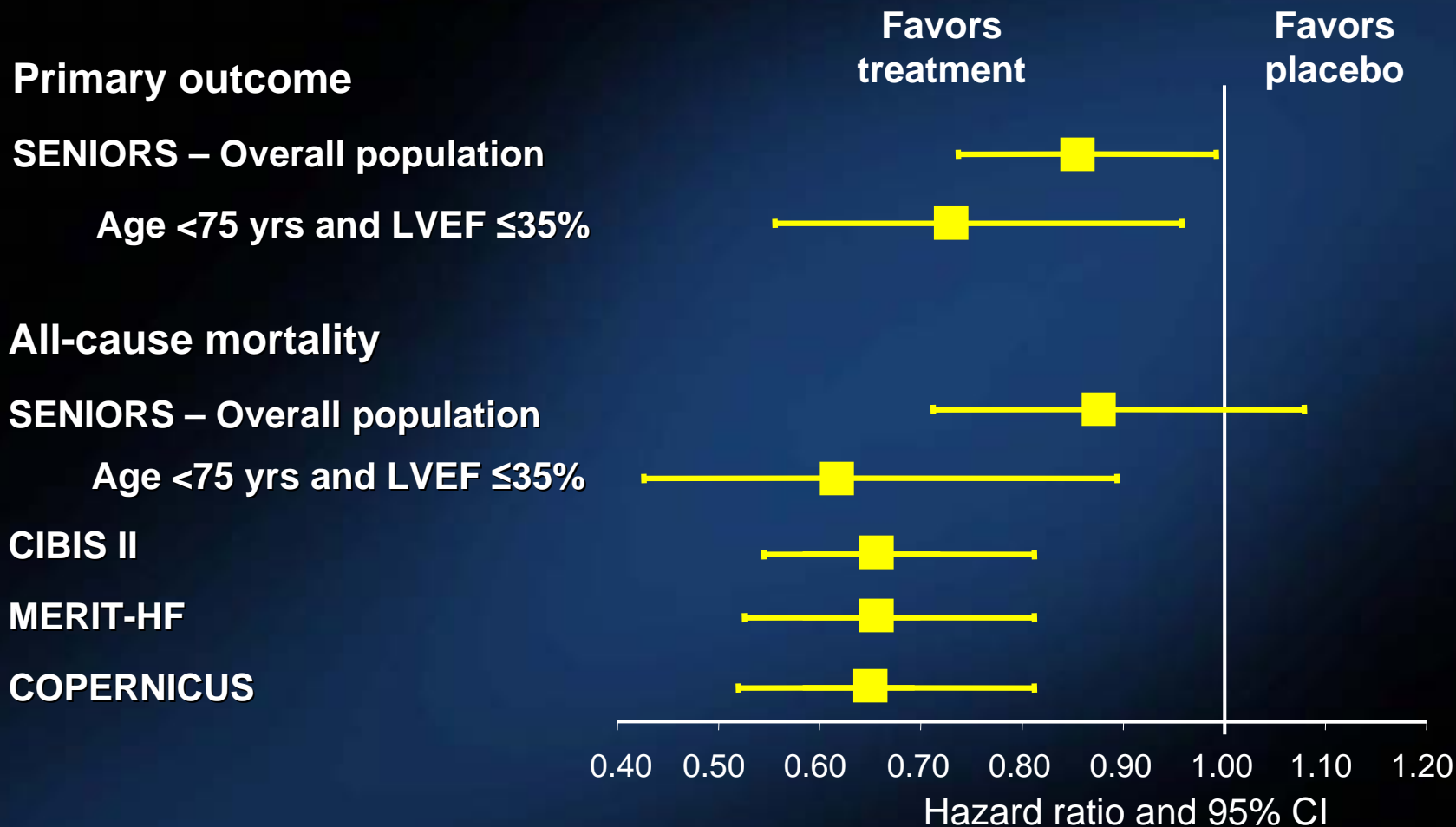
## General Tolerability



# Tolerability Profile of Nebivolol in SENIORS



# SENIORS vs Other $\beta$ -Blocker HF Trials

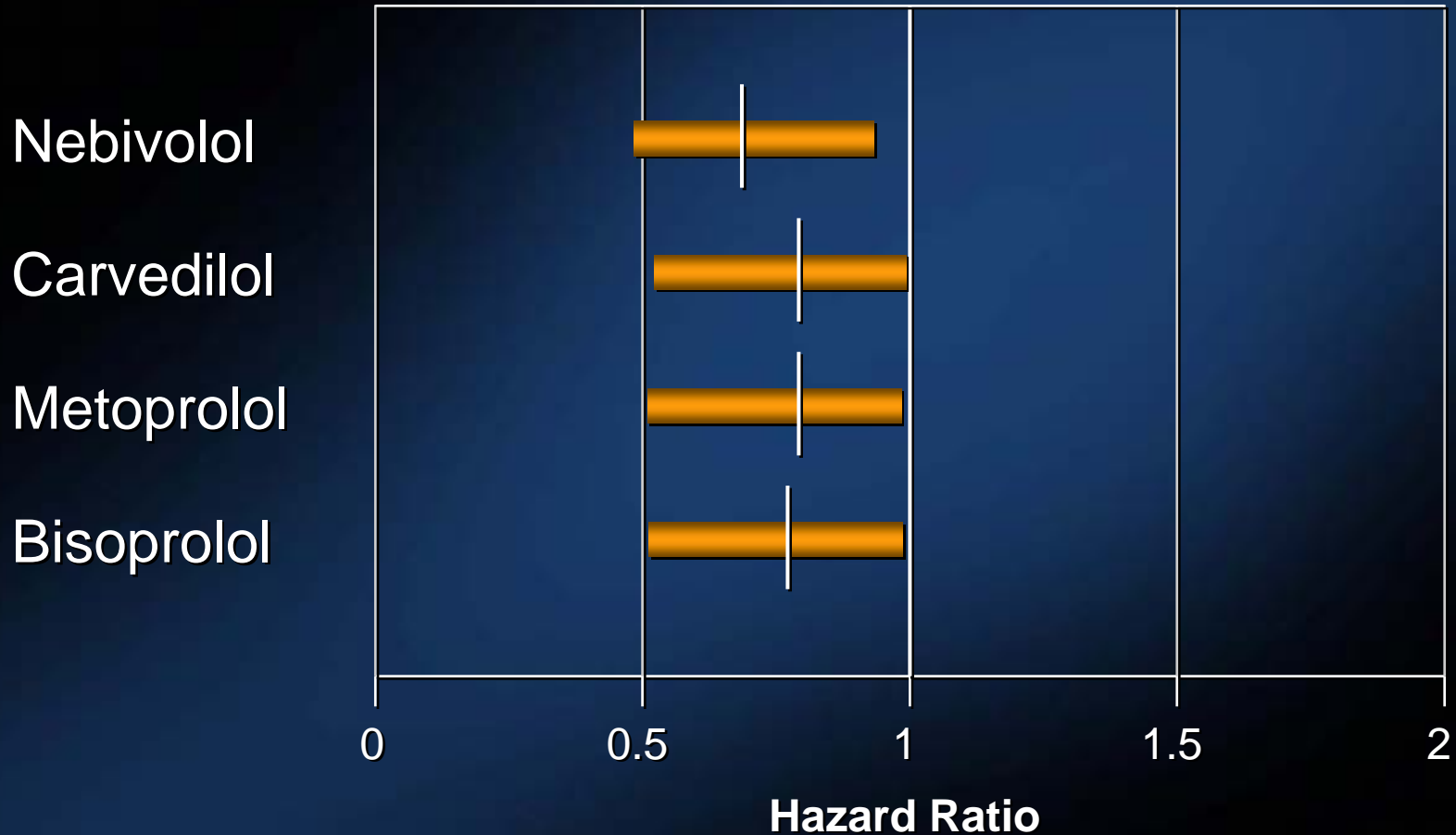


CIBIS-II Investigators and Committees. *Lancet*. 1999;353:9-13. Flather MD et al. *Eur Heart J*. 2005;26:215-225. Packer M et al. *N Engl J Med*. 2001;344:1651-1658. Packer M et al. *Circulation*. 2002;106:2194-2199. Hjalmarson A et al. *JAMA*. 2000;283:1295-1302. MERIT-HF Study Group. *Lancet*. 1999;353:2001-2007



# Hazard Ratio Plots for Total Mortality for Comparable Patient Subgroups

## $\beta$ -Blocker Trials





# CONCLUSIONS

- ▶ **Beta blockers are not all created equal**
- ▶ **Third generation, cardioselective beta blockers may produce clinical outcomes that differ from those that derive from traditional beta-blocker therapy**
- ▶ **These effects may be linked to nitric oxide production and/or other hemodynamic effects**
- ▶ **Ongoing trials will help differentiate indications, clinical roles, and optimal strategies for beta-blockers**

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—A Year 2007, Screen and Intervene Hypertension and Cardiovascular Disease Update



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