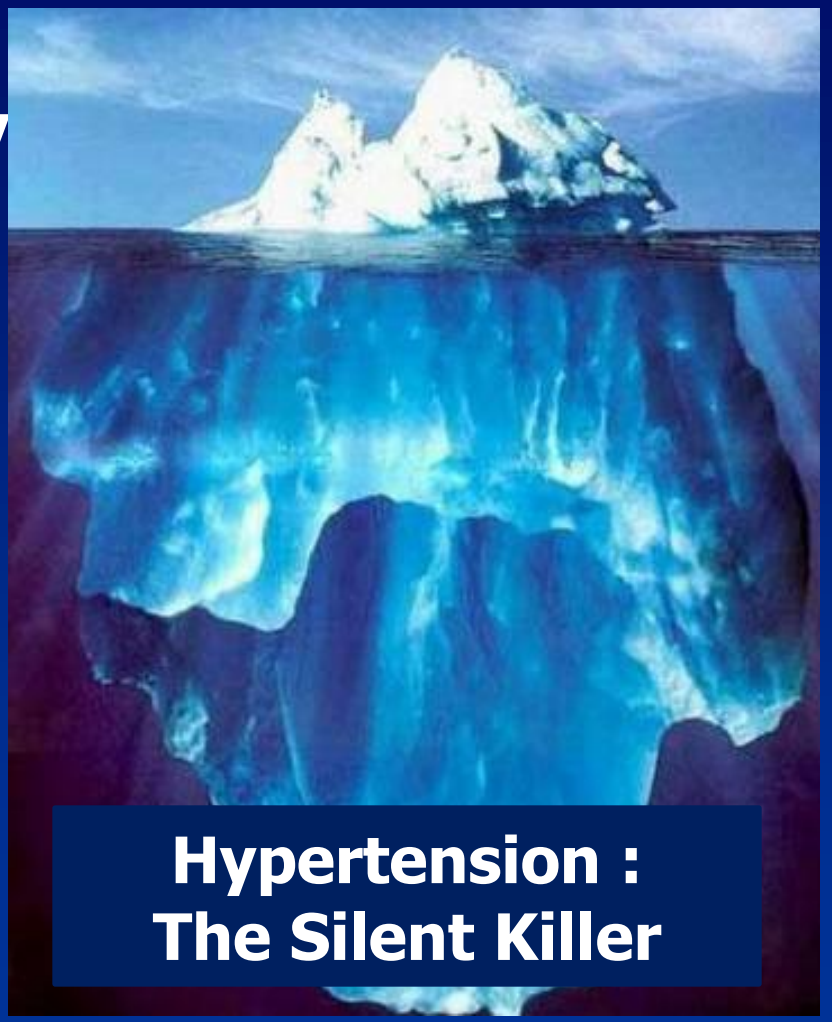
The Role of β1 Cardioselective Beta Blockers for Management of Hypertension and Related CV Conditions

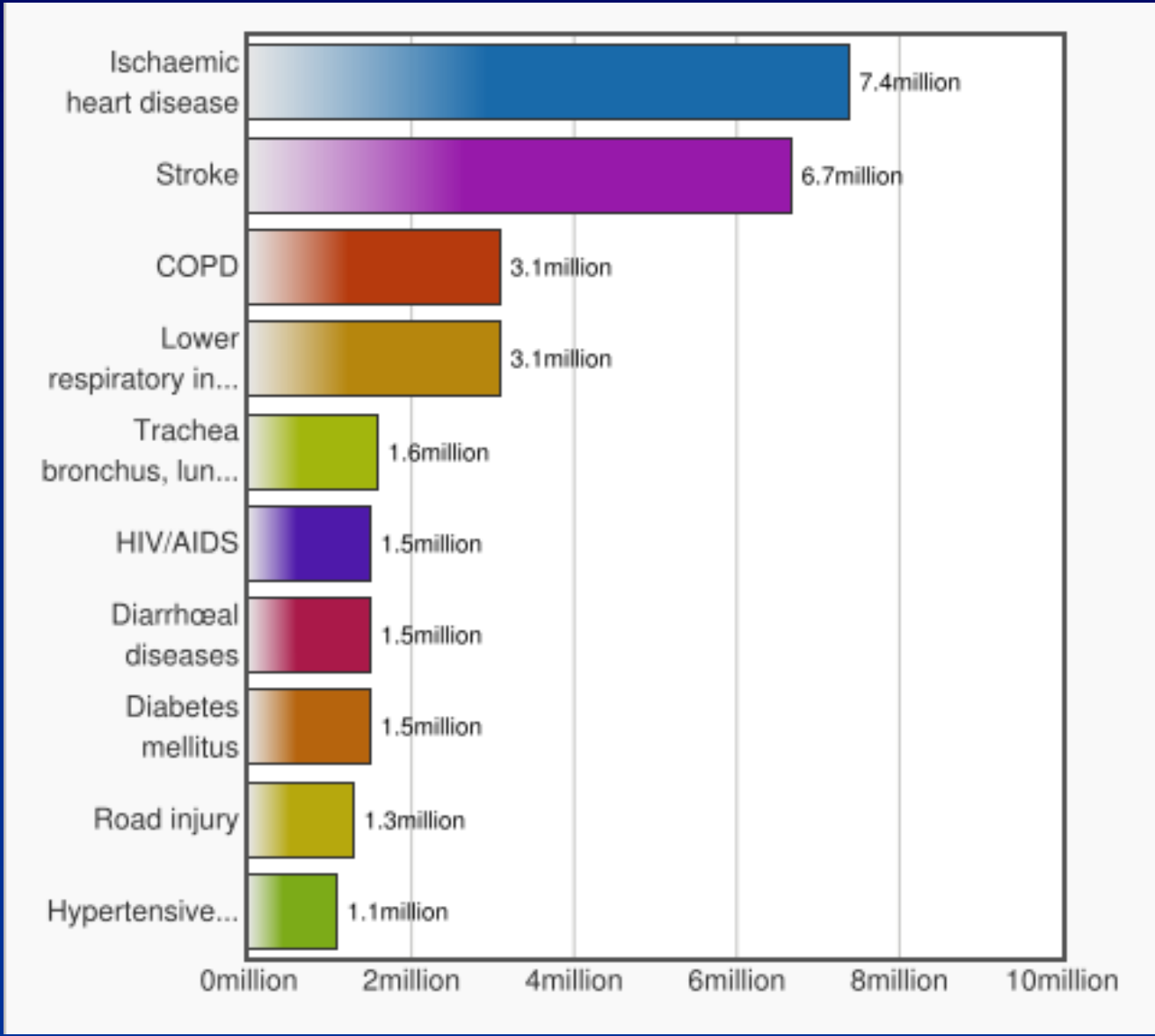
Hypertension Burden

- One of the major contributors of CV morbidity and mortality
- Undiagnosed, uncontrolled, and undertreated hypertension - responsible for increased chronic disease burden
- Worldwide Prevalence: 970 million
- Expected to affect 1.56 billion adults with hypertension by 2025



Gupta R et al. *J Hum Hypertens*. 2018 Feb;30(2):79-82
World-heart-federation.org.

Leading caused of Death: WHO Data



http://www.who.int/mediacentre/factsheets/fs310/en/index2.html

New blood pressure targets and treatment recommendations

- For years, hypertension was classified as blood pressure (BP) reading of 140/90 mm Hg or higher.
- But the updated guideline classifies hypertension as a BP reading of 130/80 mm Hg or higher.
- The updated guideline also provides new treatment recommendations, which include lifestyle changes as well as BP-lowering medications

2017 ACC/AHA Clinical Practice Guidelines . Whelton PK et al. Hypertension. 2017 Nov 13. pii: HYP.0000000000000066

New ACC/ AHA Hypertension Guidelines (2017)

BP Category	Systolic BP		Diastolic BP	Treatment or Follow-up
Normal	<120 mm Hg	**and**	<80 mm Hg	Evaluate yearly; encourage healthy lifestyle changes to maintain normal BP
Elevated	120-129 mm Hg	**and**	<80 mm Hg	Recommend healthy lifestyle changes and reassess in 3-6 months
Hypertension: stage 1	130-139 mm Hg	**or**	80-89 mm Hg	Assess the 10-year risk for heart disease and stroke using the atherosclerotic cardiovascular disease (ASCVD) risk calculator • If risk is less than 10%, start with healthy lifestyle recommendations and reassess in 3-6 months • If risk is greater than 10% or the patient has known clinical cardiovascular disease (CVD), diabetes mellitus, or chronic kidney disease, recommend lifestyle changes and BP-lowering medication (1 medication); reassess in 1 month for effectiveness of medication therapy – If goal is met after 1 month, reassess in 3-6 months – If goal is not met after 1 month, consider different medication or titration – Continue monthly follow-up until control is achieved
Hypertension: stage 2	≥140 mm Hg	**or**	≥90 mm Hg	Recommend healthy lifestyle changes and BP-lowering medication (2 medications of different classes); reassess in 1 month for effectiveness • If goal is met after 1 month, reassess in 3-6 months • If goal is not met after 1 month, consider different medications or titration • Continue monthly follow-up until control is achieved

ACC/AHA Clinical Practice Guidelines. Whelton PK et al. Hypertension. 2017 Nov 13. pii: HYP.0000000000000066

ESC/ESH 2018 Arterial Hypertension Guidelines

Changes in recommendations	
2013	**2018**
Diagnosis	**Diagnosis**
Office BP is recommended for screening and diagnosis of hypertension.	It is recommended to base the diagnosis of hypertension on: • Repeated office BP measurements; or • Out-of-office BP measurement with ABPM and/or HBPM if logistically and economically feasible.
Treatment thresholds **High normal BP (130–139/85–89 mmHg):** Unless the necessary evidence is obtained, it is not recommended to initiate antihypertensive drug therapy at high–normal BP.	**Treatment thresholds** **High normal BP (130–139/85–89 mmHg):** Drug treatment may be considered when CV risk is very high due to established CVD, especially CAD.
Treatment thresholds **Treatment of low-risk grade 1 hypertension:** Initiation of antihypertensive drug treatment should also be considered in grade 1 hypertensive patients at low–moderate-risk, when BP is within this range at several repeated visits or elevated by ambulatory BP criteria, and remains within this range despite a reasonable period of time with lifestyle measures.	**Treatment thresholds** **Treatment of low-risk grade 1 hypertension:** In patients with grade 1 hypertension at low–moderate-risk and without evidence of HMOD, BP-lowering drug treatment is recommended if the patient remains hypertensive after a period of lifestyle intervention.

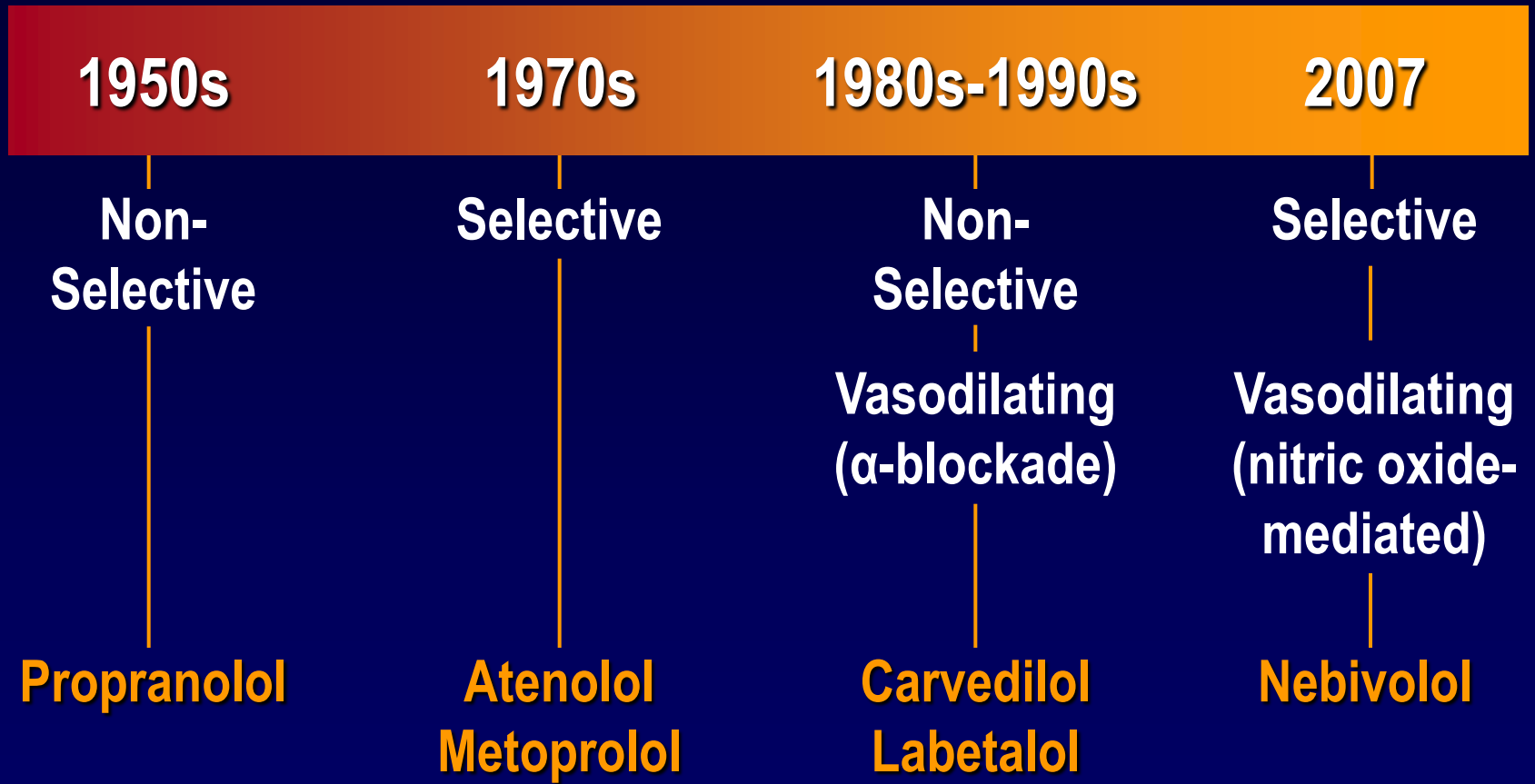
Recommendation Grading							
	Grade I		Grade IIa		Grade IIb		Grade III

ESC/ESH 2018 Arterial Hypertension Guidelines

Changes in recommendations	
2013	**2018**
Treatment thresholds **Older patients** Antihypertensive drug treatment may be considered in the elderly (at least when younger than 80 years) when SBP is in the 140–159 mmHg range, provided that antihypertensive treatment is well tolerated.	**Treatment thresholds** **Older patients** BP-lowering drug treatment and lifestyle intervention is recommended in fit older patients (>65 years but not >80 years) when SBP is in the grade 1 range (140–159 mmHg), provided that treatment is well tolerated.
BP treatment targets	**BP treatment targets**
An SBP goal of <140 mmHg is recommended.	• It is recommended that the first objective of treatment should be to lower BP to <140/90 mmHg *in all patients* and, provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower in most patients. • In patients <65 years it is recommended that SBP should be lowered to a BP range of 120–129 mmHg in most patients.

Recommendation Grading							
	Grade I		Grade IIa		Grade IIb		Grade III

The Evolution in β-blockade



Current Use of β-blockers

- First-line and Add-on Therapy for Hypertension
- Hypertension with Compelling Indications:
  - Heart Failure
  - Post-MI
  - High coronary disease risk
  - Type 2 diabetes

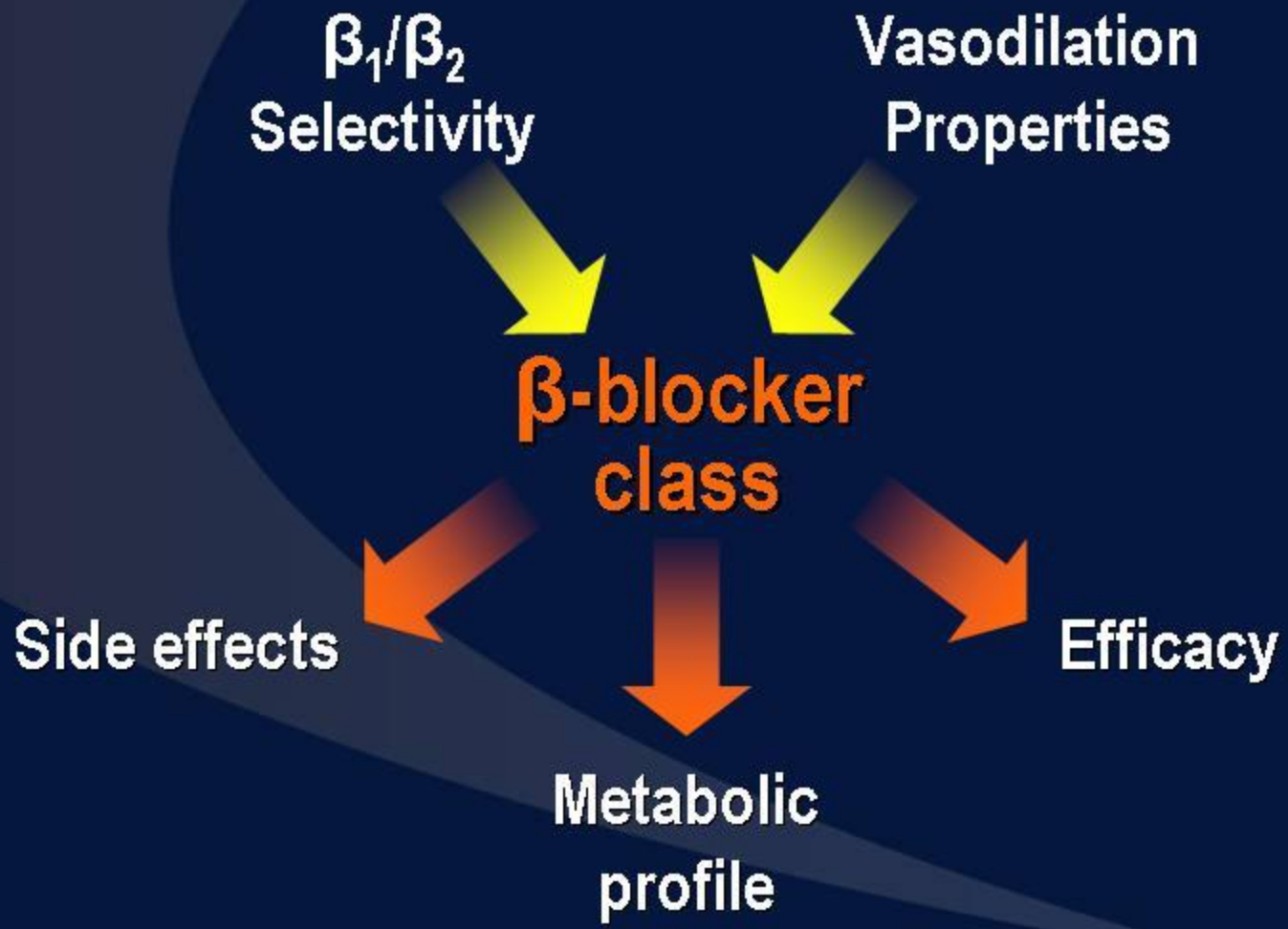
Concerns With Traditional β-blockers

- Efficacy in certain hypertensive populations
  - Blacks
  - Elderly patients
- Side Effects
  - Fatigue
  - Sexual dysfunction
  - Cold extremities
  - Depression
  - Hyperreactive airway disorder
  - Bradycardia
- Metabolic Change
  - Glucose abnormalities
  - Lipid abnormalities
- Hemodynamic Change
  - ↓ CO, ↑ PVR
  - ↓ Exercise tolerance

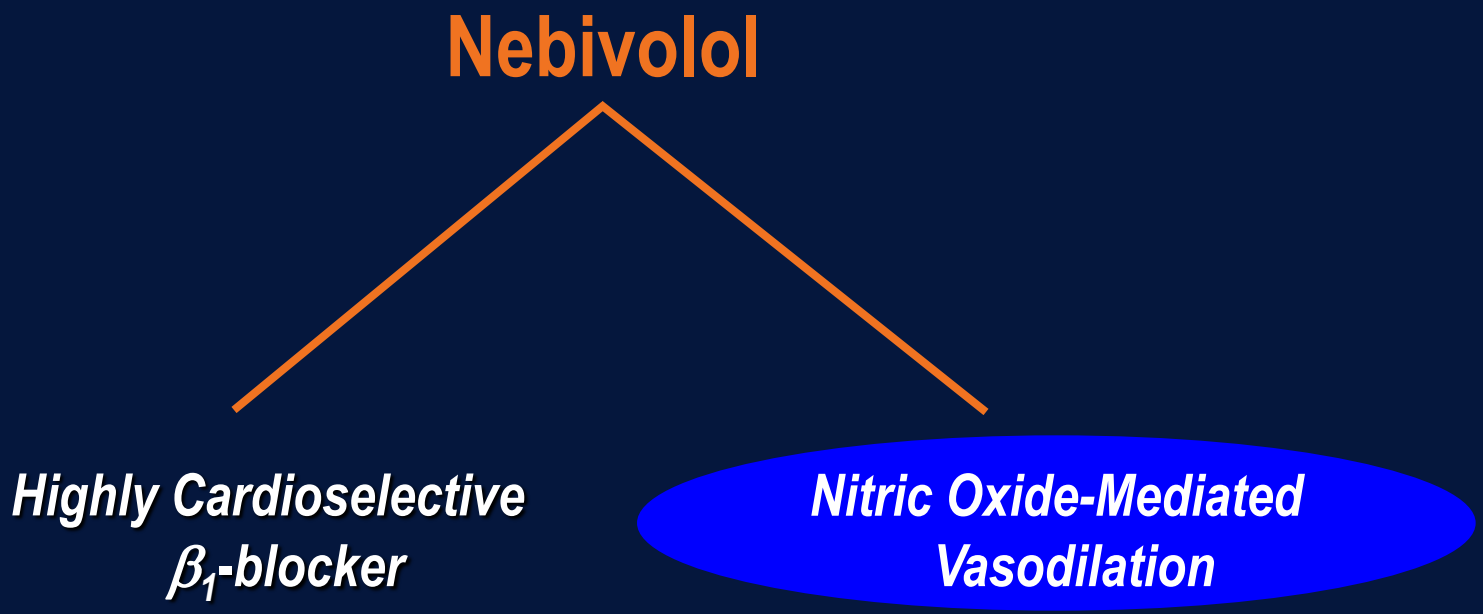
CO=cardiac output; MI=myocardial infarction; PVR=peripheral vascular resistance.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560-2572.
Moser M. Clinical Management of Hypertension. 8th ed. Professional Communications. 2007.

Main Factors Contributing to Heterogeneity Within the β-blocker Class

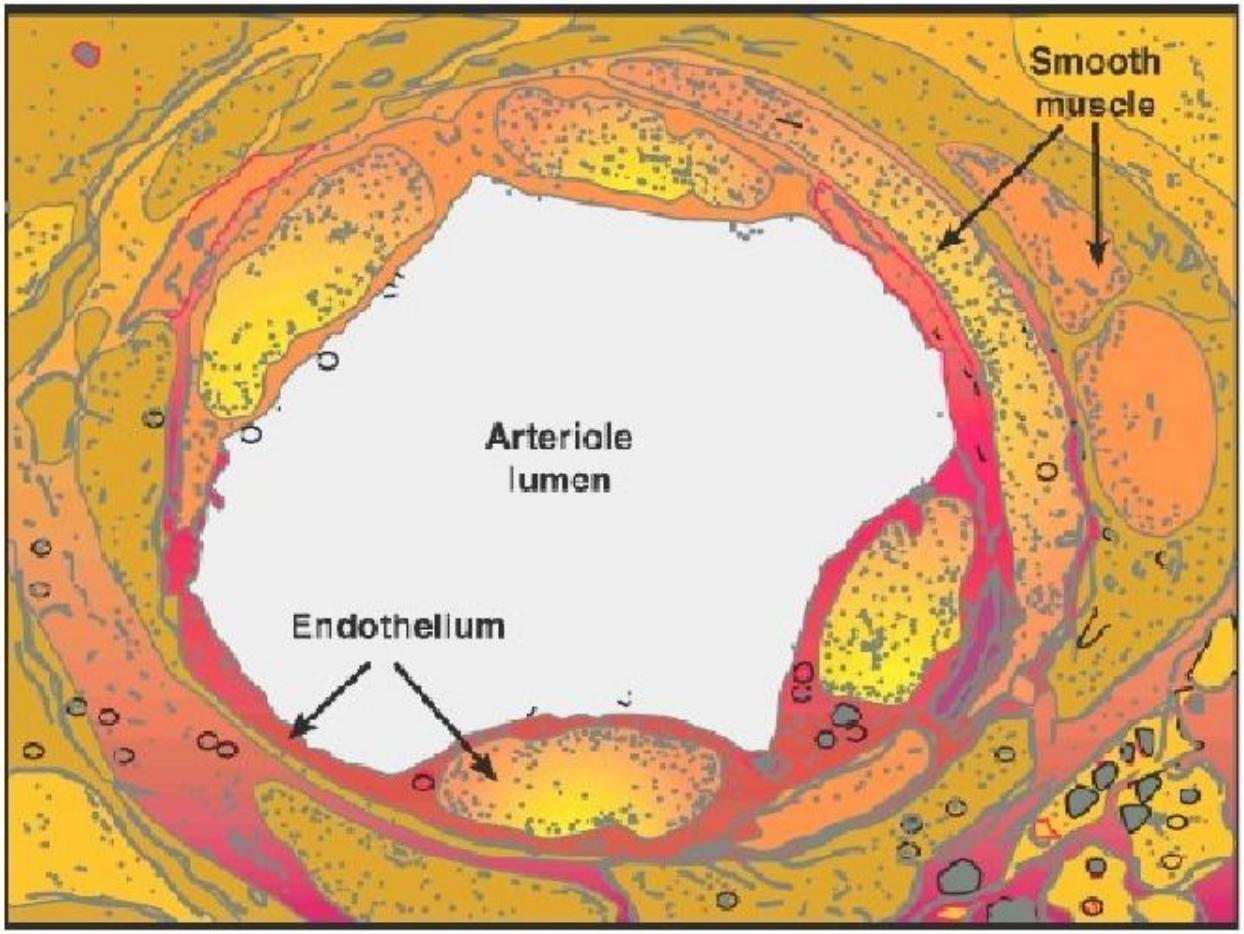


Nebivolol HCl: Dual Mechanism of Action



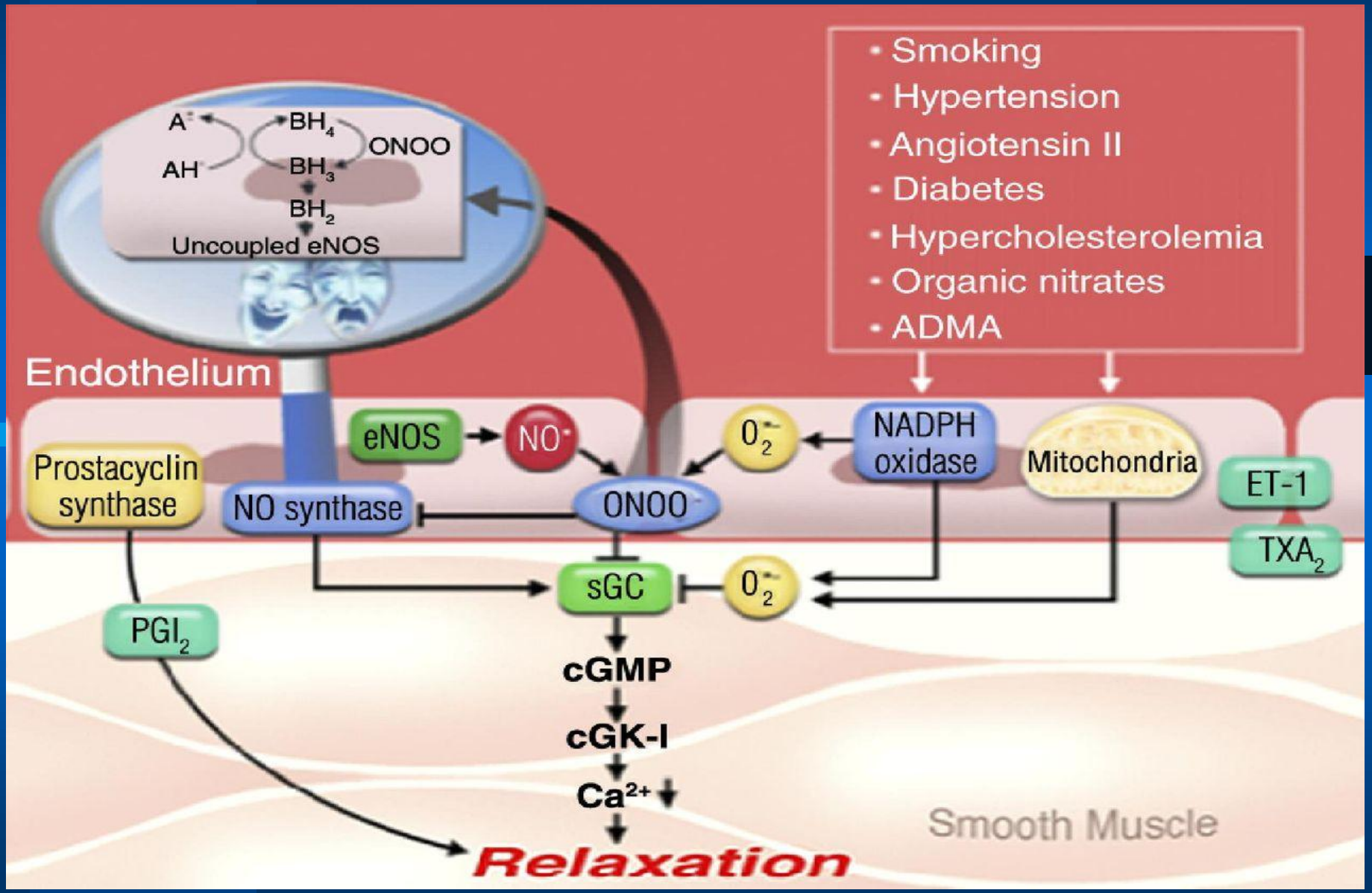
Bristow MR et al. *Am J Hypertens*. 2005;18(suppl 5):A51-A52.
Iganarro LJ. *Blood Pressure*. 2004;13(suppl 1):3-17.
Mason RP et al. *Circulation*. 2005;112:3795-3801.

The Endothelium: The largest living organ



- 1 ½ kg.
- Semi-permeable

Mechanisms Underlying Endothelial (Vascular) Dysfunction in Vascular Disease



Thomas Münzel, and Tommaso Gori JACC 2009;54:1491-1499

Nitric Oxide

- Vasodilator - Most important intrinsic dilator
- Anti-thrombotic - Prevents cell adhesion & Platelet aggregation
- Anti-atherogenic - Inhibits lipid oxidation
-
- **Actions :**

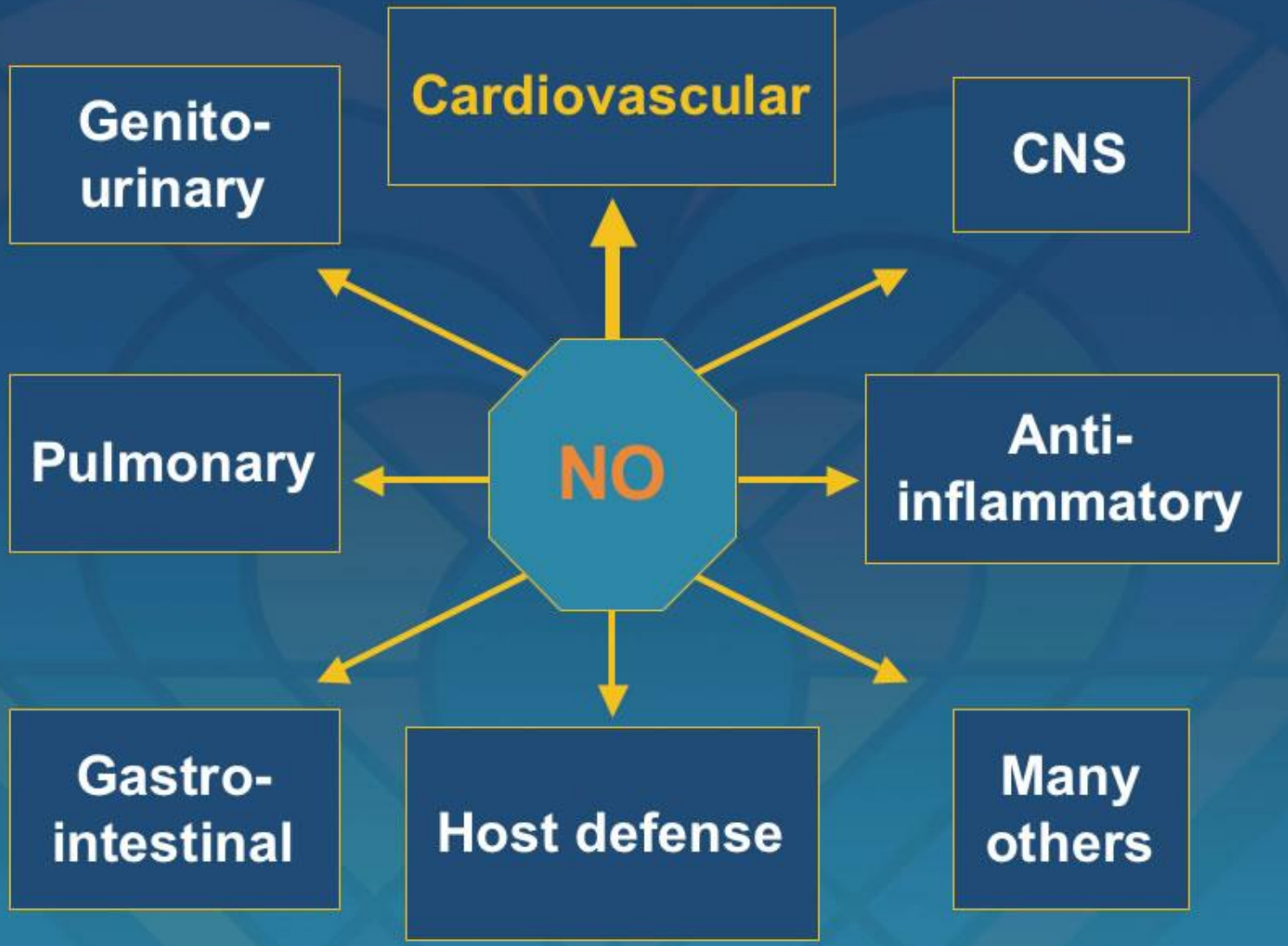
- ↓ monocyte migration
- Growth inhibitor - inhibits cellular growth & migration
- Antioxidant- Scavenges superoxide anions
- Anti inflammatory - Prevents generation of thrombosis

NO :In disease
Hypertension = endothelial dysfunction!

- Normotensive offsprings of hypertensive parents who are more at risk of developing hypertension in the future have been reported to have impaired endothelial function.
- This finding would support the notion that endothelial dysfunction precedes hypertension
- " NO · may be an important anti-inflammatory mediator and regulator of microvascular blood flow in sepsis.

Conditions have endothelial dysfunction and reduced NO production and/or bioavailability:

- Hypertension
- Obesity
- Dyslipidemias (particularly hypercholesterolemia and hypertriglyceridemia)
- Diabetes (both type I and II)
- Heart failure
- Atherosclerosis, cigarette smoking, aging, and vascular injury

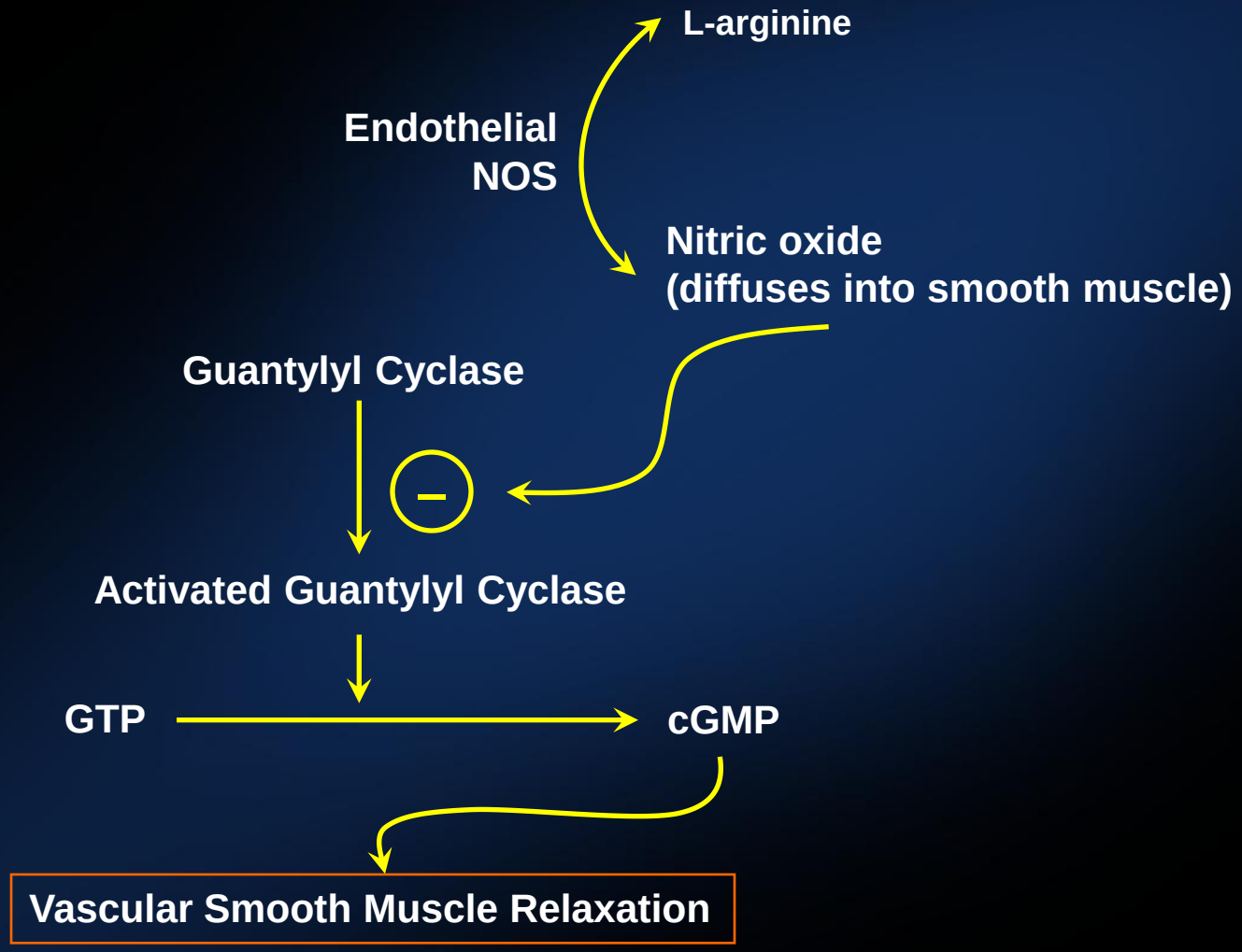

Genito-urinary
Cardiovascular
CNS
Pulmonary
NO
Anti-inflammatory
Gastro-intestinal
Host defense
Many others

Nebivolol: Potential Benefits of Nitric Oxide Potentiation

- Endothelial dysfunction is:
  - A key marker of atherosclerosis
  - Characterized by impaired 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 β-blocker nebivolol

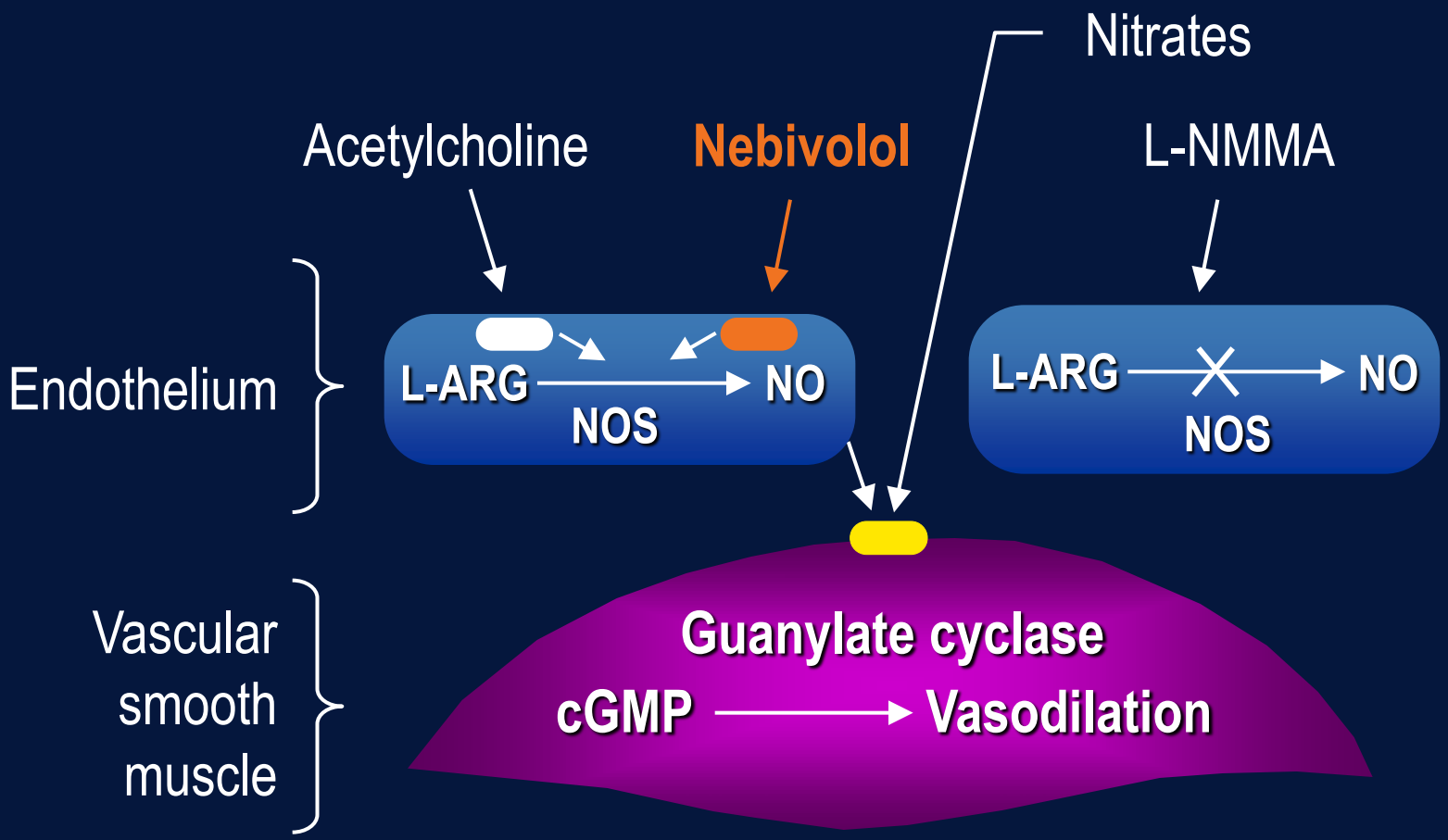
Mason RP, et al. *J Clin Hypertens.* 2006;8 (suppl 2):31-40

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



Veverka A, et al. *Am Pharmacother*. 2006;40:1353-1360

Endothelial-Dependent Vasodilation With Nebivolol



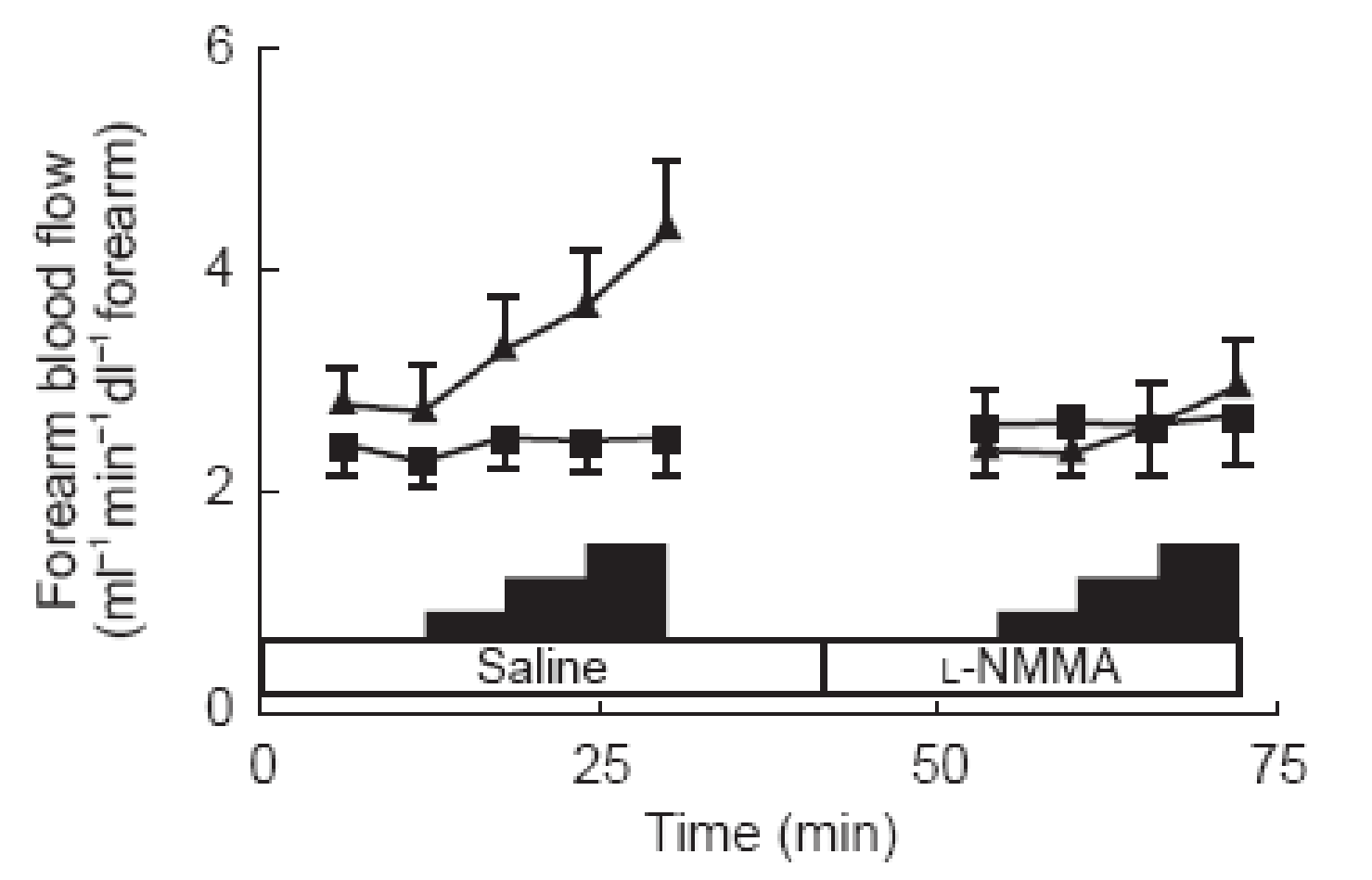
cGMP=cyclic guanosine monophosphate; L-ARG=L-arginine; NOS=nitric oxide synthase.

Nebivolol: vasodilation in healthy volunteers

Effects of nebivolol and atenolol administered intra-arterially in two distinct occasions, at equimolar doses, for 6 minutes on forearm blood flow

Cockroft JR. J Pharmacol Exp Ther 1995; 274(3):1067-71

Nebivolol Enhances Nitric Oxide-Mediated Vasodilation in Hypertensive Patients



Dawes et al. *Br. J. Clin. Pharmacol. 1999: 48:460-463.*

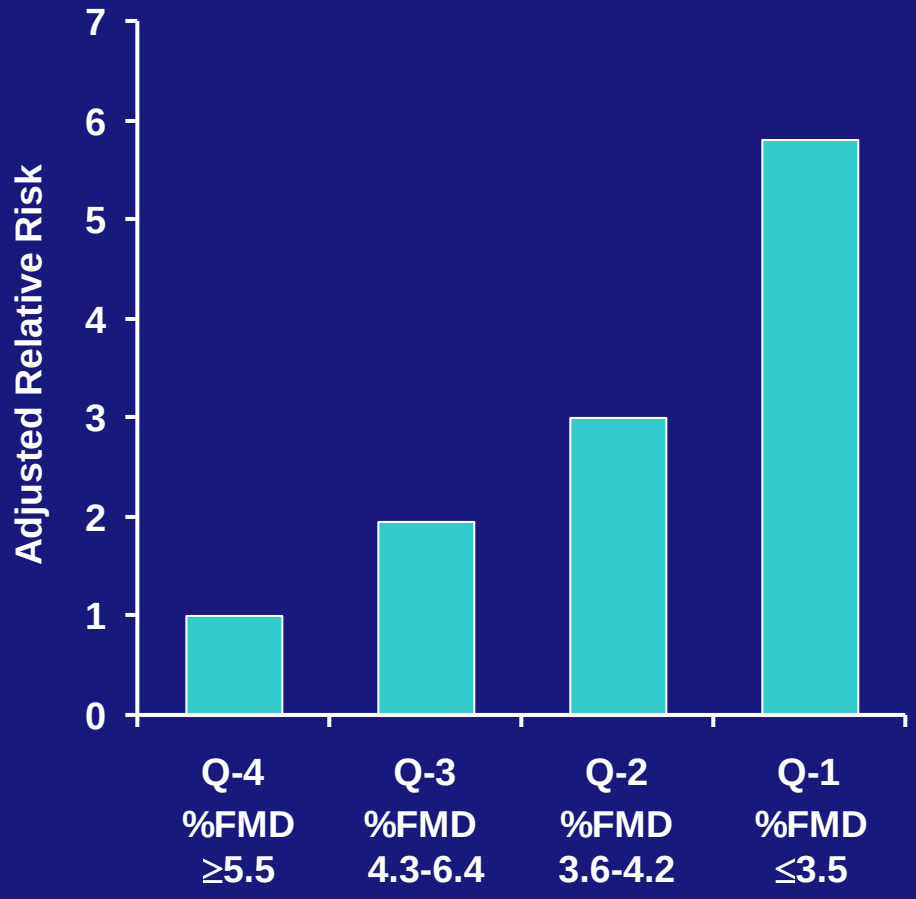
▲ - Infused left arm
■ - Non-infused right arm

Endothelial Function and Risk of Developing Hypertension

- 952 healthy postmenopausal women
- Aged 44 to 60 years
- Baseline normal blood pressure
- Follow-up for mean 3.6 years

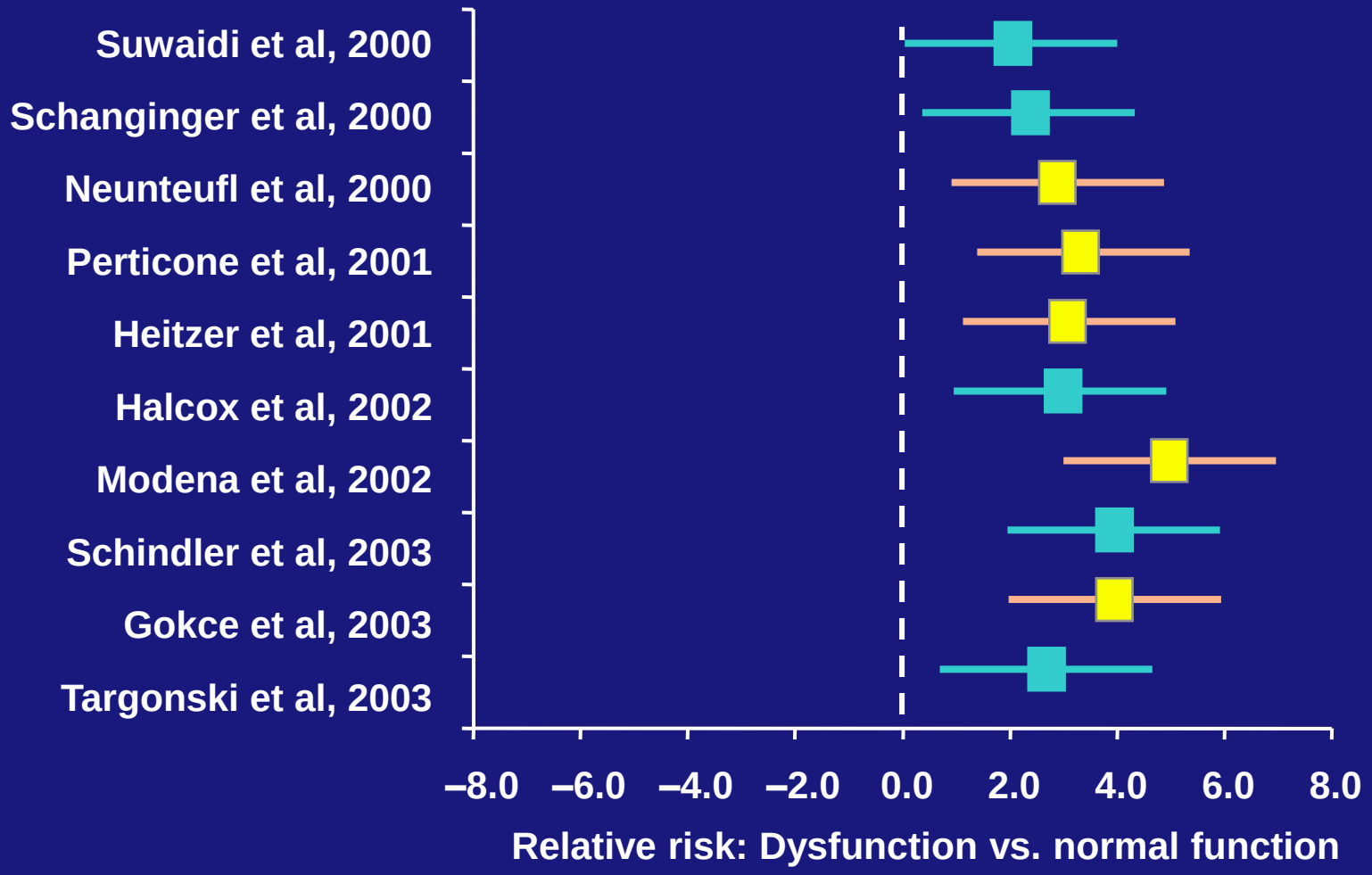
Results:

- 112 developed hypertension
- Relative risk for developing hypertension during follow-up was 5.8-fold in those in the lowest FMD quartile compared with the highest quartile.

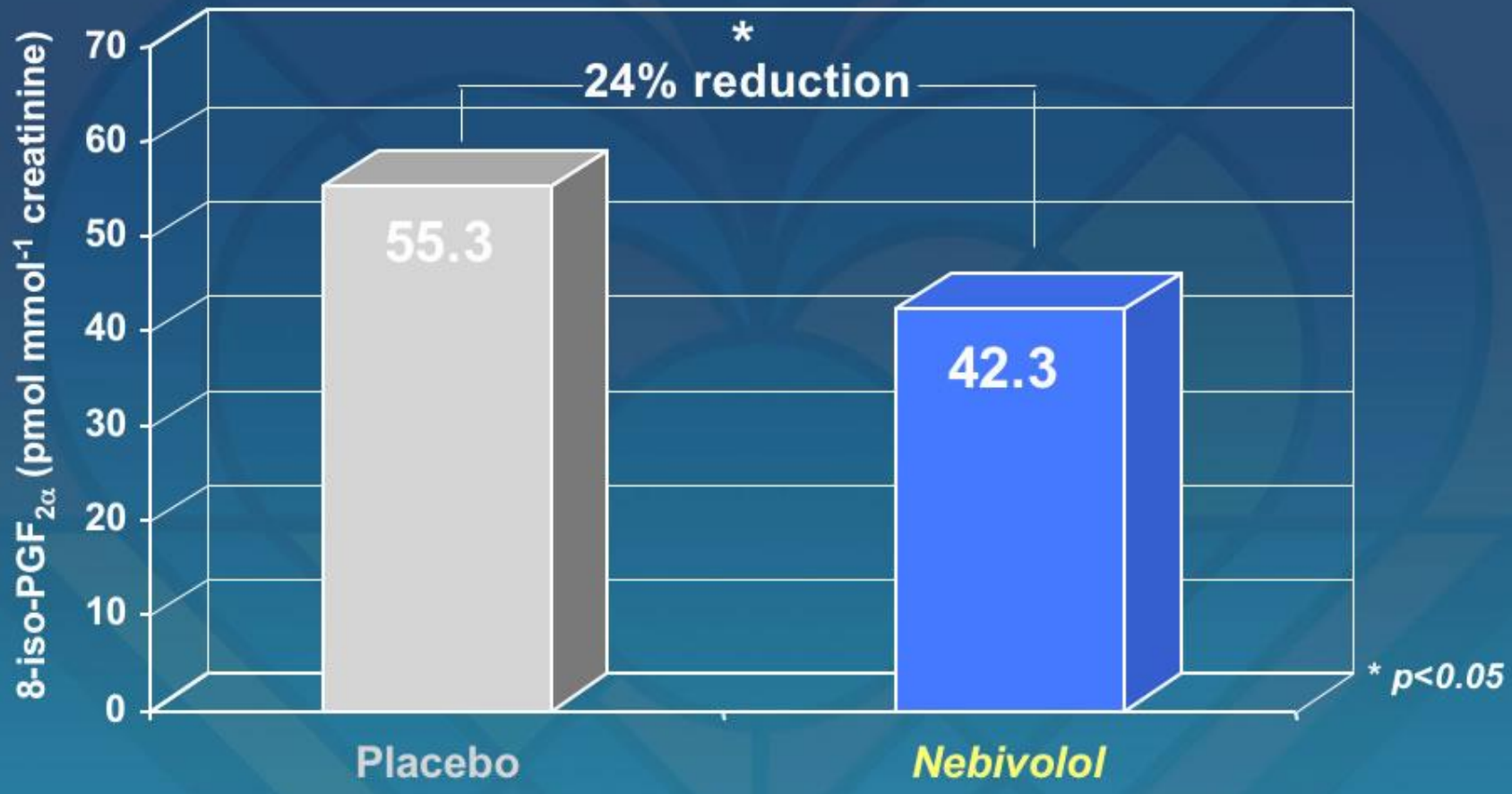


Rossi R. *J Am Coll Cardiol.* 2004;44:1636-1640.

Prediction of Future Cardiovascular Events by Measurement of Endothelial Function

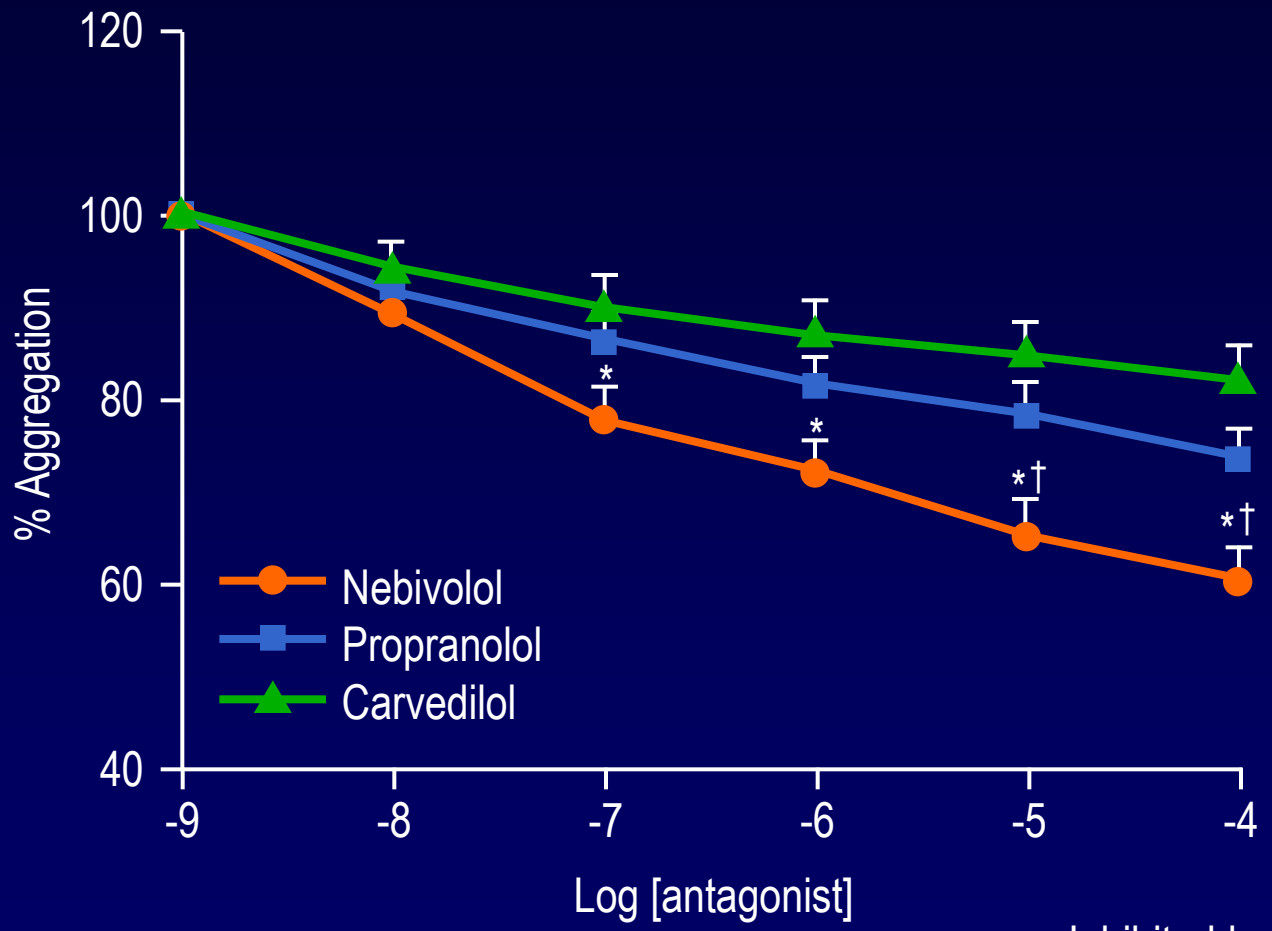


Nebivolol: decreases systemic oxidative stress



Troost R, et al. Br J Clin Pharmacol 2000; 50:377-9

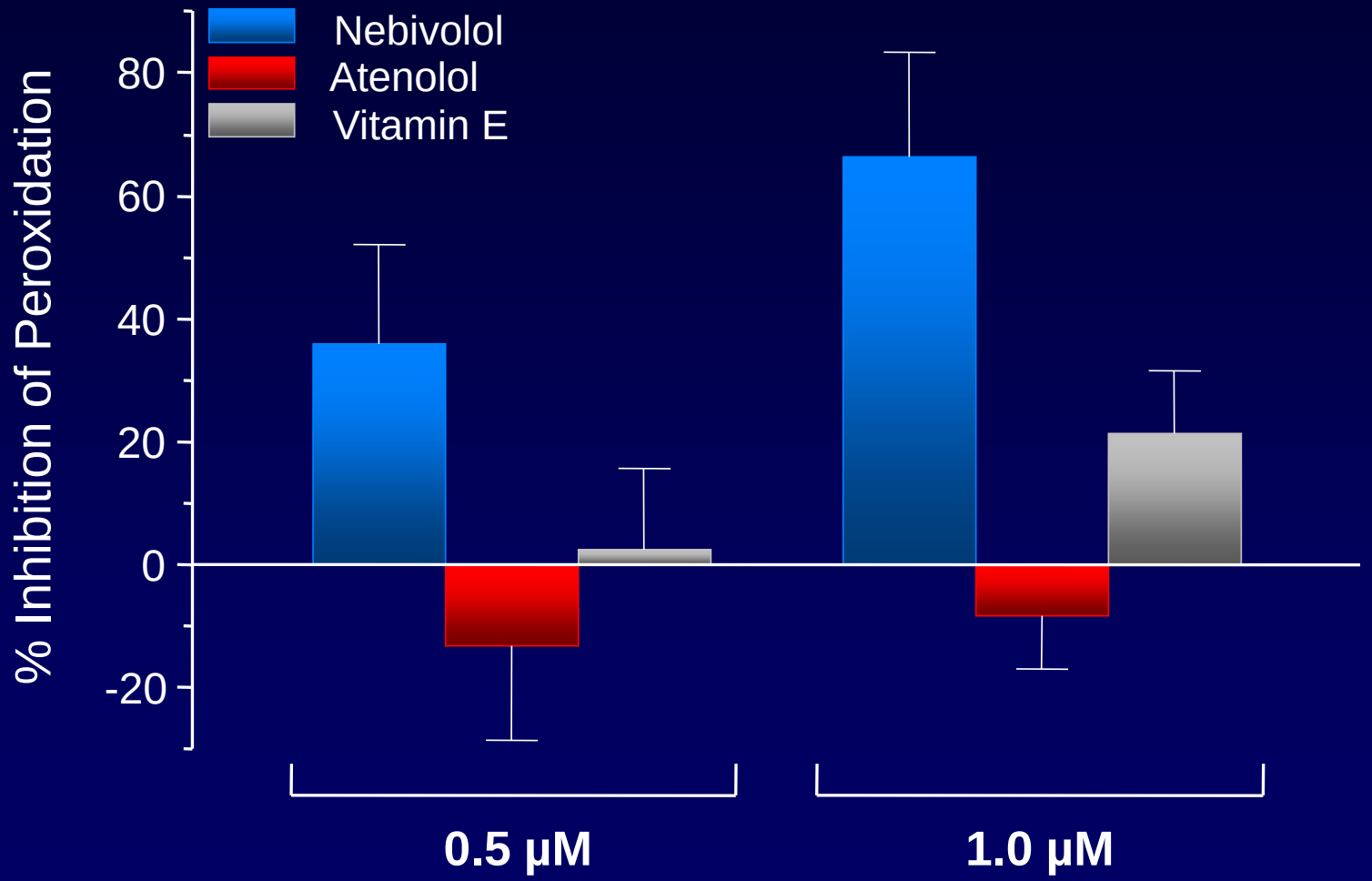
Nebivolol Inhibits Human Platelet Aggregation



Inhibited by L-NMMA
Potentiated by L-Arginine

Aggregating agent: adenosine diphosphate (3 μM).
Falciani et al. *J Cardiovasc Pharmacol.* 2001.

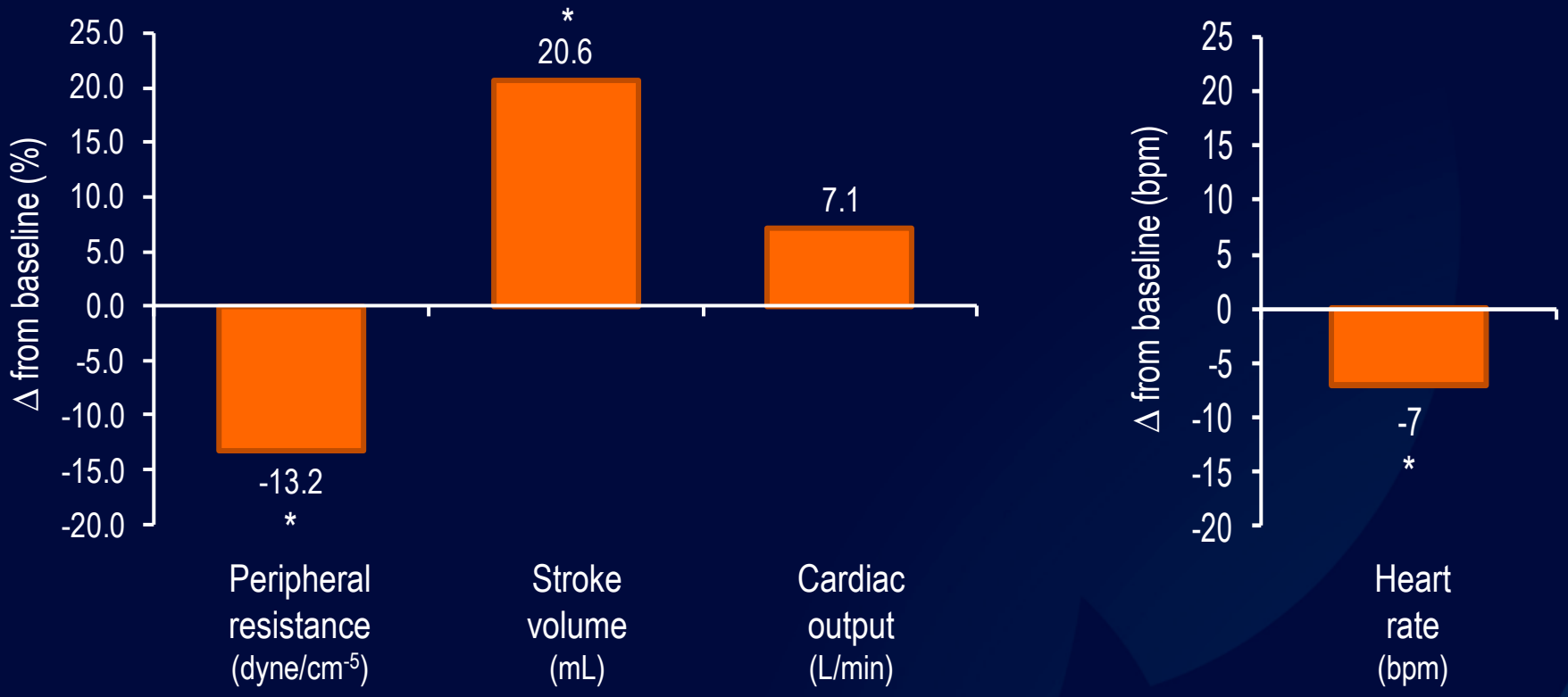
Comparative Effects of Nebivolol, Atenolol and Vitamin E on Lipid Peroxidation



Mason RP, *et al*. *J Cardiovasc Pharm*. 2006;**48**:862-869

Nebivolol: Hemodynamics

Reduced Peripheral Vascular Resistance in Patients With Hypertension (5-mg Dose)

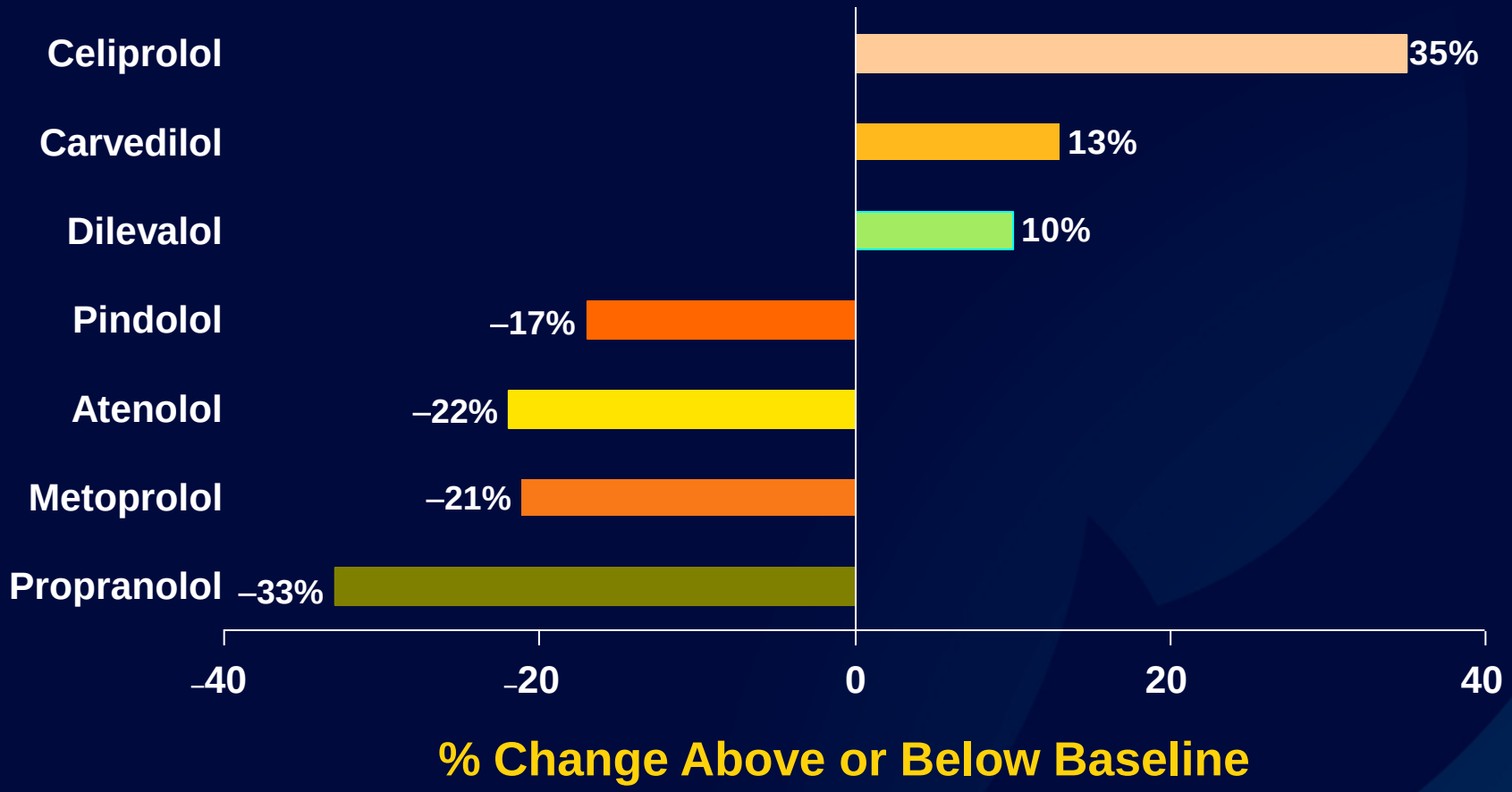


Systolic/diastolic blood pressure reductions were -19/12 mm Hg for Bystolic®.

Statistically significant changes were seen versus baseline (pretreatment) in peripheral resistance, stroke volume, and heart rate.
Cardiac output was unchanged (posttreatment versus baseline).
The clinical significance of these changes is unknown.

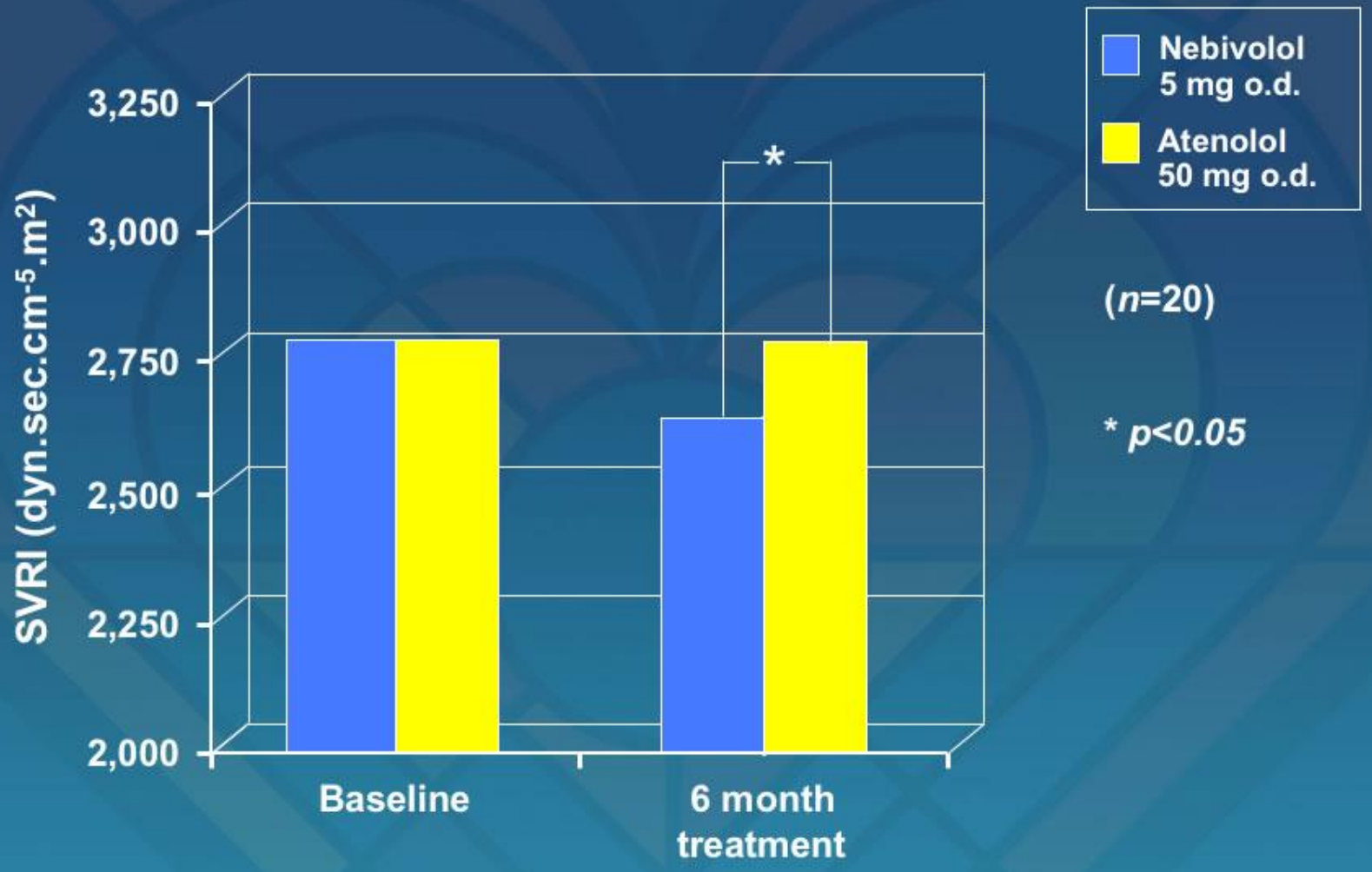
N=12. Parameters measured at 2 weeks. *P<0.05 vs pretreatment.
Adapted from Kamp O et al. *Am J Cardiol.* 2003;92:344-348.

Effect of β-Blockers on Insulin Sensitivity in Hypertensive Patients



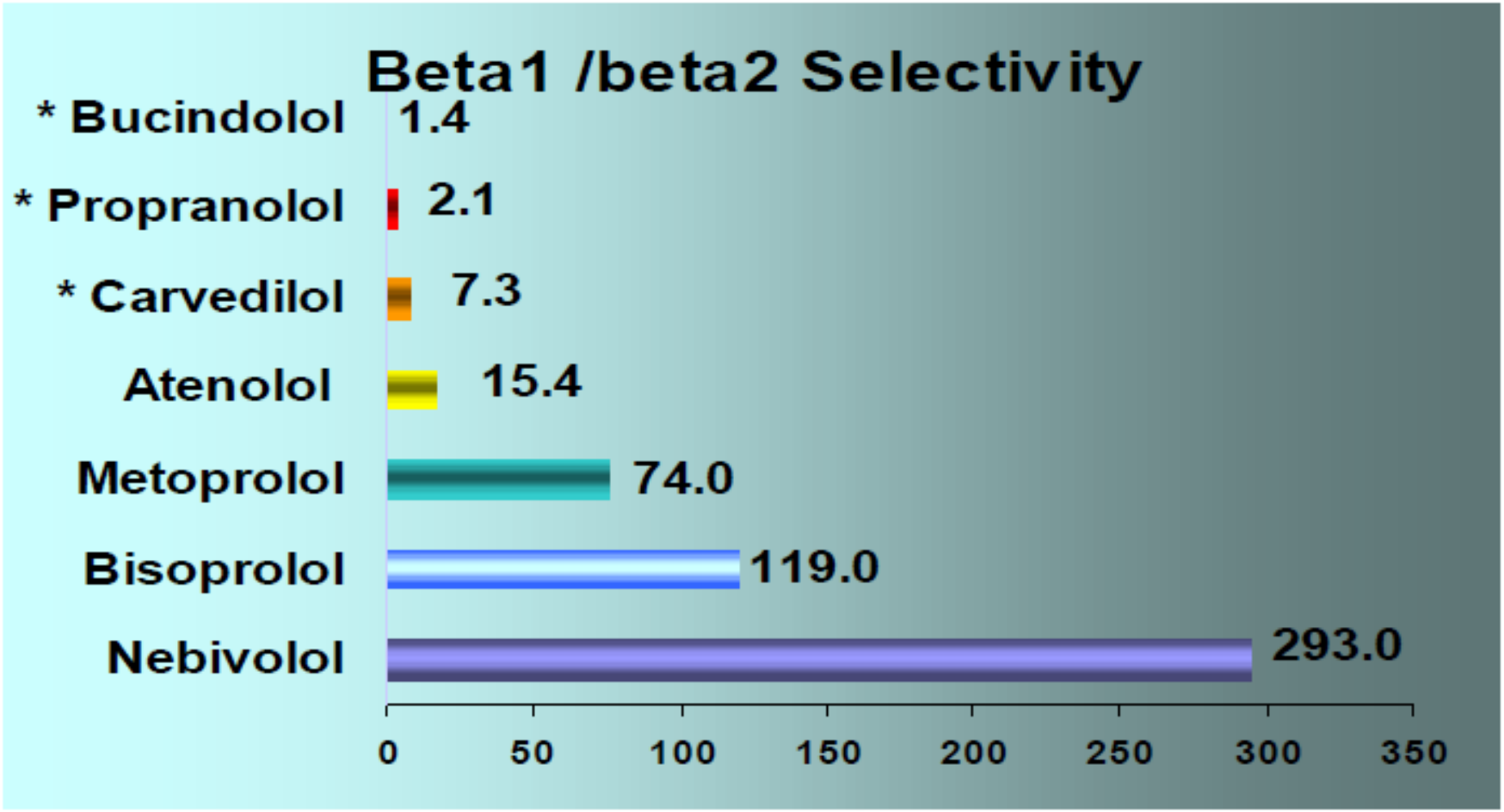
Jacob S et al. *Am J Hypertens.* 1998;11:1258-1265.

Comparative study: nebivolol *vs* atenolol



Sánchez R, et al. 1986

Highest Beta-1 selectivity

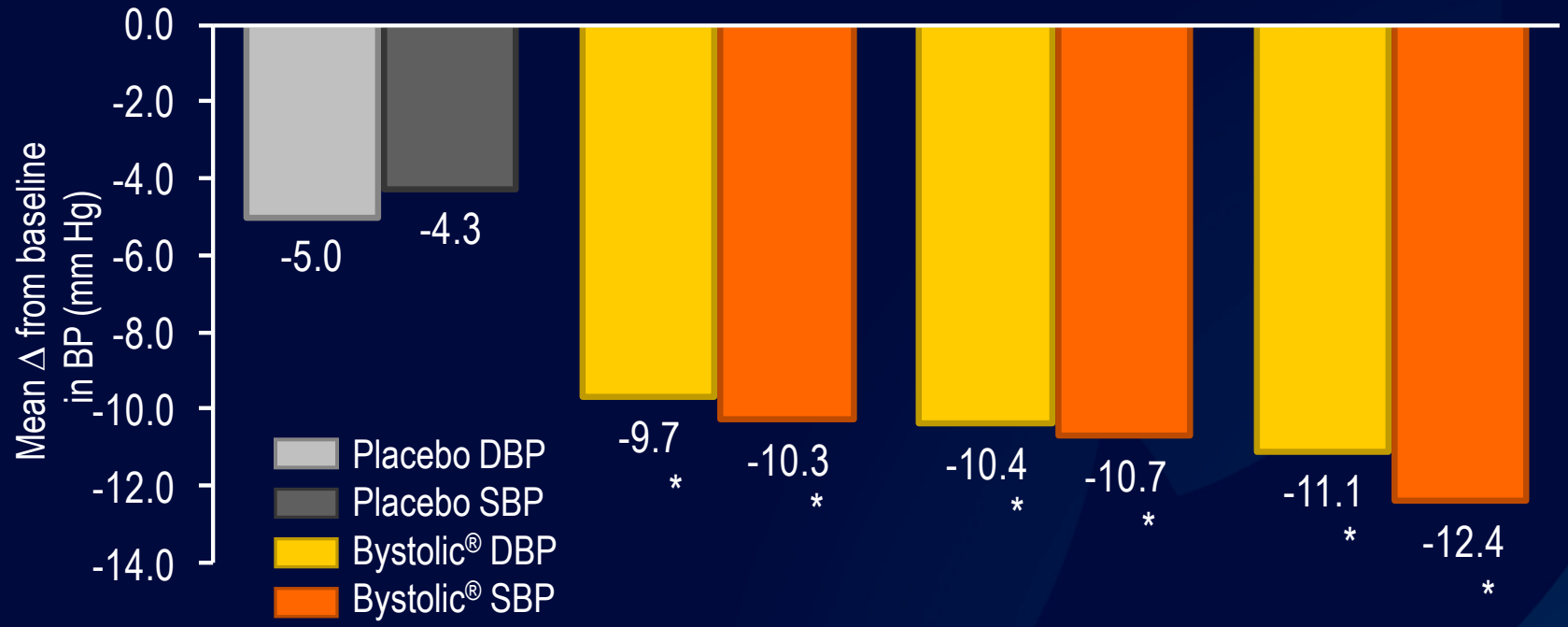


Celiprolol selectivity is 5:1

Cleophas et al, 2001, "Of the Beta-blockers, Nebivolol has the highest Beta 1-selective

Nebivolol: Efficacy
Pooled Data

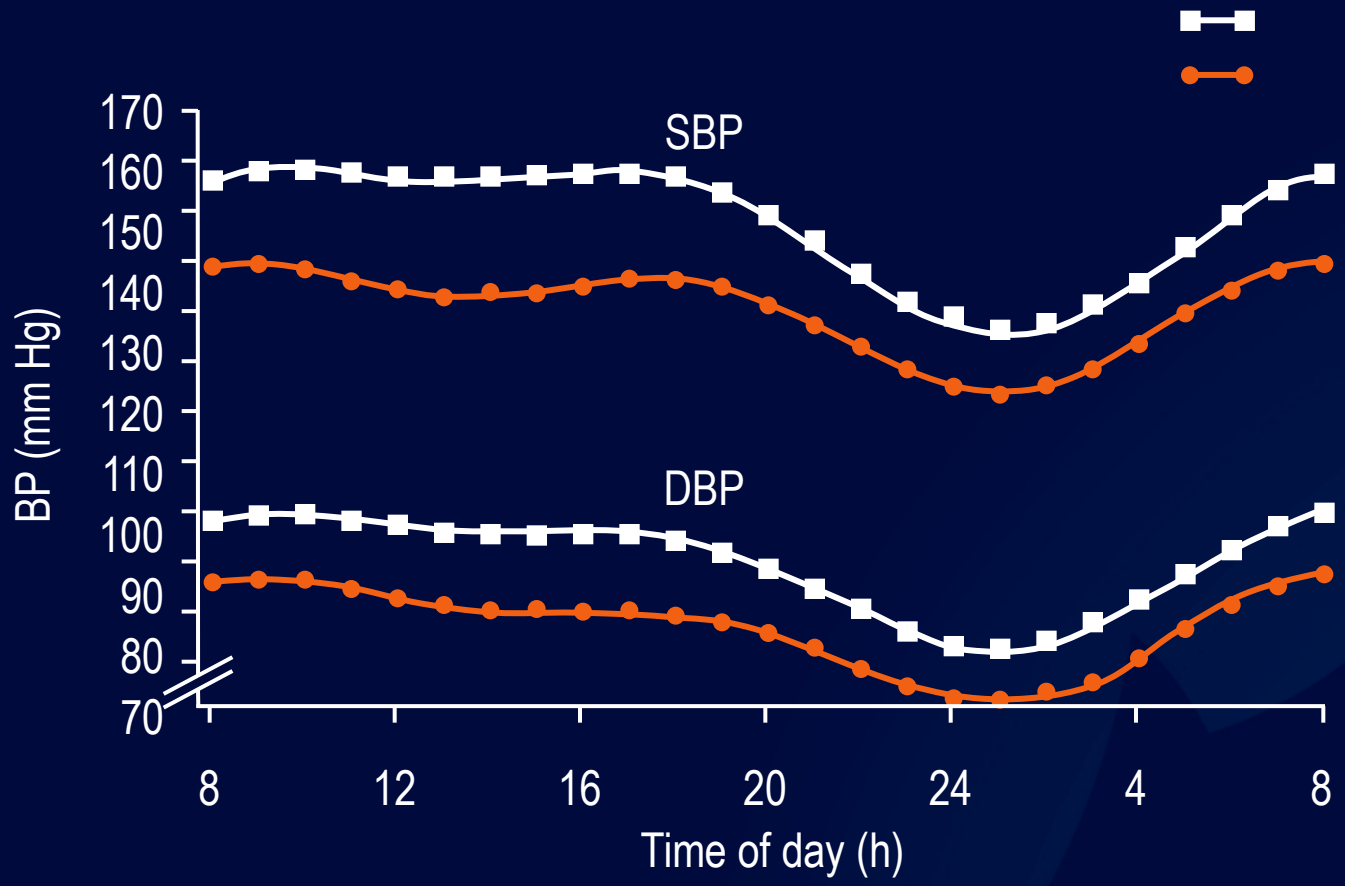
N	205	459	461	460
Baseline BP (mm Hg)	152/100	152/99	153/99	152/99
Dose	Placebo	5 mg	10 mg	20 mg



BP=sitting blood pressure; DBP=sitting diastolic BP; SBP=sitting systolic BP.
Only data for patients randomized to placebo or Bystolic® 5 mg, 10 mg, or 20 mg are shown (n=1585). *P<0.001 vs placebo.
Weiss RJ et al. *J Clin Hypertens (Greenwich).* 2009;11(suppl A):A40.
Data on file. Forest Laboratories, Inc. New York, New York.

: 24-hour BP Reduction

Ambulatory Blood Pressure Monitoring Curves



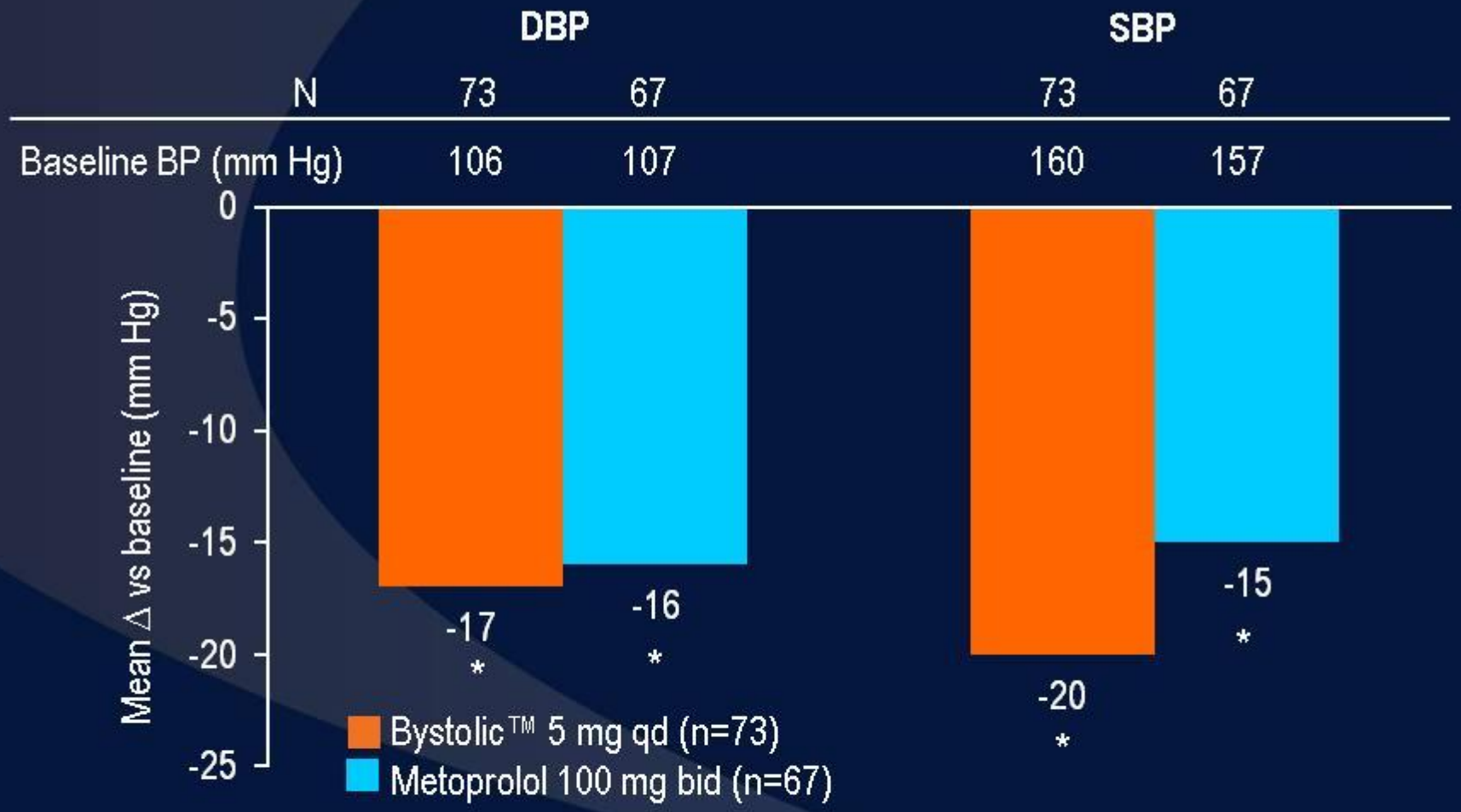
BP=blood pressure; SBP=systolic BP; DBP=diastolic BP.

Study included a 2-week to 4-week single-blind placebo run-in period, after which patients underwent baseline ambulatory blood pressure monitoring (ABPM), followed by an 8-week double-blind phase during which patients underwent another ABPM (N=29). *P*=0.0001 vs baseline.

Lacourcière Y et al. *Am J Ther*. 1994;1:74-80.

- Not all beta-blockers are equal
- Vasodilatation improves insulin sensitivity

Nebivolol and Metoprolol on Insulin Resistance

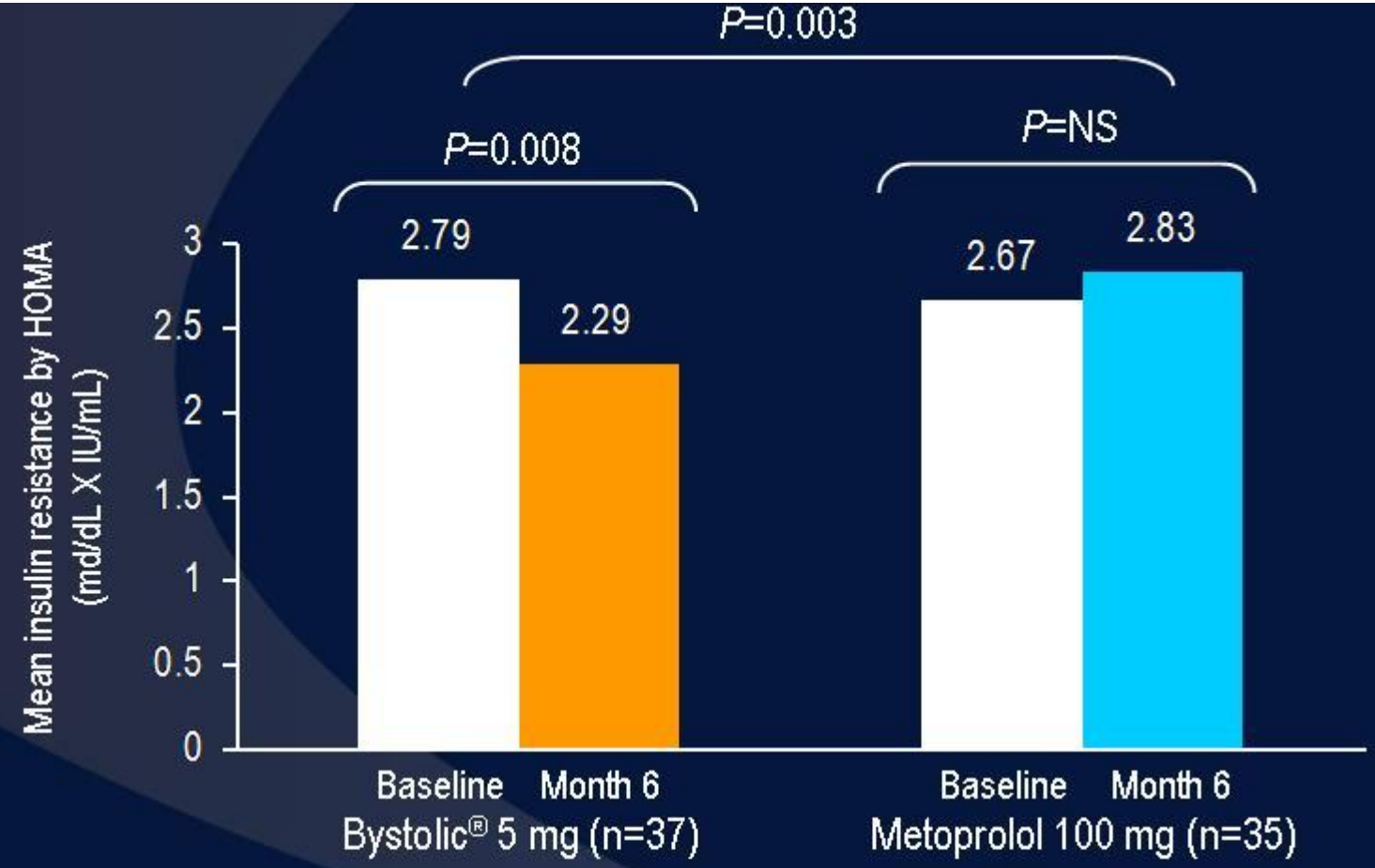


*$P<0.05$ vs baseline.

BP=sitting blood pressure; DBP=sitting diastolic blood pressure; SBP=sitting systolic blood pressure.

Uhlir O et al. *Drug Invest.* 1991;3(suppl 1):107-110.

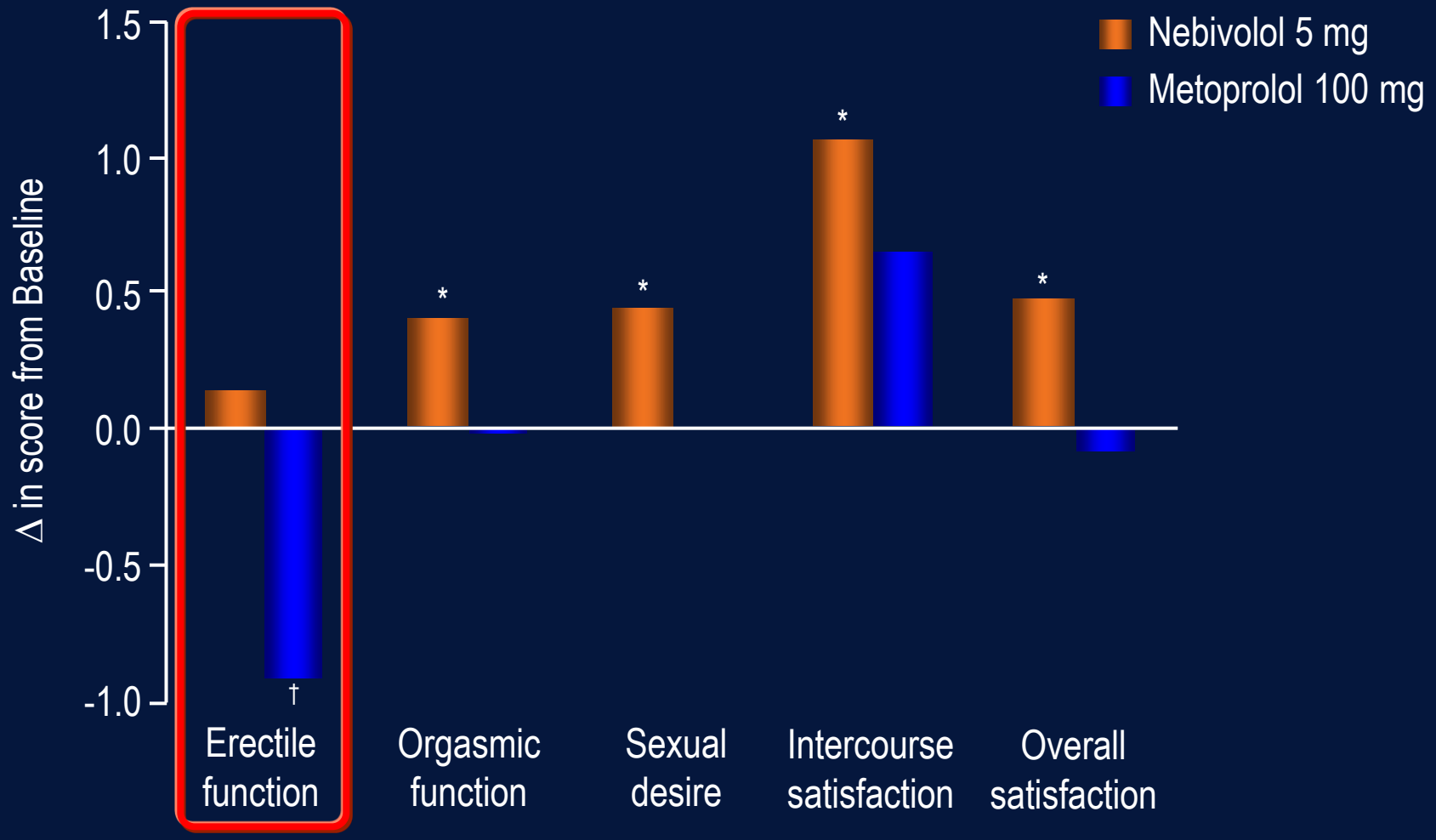
Nebivolol and Metoprolol on Insulin Resistance



Bystolic® is not indicated for glucose control. Bystolic® is indicated for the treatment of hypertension.

Baseline SBP/DBP was 153/92 mm Hg and 155/95 mm Hg in the Bystolic® and metoprolol groups, respectively. Following 6 months of therapy, BP was 131/79 mm Hg and 129/82 mm Hg in the Bystolic® and metoprolol groups, respectively.
HOMA=homeostasis model assessment: insulin resistance.
Celik T et al. *J Hypertens*. 2006;24:591-596.

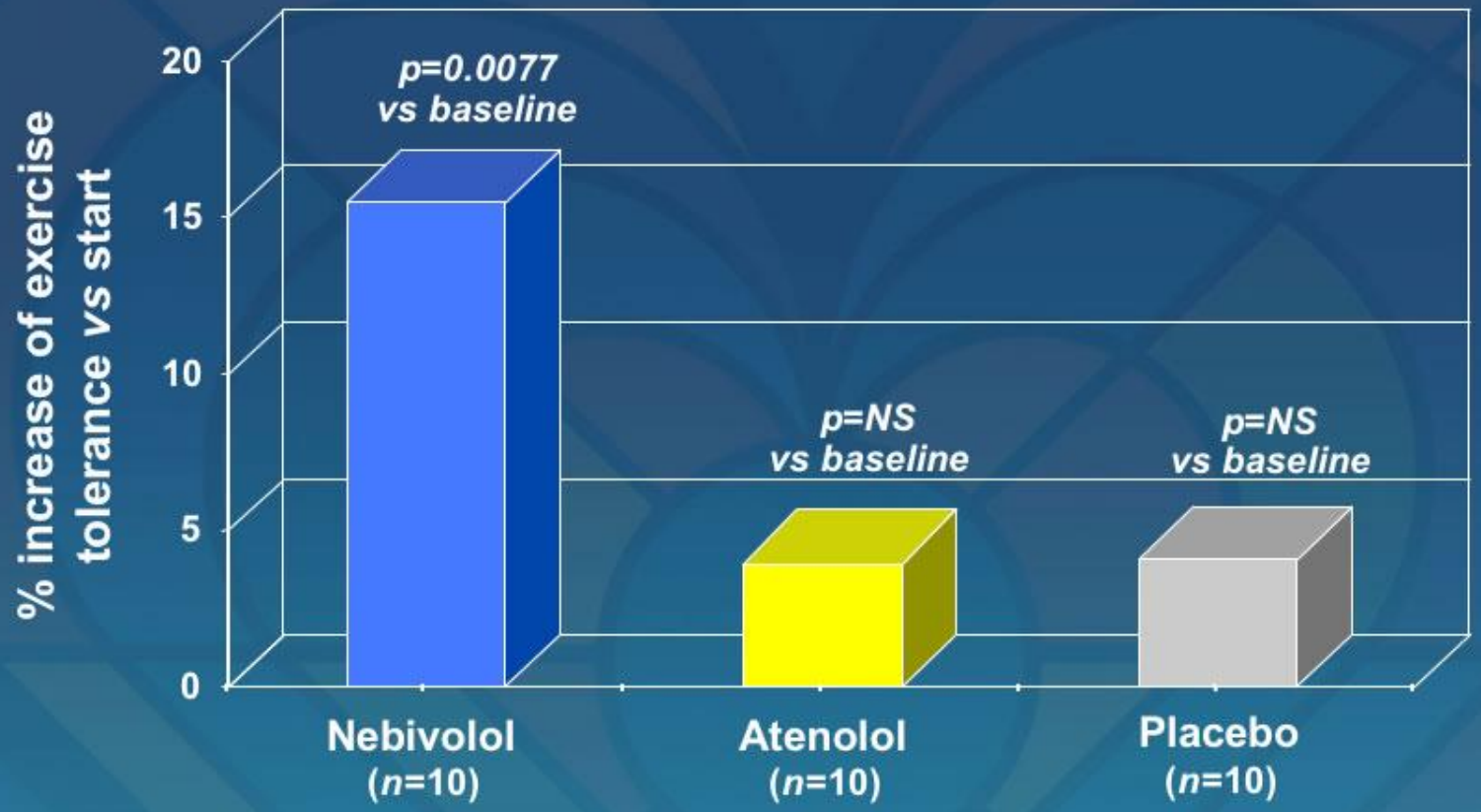
Nebivolol vs. Metoprolol on Sexual Function: IIEF



IIEF=International Index of Erectile Function.

Brixius K et al. *Clin Exper Pharmacother.* 2007;34:327-331.

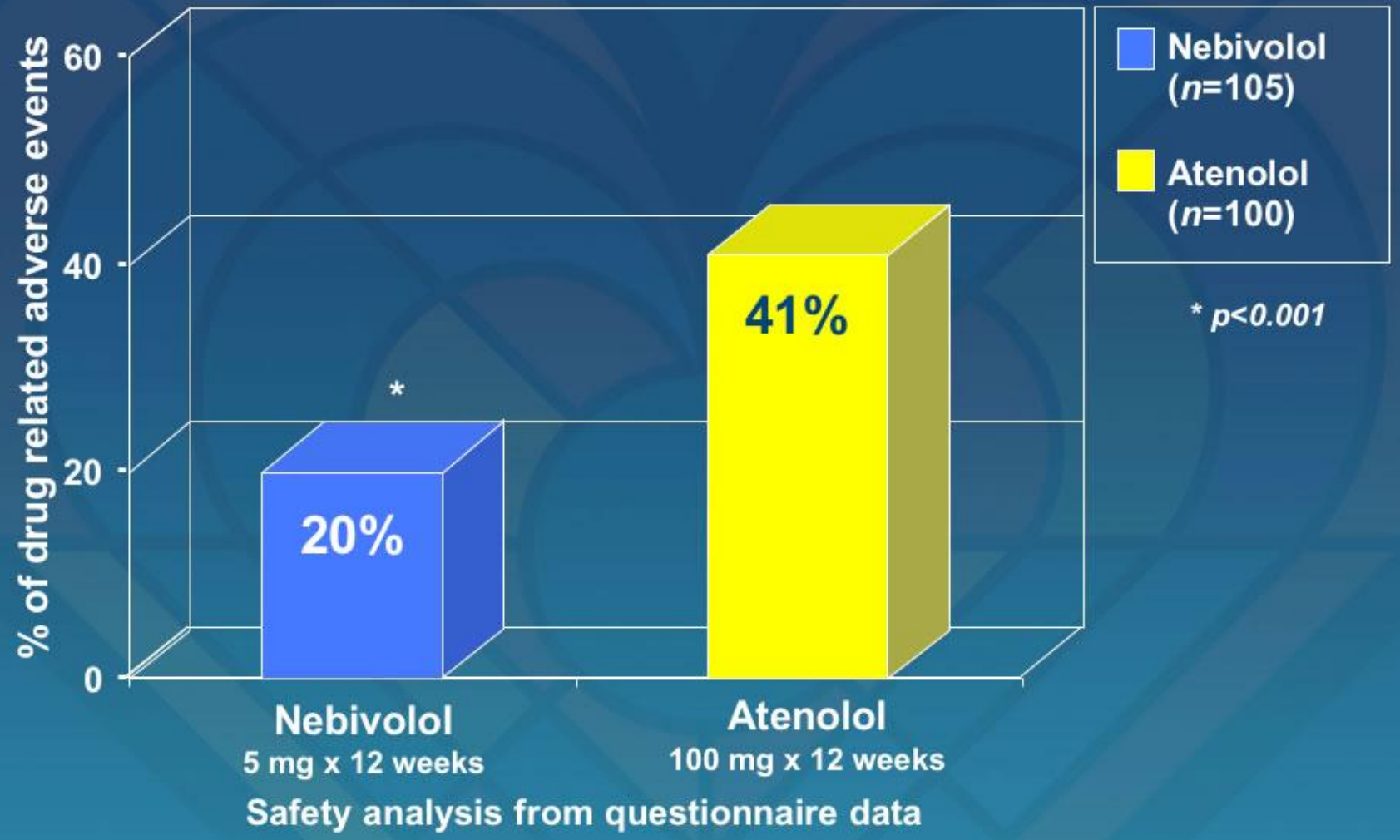
Improved physical performance



Increase of total exercise duration in patients with coronary heart disease and left ventricular dysfunction

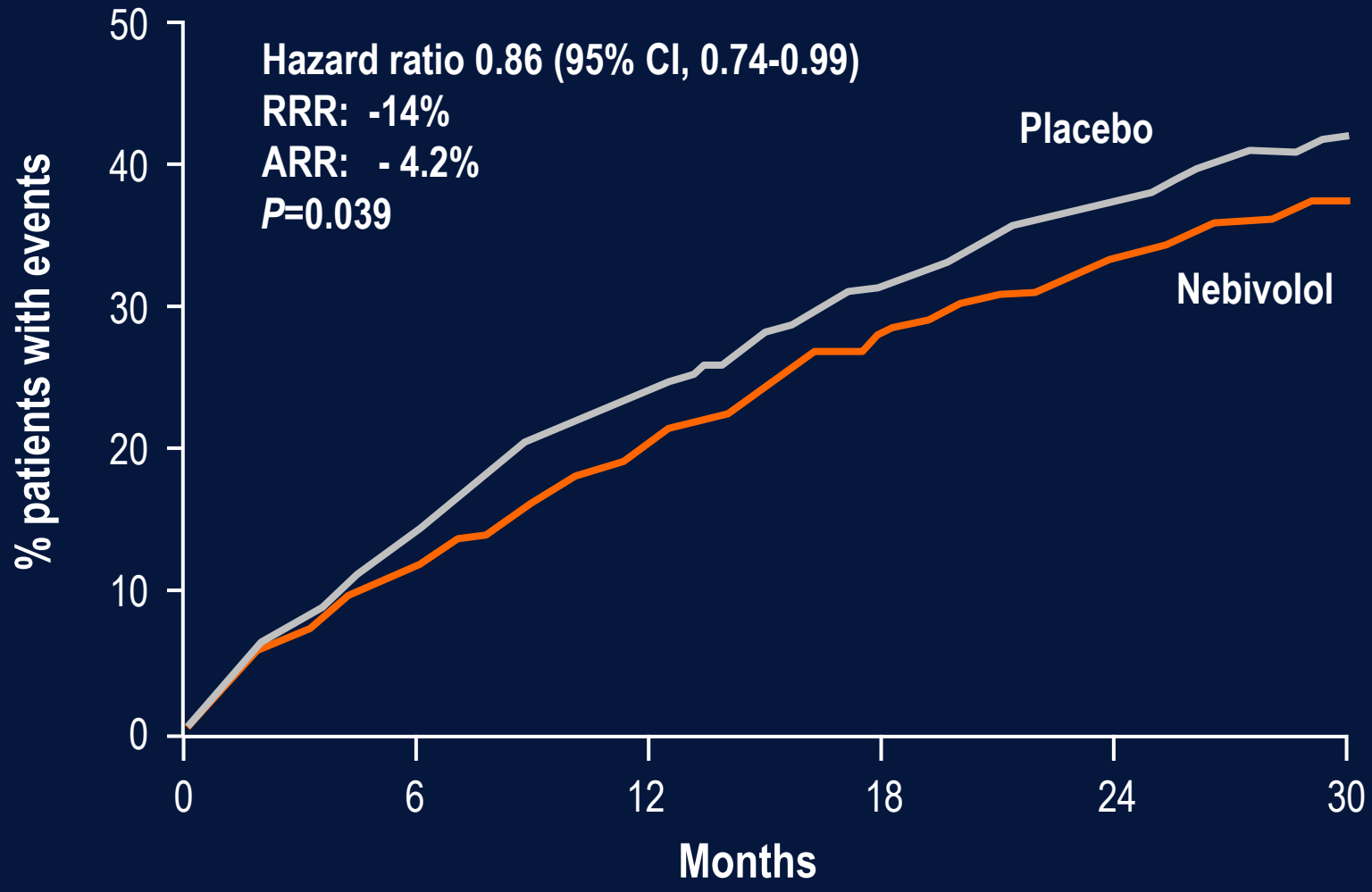
Rosseau MF, et al. J Cardiac Failure 1996; 2(1):15-23

Tolerability: nebivolol *vs* atenolol



Grassi G, et al. Blood Pressure 2003; 12:1-7

SENIORS Primary Endpoint: All-cause Mortality and CV Hospitalizations

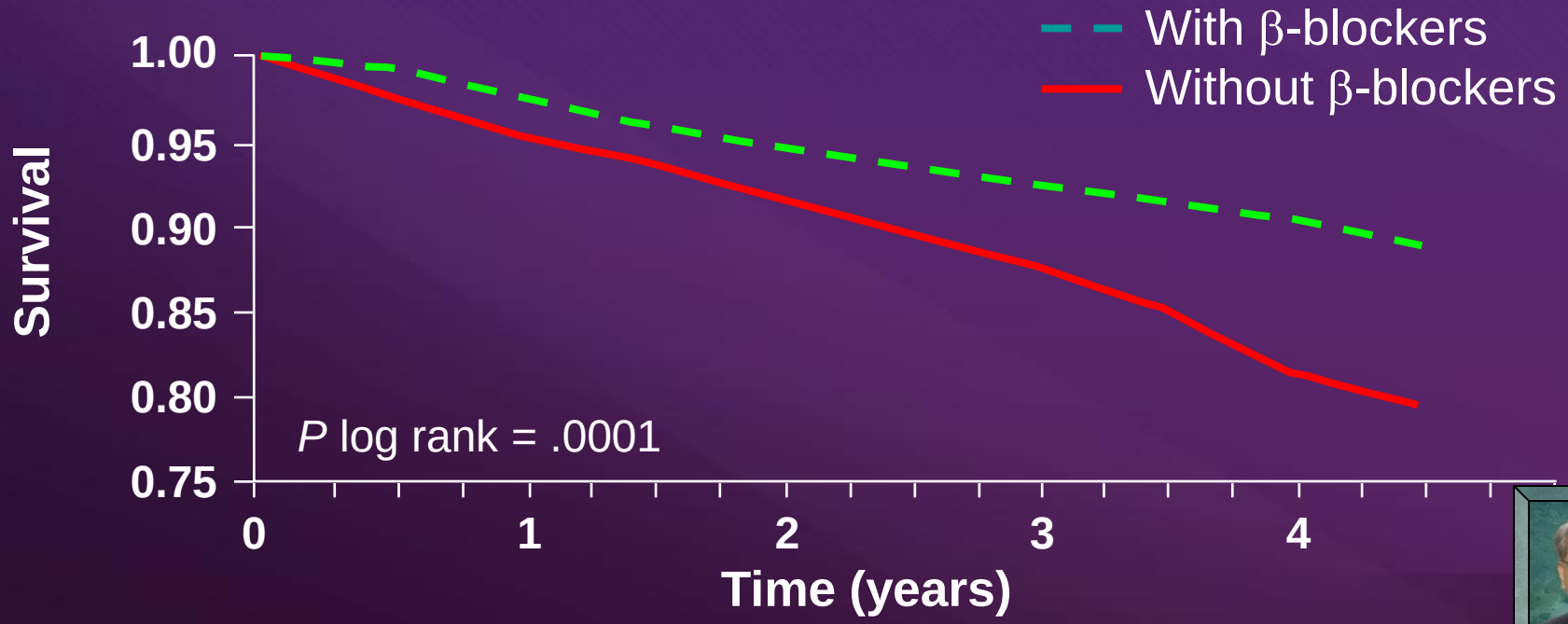


Flather MD. *EHJ.* 2005;26:215-225.

β-Blockers in Diabetic Patients with CAD

Benzafibrate Infarction Prevention Study

- 2,723 patients with type 2 diabetes and CAD
- After 3 years, there was a 44% reduction in cardiac events with β-blockers (7.8% vs. .14%)
- 42% reduction in cardiac mortality



Jonas M, et al. *Am J Cardiol*. 1996;77:1273-1277.

Not All β-Blockers are the Same

"…the β-blocker class is perhaps the most heterogeneous of all the antihypertensive drug classes."[1]

"The β-blocker class…is markedly heterogeneous, and perhaps outcomes achieved with nonvasodilating β-blockers such as atenolol should not be extrapolated to all β-blockers, and in particular to the newer, vasodilating β-blockers."[2]

Basile J. *J Clin Hypertens.* 2006;8(8 suppl 2):21-30.
Pedersen ME, Cockcroft JR. *Curr Hypertens Rep.* 2006;8:279–286

Beneficial Effects of Nebivolol in Comparison with Atenolol on Safety and Pharmacology Section Tolerability in Essential Hypertension

- Prospective, double blind, comparative controlled clinical trial.
- No of patients enrolled (N): 90 patients.
- 45 patients in each group were randomized to receive Atenolol and Nebivolol.
- Duration: 12 weeks

Results:

- The mean reduction diastolic blood pressure in Nebivolol and Atenolol group was 10.77±2.60 and 10.05±2.83 respectively.

Bhosale VV et al. Beneficial Effects of Nebivolol in Comparison with Atenolol on Safety and Tolerability in Essential Hypertension. Journal of Clinical and Diagnostic Research. 2014 Jun; 8(6): HC01-HC04.

Beneficial Effects of Nebivolol in Comparison with Atenolol on Safety and Pharmacology Section Tolerability in Essential Hypertension

- The number of patients with adverse effect events was higher in the Atenolol than in the Nebivolol group (36.84% of Atenolol Vs 12.82% of Nebivolol).
- Majority of patients in Nebivolol group than Atenolol group rated the therapy as good and excellent.

Conclusion: For the same antihypertensive effect, Nebivolol was better tolerated and excellent drug than Atenolol.

Bhosale VV et al. Beneficial Effects of Nebivolol in Comparison with Atenolol on Safety and Tolerability in Essential Hypertension. Journal of Clinical and Diagnostic Research. 2014 Jun; 8(6): HC01-HC04.

Nebivolol, But Not Metoprolol, Treatment Improves Endothelial Fibrinolytic Capacity in Adults With Elevated Blood Pressure

VBWG

- Double-blind, randomized, placebo-controlled trial comparing nebivolol (5 mg/d), metoprolol succinate (100 mg/d), and placebo.
- No. of patients: 44 middle-aged adults (36% women) with elevated BP
- Duration of study: 3-month
- Net endothelial t-PA release was determined in vivo before and after each intervention.
- At baseline, resting BP and endothelial t-PA release were comparable between the 3 groups.

Stauffer BL et al. Nebivolol, But Not Metoprolol, Treatment Improves Endothelial Fibrinolytic Capacity in Adults With Elevated Blood Pressure. J Am Heart Assoc. 2017 Nov 9;6(11).

Results:

- **BP decreased to a similar extent (10 mm Hg) in the nebivolol- and metoprolol-treated groups.**

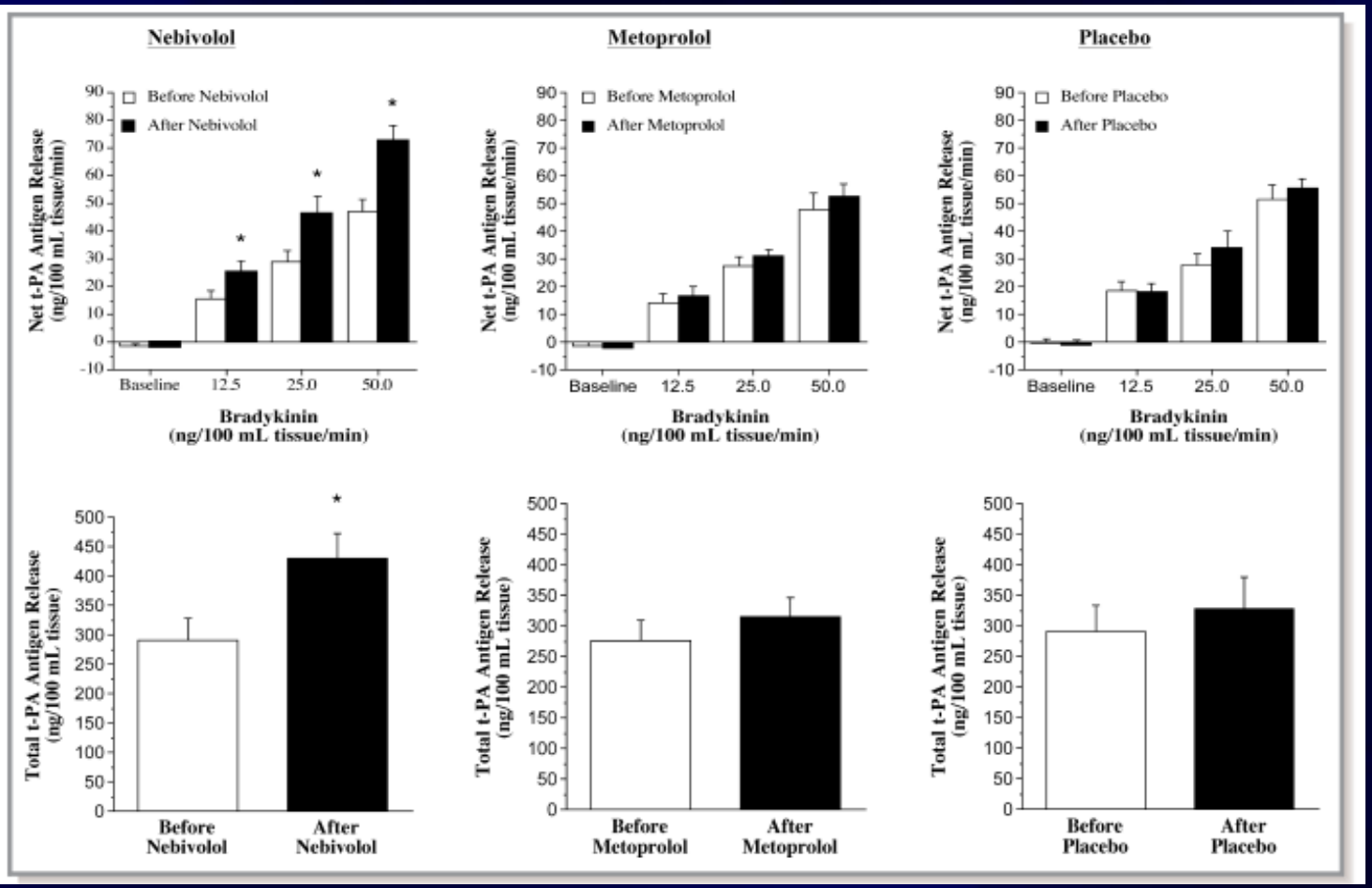


Figure 1. Nebivolol, but not metoprolol, treatment improves tissue-type plasminogen activator (t-PA) release.

Stauffer BL et al. Nebivolol, But Not Metoprolol, Treatment Improves Endothelial Fibrinolytic Capacity in Adults With Elevated Blood Pressure. J Am Heart Assoc. 2017 Nov 9;6(11).

Hypertension treatment in the Asia-Pacific: Summary of Studies

Clinical efficacy and tolerability of nebivolol:

- Study by Park S et al demonstrated that intervention with nebivolol, but not with metoprolol succinate, resulted in significantly reduced central systolic and diastolic BPs, central pulse pressure and left ventricular wall thickness in hypertensive patients (aged 30– 65 years) treated for 1 year.[1]

- Study by Dhakam Z et al showed that Nebivolol reduced aortic pulse pressure to a greater extent than atenolol, and yet affects a less pronounced impact on augmentation index (AIx).[2,]

- Study by Studinger P et al showed that as compared with carvedilol and metoprolol, nebivolol treatment resulted in a statistically significant reduction of heart rate-adjusted AIx values.[3]

1.Park S. et al. J Hypertens 2013;31:813–19.
2.Dhakam et al. J Hypertens 2008;26:351–6.
3.Redón J et al. Blood Press 2014;23:181–8.

Hypertension treatment in the Asia-Pacific: Summary of Studies

Clinical efficacy and tolerability of nebivolol:

- Nebivolol offers beneficial hemodynamic effects in hypertensive patients because of its vasodilating properties.[5]

- Study by Brett SE et al reports that In contrast to bisoprolol, nebivolol does not lead to a reduction in cardiac index. [5]

- Patrascu N et al. reports that favourable haemodynamic profile of nebivolol (ie, preservation of cardiac output and index, reduction of peripheral resistance and improved diastolic function) might provide hypertensive patients with clinically relevant benefits regarding the impairment of systolic and/or diastolic function.[6]

4.Studinger P,. J Clin Hypertens (Greenwich) 2013;15:910–17.
5.Brett SE et al. Clin. Drug Investig. 2002;22:355–9
6. Patrascu N. Maedica (Buchar) 2013;8:285–9

Nebivolol- Dosage & Administration

- **Hypertension**
  5 mg OD with or without meals
  Elderly and renal dysfunction cases – 2.5 mg OD

- **CHF**
  2.5 mg was found to be better tolerated may be increased to 5 mg OD & Max up to 10 mg OD

- **Angina**
  5 mg OD

Conclusion

- Beta blockers are not all created equally.
- Third generation, cardioselective beta blockers produce clinical outcomes that differ from traditional beta-blockers.
- These effects may be linked to nitric oxide production and other hemodynamic effects.
- Nebivilol is an effective antihypertensive and with its plieotropic benefits decreases the CV risk.

Thank You