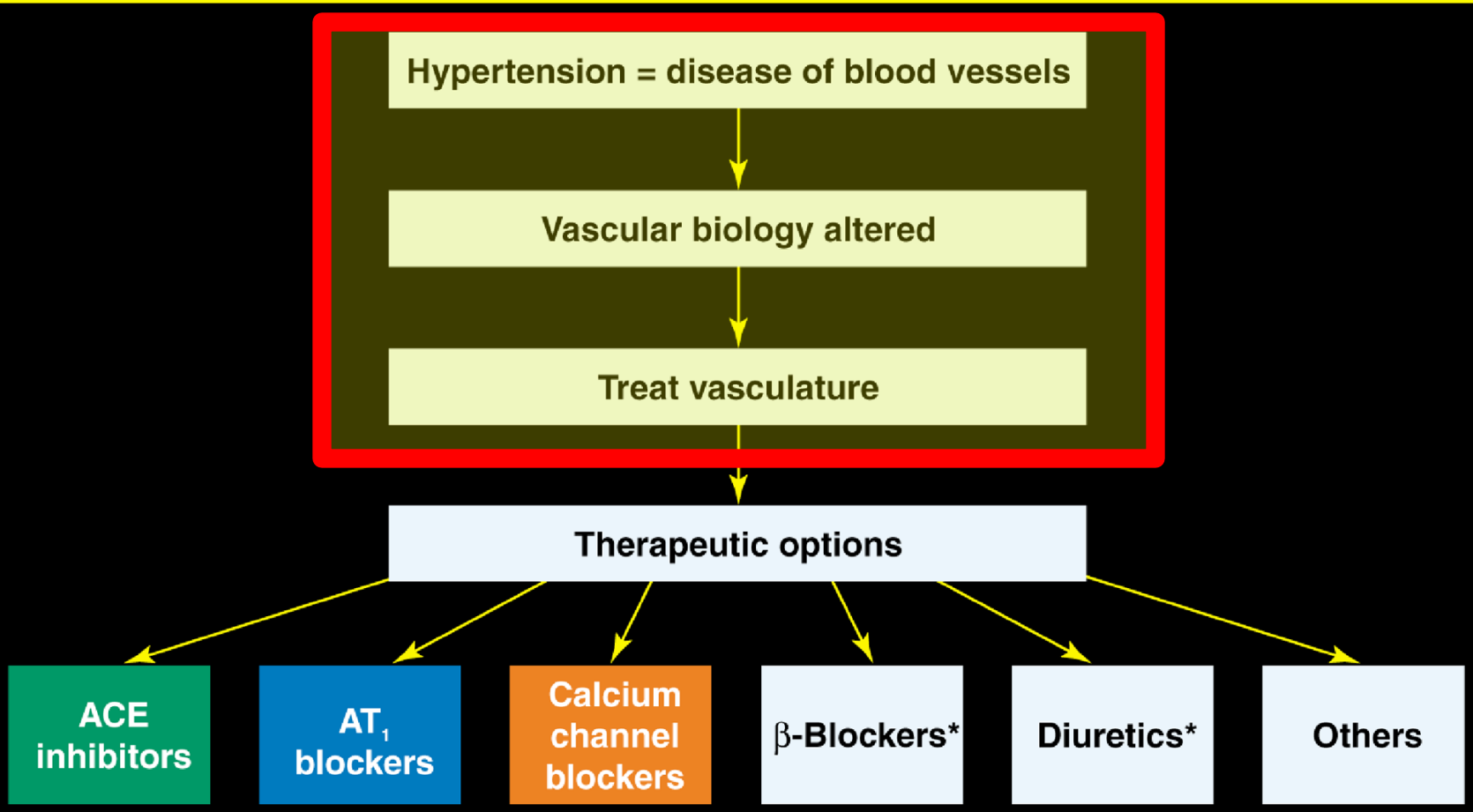
Endothelial dysfunction and Nitric Oxide in Hypertension

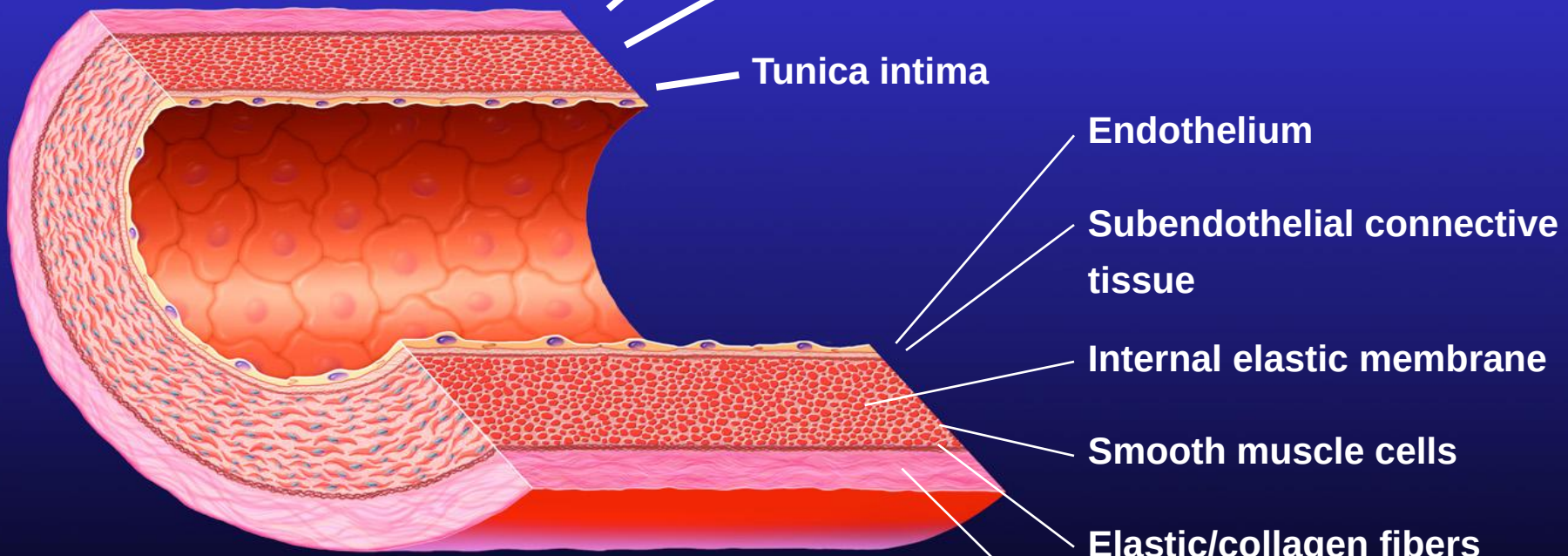
A\Prof. Truong Quang Binh MD, PhD, FSCAI
University Medical Center

New treatment approach

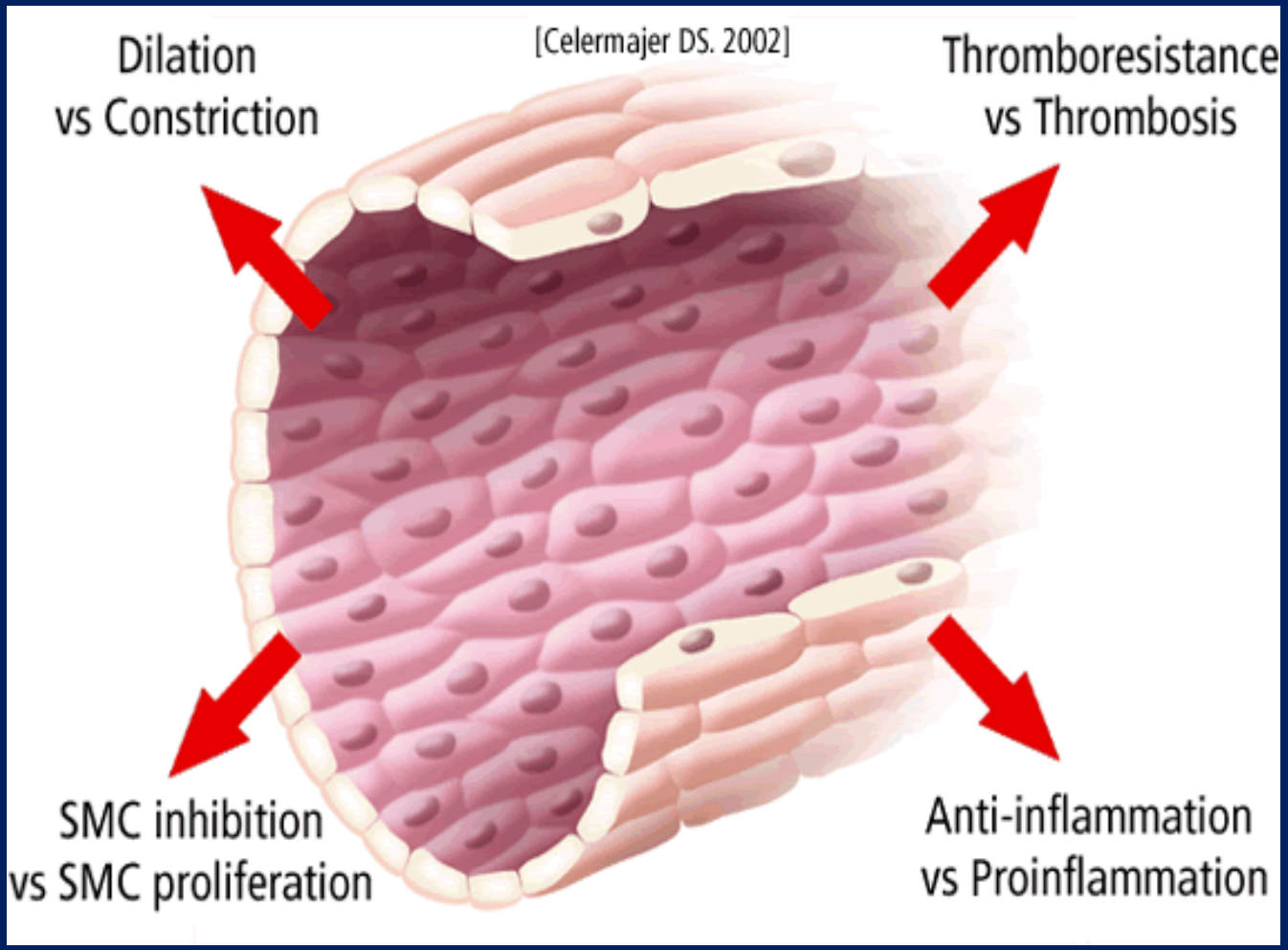


*Minimal evidence of effects on endothelial function

Endothelium:The Largest Living Organ



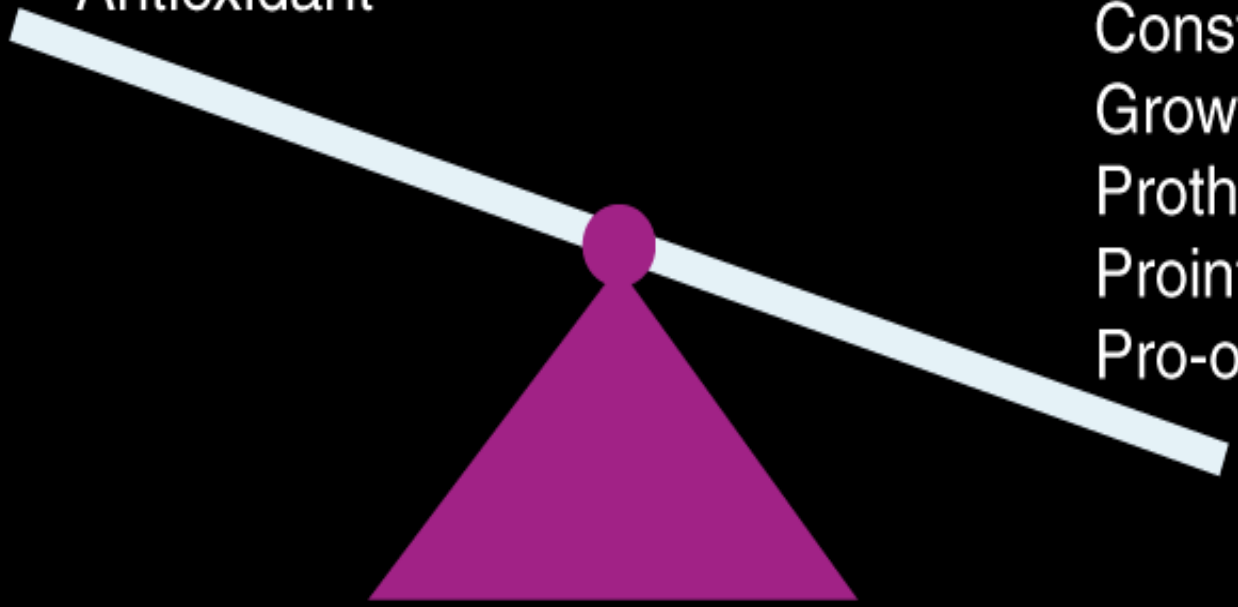
Endothelium:The Largest Living Organ



1 ½ kg. 6 tennis courts

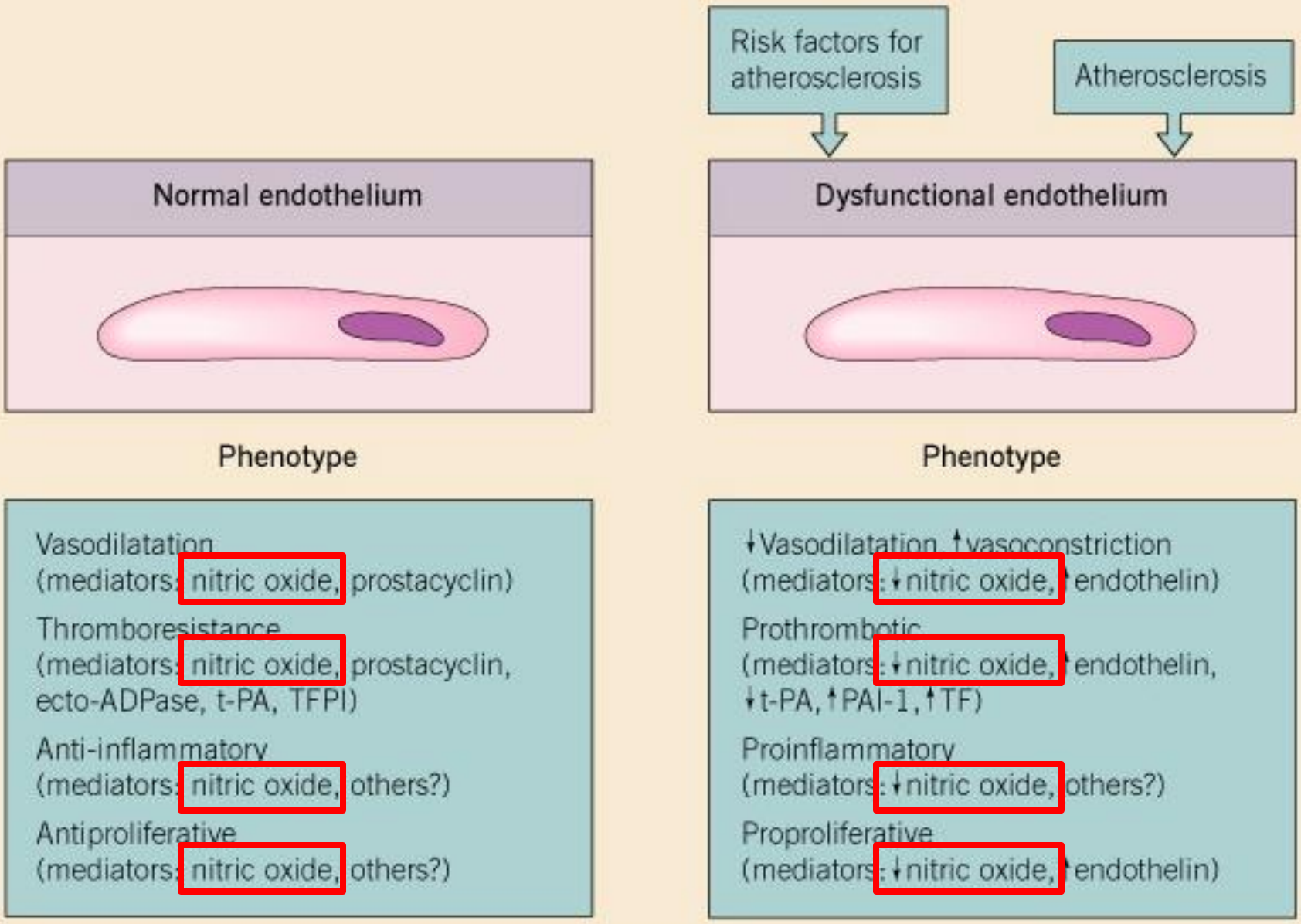
The endothelium maintains vascular health

Dilatation
Growth inhibition
Antithrombotic
Anti-inflammatory
Antioxidant



Constriction
Growth promotion
Prothrombotic
Proinflammatory
Pro-oxidant

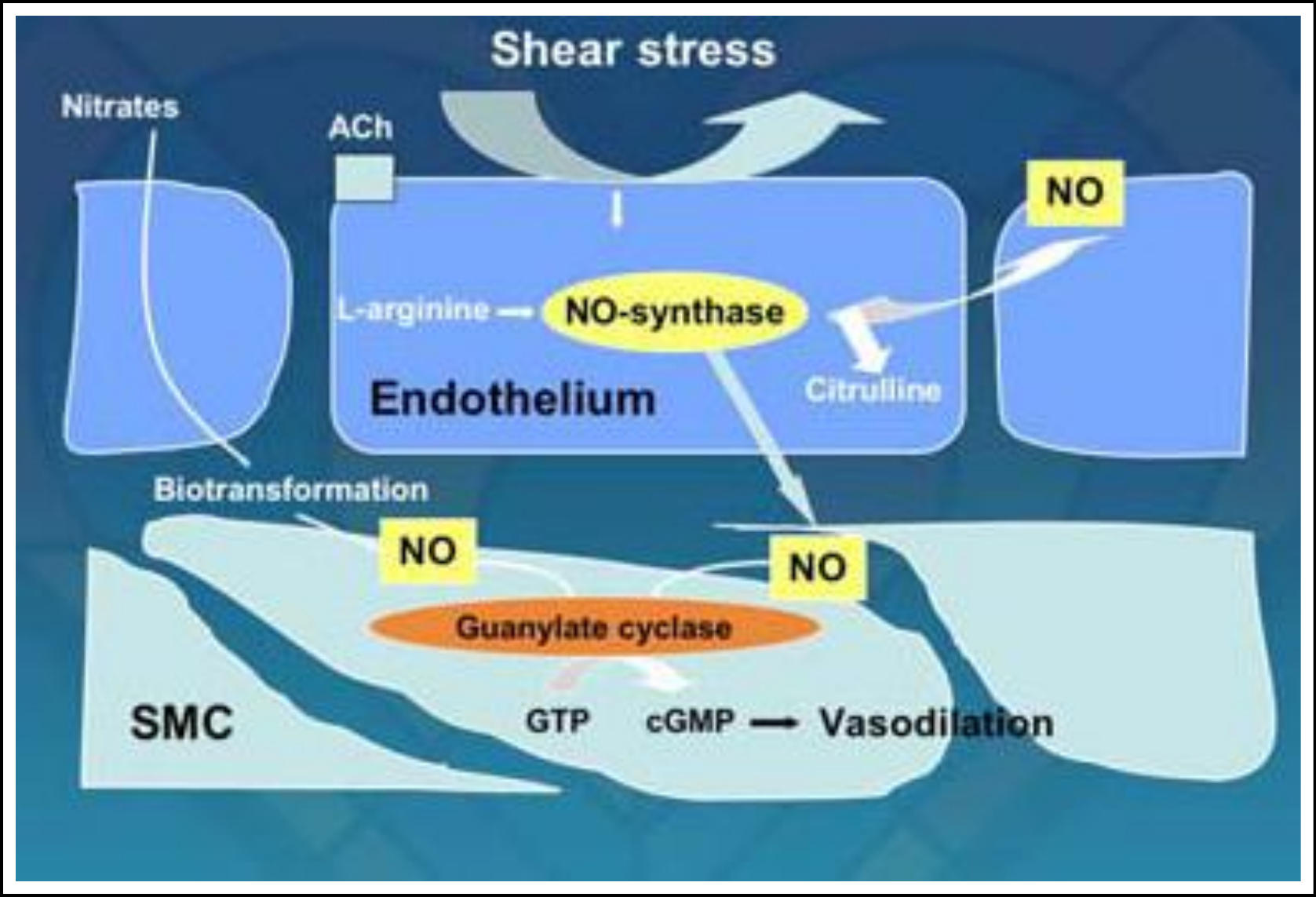
NORMAL AND DYSFUNCTIONAL ENDOTHELIUM

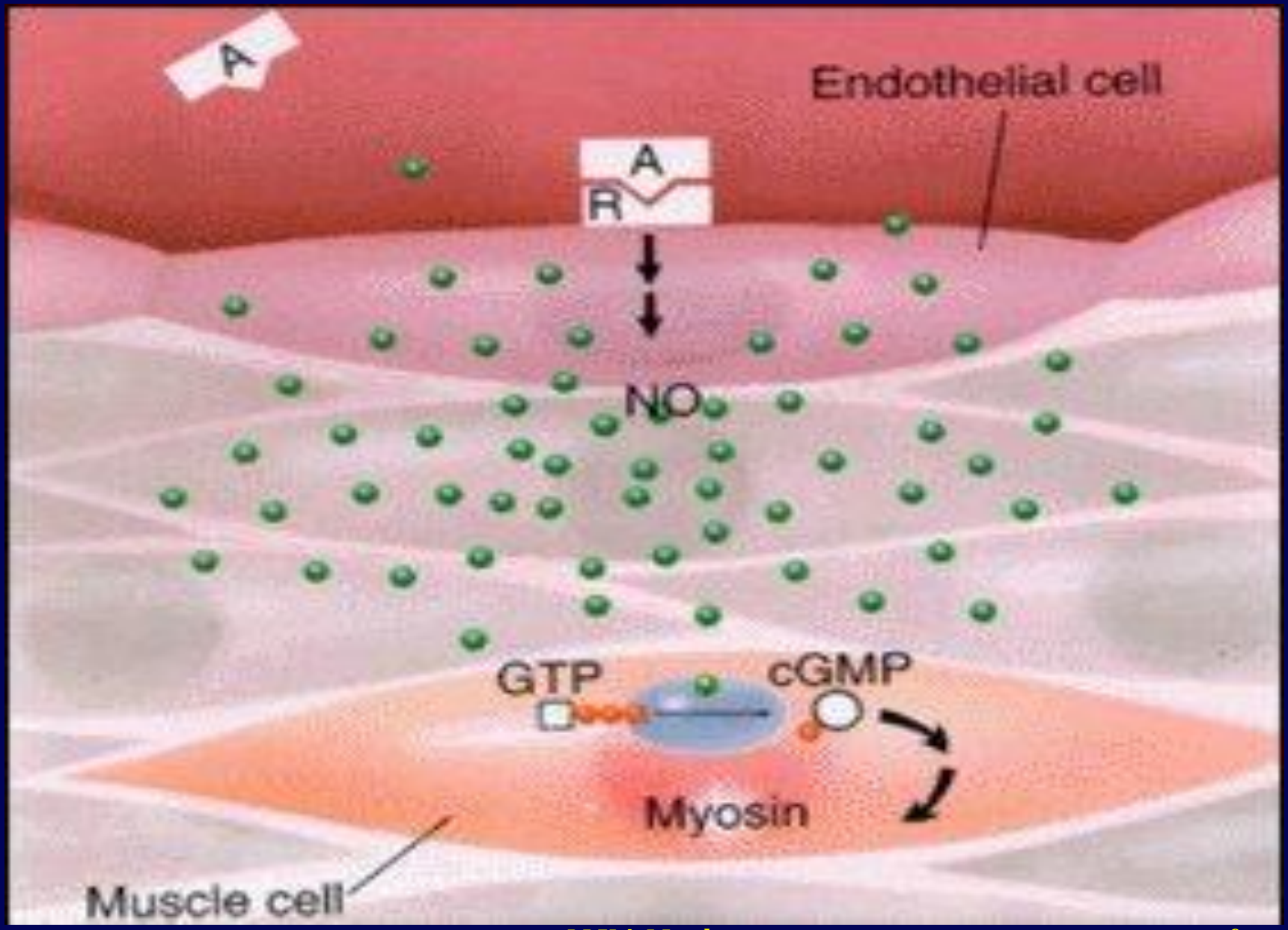


Effects of endothelium-derived NO

- Vasodilatation
- Inhibition of platelet aggregation and adhesion
- Inhibiton of white cell adhesion
- Inhibition of vascular smooth muscle cell growth
- Regulation of oxygen consumption
- Anti-atherogenesis

Synthesis and action of Nitric oxide



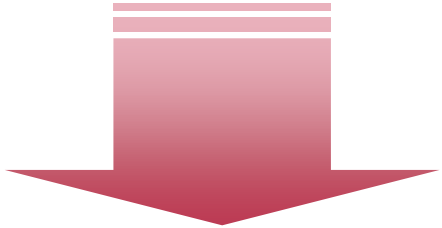

A
Endothelial cell
A
R
NO
GTP
cGMP
Myosin
Muscle cell

Nitric oxide contributes to the regulation of BP
Impaired NO bioactivity is associated with hypertension

Decreased NO production

Decreased endothelial vasodilation

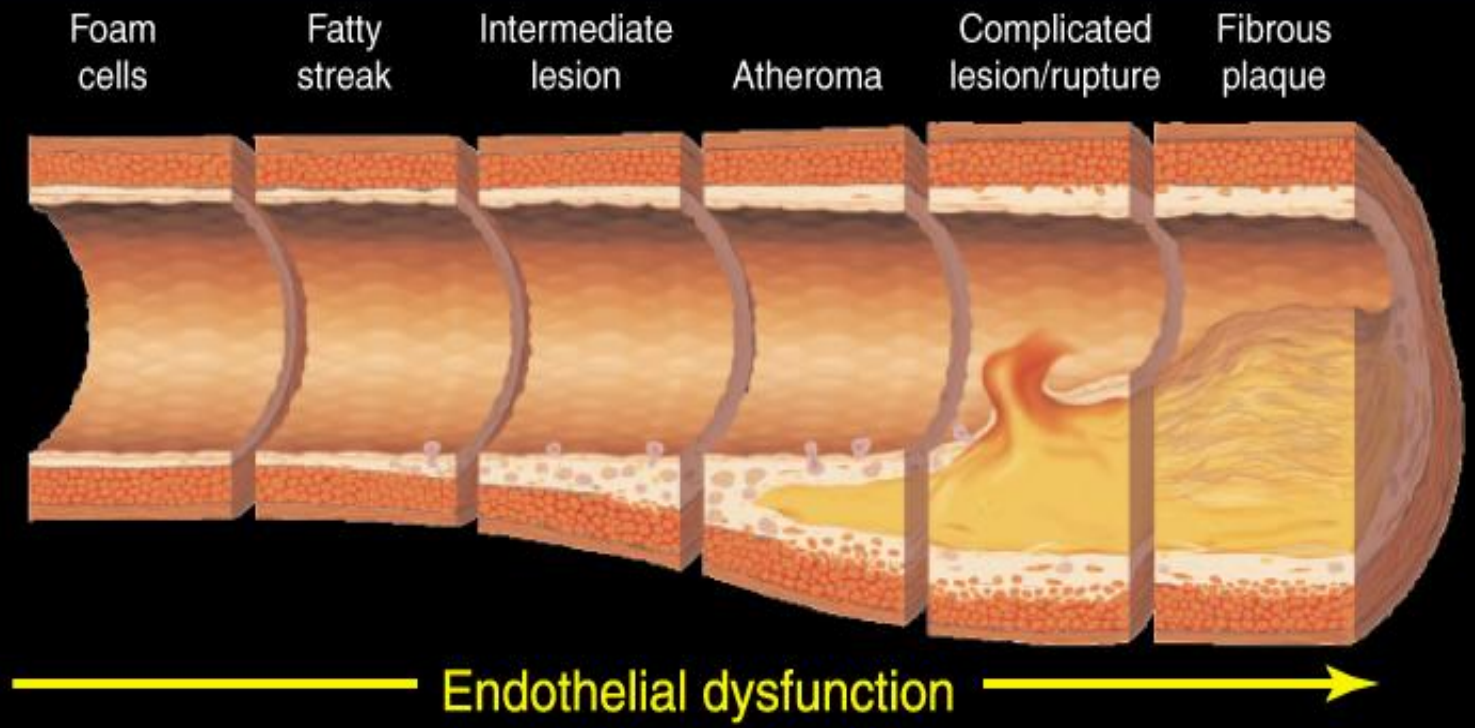
Increased vascular resistance



Essential hypertension

Calver A, et al. J Hypertens 1992; 10:1025-31.

Atherosclerosis timeline



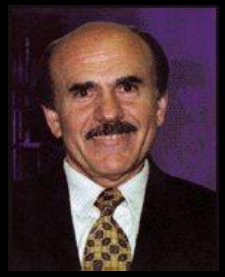
Adapted from Pepine CJ. *Am J Cardiol.* 1998;82(suppl 10A:23S-27S).

The 1998 Nobel Prize in Physiology or Medicine

The 1998 Nobel Prize in Physiology or Medicine

Discoveries concerning "the nitric oxide as a signalling molecule in the cardiovascular system".

Robert F Furchgott, born 1916
Dept. of Pharmacology, SUNY Health Science Center
New York



Louis J Ignarro, born 1941
Dept. of Molecular and Medical Pharmacology
UCLA, Los Angeles

Ferid Murad, born 1936
Dept. of Integrative Biology Pharmacology & Physiology
University of Texas, Houston

Drugs shown to improve endothelial function in patients

ACE inhibitors	↑↑↑
HMG-CoA reductase inhibitors	↑↑↑
Calcium channel blockers	↑↑
Thiazolidinediones	(↑↑)
Estrogen	(↑↑)
L-arginine	(↑↑)
Antioxidants	(↑)

( ) = Inconclusive, few studies

Kiowski W, et al. *J Hypertens*. 1994;12(suppl 1):S21-S26.
Mancini GBJ, et al. *Circulation*. 1996;96:258-265.
Treasure CB, et al. *N Engl J Med*. 1995;332:481-487.
Diaz MN, et al. *N Engl J Med*. 1997;337:408-416.
Avena R, et al. *J Vasc Surg*. 1998;28:1024-1031.
Harrison DG. *J Clin Invest*. 1997;100:2153-2157.
Cannon RO. *Clin Chem*. 1998;44:1809-1819.
Bush DE, et al. *Am J Med*. 1998;104:552-558.

B-blockers and endothelial function

- Carvedilol which has antioxidant properties may improve endothelial function,

- Nebivolol – endothelium dependent dilatation of blood vessels via L-ariginine / NO pathway.

RECOMMENDATION ON INDICATION OF BB IN TREATMENT CARDIOVASCULAR AT ASEAN COUNTRIES

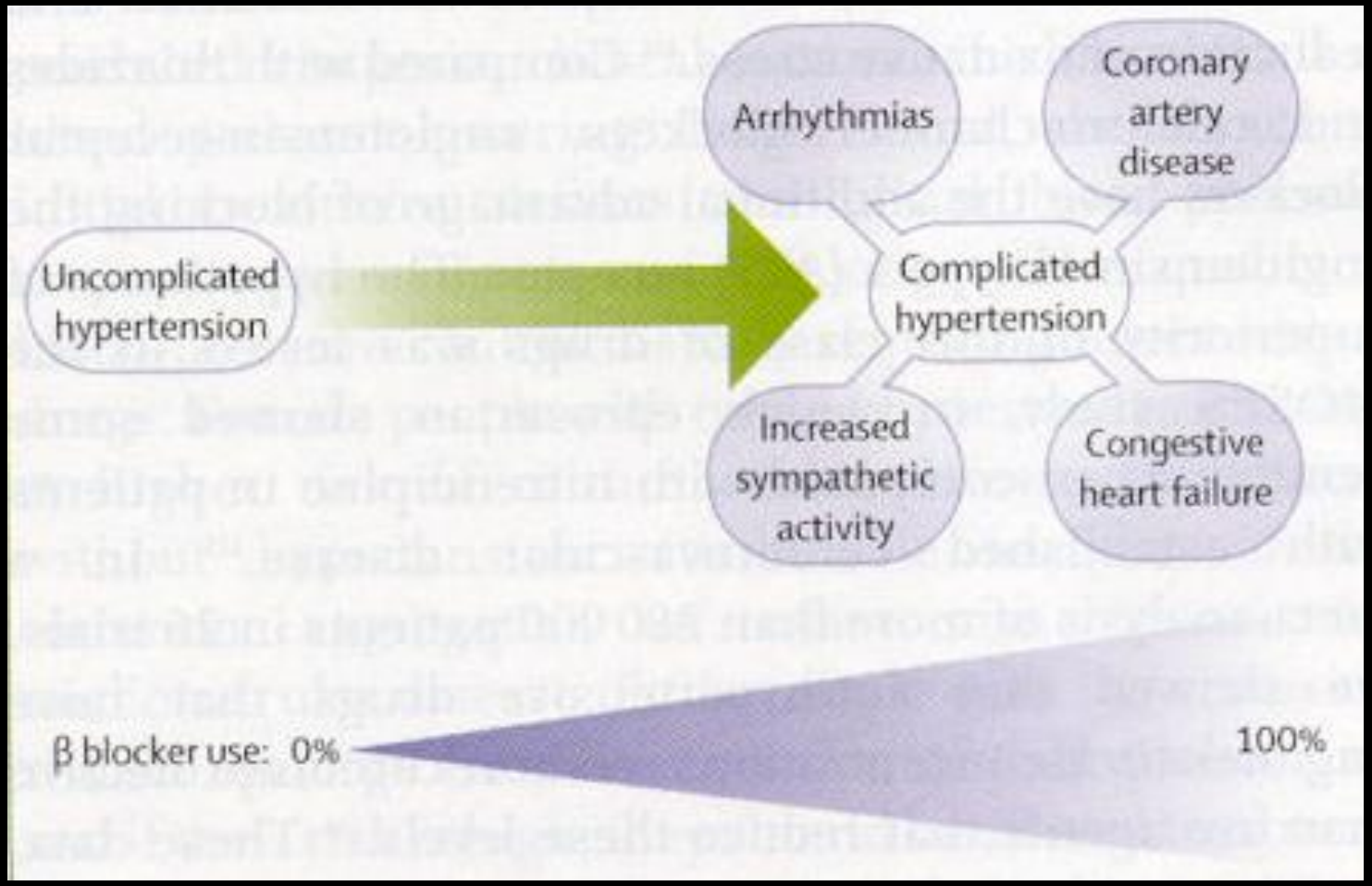
Table 3. Recommended indications for β-blocker therapy in Asian countries.

	Young patients with increased HR	Hypertension with CAD	Hypertension with HF	Tacharrhythmias	Post-MI	Hypertension with diabetes	Angina	High risk of CHD
China	+		+	+				+
Hong Kong	+	+	+	+	+	+	+	
India	+	+	+	+	+		+	
Indonesia	+	+	+	+	+	+	+	
Korea		+	+	+	+		+	
Malaysia		+	+		+		+	
Philippines		+	+	+	+		+	+
Singapore			+	+	+	+	+	

CAD, coronary artery disease; CHD, coronary heart disease; MI, myocardial infarction; HF, heart failure; HR, heart rate.

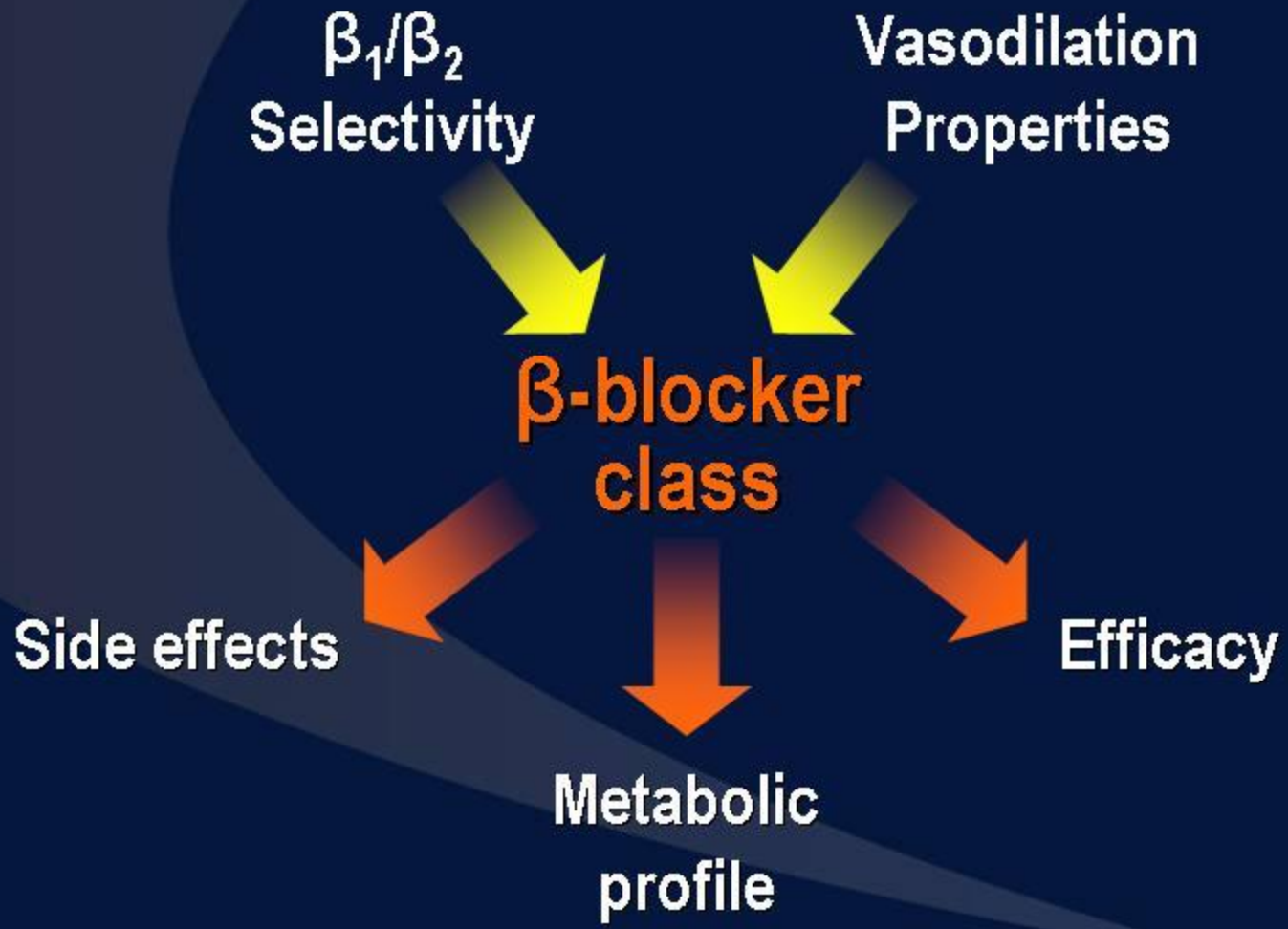
B. Tomlinson và CS. CMRO, Vol 27, No 5, 2011

Betablockers in treatment of hypertension

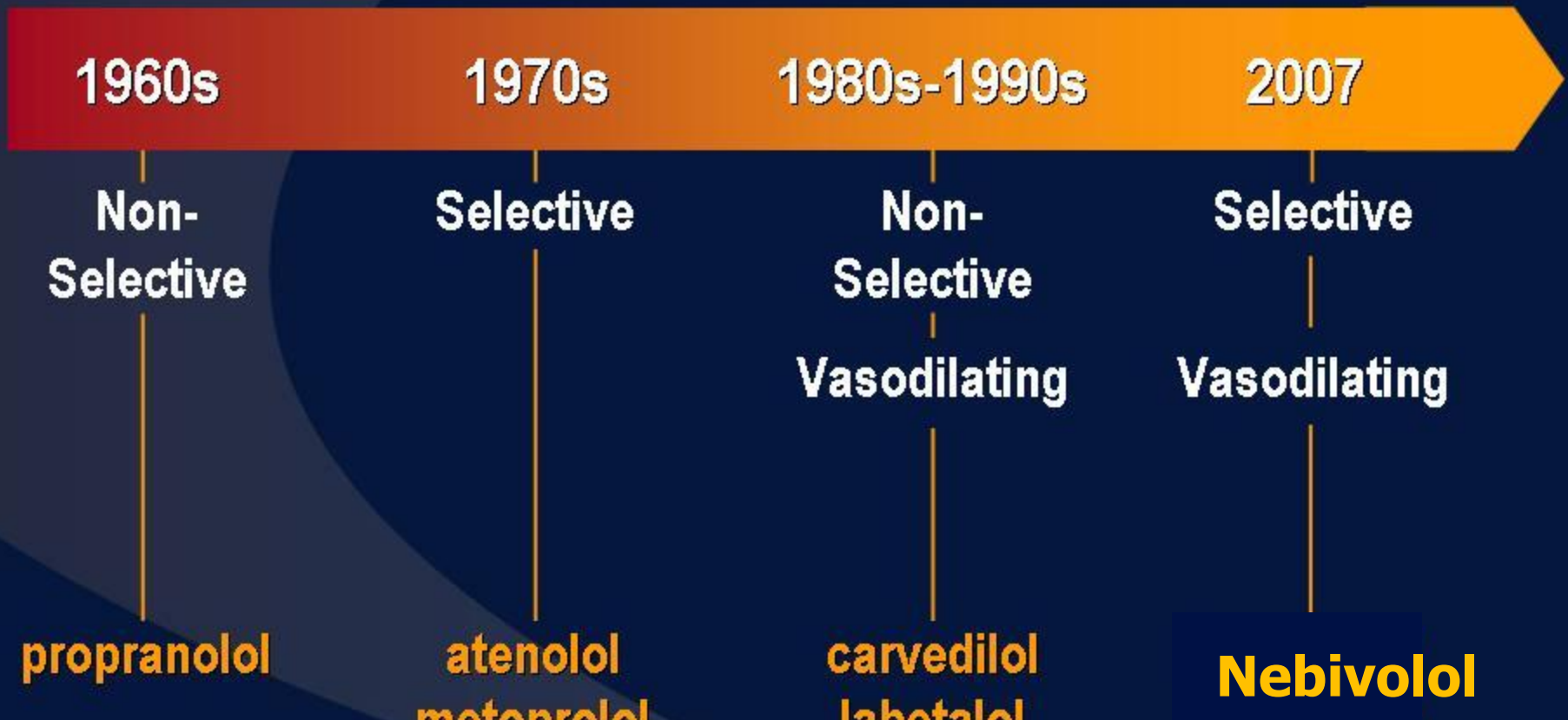


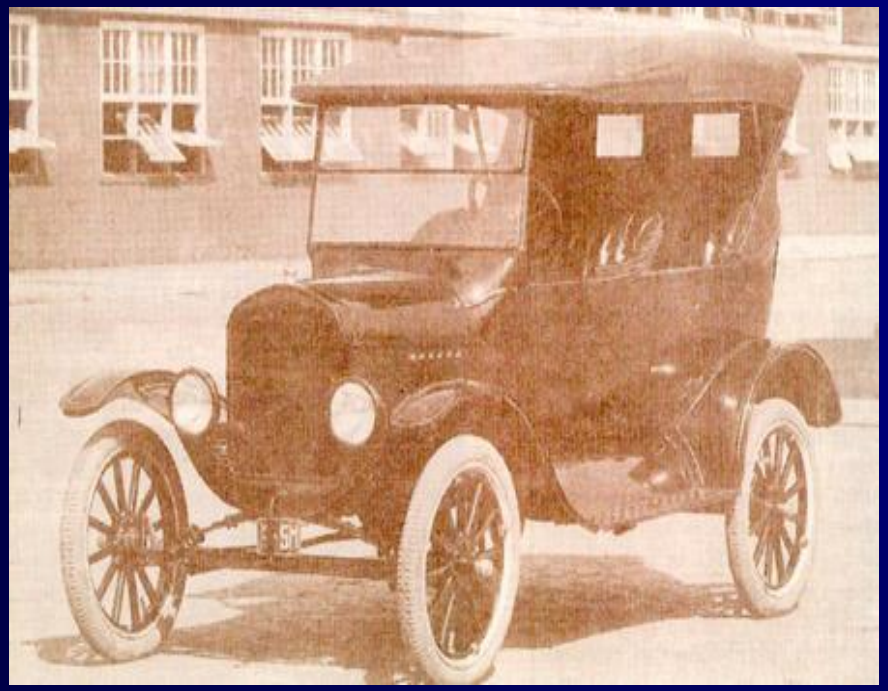
Messerli FH et al. Lancet : 370 August 18, 2007

Main Factors Contributing to Heterogeneity Within the β-blocker Class



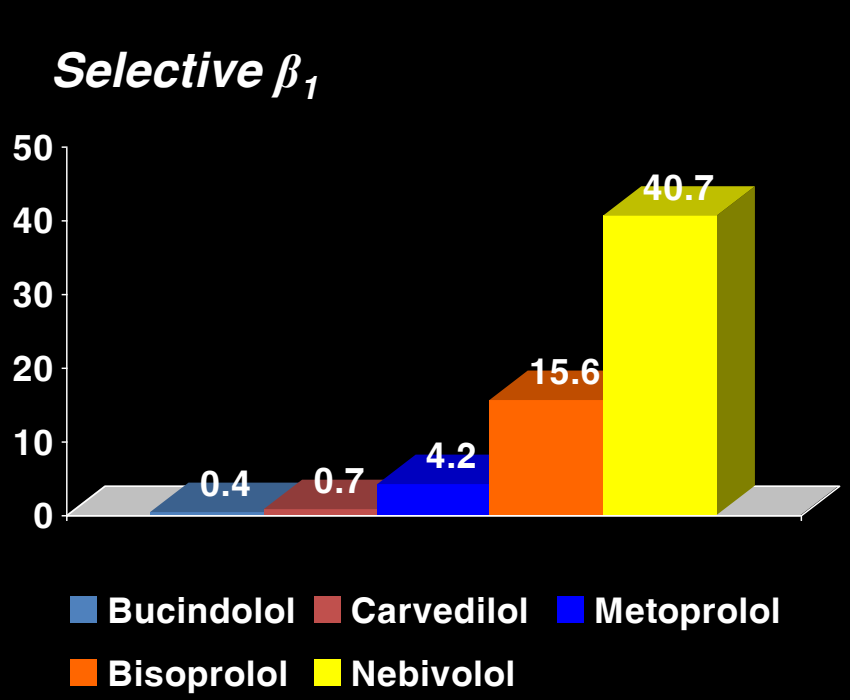
The Evolution of β-blockers

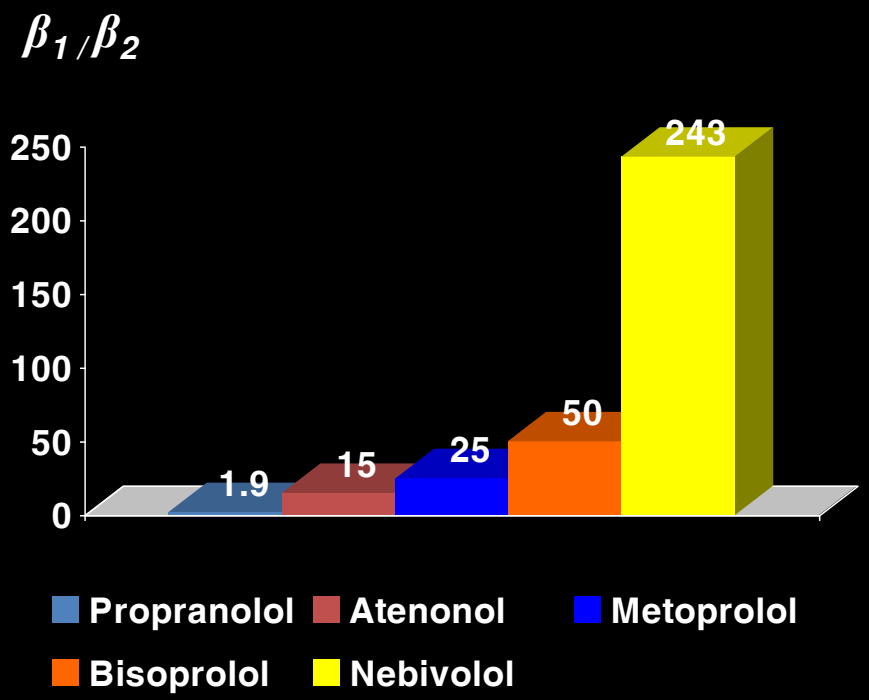




Old BetaBlockers ***New BetaBlocker***

Selective beta1 BB (1), (2)

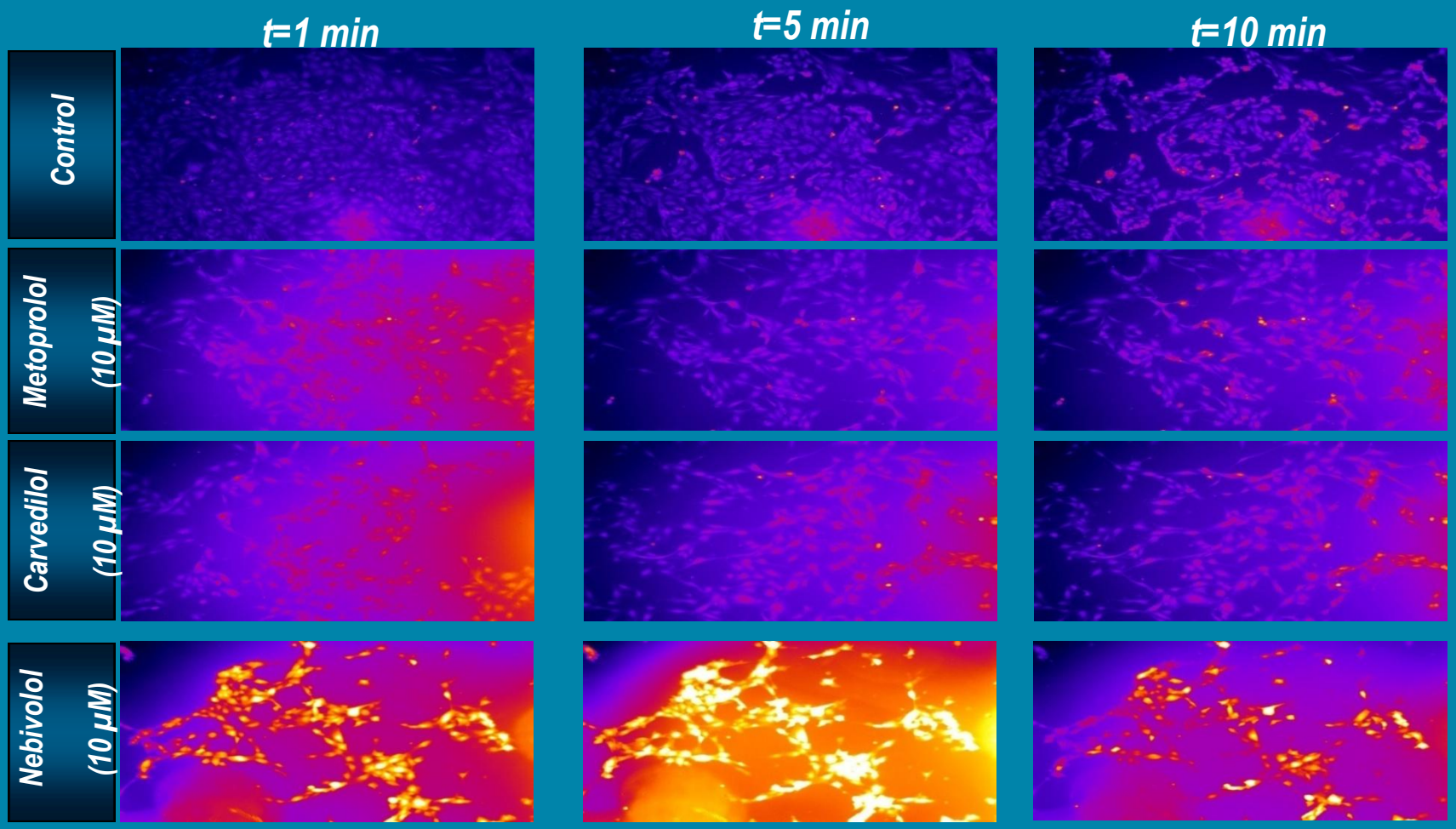




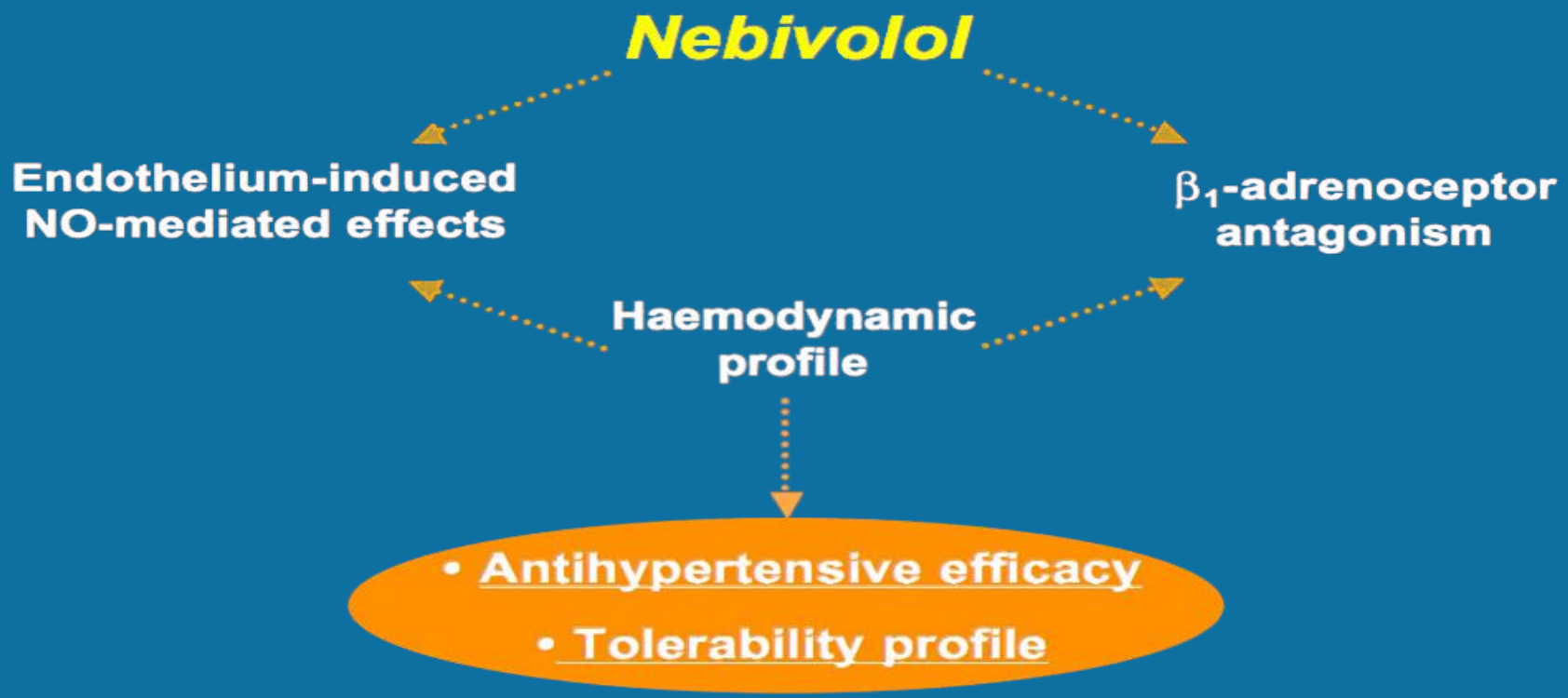
(1) Bundkirchen A et al. 2003. Eur J Pharmacol. 460 (1): 19-26

(2) Nuttall SL et al. June 2003. J Clin Pharm Ther. 28 (3): 179-86

Nebivolol induced NO release from endothelium

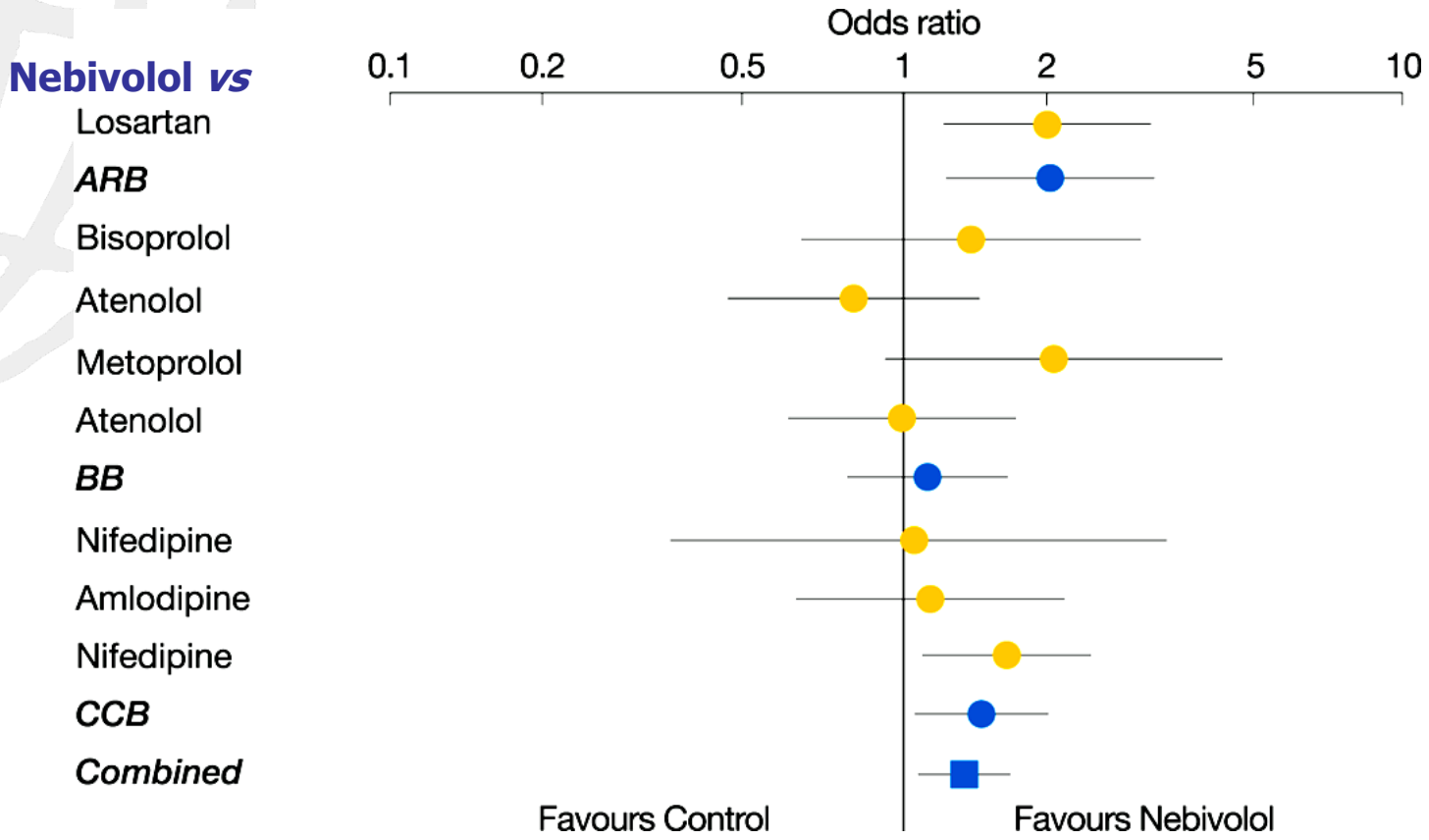


Ladage D et al. : Clin Exp Pharmacol Physiol. 2006;33(8):720-4 and Wien Med Wochenschr. 2009;159(7-8):211-8


Nebivolol
Endothelium-induced NO-mediated effects
β1-adrenoceptor antagonism
Haemodynamic profile
• Antihypertensive efficacy
• Tolerability profile

Meta-analysis of efficacy of antihypertensive agents

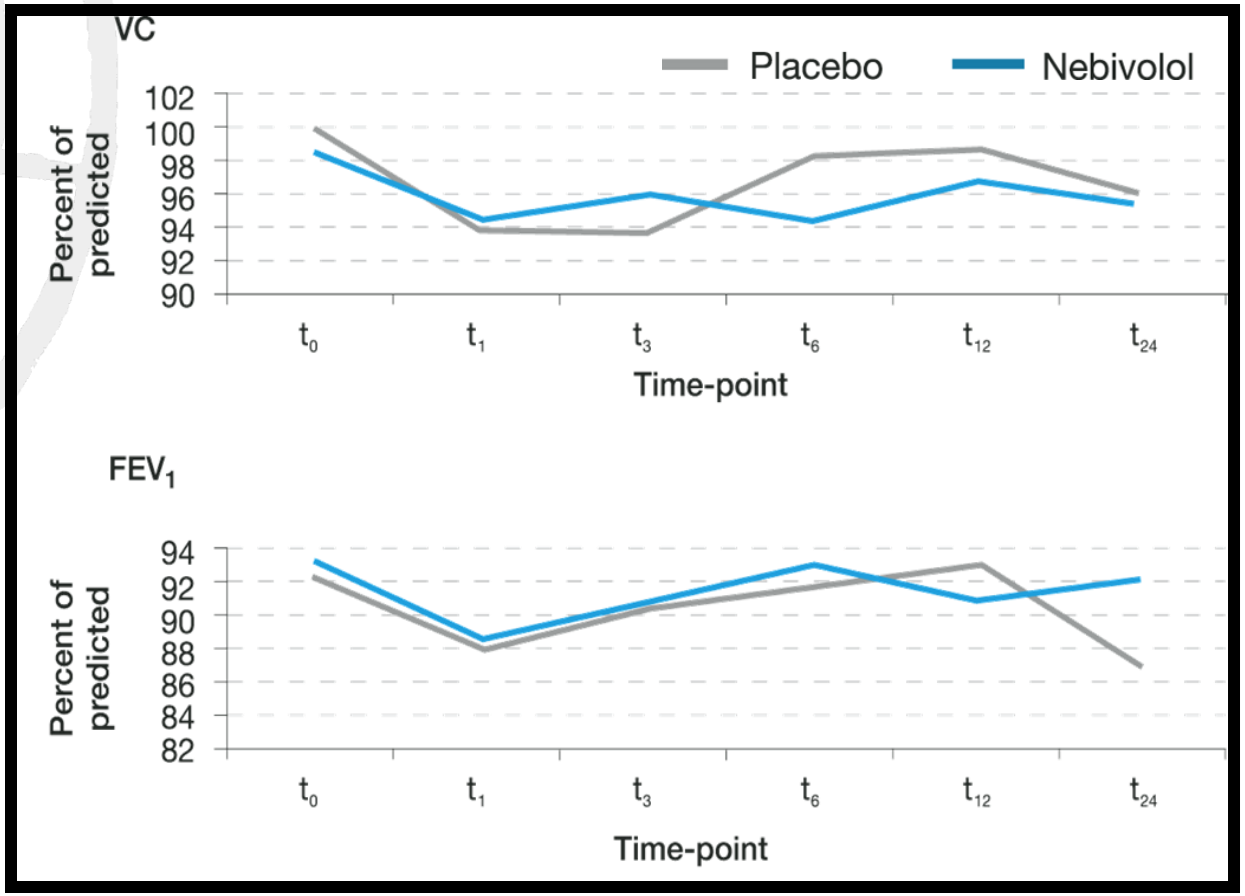
Nebivolol Treatment: Higher Proportion of patients had normalised BP than with other antihypertensive drugs



Van Bortel LA, et al. Am J Cardiovasc Drugs 2008; 8:35-44.

Airway function

Pharmacokinetic study in patients with mild to moderate asthma and arterial hypertension

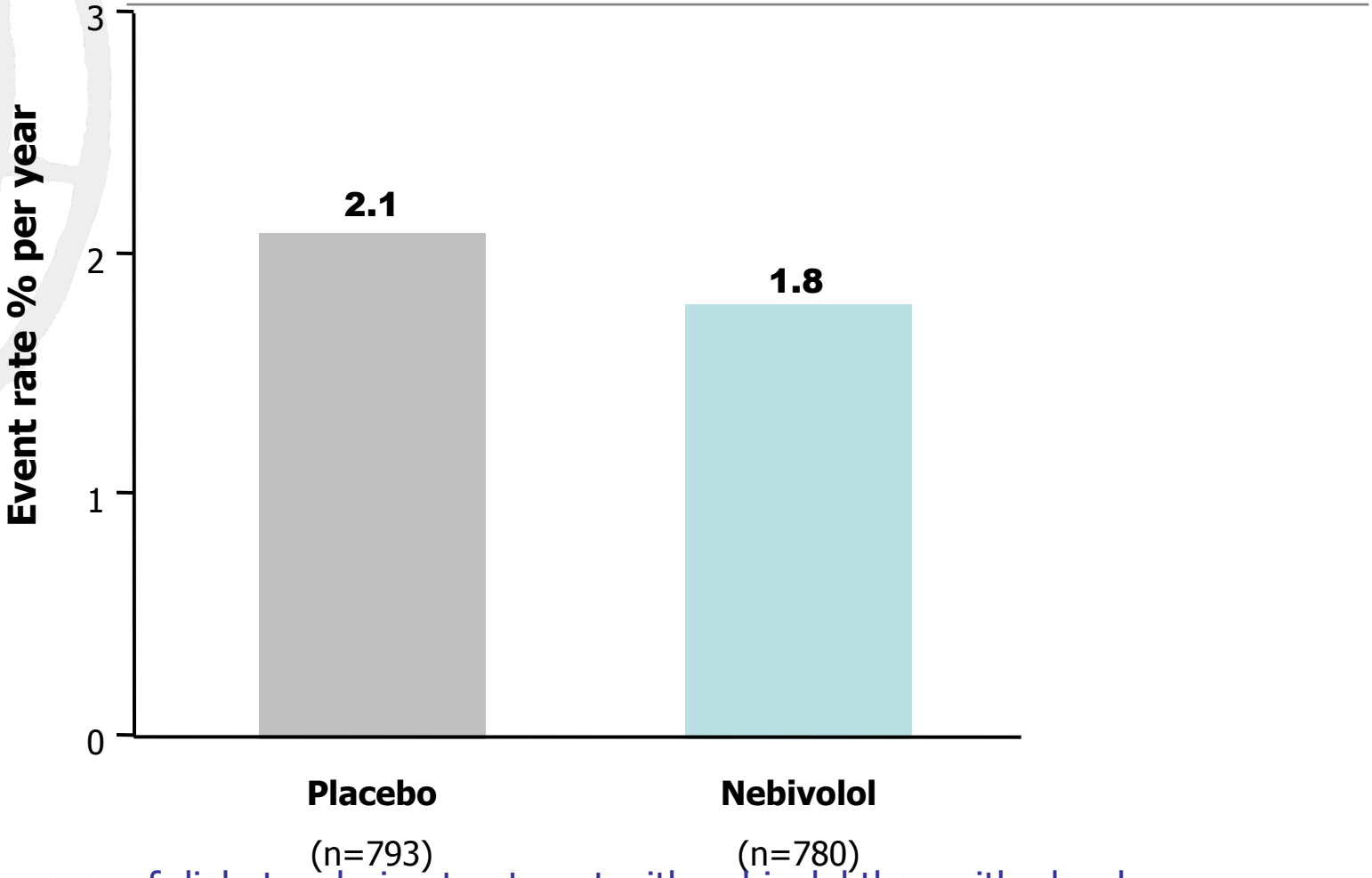


VC: vital capacity; FEV_1: forced expiratory volume in 1 sec

Dal Negro RW, et al. Clin Drug Invest 2002; 22:197-204.

Nebivolol and new-onset diabetes

Data from SENIORS



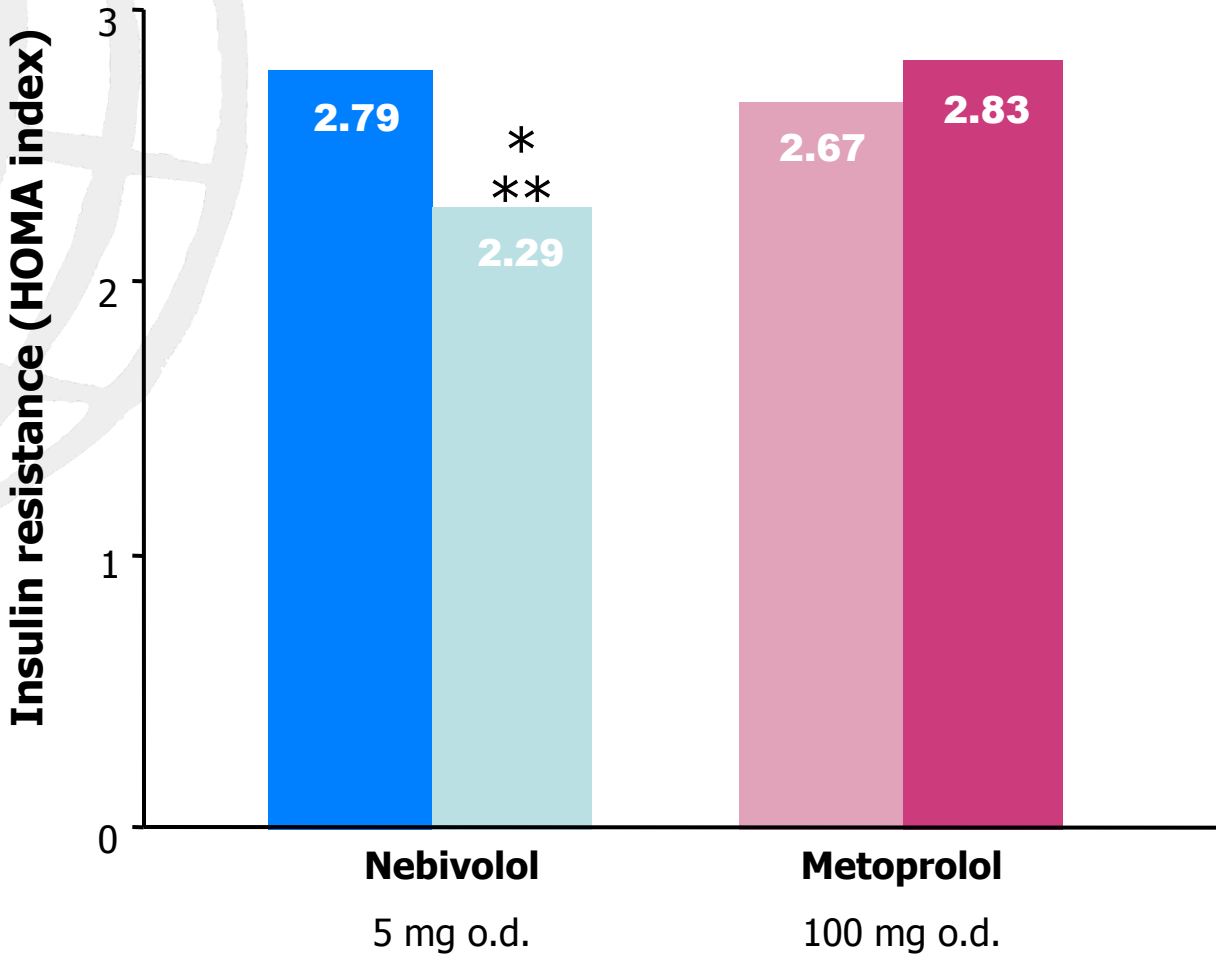
⇒ Fewer new cases of diabetes during treatment with nebivolol than with placebo;

Nebivolol metabolically neutral

Agabiti-Rosei E, et al. Drugs 2007; 67:1097-107.

Nebivolol and carbohydrate metabolism

Insulin resistance



Nebivolol (n=37)
baseline
6 months
Metoprolol (n=35)
baseline
6 months

** p<0.008 vs baseline*

*** p=0.003 vs metoprolol*

Nebivolol was found to decrease plasma insulin and insulin resistance in hypertensive patients

Celik T, et al. J Hypertens 2006; 24:591-6.

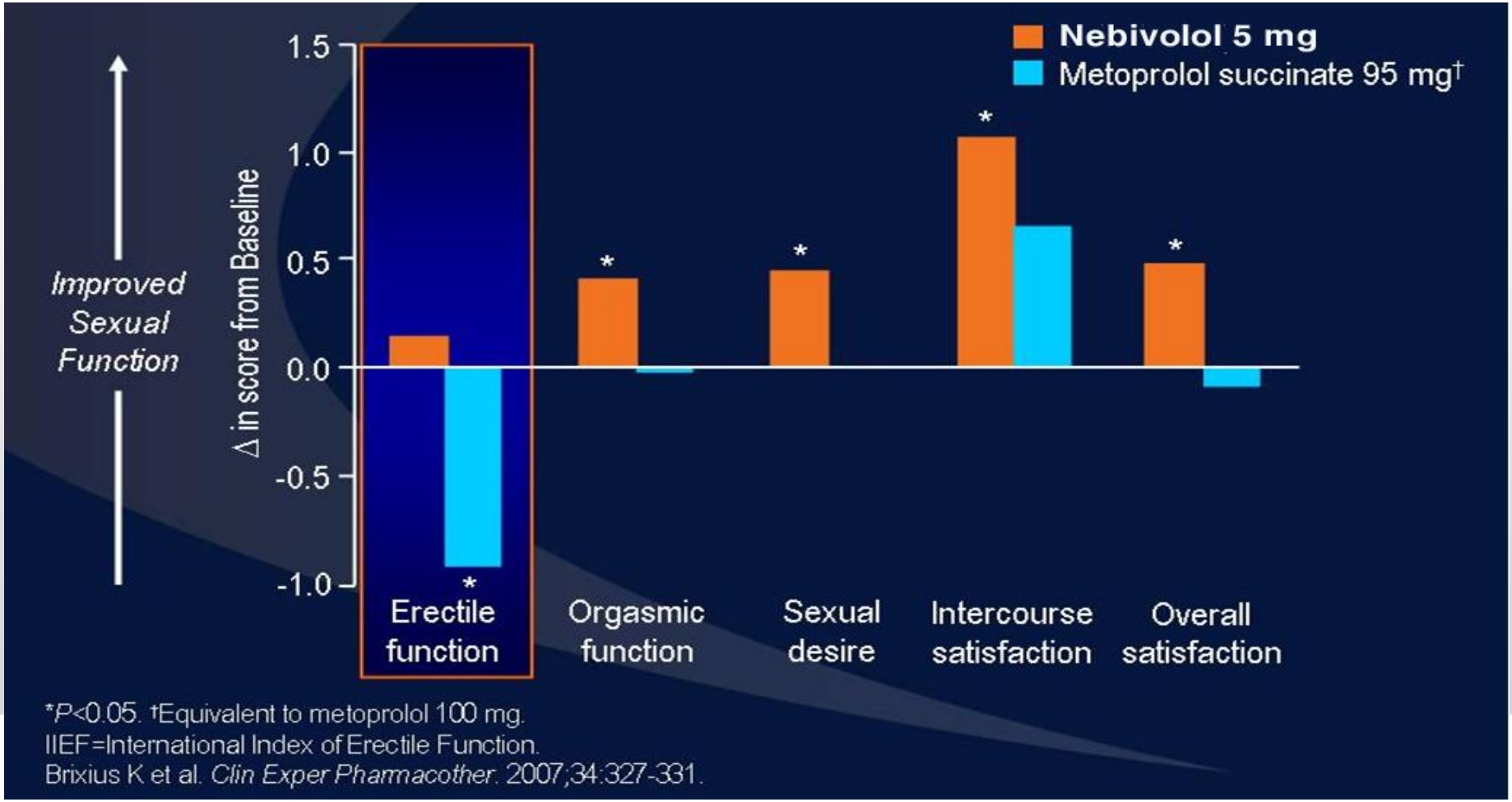
Betablocker on sexual function compare to placebo

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

NEBIVOLOL – IMPROVES SEXUAL FUNCTION

Nebivolol compare to Metoprolol

On sexual activities: IIEF



Erectile Dysfunction – Today's concept

Penis is the barometer
of Endothelial Health

Erectile Dysfunction is a
mirror of Cardiovascular Risk

ED = ED

European Guidelines on Hypertension

When discussing β-blockers, however, it should not be ignored that they are not a homogeneous class, and that vasodilating β-blockers, such as nebivolol, appear not to share some of the negative properties described for other compounds.

Older antihypertensive drugs (diuretics, β-blockers, centrally acting drugs) exert negative effects on erectile dysfunction, whereas newer drugs have neutral or beneficial effect (calcium antagonists, ACE inhibitors, angiotensin receptor antagonists, nebivolol)

Conclusions

- **ED and NO are very important in cardiovascular disease, esp hypertension.**
- **We can improve ED.**
- **BB with vasodilating properties through NO is good in management hypertensive patients**

Are all betablockers the same?

Thank you for your attention