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Can endothelial dysfunction be reversed?

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Can endothelial dysfunction be reversed?

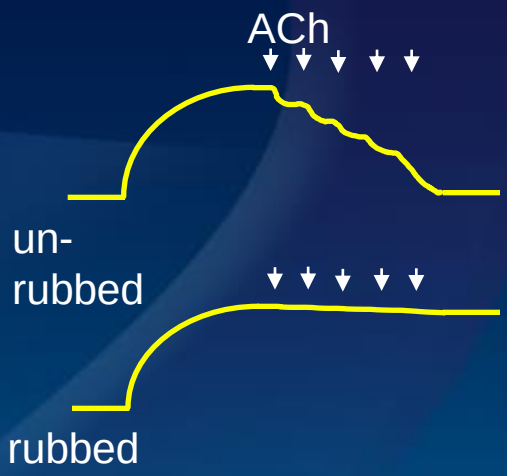
Yes:

Numerous strategies:

- clinical rationale
- points of pharmacological attack
  (- NO exclusively)
- selected examples
- overview

What is “endothelial dysfunction”?

- experimental tissue:
  - de-endothelialisation
    - mechanical
    - detergent



What is “endothelial dysfunction”?

human *in vivo*:

- Local ACh etc
  - forearm
  - coronary
- Radial FMD
- PW response to systemic β_2-agonist…

Complex:

- different vessels
- different mediators

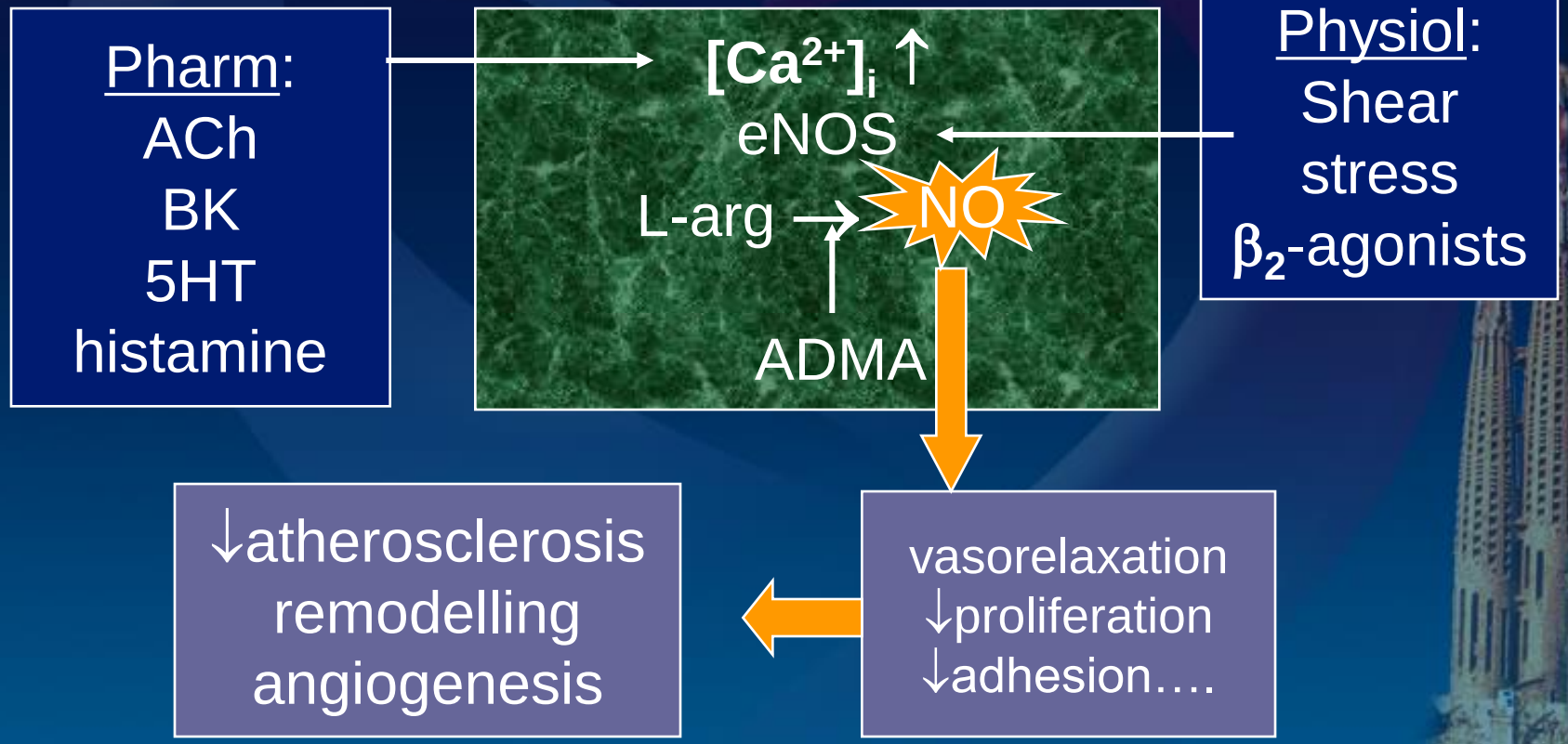
But:

- internal consistency
- predictive of outcome

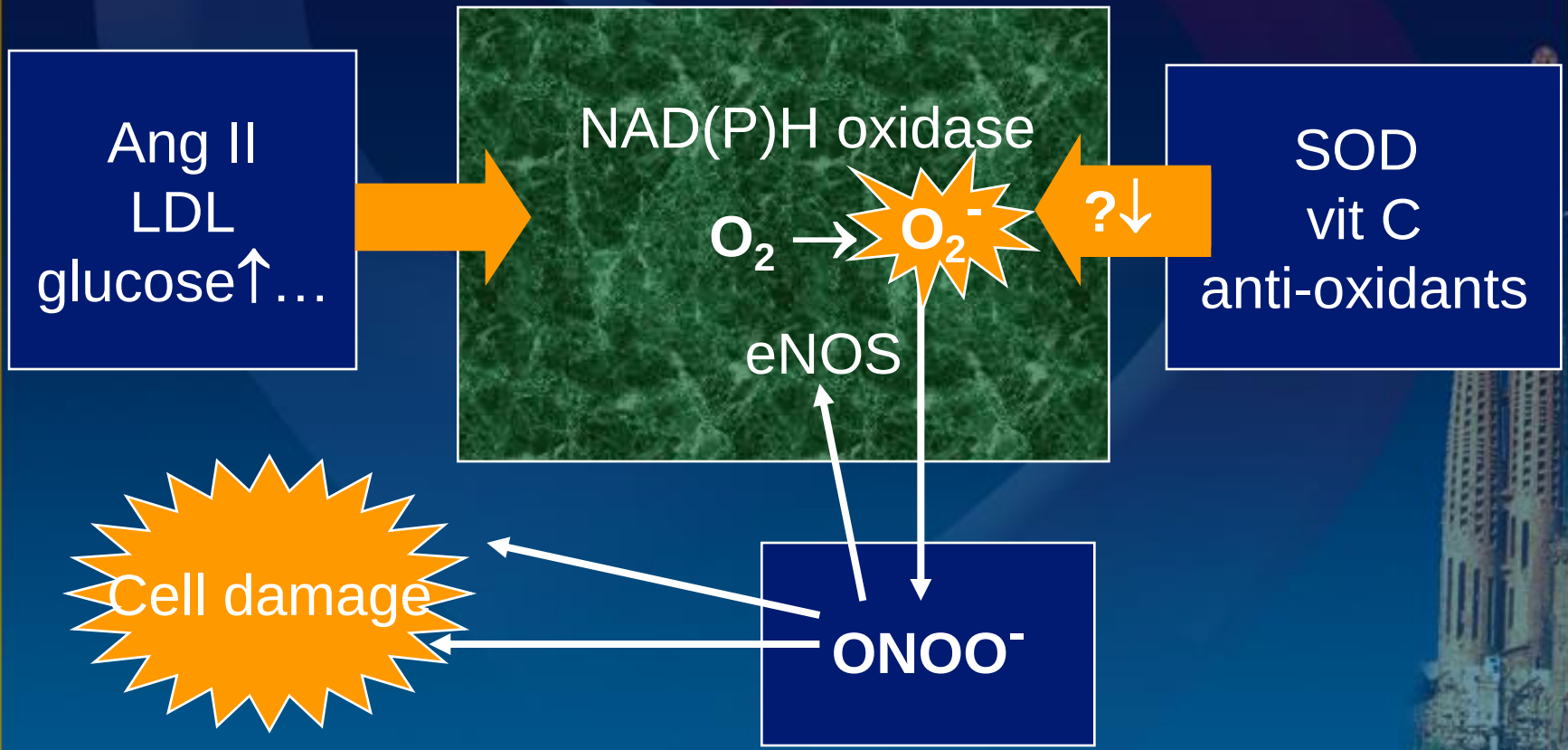
“Endothelial dysfunction” predicts events

- Coronary artery response to ACh:
  - Schachinger et al Circ 2000;101:1899-1906
  - Heitzer et al Circ 2001;104:2673-2678
- Forearm response to ACh in EH patients
  - Perticone et al Circ 2001;104:191-196
- Radial artery FMD:
  - Neunteufl et al Am J Cardiol 2000;86:207-210
  - Gokce et al Circ 2002;105:1567-1572

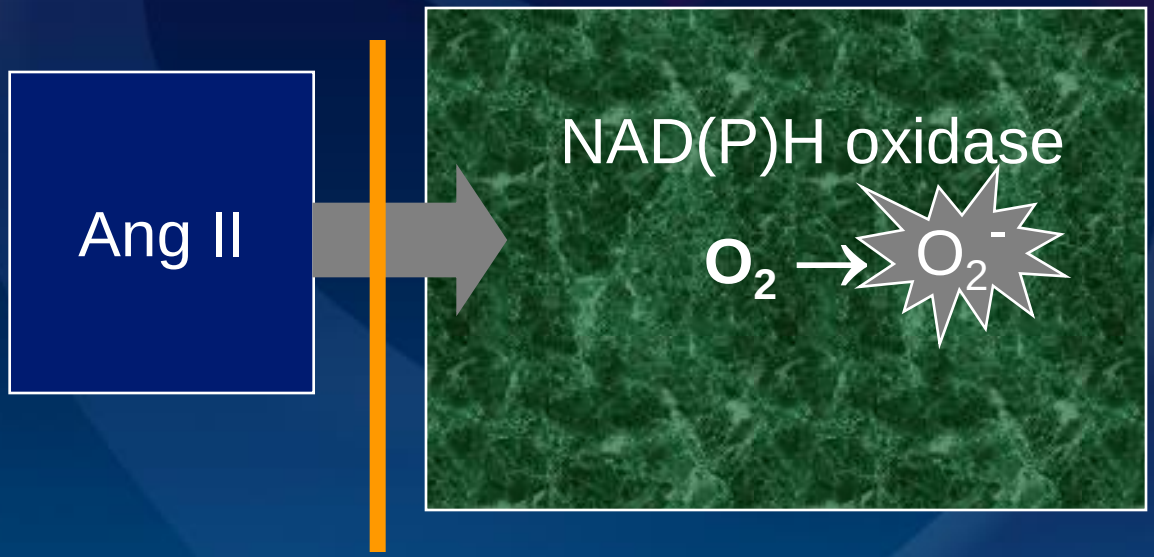
NO and EC function



EC dysfunction: ↑ superoxide formation

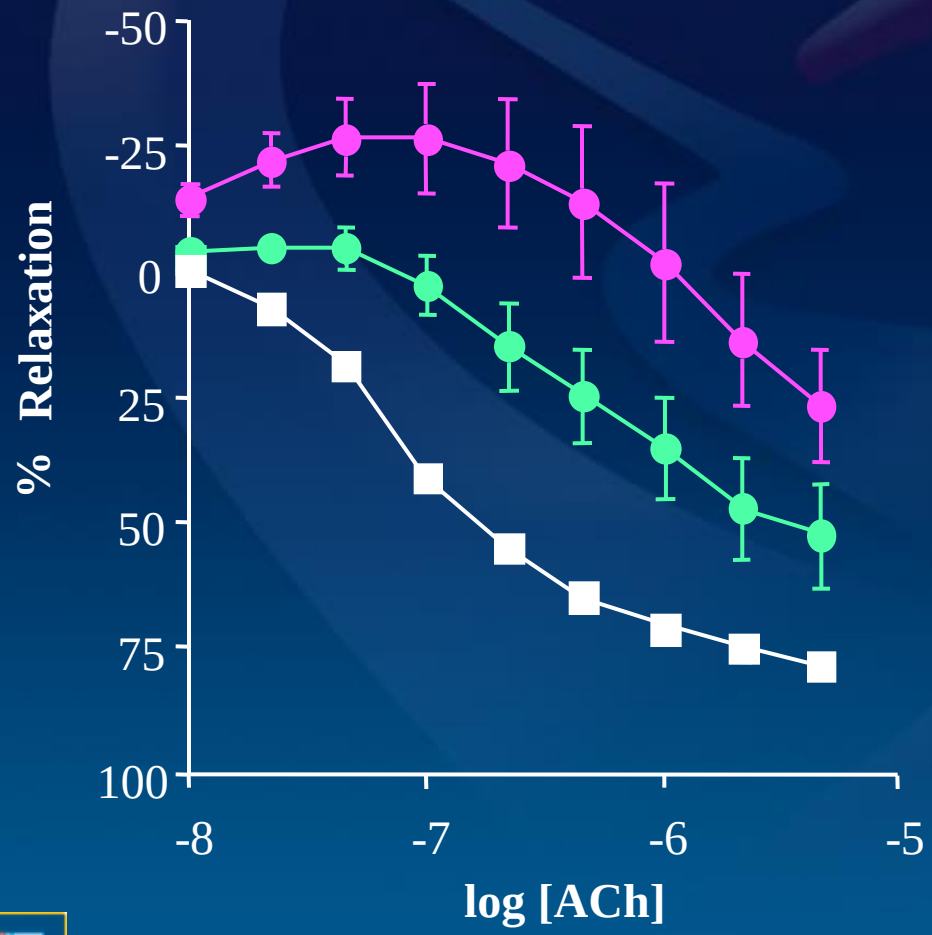


Reversing AngII-induced EC dysfunction



ACEI: TREND study
? AT1 antagonists
? β_1-antagonists

LDL-induced ED: $O_2^{-\bullet}$ is implicated



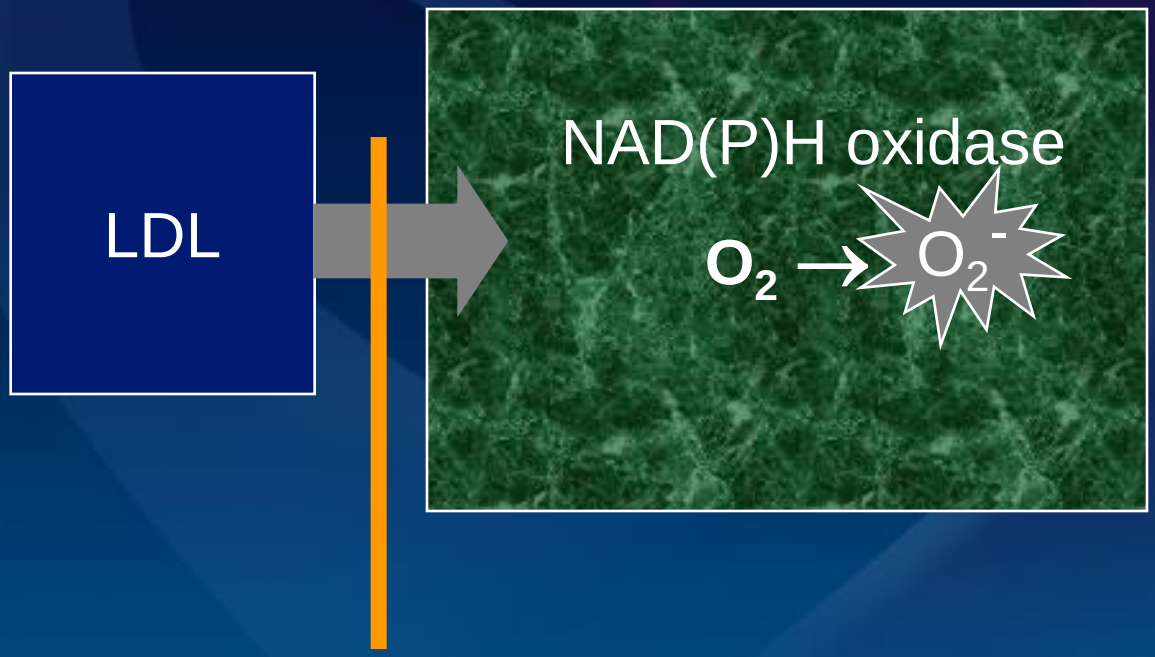
LDL (150 µg/ml)

LDL + MnTMPyP

Control

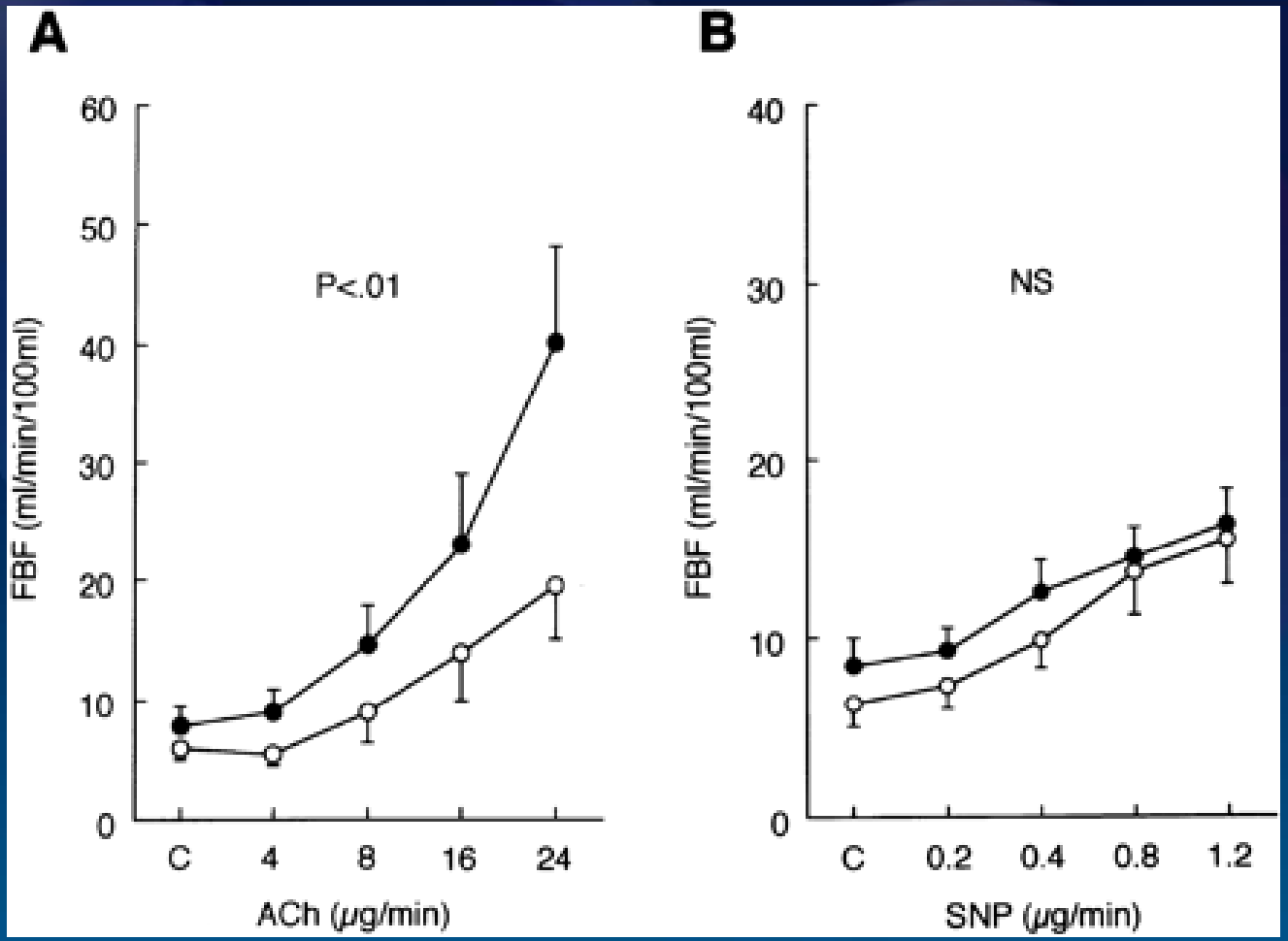
(Fontana et al BJP 1998)

Reversing LDL-induced EC dysfunction



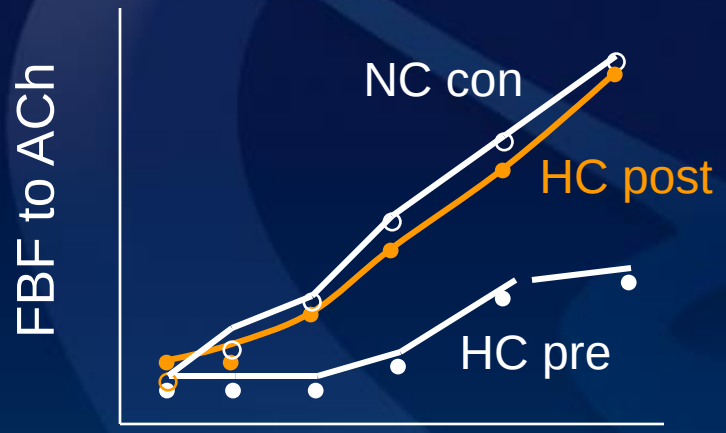
Apheresis
Statin

LDL apheresis

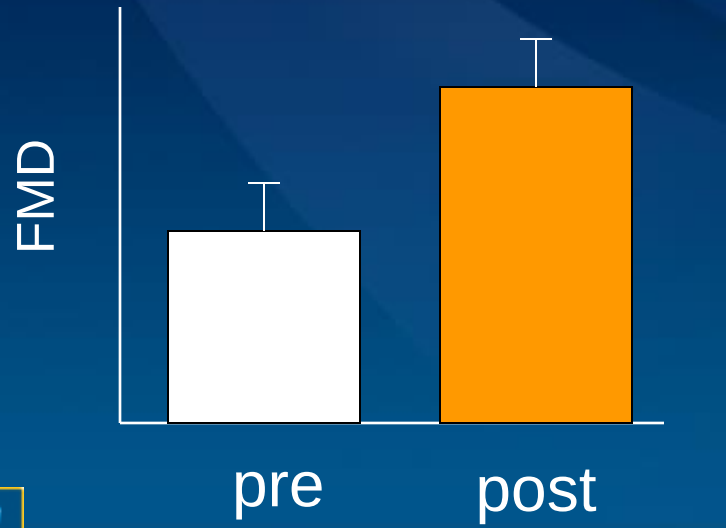


Tamai *et al.* 1997

HDL infusion



Reconstituted HDL
(apo A1:PC=1:150)
80 mg/kg iv 4h
[HDL] 1.3±0.1→2.2±0.1



(redrawn from Spieker LE et al. Circ 2002;105:1399-1402)

Statins

- ↓LDL ± ↑HDL
- ↓mevalonate synthesis →

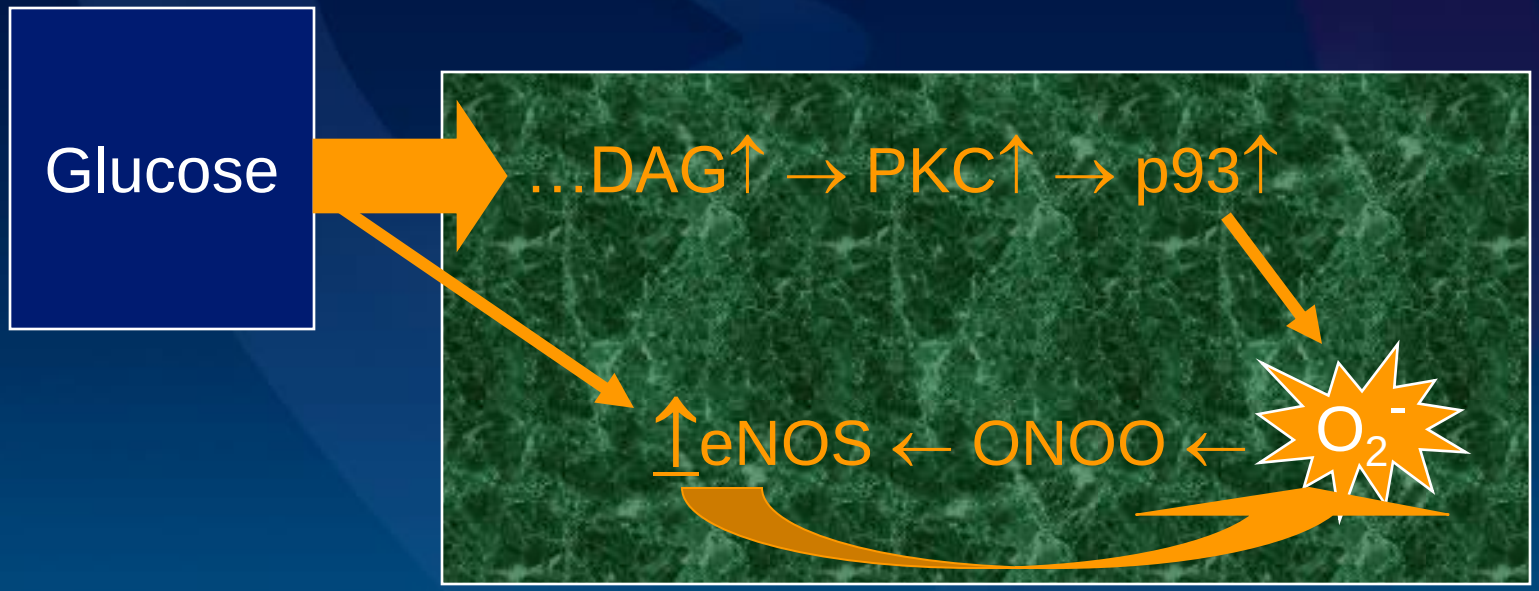
  ↓isoprenoids (farnesylPP, geranylgeranylPP) →

  alters membrane attachments of rho etc →

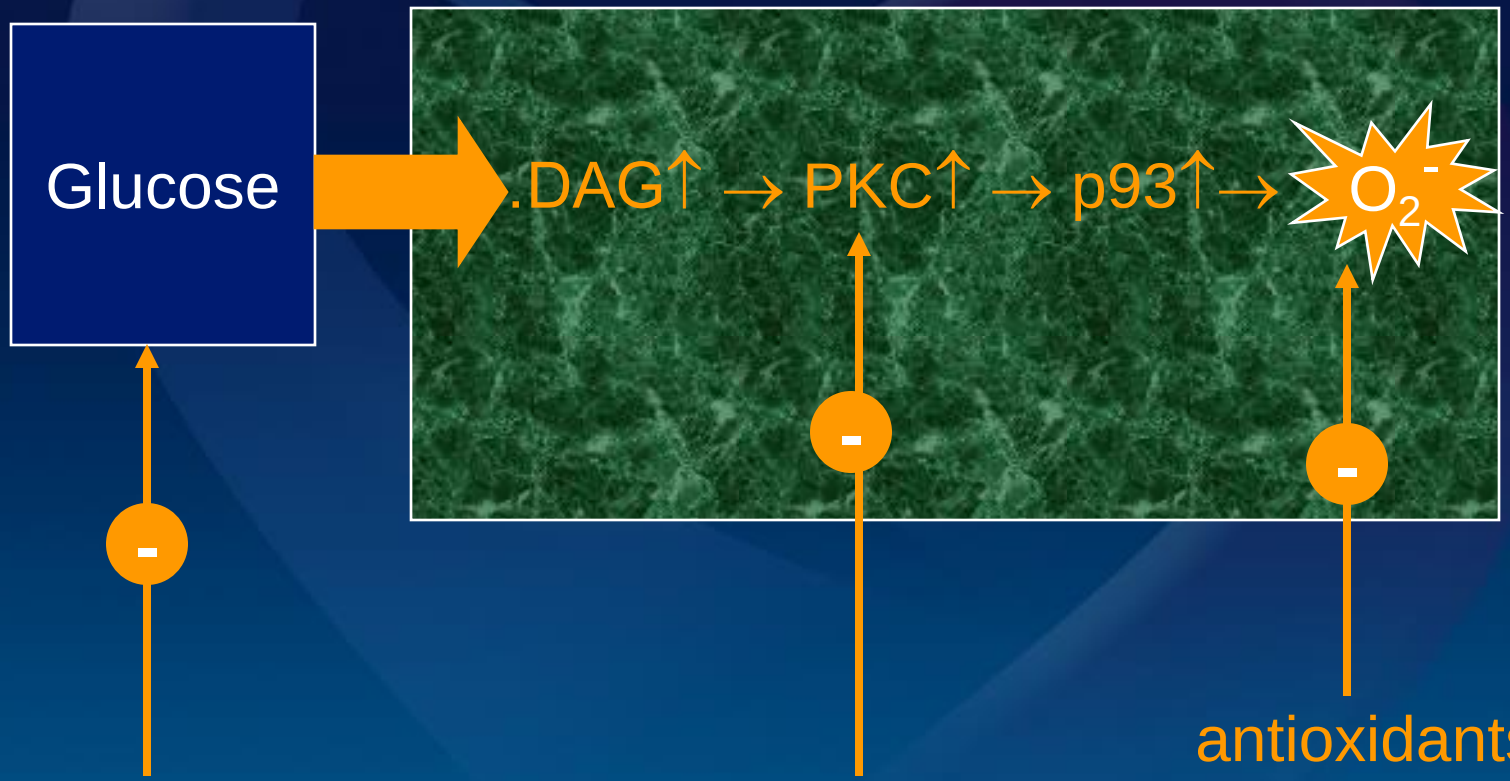
  “pleiotropic” effects including

  upregulation of eNOS via stabilisation of mRNA
- restore EC function (eg Stroes et al Lancet 1995)

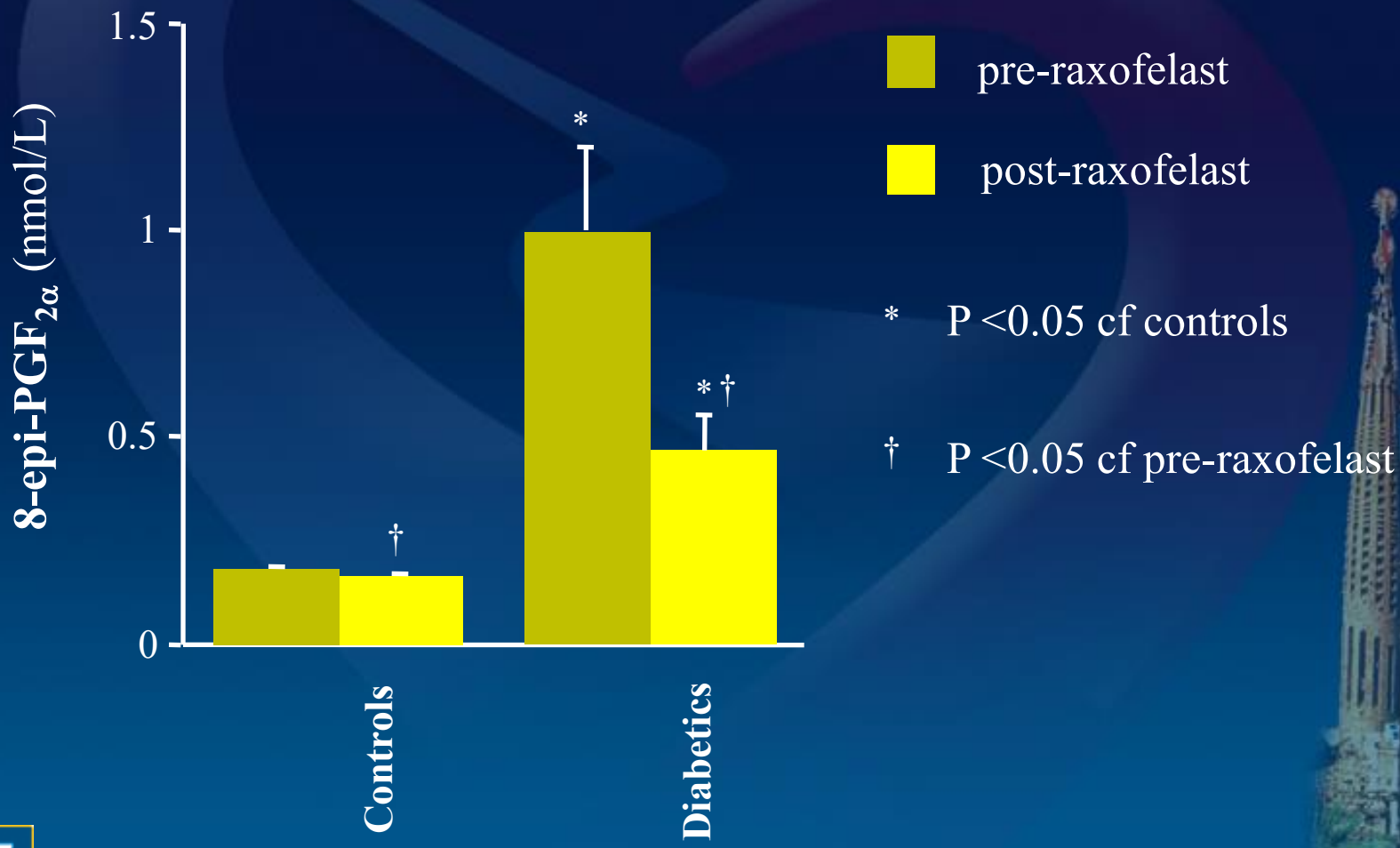
Glucose-induced EC dysfunction (acute)



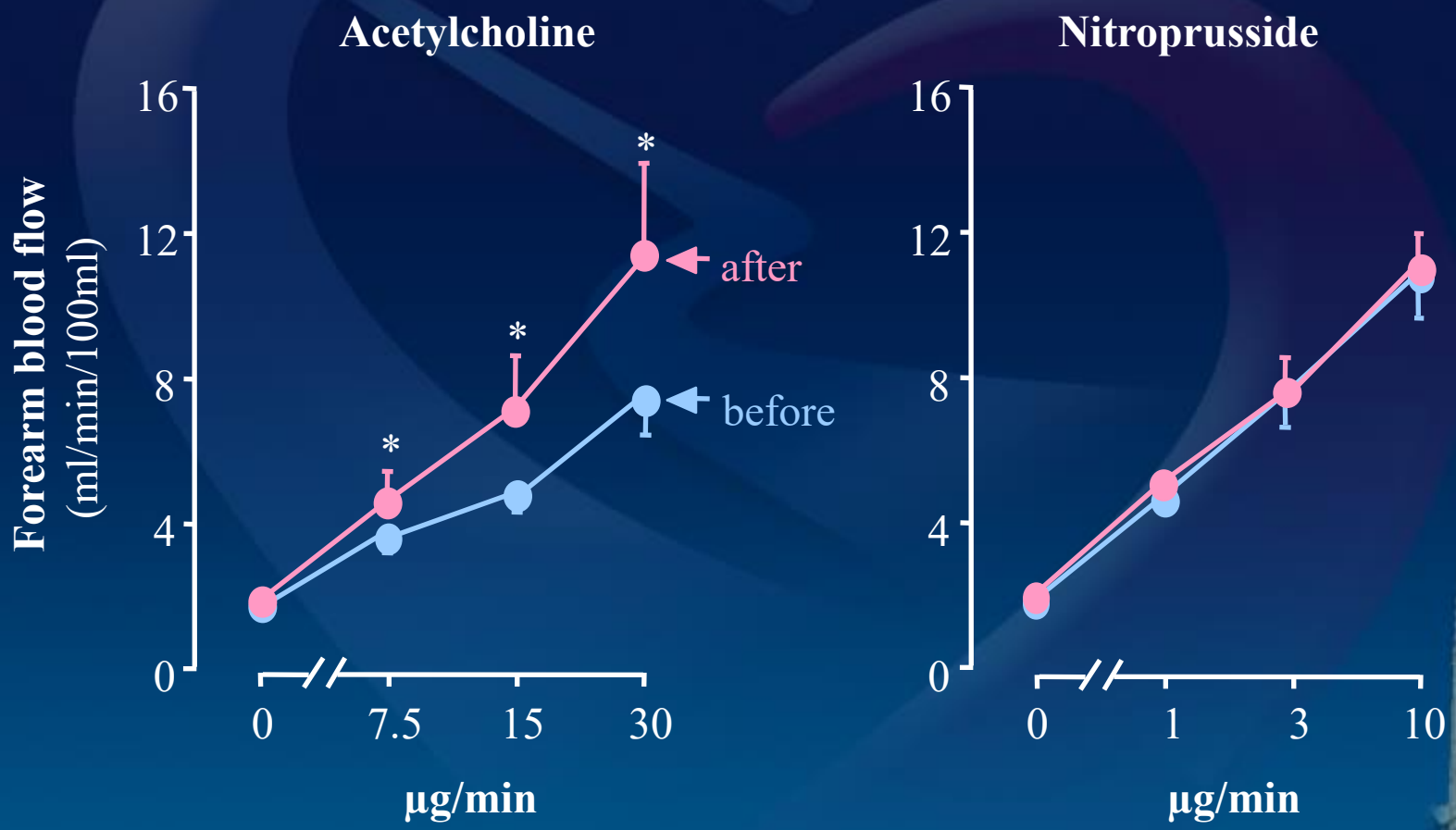
Reversing glucose-ind. EC dysfunction



Raxofelast on oxidative stress in type 2 DM



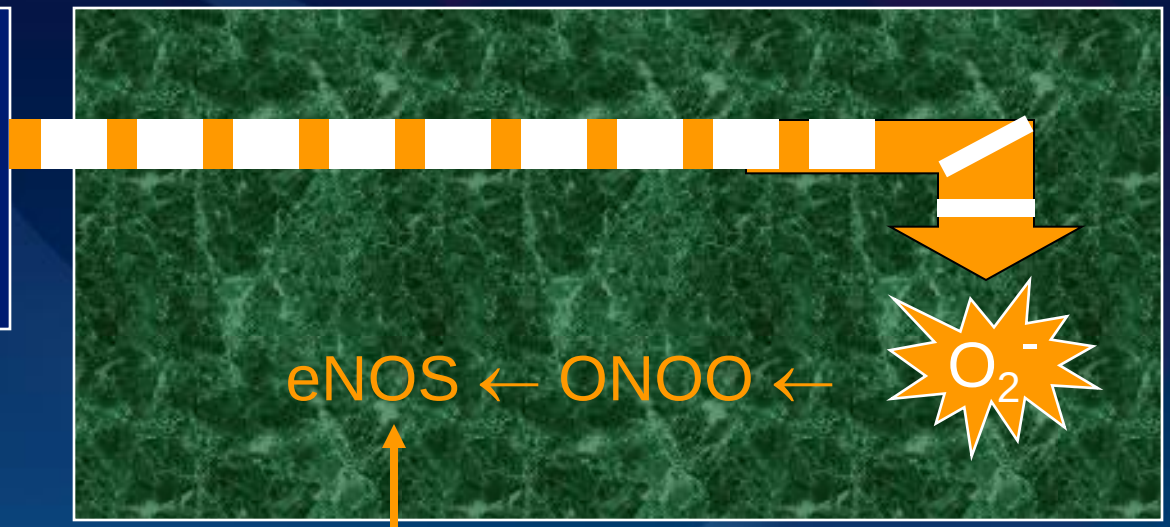
Raxofelast on EC function in type 2 DM



Chowienczyk *et al.* Diabetologia 2000

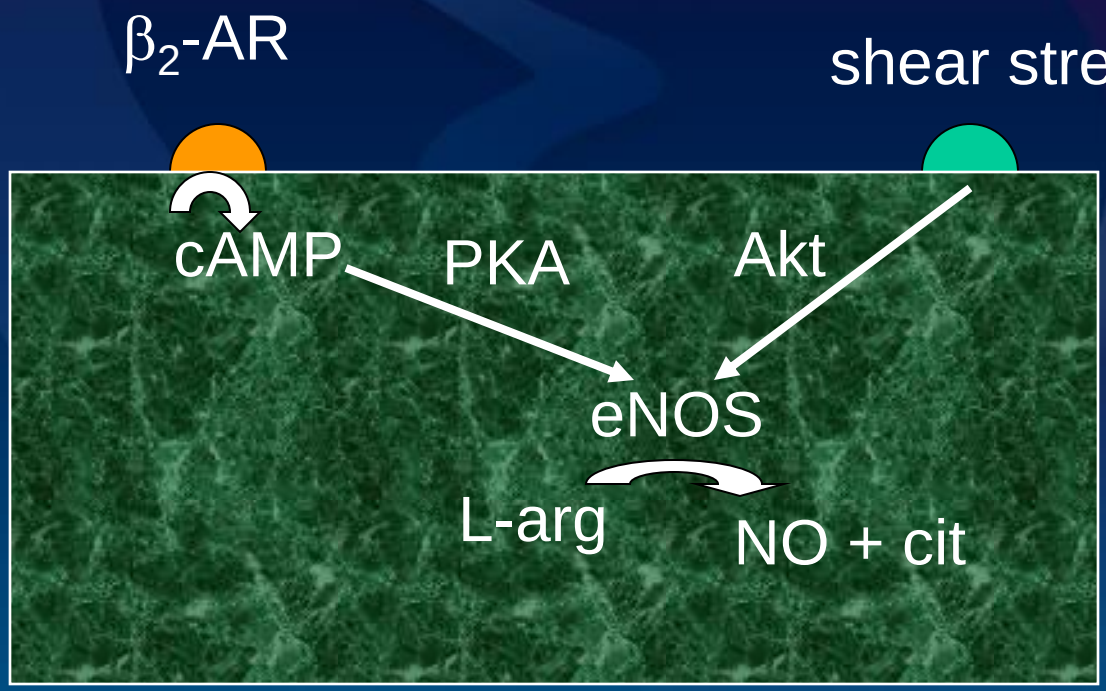
Reversing eNOS dysfunction

Glucose
Dyslipid
Smoking..



BH4, sepiapterin
5MTHF; arginine

Increasing physiological NO synthesis



Nebivolol

- highly β_1-selective antagonist
- additional ED-vasodilating properties
- *in vitro*, *in vivo*: local and systemic
- vasodilator action blocked by LNMMA
- possibly via metabolite with β_2-agonist activity
- ↑ EC function (FBF to ACh: contrast with atenolol)
- ? specific anti-atherosclerotic effects

Candidate strategies for reversing EC ↓

- increase NO directly(eg nitrates)?
- increase NO indirectly (eg nebivolol)
- promote NO actions (cf sildenafil)
- reduce superoxide anion formation
- reduce superoxide anion effects
- other strategies:
  - exercise
  - anti-inflammatory drugs
  - saunas...