# Equine Estrogens Impair Nitric Oxide Production and Endothelial Nitric Oxide Synthase Transcription in Human Cells Compared with the Natural 17β- Estradiol

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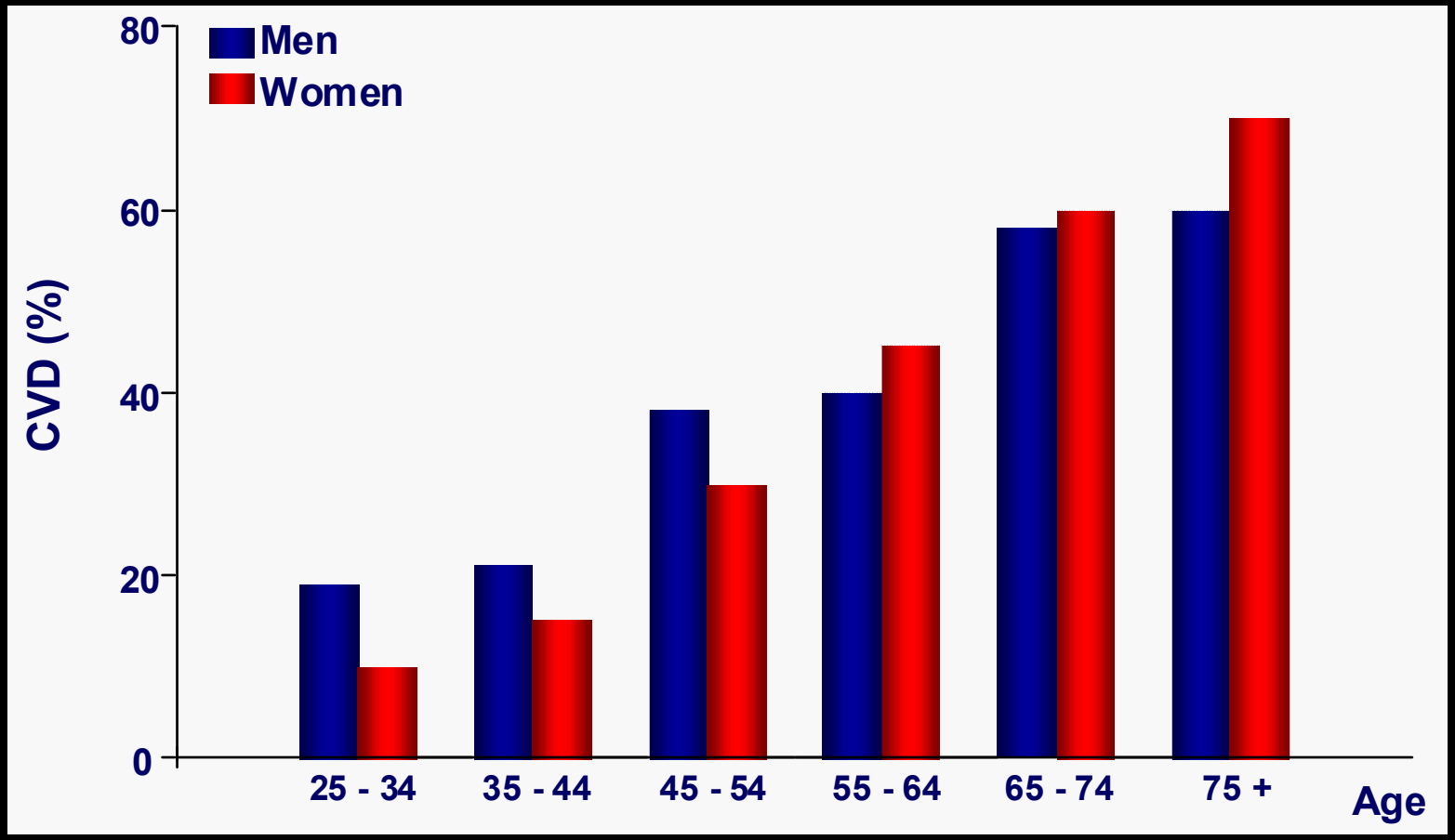
# Background

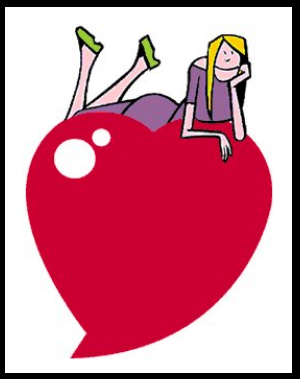
# Gender differences in CVD incidence



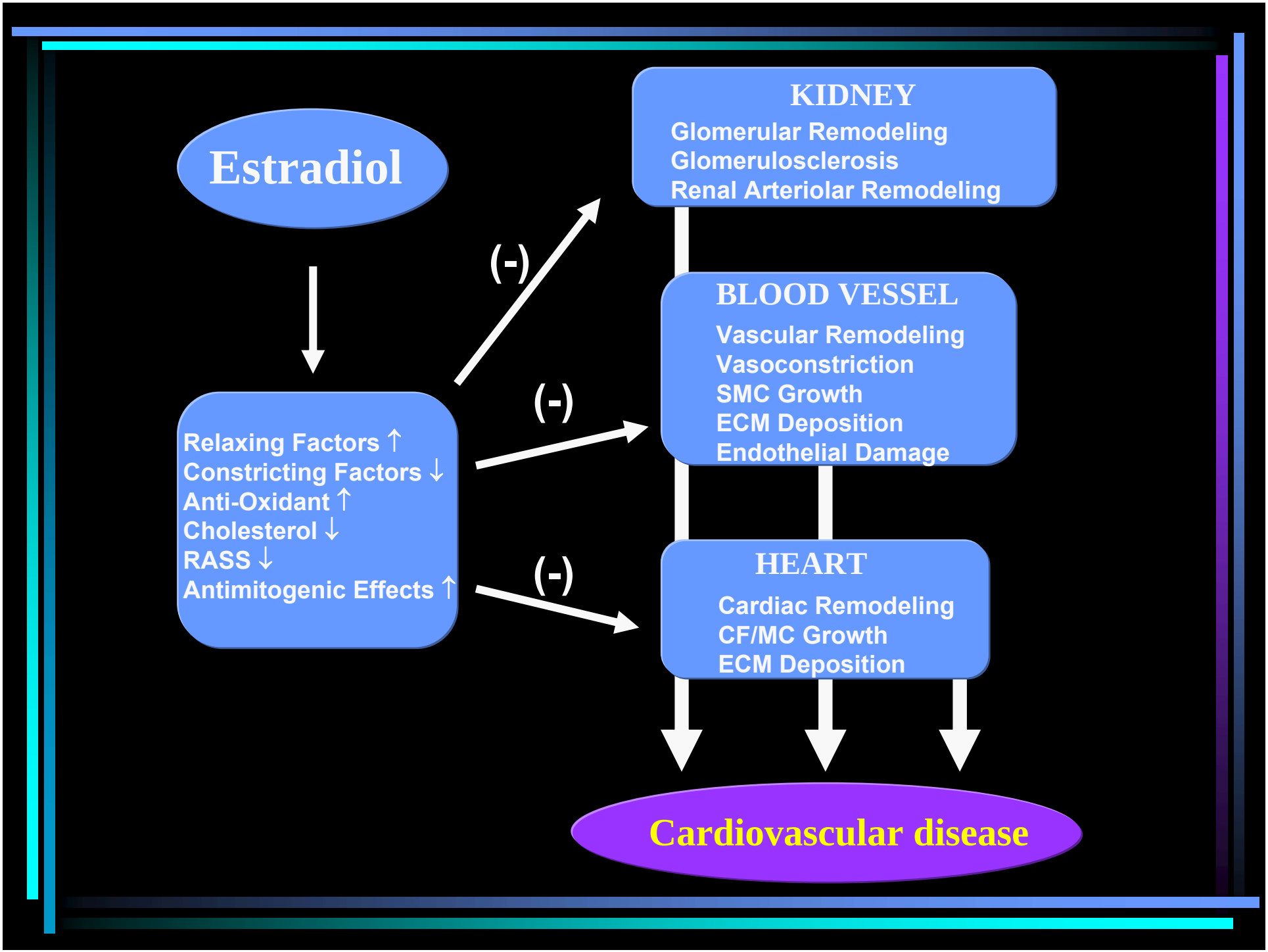

Bittner V et al. Hypertension. 1993: 63-104

# Why are the women protected?

# *The hormonal theory*



**Estrogen protects females mammals at a cellular level, so that the incidence and severity of cardiovascular disease in females (rats, dogs or humans) will be lower than in males.**


Estradiol
KIDNEY
Glomerular Remodeling
Glomerulosclerosis
Renal Arteriolar Remodeling
(-)
BLOOD VESSEL
Vascular Remodeling
Vasoconstriction
SMC Growth
ECM Deposition
Endothelial Damage
(-)
Relaxing Factors ↑
Constricting Factors ↓
Anti-Oxidant ↑
Cholesterol ↓
RASS ↓
Antimitogenic Effects ↑
(-)
HEART
Cardiac Remodeling
CF/MC Growth
ECM Deposition
Cardiovascular disease

ORIGINAL CONTRIBUTION

*JAMA* - EXPRESS

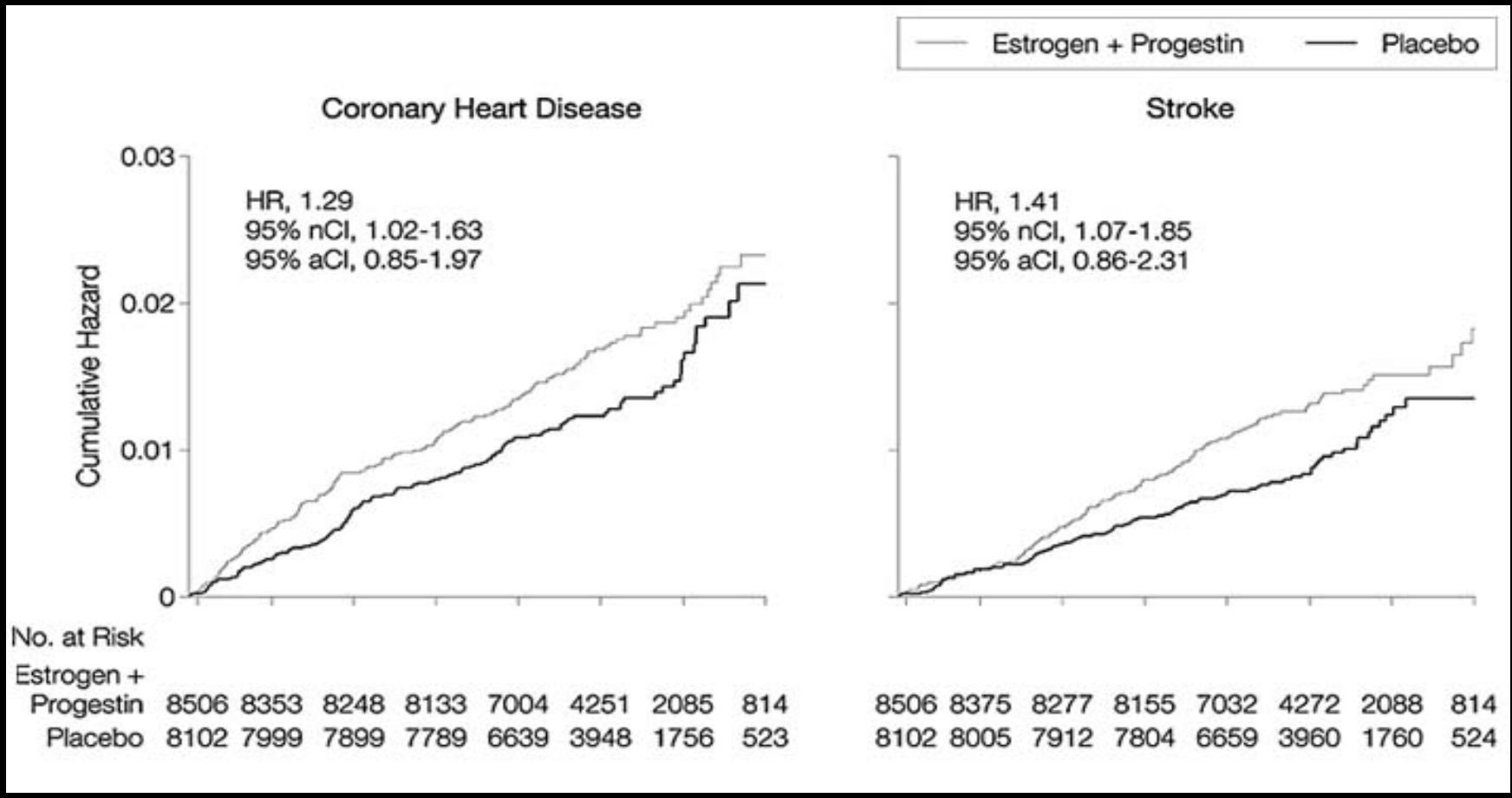
# Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women

## Principal Results From the Women's Health Initiative Randomized Controlled Trial

Writing Group for the
Women's Health Initiative
Investigators

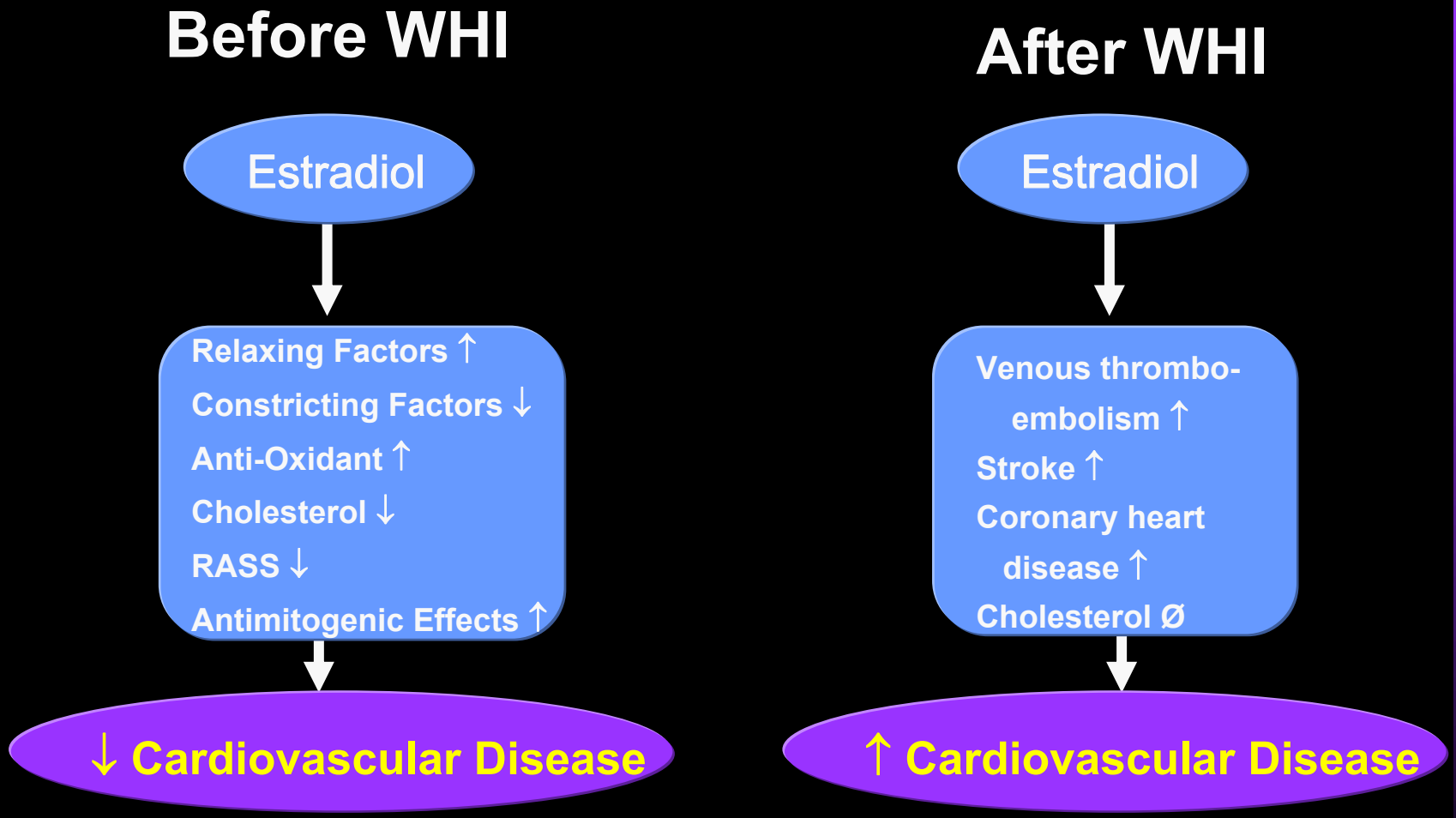
JAMA, July 17, 2002 – Vol. 288, No. 3

# Women's Health Initiative (WHI)




JAMA, July 17, 2002 – Vol. 288, No. 3

# Estrogen Replacement Therapy: before and after the Women's Health Initiative (WHI)



# *WHI?*

- ✓ Dose regimen
- ✓ Association of estrogens with progestins
- ✓ Administration route
- ✓ Type of estrogen
- ✓ Average age of women beginning the trial

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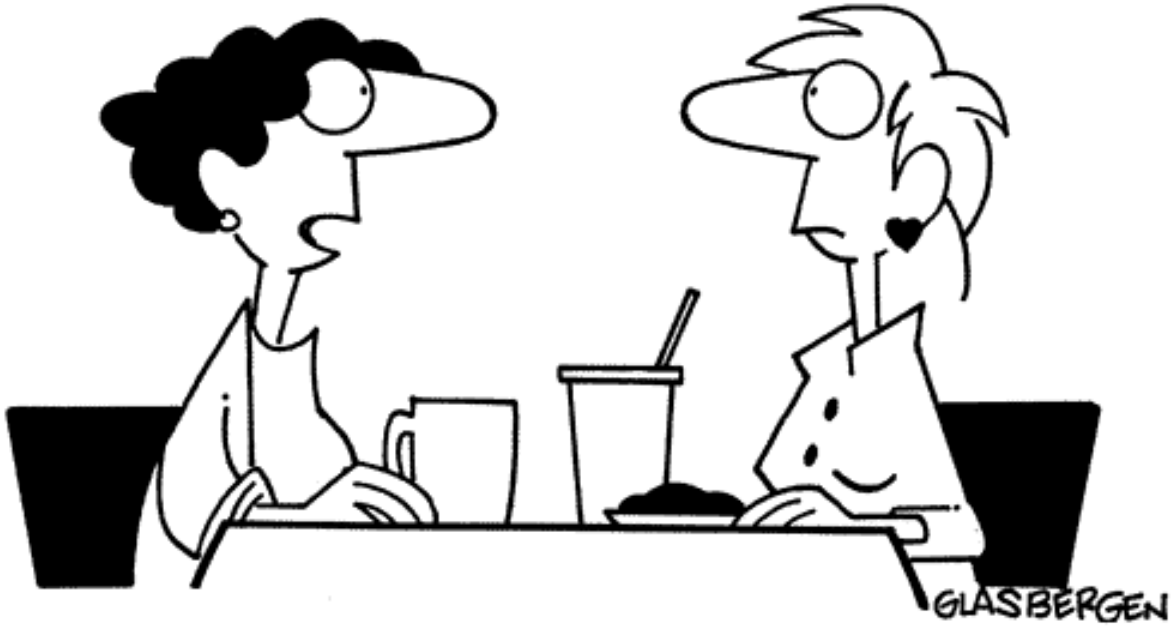
# Equine estrogens vs natural estrogens





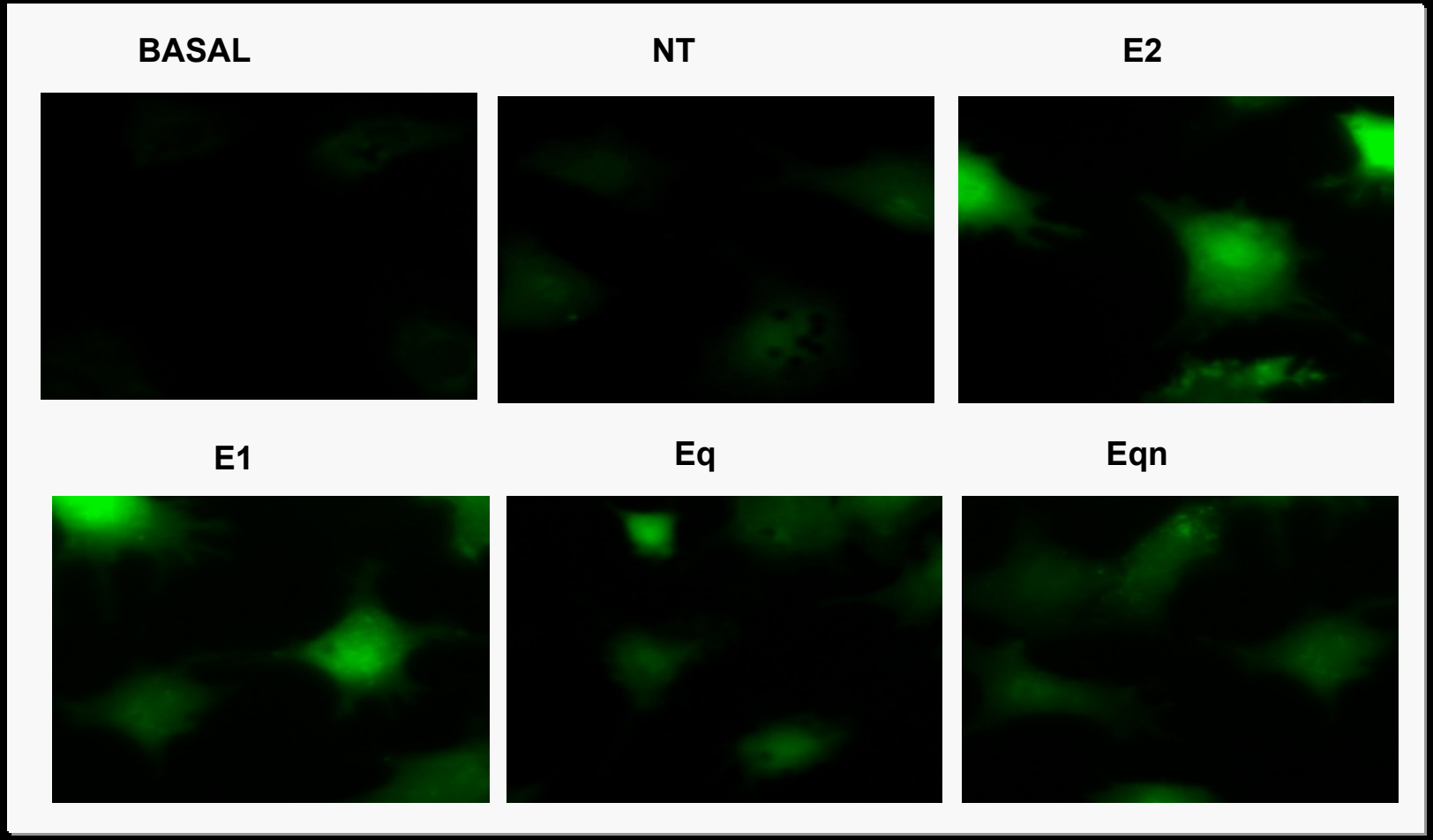

"I'm in an experimental program that
treats menopause with ostrich hormones.
Now I only get hot flashes when I'm laying an egg."

# AIMS

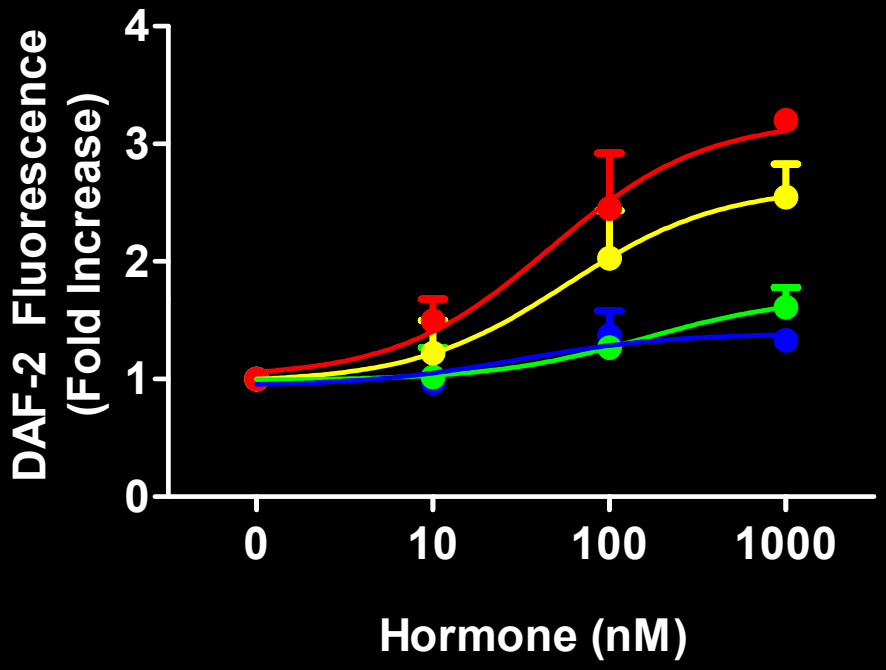
- To compare the action of CEE and human estrogens in the NO production
- To determine the mechanisms of NO modulation by the different estrogens

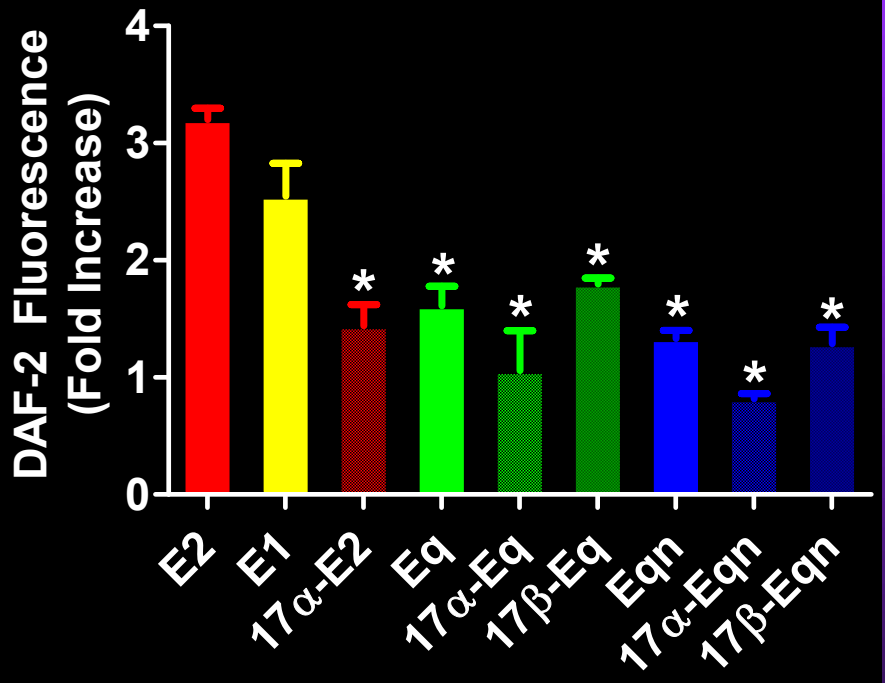
# RESULTS

# NO production in HAEC



# NO production in HAEC

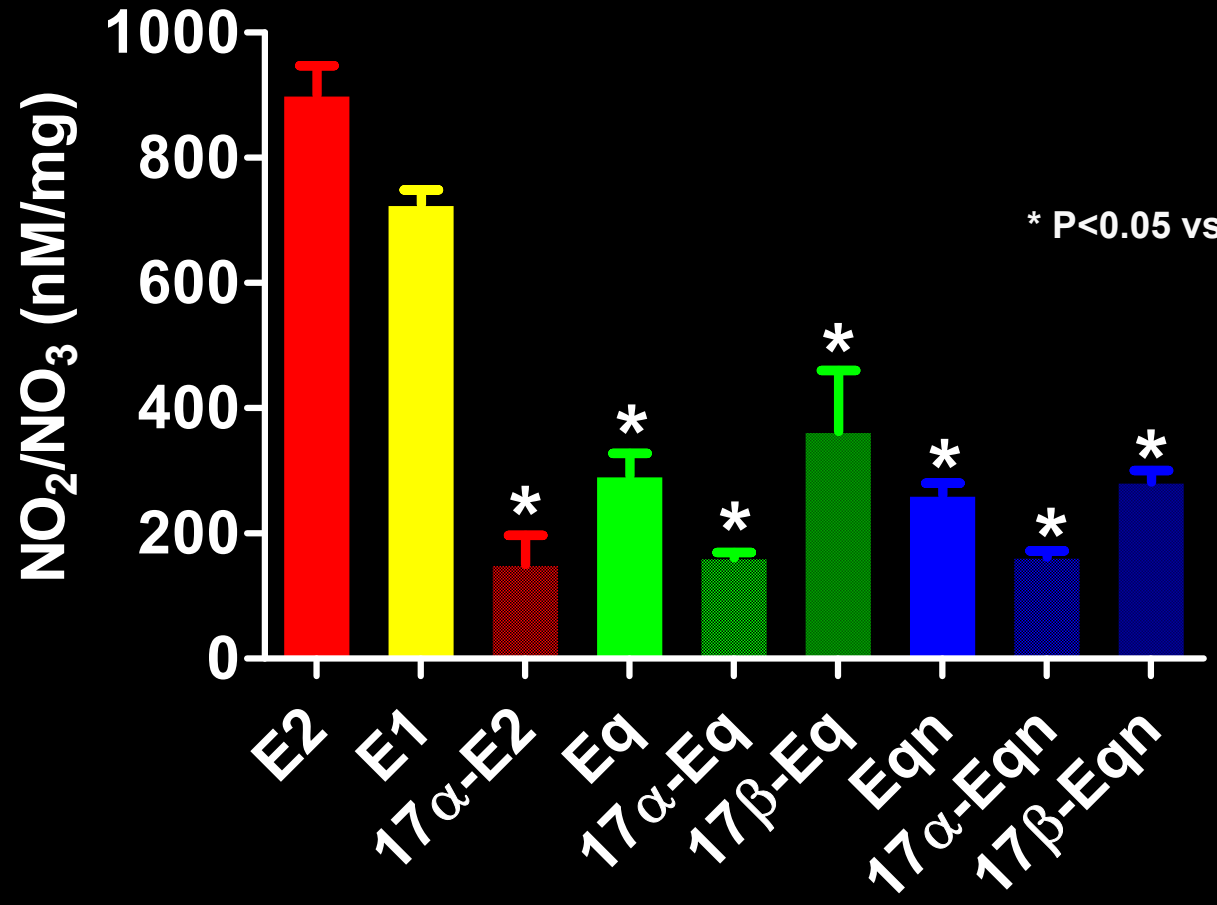


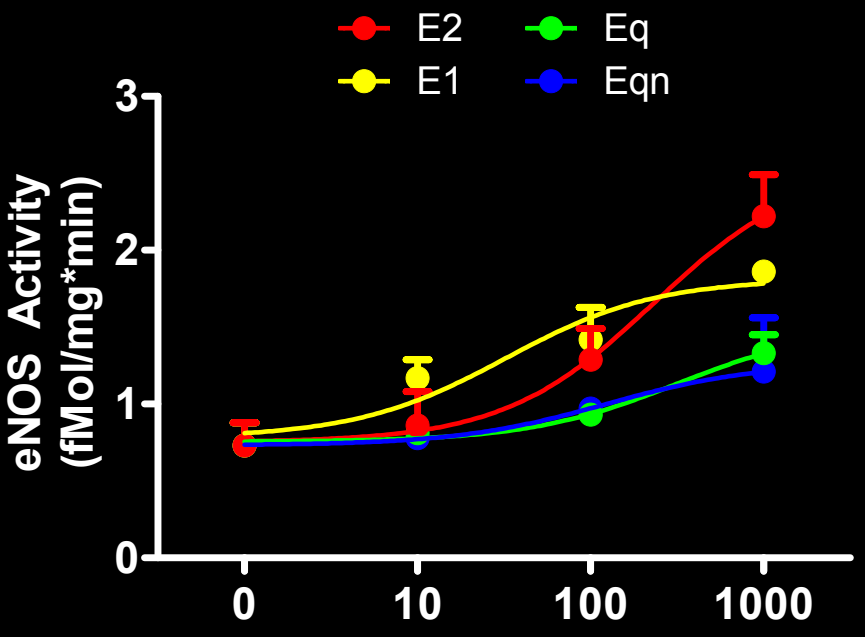

* P<0.05 vs Estradiol

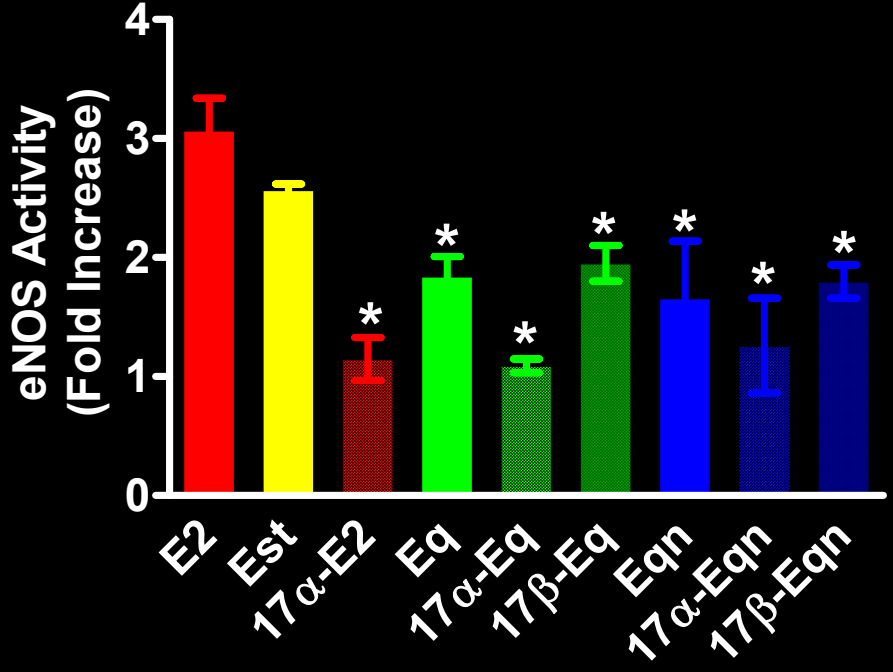
Estradiol
Estrona
Equilina
Equilenina

# Metabolites concentration $NO_2/NO_3$

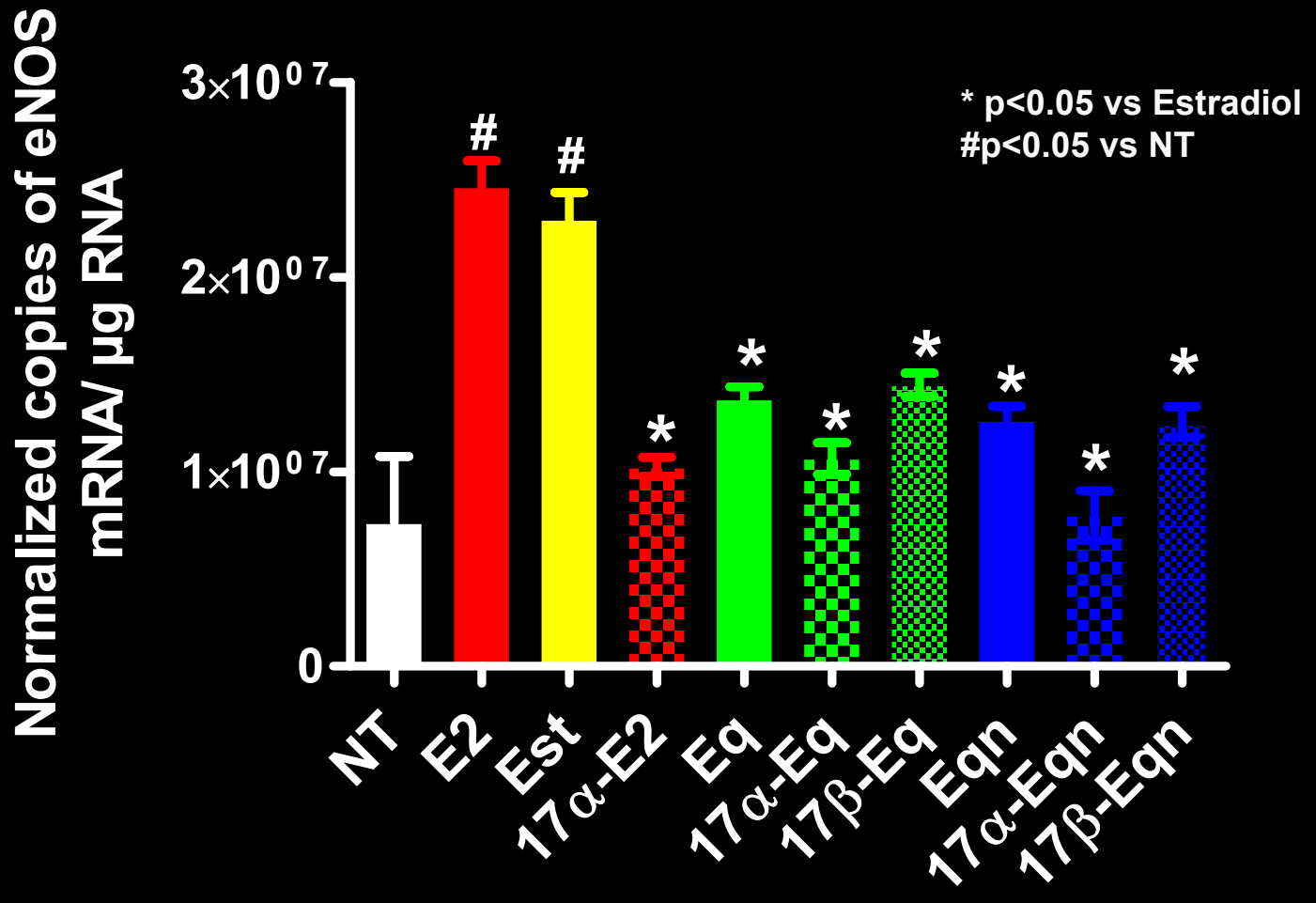


# eNOS activity

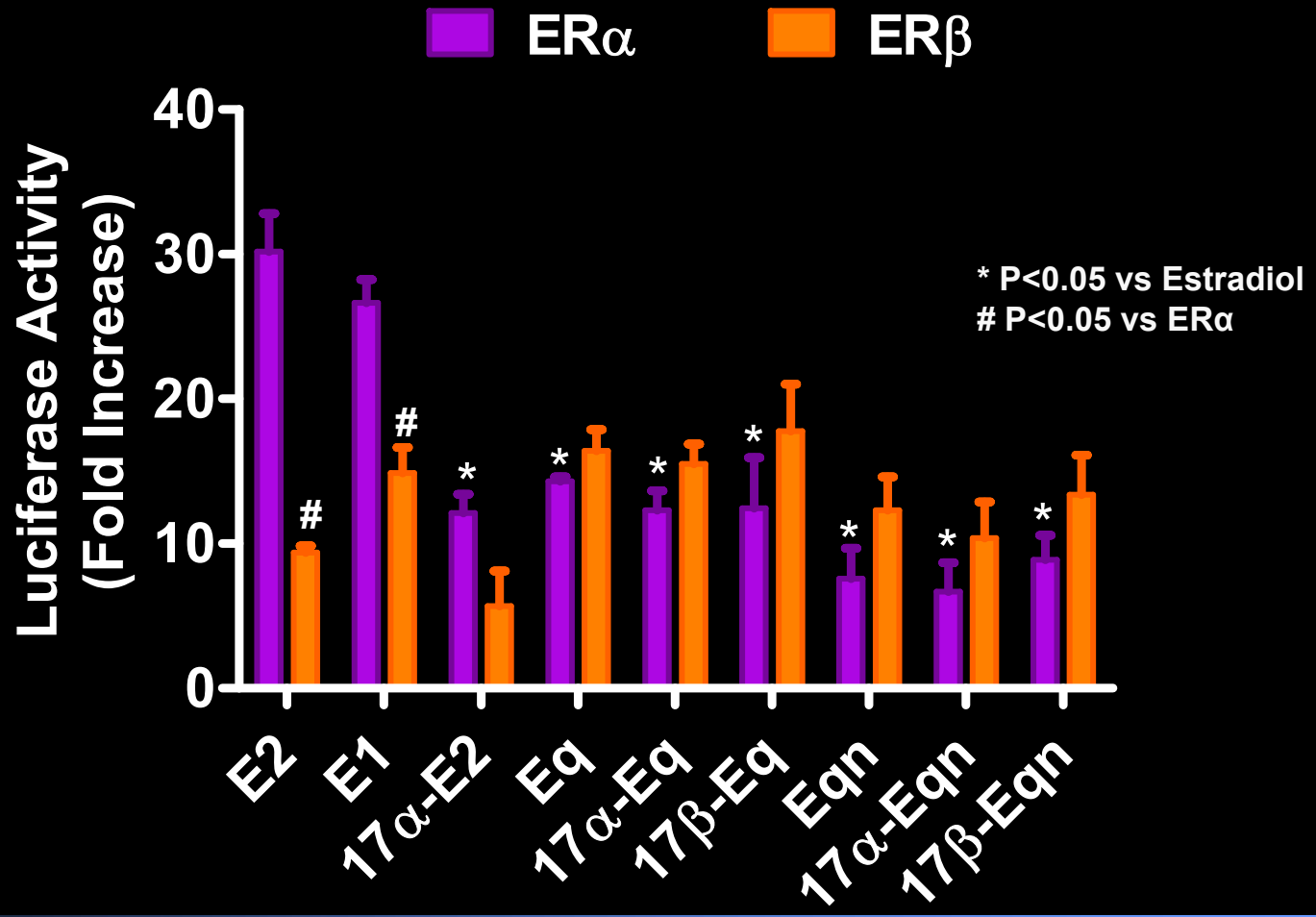


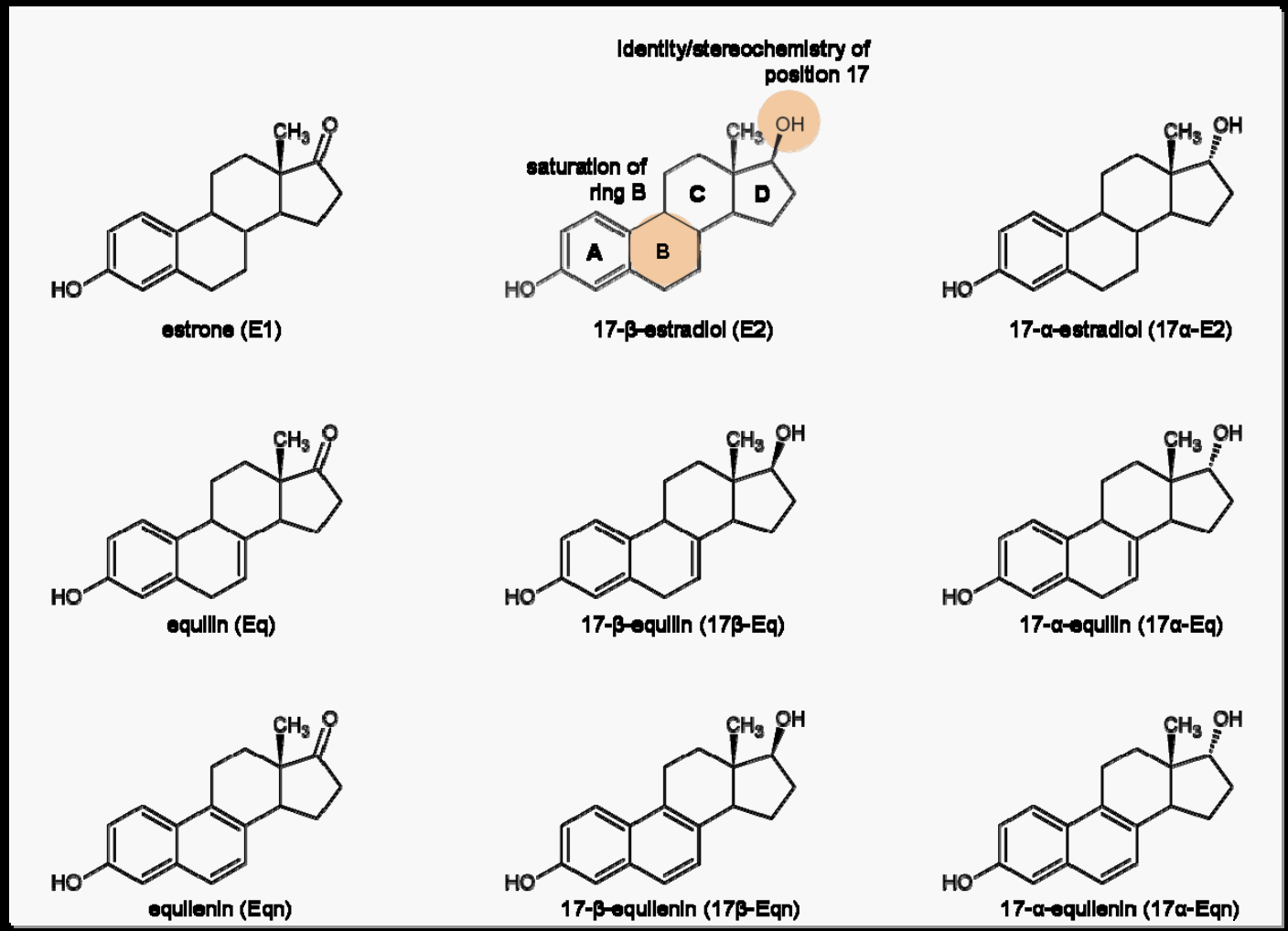
# eNOS expression



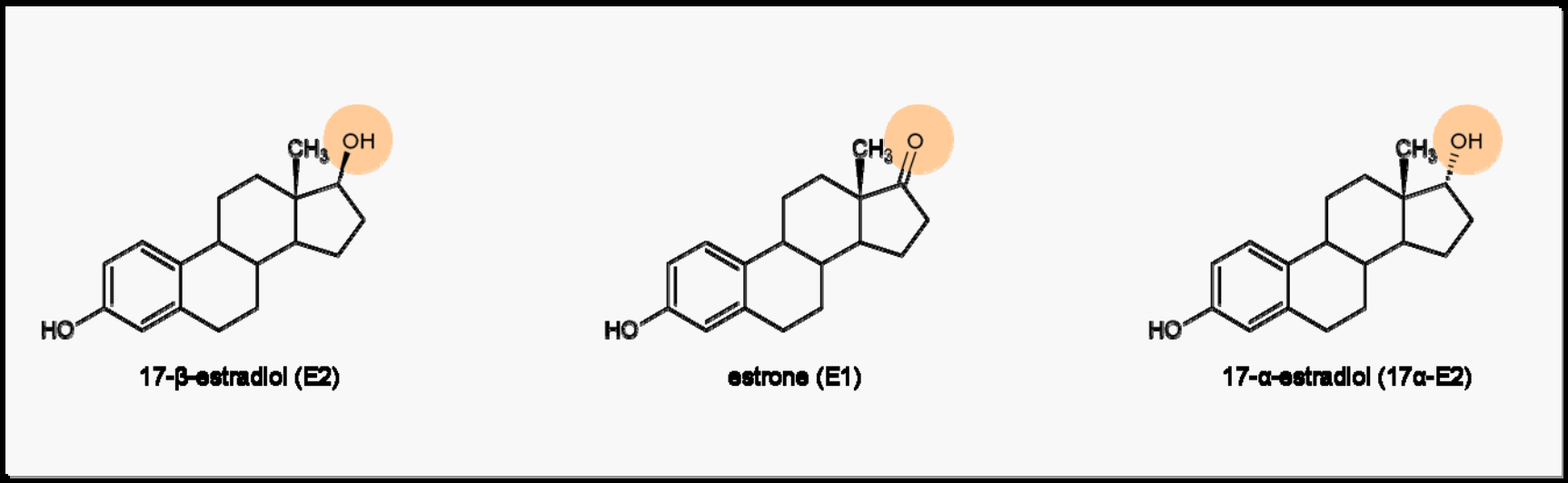
# Transcriptional activity



# Molecular structure



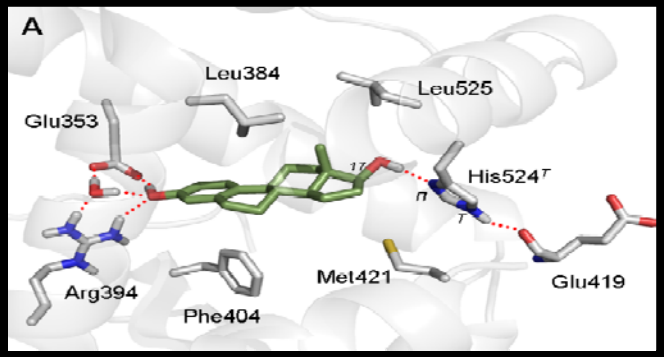
# 17 position

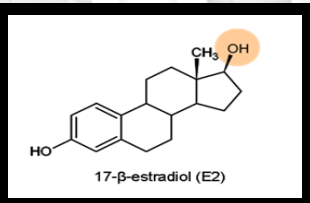



+ NO production -

# 17 position

## 17β-E2

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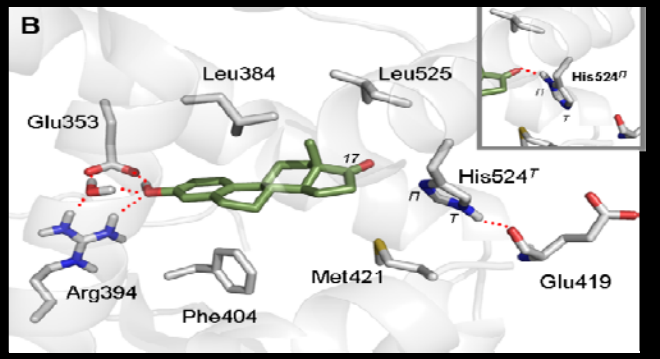
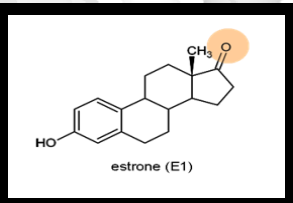
## E1

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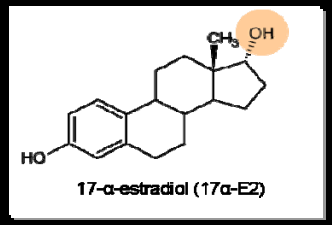
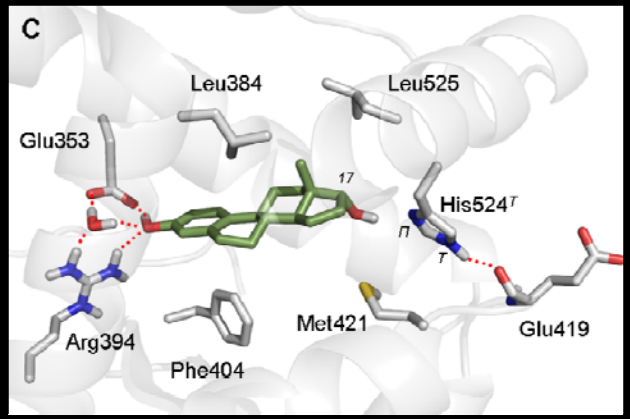
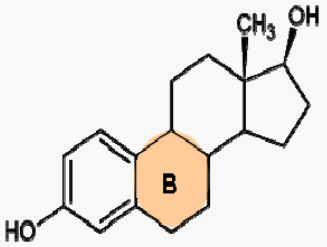
## 17α-E2

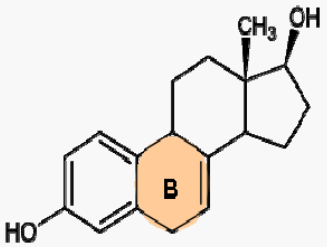


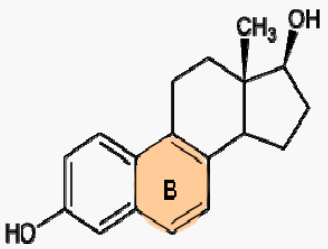
# B ring saturation




17-β-estradiol (E2)



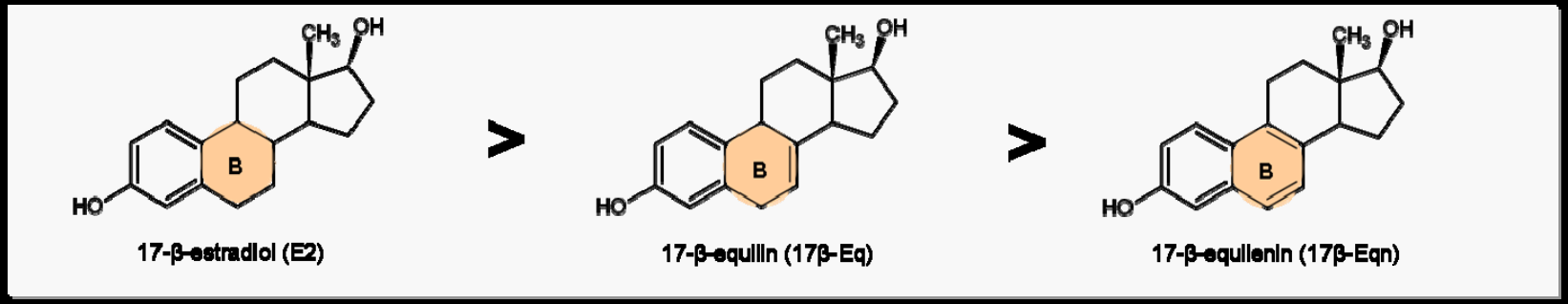

17-β-equilin (17β-Eq)

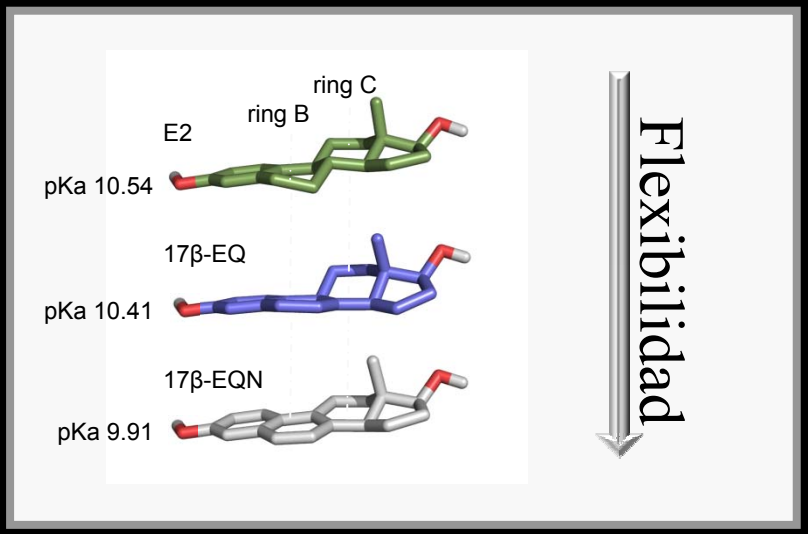


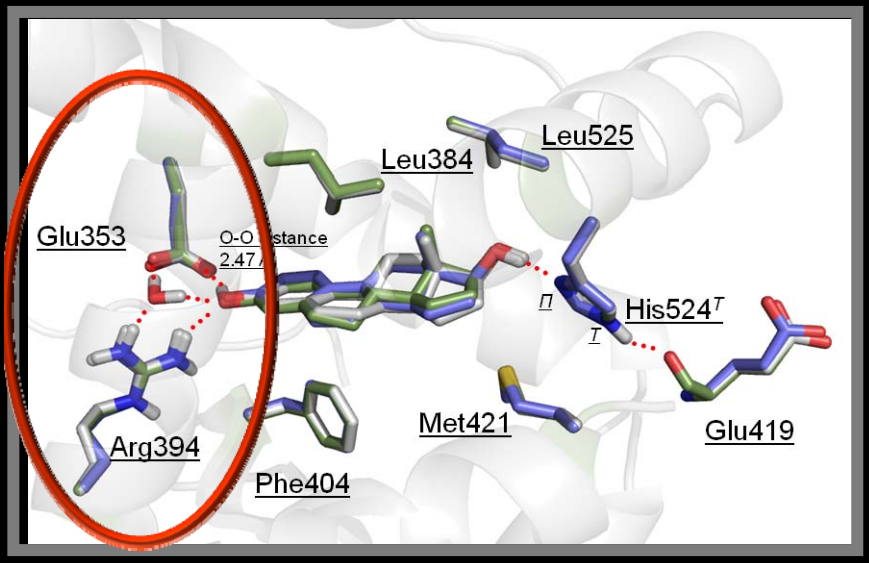

17-β-equilenin (17β-Eqn)

\+ NO production -

# B ring saturation



# CONCLUSIONS

- ✓ Equine estrogens increase NO production less effectively than naturally occurring estrogens, as a result of their lesser ability to activate the ERα-mediated increase of eNOS promoter activity and eNOS transcription.
- ✓ Chemical moiety and stereochemistry at position 17 and the degree of ring B saturation in estrogenic compounds play a significant role in ERα- transcriptional activity.

MOLTES GRÀCIES!!!