

Cardiovascular Health and Cognition: Perspectives on Using the Primate as a Model for Human Research

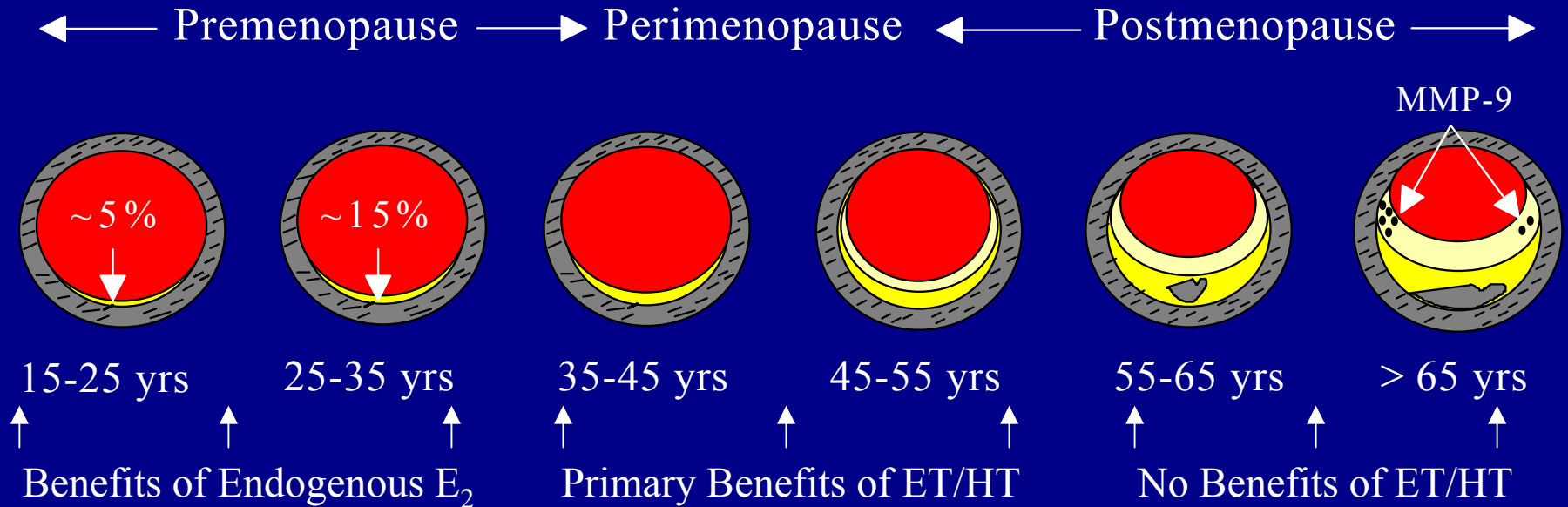
ET/HT

**I just don't
know what
to think**



Pathogenesis of Coronary Artery Atherosclerosis of North American Human Females

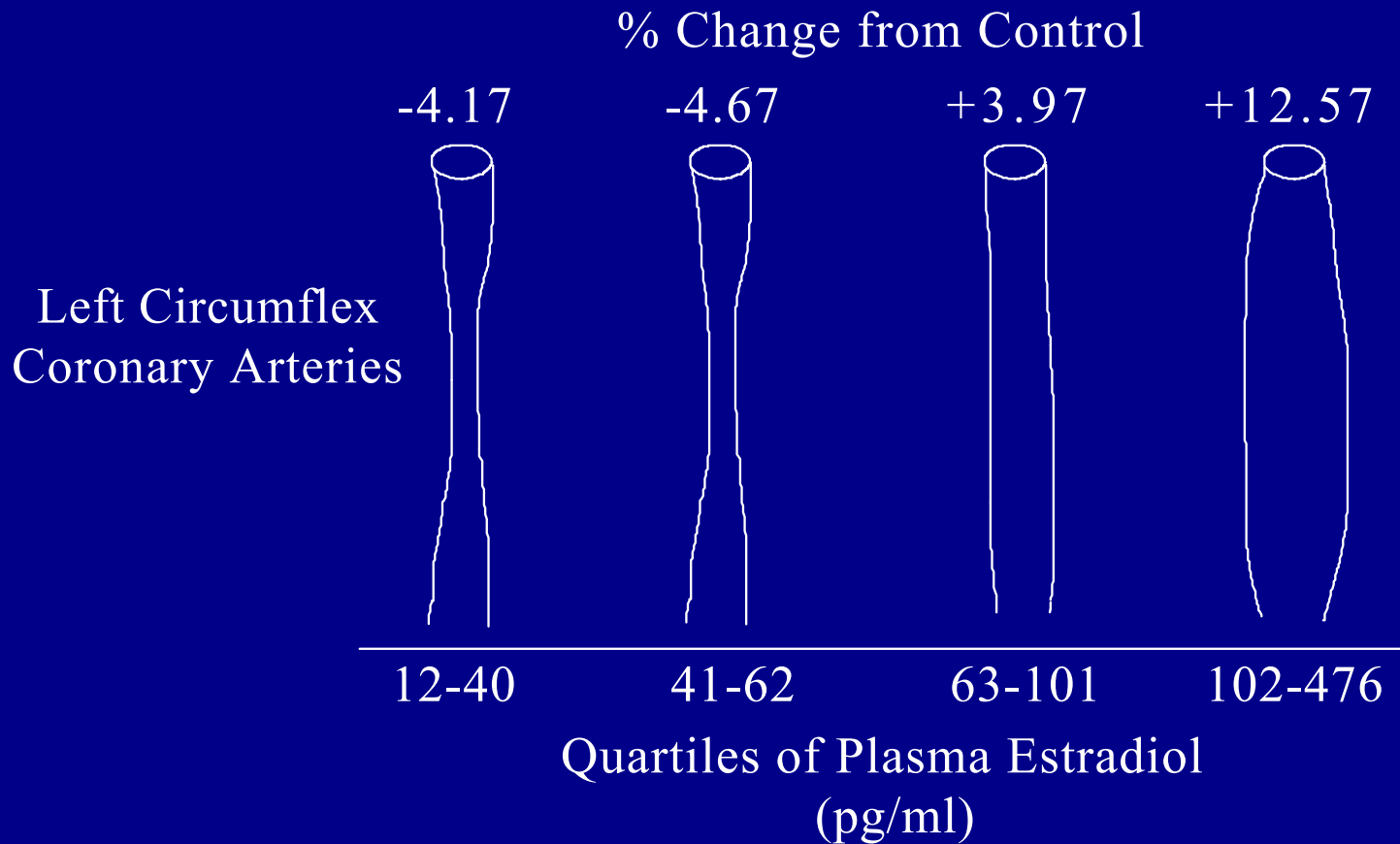
Stage of Reproductive Life



From Mikkola, Clarkson and Notelovitz, Ann Med, 2004

Premenopausal Considerations:

Association Between Plasma Estradiol and Coronary Artery Vasodilator/Constrictor Response to Acetylcholine*



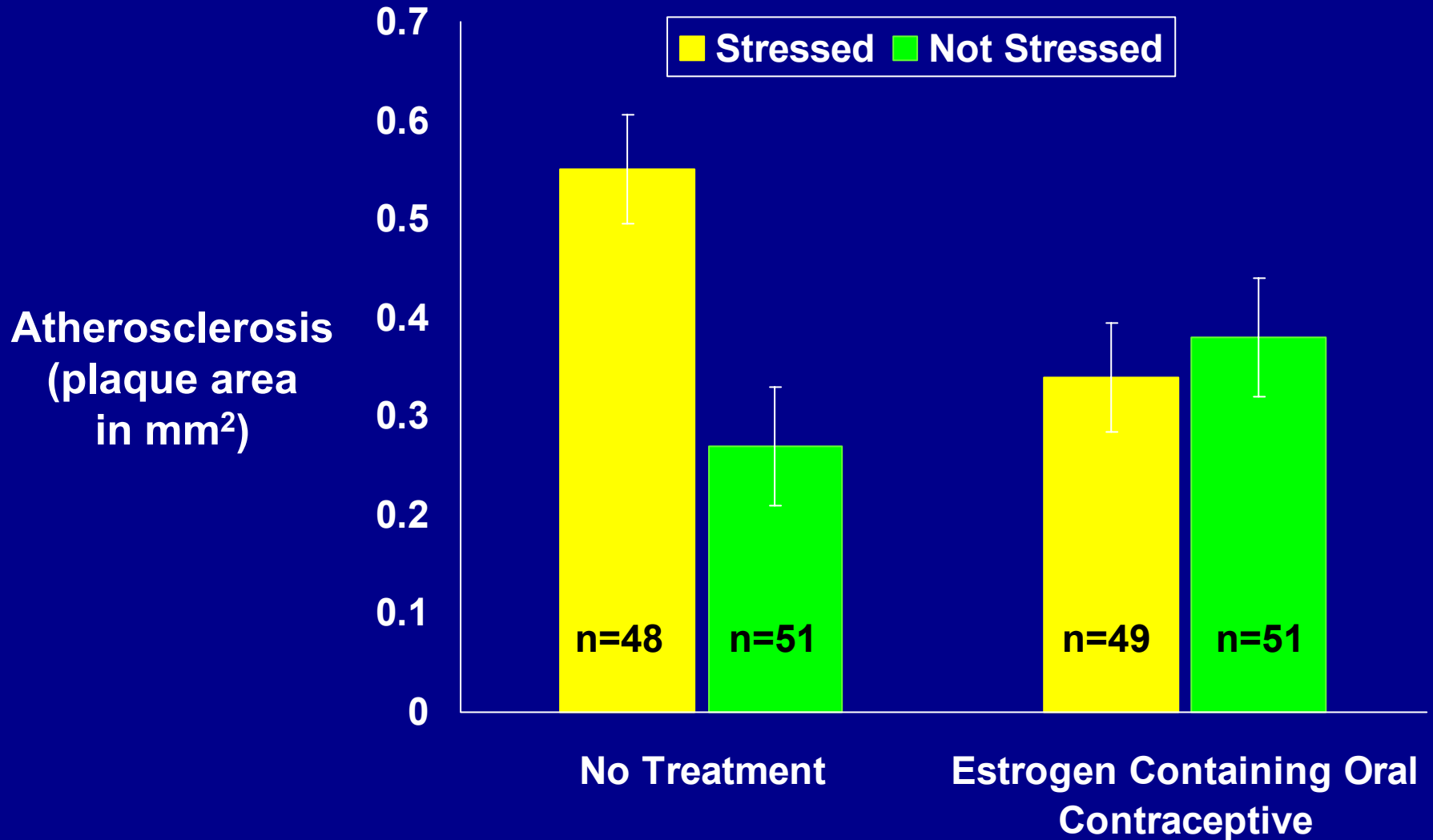
*Adapted from Williams, et al., Circulation 86(4):I-831, 1992.

Premenopausal Considerations: Effects of Premenopausal Estrogen Deficiency (Cynomolgus Model)

Observation	No Stress (dominant)	Stress (subordinate)
Follicular phase plasma estradiol (pg/ml)		
HDL cholesterol (mg/dl)		
Coronary atherosclerosis plaque area in mm ²		

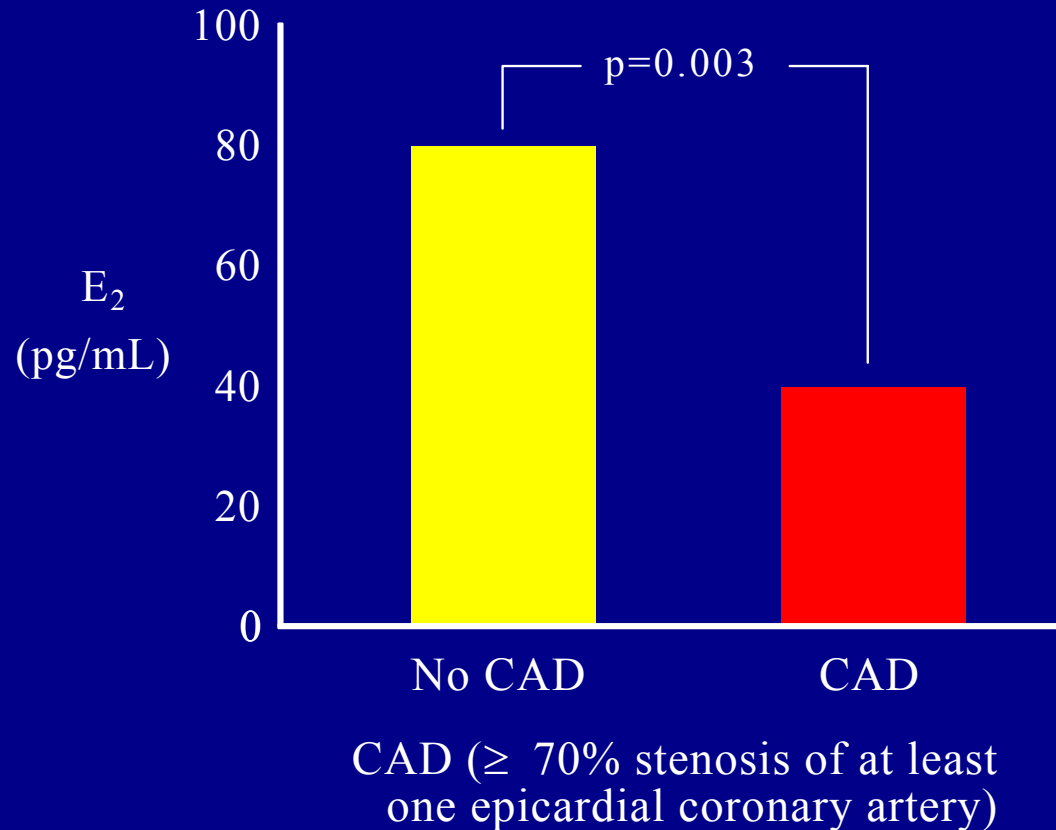
Modified from Clarkson et al, Br J Obstet Gynaecol, 1996

Effect of Exogenous Estrogen on Atherosclerosis of Estrogen Deficient (Stressed) Cynomolgus Monkeys



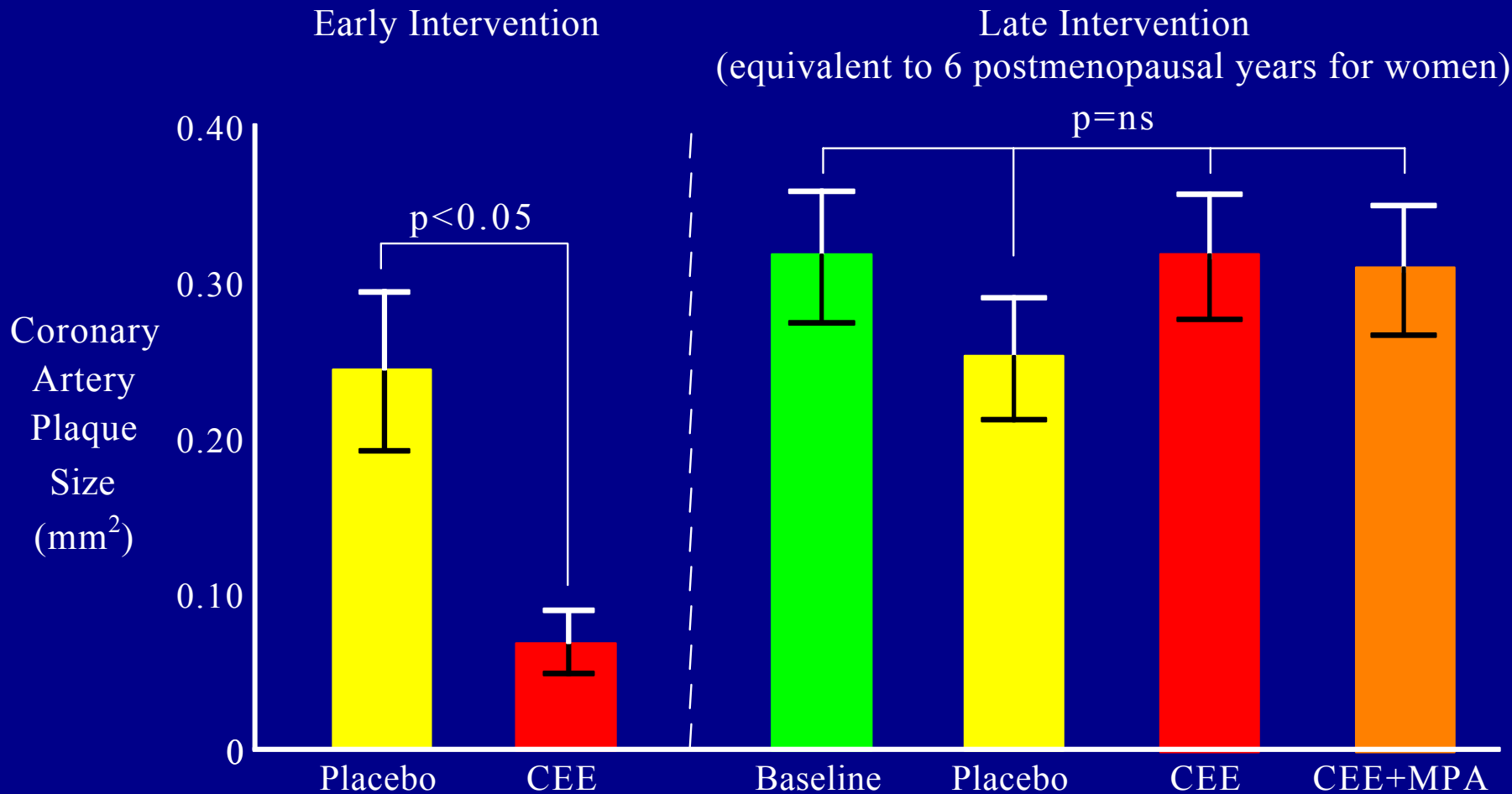
Modified from Kaplan et al, Arterioscler Thromb Vasc Biol, 1995

Median Estradiol Concentrations of Premenopausal Women With/Without CAD (WISE Study)



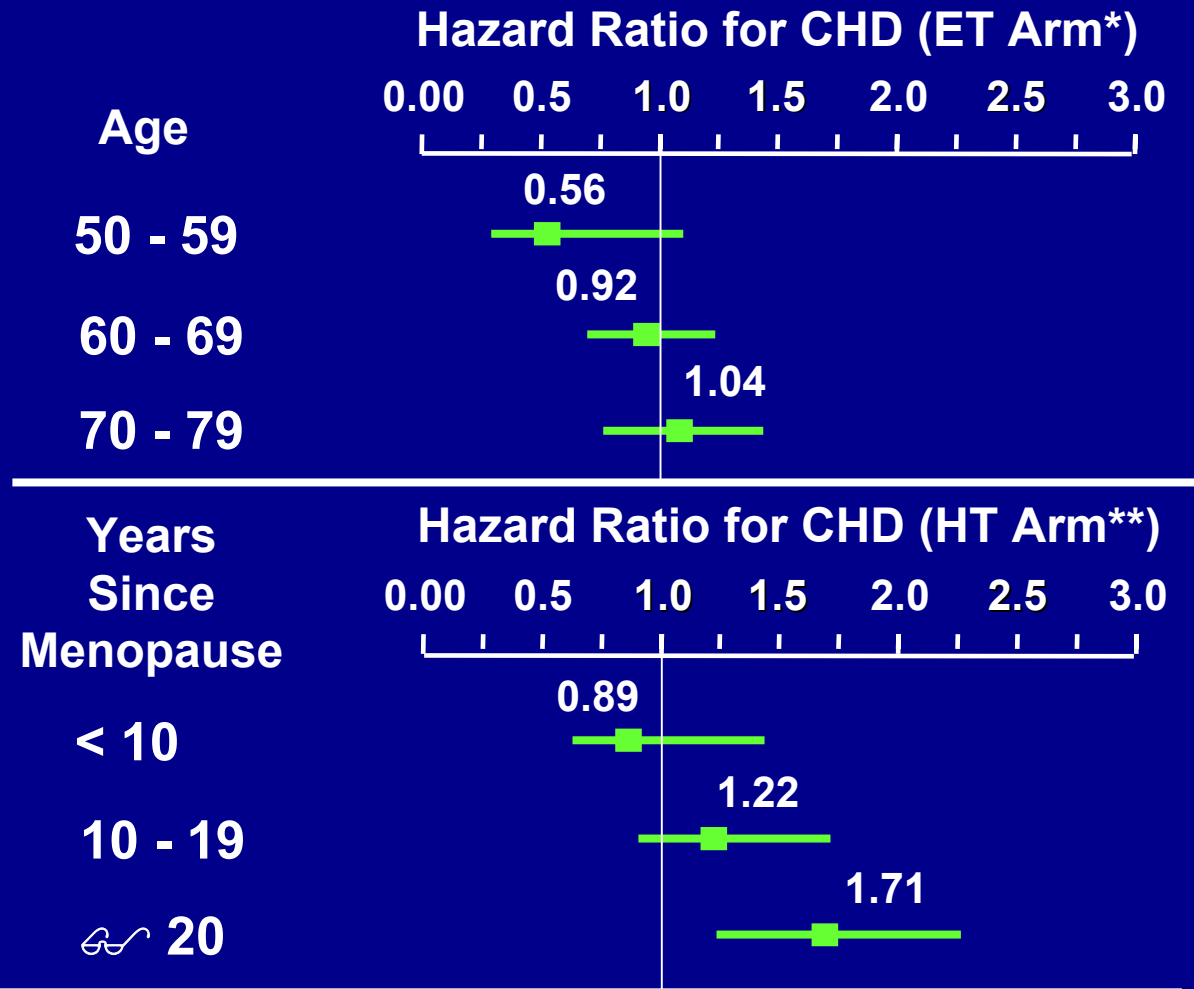
Data from Bairey-Merz et al, J Am Coll Cardiol, 2003

Effect of Time Menopausal on Effect/Lack of Effect of ET/HT on Coronary Artery Atherosclerosis of Cynomolgus Monkeys



Modified from Clarkson, Int J Fertil, 2002

Effect of ET and HT on CHD in Postmenopausal Women



*The Women's Health Initiative Steering Committee, JAMA, 2004

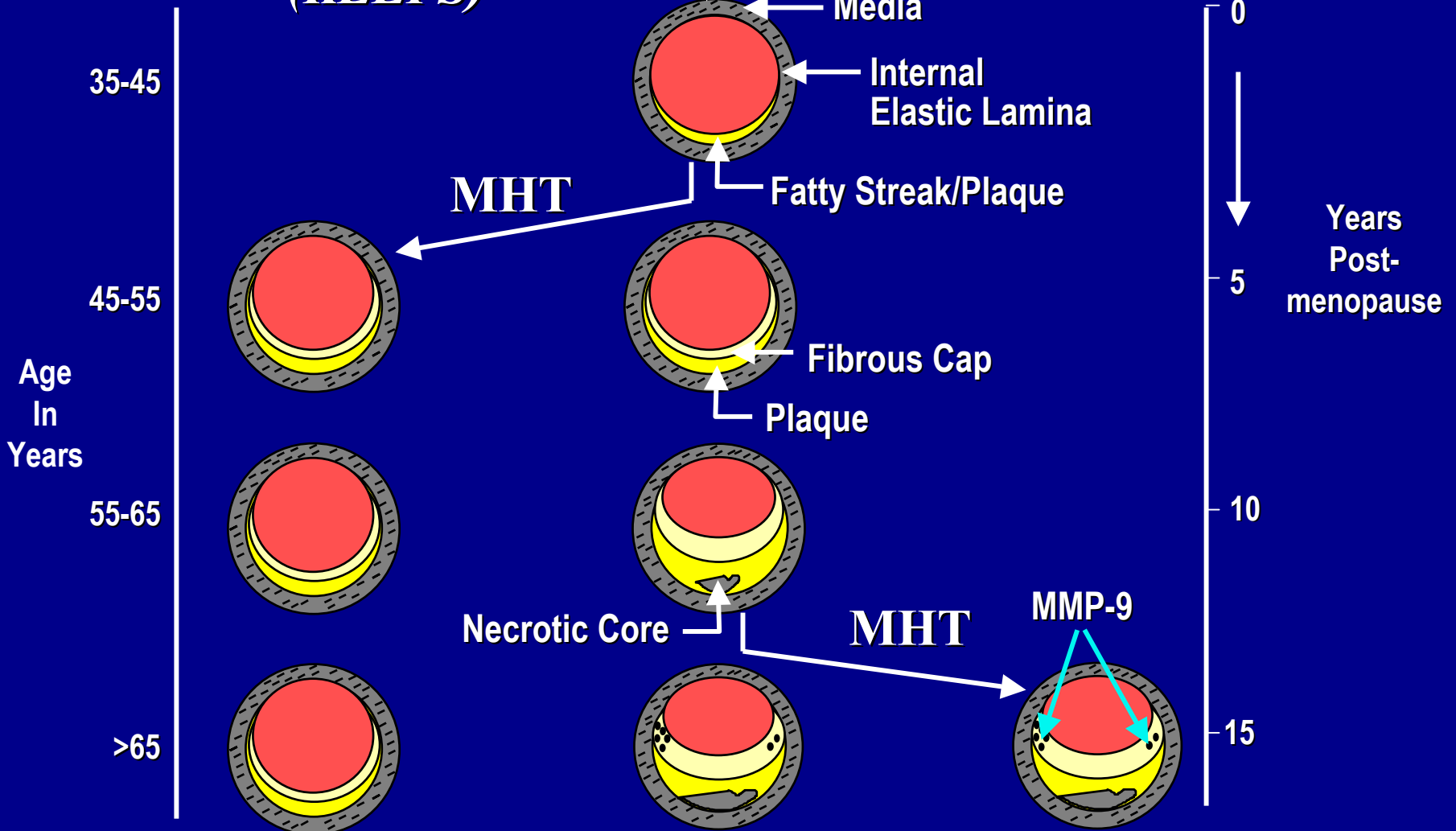
**Manson et al, N Engl J Med, 2003

HYPOTHETICAL RATIONALE FOR KEEPS

***Early Intervention
(KEEPS)***

No MHT

***Late Intervention
(HERS, WHI)***



When Should “Primary Prevention” Begin??

**With OCs During Perimenopausal
Transition Followed Directly with
HT at Postmenopause.**

**What Is the Evidence to Support
That Answer??**

Psychosocially Stressed Cynomolgus Monkeys as Models of the Perimenopausal Transition



Perimenopausal Women

Menstrual Irregularity

Anovulatory Cycles

Declining plasma estradiol concentrations

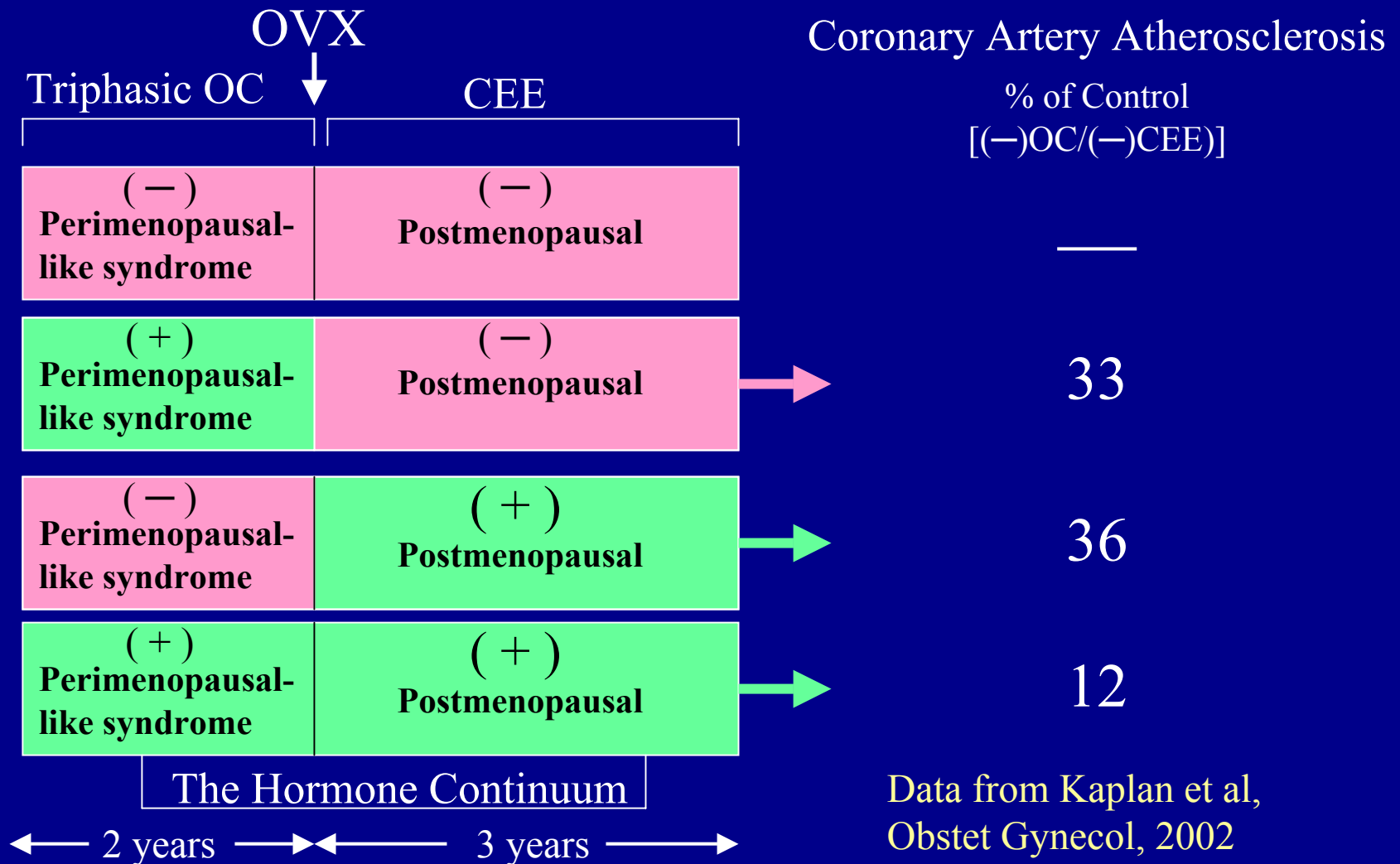
“Perimenopausal” Monkeys

Menstrual Irregularity

Anovulatory Cycles (27%)

Relative estrogen deficiency
(follicular phase peaks of ~ 80
pg/ml vs. normal of ~ 200 pg/ml)

OCs/ET and Coronary Artery Atherosclerosis



Monkey Models and Cognition Research



- Age-matched rhesus monkeys have cognitive decline associated with the peri and postmenopause (Roberts et al, Neuro Report, 1997).
- Neither OVX of cynomolgus monkeys for periods up to 6 years in women equivalents nor estrogen treatment of OVX monkeys for equivalent to 3 years had any effect on learning and memory (Voytko, Behav Neurosci, 2000).

**The Evidence Seems Strong That
ET/HT Is “Good” Early**

**and
“Bad”
Late**



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