Risk for coronary Artery Disease (CAD) in relation to estrogens

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ESTROGENS

- Estradiol is the most common type of estrogen, it is produced in both males and females .
- Estradiol, also known as 17beta-estradiol or (E2), is the most abundant form of circulating estrogens and considered the main female hormone.
- Estradiol controls development and maintainance of female sex characteristics and is often referred to as the “female hormone” .
- Estradiol levels are significantly lower in males compared to females ,estrogens nevertheless have important physiological roles in males.

- E2 is predominantly synthesized and secreted by the ovaries in premenopausal women .
- In men testes produce only 20% of circulating estrogens.
- Some E2 is also produced in other tissue types including adipose, brain, and bone tissues as well as the vascular endothelium and aortic smooth muscle cells .
- Gonadal E2 acts largely as an endocrine factor affecting distal tissues.
- Extra gonadal production of E2 acts locally as a paracrine or intracrine factor in the tissue where it is synthesized .
- This extra gonadal E2 production plays an important role, as it remains the main source of endogenous E2 production in postmenopausal women .

- Estradiol has effects on multiple tissues and organs.
- In the breast estradiol mediates development of mammary gland tissue.
- Estradiol produced by the growing ovarian follicle , drives endometrial proliferation.
- Estradiol also supports bone development

ESTROGENS – CARDIOPROTECTIVE ROLE

- Clear roles for estradiol action on the cardiovascular system have been demonstrated.

- Clinicians have long suspected that the delay of a decade or more in cardiovascular disease expression in women relative to men is due to the protective effects of estrogen during a woman's reproductive years.

- Population-based observational studies reported favorable effects of estrogen therapy on cardiovascular morbidity and mortality have led to enthusiasm for widespread use of estrogen by postmenopausal women for prevention of cardiovascular disease events.

- The guidelines for estrogen therapy issued by the American College of Physicians include the statement, **“Women who have coronary heart disease or who are at increased risk for coronary heart disease are likely to benefit from hormone therapy.”**

EFFECTS OF ESTROGEN ON LIPOPROTEINS

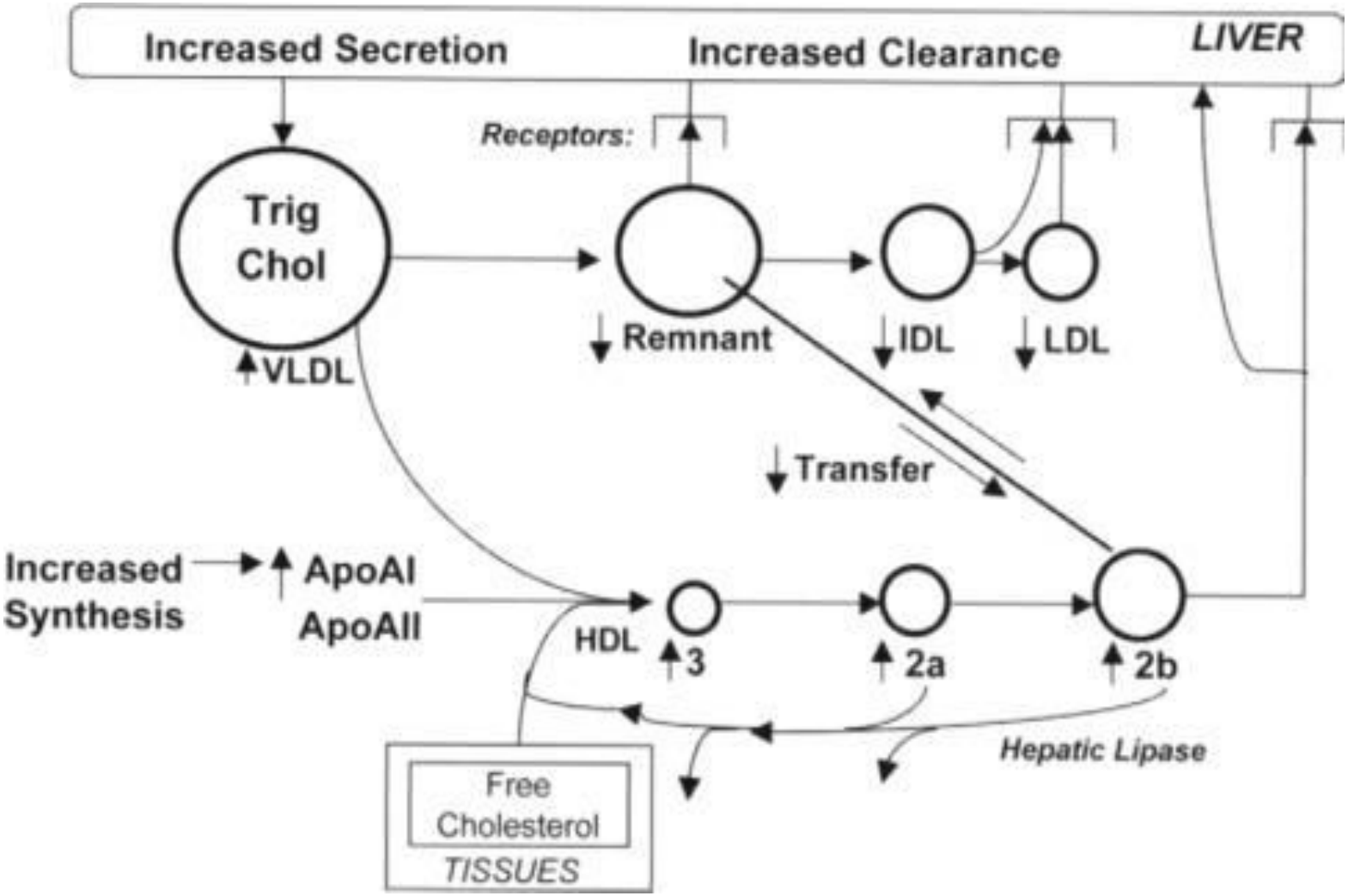
- Before menopause, plasma LDL cholesterol levels are lower and HDL cholesterol levels are higher in women compared with men of the same age.

- After menopause, LDL cholesterol levels rise, commonly exceeding those of age-matched men, and HDL cholesterol levels decline.

- Orally administered estrogen reduces LDL cholesterol levels and increases HDL cholesterol levels in postmenopausal women .

- In liver 17- beta estradiol , reduces the rate of apoB100 synthesis(apoprotein of LDL) while stimulates apoA1 and apoA2 synthesis(apo - proteins of HDL).

EFFECTS OF ESTROGEN ON LIPOPROTEIN METABOLISM



ESTROGEN AND NITRIC OXIDE

- Estrogen enhance the release or bioavailability of nitric oxide from endothelial cells, resulting in increased cGMP in underlying smooth muscle and cause vasorelaxation.

- Postmenopausal women on estrogen therapy were found to have higher serum levels of nitrite and nitrate, indicators (in part) of vascular nitric oxide release, compared with untreated controls
- **Reference: Circulating nitric oxide levels in postmenopausal women substituted with 17 beta –estradiol Hypernsion 1995;25-848-853. Crossref PubMed**

GENOMIC AND NON-GENOMIC EFFECTS OF ESTROGEN

- E2 binds to the traditional ERs, ERα and ERβ, as well as the newly identified G-protein-coupled ER (GPR30)

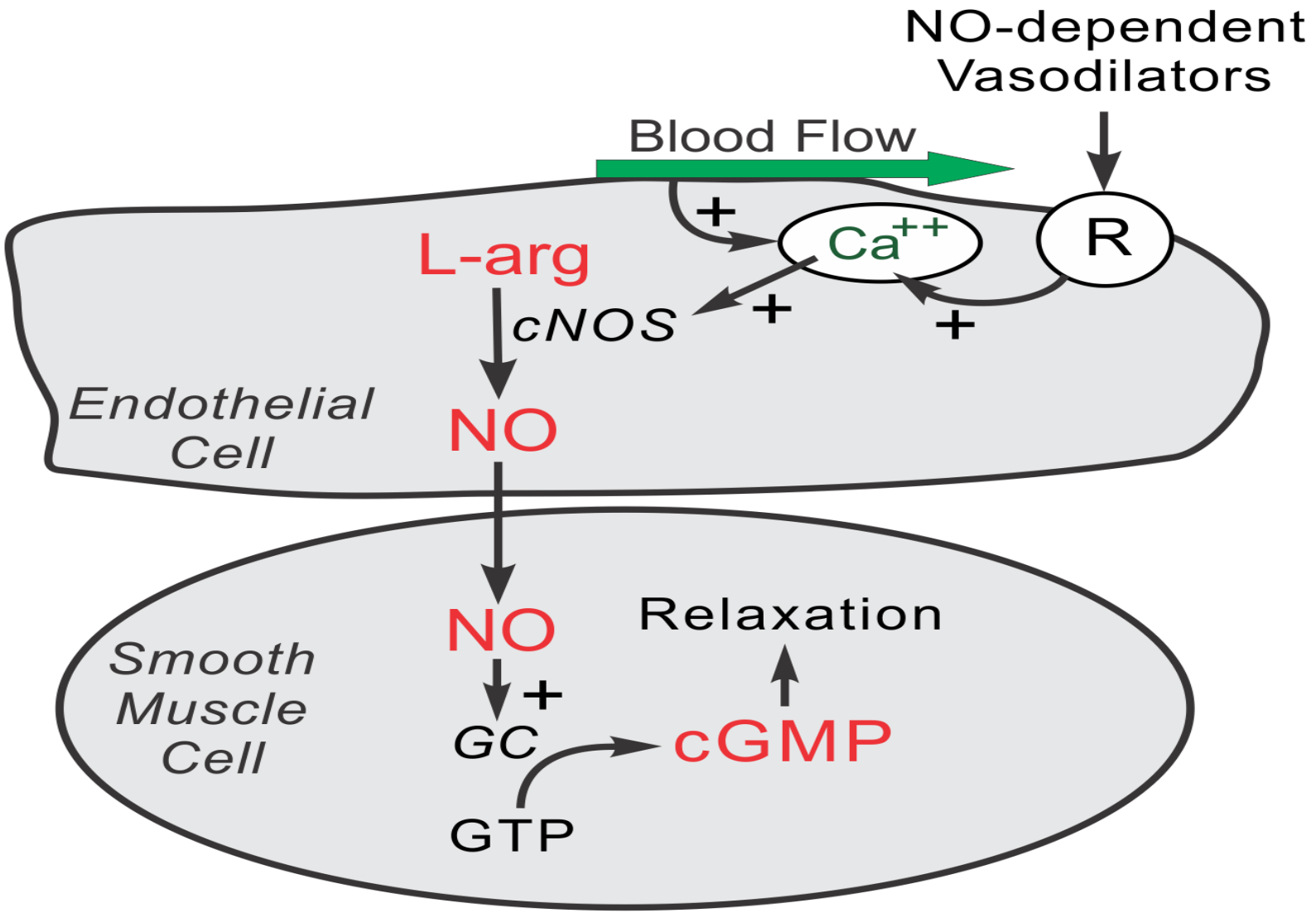
- Binding to ERα and ERβ can perform both genomic and rapid non-genomic actions

- Genomic effects include the classical intracellular estrogen receptors (ER), which after binding of E2 interact with estrogen-response element (ERE) in DNA, resulting in an increased eNOS expression.

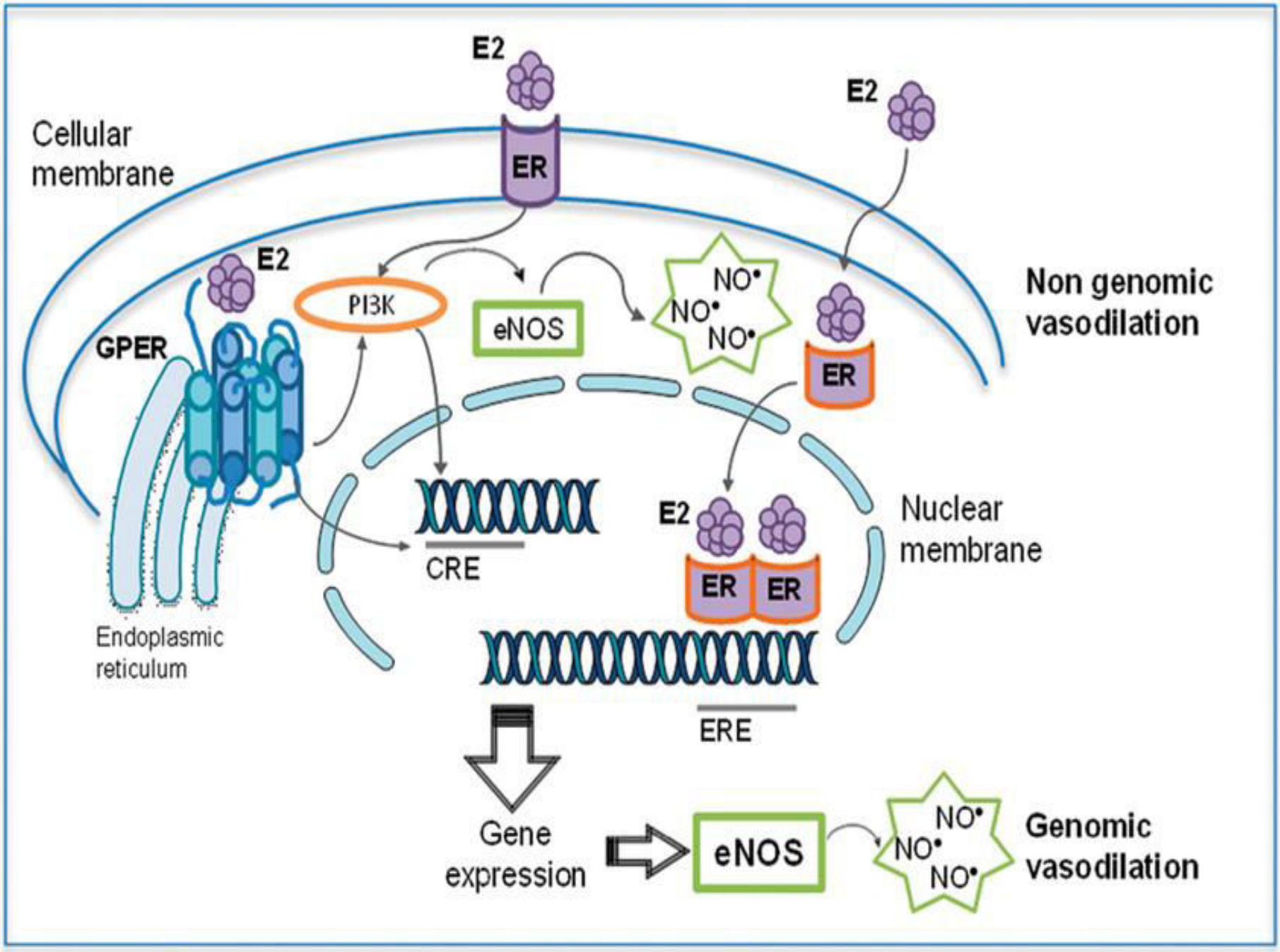
- Nongenomic actions are a common property of steroid hormones and are frequently associated with the activation of various protein-kinase cascades .

- E2 binding to GPER(G protein coupled estrogen receptor) leads to activation of different transcriptional factors such as cAMP response element (CRE) which also induces eNOS expression.

- The nongenomic actions of 17β-estradiol that have been reported include the mobilization of intracellular calcium , and the stimulation of adenylate cyclase activity and cAMP production .



R, receptor; *L-arg*, L-arginine; *cNOS*, constitutive nitric oxide synthase; *GC*, guanylyl cyclase; *GTP,* guanosine triphosphate; *cGMP,* cyclic guanosine monophosphate.


E2
E2
Cellular membrane
ER
E2
PI3K
eNOS
NO•
NO•
NO•
Non genomic vasodilation
GPER
ER
CRE
E2
ER
ER
Nuclear membrane
Endoplasmic reticulum
ERE
Gene expression
eNOS
NO•
NO•
NO•
Genomic vasodilation

- Augmented release of nitric oxide by estrogen might account not only for enhancement of endothelium-dependent vasodilation but also for much of the antiatherogenic effects of estrogen by
  - Inhibition of platelet aggregation
  - Inhibition of platelet and inflammatory cell attachment to the vessel wall
  - Inhibits release of factors that stimulate smooth muscle cells growth and migration.

ANTIOXIDANT EFFECTS OF ESTROGEN

- Over the past decade, evidence has accumulated indicating that oxidative modification of LDL greatly increases its atherogenicity and that antioxidants may reduce the extent of atherosclerosis and reduce cardiovascular events in humans.

- Researchers have found that the acute administration of 17ß-estradiol into the brachial arteries of postmenopausal women significantly delayed the onset and rate of copper-catalyzed oxidation of LDL .

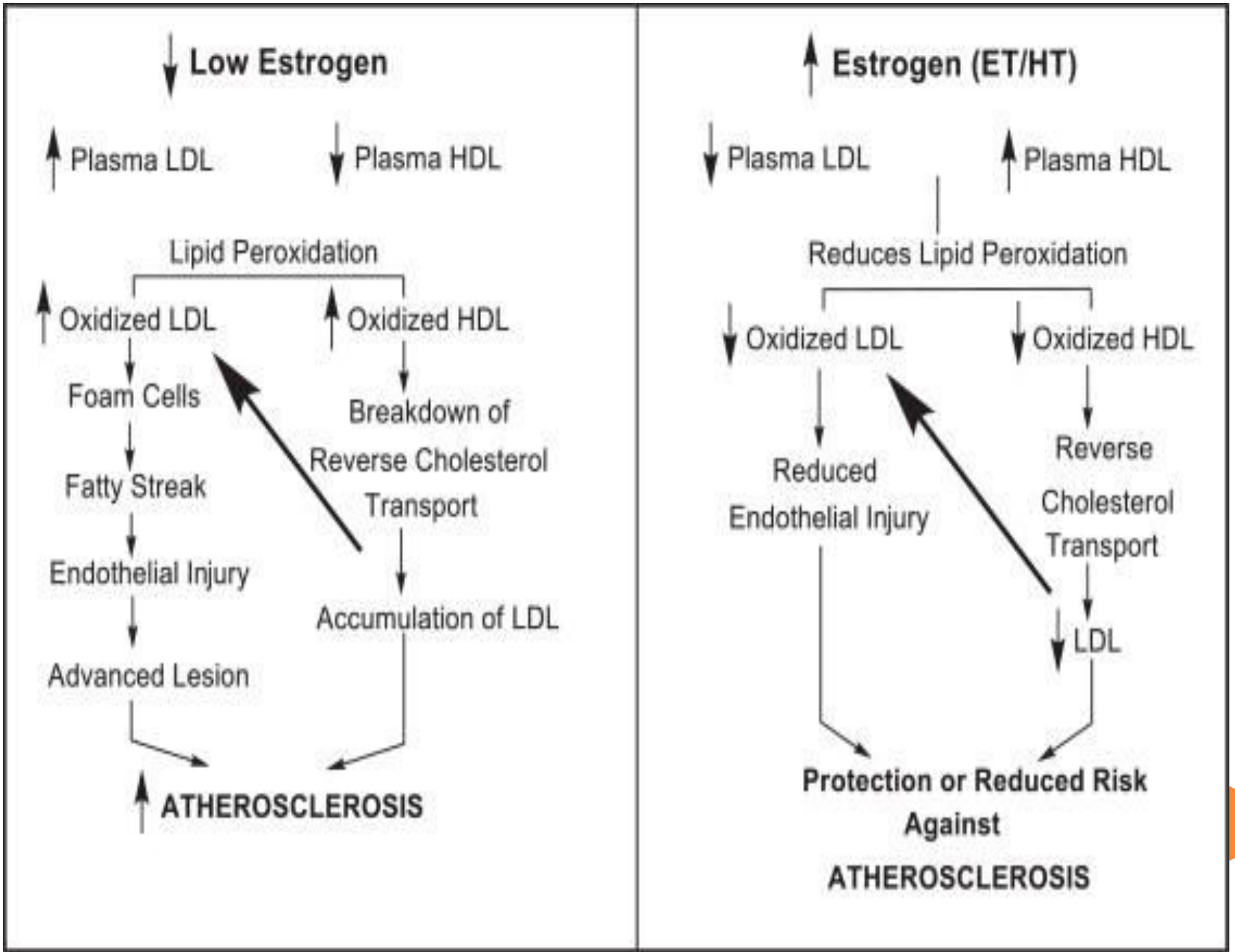
- Reference:Antioxidant potential of specific estrogens on lipid peroxidation J Clin Endocrinol Metab,1993;77:1095-1097.PubMed

- Pavón et al. also reported that E2 is protective against damaging oxidative stress resulting from lipid peroxidation and free radical formation.

- They showed that levels of thiobarbituric acid reactive substances (TBARS) were increased following I/R injury in ovarectamised females when compared to intact females.

- Intact female mice were found to have increased cardiac levels of the antioxidant mitochondrial superoxide dismutase 2 (SOD2) when compared to male mice.

- Following OVX, SOD2 expression decreased to match that of males, and E2 therapy in OVX female mice resulted in increased SOD2 expression.


Low Estrogen
Plasma LDL
Plasma HDL
Lipid Peroxidation
Oxidized LDL
Oxidized HDL
Foam Cells
Fatty Streak
Endothelial Injury
Advanced Lesion
Breakdown of
Reverse Cholesterol
Transport
Accumulation of LDL
ATHEROSCLEROSIS
Estrogen (ET/HT)
Plasma LDL
Plasma HDL
Reduces Lipid Peroxidation
Oxidized LDL
Oxidized HDL
Reduced
Endothelial Injury
Reverse
Cholesterol
Transport
LDL
Protection or Reduced Risk
Against
ATHEROSCLEROSIS

HEMOSTATIC EFFECTS OF ESTROGEN

In the Framingham Offspring Study, reproductive-age women had **lower** plasma levels of PAI-1(plasminogen activator inhibitor) and **higher** levels of TPA (tissue plasminogen activator an enzyme that dissolves clots) compared with age matched men and postmenopausal women .

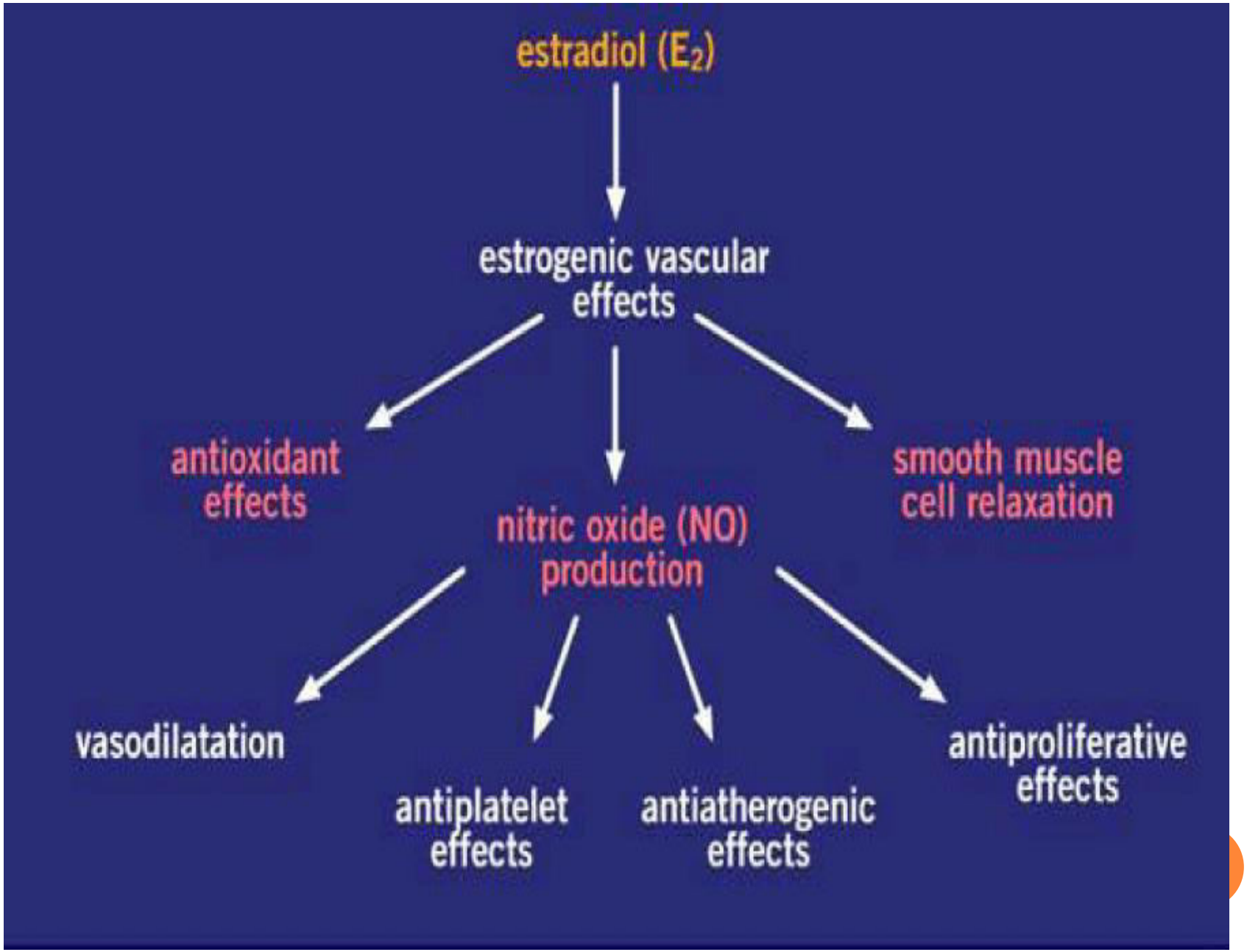
- Reference : Association between increased estrogen status and increased fibrinolytic potential in the Framingham Offspring Study : Circulation 1995-91:1952-1958. Crossref PubMed

- However, postmenopausal women on estrogen therapy had PAI-1 and TPA levels similar to those of reproductive-age women.

- The mechanism of the apparently favorable hemostatic effects of estrogen is unknown.

- Oxidatively modified LDL depresses endothelial release of TPA, and both oxidatively modified LDL and lipoprotein(a) promote synthesis of PAI- by increased transcription of PAI-1 mRNA.

- Thus, the effect of estrogen on TPA and PAI-1 may in part be due to antioxidant protection of LDL and reduction in lipoprotein(a) plasma levels


estradiol (E_2)
estrogenic vascular effects
antioxidant effects
nitric oxide (NO) production
smooth muscle cell relaxation
vasodilatation
antiplatelet effects
antiatherogenic effects
antiproliferative effects

Aromatase and the cardiovascular system

- In men estrogens are produced by aromatization of androgenic precursors from the testes and adrenal glands.

- Endogenous production of estrogens in men plays a significant role in cardiovascular health;

- The main site of E2 production in female is ovary , peripheral tissues(coronary endothelium,blood vessels, bone etc) can act as sites of local E2 production by converting androgens into E2 via the aromatase enzyme.

- Research studies on serum estradiol and testosterone levels following AMI, observed low testosterone and high estradiol levels in the acute phase of MI ,suggested enhanced conversion of testosterone to estradiol by aromatase enzyme.

Studies on estrogen levels in men with myocardial infarction

- **Serum estrogen levels in men with acute myocardial infarction.**

Klaiber EL, Broverman DM,. Am J Med. 1982 Dec;73(6):872-81.

- **Relationship between sex hormones, myocardial infarction, and occlusive coronary disease.**

Luria MH, Johnson MW, Pego R, Arch intern Med;1982 jan.

- **Sex hormone levels in young Indian patients with myocardial infarction.**

Sewdarsen M, Jialal I, Vythilingum S, Desai R. Arteriosclerosis. 1986 Jul-Aug;6(4):418-21

- Plasma sex hormones and ischemic heart disease

Clin biochem 1987 apr20(2)eldrupE .

estradiol ,testosterone,apolipoproteons,in men with MI.

Artery 1983 12(1)MendozaSG.

Thank you

- Estrogen has been shown in animal models or cell culture to reduce collagen and elastin synthesis and enhance their degradation in arterial tissue, reduce smooth muscle cell proliferation, decrease platelet aggregation, and promote angiogenesis.

- Prostacyclin, a potent vasodilator and inhibitor of platelet aggregation, has been shown in various studies to be potentiated or inhibited by estrogen.

Estrogen and angiogenesis

- By definition, angiogenesis is the physiological process by which new blood vessels form from pre-existing vessels. E2 has previously been shown to be pro-angiogenic in various tissues including the uterus, breast, brain, and limbs [53–55].
- Induction of neoangiogenesis via E2 therapy is dependent on eNOS activation, as eNOS-null mice do not exhibit the proangiogenic effects following E2 therapy.

Estrogen and fibrosis

- Myocardial extracellular matrix (ECM) proteins, matrix metalloproteinases (MMPs), growth factors, and cytokines are mainly produced by cardiac fibroblasts, all of which contribute to the myocardial structure maintainance as well as cardiac remodeling in diseased hearts .

- E2 has been demonstrated to have a significant role in ECM remodeling by acting on fibroblasts via ER and MAPK-(mitogen activated protein kinases) dependent mechanisms .

- Recent data demonstrates that E2 protects against cardiac fibrosis and harmful ECM remodeling by altering fibroblast proliferation .