DIU HTA – Toulouse Mai 2013

Oestrogènes et risque cardio-vasculaire: Où en sommes nous?

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INSERM U1048 - Team 9
CHU de Toulouse

1- Effets physiologiques de l'oestradiol (E2)

2- Etude du ttt « substitutif » à la Ménopause :

A) Etude d'observation : Nurses

B) Etude d'intervention : Woman Health Initiative (USA)

C) …Et chez l'Homme : à propos d'un cas

3- Perspectives, Traitements du futur : nouveaux

SERMs, nouvelles associations ?

1- Effets physiologiques de l'oestradiol (E2) (13 - 52 ans)

Effets physiologiques de l'oestradiol (E2) : Protecteur, neutre et délétère

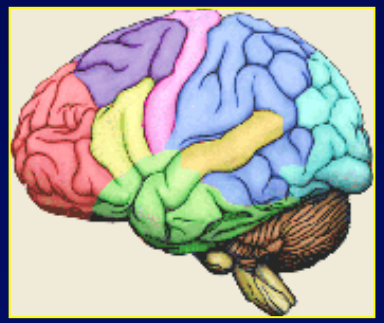
Reproduction / caractères sexuels

K du Sein

Progesterone

Uterus

Progesterone



SNC

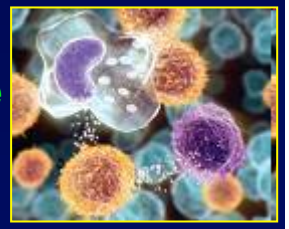
Estradiol (E2)

Sécrétion ovaires

Cycle oestral

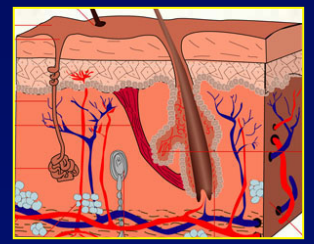
Immunité

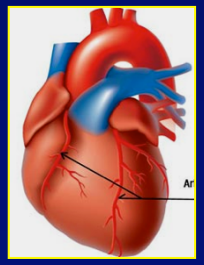
Immunité



OS

peau

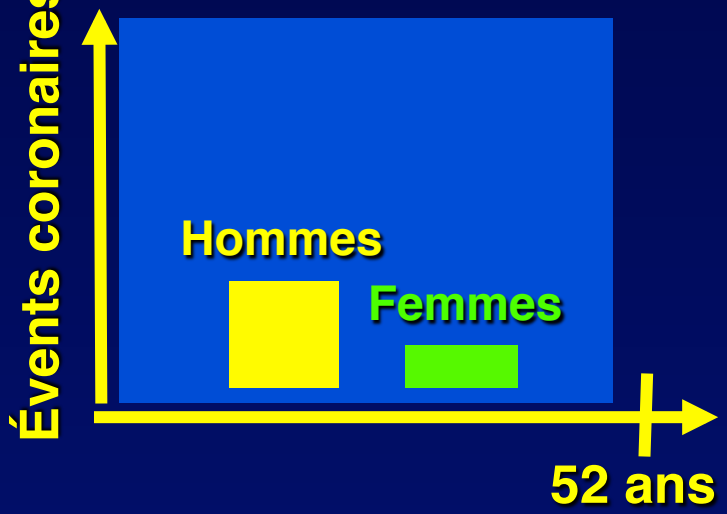




Homeostasie cardio-vasculaire et métabolique

Impact cardiovasculaire des oestrogènes (E) endogènes

Epidémiologie :
Différence entre sexes
avant la ménopause



E endogènes :
Protecteurs

…mais

protection en grande partie perdue si

facteurs de risque

(Tabac!!)

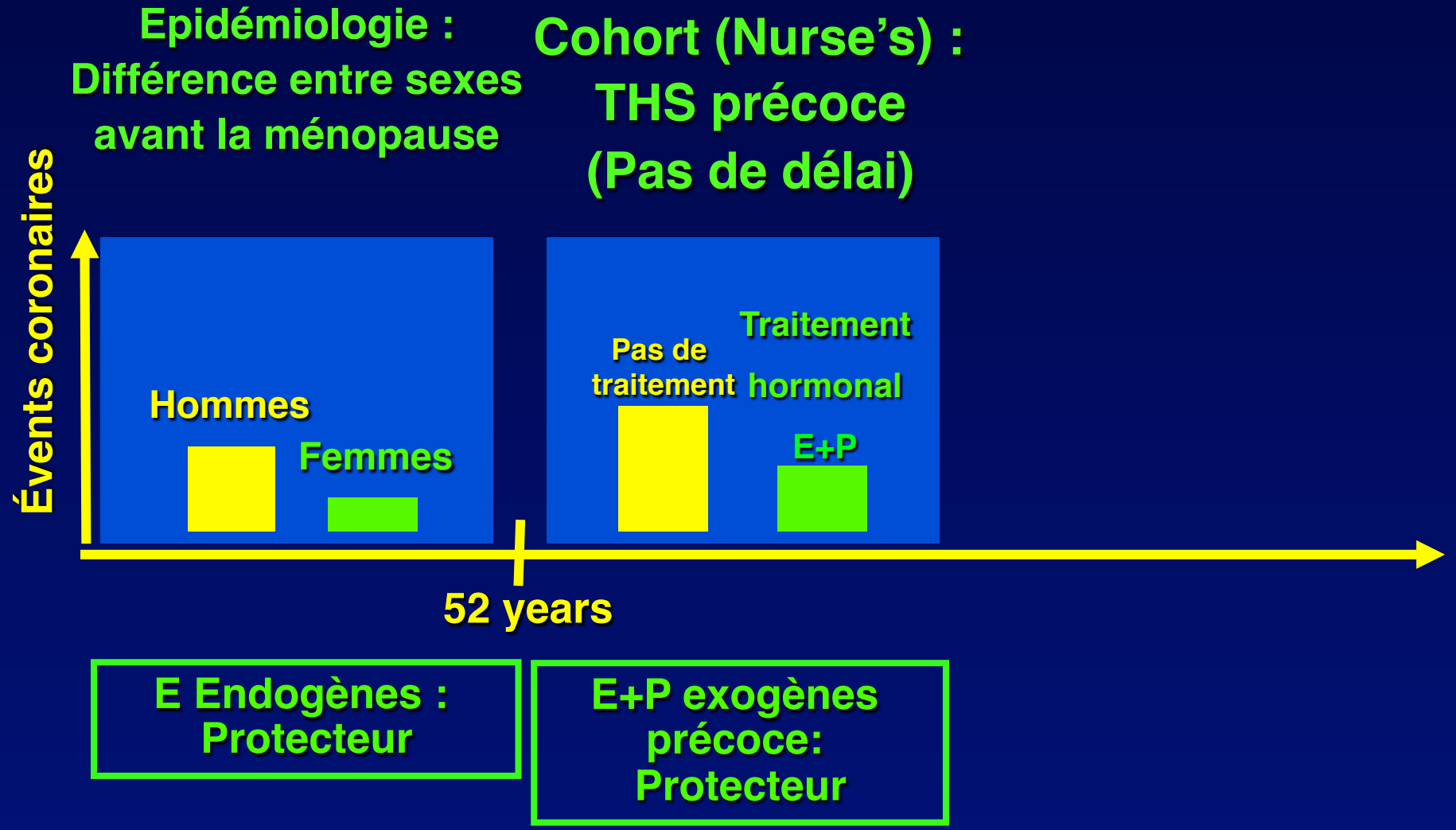
2- Oestrogènes exogènes après la ménopause :

A) Etude d'observation : Nurses

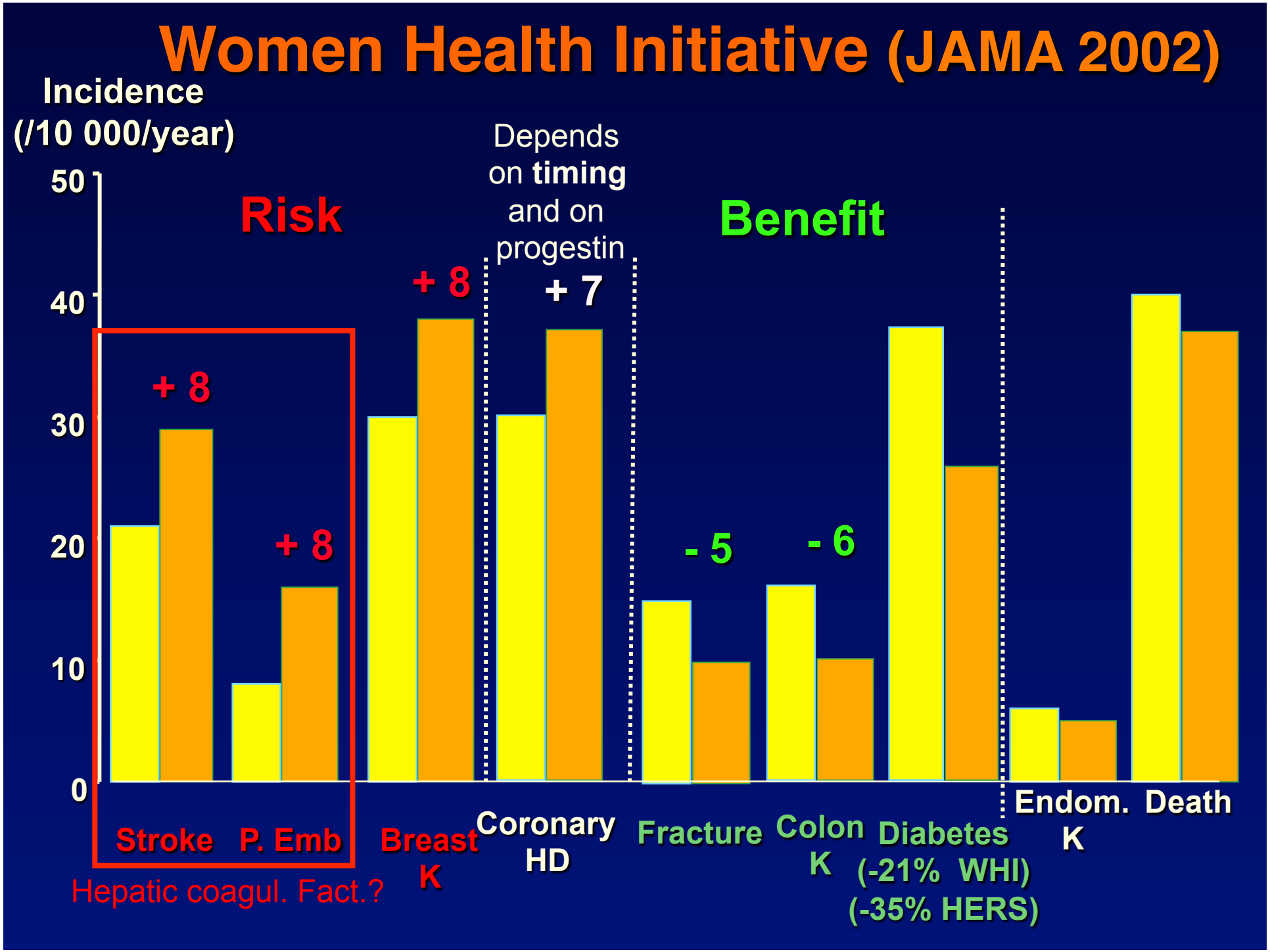
B) Etude d'intervention :

Woman Health Initiative (USA)

A) Etude d'observation : Nurses



Women Health Initiative (JAMA 2002)



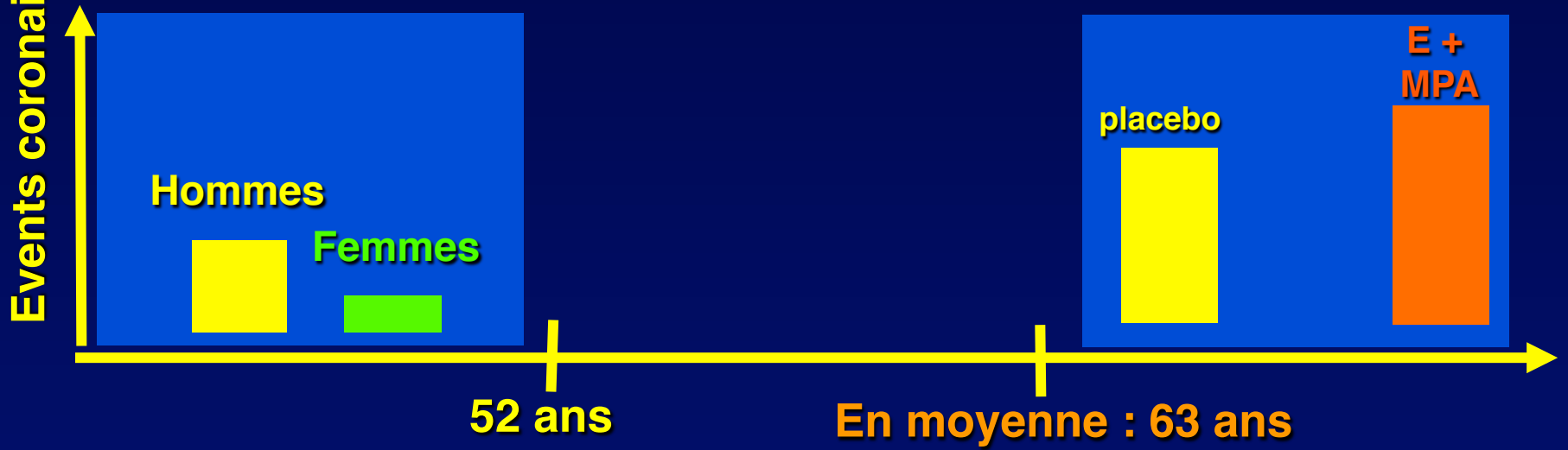
B) Etude d'intervention : Women Health Initiative

2002

Epidémiologie :
Différence entre sexes avant la ménopause

Women Health Initiative :

Non Hysterect.: E + MPA



Période sans oestrogènes

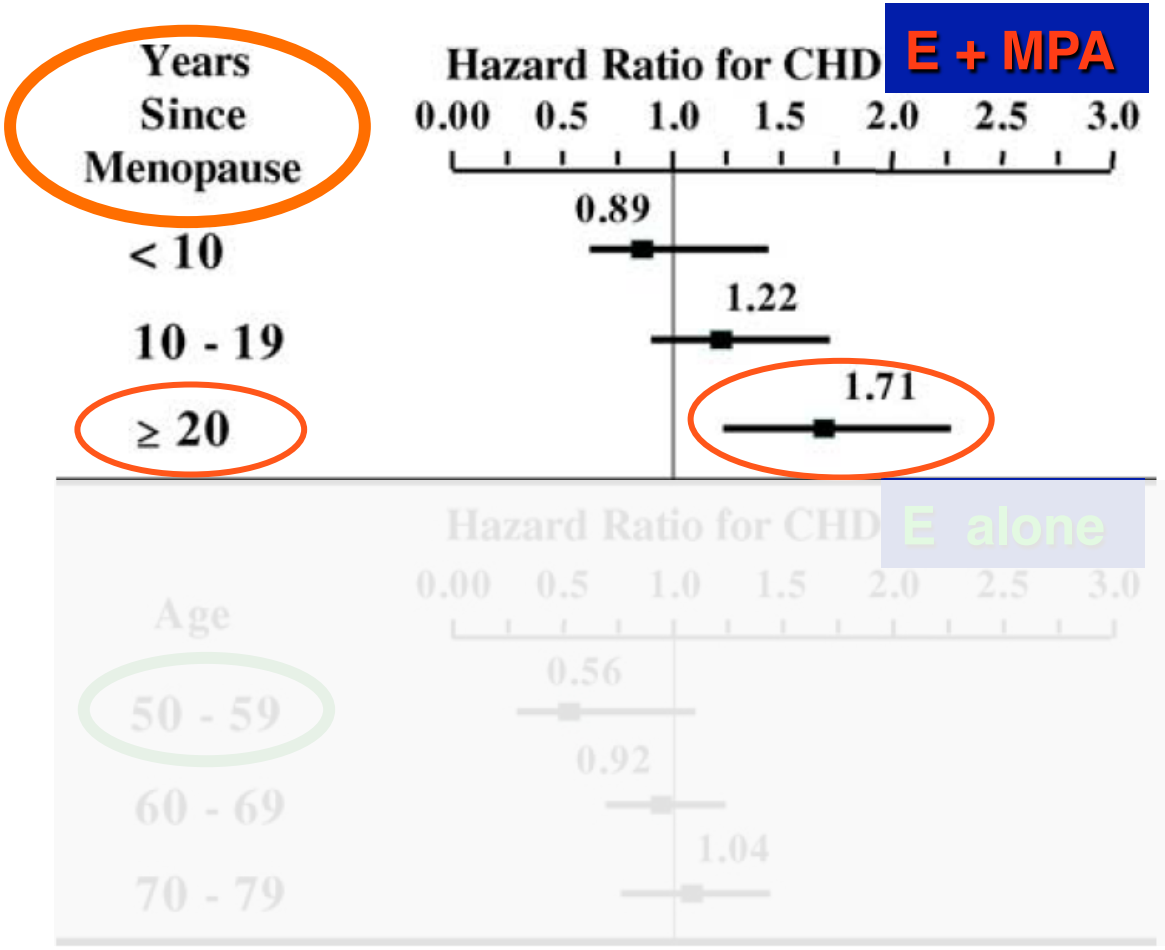
=

délai

E + MPA: délétère chez les femmes les plus agées

WHI 2002 : E + MPA increases coronary events during the 1st year following the onset of the HT in the most aged women

T.B. Clarkson, S.E. Appt / Maturitas 51 (2005) 64–74



B) Etude d'intervention : Woman Health Initiative

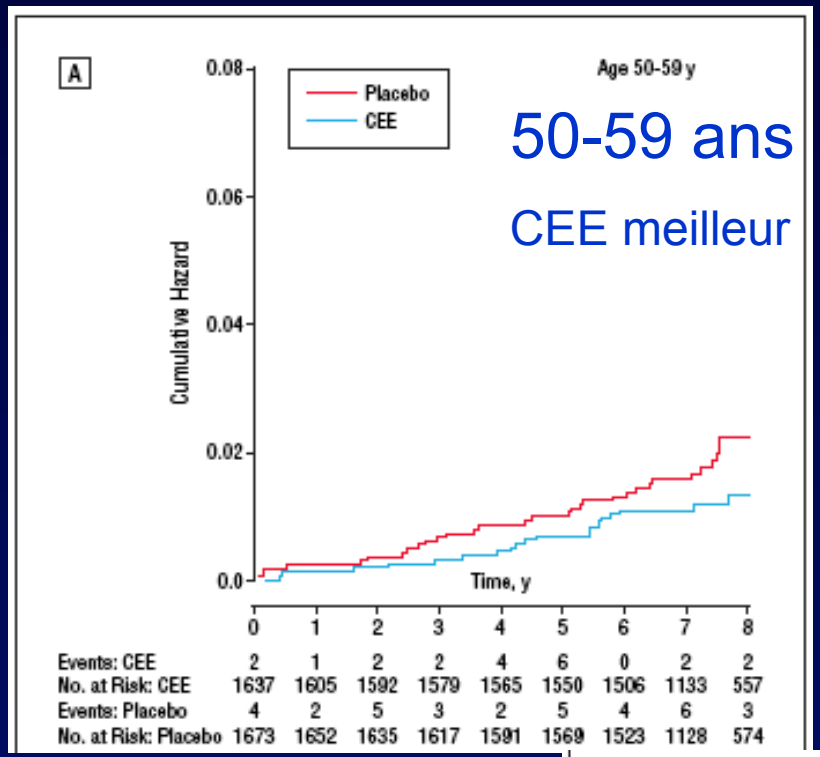
Epidémiologie :
Différence entre sexes avant la ménopause

Women Health Initiative :
Hysterectomisées : E seul
Non Hysterect.: E + MPA

Période sans oestrogènes = délai

E seuls : inefficace

E + MPA: délétère chez les femmes les plus agées

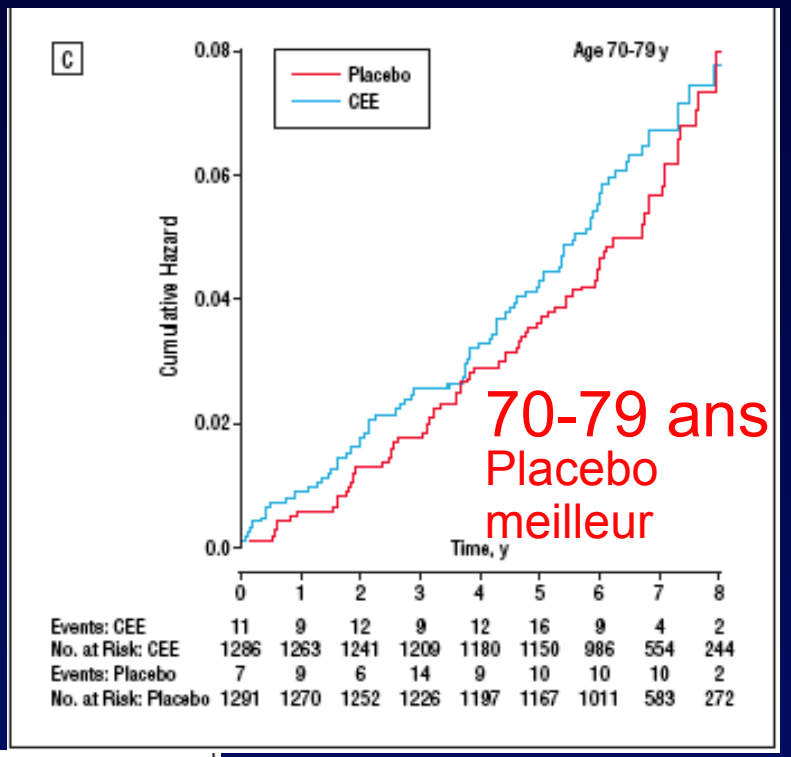


50-59 ans

CEE meilleur

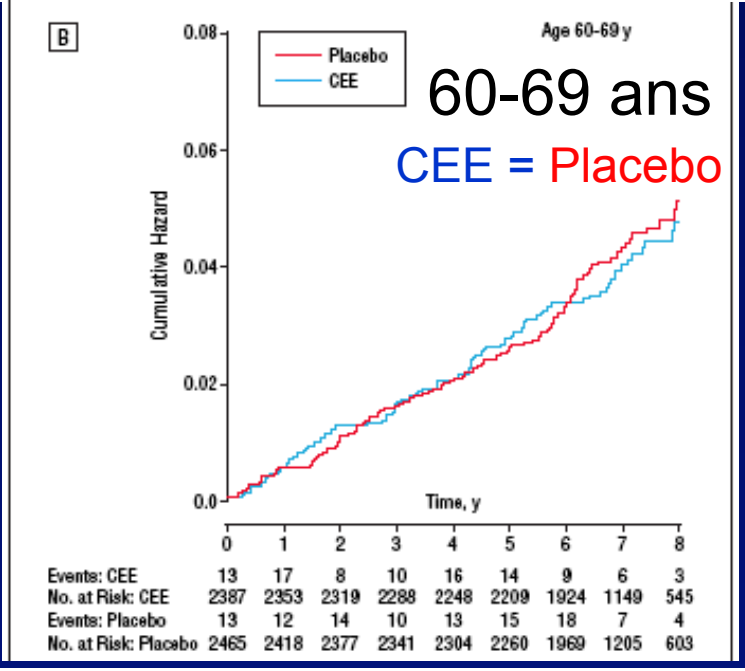
Timing

! ! !



70-79 ans

Placebo meilleur

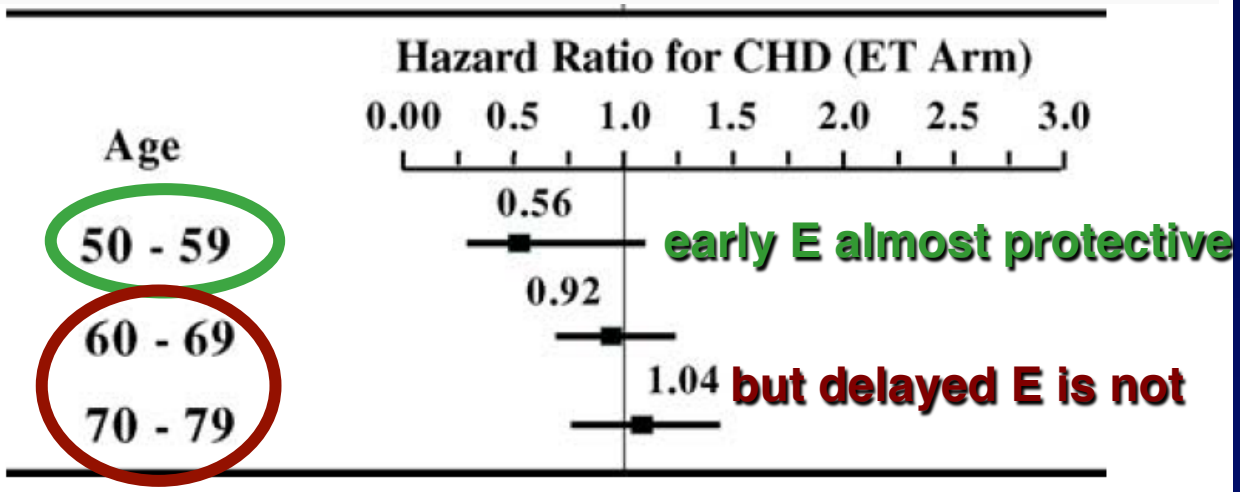


60-69 ans

CEE = Placebo

T.B. Clarkson, S.E. Appt / Maturitas 51 (2005) 64–74

WHI 2004 :
Relative Risk of Coronary Heart Desease
of Estrogen alone / placebo

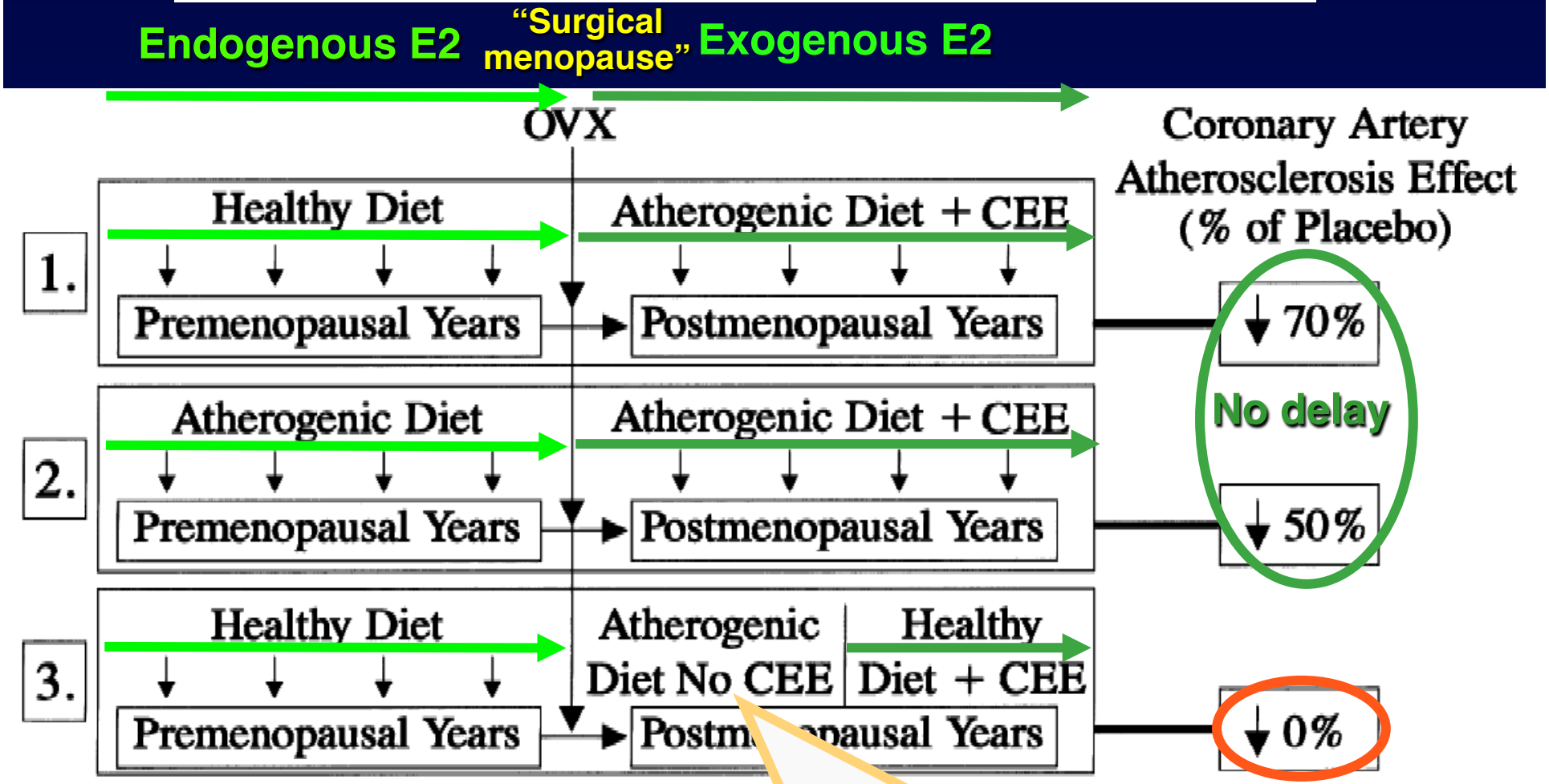


Importance du "timing"

Very similar to the Monkey studies (Cardiovasc. Res. 2002)

Estrogen replacement therapy, atherosclerosis, and vascular function

Tomi S. Mikkola[a,b], Thomas B. Clarkson[a,*]

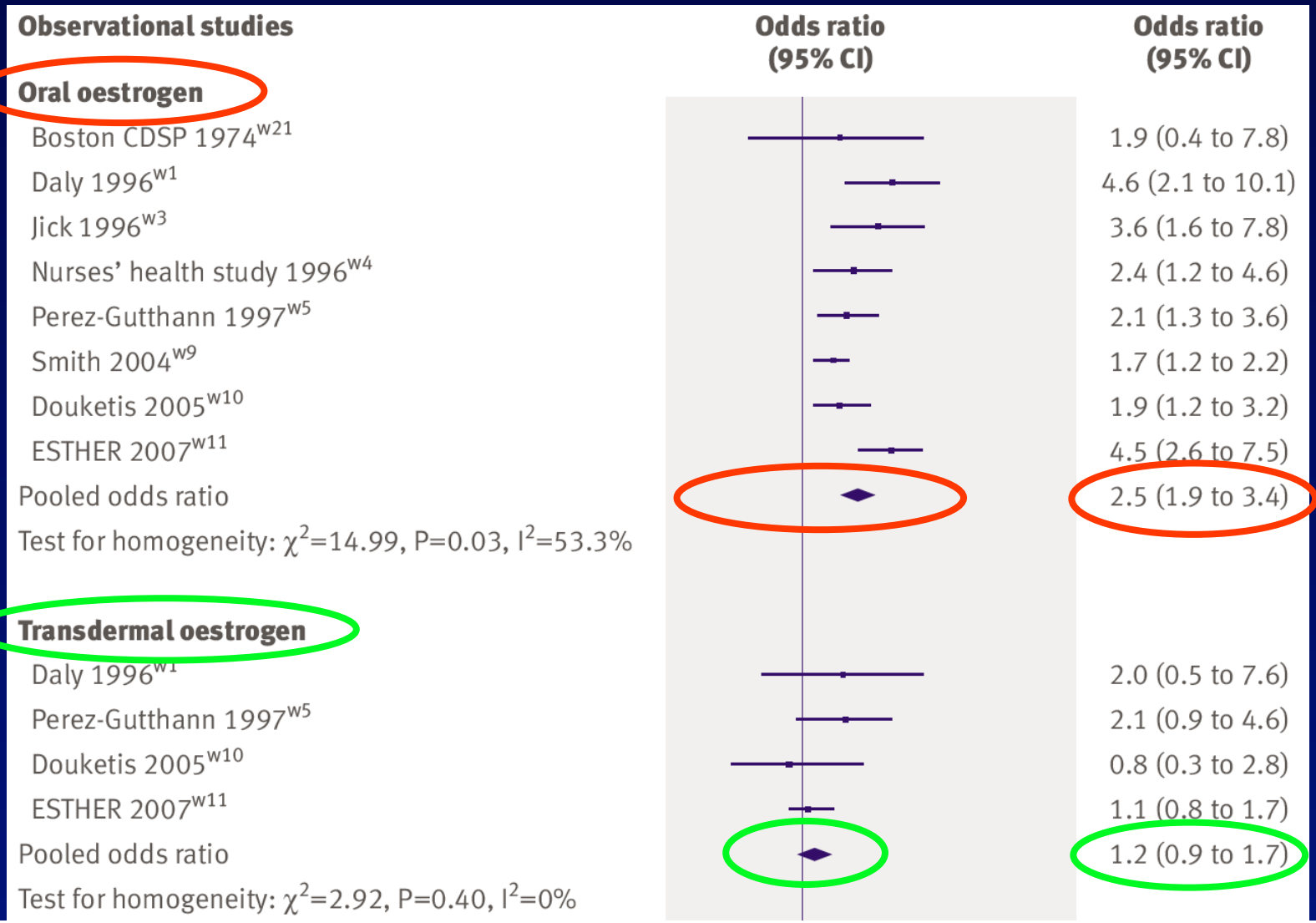


Délai "=" 6 années post-menopause chez la femme

Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis

BMJ 2008;336;1227-1231

Marianne Canonico, postdoctoral research fellow,[1,2] Geneviève Plu-Bureau, gynaecologist,[1,3]
Gordon D O Lowe, professor of vascular medicine,[4] Pierre-Yves Scarabin, director of research (Inserm)[1,2]



CCL 1: Effets des oestrogènes par voie orale (E2 ou EE) :
Nurses + WHI précocément (52-60 ans)

K du Sein (seulement si MPA!)

Syndrome climatérique

OS

peau

Tendance à la prévention du risque coronaire

+ Risque Thrombo-Embolique

Prévention du diabète de type 2

CCL 2 : Effets des oestrogènes par voie percutanée : précocément (52-60 ans)

K du Sein (seulement si MPA!)

Syndrome climatérique

OS

peau

Tendance à la prévention du risque coronaire

(Pas de Risque Thrombo-Embolique)

Prévention du diabète de type 2

Effets des oestrogènes par voie orale + MPA
débuté tardivement (avec délai) et par prudence > 60 ans

K du Sein si associé à MPA
(mais pas E2 seul)

Syndrome climatérique

Estrogènes

Voie orale

OS

peau

Risque coronaire accru si associé à MPA (mais pas E2 seul)

Risque Thrombo-Embolique accru

Prévention du diabète de type 2

C- Et chez l'Homme : à propos d'un cas Unique !

Smith et al. *NEJM* 1994, 331:1056-1061

Un homme 28 ans, puberté normale

mais poursuite de la croissance à l'age adulte

(soudure incomplète épiphyses)

Diagnostic : Gene « Knock Out » du Gène ERα

1) **Intolérance au glucose, hyperinsulinémie.**

Smith et al. *NEJM* 1994, 331:1056-1061

2) **Dysfonction endothéliale**

Sudhir K et al. *Lancet* 1997, 349: 1146–1147.

3) **Maladie coronaire prématurée**

Sudhir K et al. *Circulation* 1997, 96: 3774–3777.

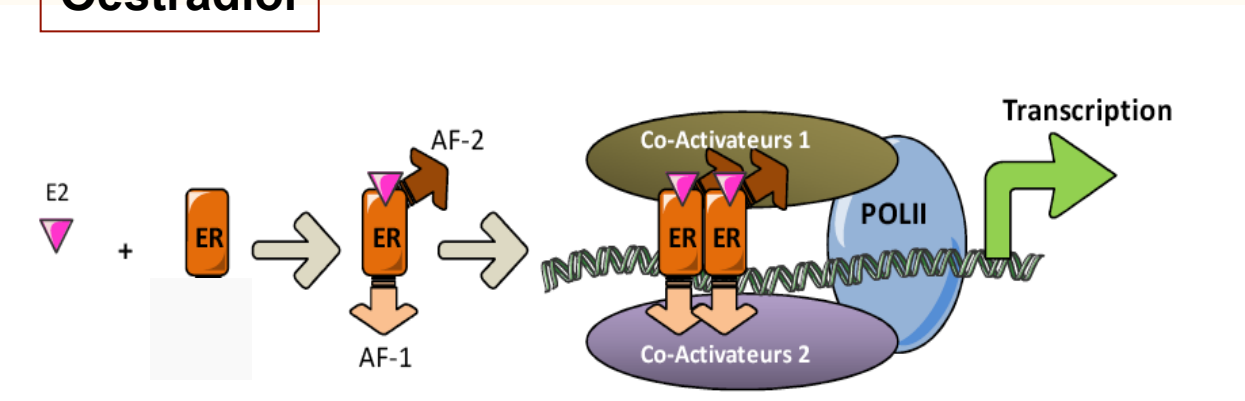
Role crucial de ERα dans l'homéostasie vasculaire et MB

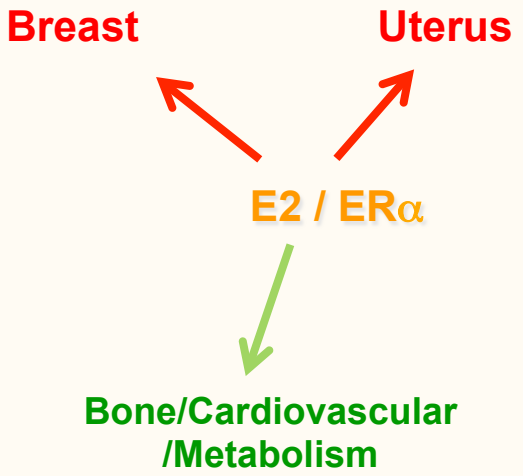
3 - Futurs traitements :

SERMs actuels et…

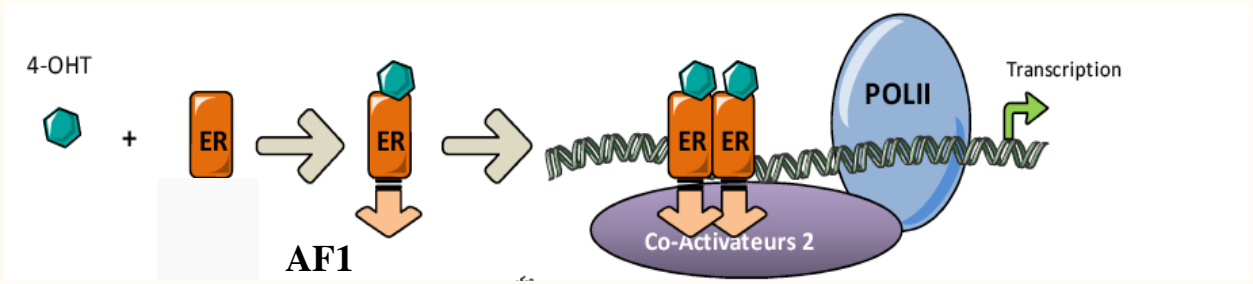
nouveaux SERMs ?

Oestradiol

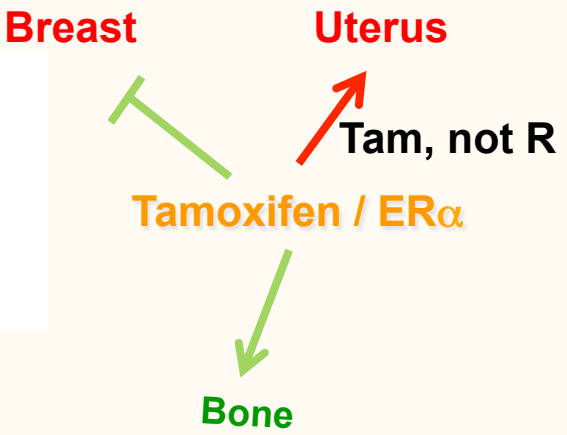




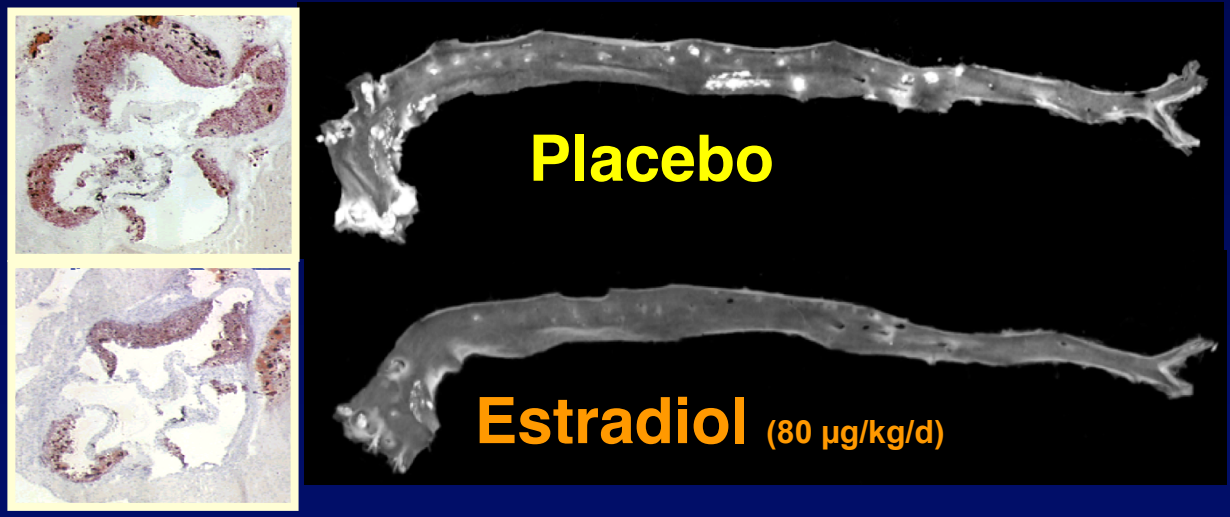
Tamoxifene | Raloxifene



AF1

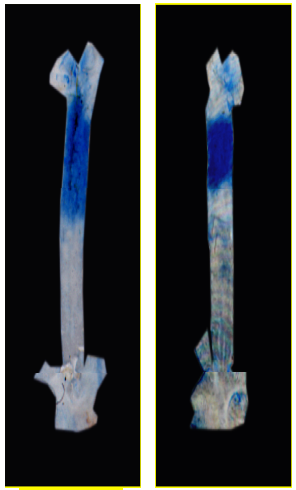


Mouse models : allow gene targeting, and thereby to study cellular and molecular mechanisms in vivo



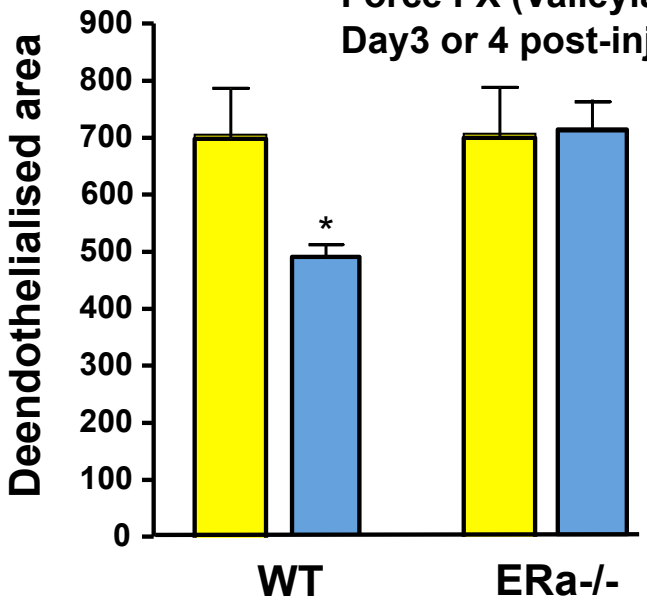
E2 prevents early atheroma in hypercholesterolemic (ApoE $^{-/-}$ or LDLr $^{-/-}$) ovariectomized mice…

Modelization of artery injury / healing in mouse



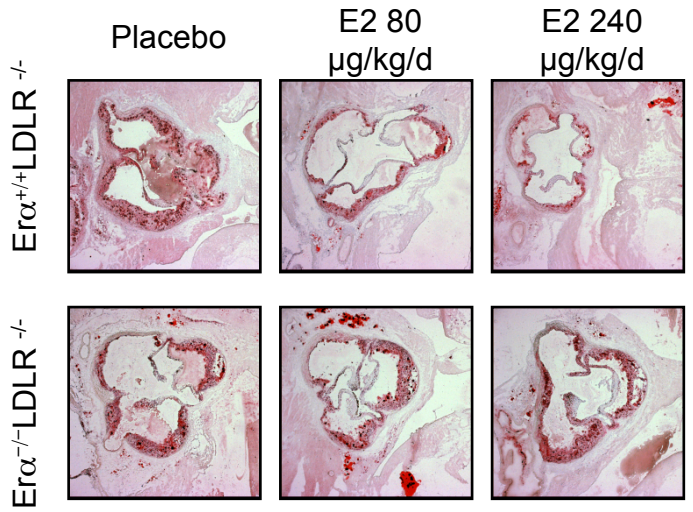
Plc E2

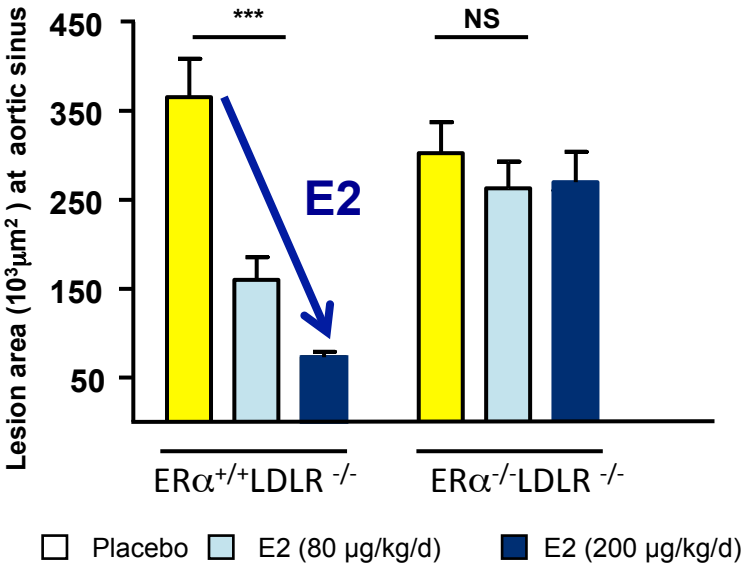
Forceps with large tips
Bipolar microregulator
Force FX (Valleylab)
Day3 or 4 post-injury



Carmeliet et al. AM J Pathol 1997
Brouchet et al. Circulation 2001

Modelization of atheroma in mouse

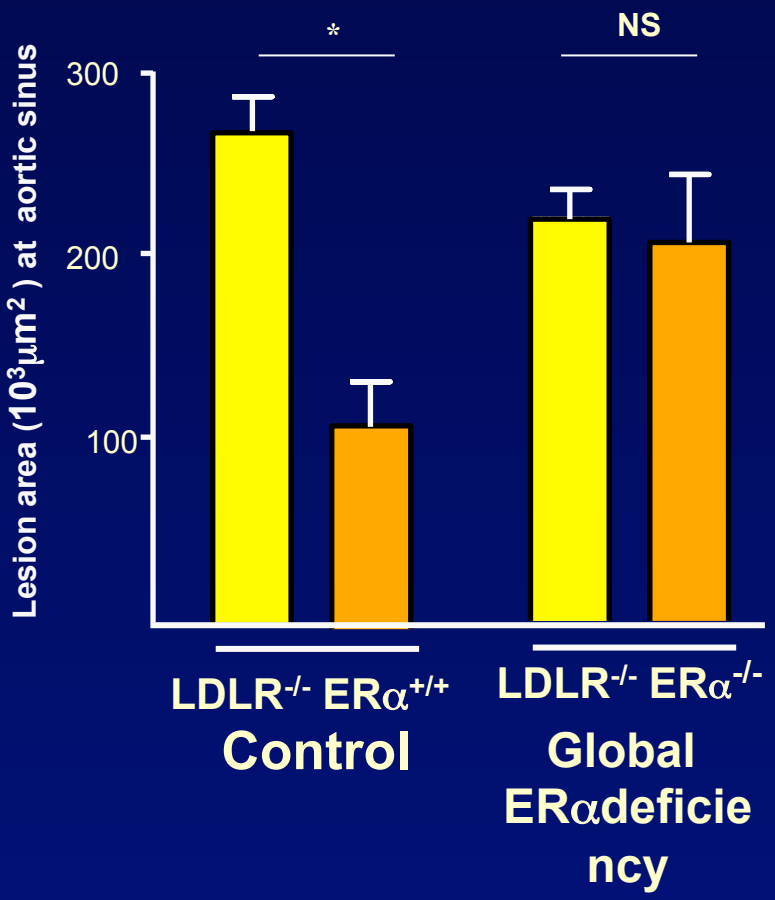




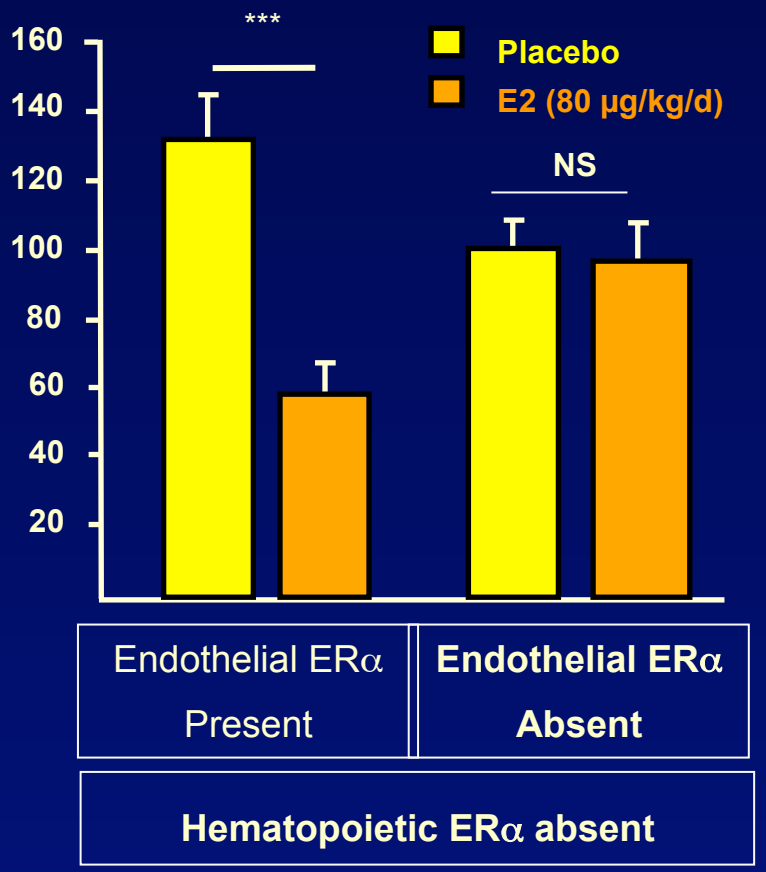
Billon et al. Circulation 2009

Estradiol (E2) prevents of early atheroma :

ERα is absolutely required (abrogation in ERα$^{-/-}$ mice)



Crucial role of endothelial ERα is absolutely required (abrogation in Tie2-Cre^{+} ERα$^{flox/flox}$)

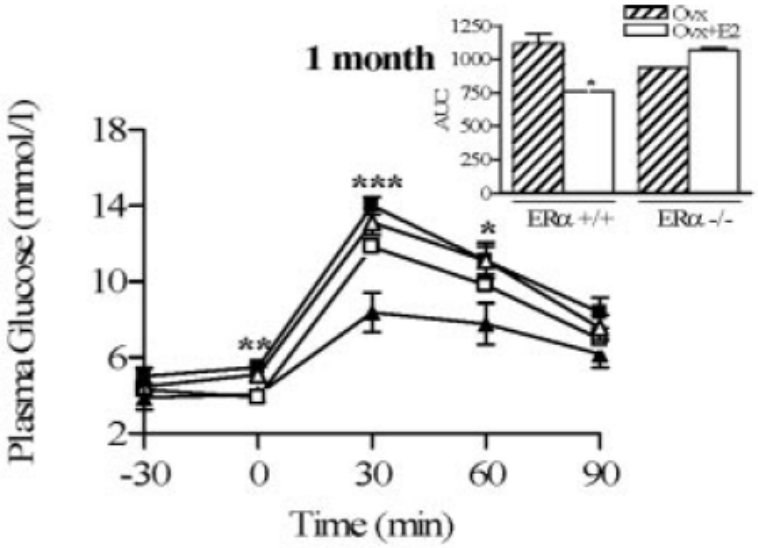


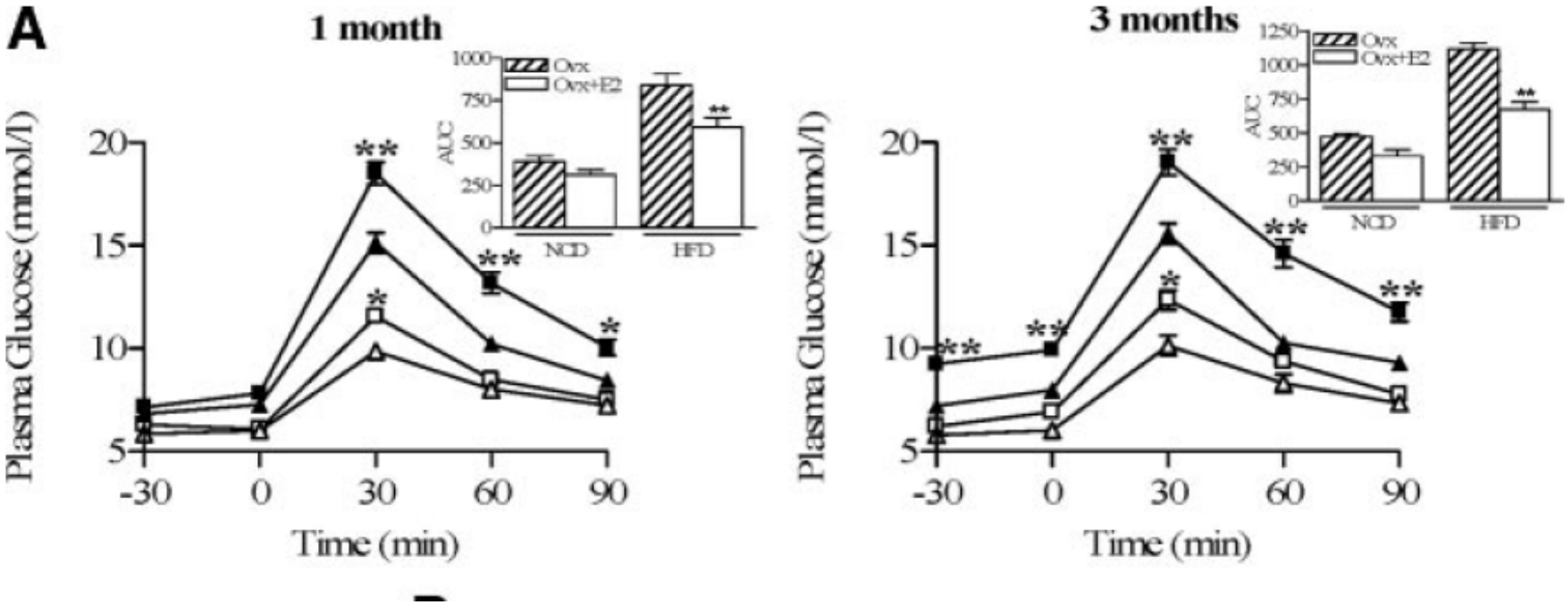
Billon-Gales, Fontaine et al. Circulation 2009

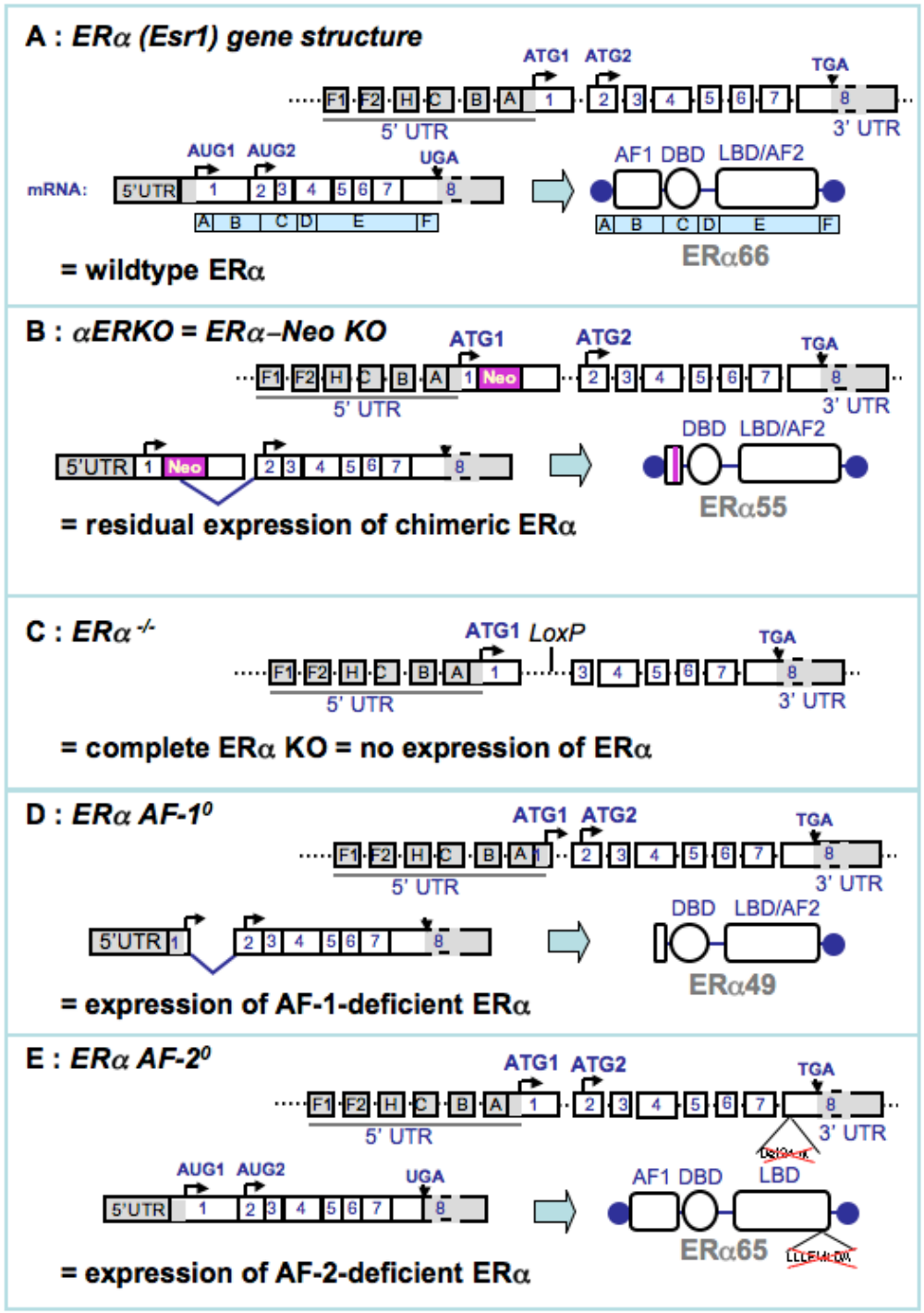
Estrogens Protect against High-Fat Diet-Induced Insulin Resistance and Glucose Intolerance in Mice

Elodie Riant, Aurélie Waget, Haude Cogo, Jean-François Arnal, Rémy Burcelin, and Pierre Gourdy

(*Endocrinology* 150: 2109–2117, 2009)







Transgenic mouse

(Team 9, INSERM U1048, Toulouse; Collab. P. Chambon, Mouse Clinic, Strasbourg)

Korach et al. PNAS 1993

1st KO but …

partial ERa KO

Pendaries et al. PNAS 2002

Dupont et al. Development 2000
Circulation 2001

1st Complete ERa KO

Billon et al. PNAS 2009

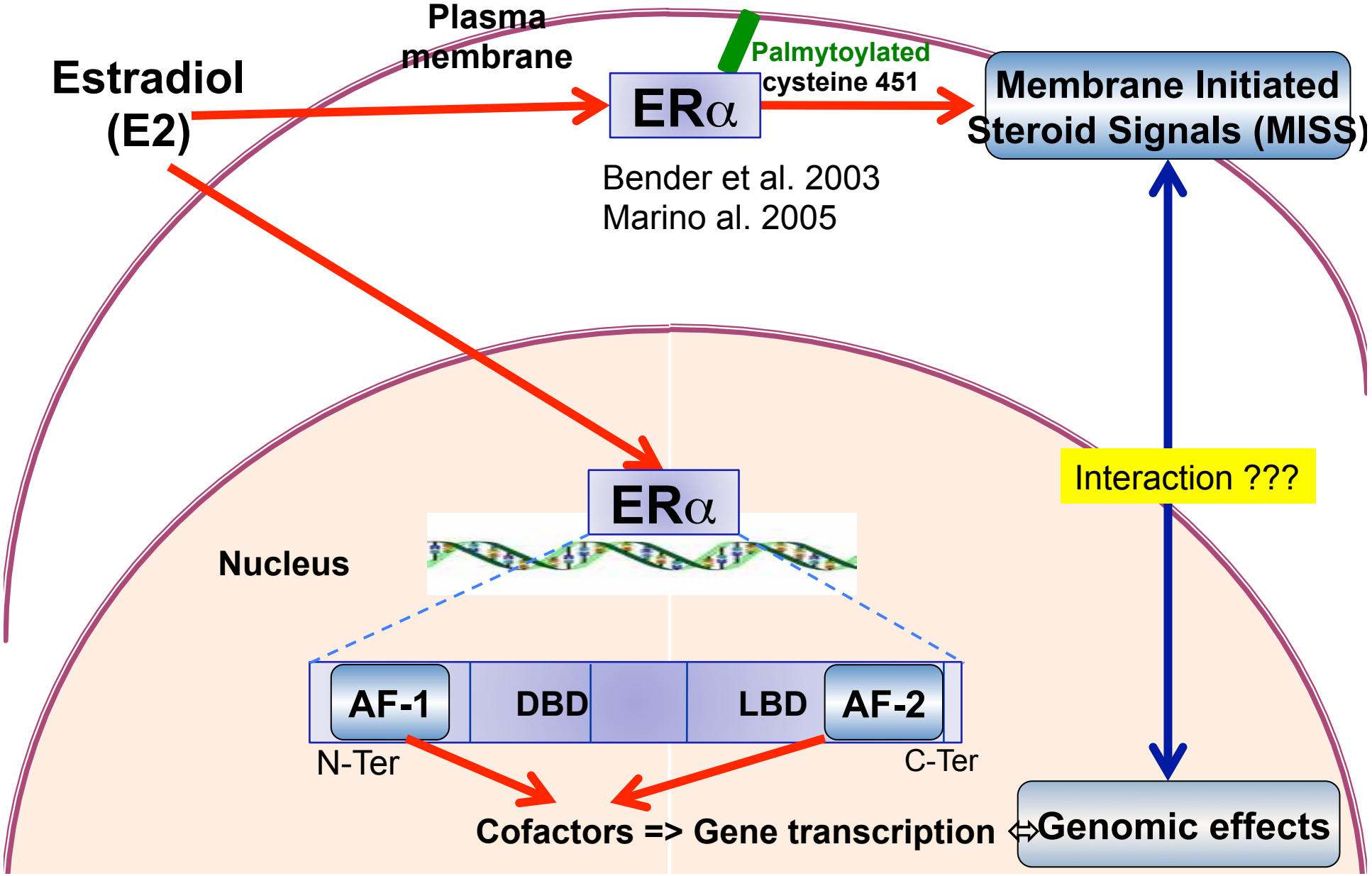
Billon et al. PNAS 2011

Role of ERa and of AFs	ERa necessary	AF1 necessary	AF2 necessary
BENEFICIAL :	YES	NO	
Atheroma	YES	NO	YES
Endothelial healing	YES	NO	NO
Diabetes T2	YES	NO	YES
Osteoporosis	YES	NO	YES
DELETERIOUS	YES	YES	YES
Hepatic Gene Expres. (// human VTE risk?)	YES	YES	YES
Endometrial prolif.	YES	YES	YES
Breast prolif.	YES	YES	YES

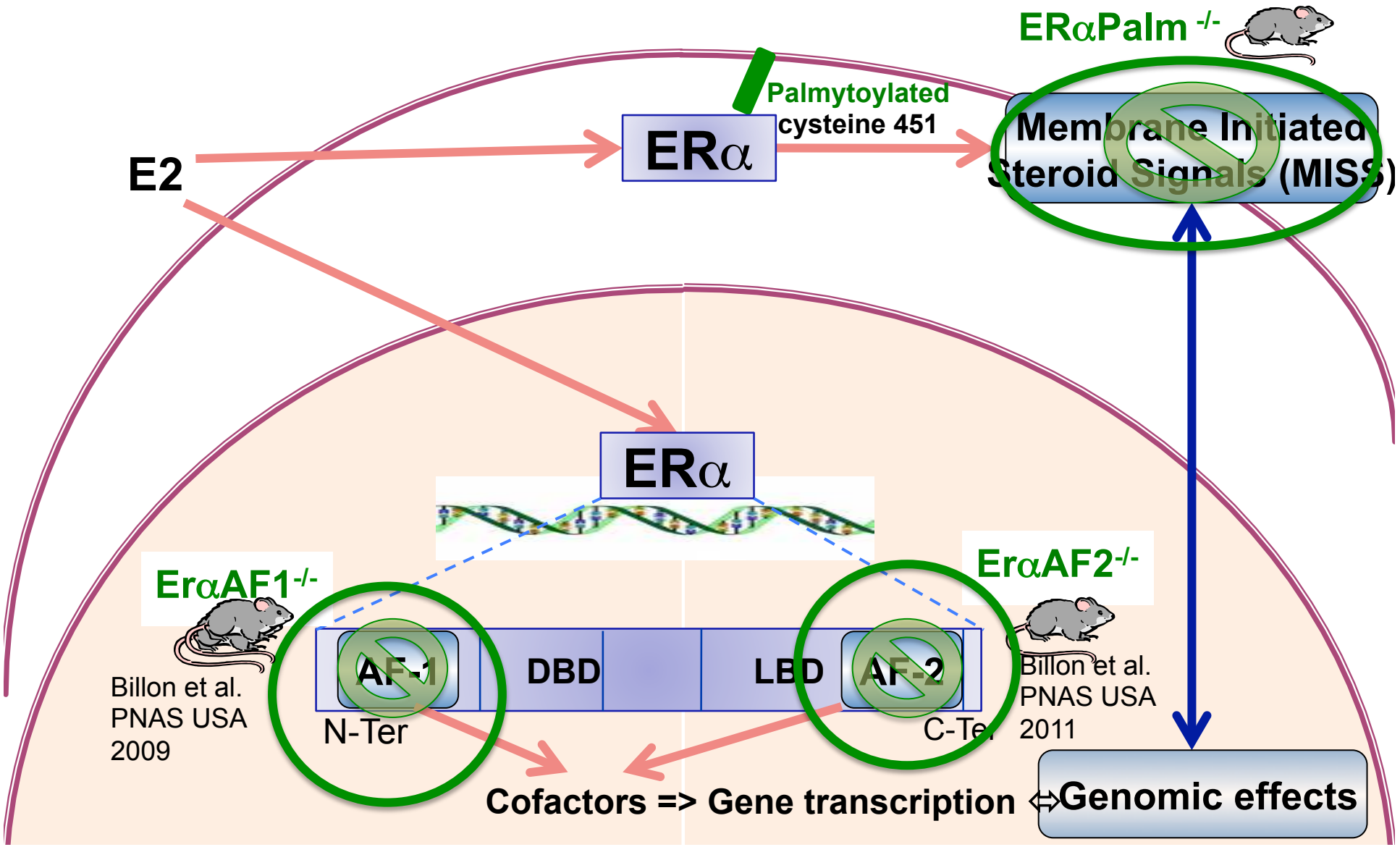
Summarized in "From in vivo gene targeting of Estrogen Receptors to Optimisation of their Modulation in Menopause" Br J Pharmacol 2012

British Journal of Pharmacology (2012) **165** 57–66

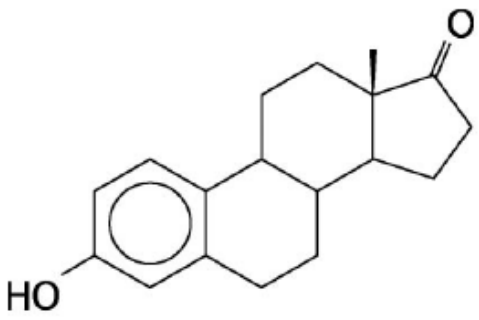
Estradiol (E2) also activates «membrane» ERα : Membrane Initiated Steroid Signals (MISS)



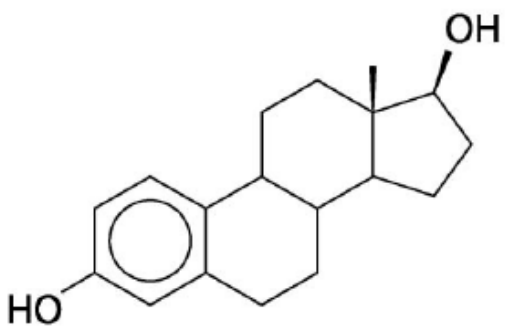
Phenotyping ERα Palm-/- (cys451=>ala) : 1st KO of MISS



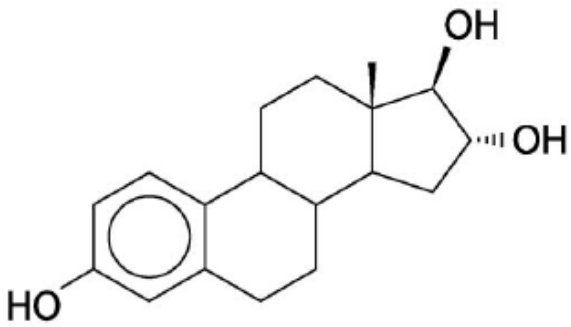
Estetrol (E4) : a « novel, liver friendly » estrogen/ SERM => *potentially* no increase in VTE



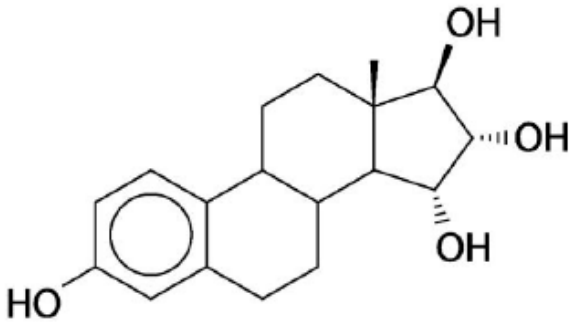
E_1 Estrone



E_2 Estradiol



E_3 Estriol



E_4 Estetrol

Merci de votre attention !