TRH: MENOPAUSIA, CÁNCER Y RIESGO CARDIOVASCULAR. IMPLICACIONES PARA LA INVESTIGACIÓN Y METODOLOGÍAS PARA LA PRÁCTICA CLÍNICA.

Aplicando la evidencia

PRIMER CONGRESO COSTARRICENSE DE BIOÉTICA
SÉPTIMA REUNIÓN ANUAL DE LA RED COCHRANE IBEROAMERICANA
QUINTA REUNIÓN ANUAL DE LA RED IBEROAMERICANA DE GUÍAS DE PRÁCTICA CLÍNICA (GPC)
SEGUNDA REUNIÓN ANUAL DE LA RED COCHRANE CENTROAMERICANA
EVIDENCIA / BIOÉTICA
IHCAI Foundation
Centro América Red Cochrane iberoamericana
Colaboración Cochrane
2008

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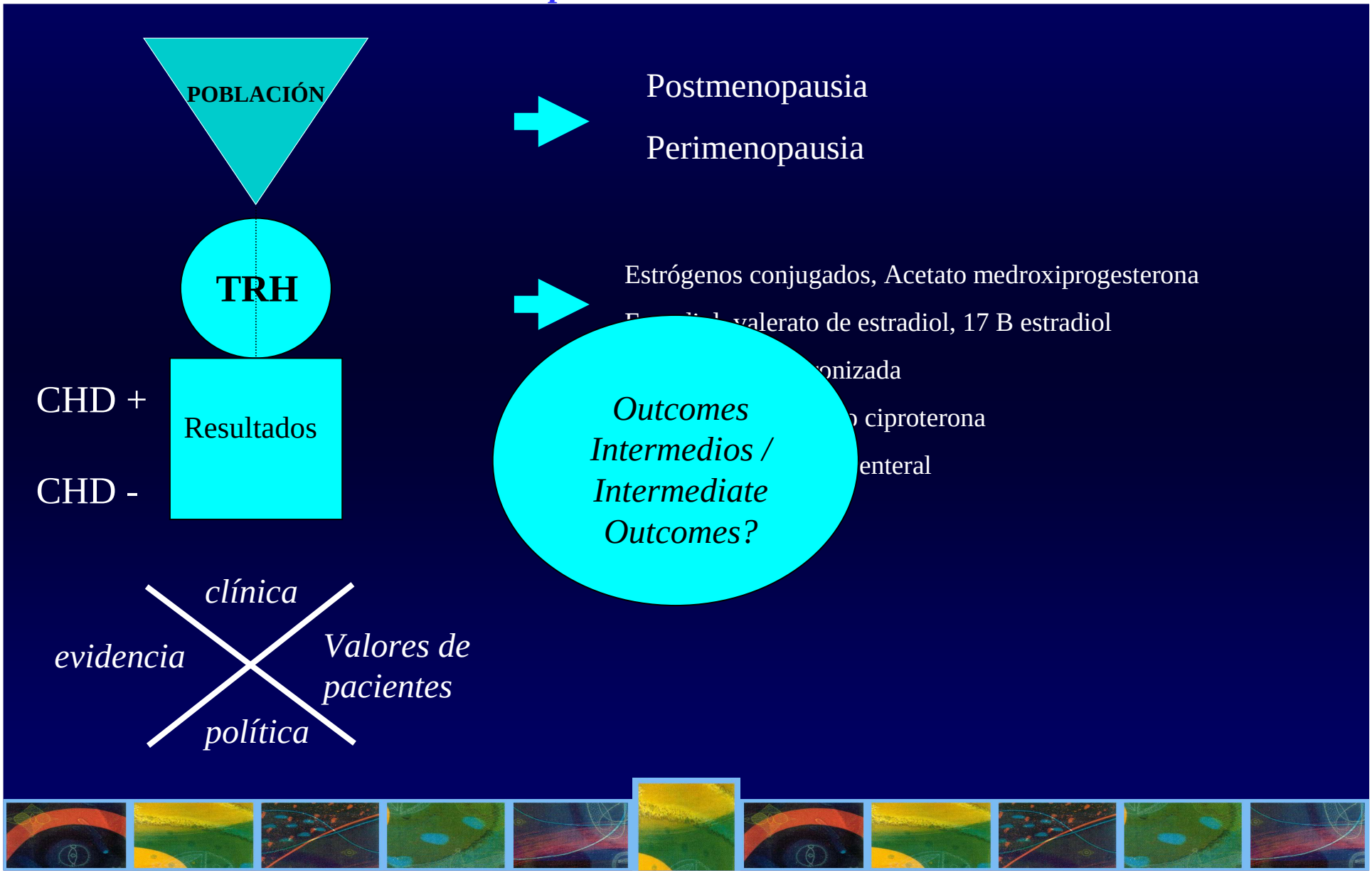

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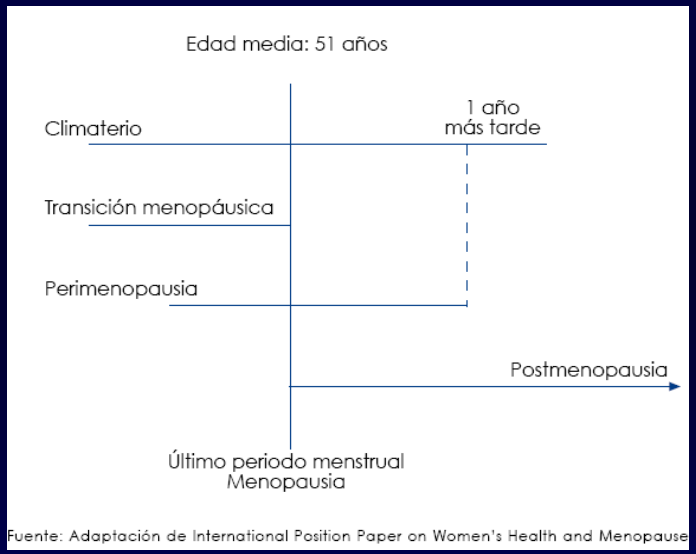
POBLACIÓN



Fuente: Adaptación de International Position Paper on Women's Health and Menopause

Ongoing discussion concerns the "timing hypothesis" or "therapeutic window of opportunity."

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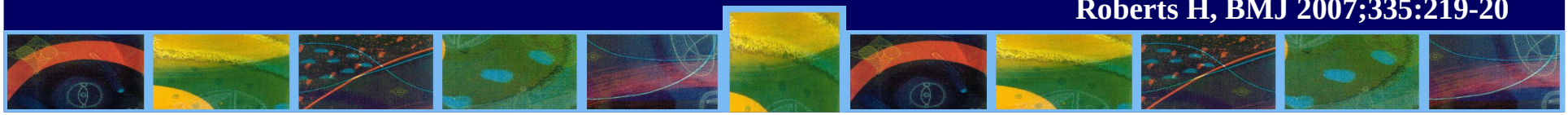
Therapeutic window of opportunity

Estrogen deficiency is a key modulator of atherosclerosis progression

CHD risk rises sharply after premature ovarian failure , or surgical or natural menopause

Roberts H, BMJ 2007;335:219-20



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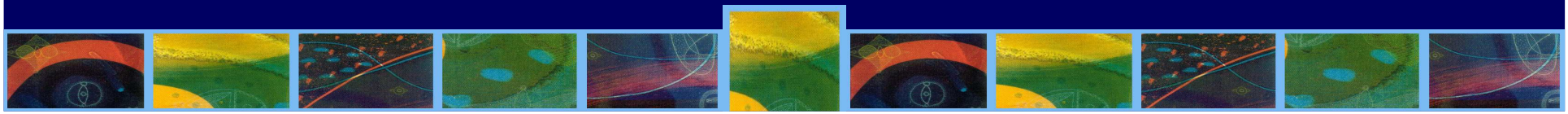
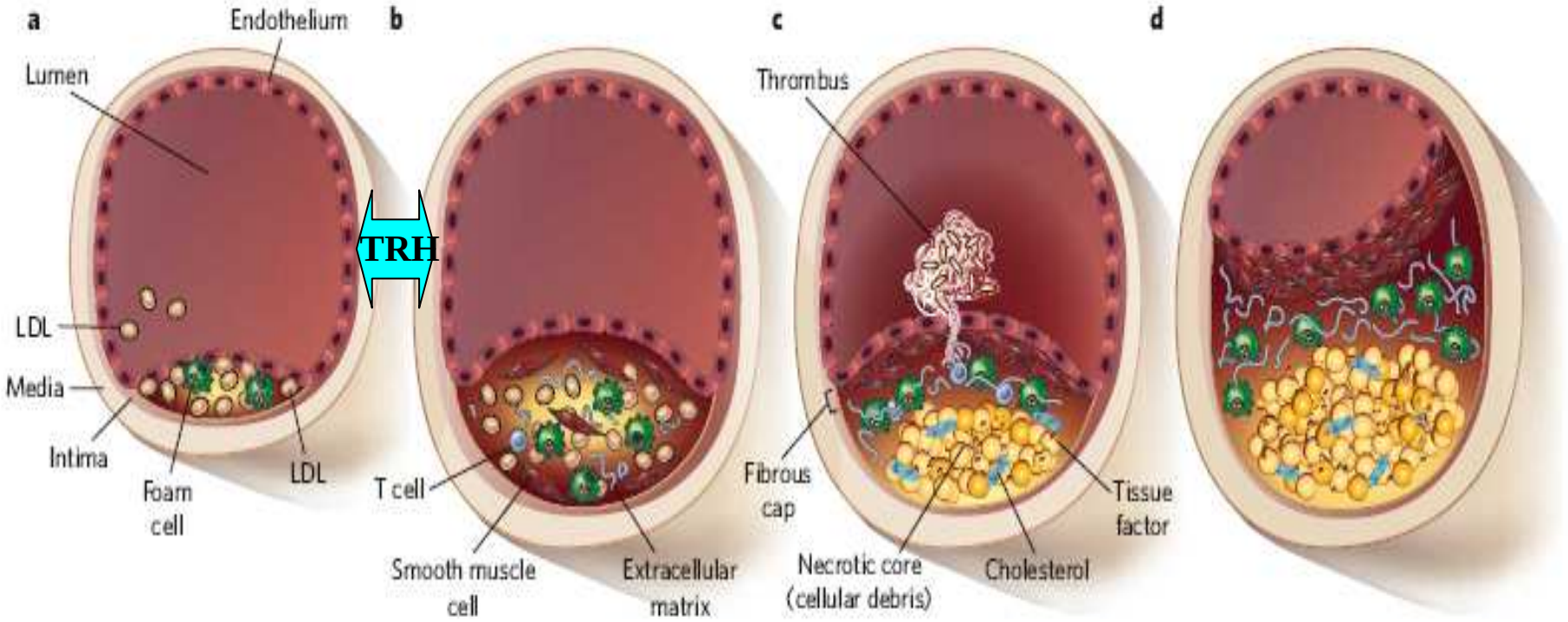
Therapeutic window of opportunity

The proposal under debate, which comes from early primate studies, is that oestrogen may be cardioprotective if treatment is started before vasculature has been compromised.

Roberts H, BMJ 2007;335:219-20



Initiation and progression of atherosclerosis



Estrogen therapy initiated in women at 50 to 59 years of age is related to a reduced plaque burden in the coronary arteries and a reduced prevalence of subclinical coronary artery disease.

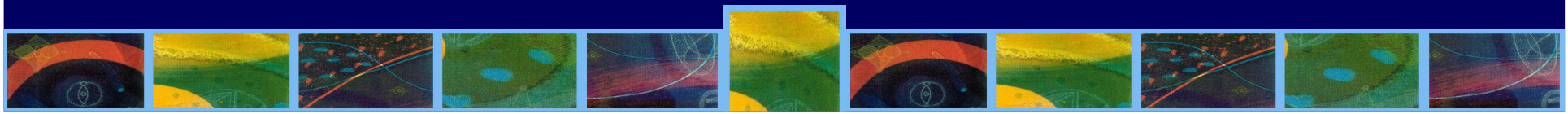
Manson JE, N Engl J Med 2007;356:2591-602

Data from studies of nonhuman primates suggest that estrogen inhibits the progression of atherosclerosis during the early period after bilateral oophorectomy and menopause.

Mikkola TS, 2002.

- Conclusions
- Among women 50 to 59 years old at enrollment, the calcified-plaque burden in the coronary arteries after trial completion was lower in women assigned to estrogen than in those assigned to placebo.
- Hormone therapy does not prevent atherosclerosis progression in high-risk women.
- Estrogen has complex biologic effects and may influence the risk of cardiovascular events and other outcomes through multiple pathways.

Manson JE, N Engl J Med 2007;356:2591-602



- **Context:** The timing of initiation of hormone therapy may influence its effect on cardiovascular disease.

ORIGINAL CONTRIBUTION

Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause

Jacques E. Rossouw, MD
Ross L. Prentice, PhD
JoAnn E. Manson, MD, DrPH
LieLing Wu, MSc
David Barad, MD
Vanessa M. Barnabei, MD, PhD
Marcia Ko, MD
Andrea Z. LaCroix, PhD
Karen L. Margolis, MD
Marcia L. Stefanick, PhD

Context The timing of initiation of hormone therapy may influence its effect on cardiovascular disease.

Objective To explore whether the effects of hormone therapy on risk of cardiovascular disease vary by age or years since menopause began.

Design, Setting, and Participants Secondary analysis of the Women's Health Initiative (WHI) randomized controlled trials of hormone therapy in which 10 739 postmenopausal women who had undergone a hysterectomy were randomized to conjugated equine estrogens (CEE) or placebo and 16 608 postmenopausal women who had not had a hysterectomy were randomized to CEE plus medroxyprogesterone acetate (CEE + MPA) or placebo. Women aged 50 to 79 years were recruited to the study from 40 US clinical centers between September 1993 and October 1998.

Main Outcome Measures Statistical test for trend of the effect of hormone therapy on coronary heart disease (CHD) and stroke across categories of age and years since menopause in the combined trials.

JAMA. 2007;297:1465-77.

WHI Summary

Effects per 10000 Women/y of ET use (ages 50-59)

- 10 fewer deaths
- 10 fewer CHD events
- 2 fewer stroke

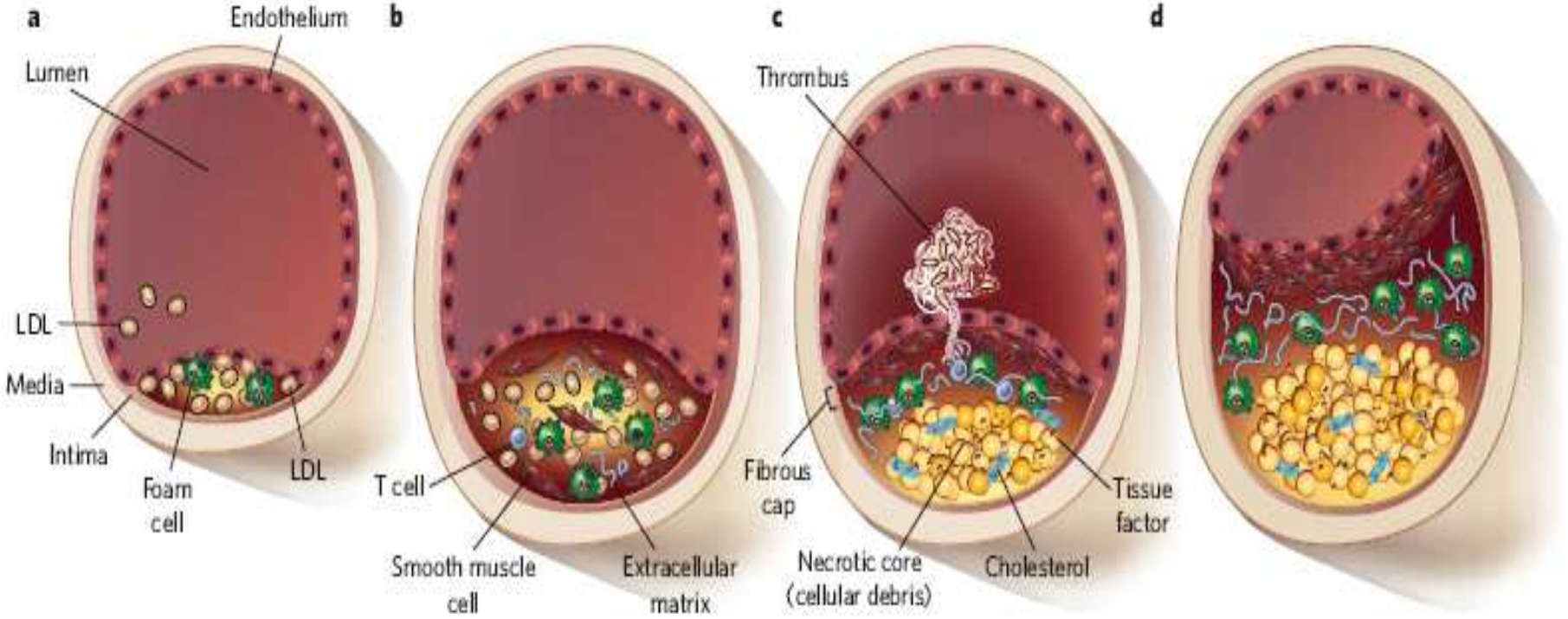
Effects per 10000 Women/y of EPT use (< 10 years postmen)

- 6 fewer deaths
- 4 fewer CHD events
- 5 more strokes

Subgroup analyses with small numbers and inadequate power.

Rossouw J. JAMA. 2007;297:1465-77.

Initiation and progression of atherosclerosis

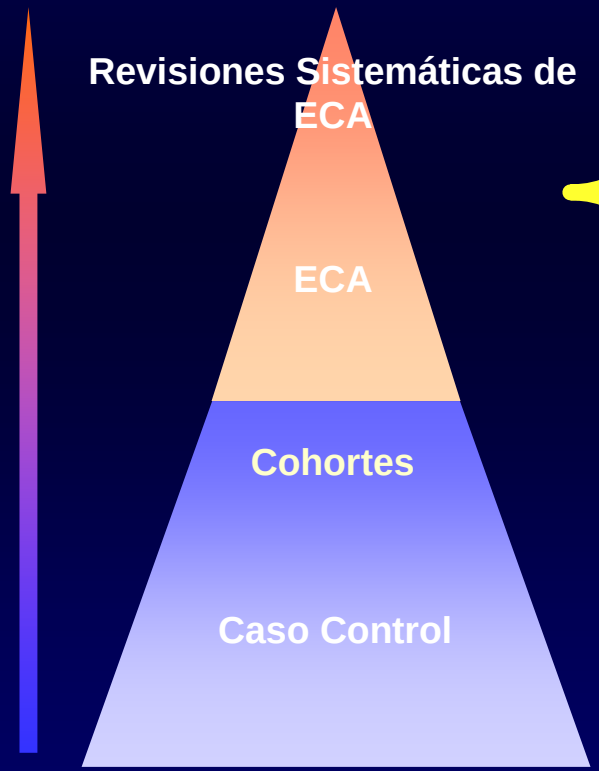


¿ If early hormone use is cardioprotective, will this benefit continue?

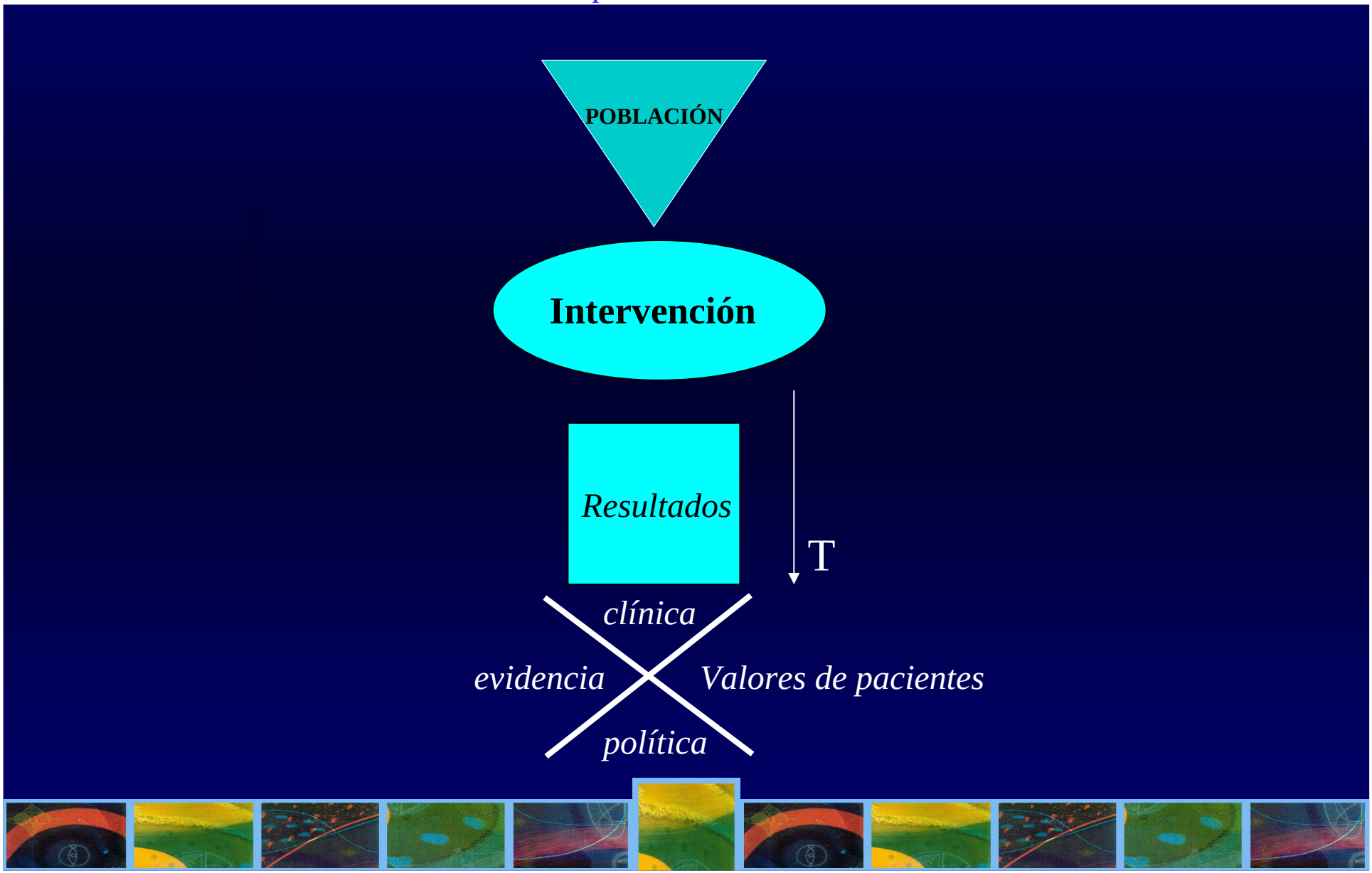
- Aún existe una pregunta importante:
- Age-related progression of atherosclerosis is likely to continue even in the face of hormone therapy.
- ¿la mejoría en estos biomarcadores se traduce en una disminución de la mortalidad cardiovascular?
- Even if ongoing imaging trials confirm a slowing of early atherosclerosis, it would be unwise to extrapolate such findings to clinical benefit with continued use into old age.”

Rossouw J. JAMA. 2007;297:1465-77.

Jerarquía de la evidencia



None of these had the power to look at outcomes amongst younger women, who are the main users of hormones for symptom relief.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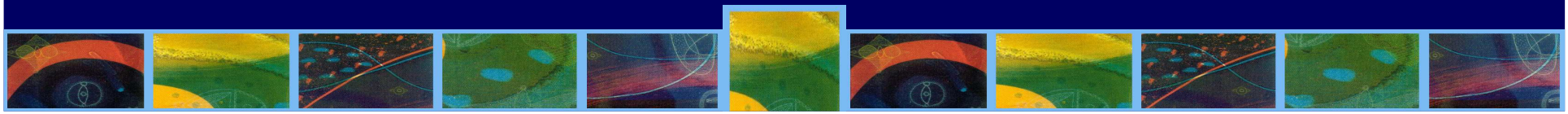
Intervención
Resultados
T
clínica
evidencia
Valores de pacientes
política

- Estradiol, un estrógeno derivado de la orina equina (caballo). Las dosis usadas fueron 1 mg (EPAT 2001; Haines 2003; WEST 2001) y 2 mg (Haines2003).

- Estrógeno equino conjugado (CEE, por sus siglas en inglés), una mezcla de estradiol con otros nueve estrógenos equinos. Las dosis usadas fueron de 0,625 mg.diarios (ERA 2000; Mulnard 2000; PEPI 1995; WAVE 2002; WHI 1998*(brazo de TH con estrógeno solo)* y 1,25 mg diarios (Mulnard 2000).



Study WHI 2002

- Mean age: 63 years (SD 7)

Intervention:

Combined HT arm: Conjugated equine oestrogen 0.625 mg and medroxyprogesterone acetate 2.5 mg.

Study HERS 1998

- Mean age: 67 years (SD 7)

Intervention:

Combined HT arm: Conjugated equine oestrogen 0.625 mg and medroxyprogesterone acetate 2.5 mg.

Todos los resultados estadísticamente significativos de esta revisión provinieron de los dos ensayos más amplios, HERS 1998 y WHI 2002;

los ensayos más pequeños que utilizaban otros tipos de TH informaron muy pocos o ningún evento clínico serio.

Farquhar CM, Marjoribanks J, Lethaby A, Lamberts Q, Suckling JA and the Cochrane HT Study Group. Tratamiento hormonal a largo plazo para mujeres perimenopáusicas y postmenopáusicas (Revisión Cochrane traducida). En: *La Biblioteca Cochrane Plus*, 2006 Número 1.

Low dose:

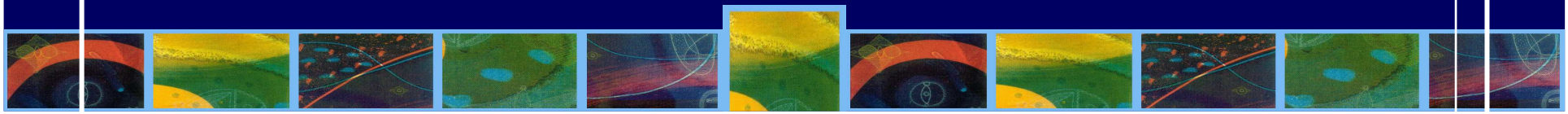
- 1 mg micronized oral 17-B estradiol.
- 0.45 mg CEE

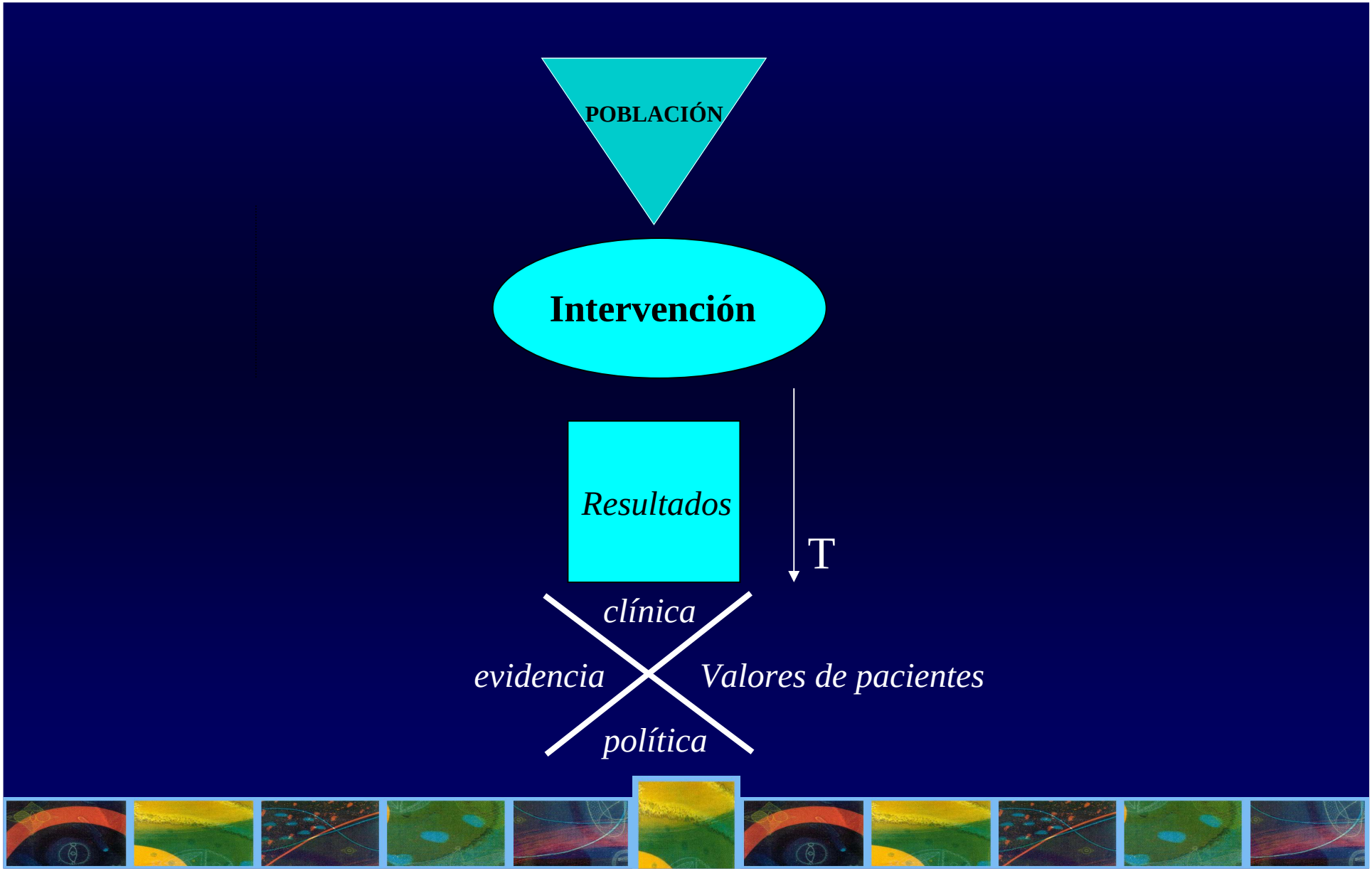
Ultra low dose:

- 0.5 mg micronized oral 17-B estradiol.
- 0.3 mg CEE.

Both were effective in reducing menopausal symptoms and effective proteccion againts postmenopausal decrease of BMD

Gambacciani M, Maturitas. 2007 Dec 1; 18063490

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Intervención
Resultados
T
clínica
evidencia
Valores de pacientes
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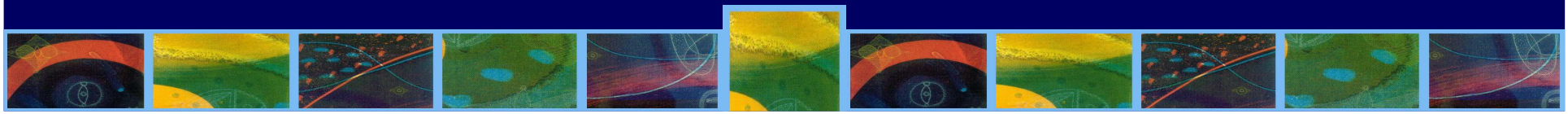
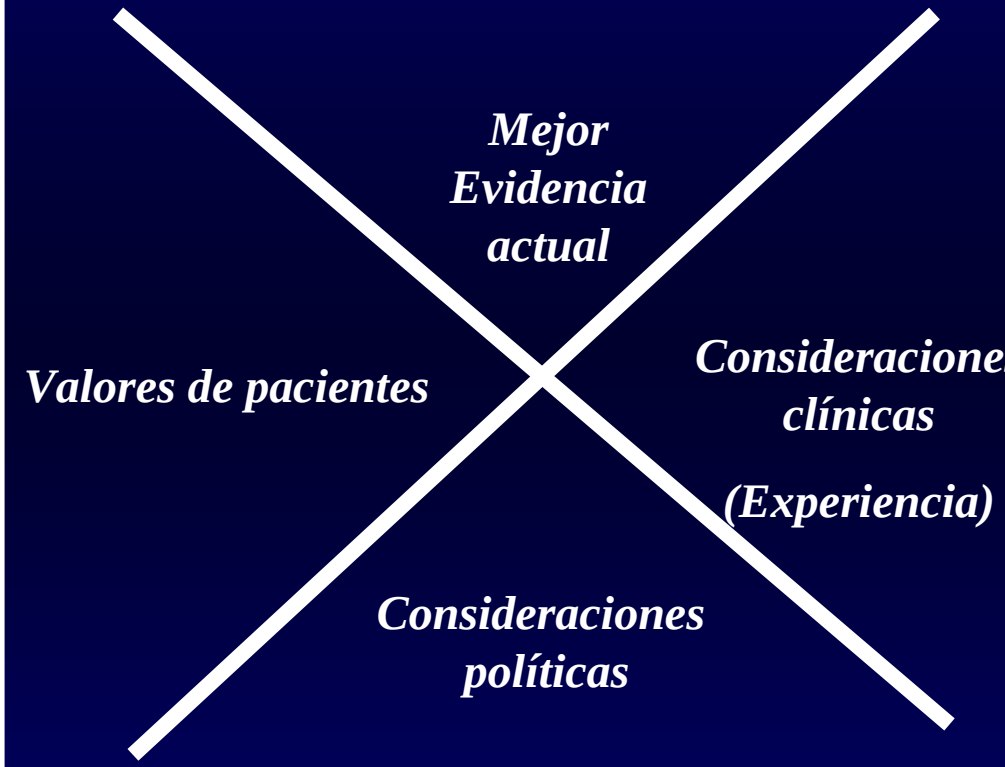
- Acetato de medroxiprogesterona (MPA): un progestágeno sintético estructuralmente relacionado con la progesterona.
- Noretisterona (noretindrona): un progestágeno sintético estructuralmente relacionado con la testosterona.
- Progesterona micronizada**:** un progestágeno natural sintetizado a partir de plantas y finamente molido para mejorar su absorción.
- Drospirenona (DRPS): una progestina sintética análogo a la espironolactona. Efecto antimineralocorticoide.



- European active surveillance study of women taking HRT (EURAS-HRT).
  - Multi-national prospective, controlled cohort study.
  - Results do not indicate a higher CV risk potencial for DRPS/Estradiol.



- Los estrógenos con o sin progestágenos son efectivos y continúan siendo apropiados en el tratamiento de los síntomas vasomotores intensos que afectan la calidad de vida.
- El TH debe administrarse a la mínima dosis eficaz y el mínimo tiempo posible.
- El TH no está indicado para la prevención de la enfermedad cardiovascular.

- **Características clínicas**
- **Biomarcadores y factores de riesgo que afectan a cada mujer.**
- **Los diversos estrógenos y progestágenos.**
- **Los diferentes períodos de uso de TH, las diferentes dosis y vías de administración.**

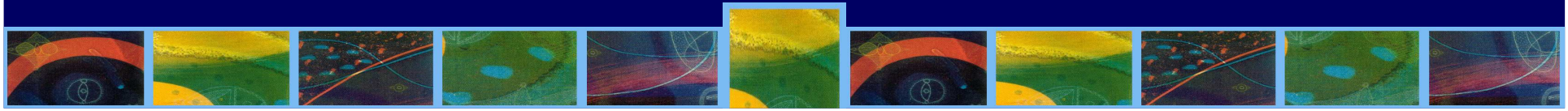
Valores de pacientes

HT Risks vs Other Drug Risks

Therapy	*Event*	*Cases/10,000 persons/year of use*
Statins (7 studies)[1]	Breast cancer	–10 to +77
EPT[2]	Breast cancer	+9
ET[2]	Breast cancer	–7
Aspirin (in men)[3]	Sudden death	+5
Fenofibrate[1]	Total mortality	+13
HT (aged 50-59)[2]	Total mortality	–10
Raloxifene[1]	Fatal stroke	+20
EPT[2]	PE events	+10
ET[2]	PE events	+4

ET = CE; EPT = CE + MPA

1. Hodis. *Menopause*. 2007;14:944.
2. Rossouw. *JAMA*. 2007;297:1465.
3. Physicians' Health Study Writing Group. *N Engl J Med*. 1984;321:129.



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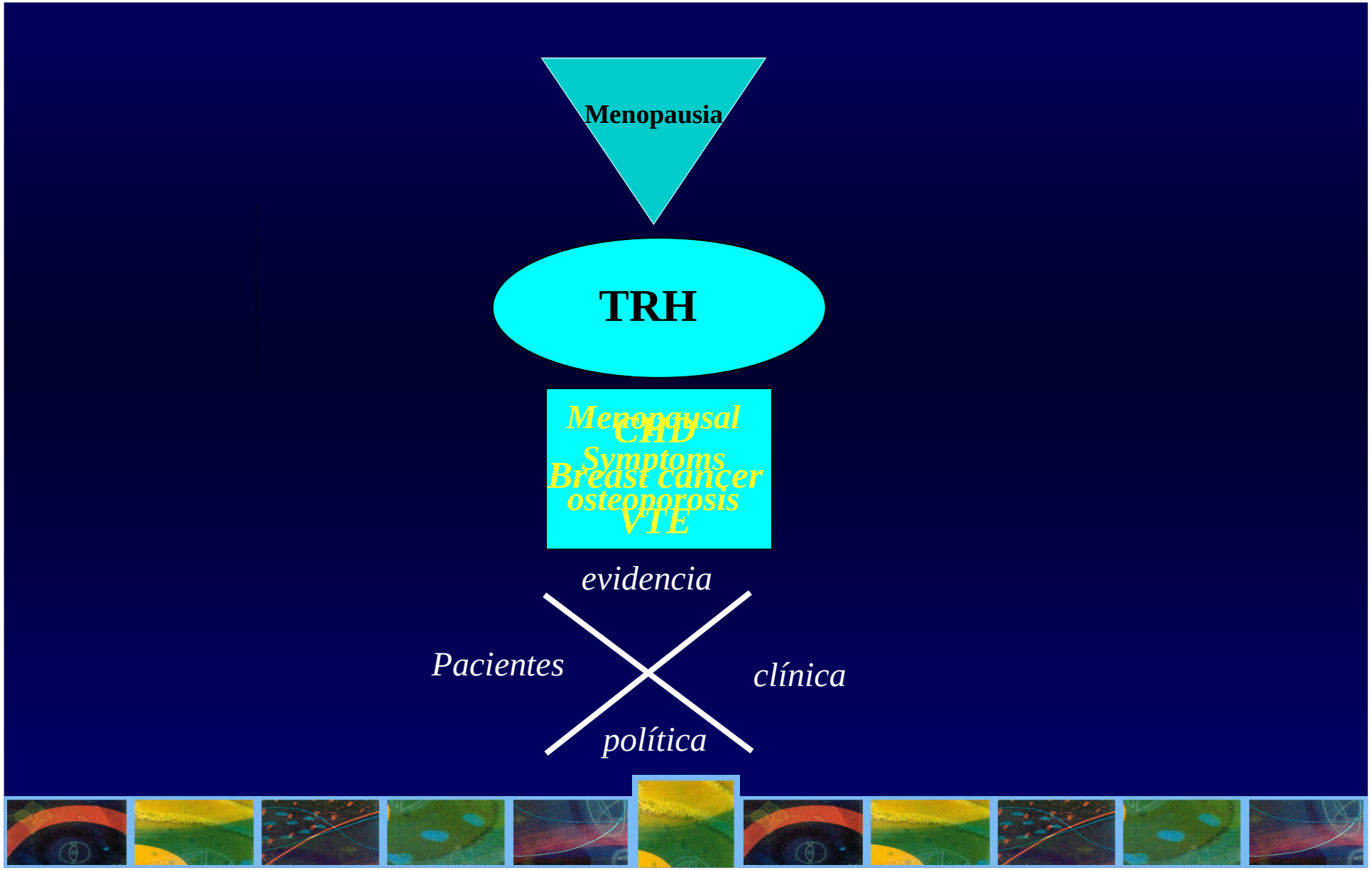

Change continues—Keep an open mind!!