ENFERMEDAD TROMBOEMBÓLICA VENOSA Y EL TRATAMIENTO HORMONAL SUSTITUTIVO

VI Forum multidisciplinar de la ETV

Granada 2010

TRATAMIENTO HORMONAL SUSTITUTIVO

- Estrógenos “naturales” + progestágenos:
  - Estrógenos: E. equinos conjugados, estradiol.
  - Progestágenos: medroxiprogesterona, levonorgestrel, noretisterona, didrogesterona, progesterona natural micronizada.
- Estrógenos solos en histerectomizadas.

VIAS DE ADMINISTRACIÓN:

- Vía oral.
- Vía transdérmica.

TRATAMIENTO HORMONAL SUSTITUTIVO EN EL SIGLO XX

- El tratamiento hormonal sustitutivo (THS) se usó frecuentemente en las mujeres menopáusicas en las últimas décadas del siglo pasado.
- Beneficios del THS:
  - Desaparición de los síntomas vasomotores y de la atrofia vaginal.
  - Prevención y el tratamiento de la osteoporosis.
  - Protección frente a las enfermedades cardiovasculares (estudios observacionales).

The New England
Journal of Medicine

VOLUME 335 AUGUST 15, 1996 NUMBER 7

POSTMENOPAUSAL ESTROGEN AND PROGESTIN USE AND THE RISK OF CARDIOVASCULAR DISEASE

FRANCINE GRODSTEIN, SC.D., MEIR J. STAMPFER, M.D., JOANN E. MANSON, M.D., GRAHAM A. COLDITZ, M.B., B.S., WALTER C. WILLETT, M.D., BERNARD ROSNER, PH.D., FRANK E. SPEIZER, M.D., AND CHARLES H. HENNEKENS, M.D.

TABLE 1. AGE-STANDARDIZED DISTRIBUTION OF CHARACTERISTICS OF WOMEN PARTICIPATING IN THE NURSES' HEALTH STUDY IN 1990, ACCORDING TO THE USE OR NONUSE OF POSTMENOPAUSAL HORMONES.

CHARACTERISTIC	HORMONE USE			
	NEVER USED (N=27,034)	USED IN PAST (N=12,503)	CURRENTLY USED	
			Estrogen Alone (N=7776)	*Estrogen with Progestin (N=6224)*
Parental MI before the age of 60 yr (%)*	29.6	26.7	21.8	20.6
Hypertension (%)	32.9	35.9	35.6	27.3
Diabetes mellitus (%)	5.8	5.6	3.8	2.7
High serum cholesterol level (%)	35.6	41.9	43.9	41.6
Moderate smoker (%)†	9.4	8.9	5.5	4.6
Bilateral oophorectomy (%)	4.2	27.6	47.9	8.9
Past use of oral contraceptives (%)	30.6	37.9	42.0	46.4
Multivitamin use (%)	24.6	29.0	41.1	42.2
Vitamin E use (%)	9.5	11.6	17.4	18.1
Aspirin use (%)	33.6	36.7	46.9	48.3
Mean age (yr)	60.1	61.6	58.5	56.7
Mean age at menopause (yr)	50.9	46.3	44.7	49.2
Mean body-mass index	26.3	25.9	25.1	24.3
Mean alcohol consumption (g/day)	4.7	5.5	6.4	6.0
Mean consumption of saturated fat (g/day)	31.2	34.4	41.9	41.4

*MI denotes myocardial infarction.

†Moderate smokers were defined as women who smoked 15 to 24 cigarettes per day.

(Gronstein. N Engl J Med 1996;335:453-61)

TABLE 2. RELATIVE RISK OF CARDIOVASCULAR DISEASE AMONG CURRENT USERS OF CONJUGATED ESTROGEN ALONE OR WITH PROGESTIN AS COMPARED WITH NONUSERS, 1978 TO 1992.*

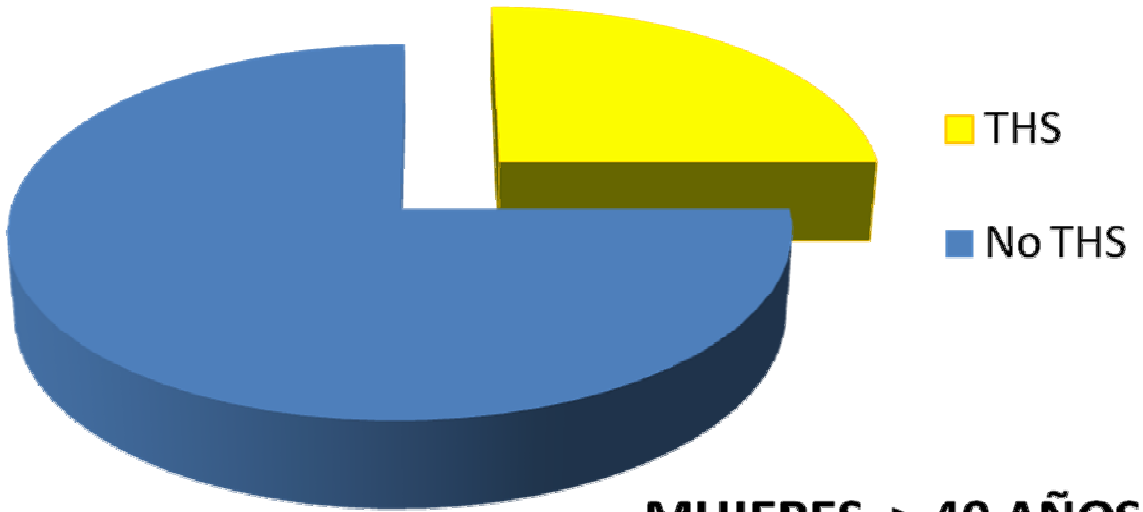
HORMONE USE	PERSON-YEARS	MAJOR CORONARY DISEASE			STROKE (ALL TYPES)		
		NO. OF CASES	RELATIVE RISK (95% CI)		NO. OF CASES	RELATIVE RISK (95% CI)	
			Age Adjusted	*Multivariate Adjusted†*		*Age Adjusted*	*Multivariate Adjusted†*
Never used	304,744	431	1.0		270	1.0	
Currently used							
Estrogen alone	82,626	47	0.45 (0.34–0.60)	0.60 (0.43–0.83)	74	1.13 (0.88–1.46)	1.27 (0.95–1.69)
Estrogen with progestin	27,161	8	0.22 (0.12–0.41)	0.39 (0.19–0.78)	17	0.74 (0.45–1.20)	1.09 (0.66–1.80)

(Gronstein. N Engl J Med 1996;335:453-61)

Prevalence of Estrogen or Estrogen–Progestin Hormone Therapy Use

Kate M. Brett, PhD, and Cynthia A. Reuben, MA

OBSTETRICS & GYNECOLOGY VOL. 102, NO. 6, DECEMBER 2003



MUJERES > 40 AÑOS

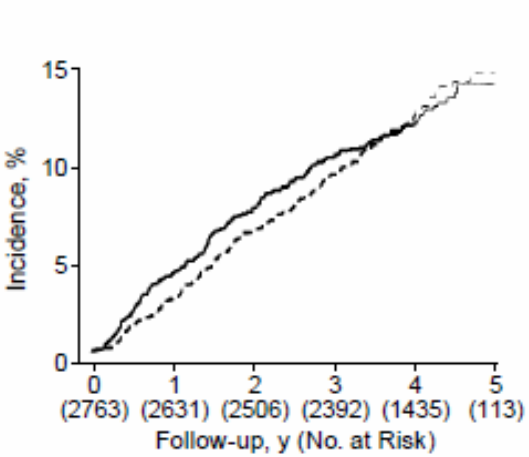
En la década de los 90, un 25% de las mujeres americanas mayores de 40 años usaban el THS, y la gran mayoría (70%) solo con estrógenos.

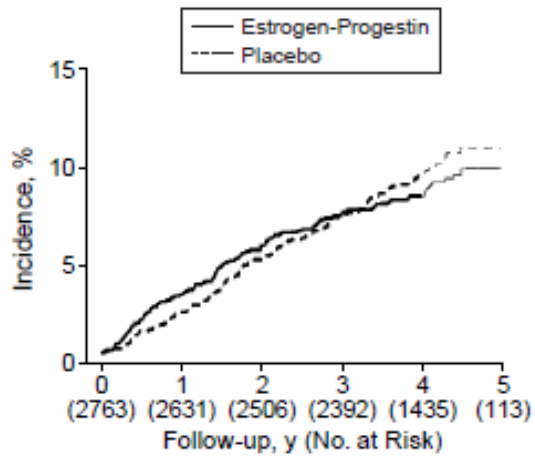
Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women

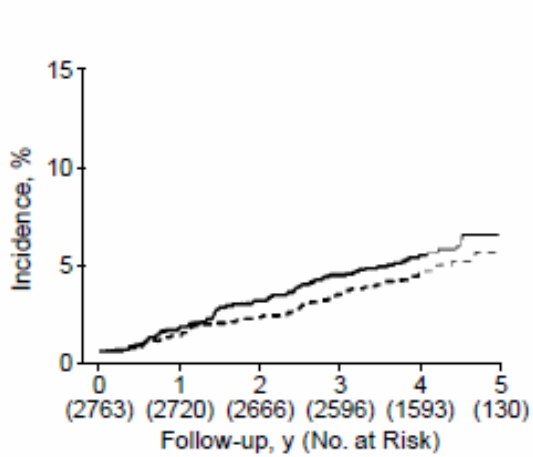
Stephen Hulley, MD; Deborah Grady, MD; Trudy Bush, PhD; Curt Furberg, MD, PhD; David Herrington, MD; Betty Riggs, MD; Eric Vittinghoff, PhD; for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group

JAMA, August 19, 1998–

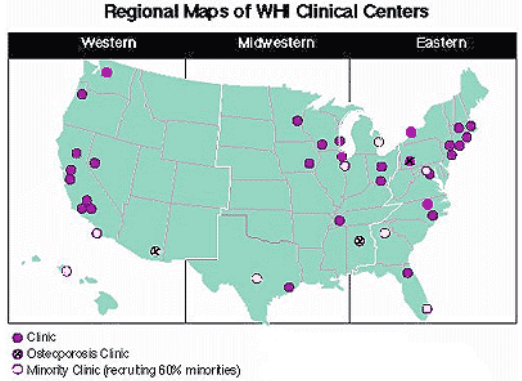
TROMBOEMBOLISMO VENOSO THS /PLACEBO : 2.89 (1.5-5.58)







CARDIOPATIA ISQUÉMICA **IAM** **MUERTE POR C. ISQUÉMICA**



THE WOMEN´S HEALTH INITIATIVE (WHI)

64.500 MUJERES MENOPAÚSICAS

Seguimiento 1992-2007

DIETA BAJA EN GRASAS:	TRATAMIENTO HORMONAL SUSTITUTIVO:	DIETA CON CALCIO Y VITAMINA D:
- Prevención Ca mama, Ca de colon y enfermedad coronaria	- Prevención enfermedad coronaria y reducción fracturas.	- Prevención fractura de cadera y Ca colorrectal.

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women

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

JAMA, July 17, 2002—Vol 288, No. 3

Writing Group for the Women's Health Initiative Investigators

Figure 1. P Plus Progestin the W

8506 Assigned to Receive Estrogen + Progestin	8102 Assigned to Receive Placebo
Status on April 30, 2002	Status on April 30, 2002
7968 Alive and Outcomes Data Submitted in Last 18 mo	7608 Alive and Outcomes Data Submitted in Last 18 mo
307 Unknown Vital Status	276 Unknown Vital Status
231 Deceased	218 Deceased

WOMEN'S HEALTH INITIATIVE

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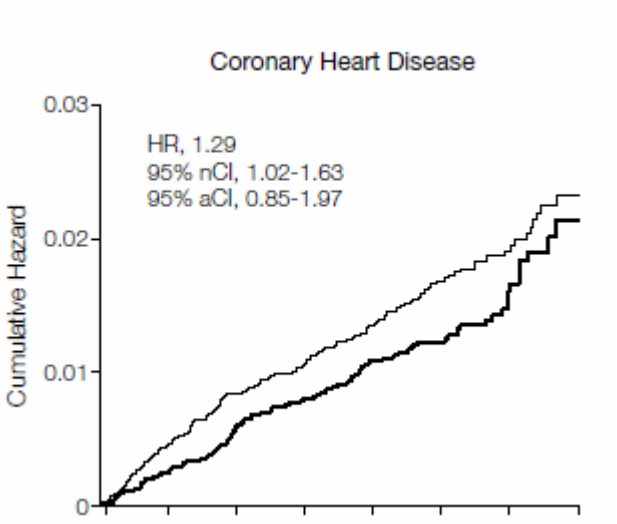

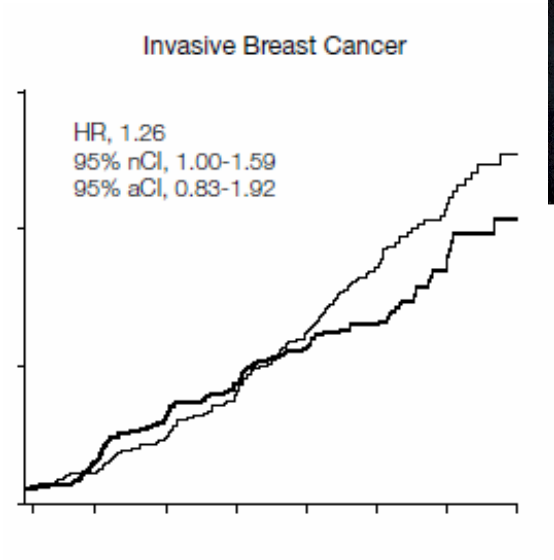

Estrogen + Progestin — Placebo

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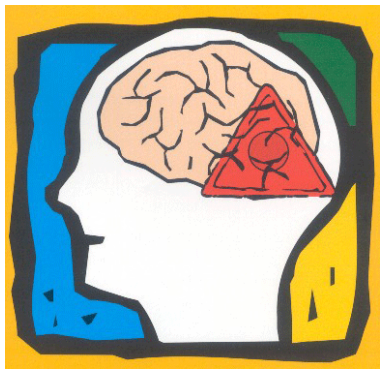
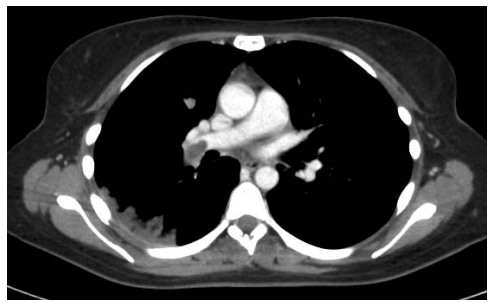
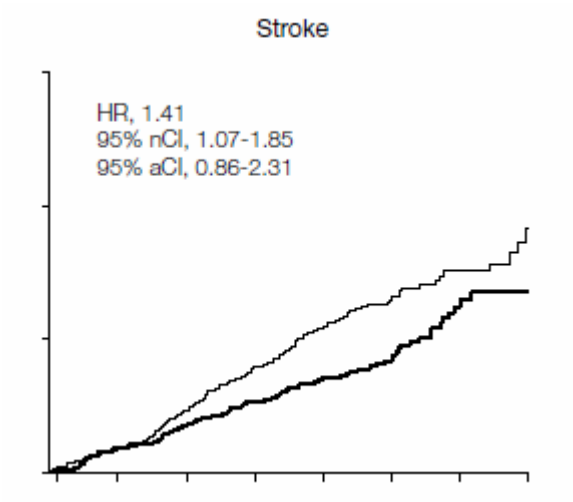
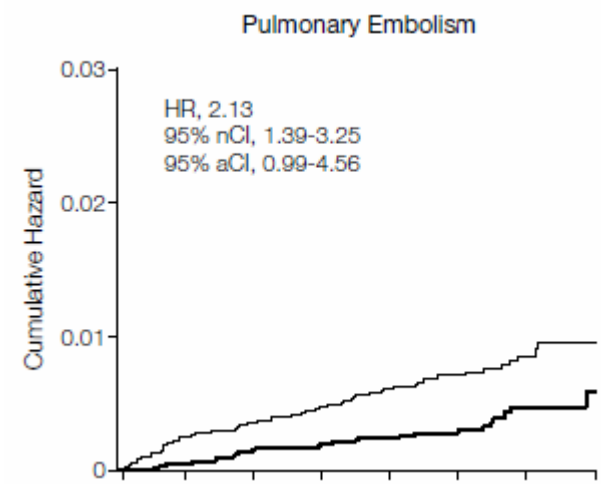








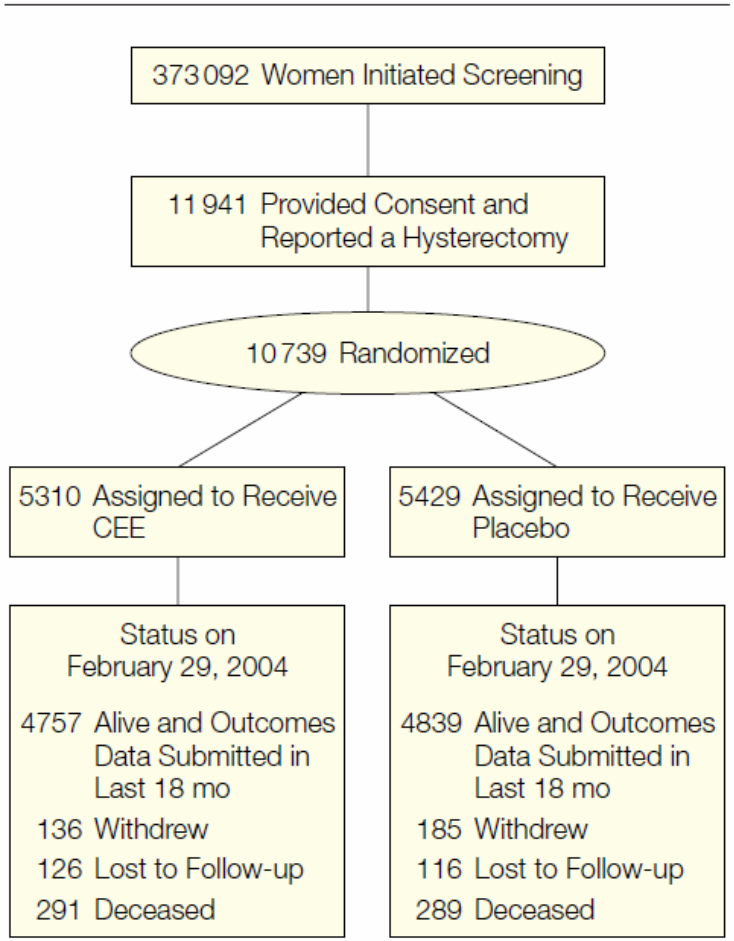
Estrogen + Progestin — Placebo

Effects of Conjugated Equine Estrogen in Postmenopausal Women With Hysterectomy

The Women's Health Initiative Randomized Controlled Trial

The Women's Health Initiative Steering Committee*

JAMA, April 14, 2004—Vol 291, No. 14



CEE indicates conjugated equine estrogen.

WOMEN'S HEALTH INITIATIVE

Effects of Conjugated Equine Estrogen in Postmenopausal Women With Hysterectomy

The Women's Health Initiative Randomized Controlled Trial

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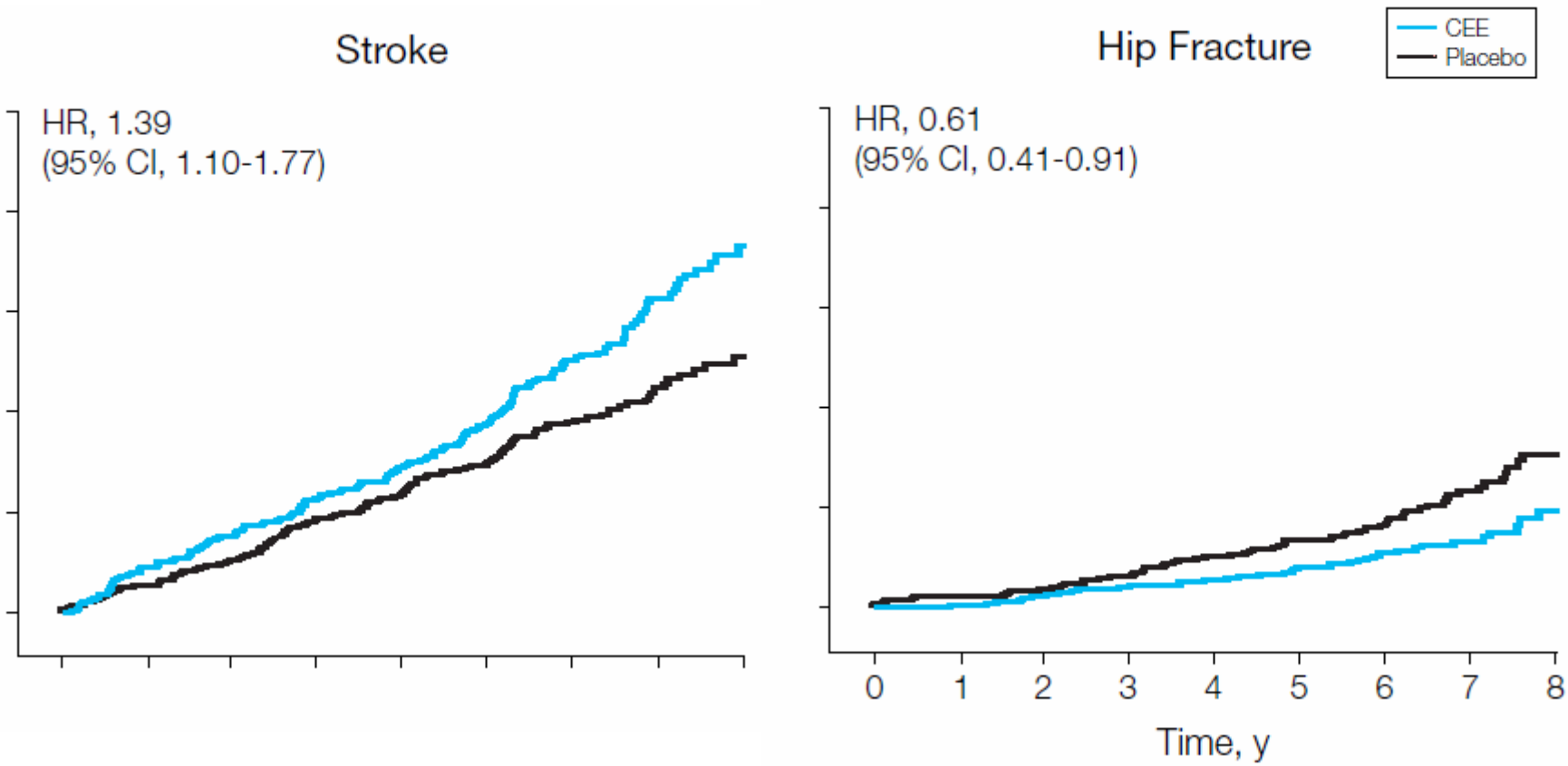
JAMA, April 14, 2004—Vol 291, No. 14

No diferencias en:
- **C. Isquémica.**
- **TEP.**
- **Ca mama.**
- **Ca colorrectal**



Estrogen Plus Progestin and Risk of Venous Thrombosis

JAMA, October 6, 2004—Vol 292, No. 13

Mary Cushman, MD, MSc
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Rebecca J. Rodabough, MS
Bruce M. Psaty, MD, PhD
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for the Women's Health Initiative Investigators

Table 1. Baseline Characteristics Based on Development of Venous Thrombosis During Follow-up

Characteristic	No. (%) of Participants*	
	Without Venous Thrombosis (n = 16 365)	With Venous Thrombosis (n = 243)
Age, mean (SD), y	63.2 (7.1)	66.4 (6.5)
White	13 724 (83.9)	221 (90.9)
Body mass index, mean (SD)†	28.4 (5.9)	30.7 (6.3)
Prior deep vein thrombosis or pulmonary embolus	133 (0.8)	8 (3.3)
Current smoking	1705 (10.5)	13 (5.4)
Diabetes	720 (4.4)	14 (5.8)
Statin use	1095 (6.7)	16 (6.6)

*Unless otherwise indicated.
†Calculated as weight in kilograms divided by the square of height in meters.

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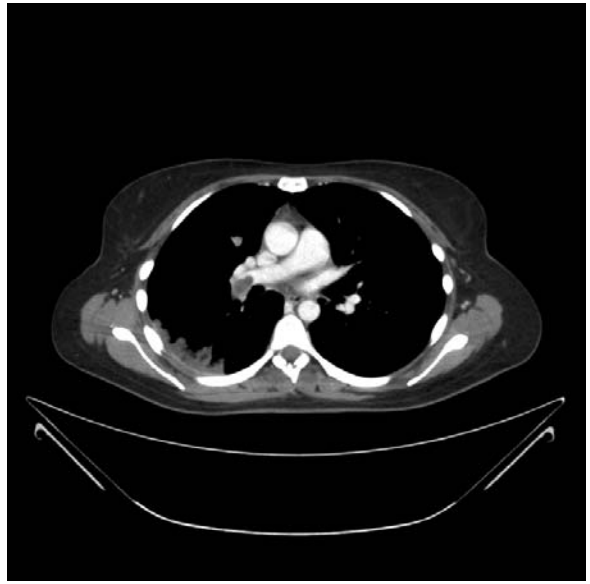

Figure 1. Cumulative Hazard of Venous Thrombosis, Deep Vein Thrombosis, and Pulmonary Embolus

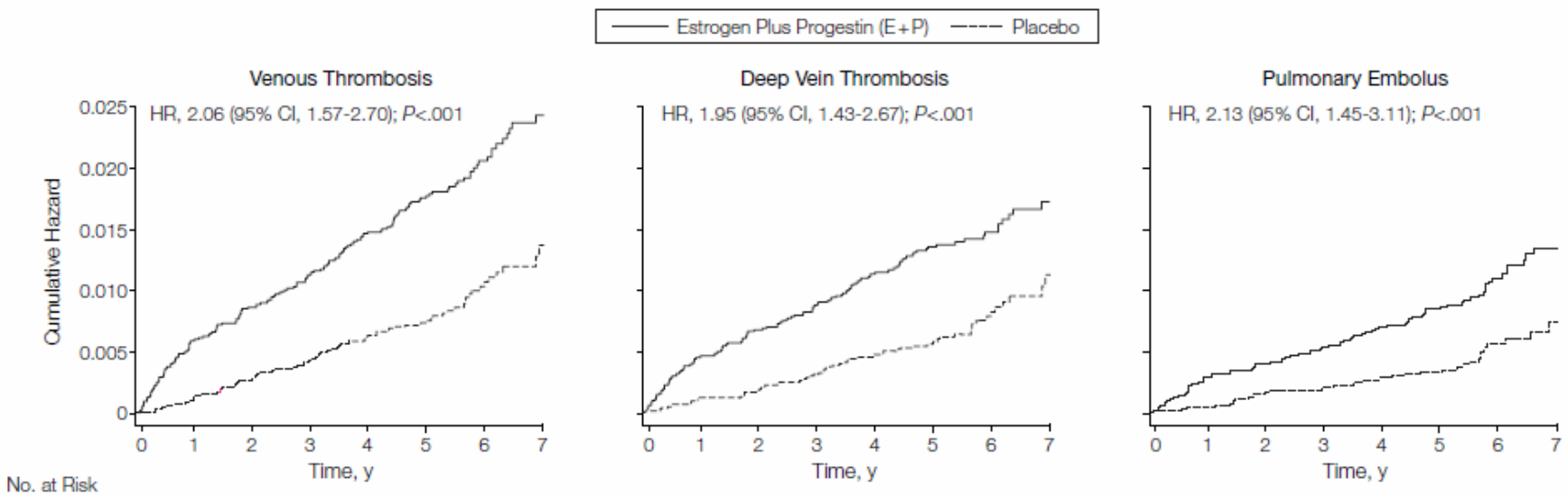

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Table 3. Age-Specific Incidence of Venous Thrombosis

	Baseline Age, y					
	50-59		60-69		70-79	
	Placebo	Estrogen + Progestin	Placebo	Estrogen + Progestin	Placebo	Estrogen + Progestin
No. of cases	13	32	38	76	25	60
Annualized rate/1000 person-years	0.8	1.9	1.9	3.5	2.7	6.2
HR (95% CI)*	1.00	2.27 (1.19-4.33)	2.31 (1.23-4.35)	4.28 (2.38-7.72)	3.37 (1.72-6.60)	7.46 (4.32-14.38)

Abbreviations: CI, confidence interval; HR, hazard ratio.
*Adjusted for prior venous thrombosis, randomization group in the dietary modification trial, age, assignment to estrogen plus progestin or placebo, and the interaction term of age and treatment assignment.

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Table 4. Incidence of Venous Thrombosis by Body Mass Index

	Body Mass Index*					
	<25		25-30		>30	
	Placebo	Estrogen + Progestin	Placebo	Estrogen + Progestin	Placebo	Estrogen + Progestin
No. of cases	13	24	24	59	38	83
Annualized rate/1000 person-years	0.9	1.6	1.5	3.5	2.5	5.1
HR (95% CI)†	1.00	1.78 (0.91-3.51)	1.63 (0.83-3.20)	3.80 (2.08-6.94)	2.87 (1.52-5.40)	5.61 (3.12-10.11)

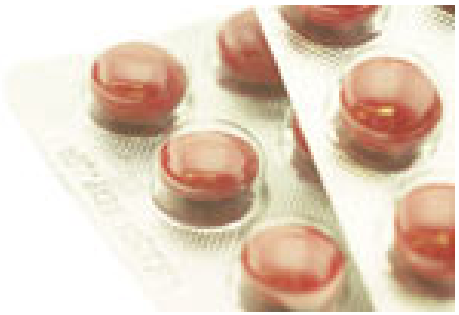
Abbreviations: CI, confidence interval; HR, hazard ratio.
*Calculated as weight in kilograms divided by the square of height in meters.
†Adjusted for prior venous thrombosis, randomization group in the dietary modification trial, body mass index, assignment to estrogen plus progestin or placebo, and the interaction term of body mass index and randomization group.

Estrogen Plus Progestin and Risk of Venous Thrombosis

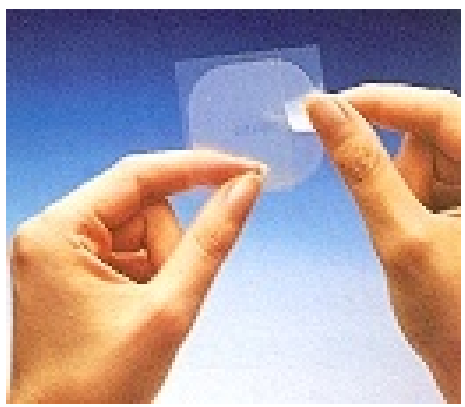
Table 5. Association of Genetic Variants With Venous Thrombosis

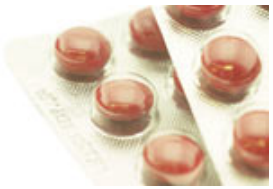
Genetic Variant	No. (%) of Controls	No. (%) of Cases	OR (95% CI)*
Factor V Leiden			
GG	455 (95.4)	119 (86.2)	1.0
GA	21 (4.4)	17 (12.3)	2.6 (1.3-5.2)
AA	1 (0.2)	2 (1.4)	7.5 (0.6-87.8)
Prothrombin 20210			
GG	458 (95.8)	133 (96.4)	1.0
AG	20 (4.2)	5 (3.6)	0.8 (0.3-2.2)
AA	0	0	
MTHFR			
CC	204 (42.5)	70 (50.4)	1.0
CT	213 (44.4)	56 (40.3)	0.8 (0.5-1.2)
TT	63 (13.1)	13 (9.4)	0.6 (0.3-1.2)
Factor XIII			
GG	255 (53.5)	75 (52.2)	1.0
GT	192 (40.3)	60 (43.5)	1.1 (0.7-1.7)
TT	30 (6.3)	6 (4.3)	0.6 (0.3-1.7)
PAI-1			
4G/4G	119 (25.4)	37 (26.8)	1.0
4G/5G	248 (52.9)	68 (49.3)	0.8 (0.5-1.2)
5G/5G	102 (21.7)	33 (23.9)	1.0 (0.6-1.8)
Factor V HR2			
AA	421 (88.4)	124 (89.9)	1.0
AG	52 (10.9)	13 (9.4)	0.8 (0.4-1.6)
GG	3 (0.6)	1 (0.7)	1.0 (0.1-10.1)

Abbreviations: CI, confidence interval; OR, odds ratio.
*Adjusted for age, year of randomization, prior venous thrombosis, and treatment assignment.

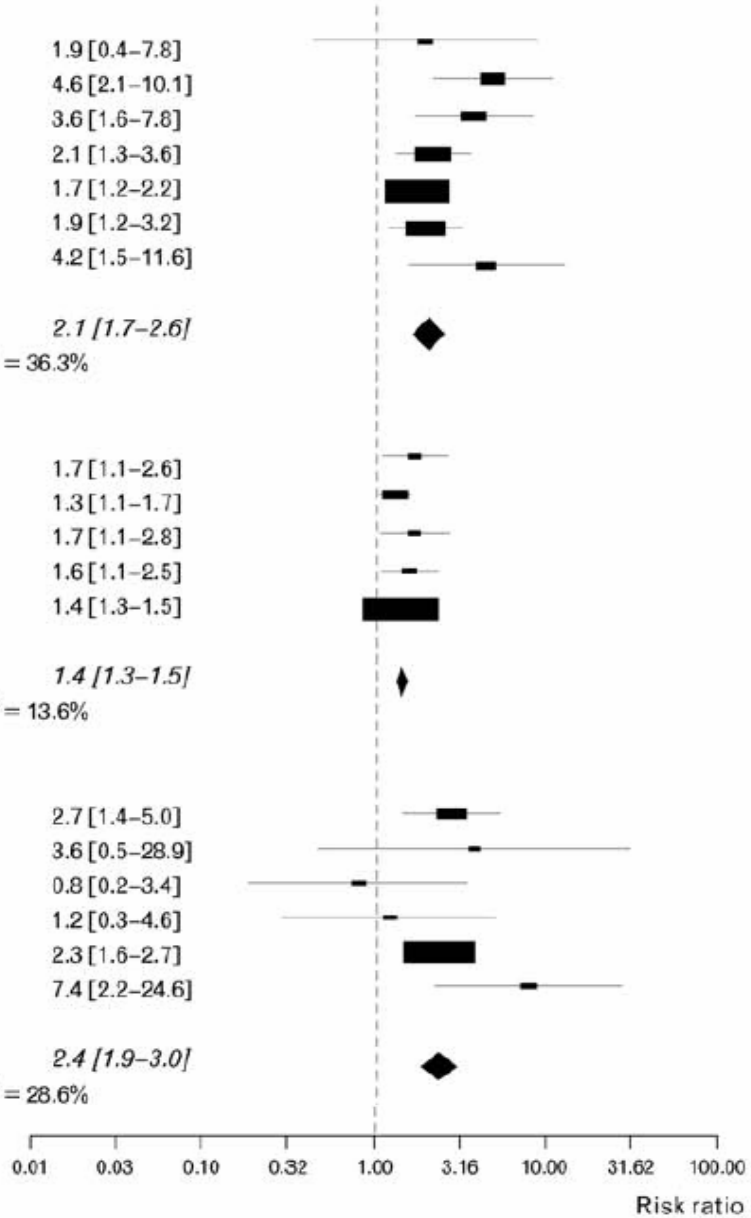


THS VÍA ORAL/ TRANSDÉRMICA





Estrogen route	Study design	Author or Study, year	Risk ratio [95% CI]
Oral	Case/control	Boston CDSP, 1974	1.9 [0.4–7.8]
		Daly, 1996	4.6 [2.1–10.1]
		Jick, 1996	3.6 [1.6–7.8]
		Perez-Gutthann, 1997	2.1 [1.3–3.6]
		Smith, 2004	1.7 [1.2–2.2]
		Douketis, 2005	1.9 [1.2–3.2]
		ESTHER, 2007	4.2 [1.5–11.6]
		Pooled risk ratio	*2.1 [1.7–2.6]*
		Test for homogeneity: $\chi^2 = 9.41$ ($P = 0.15$), $I^2 = 36.3\%$	
	Cohort	NHS, 1996	1.7 [1.1–2.6]
		Schneider, 2009*	1.3 [1.1–1.7]
		E3N, 2010	1.7 [1.1–2.8]
		Ohira, 2010	1.6 [1.1–2.5]
		Renoux, 2010*	1.4 [1.3–1.5]
		Pooled risk ratio	*1.4 [1.3–1.5]*
		Test for homogeneity: $\chi^2 = 2.32$ ($P = 0.68$), $I^2 = 13.6\%$	
	RCT	HERS, 1998	2.7 [1.4–5.0]
		ERA, 2000*	3.6 [0.5–28.9]
		WEST, 2001	0.8 [0.2–3.4]
		ESPRIT, 2002	1.2 [0.3–4.6]
		WHI I, 2004*	2.3 [1.6–2.7]
		WISDOM, 2007	7.4 [2.2–24.6]
		Pooled risk ratio	*2.4 [1.9–3.0]*
		Test for homogeneity: $\chi^2 = 7.00$ ($P = 0.22$), $I^2 = 28.6\%$	

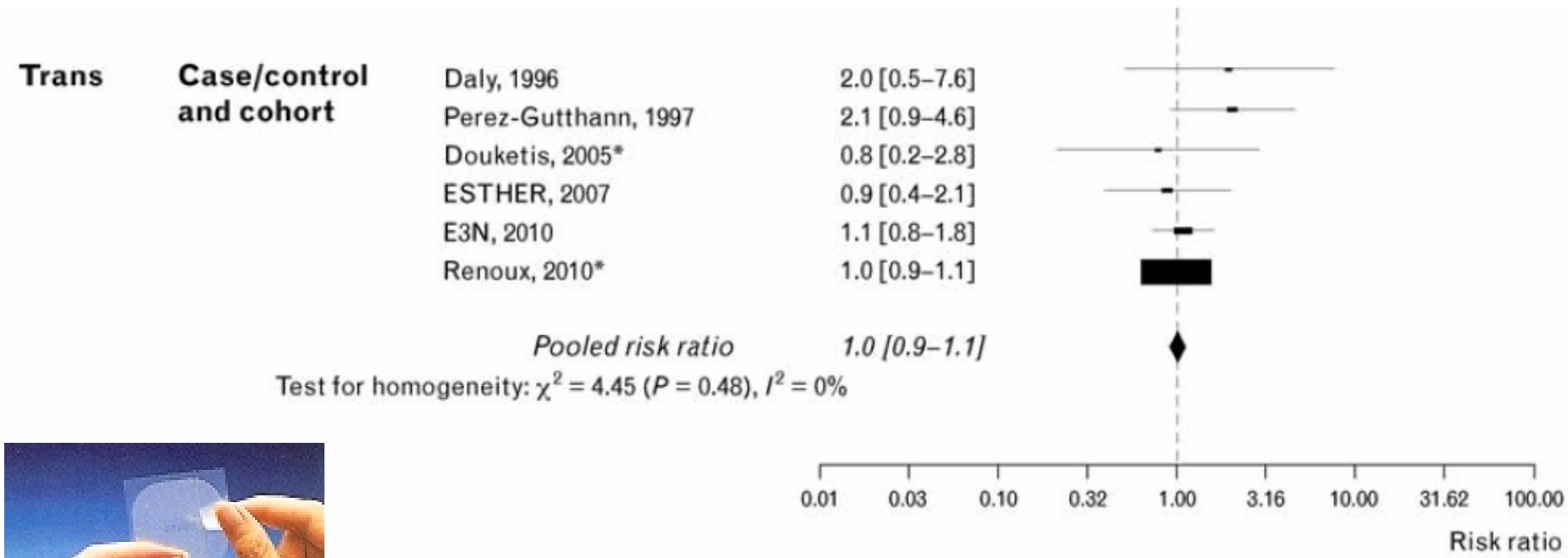


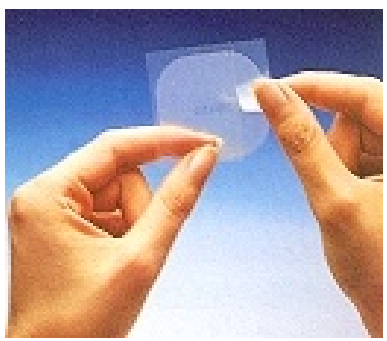
Olie´ V, Canonico M , Scarabina P. Risk of venous thrombosis with oral versus transdermal estrogen therapy among postmenopausal women.. Cur Opin Hematol 2010

Risk of venous thrombosis with oral versus transdermal estrogen therapy among postmenopausal women

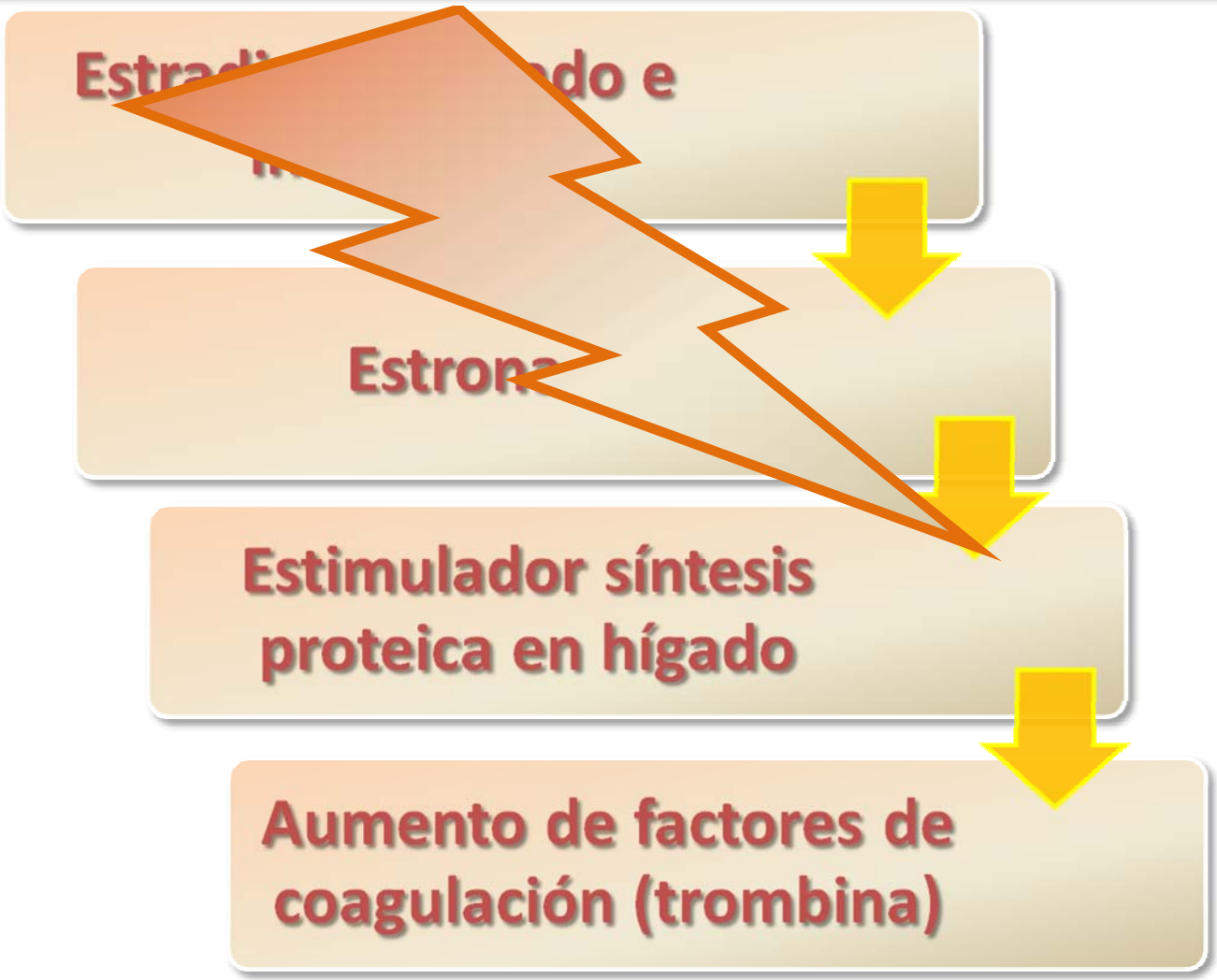
Valérie Olié[a,b], Marianne Canonico[a,b] and Pierre-Yves Scarabin[a,b]

Current Opinion in Hematology 2010, 17:457–463

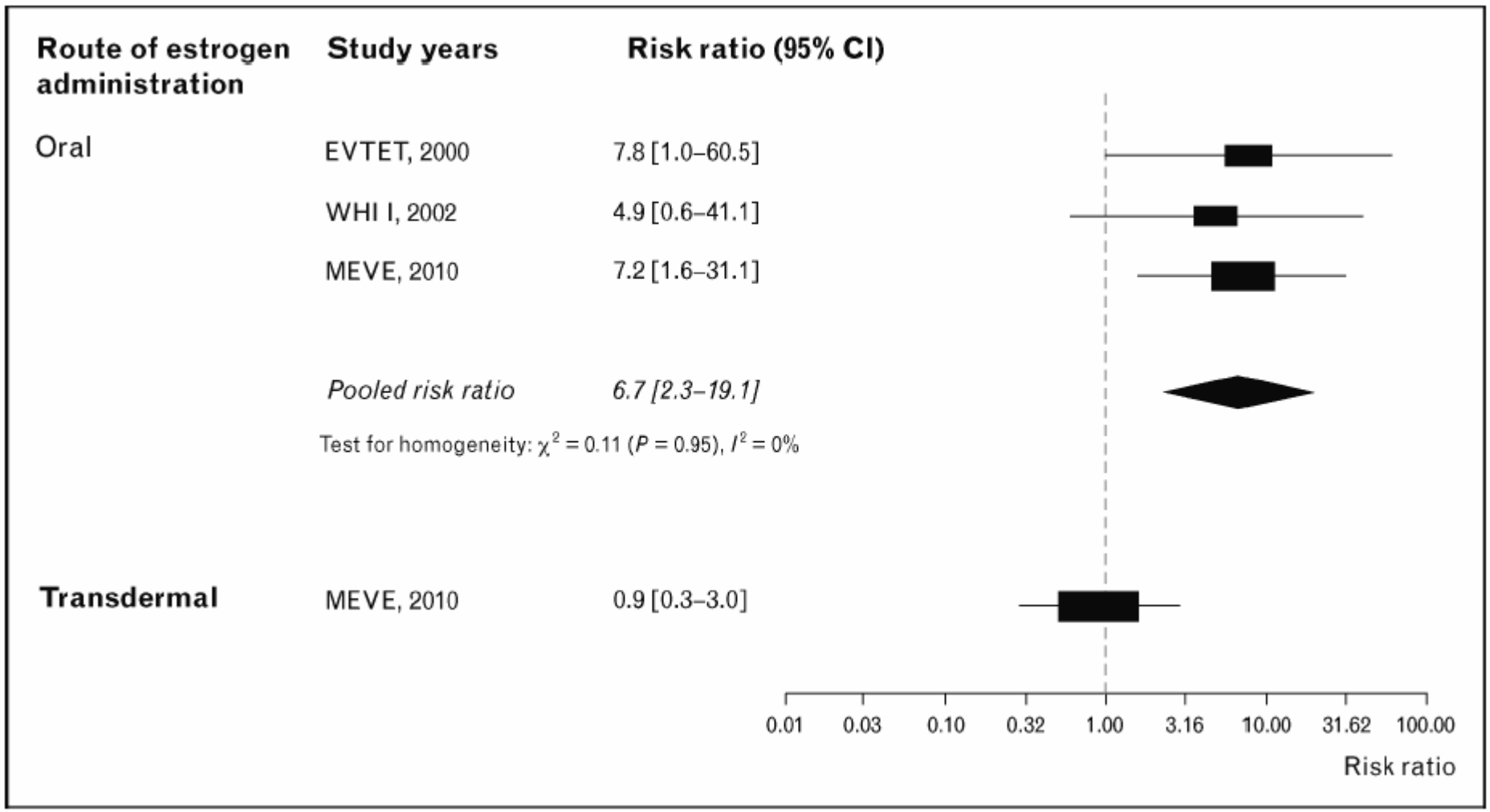




TSH VIA TRANSDÉRMICA



THS Y RECURRENCIA DE ETV



Riesgo de recurrencia de ETEV según la vía de administración del THS. Olié et al. Curr Opin Hematol 2010.

THS Y TROMBOFILIA

- El riesgo de ETV en las portadoras asintomáticas del Factor V Leiden con THS es 7-17 veces mayor que en las mujeres menopáusicas sin mutación y sin THS.
- Mutación 20210 protrombina menor riesgo que Factor V Leiden.
- No hay datos sobre Déficit de C, S, ATII y Anticuerpos antifosfolípidos. Parece sensato pensar que es similar al descrito con anticonceptivos.

Ueng J, Douketis J. Prevention and treatment of hormone-associated venous thromboembolism. Hematol Oncol Clin N Am 2010; 24: 683-694.

THS Y ESTUDIO DE TROMBOFILIA

- El riesgo de ETV es mayor en las mujeres menopáusicas con THS que en las mujeres en edad fértil que toman ACO.
- El screening **selectivo** de Trombofilia es más coste – eficaz previo al THS que al uso de anticonceptivos.
- La rentabilidad aumenta si la mujer tiene ETV previa o antecedentes familiares.

Wua O, Greer I. Is screening for thrombophilia cost-effective?. Curr Opin Hematol 2007; 14:500–503.

TRATAMIENTO HORMONAL SUSTITUTIVO EN EL SIGLO XXI

INDICACIONES DEL THS

- ✓ La FDA [1] y el American College of Obstetricians and Gynecologists [2] recomiendan que el tratamiento hormonal sustitutivo se use a las dosis más bajas y durante el menor tiempo posible para poder amortiguar los síntomas moderados-severos de la menopausia.

[1] *Stephenson J. FDA orders estrogen safety warnings: agency offers guidance for HRT use: JAMA 2003; 289: 537-8.*

[2] *Question and answers on hormone therapy: In reponse to the Women´s Health Initiative study results on estrogen and progestin hormone therapy. http://www.acog.org*

RIESGO / BENEFICIO DEL THS

- El riesgo de ETV idiopática es mayor durante el primer año de tratamiento. En este periodo la incidencia sobre el cáncer de mama y las alteraciones cardiovasculares son menores y van aumentando a más largo plazo.
- Por este motivo, en la actualidad la ETV es la complicación más importante del tratamiento hormonal sustitutivo.

RECOMENDACIONES

ANTES DE INICIAR EL THS:

- Evaluar e informar de los riesgos y beneficios en cada caso individual y contemplar otras alternativas de tratamiento (C).
- Detectar las mujeres de alto riesgo de ETV (antecedentes personales y familiares de ETV)(C).
- Instruir sobre los síntomas y signos de TVP/TEP para que consulten con rapidez.

RCOG (Royal College of Obstetricians and Gynaecologists) Guideline nº19.2004

RECOMENDACIONES

- Evitar al THS si antecedente de ETV previa, por alto riesgo de recurrencias.
- En mujeres portadoras de Trombofilia no se recomienda el THS .
- En cirugía electiva el THS no tiene que ser suspendido de forma rutinaria, pero se debe de realizar profilaxis con HBPM y medias de compresión.

RCOG (Royal College of Obstetricians and Gynaecologists) Guideline nº19. 2004

ETV AGUDA Y THS

- Retirar el THS en mujer con ETV aguda.
- Valorar en casos de síntomas climatéricos severos.
  - Recurrencia de los síntomas.
  - ¿Previene la anticoagulación del efecto protrombótico del THS?
- Duración del tratamiento anticoagulante:
  - No está definida. 3-6 meses o largo plazo.
  - Depende del momento de la ETV en relación al inicio del THS y de la coexistencia de factores de riesgo transitorios, permanentes o del carácter idiopático.

Ueng J, Douketis J. Prevention and treatment of hormone-associated venous thromboembolism.. Hematol Oncol Clin N Am 2010.

PROFILAXIS ETEV

Mujer de 51 años con bochornos frecuentes que interfieren con el sueño y el trabajo, y con sequedad vaginal que ocasiona incomodidad en sus relaciones sexuales.

CASO 1	CASO 2	CASO 3
No antecedentes de TV	Antecedente de TV [illegible] anticonceptivos.	Previamente sana.
Heterocigota para Factor V Leiden .		No antecedentes de ETV.
		No Trombofilia.
NO	**NO**	**SI**

Paciente 034-0001 Grabar Datos

Paciente Válido
(pulse el botón para ver los errores)

Factores de Riesgo

¿Ha estado con tratamiento hormonal (estrógenos, progestágenos, moduladores de receptores de estrógenos...) en los últimos 2 meses?: Sí

Motivo del tratamiento: SIN ESPECIFICAR

Inicio del tratamiento (Mes): SIN ESPECIFICAR

Inicio del tratamiento (Año):

Fármaco (Principio Activo o Nombre Comercial):

Vía de administración: SIN ESPECIFICAR

- SIN ESPECIFICAR
- Oral
- Transdérmica
- Vaginal
- Parenteral
- Implante subcutáneo

¿Está la paciente embarazada?: No

¿En que trimestre de gestación se encontraba en el momento del diagnóstico?:

¿Finalizó el embarazo?: