AAPEC, Julio 2016

DIABETES, MENOPAUSIA Y THM

Gladys Isabel Fernández

ARKHËN

2016 American Diabetes Association (ADA) Diabetes Guidelines Summary Recommendations from NDEI

1. Diabetes Diagnosis

Criteria for Diabetes Diagnosis: 4 options
FPG ≥ 126 mg/ dL (7.0 mmol/ L)*   Fasting is defined as no caloric intake for ≥ 8 hours
2-hr PG ≥ 200 mg/ dL (11.1 mmol/ L) during OGTT (75-g)*   Using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water
A1C ≥ 6.5% (48 mmol/ mol)*   Performed in a lab using NGSP-certified method and standardized to DCCT assay
Random PG ≥ 200 mg/ dL (11.1 mmol/ L)   In individuals with symptoms of hyperglycemia or hyperglycemic crisis
*In the absence of unequivocal hyperglycemia results should be confirmed using repeat testing
No clear clinical diagnosis? Immediately repeat the same test using a new blood sample.   Same test with same or similar results? Diagnosis confirmed.   Different tests above diagnostic threshold? Diagnosis confirmed.   Discordant results from two separate tests? Repeat the test with a result above diagnostic cut-point.

Diabetes Care 2016;39(suppl 1):S1-S106

Testing for Type 2 Diabetes and Prediabetes in Asymptomatic Adults

Type 2 diabetes screening should be performed in adults of any age who are overweight or obese, and who have one or more diabetes risk factor (See Diabetes Risk Factors)

- Testing should begin at age 45
- If test is normal? Repeat it at least every 3 years (See Diabetes Risk Factors):

Screening for prediabetes can be done using A1C, FPG, or 2-hr PG after 75-g OGTT criteria

- CVD risk factors should be identified and treated
- Testing may be considered in children and adolescents who are overweight or obese and have two or more risk factors for diabetes (See Diabetes Risk Factors)

Type 2 Diabetes Risk Factors

- Physical inactivity
- First-degree relative with diabetes
- High-risk race/ethnicity
- Women who delivered a baby >9 lb or were diagnosed with GDM
- HDL-C <35 mg/dL ± TG >250 mg/dL
- Hypertension (140/90 mm Hg or on therapy)
- A1C 5.7%, IGT, or IFG on previous testing
- Conditions associated with insulin resistance: severe obesity, acanthosis nigricans, PCOS
- History of CVD

Diabetes Care 2016;39(suppl 1):S1-S106

2016 American Diabetes Association (ADA) Diabetes Guidelines Summary Recommendations from NDEI

Categories of Increased Risk for Diabetes (Prediabetes)		
FPG	**2-hr PG**	**A1C**
100-125 mg/dL (5.6-6.9 mmol/L) Impaired fasting glucose (IFG)	140-199 mg/dL (7.8-11.0 mmol/L) Impaired glucose tolerance (IGT)	5.7-6.4% (39-46 mmol/mol)
For all tests, risk is continuous, extending below lower limit of range and becoming disproportionately greater at higher ends of range		

Diabetes Care 2016;39(suppl 1):S1-S106

CASO CLINICO

Paciente de 53 años. Arquitecta. Sedentaria. No fuma.

MC: Tuforadas de calor, insomnio y depresión de más de 2 años de evolución, que alteran su calidad de vida.

Antecedentes Familiares:

Padre fallecido por cáncer de pulmón. Madre con HTA, fallecida por ACV.

Antecedentes Personales:

- **HTA tratada con Enalapril 10 mg/día**
- **Dislipemia en tratamiento con 10 mg/día de Atorvastatina**
- **Diabética tipo 2 diagnosticada a los 48 años, en tratamiento con metformina (1700 mg diarios)**

- Antecedentes tocoginecológicos:

Menarca: 14 años

RM: regulares

G: 2 PN:2 (el último con DG, no requirió insulina)

Menopausia a los 52 años.

A los 51 años comenzó con severos sofocos que la despiertan por la noche, que no cedieron con tratamiento no hormonal (intentó isoflavonas, venlafaxina, β- alanina con oxazepam y hasta gabapentin).

<u>Examen físico</u>:

Peso: 84kg Talla: 1.62 mt IMC: 32.06 Cintura: 107 cm

TA 130/80mmHg. Acantosis nigricans grado 2-3.

Resto del examen físico normal.

Laboratorio: (datos de relevancia solamente)

- **HbA1C 6.5%**
- **Glucemia 126 mg%**
- **Creatinina 1.0 mg/dl**
- **LDL 120mg/dl**
- **HDL 35 mg/dl**
- **Triglicéridos 179 mg/dl**
- **Colesterol total 201mg/dl**
- **Albuminuria: negativa**

Trae fondo de ojos: sin retinopatía diabética

Trae estudios ginecológicos:

- **Ecografía mamaria y mamografía que informan Bi-rads 2**
- **Ecografía transvaginal con endometrio de 4 mm**

Ante esta paciente las preguntas que nos hacemos son:

1-¿A esta paciente con DM2 y severos síntomas climatéricos que alteran su calidad le indicaría THM?

2-De indicarle THM:

-¿Qué THM le indicaría?

THM: Contraindicaciones

- Cánceres hormono-dependientes
- Hemorragia genital de origen no determinado
- Enfermedad hepática, renal o cardíaca aguda
- Trombosis venosa profunda o TEV (actual o pasado)
- Historia de enfermedad coronaria arterial o de ACV
- Hipertrigliceridemia >750mg%
- Hipertensión arterial no controlada
- Migrañas con aura
- Porfiria

Fertil Steril 2014;101(4):905-915

Table 4 Tailoring hormone replacement therapy (HRT) in higher-risk cases

Obese	Use non-oral routes to reduce risk of venous thromboembolism
High triglycerides	Use non-oral route
Hypertensive	Consider drospirenone if woman has uterus
Skin allergy	Consider gel, spray or implant
Implants required	Use low dose and sparingly to avoid tachyphylaxis
Diabetes	Is not a contraindication to HRT

Climateric 2011;14:409-417

Table 4. Specific Cautions to Use of Systemic MHT or SERMs[a,b] for Treatment of Menopausal Symptoms

In general, ET should not be used in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of cancer of the breast
- Known or suspected estrogen-dependent neoplasia including endometrial cancer
- Active DVT, pulmonary embolism, or history of these conditions
- Active arterial thromboembolic disease (for example, stroke, MI) or a history of these conditions
- Known anaphylactic reaction or angioedema in response to any ingredient in the medication[c]
- Known liver impairment or disease
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders[c]
- Known or suspected pregnancy

Caution should also be exercised in women with:

- Gallbladder disease (oral ET)
- Hypertriglyceridemia (>400 mg/d) (oral ET)
- Diabetes
- Hypoparathyroidism (risk of hypocalcemia)
- Benign meningioma
- Intermediate or high risk of breast cancer
- High risk of heart disease
- Migraine with aura (oral ET)
- Other conditions[d]

J Clin Endocrinol Metab 2015;100(11):3975-4011

Review article

Managing the menopause: An update

Helen Roberts[a,*], Martha Hickey[b]

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[b] *Department of Obstetrics & Gynaecology, University of Melbourne and the Royal Women's Hospital, Parkville Vic 3052, Australia*

Maturitas 2016;86:53-58

Table 1
Recommendations for HT use (6).

Outcome	Recommendation	Level of Evidence
Prevention of CVD	Do not use	I-A
Menopausal symptoms	Moderate dose HT most effective for VMS therapy	I-A
	Progestin alone	I-A
	Selected Antidepressants/clonidine/gabapentin	I-B
Vaginal dryness	Low dose vaginal estrogen.	I-A
	Progestin not required	III-C
Recurrent UTIUrge incontinence	Low dose vaginal estrogen	I-B
		II-1A

Table 2
Recommendations for HT use in women with particular conditions (6).

Medical history	Recommendation to use for symptom relief	Level of Evidence[a]
Personal history or	Do not use oral HT	I-A
high risk of VTE	consider transdermal	III-C
Diabetes	Can use HT	I-A
Breast cancer	Uncertainty re risks of HT	I-B
Surgical menopause	Offer HT	I-A
Premature ovarian insufficiency	Offer HT	I-A
	Recommend use to average age of menopause	III-B

[a] I: Evidence obtained from at least one properly randomized controlled trial. II-1: Evidence from well-designed controlled trials without randomization. III: Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees. A: There is good evidence to recommend the clinical preventive action B. There is fair evidence to recommend the clinical preventive action. C: The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making.

Hormone Replacement Therapy Is Associated With Better Glycemic Control in Women With Type 2 Diabetes

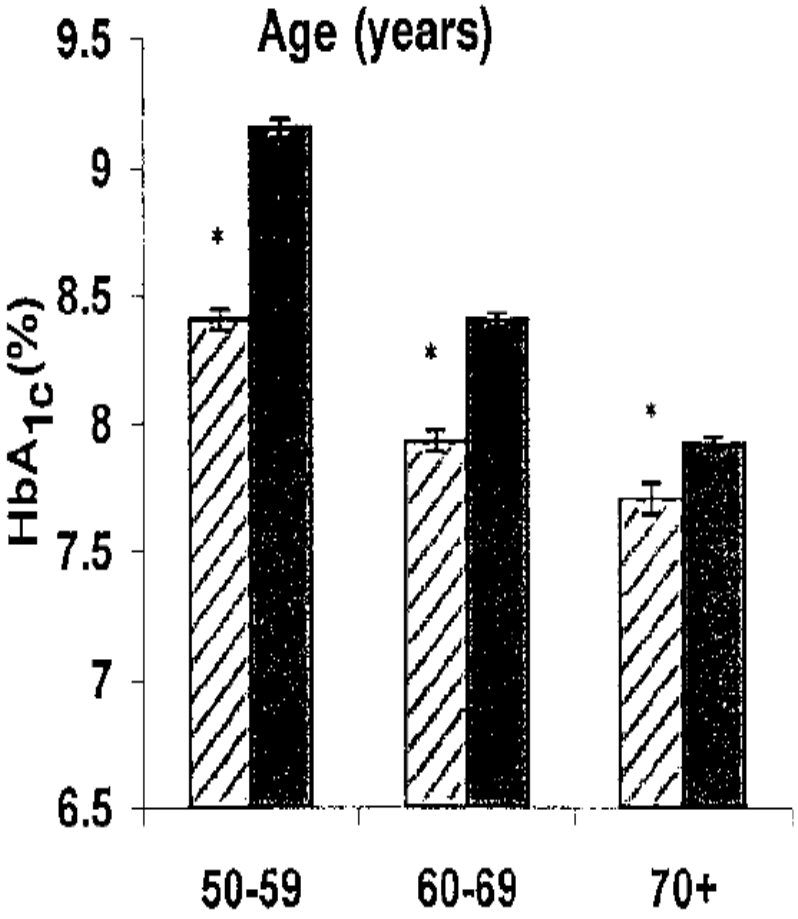
The Northern California Kaiser Permanente Diabetes Registry

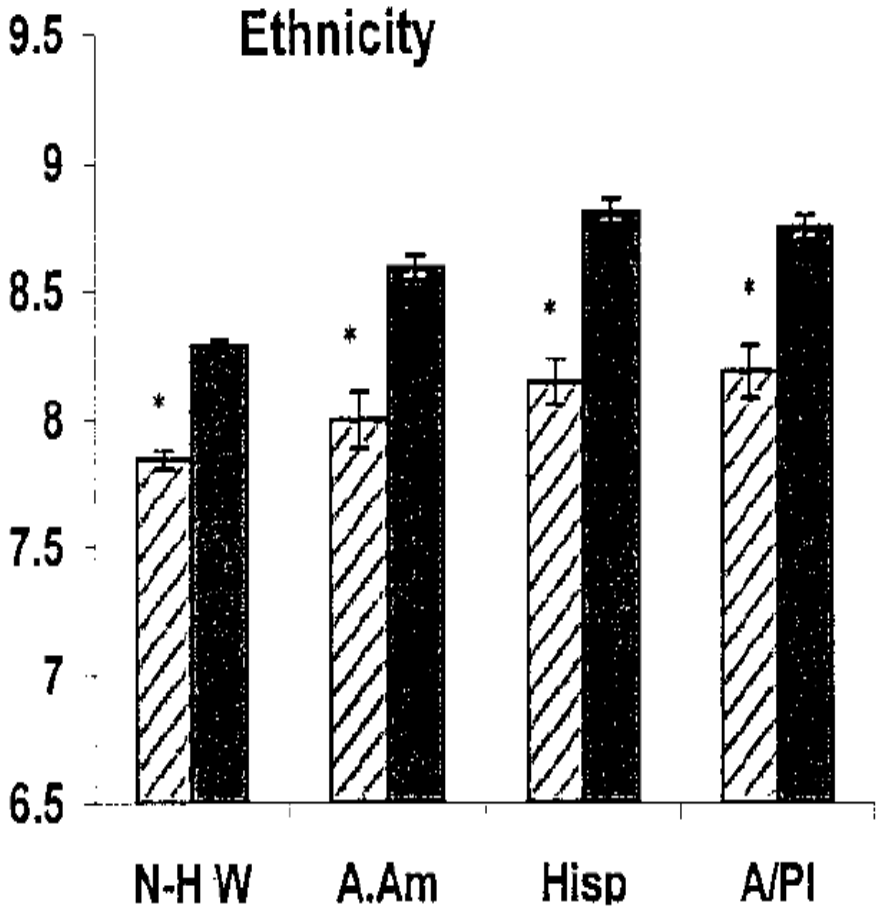
En una cohorte de 15435 mujeres con DBT2 de ≥50 años, identificadas por el Northern California Kaiser Permanente Diabetes Registry, se observó que la THM fue significativamente (e independientemente) asociada con mejor control glucémico reflejado por descenso significativo de HbA1c.

Diabetes Care 2001;24:1144-1150

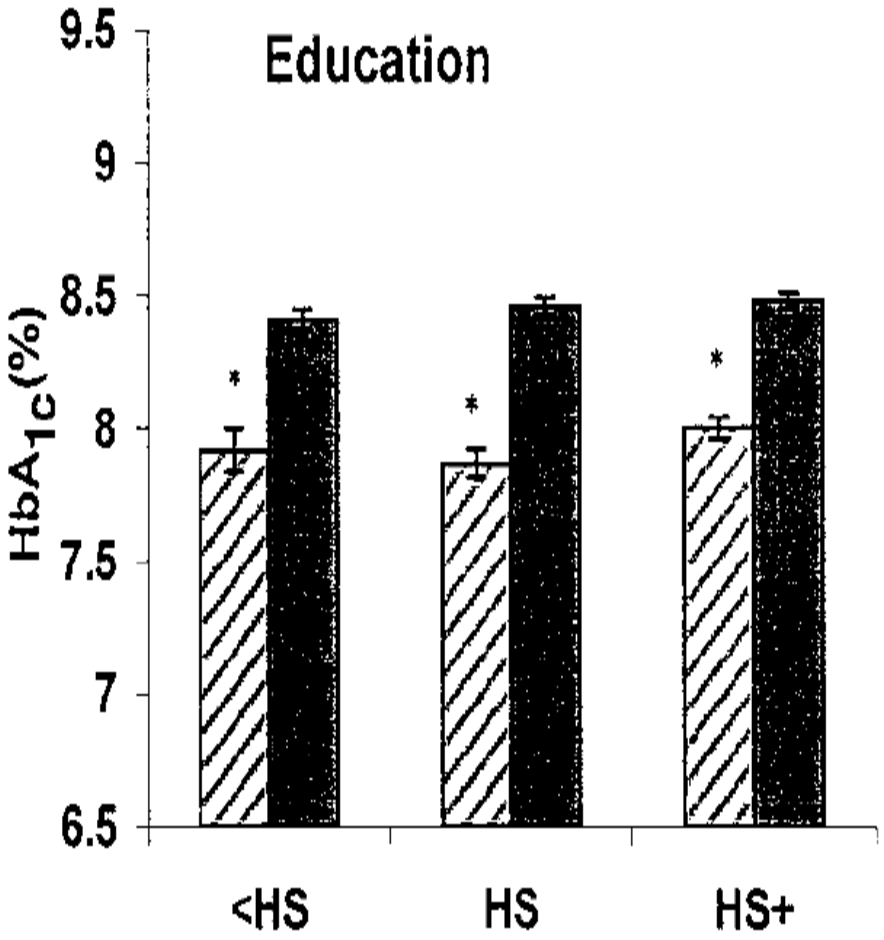
Table 1—*Characteristics of 15,435 women with type 2 diabetes by HRT: the Northern California Kaiser Permanente Diabetes Registry, 1995–1996*

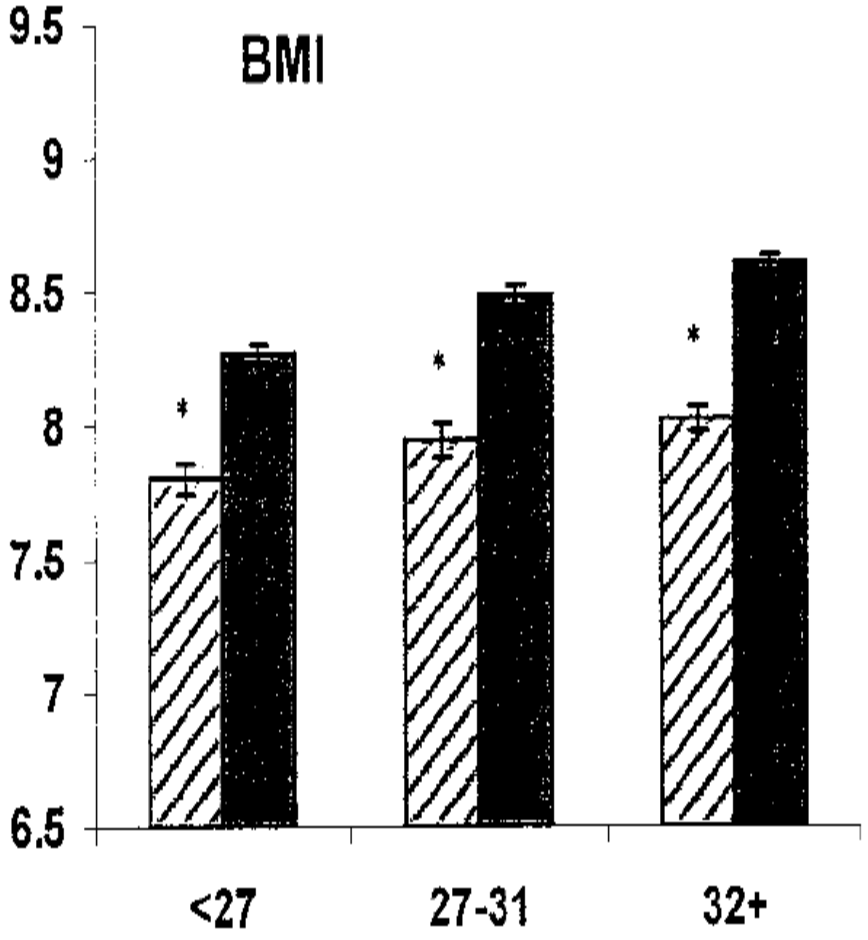
	Women using HRT (n = 3,406)	Women not using HRT (n = 11,583)	P
Age (years)			
Means (SD)	61.2 (7.6)	65.9 (8.8)	0.0001
BMI (kg/m^2)			
Crude means (SD)	30.7 (6.5)	30.4 (6.8)	0.01
Age-adjusted means (SE)	30.0 (0.1)	30.6 (0.1)	0.0001
HbA_{1c} (%)			
Crude means (SD)	8.1 (1.7)	8.4 (2.0)	0.001
Age-adjusted means (SE)	7.9 (0.03)	8.5 (0.02)	0.0001
Ethnicity (%)			0.001
Non-Hispanic Whites	60.9	53.2	
African-Americans	9.4	15.0	
Hispanics	12.9	12.3	
Asian/Pacific Islanders	9.4	11.5	
Other/unknown	7.4	8.0	
Education (%)			0.001
High school or less	48.2	57.2	
Some college	32.5	27.7	
College	19.3	15.1	
Therapy (%)			0.01
Diet	13.9	12.2	
OHA	51.5	53.4	
Insulin	34.6	34.4	
Diabetes duration (%)			0.001
<5 years	38.0	36.2	
5–9 years	23.9	21.6	
≥10 years	38.1	42.2	
SMBG practice (%)			0.001
Never	19.9	26.4	
<1/week	18.2	17.1	
≥1/week	61.8	56.5	
Smoking (%)			0.001
Current	9.7	8.9	
Former	36.0	31.6	
Never	54.3	59.5	
Exercise (%)	52.4	46.9	0.001
Medication benefit (%)	87.9	83.9	0.001



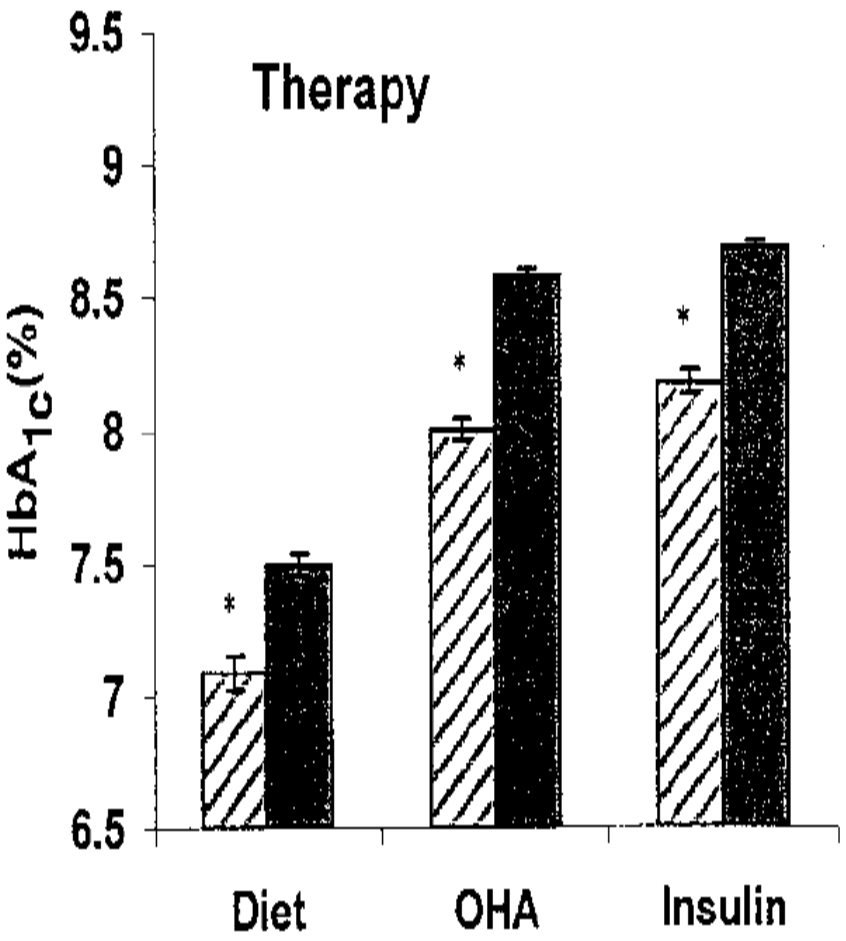


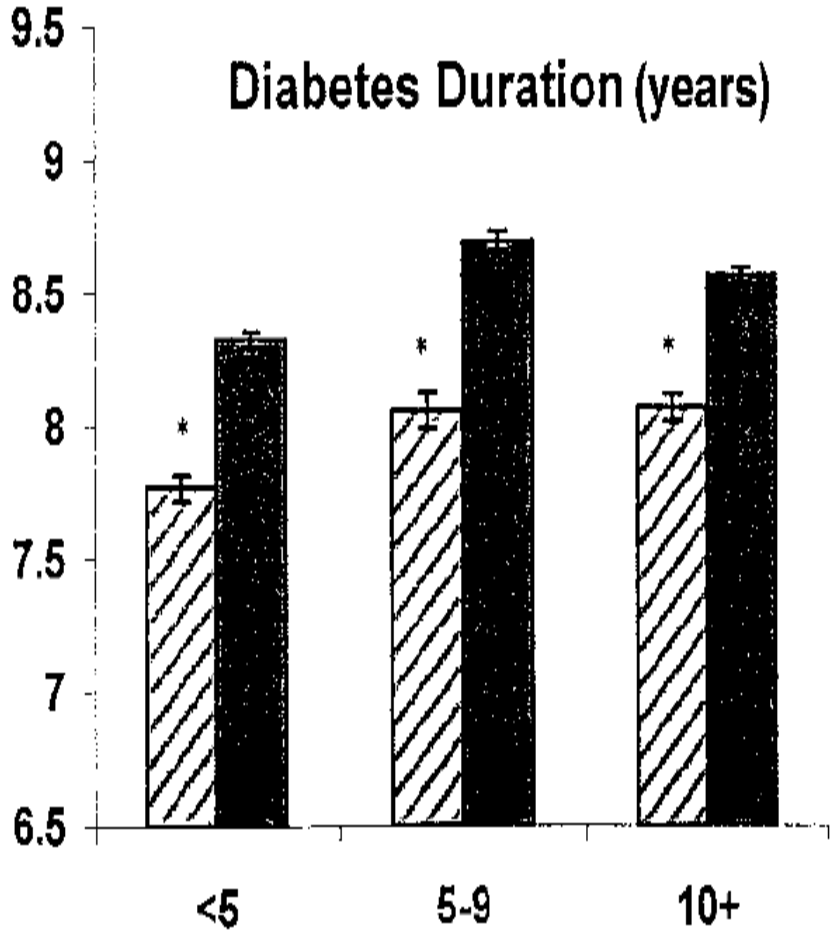
Diabetes Care 2001;24:1144-1150





Diabetes Care 2001;24:1144-1150





Diabetes Care 2001;24:1144-1150

Estrogen Therapy and Risk of Cardiovascular Events Among Women With Type 2 Diabetes

KATHERINE M. NEWTON, PHD[1,2]
ANDREA Z. LACROIX, PHD[1,2,3]
SUSAN R. HECKBERT, MD, PHD[1,2]
LINN ABRAHAM, MS[1]
DAVID MCCULLOCH, MD[1]
WILLIAM BARLOW, PHD[1,4]

Estudio retrospectivo, caso-control, de 6017 mujeres de 45-80 años DBT 2 que evaluó riesgo de eventos cardiovasculares en usuarias de THM.

	RR (95%IC)
Nunca Usuarias de THM	1
Actuales usuarias de E	0.48 (0.30-0.78)
Actuales usuarias de E+P	0.43 (0.22-0.85)
Usuarias pasadas de THM	0.88 (0.65-1.19)

Diabetes Care 2003;26(10):2810-2816

ORIGINAL ARTICLE

Combined estrogen replacement therapy on metabolic control in postmenopausal women with diabetes mellitus

Youhua Xu [a,*], Jing Lin [b], Shanshan Wang [a,c], Jianfeng Xiong [a], Quan Zhu [a]

Revisión sistemática y meta-análisis de artículos que examinaron el efecto de la THM sobre la incidencia de DM2 y sobre índices metabólicos en mujeres postmenopáusicas con DBT tipo2.

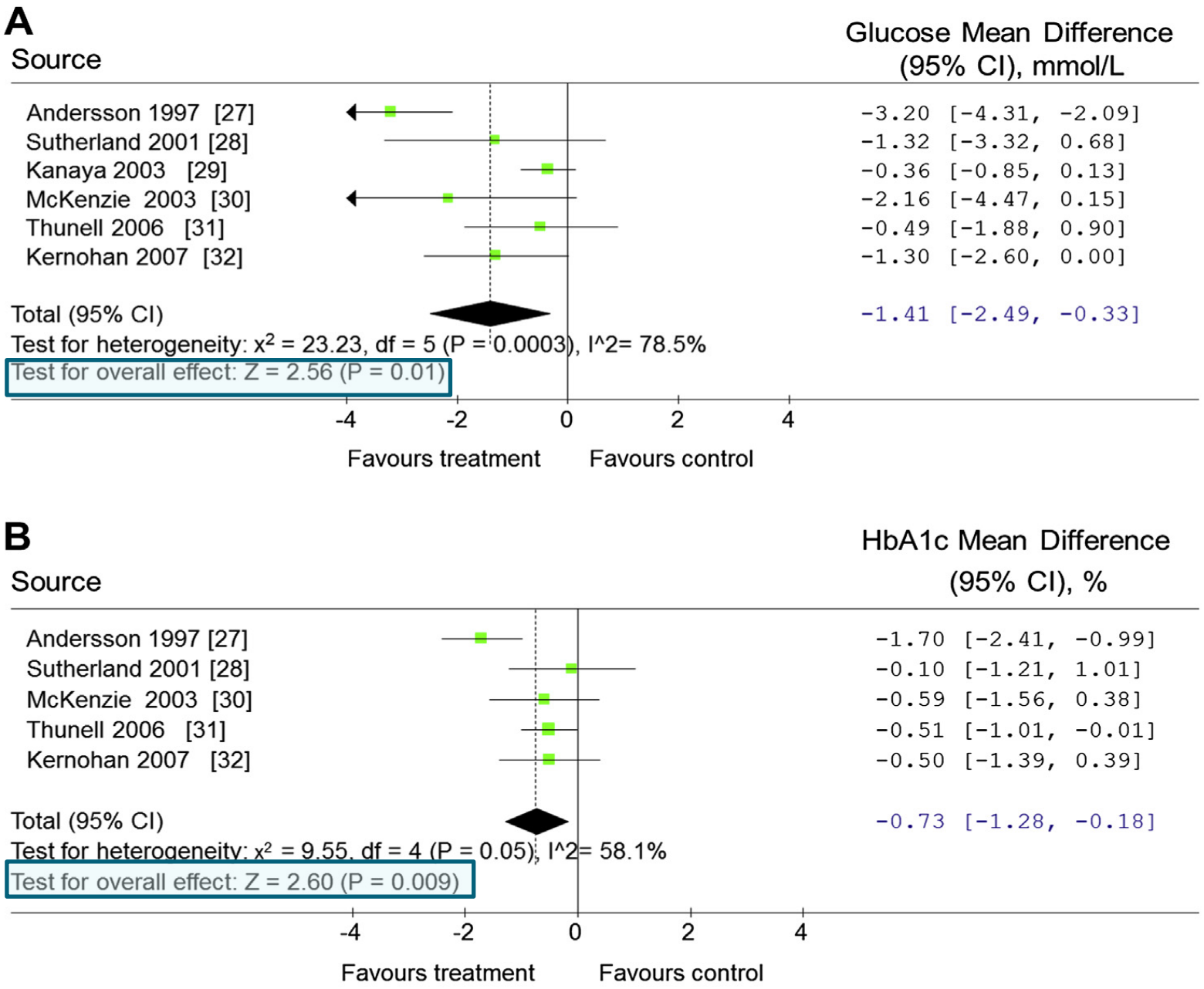
Kaohsiung J Med Sci 2014;30(7):350-361

Table 2 Study characteristics of combined ERT on diabetic indices in postmenopausal women.

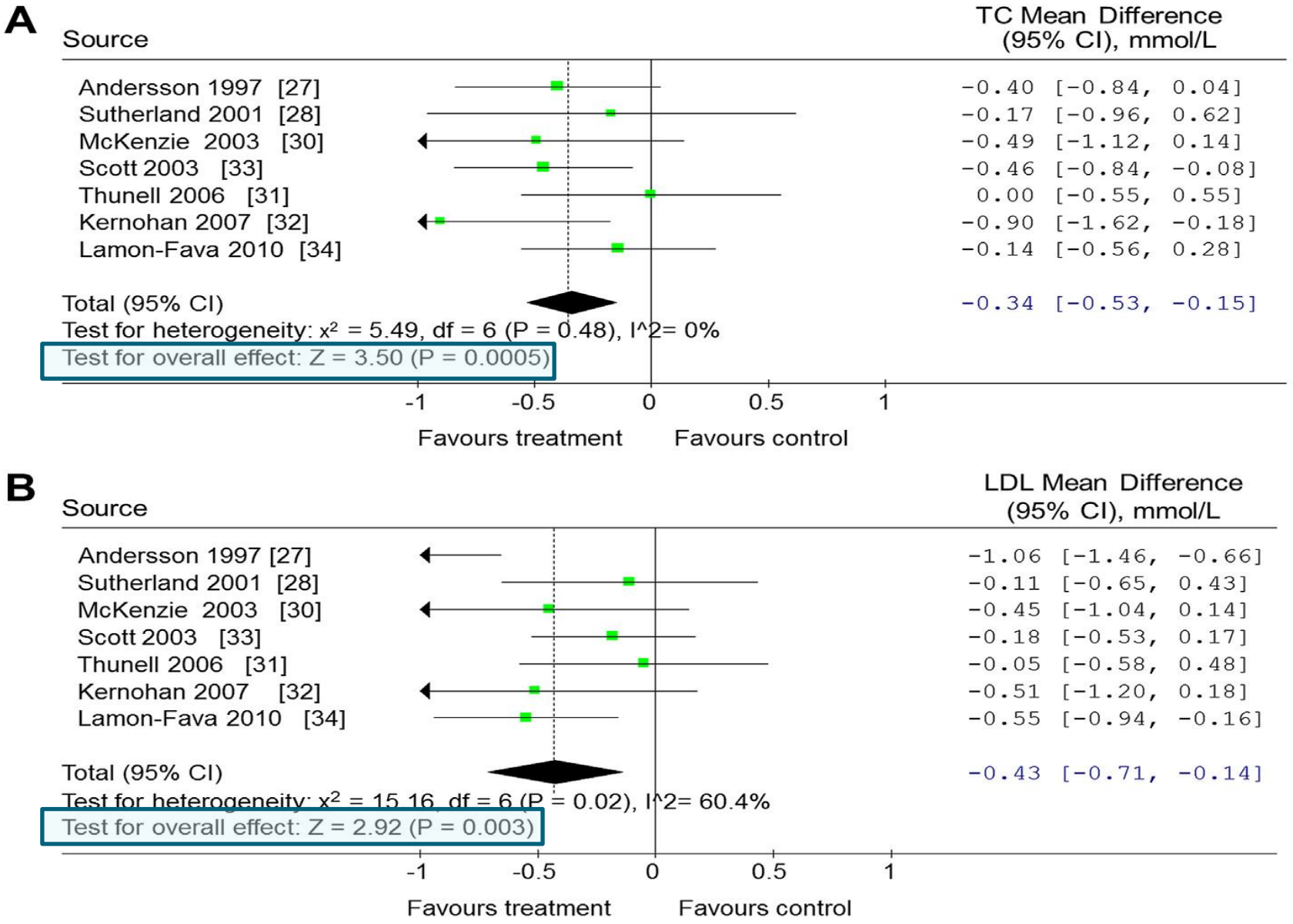
Source	Location	Follow-up (m)	Study design	Estrogen therapy	Age (y)		Case (*n*)	
					Placebo	ERT	Placebo	ERT
Andersson et al. [27]	Sweden	3	Crossover	E2 (2 mg/d) + NEA (1 mg/d)	59 (5)		25	
Sutherland et al. [28]	New Zealand	6	Parallel	CEE (0.625 mg/d) + MPA (2.5 mg/d)	61 (8)	65 (7)	19	28
Kanaya et al. [29]	USA	4.1 y	Parallel	CEE (0.625 mg/d) + MPA (2.5 mg/d)	66.0 (6.3)		353	381
McKenzie et al. [30]	UK	6	Parallel	E2 (1 mg/d) + NE (0.5 mg/d)	61.3 (4.8)	60.7 (5.5)	22	19
Scott et al. [33]	UK	12	Parallel	E2 (2 mg/d) + NEA (1 mg/d)	61 (6)		76	74
Thunell et al. [31]	Sweden	6	Crossover	E2 (2 mg/d) + NEA (1 mg/d)	62 (5.3)		23	
Kernohan et al. [32]	UK	3	Parallel	E2 (1 mg/d) + NE (0.5 mg/d)	62.1 (3.8)	62.2 (5.8)	14	14
Lamon-Fava et al. [34]	USA	3.2 y	Parallel	CEE (0.625 mg/d) + MPA (2.5 mg/d)	64 (7)		27	41

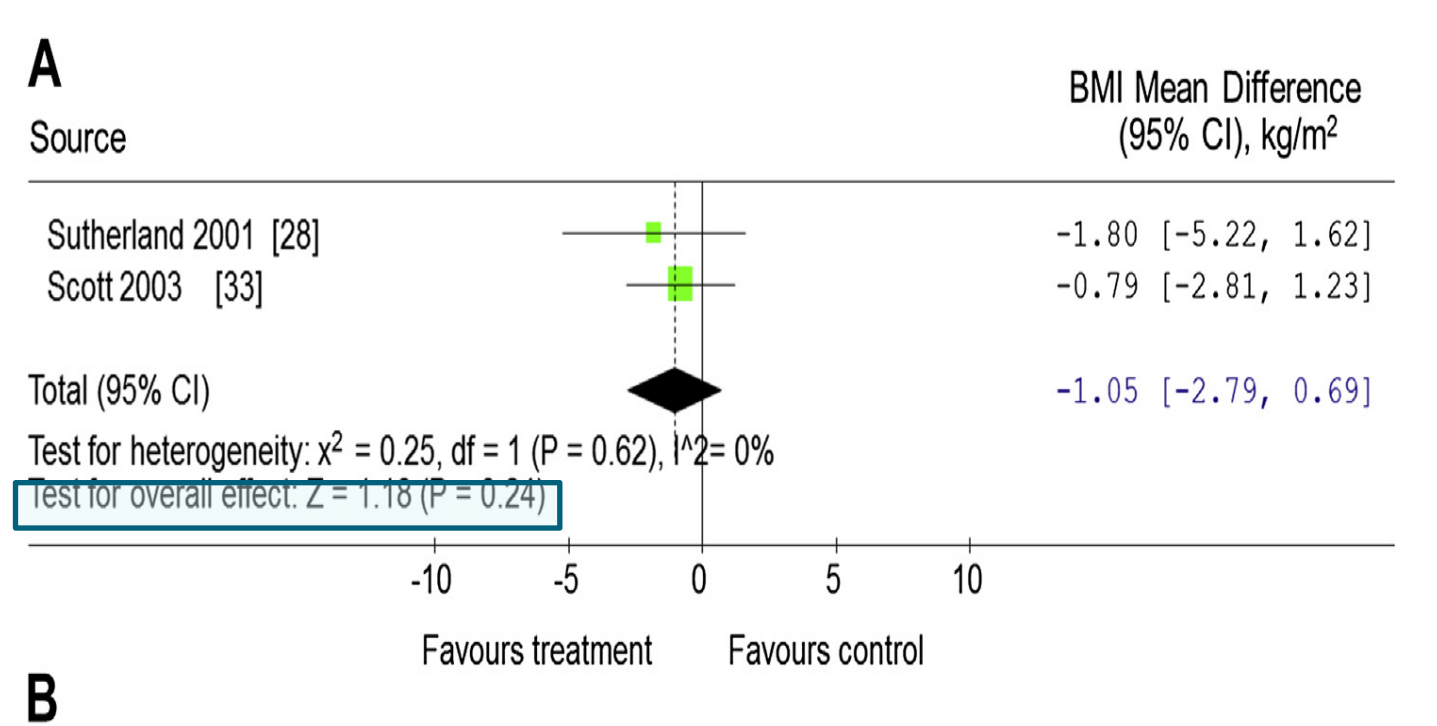
Values are shown as mean (standard deviation).

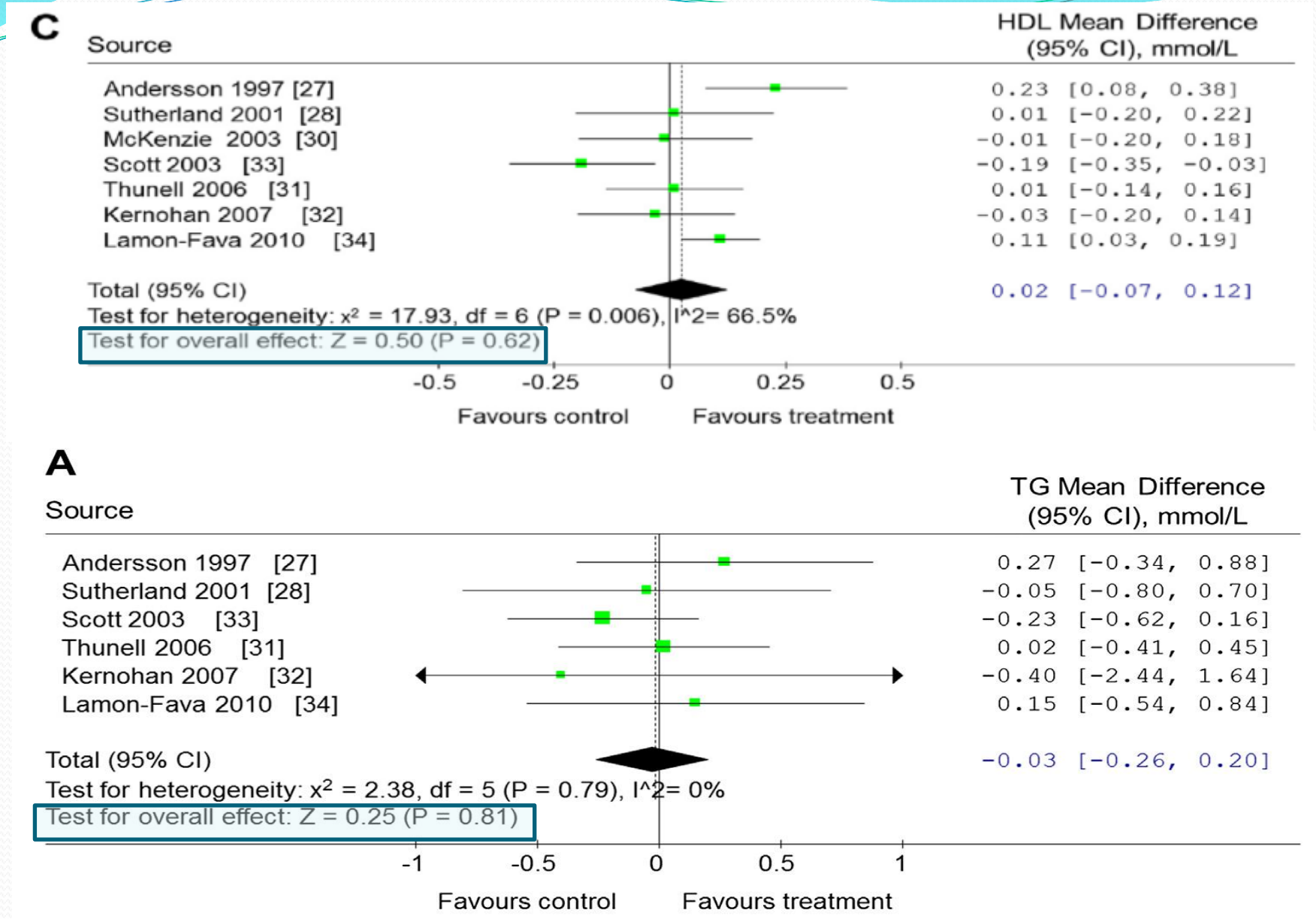
CEE = conjugated equine estrogen; E2 = 17beta-estradiol; MPA = medroxyprogesterone acetate; NE = norethisterone; NEA = norethisterone acetate.



Kaohsiung J Med Sci 2014;30(7):350-361


A
Source
TC Mean Difference
(95% CI), mmol/L
Andersson 1997 [27]
Sutherland 2001 [28]
McKenzie 2003 [30]
Scott 2003 [33]
Thunell 2006 [31]
Kernohan 2007 [32]
Lamon-Fava 2010 [34]
-0.40 [-0.84, 0.04]
-0.17 [-0.96, 0.62]
-0.49 [-1.12, 0.14]
-0.46 [-0.84, -0.08]
0.00 [-0.55, 0.55]
-0.90 [-1.62, -0.18]
-0.14 [-0.56, 0.28]
Total (95% CI)
-0.34 [-0.53, -0.15]
Test for heterogeneity: x² = 5.49, df = 6 (P = 0.48), I^2= 0%
Test for overall effect: Z = 3.50 (P = 0.0005)
-1
-0.5
0
0.5
1
Favours treatment
Favours control
B
Source
LDL Mean Difference
(95% CI), mmol/L
Andersson 1997 [27]
Sutherland 2001 [28]
McKenzie 2003 [30]
Scott 2003 [33]
Thunell 2006 [31]
Kernohan 2007 [32]
Lamon-Fava 2010 [34]
-1.06 [-1.46, -0.66]
-0.11 [-0.65, 0.43]
-0.45 [-1.04, 0.14]
-0.18 [-0.53, 0.17]
-0.05 [-0.58, 0.48]
-0.51 [-1.20, 0.18]
-0.55 [-0.94, -0.16]
Total (95% CI)
-0.43 [-0.71, -0.14]
Test for heterogeneity: x² = 15.16, df = 6 (P = 0.02), I^2= 60.4%
Test for overall effect: Z = 2.92 (P = 0.003)
-1
-0.5
0
0.5
1
Favours treatment
Favours control


A
Source
BMI Mean Difference
(95% CI), kg/m2
Sutherland 2001 [28]
-1.80 [-5.22, 1.62]
Scott 2003 [33]
-0.79 [-2.81, 1.23]
Total (95% CI)
-1.05 [-2.79, 0.69]
Test for heterogeneity: x2 = 0.25, df = 1 (P = 0.62), I^2= 0%
Test for overall effect: Z = 1.18 (P = 0.24)
-10
-5
0
5
10
Favours treatment
Favours control
B



Kaohsiung J Med Sci 2014;30(7):350-361

Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline

Cynthia A. Stuenkel, Susan R. Davis, Anne Gompel, Mary Ann Lumsden, M. Hassan Murad, JoAnn V. Pinkerton, and Richard J. Santen

University of California, San Diego, Endocrine/Metabolism (C.A.S.), La Jolla, California 92093; Monash University, School of Public Health and Preventive Medicine (S.R.D.), Melbourne 03004, Australia; Université Paris Descartes, Hôpitaux Universitaires Port Royal-Cochin Unit de Gynécologie Endocrnienne (A.G.), Paris 75014, France; University of Glasgow School of Medicine (M.A.L.), Glasgow G31 2ER, Scotland; Mayo Clinic, Division of Preventive Medicine (M.H.M.), Rochester, Minnesota 55905; University of Virginia, Obstetrics and Gynecology (J.V.P.), Charlottesville, Virginia 22908; and University of Virginia Health System (R.J.S.), Charlottesville, Virginia 22903

J Clin Endocrinol Metab 2015;100(11):3975-4011

Diabetes. Diabetes is considered by the AHA to be a CHD risk equivalent (40), which would suggest that women with diabetes should not take MHT. However, clinical trial evidence of CVD outcomes associated with MHT in women with diabetes is mostly lacking. Some diabetic women were included in RCTs (Heart and Estrogen/Progestin Replacement Study [19%]; WHI [4.4–7.7%]), but these trials were not powered to assess differences in CVD

J Clin Endocrinol Metab 2015;100(11):3975-4011

outcomes. A few short-term RCTs have evaluated glucose control in diabetic women taking a variety of MHT preparations and showed either no effect or improved control (148). The evidence at this time is inadequate to make firm recommendations. An individualized approach to treating menopausal symptoms could be considered, with a low threshold to recommend nonhormonal therapies, particularly in women with concurrent CVD. However, some diabetic women, after careful evaluation of cardiovascular risk, may be candidates for MHT, preferably transdermal estrogen and micronized progesterone or another less metabolically active progestogen.

J Clin Endocrinol Metab 2015;100(11):3975-4011

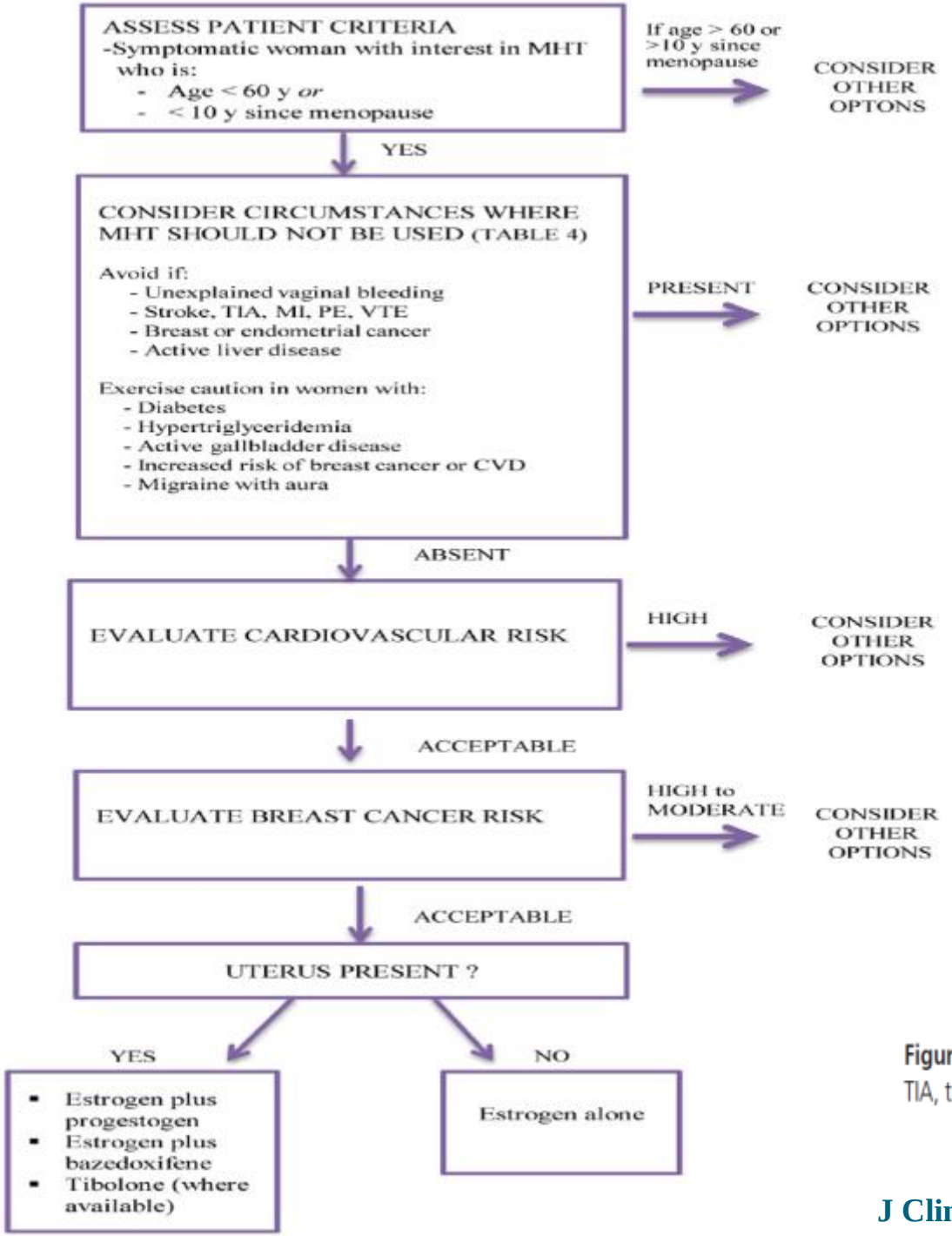


Figure 2. Approach to the patient with VMS contemplating MHT. TIA, transient ischemic attack.

J Clin Endocrinol Metab 2015;100(11):3975-4011

Ante esta paciente las preguntas que nos hacemos son:

1-¿A esta paciente con DM2 y severos síntomas climatéricos que alteran su calidad le indicaría THM?

2-De indicarle THM:

-¿Qué THM le indicaría?

THM EN MUJERES DIABETICAS

A la hora de elegir la THM en mujeres diabéticas se deberá tener en cuenta principalmente el efecto sobre:

- **El perfil lipídico (recordar que poseen dislipemia)**
- **La presión arterial**
- **La sensibilidad a insulina**
- **Los factores de coagulación e inflamatorios (ACV y TEV son más comunes en mujeres DM)**

TERAPIA HORMONAL MENOPAUSICA (THM)

PERFIL LIPIDICO

El efecto de la THM sobre los lípidos depende de:

- **Tipo de estrógeno y de progestágeno**
- **Dosis de estrógeno y de progestágeno**
- **Vía de administración**
- **Forma de administración (cíclica o contínua)**

TERAPIA HORMONAL MENOPAUSICA (THM)

PERFIL LIPIDICO

En términos generales se dice que:

- **Todos los estrógenos tienen efecto benéfico, en mayor o menor grado, sobre el metabolismo lipídico dependiendo principalmente de la ruta de administración**
- **Los progestágenos tienen efecto deletéreo sobre los lípidos, dependiendo de su androgenicidad**

TERAPIA HORMONAL MENOPAUSICA (THM)

ENZIMA "LIPASA HEPATICA"

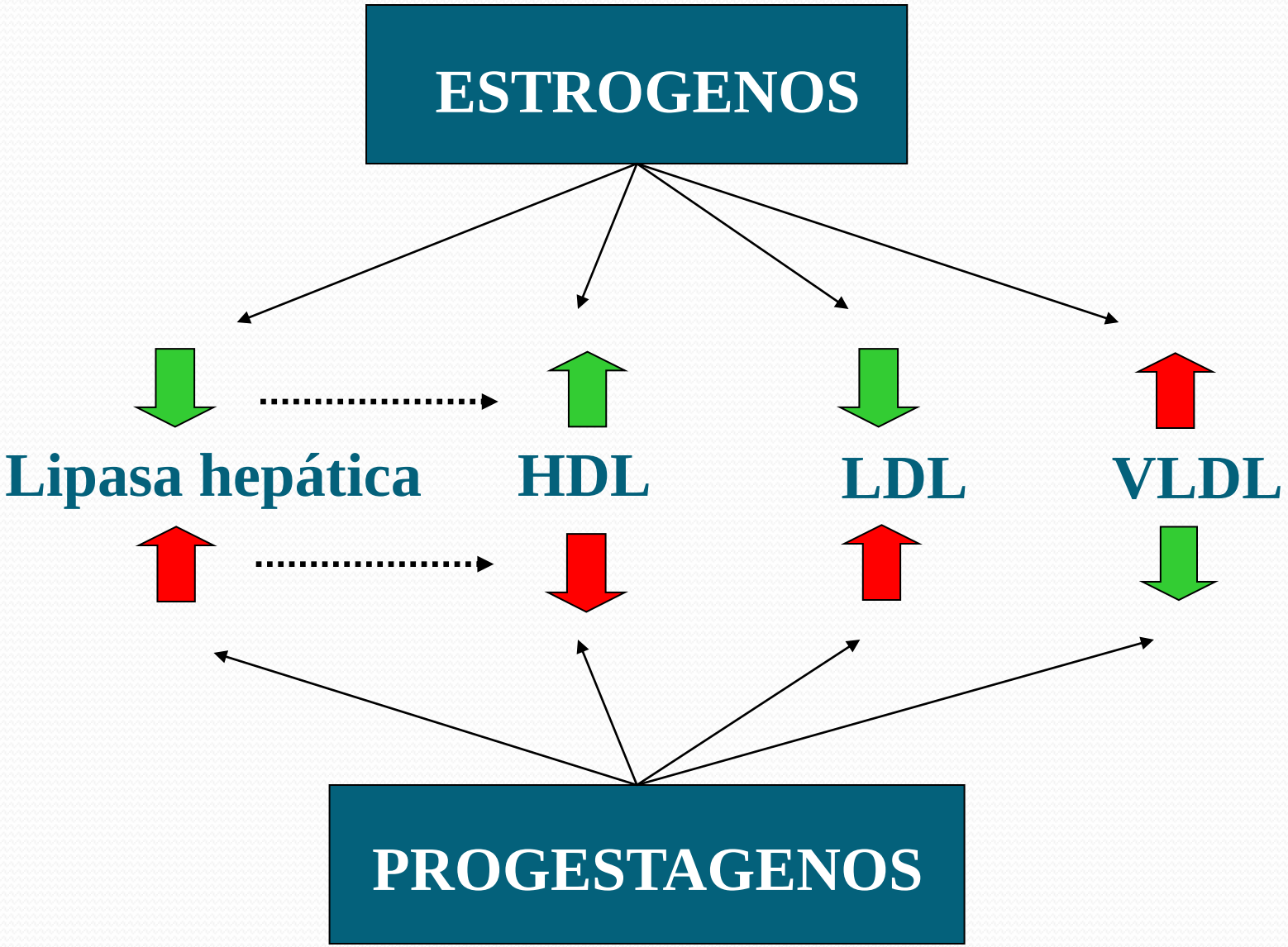
Esta enzima se caracteriza por ser sensiblemente regulada por los esteroides sexuales. Sus funciones son:

- **Cataboliza HDLc2**
- **Transforma VLDLc en LDLc**
- **Transforma IDLc en LDLc**

} **aumentando la LDLc**

- **Origina partículas más densas de** → **LDLc (LDLc p&d)**, **HDLc (HDLc3)**

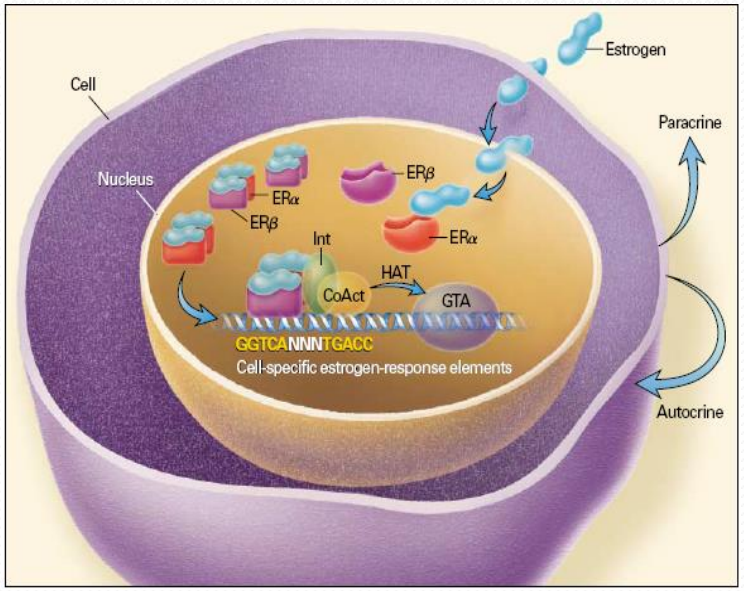
J Clin Endocrinol Metab 2003;88:2404


ESTROGENOS
Lipasa hepática
HDL
LDL
VLDL
PROGESTAGENOS

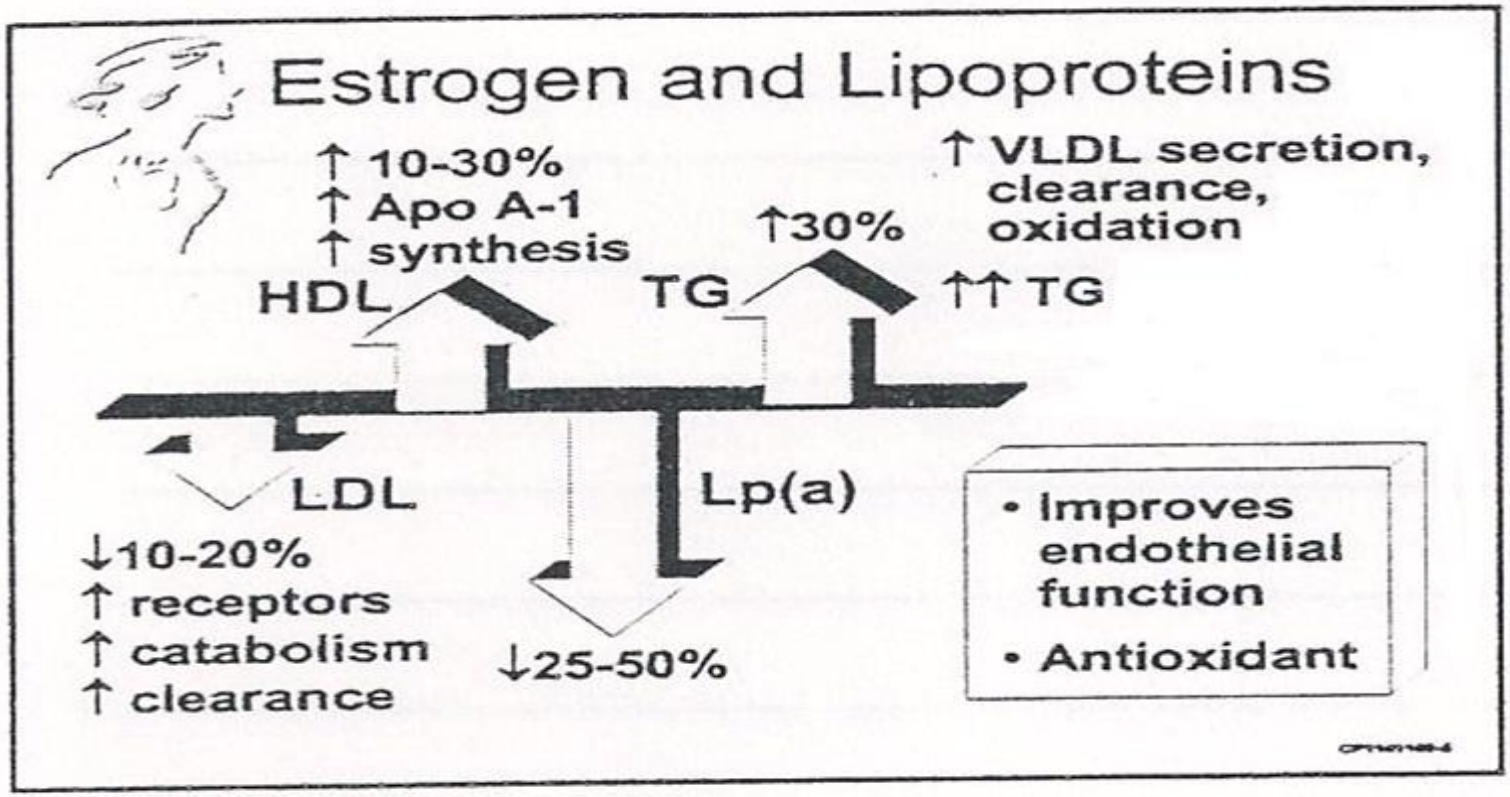
EFECTO DE ESTROGENOS SOBRE LOS LIPIDOS

- ↓ Col t
- ↓ LDLc
- ↓ apo B
- ↑ HDLc
- ↑ HDL_2
- ↑ Apo A_1

“Regulación de la expresión de genes de apoproteínas a nivel hepático a través de ER”



EFECTO DE ESTROGENOS SOBRE LIPIDOS



ESTROGENOS

Vías de administración

VIA ORAL

- ↓↓ col t
- ↑↑ HLDc
- ↓↓LDLc
- ↑ TG (dosis dependiente)
- ↑VLDL

VIA NO ORAL

- ↓ col t
- ↑ HLDc
- ↓LDLc
- No varía o ↓TG
- No varía o ↓ VLDL

Table 1
Hormonal effect of the different progestogens used among postmenopausal women.

Pharmacological class	Molecules	Progestogenic activity	Estrogenic activity	Androgenic activity	Anti-androgenic activity	Gluco-corticoid activity	Anti mineralo-corticoid
Micronised progesterone	Micronised progesterone	+	–	–	±	±	+
Pregnanes	Dydrogesterone	+	–	–	–	–	–
	Medrogestone	+	–	–	–	–	–
	Chlormadinone acetate	++	–	–	+	+	–
	Cyproterone acetate	++	–	–	+++	+	–
	Medroxyprogesterone acetate	+	–	+	–	+	–
Norpregnanes	Nomegestrol acetate	+	–	–	+	–	–
	Promegestone	+	–	–	–	+	–
	Trimegestone	+	–	–	±	–	–
	Nestorone	+	–	–	–	–	–
19 Nortestosterone ethinylated							
Estranes	Norethisterone acetate	++	+	+	–	–	–
Gonanes	Levonorgestrel	++	–	+	–	±	–
	Gestodene	++	–	+	–	±	–
19 Nortestosterone non ethinylated	Dienogest	++	–	–	+	–	–
Spironolactone derivatives	Drospirenone	+	–	–	+	–	++
Tibolone	Tibolone	+	+	++	–	–	–

Maturitas 2011;70(4):354-360

EFECTO DE PROGESTAGENOS SOBRE LIPIDOS

- ↓HDLc
- ↑ LDLc

Estos efectos deletéreos son mayores cuanto mayor actividad androgénica y se evitan con progesterona natural micronizada

Todos los progestágenos tienen la ventaja de ↓ TG y ↓ VLDL

(más cuanto mayor androgenicidad)

Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Interventions (PEPI) Trial.

The Writing Group for the PEPI Trial.

JAMA 1995;273(3):199-208

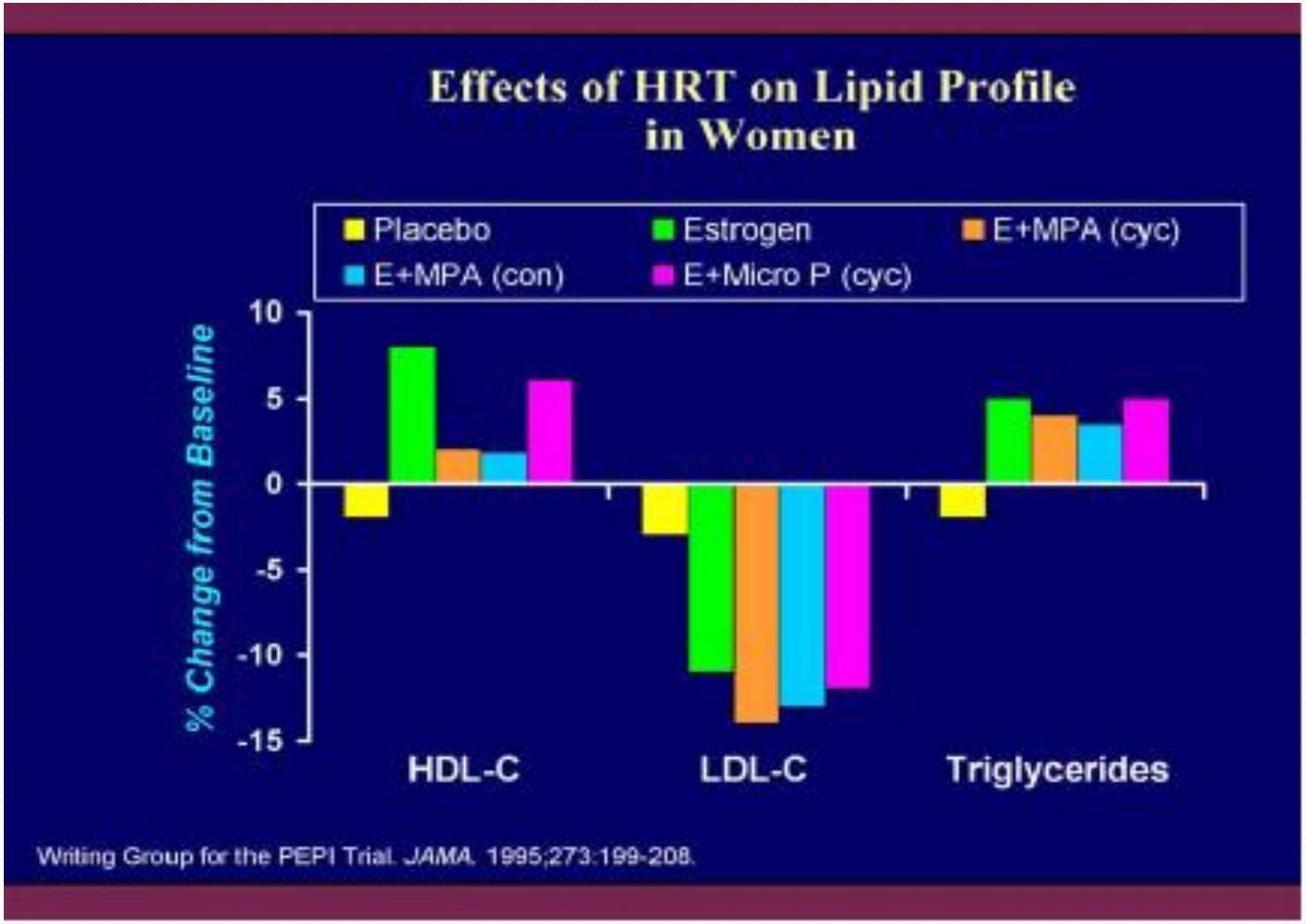
Estudio doble ciego, prospectivo, placebo-control, que se realizó en 7 centros de USA con 875 mujeres postmenopáusicas de 45-64 años seguidas por 3 años que fueron randomizadas a recibir:

- **placebo**
- **EEC 0.625 mg/día**
- **EEC asociado a**
  - **MAP cíclico**
  - **MAP contínuo**
  - **PM cíclica**

Se compararon niveles lipídicos con intervalos de 6 meses durante los 3 años de seguimiento.

JAMA 1995;273(3):199-208

POST MENOPAUSAL ESTROGEN/PROGESTIN INTERVENTION STUDY



Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women

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

JAMA 2002;288:321-333

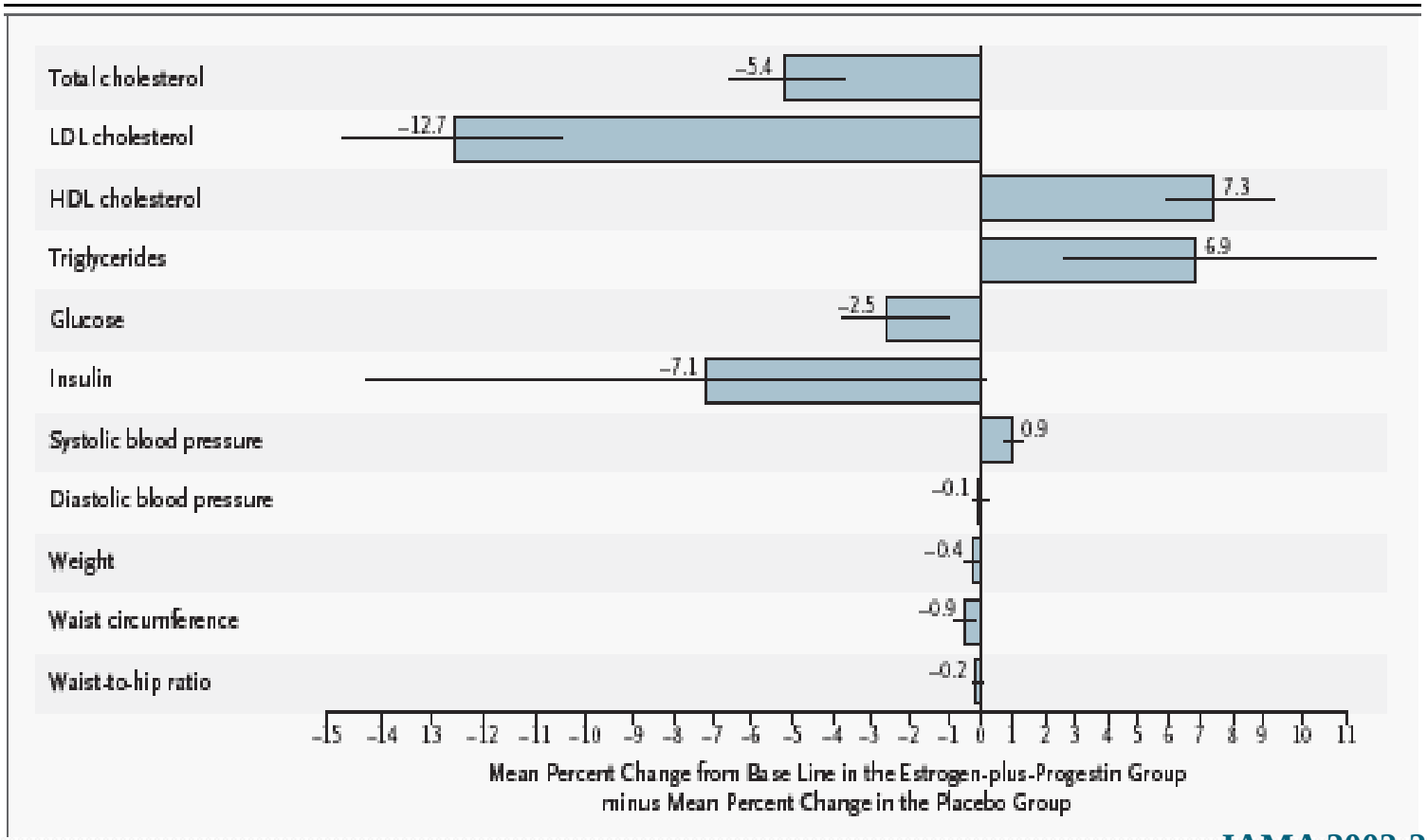
WHI E+P
EFECTO DE LA THM SOBRE LIPIDOS

El tratamiento con 0.625 mg EEC/2.5 mg MAP provocó en relación al placebo:

- ↓ **Colesterol total -5.4%**
- ↓ **LDLc de -12.7%**
- ↑ **HDLc de +7.3%**
- ↑ **TG de +6.9%**

JAMA 2002;288:321-333

WOMEN´S HEALTH INICIATIVE (WHI E+P)



JAMA 2002;288(3):321-333

ESTROGENOS

Vías de administración

VIA ORAL

- ↓↓ col t
- ↑↑ HLDc
- ↓↓LDLc
- ↑ TG (dosis dependiente)
- ↑VLDL
- ⊕ SRA-A (dosis dependiente)

VIA NO ORAL

- ↓ col t
- ↑ HLDc
- ↓LDLc
- No varía o ↓TG
- No varía o ↓ VLDL
- No ⊕ SRA-A

Table 3 Relative potency of various estrogens concerning several clinical (relief of hot flushes) and metabolic parameters (suppression of follicle stimulating hormone (FSH) levels; increase in the serum levels of high density lipoprotein (HDL) cholesterol, sex hormone-binding globulin (SHBG), corticosteroid-binding globulin (CBG) and angiotensinogen). The values are estimated on a weight basis[12–14]

Estrogen	*Hot flushes*	*FSH*	*HDL cholesterol*	*SHBG*	*CBG*	*Angiotensinogen*
Estradiol-17β	100	100	100	100	100	100
Estriol	30	30	20			
Estrone sulfate		90	50	90	70	150
CEE	120	110	150	300	150	500
Equilin sulfate			600	750	600	750
Diethylstilbestrol		340		2 560	2 450	1 950
Ethinylestradiol	12 000	12 000	40 000	50 000	60 000	35 000

CEE, conjugated equine estrogens

Climateric 2005;8(Suppl 1):3-63

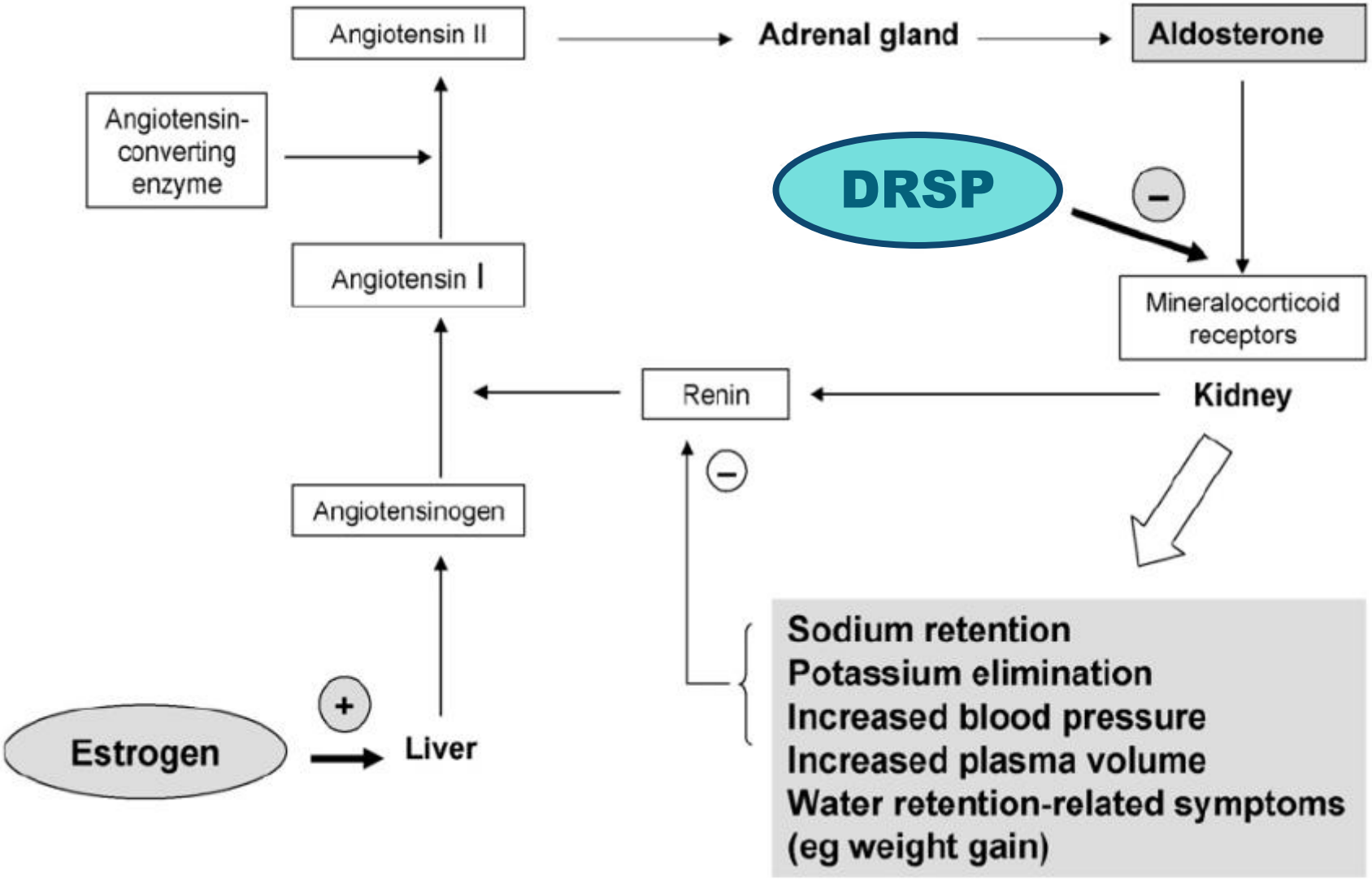
Table 2: **Effect of Postmenopausal Estrogen on Liver Proteins**

Liver Protein Target	ESTROGEN *DELIVERY ROUTE* Transdermal E_2 [a]	Oral E_2 [b]	Oral CEE [c]	Potential Consequences	Ref. example
C-reactive protein	No change	↑	↑	*Risk for atherosclerosis, ischemic stroke*	(56, 190, 407-409)
Lipoproteins					
LDL	↓ or No change	↓	↓	*Anti-atheroma formation*	(83, 407, 408, 410, 411)
HDL	↑ or No change	↑	↑		
Serum amyloid A (SAA)	↓		↑	*Elevated SAA - can promote atherosclerosis, vascular inflammation - may interfere with HDL function*	(195)
Activated protein C resistance	No change	↑	↑	*Increased risk for venous thrombosis*	(100, 101, 412, 413)
GH-induced IGF-1	No change	↓	↓	*Decrease in lean body mass*	(409, 414, 415)
Serum binding proteins					
SHBG	No change	↑	↑	*Change in bioavailability of estrogens, androgens, corticosteroids, and thyroid hormones*	(410, 416, 417)
TBG	No change		↑		
CBG	No change	↑	↑		
Angiotensinogen	No change	↑	↑	*Sodium retention, vasoconstriction*	(410, 418)

[a] 0.05 or 0.10 mg/day [b] 1-2 mg/day [c] 0.625 mg/day

Endocr Rev 2006;27(6):575-605

INFLUENCIA DE THM EN SRA-A



Maturitas 2006;55(4):297-307

INSULINA Y ESTROGENOS

Los estrógenos naturales se caracterizan por:

Esto hace que la menopausia en humanos se asocie con:

1- aumento del riesgo de DM2

2- reducción de la respuesta pancreática de insulina a la glucosa

Ann Endocrinol (Paris) 2003;64:170-177

ESTROGENOS Y SENSIBILIDAD A LA INSULINA

En 1993 Lindheim y colaboradores observaron el llamado *"efecto bimodal"* del EEC

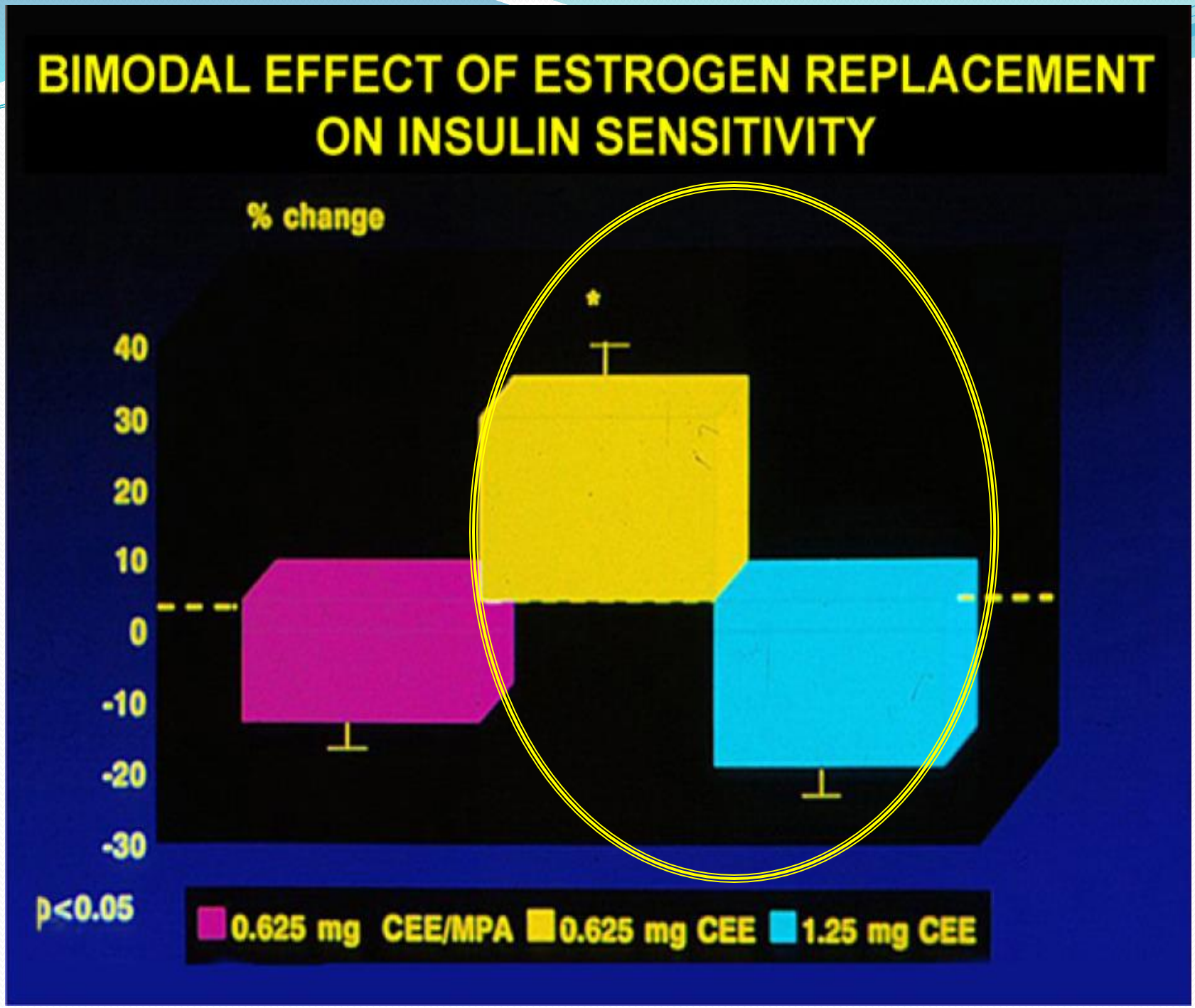
- **0.625 mg/día de EEC mejora sensibilidad a insulina en 25%**
- **1.25 mg/día de EEC desciende la sensibilidad a la insulina aproximadamente 24.7% y deteriora la tolerancia a glucosa**

Ann Endocrinol (Paris) 2003;64:170-177

ESTROGENOS Y SENSIBILIDAD A LA INSULINA

- 1994 Lindheim y col. observaron que el uso de parches de 100 μg/día de estradiol tenía efecto benéfico sobre la sensibilidad a insulina
- 1995 O´Sullivan y col. comparó 1.25 mg/día de EEC con parches de 100 μg/día de estradiol y corroboró los hallazgos previos

Ann Endocrinol (Paris) 2003;64:170-177

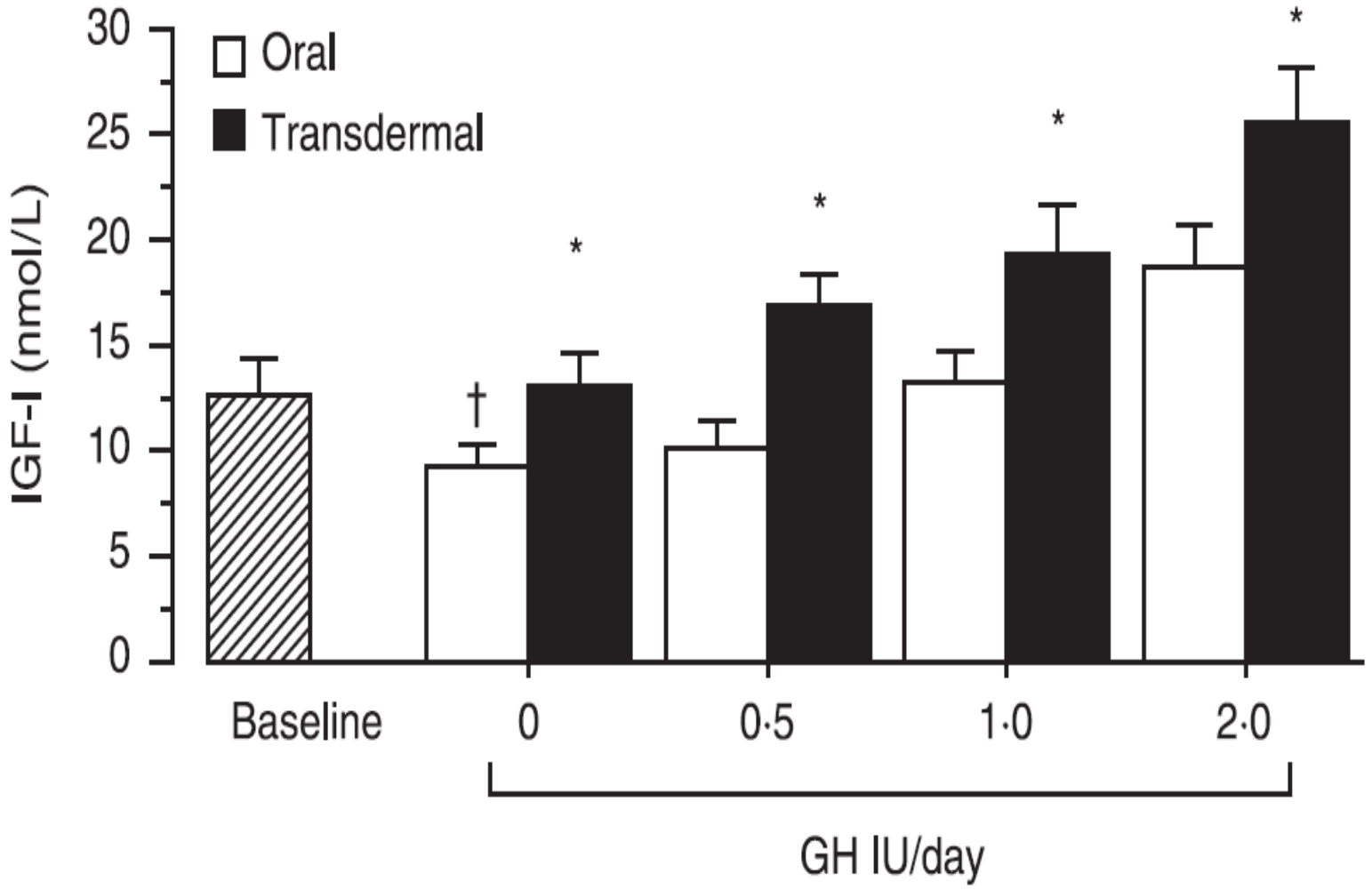

BIMODAL EFFECT OF ESTROGEN REPLACEMENT ON INSULIN SENSITIVITY
% change
40
30
20
10
0
-10
-20
-30
*
p<0.05
0.625 mg CEE/MPA
0.625 mg CEE
1.25 mg CEE

Modulation of growth hormone action by sex steroids

Udo J. Meinhardt and Ken K. Y. Ho

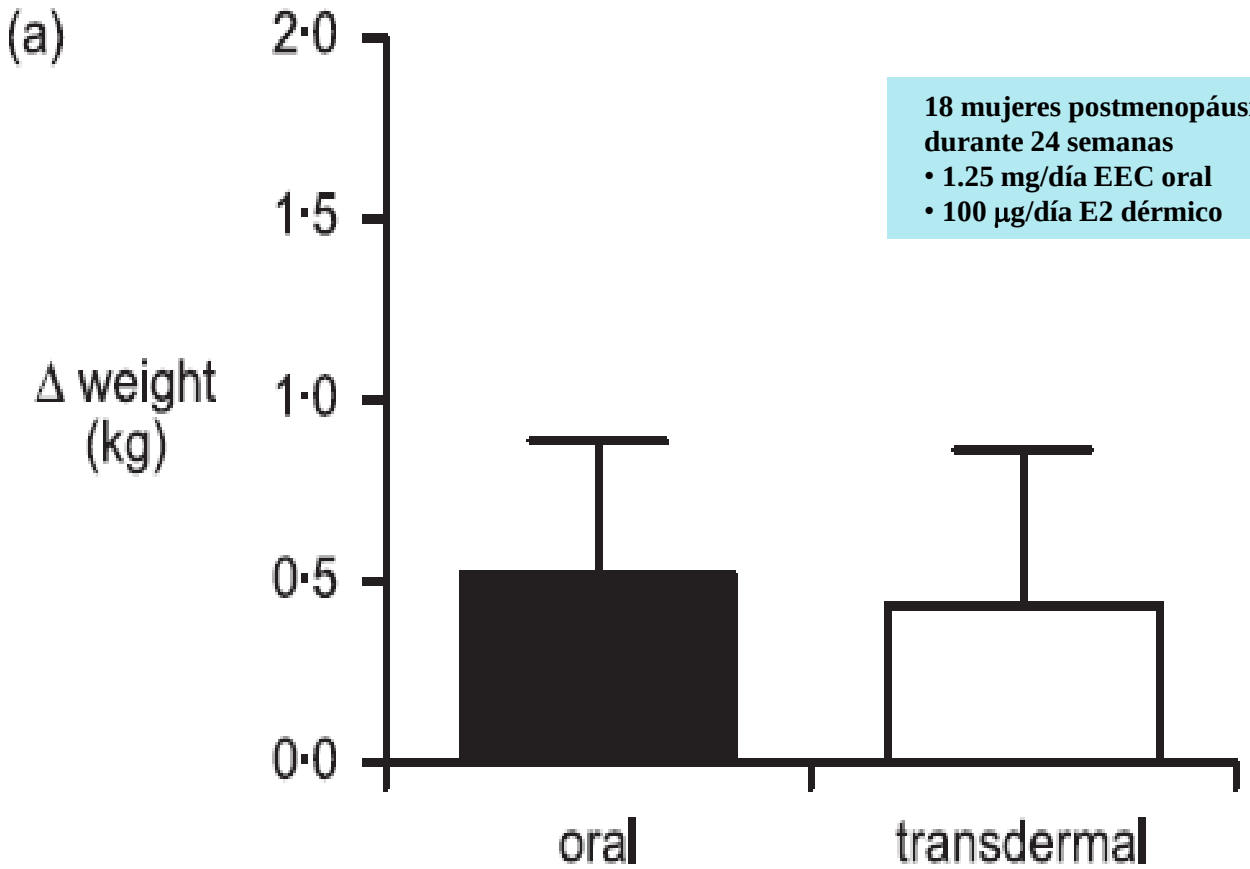
Pituitary Research Unit, Garvan Institute of Medical Research, Sydney, Department of Endocrinology, St Vincent's Hospital, Sydney and University of New South Wales, Sydney, Australia

Clinical Endocrinology 2006;65:413-422



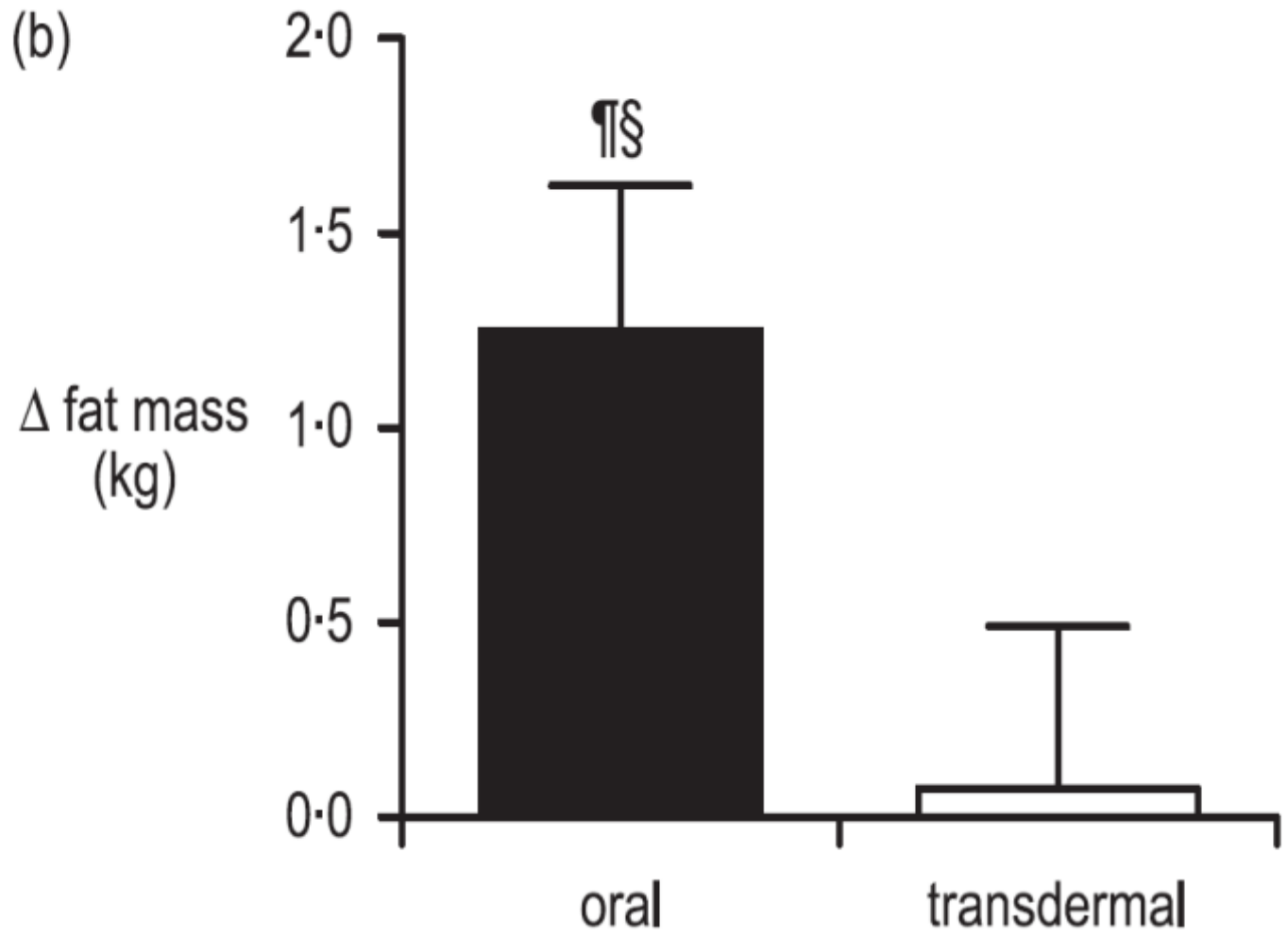
Clinical Endocrinology 2006;65:413-422

ESTROGENOS Y PESO CORPORAL

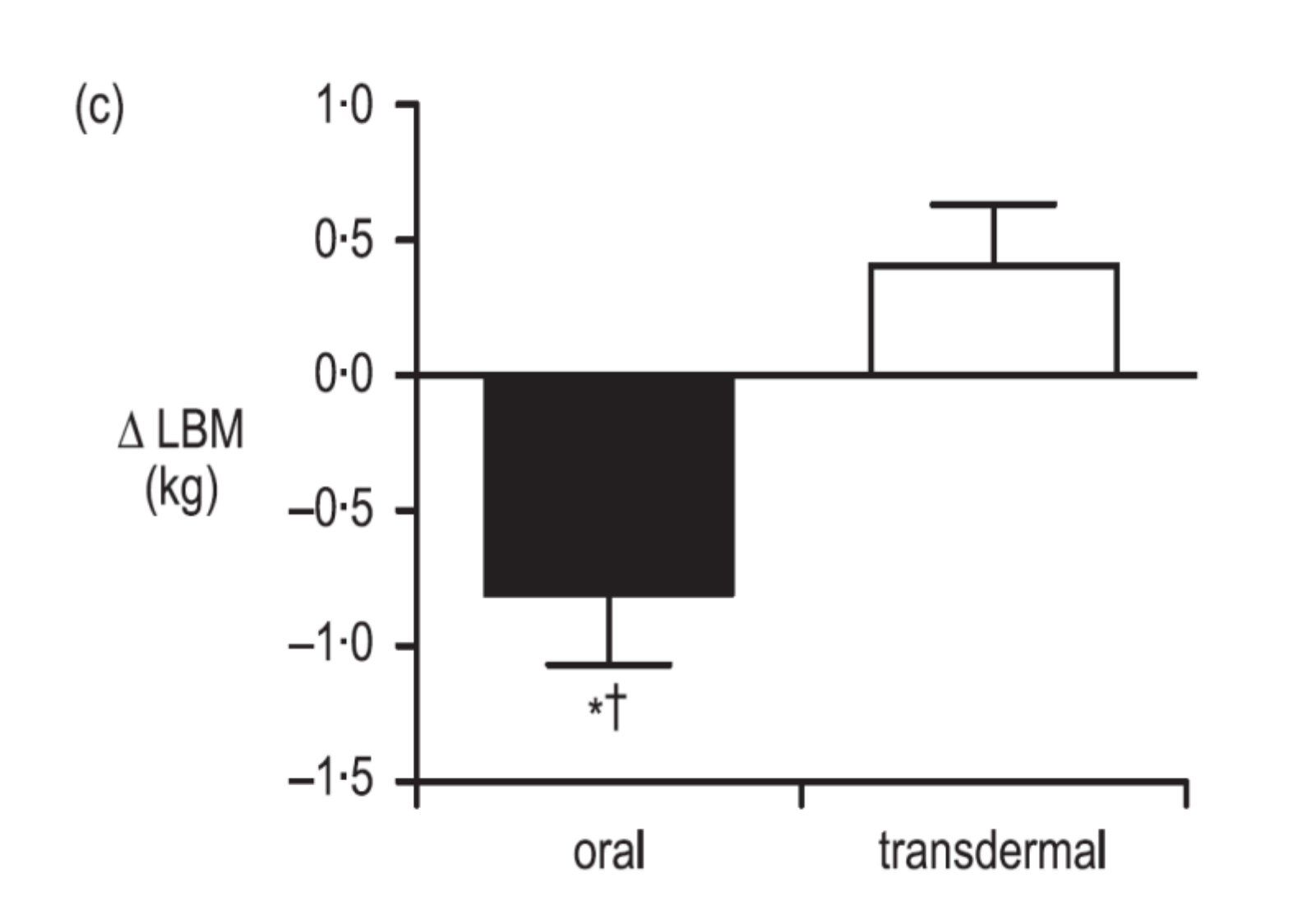


18 mujeres postmenopáusicas recibieron durante 24 semanas
- **1.25 mg/día EEC oral**
- **100 µg/día E2 dérmico**

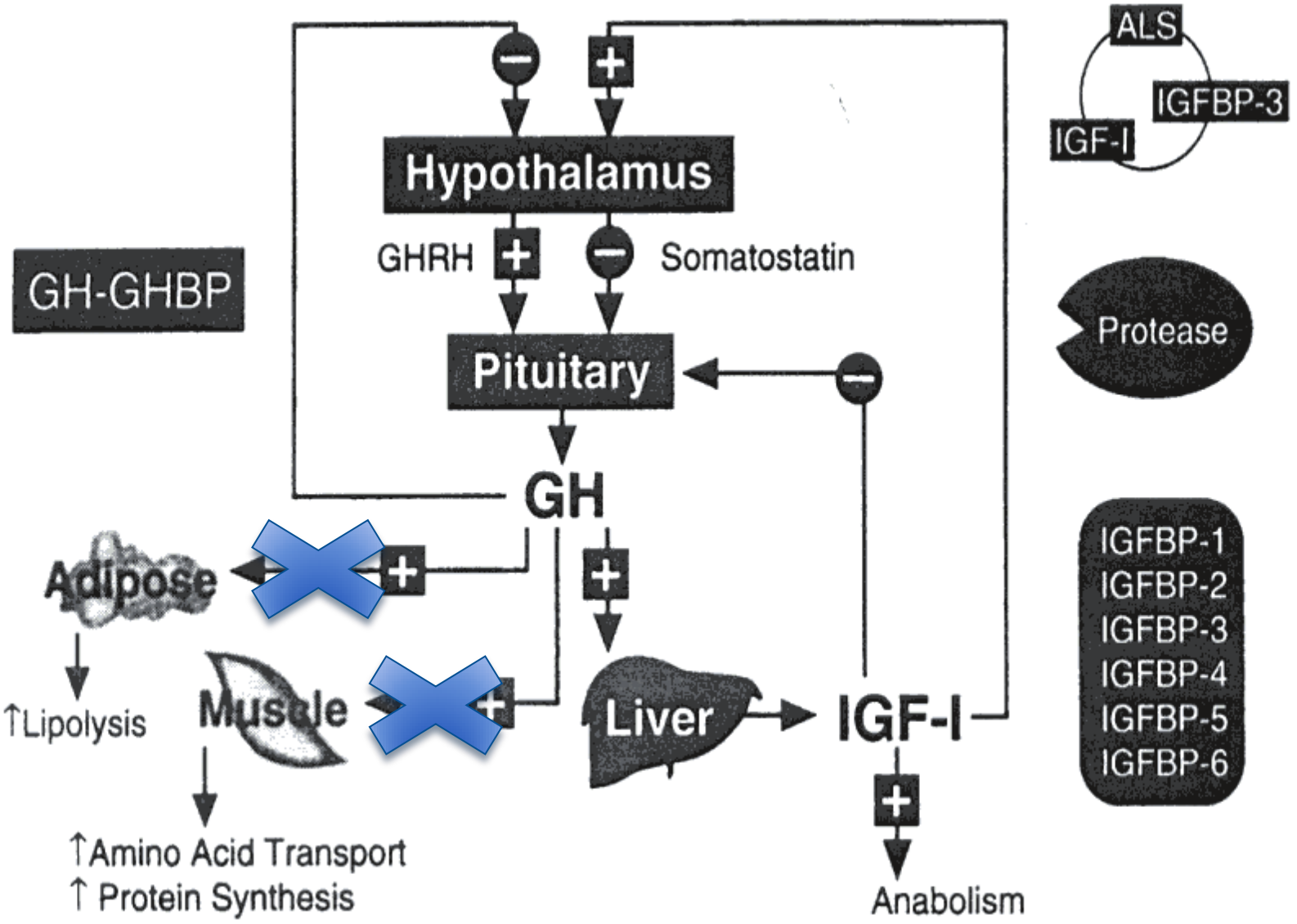
Clinical Endocrinology 2006;65:413-422



Clinical Endocrinology 2006;65:413-422



Clinical Endocrinology 2006;65:413-422


ALS
IGFBP-3
IGF-I
Hypothalamus
GHRH
Somatostatin
GH-GHBP
Protease
Pituitary
GH
Adipose
IGFBP-1
IGFBP-2
IGFBP-3
IGFBP-4
IGFBP-5
IGFBP-6
↑Lipolysis
Muscle
Liver
IGF-I
↑Amino Acid Transport
↑ Protein Synthesis
Anabolism

ORIGINAL ARTICLE

Quantification of the adverse effect of ethinylestradiol containing oral contraceptive pills when used in conjunction with growth hormone replacement in routine practice

Niamh Phelan, Sophy H. Conway, Sofia Llahana and Gerard S. Conway

Department of Endocrinology, University College London Hospitals, London, UK

Se analizaron 88 mujeres premenopáusicas con déficit combinado de GH y estrógeno, de 18 a 47 años, que fueron atendidas en el Hospital Universitario de Londres para comparar las dosis de GH requeridas según tipo de estrógeno administrado.

Clin Endocrinol 2012;76(5):729-733

Table 1. Clinical data for women receiving growth hormone (GH) treatment grouped according to the type of exogenous oestrogen taken. Data expressed as mean (SD) or number [%]. A single asterisk '*' shows the frequency distributions with significant group differences ($P < 0{\cdot}05$)

	None ($n = 31$)	Transdermal HRT ($n = 13$)	Oral HRT ($n = 27$)	Ethinylestradiol ($n = 29$)
Age (years)	31 (9)	33 (9)	31 (9)	28 (7)
Childhood onset	15 [48%]	9 [69%]	13 [48%]	23 [79%]*
Weight (Kgs)	78·7 (21·0)	83·1 (20·8)	75·6 (24·9)	68·7 (18·0)
Isolated growth hormone deficiency	16 [53%]	1 [8%]	1 [4%]	13 [45%]*
Multiple pituitary hormone deficiency	14 [47%]	12 [92%]	26 [96%]	16 [55%]*
Pituitary irradiation	10 [32%]	7 [54%]	17 [63%]	11 [38%]
GH dose (mg/day)	0·58 (0·24)†	0·72 (0·42)†	0·87 (0·52)	1·13 (0·44)‡
Insulin-like growth factor 1 (nmol/l)	32·3 (11·0)	29·8 (15·4)	26·6 (13·5)	23·8 (9·3)
GH responsivity	66·4 (42·1)§	61·4 (49·9)†	40·0 (34·6)¶	24·2 (12·5)‡
GH cost per patient per year	£4,653	£6,258	£8,472	£12,274

†Different from oral HRT and ethinylestradiol. ‡Different from ethinylestradiol. §Different from none. ¶Different from none and transdermal.

Clin Endocrinol 2012;76(5):729-733

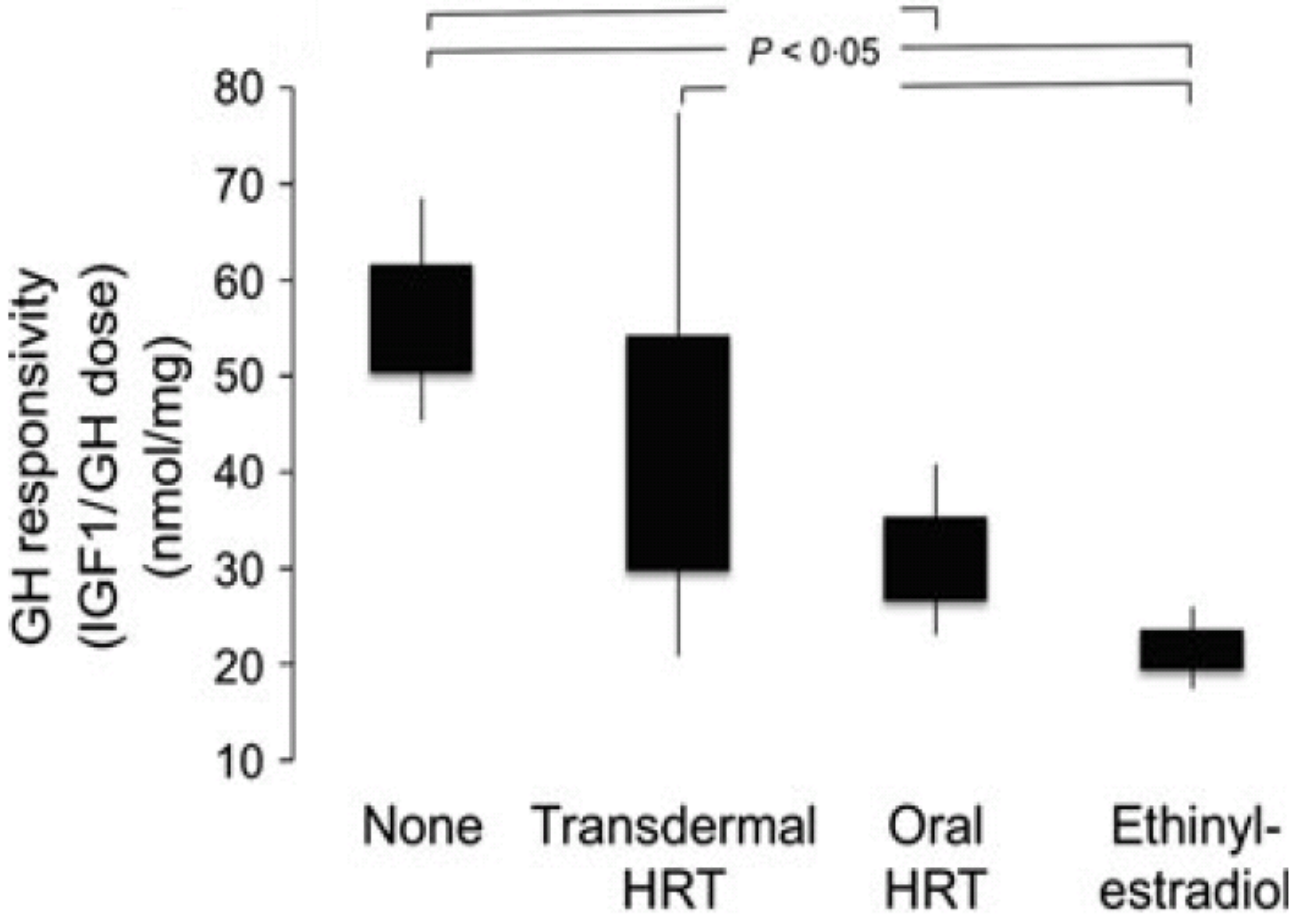


Fig. 1 Dose of growth hormone (GH), Serum IGF-I and GH responsivity (serum IGF-I concentration divided by GH dose) in women receiving GH treatment group by the type of exogenous oestrogen taken concurrently. Data shown as mean ± standard error and 95% confidence intervals.

Clinical Endocrinology 2012;76(5):729-733

Results The daily dose of GH was significantly higher and the GH responsivity was significantly lower in the EE group compared to those taking no oestrogen and transdermal oestrogen. The additional cost of GH for women using EE compared to transdermal oestradiol was £6016 per patient per year. Effectiveness of GH improved in all women changing from EE to another form of oestrogen.

Conclusion Use of oral contraceptive pills containing EE should be avoided in women receiving treatment with GH. Alternative options include oral or transdermal hormone replacement therapy (HRT) preparations for those that require oestrogen replacement or a progesterone-based regimen for contraceptive purposes.

Clin Endocrinol 2012;76(5):729-733

ESTROGENOS Y SENSIBILIDAD A LA INSULINA

Vías de administración

ESTROGENO VIA ORAL

- **inhibe la producción hepática de IGFI que provoca**
- **↑ GH (empeorando la acción de insulina)**
- **↑ cortisol (↑ CBG)**
- **↑ producción de TG**

Diabetología 2005;48:2213-2220

Timing of Estradiol Treatment After Menopause May Determine Benefit or Harm to Insulin Action

R. I. Pereira, B. A. Casey, T. A. Swibas, C. B. Erickson, P. Wolfe, and R. E. Van Pelt

Department of Medicine (T.A.S., C.B.E., R.E.V.P.), Division of Geriatric Medicine; Department of Medicine (R.I.P., B.A.C.), Division of Endocrinology, Metabolism and Diabetes; Colorado School of Public Health, Biostatistics and Informatics (P.W.), University of Colorado Anschutz Medical Campus, Aurora, Colorado 80045

Objective: We hypothesized that the timing of E_2 administration after menopause is an important determinant of its effect on insulin action.

Design: We performed a randomized, crossover, placebo-controlled study.

Participants: Study participants were early postmenopausal (EPM; ≤6 years of final menses; n = 22) and late postmenopausal (LPM; ≥10 years since last menses; n = 24) women naive to HT.

Intervention: Study interventions included short-term (1 week) transdermal E_2 and placebo.

J Clin Endocrinol Metab 2015;100(12):4456-4462

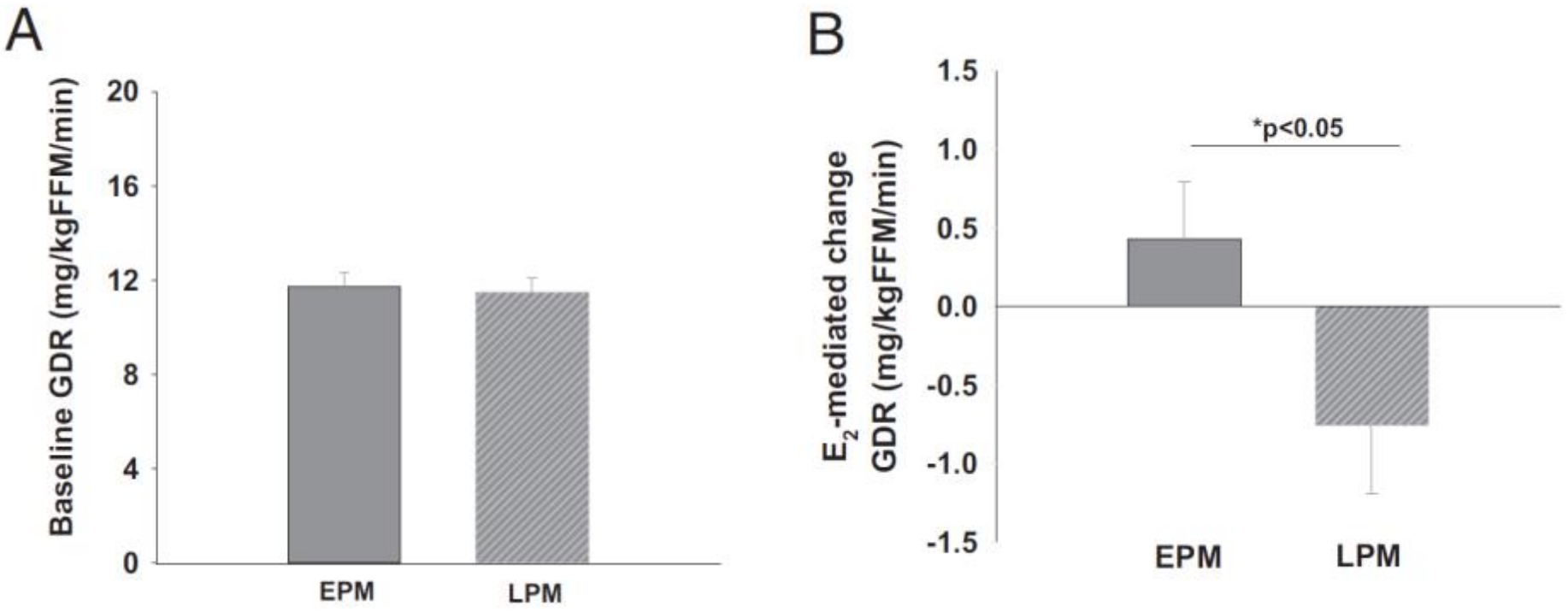


Figure 1. Baseline group differences (A, C) and estradiol (E_2)-mediated changes (B, D) in insulin-stimulated glucose disposal rate (GDR) and insulin-suppressed glycerol (lipolysis EC_{50}) in early postmenopausal (EPM; ≤6 years past menopause) and late postmenopausal (LPM; ≥10 years past menopause) women (mean ± SE).

J Clin Endocrinol Metab 2015;100(12):4456-4462

Discussion

This study is the first to demonstrate that E_2 increases insulin-stimulated glucose disposal when administered to early postmenopausal women (ie, within 6 years of menopause) compared to a decrease when administered to late postmenopausal women (ie, more than 10 years past menopause). These data suggest that the physiologic effect of E_2 on glucoregulatory insulin action (glucose disposal) depends on the timing of treatment relative to menopause. In contrast, the effect of E_2 on antilipolytic insulin action (insulin suppression of lipolysis) did not differ by time since menopause.

J Clin Endocrinol Metab 2015;100(12):4456-4462

Table 1
Hormonal effect of the different progestogens used among postmenopausal women.

Pharmacological class	Molecules	Progestogenic activity	Estrogenic activity	Androgenic activity	Anti-androgenic activity	Gluco-corticoid activity	Anti mineralo-corticoid
Micronised progesterone	Micronised progesterone	+	–	–	±	±	+
Pregnanes	Dydrogesterone	+	–	–	–	–	–
	Medrogestone	+	–	–	–	–	–
	Chlormadinone acetate	++	–	–	+	+	–
	Cyproterone acetate	++	–	–	+++	+	–
	Medroxyprogesterone acetate	+	–	+	–	+	–
Norpregnanes	Nomegestrol acetate	+	–	–	+	–	–
	Promegestone	+	–	–	–	+	–
	Trimegestone	+	–	–	±	–	–
	Nestorone	+	–	–	–	–	–
19 Nortestosterone ethinylated							
Estranes	Norethisterone acetate	++	+	+	–	–	–
Gonanes	Levonorgestrel	++	–	+	–	±	–
	Gestodene	++	–	+	–	±	–
19 Nortestosterone non ethinylated	Dienogest	++	–	–	+	–	–
Spironolactone derivatives	Drospirenone	+	–	–	+	–	++
Tibolone	Tibolone	+	+	++	–	–	–

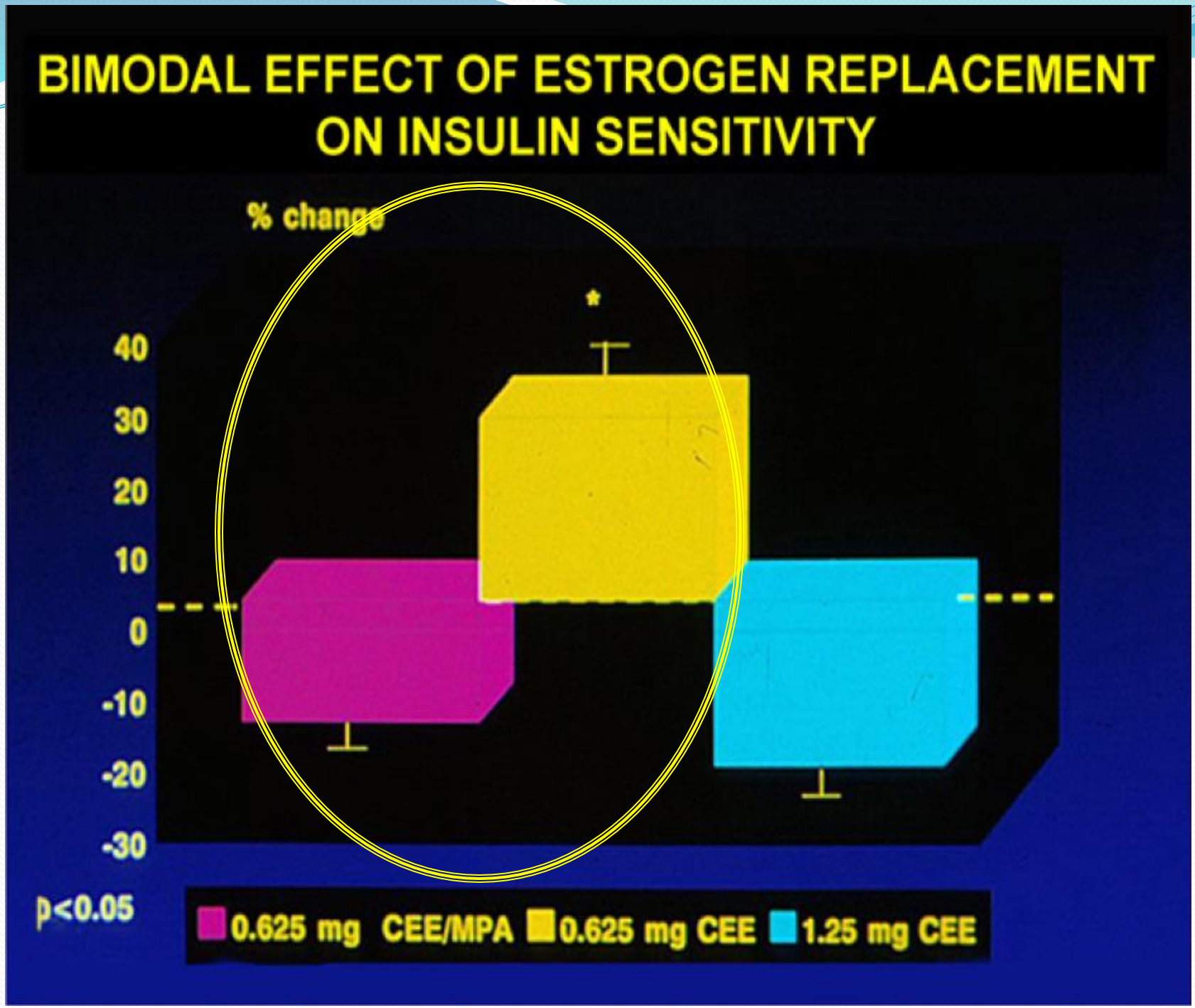
Maturitas 2011;70(4):354-360

PROGESTAGENOS Y SENSIBILIDAD A LA INSULINA

Vías de administración

GESTAGENOS VIA ORAL

- ↓ sensibilidad a la insulina (peor cuanto más androgénico)
- ↓ clearence hepático de insulina (ideal ruta no oral)
- Los más deletéreos son: LNG, MAP y CPA


BIMODAL EFFECT OF ESTROGEN REPLACEMENT ON INSULIN SENSITIVITY
% change
40
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0
-10
-20
-30
*
p<0.05
0.625 mg CEE/MPA
0.625 mg CEE
1.25 mg CEE

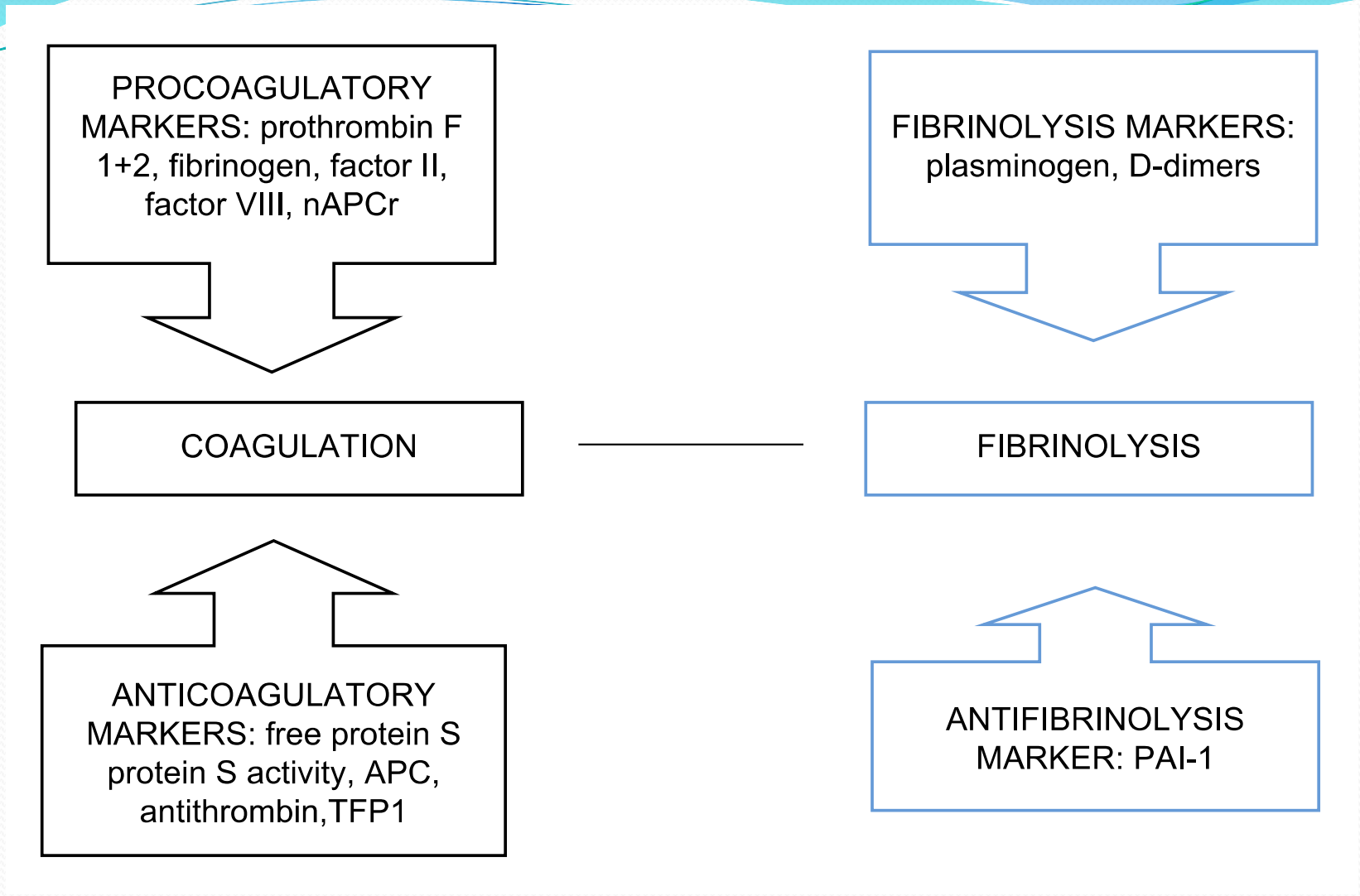


Figure 2 The dynamic balance of haemostasis. Haemostasis is a complex process resulting from a subtle balance between procoagulatory, anticoagulatory, fibrinolysis and antifibrinolysis markers. COCs have multiple effects on this dynamic balance. They alter procoagulant, anticoagulant and fibrinolytic pathways. APC (activated protein C); nAPCr, normalised APC ratio; TFP1, tissue factor pathway inhibition 1; PAI-1: plasminogen activator inhibitor-1.

Eur J Contracept Reprod Health Care 2015;28:1-15

FACTORES DE COAGULACION E INFLAMATORIOS

E VIA ORAL

- ↓ antitrombina III
- ↓ proteína S
- ↑ factor VII, protrombina y fragmento F1 protrombina
- Provoca R adquirida a la proteína C activada

E VIA NO ORAL

- Al igual que el estrógeno oral ↓ fibrinógeno y PAI-1
- No varía antitrombina III, proteína S, factor VII, protrombina ni su fragmento F1
- Menor trombosis que el estrógeno oral

BMJ 2008;336:1227-1230-Maturitas 2008;60(1):10-18

FACTORES DE COAGULACION E INFLAMATORIOS

E VIA ORAL

- ↓ ICAM-1
- ↓ VCAM-1
- ↓ Selectinas (E-selectina)
- ↓ MCP-1
- ↓ Homocisteína
- ↑PCR y MMP-9

E VIA NO ORAL

- ↓ ICAM-1
- ↓ VCAM-1
- ↓ Selectinas (E-selectina)
- ↓ MCP-1
- ↓ Homocisteína
- No varía PCR ni MMP-9
- Menor inflamación que estrógeno oral

BMJ 2008;336:1227-1230-Maturitas 2008;60(1):10-18

Hormone Therapy and Venous Thromboembolism Among Postmenopausal Women

Impact of the Route of Estrogen Administration and Progestogens: The ESTHER Study

TABLE 2. Impact of Hormone Therapy on VTE Risk by Route of Estrogen Administration and Type of Progestogens

	Cases (n=259)	Controls (n=603)	Matched OR (95% CI)		
			Crude	Adjustment 1	Adjustment 2
Nonuse	146	384	1	1	1
Oral estrogen use	45	39	3.6 (1.5–8.8)	4.0 (1.6–10.1)	4.2 (1.5–11.6)
Transdermal estrogen use	67	180	0.8 (0.4–1.6)	0.8 (0.4–1.8)	0.9 (0.4–2.1)
No progestogens	14	40	…	…	…
Micronized progesterone	19	63	1.0 (0.4–2.3)	0.9 (0.4–2.2)	0.7 (0.3–1.9)
Pregnane derivatives	39	79	1.0 (0.4–2.3)	0.9 (0.4–2.2)	0.9 (0.4–2.3)
Norpregnane derivatives	40*	37†	3.8 (1.6–8.7)	4.0 (1.7–9.4)	3.9 (1.5–10.0)

Circulation 2007;115:840-845

FACTORES INFLAMATORIOS Y COAGULACION

El estudio ESTHER reportó un incremento en el RR para el desarrollo de TEV de 3.9 para progestágenos no pregnanos:

"PROMEGESTONA y ACETATO DE NOMEGESTROL"

Esto parece deberse a que estos gestágenos:

1. **Inducen R a la proteína C activada**
2. **Aumentan la actividad protrombina**
3. **Como progestágenos inducen mayor ectasia venosa?**

Circulation 2007;115:840-845

Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women

S. R. Salpeter,[1,2] J. M. E. Walsh,[3] T. M. Ormiston,[2] E. Greyber,[2] N. S. Buckley[4] and E. E. Salpeter[5]

Meta-análisis de los estudios randomizados, controlados, de al menos 8 semanas de duración, publicados entre Abril de 1996 y Octubre del 2004, que evaluaron efecto de la THM sobre los distintos componentes del SM en mujeres postmenopáusicas con y sin DM2.

Diabetes, Obesity Metabol 2006;8:538-554

Table 1 Results for hormone-replacement therapy (HRT) combined, and for transdermal and oral agents, in women without known diabetes

Outcome	HRT – all agents (%)	Transdermal agents (%)	Oral agents (%)	p for interaction
HOMA-IR	−12.9* (−4.9 to −13.7)	−6.8 (−17 to 3.5)	−13.5* (−18.3 to −8.8)	NS
LDL/HDL	−11.0* (−12.3 to −9.6)	−8.4* (−13.8 to −2.8)	−17.4* (−20.0 to −14.9)	0.004*
Triglycerides	2.1 (−0.6 to 4.8)	−6.5 (−14.7 to 1.8)	6.0* (4.3 to 7.6)	0.004*
Lp(a)	−25.0* (−32.9 to −17.1)	−22.8* (−44.4 to −1.2)	−25.1* (−33.2 to −17.1)	NS
Mean BP	−1.7* (−2.9 to −0.5)	−0.8 (−3.3 to 1.6)	−2.2* (−4.1 to −0.3)	NS
CRP	37.7* (17.4 to 61.3)	2.0 (−23.0 to 34.0)	47.0* (29.0 to 67.0)	0.02*
E-selectin	−17.3* (−22.4 to −12.1)	−6.0 (−19.8 to 7.9)	−18.6* (−23.9 to −13.3)	NS
Fibrinogen	−5.5* (−7.8 to −3.2)	−4.7* (−7.6 to −1.8)	−5.8* (−8.7 to −2.8)	NS
PAI-1 antigen	−25.1* (−33.6 to −15.5)	−3.0 (−23.0 to 35.0)	−27.0* (−38.0 to −22.0)	0.03*
Protein C	−0.8 (−4.2 to 2.6)	−1.2 (−7.4 to 5.1)	−1.7 (−7.0 to 3.7)	NS
Protein S	−4.8 (−10.7 to 1.2)	−2.2 (−9.9 to 5.6)	−8.6* (−13.1 to −4.1)	0.01*

Diabetes, Obesity Metabol 2006;8:538-554

La THM en mujeres sin DM2 produjo:

- *Reducción de la obesidad abdominal*
- *Descenso de IR*
- *Descenso del núme*
- *Mejoría del*
  dese

“Esto significa que la THM aportó mayor beneficio en las mujeres sin DM2 comparadas con mujeres con DM2”

L jeres DM2 sólo provocó:

- *cción de IR*
- *Descenso de glucemia en ayuno*

Diabetes, Obesity Metabol 2006;8:538-554

THM comparada con placebo o ausencia de tratamiento:

- ↑HDLc 5.1%
- ↓LDLc 11%
- ↓relación LDL/HDL 15.7%
- ↓Lp(a) 25%
- ↑TG 2.1% (no significativo)
- Reducción de la grasa abdominal (6.8%)
- Descenso de IR (12.9%)
- Mejoría del perfil lipídico, de moléculas de adhesión y descenso de factores procoagulantes
- Descenso de la T.A.
- Descenso del número de casos nuevos de DM2

Diabetes, Obesity Metabol 2006;8:538-554

INCIDENCIA DE DM2 Y THM

La menor incidencia de DM2 con THM se debe a:

- ***Efecto directo sobre páncreas y músculo esquelético*:**
  - **efecto directo sobre células β aumentando secreción de insulina en respuesta a la glucosa**
  - **aumentando la eliminación de insulina**
  - **aumentando la sensibilidad a la insulina**
- ***Efecto indirecto*: Al disminuir la acumulación de grasa total y principlamente central**

Diabetología 2005;48:2213-2220

Effect of climacteric transition and hormone replacement therapy on body weight and body fat distribution

ANDREA RICCARDO GENAZZANI & MARCO GAMBACCIANI

Department of Obstetrics and Gynecology, University of Pisa, Pisa, Italy

Gynecol Endocrinol 2006;22(3):145-150

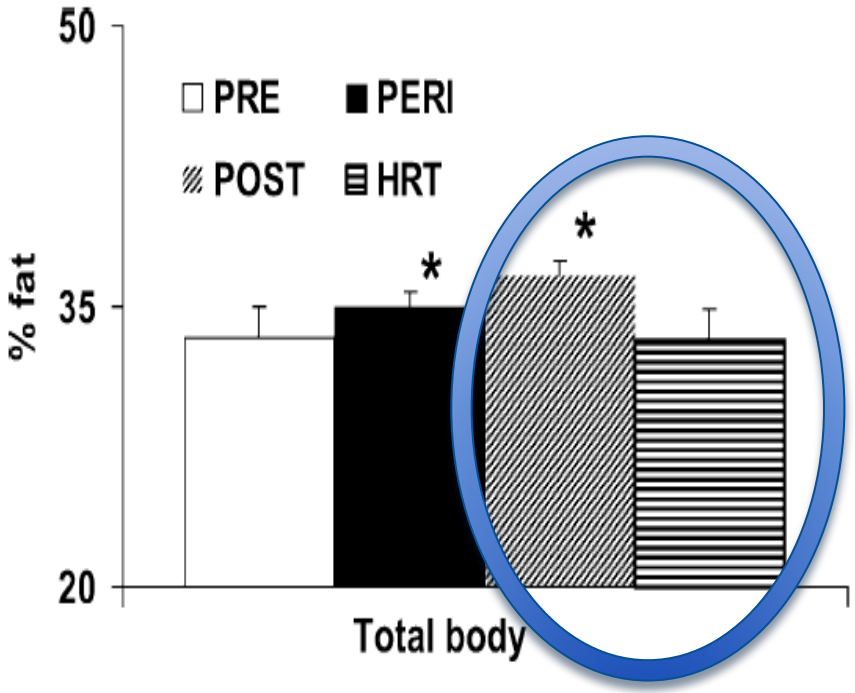
Table I. Selected characteristics (mean ± standard error, range in brackets) in normal cycling (premenopausal), oligomenorrheic (perimenopausal) and postmenopausal women, and postmenopausal women treated with hormone replacement therapy (HRT).

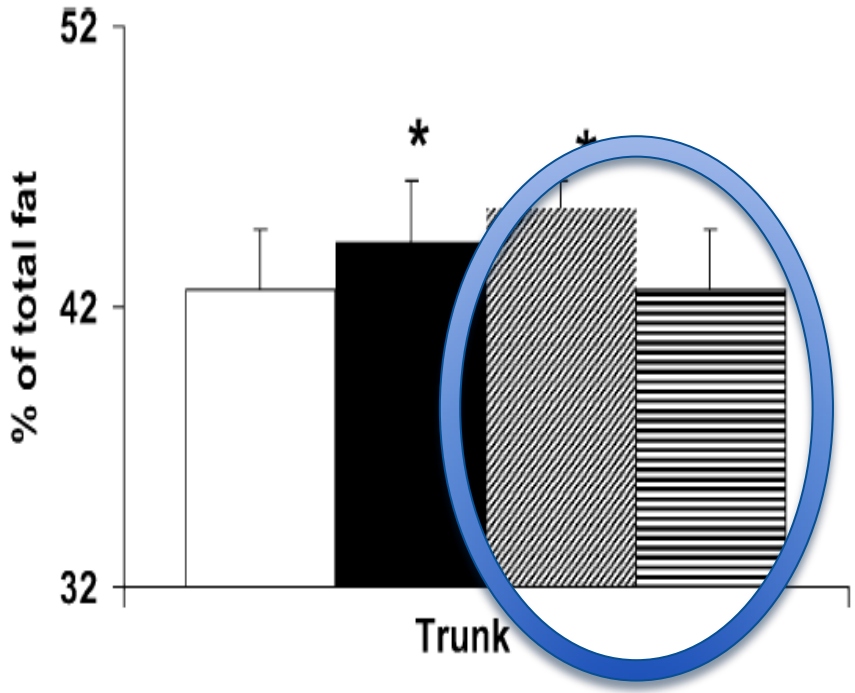
	Premenopause ($n = 540$)	Perimenopause ($n = 750$)	Postmenopause ($n = 885$)	HRT ($n = 354$)
Age (years)	42.3 ± 0.4 (25–53)	46.8 ± 0.2* (39–55)	53.0 ± 0.2* (42–70)	53.0 ± 0.2* (42–65)
Weight (kg)	60.9 ± 0.4 (43–89)	63.6 ± 0.6* (44–90)	64.3 ± 0.5* (42–86)	63.3 ± 0.5 (45–82)
Height (cm)	162.7 ± 0.3 (145–187)	161.8 ± 0.4 (145–178)	161.3 ± 0.3 (145–180)	160.3 ± 0.3 (149–186)
Body mass index (kg/m^2)	23.4 ± 0.2 (19.0–29.0)	24.1 ± 0.2* (20.5–30.5)	26.5 ± 0.2* (19.2–30.9)	24.5 ± 0.2 (20.2–31.0)
Follicle-stimulating hormone (U/l)	9.3 ± 3.8	27.7 ± 5.5*	59.7 ± 3.5**	–
Estradiol (ng/ml)	80.3 ± 10.8	45.5 ± 8.5*	23.5 ± 6.5**	–
Cycle length (days)	30.0 ± 5.0	65.0 ± 5.0*	–	–

*$p < 0.05$ vs. corresponding premenopause value; **$p < 0.05$ vs. corresponding perimenopause and premenopause values.

Gynecol Endocrinol 2006;22(3):145-150

Effect of climacteric transition and hormone replacement therapy on body weight and body fat distribution





Gynecol Endocrinol 2006;22(3):145-150

Table 1 Prospective studies of postmenopausal oestrogen hormone replacement therapy (HRT) and oral contraceptive therapy on the incidence of diabetes

Study	Design	Treatment	Women–years of observation	Current users' relative risk (95% CI)
Nurses' Health Study, Manson et al. 1992 [25]	Observational 12-year follow-up of US occupation-based cohort	Any HRT	422,991	0.80 (0.67–0.96) (age- and BMI-adjusted)
Hammond et al. 1979 [26]	Retrospective observational follow-up of hypo-oestrogenic women in US hospital clinic	Any HRT	3844	0.29 (0.14–0.60) (unadjusted: non-significant after adjustment for weight)
Rancho Bernardo Health and Chronic Diseases Study, Gabal et al. 1997 [27]	Observational 11.5-year follow-up of US community-based cohort	HRT	9752	0.83 (0.43–1.63) (age-adjusted), 1.12 (0.56–1.37) (age- and BMI-adjusted)
STRONG Heart Study, Zhang et al. 2002 [28]	Observational 4-year follow-up of Native American communities cohort	Any HRT	3428	0.66 (0.39–1.12) (unadjusted), 1.11 (0.62–1.97) (adjusted)
Heart Estrogen Replacement Study, Kanaya et al. 2003 [5]	Randomised placebo-controlled trial of HRT in secondary prevention of cardiovascular disease in US postmenopausal women, with 5.7 years' follow-up	0.625 mg/day conjugated equine oestrogens plus 2.5 mg/day medroxyproges-terone acetate	15,749	0.65 (0.48–0.89)
Women's Health Initiative, Margolis et al. 2004 [6]	Randomised placebo-controlled trial of HRT in primary prevention of cardiovascular disease in US postmenopausal women, with 5.2 years' follow-up	0.625 mg/day conjugated equine oestrogens plus 2.5 mg/day medroxyproges-terone acetate	81,333	0.79 (0.67–0.94)

Diabetología 2005;48:2213-2220

Glycemic Effects of Postmenopausal Hormone Therapy: The Heart and Estrogen/progestin Replacement Study

A Randomized, Double-Blind, Placebo-Controlled Trial

Alka M. Kanaya, MD; David Herrington, MD, MHS; Eric Vittinghoff, PhD; Feng Lin, MS; Deborah Grady, MD, MPH; Vera Bittner, MD, MSPH; Jane A. Cauley, DrPH; and Elizabeth Barrett-Connor, MD

El objetivo del estudio fue evaluar efecto de la THM sobre glucemia en ayuno e incidencia de DM2. Se realizó determinación de glucemia basal y a 1- 4 años del estudio.

Ann Intern Med 2003;138:1-9

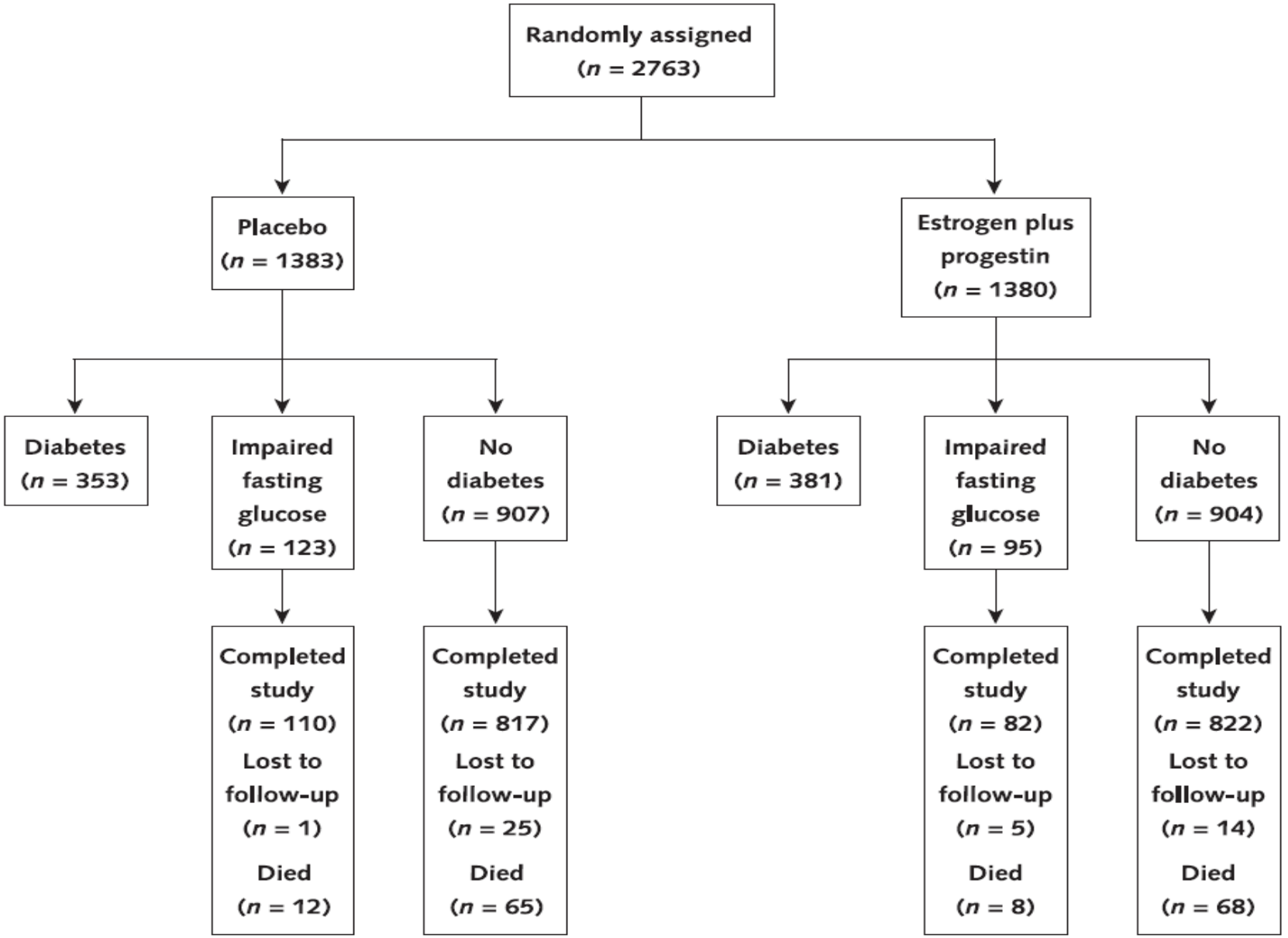

Randomly assigned
(n = 2763)
Placebo
(n = 1383)
Estrogen plus progestin
(n = 1380)
Diabetes
(n = 353)
Impaired fasting glucose
(n = 123)
No diabetes
(n = 907)
Diabetes
(n = 381)
Impaired fasting glucose
(n = 95)
No diabetes
(n = 904)
Completed study
(n = 110)
Lost to follow-up
(n = 1)
Died
(n = 12)
Completed study
(n = 817)
Lost to follow-up
(n = 25)
Died
(n = 65)
Completed study
(n = 82)
Lost to follow-up
(n = 5)
Died
(n = 8)
Completed study
(n = 822)
Lost to follow-up
(n = 14)
Died
(n = 68)

Table 3. **Effect of Treatment Assignment on Fasting Serum Glucose Level***

Diabetes Status	Participants	Visit	Fasting Serum Glucose Level		Between-Group Difference (95% CI)
			Hormone Therapy Group	Placebo Group	
	n		← *mg/dL* →		
Normal	1811	Baseline	94.2 ± 7.7	94.6 ± 7.4	0.3 (−0.4 to 1.0)
		Year 1	94.3 ± 10.0	96.7 ± 10.3	2.4 (1.4 to 3.3)
		End of trial	96.3 ± 14.5	98.7 ± 14.5	2.4 (1.0 to 3.8)
Impaired fasting glucose	218	Baseline	115.6 ± 4.5	115.1 ± 4.1	−0.5 (−1.6 to 0.7)
		Year 1	111.9 ± 15.2	115.2 ± 30.2	3.3 (−3.5 to 10.2)
		End of trial	112.4 ± 20.3	125.8 ± 42.5	13.4 (3.3 to 23.4)
Diabetes	734	Baseline	152.7 ± 48.7	157.5 ± 48.2	4.7 (−2.3 to 11.7)
		Year 1	154.9 ± 58.0	170.4 ± 64.1	15.6 (6.4 to 24.8)
		End of trial	153.7 ± 57.9	165.1 ± 63.2	11.4 (1.7 to 21.0)
Overall	2763	Baseline	111.9 ± 36.9	112.4 ± 36.8	0.6 (−2.2 to 3.3)
		Year 1	111.9 ± 41.1	117.0 ± 46.7	5.1 (1.7 to 8.5)
		End of trial	112.4 ± 40.8	117.2 ± 45.4	4.8 (1.4 to 8.3)

* Values with plus/minus signs are means ± SD. To convert mg/dL to mmol/L, multiply by 0.0555.

Ann Intern Med 2003;138:1-9

INCIDENCIA DE DM2 A LOS 4 AÑOS DEL SEGUIMIENTO:

De 2029 mujeres del HERS con enfermedad cardiovascular previa pero sin DM2 al basal desarrollaron la enfermedad:

- **6.2% en mujeres con THM**
- **9.5% en mujeres con placebo**

} **p=0.006**

HERS reveló reducción del 35% de incidencia de DM2 en las mujeres asignadas a THM en comparación con las que recibieron placebo

Ann Intern Med 2003;138:1-9

Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial

K. L. Margolis[1, 9] · D. E. Bonds[2] · R. J. Rodabough[3] · L. Tinker[3] · L. S. Phillips[4] · C. Allen[5] · T. Bassford[6] · G. Burke[2] · J. Torrens[7] · B. V. Howard[8] · for the Women's Health Initiative Investigators

El objetivo del estudio fue evaluar los efectos de la THM (E/P) sobre la incidencia de DM2 y valorar la IR en mujeres del WHI. Se determinó glucemia, insulina y HOMA.

Diabetologia 2004;47:1175-1187

Table 2. Baseline and follow-up measurements in non-diabetic women randomised to oestrogen plus progesterone or placebo in the Women's Health Initiative[a]

	Oestrogen + Progestin			Placebo			Difference	(SE)	*p* value[b]
	n	Mean	(SD)	*n*	Mean	(SD)			
Glucose (mmol/l)									
Baseline	699	5.33	(0.71)	660	5.35	(0.99)	−0.02	(0.05)	0.63
Year 1 to baseline	635	−0.12	(0.64)	592	−0.01	(0.70)	−0.11	(0.04)	<0.01
Year 3 to baseline	547	−0.12	(0.62)	507	−0.04	(0.92)	−0.08	(0.05)	0.15
Insulin (mU/l)									
Baseline	672	11.20	(5.65)	643	10.63	(5.70)	0.57	(0.35)	0.11
Year 1 to baseline	603	−0.33	(5.80)	564	0.32	(4.27)	−0.65	(0.34)	0.05
Year 3 to baseline	496	0.76	(5.82)	472	1.63	(6.36)	−0.87	(0.43)	0.04
HOMA-IR									
Baseline	672	2.73	(1.59)	642	2.63	(1.97)	0.10	(0.11)	0.37
Year 1 to baseline	602	−0.16	(1.48)	562	0.05	(1.52)	−0.22	(0.10)	0.03
Year 3 to baseline	496	0.12	(1.57)	472	0.35	(2.00)	−0.23	(0.13)	0.08

Diabetologia 2004;47:1175-1187

INCIDENCIA DE DM2 A LOS 5.2 AÑOS DEL SEGUIMIENTO:

Se observó desarrollo de DM2 en el:

- **3.5% de mujeres con THM**
- **4.2% de mujeres con placebo**

} **p=0.004**

WHI E-P reveló reducción del 21% en la incidencia de DM2 en las mujeres randomizadas a THM en comparación con las mujeres que recibieron placebo

Diabetologia 2004;47:1175-1187

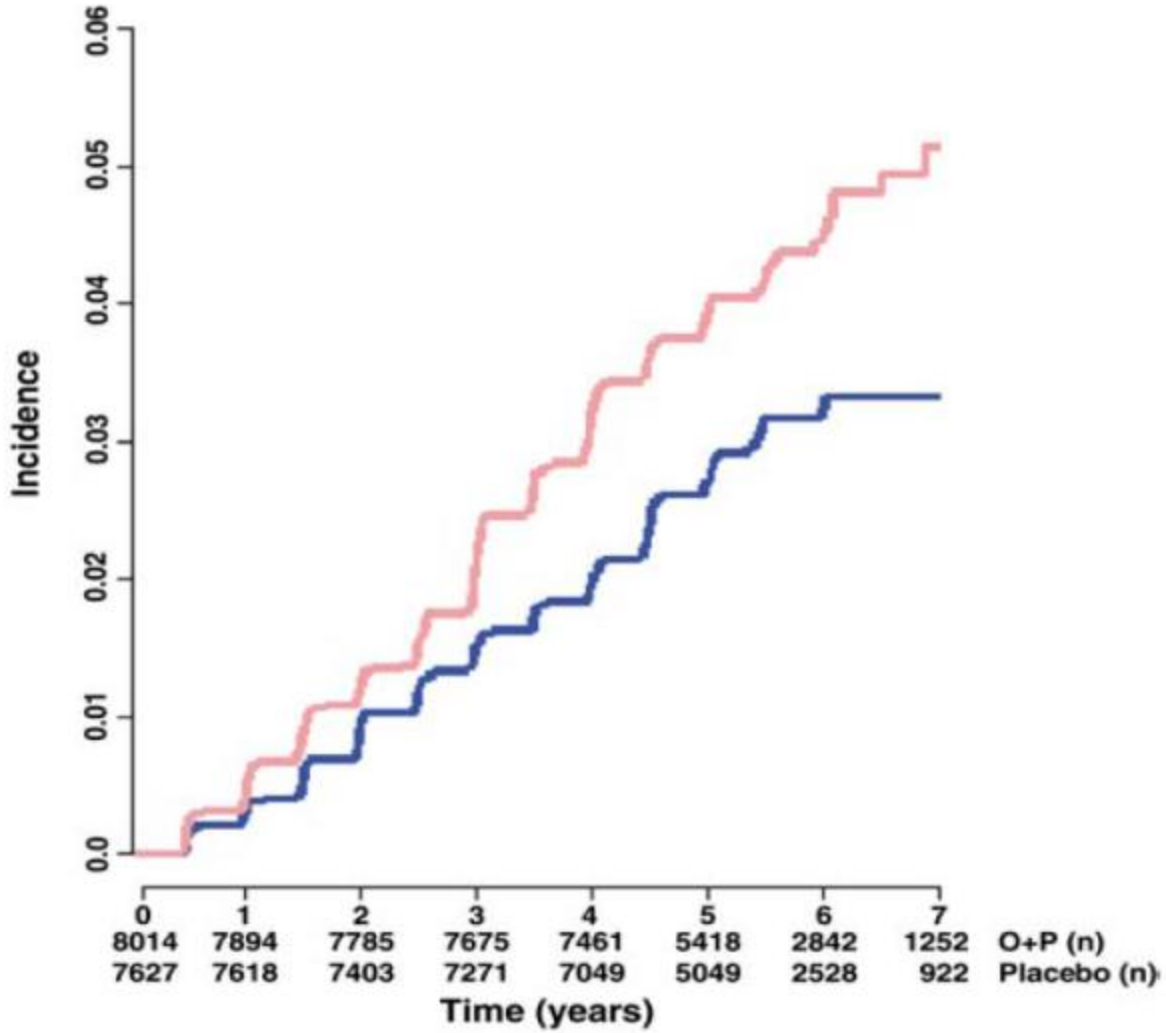


Fig. 1. Diabetes incidence by treatment arm (Oestrogen Plus Progestin [O+P] versus Placebo). Hazard ratio (95% CI), 0.79 (0.67–0.93). Blue line: Oestrogen Plus Progestin; red line: Placebo

Diabetologia 2004;47:1175-1187

Menopausal hormone therapy and new-onset diabetes in the French Etude Epidemiologique de Femmes de la Mutuelle Générale de l'Education Nationale (E3N) cohort

B. de Lauzon-Guillain · A. Fournier · A. Fabre ·
N. Simon · S. Mesrine · M-C. Boutron-Ruault ·
B. Balkau · F. Clavel-Chapelon

El objetivo del estudio fue investigar la asociación entre el uso de THM y el nuevo comienzo de DM2 en el estudio prospectivo francés de epidemiológia de las mujeres (iniciado en 1990 y con 15 años de seguimiento).

Diabetología 2009;52:2092-2100

INCIDENCIA DE DM2 EN FRANCIA:

De un total de 63.624 mujeres postmenopáusicas del estudio epidemiológico de mujeres (E3N), 1220 nuevos casos de DM2 fueron identificados:

- **702/45.394 (1.5%) en mujeres con THM**
- **518/18.230 (2.8%) en mujeres con placebo**

Se observó un menor riesgo de nuevo comienzo de DM2 entre usuarias de THM en comparación con las que nunca usaron THM, con RR de 0.82

Diabetología 2009;52:2092-2100

Position Statement

Estrogen and progestogen use in postmenopausal women: 2010 position statement of The North American Menopause Society

DIABETES:

"El meta-análisis de los datos publicados sugiere que la THM se asocia con mejoría de la insulinorresistencia en las mujeres postmenopáusicas"

"Mujeres postmenopáusicas con DBT2 que usan THM pueden requerir menores dosis de medicaciones para su control glucémico"

Menopause 2010;17(2):242-255

Position Statement

The 2012 Hormone Therapy Position Statement of The North American Menopause Society

DIABETES:

"A pesar que los grandes estudios clínicos randomizados demuestran que la THM reduce la incidencia de nuevos casos de DM2, "NO SE RECOMIENDA" su uso para prevención de DBT mellitus en mujeres peri o postmenopáusicas"

Menopause 2012;19(3):257-271

POSITION STATEMENT

Estrogen and progestogen use in postmenopausal women: 2010 position statement of The North American Menopause Society

DIABETES:

Estrógenos transdérmicos ofrecen ventajas sobre estrógenos orales, ya que:

- ***No aumentan TG***
- ***No aumentan factores trombóticos***
- ***No activa factores inflamatorios ni de coagulación***
- ***No se asocian con aumento de tensión arterial***
- ***Mas aún, mejora la sensibilidad a la insulina***

Menopause 2010;17(2):242-255

Ante esta paciente (< de 60 años de edad y con menos de 10 años desde su menopausia) que presenta:

- DM2

- Síntomas climatéricos "severos" que le alteran su calidad de vida

- No posee contraindicaciones para el uso de TH

- Que no respondió previamente a tratamientos no hormonales

<u>Se le indica</u>:

THM con elección de estrógenos transdérmicos asociados a progesterona natural micronizada vaginal

ARKHËN

Box 1
Suggested protocol for monitoring diabetic women on HRT.

- Blood pressure checks—six monthly.
- HbA_{1C}—six monthly.
- Lipid profiles—annually.
- Liver function tests—annually.
- Fundoscopy—annually.
- Screening for microvascular disease—annually.
- DXA scan—for women at risk of osteoporosis.

Note: Any abnormal uterine bleeding whist on HRT must be fully investigated to rule out endometrial neoplasia.
Adapted from Perera and co-worker [49].

Maturitas 2009;63:200-203

MUCHAS GRACIAS !!