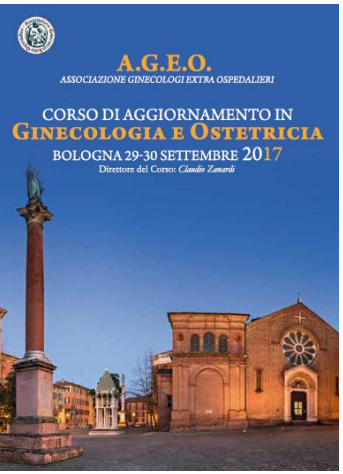


La Terapia Ormonale Sostitutiva in Menopausa:
Rivalutazione dei rischi e benefici nell'ultimo decennio

Marco Gambacciani

President Italian Menopause Society

Department of Obstetrics and Gynecology

Pisa University Hospital

Italy

http://simenopausa.it/

MENOPAUSA E TERAPIA ORMONALE SOSTITUTIVA

RACCOMANDAZIONI DELLA SOCIETÀ ITALIANA DELLA MENOPAUSA

a cura del Consiglio Direttivo della Società Italiana della Menopausa

INTERNATIONAL MENOPAUSE SOCIETY

THE SOCIETY FOR THE STUDY OF ALL ASPECTS OF THE CLIMACTERIC IN MEN AND WOMEN

2016 IMS Recommendations on women's midlife health and menopause hormone therapy

R. J. Baber, N. Panay & A. Fenton the IMS Writing Group

J. Baber, N. Panay & A. Fenton the IMS Writing Group (2016) Climacteric, 19:2, 109-150,

Menopause: The Journal of The North American Menopause Society
Vol. 24, No. 7, pp. 728-753
DOI: 10.1097/GME.0000000000000921

POSITION STATEMENT

The 2017 hormone therapy position statement of The North American Menopause Society

This NAMS position statement has been endorsed by Academy of Women's Health, American Association of Clinical Endocrinologists, American Association of Nurse Practitioners, American Medical Women's Association, American Society for Reproductive Medicine, Asociacio´n Mexicana para el Estudio del Climaterio, Association of Reproductive Health Professionals, Australasian Menopause Society, Chinese Menopause Society, Colegio Mexicano de Especialistas en Ginecologia y Obstetricia, Czech Menopause and Andropause Society, Dominican Menopause Society, European Menopause and Andropause Society, German Menopause Society, Groupe d'e´tudes de la me´nopause et du vieillissement Hormonal, HealthyWomen, Indian Menopause Society, International Menopause Society, International Osteoporosis Foundation, International Society for the Study of Women's Sexual Health, Israeli Menopause Society, Japan Society of Menopause and Women's Health, Korean Society of Menopause, Menopause Research Society of Singapore, National Association of Nurse Practitioners in Women's Health, SOBRAC and FEBRASGO, SIGMA Canadian Menopause Society, **Societa` Italiana della Menopausa**, Society of Obstetricians and Gynaecologists of Canada, South African Menopause Society, Taiwanese Menopause Society, and the Thai Menopause Society. The American College of Obstetricians and Gynecologists supports the value of this clinical document as an educational tool, June 2017. The British Menopause Society supports this Position Statement.

PRINCIPI GENERALI

- La menopausa non è una malattia e non necessita di una terapia
- Alcune donne possono risentire del calo ormonale e quindi hanno bisogno di una sostituzione

Principi Generali per una corretta TOS

- **Selezione delle donne**
  - Trattare le donne sintomatiche
- **Timing**
  - Mantenere l'effetto degli estrogeni endogeni
  - Inizio precoce
- **Personalizzazione**
  - Non esiste il dosaggio ideale
  - Diverse combinazioni hanno caratteristiche peculiari
  - Ridurre il dosaggio con l'età

Indicazioni alla TOS

- Sindrome vasomotoria
- Sindrome Genitourinaria
- Dolori muscolo-articolari migranti
- Modificazioni del ritmo sonno-veglia
- Alterazioni del tono dell'umore
- Disfunzioni sessuali
- Prevenzione dell'osteoporosi e delle fratture correlate
- Prevenzione dell'atrofia
    - Epiteli, cute
    - tessuto connettivo
    - dischi intervertebrali

Controindicazioni alla TOS

- Sanguinamento uterino anomalo non investigato
- Carcinoma della mammella
- Carcinoma endometriale ormonosensibile tipo I
- Iperplasia endometriale non trattata
- Patologia coronarica e cerebrovascolare (ad es. angina, infarto del miocardio, ictus)
- Tromboembolia venosa (trombosi venosa profonda, embolia polmonare)
- Malattie epatiche croniche o in atto, fino al ritorno alla normalità dei test di funzionalità epatica
- Porfiria cutanea tarda
- Otosclerosi
- Ipersensibilità nota al principio attivo o ad uno qualsiasi degli eccipienti
- Rifiuto della donna informata

PRINCIPI GENERALI

- Il termine TOS indica terapie con estrogeni (per via orale, transdermica e vaginale), progestinici, terapie combinate estro-progestiniche, sequenziali o continue, Tibolone, TSEC con dosaggi e profili rischi/benefici potenzialmente molto diversi
- **È inappropriato applicare alla TOS un effetto di classe evidentemente inesistente**

PRINCIPI GENERALI

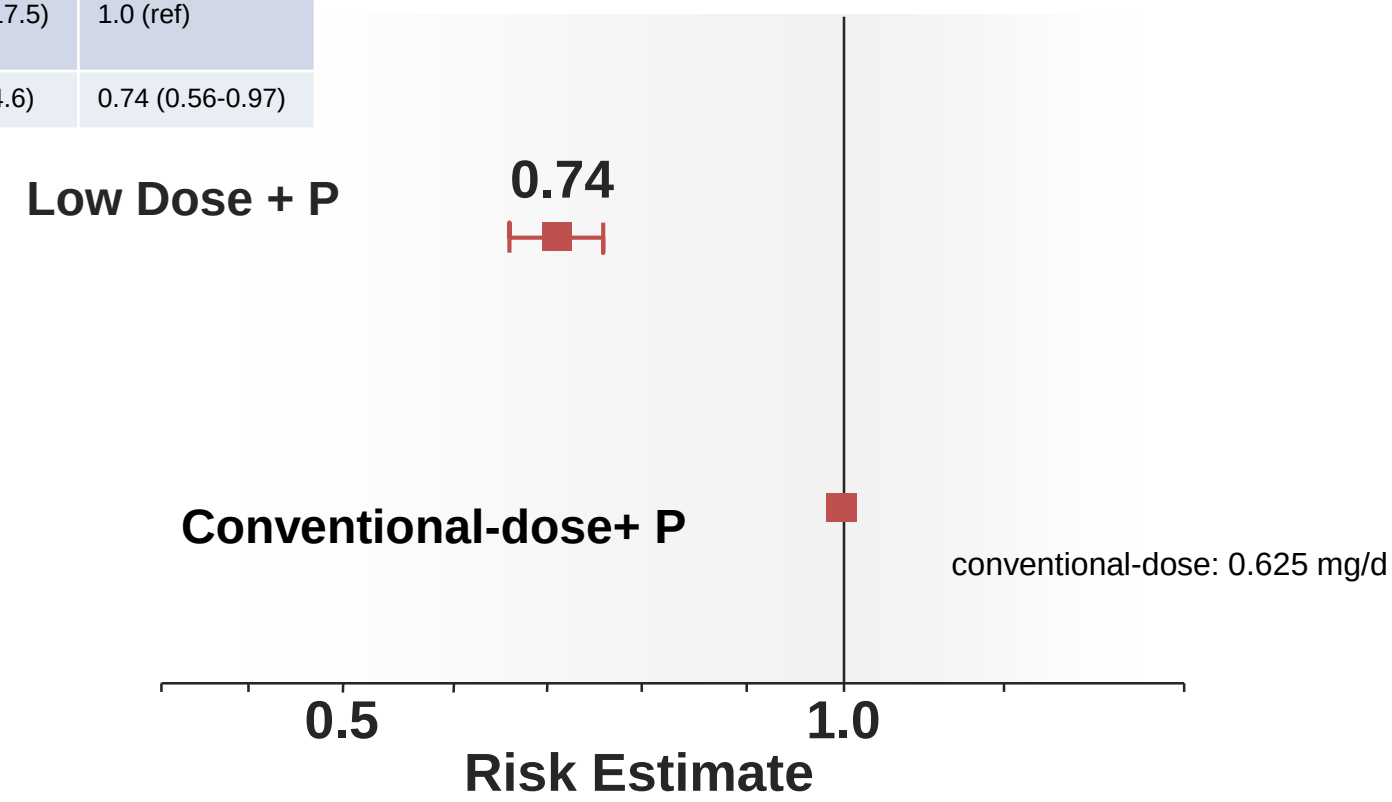
Dosaggi utilizzati per la TOS

DOSE	Estradiolo orale (mg)	Estrogeni coniugati (mg)	Estradiolo gel transcutaneo (mg)	Estradiolo cerotto (mcg)	Tibolone (mg)
Standard	2	0.625	1.5	50	2.5
Bassa	1	0.45	1	25	1.25
Ultra-Bassa	0.5	0.30	0.75	12.5	0.625

Risk of global index event by CE dose

45,112 participants of the WHI Observational Study (average follow-up 5.5 yrs)

	Events/1,000 person-years	HR (95% CI)
Conventional-dose+ P	16.5 (15.5-17.5)	1.0 (ref)
Low-dose+P	11.8 (9.0-14.6)	0.74 (0.56-0.97)



Global index event is defined as time to first CHD, breast cancer, stroke, pulmonary embolism, hip fractures, colorectal cancer, endometrial cancer, or death

conventional-dose: 0.625 mg/d

Crandall et al., Menopause 2017

Principi Generali per una corretta TOS

- **Selezione delle donne**
  - Trattare le donne sintomatiche
- **Timing**
  - Mantenere l'effetto degli estrogeni endogeni
  - Inizio precoce
- **Personalizzazione**
  - Non esiste il dosaggio ideale
  - Diverse combinazioni hanno caratteristiche peculiari
  - Ridurre il dosaggio con l'età

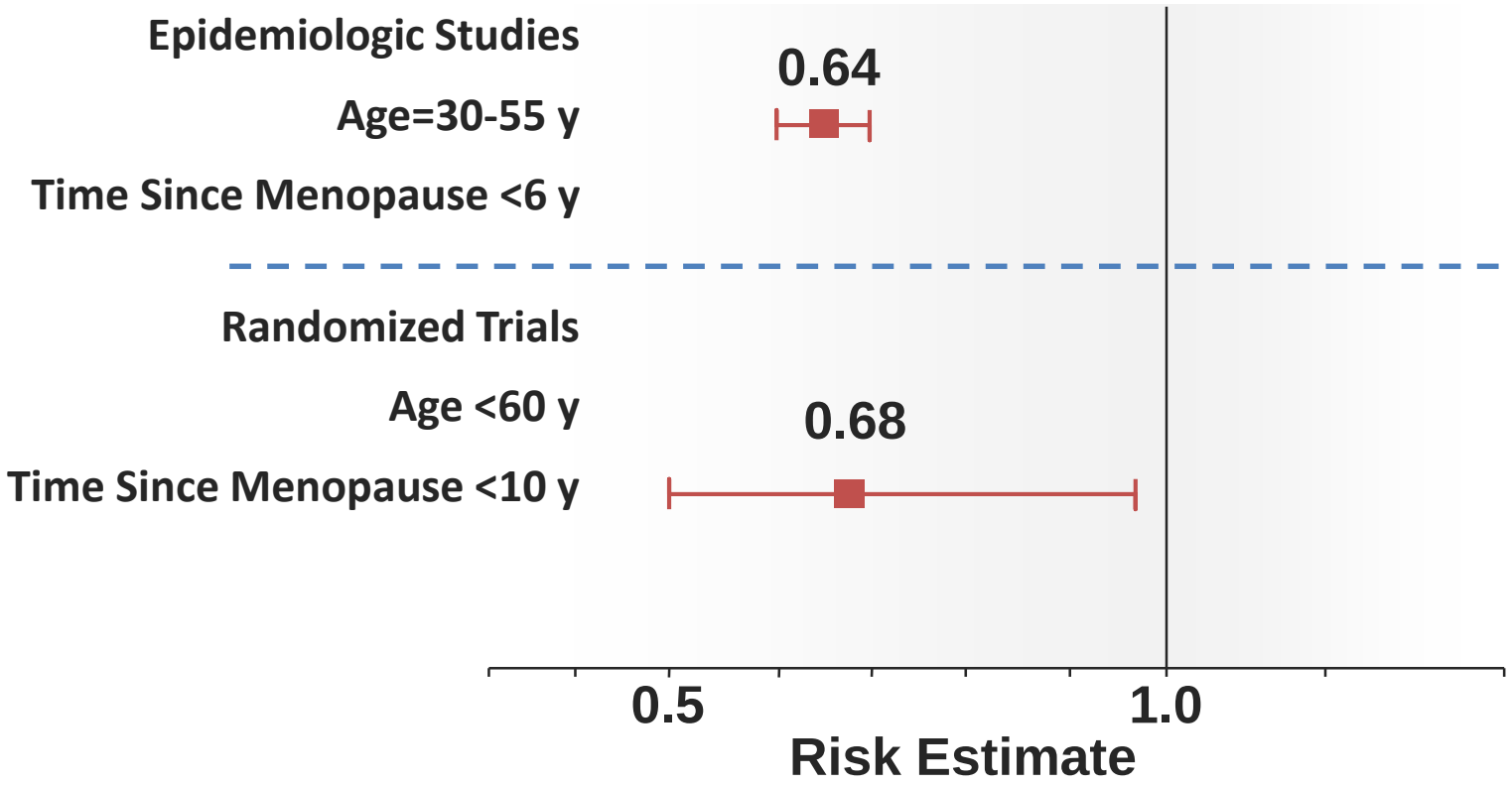
I sintomi menopausali sono un marcatore di suscettibilità alla carenza estrogenica e di maggior rischio per :

- Nel breve periodo:
  - Disturbi del sonno/Insonnia
  - Alterazioni del tono dell'umore/depressione
  - Ridotta QoL
- Nel lungo periodo
  - Alterazioni cognitive/mnemoniche
  - Osteoporosi
  - prolasso genitale/incontinenza urinaria
  - Ipertensione/Sindrome Metabolica
  - CVD

Principi Generali per una corretta TOS

- **Selezione delle donne**
  - Trattare le donne sintomatiche
- **Timing**
  - Mantenere l'effetto degli estrogeni endogeni
  - Inizio precoce
- **Personalizzazione**
  - Non esiste il dosaggio ideale
  - Diverse combinazioni hanno caratteristiche peculiari
  - Ridurre il dosaggio con l'età

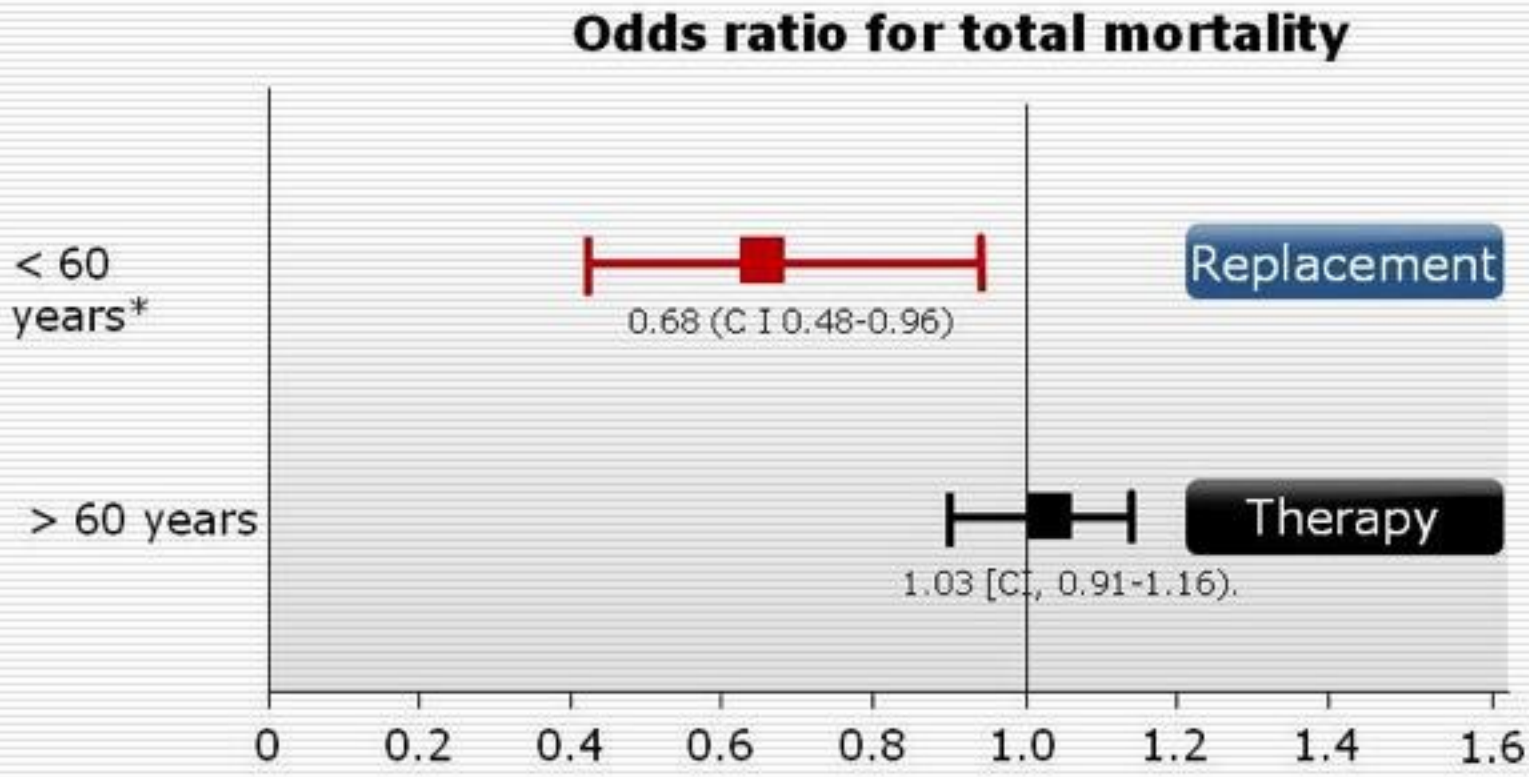
HRT and CHD: Observational Studies and RCTs



Grodstein F, et al. Prog Cardiovasc Dis 1995;38:199-210.
Salpeter S, et al. J Gen Intern Med 2006;21:363-366.

CHD events associated with hormone therapy in younger and older women: a meta-analysis

23 trials, with 39,049 participants followed for 191,340 patient-years



* Statistical significance

Salpeter SR et al., J Gen Intern Med. 2006 Apr;21(4):363-6

2015 Cochrane review

CARDIOVASCULAR DISEASE AND ALL-CAUSE MORTALITY

HRT initiated fewer than 10 yrs after menopause onset

- CHD RR = 0.52 (0.29-0.96)
- all-cause mortality RR = 0.70 (0.52-0.95)
- VTE RR= 1.74 (1.11-2.73)
- no increased risk of stroke

Boardman HM et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women. Cochrane Database Syst Rev 20152.

TOS: rapporto rischi/benefici

- Più favorevole nelle donne sintomatiche che iniziano prima dei 60 anni e comunque entro i 10 anni dalla menopausa
- Determinato dal dosaggio, dal tipo e/o dalla via di somministrazione utilizzata

The 2017 hormone therapy position statement of The North American Menopause Society

Potential risks of HT

- **breast cancer**
  - with combined EPT
- **endometrial hyperplasia and cancer**
  - if estrogen is unopposed or inadequately opposed
- **venous thromboembolism (VTE)**
- **biliary issues**

- Additional risks across ages include
  - myocardial infarction
  - Stroke
  - dementia

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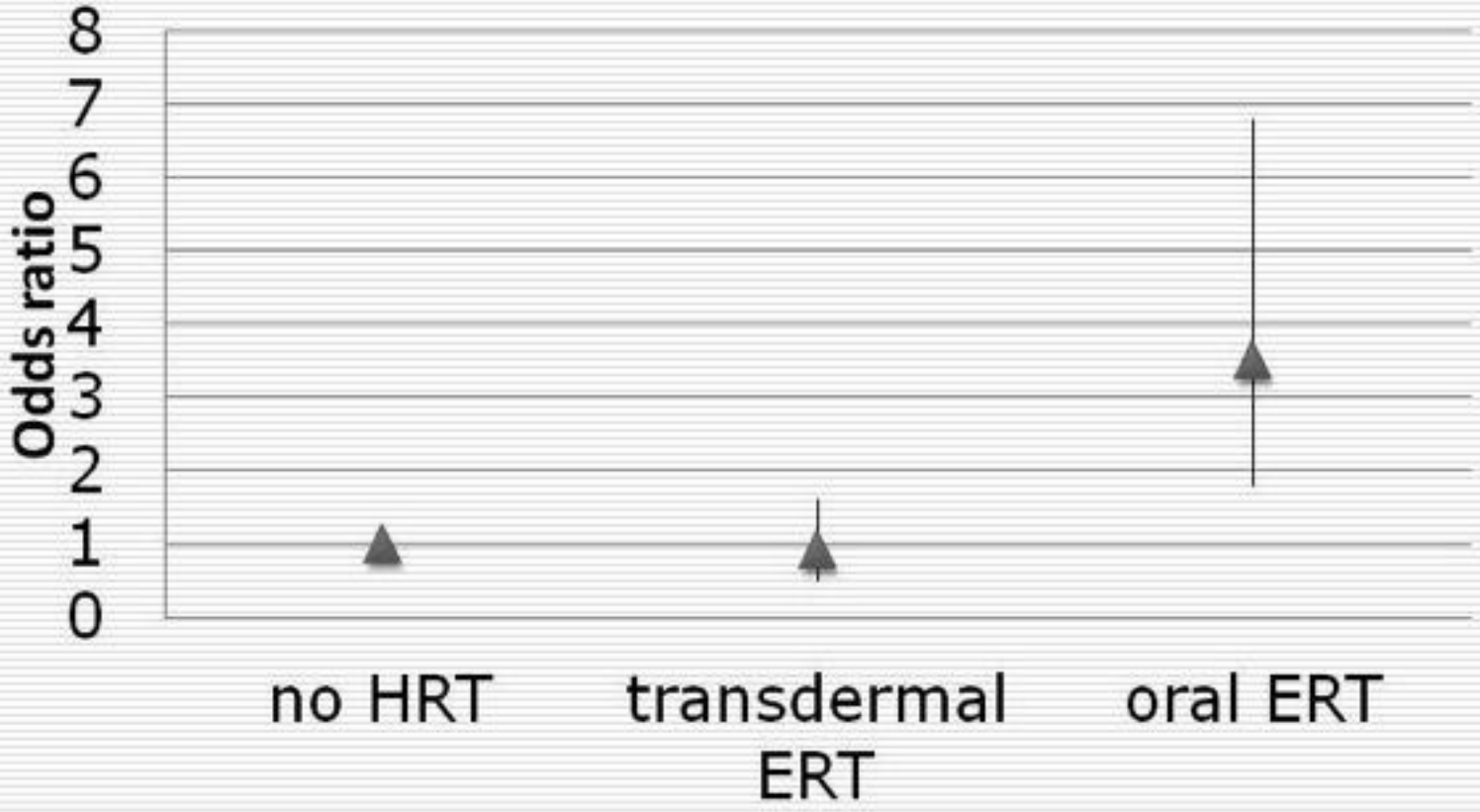
HRT RISKS

- breast cancer
- DVT/PE

HRT ROUTE & VTE



Scarabin et al. Lancet 2003; 362: 428-32

Oral versus transdermal estrogens and venous thromboembolism in postmenopausal women

1. The EStrogens THromboEmbolism Risk study case-control study
2. E3N cohort study
3. the UK General Practitioner Research Database analysis
4. Million Women Study
5. Mega Study
6. The ThromboEmbolismHormoneStudy (TEHS)
7. Retrospective matched-cohort design based on health insurance claims

1. Scarabin PY, Oger E, Plu-Bureau G; Estrogen and Thromboembolism Risk Study Group. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. Lancet 2003;362:428-432.
2. Canonico M, Fournier A, Carcaillon L, et al. Postmenopausal hormone therapy and risk of idiopathic venous thromboembolism: results from the E3N cohort study. Arterioscler Thromb Vasc Biol 2010;30:340-345.
3. Renoux C, Dell'Aniello S, Suissa S. Hormone replacement therapy and the risk of venous thromboembolism: a population-based study. J Thromb Haemost 2010;8:979-986.
4. Sweetland S, Beral V, Balkwill A, et al; Million Women Study Collaborators. Venous thromboembolism risk in relation to use of different types of postmenopausal hormone therapy in a large prospective study. J Thromb Haemost 2012;10:2277-2286.
5. Roach RE, Lijfering WM, Helmerhorst FM, Cannegieter SC, Rosendaal FR, van Hylckama Vlieg A. The risk of venous thrombosis in women over 50 years old using oral contraception or postmenopausal hormone therapy. J Thromb Haemost 2013;11:124-131.
6. Bergendal A, Kieler H, Sundström A, Hirschberg AL, Kocoska-Maras L. Risk of venous thromboembolism associated with local and systemic use of hormone therapy in peri- and postmenopausal women and in relation to type and route of administration. *Menopause* 2016; 23:593–599
7. Simon JA, Laliberté F, Duh MS, et al. Venous thromboembolism and cardiovascular disease complications in menopausal women using transdermal versus oral estrogen therapy. *Menopause* 2016; 23:600–610

Obesity and risk of venous thromboembolism among postmenopausal women

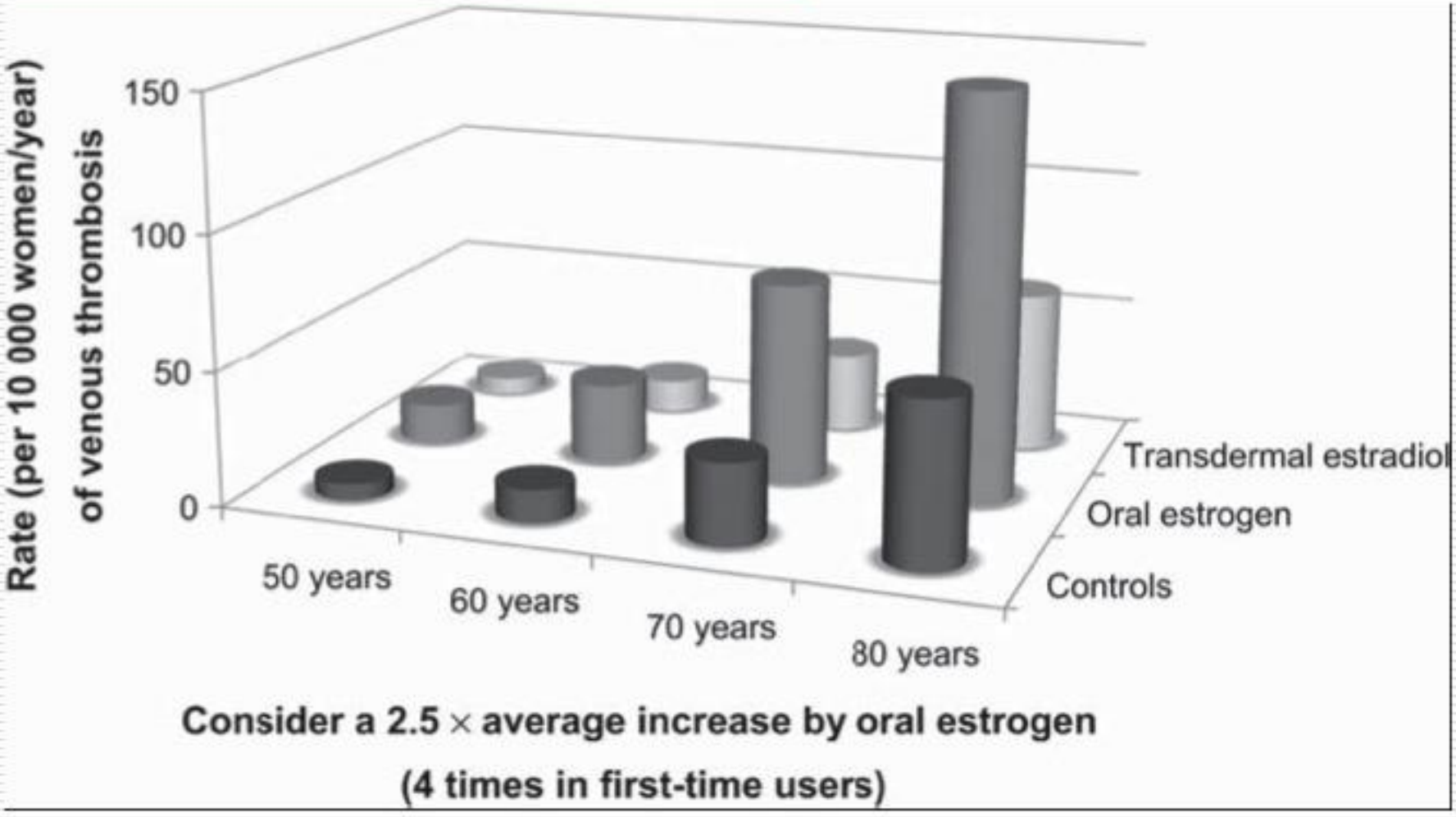
the Estrogen and Thromboembolism Risk (ESTHER) Study

Compared with non-users with normal weight

	overweight	obesity
no HRT	2.7 (1.7-4.5) NS	4.0 (2.1-7.89) NS
TD HRT	2.9 (1.5-5.8)	5.4 (2.1-14.1)
oral HRT	**10.2 (3.5-30.2)**	**20.6 (4.8-88.1)**

Canonico M, et a., J Thromb Haemost. 2006 Jun;4(6):1259-65

Effects of aging on the absolute risk of venous thromboembolism events



L'Hermite, CLIMACTERIC 2013;16(Suppl 1):44–53

ORAL ADMINISTRATION

protein synthesis

liver { Metabolic activation

Portal circulation

estrogen

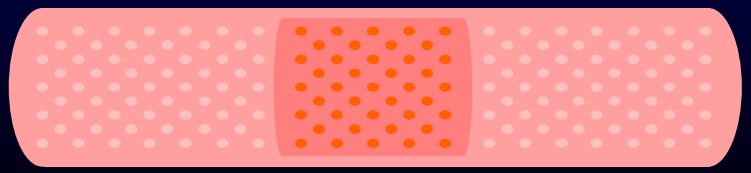
intestine

TRANSDERMAL ADMINISTRATION

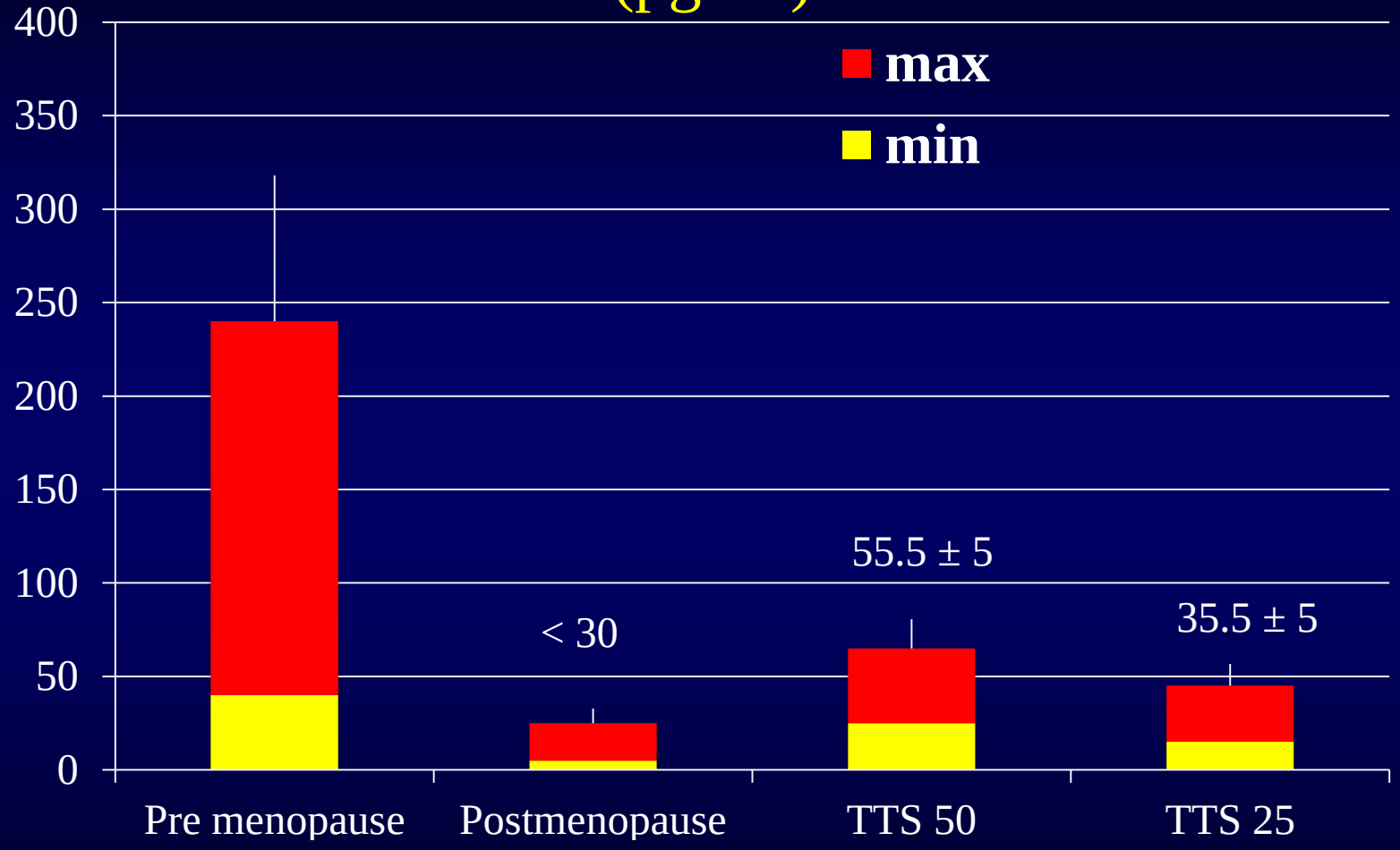
Reduced metabolic effects

No liver activation

Cutaneous circulation



Plasma Estradiol Levels (pg/ml)

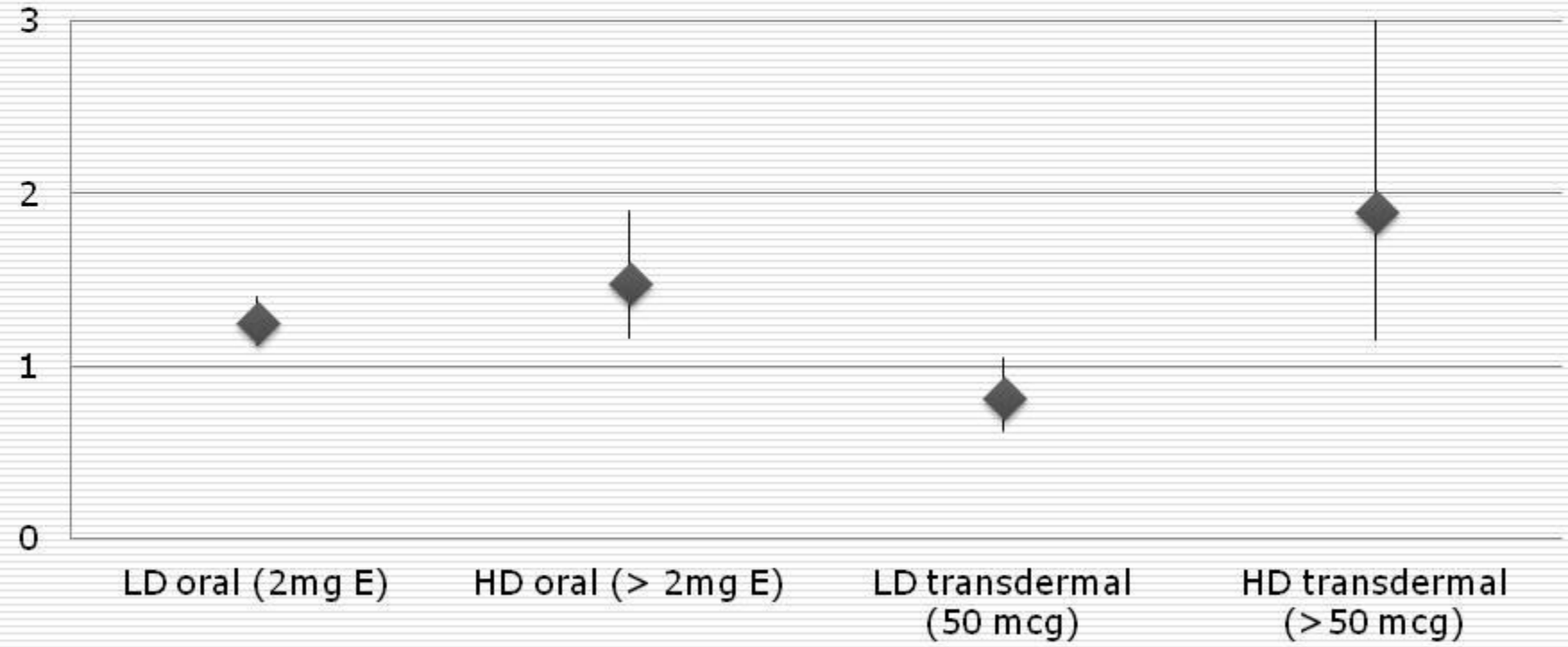


Estraderm 50: delivers a dosage of 50 microg E2/day
Estraderm 25: delivers a dosage of 25 microg E2/day

Gambacciani et al., 1995

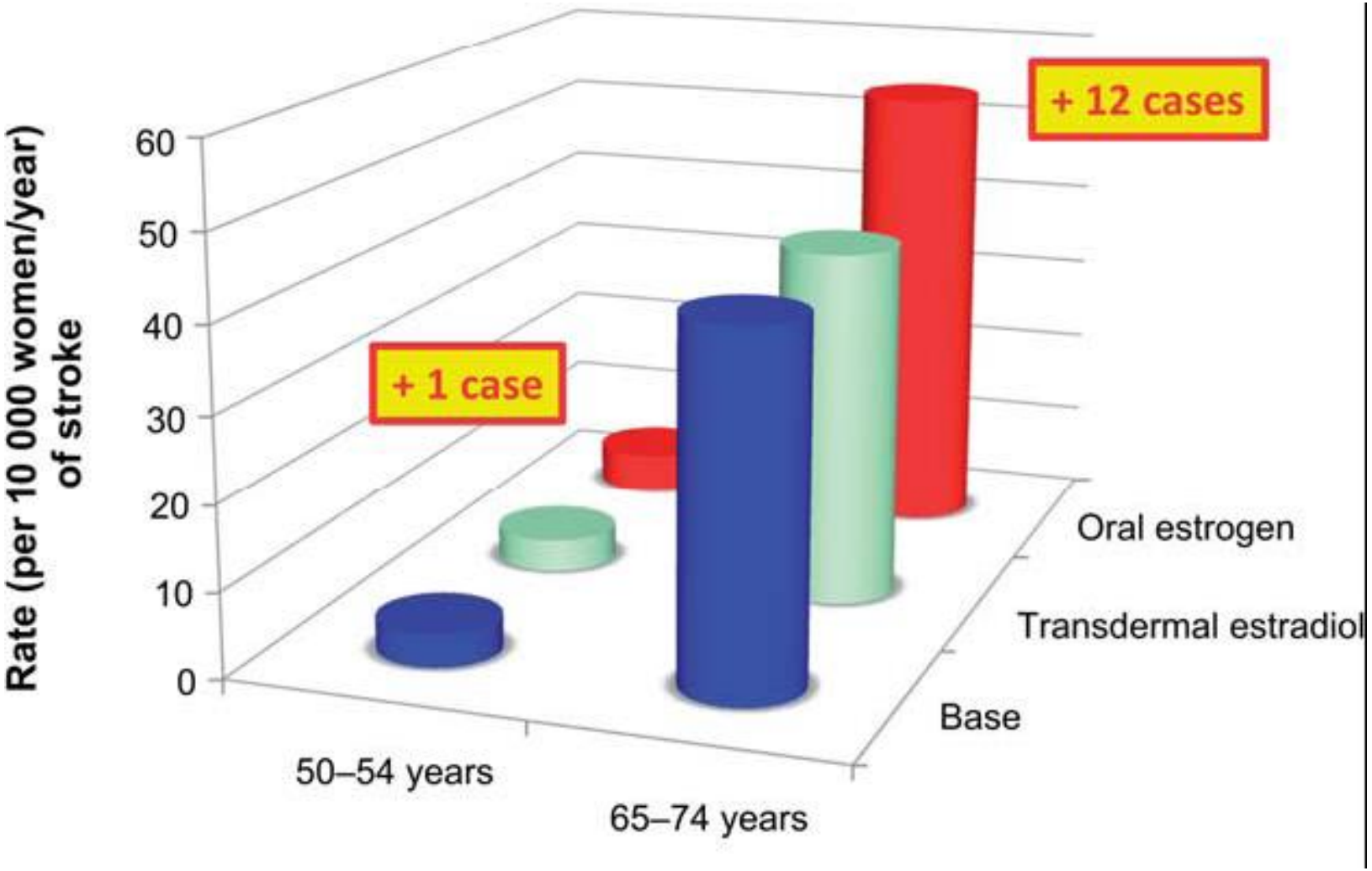
Risk of stroke associated with current use of HRT by dose and route of administration

the United Kingdom General Practice Research Database



BMJ 2010;340:c2519

Effects of aging on the absolute risk of thrombotic stroke events



L'Hermite, CLIMACTERIC 2013;16(Suppl 1):44–53

HRT RISKS

- breast cancer
- DVT/PE

Hormone therapy and breast cancer

- The effect of hormone therapy (HT) on breast cancer risk is complex and conflicting
- The effect of HT on breast cancer risk may depend on
  - Type of HT, dose, duration of use
  - Regimen, route of administration
  - Prior exposure to HT
  - Individual characteristics

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-753.

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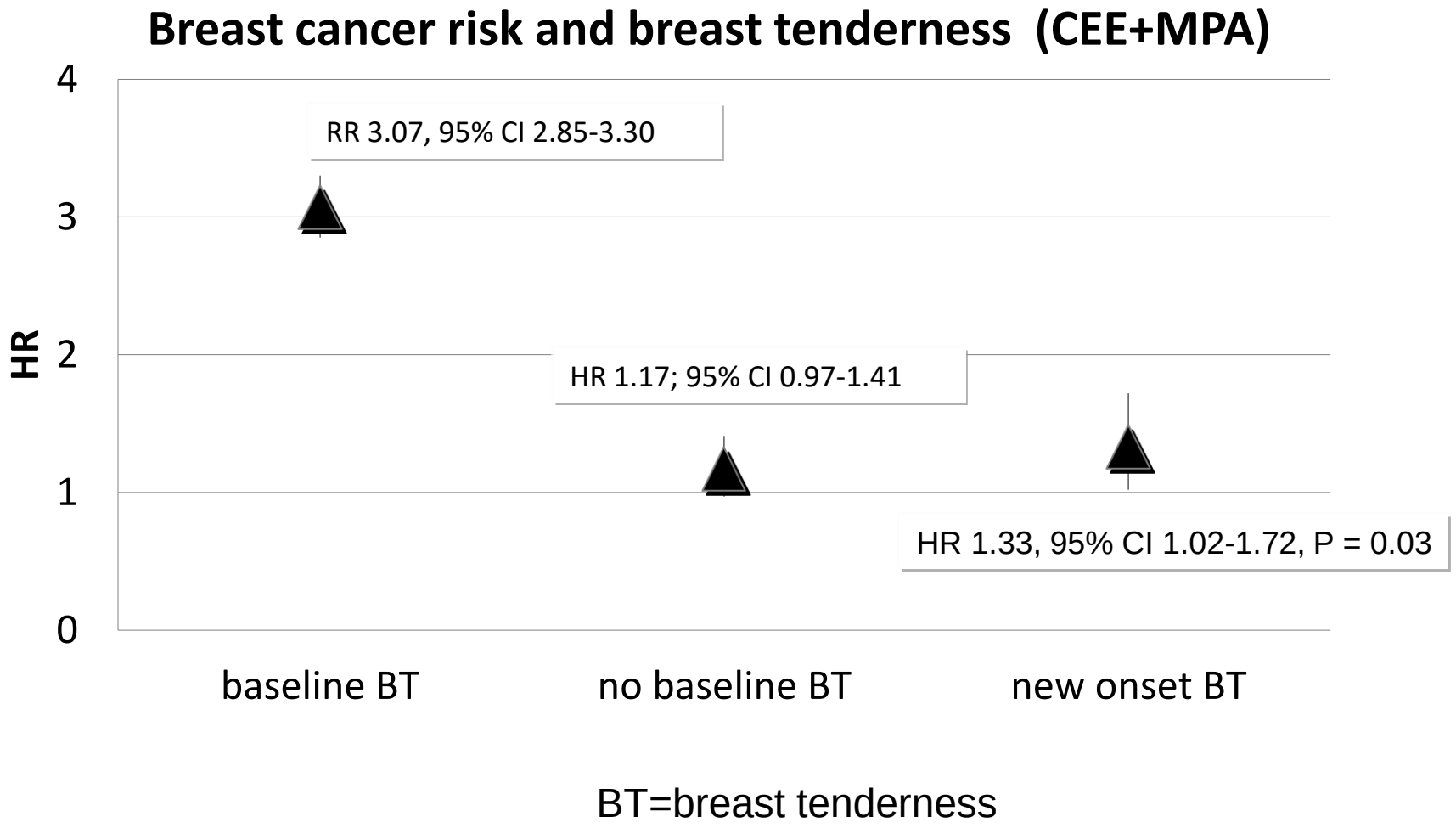
Breast tenderness and breast cancer risk

the estrogen plus progestin WHI trial



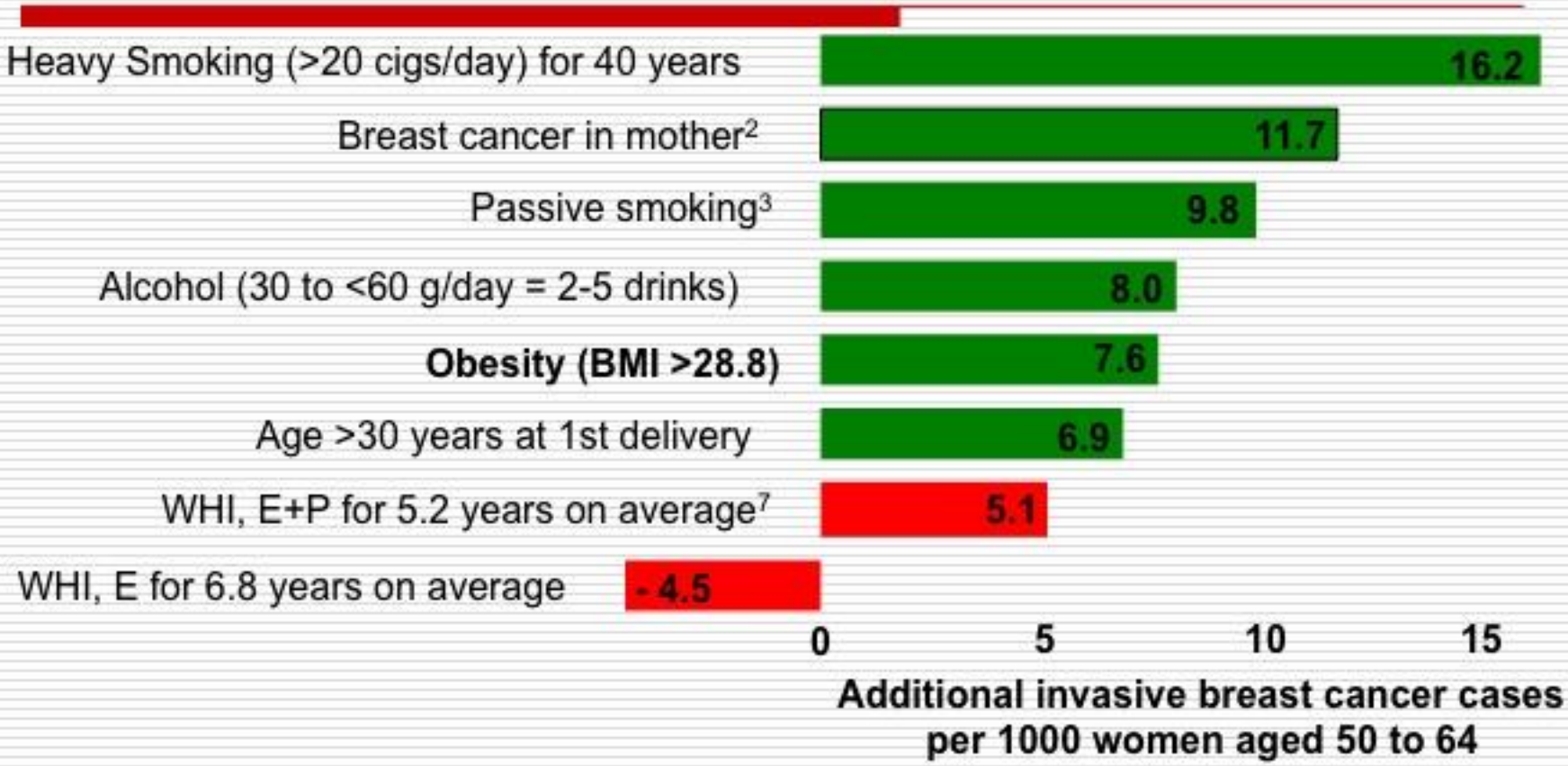
Crandall CJ, Aragaki AK, Cauley JA, McTiernan A, Manson JE, Anderson G, Chlebowski RT, ***Breast cancer research and treatment*** 2012

Breast cancer risk correlates with

- body mass index
- % body fat
- weight gain
- Insulin resistance and hyperinsulinemia
- Serum level of C-peptide

HRT does not increase risk of breast cancer in obese PMW

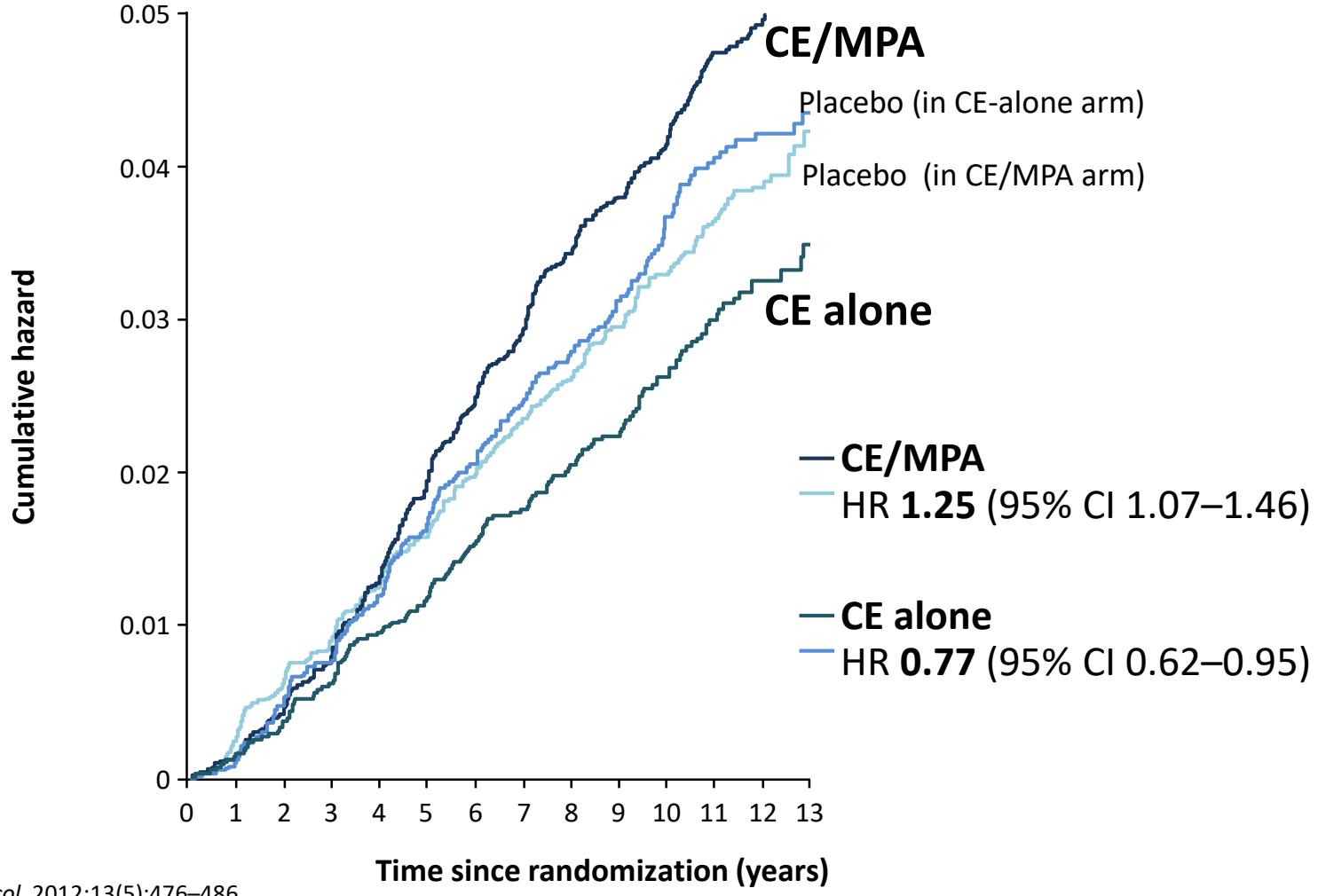
Breast Cancer Risk Factors



USA 2000 data, for all races,
19.5 cases of invasive breast cancer per 1000 women aged 50 -64 years [9]

Variations in Associated Breast Cancer Risk Between CE alone and CE/MPA

Cumulative hazards, adjusted for age and race/ethnicity, for invasive breast cancer by randomization assignment in the WHI CE-alone and CE/MPA trials



Anderson GL, et al. *Lancet Oncol*. 2012;13(5):476–486.

WHI & Breast Cancer Risk

	No. of Patients (Annualized %)				No. Additional Breast Cancer Cases per 10,000 Women per Year of Therapy
Study	**Placebo**	**Therapy**	**Relative Risk**	**95% CI**	
WHI-EP 2002 **CEE+MPA**	124 (0.30)	166 (0.38)	**1.26**	0.83-1.92	+ 8
	Annualized Absolute Risk + 0.08%				
WHI-E 2004 **CEE alone**	124 (0.33)	94 (0.26)	**0.77**	0.57-1.06	- 7
	Annualized Absolute Risk - 0.07 %				

Gambacciani 2012

Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality

Mortality Outcomes During the 18-Year Cumulative Follow-Up According to 10-Year Age Groups at Randomization

breast cancer–specific mortality

- **CE+MPA**
  - **HR, 1.44** (0.97 - 2.15; *NS*)
- **CE alone**
  - **HR, 0.55** (0.33 - 0.92; *P* = .02)

Manson et al., JAMA 2017

A Progestin is Not a Progestin

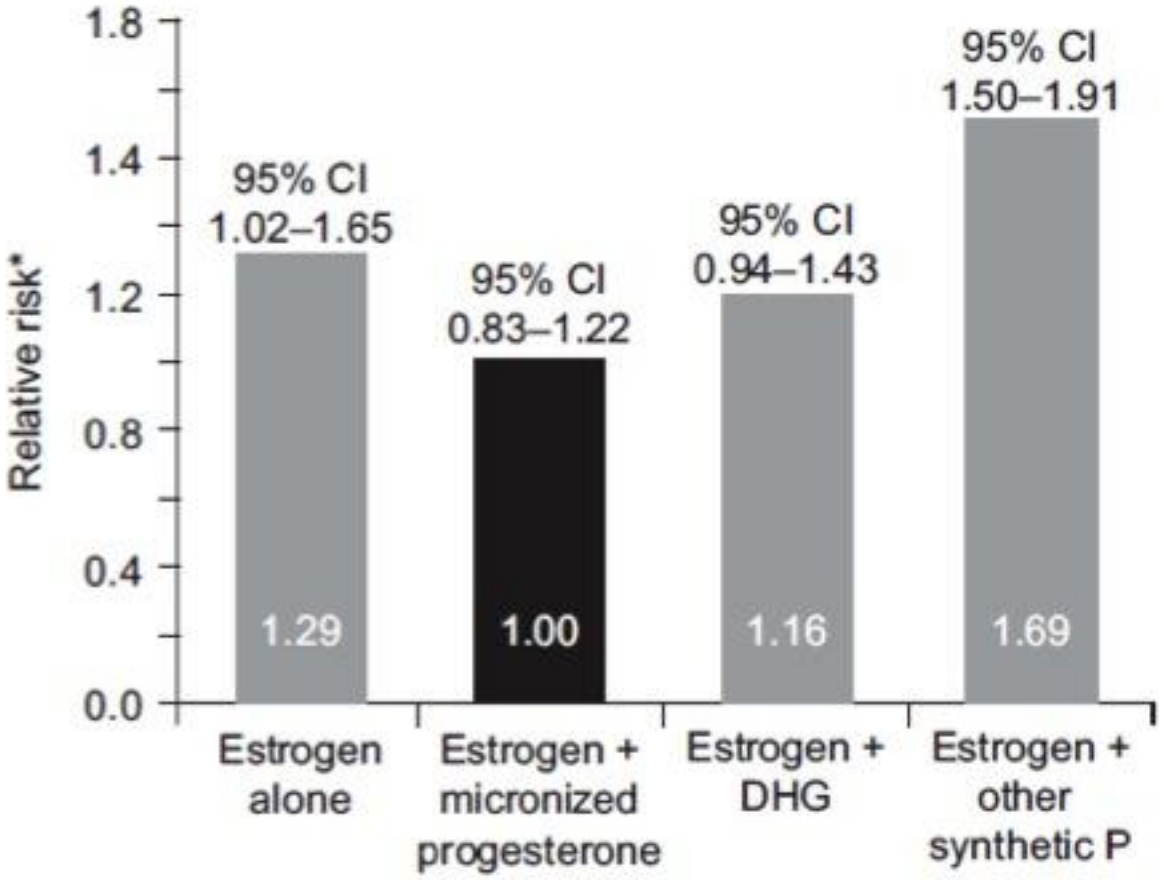
- **Endometrial effects – similar**
- **Bone effects – similar**
- Metabolic effects – different
- Vascular effects – different
- Breast Effects – different
- Side effects – different

Unequal risks for breast cancer associated with different HRT

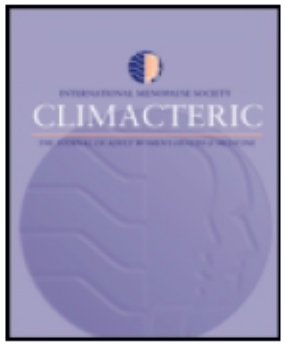
results from the E3N cohort study

The cohort comprises 100,000 women, aged 40-65 years at baseline in 1990

Invasive breast cancer with HRT vs never-users



Gompel , Climacteric 2012 (adapted from Fournier A, et al., *Breast Cancer Res Treat 2008;107:103 – 11)*



Climacteric

CLIMACTERIC 2013;16(Suppl 1):79–84

ISSN: 1369-7137 (Print) 1473-0804 (Online) Journal homepage: http://www.tandfonline.com/loi/icmt20

Are progestins really necessary as part of a combined HRT regimen?

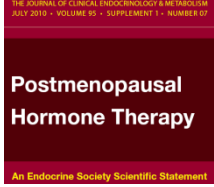
D. W. Sturdee

HRT for women with uterus should include a progestin to prevent proliferative effects of endometrial cancer

E+P regimens increase BC risk whereas unopposed estrogens may not increase risk or even reduce it

It's pertinent to reasses the merits of adding a progestin

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM
JULY 2010 • VOLUME 95 • SUPPLEMENT 1 • NUMBER 07



Tibolone as HRT

Yes: symptomatic PMW
@ risk for Fx; low libido; mood disorders

- reduces vasomotor symptoms and improves urogenital atrophy.
  - Level of evidence: A
- reduces the incidence of vertebral and nonvertebral fractures.
  - Level of evidence: A
- reduces the risk of breast cancer
  - Level of evidence: B
- reduces colon cancer.
  - Level of evidence: B
- **No increase in the risk of VTE or CHD**
  - **Level of evidence: B**
- **No increase in endometrial hyperplasia or cancer**
  - **Level of evidence: A**

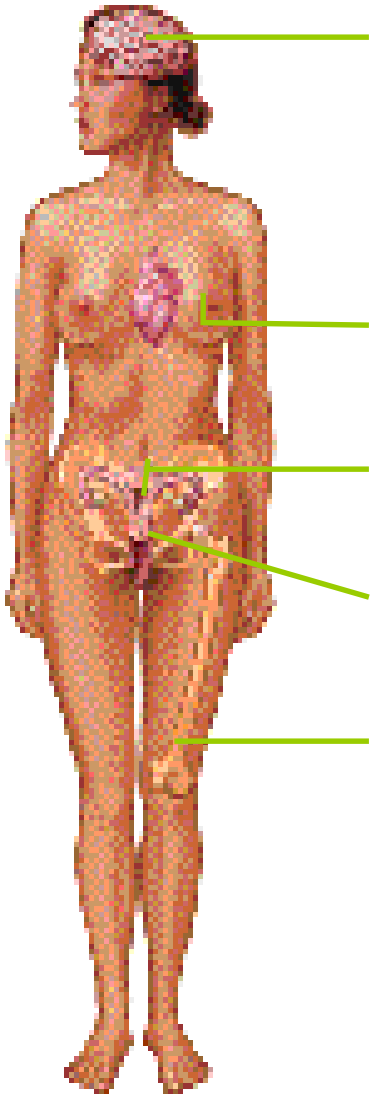
no

older women at increased risk of stroke
- Level of evidence: A

Breast cancer survivors
- Level of evidence: A

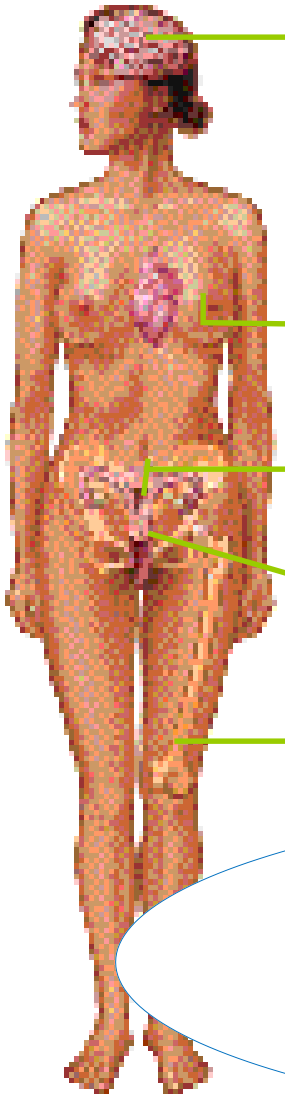
Santen RJ et al. 2010, JCE&M : 95, Supplement 1: S1-S66

Optimal Clinical Effects of an ideal Hormone Replacement



- Treat climacteric symptoms
- Beneficial effects on quality of life QOL
- No increased risk of breast cancer
- No increased risk of endometrial proliferation
- Treat vaginal atrophy
- Prevent postmenopausal bone loss

Optimal Clinical Effects of Hormone Replacement



- Treat climacteric symptoms
- Beneficial effects on quality of life QOL
- No increased risk of breast cancer
- No increased risk of endometrial proliferation
- Treat vaginal atrophy
- Prevent postmenopausal bone loss

Tissue Selective Estrogen Complex (TSEC)
(progestin-free hormone replacement)

Tissue Selective Estrogen Complex (TSEC)

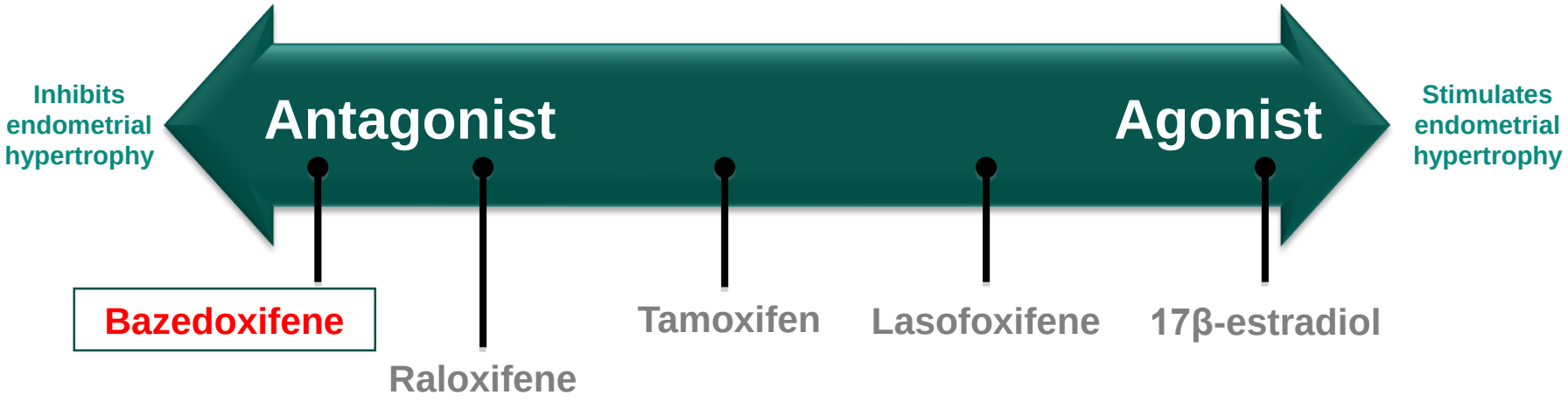
(progestin-free hormone replacement)

BZA 20 mg + EC 0.45 mg

- **CE low dose**
  - **VMS**
  - **GSM**
- **BZA antiestrogenic effect**
  - **Endometrium**
  - **Breast**

Why Bazedoxifene instead of other SERMs?

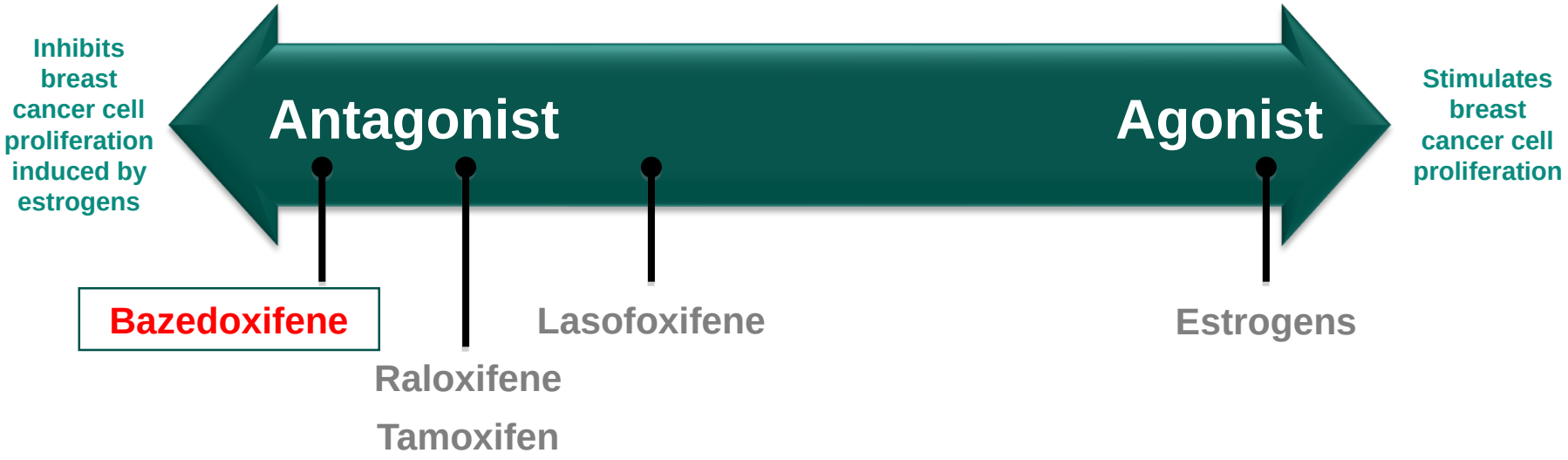
Estrogens and SERMs: Different Effect on Endometrium*



* In vivo studies
SERM: Selective Estrogen Receptor Modulator

Why Bazedoxifene instead of other SERMs?

In Vitro Studies
Cell Proliferation In Breast Cancer Cells



SERM: Selective Estrogen Receptor Modulator

TSEC

0.45 mg Conjugated Estrogens /20 mg Bazedoxifene

Clinical studies conducted worldwide in more than 7500 women

- **Relief of menopausal symptoms**
  - Efficacy comparable to other HRT preparations
- **Optimal bleeding pattern**
  - Higher prevalence of amenorrhea
- **Prevention of osteoporosis**
  - Decreased bone resorption, Increased BMD
- **Favorable safety and tolerability profile**
  - VTE, stroke and CHD incidence comparable to placebo
  - **No stimulation of the endometrium and breast**

**1. Lobo RA, et al. Fertil Steril. 2009;92:1025-1038; 2. Pinkerton JV, et al. Menopause. 2009;16:1116-1124;
3. Kagan R, et al. Menopause. 2010;17:281-289; 4. Mirkin S, et al. Climacteric. 2013;16:338-346;
5. Pinkerton JV, et al. Obstet Gynecol. 2013;121:959-968.**

BZA/Incidence of Select Gynecologic Aes 7 year data

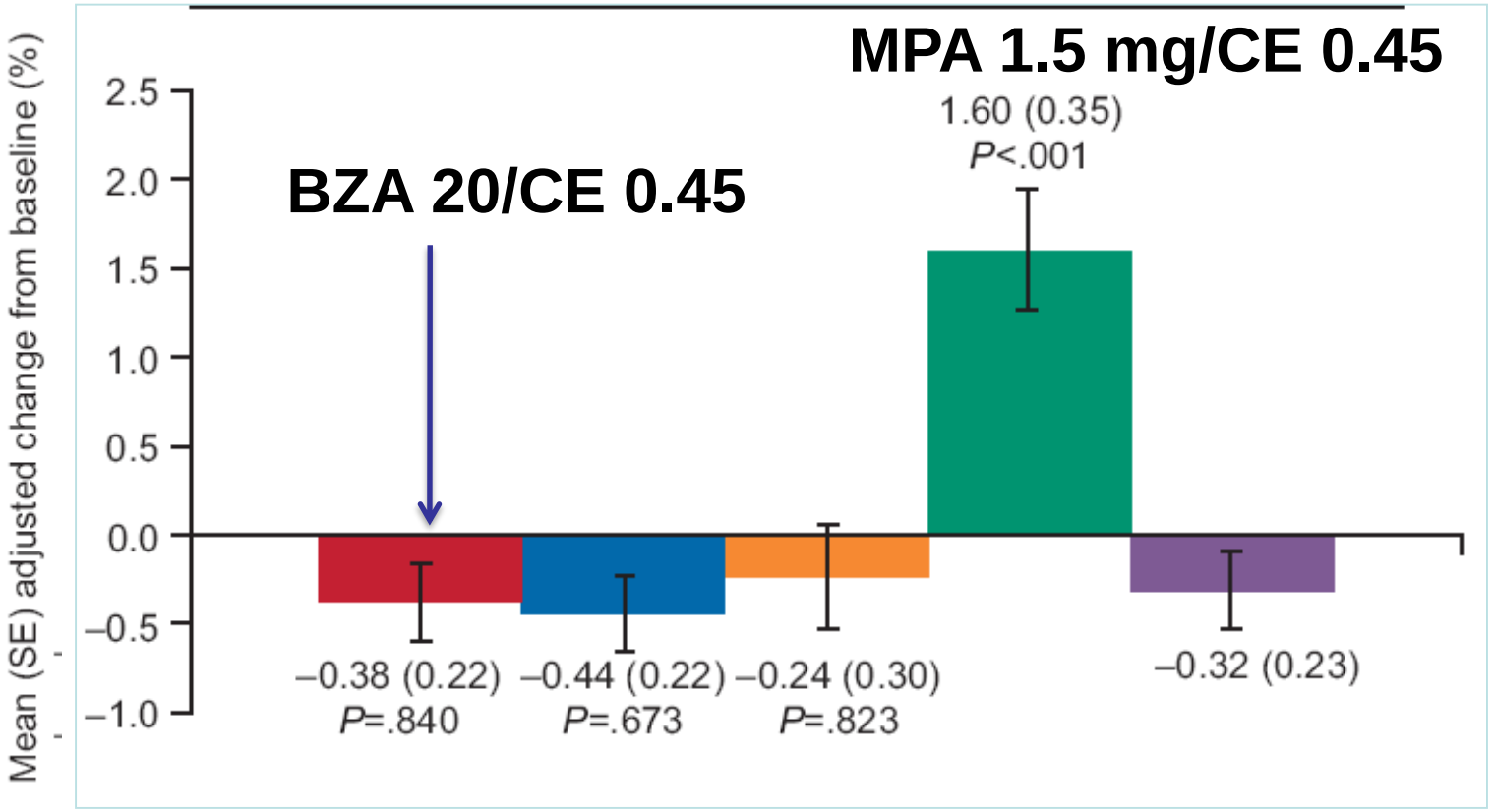
Subjects, n (%)	BZA combined (n = 3,758)	PBO (n = 1,885)
Endometrial carcinoma	3 (0.1)[a]	7 (0.4)
Endometrial hyperplasia	2 (0.1)	1 (0.1)
Endometrial neoplasia (polyps)	34 (0.9)	15 (0.8)
Ovarian cyst	35 (0.9)	17 (0.9)
Uterine hemorrhage	10 (0.3)	5 (0.3)

BZA, bazedoxifene; PBO, placebo.
[a]*P* <0.05 vs PBO (Fisher exact test).

Modified from Palacios S, et al. Maturitas. 2013 Sep;76(1): 81-87.

Breast Density

% change vs baseline



- Bazedoxifene 20 mg and conjugated estrogens 0.45 mg (n=186)
- Bazedoxifene 20 mg and conjugated estrogens 0.625 mg (n=191)
- Bazedoxifene 20 mg (n=98)
- Conjugated estrogens 0.45 mg and MPA 1.5 mg (n=68)
- Placebo (n=182)

Pinkerton, JV. et al. Obstet Gynecol 2013

BZA/Incidence of Select Breast-Related Aes
7-Year data

Subjects, n (%)	BZA + CE (n = 3,758)	PBO (n = 1,885)
Breast carcinoma	**22 (0.6)**	**11 (0.6)**
Breast cyst	22 (0.6)	16 (0.8)
Fibrocystic breast disease	19 (0.5)	16 (0.8)
Breast neoplasm[a]	38 (1.0)	22 (1.2)
Breast pain	112 (3.0)	52 (2.8)

BZA, bazedoxifene; PBO, placebo.
[a]Includes breast mass, breast lump, solid formation, lipoma, fibroadenoma, tumor, nodule, microcalcification, intracanalar papilloma, and cyst

Palacios S, et al. Maturitas. 2013 Sep;76(1): 81-87.

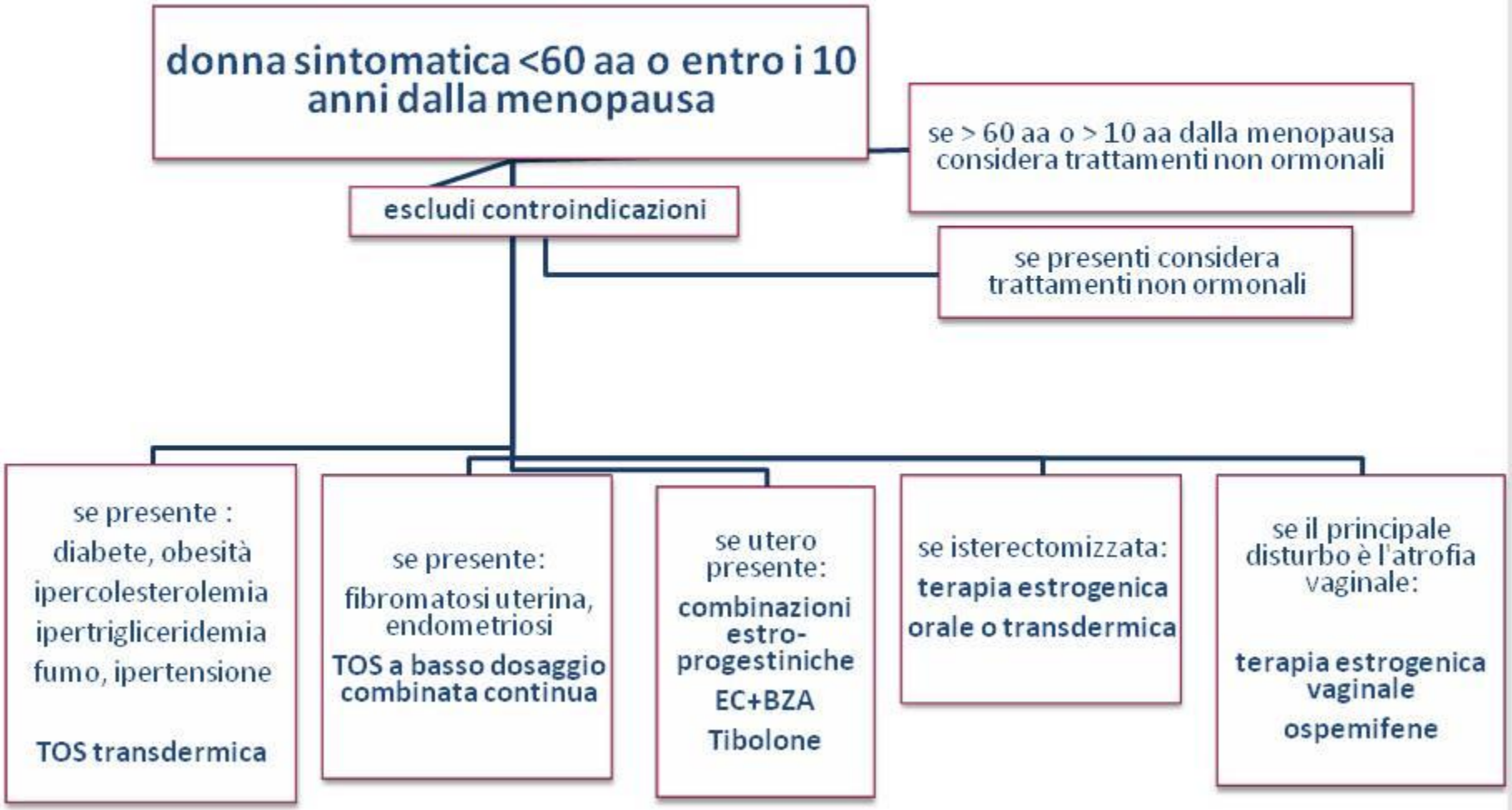
BZA, CE and BZA/CE: Attributes in Clinical Efficacy and Tolerability

Target	IDEAL HRT	BZA	CE/MPA	BZA/CE
VMS	●	●	●	●
VVA	●	●	●	●
Osteoporosis Prevention	●	●	●	● no Fx data
Breast Tenderness	●	●	●	● no BC data
Uterus Bleeding	●	●	●	●

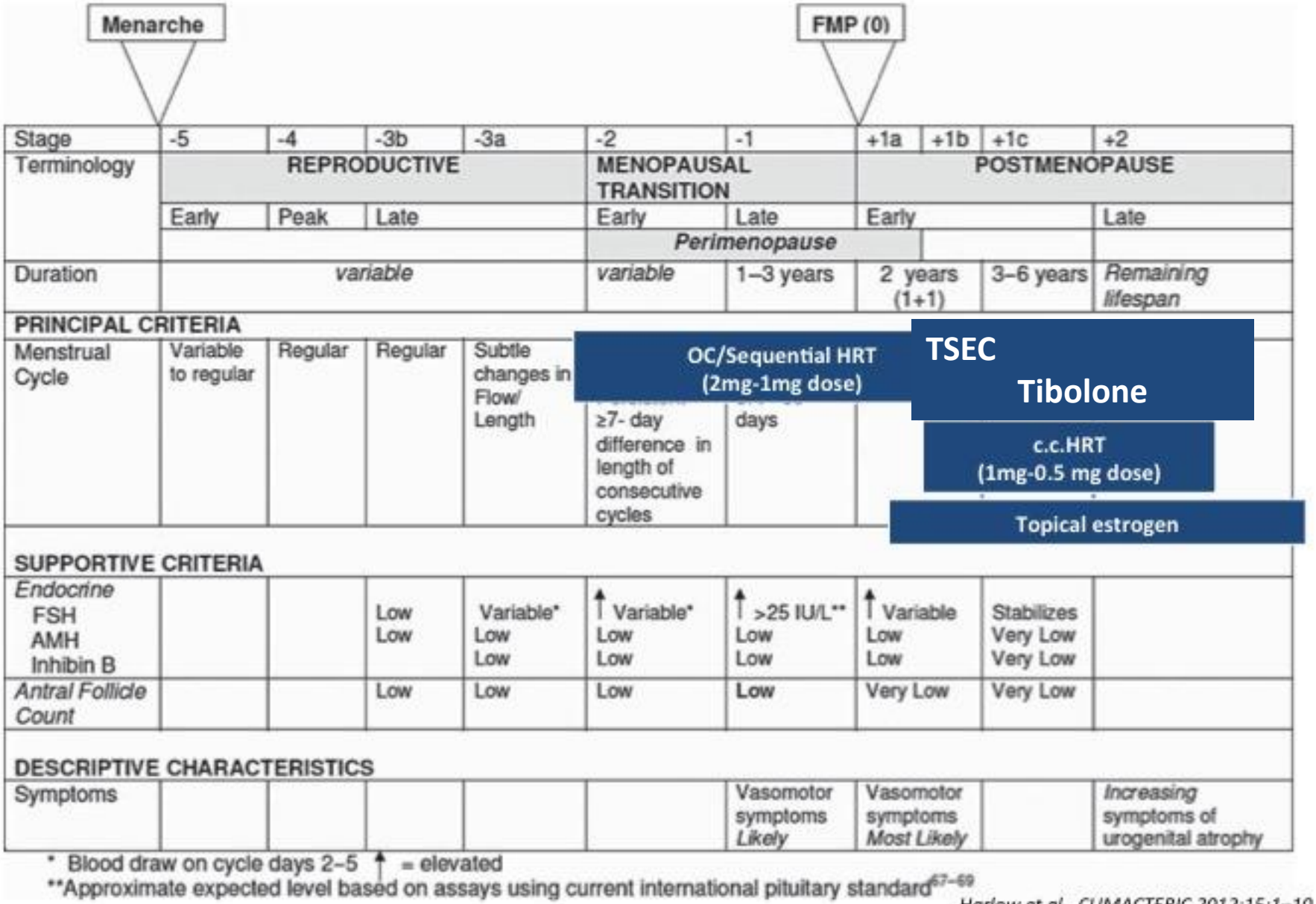
● Favorable ● Unfavorable

How can we choose HRT?

Procedimento operativo per la prescrizione della TOS



The Stages of Reproductive Aging in women



Stage	-5	-4	-3b	-3a	-2	-1	+1a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*variable*				*variable*	1–3 years	2 years (1+1)		3–6 years	*Remaining lifespan*
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/ Length	≥7- day difference in length of consecutive cycles	days				
SUPPORTIVE CRITERIA										
Endocrine										
FSH			Low	Variable*	↑ Variable*	↑ >25 IU/L**	↑ Variable		Stabilizes	
AMH			Low	Low	Low	Low	Low		Very Low	
Inhibin B				Low	Low	Low	Low		Very Low	
Antral Follicle Count			Low	Low	Low	Low	Very Low		Very Low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most Likely*			*Increasing* symptoms of urogenital atrophy

* Blood draw on cycle days 2–5 ↑ = elevated

**Approximate expected level based on assays using current international pituitary standard[67–69]

Harlow et al., CLIMACTERIC 2012;15:1–10

Menopause: The Journal of The North American Menopause Society
Vol. 24, No. 7, pp. 728-753
DOI: 10.1097/GME.0000000000000921

POSITION STATEMENT

The 2017 hormone therapy position statement of The North American Menopause Society

The experts agree about hormone therapy

- **Benefits are likely to outweigh risks for symptomatic women who initiate hormone therapy aged younger than 60 years or within 10 years of menopause onset (Level I)**

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-753.

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THE NORTH AMERICAN MENOPAUSE SOCIETY

http://simenopausa.it/