Centro Salute Donna
Azienda USL Ferrara

OSTETRICIA e GINECOLOGIA

2022

8,9 aprile 2022

Hotel Astra

V.le Cavour, Ferrara

TIBOLONE
30 anni e non sentirli

8APRILE 2022

A.Pasi (Ravenna)

Symptoms of

Menopause

Systemic
- Weight gain
- Heavy night sweats

Headache

Psychological
- Dizziness
- Interrupted sleeping patterns
- Anxiety
- Poor memory
- Inability to concentrate
- Depressive mood
- Irritability
- Mood swings
- Less interest in sexual activity

Palpitations

Breasts
- Enlargement
- Pain

Skin
- Hot flashes
- Dryness
- Itching
- Thinning
- Tingling

Joints
- Soreness
- Stiffness

Back pain

Transitional menstruations
- Shorter or longer cycles
- Bleeding between periods

Urinary
- Incontinence
- Urgency

Vaginal
- Dryness
- Painful intercourse

Principi Generali per una corretta TOS

Selezione delle pazienti

- 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

ENDOCRINE SOCIETY

IOF International Osteoporosis Foundation

European Menopause and Andropause Society EMAS

sim società italiana menopausa

NAMS The North American Menopause Society

asrm American Society for Reproductive Medicine

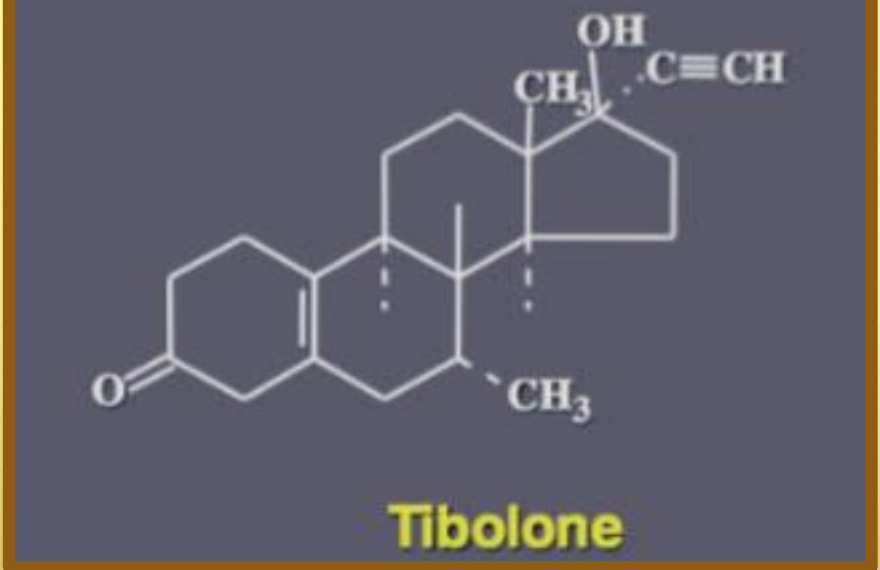
Impacting Reproductive Care Worldwide

Asia Pacific Menopause Federation

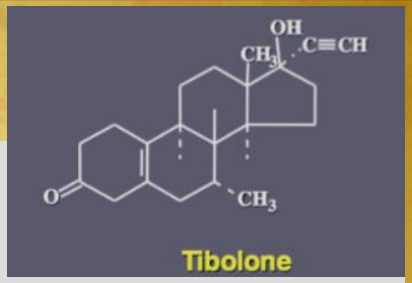
International Menopause Society IMS

A SELECTIVE, TISSUE ESTROGENIC ACTIVITY REGULATOR (STEAR)

(Regolatore Tessuto Selettivo della Attività Estrogenica)



TIBOLONE



ESTROGENIC

OH

Sulfotransferase

Sulfatase

SULFATE COMPOUNDS

3aα-HSD

HO

3a-OH-TIBOLONE

OH

3b-HSD-Isomerase

O

TIBOLONE

OH

O

Δ⁴-ISOMER

HO

3b-HSD

3α-HSD-Iso

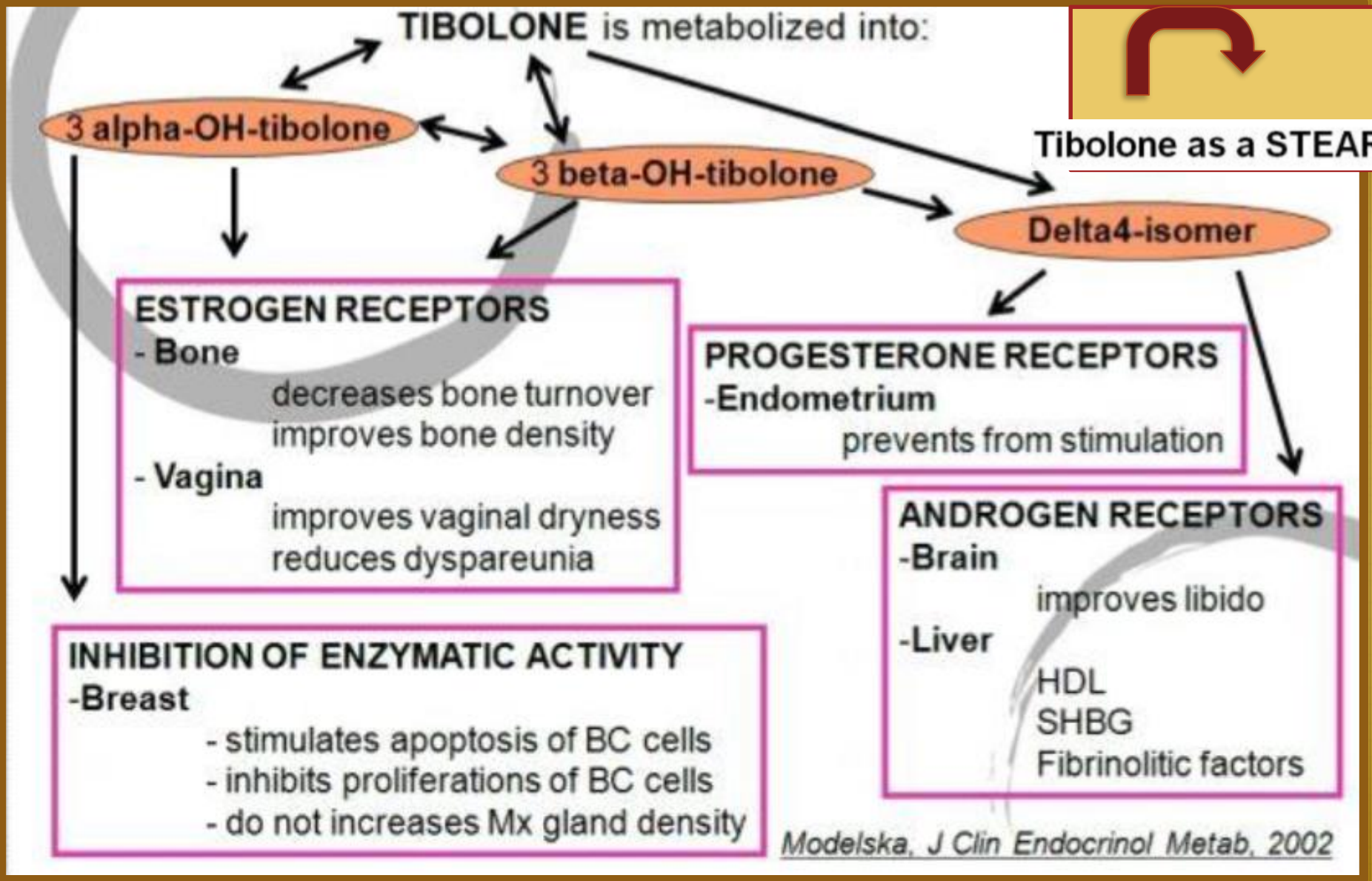
PROGESTOGENIC ANDROGENIC

ESTROGENIC

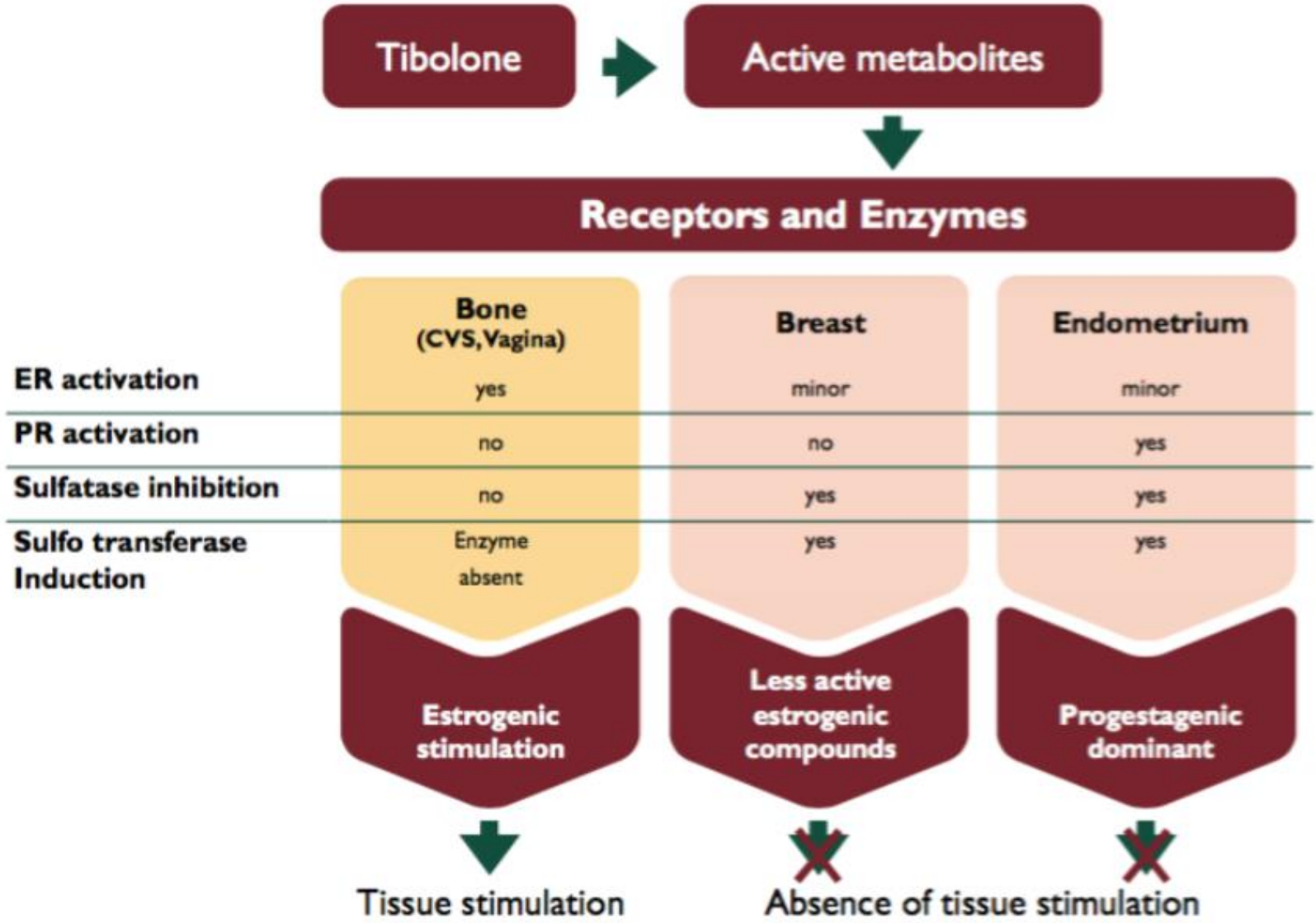
HO

3b-OH-TIBOLONE

HJ Kloosterboer, 2004


TIBOLONE is metabolized into:
3 alpha-OH-tibolone
3 beta-OH-tibolone
Delta4-isomer
Tibolone as a STEAR
ESTROGEN RECEPTORS
- Bone
decreases bone turnover
improves bone density
- Vagina
improves vaginal dryness
reduces dyspareunia
PROGESTERONE RECEPTORS
-Endometrium
prevents from stimulation
ANDROGEN RECEPTORS
-Brain
improves libido
-Liver
HDL
SHBG
Fibrinolitic factors
INHIBITION OF ENZYMATIC ACTIVITY
-Breast
- stimulates apoptosis of BC cells
- inhibits proliferations of BC cells
- do not increases Mx gland density
Modelska, J Clin Endocrinol Metab, 2002

The unique mechanism of action of tibolone



Tratto da ref. Helmond

Smith CLet al, 2004
Helmond F. 4 world Congr. Controversies Obstet. Gynecol Infertil 2003; 222 -230

Tibolone

Tibolone as a STEAR

In healthy menopausal women..

- is as effective as currently used EPT/ET regimens in the management of climacteric symptoms (hot flushes, sweating, insomnia, headache and fatigue);

- treats vaginal atrophy and relieves urogenital symptoms;

- has a positive effect on sexual well-being and is more beneficial than oral EPT/ET;

- positively affects mood;

- is as effective as EPT/ET in preventing bone loss.

P. Kenemans, Maturitas 2005

Double-blind placebo (PL) controlled trials (LISA, LIFT, OPAL, THEBES, LIBERATE) recently conducted worldwide in PMW.

Table I. Double-blind placebo (PL) controlled trials (LISA, LIFT, OPAL, THEBES, LIBERATE) recently conducted worldwide in PMW.

	Study design	Population	Study endpoints	Results
LISA study Nijland et al., 2008 [7]	Double blind randomised Treatment: 1. Tibolone 2.5 mg/day 2. Transdermal E2/NETA (50 μg/140 μg) Duration 24 weeks (June 2004–Nov2005)	403 naturally postmenopausal Women with sexual dysfunction Mean age 56 A total of 29 study centres in US, Australia, 6 in Europe	FSFI assessment at baseline, week 12 and week 24 To compare the efficacy on sexual function	Both therapies improved sexual function The increase in the FSFI scores was significantly larger in the tibolone group at week 24 The incidence of adverse events was comparable between the two groups; bleeding profile resulted to be better with tibolone
OPAL study Bots et al., 2006 [8]	Three-arm randomized placebo controlled double blind to determine 1. Tibolone 2.5 mg/day 2. CEE/MPA 0.625/2.5 mg/day 3. Placebo Duration: 3 years	866 healthy post-menopausal women from 6 US and 5 European centres Age 45–79	Arterial effect of tibolone: 1. Progression of carotid intima-media thickness (CIMT) 2. Change in meanMax CIMT	In tibolone and CEE/MPA groups significantly higher then placebo HDL cholesterol increased in CEE/MPA group and decreased in the tibolone group no statistically significant differences between groups
LIFT study, Cummings et al., 2008 [9]	Randomised double blind placebo-controlled Treatment: 1. Tibolone 1.25 mg/day 2. Placebo Recruitment: July 2001–June 2003 Duration: 3 years	4538 postmenopausal women with a BMD T score of ≤ −2.5 at the hip or spine Mean age 68	1. Annual spine radiographs were used to assess for vertebral fracture 2. Rates of cardiovascular events 3. Rates of cancer events	Decreased risk of vertebral fracture Decreased risk of non-vertebral fracture Increased risk of stroke (for which the study was stopped in Feb 2006) No differences in the risk of either coronal heart disease or venous thromboembolism Decreased risk of invasive breast cancer Decreased risk of colon
THEBES study, Archer et al., 2007 [10]	Randomised double blind comparative Treatment: 1. Tibolone 1.25 mg/day 2. Tibolone 2.5mg/day 3. Combined CEE/MPA (0.625/2.5 mg/day) in a 1:1:2 ratio Duration: 2 years	3240 healthy postmenopausal women Mean age 54.5 years; BMI ⩾18 A total of 146 centres: 73 US and 69 Europe and 4 Chile	1. Endometrial safety: incidence of hyperplasia and/or carcinoma at 1 y or 2 y endpoints 2. Vaginal bleeding pattern Additional observations:	No cases of hyperplasia or carcinoma in either tibolone group. 2 cases of endometrial hyperplasia and1 case low grade of stromal sarcoma in the CEE/MPA group Tibolone is associated with a better vaginal bleeding profile then CEE/MPA Incidence of breast pain was significantly lower in the tibolone group No stroke was reported in the tibolone group
LIBERATE study, Kenemans et al., 2009 [11]	Randomised, placebo controlled double blind parallel group Treatment: 1. Tibolone 2.5 mg/day 2. Placebo Recruitment: July 2002–Dec 2004	3098 women surgically treated for histologically confirmed breast cancer with vasomotor symptoms Mean age 52.7 years Mean time since surgery 2.1 years 245 centres in 31 countries	Safety of tibolone in: 1. Breast cancer recurrence 2. Vasomotor symptoms, BMD, HRQL	15.2% women on tibolone had cancer recurrence, compared with10.7% on placebo Study was stopped 6 months before planned NB risk of recurrence with tibolone was more evident in women with ER positive tumor status Overall significant improvement with tibolone compared with placebo Tibolone was not different from Tibolone was not different from safety outcomes

- SINTOMI VASOMOTORI
- DISTURBI UROGENITALI
- TONO DELL'UMORE
- BENESSERE SESSUALE
- RISCHIO CARDIOVASCOLARE
- RISCHIO NEOPLASTICO (MAMMELLA)
- OSTEOPOROSI

Tibolone compared with combined HT for treatment of vasomotor symptoms in postmenopausal women

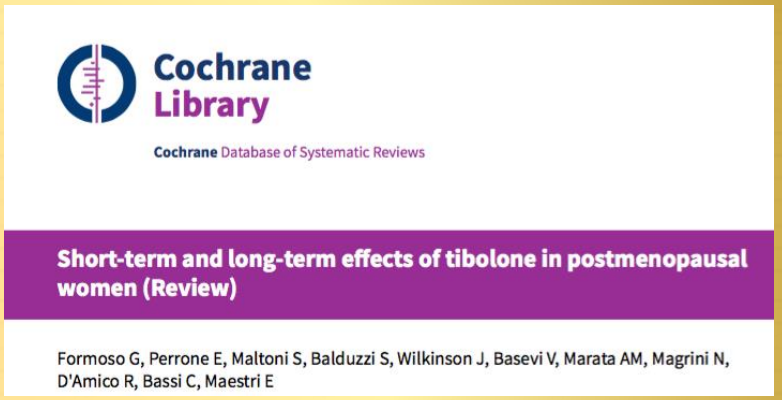
Tibolone compared with combined HT for postmenopausal women: vasomotor symptoms

Population: postmenopausal women with vasomotor symptoms

Settings: outpatient or community

Intervention: tibolone

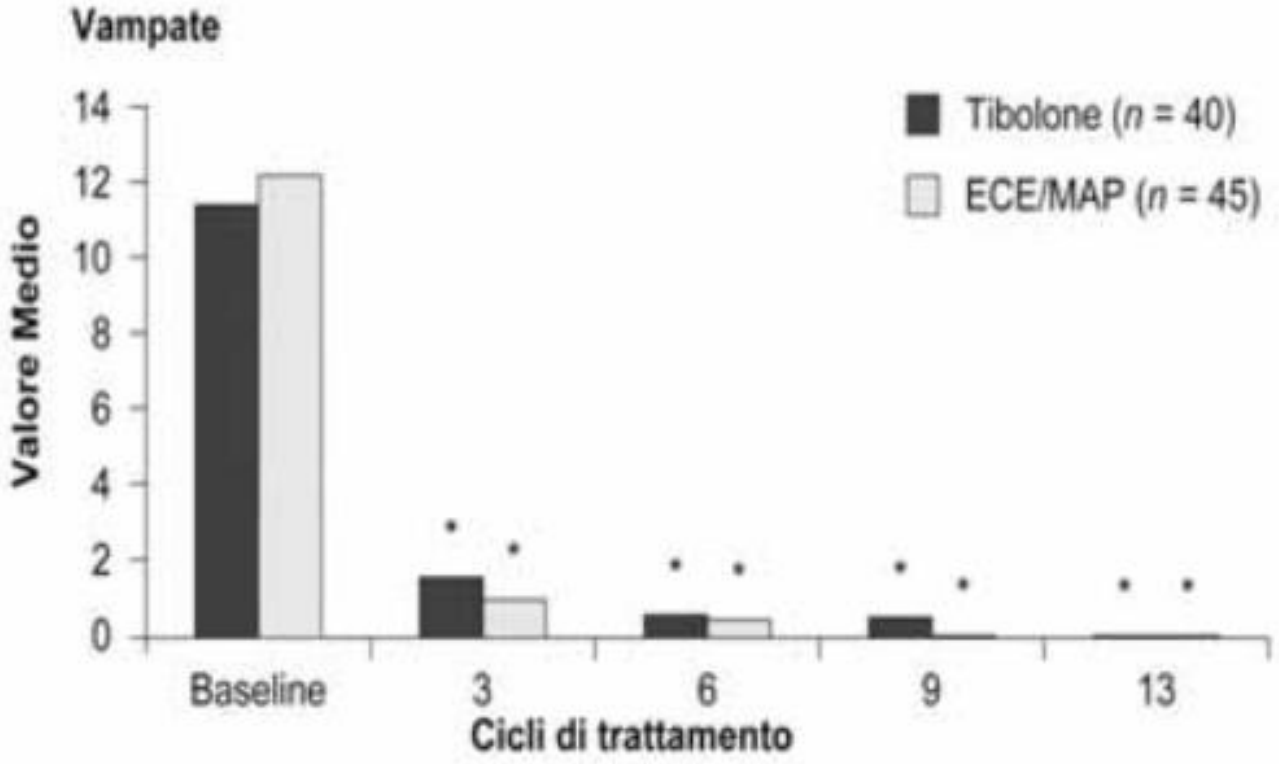
Comparison: combined HT



VASOMOTOR SYMPTOMS

Tibolone was more effective than placebo (standard mean difference (SMD) -0.99, 95% confidence interval (CI) -1.10 to -0.89; seven RCTs; 1657 women; moderate-quality evidence), but removing trials at high risk of attrition bias attenuated this effect (SMD -0.61, 95% CI -0.73 to -0.49; odds ratio (OR) 0.33, 85% CI 0.27 to 0.41). This suggests that if 67% of women taking placebo experience vasomotor symptoms, between 35% and 45% of women taking tibolone will do so.

VASOMOTOR SYMPTOMS AND TIBOLONE

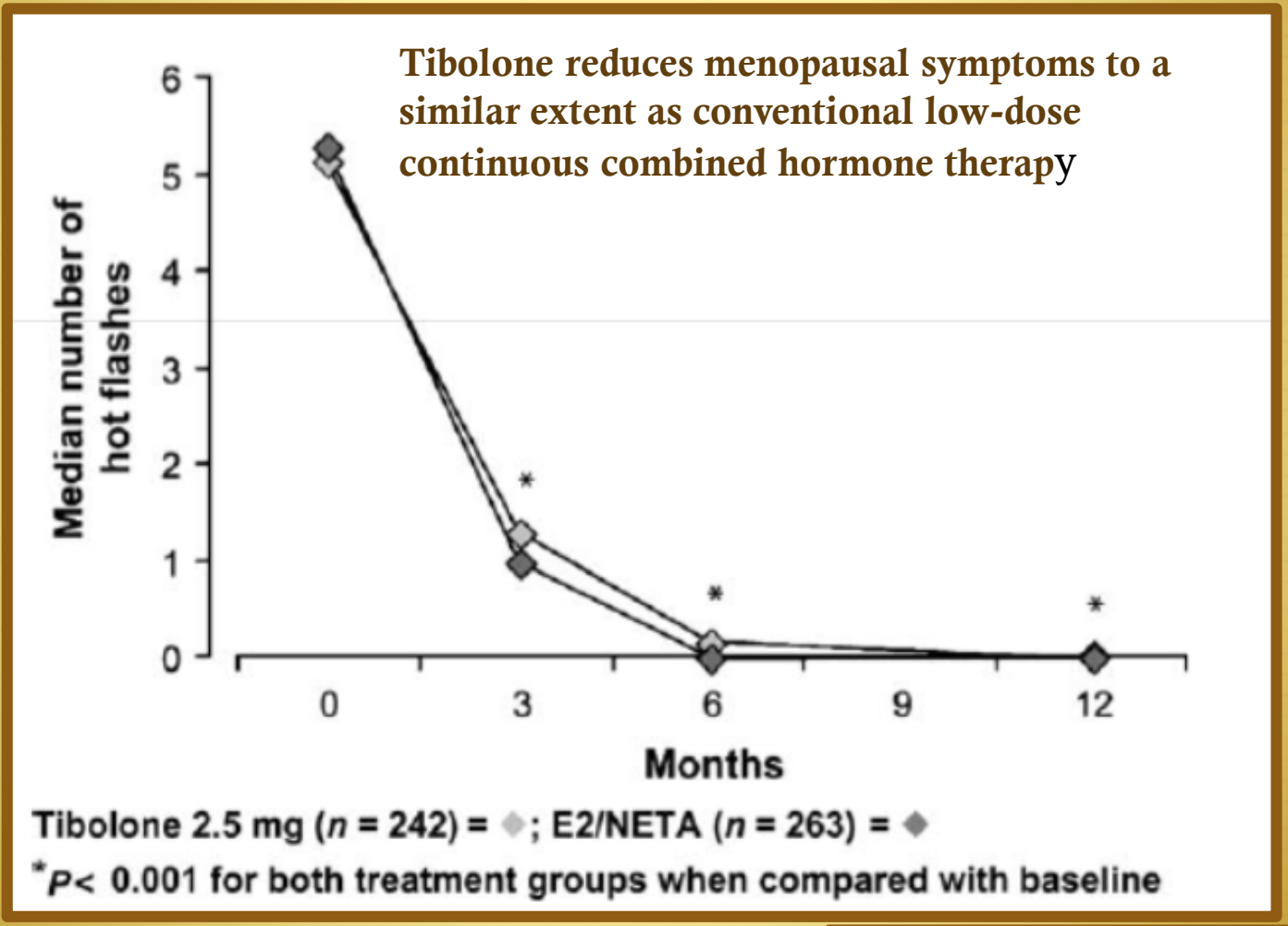


*Differenza statisticamente significativa dal baseline; ECE, estrogeni coniugati equini; MAP, medrossiprogesterone acetato

Baracat *et al.*, *Climacteric* 2002

STUDIO TOTAL

NUMERO MEDIANO DI VAMPATE DURANTE IL PERIODO DI TRATTAMENTO



Hammar et al, BJOG 2007

JSAFOMS

10.5005/jp-journals-10032-1089

RESEARCH ARTICLE

Tibolone: An Emerging Option as Hormone Replacement

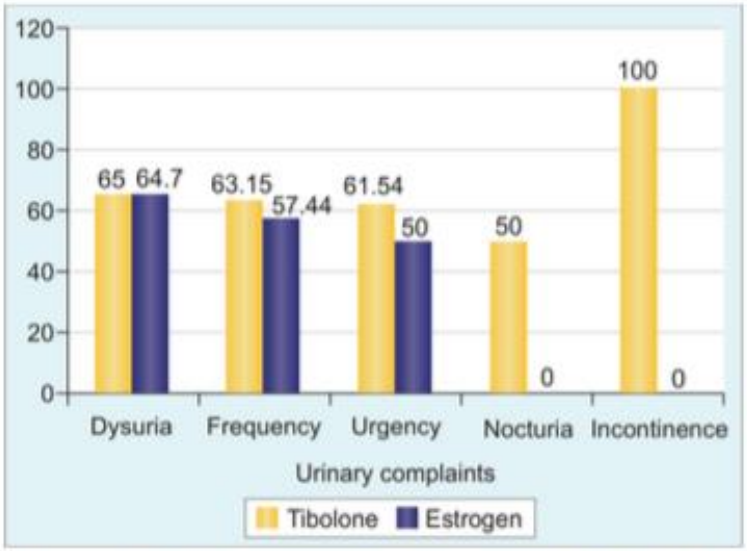
Introduction: To study efficacy and side effects of Tibolone in alleviating postmenopausal symptoms and compare it with vaginal estrogen.

Materials and methods: This prospective study was done on 100 postmenopausal women with amenorrhea of more than 1 year. All patients had one or more urogenital complaints. They were randomly assigned to receive Tibolone tablet 2.5 mg once daily (50 cases; group I) and vaginal estrogen (50 cases; group II). Both groups were compared at 1 and 6 months after starting treatment for genitourinary complaints. Chi-square test was used for comparison. A p-value of 0.05 was considered as significant.

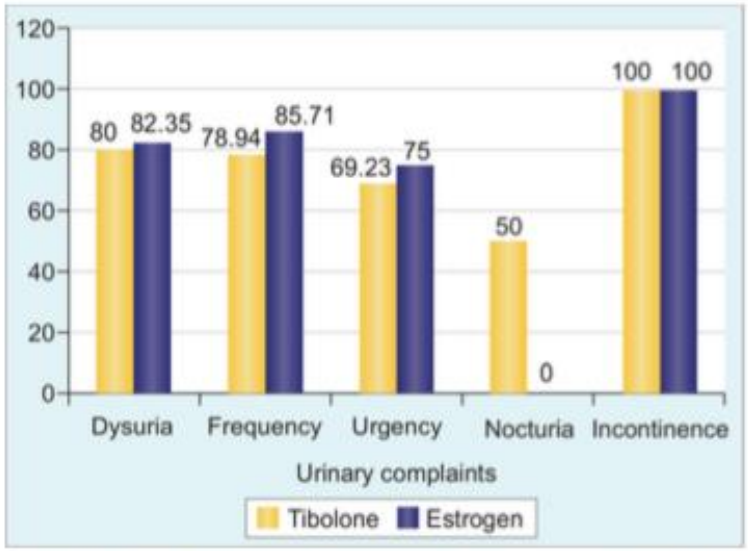
Results: After 1 month of t/t, Tibolone was slightly better in relieving genital symptoms, while significantly improved dyspareunia and dryness in vagina after 6 months as compared with estrogen. After 6 months both groups showed clinically marked improvement in dysuria, frequency, and urgency.

Conclusion: Tibolone was better than estrogen in relieving dyspareunia and dryness in vagina. Both are equally effective in relieving urogenital symptoms, decreasing the recurrence rate of vaginal and urinary infections, and bringing out improvement in general well-being. Tibolone causes less nausea, edema, breakthrough bleeding as compared with estrogen.

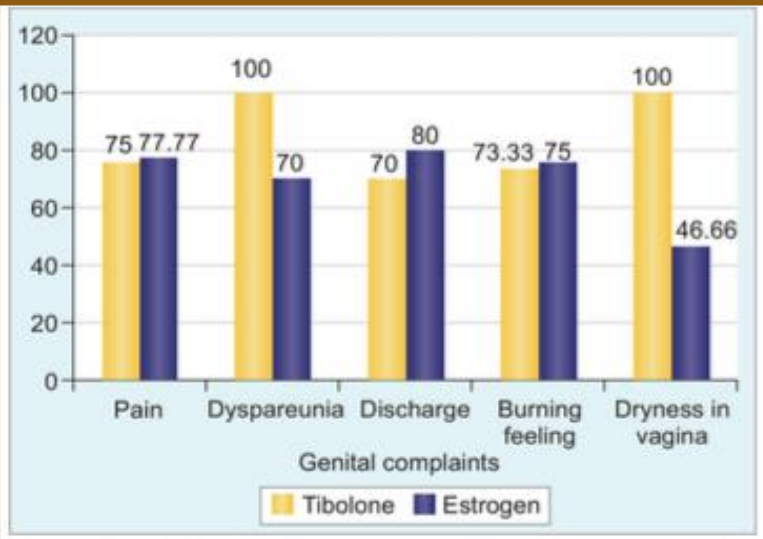
SINTOMI UROGENITALI



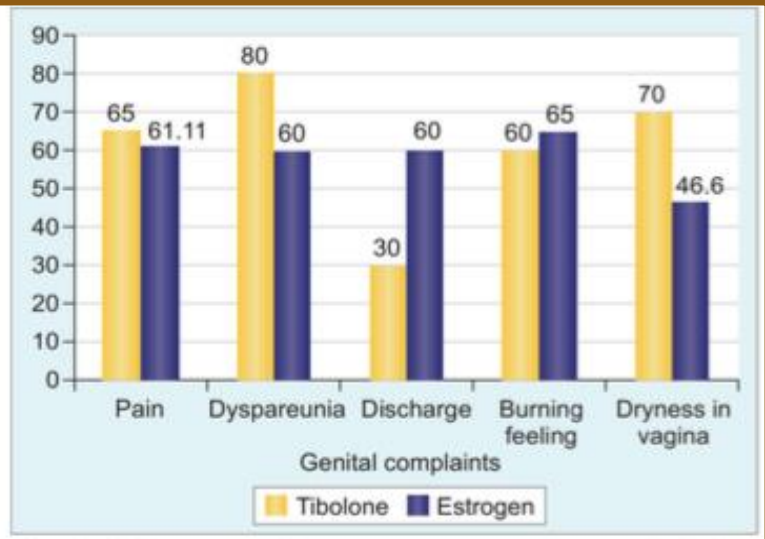
Graph 3: Distribution of patients according to degree of relief in urinary complaints after 1 month



Graph 4: Distribution of patients according to degree of relief in urinary complaints after 6 months

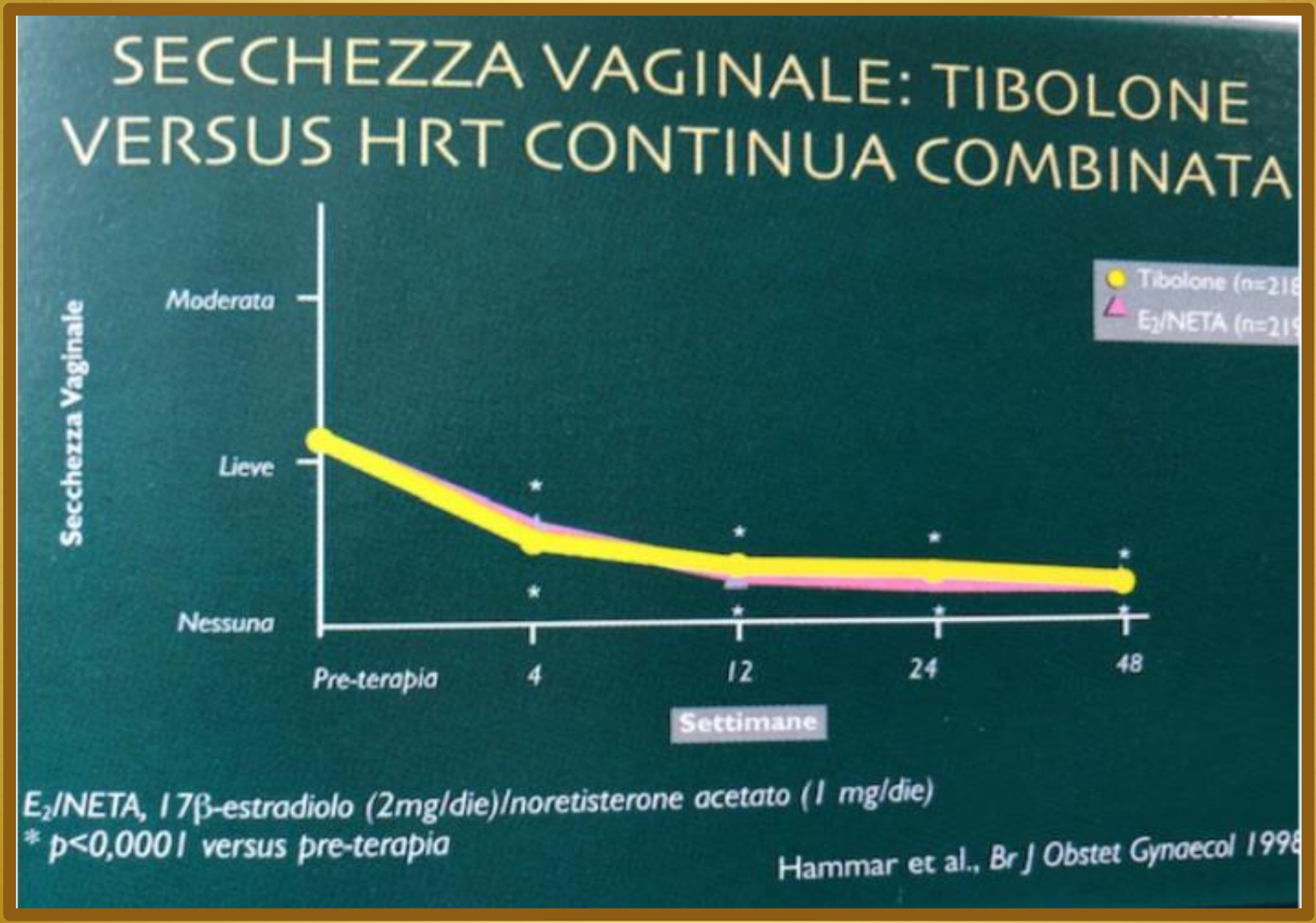


Graph 1: Distribution of patients according to degree of relief in genital symptoms after 1 month



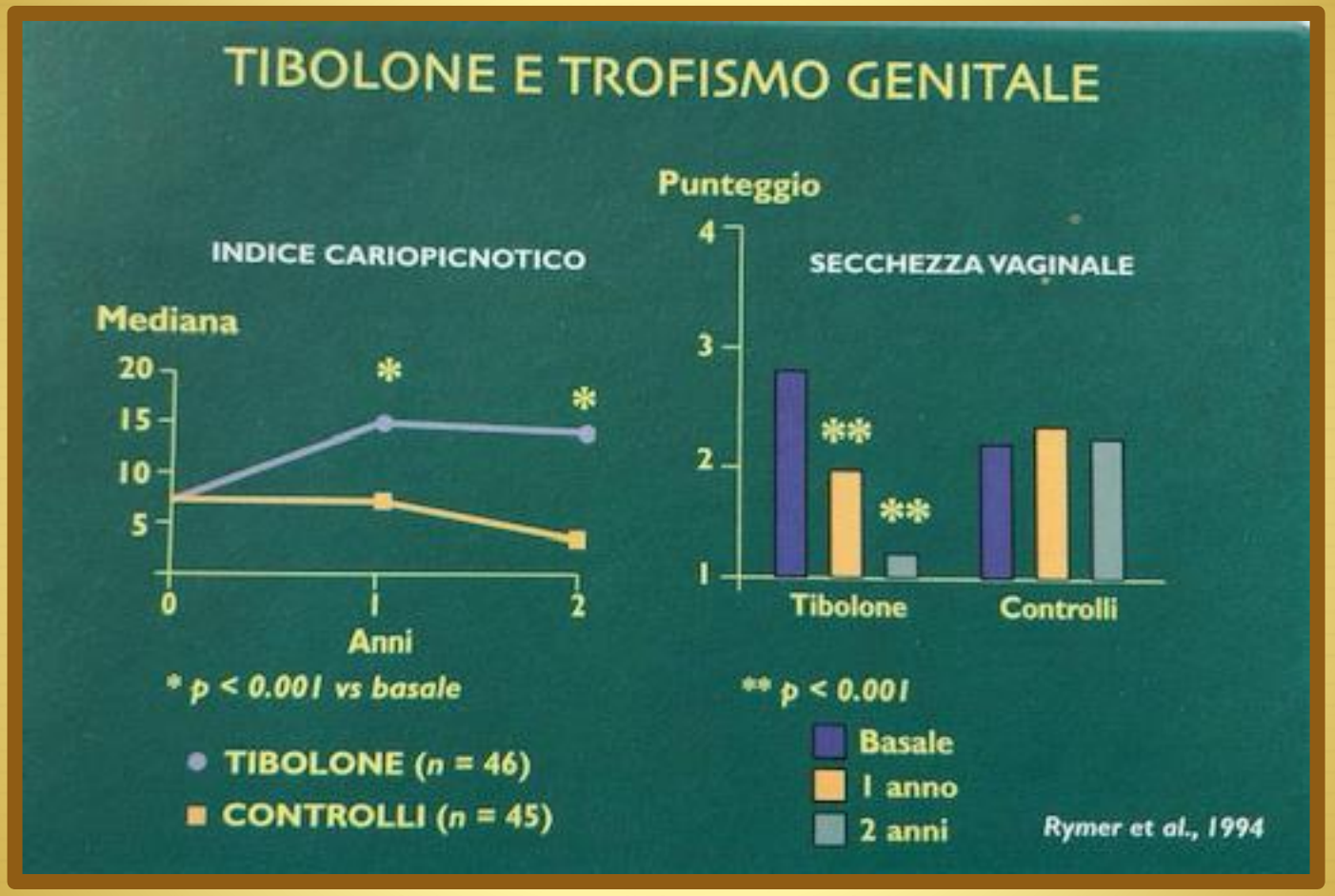
Graph 2: Distribution of patients according to degree of relief in genital complaints after 6 months

TIBOLONE E SINTOMI UROGENITALI



TIBOLONE E SINTOMI UROGENITALI

TIBOLONE E SINTOMI UROGENITALI



Tibolone and Transdermal E_2/NETA for the Treatment of Female Sexual Dysfunction in Naturally Menopausal Women: Results of a Randomized Active-Controlled Trial

Esme A. Nijland, MD,* Willibrord C.M. Weijmar Schultz, MD, PhD,* Jörgen Nathorst-Boös, MD, PhD,† Frans A. Helmond, MD, PhD,‡ Rik H.W. Van Lunsen, MD, PhD,§ Santiago Palacios, MD,¶ Robert J. Norman, MD, PhD,** Roel J. Mulder, MSc,†† and Susan R. Davis, MD, PhD‡‡ for the LISA study investigators

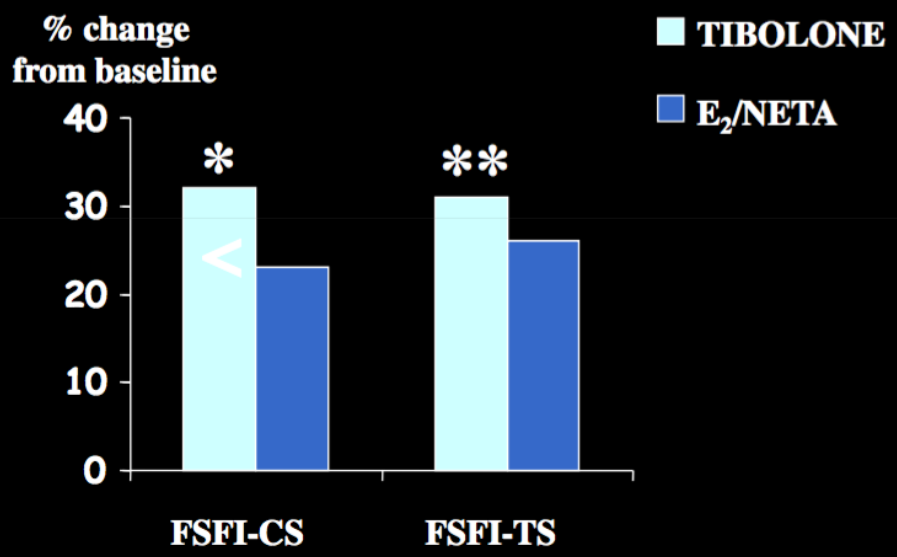
- AIM OF THE STUDY

To compare the treatment effect of tibolone (2.5 mg) to continuous combined transdermal E2/NETA (50/140μg) on sexual functioning in healthy postmenopausal women with sexual dysfunction.

- Main Outcome Measure: Female Sexual Function Index (FSFI)

J Sex Med, 2008

FSFI and TIBOLONE IN NATURALLY MENOPAUSAL WOMEN - LISA STUDY



Of the 403 women randomized 293 (73%) completed the 24-week treatment period

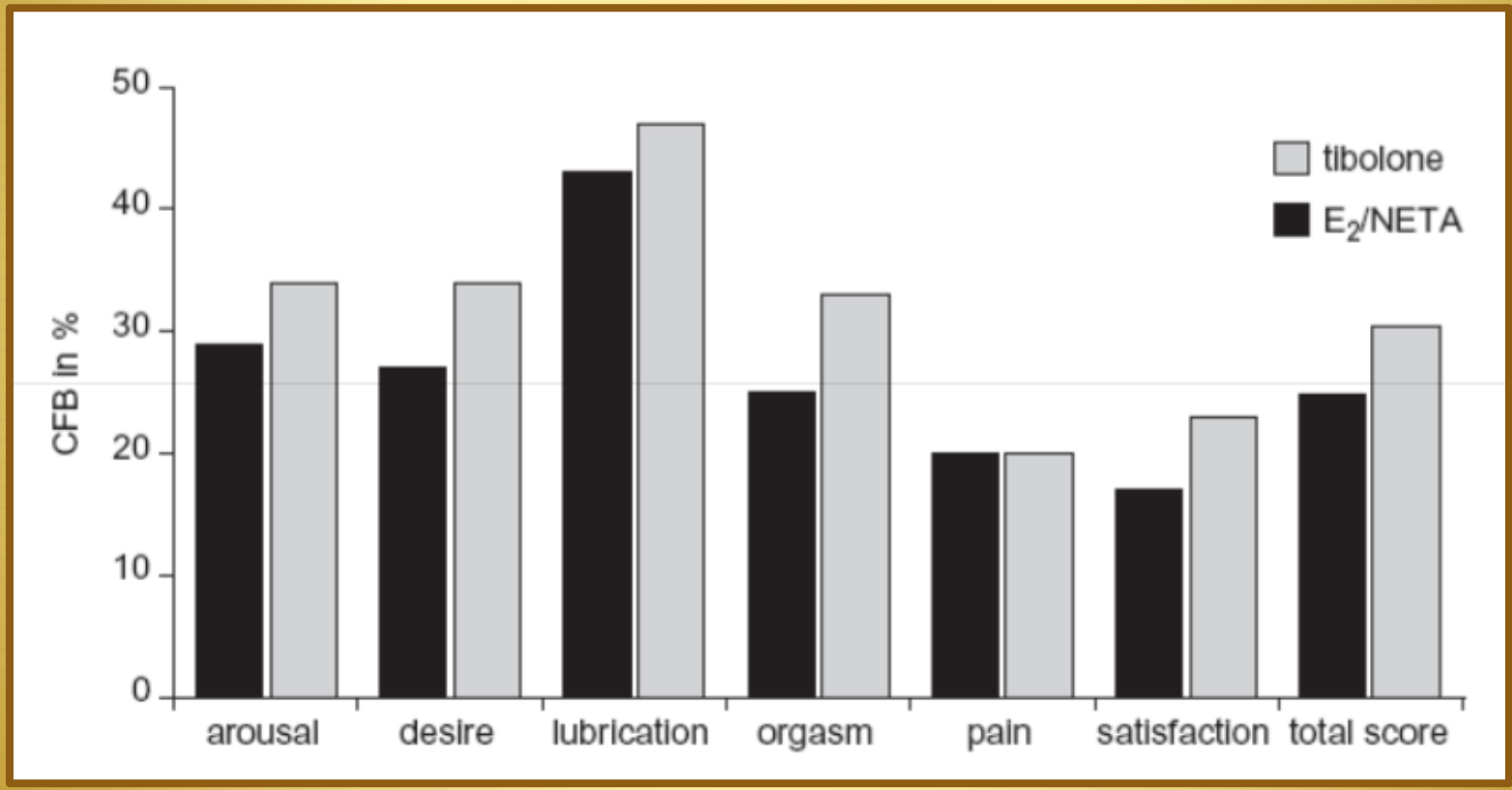
***p < 0.036 for Tib vs E2/NETA**
****p< 0.025 for Tib vs NETA**

FSFI-CS = Female Sexual Funtion Index Compositte Score: arousal, desire, satisfaction

Nijiland et al, 2008

LISA Study

Cambiamento medio % vs baseline per i diversi domini del FSFI per gruppo di trattamento alla settimana 24



Nijland et al, 2008

Lisa Study

conclusions

Both treatments resulted to improved overall sexual function, as determined by scores on the FSFI, with an increase in the frequency of sexual events, and a reduction in sexuality-related personal distress.

The statistically significant higher FSFI scores in the tibolone group, when compared to the E2/NETA group, may be because of tibolone's combined estrogenic and androgenic properties.

Emotional Impacts of Premature Ovarian Failure in Kuwait

F. E. Omu[1*], A. A. M. El Biaa[2], A. A. Ghafour[2], I. T. Gadalla[2], A. E. Omu[2,3]

[1]College of Nursing, Public Authority for Applied Education & Training, Kuwait City, Kuwait
[2]Maternity Hospital, Kuwait City, Kuwait
[3]Department of Obste ...uwait City, Kuwait

...ealth, 2016, 8, 262-278

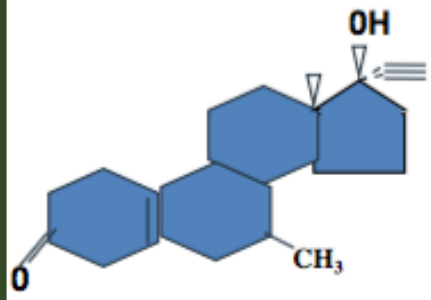
La somministrazione di tibolone è stata associata ad un aumento significativo della frequenza del coito, riduzione della dispareunia e secchezza vaginale, aumento della libido e generale soddisfazione e felicità

Abstract

Premature Ovarian F... ...age of 40 years with consequent cessation... ...o evaluate the emotional reaction and se... ...d to have Premature Ovarian Failure seen... ...study criteria, were enrolled into the study. Another group of 42 healthy women formed the control group. The instrument of data collection included three types of questionnaires to assess the depth of emotional reaction to the diagnosis... ...ientation Scale (HOS) and Stanford Chroni... ...ted at the clinic with infertility ($P < 0.01$), ...gnosis of ovarian insufficiency was a trau... ...vious loss to others), with high level of an... ...nd impaired self-esteem. Fertility was ... ...rtility was a societal landmark of woman... ...s were generally low (below 7) in coping w... ...n, loss of self-esteem and other significant emotional reactions. The present study has demonstrated that Premature Ovarian Failure is associated with severe emotional distress and impaired ability to cope with them especially low self-esteem. A multidisciplinary management team is advocated for POF.

Conclusione:L'insufficienza ovarica precoce è associata a disfunzione sessuale. Tibolone fornisce un mezzo efficace per il trattamento della disfunzione sessuale causata da insufficienza ovarica precoce.

TIBOLONE
TARGET TISSUES RELEVANT TO MENTAL & SEXUAL WELL-BEING



	affinità
3α-OH derivato	ER debole
3β-OH derivato	ER debole
Δ4 derivato	P, AR debole

NEUROENDOCRINE CIRCUITRIES

(Mental well-being, Libido, Orgasm)

VAGINAL & CLITORAL TISSUES

(Sensations, Congestion, Lubrication)

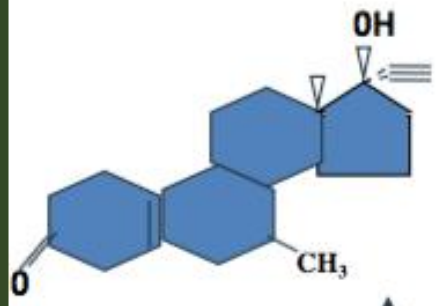
Tibolone ↑ circulating levels of Free Testosterone & DHEA-S

↓ circulating levels of SHBG

SR Davis, 2002

TIBOLONE

TARGET TISSUES RELEVANT TO MENTAL & SEXUAL WELL-BEING



	affinità
3α-OH derivato	ER debole
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Δ4 derivato	P, AR debole

NEUROENDOCRINE CIRCUITRIES

(Mental well-being, Libido, Orgasm)

VAGINAL & CLITORAL TISSUES

(Sensations, Congestion, Lubrication)

↑ **Free Testosterone & DHEA-S** ↓ **SHBG**

Effetti su umore e benessere sessuale

- ***umore e libido nelle donne in postmenopausa***

(Genazzani et al., Maturitas 1987, Nijilan et al, 2008)

- ***la funzione sessuale con un incremento del desiderio sessuale, frequenza di orgasmi, fantasie sessuali e lubrificazione vaginale***

(Laan et al, 2001, RE Nappi et al, 2006)

- ***produce significativo miglioramento del piacere sessuale vs TOS***

Nathorst-Böös and Hammar, 1997 , Dören et al., Fertil Steril 2001)

SR Davis, 2002

Gli effetti sessuali del Tibolone sono simili a quelli della terapia Estro-Androgenica

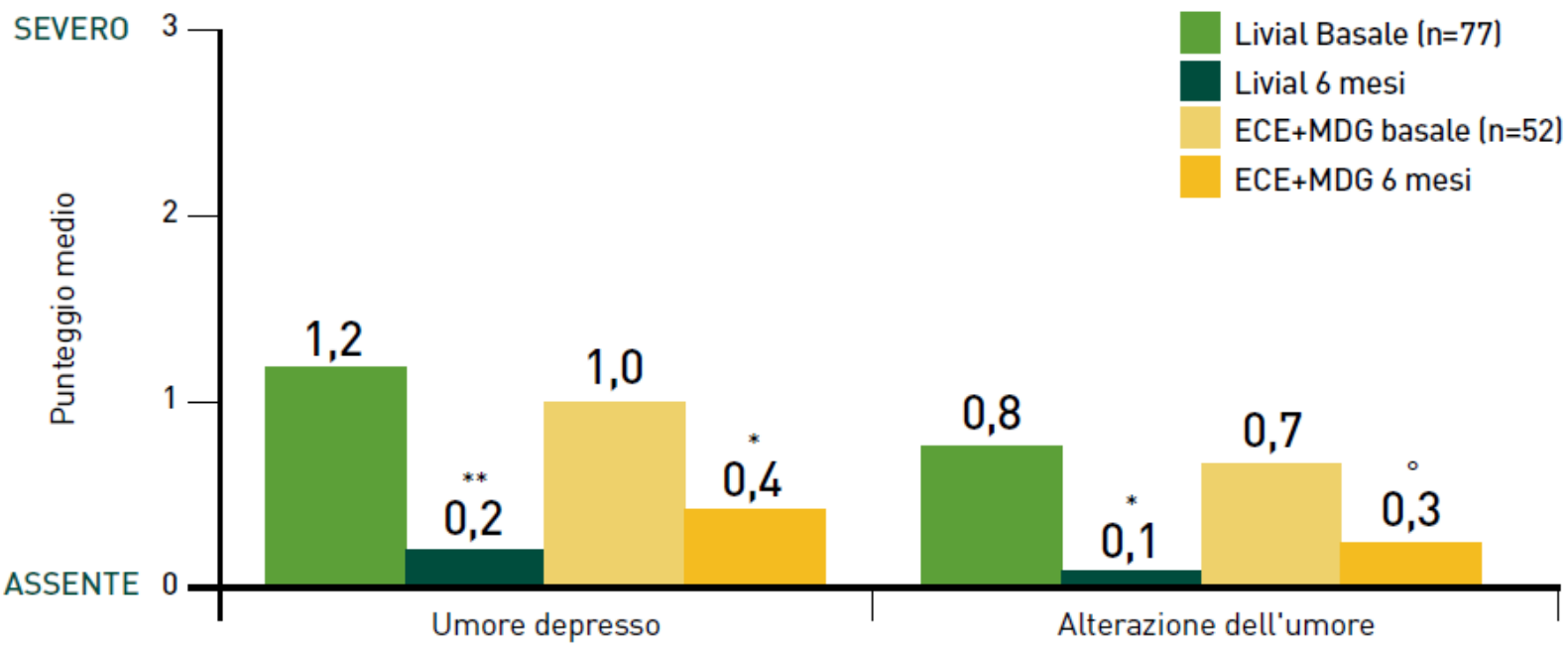
MIGLIORA LA SESSUALITA' COME HRT+ART

Opzione terapeutica per i sintomi e i segni di deficienza androgenica

- ↓ Libido/Fantasie
- ↓ Orgasmo
- ↓ Energia Vitale
- ↓ Pelo Pubico
- ↓ Eccitazione
- ↓ Sensibilità Clitoride/ Capezzoli
- ↓ Tono Muscolare
- ↑ Secchezza Cutanea

Castelo-Branco et al, 2001

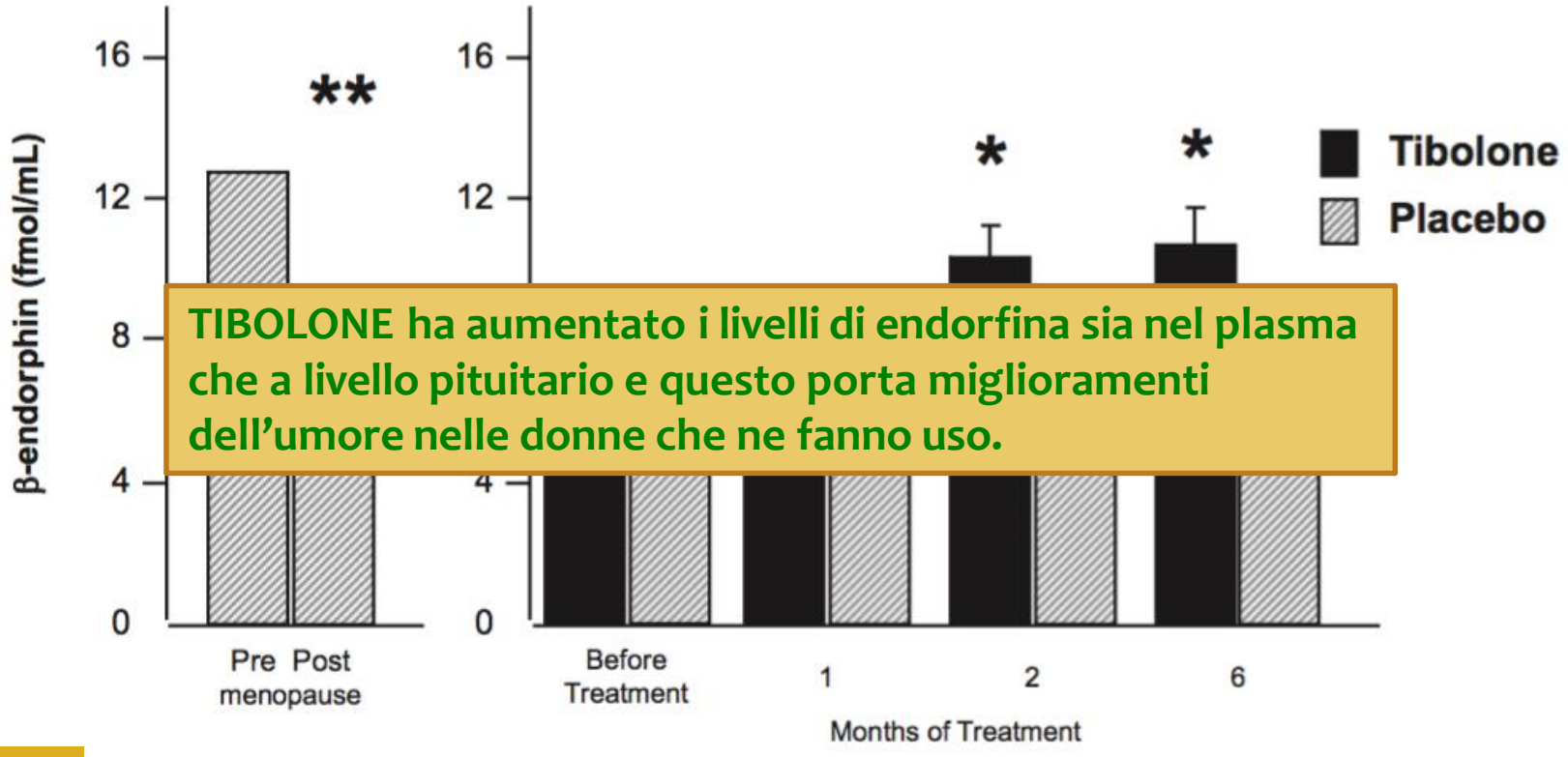
TIBOLONE E TONO DELL'UMORE



ECE + MDG, estrogeni coniugati equini (0,625 mg/die) - medrogestone (10 mg/die per 12 gg/mese)
* p<0,01 vs basale
Tibolone (2,5 mg/die); ** p<0,001 vs basale differenza non significativa tra i 2 gruppi di trattamento al baseline, a 6 mesi
° n.s. vs basale

1. EGARTER et al. Maturitas 1996; 23:55-62 - Studio randomizzato comparativo della durata di 6 mesi. 77 pazienti sono state randomizzate secondo lo schema 2:1 nel gruppo Tibolone 2.5mg/die (Livial) e 52 pazienti sono state randomizzate nel gruppo estrogeno/progesterone coniugato 0,625mg/die (Premarin) in combinazione con medrogestone (Colpron 2x5mg/dieper 12 giorni/mese). La severità dei sintomi climaterici e dello spessore endometriale sono stati determinati al basale e dopo 1, 3, 6 mesi di trattamento.

Beneficial effect of tibolone on mood, cognition, well-being, and sexuality in menopausal women



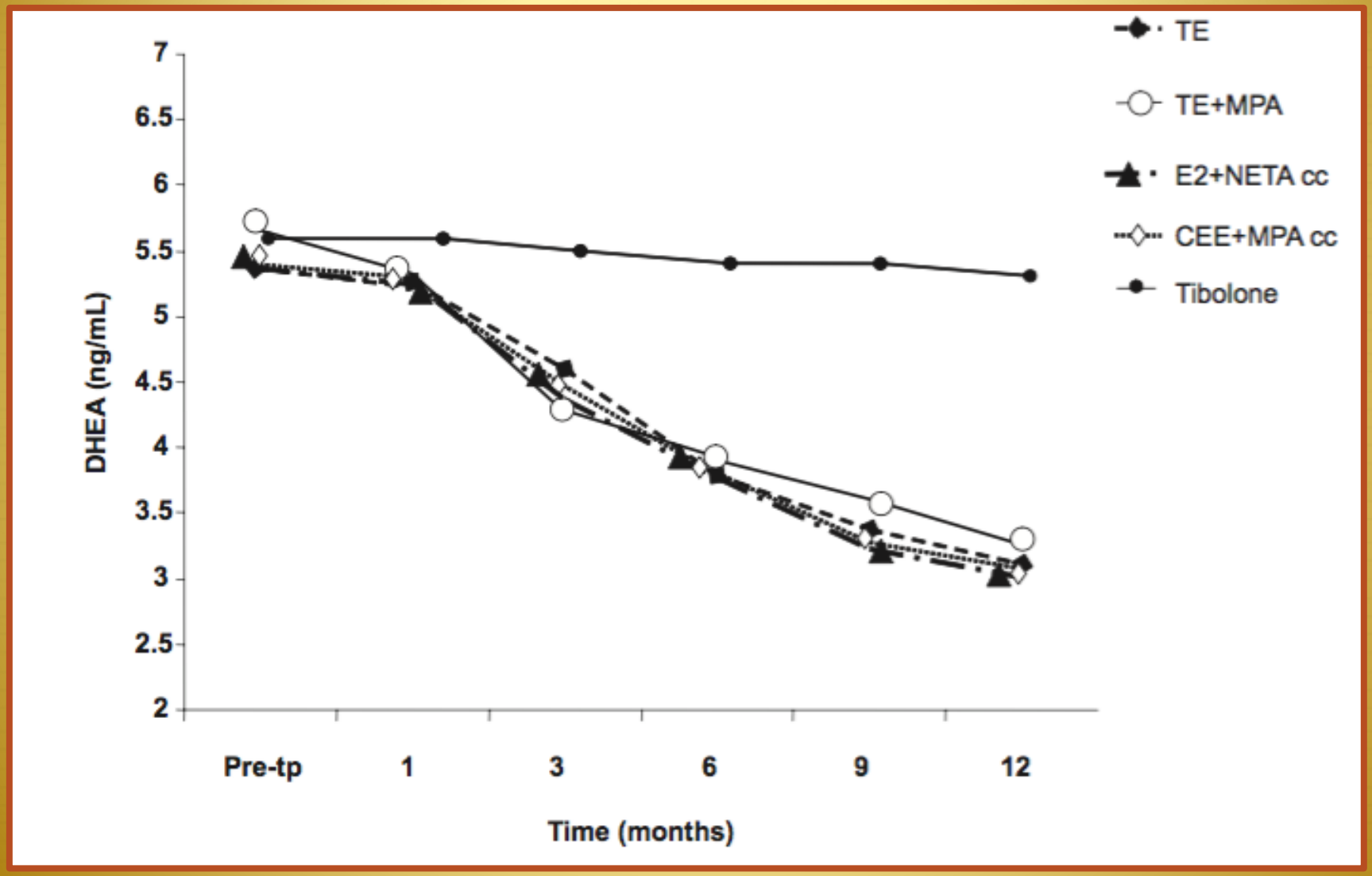
TIBOLONE ha aumentato i livelli di endorfina sia nel plasma che a livello pituitario e questo porta miglioramenti dell'umore nelle donne che ne fanno uso.

β-endorphin plasma level during tibolone administration. Adapted from Genazzani et al (2005).
*$p < 0.05$; **$p < 0.001$ among groups.

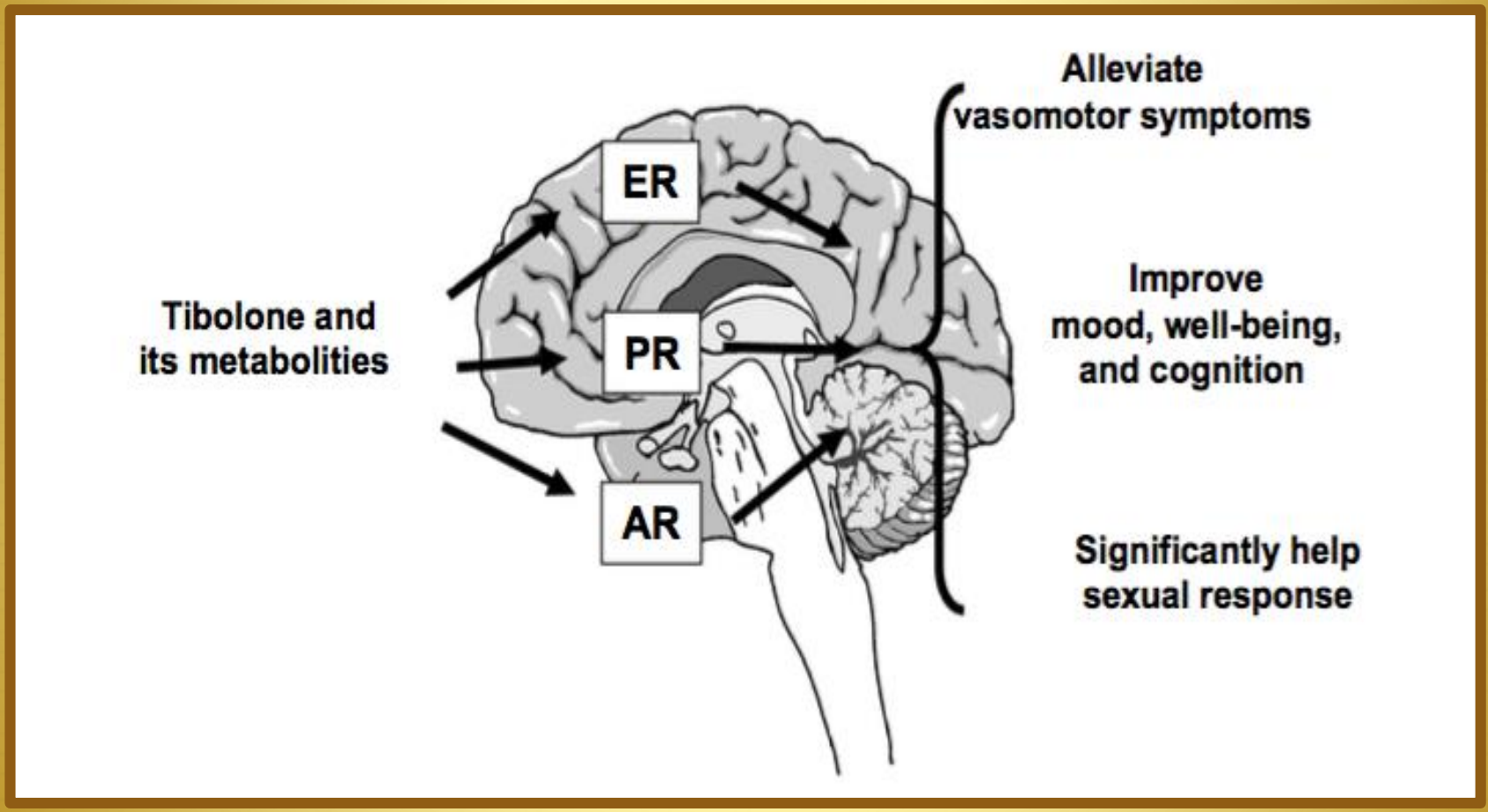
Tibolone, transdermal estradiol or oral estrogen-progestin therapies: effects on circulating allopregnanolone, cortisol and dehydroepiandrosterone levels

N Pluchino 1, A D Genazzani, F Bernardi, E Casarosa, M Pieri, M Palumbo, G Picciarelli, M Gabbanini, M Luisi, A R Genazzani

Gynecol Endocrinol2005 Mar;20(3):144-9.

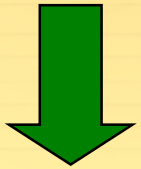


CENTRAL EFFECTS OF TIBOLONE ADMINISTRATION



Tibolone (STEAR) e Tessuto Osseo

- Azione estrogenica mediata dal legame e dall'attivazione dei recettori per gli E
- Nessuna inibizione della solfatasi (disponibilità di composti estrogenici attivi)



Prevenzione della perdita di massa ossea e aumento della densità minerale ossea

The OPAL study

BMD data from a three-year, double-blind, randomized study comparing the effects of tibolone, CEE/MPA and placebo in postmenopausal women.

Percentage of change in bone mineral density from baseline to 36 months of treatment (ITT)

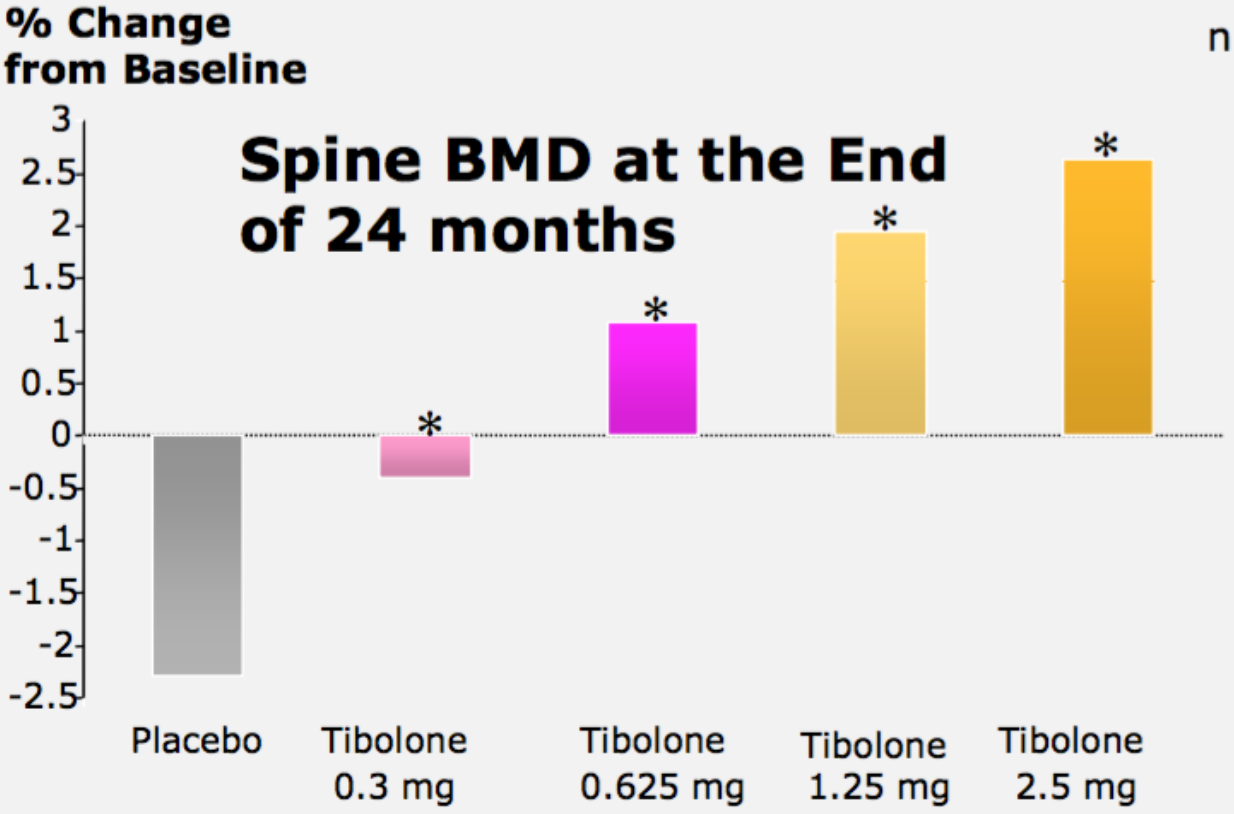
	Tibolone 2.5 mg (*n* = 247)	CEE/MPA (*n* = 255)	Placebo (n = 257)
Lumbar spine (L2–L4)	+4.22%	+4.56%	- 1.96%
Total hip	+ 3.61%	+ 3.01%	- 1.05%
Femoral neck	+ 3.10%	+ 3.31%	- 0.27%
Femoral trochanter	+ 6.18%	+ 5.61%	+ 0.36%

CEE/MPA 0.625 mg conjugated equine estrogens/ 2.5 mg medroxyprogesterone acetate

Langer *et al., 2003*

Tibolone and its effects on bone

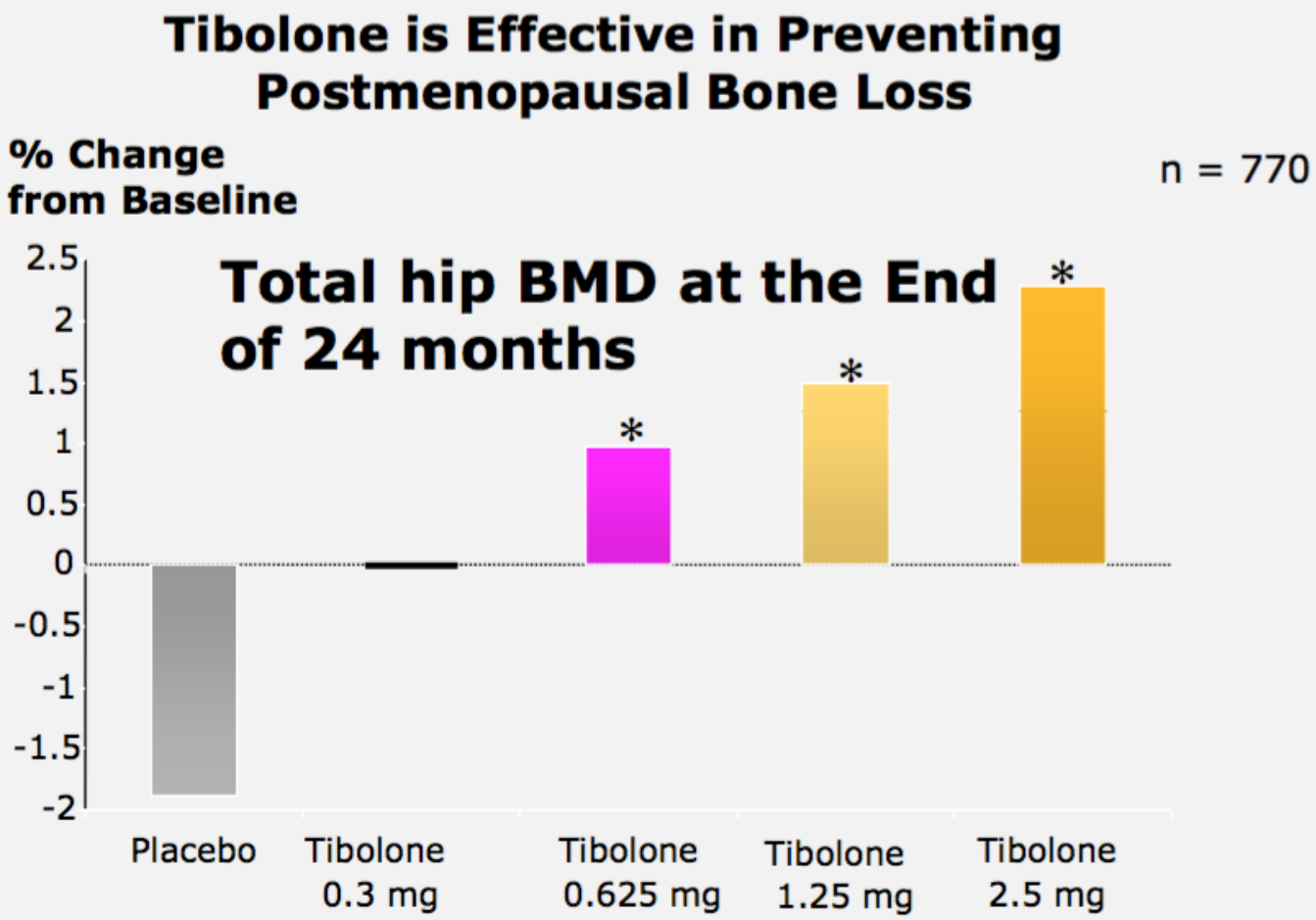
Tibolone is Effective in Preventing Postmenopausal Bone Loss



** p < 0.05 vs. placebo*

Adapted from Gallagher *et al., J Clin Endocrinol Metab 2001*

Tibolone and its effects on bone



* *p < 0.001 vs. placebo*

Adapted from Gallagher *et al., J Clin Endocrin Metab 2001*

Tibolone and its effects on bone

Change in bone markers after 24 months

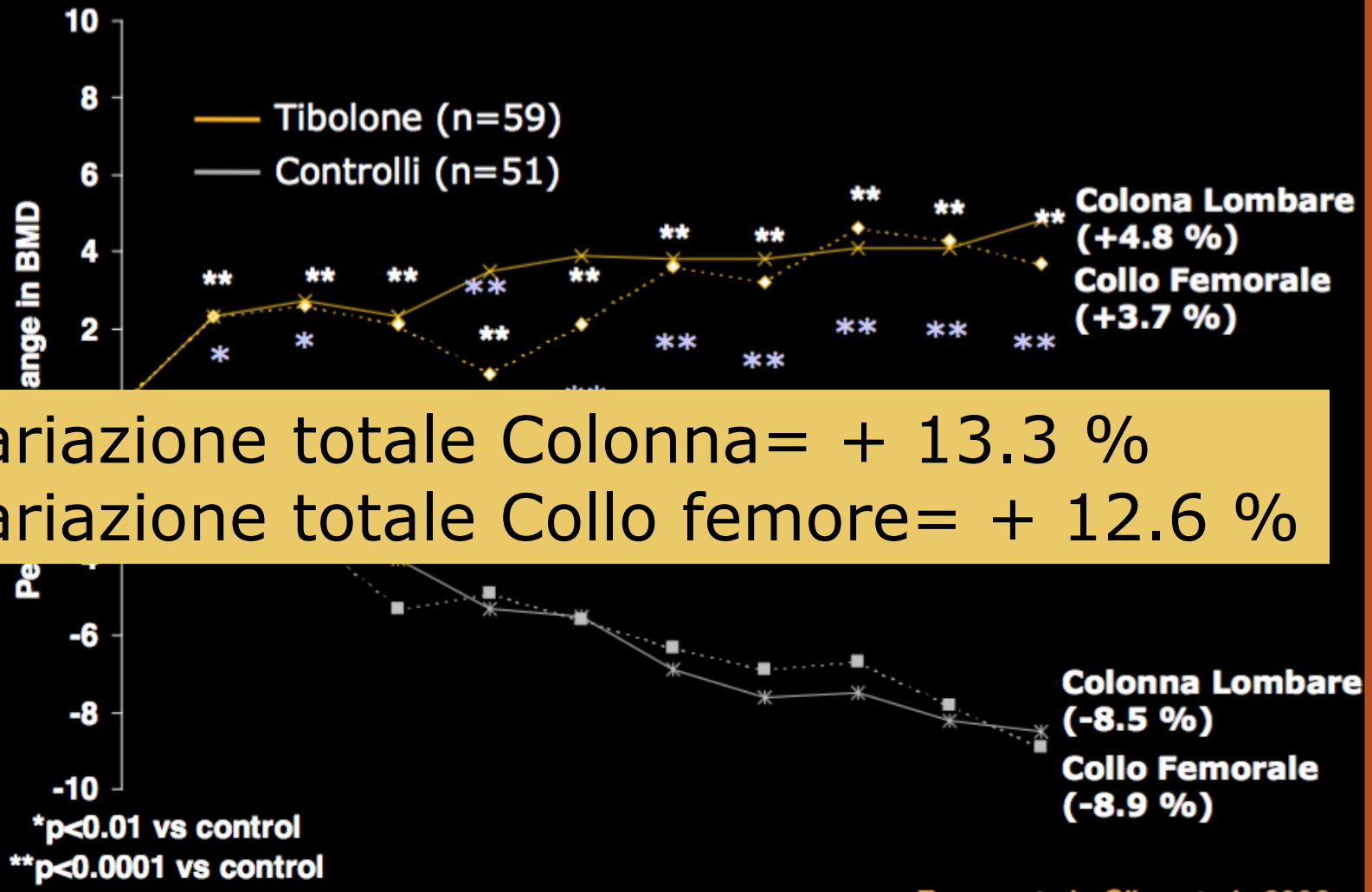
TIBOLONE previene la perdita di massa ossea, mantenendo la sua efficacia nel tempo

TIBOLONE aumenta la densità minerale ossea anche in donne con osteoporosi

TIBOLONE ha ridotto i livelli dei markers di riassorbimento osseo

Adapted from Gallagher *et al., J Clin Endocrin Metab 2001*

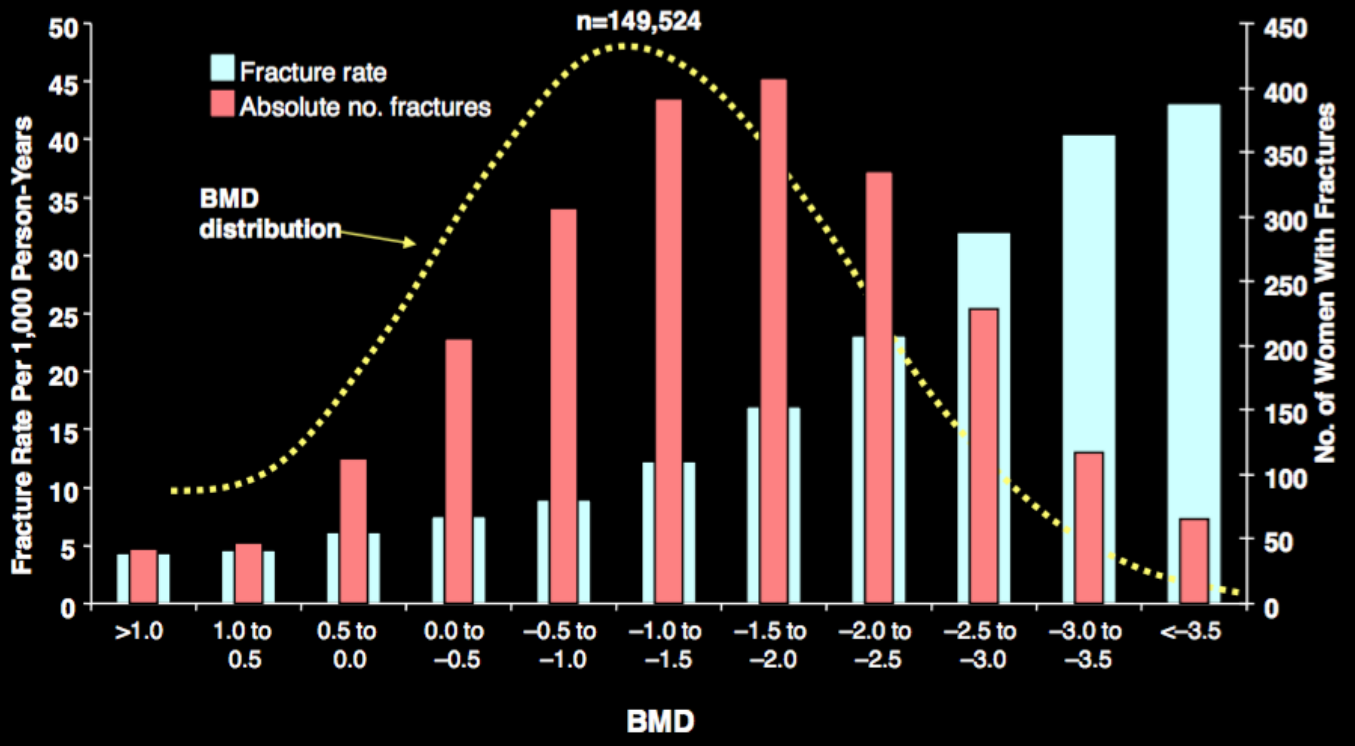
Efficacia del Tibolone



Variazione totale Colonna= + 13.3 %
Variazione totale Collo femore= + 12.6 %

Rymer *et al., Climacteric 2002,*

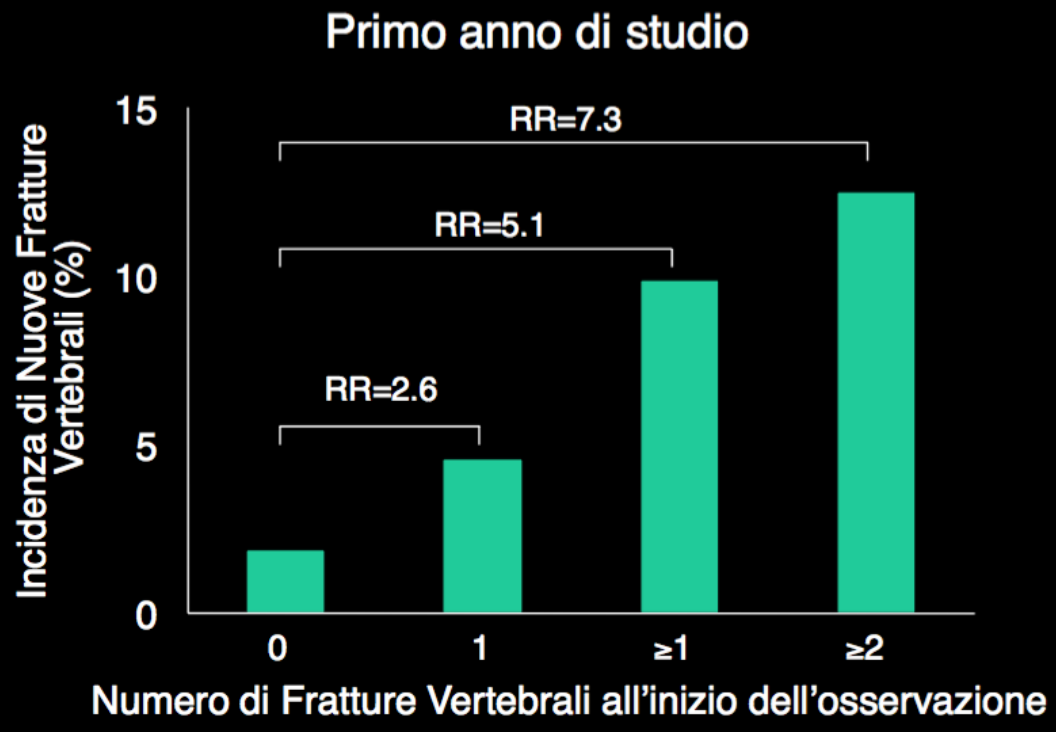
Osteoporotic Fracture Rate, BMD, and Absolute Number of Women with a Fracture by Baseline T-score



Siris ES, et al. *Arch Intern Med* 2004; 164:1108-1112.

52 % donne con Fx ha T-score tra -1.0 e -2.5

Effetti di precedenti Fratture Vertebrali sul Rischio di Fratture Vertebrali successive



Mod. da Lindsay R et al., *JAMA* 2001;285:320-23

Long-Term Intervention on Fractures with Tibolone (**LIFT**)

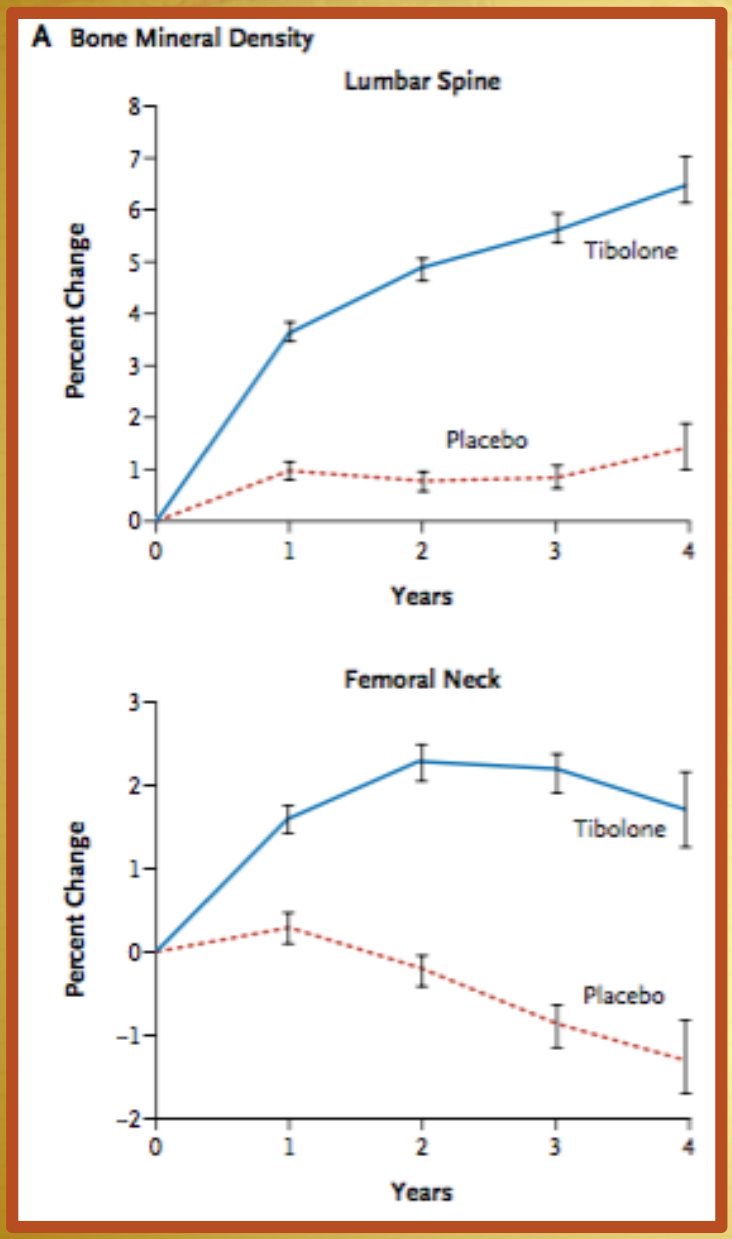
- 4.538 donne in postmenopausa con BMD T score totale femorale e/o vertebrale ≤2.5 oppure ≤2.0 con una frattura vertebrale
- età media **68.3 anni**
- Randomizzazione a **tibolone 1.25 mg** o placebo
- ***OBIETTIVO PRIMARIO***
- Riduzione dell'incidenza di **nuove fratture vertebrali** valutate mediante radiografia spinale
- ***OBIETTIVI SECONDARI***
- Incidenza di soggetti con **fratture cliniche,** comprese le fratture femorali
- **Densità minerale ossea** (BMD) delle vertebre lombari (L1-L4) e densità femorale totale misurata mediante DXA
- **Tumore mammario, malattie cardiovascolari, cancro endometriale** dopo 5 anni di trattamento

Long-Term Intervention on Fractures with Tibolone (**LIFT**)

Table 1. Characteristics of the Patients.*

Characteristic	Tibolone (N=2267)	Placebo (N=2267)
Age		
Mean — yr	68.3±5.2	68.2±5.2
≤69 yr — no. (%)	1352 (60)	1349 (60)
≥70 yr — no. (%)	915 (40)	918 (40)
Body-mass index	25.7±3.4	25.7±3.4
Previous hormone therapy — no. (%)	482 (21)	461 (20)
Family history of breast cancer — no. (%)†	208 (9)	223 (10)
Current smoker — no. (%)	289 (13)	254 (11)
Hypertension — no. (%)	807 (36)	806 (36)
Diabetes — no. (%)	106 (5)	115 (5)
Prevalent vertebral fracture — no. (%)	607 (27)	584 (26)
Previous nonvertebral fracture — no. (%)	528 (23)	479 (21)
Bone mineral density T score‡		
Total hip	−1.8±0.78	−1.8±0.79
Lumbar spine	−2.9±0.61	−2.9±0.55
Intact uterus — no. (%)	1746 (77)	1773 (78)

Long-Term Intervention on Fractures with Tibolone (**LIFT**)



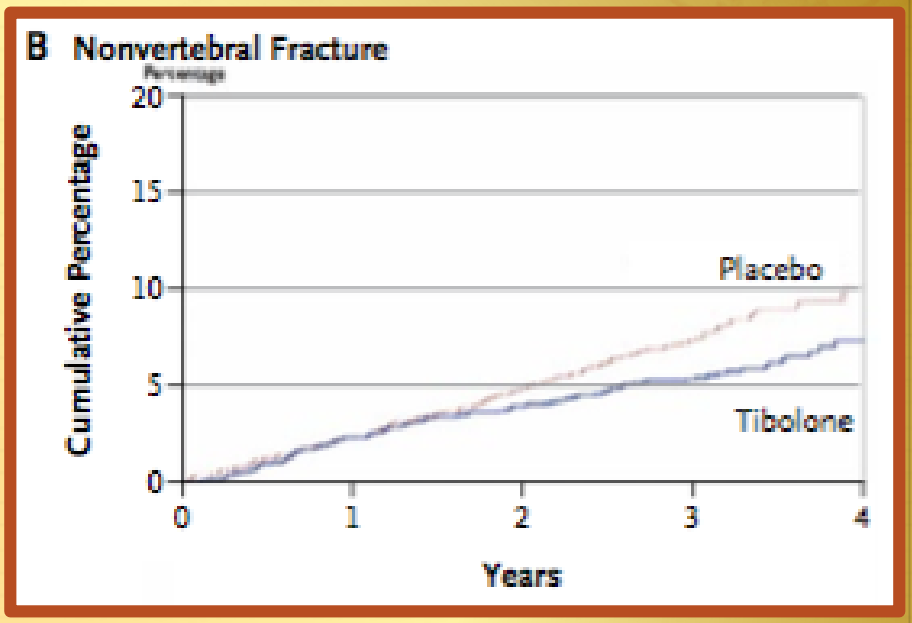


Figure 1. Percent Changes in Bone Mineral Density and Cumulative Proportions of Patients with Nonvertebral Fractures.

Panel A shows the percent changes in bone mineral density at the lumbar spine and femoral neck in the two study groups after 4 years. The differences between the tibolone group and the placebo group were significant ($P<0.001$) at each year. The I bars denote 95% confidence intervals. Panel B shows the cumulative proportions of patients in the two groups with nonvertebral fractures (relative hazard in the tibolone group, 0.75; 95% CI, 0.58 to 0.93).

Cummings et al, NEJM, 2008

Table 3. Effects of Tibolone on New Fractures, According to the Presence or Absence of a Vertebral Fracture at Baseline.*

Variable	Tibolone (N=2059)		Placebo (N=2087)		Relative Hazard (95% CI)	P Value		Risk Difference in Tibolone Group (95% CI)†
						Treatment	Interaction	
	no. of events	*no. of cases per 1000 person-years*	*no. of events*	*no. of cases per 1000 person-years*				*no. of cases per 1000 person-years*
New vertebral fracture								
No prevalent vertebral fracture	47	10.0	70	14.6	0.69 (0.48 to 1.00)	0.05	0.07	-4.6 (-9.0 to -0.1)
Prevalent vertebral fracture	23	13.6	56	34.3	0.39 (0.24 to 0.63)	<0.001		-20.8 (-31.3 to -10.2)
Nonvertebral fracture								
No prevalent vertebral fracture	89	19.3	106	22.5	0.86 (0.65 to 1.14)	0.28	0.07	-3.2 (-9.1 to 2.7)
Prevalent vertebral fracture	33	20.0	60	37.7	0.53 (0.35 to 0.81)	0.004		-17.7 (-29.4 to -6.0)

L'entità delle riduzione del rischio di FXs Vertebrali è simile a quella dimostrata con Estrogeni, Bisfosfonati e Raloxifene

Cummings et al, NEJM, 2008

Principali risultati di tibolone 1,25 mg vs PBO

Table 2. Major Outcomes.*

Outcome	Tibolone (N=2249)		Placebo (N=2257)		Relative Hazard (95% CI)	P Value	Difference in Tibolone Group (95% CI)†
	no. of events	*no. of cases per 1000 person-years*	*no. of events*	*no. of cases per 1000 person-years*			*no. of cases per 1000 person-years*
New vertebral fracture	70	10.9	126	19.6	0.55 (0.41 to 0.74)	<0.001	−8.6 (−12.9 to −4.4)
Nonvertebral fracture‡	122	19.5	166	26.3	0.74 (0.58 to 0.93)	0.01	−6.9 (−12.2 to −1.6)
Breast cancer	6	0.9	19	2.8	0.32 (0.13 to 0.80)	0.02	−1.9 (−3.4 to −0.5)
Colon cancer	4	0.6	13	1.9	0.31 (0.10 to 0.96)	0.04	−1.3 (−2.6 to −0.1)
Stroke (ischemic or hemorrhagic)	28	4.3	13	1.9	2.19 (1.14 to 4.23)	0.02	2.3 (0.4 to 4.2)
Coronary heart disease	27	4.1	20	3.0	1.37 (0.77 to 2.45)	0.28	1.1 (−0.9 to 3.2)
Venous thromboembolism	5	0.8	9	1.3	0.57 (0.19 to 1.69)	0.31	−0.6 (−1.7 to 0.5)

Long-Term Intervention on Fractures with Tibolone (**LIFT**)

Cummings et al, NEJM, 2008

Principali risultati di tibolone 1,25 mg vs PBO (Studio LIFT) (Cummings et al, NEJM, 2008)

	Rischio Relativo	Intervallo Confidenza 95%	N casi/1000 persone-anni
Nuove Fratture Vertebrali	0.55	0.41 - 0.74	-8.6
Fratture non–vertebrali	0.74	0.58 - 0.93	-6.9
Ca mammario invasivo	0.32	0.13 - 0.80	-1.9
Tromboembolismo venoso	0.57	0.19-1.69	-0.6
Malattia coronarica	1.37	0.77-2.45	+1.1
Cancro del colon	0.31	0.10-0.96	-1.3
Stroke	2.19	1.14 to 4.23	+2.3

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 359;7 WWW.NEJM.ORG AUGUST 14, 2008

The Effects of Tibolone in Older Postmenopausal Women

METHODS

In this randomized study, we assigned 4538 women, who were between the ages of 60 and 85 years and had a bone mineral density T score of –2.5 or less at the hip or spine or a T score of –2.0 or less and radiologic evidence of a vertebral fracture, to receive once-daily tibolone (at a dose of 1.25 mg) or placebo. Annual spine radiographs were used to assess for vertebral fracture. Rates of cardiovascular events and breast cancer were adjudicated by expert panels.

CONCLUSIONS

Tibolone reduced the risk of fracture and breast cancer and possibly colon cancer but increased the risk of stroke in older women with osteoporosis. (ClinicalTrials.gov number, NCT00519857.)

Steven R. Cummings, M.D., Bruce Ettinger, M.D., Pierre D. Delmas, M.D., Ph.D., Peter Kenemans, M.D., Ph.D., Victoria Stathopoulos, Ph.D., Pierre Verweij, Ph.D., Mirjam Mol-Arts, M.D., Lenus Kloosterboer, Ph.D., Lori Mosca, M.D., Ph.D., M.P.H., Claus Christiansen, M.D., John Bilezikian, M.D., Eduardo Mario Kerzberg, M.D., Susan Johnson, M.D., Jose Zanchetta, M.D., Diederich E. Grobbee, M.D., Ph.D., Wilfried Seifert, Ph.D., and Richard Eastell, M.D., for the LIFT Trial Investigators*

TIBOLONE E SISTEMA CARDIOVASCOLARE

↑ OUTPUT CARDIACO
FLUSSO EMATICO(CAPILLARI ED ARTERIE)

- NON MODIFICHE DELLA PA
- EFFETTO BENEFICO SU ECG DA SFORZO

↓ HDL,TG.LIP(A)
- STIMOLO DELLA FIBRINOLISI
- NON EFFETTI SULLA COAGULAZIONE (MINIMO EFFETTO SULLA ATTIVITA' PROCOAGULANTE ,MA I LIVELLI DI FIBRINOGENEO E FATT VII POSSONO DIMUNUIRE ; AUMENTI DI PLASMINOGENO E ATIII ; LIVELLI DI TPA E PAI-I DIMUINUSICONO DEL 30%)
- NON EFFETI SU METABOLISMO CARBOIDRATI
- NON ALTERAZIONI DELLA COMPOSIZIONE CORPOREA

TIBOLONE AND CARDIOVACULAR SYSTEM

✓ **CRP and inflammatory markers**

Conflicting data are available on the effects of T on **CRP and other inflammatory markers**

✓ **ATH**

T show

✓ **T re**

Findings
indicate
in PMW
effects
(a) leve
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✓ **EN**

Nevertheless, it is important to underline that T does not increase the risk of venous thromboembolism, as confirmed from the more recent randomised controlled trials (LIFT study and THEBES study)

Simoncini et al. showed that the D4 isomer had a neutral effect on nitric oxide (NO) synthesis, which implies that the effect of **T on endothelial NO production is likely to be mediated by estrogen receptors**

✓ **COAGULATORY SYSTEM**

Even data of the effects of T on the coagulatory system are not univocal The potential benefits were related to a decrease in fibrinogen, Factor VII, plasminogen activator inhibitor 1 (PAI-1) and tissue plasminogen activator. Such tendency towards fibrinolytic activity in the haemostatic system seemed be related to the androgenic effect of T

Hormone therapy and risk of myocardial infarction: a national register study

E. Løkkegaard,
EHJ 2008

The age-str… infarction with various Hormone Therapy regimens from multivariable model.

Tibolone
no aumento di rischio

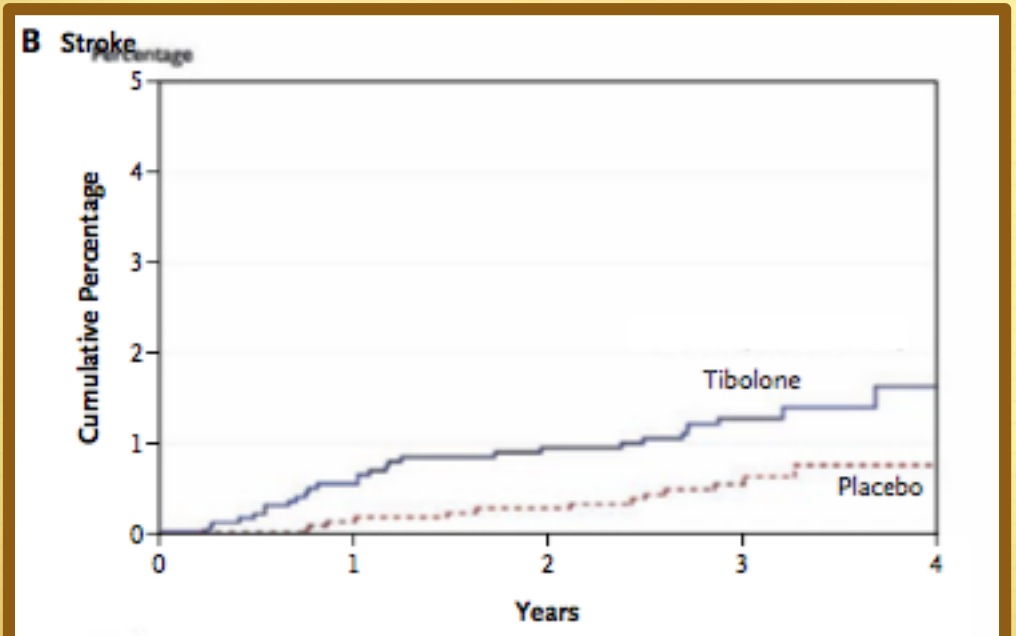
Studio THEBES

Incidenza di eventi avversi cardiovascolari (tutti i soggetti trattati)

(range età: 45-65 aa; media 54.4)

AE	Combined tibolone group	CEE/MPA
Subjects as treated	1598	1626
Women-years	2402	2415
Stroke	0	2
Transient ischemic attack	0	1
Pulmonary embolism	0	1
Deep venous thrombosis	0	2
Myocardial infarction	2	2
All adjudicated cardiovascular events	2	8

Effetti di tibolone 1,25 mg sul Rischio di Stroke (Studio LIFT)



Per 1000 donne:

- 50-59 anni → 4 casi in più
- 60-69 anni → 13 casi in più

Cummings et al, NEJM, 2008

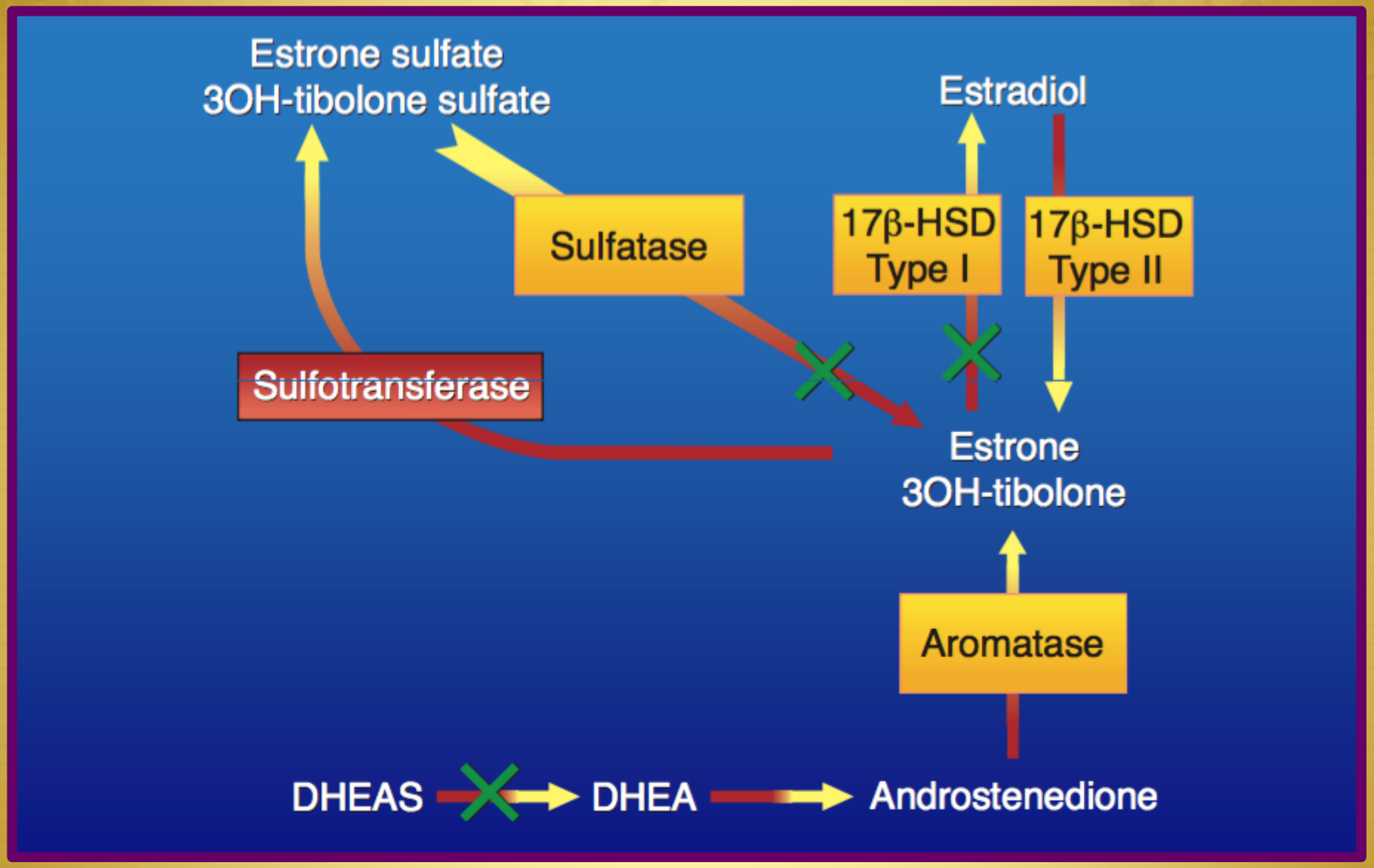
TIBOLONE E STROKE:CONSIDERAZIONI

- FATTORI DI RISCHIO :
  IPERTENSIONE ARTERIOSA
  DISLIPIDEMIA
  ATEROSCLEROSI

PIU' FREQUENTI E DI MAGGIORE ENTITA' CON L'AUMENTARE DELL'ETA'

- CONCLUSIONI : COME PER HRT E' OPPORTUNO NON UTILIZZARE T. NELLE DONNE ANZIANE O IN QUELLE CON FATTORI DI RISCHIO PER STROKE (I.A, FUMO,DIABETE ,FA)

TIBOLONE E MAMMELLA



Regolazione degli enzimi nella mammella

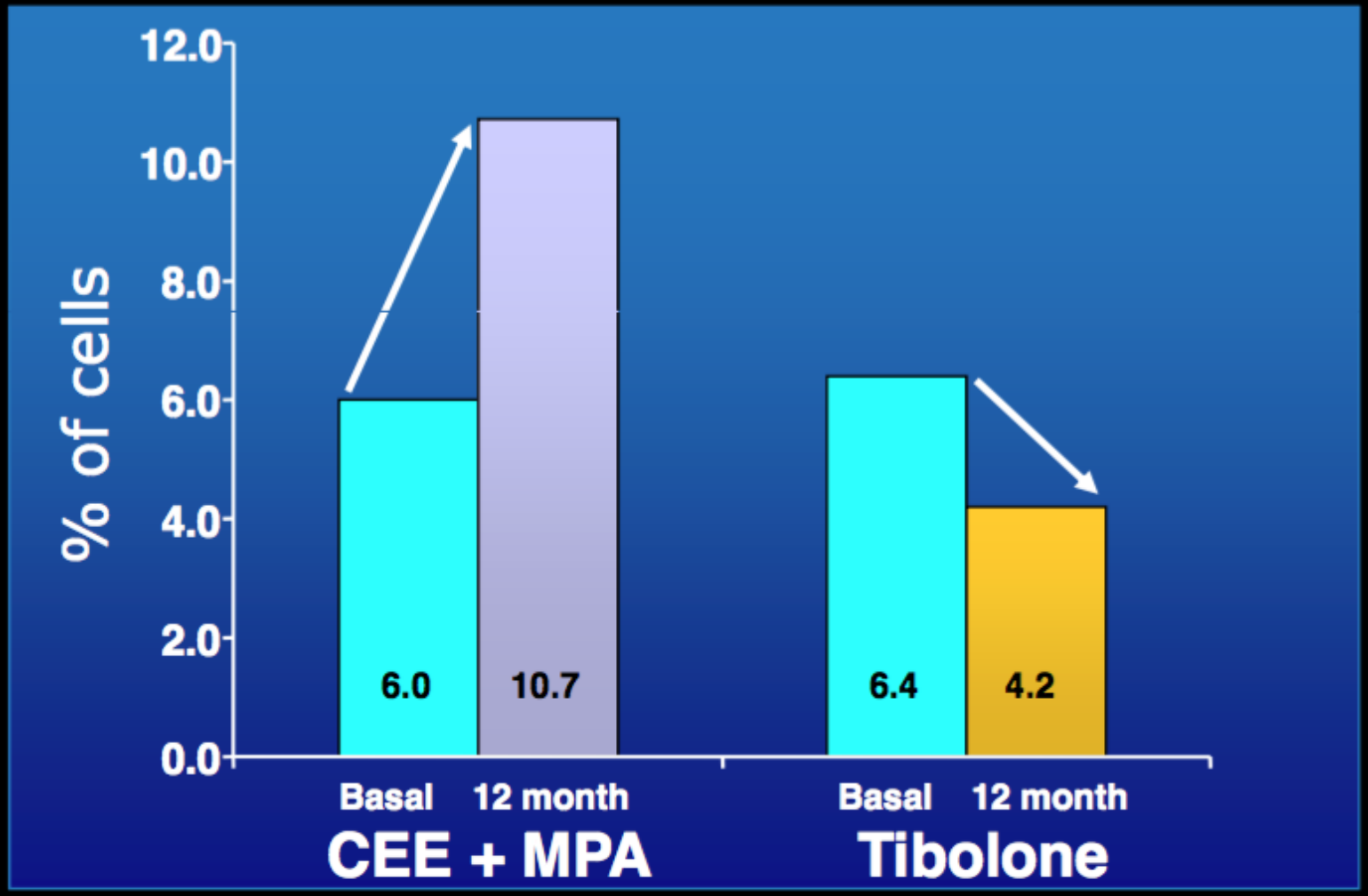
Effetti sul sistema solfotransferasi-solfatasi previene la stimolazione della mammella

Solfotrasferasi ↑

- No attività antagonista per ER
- No inibizione dell'aromatasi
- Omeostasi cellulare
  (aumento dell'apoptosi & diminuzione della proliferazione)
- Inibizione della Solfatasi

Solfatasi ↓

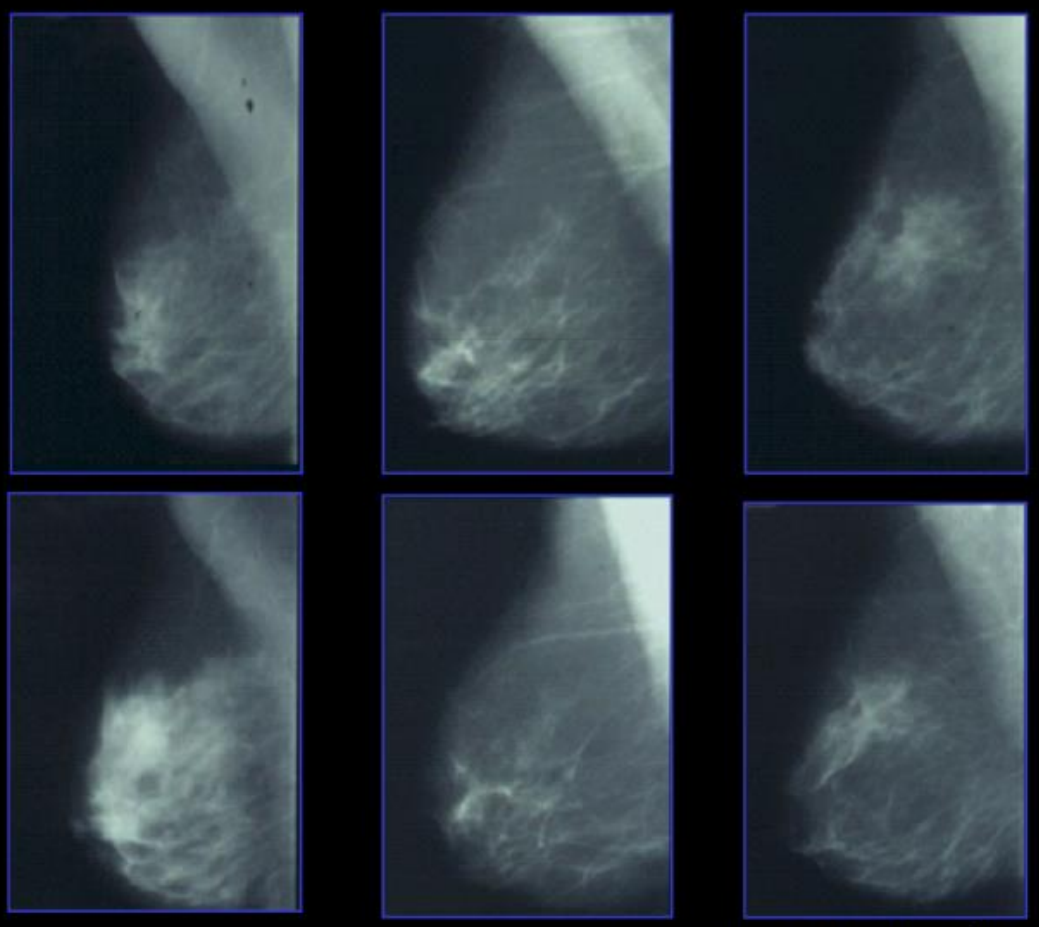
Proliferazione delle cellule mammarie
Cambiamenti del Ki67 medio dopo 12 mesi di trattamento con HRT e Tibolone



Valdivia I, Campodónico I, et al. IMS June 2002.

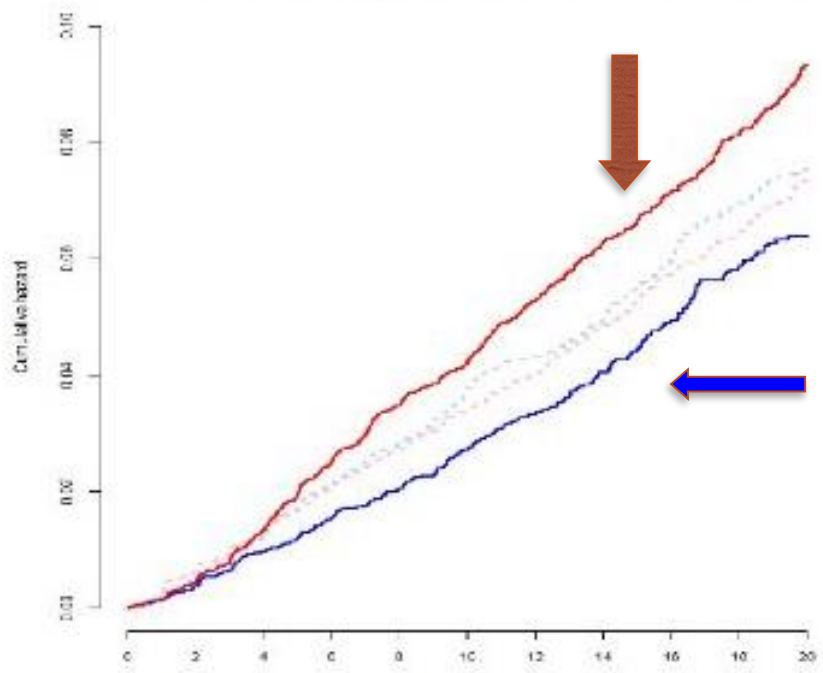
Sicurezza del Tibolone :Mammella

Studio sulla densità mammografica



Lundström *et al., Am J Obstet Gynecol 2002*

Hormone Therapy and Breast Cancer Incidence in WHI HT Randomized Trials



CEE+MPA
Placebo
572(0.45) v 431(0.36)
HR(95%CI) = 1.29 (1.14, 1.47)
P−value < 0.001

CEE−alone
Placebo
231(0.31) v 289(0.38)
HR(95%CI) = 0.77 (0.65, 0.92)
P−value = 0.005

CEE+MPA and CEE alone have opposite effects on breast cancer incidence

Tibolone ed incidenza del carcinoma della mammella

	Placebo	Tibolone
Numero di donne	1194	3343
Donne per anno	1269	3150
Cancro della mammella	4	5
Incidenza/1000 donne l'anno	3.15	1.59
Rischio relativo		0.50 (0.11-2.54)

F.Helmond, H.Kloosterboer 2002

MILLION WOMEN STUDY

Objective: to investigate the relation between various patterns of use of HRT and breast cancer incidence and mortality.

Partecipants: 1 084 110 UK women aged 50–64 years were recruited

Results: relative risk for breast cancer following **tibolone** therapy was increased **(1.45** [1·25–1·68], p<0·0001), similar to that of ET (1.3 [1·21–1·40], p<0·0001) but significantly less than that for CCHT (2.0 [1·88–2·12], p<0·0001).

HRT use at baseline	Cases/population	Relative risk (95% FCI)*
All never users	2894/392 757	1·00 (0·96–1·04)
All past users	1044/150 179	1·01 (0·95–1·08)
Current users of:		
Oestrogen only	991/115 383	1·30 (1·22–1·38)
Oestrogen-progestagen	1934/142 870	2·00 (1·91–2·09)
Tibolone	184/18 186	1·45 (1·25–1·67)
Other/unknown types	93/9548	1·44 (1·17–1·76)

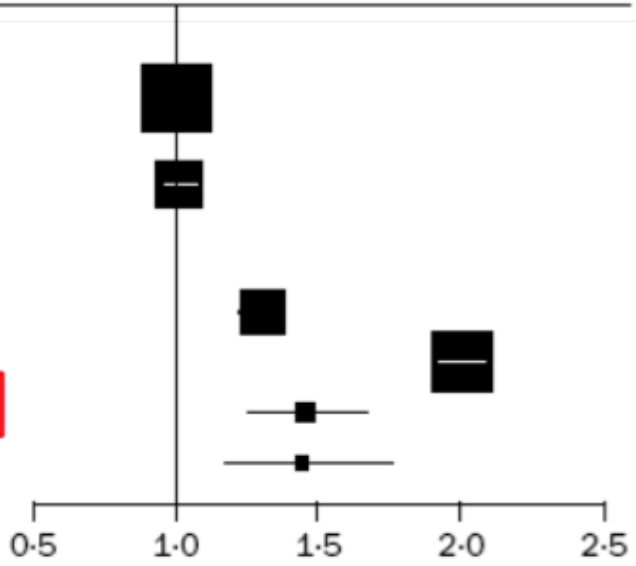


Figure 2: **Relative risk of incident invasive breast cancer in relation to recency and type of HRT used**

Lancet, 2003

Million Women Study in perspective

	Million Women Study	GPRD Study*
Observation period	1996 - 2001	1992 – 1998
Breast cancers	9364	7192
RR (95% CI)		
Oestrogen only	1.30 (1.21 – 1.40)	0.97 (0.86 – 1.08)
Oestrogen - Progestogen	2.00 (1.88 – 2.12)	1.21 (1.12 – 1.30)[1]
Tibolone	1.45 (1.25 – 1.67)	1.02 (0.78 – 1.33)
		[1] sc HRT only

General Practitioner Research Database observational study
Allen et al. Pharmacoepidemiol Drug Safety 2002;11(1):296.

HORMONE REPLACEMENT THERAPY USE AND VARIATIONS IN THE RISK OF BREAST CANCER

L. Opatrny, et al 2008

Objective: To determine the effect of different types and formulations of HRT on the risk of breast cancer in postmenopausal women.

Design: Population-based case–control study

Setting: UK, 1998-2004

Partecipants: Women 50–75 years **from GPRD (General Practice Research Database)**; 6347 incident cases of breast cancer that were matched with 31 516 controls.

Results: **The rate of breast cancer was not increased among exclusive users of unopposed estrogens (RR 0.97; 95% CI 0.86–1.09) or of tibolone (RR 0.86; 95% CI 0.65–1.13). Users of tibolone who had switched from opposed estrogens, however, had an elevated rate (RR 1.29; 95% CI 1.09–1.52).**

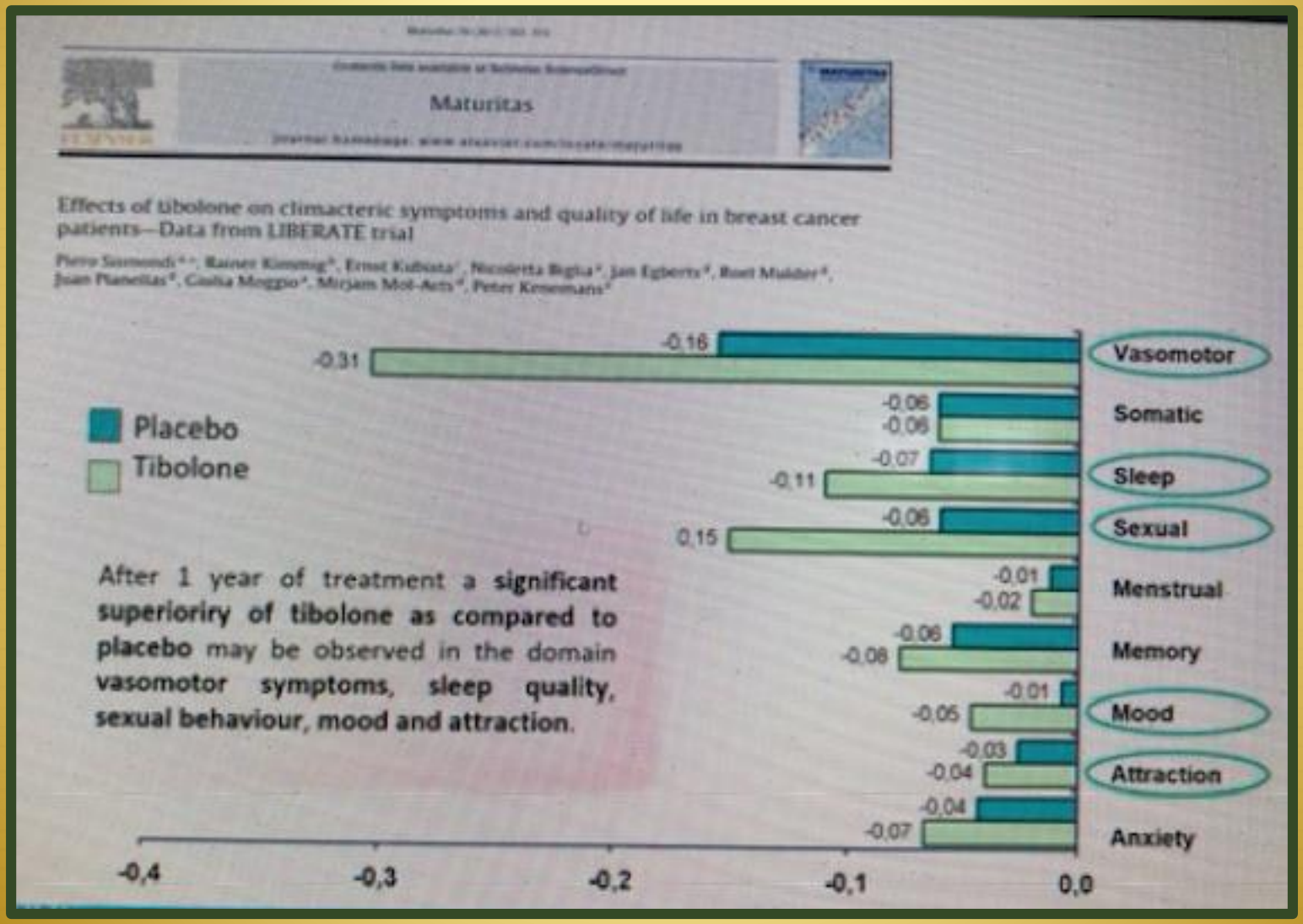
Table 2. Adjusted* odds ratios of breast cancer incidence associated with lifetime use of single hormone therapy types

Use of HRT, % (*n*)	Cases (*n* = 6347)	Controls (*n* = 31 516)	Adjusted OR (95% CI)
No use ever (reference)	60.6 (3843)	64.1 (20 200)	1.00
Opposed estrogens only	20.77 (1318)	17.35 (5469)	1.33 (1.23–1.44)
Estrogens only	8.98 (570)	9.55 (3010)	0.97 (0.86–1.09)
Tibolone only	0.96 (61)	1.22 (385)	0.86 (0.65–1.13)
Progestin only	1.70 (108)	1.78 (562)	1.05 (0.85–1.30)

*Adjusted for endometrial cancer, hysterectomy, oophorectomy, family history of breast cancer, documented oral contraceptive use, body mass index, smoking and drinking status.

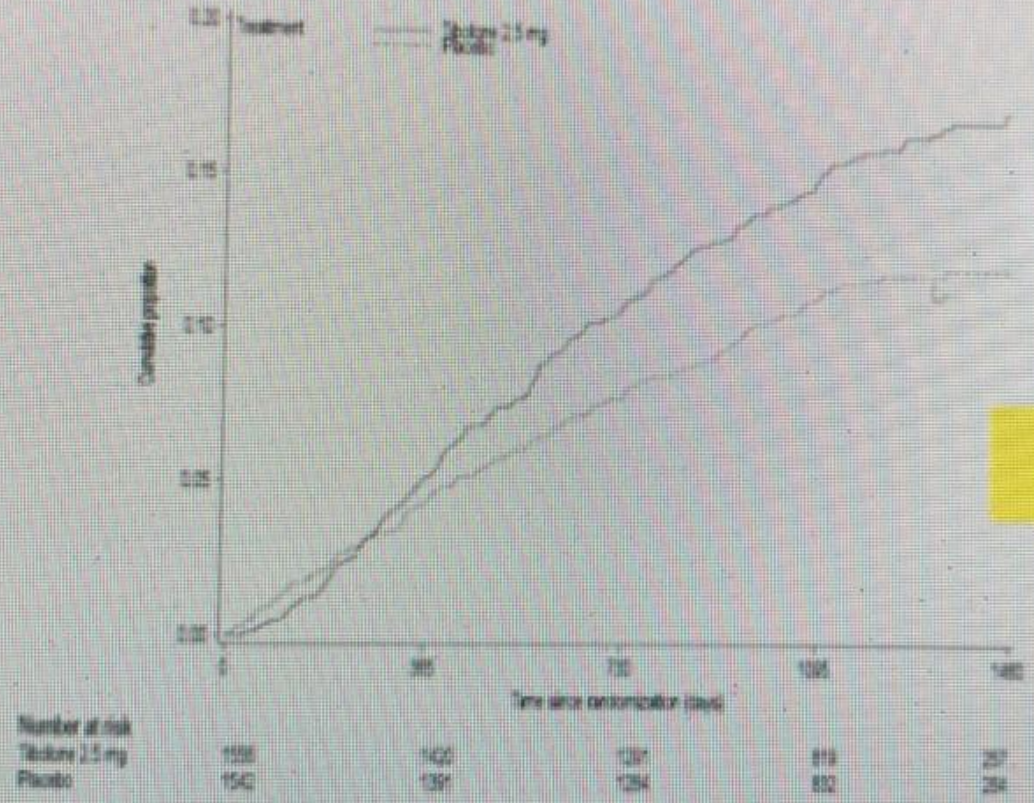

HRT after breast cancer: LIBERATE trial
Liberate
LIVIAL INTERVENTION
FOLLOWING BREAST CANCER.
EFFICACY, RECURRENCE AND
TOLERABILITY ENDPOINTS

Liberate


Maturitas
Effects of tibolone on climacteric symptoms and quality of life in breast cancer patients—Data from LIBERATE trial
Placebo
Tibolone
After 1 year of treatment a significant superioriry of tibolone as compared to placebo may be observed in the domain vasomotor symptoms, sleep quality, sexual behaviour, mood and attraction.
-0.31
-0.16
Vasomotor
-0.06
-0.06
Somatic
-0.11
-0.07
Sleep
0.15
-0.06
Sexual
-0.02
-0.01
Menstrual
-0.08
-0.06
Memory
-0.05
-0.01
Mood
-0.04
-0.03
Attraction
-0.07
-0.04
Anxiety
-0,4
-0,3
-0,2
-0,1
0,0

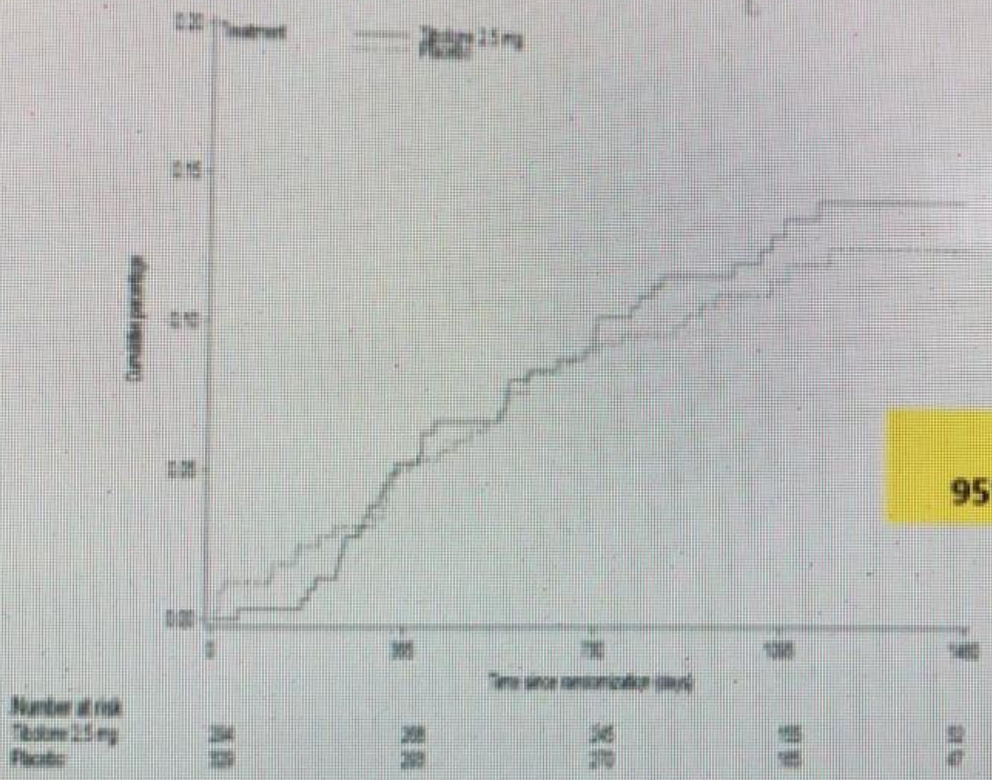
Libe Rate

Breast cancer recurrence (ITT) HR tibolone to placebo [95% IC]



Kenemans P, et al. Lancet Oncol 2009

Breast cancer recurrence (ITT) – estrogen receptor status negative (N=623)



Kenemans P. et al. Lancet Oncol 2009

Maturitas

Effects of tibolone on climacteric symptoms and quality of life in breast cancer patients—Data from LIBERATE trial

Pierre Simoncini [*], Rainer Kimmig [2], Ernst Kubista [1], Nicoletta Biglia [3], Jan Egberts [4], Roel Mulder [4], Joan Planellas [5], Giulia Moggio [3], Mirjam Mol-Arts [4], Peter Kenemans [1]

	Tibolone (N =1556) n (%)	Placebo (N =1542) n (%)	HR [95% CI]	P-value
Overall	237 (15.2%)	165 (10.7%)	1.40 [1.14;1.70]	0.001
Location				
- Local	48 (3.1%)	33 (2.1%)	1.42 [0.91;2.21]	NS
-Contralateral	25 (1.6%)	17 (1.1%)	1.39 [0.74;2.59]	NS
- Distant	171 (11.0%)	121 (7.8%)	1.38 [1.09;1.74]	0.007

Liberate

Significant increase of the recurrences in women treated with tibolone as compared to the placebo group

Overall increased risk of recurrence in the tibolone group (HR 1.4), mainly distant recurrences

Stopped prematurely 6 months before the planned

Kenemans P, et al. Lancet Oncol 2009

Liberate trial: conclusions

Tibolone, given for three years on average to women with vasomotor symptoms and a history of breast cancer, showed:

- efficacy in relief of vasomotor symptoms
- a beneficial effect on bone mineral density
- No difference in other relevant safety parameters: mortality, cardiovascular events, gynecological malignancies
- overall, an increased risk of BC recurrence vs placebo treated

Contraindication in women with known, past or suspected breast cancer must remain in the labeling of tibolone

TIBOLONE

Tabella 1 Effetti indesiderati di

Classificazione per Sistemi ed Organi	Comune >1%,<10%	Non comune >0,1%,<1%	Raro >0,01%,<0,1%
Disturbi del metabolismo e della nutrizione		Edema**	
Patologie gastrointestinali	Dolore addominale basso	Fastidio addominale**	
Patologia della cute e del tessuto sottocutaneo	Crescita anormale dei capelli	Acne	Prurito**

Classificazione per Sistemi ed Organi	Comune >1%,<10%	Non comune >0,1%,<1%	Raro >0,01%,<0,1%
Patologie dell'apparato riproduttivo e della mammella	Secrezione vaginale Ispessimento della parete dell'endometrio Emorragia postmenopausale Dolorabilità mammaria Prurito genitale Candidiasi vaginale Emorragia vaginale Dolore pelvico Displasia della cervice Secrezione genitale Vulvovaginite	Fastidio mammario Infezione fungina Micosi della vagina Dolore del capezzolo	
Esami diagnostici	Aumento del peso corporeo Striscio cervicale anormale*		

4. INFORMAZIONI CLINICHE

4.1 Indicazioni terapeutiche

- Trattamento dei sintomi da deficit di estrogeni nelle donne in post-menopausa, dopo più di un anno dalla menopausa.
- Prevenzione dell'osteoporosi in donne in post-menopausa, ad alto rischio di future fratture che presentano intolleranze o controindicazioni ad altri medicinali autorizzati per la prevenzione dell'osteoporosi.

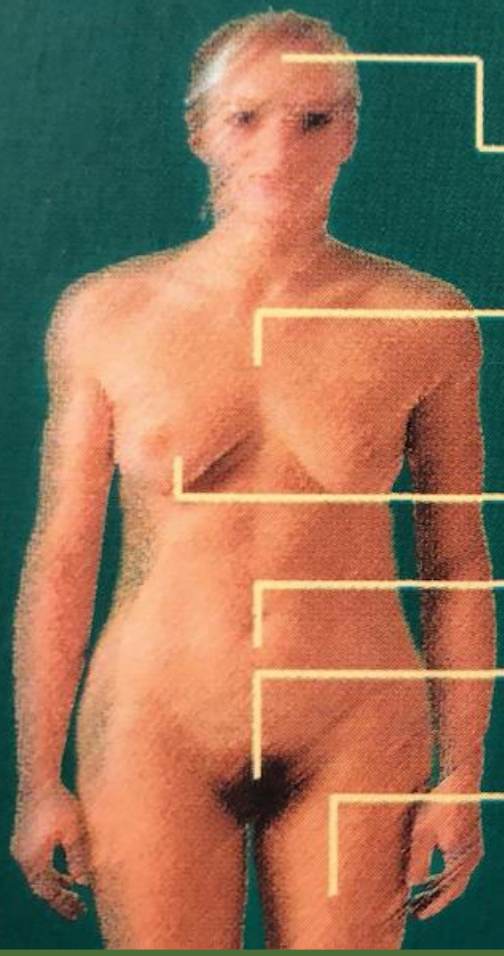
Per tutte le donne, la decisione di prescrivere Livial deve essere basata su una valutazione dei rischi individuali complessivi della paziente, in particolare nelle donne di età superiore ai 60 anni si deve tenere in considerazione il rischio di ictus (vedere paragrafi 4.4 e 4.8).

DI FRONTE ALLA MENOPAUSA

TUTTE LE TERAPIE SONO UGUALI???

- **C'E' UN RAZIONALE BIOLOGICO PER LA TERAPIA ORMONALE ???**
- **TUTTE LE DONNE IN POST MENOPAUSA SONO "CARENTI" ALLO STESSO MODO ???**
- **TUTTI I TRATTAMENTI (ORMONI) SONO UGUALI ???**

TIBOLONE: INCONTRO CON I BISOGNI SPECIFICI DELLA DONNA



TRATTA I SINTOMI CLIMATERICI
MIGLIORA UMORE E LIBIDO

EFFETTI BENEFICI
SUI PARAMETRI CARDIOVASCOLARI

BASSA INCIDENZA
DI TENSIONE MAMMARIA
NON AUMENTI DI DENSITÀ MAMMOGRAFICA

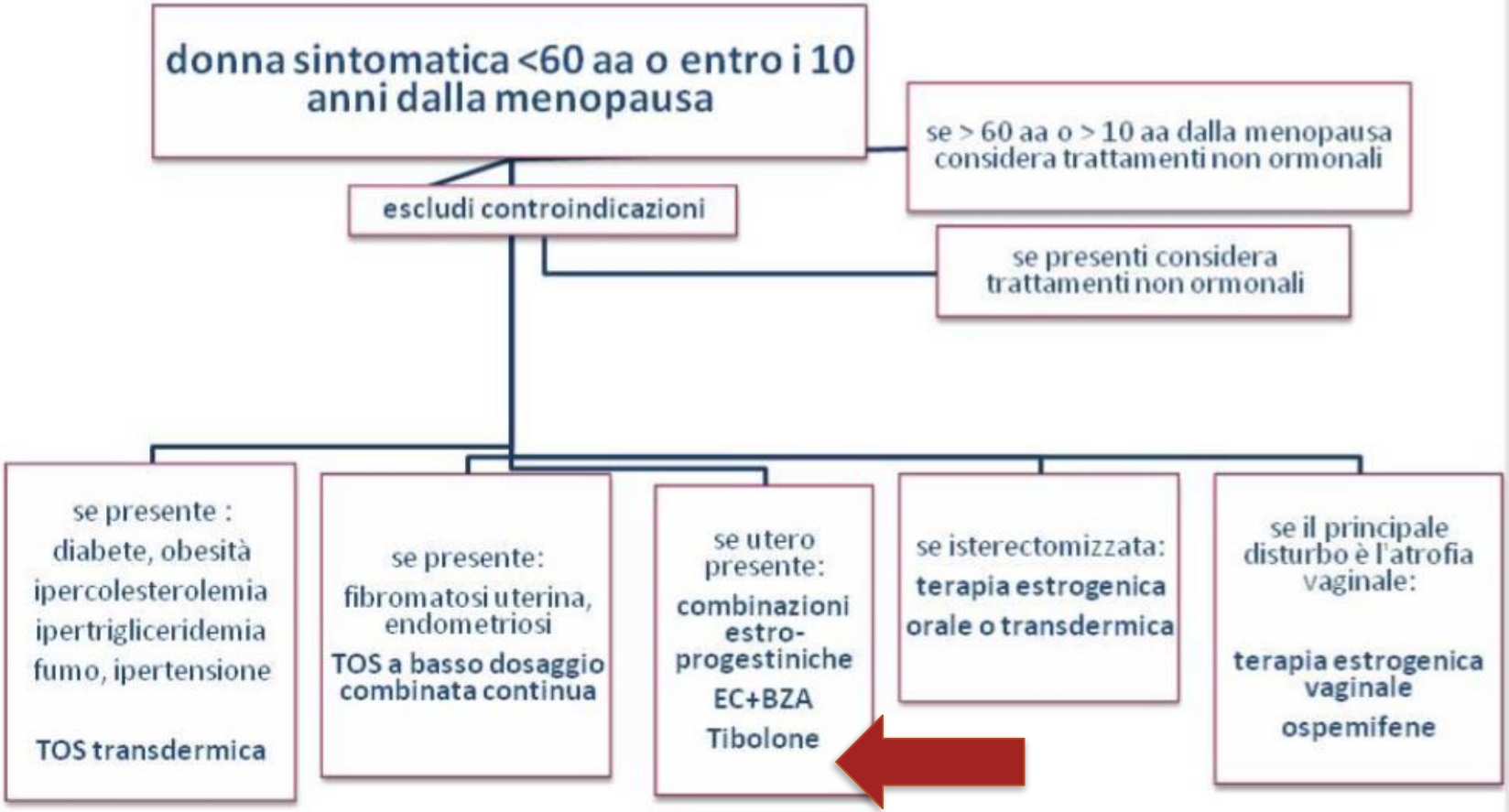
NON PROLIFERAZIONE ENDOMETRIALE

TRATTA L'ATROFIA VAGINALE

PREVIENE LA PERDITA OSSEA POST MENOPAUSALE

Jordan, *J Women s Health* 1997

Procedimento operativo per la prescrizione della TOS



If you torture the data long enough, it will confess to anything.

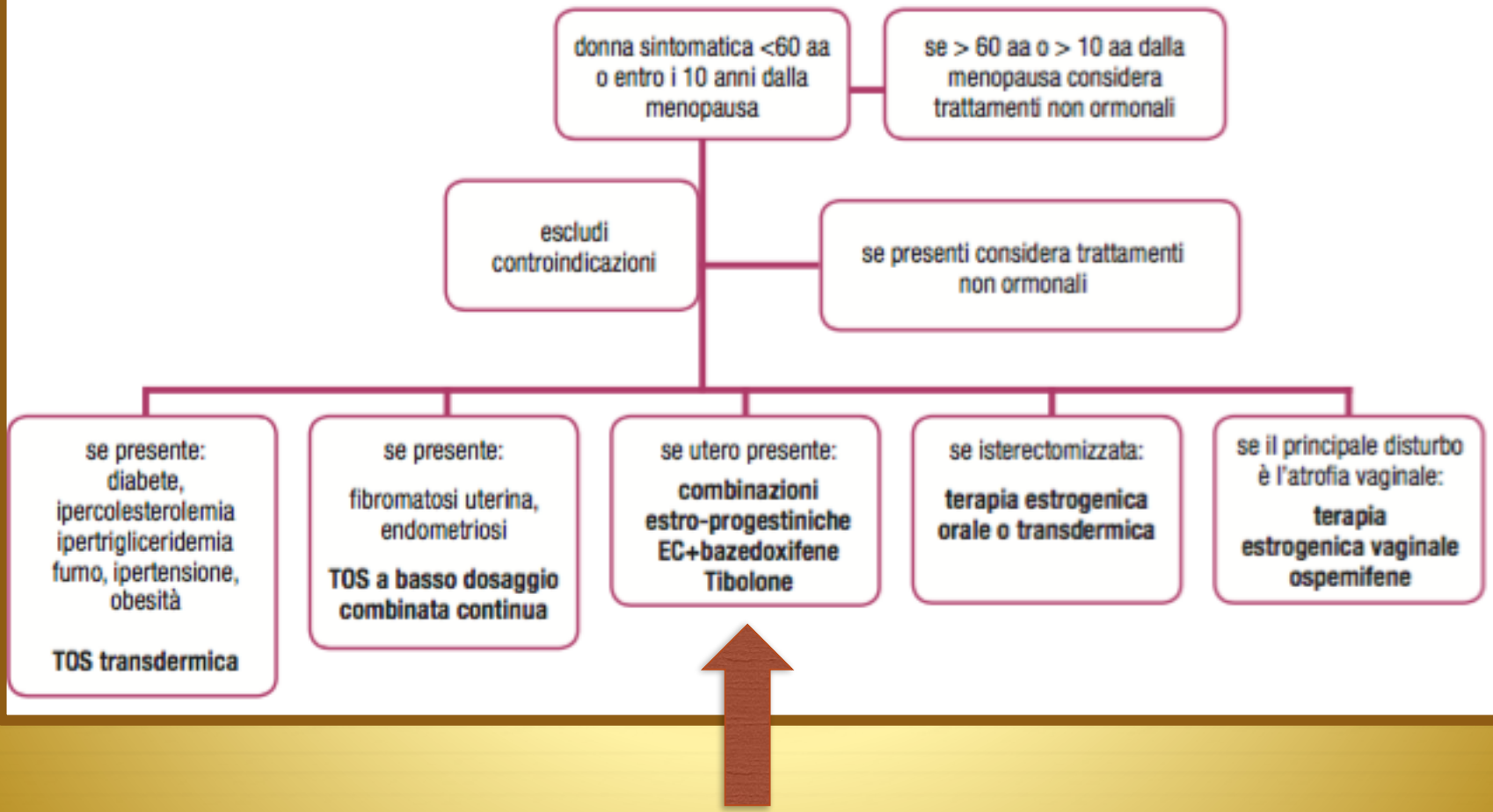
Ronald H. Coase

Studio THEBES
Conclusioni

- Il tibolone non induce iperplasia o carcinoma endometriale
- L'incidenza di endometrio atrofico/inattivo risultava maggiore nelle pazienti trattate con tibolone vs ECE/MAP (87,9 % vs 79,8 %)
- Il tibolone ha un profilo di sanguinamento migliore vs ECE/MAP: 75 % no sanguinamento/spotting con tib. vs 45 % con ECE/MAP
- Mastodinia meno frequente con tib. (2,3 %) vs ECE/MAP (9,7 %)

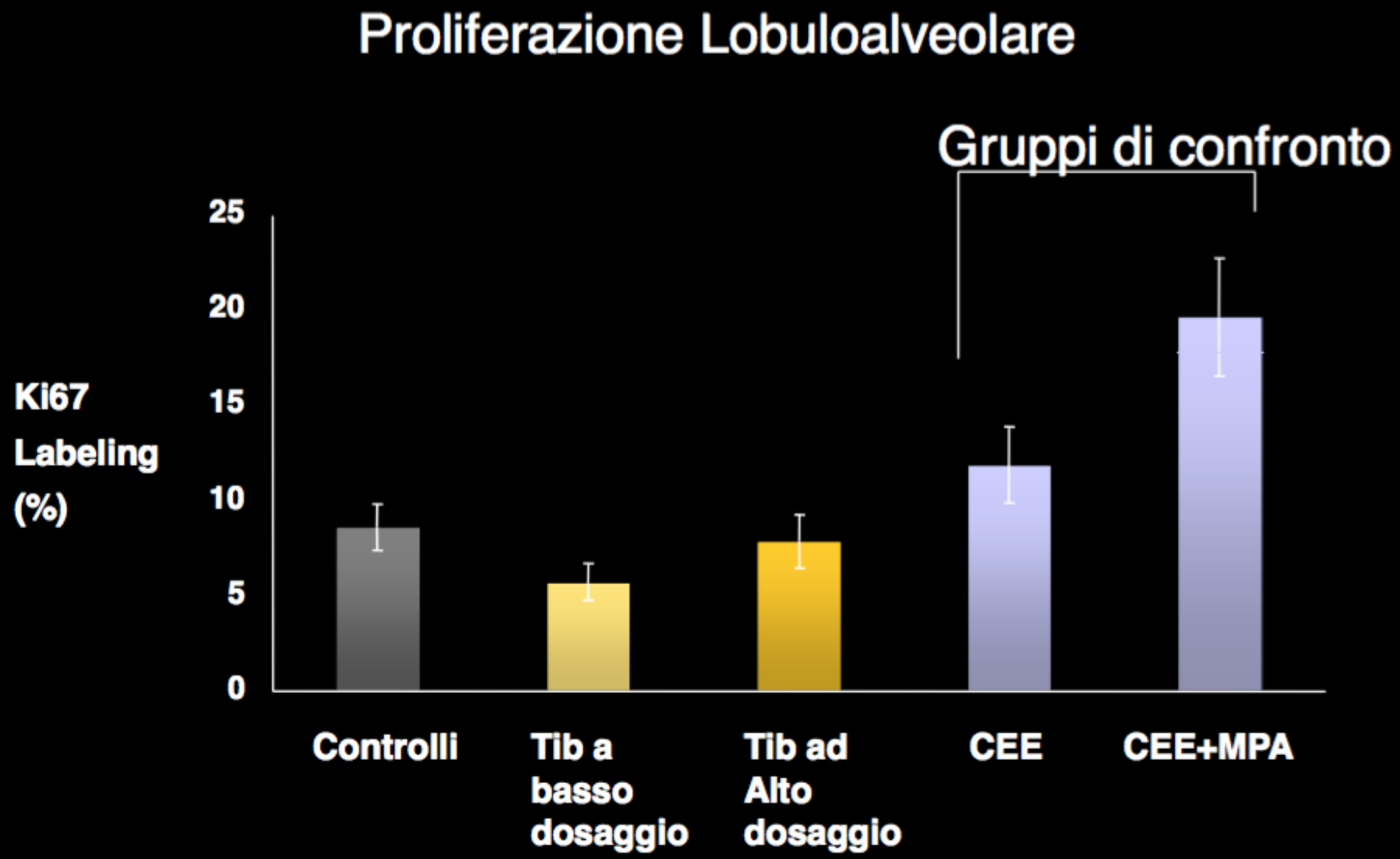
Archer et al, JCEM 2007

Procedimento operativo per la prescrizione della TOS



Sicurezza del Tibolone: Mammella

Proliferazione delle ghiandole mammarie di cynomolgus monkeys

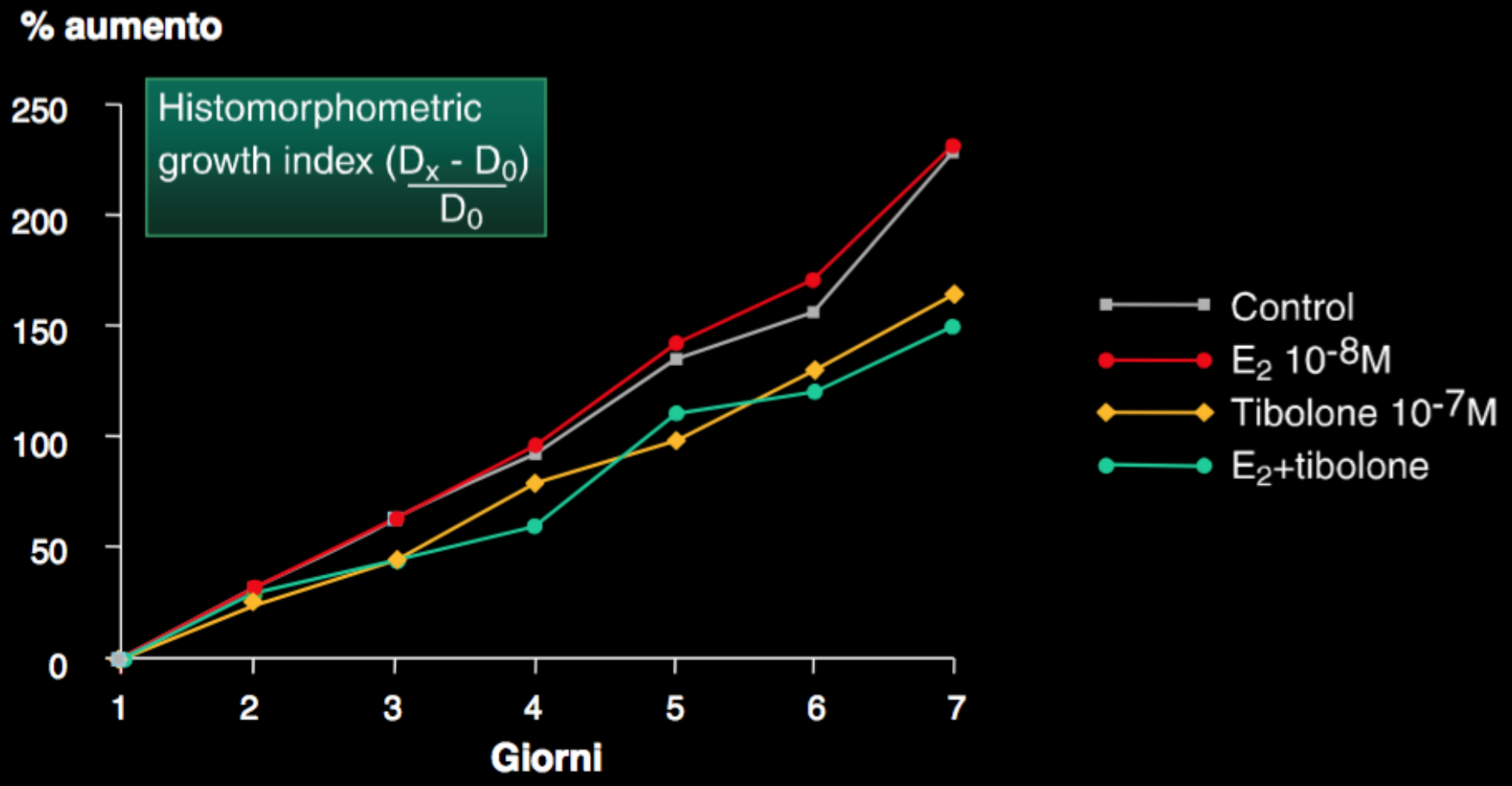


Cline et al, Menopause 2002; 9:242

TIBOLONE E OSSO

Sicurezza del Tibolone: Mammella

Effetto del tibolone sulla proliferazione delle cellule epiteliali normali umane mammarie



Adapted from Gompel *et al., Fertil Steril 1998*

SINDROME IPOANDROGENICA

SINTOMI E SEGNI

DEL DEFICIT DI TESTOSTERONE

- Perdita globale di desiderio sessuale; diminuzione di fantasie e sogni sessuali
- Diminuita sensibilità alla stimolazione sessuale dei capezzoli e del clitoride
- Diminuita eccitabilità e capacità di orgasmo
- Diminuita del senso di energia vitale e di benessere
- Perdita del tono muscolare
- Assottigliamento e diradamento della peluria pubica
- Atrofia genitale non responsiva agli estrogeni
- Secchezza e fragilità dei capelli; secchezza cutanea

Studio THEBES
(Tibolone Histology of the Endometrium and Breast Endpoints Study)

- Trial randomizzato in doppio cieco, a gruppi paralleli
- Obiettivo primario: confermare la sicurezza endometriale del tibolone (1,25 e 2,5 mg/die)
- Obiettivo secondario: valutare il profilo di tollerabilità confrontando l'incidenza di sanguinamenti vaginali e di mastodinia in pazienti trattate con tibolone vs ECE/MAP
- Trattate in tutto 3224 pazienti (range età: 45-65 aa; media 54.4)
- 792: 1,25 mg tibolone
- 806: 2,5 mg tibolone
- 1626: ECE/MAP

3 gruppi di trattamento

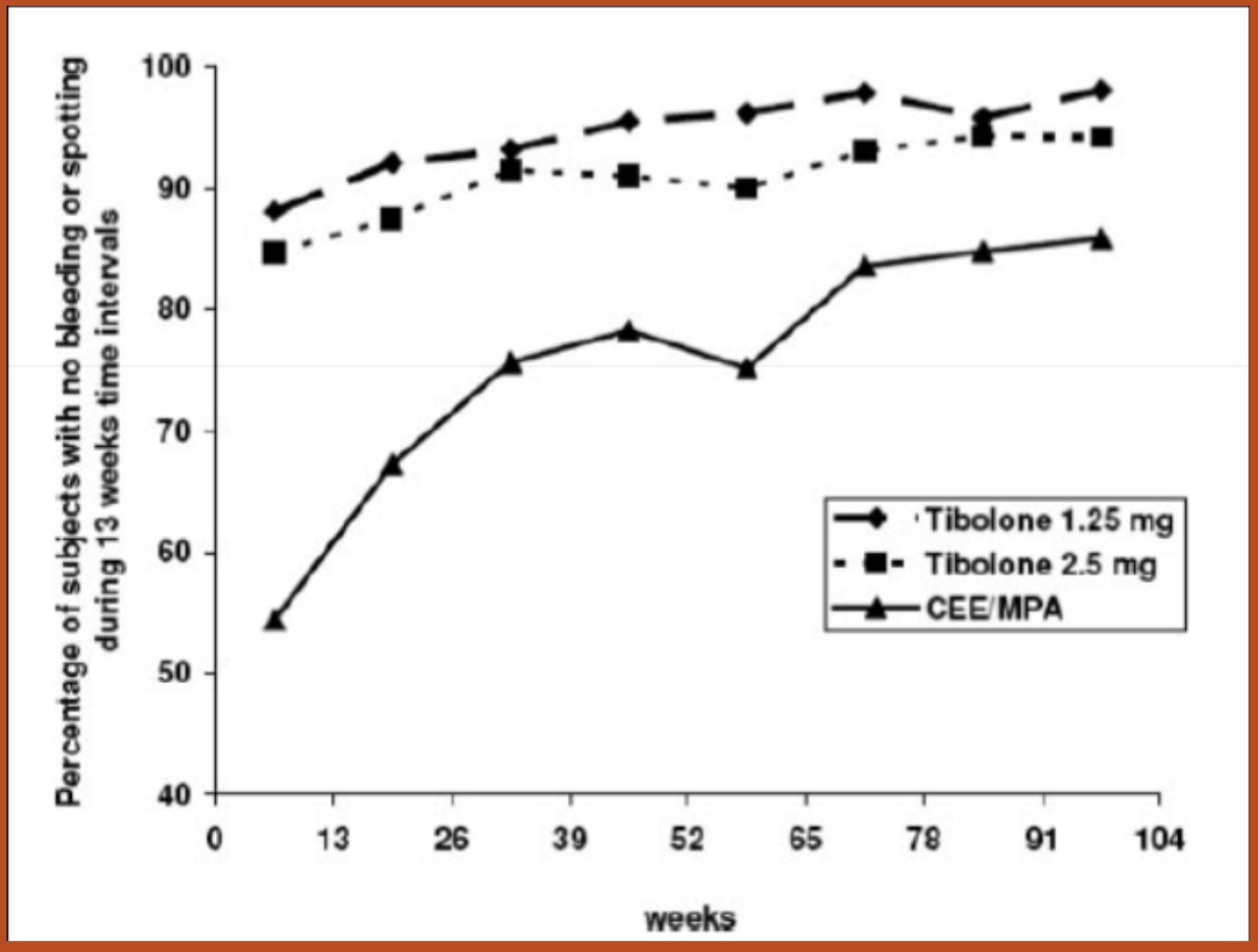
Archer et al, JCEM 2007

Studio THEBES
risultati

- Non casi di iperplasia nei due gruppi di trattamento con tibolone
- Nel gruppo con ECE/MAP 2 casi di iperplasia
- Ecopattern endometriale (TVS):
- Tibolone: basale 3,1 mm; dopo 2 aa: 3,6 mm
- ECE/MAP: 3,0 mm; dopo 2 aa: 3,4 mm

Archer et al, JCEM 2007

Percentuale di soggetti senza episodi di B/S Vaginale – Studio THEBES



Archer et al, JCEM 2007

OPAL Study

Objective: The primary objective was to compare the effect of tibolone and placebo on the progression of the common carotid artery intima-medial thickness; A secondary objective was to assess the effects of tibolone (2.5 mg), continuous combined CEE/MPAe [0.625/2.5 mg], and placebo **on the endometrium and vaginal bleeding**.

Design: 3-year, three-arm, randomized, double-blind, parallel group, placebo-controlled clinical trial

Partecipants: **866 postmenopausal women (aged 45-79 years).**

Results (I): **Endometrial thickness increased slightly during the first year with tibolone and HRT without any further progression.**

Table II Endometrial thickness (mm) assessed by TVUS at baseline and annually during treatment with tibolone, CEE/MPA, or placebo (mean ± SD)

	Tibolone	CEE/MPA	Placebo
Baseline	2.3 ± 1.1 (n = 216)	2.4 ± 1.1 (n = 219)	2.4 ± 1.1 (n = 230)
Week 52	3.8 ± 2.6 (n = 187)	3.1 ± 1.8 (n = 197)	2.4 ± 1.3 (n = 200)
Week 104	3.7 ± 2.3 (n = 167)	3.2 ± 1.6 (n = 177)	2.6 ± 1.2 (n = 178)
Week 156	3.7 ± 2.0 (n = 152)	3.0 ± 1.3 (n = 164)	2.6 ± 1.1 (n = 172)
End point	3.6 ± 2.0 (n = 191)	3.2 ± 1.7 (n = 200)	2.6 ± 1.3 (n = 211)

Table III Summary of the endometrial biopsy findings at baseline and end point during 3 years of treatment with tibolone, CEE/MPA, or placebo

Number of women with	Tibolone	CEE/MPA	Placebo	*P* value*
Baseline biopsies	114	119	118	
Evaluable	86 (75.4%)	92 (77.3%)	89 (75.4%)	
Nonevaluable				
3-year biopsies				
Evaluable				
Nonevaluable				
End point biopsie				
Evaluable				
Nonevaluable				
Proliferation at ba				1.0000†
				.2128‡
				.0661§
Proliferation at er				.4797†
				.0146‡
				.0733§
Hyperplasia at end point	0	0	0	NA
Endometrial cancer	1	0	1‖	1.0000†
at end point				.4724‡
				.4522§

Vaginal bleeding was more commonly reported as an adverse event with CEE/MPA than tibolone (26.4% vs 10.8%, P < .0001)

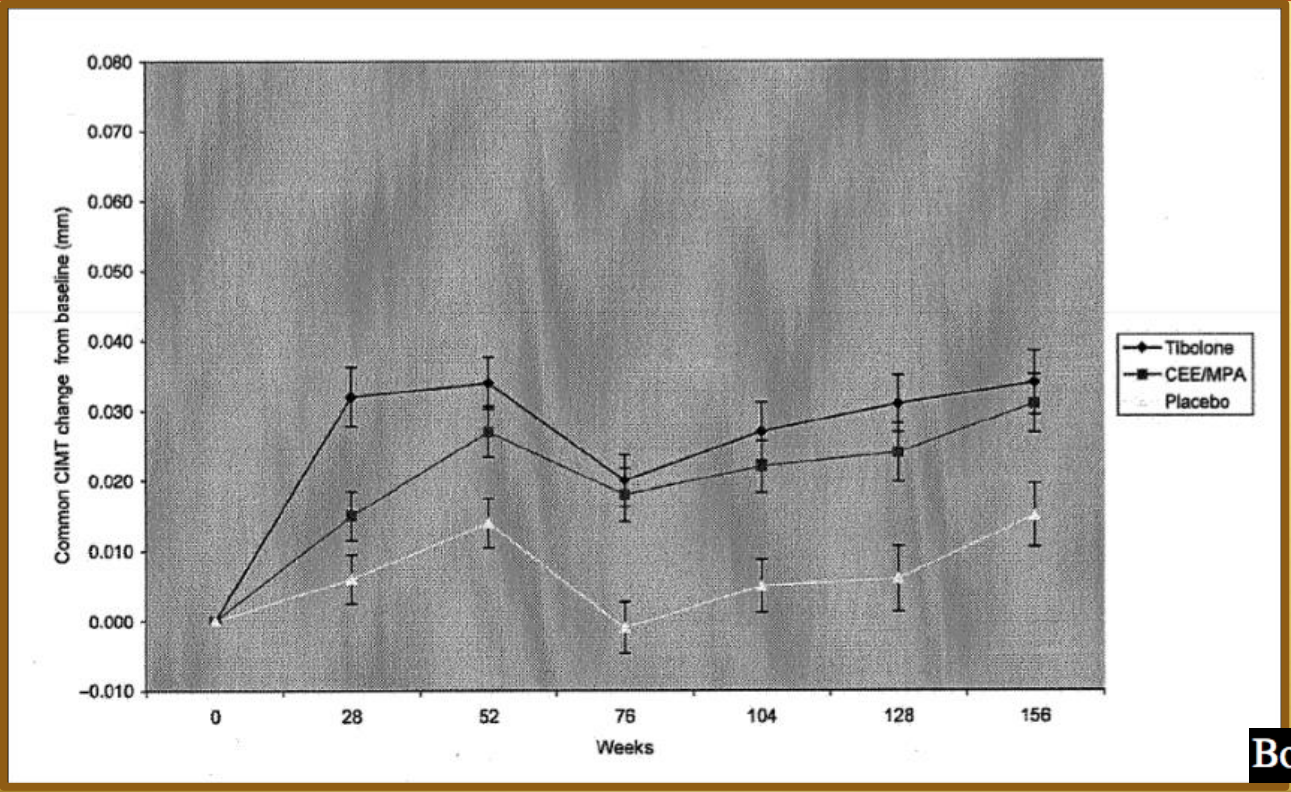
* P-values based on Fisher's exact test.
† Tibolone vs placebo.
‡ CEE/MPA vs placebo.
§ Tibolone vs CEE/MPA.
‖ Non-US/UK subject: no endometrial biopsy performed (cancer diagnosis following surgery).

Langer et al, Am J Ob Gyn, 2006

The effect of tibolone and continuous combined conjugated equine oestrogens plus medroxy-progesterone acetate on progression of carotid intima–media thickness: the Osteoporosis Prevention and Arterial effects of tiboLone (OPAL) study

Michiel L. Bots[1*], Gregory W. Evans[2], Ward Riley[3], Karen H. McBride[4], Electra D. Paskett[5], Frans A. Helmond[6], and Diederick E. Grobbee[1] for the OPAL Investigators

Eur Heart J, 2006



Bots et al, EHJ, 2006

Beneficial effect of tibolone on mood, cognition, well-being, and sexuality in menopausal women

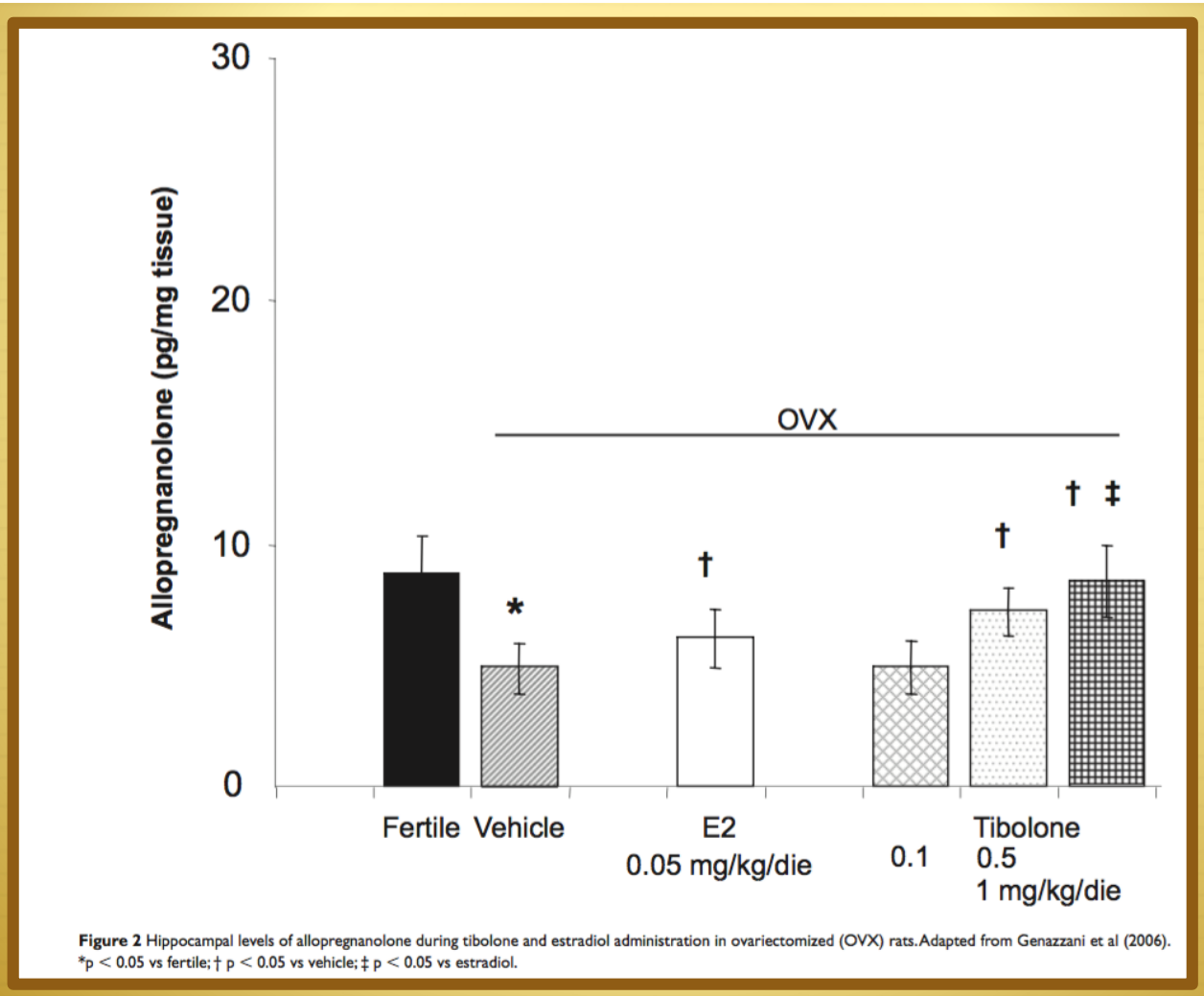


Figure 2 Hippocampal levels of allopregnanolone during tibolone and estradiol administration in ovariectomized (OVX) rats. Adapted from Genazzani et al (2006).
*$p < 0.05$ vs fertile; † $p < 0.05$ vs vehicle; ‡ $p < 0.05$ vs estradiol.

Cummings SR, et al. for the LIFT Trial Investigators. The effects of tibolone in older postmenopausal women. N Engl J Med 2008, 359: 697-708 (http://www.nejm.org/doi/full/10.1056/NEJMoa0800743).
Cummings SR for LIFT Steering Committee. LIFT study is discontinued. BMJ 2006, 332: 667 (http://www.bmj.com/content/332/7542/667.1?view=long&pmid=16543350).
Kenemans P, et al. Safety and efficacy of tibolone in breast cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. Lancet Oncol 2009, 10: 135-46. (http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045%2808%2970341-3/abstract)
Winkler UH, Altkemper R, Kwee B, et al. Effects of tibolone and continuous combined hormone replacement therapy on parameters in the clotting cascade: a multicenter, double-blind, randomized study. Fertil Steril 2000, 74: 10–9 (http://www.fertstert.org/article/S0015-0282%2800%2900587-2/abstract).
Archer DF, Hendrix S, Gallagher JC, et al. Endometrial effects of tibolone. J Clin Endocrinol Metab 2007, 92: 911–8. (http://jcem.endojournals.org/content/92/3/911.abstract)
Nijland EA, Weijmar Schultz WC, et al. Tibolone and transdermal E2/NETA for the treatment of female sexual dysfunction in naturally menopausal women: results of a randomized active-controlled trail. J Sex Med 2008, 5: 646–56. (http://onlinelibrary.wiley.com/doi/10.1111/j.1743-6109.2007.00726.x/abstract)
Delmas PD, Davis SR, Hensen J, et al. Effects of tibolone and raloxifene on bone mineral density in osteopenic postmenopausal women. Osteoporos Int 2008, 19: 1153–60 (http://www.springerlink.com/content/m28x05182t87q2x0/).

Studio THEBES
risultati

	Gruppi tibolone (n= 1317)	Gruppo ECE/MAP (n=1327)
Tessuto insuff. x dia	65 (5 %)	70 (5,3 %)
Atrofico/inattivo	1156 (87,7 %)	1059 (79,8 %)
Proliferativo	24 (1,8 %)	52 (3,9 %)
Secretivo	62 (4.7 %)	115 (8,7 %)
Tipo mestruale	9 (0,7 %)	29 (2,2 %)
Iperplasia	0 (0 %)	2 (0,2 %)

Archer et al, JCEM 2007

OPAL Study

Objective: The primary objective was to compare the effect of tibolone and placebo on the progression of the common carotid artery intima-medial thickness; A secondary objective was to assess the effects of tibolone (2.5 mg), continuous combined CEE/MPAe [0.625/2.5 mg], and placebo **on the endometrium and vaginal bleeding.**

Design: 3-year, three-arm, randomized, double-blind, parallel group, placebo-controlled clinical trial

Partecipants: **866 postmenopausal women (aged 45-79 years).**

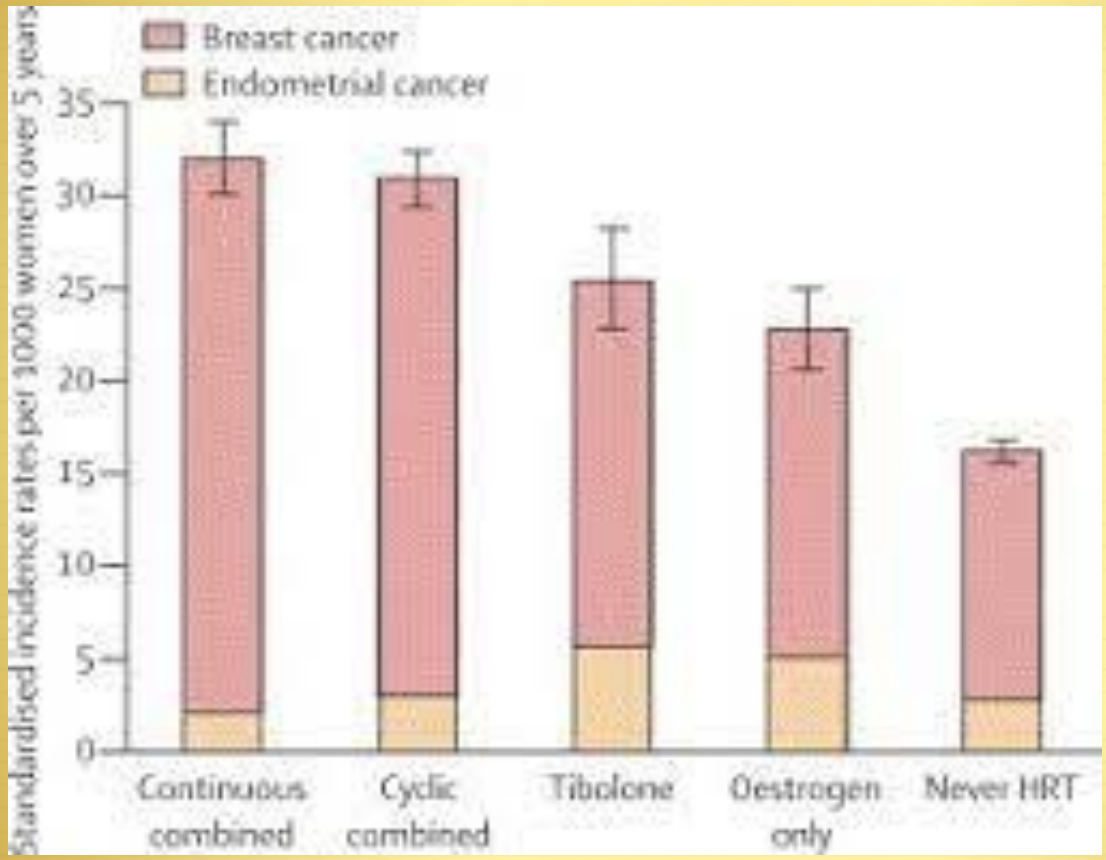
Results (I):

After 3 years, there were no significant differences between the tibolone, HRT and placebo groups in:

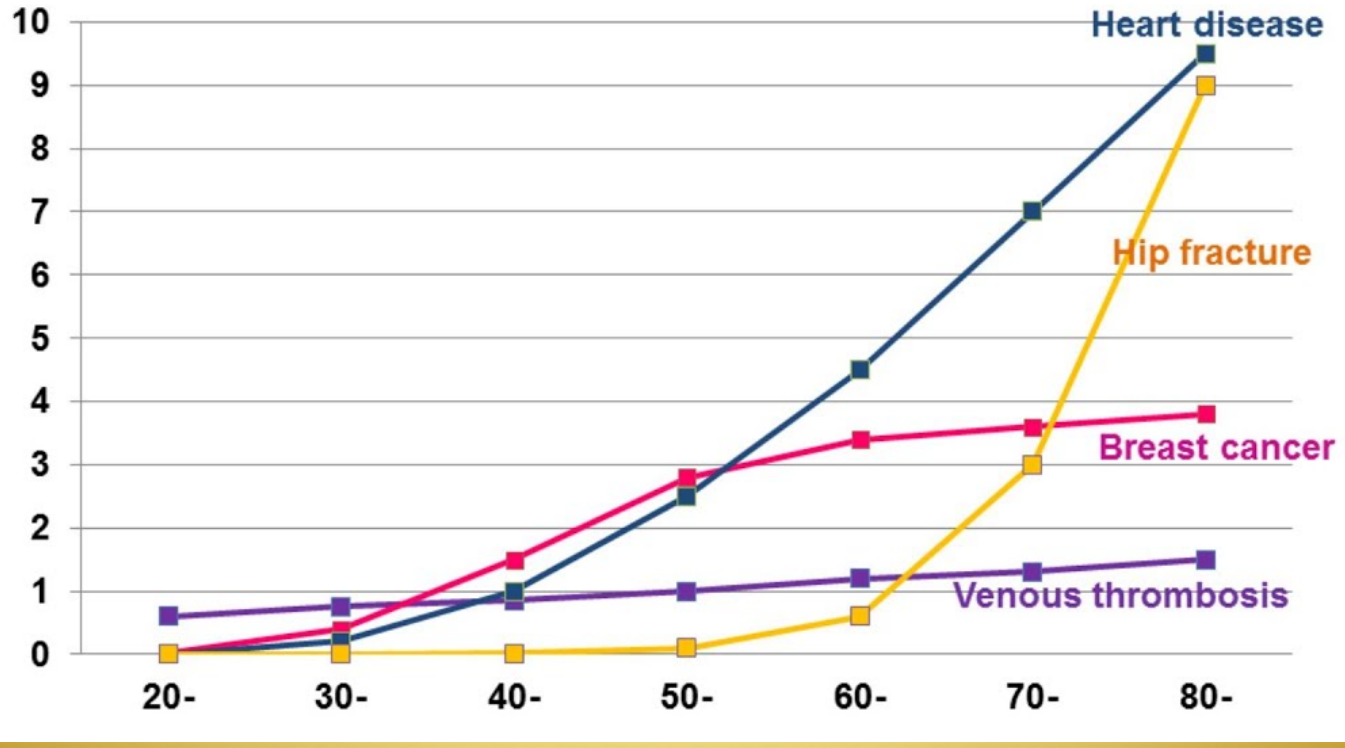
- incidence of proliferation (1.4%, 4.8%, and 0%, respectively),

- endometrial hyperplasia (0% in all groups),

- cancer (1, 0, and 1 case, respectively).


Breast cancer
Endometrial cancer
Standardised incidence rates per 1000 women over 5 years
35
30
25
20
15
10
5
0
Continuous combined
Cyclic combined
Tibolone
Oestrogen only
Never HRT

Age-specific incidence of important conditions in women (rate/1000/year)



Abstract
Objectives: The primary objective was to compare the vaginal bleeding pattern during administration of tibolone and low-dose continuous combined estradiol plus norethisterone acetate (E2/NETA). The secondary objectives were efficacy on vasomotor symptoms and vaginal atrophy.

Design: A randomised, double-blind, double-dummy, group comparative intervention trial.

Setting: Multicentre study executed in 32 centres in 7 European countries.

Sample: Five hundred and seventy-two healthy symptomatic postmenopausal women, aged 45-65 years.

Methods: Participants were randomised to receive 2.5 mg tibolone or 1 mg 17beta estradiol plus 0.5 mg norethisterone acetate (E2/NETA) daily for 48 weeks.

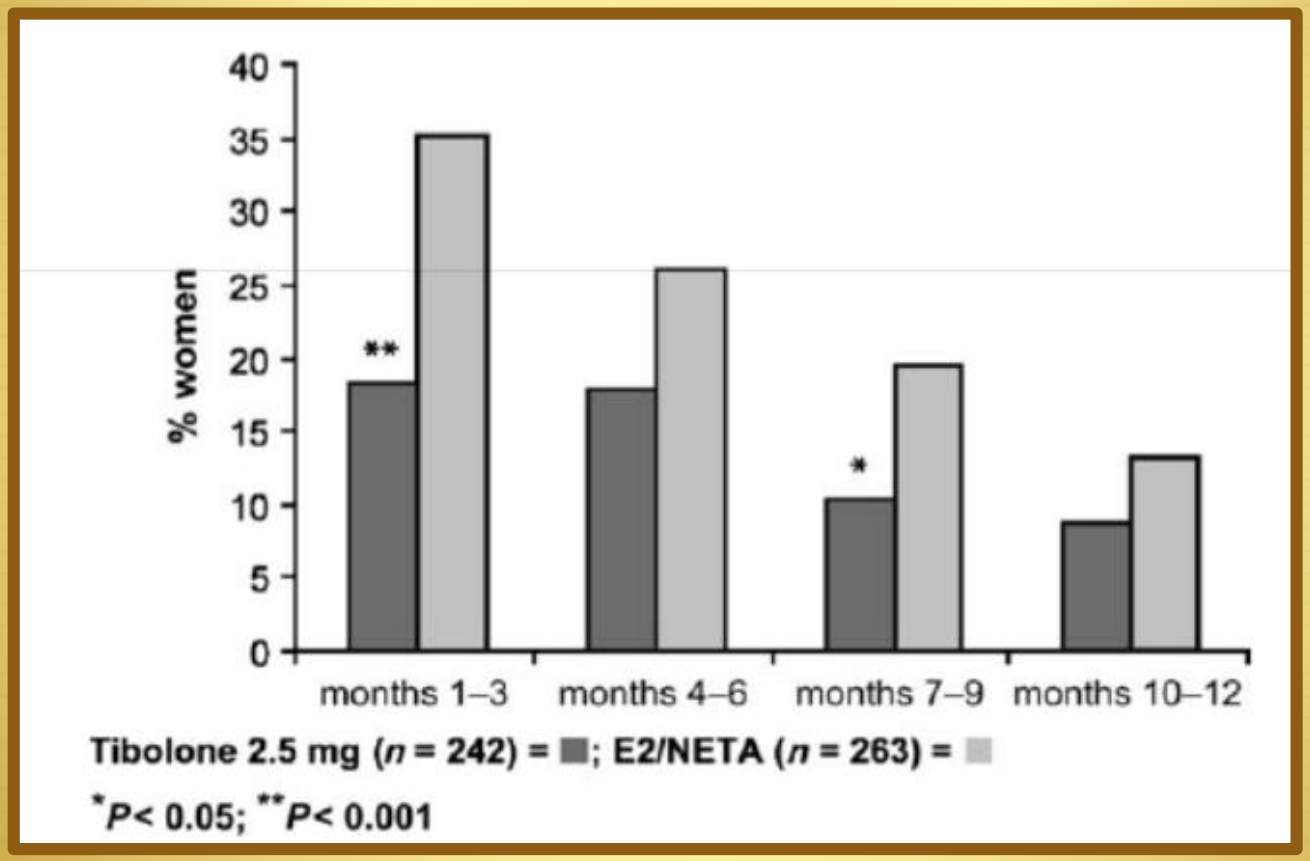
Main outcome measures: Prevalence of vaginal bleeding, hot flushes and adverse events.

Results: The incidence of bleeding was significantly lower in the tibolone group during the first 3 months of treatment (18.3 versus 33.1%; $P < 0.001$) when compared with the E2/NETA group. This effect on the bleeding pattern was sustained throughout the study, although reaching statistical significance again only in 7-9 months of treatment (11 versus 19%; $P < 0.05$). In both treatment groups, vasomotor symptoms and vaginal atrophy were significantly reduced to a similar extent when compared with baseline. The prevalence of breast pain/tenderness was significantly lower with tibolone compared with E2/NETA (3.2 versus 9.8%; $P < 0.001$).

Conclusion: Tibolone reduces menopausal symptoms to a similar extent as conventional low-dose continuous combined hormone therapy but causes significant less vaginal bleeding in the first 3 months of treatment. This constitutes an important argument for woman adherence to therapy.

STUDIO TOTAL:

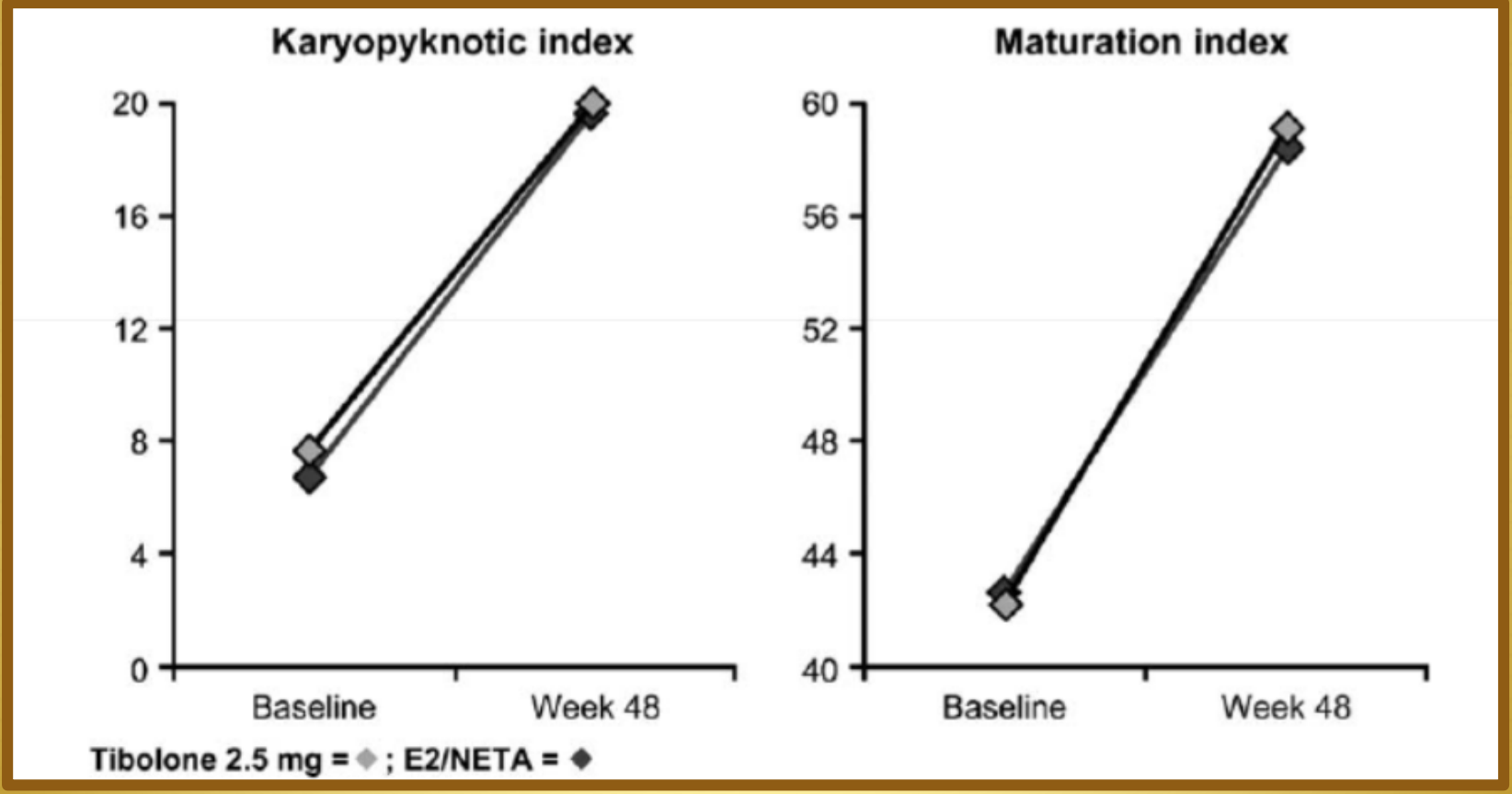
PERCENTUALE DI DONNE CON SANGUINAMENTO DURANTE IL PERIODO DI 4 TRIMESTRI DI TRATTAMENTO (B o S per almeno 1 giorno)



Hammar et al, BJOG 2007

STUDIO TOTAL

CITOLOGIA VAGINALE



Hammar et al, BJOG 2007

Studio THEBES

Incidenza di eventi avversi cardiovascolari (tutti i soggetti trattati)

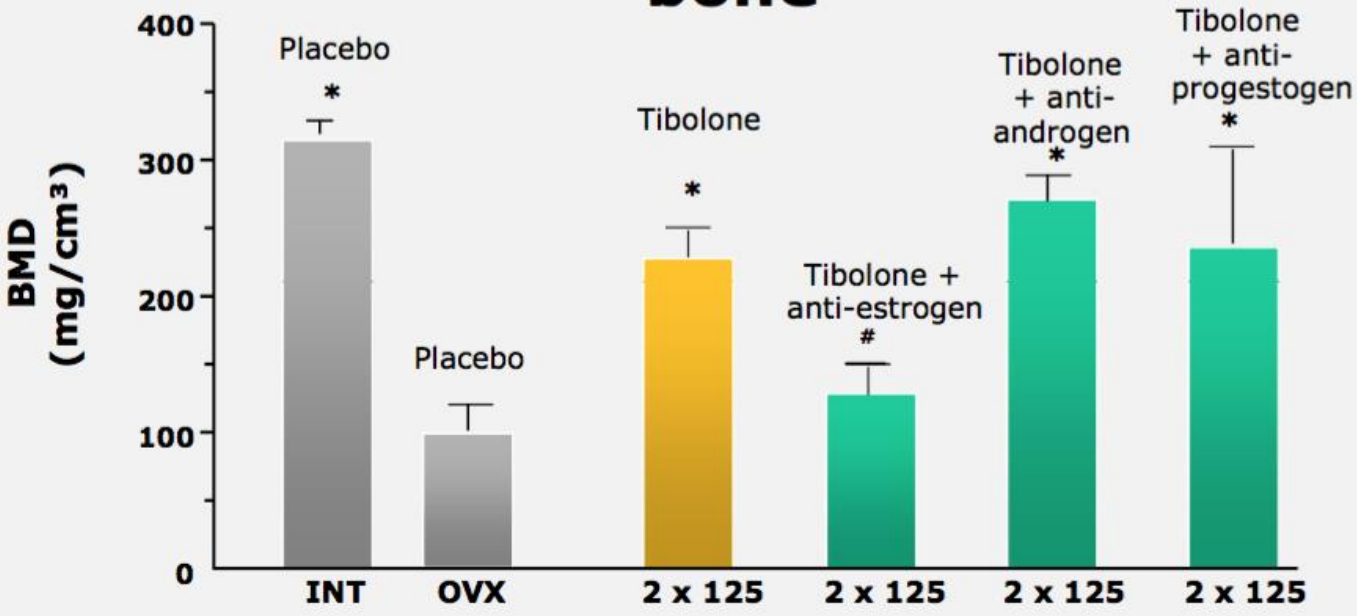
(range età: 45-65 aa; media 54.4)

AE	Combined tibolone group	CEE/MPA
Subjects as treated	1598	1626
Women-years	2402	2415
Stroke	0	2
Transient ischemic attack	0	1
Pulmonary embolism	0	1
Deep venous thrombosis	0	2
Myocardial infarction	2	2
All adjudicated cardiovascular events	2	8

Archer et al, JCEM 2007

Tibolone and its effects on bone

Effect of tibolone and anti-hormones on bone



* p<0.05 vs OVX

#p<0.05 vs Tib.

Tibolone acts as an estrogen on bone

Adapted from Ederveen and Kloosterboer, *J Bone Min Res 2001*

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Maturitas 54 (2006) 229–237
MATURITAS
THE EUROPEAN MENOPAUSE JOURNAL
www.elsevier.com/locate/maturitas

Tibolone and its metabolites inhibit invasion of human mammary carcinoma cells in vitro

B.W. Vanhoecke[a], M.E. Bracke[b], H.J. Kloosterboer[c], H.T. Depypere[a,*]

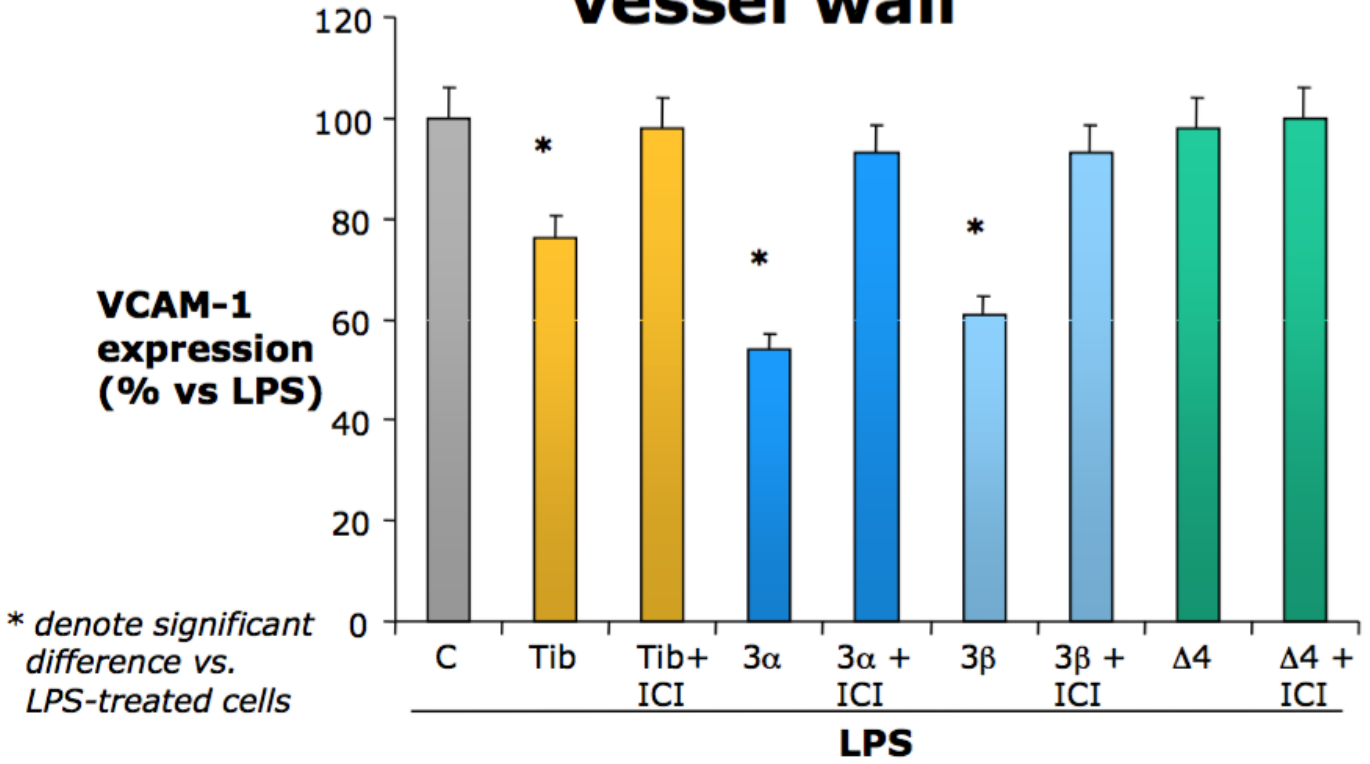
[a] *Department of Gynaecology, Ghent University Hospital, De Pintelaan 185, B-9000 Gent, Belgium*
[b] *Laboratory of Experimental Cancerology, Department of Radiotherapy and Nuclear Medicine, Ghent University Hospital, De Pintelaan 185, B-9000 Gent, Belgium*
[c] *Organon N.V., Oss, The Netherlands*

Conclusions

… tibolone and its 3betaOH metabolite have an anti-invasive effect on the tested breast cancer cell lines in vitro.
This effect on invasion is not correlated with an effect on cell-cell adhesion or motility but coincides with a decreased release of pro-MMP-9 in the medium

Tissue-Selective effects

Effect of tibolone and anti-hormones on vessel wall



* *denote significant difference vs. LPS-treated cells*

Tibolone acts as an estrogen on vessel wall

Simoncini *et al., MCE 2000; 162: 87-94*