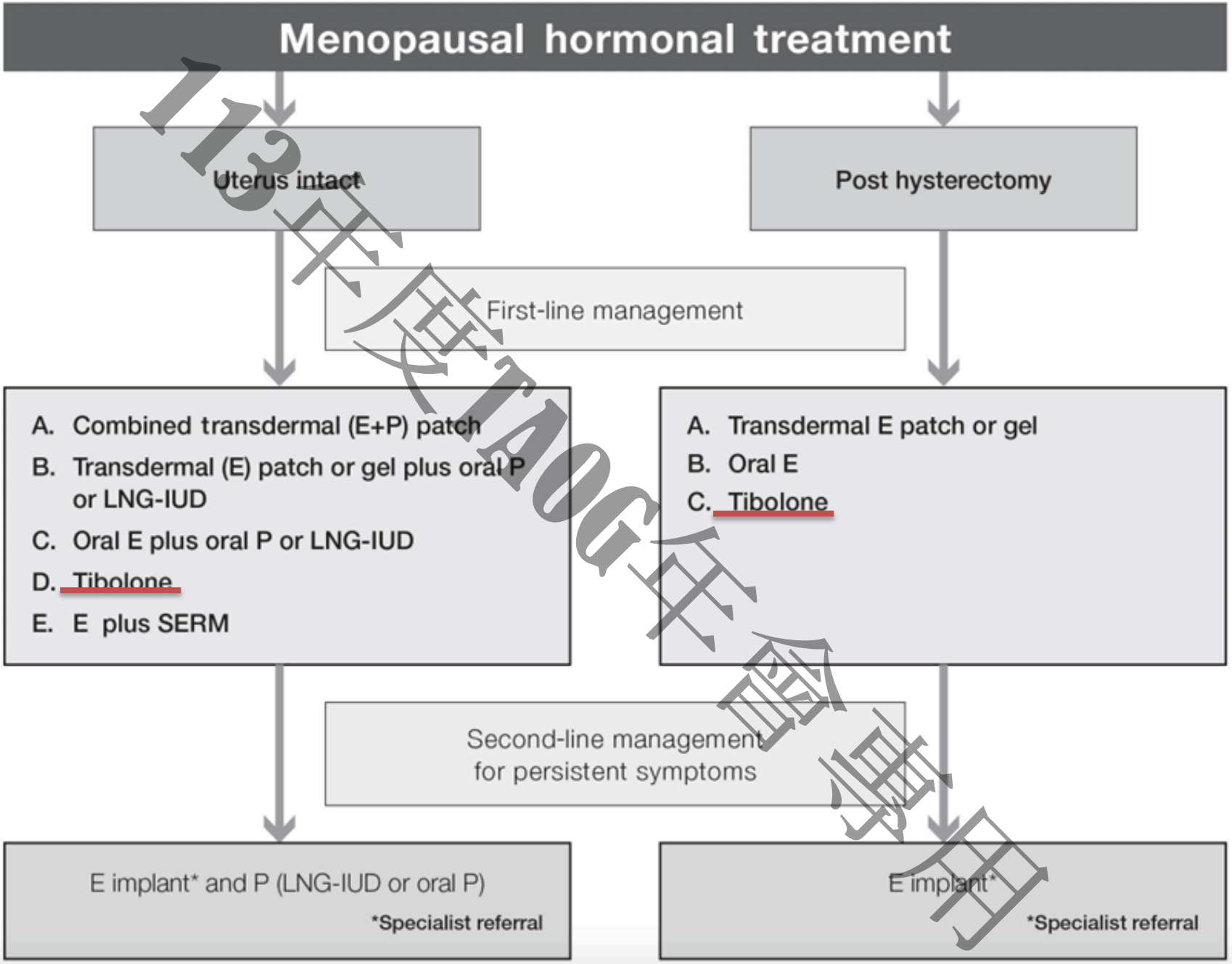
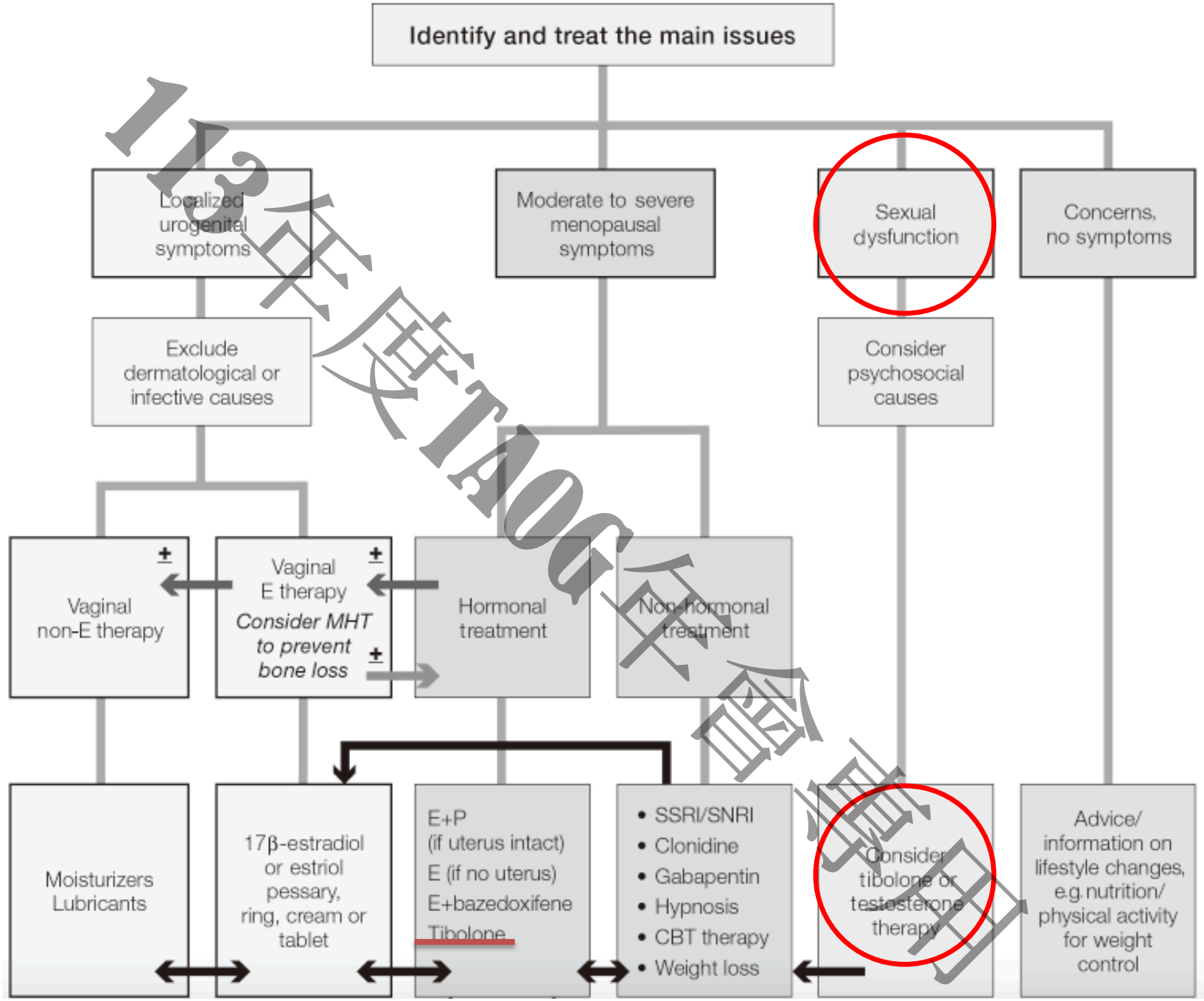
Selective Tissue Estrogenic Activity Regulator (STEAR)

奇美醫院
婦產部
徐英倫



Climacteric. 2014 Oct;17(5):564–79



Climacteric. 2014 Oct;17(5):564–79

Developed in 1964
Organon Research and Development Laboratories, Netherlands

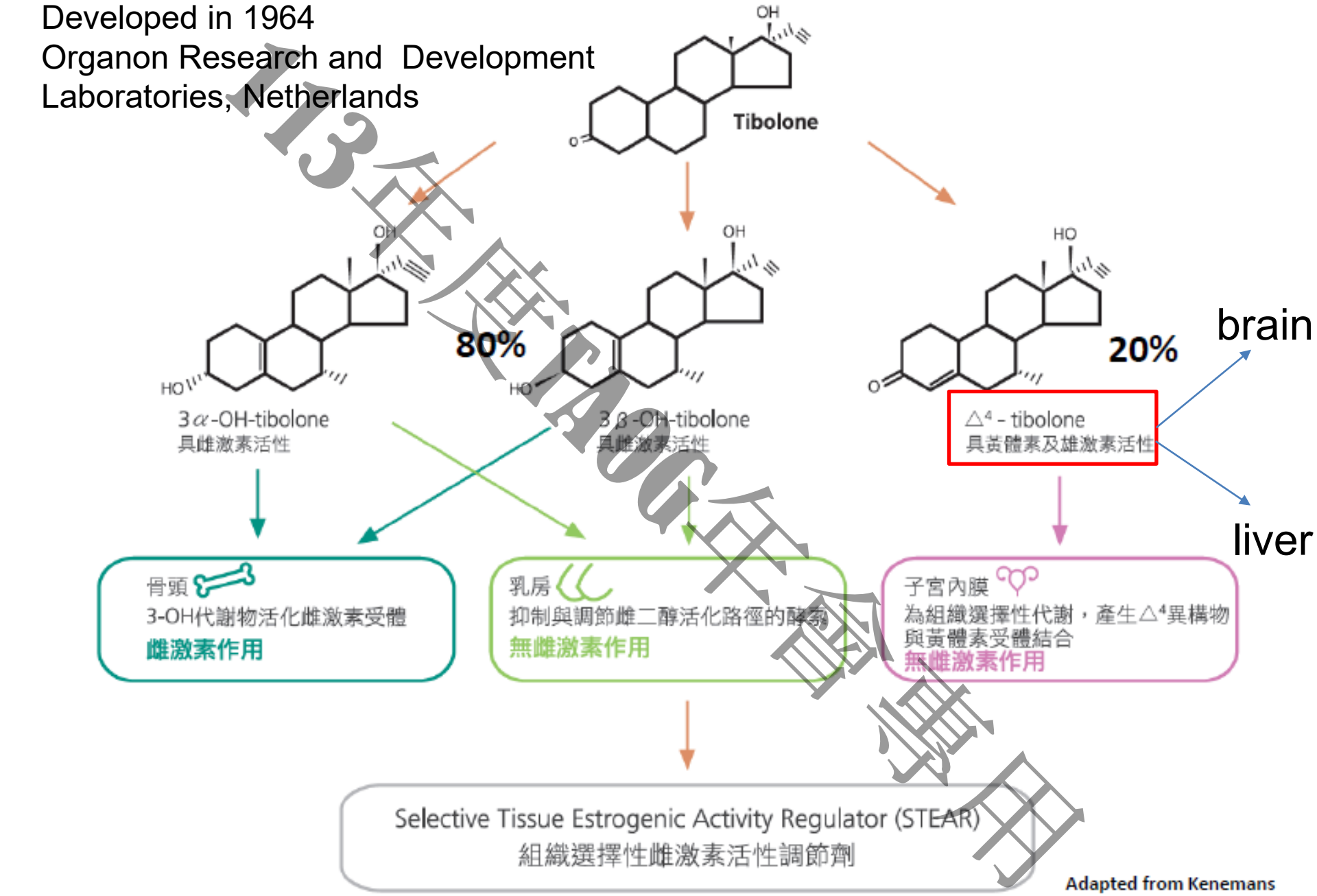
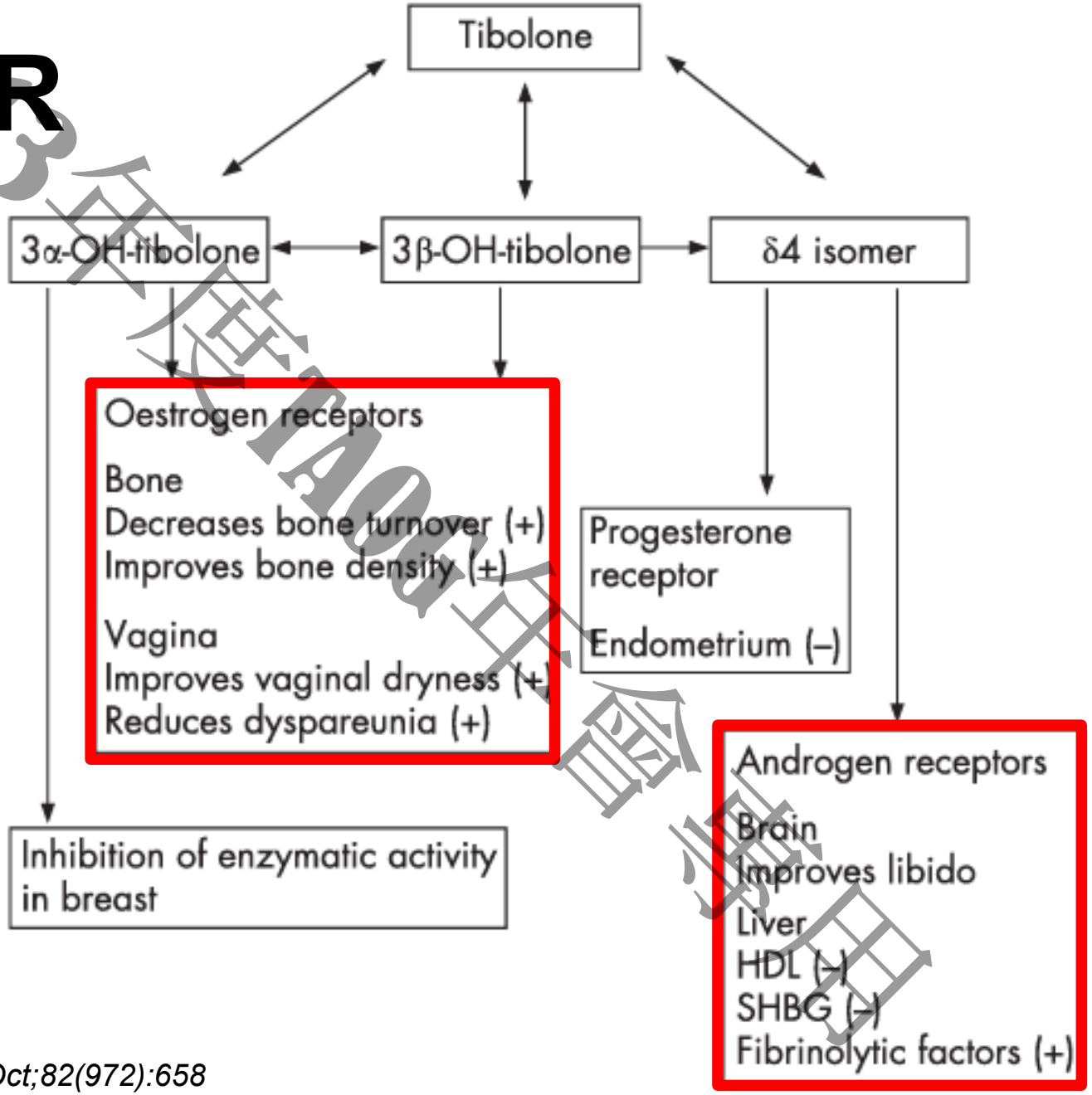


TABLE 1. *Affinities of tibolone and its metabolites for steroid receptors*

	Steroid receptor		
Steroid	Estrogen	Progesterone	Androgen
Tibolone	Weak	Weak	Weak
Isomer Δ^4	None	Moderate	Moderate
3α-OH–derived	Weak	None	None
3β-OH–derived	Weak	None	None

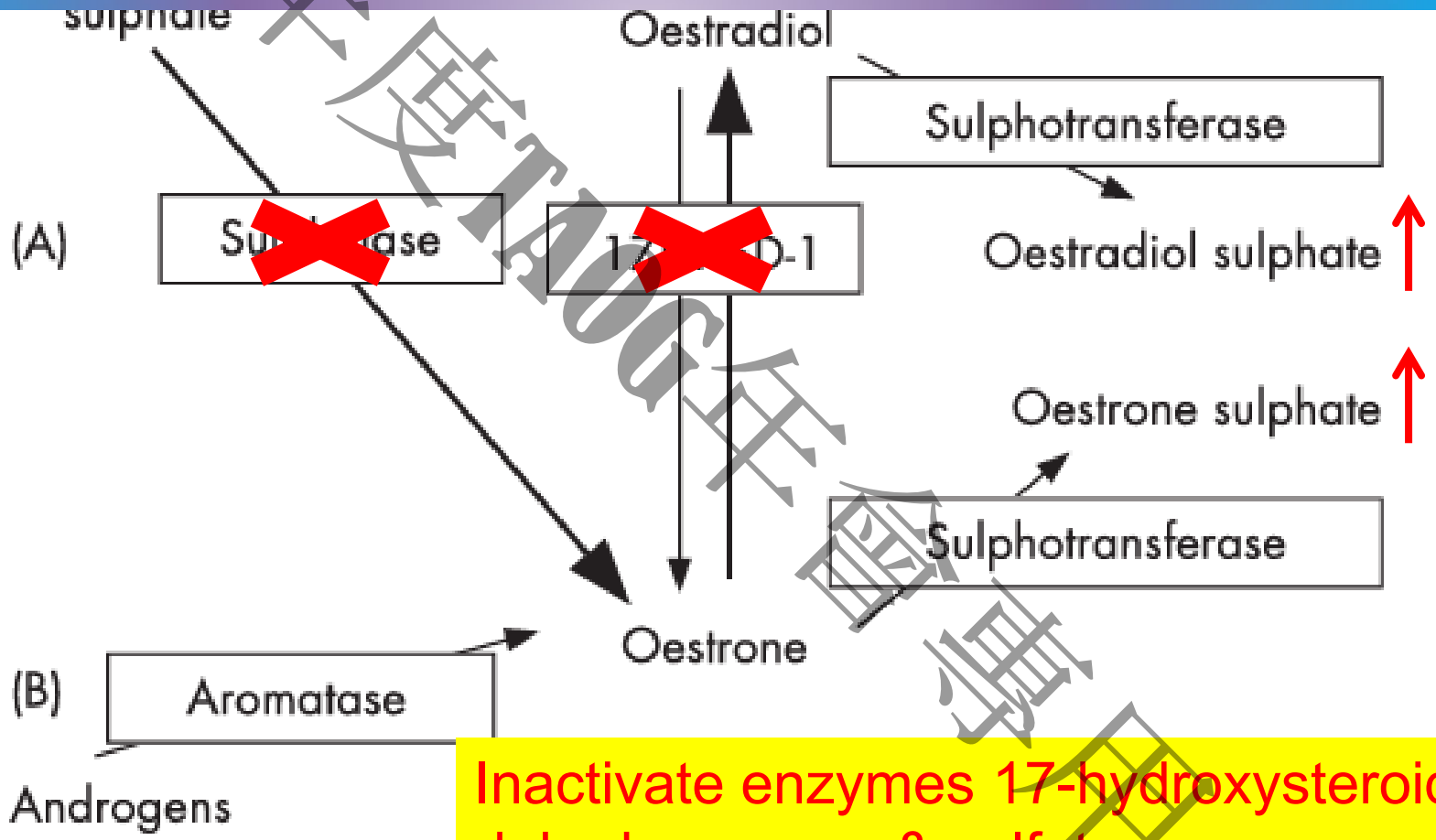
STEAR



Postgrad Med J 2006 Oct;82(972):658

In breast
17 beta-HSD inhibited by tibolone

總反應：減少Estradiol濃度

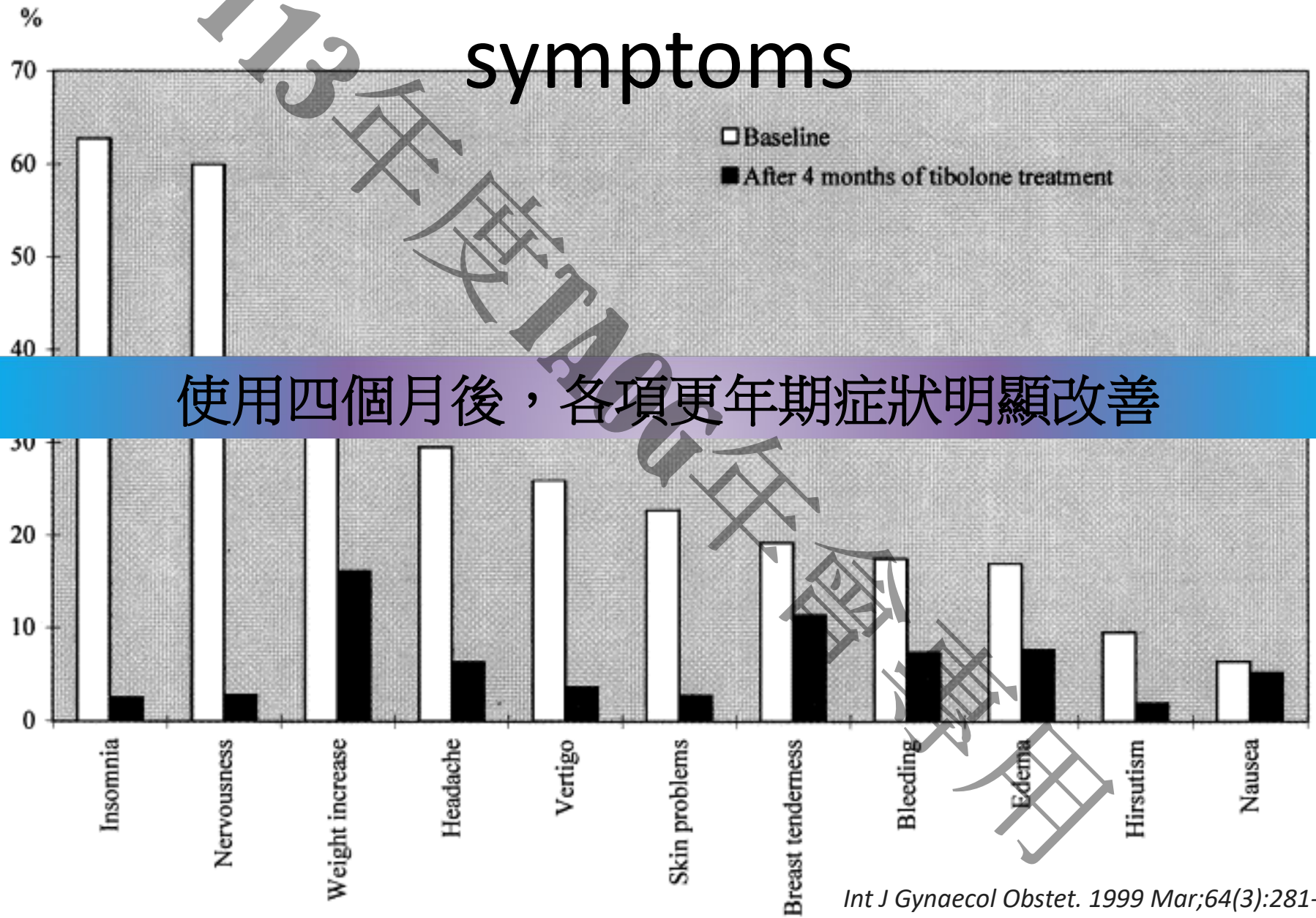


Inactivate enzymes 17-hydroxysteroid dehydrogenase & sulfatase

Postgrad Med J 2006 Oct;82(972):658

VASOMOTOR SYMPTOMS

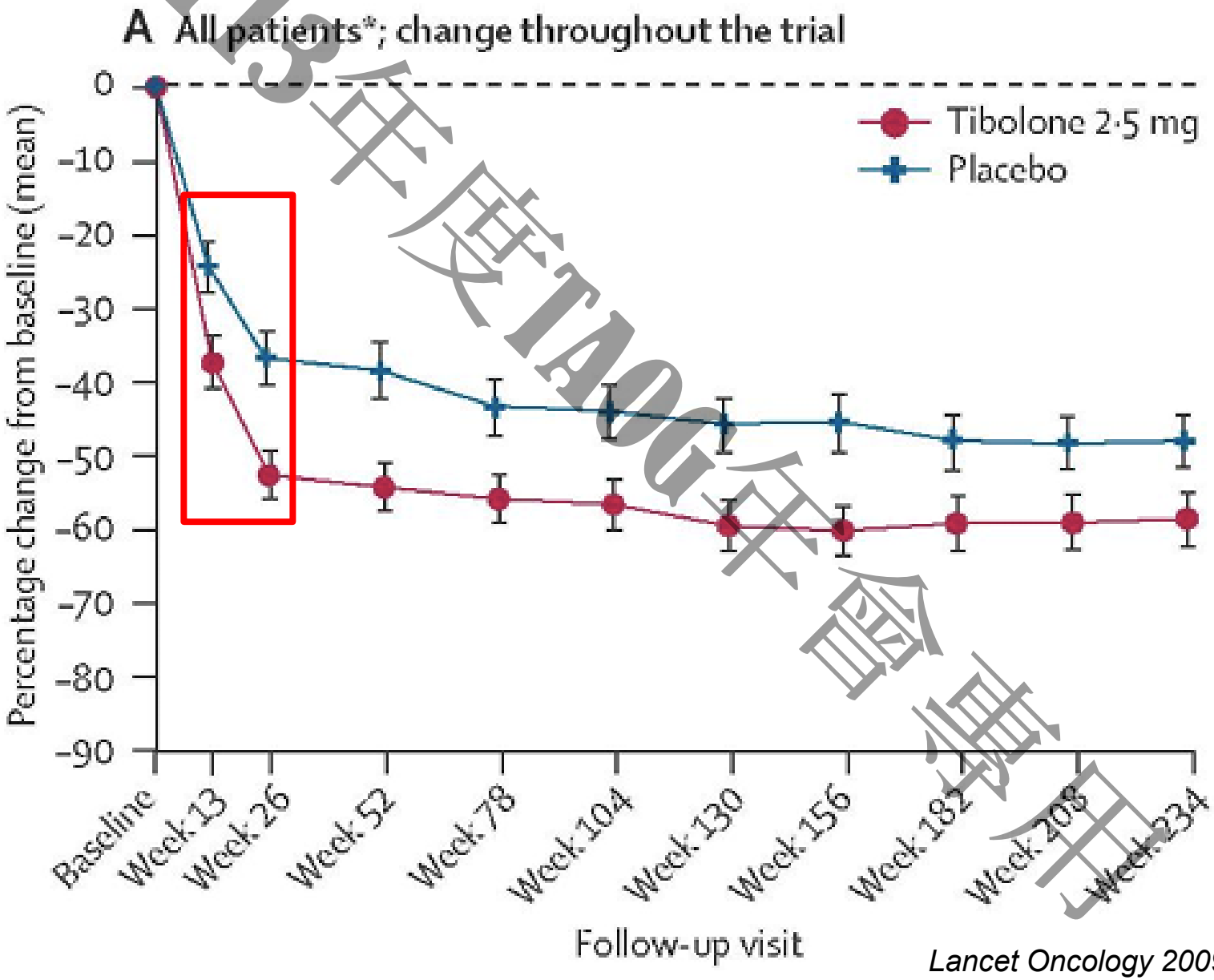
Effective in relieving climacteric symptoms



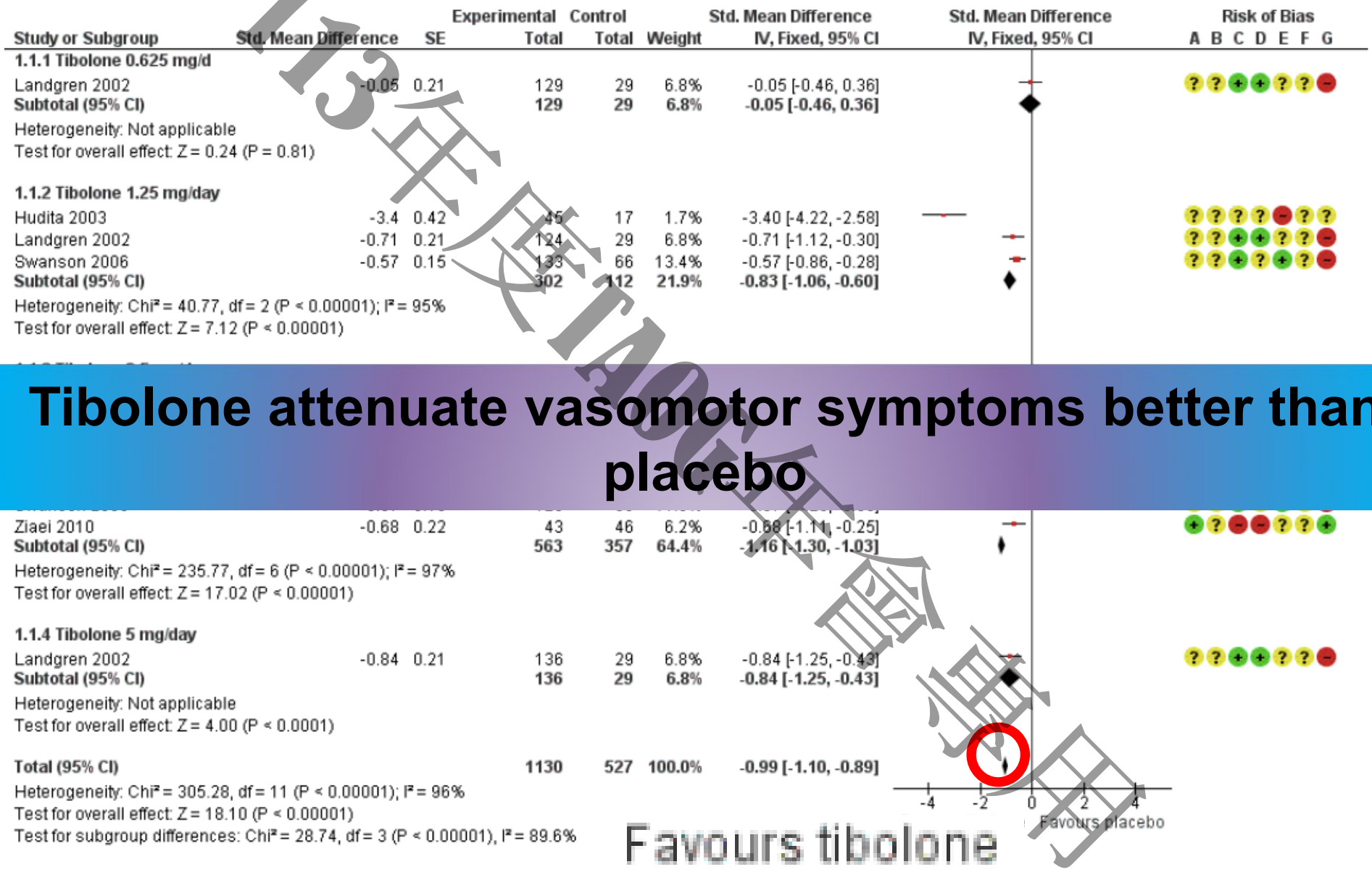
使用四個月後，各項更年期症狀明顯改善

Int J Gynaecol Obstet. 1999 Mar;64(3):281-6.

Change of hot flush

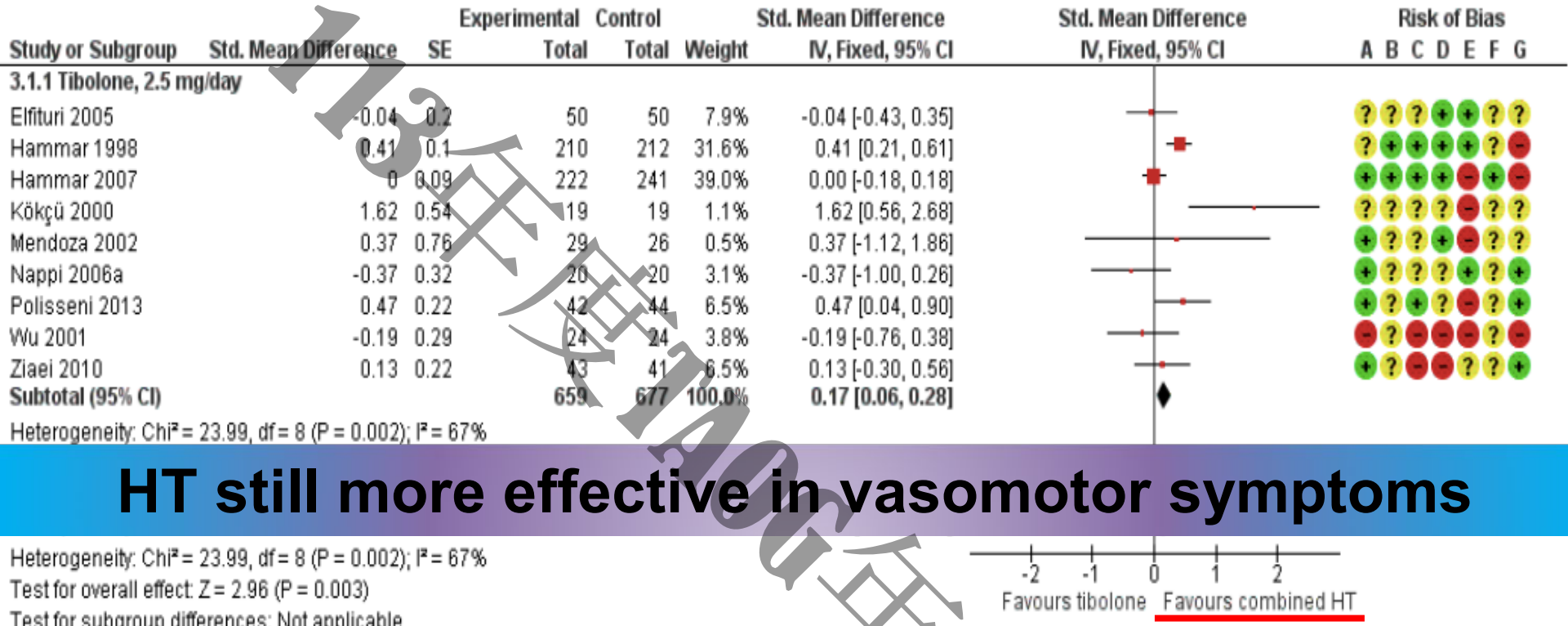


Lancet Oncology 2009;(10) 2:135-46



Tibolone attenuate vasomotor symptoms better than placebo

Cochrane Database Syst Rev. 2016 Oct 12;10:CD008536.



HT still more effective in vasomotor symptoms

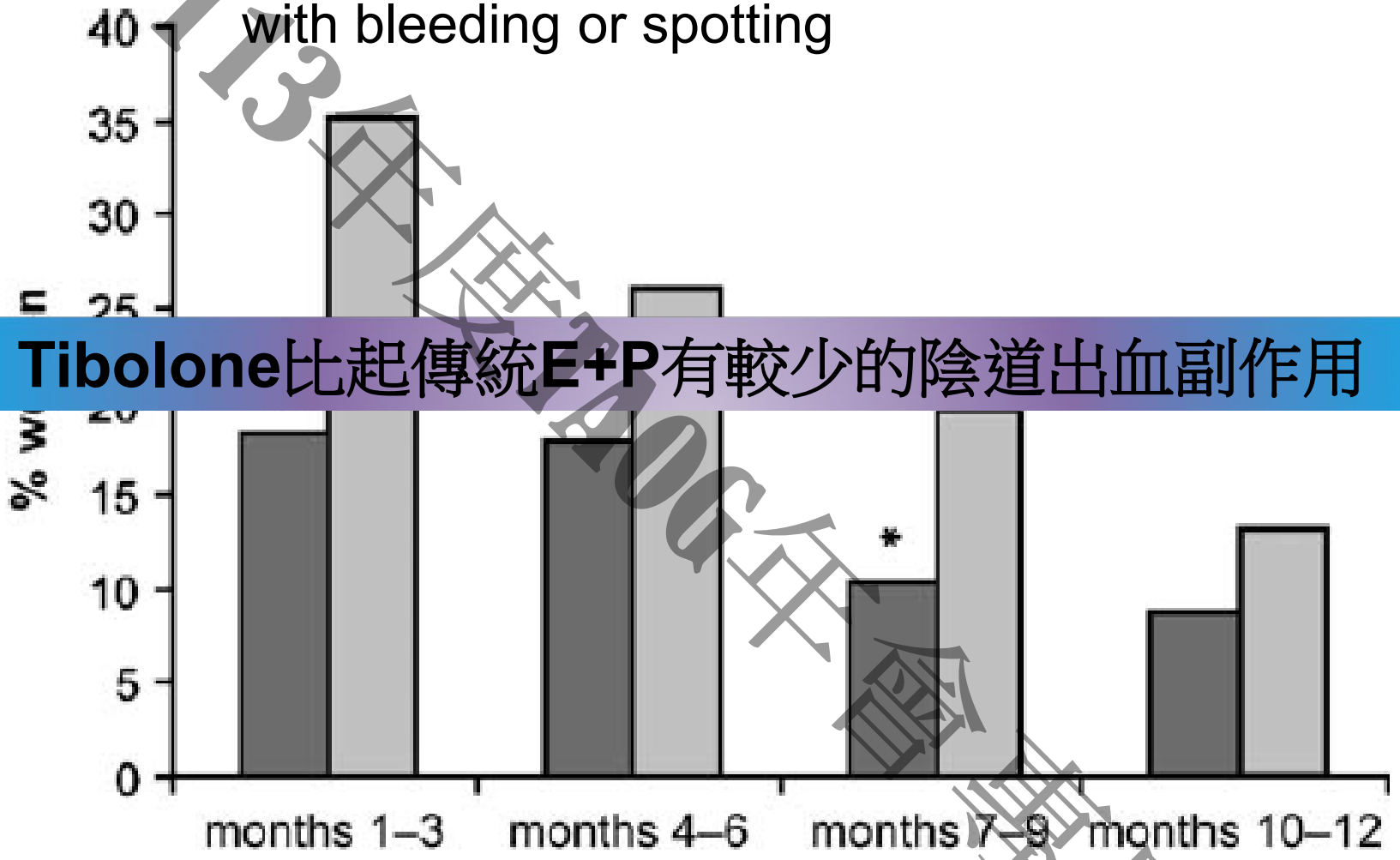
Heterogeneity: Chi² = 23.99, df = 8 (P = 0.002); I² = 67%
Test for overall effect: Z = 2.96 (P = 0.003)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Conflict of interest

Cochrane Database Syst Rev. 2016 Oct 12;10:CD008536.

TOLERABILITY

Percentage of women reporting at least 1 day with bleeding or spotting



Tibolone比起傳統E+P有較少的陰道出血副作用

Tibolone 2.5 mg (*n* = 242) = ■; E2/NETA (*n* = 263) = ■

***$P < 0.05$; **$P < 0.001$**

BJOG. 2007 Dec;114(12):1522-9.

LISA: adverse events

Livial International Study in sexual Arousal disorders

Tibolone適合使用HT之後，對於副作用難以忍受的女性

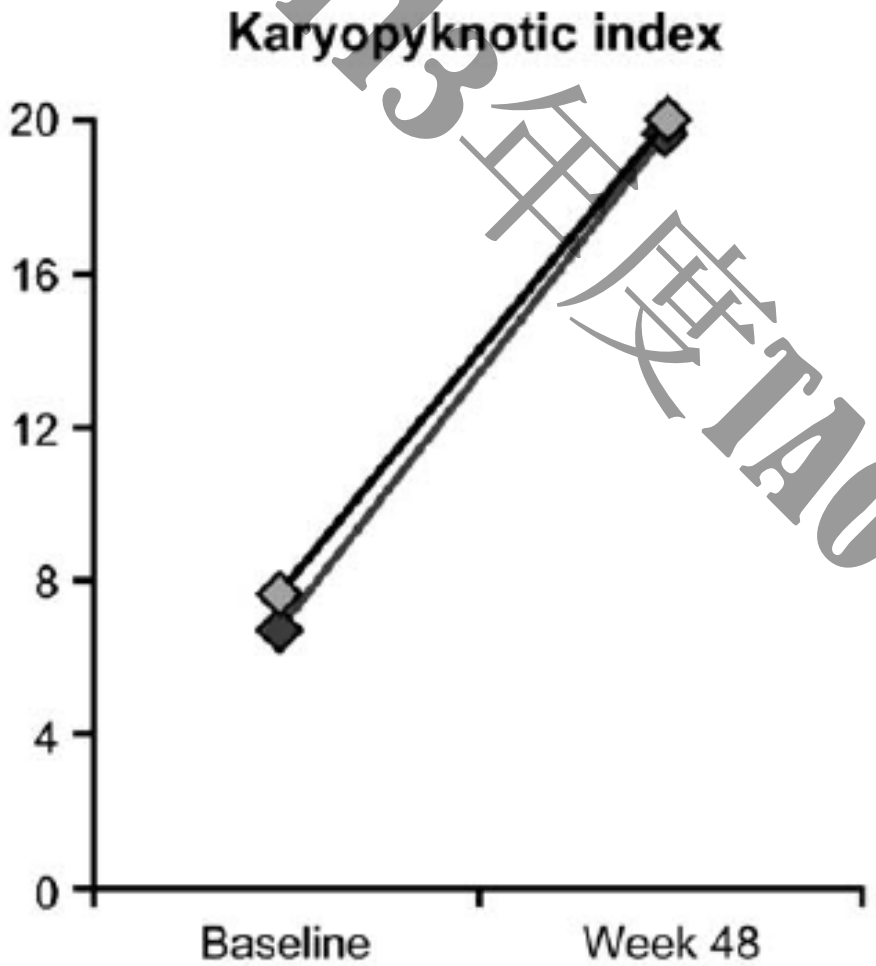
	Tibolone	E_2/NETA patch
Vaginal haemorrhage	0%**	11%
Breast signs and symptoms	4%*	11%

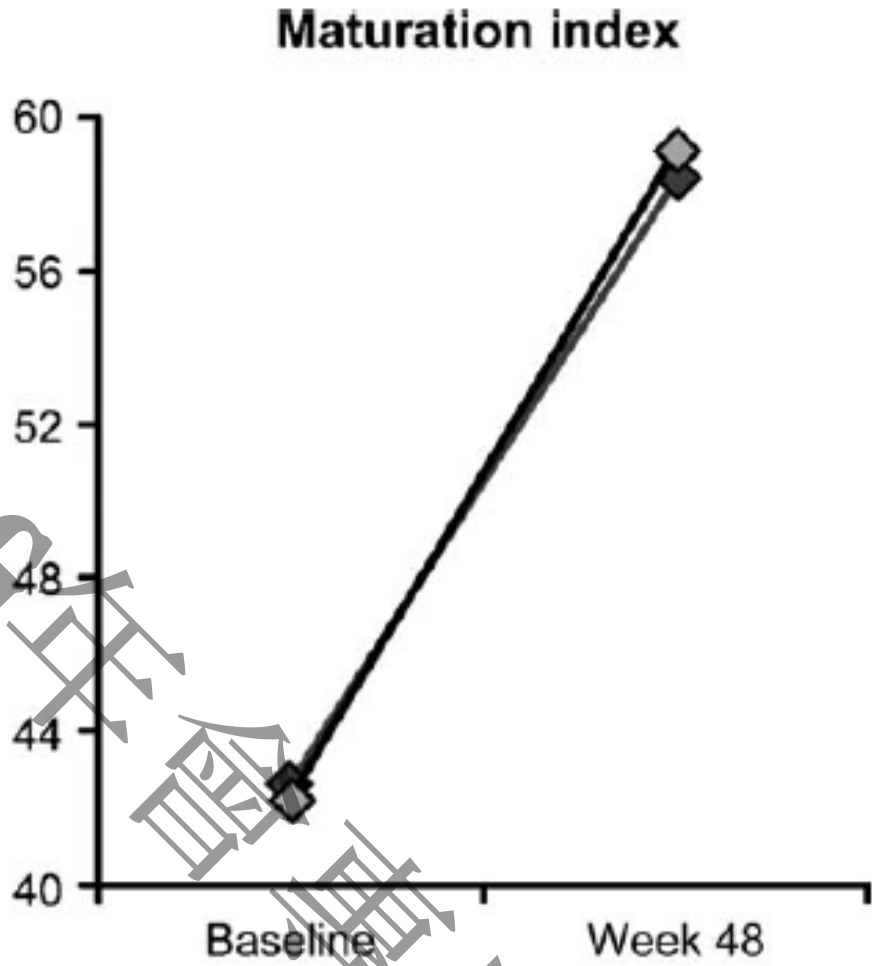
* $P = 0.015$ vs. E_2/NETA ** $P < 0.001$ vs. E_2/NETA

Nijland E *et al. Climacteric* 2009;12:114–121.

GENITAL TRACT ATROPHY
&
SEXUAL DYSFUNCTION

Similar effect in genital tract atrophy

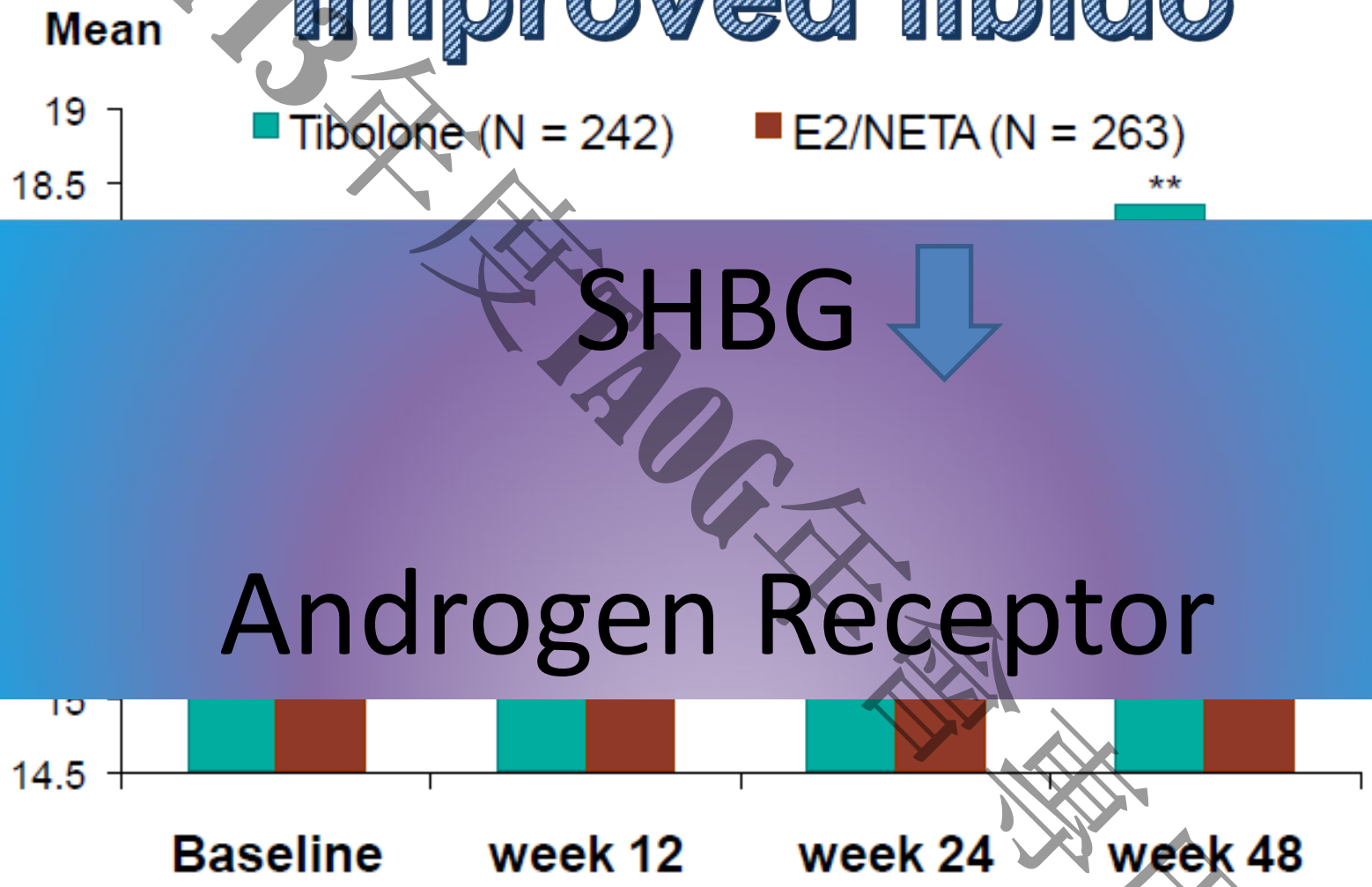




Tibolone 2.5 mg = ◆ ; E2/NETA = ◆

BJOG. 2007 Dec;114(12):1522-9.

Improved libido



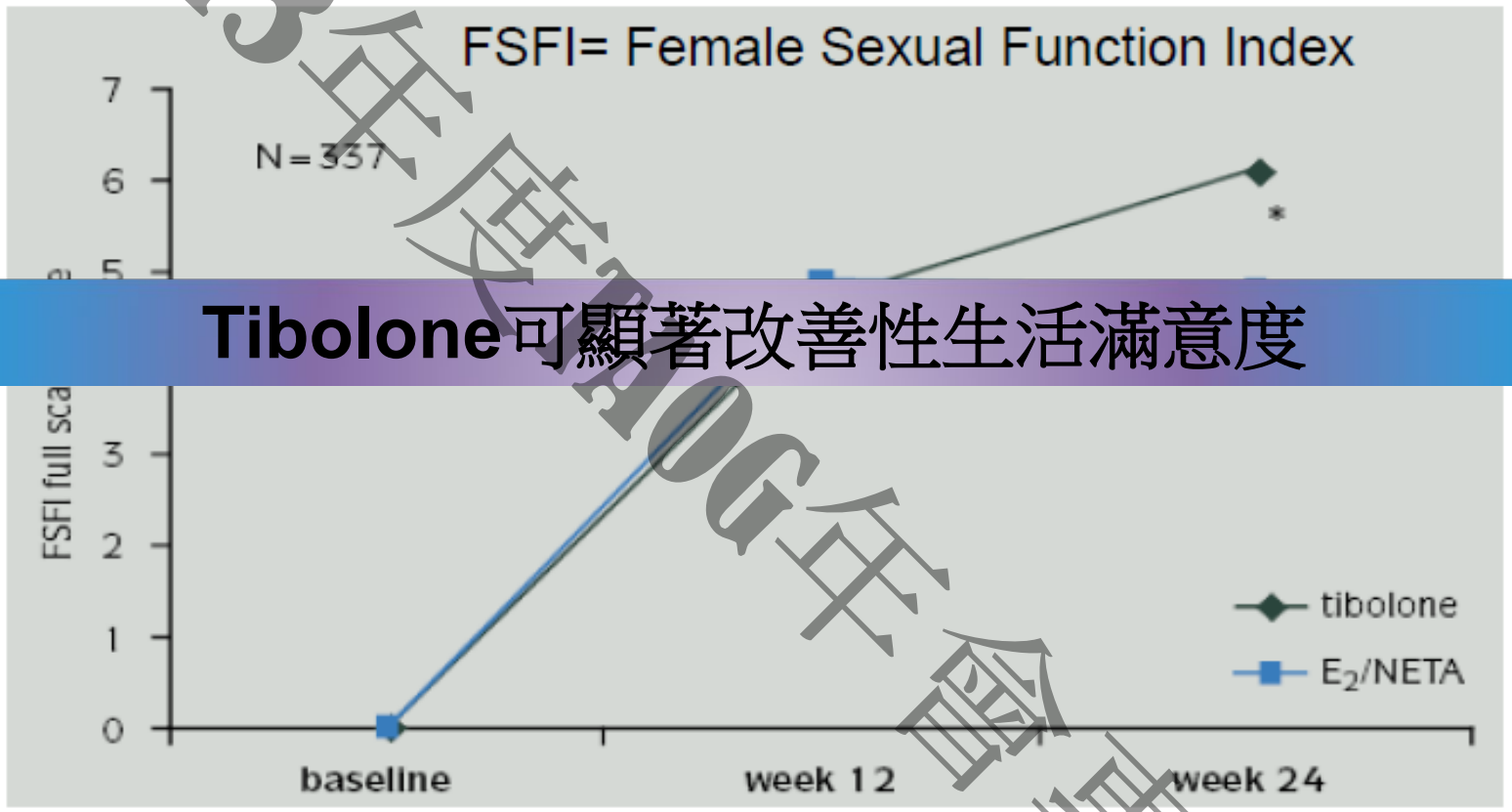
SHBG ↓

Androgen Receptor

*P<0.05 between treatment groups **P=0.003 between treatment groups

Menopause 2002;9:162–70

LISA: effects on sexual dysfunction (FSFI)



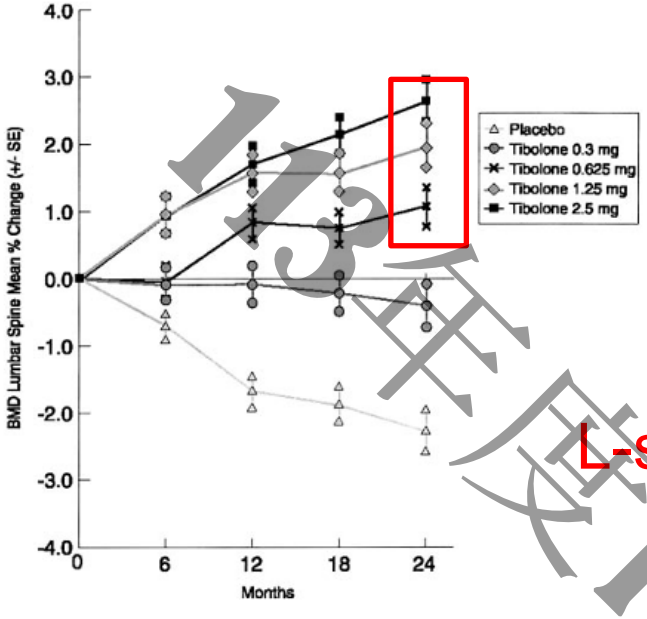
Tibolone可顯著改善性生活滿意度

*P < 0.025 vs. E_2/NETA for full scale score

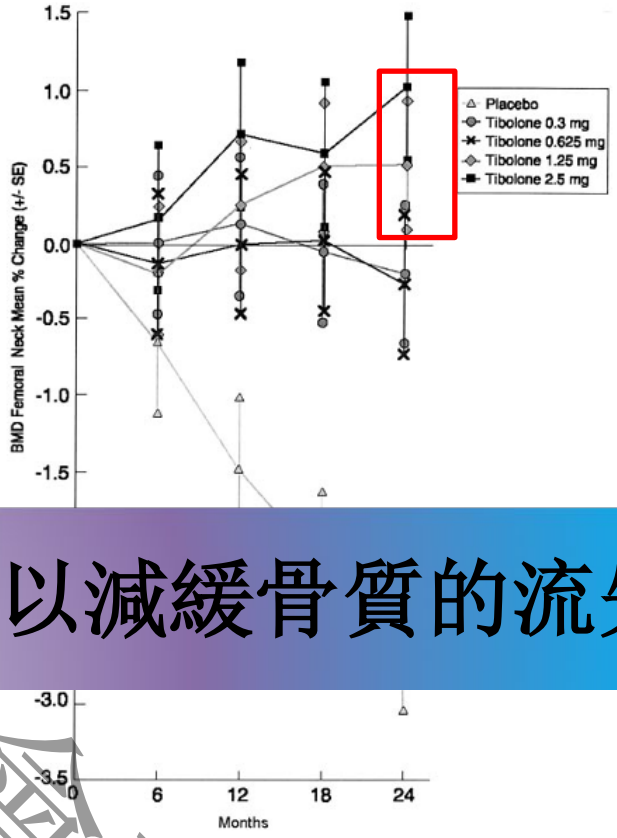
FSFI sub-scores such as arousal, desire, satisfaction also significantly more increased in tibolone group

Nijland E *et al. J Sex Med* 2008;5:646–656

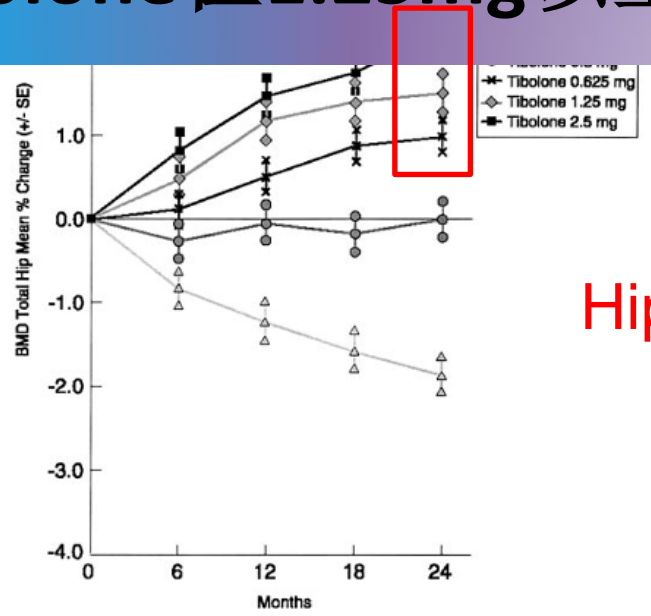
BONE DENSITY AND FRACTURE



L-spine



Tibolone在1.25mg以上的劑量可以減緩骨質的流失



Hip

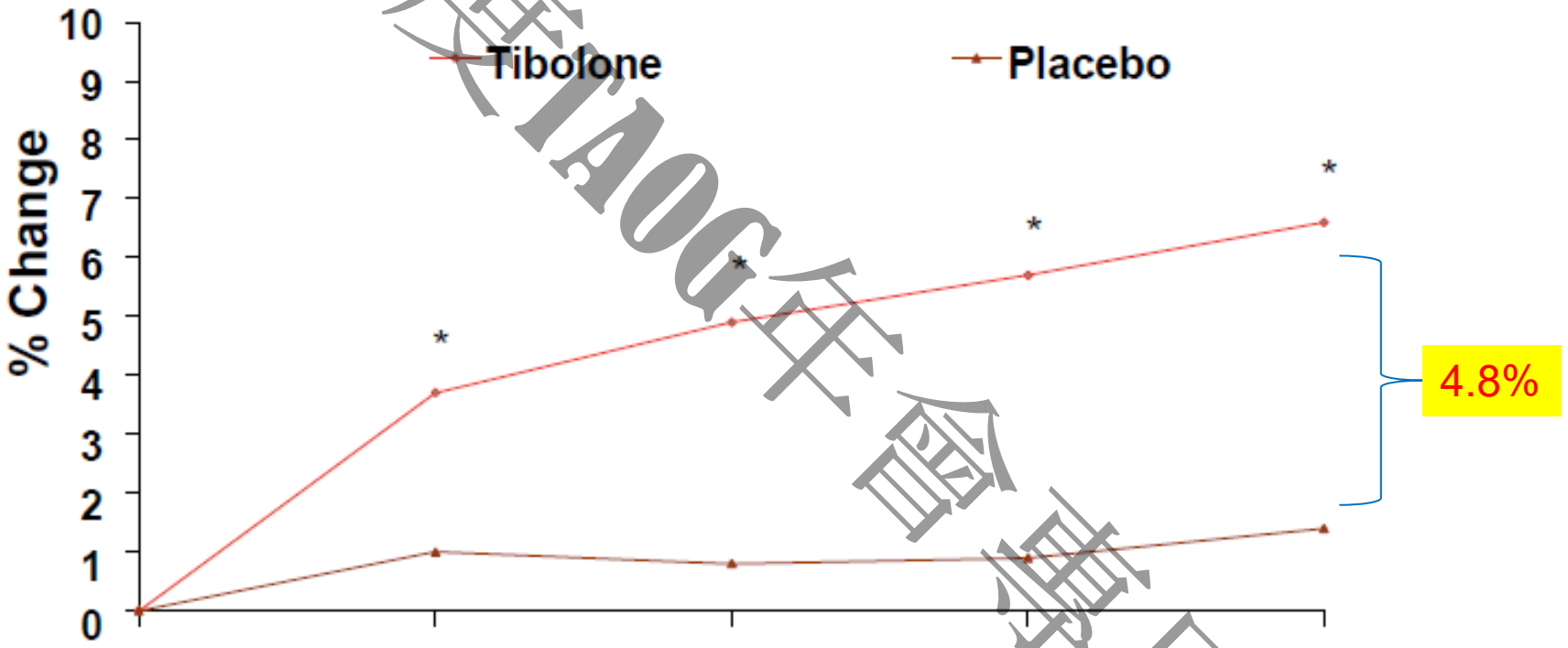
Femoral neck

J Clin Endocrinol Metab, 2001,86(10):4717–4726

LIFT: BMD lumbar spine

LIFT: Long-Term Intervention on Fractures with Tibolone

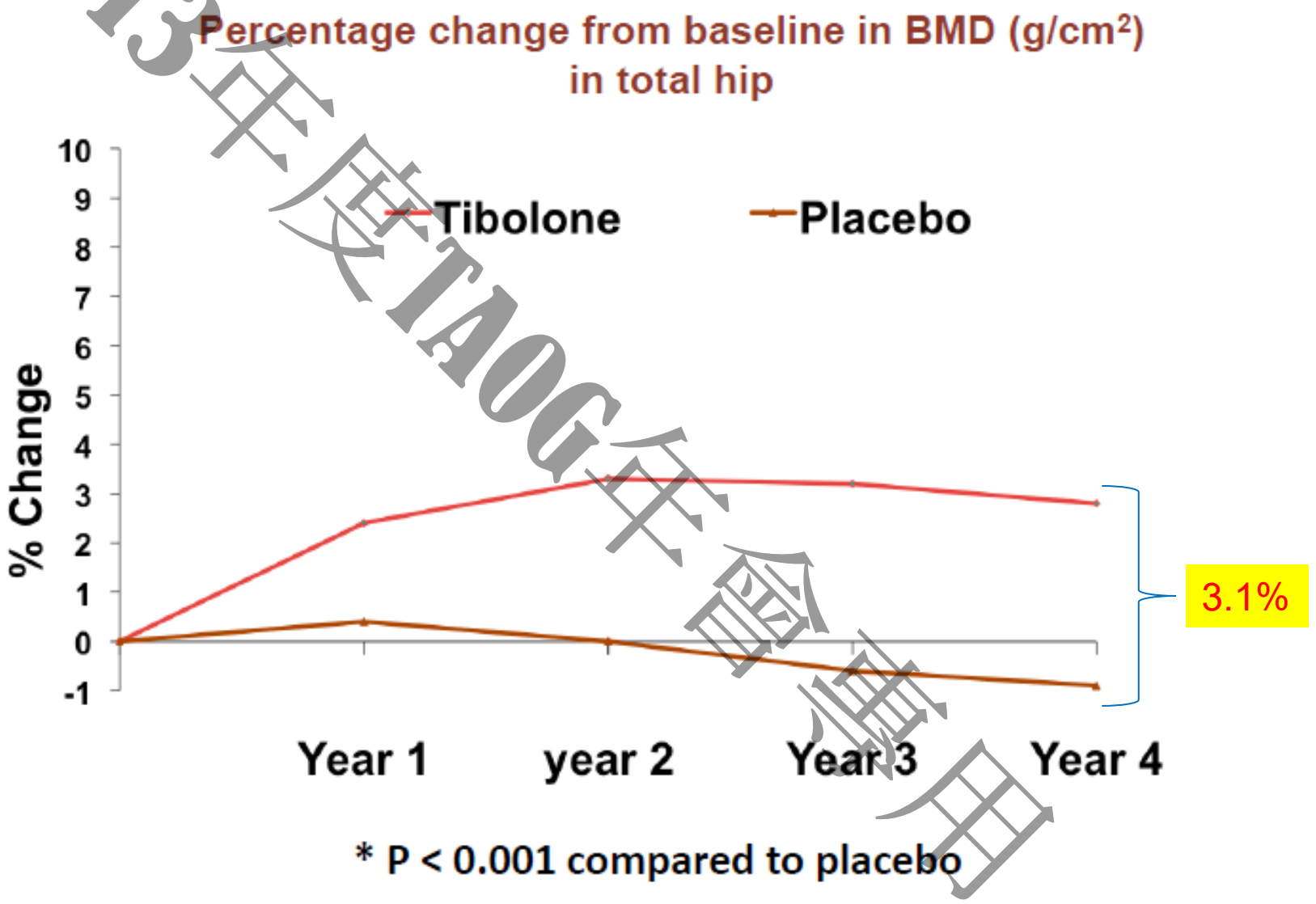
Percentage change from baseline in BMD (g/cm²) in lumbar vertebrae (L1–L4)



*** P < 0.001 compared to placebo, BMD: Bone mineral density**

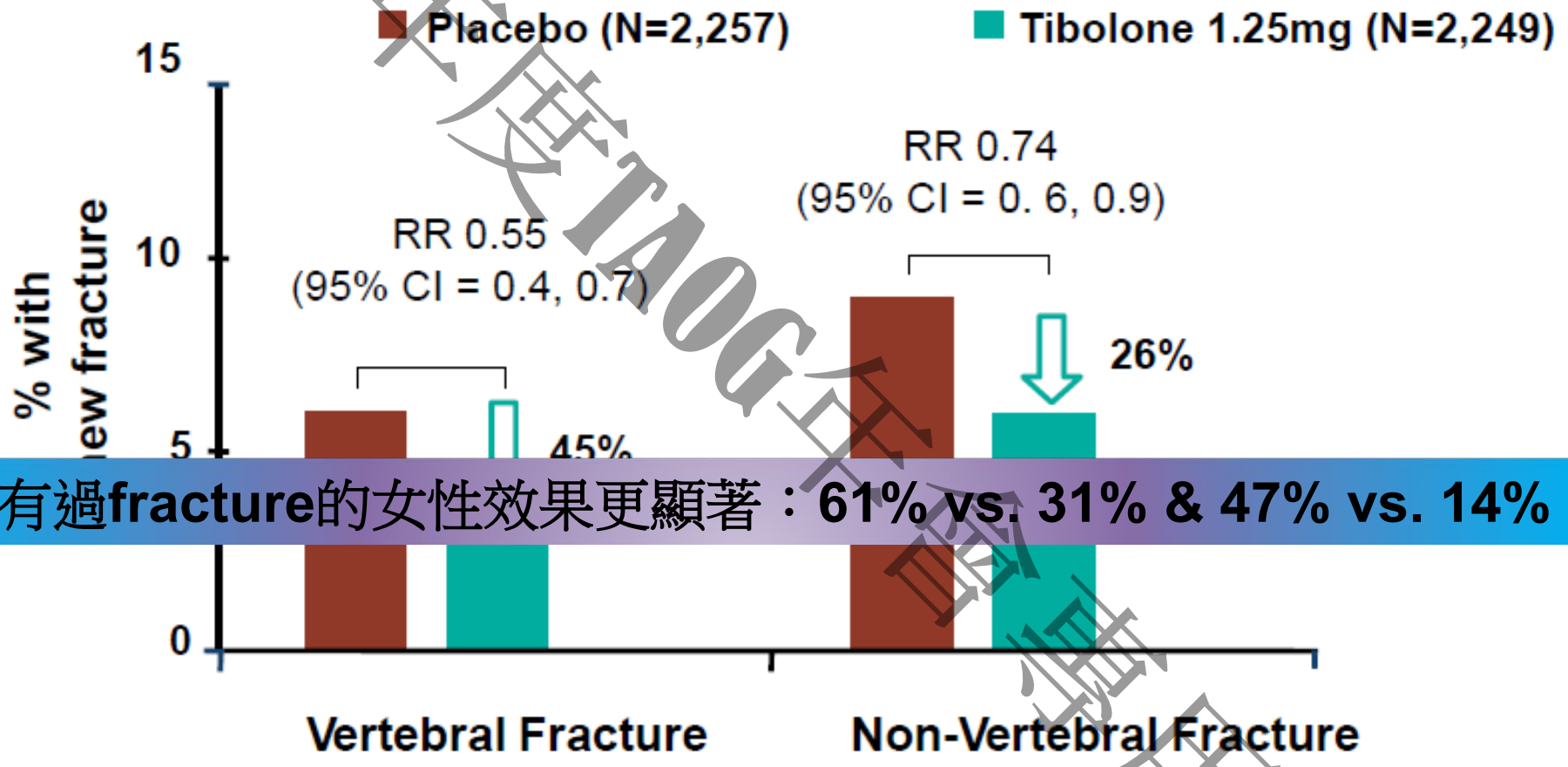
Cummings SR, *et al. N Engl J Med* 2008;359:697–708.

LIFT: BMD total hip



Cummings SR, *et al. N Engl J Med* 2008;359:697–708.

LIFT: fractures



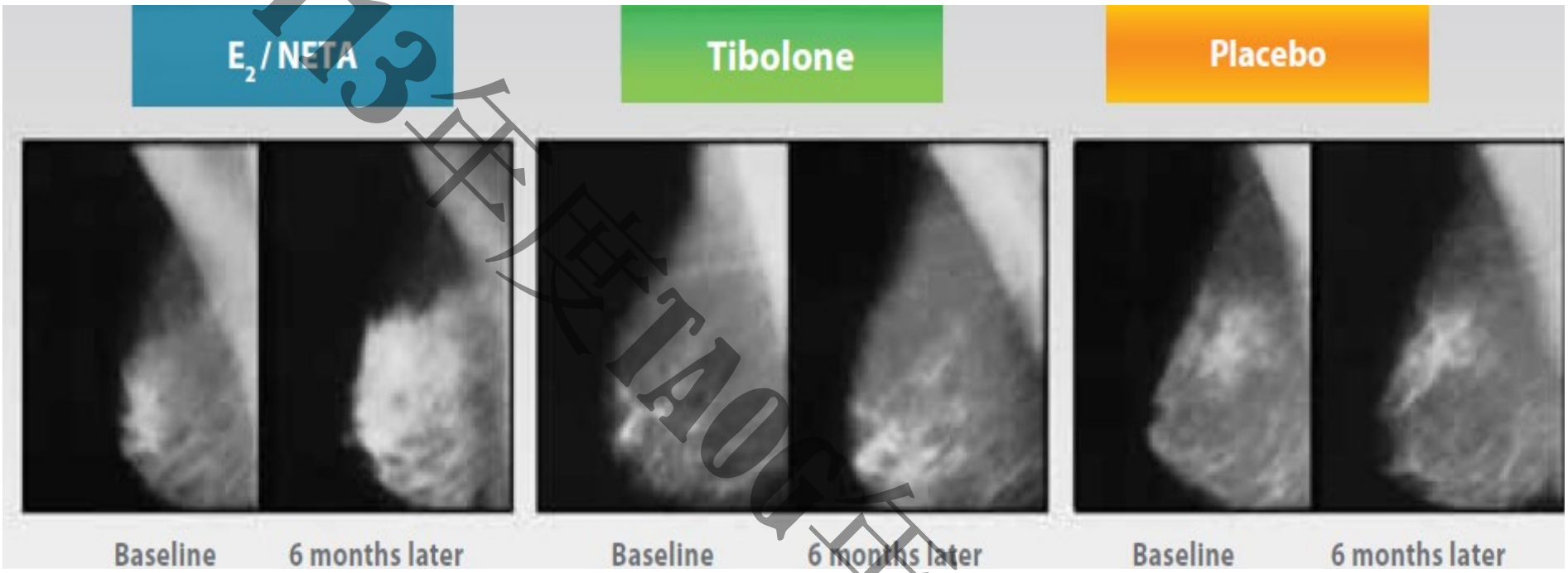
在有過**fracture**的女性效果更顯著：**61% vs. 31% & 47% vs. 14%**

Cummings SR, *et al. N Engl J Med* 2008;359:697–708.

BREAST

Minimal impact on breast density

166 postmenopausal women randomized to take Tibolone, E2/NETA, or placebo

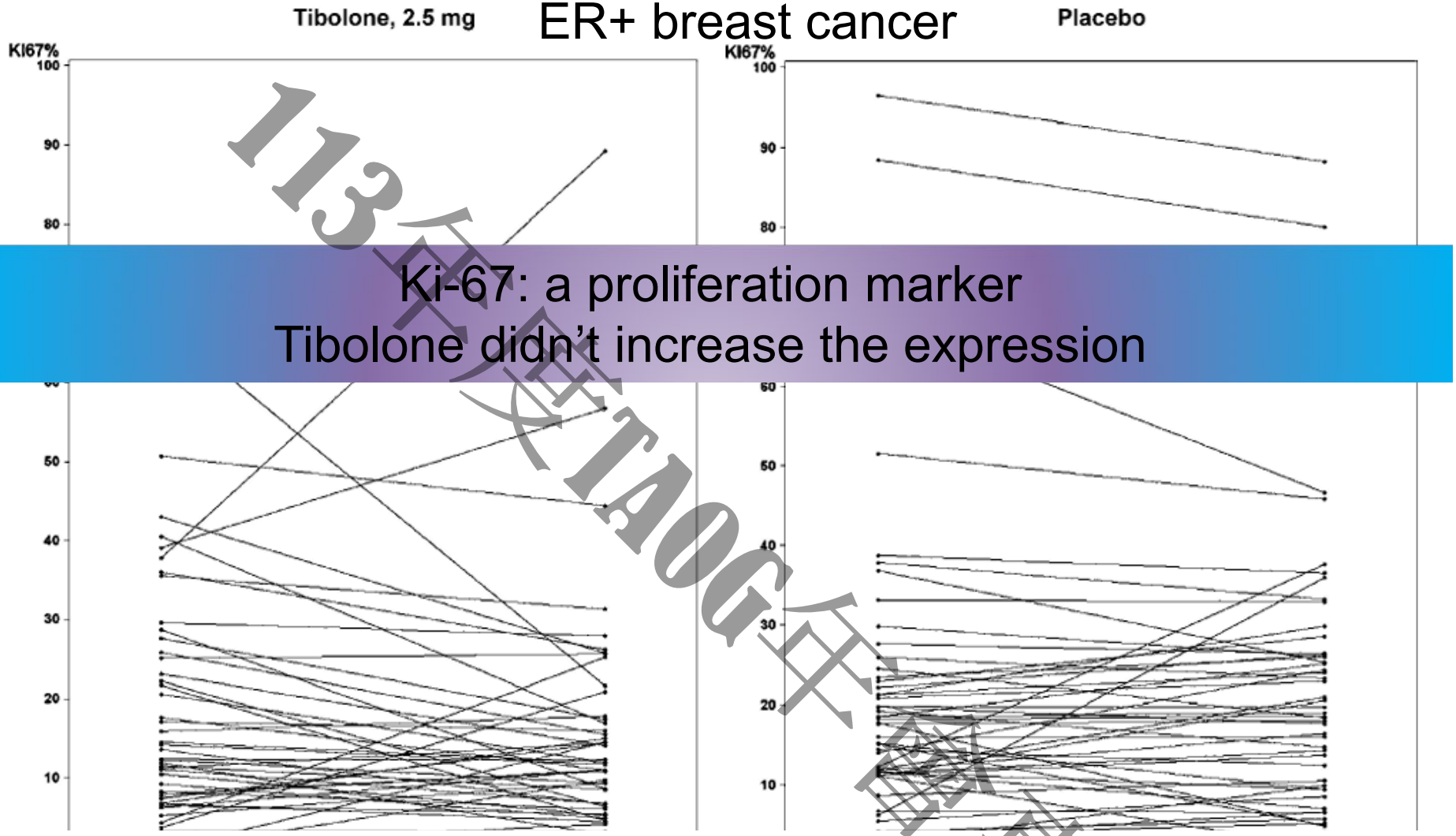


Wolfe classifiction

	Wolfe increase	*Percentage classification increase*
E_2/NETA	22/48 (46%)	24/48 (50%)
Tibolone	1/51 (2%)	3/51 (6%)
Placebo	0/55 (0%)	0/55 (0%)

Lundström et al., Am J Obstet Gynecol 2002

ER+ breast cancer



Ki-67: a proliferation marker
Tibolone didn't increase the expression

	Baseline		Surgery		Change from baseline		*P**
	Tibolone	Placebo	Tibolone	Placebo	Tibolone	Placebo	
Ki-67 (%)							0.170
n	46	49	46	49	46	49	
Median	13.0	17.8	12.0	19.0	-2.4	0.2	
Mean (SE)	18.2 (2.2)	21.6 (2.8)	16.3 (2.3)	22.0 (2.4)	-1.9 (2.1)	0.4 (1.2)	

ClinCancerRes2007;13(14)July15,2007

THE LANCET

Volume 362, Issue 9382, 9 August 2003, Pages 419–427

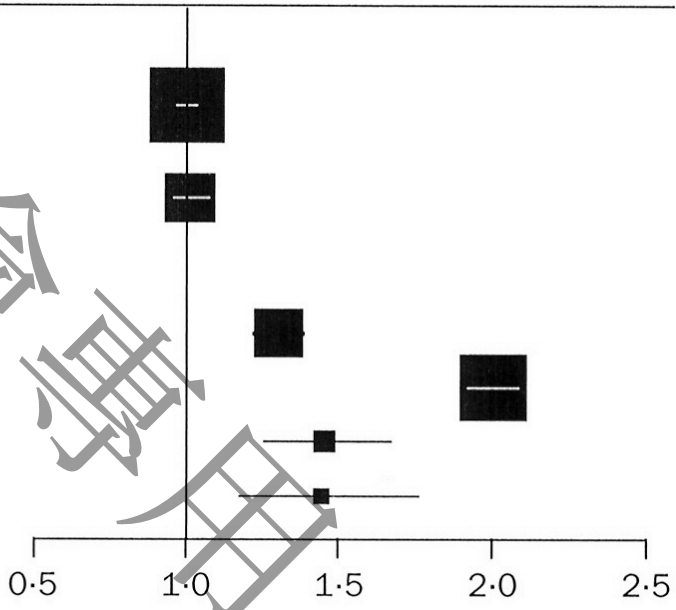
The Million Women Study (UK)

Breast cancer and hormone-replacement therapy in the Million Women Study

Million Women Study Collaborators

Design	Prospective cohort, observational study
Population	1,084,110 UK women, aged 50–64 years
Time	May 1996 – March 2001

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)



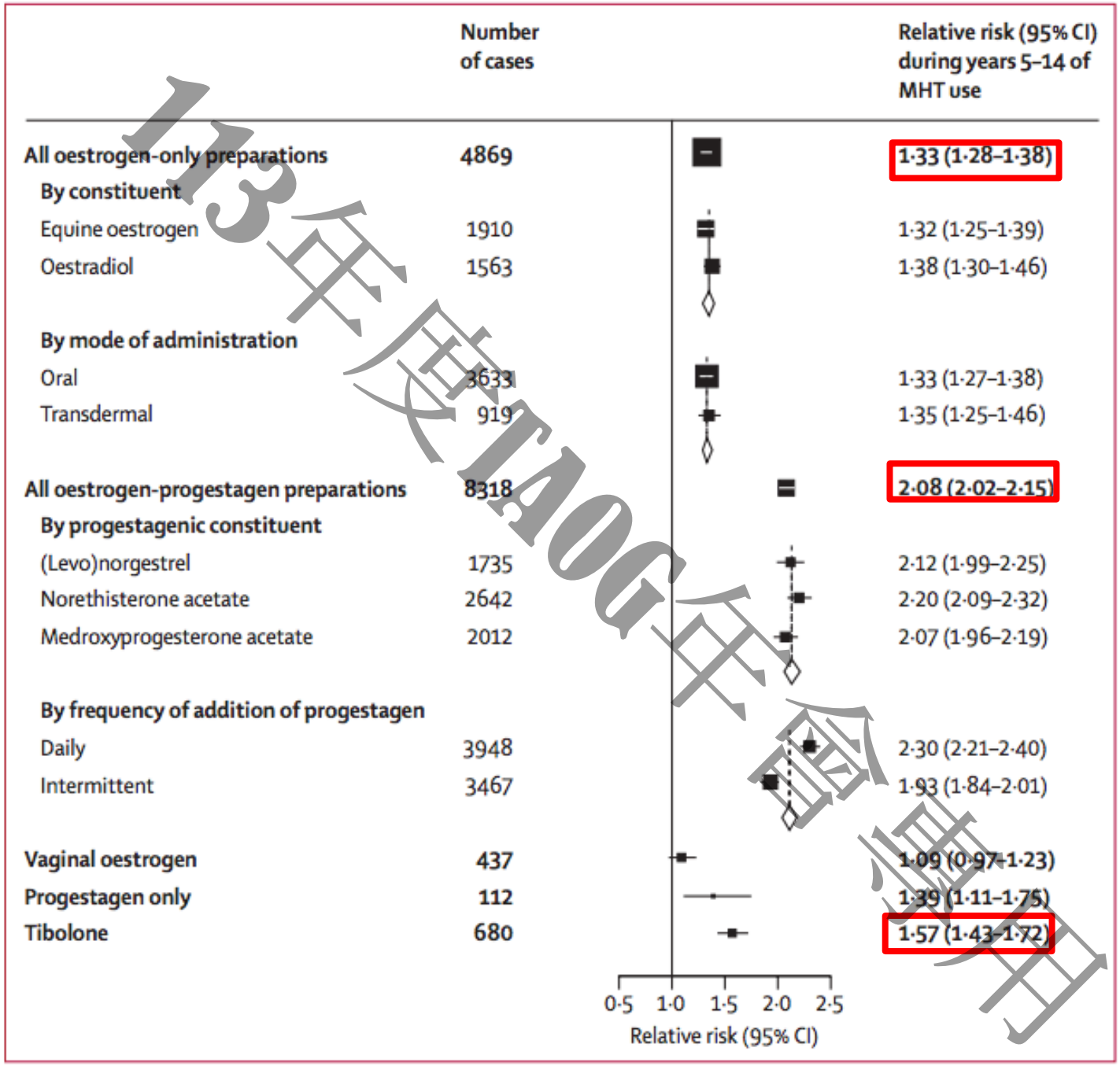
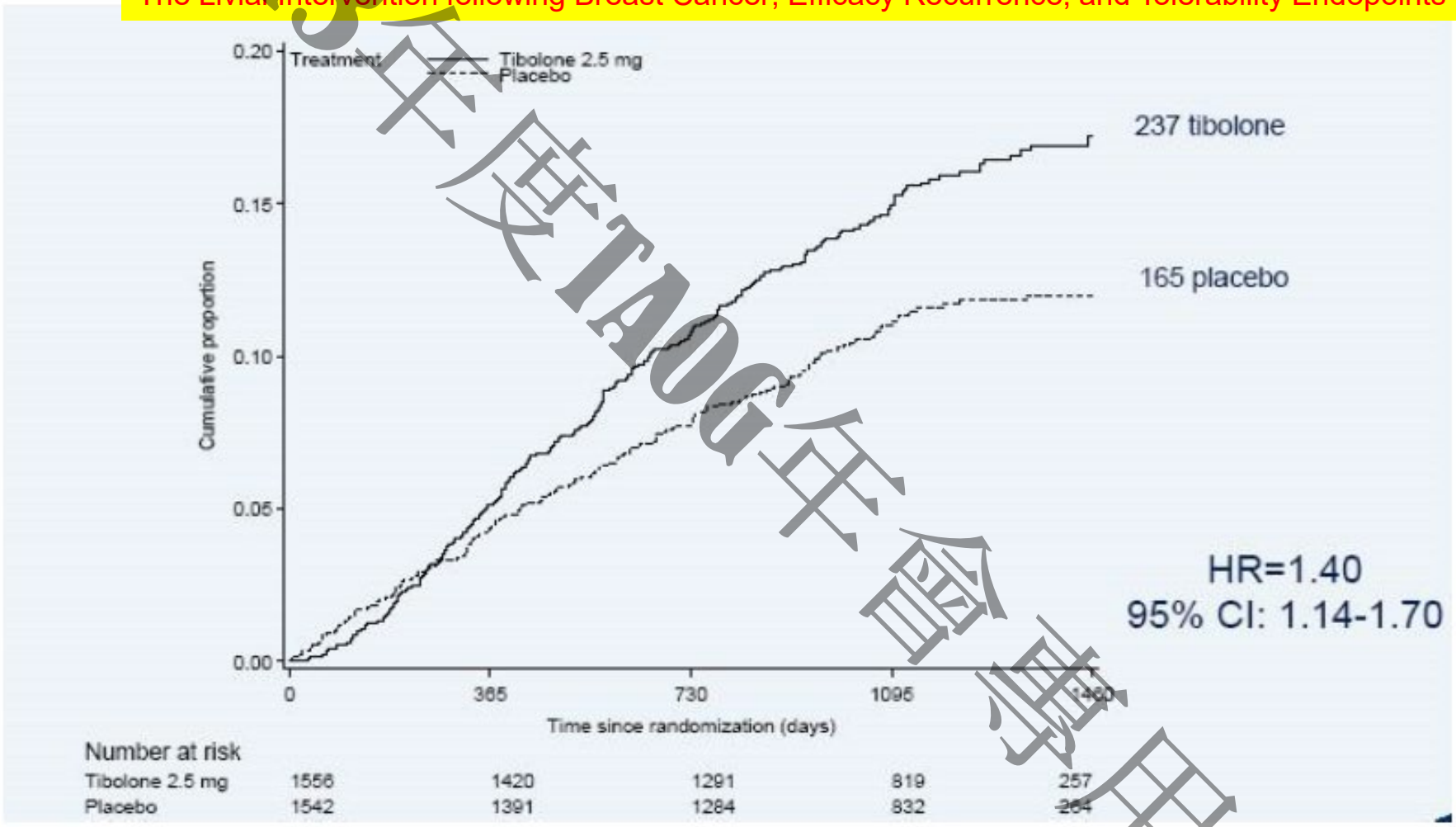


Figure 4: **Main types of MHT: relative risks during years 5–14 of current use**

Lancet 2019; 394: 1159–68

LIBERATE: breast cancer recurrence (ITT)

The Livial Intervention following Breast Cancer; Efficacy Recurrence, and Tolerability Endopoints



Kenemans P, *et al*. *Lancet Oncol*. 2009:10;135–146.

ENDOMETRIAL SAFETY

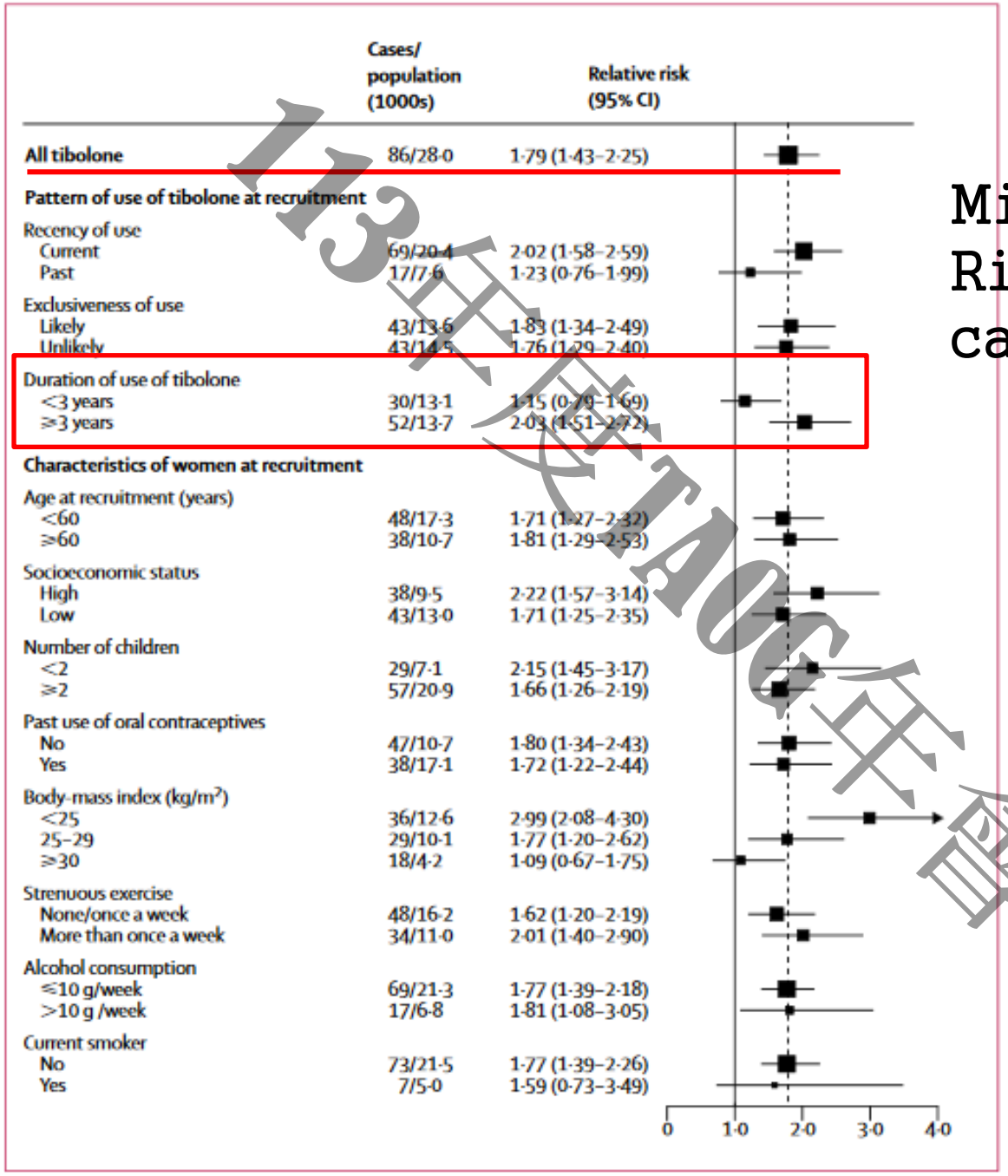
THEBES: endometrial hyperplasia and cancer

Tibolone Histology of the Endometrium and Breast Endpoints Study

Parameter	Tibolone 1.25 mg (N = 637)†	Tibolone 2.5 mg (N = 671)†	CE/MPA (N = 1,320)†
Women-years of exposure	1,179	1,223	2,415
Endometrial hyperplasia	**0 (0.0%)**	**0 (0.0%)**	**2 (0.2%)**
Endometrial cancer	**0 (0.0%)**	**0 (0.0%)**	**1 (0.08%)#**

† Evaluable subjects (90 days treatment and biopsy taken)
# Endometrial stromal sarcoma,

Archer DF *et al. J Clin Endocrinol Metab* 2007;92:911–918.



Million Women Study: Risk of endometrial cancer

Beral v, et at. Lancet 2005;365:1543–51

IJC
International Journal of Cancer

Tibolone and risk of gynecological hormone sensitive cancer

Ellen Christine Leth Løkkegaard [1] and Lina Steinrud Mørch [2,3]

[1] Department of Obstetrics and Gynecology, North Zealand Hospital, Copenhagen University Hospital, Hillerød, Denmark
[2] The Juliane Marie Centre, Gynecological Clinic, Copenhagen University Hospital, Copenhagen, Denmark
[3] Unit of Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen DK-2100, Denmark

	Person years	Cases	All endometrial cancers	Cases	Type I endometrial cancer
Tibolone use			IRR (95% CI)		IRR (95% CI)
Never any HT	6,174,059	3,411	1.00	2,685	1.00
Previous systemic HT	1,029,019	881	1.38 (1.28–1.49)	698	1.55 (1.42–1.69)
Current other HT	1,071,488	1,064	2.10 (1.96–2.25)	905	2.23 (2.07–2.40)
Current tibolone	49,850	107	3.56 (2.94–4.32)	91	3.80 (3.08–4.69)
Duration of tibolone					
Current users					
<2 years	8,383	12	3.00 (1.70–5.31)	8	2.45 (1.22–4.92)
2–4 years	13,609	24	3.31 (2.21–4.95)	20	3.42 (2.20–5.32)
5–9 years	19,131	46	3.77 (2.81–5.05)	39	4.03 (2.93–5.54)
10+ years	8,725	25	3.80 (2.56–5.64)	24	4.70 (3.13–7.04)

cohort study of >900,000 women followed for 8.9 years in average

Int. J. Cancer: 142, 2435–2440 (2018)

IJC
International Journal of Cancer

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[2] The Juliane Marie Centre, Gynecological Clinic, Copenhagen University Hospital, Copenhagen, Denmark
[3] Unit of Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen DK-2100, Denmark

	Person years	Cases	All epithelial ovarian tumors	Cases	Serous ovarian tumors
Tibolone use			IRR (95% CI)		IRR (95% CI)
Never any HT	6,598,898	2,860	1.00	1,324	1.00
Previous systemic HT	250,883	559	1.17 (1.07–1.28)	72	1.24 (1.09–1.41)
Current other HT	1,241,824	532	1.39 (1.28–1.51)	368	1.64 (1.46–1.84)
Current tibolone	46,590	31	1.42 (1.01–2.00)	24	2.21 (1.48–3.32)
Duration of tibolone					
Current users					
<2 years	8,485	5	1.40 (0.58–3.37)	2	1.49 (0.37–5.97)
2–4 years	12,973	9	1.55 (0.80–2.98)	8	3.08 (1.53–6.18)
5–9 years	18,021	9	1.08 (0.56–2.08)	8	2.04 (1.01–4.09)
10+ years	7,111	8	2.28 (1.13–4.57)	6	3.15 (1.40–7.03)

not able to adjust for body mass index, physical activity, smoking or oral contraceptive use

Int. J. Cancer: 142, 2435–2440 (2018)

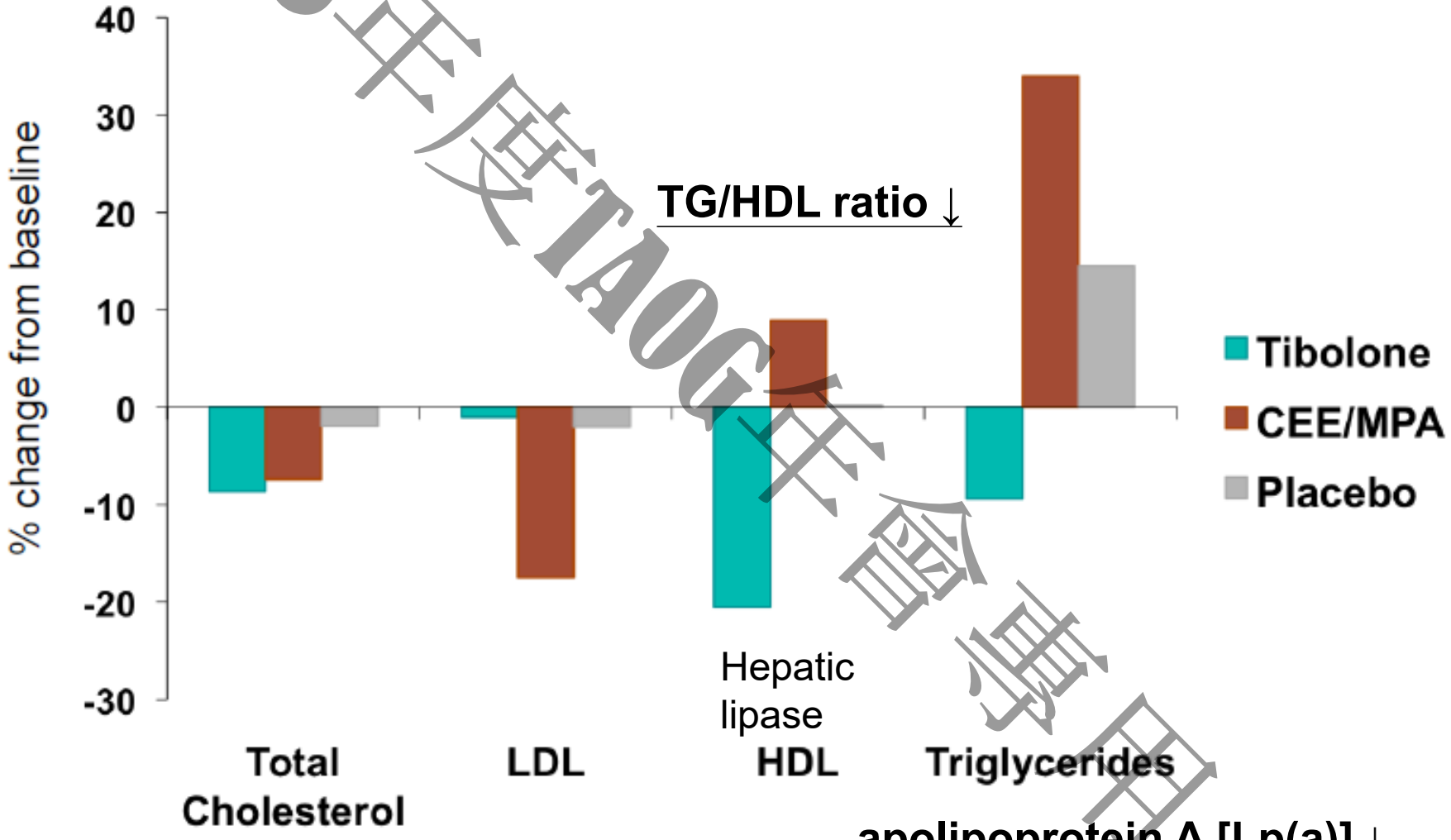
Cancer Risk

- Not recommend treatment with tibolone in patients who have a personal or first-grade relative history of a hormone-sensitive neoplasm

CARDIOVASCULAR HEALTH

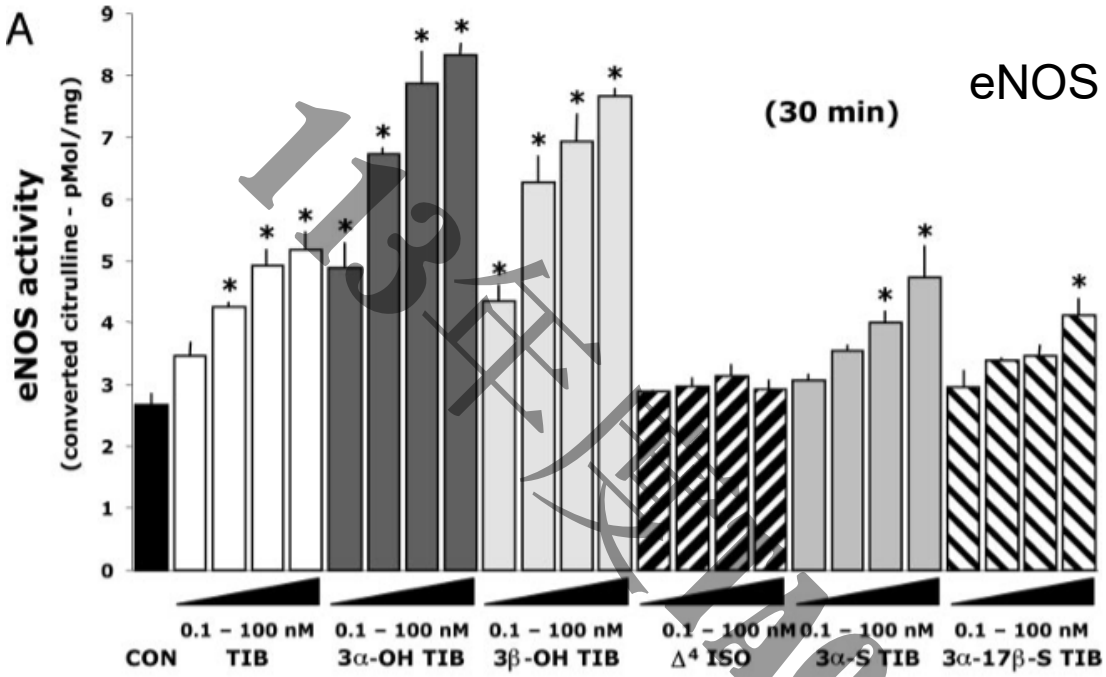
OPAL: change in CVD risk factors – lipids

The Osteoporosis Prevention and Arterial effects of tibolone (OPAL) study



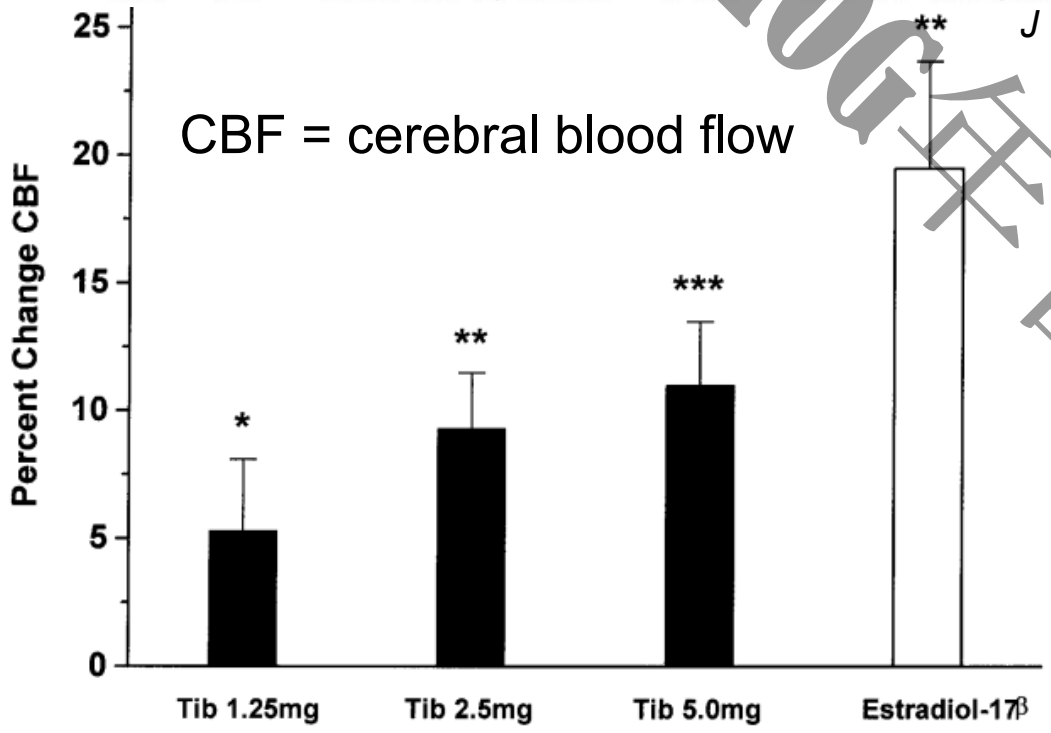
Bots ML, *et al. Eur Heart J* 2006;27:746–755.

Maturitas 99, 27–36



eNOS = Endothelial NO synthase↑

J Clin Endocrinol Metab,2004,89(9):4594–4600



CBF = cerebral blood flow

Am. J. Obstet. Gynecol. 184, 544–551

	Postmenopausal women			
	Before tibolone treatment	After tibolone treatment	Relative change %	Premenopausal women
Systolic arterial pressure (mmHg)	125 ± 12	118 ± 10*	−6	108 ± 12*
Diastolic arterial pressure (mmHg)	75 ± 9	70 ± 7*	−7	70 ± 13*
Mean arterial pressure (mmHg)	91 ± 10	86 ± 7* ✓	−5	83 ± 13*

NO release
Decreased plasma endothelin
Certain antagonistic activity on mineralocorticoid receptors (MRs)

	Postmenopausal women			
	Before tibolone treatment	After tibolone treatment	Average change %	Premenopausal women
Glucose (mg/dl)	93 ± 10	87 ± 13* ✓	−6	86 ± 13
Tot CH (mg/dl)	201 ± 41	187 ± 34	−7	191 ± 26
HDL (mg/dl)	63 ± 13	52 ± 10* ✗	−17	56 ± 9
TG (mg/dl)	75 ± 40	69 ± 39	−8	64 ± 27
LDL (mg/dl)	121 ± 31	118 ± 30	−2	121 ± 23
CRP (mg/dl)	0.09 ± 0.08	0.1 ± 0.09	11	0.1 ± 0.18
IL-6 (pg/ml)	0.24 ± 0.2	0.4 ± 0.5	60	0.12 ± 0.15*
TNFα (pg/ml)	4.1 ± 0.2	2.5 ± 1.7* ✓	−39	0.6 ± 1.0**
ROMs (AU)	269 ± 79	299 ± 86	11	283 ± 45
OXY (μmol. HClO/ml)	296 ± 62	311 ± 59 —	5	378 ± 69**

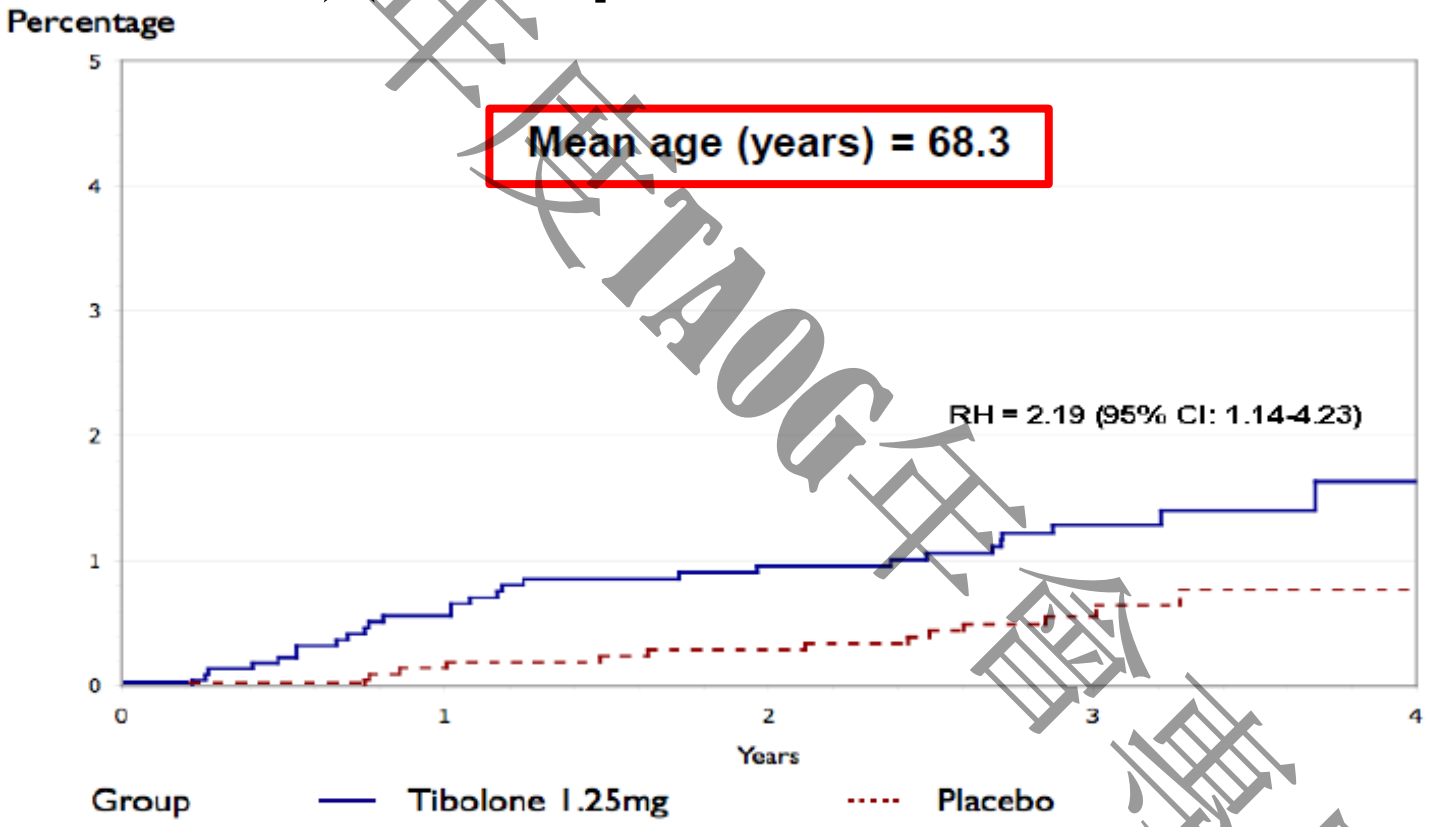
*$p < 0.05$; **$p < 0.01$ *versus* postmenopausal women baseline
Tot CH, total cholesterol; HDL, high density lipoproteins; TG, triglycerides; LDL, low-density lipoproteins; CRP, C-reactive protein, IL-6, Interleukin-6; TNFα, tumor necrosis factor; ROMs, Hydroperoxides; OXY, total antioxidant capacity, values are expressed as mean ± SD

Gynecological Endocrinology, March 2011; 27(3): 163–169

LIFT:

Cumulative Percentages of Patients with Stroke

☆Therapeutic window



Cummings SR, *et al. N Engl J Med* 2008;359:697–708.

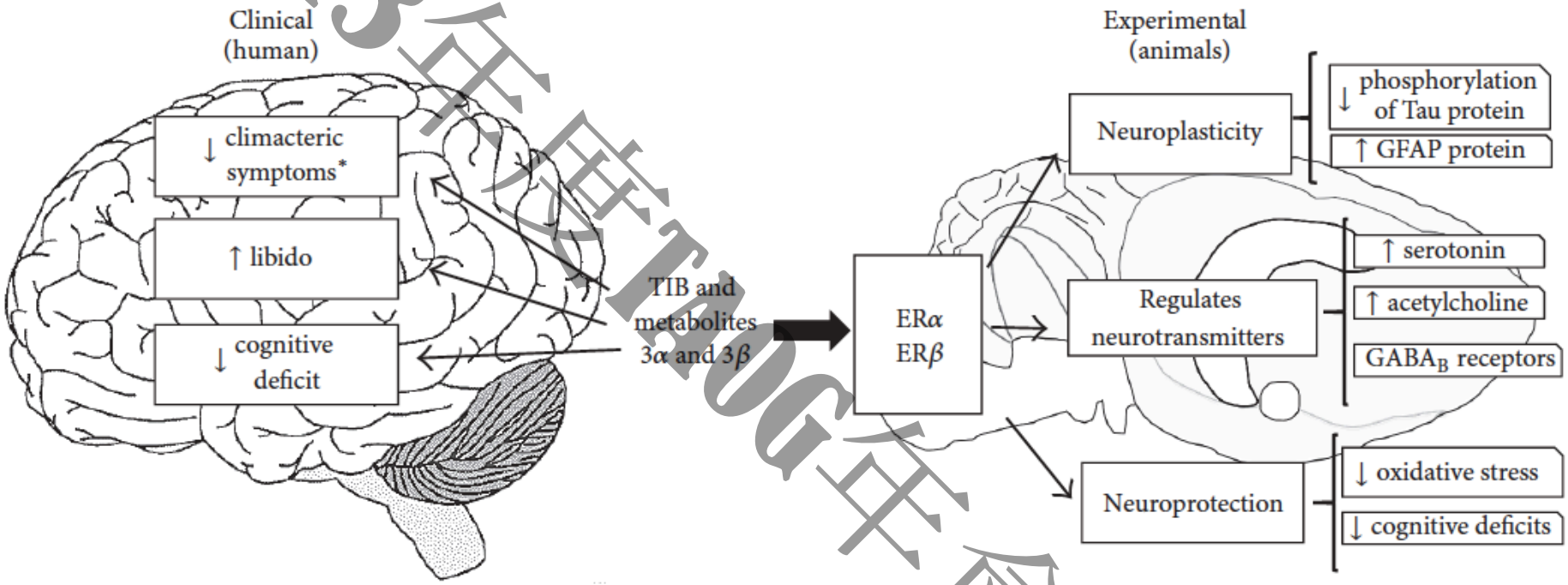
Venous thromboembolism & Coronary heart disease: no difference with placebo

CV & Coagulation Factors

- Recently menopaused women—
  no increased CV or augmented stroke risk
- Should not be used
  - Outside therapeutic window
  - High risk of cerebrovascular disease (hypertension, diabetes, atrial fibrillation, smoking habit)

CENTRAL NERVOUS SYSTEM

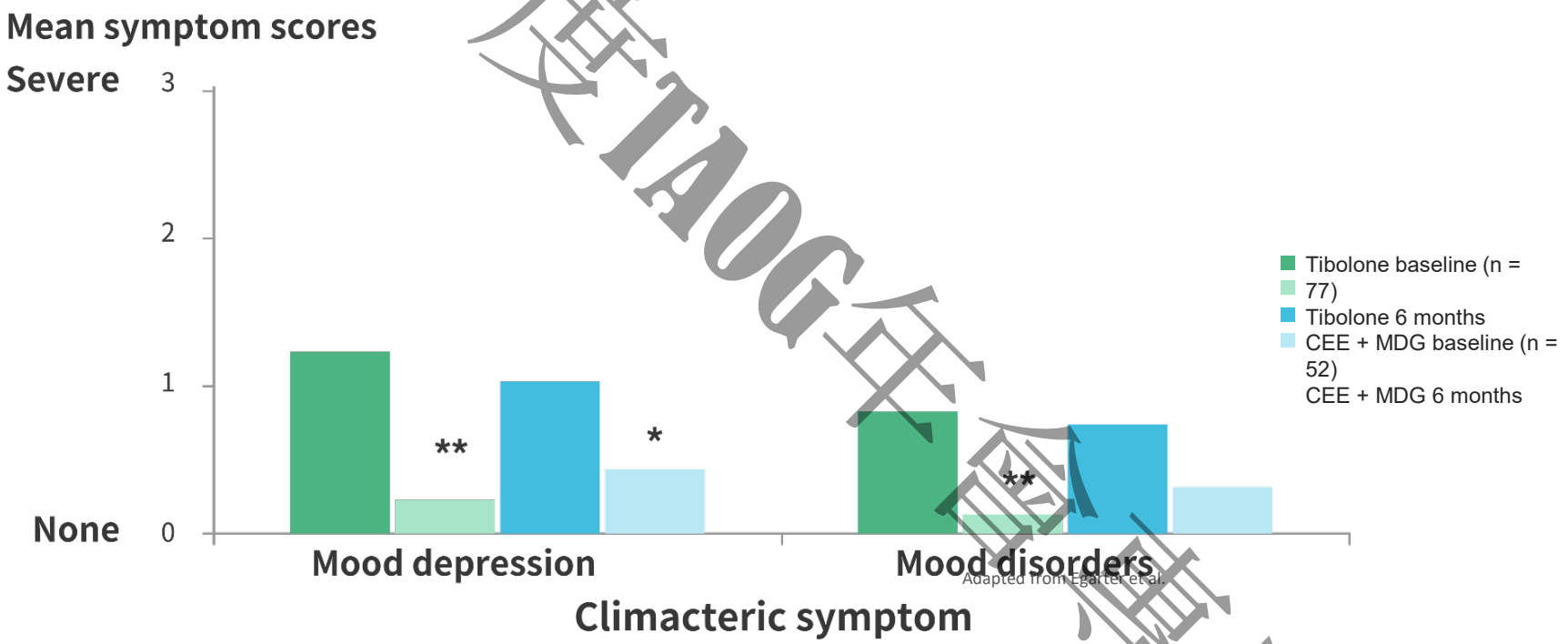
Central Nervous System



1. More lipophilic, nonsulfated metabolites across blood-brain barrier
2. Organic anion transporter proteins in brain tissue

Biomed Res Int. 2017
Drug Metab. Dispos. 35, 1105–1111

Effect on mood



CEE + MDG, conjugated equine estrogens (0.625 mg/day) + medrogestone (10 mg/day for 12 days/month): *p < 0.01 vs baseline
Tibolone (2.5 mg/day): **p < 0.001 vs. baseline

Egarter et al., *Maturitas* 1996

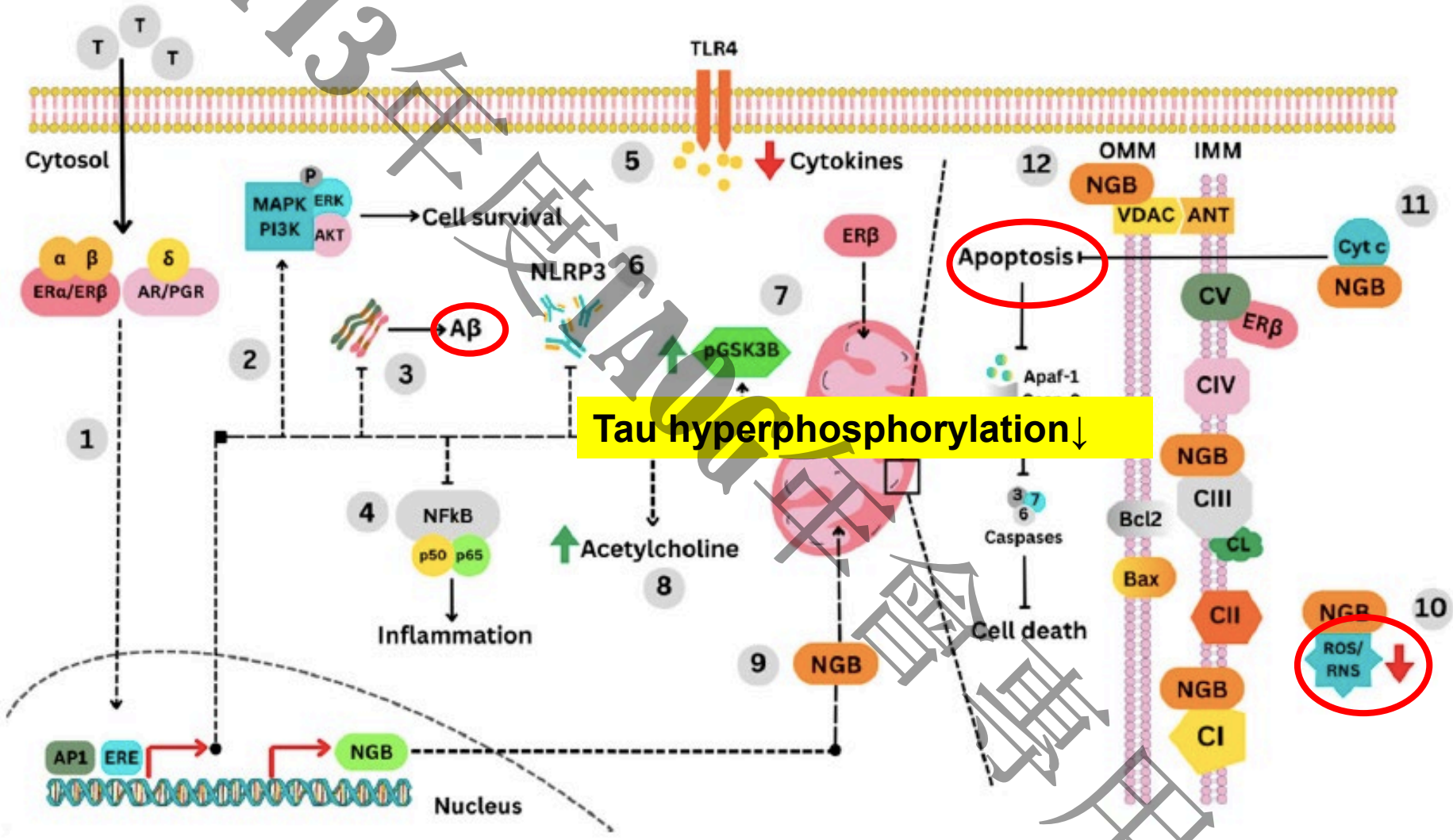
Mood

- Tibolone 2.5mg/day has positive impact on mood compared with placebo

Reproduccion 6, 81–91
Maturitas 9, 303–308

- Jayashri Kulkarni:
  RCT (12 weeks): perimenopausal depressive women with tibolone 2.5mg/day vs. placebo
  → tibolone improved depression severity

J Affect Disord 2018;15:236:88-92.



Biomolecules 2023, 13, 1115

OTHERS

Maybe safer in women with residual endometriosis

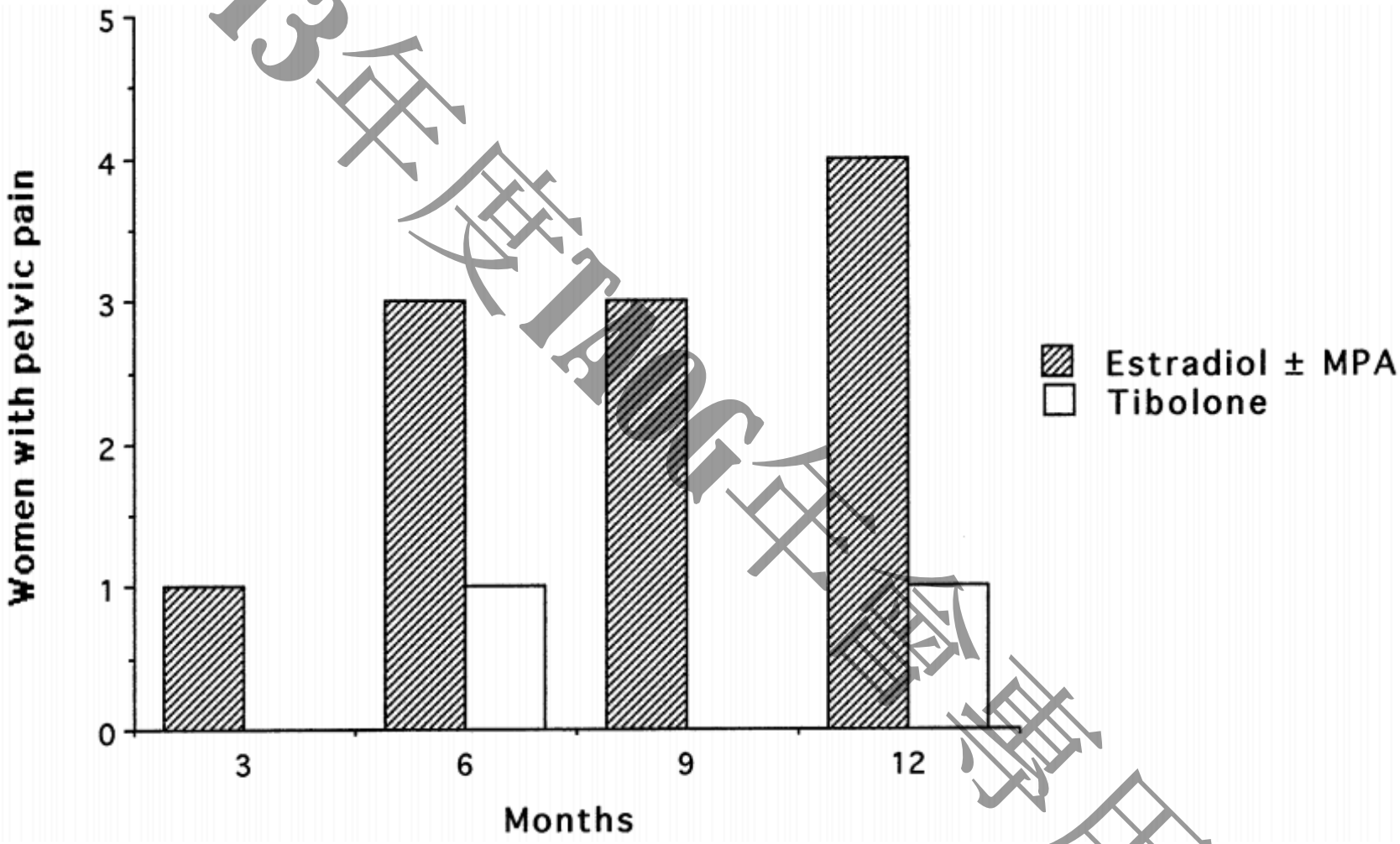


Fig. 1. Moderate pelvic pain in the two groups before and at different times during treatment.

Maturitas 1999;32:189–193

HRT & MYOMAS

TIBOLONE
5 studies – 237 women

- ✓ Conflicting results
- ✓ No significant effect on myomas growth compared to placebo or estrogen-progestin therapy [28, 30]
- ✓ Significant difference in terms of fibroids growth was found in one study [29]

ESTROGENS/PROGESTINS
13 studies – 914 women

- ✓ Conflicting results
- ✓ Significant influence on fibroids enlargement and newly detected myomas in menopause [14, 35, 39, 40]
- ✓ No significant increase in fibroids size, although a trend towards enlargement was noted [18, 33, 34, 37, 38]

SERMs
2 studies – 102 women

- ✓ Impact on uterine fibroids is still largely unknown
- ✓ Significant reduction in myomas size [31, 32]

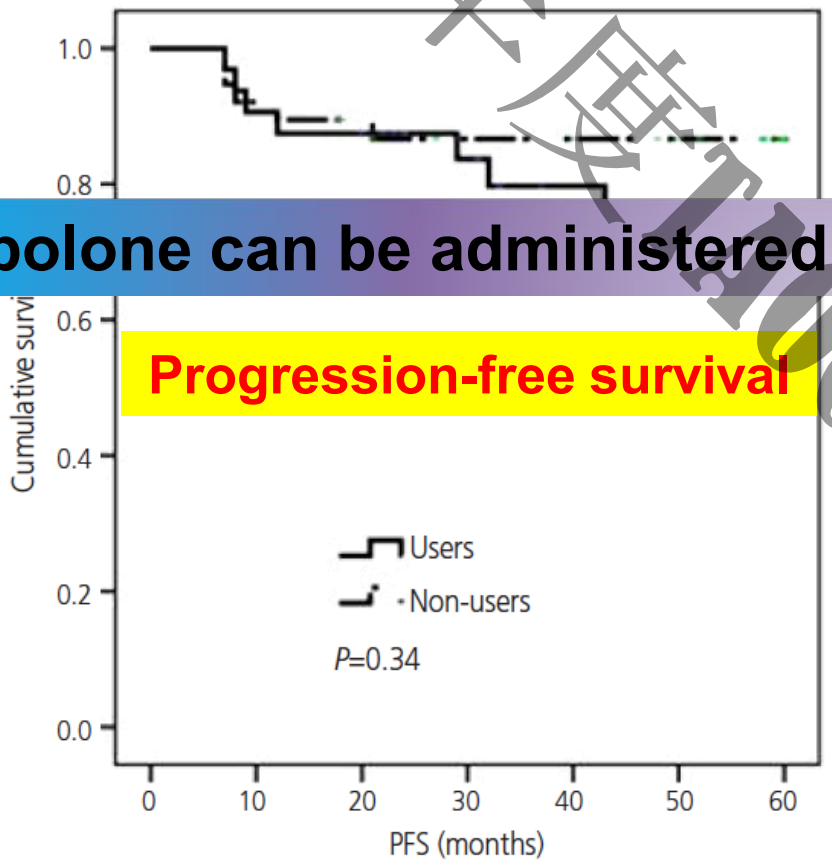
Tibolone不會促進肌瘤生長，影響也較E+P小

Medicina (Kaunas). 2019 Aug 30;55(9):549.

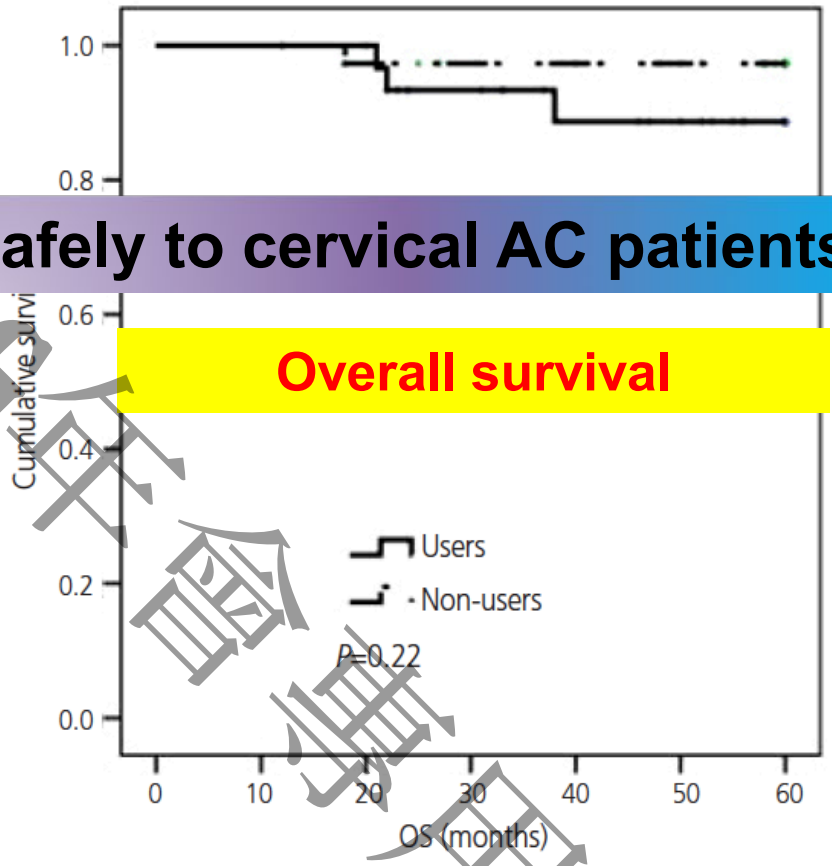
Early Stage Cervical Adenocarcinoma

tibolone can be administered safely to cervical AC patients

Progression-free survival

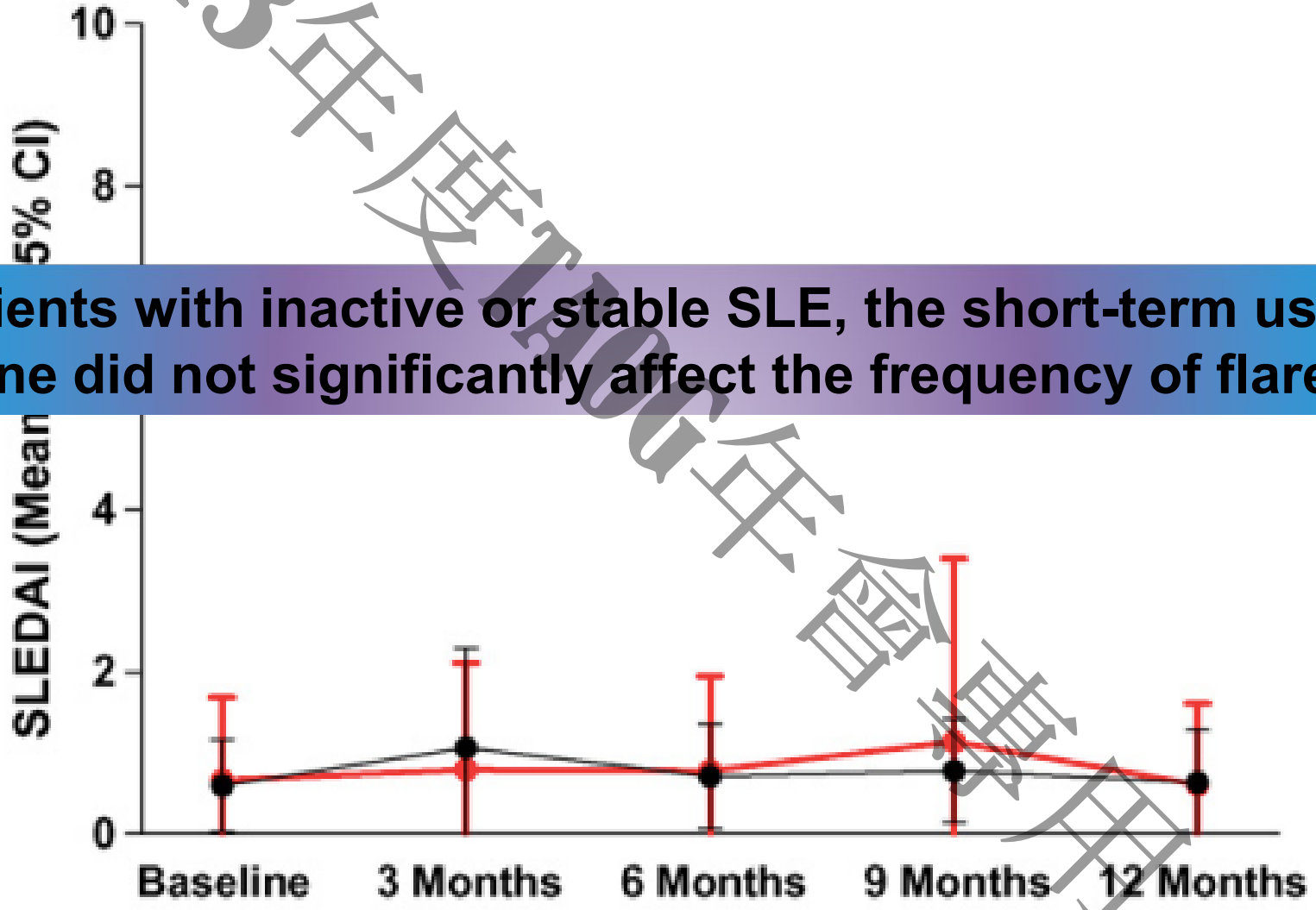


Overall survival



Obstet Gynecol Sci 2018;61(5):584-589

Systemic Lupus Erythematosus



In patients with inactive or stable SLE, the short-term use of tibolone did not significantly affect the frequency of flares

Maturitas 62 (2009) 311–316

TAKE HOME MESSAGE

CLIMACTERIC 2010;13:317–327

Updated clinical recommendations for the use of tibolone in Asian women

K-E. Huang and R. Baber, on behalf of the Asia Pacific Tibolone Consensus Group*

Center for Menopause and Reproductive Medicine Research and Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital–Kaohsiung Medical Center, Kaohsiung, Taiwan; *Sydney Medical School, The University of Sydney, Royal North Shore Hospital and North Shore Private Hospital, St. Leonards, Australia

Table 1 Consensus statements on the use of tibolone and levels of supporting evidence

Updated statements and/or new evidence published since 2005	*Level of evidence**
Tibolone is as effective as currently used EPT/ET regimens in the management of climacteric symptoms[34]	1b
Tibolone treats vaginal atrophy and alleviates local vaginal symptoms[34]	1b
Tibolone has a positive effect on sexual well-being and is more effective than oral EPT/ET in some respects, namely arousal, desire, and satisfaction[8,34]	1b
Tibolone positively affects mood and quality of life[8,34]	1b
Tibolone prevents bone loss and is as effective as standard doses of EPT/ET and more effective than raloxifene[36]	1b
Tibolone reduces the risk of vertebral and non-vertebral fracture in older osteoporotic women. The absolute reduction was greater among women who had already had a vertebral fracture than among those who had not[16]	1b

Table 1 Consensus statements on the use of tibolone and levels of supporting evidence

Updated statements and/or new evidence published since 2005	*Level of evidence**
Tibolone does not stimulate the endometrium or induce endometrial hyperplasia or carcinoma in postmenopausal women in randomized controlled clinical trials and has a low incidence of bleeding[34,35,61]	1b
In observational studies, an increased relative risk of endometrial cancer has been shown[56,57]	3b
Tibolone causes less breast tenderness and less mastalgia than EPT[34]	1b
Tibolone does not increase mammographic density	2b
Tibolone, taken by women with a personal history of breast cancer, is associated with an increased risk of recurrence[18]	1b
The evidence of tibolone use and increased risk of breast cancer from observational studies remains inconclusive[41]	3b
Tibolone 1.25 mg does not increase breast cancer risk in older osteoporotic women with no history of breast cancer[16]	1b
There are still no hard endpoint data on the effect of tibolone on cardiovascular health[38]	1b
Tibolone has different effects on lipids compared with EPT/ET[38]	1b
Tibolone increases CIMT in a manner similar to EPT[38]	1b
In one randomized, controlled trial, use of tibolone 1.25 mg in older women was associated with an increased risk of stroke[16]. Hence, tibolone should be used with caution in elderly women (i.e. over 60 years) and should not be used in those who have strong risk factors for stroke	1b
Tibolone did not increase the risk of stroke, VTE or myocardial infarction in observational studies[37,40]	2b

CIMT: carotid intima-media thickness

Climacteric. 2010 Aug;13(4):317-27.

Thanks for Your Listening