TSEC의 유용성 및 안전성: 증례 위주 접근

전성욱

의학박사/ 전문의

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Background

Tissue Selective Estrogen Complex

In postmenopausal women with intact uterus…

- Estrogen/ Progestogen therapy: *breast cancer risk* 
- Estrogen only therapy: *Endometrial cancer risk* 
- SERM: CANNOT relieve *menopausal symptom*, esp. Hot flush

IF CAN Estrogen + SERM BE USED…?

- RISK OF BREAST CANCER → ANSWER (?)
- MENOPAUSAL SYMPTOMS INCLUDING HOT FLUSH → ANSWER (?)
- RISK OF ENDOMETRIAL CANCER → ANSWER (?)

TSEC
Tissue Selective Estrogen Complex

- Pairing of **a SERM with 1 or more Estrogens**

  Estrogen + SERM(s) (instead of EPT Estrogen + Progestogen)

- Effect of TSEC
  - **Bone preservation**
  - **Relieve menopausal symptoms including hot flushes**
  - **Without stimulating EM and breast** → ***New progestin-free MP therapy***
- First TSEC
  - Bazedoxifene/conjugated estrogens
  - Duavee® (BZA 20 mg/CE 0.45 mg): **USA FDA approved (Oct 3, 2013)**
  - Duavive®: approved in **Korea (Jul 25, 2014)** & **Europe (Oct 23, 2014)**

TODAY's Issue Is…?

TSEC의 유용성 및 안정성: 증례위주 접근

증례 I

Case (I)
Concerns over breast cancer

증례

- 54세 산과력 1-0-5-1; 마지막 생리 6개월 전
- 근육통, 관절통으로 정형외과 진료 받고 부인과 진료 권유 받음
- 열성 홍조 (+: 하루 3-4회, 2-3 min/episode), 야간 발한 (+)
- 1년 전 **Breast USG> Category 4 A in both breast**

→ **Breast biopsy> both breast fibrocystic disease**

GY-USG: Multiple myoma ut (biggest 3.2 x 2.0 cm on anterofundal), other n.s

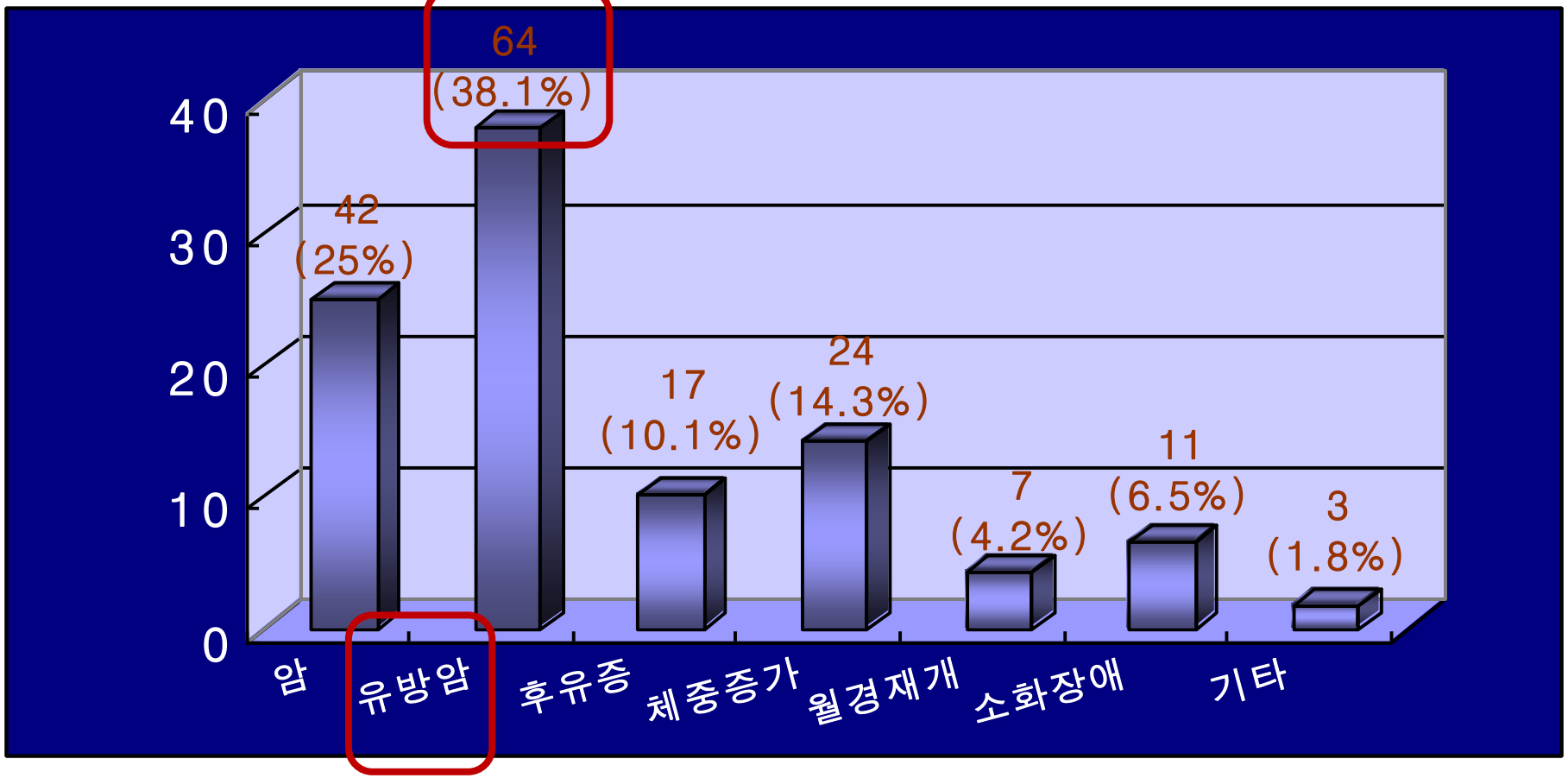
Pap smear: negative, atrophy

FSH/E2 79.1/ < 5.0, TSH/FT4 1.16/ 1.20, 25OH VIT D 19.5, CTX 0.481

DXA> L_{1-4} -0.4, FN -0.2: WNL, OT/PT 23/24, LIPID 173-165-63-89, GLC 113

폐경 호르몬 치료

환자들은 무엇을 가장 두려워하는가?



폐경역학연구회, 2008

Menopausal treatment
Women with intact uterus

Hysterectomized Postmenopausal women

ET

Progestogen

✕

Non-Hysterectomized Postmenopausal Women

EPT

Progestogen

○

Tibolone

Progestogen

△†

TSEC

Progestogen

✕

ET (Estrogen-only Therapy)

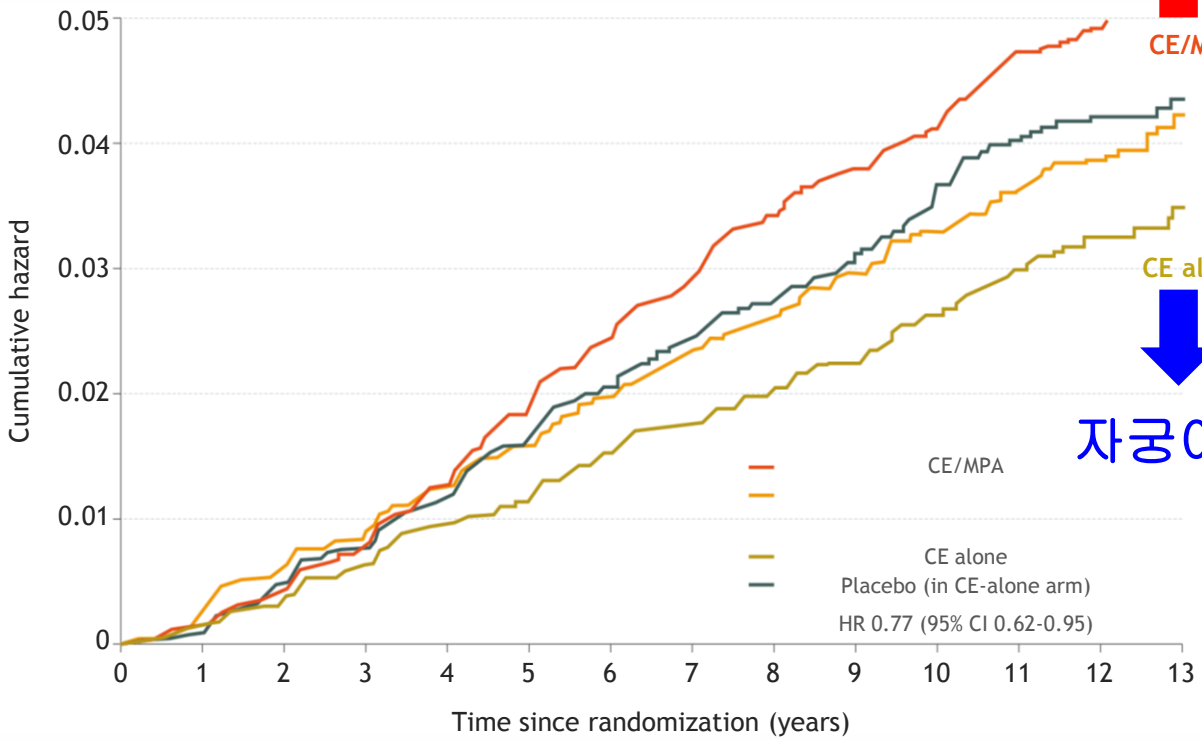
EPT (Estrogen-Progestogen Therapy)

STEAR (Selective Tissue Estrogen Activity Regulator)

TESC (Tissue Selective Estrogen Complex)

유방암 위험도
ET Vs EPT: WHI 연구

자궁이 있는 여성에서 **EPT** 사용



HR 1.25 (95% CI 1.07-1.46)

CE/MPA

CE alone

HR 0.77 (95% CI 0.62-0.95)

자궁이 없는 여성에서 **ET** 사용

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

대한폐경학회 2014

ET는 오히려 7.2년 사용 후 유방암의 위험도가 감소하였으며 13.2년간의 추적 관찰 후 유의하게 유방암의 위험도가 감소하였다.

유방암 위험도
EPT 치료 환자에서 증가... Why...?

As occult breast tumours are common and only become clinically detectable after ≥10 years, this slow doubling time is shortened by a promotional effect of oestrogen and/or oestrogen plus progestogen 'feeding' these usually ER+ tumours ➔ This promotional effect is probably greater with oestrogen plus progestogen than with oestrogen alone, particularly with certain progestogens

Lobo RA, et al. Nat Rev Endocrinol 2017;13(4):220-231.

세계폐경학회 2016

- **The increased risk is primarily associated with the addition of a synthetic progestogen to estrogen therapy and to duration of use**
- It is the **Progestogen component of MHT** that is **more significant in any increase in breast cancer risk** rather than the **Estrogen**

X 때문이야

프로게스토겐

TSEC
유방암 위험도

- ET **Estrogen** **Risk ↓**
- EPT **Estrogen** **Progestogen** **Risk ↑**

- TSEC **Estrogen** **SERM(s)** **Progestogen-free**

이론적으로 **TSEC**은 유방암에 대하여 안전하다고 사료됨. 단, 향후 장기 연구결과는 필요함 !!!

Case (I)
Symptom improvement… how long…?

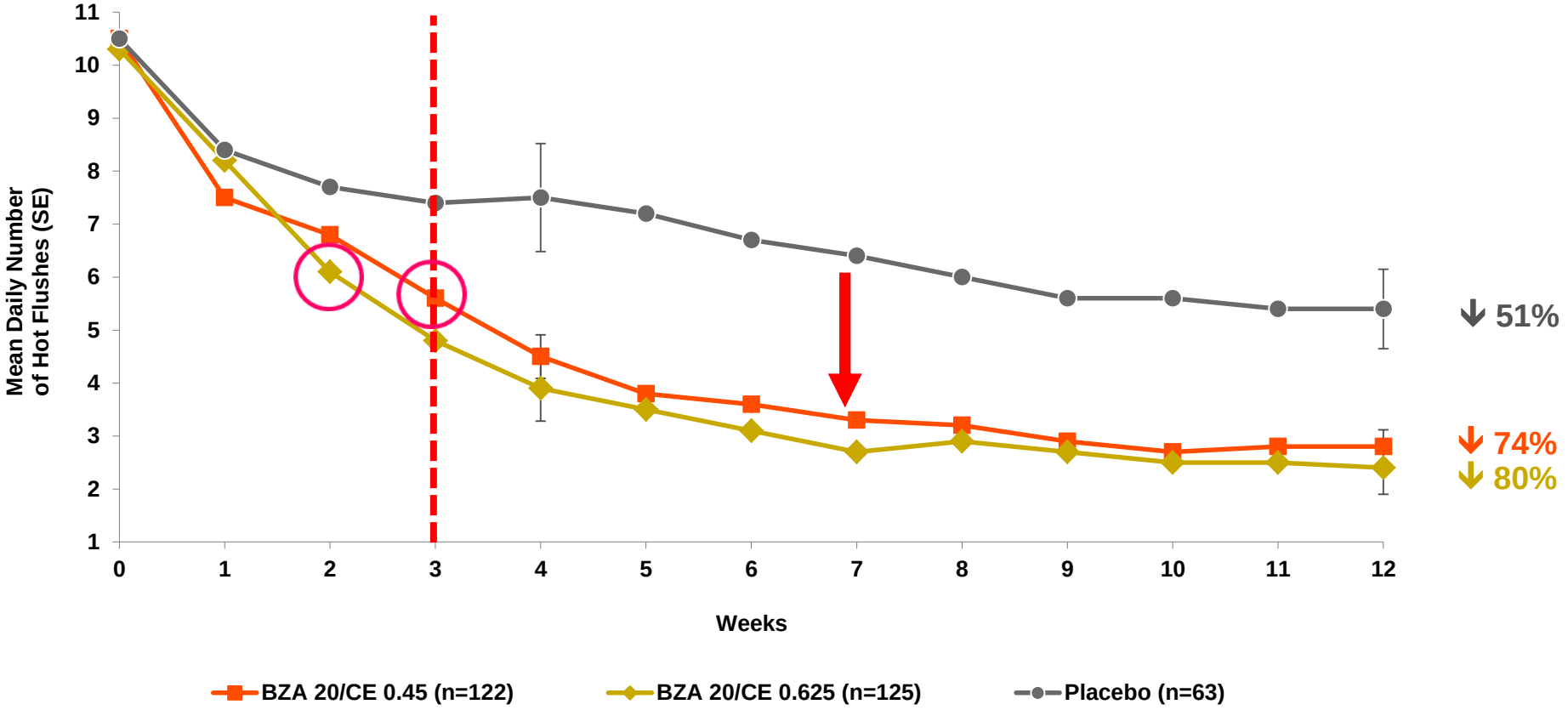
증례

- **Continued…**
- **Duavive®** start
- **2** 주 후 외래 방문: 열성 홍조 증세가 좋아지지 않으며 다른 제제로 전환 원함

How should we respond to this situation … ?

Hot Flush: Frequency
SMART-2

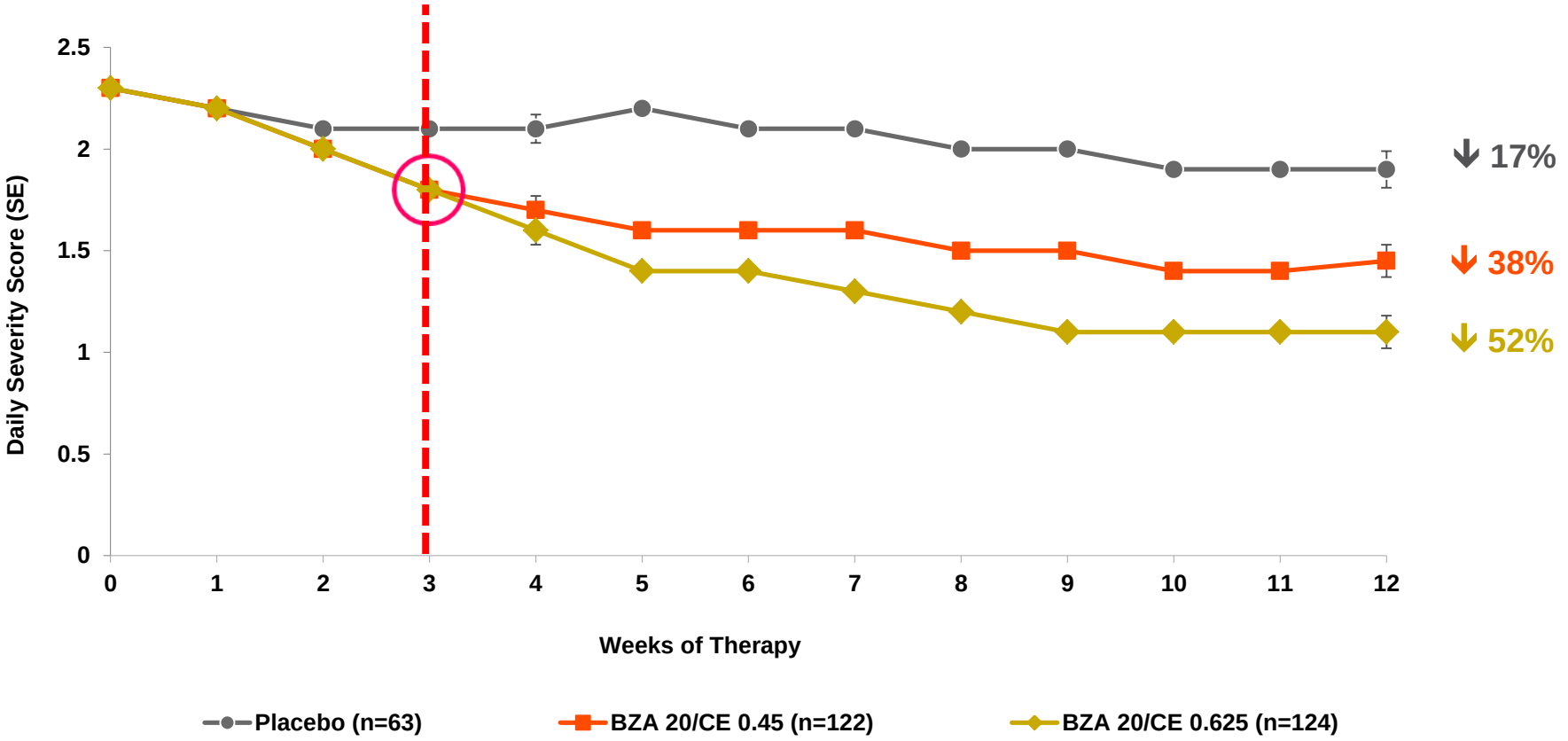
Starting at week 2 to 3, BZA/CE significantly reduced the number of hot flushes compared with placebo



Pinkerton JV, et al. Menopause 2009;16(6):1116-1124.

Hot Flush: Severity
SMART-2

Starting at week 3, BZA/CE significantly reduced the severity of hot flushes compared with placebo



Pinkerton JV, et al. Menopause 2009;16(6):1116-1124.

Case (I)

Symptom improvement… how long…?

How should we respond to this situation … ?

Continue F/U with reassurance

증례 II

Case (II)
Dense breast/ Concerns over breast cancer

증례

- 53세 산과력 2-0-2-2; 마지막 생리 1년 전
- 8개월 전부터 심한 열성 홍조 증세로 continuous EPT 시작
- 6개월전 시행한 **MMG> dense breast, microcalcification in Right breast**

→ Additional Breast USG> Category 4A in right 6' & 8' directions. --Rec.) tissue Bx

→ Breast biopsy> Right breast fibrocystic change with mild ductal hyperplasia. Fibrocystic change with columnar cell change

- 환자 자의로 호르몬 치료 중단
- 중단 1개월 후부터 다시 열성 홍조 증세 재발 및 심화되어 외래 방문

Breast cancer screening
MMG: Interval & Starting age

Annual — NCCN 2016 ⟷ **Biennial** — USPSTF 2016

40 YO — NCCN 2016 ⟷ **50 YO** — USPSTF 2016

Risk Reduction ⟷ Screening Harms

NAMS Recommendations 2014

- Current Guidelines generally include **mammograms every 1 to 2 years**, **starting at age 40 to 50 years** and continuing **until age 70**

Dense Breast
Effect on MMG Screening

Participants	Overall sensitivity	References
Women with Average risk	**About 75%**	(Barton, JAMA 1999) (Nemec, Cleve Clin J Med 2007)
Women with heterogenous dense tissue	**50%**	(Berg WA, Ann Intern Med 2003)
Women with suspected or known BRCA mutation (more likely to be younger & to have dense breasts)	**33%**	(Kuhl, J Clin Oncol 2005)

2016 NCCN Clinical Practice Guidelines

- **Dense breasts** are associated with an **increased risk for breast cancer**
- **Dense breasts limit the sensitivity of MMG**

Dense Breast
After HRT

- Reading showing an increase in BI-RADS density grade at 12 MO

Variables	Baseline to 12 Mo Readings (95% CI)
Placebo group	**0.0** (0.0 – 4.6)
CEE only	**3.5** (1.0 – 12.0)
CEE + cyclic MPA	**23.5** (11.9 – 35.1)
CEE + daily MPA	**19.4** (9.9 – 28,91)
CEE + Micronized P	**16.4** (6.6 - 26.2)

- Adjusted ORs for increase in BI-RADS density grade at 12 MO

Regimens (Vs CEE)	OR (95% CI)	P value
CEE + cyclic MPA	**13.1** (2.4 - 73.3)	0.003
CEE + daily MPA	**9.0** (1.6 - 50.1)	0.012
CEE + Micronized P	**7.2** (1.3 - 40.0)	0.024

Greendale GA, et al. Ann Intern Med 1999;130;262-269.

Increased Breast Density
By HRT

NO

Increased Risk of Breast Cancer

IMS recommendations 2013

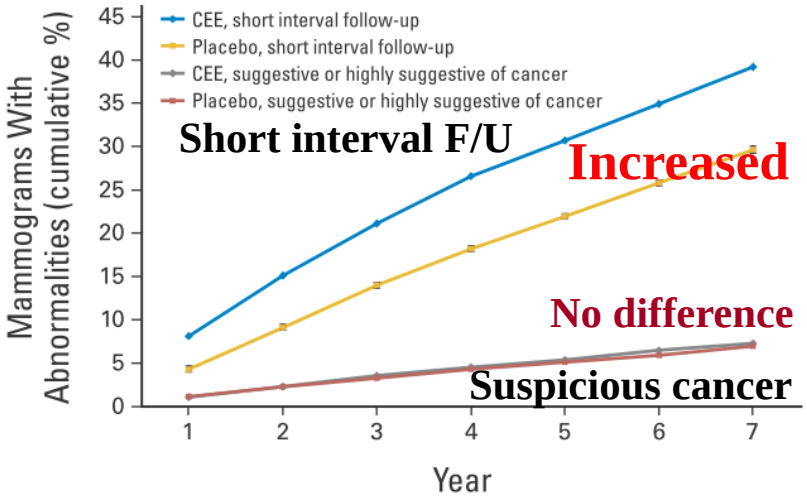
- **Baseline mammographic density *correlates with breast cancer risk***, but this is **independent** of **breast cancer association with MHT**

대한폐경학회 학술위원회 2011

- 호르몬 요법 시 유방 밀도의 증가는 유방암의 위험성과는 관련이 없으나 유방암의 진단을 어렵게 할 수 있기 때문에 주의가 필요하다.

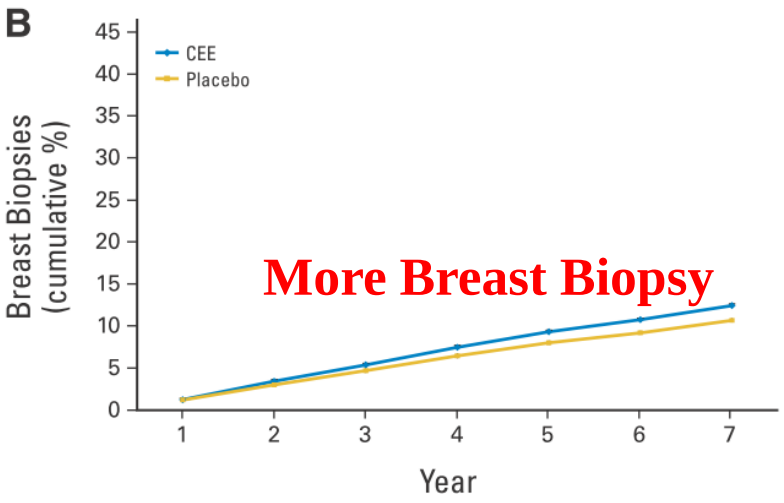
MMG Screening
HRT & Breast Biopsy: WHI-ET

- Abnormal MMG



	ET	Placebo	*P* value
Short-term interval F/U	39.2%	29.6%	<0.001

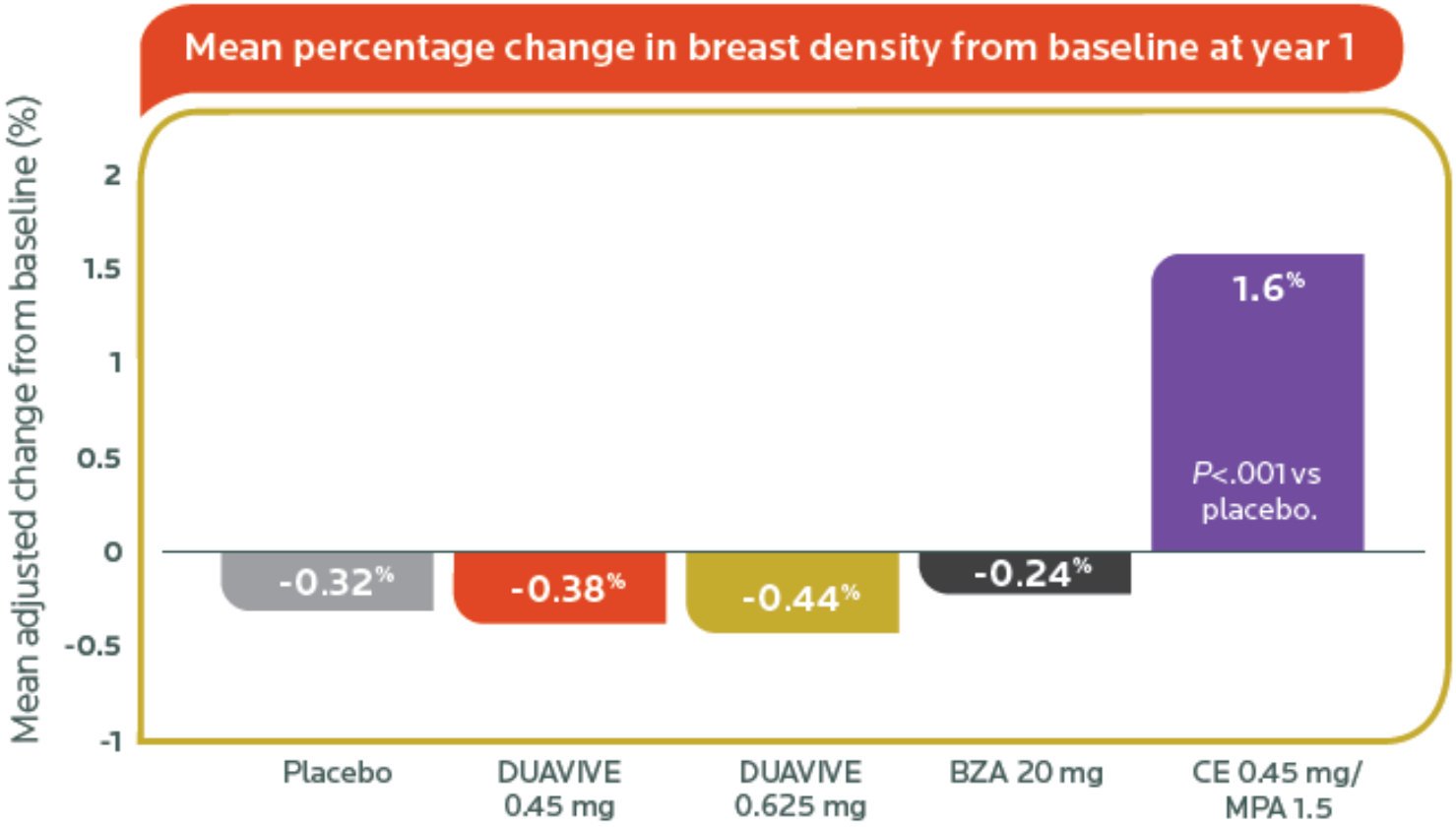
- Breast biopsy



	ET	Placebo	*P* value
Breast biopsies	12.5%	10.7%	0.004
Abnormal results by Bx	8.9%	15.8%	0.04

Chlebowski RT, et al. J Clin Oncol 2010;28:2690-72.

Breast density
TESC: SMART-5



NO significant difference** in breast density **between BZA/CE and placebo

Breast density was significantly increased with CE/MPA compared with placebo

Pinkerton JV, et al. Obstet Gynecol 2013.

Case (II)
Continued…

증례

- **Continued…**
- **Duavive®** start
- 1 달 후 외래 방문 → 증상이 조금 좋아졌지만 아직도 증상이 심한 편이라고 함

→ 기다려 보자고 하고 2개월 추가 처방

- 2개월 후 외래 방문: 증상은 이전보다 많이 좋아졌지만 아직도 가끔씩 열감이 오르면서 불편하다고 함. 이전에 복용하던 EPT 제제의 경우에는 열성 홍조 증상이 없었는데 왜 이런지 궁금해함.

Hot flush
TSEC: Limitations for guidance

Mini-review: practical Guide

Further comparative randomized controlled trials of **CE/BZA vs EPT** are needed to inform treatment selection

Palacios S, et al. Maturitas 2015;80:435-440.

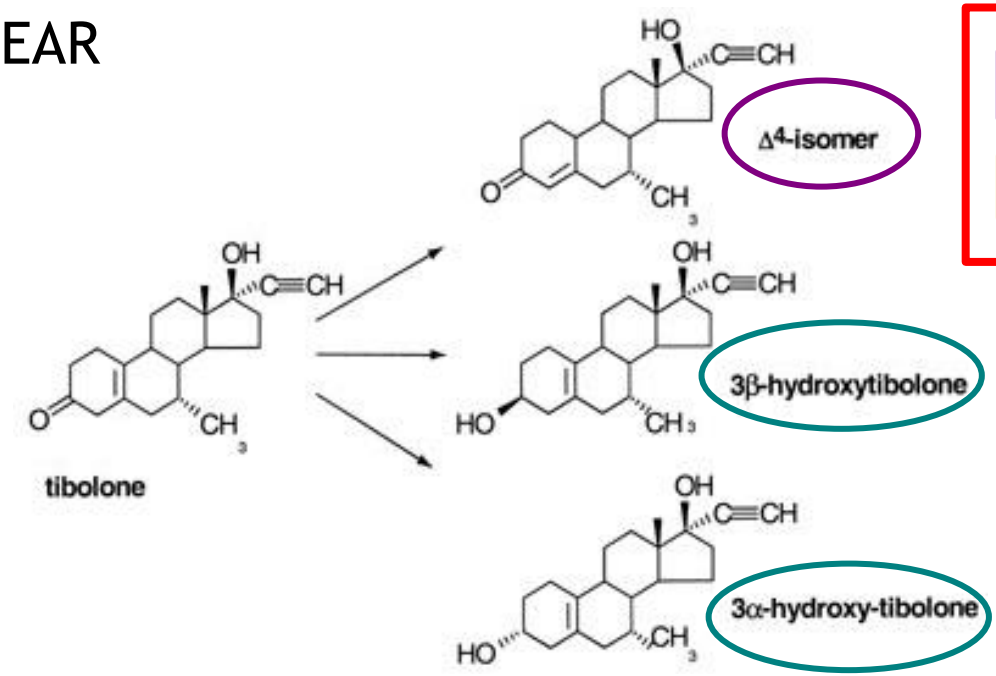
Lack of RCTS comparing the efficacies of **TSEC** on the **issues about menopausal symptoms with…**

Efficacies of EPT … ?

Efficacies of TBL … ?

Tibolone
What is the Tibolone?

- STEAR



Progestogen

Androgen

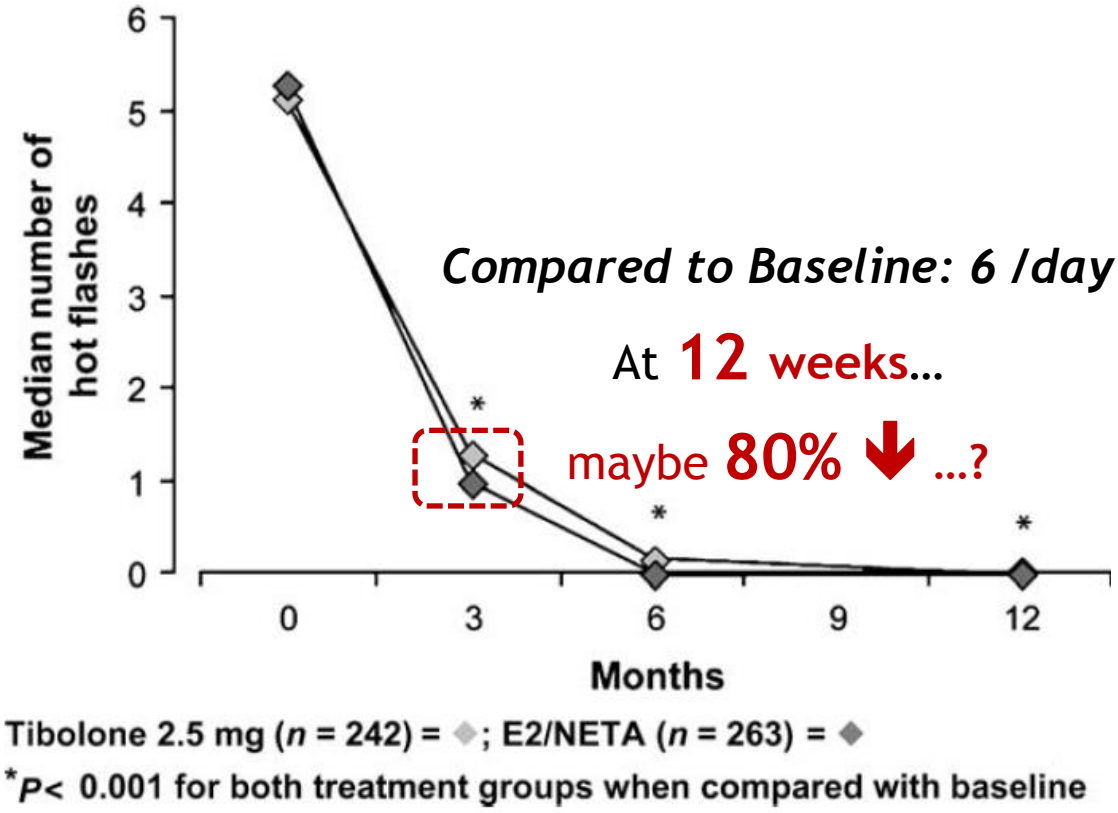
Estrogen

대한폐경학회 2014 폐경호르몬요법 치료 지침

- 티볼론은 자체적으로는 생물학적 활성이 없으나 대사물질이 인체의 조직에 따라 특정한 약리효과를 보이기 때문에 **선택적 조직 에스트로겐 활성 조절제(Selective Tissue Estrogen Activity Regulator, STEAR)**로 분류되고 있다.

Hot flush
Tibolone Vs EPT (low dose): TOTAL

- Double-blinded RCT
- Intervention for 48 weeks
  - ✓ 2.5 mg TBL
  - ✓ 17β E2 1 mg/ NETA 0.5 mg



Tibolone reduces menopausal symptoms to a **similar extent as conventional low-dose continuous EPT**

Hammar ML, et al. BJOG 2007;114:1522–1529.

Hot flush
Tibolone Vs EPT (standard dose)

- Double-blinded RCT for 12 months
- TBL 2.5 mg (n = 250) vs. CEE 0.625 mg/ MPA 5 mg (n = 251)
- Hot flush: **TBL (4.8%)** vs. **CEE/MPA (1.2%)** (*P*< 0.05)

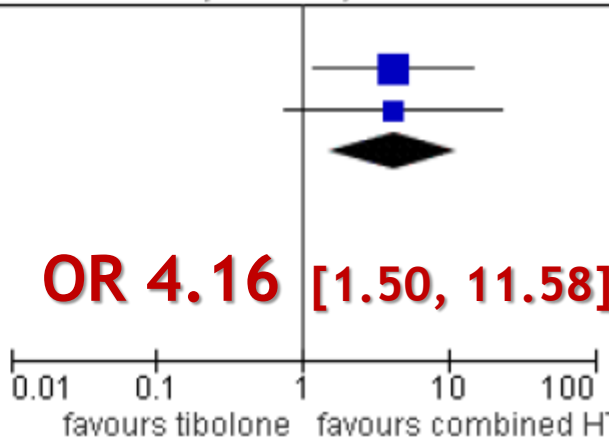
Huber J, et al. BJOG 2002; 109: 886-893.

- Cochrane Review: vasomotor symptoms

	tibolone		combined HT			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
2.1.1 Tibolone, 2.5 mg/day							
Huber 2002	12	250	3	251	64.1%	4.17 [1.16, 14.95]	
Kökçü 2000	7	23	2	21	35.9%	4.16 [0.75, 22.90]	
Subtotal (95% CI)		**273**		**272**	**100.0%**	**4.16 [1.50, 11.58]**	
Total events	19		5				

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%

Test for overall effect: Z = 2.73 (P = 0.006)

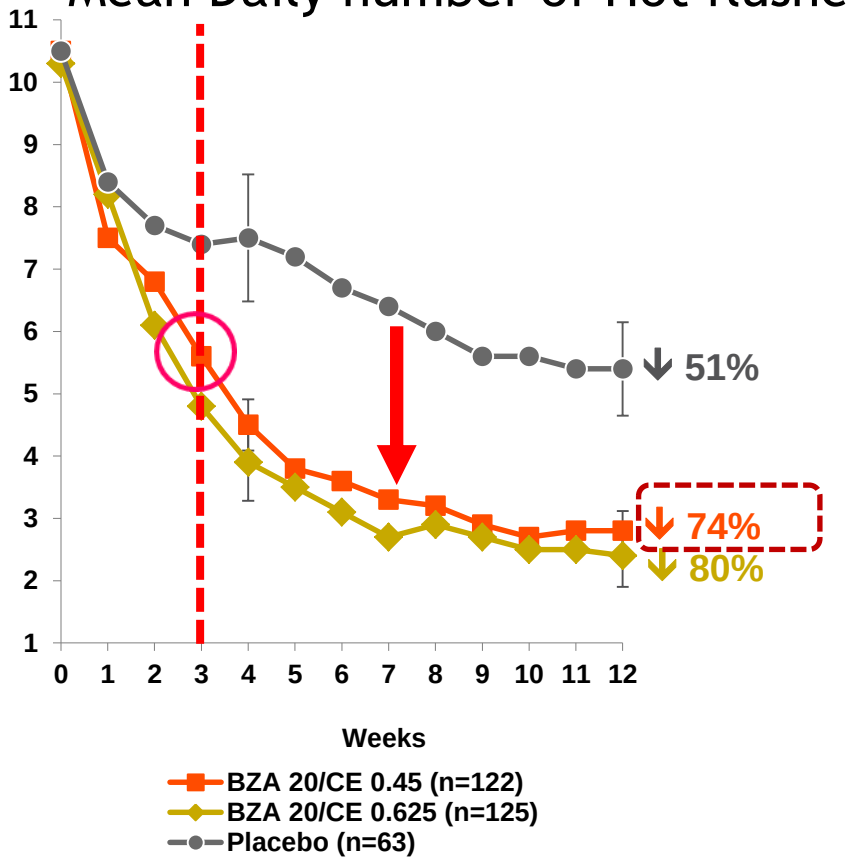


인제대학교 해운대백병원

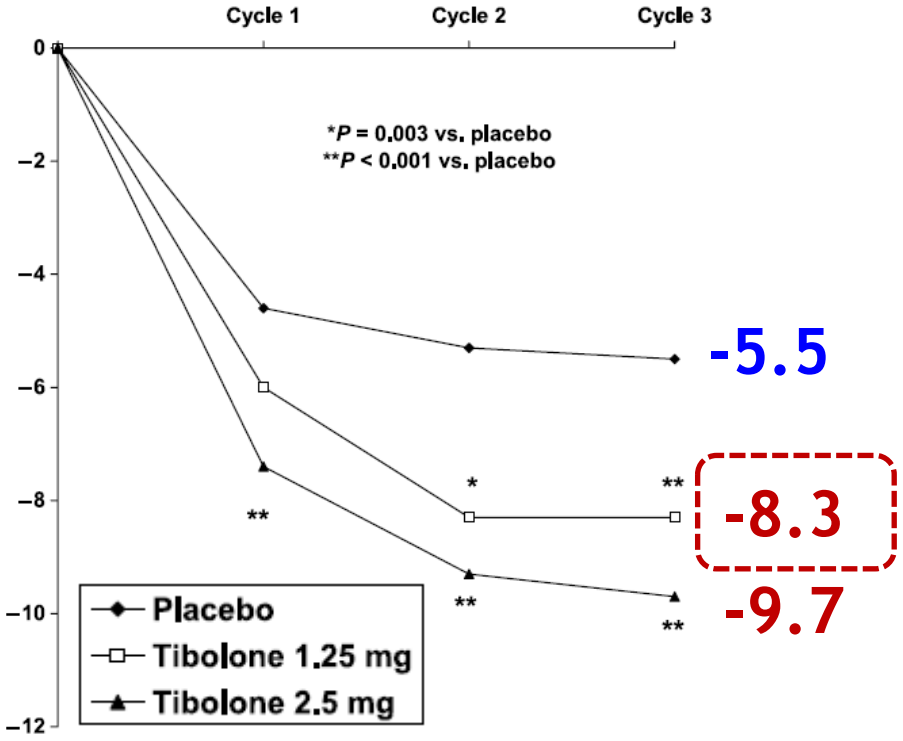
Formoso G, et al. Cochrane Database Syst Rev 2012.

Hot flush frequency
TSEC (SMART-2) Vs Tibolone

Mean Daily number of Hot flushes



Median change from baseline in average number of hot flushes/ day

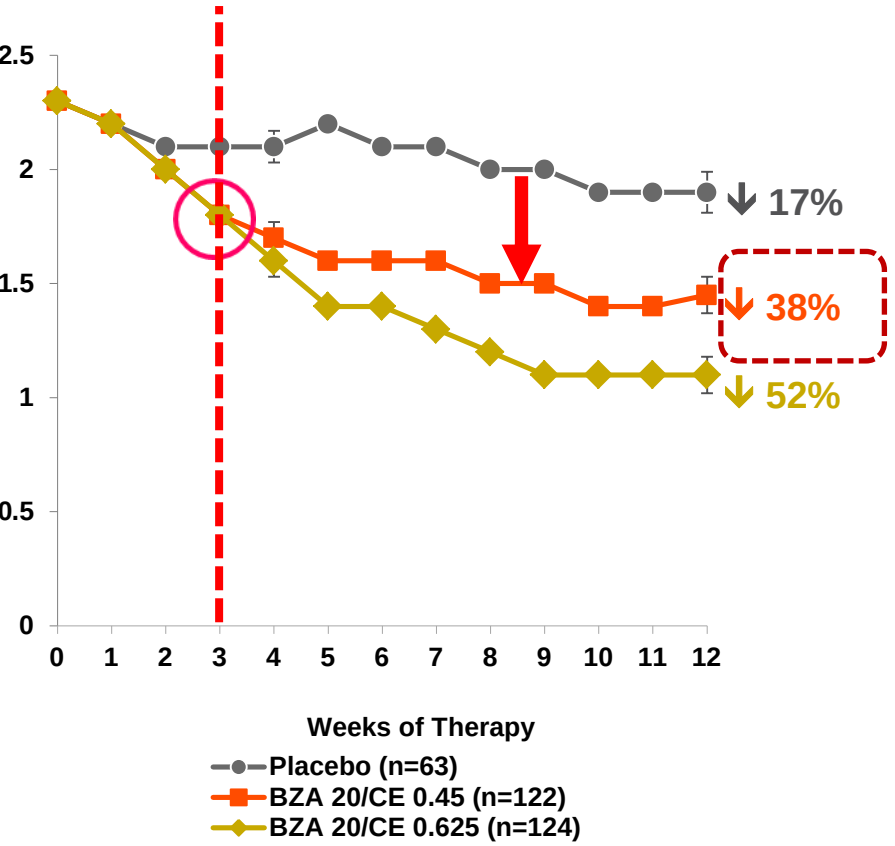


TSEC...? Comparable to... or lower than low dose TBL...?

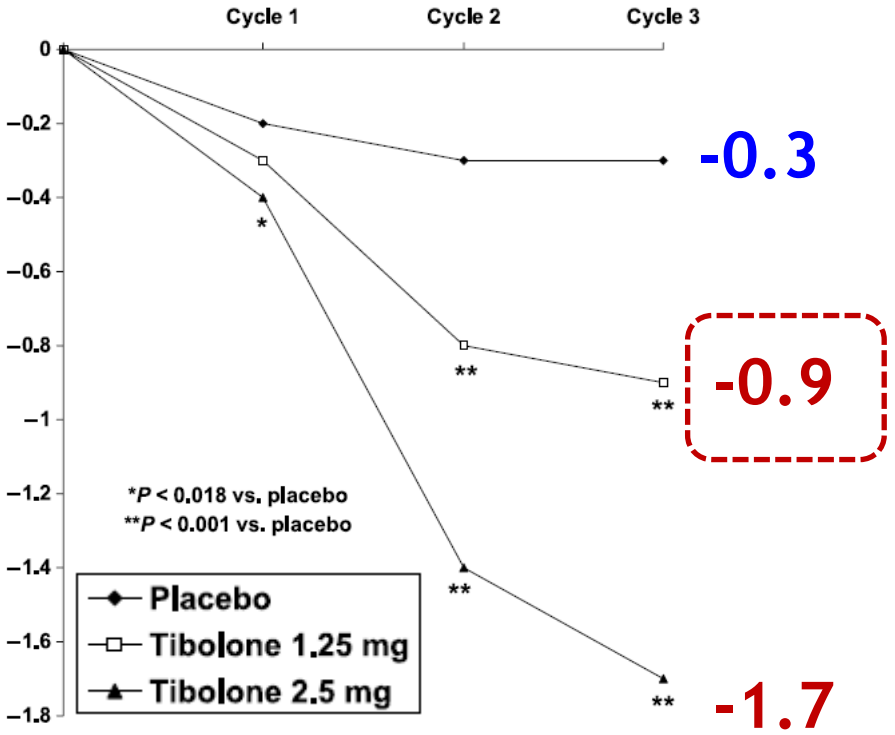
Pinkerton JV, Menopause 2009.; Swanson SG, Menopause 2006.

Hot flush severity
TSEC (SMART-2) Vs Tibolone

Daily severity scores



Median change from baseline in the average daily severity score



TSEC...? Comparable to... or lower than low dose TBL...?

Pinkerton JV, Menopause 2009.; Swanson SG, Menopause 2006.

Vasomotor symptoms
Comparison of efficacies

- Vasomotor symptoms

Standard EPT

Low dose EPT ≈ Standard TBL

Low dose TBL ≈ TSEC

Why…?

- EPT — Estrogen + Progestogen
- Tibolone (대사후) — Estrogen + Progestogen + Androgen
- TSEC — Estrogen + SERM(s)

증례 III

Case (III)
Bleeding episodes

증례

- 49세 산과력 0-1-3-1; 마지막 생리 2개월전
- 3개월전부터 1-2 시간 간격으로 열감이 있으며 땀나고 두근거리는 증세가 지속되면서 수면 장애까지 있어서 방문

GY-USG: Uterus Ant wall asymmetrical enlargement (2.52 cm vs. 1.11 cm) -> r/o adenomyosis, small myoma (+), EMT 0.48 cm

FSH/E2 64.3/ < 5.0, TSH/FT4 1.16/ 1.20, 25OH VIT D 15.1, CTX 0.481, OSC 16.5

OT/PT 17/15, LIPID 243-96-55-163, GLC 99

CPA/EKG> WNL

DXA> L_{1-4} -2.2 (-2.4), FN -1.0 (Hip -1.4): lumbar & femur osteopenia

MMG> Category 0 in Lt. upper central, Lt. lower central → rec> Lt Mag MMG, USG

Breast USG> C 3, Lt Mag MMG> C 2

Case (III)
Bleeding episodes

증례

- **Continued…**
- **Cyclic EPT with Ca-Vit D** start
- **2** 개월 후 외래 방문: 출혈이 **3**주째 지속됩니다 → **GY-USG> free**

➔ 일단 기다려 보자고 하고 2개월 추가 처방

- **1**개월 후 다시 외래 방문: 출혈이 지속되어 약제 중단 또는 변경 원함. 또한 유방 초음파 검사 결과가 불안하여 가능한 유방암에 보다 안전한 제제로 바꾸길 원함

How should we respond to this situation … ?

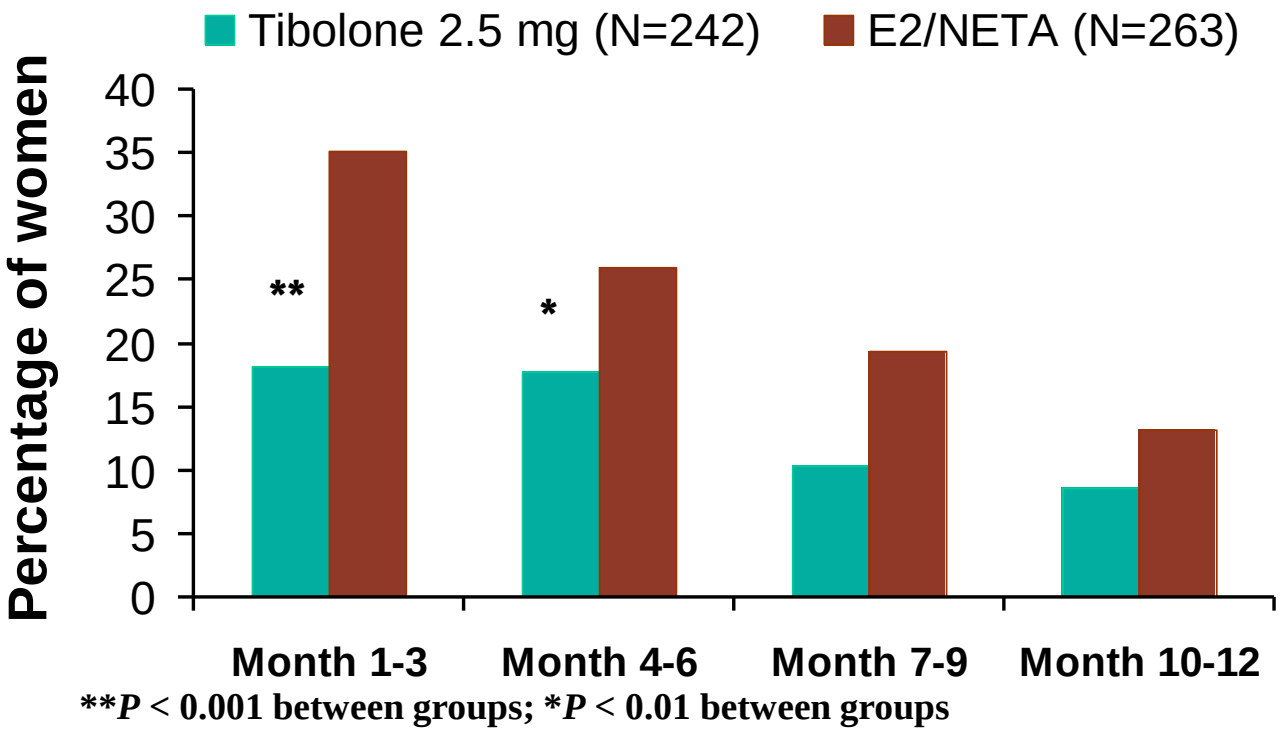
Tibolone
Patients selection: compared to EPT

AP Tibolone Consensus Group 2010 Recommendations

Those who experience:

1. An increase in breast pain despite HRT dose adjustment
2. Increased breast density that resulted in an unreadable mammogram
3. Low libido
4. Mood disorders
5. Persistent bleeding problems on EPT

Vaginal bleeding
Tibolone Vs EPT: TOTAL



**$P < 0.001$ between groups; *$P < 0.01$ between groups

Tibolone causes **less vaginal bleeding** than continuous **combined EPT**

Hammar ML, et al. BJOG 2007.

Vaginal bleeding
Tibolone Vs Placebo

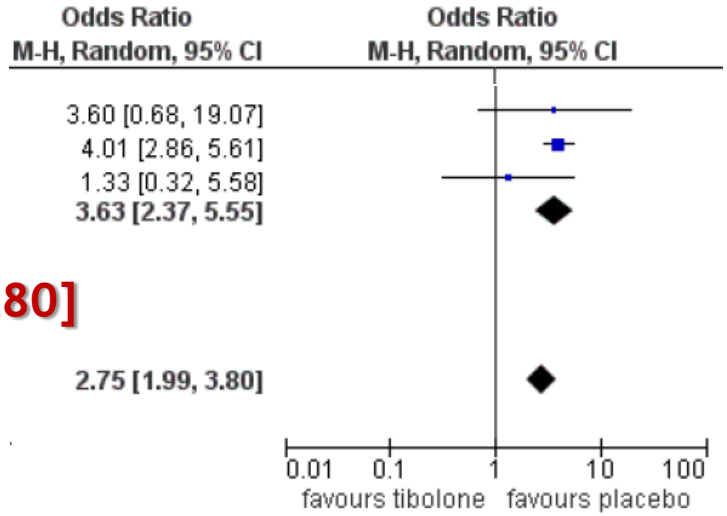
- LIFT study

Treatment (mean 34 months)	Tibolone N = 2,249	Placebo N = 2,257
Vaginal bleeding	9.5%**	2.5%

** $P < 0.001$

Cummings SR, et al. N Engl J Med 2008.

- Cochrane review: unscheduled bleeding



OR 2.75 [1.99, 3.80]

Formoso G, et al. Cochrane Database Syst Rev 2012.

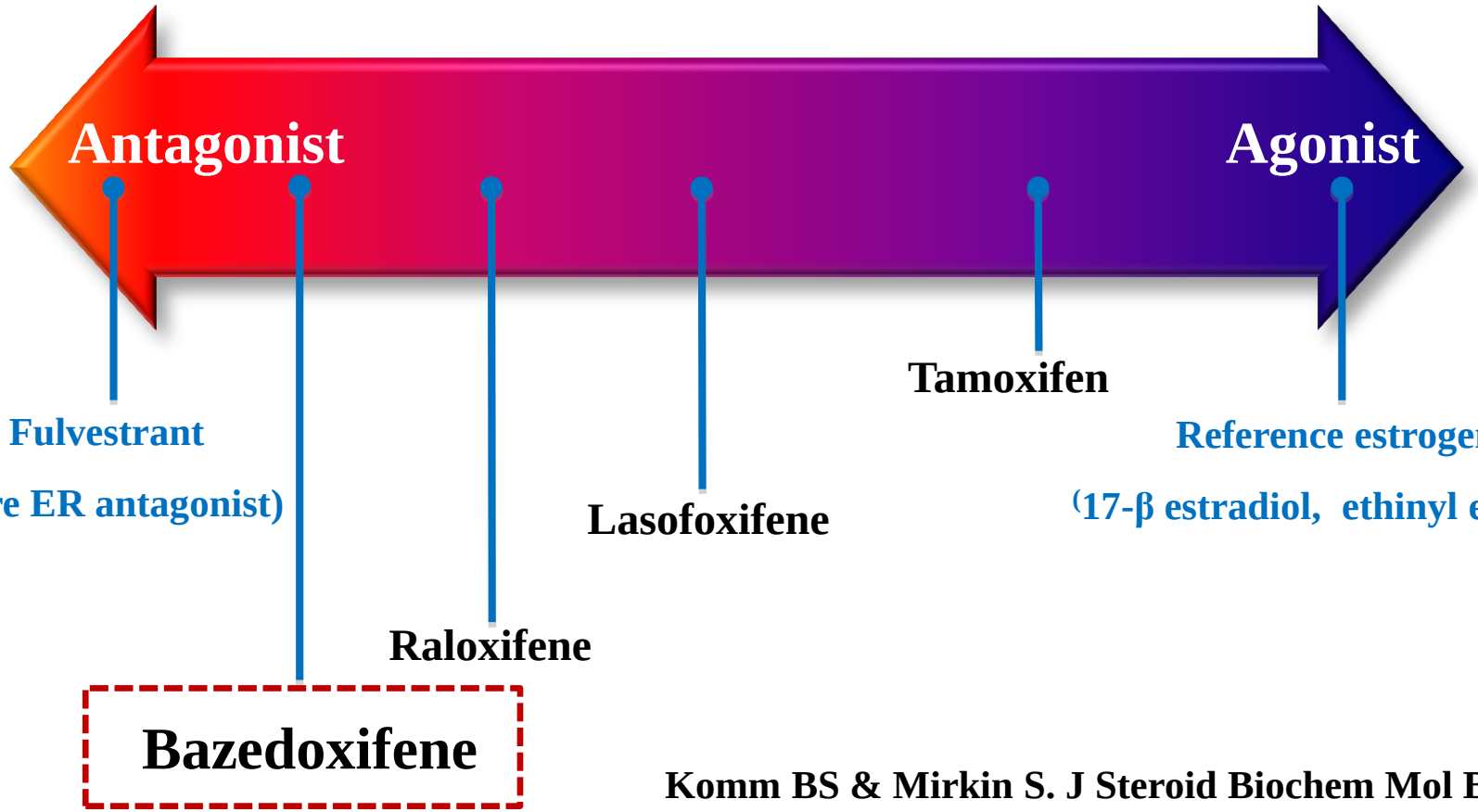
SERMs
Activity on Endometrium

- TSEC

Estrogen + SERM(s)

- EPT

Estrogen + Progestogen



Komm BS & Mirkin S. J Steroid Biochem Mol Biol 2014.

Vaginal bleeding
TSEC: SMART-5

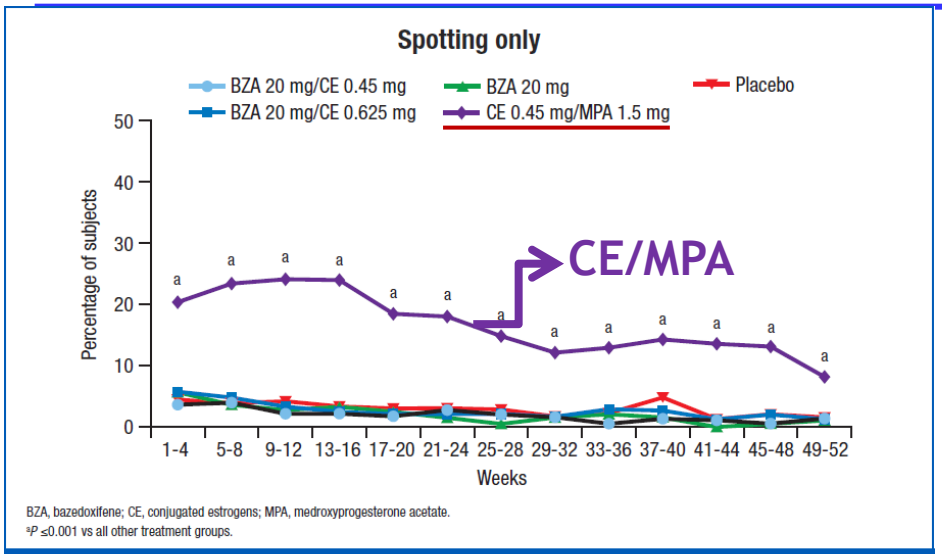


Figure 4. Percentage of subjects reporting spotting during 4-week cycles over Year 1.

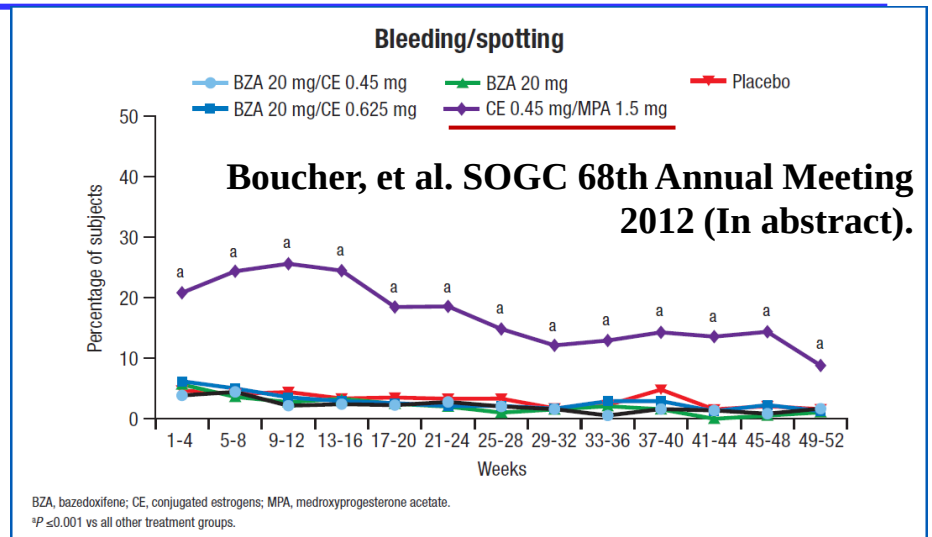


Figure 5. Percentage of subjects reporting bleeding/spotting during 4-week cycles over Year 1.

Noncumulative rates of spotting and bleeding/spotting were **similar** among women treated with **BZA 20 mg/CE 0.45 or 0.625 mg, BZA 20 mg, or placebo**, and *were consistently **higher** in women treated with **CE 0.45 mg/MPA 1.5 mg***

Pinkerton JV, et al. J Clin Endocrinol Metab 2014.

Progestin-related issues
Compliance-related

Most common adverse events leading to discontinuation are related to progestins[1,2]:

Breakthrough bleeding

- Increase in the number of **uterine procedures** (i.e., unnecessary endometrial biopsies)

Breast pain/tenderness

- Increase in the number of **breast interventions**

Other progestin-related intolerance issues[3]

- Nausea
- Depressive mood
- Poor concentration
- Hirsutism
- Headache
- Dizziness
- Fluid retention
- Weight gain

1. Steel SA, Climacteric 2003.; 2. Ettinger B, Am J Manag Care 1999.; 3. Palacios S, Maturitas 2015.

Breast pain/ tenderness
Tibolone

- TOTAL study: STEAR Vs low dose EPT

Treatment (duration 12 months)	Tibolone N = 242	E_2/NETA N = 263
Breast tenderness	3.2%**	9.8%

** *P* < 0.001

Hammar ML, *et al. BJOG* 2007;114:1522–1529.

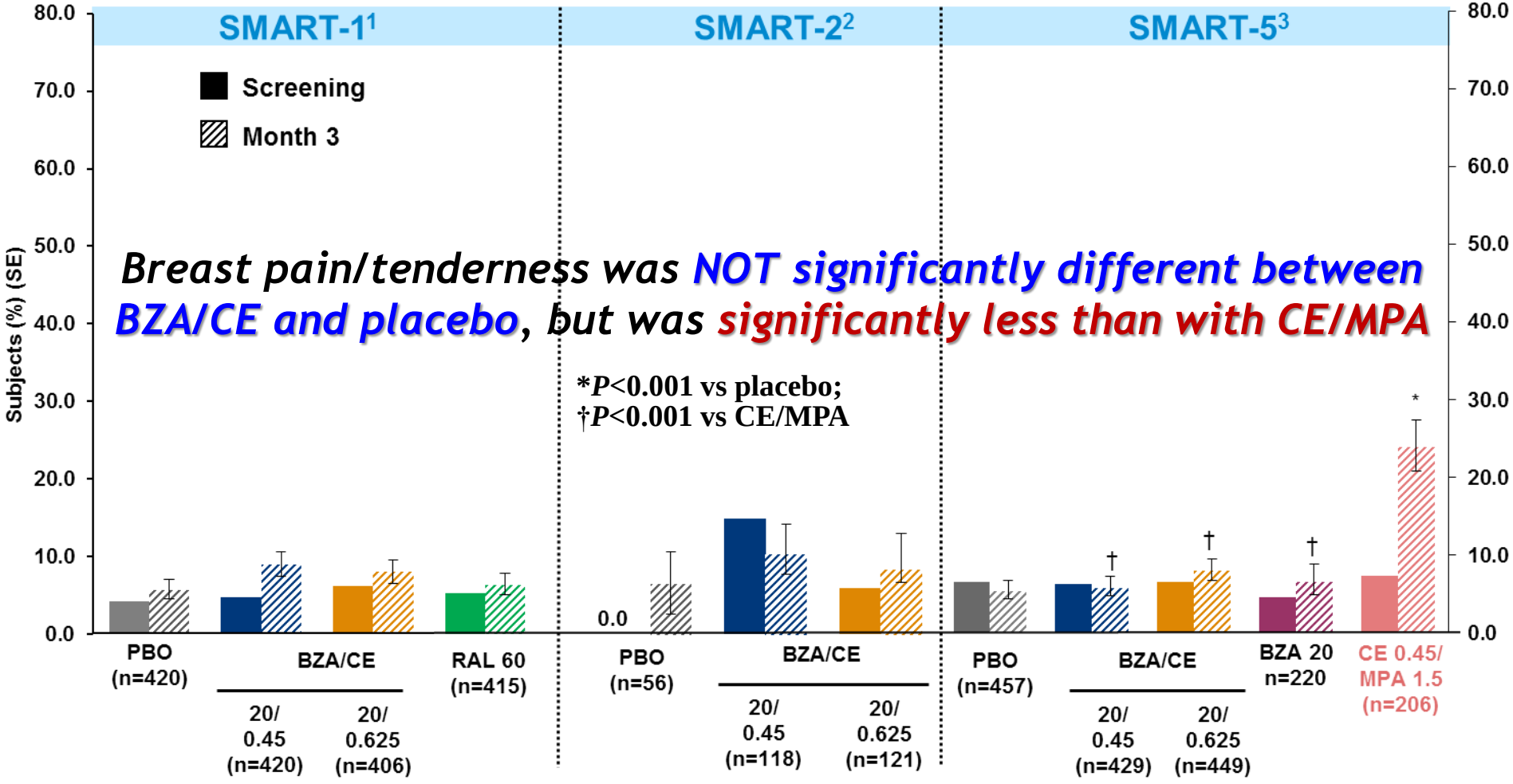
- LIFT study: STEAR Vs placebo

Treatment (mean 34 months)	Tibolone N = 2,249	Placebo N = 2,257
Breast discomfort	9.0%**	2.9%

** *P* < 0.001

Cummings SR, et al. N Engl J Med 2008.

Breast pain/ tenderness
TSEC: SMART-1, -4, & -5



1. Archer DF, *Fertil Steril* 2009; 2. Pinkerton JV, *Menopause* 2009; Pinkerton JV, *Obstet Gynecol* 2013.

TSEC
Summary of adverse events

Adverse events	TSEC
Vaginal bleeding	→
compared to EPT	↓
Endometrial cancer/ hyperplasia	→
Endometrial thickness (*compared to EPT*)	↓
Breast cancer	**Lack of data (theoretically ↓)**
Breast pain	→
compared to EPT	↓
Mammographic density	→
Strokes	→
Other cardiovascular events	→
Weight gain	→

TSEC
Patients selection: compared to EPT

Recommendations about which to use **CANNOT be made based on efficacy**…

However… CE/BZA may be considered for women with…

- **Bothersome vaginal bleeding**
- **Breast pain/tenderness**
- **Other intolerable side effects of progestin-containing therapy**

  e.g.) nausea, hirsutism, headache, dizziness, weight gain, and cyclical mild depression and mood symptoms

- **Increased breast density in MMG**
- **Concerns about breast cancer risk**

  ➔ understanding about the lack of long term data are needed

Palacios S, et al. Maturitas 2015;80:435-440.

SUMMARY

- **TSEC** is a novel, progestin-free MP treatment in women with intact uterus
- **The combination of BZA with CE (DUAVIVE)…**
  - Preserve **Bone mass**
  - Significantly improve **Perimenopausal symptoms**
  - **Acceptable Endometrial & Breast Safety/Tolerability Profile**
  - **Free from Cardiovascular events at short-term follow-up**
- **DUAVIVE** is a ***promising alternative to conventional EPT*** *for non -hysterectomized postmenopausal women*

Thank You For Your Attention !!!

TAKE-HOME MESSAGES

	STEAR	TSEC
Strength	▪ **Cost** ▪ More effective in symptom relief & bone density improvement ▪ Proven effect on fracture reduction ▪ Proven effect on sexual function ▪ **Most used MP treatment** in Korea	▪ **Progestin-free MP treatment** ▪ Less adverse effects related to compliance ▪ Free from cardiovascular events at short-term follow-up ▪ **In theory, free from breast cancer**
Weakness	▪ More vaginal bleeding, weight gain, or breast pain ▪ Increased stroke risk in older women	▪ Lack of comparative studies on efficacies of treatment ▪ Lack of RCTs on fracture risk or breast cancer incidence ▪ Lack of long-term F/U data

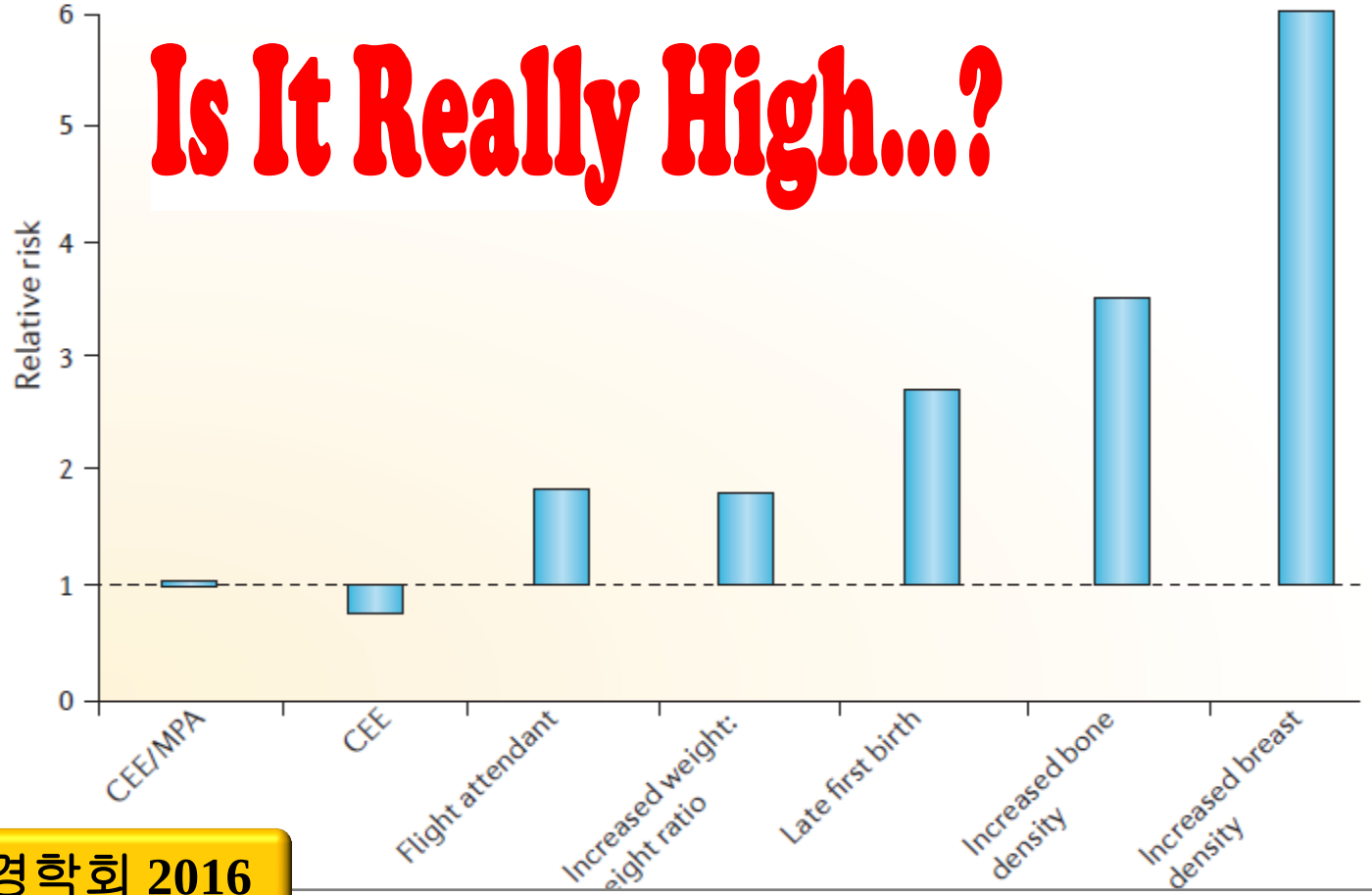
TSEC
Contraindications

킴스 온라인

1. 진단되지 않은 자궁 이상출혈 여성
2. 유방암 또는 그 의심자 및 기왕력자 여성
3. 에스트로겐-의존성 종양 혹은 그 의심자 여성
4. 활성 심부정맥혈전증·폐색전증 또는 그 기왕력자 여성
5. 활성 동맥 혈전색전성 질환 또는 그 기왕력자 여성
6. 프로게스틴·에스트로겐·에스트로겐 작용제/길항제 복용자 여성
7. 에스트로겐·바제독시펜·기타 본제 성분 과민증 여성
8. 간장애 또는 질환자 여성
9. 알려진 C단백·S단백·항트롬빈 결핍 및 기타 알려진 혈전유발 장애 있는 여성
10. 임부, 가임부, 수유부

유방암 위험도
과연 제대로 알려져 있는가...?

- Exogenous and endogenous risk factors



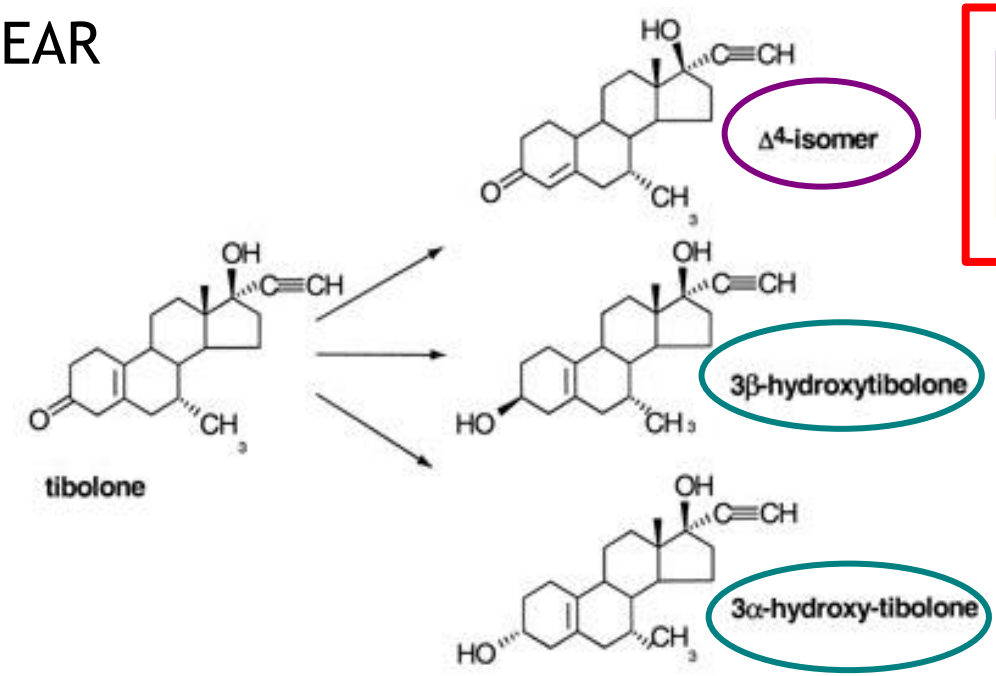
세계폐경학회 2016

호르몬치료로 인한 유방암 위험성 증가는 낮으며, 치료 중단 후 점차적으로 소실된다.

Tibolone

What is the Tibolone?

- STEAR



Progestogen

Androgen

Estrogen

- TSEC

Estrogen + SERM(s)

Progestogen-free

Theoretically, TSEC maybe superior to …?

But in real world …?

CE/BZA vs Others
Uterine/ Endometrial Profile

Combination Tested	Type of Study	Uterine Profile	
RLX + E2 (patch or oral)[1,2]	Clinical	Unfavorable	X
RLX + CE[3]	Preclinical	Unfavorable	X
LAS + CE[3]	Preclinical	Unfavorable	X
BZA + CE[3]	Preclinical / Clinical	Favorable	✓

RLX, raloxifene, LAS, lasofoxifene, BZA, bazedixifene.

[1]Stovall DW, Menopause 2007.; [2]Davis SR, Menopause 2004.; [3]Peano BJ, Endocrinology 2009.

TSEC: CE plus BZA
Clinical trials

- **SMART trials** (Selective estrogen Menopause And Response to Therapy)

Study	Duration	Main Endpoints	Treatment Arms	No. of Subjects
SMART-1	24 mo	• Dose ranging • Endometrial hyperplasia at 12 mo • Bone mineral density at 24 mo • Vasomotor symptoms • Vaginal maturation	• BZA 10, 20, 40/CE 0.45 • BZA 10, 20, 40/CE 0.625 • Raloxifene 60 • Placebo	**3,397**
SMART-2	3 mo	• Vasomotor symptoms	• BZA 20/CE 0.45 • BZA 20/CE 0.625 • Placebo	**318**
SMART-3	3 mo	• Vulvar/vaginal atrophy	• BZA 20/CE 0.45 • BZA 20/CE 0.625 • BZA 20 • Placebo	**652**
SMART-4	12 mo + 12 mo extension	• Supportive safety study • Endometrial hyperplasia • Bone mineral density	• BZA 20/CE 0.45 • BZA 20/CE 0.625 • CE 0.45/MPA 1.5 • Placebo	**1,061**
SMART-5	12 mo	• Endometrial hyperplasia • Bone mineral density • Breast density • Sleep/quality of life (substudy)	• BZA 20/CE 0.45 • BZA 20/CE 0.625 • CE 0.45/MPA 1.5 • BZA 20 • Placebo	**1,843**