새로운 폐경치료제

조직선택적에스트로겐복합제(TSEC)

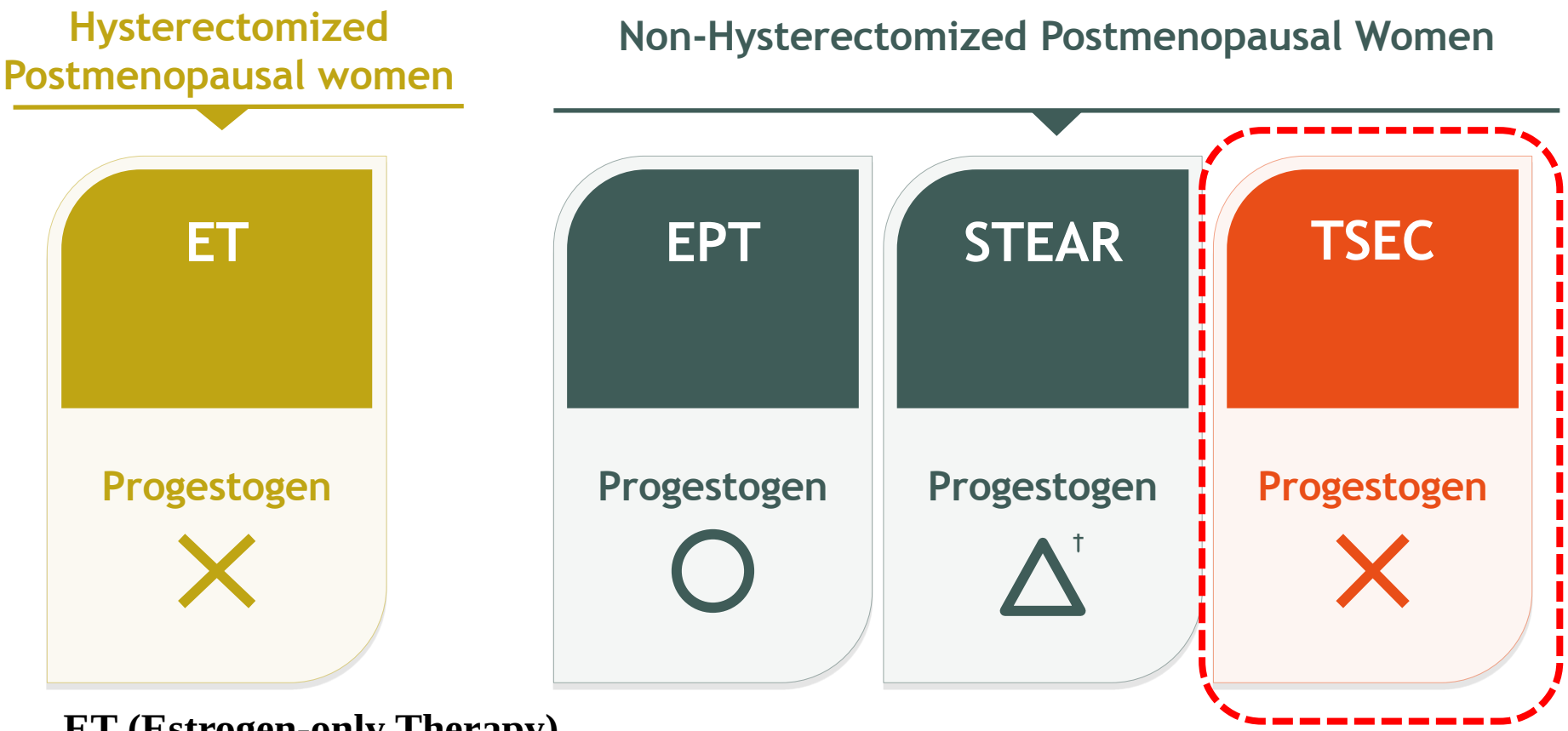
Sungwook Chun, MD, PhD

Associate Professor

Inje University Haeundae Paik Hospital

Jan 7, 2018

Menopausal treatment
Women with intact uterus



ET (Estrogen-only Therapy)

EPT (Estrogen-Progestogen Therapy)

STEAR (Selective Tissue Estrogen Activity Regulator)

TESC (Tissue Selective Estrogen Complex)

Menopausal treatment
Menopausal women with intact uterus

Conjugated Estrogens

Issue: **Endometrial hyperplasia & cancer**

Conjugated Estrogens + Progestin

Issue: some medical conditions which may be exacerbated by Progestins exist (eg. Breast cancer)

Conjugated Estrogens + SERM = TSEC (Conjugated Estrogens / Bazedoxifene)

IF CAN Estrogen + SERM BE USED INSTEAD OF EPT…?

- RISK OF BREAST CANCER → ANSWER (?)
- ISSUES ON OTHER PROGESTIN-RELATED ISSUES → ANSWER (?)

TSEC
Tissue Selective Estrogen Complex

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

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

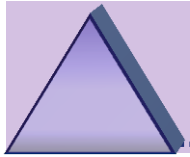
- Effect of TSEC
  - **Bone preservation**
  - **Relieve menopausal symptoms including hot flushes**
  - **Without stimulating EM and breast → *New progestin-free MP therapy***
- First TSEC
  - Bazedoxifene/conjugated estrogens
  - Duavive®: approved in **Korea (Jul 25, 2014) → launching in 2015**

TSEC: Clinical trials
SMART 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**

Today's Topics Are ...?

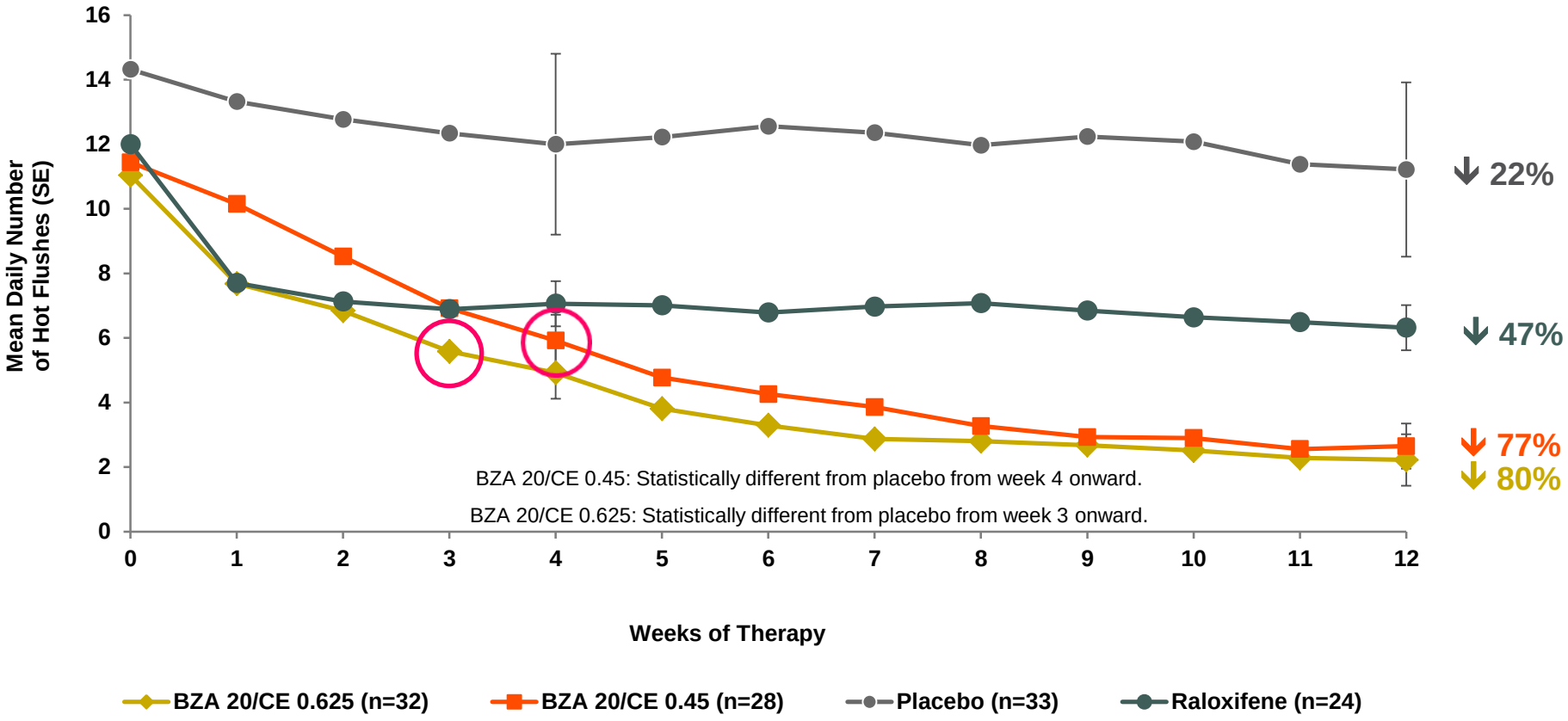


Issues on Efficacy

Issues on Safety & Tolerability

VASOMOTOR SYMPTOM

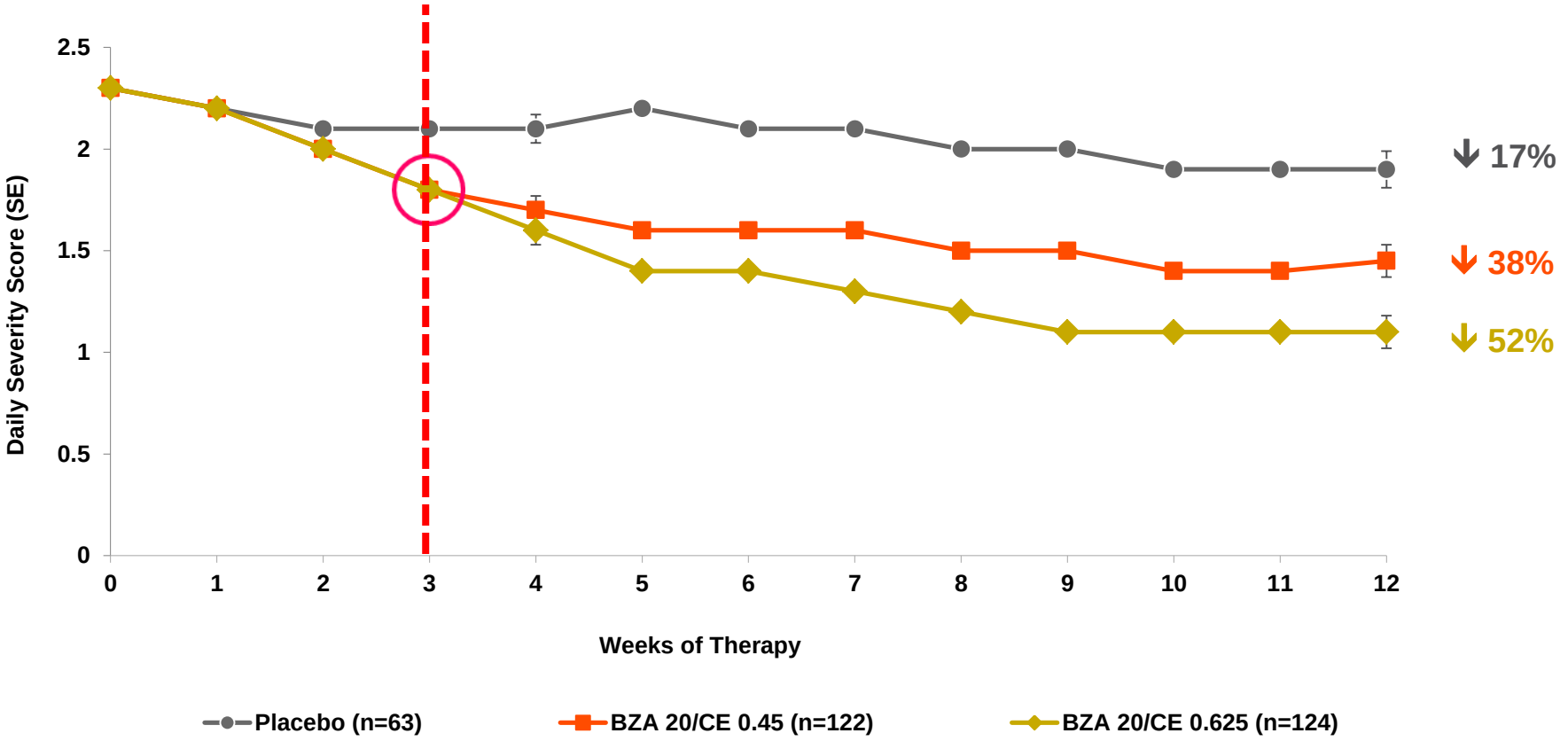
Hot Flush: Frequency
SMART-1



Archer DF, et al. *Fertil Steril*. 2009;92(3):1039-1044.

Hot Flush: Severity
SMART-2

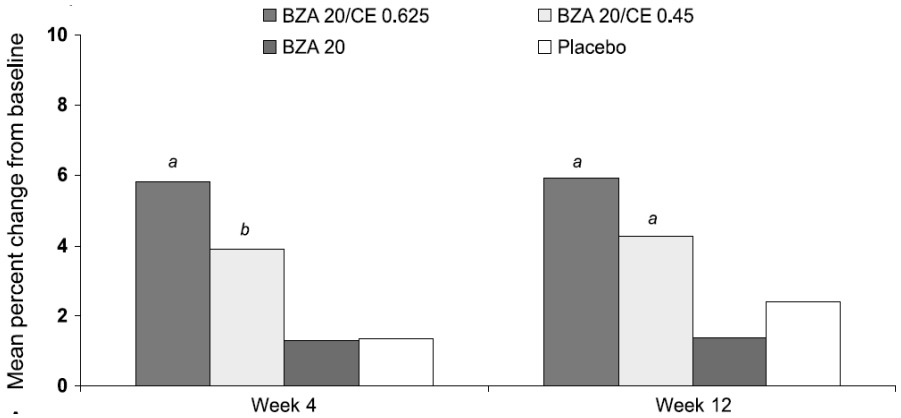
Starting at week 3, BZA/CE significantly reduced the severity of hot flushes compared with placebo



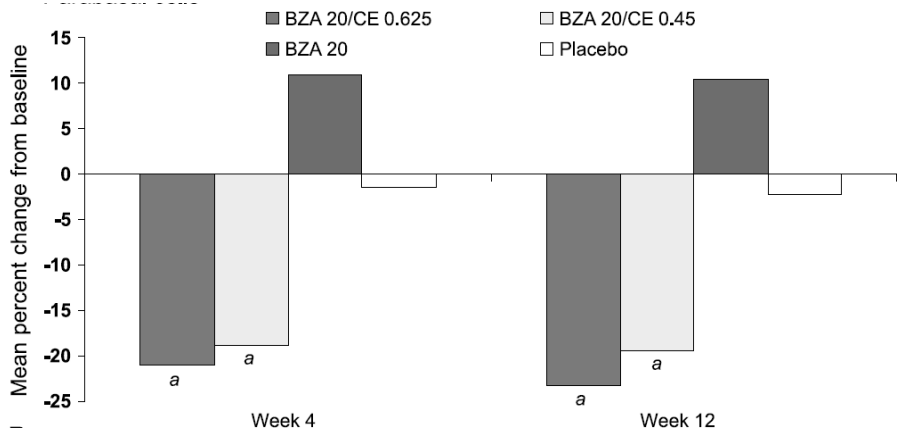
Pinkerton JV, et al. Menopause 2009;16(6):1116-1124.

VULVOVAGINAL ATROPHY

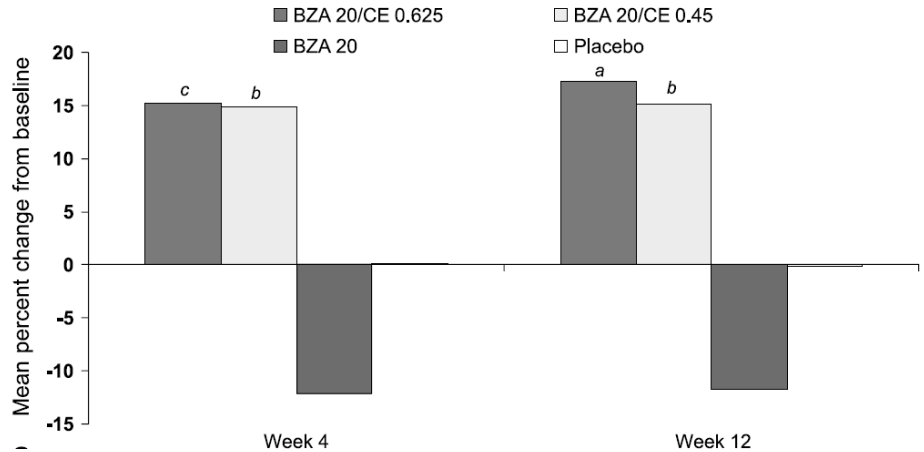
Vulvar/vaginal smear
SMART-3



Superficial cells



Parabasal cells



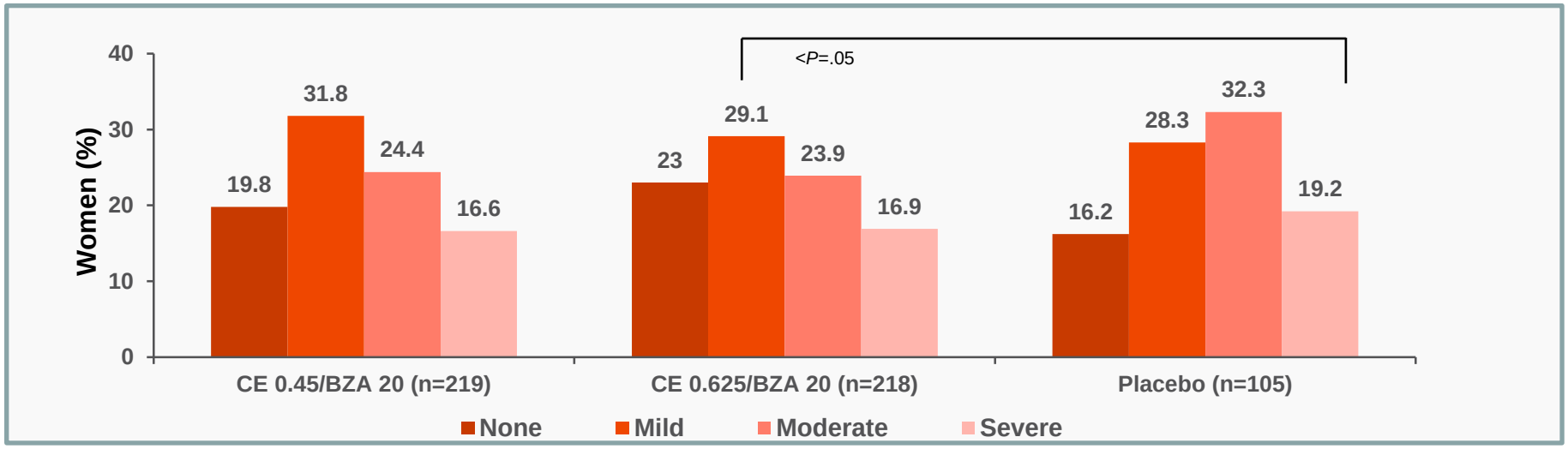
Intermediate cells

- **Superficial cells:** ↑ with both dose of BZA/CE at 4 & 12th week
- **Parabasal cells:** ↓ with both dose of BZA/CE at 4 & 12th week
- **Intermediate cells:** ↑ with both dose of BZA/CE at 4 & 12th week

Kagan R, et al. Menopause 2010.

Vaginal symptoms
SMART-3

Improvement in Incidence of most bothersome symptom of VVA at week 12 (SMART-3)



Participants treated with **BZA 20 mg/ CE 0.625 mg** had significantly **greater improvements** in their MBS compared with participants treated with placebo

(but…, **NOT BZA 20 mg/ CE 0.45 mg !!!**)

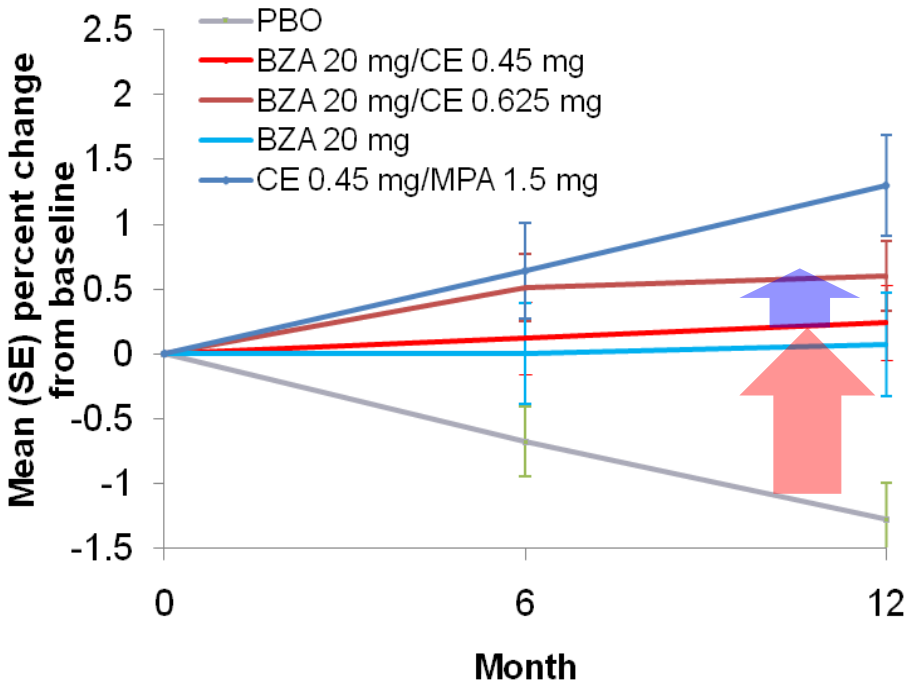
인제대학교 해운대백병원

Kagan R, et al. Menopause 2010.

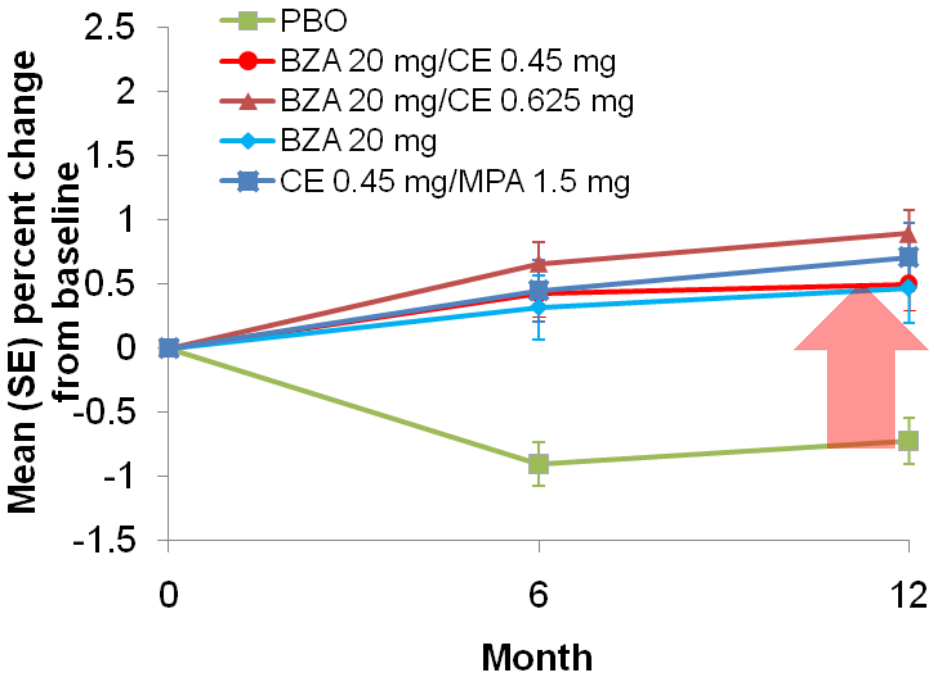
BONE

Bone density
SMART-5

Lumbar Spine



Total Hip

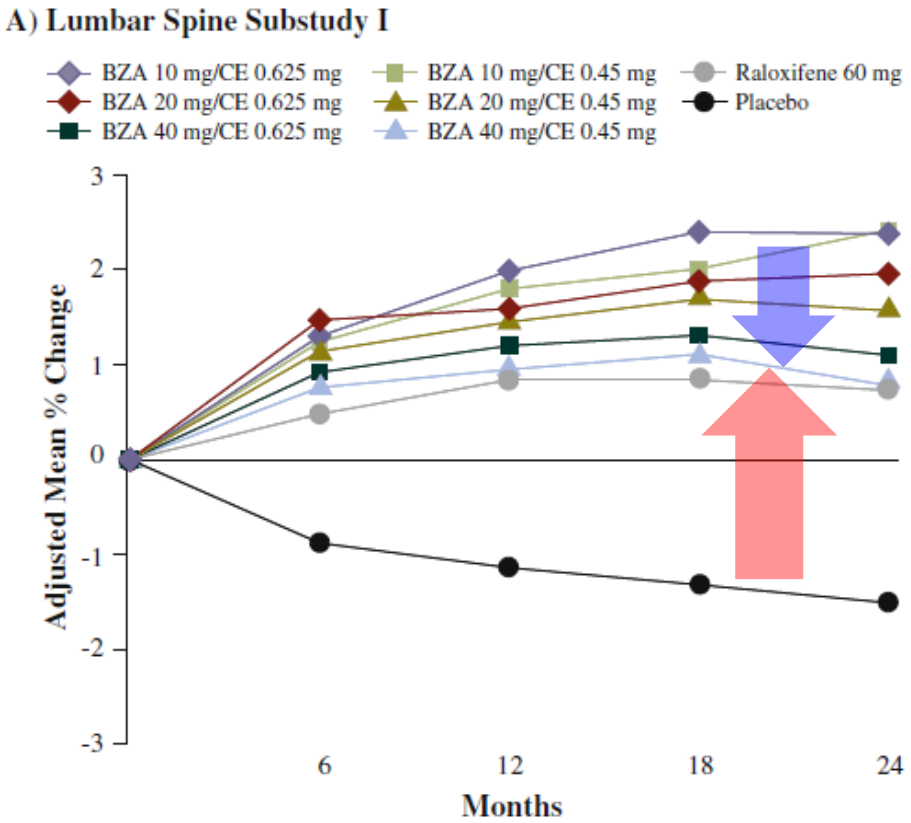


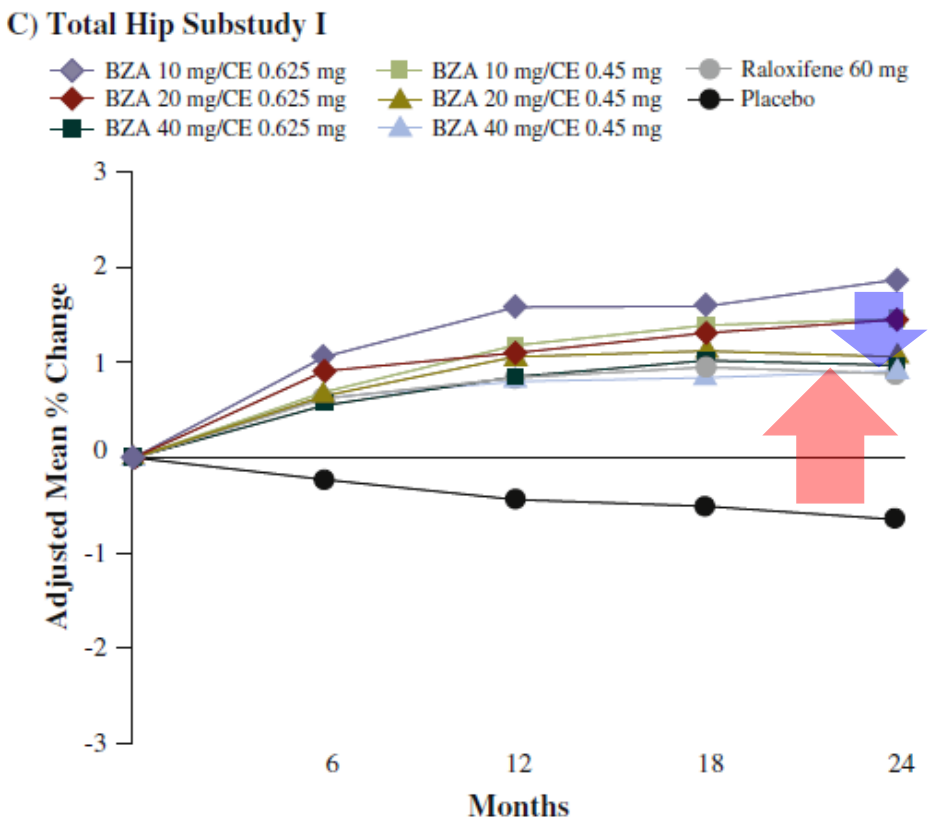
E2-dose dependent increase …?

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

Bone density
SMART-1

- Mean % change in lumbar spine & total hip BMD

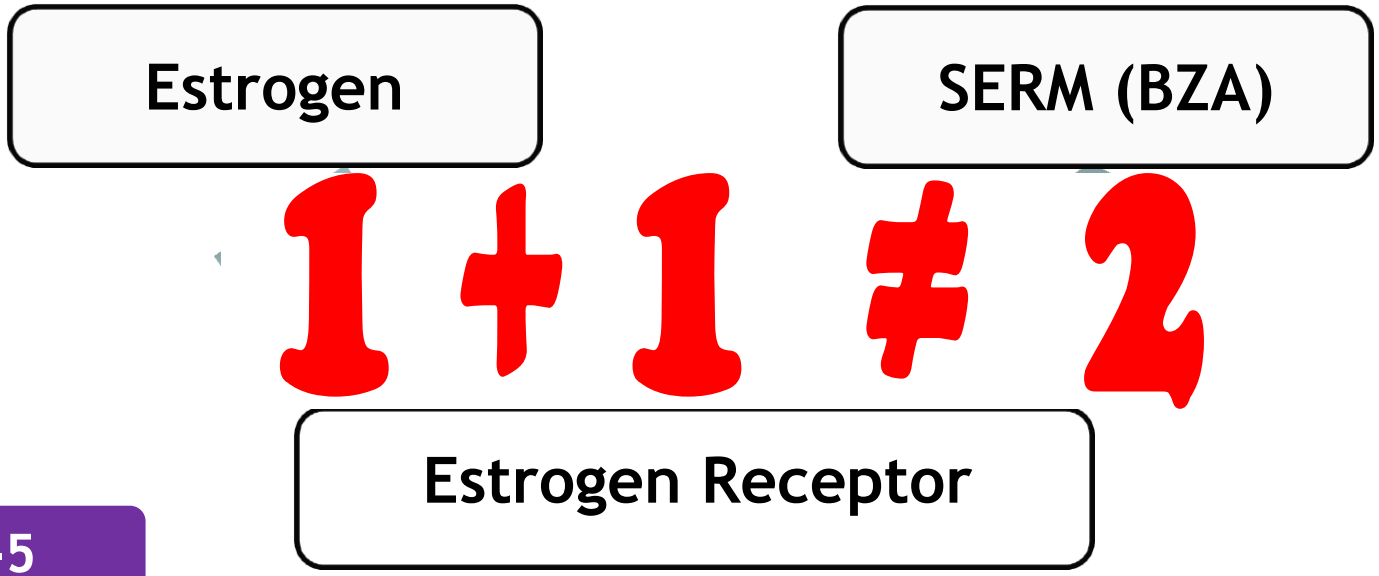




BZA-dose dependent inhibition ...?

Linsay R, et al. Fertil Steril 2009.

TSEC
Additive effect on bone density…?



SMART-5

The increase in lumbar spine BMD for ***CE 0.45 mg/MPA was significantly greater*** than that for **BZA 20mg/CE 0.45mg** at 12 months

➔ **CE** is a ***more potent anti-resorptive agent compared to BZA***, one may expect attenuation in BMD responses when BZA is added to CE

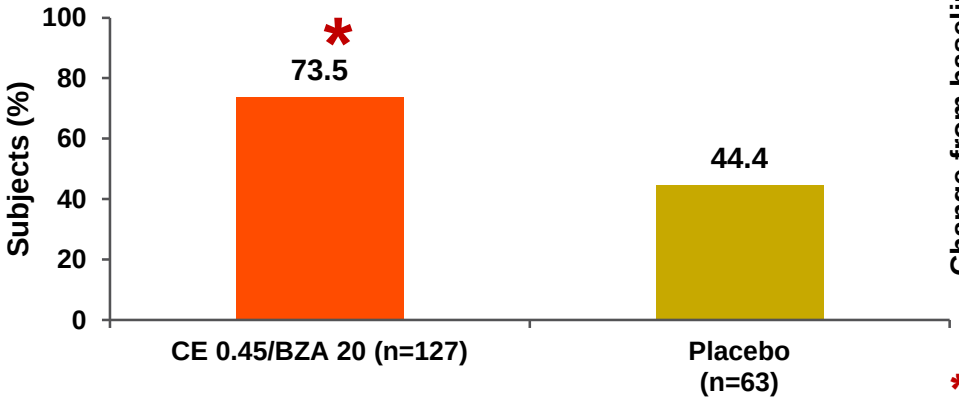
Pinkerton, et al. J Clin Endocrinol Metab 2014.

Quality Of Life

Quality Of Life
SMART-2 & SMART-5

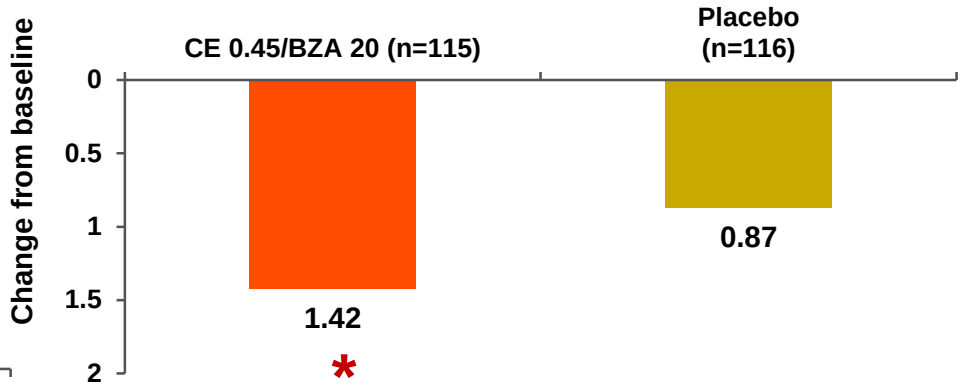
MS-TSQ[1]

Percentage of subjects reporting overall satisfaction as "extremely satisfied" or "satisfied" at week 12 Study 3 (305,SMART-2)



MENQOL[2]

Adjusted mean reduction from baseline in total score at month 12 Study 2 (3307, SMART-5)



***P<.001 vs placebo**

MS-TSQ evaluates satisfaction with treatment based on questions (related to control of hot flushes during the day, control of hot flushes and sweats at night, sleep, mood, libido, ability to concentrate, medication tolerability, and overall satisfaction)

MENQOL questionnaire assesses HR-QoL across 4 domains: 1) vasomotor, 2) psychosocial, 3) sexual, and 4) physical functioning

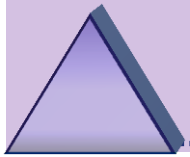
1. Utian W, et al. Maturitas 2009;63:329-335.; 2. Pinkerton JV, et al. Menopause 2014;21(3):252-259.

Efficacy of TSEC…?
Not superior to EPT…

How Can TSEC Be An Promising Alternatives to Conventional EPT or TBL in Postmenopausal Women?

Today's Topics Are ...?

Issues on Efficacy



Issues on Safety & Tolerability

ENDOMETRIAL SAFETY

Menopausal treatment

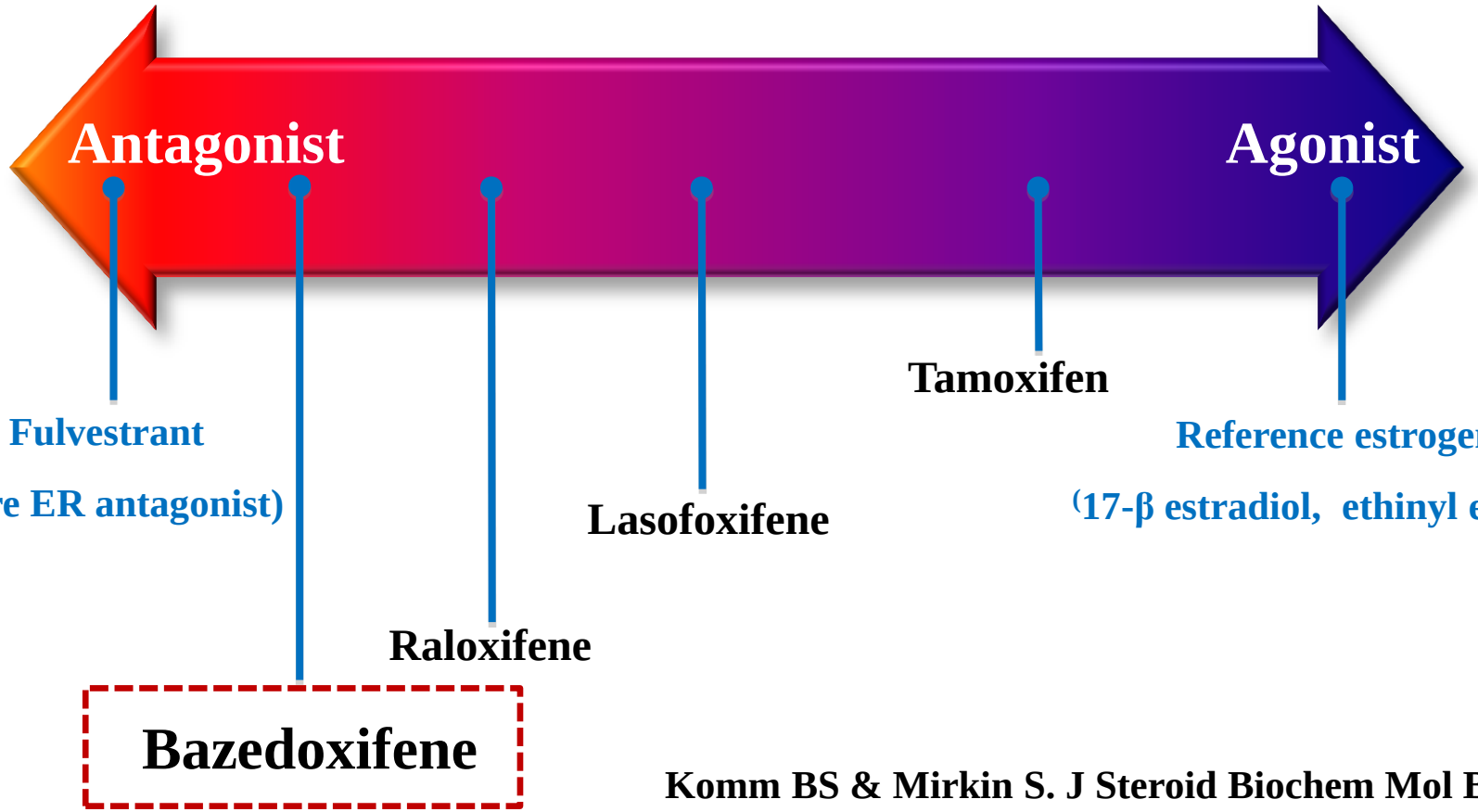
Menopausal women with intact uterus

- TSEC

Estrogen + SERM(s)

- EPT

Estrogen + Progestogen



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

Endometrial Safety
SMART-1: dose-adjustment

- Incidence of EM hyperplasia at month 12

	CE (0.625 mg)			CE (0.45 mg)		
	BZA (10 mg) n = 341	BZA (20 mg) n = 314	BZA (40 mg) n = 311	BZA (10 mg) n = 320	BZA (20 mg) n = 336	BZA (40 mg) n = 309
Total cases (%)	13 (3.81)[a]	1 (0.32)	0 (0.00)	3 (0.94)	0 (0.00)	0 (0.00)
95% CI (%)[b]	2.27–5.99[a]	0.02–1.50	0.00–0.96	0.26–2.41	0.00–1.09[c]	0.00–1.19[c]

- Incidence of urogenital adverse events

	CE (0.625 mg)			CE (0.45 mg)				
Adverse event, n (%)	BZA (10 mg)	BZA (20 mg)	BZA (40 mg)	BZA (10 mg)	BZA (20 mg)	BZA (40 mg)	Raloxifene (60 mg)	Placebo
(MedDRA term)	n = 430	n = 414	n = 417	n = 430	n = 433	n = 423	n = 423	n = 427
Any endometrial event[a]	21 (4.9)[c]	4 (1.0)	5 (1.2)	10 (2.3)[b]	8 (1.8)	2 (0.5)	1 (0.2)	2 (0.5)
Endometrial disorder	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Endometrial hyperplasia[a]	16 (3.7)[b]	1 (0.2)	0 (0.0)	4 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Endometrial hypertrophy	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Uterine Polyp	5 (1.2)	4 (1.0)	4 (1.0)	3 (0.7)	8 (1.8)	1 (0.2)	0 (0.0)	2 (0.5)
Any ovarian event	2 (0.5)	1 (0.2)	4 (1.0)	3 (0.7)	2 (0.5)	2 (0.5)	1 (0.2)	1 (0.2)
Ovarian cyst	2 (0.5)	1 (0.2)	4 (1.0)	3 (0.7)	2 (0.5)	2 (0.5)	1 (0.2)	1 (0.2)
Any cervical event	22 (5.1)	21 (5.1)	11 (2.6)	17 (4.0)	23 (5.3)	16 (3.8)	19 (4.5)	18 (4.2)
Cervicitis	2 (0.5)	1 (0.2)	0 (0.0)	1 (0.2)	2 (0.5)	1 (0.2)	0 (0.0)	1 (0.2)

BZA 20 mg was lowest dose to prevent EM hyperplasia

Pickar JH, et al. Fertil Steril 2009.

Endometrial hyperplasia
SMART-5

- In SMART-5 (at 1 year)

	BZA 20 mg/ CE 0.45 mg	BZA 20 mg/ CE 0.625 mg	BZA 20 mg	CE 0.45 mg/ MPA 1.5 mg	Placebo
Endometrial hyperplasia	1/ 335 (0.30%)	1/ 368 (0.27%)	1/ 169 (0)	0/149 (0)	1/ 354 (0.28%)
Endometrial polyps	7/ 338 (2.07%)	6/ 370 (1.62%)	1/ 171 (0.58%)	4/ 153 (2.61%)	1/ 356 (0.28%)

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

Endometrial thickness
SMART-1 & SMART-5

- TSEC in SMART-1 (at 1 and 2 year)

  - **EMT Change: For BZA (20/ 40 mg)/CE (0.625/ 0.45 mg)**

Adjusted mean (± SE) increases from baseline in endometrial thickness assessed by TVU were small (<1 mm) and NOT significantly different from that with placebo or raloxifene, respectively, at month 12 or month 24

Pickar JH, et al. Fertil Steril 2009.

- TSEC in SMART-5 (at 1 year)

Adjusted mean changes from baseline were… (compared with 9 mm in PBO)

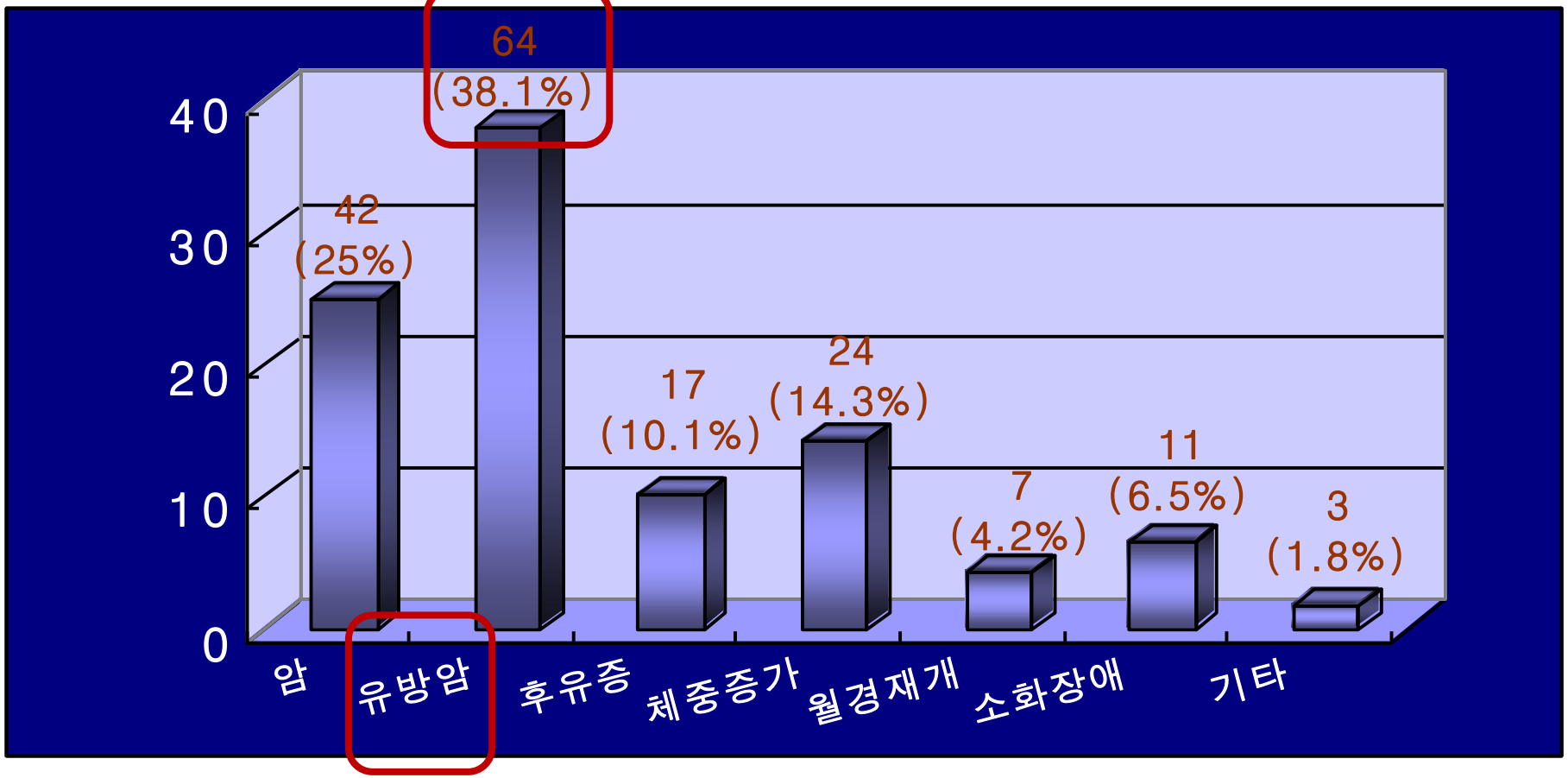
- **0.17 mm in BZA 20/CE 0.45 (*P* < 0.05)**
- **0.51 mm in BZA 20/CE 0.625 & 0.78 mm in CE 0.45/ MPA 1.5 (*P* < 0.001)**

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

BREAST CANCER

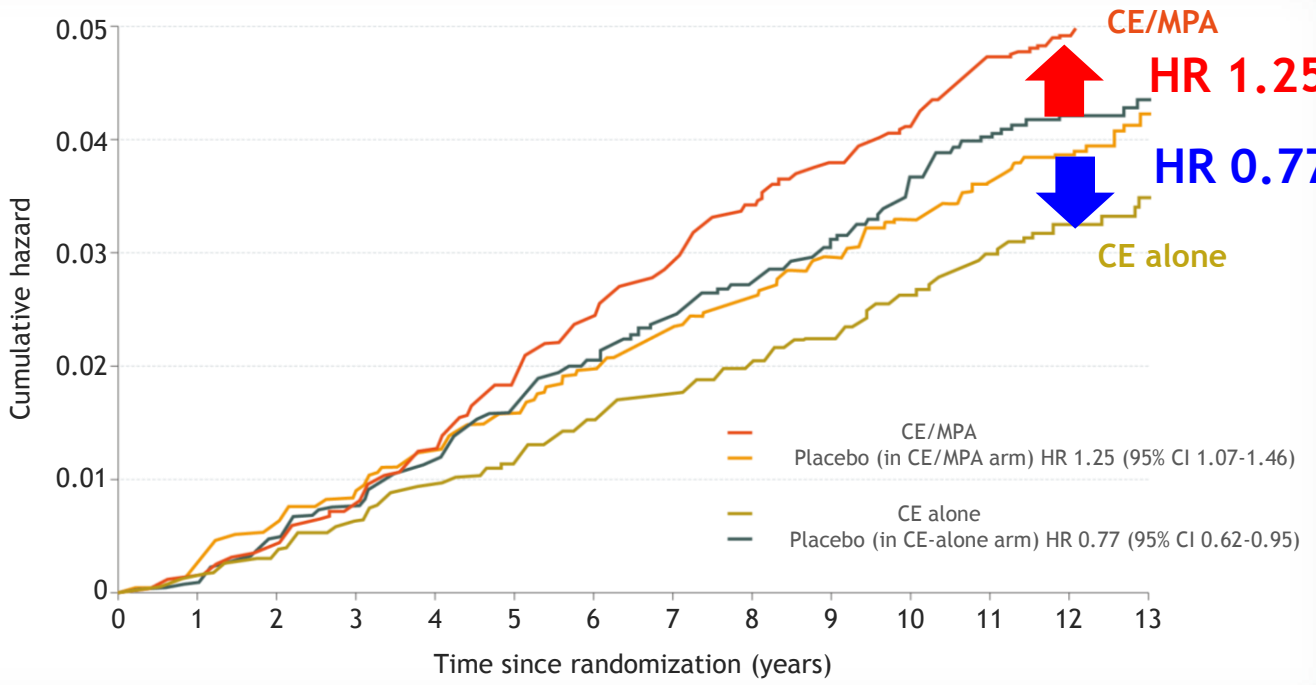
호르몬 치료

환자들은 무엇을 가장 두려워하는가?



폐경역학연구회, 2008

Breast cancer risk
ET Vs EPT: WHI trials



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

세계폐경학회 2016

- **The increased risk is primarily associated with the addition of a synthetic progestogen to estrogen therapy and to duration of use**

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 !!!

BREAST DENSITY

Case
Dense breast

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

How should we respond to this situation … ?

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

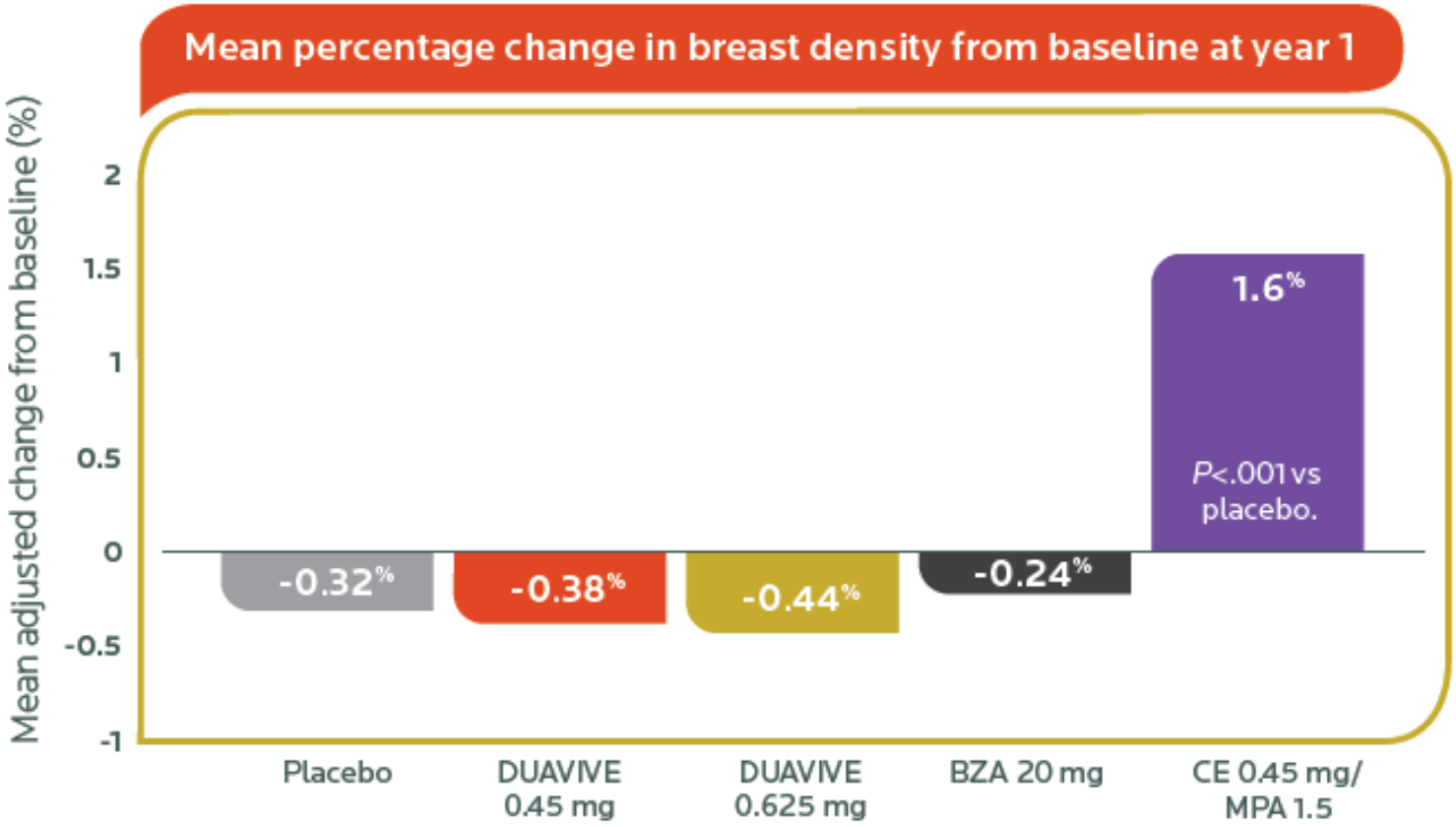
IMS recommendations 2013

- **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.

Breast density
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.

CARDIOVASCULAR SAFETY

Cardiovascular events
TSEC: Meta-analysis of SMART trials

Category	CE 0.45/ BZA 20	CE 0.625/ BZA 20	Any CE/BZA dose	PBO
	N= 1,585	N= 1,583	N= 4,868	N= 1,241
VTE	3 (0.2%)	0	6 (0.1%)	1 (0.1%)
Supf. Thrombophlebitis	1 (0.1%)	1 (0.1%)	13 (0.3%)	1 (0.1%)
Ischemic stroke	1 (0.06%)	1 (0.06%)	4 (0.08%)	0
TIA	2 (0.1%)	0	8 (0.2%)	0
Any CHD	4 (0.3%)	4 (0.3%)	14 (0.3%)	3 (0.2%)
MI	3 (0.2%)	1 (0.1%)	5 (0.1%)	2 (0.2%)

Up to 2 years of CE 0.45 or CE 0.625 mg with BZA 20 mg had an acceptable cardiovascular safety profile

Komm BS, et al. Climacteric 2015.

Cardiovascular events
SMART trials/ WHI/ BZA trial

- Incidence rate of cardiovascular events per 1000 woman-years

	Incidence rate per 1000 woman-years							
	SMART studies		*WHI (50–59-year age group)*[30,35]		*WHI (50–59-year age group)*[30,36]		*BZA Osteoporosis Trial*[*37]	
	CE 0.45 mg/BZA 20 mg	*Placebo*	*CE/MPA*	*Placebo*	*CE*	*Placebo*	*BZA 20 mg*	*Placebo*
Venous thromboembolism	0.3	0.6	1.9	0.8	1.6	1.2	2.3	1.6
Coronary heart disease	2.6	2.0	2.2	1.7	1.7	2.7	NR	NR
Ischemic stroke	0.4	0.0	1.5	1.0	1.5	1.7	1.9	2.0

BZA, bazedoxifene; CE, conjugated estrogens; MPA, medroxyprogesterone acetate; SMART, Selective estrogens, Menopause, And Response to Therapy; NR, not reported

Risks of VTE and stroke with **CE/BZA combined was comparable to placebo**, and, in fact, ***lower than*** historical rates with ***CE alone*** or ***BZA alone***

Komm BS, et al. Climacteric 2015.

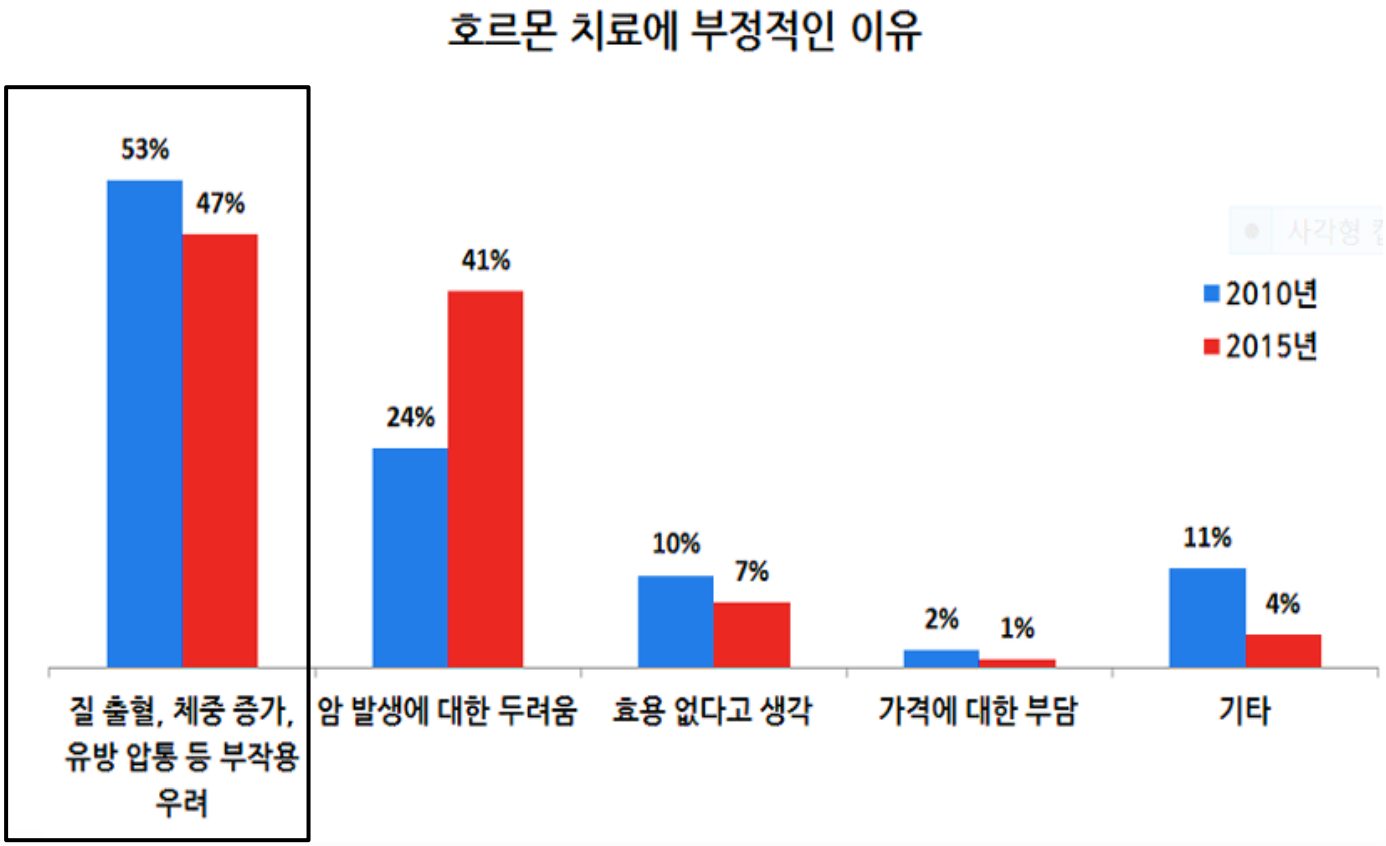
SAFETY/ TOLERABILITY

: Other PROFILES

호르몬 치료

환자들은 왜 호르몬치료에 부정적인가?

2015 대한폐경학회 호르몬 치료 인식도 조사



Compliance-related issues
Progestin-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.

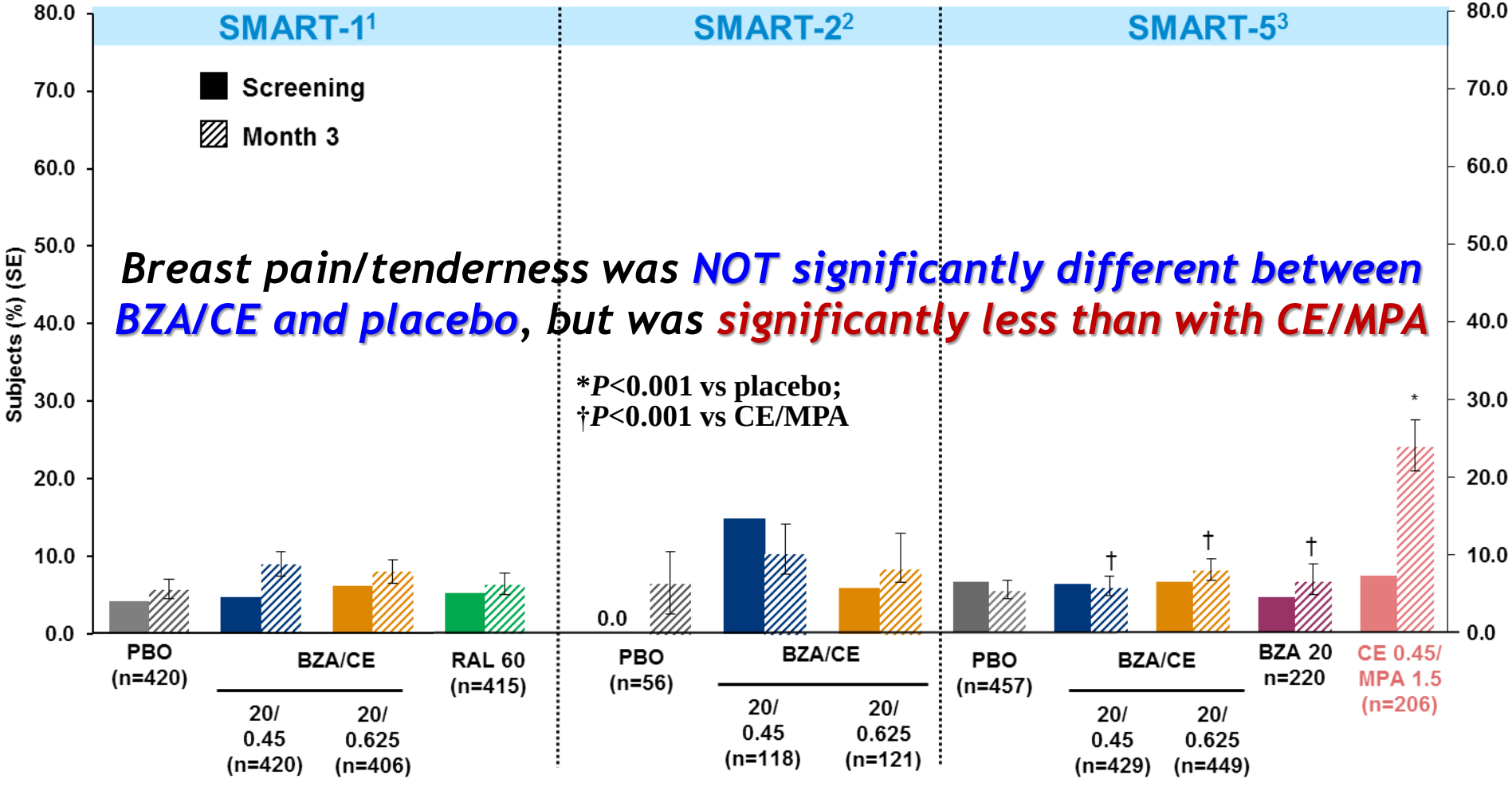
Progestin-related issues
progestin-inappropriate conditions…?

History of the following conditions may make progestin inappropriate:

- High breast density
- Bleeding profile
- Diabetes and metabolic syndrome
- Depression
- PMS/PMDD

De Villiers TJ, Climacteric 2013; Greendale GA, J Natl Cancer Inst 2003; Hickey M, et al, Hum Reprod 2003; Mirkin S, Climacteric 2003;6:273-277; Christodoulakos E, Maturitas 2006; Panay N & Studd JWW. Human Reprod Update 1997; 8. Godsland I, Metabolism 1993; Sites CK, et al. J Clin Endocrinol Metab 2005; Girdler SS, J Womens Health Gend Based Med 1999; Llanezaa P, Maturitas 2012; Hays J, N Engl J Med 2003; Traish AM, Korean J Urol 2014; Ströhle A, Biol Psychiatry 1999; Romeo E, Am J Psychiatry 1998; Nevatte T, Arch Womens Ment Health 2013; Björn I, Climacteric 2006;

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



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

Vaginal bleeding
TSEC: SMART-5

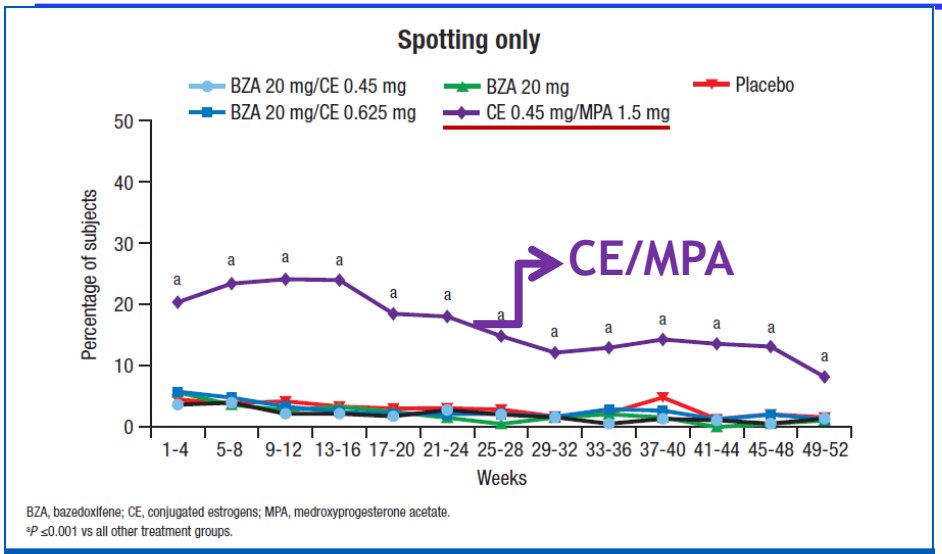


Figure 4. Percentage of subjects reporting spotting during 4-week cycles over Year 1.

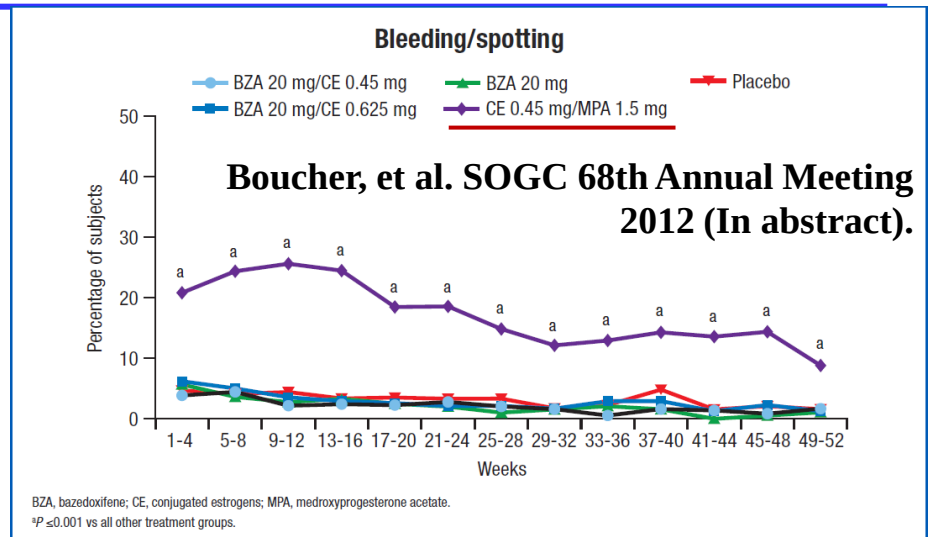


Figure 5. Percentage of subjects reporting bleeding/spotting during 4-week cycles over Year 1.

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.

Weight change
TSEC: SMART-2 & SMART-5

- Mean body weight change in SMART-2: for 12 weeks
  - BZA 20 mg/CE 0.625 mg group: 0.64 kg
  - Placebo group: 1.01 kg
  - **BZA 20 mg/CE 0.45 mg: 0.01 kg → NO significant change**

Pinkerton JV, et al. Menopause 2009.

- Mean body weight change in SMART-5: for 1 year

	CE 0.45/BZA 20	CE 0.625/BZA 20	Any CE/BSA dose	Placebo
Body weight (kg)	0.40 (3.37)	0.31 (3.64)	0.48 (3.95)	0.51 (3.59)

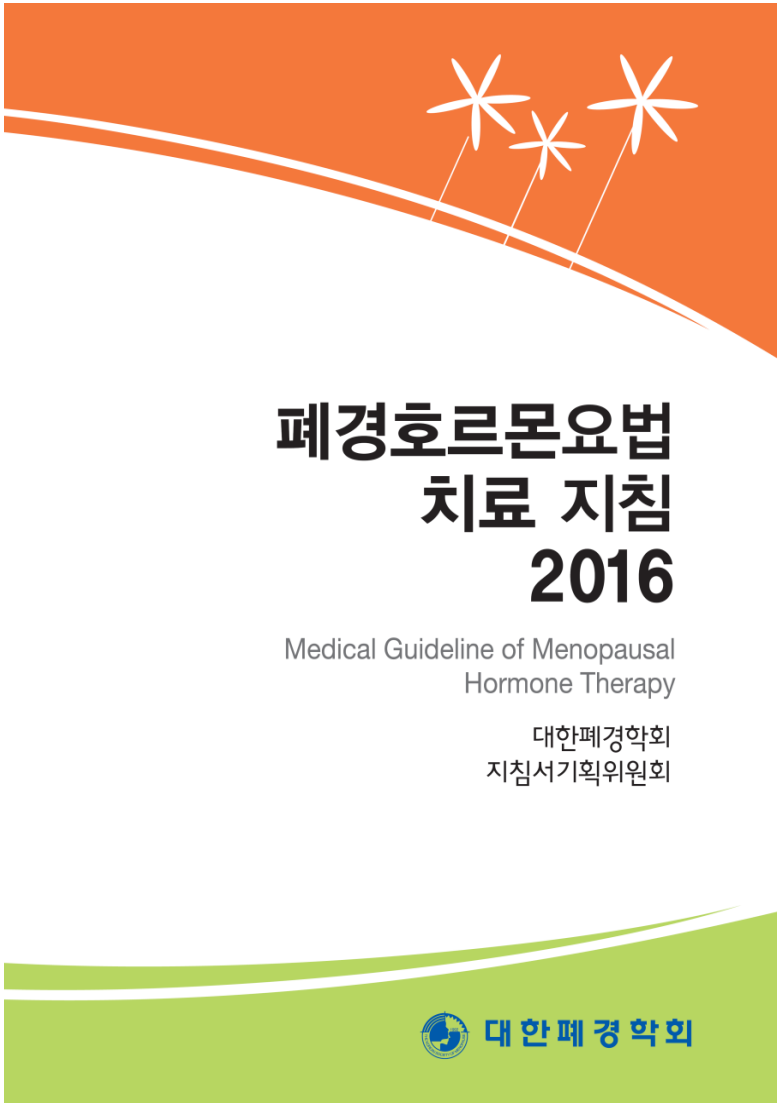
Data are given as mean (SD).

Komm BS, et al. Climacteric 2015.

SUMMARY

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

Clinical guidelines
대한폐경학회 폐경호르몬요법 치료지침



폐경 호르몬요법 치료 지침 2016

➢ 폐경기 증상에 대한 효과

결합형 에스트로겐/바제독시펜(이하 CE/BZA)은 자궁 내막에 대한 자극은 줄이면서 안면홍조, 비뇨생식기 위축 및 수면장애를 개선시켜 삶의질을 유의하게 개선시킨다.

➢ 골다공증

CE/BZA는 요추와 대퇴골의 골밀도를 증가시킨다.

➢ 안정성

CE/BZA는 유방밀도의 증가, 유방통, 질출혈 등의 호르몬치료의 이상반응이 위약과 유사한 수준으로 매우 낮으며 자궁내막에 대한 안전성을 확보하였다. 체중을 증가시키지 않으며 지질대사는 기존의 호르몬제와 유사한 변화를 보인다.

TSEC
Tips on selection of patients

CE/BZA may be considered for women with…

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

   e.g.) nausea, hirsutism, headache, dizziness, weight gain, and cyclical mild depression and mood symptoms
4. **Increased breast density in MMG**
5. **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 option for managing symptoms of estrogen deficiency in non-hysterectomized postmenopausal women
- **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**
- **TSEC** is a ***promising alternative to conventional EPT*** for **whom progestins are inappropriate** or for **whom concerns about safety of HRT, especially breast- related issues**

Thank You For Your Attention !!!

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

Hot flush
Efficacy: compared to other MHTs

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 … ?

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)

CE/BZA vs Others
Uterine/ Endometrial Profile

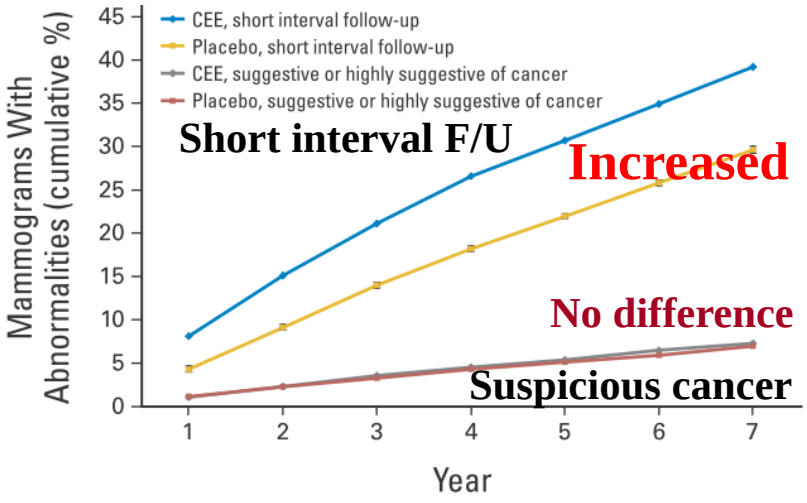
Combination Tested	Type of Study	Uterine Profile	
RLX + E2 (patch or oral)[1,2]	Clinical	Unfavorable	X
RLX + CE[3]	Preclinical	Unfavorable	X
LAS + CE[3]	Preclinical	Unfavorable	X
BZA + CE[3]	Preclinical / Clinical	Favorable	✓

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

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

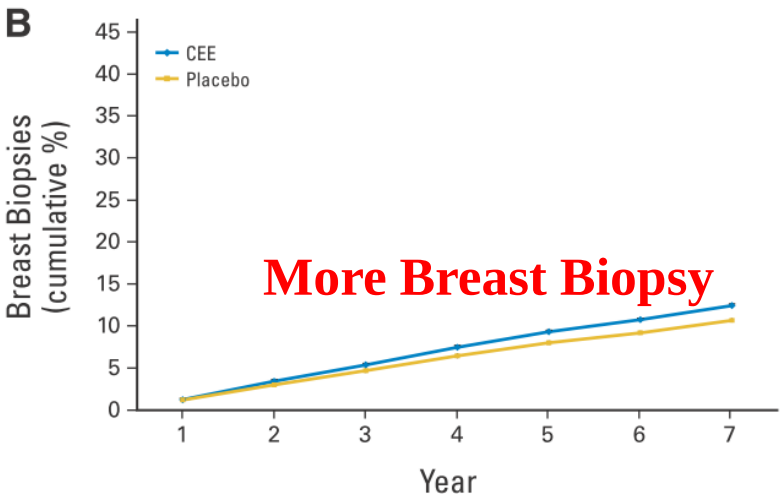
MMG Screening
HRT & Breast Biopsy: WHI-ET

- Abnormal MMG



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

- Breast biopsy

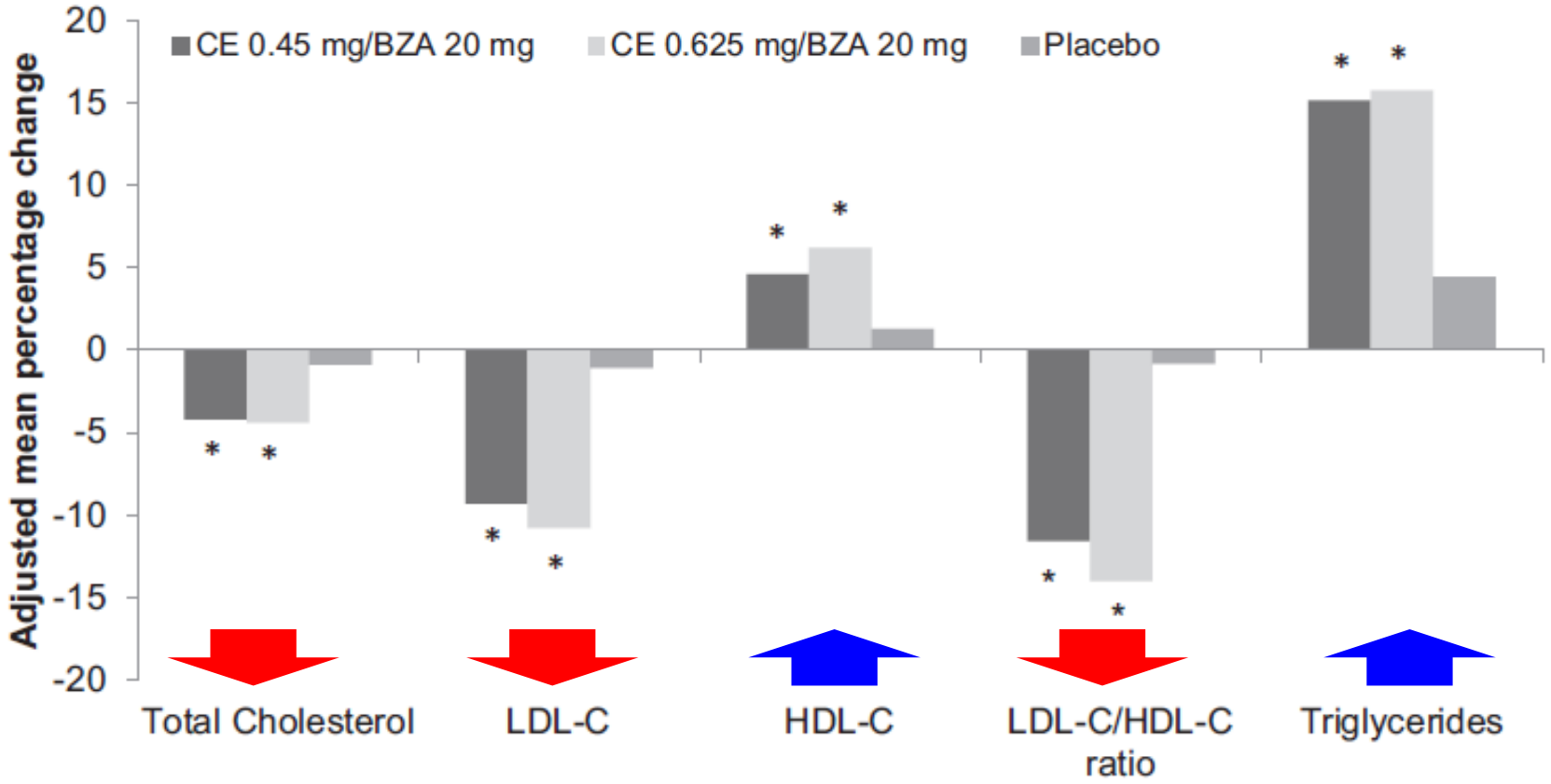


	ET	Placebo	*P* value
Breast biopsies	12.5%	10.7%	0.004
Abnormal results by Bx	8.9%	15.8%	0.04

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

Lipid parameters
TSEC: SMART-1, -4, & -5

- Pooled analysis at 12 months



These results are ***consistent with those at 24 Mos***

인제대학교 해운대백병원

Stevenson JC, et al. J Clin Endocrinol Metab 2015.

Coagulation Parameters
SMART-5

- % change from baseline in coagulation variables on month 12

Variables[a]	CE 0.45 mg/ BZA 20 mg (n = 135)	CE 0.625 mg/ BZA 20 mg (n = 154)	BZA 20 mg (n = 73)	CE 0.45 mg/ MPA 1.5 mg (n = 70)	PBO (n = 158)
Antithrombin	−2.3 (−4.3 to −0.2)[b]	−4.7 (−6.6 to −2.9)[b]	−3.4 (−6.3 to −0.5)[b]	1.8 (−1.2 to 4.8)	3.7 (1.8 to 5.6)
Protein C activity	19.3 (−10.7 to 49.4)	10.8 (−16.4 to 38.1)	−5.1 (−47.6 to 37.4)	5.2 (−38.6 to 49.0)	1.5 (−25.8 to 28.8)
Protein S activity	−9.3 (−15.4 to −3.3)	−8.9 (−14.5 to −3.4)	−5.4 (−14.0 to 3.2)	5.7 (−3.3 to 14.6)	−4.5 (−10.1 to 1.0)
PAI-1 activity	5.3 (−15.0 to 25.6)[b]	3.8 (−14.6 to 22.1)[b]	18.4 (−10.1 to 47.0)[c]	11.5 (−18.2 to 41.3)[d]	70.8 (52.4 to 89.1)
PAI-1 antigen	12.5 (−4.0 to 29.0)	11.1 (−3.8 to 26.1)	16.0 (−7.2 to 39.2)	7.6 (−16.5 to 31.7)	30.7 (15.8 to 45.6)
Fibrinogen	−7.1 (−12.2 to −2.0)[c]	−6.4 (−11.0 to −1.7)[c]	−6.3 (−13.5 to 0.8)[e]	0.5 (−6.9 to 7.9)	3.2 (−1.4 to 7.7)
Plasminogen	4.5 (2.0 to 7.1)[e]	4.5 (2.2 to 6.8)[e]	1.2 (−2.4 to 4.8)	8.9 (5.1 to 12.6)[d]	0.6 (−1.7 to 2.9)
D-dimer	11.7 (−6.7 to 30.1)	38.7 (22.0 to 55.4)[c]	−3.1 (−29.1 to 22.9)	30.1 (2.7 to 57.4)	7.0 (−9.7 to 23.7)
Prothrombin time	0.5 (−1.0 to 2.1)	1.7 (0.3 to 3.1)	0.9 (−1.3 to 3.0)	−0.2 (−2.4 to 2.1)	2.0 (0.6 to 3.4)
PTT	−1.6 (−3.8 to 0.6)[c]	0.5 (−1.5 to 2.5)	0.3 (−2.8 to 3.4)	1.8 (−1.4 to 5.0)	2.3 (0.4 to 4.3)

Both CE/BZA doses were associated with **small but significant effects on hemostasis variables**, including reductions in antithrombin, plasminogen activator inhibitor-1, and fibrinogen activity, and an increase in plasminogen activity relative to placebo at 12 months

Skouby SO, et al. Menopause 2015.

Cardiovascular events
SMART-5

Event, n (%)	BZA 20 mg/ CE 0.45 mg (n = 445)	BZA 20 mg/ CE 0.625 mg (n = 474)	BZA 20 mg (n = 230)	CE 0.45 mg/ MPA 1.5 mg (n = 220)	Placebo (n = 474)
Any AE	407 (91.5)	426 (89.9)	207 (90.0)	197 (89.5)	424 (89.5)
Any TEAE	375 (84.3)	404 (85.2)	194 (84.3)	187 (85.0)	392 (82.7)
Any serious AE	16 (3.6)	17 (3.6)	5 (2.2)	13 (5.9)	18 (3.8)
Discontinuations due to AE[a]	34 (7.6)	33 (7.0)	16 (7.0)	31 (14.1)	33 (7.0)
Deaths	0	0	0	0	1 (0.2)
Most common TEAEs[b]					
Nasopharyngitis[c]	80 (18.0)	58 (12.2)	36 (15.7)	25 (11.4)	51 (10.8)
Back pain	43 (9.7)	58 (12.2)	22 (9.6)	19 (8.6)	49 (10.3)
Pain in extremity	36 (8.1)	40 (8.4)	14 (6.1)	28 (12.7)	40 (8.4)
Headache	59 (13.3)	75 (15.8)	40 (17.4)	42 (19.1)	94 (19.8)
Breast tenderness[d]	15 (3.4)	13 (2.7)	4 (1.7)	24 (10.9)	14 (3.0)
Vaginal hemorrhage[d]	11 (2.5)	5 (1.1)	8 (3.5)	26 (11.8)	14 (3.0)
Selected cardiac disorders[e]	1 (0.2)	1 (0.2)	0	0	2 (0.4)
Venous thromboembolic events	0	0	0	1 (0.5)	0
Selected cerebrovascular AEs	0	1 (0.2)[f]	0	0	0

Overall incidence of AEs, treatment-emergent AEs, and serious AEs was **similar**

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