Low Dose HT-荷爾蒙治療的新趨勢

趙湘台

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97年3月19日上午7時30分

長庚醫院演講

Low Dose HT-荷爾蒙治療的新趨勢

Why Low Dose HT?

Postmenopausal Systemic Hormone Therapy:
Putting Risks Into Perspective

HERS STUDY 1998

WHI STUDY 2002

Postmenopausal Systemic Hormone Therapy: Putting Risks Into Perspective

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長庚醫院演講

Menopause: An Update, 2003

Therapy	*Was*	*Now*
Using estrogen with or without progestin	hormone replacement therapy (HRT)	menopausal hormone therapy (MHT)
Using estrogen alone	estrogen replacement therapy (ERT)	estrogen therapy (ET)
Using estrogen with a progestin	hormone replacement therapy (HRT)	estrogen-progestin therapy (EPT)

Risks and Benefits of Hormones

Terminology

- ET -- Estrogen therapy
- EPT or E+P -- Combined estrogen-progestogen therapy
- HT -- Hormone therapy (encompassing both ET and EPT)
- Progestogen -- Encompassing both progesterone and progestin

Milestones in Hormone Therapy

- 1920s: HT first used
- Mid-1940s: FDA approval of *Premarin* (conjugated equine estrogens)
- Estrogen used for menopause symptoms
- Mid-1970s: Unopposed estrogen use increases endometrial cancer risk
- Concomitant progestogen negates increased endometrial cancer risk

Observational Trial Results

- 1976: Lowers risk of osteoporosis
- 1981: CHD benefit, inconclusive for stroke
- 1988: Reduction in mortality
- 1994: Reduction in Alzheimer's risk
- Accelerated use of hormone therapy

臨床人體實驗
CLINICAL TRIALS

- **Randomized, Blinded, Placebo-controlled:** NHS；HERS；WHI；WHIMS； prospective cohort study
- Meta-analysis

臨床人體實驗
CLINICAL TRIALS

- Postmenopausal Estrogen/Progestin Interventions (PEPI) trial
- Nurses' Health Study (NHS)
- Heart and Estrogen/progentin Replacement Study (HERS) (HERSII) 1998
- Estrogen Replacement and Atherosclerosis (ERA)
- The Women's Health, Osteoporosis, Progestin, Estrogen (Women's HOPE) study 2001
- The National Institutes of Health Women's Health Initiative (WHI) 2002 WHI1 E P 7/02 5.2y
- Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) trial
- Multiple Outcome of Raloxifene Evaluation (MORE) trial
- The National Institutes of Health Women's Health Initiative Memory Study (WHIMS) 2003
- Million Women Study August 2003 The Lancet
- The National Institutes of Health Women's Health Initiative (WHI2) 2004 WHI2 E only, s/p H, 4/04, 6.8y

Heart and Estrogen/progestin Replacement Study (HERS)

- Conducted to determine if older women with heart disease have CVD protection with HT
- Studied postmenopausal women (mean age, 67 years)
- Used EPT for 4.1 years
- Conclusions:
  - Older women with pre-existing disease had increased CVD risk
  - Risk was observed early in treatment

Hulley. *JAMA*. 1998;280:605.

Women's Health Initiative (WHI)

- Conducted to determine if "healthy" women have CHD protection with HT
- Studied women aged 50-79 years
- Used EPT or ET for 5 to 7 years
- Conclusions:
  - No CHD benefit with HT
  - Perceived VTE and breast cancer risks

WHI Writing Group. *JAMA*. 2002;288:321.

Randomized, Blinded, Placebo-controlled Trial Results

- **The Risk of CHD/CVD** (Coronary Heart Disease)
- **The Risk of Stroke**
- **The Risk of Venous Thromboembolism**
- **The Risk of Breast Cancer**
- **The Risk of Osteoporotic Fracture** Hip
- **The Risk of Osteoporotic Fracture** Vertebral

Effect on the Risk of Coronary Heart Disease (CAD)

- WHI Significant increased risk

  RR = 1.29 (CI = 1.02 – 1.63)

  AR = 3.70%% versus 3.00 %%
- HERS Non-significant decreased risk

  RR = 0.99 (CI = 0.84 – 1.17); decreased risk by 1%

  AR = 3.66 %% versus 3.68 %%

Randomized Controlled Trial Results

- 1998: HERS found that HT does not prevent CHD[1]
- Mid-2002: WHI found that HT does not help CHD and may increase CHD and breast cancer risk[2]

1. Hully. *JAMA*. 1998;280:605.
2. WHI Writing Group. *JAMA*. 2002;288:321.

Effect on the Risk of Breast Cancer

- WHI significant increased risk

  RR = 1.26 (CI = 1.00 – 1.59); increased risk by 26%

  AR = 3.80 %% versus 3.00 %%

- HERS Non-significant increased risk

  RR = 1.27 (CI = 0.84 – 1.94); increased risk by 27%

  AR = 5.90 %% versus 4.70 %%

WHI and Breast Cancer Risk

With EPT use

- Relative risk = 1.24 (24% increased risk)
- Absolute risk = 9 more cancers per 10,000 women per year of EPT use

With ET use

- Relative risk = 0.80 (20% decreased risk)
- Absolute risk = 7 fewer cancers per 10,000 women per year of ET use
- 33% statistically significant decreased risk when adherent to treatment (ie, used ET 80% of the time)

ET = CE; EPT = CE + MPA

Stefanick. *JAMA*. 2006;295:1647.

Randomized, Blinded, Placebo-controlled Trial Results

- The Risk of Breast Cancer
- The Risk of CHD/CVD (Coronary Heart Disease)
- The Risk of Stroke
- The Risk of Venous Thromboembolism
- The Risk of Osteoporotic Fracture Hip
- The Risk of Osteoporotic Fracture Vertebral

Osteoporotic Fracture Risk

Observational data

- Relative risk = 0.6 (40% decreased risk)

RCT data (WHI) for both EPT and ET

- Relative risk = 0.60-0.70 (30% to 40% decreased risk)
- Absolute risk of hip fracture = 5-6 fewer fractures per 10,000 women per year of HT use
- Absolute risk of total fracture = 44-56 fewer fractures per 10,000 women per year of HT use

ET = CE; EPT = CE + MPA

Cauley. *JAMA*. 2003;290:1729.

Effect on the Risk of Osteoporotic Fracture Hip

- WHI Significant decreased risk

  RR = 0.66 (CI = 0.45 – 0.98); decreased risk by 34%

  AR = 1.00 %% versus 1.50 %%

- HERS Non-significant increased risk

  RR = 1.61 (CI = 0.98 – 2.66); increased risk by 61%

  AR = 4.80 %% versus 3.00 %%

Effect on the Risk of Osteoporotic Fracture Vertebral

- WHI Significant decreased risk

  RR = 0.66 (CI = 0.44 – 0.98); decreased risk by 34%

  AR = 0.90 %% versus 1.50 %%

- HERS Non-significant decreased risk

  RR = 0.87 (CI = 0.52 – 1.48); decreased risk by 13%

  AR = 3.10 %% versus 3.50 %%

美國婦女健康關懷研究 WHI

WHI 研究女性荷爾蒙與心臟病, 50-79, 1993-1998, 40 centers, 8.5y, randomized

WHI1 E P　　7/02, 5.2y, ↑乳癌

16,608(7,969/7,08)

WHI2 E only, s/p H, 4/04, 6.8y

10,739(4,757/4,839)

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women

JAMA 288:321-333, 2002

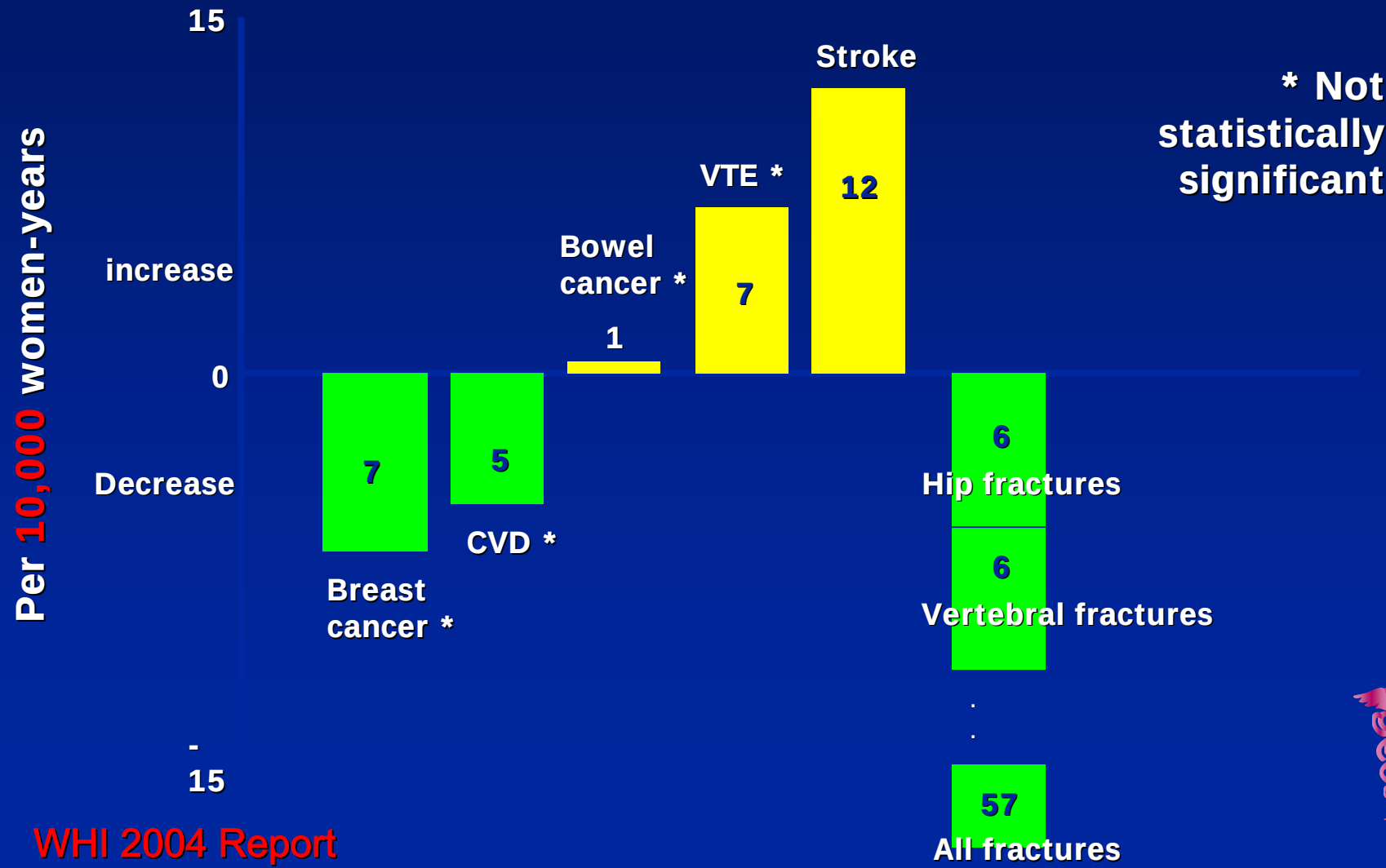
Principal Results From the Women's Health Initiative Randomized Controlled Trial

Effects of Conjugated Equine Estrogen in Postmenopausal Women with Hysterectomy

JAMA 2004;291:1701-1712

The Women's Health Initiative Randomized Controlled Trial

Annual absolute risks and benefits after 7 years of ET



WHI 2004 Report

Hazard Ratios From 3 Hormone Therapy Trials

Clinical Event	HRS E+P	WHI E+P	WHI E
CHD events	0.99	1.29	0.91
Stroke	1.23	1.41	1.39
Pulmonary embolism	2.79	2.13	1.34
Breast cancer	1.30	1.26	0.77
Colon cancer	0.69	0.63	1.08
Hip fracture	1.10	0.66	0.61
Death	1.08	0.98	1.04

WHI Limitations

- Only one estrogen was used (CEE, alone and with MPA)
- Only one route of administration was used (oral)
- Subjects were:
  - Older (mean age, 63 years)
  - Most more than 10 years beyond menopause
  - Had more risk factors than younger women who typically use HT for menopausal symptoms
  - Largely asymptomatic

More Recent WHI Analyses of Younger Women (aged 50-59 years)

- 7% decrease in CHD with ET or EPT
  (2 fewer cases/10,000/year of use)
- 24% increase in breast cancer with EPT
  (9 more cases/10,000/year of use)
- 20% decrease in breast cancer with ET
  (7 fewer cases/10,000/year of use)
- 30% decrease in total mortality with ET or EPT
  (10 fewer deaths/10,000/year of use

ET = CE; EPT = CE + MPA

Rossouw. *JAMA*. 2007;297:1465.

WHI Summary

Effects per 10,000 women/year of ET use (ages 50-59)

- 10 fewer deaths
- 10 fewer CHD events
- 2 fewer strokes

Effects per 10,000 women/year of EPT use (<10 years postmenopause)

- 6 fewer deaths
- 4 fewer CHD events
- 5 more strokes

Rossouw. *JAMA* 2007;297:1465.
ET = CE; EPT = CE + MPA

HT Risks vs Other Drug Risks

Therapy	*Event*	*Cases/10,000 persons/year of use*
Statins (7 studies)[1]	Breast cancer	–10 to +77
EPT[2]	Breast cancer	+9
ET[2]	Breast cancer	–7
Aspirin (in men)[3]	Sudden death	+5
Fenofibrate[1]	Total mortality	+13
HT (aged 50-59)[2]	Total mortality	–10
Raloxifene[1]	Fatal stroke	+20
EPT[2]	PE events	+10
ET[2]	PE events	+4

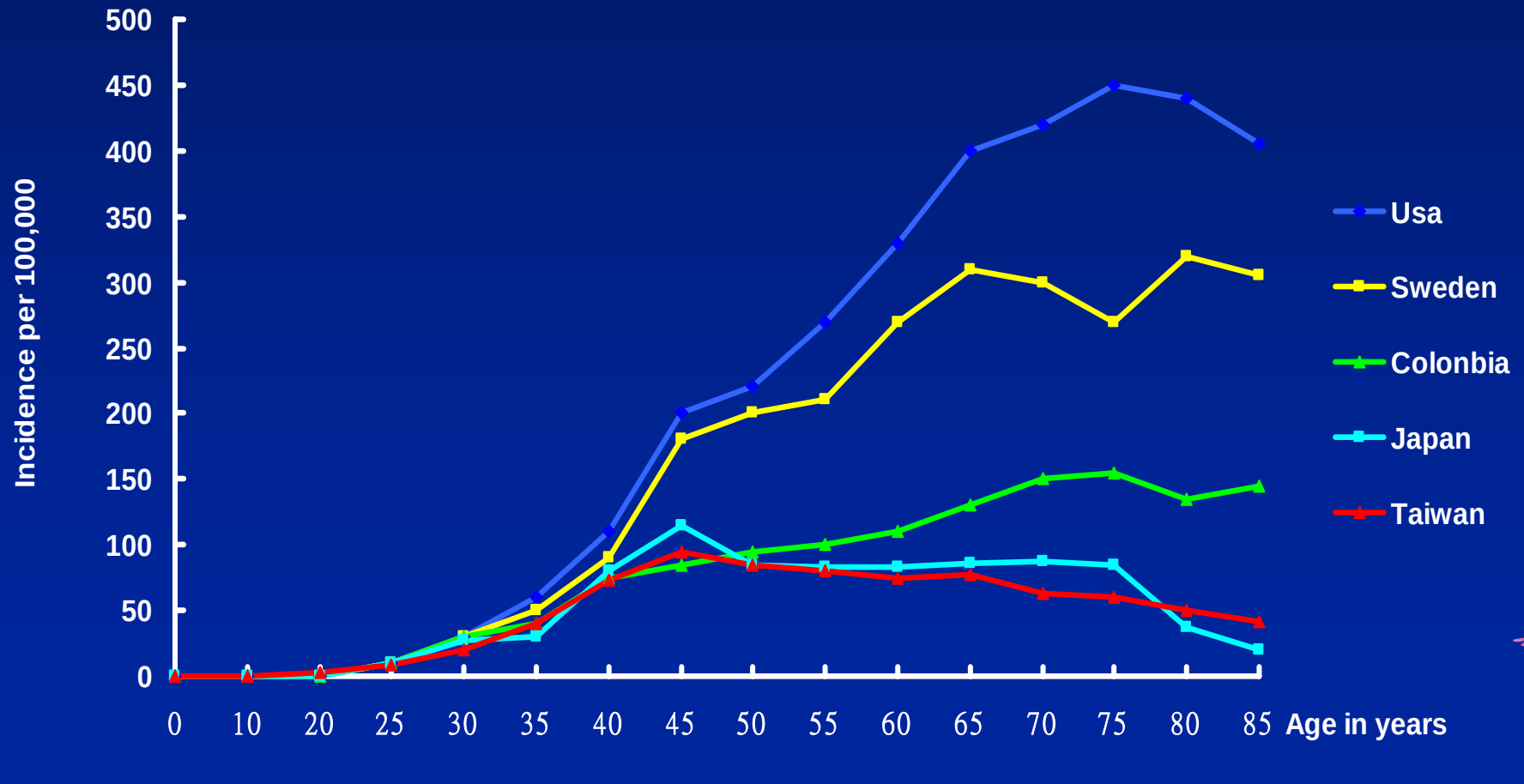
ET = CE; EPT = CE + MPA

1. Hodis. *Menopause*. 2007;14:944.
2. Rossouw. *JAMA*. 2007;297:1465.
3. Physicians' Health Study Writing Group. *N Engl J Med*. 1984;321:129.

Factors associated with an increased risk for breast cancer in women

Relative Risk	Factor
1.1-2.0	Menarche before age 12 years
	Recent and long-term use of postmenopausal HT
	High socioeconomic status
	Nulliparity
	Never having nursed an infant
	First full-term pregnancy after age 30 years
	Alcohol consumption
2.1-4.0	One first-degree relative with breast cancer
	Biopsy-confirmed atypical hyperplasia
	High bone density (postmenopausal)
> 4.0	*BRCA1* and/or *BRCA2* mutations
	Increase mammographic breast density

Breast Cancer Age- Adjusted incidence rate



Summary

- For women suffering severe menopausal symptoms, systemic HT benefits generally outweigh risks.
- It is currently not appropriate to prescribe systemic HT for the sole indication of prevention of heart disease.
- Change continues -- keep an open mind.

Therapeutic Window

Early Postmenopause ??

Change continue-keep an open mind

- **Therapeutic Window**
  Early Postmenopause ??
- **Low dose HT**

HORMONE REPLACEMENT THERAPY REGIMENS

- Standard Dose continuous oral HRT
- Standard Dose cyclic oral HRT
- Low Dose oral HRT
- Transdermal HRT
- Intravaginally HRT

Standard Dosages of Commonly Used Oral Estrogens

- Conjugated estrogens 0.625-1.25mg daily **(premelle 2.5/5 cycle)**
- Ethinyl Estradiol 5-10ug daily
- Piperazine estrone sulfate 1.0 mg daily
- Micronized 17B-estradiol 0.5-2.0 mg daily
- Estradiol valuate **(climen,divina)** 1-2 mg
- Estardiol **(covina,sevina)** 1-2 mg

Standard Dosages of Commonly Used Progestins (Oral)

Medroxyprogesterone	2.5-5.0 mg daily, or 10mg 12-14 days/month
Cyproterone acetate	1 mg (climen)
Micronized progesterone	100-300 mg daily
Norethindrone	5mg daily
Norethindrone acetate NETA	1.25-5 mg daily (servina,covina)
Norgestrel	0.015 mg daily

HORMONE REPLACEMENT THERAPY REGIMENS

- Standard Dose continuous oral HRT
- Standard Dose cyclic oral HRT
- Low Dose oral HRT
- Transdermal HRT
- Intravaginally HRT

Low Dose oral HRT of Commonly Used Oral Estrogens

- Conjugated estrogens 0.3-0.45 mg daily **(premelle lite 0.3/0.45)**
- Ethinyl Estradiol ug daily
- Piperazine estrone sulfate mg daily
- Micronized 17B-estradiol mg daily
- Estradiol valuate **(climen,divina)** 1 mg
- Estardiol **(covina,sevina)** 1 mg

Standard Dosages of Commonly Used Progestins (Oral)

- Medroxyprogesterone 1.25 mg daily (premelle lite 0.3/0.45)
- Cyproterone acetate mg (climen)
- Micronized progesterone mg daily
- Norethindrone mg daily
- Norethindrone acetate NETA 0.5 mg daily (Havina)
- Norgestrel mg daily

Standard Dosages of Commonly Used parenteral Estrogens

- Transdermal estradiol — 0.05-0.10mg patch twice weekly
- Vaginal conjugated estrogens — 0.2-0.625mg, 2-7 times per week
- Vaginal 17B-estradiol — 1.0 mg, 1-3 times per week

Low Dose HT-荷爾蒙治療的新趨勢

趙湘台

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Consensus Builds on Appropriate Use of Low Dose HT

- All HT should be prescribed at the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman[1]

  - ✓**FDA Office of Women's Health[2]**
  - ✓**North American Menopause Society[3]**
  - ✓**American College of Obstetricians and Gynecologists[4]**

Appropriate Use of Estrogen Therapy /Hormone Therapy

- Individualized therapy based on each patient's unique benefit and risk profile
- Estrogens and progestins should be prescribed at the lowest effective doses[1,2]
- Limit use to the shortest duration consistent with treatment goals and patient risks[1,2]
- Do not use for the prevention of cardiovascular disease[1,2]
- Reevaluate periodically[1,2]
- Treatment goals and risks change over time

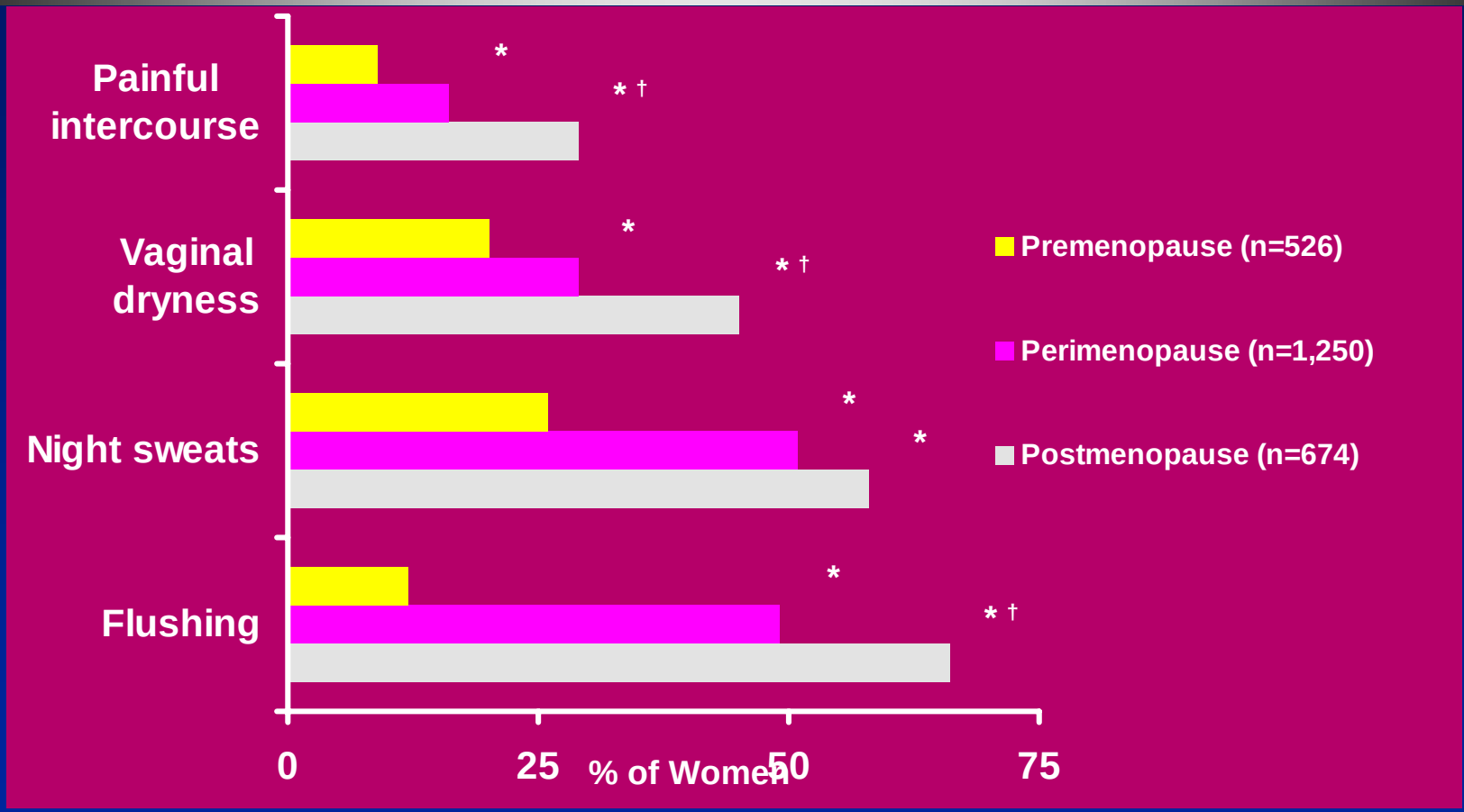
1. Conjugated equine estrogens Core Data Sheet. Wyeth Pharmaceuticals Inc.
2. Conjugated equine estrogens with medroxyprogesterone acetate (MPA) Core Data Sheet. Wyeth Pharmaceuticals Inc.

Criteria for Low Dose HT

- New low dose products should effectively:
  - Relieve vasomotor symptoms
  - Relieve symptoms of vulvar and vaginal atrophy
  - Prevent postmenopausal osteoporosis
  - Protect the endometrium

Menopause: The Journal of The North American Menopause Society 2005 Jul-Aug ; 12(4):399-404. Epub 2005 Jul 21.

Climacteric Complaints Related to Menstrual Status



Cross-sectional survey of 2,450 women. *P<.05 vs. premenopause; †P<.05 vs. perimenopause.

Maartens LW et al. Fam Pract. 2001;18:189-194.

What is the patient's care?

- Adverse events
- Cancer risk
- Long-term effects
- Symptom control

2007 HT Brand Positioning

- Premelle Lite 0.3/1.5 is the 1st choice in the treatment of menopausal symptoms and osteoporosis prevention for post-menopausal women who want amenorrhea.
- Premarin Vaginal Cream is the alternative choice in the treatment of vaginal menopausal symptoms for post-menopausal women

Women's HOPE Study

The Women's Health, Osteoporosis, Progestin, Estrogen (Women's HOPE) study

James H. Pickar, MD, FACOG
Assistant Vice President, Clinical Research & Development and Director, Menopause Research Program
Wyeth Research, Collegeville, PA, USA

Women's HOPE Study Objectives

To evaluate the safety and efficacy of lower doses of CE with and without MPA

- Primary
  - Incidence of endometrial hyperplasia at year 1
- Secondary
  - Menopausal vasomotor symptom relief
  - Vaginal Maturation Index changes
- Substudy
  - Prevention of postmenopausal osteoporosis

Source: Utian WH et al. Fertil Steril. 2001;75:1065-1079.

Women's HOPE Study Design and Population

- Methodology
  - 8-arm, double-blind, randomized, placebo-/active-drug-controlled, multicenter trial of various combinations of CE and MPA
- Inclusion criteria
  - Generally healthy, 40-65 years of age, intact uterus, within 20% ideal body weight
  - Postmenopausal (no menses within last year; FSH $\geq$30 IU/L; 17β-estradiol $\leq$50 pg/mL)
  - 8-week prestudy washout period for prior estrogen, progestin, or androgen therapy (12 weeks for BMD substudy)

Source: Utian WH et al. Fertil Steril. 2001;75:1065-1079.

Women's HOPE Study Design and Population (Cont'd)

- Exclusion criteria
  - Known hypersensitivity to estrogens or progestins
  - Hormonal therapy within the last 8 weeks (12 weeks for BMD substudy)
  - Use of concomitant drugs that affect vasomotor symptoms
- Patient evaluation
  - Physical exam
  - Endometrial biopsy
  - Papanicolaou smear with Vaginal Maturation Index
  - Laboratory safety screening
  - Mammogram
  - Daily diary

Source: Utian WH et al. Fertil Steril. 2001;75:1065-1079.

Women's HOPE Study Treatment Groups

Control
- Placebo

CE (mg/d)
- 0.625
- 0.45
- 0.3

CE/MPA (mg/d)
- 0.625/2.5
- 0.45/2.5
- 0.45/1.5
- 0.3/1.5

A double-blind, double-dummy design was used to administer study medication.
All groups received a calcium carbonate supplement (600 mg elemental calcium/d).

Source: Utian WH et al. Fertil Steril. 2001;75:1065-1079.

Women's HOPE Study Demographic Characteristics

	Total (N=2,673) Mean ± SD
Age (yr)	53.3 ± 4.9
Age at menopause (yr)	48.5 ± 4.3
Years since menopause	4.7 ± 4.2
Weight (kg)	65.5 ± 8.7
BMI (kg/m^2)	24.4 ± 2.8

No significant differences between treatment groups were observed for age, age at menopause, years since menopause, height, weight, BMI, parity, or ethnicity (*P*>.05).

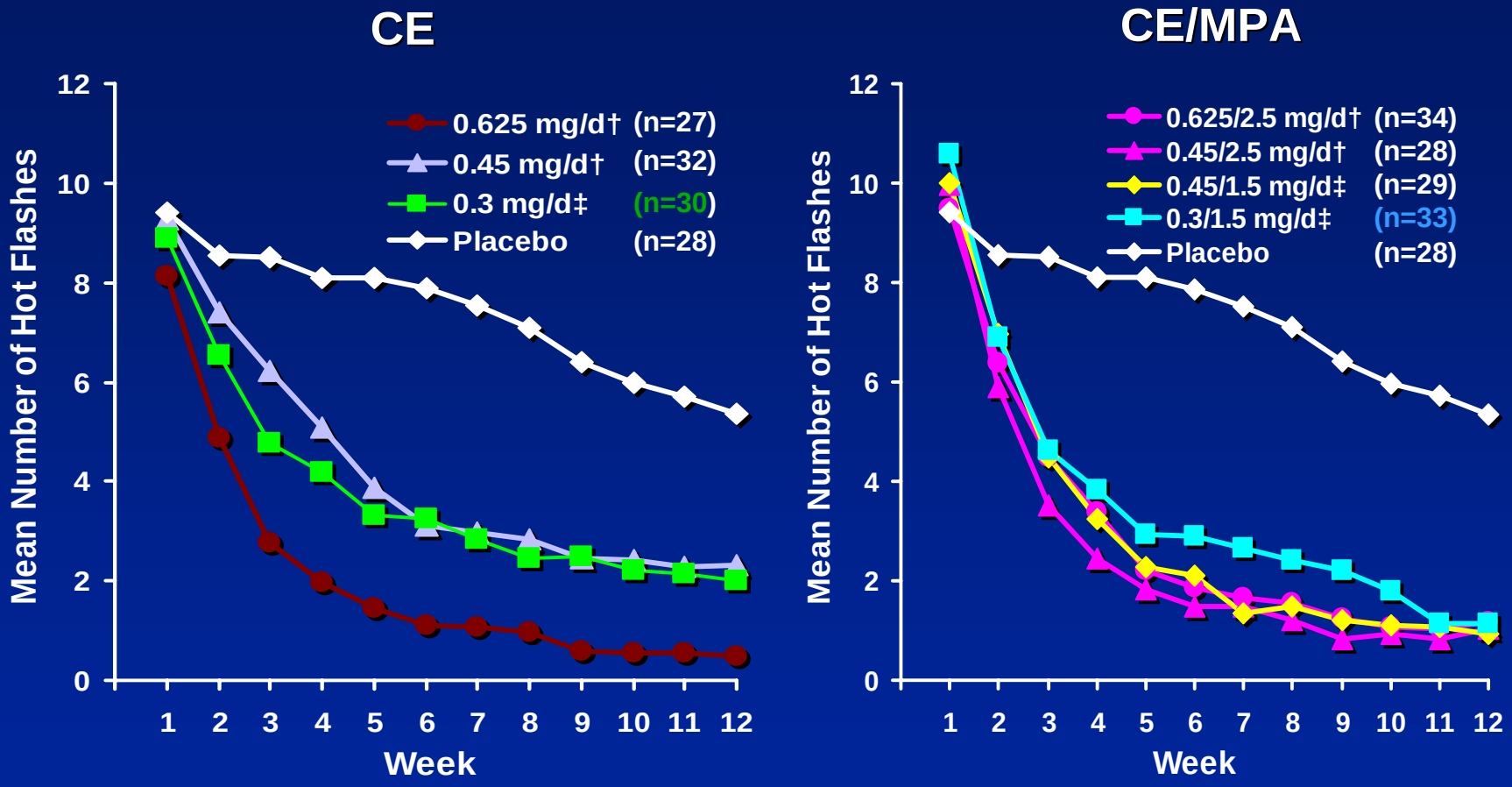
Ethnic distribution: 88% Caucasian, 6% African American, 5% Hispanic, <1% Asian, <1% Native American, and <1% Arabic.

Source: Utian WH et al. Fertil Steril. 2001;75:1065-1079.

Women's HOPE Study

Vasomotor Symptoms Associated with Menopause and Women's HOPE Study Results

Women's HOPE Study
Frequency of Hot Flashes*



Data are adjusted for baseline.

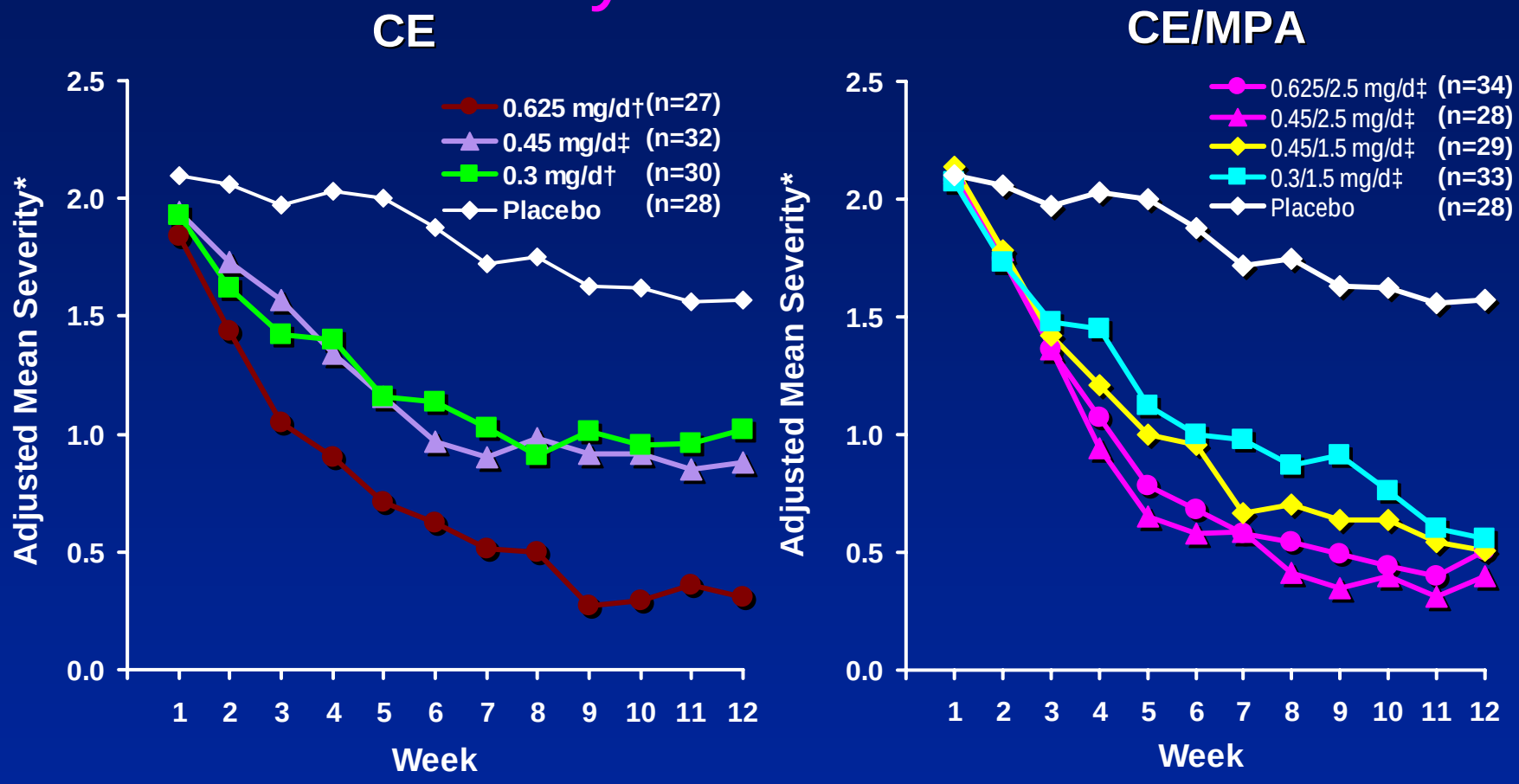
*Efficacy of evaluable population.

†Difference from placebo was significant ($P<.05$) from weeks 2-12.

‡Difference from placebo was significant ($P<.05$) from weeks 3-12.

Source: Utian WH et al. Fertil Steril. 2001;75:1065-1079.

Women's HOPE Study
Severity of Hot Flashes*



Data are adjusted for baseline. Hot flush severity: 1 = mild, 2 = moderate, 3 = severe.

*Efficacy of evaluable population.

†Difference from placebo was significant ($P<.05$) from weeks 2-12.

‡Difference from placebo was significant ($P<.05$) from weeks 3-12.

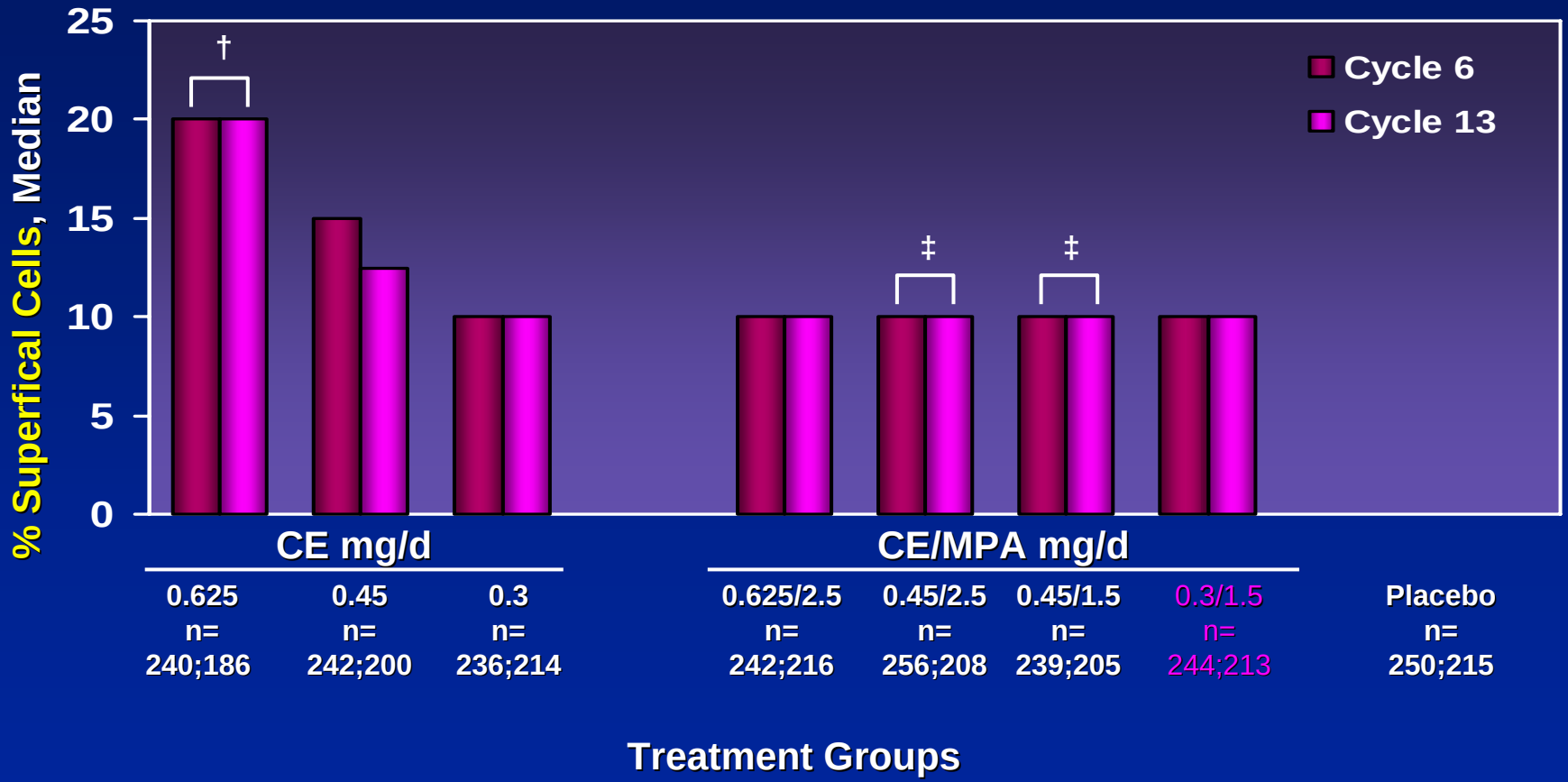
Source: Utian WH et al. Fertil Steril. 2001;75:1065-107.

Women's HOPE Study Vasomotor Summary

- The frequency and severity of vasomotor symptoms were significantly reduced by the end of week 2 for all active treatments compared to placebo
- CE/MPA 0.45 mg/1.5 mg obtained vasomotor symptom relief comparable to that seen with CE 0.625 mg/MPA 2.5 mg
- Both low doses of CE alone (0.45 mg and 0.3 mg) significantly reduced vasomotor symptoms compared to placebo

Source: Utian WH et al. Fertil Steril. 2001;75:1065-1079.

Women's HOPE Study
Vaginal Maturation Index (VMI): Change from Baseline*



*P <.05 vs. baseline and placebo for all treatment groups
†P <.05 vs. CE 0.45, 0.3, CE/MPA 0.625/2.5
‡P <.05 vs. CE/MPA 0.3/1.5

Source: Utian WH et al. Fertil Steril. 2001;75:1065-1079.
Data on file: Wyeth Pharmaceuticals Inc.

Women's HOPE Study
VMI* Summary

All CE and CE/MPA regimens, including lower doses, significantly improved the Vaginal Maturation Index (VMI), a marker for vaginal estrogenization.

***VMI reported as proportion of vaginal superficial cells relative to the number of parabasal and intermediate cells in a lateral vaginal wall smear.**

Source: Utian WH et al. Fertil Steril. 2001;75:1065-1079.

Women's HOPE Study

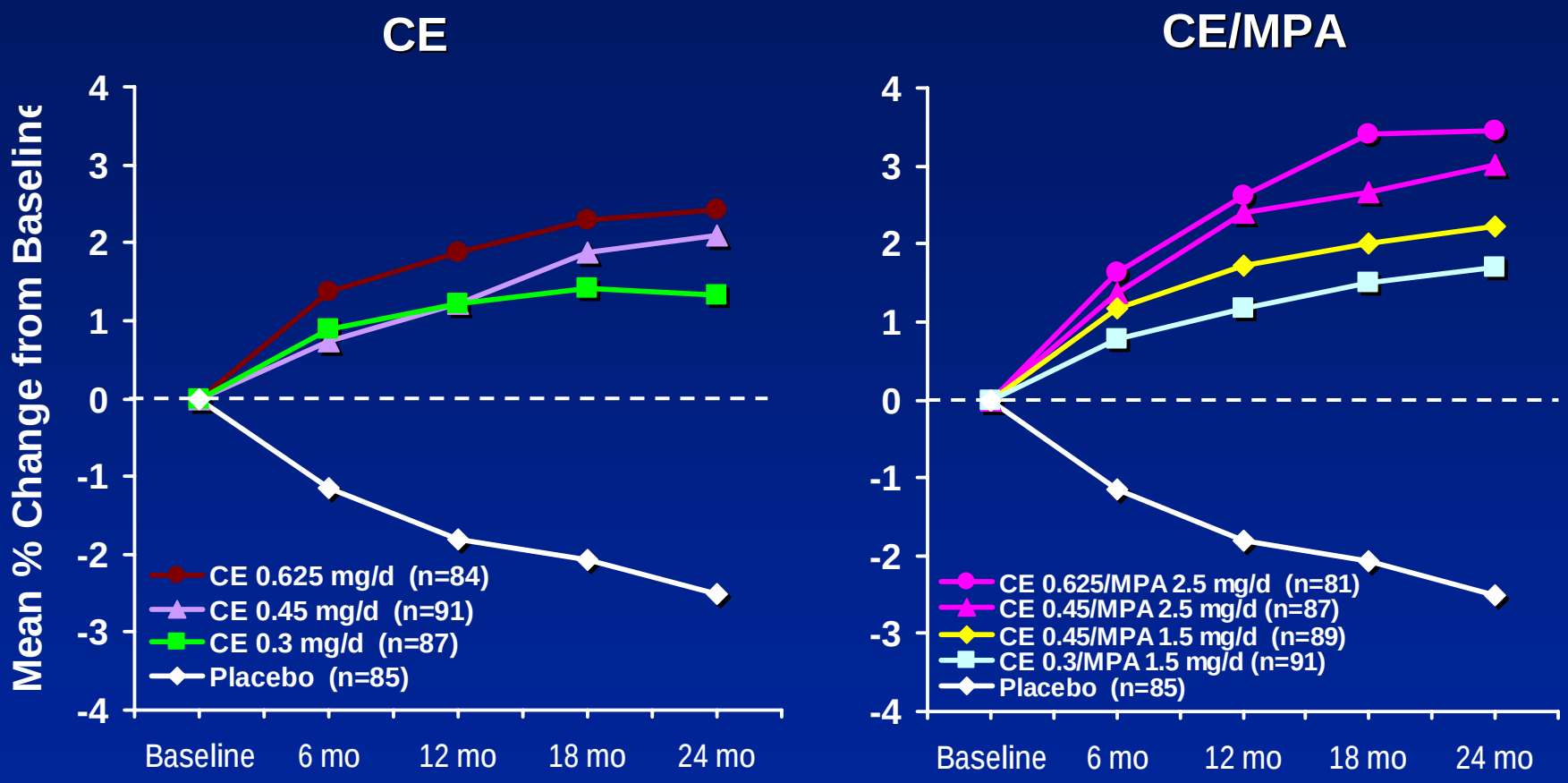
Prevention of Postmenopausal Osteoporosis

Women's HOPE Study
Bone Mineral Density (BMD) Study Design

- Utilizes a subpopulation of the Women's HOPE Study to evaluate the effects of various doses of CE alone and CE/MPA on the skeleton
- Demographically similar to the Women's HOPE Study overall population, but within 4 years of menopause
- Analysis includes 695 postmenopausal women in the Women's HOPE Study at sites with expertise in Dual Energy X-Ray Absorptiometry

Source: Lindsay R et al. JAMA. 2002;287:2668-2676.

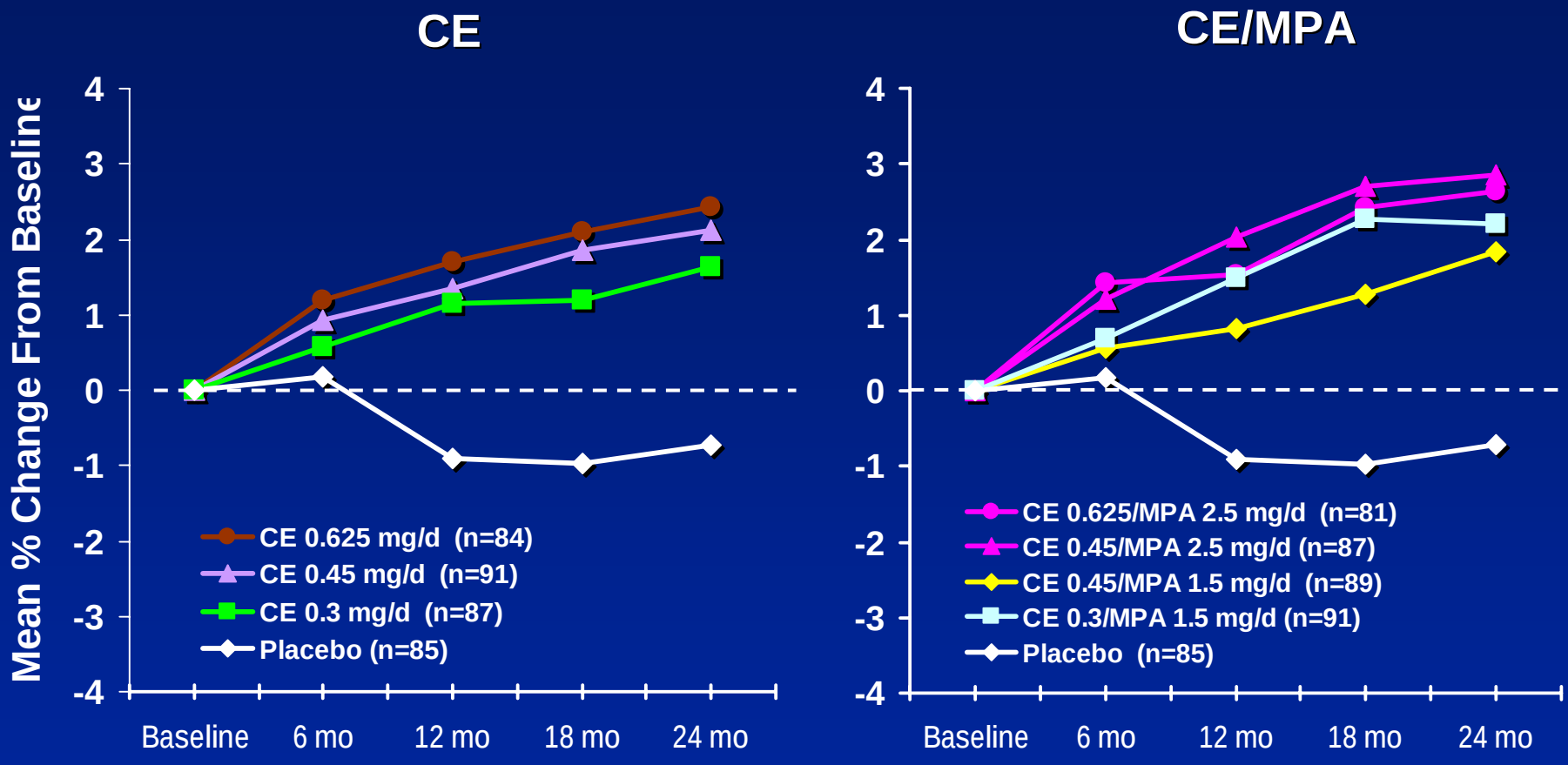
Women's HOPE Study: Spine BMD*



*** Modified intent-to-treat population**
Changes were statistically different (*P*<.05) from baseline and placebo for all active treatment groups at all time points.

Source: Lindsay R et al. JAMA. 2002;287:2668-2676.

Women's HOPE Study: Total Hip BMD*



*** Modified intent-to-treat population**
Changes were statistically different (*P*<.05) from baseline for all active treatment groups at all time points.
Changes were statistically different (*P*<.05) from placebo for all active treatment groups by 1 year.

Source: Lindsay R et al. JAMA. 2002;287:2668-2676.

Women's HOPE Study: Osteoporosis Summary

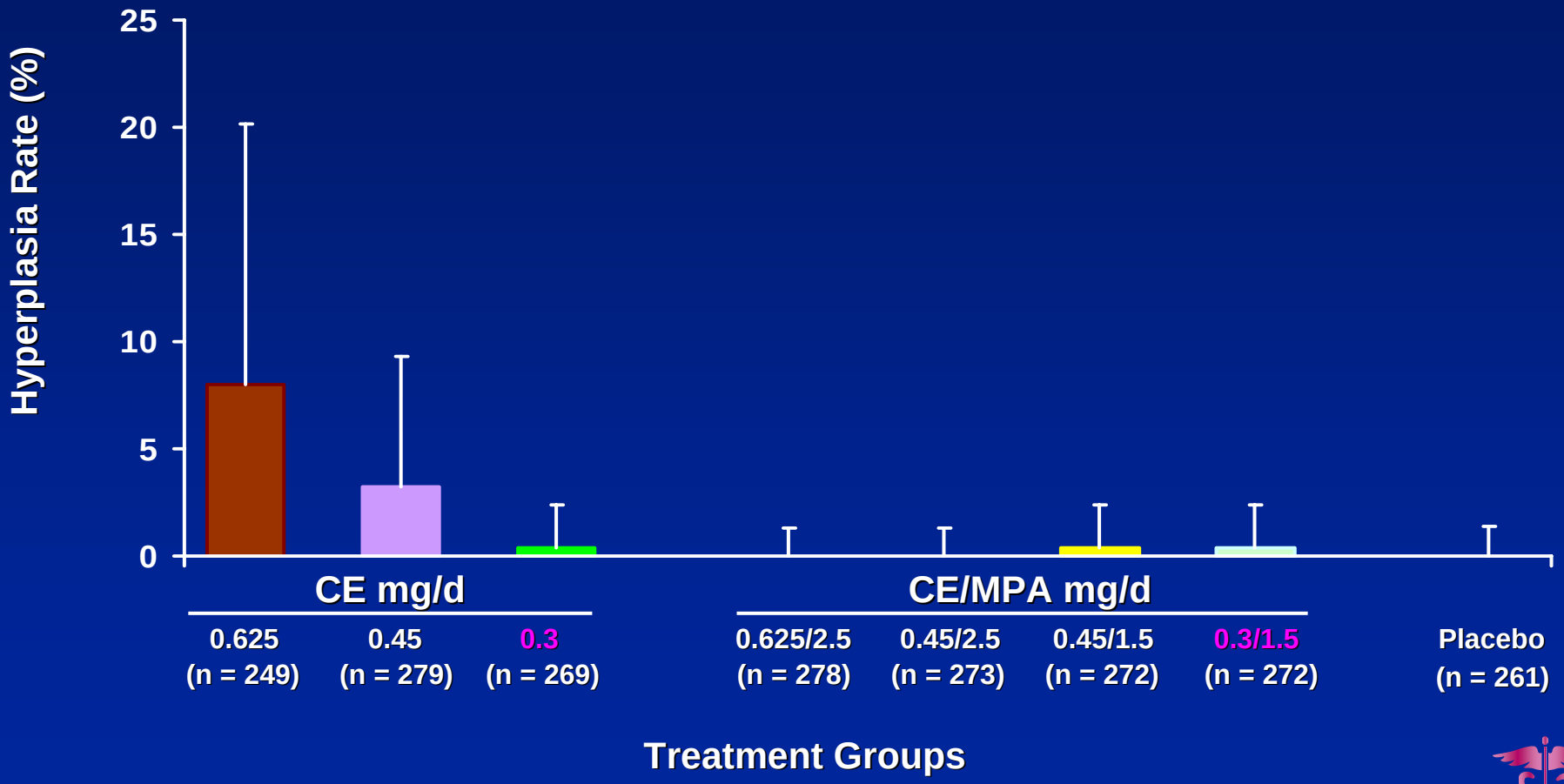
- All doses of CE and CE/MPA demonstrated a statistically significant improvement in BMD relative to placebo and baseline at 24 months
- Lower doses of CE or CE/MPA effectively reduce bone loss in early postmenopausal women

Source: Lindsay R et al. JAMA. 2002;287:2668-2676.

Low Dose HT-荷爾蒙治療的新趨勢

Safety and Tolerability of Low Dose Hormone Therapy

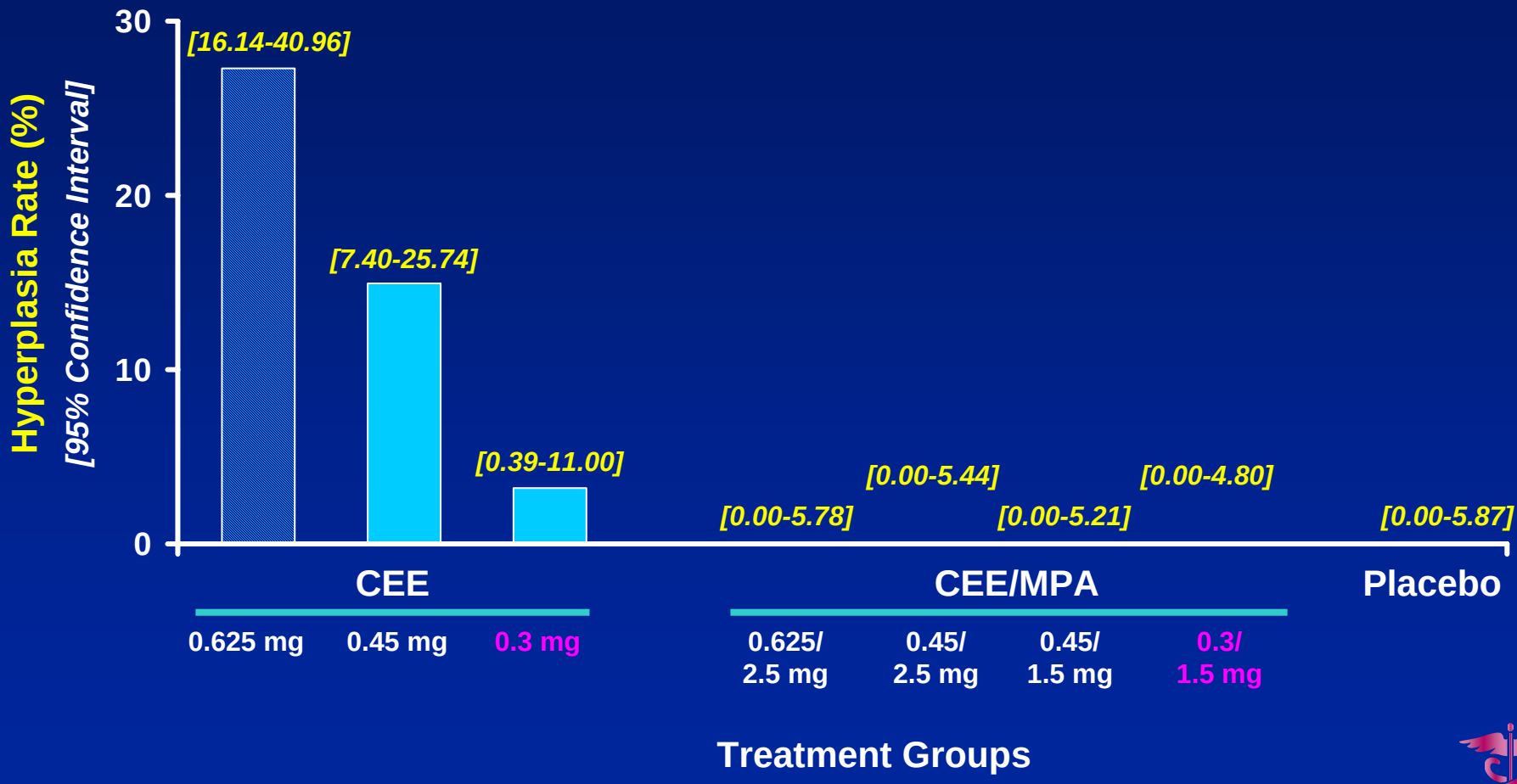
Women's HOPE Study
Endometrial Hyperplasia Rates (1 Year)



Source: Pickar JH et al. Fertil Steril. 2001;76:25-31.

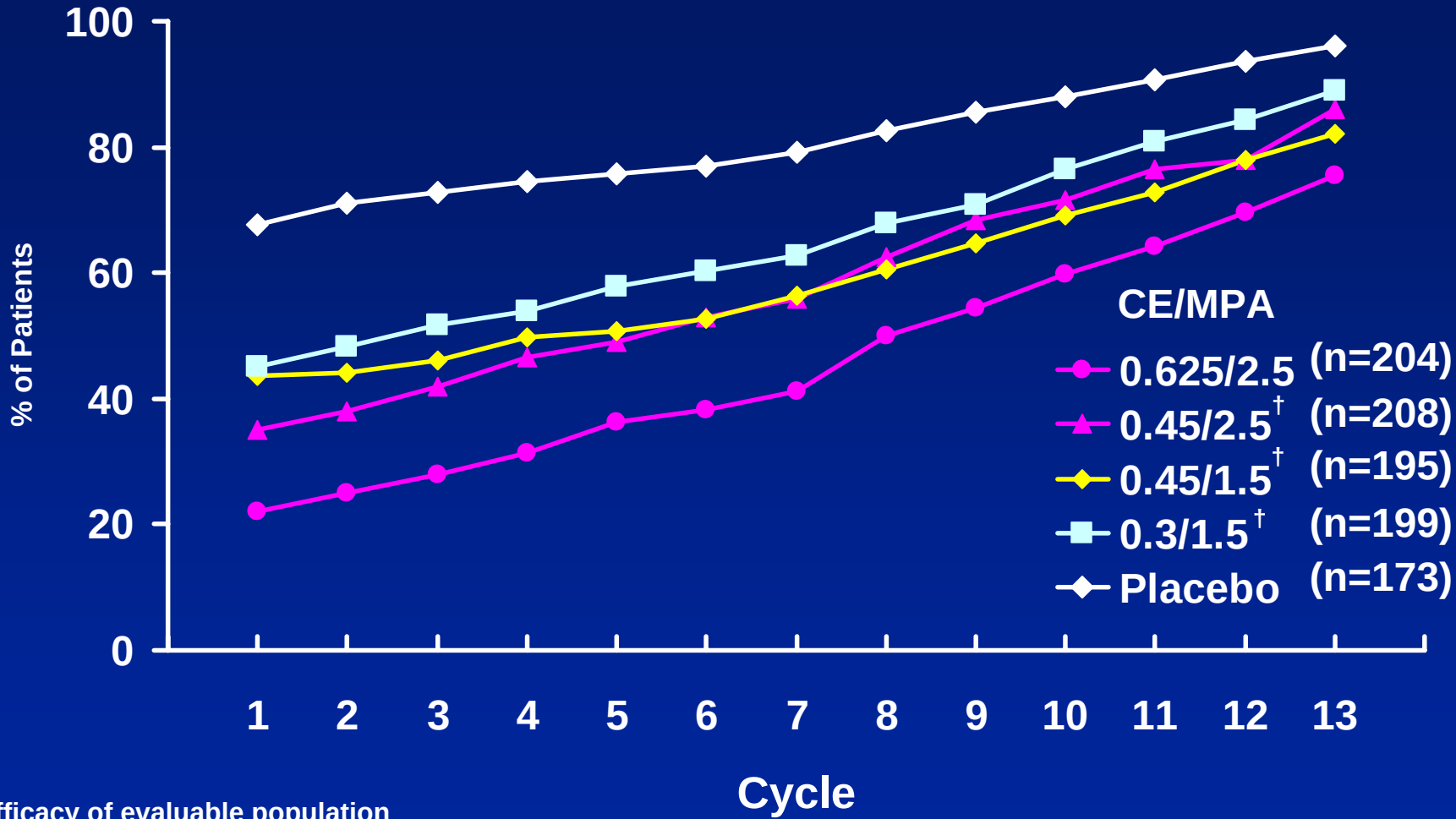
Women's HOPE Substudy

Hyperplasia Rates at Year 2: Consensus of 2 Pathologists (n = 518*)



*An evaluable patient for consensus hyperplasia at cycle 26 had a prestudy endometrial biopsy, had taken at least 1 dose of study medication, and had a biopsy performed during cycles 25 to 27, or had a diagnosis of hyperplasia by that pathologist at any time during the 2-year study.

Women's HOPE Study
Cumulative Amenorrhea Rates*: CE/MPA



Efficacy of evaluable population

*Amenorrhea defined as absence of any vaginal bleeding; Cumulative rates of amenorrhea were defined as the proportion of women who experienced consecutive cycles of amenorrhea for a given period of time.

†*P* <.05 vs 0.625/2.5 for cycles 1-13, 7-13, and 13.

Source: Archer DF et al. Fertil Steril. 2001;75:1080-1087.

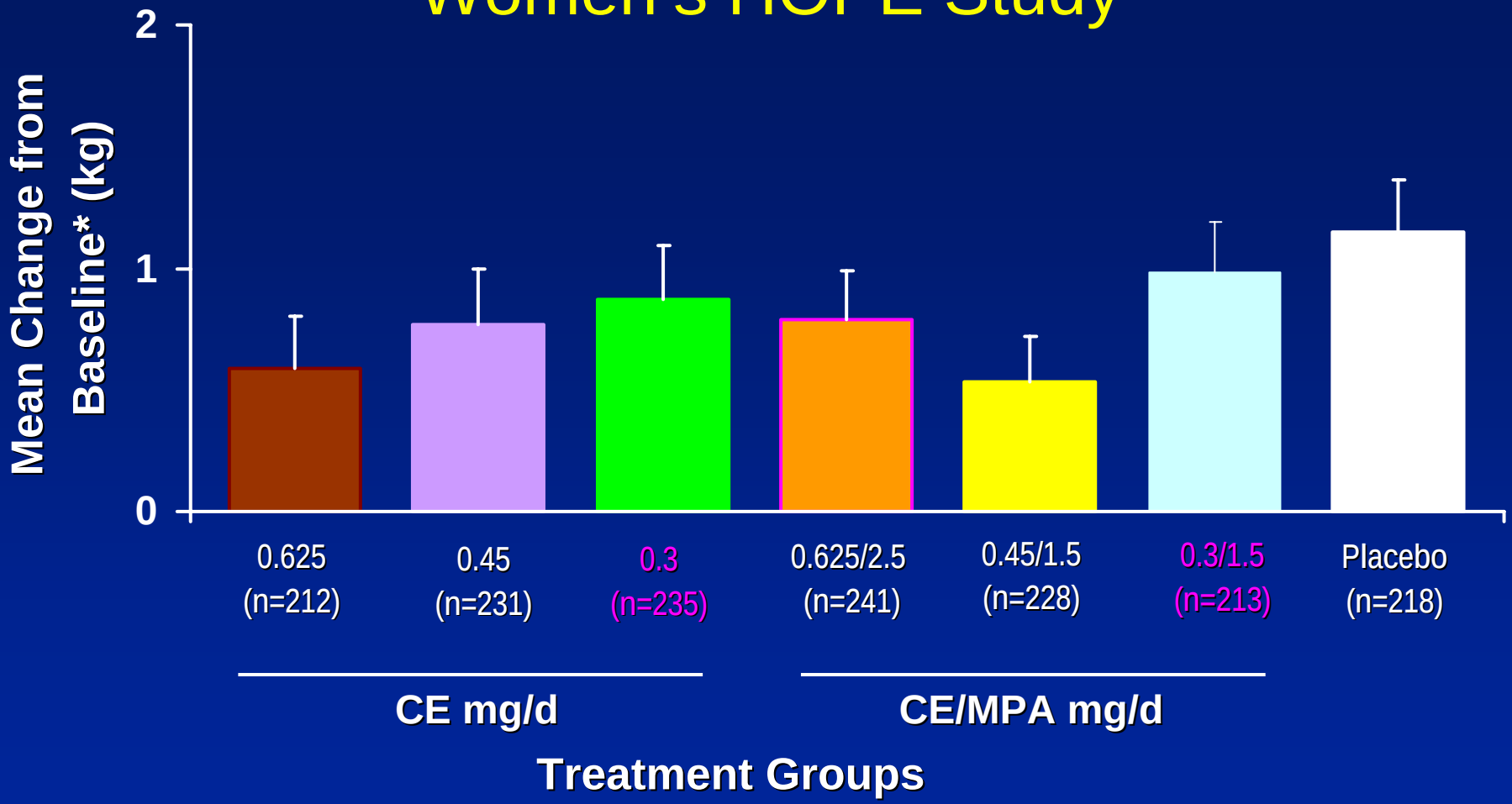
Women's HOPE Study

Most Commonly Reported Adverse Events (≥5%) That Were Greater Than Placebo

- **CE/MPA 0.45 mg/1.5 mg and CE/MPA 0.625 mg/2.5 mg:**
  - **Mastalgia**
  - **Vaginal bleeding**
  - **Vaginal moniliasis**
  - **Vaginitis**
  - **Leg cramps**
  - **Dysmenorrhea**
  - **Breast enlargement**
- **CE/MPA 0.3 mg/1.5 mg**
  - **No difference compared to placebo**

Source: Data on File, Wyeth Pharmaceuticals Inc.

Mean Change in Weight After 13 Cycles
Women's HOPE Study



*Significant increase from baseline for all treatment groups, including placebo.

Source: Utian WH et al. Obstet Gynecol. 2002;99:57S.
Data on file, Wyeth Pharmaceuticals Inc.

Women's HOPE Study
Safety and Tolerability Summary

- Lower doses of CE and MPA produced higher rates of amenorrhea compared to 0.625 CE/2.5 MPA, especially during earlier cycles of therapy
- Improved amenorrhea rates with lower doses of HT may aid in counseling when initiating therapy and reduce discontinuations due to bleeding
- All regimens of CE and MPA resulted in **<1% incidence** of endometrial hyperplasia
- Lower dose regimens of CE and MPA provide endometrial safety comparable to conventional dose therapy
- In a clinical trial, the most commonly reported adverse events (≥5%) that were significantly different from placebo for 0.45 CE/1.5 MPA and 0.625 CE/2.5 MPA were **mastalgia, vaginal bleeding, vaginal moniliasis, leg cramps, dysmenorrhea, breast enlargement, and vaginitis**

Differential prevalence of quality-of-life categories (domains) in Asian women and changes after therapy with three doses of conjugated estrogens/medroxyprogesterone acetate: the Pan-Asia Menopause (PAM) study

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Key words: MENOPAUSE, PAN-ASIA MENOPAUSE STUDY, PAM STUDY, ASIAN WOMEN, HORMONE THERAPY, QUALITY OF LIFE, MENQOL

ABSTRACT

Objectives To assess the prevalence of four categories (domains) of menopausal symptoms as markers for quality of life in nine ethnic groups of Asian women. To evaluate changes in quality of life (MENQOL scores) in Asian women following hormone therapy.

Methods A prospective, randomized, double-blind, multinational clinical trial in 1028 healthy postmenopausal women of nine ethnic groups from 11 Asian countries/regions. Following 2 weeks of baseline observation, the women received one of three conjugated estrogens (CE)/medroxyprogesterone acetate (MPA) doses (in mg) daily for 24 weeks: 0.625/2.5, 0.45/1.5, or 0.3/1.5. At baseline and at the end of weeks 4, 12 and 24 following the start of therapy, the study participants were asked to record, on a menopause-specific quality of life (MENQOL) questionnaire, 29 menopausal symptoms, as experienced during the preceding month. The symptoms were categorized into four domains: vasomotor, psychosocial, physical and sexual.

Results The baseline (pretreatment) symptom scores in each of the four domains varied substantially among the different ethnic groups, ranging from 2.21 to 5.71 in the vasomotor, 2.37–5.96 in the psychosocial, 2.66–5.39 in the physical, and 2.11–6.55 in the sexual domain. Overall, Vietnamese and Pakistani women had the highest baseline scores, i.e. were most afflicted by each set of symptoms in a given domain, and Indonesian, Malay, Taiwanese and Thai women were least afflicted. In the overall population,

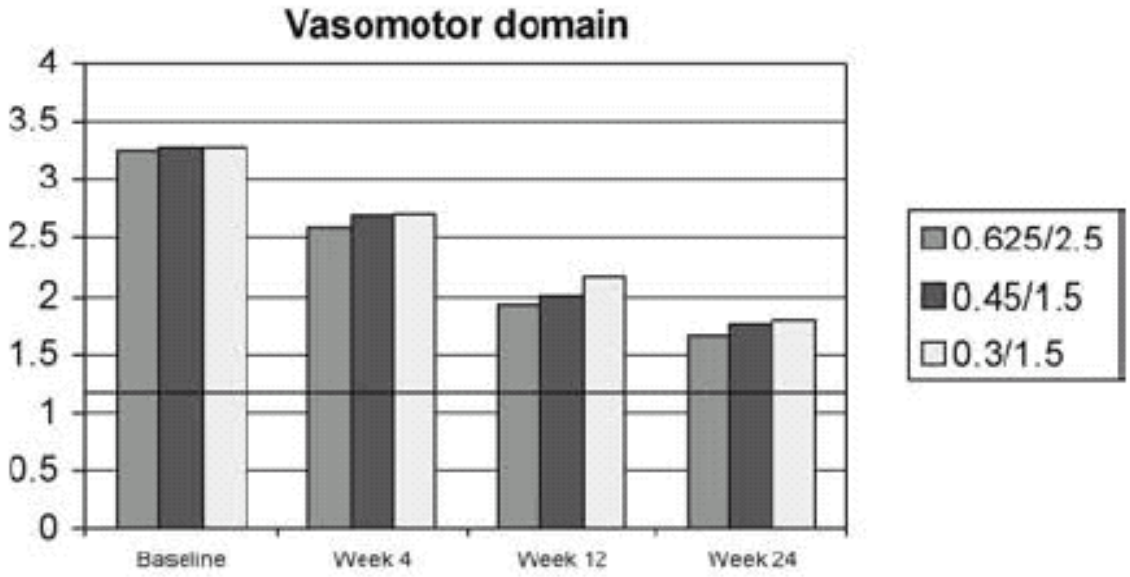
Table 1 Baseline characteristics of women in the PAM study. Data are given as mean ± standard deviation or as number (%)

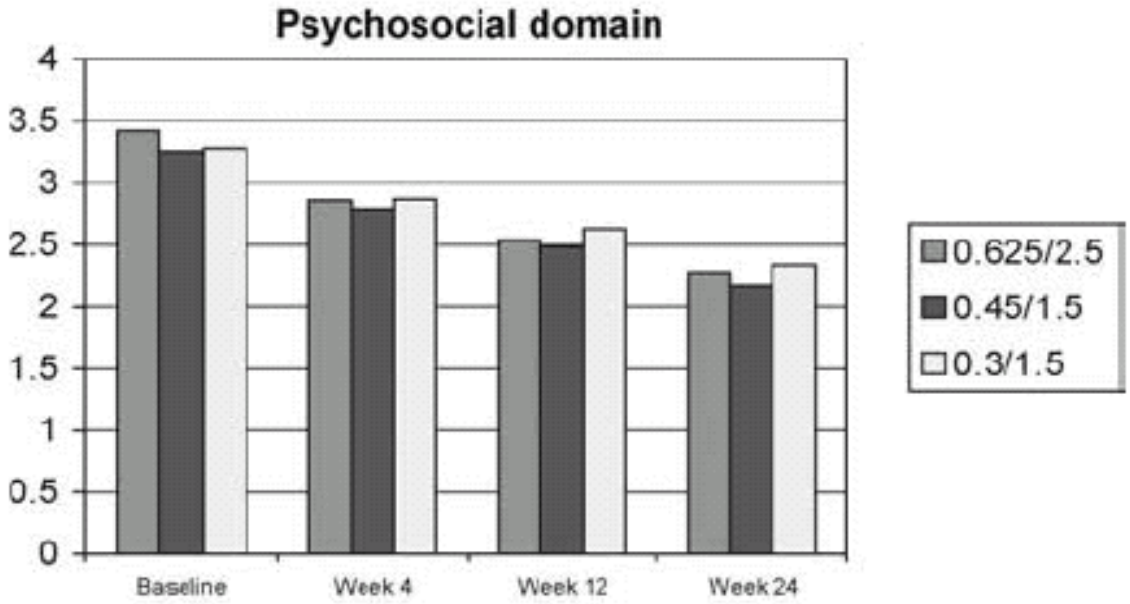
	CE/MPA (daily dose, mg)			
Characteristic	*0.625/2.5* ($n=344$)	*0.45/1.5* ($n=342$)	*0.3/1.5* ($n=342$)	*Total* ($n=1028$)
Age (years)	53.9 ± 5.3	53.1 ± 4.9	53.3 ± 4.7	53.5 ± 5.0
Age distribution (years)				
≤45	18 (5.2)	23 (6.7)	18 (5.3)	59 (5.7)
46–50	75 (21.8)	75 (21.9)	79 (23.1)	229 (22.3)
51–55	128 (37.2)	137 (40.1)	146 (42.7)	411 (40.0)
56–60	80 (23.3)	80 (23.4)	71 (20.8)	231 (22.5)
61–65	43 (12.5)	27 (7.9)	28 (8.2)	98 (9.5)
>65	0	0	0	0
Height (cm)	155.3 ± 5.6	155.1 ± 5.7	155.3 ± 6.0	155.3 ± 5.7
Weight (kg)	57.8 ± 9.1	56.2 ± 8.0	56.8 ± 8.5	57.0 ± 8.6
Body mass index (kg/m^2)	24.0 ± 3.6	23.4 ± 3.2	23.6 ± 3.4	23.6 ± 3.4
Previous pregnancy				
Yes	316 (91.9)	320 (93.6)	319 (93.3)	955 (92.9)
No	28 (8.1)	22 (6.4)	23 (6.7)	73 (7.1)
Number of pregnancies	4.0 ± 2.1	4.0 ± 2.2	4.0 ± 2.4	4.0 ± 2.2
Type of menopause				
Natural	343 (100.0)	340 (99.4)	336 (98.8)	1019 (99.4)
Surgical	0	2 (0.6)	4 (1.2)	6 (0.6)

CE, conjugated estrogen; MPA, medroxyprogesterone acetate

Table 2 Baseline domain scores by ethnic group. Data are given as mean ± standard deviation

		MENQOL domain			
Ethnic origin	*Number of women*	*Vasomotor*	*Psychosocial*	*Physical*	*Sexual*
Chinese	249	3.13 ± 1.67	2.84 ± 1.37	3.21 ± 1.15	4.04 ± 2.20
Filipino	199	3.17 ± 1.60	3.33 ± 1.41	3.20 ± 1.23	3.03 ± 2.03
Indonesian	60	2.28 ± 0.87	2.40 ± 0.68	2.66 ± 0.63	2.63 ± 1.18
Korean	97	2.21 ± 1.40	3.06 ± 1.46	3.29 ± 1.24	3.55 ± 2.29
Malay	24	3.02 ± 1.56	2.78 ± 1.11	2.93 ± 1.08	3.14 ± 1.78
Pakistani	60	4.96 ± 2.41	4.24 ± 1.64	4.84 ± 1.61	2.90 ± 1.70
Taiwanese	81	2.29 ± 1.39	2.37 ± 1.32	2.84 ± 1.23	2.11 ± 1.32
Thai	150	2.87 ± 1.61	3.10 ± 1.22	3.28 ± 1.08	2.89 ± 1.90
Vietnamese	100	5.71 ± 1.59	5.96 ± 1.48	5.39 ± 1.20	6.55 ± 1.67


Vasomotor domain
4
3.5
3
2.5
2
1.5
1
0.5
0
Baseline
Week 4
Week 12
Week 24
0.625/2.5
0.45/1.5
0.3/1.5


Psychosocial domain
4
3.5
3
2.5
2
1.5
1
0.5
0
Baseline
Week 4
Week 12
Week 24
0.625/2.5
0.45/1.5
0.3/1.5

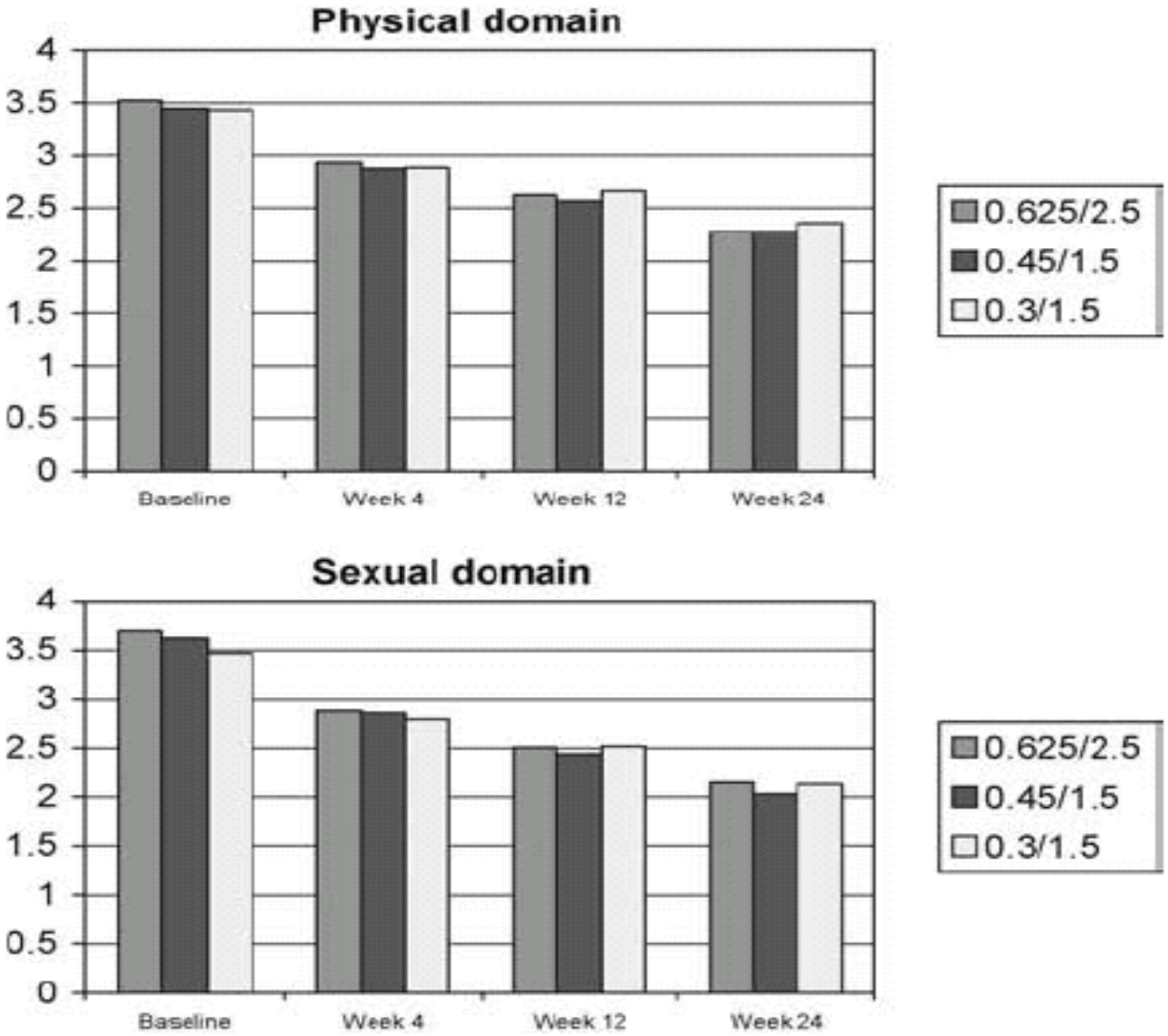


Figure 1 Changes in MENQOL scores in the overall study population

NAMS 2007 Position Statement on Vaginal ET for Vaginal Atrophy

The North American Menopause Society.

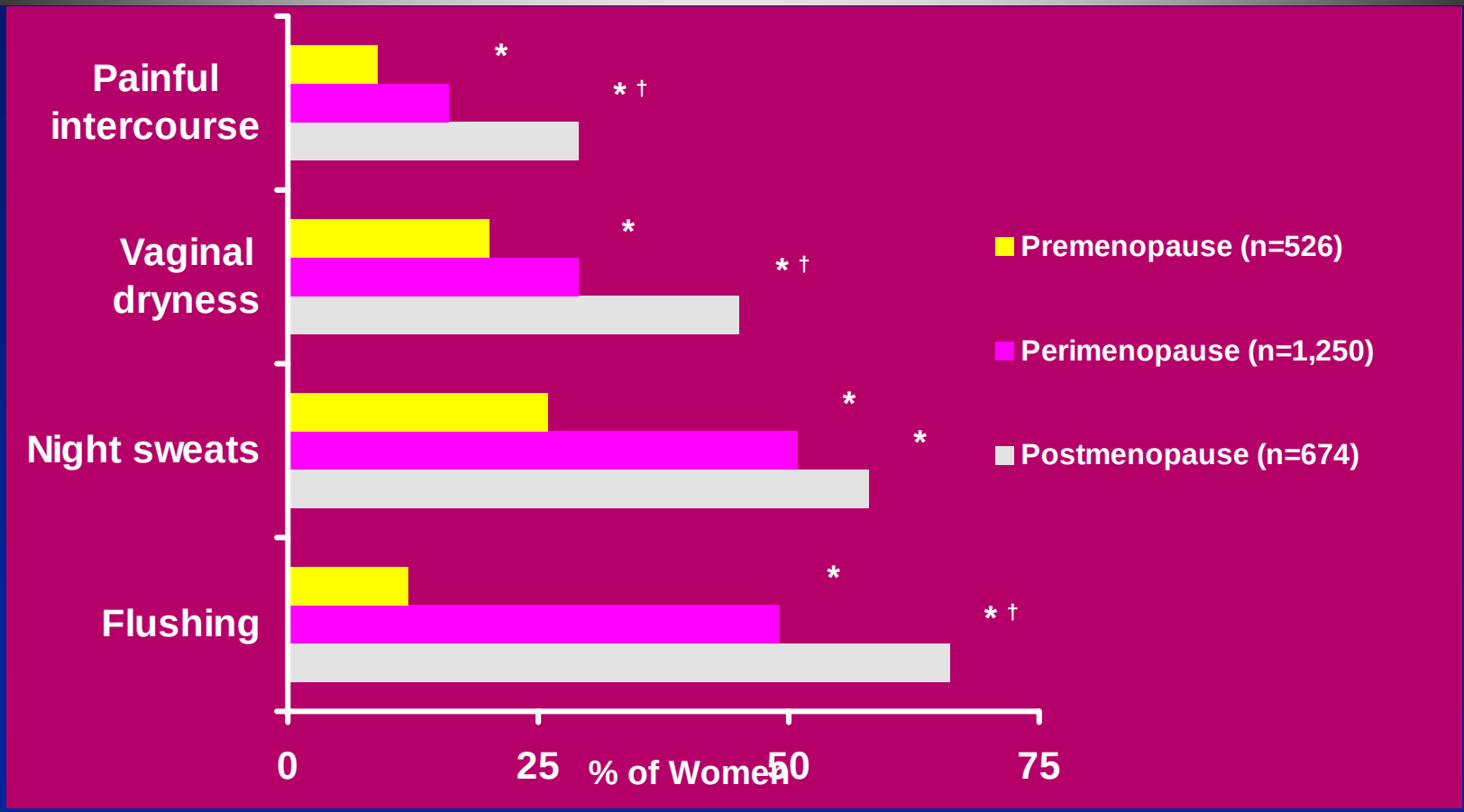
The role of local vaginal estrogen for treatment of vaginal atrophy in postmenopausal women: 2007 position statement of The North American Menopause Society. *Menopause* 2007.

Vaginal Atrophy Management: Therapeutic Goals

- Relieve symptoms
- Reverse atrophic anatomic changes

NAMS position statement. *Menopause* 2007.

Climacteric Complaints Related to Menstrual Status



Cross-sectional survey of 2,450 women. *P<.05 vs. premenopause; †P<.05 vs. perimenopause.

Maartens LW et al. Fam Pract. 2001;18:189-194.

Vaginal Atrophy Management: Treatment Options

- Nonhormonal vaginal lubricants and moisturizers are first-line therapy
- Prescription estrogen therapy (ET) may be required for symptomatic vaginal atrophy that does not respond to nonhormonal options

NAMS position statement. *Menopause* 2007.

Vaginal Atrophy Management: Vaginal Estrogen Therapy (ET)

- Low-dose, local, prescription vaginal ET:
  - is effective and well tolerated for treating vaginal atrophy
  - has limited systemic absorption
- Evidence is from RCTs, albeit limited

NAMS position statement. *Menopause* 2007.

Choosing Vaginal ET

- Low-dose, local, prescription vaginal ET products FDA-approved for treating vaginal atrophy include:
  - estradiol vaginal cream (Estrace Vaginal Cream)
  - CE vaginal cream (Premarin Vaginal Cream)
  - estradiol vaginal ring (Estring)
  - estradiol hemihydrate vaginal tablet (Vagifem)
- All are equally effective at doses recommended in labeling
- Choice depends on clinical experience and patient preference

NAMS position statement. *Menopause* 2007.

Standard Dosages of Commonly Used parenteral Estrogens

- Transdermal estradiol — 0.05-0.10mg patch twice weekly
- Vaginal conjugated estrogens — 0.2-0.625mg, 2-7 times per week
- Vaginal 17B-estradiol — 1.0 mg, 1-3 times per week

Need for Progestogen

- When low-dose, local, vaginal ET is used, concomitant progestogen is generally not indicated

NAMS position statement. *Menopause* 2007.

Need for endometrial surveillance

- There are insufficient data to recommend annual endometrial surveillance in asymptomatic women using low-dose, local vaginal ET
- Closer surveillance may be required if a woman is:
  - at high risk for endometrial cancer
  - using a greater dose of vaginal ET
  - having symptoms such as spotting, breakthrough bleeding

NAMS position statement. *Menopause* 2007.

Length of Therapy

- Vaginal ET should be continued as long as distressful symptoms remain

NAMS position statement. *Menopause* 2007.

Vaginal atrophy in cancer patients

- For women treated for non-hormone-dependent cancer, management is similar to that for women without a cancer history
- For women with a history of hormone-dependent cancer, management recommendations are dependent upon each woman's preference in consultation with her oncologist

NAMS position statement. *Menopause* 2007.

Thank You for Your Attention