국내 사용 가능한 호르몬 제제와 부작용

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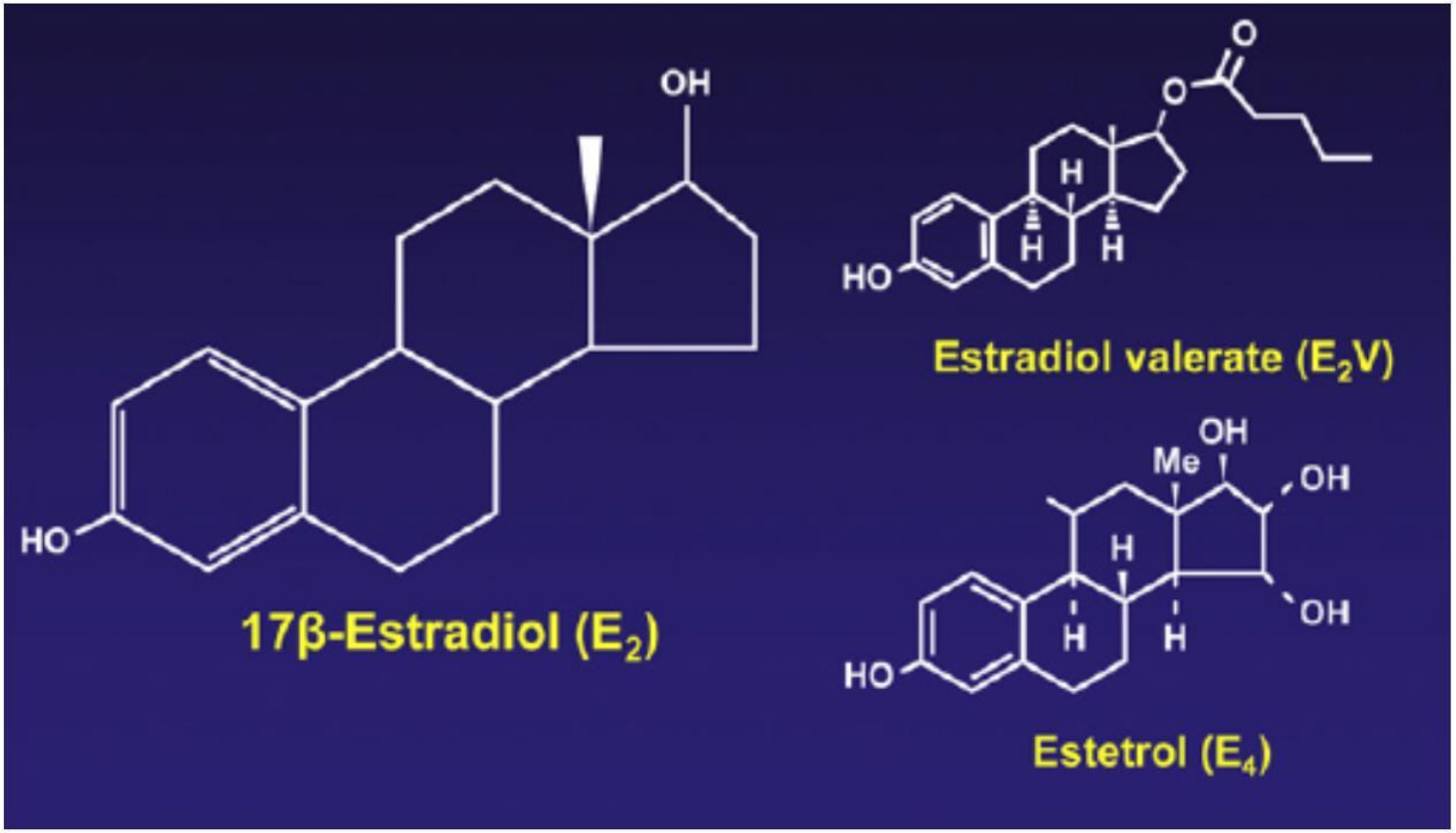
FORMULATION, DOSING, ROUTE OF ADMINISTRATION

Formulation

- 에스트로겐 : 경구 또는 경피, 경질
- 에스트로겐- 프로게스토겐 복합제재
- 티볼론
- 조직선택적 에스트로겐 복합제(TSEC)

Estrogen for Homene Therapy



Estrogen for hormonal therapy

Effects of ethinyl-estradiol on proteins produced in the liver [natural estrogens have less impact on liver proteins].

- ↑ SHBG
- ↑ HDL-C
- ↑ VLDL
- ↑ Angiotensinogen
- ± Modification of some estrogen-dependent clotting factors

Relative potency of estrogens (%) concerning various clinical and metabolic parameters. As compared to E2, EE exerts a stronger effect on hepatic proteins.

Estrogen	FSH	HDL-C	SHBG	CBG	Angio
E_2	100	100	100	100	100
Estriol	30	20			
Estrone sulfate	90	50	90	70	150
CEE	110	150	300	150	500
Equilin sulfate		600	750	600	750
EE	12,000	40,000	50,000	60,000	35,000

Estrogen dose

	일반 용량	저용량
경구 conjugated equine estrogen	0.625 mg	0.3 mg
경구 estradiol valerate	2 mg	1 mg
경구 ethinyl estradiol	5 μg	0.25 μg
경피 17β-estradiol patch	50 μg	25 μg

The therapeutic goal should be to **use the most appropriate**, often lowest, **effective dose** of systemic ET consistent with treatment goals

Estrogen

제품명	성분	용량
프레미나	**Conjugated equine estrogen**	**0.625/0.3mg**
프로지노바	**Estradiol valerate**	**2/1mg**

경피 제품	성분	투여경로
에스트레바 겔	**Estradiol hemihydrate (estradiol 0.5mg/q * 3)**	**TD**

주사제	성분	투여경로
에스트라디올-데포 주	**Estradiol valerate 10mg/ml**	**Q2W IM**

Estrogen

제품명	성분	투여경로	
오베스틴 질정	**Estriol 0.5 mg**	**TV**	**2-7/wk**
지노프로 질정	**Lactobacillus Acidophilus Lyophiliazate 10000 kIU, Estriol 30 μg**	**TV**	**2-7/wk**
에스젠 질크림	**Estropipate 1.5mg/g (estrone sulfate + piperazine)**	**TV**	**2-4g/d**

Progestogen

❖ Progestogen indication : need for endometrial protection

- 자궁이 있는 여성은 자궁내막증식증과 자궁내막암의 위험을 줄이기 위해서 에스트로겐과 함께 프로게스토젠을 반드시 함께 투여해야 한다.
- 질위축증으로 경질 에스트로겐요법을 받거나, 골소실을 막기 위해 극소량의 경피적 에스트로겐요법을 받는 경우에는 프로게스토젠을 투여하지 않을 수 있으나, 1년 이상의 장기 안정성에 대한 결과는 아직 확실하지 않다.
- **Progesterone alone for VMS**
  - MPA 10mg, megestrol acetate 20mg, MP 300mg OD.
  - No long term study for safety

자궁내막증의 과거력이 있거나 자궁절제술을 할 때 자궁체부 일부를 남겨 놓은 경우, 난소암 중 자궁내막양암이 있었던 경우 등에서는 프로게스토젠의 투여가 필요하다.

프로게스토겐 단일 제재

제품명	성분	투여경로
프로베라	**Medroxyprogesterone acetate 2.5mg daily** **5mg for 14d (>12d)**	**PO**
듀파스톤	**Dydrogesterone 10mg OD daily** **10mg bid for 14d(>12d)**	**PO**
유트로게스탄	**Micronized progesterone 100mg daily** **200mg for 14d(>12d)**	**PO**
미레나	**Levonorgestrel 52mg (for 5yr)**	**IUD**

Bazedoxifene combination provides endometrial protection without the need for a progestogen

Progestogen dosing-regimen options that provide for endometrial safety are dependent on the potency of the progestogen and vary with the estrogen dose. Different types and doses of progestogens, routes of administration, and types of regimen (sequential or continuous-combined) may have different health outcomes.

경구 복합제재

주기적 요법	에스트로겐 **(28d)**	프로게스틴 **(14d)**
크리멘	Estradiol valerate 2mg	Cyproterone acetate 1mg
페모스톤1/10	Estradiol Hemihydrate 1mg	Dydrogesterone 10 mg
페모스톤2/10	Estradiol Hemihydrate 2mg	Dydrogesterone 10 mg

지속적 요법	에스트로겐	프로게스틴
안젤릭	Estradiol hemihydrate 1mg	Drospirenone 2mg
에스디올 하프 정	Estradiol hemihydrate 1mg	Norethisterone acetate 0.5mg
페모스톤 콘티	Estradiol Hemihydrate 1mg	Dydrogesterone 5 mg
크리안	Estradiol Hemihydrate 2 mg	Norethisterone Acetate 1 mg

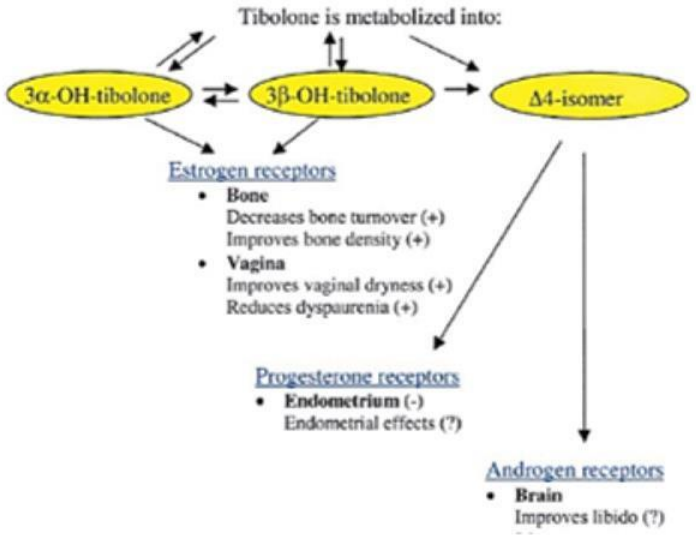
프로게스틴 프리	성분
듀아비브	CEE 0.45mg +Bazedoxifene 20mg
리비알/ 리브론	Tibolone 2.5mg /1.25mg

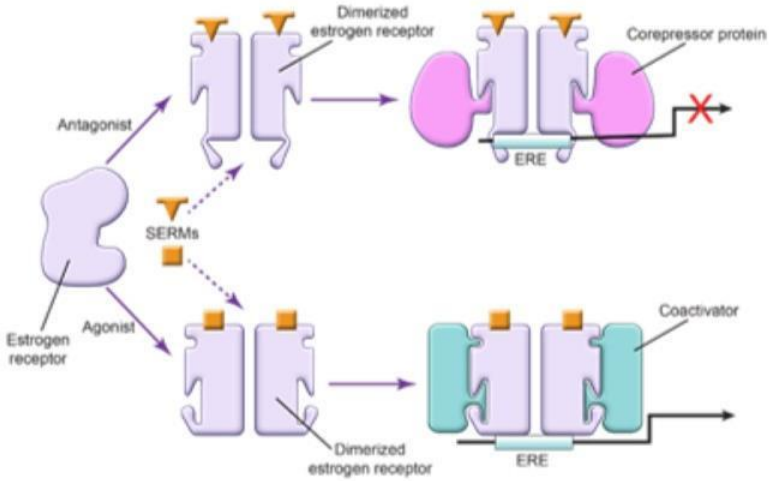
프로게스토겐 제재

	Progestogenic activity	Androgenic activity	Antiandrogen. activity	Anti-aldosterone activity	Glucocorti-coid activity
Progesterone	+	–	(+)	+	(±)
Dydrogesterone	+	-	-	-	-
Drospirenone	+	–	+	+	–
CPA	+	–	++	–	+
Desogestrel	+	(±)	–	–	–
Etonogestel	+	(±)	–	–	–
Gestodene	+	(+)	–	(+)	(+)
Levonorgestrel	+	(+)	–	–	–
(D)MPA	+	(±)	–	–	+
Norethisterone	+	(+)	–	–	–
Norgestimate	+	(+)	–	–	–
Dienogest	+	–	+	–	–

Tibolone (리비알) vs TSEC (듀아비브)

	STEAR *Selective Estrogenic Activity Regulator*	TSEC *Tissue Selective Estrogen Complex*
Compound	Synthetic Steroid	CCE + SERM (BZA)
Mechanism of action	Metabolized into Estrogen, progesterone, androgen	SERM acts as an agonist or antagonist of estrogen receptor depending on the tissue
Progestin Effect	△ (Metabolite)	X (Progestin-free)
FDA / EMEA Registration	EMEA approved	FDA/EMEA approved





Route of administration

1. 질위축증, 질건조증과 같은 증상만 있는 경우 : 국소적인 경질 에스트로겐 투여
2. 정맥혈전증의 위험성이 높은 여성, 중성지방이 높은 여성, 그리고 대사 증후군이 있는 비만 여성 : 경피적 요법
3. 흡연 여성, 고혈압이 있는 여성 : 경피적 요법

경구 투여와 비경구 투여가 있으며, 비경구 투여는 경구 투여와 비교하여 간에서의 1차 통과 효과 (first pass effect)가 없고 중성지방, CRP, 성호르몬 결합글로불린(SHBG, sex hormone binding globulin), 혈압에 미치는 영향이 거의 없는 것으로 알려져 있다

Serious Adverse Events and Risks

Intolerance

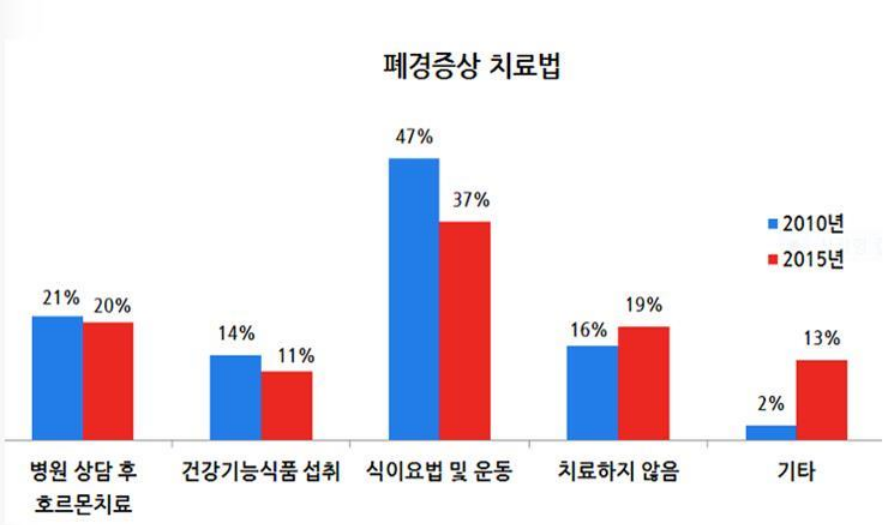
호르몬 치료의 부작용

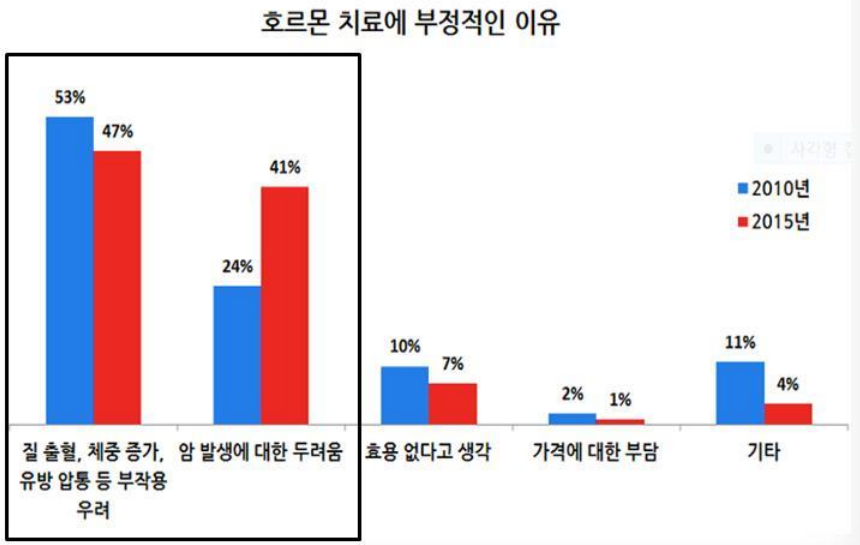
Adverse Events of Hormone Therapy

The effects were estrogen-dose and progestogen-type dependent.

Treatment Rate of HRT & Obstacles to HRT

2015 대한폐경학회 호르몬 치료 인식도 조사





The negative publicity regarding previous studies, including the Women's Health Initiative and the Million Women Study , has led to many women being concerned and anxious about the potential risks of HRT

전국 45세부터 65세 여성 2330명 대상 설문조사, Medigate New, Aug 2015

Compliance with HRT

RESEARCH ARTICLE

Poor Compliance to Hormone Therapy and Decreased Bone Mineral Density in Women with Premature Ovarian Insufficiency

Anne Bachelot[1,2], Carole Nicolas[1,2], Solenne Gricourt[1], Jérôme Dulon[1], Monique Leban[3], Jean Louis Golmard[4,2], Philippe Touraine[1,2]*

1 AP-HP, IE3M, Hôpital Pitié-Salpêtrière, Department of Endocrinology and Reproductive Medicine, Centre de Référence des Maladies Endocriniennes Rares de la Croissance, Centre de Référence des Pathologies Gynécologiques Rares, Paris, France, **2** Université Pierre et Marie Curie, Univ Paris, Paris, France, **3** AP-HP, Hôpital Pitié-Salpêtrière, Department of Hormonal Biochemistry, Paris, France, **4** AP-HP, Hôpital Pitié-Salpêtrière, Clinical Research Unit, Paris, France

- The large number of patients stop HRT and specialist care in the first year due to side effects, lack of interest, or fear of breast cancer
  - 42.6% had stopped their hormone replacement therapy (HRT) for at least one year during the follow up period

- Compliance with HRT has a direct impact on clinical outcomes
  - There was a significant loss of femoral BMD in women who had stopped their HRT for over a year

Bachelot A, et al. PLoS ONE 11(12): e0164638. 2016

Tolerability issues on HRT

- Estrogen is the most effective therapy for vasomotor symptoms and vulvovaginal atrophy
- Women with a uterus require additional therapy to counteract the effects of estrogen on the uterus
  - Endometrial protection with synthetic progestins or progester one is recommended
  - However, the tolerability and safety of **systemic progestins** and progesterone are of concern
  - Tolerability issues limit continuation of hormone therapy in m any women

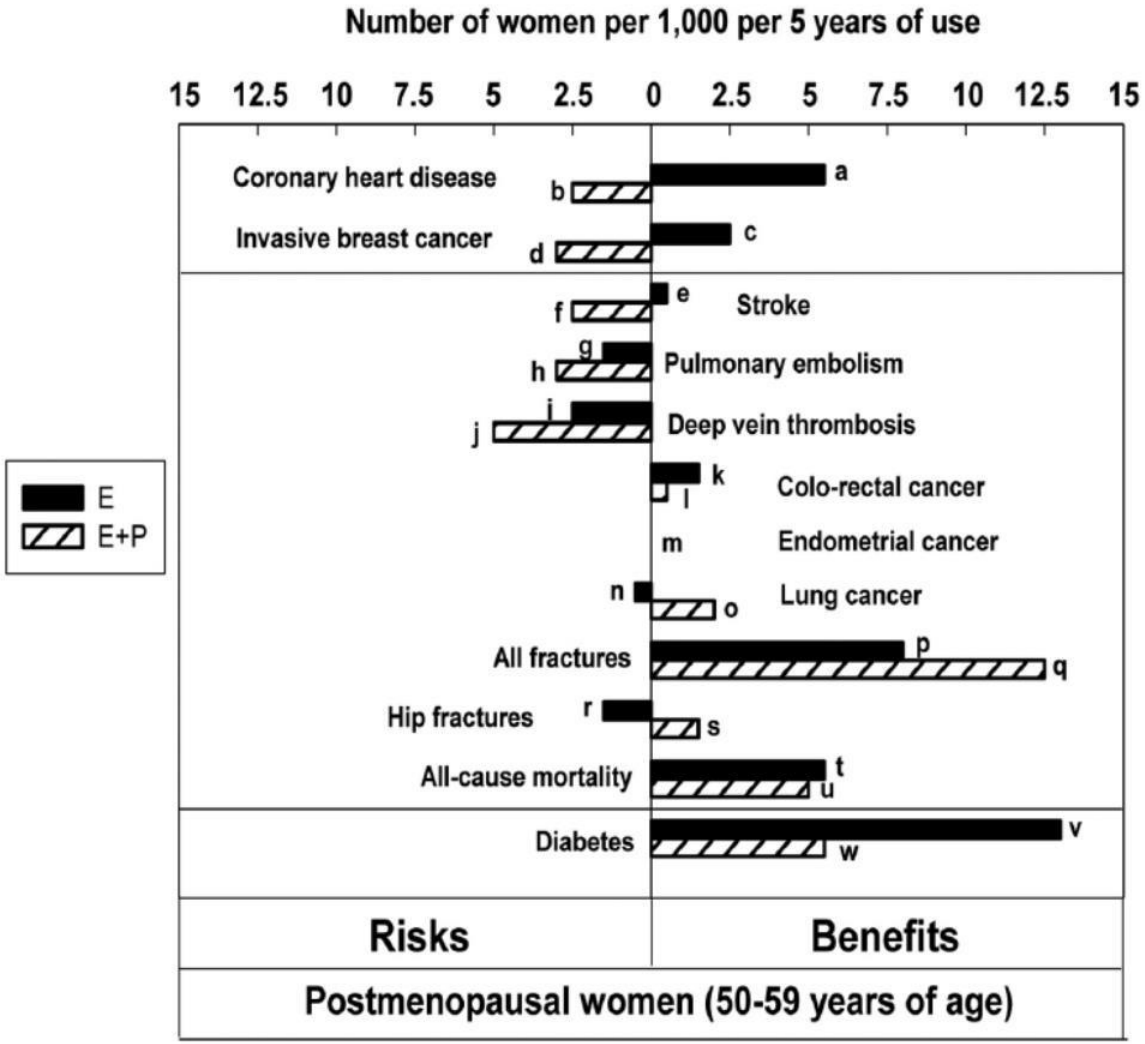
Tolerability & Safety issues limit hormone therapy in many women

Adverse effects of Hormone Treatment

Re-evaluation of WHI data (stratified by age): Risks and Benefits of HRT Cases

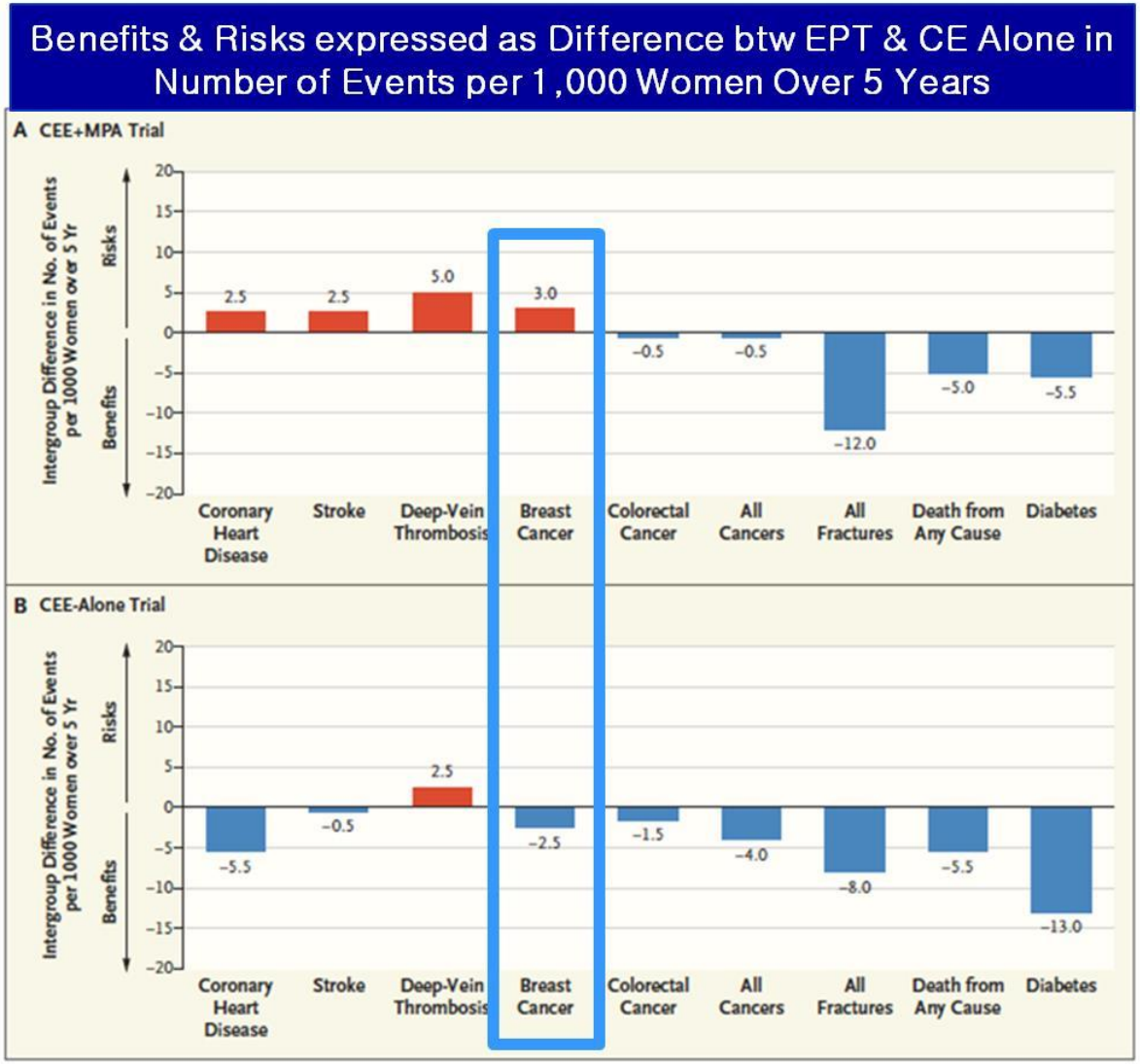
- Younger women (aged 50–59 years) had more favorable results
- There are differences between CE alone and CE/MPA arms
- Overall benefit/risk ratio of CE-alone appears to be more favourable than CE/MPA

E=estrogen; P=progestin.



The basis of the Endocrine Society scientific statement for postmenopausal hormone replacement therapy (HRT): excess risks and benefits of HRT for 5 years in women aged 50–59 years or within 10 years of the start of menopause

Safety issues on HRT Lessons Learned for CE Alone from the WHI Trial



Progestogens may…

- Decrease glucose tolerance
- Attenuate the beneficial effects of estrogen on lipids
- Attenuate any cardiovascular benefits of estrogen only therapy
- Increase mammographic density
- May increase the risk of breast cancer when used in combination with estrogen

Manson. NEJM March 2016 374(9): 803-806.

2017 NAMS HT position statement

Menopause: The Journal of The North American Menopause Society
Vol. 24, No. 7, pp. 000-000
DOI: 10.1097/GME.0000000000000921

POSITION STATEMENT

The 2017 hormone therapy position statement of The North American Menopause Society

"NAMS discovered through its review of the literature published since the 2012 Position Statement that its previous position that hormone therapy should be prescribed only for the **'lowest dose for the shortest period of time'** may be inadequate or even harmful for some women.

NAMS has clarified this position to the more fitting concept of the **'appropriate dose, duration, regimen, and route of administration'** that provides the most benefit with the minimal amount of risk."

Back To The Future

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review article

Back to the future: Hormone replacement therapy as part of a prevention strategy for women at the onset of menopause

Roger A. Lobo [a,*], James H. Pickar [a], John C. Stevenson [b], Wendy J. Mack [c], Howard N. Hodis [c]

[a] Department of Obstetrics and Gynecology, Columbia University, New York, NY 10032, USA
[b] National Heart and Lung Institute, Imperial College London, Royal Brompton Hospital, Sydney Street, London, SW3 6NP, UK
[c] Atherosclerosis Research Unit, Departments of Medicine and Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles,

Primary Prevention of CHD and All-cause Mortality in Women<60 yrs or <10 yrs since-menopause

Studies	Age; time-since-menopause	Therapy	Coronary heart disease	All-cause mortality
			% Reduction (risk ratio; 95% confidence interval)	% Reduction (risk ratio; 95% confidence interval)
DOPS, 10 year	50 yr; 7 mo-s-m	E2+NETA sequential	↓ 52% (0.48; 0.27–0.89)	↓ 43% (0.57; 0.30–1.08)
DOPS, 16 year		and E2 alone	↓ 39% (0.61; 0.39–0.94)	↓ 34% (0.66; 0.41–1.08)
WHI-E, 11-year	<60 yr	CE alone	↓ 41% (0.59; 0.38–0.90)	↓ 27% (0.73; 0.53–1.00)
WHI-E, 13-year	<10 yr-s-m	CE alone	↓ 50% (0.50; 0.22–1.18)	↓ 36% (0.64; 0.33–1.25)
WHI-E + P, 13-year	<10 yr-s-m	CE + MPA continuous	↓ 10% (0.90; 0.56–1.45)	↓ 21% (0.79; 0.52–1.21)
WHI-E, 13-year	<60 yr	CE alone	↓ 35% (0.65; 0.44–0.96)	↓ 22% (0.78; 0.59–1.03)
WHI-E + P, 13-year	<60 yr	CE + MPA continuous	↑ 27% (1.27; 0.93–1.27)	↓ 12% (0.88; 0.70–1.11)
WHI-E	<10 yr-s-m	CE alone	↓ 52% (0.48; 0.20–1.17)	↓ 35% (0.65; 0.33–1.29)
WHI-E + P	<10 yr-s-m	CE + MPA continuous	↓ 12% (0.88; 0.54–1.43)	↓ 19% (0.81; 0.52–1.24)
WHI-E/E + P	<10 yr-s-m	CE and CE + MPA	↓ 24% (0.76; 0.50–1.16)	↓ 24% (0.76; 0.53–1.09)
WHI-E	<60 yr	CE alone	↓ 37% (0.63; 0.36–1.09)	↓ 29% (0.71; 0.46–1.11)
WHI-E + P	<60 yr	CE + MPA continuous	↑ 29% (1.29; 0.79–2.12)	↓ 31% (0.69; 0.44–1.07)
WHI-E/E + P	<60 yr	CE and CE + MPA	↓ 7% (0.93; 0.65–1.33)	↓ 30% (0.70; 0.51–0.96)
Meta-analysi	<60 yr <10 yr-s-m	HT	↓ 32% (0.68; 0.48–0.96)	
Meta-analysis	54 yrs	HT		↓ 39% (0.61; 0.39–0.95)
Bayesian meta-analysis	55 yrs	HT		↓ 27% (0.73; 0.52–0.96)
Cochrane meta-analysis	<10 yr-s-m	HT	↓ 48% (0.52; 0.29–0.96)	↓ 30% (0.70; 0.52–0.95)
Observational studies	30-55 yr <5 yr-s-m	HT	↓ 30–50%	↓ 20–60%

Lobo RA, et al. Atherosclerosis. 2016

Intolerance issue

HRT Compliance Factor: Progestin-Intolerance

One of the main factors for reduced compliance with HRT is that of **progestin intolerance**.

Most common adverse events leading to discontinuation are related to progestins

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

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

Steel SA, Albertazzi P, Howarth EM, et al. Climacteric. 2003;6(2):96-103 ; Ettinger B and Pressman A, Am J Manag Care 1999; Komm BS, Mirkin S. Pharmaceuticals. 2012; Panay N & Studd JWW. Human Reprod Update 1997

Progestin intolerance is one of the main factors for reduced compliance

- About **20%** of women receiving progestin-containing HT have significant progestin intolerance, and half of these experience s erious effects that prevent treatment continuation

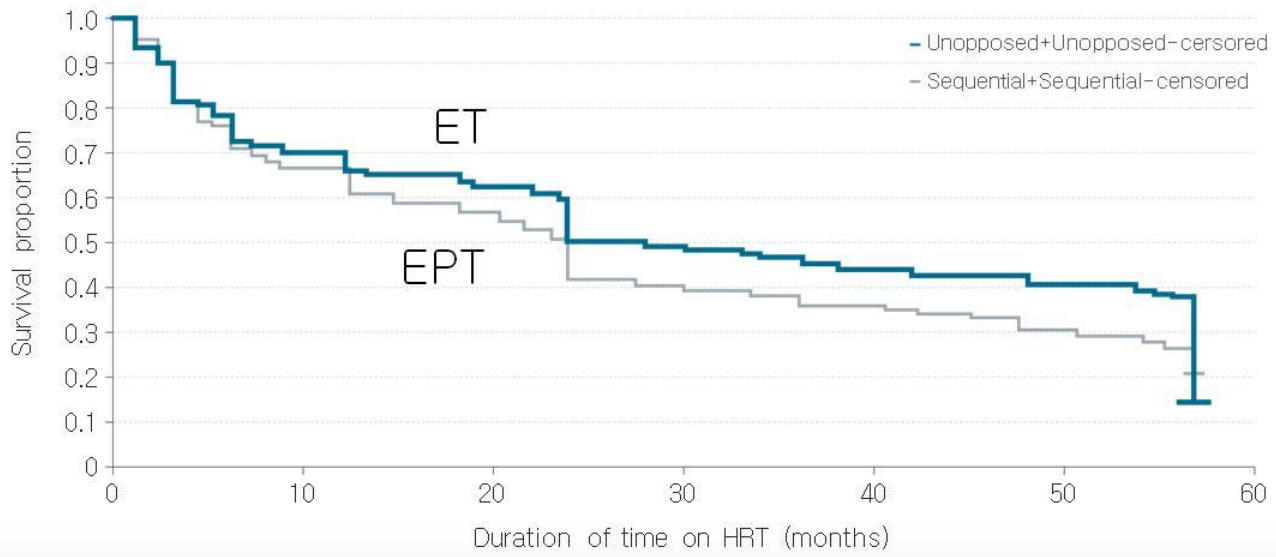
- The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy do recognise progestin intolerance as one of the main factors for reduced compliance with HT

Panay N & Studd J. Human Reprod Update 1997;
Panay N et al. on behalf of the British Menopause Society and Women's Health Concern. Menopause Int 2013;

HRT Compliance Factor: Progestin-Intolerance

- One of the main factors for reduced compliance with HRT is that of **progestin intolerance**.
- Adherence to HRT type was significantly superior in hysterectomized women taking unopposed estradiol (median 32 months) compared with those on sequential HRT(median 28 months; p = 0.011).[1]

Kaplan-Meier estimates for treatment adherence of HRT



Adapted from Steel SA, et al.

Steel SA, Albertazzi P, Howarth EM, et al. Climacteric. 2003;6(2):96-103

Medical Conditions which may be Exacerbated by Progestins

History of the following conditions may make progestin inappropriate:

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

Alternatives to progestin are needed that will protect the endometrium while avoiding other progestin-associated effects and preserving the desired effects of estrogens in postmenopausal women.

*PMS: premenstrual syndrome
**PMDD: premenstrual dysphoric disorder

Treatment adjustments

Symptom/Condition When MHT Started	Approach to Resolution
Persistent, intolerable VMS	Switch mode of administration or adjust dose of estrogen and/or progestogen.
Hot flashes that persist after treatment adjustment	Consider another etiology of flashes Ensure absorption: if transdermal, consider serum E2 determination.
Bleeding: approach depends on time since menopause, MHT regimen, duration of therapy, duration and character of bleeding	Sequential regimen may be more appropriate for recently menopausal (2 y), because unscheduled bleeding with continuous combined MHT can be problematic. Persistent irregular bleeding (6 mo) should be evaluated for endometrial pathology; if obese, diabetic, or having family history for endometrial cancer, evaluate sooner. Atrophic endometrium in women more remote from menopause may respond to increased estrogen dose if otherwise appropriate CEE/BZA may improve symptoms
Breast tenderness	Usually responds to a reduction in estrogen dose or change in progestogen preparation. CEE/BZA may improve symptoms. Changing to tibolone may be helpful in women who develop mastalgia on conventional MHT.
Baseline TG level 200 mg/dL	Review family history and seek contributing factors. Transdermal ET is preferred. If oral estrogen is selected, monitor serum TG levels 2 wk after starting therapy.
Hypothyroid on thyroid replacement	Monitor TSH 6 to 12 wk after starting oral MHT; T4 dose may need to be increased .

Cause or mimic vasomotor events

- Hormone excess
  - Thyroid hormone excess
  - Carcinoid syndrome (flushing without sweating)
  - Pheochromocytoma (hypertension, flushing, and profuse sweating)
- Dietary factors
  - Alcohol
  - Spicy food
  - Food additives (eg, monosodium glutamate, sulfites)
- Pharmaceuticals
  - Chronic opioid use
  - Opiate withdrawal
  - SSRIs (may cause sweats)
  - Nicotinic acid (intense warmth, itching lasting up to 30 min)
  - Calcium channel blockers
  - Medications that block estrogen action or biosynthesis
- Chronic infection (increased body temperature)
- Other medical conditions
  - Postgastric surgery dumping syndrome
  - Mastocytosis and mast cell disorders (usually with gastrointestinal symptoms)
  - Some cancers: medullary carcinoma of the thyroid, pancreatic islet-cell tumors, renal cell carcinoma, lymphoma
  - Anxiety disorders

감사합니다.