Menopause and Hormone Therapy

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February 1, 2019

Conflict of Interest

- Speaker, Consultant for Searchlight Pharma (*Estragyn*)
- Ad Board, Speaker for Pfizer (*Duavive*)
- Honoraria from Searchlight, Pfizer

Objectives

- Following the presentation, participants will have an understanding of the importance of caring for patients suffering from menopausal symptoms. They will feel comfortable with an initial approach to management of these symptoms, including a discussion on risks and benefits of therapy.

Outline

- Discuss the impact of menopause and its symptoms
- WHI: Refresher and Ongoing Lessons
- New Cardiovascular Trials
- Genitourinary Syndrome of Menopause - New term for a common condition
- New and Notable: TSECs

Menopause Management: Is there a consensus?

- Pendulum swings with regards to the popularity and favourability of Hormone Therapy (HT)
- Early observational trials showed benefits (e.g., Nurses Health Study)
- WHI sensationalized and misrepresented risks
- Experts are now rationally reviewing data and global consensus is being reached

Summary

GLOBAL CONSENSUS STATEMENT ON MHT (MARCH 2013)*

MHT is the most effective treatment for vasomotor symptoms associated with menopause at any age, but benefits are more likely to outweigh risks for symptomatic women before the age of 60 years or within 10 years after menopause.

*This Consensus Statement is endorsed by: The American Society for Reproductive Medicine, The Asia Pacific Menopause Federation, The Endocrine Society, The European Menopause and Andropause Society, The International Menopause Society, The International Osteoporosis Foundation and The North American Menopause Society.

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- **Discuss the impact of menopause and its symptoms**
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Impact of Menopause

- Menopause is a natural physiologic event
  - Many women sail through
  - Many others have bothersome symptoms that need management by a physician
- As our population ages, the impact of menopause-related health concerns will grow
  - Women are spending one third of their lives in menopause

Impact of Menopause

- Middle aged women are the backbone of society
- Multiple roles within families
- Often work outside the home
- Carry much of the “emotional responsibility”

Impact of Menopause

- The majority of women in peri-menopause and early post-menopause experience vasomotor symptoms
  - Influenced by certain factors - obesity, smoking, education
- VMS may be accompanied by other symptoms like poor sleep, altered mood, impact quality of life
- Attitude towards menopause may influence a woman’s experience of her symptoms

Rebecca C. Thurston, Hadine Joffe, Vasomotor Symptoms and Menopause: Findings from the Study of Women's Health across the Nation, In Obstetrics and Gynecology Clinics of North America, Volume 38, Issue 3, 2011, Pages 489-501, ISSN 0889-8545, https://doi.org/10.1016/j.ogc.2011.05.006.

Beverley Ayers, Mark Forshaw, Myra S. Hunter, The impact of attitudes towards the menopause on women's symptom experience: A systematic review, In Maturitas, Volume 65, Issue 1, 2010, Pages 28-36, ISSN 0378-5122, https://doi.org/10.1016/j.maturitas.2009.10.016.

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Heart Health - What We Know

- Observational Data:
  - Nurses Health Study, NEJM, 1996, Grodstein et al.
    - 121 700 nurses aged 30-55, data collection began 1976
    - Biennial questionnaires on hormone use, cardiovascular disease, and lifestyle
    - Outcomes measured included MI, coronary bypass or angioplasty, stroke, death

TABLE 2. RELATIVE RISK OF CARDIOVASCULAR DISEASE AMONG CURRENT USERS OF CONJUGATED ESTROGEN ALONE OR WITH PROGESTIN AS COMPARED WITH NONUSERS, 1978 TO 1992.*

HORMONE USE	PERSON-YEARS	MAJOR CORONARY DISEASE			STROKE (ALL TYPES)		
		NO. OF CASES	RELATIVE RISK (95% CI)		NO. OF CASES	RELATIVE RISK (95% CI)	
			Age Adjusted	*Multivariate Adjusted†*		*Age Adjusted*	*Multivariate Adjusted†*
Never used	304,744	431	1.0		270	1.0	
Currently used							
Estrogen alone	82,626	47	0.45 (0.34–0.60)	0.60 (0.43–0.83)	74	1.13 (0.88–1.46)	1.27 (0.95–1.69)
Estrogen with progestin	27,161	8	0.22 (0.12–0.41)	0.39 (0.19–0.78)	17	0.74 (0.45–1.20)	1.09 (0.66–1.80)

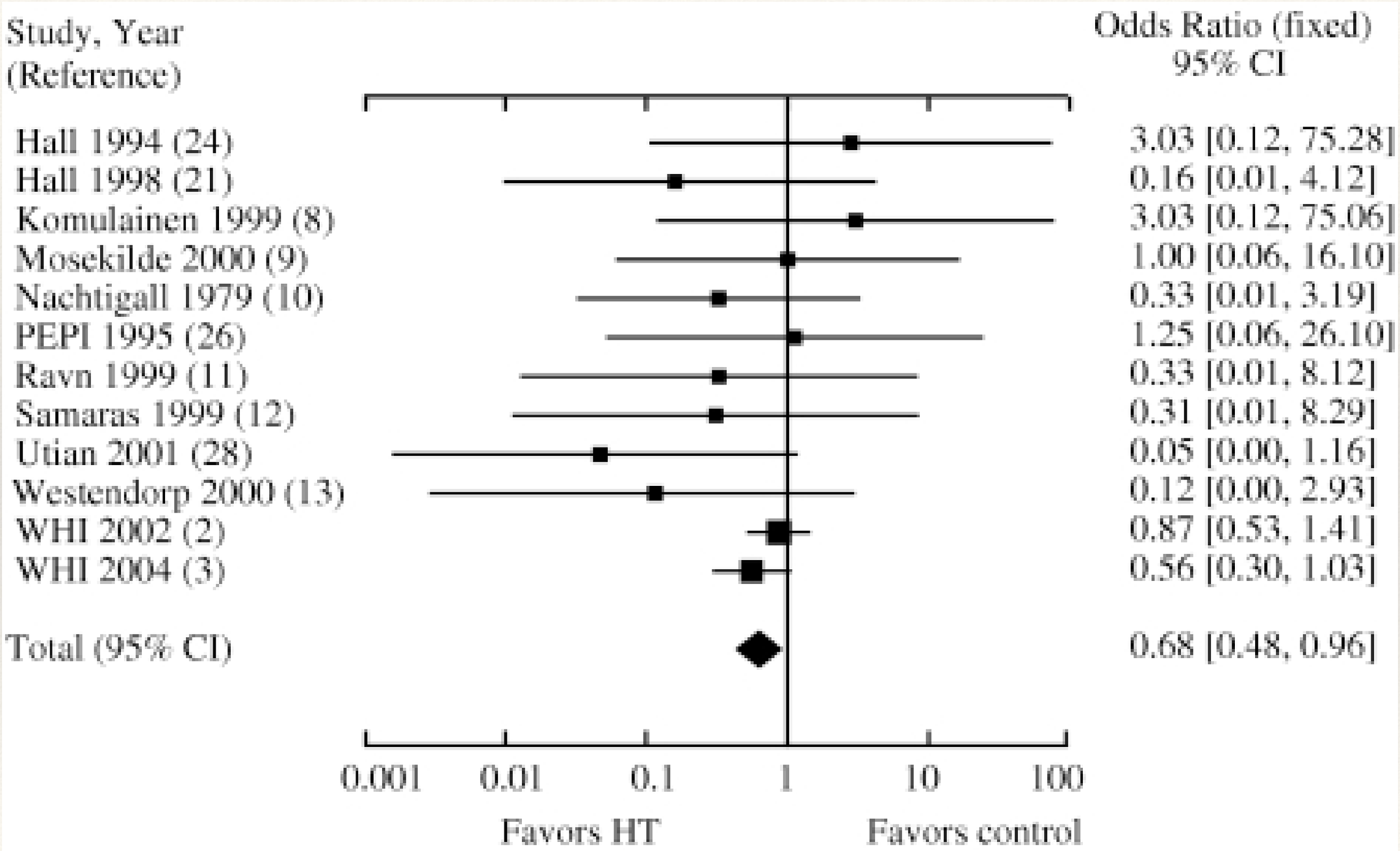
*CI denotes confidence interval.

†The analysis was adjusted for age (in five-year categories), time (in two-year categories), age at menopause (in two-year categories), body-mass index (in quintiles), diabetes (yes or no), high blood pressure (yes or no), high cholesterol level (yes or no), cigarette smoking (never, formerly, or currently [1 to 14, 15 to 24, or 25 or more cigarettes per day]), past oral-contraceptive use (yes or no), parental history of myocardial infarction before the age of 60 years (yes or no), and type of menopause (natural or surgical).

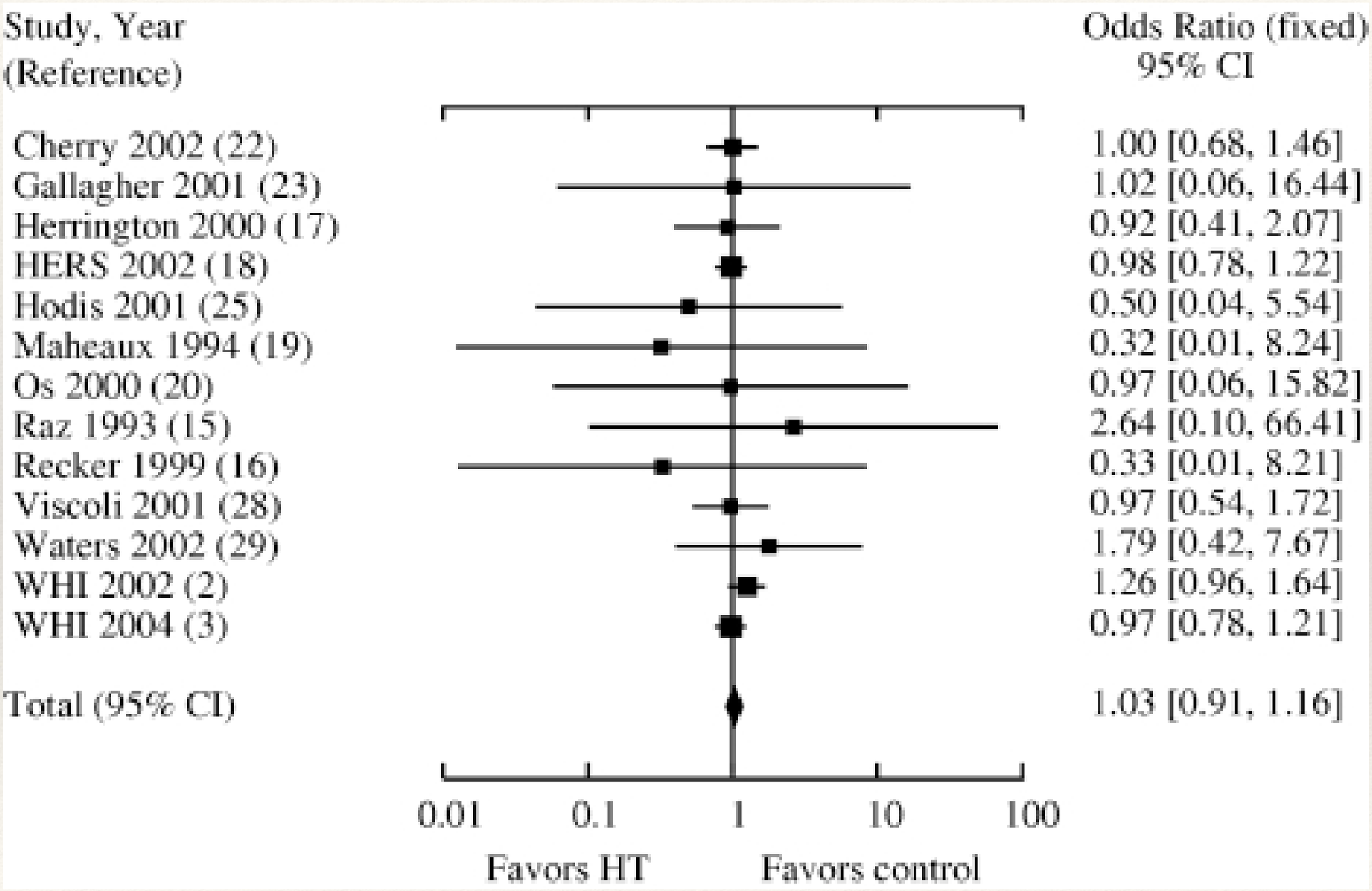
Heart Health - What We Know

- Meta-Analysis:
  - Salpeter, 2006, J Gen Internal Medicine
    - 39 049 women from 23 RCT, six months duration or longer, compared HRT to placebo or no therapy
    - Women aged older or younger than 60, or ten years greater than/less than from menopause
    - Outcomes included CHD events or death from CHD

Heart Health - What We Know



Heart Health - What We Know



Women's Health Initiative (WHI)

- The Women's Health Initiative (WHI) was conceived as a double blind RCT, designed to prove as a primary endpoint that hormone therapy reduced cardiovascular morbidity and mortality
- 16 608 recruited to the estrogen/progestin arm
- 10 739 recruited to the estrogen alone arm
- Premarin (0.625mg OD) and Provera (2.5mg OD) were the drugs chosen

WHI

- Average age 63 (50-79)
- Intervention arms stopped early:
  - CEE/MPA 5.6 years median follow up
  - CEE alone arm 7.2 years median follow up
- Post-intervention follow-up available for ~80% of participants
- 4% of women remained on HT following trial

WHI - A Brief Review

- **Estrogen plus progestin arm**:
  - Outcomes:
    - **CHD 1.29 (1.02 - 1.63) — +7 cases**
    - **Breast Cancer 1.26 (1.00 - 1.59) — +8 cases**
    - **Stroke 1.41 (1.07 - 1.85) — +8 cases**
    - **PE 2.13 (1.39 - 3.25) — +8 cases**
    - **Colorectal Cancer 0.63 (0.43 - 0.92) — -6 cases**
    - Endometrial Cancer 0.83 (0.47 - 1.47)
    - **Hip Fracture 0.66 (0.45 - 0.98) — -5 cases**
    - Death due to other causes 0.92 (0.74 - 1.14)

WHI - A Brief Review

- **Estrogen alone**
- Outcomes:
  - CHD 0.91 (0.75 - 1.12)
  - Breast Cancer 0.77 (0.59 - 1.01)
  - **Stroke 1.39 (1.10 - 1.77) — +12 extra cases**
  - PE 1.34 (0.87 - 2.06)
  - Colorectal Cancer 1.08 (0.75 - 1.55)
  - **Hip Fracture 0.61 (0.41 - 0.91) — -6 extra cases**

What are we still learning from the WHI?

- Cardiovascular Health:
  - **Intervention Phase:**
- CEE plus MPA had an HR of 1.18 (95% CI, 0.95-1.45) compared with placebo
- CEE alone had an HR of 0.94 (95% CI, 0.78-1.14) compared with placebo
  - **Post Intervention:**
- During cumulative 13-year follow-up, the HRs for CHD were 1.09 (95% CI, 0.96-1.24) for CEE plus MPA
- 0.94 (95% CI, 0.82-1.09) for CEE alone compared with the placebo groups

Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, Anderson G, Howard BV, Thomson CA, LaCroix AZ, Wactawski-Wende J, Jackson RD, Limacher M, Margolis KL, Wassertheil-Smoller S, Beresford SA, Cauley JA, Eaton CB, Gass M, Hsia J, Johnson KC, Kooperberg C, Kuller LH, Lewis CE, Liu S, Martin LW, Ockene JK, O'Sullivan MJ, Powell LH, Simon MS, Van Horn L, Vitolins MZ, Wallace RB. Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Poststopping Phases of the Women's Health Initiative Randomized Trials. *JAMA.* 2013;310(13):1353–1368.

What are we still learning from the WHI?

- Invasive Breast Cancer:
  - **Intervention Phase:**
- CEE plus MPA had an HR of 1.24 (95% CI, 1.01-1.53) for breast cancer compared with the placebo group
- CEE alone had an HR of 0.79 (95% CI, 0.61-1.02) compared with the placebo group
  - **Post-Intervention:**
- CEE plus MPA remained statistically significantly elevated during postintervention and cumulative follow-up compared with the placebo group (HR for cumulative follow-up, 1.28 [95% CI, 1.11-1.48]
- CEE alone, the risk reduction became statistically significant during cumulative follow-up (HR, 0.79 [95% CI, 0.65-0.97]

Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, Anderson G, Howard BV, Thomson CA, LaCroix AZ, Wactawski-Wende J, Jackson RD, Limacher M, Margolis KL, Wassertheil-Smoller S, Beresford SA, Cauley JA, Eaton CB, Gass M, Hsia J, Johnson KC, Kooperberg C, Kuller LH, Lewis CE, Liu S, Martin LW, Ockene JK, O'Sullivan MJ, Powell LH, Simon MS, Van Horn L, Vitolins MZ, Wallace RB. Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Poststopping Phases of the Women's Health Initiative Randomized Trials. *JAMA.* 2013;310(13):1353–1368.

A short diversion about breast cancer risk and hormone therapy….

WHI - The Fine Print

- Differences in risk exist between early initiators of hormone therapy and late initiators:
  - With the CEE/MPA group, no increased risk of breast cancer if starting HT for the first time greater than five years from menopause.
  - In the CEE group, no decreased risk of breast cancer if starting HT for the first time less than five years from menopause

Richard J. Santen, Menopausal hormone therapy and breast cancer, In The Journal of Steroid Biochemistry and Molecular Biology, Volume 1

Women’s Health Initiative

- Take Home Points:
  - CEE/MPA = increased risk
    - (unless you initiate HT >5 years after menopause)
  - CEE alone = decreased risk
    - (neutral risk if you initiate HT <5 years after menopause)

Collaborative Group on Hormonal Factors in Breast Cancer

- 51 studies, 21 countries, 52 705 women with breast cancer
- The main findings are:
  - Risk of breast cancer is increased in women using HRT and increases with increasing duration of use
  - This excess risk is reduced after use ceases and has largely, if not completely, disappeared after about 5 years.
  - The increase in the relative risk of breast cancer among current or recent users was greater for women of low than for those of high relative weight.
  - The breast cancers diagnosed in women who had used HRT were less advanced clinically than those diagnosed in never-users.

Collaborative Group on Hormonal Factors in Breast CancerBreast cancer and hormone replacement therapy: collaborative reanalysi

EPIC STUDY

- EPIC-cohort is a multi-centre prospective cohort with 23 contributing centres in 10 European countries
- More than half a million participants
- A total of 4,312 primary breast cancers were diagnosed during 1,153,747 person-years of follow-up (mean duration: 8.6 yr)
- The mean age at recruitment was 58.1 yr (ranging from 52.1 in Norway to 61.5 in the United Kingdom).
- Most women (93.3%) reported a natural menopause.

Epic study Conclusions

- Compared with never users, *current users* of both estrogen-only and combined MHT had an increased risk of breast cancer, with the latter being associated with a higher risk than the former.
- In combined MHT, *fixed continuous regimens* were found to confer a significantly increased risk compared with sequential regimens.
- Among women who used sequential regimens, risk did not vary significantly between those who used testosterone-like or progesterone-like progestins.
- Among women who used estrogen-only MHT, risk did not vary significantly according to route of administration (oral *vs*. cutaneous) or estrogen component (estradiol compounds *vs*. CEE). Past use of MHT was associated with a small increase in risk.

Conclusions: What do I tell my patients about risk?

- The risks of breast cancer with MHT use are complicated, and we are still learning about them
- Risks are small, “a few per thousand”
- Increased risks are not immediate
- Risks increase slightly over time, but also trend to baseline after discontinuation

Conclusions: what do I give my patients?

- Estrogen alone:
  - CEE
- Combined therapy:
  - Cyclical
  - Favour progesterone use
  - Consider TSEC

Back to the WHI findings….

What are we still learning from the WHI?

- Stroke:
  - **Intervention:**
    - Stroke risk was increased with CEE plus MPA (HR, 1.37) and with CEE alone (HR, 1.35) compared with the placebo groups, reflecting increased ischemic stroke (P = 0.01)
  - **Post-Intervention:**
    - The postintervention results were neutral in both trials

Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, Anderson G, Howard BV, Thomson CA, LaCroix AZ, Wactawski-Wende J, Jackson RD, Limacher M, Margolis KL, Wassertheil-Smoller S, Beresford SA, Cauley JA, Eaton CB, Gass M, Hsia J, Johnson KC, Kooperberg C, Kuller LH, Lewis CE, Liu S, Martin LW, Ockene JK, O'Sullivan MJ, Powell LH, Simon MS, Van Horn L, Vitolins MZ, Wallace RB. Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Poststopping Phases of the Women's Health Initiative Randomized Trials. JAMA. 2013;310(13):1353–1368.

What are we still learning from the WHI?

- Pulmonary Embolus:
- **Intervention:**
  - A statistically significant increase in pulmonary embolism risk was seen in women assigned to CEE plus MPA (HR, 1.98) compared with the placebo group, whereas the increase in pulmonary embolism risk was not statistically significant in women assigned to CEE alone (HR, 1.35).
- **Post-Intervention:**
  - Post-stopping results were neutral in both trials
  - HRs were 1.26 (95% CI, 1.00-1.59) for CEE plus MPA and 1.15 (95% CI, 0.87-1.51) for CEE alone compared with the placebo groups

Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, Anderson G, Howard BV, Thomson CA, LaCroix AZ, Wactawski-Wende J, Jackson RD, Limacher M, Margolis KL, Wassertheil-Smoller S, Beresford SA, Cauley JA, Eaton CB, Gass M, Hsia J, Johnson KC, Kooperberg C, Kuller LH, Lewis CE, Liu S, Martin LW, Ockene JK, O'Sullivan MJ, Powell LH, Simon MS, Van Horn L, Vitolins MZ, Wallace RB. Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Poststopping Phases of the Women's Health Initiative Randomized Trials. *JAMA.* 2013;310(13):1353–1368.

What are we still learning from the WHI?

- All-Cause Mortality:
- **Intervention:**
  - Neither CEE plus MPA nor CEE alone affected all-cause mortality
- **Post-Intervention:**
  - All-cause mortality remained neutral post-intervention and during cumulative follow-up in both trials.
  - The cumulative follow-up HR was 0.99 (95% CI, 0.91-1.08) for CEE plus MPA compared with placebo and 0.99 (95% CI, 0.90-1.10) for CEE alone compared with placebo

Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, Anderson G, Howard BV, Thomson CA, LaCroix AZ, Wactawski-Wende J, Jackson RD, Limacher M, Margolis KL, Wassertheil-Smoller S, Beresford SA, Cauley JA, Eaton CB, Gass M, Hsia J, Johnson KC, Kooperberg C, Kuller LH, Lewis CE, Liu S, Martin LW, Ockene JK, O'Sullivan MJ, Powell LH, Simon MS, Van Horn L, Vitolins MZ, Wallace RB. Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Poststopping Phases of the Women's Health Initiative Randomized Trials. *JAMA.* 2013;310(13):1353–1368.

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- Discuss the impact of menopause and its symptoms
- WHI: Refresher and Ongoing Lessons
- **New Cardiovascular Trials**
- Genitourinary Syndrome of Menopause - New term for a common condition
- New and Notable
- Case Studies

New RCT: KEEPS

- Multi-center double-blinded placebo-controlled RCT
- N = 727 women aged 42-59 (mean age, 52.7, within 3 yrs of FMP)
- Trial Duration = 48 months
- **Treatment Arms:**
  - Oral conjugated equine estrogens (o-CEE) given as Premarin®, 0.45 mg/d
  - Transdermal Estradiol (t-E2) given by Climara® patch, 50 µg/d
  - Placebo
  - Cyclical micronized progesterone [Prometrium®], 200 mg/d x 12 days/month or placebo Prometrium)

Harman et al. KEEPS Study. *Ann Intern Med* 2014;161:249-60. Slide by Dr. Elaine Jolly, modified.

Heart Health - New Trials

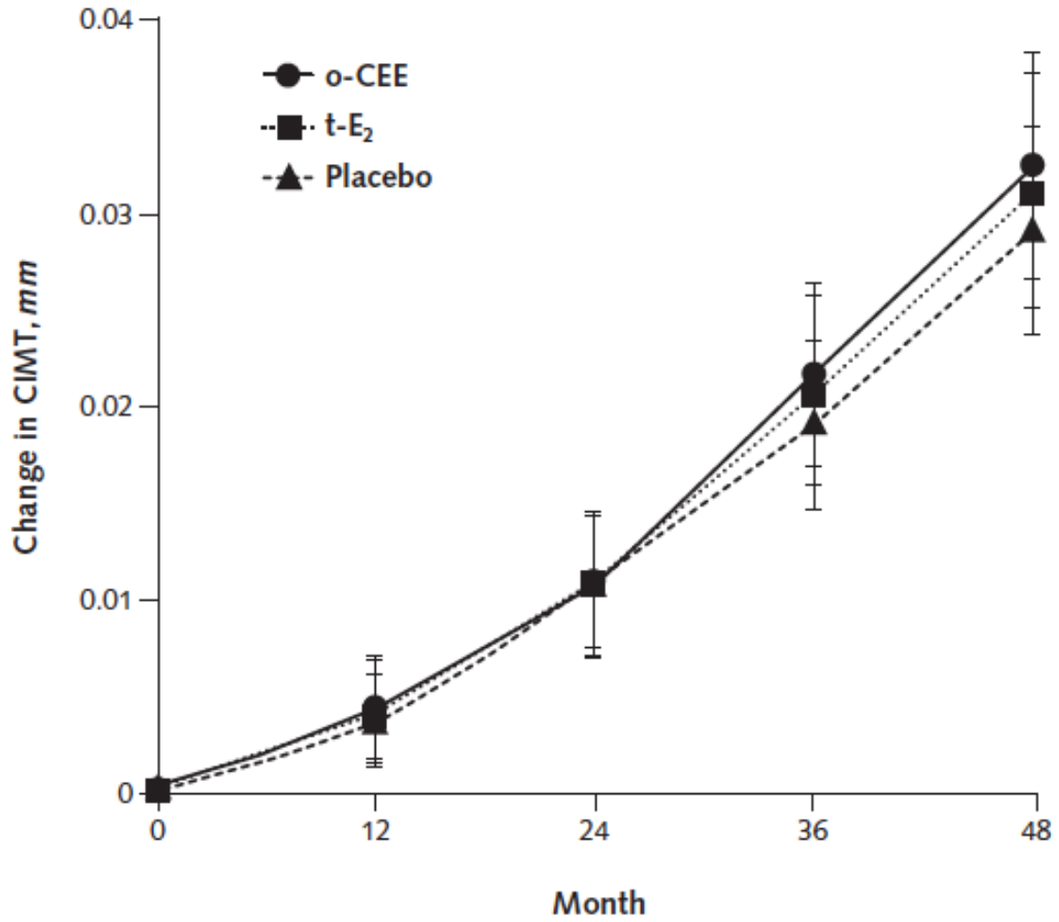
- KEEPS:
  - Outcome Measures:
    - Primary - Carotid artery intima-media thickness (CIMT) by high resolution US
    - Secondary - Coronary artery calcium (CAC) with chest CT, bloodwork
    - Followed for 3-4 years

Heart Health - New Trials

- KEEPS
  - Results:
    - CIMT increased similarly in all groups (0.0076mm/yr)
    - CAC - increased with no significant difference between any group

Heart Health - New Trials

Figure 2. **Effects of treatment on CIMT.**



The change in CIMT (primary end point) from baseline to 12, 24, 36, and 48 mo after randomization by treatment group is shown. Bars represent 95% CIs. All values are derived from the linear mixed-effects model for repeated measurements (see Methods section). CIMT = carotid artery intima–media thickness; o-CEE = oral conjugated equine estrogens; t-E_2 = transdermal 17β-estradiol.

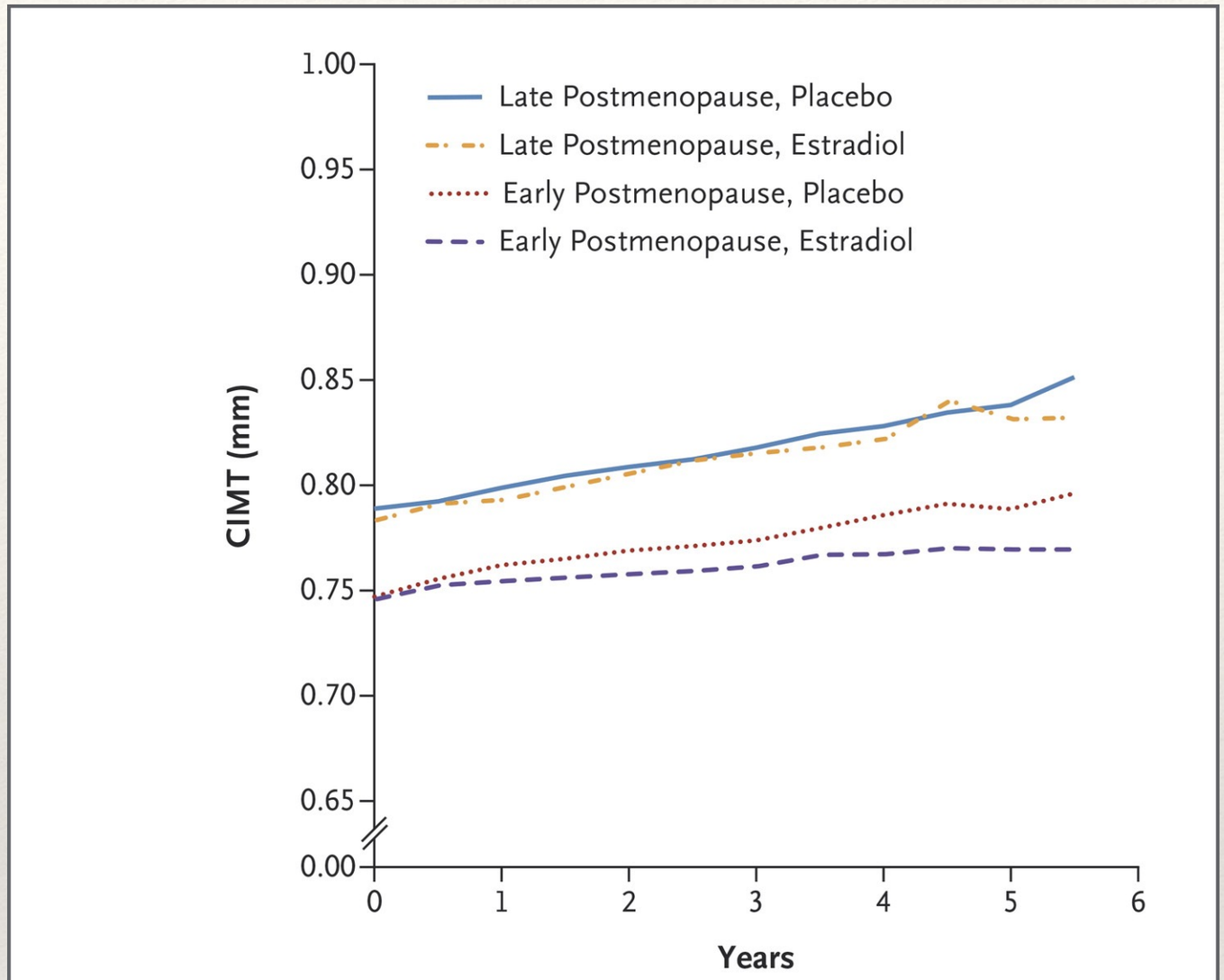
Heart Health - New Trials

- KEEPS:
  - Results:
    - No adverse events could be attributed to specific treatment group
    - Power to compare clinical adverse events insufficient

New RCT: ELITE

- 643 participants (mean age 55.4 and 65.4)
- Two groups—one <6 years from LNMP (early group), one >10 years from LNMP (late group)
- Treatment Groups:
  - In each group women were randomized to receive 17 beta estradiol 1 mg orally daily or placebo.
  - Those receiving the estradiol received active 4% progesterone vaginal gel for 10 days per month, vs placebo gel for those in the placebo arm
- Study was extended to an average of 5 years
- Primary outcome was CIMT every 6 months.

Harman et al. KEEPS Study. *Ann Intern Med* 2014;161:249-60. Slide by Dr. Elaine Jolly, modified.



No. of Participants							
With CIMT data	643	533	522	515	424	295	56
Who completed or discontinued study	0	106	119	128	215	345	582
Without CIMT data	0	4	2	0	4	3	5

ELITE Summary and Conclusions

- The **early group** treatment arm showed a **50% reduction in rate of progression of carotid intima media thickening** with $p < 0.007$

- No difference was seen in the late group

Hodis HN et. Al., *AHA Annual Congress,* 2014; 130:A13283. Slide by Dr. Elaine Jolly, modified.

Heart Health - New Trials

- Conclusions:
  - New RCT data support a *neutral or beneficial* effect on subclinical cardiac disease, from the use of estrogen in young healthy women close to the menopause.

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"Apparently I have done something to upset you."

Genitourinary Syndrome of Menopause

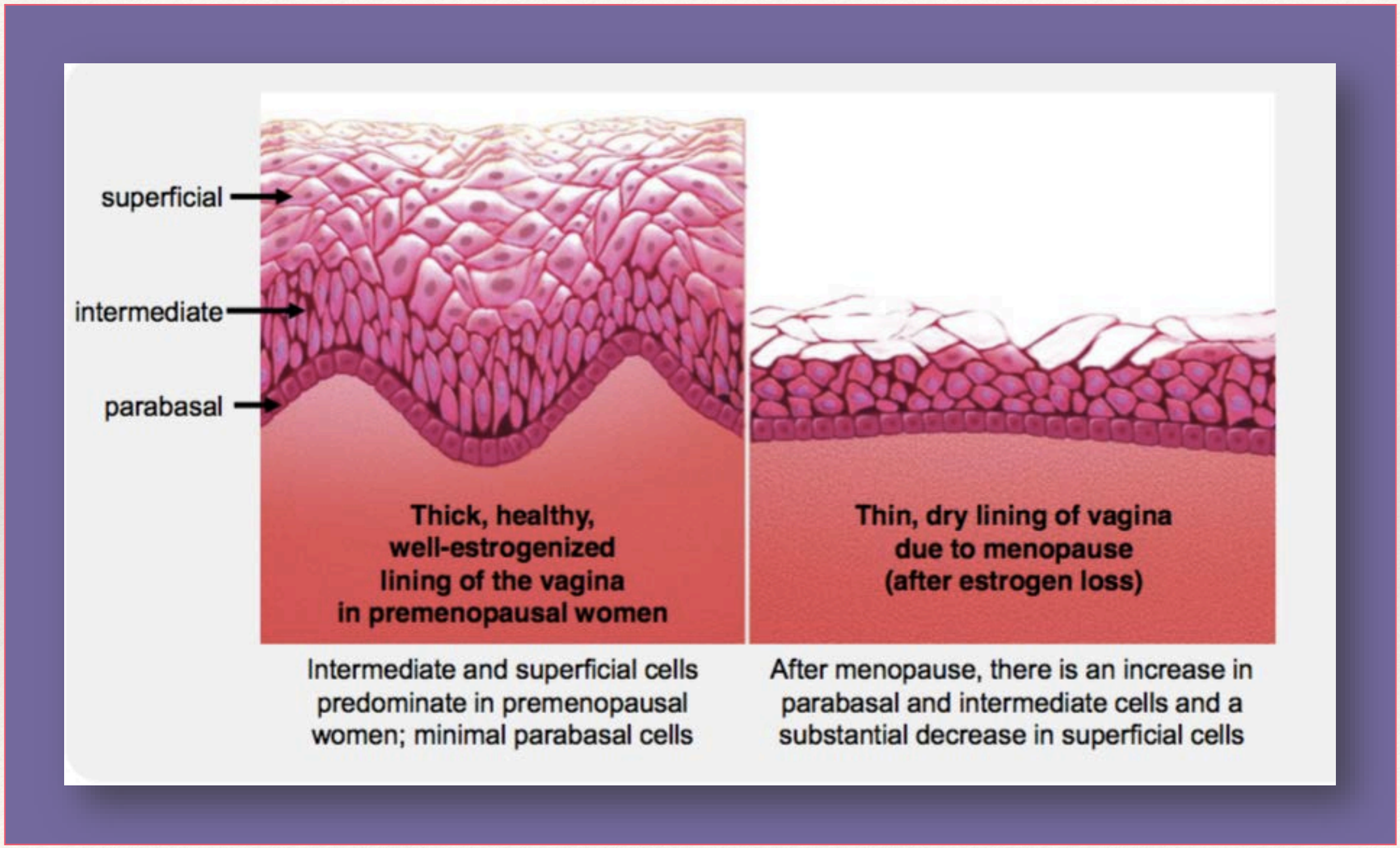
- A condition with many names:
  - Vulvovaginal atrophy, urogenital atrophy, atrophic vaginitis, senile vaginitis
- New terminology deemed necessary:
  - “Vagina” not overly popular with public and media
  - Did not address full spectrum of condition
  - “Atrophy” inaccurate and potentially offensive

Prevalence of GSM

- Up to 75% of menopausal women may experience vaginal atrophy symptoms[1,2]
- Approximately 50% of post-menopausal women have vaginal atrophy symptoms that impact on sexual function and quality of life[3]
- Despite its prevalence, vaginal atrophy is often not recognized by women as a chronic condition
  - 1/3 will not seek medical advice[3]
- The taboo status surrounding vaginal atrophy means that many women do not receive effective treatment

1. The North American Menopause Society. *Menopause*. 2007;14:357-369.
2. Labrie F, et al. *Menopause*. 2009;16:907-22.
3. Nappi RE, Kokot-Kierepa M. *Climacteric*. 2012;15:36-44.
Slide by SIGMA.

Effect on Vaginal Lining



NAMS., *Menopause*, 2007; 14:357-69. Slide by SIGMA.

Formulation	Composition	Dosages
Vaginal Cream (Estragyn)	Estrone 0.1%	0.5grams - 4grams*
Vaginal Cream (Premarin)	Conjugated equine estrogen	0.5grams PV daily for 2 weeks, then 2x/week
Vaginal Ring (Estring)	17Beta-estradiol	2mg ring releasing 7.5mcg/day for 90 days
Vaginal Tablet (Vagifem)	17Beta-estadiol	10mcg tablet daily for two weeks, then 2x/week

ESTRAGYN
vaginal cream
crème vaginale
Estrone vaginal cream – Crème vaginale à base d'estrone
0.1% w/w | 0.1% p/p

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What's New in Menopause

- Tissue Selective Estrogen Complex
  - Estrogen plus SERM
  - Very specific combination of CEE 0.45mg and basodoxefine 20mg
  - Once daily oral pill
  - Marketed in Canada as Duavive
  - Excellent bleeding profiles
  - In vivo evidence of reduction in breast stimulation compared to standard HT

SMART TRIALS

TSEC: Bazedoxifine and Conjugated equine estrogens

- Bazedoxifene has ER antagonist effects in the breast
- In the SMART trials, breast density measurements of the CEE/BZA combinations did not differ from placebo
- In a pooled analysis of the five SMART trials:
  - Four breast cancers (0.3%) among 1585 women treated with CE 0.45 mg/BZA 20 mg (RR 1.1; 95% CI, 0.3–3.8)
  - None in 1583 women treated with CE 0.625 mg/BZA 20 mg (RR 0.4; 95% CI, 0.1–2.0), and
  - Two (0.2%) among 1241 controls.
  - Maximum follow-up was only 24 months.

James H Pickar, Barry S Komm Selective estrogen receptor modulators and the combination therapy conjugated estrogens/bazedoxifene: A review of effects on the breast. Post Reproduct

How Long to Use Hormones?

- There is no longer a “lowest dose for shortest duration” dogma
- Many women continue to have bothersome symptoms of menopause into their 60’s and beyond
- North American Menopause Society supports the “judicious use of hormone replacement therapy in women over the age of 65”

How Long to Use Hormones?

- When a patient is considering discontinuing or stopping hormones:
  - Tapering is not necessary, but often preferred
  - Taper estrogen first, until a stable dose is reached
  - Stop progestin only when estrogen has been stopped completely

How Long to Use Hormones?

- Is it safe to stop?
  - Finnish study of >300 000 women stopping hormone therapy
  - Evaluated stroke and CHD risk in time after discontinuation
    - Cardiac death risk 1.26 (1.16-1.37) in first year
    - Stroke death risk 1.63 (1.47-1.79) in first year

Putting it all together: What do I Tell my Patients?

- Validate their menopausal symptoms. Many women have bothersome symptoms that negatively affect their quality of life.
- Menopausal hormone therapy is the gold standard and first line treatment for moderate to severe bothersome symptoms.
- Risks of therapy are small.

Putting it all together: What do I Give my Patients?

- Estrogens:
  - Healthy young patients may take any low dose estrogen
  - Favour transdermal for safety profiles
- Progestogens:
  - Favour progesterone for safety profiles
  - Consider cyclical regimens for breast health
- Consider CEE alone for the hysterectomized patient
- Local estrogen only for symptoms of GSM alone
- Consider TSEC

Summary

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