Northern Ontario Women's Health Conference

Thunder Bay Ontario

Friday October 14, 2022

Northern Ontario Women's Health Conference

Updates to Menopause Treatment Guidelines

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University of Toronto

St Michael's Hospital

October 14, 2022

11:00 – 11:25

DISCLOSURES

- **Faculty: University of Toronto,**
  Associate Professor ,Department of Obstetrics & Gynecology and Department of Internal Medicine (Endocrinology)

- **Relationships with for-profit and not-for-profit interests:**
- **--Advisory Boards (Not for Profit):**
- SIGMA-CMS --Board of Directors & past Executive Member;
  Canadian Osteoporosis Society –Scientific Advisory Committee

--Advisory Board /Speakers Bureau/Consultant : Amgen, Allergan, Berlex, Biosyent, Duchesnay, Lupin, NovoNordisk, Pfizer

Grants/ Clinical Research Support: NovoNordisk

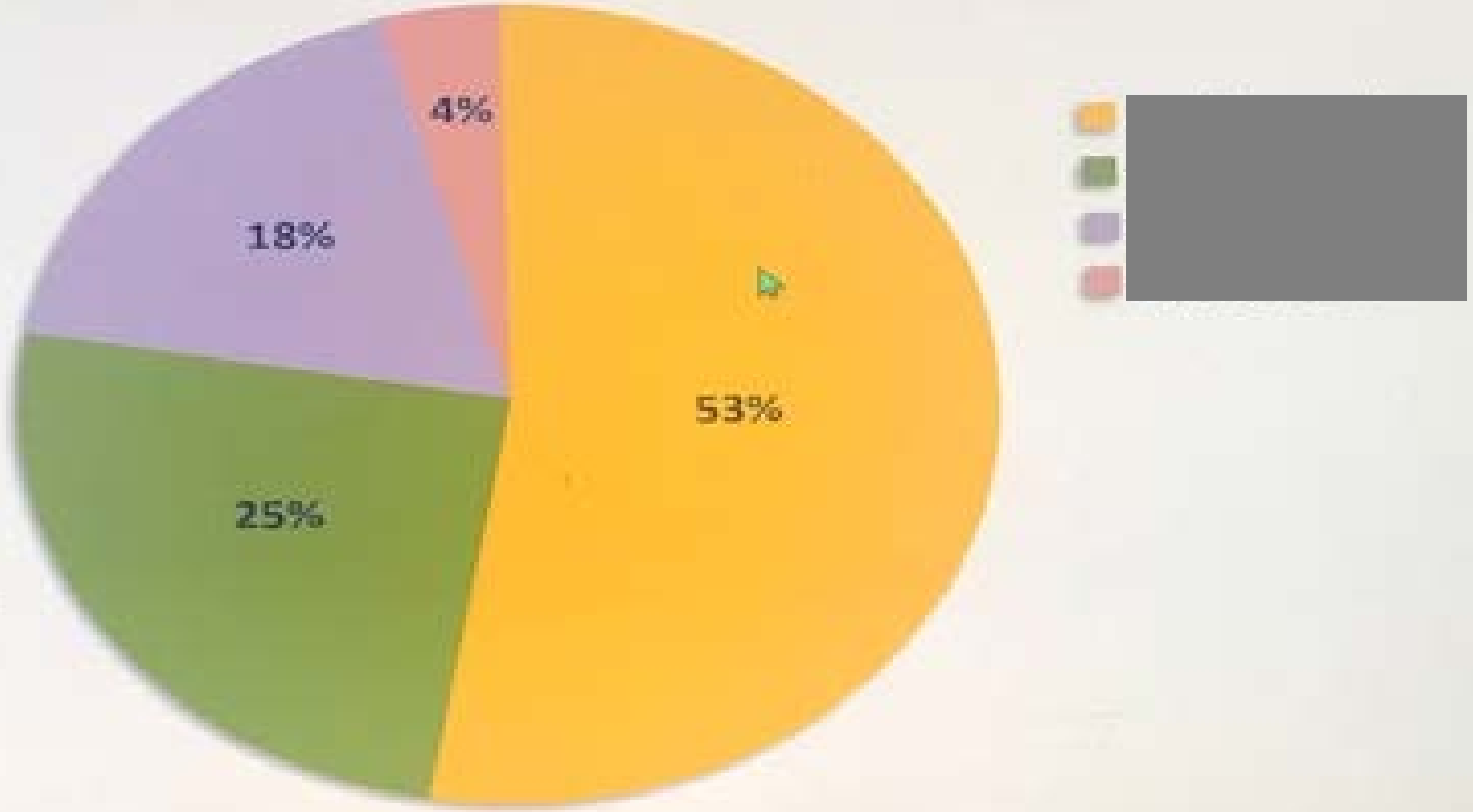
– **Patents: None**

– **Other: None**

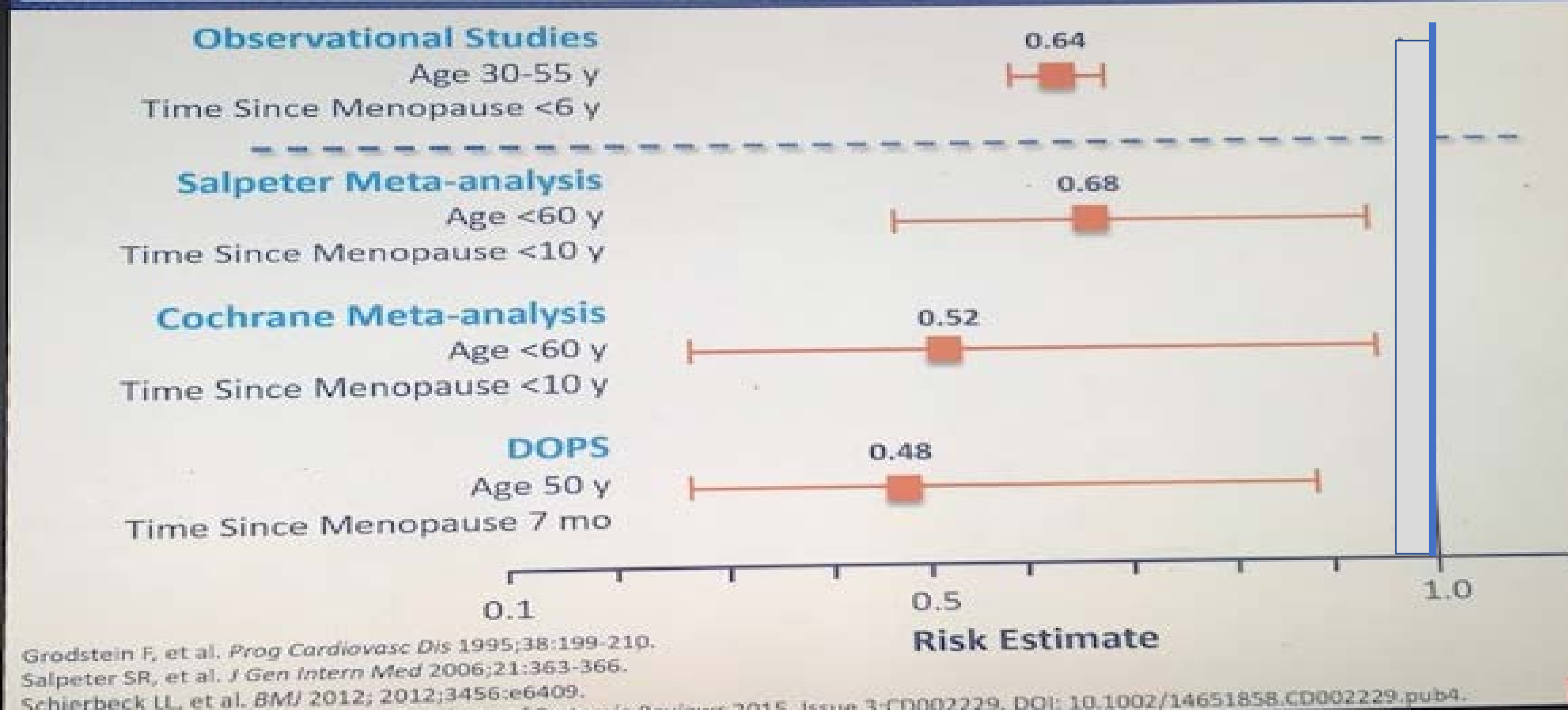
OBJECTIVES

- **To review some key findings of the Women's Health Initiative(WHI) and how they guide our use of HRT**
- **To provide an overview of the 2021 SOGC MENOPAUSE GUIDELINES including data on some new therapies**
- **Discuss strategies for management of menopause patients : Addressing the needs of menopause patients and individualizing their care**

Causes of Death in Women



Relative Risk of CHD: Observational Studies and Randomized Trials

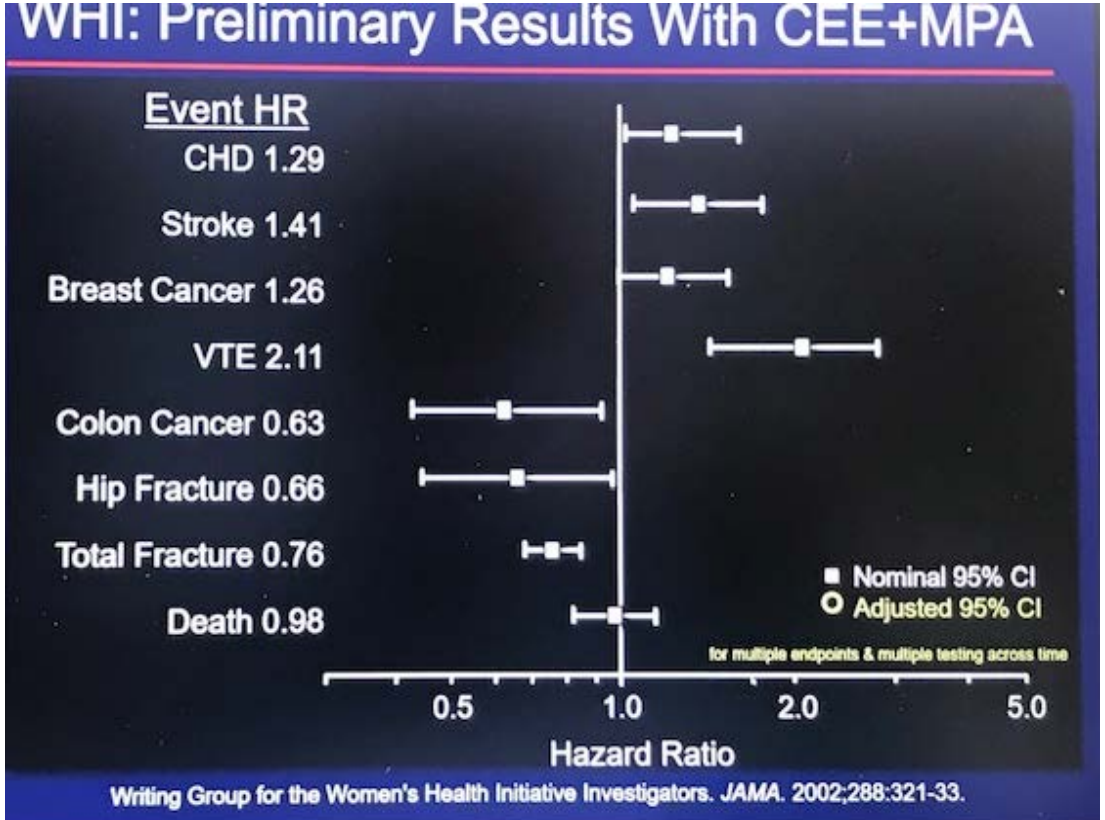


Grodstein F, et al. *Prog Cardiovasc Dis* 1995;38:199-210.
Salpeter SR, et al. *J Gen Intern Med* 2006;21:363-366.
Schierbeck LL, et al. *BMJ* 2012; 2012;3456:e6409.
Boardman HMP, et al. *Cochrane Database of Systemic Reviews* 2015, Issue 3:CD002229. DOI: 10.1002/14651858.CD002229.pub4.

Women's Health Initiative study 2002

Headline, WHI Press Release, July 8, 2002 ==>

"Major Hormone Study Stopped for Breast Cancer Harm"

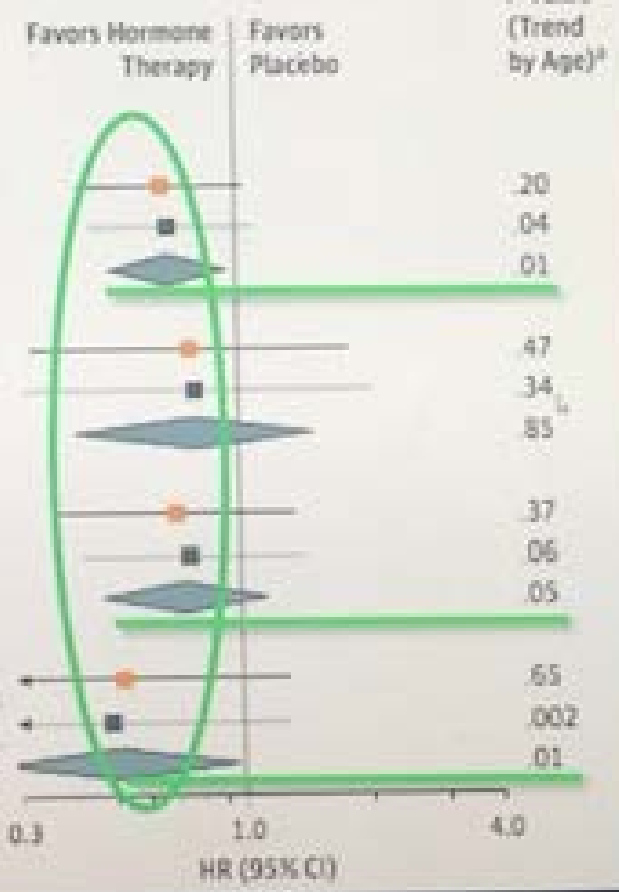



INSIDE HARKEN AND HALLIBURTON
THE OLDEST SKULL
Newsweek
A New Study Raises Fears About the Risks For Millions Of Women. Here's What You Should Do
Beyond Hormone Therapy
Use of MHT quickly plummeted worldwide

WHI Mortality Outcomes During the Intervention Phase: Women 50 to 59 at Randomization

Figure 3. Mortality Outcomes During the Intervention Phase According to 10-Year Age Groups at Randomization

Outcome by Age	No. of Deaths, Annualized Rates (%) Hormone Therapy	Placebo	HR (95% CI)	P Value (Trend by Age)[a]
Age 50-59 y				
All-cause mortality				
CEE plus MPA vs placebo	35 (0.20)	48 (0.30)	0.67 (0.43-1.04)	.20
CEE alone vs placebo	35 (0.28)	50 (0.39)	0.71 (0.46-1.09)	.04
Pooled trials	70 (0.23)	98 (0.34)	0.69 (0.51-0.94)	.01
CVD mortality[b]				
CEE plus MPA vs placebo	10 (0.058)	12 (0.075)	0.77 (0.33-1.79)	.47
CEE alone vs placebo	8 (0.063)	10 (0.077)	0.81 (0.32-2.04)	.34
Pooled trials	18 (0.060)	22 (0.076)	0.79 (0.42-1.47)	.85
Cancer mortality				
CEE plus MPA vs placebo	17 (0.099)	22 (0.14)	0.71 (0.38-1.33)	.37
CEE alone vs placebo	20 (0.16)	26 (0.20)	0.78 (0.43-1.40)	.06
Pooled trials	37 (0.12)	48 (0.17)	0.74 (0.48-1.14)	.05
Other mortality[c]				
CEE plus MPA vs placebo	8 (0.046)	14 (0.087)	0.53 (0.22-1.27)	.65
CEE alone vs placebo	7 (0.056)	14 (0.11)	0.51 (0.20-1.26)	.002
Pooled trials	15 (0.050)	28 (0.097)	0.52 (0.28-0.97)	.01



Median Follow-up:
CEE+MPA = 5.6 [interquartile range (IQR), 4.9-6.8] years;
CEE = 7.2 [IQR, 6.5-8.2]

[a]P values based on a test for trend of interaction between the randomization group and the age group.

[b]Cardiovascular disease (CVD) mortality includes deaths due to myocardial infarction, coronary heart disease (CHD), stroke, heart failure, peripheral vascular disease, venous thromboembolism, and other major causes of CVD death.

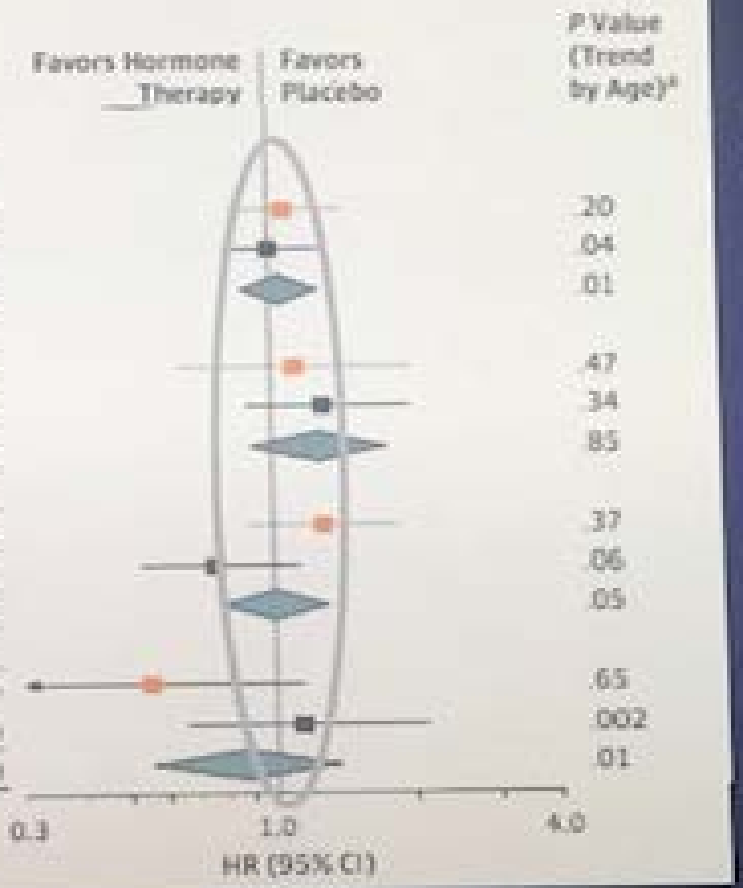
[c]Indicates mortality outcomes not due to CVD or cancer.

Manson et al. Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The WHI Randomized Trials. JAMA. 2017;318(10):927-938.

WHI Mortality Outcomes During the Intervention Phase: Women 60 to 69 at Randomization

Figure 3. Mortality Outcomes During the Intervention Phase According to 10-Year Age Groups at Randomization

Outcome by Age	No. of Deaths, Annualized Rates (%)			P Value (Trend by Age)[a]
	Hormone Therapy	Placebo	HR (95% CI)	
Age 60-69 y				
All-cause mortality				
CEE plus MPA vs placebo	111 (0.51)	94 (0.46)	1.07 (0.82-1.41)	.20
CEE alone vs placebo	130 (0.76)	134 (0.75)	1.02 (0.80-1.30)	.04
Pooled trials	241 (0.62)	228 (0.60)	1.04 (0.87-1.25)	.01
CVD mortality[b]				
CEE plus MPA vs placebo	27 (0.12)	22 (0.11)	1.11 (0.63-1.95)	.47
CEE alone vs placebo	57 (0.33)	46 (0.26)	1.30 (0.88,1.92)	.34
Pooled trials	84 (0.22)	68 (0.18)	1.24 (0.90-1.70)	.85
Cancer mortality				
CEE plus MPA vs placebo	72 (0.33)	52 (0.26)	1.26 (0.88-1.80)	.37
CEE alone vs placebo	48 (0.28)	65 (0.37)	0.77 (0.53-1.12)	.06
Pooled trials	120 (0.31)	117 (0.31)	1.00 (0.77-1.26)	.05
Other mortality[c]				
CEE plus MPA vs placebo	12 (0.055)	20 (0.098)	0.55 (0.27-1.13)	.65
CEE alone vs placebo	25 (0.15)	23 (0.13)	1.15 (0.65-2.03)	.002
Pooled trials	37 (0.095)	43 (0.11)	0.86 (0.55-1.34)	.01



Median Follow-up:
CEE+MPA = 5.6 [interquartile range (IQR), 4.9-6.5] years;
CEE = 7.2 [IQR, 6.5-8.2]

[a]P values based on a test for trend of interaction between the randomization group and the age group.

[b]Cardiovascular disease (CVD) mortality includes deaths due to myocardial infarction, coronary heart disease (CHD), stroke, heart failure, peripheral vascular disease, venous thromboembolism, and other major causes of CVD death.

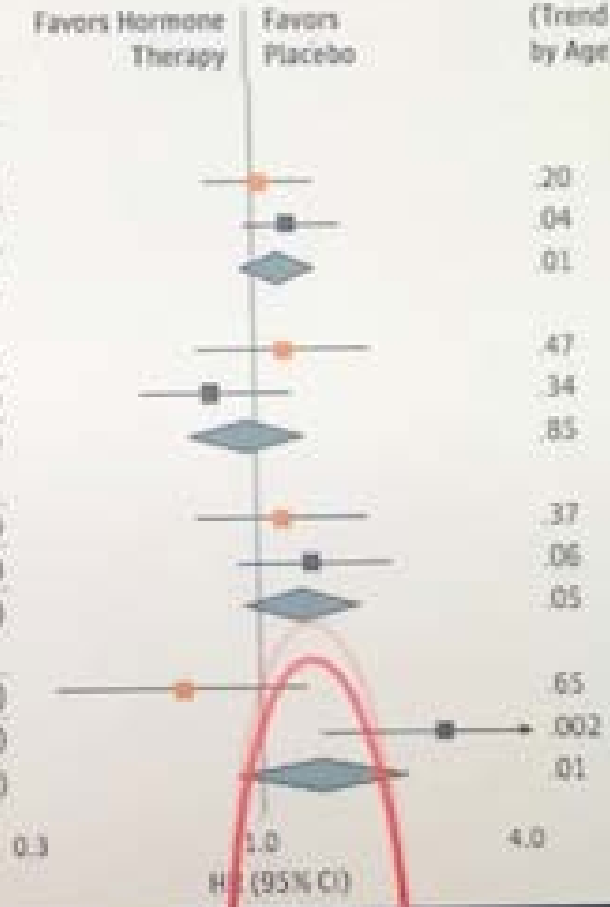
[c]Indicates mortality outcomes not due to CVD or cancer.

Manson et al. Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The WHI Randomized Trials. JAMA. 2017;318(10):927-938.

WHI Mortality Outcomes During the Intervention Phase: Women 70 to 79 at Randomization

Figure 3. Mortality Outcomes During the Intervention Phase According to 10-Year Age Groups at Randomization

Outcome by Age	No. of Deaths, Annualized Rates (%)			P Value (Trend by Age)[a]
	Hormone Therapy	Placebo	HR (95% CI)	
Age 70-79 y				
All-cause mortality				
CEE plus MPA vs placebo	104 (1.06)	96 (1.01)	1.03 (0.78-1.36)	.20
CEE alone vs placebo	136 (1.53)	115 (1.27)	1.22 (0.95-1.56)	.04
Pooled trials	240 (1.28)	211 (1.14)	1.13 (0.94-1.36)	.01
CVD mortality[b]				
CEE plus MPA vs placebo	44 (0.45)	36 (0.38)	1.16 (0.74-1.80)	.47
CEE alone vs placebo	45 (0.51)	57 (0.63)	0.81 (0.55-1.20)	.34
Pooled trials	89 (0.48)	93 (0.50)	0.95 (0.71-1.27)	.85
Cancer mortality				
CEE plus MPA vs placebo	44 (0.45)	37 (0.39)	1.13 (0.73-1.75)	.37
CEE alone vs placebo	58 (0.65)	45 (0.50)	1.34 (0.90-1.97)	.06
Pooled trials	102 (0.54)	82 (0.44)	1.24 (0.93-1.66)	.05
Other mortality[c]				
CEE plus MPA vs placebo	16 (0.16)	23 (0.24)	0.67 (0.35-1.26)	.65
CEE alone vs placebo	33 (0.37)	13 (0.14)	2.59 (1.36-4.92)	.002
Pooled trials	49 (0.26)	36 (0.19)	1.35 (0.88-2.06)	.01



Median Follow-up:
CEE+MPA = 5.6 [interquartile range (IQR), 4.9-6.5] years;
CEE = 7.2 [IQR, 6.5-8.2]

[a]P values based on a test for trend of interaction between the randomization group and the age group.

[b]Cardiovascular disease (CVD) mortality includes deaths due to myocardial infarction, coronary heart disease (CHD), stroke, heart failure, peripheral vascular disease, venous thromboembolism, and other major causes of CVD death.

[c]Indicates mortality outcomes not due to CVD or cancer.

CEE-alone Trial

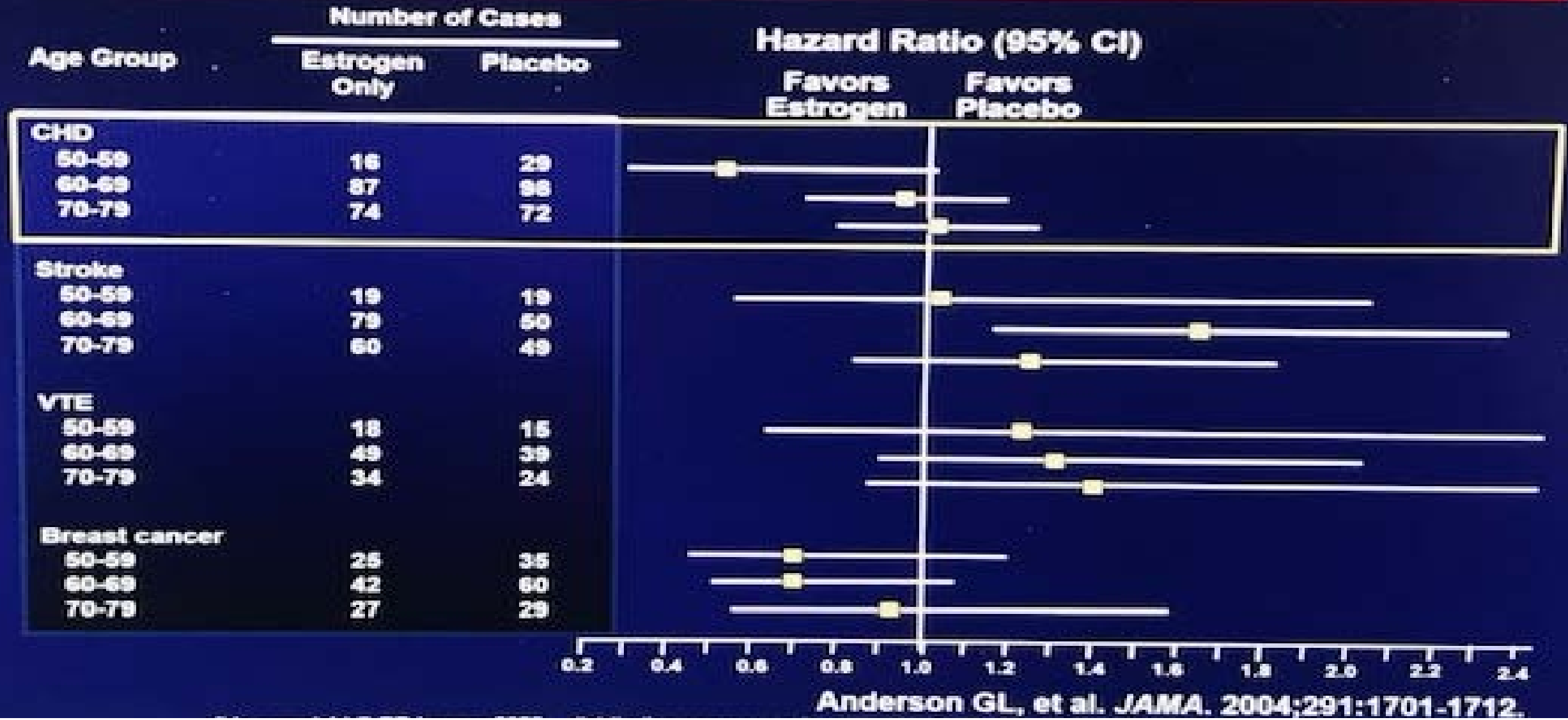
Also stopped early -- decision driven by an increase in stroke in the total cohort (HR=1.39; 95% CI, 1.10-1.77), that was not seen in women aged 50 - 59

Major contrasts in results of CEE-alone vs CEE+MPA =>

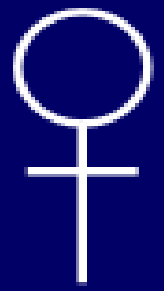
- a *reduced* rate of breast cancer was at the cusp of significance 0.77 (0.59-1.01),
- a non-significant reduction in CHD, HR = 0.91 (0.75-1.12)

In FINAL ANALYSIS :
In 50-59 yo ---↓ CHD –@ revascularization & ↓Cor A calcification
Overall ↓breast Ca in longer followup

WHI CEE-alone: Benefits Also Generally Associated With Younger Age



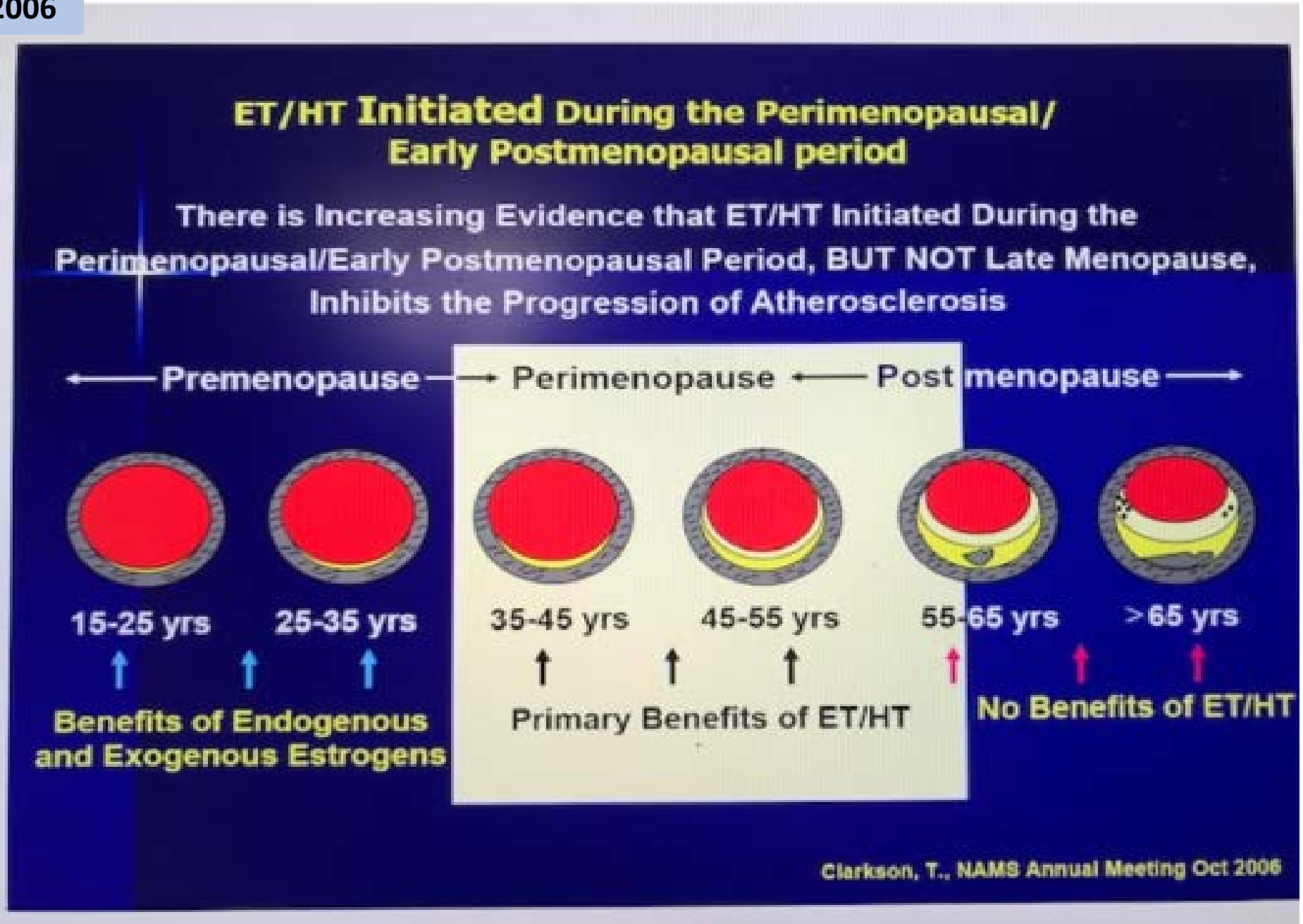
Anderson GL, et al. *JAMA*. 2004;291:1701-1712.



Hypothesis

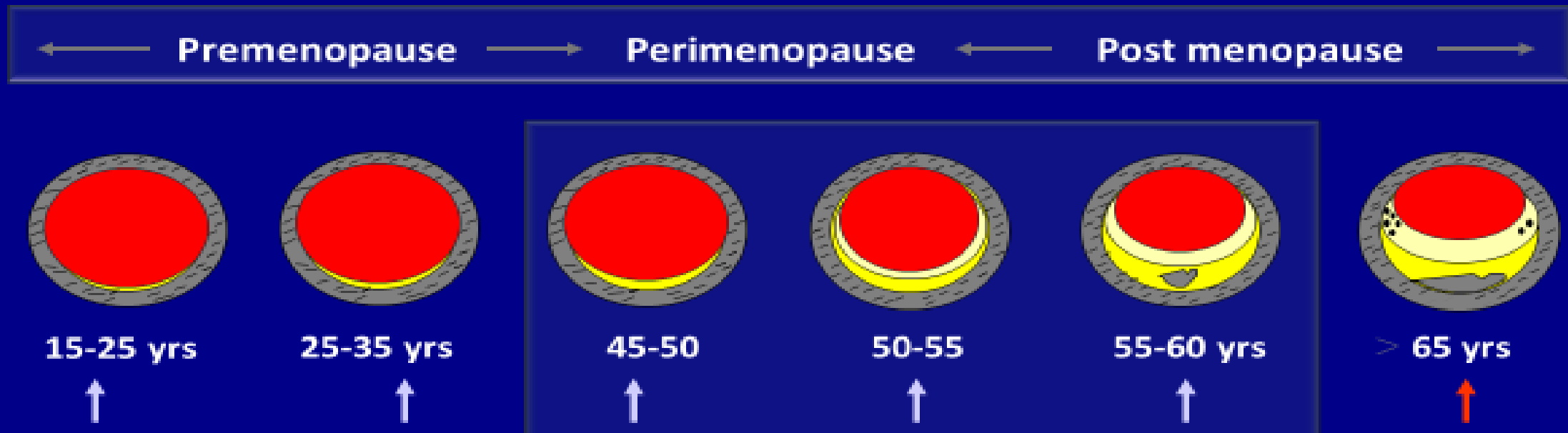
Reproductive stage is a major determinant of the effect of estrogens on atherosclerosis progression, complications and plaque vulnerability

Professor Tom Clarkson
NAMS AGM – Oct 2006



Window of Opportunity for Hormone Therapy

Reproductive stage is a major determinant of the effect of estrogens on atherosclerosis progression, complications and plaque vulnerability

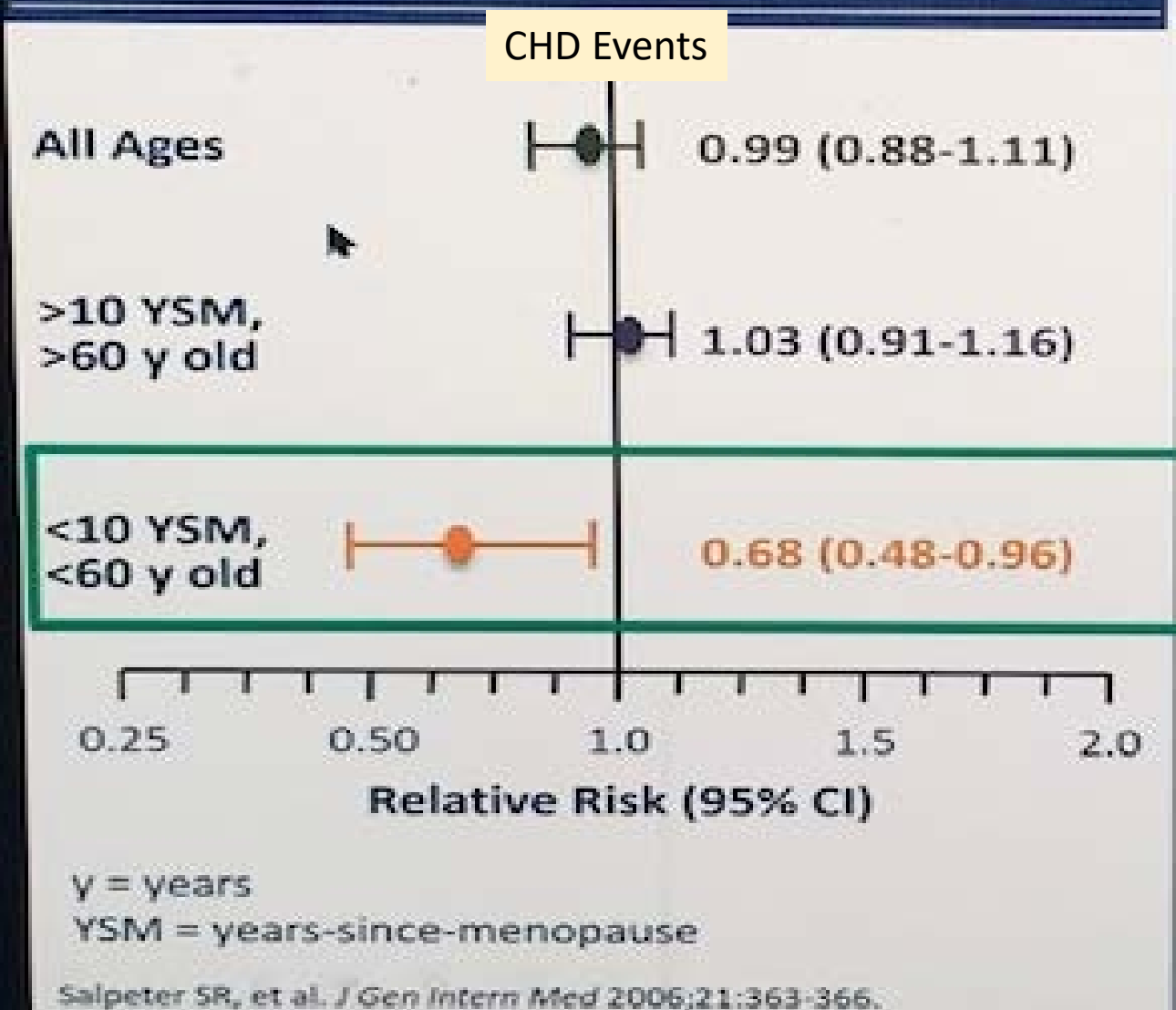


Favorable Lipid and Endothelial Effects of Estrogen Predominate

Prothrombotic and Proinflammatory Effects of Estrogen Predominate

Clarkson, T., NAMS Annual Meeting Oct 2006
Mikkola, Clarkson & Notelovitz Ann Med 2004

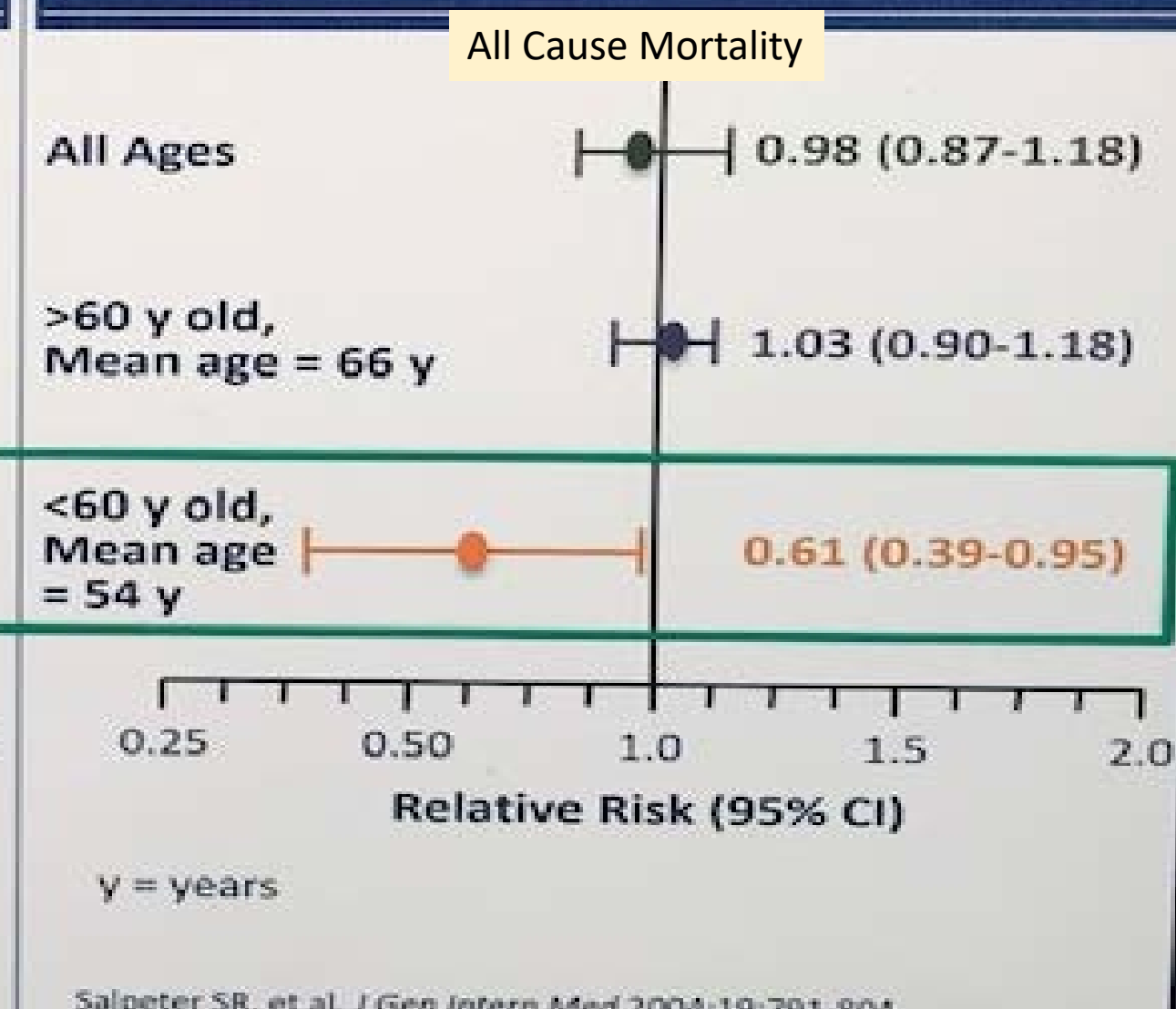
CHD Events Associated with HRT in Younger and Older Women: Meta-analysis of 23 Randomized Controlled Trials (191,340 patient-years)



y = years
YSM = years-since-menopause

Salpeter SR, et al. *J Gen Intern Med* 2006;21:363-366.

All-Cause Mortality Associated with HRT in Younger and Older Women: Meta-analysis of 30 Randomized Controlled Trials (119,118 patient-years)



y = years

Salpeter SR, et al. *J Gen Intern Med* 2004;19:791-804.

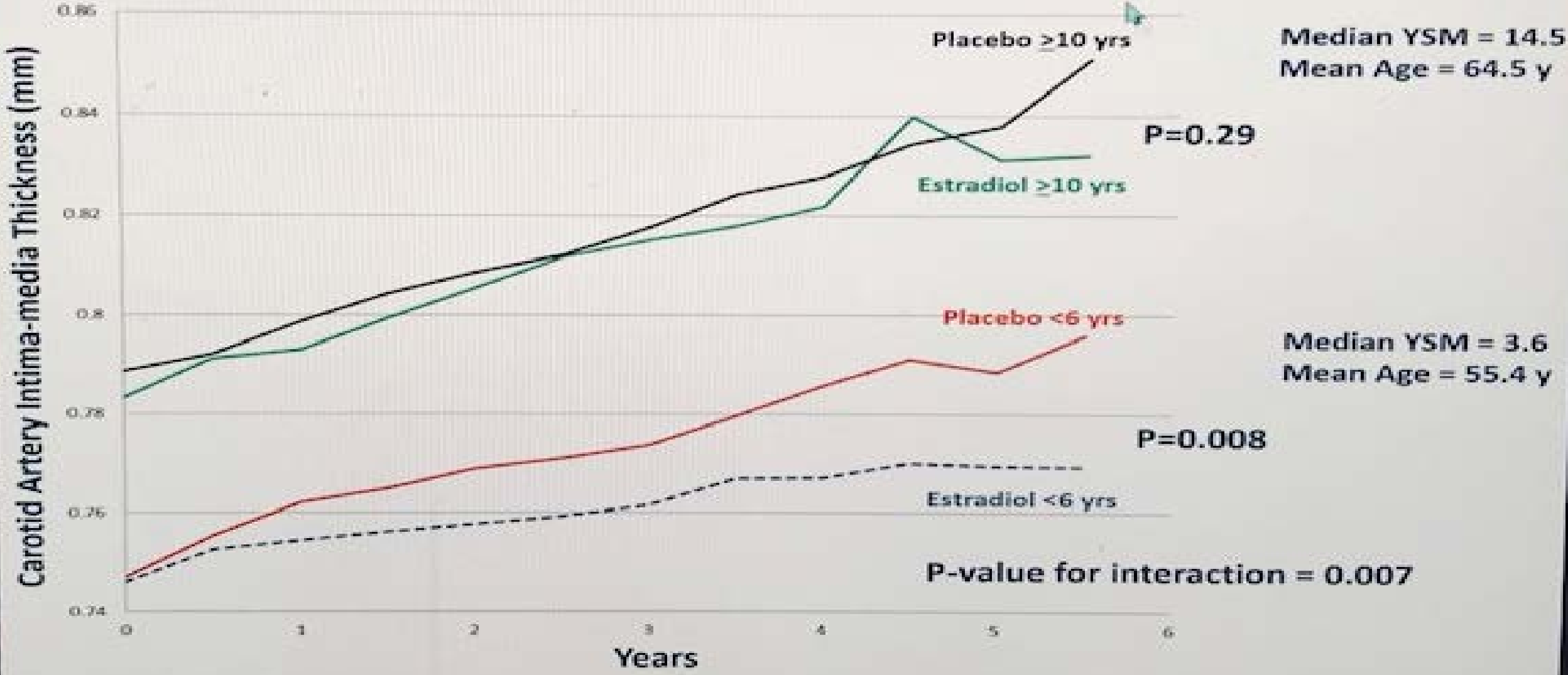
Differences between Randomized Trials and Observational Studies

	Randomized Trials	Observational Studies
Mean age or age range at enrollment (years)	>63	30-55
Time since menopause at HT initiation (years)	>10	<2
Menopausal symptoms (flushing)	excluded	predominant
Duration of therapy (years)	<7	>10-40
Body mass index (mean, kg/m^2)	28.5*	25.1

In WHI 34.1% had BM! >30 kg/m2

Hodis H et al Ann Intern Med 2001; 135:939-953

Early vs. Late Intervention Trial with Estradiol: CIMT by Treatment and Postmenopausal Strata



Hodis HN, et al. *New Engl J Med* 2016;374:1221-1231.

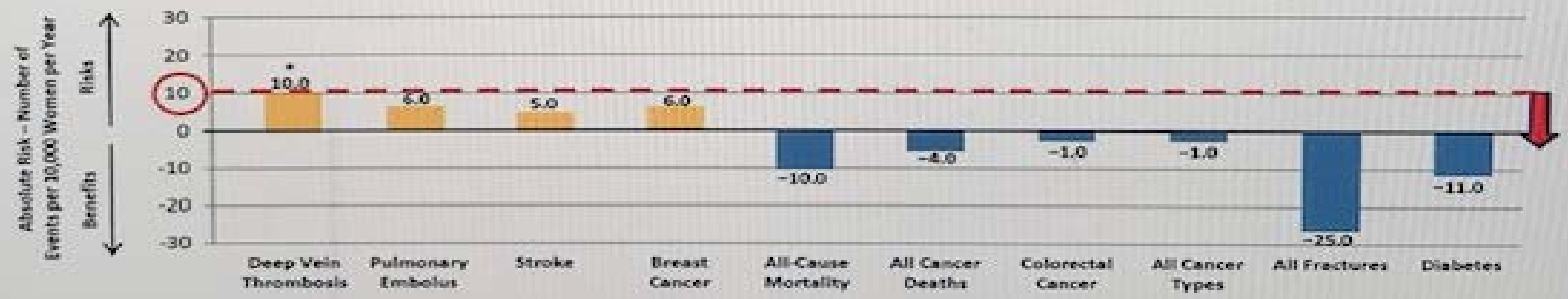
Absolute Benefits and Risks from WHI – Initiation of HT in Women 50-59 Years of Age: Number of Events per 10,000 Women per Year

World Health Organization (WHO)
Council for International Organizations of Medical Sciences (CIOMS)
Classification of Frequency of Drug Reactions

Very common	>1/10 (>10%)
Common (frequent)	>1/100 and <1/10 (>1% and <10%)
Uncommon (infrequent)	>1/1,000 and <1/100 (>0.1% and <1%)
Rare	>1/10,000 and <1/1,000 (0.01% and <0.1%)
Very rare	<1/10,000 (<0.01%)

CE Alone Trial

CE + MPA Trial



Lobo RA, et al. *Atherosclerosis* 2016;254:296-304.

Women over 60, or > 10 years post menopause

- VTE and stroke risk is increased
- Oral and combined hormone therapy preparations more close associated with risk of VTE than either with transdermal or estrogen alone

What was learned from the WHI

Valuable New Insights Not Anticipated in the WHI Trial Design ...

- CHD trends were attributable to age-related differences in the pathophysiology of atheromatous plaque that were unrecognized prior to the HERS & WHI trials
- We've learned from the WHI and subsequent studies that organs with estrogen receptors respond differently to estrogen supplementation after a long period of low estrogen levels than they do **when early replacement preserves physiologic estrogen functions**
- It, together with the HERS study, gave rise to the concept of a "window of opportunity" for prevention of cardiovascular disease
- It showed reduction in All Cause Mortality with MHT for women aged 50 to 59
- It showed that the progestogen is a critical modifier of estrogen benefits for CHD
- Outside of CVD, it showed clearly that MHT prevents fractures, even in women unselected for osteopenia

Fear continues to drive conversation about Hormone Therapy

Women's Health Initiative study 2002

- Breast cancer
- Heart Disease
- Dementia

Summary (SOGC)

- CVD is the number 1 cause of death in women and postmenopausal women are at an increased risk for CVD.
- Data strongly support reduced all-cause mortality and CHD when HRT is initiated in women <60 years old and/or <10 years since menopause.
- Compared with placebo, the risks associated with HRT are statistically non-significant and rare (<1/1,000 women per year of treatment) especially when initiated in women who are <60 years of age and/or <10 years since menopause.

SUMMARY (IMS)

- HRT reduces all-cause mortality, cancer mortality (including breast cancer), other mortality (including dementia/AD), CHD and new onset diabetes mellitus.
- In addition, HRT significantly prevents bone fractures in an unselected population of women and is the most effective therapy for significantly reducing menopausal symptoms.
- Avoidance of initiating hormone therapy (ET) in postmenopausal women aged 50-59 years results in increased disease conditions and mortality and has immen personal and societal economic consequences.

Primary Prevention of CHD in PMW

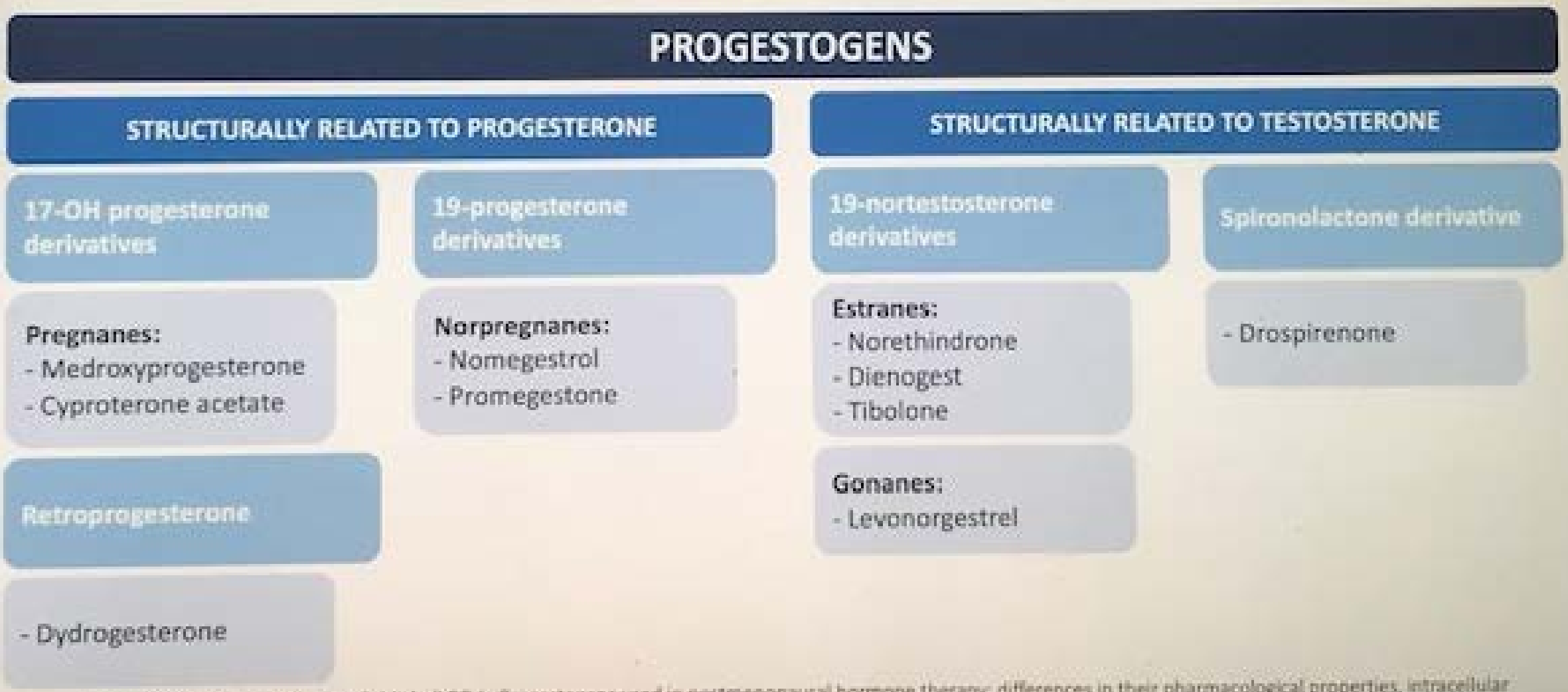
Outcome	Hormone Therapy[1,2*]	Lipid Lowering[3]	Aspirin[4]
CHD	0.68 (0.48-0.96)	0.89 (0.69-1.09)	0.91 (0.80-1.03)
Total Mortality	0.61 (0.39-0.95)	0.95 (0.62-1.46)	0.95 (0.85-1.06)

*Women <60 years old and/or <10 years since menopause when randomized

[1]Salpeter S, et al. *J Gen Intern Med* 2004;19:791-804.
[2]Salpeter S, et al. *J Gen Intern Med* 2006;21:363-366.
[3]Walsh JME, et al. *JAMA* 2004;21:363-366.
[4]Ridker PM, et al. *N Engl J Med* 2005;352:1293-1304.

ALL PROGESTOGENS ARE NOT THE SAME

Different Molecular Structures



Stanczyk FZ, Hapgood JP, Winer S, Mishell DR Jr. Progestogens used in postmenopausal hormone therapy: differences in their pharmacological properties, intracellular actions, and clinical effects. Endocr Rev. 2013 Apr;34(2):171-208.

NICE GUIDELINE – Menopause Diagnosis & Management

ET / EPT :

1.5 Long-term benefits and risks of hormone replacement therapy

Cardiovascular Disease

1.5.4 Ensure that menopausal women and healthcare professionals involved in their care understand that HRT:

- **does not increase cardiovascular disease risk when started in women aged under 60 years**
- does not affect the risk of dying from cardiovascular disease.

1.5.5 Be aware that the **presence of cardiovascular risk factors is not a contraindication to HRT** as long as they are optimally managed.

1.5.6 Using tables 1 and 2, explain to women that:

- the baseline risk of coronary heart disease and stroke for women around menopausal age varies from one woman to another according to the presence of cardiovascular risk factors
- HRT with oestrogen alone is associated with no, or reduced, risk of coronary heart disease
- HRT with **oestrogen and progestogen** is associated with **little or no increase in the risk of coronary heart disease**.

1.5.7 Explain to women that taking oral (but not transdermal) oestrogen is associated with a small increase in the risk of stroke. Also explain that the baseline population risk of stroke in women aged under 60 years is very low (see table 2).

National Institute for Health and Care Excellence (NICE). Menopause: diagnosis and management. NICE guideline [NG23]. Published November 2015. Last updated December 2019. Last accessed May 3, 2021.

NICE GUIDELINE – Menopause Diagnosis & Management

ROUTE OF THERAPY :

1.5 Long-term benefits and risks of hormone replacement therapy

Venous thromboembolism

1.5.1 Explain to women that:

- the risk of venous thromboembolism (VTE) is increased by oral HRT compared with baseline population risk
- the risk of VTE associated with HRT is greater for oral than transdermal preparations
- the risk associated with **transdermal HRT** given at standard therapeutic doses is **no greater than baseline population risk**.

1.5.2 **Consider transdermal rather than oral HRT** for menopausal women who are at increased risk of VTE, including those with a BMI over 30 kg/m^2.

1.5.3 Consider referring menopausal women at high risk of VTE (for example, those with a strong family history of VTE or a hereditary thrombophilia) to a haematologist for assessment before considering HRT.

National Institute for Health and Care Excellence (NICE). Menopause: diagnosis and management. NICE guideline [NG23]. Published November 2015. Last updated December 2019. Last accessed May 3, 2021.

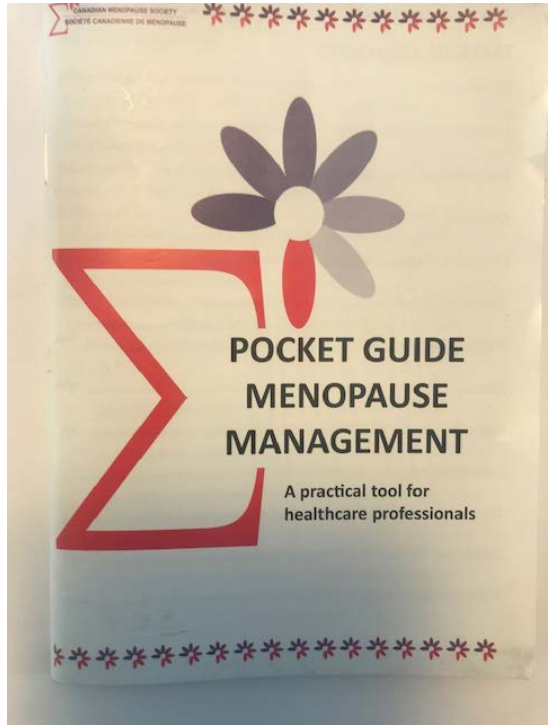
- B. AN OVERVIEW of the 2021 SOGC MENOPAUSE GUIDELINES

Benefits vs Risks

"The Bottom Line"

The recognized indications for menopausal hormone treatment are :

- **a)First-line therapy for relief of vasomotor symptoms in appropriate candidates**
- **b) For women with hypogonadism, primary ovarian insufficiency, or premature surgical menopause without contraindication, hormone therapy is recommended for health benefits until the average age of menopause**
- **c) Low-dose vaginal estrogen therapy is recommended first line for isolated genitourinary syndrome of menopause to treat symptoms of vulvovaginal atrophy**
- **d) To prevent bone loss and to reduce fractures in postmenopausal women at elevated risk of osteoporosis or fractures**



https://www.sigmamenopause.com/consumers/publications

HORMONE THERAPY PRODUCTS IN CANADA

Table 1: Estrogen Products in Canada

Type of Estrogen	Trade Names	Strengths Available	Comments
Oral Estrogen			
conjugated estrogen (CE)	Premarin®	0.3, 0.625, 1.25 mg tablets	One tablet daily
17β estradiol	Estrace®	0.5, 1, 2 mg tablets	One tablet daily
Transdermal Estrogen Patches			
17β estradiol patch	Estradot®	25, 37.5, 50, 75, 100 µg patches	Twice weekly application
	Sandoz Estradiol Derm® (generic)	50, 75, 100 µg patches	Twice weekly application
	Oesclim®	25, 50 µg patches	Twice weekly application
	Climara®	25, 50, 75, 100 µg patches	Once weekly application
Transdermal Estrogen Gel			
17β estradiol gel	Estrogel®	0.75 mg estradiol per 1.25 g metered dose(=one actuation)	Daily application, use in same area (do not rotate sites)
	Divigel®	0.25, 0.5, 1 mg individual packets	Daily application

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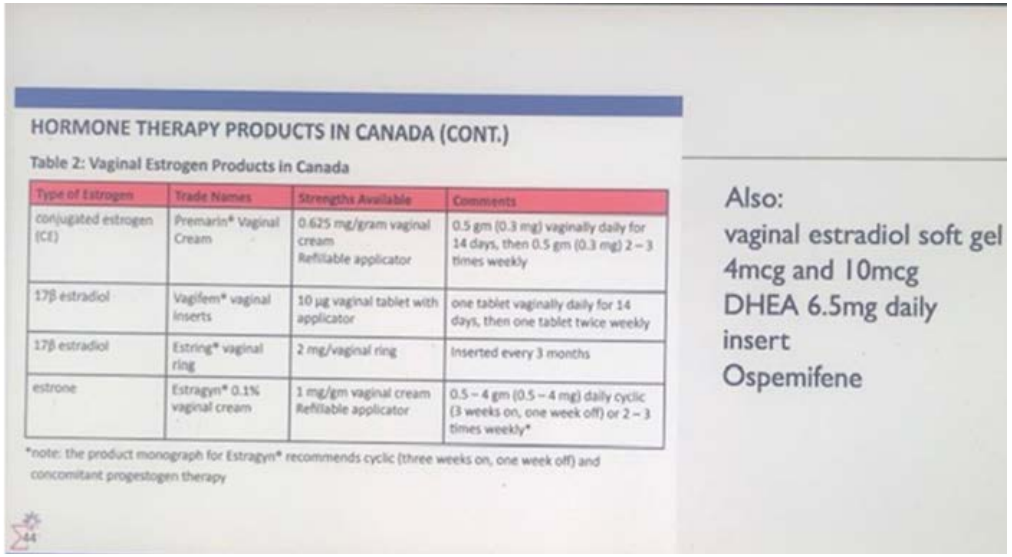


HORMONE THERAPY PRODUCTS IN CANADA (CONT.)

Table 2: Vaginal Estrogen Products in Canada

Type of Estrogen	Trade Names	Strengths Available	Comments
conjugated estrogen (CE)	Premarin® Vaginal Cream	0.625 mg/gram vaginal cream Refillable applicator	0.5 gm (0.3 mg) vaginally daily for 14 days, then 0.5 gm (0.3 mg) 2 – 3 times weekly
17β estradiol	Vagifem® vaginal inserts	10 µg vaginal tablet with applicator	one tablet vaginally daily for 14 days, then one tablet twice weekly
17β estradiol	Estring® vaginal ring	2 mg/vaginal ring	Inserted every 3 months
estrone	Estragyn® 0.1% vaginal cream	1 mg/gm vaginal cream Refillable applicator	0.5 – 4 gm (0.5 – 4 mg) daily cyclic (3 weeks on, one week off) or 2 – 3 times weekly*

*note: the product monograph for Estragyn® recommends cyclic (three weeks on, one week off) and concomitant progestogen therapy

44

Also:
vaginal estradiol soft gel 4mcg and 10mcg
DHEA 6.5mg daily insert
Ospemifene

HORMONE THERAPY PRODUCTS IN CANADA (CONT.)

Table 2: Vaginal Estrogen Products in Canada

Type of Estrogen	Trade Names	Strengths Available	Comments
conjugated estrogen (CE)	Premarin® Vaginal Cream	0.625 mg/gram vaginal cream Refillable applicator	0.5 gm (0.3 mg) vaginally daily for 14 days, then 0.5 gm (0.3 mg) 2 – 3 times weekly
17β estradiol	Vagifem® vaginal inserts	10 µg vaginal tablet with applicator	one tablet vaginally daily for 14 days, then one tablet twice weekly
17β estradiol	Estring® vaginal ring	2 mg/vaginal ring	Inserted every 3 months
estrone	Estragyn® 0.1% vaginal cream	1 mg/gm vaginal cream Refillable applicator	0.5 – 4 gm (0.5 – 4 mg) daily cyclic (3 weeks on, one week off) or 2 – 3 times weekly*

*note: the product monograph for Estragyn® recommends cyclic (three weeks on, one week off) and concomitant progestogen therapy

SOGC/CMS MENOPAUSE GUIDELINES 2021 – KEY POINTS

from each chapter

- **1. SYSTEMATIC APPROACH TO VMS Rx (422 a)**
- **2. GENITOURINARY HEALTH – GSM (422 b)**
- **3. MOOD, SLEEP COGNITION (422 c)**
- **4. SEXUALITY (422 d)**
- **5. CARDIOVASCULAR DISEASE (422 e)**
- **6. BREAST CANCER (422 f)**

1. SYSTEMATIC APPROACH TO VMS Rx (422 a)

- 1- VMS is the key reason/ THE major indication for HRT / no duration limitation
  - Individualization
- POF/POI patient needs **HRT (unless contraindicated) at least to normal menopause age** ≈ 52 yo in Canada
- VMS is more than a bother – significant effects –QOL effects
  - HRT the most effective Rx
  - Hormonal (HRT) and non EPT (Tibolone, Duavive)
    non hormonal options .....
- EPT – continuous combined or cyclic oral or transdermal; norgestrel IUCD –a P option
- LISTS & tables of available effective meds **(NB Also available in *Pocket Guide*)**
- Cultural / traditional therapies
- ***NEW*** *-- Neurokinin Receptor Antagonist -* ***Fazolinetent***

DRUGS FOR VASOMOTOR SYMPTOMS

Table 2. Drugs for Vasomotor Symptoms

Drug	Some formulations	Usual dosage	Cost[a]
Oral estrogens[b]			
Conjugated estrogens[c] - Premarin (Pfizer)[d]	0.3, 0.45, 0.625, 0.9, 1.25 mg tabs	0.3-0.625 mg PO once/d	$177.00
Estradiol[d] - generic	0.5, 1, 2 mg tabs	0.5-1 mg PO once/d	0.90
Estrace (Abbvie)			163.50
Esterified estrogen - Menest (Monarch)[d]	0.3, 0.625, 1.25, 2.5 mg tabs	0.625-1.25 mg PO once/d	74.90
Oral progestogens			
Progesterone (micronized) - generic	100, 200 mg caps	100 mg PO once/d[e]	25.90
Prometrium (Virtus)			316.70
Medroxyprogesterone - generic	2.5, 5, 10 mg tabs	5-10 mg PO once/d × 12-14 d/mo	2.60
Provera (Pfizer)			45.20
Oral estrogen/progestogen combinations			
Conjugated estrogens[c]/medroxyprogesterone - Prempro (Pfizer)[d,f]	0.3/1.5, 0.45/1.5, 0.625/2.5, 0.625/5 mg tabs	0.3/1.5-0.625/5 mg PO once/d	202.80
Estradiol/drospirenone - Angeliq (Bayer)[g]	0.5/0.25, 1/0.5 mg tabs	0.5/0.25 or 1/0.5 mg PO once/d	186.20
Estradiol/norethindrone[h] - Activella (Amneal)[g]	0.5/0.1, 1/0.5 mg tabs	0.5/0.1 or 1/0.5 mg PO once/d	255.60
Estradiol/progesterone - Bijuva (Therapeutics MD)	1/100 mg caps	1/100 mg PO once/d	214.50
Ethinyl estradiol/norethindrone[h] - Femhrt (Abbvie)	2.5 µg/0.5 mg tabs	2.5 µg/0.5 mg or 5 µg/1 mg PO once/d	156.90
Oral estrogen/selective estrogen reuptake modulator (SERM)			
Conjugated estrogens[c]/bazedoxifene - Duavee (Pfizer)	0.45/20 mg tabs	0.45/20 mg PO once/d	185.60
Transdermal estrogens[b]			
Estradiol patches[d,h] - Alora (Abbvie)	0.025, 0.05, 0.075, 0.1 mg/d patches	0.05 mg/d patch 2 ×/wk	113.00
Climara (Bayer)	0.025, 0.0375, 0.05, 0.06, 0.075, 0.1 mg/d patches	0.05 mg/d patch once/wk	138.40
Vivelle-DOT (Novartis)	0.025, 0.0375, 0.05, 0.075, 0.1 mg/d patches	0.05 mg/d patch 2 ×/wk	121.30
Estradiol gel - EstroGel (Ascend Therapeutics)[d]	0.75 mg/actuation (30 doses/unit)[i]	0.75 mg applied once/d	127.40[j]
Divigel (Osmotica)	0.25, 0.5, 0.75, 1, 1.25 mg/packets	0.25-1 mg applied once/d	87.00
Elestrin (Meda)	0.52 mg/actuation (100 doses/unit)[k]	0.52 mg applied once/d	107.50[l]
Estradiol transdermal spray - Evamist (Perrigo)	1.53 mg/spray (56 sprays/unit)	2 sprays once/d	123.80[m]
Vaginal estrogen[b]			
Estradiol intravaginal ring - Femring (Millicent)[d]	0.05, 0.1 mg/d vaginal rings	0.05 mg/d[n]	531.50[o]
Transdermal estrogen/progestin combinations			
Estradiol/levonorgestrel - Climara Pro (Bayer)	0.045/0.015 mg/d patches	0.045/0.015 mg/d patch once/wk	221.90
Estradiol/norethindrone - CombiPatch (Noven Therapeutics)[d]	0.05/0.14, 0.05/0.25 mg/d patches	0.05/0.14 or 0.05/0.25 mg/d patch 2 ×/wk[p]	207.40
Selective serotonin reuptake inhibitor (SSRI)			
Paroxetine mesylate - generic	7.5 mg caps	7.5 mg PO once/d at hs	151.20
Brisdelle (Sebela)			211.90

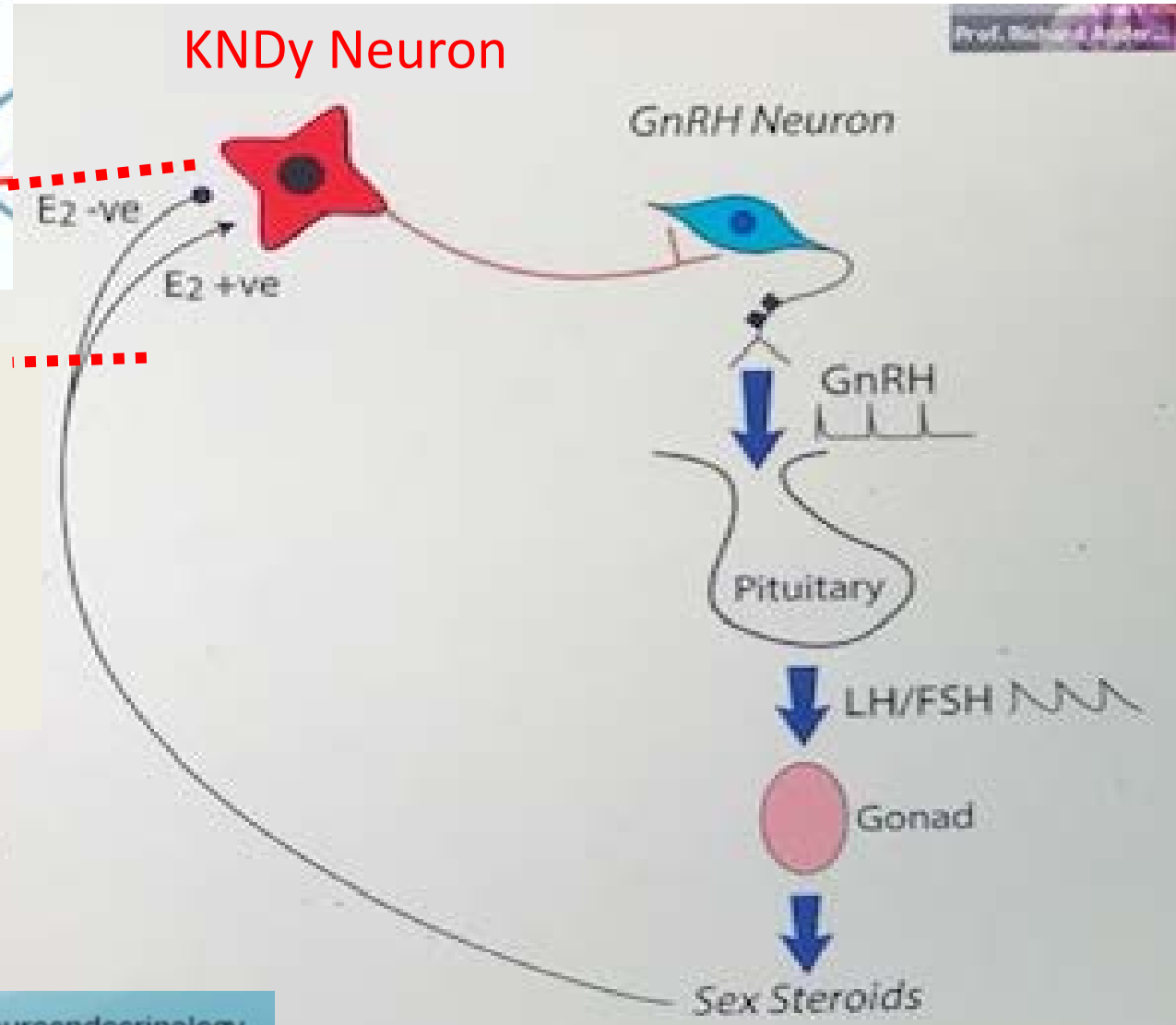
[a] Approximate WAC for 30 days' or 4 weeks' treatment at the lowest usual

[h] Available generically.

KNDy NEURONS and regulation of body temperature

FAZOLINETENT : *A Neurokinin 3 Receptor Antagonist*

VMS



Seminara, SB et al. N Eng J Med, 2003;349(17): 1614-27;Lehman M et al. J Neuroendocrinology

VMS, THERAPEUTICS, CAM & NUTRITION IN MENOPAUSE

- 1***. VMS****-a significant problem for many*
- ***2. MHT =*** **most effective Rx-- safe when started @ <60 yo & within 10 yrs LMP**
- ***3. Hormonal options :*** *EPT or ET if no uterus); -STEAR (tibolone), TSEC(duavive)*
- ***4. Compounded "BHT" –*** NO rigorous evidence to support***,*** not recommended
- ***5. "Non-hormonal" –*** *antidepressants, gabapentinoids, clonidine, oxybutynins–* *for VMS– (NB S/E's)*
- ***6. CBT*** *(cognitive behavior therapy)-****effective****;*
  Exercise, paced breathing, relaxation, accupuncture
- ***7. Natural health pdts –*** *Lack of rigorous evidence to support*
- ***8. Diet/nutrition - NB***

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GSM - VAGINAL ATROPHY

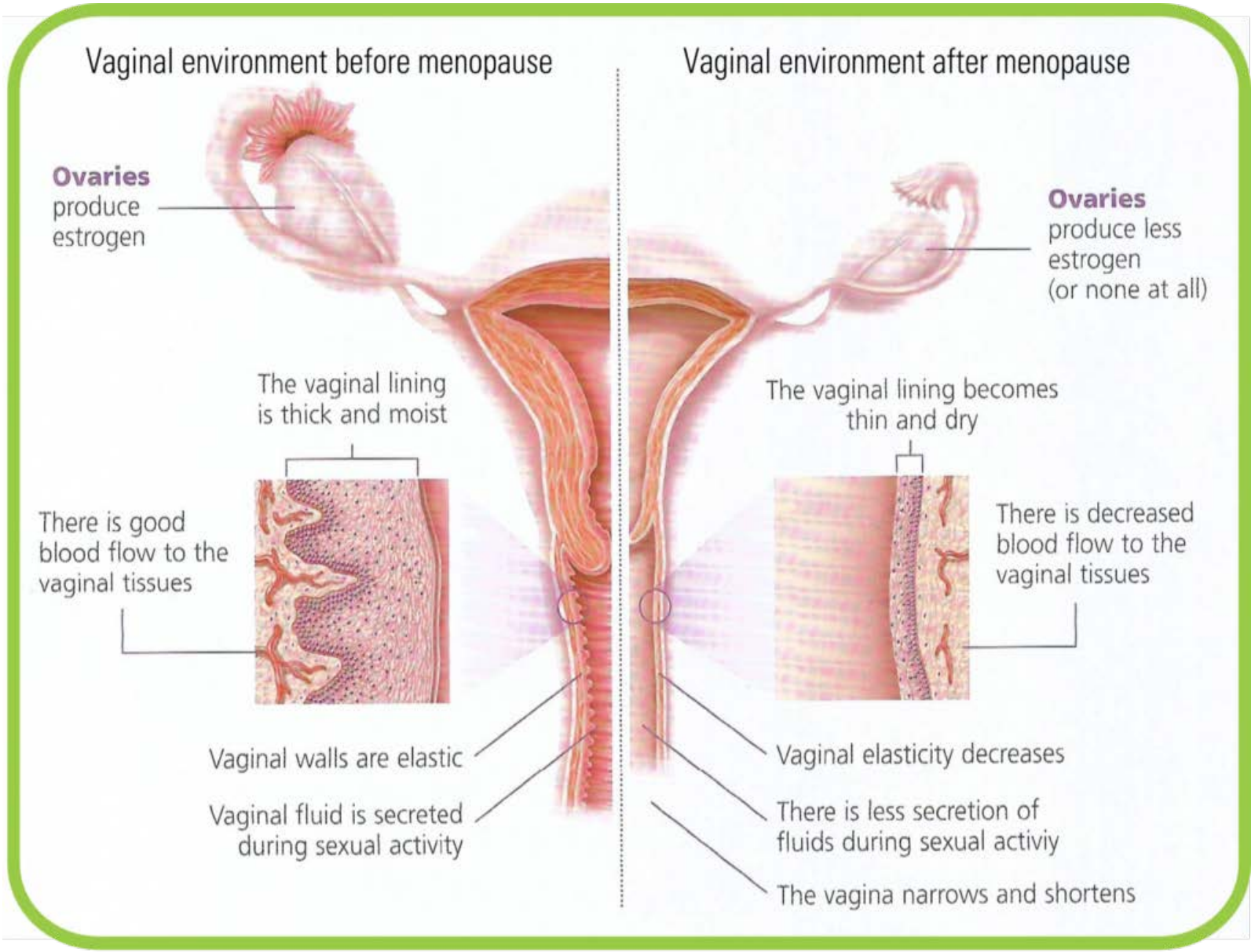
labia majora/minora,

clitoris,

vestibule/introitus,

vagina,

urethra and bladder



Reference :
Johnston L. The Recognition and Management of Atrophic Vaginitis. *Geriatrics & Aging* 2002; 5(7):9-15.

Causes of GSM / Vaginal Atrophy

- **Menopause** (most common cause)
- Lack of sexual activity
- Pregnancy or recent childbirth
- Post episiotomy
- Breast feeding
- Premenopausal periods
- Post menstruation
- Hysterectomy +/- oophorectomy
- Removal of ovaries
- Pelvic radiation therapy in women cancer patients
- Chemotherapy

- POI/ POF (spontaneous)
- Early menopause (post cancer Rx)
- Immune disorders
- Oral contraceptives
- After stopping Hormone Rx (MHT)
- Medications such as anti-depressants, allergy and cold medications
- Intolerance to douching products or harsh soaps
- Alcohol consumption
- Cigarette smoking
- Stress, Anxiety or emotional upsets

SUMMARY STATEMENTS

- GSM is common affects >50% of women-- yet most don't bring up this problem in the office ----suffer in silence – affects their QoL & relationships and their sex life)
- Women need to be made aware that it is treatable & that there are many options

  ** and We physicians need to be made aware also

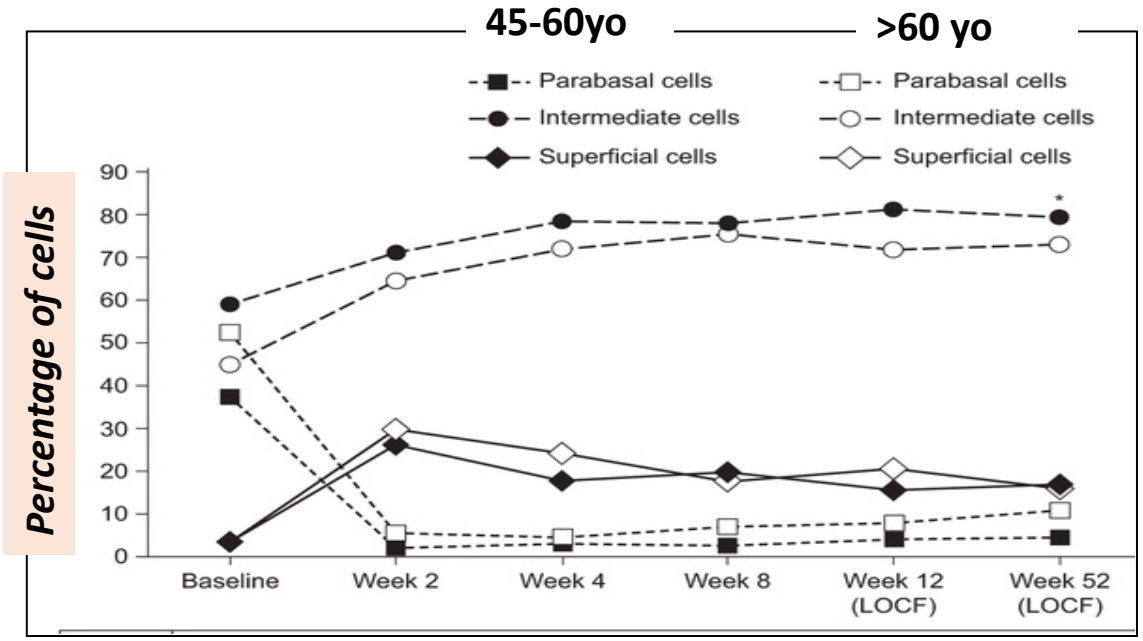
- Progressive and recurs if treatment is stopped

- NEW DATA/UPDATES
- (1)"it's never too late to start Rx" – but may take longer to reverse & correct the changes in later years
- (2) New products –recently passed by Health Canada
- (3) Vaginal Laser Rx – RCT results

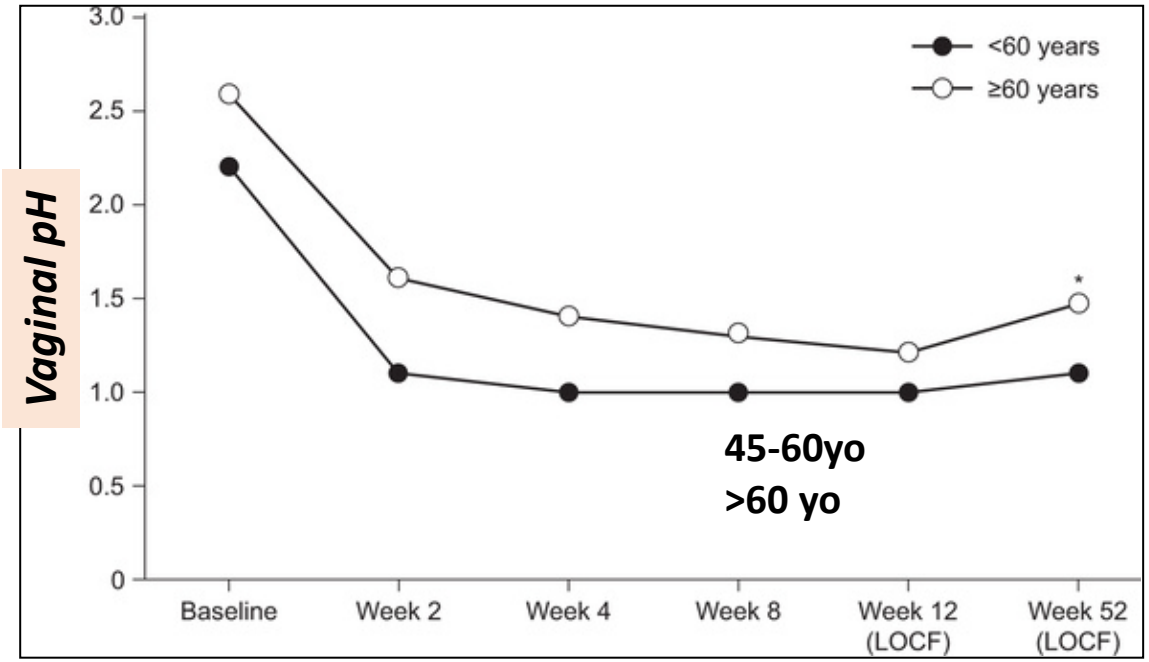
Ideal to initiate vaginal estrogen Rx early stage of vaginal atrophy BUT initiation in later post menopause is still very effective

MI : Maturation Index (MI) :

Percentage of cells : parabasal, intermediate, superficial



Vaginal pH



Does age at the start of treatment for vaginal atrophy predict response to vaginal estrogen therapy? Post hoc analysis of data from a randomized clinical trial involving 205 women treated with 10 [mu]g estradiol vaginal tablets.
Derzko, C, Rohrich, S Panay, N. **Menopause. 28(2):113-118, February 2021**.

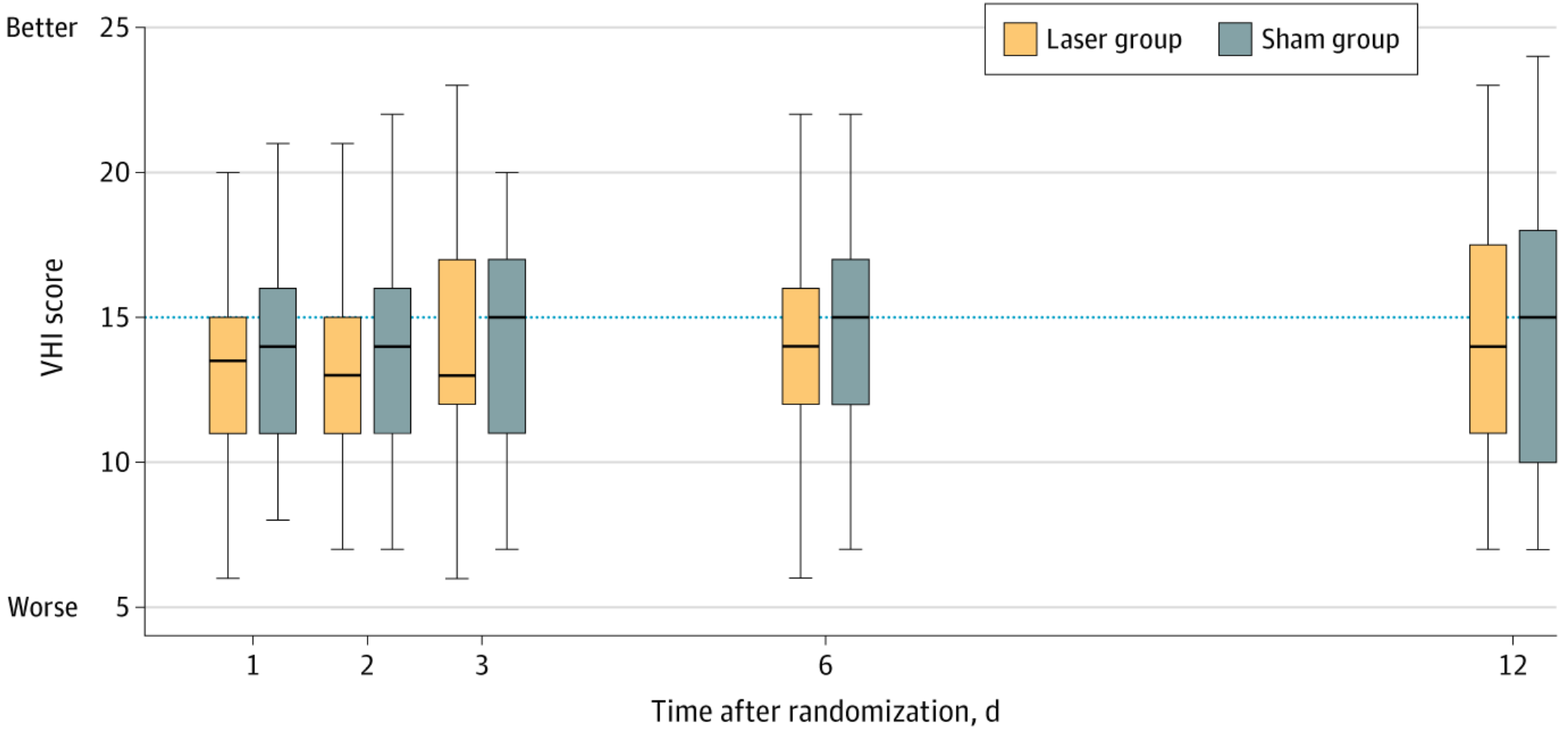
Drugs for Genitourinary Syndrome of Menopause (GSM)

Drug	Some formulations	Usual dosage	Cost[b]
VAGINAL			
Estradiol - Estring (Pfizer)	2 mg ring (7.5 µg/d)	7.5 µg/d[c]	$475.60
Estradiol - Imvexxy (Therapeutics MD)	4, 10 µg inserts	4 or 10 µg once/d × 2 wk, then 2 ×/wk	572.40
Vagifem (Novo Nordisk)	10 µg insert[d]	10 µg once/d × 2 wk, then 2 ×/wk	521.30
Generic			465.60
Yuvafem (Amneal)[e]	10 µg insert[d]		160.30
Estradiol - Estrace (Abbvie)	0.1 mg/g cream	2-4 g once/d × 1-2 wk, then 1-2 g once/d × 1-2 wk[f]	344.80[g]
Generic			271.00[g]
Conjugated estrogens - Premarin (Pfizer)	0.625 mg/g cream	0.5-2 g once/d × 3 wk followed by 7 d off, or 0.5 g 2 ×/wk	392.20[h]
Prasterone –*Intrarosa* (*Lupin*)	6.5 mg insert	6.5 mg once/d at bedtime	682.40
ORAL			
Ospemifene - *Osphena* (*Duchesnay*)	60 mg tabs	60 mg once/d	680.40

"Vaginal Rejuvenation Rx" -- Is CO_2 Laser effective ?

Effect of Fractional Carbon Dioxide Laser vs Sham Treatment on Symptom Severity in Women With Postmenopausal Vaginal Symptoms: A Randomized Clinical Trial

JAMA. 2021;326(14):1381-1389.



The Vaginal Health Index Score (VHI) ranges from 5 to 25, with a score less than 15 considered to indicate vaginal atrophy. The median is represented by the line; the interquartile range is represented by the bar (75th percentile by maximal edge; 25th percentile by minimal edge); and the range is represented by the whiskers. Values under the dotted line indicate vaginal atrophy.

VAGINAL LASER THERAPY

JAMA Network

QUESTION Is fractional carbon dioxide laser an effective treatment for vaginal symptoms associated with menopause?

CONCLUSION This trial found that among women with postmenopausal vaginal symptoms, treatment with fractional carbon dioxide laser vs sham treatment did not improve vaginal symptoms after 12 months.

POPULATION

85 Women

Postmenopausal women seeking treatment for vaginal symptoms

Mean age: 57 years

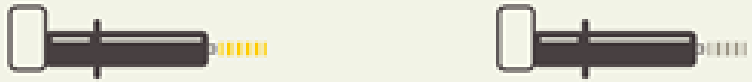
LOCATIONS

1 Hospital in Australia

INTERVENTION

85 Patients randomized

43	42
Laser treatment	**Sham treatment**
Microablative carbon dioxide laser treatment performed 4-8 wk apart at standard power (5.37 J/cm²)	Laser treatment performed at minimal energy settings with no tissue effect (0 J/cm²)



PRIMARY OUTCOME

Change in symptom severity on visual analog scale (VAS 0-100; 100 being most severe) and Vulvovaginal Symptom Questionnaire (VSQ 0-20; 20 most severe)

FINDINGS

Change in symptom severity

Change in VAS	Change in VSQ
Laser treatment: -17.2	Laser treatment: -3.1
Sham treatment: -26.6	Sham treatment: -1.6

There was no significant difference between groups

VAS, difference, **9.4** (95% CI, -28.6 to 47.5)

VSQ, difference, **-1.5** (95% CI, -5.9 to 3.0)

Li FG, Maheux-Lacroix S, Deans R, et al. Effect of fractional carbon dioxide laser vs sham treatment on symptom severity in women with postmenopausal vaginal symptoms: a randomized clinical trial. *JAMA*. Published October 12, 2021. doi:10.1001/jama.2021.14892

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SUMMARY STATEMENTS

- 1. The perimenopause =“***window of vulnerability”*** for *both depressive symptoms & major depressive episodes* even in those without a hx of depression

- 2. Other contributing factors : to the ***occurrence*** and ***severity*** of midlife mood symptoms
  - Context related – VMS, sleep disturbances and health problems
  - Longitudinal or preceding eg unemployment, smoking, hx anxiety

- 3. ***Hysterectomy +/- oophorectomy***
  - *Large scale studies show ↑ risk of depression*

- 4. ***POI ↑ risk of depression***

- 5. ***Poor sleep quality*** (objective/& subjective) –common in peri & postmenopausal

- 6. ***Cognitive symptoms*** (worsening memory/slower cognition) –shown in prospective longitudinal studies

Will postmenopausal hormone use foster better brain health?

- During perimenopause and early menopause, women report reduced quality of life due to hot flashes, insomnia, mental "fog", trouble concentrating, difficulty with word finding, irritability, and reduced libido
- Women are at increased risk for some neurodegenerative disorders, including dementia, as compared to men
- Early loss of ovarian function, including surgical menopause prior to the expected time of natural menopause, increases the risk of neurodegenerative disorders and reduces QOL

IMS

E2 use associated with reduced risk of death from both vascular dementia and AD

- 489,105 Finnish women using systemic HT from 1994-2009
- 581 died of **vascular dementia**
  - E2 oral and transdermal
  - P mostly norethindrone or MPA
  - **Risk ↓↓ ~38% by E2 or E2-P use**
- 1057 died of **AD**
  - Risk ↓ ~15% after 5 years of use
  - **Risk reduction similar regardless of age at initiation (<60 vs ≥ 60 years)**

Mikkola TS et al. JCEM 2017;102:870-877

IMS

Depression, stress and cognitive impairment at midlife

- The brain is a target of sex steroids

- Several studies have identified an association between perimenopause and increased rates of depression, stress, and cognitive "fog"
  - SWAN 4x increase in major depressive episodes

    Bromberger JT et al 2011

- Hypothesis: Hormonal management will ameliorate - but will not fully prevent - brain aging
  - Estrogens maintain brain metabolism, synapses, mood, and cognition
  - Progestins increase irritability and slow metabolism

IMS

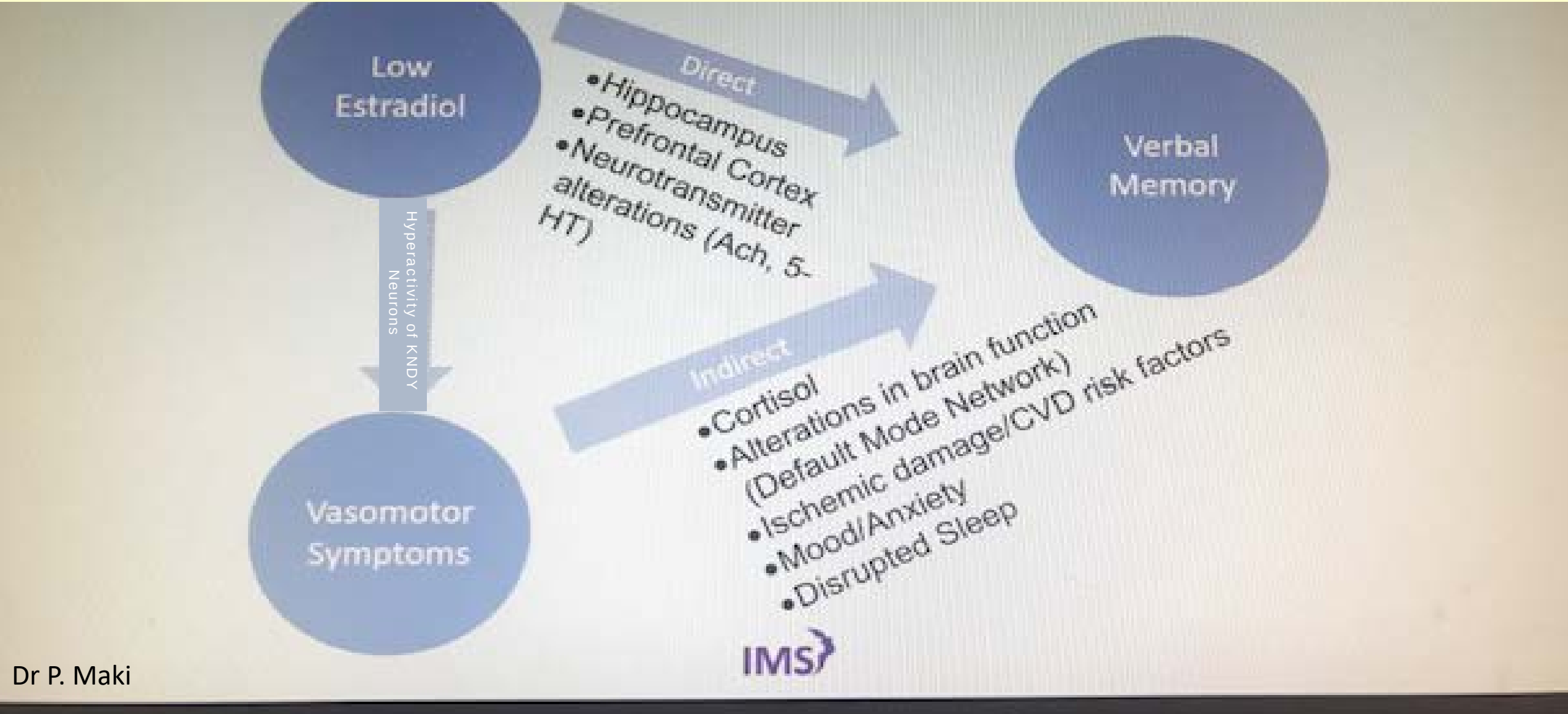
DEPRESSION

Even mild symptoms of depression are linked to memory problems at midlife.

Weber M, Mapstone M, Staskiewicz J, Maki PM. Reconciling subjective memory complaints with objective memory performance in the menopausal transition. Menopause (New York, NY). 2012 Jul;19(7):735.

IMS

Theoretical Model for Menopause-Related Changes in Verbal Memory



Dr P. Maki

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4. Menopause and sexuality

- Changes in sexual desire in menopause:
- Over 50% of women report low sexual desire and 50% report vulvovaginal discomfort within 3 years of menopause

DESIRE	AROUSAL	PAIN	ORGASM

CLASSIFICATION OF SEXUAL DYSFUNCTION IN WOMEN

Domain	Etiology of dysfunction	Available treatments
DESIRE	Psychosocial stress, HSDD, hormonal changes, aging, endocrinopathies (thyroid, prolactin), medication-induced (SSRI, OCP), other medical comorbidities	Talk therapy, correction of medical or psychosocial causes, flibanserin, off-label testosterone
AROUSAL	Psychosocial stress, diabetes, vascular disease, medication-induced (SSRI, OCP), iatrogenic (pelvic surgeries)	Talk therapy, off-label use of PDE5 inhibitor, pelvic physiotherapy
PAIN	GSM, pelvic floor muscle hypertonicity, psychosocial stress, trauma, lichen sclerosus, lichen planus	Correct underlying medical or psychosocial causes, local hormone application, pelvic physiotherapy, talk therapy
ORGASM	Psychosocial distress, medication-induced (SSRI), comorbidities, iatrogenic (pelvic and neurological surgeries)	Talk therapy, medication changes, off-label use of PDE5 inhibitor

GSM: genitourinary syndrome of menopause; HSDD: hypoactive sexual desire disorder; OCP: oral contraceptive pill; PDE5: PDE5: phosphodiesterase 5; SSRI: selective serotonin reuptake inhibitor.

HSDD SCREENER

Decreased Sexual Desire Screener

Please answer each of the following questions by circling either *Yes* or *No*

1. In the past, was your level of sexual desire or interest good and satisfying to you?	**Yes**	**No**
2. Has there been a decrease in your level of sexual desire or interest?	**Yes**	**No**
3. Are you bothered by your decreased level of sexual desire or interest?	**Yes**	**No**
4. Would you like your level of sexual desire or interest to increase?	**Yes**	**No**
5. Please circle all the factors that you feel may be contributing to your current decrease in sexual desire or interest:		
A. An operation, depression, injuries, or other medical condition	**Yes**	**No**
B. Medication, drugs, or alcohol you are currently taking	**Yes**	**No**
C. Pregnancy, recent childbirth, menopausal symptoms	**Yes**	**No**
D. Other sexual issues you may be having (pain, decreased arousal or orgasm)	**Yes**	**No**
E. Your partner's sexual problems	**Yes**	**No**
F. Dissatisfaction with your relationship or partner	**Yes**	**No**
G. Stress or fatigue	**Yes**	**No**

When completed, please give this form back to your clinician.

Clinician:

Verify with the patient each of the answers she has given.

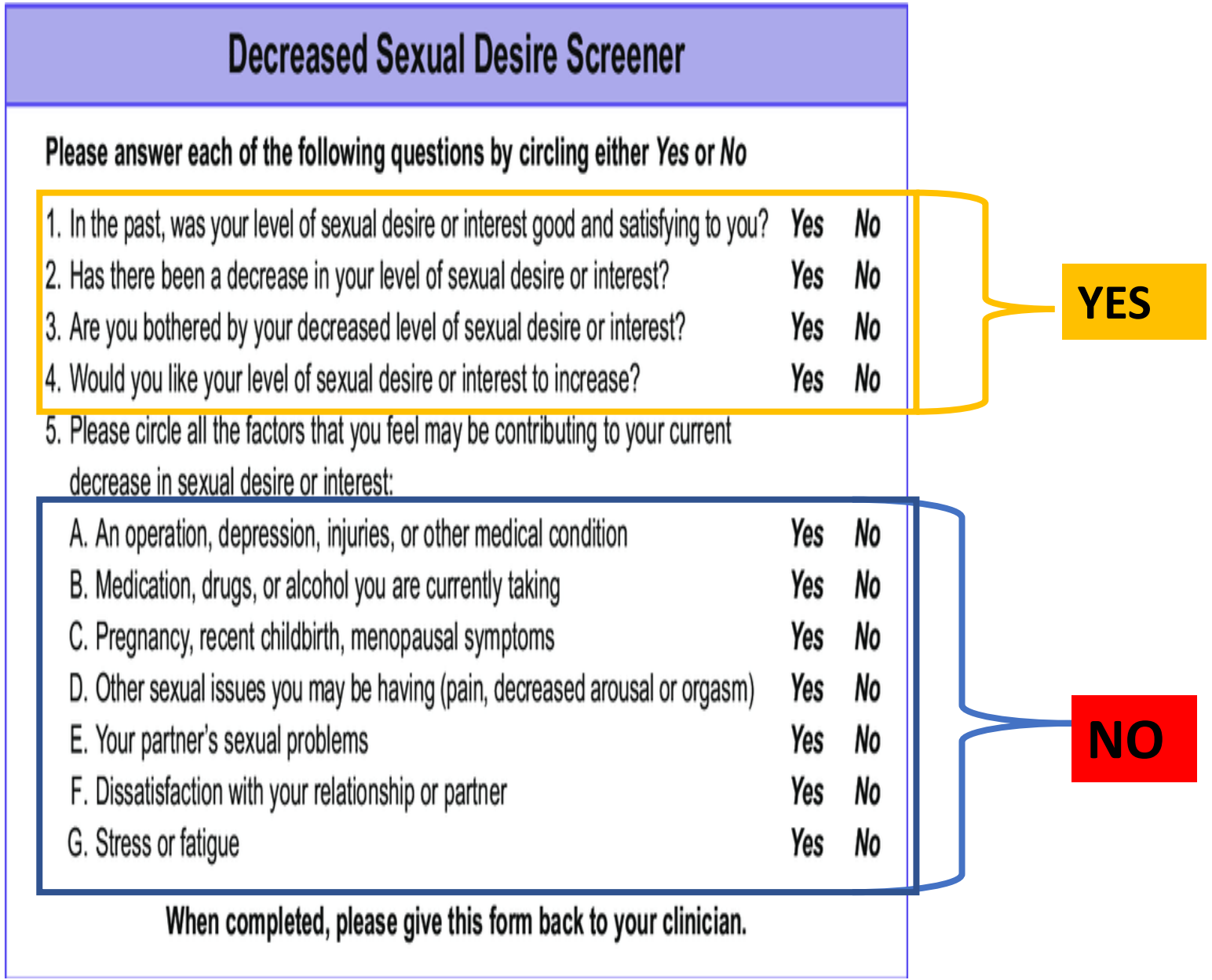
The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision, characterizes Hypoactive Sexual Desire Disorder (HSDD) as a deficiency or absence of sexual fantasies and desire for sexual activity, which causes marked distress or interpersonal difficulty, and which is not better accounted for by a medical, substance-related, psychiatric, or other sexual condition. HSDD can be either generalized (not limited to certain types of stimulation, situations, or partners) or situational, and can be either acquired (develops only after a period of normal functioning) or lifelong.

If the patient answers "YES" to all of the questions 1 through 4, and your review confirms "NO" to all of the factors in question 5, then she qualifies for the diagnosis of generalized acquired HSDD.

If the patient answers "YES" to all of the questions 1 through 4 and "YES" to any of the factors in question 5, then decide if the answers to question 5 indicate a primary diagnosis other than generalized acquired HSDD. Co-morbid conditions such as arousal or orgasmic disorder do not rule out a concurrent diagnosis of HSDD.

If the patient answers "NO" to any of the questions 1 through 4, then she does not qualify for the diagnosis of generalized acquired HSDD.

HSDD SCREENER



Decreased Sexual Desire Screener

Please answer each of the following questions by circling either *Yes* or *No*

1. In the past, was your level of sexual desire or interest good and satisfying to you?	Yes	No
2. Has there been a decrease in your level of sexual desire or interest?	Yes	No
3. Are you bothered by your decreased level of sexual desire or interest?	Yes	No
4. Would you like your level of sexual desire or interest to increase?	Yes	No

5. Please circle all the factors that you feel may be contributing to your current decrease in sexual desire or interest:

A. An operation, depression, injuries, or other medical condition	Yes	No
B. Medication, drugs, or alcohol you are currently taking	Yes	No
C. Pregnancy, recent childbirth, menopausal symptoms	Yes	No
D. Other sexual issues you may be having (pain, decreased arousal or orgasm)	Yes	No
E. Your partner's sexual problems	Yes	No
F. Dissatisfaction with your relationship or partner	Yes	No
G. Stress or fatigue	Yes	No

When completed, please give this form back to your clinician.

Low libido or hypoactive sexual desire disorder:

- Measuring androgens should not be used as a diagnostic tool
- Treatments — only after all other causes have been ruled out:
  - Transdermal testosterone, preferably ½ pump daily of a 1% male pump or 3–4 dots of 1% male cream in tube. Should not exceed levels above 2.4 nmol/L; may take up to 3 months to work
    - **Not Health Canada–approved**
    - Consider a 3–6 month short course while monitoring testosterone levels
  - Flibanserin
    - Increases sexual ideation

Medications for Sexual Dysfunction

- **PAIN** : ***for VVA*** ---Vaginal estrogens (Cream, pill)
  -- Vaginal (DHEA) ovules – Prasterone (Intrarosa)
  -- Ospemifene (Osphena)
  for Pelvic Floor Hypertonicity – Pelvic Physio
  (vaginismus) -- Onbotulinum toxin

- **LIBIDO/HSDD**: *(All treatments are "off label")*

  Testosterone : "a trial of Therapy"
  Transdermal –***1% Androgel ½ pump qhs to calf (NB monitor total Testosterone)***

  Flibanserin (po): qhs

  Bremelanotide (s/c) "on demand"

- **AROUSAL**: *(No approved medication for Rx)—possibly low dose* ***sildenafil***

- **ANORGASMIA** : **1°** r/o mechanical

  2°- *? Related to SSRI use; change SSRI to* ***bupropion;*** *-trial of* ***sildenafil***

  - +/-try ***flibanserin + TD testosterone***

****Psychological counselling, CBT, mindfulness, sexual skills training**
****Sexual counselling : individual / couple / group**

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Breast Cancer Risk in Perspective

Table. Documented risk factors for breast cancer[2]

Risk factor	Relative risk
CE and continuous medroxyprogesterone acetate use > 5 years' use compared with never having used CE + MPA	1.3
Early menarche (younger than 12 y)	1.3
Late menopause (older than 55 y)	1.2–1.5
Late first pregnancy (>30 y or nulliparous versus <20 y)	1.7–1.9
Chest radiation (fluoroscopy/chest-wall radiation compared with none)	1.6–5.2
Postmenopausal obesity >80th percentile	1.2
Alcohol use >2 drinks/d	1.2
First-degree relative with breast cancer at age >50 y	1.8
First-degree relative with breast cancer at age <50 y	3.3
Increased mammographic density >75%	6.0
BRCA1 gene mutation <40 y versus wild type	200.0

Adapted from Singletary SE. Rating the Risk Factors for Breast Cancer. Vol. 237, Annals of Surgery. 2003. p. 474–82.[2]

CE: conjugated estrogen; MPA: medroxyprogesterone acetate.

WHI HT Trials
Breast Cancer Mortality

End Points	No. of Deaths, Annualized Rates (%)		HR (95% CI)	Additional/Fewer Deaths per 10,000 Women per Year of HT
	Hormone Therapy	Placebo		
Breast cancer mortality – during intervention*				
CEE plus MPA vs placebo	5 (0.010)	4 (0.009)	1.08 (0.29-4.03)	1
CEE alone vs placebo	4 (0.010)	9 (0.023)	0.45 (0.14-1.46)	-1.3
Pooled trials			not reported	
Breast cancer mortality – 20.7-year cumulative follow-up				
CEE plus MPA vs placebo	71 (0.045)	53 (0.035)	1.35 (0.94-1.95)	1
CEE alone vs placebo	30 (0.031)	46 (0.046)	0.60 (0.37-0.97)	-1.5
Pooled trials			not reported	

*Median 5.6 years [interquartile range, 4.9-6.5 years] of intervention in CEE + MPA trial
*Median 7.2 years [interquartile range, 6.5-8.2 years] of intervention in CEE trial

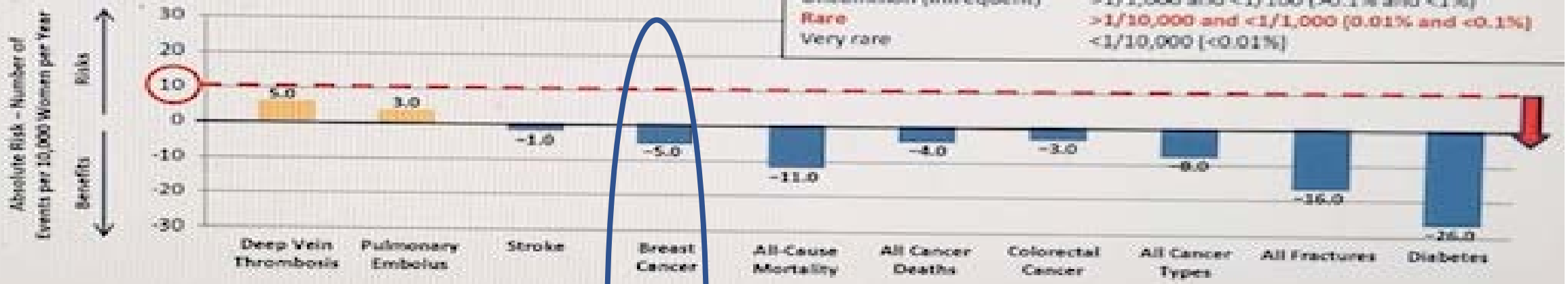
Manson JE, et al. *JAMA* 2017;318:927-938.

Absolute Benefits and Risks from WHI – Initiation of HT in Women 50-59 Years of Age: Number of Events per 10,000 Women per Year

World Health Organization (WHO)
Council for International Organizations of Medical Sciences (CIOMS)
Classification of Frequency of Drug Reactions

Very common	≥1/10 (≥10%)
Common (frequent)	≥1/100 and <1/10 (≥1% and <10%)
Uncommon (infrequent)	≥1/1,000 and <1/100 (≥0.1% and <1%)
Rare	≥1/10,000 and <1/1,000 (0.01% and <0.1%)
Very rare	<1/10,000 (<0.01%)

CE Alone Trial



CE + MPA Trial

Lobo RA, et al. *Atherosclerosis* 2016;254:296-304.

JAMA Network™ JAMA. 2020;324(4):369-380. doi:10.1001/jama.2020.9482

Association of Menopausal Hormone Therapy With Breast Cancer Incidence and Mortality During Long-term Follow-up of the Women's Health Initiative Randomized Clinical Trials

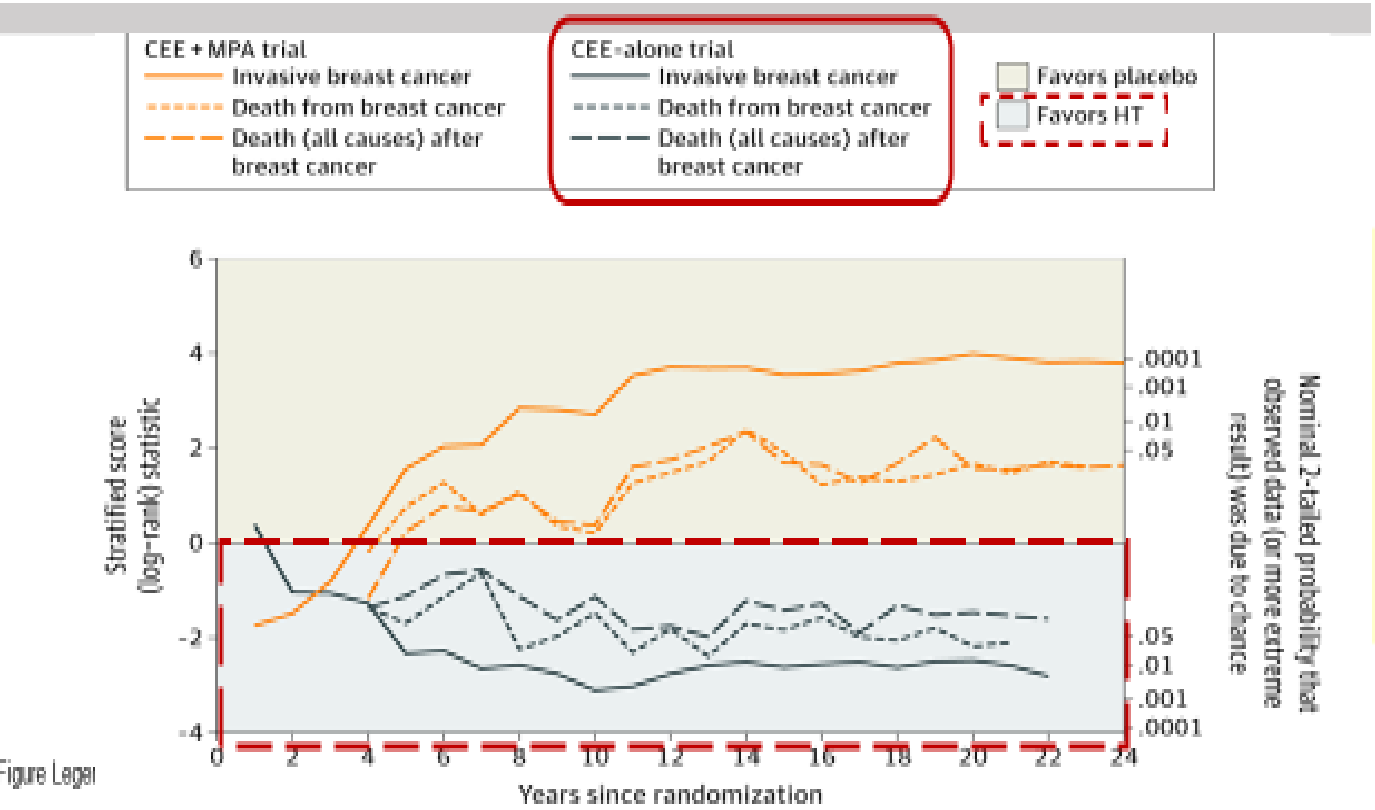


Figure Legend

Plot of Stratified Score (Log-Rank) Statistics Updated Annually Based on Cumulative DataData accumulated from randomization for breast cancer–related events in the trials evaluating conjugated equine estrogen (CEE) alone (n = 10 739) and evaluating CEE plus medroxyprogesterone acetate (MPA) (n = 16 608) during cumulative follow-up. Test statistics are 2-sided, correspond to the stratified score (log-rank) test obtained from the Cox regression model described in Figure 1, and were updated until all observed cases were included.

CONCLUSION: 20 YEAR FOLLOWUP OF WHI BREAST CANCER DATA:

CEE alone was associated with a statistically significant LOWER breast cancer incidence (hazard ratio [HR] = 0.78; 95% CI 0.65 - 0.93) and breast cancer mortality (HR = 0.60; 0.37 - 0.97).

CEE plus progestin was associated with a statistically significant higher breast cancer incidence (HR = 1.28; 1.13 - 1.45), but NO significant difference in breast cancer mortality.

Association of Menopausal Hormone Therapy with Breast Cancer Incidence & Mortality During Long-Term Follow-up of the WHI RCTs
Chelbowski RT et al JAMA 2020:324(4):369-380

RISK REDUCING STRATEGIES

- 1. **CEE alone** in women post hysterectomy significantly decreased breast Ca
- 2. **CEE +MPA** Rx in WHI : after 5 years :<1 additional BrCa/1000 women/year of use
- 3. Different **progestogens** may have different effects on the breast but still no evidence to suggest a differential effect on BrCa -- duration of exposure?
- 4. **TSEC (Duavive)** –has a potent anti-proliferative effect on the breast
- 5. **STEAR (Tibolone)** – appears to have antiprolferative effects & in some RCT was associated with less breast cancer than the placebo

BREAST CANCER : KEY MESSAGES

- 1. Menopausal hormone therapy choices and regimens should be individualized in women at risk for breast cancer, with preference given to regimens with evidence showing they do not increase breast cancer risk.

- 2. Vaginal estrogen can be offered to women with a history of breast cancer experiencing genitourinary syndrome of menopause, with careful consideration given to women on aromatase inhibitors.

- **3. Hormone therapy should be offered to women with a hereditary predisposition to breast cancer, in the absence of contraindications, to mitigate the risks of premature menopause from risk reducing sapingo-oophorectomy**

C. Strategies for Menopause Patient Management

"Individualizing Care"

Potential adverse effects of MHT

Short term:

- Fluid retention, bloating, headaches
- Vaginal spotting and bleeding

Long term:

- Thromboembolic events
- Breast Cancer

Short term:

- Related to dose and choice of regimen. *Start with low doses.*
- Unexpected bleeding is not unusual during first 6 months of therapy

Long term:

- VTE risk is increased with oral but not transdermal therapy
- Breast Cancer – risk is influenced by dose, duration of therapy and choice of progestogen

IMS Recommendations on MHT and midlife women's health. Climacteric 2016;19:109-15

CASE PRESENTATION

53 yo G2P2 healthy
Took OCP for perimenopausal DUB & contraception; d/c @ age 52 with no more bleeding

Age 53 yo presented to FD with troublesome VMS not responsive to OTCs : eg evening primrose oil; black cohosh X 1yr
Wanted to "tough it out" Afraid of HT --- "high risk breast cancer"

TRIED EVERYTHING -- SIMPLY NOT WORKING !

Common complaints at this time:

Hot flushes ***Vasomotor Symptoms (VMS)***
Night sweats

Crawling sensations on skin

Mood issues : anxiety, irritability, depression

Sleep disturbances

Cognitive issues: *↓memory; ↓concentration*

Vaginal dryness

Low libido

Fatigue

Muscle/joint pains

Overall diminished wellbeing

"Reduced Quality of Life

But ----1 yr later.. Back to FD –willing to try MHT/HT

CASE PRESENTATION

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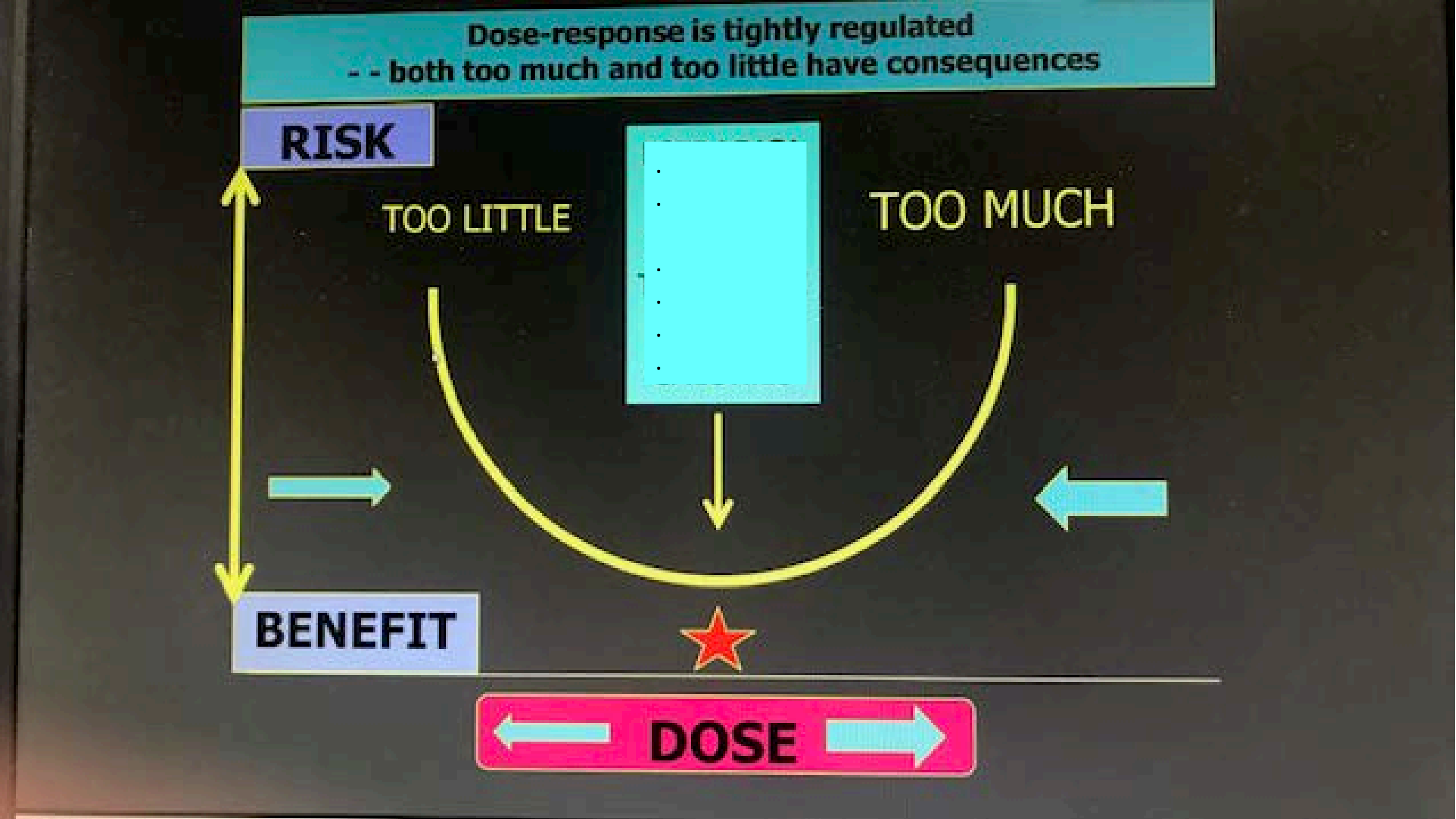
But ----1 yr later.. Back to FD –willing to try MHT/HT

54 yo Rx –Estrace 1mg + Prometrium 100 mg qd ;
At 6 mo f/u she was still having hot flushes & still not sleeping

FD called to ask if OK to increase dose to Estrace 2mg +continue Prometrium 100 mg;

Increased dose of Estrace improved VMS & sleep, but caused breast tenderness/mastalgia;
Ix: mammogram N; labs N

HT stopped after 8 weeks


Dose-response is tightly regulated
- - both too much and too little have consequences
RISK
TOO LITTLE
TOO MUCH
BENEFIT
DOSE

Vasomotor Symptoms Including Hot Flashes, Flushes and Night Sweats

Stopped HRT for mastalgia but 6 months later returns Now symptoms intolerable!

I simply can't take it anymore!

- **Night sweats**
- Has to work
- 10 flashes during day
- Nasty burning
- **Cranky**
- Exhausted

Depressed Mood, sleep disturbances, ↓Libido

Memory Issues, ↓Cognition ↓ Quality of Life

CASE PRESENTATION

- Age 54 ½ --- again off all HT X6mo : intolerable symptoms: Unable to function at work
- c/o brain fog, fatigue VMS insomnia, anxiety

- Referred for consultation ---What would you recommend next?

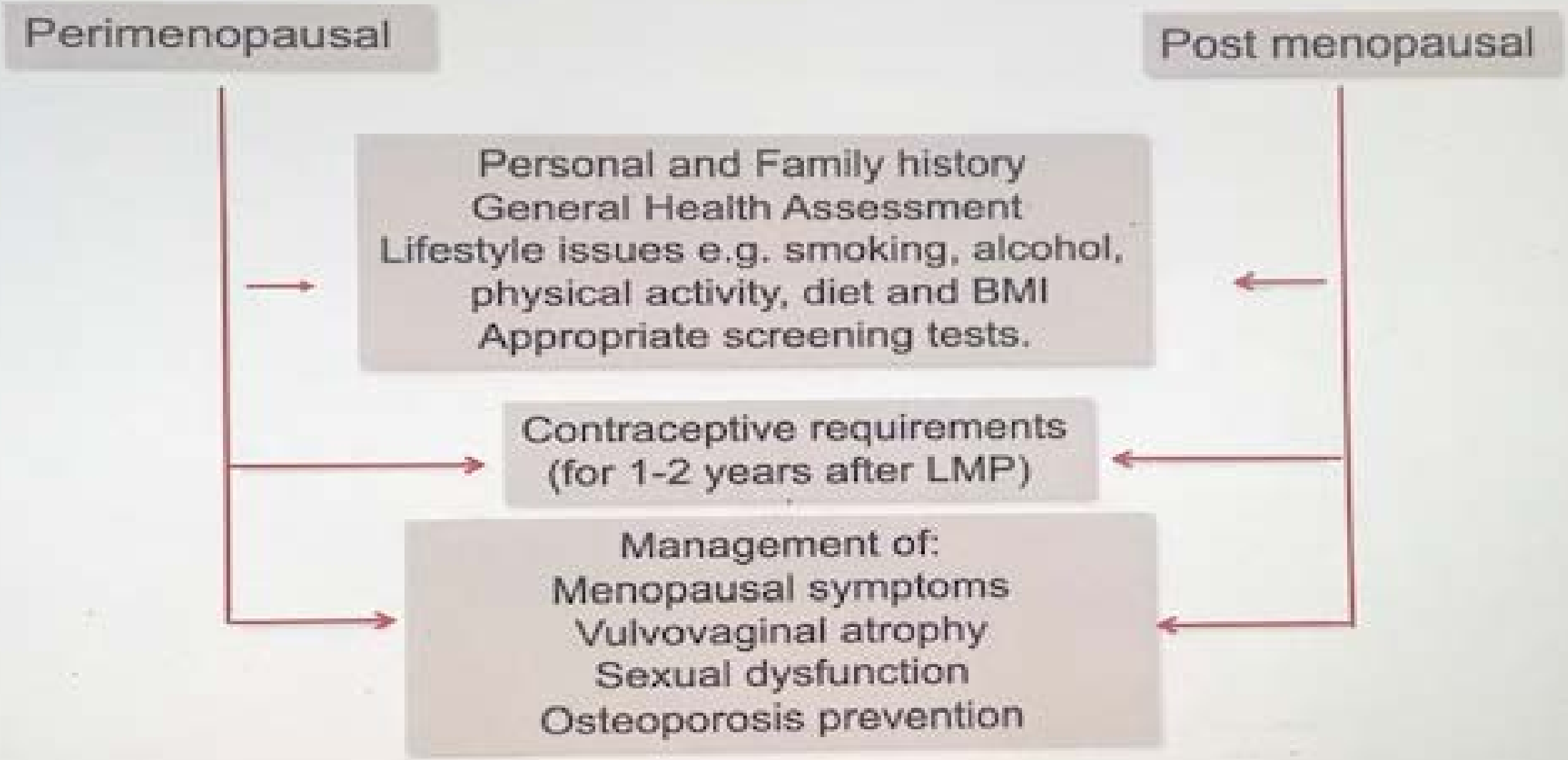
TREATMENT OPTIONS-HORMONAL TREATMENT

SOME NEW ALTERNATIVES

1. **"BIOIDENTICAL MHT"**
2. **"TSEC"** *(CEE/BZD)*
3. **"STEAR"** (tibolone)

NAMS 2015 Position Statement: Nonhormonal management of menopause-associated vasomotor symptoms, Menopause: Vol. 22, No. 11, 2015

The mid-life consultation: What to consider



A Practitioner's tool kit. Jane F
Climacteric 2014;17:1-16

OPTIONS FOR PERI-MENOPAUSAL WOMEN

Continuous E + Sequential P	Best starting option over 45 yrs Commence on Day 1 of natural cycle Doesn't control PMS Transdermal option available
E + P Contraception	Potential contra-indications to ocp Controls PMS Good cycle control Low dose and 17 B Estradiol options
Continuous E + Lng IUS	No Bleeding Doesn't control PMS Transdermal options available
Continuous E + continuous P	Likely to lead to irregular bleeding PMS may still occur May suit some women

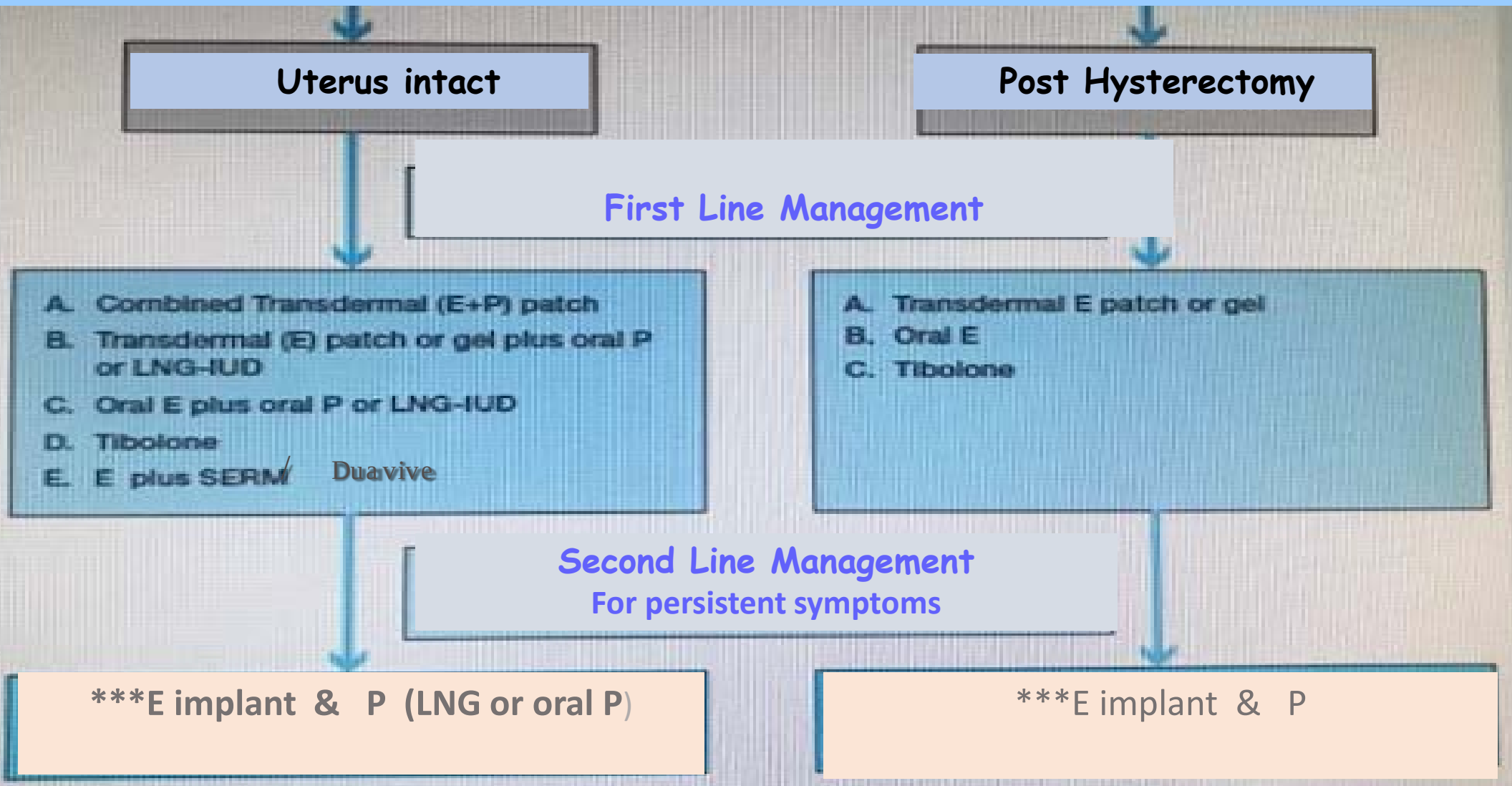
What to prescribe

Stage of Menopause transition	Treatment options
Perimenopausal	Sequential E + P MHT Combined Oral Contraceptive (if not contraindicated) Estrogen plus LNG-IUS
Post menopausal, intact uterus	Combined transdermal patch Transdermal E plus oral P or LNG IUS Oral E plus oral P or LNG IUS Tibolone TSEC
At any stage post hysterectomy	Transdermal Estrogen Oral Estrogen Tibolone

A Practitioner's tool kit. Jane F M and Davis S R Climacteric 2014;17:1-16

Choosing the Right MHT

Menopausal Hormonal Treatment



IMS Recommendations on Women's Midlife Health and Menopausal Hormone Therapy

- MHT remains the most effective therapy for vasomotor symptoms and urogenital atrophy (GSM)

- "…the potential benefits of MHT given for a clear indication are
- many and the risks are few when initiated within a few years of
- menopause"

IMS Guidelines 2016

Let's Change the Message about Hormone Therapy!

- 2002 : Post WHI ~~"Lowest dose for shortest period of time"~~

- 2022 "Appropriate hormone therapy to meet treatment goals" Individualize:
  - Type, dose and formulation
  - Route of administration
  - Duration

Not all women are the same

- **Age** – critical variable in determining hormone action at tissue level

- Weight
- Personal medical history
- Expectations
- Lifestyle
- Family history

- Molecular genotype
- Epigenetic status
- Pharmaco-kinetics
- Pharmaco-dynamics
- Pharmaco-genomics

Hypothesis: Ongoing hormonal exposure may cumulatively retard aging in tissues & thereby prolong hormonal responsiveness

Let's Change the Message about Hormone Therapy

"Shared Decision Making"

Women Need Individualized Treatment

"Shared decision making can *help women resolve their ambivalence about HT* by better understanding their options, creating more accurate expectations of possible benefits and harms, and aligning treatment with patient values. This may lead to improved adherence and satisfaction with treatment"

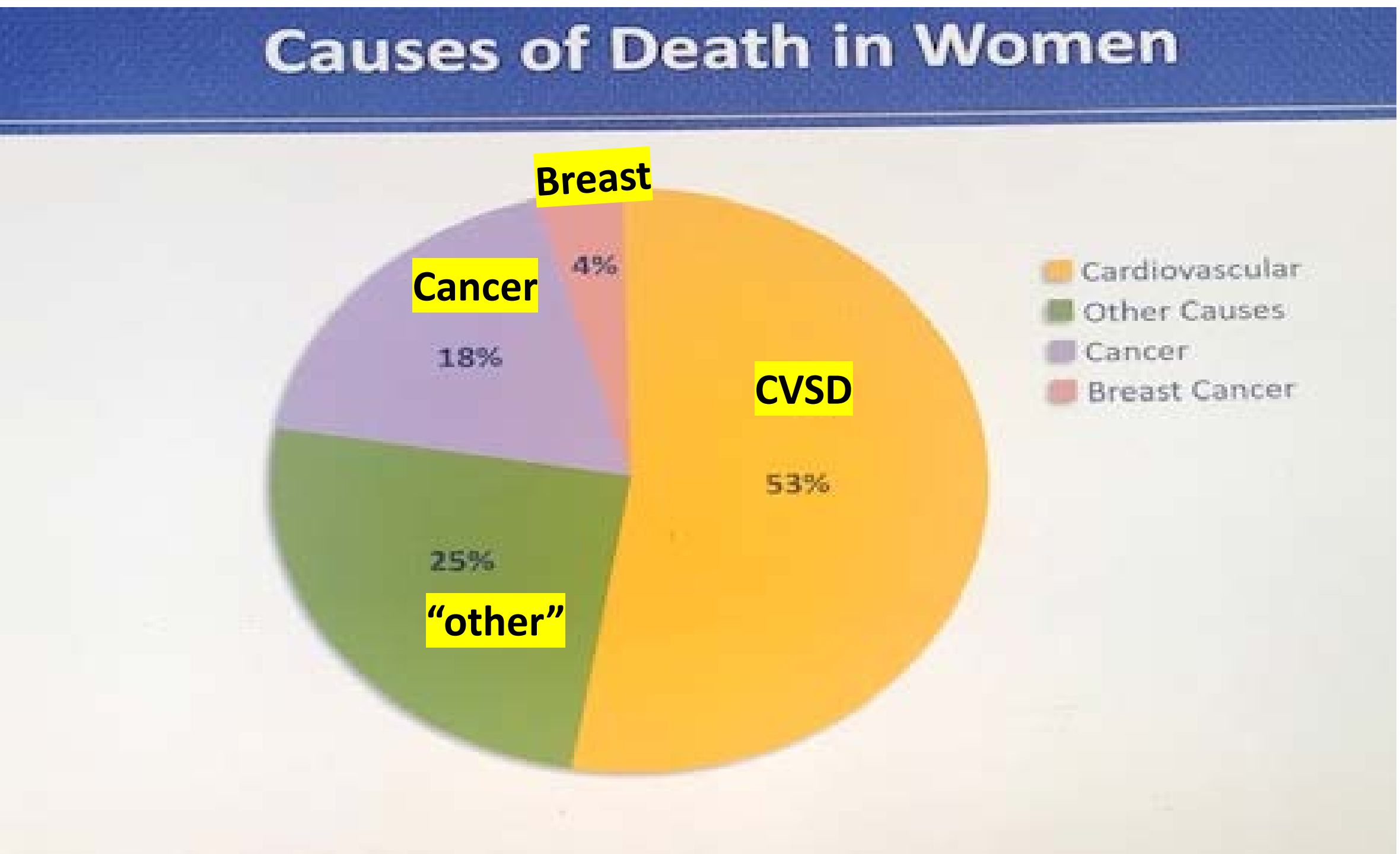
OBJECTIVES

X • To review some key findings of the Women's Health Initiative(WHI) and how they guide our use of HRT

X • To provide an overview of the 2021 SOGC MENOPAUSE GUIDELINES including data on some new therapies

X • Discuss strategies for management of menopause patients : Addressing the needs of menopause patients and individualizing their care

Causes of Death in Women



THANK YOU