Women's Health 2024 | Beyond the Annual Visit

New Horizons in Hormone Therapy: Modernizing the Management of Menopause

Faculty

- **James A. Simon, MD**
  Clinical Professor
  George Washington University
  Washington, DC

- **Jessica Shepherd, MD**
  Founder and CEO
  Sanctum Med & Wellness
  Dallas, TX

Disclosures

- **James A. Simon, MD**
  - Grant/Research Support: AbbVie, Inc., Bayer Healthcare LLC, Daré Bioscience, Ipsen, Mylan/Viatris Inc., Myovant Sciences, Sebela Pharmaceuticals Inc.
  - Consultant/Advisory Boards: Ascend Therapeutics, Bayer HealthCare Pharmaceuticals Inc., Besins Healthcare, Biote Medical, LLC, California Institute of Integral Studies (CIIS), Daré Bioscience, Femasys Inc., Khyria, Madorra Pty Ltd., Mayne Pharma, Inc., Pfizer Inc., Vella Bioscience Inc.
  - Speakers Bureau: Ascend Therapeutics, Astellas Pharma, Inc., Mayne Pharma, Inc., Myovant Sciences, Inc., Pfizer Inc., Pharmavite LLC., Scynexis Inc.
  - Stockholder (direct purchase): Sermonix Pharmaceuticals
- **Jessica Shepherd, MD**
  - No relevant financial relationships to report

Learning Objectives

- Summarize key scientific findings regarding patient selection, efficacy, and safety of menopausal hormone therapy to optimize patient outcomes
- Incorporate the most current evidence-based menopause management guidelines into clinical practice
- Utilize a patient-centered, shared decision-making approach, along with culturally relevant communication techniques, in the evaluation and management of symptoms of menopause
- Delineate the benefits and risks associated with hormone therapy options for the management of vasomotor symptoms and prevention of osteoporosis in menopausal women

Women's Health 2024 | Beyond the Annual Visit

Hormone Therapy in Menopause Management: What We Know About CVD and Breast Cancer Risk 20 Years Post-WHI

James A. Simon, MD, CCD, MSCP, IF, FACOG

Clinical Professor

George Washington University

IntimMedicine Specialists®

The Initial WHI Publication

Context Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain.

Objective To assess the major health benefits and risks of the most commonly used combined hormone preparation in the United States.

Design Estrogen plus progestin component of the Women's Health Initiative, a randomized controlled primary prevention trial (planned duration, 8.5 years) in which 16 608 postmenopausal women aged 50-79 years with an intact uterus at baseline were recruited by 40 US clinical centers in 1993-1998.

Interventions Participants received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n=8506) or placebo (n=8102).

Main Outcomes Measures The primary outcome was coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome. A global index summarizing the balance of risks and benefits included the 2 primary outcomes plus stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

Conclusions Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD.

JAMA. 2002;288:321-333 www.jama.com

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women

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

Writing Group for the Women's Health Initiative Investigators

Context Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain.

Objective To assess the major health benefits and risks of the most commonly used combined hormone preparation in the United States.

Design Estrogen plus progestin component of the Women's Health Initiative, a randomized controlled primary prevention trial (planned duration, 8.5 years) in which 16 608 postmenopausal women aged 50-79 years with an intact uterus at baseline were recruited by 40 US clinical centers in 1993-1998.

Interventions Participants received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n=8506) or placebo (n=8102).

Main Outcomes Measures The primary outcome was coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome. A global index summarizing the balance of risks and benefits included the 2 primary outcomes plus stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

Conclusions Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD.

Rossouw JE, et al; Writing Group for the Women's Health Initiative Investigators. *JAMA.* 2002;288(3):321-333.

WHI-E+P: Relative and Absolute Risk

Women 50 to 79 (mean 63.5) Years of Age at Baseline

Health Event	Overall Hazard Ratio	Confidence Interval		Absolute Risk per 10,000 Women/Year	Absolute Benefit per 10,000 Women/Year
		Nominal 95%	Adjusted 95%		
~~CHD~~	~~1.29~~	~~1.02–1.63~~	~~0.85–1.97~~	~~7~~	
CHD-Revised	1.24	1.00–1.54	0.97–1.60	6	
~~Breast cancer~~	~~1.26~~	~~1.00–1.59~~	~~0.83–1.92~~	~~8~~	
Breast cancer	1.24	1.01–1.54	0.97–1.59	8	
Strokes	1.31	1.02–1.68	0.93–1.84	7	
VTE	2.11	1.58–2.82	1.26–3.55	18	
Colorectal cancer	0.56	0.38–0.81	0.33–0.94		7
Hip fractures	0.67	0.47–0.96	0.41–1.10		5
Total fractures	0.76	0.69–0.85	0.63–0.92		47
New-onset diabetes	0.79	0.67–0.93			15

Slide courtesy of Dr. Howard Hodis.

Cauley JA, et al. *JAMA.* 2003;290(13):1729-1738. Chlebowski RT, et al. *N Engl J Med.* 2004;350(10):991-1004. Chlebowski RT, et al. *JAMA.* 2003;289(24):3243-3253. Manson JE, et al. *N Engl J Med.* 2003;349(6):523-534. Wassertheil-Smoller S, et al. *JAMA*. 2003;289(20):2673-2684. Margolis KL, et al. *Diabetologia.* 2004;47(7):1175-1187. Rossouw JE, et al; Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288(3):321-333.

WHI-E: Relative and Absolute Risk

Women 50 to 79 (mean 64) Years of Age at Baseline

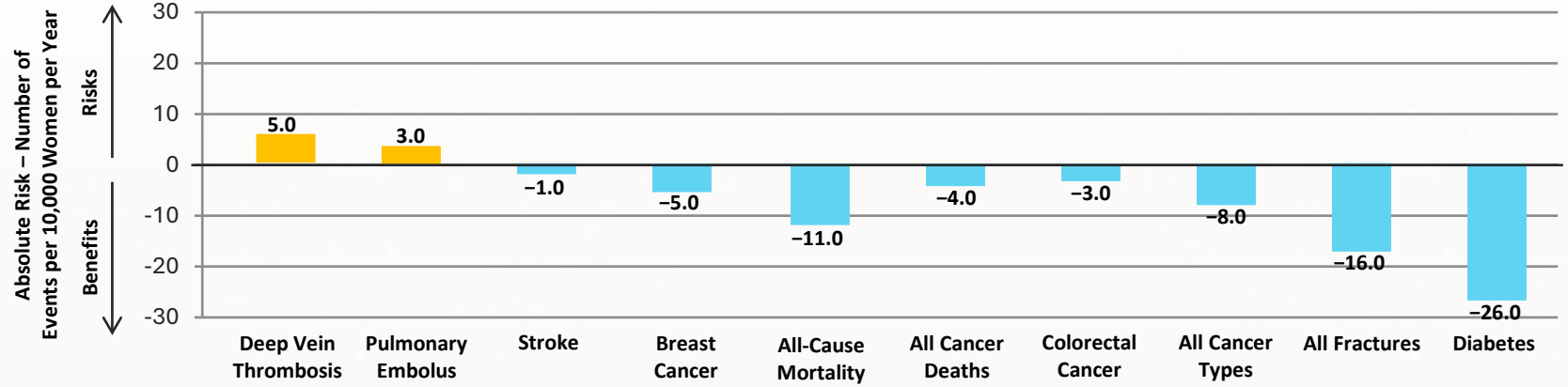
Event	Overall HR	Confidence Intervals 95% Nominal	Confidence Intervals 95% Adjusted	Absolute Risk per 10,000 Women/Year	Absolute Benefit per 10,000 Women/Year
CHD	0.91	0.75–1.12	0.72–1.15		5
Breast cancer	0.77	0.59–1.01	0.57–1.06		7
Strokes	1.39	1.10–1.77	0.97–1.99	12	
VTE	1.33	0.99–1.79	0.86–2.08	7	
PE	1.34	0.87–2.06	0.70–2.55	3	
Colorectal cancer	1.08	0.75–1.55	0.63–1.86	1	
Hip fractures	0.61	0.41–0.91	0.33–1.11		6
Total fractures	0.70	0.63–0.79	0.59–0.83		56
New-onset diabetes	0.88	0.77–1.01			14

Slide courtesy of Dr. Howard Hodis.

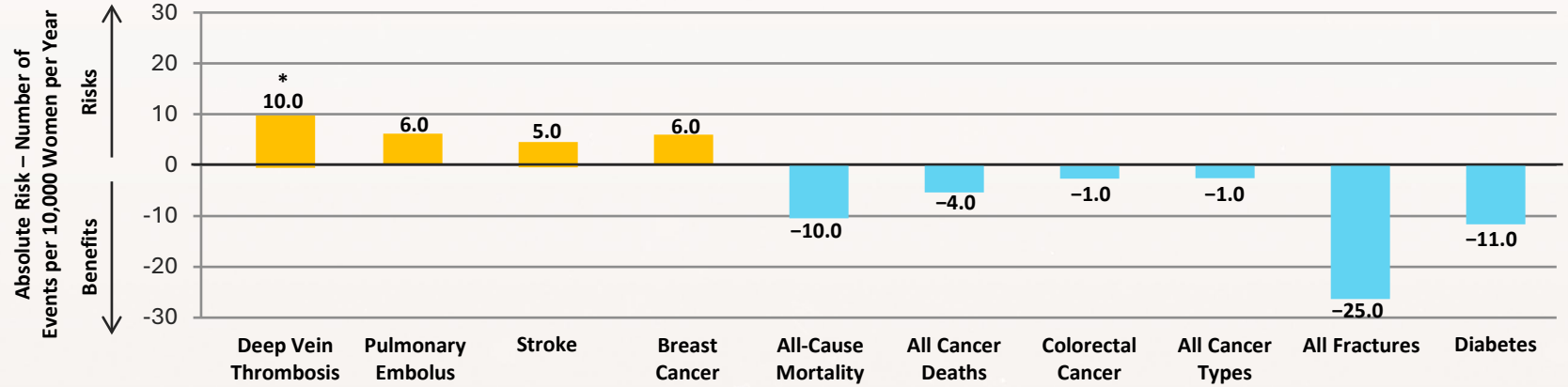
Anderson GL, et al; Women's Health Initiative Steering Committee. *JAMA*. 2004;291(14):1701-1712.

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

CEE Trial



CEE+MPA Trial



Slide courtesy of Dr. Howard Hodis.
Manson JE, et al. *JAMA* 2013;310(13):1353-1368.

WHI received enormous media coverage – more than 400 newspaper stories and 2500 television/radio stories…

And what about the embargo and the warning letters?

TIME ONLINE EDITION

The Truth About Hormones – Hormone Replacement Therapy is Riskier Than Advertised: What's a woman to do?

July 22, 2002

People.com

Hormone Hazards

July 29, 2002

The Philadelphia Inquirer

A New Blow to Hormone Therapy,

June 24, 2003

FT.com FINANCIAL TIMES

Study Dismissed HRT As Clinically Useless

March 18, 2003

Newsweek

The End of the Age of Estrogen

July 22, 2002

Another Study Slams Hormone Pills; The Replacement Regimen Doesn't Help Improve Women's Memory or Mood, Researchers Said

March 18, 2003

USA TODAY

Hormone Therapy: The Danger Assessed

May 27, 2003

DallasNews.com
The Dallas Morning News

Home Menu | Local News | SportsDay | Business | ClassifiedCenter

Bad to Worse: Major Findings by a Government Study of Hormone Therapy for Women

August 7, 2003

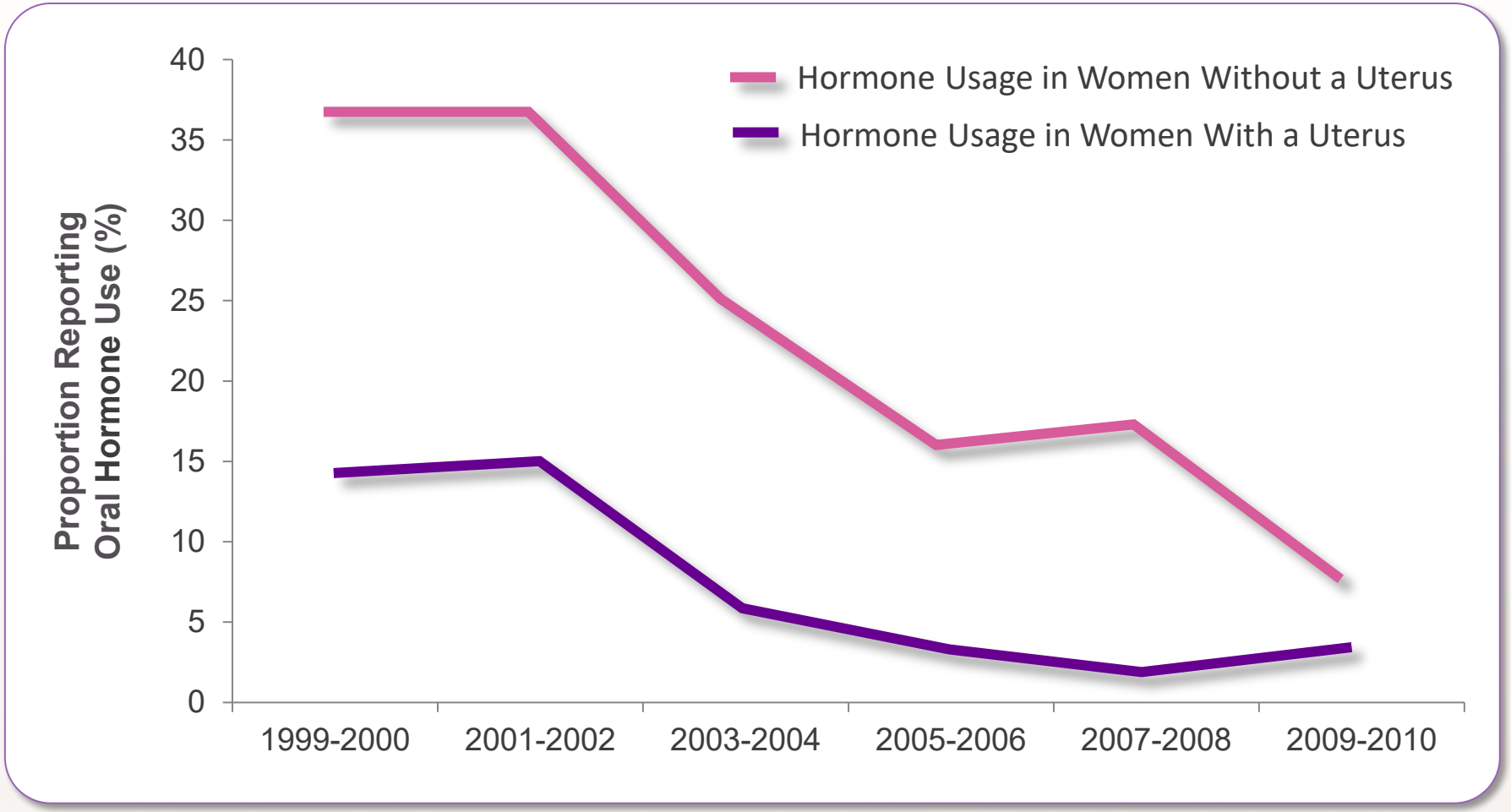
St. Petersburg Times — Florida's best newspaper sptimes.com

Hormone Therapy's Use Knocked Again

August 7, 2003

The Media Matter: A Call for Straightforward Medical Reporting.
Ann Intern Med. 2004;140(3):226-228.

Use of Estrogen and Estrogen/Progestin Has Dropped Since the WHI (July 2002): Results From NHANES



Data from 10,107 women aged ≥40 years in the National Health and Nutrition Examination Survey (NHANES).
Sprague BL, et al. *Obstet Gynecol*. 2012;120(3):595-603.

WHI Methods: Outcome Definitions

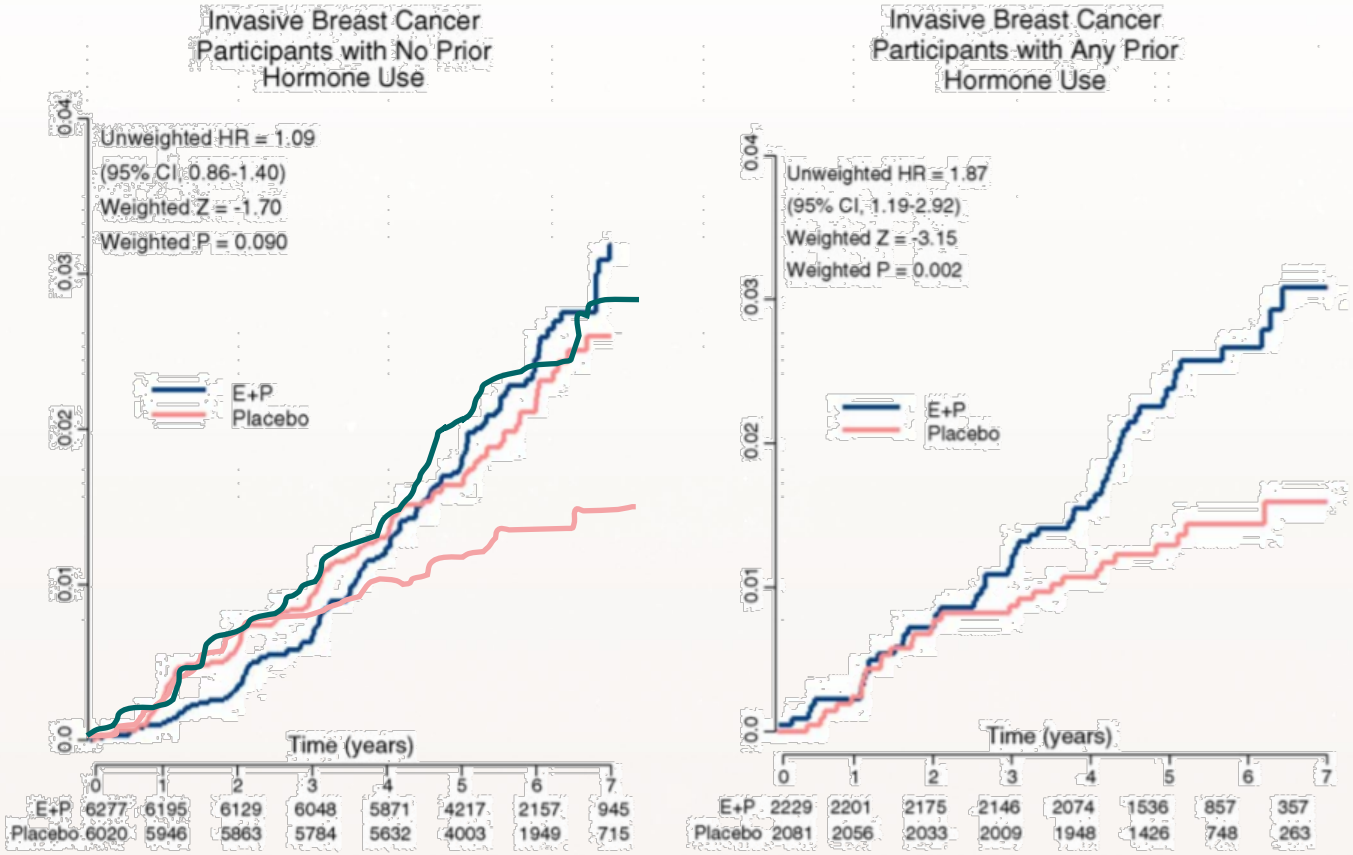
TABLE 1. Outcomes for each arm of the WHI Clinical Trial and Observational Study

Outcome	PHT	DM	CaD	OS
Cardiovascular				
Coronary heart disease	1°	2°	x	x
Stroke	2°	2°	x	x
Congestive heart failure	2°	2°	x	x
Angina	2°	2°	x	x
Peripheral vascular disease	2°	2°	x	x
Coronary revascularization	2°	2°	x	x
Venous thromboembolic disease				
Pulmonary embolism	2°	x	x	x
Deep vein thrombosis	2°	x	x	x
Total cardiovascular	2°	2°	x	x
Cancer				
Breast	2°	1°	2°	x
Colorectal	x	1°	2°	x
Endometrial	2°	2°	x	x
Ovarian	2°	2°	x	x
Total cancers	2°	2°	2°	x
Fractures				
Hip	2°	x	1°	x
Other fractures	2°	x	2°	x
Total fractures	2°	x	2°	x
Other				
Diabetes mellitus requiring therapy	x	2°	x	x
Death from any cause	2°	2°	2°	x

"1°" indicates primary outcome; "2°" secondary or safety outcomes; "x" ascertained.

Curb JD, et al. *Ann Epidemiol.* 2003;13(9 Suppl):S122-S128.

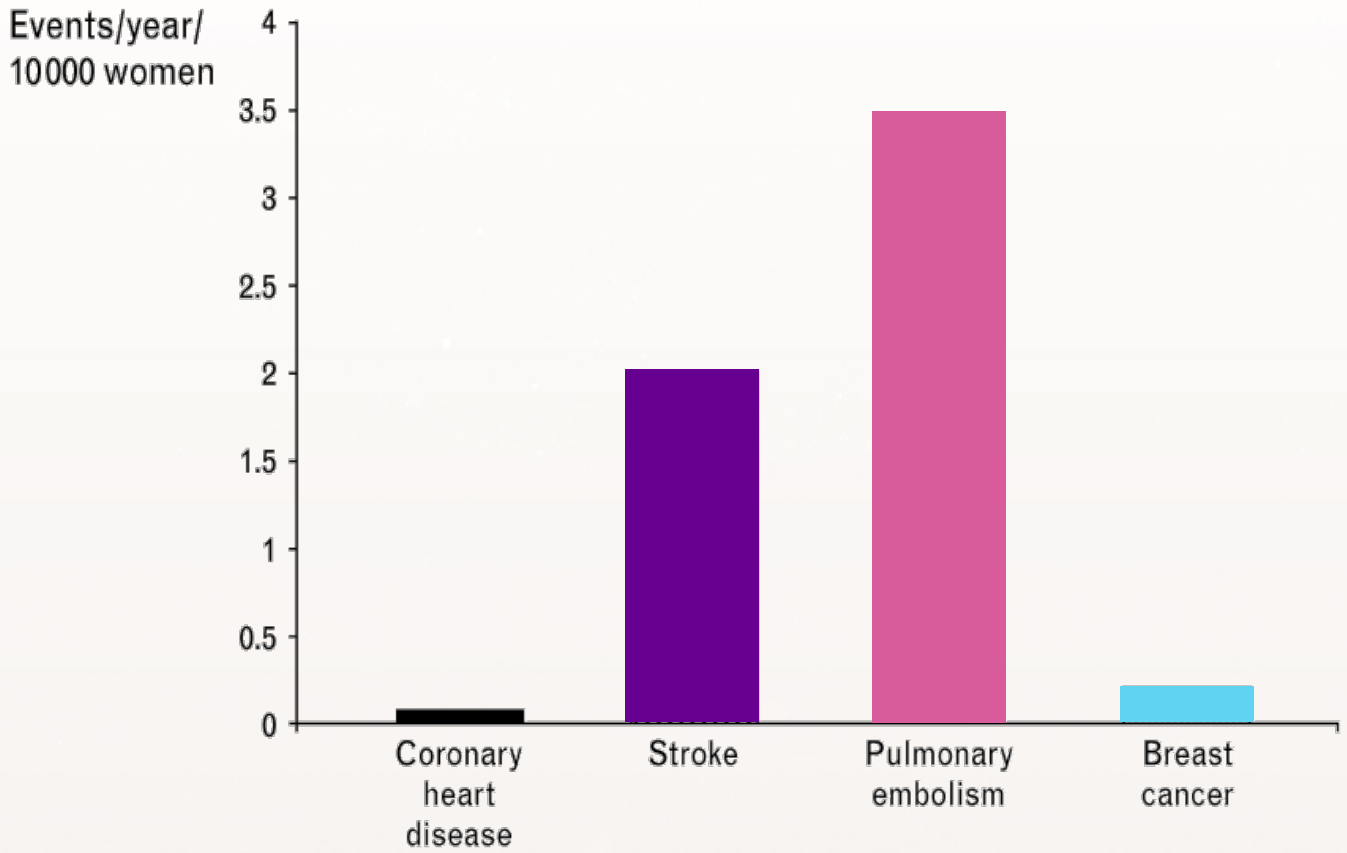
WHI CEE+MPA Breast Cancer by Prior Use Over an Average of 5.6 Years of Treatment



Modified from slide courtesy of Dr. Howard Hodis.

Anderson GL, et al. *Maturitas*. 2006;55(2):103-115.

Excess Incidence of Potentially Fatal Events Attributable to Oral ET/EPT in WHI (Women Aged 50-60 years)

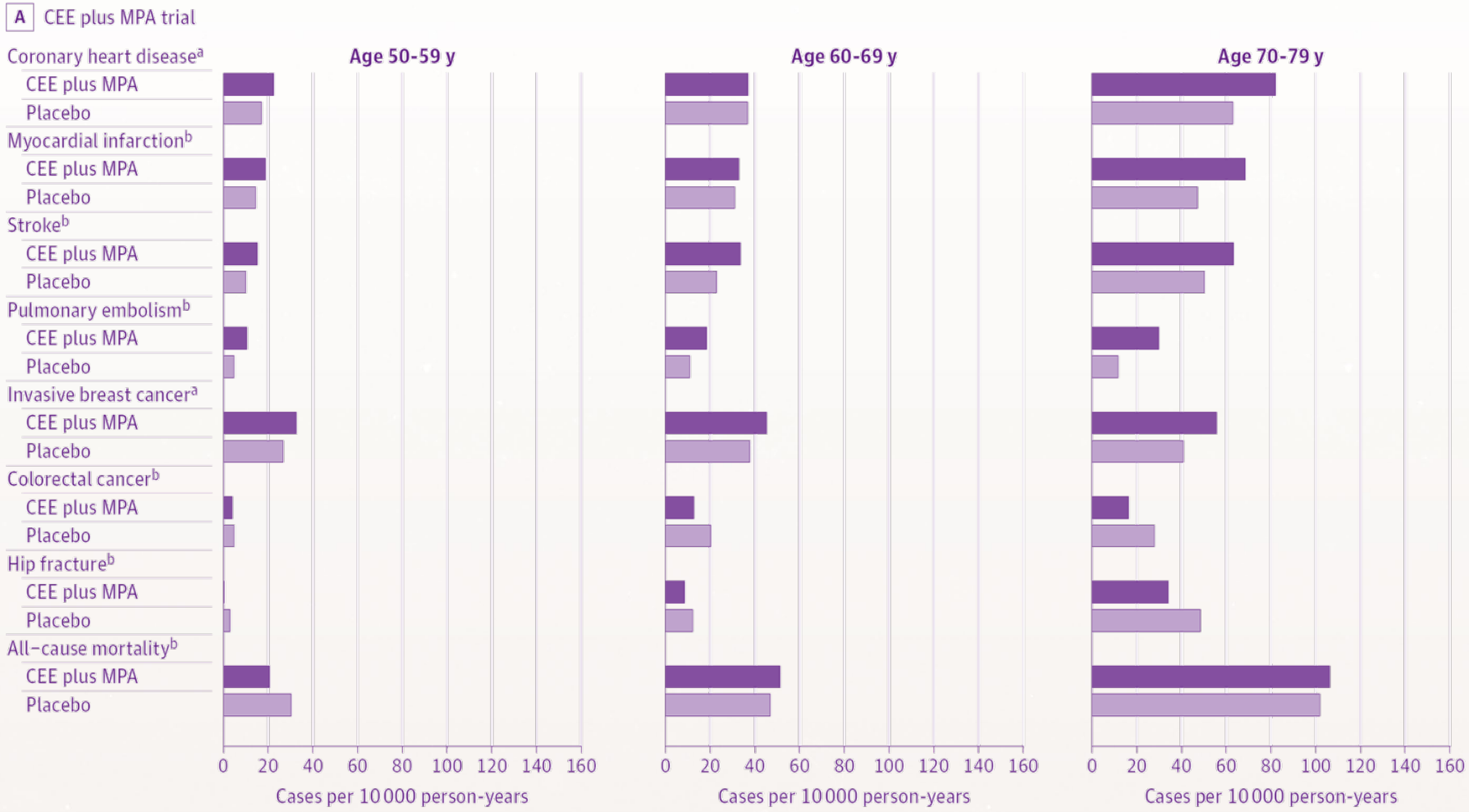


Data from both Women's Health Initiative clinical trials (CEE+MPA, CEE)

Olié V, et al. *Curr Opin Hematol*. 2010;17(5):457-463.

WHI Summary of Results: All Trials, JAMA 2024

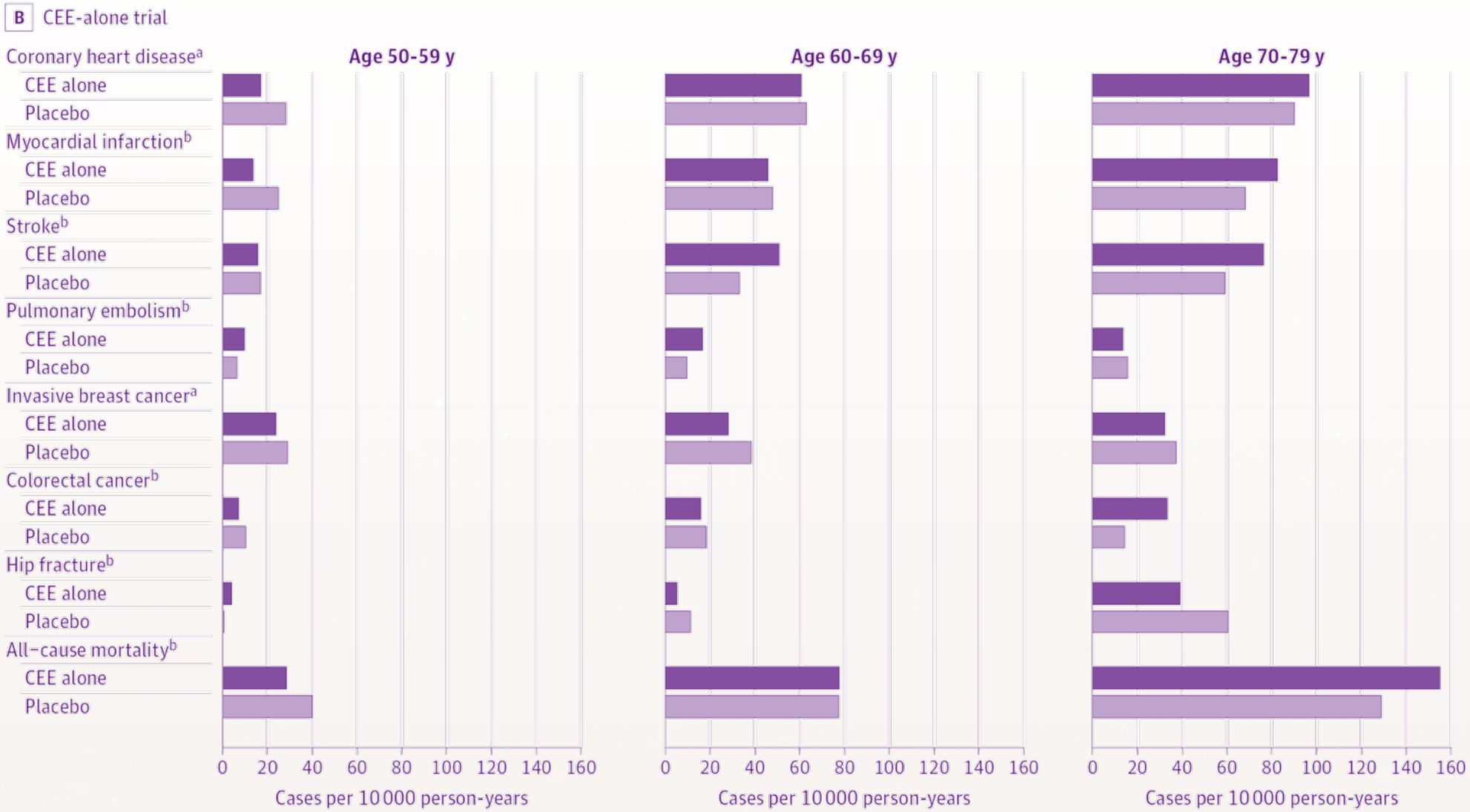
Figure 3. Absolute Risks of Health Outcomes by 10-Year Age Groups in the Women's Health Initiative Hormone Therapy Trials



Women's Health 2024 | Beyond the Annual Visit

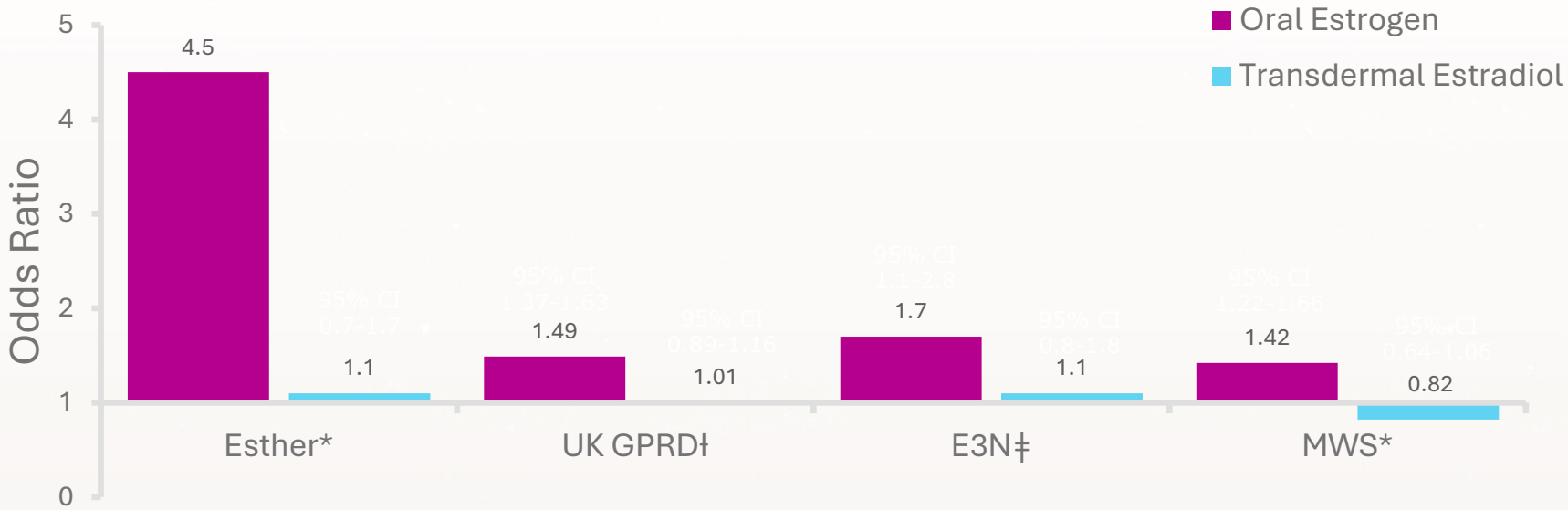
Manson JE, et al. *JAMA*. 2024;331(20):1748-1760.

WHI Summary of Results: All Trials, JAMA 2024



Manson JE, et al. *JAMA*. 2024;331(20):1748-1760.

Transdermal Estradiol Confers Reduced VTE Risk[1-5]



- **By avoiding first-pass liver metabolism, transdermal estradiol has less effect on clotting factors compared to oral estrogen[6]**
- **It is suggested that transdermal estradiol does not increase VTE risk[4,5,7-10]**

* Adjusted for family history of VTE and varicose veins, and body mass index (BMI).
† Adjusted for BMI, history of treatment for varicose veins, inherited thrombophilia.
‡ Adjusted for confounding factors (BMI, parity, education level, and time period).

1. Canonico M, et al. *J Thromb Haemost*. 2006;4(6):1259-1265. 2. Renoux C, et al. *J Thromb Haemost*. 2010;8(5):979-986. 3. Canonico M, et al. *Arterioscler Thromb Vasc Biol*. 2010;30(2):340-345. 4. Sweetland S, et al. *J Thromb Haemost*. 2012;10(11):2277-2286. 5. Mueck AO. *Climacteric*. 2012;15(sup1):11-17. 6. Olié V, et al. *Curr Opin Hematol*. 2010;17(5):457-463. 7. Canonico M, et al. *Circulation*. 2007;115(7):840-845. 8. Canonico M. *Maturitas*. 2015;82(3):304-307. 9. Canonico M, et al. *Menopause*. 2016;23(6):587-588. 10. de Villiers TJ, et al. *Climacteric*. 2016;19(4):313-315.

Arteriosclerosis, Thrombosis, and Vascular Biology
Journal of the American Heart Association
American Heart Association. Learn and Live℠

Thromboembolism. Results From the E3N Cohort Study Postmenopausal Hormone Therapy and Risk of Idiopathic Venous

Hazard Ratios of Idiopathic Venous Thromboembolism in Relation to Both Estrogens by Route of Administration and Concomitant Progestogens

			Hazard Ratios (95% Confidence Intervals)	
Treatment	n=549	811 643	Age-Adjusted	Multivariable Adjusted*
Never use	181	291399	1 [reference]	1 [reference]
Past use	66	100943	1.0 (0.7–1.3)	1.1 (0.8–1.5)
Current use of oral estrogens	81	93211	1.5 (0.9–2.3)	1.7 (1.1–2.8)
Current use of transdermal estrogens	174	268481	1.1 (0.7–1.6)	1.1 (0.8–1.8)
No progestogens use	26	46163	...	...
Current use of micronized progesterone	47	87959	0.9 (0.6–1.4)	0.9 (0.6–1.5)
Current use of pregnane derivatives	91	125804	1.3 (0.8–1.9)	1.3 (0.9–2.0)
Current use of norpregnane derivatives	69	78855	1.7 (1.1–2.6)	1.8 (1.2–2.7)
Current use of nortestosterone derivatives	22	22911	1.4 (0.8–2.5)	1.4 (0.7–2.4)
Current use of other treatment	30	47693	1.0 (0.7–1.5)	1.1 (0.7–1.8)
Unknown	17	9916	2.0 (0.5–3.9)	2.0 (0.5–3.9)

*Adjusted for age, body-mass index, parity, education level, and time-period.
Data for adjustment missing for 19 cases and for 843 non-cases.
P for homogeneity between current use of oral estrogens vs current use of transdermal estrogens is significant (*P*=0.01).
P for homogeneity between progestogen subgroups is significant (*P*<0.01).

Conclusions

In this large study, we found that route of estrogen administration and concomitant progestogens type are 2 important determinants of thrombotic risk among postmenopausal women using hormone therapy.

Transdermal estrogens alone or combined with progesterone might be safe with respect to thrombotic risk.

Slide courtesy of Paul Piette.
Canonico M, et al. *Arterioscler Thromb Vasc Biol*. 2010;30(2):340-345.

VTE and Type of Progestogen: Guidelines

- Observational studies point to **a lower risk with low-dose transdermal therapy associated with progesterone**, underlined by a strong biological plausibility.[1]
- Some progestogens, eg, MPA, norpregnane derivatives, and continuous combined regimens, may be associated with greater risk of VTE in oral MHT users.[1]
- "*The route of administration of estrogen and the dosage and* ***type of progestogen*** *used may* ***impact thrombosis risk***"[2]
- "*The* ***impact on the risk*** *of a thromboembolic event may* ***also be affected*** *by the* ***type of progestogen***"[3]

Slide courtesy of Paul Piette.

1. Baber RJ, et al. *Climacteric.* 2016;19(2):109-150.
2. Santen RJ, et al. *J Clin Endocrinol Metab.* 2010;95(7 Suppl 1):S1-S66.
3. Sturdee DW, et al. *Climacteric.* 2011;14(3):302-320.

Risks vs Benefits: Breast Cancer Risk CEE + MPA

- In WHI, CEE + MPA was associated with a 24% increased risk of invasive breast cancer.
- The RR of 1.24 with CEE/MPA translates to an excess risk of approx. 4 per 1,000 women taking HT for a **5-year time period**.
  - An approximate 11%-50% increase in breast cancer risk from 15-30 g/day of alcohol consumption (about 2 standardized drinks)
  - Same or greater risk for obesity
- Analysis from French prospective cohort study[1]
  - Synthetic progestins (medrogestone, chlormadinone acetate, cyproterone acetate, promegestone, nomegestrol acetate, norethisterone acetate, medroxyprogesterone acetate) significantly increased:
    - Breast cancer cell proliferation and
    - Breast cancer risk, whereas
    - Micronized progesterone did not affect either of these

1. Fournier A, et al. *Breast Cancer Res Treat*. 2008;107(1):103-111.

Conclusions

- Results from the WHI provided many new insights into the benefits and risks of HRT
- A reduction in the risk of heart attack (primary endpoint) is favorable in the estrogen-only arm in women who started HRT post menopause
- The outcomes of both arms of the WHI tended to persist whether risks or benefits over long periods of time, even out to 20+ years following the initial study
- Non-oral estrogen delivery, as in transdermal estradiol and micronized progesterone, versus synthetic progestogen may cause PE and have a neutral effect with the progestogen on breast cancer

Women's Health 2024 | Beyond the Annual Visit

Current Guidelines on the Management of Menopausal Symptoms

Jessica Shepherd, MD, MBA, FACOG
Chief Medical Officer, Hers
Founder, Sanctum Med

Intro

- HRT is indicated for short-term and long-term use in perimenopausal and menopausal women for symptoms due to estrogen decline
- Indications for HRT use
    1. Women with menopausal symptoms
    2. Prevention of osteoporosis
    3. Women with conditions that lead to premature estrogen deficiency (POF, gonadal dysgenesis, surgical menopause)

The Menopause Society 2022 Hormone Therapy Position Statement

Hormone therapy remains the most effective treatment for vasomotor symptoms (VMS) and the genitourinary syndrome of menopause and has been shown to prevent bone loss and fracture.

The risks of hormone therapy differ depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used.

Treatment should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation of the benefits and risks of continuing therapy.

Benefits of HRT

- Resolution of vasomotor symptoms
- Improvement in bone mineral density
- Improvement in urogenital atrophy
- Reduction of colorectal cancer
- Decreased risk in vertebral and hip fractures
- Possible cardioprotection
- Decrease in neurodegenerative disease

Benefits of HRT

- HRT prevents bone loss and stimulates new bone formation. HRT increases BMD by 2%-5% and reduces the risk of vertebral and hip fracture (25%-50%). Estrogen is found to play a direct role, as receptors have been found in the osteoblasts.
- HT is the most effective treatment for VMS. HRT reduces symptom frequency and also intensity by nearly 90%, usually within one month of initiation.

Type and Dose of HRT

- Factors to help HCP prescribers include the following:
  - Patient preference
  - Uterine presence or absence
  - Contraceptive needs
  - Symptom type and severity
  - Comorbidities

Risks of HRT

- Endometrial cancer risk factors in women taking HRT
- Risk factors for endometrial hyperplasia and cancer, with unopposed estrogen and progesterone
- A monthly progestogen dose, in proportion to the estrogen dose, is recommended in:
  - Women with a uterus
  - Women using sequential HRT as a minimum of 10 days norethisterone (NET); medroxyprogesterone acetate (MPA), can also be given in 12 days or micronized progesterone per month

Assessment of Uterine Bleeding on HRT

In the absence of risk factors for endometrial cancer, offer adjustments in the progesterone or HRT preparation, for 6 months in total.

If unscheduled bleeding (a) occurs within 6 months of starting HRT or (b) if it persists 3 months after a change in HRT dose or preparation, order a transvaginal ultrasound for endometrial lining thickness.

If unscheduled bleeding continues in low-risk women after 6 months of adjustments, discuss the options of an urgent ultrasound, weaning off HRT dosages, or consideration of nonhormonal alternatives.

Contraindications

- HRT is conventionally contraindicated in women with hormone receptor-positive breast cancer and endometrial cancer.
- In women with a past history of VTE, MHT may be considered if the VTE had been provoked by certain circumstances, eg, major surgery or prolonged immobility, and use of a concomitant anticoagulant for VTE prophylaxis could be considered.

Duration of Use of HRT

- Currently there is universal agreement amongst national and international menopause societies that arbitrary limits should not be placed on the duration of use of HRT.
- The IMS has stated: “There are no reasons to place mandatory limitations on the duration of MHT.”
- Continuation of therapy should be decided at the discretion of the well-informed woman and her HCP and is dependent upon the specific goals and an objective estimation of ongoing individual benefits and risks.

The Menopause Society Statement on Duration of Use

- For women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio is favorable for treatment of bothersome VMS and prevention of bone loss.
- For women who initiate hormone therapy more than 10 years from menopause onset or who are aged older than 60 years, the benefit-risk ratio appears less favorable because of the greater absolute risks of coronary heart disease, stroke, venous thromboembolism, and dementia.
- Longer durations of therapy should be for documented indications such as persistent VMS, with shared decision-making and periodic reevaluation.

Women's Health 2024 | Beyond the Annual Visit

Menopausal Hormone Therapy: The Management of VMS and GSM and the Prevention of Osteoporosis

James A. Simon, MD, CCD, MSCP, IF, FACOG

Clinical Professor
George Washington University
IntimMedicine Specialists®

VMS

- VMS persist for a median duration of 7 years but can last for more than a decade in some women
- VMS can have a significantly negative impact on overall health and well-being
  - Women who experience frequent VMS (>6 days in the previous 2 weeks) also experience higher rates of anxiety, depression, difficulty sleeping, and overall impaired QoL
- About 3 out of 4 postmenopausal women suffer from fatigue, and 2 out of 3 have difficulty sleeping

Khan SJ, et al. *Int J Womens Health.* 2023;15:273-287.

Common HT Formulations

- HT is the most effective treatment for VMS
- HT use reduces symptom frequency and intensity by nearly 90%, usually within one month of initiation
- Generally well tolerated; most AEs, particularly with estrogen therapy, are breast pain and uterine bleeding

HT Type	Formulation	Common Brand Names	Route of Administration	Dosing	Additional Considerations
Estrogens	17β-estradiol	Activella, Mimvey, Estrace	Oral	1–2mg/day	
		Alora, Climara, CombiPatch, Minivelle, Vivelle-Dot	Transdermal	0.025mg-0.1mg; one patch every 3–7 days	May confer less risk of VTE vs oral estrogens
		Elestrin, Divigel	Topical/Lotion	1.74g/day	Can transfer to other individuals, clothing, et cetera without proper precautions; possible alternative to transdermal patch for adhesive allergies
		Estrace	Vaginal cream	500mg-1g daily x2 weeks; then 500mg-1g 1–3x weekly	Preferred for genitourinary but not systemic symptoms
		Femring	Intravaginal ring	0.05mg/day x3 months; 0.1mg/day x3 months	
	Conjugated equine estrogen (CEE)	Premarin, Prempro	Oral	0.3mg-1.25mg/day	In women post-hysterectomy: may be associated with reduced breast cancer mortality
		Premarin	Vaginal Cream	Daily x 2 weeks; then 2x weekly	Preferred for localized genitourinary symptoms; does not treat systemic VMS
	Estrone	Estragyn	Injection	0.1–0.5mg 2–3x weekly	
	Esterified estrogens	Menest	Oral	0.3–1.25mg/day	
	Ethinyl Estradiol	FemHrt	Oral	0.02–0.05mg 1–3x daily	Dose-dependent increased risk of coagulopathy such as VTE
Progestogens	Medroxyprogesterone (MPA)	Premphase, Prempro (CEE + MPA)	Oral	30-day cycle: 5–10mg/day x10-14 days Daily: 2.5–5mg/day	
	Micronized Progesterone (MP)	Prometrium, Endometrin	Oral	28-day cycle: 200mg/day x12 days Daily: 100mg/day	Continuous dose reduces unwanted vaginal bleeding; cyclical dose more favorable for endometrial protection and reduced breast cancer risk
	Norethindrone acetate	FemHrt (ethinyl estradiol + norethindrone acetate)	Oral	5mg/day	
		CombiPatch (estradiol + norethindrone acetate)	Transdermal	0.14mg 2x weekly	
	Levonorgestrel	Climara (estradiol + levonorgestrel)	Transdermal	0.015mg weekly	
	Dydrogesterone	Duphaston	Oral	28-day cycle: 10mg/day Daily: 2.5mg-5mg/day	Nonandrogenic

Khan SJ, et al. *Int J Womens Health.* 2023;15:273-287.

Approach to Prescribing

For healthy, symptomatic women aged <60 years and <10 years from menopause onset, current evidence supports the use of HT

However, >80% of women older than 50 years have at least one chronic medical condition that impacts decision-making regarding HT use (eg, CVD)

For women with an intact uterus who experience moderate to severe VMS symptoms, treatment should include an adequate dose of progesterone/progestogen or bazedoxifene for endometrial protection

Khan SJ, et al. *Int J Women's Health.* 2023;15:273-287.

GSM/VVA: Incidence and Unmet Need

- GSM/VVA symptoms will affect at least 50% of postmenopausal women at some point in their lives
  - GSM/VVA symptoms are chronic and progressive
  - Symptoms do not improve without treatment
- Many women remain unaware that vulvar and vaginal changes can be a direct result of the menopausal transition
- Women experiencing GSM/VVA symptoms due to menopause often become depressed with a diminished QoL

FDA-Approved Products for Vaginal Changes of Menopause Include:

- Estradiol vaginal cream
- Conjugated estrogens vaginal cream
  - Also indicated for dyspareunia
- Estradiol hemihydrate vaginal tablet
- Estradiol vaginal rings can deliver:
  - "Locally" or
  - Systemically; systemic ring is also indicated for vasomotor symptoms
- Ospemifene indicated for dyspareunia and moderate to severe vaginal dryness due to VVA
- Prasterone/DHEA indicated for dyspareunia
- Estradiol vaginal insert Indicated for dyspareunia

Modified from: North American Menopause Society. *Menopause*. 2007;14(3 Pt 1):355-369.

Osteoporosis

It is well known that menopause is one of the most important risk factors for bone loss in women midlife

Women lose about 50% of their trabecular bone and 30% of their cortical bone during their lifetime—about 50% is lost during the first 10 years after menopause begins

The lack of ovarian estrogen after menopause results in significant loss in bone strength, placing women at higher risk of osteoporosis

Interventions for the Prevention and Treatment of Osteoporosis in Menopause

Hormone replacement therapy

- Estrogen alone
- Estrogen + progestogen

Bisphosphonates

- Alendronate
- Risedronate
- Ibandronate
- Zoledronate

Denosumab

SERMs

- Bazedoxifene
- Raloxifene

Stevenson J, et al. *Post Reprod Health*. 2023;29(1):11-14.

The Role of HT

- Data from the WHI study showed that HT, even at lower doses,[1] reduces the risk of both spine and hip as well as other osteoporotic fractures even in women at low risk[2] as well as in those with established osteoporosis[3]
- Continuous use of HT has been shown to be an effective method of preventing fracture, but just a few years of treatment with initiation around the time of menopause may have a long-term effect on fracture reduction[4]
- Discontinuation of hormone therapy can lead to rapid bone loss

1. Lees B, et al. *Osteoporos Int*. 2001;12(4):251-258. 2. Mason JE, et al. *JAMA*. 2013;310(13):1353-1368.
3. Lufkin EG, et al. *Ann Intern Med*. 1992;117(1):1-9. 4. Bagger YZ, et al. *Bone*. 2004;34(4):728-735.

Considerations for Choosing Therapy: The Role of SERM Therapy

- For postmenopausal women:
  - At high risk for invasive breast cancer: raloxifene should be given and is FDA-approved for chemoprevention
  - With an intact uterus: bazedoxifene may provide an added element of prevention when added to estrogen compared with synthetic progestogens

Conclusions

- HT initiated near the last menstrual period (ie, within 10 years of the last menstrual period) can be used for:
  - Prevention or treatment of GSM or vasomotor symptoms due to menopause
  - Prevention of bone loss and osteoporosis

Women's Health 2024 | Beyond the Annual Visit

Shared Decision-Making and the Elevation of the Patient Voice

Jessica Shepherd, MD

What Is SDM?

- Shared decision-making involves collaboration between clinicians and patients to understand available treatment options and their risk-benefit profile to reach a treatment decision using evidence-based information while incorporating the patient's personal preferences and values

Koysombat K, et al. Ann NY Acad Sci. 2024;1538(1):34-44.

SDM in Menopause Care: HRT

Decision-making should include overall benefits in terms of symptom management and QoL improvement, as well as improving bone and CV health for some patients

The benefit-risk profile should be weighed in the context of lifestyle factors, alcohol intake, and obesity

Recommendations for the use of the appropriate dose, route of administration, regimen, and duration need to be individualized to manage a woman's symptoms and to meet treatment goals

It is thus imperative that these benefits and risks are conveyed clearly and accurately so that patients can make an informed decision about what is important for them in the context of their values and circumstances

Koysombat K, et al. Ann NY Acad Sci. 2024;1538(1):34-44.

Factors Influencing Decision-Making Regarding HRT Use

- Women's decision-making on how to manage menopausal symptoms has been described as a nonlinear process consisting of iterative cycles in which women:
  - Consider available options
  - Evaluate benefit-risk profiles and the likely outcome of their decision
  - Reevaluate their decision
  - Instigate changes as required

Koysombat K, et al. Ann NY Acad Sci. 2024;1538(1):34-44.

Factors Related to Decision-Making in Menopause Care

Internal Factors

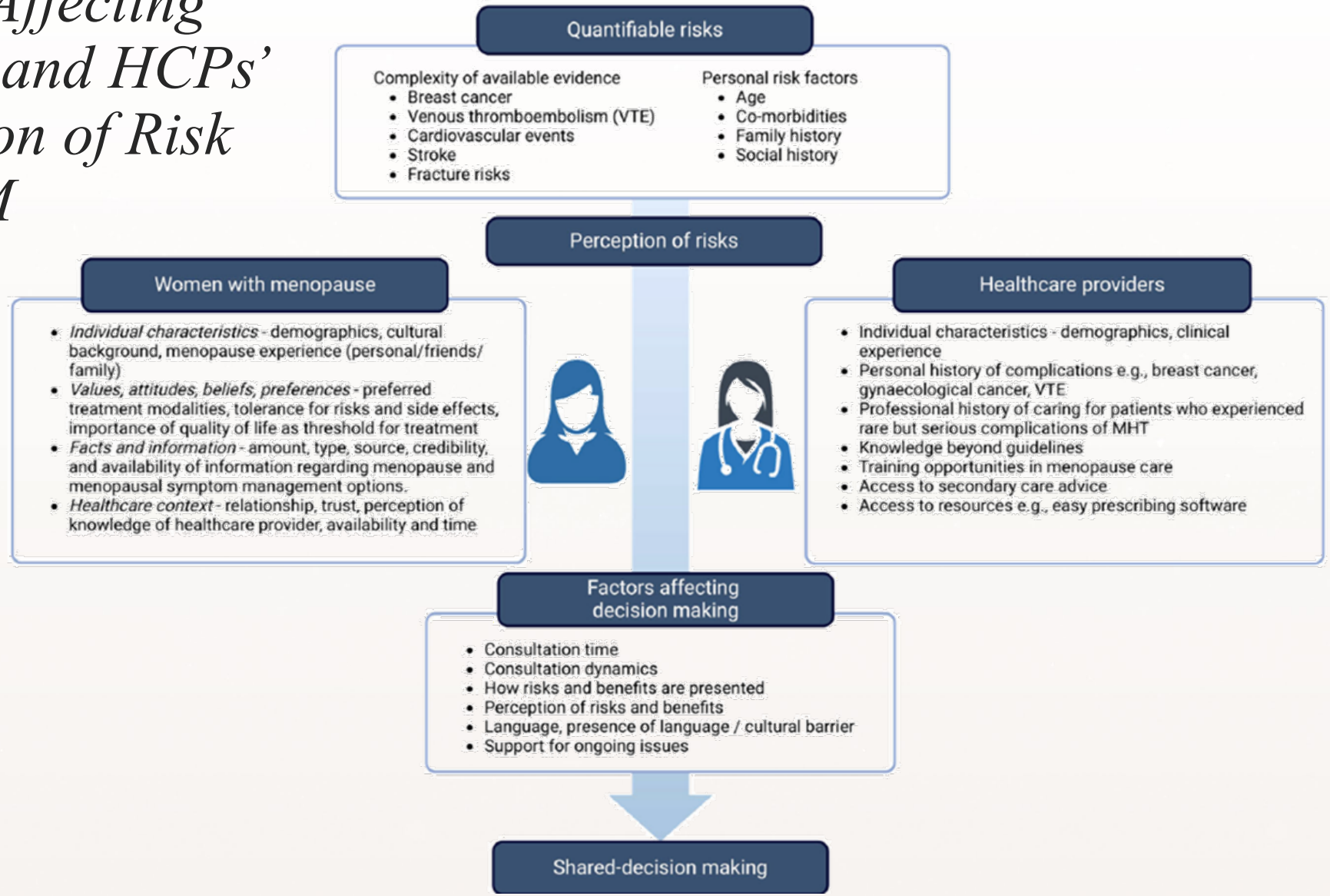
- **Individual characteristics** (demographics, menopause experience, menopause-related symptoms)
- **Values, attitudes, beliefs, and preferences** (preferred treatment modalities, tolerance for risks and side effects of treatment, and importance of quality of life as a threshold for treatment)

External Factors

- **Information about menopause and symptom management** (the amount, type, source, credibility, and availability of information regarding menopause and management options)
- **Healthcare context** (relationship, trust, perception of knowledge of HCPs, availability, and time)

Koysombat K, et al. Ann NY Acad Sci. 2024;1538(1):34-44.

Factors Affecting Patients' and HCPs' Perception of Risk and SDM



Koysombat K, et al. Ann NY Acad Sci. 2024;1538(1):34-44.

SES and Considerations for SDM

- Markers of affluence, including place of residence, education, and employment status, have been shown to influence decisions to seek menopause-related treatments[1]
- HRT use was more frequently reported among women with high levels of education and who lived in urban areas[1]
- A strong link has previously been demonstrated between health literacy score and knowledge about HRT[1]
- Women with low income reported greater severity and frequency of menopausal symptoms vs White women and women with higher income[2,3]

1. Koysombat K, et al. Ann NY Acad Sci. 2024;1538(1):34-44.
2. Pershad A, et al. Menopause. 2022;29(11):1263-1268.
3. Thurston RC, et al. Obstet Gynecol Clin North Am. 2011;38(3):489-501.

Race/Ethnicity/Cultural Considerations for SDM

- The onset of menopause varies by race/ethnicity
- The type and degree of severity varies by race/ethnicity
- The perception of menopause varies by race/ethnicity/culture

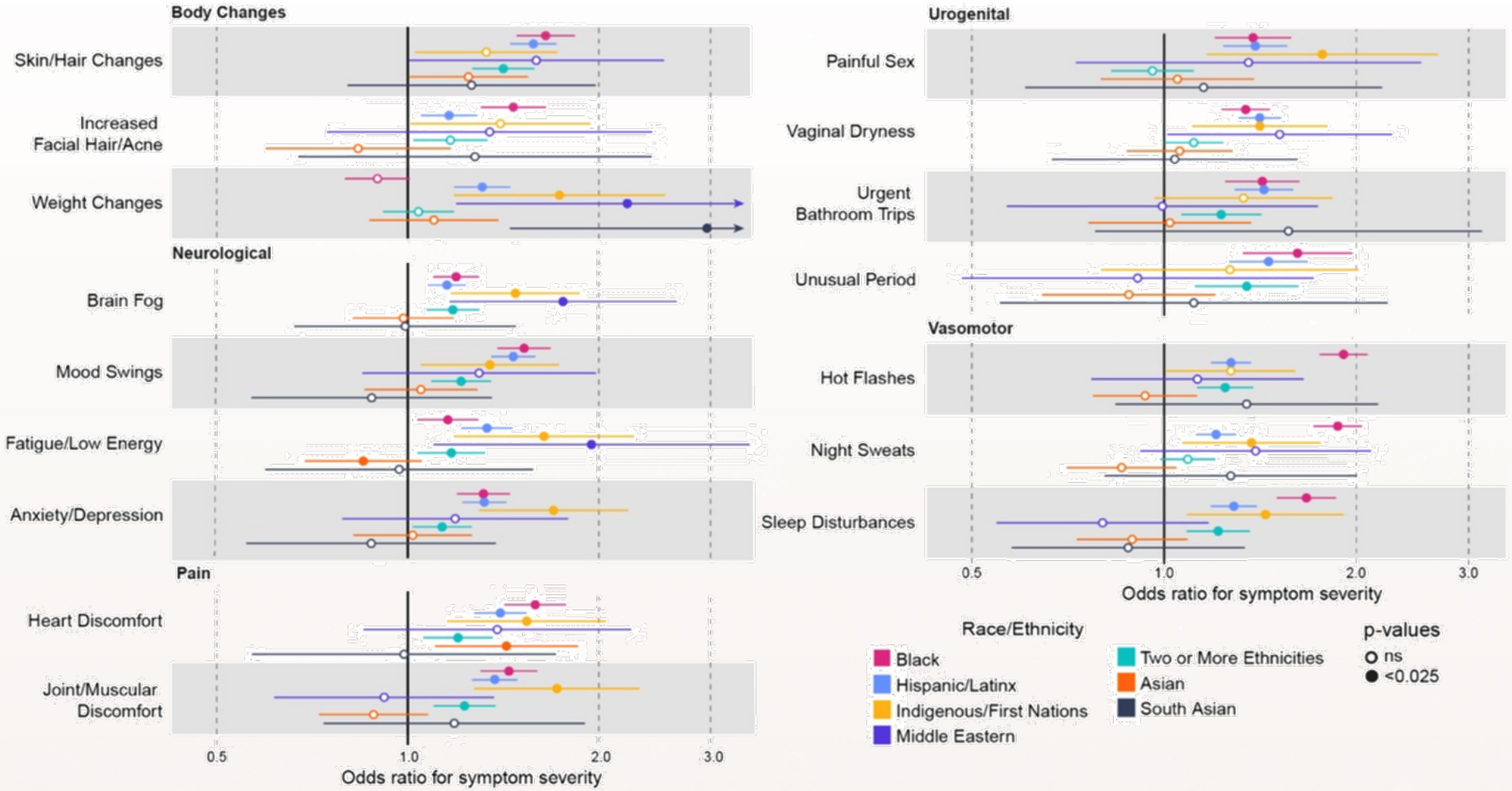
Hickey M, et al. Lancet. 2024;403(10430);947-957. Kochersberger A, et al. Menopause. 2024;31(6):476-483. Gold EB, et al. Am J Epidemiol. 2004;159(12):1189-1199. Pershad A, et al. Menopause. 2022;29(11):1263-1268. Thurston RC, et al. Obstet Gynecol Clin North Am. 2011;38(3):489-501.

VMS

- Analyses of the Study of Women's Health Across the Nation (SWAN) found that VMS were more prevalent among Black and Hispanic women; vaginal dryness was most prevalent among Hispanic women[1]
- Women with low income reported greater severity and frequency of menopausal symptoms vs White women and women with higher income
  - Caveat: these findings should be interpreted with caution, as they can be influenced by factors such as access to healthcare and use of HRT, which varies based on demographic characteristics

1. Gold EB, et al. Am J Epidemiol.2004;159(12):1189-1199.

Adjusted OR for Symptom Severity by Race/Ethnicity Including Affluence



Kochersberger A, et al. Menopause. 2024;31(6):476-483.

Considerations for SDM and Empowerment in Menopause

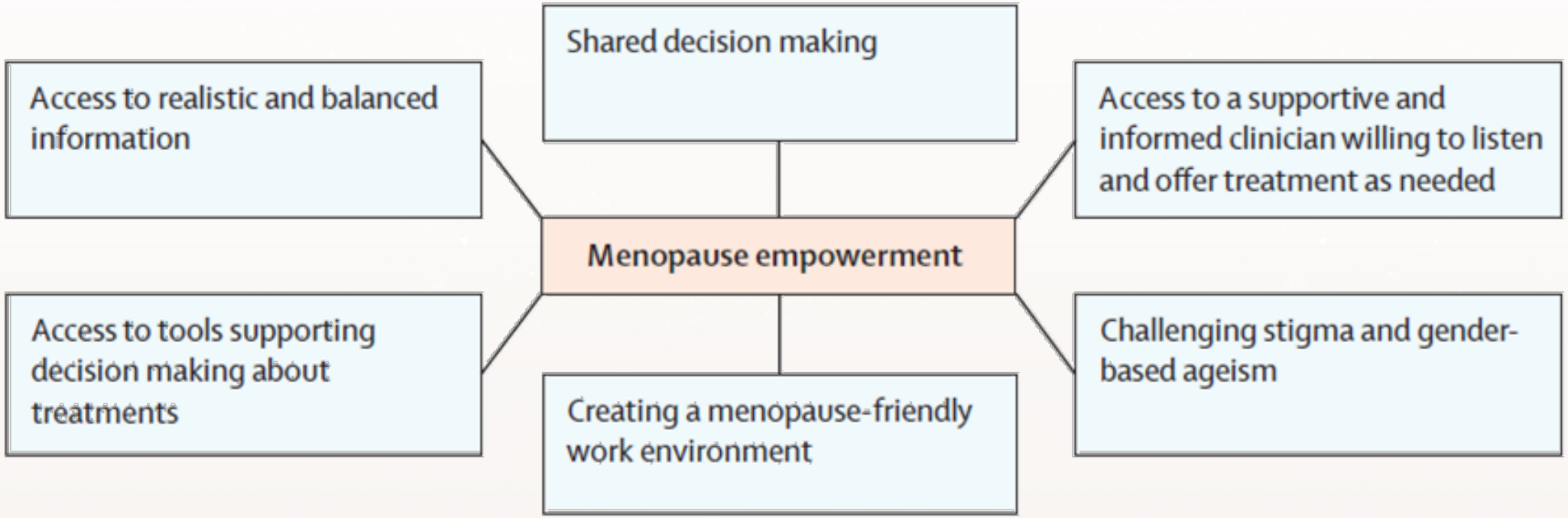
- To be empowered, women must be informed and listened to
  - Women have clearly stated that they want their voices heard and their experiences of menopause acknowledged and validated
  - Unfortunately, some women report that their concerns are dismissed, particularly those from minority groups

Health Empowerment in Menopause

- WHO defines empowerment as an active process of gaining knowledge, confidence, and self-determination to self-manage health and make informed decisions about care[1]
- In 2005 the NIH identified the need to develop and disseminate information emphasizing menopause as an ordinary, healthy phase of women's lives and promoting its demedicalization[2]

1. WHO. Health promotion glossary. Geneva, Switzerland: World Health Organization, 1998.
2. National Institutes of Health. Ann Intern Med. 2005;142(12 Pt 1):1003-1013.

Factors That Empower Women to Manage Menopause



Hickey M, et al. Lancet. 2024;403(10430);947-957.

Conclusion

- All patients have the right to be involved in decisions about their treatment and to make informed decisions if they can
- For menopausal women, this means that when discussing the risks and benefits of HRT, the information provided by healthcare professionals should be based on the best available evidence
- In a positive model of shared decision-making, the healthcare professional and the woman work together to make a decision that is the best for that individual