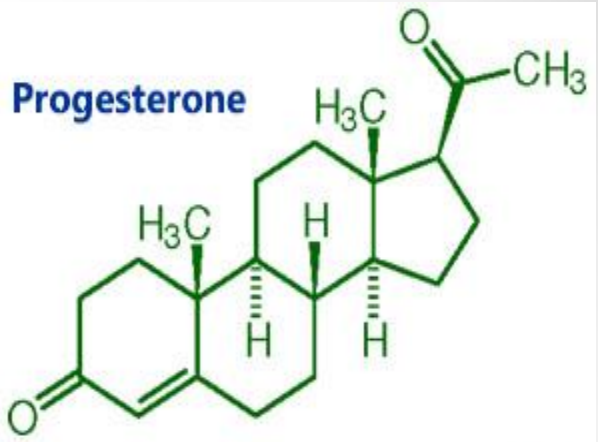
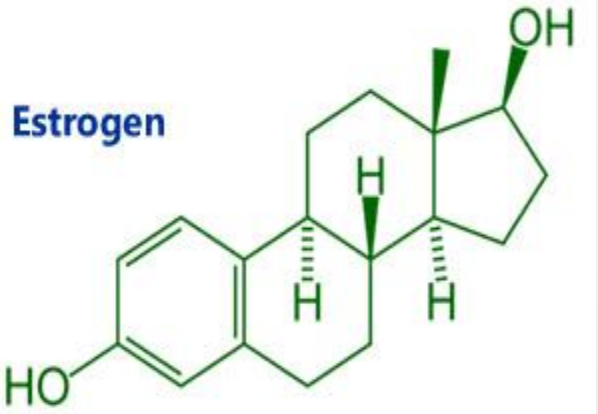
Hormone Therapy: Estrogen and Progesterone





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Disclosures

- Husband works as employee for Genomic Health

Objectives

- Review currently understanding of Risks/Benefits of HRT
- Review when to consider HRT
- Review timing of initiation
- Review formulations for various treatments

Menopause: Symptoms vs Systems

Estrogen *withdrawal*

Resolve with time

- Hot flashes
- Night sweats
- Sleeplessness
- Palpitations
- Headaches
- Mood swings
- Fatigue

Estrogen *deficiency*

Worsen with time

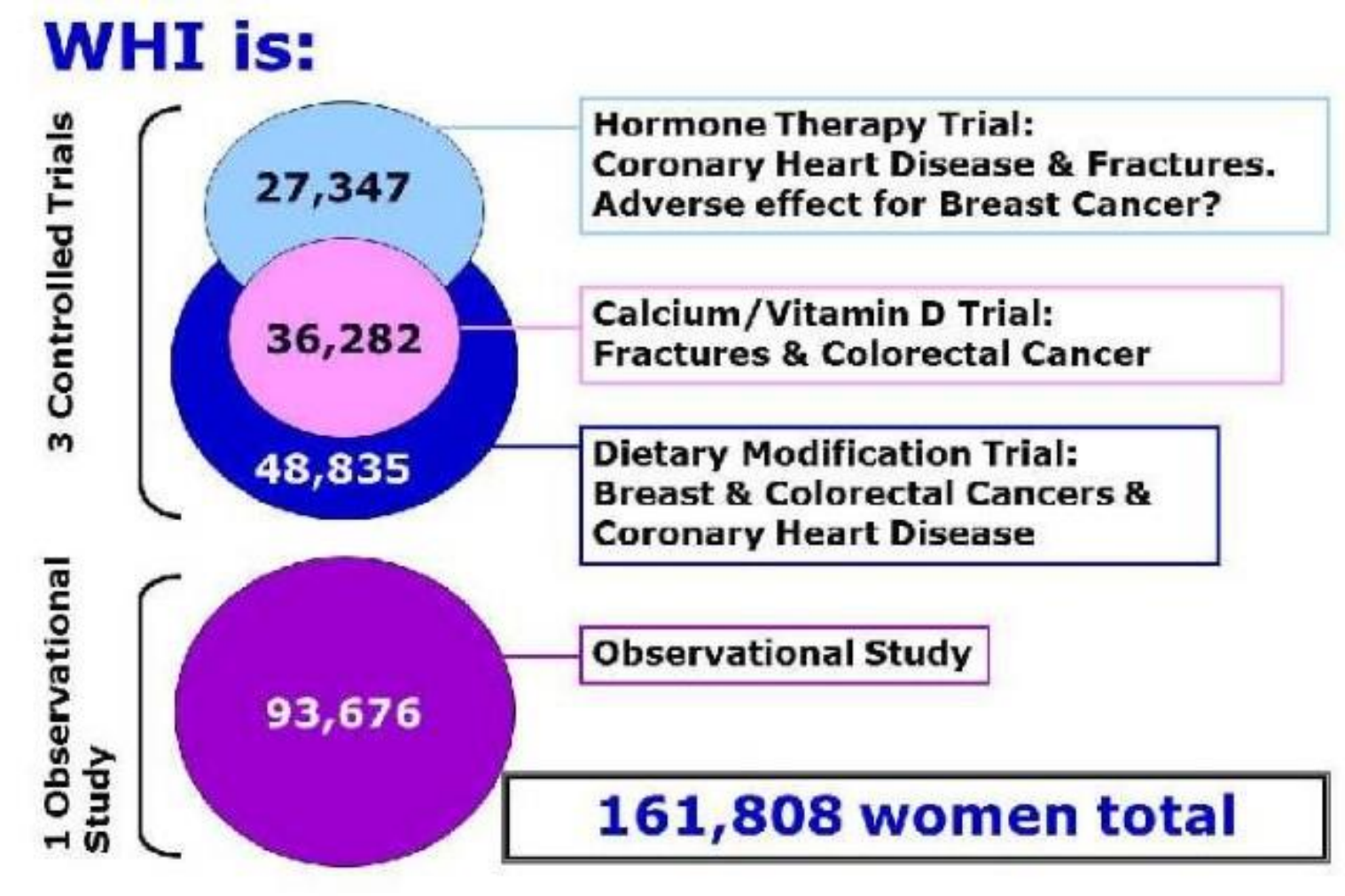
- Brain
- Bone
- Blood vessels
- Skin
- Joints
- Mucous membranes
- Genitalia

Historical Use of Hormones

- Strong basic science and clinical data suggested that estrogen benefits the cardiovascular system in older women.
- Estrogen receptor shown to improve lipids, enhance endothelial function, dilate coronary arteries, and inhibit the progression of atherosclerosis
- Multiple Studies demonstrated decrease in all cause mortality
  - Mainly attributed to decrease on CAD

Grimes and Lobo *Obstet Gynecol* 2002
Grodstein F et al *N Engl J Med* 1997

So What Happened?

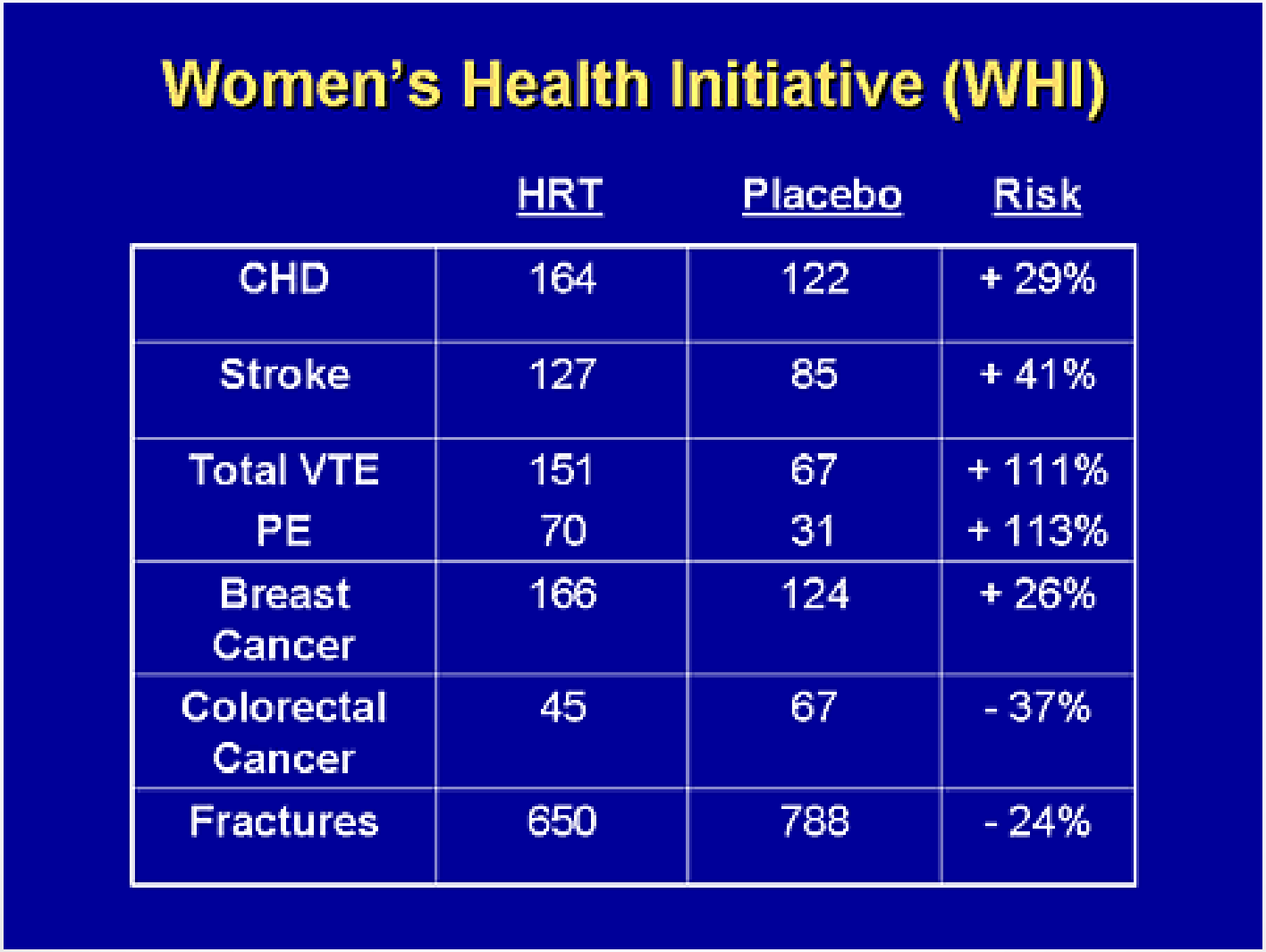


From WHI.org

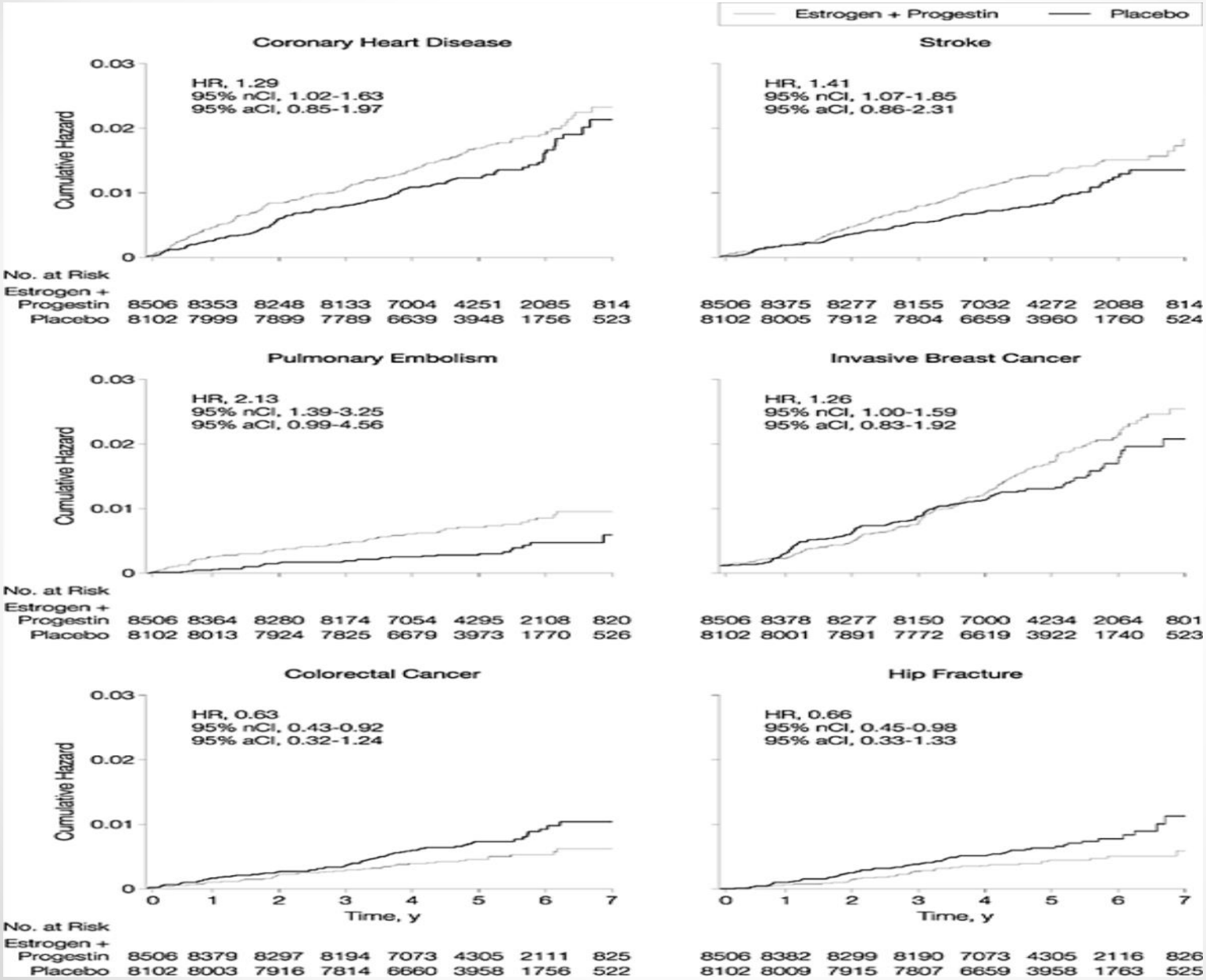
More on WHI

- Recruitment began in September 1993 continued through October 1998 for the CT
- E+P arm stopped 2002
- E only arm stopped 2004
- Close-out of the WHI CT occurred between October 2004 and March 2005
- Why stop?
  - Significant increases in CVD, VTE and BC seen in HRT arms…

WHI Risks Overall



WHI in Visual Terms



WHI in Actual Numbers

- Over 1 year 10 000 women taking estrogen plus progestin compared with placebo *might* experience:
  - 7 more CHD events
  - 8 more strokes
  - 8 more PEs
  - 8 more invasive breast cancers
  - 6 fewer colorectal cancers
  - 5 fewer hip fractures

"***Combining all the monitored outcomes, women taking estrogen plus progestin might expect 19 more events per year per 10 000 women than women taking placebo***"

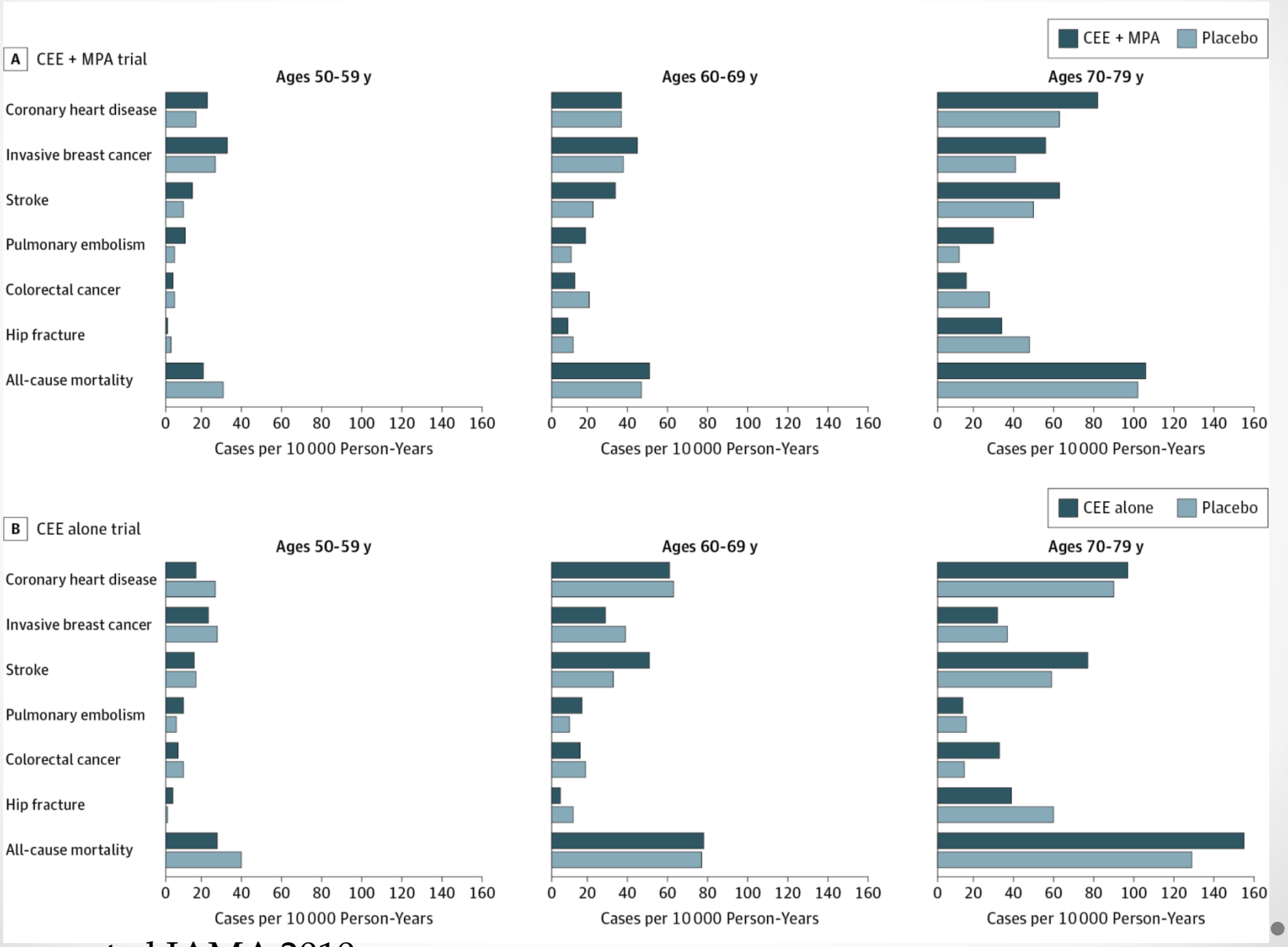
Rossouw JE et al *JAMA 2003*

Aftermath of WHI

- Do *not* use estrogen therapy for the prevention of cardiovascular disease
- *May* be used to treat vasomotor symptoms, but should be used at the *lowest effective dose, and for the shortest duration possible*
- Consider local vaginal therapy if genitourinary symptoms are sole complaint
- If prevention of osteoporosis is the primary concern, other medications such as bisphosphonates/SERMs should be considered as first-line treatment options
- Newer recommendations do support individualizing when to stop HRT(can continue >age 65)

ACOG 2013

New information: age is everything!



Manson et al JAMA 2010

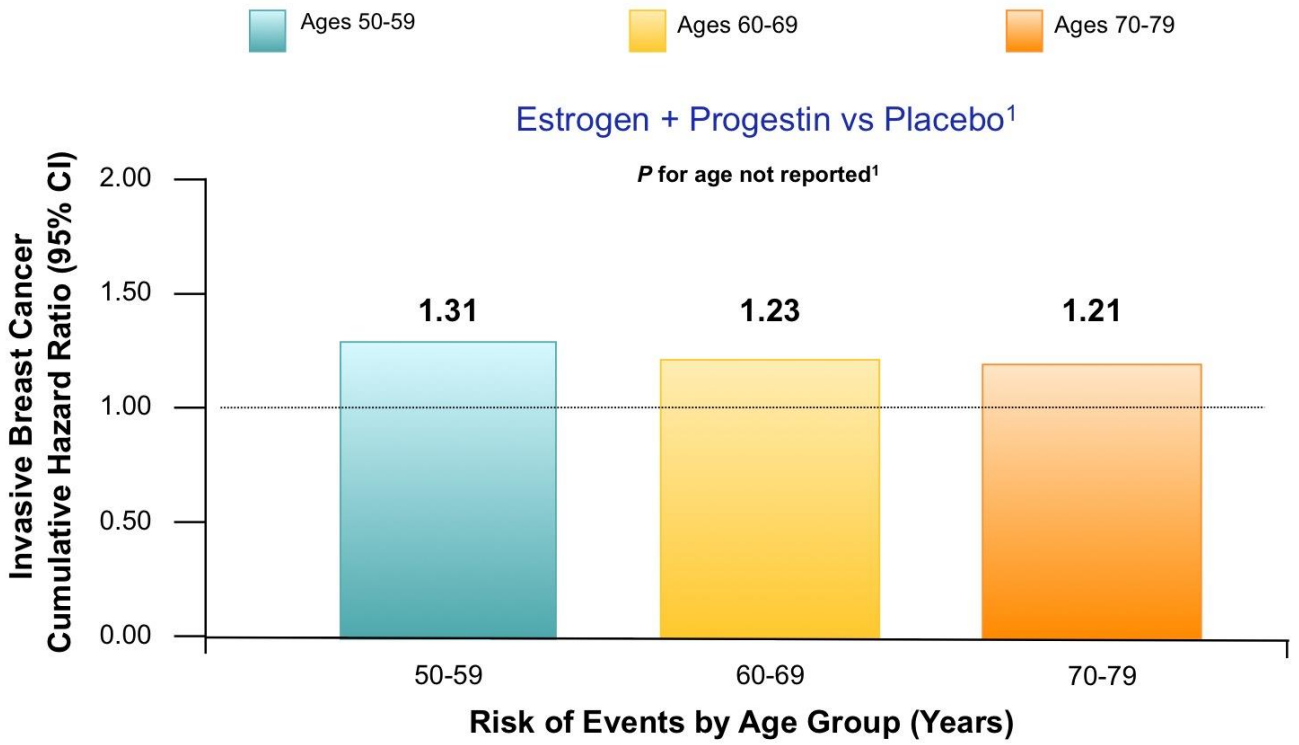
Younger Women do Better

Event	Estrogen as compared with Placebo	
	Percent difference	Absolute difference in No. of Events per 10,000 women per year of therapy
Death	-29%	-11
Coronary Heart Disease	-37%	-11
Stroke	-11%	-2
New-onset diabetes mellitus	-12%	-14
Bone Fracture	-30%	-56
Breast Cancer	-18%	-8
Venous thromboembolism	+37%	+4

- Hodis HN, et al. *NEJM*. 2007

Breast Cancer Risks

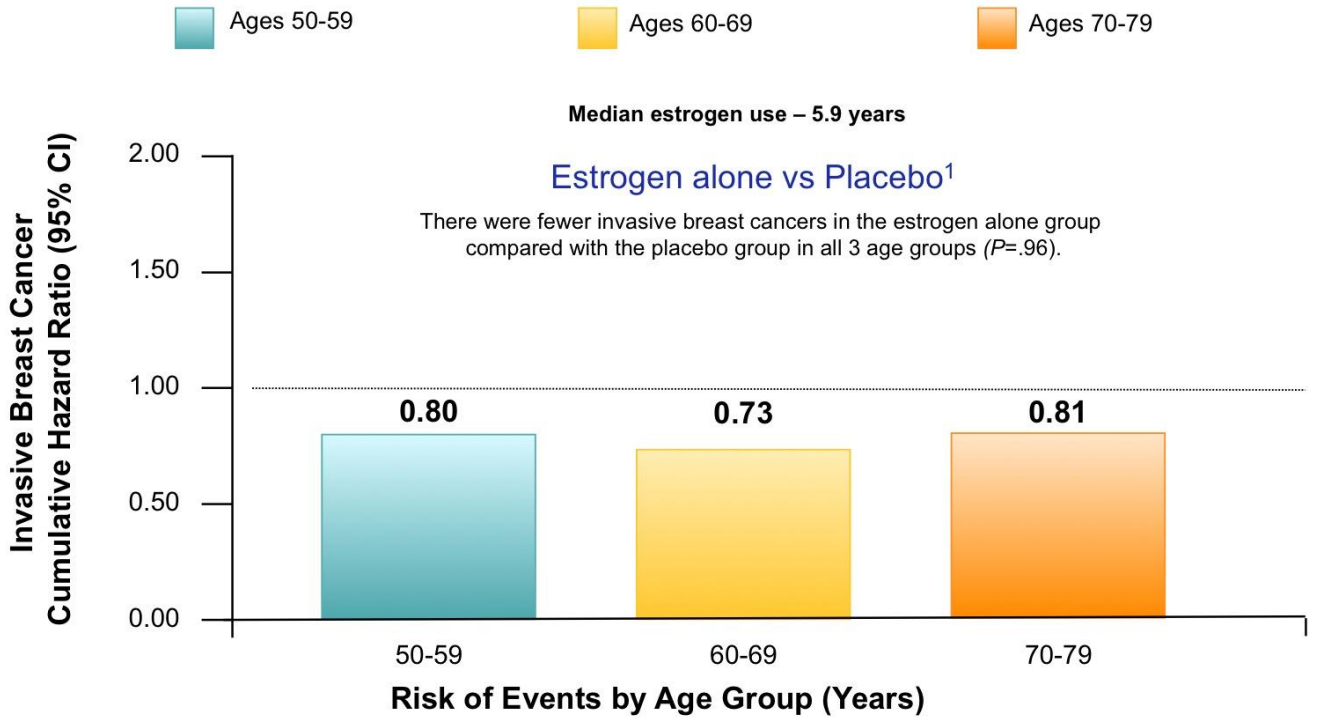
Breast Cancer Risk in WHI After Mean Follow-Up Time of 11.0[1] Years as a Function of Age Group When Therapy was Initiated



1. Chlebowski RT et al. *JAMA*. 2010;304 (15):1684-1692.

Breast Cancer and Role of Progesterone

Breast Cancer Risk in WHI After Mean Follow-Up Time of 10.7[1] Years as a Function of Age Group When Therapy was Initiated



1. LaCroix AZ et al. *JAMA*. 2011;305 (13):1305-1314.

What about Heart Health?

- KEEP (Kronos Early Estrogen prevention Study)
  - 727 Women RCT CEE
- DOPS (Danish Osteoporosis Prevention)
  - 1006 Women RCT HRT
- NHS (Nurses Health Study)
  - 48, 470 women observational

All studies showed decreased CV mortality from HRT

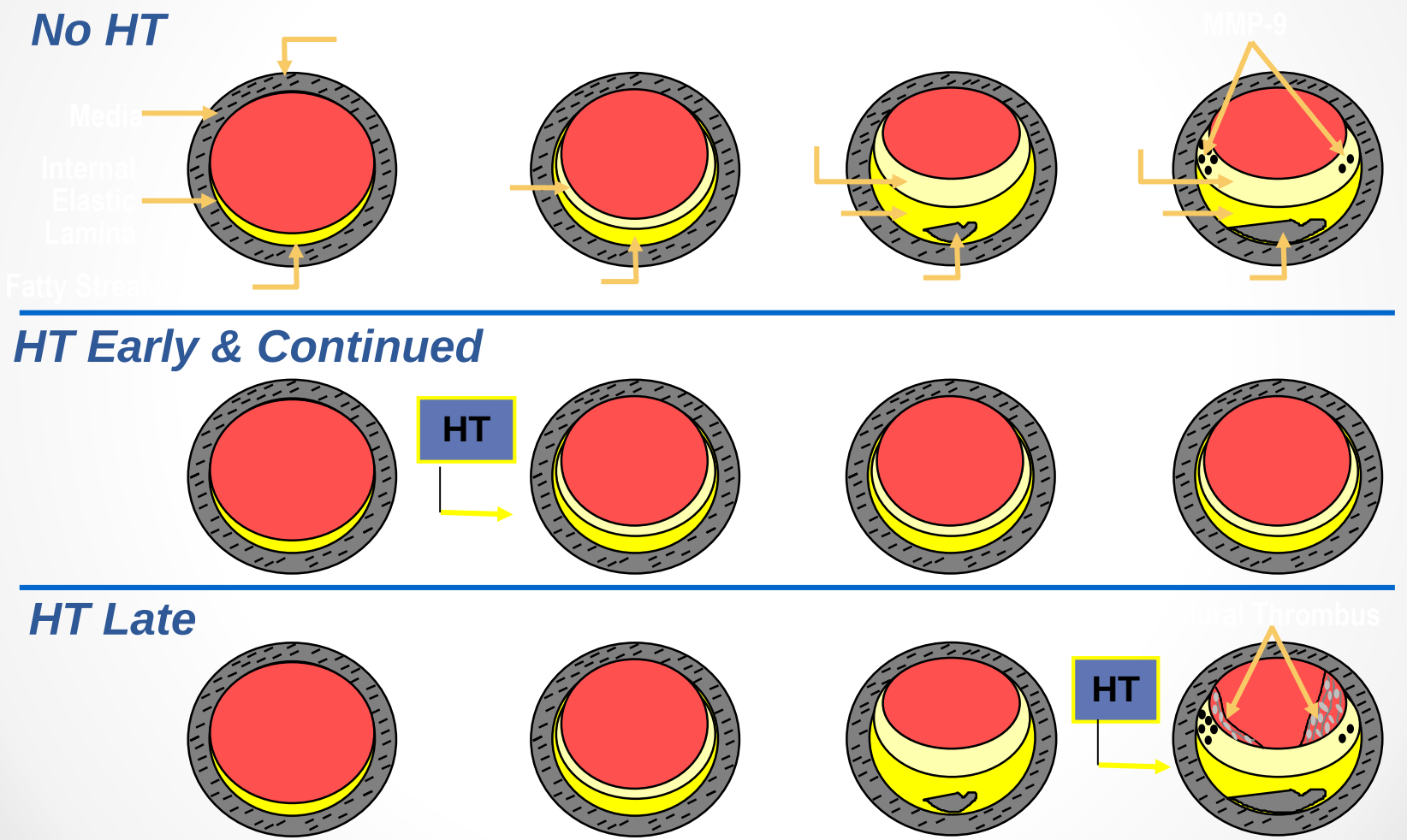
Summary of CV Risk

- Meta-analysis
  - A lower risk of CHD (composite of death from cardiovascular causes and non-fatal myocardial infarction) compared with placebo (relative risk [RR] 0.52, 95% CI 0.29 to 0.96)
  - 8 fewer cases of heart disease per 1000 women treated/year

- Lower mortality rate (RR 0.70, 95% CI 0.52 to 0.95)
  - 6 fewer deaths per 1000 women treated/year)

Boardman HM et al Cochrane Database Syst Rev. 2015

Explaining the CV Findings



What About Cognition?

- Estrogen works synergistically with many biologic systems to promote physical, cognitive, and affective function
- Administration of estrogen (E_2 alone and E_2 plus P) results in increased levels of antioxidants, reduces free radicals, and substantially lowers oxidative damage to mitochondrial DNA
- Epi research strongly suggested decreased risk AD with HRT
- WHI and HERs studies found No effect or MORE dementia in the CEE/MPA users
- KEEPs study(TD E2 and Prometrium) found NO benefit

Shumaker et al *JAMA* 2004
Grady et el *Am J Obgyn* 2012
Fischer et al *Fertil Steril i2014*

Why does MOA Matter?

	Oral Estrogen	Non-Oral Estrogen
First-pass metabolism	**Yes**	**No**
Lipid effects		
HDL-C	↑ or generally unchanged	Slight ↑ or ↓, or unchanged
Triglycerides	↑ Significantly	↓ Significantly
LDL-C	↓	↓
Total cholesterol	↓	↓
SHBG	↑	x
Clotting factors	↑	x
Thyroid binding globulin	↑	x
Glucose	↑	x
Insulin resistance	↑	x
C-reactive protein	↑	x
Renin substrate	↑	x
Estrone:estradiol ratio	↑	x

Minkin MJ. *J Reprod Med*. 2004

Why is this Important?

- **VTE and CVD**
- First-pass metabolism of oral E
- Oral E associated with an increase in production of thrombogenic proteins
- Oral E associated with an increased resistance to activated protein C (a natural anticoagulant) when compared to TD
- Systemic review and meta-analysis of 8 observational studies and 9 RCTs on HT

  Oral…but not transdermal E…was associated with a higher risk of VTE
- Canonico M et al *BMJ 2008*

To Prescribe Estrogen

- Oral
  - Estradiol , CEE, Estropitate 0.5-1mg
    - Usually covered by insurance
    - Well studied
    - Does go through 1st pass metabolism
    - Variation in blood levels
- Transdermal (all 17 B estradiol)
  - Patch, gel, emulsion or spray
  - bypasses first pass metabolism
  - Steady state of E2
  - Some women get skin reaction

A Note on "bioidenticals"

- No evidence to support use
- Not FDA approved
- Concentration varies between pharmacies and even within pharmacies
- Evidence has shown that even same concentrations result in different blood levels of E2 compared to FDA approved treatments
- Transdermal preparations and oral estradiol are in fact "bioidentical"

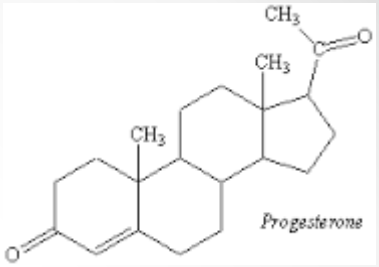
ACOG/ASRM *Fertil Steril 2012*

Beginning HT…fine points

- Start on E2 alone and adjust according to clinical response
- Add P when above stable
- Can wait up to 3 months (usually 1-2)
- Add vaginal estrogen prn

- Hold off on Testosterone until E+P given time to work
  - Usually 2-3 months

Progesterone



- Remember the difference between progesterone and progestin
  - Most "progesterone" formulation are synthetic(think CHC)
- Most commonly rx for medroxyprogesterone acetate (MPA) and micronized progesterone (MP)
- MPA has worse cardiovascular risk profile than MP
  - MPA is known vascoconstrictor compared to MP

The PEPI Writing Group. JAMA. 1995

- MPA used in WHI was the source of increased rates of breast Cancer, NOT CEE
- MP causes more drowsiness, MPA more bloating

Sites CK, et al. *J Clin Endocrinol Metab.* 2005;90:2701-2707

Progesterone Regimens

- Controversy over continuous vs sequential
- Evidence shows benefit from cont over sequential
  - Jaakol S et al *Obstetric* Gynecol 2011
  - Use of E+P >6 mo = 54% incr risk endo ca
  - Only monthly and long-cycle > 5 years contrinuted to risk
  - Monthly =69% incr, q 3 month =276% incr respectively)
  - Cont use 76%
  - NO effect of TD vs oral E2
  - Progesterones were norethistoterone acetate, MPA, dydrogesterone

- Evidence Equivocal for Progesterone Alone for tx of menopausal sx

  NAMS 2003, Whelan et al *Annals Pharmacother* 2013

A note on "bioidenticals"

- Progesterone poorly absorbed through skin
- Transdermal progestins are utero-protective when used in *transdermal combination patches*
- Transdermal micronized "natural" progesterone compounded creams have *not been shown to be utero-protective!*
- Role of salivary testing very controversial
- MP is "bioidentical"!
- Fugh Berman *J Gen Intern Med* 2007

Avoiding AE of Oral Progesterone

- Option of combination patch
- Option of LNG-IUC
- Option of CEE/SERM
  - bazedoxifene 20mg/CEE 0.45mg
  - Daily dosing
  - Well tolerated
  - Remember both oral E2 as well as not “bioidentical”

Take Home Points

- Data supports use of HRT for tx of menopausal sx
- There is a timeline on when to begin but NOT on when to stop
- Very important to consider dosing route and regimen of E2
- Critical to use Progesterone in women with intact uteri
- There is no role for "bioidentical" non FDA approved therapies
- Salivary testing without clinical basis in treatment
- There are many options now to help women!

Thank You!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