Female Reproductive Endocrinology Hirsutism and the Menopause

Internal Medicine Clinical Didactic Series

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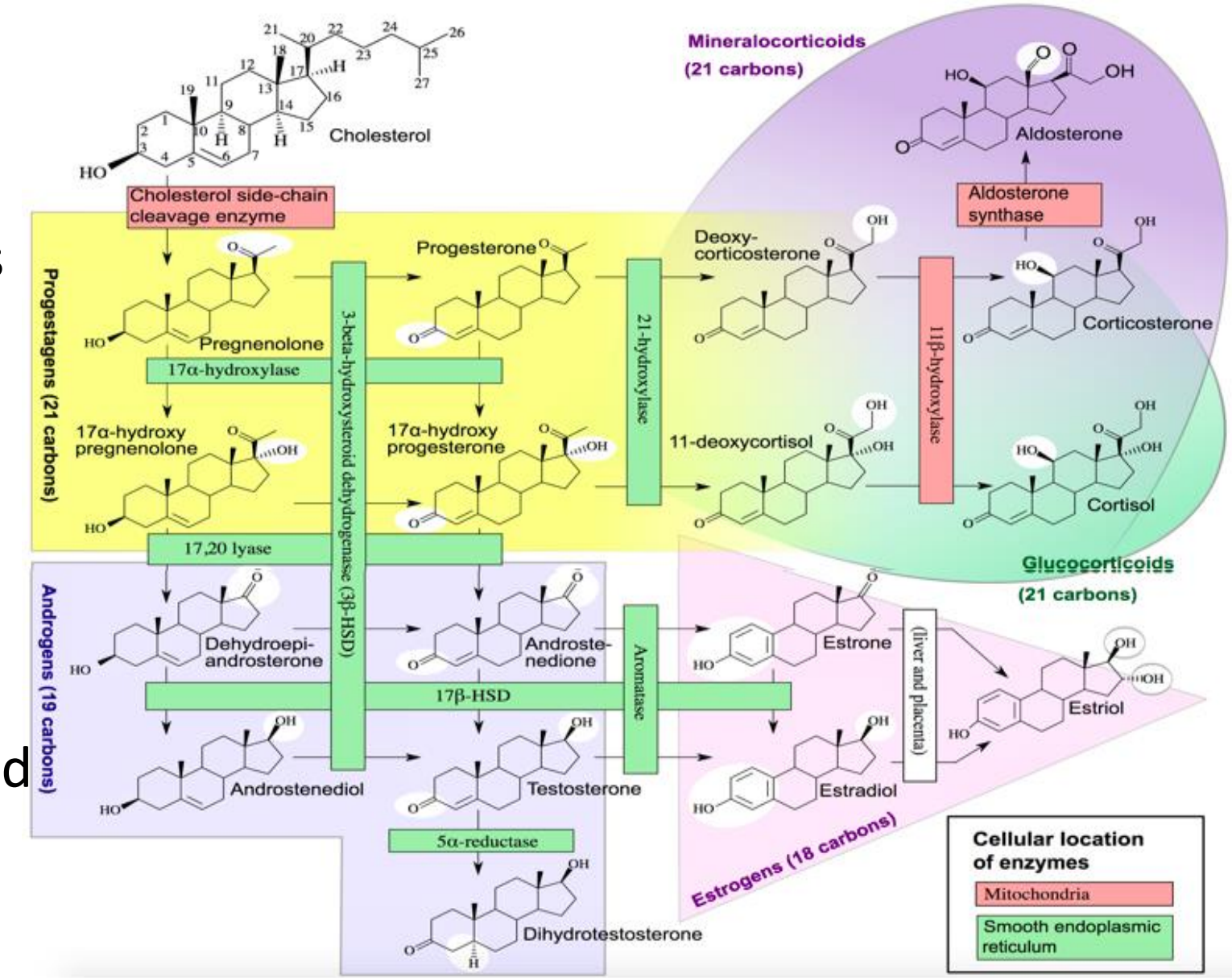
Female Hirsutism: Steroid Synthesis Pathways

- Steroid synthesis begins with cholesterol and proceeds by sequential hydroxylations and oxidations mediated by a series of cytochrome p450 enzymes.
- The full sequence of enzymes needed to synthesize active steroid hormones is found only in the:
  - Adrenal Gland
  - Gonad (ovary and testis)
- Therefore all disorders of steroid hormone physiology must involve one of these organs

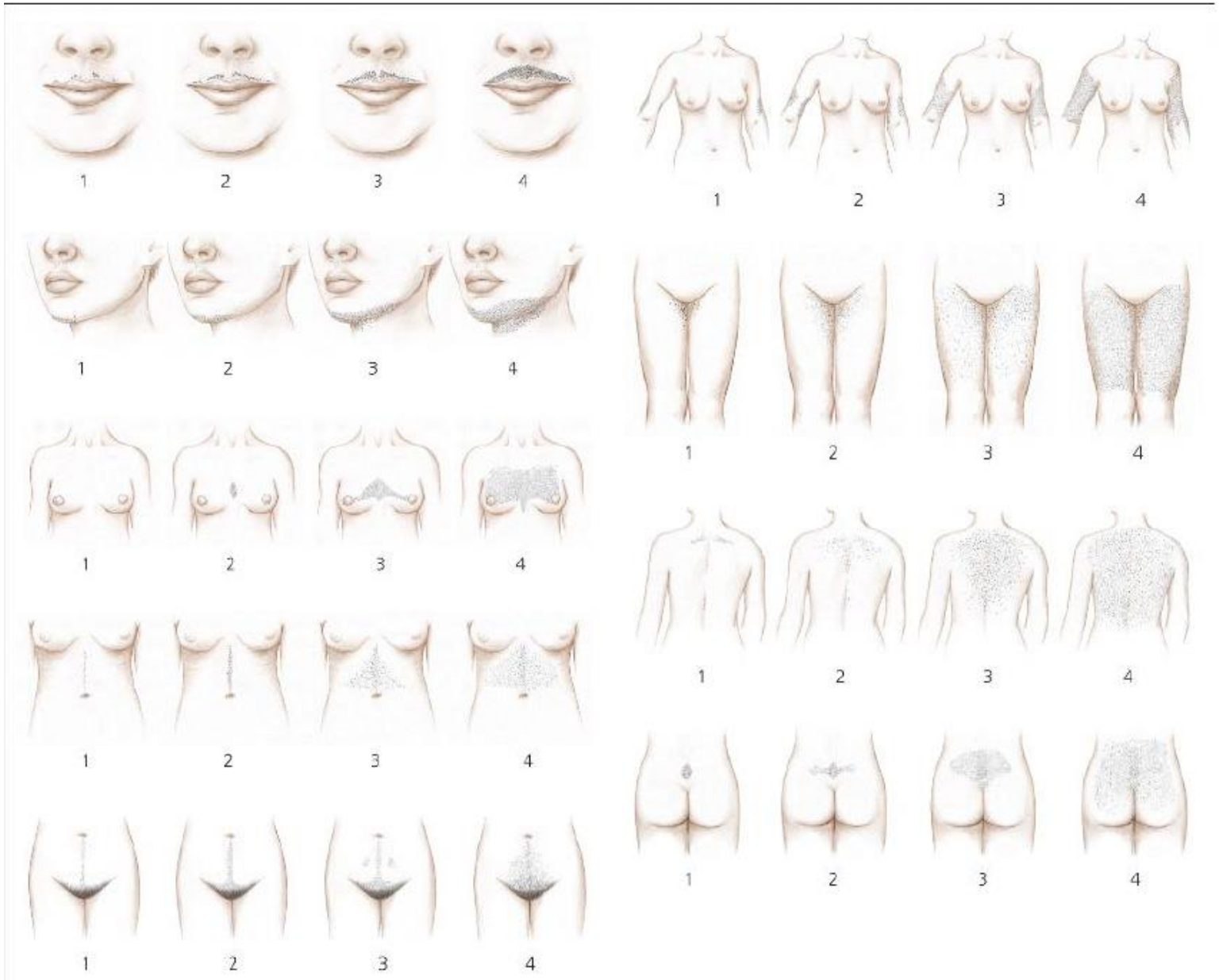


Female Hirsutism: Presentation, History, and PE

- Presentation
  - Dark coarse hair growth is a common reason for women to consult a physician
  - Chief complaint: Identify patient's primary concern (hairiness, fertility, obesity, other?)
- History
  - Hair growth: Age of onset, location(s), rate of progression, how treated
  - Other manifestations: oily skin, acne, altered sex drive (often increased), hairline recession (alopecia), deepening of voice, changes in muscle mass & habitus
  - Related symptoms: weight gain/obesity, menstrual irregularity, infertility, hypertension, glucose intolerance or diabetes, symptoms suggestive of Cushing's Dx. (weakness, fatigue, bruising, poor healing, striae), symptoms of acromegaly
- Family history: The two most common diseases producing hirsutism are
  - Familial: Polycystic ovary syndrome common in mother, aunt, sister
  - Genetic: Congenital adrenal hyperplasia, nonclassical form 21-OHase deficiency
- Physical Examination
  - General: Habitus, obesity and fat distribution, voice, hairline (? male pattern)
  - Skin: oiliness, comedones, striae, flush/plethora, acanthosis nigricans
  - Hair distribution - extent and density (next slide)
  - Abdominal and pelvic examination (palpate for mass lesion, look for clitoromegaly)

Grading Hirsutism: The Ferriman-Gallwey Scale

- A score of 1 to 4 is given for density of coarse dark hair on nine areas of the body.
  - A total score of less than 8 is considered normal
  - A score of 8-15 indicates mild hirsutism
  - A score greater than 15 indicates moderate or severe hirsutism



Intrinsic Etiologies of Female Hirsutism

Common

Diagnosis	*Percentage of hirsutism cases*	*Distinguishing historical and clinical clues*
Polycystic ovary syndrome	72 to 82	Irregular menses Normal to mildly elevated androgen levels Polycystic ovaries on ultrasonography Central obesity Infertility Insulin resistance Acanthosis nigricans
Idiopathic hyperandrogenemia	6 to 15	Normal menses Normal ovaries on ultrasonography Elevated androgen levels No other explainable cause
Idiopathic hirsutism	4 to 7	Normal menses, androgen levels, and ovaries on ultrasonography No other explainable cause
Adrenal hyperplasia	2 to 4	Family history of congenital adrenal hyperplasia High-risk ethnic group (e.g., Ashkenazi Jews [1 in 27], Hispanic persons [1 in 40], Slavs [1 in 50]) Classic form: ambiguous genitalia at birth Nonclassic, late-onset form: menstrual dysfunction, oligoanovulation, infertility Elevated 17-hydroxyprogesterone level before and after corticotropin stimulation test

Uncommon or Rare

Diagnosis	*Percentage of hirsutism cases*	*Distinguishing historical and clinical clues*
Androgen-secreting tumors	0.2	Rapid onset of hirsutism Progression of hirsutism despite treatment Virilization (e.g., clitoromegaly, increased muscle mass, loss of female body contour) Palpable abdominal or pelvic mass Early morning total testosterone level greater than 200 ng per dL (6.94 nmol per L)
Iatrogenic hirsutism	Uncommon (exact percentage not well-defined in the literature)	Medication history (see Table 2)
Acromegaly	Rare to present with isolated hirsutism	Frontal bossing, increased hand and foot size, mandibular enlargement, coarse facial features, hyperhidrosis, deepened voice Elevated serum insulin-like growth factor 1
Cushing syndrome	Rare to present with isolated hirsutism	Central obesity, moon facies, purple skin striae, proximal muscle weakness, acne Hypertension, impaired glucose tolerance Elevated 24-hour urine free cortisol level
Hyperprolactinemia	Rare to present with isolated hirsutism	Galactorrhea, amenorrhea, infertility Elevated prolactin level

Bode D, et al. Hirsutism in Women. Am Fam Physician. 2012, 85: 373

Medications Associated with Excess Hair Growth

Hirsutism

Aripiprazole (Abilify)
Bimatoprost (Lumigan)*
Bupropion (Wellbutrin)
Carbamazepine (Tegretol)
Clonazepam (Klonopin)
Corticosteroids (systemic)
Cyclosporine (Sandimmune)
Dantrolene (Dantrium)
Diazoxide (Proglycem)
Donepezil (Aricept)
Estrogens
Eszopiclone (Lunesta)
Fluoxetine (Prozac)
Interferon alfa*
Isotretinoin
Lamotrigine (Lamictal)
Leuprolide (Lupron)
Mycophenolate (Cellcept)*
Olanzapine (Zyprexa)

Hirsutism *(continued)*

Paroxetine (Paxil)
Pregabalin (Lyrica)
Progestins
Selegiline (Eldepryl)
Tacrolimus (Prograf)*
Testosterones
Tiagabine (Gabitril)
Trazodone
Venlafaxine (Effexor)
Zonisamide (Zonegran)

Hypertrichosis

Acitretin (Soriatane)
Azelaic acid (Finacea)
Cetirizine (Zyrtec)
Citalopram (Celexa)
Corticosteroids (topical)
Cyclosporine*
Etonogestrel implant (Implanon)
Phenytoin (Dilantin)

Bode D, et al. Hirsutism in Women. Am Fam Physician. 2012, 85: 373

Female Hirsutism: Laboratory Testing

- Measure early morning total testosterone (T) level, LH, FSH
  - If T mildly elevated (>60 ng/dL but <200 ng/dL) PCOS is likely
    - Most PCOS patients have h/o obesity and menstrual irregularity, but both conditions need not be present to make diagnosis
  - If T normal but near ULN obtain free/bioavailable T
    - Elevated free and/or bioavailable testosterone without elevated total free T occurs in about 50% of PCOS patients
  - If T is > 200 ng/dL, ovarian T secreting tumor or (rarely) adrenal tumor should be suspected.
- Measure Adrenal Androgens
  - 17-hydroxyprogesterone
    - If unequivocally elevated (>400 ng/dL) Dx. of 21-OHase CAH is made
    - If mildly elevated 180-400 ng/dL perform ACTH stimulation test
  - Androstenedione and DHEA or DHEAS if neither PCOS nor CAH is diagnosed, or adrenal tumor/Cushing's syndrome is suspected

Polycystic Ovary Syndrome (PCOS)

- Common disease found in 6-10% of females in developed countries
- Characterized by (2 of 3 must be present to make Dx):
  - **Hyperandrogenism-** hirsutism but NOT virilization
  - **Polycystic ovaries**- cysts may or may not be visible on ultrasound
  - **Anovulation-** irregular menses and impaired fertility (may ovulate intermittently)
    - Cause of up to 30% of infertility in couples seeking treatment
- Usual onset in late teens to early 20's
- Associated with other disorders
  - Obesity (61-76%)
  - Insulin resistance often progressing to diabetes
  - Premature cardiovascular disease
  - Increased rates of endometrial and breast cancer
- Familial- Commonly one or more first degree relatives has PCOS

Barthelmess EK and Naz RK. Front Biosci (Elite Ed). 2014; 6: 104

Genetics of 21-OHase Deficiency

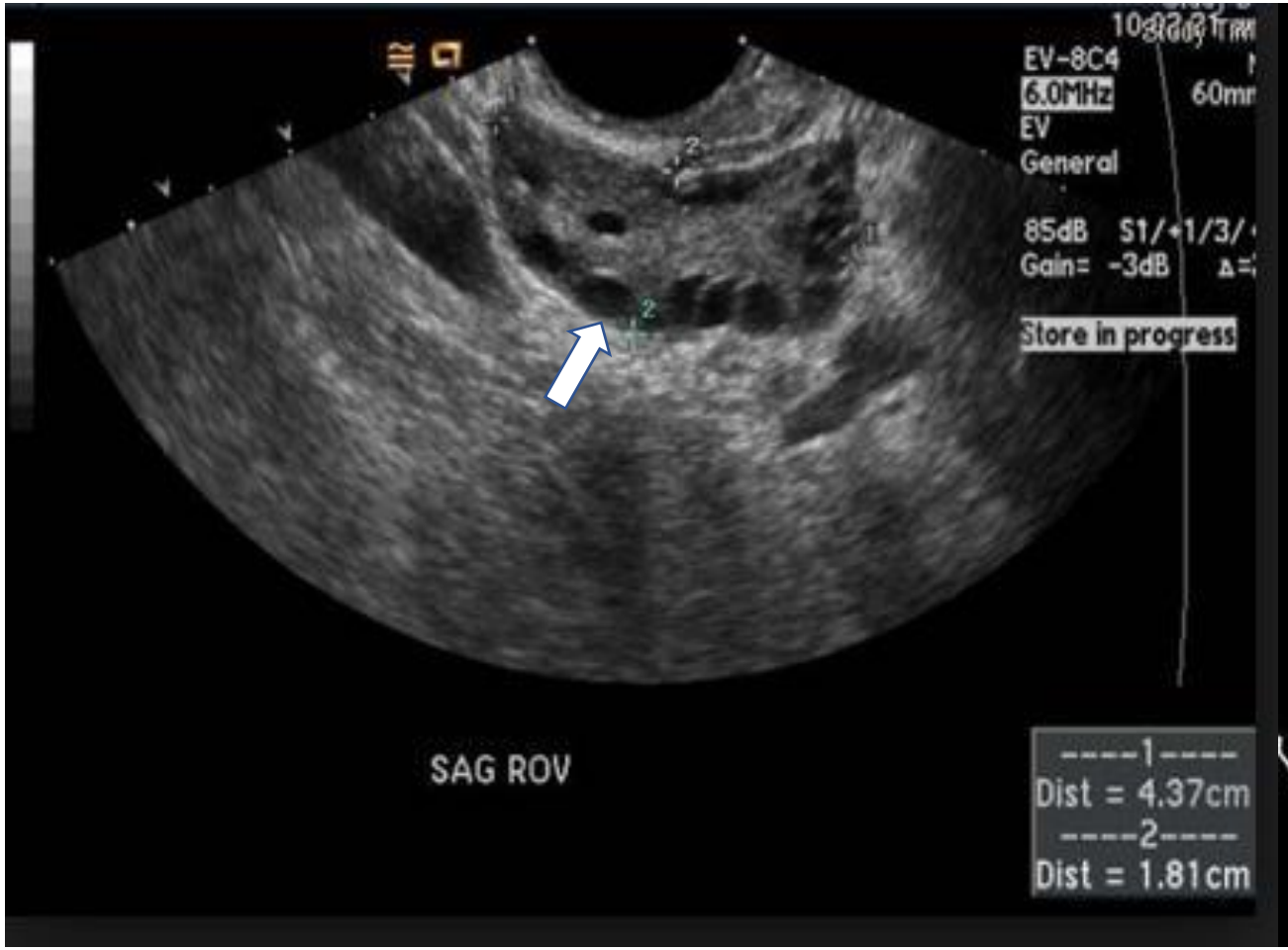
- Autosomal recessive trait
- Humans have two CYP21A genes: both located on chromosome 6p21.3 within HLA locus
  - nonfunctional pseudogene (*CYP21A1* or *CYP21P*)
  - active gene (*CYP21A2* or *CYP21*)
  - Both are > 90% homologous
  - Most of the 21OHD is due to gene conversion events
- > 100 mutations in CYP21A2 gene known
  - Disease severity correlates with CYP21A2 allelic variation
  - Clinical Phenotype correlates with less severely mutated allele &, consequently, with residual 21OH activity

Non-Classical (Late Onset) 21OHase Deficiency

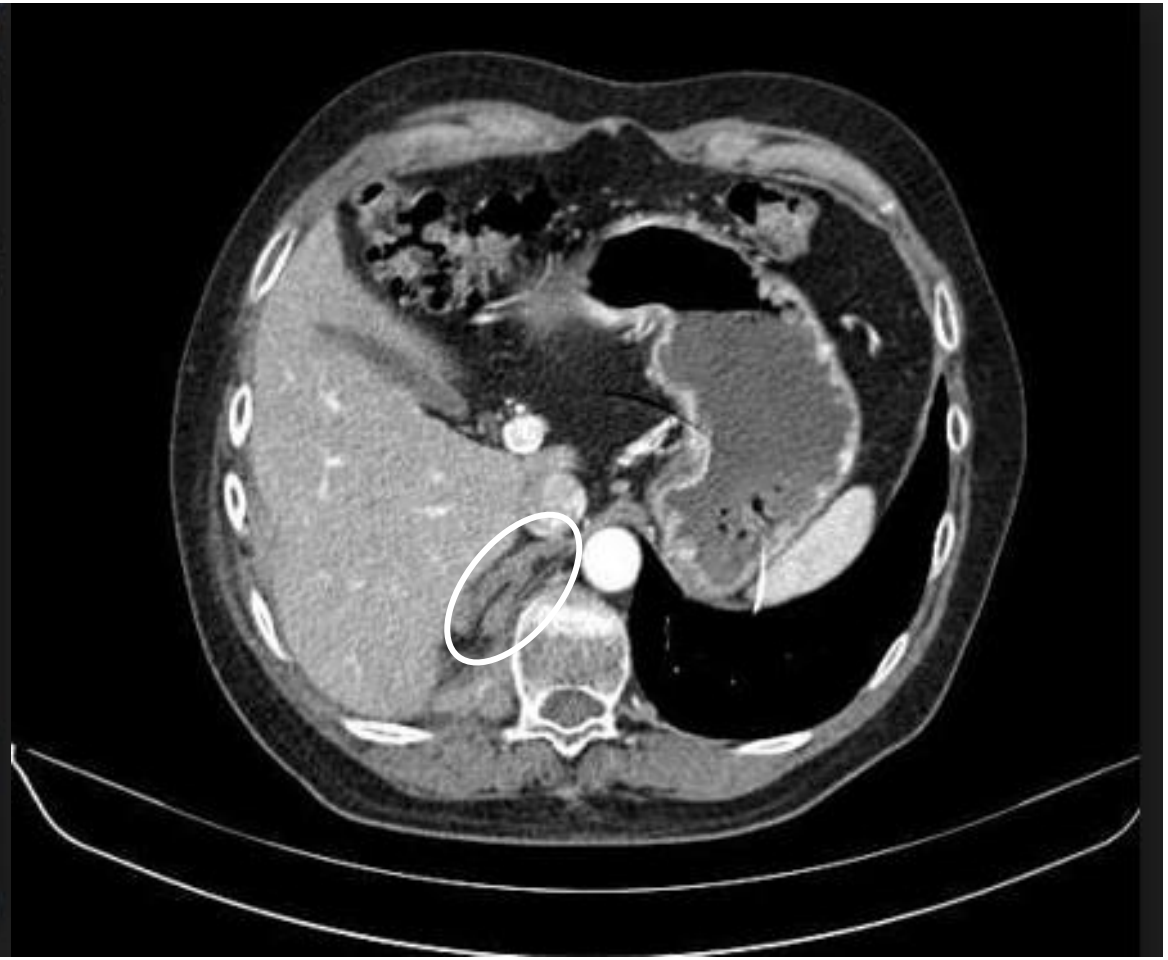
- One of the most common causes of female hirsutism
- Mild enzyme deficiency: sufficient to maintain normal glucocorticoid and mineralocorticoid production, at the expense of excessive androgen production
- Postnatal onset: childhood or early adulthood
- Clinical Features:
  - Late childhood: premature pubarche, acne, & accelerated bone age
  - Adolescent and adult females: acne, hirsutism, menstrual irregularity in young women (D/D PCOS)
  - Adult males: early balding, acne, or impaired fertility & fecundity
  - May be asymptomatic
  - May be prone to stress-induced adrenal insufficiency

Imaging of Ovary and Adrenal in PCOS and CAH

Pelvic ultrasound of ovary in PCOS. Note semilunar Rim of medium sized cystic follicles (arrows).



CT of abdomen showing thickening of both arms of right adrenal gland (white oval)



Pharmacologic Treatment of Hirsutism in Women

Treatment depends on the etiology

- Polycystic Ovary Syndrome
  - Initial treatment is with OCP unless contraindicated (age, smoking, h/o DVT/PE, or desire for fertility)
    - Suppresses LH secretion
    - Increases SHBG binding of androgen
  - If hirsutism not improved after 6-12 months add spironolactone (50-100 mg/day.
  - Other antiandrogens (e.g. flutamide) may be considered
  - If fertility is goal, treatment is ovulation induction with antiestrogen (clomiphene) or aromatase inhibitor
  - Metformin is effect for glucose intolerance and may improve ovarian function
- Congenital Adrenal Hyperplasia (non-classical 21 OHase deficiency)
  - Treatment is suppression of ACTH using a glucocorticoid
  - Dexamethasone is preferred
    - Long acting
    - No mineralocorticoid activity
  - Dosing is 1-2 mg at bedtime
    - In order to suppress AM peak ACTH
    - Dose adjusted to get 17 OH progesterone into normal range and reduce hair growth
    - Dose should be minimized to avoid Cushing's syndrome

Fertility Induction in Polycystic Ovary Syndrome Clomiphene Citrate vs. an Aromatase Inhibitor (Letrozole)

Outcome	Letrozole (N = 80)	CC (N = 79)	Rate ratio (95% CI)	Absolute difference (95% CI)	P
Pregnancy rate	49/80 (61.2%)	34/79 (43.0%)	1.4 (1.1, 2.0)	18% (3–33%)	0.022
Live birth rate	39/80 (48.8%)	28/79 (35.4%)	1.4 (0.95, 2.0)	13% (−2 to 28%)	0.089
Ovulation rate	67/80 (83.8%)	63/79 (79.7%)	1.1 (0.9, 1.2)	4% (−8 to 16%)	0.513
Pregnancies per ovulating patient	47/67 (70.1%)	32/63 (50.8%)	1.4 (1.04, 1.9)	20% (3–30%)	0.024
Pregnancies—strata 1 (BMI <30)	37/54 (68.5%)	25/53 (47.2%)	1.5 (1.04, 2.1)	21% (3–38%)	0.025
Pregnancies—strata 2 (BMI 30–35)	12/26 (46.2%)	9/26 (34.6%)	1.3 (0.7, 2.7)	12% (−14 to 35%)	0.397
Live births—strata 1 (BMI <30)	29/54 (53.7%)	20/53 (37.7%)	1.4 (0.9, 2.2)	15% (−3 to 30%)	0.122
Live births—strata 2 (BMI 30–35)	10/26 (38.5%)	8/26 (30.8%)	1.3 (0.6, 2.7)	8% (−20 to 30%)	0.771
Pregnancies per cycle	49/261 (19.0%)	34/278 (12%)	1.5 (1.03, 2.3)	7% (0.4–13%)	0.036
Live births per cycle	39/261 (15%)	28/278 (10%)	1.48 (0.95, 2.33)	5% (−0.7 to 11%)	0.087
Ovulation per cycle	196/261 (75%)	187/278 (67%)	1.1 (1.01, 1.2)	8% (1–15%)	0.045
Mono-ovulation*	80/94 (85.1%)	64/77 (83.1%)	0.88 (0.4, 1.7)	−2% (−13 to 9%)	0.723

Amer SA, et al. Hum Reprod. 2017 Aug 1;32(8):1631-1638.

The Menopause: Diagnosis and Symptoms

- Definition: Menopause is a natural cessation of ovarian function, both ovulation and hormone secretion, occurring at midlife
  - Due to depletion of follicles
  - Occurs between ages 44-64, average age 51 years
  - Loss of ovarian function at <44 years of age = premature ovarian failure (POF)
- Symptoms
  - Period of gradually diminishing frequency of menses (perimenopause)
  - Cessation of menses
  - Symptoms of estrogen deficiency
    - Vaginal dryness and dyspareunia
    - Vasomotor episodes (“hot flashes)
- Diagnosis of menopause
  - Should be based on clinical criteria
    - Absence of menstrual cycle
    - Vasomotor symptoms (VMS)- typically sensation of heat, flushing, followed by sweating
  - FSH level > 15 mIU/ml and/or E2 levels < 20 pg/ml are consistent with menopause

Treatment of the Menopause

- Hormone therapy- considerations
  - According to FDA, hormones are indicated only for treatment of VMS in women <60 years of age or <10 years past menopause
  - Treatment modalities
    - Estrogen
      - Transdermal estrogen 50-200 ug/day (no excess risk of DVT/PE)
      - oral micronized estradiol 100-200 mg/day
      - Conjugated equine estrogen (Premarin®, others)- 0.45 or 0.625 mg/day
    - Plus progestogen therapy for women with a uterus to prevent endometrial Ca
      - Micronized progesterone 200-300 mg/day either constantly or 12 days/month
      - Progesterone releasing intra-uterine device
      - Bazedoxifene can be given with conjugated estrogens (available as combination)
      - Medroxyprogesterone acetate (Provera®) is no longer recommended
  - For women with VMS unable to take estrogen, alternative therapies include:
      - Gabapentin, pregabalin, SSRI's, SNRI's, clonidine
      - Local vaginal estrogen (for vaginal atrophy/dyspareunia)
      - Evidence for botanicals (black cohosh, red clover, etc.) is that they are ineffective

FDA Black Box Warning for HT

Endometrial Cancer Risk

- Unopposed estrogen use increases risk in women with intact uteri; adding progestin may decrease risk of endometrial hyperplasia (possible precursor to endometrial CA); use adequate diagnostic measures such as endometrial sampling to rule out malignancy if undiagnosed persistent or recurrent abnormal genital bleeding occurs

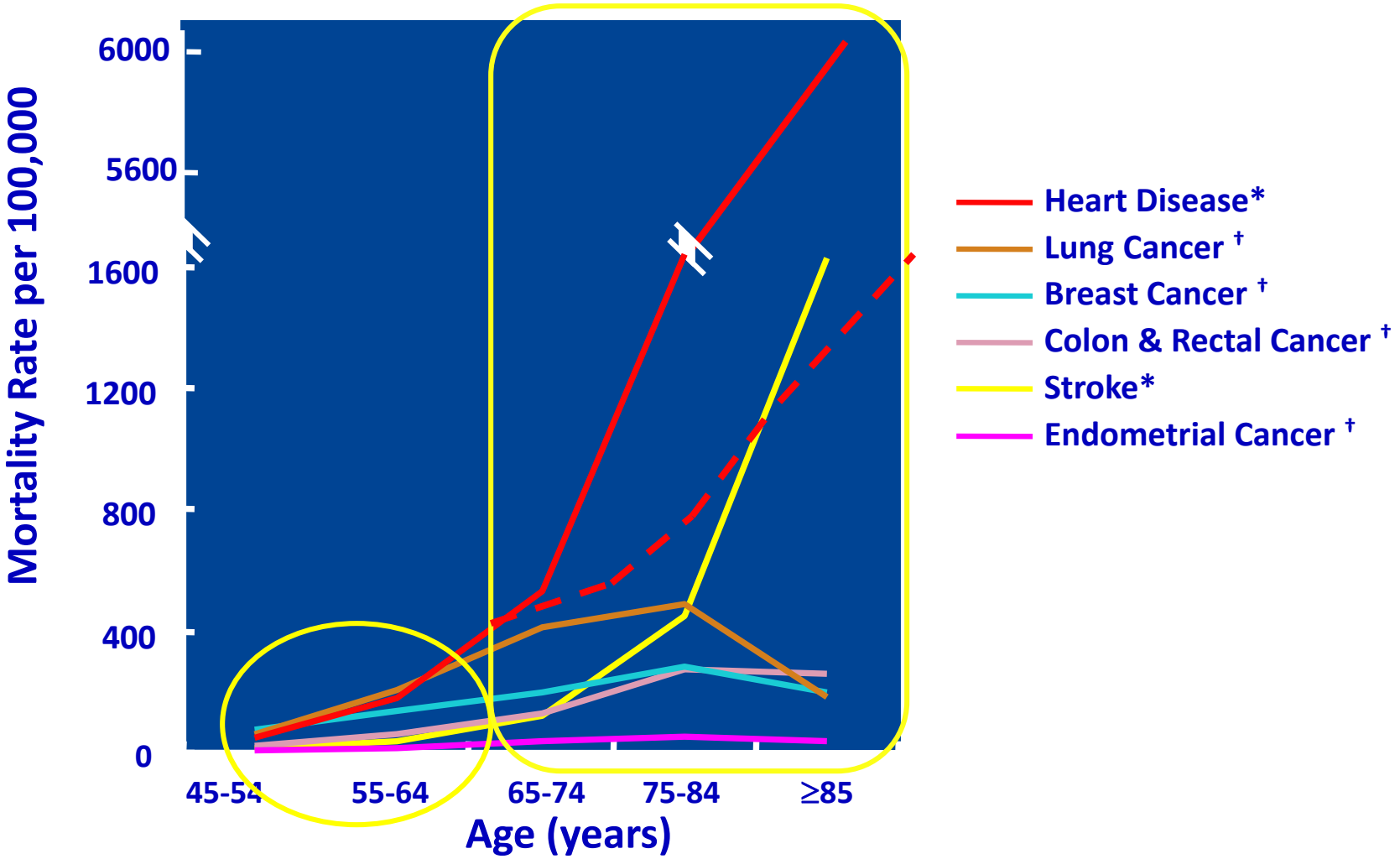
Cardiovascular and Other Risks

- Estrogens +/- progestins are not indicated for cardiovascular disease or dementia prevention; increased risk of stroke and DVT (from WHI estrogen-alone substudy) and MI, stroke, PE/DVT, and invasive breast CA (from WHI estrogen/progestin substudy) in postmenopausal women; increased risk of probable dementia in postmenopausal women >65 yo on a WHI regimen x 4-5years; WHI regimens = conjugated estrogens 0.625 mg/day with or w/o medroxyprogesterone 2.5 mg/day, other doses or estrogen/progestin combos were not studied, but assume similar risk; use lowest effective estrogen dose and shortest duration based on individual therapeutic goals and risks

Menopause and Cardiovascular Disease History of the Research

- Evidence that menopause is related to CVD
- Epidemiologic/observational studies
- The Heart and Estrogen/Progestin Replacement Study (HERS) and the Women's Health Initiative (WHI) Hormone Trials, initial interpretations
- The WHI Hormone Trials, revisited: Revisionist views and follow-up studies
- New RCT data since the WHI

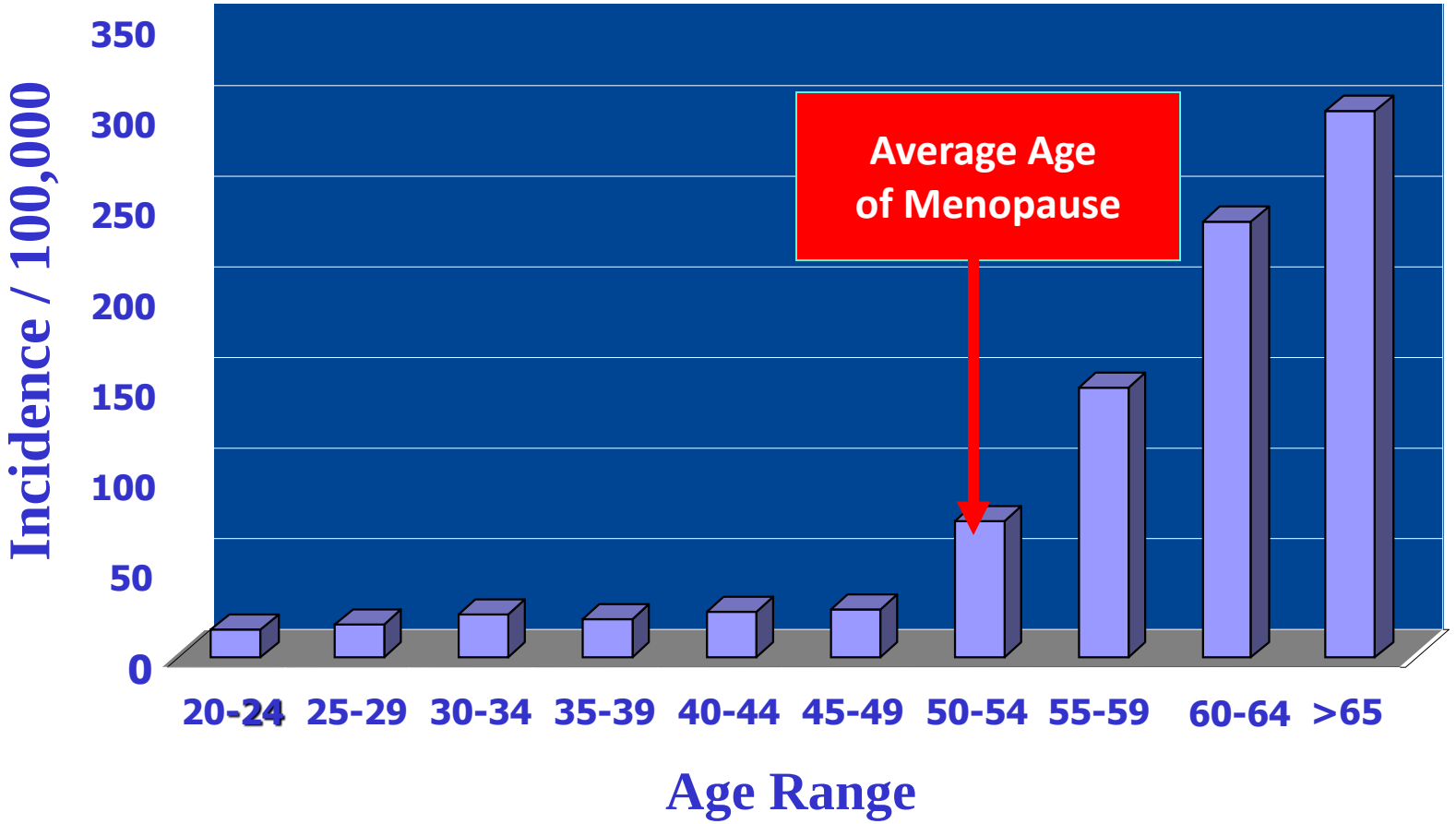
Mortality Rates in Women for Different Diseases by Age in Five Year Groups



*Mean of years 1995-1998; †1994-1998. Eberhardt MS, et al. *Health, United States, 2001*. Hyattsville, Md: National Ctr for Health Statistics; 2001:189,192.

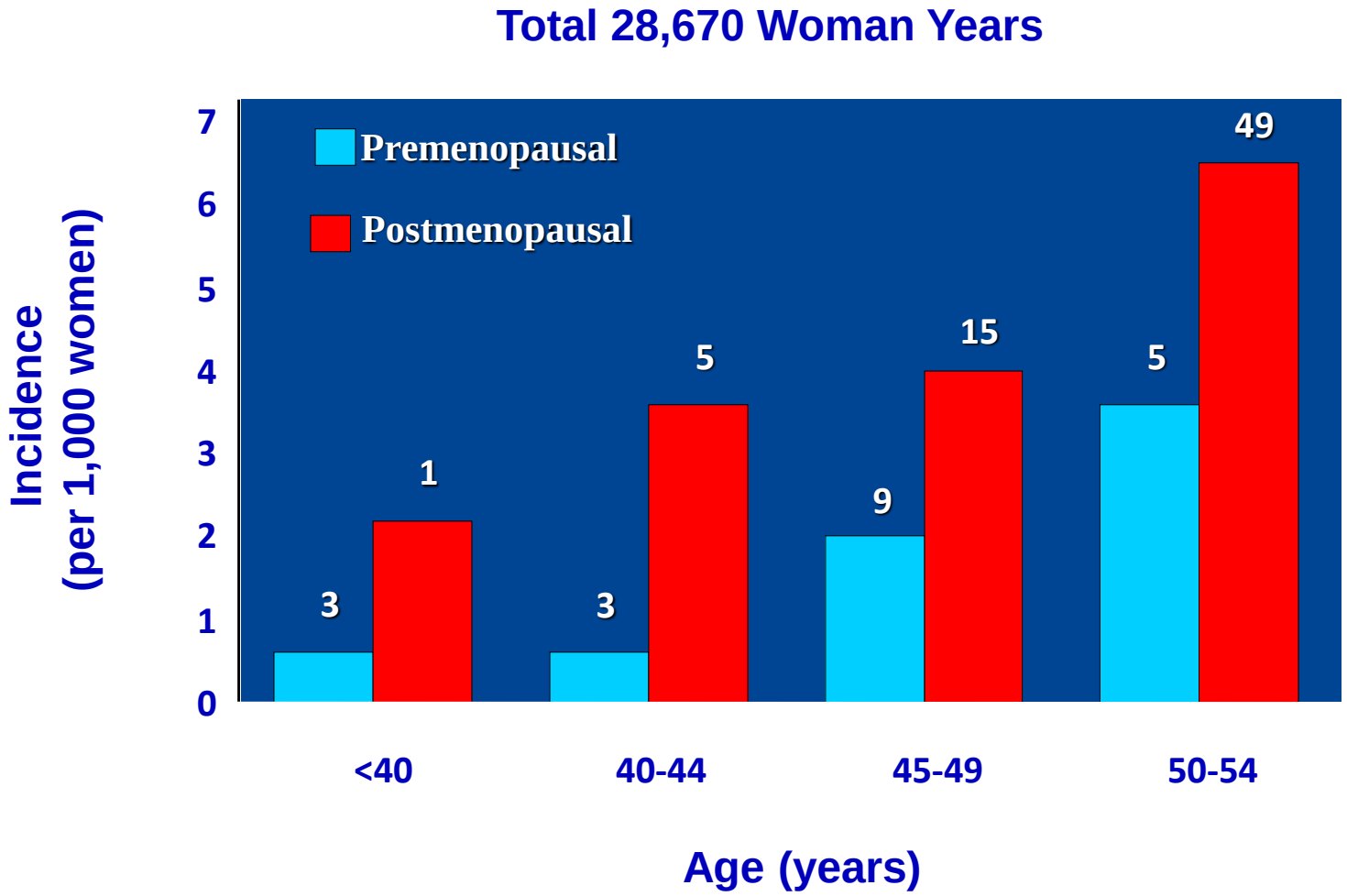
†Ries LAG, et al. *SEER Cancer Statistics Review, 1973-1998*. Bethesda, Md: National Cancer Institute; 2001.

Incidence of Cardiovascular Events in Women Before and After the Menopause



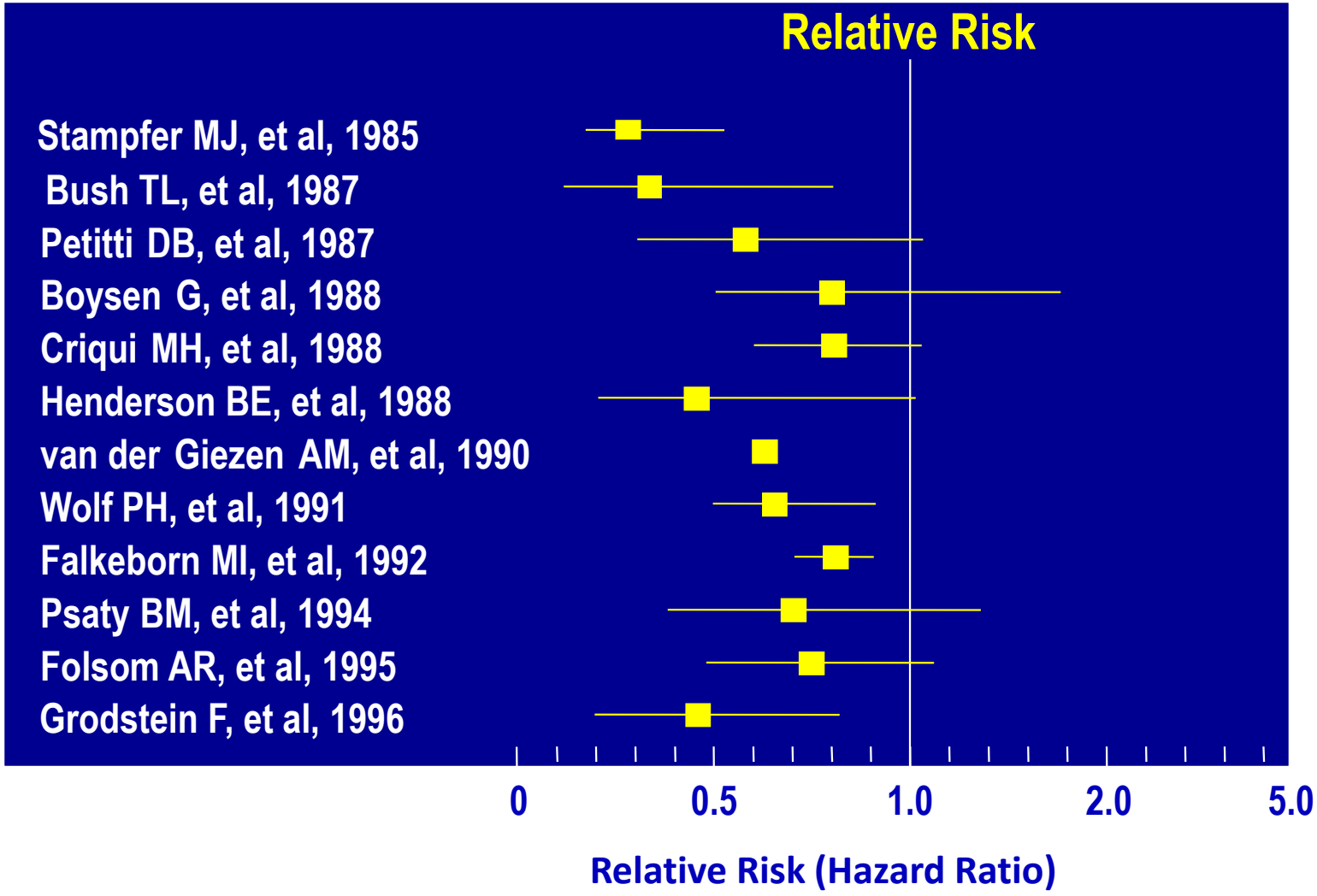
F. B. Hu et al. New Engl J Med, 2000; 343:530-7

Incidence of Cardiovascular Disease: Relation to Menopause Status



Kannel W, et al. *Ann Intern Med.* 1976;85:447-52.

Observational Studies of ERT/HRT and CHD



Adjusted* Relative Risk of Death Among All Postmenopausal Women in the Nurses Health Study

Cause of Death	Hormone Use		
	NEVER	CURRENT	PAST
All Causes			
No. of cases	2051	574	1012
Relative risk (95% CI)	1.0	0.63 (0.56-0.70)	1.03 (0.94-1.12)
Coronary Heart Disease			
No. of cases	289	43	129
Relative risk (95% CI)	1.0	0.47 (0.32-0.69)	0.99 (0.75-1.30)
Stroke			
No. of cases	91	28	48
Relative risk (95% CI)	1.0	0.68 (0.39-1.16)	1.07 (0.68-1.69)
All Cancer			
No. of cases	1103	353	529
Relative risk (95% CI)	1.0	0.71 (0.62-0.81)	1.04 (0.92-1.17)
Breast Cancer			
No. of cases	246	85	94
Relative risk (95% CI)	1.0	0.77 (0.59-1.00)	0.83 (0.63-1.09)

*CI = Confidence Interval. Values are adjusted for age, age at menopause, type of menopause, BMI, DM, high BP, high cholesterol, smoking, OC use, family H/O MI or breast Ca, parity

From: Colditz, et al. N Engl J Med;336:1769-75 (1997)

Circumstantial Evidence for Cardioprotection by Estrogen?

- **There are <u>multiple plausible mechanisms</u> by which estrogens could help prevent or delay CVD:**
  - Lipid effects- lower LDL and $Lp_{(a)}$, higher HDL
  - Antioxidant effects- decreased lipid oxidation
  - Vascular effects- ENOS upregulation, vasodilation
  - Inhibition of platelet aggregation
  - Increased prostacyclin (COX-2 activity)
  - Decreases in cell adhesion molecules (CAMs)
  - Impaired CAM tethering of leucocytes
  - Decreases in inflammatory factors (TNF-α, IL-6, MCP-1, fibrinogen)
- **Epidemiologic/Observational Studies suggested 40-50% reduction in CHD rates in women taking estrogen**

Inherent Biases in Observational Studies

- Selection bias
  - Healthier women prescribed HT
- Prevention bias
  - Monitoring and treatment of CVD risk factors more intensive in women prescribed HT
- Compliance bias
  - Patients with greater adherence (even to placebo) may have better outcomes
- Survivor bias
  - HT may be stopped due to illness and those women counted as non-treated
- Prevalence-incidence bias
  - Early adverse effects of HT not observed if user dies before becoming eligible for inclusion in cohort

HERS: A Secondary Prevention Trial

- Goal: Determine CHD event risk in women with documented CHD
  - MI, CABG, cutaneous angioplasty, or 50% narrowing of coronary artery
- 2763 postmenopausal women (average age 67) randomized to receive either CEE 0.625, CEE with MPA 2.5 mg daily, or placebo
- During the average follow-up of 6.8 yrs, the incidence of myocardial infarctions and coronary deaths were about the same in both groups

HERS Trial: Clinical Outcomes

Outcome	RR	(95% CI)
Total mortality	1.08	(0.84-1.38)
Nonfatal and fatal MI	0.99	(0.80-1.22)
CABG	0.87	(0.66-1.16)
Percutaneous revascularization	0.95	(0.77-1.17)
Stroke / TIA	1.13	(0.85-1.48)
Venous thromboembolism	2.89	(1.50-5.58)
Gallbladder disease	1.38	(1.00-1.92)
All cancers	1.12	(0.84-1.50)
Breast cancer	1.30	(0.77-2.19)

JAMA. 1998;280(7):605-613.

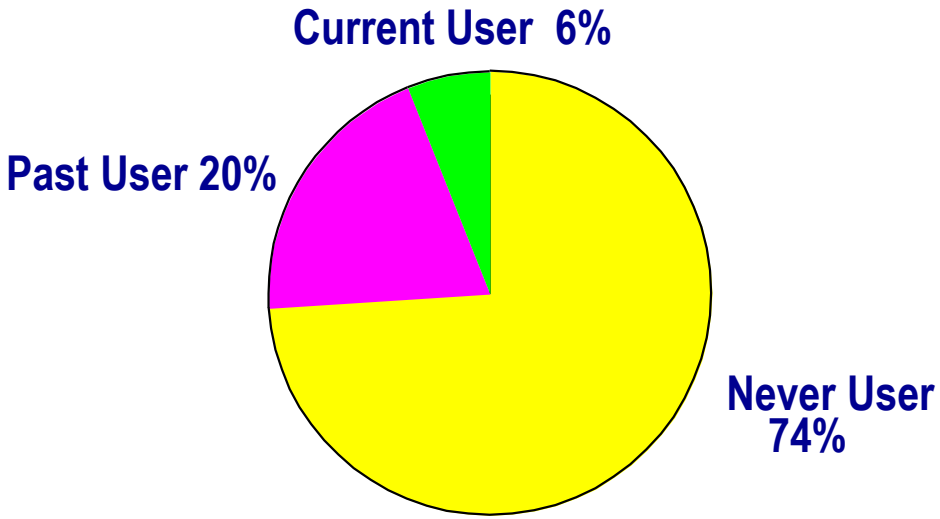
Women's Heath Initiative (WHI) Hormone Trials

- Randomized, double-blinded placebo-controlled trials- intended as test of primary prevention in women ages 50-79, planned for 8.5 years
- Estrogen + Progestin (uterus intact); stopped at 5.2 years
    - PremPro® 0.625 CEE/2.5 MPA daily); n=8506
    - Placebo; n=8102
- Estrogen alone (hysterectomized); stopped at 6.8 years
    - Premarin® 0.625 CEE daily; n=5310
    - Placebo; n=5429
- Endpoints
    - Cardiovascular events (new heart attack, cardiac death,)
    - Other clinical events (fractures, cancers, VTE, stroke)

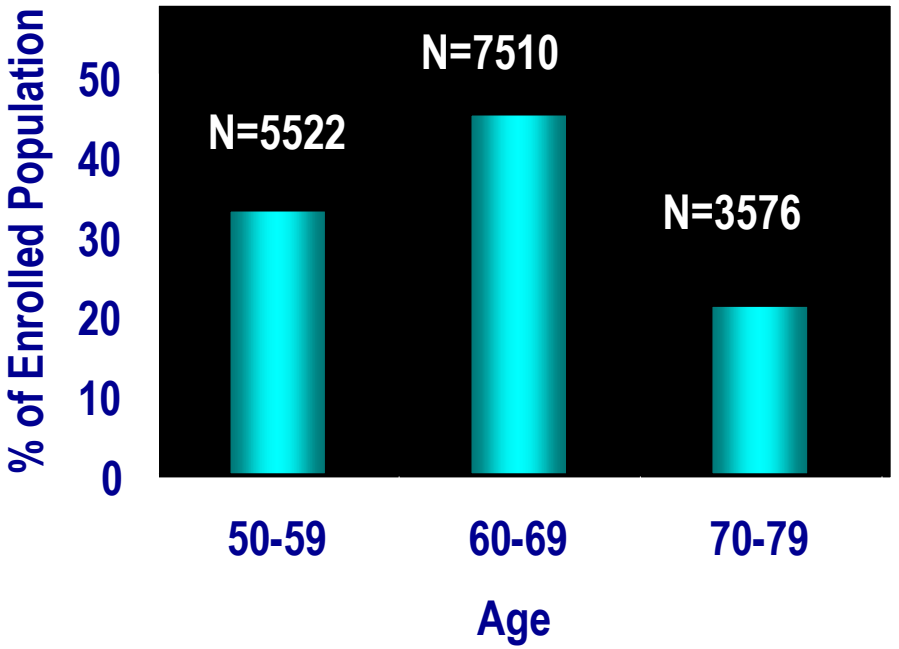
WHI E+P Trial: Subject Characteristics

Mean age 63

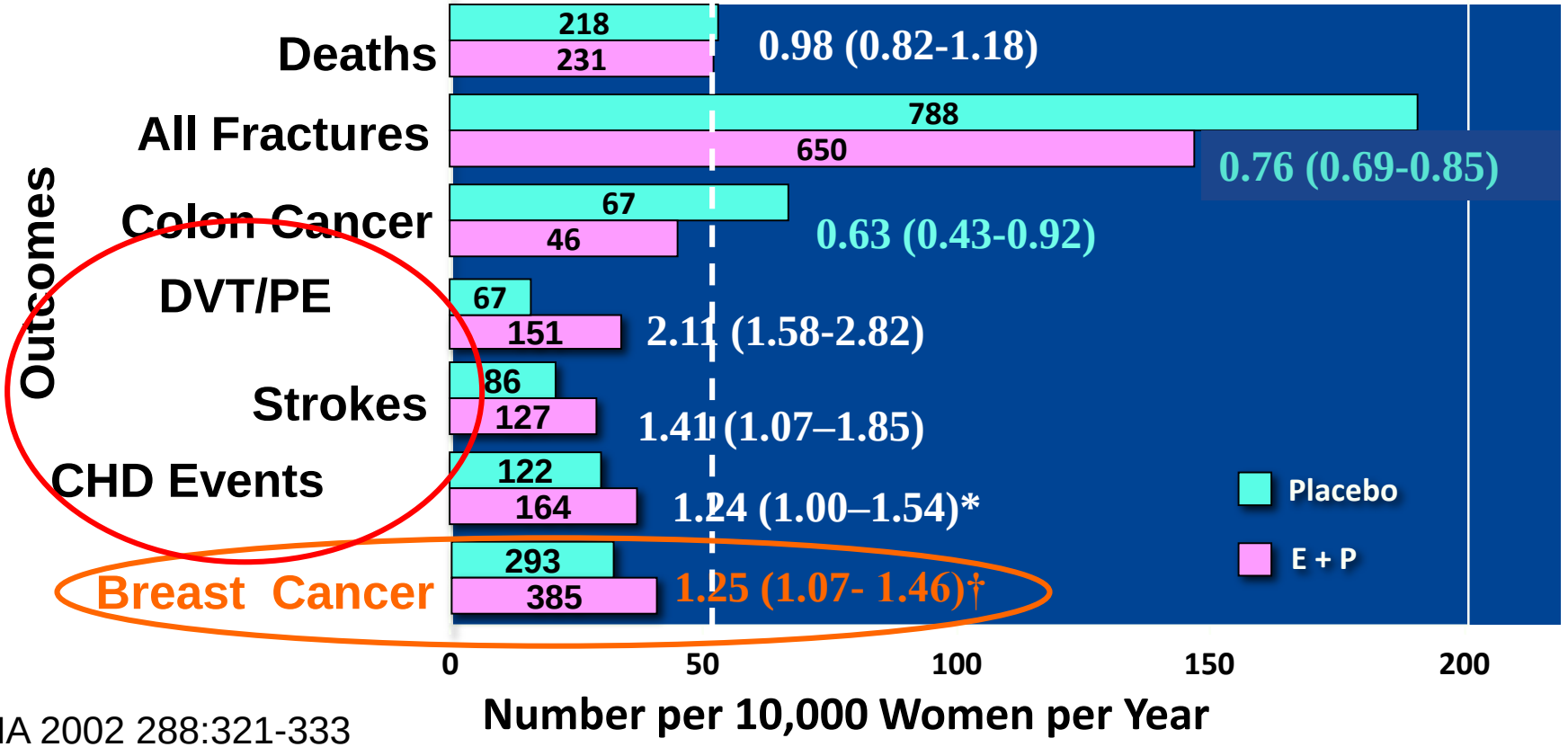
BMI 28.5 kg/m ^{2}



Hormone Use Prior to Study Entry



Clinical Event Incidences in the WHI Estrogen + Progestin Arm vs. Placebo

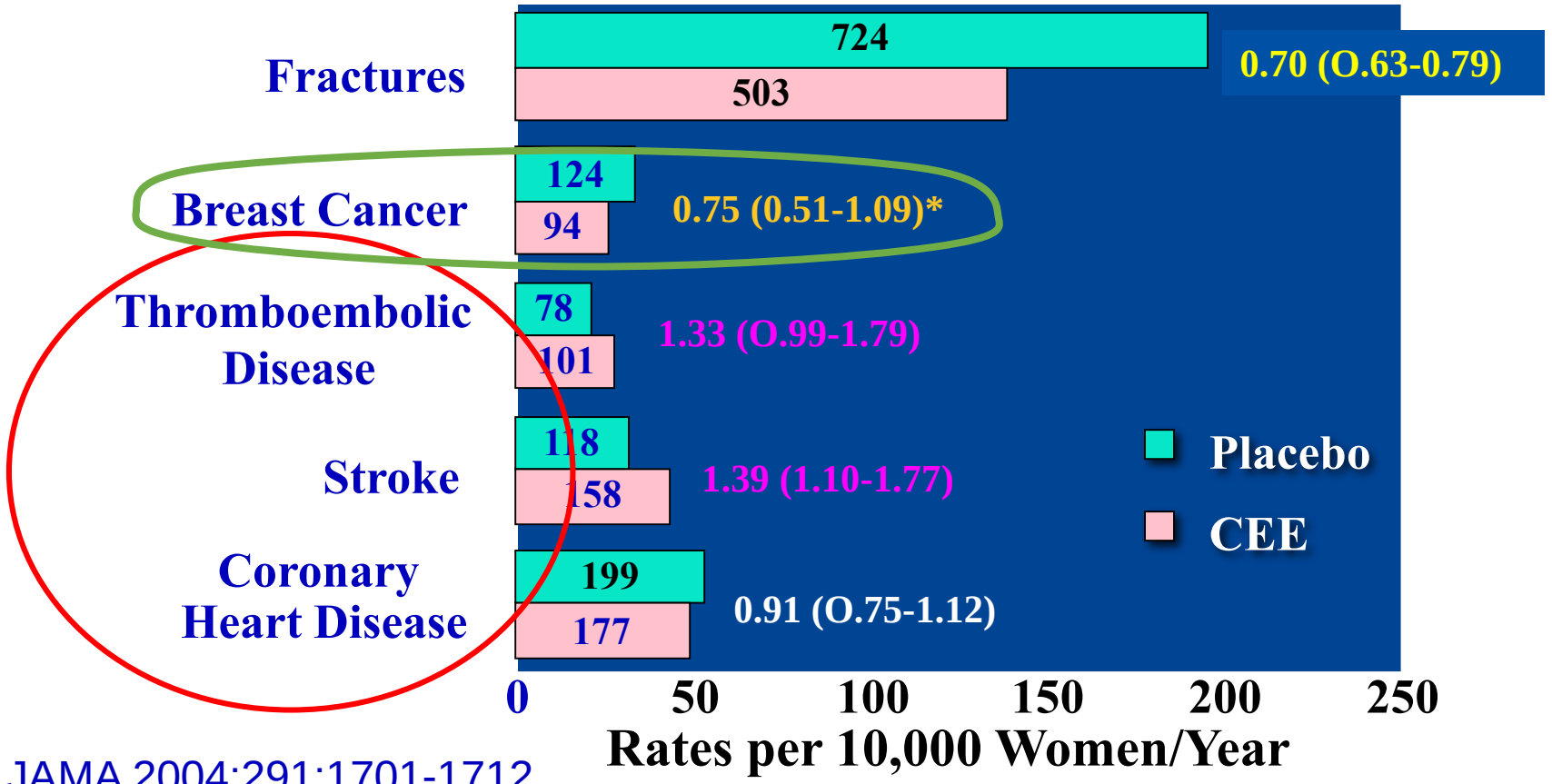


JAMA 2002 288:321-333

* Manson, et al. New Engl J Med, 2003;349:530

† Chlebowski RT, et al. JAMA 2010;304:1684 (12 y follow-up data)

Clinical Outcomes in the E-only Arm of the WHI HT Trial



JAMA 2004:291;1701-1712

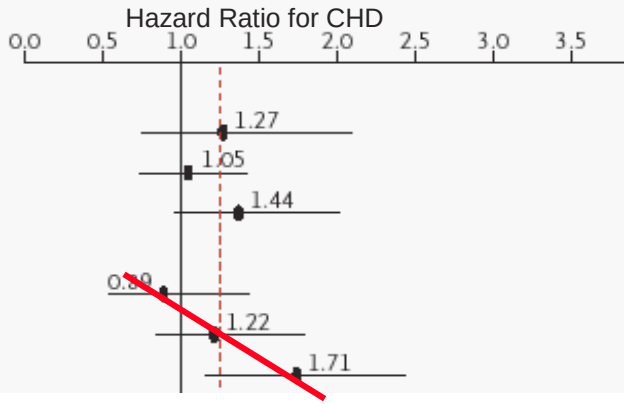
* LaCroix, JAMA 2011:305:1305-1314 (10.7year f/u)

Differences Between Prior MHT Studies and the WHI E and E+ P Trials

Characteristic	Prior Studies	E+P Trial	E Trial
Study Design	Observational Cohort Case Control	Prospective Randomized Blinded	
Age at Onset of Therapy	40-55 years (mean 51.1)	55-79 years (mean 62.7)	55-79 years (mean 63.6)
Treatment Modality	Mainly CE Some + MPA	PremPro® CE 0.625 mg +MPA 2.5 mg	Premarin® CE 0.625 mg
Duration Rx	10-15 years	5 years	7 years

Estrogen plus Progestin and the Risk of CHD in Various Subgroups of WHI Women*

Subgroup	No. of cases of CHD (annualized percentage)		P value for Interaction
	E + P	Placebo	
Age			0.36
50–59 yr	37 (0.22)	27 (0.17)	
60–69 yr	75 (0.35)	68 (0.34)	
70–79 yr	76 (0.78)	52 (0.55)	
Years since menopause			0.33
<10	31 (0.19)	34 (0.22)	
10–19	63 (0.38)	51 (0.32)	
≥20	74 (0.75)	44 (0.46)	

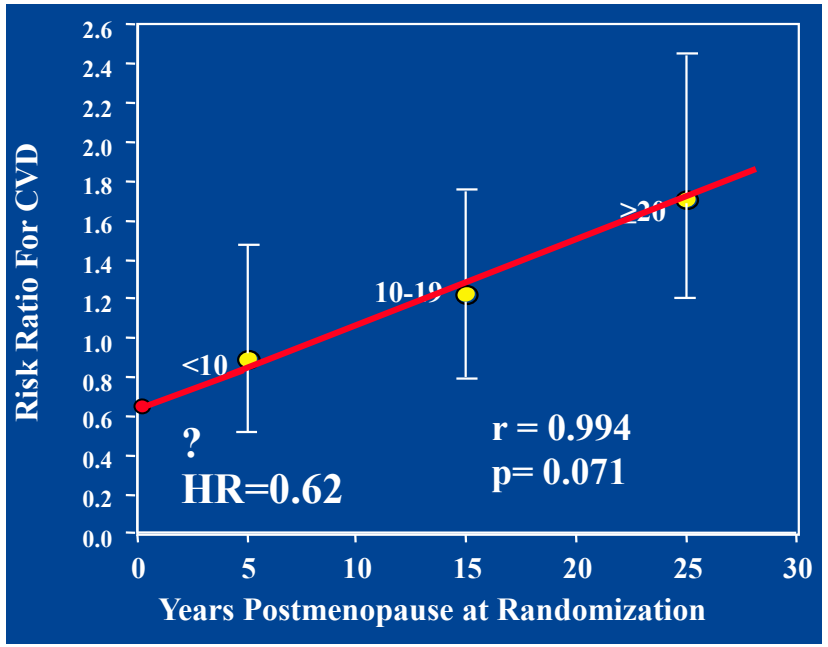


*From Manson, et al. New Engl J Med, 2003;349:530 (Fig. 3)

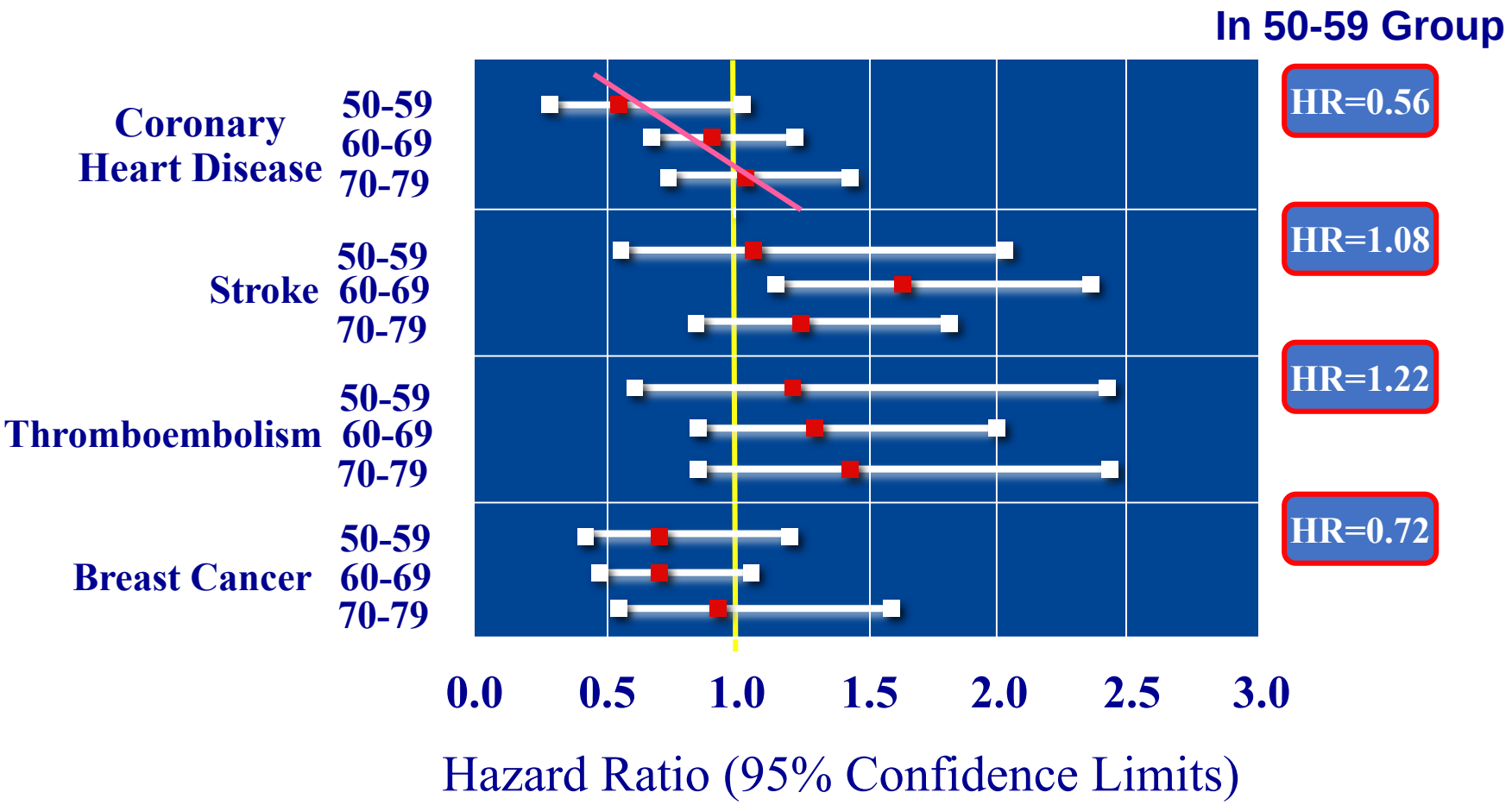
Assume mean postmenopausal durations of 5, 15, and 25 years for the <10, 10-20, and ≥20 year groups, respectively (actual means not provided).

Draw best fit regression line

Extrapolate the best fit regression line to a value of 0 postmenopausal years.



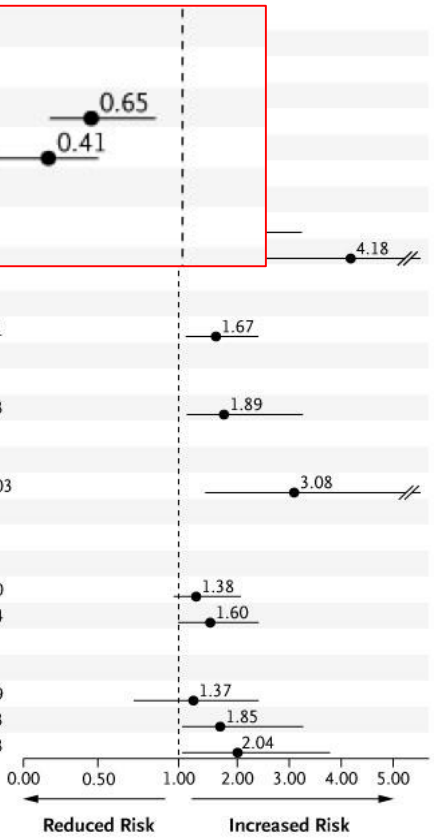
Event Hazard Ratios by Age Subgroups in WHI Estrogen-only Arm



JAMA 2004:291;1701-1712

Multivariate Odds Ratios for a Coronary-Artery Calcium Score of More Than 100, According to Randomized-Group Assignment and Coronary-Risk-Factor Status

Variable	No. of Participants	Coronary-Artery Calcium Score ≥10	Coronary-Artery Calcium Score >100	P Value
Study group		*percen*		
Placebo (referent)	527	43		
Conjugated equine estrogens				
Intention-to-treat group	537	35		0.03
Group with adherence of ≥80% for ≥5 yr	387	32		<0.001
Coronary risk factor				
Smoking status				
Never (referent)	515	34		
Past	416	40		
Current	127	53		
Hypertension				
No (referent)	609	34	16	
Yes	335	45	25	0.01
High cholesterol level				
No (referent)	818	36	17	
Yes	91	53	30	0.03
Diabetes				
No (referent)	997	38	19	
Yes	53	56	39	0.003
Family history of myocardial infarction				
No (referent)	529	37	16	
Yes				
At any age	481	42	24	0.10
At a premature age	130	41	24	0.04
Body-mass index				
<25.0 (referent)	184	29	13	
25.0–29.9	359	34	18	0.29
≥30.0	516	44	22	0.03
≥35.0	232	47	21	0.03



Manson JE, et al. N Engl J Med 2007;356:2591-2602

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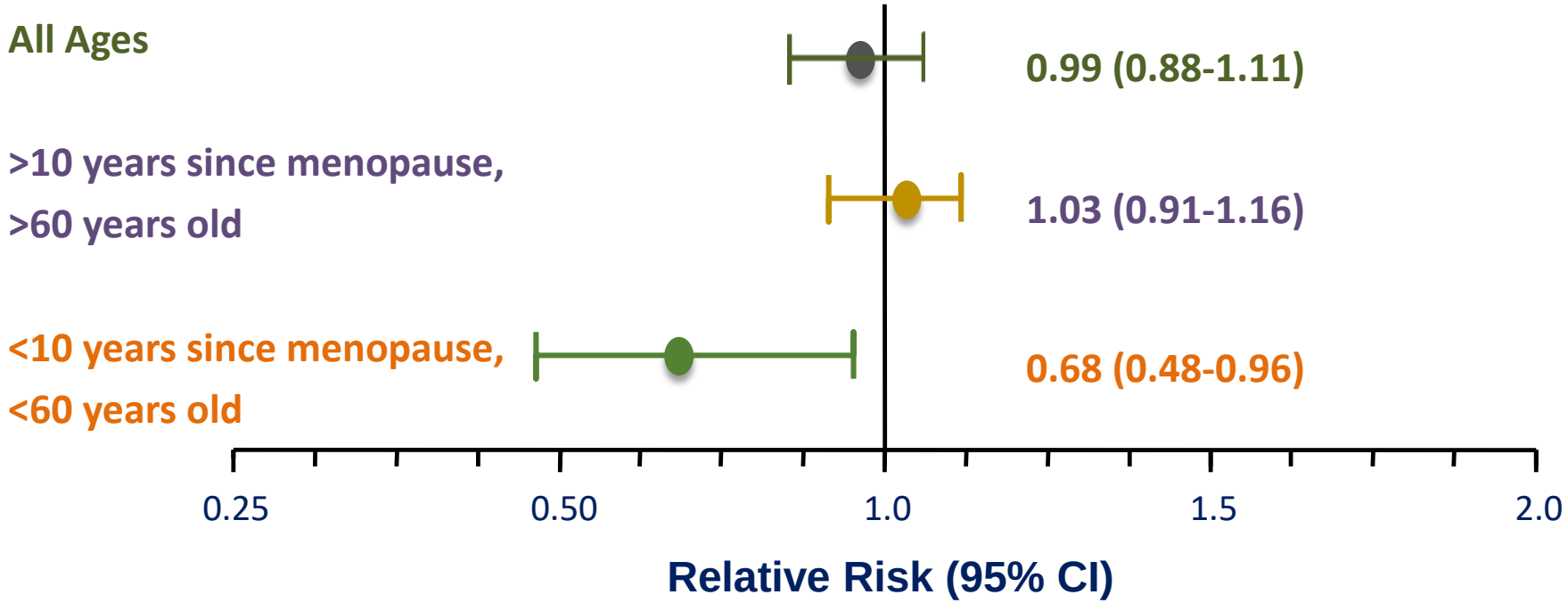
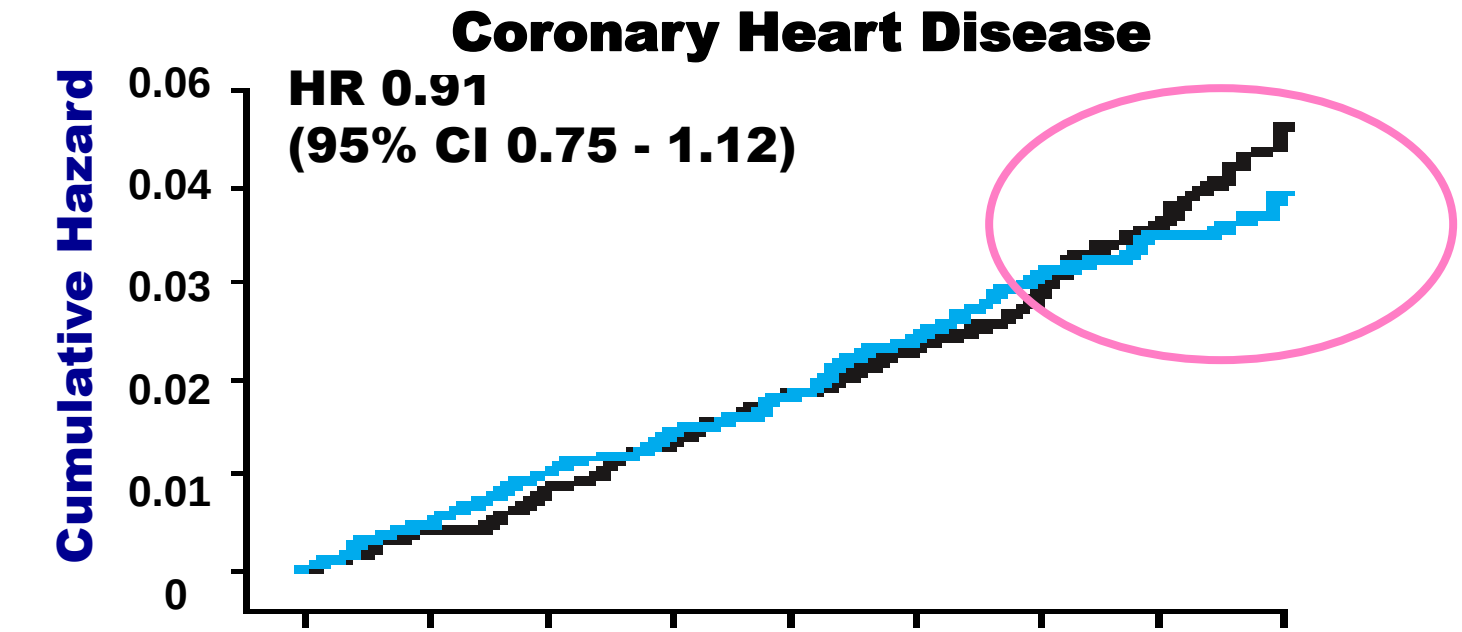
CHD Events Associated with HRT in Younger and Older Women: Meta-analysis of 23 Randomized Controlled Trials (191,340 patient-years)



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

Kaplan-Meier Estimates of Cumulative Hazards for CHD Events by Follow-up Year in the WHI E-Only Arm vs. Placebo

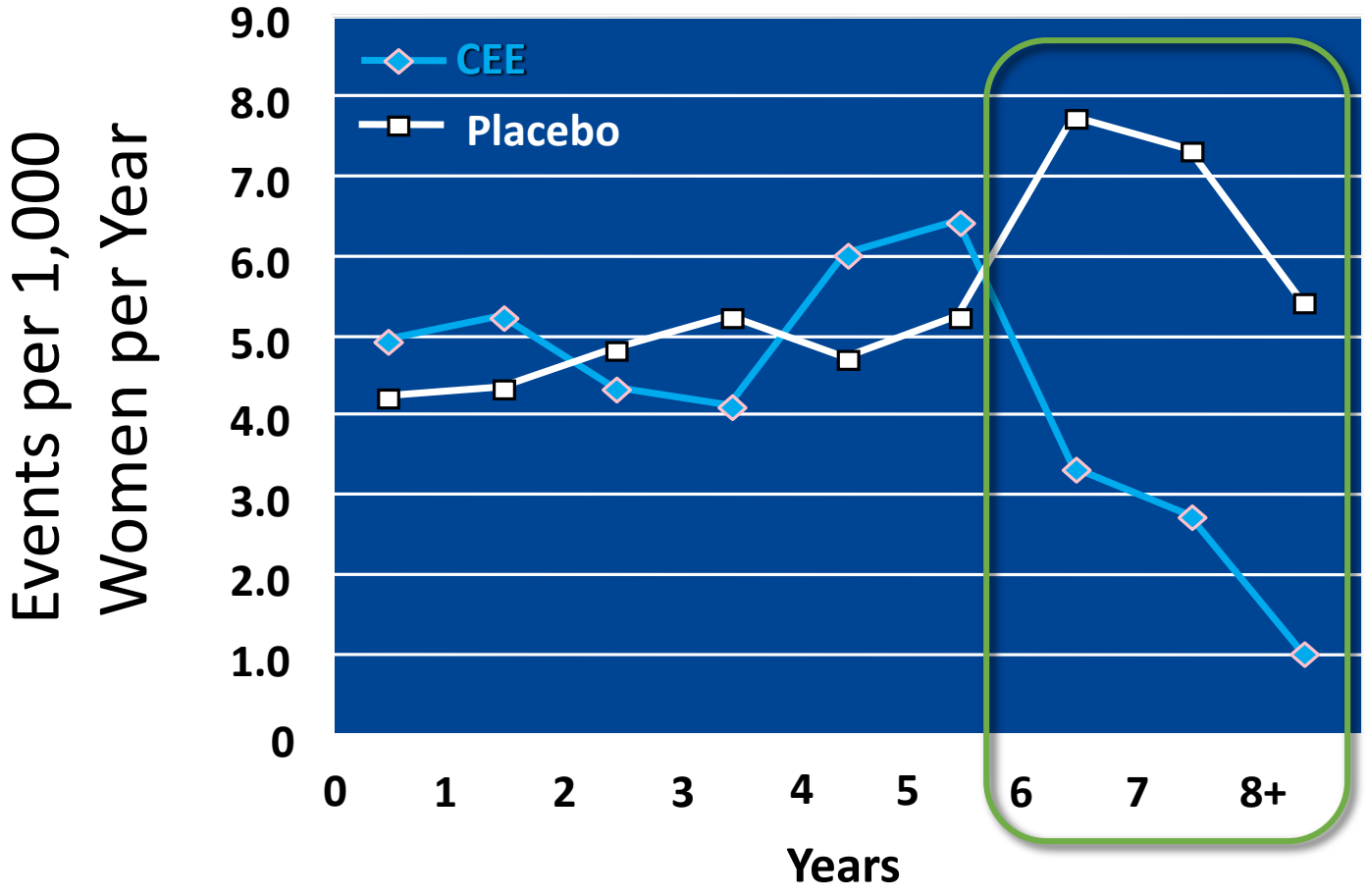


Events	1	2	3	4	5	6	7	8
CEE	26	27	22	21	30	31	13	6	1
Placebo	23	23	25	27	24	26	28	17	6

No. at Risk									
CEE	5310	5210	5147	5067	4978	4874	3034	2248	999
Placebo	5429	5336	5254	5171	5072	4950	4015	2331	1106

JAMA 2004:291;1701-1712

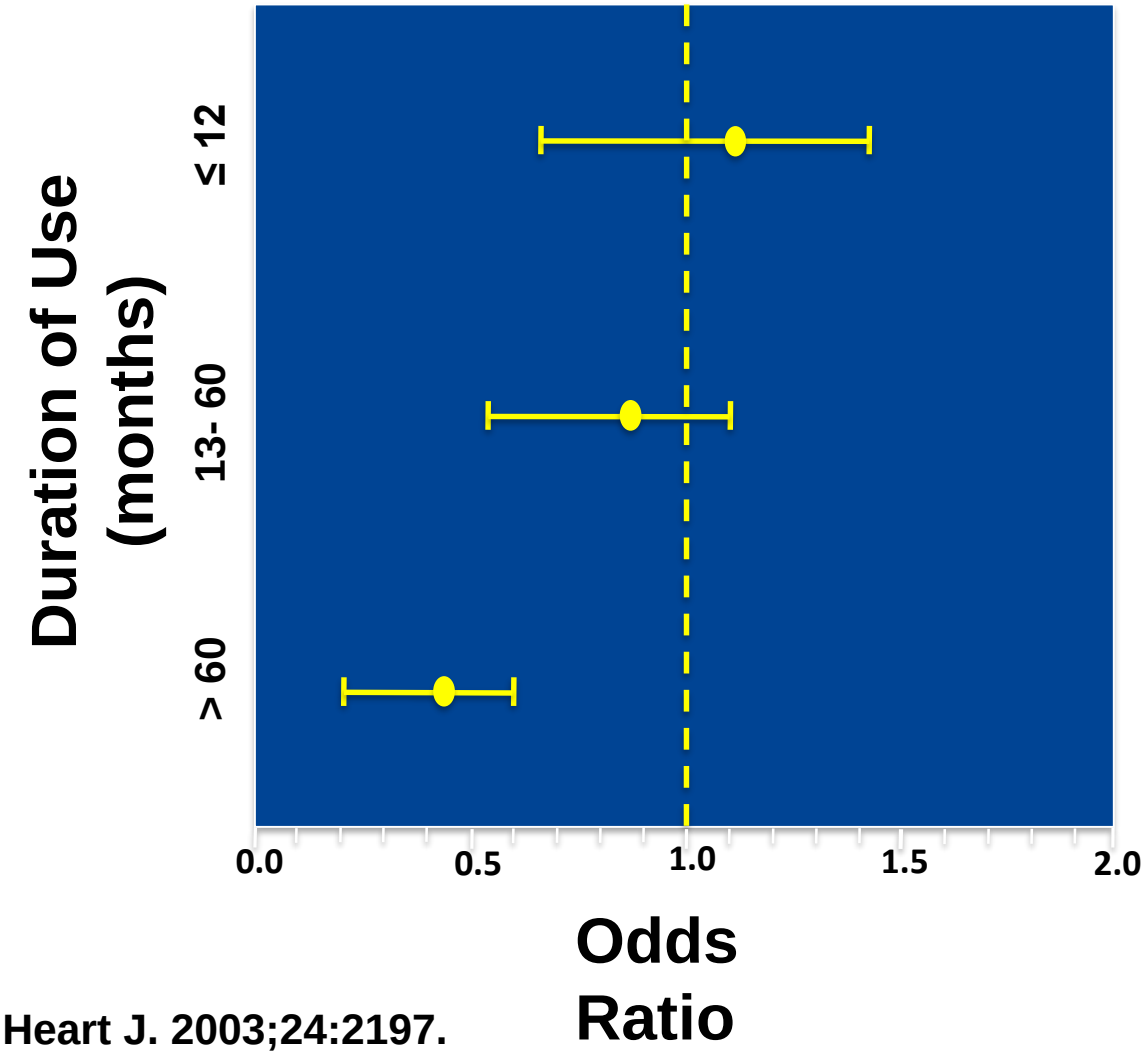
Coronary Heart Disease Event Rates per Thousand Women Active by Follow-up Year in the WHI E-Only Arm vs. Placebo



CHD
Hazard Ratio
Years 6 - 8+
0.41

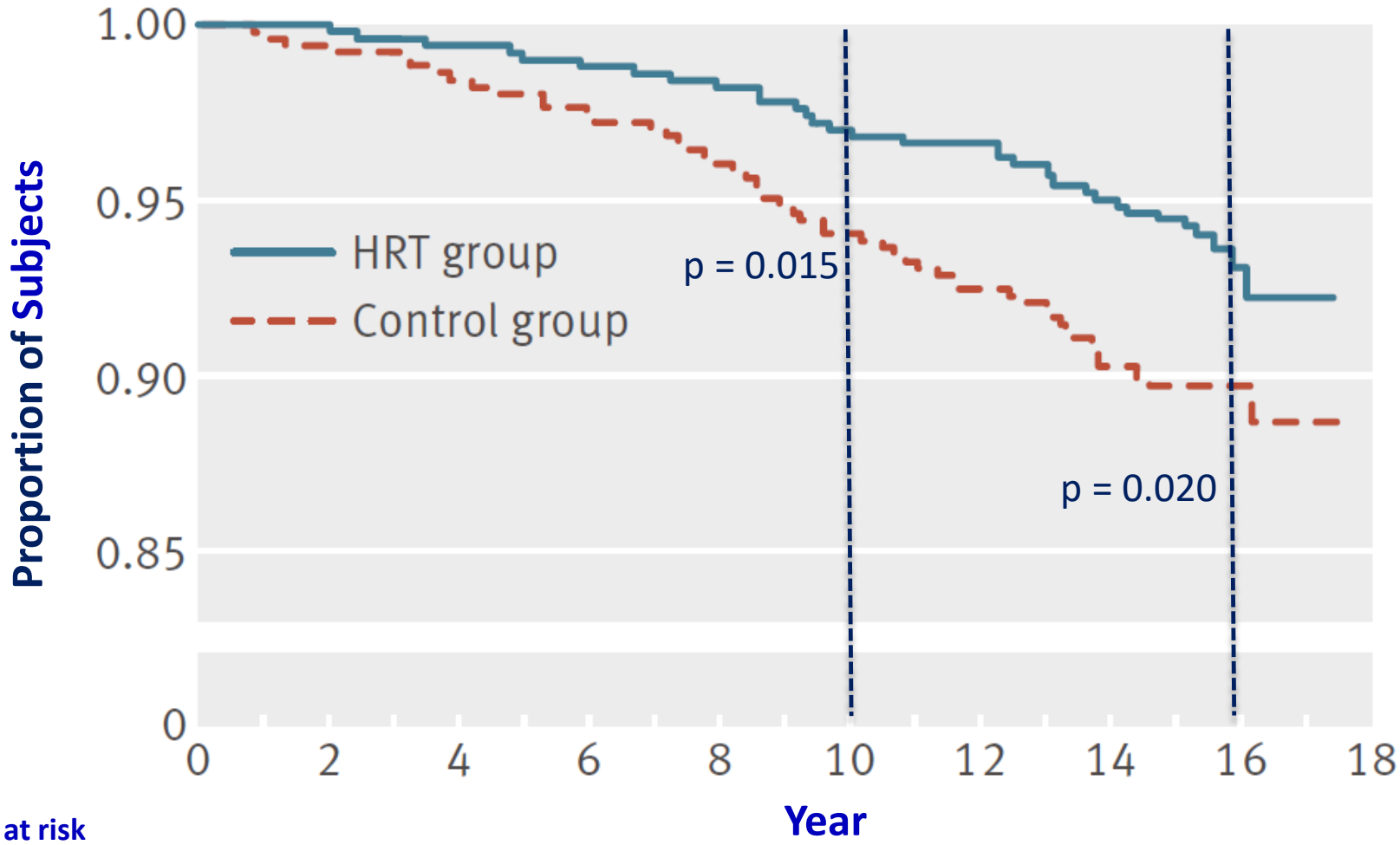
Data from JAMA 2004:291;1701-1712

Odds Ratios for Acute MI in 864 Women with or without HT Use by Duration of Use



Chilvers CE, et al.. Eur Heart J. 2003;24:2197.

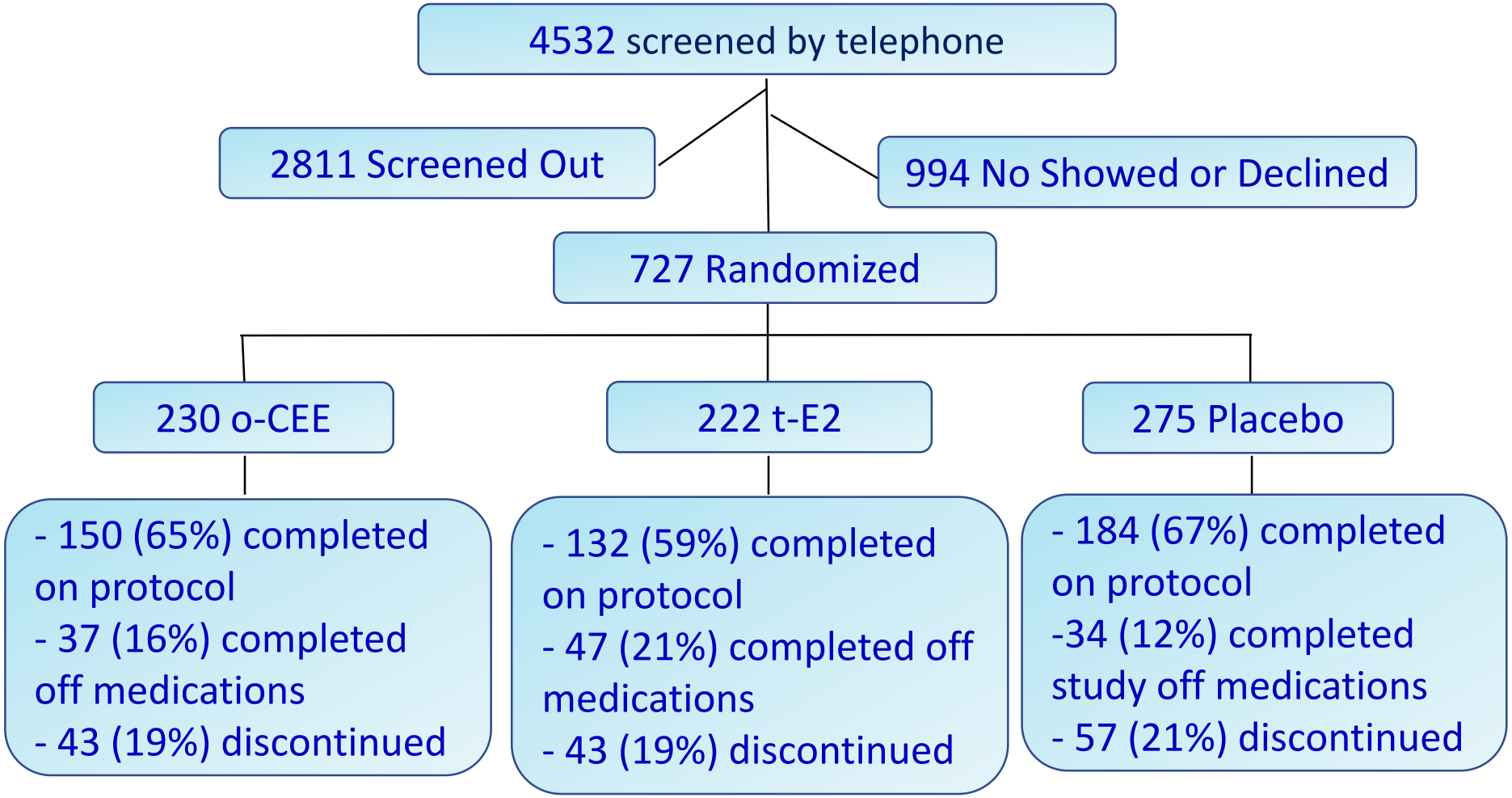
Danish Osteoporosis Prevention Study (DOPS) CVD Outcome



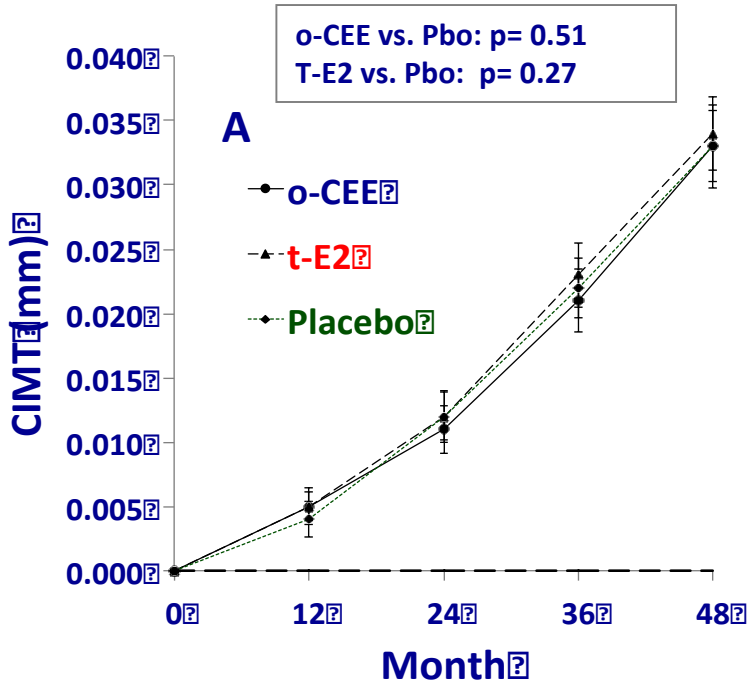
No. at risk									
HRT	502	502	498	496	483	487	484	477	155
Control	504	502	497	492	484	475	466	455	90

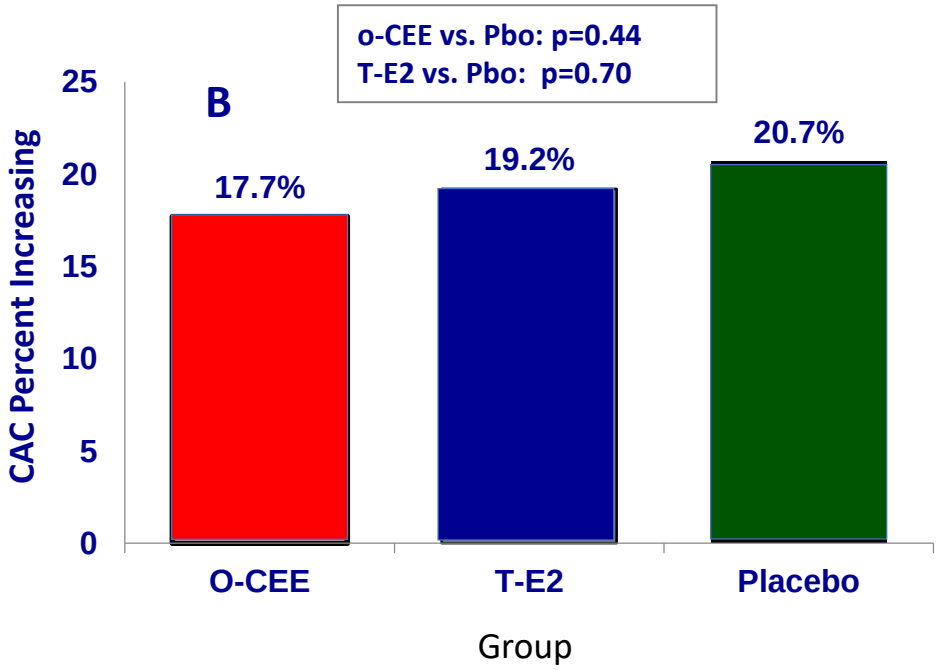
Schierbeck LL, et al. *BMJ* 2012;3456:e6409.

KEEPS Subjects Study Flow



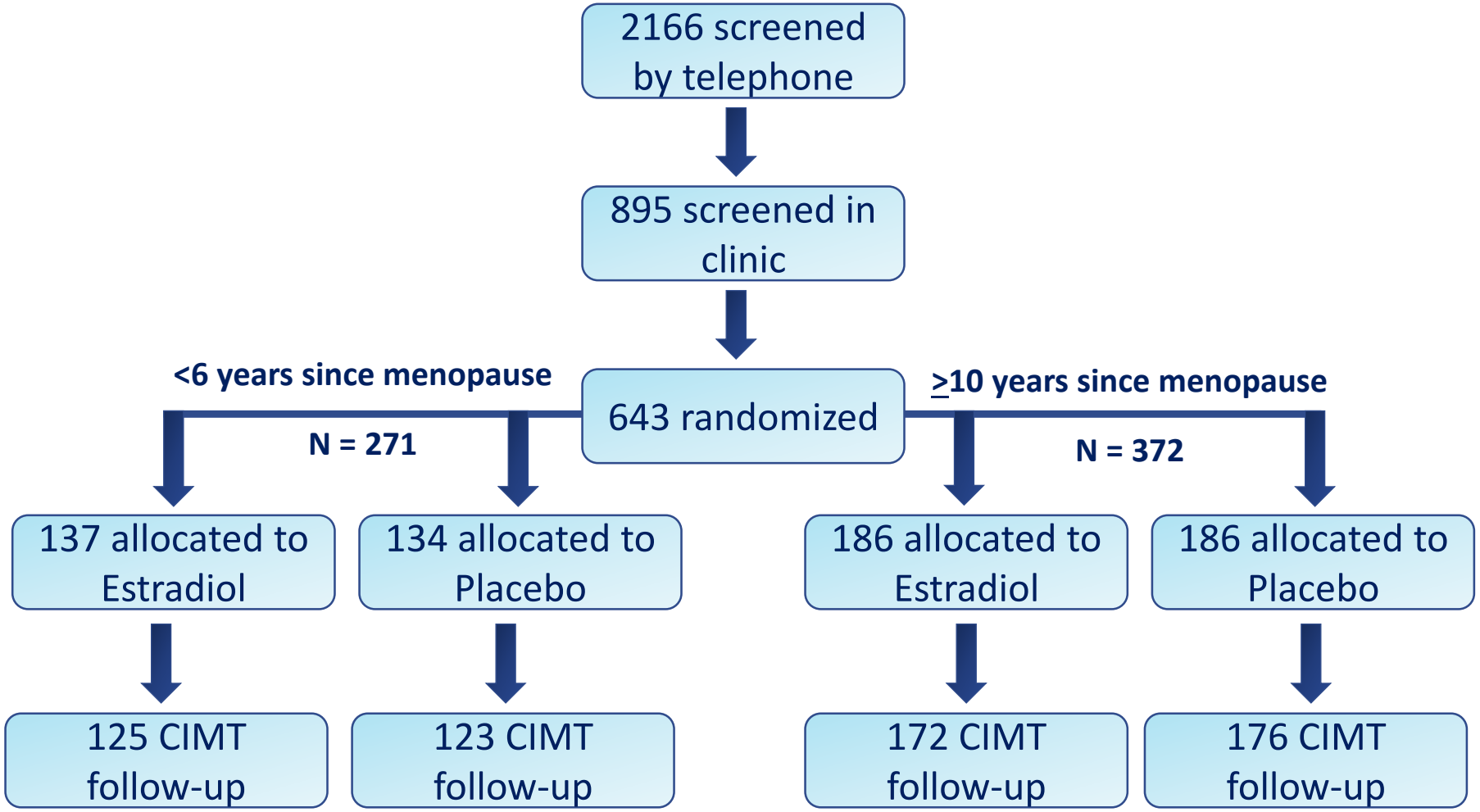
KEEPS: Effects of Treatment on Imaging Endpoints





Harman, SM, et al.
Ann Int Med.
2014, 161:249

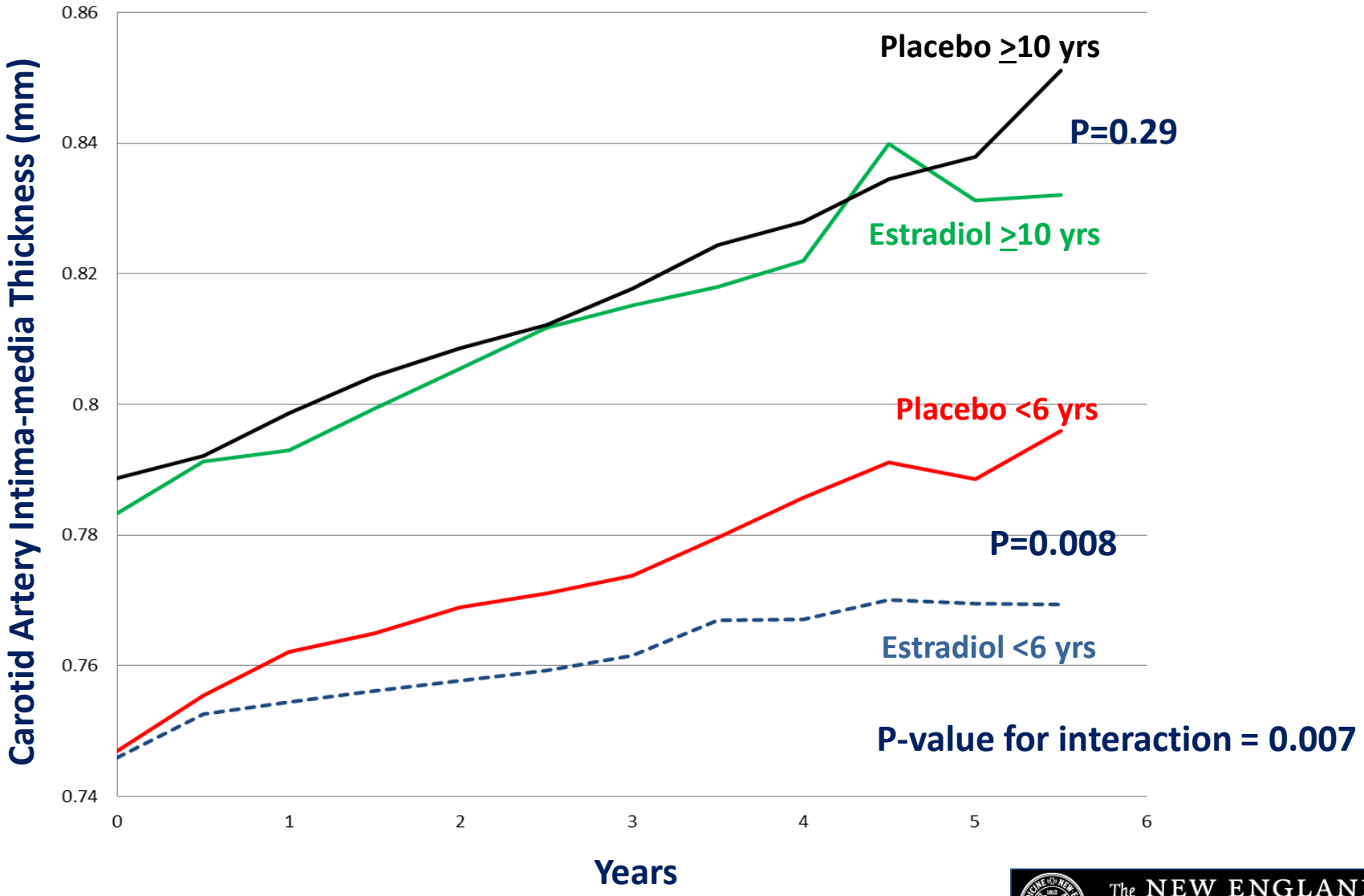
Early versus Late Intervention Trial with Estradiol (ELITE); Enrollment, Randomization, and Follow-up.



Hodis HN et al. N Engl J Med 2016;374:1221-1231.

elite

ELITE: CIMT Progression According to Study Group and Postmenopause Stratum.

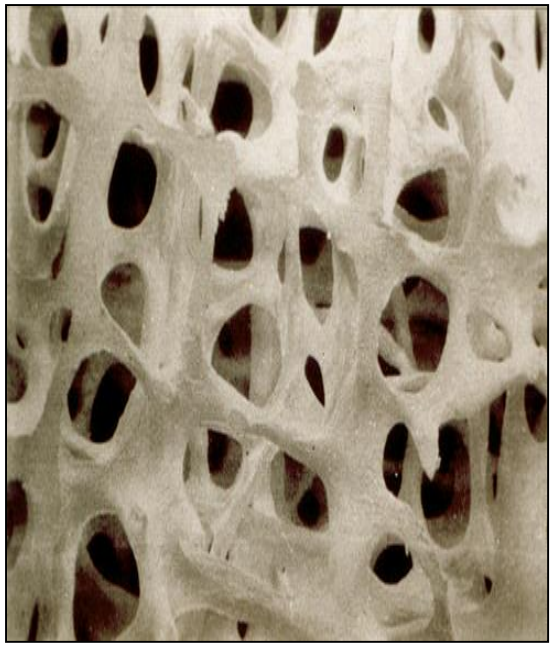


Hodis HN et al. N Engl J Med 2016;374:1221-1231.

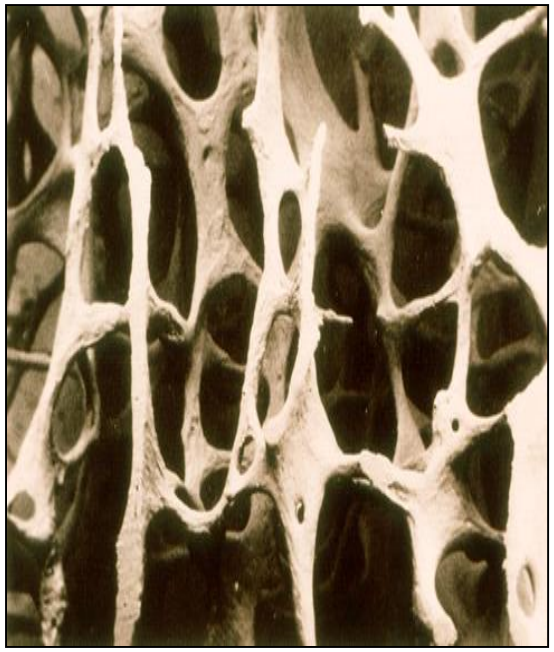
The NEW ENGLAND JOURNAL of MEDICINE

What About Osteoporosis

A disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk



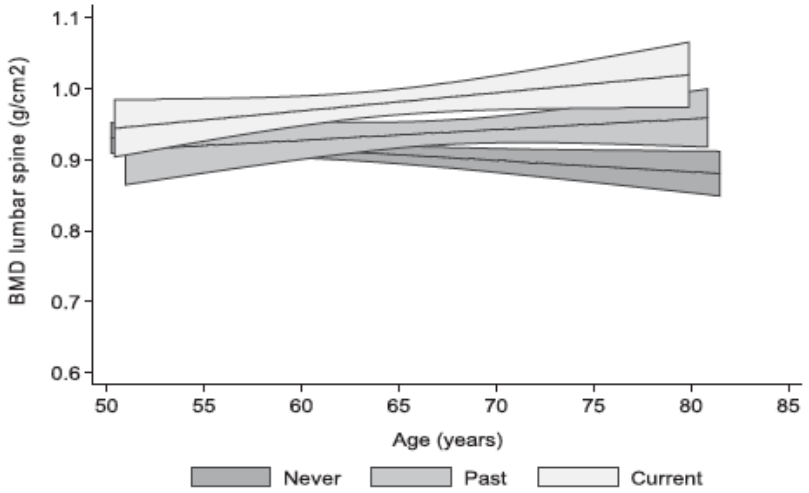
Normal Bone

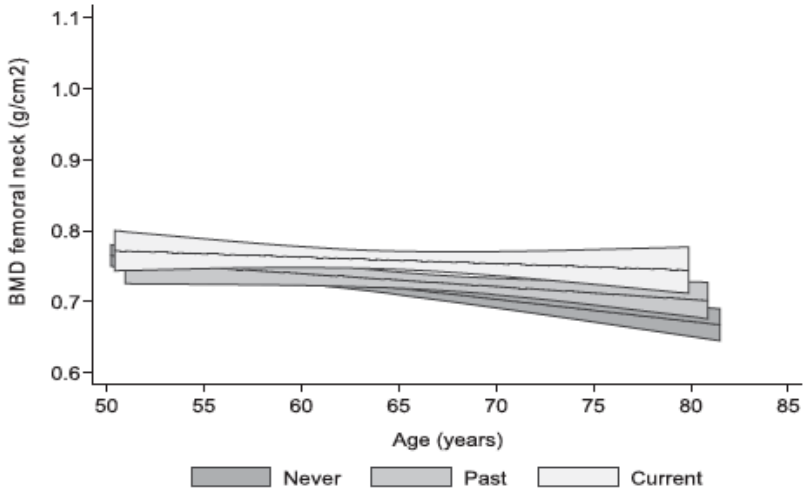


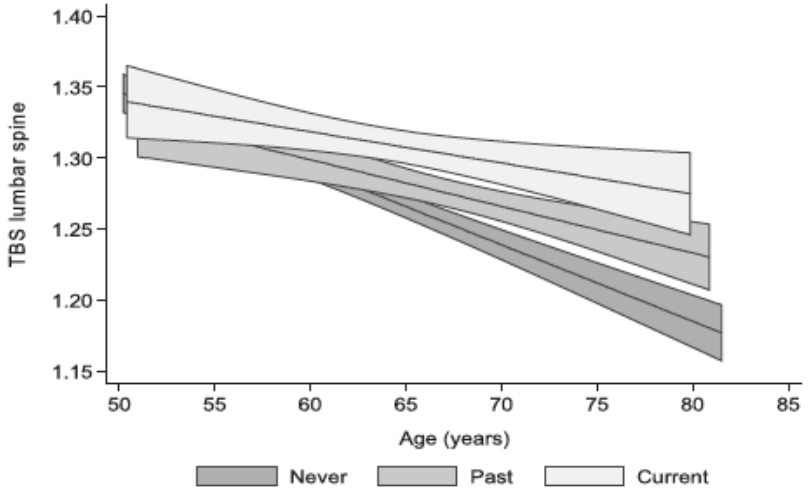
Osteoporosis

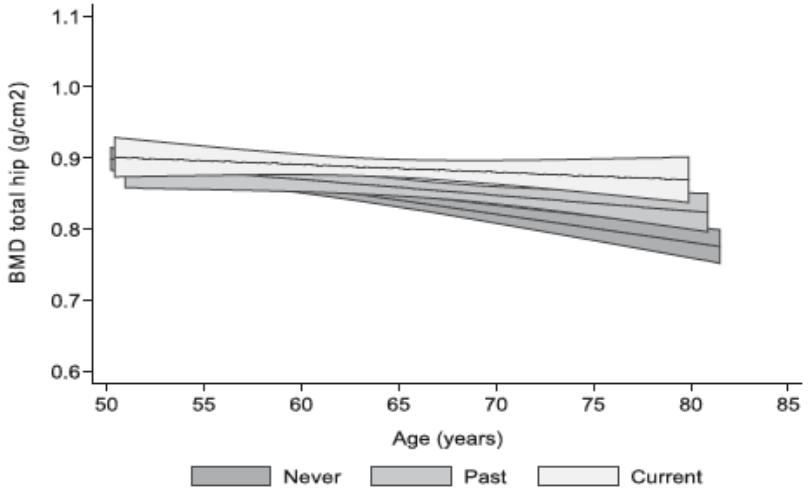
Pentice A *Public Health Nutr* 2004;7:227-43; WHO Study Group In *Assessement of Facture Risk and Its Application to Screening for Postmenopausal Osteoporosis*. Geneva: WHO, 1994

Effects of Estrogen Treatment on Bone Mineral Density and Bone Quality



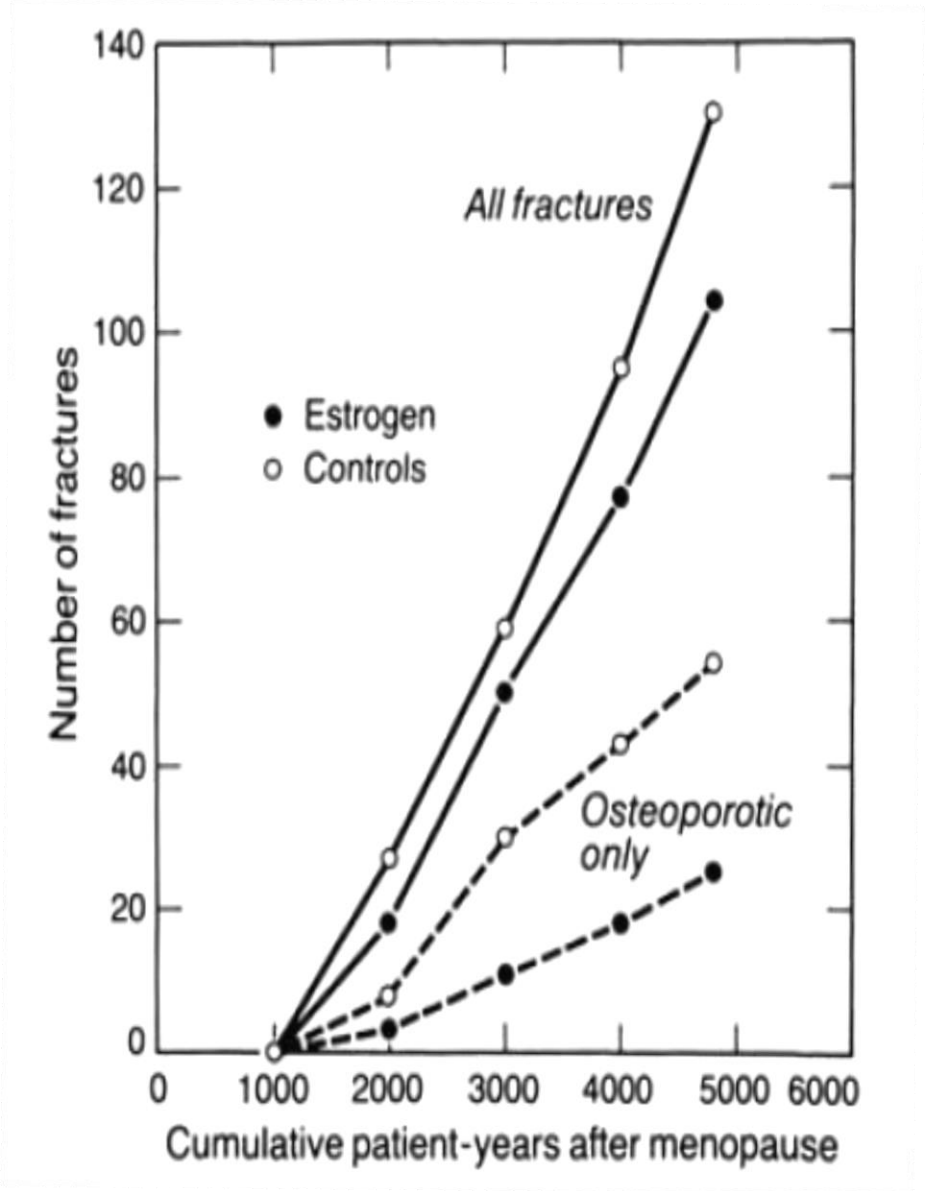






Papadakis et al. J Clin Endocrinol Metab, 2016, 101:5004–5011

Effects of HT on Fractures



Ettinger, et al. Annals of Internal Medicine. 1985;102:319-324.

Conclusions

- Results of the WHI parsed and reanalyzed do not justify the current black box warning* and suggest no harm, or even CVD protection, in younger, more recently menopausal women
- Newer data, consistent with long term observational studies, show no harm (KEEPS) or protection against subclinical CVD progression (ELITE) and CVD events (DOPS) when estrogen treatment is initiated early in the menopause
- Hormone therapy protects against bone loss and fractures
- Further research on menopausal HT should be pursued to clarify effects of:
  - Doses and agents (especially progestogens)
  - Route of administration
  - Timing/Age

***Opinion of the author and <u>not</u> the Phoenix VAHCS or the U.S. Veterans Administration**