# Timing of Menopausal Hormone Therapy and Reduction of All-Cause Mortality and Cardiovascular Disease

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# Disclosures

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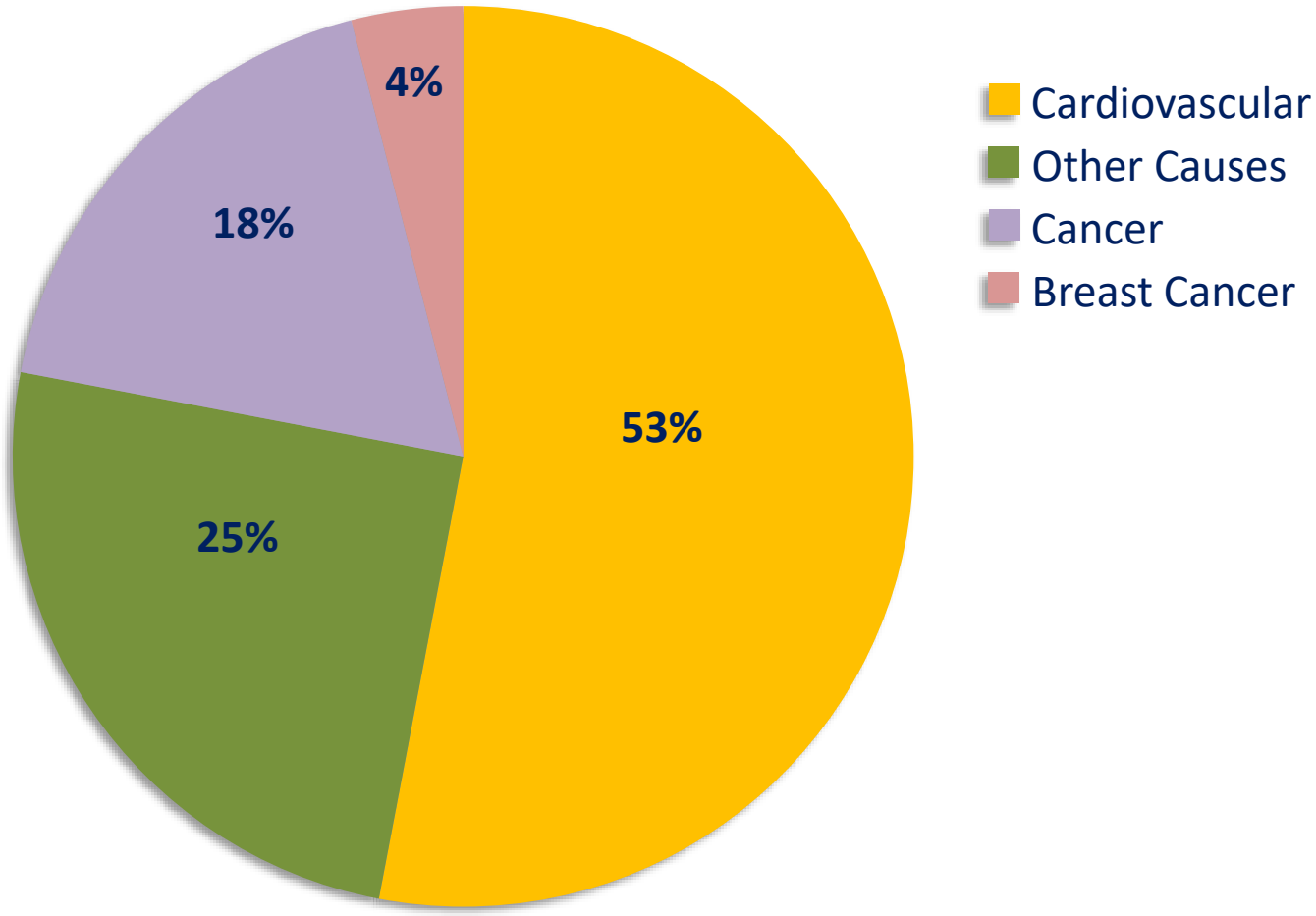
R01ES-033705
R01ES-033707
NIH - MACS-WIHS combined cohort study

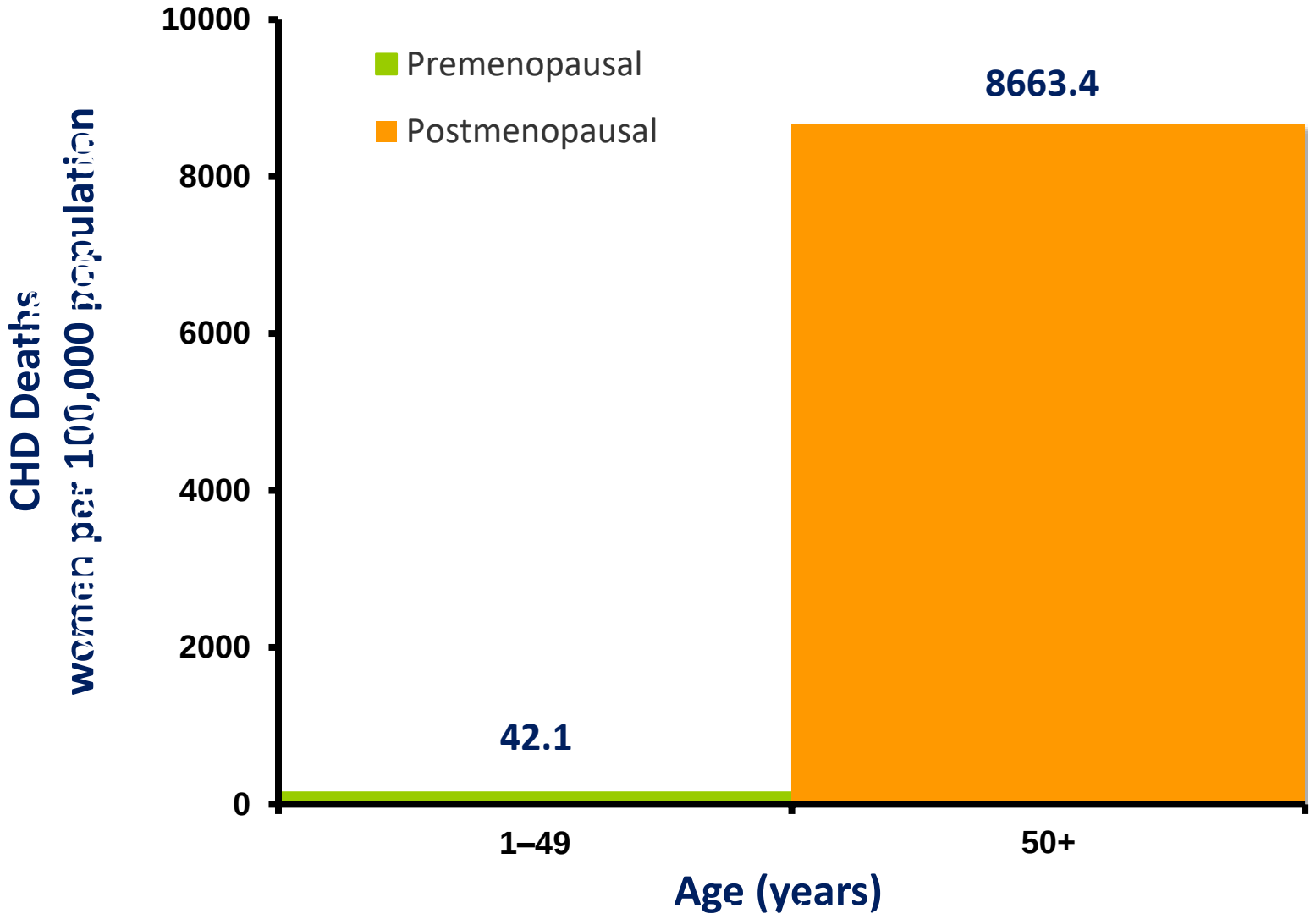
ELITE and EPAT funded by the National Institute on Aging, NIH
ClinicalTrials.gov number NCT00114517 and NCT00115024, respectively

WELL-HART funded by the National Heart, Lung, and Blood Institute, NIH
ClinicalTrials.gov number NCT00000559

# Causes of Death in Women

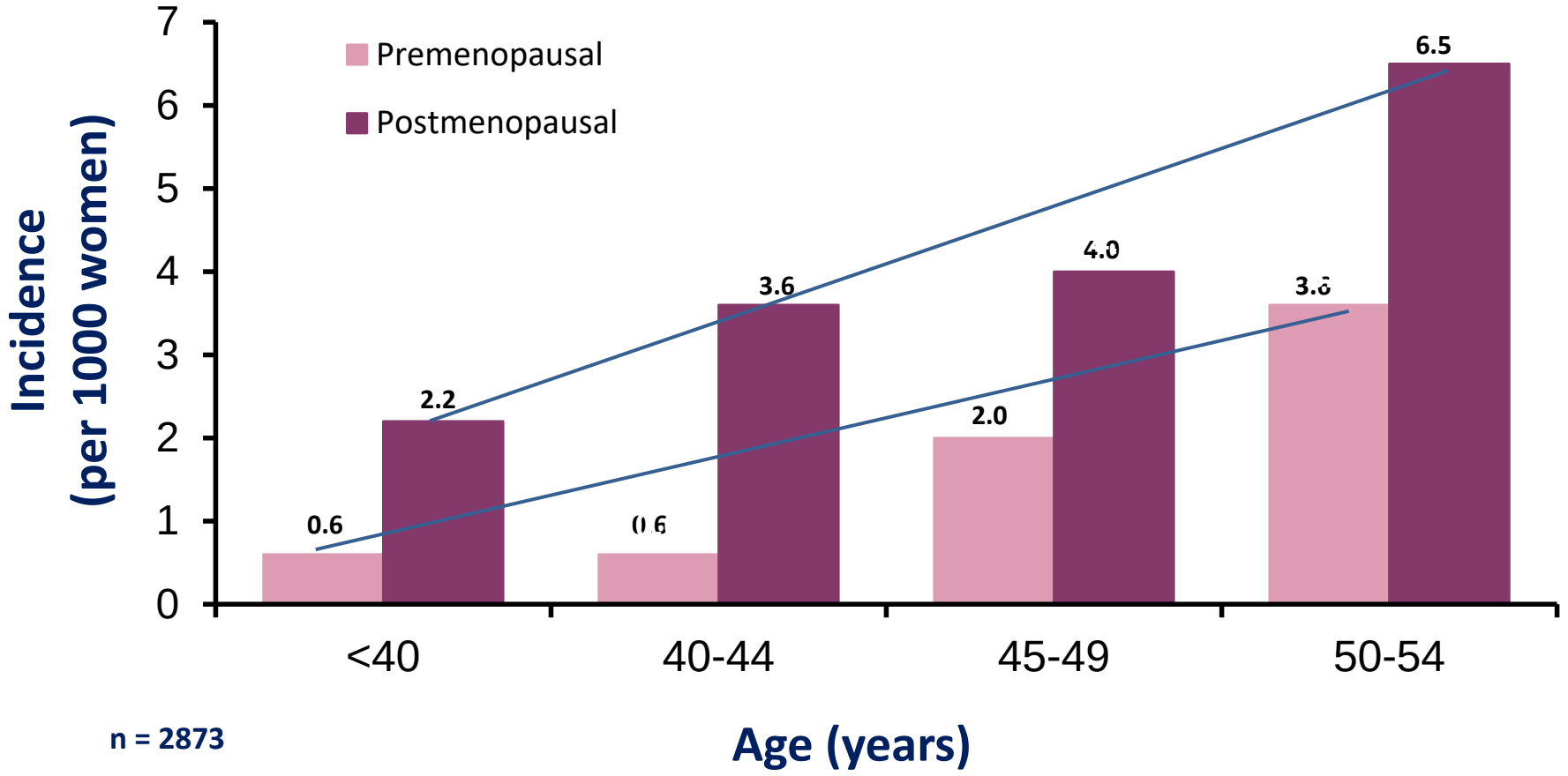


# CHD Death in Women by Menopausal Status



# Incidence of Cardiovascular Disease in Relation to Menopause Status

## The Framingham Study

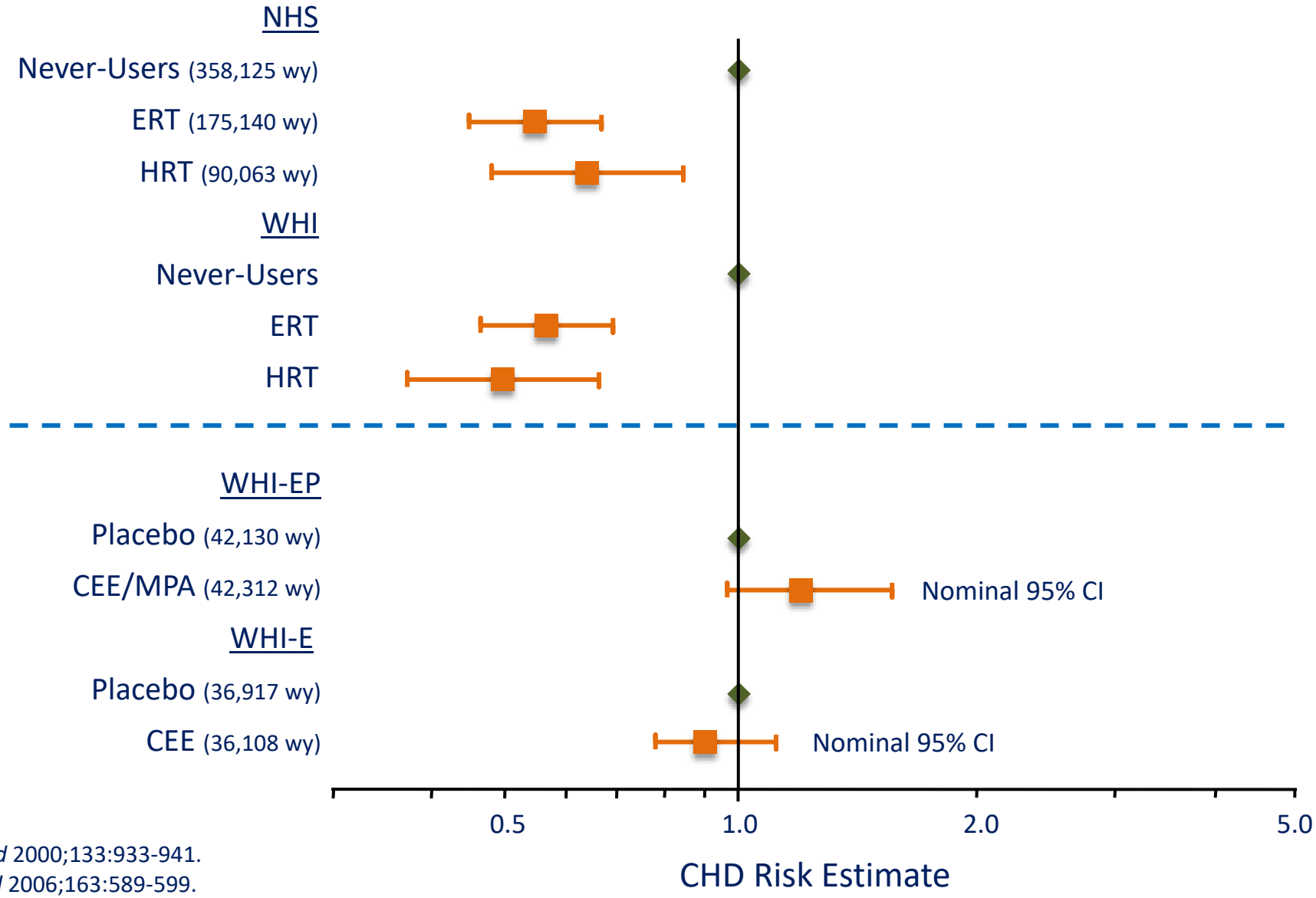



n = 2873

Kannel WB, et al. *Ann Intern Med* 1976;85:447-552.

# Who are the Women Most Likely Protected with Menopausal Hormone Replacement Therapy?

# CHD: Observational Studies vs. Randomized Trials




wy = woman-years


Grodstein F, et al. *Ann Intern Med* 2000;133:933-941.
Prentice RL, et al. *Am J Epidemiol* 2006;163:589-599.
Prentice RL, et al. *Am J Epidemiol* 2005;162:404-414.
Rossouw JE, et al. *JAMA* 2007;297:1465-1477.

# Differences between Randomized Trials and Observational Studies

| | Observational Studies | Randomized Trials |
|---|---|---|
| Mean age or age range at enrollment (years) | 30-55 | >63 |
| Time since menopause at HT initiation (years) | <2 | >10-25 |
| Menopausal symptoms (flushing) | predominant | excluded |
| Duration of therapy (years) | >10-40 | <7 |
| Body mass index (mean, $kg/m^2$) | 25.1 | 28.5* |

*For example, WHI: 34.1% had BMI ≥30 $kg/m^2$

Hodis HN, et al. *Ann Intern Med* 2001;135:939-953.
Hodis HN, et al. *N Engl J Med* 2003;349:535-545.
Hodis HN, et al. *Clin Obstet Gynecol* 2008;51:564-586.

# Timing of Menopausal HRT
# Window of Opportunity

**The effects of menopausal HRT on atherosclerosis and clinical events are dependent upon when HRT is initiated in relation to menopause and/or age.**

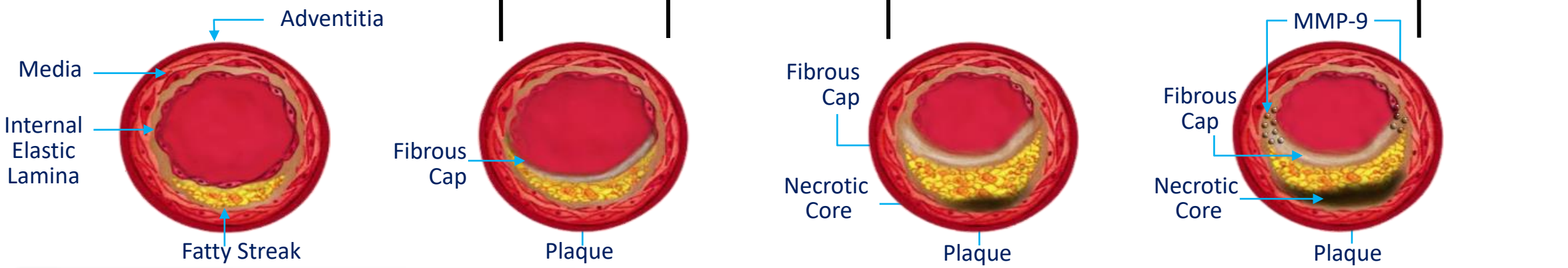
**Athero imaging RCTs**
**Animal studies**
**RCTs/Obs studies**

Hodis HN, et al. *J Am Geriatr Soc* 2013;61:1005-1010.
Hodis HN, et al. *J Am Geriatr Soc* 2013;61:1011-1018.

# Healthy Endothelium Hypothesis
# Duality of Estrogen on Natural History of Atherosclerosis

## Relation of Age Distribution in WHI to Stage of Atherosclerosis Progression

| 0% | 10% | 20% | 70% | |
|---|---|---|---|---|
| Years of age → | 50-54 | 55-59 | 60-69 | 70-79 |
| | | | 45% | 25% |




**Age 35-45 years** | **Age 45-55 years** | **Age 55-65 years** | **Age >65 years**

51

menopause | early postmenopause (<6 years since menopause) | late postmenopause (≥6 years since menopause)

### *Beneficial Effects on Atherogenesis*

↓LDL oxidation ⇒ ↓LDL atherogenicity
↓LDL binding/accum ⇒ ↓lesion progression
↓CAMs ⇒ ↓monocyte adhesion/
↓macrophage accumulation
↓SMC proliferation ⇒ ↓lesion progression
↑Endothelial function ⇒ ↑vasodilation

### *Loss of Estrogen Benefits on Aging/Diseased Vessels*

↓Vascular responsivity
↓Expression of estrogen receptors
↑ERα gene methylation

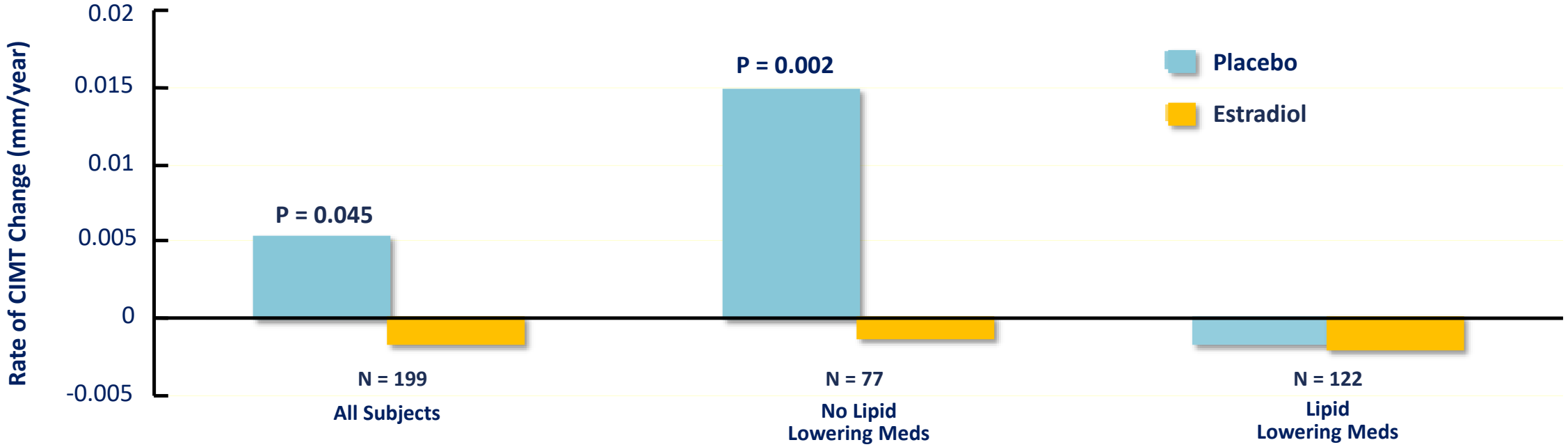
### *Adverse Effects on Established Plaques*

↑MMP expression ⇒
↑PQ instability/rupture
↑lesion progression

Hodis HN, et al. *N Eng J Med* 2003;349:535–545.

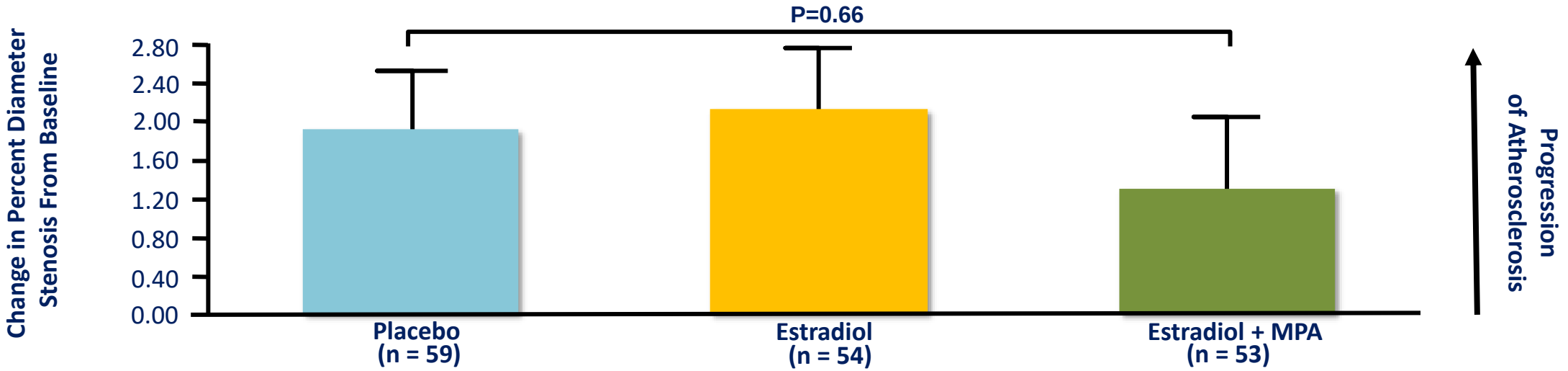
# EPAT: Rate of CIMT Change

Hodis HN, et al. *Ann Intern Med* 2001;135:939-953.

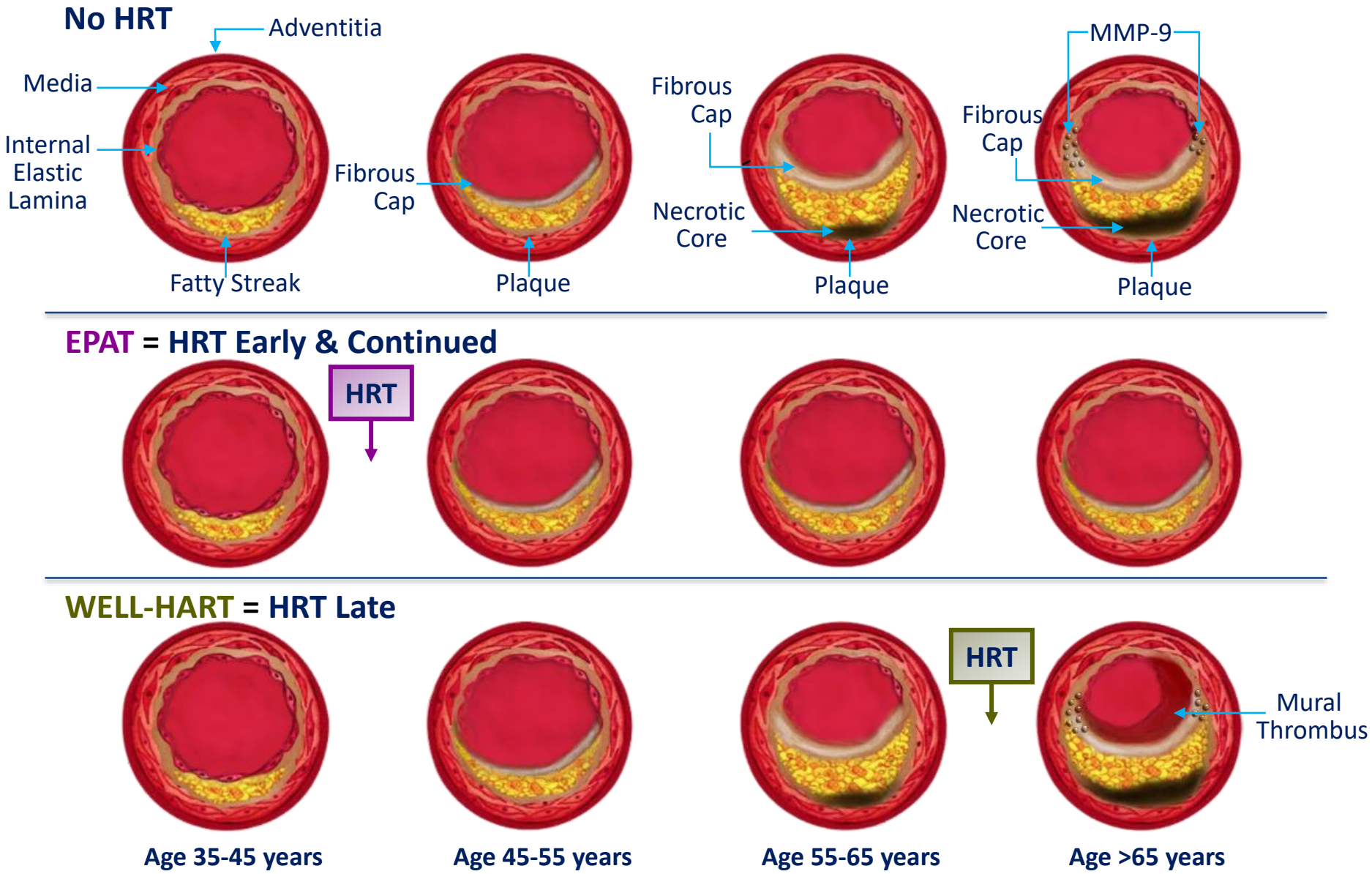



# WELL-HART: Change in Percent Diameter Stenosis

Hodis HN, et al. *N Engl J Med* 2003;349:535-545.

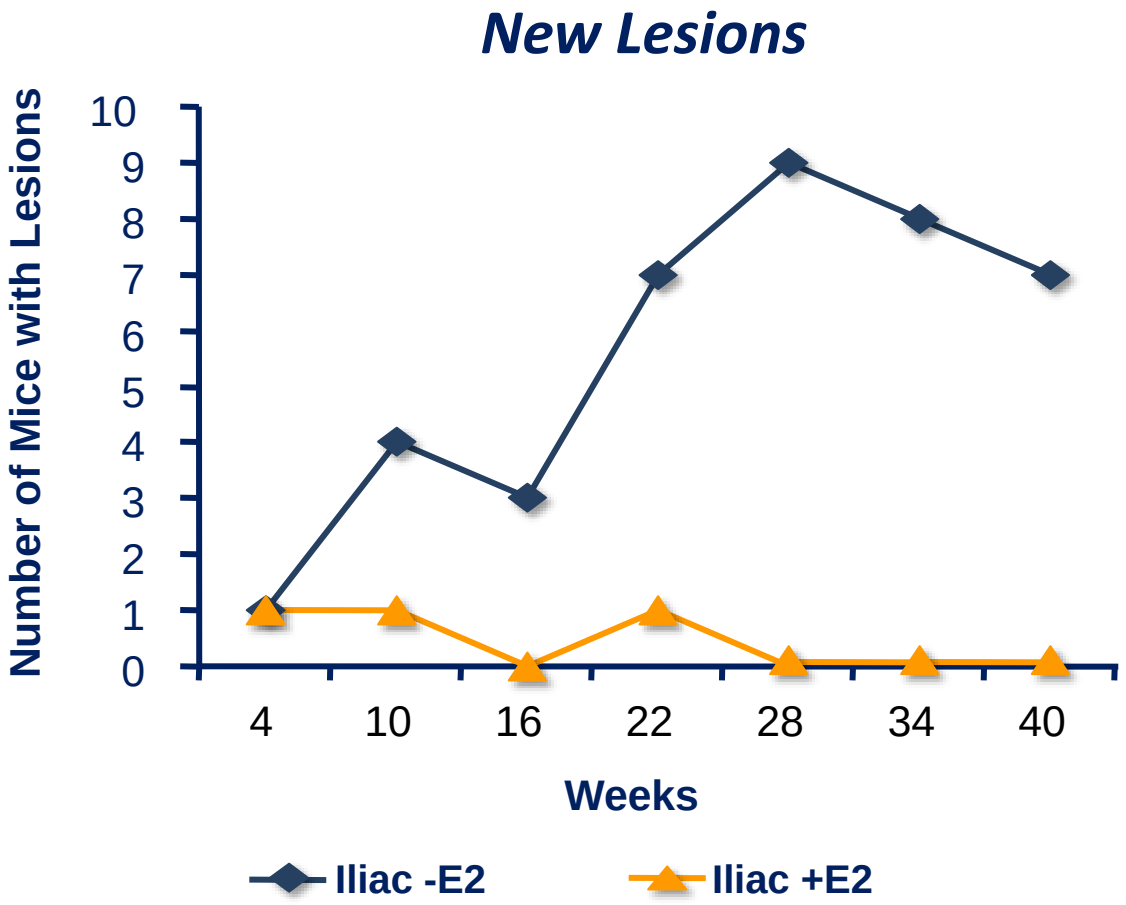


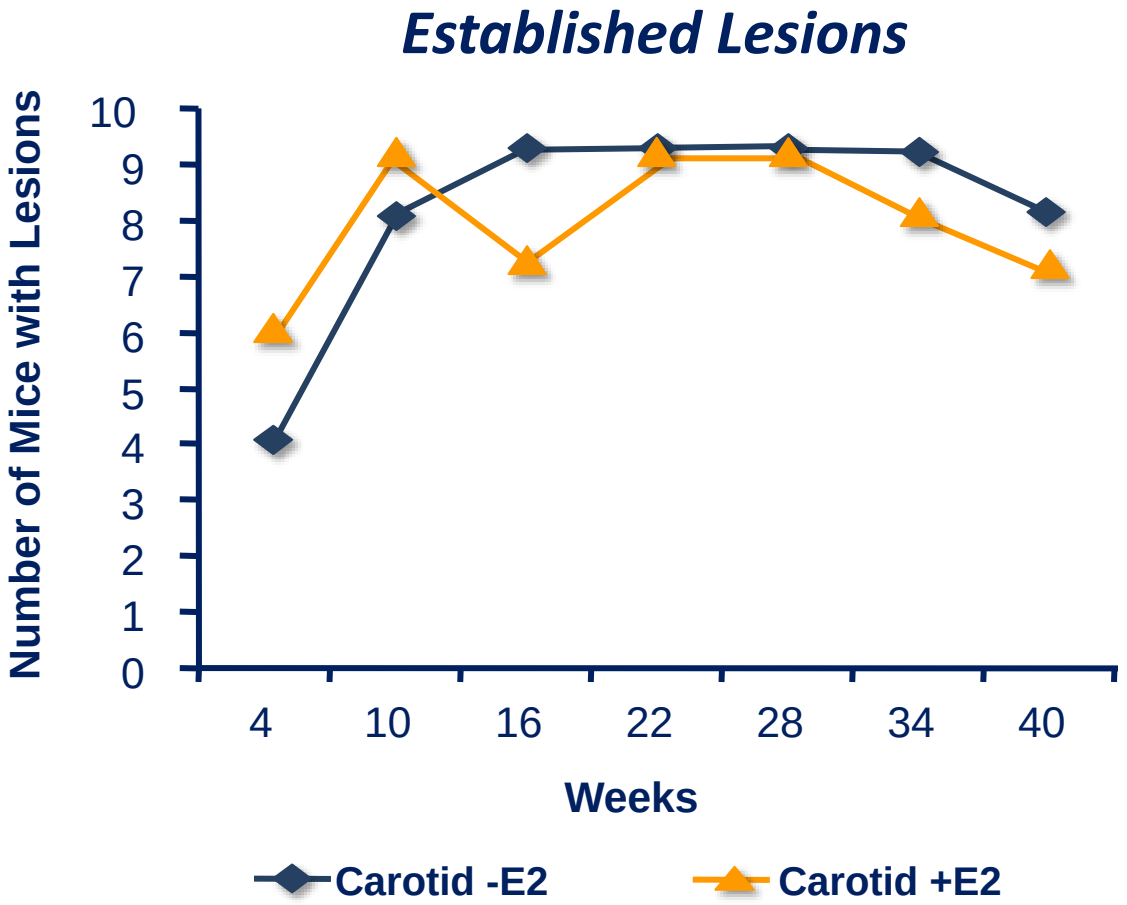
# Pathogenic Sequence of Vascular Aging




Hodis HN, et al. *N Eng J Med* 2003;349:535–545.

# Estrogen Inhibits Initiation but not Progression of Established Lesions in Mice




Rosenfeld ME, et al. *Atherosclerosis* 2002;164:251-259.

# HRT and Prevention of Cardiovascular Disease and Reduction of Mortality

# Early versus Late Intervention Trial with Estradiol (ELITE)
# Direct Test of the Timing Hypothesis

| | |
|---|---|
| *Study design:* | Single-center, randomized, double-blinded, placebo-controlled trial |
| *Trial factors:* | Randomized treatment (estradiol, placebo) x time since menopause (<6 years, ≥10 years) |
| *Participants:* | 643 healthy postmenopausal women without preexisting CVD and diabetes mellitus |
| *Intervention:* | Oral micronized 17β-estradiol 1 mg/d (+ vaginal micronized progesterone gel x 12 days every month in women with a uterus) |
| | Placebos |
| *Follow-up:* | Every month for the first 6 months and then every 2 months for up to 6 years |

Hodis HN, et al. *Menopause* 2015;22:391-401.

# Baseline Characteristics

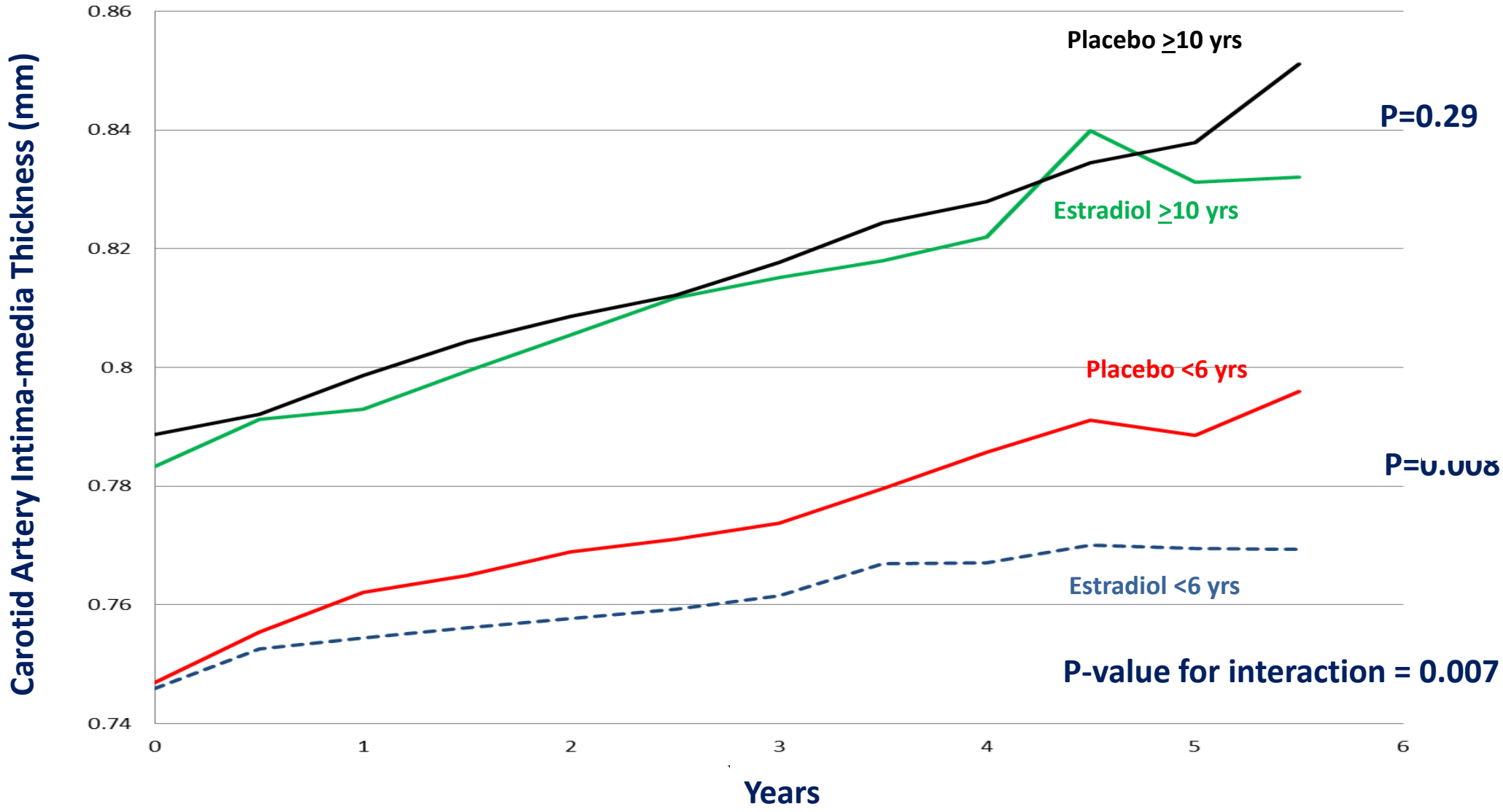
| Characteristic | <6 Years-Since-Menopause (n=271) | | ≥10 Years-Since-Menopause (n=372) | |
|---|---|---|---|---|
| | Placebo (134) | Active (137) | Placebo (186) | Active (186) |
| | | | | |
| Time since menopause, years (median, IQR) | 3.7 (1.9,5.0) | 3.5 (1.9,5.2) | 14.0 (11.4,18.1) | 14.9 (11.5,19.0) |
| | | | | |
| Mean age, years | 55.3 (4.1)[1] | 55.6 (4.1) | 63.8 (6.5) | 64.9 (5.5) |
| | | | | |

IQR = interquartile range

[1] Mean (SD)

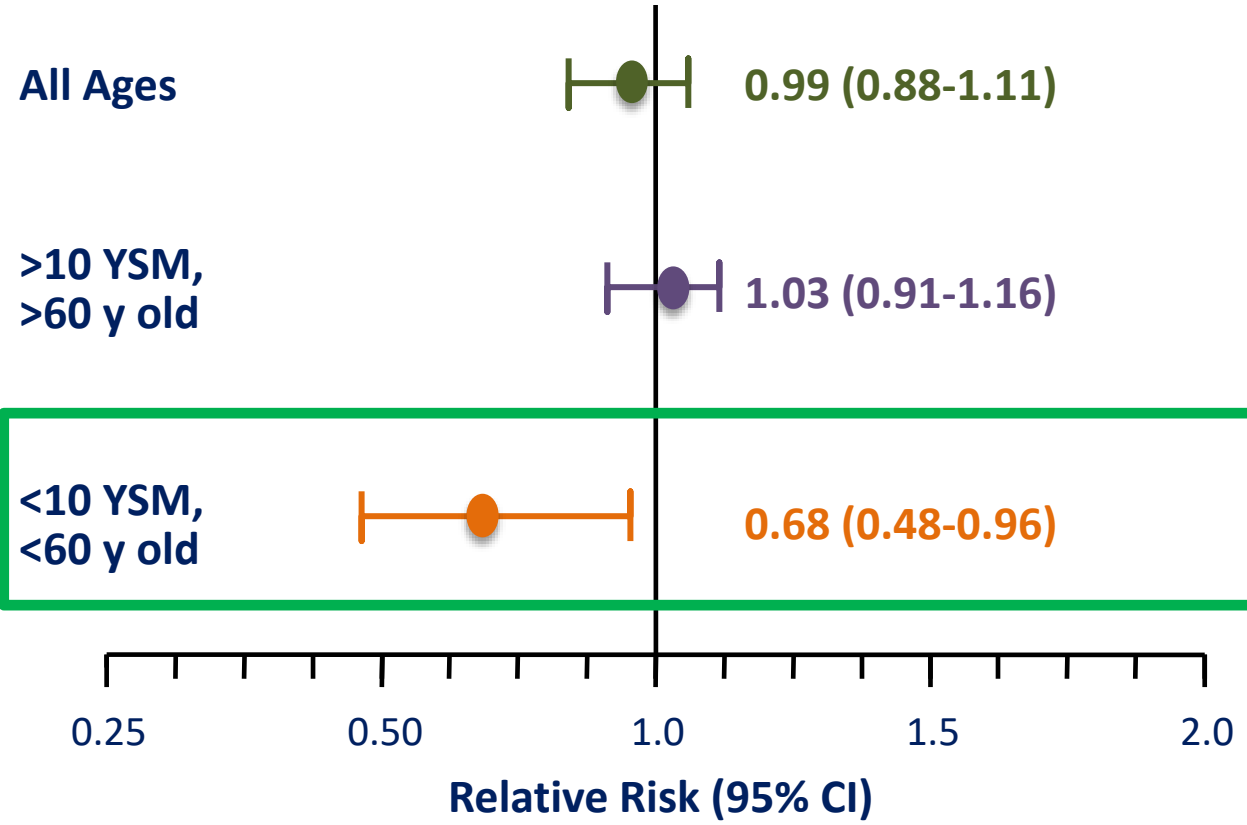
Hodis HN, et al. *New Engl J Med* 2016;374:1221-1231.

# Early vs. Late Intervention Trial with Estradiol (ELITE) CIMT by Treatment and Postmenopausal Strata




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

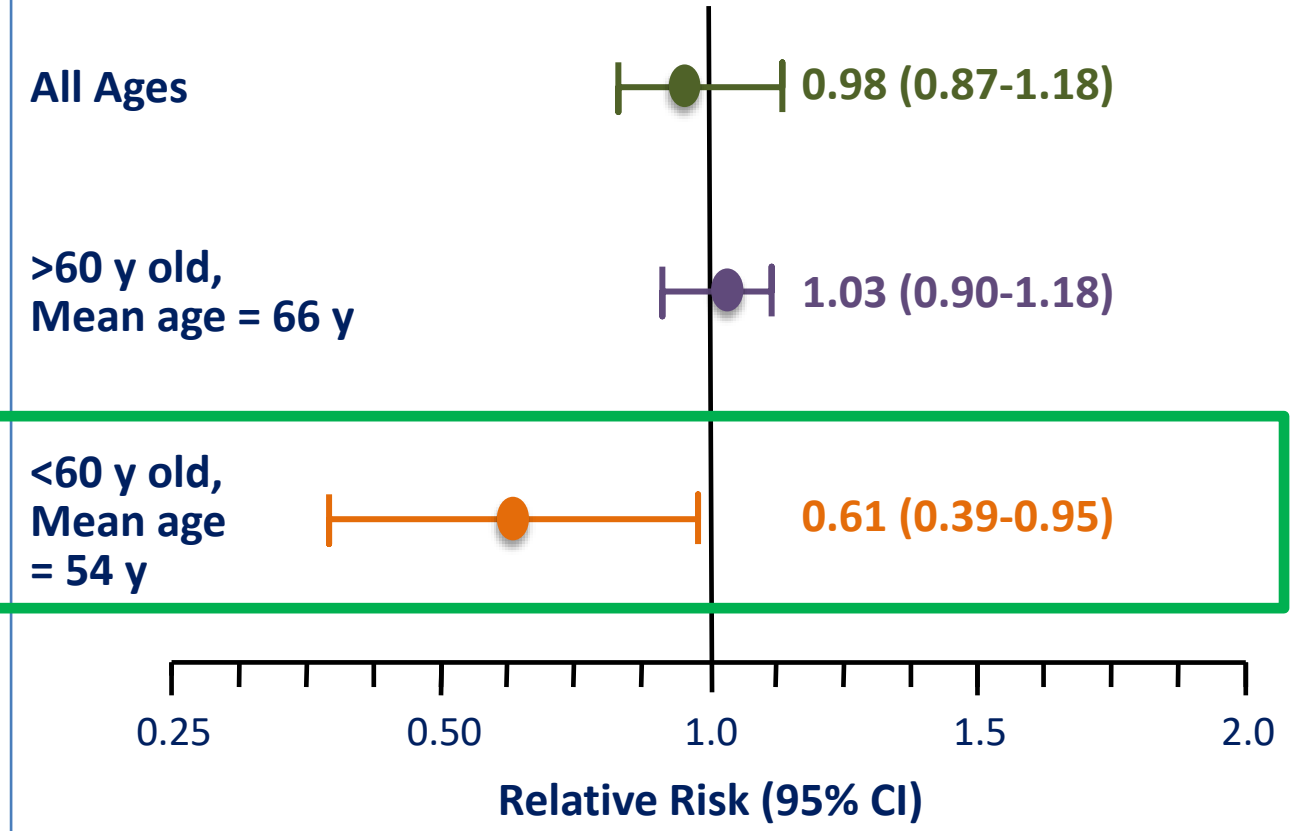
# CHD Events Associated with HRT in Younger and Older Women: Meta-analysis of 23 Randomized Controlled Trials (191,340 patient-years)




y = years
YSM = years-since-menopause

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

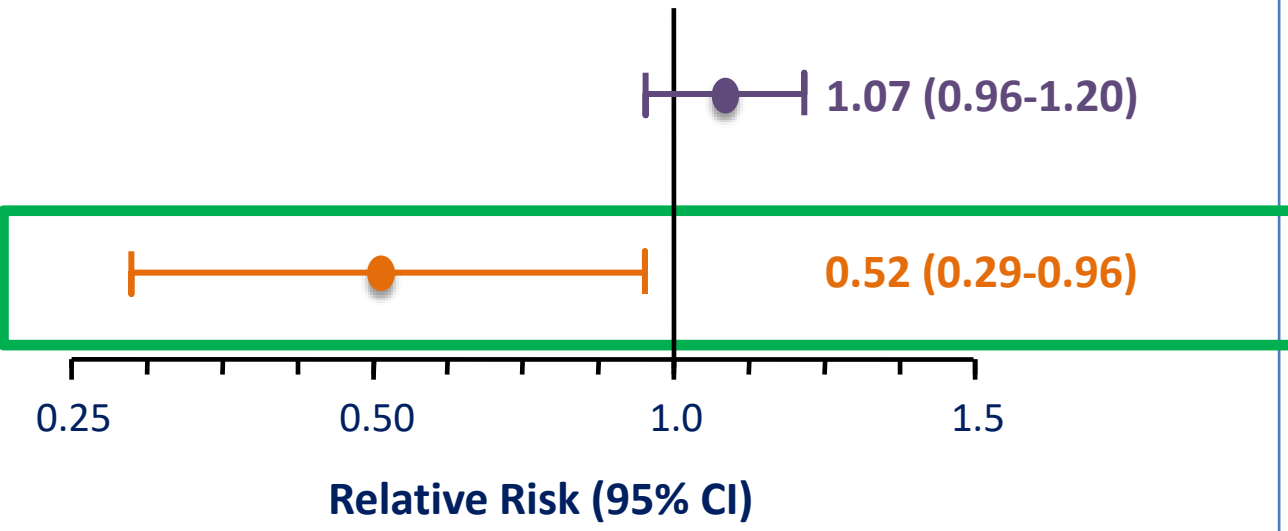
# All-Cause Mortality Associated with HRT in Younger and Older Women: Meta-analysis of 30 Randomized Controlled Trials (119,118 patient-years)



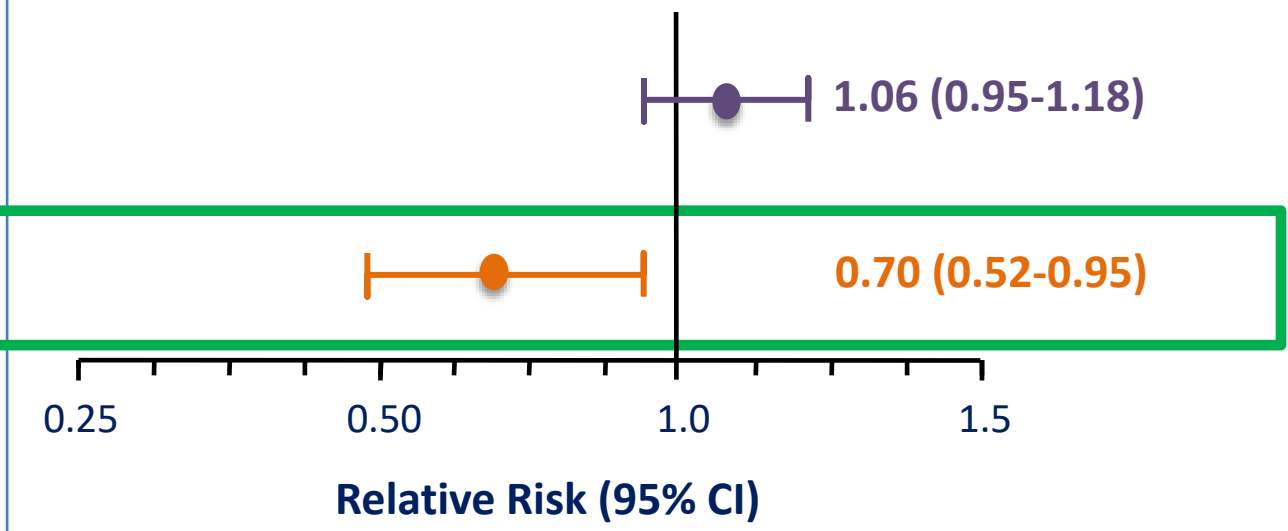

y = years

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

# Cochrane Meta-analysis: Randomized Controlled Trials of CHD Events Associated with HRT in Younger and Older Postmenopausal Women




# Cochrane Meta-analysis: All-Cause Mortality from Randomized Controlled Trials of HRT in Younger and Older Postmenopausal Women



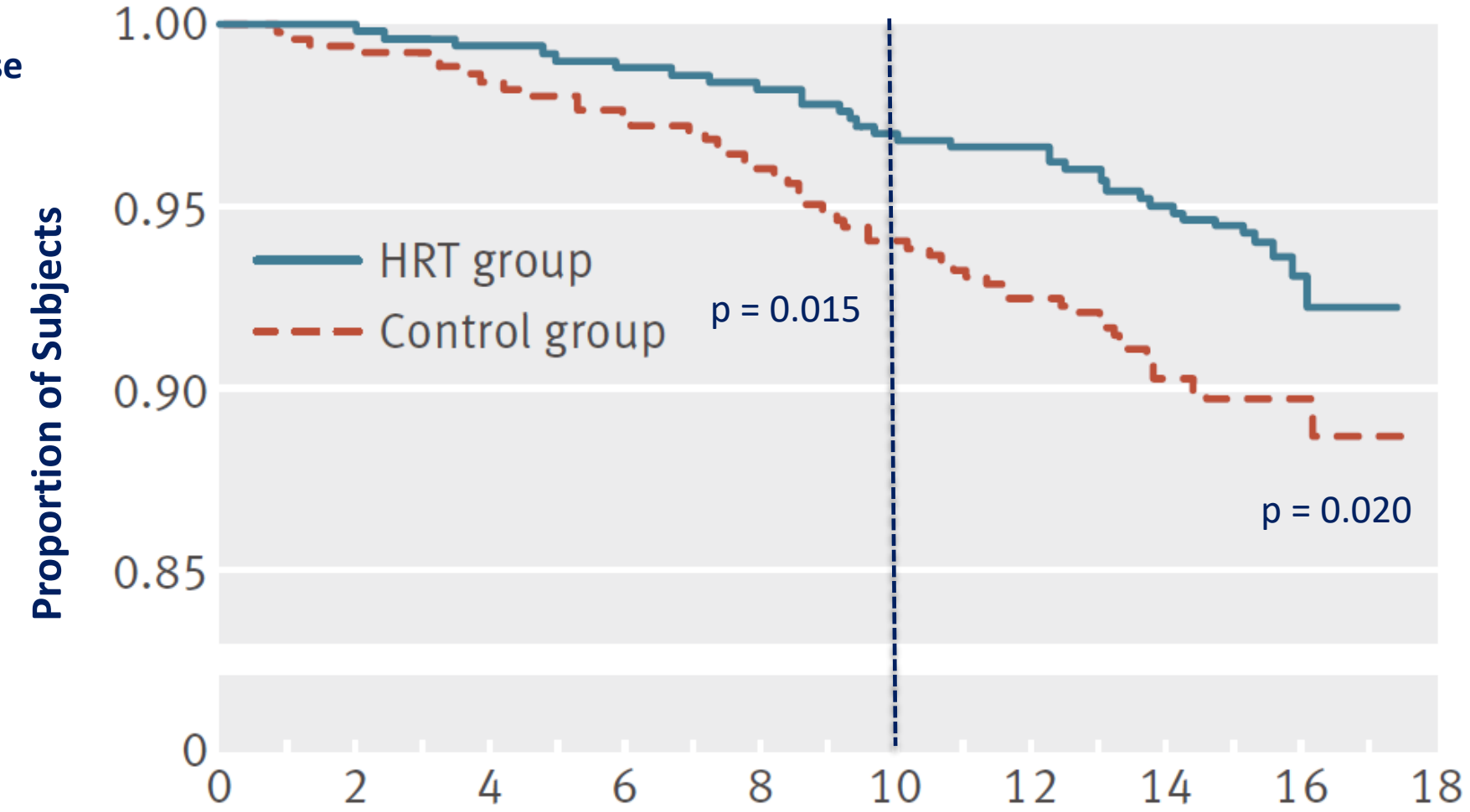

>10 years since menopause, >60 years old

<10 years since menopause, <60 years old

Boardman HMP, et al. *Cochrane Database of Systemic Reviews* 2015, Issue 3:CD002229. DOI: 10.1002/14651858.CD002229.pub4.

# DOPS Cardiovascular Disease Outcome

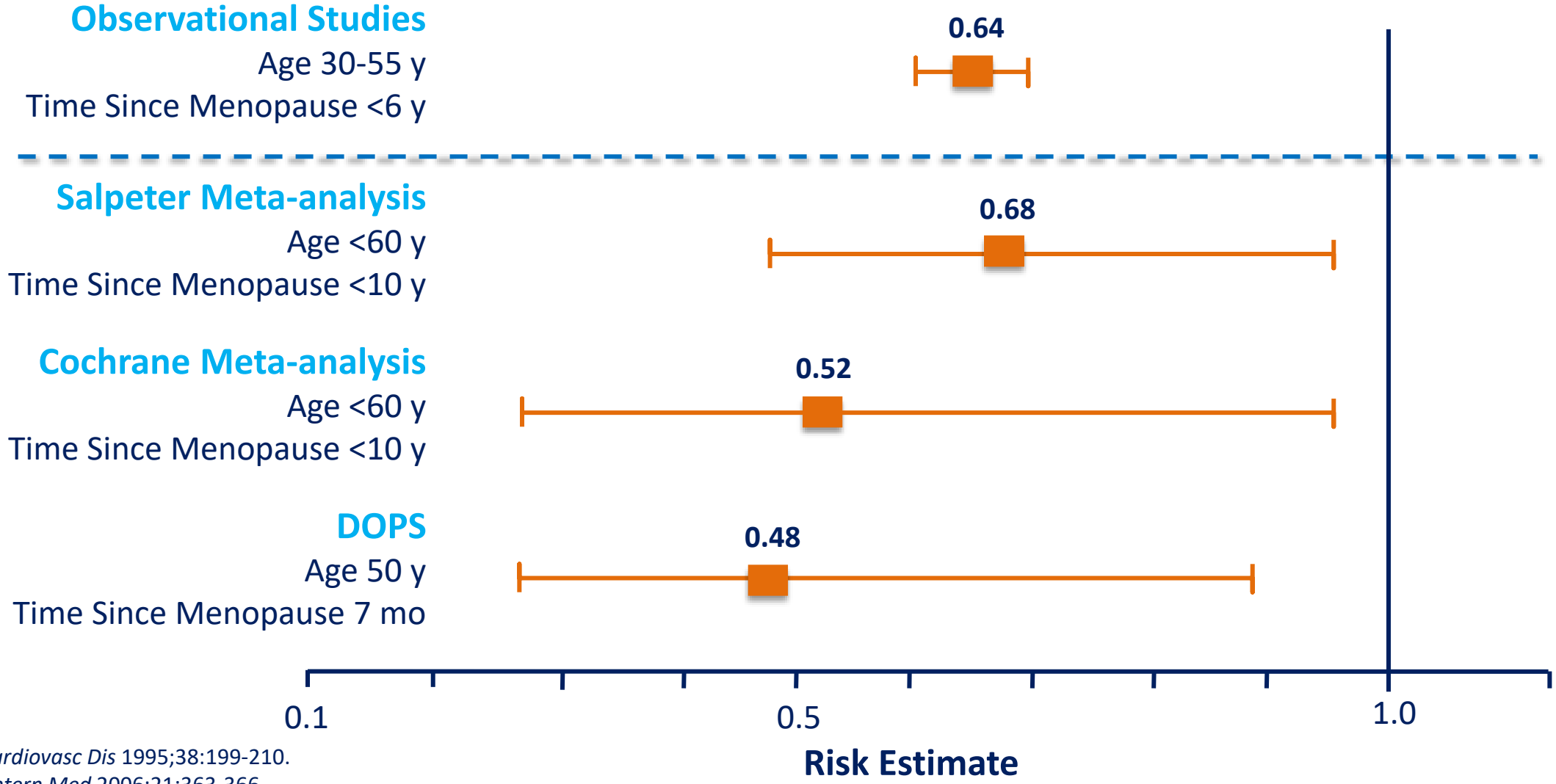
**7 months = mean time from menopause**
**50 years = mean age**
**25.2 kg/m$^2$ = mean BMI**




| 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.

# Relative Risk of CHD
# Observational Studies and Randomized Trials



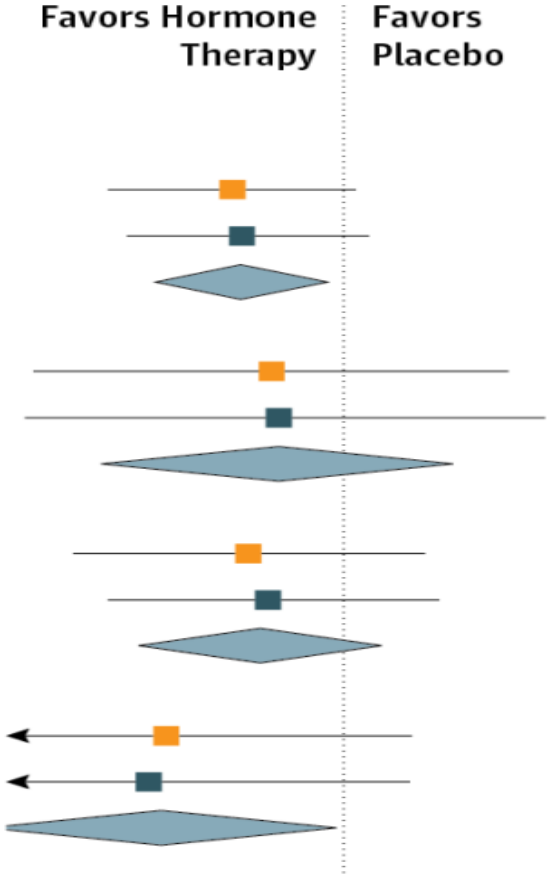


Grodstein F, et al. *Prog Cardiovasc Dis* 1995;38:199-210.
Salpeter SR, et al. *J Gen Intern Med* 2006;21:363-366.
Schierbeck LL, et al. *BMJ* 2012; 2012;3456:e6409.
Boardman HMP, et al. *Cochrane Database of Systemic Reviews* 2015, Issue 3:CD002229. DOI: 10.1002/14651858.CD002229.pub4.

# Mortality

# Mortality Outcomes During the WHI Intervention Phase in 50-59 Year Old Women at Randomization*

| Outcome by Age | No. of Deaths, Annualized Rates (%) | | HR (95% CI) | *P* Value (Trend by Age)[a] |
|---|---|---|---|---|
| | Hormone Therapy | Placebo | | |
| **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 |

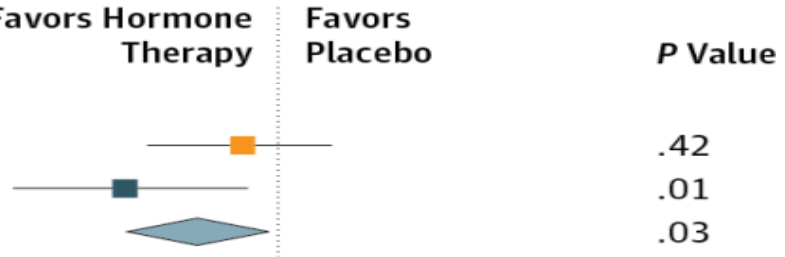



*Median 5.6 years [interquartile range, 4.9-6.5 years] of intervention in CEE + MPA trial
*Median 7.2 years [interquartile range, 6.5-8.2 years] of intervention in CEE trial
*Median 6.3 years [interquartile range, 5.3-7.3 years] of intervention in pooled analysis

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

# Alzheimer's Disease or Dementia Mortality During WHI 18-Year Cumulative Follow-up*

| End Points | No. of Deaths, Annualized Rates (%) Hormone Therapy | Placebo | HR (95% CI) | *P* Value |
|---|---|---|---|---|
| **Alzheimer's or dementia mortality** | | | | |
| CEE plus MPA vs placebo | 223 (0.16) | 233 (0.17) | 0.93 (0.77-1.11) | .42 |
| CEE alone | 127 (0.15) | 175 (0.20) | 0.74 (0.59-0.94) | .01 |
| Pooled trials | | | 0.85 (0.74-0.98) | .03 |

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

# All-Cause Mortality in Women Initiating Hormone Therapy before Age 60 Years and/or within 10 Years of Menopause

| Studies | Age; Time-Since-Menopause | Therapy | % Reduction (Risk Ratio; 95% Confidence Interval) |
|---|---|---|---|
| DOPS, 10 year[1] | 50 yrs; 7 mo-s-m | E2+NETA sequential and E2 alone | ↓ 43% (0.57; 0.30-1.08) |
| DOPS, 16 year[1] | | | ↓ 34% (0.66; 0.41-1.08) |
| WHI-E, 11-year[2] | <60 yrs | CEE alone | ↓ 27% (0.73; 0.53-1.00) |
| WHI-E, 13-year[3] | <10 yrs-s-m | CEE alone | ↓ 36% (0.64; 0.33-1.25) |
| WHI-E, 13-year[3] | <10 yrs-s-m | CEE+MPA continuous | ↓ 21% (0.79; 0.52-1.21) |
| WHI-E, 13-year[3] | <60 yrs | CEE alone | ↓ 22% (0.78; 0.59-1.03) |
| WHI-E+P, 13-year[3] | <60 yrs | CEE+MPA continuous | ↓ 12% (0.88; 0.70-1.11) |
| WHI-E[4] | <10 yrs-s-m | CEE alone | ↓ 35% (0.65; 0.33-1.29) |
| WHI-E+P[4] | <10 yrs-s-m | CEE+MPA continuous | ↓ 19% (0.81; 0.52-1.24) |
| WHI-E/E+P[4] | <10 yrs-s-m | CEE and CEE+MPA | ↓ 24% (0.76; 0.53-1.09) |
| WHI-E[4] | <60 yrs | CEE alone | ↓ 29% (0.71; 0.46-1.11) |
| WHI-E+P[4] | <60 yrs | CEE+MPA continuous | ↓ 31% (0.69; 0.44-1.07) |
| WHI-E/E+P[4] | <60 yrs | CEE and CEE+MPA | ↓ 30% (0.70; 0.51-0.96) |
| Meta-analysis[5] | 54 yrs | HT | ↓ 39% (0.61; 0.39-0.95) |
| Bayesian meta-analysis[6] | 55 yrs | HT | ↓ 27% (0.73; 0.52-0.96) |
| Cochrane meta-analysis[7] | <10 yrs-s-m | HT | ↓ 30% (0.70; 0.52-0.95) |
| Observational studies[8,9] | 30-55 yrs; <5 yrs-s-m | HT | ↓ 20-60% |

**WHI-E=1,530 & WHI-E+P=1,298 women with pre-existing cardiovascular disease**

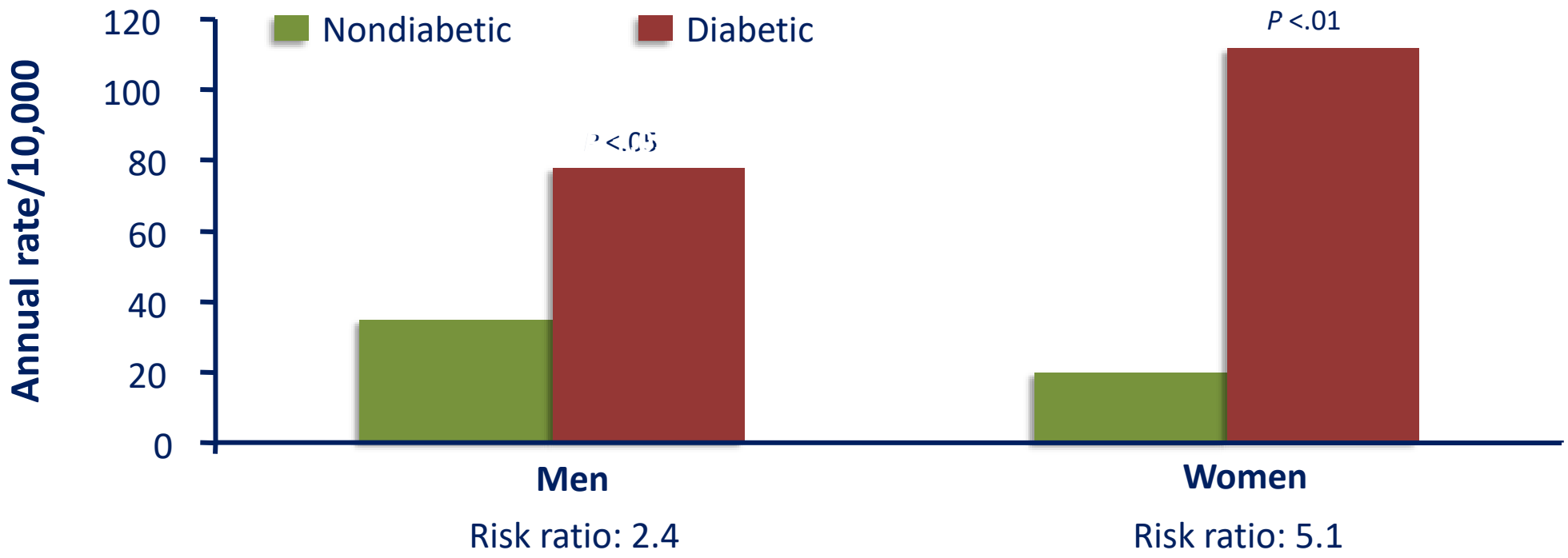
Hodis HN, et al. *J Steroid Biochem Mol Biol* 2014;142:68-75.

mo-s-m = months-since-menopause
yrs-s-m = years-since-menopause


[1] Schierbeck LL, et al. *BMJ* 2012;3456:e6409.
[2] LaCroix AZ, et al. *JAMA* 2011;305:1305-1314.
[3] Manson JE, et al. *JAMA* 2013;310:1353-1368.
[4] Rossouw JE, et al. *JAMA* 2007;297:1465-1477.
[5] Salpeter SR, et al. *J Gen Intern Med* 2004;19:791-804
[6] Salpeter SR, et al. *Am J Med* 2009;122:1016-1022.
[7] Boardman HMP, et al. *Cochrane Database of Systemic Reviews* 2015, Issue 3: CD002229. DOI: 10.1002/14651858.CD002229.pub4.
[8] Grodstein F, et al. *Prog Cardiol Dis* 1995;38:199-210.
[9] Grodstein F, et al. *Maturitas* 1998;30:19-26.

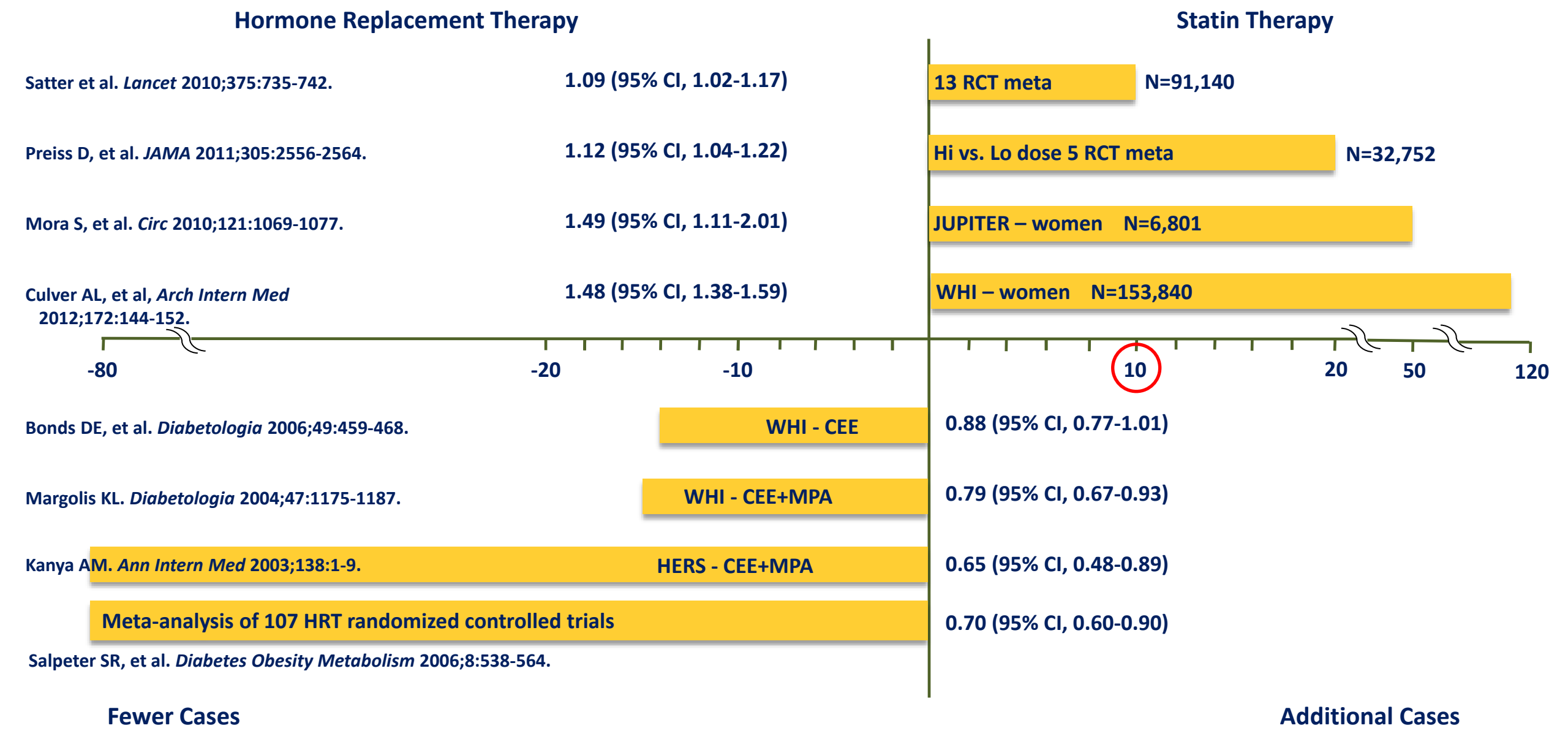
# Age-Adjusted Risk of CHD for Men and Women Ages 45-74 Years by Diabetic Status

## Framingham 18-Year Follow-up



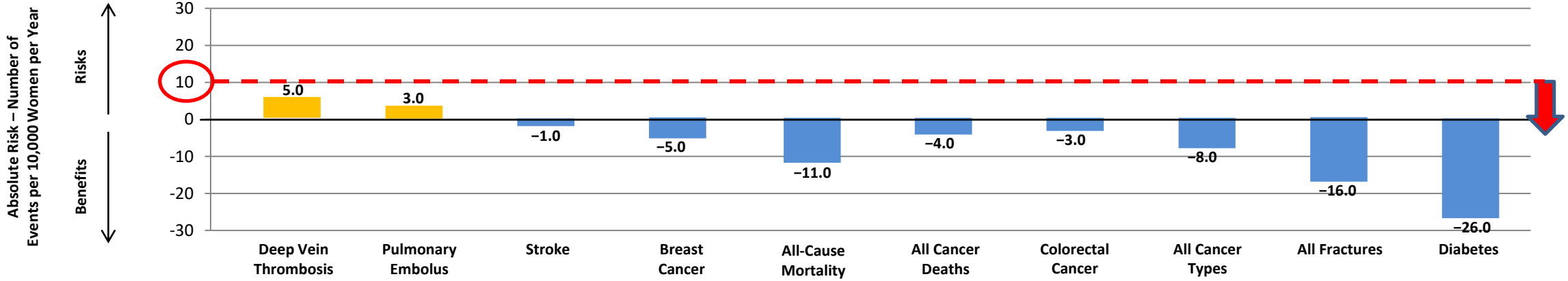

Kannel WB. *Am Heart J* 1985;110:1100-1107.

# Absolute Number (Difference from Placebo) of New Onset Diabetes Mellitus Cases per 10,000 Persons per Year of HRT or Statin Therapy

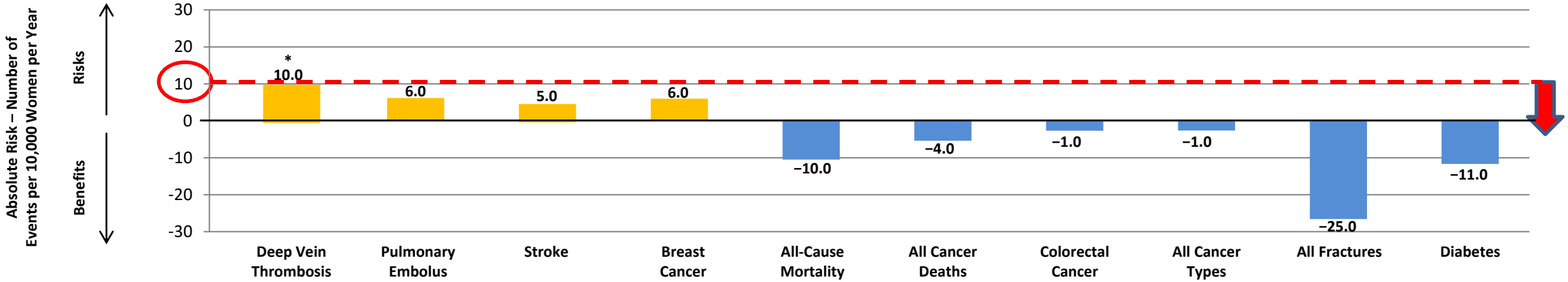


# Absolute Benefits and Risks from WHI – Initiation of HT in Women 50-59 Years of Age: Number of Events per 10,000 Women per Year

## CE Alone Trial




## CE + MPA Trial




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

# Conclusion

- **CVD is the number 1 cause of death in women.**
- **Postmenopausal women are at an increased risk for CVD.**
- **Menopausal HRT is a cost-effective sex-specific therapy that reduces all-cause mortality (including CVD, cancer, dementia/AD), CHD, bone fracture, and new onset diabetes mellitus with rare risks when initiated around the time of menopause.**
- **Benefits of menopausal HRT outweigh risks when initiated around the time of menopause.**

**<u>Many Unanswered Questions – Future Directions</u>**

**TSEC therapy – Advancing Postmenopausal Prevention Therapy – NIA**

Hodis HN, Mack WJ. *Cancer J* 2022;28:208-223.

*Cancer J* 2022;28:208-223.

REVIEW ARTICLE

# Menopausal Hormone Replacement Therapy and Reduction of All-Cause Mortality and Cardiovascular Disease

## *It Is About Time and Timing*

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**Abstract:** The totality of evidence indicates menopausal hormone replacement therapy (HRT) effects are determined by timing of initiation according to age and/or time since menopause, underlying health of target tissue, and duration of therapy. Initiated in women at younger than 60 years and/or at or near menopause, HRT significantly reduces all-cause mortality and cardiovascular disease (CVD), whereas other primary CVD prevention therapies such as lipid-lowering fail to do so. The magnitude and type of HRT-associated risks, including breast cancer, stroke, and venous thromboembolism, are rare (<10 events/10,000 women), not unique to HRT, and comparable with other medications. Hormone replacement therapy is a sex-specific and time-dependent primary CVD prevention therapy that concomitantly reduces all-cause mortality, as well as other aging-related diseases with an excellent risk profile. Keeping in mind that prevention strategies must be personalized, health care providers and patients can use cumulated HRT data in making clinical decisions concerning chronic disease prevention including CVD and mortality reduction.

**Key Words:** All-cause mortality, cardiovascular disease, estrogen, hormone replacement therapy, menopause, meta-analysis, observational studies, prevention, randomized trials

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Pathophysiologically, incidence of CHD in women lags behind men by 10 years, and incidence of MI and sudden death in women lags behind men by 20 years.[1] This delay in onset of CVD seems to be due to the cardioprotective effects of endogenous estrogen where women exhibit 2 patterns of cardiovascular risk during their life span. Whereas premenopausal women are protected from clinical manifestations of CVD relative to men, after menopause CVD complications exceed those of men. Although there is an age-associated increase in CVD incidence for women as there is for men, age-specific CVD incidence is 2- to 6-fold greater for postmenopausal than premenopausal women across the age range <40 to 54 years (Fig. 1).[4]

Development of substantial CVD risk after menopause provides a window of opportunity for extension of cardioprotection from endogenous estrogen in postmenopausal women with hormone replacement therapy (HRT) as a sex-specific primary preventive therapy for CVD and reduction of all-cause mortality.

## THE PREMISE OF THE TIMING HYPOTHESIS

The "timing hypothesis" posits that the effects of menopausal HRT on atherosclerosis and clinical events are dependent on when HRT is initiated in relation to age and/or menopause. The