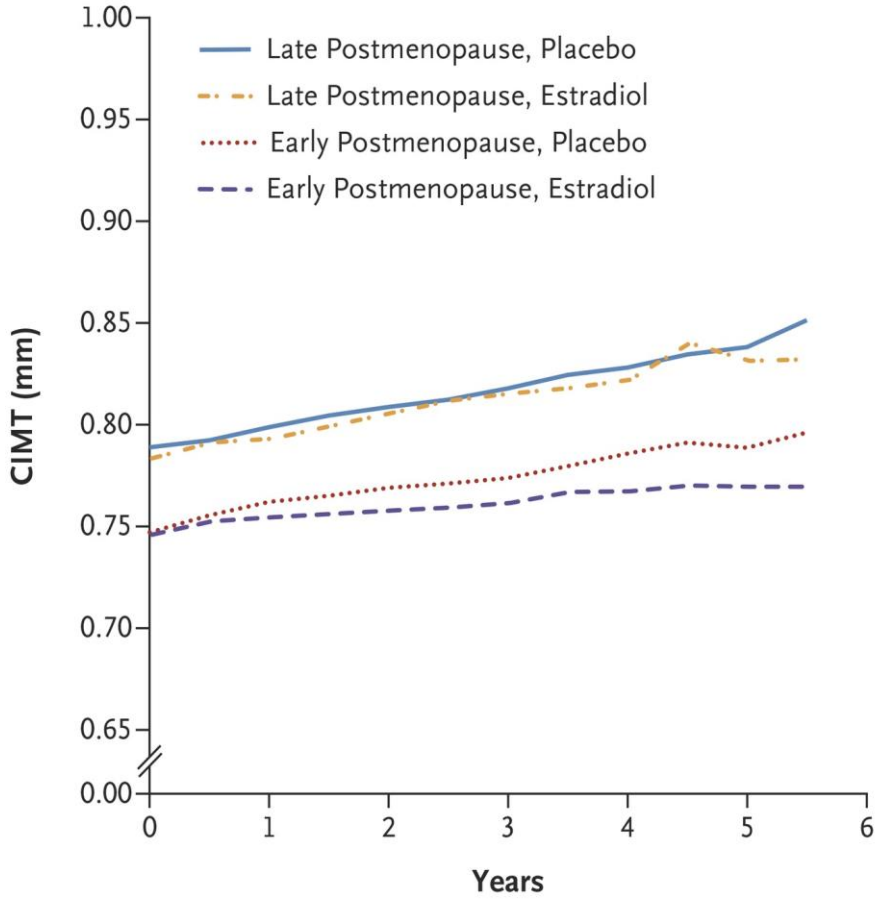
Original Article

# Vascular Effects of Early versus Late Postmenopausal Treatment with Estradiol

Howard N. Hodis, M.D., Wendy J. Mack, Ph.D., Victor W. Henderson, M.D., Donna Shoupe, M.D., Matthew J. Budoff, M.D., Juliana Hwang-Levine, Pharm.D., Yanjie Li, M.D., Mei Feng, M.D., Laurie Dustin, M.S., Naoko Kono, M.P.H., Frank Z. Stanczyk, Ph.D., Robert H. Selzer, M.S., Stanley P. Azen, Ph.D., for the ELITE Research Group

N Engl J Med
Volume 374(13):1221-1231
March 31, 2016

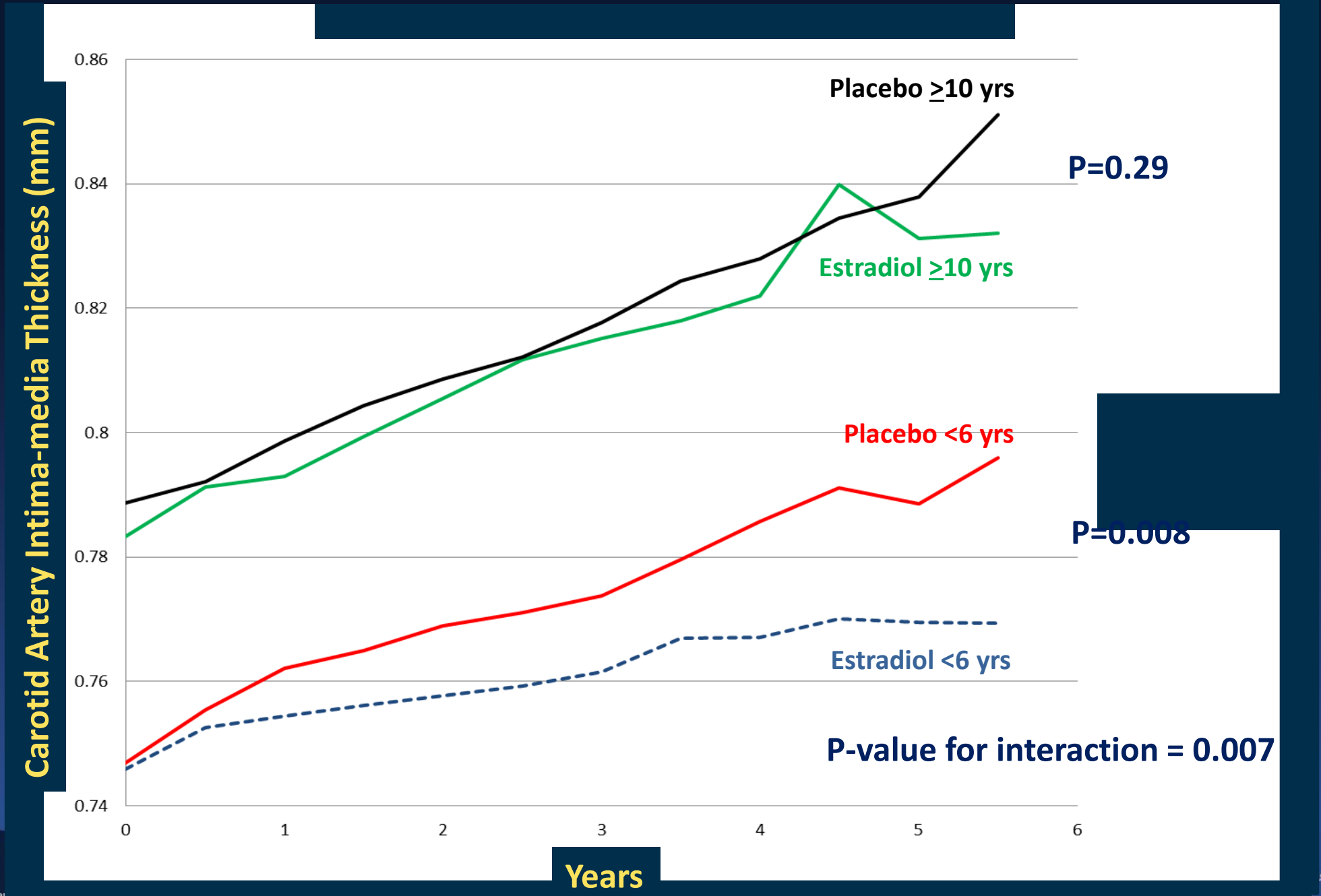
# CIMT Progression According to Study Group and Postmenopause Stratum.




| No. of Participants | | | | | | | |
|---|---|---|---|---|---|---|---|
| With CIMT data | 643 | 533 | 522 | 515 | 424 | 295 | 56 |
| Who completed or discontinued study | 0 | 106 | 119 | 128 | 215 | 345 | 582 |
| Without CIMT data | 0 | 4 | 2 | 0 | 4 | 3 | 5 |

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

# CIMT by Treatment and Postmenopausal Strata




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

NewYork-Presbyterian

# Conclusions

Oral estradiol therapy was associated with less progression of subclinical atherosclerosis (measured as CIMT) than was placebo when therapy was initiated within 6 years after menopause but not when it was initiated 10 or more years after menopause.

Estradiol had no significant effect on cardiac CT measures of atherosclerosis in either postmenopause stratum.

# J Am Coll Cardiol Img 2017

## Impact of Exercise on the Relationship Between CAC Scores and All-Cause Mortality

Yoav Arnson, MD,[a,b] Alan Rozanski, MD,[c] Heidi Gransar, MS,[a,b] Sean W. Hayes, MD,[a,b] John D. Friedman, MD,[a,b] Louise E.J. Thomson, MBChB,[a,b] Daniel S. Berman, MD[a,b]

# CONCLUSIONS

In asymptomatic patients, self-reported exercise is a significant predictor of long-term outcomes. Prognostic value of the reported exercise is additive to the increasing degree of underlying atherosclerosis. Among patients with high CAC scores, exercise may play a protective role, whereas reported minimal or no exercise substantially increases clinical risk.

J Am Coll Cardiol Img 2017

# J Am Geriatr Soc 2017;65:200-6

DRUGS AND PHARMACOLOGY

## Long-Term Hormone Replacement Therapy Is Associated with Low Coronary Artery Calcium Levels in a Cohort of Older Women: The Age, Gene/Environment Susceptibility—Reykjavik Study

*Adalsteinn Gudmundsson, MD,*[*†] *Thor Aspelund, PhD,*[†‡] *Gunnar Sigurdsson, MD, PhD,*[*†‡] *Tamara Harris, MD, MS,*[§] *Lenore J. Launer, PhD,*[§] *Vilmundur Gudnason, MD, PhD,*[†‡] *and Helgi Jonsson, MD, PhD*[*†]

# J Am Geriatr Soc 2017;65:200-6

**Long-term hormone replacement therapy is associated with low coronary artery calcium levels in a cohort of older women: the Age, Gene/Environment Susceptibility-Reykjavik Study.**

# J Am Geriatr Soc 2017;65:200-6

- Coronary calcium score is an established marker of atherosclerosis.
- The (AGES) population had longitudinal information on lifestyle, HRT use, risk factors, and calcium scoring with which to explore the association between HRT and coronary artery calcification (CAC).

# J Am Geriatr Soc 2017;65:200-6

- Large population-based cohort study
- OBSERVATIONAL STUDY
- older Icelandic women (ages 67-93)
- between 2002 and 2006, with follow up in the Icelandic Heart Association Registry.

# American College of Cardiology Annual Scientific Sessions "2017"

- Does Hormone Replacement Therapy Curb Atherosclerosis?
- New Imaging Study Opens Old Questions
- It's been 15 years since the Women's Health Initiative dashed hopes that HRT could keep CVD at bay.
- Now a CAC study reveals the following.

- Arnson and colleagues retrospectively analyzed medical records for 4,286 postmenopausal women with no symptoms of cardiovascular disease who had undergone CAC scanning at their institution between 1998 and 2012.
- 41% of patients were using HRT at the time of their CAC scan.
- 8.4 years of follow up

# RESULTS

- Women using HRT were younger, with less hypertension and diabetes, and had similar LDL cholesterol levels but higher HDL cholesterol levels than women not taking HRT.
- CAC scores were significantly lower in the HRT group (119.2 vs 322.2, $P < 0.001$), with significantly more women on HRT having CAC scores of 0 (HR 1.2; 95% CI 1.03-1.41).

# RESULTS

- Over the follow-up period, HRT usage was associated with lower mortality (5.8% vs 6.8%), even after controlling for age, cardiac risk factors, and CAC score (HR 0.7; 95% CI 0.49-0.98).
- "There have been randomized trials that have shown that there is no benefit in terms of cardiovascular events and there have been observational studies that have shown there is benefit, so it's a controversial area."

# Results

- In the current study Arnson and colleagues were able to stratify patients according to the amount of baseline plaque. This has never been done before.
- Women who started off with moderate-to-extensive amounts of coronary calcium, or coronary atherosclerosis, are the ones in whom the greatest benefit of HRT was observed.

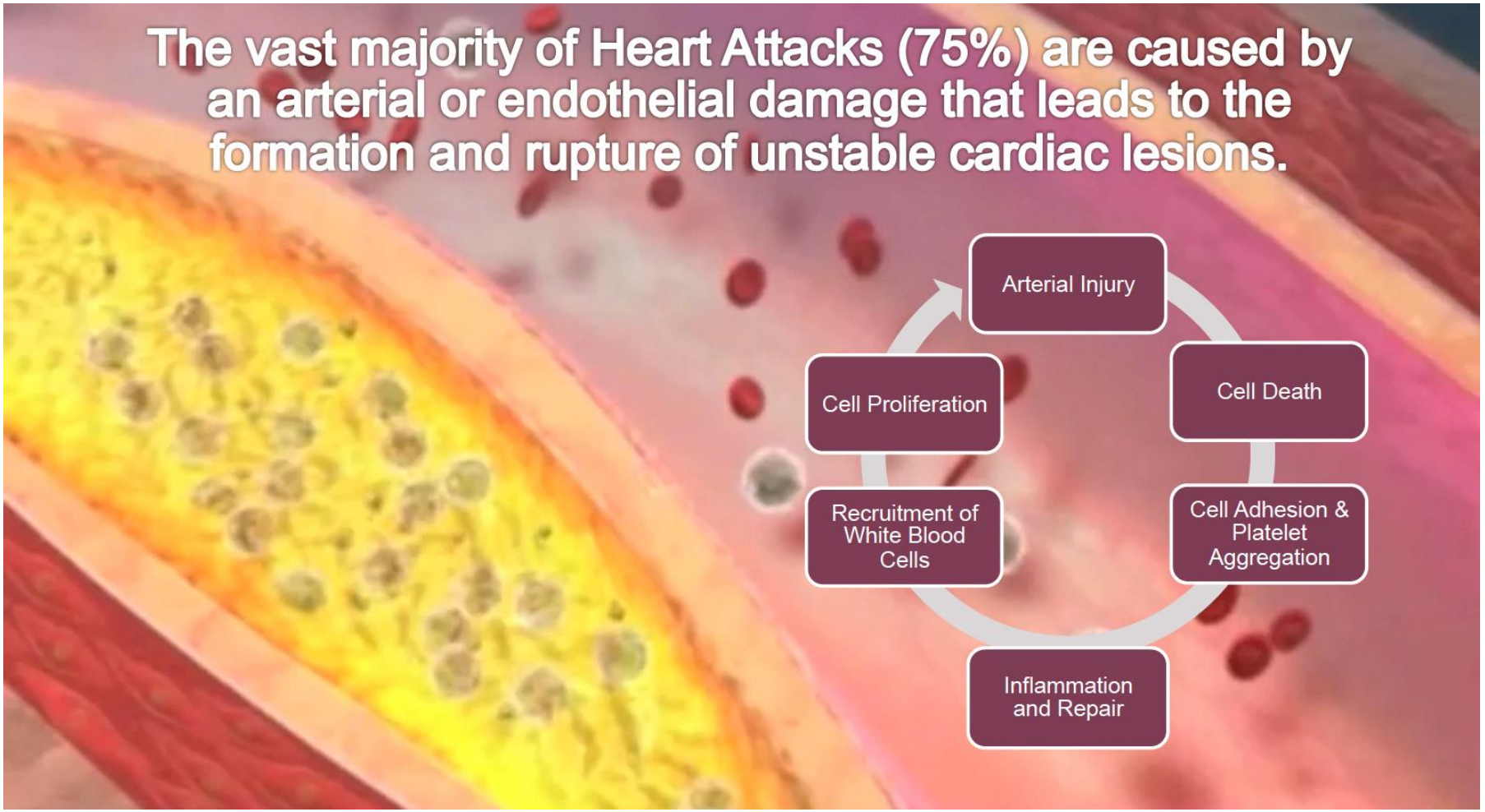
# Conclusion

- Similar to HRT, cumulated data indicate that over all ages, lipid-lowering therapy and aspirin have a null effect on the incidence of all-cause mortality and CHD in women.
- Data supporting the effectiveness of primary prevention of CHD with lipid-lowering therapy and aspirin is limited to men.
- However, data consistently support reduced all-cause mortality and CHD when HRT is initiated in women <60 years old and/or <10 years since menopause.
- HRT started in women in their 50's and continued for 15-30 years results in a significant gain of 1.5 quality adjusted life years (QALY) and is highly cost-effective

# Conclusion

- The magnitude and type of risks associated with HRT are less than or similar to other commonly used medications and therapies.
- HRT risks are rare and even more rare (<1/1,000 women per year of treatment) when initiated in women who are <60 years of age and/or <10 years since menopause.
- On the other hand, HRT reduces all-cause mortality, CHD and new onset diabetes mellitus.
- In addition, HRT significantly prevents bone fractures in an unselected population of women and is the only effective therapy for significantly reducing menopausal symptoms.

# New Biomarker Test to Evaluate Vulnerable plaques



# PULS

PULS™
CARDIAC TEST

## CONQUERING HEART DISEASE

PULS (Protein Unstable Lesion Signature)

- ✓ Quantifies Endothelial Damage
- ✓ Predicts ACS
- ✓ Improves Patient Care

# PULS

## 9 Proteins Are Signficant

*9 clinically-significant protein biomarkers measure the body's immune response to arterial or endothelial damage leading to unstable lesion formation and potential rupture.*

| PULS Biomarker | Relation to Arterial Damage & Unstable Cardiac Lesions |
|---|---|
| MCP-3 | Guides immune cell direction & activity |
| sFas | Prevents cell death |
| Fas Ligand | Initiates cell death and recycling |
| Eotaxin | Activates immune cells at areas of damage |
| CTACK | Helps clean up damaged tissue |
| IL-16 | Recruits & activates immune cells |
| HGF | Stimulates tissue and repair |
| HDL | Helps remove bad cholesterol |
| HbA1c | Diabetes marker |

# ADDITIONAL SLIDES

# Primary Prevention of CHD in Women

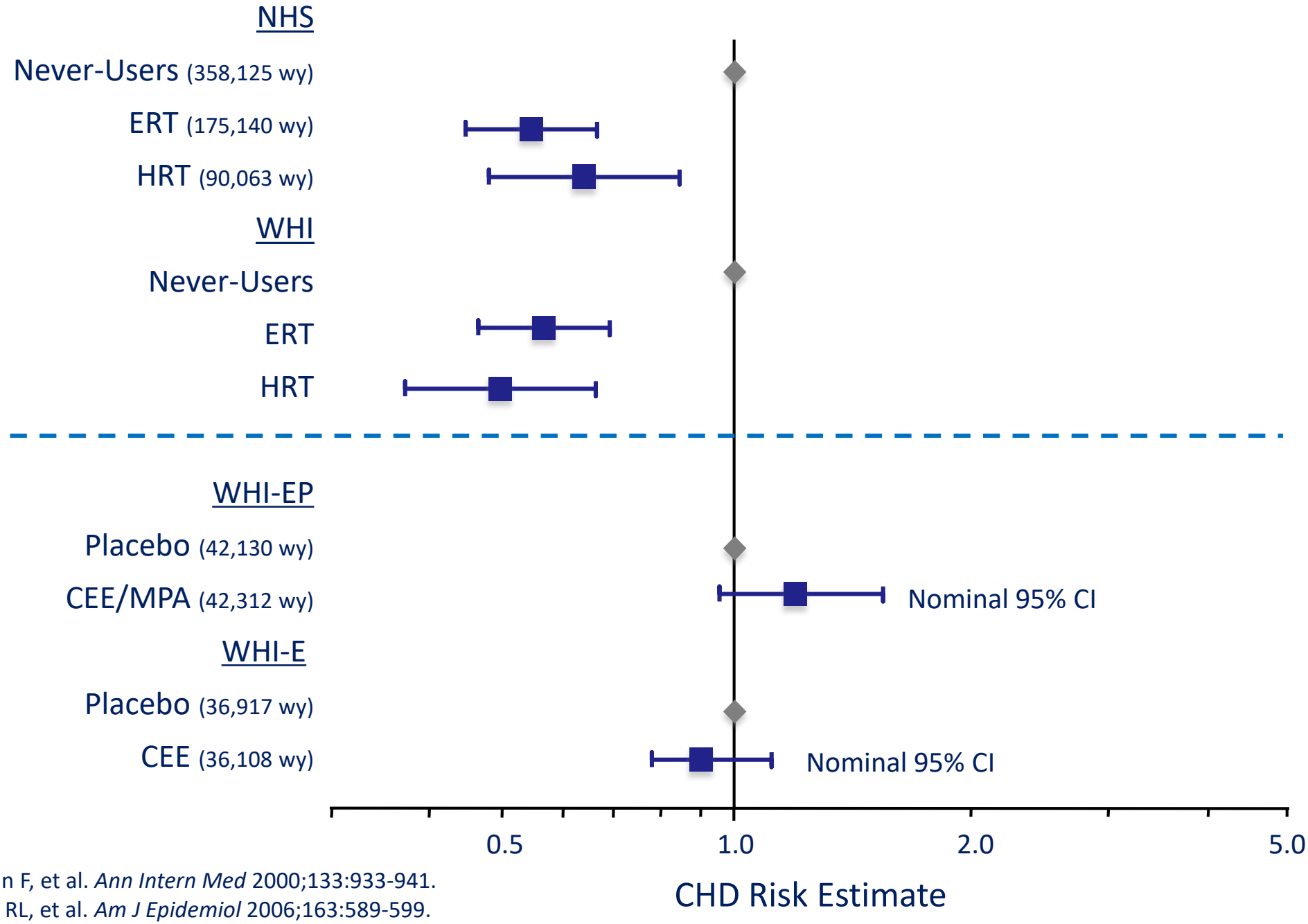
| Outcome | Hormone Therapy* | Lipid Lowering | Aspirin |
|---|---|---|---|
| CHD | **0.68 (0.48-0.96)** | 0.89 (0.69-1.09) | 1.01 (0.84-1.21) |
| | **0.52 (0.29-0.96)**‡ | 0.95 (0.78-1.16) | 0.91 (0.80-1.03) |
| | 0.79 (0.56-1.13) | | |
| Total Mortality | **0.61 (0.39-0.95)** | 0.95 (0.62-1.46) | 0.95 (0.85-1.06) |
| | **0.73 (0.52-0.96)** | 0.96 (0.81-1.13) | 0.95 (0.85-1.06) |
| | **0.70 (0.52-0.95)**‡ | 0.91 (0.76-1.08) | |
| QALY | 1.5 | 0.9 men with DM | |
| Cost per QALY | $2438 men with DM | $140,000 | |
| Breast Cancer per 1,000 women per year | -1.4 to 0.8 | -0.1 to 7.7 | |
| Incident Diabetes per 1,000 women per year | -8.1 to -1.4 | 5.0 to 11.7 | |

#Cost effectiveness ratios per QALY gained:
<$5,000 highly cost effective
<$50,000 worthwhile
>$100,000 unattractive

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


Hodis HN, et al. *Climacteric* 2012;15:217-228.
‡Cochrane Meta-analysis 2015
#Jacobs-van der Bruggen MAM, et al. *Cardiovas Prev Rehab* 2008;26:329-339.
#Ramsey SD, et al. *Pharmacoeconomics* 2008;26:329-339.
#Cohen DJ, et al. *J Am Coll Cardiol* 2008;52:2119-2126.

# 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.

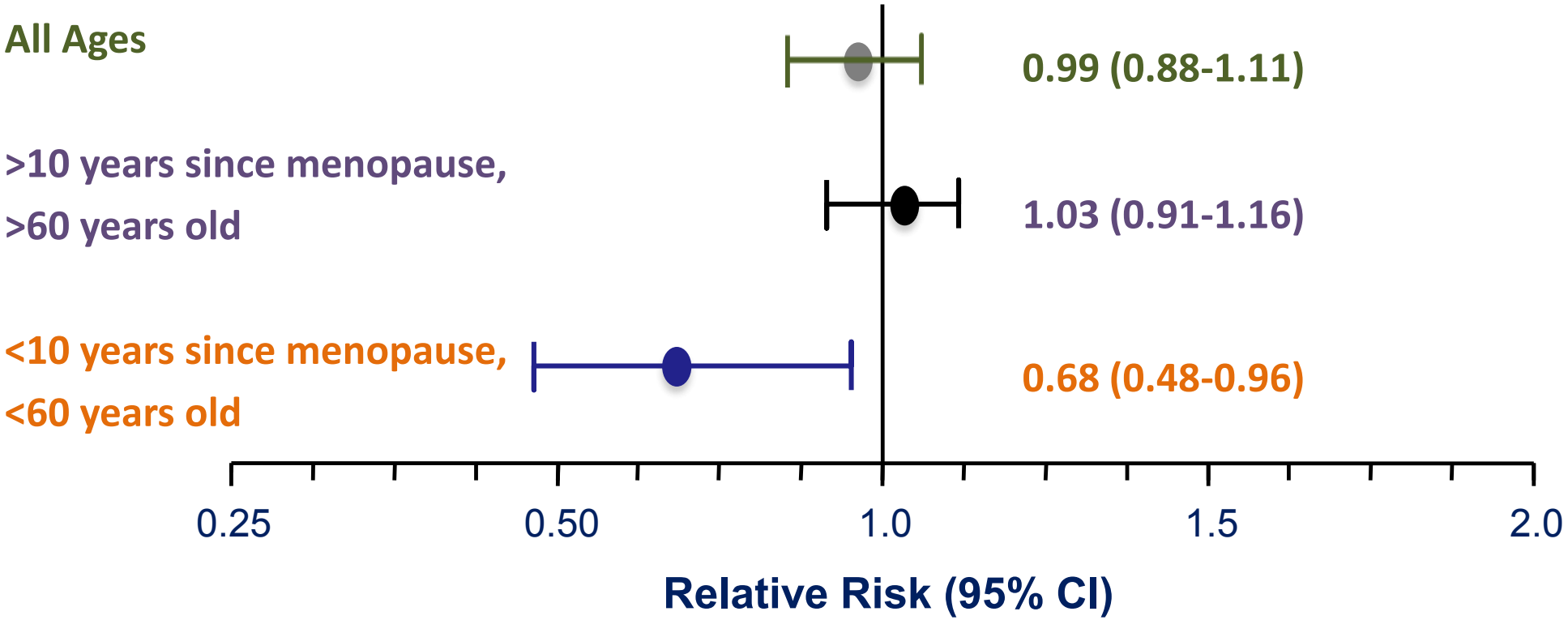
# Differences between Randomized Trials and Observational Studies

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

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

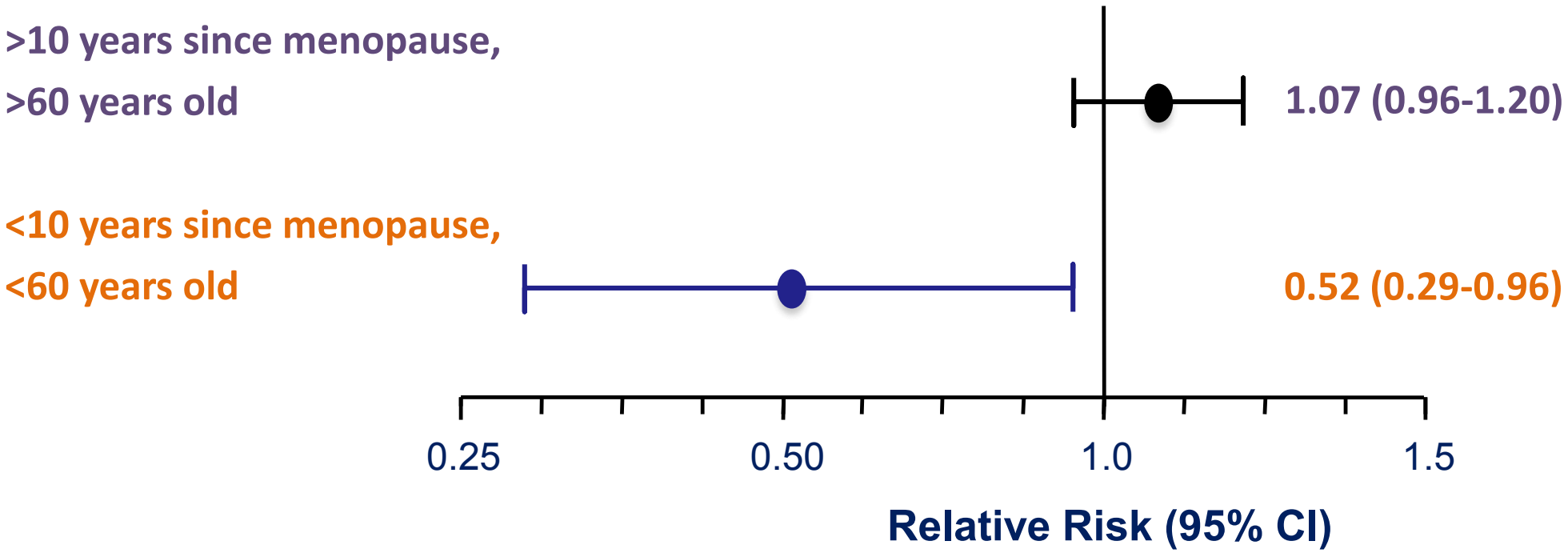
Hodis HN, et al. *Ann Intern Med* 2001;135:939-953.
Hodis HN, et al. *N Engl J Med* 2003;349:535-545.
Hodis HN, et al. *Clin Obstet Gynecol* 2008;51:564-586.

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



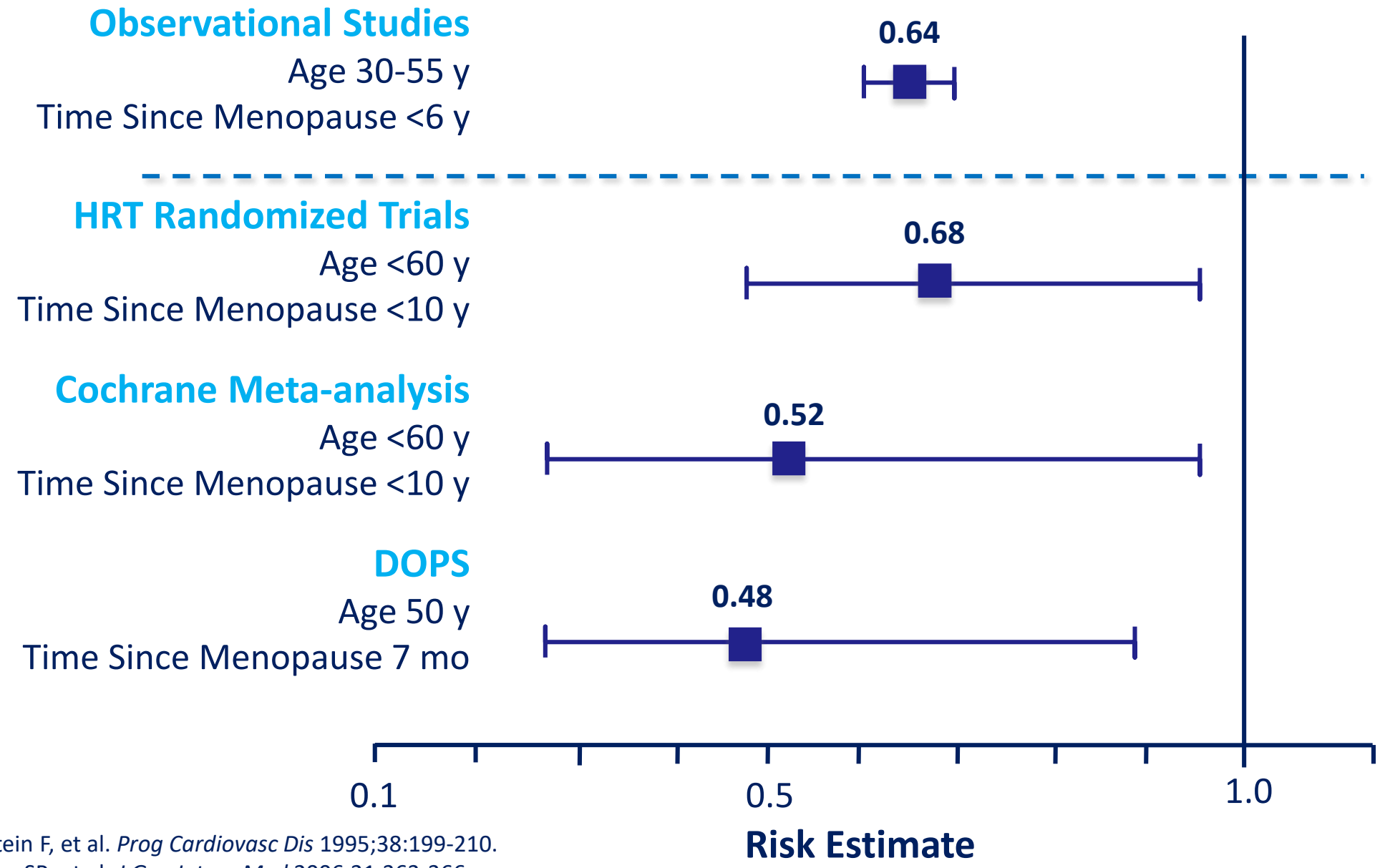

Salpeter SR, et al. *J Gen Intern Med* 2006;21:363-366.

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




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

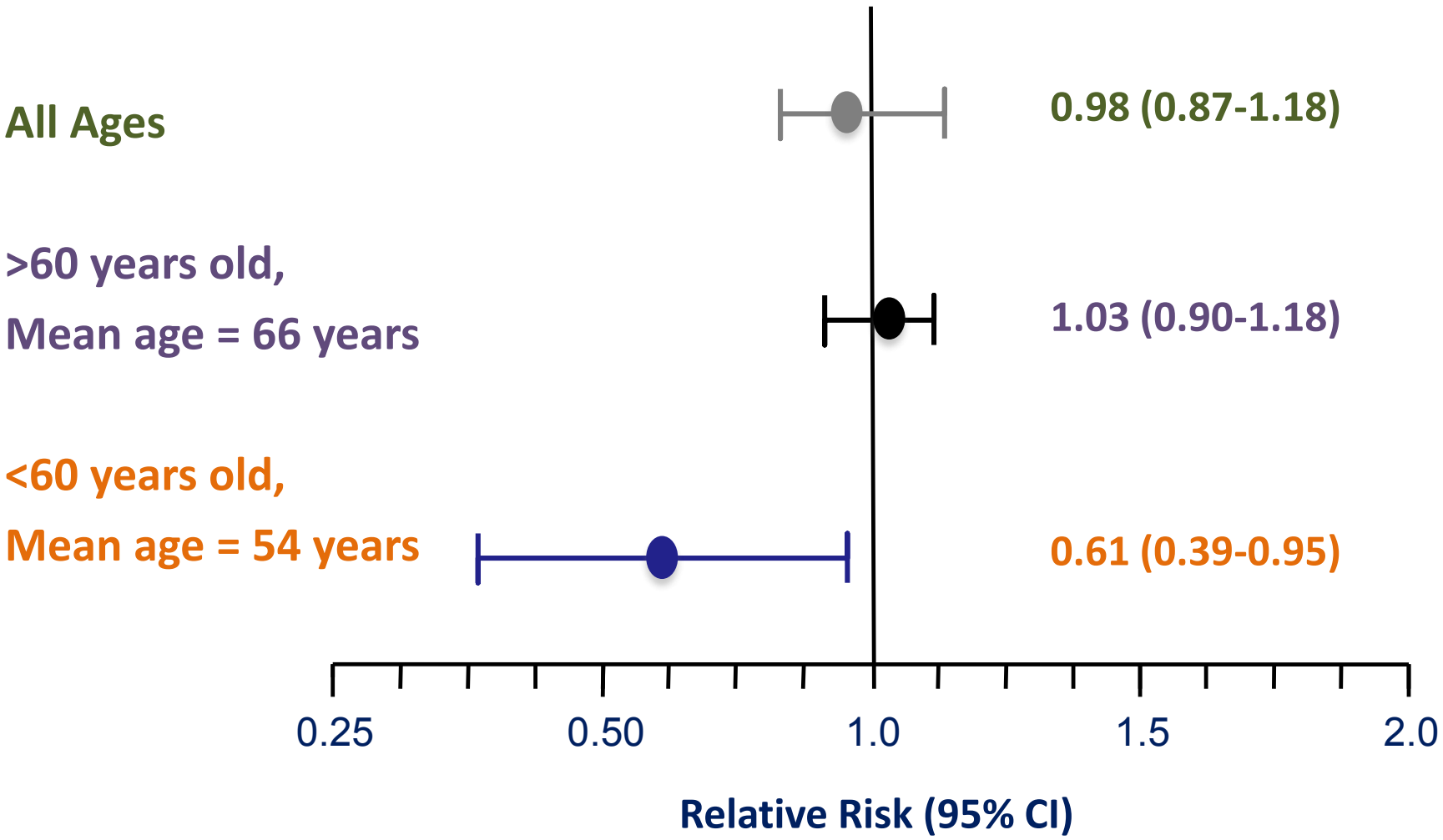
# Relative Risk of CHD: Observational Studies and Randomized Trials





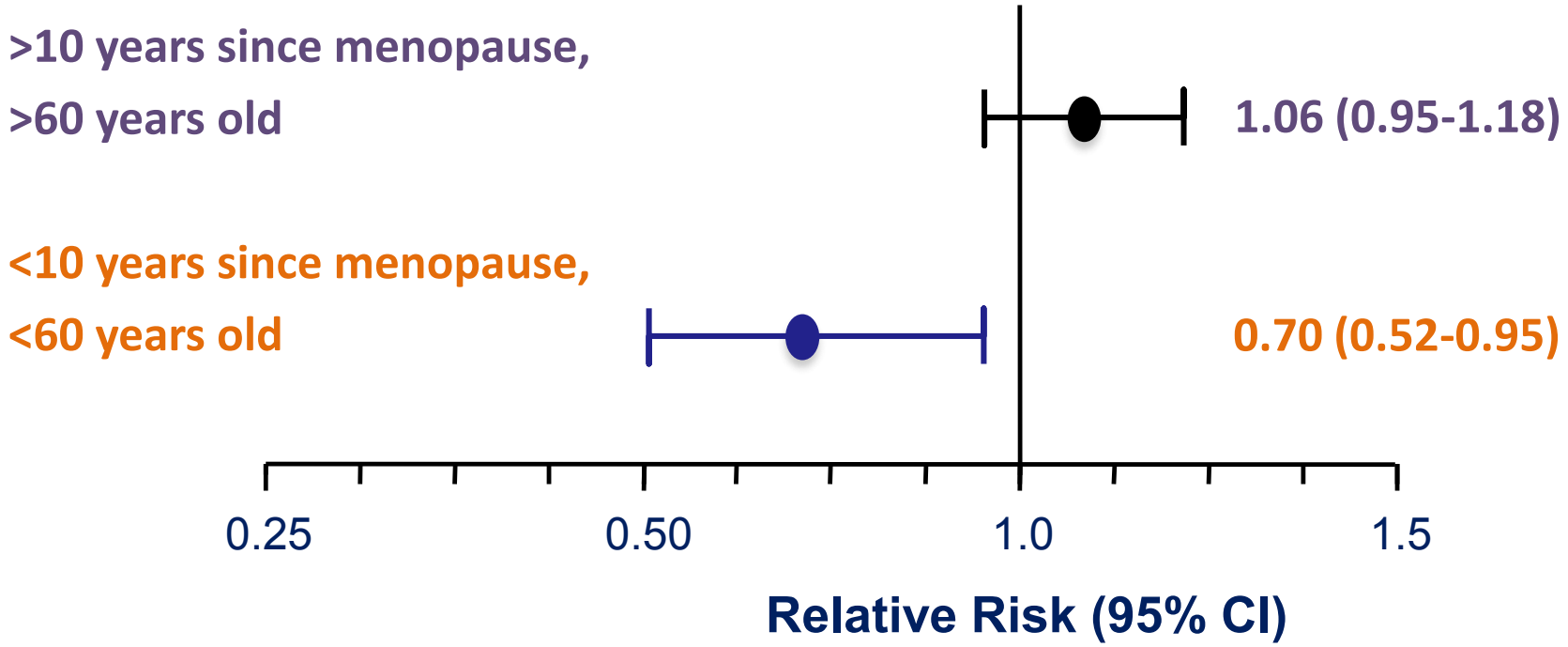
Grodstein F, et al. *Prog Cardiovasc Dis* 1995;38:199-210.
Salpeter SR, et al. *J Gen Intern Med* 2006;21:363-366.
Schierbeck LL, et al. *BMJ* 2012; 2012;3456:e6409.
Boardman HMP, et al. *Cochrane Database of Systemic Reviews* 2015, Issue 3:CD002229. DOI: 10.1002/14651858.CD002229.pub4.

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




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

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



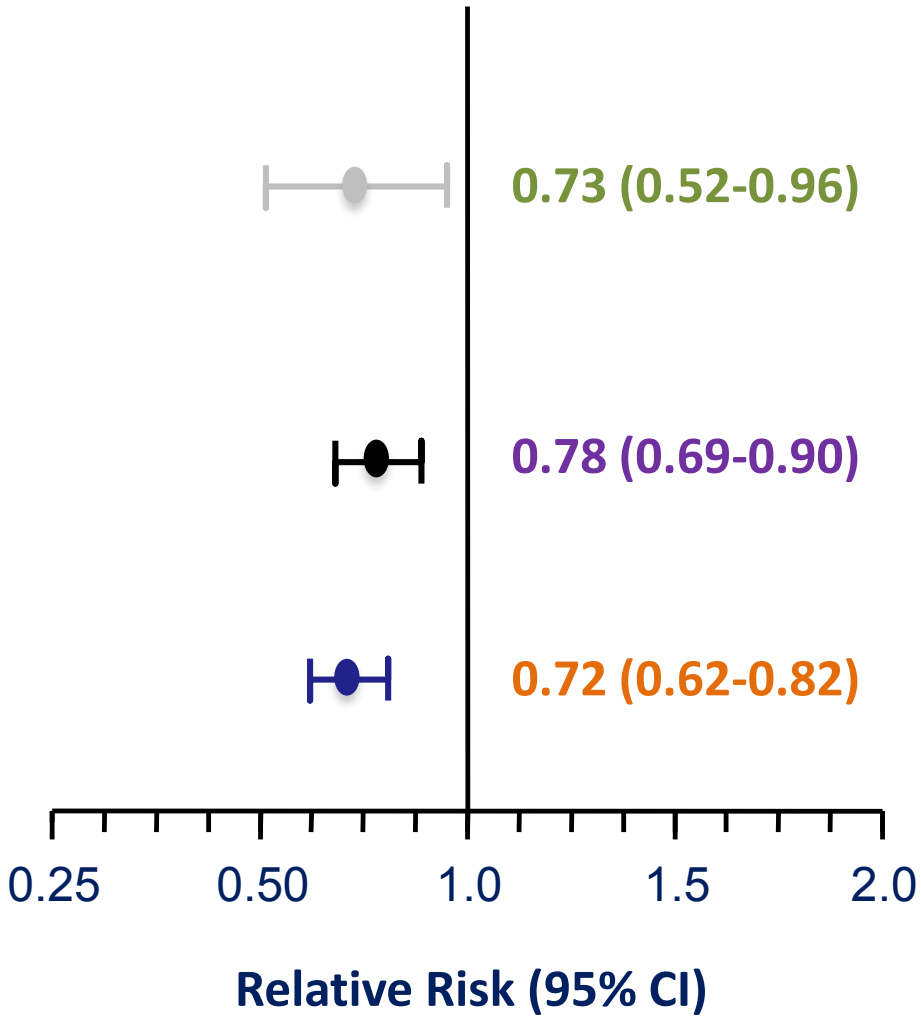

Boardman HMP, et al. *Cochrane Database of Systemic Reviews* 2015, Issue 3:CD002229. DOI: 10.1002/14651858.CD002229.pub4.

# Bayesian Meta-Analysis of HRT and All-Cause Mortality in Younger (mean age 54.5 years) Postmenopausal Women

**19 randomized controlled trials**
- 16,283 women
- 83,043 patient-years
- mean 5.1 years (1-6.8 years)

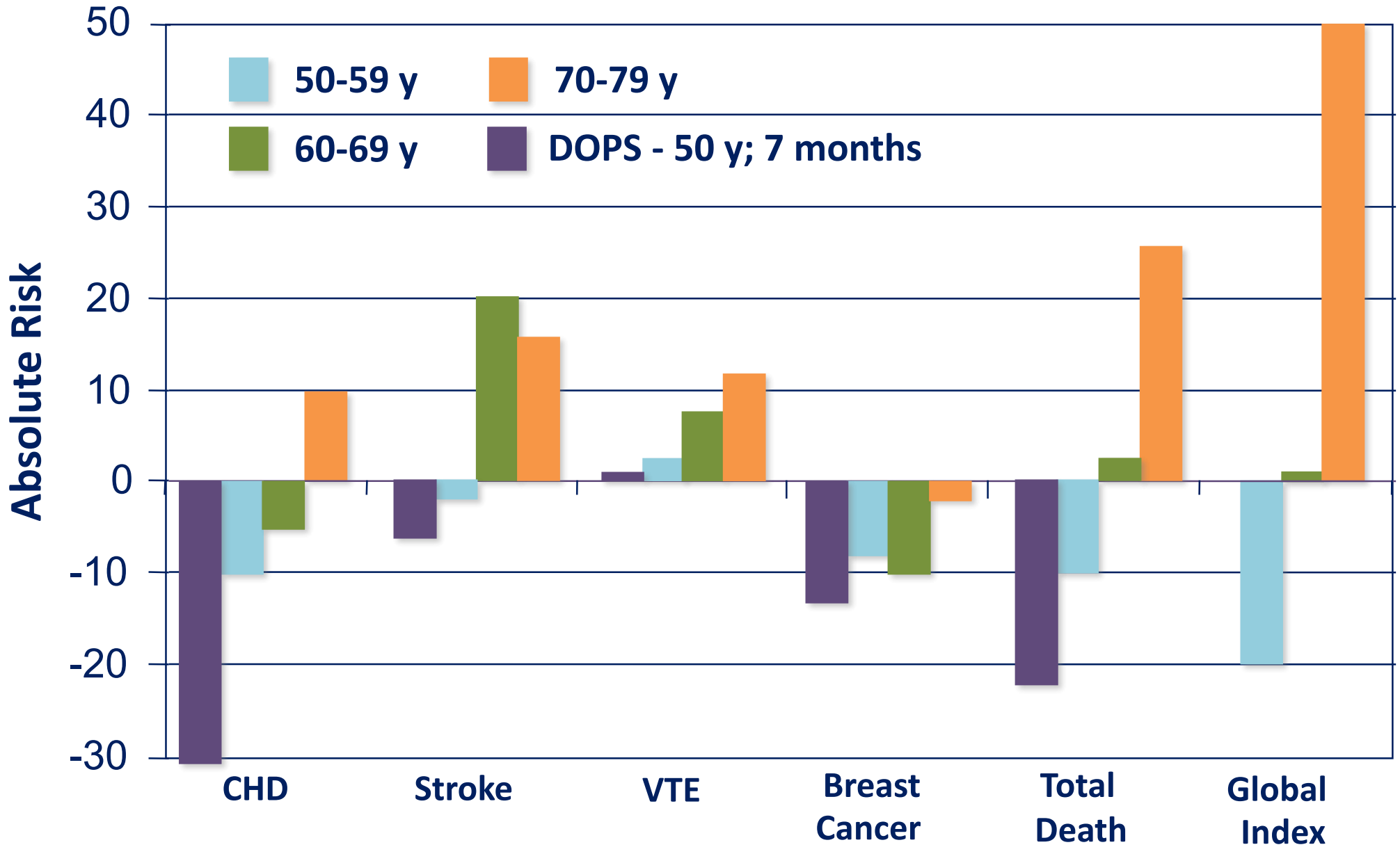
**8 prospective observational studies**
- 212,717 women
- 2,935,495 patient-years
- 13.8 years (6-22 years)

**Randomized controlled trials and observational studies combined**




Salpeter SR, et al. *Am J Med* 2009;122:1016-1022.

# Number of Events per 10,000 Women per Year of HT: WHI-E and DOPS





Rossouw JE, et al. *JAMA* 2007;297:1465-1477.

Writing Group for the Women's Health Initiative Investigators. *JAMA* 2004;291:1701-1712.

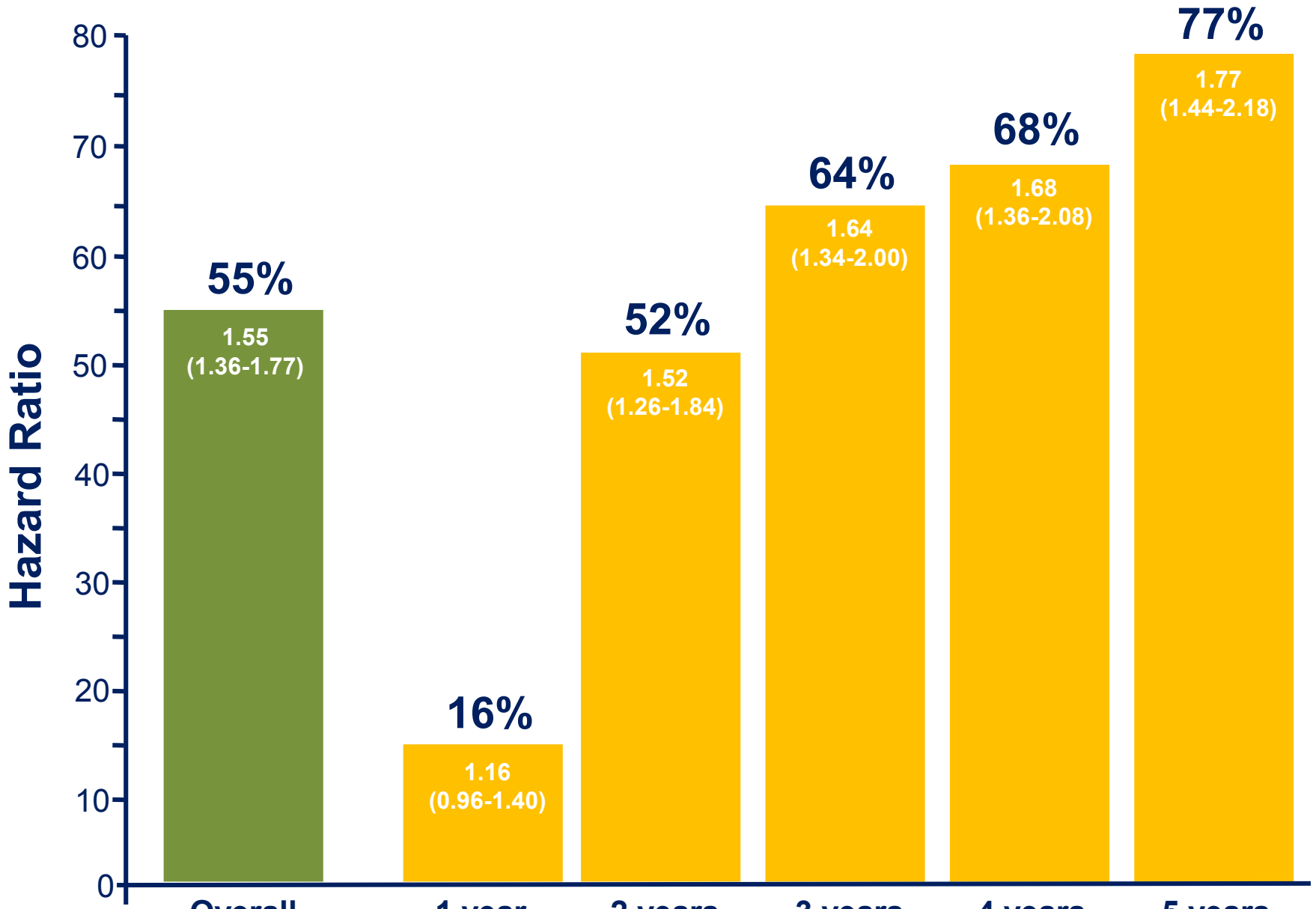
Schierbeck LL, et al. *BMJ* 2012;3456:e6409 .

# FDA Approved

- Menopausal symptoms – moderate to severe vasomotor symptoms and/or moderate to severe symptoms of vulvar and vaginal atrophy due to menopause.

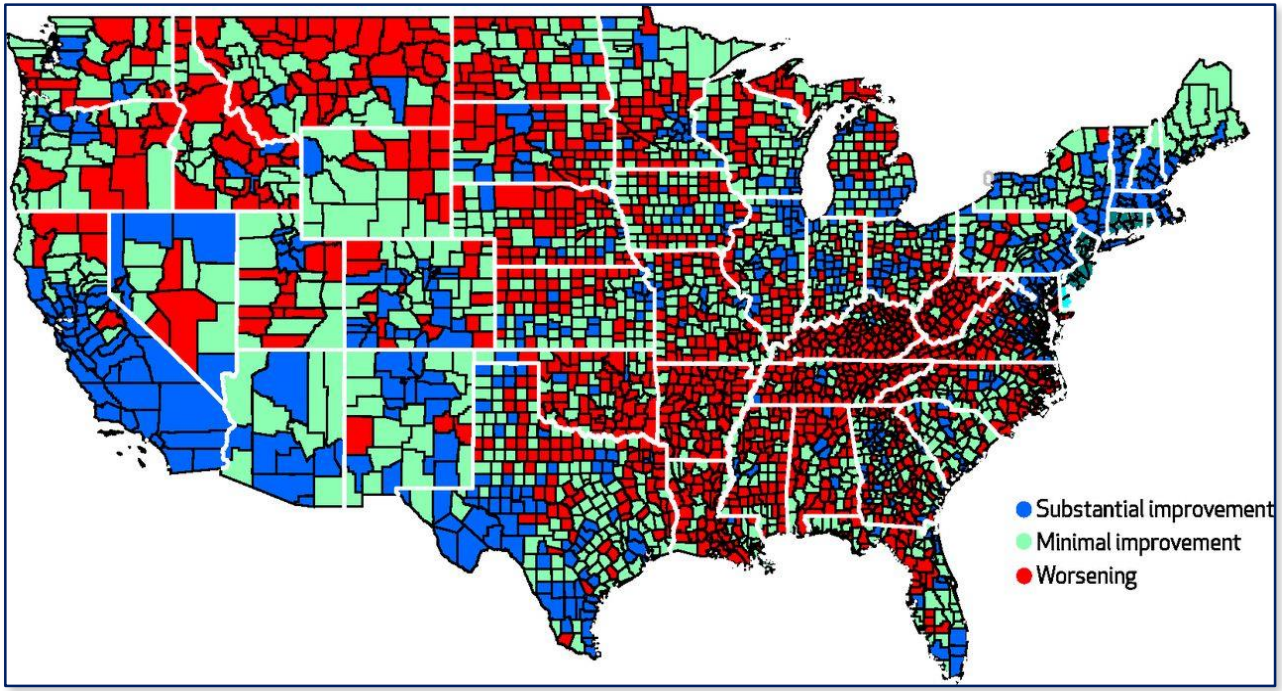
- Prevention of postmenopausal osteoporosis

# Hip Fracture in 80,955 Postmenopausal HMO Women after Cessation of HT: Longitudinal Observational Study 2002 to 2009



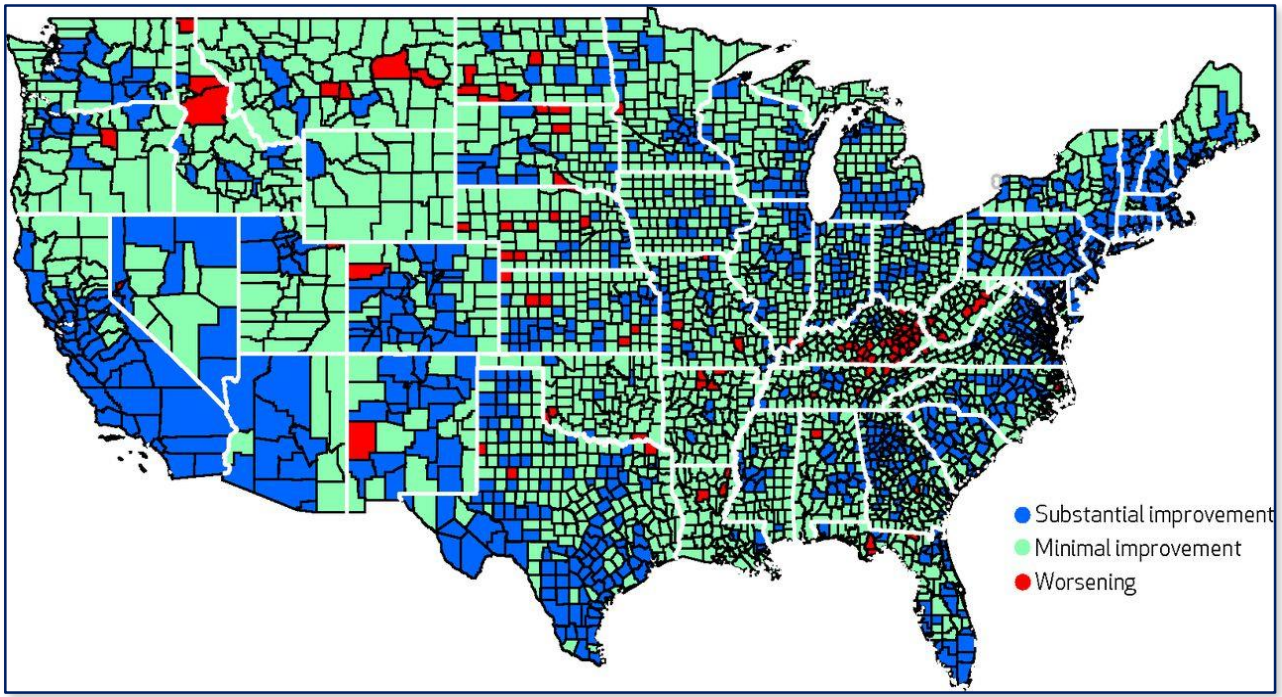

Karim R, et al. *Menopause* 2011;18:1172-1177.

# Change in Male and Female Mortality Rates From 1992–96 to 2002–06 in 3140 United States Counties




**Female**

**Mortality rate increased in 42.8% of counties**

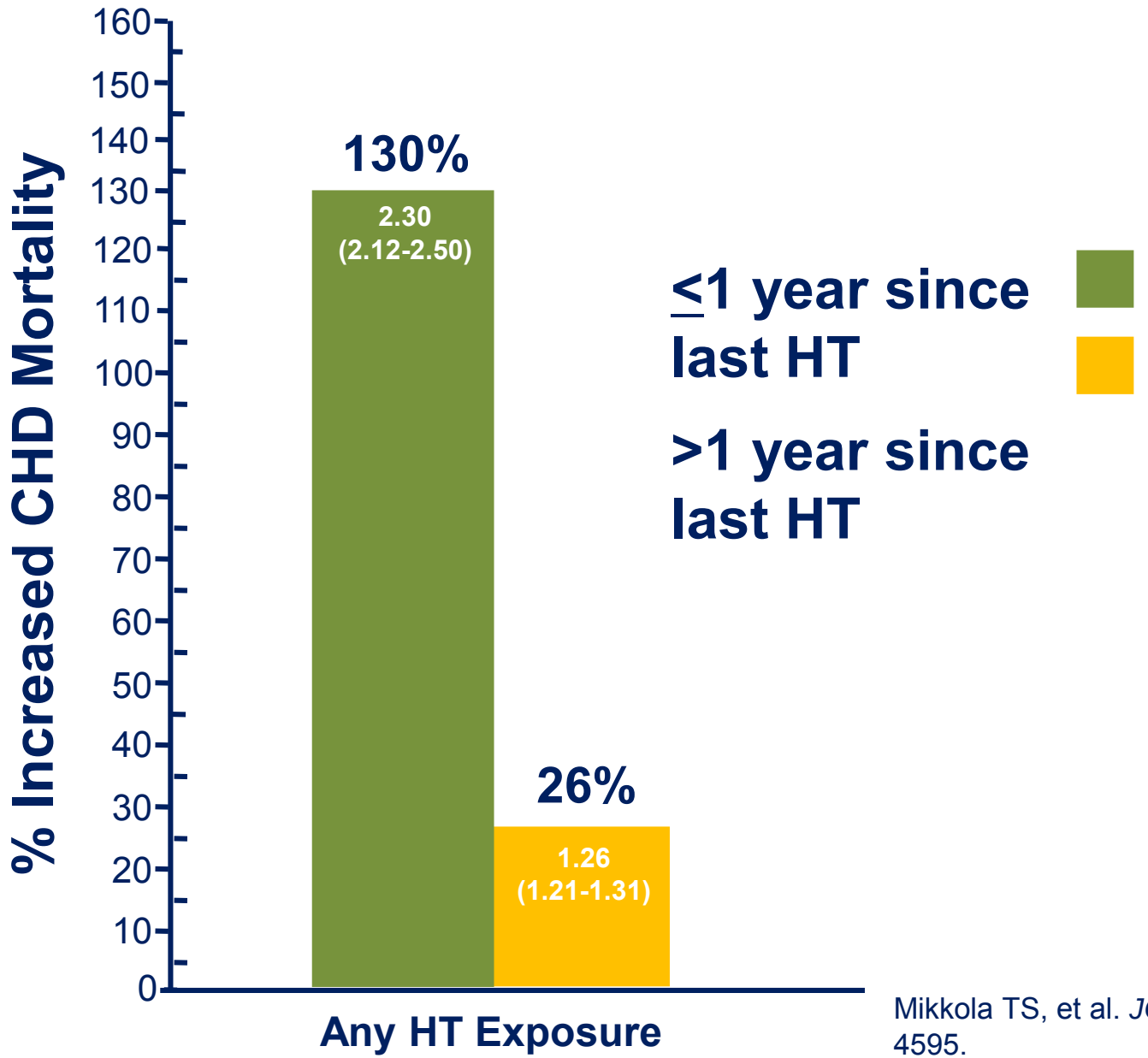



**Male**

**Mortality rate increased in 3.4% of counties**

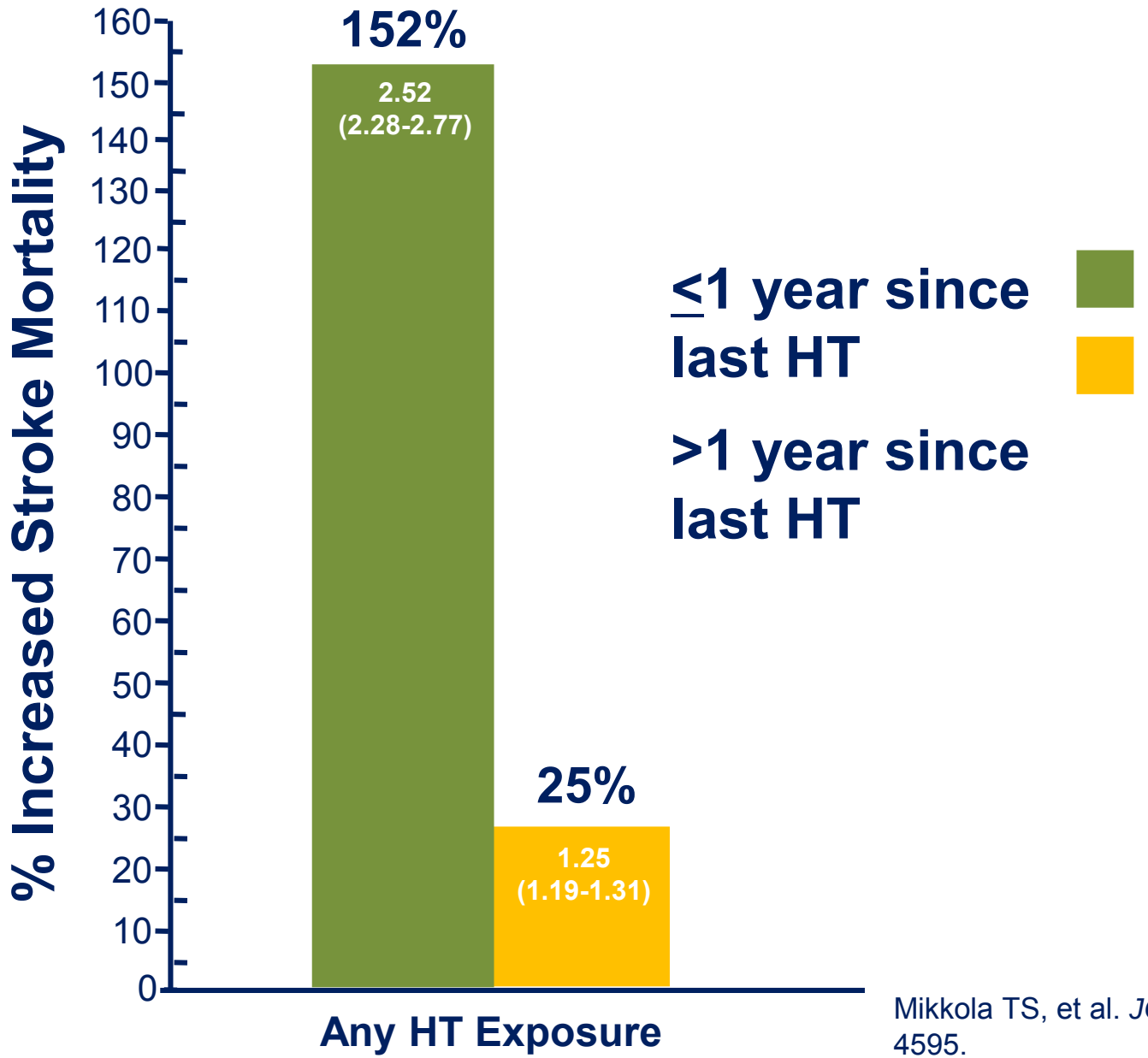
Kindig DA, et al. *Health Affairs* 2013;32:451-458.

# CHD Mortality Risk in 330,000 Women Discontinuing Postmenopausal HT Compared with HT Users (Finnish Death Register)




Mikkola TS, et al. *JCEM* 2015;100:4588-4595.

# Stroke Mortality Risk in 330,000 Women Discontinuing Postmenopausal HT Compared with HT Users (Finnish Death Register)




Mikkola TS, et al. *JCEM* 2015;100:4588-4595.

# Evidence for Current Cardiovascular Disease Prevention Guidelines

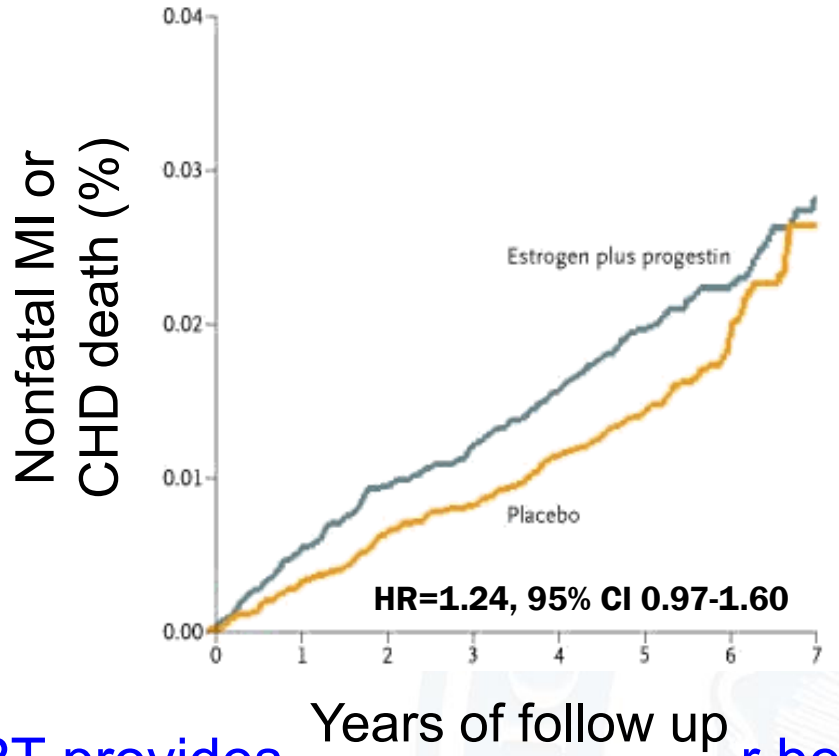
## Hormone Replacement Therapy Evidence and Guidelines


*Helping Cardiovascular Professionals*
*Learn. Advance. Heal.*

# Hormone Replacement Therapy: Primary Prevention

## Women's Health Initiative (WHI)

16,608 postmenopausal women aged 50-79 years randomized to conjugated equine estrogen (0.625 mg) plus medroxyprogesterole acetate (2.5 mg) or placebo for 5.2 years




HRT provides no cardiovascular benefit



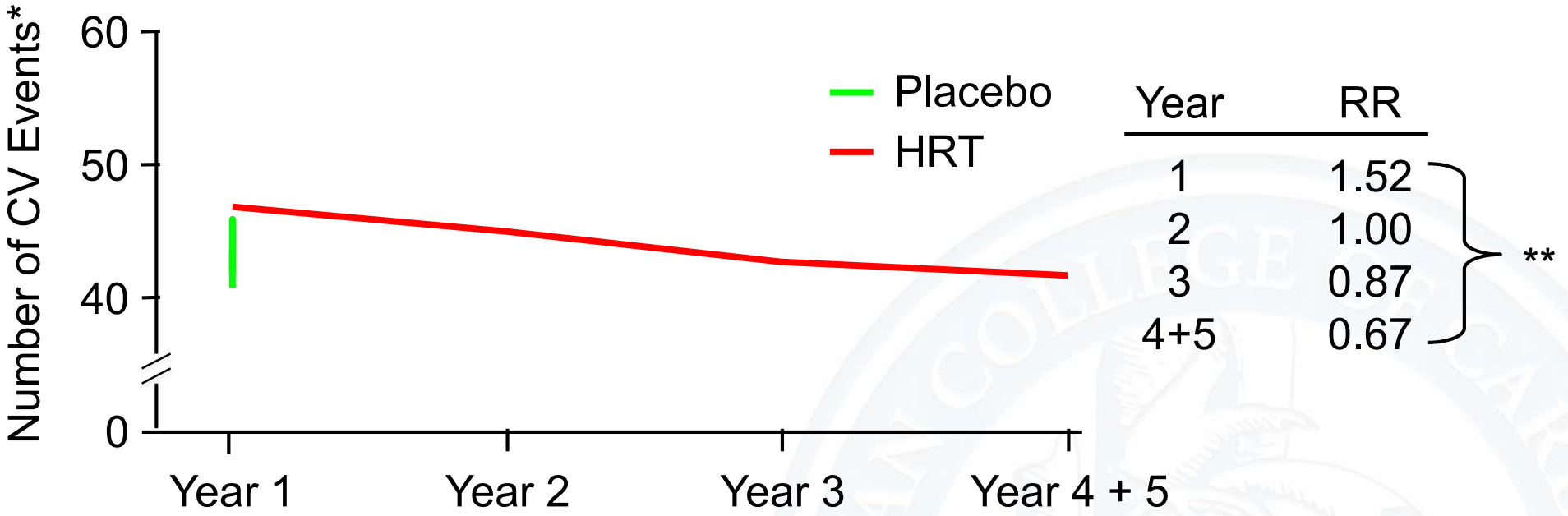
CHD=Coronary heart disease, HRT=Hormone replacement therapy, MI=Myocardial infarction

Manson JE et al. *NEJM* 2003;349:523-534

# Hormone Replacement Therapy: Secondary Prevention

## Heart and Estrogen/progestin Replacement Study (HERS)

2,763 postmenopausal women with known CAD randomized to conjugated equine estrogen (0.625 mg) and medroxyprogesterone acetate (2.5 mg) or placebo for 4.1 years




| Year | RR |
|---|---|
| 1 | 1.52 |
| 2 | 1.00 |
| 3 | 0.87 |
| 4+5 | 0.67 |

**

HRT provides no CV benefit in women with known CAD

*Includes coronary revascularization, unstable angina, congestive heart failure, resuscitated cardiac arrest, transient ischemic attack or stroke, peripheral arterial disease, and all-cause mortality

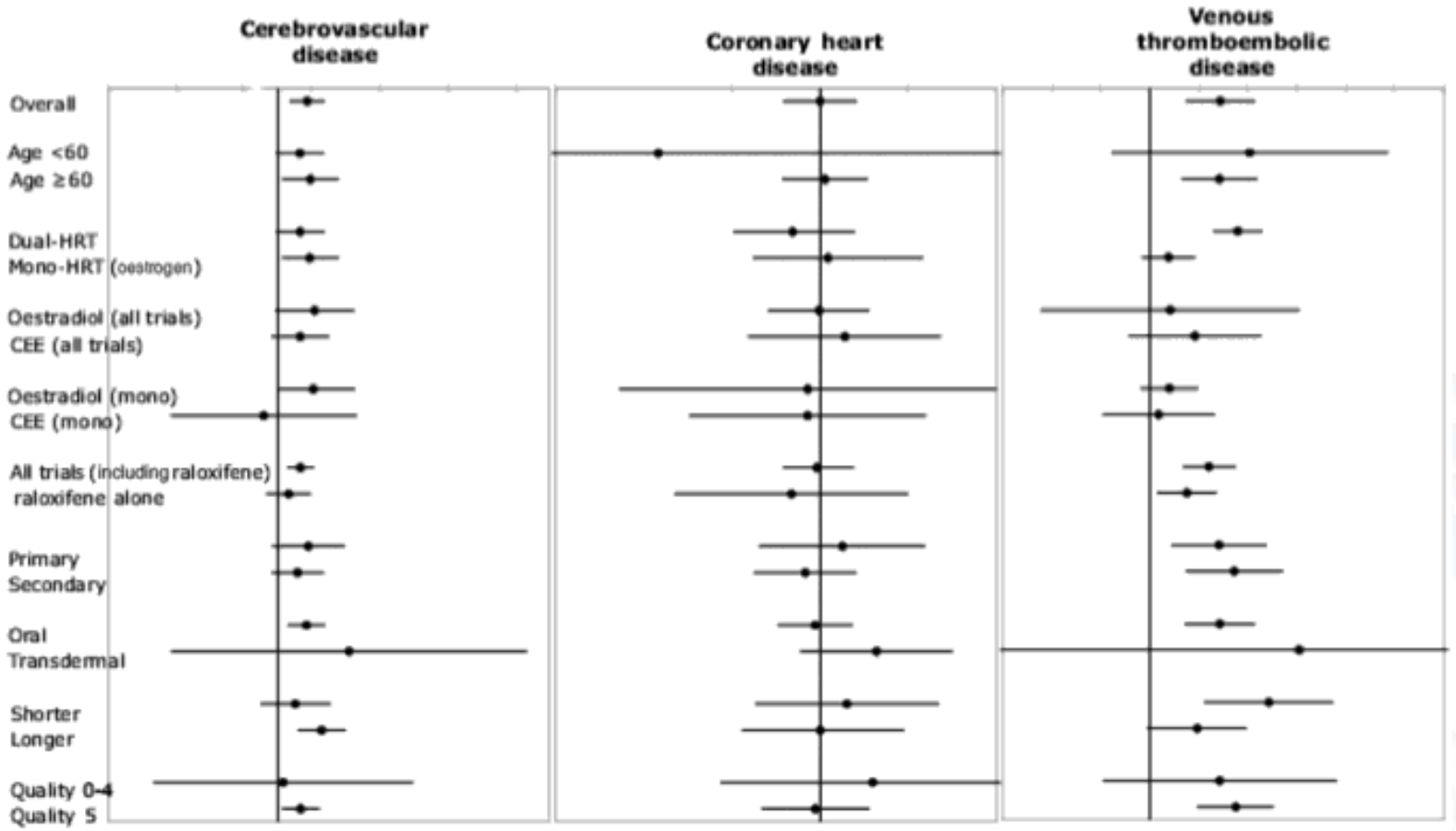
**P=0.009 for trend-time analysis

CAD=Coronary artery disease, CV=Cardiovascular, HRT=Hormone replacement therapy

Hulley S et al. *JAMA* 1998;280:605-613

# Hormone Replacement Therapy: Primary and Secondary Prevention

Meta-analysis of 35 randomized clinical trials evaluating the effect of hormone replacement therapy on cardiovascular outcomes




HRT provides no cardiovascular benefit in primary and secondary prevention



Sare GM et al. *Eur Heart J* 2008;29:2031-2041

# Hormone Replacement Therapy Guidelines

## Secondary Prevention


HRT with estrogen plus progestin, or estrogen alone, should not be given de novo to postmenopausal women after NSTE-ACS for secondary prevention of coronary events.


Postmenopausal women who are already taking estrogen plus progestin, or estrogen alone, at the time of NSTE-ACS in general should not continue HRT. Women who are more than 1-2 years past the initiation of HRT who wish to continue therapy for another compelling indication should weigh the risks and benefits, recognizing the greater risk of CV events and breast cancer (combination therapy) or stroke (estrogen).



CV=Cardiovascular, HRT=Hormone replacement therapy, NSTE-ACS=Non-ST-segment elevation acute coronary syndrome

Anderson JL et al. *JACC* 2007;50:652-726

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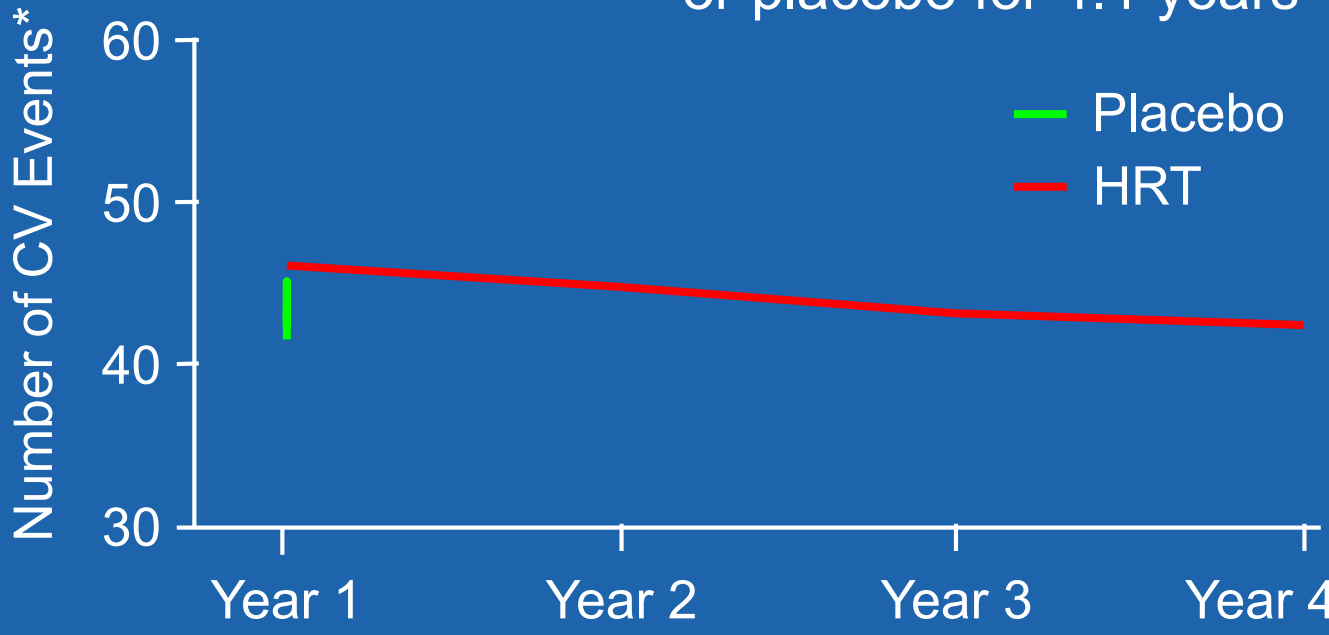


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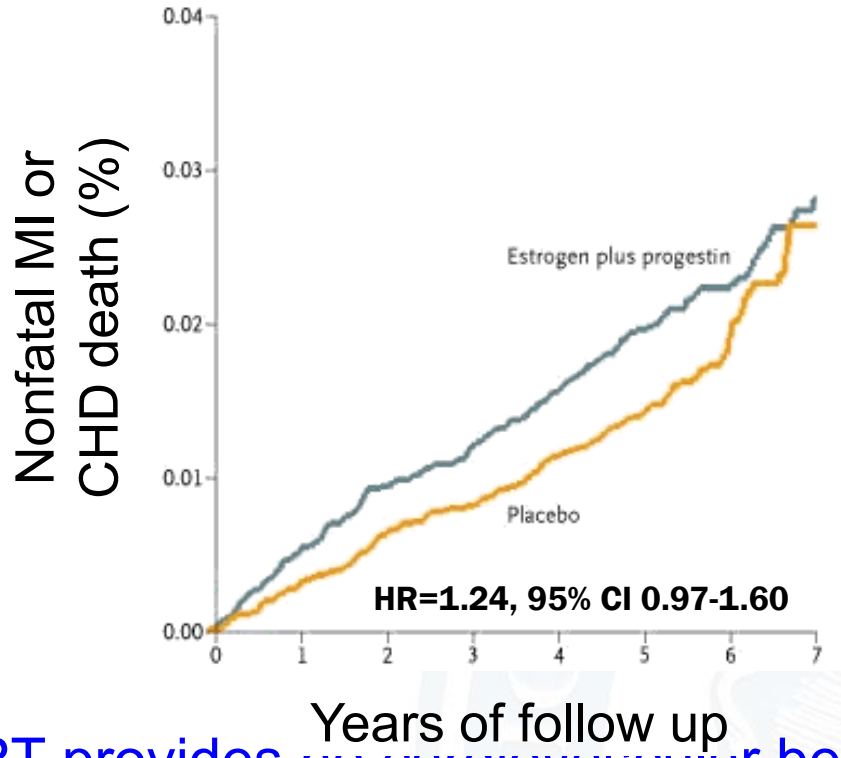


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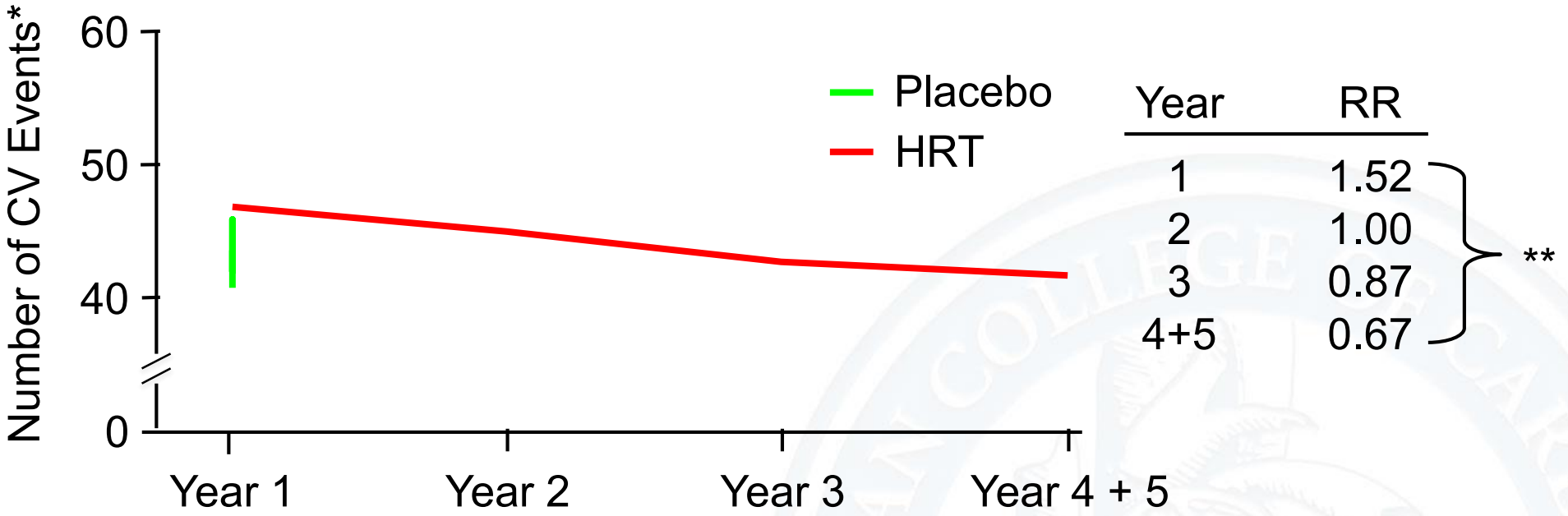


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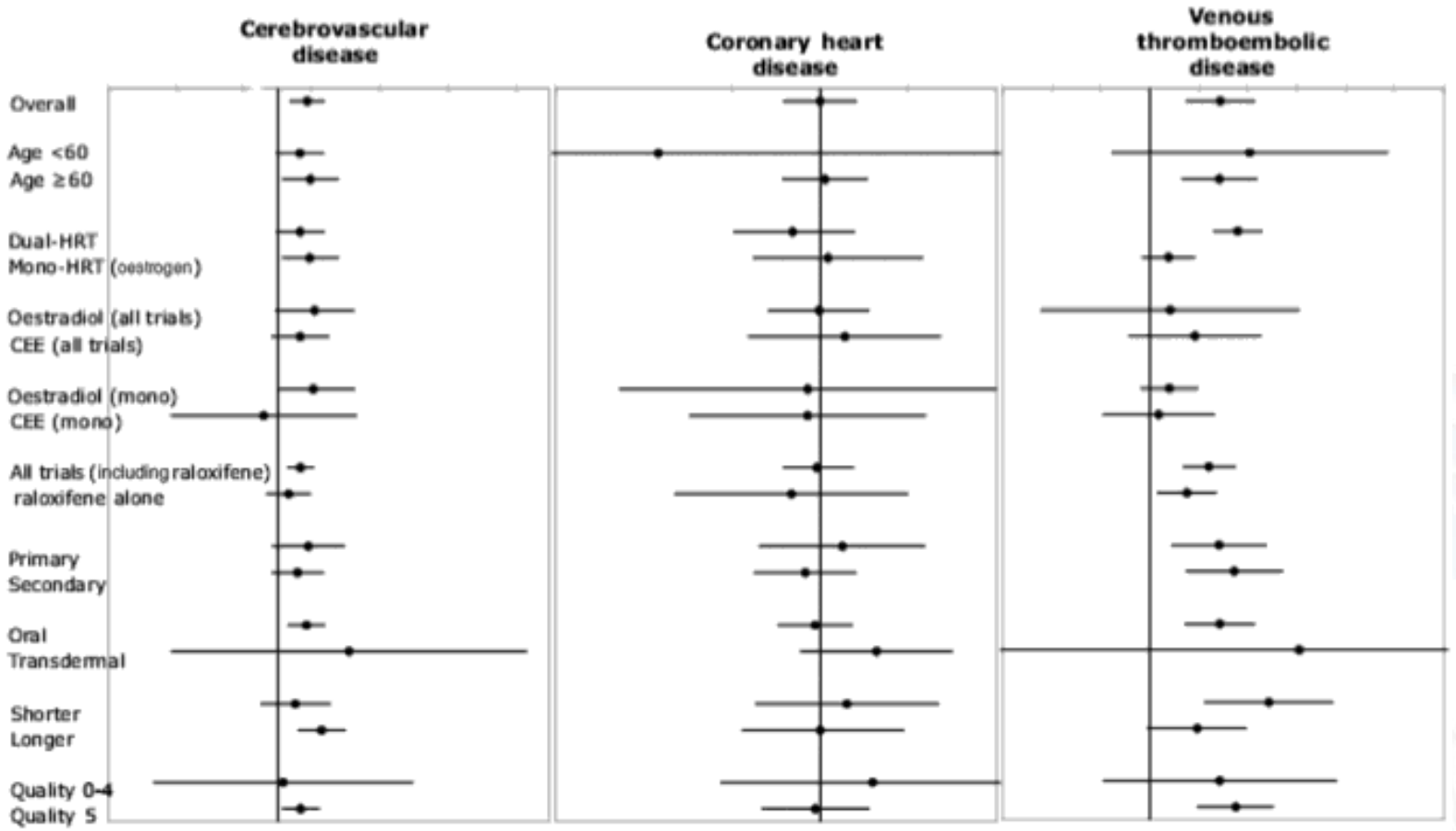
Meta-analysis of 35 randomized clinical trials evaluating the effect of hormone replacement therapy on cardiovascular outcomes




HRT provides no cardiovascular benefit in primary and secondary prevention

*Helping Cardiovascular Professionals Learn. Advance. Heal.*

Sare GM et al. *Eur Heart J* 2008;29:2031-2041

# Hormone Replacement Therapy Guidelines

## Secondary Prevention


HRT with estrogen plus progestin, or estrogen alone, should not be given de novo to postmenopausal women after NSTE-ACS for secondary prevention of coronary events.

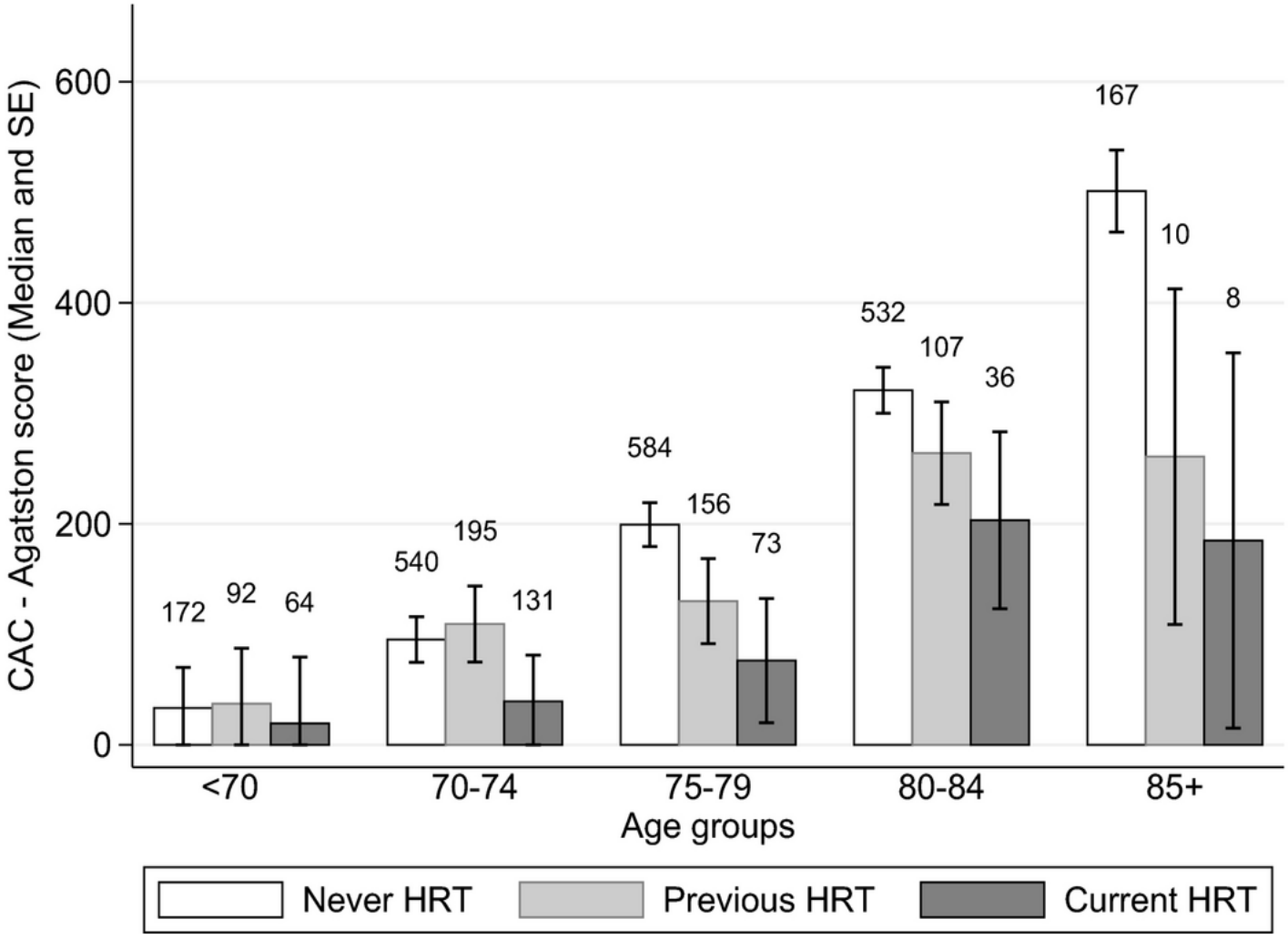

Postmenopausal women who are already taking estrogen plus progestin, or estrogen alone, at the time of NSTE-ACS in general should not continue HRT. Women who are more than 1-2 years past the initiation of HRT who wish to continue therapy for another compelling indication should weigh the risks and benefits, recognizing the greater risk of CV events and breast cancer (combination therapy) or stroke (estrogen).



CV=Cardiovascular, HRT=Hormone replacement therapy, NSTE-ACS=Non-ST-segment elevation acute coronary syndrome

Anderson JL et al. *JACC* 2007;50:652-726

# Long-Term Hormone Replacement Therapy Is Associated with Low Coronary Artery Calcium Levels in a Cohort of Older Women: The Age, Gene/Environment Susceptibility—Reykjavik Study




**Journal of the American Geriatrics Society**
Volume 65, Issue 1, pages 200-206, 11 NOV 2016 DOI: 10.1111/jgs.14461
http://onlinelibrary.wiley.com/doi/10.1111/jgs.14461/full#jgs14461-fig-0002

# Hormone Therapy (HT): Does the Timing and Type of Estrogen Matter?

- KEEPS: Kronos Early Estrogen Prevention Study
  - 660 women aged 48-52, randomized to placebo, oral conjugated equine estrogen, or transdermal 17 beta-estradiol patch with placebo or pulsed progesterone for 12 days/month
  - Endpoint: Progression of atherosclerosis measured by carotid intima media thickness and coronary artery calcification

Source: Miller 2009, clinicaltrials.gov

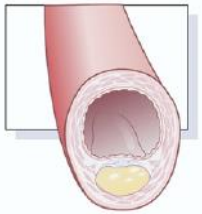
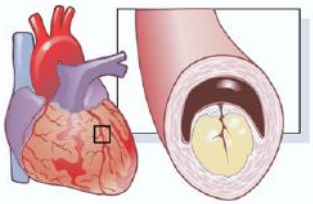
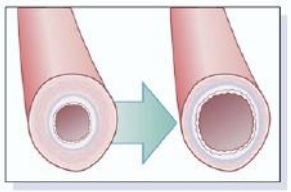
# J Am Coll Cardiol 2009;53:221–31

STATE-OF-THE-ART PAPER

## Contraceptive Hormone Use and Cardiovascular Disease

Chrisandra L. Shufelt, MD, MS, C. Noel Bairey Merz, MD, FACC

*Los Angeles, California*

| Estrogens | | Progestins |
|---|---|---|
| ↓ LDL oxidation<br>↓ LDL binding<br>↑↓ lipoprotein* ***<br>↑ blood pressure<br>↓ oxidation damage<br>↓ VSMC proliferation<br>↓ glucose tolerance*** | **Atherosclerosis**<br>  | ↑↓ HDL effect* **<br>↑↓ blood pressure**<br>↑ glucose tolerance** |
| ↑ coagulation factors<br>↓ platelet aggregation | **Thrombosis**<br>  | ↑ coagulation factors<br>↓ platelet aggregation<br>↓ nitric oxide** |
| ↑ nitric oxide<br>↓ endothelin<br>↑ Cox-2<br>↓ neuroendocrine response<br>↓ VSMC proliferation | **Vasomotion**<br>  | ↑ vasoconstriction**<br>↓ nitric oxide** |
| | **Arrhythmogenesis** | |

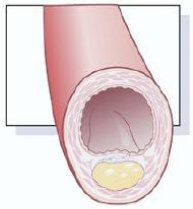
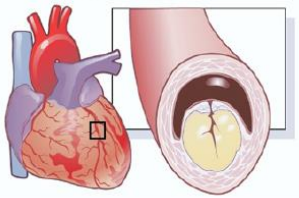
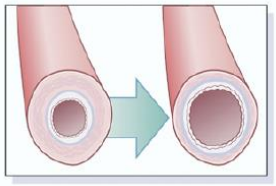
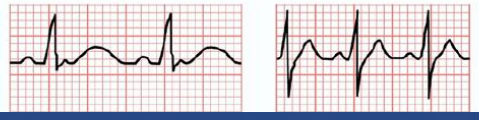
| Estrogens | | Progestins |
|---|---|---|
| ↓ LDL oxidation<br>↓ LDL binding<br>↑↓ lipoprotein* ***<br>↑ blood pressure<br>↓ oxidation damage<br>↓ VSMC proliferation<br>↓ glucose tolerance*** | **Atherosclerosis**<br>  | ↑↓ HDL effect* **<br>↑↓ blood pressure**<br>↑ glucose tolerance** |
| ↑ coagulation factors<br>↓ platelet aggregation | **Thrombosis**<br>  | ↑ coagulation factors<br>↓ platelet aggregation<br>↓ nitric oxide** |
| ↑ nitric oxide<br>↓ endothelin<br>↑ Cox-2<br>↓ neuroendocrine response<br>↓ VSMC proliferation | **Vasomotion**<br>  | ↑ vasoconstriction**<br>↓ nitric oxide** |
| ↑ QT prolongation | **Arrhythmogenesis**<br>  | ↓ QT prolongation |

**Table 3** Summary of Hormonal Contraceptive Prescribing Guidelines for Women With Elevated Cardiovascular Risk

| | |
|---|---|
| Hypertension | Well-controlled BP in women <35 yrs of age and otherwise healthy, nonsmoking → trial of OC.<br>Monitor BP and if controlled after starting, OC may be continued.<br>If BP not well controlled, alternative methods such as progestin-only pills or IUD may be started. |
| Dyslipidemia | LDL-C >160 mg/dl or multiple cardiac risk factors → alternative nonhormonal contraceptive methods, such as an IUD. |
| Diabetes | Diabetes type I or II, OC is *only* appropriate for use in otherwise healthy, nonsmokers <35 yrs of age. Otherwise progestin-only or IUD may be started. |
| Smoking | Smoking and >35 yrs of age → alternative nonhormonal contraceptive methods, such as an IUD.<br>Smokers <35 yrs of age are not addressed. |
| Obesity | Obesity (BMI >30 kg/m$^2$) → alternative nonhormonal contraceptive methods such as progestin-only contraception or IUD. Obesity is felt to be an independent risk factor for VTE. |
| Women older than 35 yrs of age | Healthy, nonsmoking women → OC with <50 $\mu$g EE remain safer than pregnancy, and can be continued until 50 to 55 yrs of age or until menopause after reviewing risks and benefits. |

# Twelve-Year Follow-Up of American Women's Awareness of Cardiovascular Disease Risk and Barriers to Heart Health

Lori Mosca, MD, MPH, PhD; Heidi Mochari-Greenberger, MPH, RD; Rowena J. Dolor, MD, MHS; L. Kristin Newby, MD, MHS; Karen J. Robb, MBA

***Background***—Awareness of cardiovascular disease (CVD) risk has been linked to taking preventive action in women. The purpose of this study was to assess contemporary awareness of CVD risk and barriers to prevention in a nationally representative sample of women and to evaluate trends since 1997 from similar triennial surveys.

***Methods and Results***—A standardized survey about awareness of CVD risk was completed in 2009 by 1142 women ≥25 years of age, contacted through random digit dialing oversampled for racial/ethnic minorities, and by 1158 women contacted online. There was a significant increase in the proportion of women aware that CVD is the leading cause of death since 1997 ($P$ for trend=<0.0001). Awareness among telephone participants was greater in 2009 compared with 1997 (54% versus 30%, $P<0.0001$) but not different from 2006 (57%). In multivariate analysis, African American and Hispanic women were significantly less aware than white women, although the gap has narrowed since 1997. Only 53% of women said they would call 9-1-1 if they thought they were having symptoms of a heart attack. The majority of women cited therapies to prevent CVD that are not evidence-based. Common barriers to prevention were family/caretaking responsibilities (51%) and confusion in the media (42%). Community-level changes women thought would be helpful were access to healthy foods (91%), public recreation facilities (80%), and nutrition information in restaurants (79%).

***Conclusions***—Awareness of CVD as the leading cause of death among women has nearly doubled since 1997 but is stabilizing and continues to lag in racial/ethnic minorities. Numerous misperceptions and barriers to prevention persist and women strongly favored environmental approaches to facilitate preventive action. (***Circ Cardiovasc Qual Outcomes*. 2010;3:120-127.**)