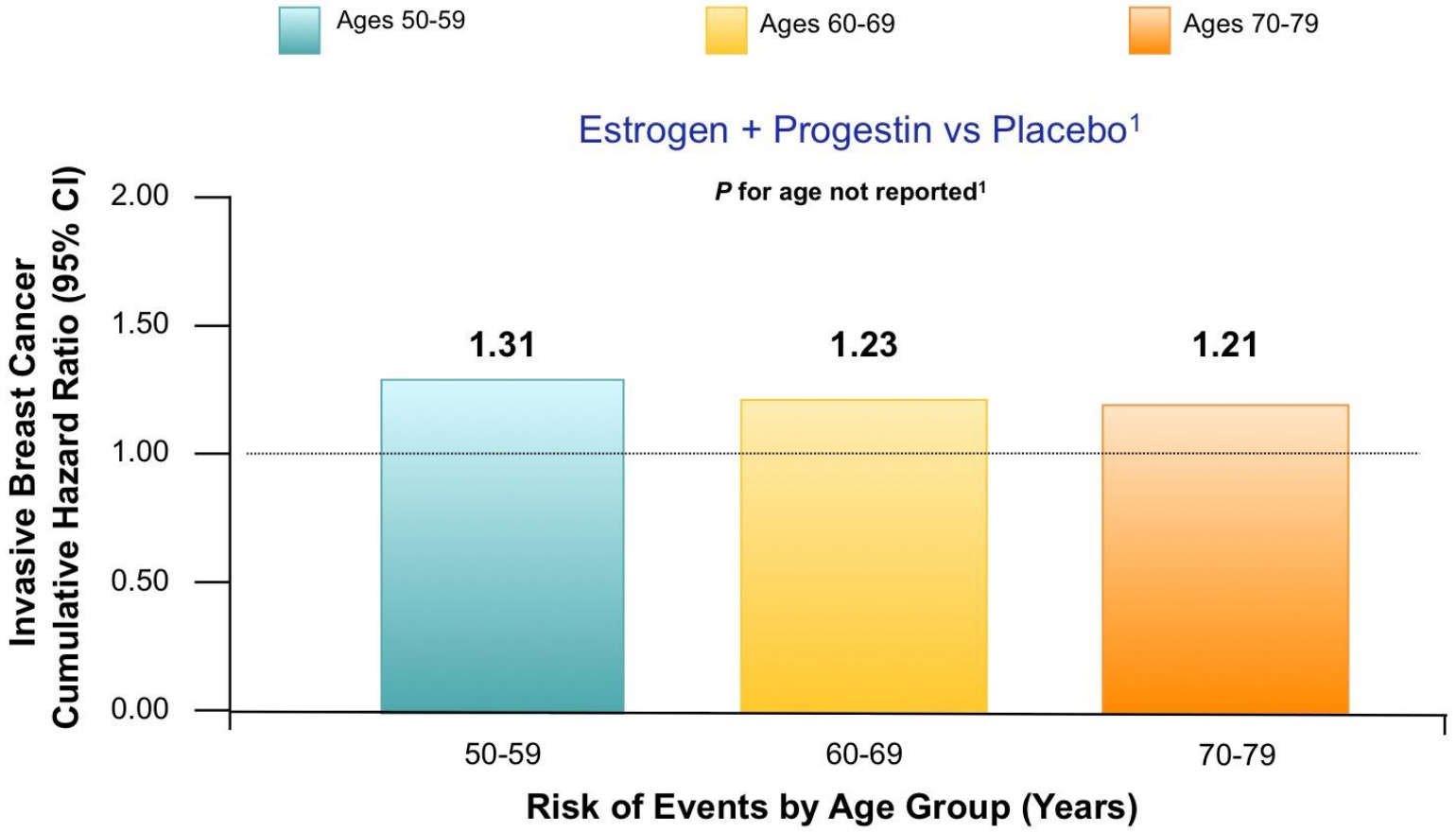
Disclosure

- Shionogi: Speakers Bureau

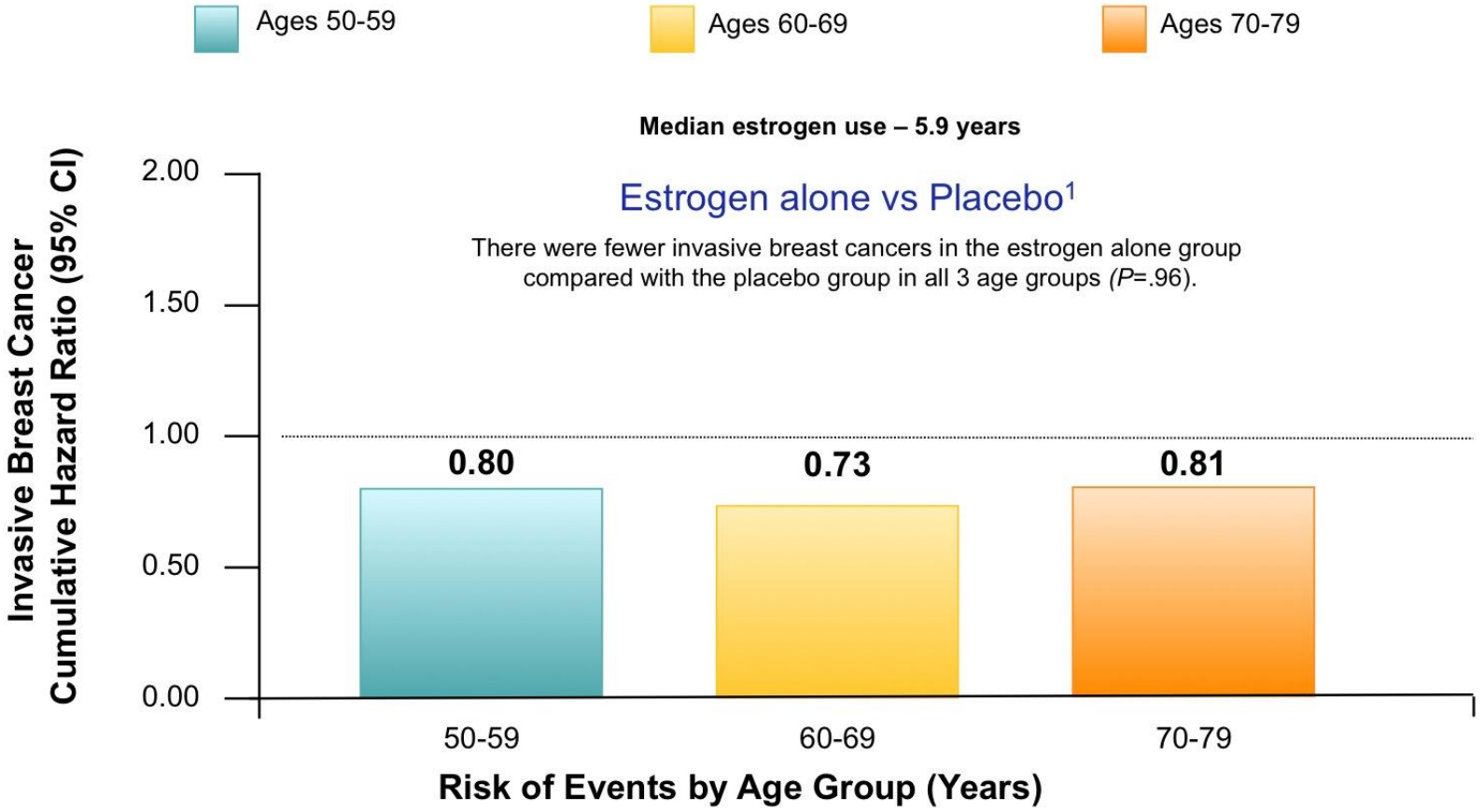
- Family investments include:
  - Sermonix Pharmaceutical
  - MHB Labs
  - Sprout Pharmaceutical (formerly)

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



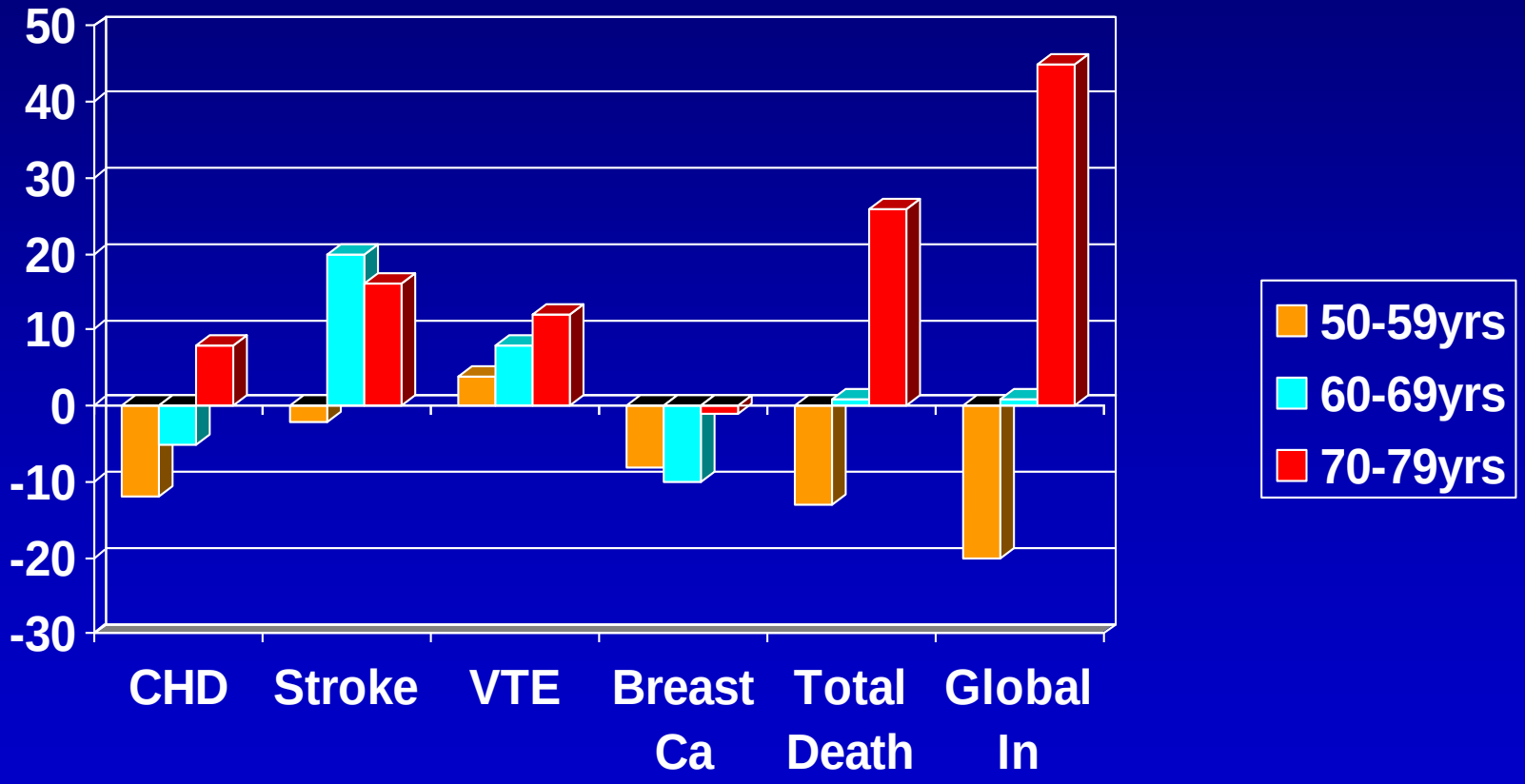
1. LaCroix AZ et al. *JAMA*. 2011;305 (13):1305-1314.

Effect of Therapy with CEE on Major Outcomes in Women under the Age of 60 Years from WHI

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;357(12):1252-3.

Absolute risk/10,000 women per year on ET; WHI



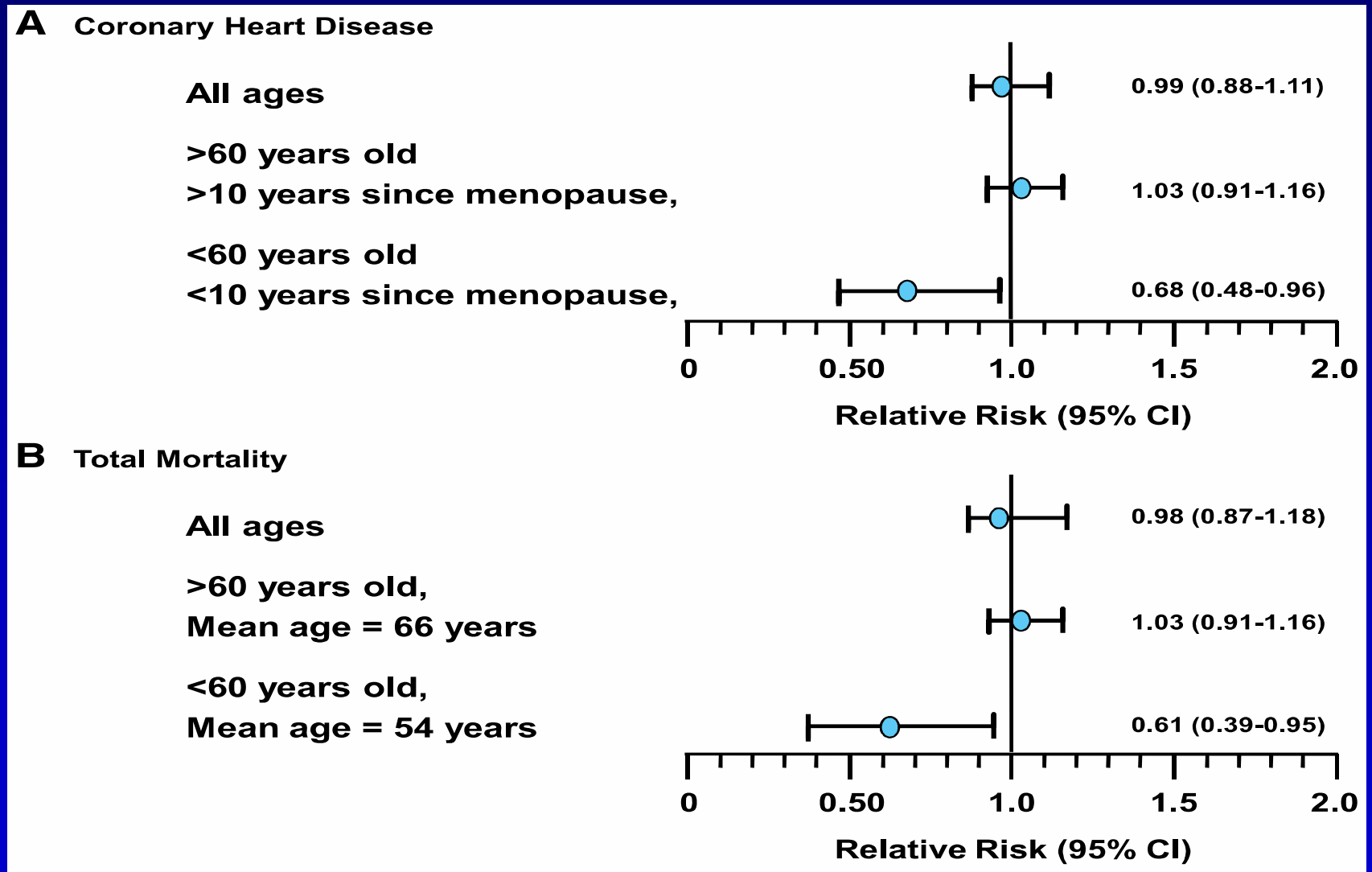
Important Studies since WHI; Media worthy???

- **Observational studies 10-40 years**
- **Randomized studies 7-8 years**
- **WHI Observ. Study; ET >5yrs. CHD *HR= 0.73 (0.61-0.84)***

- **Meta analysis 23 trials (Stanford) 40,000 w (191,000pt yrs)**
  CHD <60 & w/in 10 yrs of MP *HR 0.68 (0.48-0.96)*
  Younger <60 vs older>60 *HR 0.66 (0.46-0.95)*
- **30 trials (Stanford) 26,700 w (119,118 pt yrs)**
  Total mortality <60 on HT *HR 0.61 (0.39-0.95)*
  >60 no effect
- **WHI EPT + ET combined; *ages 50-59; Overall mortality 0.70 (0.51-0.96)***

Hodis H; Assessing benefits and risks of Hormone Trerapy in 2008: New evidence, especially with regard to heart; Cleve Clin Jnl Med;75;Suppl 4;May 2008

Meta-analysis CHD and Total Mortality ibid



Sex Specific Statin Therapy

Hodis and Mack;JAGS 2013

Table 1. Comparison of Statin Therapy on Coronary Heart Disease and Total Mortality in Primary Prevention in Women and Men

	Women		Men	
Outcome	**HR (95% CI)**	**N**	**HR (95% CI)**	**N**
Coronary heart disease				
Walsh and Pignone[1]	0.89 (0.69–1.09)	11,435		
Petretta et al.[2]	0.95 (0.78–1.16)	13,346	0.55 (0.41–0.75)	28,346
Brugts et al.[4]	0.79 (0.56–1.13)	20,817	0.72 (0.61–0.86)	26,921
Total mortality				
Walsh and Pignone[1]	0.95 (0.62–1.46)	11,435		
Petretta et al.[2]	0.96 (0.81–1.13)	11,849	0.93 (0.83–1.04)	20,426
Brugts et al.[4]	0.91 (0.76–1.08)	20,817	0.95 (0.86–1.06)	26,921

HR = hazard ratio; CI = confidence interval.

Decide for yourself: HRT vs Statin vs ASA

Hodis and Mack; JAGS 2013

Table 2. Comparison of the Effect of Initiation of Hormone Replacement Therapy in Young Postmenopausal Women with that of Statin and Aspirin Therapy on Coronary Heart Disease and Total Mortality in Primary Prevention

	Hormone Replacement Therapy[a]	Statin Therapy	Aspirin Therapy
Outcome	**Hazard Ratio (95% Confidence Interval)**		
Coronary heart disease			
Salpeter et al.[14]	0.68 (0.48–0.96)		
Schierbeck et al.[19]	0.48 (0.26–0.87)		
Walsh and Pignone[1]		0.89 (0.69–1.09)	
Petretta et al.[2]		0.95 (0.78–1.16)	
Brugts et al.[4]		0.79 (0.56–1.13)	
Berger et al.[8]			1.01 (0.84–1.21)
Ridker et al.[9]			0.91 (0.80–1.03)
Total mortality			
Salpeter et al.[20]	0.61 (0.39–0.95)		
Salpeter et al.[21]	0.72 (0.62–0.82)		
Schierbeck et al.[19]	0.57 (0.30–1.08)		
Walsh and Pignone[1]		0.95 (0.62–1.46)	
Petretta et al.[2]		0.96 (0.81–1.13)	
Brugts et al.[4]		0.91 (0.76–1.08)	
Berger et al.[8]			0.94 (0.74–1.19)
Ridker et al.[9]			0.95 (0.85–1.06)

[a]Initiation in women younger than 60 or less than 10 years after menopause.

Danish Osteoporosis Prevention Study (DOPS) BMJ 2012

- Only PLRT to look at clinical outcomes in women who were randomized to HT while peri or early post menopausal.
- 45-58 y.o. and 7 mos. postmenopausal
- 10 yrs + f/u 6 yrs = total 16 yrs
- Looked at composite primary trial endpoint (CPTE) of:
  1) mortality, MI, or heart failure (HF)

  and

  2) total mortality

Danish Osteoporosis Prevention Study (DOPS) BMJ 2012

- 10 yrs: CPTE signif. 52% lower; HR 0.48 (0.27-0.89)

  Total mortality 43% lower; HR 0.57 (0.30-1.08)
- 16 yrs: CPTE 49% lower; HR 0.51 (0.39-0.94)

  Total mortality 34% lower; HR 0.66 (0.41-1.08)
- No statistically signif differences in incident breast cancer, stroke, or VTE between groups
- Similar to WHI CEE 50-59 and to the meta-analyses of RCTs of women <60 or <10 yrs post menopausal

Danish Osteoporosis Prevention Study (DOPS) BMJ 2012

- DOPS is the only randomized trial to appropriately test the "estrogen cardio-protective" hypothesis in the same population of women in which this hypothesis was generated.
- Few prevention therapies other than HT have been studied under randomized conditions for over ten years!

Statin and HT study

Berglind, Andersen et al; Menopause,April 2015

- HT & risks of CV outcomes & mortality in **women treated with statins**
- N=40,958; 40-74 years of age
- 7%HT users; 93% non-users
- National registry-based cohort study; Sweden
- National health register and pharma records
- **70% used statins as primary prevention**

Statin and HT study

Berglind, Andersen et al; Menopause,April 2015

- HT users; 5 CV deaths per 10,000 women yrs.
- Non-HT users; 18 CV deaths / 10,000 w y
- RR or Hazard ratio: 0.38 (0.12-1.19)
- All cause mortality rate; 33 vs 87 /10,000 w y
- RR or Hazard ratio: 0.53 (0.34-0.81)
- HT is associated w/ a ss reduced risk of all-cause mortality in women rx'd w/ statins
- HT (at the very least) is not detrimental to statin rx'd women

Hodis editorial discussion; Ibid

- Statins do not reduce CHD or all–cause mort.
- HT in young w; redux. CHD/all-cause mortality
- HT in older w; null effect

- HERS; early increase in MI; first 6 mos. Then a signif redux during remaining 4 yr intervent.
- E increases MMP-9; plaque rupture
- But statins suppress MMP-9; no increase yr 1

Hodis editorial discussion; Menopause; April 2015

- HT and statins reduce all cause mortality and reduce each other's side effects
- Statins reduce HT induced plaque rupture in secondary prevention (suppress MMP-9)
- HT has the potential to reduce new-onset DM caused by statin rx
- Statins may reduce VTE adverse effect of oral estrogen

Hodis editorial discussion; Ibid

- Consistant with the prevailing literature
- Lends further support for the progressive, but unpopular, position that combined HT and statin rx may be the optimum option for reducing CHD and all-cause mortality in women!

Summary; Hodis and Mack; JAGS 2013

- The totality of evidence indicates that the **benefits of the initiation of HT at or near menopause outweigh the risks**, with the weight of evidence **supporting downstream prevention of morbidity and mortality.**

- Cumulative data provide **not only strong evidence of the beneficial effects** of HT when initiated in close proximity to menopause, **but also reassurance of their safety.**

CVD & stroke risk after D/C HT Mikkola et al; JClinEndocrinlMetab;9-2015 Hodis summary NAMS

- 15 yrs w 2million f/u years in >330,000 Finnish w
- Both CHD and stroke mortality **significantly increased in the first year after stopping HT**
- When compared to those who continued HT, **both mortalities continued beyond the 1st yr.**
- 3 lines of published evidence confirm that HT reduces CV mortality **more than any other 1^0 prevention rx in use today:**

a) Starting HT w/in 10 yrs of MP and <60 reduces mortality
b) Avoiding HT results in excess mortality
c) Stopping HT is associated w/ cardiac and stroke mortality

Starting HT w/in 10 yrs of MP and <60 reduces mortality

Hodis summary NAMS

- Observational studies and randomized trials in w <60 and <10 yrs post MP show reduction in total mortality
- Meta of 30 RCTs w/ 120,000 w yrs of f/u: signif 39% redux in total mortality (0.61; 0.30-0.95) in w who averaged 54 yrs when randomized to HT/placebo
- WHI ET and HT arms both showed 30% redux in total mortality in <60 and <10 compared to placebo (0.70; 0.51-0.96)
- DOPS; 43% redux in mortality, with persistent redux of 34% after 16 yrs of f/u
- Observational + RCTs combined: total mortality signif reduced 28% (0.72; 0.62-0.82)

Avoiding HT results in excess mortality

Hodis summary NAMS

- Avoiding ET adversely affected mortality rates among hysterectomized women <60
- Using WHI ET data of 10-12 fewer deaths per 10,000 women years of use, Sarrel et al estimated that over a 10 yr period since 2002, **a minimum of 18,601 and a maximum of 91,610 postmenopausal women died prematurely because of ET avoidance**

Stopping HT is associated w/ cardiac and stroke mortality

Hodis summary NAMS

- Demonstration of stopping rx (HT) with resultant death unheard of in 1^0 prevention of CVD
- 2 well-understood nongenomic mechanisms:

a) Immediate withdrawal HT… decr NO production…vasoconstrictive reactive arteries…cardiac and stroke death

b) Rapid rise and continued exposure of vascular system to activated inflammatory processes; (acute events and long term plaque induction normalized with HT)