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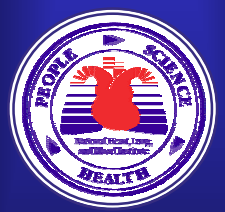

National Heart, Lung, and Blood Institute

Hormomes and CHD: Discrepancies between Laboratory Studies, Observational Studies, and Clinical Trials

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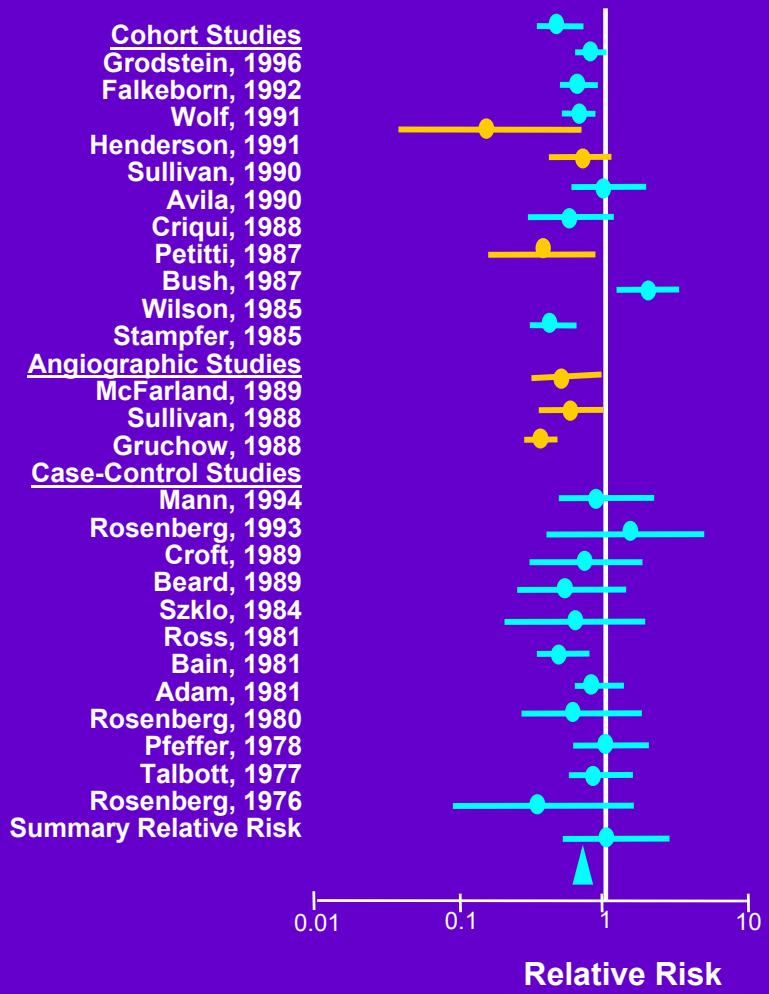
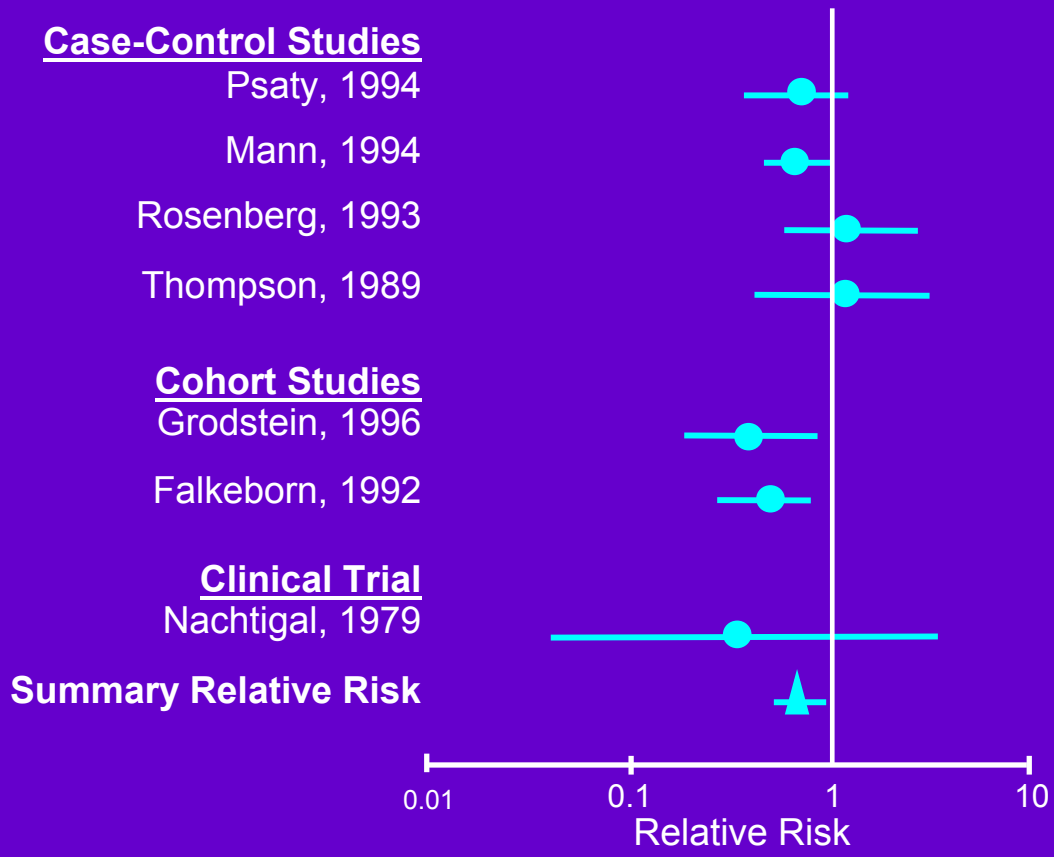
Risk for Coronary Heart Disease: Estrogen Users vs. Nonusers



Barrett-Connor. **Annu Rev Public Health. 1998;19:55-72.**

Risk for Coronary Heart Disease: Estrogen+Progestin Users vs Nonusers



Barrett-Connor. **Annu Rev Public Health. 1998;19:55-72.**

Observational studies suggest HT use is associated with reduced risk of CHD in…

- users of estrogen
- users of estrogen plus progestin
- irrespective of type of estrogen or progestin
- women without prior heart disease (primary prevention)
- women with prior heart disease (secondary prevention)

A variety of biases in hormone users may explain all, or a large proportion of the apparent benefit for CHD…..

- At start HT
  - Users healthier
- During HT
  - Compliant pill takers have better health
  - Are under medical surveillance
  - Early CHD events missed in some studies
- On stopping HT
  - Illness often reason for stopping

Trials of Hormones and CVD with Clinical Outcomes

Primary Prevention

- WHI (CEE+MPA)
- Hemminki (various)
- WHI (CEE)
- WISDOM (CEE+MPA, CEE)
- RUTH (raloxifene)

Secondary Prevention

- HERS (CEE+MPA)
- WAVE (CEE, CEE+MPA)
- PHASE (transdermal estradiol/NETA)
- WEST (estradiol)
- ESPRIT (estradiol)

Clinical trials have not shown CHD risk reduction with …

- estrogen
- estrogen plus progestin
- women without prior heart disease (primary prevention)
- women with prior heart disease (secondary prevention)

Could both observational studies and clinical trials be right?

Different Populations and Exposures

Nurses Health Study

- Age 30-63
- Hormones started at menopause
- Symptomatic
- No prevalent CVD
- 2/3 of estrogen data based on CEE
- CEE 0.625 mg most common dose
- MPA cyclic

WHI

- Age 50-79
- Hormones started after menopause
  - <5 years 17%
  - 5-9 years 19%
  - 10-14 years 21%
  - ≥15 years 43%
- Mostly asymptomatic
- Some prevalent CVD
- CEE 0.625 mg/day
- MPA continuous

Differences in Populations and Exposures: Subgroup Analyses in WHI

- Hints that younger women, recently postmenopausal women, women with symptoms, and those using aspirin and statins may not be at increased risk for CHD
- Trends not statistically significant
- Further analyses underway

How can we reconcile the findings from basic science, animal studies, and clinical trials?

Stages of Atherosclerosis

Initiation (endothelium, fatty streaks)

Progression (raised lesions)

Complicated lesions (unstable plaque)

Atherosclerosis versus AMI

- Do hormones retard atherosclerosis?
  - POSSIBLY, if minimal or no pre-existing atherosclerosis (EPAT, animal models, cell studies)
  - NO, in presence of existing atherosclerosis (ERA, WAVE, WELL-HART, PHOREA)
- Do hormones trigger AMI events in presence of complicated lesions?
  - YES (HERS, WAVE, PHASE, possibly WHI)

Is it possible that recently postmenopausal women will have a different response to hormones?

Menopausal women are not necessarily free of coronary atherosclerosis (at age 45-55 about 40% have raised lesions, and about 6% have complicated lesions)

A Trifurcated Response?

- Retardation in women with no or very early atherosclerosis, with reduction in CHD events after several years
- No effect in women with raised lesions
- Immediate increase in CHD events in a smaller subset of women with complicated lesions

Is it possible that recently postmenopausal women will have a different response to hormones?

- Conclusion: Even if hormones retard initiation of atherosclerosis, they may not be of value for prevention of CHD
  - Unless the subset with vulnerable lesions can be identified
  - Or unless the triggering of events can be prevented
- Corollary: Short-term relief of menopausal symptoms with hormones may come at a price: a small and immediate increase in the risk of CHD (and stroke,VT)

Some differences between oral conjugated equine estrogens (CEE) and transdermal estradiol (E_2)

	Oral CEE	Transdermal E_2
LDL	--	-
HDL	++	0
Triglycerides	++	0/-
LDL particle size	--	0
Coagulation	++	0/+
Inflammation	+/-	0/-
Endothelial function	++	++

- = decrease **+** = increase **0** = no effect

Research questions: Hormone Therapy and Coronary Heart Disease

- Identify mechanisms/markers of early harm
  - Screen out susceptibles
  - Therapies to prevent harm
- Hormone effects in younger women with symptoms
  - Surrogate outcomes
  - Consider large trial
- Transdermal estradiol/non-oral progesterone
- Lower doses of oral estrogens
  - Effective for osteoporosis
  - Effect on coronary heart disease/stroke unknown