

ICPPR

October 17, 2007

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Overview:

Meta-analysis

Secondary data analysis

Participant selection

Ads

Meta-analysis:

Objective: Understand what a meta-analysis is, how to interpret, and where to go for further guidance

Evidence-based medicine: Clinical practice should follow the best supported information on outcomes.

Presumption— no one definitive study as any study is unlikely to address all known and unknown sources of bias.

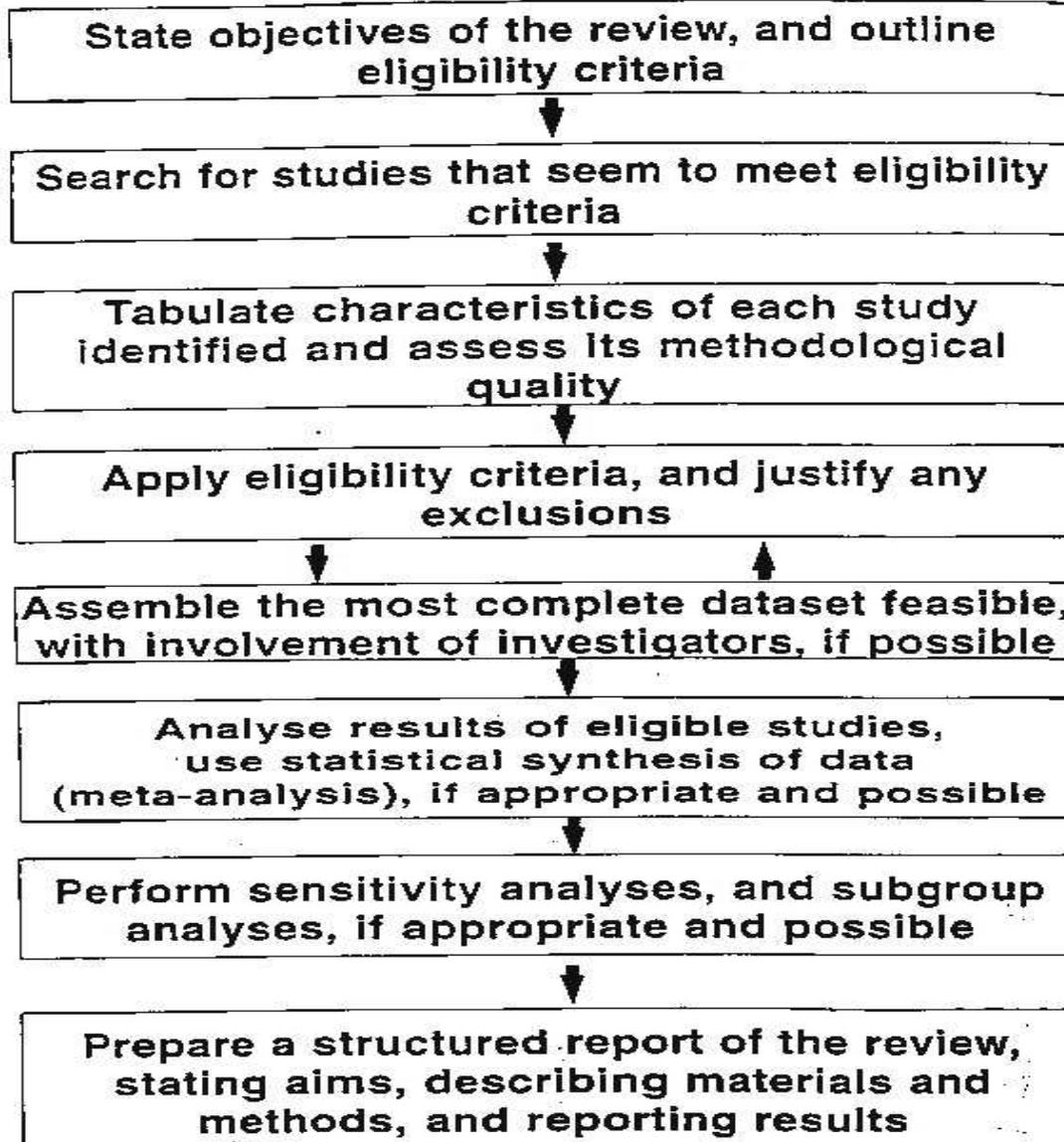
Meta-analysis is a systematic review and statistical analysis of data from studies relevant to the question.

Two major types:

- 1. Studies themselves are “units” of an analysis**
- 2. Subjects within studies are pooled**

Should be as carefully planned as any other research project with a detailed, written protocol in advance and a priori definitions of eligibility for studies

WHAT IS A SYSTEMATIC REVIEW?



For more information:

Egger, Smith, Phillips. Meta-analysis: Principles and procedures. BMJ 1997;315:1533-1537 (series)

Simple issues:

1. Inclusion criteria

- a. Independent of results**
- b. Publication bias**

2. Statistical issues

- a. Big vs. small studies**
- b. How present data**

3. Precision does not = truth if there is a systematic bias.

Recent past:

Cox-2 inhibitors and risk of myocardial infarction

Next up:

Rosiglitazone and cardiovascular events

Rosiglitazone and pioglitazone are potent inhibitors of peroxisome-proliferator activator-receptor γ .

Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy

RESULTS

Kaplan–Meier analysis showed a cumulative incidence of monotherapy failure at 5 years of 15% with rosiglitazone, 21% with metformin, and 34% with glyburide. This represents a risk reduction of 32% for rosiglitazone, as compared with metformin, and 63%, as compared with glyburide ($P < 0.001$ for both comparisons). The difference in the durability of the treatment effect was greater between rosiglitazone and glyburide than between rosiglitazone and metformin. Glyburide was associated with a lower risk of cardiovascular events (including congestive heart failure) than was rosiglitazone ($P < 0.05$), and the risk associated with metformin was similar to that with rosiglitazone. Rosiglitazone was associated with more weight gain and edema than either metformin or glyburide but with fewer gastrointestinal events than metformin and with less hypoglycemia than glyburide ($P < 0.001$ for all comparisons).

CONCLUSIONS

The potential risks and benefits, the profile of adverse events, and the costs of these three drugs should all be considered to help inform the choice of pharmacotherapy for patients with type 2 diabetes. (ClinicalTrials.gov number, NCT00279045.)

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group <i>no. of events/total no. (%)</i>	Control Group <i>no. of events/total no. (%)</i>	Odds Ratio (95% CI)	P Value
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

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Table 5. Risk of Myocardial Infarction and Death from Cardiovascular Causes for Patients Receiving Rosiglitazone versus Several Comparator Drugs.

Comparator Drug	Odds Ratio (95% CI)	P Value
Myocardial infarction		
Metformin	1.14 (0.70–1.86)	0.59
Sulfonylurea	1.24 (0.78–1.98)	0.36
Insulin	2.78 (0.58–13.3)	0.20
Placebo	1.80 (0.95–3.39)	0.07
Combined comparator drugs	1.43 (1.03–1.98)	0.03
Death from cardiovascular causes		
Metformin	1.13 (0.34–3.71)	0.84
Sulfonylurea	1.42 (0.60–3.33)	0.43
Insulin	5.37 (0.51–56.52)	0.16
Placebo	1.22 (0.64–2.34)	0.55
Combined comparator drugs	1.64 (0.98–2.74)	0.06



GlaxoSmithKline Responds to NEJM Article on Avandia

Philadelphia, PA (May 21, 2007) – GlaxoSmithKline [NYSE:GSK] today issued the following response to an article in the New England Journal of Medicine (NEJM) on Avandia® (rosiglitazone maleate), a widely used and highly effective treatment for type 2 diabetes:

GSK strongly disagrees with the conclusions reached in the NEJM article, which are based on incomplete evidence and a methodology that the author admits has significant limitations.

The NEJM paper is based on an analysis of summary information that combines a number of studies – a meta-analysis - which is not the most rigorous way to reach definite conclusions about adverse events. Each study is designed differently and looks at unique questions: for example, individual studies vary in size and length, in the type of patients who participated, and in the outcomes they investigate. The data compiled from these varied studies is complex and can be conflicting.

Importantly, the editorial in the NEJM states: “A few events either way might have changed the findings for myocardial infarction or for death from cardiovascular causes. In this setting, the possibility that the findings were due to chance cannot be excluded. In their discussion, the authors properly emphasize the fragility of their findings.”

Rosiglitazone Evaluated for Cardiovascular Outcomes — An Interim Analysis

Table 2. Hospitalization or Death from Cardiovascular Causes.*

Variable	Rosiglitazone Group (N = 2220) <i>no. of patients</i>	Control Group (N = 2227) <i>no. of patients</i>	Hazard Ratio (95% CI)	P Value
Adjudicated events				
Primary end point	217	202	1.08 (0.89–1.31)	0.43
Death				
From cardiovascular causes†	29	35	0.83 (0.51–1.36)	0.46
From any cause	74	80	0.93 (0.67–1.27)	0.63
Acute myocardial infarction‡	43	37	1.16 (0.75–1.81)	0.50
Congestive heart failure‡	38	17	2.24 (1.27–3.97)	0.006
Death from cardiovascular causes, myocardial infarction, and stroke	93	96	0.97 (0.73–1.29)	0.83
Events adjudicated and pending adjudication				
Primary end point	267	243	1.11 (0.93–1.32)	0.26
Death				
From cardiovascular causes†	37	46	0.80 (0.52–1.24)	0.32
Acute myocardial infarction‡	49	40	1.23 (0.81–1.86)	0.34
Congestive heart failure‡	47	22	2.15 (1.30–3.57)	0.003
Death from cardiovascular causes, myocardial infarction, and stroke	109	114	0.96 (0.74–1.24)	0.74

Rosiglitazone for type 2 diabetes mellitus (Review)

<http://www.thecochranelibrary.com>

Summary

This systematic review shows that published studies of at least 24 weeks rosiglitazone treatment in people with type 2 diabetes mellitus did not provide evidence that patient-oriented outcomes like mortality, morbidity, adverse effects and health-related quality of life are positively influenced by this compound. Metabolic control measured by glycosylated haemoglobin A1c (HbA1c) as a surrogate endpoint did not demonstrate clinically significant differences to other oral antidiabetic drugs. One study investigated economic costs of rosiglitazone versus insulin glargine therapy indicating lower costs of insulin glargine treatment. Occurrence of oedema was approximately doubled.

Rosiglitazone for type 2 diabetes mellitus (Review)

Moreover, it is disturbing to hear that the manufacturer of rosiglitazone (Avandia) provided the FDA with a pooled analysis of 42 RCTs in which rosiglitazone was compared to either placebo or other antidiabetic therapies in patients with type 2 diabetes. The meta-analysis suggested that patients receiving short-term (most studies were of six months duration) treatment with rosiglitazone may have a 30% greater relative risk of heart attacks and other heart-related adverse events than patients treated with placebo or another antidiabetic therapy. Questions of timing of this information and how it was circled arise. Ongoing trials using rosiglitazone (RECORD) may provide additional data but for a drug which was approved in 1999, the delay in obtaining information about the benefit-risk ratio is considerable.



PHILADELPHIA, PA – July 17, 2007

GSK Responds to Online Review of Rosiglitazone by The Cochrane Collaboration

The following is GlaxoSmithKline's [NYSE: GSK] response to an online review published by The Cochrane Collaboration titled "Rosiglitazone for type 2 diabetes mellitus."

This review is another analysis of existing data that have previously been reported. GSK believes that the limited number of studies evaluated generate misleading conclusions and provide no new evidence about the use of rosiglitazone in clinical practice and research.

Questions about the safety of rosiglitazone should be answered by reviewing the totality of the evidence, in particular long-term prospective studies. In ADOPT, all major adverse cardiovascular events (MACE) were analysed and such events were rare in this population and comparable for all treatments - rosiglitazone, metformin and glibenclamide. Furthermore, RECORD, the only study specifically designed to look at cardiovascular outcomes, was not included in the review. Though RECORD is ongoing, the interim findings do not show evidence of a difference in cardiovascular death between rosiglitazone and control groups and showed no significant difference for heart attack.

Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials

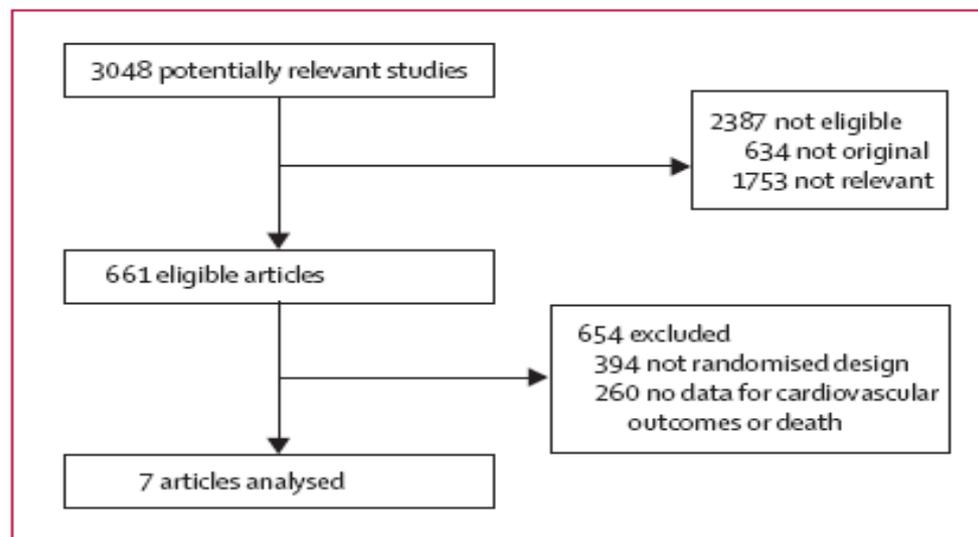
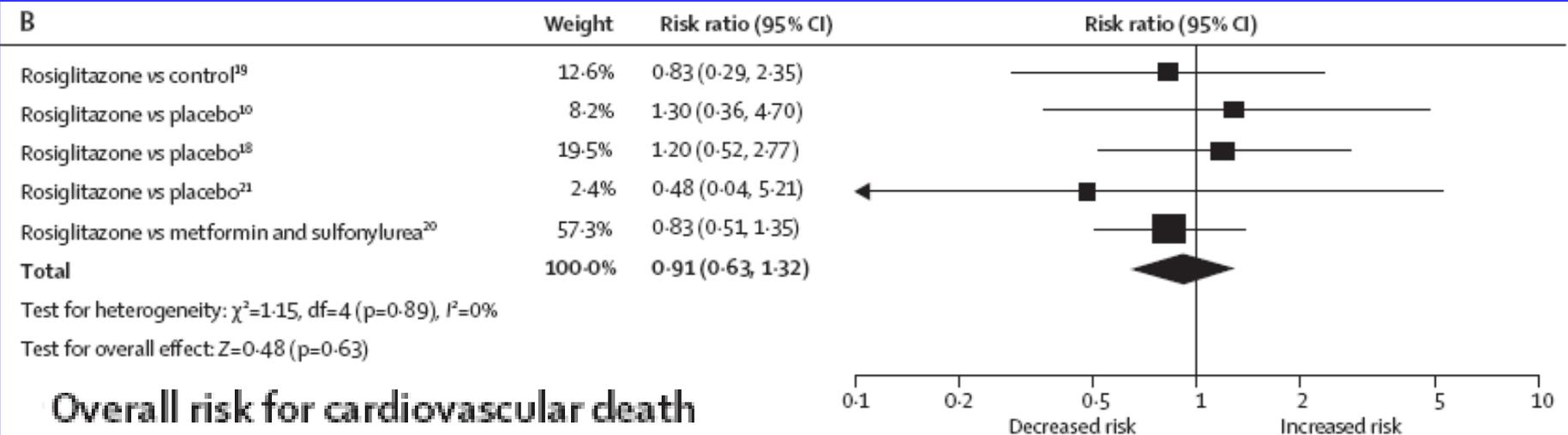
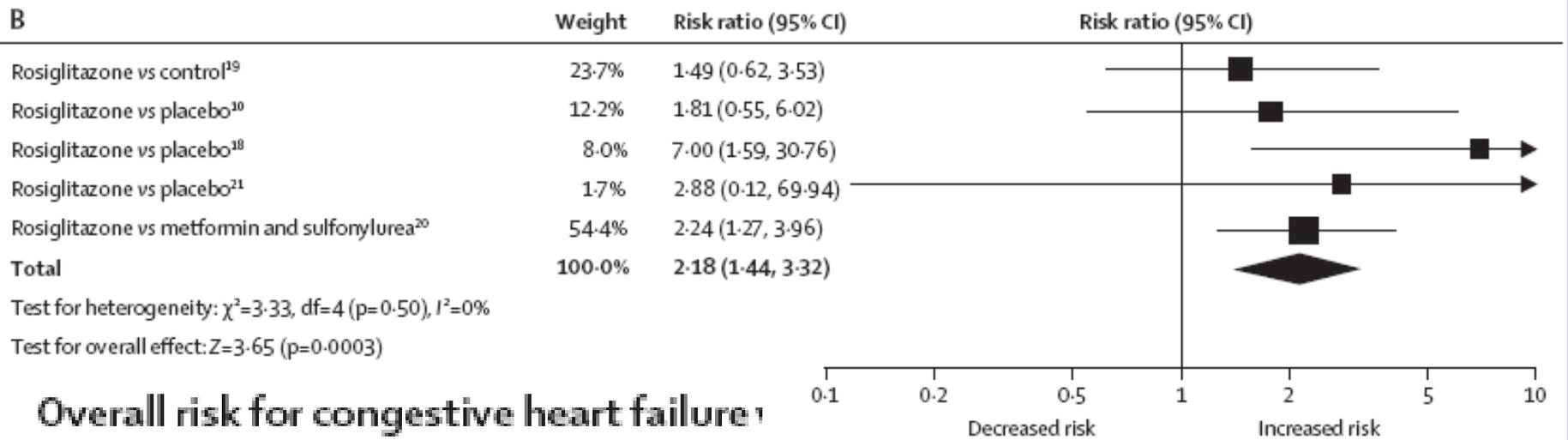


Figure 1: Search strategy profile

Daily TZD dosage (mg)	Participants	CHF definition criteria	Trial duration (months)	Mean age (years)	Sex (men)	BMI (kg/m ²)	Baseline HbA _{1c}	Baseline medical history				
								HTN	HLD	CAD	CHF	CKD or nephropathy

Interpretation Congestive heart failure in patients given TZDs might not carry the risk that is usually associated with congestive heart failure which is caused by progressive systolic or diastolic dysfunction of the left ventricle. Longer follow-up and better characterisation of such patients is needed to determine the effect of TZDs on overall cardiovascular outcome.



Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy

Note added in proof: While this article was in production, further examination of data on adverse events identified a higher rate of fractures in the group receiving rosiglitazone. This was an unexpected event that was not part of the prespecified analysis plan.

	Rosiglitazone	Metformin	Glyburide
	<i>number of patients (percent)</i>		
Men	32 (3.95)	29 (3.36)	28 (3.35)
Women	60 (9.30)	30 (5.08)*	21 (3.47)*
Lower limb	36 (5.58)	18 (3.05)†	8 (1.32)*
Upper limb	22 (3.41)	10 (1.69)	9 (1.49)†
Spinal	1 (0.16)	1 (0.17)	1 (0.17)

* $P < 0.01$ for the comparison with rosiglitazone (unadjusted, contingency chi-square test).

† $P < 0.05$ for the comparison with rosiglitazone (unadjusted, contingency chi-square test).

Figure 1. Flowchart of Pioglitazone Trials Used for the Meta-analysis

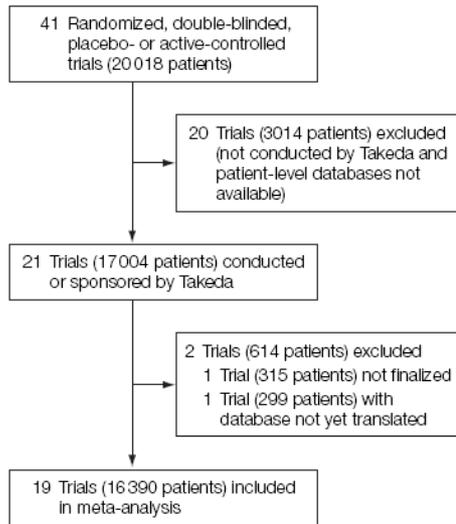
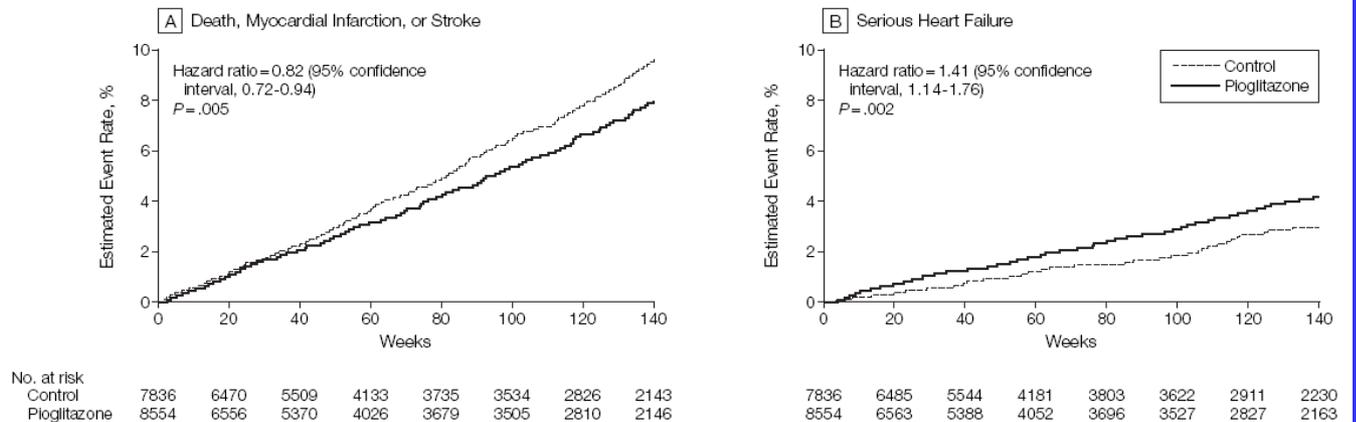


Figure 2. Estimates of the Incidence of the Cardiovascular End Points According to Randomized Treatment Assignment to Pioglitazone or Control



A, Kaplan-Meier curve of time to death from any cause, nonfatal myocardial infarction, or nonfatal stroke. B, Shows curve of time to serious congestive heart failure.

Rosiglitazone and Cardiovascular Risk

Rosiglitazone — Continued Uncertainty about Safety

Rosiglitazone and Cardiotoxicity — Weighing the Evidence

**Cardiovascular Risk
and the Thiazolidinediones**
Déjà Vu All Over Again?

Thiazolidinediones, deadly sins, surrogates, and elephants

Overview:

Meta-analysis

Secondary data analysis

Participant selection

Ads

Secondary data analysis:

Objectives:

Open up possibilities for obtaining preliminary data

Consider the range of secondary data analysis in addition to meta-analysis

Benefits:

Data often available, therefore study should be cheap to perform.

Good way to work through the problems of the study design including case definition, controls, potential biases and develop statistical techniques.

Preliminary data for applications

Networking and collaborations

Asking for data:

Sharing and collaborating, not appropriating.

Most large studies have data resources available or have standard procedures for collaborations.

Creative add-ons to existing studies—nested studies—use the original sample to answer a different but related questions. May involve using laboratory specimens.

Don't be shy!

Sources of data:

Published statistics

Federal or local survey data (geocoding)

Computerized medical records

Industrial records

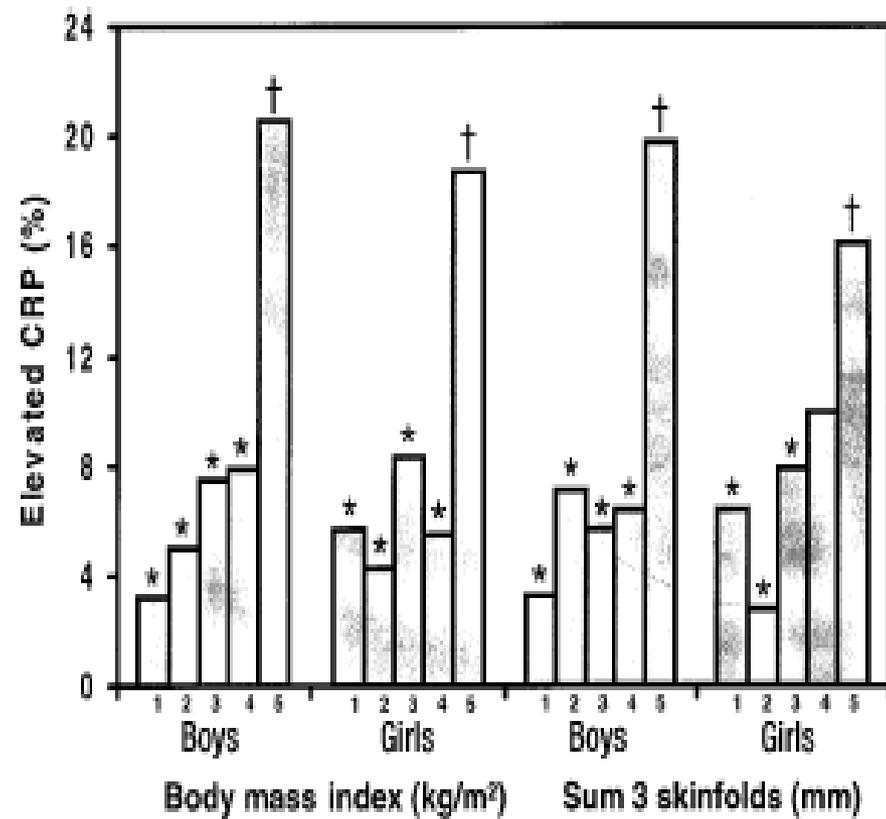
Published studies

Observation studies – case/control

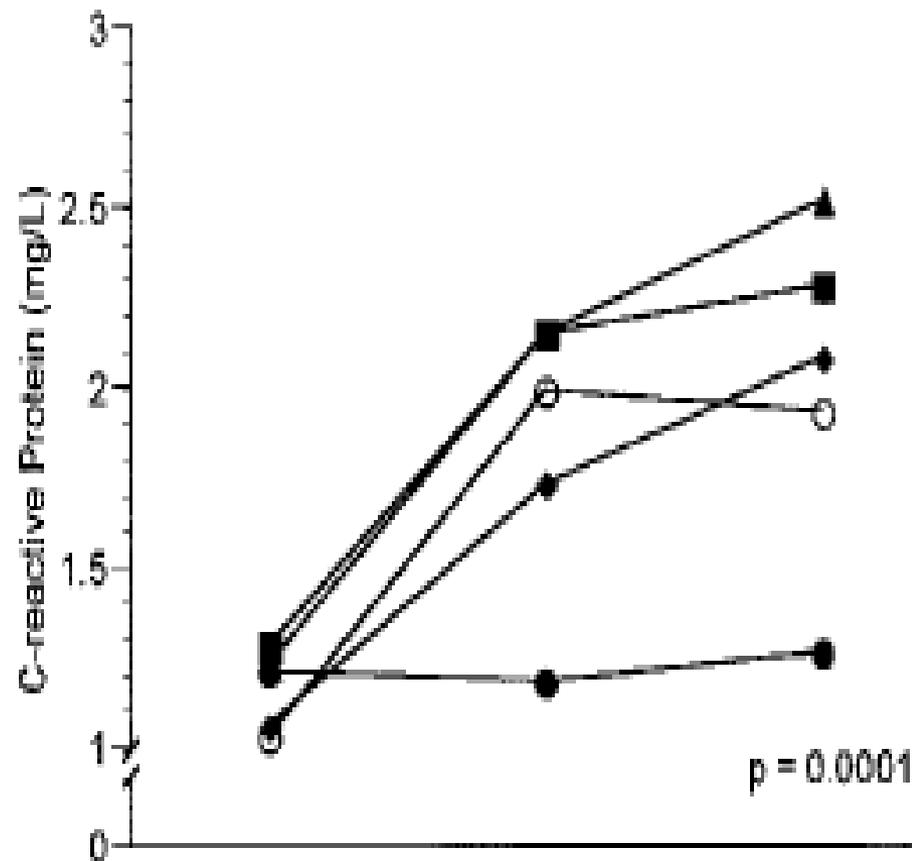
Trials – pre and post

Collected data – new hypothesis –CRP and obesity in children

Fig 1. Prevalence of elevated (≥ 22 mg/dL) serum CRP concentration by categories of BMI and sum of 3 skinfolds (triceps, subscapula, and supra-iliac skinfold) in 3512 children 8 to 16 years of age, NHANES III, 1988–1994. The categories were defined according to percentiles of the distribution: ≤ 25 th percentile = 1; 25.1–50th = 2; 50.1–75th = 3; 75.1–85 = 4; and >85 th = 5 = overweight. * $P < .05$ versus highest category; † $P < .05$ versus lowest category.



Novel marker – measure change before and after intervention



Estimated mean level of each inflammation factor over time by randomized treatment assignment. ● indicates placebo; ○, CEE; ▲, CEE + MPA cyc; ■, CEE + MPA con; ◆, CEE + MP. Probability value from log-transformed data, adjusted for clinical center and hysterectomy status, and for 10 pairwise comparisons. For C-reactive protein and E-selectin, the significant differences were between the placebo group and each active treatment arm. For fibrinogen, analyses were adjusted for the baseline value, and the significant difference was between CEE and placebo.

**Ridker et al. Nested case-control WHI
C-reactive protein and HRT-synergistic effect?**

	C-Reactive Protein, Median (Interquartile Range), mg/dL	
	Cases	Controls
Nonusers	0.27 (0.11-0.62)	0.20 (0.08-0.40)
Current users	0.42 (0.21-0.78)	0.34 (0.15-0.55)
<i>P</i> value†	.001	<.001

Novel marker in cases and controls--?? risk

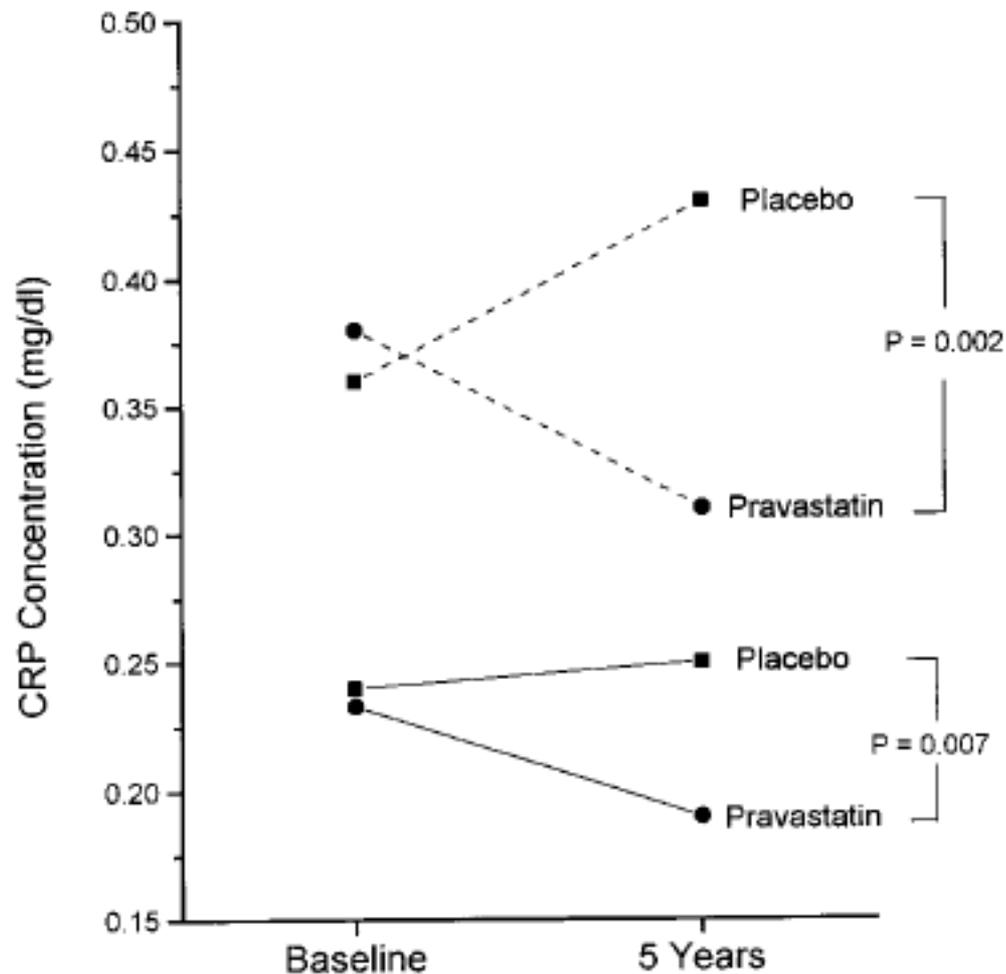


Figure 2. Median (solid lines) and mean (dotted lines) levels of CRP at baseline and at 60 months, according to placebo or pravastatin assignment.

Do statins reduce both lipids and CRP?

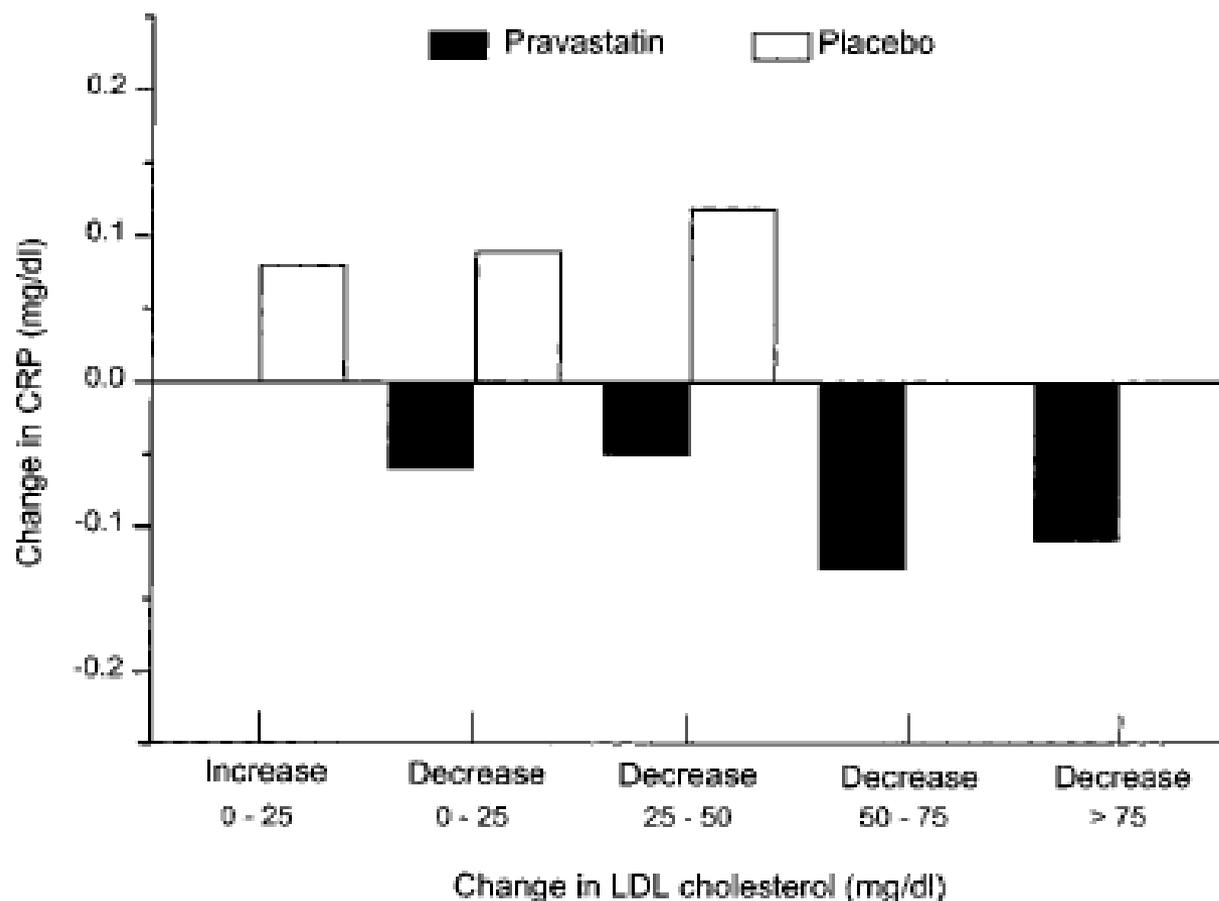


Figure 3. Mean change in CRP levels over time according to observed changes in LDL cholesterol. Data are shown for those allocated to pravastatin (solid bars) or to placebo (open bars).

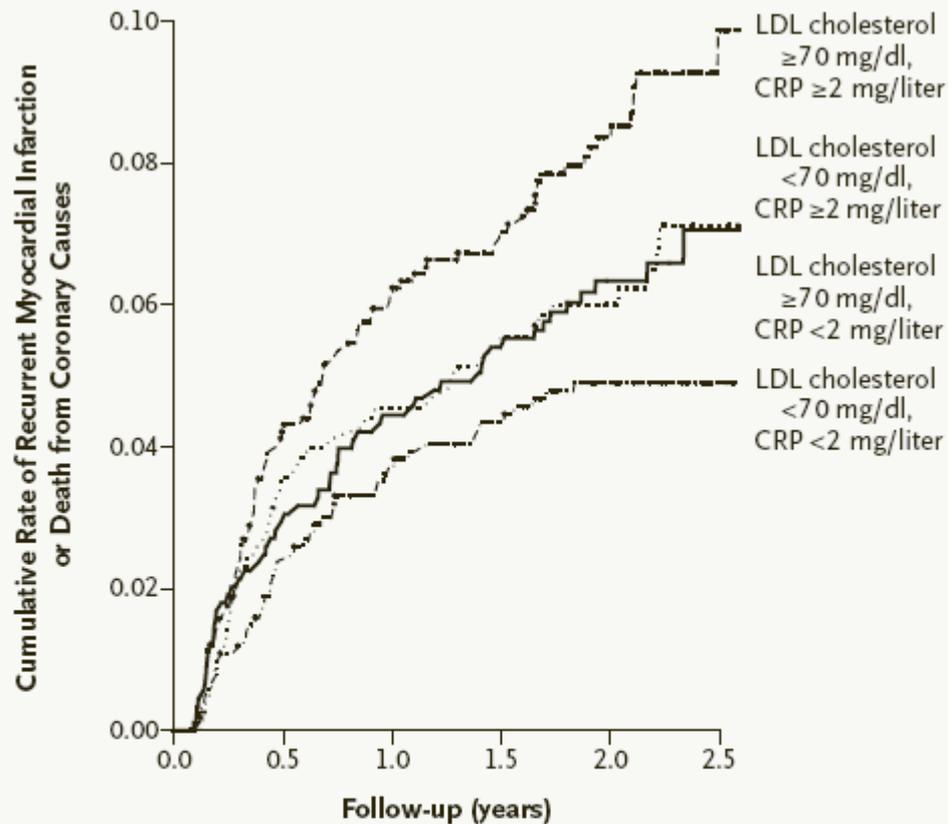


Figure 3. Cumulative Incidence of Recurrent Myocardial Infarction or Death from Coronary Causes, According to the Achieved Levels of Both LDL Cholesterol and CRP.

The median value of each marker is included for the sake of completeness, since no patient had the exact median value of either marker.

Result from clinical trial – lowering LDL cholesterol and CRP is synergistic

Downside:

Hypothesis-generating, power, compromises in design and problems of data-dredging

Easy to make errors because you didn't design study-need to learn as much as you can before starting to use data

Statistical help

Still need to assess the validity of the results

Does the literature support your observation?

Is the result biologically plausible?

Overview:

Meta-analysis

Secondary data analysis

Participant selection

Ads

Overview:

Your research question:

What are the health effects of estrogen therapy for postmenopausal women?

Meta-analysis: Estrogen use and CHD risk, 1991

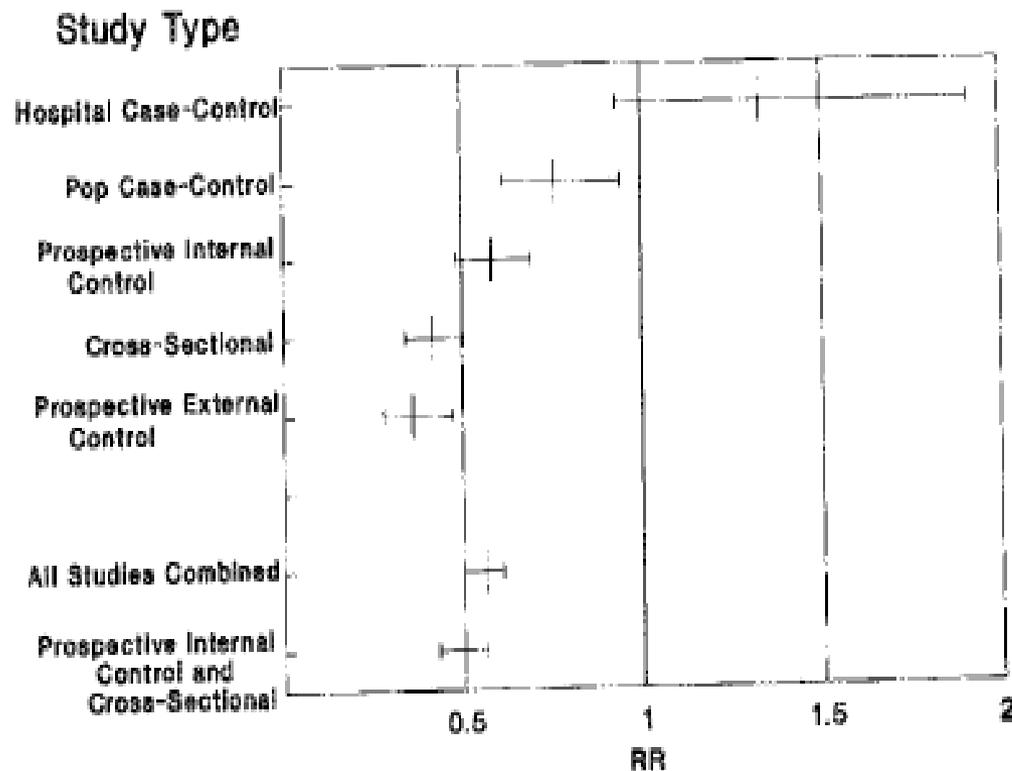


FIG. 2. Summary relative risks and 95% confidence interval estimates for studies of estrogen use and risk of coronary disease, by study design. There was significant ($P < 0.001$) heterogeneity by study design.

Meta-analysis: Estrogen and Breast Cancer, 1991

Table 3.—Effect of Estrogen Replacement Therapy on Breast Cancer Risk in Women: Data From 15 Case-Control Studies Stratified and Pooled by High, Moderate, and Low Quality Scores, 1976 Through 1989

Reference, y	Quality Score	Proportional Increase in Risk for Each Year of Estrogen Use	Mean Proportional Increase in Risk for Each Year of Estrogen Use by Quality Score (95% Confidence Interval)*
High Quality Score: 71-83			
Wingo et al, ²⁶ 1987	83	0.003	
Bergkvist et al, ¹¹ 1989	82	0.060	
Ross et al, ²⁷ 1980	75	0.060	
Hoover et al, ²⁸ 1981	72	0.060	
Hill et al, ²⁹ 1984	71	0.053	
	77 (60-88)†		0.040 (0.030-0.050)
Moderate Quality Score: 40-57			
Nomura et al, ³⁰ 1986	57	-0.002	
Bilmon et al, ³¹ 1986	51	0.001	
Kaufman et al, ³² 1984	45	-0.007	
LaVecchia et al, ³³ 1986	43	0.008	
Kelsey et al, ³⁴ 1981	40	-0.081	
	47 (33-61)†		-0.008 (-0.017-0.009)
Low Quality Score: 15-38			
Hulka et al, ³⁵ 1982	38	0.068	
Jick et al, ³⁶ 1986	35	0.007	
Ravlnhar et al, ³⁷ 1979	26	-0.016	
Wynder et al, ³⁸ 1978	25	-0.200	
Saithveit et al, ³⁹ 1977	15	-0.084	
	28 (0-47)†		0.006 (0.000-0.012)

*Results obtained by combining dose-response slopes across studies for each quality score category, then converting the results to mean proportional increase in risk per year of estrogen use as described in "Methods" section.

†Mean quality score (95% confidence interval).

Can a meta-analysis reach the wrong conclusion??

Even if biologically plausible, may be wrong

Biases may overestimate benefit, underestimate risk

Healthy use selection bias

Better health=usage=better outcomes

Compliance bias

Good adherers=good health=good outcomes

Surveillance bias

See doctor more often=better outcomes

Survivor bias

Continue to use=better health=better outcomes

Participant selection:

Clinicians: Clinical judgment- I “know” who I need.

**Biologists: Everything is already so uncontrolled
One person=all people**

Why do you need to get it right?

Power

Participant recruitment/retention costs

Validity

What to consider?

Alternative explanations for outcome you hope for

Design study to minimize alternative explanations

Choosing subjects to address potential bias

THE HERS STUDY

Heart and Estrogen/progestin Replacement Study

Randomized double-blind placebo-controlled trial of daily use of conjugated equine estrogens plus medroxyprogesterone acetate on combined rate of nonfatal MI and CHD death among postmenopausal women with coronary disease.

Postmenopausal: Age at least 55, no natural menses for at least 5 years OR
No natural menses for at least 1 year and FSH level > 40 IU/L OR
Documented oophorectomy OR
Reported oophorectomy with FSH level > 40 IU/L and
estradiol < 25 pg/mL

Established heart disease: Evidence of one or more of the following:
MI, coronary artery bypass graft surgery,
Percutaneous coronary revascularization,
Angiogram proven 50% occlusion of 1 or more
major coronary arteries

Exclusions:

EXCLUSIONS FROM HERS:

- CHS event within 6 months of randomization
- Serum triglycerides >300 mg/dL
- Use of hormones within 3 months of screening
- History of DVT or pulmonary embolism
- History of breast cancer or suggestive mammogram
- History of endometrial cancer, abnormal uterine bleeding, endometrial thickness of greater than 5 mm on screening
- Abnormal PAP test
- Serum aspartate aminotransferase level > 1.2 times normal
- Planning to move within 4 years
- Disease other than CHD deemed likely to be fatal within 4 years
- NYHA Class III or IV congestive failure
- Alcoholism
- Uncontrolled hypertension, diabetes
- Participation in another clinical study
- Less than 80% compliance with placebo run-in prior to randomization
- History of intolerance to hormone therapy

Participant selection:

On exposure:

Say HRT....

“Are you currently using HRT?”

Criteria:

What type of HRT? [Is it really an HRT?]

Which formulation? [Response may vary by type]

How long has it been taken?

Taken continuously or intermittently? [Years taken may affect the effect]

Has she taken the same type for the whole time?

Participant selection:

On “case” status:

Defining a case also identifies your controls

You want your controls from the same reference population, but to truly differ from your cases in terms of the underlying feature you are studying

Mixing of “cases” in your “control” group pushes toward a null result!

Technoepidemiology:

Low tech:

MI on ECG (40% MI silent)
Ischemic pattern on ECG
Peripheral vascular disease by
ankle/arm blood pressure
Arterial pulse-wave velocity
Carotid thickening,
distensibility, plaque

High tech:

Electron-beam CT for calcium
Angiography
Echo-wall motion studies
MRI studies of the heart or
carotids

Table 1.—Baseline Characteristics of HERS Participants (n=2763) by Treatment Group*

Characteristic	Treatment Group		P Value
	Estrogen-Progestin (n=1380)	Placebo (n=1383)	
Demographics			
Age, mean±SD, y	67±7	67±7	.32
White, %	88	90	.14
Education, mean±SD, y	13±3	13±3	.84
CHD risk factors			
Current smoker, %	13	13	.84
Diabetes on oral medication or insulin, %	19	18	.44
Systolic blood pressure, mean±SD, mm Hg	135±19	135±19	.88
Diastolic blood pressure, mean±SD, mm Hg	73±10	73±10	.89
LDL cholesterol, mean±SD, mmol/L (mg/dL)	3.75±0.96 (145±37)	3.75±0.98 (145±38)	.83
HDL cholesterol, mean±SD, mmol/L (mg/dL)	1.29±0.34 (50±13)	1.29±0.34 (50±13)	.41
Triglyceride, mean±SD, mmol/L (mg/dL)	1.90±0.72 (168±64)	1.86±0.72 (165±64)	.25
Time since last menstrual period, mean ± SD, y	18±8	18±8	.31
Body mass index >27 kg/m ² , %	57	55	.44
Exercise >3 times weekly, %	39	38	.72
No. of drinks per week, mean±SD	1.4±4	1.3±4	.83
General health poor or fair, %	24	24	.94
Postmenopausal estrogen use, %†	24	23	.43
CHD manifestations			
Signs of congestive heart failure, %‡	10	9	.38
Q-wave myocardial infarction, %	17	17	.94
Percutaneous coronary revascularization, %	45	45	.96
Coronary artery bypass graft surgery, %	42	41	.64
Medication use			
Aspirin, %	78	78	.73
β-Blockers, %	33	32	.72
Lipid-lowering medications, %	45	47	.26
Calcium channel blockers, %	55	55	.83
Angiotensin-converting enzyme inhibitors, %	17	18	.57
Diuretics, %	28	28	.79
Multivitamins, %	29	30	.45

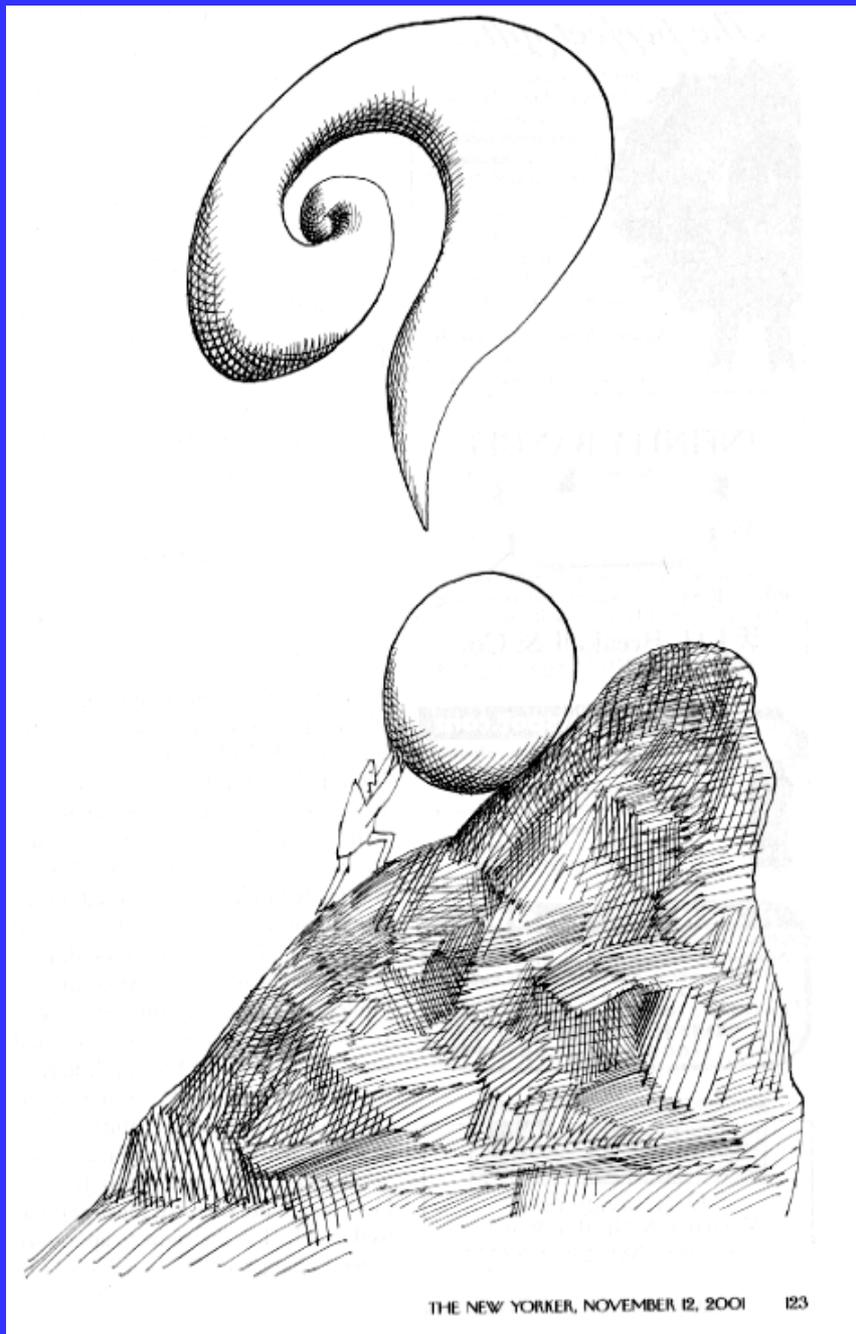
*HERS indicates Heart and Estrogen/progestin Replacement Study; CHD, coronary heart disease; LDL, low-density lipoprotein; and HDL, high-density lipoprotein. P values are for difference between treatment groups by *t* test or χ^2 .

†Estrogen use refers to use after menopause but not within 3 months of HERS screening.

‡Presence of jugular venous distention more than 8 cm H₂O, S₃ heart sound, rales, or pitting peripheral edema.

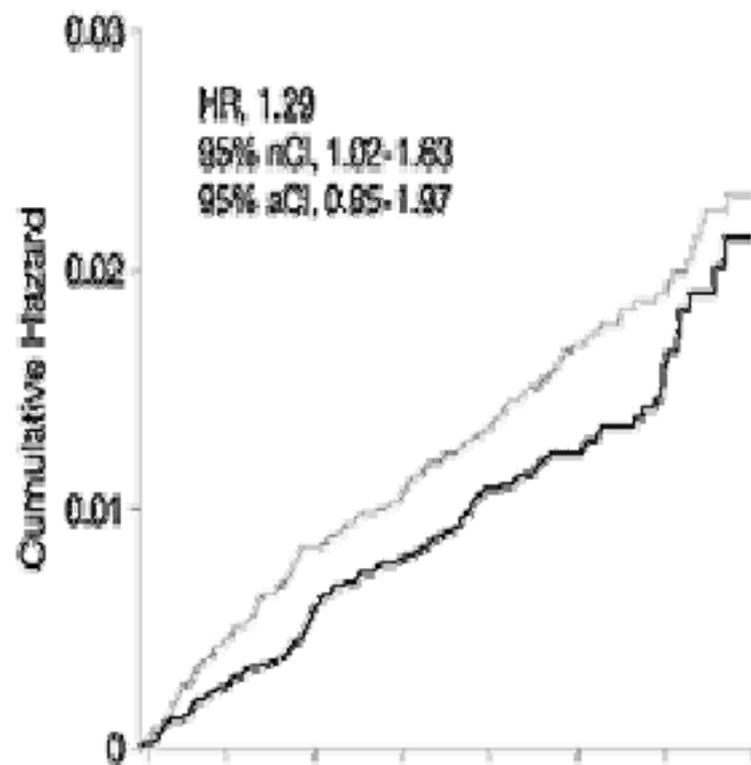
Table 3.—Outcomes by Treatment Group and Year Since Randomization*

Outcome and Period	Estrogen-Progestin		Placebo		RH (95% CI)	<i>P</i> Value‡
	No.	Rate†	No.	Rate†		
Primary CHD event§						
Year 1	57	42.5	38	28.0	1.52 (1.01-2.29)	.009
Year 2	47	37.0	48	37.1	1.00 (0.67-1.49)	
Year 3	35	28.8	41	33.1	0.87 (0.55-1.37)	
Years 4 and 5	33	23.0	49	34.4	0.67 (0.43-1.04)	
Nonfatal myocardial infarction						
Year 1	42	31.3	29	21.4	1.47 (0.91-2.36)	.01
Year 2	34	26.8	37	28.6	0.94 (0.59-1.49)	
Year 3	20	16.5	29	23.4	0.70 (0.40-1.24)	
Years 4 and 5	20	13.9	34	23.9	0.58 (0.34-1.02)	
CHD death						
Year 1	17	12.5	11	8.0	1.56 (0.73-3.32)	.34
Year 2	19	14.4	13	9.7	1.48 (0.73-2.99)	
Year 3	18	14.0	16	12.3	1.14 (0.58-2.24)	
Years 4 and 5	17	11.0	18	11.6	0.95 (0.49-1.84)	
Unstable angina or coronary revascularization¶						

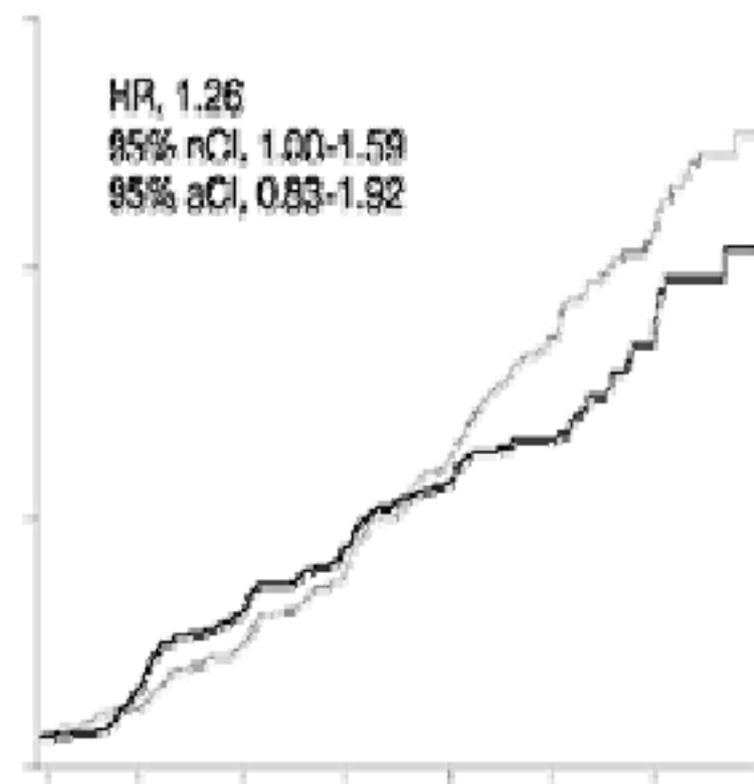


WHI Results for CHD and Breast Cancer

Coronary Heart Disease



Invasive Breast Cancer



No. at Risk

Estrogen +

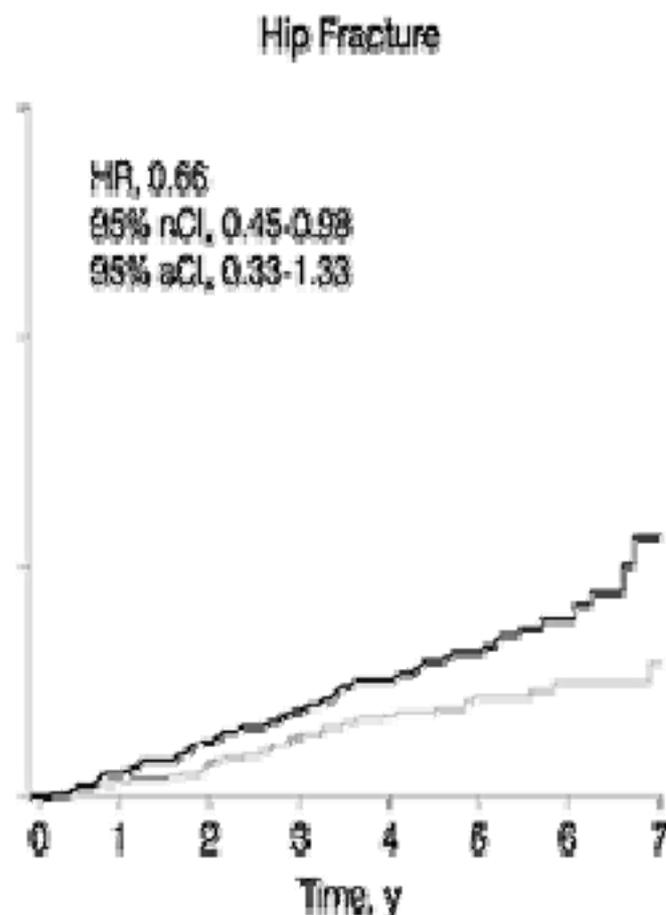
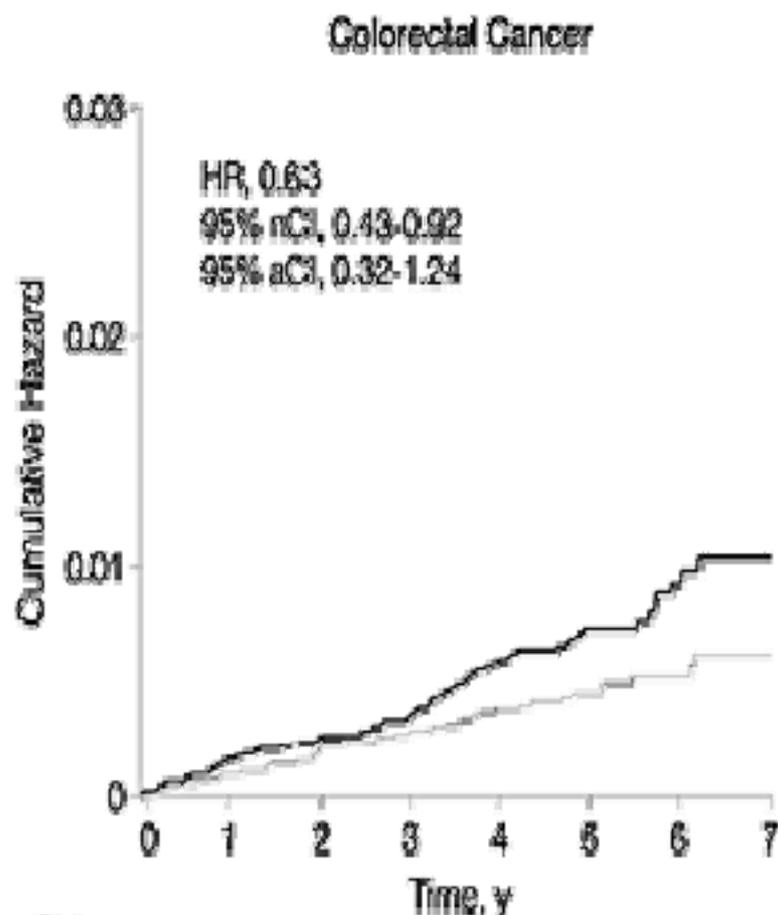
Progestin 8506 8353 8248 8133 7904 4251 2085 814

Placebo 8102 7999 7899 7789 8639 3949 1756 523

8506 8378 8277 8160 7000 4234 2064 801

8102 8001 7891 7772 6619 3922 1740 523

WHI Results for colorectal cancer and hip fracture



No. at Risk

Estrogen +

Progestin 8506 8378 8297 8194 7073 4305 2111 825

Placebo 8102 8003 7916 7814 6660 3958 1756 522

8506 8382 8299 8190 7073 4305 2116 826

8102 8009 7915 7807 6659 3958 1763 525

Updated meta-analysis of estrogen risks, 2003

Table 4. Hormone Replacement Therapy Use in 10 000 Women: Benefits and Harms per Year

	Relative Risk (95% Confidence Interval [CI]) From Review and Meta-analysis	Hazard Ratio (95% CI) From WHI*	Events Prevented or Caused per Year, No.					
			Aged 55-64 Years		Aged 65-74 Years		Aged 75-84 Years	
			Review	WHI	Review	WHI	Review	WHI
Benefits (prevention)								
Hip fractures	0.76 (0.56-1.01)	0.66 (0.33-1.33)	3	4	9	13	33	47
Wrist fractures	0.44 (0.23-0.84)	NA	34	...	37.5	...	45	...
Vertebral fractures	0.60 (0.36-0.99)	0.66 (0.32-1.34)	32	27	57	49	91	78
Cases of colon cancer	0.80 (0.74-0.86)	0.63 (0.32-1.24)	2	3	4	7	7	12.5
Uncertain benefits								
Cases of dementia prevented	0.66 (0.53-0.82)	NA	17†	...	34	...	68†	...
Harms (caused)								
Coronary heart disease events	0.91 (0.67-1.33)	1.29 (1.02-1.63)	0	6	0	9	0	11.5
Strokes	1.12 (1.01-1.23)	1.41 (0.86-2.31)	1†	4†	3	9	6†	19†
Thromboembolic events	2.14 (1.64-2.81)	2.11 (1.26-3.55)	1.5	1.4	1.5	1.4	1.5	1.4
Thromboembolic events during first year	3.49 (2.33-5.59)	NA	3	...	3	...	3	...
Breast cancer cases (<5 years' use)	1.0 to 1.14	NA	0 to 2.5	...	0 to 6	...	0 to 7	...
Breast cancer cases (≥5 years' use)	1.23 to 1.35	1.26 (1.00-1.59)	7 to 11	8	10 to 15	11	11 to 17	12
Cholecystitis cases (<5 years' use)	1.8 (1.6-2.0)	NA	25	...	25	...	25	...
Cholecystitis cases (≥5 years' use)	2.5 (2.0-2.9)	NA	53.5	...	53.5	...	53.5	...

*WHI indicates Women's Health Initiative; NA, not applicable; and ellipses, data not computed. Nominal CIs are indicated for main outcomes of the trial (breast cancer and coronary heart disease); adjusted CIs, for secondary outcomes.

†Estimates are based on extrapolations.

Table 4. Results of Randomized Trials of the Effect of Hormone Replacement Therapy on Atherosclerosis Progression Measured by Coronary Angiography

Study	Regimen	Change in Minimum Coronary Artery Lumen Diameter	<i>P</i> ¹	Change in % Stenosis	<i>P</i> ¹	Change in Average Coronary Artery Lumen Diameter Mean	<i>P</i> ¹
ERA	ERT	-0.09 mm (+0.02 SE)	.97	4.01 (0.92)	.93	NR	—
	PERT	-0.12 mm (+0.02 SE)	.38	4.75 (0.92)	.56	NR	—
	Placebo	-0.09 mm (+0.02 SE)		4.11 (0.92)			
WAVE	ERT/PERT	-0.047 mm/y (+0.15 SD)	.17	NR		0.027 mm/y (+0.11 SD)	6.20
	Placebo	-0.024 mm/y (+0.15 SD)				0.007 mm/y (+0.16 SD)	

¹Compared with placebo.

Abbreviations: ERA, Estrogen Replacement and Atherosclerosis Trial; ERT, estrogen only replacement therapy; SE, standard error; NR, not reported; PERT, progestin/estrogen replacement therapy; WAVE, Womens Angiographic Vitamin and Estrogen Trial; SD, Standard deviation.

Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women

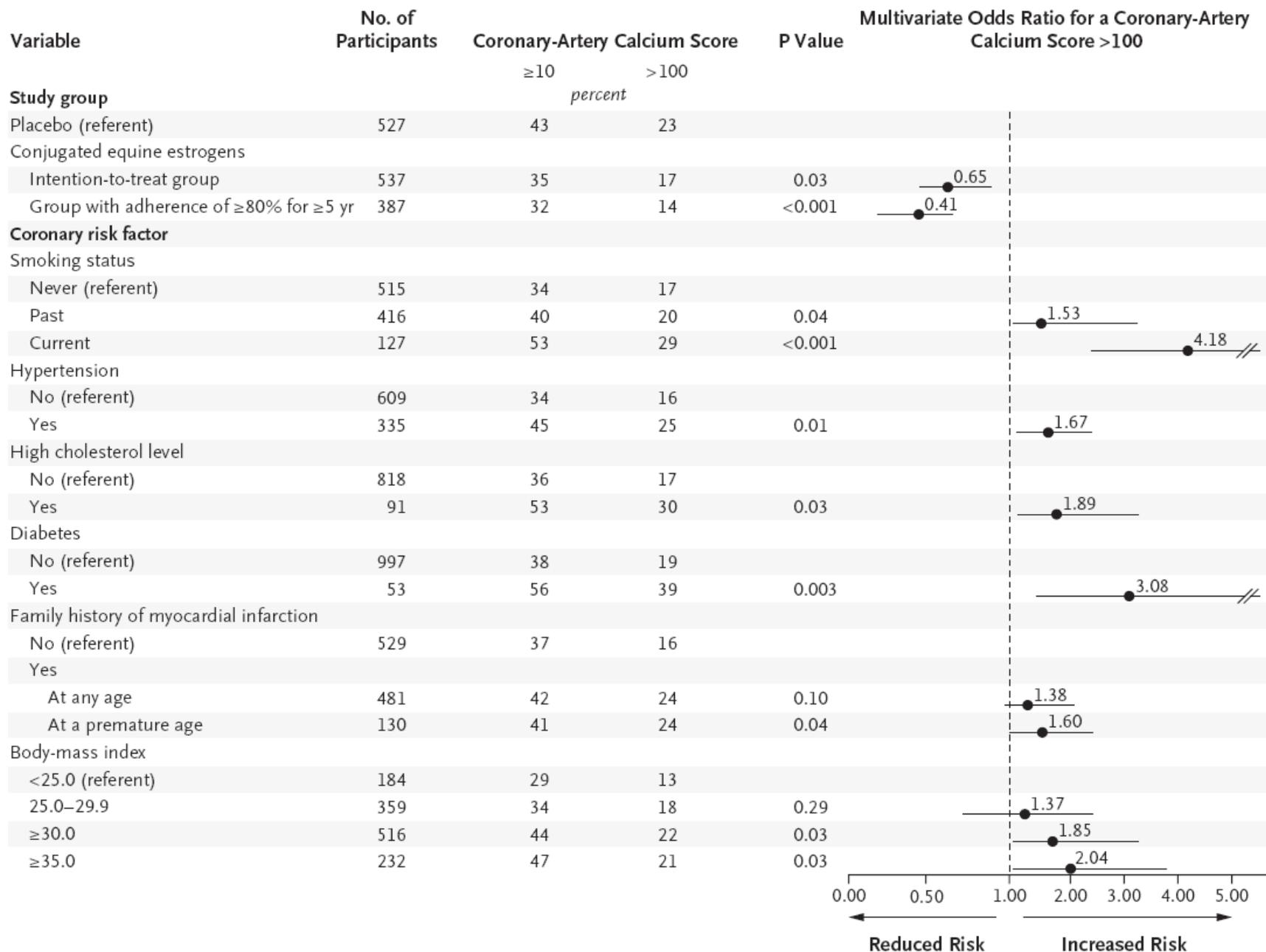
Breast cancer				
Invasive breast cancer	40 (0.15)	70 (0.27)	0.56 (0.38–0.83)	0.003
Estrogen-receptor–positive	25 (0.09)	55 (0.21)	0.45 (0.28–0.72)	<0.001
Estrogen-receptor–negative	13 (0.05)	9 (0.03)	1.44 (0.61–3.36)	0.40
Unknown estrogen-receptor status	2 (0.007)	6 (0.02)	0.33 (0.07–1.63)	0.15
Noninvasive breast cancer‡	11 (0.04)	5 (0.02)	2.17 (0.75–6.24)	0.14
All breast cancers§	52 (0.20)	76 (0.29)	0.67 (0.47–0.96)	0.03
Fracture				
Clinical nonvertebral	428 (1.67)	438 (1.73)	0.96 (0.84–1.10)	0.59
Clinical vertebral	64 (0.24)	97 (0.37)	0.65 (0.47–0.89)	0.007
Death				
Any cause	554 (2.07)	595 (2.25)	0.92 (0.82–1.03)	0.16
Cardiovascular cause	362 (1.35)	355 (1.34)	1.01 (0.87–1.17)	0.91
Noncoronary	107 (0.40)	81 (0.31)	1.31 (0.98–1.74)	0.07
Cerebrovascular (stroke)¶	59 (0.22)	39 (0.15)	1.49 (1.00–2.24)	0.05
Venous thromboembolism	10 (0.04)	5 (0.02)	1.98 (0.68–5.79)	0.20
Noncardiovascular cause	188 (0.70)	231 (0.87)	0.80 (0.66–0.98)	0.03
Cancers	97 (0.36)	103 (0.39)	0.93 (0.70–1.23)	0.61
Noncancer	91 (0.34)	128 (0.48)	0.70 (0.54–0.92)	0.01
Cause unavailable	4 (0.02)	9 (0.03)	0.44 (0.14–1.43)	0.16

Raloxifene is a selective estrogen-receptor modulator

Estrogen Therapy and Coronary-Artery Calcification

CONCLUSIONS

Among women 50 to 59 years old at enrollment, the calcified-plaque burden in the coronary arteries after trial completion was lower in women assigned to estrogen than in those assigned to placebo. However, estrogen has complex biologic effects and may influence the risk of cardiovascular events and other outcomes through multiple pathways. (ClinicalTrials.gov number, NCT00000611.)



HRT and the Young at Heart

The translation of basic research to the bedside and to public guidelines requires a collaborative and interactive process conducted with patience and persistence. Just such an iterative process has enabled our emerging appreciation for the potential cardiovascular benefits of hormone-replacement therapy in younger women who have recently undergone menopause.

For the class assignment, look over these ads from the Washington Post Health Section and elsewhere.

Part 1 Grade the 6 ads for depression (starting with second ad). Grade each ad on a scale of one (least) to five (most) for how likely you would be to enter this study if you were eligible.

Is the ad likely to catch your eye? Is the ad clear as to what the study needs? Is it clear what participation would mean?

Depressed 1

Are you Depressed?

Do you suffer from the following symptoms:

- Depressed mood
- Diminished interest or pleasure in activities
- Change in appetite
- Poor sleep
- Restlessness or feeling slowed down
- Fatigue
- Low self-esteem
- Poor concentration

If you have two or more of these symptoms, are between the ages of 18 and 65 and have not responded to an antidepressant medication, you may be eligible to participate in a research study being conducted at CNS Clinical Trials.

For more information, please call 202-885-5710

~ All inquiries are kept strictly confidential. ~



Clinical Trials

Psychiatric Institute of Washington
4228 Wisconsin Avenue, NW
Washington, D.C. 20016

www.clinicalstudies.net

Depressed 2

Depressed Again?

*If you have been depressed before
and were treated
but are now*

Depressed Again



You may be eligible for a depression research study.
Subjects should be between 18 and 65
and not currently on antidepressant medications.
Participants will be compensated for their time.

To learn more about this study, please call

CAPITAL CLINICAL RESEARCH ASSOCIATES

301-770-7375



Have You Been Depressed in the Past?

The NIMH is looking for volunteers to help better understand the causes of depression. The research study includes 6 outpatient visits at the NIH Clinical Center in Bethesda, Maryland.

Patients should be:

- Ages 18-60
- Not currently depressed
- Medication-free
- Otherwise medically healthy

The study includes medical and psychiatric evaluations. Financial compensation and transportation reimbursement provided.

Call: **301-496-5645**
(TTY: 1-866-411-1010)



The National Institute of Mental Health
National Institutes of Health, Department of Health & Human Services

NIMH
National Institute
of Mental Health

Depressed 3

Is the world getting you down?

Is life no fun anymore?
Is your energy level low?
Is your sleeping or eating
out of whack?

If so, you may be eligible for a
clinical research study on
depression at no cost to you.

Call CCRA at 301.770.7375



Capital Clinical Research Associates
Healing Through Knowledge



Depressed 4

ARE YOUR GOLDEN YEARS TURNING BLUE?

DEPRESSION is a significant problem for older Americans, but the symptoms can be difficult to recognize. If you or someone you love is over 60 and has:

- Feelings of sadness and anxiety
- Loss of interest in things previously enjoyed
- Significant changes in eating and/or sleeping patterns
- Feelings of worthlessness

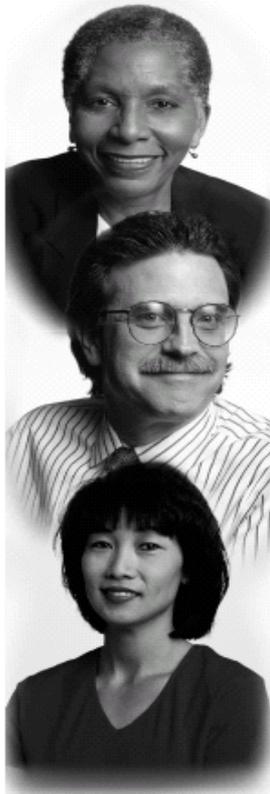
...you may be interested in learning about a research study of an investigational medication for depression. Please call

DUPONT CLINICAL RESEARCH

1-800-999-6955

Depressed 5

Depressed 6



The NIH Clinical Center is currently conducting approximately 1,000 studies. All studies are conducted under the safety and testing standards of the U.S. Food and Drug Administration.

NATIONAL INSTITUTES OF HEALTH NIH Clinical Center Bethesda, Maryland

The NIH Clinical Center is the world's largest hospital devoted entirely to research on common and rare disorders. All study-related tests and medications at the NIH Clinical Center are provided at **no cost**. Please consider participating in a study.

A sample of some of the conditions being studied are:

Inflammatory Bowel Diseases

- Common Variable Immunodeficiency Syndrome
- Crohn's Disease
- Ulcerative Colitis

Liver Disorders

- Hepatitis B or D
- NASH (Non-alcohol related fatty liver disease)

Mental Health Disorders

- Anxiety and Panic Disorders
- Postpartum Depression
- Schizophrenia

Neurological Disorders

- Parkinson's Disease
- Stroke
- Swallowing Disorders



To participate in a study, contact us at:

1-866-444-8805

TTY#: 1-866-411-1010

<http://clinicalcenter.nih.gov> • Se habla español