

ICPPR 2008 - Tamara Harris, M.D., M.S.
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Overview:
Meta-analysis
Secondary data analysis
Participant selection
Ads

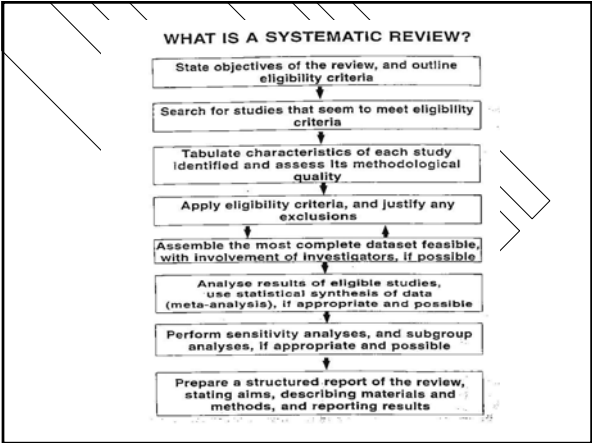
Meta-analysis:
Objective: Understand what a meta-analysis is, how to interpret, and where to go for further guidance
Evidence-based medicine: Clinical practice should follow the best supported information on outcomes.
Presumption- no one definitive study as any study is unlikely to address all known 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



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.)

N Engl J Med 2006;355:2427-43.

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 no. of events/total no. (%)	Control Group no. of events/total no. (%)	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

N Engl J Med 2007;356:2457-71.

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.

<http://www.thecochranelibrary.com>

Press Release



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

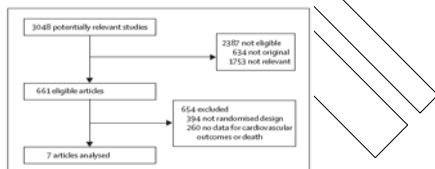
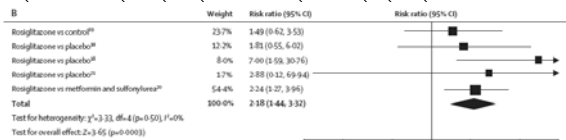


Figure 1: Search strategy profile

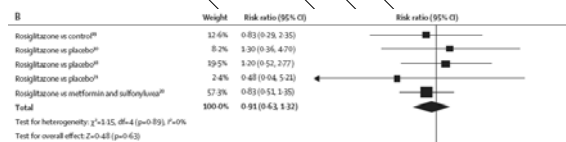
Daily TZD dosage (mg)	Participants	CHF definition criteria	Trial duration (months)	Mean age (years)	Sex (men)	BMI (kg/m ²)	Baseline HbA _{1c}	Baseline medical history
								HTN HLD CAD CHF CVD or nephropathy

Lancet 2005; 376: 1329-38

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 outcomes.



Overall risk for congestive heart failure



Overall risk for cardiovascular death

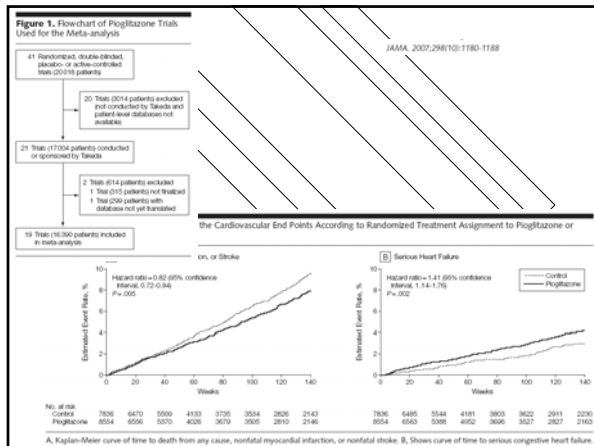
Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy

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
	number of patients (percent)		
Men	32 (3.95)	29 (3.36)	28 (3.35)
Women	60 (9.30)	30 (5.08) ^a	21 (3.47) ^a
Lower limb	36 (5.58)	18 (3.05) [†]	8 (1.32) ^a
Upper limb	22 (3.41)	10 (1.69)	9 (1.49) [†]
Spinal	1 (0.16)	1 (0.17)	1 (0.17)

^a $P<0.01$ for the comparison with rosiglitazone (unadjusted, contingency chi-square test).
[†] $P<0.05$ for the comparison with rosiglitazone (unadjusted, contingency chi-square test).

N Engl J Med 2006;355:2427-43.



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

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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.

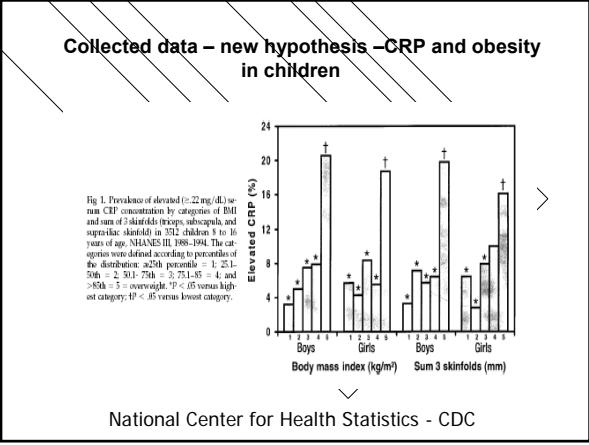
Don't be shy!

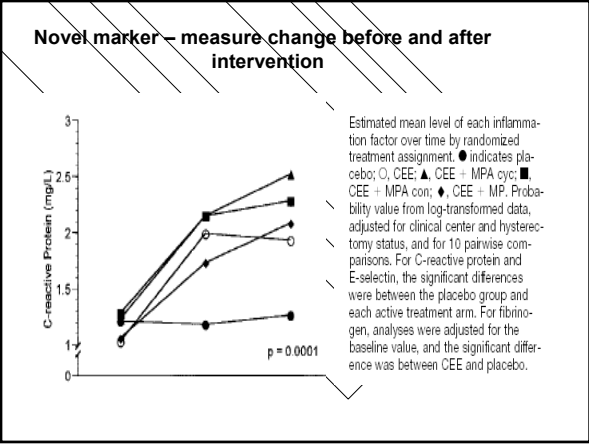
Sources of data:

- Published statistics
- Federal or local survey data (geocoding)
- Computerized medical records
- Industrial records

Published studies

- Observation studies – case/control
- Trials – pre and post





**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)
P value†	.001	<.001

Novel marker in cases and controls--?? risk

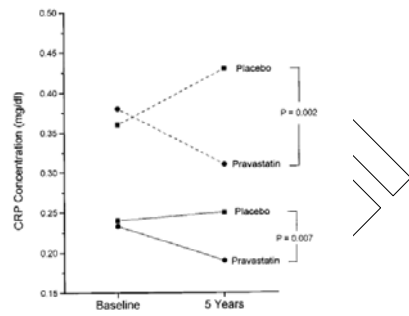


Figure 2. Median (solid lines) and mean (dotted lines) levels of CRP at baseline and at 60 months, according to placebo or pravastatin assignment.

Do statins reduce both lipids and CRP?

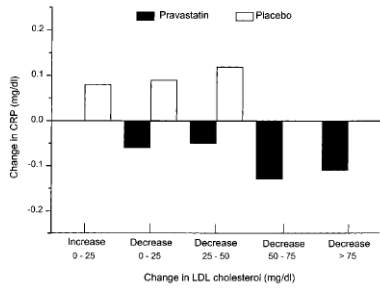
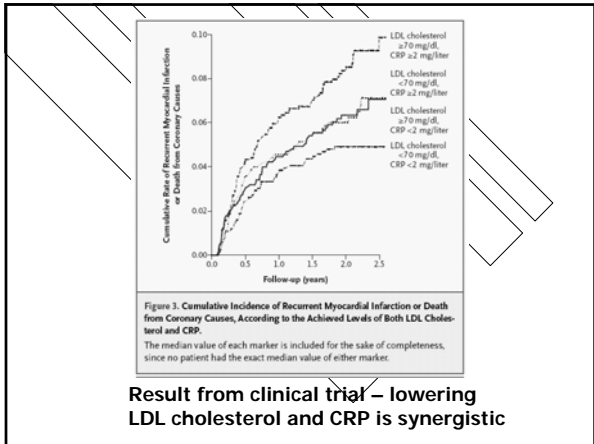


Figure 3. Mean change in CRP levels over time according to observed changes in LDL cholesterol. Data are shown for those allocated to pravastatin (solid bars) or to placebo (open bars).



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:

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Overview:

Your research question:

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

Meta-analysis: Estrogen use and CHD risk, 1991

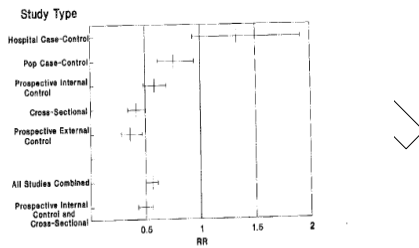


FIG. 2. Summary relative risks and 95% confidence interval estimates for studies of estrogen use and risk of coronary disease, by study design. There was significant ($P < 0.001$) heterogeneity by study design.

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. ¹⁶ 1987	83	0.903	
Bergman et al. ¹⁷ 1986	82	0.050	
Rice et al. ¹⁸ 1986	75	0.060	
Hogwerf et al. ¹⁹ 1981	73	0.060	
Hill et al. ²⁰ 1984	71	0.055	
	72 (86-98)†		0.040 (0.030-0.050)
Moderate Quality Score: 40-67			
Nomura et al. ²¹ 1986	67	-0.002	
Bedrossian et al. ²² 1986	51	-0.001	
Kauhanen et al. ²³ 1984	49	-0.007	
Layton et al. ²⁴ 1986	43	0.308	
Kelsey et al. ²⁵ 1981	40	0.081	
	47 (52-61)†		-0.060 (-0.0717-0.000)
Low Quality Score: 15-36			
Hulka et al. ²⁶ 1982	36	0.069	
Jick et al. ²⁷ 1988	26	0.007	
Reinherz et al. ²⁸ 1979	26	-0.016	
Meyer et al. ²⁹ 1976	25	-0.240	
Earfwell et al. ³⁰ 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: results."
[†]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<25pg/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 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:

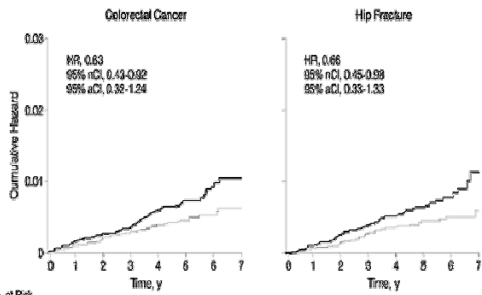
On “case” status:

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!

WHI Results for colorectal cancer and hip fracture



No. at Risk	Colorectal Cancer										Hip Fracture									
Estrogen+																				
Progestin+	8508	8370	8397	8194	7073	4303	2111	825	8508	8392	8298	8190	7073	4325	2110	836				
Placebo	8102	8000	7916	7814	6660	3958	1755	522	8102	8009	7915	7807	6559	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 (prevented)								
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	0.60 (0.74-0.89)	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 (0.89-2.21)	11	4†	3	9	6†	19†
Thromboembolic events	2.14 (1.64-2.81)	2.11 (1.29-3.55)	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 (1.00-1.58)	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 WHI (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	P ¹	Change in % Stenosis		Change in Average Coronary Artery Lumen Diameter Mean	
				P ¹	P ¹	P 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, Women's Angiographic Vitamin and Estrogen Trial; SD, Standard deviation.

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



Psychiatric Institute of Washington
428 Wisconsin Avenue, NW
Washington, D.C. 20016
www.cnsclinicaltrials.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



Depressed 3

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 NIMH
 National Institutes of Health, Department of Health & Human Services




Depressed 4

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



Depressed 5

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 6



**NATIONAL INSTITUTES OF HEALTH
 NIH Clinical Center
 Bethesda, Maryland**

The NIH Clinical Center is the world's largest hospital devoted entirely to research on complex 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 C
- NASH (non-alcohol related fatty liver disease)

Mental Health Disorders

- Anxiety and Panic Disorders
- Postpartum Depression
- Schizophrenia

Neurological Disorders

- Parkinson's Disease
- Stroke
- Dementing Disorders

The NIH Clinical Center is currently conducting approximately 1,000 studies. All studies use medical tests that are safe and tested standards of the U.S. Food and Drug Administration.

To participate in a study, contact us at
1-866-464-2869
TTY: 1-866-411-1010
<http://clinicalcenter.nih.gov> • for health experts

ICPPR 2008 - Tamara Harris, M.D., M.S.
 harris99@mail.nih.gov
