

Adherence Main Effects

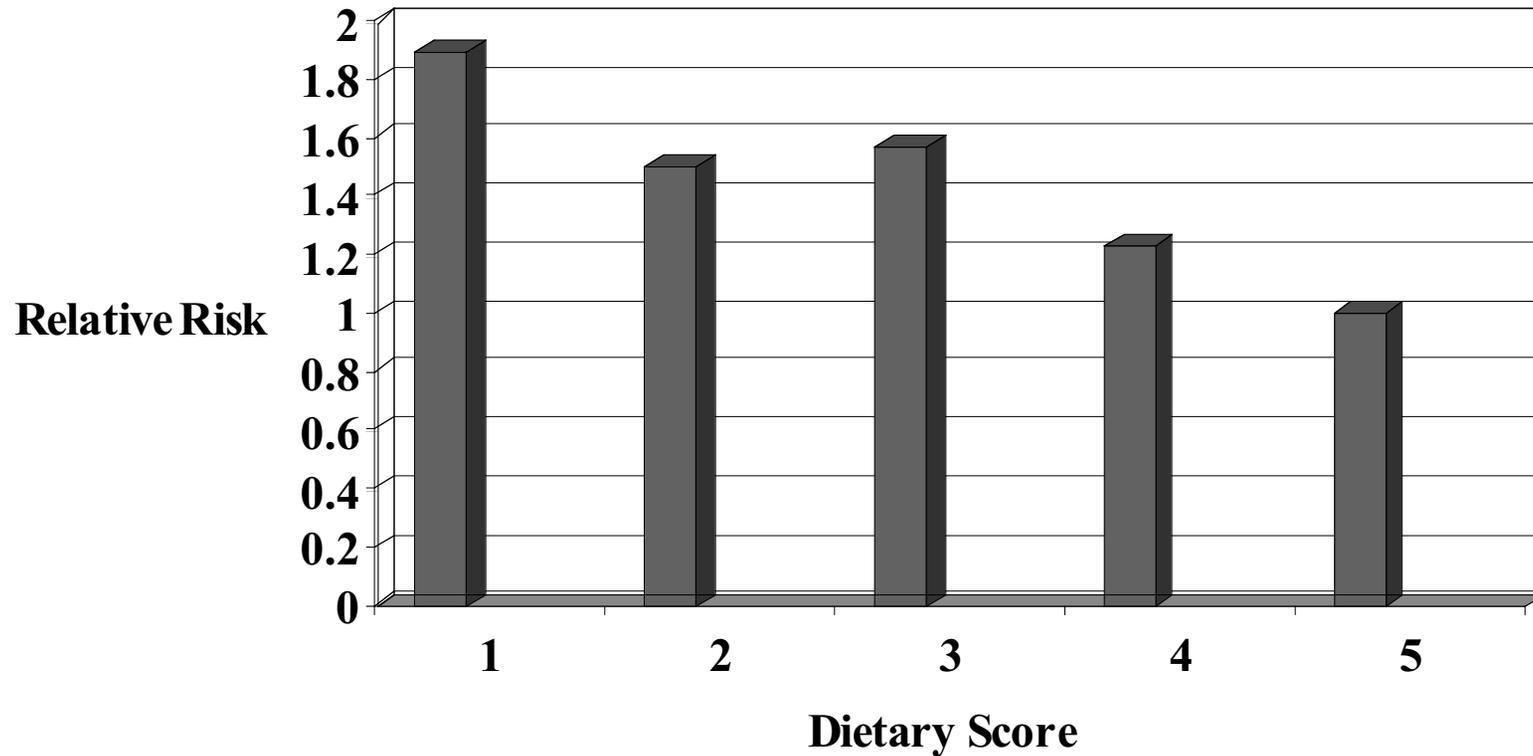
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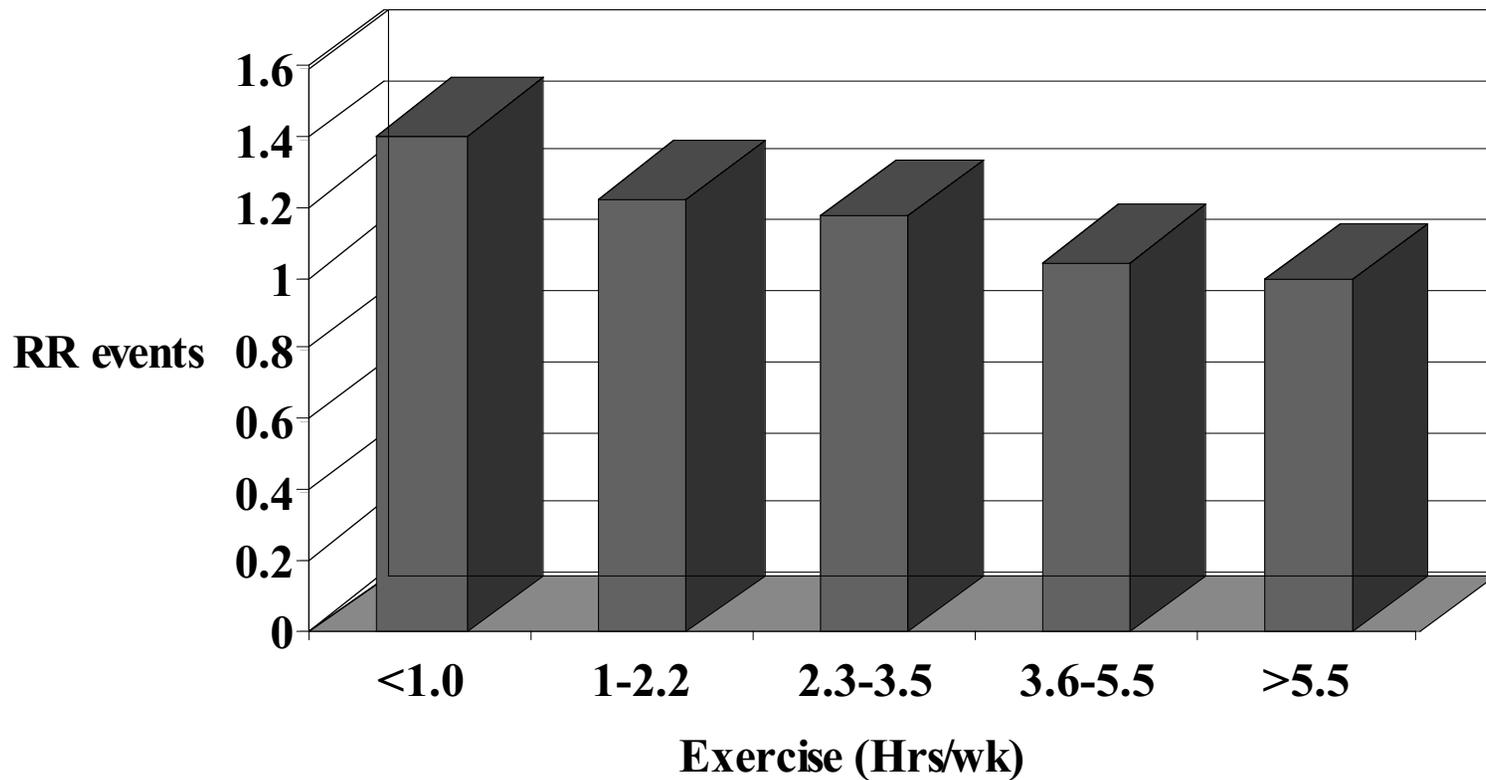
Stampfer et al, 2000 NEJM Nurses Health Study

- N = 18,129 nurses
- All disease free at baseline
- 14 year follow-up
- 1,128 major CHD events
- 296 fatal
- 832 non-fatal

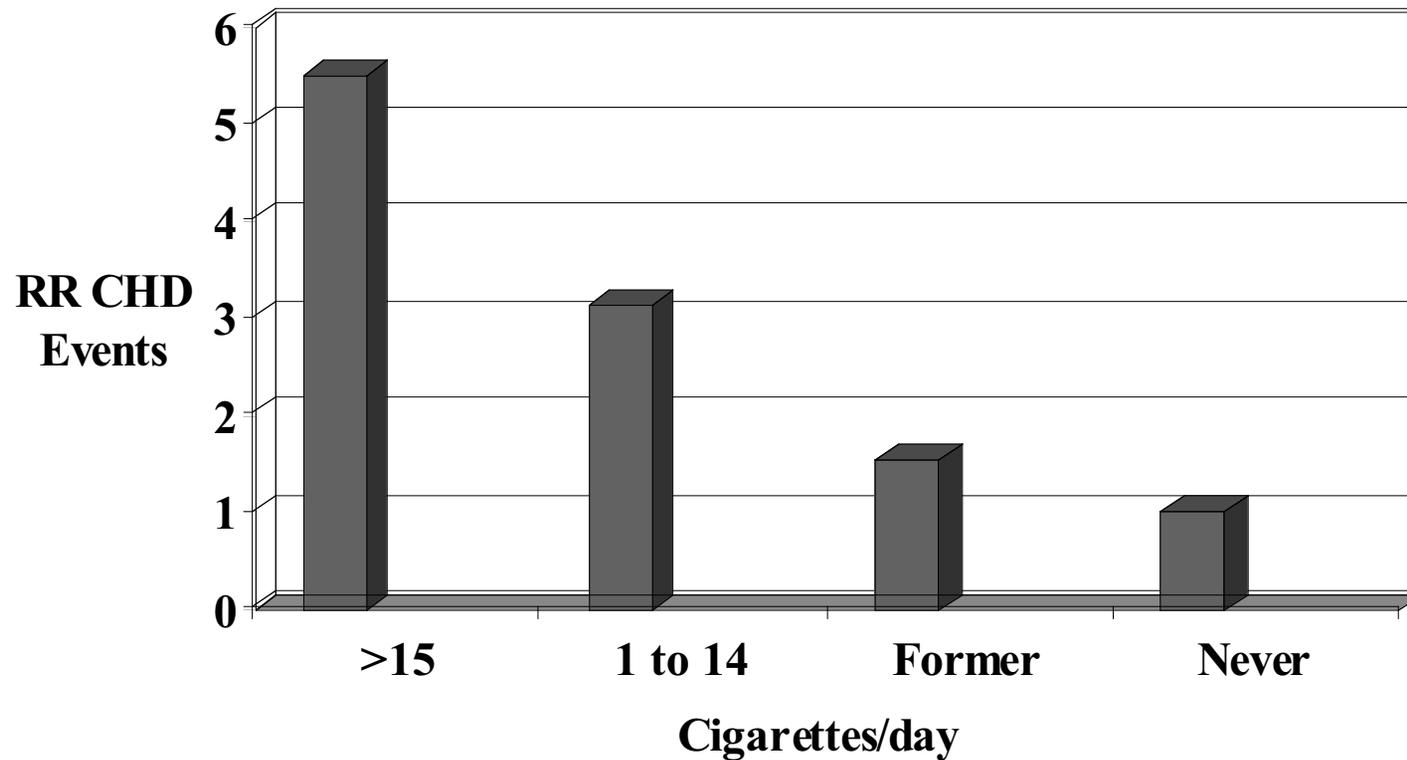
Dietary Score and RR for CHD Events: Nurses' Health Study



Exercise and CHD events: Nurses' Health Study



Smoking and Event Rates: Nurses' Health Study



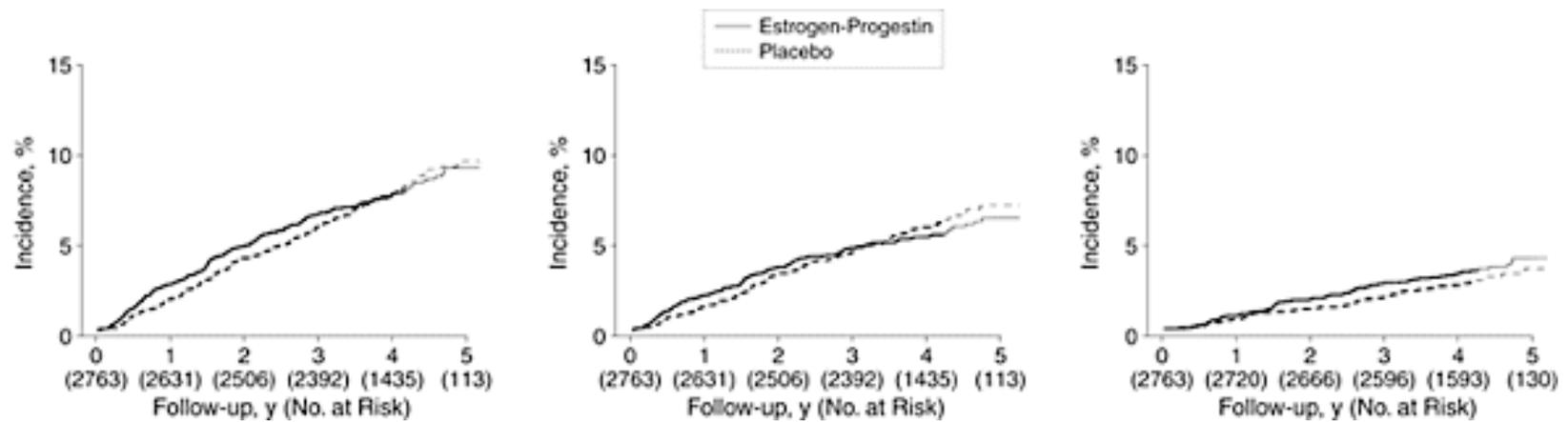
Hormone Replacement Studies

- Observational studies consistently show benefits of opposed HRT for women with uterus
- However, Matthews et al (Pittsburgh Women's Health Study) showed that choosing to use HRT was associated with better health habits, higher SES, fewer risk factors

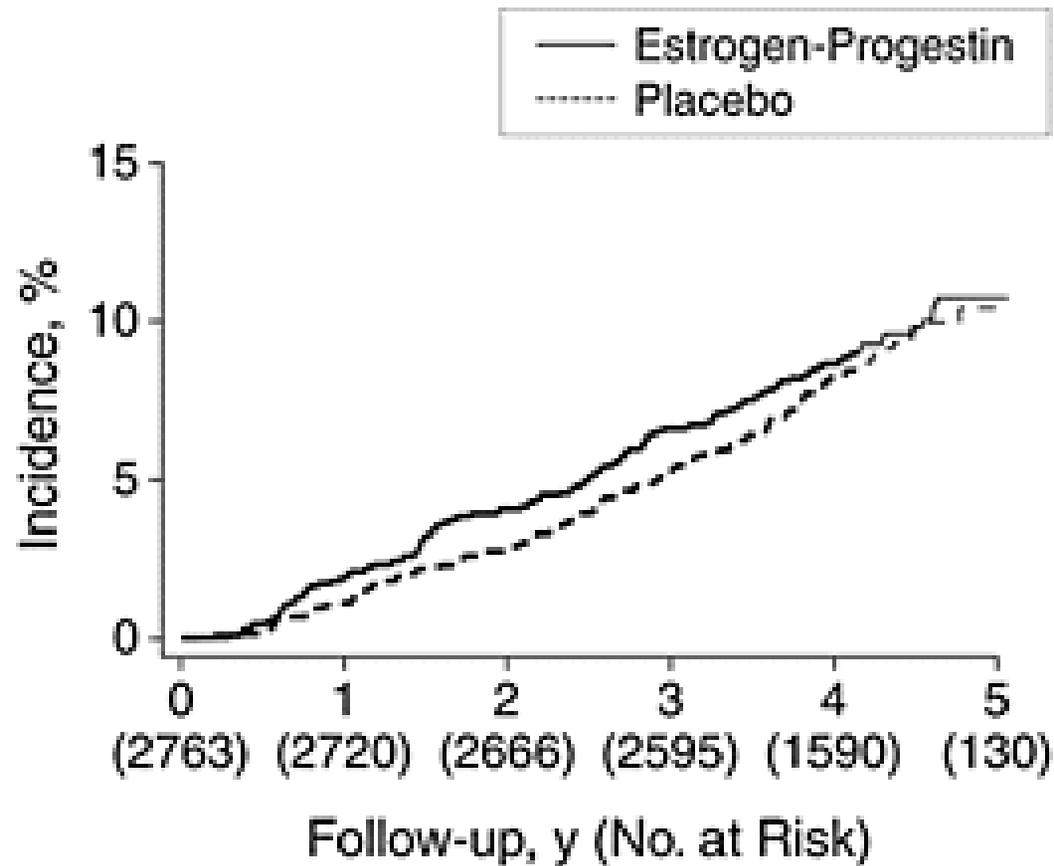
Trials

- HERS, RCT for women with uterus with established heart disease
- WHI, RCT 30K women
 - HRT
 - Calcium and Vitamin D
 - Low fat diet
- Observational Study 100+K women

Outcomes in HERS



HERS All Cause Mortality (Hulley et al, 1998)



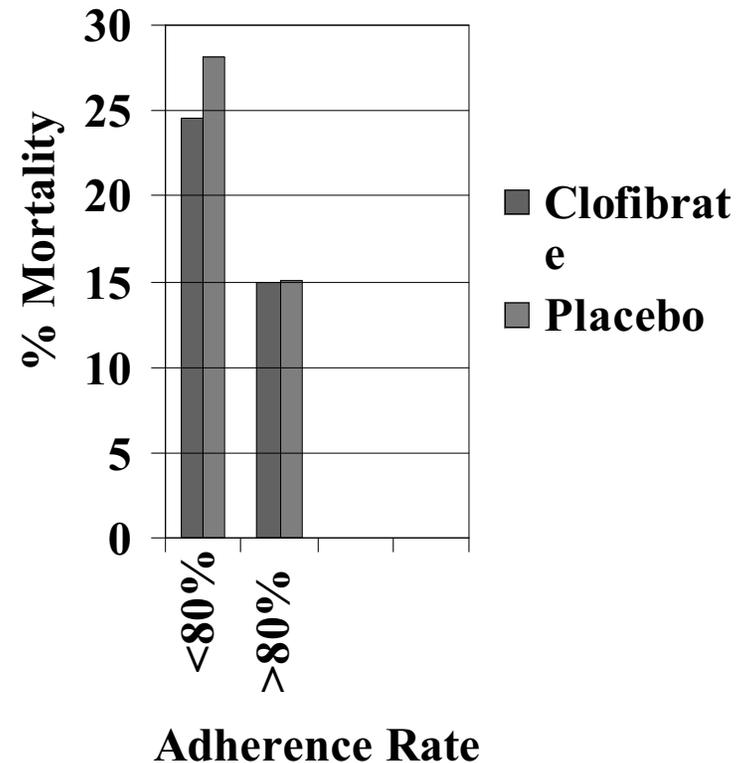
Coronary Drug Project

NEJM, 1980, 303, 1038-41

- Designed to evaluate the efficacy and safety of lipid lowering drugs for CHD events
- 53 participating centers
- 8,341 participants
- Approximately 1,100 to each of 5 drugs
- 2789 assigned to placebo
- Followed every 4 months for minimum of 5 years (up to 8.5 years)

Coronary Drug Project Results for Clofibrate

- No overall effect for clofibrate arm (in comparison to placebo)
- But, those who complied with the drug (>80%) had better outcomes than non compliers

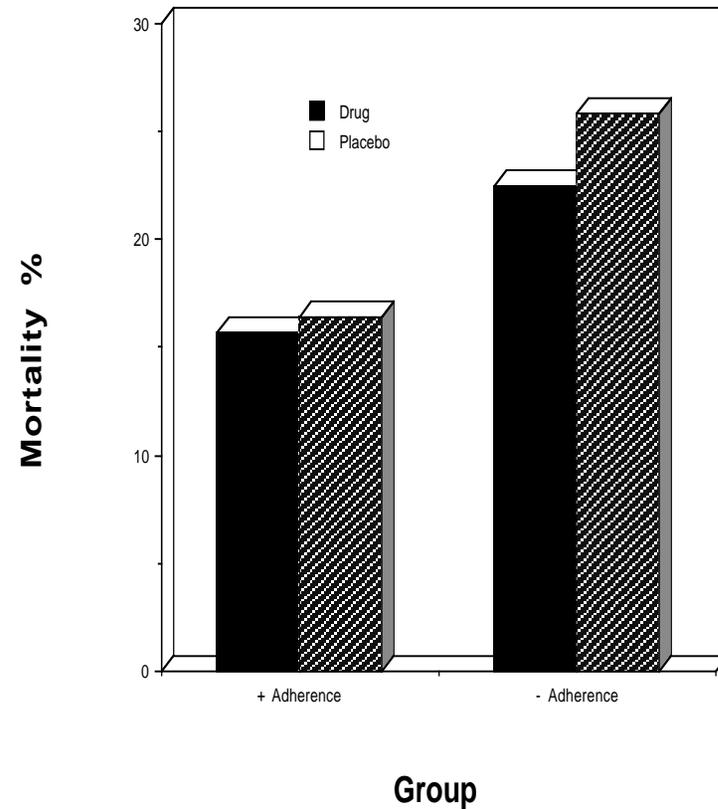


Base-line Risks by Adherence in Coronary Drug Project

Base-Line Characteristics	<80%	>80%
ST Seg Depression	31.4	21.6
Diuretics	20.0	14.7
NY Heart 2	58.7	50.5
>2 previous MIs	22.9	18.2

Coronary Drug Project (1980)

- Drug: Clofibrate
- Outcome: Mortality
- Drug Effect: -
- Adherence: +
- Interaction -



Example Study:

Gallagher et al, JAMA 1993, 270 (6), 742-744)

- Beta Blocker Heart Attack Trial (B-Hat)
- Subjects: 602 women age 30-69 years
- Assigned to Propranolol or placebo following MI
- Followed for mortality-- average 26 months

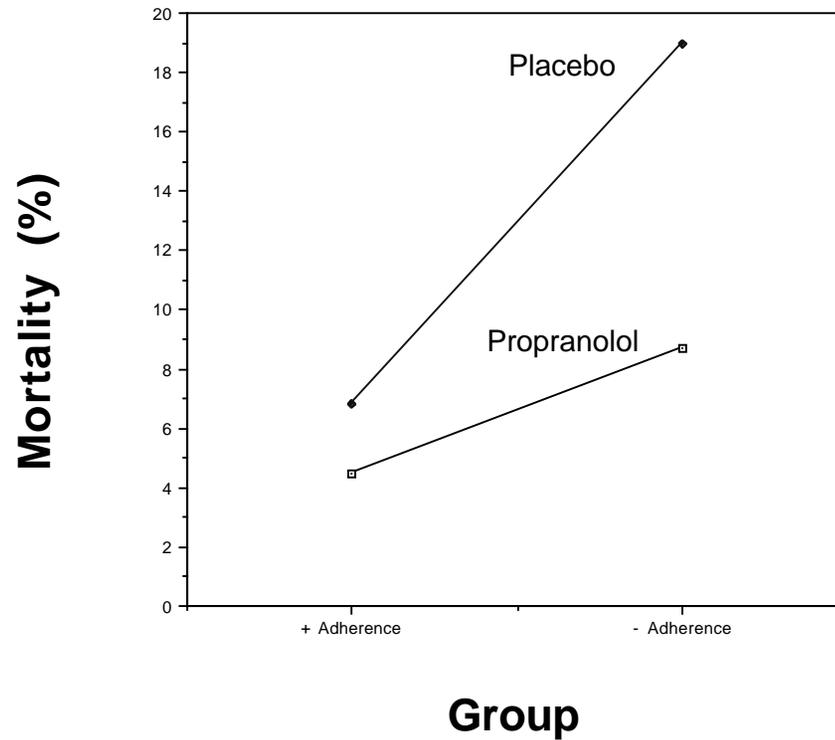
Adherence in B-Hat

- Good $>75\%$ meds
- Poor $<75\%$ meds

Poor Adherence Rates

- Propranolol 8.7%
- Placebo 8.7%
- Overall 8.7%

Results of Gallagher Analysis: B-Hat

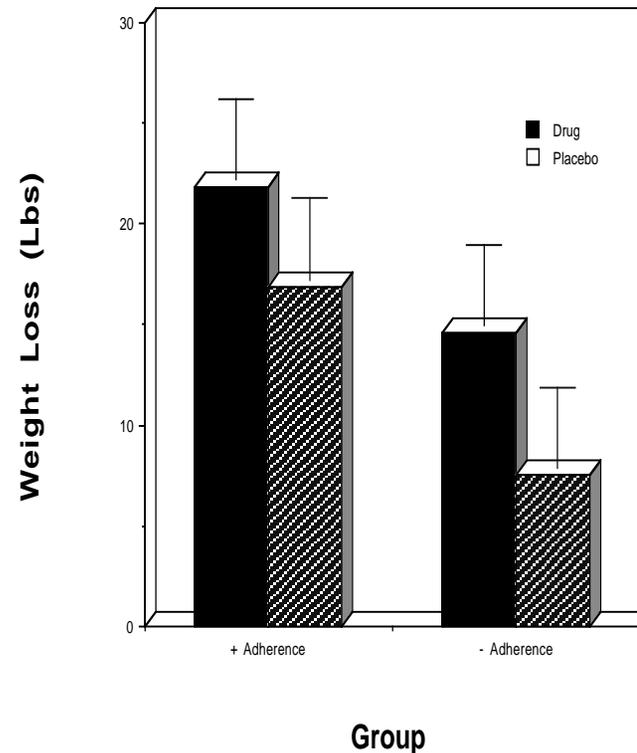


Proportional Hazards in Multivariate Analysis: B-HAT

Variable	Coefficient	RR
Adherence	.997	2.7
Ad. + treatment	1.01	2.8
Ad + Treat + MI severity	1.01	2.8
Ad + Treat + CHF	1.05	2.9
Ad + Treat + Age	1.01	2.7
Ad + Treat + Smoking	1.02	2.8

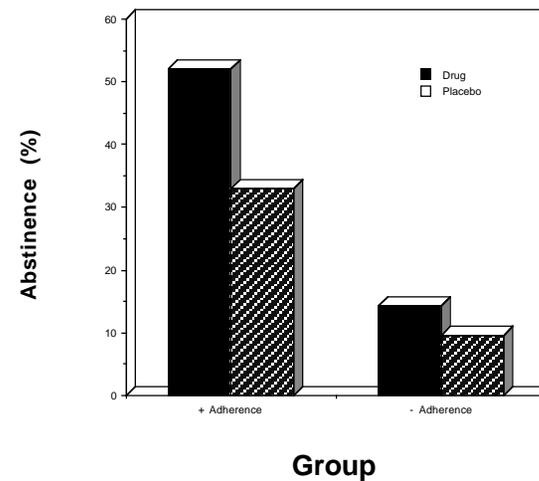
Asher & Harper (1973)

- Drug: Human Chorionic Gonadotropin (HCG)
- Outcome: Weight loss (lbs)
- Drug effect: +
- Adherence: +
- Interaction: -



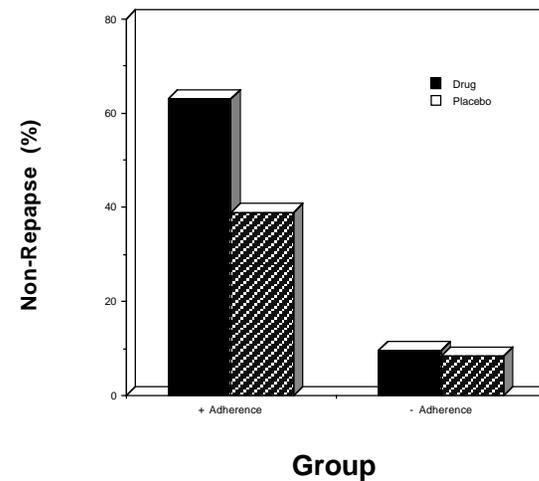
Fuller et al (1983)

- Drug: Disulfiram
- Outcome: Alcohol abstinence (%)
- Drug effect: NS
- Adherence: +
- Interaction: NS



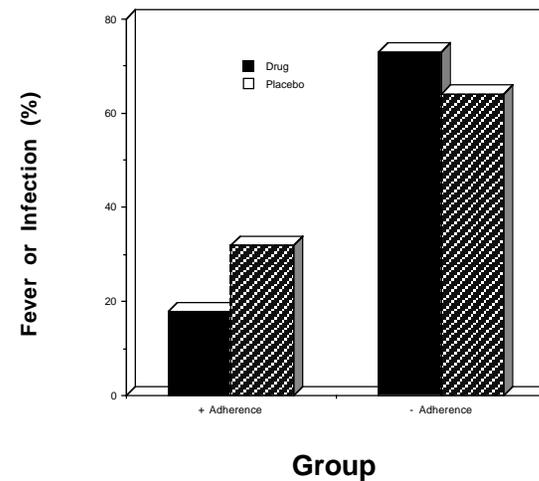
Hogarty et al (1973)

- Drug:
Chlorpromazine
- Outcome: Non-relapse
(%)
- Drug effect: +
- Adherence: +
- Interaction: +



Pizzo et al (1983)

- Drug: TMP/SMX
- Outcome: Fever or infection in cancer patients
- Drug effect: NS
- Adherence: +
- Interaction: +



Explanations

- Selection Bias
- Personal Control
- Stress and Adaptation
- Spurious

Selection Bias

- Healthy people may be more likely to adhere to treatment
- Unlikely to be correct. In B-HAT and other studies, statistical control for seriousness of illness did not modify the result

Personal Control

- People who adhere to protocol may be more likely to change other aspects of their lives and risk factors for poor health outcomes.
- Studies show that sense of control is related to positive health outcomes.....or do they?

Rodin & Langer: Control and Mortality

- Subjects 91 elderly nursing home residents
- Randomized to
 - Responsibility for daily events (watering a plant)
 - Non-responsible (nurse watered plant)
- Followed for mortality for 18 months

Mean Nurse Ratings 18 Months After Intervention (Rodin & Langer, 1977)

Nurse Rating	Responsibility (N=20)	Comparison (N=14)
Happy	4.35	3.68
Sociable	5.00	3.96
Self-Initiating	5.15	3.90
Vigorous	4.75	3.39

Mortality 18 Months After Intervention (Rodin & Langer, 1977)

Group	Number	Percent
Responsibility	7/44	15%
Comparison	13/44	30%

Rodin & Langer: Relative Risk Reduction

	Dead	Alive
Responsible	7	40
Control	13	31

Rodin & Langer: Relative Risk Reduction

- $(E-C)/E$ -98%
- Reduced risk of dying by nearly 100%!
- Could be one of the largest effects known to experimental medicine
- Could it be right?

Rodin & Langer: Statistical Analysis

- Reported as frequency test, $Z=3.14$, $p<.01$
- However, using their observations does not give the same result

$$\chi^2 = 2.84, df = 1, p > .09$$

- CI for Responsibility Group .05-.25
- CI for Control Group .13-.47

Stress

- Development of serious illness is a stressful event.
- Adherence is a proxy for adaptive coping.

Spurious

- Most studies use self-report measures of adherence
- Those who are in better health might be more likely to be regarded as adherent
- Finding unlikely to be spurious because it has occurred in different trials with different measures of adherence

Current Problems

- Literature seemed to die around 1993
- Few new examples
- Newer clinical trials often have run in phases and eliminate people who are low in adherence
- However, in clinical practice, adherence rates are usually much lower than they are in trials.

Methodology: Preference Trial

- Are outcomes better when participants self select into treatment
- Personal control and expectation may lead to better outcomes
- In RCTs, participants give up the opportunity to choose
- Can the value of choice be evaluated?

Modeling the Preference Effect

- Assume two treatments, A and B
- A portion of people (p) benefit from A
 - Suppose $p(A) = .50$
- The benefit of B is defined as $p(A) + x$
 - If $x = .10$
 - Then $p(B) = .60$

Modeling Preference

- Preference for either treatment bestows an extra advantage of y
- For example if someone preferred and received treatment B, they would have $p(A)+x+y$
- A person who prefers A, but gets B is $p(A)+x-y$

Effects of Different Assignments and Preferences

Treatment	Indifferent	Prefer A	Prefer B
On A	P	$P+y$	$P-y$
On B	$P+x$	$P+x-y$	$P+x+y$

Treatment Effects With Preferences

- If proportion who prefer A is α
- And proportion who prefer B is β
- And proportion indifferent is ψ
 $\alpha + \beta + \psi = 1$
- The effect of Treatment B over A in a well-controlled trial is
 $x + 2y (\beta + \alpha)$

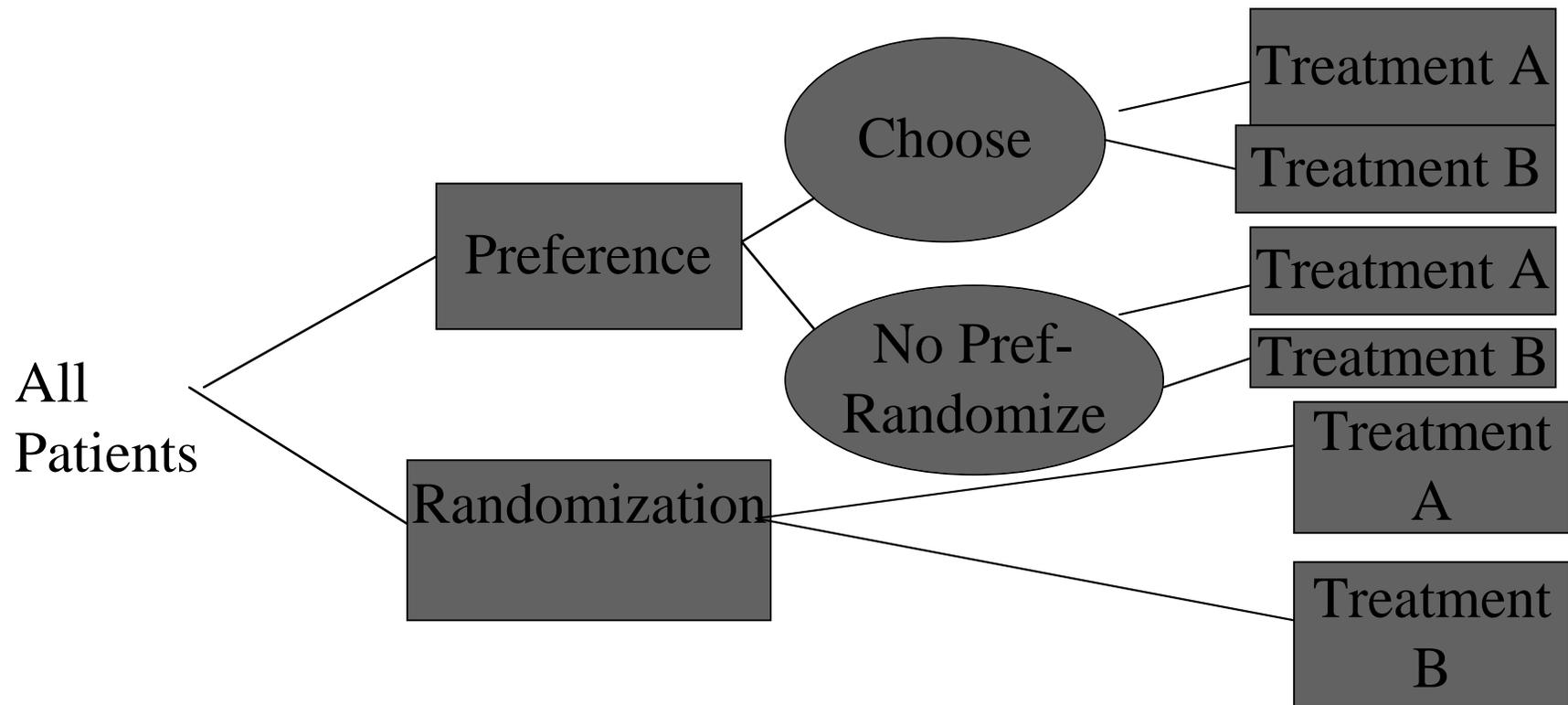
Example

- Preference for treatment
 - A 60%
 - B 35%
 - $(\beta - \alpha) = -.025$
- Physiological Effect of Treatment
 - A 50%
 - B 60%

Effects of Treatment and Preference Example

Treatment	Indifferent	Prefer A	Prefer B
On A	50%	55%	45%
On B	60%	55%	65%

Rucker's Two State Design



Summary

- Adherence main effect has been observed in several major clinical trials
- Mechanism for effect is unknown
- Preference for treatment may be an important factor
- Research on the adherence main effect and the preference effect is needed

Key References

- Epstein, L. H. (1984). The direct effects of compliance on health outcome. *Health Psychology, 3*(4), 385-393.
- Gallagher, E. J., Viscoli, C. M., & Horwitz, R. I. (1993). The relationship of treatment adherence to the risk of death after myocardial infarction in women. *Jama, 270*(6), 742-744.
- Horwitz, R. I., & Horwitz, S. M. (1993). Adherence to treatment and health outcomes. *Archives of Internal Medicine, 153*(16), 1863-1868.
- McPherson, K., Britton, A. R., & Wennberg, J. E. (1997). Are randomized controlled trials controlled? Patient preferences and unblind trials. *Journal of the Royal Society of Medicine, 90*(12), 652-656.