

A Selected History of Behavioral Clinical Trials: What Have We Learned?

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“The wrong view of science betrays
itself in the craving to be right.”

Karl Popper,

The Logic of Scientific Discovery, 1934

HYPOTHESES

- Epidemiology:

The policy of offering the proposed intervention results in improvement in the clinical endpoint.

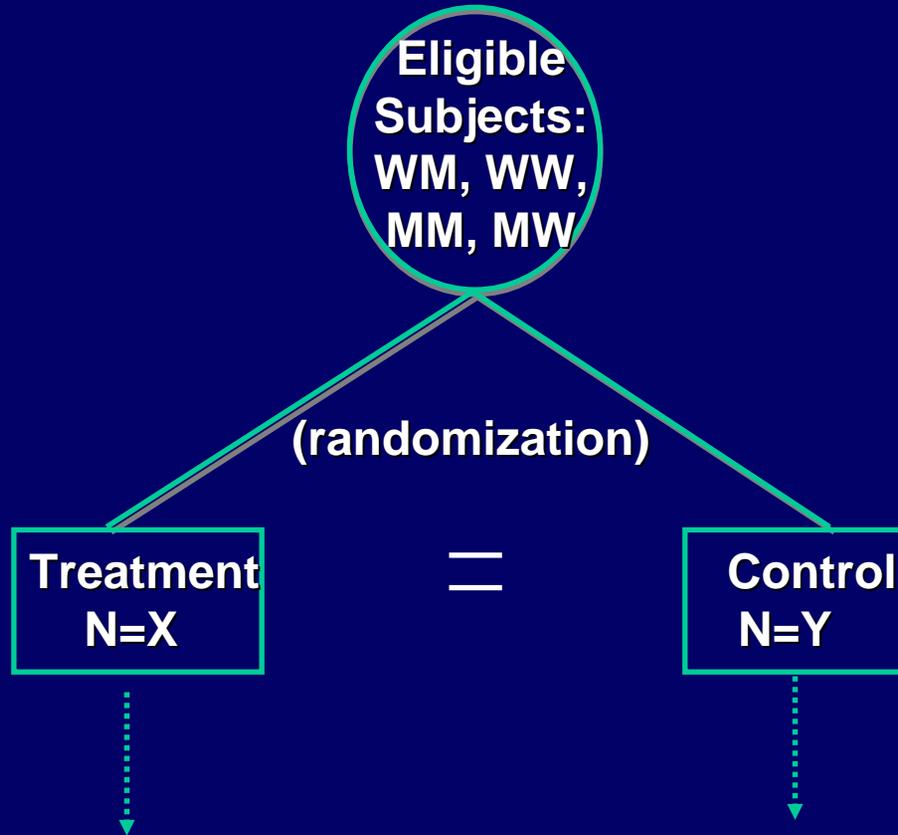
- Behavioral Sciences:

Improvement in the behavioral risk factor results in improvement in the clinical endpoint.

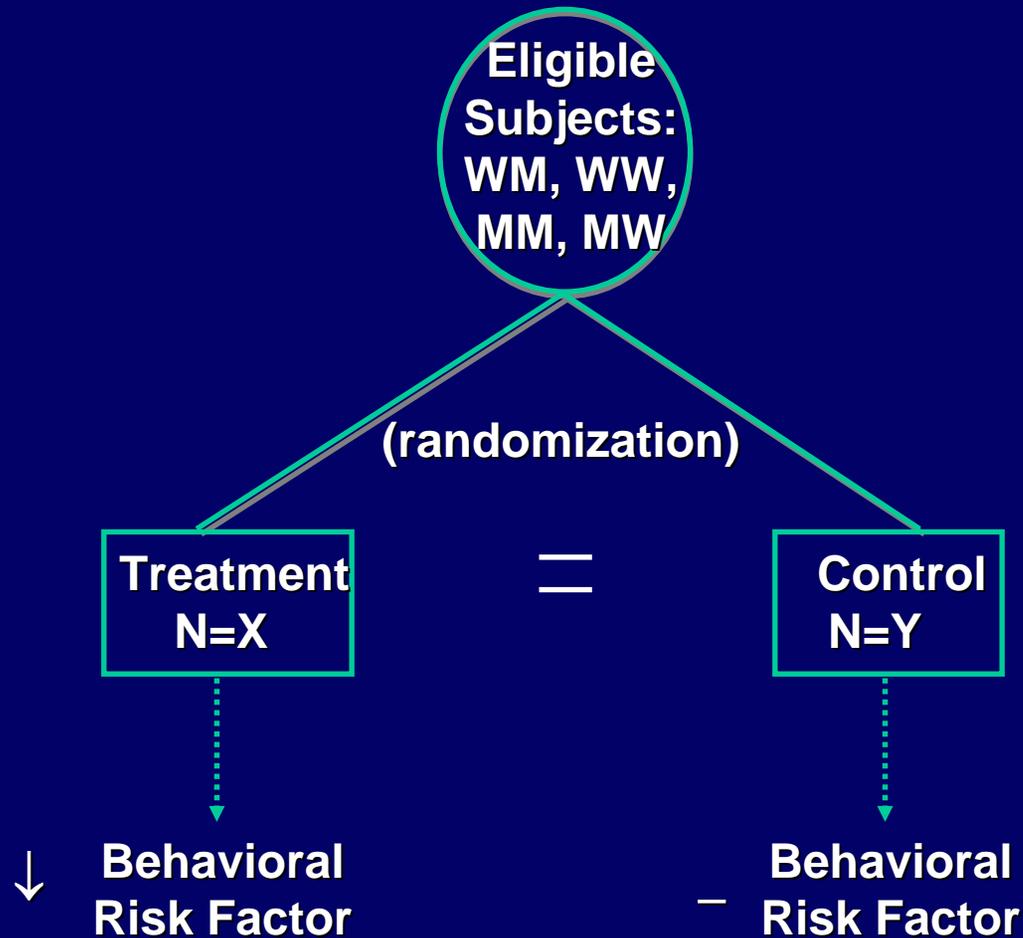
Clinical Trial Design

Eligible
Subjects:
WM, WW,
MM, MW

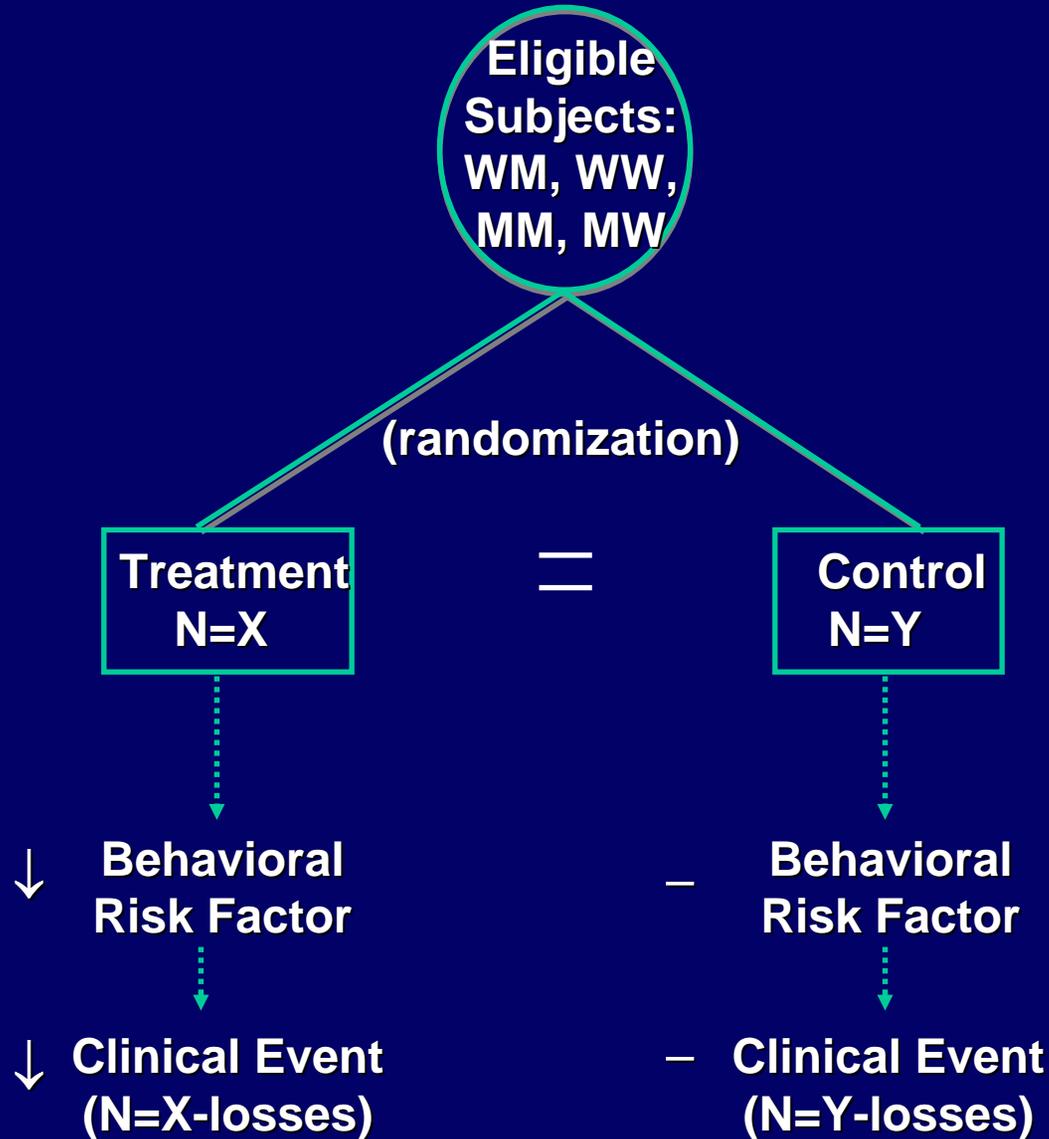
Clinical Trial Design



Clinical Trial Design

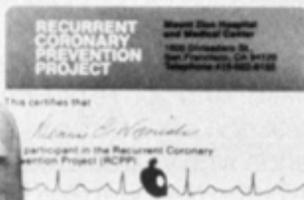


Clinical Trial Design



TIME, JULY 17, 1978

THIS CARD JUST MIGHT SAVE YOUR LIFE.



For every 100 people who have had one or more heart attacks, within five years 45% will have a second heart attack—and half of these people will die.

Frightening? You bet. These are alarming statistics. But something is being done to substantially reduce these odds, and it's being done in San Francisco.

Called the Recurrent Coronary Prevention Project, it's a program

currently underway at Mount Zion Hospital.

Earlier work done by the Mount Zion research group under the direction of Meyer Friedman, M.D., Director of the Harold Brunn Institute at Mount Zion Hospital and Medical Center, has shown that the number of fatalities from a second heart attack can be reduced from five out of ten people to one out of ten.

If you have had a heart attack, here's what you can do. If you are currently a non-smoker, and do not suffer from diabetes, you are eligible to become a part of this program and receive your recurrent coronary prevention card which entitles you to all of the benefits of this project. There's no charge as the project is funded by the National Heart, Lung and Blood Institute.

**Act now
before it's too late.**

For full details, call the
RECURRENT CORONARY
PREVENTION PROJECT
(415) 922-8155

Typography:
Cohncomp, San Francisco

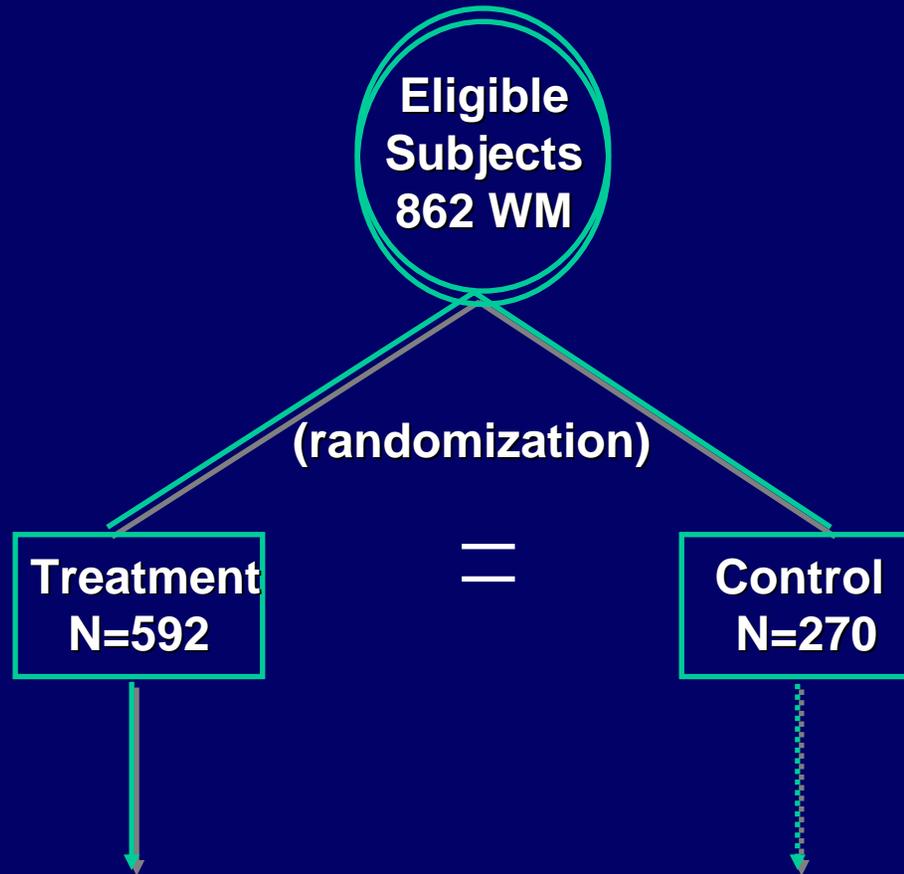
This ad prepared as a public service for the Recurrent Coronary Prevention Project by Scroggin, Reed Advertising, 843 Montgomery Street, San Francisco, California.

The Recurrent Coronary Prevention Project 1977-1985

Principal Investigator: Meyer Friedman, MD

HYPOTHESIS: Type A behavior can be reduced and this reduction will result in reduced cardiac deaths or nonfatal MI.

RCPP Clinical Trial Design





Russell

"If you can't relax, pretend to relax."

I. 1. Walk more slowly than wife/friend

--	--	--	--	--	--	--	--

2. Speak more slowly

--	--	--	--	--	--	--	--

3. Eat more slowly

--	--	--	--	--	--	--	--

4. Discontinue fist clenching/knee jiggling

--	--	--	--	--	--	--	--

5. Leave watch off 2 of 5 working days

--	--	--	--	--	--	--	--

6. Seek longest line in bank/shop

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7. Linger at table

--	--	--	--	--	--	--	--

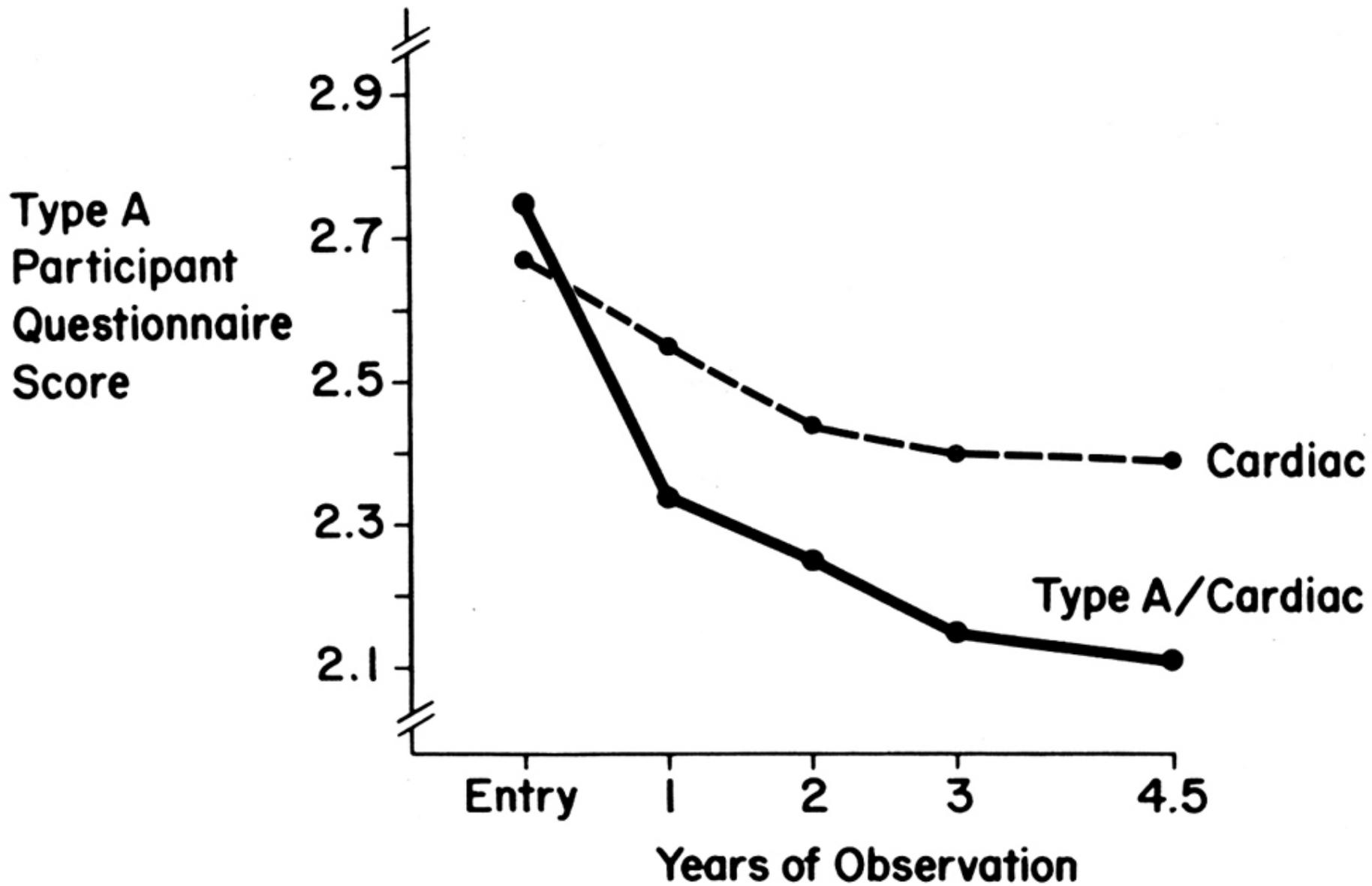
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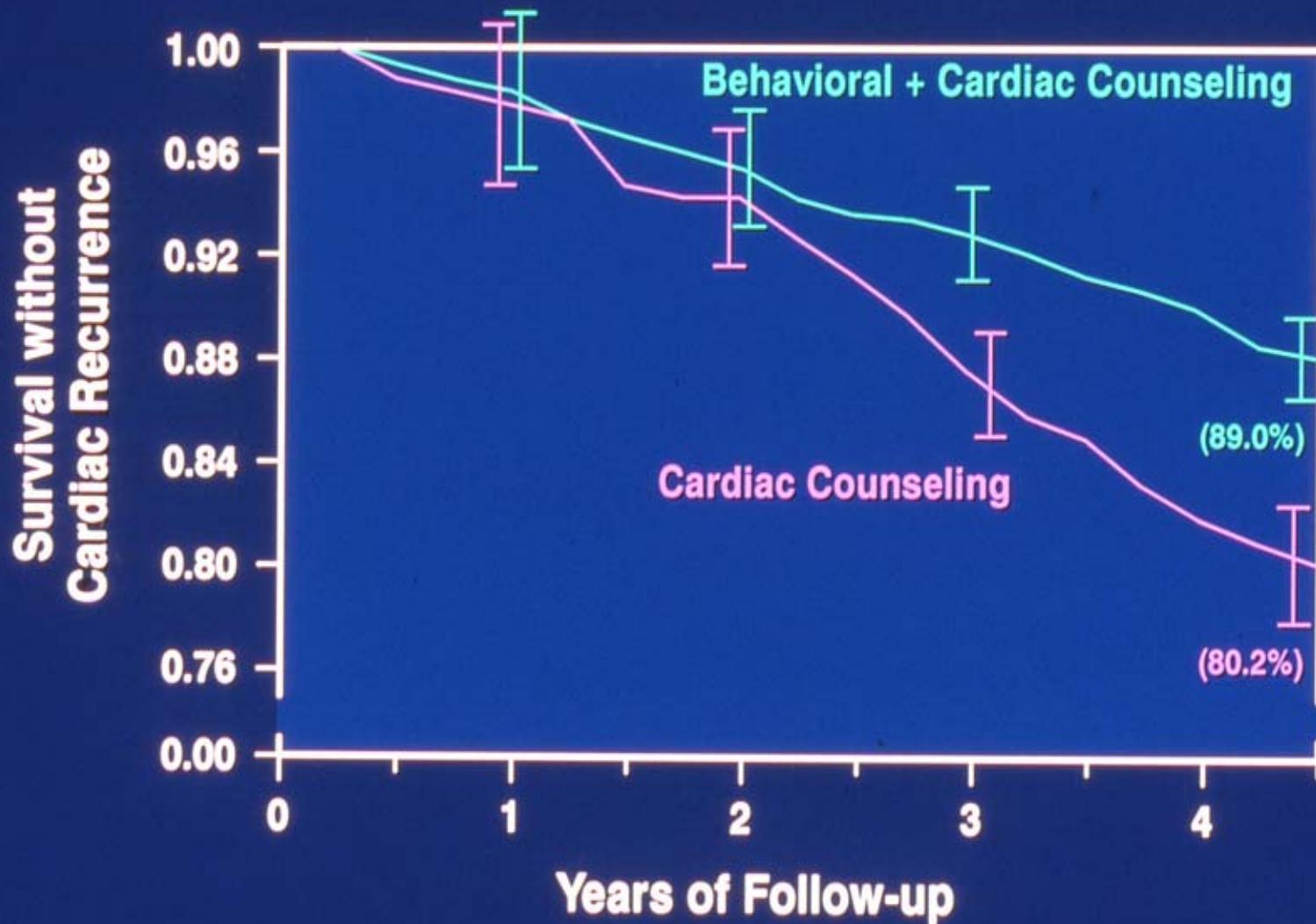
OFF HAND,
I'D SAY
YOU'RE
HOOKED!



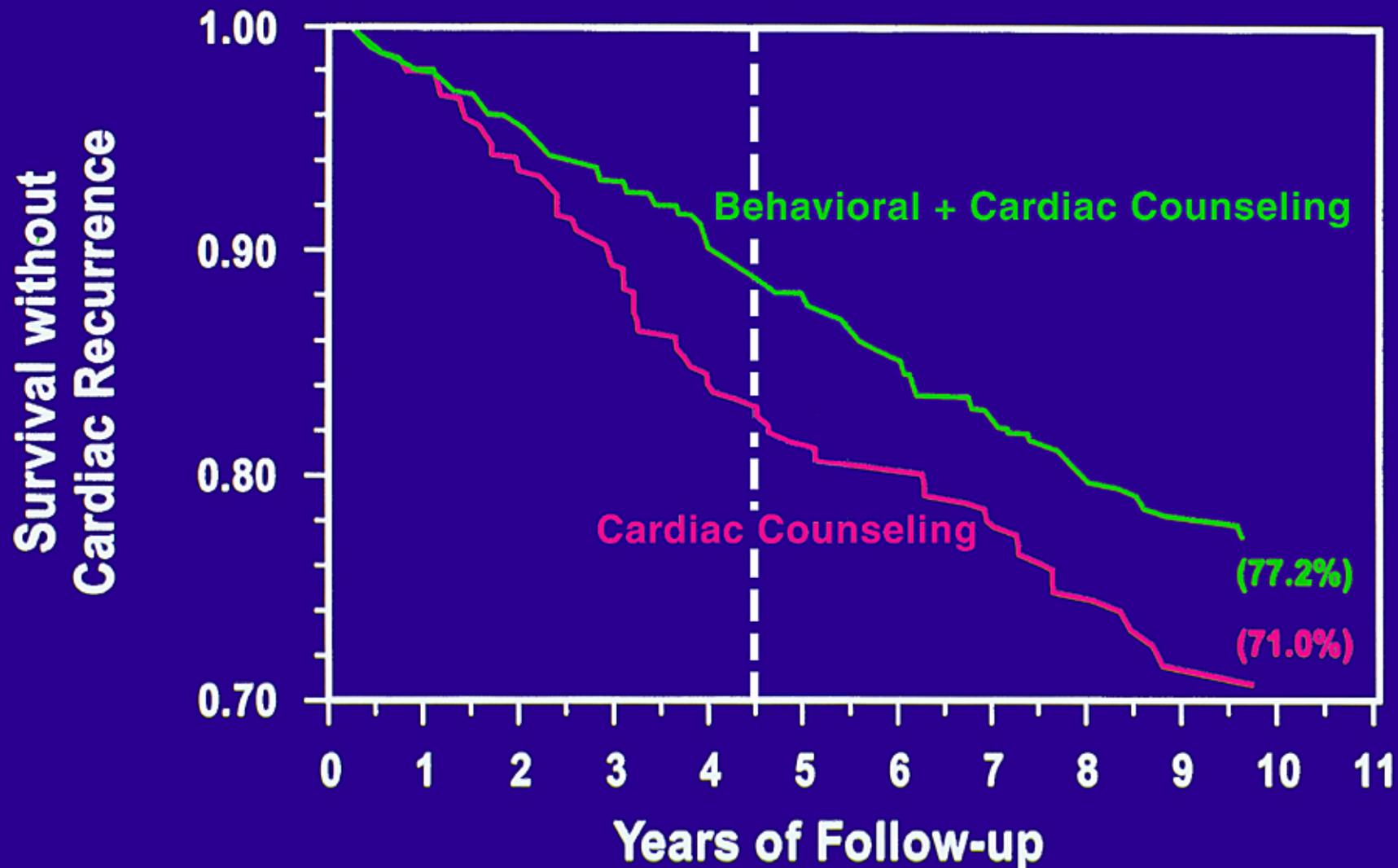
mal 25



Cardiac Recurrence at 4.5 Years



Cardiac Recurrence at 8.5 Years



Impact of RCPP Intervention on Psychosocial Risk Factors

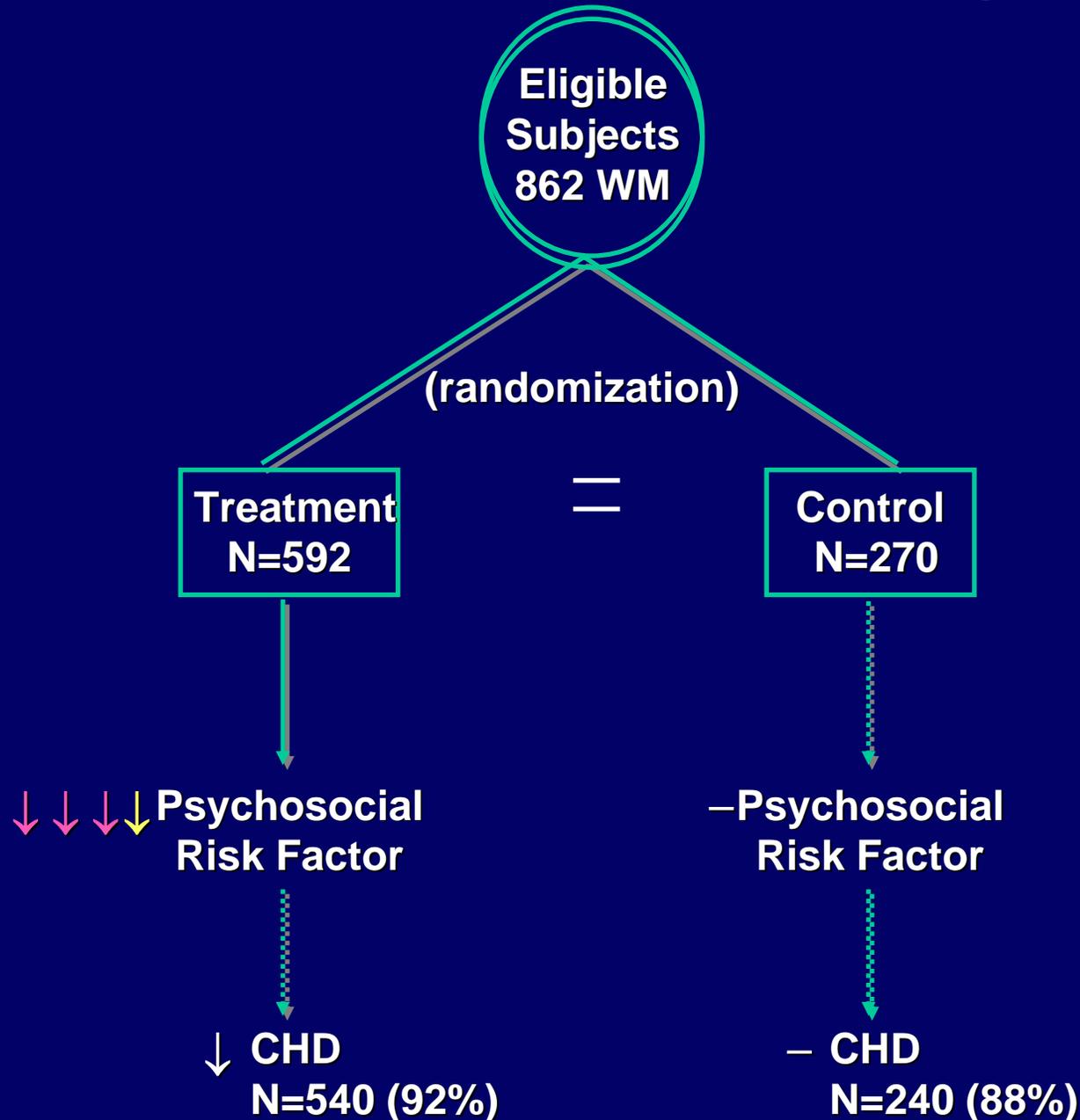
	Improved at End of Treatment	Improvement Predicted Subsequent CHD Events
Type A Behavior	***	ns
Hostility	***	ns
Anger	***	ns
Impatience	***	ns
Life Satisfaction	***	ns
Self-Efficacy at Managing Stress	***	*
Social Support	***	ns
Depression	***	**

*** $p < 0.001$

** $p < 0.01$

* $p < 0.05$

RCPP Clinical Trial Design



WHAT WE LEARNED

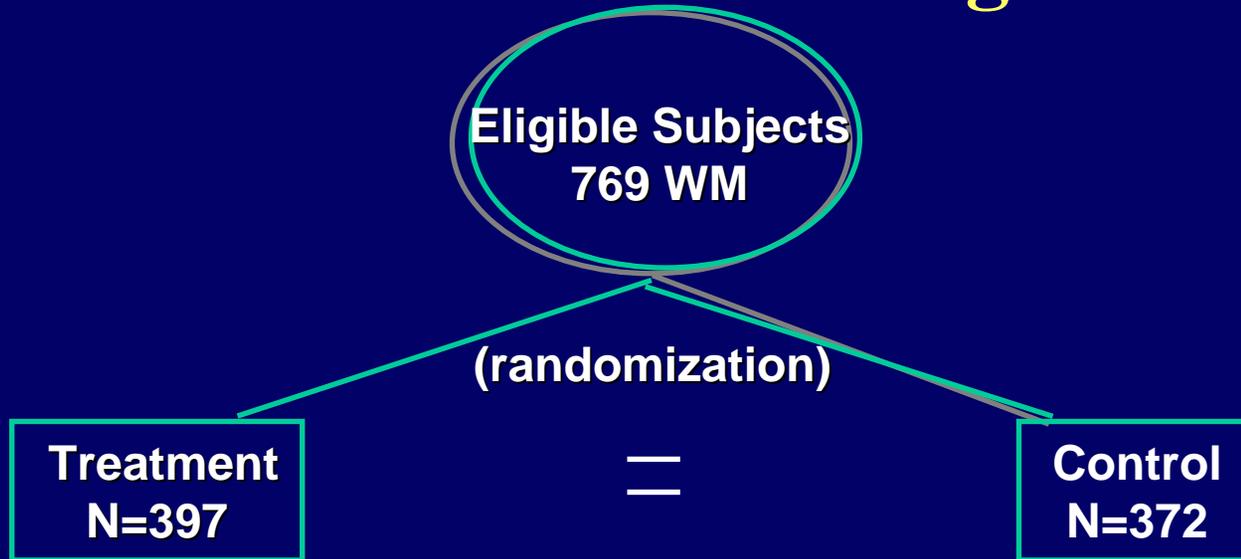
- Value of strong intervention.
- Many things can change during the course of a behavioral intervention. The intended treatment target may not be the real mechanism of effectiveness.

The Ischemic Heart Disease Stress Monitoring Trial 1983-1986

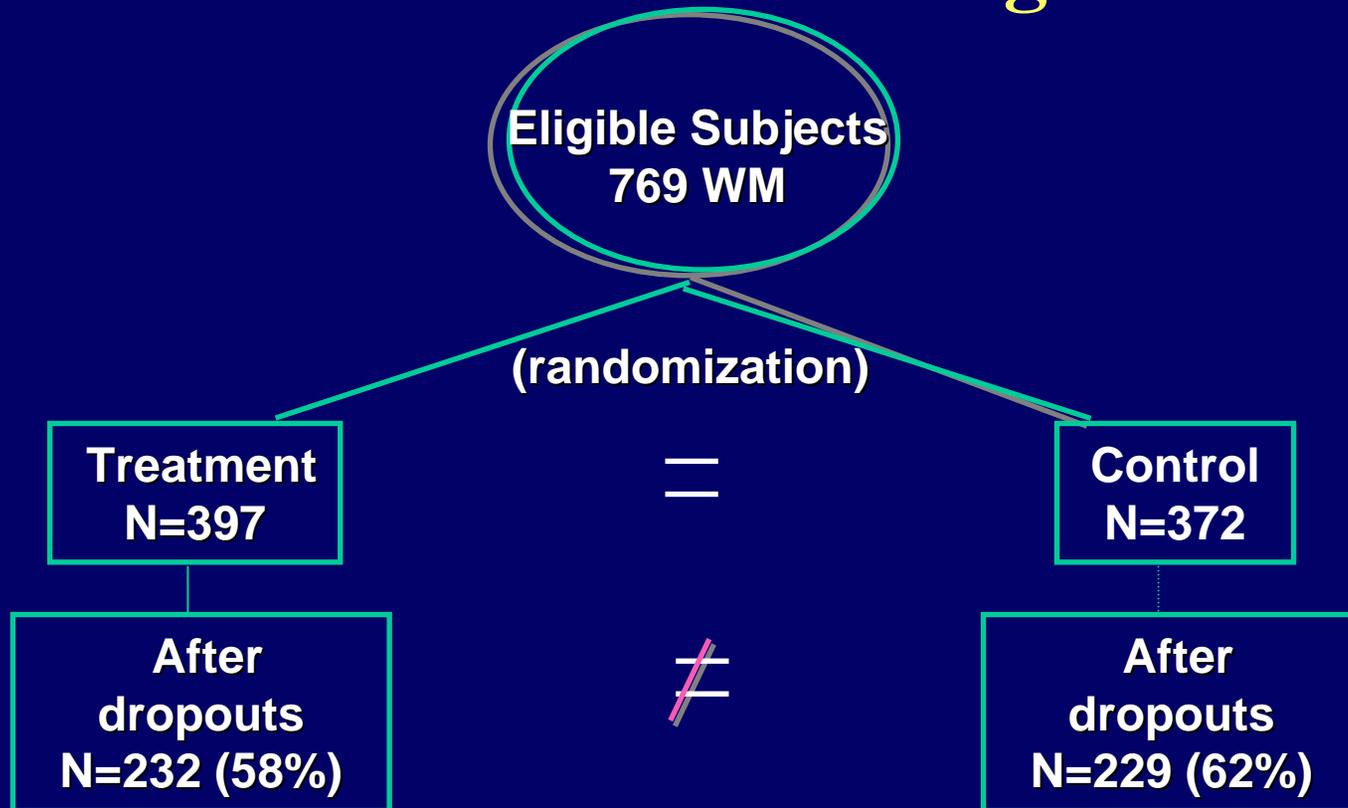
Principal Investigator: Nancy Frasure-Smith, PhD

HYPOTHESIS: The provision of emotional support at a time of high vulnerability to stress results in a reduction in cardiac deaths or nonfatal MI in male post-MI patients.

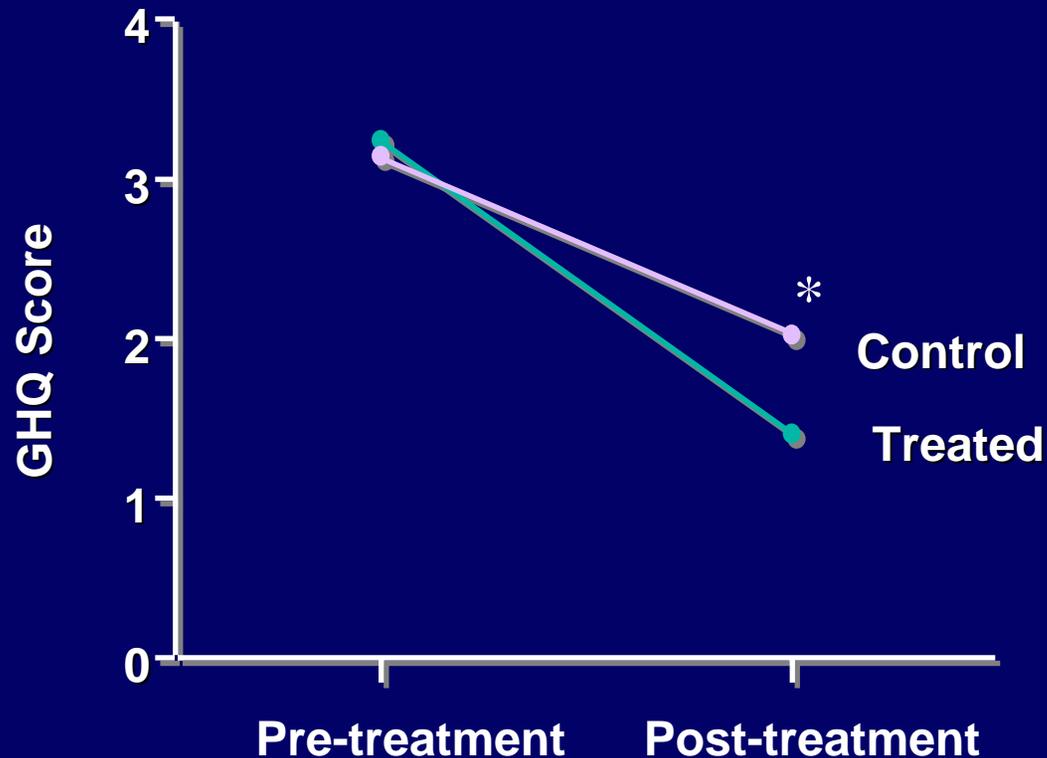
IHD Stress Monitoring Clinical Trial Design



IHD Stress Monitoring Clinical Trial Design



Reduction in Distress at 1-Year Follow-up



* $p < 0.05$

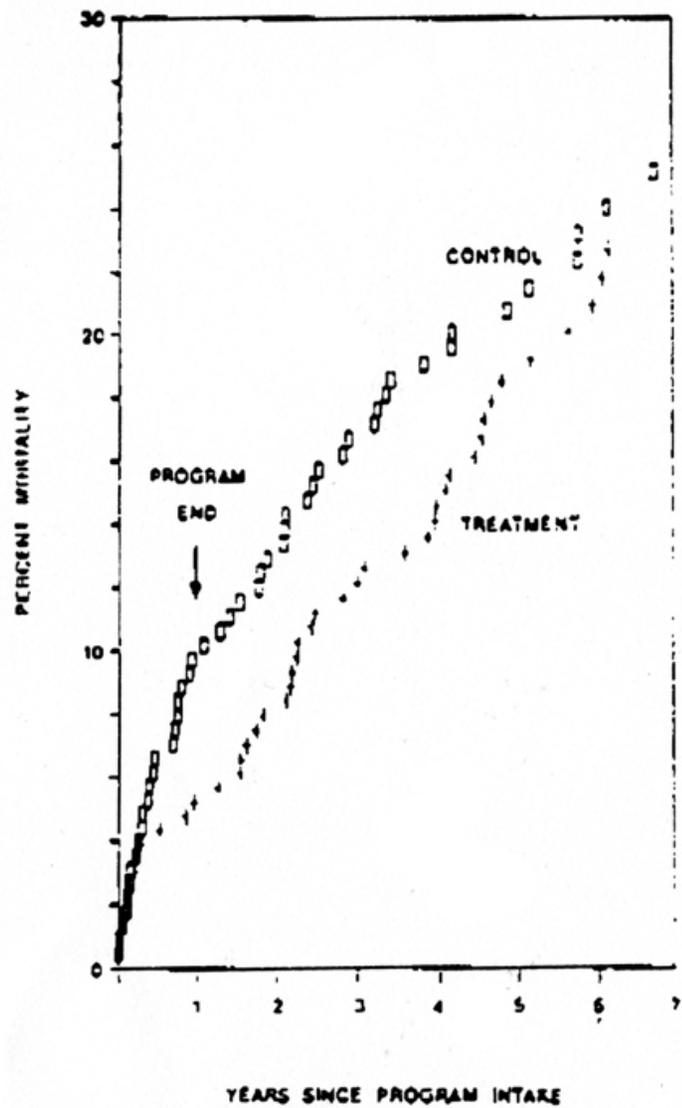


Fig. 1. Cumulative cardiac mortality in the treatment and control groups.

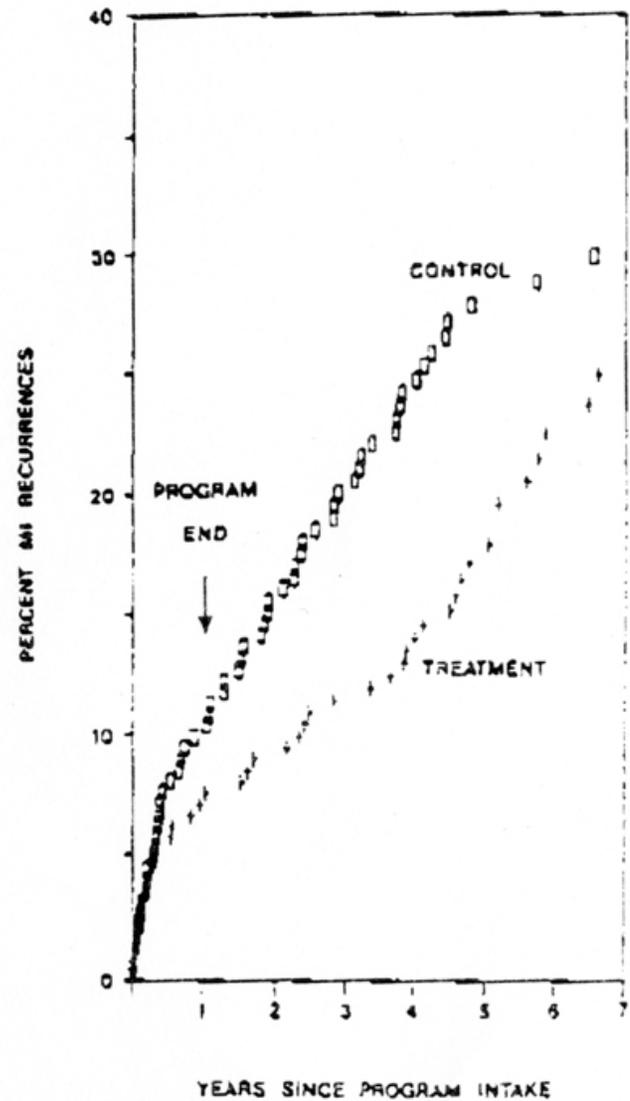
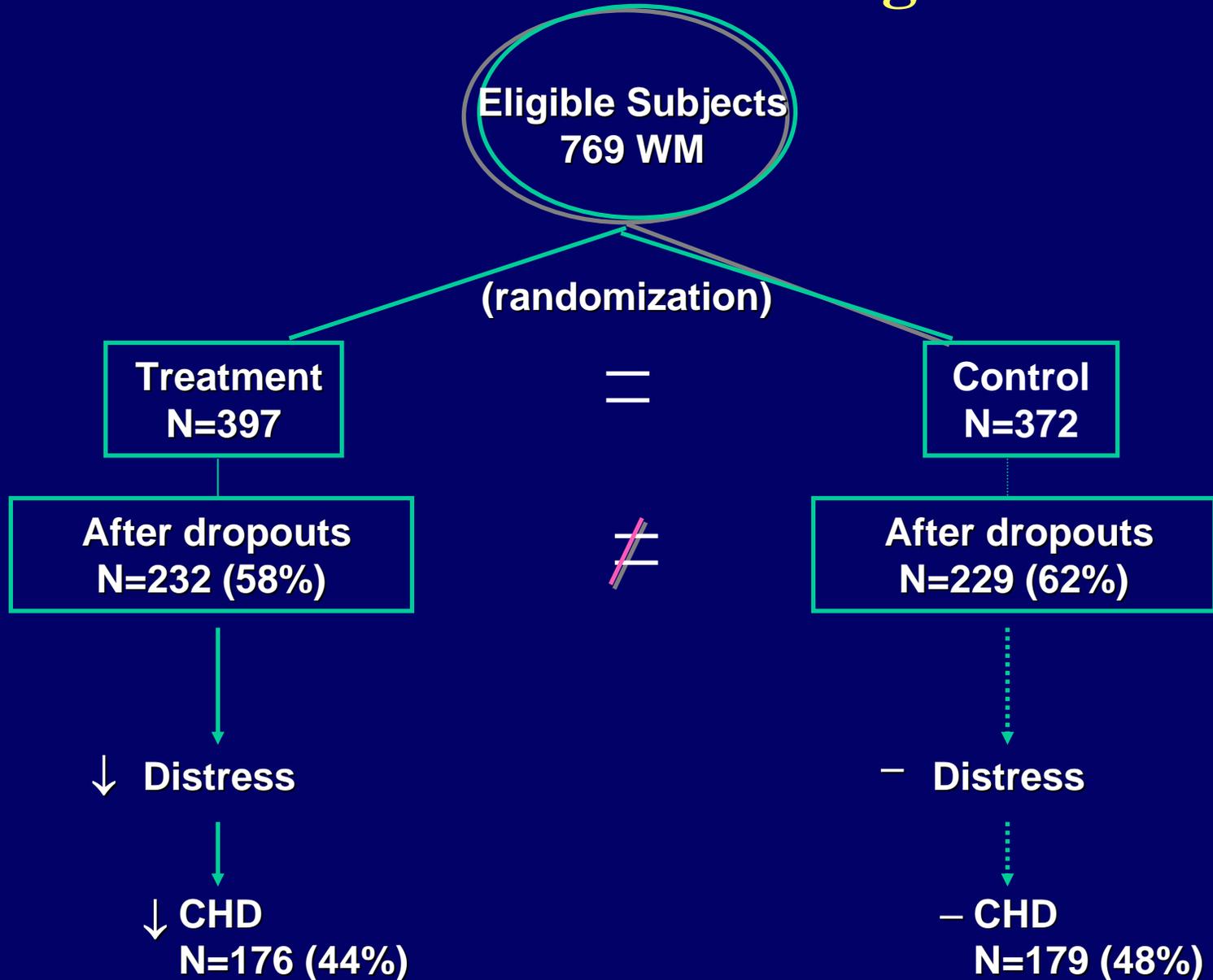


Fig. 3. Cumulative MI recurrences in the treatment and control groups.

IHD Stress Monitoring Trial: Baseline Comparability

	Treatment	Control
Education	↑	↓
Occupation: White Collar	↑	↓
Income	↑	↓

IHD Stress Monitoring Clinical Trial Design



WHAT WE LEARNED

Guard the randomization
throughout the trial.

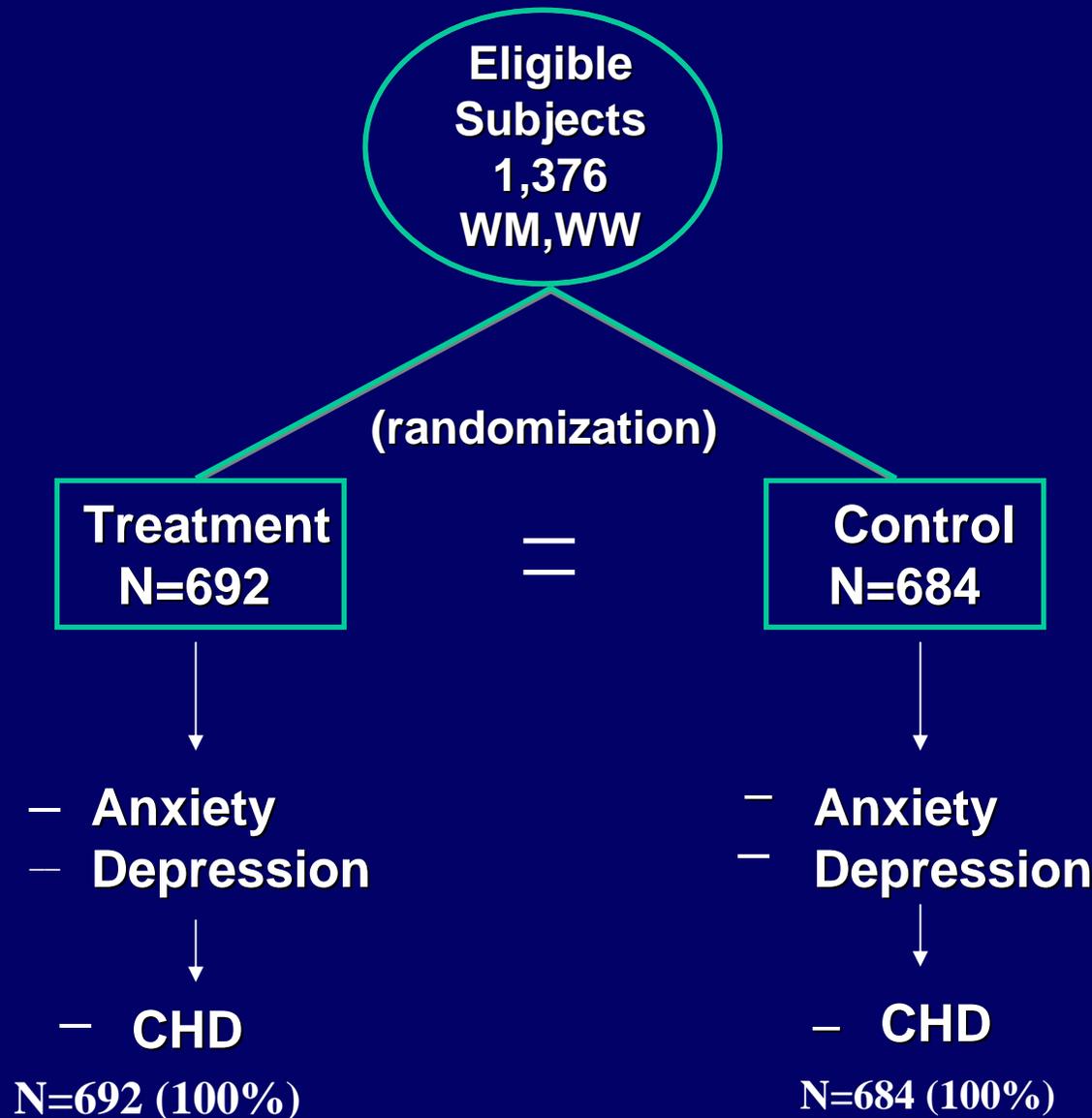
Montreal Heart Attack Readjustment Trial (M-HART) 1992-1997

Principal Investigator: Nancy Frasure-Smith, PhD

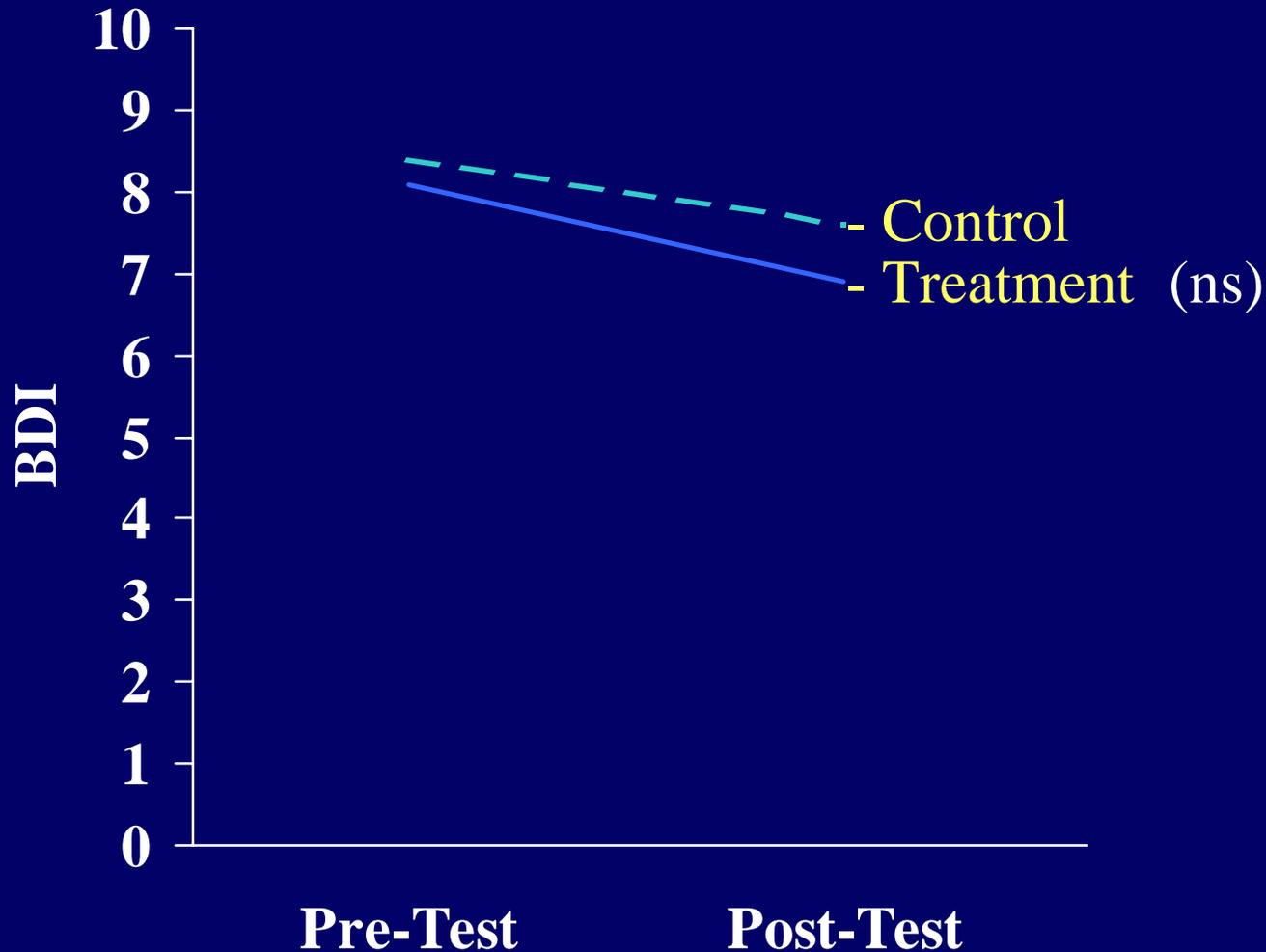
HYPOTHESIS:

- The provision of emotional support at a time of high vulnerability to stress results in a reduction in cardiac deaths or nonfatal MIs in *male and female* post-MI patients.

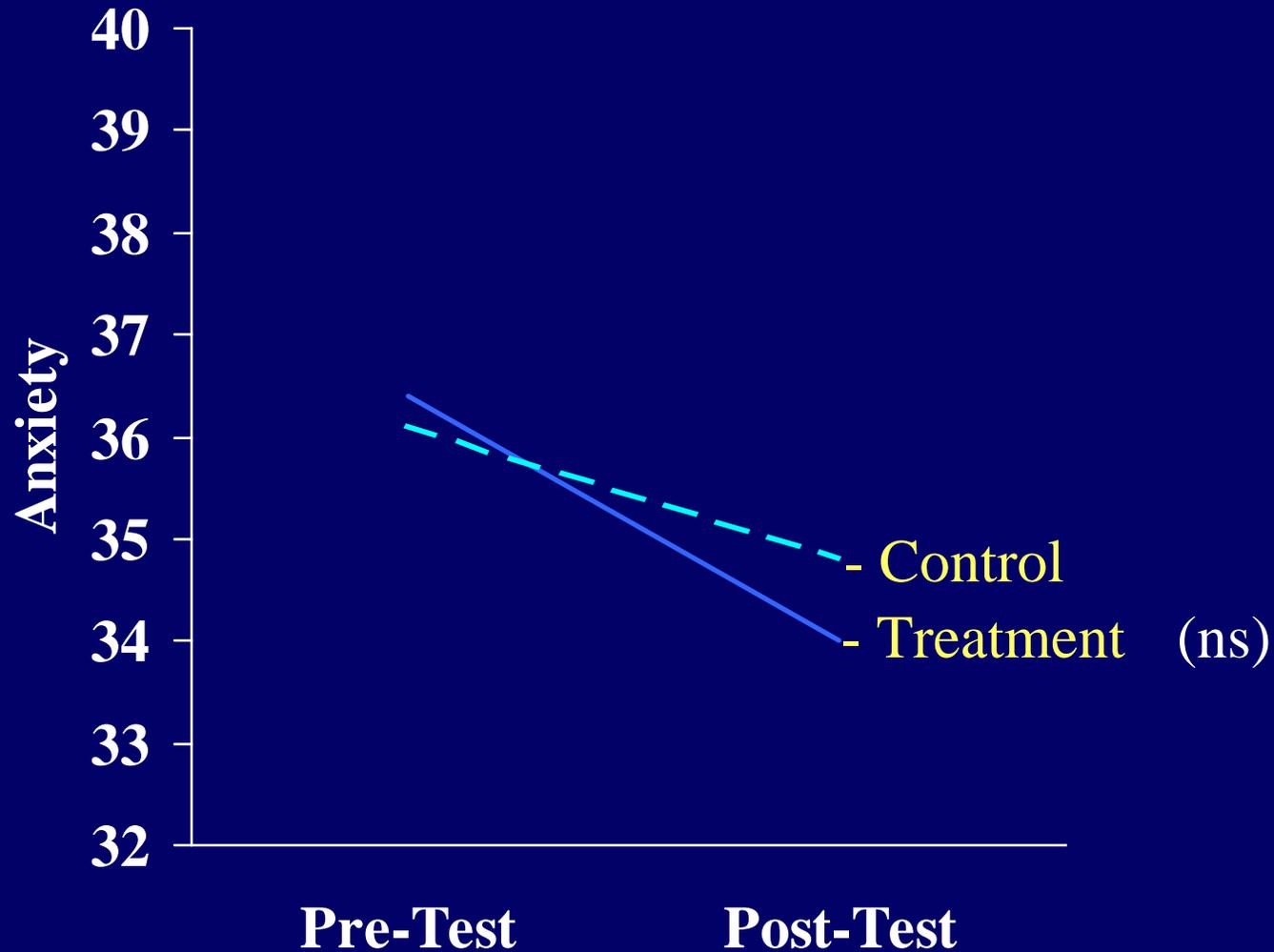
M-HART Clinical Trial Design

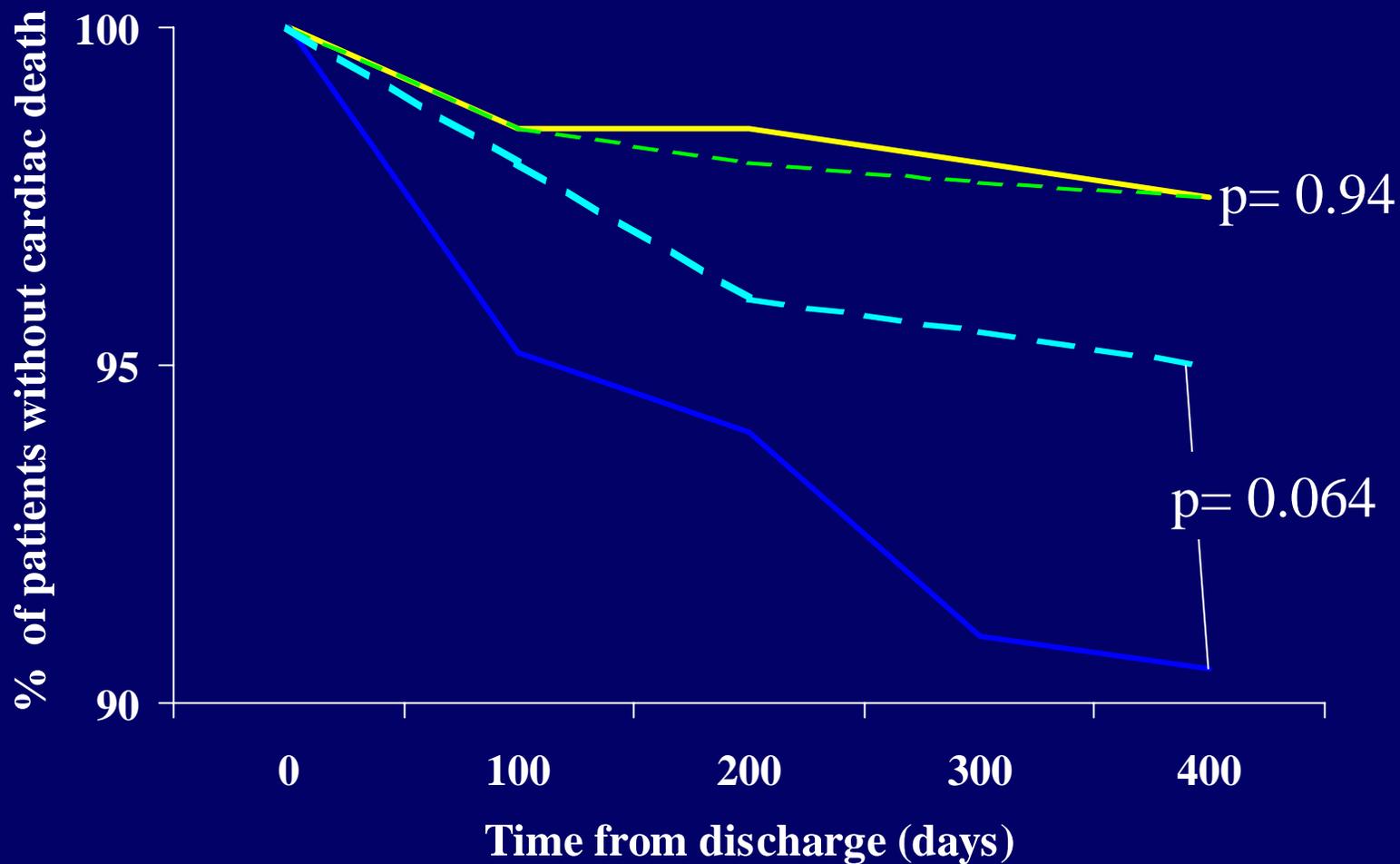


M-HART Change in Depression



M-HART Change in Anxiety





WHAT WE LEARNED

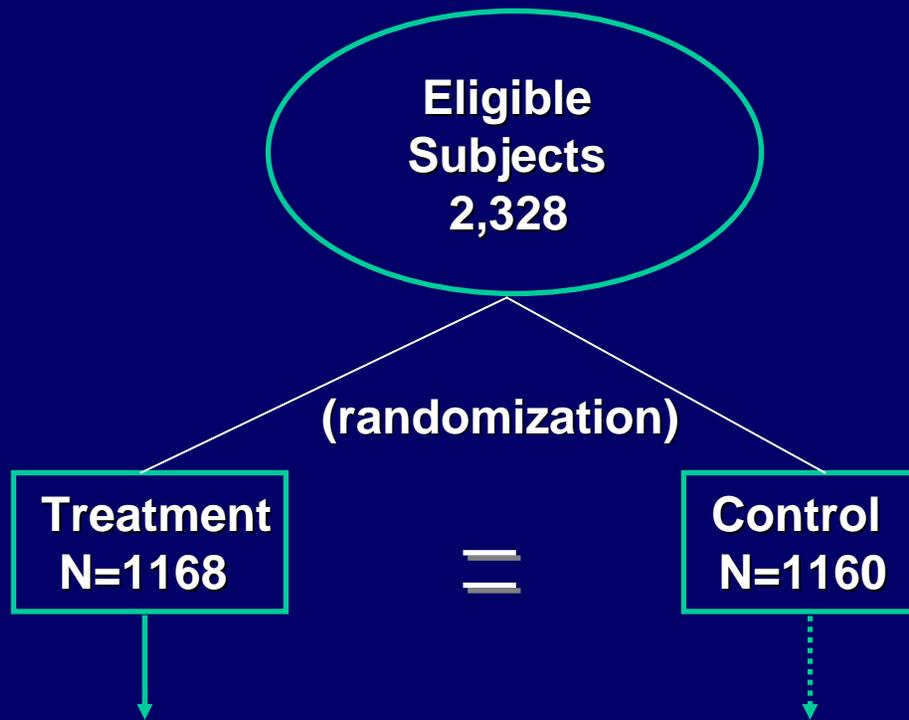
- Replication of treatment benefits is essential to minimize effects of bias.
- Behavioral treatments *can* harm.

Jones and West Rehabilitation Program 1990-1996

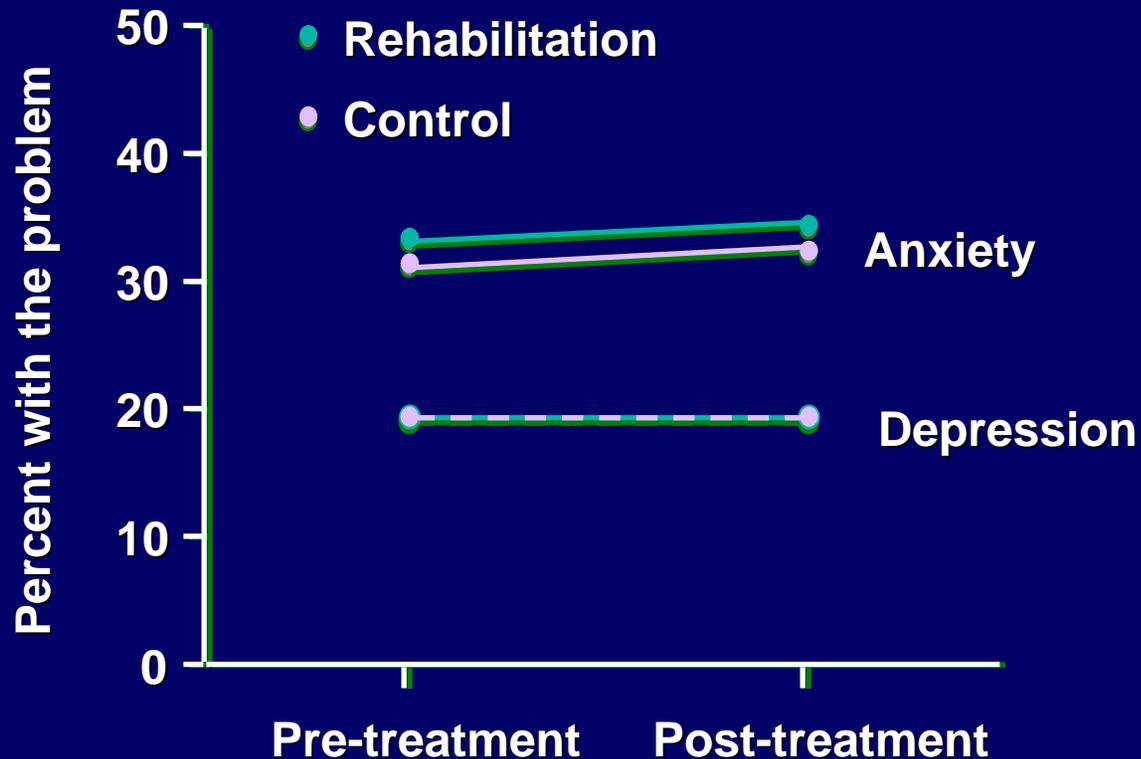
Principal Investigator: DA Jones, MD

HYPOTHESIS: Reduction in anxiety and depression results in reduction in mortality in post-MI patients.

Jones & West Rehabilitation Program Clinical Trial Design



Reduction in Anxiety and Depression at 6-Month Follow-up



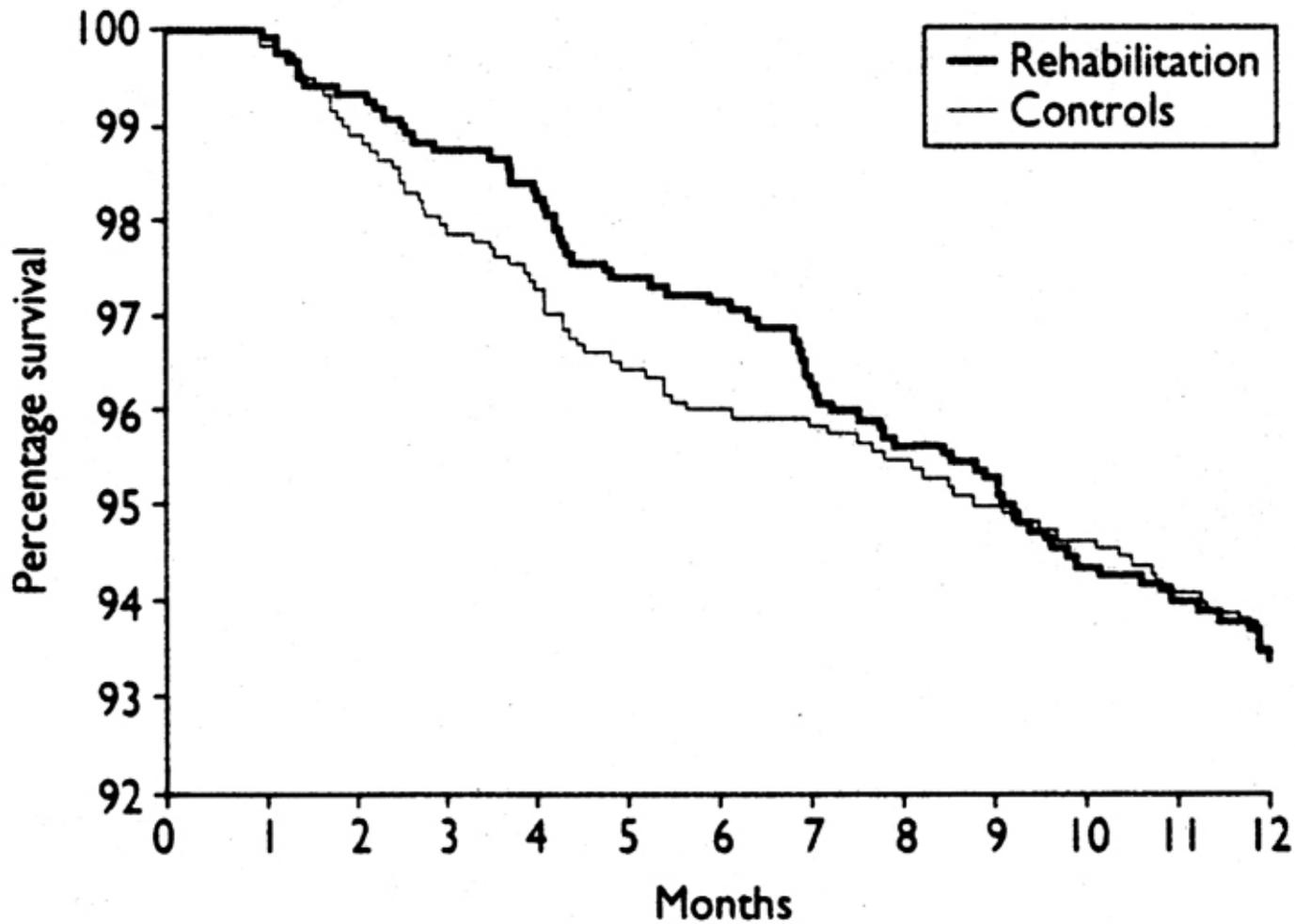
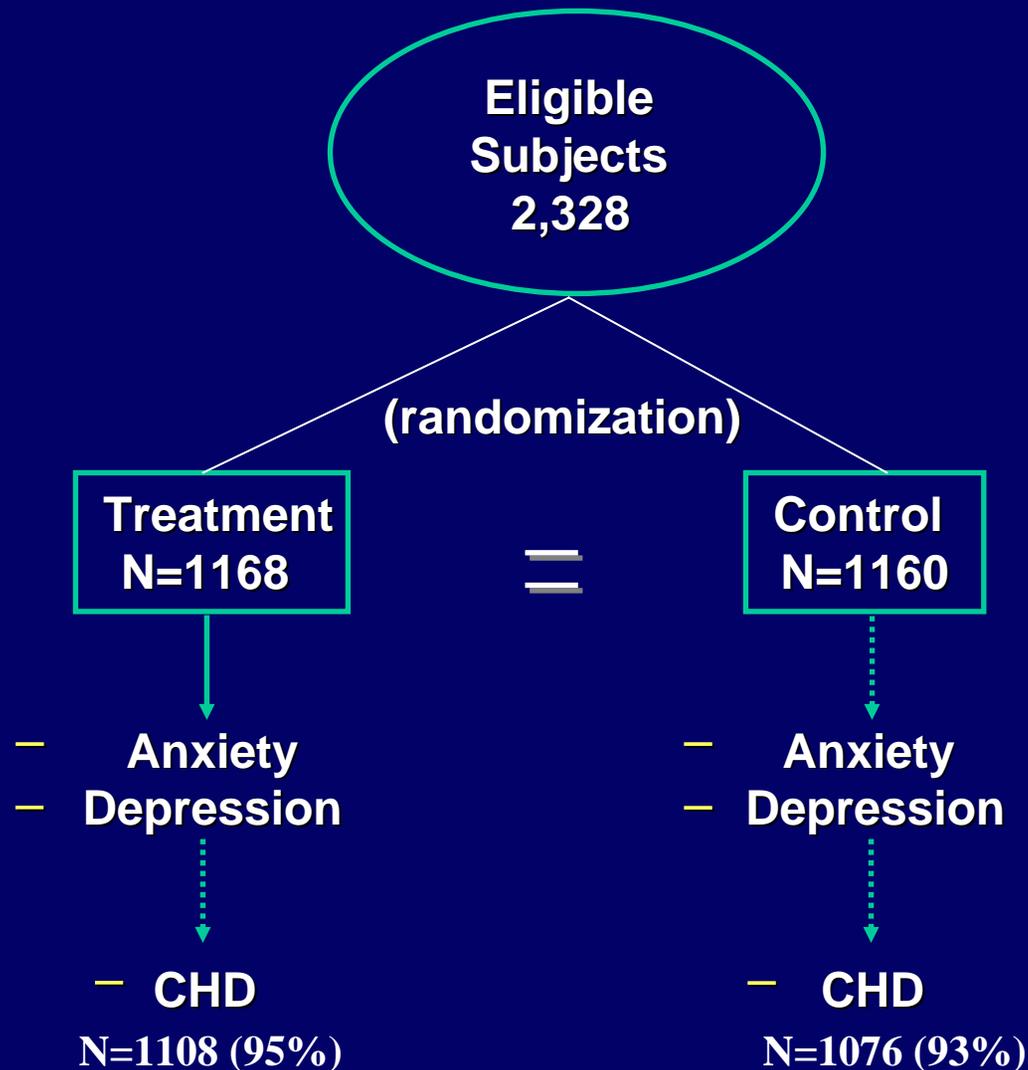


Fig 2—Percentage survival after 28 days in rehabilitation and control groups

Jones & West Rehabilitation Program Clinical Trial Design



WHAT WE LEARNED

Pilot the intervention to insure that it can improve behavioral targets *before* undertaking a trial.



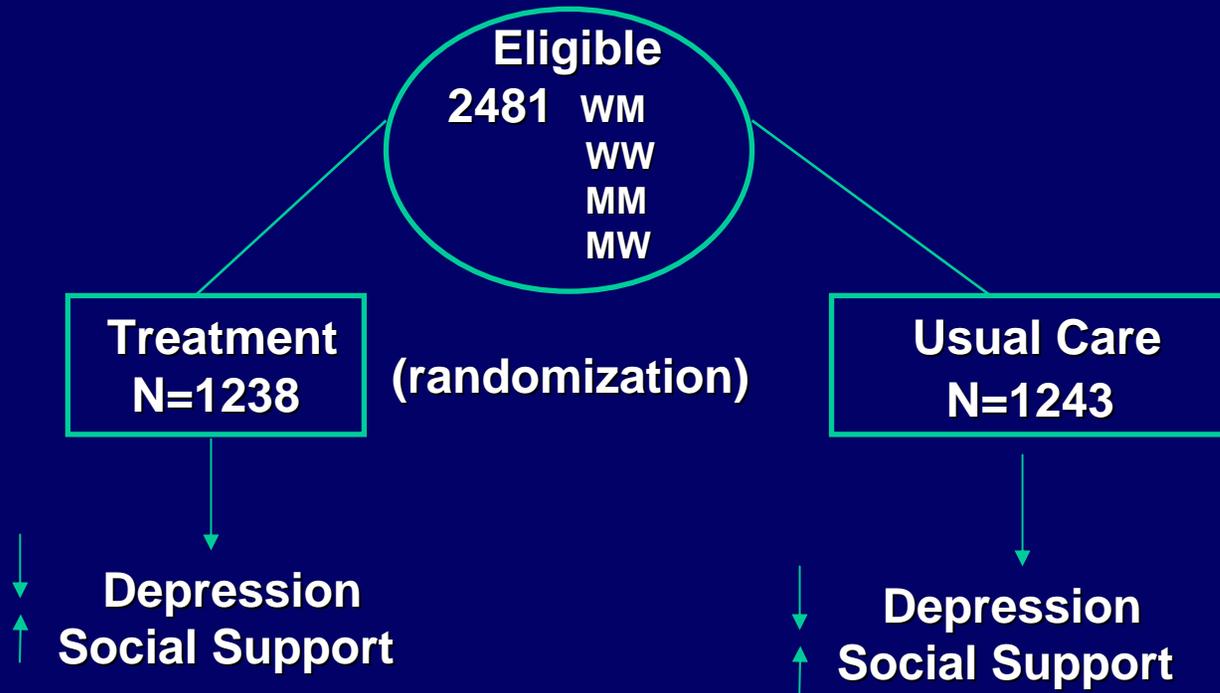
enrichd

Enhancing Recovery in Coronary Heart Disease (ENRICHD) Trial 1996-2003

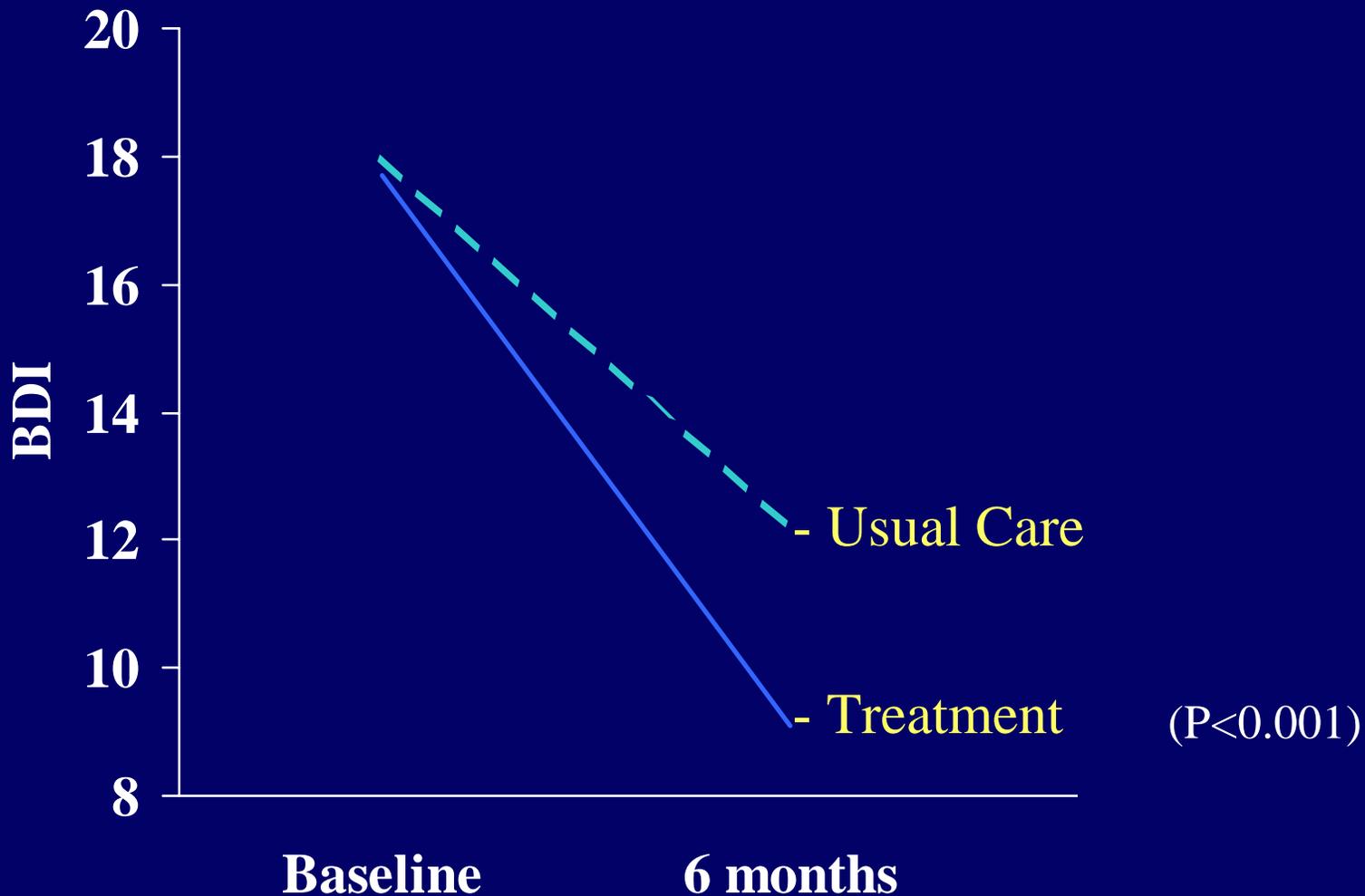
Principal Investigator: The ENRICHD Investigators

HYPOTHESIS: In post-MI patients who are depressed or have low social support, reduction in these psychosocial factors will reduce mortality or nonfatal MI.

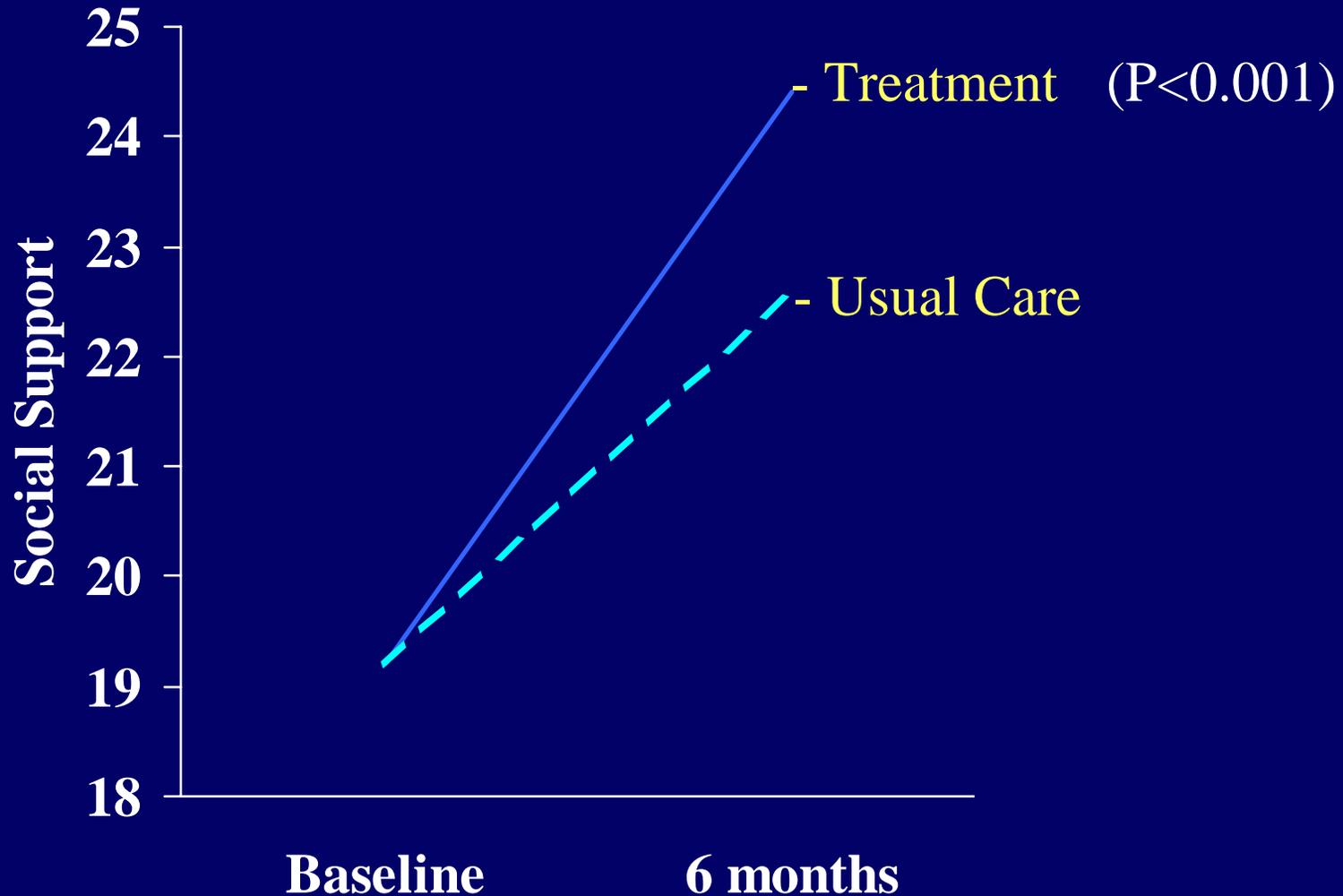
ENRICHD



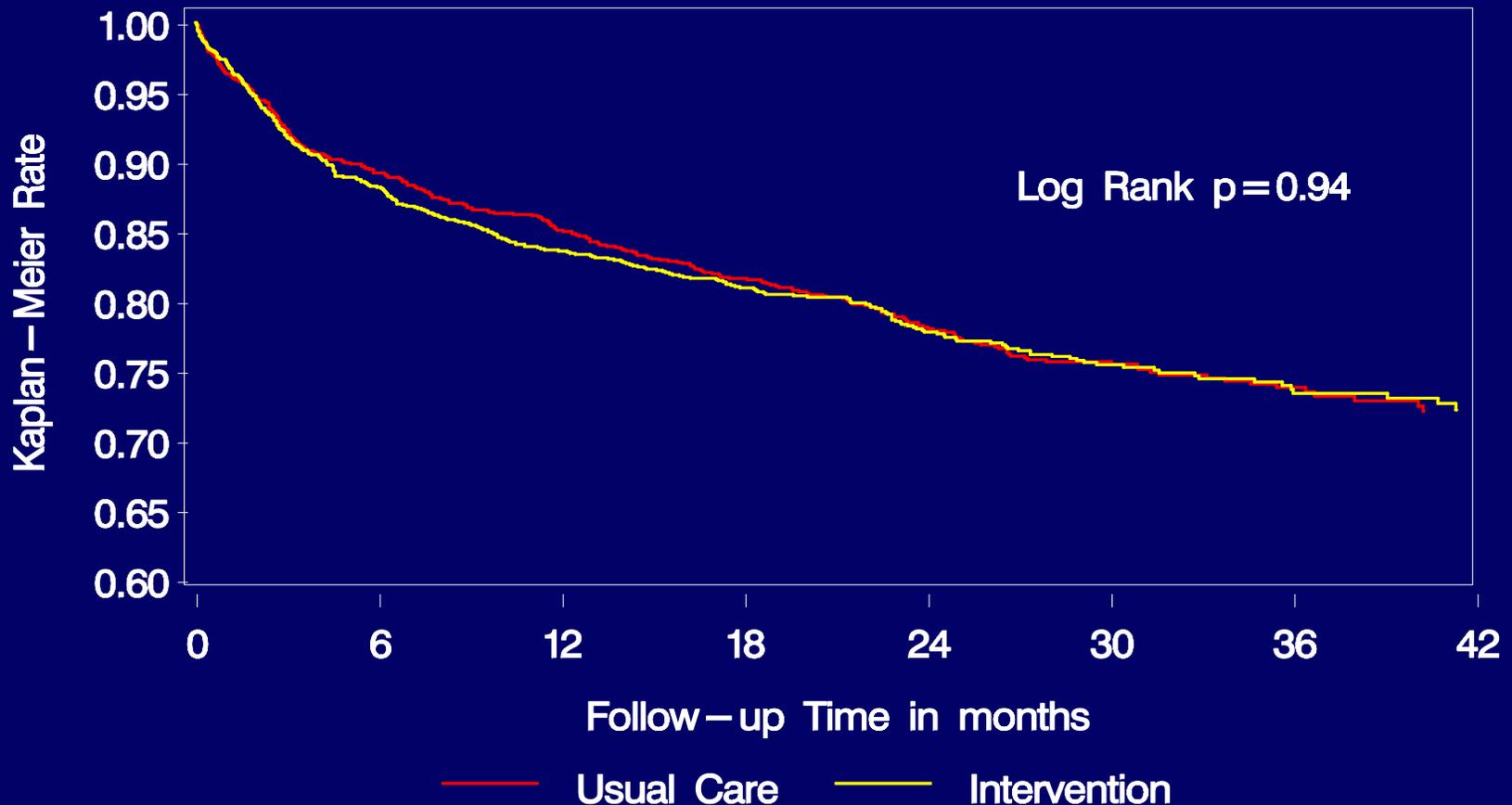
ENRICHD: Change in Depression



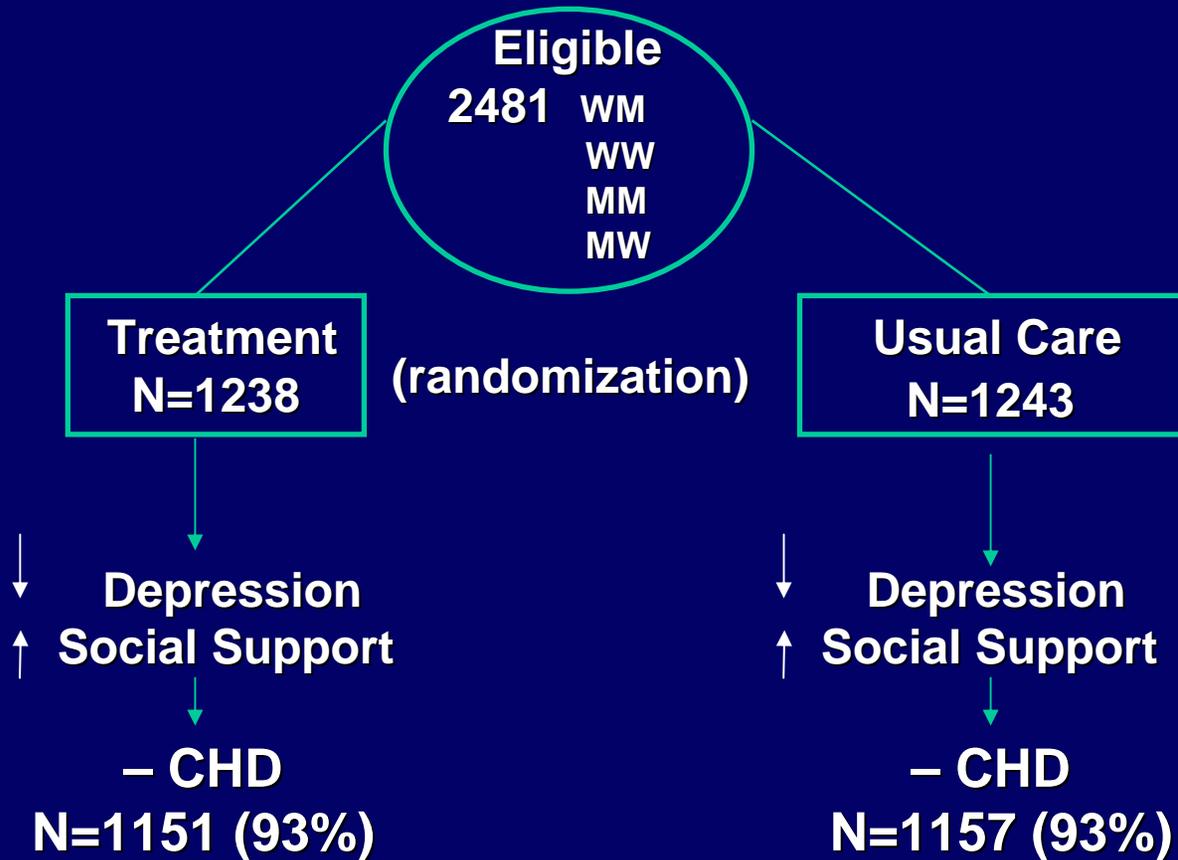
ENRICHD: Change in Social Support



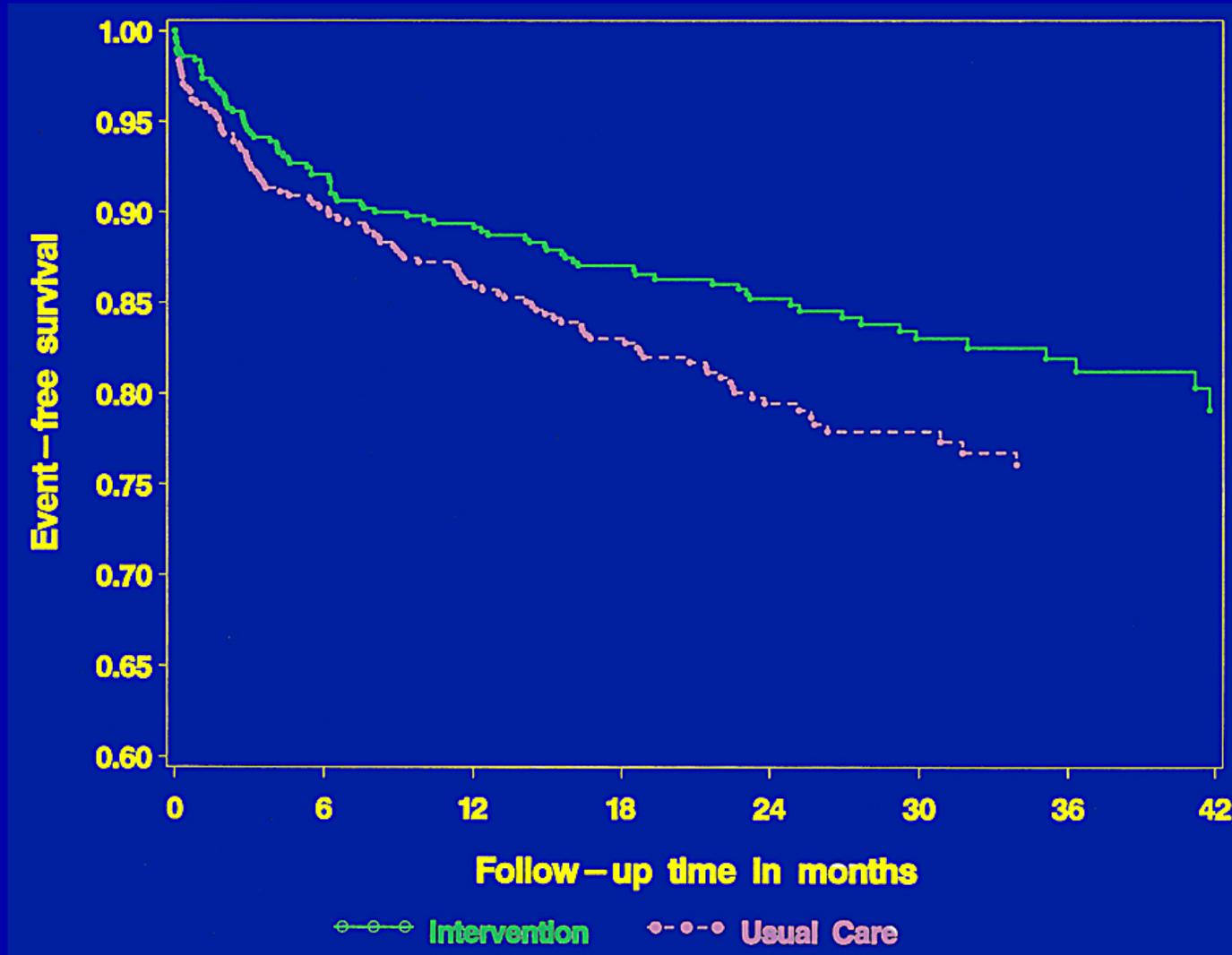
Kaplan-Meier Survival Curves



ENRICHD



Impact of Treatment for White Males



ENRICHD: Primary Endpoint



Adherence in the Treatment Group

	Goal	Observed
Median number of sessions	18-24	10
Received group intervention	100%	31%
Received ≥ 6 sessions	100%	74%
Improved on depression or social support	100%	56%
Ability to perform Beck self-therapy	100%	44%
Availability of ≥ 1 supportive relationship [for social support participants only]	100%	80%

WHAT WE LEARNED

- Value of strong intervention.
- One size may not fit all.
Understand cultural variability in response to treatment.

“An error doesn’t become a mistake until you refuse to correct it .”

- OrlandoA. Battista

Heart Failure
Adherence &
Retention Trial



Heart Failure Adherence and Retention Trial (HART) 2001-Present

Principal Investigator: Lynda H. Powell, PhD

HYPOTHESIS: Improvement in self-management skills prevents hospitalizations or death in patients with heart failure.

Self-Management
Intervention



Improved
Self-Efficacy at
Self-Management



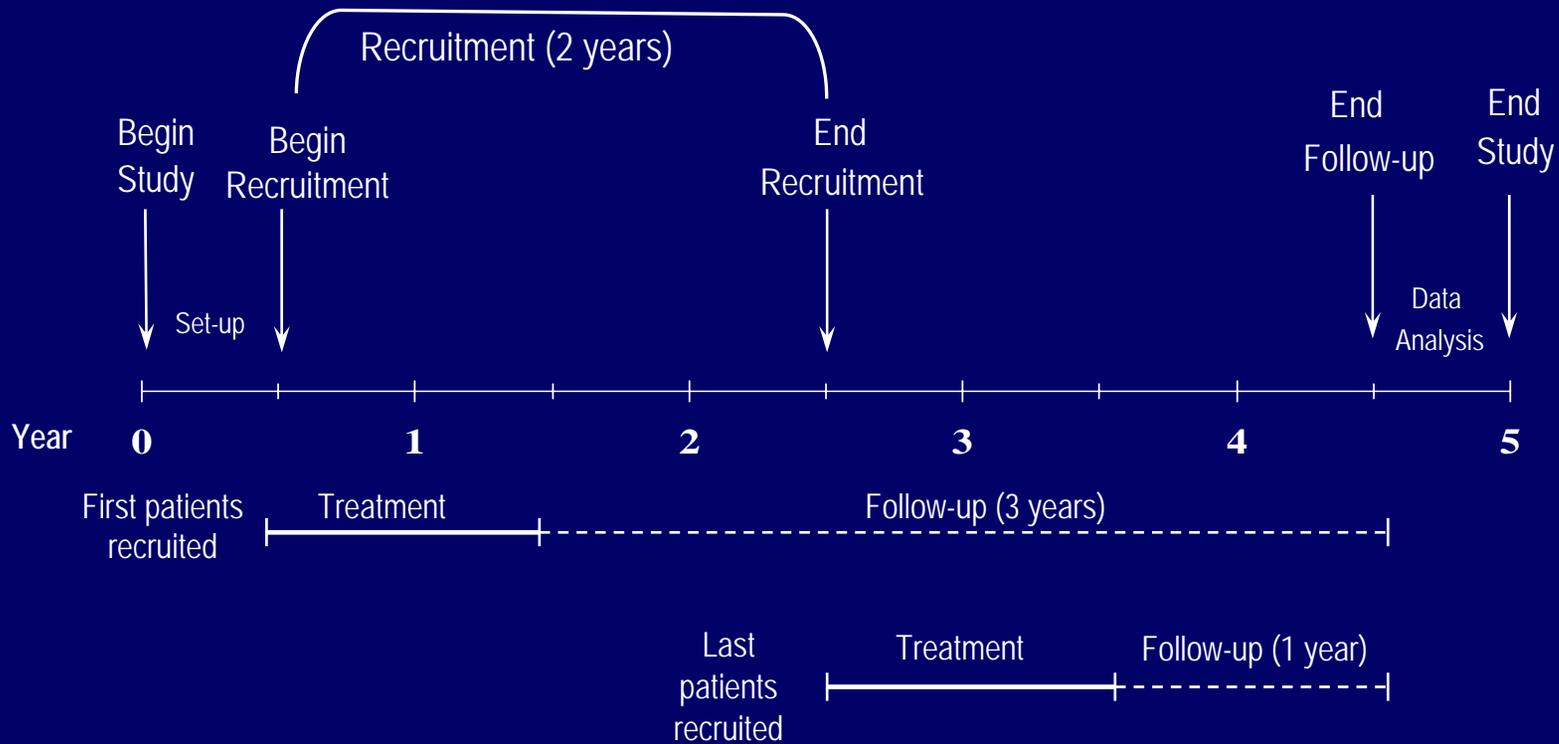
- Improved Adherence
- Improved Psychosocial
Function



- Improved Clinical
Outcome
- Slowed Progression
- Improved Quality
of Life
- Reduced Health
Care Costs

SAMPLE SIZE

- Treatment effectiveness: 15% difference
- Event rate for primary endpoint: 15% per year
- Drop-out and loss rate: 15%
- Adjustment for interim analyses



Treatment Fidelity:

- Protocol
- Team Meetings
- Local Supervisor

The Data and Safety Monitoring Committee:

Competitor or Collaborator?

Comments from the DSMB:

“It was a very good meeting. Stay in touch.”

“We had a great meeting. Keep up your good work.”

Comments from the DSMB:

“HART seems to be making good progress. You have identified the problem areas and seem to have reasonable solutions. **It takes a long time to change the course of a large ship, but I sense that this is beginning to happen.**”

ISSUE: Choice of Appropriate Control Group

Usual Care:

To determine treatment efficacy over the standard of care.

Attention Control:

To determine whether treatment was efficacious over the simple provision of attention.

ISSUE: Delay Time Between Randomization and Start of Treatment

Logistical difficulties in the formation of groups result in delay before start of treatment. Focused recruiting and case management of “waiters” is needed.

ISSUE: Poorer attendance early in treatment in the disadvantaged minorities results in differential exposure to full treatment package.

Make-up sessions for missed meetings in later phase of treatment may minimize differential exposure to treatment by ethnicity.

Summary

1. A behavioral intervention can harm. Understand the beliefs and attitudes of all targeted subgroups including women, minorities, and people of lower educational levels.
 2. Pilot the intervention first. Be completely confident in its efficacy before undertaking a clinical trial of its impact on health. Be particularly sensitive to gender and minority variation in response.
 3. Randomize and guard the randomization throughout the trial. Randomization provides the best control for the measured and unmeasured confounders available.
 4. Be objective and humble. Science moves slowly. Remain open to the possibility that the behavioral intervention:
 - will not work;
 - may work due to unintended mechanisms;
 - will be misinterpreted;
 - will not be accepted in the larger community if it does work.
-