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Department of Health and Human Services



The Challenge of Randomized Clinical Trials:

**The Enhancing Recovery in Coronary
Heart Disease Patients Trial (ENRICHD)**

January 10, 2003

Disclosure

I have no conflicts of interest to disclose.

The interpretations I present are mine, and do not necessarily reflect those of the NHLBI or of others who participated in the ENRICHD clinical trial.

Sertraline was donated to NHLBI by Pfizer.

Evidence-Based Medicine

“the conscientious, explicit, and
judicious use of current best
evidence in making decisions
about the care of individual
patients...”

David L. Sackett

BMJ, 1996

What contributes to decisions about care of patients?

- Diagnosis
- Prognostic markers
- Clinical research data, esp. from RCTs.
- Clinical experience
- Patient's preferences

“Clinical Trial”

“A properly planned and executed clinical trial is a powerful experimental technique for assessing the effectiveness of an intervention.”

Friedman, Furberg and DeMets, 1998

Characteristics of RCTs

- A clinically important and scientifically justified a-priori hypothesis.
- A well-defined population, and representative sample of sufficient size to detect clinically important differences between treatments.
- One or more comparison groups whose care is specified sufficiently well to allow replication. (Adapted from Meinert/Kraemer, 2002)

Characteristics of RCTs

- Random assignment to treatment and control group(s).

“Randomization properly carried out...relieves the experimenter from the anxiety of considering and estimating the magnitude of the innumerable causes by which ... data may be disturbed.”

R.A. Fisher, 1935

Characteristics of RCTs

- A few well-justified outcome measures, defined a-priori and obtained either blind to treatment group or with safeguards to avoid confusing the opinions or expectations of patients or researchers with treatment effects.

Characteristics of RCTs

- A primary analysis which includes data from all randomized subjects (intent-to-treat) and pre-specified subgroups.
- A valid test for statistical significance and estimates of effect sizes to guide clinical and policy decisions.

ENRICHD

Enhancing Recovery
in Coronary Heart
Disease Patients

Study Organization

- Study Chair and Co-Chair
 - L Berkman, Harvard University, Boston, MA
 - A Jaffe, Mayo Clinic, Rochester, MN
- Coordinating Center
 - J Hosking & D Catellier, U. North Carolina at Chapel Hill
- Project Office
 - S Czajkowski, NHLBI, Bethesda, MD
- Data and Safety Monitoring Board
 - N Wenger, Emory University, Atlanta GA, Chair

Study Organization

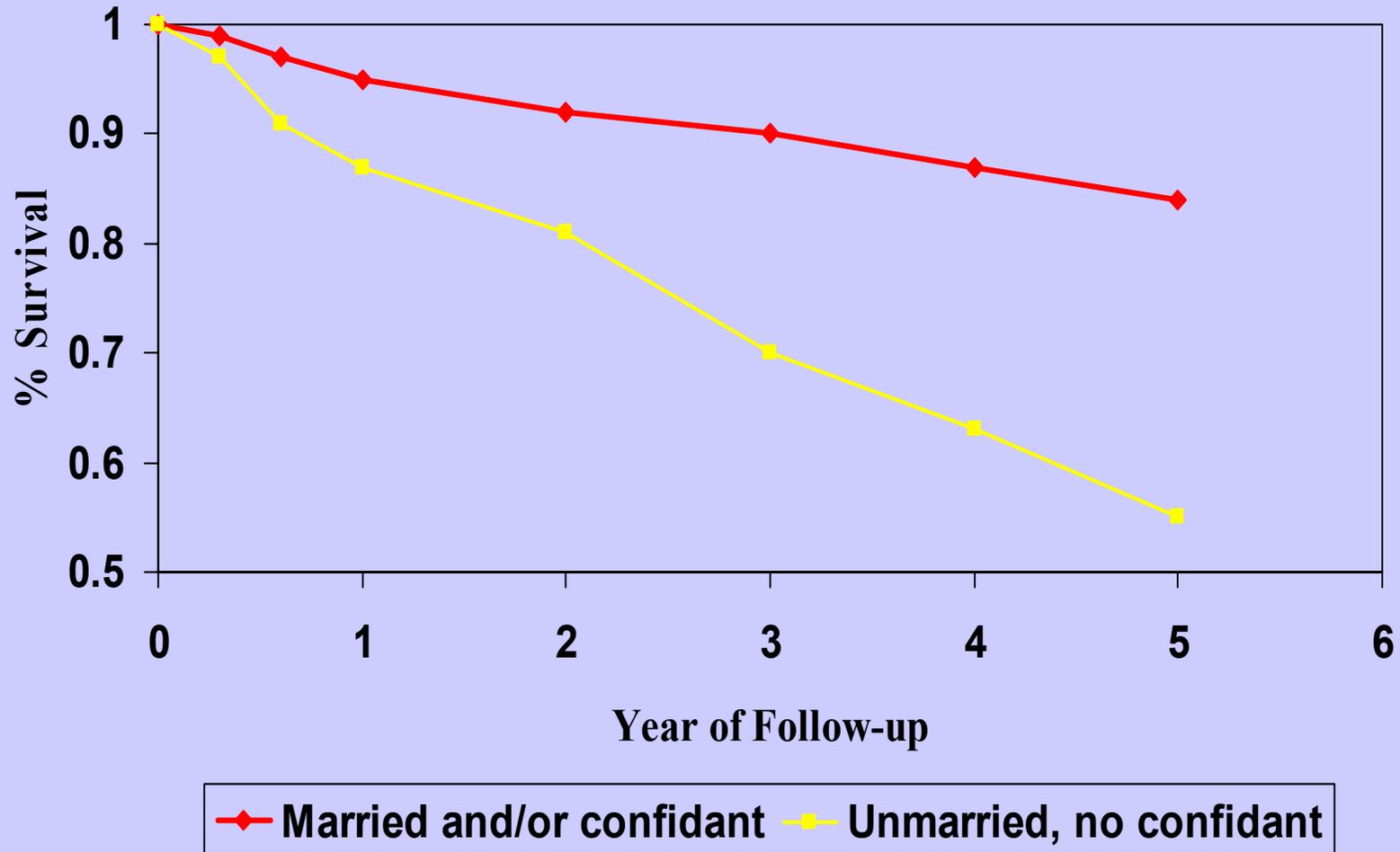
- Clinical sites

- J Blumenthal, Duke University, Durham, NC
- M Burg, Yale University, New Haven, CT
- R Carney, Washington University, St. Louis, MO
- R DeBusk, Stanford University, Palo Alto, CA
- P Mitchell, Univ. of Washington, Seattle, WA
- L Powell, Rush-Presbyterian-St. Lukes Med. Ctr, Chicago, IL
- J Raczynski, Univ. of Alabama at Birmingham, AL
- N Schneiderman, Univ. of Miami, Coral Gables, FL

Background

- Low social support also is associated with an increased risk of death and recurrent infarction
- Adjusted risks range from 2.0 – 4.0
 - Williams *JAMA*, 1992; Case, *JAMA*, 1992; Berkman, *Ann Int Med.* 1992; Gorkin, *AJC*, 1993; Kawachi, *J Epid & Comm. Hlth*, 1996.

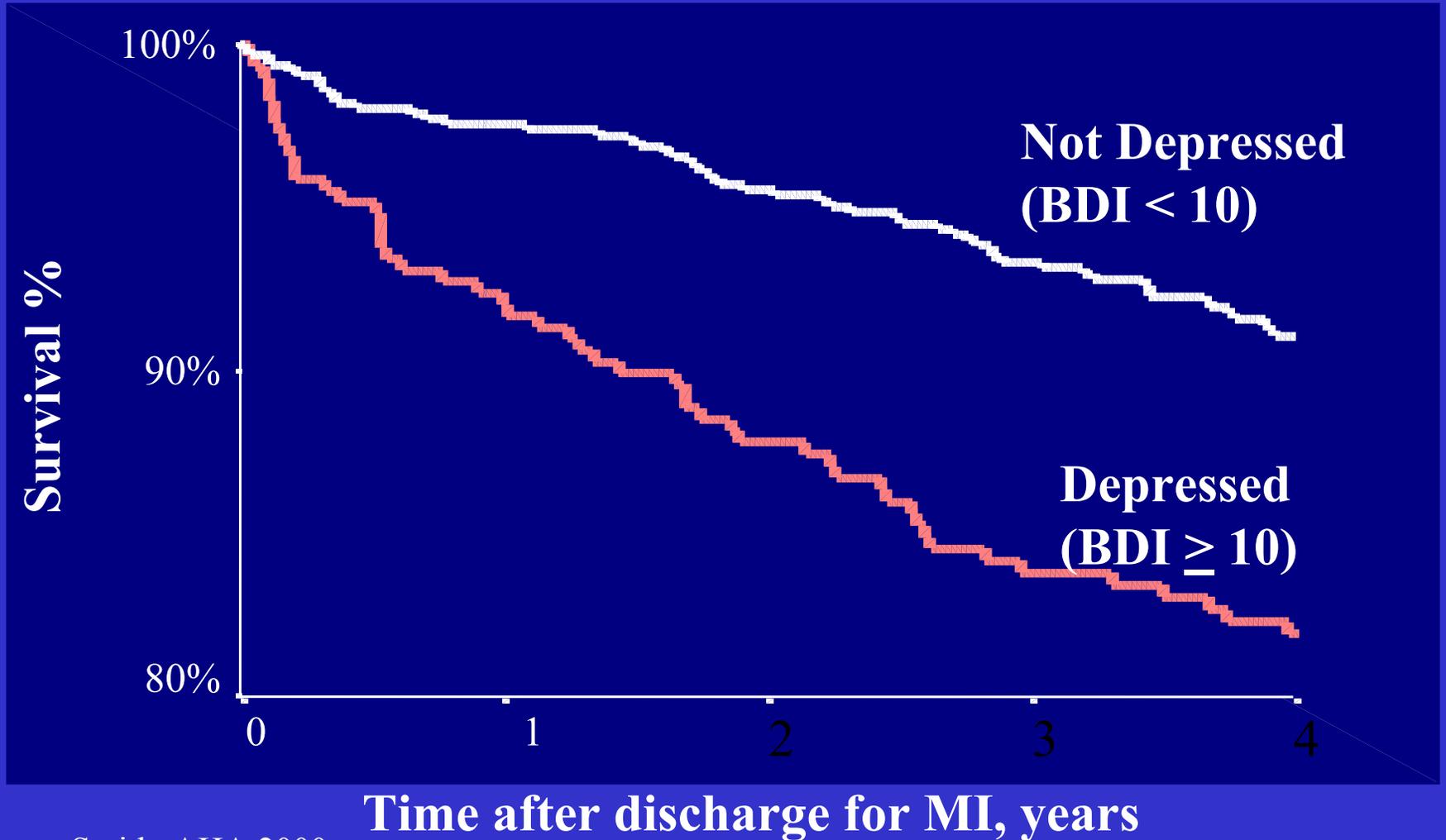
Social Support and Post-MI Cardiac Mortality.



Background

- Depression before or after MI is associated with an increased risk of death and recurrent infarction
- Adjusted risks range from 2.2 – 4.4
 - Bush, *AJC*, 2001; Irvine, *Psych Med*, 1999; Frasure-Smith, *JAMA*, 1993; Ahern, *AJC* 1990; Carney, *Psych Med*, 1988.

Depression and Post-MI Cardiac Mortality



Hypothesis

That treating of depression and low social support early after an acute myocardial infarction will reduce recurrent infarctions and death.

Inclusion Criteria

- Recruitment within 28 days after MI
- Review of medical records to verify MI
 - Characteristic increases in enzymes indicating MI (2 x ULN), and:
 - Symptoms compatible with acute MI, or
 - Characteristic evolution electrocardiographic S-T changes or new Q waves
- Diagnosis of
 - major or minor depression by DIS/HamD or
 - low social support by ESSI

Exclusion Criteria

- MI due to cardiac procedures (CABG or PTCA)
- Non-cardiac illness likely to be fatal within 1 year
- Medical condition limiting participation
- Major psychiatric comorbidity (e.g., schizophrenia, dementia)
- Imminent suicide risk
- Unwilling to provide informed consent
- Unable to complete screening visits
- Inaccessible for treatment and follow-up

Control Group

Control group: Usual cardiac and rehabilitation care; physicians notified of psychosocial test scores.

All patients: Written instructions concerning CHD risk factor modification via “An Active Partnership for the Health of Your Heart” (AHA, 1990).

Treatment Group

- Behavioral Treatment (CBT) for Depression and Low Social Support
 - Individual Sessions
 - Group Sessions
 - SSRI for non-responders and severely depressed (HamD > 24)

Assuring Intervention Integrity

Centralized training for delivery of CBT.

Treatment manual, with specific CBT goals.

Audiotaping of all therapy sessions, with expert review of randomly selected tapes.

Regularly scheduled conference calls among therapists.

Site visits and therapy goals review by expert staff.

Primary Endpoint

- All-cause mortality plus non-fatal myocardial infarction
- Assumptions:
 - usual care event rate = 23% over 3.5 years
 - 25% non-compliance
 - alpha = .05, adjusted for multiple looks
- 88% power to detect 30% reduction in events for complying patients, N = 3,000

Secondary Endpoints

- All-cause mortality
- Cause-specific mortality
- Recurrent nonfatal MI
- Revascularization procedures
- Cardiovascular hospitalization

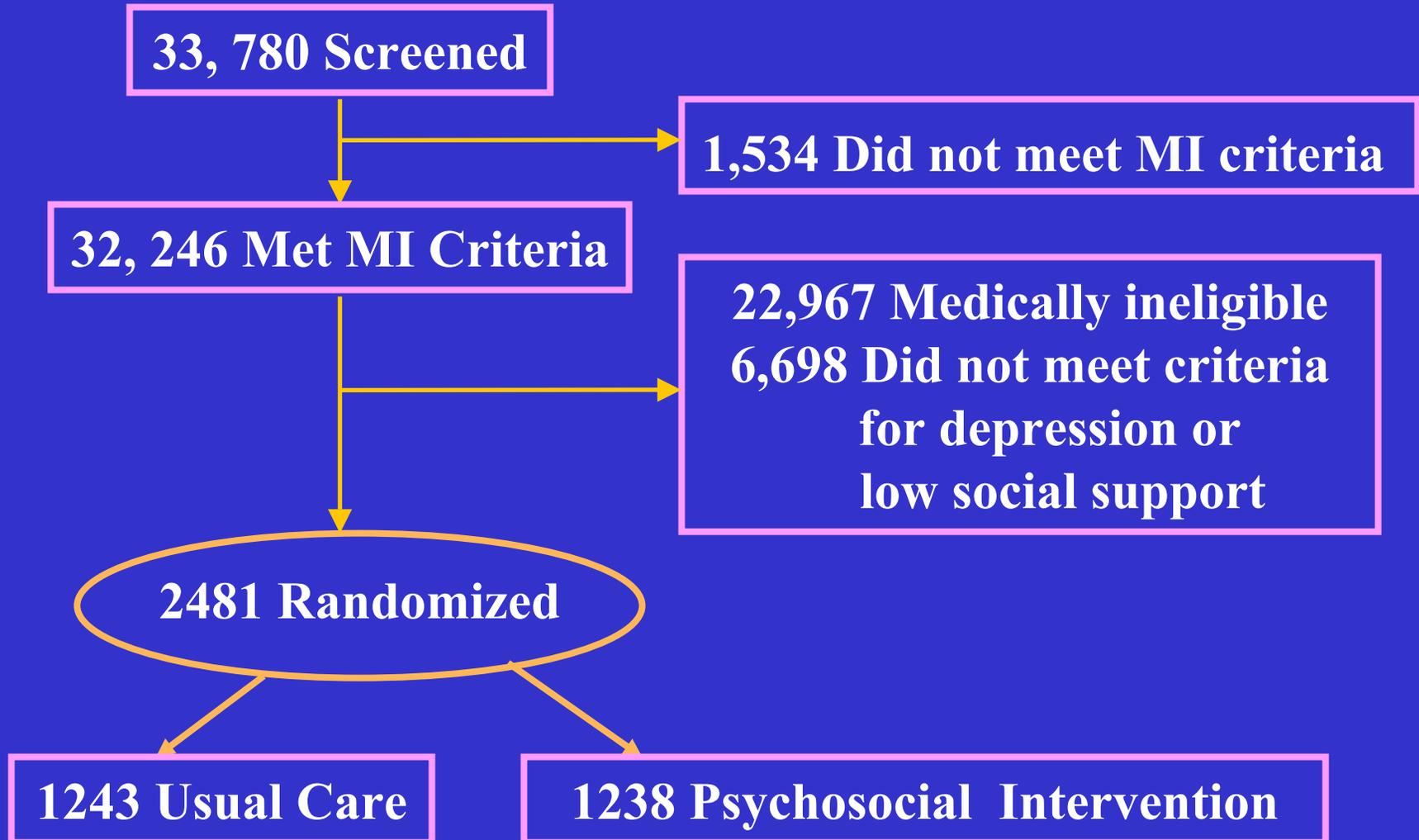
Assuring Objective Endpoints

- Endpoints reviewed by two members of a committee masked to treatment assignment
- Differences of opinion adjudicated by committee discussion
- Psychosocial outcomes evaluated by staff masked to treatment assignment

Study Design Summary

- Randomized, parallel-group clinical trial
- Post-MI patients randomly assigned to special intervention or usual care
- Average follow-up for 2.4 years
- Masked ascertainment of primary endpoint
- Intention-to-treat analysis

Screening and Enrollment



Control of Randomization

- Centralized, automated, telephone based system
- Entry of specifically required data
- Available at all times

Assuring Proper and Adequate Recruitment

- Weekly reports to PIs, with demographic subgroup information.
- Conference calls to problem sites.
- Recruitment coordinators' conference calls
- Site visits to review cardiology support, enlist additional sources, evaluate enrollment integrity
- Re-allocation of resources

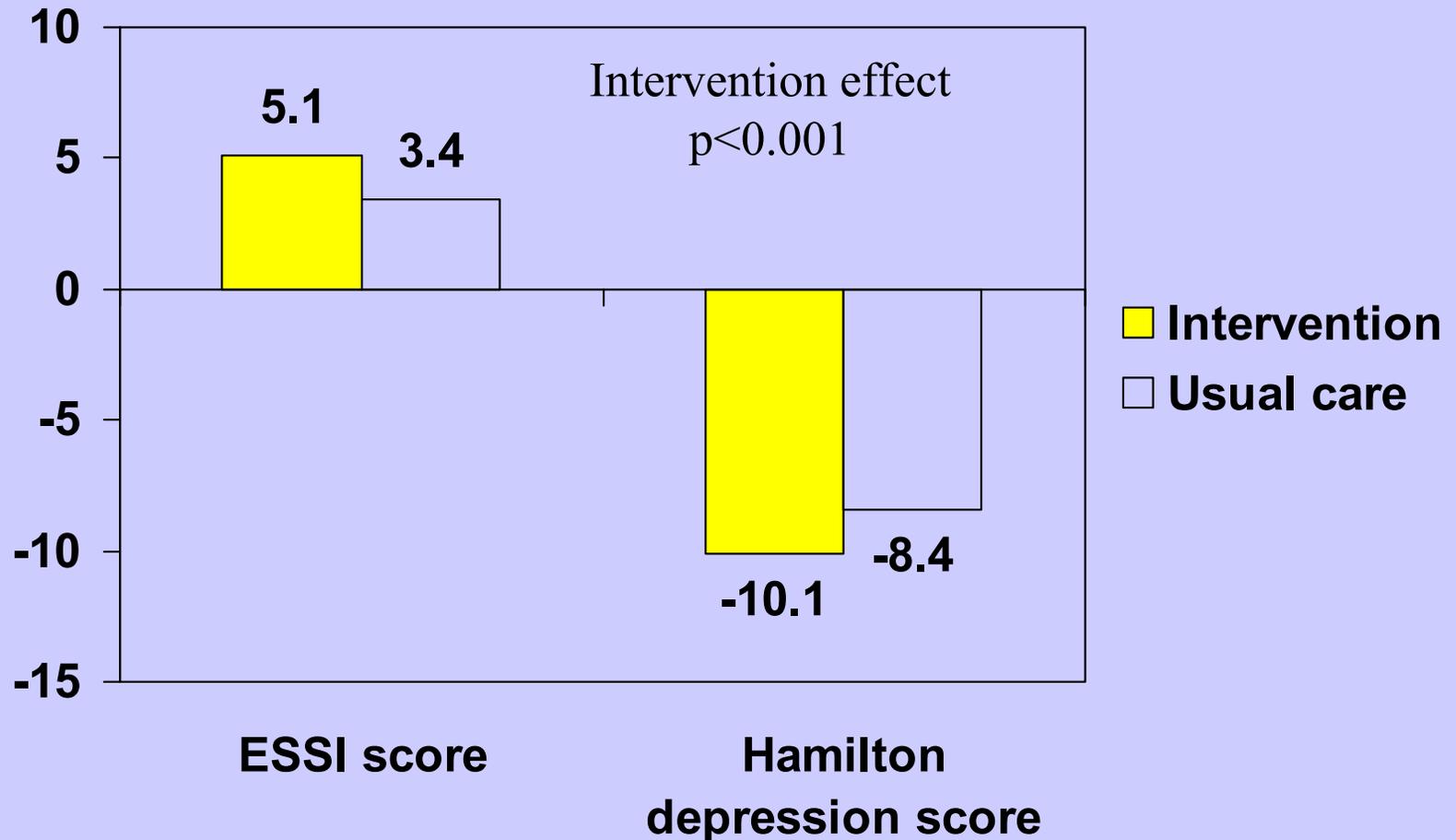
Assuring Data Completeness and Quality

- Centralized training for data collection process, forms, laboratory procedures
- Monthly reports to PIs
- Conference calls
- Site visits, with random chart review, including source documents
- Site visits for participant retention
- Site visits of Coordinating Center

Overall Monitoring

- Data and Safety Monitoring Board
 - Approval of protocol and any revisions
 - Bi-annual meetings, conference calls as needed
 - Review of recruitment, outcome data, all aspects of performance, side effects, special issues
 - Recommend continuing/stopping trial

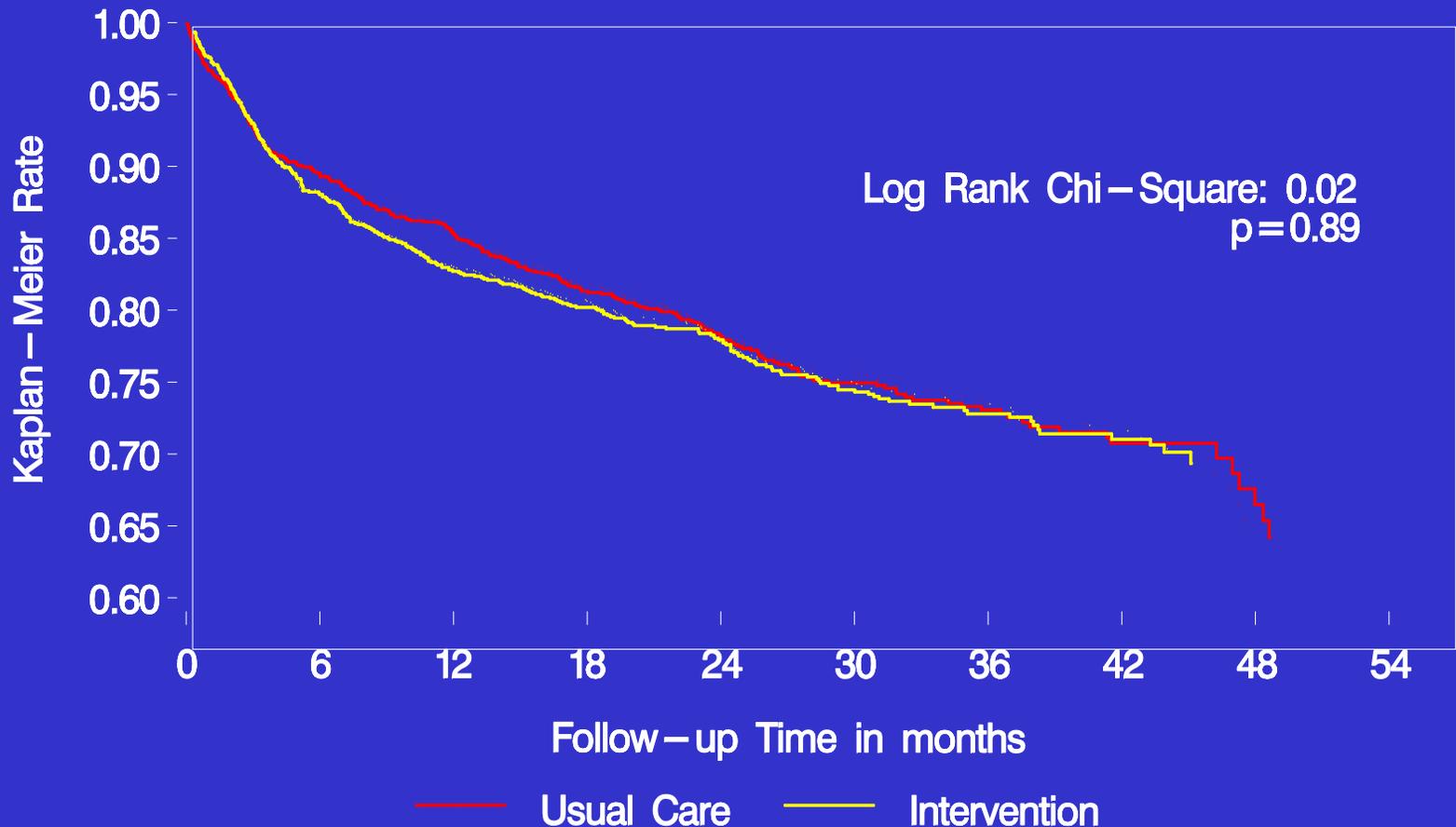
Changes in Social Support and Depression after 6 months



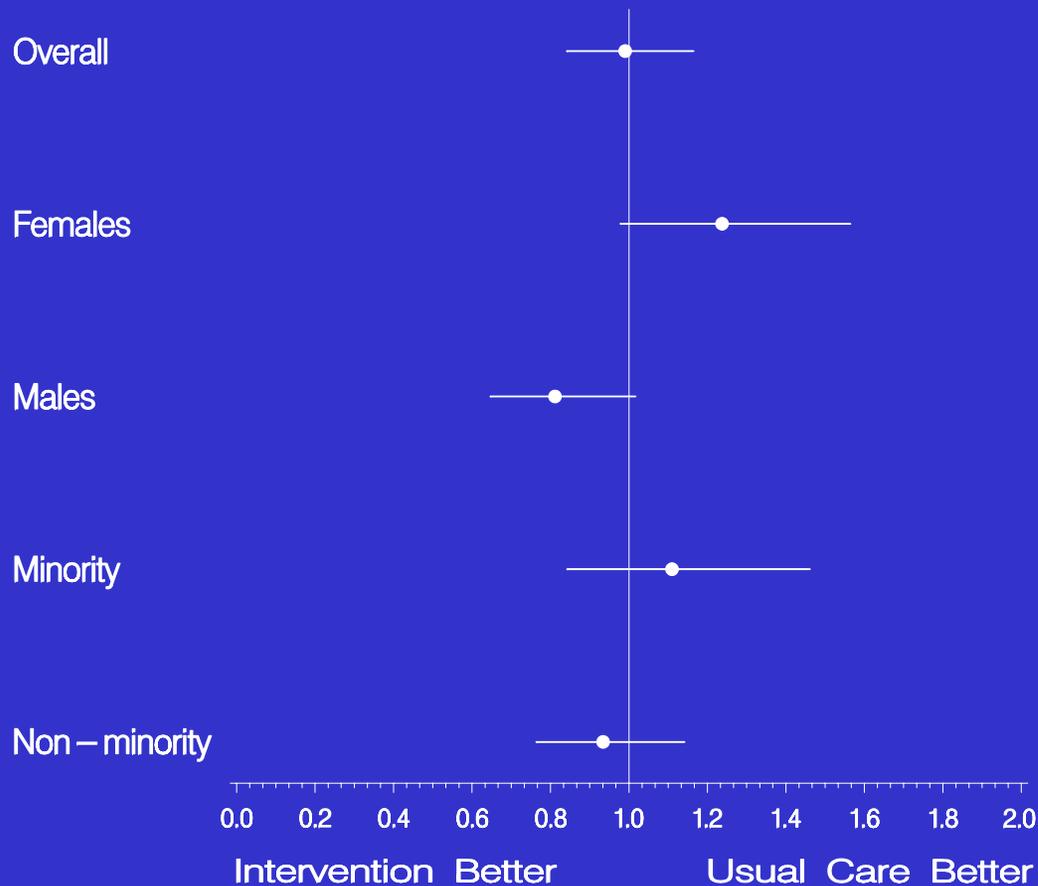
ESSI reported for patients with low social support only

Hamilton depression score reported for depressed patients only

Kaplan-Meier Survival Curves



Hazard Ratios for Pre-specified Subgroups



Conclusions

- Treating depression and low social support immediately after myocardial infarction:
 - Improves symptoms of depression and improves social support.
 - Does not reduce the higher death rate and recurrence of infarction in these patients.

Comments

- Hypothesis: was timing of intervention appropriate?
- Remission of symptoms in usual care:
Role of informing physicians of results psychosocial screening results?

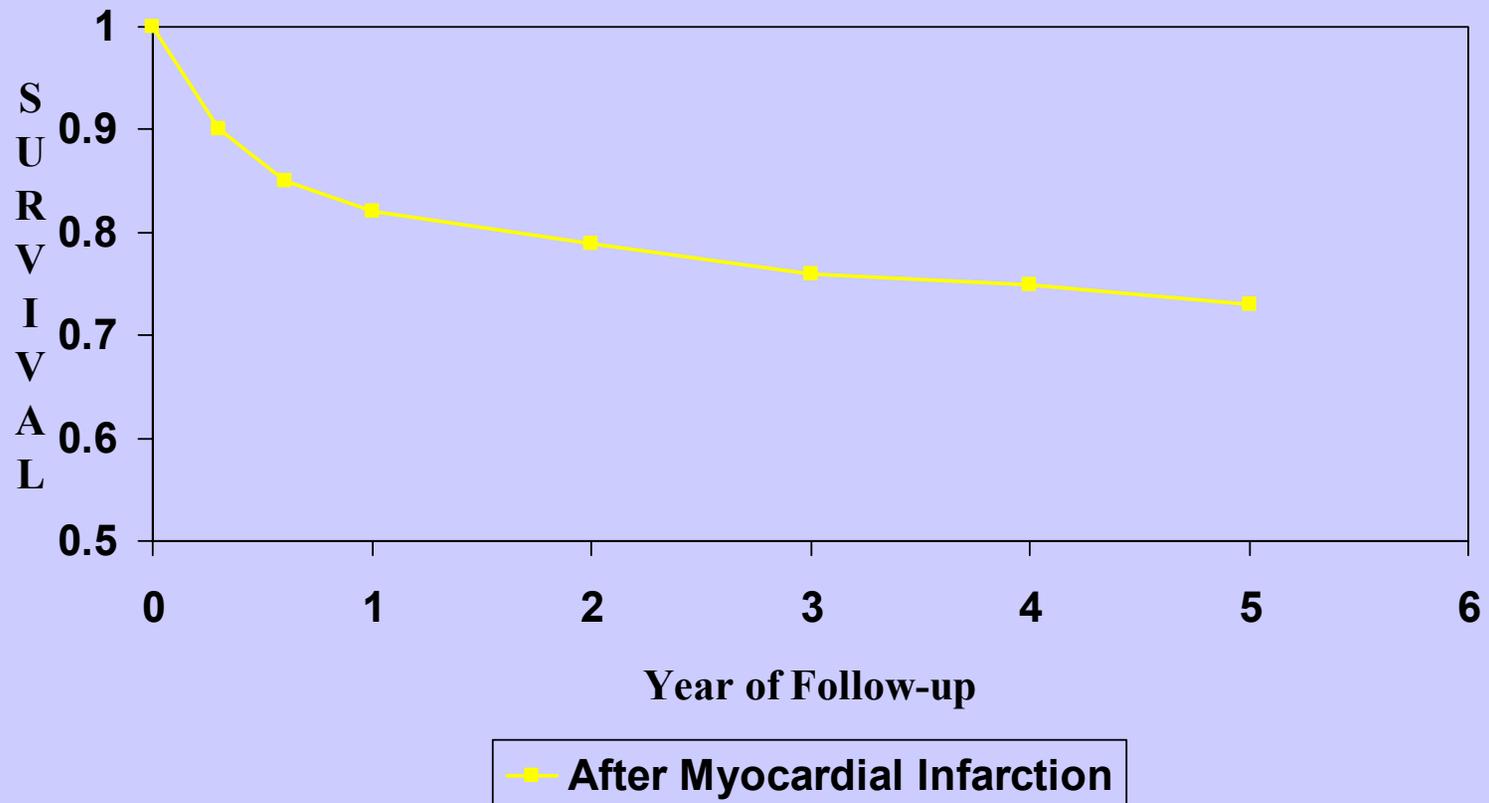
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- External vs. Self-referral by patients?
- Demographic subgroup results?
- Back to basic research?
- Do results inform clinical care?

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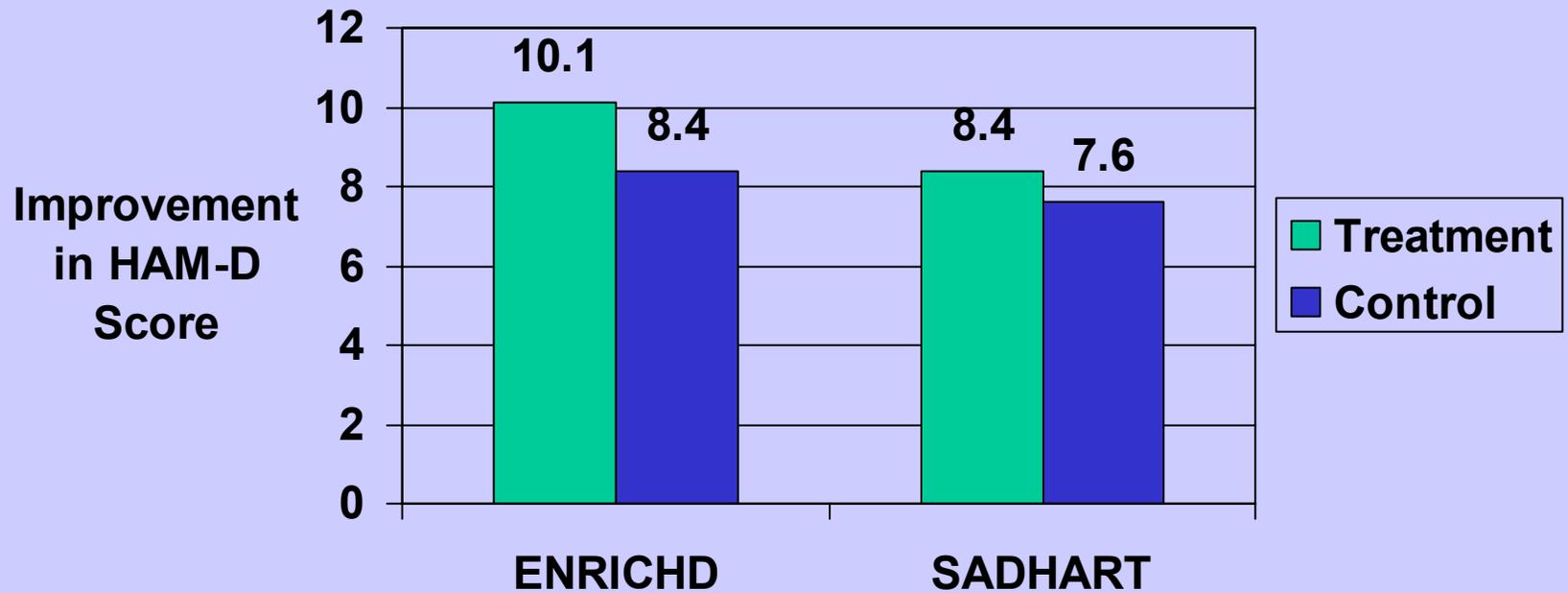
Pattern of post-MI risk



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Change in HAM-D after treatment



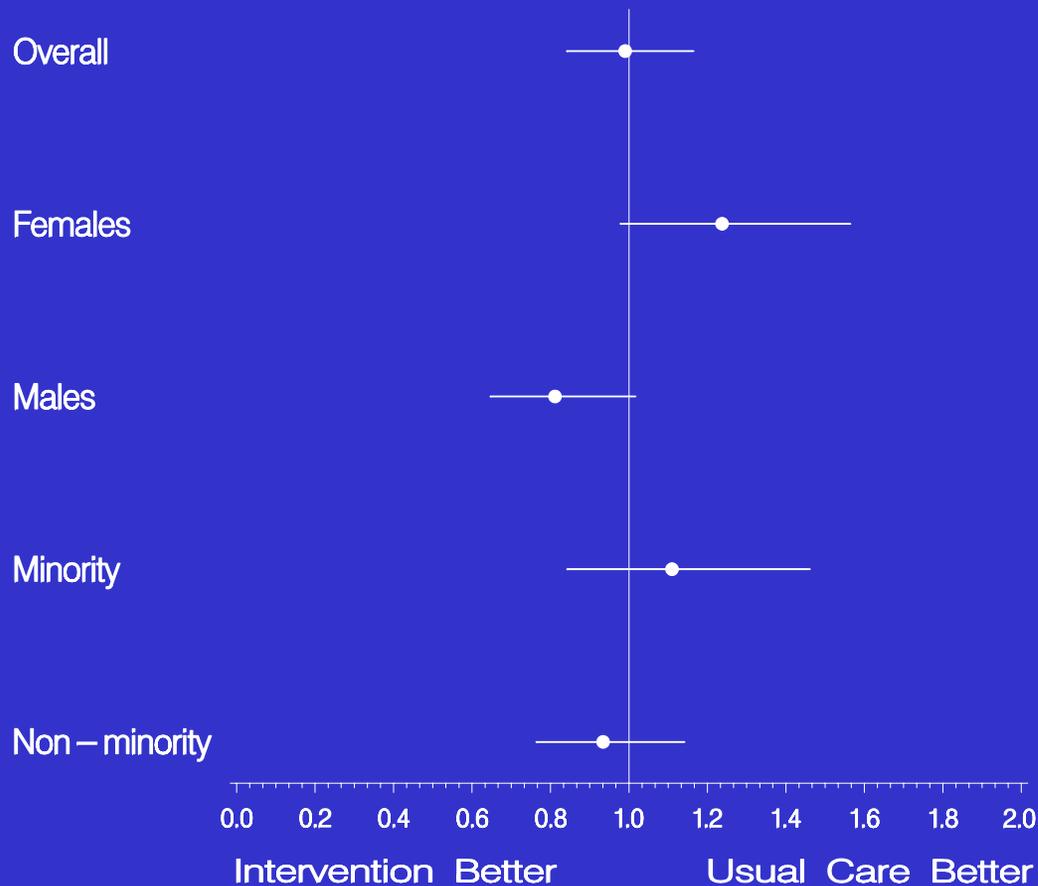
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Hazard Ratios for Pre-specified Subgroups



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“A remedy which is known to work,
though nobody knows why, is
preferable to a remedy which has
the support of theory without
confirmation in practice.”

Richard Asher
Lancet, 1961

Comments

- External vs. Self-referral by patients?
- Demographic subgroup results?
- Back to basic research?
- Do results inform policy and clinical care?

Recommendation

- Depression in patients after myocardial infarction should be treated under existing guidelines for treating depression in the general population.