Effects of Treating Depression and Low Perceived Social Support on Clinical Events After Myocardial Infarction

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

Writing Committee for the ENRICHD Investigators

Context Depression and low perceived social support (LPSS) after myocardial infarction (MI) are associated with higher morbidity and mortality, but little is known about whether this excess risk can be reduced through treatment.

Objective To determine whether mortality and recurrent infarction are reduced by treatment of depression and LPSS with cognitive behavior therapy (CBT), supplemented with a selective serotonin reuptake inhibitor (SSRI) antidepressant when indicated, in patients enrolled within 28 days after MI.

Design, Setting, and Patients Randomized clinical trial conducted from October 1996 to April 2001 in 2481 MI patients (1084 women, 1397 men) enrolled from 8 clinical centers. Major or minor depression was diagnosed by modified *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria and severity by the 17-item Hamilton Rating Scale for Depression (HRSD); LPSS was determined by the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Social Support Instrument (ESSI). Random allocation was to usual medical care or CBT-based psychosocial intervention.

Intervention Cognitive behavior therapy was initiated at a median of 17 days after the index MI for a median of 11 individual sessions throughout 6 months, plus group therapy when feasible, with SSRIs for patients scoring higher than 24 on the HRSD or having a less than 50% reduction in Beck Depression Inventory scores after 5 weeks.

Main Outcome Measures Composite primary end point of death or recurrent MI; secondary outcomes included change in HRSD (for depression) or ESSI scores (for LPSS) at 6 months.

Results Improvement in psychosocial outcomes at 6 months favored treatment: mean (SD) change in HRSD score, –10.1 (7.8) in the depression and psychosocial intervention group vs –8.4 (7.7) in the depression and usual care group ($P<.001$); mean (SD) change in ESSI score, 5.1 (5.9) in the LPSS and psychosocial intervention group vs 3.4 (6.0) in the LPSS and usual care group ($P<.001$). After an average follow-up of 29 months, there was no significant difference in event-free survival between usual care (75.9%) and psychosocial intervention (75.8%). There were also no differences in survival between the psychosocial intervention and usual care arms in any of the 3 psychosocial risk groups (depression, LPSS, and depression and LPSS patients).

Conclusions The intervention did not increase event-free survival. The intervention improved depression and social isolation, although the relative improvement in the psychosocial intervention group compared with the usual care group was less than expected due to substantial improvement in usual care patients.

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CARDIOVASCULAR DISEASE IS THE leading cause of death and a major cause of morbidity and disability in the United States, with an estimated 6 million people having symptomatic coronary heart disease (CHD).[1] Recent studies[2-7] have shown that depression and low perceived social support (LPSS) are associated with increased cardiac morbidity and mortality in CHD patients.

In patients with CHD, the prevalence of major depression is nearly 20% and the prevalence of minor depression is approximately 27%.[8-10] After an acute myocardial infarction (MI), depression is a risk factor for mortality independent of cardiac disease severity.[4,6] A recent randomized clinical trial found that the antidepressant sertraline hydrochloride was effective in treating recurrent depression in patients with either an acute MI or an episode of unstable angina.[11] However, no clinical trial has examined whether treating depression with counseling or antidepressants after an acute MI improves survival or reduces cardiac risk.

The absence of social support is also a risk factor for cardiac morbidity and mortality in patients with CHD.[2,3,5,7] No clinical trial has tested the effects of increasing social support on clinical end points following acute MI, although

For editorial comment see p 3171.

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several small trials that tested psychologically supportive interventions found these to reduce mortality and recurrent events.[12-15]

Although results of individual trials have been mixed, 2 meta-analyses of psychosocial interventions following MI reported a reduction in all-cause mortality and cardiac morbidity.[16,17] The major study reporting positive results was the Recurrent Coronary Prevention Project,[18] which enrolled 1013 MI patients, of whom 592 were randomized to receive up to 4½ years of psychosocial treatment. The targeted psychosocial end points (eg, type A behavior, hostility) were improved and accompanied by a 44% reduction in cardiac death and nonfatal MI. In contrast, the Montreal Heart Attack Readjustment Trial (M-HART),[19] which enrolled 1376 post-MI patients, found that a supportive and educational home health nursing intervention for patients in distress did not reduce medical events. Another trial that compared group counseling with standard care in 2328 MI patients found no improvement in either the psychosocial variables or the medical outcomes measured.[20]

No study has evaluated the effects of treatments designed to lessen depression or increase social support early after the onset of acute MI. Given the strength of the evidence that suggests a relationship between both depression and LPSS and clinical outcomes following acute MI, the objective of this randomized, controlled, multicenter clinical trial, sponsored by the National Heart, Lung, and Blood Institute, was to determine whether treating depression and increasing social support as soon as possible after acute MI reduces the risk of recurrent nonfatal infarction and death.[21]

METHODS

Study Organization

Patients were recruited from 73 hospitals affiliated with 8 clinical centers: Duke University, Durham, NC, Rush Presbyterian–St Luke's Medical Center, Chicago, Ill, Stanford University, Palo Alto, Calif, University of Alabama at Birmingham, University of Miami, Coral Gables, Fla, University of Washington, Seattle, Washington University, St Louis, Mo, and a combined Yale University, New Haven, Conn, and Harvard University, Boston, Mass, site. The Project Office, which was responsible for overall trial management, was the National, Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md. The Data Coordinating Center was at the University of North Carolina at Chapel Hill; the electrocardiography (ECG) core laboratory was at St Louis University, St Louis, Mo; the Beck Institute for Cognitive Therapy and Research, Bala Cynwyd, Pa, provided training and quality assurance for the intervention; and an independent Data and Safety Monitoring Board (DSMB) provided oversight. Protocol approval was obtained by local institutional review boards before beginning recruitment.

Patient Eligibility and Recruitment

Recruitment began in October 1996 and ended in October 1999. All patients with an acute MI admitted to the participating hospitals were considered for enrollment. The criteria for acute MI required characteristic elevation in 1 or more biomarkers of myocardial injury to twice the institution-specific upper limit, except for creatine kinase–MB fraction, for which any elevation with a rising and falling pattern deemed indicative of acute MI by the attending physician was considered acceptable. Symptoms compatible with acute MI or characteristic evolutionary ECG ST-T changes or new Q waves were also required.[22]

Patients who underwent intervention for ST elevation could be included even if marker criteria were not met. Patients with acute MI following percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery or those receiving psychotherapy for depression were excluded. Before April 1998, patients were also excluded if they were taking an antidepressant medication. In April 1998, the protocol was changed to allow enrollment of patients who were taking an antidepressant for longer than 14 days but remained depressed.

Patients were also excluded if they had noncardiac conditions likely to be fatal within 1 year; were too ill to participate; were participating in another research protocol that posed a significant logistic burden or that might confound evaluation of the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) intervention; had major psychiatric comorbidity (including schizophrenia, bipolar disorder, severe dementia, or active substance abuse); were at imminent risk for suicide; refused to participate or their attending physician disallowed participation; could not be enrolled within 28 days of the acute event; or were inaccessible for intervention or follow-up.

Patients who fulfilled the eligibility criteria and gave written informed consent were screened for presence of depression and/or LPSS. The Depression Interview and Structured Hamilton (DISH),[23] a semistructured diagnostic interview developed for ENRICHD, was used to diagnose current depressive episodes according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria[24] and to screen for other psychiatric disorders. The DISH also yields a depression severity score on the 17-item Hamilton Rating Scale for Depression (HRSD).[25] Patients were classified as depressed if they met the ENRICHD-modified *DSM-IV* diagnostic criteria for major or minor depression or dysthymia. Under these criteria, patients were eligible if depressive symptoms had been present for at least 7 (rather than 14) days, provided that there was at least 1 prior episode of major depression. Where no prior episode of major depression existed, the usual 14-day criterion was applied. Nurse coordinators were trained to administer the interview and evaluated on at least 20 interviews by trial psychiatrists and psychologists.[23]

The criteria for LPSS were based on the ENRICHD Social Support Instrument (ESSI), developed for ENRICHD and composed of 5 items derived from well-validated social support scales found in prior studies to be individually predictive of death in cardiac patients.[21] A score

of less than 3 on 2 or more items and a total score of less than 18, or a score of 2 on 2 items without regard to total score, were required to classify a patient as having LPSS.[26] The ESSI was found to be both reliable (α coefficient of .87) and valid (correlation of .62, $P < .001$ with the Perceived Social Support Scale [PSSS]) in psychometric analyses. Design, methods, screening measures, and the numbers of patients who met specific enrollment criteria are described elsewhere in detail.[21,26]

Randomization and Blinding

Randomization was stratified by clinical center and used a permuted block algorithm with blocks of varying sizes 2, 4, and 6. Following eligibility determination, study coordinators obtained treatment allocation using an automated telephone randomization system maintained at the ENRICHD Coordinating Center.

Although participants and interventionists were aware of the patients' treatment assignment, all staff who collected, verified, or classified end point data or follow-up assessments were masked as much as possible. To test for the potential for selection bias that results from research staff being able to predict the next treatment assignment based on unmasking of previous assignments, we used methods developed by Berger and Exner[27] to test for selection bias by examining the association between the predicted probabilities of assignment to the intervention arm (assuming knowledge of the sequence of prior allocations) and selected baseline characteristics and event-free survival within each treatment group. All tests were nonsignificant, providing some assurance that any treatment group imbalances on baseline factors and observed treatment effects are not due to selection bias.

Baseline Measurements

At baseline, an ECG was performed, and demographic, medical history, current medication use (including antidepressants), and physical examination data were recorded. In addition to the DISH and the ESSI, the Beck Depression Inventory (BDI)[28] and the PSSS[29] were administered. The BDI is a 21-item measure of self-reported severity of depressive symptoms with scores between 0 and 64; a score of 10 or higher is the threshold for considering clinical depression.[28] The PSSS is a 12-item scale that assesses perceived social support from family, friends, and others.[29] Other psychosocial assessments made during the trial are described elsewhere.[21,30]

Treatment

Patients were assigned randomly either to the intervention or usual care group. The period of highest risk for reinfarction and death is during the initial 6 months after acute MI. Therefore, patients were enrolled within 28 days, and those in the intervention arm were treated as soon as possible after the index MI in the belief that the optimal time for intervention would be during this period. Both groups received written materials about risk factors based on the American Heart Association Active Partnership Program.[31] Otherwise, patients in usual care received only the care provided by their physicians. Physicians were notified in writing that their patients were enrolled in the study with either depression or LPSS or both. Physicians were notified immediately if their patient was found to be suicidal or to have severe depression.

Cognitive behavior therapy (CBT)[32] was used as the basis for the ENRICHD intervention because of its efficacy in treating depressed noncardiac patients[33,34] and its ability to address a range of issues involving distress and behavioral problems. For depressed patients, CBT was given as described by Beck et al[28] and Beck.[32] For patients with LPSS, CBT techniques were used to address the cognitions, behaviors, and affect that accompany LPSS, supplemented with techniques based on social learning theory and adopted from other psychotherapeutic support trials. For patients with LPSS, a detailed assessment of the patient's social needs, relationships, and deficits was performed during the first therapy session, including assessment of participants' social planning, communication, and problem-solving skills and social anxiety or phobia. Counseling sessions were tailored to address patients' specific needs through the use of modular intervention components that addressed (1) behavioral and social skill deficits, (2) cognitive factors that contribute to the perception or maintenance of unsatisfying levels of social support, and (3) social outreach and network development. The major thrust of the intervention was on strengthening network ties to be more functional, supportive, and satisfying, although sometimes patients were encouraged to create new relationships. Patients with both depression and LPSS received an intervention in which elements of both treatments were integrated across treatment sessions. A detailed description of the depression and social support interventions is provided elsewhere.[35]

Therapists were trained by study psychologists and trainers from the Beck Institute for Cognitive Therapy and Research. The Beck Institute also monitored quality and adherence to the treatment protocol by evaluating randomly selected therapy session audiotapes. Training and quality control procedures have been described elsewhere.[21]

Intervention group patients with scores higher than 24 on the HRSD or those who showed a less than 50% reduction in BDI scores after 5 weeks were referred to study psychiatrists for consideration of pharmacotherapy. Unless contraindicated, sertraline hydrochloride (donated by Pfizer Inc, New York, NY, and provided without charge to intervention group patients, as needed) was initiated at 50 mg/d and adjusted to a maximum of 200 mg/d if deemed necessary by the treating psychiatrist. Alternative medications (another SSRI or nortriptyline hydrochloride) were considered for patients unable to tolerate sertraline or judged unresponsive. The maximum duration of the behavioral intervention was 6 months. Group therapy could extend an additional 12 weeks and adjunctive pharmacotherapy for up to 12

months, at which time the patient was reevaluated by the ENRICHD psychiatrist. If antidepressants were deemed still to be needed, the patient was referred to his or her physician.

Therapy was initiated as soon as possible after randomization. If indicated, therapists were permitted to schedule sessions more than once weekly. To overcome logistic barriers to prompt intervention, home visits were common soon after discharge. If possible, group therapy began as soon as was practical after the patient completed at least 3 sessions of individual CBT. When in group therapy, some patients discontinued individual CBT. Individual CBT continued until patients either met ENRICHD criteria for optimal treatment outcome or 6 months had elapsed. The criteria for optimal treatment outcome established a high standard to guide therapists and patients who sought to end the intervention before 6 months. Criteria were (1) completing at least 6 individual or group therapy sessions; (2) demonstrating adequate self-therapy skills (eg, cognitive behavioral skills to maintain treatment gains and prevent relapse); (3) reporting at least 1 sustainable, supportive relationship outside therapy (for patients qualifying for LPSS); and (4) 2 consecutive BDI scores of 7 or less (for patients qualifying for depression) or 2 consecutive scores of 4 or more on at least 2 items of the short-form PSSS (for patients qualifying for LPSS).

Follow-up Evaluations

Follow-up visits occurred 6 months after randomization and annually thereafter and included all baseline assessments, except for the DISH, which was administered by interview at the 6-month visit and by phone at 12 months to assess relapse. A resting ECG was recorded to detect otherwise unrecognized acute MI.

End Points

Potential end points were identified through patients, hospital records, or the patients' physicians. Records of every identified hospitalization were obtained for review. Classification of the primary end point (recurrent MI or death from any cause) was made using standardized criteria by a member of the treatment-masked End Points Committee, which adjudicated ambiguous cases. An ECG core laboratory classified ECGs by Minnesota code serial change rules.[36] Criteria for recurrent MI were as defined for enrollment except that periprocedural MI was diagnosed if biomarkers of cardiac injury were 3-fold above baseline after PCI or if new Q waves developed in 2 or more leads after CABG. Secondary end points, including revascularization procedures and cardiovascular hospitalizations, were also collected.

Statistical Analysis

The target sample size of 3000 patients was calculated to yield 88% power to detect a difference in proportion of events between the treatment groups of 30% in complying patients (or an observed treatment effect of 24% in all patients). Assumptions incorporated in calculations were a 2-sided $\alpha = .05$ test, a 3-year cumulative event rate of 23% in usual care, that 67% of first events would be deaths, and that 25% of patients would be noncompliant without treatment effect. Recruitment of fewer patients (2481 vs 3000 patients) reduced power to detect a 30% difference between treatment groups from 88% to 78%. However, the DSMB recommended that recruitment not be extended beyond its originally planned time frame, based on conditional power calculations that projected less than 5% power for showing potential benefit even if the original enrollment target of 3000 patients was met.

The Cox regression model[37] was used to analyze time elapsed to the primary and secondary events, and log-rank statistics were used to compare survival curves for the intervention and usual care arms. Survival curves were generated by the Kaplan-Meier method. Prespecified subgroup analyses included subpopulations defined by sex, race/ethnicity, and psychosocial and biomedical risk. All treatment group comparisons were based on the intention-to-treat principle that includes all randomized patients as randomized. Supplemental analyses were performed to assess whether treatment with an antidepressant, independent of treatment group assignment, was related to the risk of a primary event or all-cause mortality. Antidepressant use was treated as a time-dependent covariate in a Cox regression model and excluded those eligible on the basis of LPSS alone. Because the exact start date of drug use was not known, change in the covariate from 0 to 1 was estimated to have occurred at the midpoint of the interval between the visit at which drug use was reported and the previous visit or on the date of the visit if an antidepressant was prescribed at the visit. Adjustment was made for potential baseline confounders, including age, baseline BDI score, Killip class, ejection fraction, creatinine level, previous MI, and prior diagnosis of congestive heart failure, stroke or transient ischemic attack, pulmonary disease, or diabetes.

All statistical analyses were performed using SAS statistical software version 8 (SAS Institute Inc, Cary, NC, 1999).

RESULTS

Baseline Characteristics and Follow-up

The study population has been previously described in detail.[26] TABLE 1 shows that treatment groups were balanced on key baseline characteristics and prognostic factors with the exception of angiotensin-converting enzyme (ACE) inhibitor use. During the 3-year recruitment from October 1996 through October 1999, 2481 patients were randomized; 39% were depressed, 26% had LPSS, and 34% met both criteria. Twelve hundred thirty-eight patients were randomized to the intervention arm, 1145 of whom received at least 1 therapeutic session. Baseline data collection was completed in October 1999 and treatment ended in April 2000. Vital status was obtained for 2308 randomized participants (93%) in the 6 months before the April 2001 trial termination, including 340 (14%) known to be deceased. End point information from the last available contact was used for 173 patients

lost to follow-up (FIGURE 1). All patients were followed up for at least 18 months (average, 29 months).

Treatment Effect on Clinical Events

Four-year survival curves showed no significant difference between treatments in recurrence of MI or death (log-rank $P=.94$; FIGURE 2). This null effect was consistent for all secondary end points, including recurrent nonfatal MI, death from any cause, and cardiac death (TABLE 2).

Hazard ratios (HRs) for the primary end point and associated 95% confidence intervals (CIs) summarize the relative survival benefits in preplanned subgroups (FIGURE 3). None of these were significant. There was some evidence of a treatment group-by-sex interaction ($P=.03$). Post hoc adjustment for age and Charlson comorbidity index[38] (factors known to predict the primary end point) attenuated the interaction considerably ($P=.20$). Other interaction tests between treatment assignment and psychosocial risk groups (patients who met criteria for depression only, LPSS only, or both) or ethnic group (minority, nonminority) were nonsignificant ($P=.77$ and $P=.20$, respectively).

Table 1. Key Demographic and Prognostic Characteristics on Admission by Treatment*

Characteristics	Usual Care (n = 1243)	Intervention (n = 1238)
Demographics		
Age, mean (SD), y	61 (12.5)	61 (12.6)
Sex, female	552 (44)	532 (43)
Race, nonwhite	425 (34)	409 (33)
Marital status, married	625 (51)	656 (53)
Education, high school or higher	558 (46)	573 (48)
Medical characteristics		
Diabetes	414 (33)	400 (32)
Hypertension	752 (61)	741 (60)
Smoking history	810 (65)	789 (64)
Hypercholesterolemia	698 (56)	719 (58)
Cerebrovascular disease	123 (10)	111 (9)
Renal insufficiency	117 (9)	124 (10)
Previous MI	341 (27)	318 (26)
Previous CABG surgery	166 (13)	154 (12)
Previous PTCA	199 (16)	177 (14)
CHF history	170 (14)	164 (13)
Comorbidity score, mean (SD)†	2.24 (2.11)	2.16 (2.03)
Peripheral vascular disease	150 (12)	152 (12)
Systolic blood pressure, mean (SD), mm Hg	124 (19)	123 (19)
Body mass index, mean (SD)‡	29 (6.6)	29 (6.7)
Characteristics of the index MI		
Infarct type		
Q wave	378 (32)	357 (30)
Non–Q wave	650 (54)	674 (57)
Indeterminate or unknown	165 (14)	152 (13)
Infarct location		
Anterior	385 (31)	355 (29)
Inferior	484 (39)	494 (40)
Ejection fraction category		
Severe dysfunction	249 (25)	263 (26)
Moderate dysfunction	252 (26)	238 (24)
Mild dysfunction or normal	483 (49)	508 (50)
Killip class III-IV	89 (7)	86 (7)
Treatment of the index MI		
Thrombolytic therapy	478 (39)	440 (36)
CABG surgery	218 (17)	212 (17)
Cardiac catheterization	1025 (83)	997 (81)
PTCA <24 h	293 (24)	288 (23)
Current prescribed medications		
ACE inhibitors	588 (47)	524 (42)
Anticoagulants	232 (19)	248 (20)
Aspirin	1046 (84)	1027 (83)
β-Blockers	884 (71)	901 (73)
Lipid-lowering drugs	530 (43)	492 (40)
Psychosocial risk factors		
Depressed only	480 (39)	498 (40)
Low perceived social support only	334 (27)	313 (25)
Depressed and low perceived social support	429 (34)	427 (35)

Abbreviations: ACE, angiotensin-converting enzyme; CABG, coronary artery bypass graft; CHF, congestive heart failure; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.
*Data are presented as No. (%) unless otherwise indicated. Denominator may vary due to missing values.
†Based on Charlson comorbidity index (range in sample, 0-11).
‡Calculated as weight in kilograms divided by the square of height in meters.

Treatment Effect on Psychosocial Measures

The intervention produced significant but modest differences in depression and social support (TABLE 3). At 6 months after randomization, the mean BDI score for patients enrolled on the basis of depression in the intervention group was 9.1 vs 12.2 in the usual care group ($P<.001$), a mean decrease in BDI score of 49% vs 33%, respectively. A comparable difference was observed for the structured interview assessment of depression severity, the HRSD (7.6 in the intervention group vs 9.4 in the usual care group; $P<.001$). For patients enrolled on the basis of LPSS, the mean ESSI score at 6 months and the mean increase in ESSI score from baseline were significantly higher in the intervention than the usual care group (24.4 vs 22.6 and 27% vs 18%, respectively). Between-group differences in BDI and ESSI scores diminished over time, primarily because of improvement in the usual care group. No benefit of the intervention remained by 30 months of follow-up for the BDI and by 42 months for the ESSI ($P=.61$ and $P=.10$, respectively).

Protocol Adherence

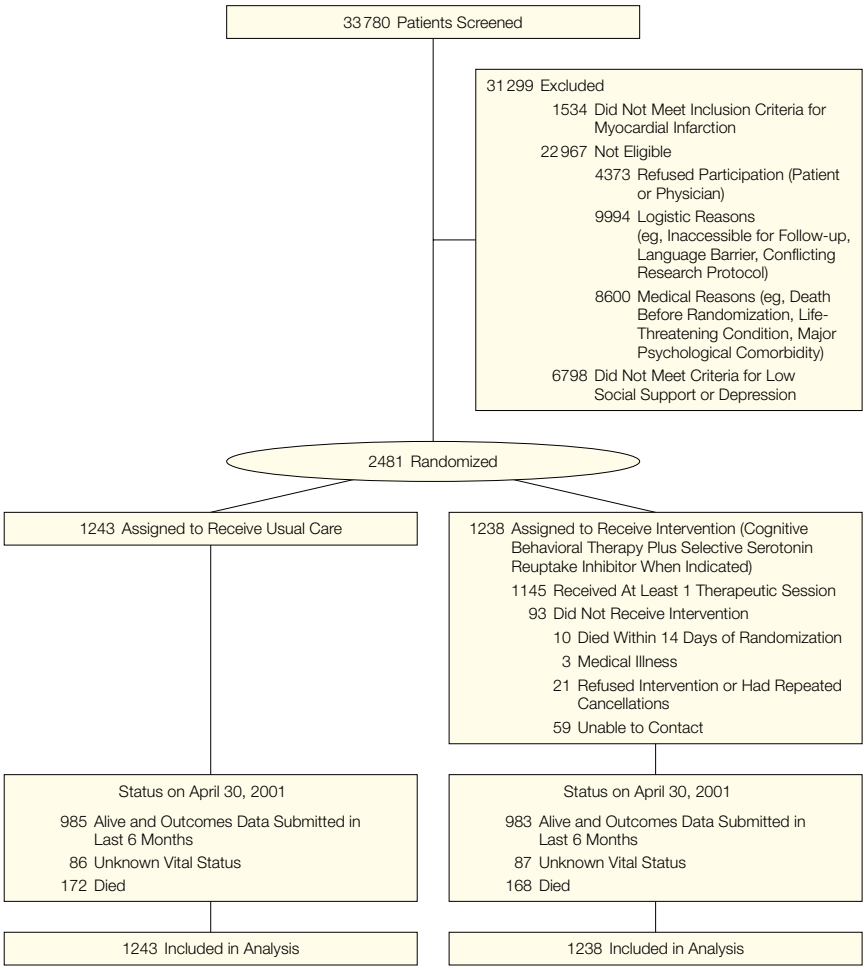
Of the 1238 patients randomized to the intervention arm, 1145 (92%) received the intervention as assigned. TABLE 4 presents key indicators of treatment adherence by psychosocial risk group. The median time from the qualifying acute MI to enrollment was 6 days (interquartile range [IQR], 3-11 days; mean, 8 days), and the median time to the first treatment session was 17 days (IQR, 10-27 days; mean, 20 days). Patients attended a median of 11 sessions (IQR, 6-19 sessions). The timing or amount of individual therapy received by depressed or LPSS patients did not differ.

Antidepressant Drug Use

Among patients who were depressed at enrollment, the cumulative rates of any antidepressant use in the usual care and intervention arms, respectively, were 4.8% and 9.1% at baseline, 13.4% and 20.5% at the 6-month visit, and 20.6% and 28% by the end of follow-up. The most often prescribed antidepressant class was SSRIs, with use rates in the usual care and intervention arms, respectively, of 3.8% and 6.9% at baseline, 9.4% and 15.3% at the 6-month visit, and 14.6% and 21.0% by the end of follow-up. Median duration of antidepressant treatment was approximately 12 months for both groups.

Antidepressant drug use was associated with a lower risk of the primary outcome with a crude HR for death or nonfatal MI of 0.67 (95% CI, 0.49-0.92) and an adjusted HR of 0.63 (95% CI, 0.46-0.87). Antidepressant use was also associated with a decreased risk of dying, with a crude HR of 0.71 (95% CI, 0.48-1.06) and an adjusted HR of 0.63 (95% CI, 0.42-0.94). Similarly, the risk of death or nonfatal MI was significantly lower in patients taking SSRIs (adjusted HR, 0.57; 95% CI, 0.38-0.85), as was the risk of death (adjusted HR, 0.58; 95% CI, 0.36-0.94). In light of these findings, there was concern that the effect of CBT therapy on clinical outcomes may have been masked by the beneficial effects of pharmacotherapy among a relatively large number of patients in the usual care group taking antidepressants. However, analysis of the intervention effect on clinical outcomes among depressed patients who did not receive antidepressants did not suggest a treatment benefit, with HRs of 0.94 (95% CI, 0.77-1.16) and 0.97 (95% CI, 0.76-1.26) for the primary outcome and all-cause mortality, respectively. At the 6-month visit, the mean change from baseline in BDI score among reported users and nonusers of antidepressants was –6.6 and –7.4, respectively.

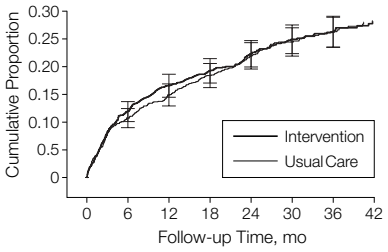
Figure 1. Profile of the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Trial



COMMENT

ENRICHD was the first clinical trial to test whether intervening on depression and LPSS soon after acute MI reduces mortality and reinfarction. The intervention decreased depression and improved social support more than was observed in usual care but did not affect

Figure 2. Estimated Probability of Death or Nonfatal Myocardial Infarction



No. at Risk

Usual Care	1243	1099	1031	898	670	460	265	130
Intervention	1238	1083	1010	886	669	439	280	122

Error bars represent SEs.

the primary end point of death and nonfatal infarction.

Analyses of the time-dependent effect of pharmacologic therapy showed that antidepressant use was associated with a lower risk of reinfarction and/or mortality. It is interesting that patients who reported taking an antidepressant before the 6-month assessment showed less improvement on the BDI from baseline to 6 months than patients who reported not taking an antidepressant (–7.4 vs –6.6). In interpreting this result, it is important to keep in mind that patients in ENRICHD were not assigned randomly to receive antidepressants, and this analysis, although interesting, is post hoc. Therefore, the disassociation between the effects of pharmacotherapy on change in BDI and on the primary end point of mortality and reinfarction may be either due to chance or reflect a beneficial effect of pharmacotherapy on cardiac end points not mediated by change in depression. The finding of a reduced risk for recurrent infarction or death is consistent with earlier observational studies that show that antidepressants, in particular SSRIs, are associated with a reduction in risk of MI,[39] perhaps due to the inhibitory effects of SSRIs on platelets[40] or combinations of other effects. In addition, there was a trend toward improved outcomes in the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) study for depressed post-MI patients who received the SSRI sertraline compared with those patients who received placebo.[11] Although these data are intriguing, the potential benefits of SSRIs on cardiac end points should be ascertained in a study with random assignment to pharmacotherapy.

The apparent treatment group-by-sex interaction on the risk of death or recurrent nonfatal MI (unadjusted $P = .03$; adjusted $P = .20$) may be due to true differences in treatment response between men and women or to chance, particularly since we did not correct for multiple comparisons. Whether it is appropriate to adjust for imbalances in clinical trials is debatable. The likelihood of imbalance increases when subgroups are examined, arguing for adjustment. The observed interaction may be due to disparities between the treatment groups on background factors associated with sex, such as age or comorbidities. On the other hand, adverse findings for women reported for the M-HART trial[19] support the view that there may indeed be something important about the observed sex-by-treatment group interaction. Future research should seek to gain a better understanding of possible differential effects of psychosocial treatments by sex.

We found statistically significant treatment group differences in depression and social support scores after the 6-month intervention period, but the magnitude of the effect may not have been sufficient to influence medical morbidity or mortality. The decline in HRSD scores for depressed patients in the intervention group was comparable to the reduction in depression observed in other clinical trials of depression in post-MI patients.[11,41-44] However, patients in the usual care group also improved substantially, resulting in a difference of only 1.7 points (2.7 on the BDI) between groups. Similar results were seen in the SADHART trial following antidepressant therapy.[11]

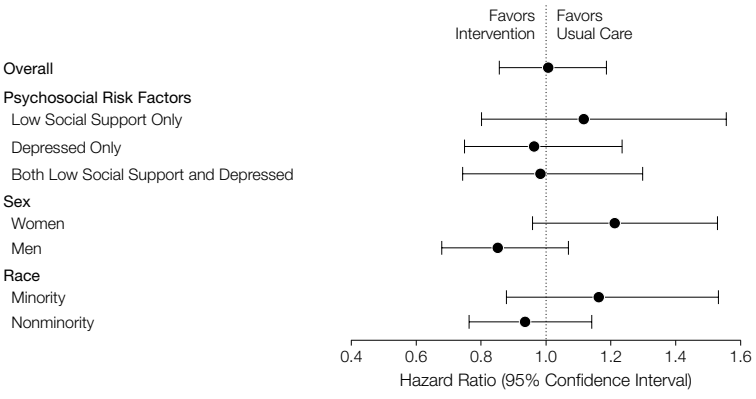
Since few interventions have been developed and tested for patients with LPSS, the social support intervention used in ENRICHD was created specifically for this study, and no data are available with which to compare the efficacy of the ENRICHD social support intervention. It is notable that, like BDI scores, ESSI social support scores improved in both the intervention and usual care groups, resulting in a treatment benefit of only 2 points. Previously, and inconsistent with our results, social support was found to be high during and immediately after hospitalization and remain stable or decline during the next year.[2] Additional research is needed to determine the amount of improvement in depres-

Table 2. Intervention Effect on Primary and Secondary Clinical Events for All Participants

Event	No. (%) of Participants		Hazard Ratio (95% CI)
	Usual Care	Intervention	
Death or nonfatal MI	300 (24.1)	299 (24.2)	1.01 (0.86-1.18)
All-cause mortality	172 (13.8)	168 (13.6)	0.98 (0.79-1.21)
Cardiovascular mortality	115 (9.3)	96 (7.8)	0.83 (0.64-1.10)
Recurrent nonfatal MI	170 (13.7)	168 (13.6)	0.90 (0.71-1.14)
Revascularization procedures	230 (18.5)	216 (17.4)	0.94 (0.78-1.14)
Cardiovascular hospitalization	467 (37.6)	442 (35.7)	0.95 (0.83-1.08)

Abbreviations: CI, confidence interval; MI, myocardial infarction.

Figure 3. Effect of Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Intervention on Risk of Death or Nonfatal Myocardial Infarction



Error bars indicate 95% confidence intervals.

sion and social support needed to affect survival and to determine the relationship between duration of depression or LPSS and medical outcomes.

Information about stress management and the patients' risk status obtained from the American Heart Association's Active Partnership health booklet,[31] spontaneous remission, or obtaining treatment outside the study may have contributed to improvement in usual care patients. Mild to moderate depression, typical of ENRICHD patients (average HRSD score was 17.8 at baseline), is more likely to remit spontaneously than more severe depression. Moreover, cumulative use of antidepressants increased steadily in both treatment arms from 4.8% at baseline to 20.6% at the end of the trial in the usual care group and from 9.1% to

Table 3. Psychological Measures at Baseline Through 6 Months by Treatment*

	No. of Patients	Scores, Mean (SD)			Mean (95% CI) Treatment Difference
		Baseline	6 Months	Change	
BDI					
Depressed participants only					
Usual care	635	18.0 (7.6)	12.2 (9.1)	−5.8 (8.9)	−2.7 (−3.7 to −1.7)
Intervention	697	17.7 (8.1)	9.1 (8.6)	−8.6 (9.2)	
All					
Usual care	869	15.7 (8.1)	11.0 (8.7)	−4.7 (8.6)	−2.8 (−3.7 to −2.0)
Intervention	916	15.7 (8.5)	8.2 (8.3)	−7.6 (8.8)	
HRSD					
Depressed participants only					
Usual care	646	17.8 (6.4)	9.4 (6.9)	−8.4 (7.7)	−1.7 (−2.5 to −0.9)
Intervention	697	17.7 (6.4)	7.6 (6.7)	−10.1 (7.8)	
All					
Usual care	876	15.5 (7.4)	8.4 (6.8)	−7.1 (7.8)	−1.5 (−2.3 to −0.8)
Intervention	926	15.5 (7.4)	6.9 (6.5)	−8.6 (7.9)	
ESSI					
Participants with LPSS					
Usual care	535	19.2 (4.2)	22.6 (6.7)	3.4 (6.0)	1.8 (1.0 to 2.5)
Intervention	556	19.2 (4.4)	24.4 (6.2)	5.1 (5.9)	
All					
Usual care	886	23.3 (6.3)	25.0 (6.7)	1.7 (6.0)	1.5 (1.0 to 2.0)
Intervention	929	23.1 (6.3)	26.3 (6.2)	3.2 (5.8)	
PSSS					
Participants with LPSS					
Usual care	513	54.4 (14.2)	58.9 (15.7)	4.5 (14.9)	4.5 (2.7 to 6.3)
Intervention	533	53.4 (14.1)	62.4 (15.2)	9.0 (14.9)	
All					
Usual care	859	60.5 (14.9)	62.8 (15.2)	2.3 (13.9)	3.9 (2.6 to 5.2)
Intervention	896	60.1 (15.2)	66.4 (14.3)	6.3 (13.9)	

Abbreviations: BDI, Beck Depression Inventory; CI, confidence interval; ESSI, Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Social Support Instrument; HRSD, Hamilton Rating Scale for Depression; LPSS, low perceived social support; and PSSS, Perceived Social Support Scale.
*All *P* values are <.001 (for comparison between 6 months vs baseline and for group differences in change scores).

Table 4. Adherence to the Protocol by Psychosocial Risk Group

Characteristics	Depressed (n = 498)	Low Perceived Social Support (n = 313)	Depressed and Low Perceived Social Support (n = 427)	Overall (n = 1238)
Days from MI to first therapy session, median (IQR)	18 (11-28)	17 (11-25)	15 (8-25)	17 (10-27)
No. of sessions, median (IQR)	11 (5-17)	11 (6-18)	13 (6-20)	11 (6-19)
Received group therapy, No. (%)	119 (25)	100 (33)	151 (36)	370 (31)
Met optimal achievement of therapy goals, No. (%)				
Received ≥6 sessions	370 (77)	237 (77)	324 (77)	931 (77)
Met goals for decrease in depression or increase in social support*	271 (56)	229 (74)	182 (43)	682 (56)
Ability to perform Beck self-therapy†	228 (47)	128 (42)	170 (41)	526 (44)
Availability of ≥1 supportive relationships outside therapy	NA	250 (81)	324 (77)	959 (79)

Abbreviations: IQR, interquartile range; MI, myocardial infarction; NA, not applicable.
*Depression criterion: scored ≤7 on the Beck Depression Inventory for 2 consecutive sessions; social support criterion: scored ≥4 on at least 2 items of the Perceived Social Support Scale for 2 consecutive sessions. Denominator may vary due to missing values.
†Ability and willingness to apply problem-solving skills to new problems, as judged by therapist.

28% in the intervention group. It seems likely that referring physicians who were informed initially when patients were diagnosed as having depression increased referrals or prescribing of antidepressants throughout the trial.

Success in recruiting a diverse population, a major objective of the trial, also led to enrolling many patients with limited social and economic resources and limited ability to participate in the intervention. Successful delivery of CBT, whether involving clinic or home visits, requires time, effort, and family support, such as arranging transportation, child care, and completion of homework assignments. Even though logistic support was provided, difficulties may have remained in families from lower socioeconomic strata. Finally, in contrast to clinical practice or many clinical trials, participants in this study did not initially anticipate or seek treatment for either depression or LPSS but were recruited based on eligibility criteria specific to those conditions. Thus, they may have been less motivated to engage in therapy than patients who seek treatment for these conditions.

The duration and timing of intervention may also have affected the outcome. We attempted to intervene as soon as possible after acute MI. Psychosocial eligibility criteria had to be met within 28 days of the index infarction and treatment completed within the first 6 months, the period of greatest risk for death and (re)infarction. Yet, in most individuals, recurrent and chronic depression and social isolation and their influence on cardiac risk may be mediated by mechanisms that require more prolonged treatment. An analogy is found with some medical therapies, such as ACE inhibitors and statins, where some of the effects on mortality and recurrent infarction only occur long term. The benefits of ACE inhibitors on left ventricular remodeling are not substantial early after acute MI, but, over time, the effects on mortality and recurrent infarction are robust.[45] Similarly, statins manifest benefits long term after acute infarction but have not been proven to reduce mortality and/or recurrent infarction early after treatment for acute coronary syndromes.[46-51] Thus, early initiation of treatment for depression and provision of social support after the index infarction, as in this study, may not reduce medical morbidity and mortality substantially unless treatment is provided longer than the first 6 months after the acute event or outside the window of greatest medical risk.

Previous studies have found depression and LPSS to be independent risk factors for cardiac events. However, treatments that mitigate depression and LPSS might not reduce cardiac morbidity and mortality unless they also influence the underlying pathophysiologic or behavioral mechanisms. Mechanisms proposed to explain the influence of depression on CHD mortality include altered autonomic tone[52] and altered platelet function,[53,54] whereas social isolation has been found to be associated with altered neuroendocrine function.[55] It is possible that pharmacologic agents prescribed for treatment of CHD or depression may have acted on these mechanisms, resulting in a failure to observe psychosocial treatment differences in ENRICHD. Further studies should investigate the potential pathophysiologic and behavioral pathways linking depression and social isolation to poor cardiac outcomes and their interaction with pharmacologic agents used to treat these patients.

Post[56] has proposed that, even when it is effective, treatment may not remedy all neuropathologic conditions that result from long-standing depression. If residual risk remains, treatment may improve quality of life without affecting cardiac events. Similarly, patients who lack social support may have had this condition for years or even decades, involving behavioral or physiologic adaptations that are difficult to alter. Primary prevention strategies may be more effective than secondary prevention strategies

Patients in this trial generally received early and aggressive cardiologic care. During the past several years, the evolution of this aggressive approach has lowered reinfarction rates, which diminishes the ability to discern potential beneficial effects of additional therapies, whether behavioral or medical. Thrombolytics were administered to 37% of patients and 39% underwent revascularization (PCI or CABG) within 12 weeks after acute MI. A high proportion of patients received aspirin (84%), β-blockers (72%), and ACE inhibitors (45%) during the later phases of recovery. The fact that our patients received aggressive state-of-the-art care confirms the applicability of our data to contemporary MI patients. Intensive clinical care was applied equally to both groups, and the predicted event rates in the study were as projected,[1,21] suggesting that the null results of the trial are unlikely to be attributable to group differences in concomitant medical therapy.

Depression in cardiac patients is associated with significant psychological, social, and physical disability,[57,58] and its effective treatment enhances quality of life and improves overall functioning.[59] Low perceived social support is associated with psychological distress and lowered physical functioning in patients with heart disease.[60-62] Although the ENRICHD intervention did not impart survival benefit for primary and secondary medical end points up to 30 months, it succeeded in decreasing depression and increasing social support, especially during the first 6 months. Accordingly, patients who exhibit depression or LPSS following acute MI should be followed up and, if symptoms do not remit, considered for treatment.

ENRICHD achieved significant improvements in depression and LPSS yet did not demonstrate a parallel benefit on mortality and recurrent infarction. The risk associated with these conditions remains significant[63,64] and is proportional to their severity.[65-67] Additional research is needed to determine the optimal timing and duration of interventions for these psychosocial risk factors; to identify the biological and behavioral pathways that link psychosocial conditions, such as depression and LPSS, to cardiovascular health; and to develop preventive strategies for reduc-

ing the burden of depression and LPSS on morbidity and mortality.

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