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The impact of cognitive behavioral group training on event-free survival in patients with myocardial infarction: The ENRICHD experience

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Abstract

Objective—Although the ENRICHD treatment was designed to include individual therapy and cognitive behavioral group training for patients with depression and/or low perceived social support, only 31% of treated participants received group training. Secondary analyses classified intervention participants into two subgroups: 1) individual therapy only or 2) group training (i.e., coping skills training) plus individual therapy; to determine whether medical outcomes differed in participants who received the combination of group training and individual therapy compared to participants who received individual therapy only or usual care.

Methods—Secondary analyses of 1,243 usual care, 781 individual therapy only, and 356 group plus individual therapy myocardial infarction patients. Depression was diagnosed using modified DSM-IV criteria; low perceived social support was determined by the ENRICHD Social Support Instrument. Psychosocial treatment followed myocardial infarction and, for participants with severe or unremitting depression, was supplemented with a selective serotonin reuptake inhibitor. Cox proportional hazards regression was used to estimate intervention effects on time to first occurrence

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of the composite end point of death plus nonfatal myocardial infarction. To control for confounding of group participation with survival (because individual sessions preceded group), risk set sampling matched minimal survival time of those receiving or not receiving group training.

Results—Analyses correcting for differential survival among comparison groups showed group plus individual therapy was associated with a 33% reduction (hazard ratio = .67; 95% confidence interval: .49–.92, $p = .01$) in medical outcome compared to usual care. No significant effect on event-free survival was associated with individual therapy alone. The group training benefit was reduced to 23% (hazard ratio = .77; 95% confidence interval: .56–1.07, $p = .11$) in the multivariate-adjusted model.

Conclusions—Findings suggest that adding group training to individual therapy may be associated with reduction in the composite end point. A randomized controlled trial is warranted to definitively resolve this issue.

Keywords

group self-management training; myocardial infarction; cognitive behavioral therapy; depression; social support; ENRICHD

INTRODUCTION

The aim of the ENRICHD randomized controlled trial was to assess whether a psychosocial intervention, designed to decrease depression and increase social support, would improve the trial's primary medical end point of all cause mortality and/or recurrent nonfatal myocardial infarction (MI) in acute post-MI patients. The main findings in ENRICHD were that the intervention modestly decreased depression and increased social support compared to the usual care control condition, but did not significantly influence the combined medical end point¹. Although other post-MI psychosocial intervention trials have likewise not shown a positive effect upon medical end points^{2,3}, meta-analyses have concluded that psychosocial interventions are associated with significant reductions in mortality and cardiac morbidity^{4,5} though mortality benefits may differ by gender⁶.

Of the three large (>1,000 patients randomized) trials examined in these meta-analyses, the major trial reporting positive results was the Recurrent Coronary Prevention Project, which employed biweekly group-based cognitive behavior therapy (CBT) over one year's time, and decreased hostility and depressed affect⁷ as well as the combined medical end point of cardiac death plus nonfatal MI⁸ in a sample of patients recruited from the local community whose index MI had occurred more than six months ago and who were not selected for any psychosocial factor. Conversely, in the past decade, two other large studies^{2,3} did not show a positive effect upon medical end points. In M-HART² patients recruited while in the hospital for the index MI were randomized to usual care or to an arm in which they were assessed for psychological distress on a monthly basis over one year. If their distress level was above a set criterion, patients were visited by an experienced nurse who had been given no special training and who worked with them in a general way to reduce the distress. There, however, was no impact of the M-HART intervention on depression or anxiety. The other large trial³ recruited patients discharged from the hospital within 28 days of the index MI and randomized them to either usual care or a rehabilitation program consisting of seven two-hour group sessions led by clinical psychologists and health visitors. In addition to information about the heart, circulation, and recovery from a heart attack, "practical exercises with patient participation" and home practice aimed at enhancing relaxation and coping skills to "improve responses to stressful situations" were central to the intervention. Despite this apparently strong design, there were no differences between rehabilitation patients and control patients on anxiety or depression at six months follow-up. Because these trials differed in format, content, number

of patient contacts, and background of those delivering the interventions, these findings do not provide a clear indication of which features of psychosocial interventions are required to effect improvements in medical or psychological outcomes.

In the ENRICHD randomized controlled trial, the protocol specified that all patients randomized to the psychosocial intervention would begin treatment with individual therapy and transition to group self-management training. However, largely due to logistical issues (e.g., use of multiple outlying hospitals by many of the clinical centers and/or patient flow too low to provide adequate numbers to form groups), only 31% of treated patients received the combination of individual therapy plus group training. This provided the opportunity to conduct secondary post hoc analyses to explore whether outcomes differed in those participants exposed to group training relative to those who received individual therapy alone or to those randomized to usual care.

METHODS

Participants

A total of 2,481 participants were recruited from October 1996 to October 1999. Inclusion and exclusion criteria for the study have been previously described⁹. Briefly, participants were screened within 28 days of acute MI. Psychosocial eligibility required that patients meet the ENRICHD modified DSM-IV diagnostic criteria for major or minor depression or dysthymia determined by the Depression Interview and Structured Hamilton¹⁰, and/or report the experience of low social support based on the ENRICHD Social Support Instrument (ESSI)⁹. Medical eligibility required that patients show either symptoms consistent with acute MI, or characteristic evolutionary electrocardiographic (ECG) ST-T changes or new Q waves¹¹. Acceptable elevations of biomarkers of myocardial injury were twice the institution-specific upper limit, or for CKMB, any elevation with a rising and falling pattern deemed indicative of acute MI by the attending physician. Patients who underwent intervention for ST elevation upon presentation were eligible whether or not biomarker criteria were met. Exclusion criteria were as follows: a) acute MI following invasive cardiac procedures such as coronary artery bypass graft; b) a non-cardiac condition likely to be fatal within one year; c) a medical condition limiting ability to participate in the trial; d) participation in a concurrent behavioral research protocol that conflicted with the aims of ENRICHD and/or current participation in psychotherapy; e) major psychiatric morbidity other than major depression; f) imminent suicide risk; g) unwillingness to provide informed consent; h) inability to complete screening visits; i) inaccessibility for intervention and/or planned follow-up; or j) antidepressant medication usage for less than 14 days.

An additional 101 participants were excluded from the analyses reported here for the following reasons: a) 93 participants randomized to treatment did not participate in any aspect of the intervention due to early death (n = 10), medical illness (n = 3), refusal to participate and/or cancellations (n = 21), and inability to contact (n = 59); b) 4 participants were excluded because they had an event prior to the first treatment session; and c) 4 participants were excluded because they entered group training after the protocol permitted time limit. As such, the sample for this paper was comprised of 1,243 usual care participants, 781 individual therapy only participants (i.e., referred to as individual therapy participants), and 356 group plus individual therapy participants (i.e., referred to as group training participants).

Procedures

The study protocol and informed consent procedures were endorsed and approved by the Institutional Review Boards at each of 73 hospitals affiliated with 8 university clinical centers. The study was overseen by an independent Data and Safety Monitoring Board appointed by

the National Heart, Lung, and Blood Institute. A detailed description of methods has been reported previously ¹².

Treatment

All ENRICHHD participants received minimal risk factor education in the form of the American Heart Association *An Active Partnership for the Health of Your Heart* patient workbook ¹³. Usual care participants received no other trial-related intervention. A detailed description of the psychosocial intervention, including therapist training, supervision, and quality assurance procedures, has been previously reported ¹⁴. Briefly, up to 6 months of therapy was initiated immediately after randomization. Patients were eligible to begin group training within 6 months of randomization and after 3 sessions of individual therapy, if there were no psychosocial contraindications (e.g., schizotypal personality disorder). In a series of workshops, therapists (clinical and counseling psychologists, psychiatrists, clinical social workers, and psychiatric nurses) received extensive training in the implementation of the individual therapy and group training protocols from the Beck Institute and ENRICHHD investigators. The Beck Institute and ENRICHHD site clinical supervisors regularly reviewed session tapes to assess therapist proficiency and treatment fidelity and to provide supervision and feedback. Two hours of individual and/or group supervision was provided to therapists on a weekly basis. In addition, weekly supervisor conference calls, chaired by the Beck Institute, provided additional intervention protocol oversight.

The format of the individual sessions was standardized and included a mood check, homework review, establishment and discussion of the agenda, homework assignment, session summary, and participant feedback following the procedures of A. Beck ¹⁵ and J. Beck ¹⁶. Treatment session emphasis was dictated by participants' psychosocial eligibility criteria. Specifically, individual treatment for depression emphasized alteration of dysfunctional automatic thoughts, problem solving, behavioral activation, and relapse prevention while individual treatment for low perceived social support stressed social outreach, social network development, and behavioral and social skills training. Participants who met criteria for both depression and low perceived social support received individual treatment designed to target both depression and low perceived social support. Depressed intervention participants, with a Hamilton Rating Scale for Depression score of 24 or higher, or who failed to show $\geq 50\%$ reduction in Beck Depression Inventory (BDI) scores after 5 weeks of treatment, were also evaluated by the study psychiatrists for adjuvant pharmacotherapy with a selective serotonin reuptake inhibitor, following a standardized protocol. As such, antidepressant medication usage was not randomly assigned.

The inclusion of the group training component follows a tradition of using group-based interventions to treat medical patients ^{17–19}, in general, and heart disease patients ^{8,20–22}, in particular to favorably influence proximal and distal medical outcomes and to reduce distress. While group cognitive behavioral self-management training was designed to reinforce and extend the progress made in individual therapy, it is important to note that it differed in both format and content from the therapy provided in the individual sessions. Rather than focusing on depression and low perceived social support, the content was expanded to address distress more generally. Specifically, the emphasis was on coping skills training and acquisition essential to prepare patients to manage stressors involved in living with heart disease as well as with stressors encountered in everyday life. The group provided a social context in which to learn, rehearse, and consolidate these new skills. Incorporating new skills into the participants' behavioral repertoire was intended to enhance self-management and to prevent relapse. A major feature of the group training as opposed to individual therapy was that it focused on normalizing the experience and concerns associated with the MI within a social setting and emphasized enhancing psychosocial strengths, i.e., coping skills, rather than

remediating psychosocial deficits, i.e., depression and low perceived social support. An added benefit of group training may have been to diminish any perceived stigma associated with study eligibility, i.e., besides suffering the effects of an MI, participants learned that they had a psychosocial problem as well.

The group component consisted of 12 two-hour sessions and was largely influenced by the work of Antoni²³, Bandura²⁴, Marlatt and Gordon²⁵, Powell and Thoresen²⁶, and Williams and Williams²⁷. Skill guidelines were articulated in each session and content was presented according to a standardized protocol using structured exercises. The following topics were addressed in order across the 12 sessions: a) the influence of thoughts, behaviors, and emotions on the cardiovascular system; b) emotion identification and management; c) negative thinking; d) social support; e) communication; f) assertion; g) anger management; h) problem-solving; i) relapse prevention; j) personal values; k) life goals; and l) maintenance of behavior change. Each session adhered to a standard format involving agenda setting, brief relaxation training, homework review, sharing among group members, planned practice with training for each skill, session summary, homework assignment, next session preview, and participant feedback.

Participants were not randomly assigned to receive group training. The study protocol specified that participants begin with individual therapy and transition to group training. The original protocol specified that participants could be involved in group training concurrently or subsequently to individual therapy as well as continue individual therapy after group termination. The protocol also recognized that participation in group training required the following: a) the availability of a group to enter; b) therapist judgment; and c) the absence of psychosocial contraindications (e.g., character pathology that would disrupt group functioning, social phobia). One-half of the participants who received any group training entered a group within 85 days of randomization. Approximately one-third of the participants randomized to the psychosocial intervention participated in at least 1 group session; attendance at a least one group session was sufficient for classification as a group training participant.

Although each center conducted groups, 71% of group participants were run at 3 of the 8 centers. The clinical event rate for those 3 centers was 22.6% compared to 25.6% at the remaining 5 centers and did not differ appreciably. Lack of group participation was primarily determined by each center's capacity to comprise a group rather than participants' unwillingness to be involved in group training. A common reason expressed for the failure to offer groups was the inability to form groups for patients living over wide geographical areas (selection of clinical centers occurred before a decision was made to include group training in the protocol.)

The planned intervention termination occurred when predetermined treatment criteria were met or at 6 months post randomization, whichever occurred first. The treatment criteria were as follows: 1) completion of at least 6 individual therapy and/or group training sessions; 2) demonstration of adequate self-therapy skills (e.g., CBT skills to identify and change maladaptive thoughts and to prevent relapse); 3) report by the patient of at least one sustainable, supportive relationship outside of therapy (for patients enrolled for low perceived social support); 4) two consecutive scores of 7 or less on the BDI (for patients enrolled for depression), consistent with remission of depression; and 5) two consecutive scores of 4 or more on 2 items of the Perceived Social Support Scale-modified (for patients enrolled for low perceived social support), indicating a current source of emotional support. An exception was made for participants receiving group training. If a participant started group treatment within the 6 month treatment window, they were able to complete the group protocol, even if this went beyond the 6 month treatment window (n = 124).

End point ascertainment

The combined end point, all cause mortality and/or nonfatal MI, was the prespecified primary outcome in the ENRICH trial. Study staff that performed end point data collection, verification, and classification, and those who conducted the follow-up psychosocial assessments, were masked to treatment assignment insofar as possible. Follow-up assessments were performed annually beginning at 6 months after randomization. In most cases, this corresponded to the conclusion of treatment for those randomized to the psychosocial intervention. The assessments included a brief medical history, physical examination, resting ECG to detect otherwise unrecognized acute MI, and completion of the BDI and ESS. A treatment-masked End Points Review Committee evaluated records for every hospitalization using standardized criteria. An ECG core laboratory classified ECGs by the Minnesota code using serial change rules²⁸. Additional details concerning the ascertainment of end points are described elsewhere¹.

Statistical methods

Differences in demographic and baseline characteristics, comorbidities, psychosocial factors, and treatment participation among the 3 treatment categories were assessed using the Wilcoxon test for continuous variables and the Chi-square test for categorical variables. For post-hoc multiple comparisons, Tukey's test was employed²⁹. Cox proportional hazards regression was used to estimate intervention effects on the time to the first occurrence of the combined primary end point, all cause mortality and/or recurrent nonfatal MI, and to obtain survival estimates adjusted for baseline confounders.

Because participants were not randomized to group training, it is possible that any differences in outcomes between those receiving group training and either individual therapy alone or usual care could be due to differences in baseline psychosocial and medical characteristics or to the additional survival time required for some patients to make it into a group. While only a truly randomized trial of group training can provide a definitive test, it is possible to use statistical approaches to minimize the influence of potential confounders. Our first approach was to adjust for the individual covariates (baseline characteristics) that were associated with the primary outcome as well as treatment condition (by the definition of confounder) in Cox regression. In addition, a model was also fitted adjusting a single summary score of medical predictors. This univariate risk score was defined as a weighted linear combination of statistically significant medical conditions, where the corresponding weight was derived as the regression coefficient from the proportional hazards model³⁰.

Our second, conservative and potentially more valid approach to control for any confounding of group participation and survival was based on the recognition that group participation could be confounded with longer survival because half of the participants began group training about 85 days after randomization and those patients who died early had no opportunity to participate in group sessions. To address any potential selection bias resulting from this type of staggered entry into group training, a statistical method based on risk set sampling methodology was employed³¹.

The goal of the risk set sampling was to match the minimum survival time of the usual care and individual therapy participants to the actual group starting times of participants who received group training. First, the distribution of the start times for group training was examined and divided into deciles. Using simple random sampling, the same proportions of usual care and individual therapy participants who were alive and had not had an event were selected for each decile corresponding to a group start time. To illustrate, 10% of the group training participants started group within the first 27 days post randomization. Therefore, 10% of the participants in usual care and 10% of the participants in individual therapy were randomly

selected from all the eligible participants at baseline. An additional 10% started group between 28–55 days (and were verified as alive and event-free on the 28th day). Thus, another 10% of the usual care and individual therapy participants who survived without the occurrence of an event on the 28th day were randomly selected. This procedure continued until all group training participants were included and the two comparison cohorts were assembled. In this way, survival up to the time of group entry was controlled and, as a result, the sickest patients and/or early events were eliminated among the usual care and individual therapy participants. This strategy removed 60% of the events in the usual care and in the individual therapy cohorts. By constructing and using these comparable risk sets among the 3 treatment categories for Cox regression, a comparison could be conducted with excellent control for the longer survival time required to participate in group training. The analyses were repeated 100 times with different random selections of the usual care and individual therapy alone conditions to ascertain the robustness and random variability of the estimation of the treatment effect. This risk set sampling approach will control for any factors that influence survival, including not only those that were measured and could be adjusted for in traditional adjusted models, but also unmeasured factors that also affect survival.

Lastly, to provide the most stringent control for all potential confounders that might account for any apparent benefits of group training, we performed an analysis that used both the risk set sampling approach and full adjustment for all potential confounders.

Two-sided hypothesis and a type I error of 5% were used for all statistical inference. A familywise error rate of 5% was also adopted for Tukey's multiple comparisons.

RESULTS

Demographic and psychosocial characteristics of the usual care, individual therapy, and group training participants are presented in Table 1. Baseline differences were apparent for age ($p = .004$), education ($p < .0001$), ethnic minority status ($p = .01$), and psychosocial entry criteria ($p = .007$). Tukey's post hoc pairwise comparisons indicated that group training participants were younger and more likely to have more than a high school education than usual care and individual therapy participants. The representation of ethnic minorities was more common among participants who received group compared to participants who only received individual therapy. Relative to individual therapy participants, group training participants were less likely to have met the psychosocial eligibility criterion of depression alone and more likely to have reported both depression and low perceived social support, suggesting a poorer psychological profile. The prevalence of women and married individuals was comparable across conditions. Baseline antidepressant use was also compared. The prevalence of participants reporting use of antidepressants (whether or not they reported a specific antidepressant medication) was also similar for the usual care (7.5%), individual therapy (8.6%), and group training participants (7%) ($p = .57$).

The frequency of medical comorbidities across conditions is presented in Table 2. For most parameters, no differences were apparent. Similar rates were reported for diabetes, hypertension, past history of smoking, hypercholesterolemia, peripheral vascular disease, history of percutaneous transluminal coronary angioplasty, ejection fraction dysfunction, and bypass surgery. Creatinine levels also did not differ. Significant baseline differences were observed for past history of MI, cerebrovascular disease, and history of congestive heart failure (CHF) ($p < .05$), and trends were apparent for the severity of the MI, and renal and pulmonary disease ($p \leq .10$). Tukey's post hoc analyses showed that group training participants had lower rates of cerebrovascular disease and CHF than individual therapy participants. A lower prevalence of patients with a past history of MI was observed among the group training participants relative to usual care participants.

The BDI scores for participants meeting the entry criterion for depression and the ESSi scores for participants meeting the entry criterion for low perceived social support are reported in Table 3. Although there is no variation in baseline scores across treatment categories, the change from baseline to the last available follow-up shows significant overall differences in depression ($p = .015$) and in social support ($p = .003$). Tukey's multiple tests indicated that the decrease from baseline BDI was greater for participants who received group training relative to usual care. Usual care participants showed smaller improvements in ESSi scores than individual therapy participants.

Data pertaining to treatment participation and achievement of criteria for treatment success are presented in Table 4. The 'met all criteria for success' category provides an index of the percentage of participants who fulfilled all of the relevant specified treatment criteria. Participants who received group training attended more sessions, and were more likely to be successful and to be retained than participants who received only individual therapy.

In our first approach to evaluating the effect of group participation on the primary medical outcome, crude Cox regression analyses fitted to the study population provided a hazard ratio of 0.50 ($p < .0001$) in the unadjusted model and a hazard ratio of 0.59 ($p = .0009$) in the fully adjusted model. To reduce the possible impact of the longer survival time required to enter a group, we next used the risk set sampling method to estimate the effect of group training on event-free survival with greatly reduced bias. Age, cerebrovascular disease and history of CHF were identified as confounders. The results of the minimal survival time-matched analyses show (see Table 5) that group training was associated with a 33% reduction in all cause mortality plus nonfatal MI (average $p = .012$). This effect was reduced to a 23% benefit in two adjusted analyses (average $p = .11$); the hazard ratios were virtually identical for the two different types of adjustment. Thus, the benefit of group training persisted after control for either all potential confounders or for survival time, but was reduced to a trend level when both were controlled. The resulting survival probability estimates are presented in Figure 1.

Because group training participants completed more treatment sessions and reported the highest rates of antidepressant medication usage, we performed two secondary analyses to address the quantitative aspect of sessions and the effect of psychopharmacology treatment. As these two factors are not major exposures and entail subgroup analyses, we investigated these issues with a confirmatory purpose. As indicated in Table 4, we acknowledge that the protocol might confound number of treatment sessions with the added participation in group training compared to individual therapy alone. To examine the potential beneficial effect of a larger number of sessions administered to participants receiving group training and to address the treatment and dose relationship adequately, we conducted an analysis restricted to those individual therapy participants who received greater than 16 sessions ($n=102$), while other cohorts remained unchanged. By doing this, the average number of total sessions completed was comparable for the individual therapy only and group training participants. This analysis demonstrated a 25% ($p = .08$) reduction in risk attributable to additional group participation and an 18% ($p = .48$) reduction for the individual therapy only participants, relative to usual care in the adjusted model.

Previously published findings from the ENRICH study³² indicated that nonrandomized antidepressant use was also associated with decreased risk of death or nonfatal MI. Thus, we examined the possible contribution of antidepressant medication usage to event-free survival. Although there were no baseline differences in reported usage of any antidepressant medication among the three treatment cohorts, at six months there was a significant difference ($p < .0001$) in reported usage among usual care (10%), individual therapy (13%), and group training participants (20%). To address whether the apparent benefit associated with the addition of group training could be explained by increased antidepressant usage, the analysis was limited

to participants who met the entry criteria for depression, and antidepressant medication usage was added in the final adjusted model as a time-dependent covariate. Use of antidepressants was associated with a 24% ($p = .15$) reduction in all cause mortality and nonfatal MI, whereas the beneficial effect of group treatment was virtually unchanged with a 27% reduction ($p = .09$).

Lastly, exploratory analyses were completed to evaluate whether event-free survival was modified by gender as suggested by a recent meta-analysis⁶. Minimal survival time matched analyses were conducted separately for men and for women. The adjustment strategy used in the main analyses was applied. The results of analyses adjusting for age, CVD, and CHF history, showed that the benefit associated with group training on the primary medical endpoint of all cause mortality and/recurrent MI was 26% in men ($p = .17$) and 22% in women ($p = .30$). Similarly, for analyses adjusting for a single risk factor of medical predictors³⁰, group training was associated with a 16% advantage in men ($p = .42$) and a 30% in women ($p = .13$). Although not significant, the findings suggest that the benefits associated with group training on the primary medical end point were comparable for men and women.

DISCUSSION

The ENRICHD clinical trial failed to demonstrate an effect of the intervention on the primary end point (all-cause mortality and/or nonfatal MI)¹. In standard unadjusted and fully adjusted proportional hazard regression analyses, group training was associated with a 50% and 41% reduction in the primary end point, respectively, relative to usual care while no benefit was associated with individual therapy alone. These findings, however, are tempered by the recognition that the patients who participated in group training were not a random subset of those randomized to the psychosocial treatment arm of ENRICHD, but had survived event-free until they attended their first group session, on average, approximately 3 months following their randomization into study intervention. We acknowledge that it is possible that this may have introduced a selection bias, insofar as patients who received individual therapy alone or usual care may have had clinical events during the interval prior to the average time of 3 months post randomization that the group training participants survived event-free. Given this possibility, efforts were directed at minimizing the impact of systematic differences in survival by approximating intention-to-treat analyses using proportionate subsamples from all treatment categories to match minimal survival times as similarly as possible.

Our statistical approach relying on risk set-based sampling plus Cox model would remove this time-varying selection bias as much as possible, resulting in the exclusion of approximately 60% of these early events during the first six months in the usual care and individual therapy cohorts. This strategy indicated that the benefit of group self-management training in post-MI patients likely lies somewhere between 23–33% reduction in risk of death or recurrent nonfatal infarction. While the current findings do not warrant the recommendation for a change in clinical practice, they underscore the need to generate and test hypotheses concerning the potential value of group training, emphasizing coping skill acquisition and stress reduction, to improve event free survival.

The only way to unequivocally determine the true benefit of group self-management training on prognosis in depressed and/or socially isolated post-MI patients will be to conduct a well-designed and well-managed randomized controlled trial in which patients are randomized to the group training and control condition(s). In considering whether such a trial should be done, it is interesting to note that in the Beta-Blocker Heart Attack Trial³³, and in pooled analyses of multiple trials^{34,35} highly reliable 23% to 28% reductions in various clinical end points were observed, respectively, with beta-blocker treatment. If the current conservative estimate of a 23% reduction in the primary end point is found in a randomized trial to be a valid indicator

of the impact of the full ENRICHD intervention protocol (individual plus group training with adjuvant pharmacotherapy when indicated), it would suggest that such an approach in post-MI patients may have a benefit comparable to that of beta-blocker therapy – now a standard part of the management of the post-MI patient in good clinical practice.

The potential benefit associated with the addition of the ENRICHD group training protocol on cardiac recurrences could stem from both the format and content of the group training and is consistent with findings from past trials that found group-based behavioral interventions effective in reducing clinical coronary events^{8,20,21}. There are several reasons why the group training protocol may be of value. First, the group training format featured numerous opportunities for the observation of peers struggling with problems that were common to all. According to social cognitive theory²⁴, one of the most effective modalities by which behavior change takes place is the vicarious experience of a new behavior that occurs when it is modeled by a peer. Second, the ENRICHD group training content focused on general emotional adaptation, targeting stress and social functioning rather than depression and low perceived social support. The group featured training in a series of skills such as relaxation, management of negative emotions, communication, assertion, relapse prevention, and time management; reinforcing and supplementing work that may have begun in individual therapy. These skills targeted cognitive, emotional, environmental, and physiological domains. Because these domains reciprocally influence each other²⁴, change in one domain may have promoted change in others. Third, the skills taught in the group were framed as skills that could be used to prevent distress (that would be expected to co-occur with depression and low perceived social support), to increase resiliency, and improve the ability to cope with a variety of stressors of daily life in addition to stressors associated with the MI. The results of a recent meta-analysis shows that psychosocial interventions that are effective in modifying distress are associated with significant decreases in all cause mortality within a 2 year follow-up period⁶.

This self-management coping skills emphasis is likely to have resonated with medically ill patients who did not view themselves as having any psychological difficulties or in need of the psychotherapy offered by the individual therapy component of the ENRICHD trial. Moreover, it may have had the added benefit of reducing any stigma that participants experienced as a result of having been labeled as depressed or as having low perceived social support. Clearly, future research will need to determine whether group-based coping skills training that enhances resistance to the negative health effects of stress and emotional distress and reinforces interpersonal and communication skills has the potential to significantly improve treatment outcomes. Such evidence would be necessary to justify changes in standard clinical practice.

Informing patients who were randomized to usual care that they were depressed and/or socially isolated could have been in effect an intervention that stimulated them to use the American Heart Association workbook, *An Active Partnership for the Health of Your Heart* 13, with a level of commitment that would not otherwise have been present. It is interesting to note that *Active Partnership* does contain a section on stress management based on principles similar to those used in the design of the ENRICHD group training protocol. It is tempting to speculate that the improvements in depression and social support observed in the usual care patients resulted from their having been motivated by the information they were given regarding their psychosocial distress to use the *Active Partnership* material more faithfully than the average post-MI patient. It is also noteworthy that in two randomized trials that did not select cardiac patients on the basis of (or inform them about) any psychosocial criteria, there was either no improvement or even a worsening of anxiety and depression among those randomized to usual care during the trial^{2,22}.

There are several limitations that mandate caution in interpreting the findings of this study. First, and most important, participants were not randomly assigned to group training. Although the original plan for the ENRICHD protocol intended that all patients randomized to psychosocial treatment would begin with individual therapy and then transition to group training, in practice, problems such as logistics resulted in approximately a third of the patients randomized to the psychosocial intervention ever participating in group training. This nonrandom participation in group training resulted in an imbalance in baseline characteristics in most cases favoring group training (i.e., although patients had a poorer psychosocial profile, they were younger, better educated, and had lower rates of previous MI, stroke, and MI) that could have contributed to differences in clinical outcome. While we believe that the conservative statistical approaches we took to control for these potential confounds (e.g., eliminating the majority of early events in the usual care and individual therapy cohorts) minimize the likelihood that they are responsible for the observed benefits of group treatment, only a more carefully planned and conducted randomized controlled trial specifically designed to address the influence of self-management coping skills group training can resolve this issue.

The nonrandom participation in group training, when added to individual therapy, means we cannot be sure whether its apparent improvement on the primary end point stems from the qualitative differences between the individual and group components that we noted above, baseline differences, or is simply a function of quantitative differences in the number of sessions. On average, those who received individual therapy alone had only 9.5 treatment contacts, whereas those who also received group training had 20.7 contacts. We, however, examined this issue in a multivariate model, where patients who received only individual therapy were restricted to those who received at least 17 treatment contacts. This analysis revealed that both the number of sessions and group training had an impact on the clinical outcome, however, the impact of group was stronger suggesting that the benefits attributable to group training are not explained by treatment dose. There was an 18% reduction in clinical events among those who received at least 17 sessions of individual therapy, compared to a 25% reduction among those who participated in at least one group session relative to the usual care condition to whom participation in treatment sessions was not an option (result not shown). Similarly, reported differential use of antidepressant medication for depressed patients receiving usual care, individual therapy alone, and group training plus individual therapy did not explain the beneficial effect of group training on all cause mortality plus nonfatal MI. Rather, antidepressant use and participation in group training had comparable effects, reducing the hazard ratios independently. This suggests that the addition of group training is as effective as the addition of pharmacologic depression management in modifying clinical outcomes in depressed post-MI patients and that their combination has the potential to further reduce the primary end point.

Recent meta-analytic evidence suggests that psychosocial interventions may reduce mortality in men but not women⁶ for follow-up periods of 2 years or less. This meta-analysis did not, however, address this trial's primary combined medical end point of all cause mortality and/or recurrent nonfatal MI. Previously reported unadjusted post hoc exploratory analyses examining the ENRICHD trial's primary medical end point suggested that white men (who were healthier and more aggressively treated) showed a 'marginally positive effect' to treatment whereas other gender by ethnicity subgroups did not³⁷. In adjusted exploratory analyses, we found no appreciable gender difference in the effects of group training on event-free survival in approximately 4 years of follow-up. Future research with adequately powered studies is warranted to unequivocally clarify issue.

In conclusion, the findings of this study suggest that inclusion of a group intervention that teaches patients with a recent MI to use skills that will likely help them cope better with the stresses imposed by their illness as well as their general life circumstances may hold promise

to improve prognosis in the 650,000 people who suffer MI in the U.S. each year³⁸. The limitations of the current study will make it necessary, in order to demonstrate such a benefit in a scientifically rigorous manner, to undertake a sufficiently powered randomized controlled trial in which patients are randomly assigned to a group intervention like that designed for ENRICHD and to appropriate control conditions.

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Glossary

ENRICHD	Enhancing Recovery in Coronary Heart Disease
MI	myocardial infarction
CBT	cognitive behavior therapy
ESSI	ENRICHD Social Support Instrument
ECG	electrocardiograph
BDI	Beck Depression Inventory
CHF	congestive heart failure
PTCA	percutaneous transluminal coronary angioplasty
CVD	cerebrovascular disease
CABG	coronary artery bypass graft

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Figure 1.

Estimated survival probability for 60 year old person without CVD and CHF history⁺

⁺Mean conditions were used. Estimated probability was derived from Model 1 in Table 5.

Table 1

Demographic and Psychosocial Characteristics

	Usual Care (n=1243)	Individual therapy (n=781)	Group training ^a (n=356)	p-value
Age in years (mean)	60.8	61.3	58.7	.004
Women (%)	44.4	44.6	38.8	.13
Minorities (%)	34.2	30.6	39.6	.01
Education > High school (%)	46.4	44.1	60.7	< .0001
Entry criteria				.007
Depression (%)	38.6	43.4	32.3	
Low Social Support (%)	26.9	24.7	27.5	
Depressed and low social support (%)	34.5	31.9	40.2	

^aParticipants received group training in addition to individual therapy.

Table 2**Baseline Medical History Characteristics**

	Usual Care (n=1243)	Individual therapy (n=781)	Group training ^a (n=356)	p-value
Cerebrovascular disease (%)	9.9	10.2	5.6	.02
Previous MI ^b (%)	27.4	26.5	21.1	.04
CHF ^c History (%)	13.7	14.9	7.6	.001
Renal Insufficiency (%)	9.4	11.5	7.3	.07
Diabetes (%)	33.3	33.2	29.5	.33
Hypertension (%)	60.5	59.9	59.0	.77
Smoking History (%)	65.2	64.1	63.5	.68
Hypercholesterolemia (%)	56.2	57.5	59.6	.45
Peripheral Vascular Disease (%)	12.1	12.0	12.1	.99
Pulmonary Disease (%)	19.3	18.2	14.9	.10
Previous Cardiac Arrest (%)	1.7	1.5	3.4	.11
Previous PTCA ^d (%)	16.0	14.7	12.4	.19
Ejection Fraction				
Severe Dysfunction (%)	25.3	26.5	22.6	.37
Killip Class III–IV (%)	7.2	8.5	4.5	.06
Vasodilator use (%)	42.9	41.1	36.3	.11
CABG ^e (%)	18.1	17.0	19.7	.55
Creatinine level in mg/dl (mean)	1.17	1.21	1.12	.31

^aParticipants received group training in addition to individual therapy.

^bMI (myocardial infarction)

^cCHF (congestive heart failure)

^dPTCA (percutaneous transluminal coronary angioplasty)

^eCABG (coronary artery bypass graft)

Table 3Baseline, Follow-up, and Change from Baseline in BDI^a and ESSI^b [mean (s.d.)]

	Usual Care	Individual therapy	Group training ^c	p-value
BDI [§]	(n=792)	(n=525)	(n=242)	
Baseline	17.8 (7.6)	17.8 (8.1)	17.7 (8.2)	
Last follow-up	10.4 (8.4)	9.7 (8.6)	8.4 (7.9)	
Change from baseline	-7.4 (9.0)	-8.1 (9.2)	-9.3 (9.2)	.015
ESSI [¶]	(n=654)	(n=387)	(n=238)	
Baseline	19.1 (4.3)	19.3 (4.5)	19.4 (4.3)	
Last follow-up	23.4 (6.7)	24.9 (6.4)	24.6 (6.6)	
Change from baseline	4.3 (6.0)	5.6 (6.5)	5.2 (6.2)	.003

Note: Sample sizes reported in the table were reduced due to missing data.

^aBDI (Beck Depression Inventory)^bESSI (ENRICH Social Support Instrument)^cParticipants received group training in addition to individual therapy.[§]Restricted to those who met the eligibility criteria for depression only.[¶]Restricted to those who met the eligibility criteria for low perceived social support only.

Table 4

Treatment Participation and Achievement of Treatment Criteria

	Individual therapy (n=781)	Group training ^a (n=356)
Days to first session (mean)	13.9	9.3
Number of sessions completed (mean)		
Individual	9.5	13.0
Group	–	7.6
Total	9.5	20.7
Dropouts (%)	12.2	1.6
Criteria for Success		
≥6 sessions completed (%)	72.5	99.4
Ability to perform self-therapy (%)	39.6	59.5
Met goal(s) for depression and/or social support (%)	54.9	69.6
Met all criteria for success (%)	34.4	47.4

^a Participants received group training in addition to individual therapy.

Table 5

Estimates of the Treatment Effect ^a : Risk Set Sampling Method with Cox Proportional Hazards Regression
(Average of 100 Iterations, n=2236)

	Hazard Ratio	95% Confidence Interval	p-value
<u>Minimal survival time-matched analysis</u>			
Individual therapy	1.10	[0.89, 1.36]	.38
Group training ^b	.67	[0.49, 0.92]	.012
<u>Minimal survival time-matched analyses with covariates-adjustment</u>			
Model 1 ^c . Individual therapy	1.03	[0.84, 1.27]	.74
Group training	.77	[0.56, 1.07]	.11
Model 2 ^d . Individual therapy	1.08	[0.88, 1.33]	.48
Group training	.77	[0.56, 1.05]	.10

^aReferent is usual care condition.

^bParticipants received group training in addition to individual therapy.

^cModel 1: Adjusts confounders which are significantly associated with exposure and outcome; age, CVD and CHF history.

^dModel 2: Adjusts a single risk score of medical predictors ³⁰ (i.e. weighted sum of age, MI history, CHF history, CVD, pulmonary disease, diabetes, Killip class, Ejection fraction, creatinine, BDI score, coronary artery bypass grafts, and vasodilator use).