Appendix C.3

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Evaluation of Lifestyle Modification and Cardiac Rehabilitation in Medicare Beneficiaries*

Benefits of Stress Management in Coronary Heart Disease

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April 30, 2009

*Supported by the Centers for Medicare & Medicaid Services under contract number 500-95-0060, Task Order 02 to Brandeis University and number 500-02-0012-MDBU to the Delmarva Foundation for Medical Care

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Abstract

Stress is an important risk factor both for the initial development of coronary heart disease (CHD) and for increasing the risks of mortality and subsequent cardiac events in people with established disease. Epidemiological cohort studies document two- to four-fold increases in the risk of CHD due to depression, anxiety, social isolation, chronic stress due to job or other life stresses, hostility, and Type A personality traits. Stress also plays a role in adversely affecting health behaviors such as diet, smoking, or inactivity and physiologic functions in the autonomic nervous and neuroendocrine systems, while predisposing individuals to endothelial damage and platelet activation.

A large number of controlled clinical trials have been conducted over the past 30 years to evaluate the effects of interventions aimed at alleviating the manifestations of stress. These studies vary widely in design, size, and the specific interventions tested. Our report focuses on meta-analyses of studies published between 1973 and 1998 and on analyses of individual studies published between 1995 and 2004. Four meta-analyses (Dusseldorp, et al., 1999; Linden, et al. 1996, Mullen, et al 1992; and Nunes, et al 1987) found statistically significant effect sizes for the benefits of psychosocial interventions in reducing mortality and risk of myocardial infarction in people with established coronary heart disease. Only the Dusseldorp study also found reductions in blood cholesterol, body weight, systolic blood pressure, and smoking behavior.

However, recent large studies have failed to replicate these encouraging results. The Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) study (ENRICHD, 2003) included 2481 men and women with acute myocardial infarctions who were also depressed and/or had low social support. This study found no significant gains in survival or reductions in recurrent myocardial infarctions after six months of cognitive behavioral therapy. Similarly, Jones et al. did not find significant benefits from outpatient interventions that included education, relaxation, and efforts to facilitate psychological adjustment in 2328 patients with acute myocardial infarctions (Jones et al., 1996). Frasure-Smith and co-workers (Frasure-Smith et al., 1997), replicating a 1989 study in which she found significant benefits of a home-based psychosocial nursing intervention in men, found no significant benefits in 903 men, and only marginally significant increases in all-cause and cardiac mortality in 473 women. Reasons for the latter findings have not been explained.

Although recent studies have been more rigorously designed, they have also been of shorter duration that some earlier studies. Time and intensity of treatment effects cannot be ruled out as possible causes for their equivocal or negative results.

We conclude that there is a convincing body of evidence that supports a relationship between stress and the occurrence and clinical course of heart disease, but that the benefits of psychosocial interventions to reduce stress when considered alone are equivocal. Analysis of lifestyle interventions and longer follow up periods are required to identify the potential beneficial role of psychosocial interventions as components of a comprehensive approach to lifestyle modification in patients with CHD.

I. Introduction

Stress is an important risk factor for the development of coronary heart disease (CHD) in healthy people and also increases mortality and morbidity risks in individuals with established disease. In this paper, we provide a framework for interpreting the impact of stress-directed psychosocial interventions on patients with coronary heart disease and review recent evidence of the benefits of stress management. We first define stress and its underlying mechanisms and then describe its effects on CHD. Finally, we review evidence of the benefits of psychosocial treatments and educational programs in alleviating symptoms and improving medical outcomes. This synthesis is based on an extensive review of published literature. Results of meta-analyses that included papers published through 1998 are supplemented by findings from more recent studies. Conclusions are based on the weight of current evidence, and recommendations focus on high priority targets for future research.

II. Stress and Stress Management – an Overview

Stress is defined as the responses that humans (and other living organisms) make to environmental demands or other pressures in their lives. Stress is a normal part of life that spares no age group, gender, or race. Stressors include exposures to acute external events such as earthquakes or car crashes, to personal events such as divorces or the loss of loved ones or a job, and to chronic stresses from disease, work, or marital discord. Healthy coping mechanisms can help one to avoid stress-producing situations all together or, when this is not possible, to manage them better when they occur.

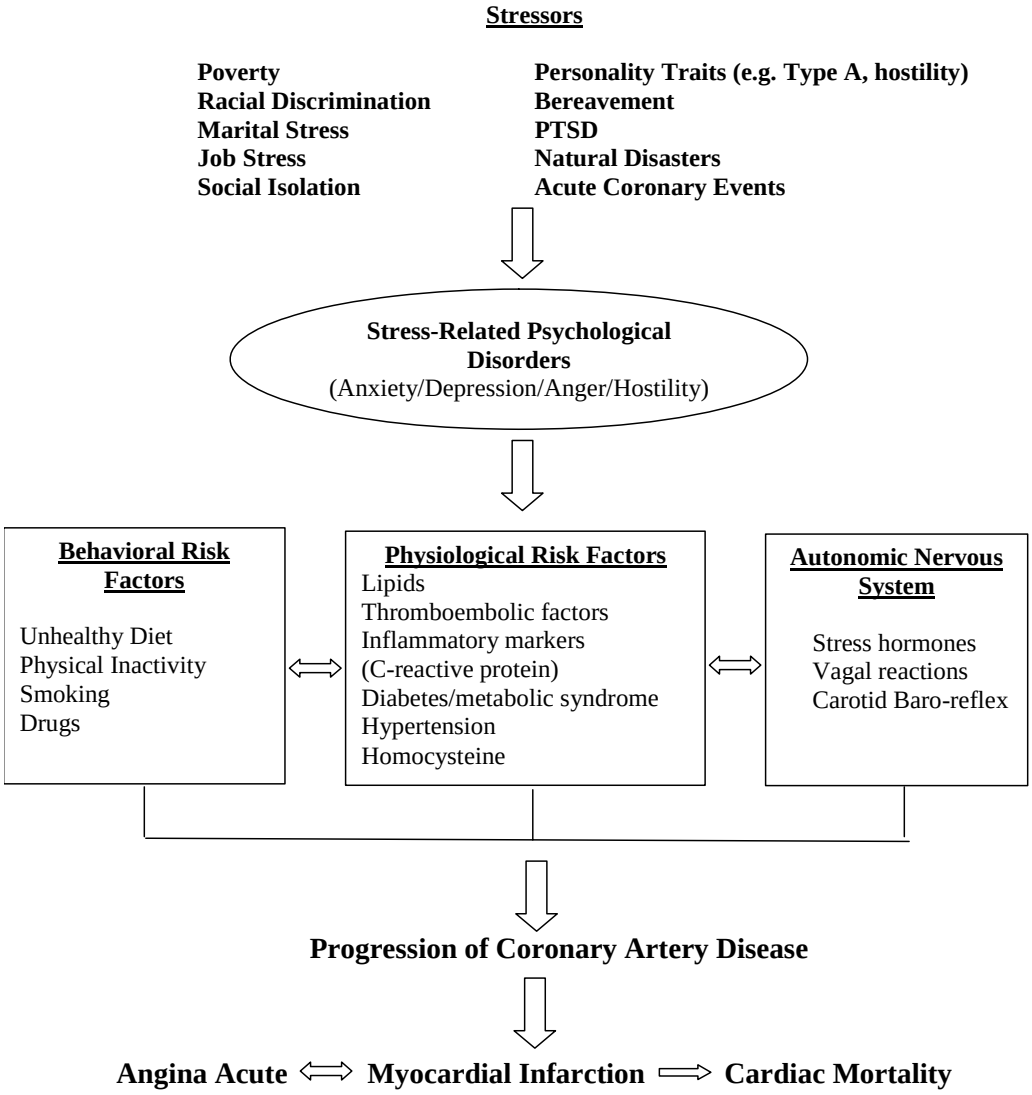
Many responses to stress are handled automatically through a delicate balance between the sympathetic and parasympathetic components of the autonomic nervous system. The former controls daily stressors and, in the extreme, ”fight or flight” responses; while the latter modulates relaxation responses. Beyond physiologic responses are psychological responses including anger, anxiety, irritability, loss of concentration or memory, and depression. Behavioral responses to stress such as overeating, overwork, addiction to alcohol, drugs, or cigarettes, insomnia, or isolation may also increase the risk of CHD.

Figure 1 provides an overview of the multi-directional relationships between environmental stressors, stress-related disorders such as depression, anxiety, and hostility, effects on behavioral and physiological risk factors, and the potential adverse effects of stress on the progression of coronary artery disease. Figure 1 emphasizes that environmental stressors and stress-related disorders may influence development and progression of CHD through multiple pathways. This framework provides important insights into challenges of designing and

evaluating interventions to reduce the effects of stress on CHD. To be successful, such interventions may need to address basic mechanisms as well as expressed manifestations of stress.

When the effects of stress spiral out of control, psychological counseling, behavior modification techniques such as the relaxation response, meditation, yoga, cognitive restructuring, support from others, and selective use of medications offer promise for

Figure 1 – Conceptual Framework for Relationships Between Stressors, Physiological Responses, and Coronary Heart Disease Outcomes



relief. No one approach is a panacea, but each may have a valuable role to play in stress reduction. Certain personality types, such as Type A personality, have attracted particular attention and have spawned controversy over whether they represent global risk factors for CHD or merely represent expressions of anger and hostility. Table 1 identifies common types of interventions that have been used to facilitate stress management and summarizes the types of clinical, quality of life, and economic endpoints that have been used in clinical trials aimed at reducing stress. Intervention strategies range from single psychosocial treatments to multi-faceted treatments involving both psychosocial and lifestyle modification interventions. Target outcomes range from proximal changes in behaviors (diet, exercise, use of stress relieving techniques); to changes in psychological and physical risk factors such as relief of symptoms of depression or reductions in serum lipids; to more distal endpoints, such as cardiac mortality and myocardial infarction. Therefore, demonstrating the benefits of stress management interventions requires measurement of a variety of proximal, intermediate, and distal endpoints.

III. Methods

A. Literature Search

MEDLINE , PyschLIT and the Social Science Index computerized searches were performed to identify relevant studies published between 1980 and 2004. The bibliographies of qualifying published studies were examined to identify additional studies. Criteria and keywords that guided the literature search were:

(1) Heart disease diagnosis (including coronary heart disease, myocardial infarction, and treatments including coronary artery bypass surgery, percutaneous transluminal coronary angioplasty, and heart surgery);
(2) Patient symptoms (including stress, depression, anxiety, anger, hostility, emotional distress, social isolation, and personality type);
(3) Outcomes (including mortality, morbidity, recurrent non-fatal cardiac events, blood pressure, cholesterol, being overweight or obese, well-being, and quality of life);

(4) Types of interventions (including stress management treatments, psychological counseling, cognitive restructuring, group therapy, relaxation response, yoga, spirituality interventions, social support and medications).

(5) Types of study methodologies included controlled clinical trials, case-control studies, population-based observational studies, review articles, and meta-analyses.

The search was limited to studies on human subjects that were published in English.

B. Study Inclusion Criteria

To be included in our review, all clinical studies involved individuals with coronary heart disease; examined at least one type of stress management intervention; included a minimum of twenty subjects; and were of at least two months duration. Quasi-experimental studies were included only when controls were matched or differences were otherwise controlled by regression techniques. Review articles were required to include a minimum of fifty citations to scientific articles. Meta-analyses were limited to those studies assessing the results of randomized clinical trials (RCTs) or otherwise controlled clinical studies. When multiple articles reported on the same or closely related study populations, we focused on the primary study and primary outcome measures, and augmented this with findings from related studies.

Table 1: Conceptual Framework: Interventions and Impacts

Stage	Examples
Inter-ventions	Single Modality
	Health education or counseling
	Nutrition counseling
	Aerobic exercise
	Relaxation response, meditation, yoga, imagery
	Social support
	Cognitive behavioral therapy
	Psychotherapy
	Multiple Modalities
	May include combinations of two or more of the above
Impacts	Medical Endpoints
	Psychological risk factors (depression, anxiety, hostility)
	Behavioral risk factors
	Endocrine/autonomic nervous system function
	Cardiac risk factors (lipids, blood pressure, smoking)
	Cardiac ischemia (angina)
	Cardiac events (MI) and procedures (CABG, angioplasty)
	Mortality (cardiac, all causes)
	Patient Perceived Outcomes
	Adherence to recommended care
	Satisfaction with health care
	Quality of life/health status
	Social adjustment
	Economic Endpoints
	Costs of ambulatory care: visits, testing, medications
	Utilization and cost of inpatient hospital care
	Cost-effectiveness of behavioral interventions

C. Abstraction of Papers

Each qualifying paper was abstracted by at least one medically trained scientist according to a pre-determined abstraction protocol. A second reader reviewed abstractions, and corrections and additions were made with the agreement of the primary reviewer.

D. Report of Findings

Associations between psychosocial factors and occurrence of CHD or the clinical course of established CHD are derived from published review articles and from individual observational studies. The results of prospective clinical trials are assessed from published meta-analyses for older studies and from analysis of individual controlled clinical studies published between 1996 and 2004. The limited number of recently published clinical trials did not permit formal updating of existing meta-analyses. Hence, conclusions are based on systematic review of the existing literature rather than quantitative evaluation.

E. Results of Literature Search

Table 2 summarizes the results of both electronic and manual searches. A total of 64 qualifying studies were selected, including 26 reviews or meta-analyses and 38 controlled clinical trials. These 64 studies provide the basis of this literature review.

Table 2. Results of Literature Search for Stress Management Studies (Psychosocial Stress, Depression, and Social Support) for Individuals with Coronary Heart Disease (CHD)

Type of Paper	Psycho-social Stress	Depression	Social Support	Total
Electronic Searches				
Initial identified	543	200	212	955
Abstracts retained	128	40	28	196
Papers Included:				
Review articles	3	15	3	21
Meta-analyses	4	1	0	5
RCT / Controlled studies	17	10	11	38
Totals	24	26	14	64

IV. Stress and Coronary Heart Disease

A. Psychosocial Factors as Risk Factors for the Initial Development of Coronary Heart Disease among "Healthy Individuals"

A wealth of studies provides convincing evidence that psychosocial factors contribute importantly to the pathogenesis of CHD. Depression, anxiety, personality factors such as Type A personality or hostility, social isolation, and job and other chronic stress situations are consistently associated with a higher incidence of cardiac symptoms and events. Causal relationships exist which include adverse health behaviors such as smoking, inactivity, unhealthy diets, and basic pathophysiological mechanisms such as neuroendocrine factors, endothelial damage, or platelet activation. This section summarizes the findings from existing literature. Excellent review articles provide the starting point (Hemingway et al., 1999; Rozanski et al., 1999) and are buttressed by population-based observational studies. Results are summarized in Table 3.

1. Depression. Episodes of major depression occur in about five percent of the population at large, based on one-month community-based prevalence (Blazer et al., 1994), and less severe depression is much more frequent. Symptoms include fatigue, sleep disturbances, changes in appetite, feelings of guilt or worthlessness, and, in the extreme, suicidal thoughts. Several large cohort studies have demonstrated two-fold or greater increases in the risk of non-fatal myocardial infarctions, stroke, and cardiac or all-cause mortality in people with depression (Arooma et al., 1994; Vogt et al., 1994; Anda et al., 1996; Barefoot et al., 1996a; Everson et al., 1996; Pratt et al., 1996; Wasserthal-Smoller et al., 1996; Ford et al., 1998). Both behavioral and physiological mechanisms appear to be involved. On the one hand, depression may contribute to adverse lifestyles such as smoking, inactivity, and overeating. Moreover, it is associated with risk factors such as increased blood cortisol levels, increased corticotropin-releasing factors in the brain, and impaired platelet function. The combination of these factors contributes to accelerated atherogenesis.

2. Anxiety. Increased anxiety was associated with higher sudden cardiac death rates in three large community-based studies with risk ratios ranging from 1.9 to 3.8 (Haines et al., 1987; Kawachi et al., 1994a; Kawachi et al., 1994b). These relationships appeared to be dose-related, that is, the greater the anxiety the higher the risk. However, anxiety does not appear to lead to an increased risk of acute myocardial infarctions. Notably, available studies do not include women despite the higher prevalence of anxiety among women. Significant relationships have also been demonstrated between "worry" and panic disorders and acute myocardial infarctions, but not with

cardiac deaths. Physiologic causal mechanisms appear to involve increased activity of the sympathetic nervous system and impaired vagal control.

3. Personality traits. In the 1950's, Friedman and Rosenman explored the role of personality type, and especially Type A behavior patterns in the occurrence of cardiac events (Friedman et al., 1959). The Type A pattern is characterized by competitiveness, hostility, and exaggerated commitment to work. Initial reports from the Western Collaborative Group in 1975 pointed to a two-fold increased risk of CHD and a five-fold increase in risk of recurrent MI in men with Type A personalities. However, more recent studies have questioned this relationship and have focused instead on specific personality traits such as hostility, anger, and cynical mistrust. (Barefoot et al., 1983; Shekelle et al., 1983; McCranie et al., 1986; Koskenvuo et al., 1988; Leon et al., 1988; Hearn et al., 1989; Maruta et al., 1993; Barefoot et al., 1995; Kawachi et al., 1996; Everson et al., 1997). The results are highly suggestive of associations between these personality traits and increased rates of cardiac or all-cause deaths and myocardial infarctions. Proposed mechanisms explaining this association include unhealthy lifestyle behaviors, increased sympathetic activity, increased cortisol levels, and, perhaps, increased platelet reactivity. Hostile individuals are also more likely to suffer from the ill effects of social isolation.

4. Social support and social isolation. A number of studies have examined the effects of social support or, conversely, social isolation on the incidence of cardiac events. People who are isolated or have limited social networks or emotional support have 2 to 3-fold increases in CHD rates. Moreover, convincing evidence supports an inverse relationship between the level of support and the frequency of cardiac deaths or future cardiac events in individuals with established CHD (Rozanski et al., 1999). Underlying the effects of social isolation are increases in unhealthy lifestyles, reductions in buffers against various environmental stressors, and the presence of physiological abnormalities such as elevated blood cortisol levels. Age and sex specific all-cause mortality rates are strongly linked to the strength of social networks, independent of other risk factors in four important population-based studies (Berkman et al., 1979; Blazer, 1982; House et al., 1982; Seeman et al., 1987). These correlations are stronger among men than among women.

5. Socioeconomic status. Low socioeconomic status appears to contribute to an increased incidence of CHD, whether measured by education level, income, or occupation (Winkleby et al., 1990; Barefoot et al., 1991; Kaplan et al., 1993).

6. Work-related and other chronic stresses. Job stress (high work demand, having little control, and low reward) has been associated with increased risk of cardiac death and cardiac

events. Similarly, recent life changes such as divorce, loss of a job, or death of spouse frequently precede myocardial infarctions or sudden cardiac deaths.

Table 3: Summary of Cardiac Risks Associated with Psychological Conditions in Healthy Individuals versus Individuals with Coronary Heart Disease (CHD)*

Psychosocial Condition	Risk in Healthy Individuals	Risk in Individuals with CHD
Depression	10 studies published 1986-1998 Follow-up: 6-37 years Risk ratios (RRs): 1.3-3.5 for major cardiac event for depressed vs. not depressed Results statistically significant in 9 of 10 studies	10 studies published 1987- 1999 N=3,874 individuals with various manifestations of CHD Follow-up: 1-15 years. RRs 1.3-7.5 for subsequent cardiac events for depressed people Results statistically significant in all studies
Anxiety Disorders	4 studies published 1987-1994 N=43,462 Follow-up: 2-32 years RRs for MI: 0.9-1.3 - not statistically significant RRs for cardiac death: 1.9-3.8 (significant in 2 studies)	4 studies published 1995-1998 N=849 RRs for death and combined cardiac endpoints 2.5-4.9 Results statistically significant
Personality Traits Hostility (including Type A personality)	11 studies published 1983-1997 N= 12,072 Follow-up: 3-33 years. Statistically significant for cardiac events or death in 3 of 8 studies	4 studies published 1988-1996 N= 695 RRs for cardiac events 1.7-2.1 Results statistically significant in 3 studies. In the 4th study, RR for restenosis was 14.6 between the highest and lowest quintiles.
Social Influences (includes social support, integration, network, and activities)	17 studies published 1979-1998 N=109,834 RRs for cardiac events or death 1.4-3.8. Statistically significant in 13/17 studies	13 studies published 1983-1998 N=10,730 Follow-up: 0.5-10 years RRs for MI or death 1.5- 6.5 Results statistically significant in all studies

* CHD defined by angiographic results, documented MIs, post-percutaneous transluminal coronary angiography (PTCA), cardiac arrhythmias, or congestive heart failure.

B. Effects of Psychosocial Factors on Prognosis in Established Coronary Heart Disease

Psychological factors also have impressive effects on the clinical course of individuals with established CHD, as shown in Table 3**.** Major depressive episodes occur at least three times more frequently in people who have suffered a cardiac event and are uniformly associated with increased rates of subsequent cardiac events and cardiac deaths (Kennedy et al., 1987; Ahern et al., 1990; Frasure-Smith et al., 1995; Barefoot et al., 1996b; Denollet et al., 1998; Hermann et al., 1998; Frasure-Smith et al., 1999; Carney et al., 2000). Anxiety is associated with a two- to five-fold increase in combined cardiac event rates (Denollet et al., 1998; Hermann et al., 1998) and small studies have found significant increases in cardiac deaths and myocardial infarctions in patients manifesting hostility traits (Hecker et al., 1988; Koskenvuo et al., 1988; Dembroski et al., 1989; De Leon et al., 1996). Interestingly, accelerated rates of restenosis after angioplasty and more rapid progression of atherosclerosis detected by serial carotid ultrasounds have been found in patients with high levels of hostility (Matsumoto et al., 1993; Julkunen et al., 1994; Goodman et al., 1996). Low levels of emotional support are associated with increased cardiac mortality and/or increased rates of myocardial infarction in a number of studies. Moreover, high work stress and perceived low levels of control over one's work environment have been significantly related to increased mortality, increased rates of recurrent MIs, or increased symptom severity in patients after acute myocardial infarctions (Siegrist et al., 1990; Lynch et al., 1997; Bosma et al., 1998).

V. Treatment of Psychosocial Factors in Patients with Coronary Artery Disease

Traditional medical treatment of individuals who have had a myocardial infarction or undergone coronary artery bypass surgery (CABG) or percutaneous interventions (PTCA or stent placements) has focused on a variety of interventions. These include the use of medications such as beta-blockers and statins, increased physical activity often initiated during cardiac rehabilitation programs, cardiac risk factor reduction, diet low in saturated fat, increased attention to control of coronary risk factors such as smoking and hypertension, and selective use of cardiac revascularization procedures to correct or bypass coronary artery obstructions.

The important influence of psychosocial factors on the clinical course of CHD, however, suggests that treatments aimed at their amelioration might achieve important health benefits. The following section describes the array of psychosocial interventions that have been reported in the literature.

We then summarize the results of meta-analyses that have evaluated controlled clinical studies involving these interventions, and finally, we describe the results of more recent studies focusing on stress management.

A. Types of Psychosocial Interventions

Psychosocial interventions include a broad array of treatment modalities. They may improve clinical outcomes by helping individuals manage stress, by increasing adherence to medications or other treatments, or by facilitating lifestyle changes aimed at risk factor reduction.

Broadly, stress management treatments may be categorized as: (1) education; (2) relaxation training; (3) psychosocial treatments; or (4) group support. Treatments utilized in clinical practice may be limited to a single modality or, more often, will involve a combination of these approaches. These modalities are briefly described below:

1. Education. Education commonly focuses on increasing a patient's knowledge of CHD, its risk factors, and treatment and laying the groundwork for achieving behavior changes that reduce cardiac risk factors such as diet, overweight, physical inactivity, smoking, blood pressure, and diabetes. It may also target behavioral strategies aimed at helping the patient better understand and manage stress.

2. Relaxation Training. A variety of approaches are used to facilitate relaxation. Yoga and transcendental meditation (TM) or the "relaxation response" are the most widely used and share common features. Yoga is a holistic health system that originated thousands of years ago, evolved as an art and science in India, and, more recently, has gained increasing popularity in the United States. There are many variants, or schools, but the basic focus is on performing a series of poses and stretches, slow breathing, meditation, and deep relaxation. Goals are directed to gaining control over mind and body, achieving inner peace, and releasing tension. Small studies in healthy males have found that yoga practice lowers heart and respiratory rates, increases lung tidal volume and vital capacity, reduces electrical activity in muscles, and increases peripheral blood flow.

3. The Relaxation Response is a term coined by Dr. Herbert Benson and colleagues that grew out of the practice of transcendental meditation (TM) (Benson et al., 1975). In the early 1970s, Benson conducted studies on trained mediators that demonstrated striking decreases in oxygen consumption and blood lactate levels during meditation. Encouraged by these findings, he defined the four essential elements of the Relaxation Response: (1) a quiet environment; (2) a mental device such as a word or phrase which is repeated over and over again in a specific

fashion; (3) adoption of a passive attitude; and (4) a comfortable position. The technique is typically practiced for 10 to 20 minutes once or twice daily.

4. Psychosocial Interventions. These treatments encompass a wide variety of approaches and include the direct provision of emotional support or psychotherapy, cognitive behavioral therapy, cognitive restructuring or imaging, and psychodynamic interpretation of unconscious motives or conflicts. Cognitive behavioral therapy helps the patient identify problem situations and develop skills aimed at avoiding or coping with these situations. Cognitive restructuring is part of a paradigm that focuses on analyzing and changing the ways in which a person responds to stressful situations such as work, stress or anger. Imaging utilizes the vehicle of imagined stressful situations to help individuals develop successful coping strategies. Treatments may be offered in individual or group sessions. Group sessions often include both the patient and a significant other. Medications may be used to supplement psychosocial interventions, especially in patients with severe depression or anxiety.

5. Group Support. These approaches take advantage of the educational value and positive reinforcement that may occur when individuals with similar problems such as CHD or social isolation, meet together to discuss their situations and identify potential solutions. A trained facilitator usually leads sessions, and networks or buddy systems may evolve.

B. Meta-Analyses of Studies Assessing the Effectiveness of Psychosocial Interventions

Stress management treatments have been evaluated in a moderate number of clinical trials over the past 30 years. These studies are heterogeneous both in terms of the interventions they examine and in the design and quality of included studies. While some well-controlled studies report encouraging effects on mortality, rates of recurrence of myocardial infarction, and reduction in cardiac risk factors, other studies do not support these findings. Published meta-analyses by Dusseldorp (Dusseldorp et al., 1999), Linden (Linden et al., 1996), Mullen (Mullen et al., 1992), and Nunes et al. (Nunes et al., 1987), provide useful summaries of results of intervention studies published between 1971 and 1997. Tables 4A through 4D report selected findings from these meta-analyses ordered chronologically from earliest to most recent.

The first meta-analysis, by Nunes, Frank, and Kornfeld, (Nunes et al., 1987) examined the effects of various combinations of educational and psychosocial interventions aimed at modifying Type A behavior patterns in 18 controlled studies published between 1968 and 1984. Table 4A displays the results. Outcomes included changes in Type A behavior patterns (TABP) based on self-reports, mortality, recurrent MIs, and angina. Reports on clinical outcomes were limited to five

"methodologically acceptable" studies in a "corrected" analysis. Other studies were compromised by self-selection into treatment or control groups, short follow-up, or inadequately reported outcomes. Results for mortality and recurrent MIs in the "corrected analysis" are summarized in Table 4A. Results for recurrent MIs and the combined endpoint of mortality plus recurrent MIs were marginally significant at 1 year (p = 0.05), but by 3-years effect sizes for the combined endpoint were highly significant and represented a 50 percent reduction in rates. However, the longer-term morbidity and mortality benefits should be interpreted with caution because they were based on only two studies. Combinations of educational and psychosocial interventions appeared to be more effective in reducing Type A behaviors and cardiac event recurrences than either considered alone.

Table 4A: Meta-Analysis of Educational and Psychosocial Treatments for Type A Behavior Pattern and Coronary Heart Disease (Nunes, et al, 1987)

End Points	F/U	Study Design	No. Studies	N	ES	p-value
Mortality	1 yr.	RCT/CT	5	1263	0.34	p=0.15
MI	1 yr.		5	1263	0.45	p=0.05
Mortality + MI	1 yr.		5	1263	0.57	p=0.05
Mortality + MI	3 yr.		2	1064	0.97	p=0.0001

Notes: Boniferroni (multiple comparison) criterion of 0.001 was used to determine statistical significance.
Effect sizes (ES) were calculated using probit transform to obtain Z-scores

The meta-analysis performed by Mullen, Mains, and Velez (Mullen et al., 1992) examined the effects of patient education programs as components of cardiac care. Thirty-eight studies with controlled, quasi-experimental, or pre/post designs were included, but 10 studies with pre/post designs were excluded from their analysis. Interventions included one-on-one or group sessions targeted at exercise (18 studies), cardiac risk factor modification (11 studies), and/or stress reduction (9 studies). Positive effects were observed for mortality, systolic blood pressure, exercise, and diet while "other parameters are positively affected although less consistently" (Mullen et al., 1992). Impacts were measured by "effect sizes", that is, the change in the dependent variable divided by its standard deviation. Table 4B displays effect sizes after 6 months follow-up for mortality and recurrent myocardial infarction or rehospitalization. Mortality rates were lower in the intervention groups and were marginally significant. Program quality (a

total score based on five educational principles--individualization, feedback, facilitation, relevance, and reinforcement) was positively associated with effect size, but the duration of the intervention and length of the follow-up period were not associated with effect size.

Table 4B: Meta-analysis of Controlled Studies of Cardiac Patient Education (Mullen, et al 1992)

End Points	F/U	Study Design	No. Studies	N	ES	OR/ p-value
Mortality	6 mos.	RCT/CT	7	2158	0.24	Signif.
Recurrent MI or Rehosp.	6 mos.		9	1885	0.05	NS

Notes: Significant effects were also found at 6 months for mortality, diet, exercise, and blood pressure.
Effect sizes (ES) for proportions were calculated using probit transforms and adjusted for sample sizes and variances.

Linden, Stossel, and Maurice (Linden et al., 1996) performed a meta-analysis of 23 randomized controlled trials (RCTs) that examined the effects of various group and individual psychosocial interventions or relaxation therapy on mortality and recurrent MI., as well as other psychosocial and biological risk factors. Controls received usual cardiac care with or without exercise. Studies of education-only interventions were not included. Three-quarters of the studies enrolled patients recovering from MIs. Endpoints were anxiety, depression, biological risk factors, recurrence of cardiac events, and mortality.

The analysis was performed with and without inclusion of the Recurrent Coronary Prevention Project (RCPP) (Friedman et al., 1986). This study, while the largest extant study (N = 1013), was not strictly a RCT because patients were randomized to one of two psychological interventions, but controls were not randomized "because of ethical reasons". In the meta-analysis, effect sizes for psychological distress (anxiety and depression) were lower in the experimental groups ($p < 0.001$) in the15 studies in which it was measured, and biological risk factors were significantly reduced in 5 studies. Table 4C displays results for nonfatal cardiac events and mortality. Odds ratios in fully randomized studies demonstrated a 46 percent reduction in non-fatal cardiac events in experimental groups after 2 years of follow-up and a 39 percent reduction during longer periods of follow-up. Corresponding odds ratios for mortality were 1.70 ($p=0.02$) and 1.35 (NS). When results of the RCPP are included, odds ratios and levels of significance are increased for mortality and recurrent MIs during the shorter, but not the

longer, period of follow-up. A limitation of the Linden meta-analysis is that most included studies have small sample sizes.

Table 4C: Meta-Analysis of Controlled Clinical Trials of Psychosocial Interventions or Relaxation Therapy in Patients with Coronary Artery Disease (Linden, et al, 1996)

End Points	F/U	Study Design	No. Studies	N	ES	OR/ p-value
Mortality	≤ 2 yr.	RCT	10	1150	1.70	0.02
	> 2 yr.		3	595	1.35	0.13 NS
MI	≤ 2 yr.		8	852	1.84	0.02
	> 2 yr.		3	595	1.64	0.02
Mortality	≤ 2 yr.	RCT/CT	12	2040	1.76	0.001
	> 2yr.		5	1475	1.39	0.04
MI	≤ 2 yr.		10	732	2.29	0.001
	> 2yr.		5	1475	1.28	0.16

Notes: The top panel does not include the Recurrent Coronary Prevention Project (RCPP); the bottom panel does include this large study in which subjects were randomized to one of two interventions, but controls were not randomly assigned. ES is effect size.

The meta-analysis by Dusseldorp, van Elderen, Maes, Meulman, Kraaij, (Dusseldorp et al., 1999) is the largest and the most methodologically rigorous of all the evaluations. Its objectives were: (1) to assess the effects of psycho-educational programs in patients with CHD; (2) to test the hypothesis that success on proximal endpoints such as serum lipids leads to reduction of cardiac mortality and cardiac event recurrences; and (3) to explore moderating effects of study features. Another important objective was to distinguish stress management from health education interventions and from combined modalities. Thirty-seven studies published between 1974 and 1997 were included in this meta-analysis. Over half of the studies were performed in Europe. Twenty-eight studies were RCTs; 9 had quasi-experimental designs; and 9 studies overlapped with those used in the Linden meta-analysis. Thirty-one studies included only patients with MIs, and, in the remaining studies, patients either had received CABG surgery or had mixed manifestations of CHD. The sample totaled 8,988 patients. Males predominated with women comprising from 0 to 34 percent of study populations. Partners were involved in 21 studies, and patient groups in 26 studies. Interventions were provided by a multidisciplinary team in 22 studies and 15 included a mental health professional. On average, interventions lasted 28 weeks

(range 1-234 weeks) and included 18 sessions (range 2- 62). Distal outcomes of interest were cardiac mortality, recurrent MIs, CABG, and frequency of anginal episodes. Effects on biological cardiac risk factors, body weight, exercise, eating habits, and emotional distress (anxiety and depression) were also reported. This analysis is impressive for its meticulous attention to effect size estimation and statistical methods. Table 4D summarizes results for mortality, recurrent myocardial infarction, total cholesterol, and body weight.

Table 4D: Meta-Analysis of Controlled Clinical Trials of Psycho-educational Interventions for Coronary Artery Disease Patients (Dusseldorp, et al, 1999)

End Points	F/U	Study Design	No. Studies	N	ES
Mortality	< 1 yr.	RCT/CT	3	237	0.017
	1- 2 yr.		8	3767	-0.003
	> 2 yr.		6	1999	0.070*
MI	< 1 yr.		3	318	-0.27
	1- 2 yr.		15	6739	0.036*
	> 2 yr.		7	2209	0.065*
Total Cholesterol	< 1 yr.		4	812	0.299*
	1- 2 yr.		7	1206	0.49*
Body Wt.	< 1 yr.		5	812	0.299*
	1- 2 yr.		7	1206	0.249*

Notes: Effect sizes (ES) for mortality and morbidity were calculated using odds ratios. ESs for cholesterol and body weight were calculated using Cohen's d. ES were weighted for the sample sizes within each measurement period.
*One-tailed p-value significant at <0.025.

Statistically significant benefits of interventions were also found for smoking habits and systolic blood pressure, but not for anxiety or depression levels. The benefits of psycho-educational interventions were statistically significant for mortality when follow-up was 2 years or longer, for recurrent myocardial infarctions when follow-up was 1 year or longer; and for total cholesterol and body weight for both shorter and longer periods of follow-up. Overall, results indicated a 34 percent reduction in cardiac mortality and a 29 percent reduction in recurrence of myocardial infarctions.

Dusseldorp (Dusseldorp et al., 1999) concluded “programs that were successful on proximal targets such as systolic blood pressure, smoking behavior, physical exercise, and emotional distress were also successful on distal targets (cardiac mortality and recurrent MI)”. For example, they found a 36% reduction in MI recurrence in studies that were successful in achieving proximal targets (physiological and behavioral risk factors) compared to a 2% reduction in programs that were not successful.

Both Linden and Dusseldorp (Linden et al., 1996; Dusseldorp et al., 1999) concluded that psycho-educational programs should become intrinsic components of comprehensive cardiac rehabilitation and should target patient-specific needs for risk factor modification and reduction of emotional distress. Furthermore, Dusseldorp emphasized that psycho-educational programs should be theory-driven and focus on relationships between specific intervention components and changes in the proximal and distal endpoints.

C. Evidence from Recent Controlled Studies of Psychosocial Interventions

Only a small number of well-controlled clinical trials published since 1995 have examined the incremental effects of psychosocial interventions in patients with CHD. The characteristics of these studies are summarized in Table 5 and described more completely in Appendix A. They are listed in the chronological order of publication date starting with the most recent. Broadly, they fall into four clusters: (1) studies focused on patients with evidence of emotional distress at the time of entry into the study (ENRICHD 2003); (2) studies comparing two interventions of varying characteristics, duration, or intensity (Blumenthal et al., 1997; Johnston et al., 1999; Blumenthal et al., 2002); (3) studies testing the effectiveness of yoga (Mahajan et al., 1999; Manchanda et al., 2000)) or relaxation (van Dixhoorn et al., 1999; Lewin et al., 2002) as part of a broader lifestyle modification intervention; and (4) a miscellaneous group of studies that use a home-based nursing intervention (Frasure-Smith et al., 1997); a study of outpatient psychosocial group sessions that include both patients and spouses(Jones et al., 1996); or intense psychosocial interventions as a part of comprehensive cardiac rehabilitation (Denollet et al., 2001). While no one study is definitive, each provides important insights into the challenges of designing and evaluating the efficacy of psychosocial interventions in patients with CHD.

The outcomes identified in these studies include proximal measures such as improvements in adherence to medical regimens; changes in health-related behaviors such as diet, physical activity, smoking, and alcohol intake; and improvement in psychosocial function (depression, anxiety, anger, hostility, and social isolation). Intermediate measures include changes in cardiac risk factors (serum lipids, body weight, and blood pressure levels) and effects on perceived health and quality of life. Final outcomes include reduction in mortality or morbidity (frequency of angina pectoris, recurrent myocardial infarctions, the need for revascularization procedures such as coronary angioplasty, and stent placement or CABG).

1. Morbidity and Mortality Outcomes. ENRICHD was a large RCT (N=2481) that targeted patients with recent MIs who were depressed, had low perceived social support, or both. Individualized cognitive behavioral therapy coupled, if necessary, with antidepressive medications was provided during 6 months of treatment (median of 11 individual sessions with an interquartile

range of 6 to 19 sessions). This study is at least as important for its insights into the challenges to psychosocial research in patients with coronary heart disease as it is for its results.
The study was designed with considerable attention to detail and was implemented in 8 major teaching centers throughout the United States. Patients were enrolled within 28 days after their MIs and randomly assigned either to the intervention or usual care groups. It is important to emphasize that both the usual care group and the experimental group received early and aggressive cardiac care including the use of thrombolytics (37%), aspirin (84%), beta-blockers (72%), ACE inhibition (45%), and 39% of participants underwent early revascularization. No statement is made about subjects' concurrent participation in comprehensive cardiac rehabilitation programs, but it is likely that the majority participated in some kind of organized exercise and lifestyle program, since these comprised "usual care" at that time. The state-of-the-art intensive cardiac care received by all patients may well have narrowed differences in outcomes between the experimental and control groups.

Table 5 displays mortality and morbidity outcomes from the ENRICHD study. No statistically significant differences nor trends were found for mortality, recurrent MI, cardiac revascularization, or the composite outcome of death or recurrent MI between experimental and control groups. There was some evidence of a treatment group by sex interaction with more statistically significant results of the intervention occurring among men ($p=0.03$). However, the interaction was attenuated after adjustment for age and the Charlson comorbidity index ($p=0.20$) (Charlson et al., 1987). The authors speculate that these findings may be do to chance or may reflect true differences in response to treatment. This finding is also discussed below under the Montreal Heart Attack Readjustment Trial (M-HART) study.

Overall, the ENRICHD study did not demonstrate significant results. At the same time, it provides extremely valuable insights. One possible explanation of its failure to find statistically significant effects on recurrent MIs or mortality may be that all patients received comprehensive, state-of-the-art, cardiac care. Under these circumstances, marginal benefits of psychosocial interventions may well not further improve distal outcomes. Rather, their true value may be to reduce emotional stress and improve quality of life. Another possible explanation for the lack of significant results is that sensitization from enrollment and support provided by data collection may have provided positive impacts to the control as well as the experimental group. Further research is needed to understand gender differences in responses to psychosocial interventions, to determine optimal timing and durations of interventions, and to develop preventive strategies for reducing the impact of depression, anxiety, and low social support on coronary heart disease.

The next study displayed on Table 5, conducted by Blumenthal (Blumenthal et al., 1997; Blumenthal et al., 2002) compares stress management using a cognitive-social learning model in 16 weekly small-group sessions with exercise training (3 days per week for 16 weeks) and a usual care control group. Participants had documented CHD (prior MIs, CABG surgery or angioplasty, or severe coronary artery disease documented by coronary angiography) and had myocardial ischemia induced by mental stress or exercise. All had previously received cardiac rehabilitation. Subjects were randomly assigned to one of the two experimental groups. The control group was comprised of individuals who lived too far away to participate in the intervention. However, controls and experimental subjects were similar in their baseline clinical characteristics.