Journal of the American College of Cardiology Vol. 45, No. 5, 2005

Published by Elsevier Inc.
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2004.12.005

STATE-OF-THE-ART PAPER

The Epidemiology, Pathophysiology, and Management of Psychosocial Risk Factors in Cardiac Practice

The Emerging Field of Behavioral Cardiology

Alan Rozanski, MD, FACC,* James A. Blumenthal, PHD,† Karina W. Davidson, PHD,‡ Patrice G. Saab, PHD,§ Laura Kubzansky, PHD‖

New York, New York; Durham, North Carolina; Coral Gables, Florida; and Boston, Massachusetts

Observational studies indicate that psychologic factors strongly influence the course of coronary artery disease (CAD). In this review, we examine new epidemiologic evidence for the association between psychosocial risk factors and CAD, identify pathologic mechanisms that may be responsible for this association, and describe a paradigm for studying positive psychologic factors that may act as a buffer. Because psychosocial risk factors are highly prevalent and are associated with unhealthy lifestyles, we describe the potential role of cardiologists in managing such factors. Management approaches include routinely screening for psychosocial risk factors, referring patients with severe psychologic distress to behavioral specialists, and directly treating patients with milder forms of psychologic distress with brief targeted interventions. A number of behavioral interventions have been evaluated for their ability to reduce adverse cardiac events among patients presenting with psychosocial risk factors. Although the efficacy of stand-alone psychosocial interventions remains unclear, both exercise and multifactorial cardiac rehabilitation with psychosocial interventions have demonstrated a reduction in cardiac events. Furthermore, recent data suggest that psychopharmacologic interventions may also be effective. Despite these promising findings, clinical practice guidelines for managing psychosocial risk factors in cardiac practice are lacking. Thus, we review new approaches to improve the delivery of behavioral services and patient adherence to behavioral recommendations. These efforts are part of an emerging field of behavioral cardiology, which is based on the understanding that psychosocial and behavioral risk factors for CAD are not only highly interrelated, but also require a sophisticated health care delivery system to optimize their effectiveness. (J Am Coll Cardiol 2005;45:637–51)

Various lifestyle behaviors promote the development and clinical manifestations of coronary artery disease (CAD), including an unhealthy diet, physical inactivity, and smoking. Emotional factors and the experience of chronic stress also promote atherosclerosis and cardiac events, as previously reviewed (1). However, although cardiologists are accustomed to managing lifestyle behaviors such as overeating and physical inactivity, they are less likely to assess and treat psychosocial risk factors, perhaps because of their limited familiarity with effective strategies and recommendations. A potential dilemma is that, on the one hand, it is not the function of cardiologists to serve as mental health professionals; on the other hand, the strong and robust relationship between psychosocial risk factors and CAD suggests that cardiologists need to be proactive in addressing this important aspect of patient care. What then should the cardiologist's role be? Herein, we address the question of the role of the cardiologist by exploring various ways for effective clinical involvement. We also provide an update on the epidemiologic and pathophysiologic evidence linking psychosocial factors and the progression of CAD, emphasizing recent select studies rather than providing a comprehensive review, and suggesting areas for future research. Thus, this review is designed to provide an integrated understanding of how psychosocial risk factors influence the current and future practice of cardiology.

From the *Division of Cardiology, St Luke's-Roosevelt Hospital Center, and the Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York; †Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina; ‡Division of General Medicine, Columbia College of Physicians and Surgeons, and Cardiovascular Institute, Mount Sinai School of Medicine, New York, New York; §Department of Psychology, University of Miami, Coral Gables, Florida; and the ‖Department of Society, Human Development and Health, Harvard School of Public Health, Boston, Massachusetts.

Manuscript received September 29, 2004, accepted October 6, 2004.

EPIDEMIOLOGY

Psychosocial factors that promote atherosclerosis and adverse cardiac events can be divided into two general categories: emotional factors and chronic stressors. Emotional factors include affective disorders such as major depression and anxiety disorders as well as hostility and anger. Chronic stressors include factors such as low social support, low socioeconomic status, work stress, marital stress, and caregiver strain.

Abbreviations and Acronyms

CAD = coronary artery disease
HPA = hypothalamic-pituitary-adrenocorticol
MI = myocardial infarction
SES = socioeconomic status
SSRI = selective serotonin reuptake inhibitor
PET = positron emission tomography

Emotional factors. Among emotional factors, depression has been most studied in recent years. Depressive disorders vary from mild (subclinical) depressive symptoms to classic major depression. According to the *Diagnostic and Statistical Manual of Mental Disorders-4th edition*, depression is characterized by severely depressed mood and/or anhedonia (inability to take pleasure in life) that lasts for two weeks or more and is accompanied by significant functional impairment and somatic complaints. Research in this area has evaluated the effects of depression in both initially healthy individuals and in patients with known CAD. Depression plays a role in promoting CAD events in both cohorts (1). Most epidemiologic studies have primarily assessed depressive symptoms rather than major depression. Data indicate the presence of a strong consistent gradient between the level of depressive symptoms and the likelihood of adverse cardiac events, beginning at relatively low levels of depressive symptoms (2) (Fig. 1). Such data suggest that the pathophysiologic effects of depression may be triggered by even mild subclinical symptoms.

Major depression has been studied less commonly, partly because its identification requires a formal interview performed by trained professionals. However, consistent with the evidence derived from assessing symptom measures, major depression has also been found to be associated with a highly significant increase in adverse cardiac events, over and above that observed for the presence of depressive symptoms alone (3).

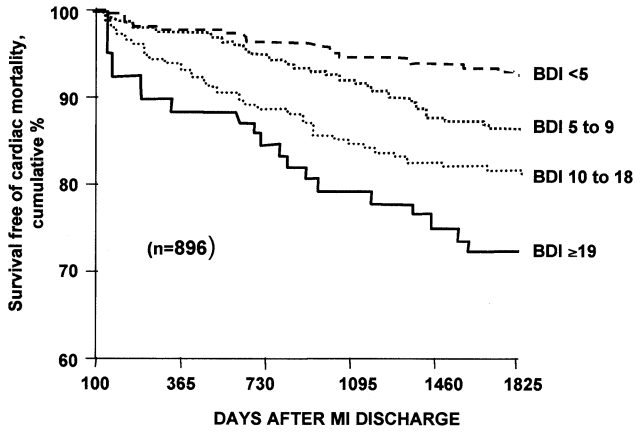

Figure 1. Post-myocardial infarction (MI) patients were recruited and assigned to one of four categories based on the Beck Depression Inventory (BDI), ranging from no depressive symptoms (BDI <5) to moderate to severe depressive symptoms (BDI ≥19). During the five-year follow-up period, a gradient relationship was observed between the magnitude of depressive symptoms and the frequency of deaths, with increased events occurring even in patients with mild depressive symptoms (BDI 5 to 9) (2).

Epidemiologic studies have also considered two other emotional factors relative to prognosis: anxiety and anger/hostility. Those that have examined the risk of cardiovascular outcomes associated with anxiety disorders are limited. Three large studies have shown a significant relationship between phobias and sudden cardiac death (1), but data linking other forms of anxiety to CAD are relatively scant or conflicting and more work is needed. Although hostility and chronic anger have been linked to cardiovascular outcomes in a number of studies, results have been generally mixed. Several factors may contribute to inconsistent findings in this area. Measures used to assess anger and hostility have varied widely, making it difficult to compare results. A recent study suggests that there is some self-denial and lack of self-awareness associated with self-reported hostility (4). This may be overcome by using a structured interview approach (4), but the approach has not been widely tested. Interestingly, a number of recent studies have demonstrated a relationship between hostility or anger and measurements of subclinical atherosclerosis (5–8) and also have linked hostility to progression of atherosclerosis during serial coronary angiography (9). Such findings suggest that hostility and chronic anger merit further study as potential psychosocial risk factors.

Chronic stressors. A variety of adverse life circumstances that promote chronic stress have been evaluated for their relationship to adverse cardiac outcomes. For instance, whereas the presence of high levels of social support is known to promote psychologic and physical well being, a consistent literature indicates that low levels of social support are health damaging. Although historically there has been little integration of differing theories of social support, there is increasing agreement that social support can be divided into two broad categories: social networks, which describe the size, structure, and frequency of contact with the network of people surrounding an individual; and functional support, which may be further divided into received social support, which highlights the type and amount of resources provided by the social network, and perceived social support, which focuses on the subjective satisfaction with available support or the perception that support would be available if needed. Received and perceived social support are often further delineated by type, including instrumental (e.g., help getting tangible tasks done), financial (economic support), informational (providing needed information), appraisal (help evaluating a situation), and emotional support (e.g., providing emotional support, feelings of being loved). The term "tangible support" also is used to describe types of support that are readily seen or quantified, such as instrumental or financial support. Both inadequate structural and functional support have been consistently linked to the occurrence of cardiac death and all-cause mortality in many studies (1). For example, low structural support has been associated with increased mor-

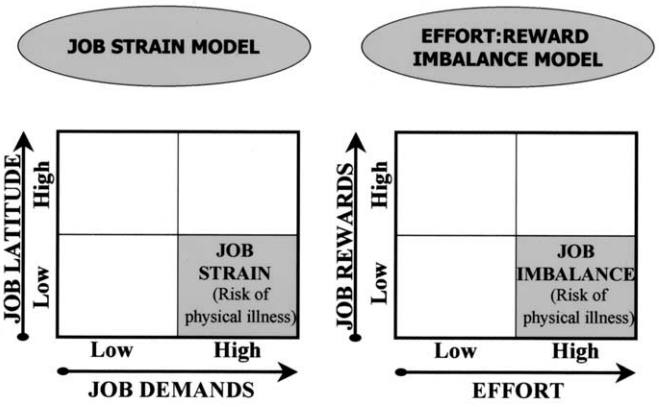

Figure 2. Two leading conceptual models of work stress. In the job strain model **(left)**, the amount of job demand and decision latitude determines the degree of job strain. High demand but low decision latitude characterizes job strain. In the effort-reward imbalance model **(right)**, increased job effort may result from either extrinsic demands or personal overcommitment, and "reward" may occur in the form of money, recognition, prestige, security, or career opportunities. High effort with low reward characterizes job imbalance.

tality within cardiac populations, including such factors as living alone (10), lacking a confidant (11), and suffering from social isolation (12). Furthermore, low emotional support (13), lack of available support (14), and low perceived social support (15) also have been associated with increased mortality, and preliminary evidence suggests that functional support may be more important than structured support in cardiac populations (16). As with depression, a strong and consistent inverse gradient consistently characterizes the relationship between the magnitude of social support and adverse clinical outcomes among both initially healthy subjects and those with known CAD (1).

Socioeconomic status (SES), generally characterized as a composite of factors such as occupational status, economic resources, education, and social status, has also attracted attention because longitudinal studies indicate a strong inverse gradient between SES level and adverse cardiac events. Low SES is characteristically accompanied by poorer health habits and higher frequencies of coronary risk factors, which account for half or less of the SES-CAD gradient (17). More financial hardship, poorer housing conditions, and increased levels of chronic stress also characterize low SES, as does poorer and more physically repetitious working conditions and less job security and job latitude (17). Thus, low SES can be viewed as a composite chronic psychologic stressor (18), a perspective that is supported by pathophysiologic evidence. Hypothalamic-pituitary-adrenal (HPA) dysfunction frequently accompanies chronic stress, and increased dysfunction is observed as SES levels decline. For example, this relationship has been documented by an inverse relationship between SES levels and measurements of cortisol variability (more variability being healthy) and measurements of central obesity (19).

Work stress is another form of chronic stress that has been increasingly studied for its potential adverse cardiovascular effects. Various aspects of work stress have been studied, but two leading epidemiologic models have received the most attention (Fig. 2). One model is the "job strain" model developed by Karasek et al. (20), in which individuals are evaluated according to two factors: "job demand" and "job latitude." Individuals with high job demand but low job latitude are categorized as being under "job strain," performing excessive routine work with a lack of creative outlets or a sense of rigid confinement. The other model is the effort-reward imbalance model developed by Siegrist et al. (21), but extensively evaluated so far only in Europe. In this model, job "effort" is compared with job "reward," with effort measured in terms of either extrinsic demands (e.g., having a demanding employer) or one's intrinsic pattern of responding to work demands, and rewards measured in terms of financial incentive, self-esteem, career opportunity, or security. Three lines of evidence link work stress to adverse clinical outcomes. First, an increasing epidemiologic literature indicates that job strain and effort-reward imbalance (22–25), as well as other work parameters (26–28), are associated with an increased frequency of adverse clinical outcomes. Both the job strain and effort-reward imbalance model appear comparable for their ability to predict adverse events (25). Second, work parameters, such as low job control, account for a substantial portion of the inverse gradient noted between SES status and cardiovascular disease (17). Third, several recent studies have also linked work stress to measures of subclinical atherosclerosis (29–31), with findings varying between genders and/or among ethnic groups (30,31). Because most epidemiologic studies that showed an association between work stress and adverse clinical outcomes have focused primarily on white men, prospective studies in women and other ethnic groups are needed.

Marital stress also represents a chronic stressor with apparent pathophysiologic effects (27,32,33). For instance, Orth-Gomer et al. (32) reported that following myocardial infarction (MI), women with concomitant marital stress had a higher frequency of recurrent cardiac events during a five-year follow-up compared to those with less marital stress. These data are supported by a recent study that found a higher prevalence of subclinical atherosclerosis, and accelerated progression over time, among healthy women reporting marital dissatisfaction (Fig. 3) (34), supporting the assertion that marital stress is atherogenic.

Caregiving strain is an increasingly prevalent stressor that has recently been studied for potential cardiovascular sequelae (35,36). In the Nurses' Health Study, caregiving for an ill or disabled spouse was associated with a nearly twofold adjusted risk ratio for experiencing an adverse cardiac event during a four-year follow-up period (35). However, this report did not stratify patients based on the emotional appraisal of their caregiving experience. Because other research indicates that highly meaningful and altruistic experiences can be of psychologic benefit (37), it is possible that the effects of caregiving are dependent on the meaning

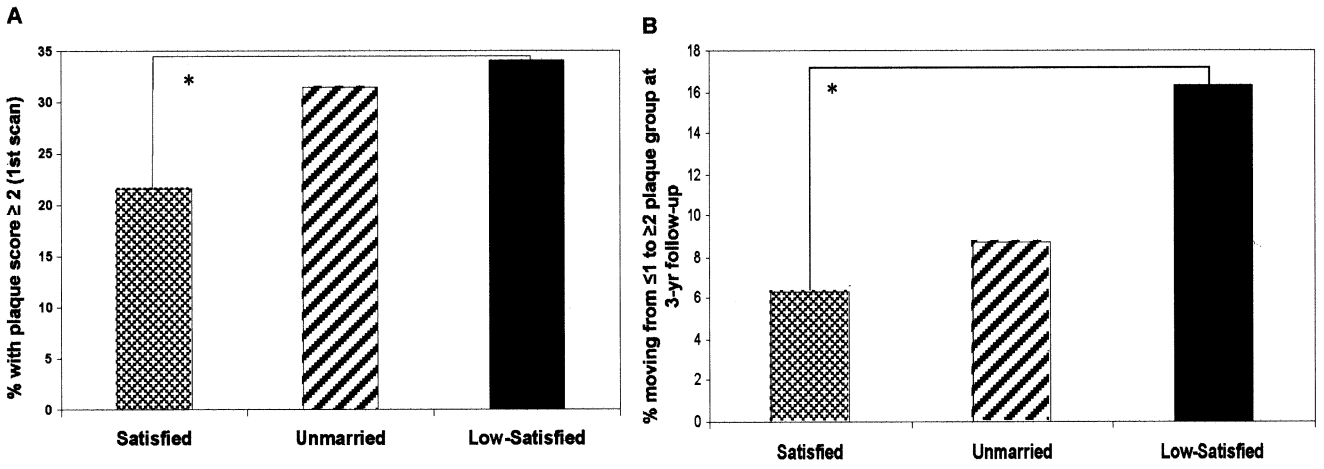

Figure 3. Postmenopausal females (n = 390) were divided into those in satisfying marriages **(left of each panel)**, unmarried **(middle of each panel)**, and in low-satisfying marriages **(right of each panel)**. After 11 years of follow-up, the women in satisfied marriages had the lowest and the women in unsatisfying marriages had the highest percentage of significant plaque (left panel). Serial carotid ultrasonography was performed after three years in a subgroup of this patient population (n = 206) and revealed that women in low-satisfying marriages also had the greatest progression of plaque during follow-up (right panel). Reprinted with permission from Gallo et al. Psychosom Med 2003;65:952–62 (34). *Groups differ significantly at $p < 0.05$.

attached to such activities. In support, another study observed that when caregivers were divided into those with and without a sense of emotional strain during caregiving, only those reporting strain had an increased death rate during follow-up (36).

Clustering of psychosocial risk factors. Although we have discussed emotional factors and chronic stressors as separate entities, they frequently cluster. For example, individuals who experience job strain tend to have higher rates of depression compared to those who do not report strain (38). The strong overlap between chronic stress and emotional factors suggests that any life situation that has the capacity to evoke chronic negative emotional responses may promote heart disease. For instance, a recent study found that childhood maltreatment (39) was associated with a significant increase in both depression and cardiovascular disease among adult women. Similarly, exposures ranging from the death of a child to adverse wartime experiences may potentially affect the risk of CAD development and should be candidates for study.

Comparison of psychosocial risk factors with traditional CAD risk factors. The characterization of psychosocial risk factors as "major" CAD risk factors has been debated. However, more consistent and reproducible outcome studies confirm that psychosocial risk factors such as depression, poor social support, and low SES represent potent CAD risk factors. Furthermore, many reported studies now link psychosocial risk factors to the presence of subclinical atherosclerosis or its progression, as measured by carotid ultrasonography (5–8,29–31,34,40,41). Meta-analyses of psychosocial studies have been limited by the use of varying measures and inconsistent methods for calculating risk ratios. However, a recent meta-analysis of outcomes associated with depressive symptoms indicates a relative risk that is comparable to those noted for traditional CAD risk factors reported from the Framingham study (Fig. 4) (3,42).

This observation is supported by the recently reported INTERHEART case-control study, which uniquely assessed eight coronary risk factors and a composite index of psychosocial factors within a single standardized international population of 12,461 acute post-MI patients and 14,637 matched controls gathered from 52 countries (43). The psychologic index was necessarily limited by the study's design to either brief or even single-item assessments of depression, locus of control, perceived stress at home or

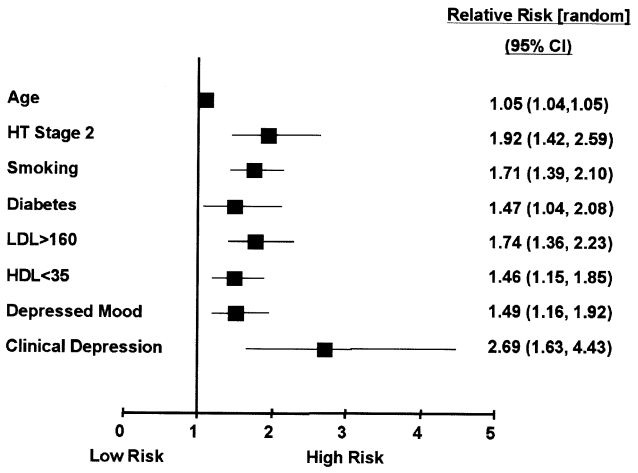

Figure 4. The risk ratios for traditional risk factors reported for men in the Framingham study (28). The risk ratios for depressive symptoms and clinical depression are from a recent meta-analysis by Rugulies et al. (3). The risk ratios for traditional risk factors are for death due to cardiac disease, myocardial infarction, coronary artery insufficiency, and development of angina. For depressive symptoms and clinical depression, the risk ratios are for death due to cardiac disease and myocardial infarction. CI = confidence interval; HT = hypertension; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

Risk Factor	Gender	Cont %	Case %	OR (99%CI)	PAR (99%CI)
Curr Smok	female	9.3	20.1	2.86 (2.36,3.48)	15.8 (12.9, 19.3)
	male	33.0	53.1	3.05 (2.78,3.33)	44.0 (40.9, 47.2)
Diabetes	female	7.9	25.5	4.26 (3.51,5.18)	19.1 (16.8, 21.7)
	male	7.4	16.2	2.67 (2.36,3.02)	10.1 (8.9, 11.4)
Hypertension	female	28.3	53.0	2.95 (2.57,3.39)	35.8 (32.1, 39.6)
	male	19.7	34.6	2.32 (2.12,2.53)	19.5 (17.7, 21.5)
Abd Obesity	female	33.3	45.6	2.26 (1.90,2.68)	35.9 (28.9, 43.6)
	male	33.3	46.5	2.24 (2.03,2.47)	32.1 (28.0, 36.5)
PS Index	female	-	-	3.49 (2.41,5.04)	40.0 (28.6, 52.6)
	male	-	-	2.58 (2.11,3.14)	25.3 (18.2, 34.0)
Fruits/Veg	female	50.3	39.4	0.58 (0.48,0.71)	17.8 (12.9, 24.1)
	male	39.6	34.7	0.74 (0.66,0.83)	10.3 (6.9, 15.2)
Exercise	female	16.5	9.3	0.48 (0.39,0.59)	37.3 (26.1, 50.0)
	male	20.3	15.8	0.77 (0.69,0.85)	22.9 (16.9, 30.2)
Alcohol	female	11.2	6.3	0.41 (0.32,0.53)	46.9 (34.3, 60.0)
	male	29.1	29.6	0.88 (0.81,0.96)	10.5 (6.1, 17.5)
ApoB/ApoA-1 Ratio	female	14.1	27.0	4.42 (3.43,5.70)	52.1 (44.0, 60.2)
	male	21.9	35.5	3.76 (3.23,4.38)	53.8 (48.3, 59.2)

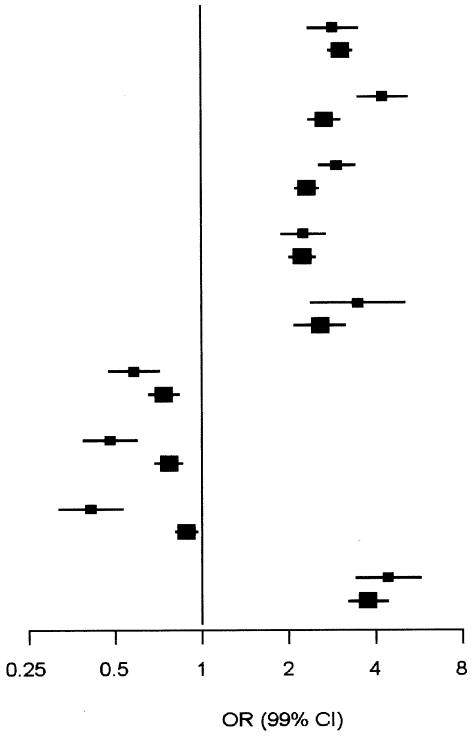

Figure 5. Risk of acute myocardial infarction for men and women for each of nine coronary artery disease (CAD) risk factors evaluated in the international INTERHEART case-control study. Results are adjusted for age, gender, and geographic location. The prevalence of each CAD risk factor is presented for controls and cases in the third and fourth columns; prevalence rates are not calculated for the psychosocial (PS) index as it is derived from a statistical model. Reprinted with permission from Yusuf et al. Lancet 2004;364:937–52 (43). Abd = abdominal; CI = confidence interval; Curr = current; OR = odds ratio; PAR = population-attributable risk; Smok = smoking; Veg = vegetables.

work, moderate to severe financial stress, and experience of adverse life events. Nevertheless, the odds ratios and population-attributable risk for acute MI by this limited subjective measure of psychosocial stress was substantial, comparable to those noted for other major CAD risk factors (Fig. 5). In addition, this psychosocial index remained a robust predictor of MI independent of geographic or ethnic context (26).

Moreover, for a variety of reasons, the risk associated with psychosocial factors may actually be greater than such statistical evidence suggests. First, behavioral and metabolic risk factors tend to aggregate disproportionately among individuals with psychosocial stress (1). However, this potentially powerful effect is reduced because of the statistical convention to adjust psychosocial risk ratios for behavioral and metabolic risk factors. Second, because measures of psychosocial stress may be imprecise, they may underestimate the relationship between psychosocial stress and CAD outcomes. For example, although depressive disorders are generally episodic, the scales used to measure self-reported depressive symptoms assess only the presence of relatively current depressive symptoms. Thus, it is not surprising to find that the chronicity and level of depressive symptoms are together more strongly associated with measures of atherosclerosis compared with symptom levels alone (40). Third, psychosocial risk factors tend to aggregate. Such clustering is associated with an increased likelihood of cardiac events (1) and more subclinical atherosclerosis (8,9).

Future epidemiologic directions. In contrast to the data linking negative emotional states and chronic stress to CAD, the potential protective effect of positive psychologic factors has not been extensively investigated. Building on work in other areas, we suggest that one potential direction for clinical investigations in this neglected area could be to explore the notion of flexibility as it relates to mental health (44). In the physical domain, the ability to demonstrate variability in response to stressors may be associated with better clinical outcomes (45). Similarly, having the capacity to respond to situations in a variety of different ways (i.e., to flexibly adapt one's emotional and coping responses to any given situation) may be associated with better mental health. We consider three psychologic components that may be central to developing emotional and coping flexibility (Fig. 6). One key component is "vitality," which refers to the presence of energy and enthusiasm and a sense of aliveness (46). It is characterized by two positive emotions, joy and interest, and is fueled by both a sense of purpose and a sense of self-worth. Vitality may be considered both restorative and regenerative and, as such, connotes a sense of freshness and positive excitement. Conversely, when someone lacks vitality, the likelihood of becoming excited and investing energy toward goals and in interactions with others is

JACC Vol. 45, No. 5, 2005
March 1, 2005:637–51

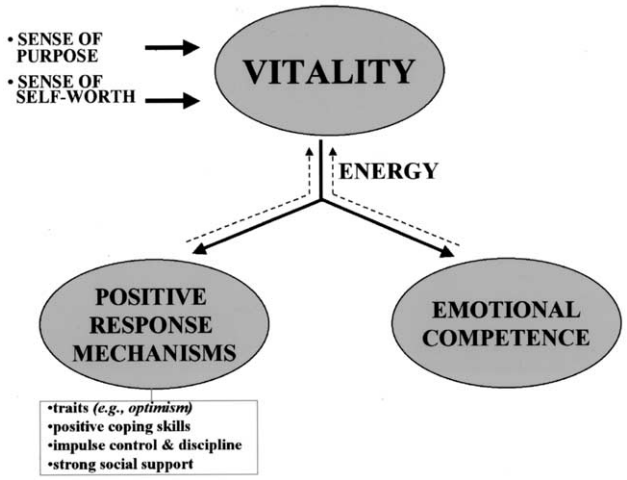

Figure 6. The mental health paradigm in which individuals who have a strong sense of purpose coupled with a sense of self-worth derive benefit in terms of a greater sense of vitality. The positive emotion associated with vitality provides energy needed to develop and maintain greater emotional competence and positive response mechanisms. In turn, the presence of emotional competence and positive response mechanisms provide a stabilizing force for maintaining a sense of vitality.

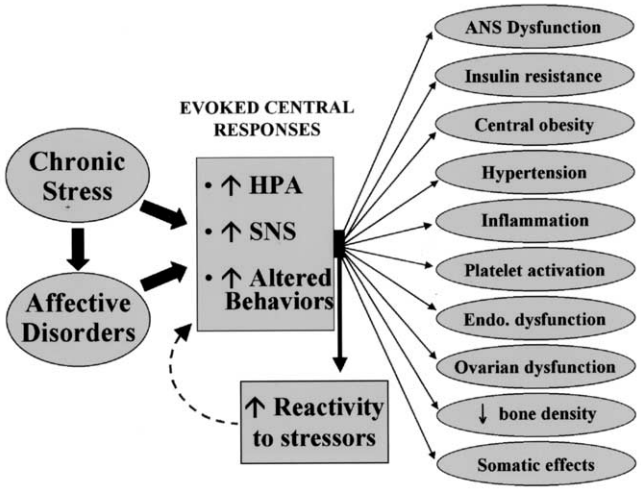

Figure 7. Pathophysiologic mechanisms by which chronic stress and affective disorders, such as depression, appear to promote atherosclerosis. These stressors activate the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) and affect behaviors. Multiple adverse peripheral effects can ensue from this neuroendocrine, sympathetic, and behavioral activation, as shown. The neuroendocrine and neuroplastic changes emanating from these stressors can also induce a state of heightened physiologic responsivity to acute stress which may interact with chronic stressors to cause more adverse effects. ANS = autonomic nervous system; Endo. = endothelial.

diminished. The availability of this energy promotes two key adaptive responses (which may in turn promote vitality): development of various positive response mechanisms (such as patience, discipline, and maintaining friendships) and emotional competence, or the ability to regulate emotions across a range of situations (47). An important aspect of emotional competence is the ability to either enhance or suppress emotional expression, a trait that may be termed "emotional flexibility," as discussed by Bonanno et al. (48) and others.

From this perspective, depression and various exhaustive states can be viewed as a long-term deficit in vitality and an escalating inability to be flexible and responsive to life and daily challenges. Anxiety and anger can also be viewed as emotionally inflexible responses, with the constant negative emotions dissipating energy and taxing positive coping mechanisms. Job strain is also an excellent example of a situation that can drain energy and vitality. For example, a recent study has demonstrated that chronic job strain can lead to exhaustion and an inability to unwind after work (28). Such sequelae can increase the risk for adverse cardiac events (49). By contrast, professional, marital, interpersonal, and avocational activities that require effort but that also promote joy and interest serve to preserve vitality and flexibility.

Early emotional theorists suggested that positive emotions such as joy might provide recuperative power. Support for this concept is provided by recent data showing that positive psychologic factors can dampen physiologic reactivity to negative emotional stimuli (50). Similarly, individuals who score high on the trait of forgiveness (51) or who are provided with social support (52) demonstrate lower heart rate and blood pressure elevations during laboratory mental stress. Other data indicate that positive emotions can enhance immune function (53). Evaluation of the impact of positive psychologic factors upon clinical outcomes is also limited and recent. In the largest study to date, Kubzansky et al. (54) conducted a 10-year follow-up study of 1,306 men from the Normative Aging Study, who were assessed for optimistic versus pessimistic "explanatory style" (i.e., how one explains the causes of bad events). Stratification of individuals according to optimistic, neutral, and pessimistic explanatory styles revealed a gradient relationship between levels of optimism and cardiac outcomes, with optimism halving the risk for cardiac events. A separate measure of dispositional optimism has been linked to more favorable outcomes following bypass surgery (55). A strong relationship has also been noted between positive emotions and longevity in the long-term follow-up of nuns whose diaries in early adult life were assessed for positive emotional content (56). Such findings suggest the value of further exploring positive psychologic factors that may promote health or protect against disease.

PATHOPHYSIOLOGY

Emotional disturbance and chronic stress can have a profound impact on the central nervous system, including increased output from the sympathetic nervous system and the HPA axis. Chronic stimulation from these central outputs can induce a wide variety of pathophysiologic responses, as displayed in Figure 7. Depression has been particularly studied in this regard. Chronic stimulation of the HPA axis by depression frequently results in hypercortisolemia, blunted HPA activity, and diminished feedback control, as evidenced by nonsuppression of cortisol secretion

following dexamethasone suppression. When present, hypercortisolemia is associated with suppression of growth and sex hormones. Heightened stimulation of the sympathetic nervous system is also common in depression and is associated with higher concentrations of circulating plasma norepinephrine and an increase in total body sympathetic activity (57). As a consequence, depressed patients commonly manifest higher resting heart rates than healthy controls and exhibit autonomic nervous system dysfunction, including diminished heart rate variability, baroreflex dysfunction, and increased QT variability (57).

Hypercortisolemia, in association with blunted growth and sex hormones, promotes central obesity (58), which may occur despite overall weight loss, and an increase in peripheral and portal fatty acids. These metabolic changes also contribute to more insulin resistance and diabetes among depressed subjects, and a higher frequency of diabetic complications (59). Depressed patients manifest substantial platelet abnormalities, including increased concentrations of beta-thromboglobulin and platelet factor 4 and increased concentration of functional glycoprotein IIb/IIIa receptors. In addition, there is evidence that depression is associated with a hyperactive 5-hydroxytryptamine (5-HT) transporter$_{2A}$ receptor signal transduction system and, relatedly, increased responsiveness of platelets to serotonin (60). Other recent studies indicate that depression is associated with increases in C-reactive protein, interleukin-6, tumor necrosis factor, and other inflammatory proteins (61). The potential mechanism for this association may be complex, involving not only stimulation of the HPA axis and the sympathetic nervous system but also potential synergy induced by peripheral effects, such as hyperglycemia (62). More recent data indicate that depression is associated with a heightened incidence of endothelial dysfunction among various cohorts, including young and otherwise healthy depressed patients (63). Finally, depression is also associated with decreased bone mineralization, which is the result of increased cortisol and decreased concentrations of growth and sex hormone concentrations, and probable interaction with local inflammatory proteins. Thus, depression is capable of inducing virtually the full spectrum of pathophysiologic effects noted in Figure 6.

Future research directions. Because other psychosocial risk factors have not yet been investigated as extensively as depression, the full spectrum of their pathophysiologic effects requires further study. In addition, we highlight three areas where clinical observations provide new research directions. First, the observation that cardiac event rates increase when psychosocial risk factors cluster has focused interest on explanatory mechanisms. Whether this increase is due to greater overall stress or the synergistic effects of stressors that evoke different pathophysiologies needs to be determined. The latter possibility is supported by recent data indicating distinct pathophysiologic differences according to the exposure of Watanabe Heritable Hyperlipidemic rabbits to two different chronic stressors: an unstable social environment versus social isolation. Both forms of stress produced more atherosclerosis compared to a control group, but the groups exposed to different forms of stress exhibited different metabolic consequences and patterns of accrued atherosclerosis (64).

Second, various data suggest links between chronic psychologic distress and certain adverse behaviors, such as overeating (65,66). New technologies that study brain function suggest that such links may be centrally mediated. Immunohistochemistry has been used to identify an anatomic chronic stress response network, localized to several specific brain centers, in a rat model of chronic stress (67). Whereas glucocorticoids help end acute stress responses by exerting negative feedback upon the HPA axis, glucocorticoids occupy central glucocorticoid receptors during chronic stress, with resultant activation of the chronic stress response network, including continued glucocorticoid production, in these experimental animals (66,67). This combination of chronic stress and high glucocorticoid levels appears to stimulate a preferential desire to ingest sweet and fatty foods (66). Further study indicates that glucocorticoids affect dopaminergic transmission in areas of the brain associated with motivation and reward (68). Positron emission tomography (PET) has been used to identify the presence of diminished dopamine D_2 binding potential within midbrain systems under conditions of chronic stress in the cynomolgus monkey (69). In humans, PET studies have revealed that this area is involved specifically in food motivation (70), and that, like stressed monkeys, obese individuals also have decreased D_2 receptor function in this same reward area of the brain, varying inversely with body mass index (71).

Third, data suggest that enhanced physiologic reactivity to acute stress is clinically important, linked to subclinical atherosclerosis (72,73) and interacting with known psychosocial risk factors to produce greater degrees of subclinical atherosclerosis (41). Clinical observations suggest that chronic stress, per se, may be an important cause for such enhanced physiologic reactivity (as exemplified in Fig. 7). For instance, depressed (57), hostile (74), and low-SES subjects (19) all manifest exaggerated physiologic responses to acute stressors. These observations are complemented by experimental animal studies that indicate that repeated exposure to a chronic stressor results in increased adrenal and pressor responses to acute novel stressors (66,75). Other animal research indicates that the mimicking of chronic stress by experimentally elevating glucocorticoids within the brain produces enhanced adrenocorticotropic hormone responses (76) and increases in both baseline arterial blood pressure (77) and blood pressure and heart rate responses to an acute novel stressor (78). Research that further elucidates the neurophysiology of the chronic stress circuitry, and the mechanisms of neuroplasticity that produce long-term stress-induced changes in the control of physiologic functions, could pave the way for understanding

JACC Vol. 45, No. 5, 2005
March 1, 2005:637–51

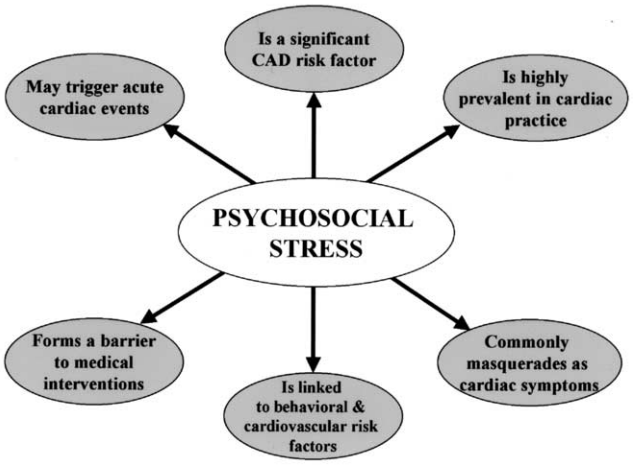

Figure 8. Six reasons that promote interest in the evaluation and management of psychosocial stress in cardiac practice.

and mitigating the adverse effects of chronic stress in cardiovascular disease.

FACTORS LINKING PSYCHOSOCIAL RISK FACTORS AND CARDIAC PRACTICE

As illustrated in Figure 8, there are important reasons that cardiologists should be interested and skilled in recognizing and managing psychosocial risk factors in practice. We have already discussed two compelling reasons: psychosocial risk factors are strongly linked to the development of adverse cardiac events and cluster with adverse behaviors that promote CAD. We now discuss four additional factors that link psychosocial risk factors to cardiac practice.

First, psychosocial risk factors are highly prevalent within cardiac populations. For instance, the National Comorbidity Survey (79) assessed the frequency of serious psychiatric illness and found that the 12-month and lifetime prevalence rates of certain depressive and anxiety disorders, as well as serious substance abuse, were remarkably high, with 48% reporting at least one of these disorders in their lifetime. To compare these prevalence rates with those noted in general medical and CAD populations, it is also useful to examine point prevalence rates, the percentage of persons with psychiatric disorders at a specific point in time. For example, the prevalence rate of major depression disorder in the National Comorbidity Survey was approximately 5%, compared with a prevalence of 15% or greater in populations with CAD (1). In addition, at least another 15% to 20% of patients with cardiac disease exhibit depressive symptoms that do not necessarily meet criteria for major depressive disorder (1). Similarly, anxiety disorders, such as phobic anxiety or panic disorder, are relatively common among patients with CAD. As a consequence, cardiologists are likely to encounter a significant number of psychologically distressed patients in clinical practice.

Second, psychologic distress commonly presents as symptoms of cardiac disease in clinical practice. Notably, whereas certain psychosocial risk factors such as depression and anxiety can present with either psychologic and/or somatic manifestations, it is those with primarily somatic symptoms, such as chest pain or palpitations, who seek medical evaluation preferentially, thus exacerbating this tendency. In fact, estimates indicate that more than three-fourths of patients with major depression or panic disorder seen in primary care settings present with somatic complaints only (80,81). Because chest pain and palpitations are common somatic complaints, a high proportion of patients presenting with such symptoms in medical settings have psychologic distress in the absence of objective evidence of organic heart disease. For instance, whereas panic disorder occurs in <4% of the general population (79), it occurs in more than 15% to 20% of patients presenting with chest pain complaints in emergency departments, reflecting the high rate of medical care use by these patients (82). Physician awareness of these relationships is important, because psychologic distress is frequently underdiagnosed in medical evaluations of cardiac symptoms. For example, in a prospective evaluation of 441 patients presenting to a cardiac care emergency department with chest pain and evaluated blindly for psychiatric diagnosis, approximately 25% had panic disorder, but in 98% of the patients with panic disorder, the diagnosis was missed by the cardiologists in the cardiac care emergency department (83).

Third, psychosocial risk factors can adversely affect treatment adherence. For instance, a meta-analysis has demonstrated that patients with depression were three times more likely to be nonadherent with treatment recommendations (84). Similarly, a recent meta-analysis of 122 social support studies (85) has revealed that patient adherence is strongly influenced by the magnitude of adequate functional or structural social support. However, although it seems intuitively reasonable, it has not yet been conclusively demonstrated that alleviation of psychologic distress improves treatment adherence.

Fourth, acute psychologic stress shapes the course of cardiac disease in both positive and negative fashion. On the one hand, acute emotional stress represents an important trigger for exacerbating pathophysiologic processes, ranging from the induction of endothelial dysfunction to the precipitation of myocardial ischemia. The latter occurs during laboratory mental stress in approximately 50% of patients with exercise-induced ischemia (1). On the other hand, patients' experience of acute cardiac events and premonitory symptoms, such as angina pectoris, is itself a form of acute psychologic stress that can sometimes transform patients' lives by signaling a need for personal reflection, inducing a reevaluation of values and/or shifting the perspective of time from "years since birth" to "years remaining" (86). Such events may cause patients to be more receptive to adopting new attitudes and be more successful in altering unhealthy behaviors, as indicated by various studies. Because cardiologists commonly treat patients who experience acute life-threatening events and who may be more receptive to

physician advice, cardiologists may be ideally positioned to initiate these interventions.

IDENTIFICATION AND MANAGEMENT OF PSYCHOSOCIAL RISK FACTORS

Given that psychologic distress is often first detected in clinical health care settings, the cardiologist can play a critical role in the identification and management of psychosocial risk factors. This role can be divided into three broad categories: screening for psychosocial risk factors, referring of appropriate patients to behavioral health care providers, and managing milder forms of psychologic distress in the context of clinical practice.

Screening for psychosocial risk factors. Cardiologists can increase the detection of psychosocial risk factors by systematically screening for them. Querying patients about psychosocial risk factors conveys the message that these factors are important and relevant to providing optimal care. Screening can be accomplished by structured interviews and/or by validated questionnaires. Although questionnaire measures are easily administered and objectively scored, interviews allow greater flexibility and offer richer clinical information than that provided by written inventories. Because cardiologists are accustomed to obtaining medical histories through a brief review of systems, additional questions about psychosocial risk factors could easily be incorporated into such assessment. These questions should cover three kinds of experiences that may help to identify psychologic distress: 1) emotional factors, such as depression, anxiety, and anger; 2) chronic stressors, such as work strain and home stress; and 3) somatic complaints that may be stress-related, such as fatigue and disrupted sleep. Some questions for screening patients' psychosocial status are suggested in Table 1.

The identification of emotional distress can often be challenging in the medical setting. Hallmarks of disorders such as depression (e.g., changes in appetite and/or significant changes in weight) and panic disorder (e.g., palpitations, and/or shortness of breath) can indicate either a cardiac or psychiatric condition. Inaccuracy in determining the cause of such symptoms can result in misdiagnosis and mistreatment. Moreover, because physicians' time is often limited, psychosocial problems need to be assessed relatively quickly and efficiently. However, research suggests that such skills can be learned and effectively implemented. Finally, following acute events or surgical interventions, cardiac patients may feel especially vulnerable and helpless. During such times, inquiries about mental health and psychosocial functioning can be perceived as highly threatening, and may elicit defensiveness, resentment, and denial. The cardiologist can help preempt this response by openly addressing the patient's concerns and establishing rapport.

Referring patients to behavioral health care providers. The benefits of screening for psychosocial risk factors will be realized only if proper identification leads to appropriate intervention and follow-up. Patients with apparently significant psychologic distress or behavioral maladjustment should be referred to appropriate specialists for counseling and/or psychiatric treatment (87). Thus, part of the cardiologist's role in managing psychologic distress may be the development of a referral network of specialists. However, close follow-up of patients even after referral is highly advisable because early dropout from both pharmacotherapy and psychotherapy is common (87).

Table 1. Suggested Open-Ended Questions to Screen for Psychosocial Risk Factors

1. How would you describe your energy level?
2. How have you been sleeping?
3. How has your mood been recently?
4. What kind of pressure have you been under at work or at home?
5. What do you do to unwind after work or at the end of the day? Do you have difficulty unwinding?
6. Who do you turn to for support?
7. Are there any personal issues that we have not covered that you would like to share with me?

Managing psychologic distress in clinical practice. Subclinical presentations of psychologic distress, such as minor depression, work stress, inability to relax, and difficulty sleeping, may be appropriately handled in routine cardiac practice. Tools that are readily available to cardiologists for direct management of psychosocial risk factors are practical behavioral interventions, as outlined in Table 2. Cardiologists are familiar with some of these interventions, such as exercise and nutritional counseling, but physicians may underestimate the potential effectiveness of such counseling techniques (88) and the other tools listed in Table 2.

As for the treatment of obesity, poor nutritional habits, smoking, and sedentary lifestyles, patient non-adherence can complicate physician attempts to modify psychosocial risk factors. Helping patients to initiate behavior change is challenging, requiring mastery of techniques and approaches derived from psychology and the behavioral and social sciences, and recommendations stemming from the American Heart Association's Expert Panel on Compliance (89). Representative techniques that cardiologists can use to promote patient adherence are summarized in Table 3. For example, the use of "micro goals" for poorly adherent patients, such as those who may claim to not have the time, willingness, or belief that they can exercise, can be applied. In such patients, initiating a modest exercise program requiring only 5 to 10 min of walking per day may be useful, increasing exercise at a measured pace. All new behaviors represent transitional intentional practices that initially require more intense physician monitoring and personal feedback before becoming more automatic and habitual. Because no single approach is effective for all patients, mastery of multiple approaches and diverse strategies may improve behavioral adherence rates typically reported in clinical practice.

Although mastery of techniques to promote adherence may be highly desirable, these add to the time, diligence,

JACC Vol. 45, No. 5, 2005
March 1, 2005:637–51

Table 2. Behavioral and Medical Interventions for Psychosocial Risk Factors

Type of Intervention	Targeted Condition	Intensity of Intervention	
		Less Intense*	More Intense
Exercise training	Psychologic distress	Exercise prescription plus general guidelines	Supervised exercise
Nutritional counseling	Management of stress by overeating	Provide nutritional advice	Supervised dietary instruction, weight management, and behavior modification
Relaxation training	General stress and stress caused by specific situations	Advise patient to initiate relaxation training; provide audiotapes, videotapes, or instructional scripts	Teach muscle relaxation, imagery, autogenic training, diaphragmatic breathing, or biofeedback.
Stress management	General stress and stress caused by specific situations	Recommend vacations, hobbies, yoga, relaxing music, pets, or pleasurable activities	Teach behavioral strategies (e.g., problem-solving, self-monitoring, appropriate goal-setting, relapse-prevention techniques)
Social support	Poor structural or functional support	Provide specific social suggestions (e.g., join walking groups or engage in socially altruistic activities)	Use staff as a support base, enroll patient in support group, or facilitate family involvement
Health information	Specific stress situations (e.g., at work or home) or low health literacy	Provide situation-specific information in form of book, articles, pamphlet, audiotapes, videotapes, or Web sites	Discuss and answer patient questions regarding materials related to health and treatment recommendations

*Most amenable to direct cardiologist management.

training, and complexity required to manage multiple risk factors in cardiac practice. As a consequence, cardiologists may rely on a nurse or other qualified office personnel, an organized community or hospital program, and/or complementary instructional material to assist them in managing psychosocial risk factors, particularly for the more intense interventions noted in Table 3.

Table 3. Steps to Promote Effective Adherence to Behavioral Suggestions

1. Use clear and effective communication, including making recommendations that are as specific and simple as possible.
2. Schedule follow-up visits to check adherence, especially during the early practice phase, as opposed to the later, more ingrained habit phase.
3. Provide a motivating rationale for the patient's treatment regimen, with consideration of explanations that befit the patient's health literacy.
4. Follow oral suggestions with written ones to reinforce the cardiologist's message and aid memory and concentration.
5. Begin with "micro" goals for patients who are resistant to behavior change or who have fewer available personal resources.
6. Help patients establish realistic goals and expectations.
7. Involve patients in tailoring behavioral suggestions rather than dictating change.
8. Suggest activities that are commensurate with patients' abilities and that provide positive feedback (factors that tend to promote a sense of pleasure).
9. Openly and candidly explore potential patient barriers to adherence (such as lack of personal motivation, time, family support, facilities, or knowledge; fears; job, home or other pressures; and cultural issues) and assist patients with problem-solving and developing strategies (e.g., self-monitoring approaches, written agreements, and relapse prevention) at the time of recommendations.
10. Refer patients with poor structural or functional social support to programs or activities that will enhance adherence by providing social support.

Results of behavior and psychopharmacologic intervention trials. A variety of behavioral and psychosocial interventions have been implemented in cardiac patients, including exercise training, psychosocial interventions as part of multifactorial risk factor modification, organized psychosocial interventions designed to reduce psychosocial risk factors, and psychopharmacotherapy. The results of cardiac outcome studies involving these approaches are reviewed here.

Exercise is commonly recommended by cardiologists to promote both primary and secondary CAD prevention, but evidence suggests that exercise may also modify psychosocial risk factors, including depression. For instance, cross-sectional studies of both medical populations and healthy cohorts have consistently demonstrated lower depression scores among those who are most active. The ability of exercise to reduce depression also has been demonstrated in randomized controlled trials, although many of these studies have had methodologic limitations (90). More recently, a randomized controlled comparison between antidepressant medication versus exercise was performed in a group of 156 men and women with depression (91). After 16 weeks, exercise was just as effective as sertraline hydrochloride in reducing depressive symptoms. Follow-up of these patients after six months revealed a low rate of relapse in the exercise group (92). Although the study may have had some methodologic limitations, these intriguing data suggest the need for additional prospective trials.

The utility of organized psychosocial interventions has been most commonly assessed by evaluating their incremental impact upon prognosis among patients referred to formal cardiac rehabilitation programs. For instance, Linden et al. (93) performed a meta-analysis of 23 randomized controlled

trials that evaluated the impact associated with adding psychosocial interventions to standard cardiac rehabilitation regimens. During the first two years of follow-up, lack of psychosocial intervention was associated with greater rates for mortality and recurrent infarction. In a separate meta-analysis of psychosocial interventions and cardiac rehabilitation, Dusseldorp et al. (94) observed differential effects depending on the efficacy of the psychosocial intervention. When psychologic distress was reduced, the odds ratio for mortality and recurrent MI also was reduced, but when no reduction in psychologic stress occurred, mortality was higher in intervention than in control rehabilitation patients. Along these lines, recent data suggest that the failure to respond to psychosocial interventions may identify a subgroup of patients who are particularly susceptible to adverse clinical events (95).

The utility of stand-alone psychosocial interventions has also been evaluated in five large-scale behavioral intervention trials in cardiac patients, with mixed results. The Recurrent Coronary Prevention Project Study was a group therapy behavior modification program that succeeded in decreasing both Type A behavior and negative affect and also reduced the rates of cardiovascular mortality and nonfatal MI (96). The Ischemic Heart Disease study was a second successful intervention trial, using a unique home-based stress-reduction program to reduce cardiac events (97). Two other large trials did not reduce subsequent cardiac events in the treatment groups, but neither intervention successfully reduced psychosocial distress (98,99). In fact, one of these trials was a follow-up of the approach used in the Ischemic Heart Disease trial, and secondary analysis of the data from this trial revealed that the results could be attributed to inadequate psychologic intervention in the experimental group (100). Indeed, cardiac mortality was significantly reduced at one year among the subgroup of experimental treatment patients who experienced an early reduction in psychologic distress. The Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) study was the fifth and largest stand-alone psychosocial intervention trial to date. It evaluated the effect of psychologic treatment on the composite end point of all-cause mortality and nonfatal MI in post-MI patients who were either depressed and/or who reported low perceived social support (101). Patients were randomized within four weeks of the index MI, and treatment consisted of individual cognitive therapy and, when possible, group therapy supplemented by the use of a selective serotonin reuptake inhibitor (SSRI) for severe or unremitting depression. Primary analyses found no treatment differences in event-free survival (101). However, analyses suggested only a modest difference in psychosocial functioning between the treatment and control groups. Psychosocial functioning was better than anticipated in the control group, perhaps due to aggressive treatment as part of routine medical care, including participation in cardiac rehabilitation and psychologic therapies, thereby reducing treatment group differences.

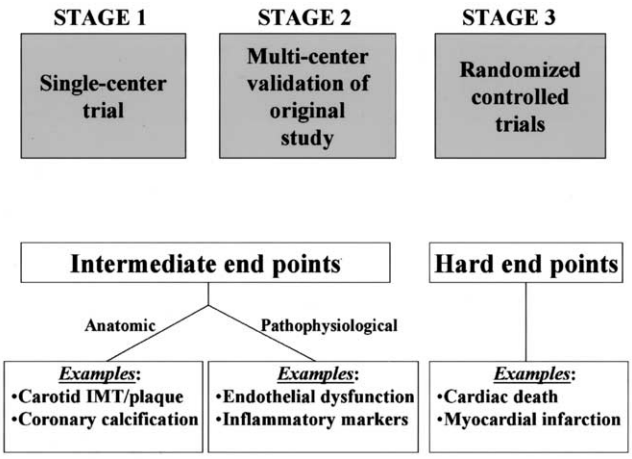

Figure 9. Proposed three-stage approach for developing behavioral intervention trials. Stage 1 consists of a single-center evaluation of a specific behavioral intervention. If successful, this intervention would be repeated at multiple centers to assess the reproducibility of findings (stage 2). In both stages, intermediate end points, such as change in carotid intimal wall thickening or plaque size during carotid ultrasonography, would be used to minimize necessary sample size and follow-up time. If reproducible results are obtained during stage 2, a multicenter intervention trial would be performed in stage 3, during which subjects would be observed for the occurrence of hard cardiac events. IMT = intima medial thickness.

The paucity of stand-alone behavioral intervention trials is partly due to the large sample sizes, long follow-up, and high costs required of such trials. One way to reduce this problem would be to use a three-stage approach for developing future interventions (Fig. 9) based on initial evaluations of surrogate end points, such as measures of subclinical atherosclerosis, myocardial ischemia, or flow-mediated dilation in smaller samples. Although there are limitations to the use of surrogate end points, they can be effective for developing new and innovative interventions for CAD before launching large multicenter randomized trials.

The impact of psychopharmacologic therapies upon cardiac outcomes represents an area of new interest. An initial trial in this arena, the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), demonstrated that an SSRI (sertraline) could be safely prescribed for the treatment of clinical depression in patients with known CAD (102). However, this trial was not powered to evaluate the influence of sertraline use on adverse cardiac events, as it was a safety study. Cohen et al. (103) assessed antidepressant use in a large group of union health plan members divided into those who were taking antidepressants and those who were not. Participants using tricyclic antidepressants had a more than a twofold increased risk of subsequent MI, but there was no increase in adverse cardiac events among the patients taking SSRIs. A recent case-control study suggests that the protective effect of SSRIs may be related to their degree of serotonin transporter affinity (104). If confirmed, these findings suggest that SSRIs with high serotonin transporter affinity may be the preferred pharmacologic means for treating depression in CAD patients because of a biologic antiplatelet effect. A biologic protective

effect for depressed patients also may be introduced by the use of statin therapy, as suggested by preliminary data indicating that statin therapy lowers the high levels of C-reactive protein associated with depression (105).

Future directions in behavioral interventions. Although clinical practice guidelines advocate psychosocial interventions in the context of cardiac rehabilitation programs, there are no existing recommendations to guide the delivery of psychosocial interventions in cardiac practice. Cardiac rehabilitation programs are widely recognized as effective in providing multifactorial multidisciplinary treatment for cardiac patients (106), but these programs are geographically limited and third-party reimbursement policies may limit patient participation. Overall, only 10% to 20% of eligible cardiac patients are referred to cardiac rehabilitation programs (106). Thus, these programs represent an incomplete delivery system for behavioral health care in cardiac practice. Moreover, because of time constraints and lack of formal training in behavioral techniques, many cardiologists may find it difficult to provide psychosocial interventions to their patients. In addition, even though cardiologists commonly manage behavioral risk factors, such as physical inactivity, poor diets, and smoking, lack of patient adherence to their behavioral recommendations remains an important problem (89) for which there is no easy solution. For all these reasons, development of effective models for the provision of psychologic and behavior services for cardiologists is needed.

Accordingly, programs of various complexities have been examined for their ability to improve physician management of behavioral risk factors. These programs include providing brief targeted physician training, monitoring patients by telephone follow-ups, using nurse managers in cardiology practice, and involving patients' primary care physicians in collaboration with mental health professionals such as psychologists and psychiatrists. This latter approach has shown promise for optimizing primary care physician management of serious psychologic illnesses such as depression (107) and panic disorder (108). Although critical assessment of these approaches is beyond the scope of our review, a conceptual approach for organizing behavioral health care interventions for cardiac patients, based on the collective experience garnered from these approaches, is shown in Figure 10. In this approach, guidelines would be developed for stepped collaborative care interventions, based on the complexity of patients' psychosocial and behavioral problems and their ability to adhere to behavioral recommendations.

The difficulty in maintaining long-term behavioral change among cardiac patients, coupled with the growing epidemic in obesity and type 2 diabetes, makes it imperative to develop more effective adherence strategies. Bellg (109) suggests that standard efforts to optimize treatment adherence most commonly view nonadherence as a form of patient deficit that can be overcome by using external forms of behavioral regulation, such as use of incentives or structured provider support (Fig. 11). Such controlled behavior regulation may be very effective in eliciting short-term behavioral change, but fostering patient autonomy is critical to maintain long-term change (110). Conversely, lack of internal motivation is a primary reason why patients continue to engage in unhealthy shortsighted behaviors after being informed about the long-term adverse consequences. Approaches for fostering internal motivation are suggested in Figure 11. An approach that incorporates many of these principles is "motivational interviewing," which is designed to enhance patients' intrinsic motivation to change unhealthful behaviors by exploring and resolving ambivalence

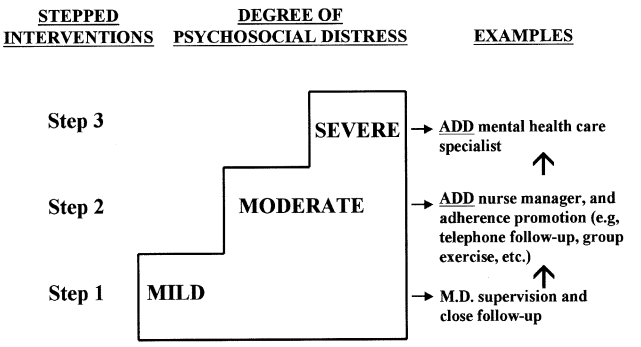

Figure 10. Stepped collaborative care for cardiac patients depending on the degree of psychological distress. Patients with mild psychologic distress (step 1) would generally be treated by cardiologists without additional collaborative intervention. The greater the degree of psychosocial distress, the greater the need for collaborative intervention.

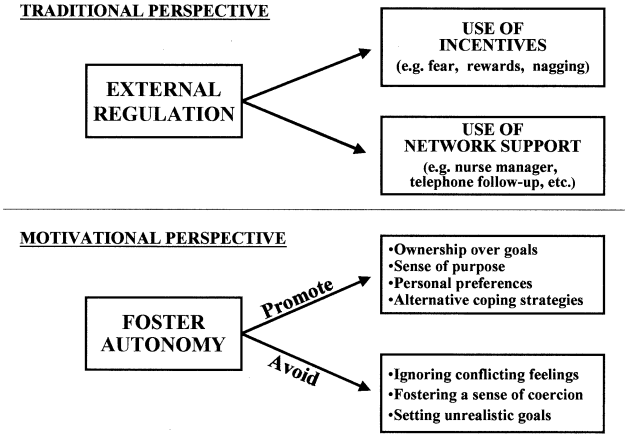

Figure 11. Approaches to promoting treatment adherence commonly make use of techniques that involve external regulation, such as the use of incentives or external network support. An alternative motivational paradigm to such controlled behavior regulation focuses on attempts to promote autonomy by fostering greater intrinsic motivation. Health providers can foster this motivational process through a variety of steps, including promoting patient ownership over recommended behavioral changes (i.e., getting patients to voice their own reasons for initiating change), helping patients to find a meaningful purpose for suggested changes, formatting the specifics of behavior recommendations in a manner most consistent with patients' personal preferences, and recognizing what coping mechanisms were best served by the old adverse behaviors (e.g., eating to decrease a sense of tension) and finding alternative solutions. At the same time it is important to avoid ignoring a sense of conflict (which can occur if behavioral recommendations are made without considering the relationship of physician advice to patients' internal values and preferences), fostering a sense of coercion, or setting goals that are not readily achievable.

to change (111). In this approach, the interviewer uses empathy to help patients focus on discrepancies between present behavior and long-term aspirations and values, and avoids confrontation or playing an authoritarian role. This approach has been applied to various behavior settings (99), and is promising for treating cardiac patients. Other novel strategies also may be used to create "teachable moments," for example, by showing patients personally relevant clinical images of calcium deposits in their coronary arteries (112). To date, this motivational approach has not yet been tested in a sufficiently broad spectrum of patient populations.

THE EMERGING FIELD OF BEHAVIORAL CARDIOLOGY

Behavioral cardiology is an emerging field of clinical practice based on the recognition that adverse lifestyle behaviors, emotional factors, and chronic life stress can all promote atherosclerosis and adverse cardiac events. In recent years, the pathophysiologic understanding of how psychosocial risk factors contribute to atherosclerosis and adverse cardiac events has broadened substantially. By contrast, the development of effective therapeutic interventions both for modifying high-risk lifestyles and behaviors and for reducing psychosocial risk factors for CAD patients remains a challenge. There have been few large-scale psychosocial intervention trials, and the design of future trials is under debate. Moreover, the lack of patient adherence to behavioral interventions remains a significant problem. Nevertheless, there is increasing evidence that interventions such as exercise training, multifactorial secondary prevention efforts that incorporate psychosocial interventions, and antidepressant medication may be effective in treating psychologic distress and improving outcomes among patients with cardiac disease. Other preliminary evidence suggests that stress management programs can improve surrogate markers for CAD. Prospective investigations are needed to determine which patients may respond best to specific forms of behavioral interventions and also define how cardiologists can best collaborate with other health care providers and health care delivery systems to reduce psychologic distress in a cost-effective and practical manner. The field of behavioral cardiology requires the development of such practical solutions because the etiologic links among psychosocial risk factors, behavioral risk factors, and atherosclerosis suggest that cardiologists will consistently encounter many patients with psychologic distress and unhealthy behaviors in clinical practice.

Acknowledgments

We thank Elliot Brown, Tara Hannon, Elizabeth Mostofsky, Nina Rieckmann, Deborah A. Scheuer, and Kimberlee Trudeau for their assistance and/or comments on prior drafts. We also thank Mindy Weingarten for her secretarial assistance.

Reprint requests and correspondence: Dr. Alan Rozanski, Division of Cardiology, St. Luke's-Roosevelt Hospital Center, 1111 Amsterdam Avenue, New York, New York 10025. E-mail: AR77@columbia.edu.

REFERENCES

1. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation 1999;99:2192–217.
2. Lesperance F, Frasure-Smith N, Talajic M, Bourassa MG. Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. Circulation 2002;105:1049–53.
3. Rugulies R. Depression as a predictor for coronary heart disease. a review and meta-analysis. Am J Prev Med 2002;23:51–61.
4. Matthews KA, Gump BB, Harris KF, Haney TL, Barefoot JC. Hostile behaviors predict cardiovascular mortality among men enrolled in the Multiple Risk Factor Intervention Trial. Circulation 2004;109:66–70.
5. Matsumoto Y, Uyama O, Shimizu S, Michishita H, Mori R, Owada T, Sugita M. Do anger and aggression affect carotid atherosclerosis? Stroke 1993;24:983–6.
6. Julkunen J, Salonen R, Kaplan GA, Chesney MA, Salonen JT. Hostility and the progression of carotid atherosclerosis. Psychosom Med 1994;56:519–25.
7. Matthews KA, Owens JF, Kuller LH, Sutton-Tyrrell K, Jansen-McWilliams L. Are hostility and anxiety associated with carotid atherosclerosis in healthy postmenopausal women? Psychosom Med 1998;60:633–8.
8. Knox SS, Adelman A, Ellison RC, et al. Hostility, social support, and carotid artery atherosclerosis in the National Heart, Lung, and Blood Institute Family Heart Study. Am J Cardiol 2000;86:1086–9.
9. Angerer P, Siebert U, Kothny W, Muhlbauer D, Mudra H, von Schacky C. Impact of social support, cynical hostility and anger expression on progression of coronary atherosclerosis. J Am Coll Cardiol 2000;36:1781–8.
10. Case RB, Moss AJ, Case N, et al. Living alone after myocardial infarction. JAMA 1992;267:515–9.
11. Williams RB, Barefoot J, Califf R, et al. Prognostic importance of social and economic resources among medically treated patients with angiographically documented coronary artery disease. JAMA 1992; 267:520–4.
12. Ruberman W, Weinblatt E, Goldberg J, et al. Psychosocial influences on mortality after myocardial infarction. N Engl J Med 1984;311: 552–9.
13. Berkman LF, Leo-Summers L, Howwitz RI. Emotional support and survival after myocardial infarction: a prospective, population-based study of the elderly. Ann Intern Med 1992;117:1003–9.
14. Gorkin L, Schron EB, Brooks MM, et al. Psychosocial predictors of mortality in the cardiac Arrhythmia Suppression Trial-1 (CAST-1) Am J Cardiol 1993;71:263–7.
15. Frasure-Smith N, Lesperance F, Gravel G, et al. Social support, depression, and mortality during the first year after myocardial infarction. Circulation 2000;101:1919–24.
16. Seeman TE, Syme L. Social networks and coronary artery disease: a comparison of the structure and function of social relations as predictors of disease. Psychosom Med 1987;49:341–54.
17. Marmot MG, Bosma H, Hemingway H, Brunner E, Stansfeld S. Contribution of job control and other risk factors to social variations in coronary heart disease incidence. Lancet 1997;350:235–9.
18. Baum A, Garofalo JP, Yali AM. Socioeconomic status and chronic stress: does stress account for SES effects on health? In: Adler N, Marmot M, McEwen BS, Steward J, editors. Socioeconomic Status and Health in Industrial Nations: Social, Psychological, and Biological Pathways, Annals of the New York Academy of Sciences. New York, NY: New York Academy of Sciences, 1999;131–44.
19. Rosmond R, Bjorntorp P. Occupational status, cortisol secretory pattern, and visceral obesity in middle-aged men. Obesity Res 2000;8:445–50.
20. Karasek R, Baker D, Marxer F, Ahlbom A, Theorell T. Job decision latitude, job demands, and cardiovascular disease: a prospective study of Swedish men. Am J Public Health 1981;71:694–705.

21. Siegrist J. Adverse health effects of high-effort/low-reward conditions. J Occup Health Psychol 1996;71:694–705.
22. Johnson JV, Hall EM, Theorell T. Combined effects of job strain and social isolation on cardiovascular disease morbidity and mortality in a random sample of the Swedish male working population. Scand J Work Environ Health 1989;15:271–9.
23. Kivimaki M, Leino-Arjas P, Luukkonen R, Riihimaki H, Vahtera J, Kirjonen J. Work stress and risk of cardiovascular mortality: prospective cohort study of industrial employees (erratum appears in BMJ 2002;325:1386). BMJ 2002;325:857.
24. Johnson JV, Stewart W, Hall EM, Fredlund P, Theorell T. Long-term psychosocial work environment and cardiovascular mortality among Swedish men. Am J Public Health 1996;86:324–31.
25. Peter R, Siegrist J, Hallqvist J, Reuterwall C, Theorell T, Group SS. Psychosocial work environment and myocardial infarction: improving risk estimation by combining two complementary job stress models in the SHEEP Study. J Epidemiol Community Health 2002;56:294–300.
26. Rosengren A, Hawkin S, Ounpuu S, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11,119 cases and 13,648 controls from 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:953–62.
27. Matthews KA, Gump BB. Chronic work stress and marital dissolution increase risk of posttrial mortality in men from the Multiple Risk Factor Intervention Trial. Arch Intern Med 2002;162:309–15.
28. Suadicani P, Hein HO, Gyntelberg F. Are social inequalities associated with the risk of ischaemic heart disease a result of psychosocial working conditions? Atherosclerosis 1993;101:165–75.
29. Lynch J, Krause N, Kaplan GA, Salonen R, Salonen JT. Workplace demands, economic reward, and progression of carotid atherosclerosis. Circulation 1997;96:302–7.
30. Muntaner C, Nieto FJ, Cooper L, Meyer J, Szklo M, Tyroler HA. Work organization and atherosclerosis: findings from the ARIC study. Atherosclerosis Risk in Communities. Am J Prev Med 1998;14:9–18.
31. Nordstrom CK, Dwyer KM, Merz CN, Shircore A, Dwyer JH. Work-related stress and early atherosclerosis. Epidemiology 2001;12:180–5.
32. Orth-Gomer K, Wamala SP, Horsten M, Schenck-Gustafsson K, Schneiderman N, Mittleman MA. Marital stress worsens prognosis in women with coronary heart disease: the Stockholm Female Coronary Risk Study. JAMA 2000;284:3008–14.
33. Coyne JC, Rohrbaugh MJ, Shoham V, Sonnega JS, Nicklas JM, Cranford JA. Prognostic importance of marital quality for survival of congestive heart failure. Am J Cardiol 2001;88:526–9.
34. Gallo LC, Troxel WM, Kuller LH, et al. Marital status, marital quality, and atherosclerotic burden in postmenopausal women. Psychosom Med 2003;65:952–62.
35. Lee S, Colditz GA, Berkman LF, Kawachi I. Caregiving and risk of coronary heart disease in U.S. women: a prospective study. Am J Prev Med 2003;24:113–9.
36. Schulz R, Beach SR. Caregiving as a risk factor for mortality: the Caregiver Health Effects Study. JAMA 1999;282:2215–9.
37. Schwartz C, Meisenhelder JB, Ma Y, Reed G. Altruistic social interest behaviors are associated with better mental health. Psychosom Med 2003;65:778–85.
38. Mausner-Dorsch H, Eaton WW. Psychosocial work environment and depression: epidemiologic assessment of the demand-control model. Am J Public Health 2000;90:1765–70.
39. Batten S, Aslan M, Maciejewski PK, Mazure CM. Childhood maltreatment as a risk factor for adult cardiovascular disease and depression. J Clin Psychiatry 2004;65:249–54.
40. Jones DJ, Bromberger JT, Sutton-Tyrrell K, Matthews KA. Lifetime history of depression and carotid atherosclerosis in middle-aged women. Arch Gen Psychiatry 2003;60:153–60.
41. Everson SA, Lynch JW, Chesney MA, et al. Interaction of workplace demands and cardiovascular reactivity in progression of carotid atherosclerosis: population based study. BMJ 1997;314:553–8.
42. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837–47.
43. Yusuf S, Hawkin S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937–52.
44. Rozanski A, Kubzansky LD. Psychological functioning and physical health: a paradigm of flexibility. Psychosom Med 2005. In press.
45. Goldberger AL. Non-linear dynamics for clinicians: chaos theory, fractals, and complexity at the bedside. Lancet 1996;347:1312–4.
46. Ryan RM, Frederick C. On energy, personality, and health: subjective vitality as a dynamic reflection of well-being. J Pers 1997;65:529–65.
47. Gross JJ. Antecedent- and response-focused emotion regulation: divergent consequences for experience, expression, and physiology. J Pers Social Psychol 1998;74:224–37.
48. Bonanno GA, Papa A, O'Neil K, Westphal M, Coifman K. The importance of being flexible: the ability to enhance and suppress emotional expression predicts long-term adjustment. Psychol Sci 2004;15:482–7.
49. Kant IJ, Bultmann U, Schroer KAP, Beurskems AJHM, Van Amelsvoort LGPM, Swaen GMH. An epidemiological approach to study fatigue in the working population: the Maastricht cohort study. Occup Environ Med 2003;23;60:i32–9.
50. Fredrickson BL, Levenson RW. Positive emotions speed recovery from the cardiovascular sequelae of negative emotions. Cogn Emotion 1998;12:191–220.
51. Lawler KA, Younger JW, Piferi RL, et al. A change of heart: cardiovascular correlates of forgiveness in response to interpersonal conflict. J Behav Med 2003;26:373–93.
52. Gerin W, Pieper C, Levy R, Pickering TG. Social support in social interaction: a moderator of cardiovascular reactivity. Psychosom Med 1992;54:324–36.
53. Cohen S, Doyle WJ, Turner RB, Alper CM, Skoner DP. Emotional style and susceptibility to the common cold. Psychosom Med 2003;65:652–7.
54. Kubzansky LD, Sparrow D, Vokonas P, Kawachi I. Is the glass half empty or half full? A prospective study of optimism and coronary heart disease in the normative aging study. Psychosom Med 2001;63:910–6.
55. Scheier MF, Matthews KA, Owens JF, et al. Optimism and rehospitalization after coronary artery bypass graft surgery. Arch Intern Med 1999;159:829–35.
56. Danner DD, Snowdon DA, Friesen WV. Positive emotions in early life and longevity: findings from the nun study. J Pers Social Psychol 2001;80:804–13.
57. Carney RM, Freedland KE, Veith RC. Depression, the autonomic nervous system, and coronary heart disease. Psychosom Med 2005. In press.
58. Weber-Hamann B, Hentschel F, Kniest A, et al. Hypercortisolemic depression is associated with increased intra-abdominal fat. Psychosom Med 2002;64:274–7.
59. De Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: a meta-analysis. Psychosom Med 2001;63:619–30.
60. Schins A, Honig A, Crijns H, Baur L, Hamulyak K. Increased coronary events in depressed cardiovascular patients: 5-HT_{2A} receptor as missing link? Psychosom Med 2003;65:729–37.
61. Anisman H, Merali Z. Cytokines, stress, and depressive illness. Brain Behav Immun 2002;16:513–24.
62. Esposito K, Nappo F, Marfella R, et al. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. Circulation 2002;106:2067–72.
63. Rajagopalan S, Brook R, Rubenfire M, Pitt E, Young E, Pitt B. Abnormal brachial artery flow-mediated vasodilation in young adults with major depression (erratum appears in Am J Cardiol 2001;88:722). Am J Cardiol 2001;88:196–8.
64. McCabe PM, Gonzales JA, Zaias J, et al. Social environment influences the progression of atherosclerosis in the Watanabe heritable hyperlipidemic rabbit. Circulation 2002;105:354–9.
65. McElroy SL, Kotwal R, Malhotra S, Nelson EB, Keck PE Jr., Nemeroff CB. Are mood disorders and obesity related? A review for the mental health professional. J Clin Psychiatry 2004;65:634–51.
66. Dallman MF, La Fluer S, Pecoraro NC, Gomez F, Houshyar H, Akana SF. Minireview: glucorcorticoids—food intake, abdominal obesity, and wealthy nations in 2004. Endocrinology 2004;145:2633–8.
67. Bhatnagar S, Dallman M. Neuroanatomical basis for facilitation of hypothalamic-pituitary-adrenal responses to a novel stressor after chronic stress. Neuroscience 1998;84:1025–39.

68. Lindley SE, Bengoechea TG, Schatzberg AF, Wong DL. Glucocorticoid effects on mesotelencephalic dopamine neurotransmission. Neuropsychopharmacology 1999;21:399–407.
69. Morgan D, Grant KA, Gage HD, et al. Social dominance in monkeys: dopamine D_2 receptors and cocaine self-administration. Nature Neurosci 2002;5:169–74.
70. Volkow ND, Wang GJ, Fowler JS, et al. "Nonhedonic" food motivation in humans involves dopamine in the dorsal striatum and methylphenidate amplifies this effect. Synapse 2002;44:175–80.
71. Wang GJ, Volkow ND, Logan J, et al. Brain dopamine and obesity. Lancet 2001;357:354–7.
72. Kamarck TW, Everson SA, Kaplan GA, et al. Exaggerated blood pressure responses during mental stress are associated with enhanced carotid atherosclerosis in middle-aged Finnish men: findings from the Kuopio Ischemic Heart Disease Study. Circulation 1997;96:3842–8.
73. Matthews KA, Owens JF, Kuller LH, Sutton-Tyrrell K, et al. Stress induced pulse pressure change predicts women's carotid atherosclerosis. Stroke 1998;29:1525–30.
74. Suarez EC, Kuhn CM, Schanberg SM, Williams RB, Jr., Zimmermann EA. Neuroendocrine, cardiovascular, and emotional responses of hostile men: the role of interpersonal challenge. Psychosom Med 1998;60:78–88.
75. Grippo AJ, Moffitt JA, Johnson AK. Cardiovascular alterations and autonomic imbalance in an experimental model of depression. Am J Physiol 2002;282:R1333–41.
76. Laugero KD, Gomez F, Manalo S, Dallman M. Corticosterone infused intracerebroventricularly inhibits energy storage and stimulates the hypothalamo-pituitary axis in adrenalectomized rats drinking sucrose. Endocrinology 2002;143:4552–62.
77. Scheuer DA, Bechtold AG, Shank SS, Akana SF. Glucocorticoids act in the dorsal hindbrain to increase arterial pressure. Am J Physiol 2004;286:H458–67.
78. Scheuer DA, Bechtold AG. Activation of dorsal hindbrain glucocorticoid receptors enhances the arterial pressure response to acute stress (abstr). FASEB J 2004;18:A675.
79. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psych 1994;51:8–19.
80. Fleet RP, Dupuis G, Marchand A, Kaczorowski J, et al. Panic disorder in coronary artery disease patients with noncardiac chest pain. J Psychosom Res 1998;44:81–90.
81. Kirmayer LJ, Robbins JM, Dworkin M, Yaffe MJ. Somatization and the recognition of depression and anxiety in primary care. Am J Psychiatry 1993;150:734–41.
82. Katon WJ, Von Korff M, Lin E. Panic disorder: relationship to high medical utilization. Am J Med 1992;92:Suppl 1A:7S–11S.
83. Fleet RP, Dupuis G, Marchand A, Burelle D, Arsenault A, Beitman BD. Panic disorder in emergency department chest pain patients: prevalence, comorbidity, suicidal ideation, and physician recognition. Am J Med 1996;101:371–80.
84. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment. Meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med 2000;160:2101–7.
85. DiMatteo, MR. Social support and patient adherence to medical treatment: a meta-analysis. Health Psychol 2004;23:207–18.
86. Neugarten BJ. Adult personality: towards a psychology of the life cycle. In: Neugarten BL, editor. Middle Age and Aging. Chicago, IL: University of Chicago Press, 1968.
87. Whooley MA, Simon GE. Managing depression in medical outpatients. N Engl J Med 2000;343:1942–50.
88. Joos SK, Hickam DH. How health professionals influence health behavior: patient provider interaction and health care outcomes. In: Glanz K, Lewis FM, Rimer BK, editors. Health Behavior and Health Education: Theory Research and Practice. San Fransisco, CA: Jossey-Bass, 1990;216–41.
89. Miller NH, Hill M, Kottke T, Ockene IS. The multilevel compliance challenge: recommendations for a call to action. A statement for healthcare professionals. Circulation 1997;95:1085–90.
90. Lawlor DA, Hopker SW. The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomised controlled trials. Br Med J 2001;322:763–7.
91. Blumenthal JA, Babyak MA, Moore KA, et al. Effects of exercise training on older patients with major depression. Arch Intern Med 1999;159:2349–56.
92. Babyak M, Blumenthal JA, Herman S, et al. Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. Psychosom Med 2000;62:633–8.
93. Linden W, Stossel C, Maurice J. Psychosocial interventions for patients with coronary artery disease: a meta analysis. Arch Intern Med 1996;156:745–52.
94. Dusseldorp E, van Elderen T, Maes S, Meulman J, Kraaij V. A meta-analysis of psychoeducational programs for coronary heart disease patients. Health Psychol 1999;18:506–19.
95. Carney RM, Blumenthal JA, Freedland KE, et al. Depression and late mortality after myocardial infarction in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) Study. Psychosom Med 2004;66:466–74.
96. Friedman M, Thoresen CE, Gill J, et al. Alteration of type A behavior and its effect on cardiac recurrences in postmyocardial infarction patients: summary results of the Recurrent Coronary Prevention Project. Am Heart J 1986;112:653–65.
97. Frasure-Smith N, Prince R. The ischemic heart disease life stress monitoring program: impact on mortality. Psychosom Med 1985;47:431–45.
98. Jones DA, West RR. Psychological rehabilitation after myocardial infarction: multicenter randomized control trial. Br Med J 1996;313:1517–21.
99. Frasure-Smith N, Lesperance F, Prince RH, et al. Randomized trial of home-based psychosocial nursing intervention for patients recovering from myocardial infarction. Lancet 1997;350:473–9.
100. Cossette S, Frasure-Smith N, Lesperance F. Clinical implications of a reduction in psychological distress on cardiac prognosis in patients participating in a psychosocial intervention program. Psychosom Med 2001;63:257–66.
101. The ENRICHD Investigators. Effects of treating depression and low perceived social support on clinical events after a myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) randomized trial. JAMA 2003;289:3106–16.
102. Glassman AH, O'Connor CM, Califf RM, et al. Setraline treatment of major depression in patients with acute MI or unstable angina. JAMA 2002;288:701–9.
103. Cohen HW, Gibson G, Alderman MH. Excess risk of myocardial infarction in patients treated with antidepressant medications: association with use of tricyclic agents. Am J Med 2000;108:2–8.
104. Sauer WH, Berlin JA, Kimmel SE. Selective serotonin reuptake inhibitors and myocardial infarction. Circulation 2001;104:1894–8.
105. Lesperance F, Frasure-Smith N, Theroux P, Irwin M. The association between major depression and levels of soluble intercellular adhesion molecule 1, interleukin-6, and C-reactive protein in patients with recent acute coronary syndromes. Am J Psychiatry 2004;161:271–7.
106. Ades PA. Cardiac rehabilitation and secondary prevention of coronary heart disease. N Engl J Med 2001;345:892–902.
107. Katon W, Von Korff M, Line E, Simon G, et al. Stepped collaborative care for primary care patients with persistent symptoms of depression: a randomized trial. Arch Gen Psychiatry 1999;56:119–1115.
108. Katon WJ, Roy-Byrne P, Russo J, Cowley D. Cost-effectiveness and cost offset of a collaborative care intervention for primary care patients with panic disorder. Arch Gen Psychiatry 2002;59:1098–104.
109. Bellg AJ. Maintenance of health behavior change in preventative cardiology: internalization and self-regulation of new behaviors. Behav Modif 2003;27:103–31.
110. Williams GC, Rodin GC, Ryan RM, Grolnick WS, Deci EL. Autonomous regulation and long-term medication adherence in adult outpatients. Health Psychol 1998;17:269–76.
111. Miller WR, Rollnick S. Motivational Interviewing: Preparing People To Change Addictive Behavior. New York, NY: Guilford, 1991.
112. O'Malley PG, Feuerstein IM, Taylor AJ. Impact of electron beam tomography, with and without case management, on motivation, behavioral change, and cardiovascular risk profile. A randomized controlled trial. JAMA 2003;289:2215–23.