Anxiety and cardiovascular risk: Review of Epidemiological and Clinical Evidence

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Abstract

An increasing body of evidence suggests that anxiety is an independent predictor of adverse cardiovascular (CV) events. Individuals with high levels of anxiety are at increased risk of coronary heart disease, congestive heart failure, stroke, fatal ventricular arrhythmias, and sudden cardiac death. Anxiety following a major cardiac event can impede recovery, and is associated with a higher morbidity and mortality. This linkage between anxiety and CV disease is further corroborated by evidence suggesting that treatment of anxiety may improve cardiac symptoms. However, the mechanisms underlying the observed associations are not entirely delineated. Several intermediary mechanisms have been suggested, including sympathetic activation, impaired vagal control, reduced heart rate variability, stimulation of the hypothalamic–pituitary axis, hyperventilation-induced coronary spasm, oxidative stress, increased inflammatory mediators, and unhealthy lifestyle. There is a need for several clinical trials to explicate the complex associations between anxiety and CV disease, which may be compounded by the involvement of other psychosocial factors. In this review, we examine the epidemiological evidence for the association between anxiety and CV disease, and discuss the proposed mechanisms that may be responsible for this association.

Keywords

BACKGROUND

Coronary heart disease (CHD) is the leading cause of death and disability in the United States (US) and other developed countries [1]. By the year 2020, CHD is projected to be the leading cause of death, not only in the developed world but also in the developing world [2–4]. It is well known in the psychological literature that negative emotions such as anxiety are common among patients with cardiovascular (CV) symptoms, but few studies have examined associations between these two conditions.

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Anxiety is defined as an unpleasant emotion that is triggered by anticipation of future events and memories of past events, and it could manifest in different forms (panic disorder, phobic anxiety, generalized anxiety, anxiety reactions, and chronic anxiety) [5, 6]. Anxiety affects about 24.9% of the population at some time in their lives [7] with reported worldwide prevalence of 16.6% [8]. Studies suggest that 38–70% of all persons with congestive heart failure (CHF) have some form of anxiety, and older adults with CHF report anxiety levels that are estimated to be 60% higher than those without such symptoms [9–13]. Among independently living women, our group observed a greater likelihood for highly anxious women to report CV symptoms [14].

Although the association of traditional CV risk factors with adverse outcomes has been well delineated [15], recent research indicates that the impact of psychosocial distress on CV morbidity and mortality is almost equal to the impact of demographic characteristics (age, sex, and race) and risk markers (smoking, alcohol, obesity, diabetes, dyslipidemia, and hypertension) [16]. Despite this observation, only a few studies have focused on the impact of anxiety and other psychosocial factors on CV outcomes. Underappreciation of the role of psychosocial factors in the development and progression of cardiac diseases may be one reason why they remain the number one cause of death in most developed countries. Although most of the studies exploring the relationship between CV disease and negative emotions have focused on depression, most patients with confirmed or suspected CV disease have some degree of anxiety [9–13]. Anxiety following a major cardiac event can impede recovery, and is associated with higher morbidity and mortality [17–21]. Although several studies have found that anxiety is related to increased mortality [17, 18, 22–25], some studies have found no difference or even a decrease in morbidity and mortality following myocardial infarction (MI) [26–29].

The evidence suggests that treatment of psychosocial distress may decrease CV events [30–33]. However, the mechanisms underlying the observed associations are not entirely delineated. Several intermediary mechanisms have been suggested, including sustained sympathetic activation, hyperventilation-induced coronary spasm, oxidative stress, increased inflammatory mediators, and unhealthy lifestyle changes [34–39]. There is a need for several randomized clinical trials to explicate the complex associations between anxiety and CV disease, which may be compounded by the involvement of other psychosocial factors. In this review, we examine the evidence linking anxiety to CV disease, and discuss the proposed mechanisms that may be responsible for this association.

LINK BETWEEN ANXIETY AND CARDIOVASCULAR SYMPTOMS

Evidence from CHD studies

Epidemiological evidence indicates that pathophysiological correlates of negative emotions may contribute to atherosclerosis [3]. However, several studies evaluating the link between negative emotions and cardiac disease have focused on depression [4]. Recent studies have demonstrated a relationship between hostility or anger and measurements of subclinical atherosclerosis [40–43], and have also linked hostility to progression of atherosclerosis during serial coronary angiography [44]. In a population-based sample of 726 men and women who were healthy at baseline, Paterniti and colleagues [45] showed that high levels of sustained anxiety were independently associated with increased progression of atherosclerosis over a 4-year period, as measured by changes in common carotid artery intima media thickness. Among hypertensive patients, White and Baker [46] found a mean increase of 27 mmHg in systolic blood pressure (SBP) and 5 mmHg in diastolic blood pressure (DBP), and an increase of 14 beats/min in the heart rate during the hour of a panic attack. In other studies, anxiety level was positively correlated with SBP [47–49], but not with DBP [50].

Three large-scale, community-based studies including one involving 34000 men showed significant relationships between anxiety disorders and CV death [17, 18, 25]. Haines and colleagues [25] followed 1457 initially healthy men for about 10 years in the Northwick Park heart study. Those with the highest levels of phobic anxiety had a higher risk of fatal CHD than men reporting no anxiety, after controlling for a range of known coronary risk factors [25]. Furthermore, a recent study from a US population showed that anxiety was associated with 60% excess risk of CHD among men and women, an effect that was independent of traditional CHD risk factors [51]. Chronic anxiety appears to increase the risk of incident CHD, with risk estimates from 1.5 to 7, depending on the type of anxiety measure used and the form of the analysis [17, 18, 25, 51–58]. Among healthy individuals, higher levels of anger symptoms were significantly associated with a 1.5- to threefold excess risk of incident CHD over a 5- to 15-year follow-up period [59–63].

In two studies involving patients participating in cardiac rehabilitation programs, anxiety symptoms predicted worse long-term prognosis [19, 20]. As these studies included psychological treatment components during follow-up, it is difficult to interpret the results. In another study, 222 patients who received usual care for 1 year were examined during hospitalization for MI. The results of that study indicated an increase in CV risk associated with anxiety symptoms that was independent of history of major depression and previous MI [21]. Other studies have also shown associations of anxiety with cardiovascular events [23, 64–69], but differences in the measures used, timing of measurement, and variations in sample sizes make it difficult to establish a head-to-head comparison of those findings.

Findings of positive relationships between anxiety and CV disease are not universal. One large study involving over 2000 patients with CAD assessed before routine stress tests found that anxiety, measured with the anxiety subscale of the Hospital Anxiety and Depression Scale [70], was associated with lower mortality rates [27]. Investigators in that study speculated that anxiety might be related to increased tendencies to seek medical attention or alter risk factors [27]. Another study that evaluated 344 patients after MI reported no relationship between either anxiety or depression and 1-year mortality [26]. However, the mortality rate was low (4%) in that study.

Evidence from CHF studies

Evidence supporting a prognostic impact of anxiety on CHF is scant and not entirely consistent. Riedinger and colleagues [71] demonstrated that anxiety was an independent predictor of adverse cardiac events among patients with recent MI and low ejection fraction. In another study, anxiety was directly related to brain natriuretic peptide level [72], suggesting a relationship between anxiety and CHF [72]. However, these findings are not consistent with other studies showing that poor outcomes and rehospitalization were associated with depression, but not with anxiety [73–78]. Friedman *et al* [73] found an association between anxiety and outcomes among patients with heart failure, but this association was not maintained after controlling for potential confounders. Jiang *et al* [74] did not find a significant association between anxiety symptoms and mortality in hospitalized patients with heart failure. The reasons for these discrepancies are not completely understood, but they may be related to differences in study population and methodology.

Evidence from psychosocial intervention studies

The impact of psychosocial interventions on CV outcomes represents a new area of interest. Epidemiological evidence suggesting that treatment of anxiety and other psychosocial factors may improve CV symptoms and decrease adverse outcomes corroborate the link between psychosocial risks and CV disease. In the initial successful intervention trial in this

arena, the Ischemic Heart Disease study, a unique home-based stress reduction program, showed that treatment was associated with reduction in cardiac events [30]. The Recurrent Coronary Prevention Project Study succeeded in decreasing both type A behavior and negative affect, and also reduced the rates of CV mortality and non-fatal MI by using behavior modification [31]. Furthermore, among patients referred to cardiac rehabilitation programs, Dusseldorp *et al* [32] observed differential reduction in the odds ratio for mortality and recurrent MI following reduction in psychological stress. In a meta-analysis of 23 randomized controlled trials that evaluated the impact of adding psychosocial interventions to standard cardiac rehabilitation regimens, Linden *et al* [33] observed that, during the first 2 years of follow-up, lack of psychosocial intervention was associated with greater rates of mortality and recurrent MI.

PROPOSED MECHANISMS EXPLAINING THE LINK BETWEEN ANXIETY CV DISEASE

Mechanisms linking anxiety to CV disease can be categorized into two pathways: neurohormonal and behavioral pathways. Below, we discuss the significance and evidence in support of both pathways.

Neurohormonal pathway

Activation of the sympathetic nervous system, as manifested by impaired vagal control, reduction in heart rate variability [34], elevated levels of proinflammatory cytokines [5], and hypercortisolemia from activation of the hypothalamic–pituitary axis (HPA) [35], is increasingly recognized as a favorable link between anxiety and CV disease [34–36]. Epidemiological evidence indicates that negative emotions have cumulative pathophysiological effects that can ultimately lead to CHD events through damage from persistent activation of the neurohormonal systems and other mechanisms [37–39]. Increased output from the sympathetic nervous system and HPA can induce a wide variety of physiologic responses [22]. Studies have shown that the number of lymphocyte b-adrenergic receptors [79–81] and b-adrenergic-mediated cyclic AMP generation are decreased among patients with anxiety disorder, especially in the context of panic disorder [82, 83]. Aronson *et al* [80] demonstrated a negative correlation between trait anxiety and the number of lymphocyte b-adrenergic receptors. Among patients experiencing panic attacks, baseline catecholamine and 3-methoxy-4-hydroxyphenylglycol levels appear to be either normal or mildly elevated [84–86]. Following infusion of isoproterenol, a smaller change in the heart rate was observed among patients with panic disorder [87], suggesting that chronic anxiety, by increasing sympathetic outflow, can lead to b-adrenergic receptor downregulation.

Data from the Normative Aging Study, which previously identified an excess risk of CHD associated with anxiety, also showed a link between high levels of anxiety and reduced heart rate variability [34]. With increased anxiety symptoms, there was a corresponding decrease in heart rate variability. This finding supports studies suggesting that the association of anxiety with sudden cardiac death, but not MI [17, 18, 25], may be related to ventricular arrhythmias. Autonomic alteration could involve either increased sympathetic stimulation, which has been linked to the occurrence of arrhythmias and sudden death [88], or impaired vagal control, which has also been linked to increased cardiac mortality [89, 90]. Specifically, reduced vagal control has been linked to impaired vagally mediated baroreflex control of the heart [91]. Such impairment appears to be a particularly important risk factor for sudden death [92, 93]. Watkins *et al* [94] reported reduced baroreflex cardiac control among patients with anxiety, but prospective work is needed to determine whether this is a common operative mechanism for sudden deaths among patients with anxiety syndromes.

Consistent with these findings, we previously observed that insomnia, which has been shown to be a form of chronic stress and sympathetic disorder, is in part responsible for the association between anxiety and CV symptoms [14]. Furthermore, an atherogenic pathway, promoted by recurring activation of the neurohormonal system with subsequent endothelial injury and atherosclerosis, has also been suggested [45].

Behavioral pathway

Various lifestyle behaviors, including unhealthy diet, physical inactivity, and smoking, promote the development and clinical manifestations of CHD [22]. Studies suggest that individuals with anxiety disorders are prone to unhealthy lifestyle behaviors [16, 95]. Negative emotions may exacerbate disease progression or reduce survival, either via direct physiological effects or through reduced compliance with recommended medical regimens [96, 97]. Among patients with CHF, negative emotions are associated with unhealthy lifestyle [98], and have been shown to be predictors of dietary and exercise adherence [11, 99, 100].

Riegel *et al* [101] suggest that the impact of anxiety on cardiac diseases may be related to the associated poor uptake of self-care behaviors. Anxiety may impair energy, cognition, and motivation to engage in self-care behaviors [96]. Patients with high levels of anxiety have difficulty making lifestyle changes, coping with challenges, and encounter more problems during cardiac rehabilitation [102–104]. Evidence suggests that anxiety is a predictor of poor adherence to lifestyle change recommendations and adherence to medical therapy [105]. Among highly anxious patients with recent hospitalization for acute exacerbation of CHF, adherence to a number of self-care behaviors was extremely poor [11]. In that study, only 9% of patients reported self-monitoring for symptoms of worsening CHF, 14% of patients were weighing themselves daily, 31% could not name even one symptom of CHF, and only 34% of patients were taking all the medications as prescribed. These findings suggest that unhealthy lifestyle behaviors may contribute to cardiac risks associated with anxiety.

A general effect of distress

The clustering of psychosocial factors and the similarity of findings between the three negative emotions and CV outcome raise the question as to whether the effects of anxiety, depression, or anger are unique, or just a general effect of distress. It has been suggested that general distress shared by these negative emotional states is a key factor [106], but little work has been done to tease apart these relationships. Recently, the uniqueness of these three negative emotions as risk factors for incident CHD was explored in a prospective study of a disease-free population, which was followed for 11 years [96]. General stress, anxiety, and depression measured at study entry were each strong predictors of incident CHD over the follow-up period. At the end of the follow-up period, anxiety and depression, but not anger, remained independent predictors. These findings support the need to consider these specific emotions separately. It may also be that general distress in and of itself is an important CV risk factor.

ANXIETY AND TRADITIONAL CORONARY RISK FACTORS

A growing body of evidence indicates that psychosocial factors may be considered as major CHD risk factors in a similar way to the traditional risk factors (hypertension, diabetes, hyperlipidemia, smoking, obesity, physical inactivity, and age). This notion is supported by the multinational INTERHEART case–control study of 29972 patients from 52 countries, which uniquely assessed the impact of eight coronary risk factors and a composite index of psychosocial factors on incident acute MI [16]. Psychosocial distress conferred a greater

adjusted relative risk of acute MI than hypertension, abdominal obesity, diabetes, and several other traditional risk factors. In addition, psychosocial distress was a predictor of acute MI independent of ethnic or geographic context [107]. This important finding, along with reports from the Framingham study [95, 108], suggests that psychosocial factors may be equivalent to traditional risk factors in predicting CV events, although more studies are needed in this area.

CONCLUSION

With the limited evidence available, anxiety appears to predict more CV symptoms, poorer functional status, and increased CV events. More experimental and randomized clinical trials are needed to fully understand the relationship between anxiety and CV disease, as well as to determine whether the proposed pathophysiological mechanisms are truly causal. Clinical evaluation of cardiac patients should include assessment of psychosocial factors, most especially anxiety and depression. Further research in this area should concentrate on teasing out the mechanisms by which individual psychosocial factors increase CV risk, and also focus on interventions that decrease both anxiety and adverse CV events.

Acknowledgments

REFERENCES

1. American Heart Association. Heart Disease and Stroke Statistics. American Heart Association; Dallas, TX: 2007. p. 9-17.2007 Update

2. Grippo AJ, Johnson AK. Biological mechanisms in the relationship between depression and heart disease. Neurosci Biobehav Rev. 2002; 26(8):941–962. [PubMed: 12667498]

3. Januzzi JL, Stern TA, Pasternak RC, DeSanctis RW. The influence of anxiety and depression on outcomes of patients with coronary artery disease. Arch Intern Med. 2000; 160(13):1913–1921. [PubMed: 10888966]

4. Denollet J, Strik JJ, Lousberg R, Honig A. Recognizing increased risk of depressive comorbidity after myocardial infarction: looking for 4 symptoms of anxiety–depression. Psychother Psychosom. 2006; 75(6):346–352. [PubMed: 17053335]

5. Boyd JH, Burke JD Jr. Gruenberg E, et al. Exclusion criteria of DSM-III: a study of cooccurrence of hierarchy-free syndromes. Arch Gen Psychiatry. 1984; 41(10):983–989. [PubMed: 6477056]

6. Zimmerman M, Chelminski I. Generalized anxiety disorder in patients with major depression: is DSM-IV's hierarchy correct? Am J Psychiatry. 2003; 160(3):504–512. [PubMed: 12611832]

7. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSMIII-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry. 1994; 51:8–19. [PubMed: 8279933]

8. Somers JM, Goldner EM, Waraich P, et al. Prevalence and incidence studies of anxiety disorders: a systematic review of the literature. Can J Psychiatry. 2006; 51:100–3. [PubMed: 16989109]

9. De Jong MJ, Moser DK, An K, Chung ML. Anxiety is not manifested by elevated heart rate and blood pressure in acutely ill cardiac patients. Eur J Cardiovasc Nurs. 2004; 3:247–253. [PubMed: 15350235]

10. Lainscak M, Cleland JG, Lenzen MJ, et al. Recall of lifestyle advice in patients recently hospitalised with heart failure: a EuroHeart Failure Survey analysis. Eur J Heart Fail. 2007; 9:1095–1103. [PubMed: 17888721]

11. Moser DK, Doering LV, Chung ML. Vulnerabilities of patients recovering from an exacerbation of chronic heart failure. Am Heart J. 2005; 150:984. [PubMed: 16290979]

12. Moser DK, Zambroski CH, Lennie TA, et al. Aging with a broken heart: the effect of heart disease on psychological distress in the elderly. Circulation. 2004; 110(Suppl III):III–416.

13. Smith OR, Michielsen HJ, Pelle AJ, Schiffer AA, Winter JB, Denollet J. Symptoms of fatigue in chronic heart failure patients: clinical and psychological predictors. Eur J Heart Fail. 2007; 9:922–927. [PubMed: 17631047]

14. Olafiranye O, Jean-Louis G, Magai C, et al. Anxiety and cardiovascular symptoms: the modulating role of insomnia. Cardiology. 2010; 115(2):114–119. [PubMed: 19907174]

15. Suls J, Bunde J. Anger, anxiety, and depression as risk factors for cardiovascular disease: the problems and implications of overlapping affective dispositions. Psychol Bull. 2005; 131(2):260–300. [PubMed: 15740422]

16. 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; 364:937–952. [PubMed: 15364185]

17. Kawachi I, Colditz GA, Ascherio A, et al. Prospective study of phobic anxiety and risk of coronary heart disease in men. Circulation. 1994; 89:1992–1997. [PubMed: 8181122]

18. Kawachi I, Sparrow D, Vokonas PS, Weiss ST. Symptoms of anxiety and risk of coronary heart disease: the Normative Aging Study. Circulation. 1994; 90:2225–2229. [PubMed: 7955177]

19. Denollet J, Brutsaert DL. Personality, disease severity, and the risk of long-term cardiac events in patients with a decreased ejection fraction after myocardial infarction. Circulation. 1998; 97(2):167–173. [PubMed: 9445169]

20. Denollet J, Vaes J, Brutsaert DL. Inadequate response to treatment in coronary heart disease: adverse effects of type D personality and younger age on 5-year prognosis and quality of life. Circulation. 2000; 102(6):630–635. [PubMed: 10931802]

21. Frasure-Smith N, Lespérance F, Talajic M. The impact of negative emotions on prognosis following myocardial infarction: is it more than depression? Health Psychol. 1995; 14(5):388–398. [PubMed: 7498109]

22. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation. 1999; 99(16):2192–2217. [PubMed: 10217662]

23. Grace SL, Abbey SE, Irvine J, Shnek ZM, Stewart DE. Prospective examination of anxiety persistence and its relationship to cardiac symptoms and recurrent cardiac events. Psychother Psychosom. 2004; 73(6):344–352. [PubMed: 15479989]

24. Lavie CJ, Milani RV. Prevalence of anxiety in coronary patients with improvement following cardiac rehabilitation and exercise training. Am J Cardiol. 2004; 93(3):336–339. [PubMed: 14759385]

25. Haines AP, Imeson JD, Meade TW. Phobic anxiety and ischaemic heart disease. BMJ (Clin Res Ed). 1987; 295(6593):297–299.

26. Mayou RA, Gill D, Thompson DR, et al. Depression and anxiety as predictors of outcome after myocardial infarction. Psychosom Med. 2000; 62(2):212–219. [PubMed: 10772399]

27. Herrmann C, Brand-Driehorst S, Buss U, Rüger U. Effects of anxiety and depression on 5-year mortality in 5057 patients referred for exercise testing. J Psychosom Res. 2000; 48(4–5):455–462. [PubMed: 10880666]

28. Frasure-Smith N, Lesperance F, Gravel G, Masson A, Juneau M, Bourassa MG. Long-term survival differences among low-anxious, high-anxious and repressive copers enrolled in the Montreal heart attack readjustment trial. Psychosom Med. 2002; 64(4):571–579. [PubMed: 12140346]

29. Carinci F, Nicolucci A, Ciampi A, et al. for the Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico. Role of interactions between psychological and clinical factors in determining 6-month mortality among patients with acute myocardial infarction. Application of recursive partitioning techniques to the GISSI-2 database. Eur Heart J. 1997; 18(5):835–845. [PubMed: 9152654]

30. Frasure-Smith N, Prince R. The ischemic heart disease life stress monitoring program: impact on mortality. Psychosom Med. 1985; 47:431–445. [PubMed: 4059478]

31. 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; 112:653–665. [PubMed: 3766365]

32. 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; 18:506–519. [PubMed: 10519467]

33. Linden W, Stossel C, Maurice J. Psychosocial interventions for patients with coronary artery disease: a meta analysis. Arch Intern Med. 1996; 156:745–752. [PubMed: 8615707]

34. Kawachi I, Sparrow D, Vokonas PS, Weiss ST. Decreased heart rate variability in men with phobic anxiety (data from the Normative Aging Study). Am J Cardiol. 1995; 75:882–885. [PubMed: 7732994]

35. Gold PW, Loriaux DL, Roy A, et al. Responses to corticotropin-releasing hormone in the hypercortisolism of depression and Cushing's disease: pathophysiologic and diagnostic implications. N Engl J Med. 1986; 314:1329–1335. [PubMed: 3010108]

36. Roberts AB, Roche NS, Winokur TS, Burmester JK, Sporn MB. Role of transforming growth factor-beta in maintenance of function of cultured neonatal cardiac myocytes: autocrine action and reversal of damaging effects of interleukin-1. J Clin Invest. 1992; 90:2056–2062. [PubMed: 1430228]

37. Everson-Rose SA, Lewis TT. Psychosocial factors and cardiovascular diseases. Annu Rev Public Health. 2005; 26:469–500. [PubMed: 15760298]

38. Kubzansky LD, Kawachi I. Going to the heart of the matter: do negative emotions cause coronary heart disease? J Psychosom Res. 2000; 48:323–337. [PubMed: 10880655]

39. Rozanski A, Blumenthal JA, Davidson KW, Saab P, Kubzansky LD. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. J Am Coll Cardiol. 2005; 45:637–651. [PubMed: 15734605]

40. Matsumoto Y, Uyama O, Shimizu S, et al. Do anger and aggression affect carotid atherosclerosis? Stroke. 1993; 24:983–986. [PubMed: 8322399]

41. Julkunen J, Salonen R, Kaplan GA, Chesney MA, Salonen JT. Hostility and the progression of carotid atherosclerosis. Psychosom Med. 1994; 56:519–525. [PubMed: 7871107]

42. 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; 60:633–638. [PubMed: 9773770]

43. Knox SS, Adelman A, Ellison RC. Hostility, social support, and carotid artery atherosclerosis in the National Heart, Lung, and Blood Institute Family Heart Study. Am J Cardiol. 2000; 86:1086–1089. [PubMed: 11074204]

44. 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; 36:1781–1788. [PubMed: 11092644]

45. Paterniti S, Zureik M, Ducimetiere PJT, Feve JM, Alperovitch A. Sustained anxiety and 4-year progression of carotid atherosclerosis. Arterioscler Thromb Vasc Biol. 2001; 21:136–141. [PubMed: 11145945]

46. White B, Baker LH. Ambulatory blood pressure monitoring in patients with panic disorder. Arch Intern Med. 1987; 147:1973–1975. [PubMed: 3675099]

47. Bahnahan BF, Sharpe TR, Baker JA, Liao WC, Smith MC. Hypertension and stress: a preventive approach. J Psychosom Res. 1979; 23:69–75. [PubMed: 480283]

48. Whitehead WE, Blackwell B, Desilva H, Robinson A. Anxiety and anger in hypertension. J Psychosom Res. 1977; 21:383–389. [PubMed: 592229]

49. Johnson, EH. Doctoral dissertation. University of South Florida; Tampa, FL: 1984. Anger and anxiety as determinants of elevated blood pressure in adolescents.

50. Spielberger, CD.; Rickman, RL. Assessment of state and trait anxiety in cardiovascular disorders. In: Byrne, DG.; Rosenman, RH., editors. Anxiety and the Heart. Hemisphere Publishing Corporation; New York: 1990. p. 73-92.

51. Thurston R, Kubzansky LD, Kawachi I, Berkman L. Do depression and anxiety mediate the link between educational attainment and coronary heart disease? Psychosom Med. 2006; 68:25–32. [PubMed: 16449408]

52. Albert CM, Chae CU, Rexrode KM, Manson JE, Kawachi I. Phobic anxiety and risk of coronary heart disease and sudden cardiac death among women. Circulation. 2005; 111:480–487. [PubMed: 15687137]

53. Eaker ED, Pinsky J, Castelli WP. Myocardial infarction and coronary death among women: psychosocial predictors from a 20-year follow-up of women in the Framingham Study. Am J Epidemiol. 1992; 135:854–864. [PubMed: 1585898]

54. Eaker ED, Sullivan LM, Kelly-Hayes M, D'Agostino RB Sr. Benjamin EJ. Tension and anxiety and the prediction of the 10-year incidence of coronary heart disease, atrial fibrillationand total mortality: the Framingham Offspring Study. Psychosom Med. 2005; 67:692–696. [PubMed: 16204425]

55. Haines A, Cooper J, Meade TW. Psychological characteristics and fatal ischemic heart disease. Heart. 2001; 85:385–389. [PubMed: 11250959]

56. Kubzansky LD, Kawachi I, Spiro A III, Weiss ST, Vokonas PT, Sparrow D. Is worrying bad for your heart? A prospective study of worry and coronary heart disease in the Normative Aging Study. Circulation. 1997; 95:818–824. [PubMed: 9054737]

57. Nicholson A, Fuhrer R, Marmot M. Psychological distress as a predictor of CHD events in men: the effect of persistence and components of risk. Psychosom Med. 2005; 67:522–530. [PubMed: 16046363]

58. Weitoft, G Ringback; Rosen, M. Is perceived nervousness and anxiety a predictor of premature mortality and severe morbidity? A longitudinal follow up of the Swedish survey of living conditions. J Epidemiol Community Health. 2005; 59:794–798. [PubMed: 16100319]

59. Chang PP, Ford DE, Meoni LA, Wang NY, Klag MJ. Anger in young men and subsequent premature cardiovascular disease: the precursors study. Arch Intern Med. 2002; 162:901–906. [PubMed: 11966341]

60. Eaker ED, Sullivan LM, Kelly-Hayes M, D'Agostino RB Sr, Benjamin EJ. Anger and hostility predict the development of atrial fibrillation in men in the Framingham Offspring Study. Circulation. 2004; 109:1267–1271. [PubMed: 14993133]

61. Kawachi I, Sparrow D, Spiro A, Vokonas P, Weiss ST. A prospective study of anger and coronary heart disease. The Normative Aging Study. Circulation. 1996; 94:2090–2095. [PubMed: 8901656]

62. Williams JE, Nieto FJ, Sanford CP, Tyroler HA. Effects of an angry temperament on coronary heart disease risk: the Atherosclerosis Risk in Communities Study. Am J Epidemiol. 2001; 154:230–235. [PubMed: 11479187]

63. Williams JE, Paton CC, Siegler IC, Eigenbrodt ML, Nieto FJ, Tyroler HA. Anger proneness predicts coronary heart disease risk: prospective analysis from the Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2000; 101:2034–2039. [PubMed: 10790343]

64. Strik JJMH, Denollet J, Lousberg R, Honig A. Comparing symptoms of depression and anxiety as predictors of cardiac events and increased health care consumption after myocardial infarction. J Am Coll Cardiol. 2003; 42(10):1801–1807. [PubMed: 14642691]

65. Jiang W, Kuchibhatla M, Cuffe MS, et al. Prognostic value of anxiety and depression in patients with chronic heart failure. Circulation. 2004; 110(22):3452–3456. [PubMed: 15557372]

66. Benninghoven D, Kaduk A, Wiegand U, Specht T, Kunzendorf S, Jantschek G. Influence of anxiety on the course of heart disease after acute myocardial infarction: risk factor or protective function? Psychother Psychosom. 2006; 75(1):56–61. [PubMed: 16361875]

67. Shibeshi WA, Young-Xu Y, Blatt CM. Anxiety worsens prognosis in patients with coronary artery disease. J Am Coll Cardiol. 2007; 49(20):2021–2027. [PubMed: 17512358]

68. Hermann C, Brand-Driehorst S, Kaminsky B, Leibing E, Staats H, Ruger U. Diagnosis groups and depressed mood as predictors of 22-month mortality in medical patients. Psychosom Med. 1998; 60:570–577. [PubMed: 9773760]

69. Moser DK, Dracup K. Is anxiety early after myocardial infarction associated with subsequent ischemic and arrhythmic events? Psychosom Med. 1996; 58:395–401. [PubMed: 8902890]

70. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand. 1983; 67(6):361–370. [PubMed: 6880820]

71. Riedinger MS, Dracup KA, Brecht ML. Quality of life in women with heart failure, normative groups, and patients with other chronic conditions. Am J Crit Care. 2002; 11:211–219. [PubMed: 12022484]

72. Tsuchihashi-Makaya M, Kato N, Chishaki A, Takeshita A, Tsutsui H. Anxiety and poor social support are independently associated with adverse outcomes in patients with mild heart failure. Circ J. 2009; 73(2):280–287. [PubMed: 19096191]

73. Friedmann E, Thomas SA, Liu F, Morton PG, Chapa D, Gottlieb SS. Relationship of depression, anxiety, and social isolation to chronic heart failure outpatient mortality. Am Heart J. 2006; 152:940, e1–e8. [PubMed: 17070164]

74. Jiang W, Kuchibhatla M, Cuffe MS, et al. Prognostic value of anxiety and depression in patients with chronic heart failure. Circulation. 2004; 110:3452–3456. [PubMed: 15557372]

75. Haworth JE, Moniz-Cook E, Clark AL, Wang M, Waddington R, Cleland JG. Prevalence and predictors of anxiety and depression in a sample of chronic heart failure patients with left ventricular systolic dysfunction. Eur J Heart Fail. 2005; 7:803–808. [PubMed: 16054436]

76. Junger J, Schellberg D, Muller-Tasch T, et al. Depression increasingly predicts mortality in the course of congestive heart failure. Eur J Heart Fail. 2005; 7:261–267. [PubMed: 15701476]

77. Vaccarino V, Kasl SV, Abramson J, Krumholz HM. Depressive symptoms and risk of functional decline and death in patients with heart failure. J Am Coll Cardiol. 2001; 38:199–205. [PubMed: 11451275]

78. Konstam V, Salem D, Pouleur H, et al. Baseline quality of life as a predictor of mortality and hospitalization in 5,025 patients with congestive heart failure: SOLVD Investigations (Studies of Left Ventricular Dysfunction Investigators). Am J Cardiol. 1996; 78:890–895. [PubMed: 8888661]

79. Albus M, Bondy B, Ackenheil M. Adrenergic receptors on blood cells:relation to the pathophysiology of anxiety. Clin Neuropharmacol. 1986; 9(Suppl 4):359–361.

80. Aronson TA, Carasiti I, McBane D, Whitaker-Axmitia P. Biological correlates of lactate sensitivity in panic disorder. Biol Psychiatry. 1989; 26:463–477. [PubMed: 2551398]

81. Brown SL, Charney DS, Woods SW, Heninger GR, Tallman J. Lymphocyte beta-adrenergic receptor binding in panic disorder. Psychopharmacology (Berl). 1988; 94:24–28. [PubMed: 2894700]

82. Charney DS, Innis RB, Duman RS, Woods SW, Heninger GR. Platelet alpha-2-receptor binding and adenylate cyclase activity in panic disorder. Psychopharmacology (Berl). 1989; 98:102–107. [PubMed: 2543016]

83. Lima DR, Turner P. Propranolol increases reduced beta-receptor function in severely anxious patients (letter). Lancet. 1983; ii:1505. [PubMed: 6140598]

84. Cameron OG, Nesse RM. Systematic hormonal and physiological abnormalities in anxiety disorders. Psychoneuroendocrinology. 1988; 13:287–307. [PubMed: 2906440]

85. Cameron OG, Smith CB, Lee MA, Hollingsworth PJ, Hill EM, Curtis GC. Adrenergic status in anxiety disorders: platelet a2-adrenergic receptor binding, blood pressure, and plasma catecholamines in panic and generalized anxiety disorder patients and normal subjects. Biol Psychiatry. 1990; 28:3–20. [PubMed: 2165422]

86. Stein MB, Tancer ME, Uhde TW. Heart rate and plasma norepinephrine responsivity to orthostatic challenge in anxiety disorders: comparison of patients with panic disorder and social phobia and normal control subjects. Arch Gen Psychiatry. 1992; 49:311–317. [PubMed: 1558465]

87. Nesse RM, Cameron OG, Curtis GC, McCann DS, Huber-Smith MJ. Adrenergic function in panic anxiety patients. Arch Gen Psychiatry. 1984; 41:771–776. [PubMed: 6331337]

88. Lown B, Verrier RL, Corbalan R. Psychologic stress and threshold for repetitive ventricular response. Science. 1973; 182:834–836. [PubMed: 4795748]

89. Rich MW, Saini J, Kleiger RE, Carney RM, TeVelde A, Freedland KE. Correlation of heart rate variability with clinical and angiographic variables and late mortality after coronary angiography. Am J Cardiol. 1988; 62:59–66. [PubMed: 2968043]

90. Farrell TG, Bashir Y, Cripps TR, et al. Heart rate variability and sudden death secondary to coronary artery disease during ambulatory electrocardiographic monitoring. Am J Cardiol. 1987; 60:86–89. [PubMed: 3300247]

91. Vanoli E, DeFerrari GM, Stramba-Badiale M, Hull SS, Foreman RD, Schwartz PJ. Vagal stimulation and prevention of sudden death in conscious death with a healed myocardial infarction. Circ Res. 1991; 68:1471–1481. [PubMed: 2019002]

92. Billman GE, Schwartz PJ, Stone HL. Baroreceptor reflex control of heart rate: a predictor of sudden cardiac death. Circulation. 1982; 66:874–880. [PubMed: 7116603]

93. DeFerrari GM, Landolina M, Mantica M, Manfredini R, Schawartz PJ, Lotto A. Baroreflex sensitivity, but not heart rate variability, is reduced in patients with life threatening ventricular arrhythmias long after myocardial infarction. Am Heart J. 1995; 130:473–480. [PubMed: 7661063]

94. Watkins LL, Grossman P, Krishnan R, Sherwood A. Anxiety and vagal control of heart risk. Psychosom Med. 1998; 60:498–502. [PubMed: 9710297]

95. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998; 97:1837–1847. [PubMed: 9603539]

96. Kubzansky LD, Cole SR, Kawachi I, Vokonas PS, Sparrow D. Shared and unique contributions of anger, anxiety, and depression to coronary heart disease: a prospective study in the Normative Aging Study. Ann Behav Med. 2006; 31:21–29. [PubMed: 16472035]

97. 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; 160:2101–2107. [PubMed: 10904452]

98. Konstam V, Moser DK, De Jong MJ. Depression and anxiety in heart failure. J Card Fail. 2005; 11:455–463. [PubMed: 16105637]

99. Horwitz RI, Viscoli CM, Berkman L, et al. Treatment adherence and risk of death after a myocardial infarction. Lancet. 1990; 336:542–545. [PubMed: 1975045]

100. Dracup K, Evangelista LS, Hamilton MA, et al. Effects of a home-based exercise program on clinical outcomes in heart failure. Am Heart J. 2007; 154:877–883. [PubMed: 17967593]

101. Riegel B, Moser DK, Anker SD, et al. American Heart Association Council on Cardiovascular Nursing; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Nutrition, Physical Activity, and Metabolism; American Heart Association Interdisciplinary Council on Quality of Care and Outcomes Research. State of the science: promoting self-care in persons with heart failure: a scientific statement from the American Heart Association. Circulation. 2009; 120(12):1141–1163. [PubMed: 19720935]

102. Rose SK, Conn VS, Rodeman BJ. Anxiety and self-care following myocardial infarction. Issues Ment Health Nurs. 1994; 15:433–444. [PubMed: 8056572]

103. Maeland JG, Havik OE. After the myocardial infarction: a medical and psychological study with special emphasis on perceived illness. Scand J Rehabil Med Suppl. 1989; 22:1–87. [PubMed: 2649976]

104. Lane D, Carroll D, Ring C, Beevers DG, Lip GY. Predictors of attendance at cardiac rehabilitation after myocardial infarction. J Psychosom Res. 2001; 51:497–501. [PubMed: 11602219]

105. Schweitzer RD, Head K, Dwyer JW. Psychological factors and treatment adherence behavior in patients with chronic heart failure. J Cardiovasc Nurs. 2007; 22:76–83. [PubMed: 17224702]

106. Todaro JF, Shen BJ, Niaura R, Spiro A, Ward KD. Effect of negative emotions on frequency of coronary heart disease (the Normative Aging Study). Am J Cardiol. 2003; 92:901–906. [PubMed: 14556863]

107. Rosengren S, 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; 364:953–962. [PubMed: 15364186]

108. Rugulies R. Depression as a predictor for coronary heart disease. a review and meta-analysis. Am J Prev Med. 2002; 23:51–61. [PubMed: 12093424]