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Risk Factors: Anxiety and Risk of Cardiac Events

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Abstract

Two recent studies published in the *Journal of the American College of Cardiology* report the prognostic significance of anxiety in the development of coronary heart disease in initially healthy adults. These findings are placed in the context of other published reports and highlight the need for future research that includes representative samples of women and minorities using precise assessment tools and careful ascertainment of clinical endpoints.

It now is widely recognized that clinical depression or elevated depressive symptoms are prospectively related to increased mortality and morbidity in healthy adults¹ and in patients with coronary heart disease (CHD)²⁻⁴. As a result of this evidence, the American Heart Association has recommended that clinicians assess depression in patients with CHD⁵.

To date, there has been no such recommendation for anxiety, as there is no consensus regarding the relationship between anxiety and CHD. Anxiety is a ubiquitous condition that is the most common psychiatric disorder recognized by the Diagnostic and Statistical Manual-IV of the American Psychiatric Association⁶. The one year prevalence of anxiety disorders is 18% in American adults⁷. Anxiety disorders take many forms, including panic attacks, generalized anxiety disorder, various phobias, social anxiety disorder, obsessive-compulsive disorder, and post-traumatic stress disorder⁶. Diagnosis is typically based upon subjective mood and physiological correlates including excessive worry and rumination, difficulty controlling anxious thoughts, hypervigilance, excessive sweating, heart palpitations, and increased urinary urgency, and may be assessed by a wide range of psychometric questionnaires with no universally accepted “gold standard.” Many patients with chronically high levels of anxiety may not meet diagnostic criteria for an anxiety disorder because their symptoms may fluctuate over time or may not be associated with the psychophysiologic symptoms required to meet diagnostic criteria. Further complicating the clinical picture is the extent to which chronic worry affects help-seeking behavior. Concerns about health can lead to the adoption of healthy lifestyle behaviors or more frequent doctor visits, which could reduce risk for CHD, or it could result in avoidance of the health care system, and generalized anxiety disorder has been reportedly associated with a low rate of help seeking⁸.

Because there is considerable overlap between anxiety and depressive symptoms with regard to their clinical presentation, some have suggested that anxiety and depression may share a common dimension of ‘negative affect’,⁹⁻¹¹ although aspects of anxiety may independently increase CHD risk¹¹. Despite these common features, however, there is considerably less consistent evidence that anxiety is predictive of adverse events in CHD patients or that anxiety predisposes healthy individuals to develop CHD¹². In fact, a number of studies have found an inverse relationship between levels of anxiety and cardiac outcomes. For example,

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data from the Norwegian HUNT study¹³, a large ($n > 60,000$) population-based sample, found reduced rates of CHD and all-cause mortality in patients with *higher* anxiety scores. Meyer et al.¹⁴ recently reported that among patients with no CHD, anxiety was associated with *better* survival, even after controlling for physical risk factors. The beneficial effect of anxiety on survival was also seen in patients diagnosed with CHD, as long as they had no history of myocardial infarction (MI). In post-MI patients with reduced left ventricular function, higher anxiety scores were associated with greater mortality. Thus, the prognostic value of anxiety is complex and, for reasons that are not entirely clear, may depend on the presence and severity of CHD.

Two papers published in the *Journal* add to this growing literature and provide further evidence that anxiety is prospectively related to the subsequent development of CHD. In part because of inconsistencies in the literature, Roest and colleagues¹⁵ performed a meta analysis involving 20 prospective studies comprising 249,846 initially healthy men and women age 38-72 years, followed over an average of more than 11 years. Anxiety was assessed by a variety of measures. Results indicated that anxious individuals were at increased risk for CHD events (hazard ratio [HR]=1.26; 95% CI=1.15-1.38) and cardiac death (HR=1.48; 95% CI=1.14-1.92) but not for non-fatal MI (HR=1.43; 95% CI= 0.85-2.40).

In a second study, Janszky and colleagues¹⁶ followed 49,321 Swedish men age 18 to 20 years who were screened for military service in 1969-70 and followed for CHD for 37 years. Almost 20% of conscripts were examined by a psychiatrist; depression, defined as having a diagnosis of psychotic or neurotic depression, was present in 1% of the sample, while anxiety defined as anxiety neurosis was present in 0.3% of the sample. Results indicated that men diagnosed with anxiety, but not depression, were more than twice as likely to develop CHD compared to their non-anxious counterparts. The study had a number of strengths including a large sample with complete follow-up information for virtually all participants. Statistical analyses adjusted for key CHD risk factors including clinic blood pressure, reported smoking, and physical activity (inferred from membership in sport clubs). However, because the CHD event rate was only 4%, the study lacked adequate power to examine the potential interaction of anxiety and depression, and did not include women. This latter limitation is important because women are more than twice as likely to be diagnosed with depression or anxiety disorders compared to men¹⁷. Moreover, because anxiety and depression frequently co-occur⁷ the two conditions may interact to potentiate cardiac risk. For example, Phillips et al.¹⁸ reported that individuals with generalized anxiety disorder and depression were at greatest risk for subsequent cardiac death and a report from the WISE study of 489 women with suspected CHD reported that depression predicted CHD events in women with low anxiety but not in women with high anxiety¹⁹.

Janszky et al.¹⁶ also had to rely on an outdated psychiatric diagnostic system; newer diagnostic formulations distinguish between various subtypes of anxiety disorders. Indeed, it is not clear if subtypes of anxiety disorders are differentially associated with varying levels of risk of different clinical manifestations of CHD or whether the entire spectrum of anxiety disorders place individuals at higher risk for CHD events. In the Women's Health Initiative study of 3,369 medically healthy community-dwelling postmenopausal women, for example, panic disorder was associated with a 1.8 fold increased risk of all-cause mortality²⁰. Similarly, in the Nurses' Health Study cohort of 72,359 women with no history of CHD, women with high phobic anxiety scores were at a 1.3-fold increased risk of fatal CHD and a 1.6-fold increased risk of sudden cardiac death compared with those women with low phobic anxiety²¹. Gender also may be an important moderator or risk. Watkins and colleagues²² recently reported results from a prospective cohort study in 947 CHD patients in which female CHD patients with high levels of phobic anxiety had a 1.6-fold

increased risk of cardiac mortality (HR=1.56; 95% CI= 1.15-2.11) and a 2.0-fold increased risk of sudden cardiac death (HR=2.02; 95% CI, 1.16-3.52); in contrast, no such relationship was observed in men.

In summary, the two reports published in the *Journal* provide evidence for the prognostic value of anxiety in the development of CHD in apparently healthy adults. However, there remains uncertainty about the role of anxiety in cardiac health. Inconsistencies in the literature result from non-standardized assessment tools and complex interactions with CHD disease severity, gender, and comorbid conditions such as depression. Research in this field will progress if studies use common instruments for assessing anxiety so that results can be compared across studies. Because of the high prevalence of comorbidity of anxiety and depression, it will be important to evaluate the separate and joint effects of these two conditions on clinical outcomes. It also will be important to quantify participants' actual exposure to determine the relative importance of duration, severity, frequency of recurrence of symptoms, and any treatment that participants may receive over the course of the follow-up period. Future studies also will need to include diverse, healthy and CHD patient groups, and consider potential mechanisms by which different types of anxiety disorders may be associated with clinical CHD events.

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