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A Narrative Review of the Relationship Between Coronary Heart Disease and Anxiety

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Abstract

Context: Coronary heart disease (CHD) is the most common cause of death and disability in the world. While the relationship between depression and CHD is well documented, anxiety remains understudied, despite its common cooccurrence.
Evidence Acquisition: A PubMed (MEDLINE) search was conducted in order to find articles published between January 2000 and December 2015, using the following keywords: "coronary heart disease" and "anxiety". In total, 79 out of 1138 articles were considered relevant by consensus between the authors and were reviewed.
Results: According to previous studies, anxiety is suggested to increase the risk of CHD. Anxiety is associated with an increase in cardiac complications, morbidity and mortality. Also, a lower quality of life has been described among patients after acute coronary syndrome, with a few studies reporting contradictory findings. Although studies on anxiety management in CHD are sparse, selective serotonin reuptake inhibitors have been shown to be relatively safe for patients. On the other hand, psychological interventions have not been adequately evaluated, although some studies have revealed their advantages.
Conclusions: Evidence suggests that anxiety is associated with the development and course of CHD. Awareness and appropriate training in cardiology settings need to be prioritized to improve early identification and initiation of effective management.

Keywords: Anxiety, Coronary Heart Disease, Etiology, Outcomes, Panic Disord

1. Context

Coronary heart disease (CHD) is the most common cause of death and disability in the world (1). A number of recent studies have reported the role of psychological factors in morbidity and mortality among patients with cardiac diseases (2-5). The results of these studies, though with some inconsistencies, suggest that a wide spectrum of psychiatric conditions can negatively influence cardiac outcomes and lead to a higher risk of death and disability, lower quality of life, and poor compliance with medications.

The most robust evidence among psychological disorders is for the relationship between CHD and depressive disorders and suggests a consistent association with adverse outcomes. Major depression following myocardial infarction (MI) is common, affecting approximately 20% of all MI patients (5, 6). Although equally common, anxiety is understudied in patients with cardiovascular diseases. According to the literature, approximately 19% of patients with MI experience elevated anxiety (7).

Due to the common cooccurrence of anxiety and CHD, there is an increasing interest in research regarding the effects of anxiety on cardiac events and subsequent mortality and morbidity. Better detection and treatment of anxiety is warranted if evidence confirms that anxiety is independently associated with in-hospital complications and prognosis of CHD. Additionally, there is evidence revealing the availability, efficacy, and safety of various treatment modalities for anxiety in acute medical settings (8, 9). If identification and proper management of anxiety in various phases of CHD can reduce the associated mortality and morbidity, attention to this aspect can be of immense public health importance.

With this background in mind, the present narrative review was performed to assess the available evidence with regard to the relationship between anxiety and cardiac events. The following aspects will be specifically scrutinized in this study: the etiological role of anxiety in CHD, the effect of anxiety on different phases of CHD, the confounding effects of other psychological conditions (especially depression) and anxiety, postulated mechanisms, management strategies, and future directions.

2. Evidence Acquisition

Articles published from January 2000 to December 2015 were searched on PubMed (MEDLINE), using the fol-

lowing keywords: "coronary heart disease" and "anxiety". Furthermore, complementary topic-specific search was conducted, using some other keywords, ie, "etiology", "treatment", and "prognosis". A total of 1138 articles were retrieved. The titles and abstracts of the articles were evaluated, and irrelevant ones in the authors' opinions were excluded. Finally, a total of 79 articles were considered relevant by consensus between the authors and were reviewed. There were no ethical issues in performing this article.

3. Results

3.1. Anxiety as an Etiological Factor for CHD

Multiple studies have found an association between anxiety and incident cardiovascular diseases. In this regard, a study, which assessed a total of 39 920 panic disorder (PD) patients and an equal number of patients without PD, showed that PD patients had a 2-fold increased risk of CHD in the prospective follow-ups (hazard ratio (HR), 1.87; 95% CI, 1.80 - 1.91). Also, after controlling for the covariates, PD patients with depression were nearly 3 times more likely to develop CHD (HR, 2.60; 95% CI, 2.30 - 3.01) (10).

Another study on PD patients reported the increased risk of MI in patients under 50 years (HR, 1.38; 95% CI, 1.06-1.79) and CHD at all ages (< 50 years: HR, 1.44; 95% CI, 1.25 - 1.65; > 50 years: HR, 1.11; 95% CI, 1.03 - 1.20). However, they did not report any increase in the risk of MI in subjects over 50 years (HR, 0.92; 95% CI, 0.82 - 1.03), while they found a slightly reduced CHD mortality at all ages (HR, 0.76; 95% CI, 0.66 - 0.88) (11). The disparate findings could be attributed to the initial misdiagnosis of CHD as panic in young people, which could lead to increased mortality. Also, the health-seeking behaviors of PD patients could have contributed to a slight decline in the overall mortality.

In a study on postmenopausal women (Women's Health Initiative Observational Study), subjects reporting at least 1 panic attack in the past 6 months were at the increased risk of future cardiovascular events during a follow-up period of 5.3 years. Even after adjusting for multiple confounding factors, a recent history of full-blown panic attack was independently associated with a nearly 4-fold increase in the risk of MI and a nearly 3-fold increase in the combined risk of CHD or stroke (12). In addition, a recent meta-analysis showed that PD could predict incident CHD. The risk continued to be significant even after adjusting for depression; however, this study could not rule out reverse causality (13).

In a cross sectional survey of 3032 adults, aged 25 - 74 years, diagnosis of generalized anxiety disorder (GAD) independently predicted the increased risk of CHD ($F(1, 3018)$, 5.14; b = 0.39; 95% CI, 0.05 - 0.72) (14). Furthermore, in the Normative Aging Study (NAS) among subjects with symptoms of posttraumatic stress disorder (PTSD), by each standard deviation (SD) increase in the symptom level, the age-adjusted combined relative risk of nonfatal MI and fatal CHD raised by 1.26 (95% CI, 1.05 - 1.51) and 1.21 (95% CI, 1.05 - 1.41) folds, respectively (15).

A 37-year follow-up study of 49 321 young Swedish men showed that anxiety, which was diagnosed based on the international classification of diseases, revision 8 (ICD-8) criteria, independently predicted subsequent CHD (16). Also, in a study on 72 359 women with no history of CHD, those with scores $\geq$ 4 (the highest level of phobic anxiety) on the Crown Crisp Index (CCI) did not experience a major increase in the risk of sudden cardiac death (SCD) (HR, 1.59; 95% CI, 0.97 - 2.60) or fatal CHD (HR, 1.31; 95% CI, 0.97 - 1.75), compared with those who scored 0 or 1 (17).

In addition, a meta-analysis of 20 studies evaluated incident CHD in 249,846 subjects during a mean follow-up of 11.2 years. After controlling for major confounding variables, the results suggested that anxious people are at a risk of CHD (random HR, 1.26; 95% CI, 1.15 - 1.38; P < 0.0001) and cardiac death (HR, 1.48; 95% CI, 1.14 - 1.92; P = 0.003). Also, the association between anxiety and nonfatal MI was insignificant (HR, 1.43; 95% CI, 0.85 - 2.40; P = 0.180) (18). Therefore, multiple studies have reported anxiety as a symptom rather than a diagnosis, thus suggesting its etiological role in the development of CHD. Furthermore, evidence suggests that the risk of CHD can be extended to different diagnostic categories, including PD, PTSD, and GAD.

3.2. Anxiety During Acute Coronary Syndrome (ACS) and Immediate Cardiac Complications

ACS includes any condition in which there is a sudden reduction in the blood flow to the heart, leading to features of MI. Unstable angina and MI are both categorized as ACS (19). Multiple studies have evaluated the relationship between anxiety, ACS, and its consequences. In a study conducted in Massachusetts General hospital, 110 MI patients were assessed using Beck Anxiety Inventory (BAI) within 72 hours of admission. After controlling for the known cardiac risk factors, subjects with higher levels of post-MI anxiety had more in-hospital cardiac complications. Furthermore, post-MI anxiety remained an independent predictor of cardiac complications, even after controlling for depressive symptoms (20).

Similar results have been reported in a study assessing anxiety, using Brief Symptom Inventory (BSI) within 72 hours of admission in 322 MI patients. Anxious patients had more complications, such as recurrent ischemia and ventricular fibrillation (mean $\pm$ SD, 1.43 $\pm$ 0.15 vs. 0.73 $\pm$ 0.09; P $\leq$ 0.01) and longer hospital stays (7.0 $\pm$ 0.49 vs. 5.7

± 0.36 days; P < 0.05) (21). Poor outcomes, both with regard to mortality and nonfatal MI, have been also reported in patients of Chinese Han ethnicity with coronary artery disease (CAD) and anxiety (22).

In a multicenter study, involving 536 hospitalized MI patients, those with higher levels of perceived control had substantially lower levels of anxiety (P = 0.001). Nearly 27% of patients in the study experienced 1 or more in-hospital complications, with the proportion being higher among patients with higher levels of anxiety (P < 0.01); also, the risk was the greatest in the group with high anxiety and low perceived control (23). Therefore, there is robust evidence linking immediate post-ACS anxiety to more severe cardiac complications.

3.3. Anxiety in CHD and Long-Term Cardiac Outcomes

Many studies have assessed long-term outcomes in patients with anxiety and CHD. In a follow-up study of 76 MI patients, anxiety was assessed, using Leubeck Interview for Psychosocial Screening (LIPS) within the first week and 31 months after MI; cardiac events were documented during this period. Among 23 patients with LIPS scores of 4 or 5, the cumulative incidence of cardiac events was significantly higher than patients with low anxiety levels (Mann-Whitney U = 447.5; P < 0.05). Based on the findings, the group with higher anxiety scores developed cardiac events earlier and more often than others. Incidentally, this study also reported that subjects with higher anxiety scores were more likely to continue smoking (24).

Furthermore, in a study on 133 Korean patients with CHD, who had undergone percutaneous coronary intervention, a moderate or severe level of anxiety, assessed by hospital anxiety depression scale (HADS), increased the risk of recurrent cardiac events, even after controlling for the confounding variables over a 12-month follow-up period (HR, 6.21; 95% CI, 1.64 - 23.54) (25).

In a prospective study conducted over 1 year, anxiety remained a significant predictor of self-reported, recurrent coronary events, even after controlling for depression and smoking (26). Another prospective 2-year follow-up study assessed 804 patients with CHD regarding depression (using BDI) and GAD (using HADS and structured clinical interview for DSM-IV). The incidence of major cardiac events was higher in subjects with major depressive disorder (MDD) (OR, 2.55; 95% CI, 1.38 - 4.73), GAD (OR, 2.47; 95% CI, 1.23 - 4.97), high BDI-II scores (OR, 1.81; 95%CI, 1.20 - 2.73), and increased HADS-A scores (OR, 1.66; 95% CI, 1.12 - 2.47) (27). Similar results were also reported in stable CHD outpatients with GAD, who were followed-up for 5.6 years (28).

In the VAGUS research, which was a prospective observational study with a median follow-up of 3 years among known CHD patients, higher risk of phobic anxiety was associated with ventricular arrhythmias even after controlling for sociodemographic and cardiac variables (OR, 1.4; CI, 1.1 - 1.8; P = 0.012) (29). Furthermore, in another study, female CHD patients with phobic anxiety had a 1.6-fold increased risk of cardiac mortality (HR, 1.56; 95% CI, 1.15 - 2.11; P = 0.004) and a 2-fold increased risk of SCD (HR, 2.02; 95% CI, 1.16 - 3.52; P = 0.01). However, phobic anxiety did not increase mortality among men (P = 0.56). A poor association with reduced heart rate variability (HRV) was reported in female patients with phobic anxiety; however, this finding could not explain the association between phobic anxiety and mortality (30).

A 2-year follow-up study, which examined anxiety at various points during the follow-up period, showed that persistent anxiety remained an independent predictor of cardiac events after controlling for multiple variables (HR, 1.27; 95% CI, 1.1 - 1.5) (31). Also, in another study, persistence of comorbid depression and anxiety was noted to significantly contribute to mortality (32). In addition, a recent 3-year follow-up study revealed that anxiety and depression were both independently associated with the increased risk of mortality, and cooccurrence of these conditions showed an additive 3-fold increased risk (33).

Anxiety in MI patients is also predictive of poor quality of life. In a previous study, MI patients with concomitant anxiety and depression at baseline were more likely to report pre-infarct distress and poor adjustment. These subjects also reported poor outcomes within 1 year on all dimensions of the 36-item short-form quality of life questionnaire and specific measures of daily activities, with no significant increase in the overall mortality (34). Similar findings have been also reported in another study, which assessed the effect of anxiety on the quality of life and mortality at 12 months following MI. While anxiety and depression did not deteriorate either cardiac or all-cause mortality, they predicted poor 12-month quality of life among the survivors (35).

Not all studies have reported poor long-term outcomes in patients with anxiety and ACS. In this regard, a follow-up study showed that depression and anxiety did not predict recurrent coronary events within 12 months after MI (36). Another study in Canada (Depression Effects on Coronary Artery Disease Events or DECADE) reported that depression rather than anxiety contributed to poor cardiac outcomes during the follow-up period of 8.8 years (37). Additionally, in a recent meta-analysis, anxiety was associated with a moderate increase in the risk of mortality, based on the unadjusted evaluations (OR, 1.21 per SD increase in anxiety). However, by adjusting for the covariates, the association became insignificant (38).

Furthermore, a previous study assessed 489 patients

with ACS for current and lifetime anxiety disorders, using Composite International Diagnostic Interview (CIDI), complemented with clinical judgment, and reassessed the cardiac outcomes during 1 year. After controlling for depression, demographics, and cardiac covariates, there was a trend for lifetime diagnosis of agarophobia to predict poorer outcomes, whereas diagnosis of lifetime GAD predicted better outcomes. Paradoxically, "apprehensive worrying" in subjects with GAD might have improved the outcomes through greater adherence to treatment and self-management (39). Furthermore, a few other studies have suggested the protective effects of anxiety on CHD (40, 41).

While negative long-term outcomes have been reported in anxious patients with CHD, the findings have not been universally replicated. Studies also vary with respect to parameters of poor outcomes. While some studies have reported higher morbidity and mortality, others have found no difference in morbidity or mortality and only showed poor quality of life. In addition, according to some studies, anxiety could contribute to better outcomes, suggesting the need for further evaluations.

3.4. The Postulated Mechanisms

Different mechanisms have been proposed regarding the effects of anxiety on cardiac function. Anxiety has been reported to produce a reversible myocardial perfusion defect in the blood supply, which can further deteriorate perfusion defects in patients with CHD (42). HRV is considered a non-invasive marker of autonomic dysfunction and seems to be affected in patients with anxiety and cardiac illness.

Various studies have noted a lower HRV (43), lower parasympathetic activity, higher sympathetic/parasympathetic ratio (44), and lower sympathetic modulation in daily life activities among anxious patients, compared to healthy controls (45). All these factors can increase the risk of fatal arrhythmias and mortality in patients with anxiety disorders in case of a cardiac event. During panic attacks, large sympathetic bursts, a major increase in cardiac norepinephrine spillover, and a surge of adrenal medulla epinephrine secretion (suggestive of sympathetic dysfunction) have been reported (46).

Previous studies have assessed the relationship between anxiety and the process of atherosclerosis. A study on CHD patients at baseline showed that men and women with sustained anxiety experienced a greater increase in common carotid intima-media thickness over 4 years; additionally, men showed a higher risk of 4-year plaque occurrence (47). Other studies have shown that anxiety disorders are associated with coronary artery calcification, subclinical atherosclerosis, and greater arterial stiffness, all of which are known to be associated with the development and deterioration of atherosclerosis and the associated conditions (48-50).

Moreover, the ATTICA study found that Spielberger State Trait Anxiety Inventory (STAI) score was positively correlated with higher levels of coagulation and inflammatory factors, such as C-reactive protein, interleukin-6, homocysteine, and fibrinogen levels (51). Anxiety in individuals with atherosclerosis was also associated with poorer resistance vessel function (both endothelial and vascular smooth muscle functions) (52). Therefore, a unique combination of weaker resistance vessel function and higher risk of inflammation and coagulation in patients with chronic anxiety might contribute to the accelerated development of coronary atherosclerosis.

Hormonal factors are also involved in the relationship between anxiety and cardiovascular diseases. Activation of the hypothalamo-pituitary-adrenal axis (including the corticosteroid hormone pathway), along with secondary sympathetic activation, is noted in stress responses such as anxiety, which can affect cardiovascular functioning (53, 54). Also, hypocortisolemia, supersuppression following dexamethasone test, and increased frequency of glucocorticoid receptor changes, which are postulated to disturb cardiac function, are also characteristic features of chronic anxiety (55).

Moreover, behavioral factors are involved in the relationship between anxiety and cardiovascular functioning. Behavioral changes, such as increased smoking, low physical activity, and unhealthy diet are found to be associated with anxiety disorders and psychological distress, both of which can increase the risk of cardiovascular diseases (56, 57).

3.5. Management

3.5.1. Pharmacotherapy

Overall, 2 major classes of drugs, ie, benzodiazepines and antidepressants, have been used to manage anxiety disorders in cardiac diseases. Trials have been performed on the use of benzodiazepines in CHD (8). However, a major part of the available data on the use of antidepressants for the management of anxiety during cardiac events is based on studies on the management of depression in CHD (58).

Benzodiazepines are rapidly effective in the reduction of anxiety states (8). Rapid reduction of anxiety is specifically beneficial, as anxiety in ongoing or recent MI leads to elevated heart rate and blood pressure, which can in turn cause poor acute outcomes. Furthermore, positive acute physiological effects of benzodiazepines include acute lowering of sympathetic activation, increasing

coronary vascular dilatation, preventing dysrhythmia and block platelet aggregation (8). Nevertheless, the use of benzodiazepines is limited, owing to their association with sedation, respiratory depression, and dependence following prolonged use (59). In addition, benzodiazepines have limited benefits for comorbid depression, which is common in CHD patients.

The effectiveness of antidepressants has been confirmed in the treatment of patients with depression and anxiety disorders. Among these agents, selective serotonin reuptake inhibitors (SSRIs) are most widely studied and appear to be safe and effective in CHD patients. They do not commonly lead to adverse cardiovascular effects, can reduce recurrent cardiac events, and are well-tolerated in this population (9). Increased anxiety, insomnia, and restlessness, reported in the first few days after the onset of treatment, are generally mild and self-limiting.

The SADHAT trial, as an open-label study, followed by SADHEART, a double-blind randomized controlled trial (RCT), found that sertraline was safe and efficacious in MDD patients who began post-ACS treatment (60). Another RCT found fluoxetine to be safe and useful for MI patients with depression (61). Further evidence on the effectiveness of SSRI has been reported in a post hoc analysis of Enhancing Recovery in Coronary Heart Disease (ENRICHD), where patients receiving SSRIs, experienced more than trial, a 40% decline in the risk of cardiac mortality and reinfarction over a mean follow-up of 29 months, compared to those not taking SSRIs (62).

Similarly, the Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial introduced citalopram as a safe and efficacious agent for patients with depression (63). It has been also shown that escitalopram can reduce the risk of post-ACS depression and improve quality of life among patients with ACS and depression (64, 65). However, there is a possibility of SSRI increasing the risk of bleeding events, especially if used concurrently with nonsteroidal anti-inflammatory drugs or aspirin (9, 66).

Tricyclic antidepressants (eg, amitriptyline, imipramine, and nortriptyline) are generally not preferred for patients with cardiac diseases. Many cardiac side effects of tricyclic antidepressants, such as tachycardia, orthostatic hypotension, and proarrhythmic properties make them unsuitable for patients with underlying cardiac diseases. Higher rates of subsequent MI are also reported in patients receiving tricyclic antidepressants, compared to SSRIs (67). Similarly, venlafaxine, which can cause an increase in blood pressure especially at higher doses, may not be appropriate for patients with cardiac diseases (68).

Contradictory findings have been reported with respect to mirtazapine. In this regard, the MIND-IT study reported no improvement in long-term depression or cardiac prognosis, compared with usual care among post-MI patients, whereas another RCT found mirtazapine to be efficacious and safe (69, 70). Some side effects, such as weight gain and increased lipid level, may limit the use of this agent for the management of patients with a history of MI.

3.5.2. Psychotherapy

Psychotherapeutic interventions are appealing to cardiac patients, given the absence of physical side effects and drug interactions. To the best of our knowledge, no psychotherapeutic trials have evaluated anxiety in cardiac patients, although there are studies on psychosocial interventions in depressed cardiac patients. However, since many psychotherapeutic principles overlap in the management of anxiety and depression, the outcomes of trials on depression are suggested to be extended to anxiety, as well.

ENRICHD trial, which is the largest study on psychotherapy in post-MI patients, revealed that treatment with cognitive behavioral therapy (CBT) significantly lowered depressive symptoms and improved quality of life among post-MI patients. However, CBT, in contrast to antidepressants, did not improve the cardiac outcomes (71). Also, the CREATE trial, in addition to studying citalopram, found that interpersonal psychotherapy did not improve depressive symptoms, compared to active controls (63).

A recent Cochrane review and meta-analysis showed that psychological interventions resulted in small or moderate improvements in depression and anxiety and had a small effect on cardiac mortality (72). Many less vigorous studies have reported a variety of other supportive and psychotherapeutic interventions, which have been used in CHD patients for different psychological conditions; overall, these interventions appear to improve the outcomes (73, 74). Although psychotherapy can be individualized to highlight a patient's specific problems, availability of these interventions remains a serious restriction.

Exercise has been also noted to be effective in reducing depressive and anxiety symptoms and can have substantial cardiovascular benefits (75). Regular exercise is shown to have substantial advantages which tend to persist beyond 6 months. Nevertheless, improving the patient's depression or anxiety with medication or psychotherapy is often necessary before patients are motivated to adhere to regular exercise (76). It can be concluded that there is a paucity of evidence concerning the psychotherapy of anxiety in patients with CHD.

4. Conclusion

The findings of the present study were based on the review of articles published in PubMed during 2000 - 2015. Other relevant articles published in other resources, grey literature, or prior to year 2000 in PubMed might have been missed out, leading to possible selection bias. In addition, the finding presenting anxiety as an independent predictor of cardiac events and poor outcomes should be considered in the light of the following issues. Although we reported findings from previous studies on the relationship between pure anxiety and CHD, anxiety and depression themselves seem to have a moderate to strong correlation, meaning that it is not entirely possible to disentangle their effects on one another (77).

In addition, anxiety and depression are suggested to have potential additive effects. They may also be part of a larger and more stable psychological factor affecting CHD, such as negative affectivity (78, 79). Studies adjusting for coronary risk factors seldom included all major coronary risk factors, indicating that the overall association between adjusted anxiety and CHD could have been poorer. The meta-analysis of studies on anxiety in CHD indicates the possibility of publication bias, suggesting that the association between anxiety and CHD might be less significant than reported (18).

It should be noted that most previous studies have been conducted in Western populations, which might limit the generalization of the findings. Future research should focus on the specific aspects of anxiety which may contribute to cardiac outcomes. Also, there is a need to study mechanisms through which anxiety might affect the development of CHD from across the world.

In conclusion, evidence suggests that anxiety is associated with CHD. While the prevalence of anxiety is common among CHD patients, the major challenge is to ensure that anxious patients are detected early in cardiology settings and appropriate management is initiated. This can be facilitated only if cardiologists are trained to be proactive in addressing psychological and social factors, which affect morbidity and mortality among CHD patients. Also, further development of behavioral cardiology subspecialty in research areas and clinical practice can help achieve this goal.

Footnotes

Authors' Contribution: Jaisoorya T S and Ajit Bhalchandra Dahale conceived and designed the evaluation. Ajit Bhalchandra Dahale made the index search. Jaisoorya T S made the secondary search and interpreted the data. Ajit Bhalchandra Dahale wrote the first draft which was revised by Jaideep C Menon and Jaisoorya T S. Jaideep C Menon revised it critically for important intellectual content. All authors read and approved the final manuscript.

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