Published in final edited form as:

Psychosomatics. 2018 ; 59(4): 318–332. doi:10.1016/j.psych.2018.03.008.

Treatment of Anxiety in Patients with Coronary Heart Disease: A Systematic Review

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Abstract

Objective—Anxiety is common in patients with coronary heart disease (CHD) and is associated with increased risk for adverse outcomes. There has been a relative paucity of studies concerning treatment of anxiety in CHD patients. We conducted a systematic review to organize and assess research into the treatment of anxiety in CHD patients.

Methods—We searched CCTR/CENTRAL, MEDLINE, EMBASE, PsycINFO, and CINAHL for randomized clinical trials (RCTs) conducted before October 2016 that measured anxiety before and after an intervention for CHD patients.

Results—475 records were subjected to full text review, yielding 112 publications that met inclusion criteria plus an additional 7 studies from reference lists and published reviews, yielding 119 studies. Sample size, country of origin, study quality, and demographics varied widely between studies. The majority of studies were conducted with non-anxious patients. The Hospital Anxiety and Depression Scale and State-Trait Anxiety Inventory were the most frequently used instruments to assess anxiety. Interventions included pharmacological, counseling, relaxation-based, educational, or “alternative” therapies. Forty (33% of total) studies reported that the interventions reduced anxiety; treatment efficacy varied by study and type of intervention. Elevated anxiety was an inclusion criterion in only 4 studies, with inconsistent results.

Conclusion—Although there have been a number of RCTs of CHD patients that assessed anxiety, in most cases anxiety was a secondary outcome, and only one third found that symptoms of anxiety were reduced with treatment. Future studies need to target anxious patients and evaluate the effects of treatment on anxiety and relevant clinical endpoints.

Introduction

Coronary heart disease (CHD) is among the most prevalent diseases in developed countries and remains a leading cause of hospitalization, mortality, and healthcare expenditure

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Declarations of interest: None

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worldwide (1, 2). A number of risk factors contribute to the development and progression of CHD, including smoking, hypertension, dyslipidemia, and diabetes. There is growing recognition that psychosocial factors also have prognostic significance (3-5), with anxiety and depression in particular frequently studied in relation to heart disease.

Anxiety appears to be common among CHD patients. The prevalence of generalized anxiety disorder (GAD) in the CHD population has been estimated to be approximately be 8%, panic disorder 7%, agoraphobia 4%, social phobia 5%, and other phobias 4%; the prevalence of any anxiety disorder is around 15% in CHD patients, and is higher among CHD patients in inpatient settings.(6, 7) Perhaps due to its prevalence in the CHD population, anxiety has been increasingly studied as a prognostic factor in patients with CHD.

Pre-operative anxiety in patients undergoing coronary artery bypass graft surgery (CABG) has been associated with greater post-operative mortality (8), more readmissions (8), and more frequent outpatient clinic visits (9). In patients with stable CHD, both GAD and elevated anxiety symptoms are predictive of major adverse cardiac events (MACEs) (6, 10, 11) and all-cause mortality (10, 12-14). Anxiety appears to be associated with a 36% increased risk of adverse cardiac outcomes in post-ACS patients, as well as increased all-cause mortality, cardiac mortality, and cardiac events (15). Anxiety has also been independently associated with CHD risk factors, such as hypertension and tobacco use (16).

However, not all studies have confirmed a negative effect of anxiety on prognosis. For example, one meta-analysis of panic disorder in CHD found an inverse relationship between panic disorder and CHD in cardiology settings; ⁵ another recent meta-analysis reported no significant relationship between any subtype of anxiety and the development of MACEs in CHD patients (6, 17). Higher anxiety has also been associated with reduced incidence of CHD and mortality in at least two cohort studies (18, 19), and it has been suggested that some amount of anxiety, e.g. health-related concerns, may pre-empt patients to improve lifestyle factors related to CHD development (20). Thus, there may be factors that modify the relationship between anxiety and CHD, such as the level of anxiety or specific diagnosis, that deserve further attention.

In addition to anxiety, depression is common in patients with CHD, with major depressive disorder (MDD) affecting 15-20% of patients with acute coronary syndrome (ACS) and up to an additional 20% exhibiting elevated depressive symptoms (21). Moreover, MDD is associated with a two- to four-fold increase in mortality (22). In a recent systematic review, the American Heart Association recognized depression as a risk factor for ACS patients.(23) As MDD is widely recognized as a negative prognostic factor for CHD patients, there have been a number of randomized clinical trials (RCTs) treating depression in CHD patients (24-28); however to date, there has been little evidence that treating depression improves clinical outcomes (29).

Although anxiety is common in the CHD population and has been associated with increased risk for adverse events in some studies, the value of treating anxiety in these patients has received considerably less attention compared to depression(30, 31). Several meta-analyses show that exercise-based cardiac rehabilitation programs (CR) (32, 33), and music therapy

(34) may reduce anxiety in CHD patients, but these reports are based on relatively few published studies employing a variety of different interventions. Therefore, in order to compile and evaluate the existing interventions to reduce anxiety in CHD patients, we conducted a systematic review to examine the extant literature reporting the effects of treatment on anxiety in patients with CHD.

Methods

We systematically searched for RCTs that included a) outpatient interventions for patients with CHD; b) established measures of anxiety; and c) measures of anxiety pre-treatment and after the interventions were completed. Criteria for inclusion in our review were: (1) the study was a RCT; (2) all, or at least a significant proportion of patients, had CHD; (3) anxiety was measured and reported as an outcome; (4) the intervention occurred in an outpatient setting; and (5) the article was published in English in a peer-reviewed journal (i.e., conference abstracts and dissertations were excluded). Articles also were excluded from our review for the following reasons: (1) the study was conducted on non-humans; (2) the study involved children (age <18 years); (3) the treatment involved inpatient participants only; and (4) the article was a 'methods' or process paper that did not report results of the intervention on anxiety.

Search procedure

We searched the CCTR/CENTRAL, MEDLINE, EMBASE, PsycINFO, and CINAHL databases for studies that could fit our criteria. Our search required that articles include at least one term from each of the following lists in their title or abstract: (1) *anxiety, phobia, or panic*, (2) *coronary heart disease, coronary artery disease, cardiac disease, myocardial infarction, acute coronary syndrome, coronary artery bypass graft, coronary bypass surgery, unstable angina, percutaneous coronary intervention*, and (3) *randomly, randomized, or clinical trial*. For additional references, we conducted another search in which we replaced the terms in criterion 3 with the terms *review, meta-analysis, systematic*. In this manner, we sought to identify any missing published studies by searching the reference lists of previously published review articles.

The resulting articles were then compiled into an EndNote database (version 7) and duplicate studies were removed. Next, the first author (JF) conducted a review at the abstract level and selected for full text review only those studies that appeared to fit all inclusion criteria. Twenty abstracts were selected randomly for consideration by two reviewers (GS and JAB) to determine agreement on inclusion or exclusion. Complete agreement was obtained on all 20 articles. A full-text review and data extraction was performed for the remaining studies. We searched reference sections of studies from which we extracted data and of studies identified in our database search that may have been missed in the original search. Any studies that fit all review criteria also were included in our final tables and analyses.

If all criteria were met, data were extracted from the article including the first author, journal and date of publication, country of origin, demographics and clinical characteristics of the sample, the anxiety instrument, a description of the intervention and control conditions,

primary and secondary outcomes, and anxiety-related results. One reviewer first extracted the relevant data, rated their degree of certainty in their abstraction of the data, and if there was any uncertainty, a second reviewer independently extracted data from the same article. Discrepancies between reviewers were resolved via a thorough joint re-review of the manuscript. Forty studies were jointly reviewed by two reviewers, and agreement was achieved for all studies.

Study quality was quantified using a modified PEDro scoring system for RCTs (35). Studies were evaluated based on criteria including completely random assignment, control for non-study interventions, blinding of outcome assessors, intention-to-treat analysis, and presence of a CONSORT flow chart or a detailed report of attrition. Based on our ratings for these criteria, we assigned each study an overall quality score. The scale used for the quality score was as follows: 5=Excellent; 4=Good; 3=Fair; 2=Poor.

Results

Our search terms resulted in 3,660 publications, of which 617 (17%) were duplicates. Of the remaining 3,043 articles, 2,568 (84%) did not meet inclusion criteria during the abstract-level review; this included 57 review articles or meta-analyses published between 1979 and 2016. Of the remaining 475 RCTs, 363 (76%) did not meet our inclusion criteria during full text review, leaving 112 remaining studies (Figure 1). Our additional review of citations from reference sections of included studies and review articles yielded another 7 studies (36-42). We determined that our original search terms did not identify these studies because the title and abstract failed to include terms for anxiety (5 studies), CHD (1 study), or randomization (1 study). Ultimately, 119 studies were included in our review.

Study characteristics

Country of origin—The included studies originated from 25 countries. Most studies were conducted in the United Kingdom (30 studies) and United States (24 studies). Of the remaining studies, 10 were conducted in Canada, 9 in the Netherlands, 6 each in Iran and Australia, 4 in India, and the remainder in Belgium (1 study), Brazil (1), China (3), Denmark (2), Germany (3), Greece (1), Hong Kong (1), Ireland (1), Italy (2), Japan (2), New Zealand (2), Norway (1), Poland (1), South Korea (1), Saudi Arabia (1), Singapore (2), Sweden (2), and Thailand (1). Two studies were conducted in multiple countries.

Sample Characteristics

Inclusion criteria: For the majority of studies (93 studies, out of 119), the inclusion criteria did not specifically include a psychiatric diagnosis of an anxiety disorder. Of the remaining 26 studies, 4 included elevated anxiety in their inclusion criteria (30, 31, 39, 43), 9 included patients with anxiety and/or depression (44-52), 8 included patients with depression, depressive symptoms, or mood disorder only (36, 37, 40, 53-57), 3 included patients with 'distress' (10, 58, 59), one included patients with "psychosomatic symptoms" including restlessness, anxiety, altered mood, and insomnia (60), and another included patients with "exhaustion" (61).

Sample size: Sample sizes ranged from 10 (62) to 3,822 (63) participants. The average number of participants analyzed per study was 204 (median N = 107). Thirty-eight studies reported analyzing a smaller number of patients than were initially randomized (i.e., failed to analyze data adhering to the intent-to-treat principle).

Demographic characteristics: The average age of participants ranged from 49 (64) to 81 (65) years; 10 studies did not report a mean or median age for their participants, but rather reported an age range. The majority of studies did not report the race or ethnicity of participants, particularly studies conducted outside of the United States, the United Kingdom, and Canada. Of studies that reported participant race, participants ranged from 0% (66) to 100% (67) Caucasian. Sex of participants was primarily male (median 80% male). Eight studies did not report participant sex.

Clinical characteristics: Patients were primarily post-acute coronary syndrome (ACS) or post-revascularization procedure (74 studies), and included patients who had recently had an MI, an episode of unstable angina, or a coronary revascularization procedure such as coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI). Participants were considered to have had 'stable' CHD in 26 studies. Participants were awaiting a coronary procedure, such as a PCI or CABG, in 10 studies. Nine studies reported that participants fit into more than one of these categories. Three studies (3%) included patients who did not have CHD. One was split evenly between patients hospitalized with MI (23%), unstable angina (26%), congestive heart failure, and arrhythmia (68). Another included patients hospitalized with primary diagnoses of acute coronary syndrome (22%), unspecified heart failure (68%), or aortic stenosis (10%) (65). The final paper used a sample of patients with coronary artery disease or cardiomyopathy but did not specify how many patients fell into either category (69).

Instruments to assess anxiety—A wide array of instruments was used to assess anxiety. The most frequently used scales were the Hospital Anxiety and Depression Scale-Anxiety (HADS) scale (70) used in 45 studies, and the State-Trait Anxiety Inventory (STAI) (71) used in 36 studies. Of the studies that used the STAI, the majority (N=18) used the STAI-State, 4 used the STAI-Trait, and 12 used both the STAI-State and STAI-Trait; two studies did not specify which form was used. Other scales used less frequently (i.e., used in <4 studies) included the Anxiety Scale Questionnaire, Beck Anxiety Inventory, Brief Symptom Inventory Anxiety Subscale, Cattell Self-Analysis form, Covi Scale, Derogatis Stress Profile, General Practitioner Research Group Nine-Item Anxiety Rating Scale, General Health Questionnaire-Anxiety, Hamilton Anxiety Rating Scale, Hopkins Symptom Check-List Self Rating Scale for Anxiety, Kessler scale, Multiple Affect Adjective Checklist, Profile of Mood States-Anxiety, the Patient-Reported Outcomes Measurement Information System anxiety items, Self-Rating Anxiety Scale, Symptoms of Anxiety-Depression Index, the anxiety subscale of the Symptom Checklist-90 form, Symptom Rating Test, Symptom Questionnaire, Taylor Manifest Anxiety scale, Welsh's Anxiety Scale, and a single anxiety item using a Likert scale. While our EndNote search included terms for panic disorder and phobia, the resulting articles only used instruments measuring generalized anxiety or health-related anxiety.

Interventions

Interventions varied widely and were categorized into five different types of treatments: (1) Pharmacological; (2) Relaxation; (3) Counseling; (4) Education and risk factor management; and (5) Alternative therapies. Some studies fit into more than category, e.g., offering both education and counseling in at-home nursing visits (58): these studies were considered in the treatment category that the study authors characterized as the primary intervention type.

Pharmacological interventions—Twelve studies primarily involved pharmacotherapy (Table 1). Intervention duration ranged from 2 days to 4 years, with median length being 8 weeks.

Medications were compared to placebo in 11 of 12 studies.

Psychoactive medications: 7 were psychoactive medications: alprazolam (45, 72), clorazepate (31, 43, 73), hydroxyzine (74), and escitalopram (75).

Coronary Heart Disease Medications: Other studies examined the effects of medications that treat CHD or CHD risk factors, including two studies using beta-blockers (e.g., propranolol and atenolol) (76, 77), and one using a statin (pravastatin) (78). Another study examined the effects of diltiazem and dibromotyrosine compared to diltiazem alone (60). The remaining study compared psychosocial functioning, including anxiety, between patients undergoing either medical or surgical management of ACS (79).

Regarding efficacy, only one of the 12 intervention studies that were primarily pharmacological reported lower anxiety in the intervention group compared to controls (60). One study reported lower anxiety in the placebo group (77), and the remainder reported no differences between groups.

Relaxation interventions—Fourteen studies primarily involved relaxation therapies (Table 2), at times delivered as adjunct to exercise-based CR. Length of the interventions ranged from one week to 12 months; the median intervention length was six weeks.

The kinds of relaxation therapies were varied: two studies involved deep breathing interventions (44, 80); four examined autogenic training, alone (81, 82) or combined with cardiac coherence biofeedback (83) or EMG feedback (84); two used muscle relaxation therapy (85) (one also included guided imagery (86)); two used mindfulness-based interventions (64, 67); one used a music tape during aerobic exercise compared to similar exercise without music (87); one used guided imagery compared to a music tape during exercise (88); and one gave participants their choice of relaxation therapy (e.g., yoga, mindfulness) (89). Another study compared a group receiving progressive muscle relaxation instruction with another receiving mindfulness-based meditation instruction (57).

In terms of efficacy of the interventions that prominently featured relaxation, 6 resulted in a greater reduction in anxiety for the intervention group compared to a control group (44, 64, 80-82, 85) and the remaining 8 studies reported a nonsignificant difference in anxiety between treatment groups.

Counseling and support interventions—Twenty-five interventions primarily involved counseling (Table 3). Intervention length ranged from 4 weeks to one year (median length 10 weeks).

Interventions often involved multiple components of treatment; for example, behavioral counseling combined with listening to a relaxation tape (62). Ten interventions primarily involved forms of cognitive-behavioral therapy (CBT) (47, 48, 54, 55, 90-92). Two of these CBT-focused studies also provided stress management training (53, 93) and one included antidepressant medication (68); eight involved skills training such as problem-solving and self-management strategies (10, 36, 61, 62, 94-97); three studies provided social support or ‘mentorship’ to patients (38, 98, 99), two provided psychotherapy (30, 100); and one involved future care planning and related counseling (65). One offered patients a choice between problem solving counseling, antidepressant therapy, or both (37).

Of the 25 studies categorized as counseling interventions, 9 were effective in decreasing anxiety in the intervention group compared to control (36, 47, 48, 53, 93, 96-99), while 16 studies reported non-significant differences between groups.

Education and risk factor management interventions—Thirty-four interventions were primarily educational (Table 4). The length of the interventions ranged from 15 minutes (a video-based intervention (101)) to one year (median length 7 weeks).

The educational topics varied between studies. Education sessions that focused on CHD awareness or risk factor/heart health and treatment were most common, with 25 overall studies applying this approach. Of these, seven were conducted in post-CABG/PCI patients (66, 102-107), ten for post-MI patients (58, 59, 108-115), five in patients with CHD or angina diagnosis (63, 116-120), one in patients with unstable angina (121) and two in patients with angina or acute MI (122, 123). Two studies used “frequently asked question” checklists prior to cardiology clinic visits (124, 125). Other interventions included four studies providing education prior to elective CABG on what to expect after surgery (126-129), one providing education in cardiopulmonary resuscitation (CPR) provided to patients and family (69), and one providing a videotape on sexual functioning after MI (101).

Seventeen of the 34 primarily educational programs reported a greater reduction in anxiety for the intervention groups compared to controls (59, 63, 66, 69, 103, 105-110, 113, 120, 124, 125, 127, 129). Of the remaining studies, two reported greater anxiety reductions in control groups compared to intervention groups (101, 116), and 10 reported no significant differences between intervention groups and controls.

Alternative therapies—Thirty-four interventions were considered ‘alternative therapies.’ Thirty-one involved physical exercise, and three involved omega-3 or herbal therapy. Length of the interventions ranged from 4 weeks to 2 years (median length 2 months).

Exercise interventions: Eleven studies compared an exercise program to usual care (with no exercise) (130-139) including one that compared a yoga-based regimen to a no-exercise

control (140). Six studies compared an exercise intervention paired with education or counseling, to a control group with usual care (receiving neither exercise training nor education/counseling) (50, 51, 141-144). Seven studies compared types of exercise: yoga compared to physiotherapy-based cardiac rehabilitation (145), an outdoor walking program compared to indoor cycling (39), low- compared to high-intensity exercise regimens (146, 147), supervised hospital-based CR compared to unsupervised home-based CR (32), and routine CR compared to an expanded program (148, 149). Center-based or hospital-based CR was compared to home-based CR in two studies (150, 151). One study compared two CR programs of different length (152). Another compared exercise to dietary changes (153). Finally, two studies compared exercise to counseling (42, 49) and one compared exercise to cardiac education (154).

Supplemental interventions: Two additional alternative therapy trials examined fatty acids compared to placebo (41) or omega 3 compared to placebo as an augmentation to the selective serotonin reuptake inhibitor (SSRI), sertraline (40). Another study compared Xinkeshu tablets (a traditional Eastern supplement comprised of *salvia miltiorrhiza*, *pseudo-ginseng*, *radix puerariae*, *radices saussureae*, and *hawthorn*) (56) along with traditional Western medicine (aspirin, beta-blocker, and a “lipid blocker,” most often a statin), to Western medicine alone.

Regarding study efficacy, of the 34 interventions that involved physical exercise, 10 resulted in a greater reduction in anxiety in the intervention group compared to the control group (32, 39, 41, 49, 50, 56, 137, 139, 141, 143), while 24 reported no differences between exercise and control groups.

Quality of Studies

Study quality was highly variable. Twelve studies received a quality rating of “5” (Excellent), 18 received a rating of “4” (Good), 57 received a rating of “3” (Fair), and 32 a rating of “2” (Poor). Two of the 12 studies rated “excellent” (17%) resulted in a greater decrease in anxiety for the intervention group (110, 155) as did six of the 18 studies rated “good” (33%) (36, 53, 103, 108-110).

In aggregate, twenty-eight studies controlled for non-study interventions, 45 specifically mentioned that the outcome assessors were blinded to treatment group, 41 mentioned using an intention-to-treat analysis, and 88 included a CONSORT diagram or a detailed description of attrition.

Results of interventions targeting patients with anxiety

Only four of the 119 studies (3%) specifically targeted patients with an anxiety disorder or elevated anxiety symptoms. Of those, one RCT was effective in reducing anxiety for the intervention group compared to controls. This study (39) examined walking versus cycling in patients with anxiety specific to exercise, and found exercise-related anxiety in the walking group decreased more than in the cycling group. In contrast, three studies showed minimal benefit: In a 6-month, group therapy intervention for patients scoring >7 on the HADS Anxiety subscale, Merswolken et al. (30) reported a non-significant reduction in

anxiety for CHD or post-MI patients compared to controls receiving usual care. In two separate studies, apparently of the same sample (31, 43), Wheatley and colleagues reported that nightly clorazepate for patients with a “sufficient level of anxiety” resulted in no differences in anxiety compared to placebo controls after three months of treatment.

In addition to the above, 9 studies targeted patients with either anxiety or depression. Of these, 7 reported decreased anxiety in the intervention groups compared to controls. Bambauer et al. (52) provided 6 sessions of weekly telephone counseling addressing cardiac-related fears and reported greater reductions in anxiety for the intervention group to a control group who received a booklet on coping with chronic illness. McLaughlin et al. (48) reported that an 8-week intervention involving telephone-based CBT, addressing common illness-related fears for patients with elevated anxiety or depressive symptoms, resulted in lower anxiety scores compared to a control group who received a booklet on coping with illness. Lv et al. (47) examined the effects of a 6-session CBT-based intervention aimed at modifying irrational beliefs about illness in patients with diagnosed anxiety and/or depression; compared to controls receiving no therapy, the intervention group experienced a greater decrease in anxiety. Freeman et al. examined the effects of 30 days of treatment with alprazolam compared to placebo in post-CABG patients with anxiety and/or depressive symptoms and reported greater decreases in anxiety for the intervention group (45). Stern (49) compared a 12-week group counseling intervention to a 12-week exercise program for participants who were anxious, depressed, or who ‘had a mean workload less than 7 metabolic equivalents (METS) on a treadmill test.’ The exercise group had greater reductions in anxiety compared to controls receiving ‘routine care’ at 3 months, the group counseling intervention group had a greater reduction in anxiety compared to controls at 6 months, and there were no between-group differences at 1 year. In another CR study, Oldridge et al. compared weekly exercise for 8 weeks to a usual care control group, and anxiety improved for patients in the intervention group with elevated anxiety scores at baseline compared to controls (51). D'Silva et al. compared a 2-week deep breathing intervention to a usual care control group for patients with anxious or depressive symptoms, and reported that anxiety scores were lower in the experimental group (44).

Two studies showed group differences in anxiety after treatment. Oldridge et al. performed an 8-week exercise intervention combined with group CBT (50) in patients who had anxiety or depressive symptoms; anxiety decreased similarly over time for both the CBT intervention group and the control group receiving exercise without therapy. Huffman et al. (46, 68) examined the effects of a telephone counseling intervention delivered by a social work case manager performing CBT as well providing SSRI medication compared to a control group receiving ‘enhanced usual care,’ in patients with diagnosed MDD, GAD, or Panic Disorder, and there were no group differences in anxiety scores after the intervention.

Discussion

In the present review, we aimed to provide a broad, comprehensive review of all studies of patients with CHD that assessed anxiety before and after any intervention. Out of literally thousands of publications initially identified by our search, only 119 studies met criteria for detailed review. Although treatment-related changes in anxiety in patients with CHD were

reported, only a minority of the studies specifically targeted patients with anxiety disorders or elevated anxiety symptoms. Most studies measured anxiety as a secondary outcome, with other outcomes (e.g., depression, quality of life, CHD events) typically serving as the primary outcome. The paucity of treatment studies specifically targeting patients with anxiety is surprising, especially in light of the relatively large number of studies targeting depression (24-29). Moreover, in those studies that measured anxiety, methodology and quality varied, and only one-third of studies actually reported a benefit in reducing anxiety in the respective intervention groups compared to controls.

The inconclusive evidence for the efficacy of the interventions can be attributed to a number of factors. The kinds of interventions were highly varied, ranging from traditional CBT to exercise therapy. Moreover, even within treatment classes, the actual interventions were highly variable. For example, the interventions subsumed under the category of 'relaxation' therapies included progressive muscle relaxation training, biofeedback, meditation, and autogenic training. In the pharmacological studies, treatments were given for varying time periods and at different doses. Additionally, the measures used for anxiety varied between studies, which makes comparison difficult. Clearly, there is no one universally accepted treatment for anxiety, and even studies of medications designed specifically to reduce anxiety yielded inconsistent results. It may be useful for future research to focus on one or two well validated instruments. Our review found that the STAI and HADS scales were utilized most often in the CHD population, and it may be beneficial for future studies utilize these instruments to facilitate better comparison between studies.

Variations in study characteristics also undoubtedly contributed to some of the inconsistencies in findings. Interventions varied in length (from a 15-minute video to a 4-year intervention) and intensity (meeting daily, weekly, or monthly). Follow-up was also variable between studies and the persistence of treatment benefits could not be determined. The majority of studies did not include any follow-up after the conclusion of the intervention, and studies with follow-up reported high numbers of patients lost to follow-up which may have served to bias results towards significance (156). Most importantly, the interventions for the majority of studies were not designed to reduce anxiety, as anxiety was rarely a primary endpoint. Studies designed to treat anxiety and targeting individuals with high anxiety could yield different results.

The quality of studies was also highly variable. The quality of the majority of studies was only "fair," with only 10 % of published studies considered "excellent." Higher quality evidence is needed before any particular treatment can be called effective for CHD patients with anxiety. Additionally, of the interventions that were considered "excellent" quality, only 2 (17%) were effective, which may suggest that better quality studies could show more modest benefit compared to those studies with weaker methodologies.

There was also a conspicuous lack of research in expected areas, and a focus on non-traditional treatments for anxiety. For example, there was only one study in the 119 we reviewed that utilized SSRI medications as a primary intervention. This is particularly interesting given that there are a number of studies that research the effects of SSRIs on depression in CHD patients (24, 25, 37). It may be that similar research has not been

conducted in patients with anxiety because anxiety has received less attention as a risk factor in CHD until recently, and therefore receives less attention and funding for treatment. Recent research generally shows that anxiety has some prognostic significance (6, 10, 11), and research on the effects of the first line anxiety medications (SSRIs, SNRIs) on anxiety and heart disease in patients with both illnesses will be important in the future.

Although there have been several large, multi-center RCTs examining treatment of MDD in cardiac patients (24, 25) and one study that examined the effects of exercise on depressive symptoms in depressed patients with stable CHD (157), we identified only four studies targeted patients with high anxiety and none with a diagnosed anxiety disorder. Moreover, in the only study that showed an effective intervention, Faulkner et al, (39) focused only on narrow, exercise-specific anxiety, rather than generalized anxiety symptoms. Of the nine studies we identified that targeted patients with anxiety and/or depression, seven reported reduction in anxiety in their intervention group. These studies spanned intervention types, including an anxiolytic, multiple CBT studies, exercise therapy, and counseling. It is interesting that these studies reported improvements in anxiety at a much greater rate than studies of patients with anxiety alone, or studies targeting patients with neither. While further analysis is difficult given study heterogeneity and the limited number of existing articles, it will be interesting to see whether this trend continues for future studies investigating treatment of anxiety in CHD patients with mood or anxiety disorders, compared to patients with anxiety disorders alone.

Additionally, although the literature includes a number of RCTs treating depression in CHD patients (24-28), there have been few RCTs targeting anxiety, and to our knowledge, no multi-site RCTs. Depression has received more attention as a prognostic factor in CHD compared to anxiety which may explain the paucity of research treating anxiety in patients with CHD. Additionally, aspects of anxiety may make it more difficult to study in CHD patients. Unlike many depression studies that focus on MDD (or in some cases elevated depressive symptoms), anxiety disorders are more heterogeneous (e.g., panic disorder, GAD, phobia, social anxiety disorder, agoraphobia, etc.), and different disorders may not have the same prognostic value and may respond differently to treatment (158). Interestingly, in the articles we found for review, only generalized and health-related anxiety were assessed, leaving the effects of treatment of other forms of anxiety (phobia, etc.) unknown. Anxiety disorders and CHD also may be more difficult to differentiate as they share comorbid symptoms; for example, tachycardia, shortness of breath, and chest pain are symptomatic of both panic disorder and angina (17). Additionally, existing treatments for heart disease may be a source of anxiety-like symptoms, such as digoxin toxicity causing palpitations and panic attack-like symptoms. There is also a possibility that during an acute event, patients experience anxiety related to the event which resolves on its own with treatment of the event independent of treatment, mitigating the effects of any treatment for anxiety in particular.

Limitations

Because we searched for mentions of anxiety only in abstracts, our search may have missed some studies that only reported anxiety-related results in the body of the article. However, we also manually searched existing meta-analyses and reviews in order to identify as many

additional studies as possible. Thus, we are confident that we included all relevant studies reporting the effects treatments on anxiety in CHD patients. We also recognize that interventions that were ineffective are less likely to be published, and anxiety may have been measured but not reported as a result if a study resulted in a null finding. Importantly, we included studies that not only measured anxiety as a primary outcome but also as a secondary outcome. The extent to which negligible effects of treatment of anxiety were due to its measurement as a secondary outcome cannot be determined. Finally, as there was significant between-study variation in intervention length, duration, and quality, intervention type, and control group conditions, a meta-analytical approach was not considered appropriate.

Conclusion

Heightened symptoms of anxiety are not uncommon among cardiac patients, and may also be associated with worse clinical CHD outcomes. Unfortunately, we identified relatively few intervention studies designed specifically to reduce anxiety in CHD patients, and results of the effectiveness of treatment have been mixed. Because of the paucity of research in this area, it is not clear what interventions are most effective in treating anxiety in CHD patients. Many published studies were conducted in non-anxious CHD samples. The lack of benefit reported in many studies could be the result of ineffective treatments or may be due to a potential floor effect in which patients had low anxiety to begin with. Moreover, the few existing interventions targeting anxiety focused on elevated symptoms or GAD, so interventions for treating patients with other anxiety disorders such as panic disorder or phobias are understudied (6). Because studies used a variety of different instruments for assessing anxiety, comparisons between studies are difficult. Selecting common instruments to measure anxiety may facilitate comparison of treatment efficacy across studies. Finally, unlike studies of depression in CHD patients, to our knowledge, no study has examined the effects of treating anxiety on clinical outcomes. It is important for clinicians to know the effects of anxiety treatment on clinically relevant outcomes such as symptom burden, utilization of healthcare services, and further acute cardiac events and death. Such research will help in determining the added value of treatment of anxiety in patients with CHD at risk for adverse cardiac events.

Acknowledgments

Funding: This research is supported, in part, by a grant (HL125522) from the National Heart, Lung, and Blood Institute.

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Acronyms

ACS	Acute coronary syndrome
CABG	Coronary artery bypass graft
CBT	Cognitive behavior therapy
CHD	Coronary heart disease
CPR	Cardiopulmonary resuscitation
CR	Cardiac rehabilitation
GAD	Generalized anxiety disorder
HADS	Hospital anxiety and depression scale
HAM-A	Hamilton Rating Scale-Anxiety
MACE	Major adverse cardiac events
MDD	Major depressive disorder
MI	Myocardial infarction
RCT	Randomized clinical trial
SSRI	Selective serotonin reuptake inhibitor
STAI	Spielberger State-Trait Anxiety Inventory

Figure 1.
Search process for studies to include in the review and reasons for exclusion.

Table 1

Description and anxiety-related results of pharmacologic interventions.

First Author	Year	Journal	Country	N*	Age	% Male	CAD inclusion criteria	Psychological diagnoses in inclusion criteria	Intervention performed	Intervention Duration	Control condition(s)	Follow-up interval	Anxiety-related outcome
Bass	1987	J Psychosom Res	UK	88	NA	88	Post-elective CABG for stable angina		Atenolol	12 months	Placebo		At 12 months post-op, lower anxiety in placebo group, no change in atenolol group
Brown	1979	Am J Cardiol	USA	51	54	94	Chronic stable angina		Medical compared to surgical therapy	Variable based on group	NA	>9 months	No group differences
Freeman	1986	J ClinBiopharm	USA	60	52	NA	Post-CABG	Anxiety (STAI >/= 36), and or depression (Center for Epidemiological Studies-Depression Score >/= 13)	Alprazolam	30 days	Placebo		At 1 month post-op, lower anxiety for alprazolam; no other group differences
Jiang	2013	JAMA	USA	127	64	21	Clinically stable CHD and mental stress-induced myocardial ischemia		Escitalopram	6 weeks	Placebo		No group differences; anxiety decreased in all groups
Karakostas	1988	Acta Therapeutica	Greece	60	49	88	Prior MI or diagnosed coronary insufficiency		Hydroxyzine	28 days	Placebo		Decrease in anxiety for treatment group but no change for placebo group; no between-group comparison
Mazzuero	1987	ClinCardiol	Italy	64	51	100	History of Q-wave infarction		Propanolol, atenolol, or chlordesmethyldiazepam	2 days	Placebo		No group differences
Mendels	1986	J Clin Psychiatry	USA	27	61	NA	Angina pectoris, taking propranolol		Alprazolam with propranolol	6 weeks alprazolam, 6 placebo	Placebo with propranolol		No group differences; anxiety decreased in all groups
Merchan	1987	Clinical Trials Journal	Italy	60	“Elderly”	NA	Angina pectoris	“Psychosomatic symptoms” (restlessness, anxiety, altered mood, insomnia)	Diltiazem and dibromotyroline	14 days + 14 day washout period	Diltiazem only		No group differences

First Author	Year	Journal	Country	N*	Age	% Male	CAD inclusion criteria	Psychological diagnoses in inclusion criteria	Intervention performed	Intervention Duration	Control condition(s)	Follow-up interval	Anxiety-related outcome
Wheatley	1979	Psychosomatics	UK	41	NA	Not reported	Post-MI (first)	“A sufficient level of anxiety”	Clorazepate nightly	3 months	Placebo		No group differences; anxiety decreased in all groups
Wheatley	1980	Progress in Neuro-psychopharmacology	UK	41	NA	Not reported	Post-MI (first)	“A sufficient degree of anxiety symptoms”	Clorazepate nightly	3 months	Placebo		No group differences; anxiety decreased in all groups
Wheatley	1982	Acta Med Scandinavia	UK	41	NA	NA	Pre-MI (1); Post-MI (2)		Clorazepate (1); diazepam (2)	10 weeks	Placebo (1); placebo and verapamil (2)		No group differences
Stewart	2000	Arch Int Med	USA	1130	31-74	80	Stable CAD		Pravastatin	> 4 years	Placebo		No group differences

* Number of patients randomized, if available in text

Table 2

Description and anxiety-related results of relaxation interventions.

First Author	Year	Journ _a l	Country	N	Age	% Male	CAD inclusion criteria	Psychological diagnoses in inclusion criteria	Intervention performed	Interventio n Duration	Control condition(s)	Follow- up interval	Anxiety-related outcome
Climov	2014	Acta Cardiol	Belgium	31	NA	100	Post-CABG or angioplasty		Cardiac coherence biofeedback plus CR	6 weeks	CR only		No group differences
Collins	1997	Heart Lung	USA	50	59	78	<12 weeks post-acute MI or CABG		Progressive muscle relaxation and guided imagery as adjunct to CR	6 weeks	Usual care and CR		No group differences
DSilva	2014	Nitte University Journal of Health Science	India	45	NA	75	Stable angina or post-MI	Identified with anxiety or depressive symptoms	Deep breathing	2 weeks	Usual care	1 month	Anxiety lower in experimental group
Dehdari	2009	Indian J Med Res	Iran	110	59		Post-CABG		Progressive muscle relaxation	6 weeks	Usual care	1 month after intervention completion	Lower state and trait anxiety in relaxation group compared to control at 1 month post-intervention
Delui	2013	Open Cardiovasc Med J	Iran	45	NA	60	Known cardiovascular disease	Depression	Progressive muscle relaxation group and mindfulness based meditation group	10 sessions of relaxation or meditation	Usual care		No group differences; anxiety decreased in all groups
Emery	2003	Heart Lung	USA	33	63	58	CHD		2 exercise treadmill sessions, 1 with music vs. 1 without	1 week	Exercise session without music		No group differences; no anxiety reduction in any group
Kanji	2004	Am Heart J	UK	59	NA	67	Post-angioplasty		Autogenic training	5 months	Standard care		Lower state anxiety in intervention group compared to control at 2 and 5 months
Michalsen	2005	Psychother Psychosom	Germany	101	59	77	Documented CHD, without ACS or CABG in prior 3 months		Lifestyle therapy: group-based intervention focused on stress reduction (patient choice of relaxation therapy), dietary recommendations, with elements of mindfulness- based stress reduction, CBT, coping skills training	1 year, 3- day retreat followed by 10 weeks of 3-hour sessions and biweekly 2- hour meetings	Advice-only: written information with no follow-up		No group differences
Nyklicek	2014	J Behav Med	Netherlands	114	55	82	Post-angioplasty		Mindfulness based stress reduction	3 weeks	Self-help booklet	6 weeks	No group differences; larger increases in anxiety in intervention group

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First Author	Year	Journa l	Country	N	Age	% Male	CAD inclusion criteria	Psychological diagnoses in inclusion criteria	Intervention performed	Interventio n Duration	Control condition(s)	Follow- up interval	Anxiety-related outcome
													than control in patients <60 years
Parswani	2013	Int J Yoga	India	30	49	100	Hospitalized or symptoms of heart disease within last year		Mindfulness based stress reduction	8 weeks	Usual care	3 months after assessment	Lower anxiety in intervention group than control post- intervention, at 3 month post-test
Stein	2010	Holist Nurs Pract	USA	70	66	70	Scheduled to undergo CABG or CABG plus aortic valve repair		Audiotape of guided imagery with music; audiotape of music alone	Daily for 2-4 weeks prior to surgery	No intervention	1 week, 6 months	No group differences
Trzcieńiecka-Green	1996	Eur Heart J	UK	100	60	87	<3 months post-acute MI or CABG		Relaxation based stress management (autogenic training, audiotape)	11 weeks	Usual care waitlist group	6 months	Lower anxiety in experimental group after 10 weeks
van Dixhoorn	1990	J Psychosom Res	Netherlands	156	56 (median)	94	Post-MI		Exercise plus relaxation and breathing therapy	5 weeks	Exercise training only		Experimental group had improvements on anxiety state score, control did not
van Dixhoorn	1983	Psychother Psychosom	Netherlands	69	56	93	Post-MI		Relaxation training during CR with EMG feedback	6 weeks	Regular CR		No group differences; anxiety decreased in all groups

Table 3

Description and anxiety-related results of counseling interventions.

First Author	Year	Journal	Countr y	N	Age	% Male	CAD inclusion criteria	Psychological diagnoses in inclusion criteria	Intervention performed	Interventio n Duration	Control condition(s)	Follow- up interval	Anxiety-related outcome
Appels	2006	J Psychosom Res	Netherlands	727	53	77	Post-angioplasty	Exhaustion	Group psychosocial counseling to improve coping, examining stressors leading to exhaustion and support for recovery	6 months	Usual care	18 months	No group differences
Bambauer	2005	Psychosom Med	USA	79	60	67	Post-ACS	HADS Anxiety or Depression >/= 7	Telephone counseling sessions focused on self-management of cardiac / illness related fears	6 weeks	Booklet on coping with chronic illness and usual treatment	6 months	Greater reductions in anxiety for intervention group
Barley	2014	PLOS One	UK	81	65	64	CAD with chest pain	>/=8 on HADS-Depression subscale	Personalized psychosocial counseling, including behavioral change for depression treatment and care with calls from nurse	6 months	Treatment as usual	1 year	Greater reduction in anxiety for treatment group
Barlow	2009	Eur J Cardiovasc Nurs	UK	192	66	72	MI, Post-CR		Expert Patient Programme (EPP): post-MI peer-led self-management program (problem solving, relaxation, coping, disease counseling)	4 months	Waitlist with usual care		No group differences
Bashiri	2016	Iran Red Crescent Med J	Iran	70	NA	NA	Hospitalized with CHD, no history of angioplasty or CABG		Psychoeducation including lifestyle, anger management, problem solving, muscular relaxation	1 month	Routine care and pamphlet with information on general cardiac healthcare		Anxiety lower in study group at end of study
Bishop	2005	Am Heart J	Singapore	68	54	100	Post-CABG		Psychosocial skills training workshop	6 weeks	2 hour bedside information session	3 months	No group differences
Blumenthal	2016	Circulation	USA	226	61	63	Stable CHD with recent ACS, angiographic evidence of CHD, or recent coronary revascularization		Comprehensive CR vs. stress management training: education, group support, CBT	12 weeks	No CR	Mean 3.2 years	Greater improvements in anxiety in the CR-SMT group
Davidson	2013	JAMA	USA	150	60	68	Post-ACS	Beck Depression Inventory >/=10	Centralized depression care including problem solving, pharmacotherapy, both, or neither based on patient preference	6 months	Locally determined depression care		No group differences
Fielding	1980	Br J Soc Psychol	UK	10	NA	100	Post-MI		Behavioral counseling discussing illness-related concerns followed by relaxation tape	10 weeks	Waitlist with usual care		Experimental group had lower post-intervention anxiety than pre on the Cattell SAF; no difference

First Author	Year	Journal	Countr y	N	Age	% Male	CAD inclusion criteria	Psychological diagnoses in inclusion criteria	Intervention performed	Interventio n Duration	Control condition(s)	Follow- up interval	Anxiety-related outcome
									Monthly calls and visits as needed, advice, problem solving	1 year	Usual care		for control; no between group comparison
Frasure-Smith	1997	Lancet	Canada	1376	59	66	Post-MI	>/=5 on General Health Questionnaire	CBT, supportive stress management	12 weeks	Usual care	3, 6, 12 months	No group differences
Freedland	2009	Arch Gen Psychiatry	USA	123	61	51	CABG	Beck Depression Inventory >/ =10, major or minor depression	Brief CBT intervention added to routine nurse counselling	8 weeks	Routine nurse education and counseling	8 weeks or 6 months	CBT group and stress management group both experienced greater improvement in anxiety compared to control at 9 months
Furze	2009	Int J Cardiol	UK	204	65	80	Awaiting first CABG		Future care planning	12 weeks	Usual care	24 weeks	No group differences
Hajjesmaïeli	2016	Open Heart	UK	50	81	60	ACS or heart failure		Telephone intervention with social work case manager including antidepressant and CBT	24 weeks	Usual care		No group differences
Huffman	2014	JAMA Intern Med	USA	183	60	47	ACS, arrhythmia or heart failure	Depression, GAD or panic disorder	Psychological therapy including counseling, relaxation training, stress management techniques and coping skills	7 weeks	Usual care	6, 12 months	No group differences
Jones	1996	BMJ	UK	2238	NA	NA	Post-MI		Angina Plan: Cognitive- behavioral disease management program. Workbook including psychoeducation, and audiotaped relaxation program. Calls from a nurse to clear up misconceptions about angina and to reinforce behavior changes.	12 weeks	Typical education, one- time session with Q&A with a nurse and written information	6 months. Intervention group received phone calls from nurses 4, 8, and 12 months.	No significant between group differences but anxiety lower in experimental group and unchanged in control at end study
Lewin	2002	Br J of Gen Prac	UK	142	76	60	<12 months since angina diagnosed		Home-based psychological support program from nurses including coping strategies and psychoeducation	4 weeks	Standard discharge care	6 months	No group difference; anxiety decreased in all groups; greater improvement for previously anxious or depressed patients compared to control group
Lie	2007	J Psychosom Res	Norway	203	62	90	Post-CABG		CBT, aimed at correcting irrational beliefs; family encouraged to attend.	2 months	Medication only		Both groups decreased in anxiety, but more in intervention group

First Author	Year	Journal	Countr y	N	Age	% Male	CAD inclusion criteria	Psychological diagnoses in inclusion criteria	Intervention performed	Interventio n Duration	Control condition(s)	Follow- up interval	Anxiety-related outcome
								diagnosed by psychiatrists	Providers establish alliance, identify goals, conduct psychoeducation, develop treatment course, correct cognitive distortions, develop daily plans for activities, and summarize treatment per session and at termination.				
McLaughlin	2005	J of Gen Intern Med	USA	100	60	67	Post-ACS	No diagnoses; 7 or greater on any HADS subscale	Telephone-based cognitive- behavioral intervention addressing common fears of individuals with chronic illness	8 weeks	Booklet on coping with cardiac illness and instructions to follow up with primary care/ specialty physicians	2, 3, 6 months	Lower score of in experimental group compared to control at month 6
Merswolken	2011	Psychother Psychosom	Germany	62	61	73	History of MI or CHD, no MI/CABG/ACS in prior 3 months	>8 on HADS Anxiety subscale	Group-based psychotherapy intervention, carried out by clinical psychologists, including information on CHD and anxiety, stress management techniques, cognitive restructuring	6 months; 12 weekly sessions plus 3 monthly 'boosters'	No intervention		No group differences
Parent	2000	Heart Lung	Canada	56	57	100	CABG		Supporting visits by volunteer former patient	3 visits	No supporting visits	4 weeks	Lower anxiety in intervention group at 24 hours, 5 days, 4 weeks after surgery
Turner	2014	Eur J Prev Cardiol	Australia	42	56	78	Post-MI, CABG, or angioplasty	Beck Depression Inventory score >13	CBT and motivational interviewing based program	8 weeks	Usual care	4, 12 months	No group differences
Turner	2013	Aus N Z J Psychiatry	Australia	57	62	72	Established cardiac disease, >2 months post-cardiac event	Beck Depression Inventory score > 13 at screening	Cognitive-behavioral group therapy including psychoeducation, activity planning, thought monitoring and challenging, problem solving, motivation strategies	6 weeks	Single brief intervention with individualized verbal feedback	2, 6, 12 months	No group differences
Vahedian-Azimi	2016	Open Heart	Iran	70	61	66	Diagnosed with MI, first hospitalization MI		Family-centered empowerment model: group support sessions concerning awareness/cognition about illness, expectations, acceptance, evaluation	9-15 sessions of 45-60 minutes	Standard care	3 months post- intervention, then every 3 months for 24 months	significant main effect of group and time $\times$ group interaction in state anxiety, with greater improvement in intervention group; NS for trait anxiety
Zetta	2011	Cardiovasc Ther	UK	233	65	68	Definite angina		Angina plan, a cognitive- behavioral, nurse-facilitated self-help intervention	12 weeks	Usual care and education	6 months	No group differences

Table 4

Description and anxiety-related results of education interventions.

First Author	Year	Journal	Country	N	Age	% Male	CAD inclusion criteria	Psychological diagnoses in inclusion criteria	Intervention performed	Intervention Duration	Control condition(s)	Follow-up interval	Anxiety-related outcome
Allison	2000	Am J Cardiol	USA	441	58	56	Unstable angina		Coronary risk factor management sessions with nurse	1 month	Usual care	6 months	No group differences
Beckie	1989	Heart Lung	Canada	74	NA	87	First CABG		Educational and supportive calls with CR nurse during home period	6 weeks	Usual care		Anxiety lower in treatment group compared with control at end of study
Bolman	2005	Patient Educ Couns	Netherlands	118	62	81	Angina, MI, post-angioplasty or post CABG		FAQ checklist	1 year	Usual care		Anxiety lower in treatment group after 1 month, not after 4 months or 1 year
Cossette	2012	Nurs Res	Canada	242	59	86	MI or unstable angina		Meetings with a nurse focused on patient perceptions of their disease	10 days	Usual care	6 weeks after discharge	No group differences
Cossette	2000	Psychosom Med	Canada	433	59	64	Post-MI	High psychological distress score on GHQ	Home visits from nurses including education and counseling	Up to 1 year	Usual care		Subjects with improvement in their GHQ scores had lower anxiety at 1 year compared to those without improvement
Coull	2004	Age Ageing	UK	319	68	61	Angina or acute MI		Mentoring groups, meetings led by trained health mentors	1 year	Usual care		No group differences
Dracup	1997	Am J Public Health	USA	453	63	84	CHD or cardiomyopathy		Patients and families attended one group CPR session, then families attended further sessions in one of 3 groups: CPR-social support; CPR-education about heart disease and risk factors; CPR-only	90 minute class in CPR, plus 30-45 minute group discussion	Completed a questionnaire, family member did not attend class	2 weeks, 3 months, 6 months	CPR-social support had greatest reduction in anxiety at 6 months compared to other groups
Furuya	2015	J Adv Nurs	Brazil	60	62	57	Pre-angioplasty		Education session and telephone follow-up	16 weeks	Usual care	6 month	Reduced anxiety in educational group compared to control;

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First Author	Year	Journal	Country	N	Age	% Male	CAD inclusion criteria	Psychological diagnoses in inclusion criteria	Intervention performed	Intervention Duration	Control condition(s)	Follow-up interval	Anxiety-related outcome
													anxiety decreased in intervention group but increased in control group
Furze	2012	J Adv Nurs	UK	142	64	53	New stable angina		Angina plan delivered by lay facilitators, relaxation, workbook, telephone calls	12 weeks	Angina nurse specialist meeting and written information	6 month	Lower anxiety in intervention group at 3,6 months
Gallagher	2003	Heart Lung	Australia	196	67	0	Hospitalized for MI, CABG, angioplasty, stable angina		Individualized information and support via telephone counseling	Up to 6 weeks after discharge	Usual care	12 weeks	No group differences
Goodman	2008	Eur J Cardiov Nurs	UK	188	64	81	Pre-CABG, at least one poorly controlled risk factor		Psychoeducational lifestyle counseling around illness related concerns, risk factors, and preparation for surgery at monthly intervals	9 months	Standard care	3 months after discharge	No group differences
Hartford	2002	Heart Lung	Canada	166	63	86	Post-CABG patients and their partners		Telephone information and support calls	7 weeks	Not disclosed		Anxiety lowered in treatment group at day 2 at home, otherwise no group differences
Horlick	1984	J Psychosom Res	UK	160	53	91	Post-MI		Education and group discussion classes led by nurse	6 weeks	Usual care and standardized educational program	6 months	No group differences
Keeping-Burke	2013	Res Nurs Health	Canada	182	63	85	Post-CABG		Telephone based health program after hospital discharge	1 week after discharge	Standard care	3 weeks after discharge	No group differences
Leemrijse	2016	Eur J Prev Cardiol	Netherlands	374	60	81	< 8 weeks since hospitalization for acute MI or unstable angina		Telephone lifestyle coaching intervention related to cardiac risk factors	6 months	Usual care		Greater reduction in anxiety at 6 months in experimental group
Martinali	2001	Patient Educ Couns	Netherlands	103	64	81	CHD, no clinic visits within last 6 months		Frequently asked questions checklist provided at home before outpatient cardiology visit	3 1 hour session	Provided brochure		State anxiety lower in experimental group compared to controls before their cardiology visit

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McHugh	2001	Heart	UK	98	62	77	< 1 month on waiting list for elective CABG		Monthly health education sessions, customized by patients' motivation and readiness to change, carried out by liaison nurse at the patient's home and nurse in clinic (alternating)	Average of 8.5 months, maximum of 1 year, minimum of 2 sessions to have 'completed' intervention	Usual care		Definite cases of anxiety increased in the control group between baseline and CABG, but reduced among individuals in the intervention group
Mittag	2006	Int J Rehabil Res	Germany	343	60	82	Prior MI, CABG, or PCI		Manual-based, telephone-based individual counseling on health behaviors and psychosocial issues, as well as 6 written flyers concerning those topics	1 year	6 flyers provided, one every 2 months		Anxiety scores increased in control group but decreased in intervention group at a non-significant level; for women specifically, p = 0.05
Moattari	2014	Iran Red Crescent Med J	Iran	80	54	86	Post-angioplasty		Angina Plan manual; address misconceptions on angina, set goals for physical activity and relaxation, dietary advice	12 weeks	Routine care		Anxiety change greater in intervention group than control group
Moser	2012	Eur J Cardiovasc Nurs	USA, Australia, New Zealand	3822	68	68	CHD		Educational session and one follow-up phone call	45 educational sessions	Not disclosed	12 month	Reduced anxiety after 12 months but not at 3 months in men (not in women); reduced anxiety over time in intervention group but not control
Murchie	2004	Fam Pract	UK	961	66	58	Diagnosis of CHD		Secondary prevention clinic; review of symptoms, treatment, blood pressure and lipid management, and lifestyle factors, as well as behavioral change negotiated	Indefinite (ecological study)	Usual care by GP	secondary clinics every 2 to 6 months depending on patient's needs	No group differences
Ness	2003	Nutr Neurosci	UK	452	61	100	Treated angina		Advice to eat fatty fish or fish oil	6 months	No advice		No group differences

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									capsules if fish unpalatable				
O'Neil	2014	Eur J Prev Cardiol	Australia	430	61	79	Diagnosed MI		Scripted telephone sessions with a health coach encouraging self- management strategies	10 sessions	Usual care - written materials and a newsletter every 3 months		Intervention group showed decreased anxiety at 6 months compared to controls
Park	2013	Int J Nurs Pract	South Korea	63	58	83	Post-angioplasty		Psychoeducational intervention--risk factor advice and telehealth coaching	12 weeks	Usual care	6 months	intervention group had significantly lower anxiety at 6 months compared to controls
Pfaffli	2015	J Med Internet Res	New Zealand	123	60	81	CHD diagnosis		Mobile phone- based comprehensive CR program	24 weeks	Traditional CR		Intervention group had significantly greater anxiety than control group at 6 months
Shuldham	2002	Eur Heart J	UK	374	63	88	Awaiting first CABG		Pre-operative education program, with videos and written information	4 hours	Usual education	6 weeks, 3 months, 6 months	No group differences
Steinke	2004	Res Nurs Health	USA	115	54	80	Post-MI		Videotape on sexual education after MI at home	15 minutes	Standard written instructions alone	5 months	Greater anxiety in the experimental group at 1 month, no group differences at 3 or 5 months
Taylor	1997	J Cardiopulm Rehabil	USA	585	57	78	Post-MI	Stratified by patients who had high distress levels at baseline	Telephone-based nurse case managed, home based, multifactorial, risk reduction program	6 months (possibly longer depending on patient factors)	Usual care	6, 12 months	Intervention reported significantly reduced anxiety compared to controls in patients with low anxiety; no difference between groups for those with existing anxiety
Tullmann	2007	Res Nurs Health	USA	120	74	48	Self-report history of cardiovascular disease		Individual education and counseling concerning signs of MI, typical emotional responses, and actions to take	30-60 minutes	No intervention	3 months	No group differences
Utriyaprasit	2010	J Adv Nurs	Thailand	120	63	70	<9 days since first CABG		Audiotape for in- hospital and home	30 minutes, repeated ad lib	Usual care plus visits/calls from	2 weeks and 4 weeks	No group differences

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									use, with information on CABG recovery plus relaxation exercises and music		researcher matching intervention group timetable	after discharge	
Vale	2005	Dis Manag Health Out	Australia	219	61	75	Hospitalized for CABG or angioplasty		Psychoeducational telephone coaching sessionstargeting risk factors and illness awareness	24 weeks	Usual care with telephone check- in at 2 weeks	6 months	Anxiety reduced in both groups, significantly larger reduction in treatment group
van Elderen-van Kemenade	1994	Br J Clin Psychol	Netherlands	60	57	85	Post-MI		Psychoeducational health education and counseling program--individual and group counseling and health education programs around risk factors, anxiety, depression	6 weeks	Usual care	2 months, 12 months after discharge	No group differences
Wang	2015	Eur J Cardiovasc Nurs	Singapore	128	55	90	Post-MI		Education session, with a home-based self-management manual plus telephone follow-up	4 weeks with weekly calls	Usual care	16 weeks	Intervention group with greater decrease in anxiety over time; main effects not reported
Wang	2012	Heart Lung	China	160	58	84	Documented acute MI		Self-help heart health behavior manual, with introduction by principal investigator	6 weeks	Usual care	3 months and 6 months	Significant main effect of time and time × group interaction; intervention group with lower anxiety scores at all follow-up points

Table 5

Description and anxiety-related results of alternative interventions.

First Author	Year	Journal	Country	N	Age	% Male	CAD inclusion criteria	Psychological diagnoses in inclusion criteria	Intervention performed	Intervention Duration	Control condition(s)	Follow-up interval	Anxiety-related outcome
Arthur	2000	Ann Intern Med	Canada	249	63	85	Waiting list for first elective CABG		Twice weekly exercise training, education and reinforcement, monthly phone call from nurse	8 weeks	Usual care	6-8 weeks after surgery, 6 months after surgery	No group differences
Asbury	2012	Cardiology	UK	42	65	83	Refractory angina>6 months; history of MI, CABG, or angioplasty; >2 episodes per week		CR	8 weeks	Daily symptom monitoring		No between group differences on HADS
Bertie	1992	J R Coll Physicians Lond	UK	110	52		Admitted for acute MI		CR program with exercise	4 weeks	Standard care	4 months, 12-24 months after infarct	No group differences
Blumenthal	1988	J Cardiopulm Rehabil	USA	70	54 (median)	100	<1 year post-MI		Low compared to high intensity exercise regimen	12 weeks	None		No group differences
Blumenthal	2005	JAMA	USA	134	63	69	Ischemic heart disease and exercise induced myocardial ischemia		Usual care with supervised aerobic exercise training, or usual care with weekly stress management	16 weeks	Usual medical care		No group differences
Carney	2009	JAMA	USA	122	58	66	CHD	Major depression	Omega 3 fatty acids as augmentation to sertraline	10 weeks	Corn oil placebo		No group differences
Dalal	2007	Int J Cardiol	UK	104	NA		Uncomplicated MI		Patient choice of hospital CR or self-help package of 6 weeks supported by nurse	6 or 10 weeks	Self-choice (randomized vs. self-choice)	9 months	No group differences
Devi	2014	J Med Internet Res	UK	94	66	35	Stable angina		Internet based CR program	6 weeks	Usual care	6 months	No group differences
Erdman	1983	J Cardiac Rehabil	Netherlands	80	51	100	<6 months post-MI		Outpatient CR	6 months	Home-based CR		No group differences
Faulkner	2013	J Cardiopulm Rehabil Prev	New Zealand	22	62	60	Experienced a cardiac event	Moderate to high level of anxiety for outdoor walking	Outdoor walking intervention	4 weeks	Stationary cycling		Walking group had significantly greater decrease in task specific anxiety
Frizelle	2004	Br J Health Psychol	UK	22	62	NA	Patients with implantable cardioverter defibrillator due to chronic heart disease		CR	6 weeks	Waitlist	3 months post treatment	Experimental group with lower anxiety end-intervention compared to control; lower post-treatment

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First Author	Year	Journal	Countr y	N	Age	% Male	CAD inclusion criteria	Psychological diagnoses in inclusion criteria	Intervention performed	Interventio n Duration	Control condition(s)	Follow- up interval	Anxiety-related outcome
													anxiety compared to pre-treatment in all patients
Haberka	2013	Pharmacol Rep	Poland	52	58	85	Acute MI		N-3 polyunsaturated fatty acids	1 month	Standard care		Significantly lower state- and trait- anxiety for both groups over time; STAI-S significantly decreased for intervention group after adjusting for baseline variables
Hevey	2003	J Cardiopulm Rehab	Ireland	60	61	81	MI and/or CABG		CR	4-10 weeks	4-week CR	6 moths	No group differences
Jolly	2009	Heart	UK	525	61	77	MI, angioplasty, or CABG		Center based CR	8-12 weeks	Home-based CR	1 year	No group differences; improvement in all groups
Karlsson	2007	J Behav Med	Sweden	224	63	77	Post-MI with planned CABG		Expanded CR--stress management, increased physical training, stay at patient hotel, cooking sessions	1 year	Routine rehabilitation		Type D patients in intervention group had significantly lower anxiety (not significant in type D control patients)
Kugler	1990	Arch Phys Med Rehabil	USA or Germany; not specified	52	32-66	100	Post-MI		Hospital supervised or home- based CR	8 weeks	Home-based CR with no instruction		Hospital biking/ home walking, unsupervised exercise groups with more anxiety improvement than hospital/home biking
Lewin	1992	Lancet	UK	176	56	72	Acute MI	Subgroup of “psychologically distressed” patients based on clinically significant depression or anxiety from HADS score	Self-help home rehabilitation program based on a cardiac manual- sections including education, home exercise program, tape-based stress management and relaxation program	6 weeks	Standard care with information package and informal counselling	1 year	Anxiety lower in treatment group than control group at 6 weeks, 1 year; in those who were psychologically distressed at baseline, anxiety was lower in treatment group at 6 weeks, 6 months, 1 year
Li	2014	Int J Clin Exp Med	China	100	45-75	71	Post-angioplasty	Mood disorder-- poor adherence, fatigue,	Western medicine (aspirin, beta-blocker, and a “lipid	8 weeks	Western medicine		Reduced anxiety in the group receiving xinkeshu tablets

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First Author	Year	Journal	Countr y	N	Age	% Male	CAD inclusion criteria	Psychological diagnoses in inclusion criteria	Intervention performed	Interventio n Duration	Control condition(s)	Follow- up interval	Anxiety-related outcome
								insomnia, somatoform symptoms	blocker," most often a statin) plus Xinkeshu tablets				
Linden	1995	Intensive Crit Care Nurs	UK	41	62	68	Post-MI		Home based CR in a cardiac care unit	6 weeks	Usual care, information leaflets		Improved anxiety scores in intervention group, no change in scores in control; no between-group differences reported although higher proportion of patients with decreased anxiety in intervention group
Mutwalli	2012	Saudi Med J	Saudi Arabia	49	57	100	Post-CABG		Home based CR program	6 months	Standard hospital treatment		Intervention group showed greater improvement in HADS
Nagarathna	2013	Indian Heart J	India	250	53	100	Post-CABG		Yoga based CR program	12 months after discharge	Physiotherapy based CR		No group differences; improvement in all groups
Oerkild	2012	BMJ Open	Denmark	40	77 (median)	58	>65 years old with recent coronary event including MI, angioplasty, or CABG, declined center-based CR		Home visits from physiotherapist to create home physical training program	6 weeks	Usual care	3 months, 6 months, 12 months	No group differences
Oldridge	1995	Med Sci Sports Exerc	Canada	201	54	89	Diagnosis of MI	Presence of anxiety or depressive symptoms measured prior to hospital discharge (STAI- State > 42)	Low-level exercise prescription plus group cognitive-behavioral counseling focusing on coping strategies	8 weeks	Usual care	12 months	No group differences; improvement in all groups
Oldridge	1991	Am J Cardiol	Canada	201	53	89	Post-MI	Depression, anxiety, or both	Program of exercise conditioning and behavioral counseling	8 weeks	Conventional care	12 month	Decreased state anxiety at 8 weeks for intervention group compared to controls
Pedersen	2015	EurJ Prev Cardiol	Denmark	70	63	78	>6 months since MI, angioplasty, CABG, or classic angina pectoris		Aerobic interval training (exercise bike), three sessions/week	12 weeks	Low energy diet		No group differences; improvement in all groups

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First Author	Year	Journal	Countr y	N	Age	% Male	CAD inclusion criteria	Psychological diagnoses in inclusion criteria	Intervention performed	Interventio n Duration	Control condition(s)	Follow- up interval	Anxiety-related outcome
Seki	2003	Circulation	Japan	38	70	100	>6 months after a major coronary event (acute MI, CABG, ACS); chronic CHD		Outpatient CR	6 months	Usual outpatient care		Nonsignificant change for trait, significant change in state anxiety at 6 months for intervention group; no between-groups comparison found
Sharif	2012	BMC Cardiovasc Disord	Iran	80	59	70	Patients scheduled for CABG		CR plus educational programs (diet, weight, stress management, smoking cessation, relaxation)	4 weeks	No intervention	2 months	Significant main effect of time such that all participants' anxiety decreased; no main effect of Group; significant Time × Group interaction such that individuals in intervention group saw steeper decrease in anxiety (9 points vs 6 for controls)
Stern	1983	JAMA Intern Med	USA	106	54	86	MI	Rated as anxious/ depressed and/or mean workload <7mets on treadmill test	Exercise sessions; or group counseling	12 weeks	Routine care	3 months, 6 months, 1 year	Exercise greater reduction compared to control at 3 months; group counseling less anxiety compared to controls at 6 months; no difference at 1 year
Sundin	2003	Int J Behav Med	Sweden	132	59	100	Post-angioplasty, CABG, or AMI		Residential multifactorial CR, outpatient multifactorial CR, stress management	12 month	Standard CR	HAD	No group differences; improvement in all groups
Taylor	1986	J Psychosomatic Research	USA	210	52	100	Hospitalized for AMI		Symptom limited treadmill plus home exercise training, treadmill plus medically supervised gym training, treadmill without formal exercise program	8 or 23 weeks	Patients seen 6 months after MI	6 months	No group differences; improvement in all groups
Worcester	1993	BMJ	Australia	224	54	100	Admitted to coronary care unit with acute MI		High intensity exercise training	8 weeks	Low intensity exercise	4 and 12 months post-MI	No group differences
Yogendra	2004	J Assoc Physicians India	India	113	NA	NA	CHD proven by angiogram		Family based yoga program with control of risk factors,	1 year	Conventional medical treatment		No group differences

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First Author	Year	Journal	Countr y	N	Age	% Male	C/AD inclusion criteria	Psychological diagnoses in inclusion criteria	Intervention performed	Interventio n Duration	Control condition(s)	Follow- up interval	Anxiety-related outcome
									dietary modifications, stress management				
Yonezawa	2009	Int Heart J	Japan	109	57	83	Post-MI		CR	5 months	Usual care		No group differences
Yu	2004	Arch Phys Med Rehabil	Hong Kong	269 randomized, 204 analyzed	64	76	<6 weeks post- AMI or post-angioplasty for angina pectoris		CR: inpatient ambulation, outpatient education and exercise; followed by home exercise program and long- term maintenance	2 years total: 1-2 weeks inpatient, then twice weekly for 8 weeks; home exercise for 6 months; long-term maintenance through end of 2 years	conventional therapy		Lower anxiety at follow-up assessments than baseline for intervention group (p < .05) and no change in control group; no between group differences