Association between anxiety and mortality in patients with coronary artery disease: A meta-analysis

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Background Depression and anxiety are common in patients with coronary artery disease (CAD). Although depression clearly has been associated with mortality in this population, the relationship between anxiety and mortality is less clear. Accordingly, we performed a series of meta-analyses to (1) examine the relationship between anxiety and mortality in patients with established CAD and (2) determine if this relationship differs in patients with stable CAD compared to those who have just had an acute coronary syndrome (ACS).

Methods and results Systematic literature searches identified 44 articles (total N = 30,527) evaluating the prospective relationship between anxiety and mortality in individuals with established CAD. A series of 8 adjusted and unadjusted meta-analyses were performed to examine this relationship across all patients, with sensitivity analyses completed in post-ACS and stable CAD cohorts. In unadjusted analyses, anxiety was associated with a moderate increase in mortality risk (odds ratio 1.21 per SD increase in anxiety). However, when adjusting for covariates, nearly all associations became nonsignificant. In sensitivity analyses, anxiety was associated with an increased risk of poor outcomes in the stable CAD—but not post-ACS—cohort.

Conclusions These analyses confirm that anxiety is associated with increased risk of mortality in patients with CAD; however, this relationship is not as strong as that of depression and may be explained partly by other clinical factors. If anxiety screening is performed, it should be performed during a period of clinical stability and should target anxiety disorders rather than anxiety symptoms alone. (Am Heart J 2015;170:1105-15.)

Among individuals with coronary artery disease (CAD), negative psychological states are common, persistent, and associated with poor medical outcomes, including reduced functioning, recurrent cardiac events, and mortality.[1] Depression, the most commonly studied psychological syndrome in cardiac patients, has been linked to the development and progression of CAD[2,3] and, in patients who have an acute coronary syndrome (ACS), has been associated with a 2- to 2.7-fold increased risk of mortality.[4-6] These findings led to the American Heart Association's recommendation that depression be considered a risk factor for poor outcomes in patients in the post-ACS period.[7]

The relationship between anxiety and mortality is less well established. Although anxiety symptoms and anxiety disorders are highly prevalent in patients with CAD,[8] studies evaluating the impact of anxiety on cardiac health have yielded mixed results. Five years ago, Roest et al[9] published 2 meta-analyses, which aimed to determine the relationship between anxiety and medical outcomes in patients with and without CAD. These analyses found that anxiety was prospectively related to the development of CAD[9] and, in patients who have had an ACS, associated with recurrent cardiac events and mortality.[10] Since those analyses were performed, however, more recent studies have suggested that anxiety may have differential effects in patients with different types of cardiac disease, with some suggesting that anxiety may act as a protective factor in certain instances.[11]

Several questions remain regarding how anxiety is linked to outcomes in cardiac patients. First, what is the relationship between anxiety and mortality in patients with CAD, and does it apply equally across the spectrum of CAD patients (from stable CAD to post-ACS patients)? Second, does the relationship between anxiety and mortality persist when controlling for other important covariates, such as depression or severity of cardiac disease? Finally, how does the relationship between anxiety and mortality change when including other outcomes, such as recurrent cardiac events or rehospitalizations, with mortality (ie, a composite outcome)? To answer these questions, we performed a series of meta-analyses and sensitivity analyses to determine the

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Table I. Search terms used in search strategy

Any of the following:	AND any of the following:	AND any of the following:
Anxiety	Mortality	Coronary heart disease
Tension	Survival	Coronary artery disease
Posttraumatic stress disorder	Prognosis	Ischemic heart disease
Panic	Adverse	Myocardial infarction
Phobic anxiety	Event*	Unstable angina
Phobia		Acute coronary syndrome
Worry		Coronary artery bypass graft
		Atherosclerosis
		Sudden death
		Ventricular fibrillation
		Ventricular tachycardia

Note: This was entered into PubMed as a single search, as follows: ((((((((anxiety) OR tension) OR "post-traumatic stress disorder") OR panic) OR "phobic anxiety") OR phobia) OR worry)) AND (((((mortality) OR survival) OR prognosis) OR event*) OR adverse)) AND ((((((((((("coronary heart disease") OR "coronary artery disease") OR "ischemic heart disease") OR "coronary artery bypass graft") OR atherosclerosis) OR "sudden death") OR "ventricular fibrillation") OR "ventricular tachycardia") OR "acute coronary syndrome") OR "myocardial infarction") OR "unstable angina").

prospective relationship between anxiety and mortality in individuals with established CAD.

Methods

The guidelines and criteria outlined in Preferred Reporting Items for Systematic Reviews and Meta-Analyses were applied to ensure proper reporting of the data (see online Appendix Supplementary Table I).[12]

Search strategy

The literature search was conducted by 2 authors (C.C. and C.A.B.). A systematic review was completed using keyword-based queries in the PubMed and PsycInfo electronic databases. Keywords related to the population of interest (patients with CAD) were combined with keywords related to anxiety, as outlined in Table I. An advanced search was performed in each database, with each subsearch consisting of 3 keywords, such as "anxiety AND unstable angina AND mortality." The search was conducted in March 2014 and included articles from the earliest covered dates of the electronic databases (1945 for PubMed, 1967 for PsycInfo) to March 10, 2014.

Selection procedure

English and Spanish language manuscripts published in peer-reviewed journals were eligible for this review. Eligible studies were assessed with criteria in line with the Participants, Interventions, Comparators, Outcomes, and Study Design search strategy.[13] Inclusion criteria were the following: (1) studies were prospective and enrolled at least 75 patients with established CAD (stable CAD, patients awaiting coronary artery bypass graft [CABG] surgery, post-ACS, or post–percutaneous coronary intervention [PCI]) but without any predefined psychiatric illness, (2) studies included at least 1 self-report or interview-based assessment of anxiety symptoms or anxiety disorder at baseline, (3) studies included at least 1 measure of mortality (cardiac mortality, all-cause mortality, or a composite outcome including mortality and other cardiac events) as an outcome, and (4) studies measured outcomes at least 30 days after the baseline assessment. These inclusion criteria largely mirrored those in the American Heart Association's systematic review of depression as a risk factor for poor prognosis in the post-ACS period.[7]

Data extraction

Article review proceeded in several steps. First, 2 authors (C.C. and C.A.B.) removed duplicate articles and screened the titles and abstracts of the remaining articles to rule out excluded studies. Next, full texts were read and screened for eligibility criteria by 3 authors (C.C., C.A.B., and R.M.). Once eligible studies were identified, relevant data were extracted independently by the same 3 authors and entered into a database. All extracted data were reviewed by the first author to ensure that the data were transferred accurately and consistently across studies. If sufficient data were not provided in potentially eligible studies, authors were contacted for additional data.

Data abstraction

To assess the quantitative relationships between anxiety and the outcome variables (mortality or a composite outcome), data were abstracted from articles in the following categories: patient/study characteristics, measures of anxiety, outcome measures, adjusted and unadjusted effect estimates with 95% CIs, and *P* values. In those studies that examined anxiety as a continuous variable, analyses were standardized to assess the odds ratio (OR) of a 1 SD change in the anxiety measure. When the SD of an anxiety measure (eg, Hospital Anxiety and Depression Scale, anxiety subscale [HADS-A]) was not available in the manuscript or through contact with the authors, it was estimated using the pooled SD of the other included studies that used the same measure.[14-17]

If an OR or hazard ratio was not provided in a manuscript, an OR was calculated using the available information. In 3 articles,[18-20] we calculated the OR by using the mean anxiety score in survivors versus nonsurvivors, and in another 4,[15,19,21,22] we used the mortality rates in anxious versus nonanxious individuals.

If a study used anxiety as both a continuous and dichotomized variable, we included them separately in different meta-analyses so that no study's data were counted twice in a single meta-analysis. To obtain a global assessment of effect size, the effect sizes in individual studies were weighted by the magnitude of the SE, to account for the precision of the effect size estimate in each study.[23]