Impact of anxiety on the post-discharge outcomes of patients discharged from the hospital after an acute coronary syndrome

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ABSTRACT

Background: Symptoms of anxiety are highly prevalent among survivors of an acute coronary syndrome (ACS), but do not necessarily indicate an anxiety disorder. The extent to which symptoms of anxiety or a diagnosis of this condition impacts hospital readmission and post-discharge mortality among patients with an ACS remains unclear.
Methods: We used data from 1909 patients discharged from six hospitals in Massachusetts and Georgia after an ACS. Moderate/severe symptoms of anxiety were defined based on responses to a Generalized Anxiety Disorder questionnaire during the patient's index hospitalization. The diagnosis of an anxiety disorder was based on review of hospital medical records. Multivariable adjusted Poisson regression and Cox proportional-hazards models were used to estimate the risk of 30-day hospital readmissions and 2-year total mortality.
Results: The mean age of the study population was 61 years, two thirds were men, and 78% were non-Hispanic whites. In this population, 10.4% had a documented diagnosis of an anxiety disorder, 18.8% had moderate/severe symptoms of anxiety, and 70.8% had neither a diagnosis nor symptoms of anxiety. Neither a diagnosis of an anxiety disorder nor symptoms of anxiety were associated with 30-day all-cause or cardiovascular-related rehospitalizations. Patients with an anxiety disorder (multivariable adjusted HR = 1.95, 95%CI = 1.11–3.42) were at greatest risk for dying during the 2-year follow-up period.
Conclusions: We identified patients with an anxiety disorder as being at greater risk for dying after hospital discharge for an ACS. Interventions may be more appropriately targeted to those with a history of, rather than acute symptoms of, anxiety.

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1. Introduction

Between one quarter to one half of patients hospitalized for an acute coronary syndrome (ACS) may have an anxiety disorder [1–4]. The presence of an anxiety disorder in patients with coronary artery disease has been associated with several adverse outcomes [3,5,6] including higher mortality [7], recurrent coronary events, and impaired quality of life [2,8]. The Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria for the diagnosis of an anxiety disorder requires the presence of anxiety symptoms for upwards of six months [9]. However,

many patients with coronary artery disease are discharged from the hospital relatively soon [10], which raises challenges to the systematic assessment of anxiety and/or anxiety related disorders in this patient population. In addition, healthcare providers may not be aware of, or pay attention to, the symptoms of anxiety in patients who are hospitalized for an ACS, or may not have the necessary knowledge or skills to assess or manage patients who have an anxiety disorder [11,12]. Since healthcare providers are increasingly accountable for patients' outcomes, and given the variety of treatments available for the management of patients with either acute symptoms of anxiety or an anxiety disorder, better knowledge about the extent to which symptoms of anxiety, or the presence of an anxiety disorder, is associated with adverse outcomes after hospitalization for an ACS may help optimize patient's acute and long-term care and their prognosis.

Using data from a large and sociodemographically diverse population of patients discharged from the hospital after an ACS, we examined the association between 30-day hospital readmissions and long-term

mortality among patients discharged from the hospital after an ACS who had symptoms of anxiety or a prior diagnosis of an anxiety disorder.

2. Methods

2.1. Study design and population

We used data from the Transitions, Risks, and Action in Coronary Events – Center for Outcomes Research and Education (*TRACE-CORE*) study for this investigation [13–15]. In brief, TRACE-CORE is a multicenter prospective cohort study which included adult men and women hospitalized with an ACS at three tertiary care and community medical centers in Worcester, MA, two hospitals in Atlanta, GA, and one hospital in Macon, GA, between April 2011 and May 2013. Two cardiologists independently validated the diagnosis of an ACS based on the presence of at least two out of the three following criteria: (1) typical chest pain, (2) change in serial ECG tracings, (3), elevated serum troponin levels. Discrepancies were discussed between the two cardiologists until consensus was achieved. Each validated episode of an ACS was categorized as either an ST-segment elevation acute myocardial infarction (STEMI), a Non ST-segment elevation myocardial infarction (NSTEMI), or as unstable angina [13,14]. IRB approval was obtained from all participating sites and study subjects provided written informed consent.

Trained study staff collected a wide range of patient sociodemographic, lifestyle, and psychosocial characteristics at baseline (in-person interview) and at 1, 3, 6, and 12 months after hospital discharge (via phone interview). We also collected information about patient's clinical presentation, laboratory test results, and their receipt of cardiac medications and coronary reperfusion therapy from hospital electronic medical records [13].

We excluded 7 patients whose type of ACS was not able to be classified and 68 patients who did not complete the anxiety questionnaire. We additionally excluded patients who had data missing on race ($n = 32$), marital status ($n = 2$), educational attainment ($n = 1$), body mass index ($n = 20$), blood pressure ($n = 17$), heart rate ($n = 4$), serum creatinine ($n = 49$), and serum glucose ($n = 51$), potassium ($n = 5$), and white blood cell count findings ($n = 9$). The final study sample consisted of 1909 patients with an independently confirmed ACS.

2.2. Symptoms and diagnosis of anxiety

The presence of an anxiety disorder was based on the review of each patient's medical history and hospital discharge diagnostic codes. We used International Classification of Diseases (ICD)-9 diagnostic codes for anxiety disorders, including 300.0 (anxiety disorder unspecified), 300.02 (generalized anxiety disorder), 300.1 (panic disorder), 300.23 (social phobia), 300.3 (obsessive compulsive disorder), and 309.81 (post-traumatic stress disorder-PTSD) [16]. Given the strong and consistent evidence linking PTSD and cardiovascular disease, including coronary artery disease and cerebrovascular disease, as well as its risk factors, such as hypertension and hyperlipidemia, although PTSD is not included in the category of anxiety disorders in DSM-5, we included this condition in our working definition of anxiety as many patients who had PTSD would also exhibit symptoms of anxiety.

Patient's current symptoms of anxiety were assessed through use of the validated 7-item Generalized Anxiety Disorder (GAD-7) questionnaire during an in-person interview while patients were hospitalized for an ACS [17]. The GAD-7 captures symptoms of anxiety, including PTSD, during the past 2 weeks, with sensitivities and specificities ranging from 66% to 89% and 80 to 88%, respectively [18]. Patients were classified as having moderate/severe symptoms of anxiety if their GAD-7 score was ≥10 [17].

2.3. Hospital readmission

Patients were asked over the telephone whether they had been admitted to the hospital for any reason after their index hospitalization during several follow-up interviews. Trained research staff reviewed patient's medical records at participating hospitals to verify the occurrence of these readmissions and to determine if a readmission was scheduled before hospital discharge [15]. The cause of hospital readmission was identified based on the primary discharge code. We used codes 300.0, 300.02, 300.1, 300.23, 300.3, and 309.81 for purposes of defining an anxiety disorder related hospital readmission and codes 390–459 for classifying the occurrence of a cardiovascular related hospital readmission. Among 232 verified hospital readmissions, 43 were scheduled prior to hospital discharge, and were subsequently excluded from the present analyses, resulting in a total of 189 unplanned hospital readmissions in this patient population. We have previously shown that these hospitals captured the majority of 30-day hospital readmissions in our study population.

2.4. Mortality

Trained research staff reviewed medical records at participating hospitals to identify patients who may have died from any cause during the 2-year follow-up period. Death certificates were also examined at local, state and national vital registries to identify additional deaths. Patients were considered alive if, after 2 years of follow up, they were not found to have died in either hospital medical records or in the review of death certificates.

This rigorous follow-up process reduced the risk of losses to follow-up with regards to our mortality data.

2.5. Other variables

The GRACE-risk scores were calculated based on patient's age, heart rate, systolic blood pressure, creatinine levels, ST-segment deviation, elevated cardiac enzymes, and the presence of cardiac arrest and congestive heart failure at the time of hospital presentation [19]. Symptoms of depression were measured using the Patient Health Questionnaire-9 on a numerical scale of 0–27 [20]. Pharmacotherapy for anxiety included (1) the receipt of serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), or atypical antidepressants (bupropion, mirtazapine, nefazodone) and (2) the use of benzodiazepines (lorazepam, diazepam, clonazepam, alprazolam, clorazepate, oxazepam, chlordiazepoxide) as documented in patient's medical records at the time of hospital discharge. The receipt of cardiac medications during the patient's index hospital admission included aspirin, P2Y12 inhibitors (clopidogrel, prasugrel, ticagrelor, cangrelor), beta blockers, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers (ACE-I/ARBs), and statins.

2.6. Data analysis

For purposes of analysis, we considered 3 mutually exclusive groups of patients according to their symptoms of anxiety or history of an anxiety disorder: (1) patients who had no/mild symptoms of anxiety and did not have a diagnosis of an anxiety disorder during their index hospitalization, (2) patients who reported moderate/severe symptoms of anxiety but were without a diagnosis of an anxiety disorder, and (3) patients who had an established diagnosis of an anxiety disorder, irrespective of their symptoms of anxiety during their acute hospital admission.

We described and compared the distribution of data in our 3 study groups using the Chi-square test or Kruskal–Wallis test for categorical and continuous variables as appropriate. We used modified-Poisson regression modelling with robust error variance estimation to estimate differences in the relative risk of a 30-day hospital readmission while adjusting for several potentially confounding demographic and clinical variables [21]. Due to their prognostic impact, GRACE-risk scores were calculated and included in each of our multivariable adjusted regression models [19]. All other variables were then tested in an iterative fashion and variables which materially changed the estimates of relative risk by >10% were retained in the final regression models [22].

We calculated Kaplan Meier survival curves for purposes of describing the post discharge survival experiences in each of our 3 comparison groups. We compared 2 year post-discharge all-cause death rates among these groups using the Logrank test. To estimate the effect of symptoms of anxiety, or a documented diagnosis of an anxiety disorder, on post-discharge survival while adjusting for several potentially confounding factors of prognostic importance, we used Cox proportional-hazards models [23]. Assumptions of proportional hazards for each variable included in the model were checked with log [−log] graph and with Schoenfeld residuals [23,24]. Similar to the modified-Poisson models, we included the GRACE-risk scores in all models; other variables were only included if they materially changed the estimates by >10%. All analyses were conducted in Stata 13.0 with a 2-sided $\alpha = 0.05$ used for statistical significance.

3. Results

The mean age of the study population was 61 years, 67% were men, 78% were non-Hispanic whites, and 16% were black. Approximately one half of study patients developed an NSTEMI during their acute index hospitalization and 30% had unstable angina. At baseline, 10.4% of patients had an established diagnosis of an anxiety disorder, 18.8% exhibited moderate/severe symptoms of anxiety as measured by the GAD-7 questionnaire, and 70.8% had no/mild symptoms of anxiety. The mean (SD) GAD-7 scores were highest in patients who had moderate/severe symptoms of anxiety without a diagnosis of an anxiety disorder (14.7 (3.8)), and were higher among patients who had a documented diagnosis of an anxiety disorder (9.8 (6.6)) than in patients who had no/mild symptoms of anxiety without a diagnosis of an anxiety disorder (3.1 (2.7)).

3.1. Baseline characteristics of study participants

Patients who had a diagnosis of an anxiety disorder, or moderate/severe symptoms of anxiety, were older, more likely to be women, and unemployed compared with patients who had no/mild symptoms of anxiety (Table 1). These patients were also more likely to have a history of depression, higher depression symptom severity, or received benzodiazepines or other anti-anxiety medications during their acute hospitalization. On the other hand, patients with a diagnosis of an

Table 1

Baseline characteristics of patients discharged from the hospital after an acute coronary syndrome according to symptoms/diagnosis of anxiety.

	No/mild symptoms of anxiety without a diagnosis of an anxiety disorder	Moderate/severe symptoms of anxiety without a diagnosis of an anxiety disorder	Documented diagnosis of an anxiety disorder
	(n = 1353)	(n = 358)	(n = 198)
Age (mean, years)	62 [54–70]	58 [51–65]	60 [52–67]
Age group (%)			
<55	26.8	38.8	34.9
55–64	31.6	33.2	31.3
65–75	26.8	21.8	22.2
≥75	14.8	6.2	11.6
Women (%)	28.8	39.9	47.5
Race/ethnicity (%)			
White	78.3	72.9	85.4
Black	15.8	21.2	8.6
Other	5.8	5.9	6.1
Marital status (%)			
Married/lived as married	60.3	53.4	53.0
Separate/divorced/widowed	28.7	30.5	39.4
Single/never married	11.0	16.2	7.6
Educational attainment (%)			
College graduate or higher	28.2	14.3	20.7
Some technical school or college	30.8	22.6	27.3
High school graduate	28.4	36.3	32.8
Less than high school	12.7	26.8	19.2
Insurance coverage (%)			
Medicare plus private insurance	21.2	12.3	15.7
Private insurance only	52.0	40.8	47.5
Medicare only	12.3	14.5	14.7
Medicaid	8.0	17.9	13.1
Uninsured	6.5	14.5	9.1
Unemployed (%)	54.1	68.4	68.7
Previously diagnosed (%)			
Chronic kidney disease	10.4	12.6	9.1
Congestive heart failure	12.6	19.0	13.1
Coronary artery disease	26.0	28.2	28.8
Depression	7.5	14.5	48.5
Diabetes	36.4	44.4	37.9
Hypertension	73.8	82.7	77.8
Physiologic findings at admission			
Systolic blood pressure (mmHg)	142 [125–158]	140 [123–157]	137 [123–152]
Diastolic blood pressure (mmHg)	80 [70–91]	78 [68–90]	77 [67–88]
Heart rate (beat/min)	75 [64–88]	75 [67–87]	77 [66–90]
Patient Health Questionnaire-9 score	3 [1–6]	11 [8–16]	8 [4–14]
Laboratory findings at admission			
Creatinine (mg/dl)	1.0 [0.8–1.2]	1.0 [0.8–1.2]	0.9 [0.8–1.1]
Glucose (mg/dl)	126 [105–166]	130 [105–171]	123 [105–171]
GRACE risk score	94 [76–115]	90 [72–111]	92 [73–112]
Potassium (mmol/l)	4.0 [3.8–4.3]	4.0 [3.7–4.4]	4.0 [3.6–4.3]
White blood cell count$^{(109cell/L)}$	8.4 [6.8–10.8]	8.8 [6.7–11.3]	8.6 [6.7–11.0]
In hospital complications (%)			
Acute kidney injury	5.8	6.4	5.6
Heart failure/cardiogenic shock	1.8	1.4	4.6
Ventricular tachycardia/fibrillation	4.8	6.2	4.0
Atrial fibrillation/flutter	8.1	6.4	6.6
ACS Type (%)			
Unstable angina	28.0	32.1	35.9
STEMI	20.3	15.9	9.6
NSTEMI	51.7	52.0	54.6
Reperfusion treatment received (%)			
Medical treatment	19.0	22.9	24.8
PCI	69.6	64.0	59.6
CABG	11.5	13.1	15.7

Table 1 (*continued*)

	No/mild symptoms of anxiety without a diagnosis of an anxiety disorder	Moderate/severe symptoms of anxiety without a diagnosis of an anxiety disorder	Documented diagnosis of an anxiety disorder
	(n = 1353)	(n = 358)	(n = 198)
Medications at hospital discharge (%)			
Aspirin	96.9	96.7	98.0
P2Y12 inhibitors	86.4	83.5	79.8
ACE-I/ARBs	61.6	67.0	56.6
Beta-blockers	89.9	91.1	91.9
Statins	88.1	86.0	88.9
SSRI/SNRI/atypical antidepressants	10.4	25.4	45.0
Benzodiazepines	22.2	36.9	66.2
Length of hospital stay (days)	3 [2–5]	3 [2–6]	3 [2–6]

Note: continuous variables were reported in median [interquartile range], p1 compared no/mild symptoms with moderate/severe symptoms of anxiety, p2 compared no/mild symptoms with a documented diagnosis of anxiety.

NSTEMI: non-ST-segment elevation myocardial infarction, STEMI: ST-segment elevation myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft surgery, ACE-I/ARBs: Angiotensin converting enzyme inhibitor/Angiotensin receptor blockers, SSRI: selective serotonin reuptake inhibitors, SNRI: serotonin and norepinephrine reuptake inhibitors.

Atypical antidepressants included bupropion, mirtazapine, nefazodone. Benzodiazepines included lorazepam, diazepam, clonazepam, alprazolam, clorazepate, oxazepam, chlordiazepoxide.

anxiety disorder or who exhibited moderate/severe symptoms of anxiety during their acute hospitalization were less likely to have been married, have insurance, have a high school or lower education, and were less likely to have received coronary reperfusion therapy (PCI or CABG surgery) during their index hospitalization. Compared with patients who had no/mild symptoms of anxiety, patients who reported moderate/severe symptoms of anxiety were more likely to have a history of heart failure, diabetes, or hypertension, and were more likely to have received ACE-I/ARBs during their hospitalization for an ACS. Patients who had an anxiety disorder were more likely to have developed heart failure and cardiogenic shock during their acute hospitalization and were less likely to have received P2Y12 inhibitors.

3.2. Association between symptoms and diagnosis of anxiety with hospital readmission

During the first 30 days after hospital discharge, a total of 189 (9.9%) patients were readmitted to the hospital. Among the 189 unplanned hospital readmissions, none was anxiety-related and 76 (40.2%) were cardiovascular-related. Unscheduled, all-cause, 30-day hospital readmission rates were significantly higher among patients who had a previously diagnosed anxiety disorder (13.7%) or moderate/severe symptoms of anxiety (12.1%) compared to patients with no/mild symptoms of anxiety (8.4%, p = 0.007).

In our unadjusted regression analyses, patients who had an anxiety disorder, or who exhibited moderate/severe symptoms of anxiety, had a 1.58 (95% Confidence interval [CI] = 1.07–2.33) and 1.45 (95%CI = 1.05–2.01) folds higher risk of an unplanned all-cause hospital readmission within 30 days post discharge compared with patients who had no/mild symptoms of anxiety, respectively (Table 2). However, after adjusting for current symptoms of depression, in addition to the GRACE risk scores, these elevated risks were attenuated and became nonsignificant (relative risk [RR] = 1.01, 95%CI = 0.67–1.52, and RR = 1.21, 95%CI = 0.79–1.88); adjustment for other variables did not materially change these estimates. When cardiovascular-related hospital readmissions were separately examined, neither a previous diagnosis of

Table 2
Risk of an unscheduled 30-day hospital readmission among patients discharged from the hospital after an acute coronary syndrome according to symptoms/diagnosis of anxiety.

	No/Mild symptoms of anxiety without a diagnosis of an anxiety disorder	Moderate/severe symptoms of anxiety without a diagnosis of an anxiety disorder		Documented diagnosis of an anxiety disorder	
	RR	RR	95%CI	RR	95%CI
All-cause hospital readmission					
Unadjusted	Reference	1.45[b]	1.05–2.01	1.58[c]	1.07–2.33
Adjusted[a]	Reference	1.01	0.67–1.52	1.21	0.79–1.88
Cardiovascular-related hospital readmission					
Unadjusted	Reference	1.39	0.82–2.35	1.26	0.63–2.52
Adjusted[a]	Reference	0.92	0.48–1.76	0.94	0.45–1.95

RR: relative risk, CI: confidence interval.
[a] Adjusted for GRACE risk score and symptoms of depression.
[b] $p = 0.023$.
[c] $p = 0.022$.

an anxiety disorder, or current moderate/severe symptoms of anxiety, were associated with an increased risk of hospital readmission (Table 2).

3.3. Association between symptoms and diagnosis of anxiety with post-discharge mortality

A total of 97 patients (5.1%) died during the 2-year follow up period, with only 13 deaths occurring during the first 30 days after hospital discharge. Overall, the risk of dying was 3.9% at 1 year and 5.7% at 2 years post discharge. Among our 3 primary comparison groups, the risk of dying from all causes at 1 and 2 years post discharge was lowest (3.1% and 4.6%, respectively) in patients with no/mild symptoms of anxiety, slightly higher (4.6% and 7.1%) in patients with moderate/severe symptoms of anxiety, and highest (8.2% and 11.3%, respectively) in patients who had been previously diagnosed with an anxiety disorder.

Patients who had been previously diagnosed with an anxiety disorder had a 2.55 (95%CI = 1.53–4.26) times higher risk of dying over the course of 2 years compared with patients who had no/mild symptoms of anxiety (Table 3). This elevated risk remained even after multivariable adjustment. On the other hand, patients who had moderate/severe symptoms of anxiety had a similar risk of dying over the 2 year follow up period (HR = 1.00, 95%CI = 0.56–1.81) compared with patients who had no/mild symptoms of anxiety. Adjustment for other sociodemographic and clinical factors and hospital management practices did not materially change these estimates (Table 3).

Table 3
Risk of 2-year all-cause mortality among patients discharged from the hospital after an acute coronary syndrome according to symptoms/diagnosis of anxiety.

	No/Mild symptoms of anxiety without a diagnosis of an anxiety disorder	Moderate/severe symptoms of anxiety without a diagnosis of an anxiety disorder		Documented diagnosis of an anxiety disorder	
	HR	HR	95%CI	HR	95%CI
All-cause mortality					
Unadjusted	Reference	1.54	0.94–2.52	2.55[b]	1.53–4.26
Adjusted[a]	Reference	1.00	0.56–1.81	1.95[c]	1.11–3.42

HR: hazard ratio, CI: confidence interval.
[a] Adjusted for GRACE risk score, symptoms of depression, serum creatinine levels, and diastolic blood pressure at hospital presentation.
[b] $p < 0.001$.
[c] $p = 0.019$.

4. Discussion

Despite a considerable published literature which has examined the relationship between anxiety and adverse clinical outcomes in patients with coronary artery disease (CAD) [4,25–27], to our knowledge, the present study is the first to examine and compare the effects of current symptoms of anxiety with that of an established diagnosis of an anxiety disorder on short and long-term clinical outcomes among patients discharged from the hospital after an ACS. We found that patients with a previously diagnosed anxiety disorder were at greater risk for dying after hospital discharge but neither the acute symptoms of anxiety or the presence of a previously diagnosed anxiety disorder were associated with 30-day hospital readmissions after adjustment for several variables of prognostic importance.

4.1. Association between symptoms and diagnosis of anxiety with hospital readmission

In our sociodemographically diverse patient population, we initially found a higher risk of all-cause 30-day hospital readmissions in patients with an established diagnosis of anxiety as well as in patients who reported moderate/severe symptoms of anxiety at the time of hospital discharge for an ACS. However, this elevated risk was markedly attenuated and became statistically nonsignificant after adjusting for concurrent symptoms of depression in addition to the GRACE risk scores. Our findings suggest that the higher risk of unscheduled hospital readmissions in patients who had a prior diagnosis of an anxiety disorder, or who reported moderate/severe symptoms of anxiety during their hospitalization for an ACS, may be due to the negative impact of concurrent symptoms of depression, which were highly prevalent in these patients, and the severity of the ACS as reflected by the GRACE risk score [4].

When the cause-specific hospital readmissions were separately examined, we did not observe an association between patient's current symptoms of anxiety and cardiovascular-related 30-day hospital readmissions despite our hypothesis that patients with anxiety might be more likely to seek care for milder cardiac symptoms compared with patients who were not anxious. None of the hospital readmissions in the present study population were apparently attributed to an anxiety-related condition, even when we examined diagnoses beyond the primary discharge codes. This finding may be, in part, explained by the fact that anxiety disorders or symptoms of anxiety are usually managed in the outpatient setting. It is, however, possible that anxiety-related readmissions were not reported or considered in discharge codes by patient's attending physicians and were markedly underestimated.

Few studies have examined the association between anxiety and hospital readmission following an ACS. Two studies showed a higher risk of hospital readmission in patients with stable coronary artery disease who had symptoms of anxiety or an anxiety disorder [25]. In a study of 2664 patients with acute or stable CAD who underwent a PCI in the Partners PCI Readmission Project between 2007 and 2011, patients with a current diagnosis of anxiety were at a 26% higher odds of being readmitted to the hospital over the following 30 days than patients who were not previously diagnosed with an anxiety disorder [25]. Another study of 226 patients who underwent CABG surgery between 1999 and 2005 at a large medical center in Southern Australia found that patients who were classified as having preoperative anxiety were at a 2-folds higher risk for an unscheduled 6-month hospital readmission compared to patients without this condition [26]. These studies, however, had several limitations compared with the present study which may have limited their generalizability. For example, these investigations did not selectively examine patients with an ACS [25,26], measured anxiety prior to surgery [26], did not adjust for concurrent depression, other important socio-demographic factors of prognostic importance, severity of CAD, or pharmacologic treatment

practices [25,26], and did not concurrently examine self-reported symptoms of anxiety during the patient's acute hospital stay [25].

4.2. Association between symptoms and diagnosis of anxiety with post-discharge mortality

In the present study, we found that patients who had been previously diagnosed with anxiety had a higher risk of dying over the 2-year follow-up period, even after adjusting for several factors of prognostic importance, than patients who did not exhibit either moderate/severe symptoms of anxiety or had none or only mild symptoms of anxiety during their acute hospitalization. These findings are consistent with the results of several prior studies [4]. In a recent meta-analysis of 43 observational studies, patients with either stable or acute CAD, and who had a generalized anxiety disorder, were at greater risk for all-cause or cardiac mortality, undergoing coronary revascularization, being re-hospitalized, or developing a subsequent myocardial infarction compared to patients who did not have this psychiatric disorder [4].

The underlying mechanisms contributing to a greater risk of dying among patients with an established anxiety disorder are unclear but likely multifactorial. Both biological and behavioral mechanisms have been proposed to explain the increased risk of adverse clinical outcomes in these patients. Anxiety may accelerate atherosclerosis and worsen the extent and severity of underlying CAD [28,29]. In a study of 726 healthy men and women, persons with sustained symptoms of anxiety over the course of 2 years had greater carotid intima-media thickness and atherosclerotic plaque formation than persons without symptoms of anxiety [30]. These and other mechanisms may also explain the higher risk of developing heart failure and cardiogenic shock in patients who had a diagnosis of an anxiety disorder compared with other patients in the present study. In addition, patients with cardiac disease and an anxiety disorder have been shown to be less likely to engage in self-care practices including medication adherence, exercise, smoking cessation, and attending cardiac rehabilitation [31,32], which in turn may place them at greater risk for dying.

The American Heart Association (AHA) in a scientific statement issued in 2014 recommended that depression be considered as a risk factor for adverse medical outcomes in patients with an ACS [33]. However, national guidelines have not discussed the importance of, and need for, enhanced surveillance and treatment in patients who have an established anxiety disorder. The findings from our study show that patients with a previously diagnosed anxiety disorder are at greater risk for dying over the subsequent 2 years compared with patients discharged from the hospital after an ACS who did not have this disorder. Inasmuch, health care practitioners may consider comorbid anxiety disorders as important risk factors for future adverse outcomes among patients admitted to the hospital for an ACS.

On the other hand, the risk of dying during our extended period of follow-up was similar between patients who reported current moderate/severe symptoms and in patients who had no or minimal symptoms of anxiety. While an established anxiety disorder may have a persistent adverse impact on the pathophysiology of CAD and unhealthy lifestyle and psychosocial behaviors, and lead to a greater risk of dying over the long-term, the symptoms of anxiety reported during hospitalization for an ACS may reflect an acute psychological and physiologic stress reaction to the coronary event. Thus, the impact of these acute symptoms may be temporary and not translate into a higher risk of dying over a prolonged follow up period.

Our findings were somewhat different from the results of a meta-analysis of 12 observational studies which included 5750 patients who had been discharged from the hospital after an AMI [27]. This meta-analysis found that symptoms of anxiety after the acute ischemic event, as measured by several types of questionnaires, were associated with a 23–47% higher odds of all-cause and cardiac-related mortality over the course of 6 months to 4 years. However, most of the studies included in this meta-analysis did not separately analyze patients who already had, or did not have, an anxiety disorder and failed to differentiate effects of this psychologic disorder from those of the acute symptoms of anxiety. In addition, several studies included in this pooled analysis measured symptoms of anxiety remotely from the cardiac event [35,36]. Inasmuch, they might have reflected the effect of sustained symptoms of anxiety after the acute coronary event rather than reactive acute symptoms as in our study.

It is noteworthy that despite the observation that a higher proportion of patients who had an anxiety disorder received pharmacotherapies for anxiety, adjustment for these treatments (e.g., SSRIs, SNRIs, benzodiazepines) did not change the estimates for mortality that we observed. In a recent meta-analysis of 35 randomized controlled trials with >10,000 patients with stable or acute CAD and either depression or anxiety, treatment with these agents did not reduce all-cause mortality or non-fatal cardiac events despite improving patient's symptoms of depression, anxiety, or stress [36]. Thus, while our findings need to be interpreted cautiously, they may suggest that the conventional pharmacologic treatments for patients with anxiety disorders may not effectively prevent long-term adverse events.

4.3. Study strengths and limitations

Our study has several strengths that are noteworthy. We collected data which allowed us to investigate the separate effects of current symptoms of anxiety during hospitalization for an ACS from those associated with an established anxiety disorder, as well as analytically control for the effects of a number of factors that can affect the outcomes under study. The study population was sociodemographically diverse, thereby enhancing the generalizability of our study findings. Readmission data were verified with hospital medical records, thereby minimizing the possibility of misclassification bias. On the other hand, the present study had several limitations that should be considered in interpreting the present findings. We were not able to examine the persistence of, and/or changes in, symptoms of anxiety over time and could not differentiate patients who only had transient symptoms of anxiety from patients whose symptoms became persistent. We could not examine patients who had a documented diagnosis of an anxiety disorder, with or without symptoms of anxiety separately, as well as patients with different subtypes of anxiety disorders such as panic disorder, PTSD, or social anxiety disorder. We also did not collect data on dose of pharmacological treatments, as well as non-pharmacological treatments for anxiety, including cognitive behavioral therapy, hypnotherapy, and supportive therapy, and could not fully examine the impact of these treatment approaches on long-term mortality in patients with an anxiety disorder. The use of ICD-9 discharge codes may have missed unreported events in this patient population following hospital discharge and the role of unmeasured residual confounding could have affected our observed study outcomes.

5. Conclusions

Patients with a previously diagnosed anxiety disorder in the setting of an ACS are at increased risk for dying during the first 2 years after hospital discharge for an ACS whereas patients who exhibit moderate/severe symptoms of anxiety during their acute hospital admission are not at increased risk for worse short and long-term outcomes compared to patients with no/mild symptoms of anxiety. Future studies are needed to examine the association between persistent symptoms of anxiety and long-term clinical and patient-centered outcomes and the best ways to manage patients with anxiety disorders, including the effectiveness of non-pharmacologic therapies, to improve their long-term clinical and quality of life outcomes.

Disclosures

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