Published in final edited form as:

Psychosom Med. 2017 April ; 79(3): 318–326. doi:10.1097/PSY.0000000000000404.

Associations between psychological constructs and cardiac biomarkers following acute coronary syndrome

Christopher M. Celano, M.D.[1,2], **Eleanor E. Beale, B.A.**[2], **Scott R. Beach, M.D.**[1,2], **Arianna M. Belcher, B.S.**[3], **Laura Suarez, M.D.**[1,2], **Shweta R. Motiwala, M.D.**[1,4], **Parul U. Gandhi, M.D.**[1,3], **Hanna Gaggin, M.D.**[1,3], **James L. Januzzi Jr., M.D.**[1,3], **Brian C. Healy, Ph.D.**[1,5], and **Jeff C. Huffman, M.D.**[1,2]

[1]Harvard Medical School, Boston, MA

[2]Department of Psychiatry, Massachusetts General Hospital, Boston, MA

[3]Department of Medicine, Division of Cardiology, Massachusetts General Hospital, Boston, MA

[4]Department of Medicine, Division of Cardiology, Beth Israel Deaconess Medical Center, Boston, MA

[5]Biostatistics Center, Massachusetts General Hospital, Boston, MA

Abstract

Objective—Psychological constructs are associated with cardiovascular health, but the biological mechanisms mediating these relationships are unknown. We examined relationships between psychological constructs and markers of inflammation, endothelial function, and myocardial strain in a cohort of post-acute coronary syndrome (ACS) patients.

Methods—Participants (N=164) attended study visits 2 weeks and 6 months post-ACS. During these visits, they completed self-report measures of depressive symptoms, anxiety, optimism, and gratitude, and blood samples were collected for measurement of biomarkers reflecting inflammation, endothelial function, and myocardial strain. Generalized estimating equations and linear regression analyses were performed to examine concurrent and prospective relationships between psychological constructs and biomarkers.

Results—In concurrent analyses, depressive symptoms were associated with elevated markers of inflammation (interleukin-17: β=.047, 95% confidence interval [.010, .083]), endothelial dysfunction (endothelin-1: β=.020, [.004, .037]), and myocardial strain (N-terminal pro-B-type natriuretic peptide: β=.045, [.008, .083]), independent of age, sex, medical variables, and anxiety, while anxiety was not associated with these markers in multivariable adjusted models. Optimism and gratitude were associated with lower levels of markers of endothelial dysfunction (endothelin-1: gratitude: β=−.009, [−.017, −.001]; optimism: β=−.009, [−.016, −.001]; soluble

Corresponding Author and Address for Correspondence: Christopher M. Celano, M.D., Massachusetts General Hospital/Blake 11, 55 Fruit Street Boston, MA 02114, Phone: 617-726-6485, Fax: 617-724-9150, ccelano@partners.org.

Conflicts of Interest:

The authors have no other conflicts of interest to disclose regarding this research to disclose.

Clinical Trial Registration: Clinicaltrials.gov identifier NCT01709669

URL: http://www.clinicaltrials.gov/ct2/show/NCT01709669

intercellular adhesion molecule-1: gratitude: β=−.007, [−.014, −.000]), independent of depressive and anxiety symptoms. Psychological constructs at 2 weeks were not prospectively associated with biomarkers at 6 months.

Conclusions—Depressive symptoms were associated with more inflammation, myocardial strain, and endothelial dysfunction in the 6 months post-ACS, while positive psychological constructs were linked to better endothelial function. Larger, prospective studies may clarify the directionality of these relationships.

Keywords

depression; anxiety; optimism; gratitude; inflammation; endothelial function

Introduction

Acute coronary syndromes (ACS; myocardial infarction [MI] or unstable angina [UA]) affect 1.3 million Americans each year (1) and are associated with substantial rates of readmission and death in the following year (2). Inflammation, endothelial dysfunction, and myocardial strain, three physiologic processes underlying CAD, have been linked to poor outcomes post-ACS (3, 4). Inflammatory markers, such as high sensitivity C-reactive protein (hsCRP), various interleukins, and tumor necrosis factor-alpha (TNF-α), have been implicated in the development and progression of CAD (5, 6). Similarly, markers of endothelial dysfunction (e.g., soluble intercellular adhesion molecule-1 [sICAM-1]) and myocardial strain (e.g., N-terminal pro-B-type natriuretic peptide [NT-proBNP], cardiac troponin-I [cTnI]) have been linked to poor health outcomes and reduced survival in patients with ACS (7–11). Better understanding what factors are associated with these markers of heart health may help clinicians to identify those patients at highest risk for complications in the post-ACS period.

Psychological factors—both positive and negative—have also been associated with cardiac prognosis (12–14), but the mechanisms mediating these relationships are unclear. Prior studies have found that depression is associated with abnormal levels of inflammatory cytokines and other established markers of poor cardiac prognosis (15–18), and anxiety has been linked to elevated levels of inflammatory markers in some studies (19, 20) but not others (21–23). On the other hand, smaller numbers of studies have found that positive constructs, such as optimism, may be associated with improved levels of cardiac biomarkers (14, 24), and gratitude has been associated with increased parasympathetic activity (25).

However, there are numerous gaps in the literature related to psychological factors and cardiac biomarkers. First, relatively few studies have examined patients with existing heart disease (14, 15, 26–28), especially in the high-risk post-ACS period. Second, there has been minimal study of the association of anxiety with prognostic biomarkers, despite links between anxiety and post-ACS mortality (19, 21, 29). Third, despite being a commonly experienced psychological state following ACS, the effects of gratitude (“a disposition toward appreciating and being thankful for people, events, and experiences in one’s life”) (30) on biomarkers have, to our knowledge, never been studied post-ACS. Finally, very few studies (and no studies in ACS patients) have concurrently examined the effects of multiple

positive and negative constructs on key biomarkers to assess which psychological factors most strongly correlate with prognosis.

Knowledge of the relationships of depression, anxiety, optimism, and gratitude with biomarkers of cardiac health in the post-ACS period is important for several reasons. Such knowledge would allow us to confirm that these relationships are consistent across clinical populations, as prior studies have focused primarily on patients without acute manifestations of CAD. By examining these four psychological constructs that frequently are experienced in the post-ACS period, it also would allow us to determine which relationships occur independent of the others (e.g., it would allow us to confirm that the relationships between anxiety and biomarkers are not simply due to associations between depression and biomarkers). Finally, confirmation of prospective associations between psychological states and cardiac biomarkers in the post-ACS period would provide support for the notion that developing treatments to reduce depression and anxiety or promote optimism and gratitude may lead to beneficial cardiovascular outcomes.

Accordingly, in a series of ACS patients we examined: (1) concurrent relationships between psychological constructs (depressive symptoms, anxiety symptoms, gratitude, and optimism) and markers of inflammation, endothelial function, and myocardial strain/cardiac prognosis over the course of 6 months, and (2) prospective relationships between psychological states 2 weeks post-ACS and relevant cardiac biomarkers at 6 months. We hypothesized that positive psychological constructs would be associated with less inflammation, improved endothelial function, and reduced cardiac strain, while negative constructs would be associated with the reverse.

Methods

This is an analysis from the Gratitude Research in Acute Coronary Events (GRACE) study (ClinicalTrials.gov identifier NCT01709669), a prospective, observational study to determine the associations between psychological states and health behaviors, biomarkers, and cardiac outcomes in post-ACS patients. The study enrolled participants between September 2012 and January 2014, and full study methods and results have been published elsewhere (30, 31). In our main analyses, optimism, measured 2 weeks following ACS, was prospectively associated with increased physical activity and lower rates of rehospitalization —but not cardiac biomarkers—at 6 months. In contrast, baseline gratitude was not associated with physical activity, biomarkers, or cardiac outcomes over the same time period (30). Prior to the initiation of study procedures, approval was obtained from the Partners Healthcare Institutional Review Board.

Participants

Participants were recruited from one of three inpatient cardiac units at an urban academic medical center. Patients were eligible for enrollment if they were admitted for an ACS (MI or UA), diagnosed using standardized criteria (32, 33). Patients were excluded if they: (1) suffered a periprocedural ACS, (2) had a non-cardiac condition that might alter cardiac biomarkers (e.g., inflammatory diseases) or would lead to death during the subsequent 6

months, (3) were unable to perform physical activity, or (4) were unable to complete self-report questionnaires due to cognitive impairment or language barriers.

Procedures

After eligibility was confirmed, participants provided informed consent and enrolled in the study. During their hospitalization, sociodemographic and medical information was obtained from the medical record. This included body mass index, comorbid cardiac-related diagnoses (hypertension, hyperlipidemia, diabetes mellitus), history of acute coronary syndrome, and current smoking status. Information from the medical record was used to calculate an age-adjusted Charlson Comorbidity Index score. After discharge, participants returned to MGH at 2 weeks and 6 months for study visits, at which time self-report measures were administered to assess psychological, behavioral, and functional status.

Blood Collection

During study visits, blood samples were collected into tubes containing ethylenediaminotetraacetic acid or no anticoagulant for biomarker analysis. The tubes were centrifuged for 15–30 minutes, after which plasma or serum was decanted and aliquoted into 500 μl tubes; processing was performed on ice. Next, samples were immediately frozen at −80 degrees centigrade and not thawed until biomarker measurements were performed.

Study Outcomes and Measures

Negative Psychological Constructs—Depressive symptoms were measured using the Patient Health Questionnaire-9 (PHQ-9), a nine item scale that queries participants about the frequency with which they experience the nine DSM-IV criteria for depression. Scores range from 0 to 27, with higher scores indicating more frequent depressive symptoms. For anxiety, the Hospital Anxiety and Depression Scale, anxiety subscale (HADS-A) (34) was used. Responses are scored from 0–3, with the total score ranging from 0–27. Both scales have been used in numerous studies of cardiac patients (32, 35, 36), are well-validated (37, 38), and had high internal consistency in our sample (PHQ-9: α=0.82, HADS-A: α=0.85).

Positive Psychological Constructs—We measured gratitude via the Gratitude Questionnaire-6 (GQ-6) (39) and optimism via the Life Orientation Test-Revised (LOT-R) (40). Both the GQ-6 and the LOT-R are well-validated, 6-item scales that have been used in studies involving patients with cardiovascular disease (41–43) and had high internal consistency in our participants (GQ-6: α=0.84, LOT-R: α=0.85). Consistent with the literature, a total optimism score was calculated for the LOT-R, with a higher score representing greater optimism and lower pessimism (40).

Cardiac biomarkers—We measured markers of inflammation, endothelial function, and myocardial strain/injury. Inflammation was assessed using measurement of high sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), interleukin-17 (IL-17), and tumor necrosis factor-alpha (TNF-α); each biomarker has been implicated in the development or progression of CAD (5, 6). Endothelial function was measured through endothelin-1 (ET-1) and soluble intercellular adhesion molecule-1 (sICAM-1). ET-1 is known to be elevated in patients with CAD, especially in the post-MI period (44), and higher levels of sICAM-1

have been associated with cardiac events and mortality in patients with heart disease (7, 8). Finally, cardiac strain was measured through N-terminal pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponin-I (cTnI), which have been linked to subsequent survival in patients with ACS (9–11).

Samples were analyzed in batch by immunoassay kits, as per published methods (and per the team's prior experience analyzing these biomarkers) via the MGH Research Core Laboratory (hsCRP, sICAM-1) and the Singulex Corporation (IL-6, IL-17, TNF-α, ET-1, cTnI, NT-proBNP). Levels of detection for each assay were as follows: 0.5mg/dL for hsCRP, 0.096ng/mL for sICAM-1, 0.004pg/mL for IL-6, 0.01pg/mL for IL-17, 0.016pg/mL for TNF-α, 0.1pg/mL for ET-1, 0.05pg/mL for cTnI, and 5pg/mL for NT-proBNP.

Statistical Analyses

Relationships between psychological variables and biomarkers were examined in a concurrent manner (examining relationships at the same timepoint and with respect to concurrent change between timepoints within the same model) and in a prospective manner (examining whether psychological variables at baseline predicted biomarker levels at 6 months).

To assess the concurrent relationships between psychological constructs and cardiac biomarkers at baseline and 6 months, a series of generalized estimating equation models with an exchangeable working correlation structure and robust standard errors were used. Three separate models were created, each one adjusted for progressively more covariates. In the first step (Model 1), age and sex were added as covariates. Next (Model 2), medical variables (peak troponin T level [representing severity of current ACS], age-adjusted Charlson Comorbidity Index score (45) [measure of overall medical comorbidity], body mass index, hypertension, hyperlipidemia, current smoking status, admission diagnosis, length of stay, and history of prior ACS) were added to those already adjusted for in Model 1. In the final model (Model 3), measures of depressive (PHQ-9) and anxiety (HADS-A) symptoms were included, in addition to those covariates from Models 1 and 2. Within each model the cross-sectional and longitudinal effects were assumed to be equal.

To assess the prospective relationships between baseline psychological constructs and 6-month biomarker levels, linear regression models were created, adjusting for baseline biomarker levels and with hierarchical adjustment over three successive models as above. Because biomarker concentrations were not normally distributed, all biomarker levels were natural log-transformed, and robust standard errors were used to account for any residual non-normality. All results are presented as regression coefficients with natural log-transformed biomarkers as the outcome; exponentiating the regression coefficient provides an estimate of the impact of the predictor on the geometric mean (46). All tests of significance were two-tailed, with significance set at $p<.05$, given the exploratory nature of the analyses. However, since four different psychological constructs were examined in our analyses, findings with $p\geq.0125$ (threshold for significance after Bonferroni correction (47)) should be interpreted with caution. Analyses were performed using Stata statistical software (version 11.2, StataCorp, College Station, TX).

Results

Of 212 post-ACS patients who enrolled in the study, 164 completed the 2-week visit, and 156 completed the follow-up visit at 6 months. All participants who provided baseline data (N=164) were included in our analyses. Fifty-four percent of participants were admitted for an MI, and 46% with UA; 42% had experienced an ACS in the past. See Table 1 for participants' sociodemographic and medical baseline characteristics.

Negative psychological constructs

On concurrent analysis, more depressive symptoms were significantly associated with higher levels of several markers of inflammation (see Table 2). Adjusting for age and sex, depressive symptoms were significantly positively correlated with levels of TNF-α (β = .016, p < .001), IL-17 (β = .030, p = .006), and IL-6 (β = .019, p = .024), but not with hsCRP (p = .18). On adjustment for medical covariates, correlations between depressive symptoms and IL-17 and TNF-α remained significant (TNF-α: β = .012, p = .002; IL-17: β = .029, p = .007), while the correlation between depressive symptoms and IL-6 did not. Finally, when adjusting for anxiety symptoms, depressive symptoms remained significantly positively correlated with IL-17 (β = .047, p = .012), but the relationship between depressive symptoms and TNF-α became marginally significant (β = .010, p = .081).

Depressive symptoms also were correlated with higher levels of ET-1, even when adjusting for medical variables and anxiety (β = .020, p = .013); however, they were not significantly correlated with sICAM-1. Finally, more depressive symptoms were associated with higher concentrations of the prognostic marker NT-proBNP in all models (model adjusting for age, sex, medical variables, and anxiety symptoms: β = .045, p = .017). More severe depressive symptoms also were associated with greater concentrations of cTnI when adjusting for age and sex (β = .036, p = .006); however, this relationship became marginally significant when adjusting for medical variables and anxiety symptoms (β = .029, p = .075).

In contrast, there were few relationships between anxiety symptoms and biological measures. When adjusting for age and sex, more anxiety symptoms were associated with higher concentrations of TNF-α (β = .012, p = .018). This relationship persisted when adjusting for medical covariates (β = .011, p = .027) but became nonsignificant when adjusting for depressive symptoms (β = .005, p = .51).

When examining the prospective relationships between depressive/anxiety symptoms at 2 weeks and biomarkers at 6 months, no significant associations were found on fully adjusted analyses, though greater depressive symptoms at baseline did predict higher levels of sICAM-1 when sex for age and sex only (β = .015, p = .010; see Table S1, Supplemental Digital Content 1).

Positive psychological constructs

On concurrent analysis (see Table 2), optimism was significantly associated with lower concentrations of TNF-α when adjusting for age and sex (β = −.007, p = .026) and when additionally adjusting for medical covariates (β = −.008, p = .009), but this relationship became non-significant when adding depressive and anxiety symptoms to the analyses (p = .

20). When adjusting for age, sex, and medical covariates, gratitude was associated with lower levels of TNF-α ($\beta = -.007$, $p = .026$); however, this relationship became non-significant when adjusting for depressive and anxiety symptoms ($p = .36$). Neither optimism nor gratitude were associated with concentrations of hsCRP, IL-6, or IL-17.

In contrast, both optimism and gratitude were associated with lower concentrations of ET-1, even when adjusting for age, sex, medical covariates, depressive symptoms, and anxiety symptoms (optimism: $\beta = -.009$, $p = .028$; gratitude: $\beta = -.009$, $p = .033$). Furthermore, gratitude was associated with lower concentrations of sICAM-1 (model adjusting for age, sex, medical factors, depressive symptoms, and anxiety symptoms: $\beta = -.007$, $p = .037$). These positive psychological constructs were not significantly associated with NT-proBNP or cTnI.

Finally, on prospective analysis (Table S1), optimism at 2 weeks was associated with lower levels of TNF-α at 6 months, when adjusting for age and sex ($\beta = -.006$, $p = .042$). However, this association became marginally significant when adjusting for age, sex, and medical covariates ($\beta = -.005$, $p = .091$) and non-significant when adjusting for depressive and anxiety symptoms ($p = .26$). There were no other significant relationships between optimism/gratitude at 2 weeks and cardiac biomarkers at 6 months.

Discussion

Overall, we found that both positive and negative psychological states were associated with alterations in cardiac biomarkers in the post-ACS period. Specifically, depressive symptoms were linked to markers of inflammation (IL-17), endothelial functioning (ET-1), and myocardial stress/cardiac prognosis (NT-proBNP, cTnI), independent of sociodemographic variables, medical variables, and anxiety. Anxiety also had mild associations with inflammatory markers and prognosis, but these relationships became non-significant when accounting for depressive symptoms. Finally, both gratitude and optimism were associated with improved endothelial function, but not with inflammatory markers or myocardial stress, on maximally adjusted analyses.

The finding that depressive symptoms were linked to inflammation is consistent with the literature, which has frequently found associations between depression and inflammatory markers, including IL-6, TNF-α, and hsCRP, in patients with or without a history of cardiovascular disease (15, 16, 27, 28). Our study suggested possible links between depressive symptoms and TNF-α in patients with CAD and also found a relationship between depressive symptoms and IL-17, a less-studied inflammatory marker (48–50). Depressive symptoms also were significantly associated with elevated levels of ET-1, cTnI, and NT-proBNP. These findings are consistent with prior studies that link depression with impaired endothelial function (26, 51–54) and poor cardiac prognosis (12, 13). Our findings suggest that depression's relationship to poor cardiac health may in part be explained by its relationships to inflammation and endothelial dysfunction.

Unlike depression, anxiety symptoms were not associated with cardiac biomarkers when adjusting for depressive symptoms. To date, the literature examining the relationships

between anxiety and inflammation has been mixed (19–23), and the relationship between anxiety and cardiac prognosis (29, 55) appears weaker than that of depression (12, 55, 56). Our findings suggest that anxiety's relationship to cardiovascular health may be explained in part by depressive symptoms, which have been more clearly associated with both inflammatory markers and cardiac prognosis in patients with heart disease (12, 56).

In contrast to negative constructs, optimism and gratitude were associated with improved endothelial function, and less so with severity of inflammation. There has been limited study of relationships between positive psychological constructs and endothelial function (24); our results are novel, therefore, and suggest that improvements in endothelial function may be one mechanism by which these constructs are associated with improved cardiac health. More generally, this study supports the notion that while positive and negative psychological constructs are associated with cardiac outcomes, there may be distinct physiologic pathways or mechanisms by which they are linked to cardiac health.

Finally, while our analyses found significant concurrent relationships between psychological states and biomarkers, no prospective relationships were found, suggesting that the relationships between psychological states and heart health may co-vary over time. Further studies are needed to clarify the directionality of these relationships (i.e., whether cardiac health leads to changes in psychological constructs or psychological constructs lead to changes in cardiac health).

This study had several limitations. It was conducted in an urban academic hospital, and participants were predominantly White and male, which limits the generalizability of the findings. Furthermore, our sample size limited our statistical power to detect relationships between psychological states and biomarkers. In addition, moderate to strong correlations between psychological constructs (see Table S2, Supplemental Digital Content 1) may have contributed to the attenuated relationships between constructs and biomarkers in the fully adjusted (Model 3) analyses. Finally, given the concurrent nature of our analyses, we cannot make interpretations regarding causality. More prospective studies will be needed to explore these relationships further.

Despite these limitations, our study is novel, and extends the literature in several ways. First, this study solidifies the knowledge base that depression is significantly associated with elevated inflammatory markers and endothelial dysfunction in the immediate post-ACS period and suggests that the relationship between anxiety and inflammatory markers may be driven largely by the effects of comorbid depression. Furthermore, we show novel results demonstrating that positive psychological states are strongly correlated to better endothelial function, with minimal associations with inflammation. Finally, by examining both concurrent and prospective relationships in this cohort, this study supports the notion that inflammation and endothelial function may change in parallel to psychological states and calls for further research into determining the directionality of these relationships.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Source of Funding:

This research project was supported by the Expanding the Science and Practice of Gratitude Project run by UC Berkeley's Greater Good Science Center in partnership with UC Davis with funding from the John Templeton Foundation (grant 15627) to Dr. Huffman. Time for analysis and article preparation was also funded by the National Heart Lung and Blood Institute through grants K23HL123607 (to Dr. Celano) and R01HL113272 (to Dr. Huffman). Dr. Januzzi is supported in part by the Hutter Family Professorship in the Field of Cardiology. Dr. Januzzi has received grant support from Siemens, Singulex and Prevencio, consulting income from Roche Diagnostics, Critical Diagnostics, Sphingotec, Philips, and Novartis, and participates in clinical endpoint committees for Novartis, Amgen, Janssen, and Boehringer Ingelheim. The Harvard Catalyst Program and Singulex provided support for the analysis of selected biomarkers. The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health or other funders.

Acronyms used

ACS	acute coronary syndrome
CAD	coronary artery disease
cTnI	cardiac troponin I
ET-1	endothelin-1
GQ-6	Gratitude Questionnaire-6
GRACE	Gratitude Research in Acute Coronary Events
HADS-A	Hospital Anxiety and Depression Scale, anxiety subscale
hsCRP	high-sensitivity C-reactive protein
IL-6	interleukin-6
IL-17	interleukin-17
LOT-R	Life Orientation Test – Revised
MGH	Massachusetts General Hospital
MI	myocardial infarction
NT-proBNP	N-terminal pro-brain natriuretic peptide
PHQ-9	Patient Health Questionnaire-9
sICAM-1	soluble intercellular adhesion molecule-1
TNF-α	tumor necrosis factor-α
UA	unstable angina

References

1. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho PM, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM,

Marcus GM, Marelli A, Matchar DB, McDermott MM, Meigs JB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Rosamond WD, Sorlie PD, Stafford RS, Turan TN, Turner MB, Wong ND, Wylie-Rosett J. Heart disease and stroke statistics–2011 update: a report from the American Heart Association. Circulation. 2011; 123:e18–e209. [PubMed: 21160056]

2. Kolansky DM. Acute coronary syndromes: morbidity, mortality, and pharmacoeconomic burden. Am J Manag Care. 2009; 15:S36–41. [PubMed: 19355807]
3. Huffman JC, Celano CM, Beach SR, Motiwala SR, Januzzi JL. Depression and cardiac disease: epidemiology, mechanisms, and diagnosis. Cardiovasc Psychiatry Neurol. 2013; 2013:695925. [PubMed: 23653854]
4. Heeschen C, Hamm CW, Bruemmer J, Simoons ML. Predictive value of C-reactive protein and troponin T in patients with unstable angina: a comparative analysis. CAPTURE Investigators. Chimeric c7E3 AntiPlatelet Therapy in Unstable angina REfractory to standard treatment trial. J Am Coll Cardiol. 2000; 35:1535–42. [PubMed: 10807457]
5. Christodoulidis G, Vittorio TJ, Fudim M, Lerakis S, Kosmas CE. Inflammation in coronary artery disease. Cardiol Rev. 2014; 22:279–88. [PubMed: 24441047]
6. Su SA, Ma H, Shen L, Xiang MX, Wang JA. Interleukin-17 and acute coronary syndrome. J Zhejiang Univ Sci B. 2013; 14:664–9. [PubMed: 23897784]
7. Blankenberg S, Rupprecht HJ, Bickel C, Peetz D, Hafner G, Tiret L, Meyer J. Circulating cell adhesion molecules and death in patients with coronary artery disease. Circulation. 2001; 104:1336–42. [PubMed: 11560847]
8. Haim M, Tanne D, Boyko V, Reshef T, Goldbourt U, Leor J, Mekori YA, Behar S. Soluble intercellular adhesion molecule-1 and long-term risk of acute coronary events in patients with chronic coronary heart disease. Data from the Bezafibrate Infarction Prevention (BIP) Study. J Am Coll Cardiol. 2002; 39:1133–8. [PubMed: 11923036]
9. Timoteo AT, Toste A, Ramos R, Miranda F, Ferreira ML, Oliveira JA, Ferreira RC. Does admission NT-proBNP increase the prognostic accuracy of GRACE risk score in the prediction of short-term mortality after acute coronary syndromes? Acute Card Care. 2009; 11:236–42. [PubMed: 19742352]
10. Jarai R, Iordanova N, Jarai F, Raffetseder A, Woloszczuk W, Gyongyosi M, Geyer G, Wojta J, Huber K. Prediction of clinical outcome in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) using the TIMI risk score extended by N-terminal pro-brain natriuretic peptide levels. Wien Klin Wochenschr. 2007; 119:626–32. [PubMed: 18043882]
11. Ottani F, Galvani M, Nicolini FA, Ferrini D, Pozzati A, Di Pasquale G, Jaffe AS. Elevated cardiac troponin levels predict the risk of adverse outcome in patients with acute coronary syndromes. Am Heart J. 2000; 140:917–27. [PubMed: 11099996]
12. Meijer A, Conradi HJ, Bos EH, Thombs BD, van Melle JP, de Jonge P. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis of 25 years of research. Gen Hosp Psychiatry. 2011; 33:203–16. [PubMed: 21601716]
13. Meijer A, Conradi HJ, Bos EH, Anselmino M, Carney RM, Denollet J, Doyle F, Freedland KE, Grace SL, Hosseini SH, Lane DA, Pilote L, Parakh K, Rafanelli C, Sato H, Steeds RP, Welin C, de Jonge P. Adjusted prognostic association of depression following myocardial infarction with mortality and cardiovascular events: individual patient data meta-analysis. Br J Psychiatry. 2013; 203:90–102. [PubMed: 23908341]
14. Dubois CM, Beach SR, Kashdan TB, Nyer MB, Park ER, Celano CM, Huffman JC. Positive psychological attributes and cardiac outcomes: associations, mechanisms, and interventions. Psychosomatics. 2012; 53:303–18. [PubMed: 22748749]
15. Valkanova V, Ebmeier KP, Allan CL. CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. J Affect Disord. 2013; 150:736–44. [PubMed: 23870425]
16. Young JJ, Bruno D, Pomara N. A review of the relationship between proinflammatory cytokines and major depressive disorder. J Affect Disord. 2014; 169:15–20. [PubMed: 25128861]
17. Celano CM, Huffman JC. Depression and cardiac disease: a review. Cardiol Rev. 2011; 19:130–42. [PubMed: 21464641]

18. Bankier B, Barajas J, Martinez-Rumayor A, Januzzi JL. Association between major depressive disorder and C-reactive protein levels in stable coronary heart disease patients. J Psychosom Res. 2009; 66:189–94. [PubMed: 19232230]

19. Bankier B, Barajas J, Martinez-Rumayor A, Januzzi JL. Association between C-reactive protein and generalized anxiety disorder in stable coronary heart disease patients. Eur Heart J. 2008; 29:2212–7. [PubMed: 18603621]

20. Pitsavos C, Panagiotakos DB, Papageorgiou C, Tsetsekou E, Soldatos C, Stefanadis C. Anxiety in relation to inflammation and coagulation markers, among healthy adults: the ATTICA study. Atherosclerosis. 2006; 185:320–6. [PubMed: 16005881]

21. Glaus J, Vandeleur CL, von Kanel R, Lasserre AM, Strippoli MP, Gholam-Rezaee M, Castelao E, Marques-Vidal P, Bovet P, Merikangas K, Mooser V, Waeber G, Vollenweider P, Aubry JM, Preisig M. Associations between mood, anxiety or substance use disorders and inflammatory markers after adjustment for multiple covariates in a population-based study. J Psychiatr Res. 2014; 58:36–45. [PubMed: 25088287]

22. Kheirabadi GR, Toghani F, Kousha M, Hashemi M, Maracy MR, Sharifi MR, Bagherian-Sararoudi R. Is there any association of anxiety-depressive symptoms with vascular endothelial function or systemic inflammation? J Res Med Sci. 2013; 18:979–83. [PubMed: 24523785]

23. Mommersteeg PM, Meeuwis SH, Denollet J, Widdershoven JW, Aarnoudse W, Westerhuis BL, Kop WJ. C-reactive protein and fibrinogen in non-obstructive coronary artery disease as related to depressive symptoms and anxiety: findings from the TweeSteden Mild Stenosis Study (TWIST). J Psychosom Res. 2014; 77:426–9. [PubMed: 25307791]

24. Ikeda A, Schwartz J, Peters JL, Fang S, Spiro A 3rd, Sparrow D, Vokonas P, Kubzansky LD. Optimism in relation to inflammation and endothelial dysfunction in older men: the VA Normative Aging Study. Psychosom Med. 2011; 73:664–71. [PubMed: 21949417]

25. McCraty R, Atkinson M, Tiller WA, Rein G, Watkins AD. The effects of emotions on short-term power spectrum analysis of heart rate variability. Am J Cardiol. 1995; 76:1089–93. [PubMed: 7484873]

26. Dimopoulos N, Piperi C, Salonicioti A, Mitsonis C, Liappas I, Lea RW, Kalofoutis A. Elevation of plasma concentration of adhesion molecules in late-life depression. Int J Geriatr Psychiatry. 2006; 21:965–71. [PubMed: 16927406]

27. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med. 2009; 71:171–86. [PubMed: 19188531]

28. Kop WJ, Kuhl EA, Barasch E, Jenny NS, Gottlieb SS, Gottdiener JS. Association between depressive symptoms and fibrosis markers: the Cardiovascular Health Study. Brain Behav Immun. 2010; 24:229–35. [PubMed: 19800964]

29. Roest AM, Martens EJ, Denollet J, de Jonge P. Prognostic association of anxiety post myocardial infarction with mortality and new cardiac events: a meta-analysis. Psychosom Med. 2010; 72:563–9. [PubMed: 20410247]

30. Huffman JC, Beale EE, Celano CM, Beach SR, Belcher AM, Moore SV, Suarez L, Motiwala SR, Gandhi PU, Gaggin H, Januzzi JL. Effects of optimism and gratitude on physical activity, biomarkers, and readmissions after an acute coronary syndrome: The Gratitude Research in Acute Coronary Events Study. Circ Cardiovasc Qual Outcomes. 2016; 9:55–63. [PubMed: 26646818]

31. Huffman JC, Beale EE, Beach SR, Celano CM, Belcher AM, Moore SV, Suarez L, Gandhi PU, Motiwala SR, Gaggin H, Januzzi JL. Design and baseline data from the Gratitude Research in Acute Coronary Events (GRACE) study. Contemp Clin Trials. 2015; 44:11–9. [PubMed: 26166171]

32. Huffman JC, Beach SR, Suarez L, Mastromauro CA, Dubois CM, Celano CM, Rollman BL, Januzzi JL. Design and baseline data from the Management of Sadness and Anxiety in Cardiology (MOSAIC) randomized controlled trial. Contemp Clin Trials. 2013; 36:488–501. [PubMed: 24090821]

33. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Apple FS, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow JJ, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann

SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Torbicki A, Vahanian A, Windecker S, Morais J, Aguiar C, Almahmeed W, Arnar DO, Barili F, Bloch KD, Bolger AF, Botker HE, Bozkurt B, Bugiardini R, Cannon C, de Lemos J, Eberli FR, Escobar E, Hlatky M, James S, Kern KB, Moliterno DJ, Mueller C, Neskovic AN, Pieske BM, Schulman SP, Storey RF, Taubert KA, Vranckx P, Wagner DR. Third universal definition of myocardial infarction. J Am Coll Cardiol. 2012; 60:1581–98. [PubMed: 22958960]

34. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002; 52:69–77. [PubMed: 11832252]
35. Frasure-Smith N, Lesperance F. Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. Arch Gen Psychiatry. 2008; 65:62–71. [PubMed: 18180430]
36. Thombs BD, Ziegelstein RC, Whooley MA. Optimizing detection of major depression among patients with coronary artery disease using the patient health questionnaire: data from the Heart and Soul Study. J Gen Intern Med. 2008; 23:2014–7. [PubMed: 18815842]
37. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002; 52:69–77. [PubMed: 11832252]
38. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001; 16:606–13. [PubMed: 11556941]
39. McCullough ME, Emmons RA, Tsang JA. The grateful disposition: a conceptual and empirical topography. J Pers Soc Psychol. 2002; 82:112–27. [PubMed: 11811629]
40. Scheier MF, Carver CS, Bridges MW. Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. J Pers Soc Psychol. 1994; 67:1063–78. [PubMed: 7815302]
41. Scheier MF, Matthews KA, Owens JF, Schulz R, Bridges MW, Magovern GJ, Carver CS. Optimism and rehospitalization after coronary artery bypass graft surgery. Arch Intern Med. 1999; 159:829–35. [PubMed: 10219928]
42. Tindle H, Chang Y, Kuller L, Manson J, Robinson J, Rosal M, Siegle G, Matthews K. Optimism, cynical hostility, and incident coronary heart disease and mortality in the Women's Health Initiative. Circulation. 2009; 120:656–62. [PubMed: 19667234]
43. Mills PJ, Redwine L, Wilson K, Pung MA, Chinh K, Greenberg BH, Lunde O, Maisel A, Raisinghani A, Wood A, Chopra D. The role of gratitude in spiritual well-being in asymptomatic heart failure patients. Spiritual Clin Pract (Wash D C). 2015; 2:5–17. [PubMed: 26203459]
44. Mayyas F, Al-Jarrah M, Ibrahim K, Mfady D, Van Wagoner DR. The significance of circulating endothelin-1 as a predictor of coronary artery disease status and clinical outcomes following coronary artery catheterization. Cardiovasc Pathol. 2015; 24:19–25. [PubMed: 25213716]
45. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40:373–83. [PubMed: 3558716]
46. Bland JM, Altman DG. The use of transformation when comparing two means. BMJ. 1996; 312:1153. [PubMed: 8620137]
47. Dunn OJ. Multiple comparisons among means. J Am Stat Assoc. 1961; 56:52–64.
48. Liu Y, Ho RC, Mak A. The role of interleukin (IL)-17 in anxiety and depression of patients with rheumatoid arthritis. Int J Rheum Dis. 2012; 15:183–7. [PubMed: 22462422]
49. Kim JW, Kim YK, Hwang JA, Yoon HK, Ko YH, Han C, Lee HJ, Ham BJ, Lee HS. Plasma Levels of IL-23 and IL-17 before and after Antidepressant Treatment in Patients with Major Depressive Disorder. Psychiatry Investig. 2013; 10:294–9.
50. Xiong GL, Prybol K, Boyle SH, Hall R, Streilein RD, Steffens DC, Krishnan R, Rogers JG, O'Connor CM, Jiang W. Inflammation markers and major depressive disorder in patients with

chronic heart failure: results from the Sertraline Against Depression and Heart Disease in Chronic Heart Failure Study. Psychosom Med. 2015; 77:808–15. [PubMed: 26186432]

51. Burg MM, Martens EJ, Collins D, Soufer R. Depression predicts elevated endothelin-1 in patients with coronary artery disease. Psychosom Med. 2011; 73:2–6. [PubMed: 20947777]
52. Yammine L, Frazier L, Padhye NS, Burg MM, Meininger JC. Severe depressive symptoms are associated with elevated endothelin-1 in younger patients with acute coronary syndrome. J Psychosom Res. 2014; 77:430–4. [PubMed: 25129849]
53. Pizzi C, Manzoli L, Mancini S, Costa GM. Analysis of potential predictors of depression among coronary heart disease risk factors including heart rate variability, markers of inflammation, and endothelial function. Eur Heart J. 2008; 29:1110–7. [PubMed: 18400765]
54. Sherwood A, Hinderliter AL, Watkins LL, Waugh RA, Blumenthal JA. Impaired endothelial function in coronary heart disease patients with depressive symptomatology. J Am Coll Cardiol. 2005; 46:656–9. [PubMed: 16098431]
55. Celano CM, Millstein RA, Bedoya CA, Healy BC, Roest AM, Huffman JC. Association between anxiety and mortality in patients with coronary artery disease: a meta-analysis. Am Heart J. 2015; 170:1105–15. [PubMed: 26678632]
56. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. Psychosom Med. 2004; 66:802–13. [PubMed: 15564343]

Table 1

Characteristics of participants who completed the 2-week visit (N=164)

Characteristics	N (%)*
Demographics and psychosocial characteristics	
Age (mean [SD]), years	61.5 (10.6)
Male sex	137 (84)
White	137 (84)
Married	113 (69)
Living alone	38 (23)
Medical characteristics	
Body mass index (mean [SD]), kg/m^2	28.9 (5.2)
Hypertension	103 (63)
Diabetes mellitus	34 (21)
Hyperlipidemia	132 (81)
Current smoking	21 (13)
Prior acute coronary syndrome	69 (42)
Admission diagnosis of myocardial infarction	88 (54)
Length of stay (days; mean [SD])	3 (2.0)
Troponin T during index hospitalization (ng/mL)	1.5 (3.5)
Charlson Comorbidity Index (age adjusted)	3.3 (1.6)
Medications prescribed at discharge	
Aspirin	159 (97)
Beta blocker	144 (88)
Angiotensin converting enzyme inhibitor	90 (55)
Antiplatelet agent	127 (77)
Statin	153 (93)
Antidepressant	27 (16)
Anxiolytic	16 (10)
Self-report measures at baseline 2-week visit	
Patient Health Questionnaire-9 (depressive symptoms; *range: 0–27)* (mean [SD])	4.3 (4.4)
Clinically Significant Depressive Symptoms (*PHQ-9 ≥ 10*)	17 (10)
Hospital Anxiety and Depression Scale-Anxiety subscale (anxiety symptoms; *range: 0–21)* (mean [SD])	4.3 (4.0)
Clinically Significant Anxiety Symptoms (*HADS-A ≥ 8*)	32 (20)
Life Orientation Test-Revised (optimism; *range: 0–24)* (mean [SD])	17.7 (5.6)
Gratitude Questionnaire-6 (gratitude; *range: 6 – 42)* (mean [SD])	36.5 (5.8)
Biological measures at baseline 2-week visit (mean [SD])	
High sensitivity C-reactive protein (μg/mL)	5.1 (9.3)
Tumor necrosis factor-α (pg/mL)	4.0 (1.5)
Interleukin-17 (pg/mL)	0.3 (0.7)

Characteristics	N (%)*
Interleukin-6 (pg/mL)	3.7 (4.1)
Soluble intercellular adhesion molecule-1 (μg/mL)	0.5 (0.2)
Endothelin-1 (pg/mL)	4.5 (3.1)
Cardiac troponin-I (ng/mL)	5.8 (15.7)
N-terminal pro-B-type natriuretic peptide (pg/mL)	536.6 (1022.5)
Self-report measures at 6-month visit **	
Patient Health Questionnaire-9 (depression; *range: 0–27)* (mean [SD])	3.3 (4.0)
Clinically Significant Depressive Symptoms (*PHQ-9 ≥ 10*)	7 (4)
Hospital Anxiety and Depression Scale-Anxiety subscale (anxiety symptoms; *range: 0–21)* (mean [SD])	3.8 (3.8)
Clinically Significant Anxiety Symptoms (*HADS-A ≥ 8*)	22 (14)
Life Orientation Test-Revised (optimism; *range: 0–24)* (mean [SD])	18.0 (5.8)
Gratitude Questionnaire-6 (gratitude; *range: 6 – 42)* (mean [SD])	37.2 (5.1)
Cardiac biomarkers at 6-month visit (mean [SD])	
High sensitivity C-reactive protein (μg/mL)	4.0 (6.9)
Tumor necrosis factor-α (pg/mL)	3.9 (1.6)
Interleukin-17 (pg/mL)	0.3 (0.5)
Interleukin-6 (pg/mL)	3.1 (2.5)
Soluble intercellular adhesion molecule-1 (μg/mL)	0.5 (0.1)
Endothelin-1 (pg/mL)	4.4 (3.3)
Cardiac troponin-I (ng/mL)	2.3 (4.2)
N-terminal pro-B-type natriuretic peptide (pg/mL)	368.4 (817.2)

*All numbers are N (%) unless otherwise specified.

**N=156 for all 6-month self-report measures

HADS-A = Hospital Anxiety and Depression Scale-Anxiety subscale; PHQ-9 = Patient Health Questionnaire-9

Table 2

Concurrent associations between psychological constructs and biomarkers of interest

		Biomarkers (β [95% confidence interval]; biomarkers were natural log-transformed)							
Predictor	**Model**	**hsCRP**	**TNF-α**	**IL-17**	**IL-6**	**sICAM-1**	**ET-1**	**cTnI**	**NT-proBNP**
Depressive Symptoms (PHQ-9)	1	.026 (−.012, .064)	.016*** (.008, .024)	.030** (.009, .052)	.019* (.002, .036)	.004 (−.007, .014)	.015** (.005, .025)	.036** (.010, .062)	.066*** (.035, .097)
	2	−.001 (−.038, .035)	.012** (.005, .020)	.029** (.008, .050)	.007 (−.009, .022)	−.002 (−.011, .007)	.011† (−.000, .022)	.020 (−.008, .048)	.045** (.017, .074)
	3	−.021 (−.064, .021)	.010† (−.001, .021)	.047* (.010, .083)	.001 (−.017, .020)	−.000 (−.012, .011)	.020* (.004, .037)	.029† (−.003, .061)	.045* (.008, .083)
Anxiety Symptoms (HADS-A)	1	.036† (−.003, .075)	.012* (.002, .023)	−.002 (−.026, .021)	.018† (−.001, .037)	.001 (−.008, .010)	−.002 (−.015, .012)	.018 (−.018, .053)	.043† (−.001, .086)
	2	.020 (−.017, .058)	.011* (.001, .020)	−.003 (−.027, .022)	.010 (−.007, .027)	−.002 (−.010, .005)	−.004 (−.017, .009)	.003 (−.031, .036)	.029 (−.007, .065)
	3	.034 (−.009, .077)	.005 (−.009, .018)	−.032 (−.073, .009)	.010 (−.010, .030)	−.002 (−.012, .008)	−.017† (−.035, .001)	−.015 (−.054, .023)	−.000 (−.046, .045)
Optimism (LOT-R)	1	−.025† (−.052, .002)	−.007* (−.014, −.001)	.006 (−.010, .022)	−.010 (−.024, .004)	−.004 (−.011, .002)	−.009** (−.016, −.002)	.009 (−.014, .032)	−.010 (−.034, .014)
	2	−.022† (−.047, .002)	−.008** (−.014, −.002)	.004 (−.012, .020)	−.008 (−.020, .004)	−.002 (−.008, .004)	−.008* (−.014, −.001)	.005 (−.017, .027)	−.014 (−.037, .008)
	3	−.026† (−.053, .001)	−.005 (−.011, .002)	.012 (−.007, .031)	−.006 (−.019, .007)	−.004 (−.011, .002)	−.009* (−.016, −.001)	.013 (−.011, .037)	.001 (−.026, .029)
Gratitude (GQ-6)	1	−.027 (−.060, .007)	−.006 (−.013, .002)	.009 (−.008, .025)	−.007 (−.023, .009)	−.006† (−.014, .001)	−.010** (−.017, −.003)	−.018 (−.046, .010)	−.015 (−.046, .016)
	2	−.022 (−.052, .008)	−.007* (−.013, −.001)	.005 (−.012, .022)	−.004 (−.018, .010)	−.005 (−.011, .001)	−.009* (−.016, −.002)	−.019† (−.038, .001)	−.018 (−.041, .005)
	3	−.026 (−.060, .007)	−.003 (−.011, .004)	.015 (−.005, .034)	−.001 (−.017, .015)	−.007* (−.014, −.000)	−.009* (−.017, −.001)	−.017 (−.038, .004)	−.004 (−.030, .022)

Model 1: Adjusting for age and gender.

Model 2: Adjusting for Model 1 covariates plus history of prior ACS, peak troponin T, length of stay, admission diagnosis, body mass index, current smoking status, hypertension, hyperlipidemia, and age-adjusted Charlson Comorbidity Index.

Model 3: Adjusting for Model 2 covariates plus depression and anxiety, if applicable.

Key:

† = p<.10

* = p<.05

** = p<.01

*** = p<.001

Abbreviations: cTnI = cardiac troponin I; ET-1 = endothelin 1; GQ-6 = Gratitude Questionnaire-6; HADS-A = Hospital Anxiety and Depression Scale, anxiety subscale; hsCRP = C-reactive protein; IL-6 = interleukin-6; IL-17 = interleukin-17; LOT-R= Life Orientation Test-Revised; NT-proBNP = N-terminal pro-brain natriuretic peptide; PHQ-9 = Patient Health Questionnaire-9; sICAM-1 = soluble intercellular adhesion molecule-1; TNF-α = tumor necrosis factor-α