Journal of the American College of Cardiology
© 2012 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 60, No. 18, 2012
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.06.044



# Perceived Stress in Myocardial Infarction

## Long-Term Mortality and Health Status Outcomes

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**Objectives** This study sought to determine the association of chronic stress with long-term adverse outcomes after acute myocardial infarction (AMI).

**Background** Chronic stress has been shown to be associated with the development of cardiovascular disease and, in the case of particular types of stress such as job and marital strain, with recurrent adverse events after AMI. Little is known, however, about the association of chronic stress with mortality and adverse health status outcomes in a general AMI population.

**Methods** In a cohort of 4,204 AMI patients from 24 U.S. hospitals completing the Perceived Stress Scale-4 (sum scores ranging from 0 to 16) during hospitalization, moderate/high stress over the previous month was defined as scores in the top 2 quintiles (scores of 6 to 16). Detailed data on sociodemographics, psychosocial status, and clinical characteristics were collected at baseline. Outcomes included patients' 1-year health status, assessed with the Seattle Angina Questionnaire, Short Form-12, and EuroQol Visual Analog Scale, and 2-year mortality.

**Results** AMI patients with moderate/high stress had increased 2-year mortality compared with those having low levels of stress (12.9% vs. 8.6%; $p < 0.001$). This association persisted after adjusting for sociodemographics, clinical factors (including depressive symptoms), revascularization status, and GRACE (Global Registry of Acute Coronary Events) discharge risk scores (hazard ratio: 1.42: 95% confidence interval: 1.15 to 1.76). Furthermore, moderate/high stress was independently associated with poor 1-year health status, including a greater likelihood of angina, worse disease-specific and generic health status, and worse perceived health ($p < 0.01$ for all).

**Conclusions** Moderate/high perceived stress at the time of an AMI is associated with adverse long-term outcomes, even after adjustment for important confounding factors. Future studies need to examine whether stress mediates observed racial and socioeconomic disparities and whether novel interventions targeting chronic stress and coping skills can improve post-AMI outcomes. (J Am Coll Cardiol 2012;60:1756–63) © 2012 by the American College of Cardiology Foundation

Chronic stress is believed to contribute to both the development and progression of cardiovascular disease (1) and cardiovascular death (2,3). The mechanisms underlying this association are complex and include a combination of behavioral (e.g., smoking, lack of exercise, obesity [4], medication nonadherence) and physiological factors (e.g., increased blood pressure and pulse rates [5] reduced insulin sensitivity [6], increased platelet aggregation [7], endothelial dysfunction [8]). Although several studies have evaluated the adverse effect of stress on the cardiovascular system, many have focused on incident cardiac disease (1–3), restricted their analyses to select clinical populations (9,10), or have focused on particular types of stress, such as job strain (10,11), marital stress (10), and financial strain (12). Few studies have evaluated the effect of chronic stress on individuals recovering from an acute myocardial infarction (AMI), although studies have suggested that high job and marital strain can increase the risk of subsequent adverse cardiovascular events (10,11,13). Importantly, it is unknown whether high levels of chronic stress, assessed with a valid instrument that examines patient perception of stress and coping, are associated with adverse prognosis after an AMI. Given the

From the Saint Luke's Mid America Heart Institute, Kansas City, Missouri. TRIUMPH was sponsored by a grant from the National Institutes of Health (National Heart, Lung, and Blood Institute): Washington University School of Medicine SCCOR grant P50HL077113-01. The funding organization did not play a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript. Drs. Arnold and Smolderen are supported by an award from the American Heart Association Pharmaceutical Roundtable and David and Stevie Spina. Dr. Smolderen is also supported by the Netherlands Organization for Scientific Research [VENI grant no.: 916.11.179]; and received a research grant from W.L. Gore & Associates. Dr. Spertus owns the copyright to the Seattle Angina Questionnaire; received partial support from a Clinical and Translational Science Award (1UL1RR033179); received a research grant from Lilly; and is a consultant for United Healthcare. Drs. Buchanan and Li have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received March 19, 2012; revised manuscript received June 6, 2012, accepted June 12, 2012.

current focus of AMI management on optimizing prognosis, defining the prognostic import of perceived stress can illuminate an opportunity to assess and intervene in when risk-stratifying patients for subsequent treatment.

Furthermore, the association between perceived stress and post-AMI angina and health status (function and quality of life[QoL]) outcomes has not been described. Although depressive symptoms have been shown to be associated with health status after adjusting for perceived stress in a cross-sectional analysis of patients with stable coronary artery disease, the independent association of stress with outcomes was not reported (14). Moreover, depressive symptoms are associated with both increased stress and poor health status and mortality. Therefore, exploring the association of stress with outcomes independent of depressive symptoms is important to disentangle these complex relationships and understand whether stress is an important factor to consider, beyond depression, when evaluating psychological distress in AMI patients and to identify novel potential areas for interventions to improve outcomes.

To better clarify the association of chronic stress, assessed with the validated perceived stress scale (PSS) (15), on mortality and health status outcomes, we examined a large population of AMI patients in the multicenter TRIUMPH (Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients' Health status) study (16). The TRIUMPH study was an ideal population for this analysis, given its extensive collection of socioeconomic, clinical, and psychosocial factors that may confound the association between stress and outcomes.

## Methods

**Study population and protocol.** Between June 2005 and December 2008, 4,340 patients from 24 U.S. hospitals were enrolled in the TRIUMPH study (16). Patients were required to have biomarker evidence of myocardial necrosis and additional clinical evidence supporting the diagnosis of an AMI, including prolonged ischemic signs/symptoms (≥20 min) or electrocardiographic ST-segment changes during the initial 24 h of admission. Baseline data were obtained through chart abstraction and a structured interview by trained research staff within 24 to 72 h after admission. Follow-up health status data were obtained 1 year after patients' AMI with a standardized interview. Each participating hospital obtained institutional research board approval, and all patients provided written informed consent for baseline and follow-up assessments.

**Assessment of perceived stress.** Patients' levels of perceived stress were assessed at the time of AMI with the 4-item PSS (15). The PSS is a reliable and valid measure of subjects' sense of control and confidence in handling circumstances over the past month. The 4 questions ask respondents to judge their ability to control important things, their confidence in handling personal problems, a feeling of things going their way, and a feeling of being overwhelmed by difficulties piling up. Responses range from never (0 points) to very often (4 points), with the total PSS score ranging from 0 to 16 and higher scores indicating more perceived stress. Because the PSS is not a diagnostic instrument, there are no established cutoffs, only comparisons within a sample. Therefore, we divided the scores into approximate quintiles and defined the highest quintile (PSS scores 9 to 16) as high stress in accordance with previous work (14) and the fourth quintile (PSS scores 6 to 8) as representing moderate stress.

**Abbreviations and Acronyms**

**AMI** = acute myocardial infarction
**CI** = confidence interval
**MCS** = Mental Components Summary
**OR** = odds ratio
**PCS** = Physical Components Summary
**PSS** = Perceived Stress Scale
**QoL** = quality of life
**SAQ** = Seattle Angina Questionnaire
**SF-12** = Medical Outcomes Study 12-item Short Form
**VAS** = EuroQol Visual Analog Scale

**Outcomes assessment.** Two-year all-cause mortality (available for 99% of patients) was determined through a combination of follow-up interviews and a query of the Social Security Death Masterfile. Health status was assessed using the Seattle Angina Questionnaire (SAQ) (17), the EuroQol Visual Analog Scale (VAS) (18), and the Medical Outcomes Study 12-Item Short Form (SF-12) (19). The SAQ is a reliable and valid 19-item questionnaire composed of 5 clinically important dimensions of health in patients with coronary artery disease. For this study, we focused on the SAQ angina frequency, physical limitations, and QoL scales. The scores for these domains range from 0 to 100, with higher scores indicating less disease burden. Based on previous work, SAQ angina frequency was categorized as none (score of 100), monthly angina (score of 61 to 99), and weekly/daily angina (score of 0 to 60); SAQ physical limitations was categorized as slight to no limitation (score >75), mild limitation (score of 51 to 75), and moderate/severe limitation (score of 0 to 50); and SAQ QoL was categorized as excellent (score >75), good (score of 51 to 75), and fair/poor (score of 0 to 50) (20).

The VAS is a measure of perceived general health that consists of a single-item, "feeling thermometer," on which patients rate their general health state from 0 (worst imaginable) to 100 (best imaginable) (18). The SF-12 is a reliable and valid measure of generic health status (21) that provides summary component scales for overall physical (Physical Components Summary [PCS]) and mental (Mental Components Summary [MCS]) health using norm-based methods that standardize the scores to a mean of 50 and an SD of 10 (higher scores indicate better health status) (19). To facilitate the interpretation of our results, we defined poor health status as scores in the lowest quartile (VAS scores of ≤65; PCS scores of ≤35; MCS scores of ≤45).

**Statistical analysis.** Baseline factors and long-term outcomes of the patients were compared across categories of stress using 1-way analysis of variance for continuous

variables and the chi-square test for categorical variables. A multivariable logistic regression model was used to determine the factors associated with moderate/high versus low stress levels (PSS scores of 6 to 16 vs. scores of 0 to 5) among AMI patients. Variables included in the model were selected a priori and included demographics, socioeconomic status, comorbidities and clinical factors, and disease severity indices.

Cox proportional hazards regression models evaluated the impact of moderate/high stress versus low levels of stress on 2-year all-cause post-AMI mortality. Two sequential mortality models were constructed: adjusted for the GRACE (Global Registry of Acute Coronary Events) discharge score (22) to account for the clinical severity of AMI and fully adjusted with additional sociodemographic, clinical, and treatment factors. Multivariable logistic regression models assessed the independent association of moderate/high levels of stress with poor health status outcomes 1 year after AMI. Outcomes included SAQ_angina frequency (none [score = 100] vs. any [score <100]), SAQ_physical limitations (slight to no limitation [score >75] vs. mild or greater limitation [score of 0-75]), SAQ_QoL (excellent [score >75] vs. diminished [score of 0 to -75]), VAS (good [score >65] vs. poor [score ≤65]), SF-12 PCS (good [score >35] vs. poor [score ≤35]), and SF-12 MCS (good [score >45] vs. poor [score ≤45]).

Covariates in all health status models and in the fully adjusted mortality model were selected a priori given their associations with stress and poor outcomes. These included age, sex, race, marital status, self-reported avoidance of care due to costs (a measure of economic barrier to medical care that has demonstrated strong association with poor long-term AMI outcomes [23]) hypertension, previous bypass surgery, diabetes, chronic lung disease, chronic heart failure, history of stroke or transient ischemic attack, body mass index, anemia, depressive symptoms (assessed with the 9-item Patient Health Questionnaire [24]), ST-segment elevation AMI, GRACE score (22), left ventricular function (categorized as normal, mild, moderate, and severe dysfunction), in-hospital percutaneous coronary intervention, in-hospital bypass graft surgery, and the percentage of Joint Commission/Centers for Medicare and Medicaid Services quality measures received (of those for which the patient was eligible). The interaction between depressive symptoms and perceived stress was tested and found not to be significant ($p > 0.05$ for all analyses) and was not included in the final models. Smoking status and low social support (assessed with the 7-item Enhancing Recovery in Coronary Heart Disease Social Support Inventory [25]) were chosen a priori not to be included in the models to avoid overadjusting because they were thought to be markers or consequences of high stress rather than causes of it. Of note, these variables were strongly associated with higher stress levels but weakly associated with outcomes. Several sensitivity analyses were performed that included smoking, low social support, and baseline health status (to test the association between baseline stress levels and health status recovery) as additional covariates in the multivariable models. All analyses were conducted using SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina), and statistical significance was determined by a 2-sided p value of $<0.05$.

**Missing data.** Of the 4,340 patients enrolled in the TRIUMPH study, 4,204 completed the PSS and were discharged alive. Baseline covariate data were fairly complete, with 12% of patients missing 1 covariate, <1% of patients missing ≥2 covariates, and an average missing rate of 0.14 items per patient. Missing baseline covariate data were imputed using multiple imputations with IVEware (Imputation and Variance Estimation Software; University of Michigan's Survey Research Center, Institute for Social Research, Ann Arbor, Michigan). At 1 year, 279 participants (6.6%) had died, 235 (5.6%) refused the interview, 78 (1.9%) did not complete the full interview, and 971 (23.1%) could not be contacted. Although unadjusted baseline PSS scores were higher for those alive but missing follow-up health status assessments (4.9 vs. 4.4, $p < 0.001$), stress was not associated with missing follow-up in a multivariable logistic model ($p = 0.30$). To further assess for potential bias in the health status outcomes assessments, we calculated a nonparsimonious propensity score with successful follow-up as the dependent variable. An inversely weighted propensity score was assigned to each patient (26), and we then repeated our health status models to provide greater weight to the scores of patients who were most like those missing follow-up data. The results of this sensitivity analysis were consistent with the main analyses, and only the unweighted analyses are presented.

## Results

**Patient population.** Of the 4,204 patients who were discharged alive after their AMI, 1,622 (38.6%) were considered as having moderate or high levels of perceived stress in the 4 weeks preceding their AMI. The mean age of the patient population was 59 years, 67% were male, and 67% were Caucasian. Cardiac and noncardiac comorbidities were common, with 66% of patients having hypertension, 31% having diabetes, and 19% expressing depressive symptoms (Personal Health Questionnaire-9 score ≥10). Patients with higher stress levels before their AMI were younger and more likely to be female, unmarried, and non-Caucasian; have low social support, avoid care due to cost; and were less likely to have completed high school. Higher stress patients also had more hypertension, diabetes, smoking, depression, and obesity (Table 1). In terms of their clinical presentation, patients with higher stress levels were less likely to present with ST-segment elevation AMIs and had lower GRACE scores but had higher heart rates on admission and longer length of stays. Higher stress patients were less likely to undergo invasive management of their AMI, but guideline-recommended medical therapy at discharge was high and similar across categories of stress (Table 2).

**Table 1** Baseline Characteristics of Patients With Various Levels of Chronic Perceived Stress

| | Perceived Stress Level | | | |
|---|---|---|---|---|
| | Low (n = 2,582) | Moderate (n = 1,027) | High (n = 595) | p Value |
| Sociodemographics | | | | |
| Age, yrs | 60.5 ± 12.3 | 57.6 ± 11.9 | 54.2 ± 11.0 | <0.001 |
| Male | 70.4 | 64.2 | 57.0 | <0.001 |
| Caucasian race | 69.8 | 63.5 | 63.7 | <0.001 |
| Married | 56.8 | 49.8 | 38.9 | <0.001 |
| Low social support | 9.4 | 24.1 | 39.3 | <0.001 |
| Lives alone | 23.2 | 25.4 | 28.4 | 0.024 |
| High school education | 82.0 | 75.0 | 74.7 | <0.001 |
| Avoids care due to cost | 18.4 | 30.7 | 48.6 | <0.001 |
| Comorbidities | | | | |
| Hypertension | 64.2 | 69.4 | 71.4 | <0.001 |
| Previous bypass graft surgery | 11.4 | 11.8 | 10.8 | 0.822 |
| Diabetes mellitus | 27.5 | 34.8 | 36.5 | <0.001 |
| Current smoking | 34.8 | 44.1 | 51.7 | <0.001 |
| Anemia on admission | 19.7 | 23.4 | 25.6 | 0.001 |
| Chronic lung disease | 6.7 | 7.2 | 9.7 | 0.032 |
| History of heart failure | 7.1 | 9.3 | 12.9 | <0.001 |
| GFR <60 ml/min | 24.4 | 24.4 | 25.5 | 0.843 |
| Body mass index, kg/m$^2$ | 29.2 ± 6.2 | 29.8 ± 6.8 | 30.5 ± 6.8 | <0.001 |
| Stroke or TIA | 6.7 | 7.1 | 8.1 | 0.492 |
| Depressive symptoms | 6.9 | 24.4 | 60.6 | <0.001 |

Values are mean ± SD or %.
GFR = glomerular filtration rate; TIA = transient ischemic attack.

**Association between perceived stress and mortality outcomes.** Among the 4,204 patients who survived the acute hospitalization for their AMI, 432 (10.3%) died within the 2 years after hospital discharge. Patients with moderate/high perceived stress levels had increased mortality over the subsequent 2 years compared with those who reported low stress levels (12.9% vs. 8.6%; log-rank test, $p < 0.001$) (Table 3, Fig. 1). In a Cox proportional hazards model adjusting for the GRACE discharge score, moderate/high stress levels were associated with an increased hazard of dying during the 2 years after AMI (hazard ratio:1.79; 95% confidence interval [CI]: 1.48 to 2.16; $p < 0.001$). After further adjusting for sociodemographics, clinical factors including depressive symptoms, and treatment characteristics, moderate/high stress remained significantly associated with increased 2-year mortality (hazard ratio: 1.42; 95% CI: 1.15 to 1.76; $p = 0.001$) (Fig. 2).

**Association between perceived stress and health status outcomes.** Moderate/high perceived stress levels were associated with worse 1-year health status outcomes, including increased angina, more physical limitations due to angina, worse disease-specific QoL, and worse physical and mental health status (Table 3). In multivariable logistic regression models adjusting for sociodemographic and clinical factors including depressive symptoms, patients with moderate/high stress during the month preceding their AMI had a 1.41 increased odds of having angina 1 year after their AMI (95% CI: 1.14 to 1.75; $p = 0.001$) (Fig. 2) and a 1.41 increased odds of having a diminished disease-specific QoL (95% CI: 1.13 to 1.77) ($p = 0.003$). Patients with moderate/high stress were also more likely to report poor perceived health, as assessed with the VAS (odds ratio [OR]: 1.79; 95% CI: 1.45 to 2.20; $p < 0.001$), SF-12 physical health status (OR: 1.43; 95% CI: 1.14 to 1.78; $p = 0.002$), and SF-12 mental health status (OR: 2.34; 95% CI: 1.87 to 2.93; $p < 0.001$). Perceived stress was not significantly associated with angina-related physical limitations after multivariable adjustment ($p = 0.11$) (Fig. 2, Online Tables 1a and 1b).

**Sensitivity analyses.** To support the robustness of our findings, we performed a number of sensitivity analyses. Although the PSS has a 1-month recall period and would be expected to capture patients' perceived stress before their MI, it is possible that the acute stress of an AMI might alter the intended recall frame of the instrument. To address this possibility, we repeated our analyses using a 1-month post-AMI PSS assessment. Of the patients, 71% reported the same level of perceived stress at baseline and 1 month after their AMI (66% of those with moderate/high stress at baseline and 73% of those with low stress at baseline). Moderate/high stress at the 1-month follow-up was associated with an increased hazard of 2-year mortality (unadjusted HR: 1.41; 95% CI: 1.0 to 1.87; $p = 0.016$) and increased odds of poor 1-year health status across all the health status domains (Online Table 2). Second, although we explicitly excluded smoking and social support from the multivariable models to avoid overadjustment, we per-

**Table 2** AMI Presentation and Treatment Characteristics of Patients With Various Levels of Chronic Perceived Stress

| | Perceived Stress Level | | | |
|---|---|---|---|---|
| | Low (n = 2,582) | Moderate (n = 1,027) | High (n = 595) | p Value |
| Clinical presentation | | | | |
| ST-segment elevations | 45.2 | 39.5 | 39.0 | <0.001 |
| Peak troponin | 29.2 ± 76.3 | 26.5 ± 64.8 | 28.0 ± 72.2 | 0.607 |
| GRACE risk score | 102.4 ± 29.9 | 98.9 ± 30.2 | 93.3 ± 28.7 | <0.001 |
| Left ventricular systolic function | | | | 0.158 |
| Normal | 61.5 | 64.0 | 60.2 | |
| Mild dysfunction | 20.6 | 17.2 | 18.3 | |
| Moderate dysfunction | 10.7 | 11.0 | 12.8 | |
| Severe dysfunction | 7.2 | 7.8 | 8.7 | |
| Initial heart rate | 81.9 ± 21.8 | 82.7 ± 21.7 | 85.3 ± 24.0 | 0.003 |
| Initial systolic blood pressure | 142.9 ± 30.3 | 143.5 ± 29.3 | 143.4 ± 31.5 | 0.813 |
| hsCRP levels | 3.8 ± 5.1 | 3.5 ± 4.7 | 3.5 ± 4.4 | 0.471 |
| Length of stay | 5.3 ± 5.7 | 5.8 ± 7.4 | 5.9 ± 6.5 | 0.02 |
| Hospital procedures | | | | |
| Cardiac catheterization | 93.6 | 89.2 | 90.6 | <0.001 |
| PCI | 67.2 | 60.1 | 63.5 | <0.001 |
| Bypass graft surgery | 9.5 | 9.3 | 9.1 | 0.941 |
| Medications at discharge | | | | |
| Aspirin | 94.9 | 93.1 | 94.1 | 0.107 |
| Beta-blocker | 90.8 | 90.0 | 88.3 | 0.165 |
| ACE inhibitor or ARB | 74.2 | 73.3 | 76.4 | 0.372 |
| Statin | 88.5, | 86.5 | 88.6 | 0.226 |
| % of QOC indicators | 90.6 ± 14.8 | 89.0 ± 16.3 | 88.9 ± 16.1 | 0.004 |

Values are % or mean ± SD.

ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; ARB = angiotensin receptor blocker; GRACE = Global Registry of Acute Coronary Events; hsCRP = high-sensitivity C-reactive protein; PCI = percutaneous coronary intervention; QOC = quality of care.

formed sensitivity analyses including these 2 variables. The association between stress and outcomes was not materially affected by the addition of low social support or smoking to the multivariable models (Online Table 3). Third, although we were specifically interested in whether chronic stress is associated with adverse health status outcomes after an AMI, we additionally investigated whether stress is associated with poor health status recovery by additionally adjusting for baseline health status in the multivariable models. Although the relationship was attenuated, moderate/high stress at baseline remained significantly associated with poorer health status recovery 1 year after their AMI (Online Table 4). Fourth, because depressive symptoms and stress are often coexisting, we compared the outcomes of patients with low versus moderate/high stress among patients with and without depressive symptoms. Within each category of depressive symptoms, patients with moderate/high stress were more likely to die and report worse angina and QoL compared with patients reporting low stress (Online Table 5). Finally, because deaths were not adjudicated, we are only able to report all-cause mortality and not cardiac-specific mortality. However, moderate/high stress was asso-

**Table 3** Long-Term Post-AMI Outcomes of Patients With Various Levels of Chronic Perceived Stress

| | Perceived Stress Level | | | |
|---|---|---|---|---|
| | Low | Moderate | High | p Value |
| Mortality rate, 2 year | 8.6 | 13.0 | 12.8 | <0.001 |
| Health status outcomes, 1 year | | | | |
| SAQ angina frequency | 94.6 ± 13.9 | 91.6 ± 16.7 | 87.0 ± 22.1 | <0.001 |
| SAQ physical limitations | 94.2 ± 15.2 | 91.6 ± 19.0 | 82.8 ± 26.3 | <0.001 |
| SAQ quality of life | 85.2 ± 18.6 | 79.3 ± 20.9 | 68.6 ± 26.5 | <0.001 |
| EuroQol Visual Analog Scale | 78.7 ± 18.5 | 71.9 ± 20.4 | 63.1 ± 24.4 | <0.001 |
| SF-12 physical health | 45.1 ± 11.7 | 42.0 ± 11.9 | 38.6 ± 12.7 | <0.001 |
| SF-12 mental health | 54.4 ± 8.8 | 49.9 ± 10.0 | 43.2 ± 12.6 | <0.001 |

Values are % or mean ± SD.

AMI = acute myocardial infarction; SAQ = Seattle Angina Questionnaire; SF-12 = Medical Outcomes Study 12-Item Short Form.

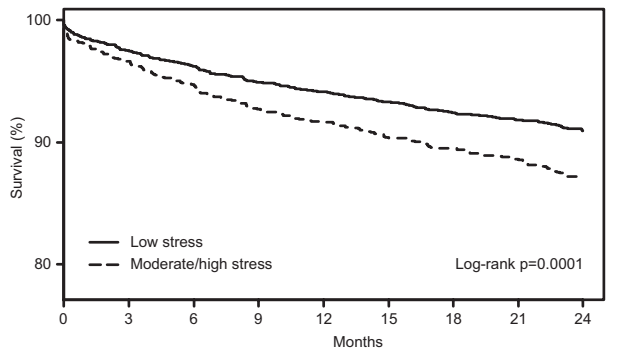


**Figure 1** **Kaplan-Meier Survival Curves for Moderate/High Versus Low Perceived Stress Levels**

Two-year survival after acute myocardial infarction in patients with moderate/high perceived stress levels (stress scores of 6 to 16) versus low stress levels (stress scores of 0 to 5).

ciated with an increased hazard of cardiac rehospitalizations. There was no significant difference between the rate of coronary revascularization over the year of follow-up between those with moderate/high and low stress levels (Online Fig. 1).

## Discussion

In a large contemporary registry of AMI patients, moderate to high perceived stress over the month before an AMI was associated with increased long-term mortality, despite the fact that patients with increased perceived stress levels were younger and less likely to have ST-segment elevation AMIs and had lower GRACE scores, all of which are generally associated with lower mortality. Although high perceived stress levels were associated with depressive symptoms, the association between increased stress and increased mortality persisted after adjustment for multiple factors, including depressive symptoms. Thus, chronic stress outside the context of depressive symptoms is independently associated with adverse outcomes. Furthermore, increased stress levels before AMI were associated with worse health status outcomes and poorer health status recovery after AMI, including more angina and worse QoL. Although the mechanisms of these associations remain unknown, these findings suggest that patients' perceived stress is an important factor to consider when evaluating patients' risk of poor long-term outcomes. In addition, many covariates that are associated with increased perceived stress have been shown in previous studies to be associated with poor outcomes post-AMI (e.g., female sex [(27] low social support [27], low socioeconomic status [23], smoking [28]), suggesting that some of the effect of these factors on outcomes may be mediated by poorer coping skills and increased stress.

**Previous studies.** Our findings substantially extend the previous literature surrounding the association between chronic stress and cardiovascular outcomes. Among working people, several studies have demonstrated that increased job strain is associated with the development and progression of cardiovascular disease (1–3,29) and the risk of recurrent adverse cardiovascular events after an AMI (9,11,29). However, this finding has not been consistent (30,31), particularly among women (10). Other studies have shown high marital (10) and financial (12) strain to be associated with an increased risk of recurrent adverse events after AMI among women. Our study extends the evaluation of stress and prognosis in a large, diverse, unselected AMI population that included patients regardless of employment, marital status, or age, further supporting the generalizability of our findings. Importantly, we were able to adjust for multiple potential confounders of the relationship between stress and mortality, including depressive symptoms and socioeconomic status, further supporting an independent relationship between perceived stress and outcomes.

Second, we have extended the literature by broadening our outcomes to include health status and QoL. Limited evidence is available demonstrating that mental stress may be related to anginal symptoms (32,33), and the cross-sectional Heart and Soul Study of 1,024 U.S. patients with stable coronary artery disease suggested that increased perceived stress was independently associated with greater physical limitations from angina and worse disease-specific and generic health status. However, our study is the first to prospectively document the independent association between perceived

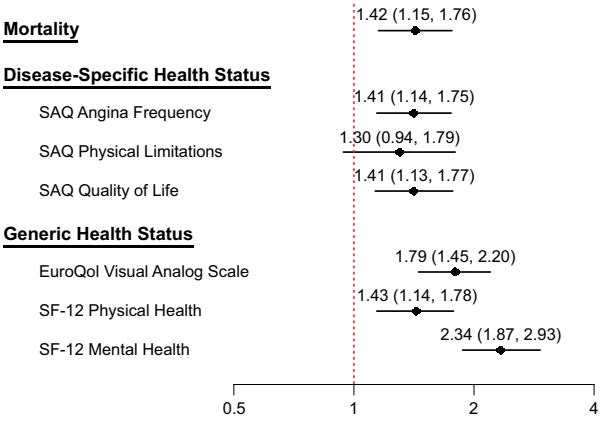


**Figure 2** **Association Between Moderate/High and Low Perceived Stress Levels and Long-Term Outcomes**

Multivariable-adjusted hazard/odds ratios of the association between moderate/high perceived stress levels (stress scores of 6 to 16) and low stress levels (stress scores of 0 to 5) and mortality and health status outcomes. Models were adjusted for age, sex, race, marital status, self-reported avoidance of care due to costs, hypertension, previous bypass surgery, diabetes, chronic lung disease, chronic heart failure, history of stroke or transient ischemic attack, body mass index, anemia, depressive symptoms, ST-segment elevations on admission, left ventricular function, Global Registry of Acute Coronary Events score (22), in-hospital bypass surgery, in-hospital percutaneous coronary intervention, and the percentage of quality of care indicators received. SAQ = Seattle Angina Questionnaire; SF-12 = Medical Outcomes Study 12-Item Short Form.

stress and a broad range of validated disease-specific and generic health status outcomes after an AMI.

**Potential mechanisms.** The mechanisms underlying the association between chronic perceived stress and poor outcomes after an AMI are complex and likely include a combination of behavioral (4) and physiological (5–8) factors. From a physiological standpoint, acute mental stress can have adverse consequences on the cardiovascular system in terms of inducing myocardial ischemia. Structured mental stress tests can provoke ischemia of similar or greater severity and extent to exercise in 40% to 70% of patients with coronary artery disease (34,35). Furthermore, myocardial ischemia induced by mental stress predicts ischemia during daily life and increases the risk of fatal and nonfatal cardiac events (36,37). These findings suggest that post-AMI patients who have high levels of mental stress may experience adverse physiological effects that may, in part, explain their poor outcomes. Furthermore, behavioral factors that are both associated with high stress and poor outcomes, such as medication nonadherence and nonparticipation in cardiac rehabilitation, should be explored as potential mediators of the effect of stress on poor outcomes.

**Perceived stress and other psychosocial distress.** Previous considerations of the psychosocial risks associated with poor post-AMI outcomes have primarily focused on recognition and treatment of depressive symptoms. Although stress is associated with other manifestations of psychological distress, our study demonstrates that an increased chronic perceived stress level at the time of an AMI is independently associated with increased mortality and worse health status after the AMI, even after accounting for depressive symptoms. Thus, significant stress that occurs outside the context of depression may also independently and adversely portend poor outcomes. Furthermore, there has been recent attention given to the adverse impact of other psychosocial factors, such as anger, anxiety, and social support on mortality (38–40) and health status (41) in patients with coronary artery disease. Although the psychological concepts of stress, anxiety, depression, anger, and hostility are not interchangeable, there is overlap among these concepts, and it is unclear how much of the PSS captures psychological distress due to these factors that are related to but distinct from chronic stress. Nevertheless, although the PSS may not be able to disentangle these psychological mechanisms, it is a simple, 4-item instrument that can be easily implemented in clinical care to identify high-risk patients with psychological distress that may benefit from a multimodal psychological evaluation and intervention. Expanding psychosocial interventions to address factors such as chronic stress, coping skills, anxiety, and other psychosocial impairments may improve post-AMI outcomes in vulnerable patients. Such multicomponent approaches have shown success on a small scale. For example, in a study of 237 Swedish women with coronary disease, patients randomized to a group-based psychosocial intervention designed to improve coping skills, reduce stress, and improve social support had significantly reduced mortality compared with patients who received usual care (42).

**Study limitations.** Our findings should be interpreted in the context of the following potential limitations. First, although the assessment of perceived stress at the time of the AMI was done with the PSS, a psychometrically appropriate instrument with a recall period of 1 month, it is unclear whether the acute stress of the AMI affected patients' recollection of their pre-AMI stress levels. However, when we repeated the analyses using the 1-month follow-up PSS scores, the results were consistent (and across most domains, the associations were even stronger), which increases our confidence in the prognostic association of perceived stress with post-AMI outcomes. Second, the PSS is not a diagnostic instrument, and thus there are no established score cutoffs. Instead, the authors of the instrument recommend using cutoffs based on the study sample. We used quintiles because the uppermost quintile in our study sample (PSS scores of 9 to 16) correlated with a threshold for high perceived stress used in the Heart and Soul Study (14). Although the use of different score cutoffs may have altered the point estimates of our findings, we found a graded, nearly continuous relationship across quintiles of PSS scores. Third, as patients missing follow-up information reported increased perceived stress and worse health status at baseline, the loss to follow-up may have biased the health status/QoL analyses, although our propensity-weighted analyses did not suggest a significant bias from loss to follow-up. Finally, given the interplay of multiple psychosocial and socioeconomic aspects with each other (including smoking, anxiety, depressive symptoms, and socioeconomic status), it is difficult to disentangle and isolate the specific relationship between stress and outcomes. Properly teasing apart the potentially causative pathway would require formal mediation or path analyses with prospective, serial measurements of stress, which are important areas for further research.

## Conclusions

We found that moderate to high levels of perceived stress over the month before an AMI were associated with increased long-term post-AMI mortality, despite the fact that patients with increased perceived stress levels were younger and less ill. Furthermore, increased stress was associated with poor long-term health status outcomes. These findings suggest that it is important to consider patients' perceived stress levels when evaluating their risk for poor long-term outcomes. Although likely resulting from a combination of multiple biological and behavioral factors, further exploration is needed to determine the mechanisms of this increased hazard. In addition, it will be important to examine whether interventions targeting chronic stress levels and coping skills in AMI populations may attenuate the increased morbidity and mortality risk from increased stress.

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**Key Words:** health status ■ mortality ■ myocardial infarction ■ stress.

## APPENDIX

**For supplemental tables and a figure, please see the online version of this article.**