HHS Public Access

Author manuscript

J Psychosom Res. Author manuscript; available in PMC 2018 February 01.

Published in final edited form as:

J Psychosom Res. 2017 February ; 93: 19–27. doi:10.1016/j.jpsychores.2016.12.001.

Anxiety and Anger Immediately Prior to Myocardial Infarction and Long-term Mortality: Characteristics of High-Risk Patients

Loes Smeijers, PhD[1], **Elizabeth Mostofsky, MPH, ScD**[2,3], **Geoffrey H. Tofler, MD**[4], **James E. Muller, MD**[5], **Willem J. Kop, PhD**[1], and **Murray A. Mittleman, MD, DrPH**[2,3]

[1]Department of Medical and Clinical Psychology, Center of Research on Psychology in Somatic diseases (CoRPS), Tilburg University, the Netherlands [2]Cardiovascular Epidemiology Research Unit, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA [3]Department of Epidemiology, Harvard School of Public Health, Boston, MA [4]Department of Cardiology, Royal North Shore Hospital, Sydney, Australia [5]InfraReDx, Burlington, MA

Abstract

Objective—Acute high levels of anger and anxiety are associated with an elevated risk of myocardial infarction (MI) in the following two hours. MIs preceded by these acute negative emotions may also have a poor long-term prognosis, but information about high-risk patients is lacking. We examined whether young age and female sex are associated with MIs that are preceded by negative emotions and whether age and sex moderate the subsequent increased mortality risk following MI preceded by negative emotions.

Methods—We conducted a secondary analysis of the Determinants of Myocardial Infarction Onset Study (N=2176, mean age=60.1±12.3 years, 29.2% women). Anxiety and anger immediately prior to (0-2 hour) MI and the day before (24-26 hour) MI were assessed using a structured interview. Subsequent 10-year all-cause mortality was determined using the US National Death Index.

Results—Anxiety during the 0-2 hour pre-MI period was associated with younger age (OR=0.98,95%CI=0.96-0.99 per year) and female sex (OR=1.50,95%CI=1.11-2.02). Anger in the 0-2 hour pre-MI period was also associated with younger age (OR=0.95,95%CI=0.94-0.96) but not with sex (OR=0.93,95%CI=0.67-1.28). During follow-up, 580 (26.7%) patients died. Mortality rate was higher if MI occurred immediately after high anxiety, particularly in patients ≥65 years

Corresponding Author: Murray A. Mittleman, MD, DrPH, Cardiovascular Epidemiology Research Unit, Beth Israel Deaconess Medical Center, 375 Longwood Avenue, Room 441, Boston, MA 02215, mmittlem@bidmc.harvard.edu, Tel: (617) 632-7653, Fax: (617) 632-7698.

Disclosures: None

Conflict of Interest:
The authors have no personal financial or institutional interest in any of the materials described in this article and none of the authors have any conflicts of interests related to this manuscript.

(HR=1.80,95%CI=1.28-2.54) vs. younger patients (HR=0.87,95%CI=0.55-1.40; p-interaction=0.015). Other interactions with sex or anger were not significant.

Conclusions—Patients with high anxiety or anger levels in the critical 2-hour period prior to MI are younger than those without such emotional precipitants. In addition, pre-MI anxiety is associated with an elevated 10-year mortality risk in patients aged ≥65 years.

Keywords

Myocardial Infarction; Mortality; Risk Factors; Anxiety; Anger; Acute Stress

INTRODUCTION

Transient exposure to physical, chemical and psychological stressors are potential triggers of cardiovascular events [1,2]. An elevated risk of myocardial infarction (MI) has been documented minutes to hours following episodes of heavy physical exertion [3], sexual activity [4,5], chemical exposures including air pollution [6], use of marijuana [7] and cocaine, [8] as well as psychological states such as high levels of anger and anxiety [9,10] and depressed mood [11]. In addition to the consistent evidence of an immediately higher cardiovascular risk associated with short-term experiences of negative emotions, the long-term prognosis may be poor among people surviving an MI following these potential acute triggers [12]. However, other studies have not found an association between acute emotional precipitants of MI and long-term mortality [13]. Clinical characteristics of patients whose MI is preceded by negative emotions may partly account for these observed differences in long-term prognosis.

Biological hyper-reactivity to physical or emotional perturbations is a plausible biobehavioral mechanism accounting for MIs that are preceded by exogenous stressors. Acute mental stress can induce myocardial ischemia in controlled laboratory settings and during daily life activities [14-17]. The cardiac demand at which psychological factors induce myocardial ischemia is lower than with physical exertion [17], suggesting that coronary supply-related processes and/or more severe underlying myocardial disease may characterize patients with emotionally triggered ischemia [18]. Mental stress-induced ischemia is also associated with an increased long-term mortality risk in patients with coronary artery disease [19,20]. These mechanistic laboratory studies are important because it is difficult to unequivocally determine whether the preceding emotions and behaviors prior to MI are actually exposures that “trigger” acute cardiac events, or whether these emotional precipitants reflect a third common factor and/or reporting bias independent of the pathophysiology of MI Knowledge about the immediate emotional precipitants of MI and the characteristics of these patients may therefore be of clinical utility because these factors may add to the long-term risk stratification of post-MI patients.

Evidence suggests that age is inversely related to emotional wellbeing such that younger adults report more negative emotions than older individuals [21,22]. This age-related pattern has also been found in patients with coronary heart disease [23] and heart failure [24]. In addition, women tend to report higher levels of anxiety and other negative emotions compared to men [25-27] whereas men tend to report higher levels of hostility [28,29]. However, there has been no research examining whether the prevalence of emotional factors in the

critical 2 hours immediately prior to MI onset varies by age and sex. Vaccarino et al. [30] showed that women ≤50 years of age with a recent history of MI had substantially more mental stress-induced myocardial ischemia compared to age-matched men (52% vs. 25%). No sex-related differences were observed for ischemia induced with physical stress or in patients older than 50 years. Therefore, younger age and female sex are likely to be associated with a higher risk of myocardial infarction preceded by acute negative emotions such as anxiety and anger. In addition, MIs that develop in the context of these acute negative emotions might have a poor subsequent long-term prognosis.

This study builds on our recent observations that immediate (0-2 hours pre-MI) [31] and distant (24-26 hours pre-MI) [32] emotional states prior to MI (particularly anxiety) are predictive of adverse long-term mortality outcomes whereas MIs preceded by exercise were not associated with a subsequent elevated mortality risk [31]. The present article builds on these observation by investigating three new aspects of emotional precipitants of MI: on (1) the identification of high-risk sub-groups of patients who experience an MI following negative emotions based on age and sex; (2) determine whether age and sex influence the higher mortality rate following MIs that occur following negative emotions; and (3) the investigation of immediate vs. distant emotional precipitants of MI as predictors of subsequent (long-term) mortality. Anxiety and anger were examined by a structured interviews derived from the State-Trait Personality Inventory at a median of 4 days post-MI; patients reported about immediate (0-2 hours pre-MI) and distant (24-26 hours pre-MI) experiences of these emotions. Patients were then followed for up until 10 years after the MI. We tested the hypothesis that: (1) younger age and female sex are associated with a higher likelihood of MI onset preceded (i.e., potentially triggered) by anxiety or anger; (2) the riska of adverse long-term mortality outcomes following MIs that are preceded by high levels of anxiety or anger are higher in young patients and women; and (3) the 10-year mortality rate is elevated in patients with high anxiety and anger levels in the *immediate* (0-2 hours pre-MI) premonitory phase compared to patients with high anxiety and anger levels occurring *distant* from the MI (24-26 hours pre-MI). These data provide important novel information as current research and clinical assessments focus on an individual's psychosocial characteristics in general, rather than focusing on the specific emotional state at the time when the actual MI occurred.

METHODS

Patients

Patients with a documented MI who participated in the Determinants of Myocardial Infarction Onset Study (MIOS) were followed up for 10 years. In total, 3886 MI patients were recruited from 64 centers between 1989 and 1996 to establish potential physical and emotional triggers of MI. Inclusion criteria were: creatine kinase levels above the upper limit of normal for the laboratory at each centre, positive MB isoenzymes, an identifiable onset of symptoms preceding MI (chest pain or other cardiac symptoms), and the ability to complete a structured interview. Eligible patients were identified by reviewing coronary care unit admission reports and patient charts.

After providing informed consent, patients were interviewed using structured forms. Interviews were administered within a median of 4 days after hospital admission (range 0-30 days). The interview for emotional state (anxiety and anger) derived from the STPI, see below) was administered in a sub-cohort of the overall MIOS sample (N=2176/3886=55.9%), comprising the study sample presented in this report. The cohort was prospectively followed for the occurrence of all-cause mortality, using the National Death Index, through December 31, 2007.

The Institutional Review Board of each center approved the protocol, and subsequent approval for the follow-up assessments based on publically available mortality records was obtained from the Beth Israel Deaconess Medical Center Committee on Clinical Investigations.

The present investigation as related to prior MIOS-based publications

Initial reports from this study were based on a subsample of the final full MIOS cohort [3,10]. These early reports were used to document the triggering potential of exposures such as exercise and anger. More recently we examined the long-term predictive value of these emotional experiences for prognosis after the incident MI [31,32]. The paper by Wrenn et al. focused on the emotional data 24-26 hours prior to MI [32] and the research letter by Smeijers et al. [31] provides only a brief evaluation of the 10-year mortality outcomes in MI patients with exercise, anxiety or anger in the 2-hour pre-MI exposure period. The present study expands these findings in three new aspects: (a) the clinical characteristics of MIs immediately (0-2 hours) prior to MI, (b) subgroup that are at disproportionately elevated risk of post-MI mortality during 10 years follow-up; and (c) the differential prognostic value of immediate (0-2 hours pre-MI) vs. distant (24-26 hours pre-MI) emotional states.

Assessment of Anxiety and Anger prior to MI

Trained research staff conducted a standardized interview to obtain information about the time, place and nature of symptom onset, health behaviors (e.g., smoking) and emotional state prior to MI. Patients were asked about several potential triggers, such as physical exertion, anxiety and anger. Patients were asked about immediate experiences during 0-2 hours prior to MI onset and more distant experiences in the 24-26 hour prior to MI (for details of the original study see [3,10,32].

Levels of anxiety and anger prior to MI were assessed using the interviewer-administered subscales of the State-Trait Personality Inventory (STPI) [33] modified to assess short-term exposures prior to MI. Patients reported about the 0-2 hours prior to MI (N=2176) and this information was compared with “distant” anxiety and anger levels during the same time period the day before (24-26 hours prior to MI; 1824/2176 patients (83.8%) had valid data for the distant pre-MI period). Participants were also asked additional questions about anger using an hour-by-hour preceding MI scale designed for this study [10], but these hourly ratings were not obtained for anxiety. This report therefore focuses on the 0-2 hour and 24-26 hour STPI-based interview data for anxiety and anger. Scores ranged from 10 to 40 and were analyzed as continuous variables and dichotomized at the 90th percentile for the primary analyses (consistent with prior reports based on this study [10,31,32] .

Assessment of Demographic and Clinical Characteristics

Patient interviews and medical records were used to collect information about demographics, health behaviors, medical history and medication use. Demographic variables included the primary subgroup variables age and sex, and information about race/ethnicity (coded as white versus "other"), marital status (married versus other). Information was also obtained about educational attainment as an individual level measure of socioeconomic position (<12, 12-14, >14 years of school), median household income as a neighborhood level measure of socioeconomic position (tertiles derived from census block groups) [34,35]. Health behaviors were assessed for smoking status (current, former, never), alcohol consumption (drinks per week), and usual frequency of physical exertion (0, 1-4, ≥5 times per week). Height and weight were self-reported and used to calculate body mass index (BMI: kg/m^2).

Medical records were reviewed for history of previous MI, congestive heart failure, angina, hypertension, diabetes mellitus, other comorbidities (stroke, cancer, respiratory disease and renal dysfunction), peak creatine kinase, and use of thrombolysis at the time of MI. Information was also obtained on patients'use of beta-adrenergic-blocking agents, calcium channel blockers, digoxin, diuretics, lipid-lowering medications and ACE inhibitors at the time of MI.

Outcome Assessment

The National Death Index was used to identify deaths of MIOS participants, and we requested death certificates from state offices of vital records for all probable matches using a validated algorithm that included name, date of birth, sex, race/ethnicity, marital status and state of residence [36]. All participants were censored on December 31, 2007 or date of death, whichever came first. The determination of death was independently verified by three physicians, and disagreements among raters were resolved by discussion. The present study examines the 10-year all-cause mortality rate as the primary outcome variable.

Statistical Analysis

Data are presented as mean ± standard deviation or sample size and proportion as appropriate. We used logistic regression analyses to examine the demographic and clinical characteristics of patients with an MI preceded by negative emotions calculating odds ratios (OR) and 95% confidence intervals (CI). We evaluated the demographics, health behaviors and clinical characteristics and examined separate multivariable models for anxiety and anger prior to MI. First, all predictor variables were tested in separate bivariate models. Then, the analyses were adjusted for age and in the third model all variables were included in the fully adjusted models: adjusting for demographic measures (age, sex, race/ethnicity, marital status, education, income), health behavior-related variables (smoking status, alcohol consumption, BMI, usual physical activity), medical history (previous history of MI, angina, hypertension, diabetes mellitus, other comorbidities) and medication use (beta-adrenergic-blocking agents, calcium-channel blockers, digoxin, diuretics, lipid-lowering medications and ACE inhibitors). Missing values were infrequent (range 0% - 1.8%) except for income (8.9%; see Table 1). For the multivariable models, the median income was imputed for the missing income values and all other cases with missing values (cumulative missing = 3.8%)

were not included. In addition, we explored models when imputing missing values using regression analysis-based imputation, which revealed essentially the same results as the models presented here.

The longitudinal association between anxiety and anger in the 0-2 hours prior to MI with all-cause mortality during follow-up was examined using Cox proportional hazards models. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated adjusted for covariates selected *a priori* based on their plausible relationship with anxiety and anger and/or with post-MI mortality[37]: demographic variables (age, sex, race/ethnicity, marital status, educational attainment, income), health behaviors (smoking status, alcohol consumption, BMI, usual frequency of physical exertion), medical history (history of MI, congestive heart failure, angina prior to MI, hypertension, diabetes mellitus, non-cardiac comorbidities (including stroke, cancer, respiratory disease and renal failure), thrombolytic therapy, peak creatine kinase, and a summary score for medication use (i.e., summing the use of beta-adrenergic-blocking agents, calcium-channel blockers, digoxin, diuretics, lipid-lowering medications, ACE inhibitors). Covariate selection for the subgroup analyses (for age and sex) also used a smaller set of covariates to minimize potential bias of overfitting [37,38] (history of MI, hypertension, smoking status and usual physical activity levels). We tested the assumption of proportional hazards by examining the statistical significance of interaction terms between exposures and the natural logarithm of time in the adjusted model, and no violations of the assumption were observed (anxiety p=0.85, anger p=0.70).

To explore whether anxiety and anger in the 0-2 hours prior to MI onset were associated with mortality independent of anxiety and anger at times outside the critical two-hour exposure period, multivariable and subgroup analyses were conducted. These analyses enabled investigation of whether exposure to an acute potential trigger only, i.e., during the 0-2 hour period prior to MI - and not during the more distant exposure period 24-26 hours prior to MI – uniquely predicted increased long-term mortality rates. Two approaches were used: (a) statistically adjusting for the levels of anxiety and anger 24-26 hours prior to MI; and (b) examining four mutually exclusive subgroups by comparing patients with “sustained/recurrent” high levels of anxiety or anger (i.e., high 0-2 hour as well as high 24-26 hour levels), “immediate” exposure (high 0-2 hour and low 24-26 hour levels; i.e., potentially triggered MI), and “distant” exposure (low 0-2 hour and high 24-26 hour levels) with the non-exposed reference group (low levels during the 0-2 hours prior to MI onset and the 24-26 hour pre-MI).

Subgroup were examined using stratified analyses for the pre-specified potentially high-risk subgroups based on age (<65 years vs. ≥65 versus) and sex. All p-values are two-sided. SAS version 9.3 (SAS Institute, Cary, NC) was used to perform the analyses.

RESULTS

Clinical characteristics of the study population are shown in Table 1. Among 2176 participants (mean age 60.1±12.5 years, 29.2% women), 204 (9.4%) reported high levels of

anxiety and 205 (9.4%) reported high levels of anger in the 2 hours prior to MI. Co-occurrence of high levels of anxiety and anger was observed in 93 participants.

1. Demographic and clinical characteristics of patients with high levels of anxiety or anger in the two hours prior to MI

Table 2 displays the results of the unadjusted, age-adjusted and fully adjusted multivariable logistic regression analyses for MI preceded by anxiety (Table 2.a.) and anger (Table 2.b.). In the unadjusted model, patients reporting high levels of anxiety were younger than patients who did not report high anxiety levels prior to MI (57.2±13.5 vs. 60.5±12.2 years; OR=0.98 per year of age, 95%CI=0.97-0.99). Female sex was associated with reporting high levels of anxiety prior to MI in the unadjusted analysis (OR=1.50, 95%CI=1.11-2.02). The interaction between age and sex for the association with pre-MI anxiety was not statistically significant (p=0.75). When examining other covariates, unadjusted analyses revealed that anxiety prior to MI was also associated with being unmarried (OR=1.39, 95%CI=1.03-1.86), low educational attainment (< 12 vs. ≥14 years, OR=1.48, 95%CI=1.01-2.16) and high usual physical activity (5 episodes or more per week vs. < 1 episode per week OR=1.56, 95%CI=1.06-2.23). Age-adjusted models revealed a similar pattern of results (Table 2.a.). The fully adjusted analyses showed that high levels of anxiety 0-2 hours prior to MI were more likely to occur in younger patients (OR=0.97, 95%CI=0.96-0.99), women (OR=1.79, 95%CI=1.27-2.54), low education (OR=1.60, 95%CI=1.06-2.44), , those who engaged in 5 or more episodes of physical activity per week (OR=1.56, 95%C=1.04-2.35) and in patients with a history of angina prior to admission (OR=1.54, 95%CI=1.05-2.25). (Table 2.a.).

As shown in Table 2.b., high levels of anger prior to MI were associated with younger age (53.4±11.9 vs. 60.8±12.2 years; OR=0.95 per year of age, 95%CI=0.94-0.96). Sex was not related to anger prior to MI and the interaction between age and sex was not statistically significant (p=0.97). Unadjusted analyses indicated that patients who reported anger prior to MI were also more likely to regularly engage in high usual physical activity (≥5 episodes vs. ≤ 1 episode per week OR=1.72, 95%CI=1.18-2.50) and to be current smokers (OR=3.12, 95%CI=2.05-4.74). Medical history and medication use were not associated with high levels of anger prior to MI.

In age-adjusted models, current smoking status (OR=2.11, 95%CI=1.36-3.26) and low educational attainment (< 12 vs ≥14 years; age-adjusted OR=1.63, 95%CI=1.10-2.43) were associated with anger immediately prior to MI onset. In fully adjusted model, the only characteristics that remained associated with high levels of anger 0-2 hours prior to MI were younger age (OR=0.95 per year of age, 95%CI=0.94-0.97) and current smoking status (OR=2.09, 95%CI=1.32-3.32).

2. Subgroups at elevated mortality risk following MI preceded by negative emotions

In total 580 (26.7%) patients died during 10 years follow-up (mean follow-up duration = 3,136 ± 1,049 days; median time until death = 1,710 days). For the full sample, anxiety prior to MI was associated with a higher mortality rate (adjusted HR=1.44, 95%CI=1.09-1.91) in multivariable models, as reported in our previous research letter [32]. Anger prior to MI was also associated with a higher mortality rate (adjusted HR=1.34, 95%CI=0.98-1.82), but this

association was not statistically significant. There was no interaction between pre-MI anxiety and anger in predicting 10-year mortality (p=0.10). Data for continuous anxiety (HR=1.01 per unit, 95%CI=1.00-1.02) and continuous anger (HR=1.01 per unit, 95%CI=0.99-1.03) scores showed parallel results as the results based on the 90% cut-off values. The purpose of the present investigation is to identify high-risk subgroups by examining whether a high level of anxiety or anger immediately prior to MI is a stronger risk factor for 10-year mortality in patients who are relatively young and in female patients.

Table 3 shows analyses stratified by age and sex. There was an 80% higher rate of all-cause mortality among patients 65 years of age and older who reported anxiety in the 0-2 hours prior to MI onset. In contrast, there was no such association among younger patients (p-interaction=0.015). There was no interaction between anger and age in 10-year mortality risk (p interaction=0.81).

In analyses stratified by sex, the association between anxiety or anger with long-term mortality was stronger for women than men, but these differences were not statistically significant (Table 3). The three-way interactions of age x sex x anxiety pre-MI ($p_{unadjusted}$ = 0.44) and age x sex x anger pre-MI ($p_{unadjusted}$ = 0.11) were not significant.

We also explored the interaction terms of the other demographic, health behavior and clinical measures with pre-MI anxiety as predictors of subsequent mortality and did not find evidence for differences in outcome as related to the joint presence or absence of these variables (p interaction > 0.10).

3. Immediate versus distant anxiety and anger prior to MI and long-term mortality

We examined whether anxiety during the critical 2-hour pre-MI exposure period (i.e., the potentially triggered MIs) was independently associated with higher mortality rates compared to anxiety that occurred outside this critical period (i.e., 24-26 hours pre-MI). The correlation between the continuous 0-2 hour and 24-26 hour pre-MI anxiety scores was 0.628 (p<0.001). Anxiety during the “immediate” 0-2 hour prior to MI remained a statistically significant predictor of mortality when adjusting for anxiety at distant 24-26 hour prior to MI (HR=1.43, 95%CI=1.01-2.04). Anger during the 0-2 hour pre-MI period was also associated with all-cause mortality when adjusting for 24-26 hour anger levels but this association was not statistically significant in the fully adjusted model (HR=1.33, 95%CI=0.90-1.96).

We then compared four subgroups of patients with high anxiety in either the 0-2 hours (potentially triggered MI) and/or the 24-26 hours (non-hazard period) prior to MI. In total, 87 patients had *immediate* exposure (i.e., high levels of anxiety only in hours 0-2; potentially triggered MI), 76 were classified as having *sustained/recurrent* anxiety (i.e., high levels of anxiety at both time points), and 91 had *distant* anxiety (i.e., high anxiety levels only in 24-26 hours pre-MI. A total of 1824/2176 (83.8%) patients had valid anxiety data for 24-26 high prior to MI (476 deaths occurred in this group). Table 4 shows that, compared to the reference group with low anxiety levels at both times (n=1570), the 10-year all-cause mortality rate was higher among the immediate exposed group (HR=1.61, 95%CI=1.08-2.40) and the sustained/recurrent high anxiety group (HR=1.69,

95%CI=1.07-2.67), whereas those with distant experiences of anxiety only did not have an elevated mortality rate (HR=1.10, 95%CI=0.70-1.1.73); because of the subgrouping, these analyses were adjusted for a subset of the covariates: age, sex, smoking status, usual physical activity levels, history of MI and hypertension. The interaction between 0-2 hour and 24-26 hour anxiety was not statistically significant (p=0.97). Parallel analyses for anger revealed similar results but the HRs per subgroup did not reach statistical significance, except for sustained anger (Table 4).

DISCUSSION

This study shows that MI preceded by episodes of heightened anxiety or anger occurred more often in relatively young patients. Women were more likely than men to report high anxiety in the two hours prior to MI onset, whereas no sex differences for anger immediately prior to MI were found. High levels of anxiety in the two hours prior to MI onset were associated with a higher rate of all-cause mortality during 10 years follow-up. This association was independent of anxiety in the non-critical exposure period (i.e., high anxiety 24-26 hours prior to MI). Moreover, subgroup analyses showed that the association between high anxiety levels in the two hours prior to MI with post-MI mortality was primarily observed among patients aged 65 and above and not in younger patients. A similar but non-significant pattern was found for high levels of anger immediately preceding MI onset. Thus, although patients aged ≥ 65 experience these emotional precipitants less often than younger MI patients, they have a disproportionately higher rate of all-cause mortality if their MI onset is preceded by high levels of anxiety.

Among the demographic and clinical characteristics, age was inversely related to experiencing both anxiety and anger in the two hours prior to MI. Other factors associated with anxiety at the time of MI were female sex, low education, high usual physical activity, and a history of angina; the only other factor associated with anger at the time of MI was current smoking status (Tables 2.a. and 2.b.). No corrections for statistical Type I error were made, but it is remarkable that prior cardiac history, medication use and cardiovascular risk factors were not associated with anxiety or anger at the time of MI. The primary focus of the present study was on age and sex as factors that may identify vulnerable subgroups for emotional precipitants of MI and we found that age is an important factor to consider. This finding is consistent with prior studies showing that younger individuals experience more negative emotions [21,22], especially in hospitalized individuals [24]. It is possible that young MI patients are more susceptible to pathophysiological changes associated with strong negative emotions because of the lack of coronary collateral supply, thereby increasing the risk of MI when plaque rupture and/or thrombus formation occurs. It is also possible that relatively young patients are exposed to more frequent or severe distressing circumstances during daily life and consequently experience more anxiety and anger. These repeated acute experiences of negative emotions may in part reflect underlying personality factors such as trait anxiety and hostility. The interaction between psychological traits and acute emotional reactivity prior to MI and other acute coronary syndromes requires further investigation.

The observed increased mortality rate in patients with high levels of anxiety in the two hours prior to MI is consistent with a recent report by Arnold et al. [12]. In a study of over 4,000 MI

patients, these investigators found that patients reporting moderate or severe perceived stress at the time of MI had a 42% (95%CI 1.15 to 1.76) higher rate of mortality during two years follow-up compared to those with lower levels of stress. They used a distress measure that assesses an individual's sense of confidence in being able to handle circumstances over the past month. Therefore, these findings may not reflect *acute* distress levels immediately prior to MI onset and may at least partially reflect sustained distress in addition to acute distress. In another study of 662 MI patients no association was found between acute physical or emotional precipitants of MI and mortality during one year follow-up [13]. It is possible that this study was underpowered as a result of the relatively limited number of events during follow-up. Bhattacharyya et al. [39] examined the long-term effects of acute potential triggers in terms of emotional and physical health status. Emotional precipitants of MI were associated with elevated anxiety levels and poor mental health status at 12 and 36 months follow-up. In addition, vigorous exertion in the two hours prior to MI onset predicted impaired physical health status whereas emotional states during that timeframe did not. In our study, heavy physical exertion was not related to the long-term rate of all-cause mortality,[32] whereas anxiety was significantly predictive of 10-year mortality, and the long-term effects of anger in the two hours prior to MI were in the expected direction, but non-significant. It is possible that the relatively adverse prognostic values of pre-MI anxiety vs. pre-MI anger reflects a higher frequency of recurrent anxiety vs. recurrent anger in the post-MI follow-up period, but this needs to be evaluated in future research.

Biobehavioral mechanisms explaining the adverse mortality rate observed in the present study include a higher magnitude and/or frequency of hemodynamic or biological responses to mental stress. Acute psychological stressors are associated with increased cardiac demand and increased coagulability and inflammation, thereby increasing the risk of MI via myocardial ischemia and thrombus formation [17,40,41]. Patients whose MI is preceded by an emotional stressor show impaired stress-induced platelet activation and delayed hemodynamic recovery [42]. Mental stress-induced hemodynamic and blood chemistry responses could therefore partially account for the higher mortality rate in patients whose index MI was preceded by high levels of anxiety.

The present study adds important new information to previous reports based on the MIOS project. Early reports addressed the identification of acute potential triggers of MI [3,10]. More recently, evidence based on this cohort has shown that that anxiety on the day prior to MI (i.e., 24-26 hours pre-MI) was associated with a trend towards a higher rate of all-cause mortality in the following 3 years [32]. In a recent short "research letter" we then showed that more proximate anxiety in the critical 0-2 hour pre-MI hazard period was associated with mortality during 10 years follow-up [31]. The present study further expands this knowledge base by demonstrating that MIs preceded by negative emotions occur more often in young patients (see Tables 2.a and 2.b.) and that the adverse long-term prognosis associated with pre-MI anxiety is primarily observed in patients aged 65 and above. Moreover, we now show that if anxiety occurred *only* in the 24-26 (non-critical hazard) period prior to MI but *not during* the 0-2 hours prior to MI onset, that then the post-MI mortality rates are not higher compared to patients with low levels of anxiety at both time points. This pattern of results indicates the emotional state *at the time of MI onset* (either acute, sustained or recurrent

negative emotions) is associated with an elevated risk of subsequent mortality during long-term follow-up.

There are limitations to this study that require consideration. There may be some misclassification of anxiety and anger because the information was ascertained by retrospective interviews in the days after hospitalization for MI. Retrospective bias (search for meaning) may have resulted in higher reports of negative emotions in the 0-2 hour vs. the 24-26 hour pre-MI period. Although retrospective bias may raise concerns about the construct validity of the emotional state assessments, the finding that these (retrospective) self-reports of anxiety immediately prior to MI have a marked impact on long-term survival is remarkable and clinically important. The assessments of anxiety and anger states may be influenced by psychological traits such as personaltiy factors. Although the analyses for anxiety and anger were adjusted for the 24-26 hours prior to MI onset, this correction may not optimally account for trait levels of these factors. Future studies are needed that assess both acute emotional states as well as traits to better characterize the psychological predictors of adverse post-MI outcomes. We assessed selected common emotional states that have been reported to precede MI (anxiety and anger) and it could be that other immediate precipitants of MI such as despair or sadness, substance abuse, and exposure to cold or pollutants may pose additional risk factors for long-term mortality. Another limitation concerns generalizability because the sample was relatively high educated, patients came from neighbourhoods with above average income, and the original cohort was enrolled in the mid 1990s. We were also specifically interested in the subgroup of premenopausal women [30], but the size of this subgroup (92 women aged ≤ 50 of whom 14 died within 10 years) did not allow reliable analyses for these potentially high-risk patients. Analyses primarily focused on dichotomized anxiety and angre scores and results were less strong when continuous measures were used, which may reflect the scaling properties of the assessment tool or a threshold effect. The present study focused on all-cause mortality and additional studies are needed to examine specific causes of death in addition to all-cause mortality. These limitations are largely outweighed by several strengths of this study, including the detailed assessments of emotional states prior to MI, the longitudinal design with complete mortality data for all participants during 10-year follow-up and the large sample size.

In conclusion, the results of this study suggest that age is inversely related to high levels of anxiety and anger in the two hours immediately prior to MI onset. Female sex was associated with anxiety, but not anger, in the two hours prior to MI. We had expected that the adverse mortality risk associated with acute anxiety would be primarily observed in relatively young MI patients. Instead, patients 65 and older, whose MI was preceded by high anxiety levels, were at elevated risk of subsequent mortality. This information could be useful in clinical practice to identify vulnerable individuals with acute coronary syndromes that are precede by negative emotions. . More knowledge is needed about prolonged episodes of psychological vulnerability such as bereavement, depression and exhaustion [43,44]. Future research on the biobehavioral mechanisms linking physical and psychological states that precede MI to long term mortality may lead to better risk stratification, long-term monitoring and the development of tailored interventions in patients with MI.

Acknowledgments

Funding Sources: This work was supported by a grant HL-120505 from the National Institutes of Health, United States (EM), and by an intramural grant from Center of Research on Psychology in Somatic diseases (*CoRPS*), Tilburg University, The Netherlands (LS and WK). This work was conducted with the support of a KL2/Catalyst Medical Research Investigator Training award (an appointed KL2 award) from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award KL2 TR001100). The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic healthcare centers, or the National Institutes of Health. The funding agencies had no influence on the scientific report in this manuscript.

Role of the Sponsor: No funding organization had any role in the design and conduct of the study; the collection, management, analysis and interpretation of the data; and preparation of the manuscript.

The research presented in this manuscript is original, not published elsewhere or submitted for publication elsewhere.

All coauthors have read the manuscript and agree with the contents and the ICMJE requirements for authorship have been met.

References

1. Nawrot TS, Perez L, Kunzli N, Munters E, Nemery B. Public health importance of triggers of myocardial infarction: a comparative risk assessment. Lancet. 2011; 377:732–40. [PubMed: 21353301]
2. Mittleman MA, Mostofsky E. Physical, psychological and chemical triggers of acute cardiovascular events: preventive strategies. Circulation. 2011; 124:346–54. [PubMed: 21768552]
3. Mittleman M, Maclure M, Tofler G, Sherwood J, Goldberg R, Muller J. Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. N Engl J Med. 1993; 329:1677–83. [PubMed: 8232456]
4. Moller J, Ahlbom A, Hulting J, et al. Sexual activity as a trigger of myocardial infarction.A case-crossover analysis in the Stockholm Heart Epidemiology Programme (SHEEP). Heart. 2001; 86:387–90. [PubMed: 11559674]
5. Muller JE, Mittleman A, Maclure M, Sherwood JB, Tofler GH. Triggering myocardial infarction by sexual activity. low absolute risk and prevention by regular physical exertion. determinants of myocardial infarction onset study investigators. JAMA. 1996; 275:1405–9. [PubMed: 8618365]
6. Mustafic H, Jabre P, Caussin C, et al. Main air pollutants and myocardial infarction: a systematic review and meta-analysis. Jama. 2012; 307:713–21. [PubMed: 22337682]
7. Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. Circulation. 2001; 103:2805–9. [PubMed: 11401936]
8. Mittleman MA, Mintzer D, Maclure M, Tofler GH, Sherwood JB, Muller JE. Triggering of myocardial infarction by cocaine. Circulation. 1999; 99:2737–41. [PubMed: 10351966]
9. Moller J, Hallqvist J, Diderichsen F, Theorell T, Reuterwall C, Ahlbom A. Do episodes of anger trigger myocardial infarction? A case-crossover analysis in the Stockholm Heart Epidemiology Program (SHEEP). Psychosom Med. 1999; 61:842–9. [PubMed: 10593637]
10. Mittleman MA, Maclure M, Sherwood JB, et al. Triggering of acute myocardial infarction onset by episodes of anger. Determinants of Myocardial Infarction Onset Study Investigators. Circulation. 1995; 92:1720–5. [PubMed: 7671353]
11. Steptoe A, Strike PC, Perkins-Porras L, McEwan JR, Whitehead DL. Acute depressed mood as a trigger of acute coronary syndromes. Biological psychiatry. 2006; 60:837–42. [PubMed: 16780810]
12. Arnold SV, Smolderen KG, Buchanan DM, Li Y, Spertus JA. Perceived stress in myocardial infarction: long-term mortality and health status outcomes. J Am Coll Cardiol. 2012; 60:1756–63. [PubMed: 23040574]

13. Brodov Y, Sandach A, Boyko V, et al. Acute myocardial infarction preceded by potential triggering activities: angiographic and clinical characteristics. Int J Cardiol. 2008; 130:180–4. [PubMed: 18068242]
14. Deanfield JE, Shea M, Kensett M, et al. Silent myocardial ischaemia due to mental stress. Lancet. 1984; 2:1001–5. [PubMed: 6149394]
15. Rozanski A, Bairey CN, Krantz DS, et al. Mental stress and the induction of silent myocardial ischemia in patients with coronary artery disease. N Engl J Med. 1988; 318:1005–12. [PubMed: 3352695]
16. Blumenthal JA, Jiang W, Waugh RA, et al. Mental stress-induced ischemia in the laboratory and ambulatory ischemia during daily life. Association and hemodynamic features. Circulation. 1995; 92:2102–8. [PubMed: 7554188]
17. Krantz DS, Kop WJ, Santiago HT, Gottdiener JS. Mental stress as a trigger of myocardial ischemia and infarction. Cardiology Clinics. 1996; 14:271–87. [PubMed: 8724559]
18. Akinboboye O, Krantz DS, Kop WJ, et al. Comparison of mental stress-induced myocardial ischemia in coronary artery disease patients with versus without left ventricular dysfunction. Am J Cardiol. 2005; 95:322–6. [PubMed: 15670538]
19. Krantz DS, Santiago HT, Kop WJ, Bairey Merz CN, Rozanski A, Gottdiener JS. Prognostic value of mental stress testing in coronary artery disease. Am J Cardiol. 1999; 84:1292–7. [PubMed: 10614793]
20. Sheps DS, McMahon RP, Becker L, et al. Mental stress-induced ischemia and all-cause mortality in patients with coronary artery disease: Results from the Psychophysiological Investigations of Myocardial Ischemia study. Circulation. 2002; 105:1780–4. [PubMed: 11956119]
21. Charles ST, Reynolds CA, Gatz M. Age-related differences and change in positive and negative affect over 23 years. J Pers Soc Psychol. 2001; 80:136–51. [PubMed: 11195886]
22. Carstensen LL, Pasupathi M, Mayr U, Nesselroade JR. Emotional experience in everyday life across the adult life span. J Pers Soc Psychol. 2000; 79:644–55. [PubMed: 11045744]
23. Walters P, Barley EA, Mann A, Phillips R, Tylee A. Depression in primary care patients with coronary heart disease: baseline findings from the UPBEAT UK study. PloS one. 2014; 9:e98342. [PubMed: 24922312]
24. Gottlieb SS, Khatta M, Friedmann E, et al. The influence of age, gender, and race on the prevalence of depression in heart failure patients. J Am Coll Cardiol. 2004; 43:1542–9. [PubMed: 15120809]
25. Weissman MM, Klerman GL. Sex differences and the epidemiology of depression. Arch Gen Psychiatry. 1977; 34:98–111. [PubMed: 319772]
26. Gater R, Tansella M, Korten A, Tiemens BG, Mavreas VG, Olatawura MO. Sex differences in the prevalence and detection of depressive and anxiety disorders in general health care settings: report from the World Health Organization Collaborative Study on Psychological Problems in General Health Care. Arch Gen Psychiatry. 1998; 55:405–13. [PubMed: 9596043]
27. Alexander JL, Dennerstein L, Kotz K, Richardson G. Women, anxiety and mood: a review of nomenclature, comorbidity and epidemiology. Expert review of neurotherapeutics. 2007; 7:S45–58. [PubMed: 18039068]
28. Barefoot JC, Peterson BL, Dahlstrom WG, Siegler IC, Anderson NB, Williams RB Jr. Hostility patterns and health implications: correlates of Cook-Medley Hostility Scale scores in a national survey. Health Psychol. 1991; 10:18–24. [PubMed: 2026126]
29. Haynes SG, Levine S, Scotch N, Feinleib M, Kannel WB. The relationship of psychosocial factors to coronary heart disease in the Framingham study. I. Methods and risk factors. Am J Epidemiol. 1978; 107:362–83. [PubMed: 665654]
30. Vaccarino V, Shah AJ, Rooks C, et al. Sex differences in mental stress-induced myocardial ischemia in young survivors of an acute myocardial infarction. Psychosom Med. 2014; 76:171–80. [PubMed: 24608039]
31. Smeijers L, Mostofsky E, Tofler GH, Muller JE, Kop WJ, Mittleman MA. Association Between High Levels of Physical Exertion, Anger, and Anxiety Immediately Before Myocardial Infarction With Mortality During 10-Year Follow-Up. J Am Coll Cardiol. 2015; 66:1083–4. [PubMed: 26314538]

32. Wrenn KC, Mostofsky E, Tofler GH, Muller JE, Mittleman MA. Anxiety, anger, and mortality risk among survivors of myocardial infarction. Am J Med. 2013; 126:1107–13. [PubMed: 24083642]
33. Spielberger, CD. Preliminary manual for the state-trait personality inventory (STPI). Tampa, FL: University of South Floria; 1971.
34. Krieger N, Chen JT, Waterman PD, Soobader MJ, Subramanian SV, Carson R. Geocoding and monitoring of US socioeconomic inequalities in mortality and cancer incidence: does the choice of area-based measure and geographic level matter?: the Public Health Disparities Geocoding Project. Am J Epidemiol. 2002; 156:471–82. [PubMed: 12196317]
35. Krieger N, Chen JT, Waterman PD, Soobader MJ, Subramanian SV, Carson R. Choosing area based socioeconomic measures to monitor social inequalities in low birth weight and childhood lead poisoning: The Public Health Disparities Geocoding Project (US). J Epidemiol Community Health. 2003; 57:186–99. [PubMed: 12594195]
36. Stampfer MJ, Willett WC, Speizer FE, et al. Test of the National Death Index. Am J Epidemiol. 1984; 119:837–9. [PubMed: 6720679]
37. Babyak MA. What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. Psychosom Med. 2004; 66:411–21. [PubMed: 15184705]
38. Steyerberg EW, Eijkemans MJ, Harrell FE Jr, Habbema JD. Prognostic modeling with logistic regression analysis: in search of a sensible strategy in small data sets. Med Decis Making. 2001; 21:45–56. [PubMed: 11206946]
39. Bhattacharyya MR, Perkins-Porras L, Wikman A, Steptoe A. The long-term effects of acute triggers of acute coronary syndromes on adaptation and quality of life. International journal of cardiology. 2010; 138:246–52. [PubMed: 18793809]
40. Muller JE, Abela GS, Nesto RW, Tofler GH. Triggers, acute risk factors and vulnerable plaques: the lexicon of a new frontier. J Am Coll Cardiol. 1994; 23:809–13. [PubMed: 8113568]
41. Dimsdale JE. Psychological stress and cardiovascular disease. J Am Coll Cardiol. 2008; 51:1237–46. [PubMed: 18371552]
42. Strike PC, Magid K, Whitehead DL, Brydon L, Bhattacharyya MR, Steptoe A. Pathophysiological processes underlying emotional triggering of acute cardiac events. Proceedings of the National Academy of Sciences of the United States of America. 2006; 103:4322–7. [PubMed: 16537529]
43. Mostofsky E, Maclure M, Sherwood JB, Tofler GH, Muller JE, Mittleman MA. Risk of acute myocardial infarction after the death of a significant person in one's life: the Determinants of Myocardial Infarction Onset Study. Circulation. 2012; 125:491–6. [PubMed: 22230481]
44. Kop WJ. Somatic depressive symptoms, vital exhaustion, and fatigue: divergent validity of overlapping constructs. Psychosom Med. 2012; 74:442–5. [PubMed: 22685237]

Highlights

- Patients younger than 65 more often a have heart attack triggered by anxiety or anger
- Anxiety and anger in the critical 2-hour period before MI predict long-term mortality
- This high mortality risk holds for immediate (0-2 hr), not distant (24-26 hr) emotions
- Mortality in 10 years after emotion-triggered MI occurs more often in older patients

Table 1

Participant characteristics

	N= 2176
Demographics	
Age	60.1 ± 12.5
Female	636 (29,2%)
Race/ethnicity (white)	1936 (89.0%)
Marital status (Married) [a]	1460 (67.1%)
Education categories [b]	
0 - 12 years	434 (19.9%)
12 - <14 years	910 (41.8%)
≥ 14 years	793 (36.4%)
Income [c]	
Low	559 (25.7%)
Medium	650 (29.9%)
High	772 (35.5%)
Health behaviors	
Smoking Status [d]	
Never	538 (24.7%)
Former	889 (40.9%)
Current	740 (34%)
Alcohol consumption (drinks/wk)	4.6 ± 12.6
BMI (kg/m^2)	27.6 ± 4.9
Physical (high exertion/week)	
None	1605 (73.8%)
1-4	270 (12.4%)
≥5	301 (13.8%)
Medical history	
Myocardial infarction [e]	566 (26.0%)
Congestive heart failure	32 (1.5%)
Angina	510 (23.4%)
Hypertension	923 (42.4%)
Diabetes mellitus	427 (19.6%)
Other non-cardiac comorbidities	115 (5.3%)
Thrombolytic therapy	900 (41.4%)
Peak creatine kinase (U/L. 10^3)	1.5 ± 1.9
Medication use	
Beta-adrenergic blocking agents	464 (21.3%)
Calcium-channel blockers	488 (22.4%)
Digoxin	120 (5.5%)
Diuretics	320 (14.7%)

	N= 2176
Lipid-lowering medications	207 (9.5%)
ACE inhibitors	273 (12.6%)

Background data of 2176 participants in the Myocardial Infarction Onset Study with information about emotional states at 0-2 hours prior to MI who were followed up for 10 years.

[a] 23 missing values (1.1%),

[b] 39 missing values (1.8%),

[c] based on median neighborhood household income derived from tertiles of census block groups; 195 missing values (8.9%),

[d] 9 missing values (0.4%);

[e] 11 missing values (0.5%)

Table 2

a. Association between demographic and clinical characteristics with high levels of anxiety in the 2 hours prior to MI

	Unadjusted		**Age-adjusted**		**Fully adjusted** [a]	
	OR (95%CI)	**p value**	**OR (95%CI)**	**p value**	**OR (95%CI)**	**p value**
Demographics						
Age (per year)	**0.98 (0.96-0.99)**	**<0.001**	-	-	**0.97 (0.96-0.99)**	**0.001**
Sex						
(female vs. male)	**1.50 (1.11-2.02)**	**0.008**	**1.82 (1.33-2.50)**	**<0.001**	**1.79 (1.27-2.54)**	**0.001**
Race/ethnicity						
(white vs. other)	1.31 (0.79-2.17)	0.29	1.41 (0.85-2.34)	0.18	1.64 (0.96-2.81)	0.070
Marital status						
Unmarried vs. married	**1.39 (1.03-1.86)**	**0.030**	**1.47 (1.09-1.98)**	**0.011**	1.33 (0.96-1.84)	0.084
Education						
0-12 vs. ≥ 14 years	**1.48 (1.01-2.16)**	**0.047**	**1.66 (1.12-2.45)**	**0.011**	**1.60 (1.06-2.44)**	**0.027**
12-<14 vs. ≥ 14 years	1.04 (0.74-1.47)	0.80	1.09 (0.60-1.29)	0.63	1.01 (0.71-1.45)	0.95
Income						
Low vs. high	1.21 (0.85-1.74)	0.29	1.36 (0.95-1.97)	0.10	1.02 (0.69-1.53)	0.91
Medium vs. high	0.92 (0.63-1.34)	0.66	0.88 (0.60-1.29)	0.52	0.77 (0.54-1.11)	0.17
Health behaviors						
Smoking status						
Current vs. never	1.45 (1.00-2.10)	0.052	1.20 (0.81-1.78)	0.36	1.22 (0.80-1.86)	0.35
Former vs. never	0.85 (0.58-1.23)	0.42	0.83 (0.56-1.22)	0.34	0.89 (0.59-1.35)	0.59
Alcohol (>75th %)	0.95 (0.68-1.33)	0.73	0.85 (0.60-1.19)	0.34	0.98 (0.68-1.42)	0.92
BMI (per kg/m^2)	1.01 (0.98-1.04)	0.67	1.00 (0.97-1.03)	0.79	0.99 (0.96-1.03)	0.72
Usual physical activity						
<1 vs. ≥ 5 episodes/wk	**1.56 (1.06-2.29)**	**0.023**	1.37 (0.92-2.02)	0.12	**1.56 (1.04-2.35)**	**0.032**
1-4 vs. ≥ 5 episodes/wk	1.35 (0.89-2.05)	0.16	1.17 (0.76-1.80)	0.47	1.29 (0.82-2.03)	0.27
Medical history						
Myocardial infarction	0.91 (0.65-1.27)	0.58	0.98 (0.70-1.37)	0.89	0.85 (0.57-1.28)	0.44
Congestive heart failure	1.00 (0.30-2.21)	1.00	1.08 (0.33-3.60)	0.90	0.97 (0.28-3.42)	0.97
Angina	1.30 (0.94-1.80)	0.11	**1.43 (1.03-1.99)**	**0.032**	**1.54 (1.05-2.25)**	**0.028**

	Unadjusted		**Age-adjusted**		**Fully adjusted** [a]	
	OR (95%CI)	**p value**	**OR (95%CI)**	**p value**	**OR (95%CI)**	**p value**
Hypertension	1.03 (0.77-1.38)	0.83	1.14 (0.85-1.53)	0.40	1.10 (0.78-1.57)	0.57
Diabetes mellitus	1.00 (0.70-1.44)	0.99	1.11 (0.77-1.60)	0.59	1.11 (0.73-1.63)	0.67
Comorbidity	1.13 (0.61-2.10)	0.69	1.26 (0.68-2.34)	0.47	1.28 (0.67-2.44)	0.45
Medication use						
Beta-blockers	1.12 (0.79-1.57)	0.53	1.19 (0.84-1.69)	0.32	1.17 (0.79-1.73)	0.45
CC blockers	1.14 (0.81-1.59)	0.45	1.30 (0.92-1.83)	0.14	1.12 (0.75-1.68)	0.57
Digoxin	0.59 (0.27-1.27)	0.18	0.70 (0.32-1.53)	0.37	0.71 (0.31-1.63)	0.42
Diuretics	0.79 (0.51-1.23)	0.30	0.94 (0.60-1.46)	0.77	0.80 (0.49-1.32)	0.38
Lipid-lowering	0.74 (0.43-1.27)	0.27	0.74 (0.43-1.28)	0.28	0.66 (0.37-1.18)	0.16
ACE inhibitors	1.12 (0.74-1.71)	0.59	1.20 (0.78-1.83)	0.40	1.27 (0.79-2.04)	0.33

b. Association between demographic and clinical characteristics with high levels of anger in the 2 hours prior to MI

	Unadjusted		Age-adjusted		Fully adjusted [a]	
	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Demographics						
Age (per year)	**0.95 (0.94-0.96)**	**<0.001**	-	-	**0.95 (0.94-0.97)**	**<0.001**
Sex (female)						
Female vs. male	0.93 (0.67-1.28)	0.64	1.32 (0.94-1.85)	0.10	1.37 (0.95-1.98)	.094
Race/ethnicity						
White vs. other	1.10 (0.68-1.76)	0.71	1.29 (0.80-2.08)	0.31	1.53 (0.91-2.55)	.11
Marital status						
Unmarried vs. married	1.23 (0.91-1.65)	0.18	1.35 (1.00-1.84)	0.052	1.22 (0.88-1.70)	.23
Education						
0-12 vs. ≥ 14 years	1.26 (0.86-1.84)	0.24	1.63 (1.10-2.43)	0.02	1.41 (0.92-2.17)	.11
12-<14 vs. ≥ 14 years	0.91 (0.63-1.34)	0.66	0.99 (0.71-1.40)	0.97	0.89 (0.62-1.28)	.54
Income						
Low vs. high	1.34 (0.93-1.92)	0.11	1.36 (0.95-1.97)	0.10	1.26 (0.84-1.91)	.27
Medium vs. high	0.92 (0.63-1.34)	0.67	0.88 (0.60-1.29)	0.52	0.93 (0.64-1.35)	.70
Health behaviors						
Smoking status						

	Unadjusted		Age-adjusted		Fully adjusted [a]	
	OR (95%CI)	**p value**	**OR (95%CI)**	**p value**	**OR (95%CI)**	**p value**
Current vs. never	**3.12 (2.05-4.74)**	**<0.001**	**2.11 (1.36-3.26)**	**<0.001**	**2.09 (1.32-3.32)**	**.002**
Former vs. never	1.23 (0.78-1.93)	0.38	1.17 (0.74-1.84)	0.50	1.19 (0.74-1.91)	.48
Alcohol (>75th %)	1.03 (0.74-1.42)	0.88	1.27 (0.93-1.75)	0.14	1.11 (0.78-1.58)	.57
BMI (kg/m^2)	1.00 (0.97-1.03)	0.79	0.97 (0.94-1.00)	0.09	0.98 (0.94-1.01)	.13
Usual physical activity						
<1 vs. ≥ 5 episodes/wk	1.72 (1.18-2.50)	0.005	1.26 (0.85-1.85)	0.25	1.35 (0.90-2.03)	.14
1-4 vs. ≥ 5 episodes/wk	1.31 (0.86-2.00)	0.21	0.94 (0.61-1.46)	0.79	1.04 (0.66-1.66)	.85
Medical history						
Myocardial infarction	0.91 (0.65-1.27)	0.58	1.08 (0.77-1.52)	0.67	1.18 (0.78-1.78)	.45
Congestive heart failure	0.64 (0.15-2.69)	0.54	0.75 (0.17-3.22)	0.70	0.69 (0.15-3.11)	.63
Angina	0.80 (0.56-1.15)	0.22	0.97 (0.67-1.40)	0.88	0.91 (0.60-1.40)	.68
Hypertension	0.90 (0.67-1.20)	0.46	1.11 (0.82-1.50)	0.51	1.21 (0.85-1.74)	.29
Diabetes mellitus	0.86 (0.59-1.25)	0.44	1.09 (0.74-1.61)	0.65	1.25 (0.82-1.90)	.30
Comorbidity	0.71 (0.34-1.47)	0.36	0.89 (0.43-1.88)	0.77	0.95 (0.45-2.04)	.90
Medication use						
Beta blocker	0.71 (0.49-1.05)	0.08	0.81 (0.55-1.20)	0.29	0.74 (0.48-1.15)	.19
CC lockers	0.85 (0.60-1.22)	0.38	1.14 (0.78-1.65)	0.50	1.03 (0.67-1.59)	.88
Digoxin	0.49 (0.21-1.12)	0.10	0.75 (0.32-1.74)	0.50	0.74 (0.30-1.83)	.52
Diuretics	0.79 (0.51-1.22)	0.29	1.17 (0.74-1.83)	0.51	1.22 (0.74-2.03)	.43
Lipid-lowering	0.97 (0.59-1.59)	0.90	0.98 (0.59-1.62)	0.93	1.07 (0.62-1.83)	.82
ACE inhibitors	0.97 (0.62-1.50)	0.88	1.13 (0.72-1.77)	0.59	1.10 (0.66-1.83)	.70

N=2176 for the unadjusted and age-adjusted models; N=2093 for the fully adjusted model (3.8% cumulative missing data)

[a]Adjusted for age, sex, race/ethnicity, marital status, education, income, smoking status, alcoholic drinks per week, BMI, episodes of physical activity per week, medical history (MI, congestive heart failure, angina, hypertension, diabetes mellitus, other comorbidities), medication use (beta blockers, calcium channel (CC) blockers, digoxin, diuretics, hypolipidemics, ACE inhibitors).

Table 3

Association between high levels of anxiety and anger in the 2 hours prior to MI and 10 year all-cause mortality, stratified by age and sex.

homogeneity	Exposed		Unexposed		Hazard Ratio* (95%CI)	p-value	p-
	No. of deaths	Person-Years	No. of deaths	Person-Years			
High Anxiety							
<65 years	21	1267	222	11,020	0.87 (0.55-1.40)	0.55	**0.015**
≥65 years	37	436	300	5,973	**1.80 (1.28-2.54)**	**0.001**	
Men	31	1091	356	12,318	1.39 (0.96-2.02)	0.060	0.58
Women	27	612	166	4,675	**1.64 (1.09-2.49)**	**0.019**	
High Anger							
<65 years	32	1509	211	10,777	1.15 (0.79-1.67)	0.48	0.81
≥65 years	16	278	321	6,131	1.06 (0.63-1.78)	0.83	
Men	30	1,321	357	12,087	1.09 (0.74-1.60)	0.67	0.30
Women	18	466	175	4,821	**1.72 (1.04-2.83)**	**0.034**	

Adjusted for smoking status, episodes of physical exertion per week, history of MI, hypertension,. Age-stratified models were also adjusted for sex and sex stratified models for (continuous) age.

Table 4

The predictive value of anxiety and anger immediately before MI onset (0-2 hours) versus distant from MI onset (24-26 hours) for subsequent mortality during 10 years follow-up sex

	N	No. of Death	Hazard Ratio (95%CI)	p
Anxiety				
Reference	1570	410	1.0	
Distant	91	20	1.10 (0.70-1.73)	0.68
Immediate	87	26	**1.61 (1.08-2.40)**	**0.020**
Sustained/recurrent	76	20	**1.69 (1.07-2.67)**	**0.024**
Anger				
Reference	1553	417	1.0	
Distant	107	20	0.90 (0.57-1.41)	0.63
Immediate	83	20	1.36 (0.86-2.17)	0.19
Sustained/recurrent	79	19	**1.64 (1.02-2.63)**	**0.039**

Subgroups are defined as follows: “sustained/recurrent” = high 0-2 hour as well as high 24-26 hour levels before MI; “immediate” = high 0-2 hour and low 24-26 hour levels; “distant” = low 0-2 hour and high 24-26 hour levels; Reference = low 0-2 hours and 24-26 hour pre-MI.

Analyses adjusted for age, sex, smoking status, usual physical activity level, previous MI, and hypertension.