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Two-Year Prognosis After Acute Coronary Syndrome in Younger Patients: Association with Feeling Depressed in the Prior Year, and BDI-II Score and Endothelin-1

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Abstract

Objective—To examine the effects of depressive symptoms and Endothelin (ET) -1 on 2-year prognosis in younger patients with acute coronary syndrome (ACS). Depression is associated with poor post-ACS prognosis; however, few investigations have focused on younger patients. Importantly, the studies that did emphasize younger patients suggested that the influence of depression on prognosis could be more robust in younger subgroups. The particular links between depression and poor prognosis in younger patients have yet to be definitively determined. ET-1 is a potent endogenous vasoconstrictor that has been previously linked to adverse post-ACS outcomes.

Methods—The sample (n=153) included male (age 50 years) and female (age 55 years) ACS patients. Blood samples for ET-1 assessment were collected within 2–3h of ACS hospital admission. Depressive symptoms were assessed with the Beck Depression Inventory (BDI) II within 2–5 days of admission. The primary outcome was defined as a composite of major adverse cardiovascular events (MACE), including recurrent myocardial infarction, emergent coronary revascularization, and all-cause mortality within 2 years after index admission.

Results—During the follow-up period, 23 patients experienced MACE. Neither the BDI-II score nor ET-1 predicted MACE in unadjusted analyses or in analyses adjusted for demographic characteristics, comorbidities and troponin levels. In the supplementary analyses, feeling depressed in the year preceding ACS predicted MACE.

Conclusions—In this cohort of younger ACS patients, feeling depressed in the year preceding ACS admission predicted MACE in the 2 years after baseline ACS event, while neither the BDI-II score, nor circulating ET-1 level predicted this outcome.

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Keywords

Acute Coronary Syndrome; Depression; Endothelin; Myocardial Infarction; Post-ACS Prognosis; Younger Patients

Introduction

Depression has consistently been independently linked to adverse post-acute coronary syndrome (ACS) events (i.e. myocardial infarction [MI], unstable angina) prognosis [1–4], with a recent investigation suggesting that the influence of depression on prognosis could be more robust in younger subgroups [5]. The particular mechanisms by which depression may contribute to poor post-event prognosis in younger patients require further elucidation; understanding of these mechanisms will facilitate secondary prevention of ACS events in younger patients.

Endothelins (ET) are 21-amino-acid peptides. Endothelin-1 (ET-1) is produced by endothelial cells [6] and activated macrophages [7] and is the most potent endogenous vasoconstrictor [8]. The role of ET-1 following ACS events can be detrimental, and in several studies, circulating ET-1 measured soon after ACS was found to strongly predict adverse post- event prognosis [9–11]. Burg et al demonstrated an association between depression and circulating ET-1 in older patients with chronic stable coronary artery disease (CAD) [12], and in a cohort of younger ACS patients (males < 50 years of age and females > 55 years of age), we have previously shown that depression symptom severity was associated with circulating ET-1 at the time of hospitalization [13]. In the current analyses we report on the 2-year follow-up of this cohort and the contribution of depression and ET-1 at the time of index ACS to subsequent major adverse events.

Methods

Participants

The sample consisted of 153 patients admitted to two tertiary-level, academic hospitals in a large U.S. medical center with a diagnosis of ACS. Patients were enrolled between 2007 and 2011 and were participants of a larger longitudinal investigation that examined the interactive effects of genetic polymorphisms, inflammatory biomarkers, and depression on ACS outcomes. The participants of the larger study were a convenience sample, with patients recruited Monday through Friday during daytime hours. Under the larger investigation, ACS was defined as hospitalization for angina or symptoms suggestive of ACS lasting more than 15 minutes with ultimate diagnosis of MI, unstable angina, or angina requiring emergent coronary revascularization.

Patients with active inflammatory conditions (human immunodeficiency virus, malignancy, hepatic disease or dialysis, surgery or trauma within the previous 2 months, inflammatory bowel disease, sepsis, rheumatoid arthritis, chronic obstructive pulmonary disease, systemic lupus, myocarditis, pericarditis, Crohn's disease or coexisting infections within the previous 2 months as noted in the electronic health record (EHR)) and/or treatment with immunosuppressant medications or systemic steroids, or antibiotic therapy within the last

two months were excluded. The criteria for participation in the present study were: 1) males 50 years of age and females 55 years of age; 2) enrolled into the previously described longitudinal study by July 2011; 3) a completed Beck Depression Inventory (BDI) II screening questionnaire; and 4) an available stored plasma sample for ET-1 analysis. The larger study and the present study were approved by the Committee for the Protection of Human Subjects associated with the recruitment hospitals and affiliated university. Informed consent was obtained from all participants during enrollment into the larger study. At the time of informed consent, all participants were informed that their de-identified plasma samples would be stored indefinitely for use in future research investigations.

Data collection

Patient interviews and EHR review were utilized to obtain information on demographics, previous hospitalization(s), cardiovascular risk factors, and current medication use and medical conditions. Depressive symptoms were measured using two approaches. The first approach was a single screening question: “Have you ever felt sad or depressed much of the time in the past year?” which was asked at the completion of the demographic data collection. The second approach was assessment of the depressive symptoms using the BDI-II questionnaire [14] which was administered by trained research nurses within 2–5 days of index admission. The BDI-II is a 21-item self-report questionnaire designed to assess depression symptom presence and severity. Each of the items in the BDI-II questionnaire describes a symptom characteristic of a depression state, and participants indicate on a 0 to 3 scale the intensity with which they have experienced the specific depressive symptom during the previous 2 weeks including the present day. The total BDI-II score is the sum of all items, and can range from 0 to 63. The BDI-II has been previously used in ACS populations and shown to have high internal consistency reliability [15, 16]. Cronbach’s alpha for the current sample was 0.92.

Blood samples for ET-1 assessment were drawn on average, within 2–3 hours of admission to the emergency department and prior to any coronary revascularization procedure. Samples were stored at 4° C immediately after collection and transported to the University’s School of Nursing’s Biosciences Laboratory. Within 24 hours of collection, the samples were centrifuged and separated; and the plasma layer of each tube was transferred to labeled aliquot tubes and frozen at –80°. The samples remained frozen until analysis. ET-1 assessment was performed at an Atherosclerosis Clinical Research Laboratory located at the Baylor College of Medicine (Houston, TX). ET-1 analysis was conducted via enzyme linked immunosorbent assay (ELISA), using a colorimetric sandwich kit (R&D Systems Inc., Minneapolis, MN). The kit has a sensitivity of 0.207 pg/mL and can be used to measure ET-1 in human plasma samples. Intra-assay and inter-assay coefficients of variation for the current sample were 4.0% and 3.9%, respectively.

The primary outcome was defined as a composite of major adverse cardiovascular events (MACE), including recurrent ACS, emergent coronary revascularization, and all-cause mortality within 2 years after index admission. MACE was ascertained by trained research personnel during annual telephone calls and EHR chart extraction within a 2-year timeframe after baseline data collection.

Statistical Analyses

In the statistical analyses, the BDI-II scores and ET-1 values were treated as continuous variables. Due to the skewed distribution of ET-1 (skewness=3.98, SE=0.96), values were transformed using square root of logarithmic transformed ET-1 – Endothelin-1 Transformed ($ET-1T; ET-1T = \sqrt{\log_{10}(1+ET-1)}$). The transformed variable did not differ significantly from normality under the Shapiro-Wilk test. The effects of the BDI-II score and ET-1T on the primary outcome were examined in simple and multivariable logistic regression models. The multivariable model controlled for factors that may have an impact on post-ACS outcomes, including sex, race, age [5], current smoking [17, 18], diabetes [19], left ventricular ejection fraction (LVEF) [18, 20], and peak troponin levels at the time of index ACS event [21].

Because prior research has described that different depression subtypes – e.g. prior history of depression versus incident depression – are differentially associated with post-ACS outcomes [22–25], we undertook the supplementary analyses to examine the effect of depression history, defined as the positive answer to the question “Have you ever felt sad or depressed much of the time in the past year?” on the primary outcome. Simple and multivariable logistic regression models were utilized for these analyses. As in the primary analyses, we adjusted for sex, race, age [5], current smoking [17, 18], diabetes [19], LVEF [18, 20], and peak troponin levels at the time of index ACS event [21].

Descriptive statistics and multivariable models of ET-1T were examined using SPSS 19 statistical package for Windows (SPSS Inc, Chicago, Illinois). All statistical tests were two-tailed with an alpha level set at 0.05.

Results

The average age of the study participants was 44.6 years (SD=4.98 years) for males and 47.6 years (SD=4.67 years) for females. Females comprised 44.4% of the sample. Forty five percent of the participants were White; 23.5%, Black; 24.2%, Hispanic, and 7.2%, of other race/ethnicity (Table 1). Overall, more than 40% of the participants had a history of previous ACS, almost 36% were active smokers, 60% had a body mass index ≥ 30 , 30% were diabetic, 63% were hypertensive, and 58% were dyslipidemic. With respect to self-reported use of medications, 76% of the patients were taking aspirin, 35% were taking beta-blockers, 45% were taking angiotensin converting enzyme inhibitors, 39% were taking statins, and 16% were taking antidepressants prior to index admission. Almost 27% of the participants reported a prior history of depression diagnosis, and 43% reported feeling depressed in the year preceding their index ACS event. The range of the BDI-II score was 0 – 46 (mean=13.67; SD=10.76; inter-quartile range: 5, 22). The range of ET-1 level was 0.402 pg/mL – 10.00 pg/mL (mean=1.68; SD=1.04; inter-quartile range: 1.09, 2.08).

During the follow-up period, 23 patients (15%) experienced MACE. There were 9 recurrent MIs, 9 urgent coronary revascularizations, and 5 deaths. In the unadjusted analyses, neither the BDI-II score, nor ET-1T level was significantly associated with MACE. Neither the BDI-

II score nor ET-1T level attained significance after the analyses were adjusted for sex, age, race, current smoking, diabetes, LVEF, and peak troponin levels.

As previously noted, we also examined the relationship between feeling depressed in the year preceding the index ACS event and MACE. In the unadjusted analyses, the odds of MACE were significantly higher (OR=4.3; 95% CI: 1.7, 11.2; $p=0.003$) in patients who reported feeling depressed in the year preceding the index ACS event compared to those who did not (Table 2). After adjusting for sex, age, race, current smoking, diabetes, LVEF, and peak troponin levels, the odds ratio of MACE in those who reported feeling depressed in the prior year was 6.6 (95% CI: 1.7, 26.3; $p=0.008$). In these latter analyses, diabetes was also a significant independent predictor of MACE (OR= 8.2; 95% CI: 1.9, 35.7; $p=0.005$).

Table 3 provides select characteristics of the patients who reported feeling depressed in the year preceding the index ACS. Compared to the patients who did not report feeling depressed in the previous year, patients who felt depressed had a higher score on the BDI-II questionnaire ($p=0.000$), were more likely to have been diagnosed with depression ($p=0.002$), were more likely to be currently taking antidepressants ($p=0.02$), and were less likely to have a history of previous ACS. There were no differences with respect to sex or age among the patients who felt depressed in the previous year and those who did not.

Discussion

Evidence accumulated over the last three decades has consistently demonstrated that depression contributes to adverse post-ACS prognosis [1–3]. Two studies in particular have shown that this risk may be particularly pronounced for younger ACS patients. Denollet et al ($n=1823$) found that the cognitive-affective depression symptom cluster independently predicted a composite of recurrent MI and mortality during a mean follow-up of 2.1 years in participants with a mean age of 55 years [5]. Similarly, Barefoot et al (2000) found the impact of depressive affect on up to 19.4-year survival was especially pronounced among younger patients (those ≤ 50 years of age) with established CAD [26]. In that study, a 2-standard deviation difference in negative affect was associated with a relative risk of 1.70 for younger patients and 1.29 for older ones. These findings underscore the importance of identifying the particular mechanisms that increase depressed younger persons' vulnerability to CAD associated morbidity and mortality.

In our previous cross-sectional study of the current sample, depression symptom severity, as determined by the BDI-II score, was associated with circulating ET-1 levels at the time of hospitalization for an ACS event [13]. Hypothesizing that pathological vascular processes may comprise one of the mechanisms by which depression contributes to adverse post-ACS outcomes, in this prospective study we examined the effects of depression and ET-1 on subsequent events. We found that neither BDI-II score nor ET-1 level in the context of the index ACS event predicted MACE in either unadjusted or adjusted analyses.

An interesting finding of this study was that while the BDI-II score did not predict post-ACS prognosis, self-report of feeling depressed during the year preceding the index event was associated with higher odds of MACE. It is possible that patients endorsing depressive

symptoms at the time of hospitalization were experiencing an adjustment reaction to the life-changing event (ACS), rather than true depression. Indeed, prior research has shown that it is persistent depressive symptoms after index ACS that predict subsequent MACE, rather than symptoms that remit within 1–3 months [22, 25]. Unfortunately, we did not assess depressive symptoms in the months after the index ACS event.

It is important to note that younger ACS patients are very different from their older counterparts with respect to clinical and psychosocial characteristics. In our recent investigation (n=1140) [27], younger ACS patients (males 50 years of age and females 55 years of age) were more likely to feel depressed during the year preceding their admission for ACS ($p<0.001$) compared to their older counterparts. In that same study, younger patients were less likely to be dyslipidemic, hypertensive ($p<0.001$ for each), or diabetic ($p=0.025$) than older patients. Others have also found younger ACS patients to be remarkably different from their older counterparts [28–34]. Generally, compared to older patients diagnosed with ACS, younger ACS patients appear to have lower prevalence of hypertension, diabetes, and dyslipidemia and higher prevalence of psychosocial (i.e. depression, anxiety) and behavioral (i.e. smoking, obesity) CAD risk factors. Although genetic predisposition is an important contributor to CAD in younger individuals, the unique psychosocial and behavioral profiles of younger patients undergoing ACS events point to the need for further exploration of the relationship between psychosocial and behavioral factors, coronary events, post-event prognosis, and the mechanisms involved in these links in younger persons.

Limitations

Our study is not without limitations. Depression assessment was not repeated in the 1–3 months post-ACS. Data regarding CAD severity, i.e. single-vessel disease versus multi-vessel disease, were not available, raising a chance of an unanticipated confounding. Although it is worth noting that younger persons generally have low prevalence of multi-vessel disease, [20, 35–37] a substantial percentage of the study participants (40.5%) had a history of previous ACS event. In addition, a significant proportion of the participants had conditions associated with pro-inflammatory state, including obesity (60.1%), dyslipidemia (57.5%), and as mentioned earlier, previous CAD (40.5%). It is possible that the underlying inflammation could have masked the relationship between depression, ET-1 and post-event prognosis in our sample.

While blood samples were collected on average within 2–3 hours after ACS admission, the time period between ACS onset and arrival to the hospital may have varied among the study participants. It has been shown previously that during ACS, ET-1 is secreted in a dynamic fashion, being markedly elevated within hours following MI and peaking at 6 hours [38]. This potential variability in timing of sample collection relative to the ACS onset could have contributed to our results.

The sample size was small, and the participants were recruited from hospitals located in a prominent medical center of a large city. Therefore, the resulted sample may not be entirely

representative of the hospitalized population of younger individuals with ACS, and thus caution should be utilized when generalizing the findings of this investigation.

Summary

In this sample of younger ACS patients, feeling depressed in the year preceding ACS admission predicted MACE in the 2 years after baseline ACS event, while neither the BDI-II score, nor circulating ET-1 level predicted this outcome. The study was limited by sample size and potential effects of time between onset of symptoms and reporting to the emergency department, which would have affected the observed levels of ET-1. Future studies of depression, ET-1, and ACS outcomes would benefit from larger ACS patient samples, assessment of both depression history and current symptoms, and follow-up assessment in the months after the index event.

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Abbreviations

ACE	angiotensin converting enzyme
ACS	acute coronary syndrome
BDI	Beck Depression Inventory
BMI	body mass index
CAD	coronary artery disease
EHR	electronic health records
ET	endothelin
LVEF	left ventricular ejection fraction
MACE	major adverse cardiovascular events
MI	myocardial infarction

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Highlights

- Depression is associated with adverse post-acute coronary syndrome (ACS) prognosis.
- Endothelin (ET)-1 has been previously linked to adverse post-ACS outcomes.
- We examined the effects of depressive symptoms (BDI-II score) and ET-1 levels at the time of hospitalization for ACS, and the self-report of feeling depressed in the year preceding hospitalization for ACS on 2-year prognosis in younger ACS patients.
- Neither the BDI-II score, nor ET-1 predicted prognosis.
- Feeling depressed in the year preceding hospitalization for ACS predicted prognosis.

Table 1**Patient Characteristics**

Variable	Total Cohort (n=153)
Age (males), mean (SD), years	44.6 (4.98)
Age (females), mean (SD), years	47.6 (6.66)
Female (%)	44.4
Race/Ethnicity (%)	
White	45.1
Black	23.5
Hispanic	24.2
Other	7.2
LVEF (%)	
<35	10.3
35–39	2.2
40–54	35.3
55	52.2
Hx of Previous ACS (%)	40.5
Diabetes (%)	30.1
Hypertension (%)	63.4
Dyslipidemia (%)	57.5
Obesity (BMI ≥30) (%)	60.1
Current Smoking (%)	35.9
Medications (%)	
Beta-blockers	34.6
ACE inhibitors	45.1
Statins	39.2
Aspirin	75.8
ET-1, mean (SD), pg/mL	1.68(1.04)
Depression Related Variables	
Depression ever been diagnosed or treated (%)	26.8
Feeling depressed in the prior year (%)	42.7
Currently taking anti-depressants (%)	16.3
BDI-II score, mean (SD)	13.67 (10.76)
Depressive symptom severity, BDI-II (%) and proportion in each group reporting depression feeling in the last year (%)	
Mild	14.4 (54.5)
Moderate	17.6 (73.1)
Severe	9.8 (86.7)

Abbreviations: ACE = angiotensin converting enzyme; BDI = Beck Depression Inventory; BMI = body mass index; ET = endothelin; Hx = history; LVEF = left ventricular ejection fraction; SD = standard deviation

Table 2

Unadjusted and Adjusted Logistic Regression Models

Variable	df	Wald Chi-Square	p-value
Unadjusted model			
Feeling depressed in the prior year	1	8.893	.003
Adjusted model			
Feeling depressed in the prior year	1	7.103	.008
Diabetes	1	8.046	.005
Sex	1	0.016	.900
Age	1	.683	.408
Race	1	1.132	.769
LVEF	3	1.813	.612
Peak Troponin	1	.897	.344
Current Smoking	1	1.406	.236

Abbreviations: LVEF = Left Ventricular Ejection Fraction.

Dependent variable is MACE; Adjusted Model: $p=0.030$, Cox & Snell $R^2 = 0.184$

Table 3

Characteristics of Patients Reporting Depression Feeling in the Year Preceding Index ACS

Variable	Feeling Depressed in the Prior Year		p-value for differences
	Yes	No	
Female (%)	32 (53)	36 (40)	ns
Age, mean (SD), years	47 (6.1)	45 (5.9)	ns
BDI-II score, mean (SD)	20.7 (10.8)	9.0 (7.9)	0.000
Depression ever been diagnosed or treated, count (%)	24 (41.4)	16 (17.8)	0.002
Currently Taking Anti-Depressants, count (%)	15 (25)	10 (11.2)	0.04
Hx of Previous ACS, count (%)	18 (30)	45 (50)	0.02

Abbreviations: ACS = Acute Coronary Syndrome; BDI = Beck Depression Inventory; Hx = history; SD = standard deviation