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Predictive value of depression and anxiety for long-term mortality: differences in outcome between acute coronary syndrome and stable angina pectoris

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ABSTRACT

Background: Since the early 2000s the treatment of choice for an acute myocardial infarction has moved from thrombolytic therapy to primary PCI (pPCI). As a result, the majority of patients undergoing PCI shifted from stable angina pectoris (SA) to acute coronary syndrome (ACS). Additionally the previously observed association between depression and anxiety and long-term outcome in patients who underwent a PCI may have been changed. The main objective of this study was to investigate the predictive value of depression and anxiety for 10-year mortality, in a cohort with post-PCI patients treated for SA versus patients treated for ACS.

Methods: This prospective single center cohort consists of a consecutive series of patients (n = 528) treated with PCI. At 1 month post-PCI, patients completed the Dutch version of the Hospital Anxiety and Depression Scale (HADS).

Results: After adjustment for baseline characteristics depression was associated with higher 10-year mortality post-PCI (HR 1.58 95% Confidence Interval [95% CI] 1.04–2.40). In the ACS population no association between depression and 10-year mortality was found (HR 1.05 95% CI 0.62–1.79), in contrast to the SA population (HR 1.97 95% CI 1.09–3.57). After additional adjustment for anxiety, depression was no longer associated with higher mortality.

Conclusions: Anxiety at baseline was associated with an increased 10-year mortality rate after PCI. Depression was also associated with higher 10-year mortality, however the association disappeared after additional adjustment for anxiety. This finding was more pronounced in patients presenting with SA as compared to those presenting with ACS, which might be a result of the increasing number of ACS patients treated with pPCI.

1. Introduction

Over the past decades, many studies have examined the relation between depression or anxiety and prognosis in patients treated for acute coronary syndrome (ACS). However, since the early 2000s treatment for ACS has moved from thrombolytic therapy to primary PCI (pPCI) and the association between depression or anxiety and long-term outcome has not been thoroughly investigated since then [1–3]. Prevalence rates of depression and anxiety in patients with coronary artery disease (CAD) in general vary from 10% to 50% [4–10]. Targeting psychological symptoms may provide improvements to the prognosis and quality of life in patients with CAD [11].

Depression and anxiety symptoms are associated with an increased mortality risk in post-PCI patients [6,7,12]. Previous research from our group showed a 77% higher 10-year mortality risk in post-PCI patients with depression compared to patients without depression. Moreover, a 50% higher 10-year mortality in anxious patients was found compared to non-anxious patients [7]. This study however, included patients in 2002, the beginning of the drug eluting stent era. At that time pPCI was a much less frequent (14%) indication for PCI than our population (31%) [3,7]. This difference is important as previous studies demonstrated that PCI indication is associated with different cardiovascular morbidity and mortality rates post-PCI [13,14].

In contrast, several other studies suggested that depression was not associated with higher 5-year mortality [9], whereas anxious patients had a lower mortality at 5 years compared to non-anxious patients after PCI [8,10]. Considering these contradictory findings, the main objective of this study was to gain further insight by investigating the predictive value of depression and anxiety for 10-year mortality post-PCI, in a large longitudinal cohort with patients treated in 2006 for stable angina pectoris (SA) versus patients treated for acute coronary syndrome (ACS).

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2. Methods

2.1. Study population

This prospective cohort consists of a consecutive series of CAD patients (n = 786) treated with PCI between February and September 2006 at the Erasmus Medical Centre, Rotterdam. In all patients, the paclitaxel-eluting stent was used as the default strategy. The design of this registry has been published previously [15]. At 1 month post-PCI, all surviving patients were contacted by mail and asked to fill in a standardized questionnaire. In total, 535 (68%) of the eligible 786 patients returned the Hospital Anxiety and Depression Scale (HADS) questionnaire. No clinical or anatomical exclusion criteria were applied. The Medical Ethics Committee of the Erasmus Medical Center reviewed the study (MEC-2005-376) and since this study was not subjected to the Dutch Medical Research Involving Human Subjects Act no approval was required. Moreover, the study was conducted according to the Helsinki Declaration [16]. All patients consented participation in this study.

2.2. Baseline characteristics

Socio-demographic characteristics included gender and age. Clinical characteristics included: cardiac history (previous myocardial infarction (MI), PCI or coronary artery bypass grafting (CABG)), indication for PCI (stable angina pectoris, unstable angina pectoris or acute MI), and CAD risk factors (hypertension, hypercholesterolemia, diabetes mellitus, family history of CAD, multi-vessel disease, self-reported smoking, body mass index (BMI)). All data on baseline and the medical history of patients were collected from the medical records.

2.3. Anxiety and depression

The Dutch version of the Hospital Anxiety and Depression Scale (HADS) was completed by patients at 1 month post-PCI. The HADS has a subscale for depression (HADS-D) and a subscale for anxiety (HADS-A). Each subscale consists of seven items (score range: 0–3). Levels of depression and anxiety were considered clinically relevant at a cut-off score of ≥8 on each subscale [17]. The Dutch HADS has been proven to be a valid and reliable instrument to detect symptoms of depression and anxiety [18].

2.4. Outcome

The endpoint was defined as all-cause mortality at 10 years post-PCI. Post-discharge survival status was collected from the Municipal Civil Registries. Survival status at follow-up was known for 528/535 patients.

2.5. Statistical analysis

Differences in baseline characteristics between patients with depression versus patients without depression, and anxious patients versus non-anxious patients, were examined using the Chi-square test for nominal variables and Student's *t*-test for independent samples for continuous variables. Cumulative mortality curves according to depression and anxiety (i.e. absent versus present, cut-off score of ≥8) were constructed using the Kaplan–Meier method. The log-rank test was used to compare cumulative mortality curves between groups.

Since women are more likely than men to report symptoms of depression [19] and anxiety [20], multivariable Cox regressions were used to test for possible interactions between depression and anxiety, depression and gender, and for anxiety and gender. Symptoms of depression and anxiety often coexist in patients [21]. To analyze the relationship between baseline depression and anxiety, Spearman correlations (r) were performed. Then, to check for multicollinearity in the Cox Regression models, the variance inflation factor (VIF) was calculated through the correlation (R) between depression and the other 'control' predictor anxiety. VIF is calculated as VIF = 1 / (1 − R2). We assumed that if VIF is <2.5, multicollinearity assumption is met. Because of the increasing number of patients treated with pPCI after acute myocardial infarction (AMI) and the widespread adoption of an early invasive strategy for non-ST-elevation ACS, we additionally tested for interaction between: depression and indication for PCI (SA or ACS), and for anxiety and indication for PCI.

Depression was entered in the first step of a Cox regression model to examine the association between depression and all-cause mortality (unadjusted) (Model 1). In a second model, the first model was adjusted for baseline characteristics (Model 2). In a third model anxiety was entered in addition to the previous model (Model 3). In multivariable analysis, we adjusted for socio-demographic characteristics (age and gender) and clinical characteristics (cardiac history, indication for PCI, hypertension, hypercholesterolemia, diabetes mellitus, family history of CAD, multi-vessel disease and smoking). Additionally we adjusted for anxiety and the interaction between anxiety and indication for PCI, which was found in multivariable cox regression. Indication for PCI was dichotomized into stable angina pectoris and acute coronary syndrome. The ACS group included unstable angina pectoris patients and AMI patients. To prevent for overfitting of the adjusted models, covariates selected for the SA and ACS groups were age, gender, diabetes mellitus, smoking and multi-vessel disease. These covariates were selected based on significance in baseline characteristics (Table 2).

Hazard ratios (HRs) with their corresponding 95% confidence intervals were reported for multivariable Cox regression analyses. All results were based on two-tailed tests and a p-value <0.05 was used to indicate statistical significance. All statistical analyses were performed using SPSS for Windows 21.0 (SPSS Inc., Chicago, Illinois, USA).

3. Results

3.1. Patient characteristics

During the study period 528 patients were able and willing to participate in this study. At baseline, 19.7% of patients scored ≥8 on the HADS-D scale and 22.9% scored ≥8 on the HADS-A scale. Patient characteristics of the total sample and stratified by depression and anxiety are presented in Table 1. Mean age in the population was 63 years and 24% was female. Patient characteristics for the SA and ACS group stratified by depression and anxiety are presented in Table 2. The median follow-up for the total patient sample was 9.5 years. The cumulative 10-year mortality for all patients was 25.4%. There was a significant and moderate positive correlation between depression and anxiety (R = 0.49), the calculated

Table 1
Baseline characteristics of patients with depression versus patients without depression and anxious versus non-anxious patients.

	Total	Depression	No depression	P	Anxiety	No anxiety	p
Number of patients (%)	n = 528	n = 104 (19.7%)	n = 424 (80.3%)		n = 121 (22.9%)	n = 407 (77.1%)	
Socio-demographic characteristics							
Age, mean ± SD	63.3 ± 10.8	64.0 ± 10.8	63.1 ± 10.8	0.47	60.9 ± 10.3	64.0 ± 10.8	**0.004**
Female gender (%)	24.1	29.8	22.6	0.13	24.0	24.1	0.98
Cardiac history							
Previous MI (%)	28.6	32.7	27.6	0.30	30.6	28.0	0.58
Previous PCI (%)	25.2	28.8	24.3	0.34	28.1	24.3	0.40
Previous CABG (%)	9.1	11.5	8.5	0.33	14.9	7.4	**0.01**
Indication for PCI							
Stable angina pectoris (%)	43.2	39.4	44.1	0.46	39.7	44.2	0.46
Unstable angina pectoris (%)	25.4	20.2	26.7	0.18	16.5	28.0	**0.01**
Acute myocardial infarction (%)	31.4	40.4	29.2	**0.028**	43.8	27.8	**0.001**
CAD risk factors							
Hypertension (%)	47.7	51.0	46.9	0.46	43.8	48.9	0.33
Hypercholesterolemia (%)	93.8	96.2	93.2	0.26	96.7	92.9	0.13
Diabetes Mellitus (%)	18.6	25.0	17.0	0.06	23.1	17.2	0.14
Family history of CAD (%)	46.8	50.0	46.0	0.46	49.6	45.9	0.48
Multi vessel disease (%)	52.5	51.9	52.6	0.90	46.3	54.3	0.12
Smoking (%)	24.2	34.6	21.7	**0.006**	30.6	22.4	0.06
BMI, mean ± SD	27.8 ± 15.1	27.9 ± 3.8	27.8 ± 16.6	0.96	27.0 ± 3.5	28.1 ± 17.0	0.50
Psychological characteristics							
Depression (%)	19.7				55.4%	9.1%	<**0.001**
Anxiety (%)	22.9	64.4%	12.7	<**0.001**			

CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; BMI, Body Mass Index.

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