European Journal of Preventive Cardiology

Original scientific paper

European Journal of Preventive Cardiology
0(00) 1–7

DOI: 10.1177/2047487315571889
ejpc.sagepub.com

Depression and anxiety symptoms as predictors of mortality in PCI patients at 10 years of follow-up

Milan R van Dijk[1], Elisabeth MWJ Utens[2], Karolijn Dulfer[2], Mustafa NA Al-Qezweny[1], Robert-Jan van Geuns[1], Joost Daemen[1] and Ron T van Domburg[1]

Abstract

Background: Depression has been shown to be an independent risk factor for short-term mortality in patients with coronary artery disease (CAD). There are studies suggesting that depression might also be associated with long-term mortality. Anxiety has also been associated with mortality. This study aimed to further investigate the predictive value of depression and anxiety symptoms on all-cause mortality, 10 years after percutaneous coronary intervention (PCI).

Methods: The study population comprised a consecutive series of CAD patients ($n = 1411$) treated with PCI between September 2001 and October 2002 at the Erasmus Medical Centre, Rotterdam. The Hospital Anxiety and Depression Scale (HADS) was completed by 1112 patients at baseline to assess levels of depression and anxiety. The endpoint was defined as all-cause mortality.

Results: The prevalence of depression and anxiety was 24.8% and 27.7%, respectively. The cumulative all-cause mortality rate in depressed patients was 37% versus 20% in non-depressed patients (log-rank $p < 0.001$). After adjustment, depression remained a predictor of all-cause mortality (hazard ratio (HR) 1.77; 95% confidence interval (CI) 1.36–2.29). Cumulative survival rates did not differ for anxious versus non-anxious patients (log-rank $p = .79$). However, after adjustment, anxiety was associated with an increased risk for all-cause mortality (HR 1.50; 95% CI 1.14–1.98). A sub-analysis showed that cumulative survival rates did not differ for depressed and anxious patients versus depressed but non-anxious patients (log-rank $p = 0.46$).

Conclusions: Depression is associated with an increased risk of 77% for all-cause mortality, 10 years post-PCI, independently of anxiety. Although anxiety was associated with all-cause mortality, it has no additional value in the case of co-occurring depression.

Keywords

Depression, anxiety, coronary artery disease, percutaneous coronary intervention, all-cause mortality

Received 19 October 2014; accepted 19 January 2015

Introduction

The survival of patients with coronary artery disease (CAD) has improved since the introduction of the drug-eluting stent (DES) in the early 2000s.[1] Known cardiac risk factors, such as hypertension, hypercholesterolaemia, diabetes mellitus, rheumatoid arthritis and renal failure, have been found to predict adverse cardiac events.[2–5] Besides these well-known conventional risk factors, psychological factors, such as symptoms of depression and anxiety, might be of similar importance in predicting adverse events post-PCI. Targeting these psychological symptoms may provide possibilities to further improve the prognosis of CAD patients.

The prevalence of depression in patients with CAD ranges from 25% to 50%.[6–9] Meta-analyses have already shown that depression is a risk factor for short-term

[1]Department of Cardiology, Thoraxcentre, Erasmus Medical Centre, The Netherlands
[2]Department of Child and Adolescent Psychiatry/Psychology, Erasmus MC – Sophia Children's Hospital, The Netherlands

Corresponding author:
Ron T van Domburg, Thoraxcentre, Erasmus Medical Centre, Department of Cardiology's Gravendijkwal 230, Room Ba561, 3015 CE Rotterdam, The Netherlands, PO box 55, 3000 WB Rotterdam, The Netherlands.
Email: r.vandomburg@erasmusmc.nl

mortality in CAD patients.[10–13] An increased mortality risk for patients with depressive symptoms after a myocardial infarction has been described, up to 5 years of follow-up.[14–16] Unfortunately, relatively little research into the impact of depression on long-term mortality (>5 years) has been done.[17,18]

In contrast to a wealth of data on the relationship between depression and outcome, much less is known on the association between anxiety and mortality. One meta-analysis on the prognostic association of anxiety after myocardial infarction showed a 36% increased risk of adverse cardiac outcomes. Regarding all-cause mortality, anxiety was associated with an almost 50% higher short-term mortality.[19] However, literature on the association between anxiety and long-term mortality is lacking.

Considering the previous indications that depression and anxiety might be risk factors of long-term mortality, this prospective study aims to further investigate the predictive value of both depression and anxiety symptoms on long-term mortality, i.e. 10 years after percutaneous coronary intervention (PCI).

Methods

Inclusion

This prospective cohort consists of a consecutive series of CAD patients ($n = 1411$) treated with PCI between September 2001 and October 2002 at the Erasmus Medical Centre, Rotterdam. The design of this registry has been published previously.[20] At 6 months post-PCI (defined as baseline) all patients received a standardized questionnaire. Assessment of 6 months post-PCI was chosen to ascertain a stable medical condition.[21] In total, 1112 (78.8%) of the eligible 1411 patients returned the Hospital Anxiety and Depression Scale (HADS) questionnaire at baseline. All patients were prospectively followed. No clinical or anatomical exclusion criteria were applied. This study was not subject to the Dutch Medical Research Involving Human Subjects Act. Approval from the local research ethics committee to conduct this prospective follow-up study was not required at the time of enrolment. Moreover, the study was conducted according to the Helsinki Declaration.[22] All patients consented to participation in this study.

Baseline characteristics

Socio-demographic characteristics included age and gender. Clinical characteristics included cardiac history (previous myocardial infarction (MI), coronary artery bypass grafting (CABG) surgery or PCI), indication for PCI (stable angina pectoris, unstable angina pectoris or acute MI), CAD risk factors (hypertension, hypercholesterolaemia, diabetes mellitus, family history of CAD, multi-vessel disease (multi-vessel disease vs. single-vessel disease), self-reported smoking, body mass index (BMI)) and medication use (aspirin, calcium-antagonists, beta-blockers, oral nitrates, diuretics, angiotensin-converting enzyme (ACE)-inhibitors, statins and psychopharmaceuticals, which comprised antidepressants and anxiolytics). Information on clinical variables was collected at the time of the index PCI and at baseline and recorded in the institutional database.

Anxiety and depression

The Dutch version of the HADS was completed by patients at baseline. 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.[23] The Dutch HADS has been proven to be a valid and reliable instrument to detect symptoms of anxiety and depression.[24]

Endpoint

The clinical endpoint was defined as all-cause mortality. Mortality status was ascertained yearly by contacting the Civil Registry. As a result, all patients had a follow-up duration between 10 and 11 years. Follow-up duration was truncated at 10 years in the analyses. Survival status was known in 99.1% of patients.

Statistical analyses

Group differences between depressed and non-depressed, and anxious 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 survival 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 survival curves between groups. Univariable and multivariable Cox regression models were used to examine the predictive value of depression and anxiety on all-cause mortality. Covariates were forced into the model. In multivariable analysis, we adjusted for socio-demographic characteristics (age and gender) and clinical characteristics (cardiac history, indication for PCI, hypertension, hypercholesterolaemia, diabetes mellitus, family history of CAD, multivessel disease, self-reported smoking and medication).

Symptoms of depression and anxiety often coexist in patients.[25] Furthermore, women are more likely than men

Table 1. Baseline characteristics of depressed versus non-depressed patients and anxious versus non-anxious patients.

	Total	Depression	No depression	*p*	Anxiety	No anxiety	*p*
Number of patients (%)	*n* = 1112	*n* = 276 (24.8%)	*n* = 836 (75.2%)		*n* = 309 (27.8%)	*n* = 803 (72.2%)	
Socio-demographic characteristics							
Age, mean ± SD	62.4 ± 11.0	63.4 ± 11.6	62.0 ± 10.8	.07	61.0 ± 11.4	62.9 ± 10.8	**.01**
Female gender	27.9%	37.0%	24.9%	**<.001**	40.1%	23.2%	**<.001**
Cardiac history							
Previous MI	38.2%	38.8%	38.0%	0.8	37.2%	38.6%	0.7
Previous PCI	21.7%	29.0%	19.3%	**.001**	25.9%	20.0%	**.03**
Previous CABG	11.3%	14.5%	10.3%	.06	11.7%	11.2%	0.8
Indication for PCI							
Stable angina pectoris	50.0%	54.7%	48.4%		53.1%	48.8%	
Unstable angina pectoris	35.7%	33.7%	36.4%		32.7%	36.9%	
Acute myocardial infarction	14.3%	11.6%	15.2%		14.2%	14.3%	
CAD risk factors							
Hypertension	40.4%	43.8%	39.3%	0.2	43.7%	39.2%	0.2
Hypercholesterolaemia	80.3%	79.0%	80.7%	0.5	78.0%	81.2%	0.2
Diabetes mellitus	14.0%	18.5%	12.6%	**.01**	16.8%	13.0%	0.1
Family history of CAD	29.5%	25.0%	31.0%	.06	32.0%	28.6%	0.3
Multi-vessel disease	53.1%	58.0%	51.4%	.06	55.7%	52.1%	0.3
Smoking	31.3%	33.7%	30.5%	0.3	37.5%	28.9%	**.006**
BMI, mean ± SD	26.8 ± 3.8	27.1 ± 4.0	26.7 ± 3.7	0.3	27.1 ± 4.1	26.7 ± 3.6	0.2
Medication							
Aspirin	94.8%	93.4%	95.3%	0.2	94.1%	95.1%	0.5
Calcium-antagonists	50.8%	52.2%	50.4%	0.6	50.5%	50.9%	0.9
Beta-blockers	66.0%	60.6%	67.8%	**.03**	60.6%	68.1%	**.02**
Oral nitrates	14.8%	17.5%	13.9%	0.1	16.6%	14.1%	0.3
Diuretics	14.9%	17.9%	13.9%	0.1	15.3%	14.7%	0.8
ACE-inhibitors	31.9%	32.1%	31.8%	0.9	31.3%	32.1%	0.8
Statins	72.8%	65.3%	75.3%	**.001**	67.4%	74.9%	**.01**
Psychopharmaceuticals	30.2%	27.9%	31.0%	0.3	29.8%	30.4%	0.8
Psychological characteristics							
Depression					63.8%	9.8%	**<.001**
Anxiety	27.8%	71.4%	13.4%	**<.001**			

p values adjusted for statistical significance.
HR, Hazard Ratio; CI, Confidence Interval; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CAD, coronary artery disease.

to experience symptoms of depression[26] and anxiety.[27] Therefore, additional multivariable Cox regressions were used to test for possible interactions between depression and anxiety; depression and gender; and anxiety and gender. In addition, a sub-analysis was performed to evaluate the predictive value of depression (D) and anxiety (A) combined on 10-years all-cause mortality. Patients were categorized into four groups: no psychological symptoms (D−A−); anxiety but no depression (D−A+), depression but no anxiety (D+A−); depression and anxiety (D+A+). Hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs) were reported for multivariable Cox regression analyses. All results were based on two-tailed tests and a *p*-value <.05 was used to indicate statistical significance. All statistical analyses were performed using SPSS for Windows 21.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Patient characteristics

The final sample consisted of 1112 patients (28% female; mean age 62 years). The prevalence of depression was 24.8% (276/1112) (Table 1). The prevalence of anxiety was 27.8% (309/1112).

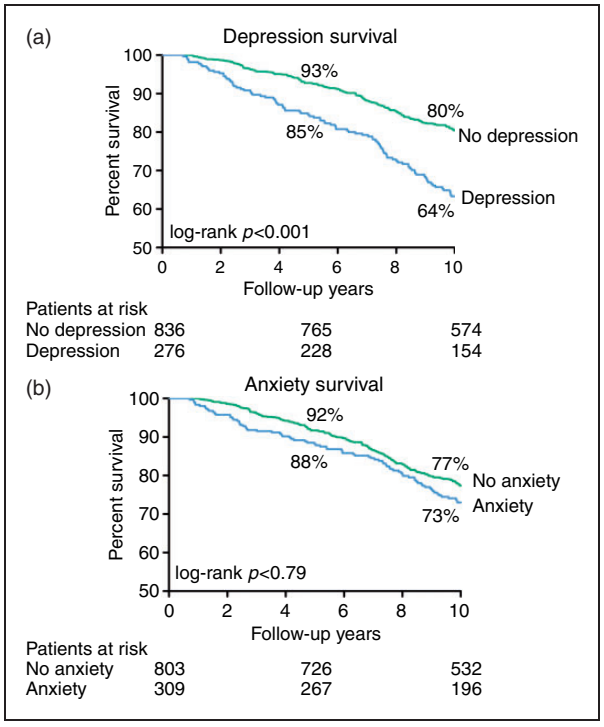

Figure 1. Cumulative survival curves of (a) depressed versus non-depressed patients; (b) anxious versus non-anxious patients.

Depression and all-cause mortality

The median follow-up was 10.6 years (range 10.0–11.2). The cumulative all-cause mortality was 15% versus 7% at 5 years and 36% versus 20% at 10 years in depressed versus non-depressed patients, respectively (log-rank $p < .001$; Figure 1). Depression was a predictor of higher all-cause mortality (HR 2.11; 95% CI 1.65–2.69). After adjustment for baseline characteristics, depression remained an independent predictor of all-cause mortality (HR 1.77; 95% CI 1.36–2.29; Table 2). Although the percentage of female patients was significantly higher in the group of depressed patients (37%) than in the group of non-depressed patients (25%), no interaction between gender and depression was found. A separate multivariable Cox regression testing for possible interactions also did not show an interaction between depression and anxiety.

Anxiety and all-cause mortality

Cumulative survival rates did not differ for anxious versus non-anxious patients (log-rank $p = 0.79$; Figure 1). Unadjusted, no association with all-cause mortality was found (HR 1.23; 95% CI 0.97–1.63). However, after adjustment for baseline characteristics, multivariable Cox regression analysis showed an increased risk for all-cause mortality (HR 1.50; 95% CI 1.14–1.98). Although the percentage of female patients was significantly higher in the group of anxious patients (40%) than in the group of non-anxious patients (23%), no interaction between gender and anxiety was found. As mentioned before, there was no interaction between anxiety and depression.

Table 2. Multivariable Cox regressions of depression and anxiety.

	Depression		Anxiety	
	HR	95% CI	HR	95% CI
Depression	1.77	1.36–2.29		
Anxiety			1.50	1.14–1.98
Socio-demographic characteristics				
Age	1.08	1.07–1.10	1.09	1.07–1.10
Female gender	1.47	1.10–1.96	1.47	1.09–1.98
Cardiac history				
Previous MI	1.27	0.98–1.66	1.28	0.98–1.66
Previous PCI	1.37	1.03–1.82	1.38	1.04–1.84
Previous CABG	1.12	0.80–1.57	1.11	0.80–1.58
Indication for PCI	0.97	0.81–1.17	0.96	0.80–1.16
CAD risk factors				
Hypertension	1.19	0.92–1.54	1.19	0.92–1.54
Hypercholesterolaemia	1.03	0.73–1.46	1.10	0.78–1.55
Diabetes mellitus	1.29	0.93–1.78	1.31	0.95–1.81
Family history of CAD	0.96	0.70–1.30	0.92	0.68–1.26
Multi-vessel disease	1.12	0.85–1.47	1.13	0.86–1.48
Smoking	1.41	1.04–1.89	1.44	1.07–1.94
Medication				
Aspirin	0.65	0.40–1.06	0.64	0.40–1.04
Calcium-antagonists	1.27	0.93–1.74	1.28	0.94–1.75
Beta-blockers	0.81	0.62–1.05	0.80	0.61–1.04
Oral nitrates	1.22	0.89–1.67	1.25	0.91–1.71
Diuretics	1.31	0.96–1.78	1.34	0.98–1.83
ACE-inhibitors	1.19	0.90–1.56	1.18	0.90–1.55
Statins	0.65	0.47–0.90	0.61	0.44–0.85
Psychopharmaceuticals	0.92	0.65–1.28	0.91	0.65–1.28

Multivariable Cox regressions were adjusted for age, gender, previous MI, previous PCI, previous CABG, indication for PCI, hypertension, hypercholesterolemia, diabetes mellitus, family history of CAD, multi-vessel disease, self-reported smoking, cardiac medication and psychopharmaceuticals, comprising antidepressants and anxiolytics.

Depression and anxiety combined

Cumulative survival rates did not differ for depressed and anxious patients versus depressed but non-anxious patients (log-rank $p = 0.46$), or for anxious but non-depressed patients versus patients without psychological symptoms (log-rank $p = .07$) (Figure 2). Both groups that included patients with symptoms of depression showed an increased risk for all-cause mortality, while patients with only symptoms of anxiety showed no significant difference in risk for all-cause mortality when compared with patients without these

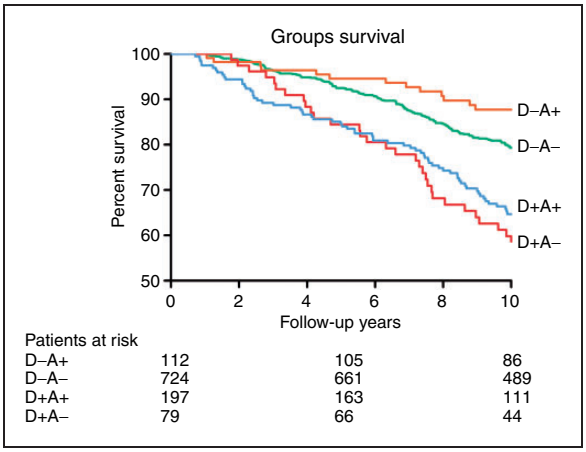

Figure 2. Cumulative survival curves of patients categorized into four groups: no psychological symptoms (D−A−); anxiety but no depression (D−A+); depression but no anxiety (D+A−); depression and anxiety (D+A+). Cumulative survival rates did not differ for D+A+ versus D+A− (log-rank $p = .46$) or for D−A+ versus D−A− (log-rank $p = .07$).

Table 3. Cox Regression of depression and anxiety combined.

	HR	95% CI
D−A− (No depression, no anxiety)	1.00	reference
D−A+ (No depression, anxiety)	.62	.36–1.05
D+A− (Depression, no anxiety)	2.22	1.52–3.25
D+A+ (Depression, anxiety)	1.90	1.43–2.53

Patients were categorized into four groups: no psychological symptoms (D−A−); anxiety but no depression (D−A+); depression but no anxiety (D+A−); depression and anxiety (D+A+).

psychological symptoms (Table 3). The 95% CIs of patients with depression and anxiety (D+A+) and patients with depression but no anxiety (D+A−) completely overlap (1.43–2.53 versus 1.52–3.25). Therefore, their HRs can be interpreted as indicating similar results.

Discussion

Symptoms of depression were associated with an almost two-fold higher risk of mortality in PCI patients after 10 years of follow-up. Furthermore, symptoms of anxiety also were associated with an increased risk of 50% higher 10-year mortality.

Our sub-analysis on the combined effect of depression and anxiety indicates that depression seems to be the main contributor to long-term mortality. It also indicates that the presence of anxiety does not influence all-cause mortality in the case of co-occurring symptoms of depression.

The strengths of our study comprise the prospective study design, the large sample size, the absence of clinical or anatomical exclusion criteria, and the follow-up duration of 10 years. To our knowledge, this is the first study to evaluate the independent predictive value of both depression and anxiety in PCI patients with a follow-up of 10 years.

The findings on depression are in concordance with earlier published studies that found an association between depression and all-cause mortality.[17,18,28] With a 77% increased risk at 10 years post-PCI, it is clear that depression is a risk factor for long-term mortality in PCI patients. Our results support the recently published statement regarding depression by the American Heart Association (AHA).[29] The AHA conducted a systematic review on depression and poor prognosis among patients with acute coronary syndrome (ACS), concluding that health organizations should consider depression as an official risk factor for poor prognosis after ACS.

Our results indicate that symptoms of anxiety at baseline are predictive of long-term mortality in patients post-PCI. This is not surprising, considering the fact that anxiety and depression have a shared component. The 'Tripartite Model of Anxiety and Depression' suggests that anxiety and depression have a common background, both stemming from the 'negative affectivity' concept.[30] Anxiety may also accelerate different direct and indirect processes involved in the pathogenesis of cardiovascular diseases, such as lifestyle risk factors and myocardial perfusion.[31] The literature on anxiety and mortality in CAD patients consists of mixed conclusions. While a recent study found no association between anxiety and all-cause mortality[32] and another claimed that anxiety reduced mortality and major adverse cardiovascular events 5 years post-PCI,[33] our study found similar results to those of a meta-analysis.[19] However, as shown by our sub-analysis, anxiety disappears as a predictor of mortality when symptoms of depression are also present.

In this study, the impact of important life events (e.g. conflicts or serious problems in the family, at work, etc.) on depression and anxiety could not be investigated. Future research should also include the impact of stressful life events on depression and anxiety and their consequences.

Depressed patients seem to use statins less than non-depressed patients (65% versus 75%). The same can be said of anxious patients versus non-anxious patients (67% versus 75%). One would also expect a higher percentage of statin use than 73% in PCI patients. This can be explained by the fact that widespread use of statins started after the publishing of the Scandinavian Simvastatin Survival Study (4S) results

in 1994.[34] Since then, the percentage of patients using statins has increased over time. Due to our inclusion period, from September 2001 to October 2002, the percentage of statin use in our study is lower than would be expected nowadays. The lower statin use in depressed patients and anxious patients might partly explain the higher mortality risk of these patients. However, we correctly adjusted for the use of statins in our multivariable analyses.

A limitation of our study is that, due to missing data, cardiovascular mortality could not be used as an endpoint in the analyses besides all-cause mortality. Another limitation is the possibility of selection bias. At baseline, 299 patients did not return the questionnaire. Perhaps symptoms of depression and anxiety were more frequent in these non-responders.

Conclusion

Our study shows that both depression and anxiety are independently associated with an increased risk of 77% and 50%, respectively, for all-cause mortality 10 years post-PCI. However, in the case of co-occurring depression and anxiety, anxiety disappears as a predictor of mortality. Depression and anxiety should be measured in PCI patients in poor health in order to optimize treatment. Future research should be aimed at investigating the effects of psychological interventions proven to be effective in targeting symptoms of depression and anxiety in patients suffering from these risk factors.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

None declared.

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