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Anxiety enhances the detrimental effect of depressive symptoms on health status following percutaneous coronary intervention

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Abstract

Objective: We examined whether anxiety has incremental value to depressive symptoms in predicting health status in patients undergoing percutaneous coronary intervention (PCI) treated in the drug-eluting stent era. **Methods:** A series of consecutive patients (n=692) undergoing PCI as part of the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital registry completed the Hospital Anxiety and Depression Scale at 6 months and the Short-Form Health Survey (SF-36) at 6 and 12 months post-PCI. **Results:** Of 692 patients, 471 (68.1%) had no symptoms of anxiety nor depression, 62 (9.0%) had anxiety only, 59 (8.5%) had depressive symptoms only, and 100 (14.5%) had co-occurring symptoms. There was an overall significant improvement in health status between 6 and 12 months post-PCI (P<.001); the interaction effect for time by psychological symptoms was also significant (P=.003). Generally, patients with co-occurring symptoms reported significantly poorer health status compared with the other three groups (Ps <.001). Patients with co-occurring symptomatology were also at greater risk of impaired health status on six of the eight subdomains of the SF-36 compared with the other three symptom groups, adjusting for baseline characteristics and health status at 6 months. **Conclusion:** Patients with co-occurring symptoms of anxiety and depression reported poorer health status compared with anxious or depressed-only patients and no-symptom patients, showing that anxiety has incremental value to depressive symptoms in identifying PCI patients at risk for impaired health status treated in the drug-eluting stent era.

Keywords: Anxiety; Depressive symptoms; Drug-eluting stents; Health status; Percutaneous coronary intervention

Introduction

The impact of depression on health outcomes has been examined extensively in patients with cardiovascular disease, with depression being associated with increased mortality [1,2], impaired health status [3], and declines in health status [4]. Hence, not surprisingly, depression is the first psychosocial factor to gain risk factor status on par with traditional biomedical factors [5]. By contrast, there has been less interest in anxiety, and available evidence on the impact of anxiety on mortality is conflicting [6–11]. Although anxiety has been shown to predict other health outcomes, such as health status [7–10], little is known about the impact of anxiety in combination with depression as a predictor of impaired health status. Health status is gaining increasing recognition as an important endpoint, and the study of health status and its determinants was recently advocated as a means by which to enhance patient-centred care and to bridge the gap between research and clinical practice [12].

Evidence shows that anxiety and depression frequently co-occur [13–17]. Not only does anxiety precede the onset

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of depression [14], but co-occurring anxiety and depression has also been associated with greater severity of emotional distress [15,16] and poor response to treatment [17] in psychiatrically depressed patients. In contrast, the impact of co-occurring anxiety and depression has received far less attention in cardiac patients. Previous studies in these patients have either examined the separate impact of anxiety and depression [7–10] or the effect of a composite of distress on health status [11].

Prior to the introduction of drug-eluting stents, restenosis following percutaneous coronary intervention (PCI) has been shown to have a negative impact on health status in some [18,19] but not in all studies [20]. However, given that the use of drug-eluting stents has led to a significant reduction in the risk of restenosis and the need for revascularisation [21–23], the health status of patients treated with PCI may have generally improved, thereby perhaps minimising the impact of psychological factors on health status. To date, no study has examined the role of anxiety and depression as predictors of health status in patients treated with PCI in the drug-eluting stent era.

The purpose of the current study was to examine whether anxiety provides added value to depressive symptoms in predicting health status in PCI patients treated in the drug-eluting stent era. We investigated whether patients with co-occurring symptoms of anxiety and depression had more impaired health status as compared to patients with no symptoms or symptoms of anxiety or depression alone.

Methods

Study design and participants

Unselected patients (n=875; 71% response rate) undergoing PCI as part of the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry participated in the current study. Details of the RESEARCH registry study design [24] and the psychological substudy have been published elsewhere [25]. In brief, the registry was designed to evaluate the efficacy of the sirolimus-eluting stent. For this purpose, no patients were excluded based on clinical or anatomical criteria in order to represent patients seen in daily clinical practice. Later analyses have shown that 68% of the RESEARCH patients would not qualify for inclusion in clinical trials due to their more complex medical profile [26].

Surviving patients at 6 and 12 months post-PCI were asked to complete a set of psychological questionnaires. Clinical variables were also obtained at 6 months. Assessment at 6 months was chosen to ensure that patients were in a stable medical condition. A similar approach has been adopted in other studies [27–29]. Moreover, psychological symptoms evaluated at the time of the PCI have been shown to be a poor indicator of later psychological morbidity [30]. Only patients (n=692) who had a score on the Short-Form Health Survey (SF-36) at both 6 and 12 months post-PCI qualified for inclusion (Fig. 1). Nonresponders on the SF-36 at 6 and 12 months were more likely to have had a previous PCI compared with responders (32% vs. 23%; P=.03), but no other differences were found between responders and nonresponders on baseline characteristics.

The local medical ethics committee approved the study protocol, and the study was conducted in accordance with the Helsinki Declaration. Every patient provided written informed consent.

Materials

Demographic and clinical variables

Demographic variables included sex and age. Clinical variables were prospectively collected at the time of the index procedure and included prior myocardial infarction (MI), prior PCI, prior coronary artery bypass graft (CABG) surgery, sirolimus-eluting stent or bare metal stent implantation, multivessel disease, hypertension, dyslipidemia, diabetes mellitus, renal impairment, smoking status, and cardiac medication [aspirin, beta-blockers, calcium antagonists, nitrates, angiotensin-converting enzyme (ACE) inhibitors, and statins].

Anxiety and depressive symptoms

Anxiety and depressive symptoms were assessed with the 14-item Hospital Anxiety and Depression Scale (HADS) [31]. Seven items contribute to each of the two subscales and are answered on a 4-point Likert scale from 0 to 3 (score range, 0–21). A cutoff score ≥8 for both subscales may be used to quantify patients with likely anxiety and depressive

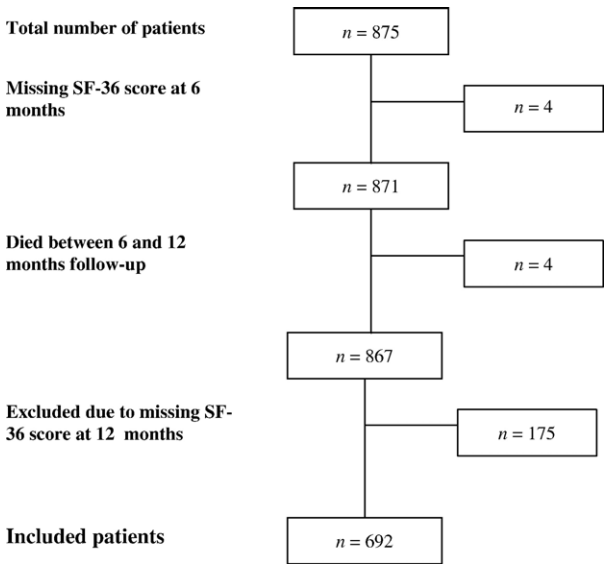

Fig. 1. Overview of patient selection for the current study.

symptomatology, as this cutoff yields an optimal balance between sensitivity and specificity [32]. The HADS is a valid and reliable instrument [32] and has been shown to predict mortality in patients referred for exercise testing [33]. The HADS was administered 6 months post-PCI.

Health status

Health status was assessed with the generic SF-36 that comprises eight health status subdomains, i.e., Role Physical Functioning, Role Emotional Functioning, Physical Functioning, Mental Health, Vitality, Social Functioning, Bodily Pain, and General Health [34]. Scale scores are obtained by summing the items together within a domain, dividing this outcome by the range of scores and then transforming the raw scores to a scale from 0 to 100. A higher score on the SF-36 subdomains represents better functioning, with a high score on the Bodily Pain scale indicating freedom from pain. The scale has good reliability, with Cronbach's alpha ranging from .65 to .96 for all subscales [35]. The SF-36 was administered 6 and 12 months following PCI.

Statistical analyses

Prior to statistical analyses, four psychological symptom groups were created on the basis of anxiety and depressive symptoms at 6 months, using a standardized cutoff ≥8 to indicate likely symptomatology [32]: (1) no symptoms, (2) anxiety, (3) depressive symptoms, and (4) co-occurring symptoms. The chi-square test (Fisher's exact test when appropriate) was used to compare the four psychological symptom groups on baseline characteristics. A post hoc Bonferroni correction was applied to all tests to adjust for multiple comparisons with $P<.003$ (0.05/17) indicating statistical significance. Analysis of variance (ANOVA) for repeated measures was used to assess the impact of the four psychological symptom groups on health status over time, using the SF-36 subscales as continuous scores. A post hoc Bonferroni correction was also used for this analysis to determine statistical significance between the four psychological symptom groups. Multivariable logistic regression analyses were performed to investigate the impact of psychological symptoms on health status, using the no-symptom group as reference group. Prior to these analyses, the subdomains of the SF-36 were dichotomised, with the lowest tertile indicating impaired health status. Others have also advocated dichotomisation of health status measures in order to enhance clinical interpretability [36]. In the multivariable analyses, we adjusted for sex, age ≥60 years, sirolimus-eluting or bare metal stent implantation, prior cardiac history, recent cardiac event (MI, PCI, and CABG occurring between 6 and 12 months post-PCI), multivessel disease, hypertension, dyslipidemia, diabetes, renal impairment, smoking, and health status at 6 months. All tests were two tailed. Odds ratios (ORs) with 95% confidence intervals (CIs) are reported. All statistical analyses were performed using SPSS 12.0.1 for Windows.

Results

Patient characteristics stratified by psychological symptoms

Baseline characteristics stratified by the four psychological symptom groups are presented in Table 1. Of 692 patients, 471 (68.1%) had no symptoms of anxiety or depression, 62 (9.0%) had anxiety only, 59 (8.5%) had depressive symptoms only, and 100 (14.5%) had co-occurring symptoms. Patients with depressive symptoms were generally older (age ≥60 years) than the other three symptom groups, whereas patients with anxiety were more likely to smoke. No other statistically significant differences were found between the four groups on demographic and clinical risk factors and cardiac medication based on a

Table 1
Patient characteristics stratified by psychological symptoms at 6 months (presented as percentages)

	No symptoms ($n=471$)	Anxiety ($n=62$)	Depressive symptoms ($n=59$)	Co-occurring symptoms ($n=100$)	P[a]
Demographics					
Females	25	34	27	42	.005
Age ≥60 years	59	32	71	52	<.001
Clinical variables					
Sirolimus-eluting stent	39	55	34	46	.05
Prior cardiac history[b]	52	50	63	48	.33
Recent cardiac event[c]	5	8	14	7	.08
Multivessel disease	51	45	56	55	.56
Hypertension[d]	36	44	29	48	.04
Dyslipidemia[e]	80	79	83	79	.93
Diabetes mellitus[d]	12	15	17	20	.13
Renal impairment[f]	31	31	34	36	.76
Current smoking[g]	29	48	24	41	.001
Medication					
Aspirin	97	95	93	95	.39
Beta-blockers	98	98	98	97	.89
Calcium antagonists	47	44	54	49	.67
Nitrates	8	18	7	14	.02
ACE inhibitors	26	15	25	29	.20
Statins	69	65	63	62	.46

[a] A post hoc Bonferroni correction was applied to all tests to adjust for multiple comparisons, with $P<.003$ (0.05/17) indicating statistical significance.
[b] MI, CABG, or PCI prior to the index PCI.
[c] MI, CABG, or PCI between 6 and 12 months post-PCI.
[d] Present if being treated for the condition.
[e] Total cholesterol levels >240 mg/dl or on lipid-lowering medication.
[f] Indicated by creatinine clearance <61 ml/min.
[g] Based on self-report.

significance level of $P<.003$ that was applied to adjust for multiple comparisons.

Health status at 6 and 12 months

There was a main effect for time, with ANOVA for repeated measures revealing a significant improvement in health status between 6 and 12 months post-PCI [$F(1,688)=24.910$; $P<.001$]. The interaction effect for time by psychological symptoms was also significant [$F(3,688)=4.671$; $P=.003$]. This indicates that improvement in health status varied according to psychological symptom group, with the depressive symptomatology group and the co-occurring anxiety and depression group generally improving more than the no-symptomatology and anxious group (Fig. 2). Of note, the four symptom groups differed markedly on the health status subdomains of the SF-36 [$F(3,688)=159.018$; $P<.001$], with all post hoc comparisons being significant ($P<.001$) except for the comparison between groups with anxiety vs. depressive symptoms only ($P=.27$) (Fig. 2). For all subdomains of the SF-36, patients who suffered from co-occurring symptoms of anxiety and depression reported significantly lower health status compared with the other three groups. Similarly, patients with depressive symptoms only reported lower health status compared with patients with anxiety (except for vitality and bodily pain). The no-symptom group reported the best health status of all groups. This pattern was consistent both at 6 and 12 months. Patients with co-occurring symptoms scored 50 or lower on all eight health status subdomains of the SF-36 at 6 months and on five of the eight subdomains at 12 months, bearing in mind that the possible score range for the subdomains is 0–100.

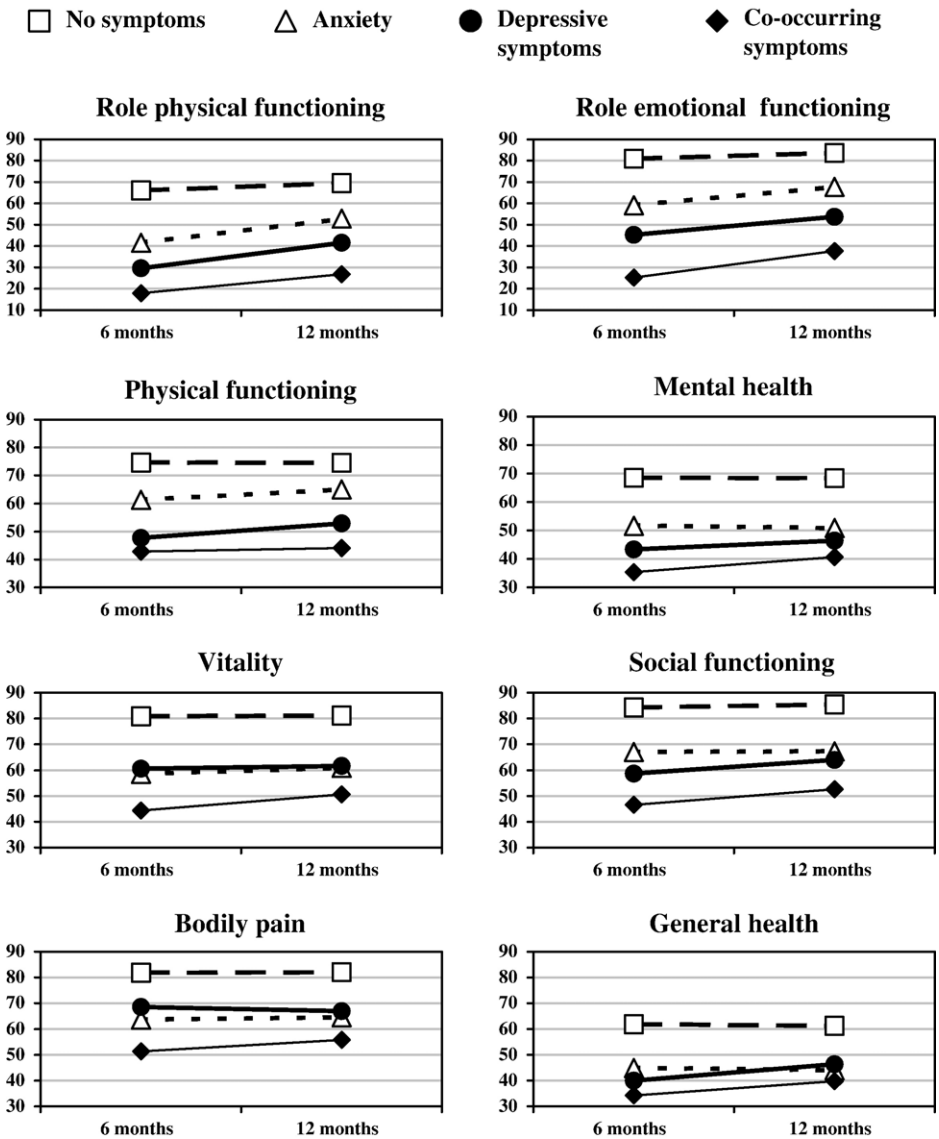

Fig. 2. Health status at 6 and 12 months stratified by psychological symptoms at 6 months. ANOVA for repeated measures (univariable analysis); a high score indicates better health status, with a high score on bodily pain representing absence of pain.

Independent impact of psychological symptoms on health status at 12 months

In multivariable logistic regression analyses, patients who had co-occurring symptoms of anxiety and depression were at increased risk of experiencing impaired health status compared with patients with no symptoms, adjusting for demographic and clinical factors and health status at 6 months (Table 2). For six of the eight subdomains of the SF-36, the risk to patients with co-occurring symptoms was larger than that to patients with depressive symptoms alone (Table 2). The largest differences in risk between patients with co-occurring symptoms and patients with depressed symptomatology were found on Role Physical Functioning (OR 4.06 vs. OR 2.13), Role Emotional Functioning (OR 4.87 vs. OR 2.70), and Vitality (OR 8.33 vs. OR 5.79). This indicates that anxiety has incremental value to depressive symptoms when wanting to identify patients with impaired health status. Other independent predictors of impaired health status were female sex, age ≥60 years, sirolimus-eluting stent implantation, prior cardiac history, recent cardiac event, renal impairment, multivessel disease, and health status at 6 months, depending on the health status subdomain in question (results not shown).

Table 2
Independent predictive value of psychological symptoms on health status at 12 months[a]

Health status subdomain	Psychological symptoms[b]	OR	[95% CI]	*P*
Role Physical Functioning	Anxiety	1.92	[1.04–3.57]	.04
	Depressive symptoms	2.13	[1.14–3.97]	.02
	Co-occurring symptoms	4.06	[2.35–7.02]	<.001
Role Emotional Functioning	Anxiety	2.38	[1.20–4.72]	.01
	Depressive symptoms	2.70	[1.40–5.19]	.003
	Co-occurring symptoms	4.87	[2.74–8.65]	<.001
Physical Functioning	Anxiety	1.63	[0.77–3.48]	.20
	Depressive symptoms	1.95	[0.90–4.22]	.09
	Co-occurring symptoms	3.80	[1.92–7.53]	<.001
Mental Health	Anxiety	2.17	[1.14–4.14]	.02
	Depressive symptoms	3.94	[2.00–7.78]	<.001
	Co-occurring symptoms	3.63	[2.03–6.48]	<.001
Vitality	Anxiety	4.53	[2.34–8.77]	<.001
	Depressive symptoms	5.79	[3.01–11.15]	<.001
	Co-occurring symptoms	8.33	[4.32–16.06]	<.001
Social Functioning	Anxiety	3.52	[1.90–6.53]	<.001
	Depressive symptoms	6.49	[3.37–12.50]	<.001
	Co-occurring symptoms	6.09	[3.41–10.85]	<.001
Bodily Pain	Anxiety	2.49	[1.32–4.70]	.005
	Depressive symptoms	2.68	[1.42–5.05]	.002
	Co-occurring symptoms	3.42	[1.98–5.91]	<.001
General Health	Anxiety	3.12	[1.66–5.86]	<.001
	Depressive symptoms	1.71	[0.90–3.22]	.10
	Co-occurring symptoms	3.19	[1.87–5.47]	<.001

[a] Multivariable analyses with adjustment for sex, age ≥60 years, sirolimus-eluting or bare metal stent implantation, prior cardiac event, recent cardiac event, multivessel disease, hypertension, dyslipidemia, diabetes mellitus, renal impairment, current smoking, and health status at 6 months.

[b] Reference group had neither symptoms of anxiety nor depression.

Discussion

To our knowledge, this is the first study to examine the impact of co-occurring symptoms of anxiety and depression on health status in patients undergoing PCI in general and in the drug-eluting stent era in particular. We found that patients with co-occurring symptoms reported a significantly poorer health status on six of the eight subdomains of the SF-36 compared with patients with depressed symptoms only or no depression.

Previous studies have found depression and anxiety to exert separate and independent detrimental effects on health status [7–11]. In the current study, we found that patients with co-occurring symptoms of anxiety and depression reported significantly poorer health status compared with patients with anxiety or depressed symptoms only or no symptoms, adjusting for demographic and clinical factors and health status at 6 months. These differences were not only statistically significant but also clinically relevant with patients with co-occurring symptoms scoring 50 or lower on a scale from 0 to 100 on all eight health status subdomains of the SF-36 at 6 months and on five of the eight subdomains at 12 months. Although patients with depressive symptomatology also were at increased risk of impaired health status compared with the anxious and no-symptom groups, their risk was lower on six of the eight subdomains than that for patients with co-occurring symptoms. Co-occurring symptoms of anxiety and depression have also been associated with greater severity of emotional distress [15,16] and poor response to treatment [17] in other patient groups and in the general population [37]. Taken together, these results show that anxiety enhances the detrimental effect of depressive symptoms on health status.

Consistent with other studies, we found a general improvement in health status between 6 and 12 months post-PCI [10,38]. Although one previous study showed that the deleterious effects of anxiety and depression on health status remained stable over time [10], in the current study, we found a significant interaction effect for time by psychological symptoms, indicating that the symptom groups had different rates of improvement. Although these improvements were somewhat larger in the depressive symptomatology and co-occurring symptom groups compared with the anxious only and no-symptom groups, neither of the former groups experienced clinically significant improvements (>10 points) in health status. An explanation for the improvements in the depressive and co-occurring symptom groups relative to the other two groups may be that their health status scores were relatively low already at 6 months; in other words, in these two groups there was still room for improvement over time, whereas the anxious and no symptom groups at 6 months may already have reached a plateau since they had higher scores.

The results of the current study have implications for research and clinical practice. Anxiety and depression should be studied in concert, as patients with co-occurring

symptoms report significantly poorer health status compared with patients with anxiety or depressive symptoms alone. Future studies are warranted that investigate whether patients with co-occurring symptoms may also be at greater risk of adverse prognosis.

This study has some limitations. Patients who died between 0 and 6 months post-PCI did not have the opportunity to complete the questionnaires, which may have biased our results, as the sickest patients were excluded. However, several have advocated that baseline is not an optimal time point to assess psychological symptoms and health status in PCI patients, as they are not medically stable at this point in time [27–30]. Second, the results may not be generalisable to the total sample due to the relatively low response rate on questionnaires. Third, we had no information on other psychiatric diagnoses, the use of psychopharmaca, treatment by a psychiatrist, or demographic variables (e.g., marital status) that may potentially have had an influence on symptoms and health status. Nevertheless, strengths of the study were the multiple assessments of health status and that patients represented those seen in daily clinical practice, as no exclusion criteria were applied based on clinical presentation. Research conducted in the "real world" has been advocated as a means by which to bridge the gap between research and clinical practice [4].

In conclusion, patients with co-occurring symptoms of anxiety and depression reported poorer health status compared with anxious or depressed-only or no-symptom patients. More importantly, health professionals frequently under-recognise the role of anxiety in depressed outpatients [39] and in cardiac patients [40]. Symptoms of anxiety may be persistent in cardiac patients, but only one out of three anxious cardiac patients are asked about such symptoms [40]. The present findings indicate that anxiety has incremental value to depressive symptoms in predicting impaired health status in PCI patients treated in the drug-eluting stent era. As recommended in a recent paper reporting on the high prevalence of psychiatric disorders in patients with stable heart disease [13], it seems timely for research and clinical practice to address this issue of co morbidity and its potential consequences for health status and prognosis.

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