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Differential Predictive Value of Depressive Versus Anxiety Symptoms in the Prediction of 8-Year Mortality After Acute Coronary Syndrome.

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Differential predictive value of depressive versus anxiety symptoms in the prediction of 8-year mortality following acute coronary syndrome

[Anhedonia and feeling slowed, but not other depressive or anxiety symptoms, predict 8-year mortality in persons with acute coronary syndrome]

Running title: Anhedonia, feeling slowed and mortality in ACS

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Abstract

Objective: Both depression and anxiety and been associated with poor prognosis in patients with acute coronary syndrome (ACS). However, certain symptoms, and how they are measured, may be more important than others. We investigated 3 different scales to determine their predictive validity in a national sample.

Methods: Patients with ACS (N=598) completed either the Hospital Anxiety and Depression Scales **(HADS-A, HADS-D; N=316)** or the Beck Depression Inventory-Fast Screen (BDI-FS; **N=282**). Their all-cause mortality status was assessed at 8 years.

Results: **During follow-up 20% (121/598) of participants died**. Cox proportional hazards modelling showed that the HADS-D was predictive of mortality (Hazard Ratio [HR]=1.11, 95% CI 1.04–1.19), and this association **remained significant after** adjustment for major clinical/demographic factors. The HADS-A (HR=0.96, 95% CI 0.85–1.09), and the BDI-FS (HR=0.99, 95% CI 0.91–1.08) were not. **The following depression items from the HADS-D predicted mortality: "I still enjoy the things I used to enjoy" (HR=1.38, 95% CI 1.05-1.82), "I can laugh and see the funny side of things" (HR=1.48, 95% CI 1.11-1.96), "I feel as if I am slowed down" (HR=1.66, 95% CI 1.24-2.22) and "I look forward with enjoyment to things" (HR=1.36, 95% CI 1.08-1.72).**

Conclusions: Depressive symptoms related to lack of enjoyment or pleasure and physical or cognitive slowing, as measured by the HADS-D, predicted all-cause mortality over 8 years in patients with ACS. Other depressive and anxiety symptoms did

not. Whether symptoms of distress predict prognosis in ACS seems to be dependent on the measures and items used.

Keywords: Depression; mortality; coronary heart disease; prognosis; anhedonia; anxiety

Acronyms

ACS = acute coronary syndrome

BDI-FS = Beck Depression Inventory – Fast Screen

CI = confidence interval

HADS = Hospital Anxiety and Depression Scale

HADS-A = Hospital Anxiety and Depression Scale – anxiety subscale

HADS-D = Hospital Anxiety and Depression Scale – depression subscale

HR = Hazard ratio

Introduction

Depressive and anxiety symptoms have consistently been shown to predict poorer outcomes in patients with acute coronary syndrome (1, 2). However, randomised trials have failed to show any cardiovascular benefit from the treatment of depressive symptoms (3). Therefore, more recent studies on depression have begun to critique the heterogeneous concept of major depressive disorder, and unpick different symptoms as being more 'cardiotoxic' than others (4-7).

The most commonly reported finding is that clusters of 'somatic/affective' symptoms of depression predict prognosis, but that cognitive/affective symptoms do not (4, 5). Recently, Carney and Freedland (5) described several limitations with this literature on somatic versus cognitive depressive symptoms which need to be addressed. They concluded that depression (overall), and not specific symptom subtypes, was the most appropriate explanation for elevated rates of morbidity and mortality in persons who report depressive symptoms. However, they did not take account of at least three studies which suggested that anhedonia may be more important than either somatic or cognitive symptoms of depression (6, 8, 9). We first speculated on the importance of anhedonia due to one study on persons with ACS which showed that the Hospital Anxiety and Depression Scale (Depression subscale; HADS-D), predicted one-year mortality, whereas the Beck Depression Inventory – Fast Screen (BDI-FS) did not (8). As the HADS-D focusses mainly on anhedonia, we concluded that anhedonia was especially important for cardiovascular prognosis. Subsequently, Davidson et al.

showed specifically that anhedonic symptoms, either scale-assessed or interviewer-rated, predicted cardiovascular prognosis, even when controlling for somatic symptoms of depression (9).

However, our initial study was underpowered, with a low one-year mortality rate (8). Furthermore, the effect sizes for both the BDI-FS and HADS-D scales were not significantly different in post-hoc analyses. It is therefore possible that longer-term follow-up could demonstrate that both scales predict mortality equivalently. Indeed, this would be expected if depression, and not specific depressive symptoms, predict prognosis (5). Furthermore, it is unknown whether long-term prognostic ability of the HADS-D survives adjustment for symptoms of anxiety. We report eight-year follow-up data from a previously published cohort to test these assumptions.

Methods

Participants:

The methods have been described in detail previously (8). In brief, all centres nationally admitting ACS patients recruited patients to a study of treatments for ACS (10). After ethical approval, hospitals distributed the HADS (n=19) or the BDI-FS (n=19), as per random assignment. Consecutive ACS patients were recruited by hospital staff **and provided informed consent. Patients then** completed either scale during hospitalisation, and demographic and clinical data were obtained from hospital charts. Mortality outcomes were assessed via a national registry during August 2011.

Measures:

The HADS is a commonly used 14-item instrument to assess symptoms of anxiety (7-items) and depression (7-items) in hospitalised samples (11). The BDI-FS is a brief, 7-item version of the full-length BDI, which assesses sadness, anhedonia and cognitive symptoms of depression (12). Both scales attempt to minimise the possible over-inflation of depression scores by omitting somatic symptoms, and have god sensitivity and specificity for identifying major depression when adopting recommended thresholds (>7 for HADS-D and HADS-A, >3 for BDI-FS) (13, 14). For each scale, items are scored in a 0-3 format, yielding total scale scores of 0-21.

Analyses

As data clustered within hospitals, Huber-White robust variance estimation commands were used in Stata version 12.0 to adjust standard errors. The X^2-test or Student's t-test was used to assess differences between HADS and BDI-FS groups, as appropriate. Pearson's correlation showed the relationship between HADS subscales. Cox proportional hazards regression estimated hazard ratios (HRs) for all-cause mortality. Scales were analysed as continuous **and dichotomous** variables, **using** recommended thresholds, **and these thresholds** were used for drawing Kaplan-Meier curves. Demographic and clinical variables were investigated as predictors of mortality, and were used for co-variate adjustment. Adjusted model 1 used demographic variables along with length of hospital stay as a proxy indicator of disease severity. Model 2 adjusted for all variables except the following: total cholesterol (too many missing values), prior revascularisation, prior myocardial infarction or prior unstable angina (these correlated with or are subsets of prior ACS, which was included in the model).

Results

Baseline characteristics are shown in Table 1, stratified by group. The HADS was completed by 316 participants, with the BDI-FS being completed by 282. Total cholesterol was the only variable which showed a difference between groups. The HADS-D and HADS-A were significantly correlated ($r=0.55$, $p<0.001$), and previous research suggests these formed a single dimension (15).

Table 1 about here

At 8 years, 20.2% (121/598) of participants had died, but there was no difference in mortality rate between those who completed the HADS or those who completed the BDI-FS (OR=1.05, 95% CI 0.65-1.67, p=0.853). Univariate predictors of mortality are shown in Table 1.Of the demographic and clinical variables, only prior myocardial infarction or prior revascularisation did not predict outcome. Mortality was not predicted by scoring above threshold on either depression scale, or the individual BDI-FS or HADS-A scales. Only the HADS-D scale predicted outcome, and this association remained when adjusting for the HADS-A (HR=1.17, 95% CI 1.08-1.27, $p<0.001$). Fig 1 shows the survival curves.

Fig 1 about here

When adjusting for other co-variates, scoring above threshold on either depression scale became significant (Table 2). However, this association was driven by the HADS-D subscale, as the HADS-D remained a significant predictor of prognosis in both multivariate models. **These findings were unchanged when scales were analysed as dichotomous variables.**

Table 2 about here

We conducted item-level analysis to determine which components of the scales were predicting outcomes (Table 3). For the HADS-D, anhedonic symptoms, as well as feeling slowed, were predictive of mortality. No items from the HADS-A or BDI-FS were associated with outcomes.

Discussion

The present study shows that only symptoms of anhedonia and feeling slowed, but not other depressive or anxiety symptoms, predict prognosis in persons with ACS. This supports previous work in that symptoms of anhedonia were predictive of outcomes, and that the HADS-D scale was predictive of outcomes, but the BDI-FS was not (6, 9). It also adds to this work as the association between the HADS-D and 8-year mortality survived adjustment for HADS-A, despite the high correlation between these scales, and the fact that they may be better seen as a single dimension (15, 16). This may suggest that, for cardiovascular prognosis, the dimension of distress may be less important than particular symptoms within a dimension. Previous theoretical work has suggested a tripartite model of distress (17), incorporating a general dimension of distress, but also core symptoms representing either depression (anhedonia) or anxiety (autonomic arousal). Our findings support this model, in terms of these general and core symptoms of distress, but extend it in the cardiovascular sphere in that anhedonia appeared to be pertinent for prognosis, but other symptoms of general distress were not. While recent findings suggest that anxiety is predictive of cardiovascular prognosis (2), it may be that most of the symptoms assessed by the HADS-A are not particularly cardiotoxic.

Therefore, in contrast to recent comment (5), the present findings do suggest that certain depressive symptoms are more important than others. If depression *per se* was important for prognosis, then the BDI-FS should have predicted at least some levels of

increased risk – especially since it has excellent sensitivity and specificity for major depression (14). The present study showed no association, and the direction of the association was negative for 4 of the six items. However, the fact that the anhedonia item from the BDI-FS did not predict outcomes is in contrast to the above conclusions. Although this item was not associated with outcomes, its effect size was in the predicted direction. One reason for this may be the language used, or the manner in which the items are scored. The HADS had higher average scores for its subscales, and this may indicate that it is more sensitive to lower threshold levels of symptoms of distress. The BDI-FS, however, leads to very skewed data, with the majority scoring zero on the anhedonia item. The BDI-FS item may not therefore be sensitive enough to capture low levels of anhedonia, which seems to be prevalent even in those not reporting high levels of distress (18), possibly because it is a symptom that patients do not fear reporting (5). Future research investigating this item should supplement it with other items assessing anhedonia. As outlined by Davidson et al. (9), anhedonia has specifically been associated with behavioural (e.g. sleep, appetite) and biological mechanisms (e.g. elevated catecholamine levels, disrupted inflammatory processes and circadian rhythms) which are purported to explain the association between depression and cardiovascular disease. Importantly, as anhedonia exists in other psychological disorders and general distress (18, 19), it is possible that it may explain the association with other disorders and cardiovascular prognosis (9).

We cannot rule out the possibility that culture may affect the reported findings (20). It is possible that the Irish population may be more responsive to the more colloquial

questions of the HADS, and therefore may be more likely to respond to such questions. If this is the case, it may be that researchers investigating the association between depressive symptoms and prognosis should use scales with predictive validity in their own setting.

That the symptom of feeling slowed predicted prognosis, alongside anhedonic symptoms, is particularly intriguing. While this item may refer to fatigue, it is also possible that it could also be interpreted to mean feeling cognitively slowed. Cognitive decline has been associated with cardiovascular disease (21, 22), and further research into this possibility is warranted.

The study has a number of limitations. We cannot rule out other factors that may explain the association between the HADS-D and prognosis, despite the fact that the hospitals were randomised to these scales, and the fact that there was no difference in mortality rate between groups. For example, left ventricular function was not recorded, and has been shown in some studies to attenuate the depression-outcomes association (23), and somatic symptoms of depression were not measured. Furthermore, patients only competed one of the scales, however, we have shown similar findings in a one-year follow-up of a different sample where patients completed both the HADS-D and BDI-FS (6). The use of independent samples also limits the study in that it prevents direct comparison of each scale and adjustment for each other, and biases to null findings by reducing study power. There is also the possibility that the effect of anhedonia are

accounted for by their association with somatic symptoms, which were not assessed in the present study. While this was not shown to be the case in another study (9), a mixture of dissatisfaction/anhedonia has tended to load on a somatic factor in other research (4, 24).

Other constructs, such as fatigue and vital exhaustion, have also been associated with cardiovascular prognosis (3, 25, 26). Given the current scientific interest in depressive subtypes in cardiac patients (5, 25-28), it is important to critically evaluate the overlap between constructs and the factor analytic techniques used to differentiate these (3, 5, 6, 26, 29). With reference to the current findings, and those by Davidson et al. (9), it appears especially pertinent for future work to establish the relationship between anhedonia and fatigue/somatic depressive subtypes. Such work may also be of further theoretical value if based on the tripartite model of distress (17), incorporating specific measures of anxiety, but also a broader range of general distress measures (26).

In conclusion, the HADS-D scale seems to assess symptoms which are important for predicting cardiovascular prognosis, despite these symptoms being highly correlated with other symptoms of anxiety. Specifically, anhedonia and feeling physically or cognitively slowed were especially pertinent for cardiovascular prognosis, but other depressive and anxiety symptoms were not. Whether symptoms of distress predict

prognosis in ACS may be dependent on the symptoms reported, or on the measures and items used.

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Table 1: Baseline characteristics of sample (n, % unless otherwise stated), with univariate predictors of 8-year mortality

	Completed HADS (n=316)	Completed BDI-FS (n=282)	P-value	Hazard Ratio (HR)	95% Confidence Interval (CI)	P-value
Demographics						
Age (years) (mean) (SD)	63 (13)	62 (12)	0.331	1.10	1.08–1.12	<0.001***
Men	235 (74)	221 (78)	0.343	0.50	0.33–0.79	0.003**
Health insurance (private)	116 (37)	101 (37)	0.963	0.57	0.37–0.85	0.006**
Previous risk factor history						
Prior diabetes	37 (12)	35 (12)	0.826	1.96	1.15–3.33	0.013*
Total cholesterol (mmol/l) (mean) (SD)	4.9 (1.2)	5.1 (1.1)	0.014*	0.66	0.57–0.78	<0.001***
Ever smoker	241 (77)	215 (78)	0.949	0.62	0.43–0.90	0.011*
Prior ACS	112 (35)	111 (37)	0.440	1.74	1.24–2.46	0.002**
Myocardial infarction	60 (19)	59 (20)	0.509	1.37	0.91–2.07	0.133
Unstable angina	57 (18)	53 (18)	0.849	2.29	1.50–3.50	<0.001***
Prior revascularisation	47 (15)	56 (19)	0.165	0.81	0.53–1.25	0.342
Prior hypertension	132 (41)	115 (41)	0.832	1.79	1.23–2.59	0.002**
Reperfusion received	109 (34)	89 (32)	0.533	0.52	0.33–0.80	0.003**
Hospital stay (days, median, interquartile range)	9 (5-13)	8 (6-13)	0.159	1.03	1.02–1.05	<0.001***
Psychometrics						
Depressed (above threshold on either scale)				1.45	0.93–2.25	0.101
HADS-D (mean, SD)	4.23 (3.26)	-	-	1.11	1.04–1.19	0.003**
HADS-A (mean, SD)	6.83 (4.03)	-	-	0.96	0.85–1.09	0.564
BDI-FS (mean, SD)	-	1.95 (2.67)	-	0.99	0.91–1.08	0.886

*p<0.05

Table 2: Adjusted predictors of 8-year mortality

	Model 1			Model 2		
	Hazard Ratio (HR)	95% Confidence Interval (CI)	p-value	Hazard Ratio (HR)	95% Confidence Interval (CI)	p-value
Depressed (above threshold on either scale)	1.91	1.16–3.14	0.011*	1.61	1.03–2.53	0.036*
HADS-D **(continuous)** (n=302)	1.11	1.03–1.21	0.007**	1.09	1.00–1.09	0.045*
HADS-D (dichotomous)	**2.64**	**1.38–5.05**	**0.003****	**2.47**	**1.38–4.40**	**0.002***
BDI-FS **(continuous)** (n=272)	1.02	0.88–1.15	0.799	1.01	0.90–1.14	0.834
BDI-FS (dichotomous)	**1.43**	**0.68–2.98**	**0.344**	**1.24**	**0.61–2.49**	**0.553**
Anxiety HADS-A **(continuous)** (n=302)	1.05	0.95–1.15	0.339	1.03	0.94–1.12	0.558
HADS-A (dichotomous)	**1.48**	**0.72–3.02**	**0.283**	**1.26**	**0.63–2.51**	**0.518**

Model 1 – Adjusted for age, sex, private health insurance, length of hospital stay

Model 2 - Adjusted for age, sex, private health insurance, diabetes, ever smoker, prior ACS, hypertension, reperfusion and length of hospital stay

*p<0.05

Table 3: Mean score of items, and item-level prediction of 8-year mortality

	Mean score	HR	95% Confidence Interval (CI)	p-value
HADS-D				
2 – I still enjoy the things I used to enjoy~	0.63	1.38	1.05–1.82	0.021*
4 – I can laugh and see the funny side of things~	0.34	1.48	1.11–1.96	0.007**
6 – I feel cheerful~	0.47	1.30	0.99–1.72	0.059
8 – I feel as if I am slowed down	1.39	1.66	1.24–2.22	0.001**
10 – I have lost interest in my appearance	0.49	0.86	0.62–1.19	0.361
12 – I look forward with enjoyment to things~	0.54	1.36	1.08–1.72	0.010*
14 – I can enjoy a good book, radio or TV programme~	0.39	1.08	0.79–1.46	0.645
HADS-A				
1 – I feel tense or wound up	1.05	0.90	0.61–1.33	0.608
3 – I get a sort of frightened feeling as if something awful is about to happen	1.14	0.99	0.75–1.30	0.934
5 – Worrying thoughts go through my mind	1.12	1.02	0.82–1.28	0.842
7 – I can sit at ease and feel relaxed~	0.78	0.80	0.52–1.21	0.287
9 – I get a sort of frightened feeling like ‘butterflies’ in my stomach	0.67	0.96	0.64–1.44	0.842
11 – I feel restless as if I have to be on the move	1.23	0.91	0.67–1.24	0.551
13 – I get sudden feelings of panic	0.79	1.35	0.95–1.93	0.096
BDI–FS items				
1 – Sadness	0.18	0.69	0.26–1.82	0.451
2 – Pessimism	0.32	0.80	0.41–1.56	0.512
3 – Past failure	0.29	0.93	0.57–1.52	0.784
4 – Loss of pleasure	0.41	1.12	0.73–1.72	0.609
5 – Self-dislike	0.26	1.14	0.76–1.70	0.539
6 – Self-criticalness	0.41	0.85	0.60–1.21	0.364
7 – Suicidality[$]	0.06	–	–	–

[$]No patient who indicated suicidality had died at follow–up

~Items which have negatively-worded responses

*p<0.05

Figure 1: Kaplan–Meier survival curves for depression and anxiety, using recommended thresholds