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Abstract

Background: Depression is a well-known risk factor for recurrent cardiac events (RCEs) but findings are less consistent for anxiety, not previously reported on using a time-dependent approach. We aimed to study the prognostic effect of anxiety and depression symptom levels on RCEs.

Methods: Data (N=595) were drawn from the UPBEAT-UK heart disease patient cohort with 6-monthly follow-ups over 3 years. Hospital Anxiety and Depression Scale symptoms were grouped into: agitation (3 items), anxiety (4 items), depression (7 items) subscales. We performed two types of multivariate analyses using Cox proportional hazard models with delayed entry: with baseline variables (long-term analysis), and with variables measured 12-to-18 months prior to the event (short-term time-dependent analysis), as RCE risk factors.

Results: In the baseline analysis, both anxiety and depression, but not agitation, were separate RCE risk factors, with a moderating effect when considered jointly. In the short-term time-dependent analysis, elevated scores on the anxiety subscale were associated with increased RCE risk even when adjusted for depression [HR (95% CI): 1.22 (1.05-1.41), p=0.009]. Depression was no longer a significant predictor when adjusted for anxiety [1.05 (0.87-1.27), p=0.61]. For anxiety, individual items associated with RCEs differed between the two approaches: item 5 'worrying thoughts' was the most significant long-term risk factor [1.52 (1.21-1.91), p=0.0004] whereas item 13 'feelings of panic' was the most significant time-dependent short-term risk factor [1.52 (1.18-1.95), p=0.001].

Conclusions: Anxiety is an important short-term preventable and potentially causal risk factor for RCEs, to be targeted in secondary cardiac disease prevention programmes.

248 words

Key words: cardiac disease; recurrent cardiac event; depression; anxiety; time-dependent analysis

Introduction

Secondary cardiovascular disease (CVD) prevention in heart disease patients is a major public health concern given the high occurrence of heart disease worldwide (Khan, Hashim, Mustafa, Baniyas, Al Suwaidi, 2020). There is widespread evidence that depression constitutes an important risk factor for recurrent cardiac events (RCEs) in heart disease patients (Freedland and Carney, 2013, Meijer, Conradi, Bos, Thombs, van Melle, 2011, Nicholson, Kuper and Hemingway, 2006). However, less attention has been paid to anxiety for which findings are inconsistent. Some studies suggest that anxiety symptoms increase the risk of RCEs (Frasure-Smith and Lesperance, 2008, Roest, Martens, Denollet and de Jonge, 2010, Tully, Winefield, Baker, Denollet, Pedersen, 2015, Van Beek, Zuidersma, Lappenschaar, Pop, Roest, 2016), in stable coronary heart disease (CHD) (Frasure-Smith and Lesperance, 2008) and myocardial infarction (MI) patients (Van Beek *et al.*, 2016). An increased risk of cerebro-cardiovascular events with anxiety has been reported in coronary artery bypass surgery patients (Tully *et al.*, 2015). Furthermore, anxiety is associated with a greater risk of all-cause mortality in CHD patients, particularly when comorbid with depression (Watkins, Koch, Sherwood, Blumenthal, Davidson, 2013). A link between persistence of anxiety symptoms over time and adverse cardiac outcomes has also been shown (Moser, McKinley, Riegel, Doering, Meischke, 2011, Shibeshi, Young-Xu and Blatt, 2007).

Yet, some studies fail to show an association between anxiety symptoms and RCEs in CHD patients (Kornerup, Zwisler, Prescott and Danrehab Group, 2011, Versteeg, Hoogwegt, Hansen, Pedersen, Zwisler, 2013), or between anxiety and depressive symptoms and mortality in MI hospitalised patients (Lane, Carroll, Ring, Beevers and Lip, 2001). Other studies have even suggested that anxiety symptoms may confer a protective effect in stable CHD patients (Meyer, Buss and Herrmann-Lingen, 2010, Meyer, Hussein, Lange and Herrmann-Lingen, 2015). Indeed, anxiety symptoms were found to have opposite effects on survival in different subgroups of cardiovascular disease (CVD) patients,

with a protective effect for those with a stable condition, an increased risk for post MI left-ventricular patients and a lack of effect for other MI patients (Meyer *et al.*, 2010). Furthermore, evidence points to a differential effect according to the type of symptoms. One study reports a stronger prognostic association with RCEs for somatic anxiety than for psychological anxiety symptoms (Roest, Heideveld, Martens, de Jonge and Denollet, 2014).

However, comparison between studies is hampered by methodological differences, in the choice of clinical populations, assessment tools, outcomes and time-frames. In addition, choice of confounders and adjusting or not for cardiac-disease severity (Frasure-Smith and Lesperance, 2003) and depression (Frasure-Smith and Lesperance, 2008, Martens, de Jonge, Na, Cohen, Lett, 2010, Strik, Denollet, Lousberg and Honig, 2003, Van Beek *et al.*, 2016, Watkins *et al.*, 2013) can substantially modify the associations. Moreover, there is also considerable variability in the length of follow-up between studies (Roest *et al.*, 2010), along with intra-study variability in duration of time between anxiety assessment and endpoint (Meyer *et al.*, 2010, Van Beek *et al.*, 2016). A time-dependent approach allows the assessment of risk within a standardised time-window, taking into account the potential time-varying effect of the exposure. In contrast to depression (Li, Van Halm-Lutterodt, Zheng, Liu, Guo, 2018, Norton, Pastore, Ancelin, Hotopf, Tylee, 2020, Pequignot, Dufouil, Prugger, Peres, Artero, 2016), this approach has so far not been reported on for anxiety which is known to fluctuate considerably over time, especially in the elderly (Palacios, Khondoker, Mann, Tylee and Hotopf, 2018).

The current study draws on data from the UPBEAT-UK cohort of heart disease patients followed up at six-month intervals over three years. The aim was to examine the Hospital Anxiety and Depression Scale (HADS) subscales identified as psychomotor agitation, psychic anxiety and depression (Friedman, Samuelian, Lancrenon, Even and Chiarelli, 2001), measured at baseline (long-term) and 12-to-18 months prior to the RCE (short-term standardised for time-to-event) as predictors of RCEs

including mortality. Individual HADS items were also examined. It was hypothesised that psychic anxiety would be more likely than agitation to be a risk factor for RCEs, given that it reflected the most anxiety-specific fear and panic symptoms of anxiety. An association was also expected for depression, as shown previously for both cognitive and somatic symptom dimensions (Norton *et al.*, 2020).

Methods

Study design and sample

The UPBEAT-UK cohort was set up in 2008, drawing on patients from CHD registers of 16 general practices in South East London (Tylee, Ashworth, Barley, Brown, Chambers, 2011). Participating general practitioners invited all of their patients registered long-term on their CHD registers and aged 18 and above to be contacted by the research team for the study. Of the 2938 registered patients, 917 agreed to be contacted and 803 (87.6%) participated. Participants were interviewed at inclusion and followed up for three years, undergoing six-monthly assessments. Written informed consent was obtained from all patients before the initial assessment. Ethics approval was granted through the Bexley and Greenwich Research Ethics Committee (REC reference number: 07/H0809/38). The analysis was performed on 595 patients with data on cardiac status at the 18, 24, 30 and 36 months follow-ups and no missing data for the main covariates (Norton *et al.*, 2020).

Measures

Socio-demographic and lifestyle characteristics, including relationship status, smoking, alcohol consumption and body mass index (BMI) were collected at baseline only. At baseline and each follow-up, severity of chest pain was measured using the Rose Angina Questionnaire (Rose, 1962)

and was classified as: no angina (none or mild); chest pain when walking uphill only (moderate); chest pain when walking on the level and uphill (severe). In addition, quality of life scores were obtained using the EuroQol EQ-5D scale, excluding the pain/discomfort and depression/anxiety subscales (Rabin and de Charro, 2001), and social problems from the Social Problems Questionnaire (SPQ) (Corney and Clare, 1985).

Outcome variable: recurrent cardiac event (RCE).

RCEs included: any visit to the rapid access chest pain clinic, accident and emergency department (A&E) or emergency hospital admittance, where cardiac-related chest pain was the diagnosis (rapid access); bypass graft or angioplasty; MI and any cardiovascular cause of death. Events were coded and dated by a medical doctor on the team after examination of the general practitioner's notes, which included all cardiology notes, investigations and interventions.

Hospital and Anxiety Depression Scale (HADS)

The HADS is a self-report scale composed of 14 items, rated on a 0-to-3 scale, measuring symptoms of anxiety and depression. The original authors suggested a 2-factor scale with 7 items relating to anxiety (HADS-A), and 7 items to depression (HADS-D) (Zigmond and Snaith, 1983). A 3-factor solution subdividing HADS-A has since been reported as more appropriate for cardiac patients (Barth and Martin, 2005, Hunt-Shanks, Blanchard, Reid, Fortier and Cappelli, 2010, Martin, Lewin and Thompson, 2003), with evidence for either Dunbar et al (Dunbar, Ford, Hunt and Der, 2000) or Friedman et al's model (Barth and Martin, 2005, Martin *et al.*, 2003), as providing the best fit. We performed confirmatory factor analysis on our data and found similar fit statistics for both models. We chose to apply Friedman's 3-factor model with items grouped into the following subscales:
-Psychomotor Agitation (referred to as agitation): items 1, 7, 11

-Psychic Anxiety (referred to as anxiety): items 3, 5, 9, 13

-Depression: items 2, 4, 6, 8, 10, 12, 14

Statistical analysis

All analyses were performed using Cox proportional hazard models with delayed entry with age as the time scale (Lamarca, Alonso, Gomez and Munoz, 1998). The assumption of proportional hazards over time was tested for baseline variables and the linearity of continuous variables was verified. Results are expressed as hazard ratios (HR) with 95% confidence intervals (CI). For comparative purposes, the agitation, depression and anxiety subscales were standardised according to the number of items, with HRs for the anxiety and depression subscales expressed for a 1.33 and 2.33 point increase, respectively.

We performed two types of analysis:

(i) with HADS subscales analysed as baseline variables in order to examine the long-term risk, allowing for variability in time-to-event as events could occur at either the 18, 24, 30 or 36 month follow-ups.

(ii) with HADS subscales analysed as time-dependent variables measured 12-to-18 months prior to the event in order to examine the short-term time-standardised risk.

We excluded participants with RCEs at the baseline, 6- and 12-month follow-ups. This ensured a gap of at least 12-months between baseline HADS assessment and outcome. In the short-term time-dependent analysis, HADS scores and available covariates were selected at the N-3 follow-up, allowing for this 12-month RCE-free gap.

We adjusted for baseline and available time-dependent covariates associated with RCE with p-values<0.25 (see Table 1), along with well-established risk factors (Model 1). Moreover, interactions between subscales and sex, chest pain and diagnosis at registry entry were tested and were not significant. The agitation subscale was not explored further as it was not significantly associated with

the outcome in Model 1, Table 1 and Model 1, Table 2. For anxiety and depression, we did not to test the interaction between the subscales as continuous scores, given the high correlation between the two (r=0.71). Instead, we tested two separate interactions: between anxiety and depression grouped into terciles (DEP3) and between depression and anxiety grouped into terciles (ANX3). Interactions were significant (with p-value set at <0.15) in the baseline analysis only and were retained in the models, with anxiety stratified by DEP3 and depression by ANX3. In the time-dependent analysis, we further adjusted anxiety for DEP3 and depression for ANX3 (Model 2). When examining individual HADS items, we used Bonferroni correction to correct for multiple comparisons. Statistical analyses were performed using SAS Enterprise Guide Version 7.15 (SAS Institute, Inc. Cary, North Carolina).

Results

Sample description

The cohort (Walters, Barley, Mann, Phillips and Tylee, 2014), the study sample and how it compares to those excluded from the analysis (Norton *et al.*, 2020) have been described in detail elsewhere. Of the sample, 70.6% were male with a median age of 72 years (range: 27 to 98). The main diagnoses at entry to the registry were: documented MI (42.4%), CHD (48.2%) and angina (6.9%). Median time from baseline to event was 22.3 months (Inter-quartile range (IQR): 13.4, min-max: 12.1-36.2). Events ranged from rapid access (47.4%), to cardio-cerebrovascular cause of death (26.3%), bypass graft or angioplasty (24.2%), and MI (2.1%). The baseline sample is further described according to the occurrence of a RCE at follow-up (Table 1).

Baseline HADS subscales as RCE risk factors

In the baseline analysis, taken separately, both anxiety and depression, but not agitation, were significantly associated with a RCE risk in Model 1 (Table 2). We found interacting effects between anxiety and DEP3 and between depression and ANX3 (Model 1: p=0.06 and p=0.11, respectively). Anxiety was a significant RCE risk factor only in the lowest depression tercile (p=0.02) and depression only in the lowest anxiety tercile (p=0.03).

Time-dependent HADS subscales as RCE risk factors

In the time-dependent analysis, only anxiety and depression significantly increased the RCE risk (Table 3). The association for agitation was not significant (p=0.11). Interactions between anxiety and DEP3 and depression and ANX3 were not significant (Model 1: p=0.43 and p=0.67, respectively). When further adjusting for DEP3 in Model 2, anxiety remained significantly associated with RCE. The association also remained significant when adding quality of life to the model (HR: 1.19; 95% CI: 1.02-1.38), p=0.02). Conversely, depression was no longer associated with an increased RCE risk when adjusted for ANX3 (HR: 1.05; 95% CI: 0.87-1.27, p=0.61) or for quality of life (HR: 1.11; 95% CI: 0.94-1.29, p=0.21).

Individual HADS items as RCE risk factors

Specific subscale items associated with RCE differed between the baseline and time-dependent analysis. For anxiety, item 5 (worrying thoughts) was the only multiple-comparison corrected significant item in the baseline analysis (HR: 1.52; 95% CI: 1.21-1.91, p=0.0004) (Figure 1). Conversely, item 13 (feelings of panic) was the only item to reach significance in the time-dependent analysis (HR: 1.52; 95% CI: 1.18-1.95, p=0.001). For depression, item 10 (lost interest in appearance) was the only significant item in the baseline analysis (HR: 1.56; 95% CI: 1.23-1.97, p=0.0002), and item 4 (laughing at things) in the time-dependent analysis (HR: 1.54; 95% CI: 1.15-2.07, p=0.004). When

further adjusted for quality of life, findings were unchanged for the anxiety items, but time-dependent depression item 4 was no longer significant (p=0.01).

Discussion

Our study suggests that psychic anxiety and not depression is an independent short-term RCE risk factor, when considering both dimensions simultaneously. Indeed, the association between anxiety and RCE risk remained significant when further adjusted for depression, with a 22% increased risk (HR: 1.22, 95% CI: 1.05-1.41) in the following 12-to-18 month time-window for every one-point increase in psychic anxiety score (scale: 0-to-9). Our findings add evidence to a potential causal relationship as many of the causality principles of Bradford-Hill (Hill, 1965) are verified, such a strength, temporality and dose-response relationship. To our knowledge, this is the first time anxiety as a RCE risk factor has been examined standardising for time-to-event. In addition, the different individual HADS items associated in the two types of analyses suggest specific symptoms may be related differently to RCEs depending on the time-frame.

Anxiety as a RCE risk factor

Despite inconsistencies regarding anxiety as a RCE risk factor, with some studies reporting no association (Kornerup *et al.*, 2011, Lane *et al.*, 2001, Tully *et al.*, 2015, Versteeg *et al.*, 2013) and one a protective effect (Meyer *et al.*, 2015), our findings add to a body of evidence suggesting an increased long-term RCE risk with anxiety disorders (Tully, Cosh and Baumeister, 2014, Tully *et al.*, 2015) or symptoms (Frasure-Smith and Lesperance, 2008, Van Beek *et al.*, 2016, Watkins *et al.*, 2013). Two other studies found positive associations between anxiety symptoms and RCEs using the 7-item HADS-A, dichotomised by applying the 8+ threshold (Zigmond and Snaith, 1983). In one,

anxiety was measured in 804 stable CHD patients approximately 2 months after hospital discharge for an acute coronary syndrome with a 2-year follow-up for RCEs (Frasure-Smith and Lesperance, 2008). In the other, anxiety assessed during hospitalisation for coronary angiography increased the three-year risk of all-cause mortality in 934 patients (Watkins *et al.*, 2013). In a recent study of 396 MI patients, cardiac anxiety was associated with an increased four-year RCE risk. Anxiety was assessed using the Cardiac Anxiety Questionnaire, which focuses on symptoms typically triggered by MI, namely fear, attention, avoidance of physical exercise and safety-seeking behaviour (Van Beek *et al.*, 2016). In keeping with these studies, we found the association between anxiety and both short-term and long-term RCE to be robust to the effect of cardiac disease severity. We adjusted for severity in our study using diagnosis at registry entry and chest pain as proxies.

In addition, we found the anxiety but not the agitation subscale to be associated with an increased RCE risk. The agitation subscale can be considered less 'anxiety-specific' than the anxiety subscale. Indeed it focuses on restlessness, tenseness and difficulties in relaxing whilst the anxiety items capture fear and panic responses related to physical hyperarousal of anxiety. Intuitively, feeling 'wound-up' could be thought of as risk inducing, especially as relaxation therapy is a common feature of secondary CVD prevention programmes (Whalley, Thompson and Taylor, 2014). However, these symptoms alone distinguished from the other more anxiety-specific ones may not be sufficient, nor meet alone plausibility criteria for the pathophysiological processes linking anxiety to cardiac events. To the best of our knowledge, only one other study has looked at the different subtypes of anxiety and no other has used any of the HADS three-factor structures. Roest et al (2014) examined the Hamilton Anxiety and Depression Rating Scale symptom dimensions in 418 patients in relation to recurrent MI and all-cause mortality (Roest *et al.*, 2014). Associations were significant for somatic anxiety, but a trend only was found for psychological anxiety. Comparison with the HADS is limited due to the partial overlap of items covered by the different scales. For instance, there are no questions in the HADS on somatic anxiety, and no assessment of insomnia. In a previous analysis, we

found the somatic depression dimension of the PHQ-9 which includes insomnia to be a short-term RCE predictor (Norton *et al.*, 2020).

With some exceptions where, for instance, the prognostic effect of anxiety on survival was examined over 12 months (Lane *et al.*, 2001), most studies focus on the longer-term effect over two (Frasure-Smith and Lesperance, 2008), three (Shibeshi *et al.*, 2007, Watkins *et al.*, 2013) or four to five years (Frasure-Smith and Lesperance, 2003, Martens *et al.*, 2010, Meyer *et al.*, 2010, Meyer *et al.*, 2015, Strik *et al.*, 2003, Van Beek *et al.*, 2016, Versteeg *et al.*, 2013). When reported, intra-study variability in follow-up is considerable; with, for example, mean (sd) follow-up durations of 5.7 (0.8) (Meyer *et al.*, 2010) and 4.2 (2) (Van Beek *et al.*, 2016) years. In our study, patients were followed for three years with a median time-to-event from baseline of 22.3 months (IQR: 13.4) and in the time-dependent analysis, the median time-to-event was 14.1 months (IQR: 3.5). Associations shown for anxiety in the two longitudinal analyses managing time-to-event differently, and allowing for an event-free period between exposure and outcome, lends support to the temporality principle for causality (Hill, 1965). Furthermore, so far, no studies have examined the short-term effect of anxiety coupled with a time-dependent approach. Yet restricting the risk to a specific time window (12-to-18 months) can be particularly useful to clinicians for anticipating RCE risk and setting up preventative measures and interventions.

The effect of anxiety moderated by or adjusted for depression

Previous studies on the independent associations of anxiety and depression with long-term RCEs have shown mixed results, some retaining anxiety alone (Shibeshi *et al.*, 2007, Watkins *et al.*, 2013), some depression alone (Versteeg *et al.*, 2013), some both (for DSM-IV disorders only (Frasure-Smith and Lesperance, 2003)) and some neither (Lane *et al.*, 2001, Roest *et al.*, 2014). Some studies only report findings for anxiety, robust to adjustment for depression (Martens *et al.*, 2010, Van Beek *et al.*, 2016). Whilst most examined depression and anxiety entered simultaneously as covariates into a

same model (Roest *et al.*, 2014, Van Beek *et al.*, 2016) or constructed composite variables (Frasure-Smith and Lesperance, 2008), few tested the interaction between the two (Martens *et al.*, 2010, Watkins *et al.*, 2013).

To our knowledge, three other studies have administered both HADS subscales to compare the effects of anxiety and depression on cardiac prognosis (Kornerup *et al.*, 2011, Versteeg *et al.*, 2013, Watkins *et al.*, 2013). In a sample of 536 hospitalised CVD patients, Kornerup et al (2011) found no evidence of an association between HADS-A or HADS-D 11+ scores, CVD and all-cause mortality over a 5-year follow-up. Conversely, Versteeg et al (2013) found depression but not anxiety to be associated with rehospitalisations and 5-year mortality in 610 CHD patients. Moreover, in the absence of a moderating effect (p=0.66), Watkins et al (2013) found anxiety only to be a significant independent predictor of all-cause mortality in an extended multi-adjusted model. These latter two studies examined HADS-A and HADS-D as binary variables using the 8+ score threshold (Zigmond and Snaith, 1983). In our baseline analysis, the interaction terms for anxiety with depression in terciles and for depression with anxiety in terciles were above the set significance thresholds and therefore retained in the models. Hazard ratios were presented for each tercile of the moderating factor. We found that anxiety was a significant RCE risk factor in patients with a low depression level (score 0-1), with a trend in those with a moderate level (score 2-4). Depression was a weaker RCE risk factor, both before and after stratification by anxiety level. Overall, this suggests a more complex effect of anxiety and depression symptoms as long-term RCE risk factors when symptoms are not limited to those specific to one of the dimensions only. This is in keeping with Frasure-Smith and Lesperance's underlying negative affectivity dimension, shared by scales measuring depression, anxiety and anger, which was shown to be associated with long-term cardiac-related mortality (Frasure-Smith and Lesperance, 2003).

In the time-dependent analysis, the lack of significance of the interactions between anxiety and depression in terciles and depression and anxiety in terciles suggests that psychic anxiety and depression act as independent risk factors, whose effects are not moderated by their respective

levels. Our findings highlight the strong role of anxiety as an independent short-term RCE risk factor, even when controlling for depression. This is in keeping with a greater effect found for anxiety as an all-cause mortality risk factor in CHD patients (Watkins *et al.*, 2013). To our knowledge, there is no other study of the joint effects of anxiety and depression on RCEs using a time-dependent approach to which our findings can be compared.

Individual psychic anxiety items as RCE risk factors

The analysis of specific subscale items reveals different associations for long-term and short-term risks. For anxiety, whereas item 5 (worrying thoughts) was associated with RCE in the baseline analysis, item 13 (feelings of panic) was the only significant item in the time-dependent approach. It has been suggested that the HADS has poor trait coverage due to its narrow focus (Norton, Cosco, Doyle, Done and Sacker, 2013). However, the 'worrying thoughts' item could tentatively be measuring trait rather than state-worry, thus increasing the RCE risk regardless of the variability in time-to-event. Its effect may be modulated by state items that would have a greater short-term impact on outcome. This lends support to a differential effect of anxiety types - extended to specific symptoms - on RCEs, further modulated by the timing of the exposure-outcome matrix.

Mechanisms for anxiety as a RCE risk factor

There are several potential direct mechanisms that could explain the adverse effect of anxiety on RCE, especially as a short-term risk factor. Pathophysiological processes are well documented and include notably arrhythmic mechanisms and dysfunction of the autonomic nervous system and hypothalamic-pituitary-adrenal axis, leading to increased catecholamine stimulation of the myocardium (Chrousos, 2009, Fisher and Newman, 2013, Pereira, Cerqueira, Palha and Sousa, 2013). Indirect behavioural pathways include unhealthy lifestyle (inactivity, diet, as well as alcohol and

smoking, which were taken into account in the current study) (Bonnet, Irving, Terra, Nony, Berthezene, 2005). Regarding health-seeking behaviour, anxiety can confer both a protective effect by inducing more regular follow-ups and engagement in preventive care strategies, as well as a negative effect, by triggering social inhibition and a negative coping strategy. One small study on 76 patients found no effect of anxiety on compliance to medical follow-up and medication (Benninghoven, Kaduk, Wiegand, Specht, Kunzendorf, 2006). This is in keeping with the inconsistent findings as to the prognostic long-term effect of anxiety on RCEs. A recent study from the UPBEAT-UK cohort investigated the direction of the association between chest pain, anxiety and depression and concluded that anxiety and depression tended to be consequences rather than causes of chest pain in CHD patients (de Heer, Palacios, Ader, van Marwijk, Tylee, 2020).

Limitations

One of the main limitations was the heterogeneity of cardiac events, both at registry entry and as the outcome variable. Indeed, anxiety has been shown to have opposite effects on 5-year survival in different types of patients, with a protective effect for those with a stable CHD condition, an increased risk for post MI left-ventricular patients and a lack of effect for other MI patients (Meyer *et al.*, 2010). Regarding the outcome, there is always a risk of misclassification of anxiety-related symptoms or disorders such as panic as cardiac-related chest pain, especially when examining anxiety as a short-term predictor. To minimise this, we left a 12-month event-free period between exposure assessment and outcome. We thus aimed to reduce the risk of a simultaneous onset of the two, with anxiety acting as a marker of disease rather than as a risk factor. It could be argued that in addition to a possible causal mechanism, anxiety could result in a lower threshold for rapid access consultation. This cannot be excluded, but we believe that the 12-month RCE-free gap between assessment and event reduces this possibility. In addition, we performed a sensitivity analysis, removing the 40 less severe 'rapid access' events from the 95 RCEs. Whilst effect sizes for baseline

HADS remained unchanged, there was a reduction in effect size for time-dependent anxiety, which no longer remained statistically significant. Another limitation was the absence of data on measures of disease severity. For example, we had no data on left ventricular ejection fraction, which would have provided a better adjustment for cardiac severity than chest pain used as a proxy, along with diagnosis at registry entry. In addition, we were not able to adjust for medication, psychotropic or cardiac-related, nor for treatment compliance.

Strengths

An important strength of our study is the use of the HADS, which despite some controversy (Cosco, Doyle, Ward and McGee, 2012, Norton *et al.*, 2013, Straat, van der Ark and Sijtsma, 2013) is still today recognised as a useful well-validated tool for assessing depression and anxiety symptoms in medically ill patients (Bjelland, Dahl, Haug and Neckelmann, 2002). Indeed, it focuses on psychosocial rather than somatic symptoms, sleep or appetite (which we studied previously (Norton *et al.*, 2020)) and thus avoids false-positives in clinical settings. Furthermore, we used the 3-factor symptom classification, identified as being the best fit for cardiac disease patients (Barth and Martin, 2005, Hunt-Shanks *et al.*, 2010, Martin *et al.*, 2003, Martin and Thompson, 2000, Martin, Thompson and Barth, 2008). We chose Friedman et al's classification (Friedman *et al.*, 2001) rather than Dunbar et al's (Dunbar *et al.*, 2000), as the item distinguishing the two, worry, is recognised as an important aspect of general anxiety rather than a sign of restlessness and agitation. This choice allowed us to extract the most anxiety-specific symptoms from the initial 7 HADS-A items and our differential findings for the subscales adds to the plausibility of the mechanisms explaining the anxiety-RCE association. Moreover, we believe that the careful choice of the time-span during which exposure and outcome were measured gives further strength to our study. In addition to the 12-month event-free period between exposure assessment and outcome, we removed patients who entered the register in the 6-months preceding baseline to avoid reverse-causality. But, above all, the time-

dependent approach allowed us to examine the time-to-event standardised effect of symptoms on RCEs. The overall design allowed us to verify causality principles of temporality and dose-response relationship, which along with the strength of the association lends support to a causal relationship. Further studies are required to explore potential mediating effects on the causal pathway.

Conclusion

Our study suggests that anxiety is an independent short-term risk factor for RCEs in heart disease patients as well as a stronger risk factor than depression. This effect is specific to a set of symptoms reflecting more general anxiety, fear and panic, rather than symptoms of restlessness and agitation. The two analytical approaches indicate a differential effect of anxiety according to the presence of concomitant depressive symptoms, over the long and short-term. Our findings highlight the need for regular assessments of anxiety, focusing on specific symptoms, in order to evaluate both the long and short-term risk. Assessing risk narrowed down to a specific time-window can be particularly useful to clinicians for referring patients to secondary CVD prevention programmes. The timing and regularity of these interventions, with for example personalized care (Barley, Walters, Haddad, Phillips, Achilla, 2014) focusing on the psychological treatment for the management of fear, worry and panic symptoms is crucial.

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Table 1. Sample description at baseline according to the occurrence of a recurrent cardiac event (RCE) at follow-up (N=595)

	RCE=no (N=500)	RCE=yes (N=95)		
Variables	**%**	**%**	**p[a]**	**p[b]**
Age at cohort entry[c]	71.7 (13.9)	71.8 (18.4)	0.34	NA
Sex (Male)	70.4	71.6	0.50	NA
Education (> 10 years)	52.0	52.6	0.87	NA
Ethnicity (White)	89.0	88.4	0.42	NA
Living alone (Yes)	35.2	36.8	0.56	NA
Smoking status				
Never	30.4	28.4		
Former	54.2	61.1		
Current	15.4	10.5	0.49	NA
Alcohol (units per week)				
None	26.8	27.4		
0-10 units	47.8	49.5		
>10 units	25.4	23.2	0.86	NA
Body mass index				
Normal	21.8	25.2		
Overweight	45.2	47.4		
Obese	33.0	27.4	0.75	NA
Diabetes	26.0	19.0	0.32	0.30
Hypertension	55.8	49.5	0.12	0.13
Arthritis	16.6	15.8	0.82	0.69
COPD	10.0	14.7	0.13	0.12
active cancer	10.8	13.7	0.32	0.25
CKD	18.4	22.1	0.47	0.42
Asthma	7.6	4.2	0.34	0.34
Chest pain				
None, mild	77.4	67.4		
Moderate	13.4	20.0		
Severe	9.2	12.6	0.03	0.16
Social problems				
No problems	49.0	37.9		
1 problem	31.8	40.0		
2 to 7 problems	19.2	22.1	0.50	0.35
Diagnosis at registry entry				
Myocardial infarction	40.8	49.5		
Ischemic heart disease	48.4	48.4		
Other	10.8	2.1	0.08	NA
Age at registry entry[c]	60.4 (17.2)	58.8 (21.2)	0.02	NA
Quality of life score[c]	3 (2)	4 (2)	0.04	0.001
Psychomotor Agitation (0-9)[c]	1 (2)	1 (2)	0.12	0.13
Psychic anxiety (0-12)[c,d]	2 (3)	3 (3)	0.001	0.001
Depression (0-21)[c,d]	2 (3)	3 (5)	0.007	0.01

COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; NA not applicable or unavailable at follow-up

[a] Cox Proportional Hazard Model adjusted for sex, for baseline variables

[b] Cox Proportional Hazard Model adjusted for sex, for time-dependent variables

[c] Median (IQR)

[d] For a 1.33 point increase in risk for ANX and a 2.33 point increase in risk for DEP, for comparability purposes between the three sub-scales (see Methods).

Table 2. Associations between baseline HADS sub-scales and recurrent cardiac event at follow-up (95 events/595)

	Model 1 [a]	
Baseline HADS Sub-scales	HR (95% CI)	p
Psychomotor agitation (0-9)	1.09 (0.96-1.25)	0.20
Psychic anxiety (0-12)[b]	1.18 (1.06-1.32)	0.002
Depression (0-21)[b]	1.19 (1.04-1.36)	0.01
Interaction models:		
Psychic anxiety[b] where:		
Depression score 0-1	1.45 (1.07-1.96)	0.02
Depression score 2-4	1.25 (0.98-1.61)	0.08
Depression score 5+	0.99 (0.83-1.18)	0.92
Depression[b] where:		
Anxiety score 0-1	1.77 (1.04-2.99)	0.03
Anxiety score 2-4	1.18 (0.92-1.51)	0.19
Anxiety score 5+	0.95 (0.71-1.26)	0.71

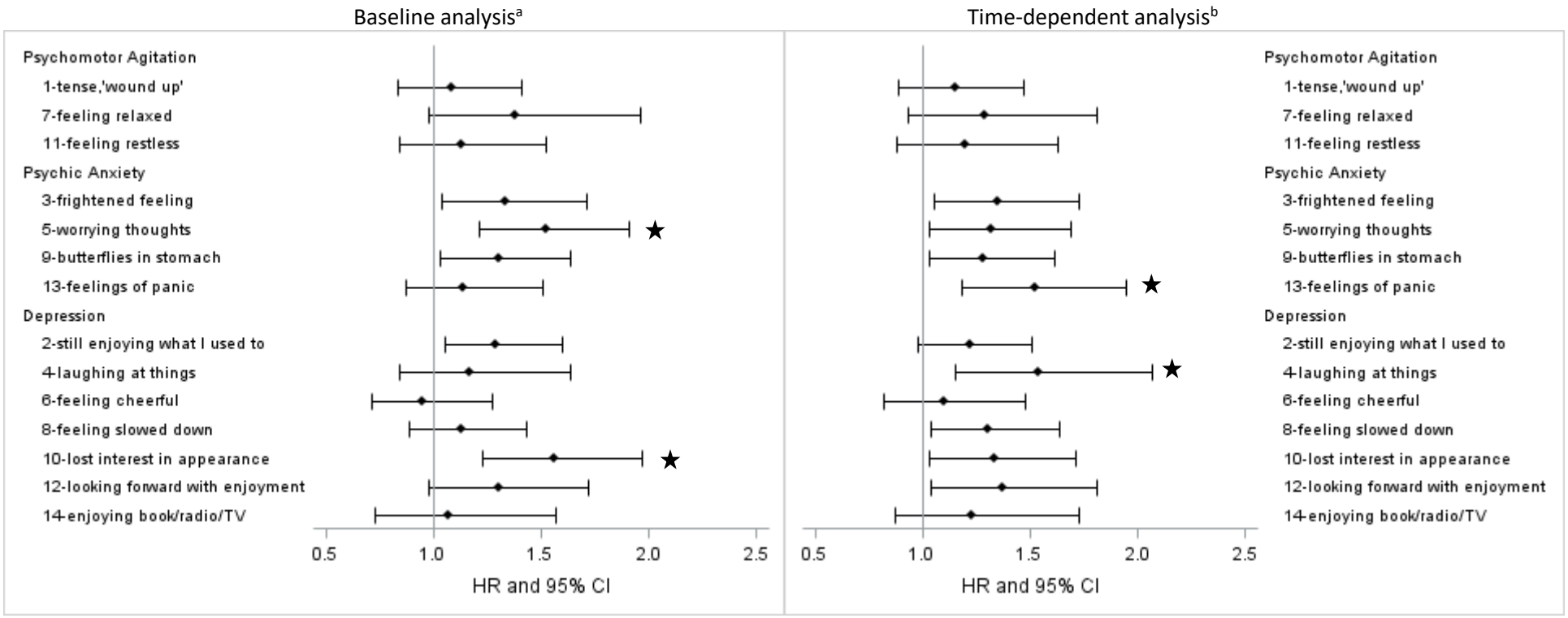
[a] Adjusted for sex, diagnosis at entry (MI no/yes), smoking, chest pain, hypertension and chronic obstructive pulmonary disease
[b] For a 1.33 point increase in risk for ANX and a 2.33 point increase in risk for DEP, for comparability purposes between the 3 sub-scales.

Table 3. Associations between time-dependent HADS sub-scales and recurrent cardiac event at follow-up (95 events/595)

	Model 1[a]		Model 2[b]	
HADS Sub-scales	HR (95% CI)	p	HR (95% CI)	p
Psychomotor agitation (0-9)	1.11 (0.98-1.26)	0.11	-	
Psychic anxiety (0-12)[c]	1.21 (1.09-1.36)	0.0007	1.22 (1.05-1.41)	0.009
Depression (0-21)[c]	1.19 (1.03-1.37)	0.02	1.05 (0.87-1.27)	0.61

[a] Model 1: adjusted for sex, diagnosis at entry (MI no/yes), smoking, and time-dependent chest pain, hypertension and chronic obstructive pulmonary disease
[b] Model 2: Model 1 further adjusted for depression in terciles for ANX and anxiety in terciles for DEP
[c] For a 1.33 point increase in risk for ANX and a 2.33 point increase in risk for DEP, for comparability purposes between the 3 sub-scales.

Figure 1. Associations between baseline and time-dependent HADS items and recurrent cardiac event at follow-up (95 events/595)



Note: scoring reversed for positively phrased items 2, 4, 6, 7, 12 and 14

[a] Adjusted for sex, diagnosis at entry (MI no/yes), smoking, chest pain, hypertension and chronic obstructive pulmonary disease
[b] Adjusted for sex, diagnosis at entry (MI no/yes), smoking, and time-dependent chest pain, hypertension and chronic obstructive pulmonary disease

* significant association when applying Bonferroni correction with p-values set at p=0.0125 for psychic anxiety and p=0.007 for depression