



Symptoms of depression and anxiety and 11-year all-cause mortality in men and women undergoing coronary artery bypass graft (CABG) surgery

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ARTICLE INFO

Keywords:

Anxiety
Depression
Cardiovascular disease
Mortality
Multicenter study
Sex

ABSTRACT

Objectives: To investigate the overall and the sex-specific association of preoperative and one-year post coronary artery bypass (CABG) surgery symptoms of depression and anxiety with 11-year all-cause mortality.

Methods: A multicenter prospective study including 1125 patients who completed the Hospital Anxiety and Depression Scale (HADS) before an elective CABG surgery, of whom 850 completed the HADS again at one-year follow-up. Information on all-cause mortality was obtained through the Israeli Ministry of Internal Affairs Register. Multivariable adjusted Cox regression models quantified the association of symptoms of depression and anxiety with all-cause mortality.

Results: Females comprised 22.7% of the cohort and were 5.5 years older than males (70.0 ± 9.3 and 64.4 ± 10.3 years, respectively). Controlling for sociodemographic and lifestyle factors, illness severity and post-surgery participation in cardiac rehabilitation, there was little evidence of an association between preoperative symptoms of depression and mortality in males [adjusted hazard ratio (aHR_{males}) = 1.03, 95% CI 0.99–1.07, $p = 0.21$] or females (aHR_{females} = 1.01, 95% CI 0.95–1.08, $p = 0.7$). One-year postoperative symptoms of depression were associated with mortality in both males (aHR_{males} = 1.05, 95% CI 1.01–1.10, $p = 0.03$) and females (aHR_{females} = 1.07, 95% CI 1.02–1.13, $p = 0.013$). Preoperative symptoms of anxiety were unrelated to mortality overall, but among females postoperative symptoms of anxiety predicted 11-year mortality (aHR_{females} = 1.07, 95% CI 1.00–1.14, $p = 0.049$). There was no HADS by sex interaction (p for interaction = 0.12–0.99).

Conclusions: Symptoms of depression one-year after surgery were positively related to mortality with little evidence for sex differences. These findings underscore the need for identification and treatment of psychiatric symptoms in patients undergoing CABG surgery.

Clinical Trial Registration: ClinicalTrials.gov: NCT00356863

1. Introduction

Coronary artery bypass graft (CABG) surgery is a common treatment for coronary artery disease (CAD) and is usually associated with improved clinical outcomes. However, a significant proportion of patients experience depression and anxiety both pre- and postoperatively. Depression has been reported in 14%–47% [1] and anxiety in 15%–52% of patients [2].

Evidence suggests that depression and anxiety are associated with postsurgical outcomes such as cardiac events, level of function and quality of life [3]. Moreover, some have reported increased mortality in patients with elevated levels of depression and anxiety undergoing CABG surgery although not all studies have been consistent. Major depressive disorder (MDD) at discharge from hospital was associated with twofold increased 12-month cardiac events in 309 patients but not with cardiac death. MDD and elevated symptoms of depression were

Acronyms: CABG, Coronary artery bypass graft; CR, Cardiac rehabilitation; HADS, Hospital Depression and Anxiety Scale; HADS-D, Hospital Depression and Anxiety Scale - depression subscale; HADS-A, Hospital Depression and Anxiety Scale - anxiety subscale; aHR, Adjusted hazard ratio; CAD, Coronary artery disease; MDD, Major depressive disorder; CHF, Congestive heart failure; MI, Myocardial infarction; MCMC, Markov Chain Monte Carlo

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<https://doi.org/10.1016/j.jpsychores.2017.11.017>

Received 8 May 2017; Received in revised form 28 November 2017; Accepted 29 November 2017

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associated with somewhat greater risk for cardiac-related but not with all-cause mortality at 10-year follow-up [4,5]. Elevated symptoms of depression before and after surgery were associated with a twofold increase in all-cause mortality among 817 patients undergoing CABG surgery [1] while in another study there was little evidence for an association between preoperative depressive symptoms and all-cause 6-year mortality among 440 patients [6]. A recent systematic review demonstrated an increase in all-cause mortality in relation to preoperative depression in four of the seven studies reviewed [7].

Data on the impact of anxiety on morbidity and mortality following CABG surgery are scarce. Tully and co-investigators have shown that patients who had generalized anxiety disorder (GAD) prior to surgery were at a greater risk of major adverse cardiovascular and cerebrovascular events up to five years after CABG surgery but panic disorder was not associated with greater morbidity [8]. Heightened symptoms of anxiety before surgery were associated with increased postoperative mortality [6] and preoperative trait anxiety was positively related to 8-year mortality [9] but these studies were relatively small and based on samples recruited from single centres. Furthermore, the scale utilized by Tully and co-investigators [6] to assess symptoms of anxiety (the Depression Anxiety Stress Scale (DASS)) included items describing physiological symptoms (e.g. breathing difficulties, feeling faintness) which are common to CAD and as such may reflect preoperative illness severity. Moreover, previous studies did not measure postoperative anxiety. Preoperative anxiety may have been influenced, at least in part, by the uncertainty associated with the invasive procedure, which may resolve after surgery. Anxiety measured after surgery may be a better reflection of a person's psychiatric symptomatology.

Studies have demonstrated differences between men and women undergoing CABG surgery including less favorable cardiac and psychiatric risk profiles, a delayed referral of women for surgery, gender disparities in functional gains following CABG surgery, with women showing worse outcomes, and lower referral and uptake of cardiac rehabilitation programmes (CRP) among women [10–15]. A small number of studies of patients after myocardial infarction (MI) showed gender disparities in the impact of depression on clinical outcomes with women showing more adverse effects [16–18]. However, none of the studies cited above have stratified their analysis by sex.

In this study, we investigate the associations between symptoms of depression and anxiety, using the Hospital Anxiety and Depression Scale (HADS), and all-cause mortality up to 11 years after CABG surgery in a large ($N = 1125$) and sociodemographically diverse sample of men and women undergoing CABG surgery from seven medical centres. In the present study, we used the HADS which focuses on cognitive and emotional components of depression and anxiety and is therefore well suited for patients after CABG surgery. Our analyses are stratified by sex to explore the sex-specific impact of poor mental health on mortality following CABG surgery.

2. Materials and methods

2.1. Design

This study is part of a prospective controlled multicentre study described in detail elsewhere [19,20]. In summary, it aimed to assess the effect of an educational intervention, designed to improve uptake of cardiac rehabilitation (CR), on CR participation rate and the effect of CR participation on patients' outcomes after CABG surgery. We approached consecutive patients scheduled for CABG surgery (Jan/2004–Nov/2007) in seven cardiothoracic departments across Israel. Patients were interviewed 1–2 days before (baseline) and approximately one-year after surgery (follow-up) by trained research interviewers.

Patients were excluded from the primary study if they had severe co-morbidities for which CR was contra-indicated [e.g. congestive heart failure (CHF) stage IV]; were institutionalized; had severe cognitive impairment (e.g. general stroke with severe disability); could not

understand the study languages: Hebrew, English, Russian, and Arabic; or resided farther than 30 km from a CR facility. Patients were excluded if they could not be interviewed (baseline interview) prior to surgery (e.g. due to emergency operation) since their mental or cognitive state could have been affected by surgery. No exclusion occurred in relation to the type of CABG procedure.

Informed consent was obtained from all patients. The study received approval from the Sheba Medical Centre Ethics committee.

2.2. Participants

Overall, 1816 of 3194 (57%) patients who had undergone CABG surgery in the one of the seven participating centres were eligible to participate, 1153 (64%) of whom were enrolled in the primary study. HADS was completed by 1125 patients (98%) at baseline and by 850 (76%) patients again at one-year (Fig. 1). A hundred and seventy of the 1125 patients who were included in this study had undergone valve replacement procedure together with the bypass procedure.

2.3. Measures

Sociodemographic data [age, sex, marital status, ethnicity, level of education, employment status, income level (categorized according to the national average household income)], behavioural parameters (e.g. tobacco use and physical exercise), and co-morbidities were collected through a face-to-face interview. Results of blood markers (e.g. serum creatinine) were abstracted from medical records.

Patients completed the HADS - a 14-item screening questionnaire measuring symptoms of anxiety (7 items) and depression (7 items) which enquires about the last week. The score of each sub-scale can range between 0 and 21 when a higher score indicates worse symptoms. A score of eight or above on either sub-scales is considered clinically significant [21]. The authors of a review of the psychometric properties of the HADS reported that the sensitivity and specificity for this cut-point were 0.70 and 0.90, respectively, when compared to depressive and anxiety disorders (including major depressive disorder and generalized anxiety disorder) as identified by a gold standard measure such as the Structured Clinical Interview for DSM (SCID) [21]. The Hebrew version of HADS was found to have good psychometric properties [22]. In the present study, the internal reliability of the total scale was 0.89. It was 0.81 for the depression (HADS-D) sub-scale and 0.82 for the anxiety (HADS-A) sub-scale.

Body mass index (kg/m^2) was calculated from height and weight measured during the interview.

We used Charlson's co-morbidity index [23,24] as a proxy for disease severity. It includes diabetes, MI, peripheral vascular disease, gastrointestinal tract disease, liver and kidney disease, stroke, cancer and HIV. Patients were assigned a value based on their number of co-morbidities. Patients completed a detailed and validated physical activity questionnaire and their physical fitness in Vo_2 ml/kg/min was estimated [25].

Mortality data were obtained from the Israel National Population Register, using individuals' unique national identification number. Mortality data were updated until May 2015 i.e. 11 years 5 months from study onset.

2.4. Statistical methods

We used Cronbach's alpha to assess the HADS's internal consistency. Student's *t*-tests and Pearson chi-square tests were used to compare participants on continuous and categorical variables, respectively (Table 1).

The outcome variables are death and time-to-death after completing the HADS. We examined the association of pre- and postoperative HADS with all-cause mortality using multiple Cox proportional hazard regression. Initially, we controlled for age and sex (in the overall

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