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ORIGINAL ARTICLE

Exploring the use of psychotropic medication in cardiac patients with and without anxiety and its association with 1-year mortality

Pernille Fevejle Cromhout [1]*, Anne Vinggaard Christensen[2], Martin Balslev Jørgensen[3], Ola Ekholm[4], Knud Juel[4], Jesper Hastrup Svendsen[2,5], Merete Osler[6], Trine Bernholdt Rasmussen[5,7], Britt Borregaard[8,9], Rikke Elmose Mols[10], Lars Thrysoee[9], Charlotte Brun Thorup[11], and Selina Kikkenborg Berg[2,4,5]

[1]Department of Cardiothoracic Anaesthesiology, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen, Denmark; [2]Department of Cardiology, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen, Denmark; [3]Psychiatric Centre Copenhagen, Institute of Clinical Medicine, University of Copenhagen, Blegdamsvej 3B, 2200 Copenhagen, Denmark; [4]National Institute of Public Health, University of Southern Denmark, Studiestræde 6, 1455 Copenhagen, Denmark; [5]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 3B, 2200 Copenhagen, Denmark; [6]Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospitals, Nordre Fasanvej 57, 2000 Frederiksberg, Denmark; [7]Department of Cardiology, Herlev and Gentofte University Hospital, Gentofte Hospitalsvej 1, 2900 Hellerup, Denmark; [8]Department of Cardiothoracic and Vascular Surgery, Odense University Hospital, J.B. Winsløws Vej 4, 5000 Odense, Denmark; [9]Department of Cardiology, Odense University Hospital, J.B. Winsløws Vej 4, 5000 Odense, Denmark; [10]Department of Cardiology, Aarhus University Hospital, Palle Juul-Jensens Blvd. 161, 8200 Aarhus, Denmark; and [11]Department of Cardiology, Cardiac Surgery & Clinical Nursing Research Unit, Aalborg University Hospital, Hobrovej 18, 9000 Aalborg, Denmark

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Aims Comorbid psychiatric disorders and the use of psychotropic medication are common among cardiac patients and have been found to increase the risk of mortality. The aims of this study were: (i) to describe the use of psychotropic medication among cardiac patients with and without symptoms of anxiety, (ii) to estimate the association between use of psychotropic medication prior to hospital admission and all-cause, 1-year mortality following discharge, and (iii) to estimate the risk of mortality among users and non-users of psychotropic medication with or without self-reported symptoms of anxiety.

Methods and results Cardiac patients from the DenHeart survey were included, providing information on self-reported symptoms of anxiety. From national registers, information on the use of psychotropic medication 6 months prior to hospitalization and mortality was obtained. By logistic regression analyses, the association between the use of psychotropic medication, anxiety, and all-cause, 1-year mortality was estimated. The risk of subsequent incident use of psychotropic medication among patients with and without anxiety was furthermore explored. All analyses were fully adjusted. A total of 12 913 patients were included, of whom 18% used psychotropic medication, and 3% died within 1 year. The use of psychotropic medication was found to be associated with increased 1-year all-cause mortality [odds ratio 1.90 (95% confidence interval, 1.46–2.46)]. Patients with symptoms of anxiety were significantly more likely to use psychotropic medication following hospital discharge [2.47 (2.25–2.72)].

Conclusion The use of psychotropic medication was associated with 1-year mortality. Thus, the use of psychotropic medication might explain some of the association between anxiety and mortality; however, the association is probably mainly a reflection of the underlying mental illness, rather than the use of psychotropic medication.

Keywords Health surveys • Cardiology • Patient-centred outcomes research • Population registers • Mortality

* Corresponding author. Tel: +45 3011 8120, Email: pernille.fevejle.cromhout@regionh.dk

Implications for practice

- Detection of mental disorders and the use of psychotropic medication in cardiac patients are important, since it may affect overall outcomes.
- A possible link between the use of psychotropic drugs and mortality needs to be taken seriously in daily clinical practice of patients with heart disease.
- Attention is required to reduce the risk of physical disorders, like cardiac disease, among patients with mental illness.

Introduction

Cardiac diseases, such as ischaemic heart disease, valvular heart disease, arrhythmias, and heart failure, constitute major health issues and often require lifelong treatment. Therefore, increasing attention is being paid to the psychological consequences of living with a cardiac disease.[1] It is well known that mental disorders, such as anxiety are highly prevalent among cardiac patients (20–40%)[2–5] and have been shown to be associated with mortality and worsen the prognosis for these patients.[6–8] The mechanisms behind the poorer prognostic outcomes, such as higher morbidity and mortality among cardiac patients with mental disorders, are multifactorial. Physiological processes, such as stress-related inflammation, endothelial dysfunction, activation of the hypothalamic–pituitary–adrenocortical axis, and the cardiovascular autonomic system, have been associated with poor outcomes in patients with heart disease.[9–11] Furthermore, symptoms of anxiety and depression may act as barriers to lifestyle changes and treatment adherence and reduce the effects of cardiac rehabilitation.[12,13]

When mental health issues are causing significant impairment to healthy functioning, psychotropic medication such as antidepressants or benzodiazepines, are often prescribed. In recent years, there has been a growing awareness of the increased use of psychotropic medication and the associated side effects and potential harms.[14,15] Therefore, it is relevant also to consider the possible role of psychotropic medication in the poorer prognostic outcomes in cardiac patients with anxiety.

There is accumulating evidence of a high prevalence of comorbid psychiatric disorders in patients with heart disease, which is why the use of psychotropic medication is common.[16] Known cardiovascular side effects of psychotropic medication include impact on heart rhythm, such as sinus tachycardia and delayed cardiac conduction.[17] In patients with chronic diseases other than heart disease, previous studies have reported an association between the use of psychotropic medication and mortality.[18–20] In cardiac populations, the use of psychotropic medication has been found to cause arrhythmias.[21] The use of antidepressant drugs has been found to be associated with mortality and altered effect of beta-blockers in patients with heart failure.[6] Furthermore, the use of antipsychotic drugs has been associated with a three times higher risk of sudden death following acute myocardial infarction (AMI).[22]

The association between symptoms of anxiety and all-cause mortality in cardiac patients has previously been established.[23–25] To further elucidate the association, this study aims to explore the association between the use of psychotropic medication and mortality among cardiac patients with and without self-reported symptoms of anxiety.

Purpose

The aim of this study was among patients with heart disease (i) to describe the use of psychotropic medication among cardiac patients with and without symptoms of anxiety, (ii) to estimate the association between use of psychotropic medication prior to hospital admission and all-cause, 1-year mortality following discharge, and (iii) to estimate the risk of mortality among users and non-users of psychotropic medication with or without self-reported symptoms of anxiety. Furthermore, an additional analysis explored the odds of subsequent incident use of psychotropic medication among cardiac patients with and without self-reported symptoms of anxiety.

Methods

Design

The present cohort study was based on a combination of self-reported data from the DenHeart national survey and data from the Danish national registers. The design and methods of the study have been described in detail elsewhere.[26]

Patient population

In the DenHeart survey, all patients aged 18 years or above and discharged from one of the five national heart centres in Denmark were invited to fill out a questionnaire at hospital discharge from April 2013 to April 2014. Survey data were linked to the index hospital admission from the Danish National Patient Register.[27] In the present analyses, patients with ischaemic heart disease, arrhythmias, heart failure, and valvular heart disease were included.

Data from national registers

For the included population individual information on redeemed prescriptions for psychotropic medication 6 months prior to hospitalization, as well as post-discharge for sub-analyses, was obtained from The Danish National Prescription Registry (DNPR). The DNPR contains information about all dispensed prescriptions in Denmark since 1995.[28] From DNPR, the Anatomical Therapeutic Chemical Classification (ATC) code and the date of dispensing were included. Patients were defined as users of psychotropic medication if they had dispensed at least one prescription over the 6 months prior to hospital admission of the following drugs classified by ATC codes: Benzodiazepines and benzodiazepine-like drugs (BZD_all): N05BA, N03AE01, N05CD, N05CF; antidepressants (anti_depr_all) [including Selective Serotonin Reuptake Inhibitors, Tricyclic Antidepressants, and Serotonin–norepinephrine reuptake inhibitor]: N06AB, 06AX, N06AA; and antipsychotics (anti_psyc_all): N05A, excluding N05AX08-12-13, N05AL05, N05AH02-03-04-05, N05AE03-04, N05AN01.

Data on comorbidity covering a period of 10 years, not including the index discharge, were available from the Danish National Patient Register[27] and used for the calculation of the Ontario AMI mortality prediction rules (Tu comorbidity index score)[29] and the Charlson comorbidity index, including information on primary and secondary diagnoses for all patients. A comorbidity score of zero means no comorbidities, a score of one means one of the included comorbidities, etc. All diagnoses were weighted equally. Follow-up data on all-cause mortality 1 year after discharge was obtained from The Danish Civil Registry System.[30]

Baseline information including information on the highest educational level obtained was gained from the Danish Education Registers.[31] Educational level was categorized as basic school (≤10 years), upper secondary or vocational education, and higher education. Information on sex, age, and marital status (married or living with a partner, single, divorced, or and widowed) was obtained from the Danish Civil Registry System.[30]

Patient-reported data

The Hospital Anxiety and Depression Scale (HADS) is a 14-item questionnaire that assesses symptoms of depression and anxiety in hospitalized patients admitted to non-psychiatric hospital clinics. The scale offers two sub-scales, consisting of seven questions each to assess anxiety (HADS-A) and depression (HADS-D), respectively.[32] HADS has been found to be a valid and internally consistent measure in this patient population, with a Cronbach's alpha of 0.82 and 0.87 for the HADS-D and HADS-A, respectively.[33,34] Scores below eight for either subscale are regarded as normal, whilst scores ≥8 suggest the presence of a disorder with anxiety or depression, respectively.[35] For the present study only the HADS-A sub-scale was evaluated. Anxiety symptoms were defined as a HADS-A score of ≥8.

Furthermore, self-reported information about smoking behaviour, alcohol intake, height, and weight [for calculating body mass index (BMI)] were included as part of the survey. High alcohol intake was defined according to The Danish Health Authority as an intake exceeding more than 21 standard drinks per week for men and more than 14 standard drinks per week for women.

Statistical analyses

Baseline characteristics at the time of discharge were described using means and standard deviations for continuous measures and percentages for categorical measures. Baseline differences between uses and non-users of psychotropic medication were tested using χ^2 tests for categorical variables and Student's *t*-test for continuous variables. Patients without complete answers ($n = 537$) to the HADS were excluded (*Figure 1*).

Logistic regression models were performed to investigate the association between exposure measured as either use of psychotropic medication 6 months prior to admission, or self-reported symptoms of anxiety, or both, and all-cause mortality within 1 year. The odds ratios (ORs) with 95% confidence intervals for all-cause mortality were estimated in two models, crude (Model 1) and fully adjusted (Model 2). Model 2 was adjusted for age (10-year intervals), sex, cardiac diagnosis (ischaemia, valve disease, arrhythmias, and heart failure), comorbidity (Tu-index score), smoker (current daily), obesity (BMI ≥ 30), marital status, and educational level.

Furthermore, we conducted an additional analysis exploring the odds of incident use of psychotropic medication 1 year following hospital discharge, stratified by HADS-A score, and by the same drug classifications, as the main analyses. This analysis was conducted using logistic regression analysis and was fully adjusted as the Model 2 of the main analyses. Patients were defined as users of psychotropic medication if they redeemed a prescription for psychotropic medication up to 1 year after hospital discharge.

All analyses were conducted using SAS version 9.4.

Results

Psychotropic medication, self-reported anxiety symptoms, and mortality

A total of 12 913 cardiac patients, were included in this study after admission for a cardiac disease. A participant flow-chart is presented in *Figure 1*. Among the included patients, 2335 (18%) redeemed at least one prescription for psychotropic medication during the six prior to hospital admission and a total of 362 (3%) died within the first year after hospitalization. Results revealed that there was a higher use of psychotropic medication among females, older patients, smokers, widowed, lower educated patients, and among patients who had more comorbidity (*Table 1*). Among patients with symptoms of anxiety ($n = 4085$; 32%), 1133 (28%) used psychotropic medication compared to 1202 (14%) among patients without symptoms of anxiety, *P*-value <0.0001. The most commonly used drugs were benzodiazepines (68%) and antidepressants (55%) (*Table 2*).

A total of 130 (6%) of the 2335 users of psychotropic medication in the 6 months prior to hospital admission, died within 1-year post-discharge, compared with 232 (2%) of non-users, *P*-value <0.0001. Redeeming a prescription for psychotropic medication within 6 months prior to hospitalization was associated with higher ORs of all-cause mortality after 1 year [1.90 (1.46–2.46)]. There was a significant association between a high HADS-A score and all-cause mortality 1 year after hospital discharge [1.81 (1.42–2.31)]. When including both the use of any psychotropic medication prior to hospitalization and self-reported symptoms of anxiety in the model, the associations became attenuated [use of psychotropic medication, 1.73 (1.33–2.26); and HADS-A, 1.67 (1.05–1.63)] (*Table 3*).

For the additional analysis exploring the odds of incident use of psychotropic medication, we found that patients with a HADS-A score of eight or more were more likely to redeem a prescription for any psychotropic medication in the year after hospital discharge [2.47 (2.25–2.72)].

Discussion

For the included cohort of 12 913 patients with heart disease, the use of psychotropic medication was common. The use of psychotropic medication prior to admission was associated with a higher risk of 1 year, all-cause mortality, regardless of self-reported symptoms of anxiety. The results of this study correspond with earlier findings that the use of psychotropic medication might affect clinical outcomes and morbidity among different patient populations, including cardiac ones.[21]

The previously established association between symptoms of anxiety and higher mortality[24] may be partly explained by the use of psychotropic medication, as we found associations attenuated when adjusted for this. However, from these findings, it cannot be ascertained whether the higher mortality is due to the use of psychotropic medication or the underlying illness. The use of psychotropic

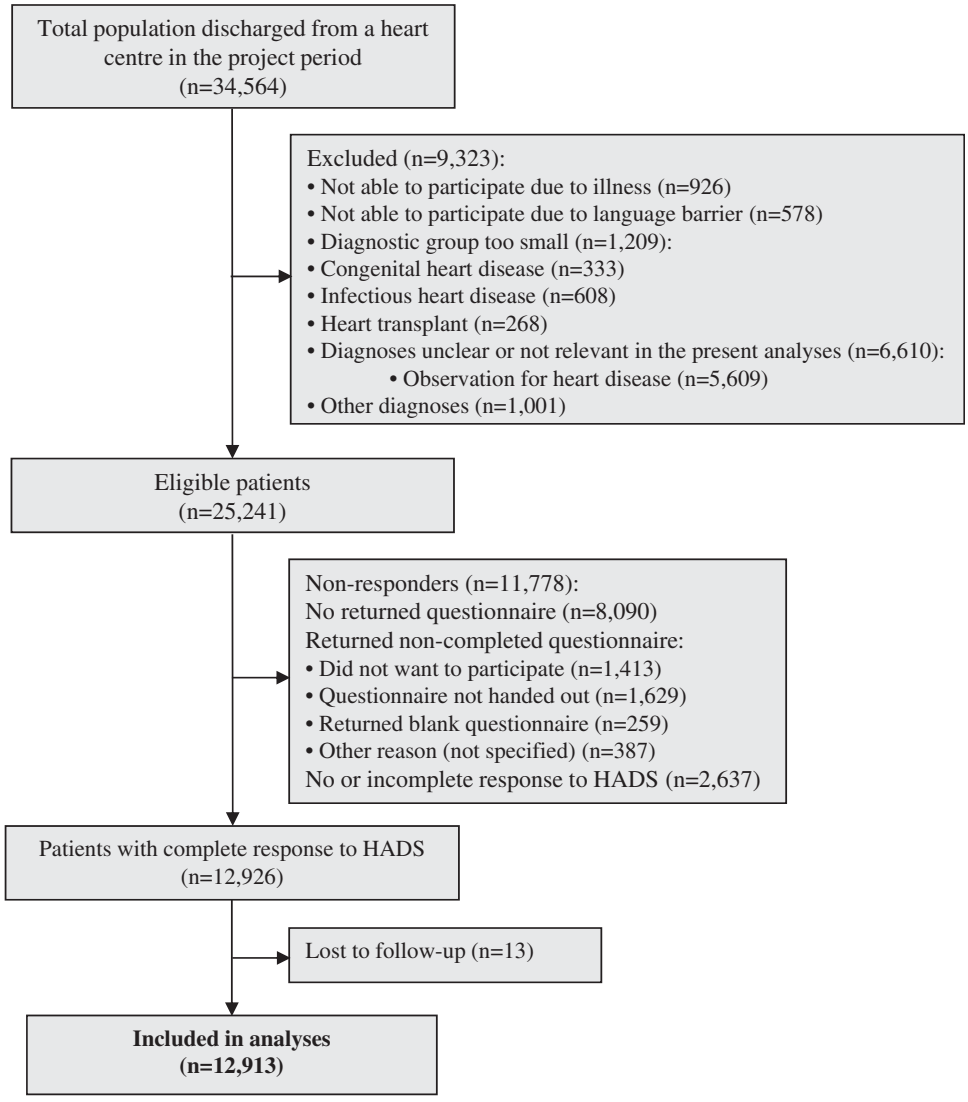

Figure 1 Flow-chart.

medication in this population is likely a proxy for the severity of psychiatric symptoms, treatment-refractory or residual mental illness, and/or other comorbidities.

The prevalence of psychotropic medication use was twice as high among cardiac patients with symptoms of anxiety compared to no symptoms of anxiety (28% vs. 14%), thus, patients reporting symptoms of anxiety had either not (yet) been diagnosed with anxiety or the treatment they were receiving was insufficient. The under-recognition and under-treatment of mood disorders in somatic patients have previously been documented.[36] A large study initiated by the World Health Organization documented that only 31% of patients recognized as 'anxious' received appropriate psychotropic treatment. The willingness to prescribe psychotropic medication was hypothesized to be influenced by diagnosis, patient age and gender, comorbidity (and severity), and the number of spontaneous psychological complaints.[37]

Our study shows that patients reporting symptoms of anxiety were significantly more likely to redeem a prescription for psychotropic medication, which suggests that patients act on the symptoms and seek help, however, as we do not in this study have any follow-up measurement of anxiety, it cannot be determined whether the use of psychotropic medication reduced the symptoms of anxiety.

Differences exist between patients who use psychotropic medication and patients who do not, since the two groups seem very different in terms of their anxiety score (21% vs. 43% of patients scored ≥8 on HADS-A among non-users and users) and mortality (2% vs. 4%, respectively). Hence, the association between symptoms of anxiety and mortality should probably be attributed to the underlying mental illness rather than the use of psychotropic medication. There is a considerable risk of confounding by indication in this study. Being prescribed with a psychotropic drug is an expression of mental morbidity, which might in itself constitute an increased risk of mortality. Therefore, it cannot be

Table 1 Demographics of 12 913 patients with heart disease who participated in the DenHeart survey, April 2013 to April 2014

	Users $n = 2335$ (18)	Non-users $n = 10\,578$ (82)	P-value[a]
	N (%)	*N* (%)	
Sex			<0.0001
Female	1023 (26)	2872 (74)	
Male	1312 (15)	7706 (85)	
Age			
Mean (SD)	67.5 (11.4)	64.9 (12.3)	<0.0001
≤49	152 (11)	1206 (89)	<0.0001
50–59	388 (16)	1969 (84)	
60–69	739 (17)	3528 (83)	
70–79	737 (20)	2901 (80)	
80–89	294 (24)	914 (76)	
90+	25 (29)	60 (71)	
Diagnosis			<0.0001
Ischaemic heart disease	1226 (18)	5658 (82)	
Valvular heart disease	176 (19)	748 (81)	
Arrhythmia	714 (17)	3445 (83)	
Heart failure	219 (23)	727 (77)	
Smoking (Daily)[b]			<0.0001
Yes	376 (23)	1288 (77)	
No	1895 (17)	9104 (83)	
Obesity (BMI ≥ 30)[c]			0.0182
Yes	567 (19)	2437 (81)	
No	1553 (17)	7588 (83)	
High alcohol intake (>national sensible drinking limits)[d]			0.1034
Yes	184 (20)	759 (80)	
No	1898 (17)	9005 (83)	
Marital status			<0.0001
Married	1329 (16)	7029 (84)	
Divorced	394 (23)	1346 (77)	
Widowed	417 (27)	1134 (73)	
Unmarried	195 (15)	1069 (85)	
Educational level[e]			<0.0001
Higher	488 (16)	2545 (84)	
Upper secondary or vocational	966 (17)	4675 (83)	
Basic	819 (21)	3135 (79)	
Tu index Ontario AMI mortality prediction rules			<0.0001
0	684 (13)	4626 (87)	
1	800 (18)	3605 (82)	
2	486 (23)	1603 (77)	
3+	365 (33)	744 (67)	
Charlson comorbidity index			<0.0001
0	741 (12)	5235 (88)	
1	575 (19)	2531 (81)	
2	439 (24)	1414 (76)	
3+	580 (29)	1398 (71)	
Anxiety			
HADS-A ≥ 8	1133 (28)	2952 (72)	<0.0001
HADS-A mean (SD)	7.6 (4.4)	5.4 (4.0)	<0.0001

Stratified by the use of psychotropic medication in the 6 months before hospital admission.
[a]χ^2 test for categorical variables and Student's *t*-test for continuous variables.
[b]$n = 250$ had missing information.
[c]$n = 768$ had missing information.
[d]$n = 1067$ had missing information.
[e]$n = 285$ had missing information.

concluded that the increased mortality risk found among users of psychotropic medication can solely be attributed to the use of that medication. Rather, it might be part of the explanation, which is most likely attributable to the underlying mental illness.

Strengths and limitations

The study included a large sample of cardiac patients with ischaemic heart disease, arrhythmias, heart failure, and heart valve disease reporting symptoms of anxiety by a subjective measure and exposure by an objective measure of the use of psychotropic medication. This adds to the existing body of evidence of the association between the use of psychotropic medication and mortality, which has previously been focused on patient groups other than cardiac. Symptoms of anxiety were for this study measured by HADS at hospital discharge. The addition of patient-reported symptoms of anxiety provides an even more nuanced picture of the association. However, multiple possible factors may affect patients' self-reported mental health at discharge. A repeated follow-up assessment of symptoms of anxiety would have provided validation of the classification of anxiety.

In this study, we used an objective measure of the use of psychotropic medication as information on redeemed prescriptions from the DNPR. We defined users of psychotropic medication by a redeemed prescription up to 6 months prior to hospital admission for the main analysis. Thus, there is a risk of misclassification of the definition of users, since we cannot be certain that the patients classified as users were current users. Furthermore, by including prevalent users of psychotropic medication, not taking into account, the fact that risk varies over time, there is a risk of selection bias, and additionally, the covariates defined at study entry might be influenced by the use of psychotropic medication. However, the validity of the registers used in this study is high and secured through quality control routines and clinical verification. Information from the registers was collected independently from the outcome examined and without relying on the participants' memories or adherence, thus the registers furnished the study with overall very reliable and valid data limiting both selection- and information bias.[30,38,39] In the DNPR, data on indication for use is not available. Certain types of psychotropic medication, e.g. benzodiazepines-like drugs, are not prescribed only with mental illness as an indication, which might lead to information bias in this

Table 2 Distribution of the use of psychotropic medication prior to hospital admission among patients with a HADS-A score ≥8 and <8

	HADS-A ≥ 8 *n* = 1133	HADS-A < 8 *n* = 1202	Total *n* = 2335
Drug group	*N* (%)	*N* (%)	*N* (%)
Antidepressants	665 (59)	625 (52)	1290 (55)
Benzodiazepines and benzodiazepine-like	804 (71)	781 (65)	1585 (68)
Antipsychotics	114 (10)	78 (6)	192 (8)
Combi1	357 (32)	230 (19)	587 (25)
Combi2	88 (8)	43 (4)	131 (6)
Combi3	62 (5)	36 (3)	98 (4)
Combi4	47 (4)	19 (2)	66 (3)

Antidepressants, including Selective Serotonin Reuptake Inhibitors (SSRI), Tricyclic Antidepressants (TCA), and Serotonin–norepinephrine reuptake inhibitor (SNRI).
Antipsychotics, including first (FGA) and second-generation antipsychotics (SGA).
Combi1, combination therapy including Antidepressants and Benzodiazepines and benzodiazepine-like drugs.
Combi2, combination therapy including Antidepressants and antipsychotics.
Combi3, combination therapy including Benzodiazepines and benzodiazepine-like drugs and antipsychotics.
Combi4, combination therapy including Antidepressants, Benzodiazepines, and benzodiazepine-like drugs and antipsychotics.

Table 3 Associations between the use of psychotropic medication, anxiety symptoms, and all-cause mortality 1 year after hospital discharge

	Mortality	
	Model 1[a]	Model 2[b]
	OR[c] (95% CI)	OR (95% CI)
Use of any psychotropic medication		
Yes	2.63 (2.11–3.28)	1.90 (1.46–2.46)
No	1.00 (reference)	1.00 (reference)
HADS-A		
≥8	1.53 (1.24–1.89)	1.81 (1.42–2.31)
<8	1.00 (reference)	1.00 (reference)
Use of psychotropic medication and HADS-A[d]		
Users of psychotropic medication	2.49 (1.99–3.11)	1.73 (1.33–2.26)
Non-users	1.00 (reference)	1.00 (reference)
HADS-A ≥ 8	1.31 (1.05–1.63)	1.67 (1.30–2.14)
HADS-A < 8	1.00 (reference)	1.00 (reference)

[a]Crude.
[b]Adjusted for age, sex, cardiac diagnosis, comorbidity (Tu-index), smoking, BMI, educational level, and marital status.
[c]OR = odds ratio.
[d]Both the crude and fully adjusted model include HADS-A and use of psychotropic medication.

study. Furthermore, information on adherence is not available from the DNPR, which again might lead to misclassification of users.[28]

As mental illness is both underrecognized and undertreated in non-psychiatric settings,[40] we expect that the true incidence was underestimated in both exposed and unexposed cardiac patients, which might have resulted in an underestimation of the associations.

Self-reported survey-based data are not objective and thus, bias may exist. In self-reporting of e.g. physical activity, alcohol consumption, smoking and weight, underreporting or social desirability bias can occur, as respondents omits answering or answer according to what they believe is socially acceptable.[41] To ensure transparency regarding this, all missing data has been reported for each variable.

This study does not distinguish between patients with known heart disease and newly diagnosed patients, which might bias the findings. It could be expected that newly diagnosed patients might experience pronounced symptoms of anxiety since they have not yet had the time to process the reality of their diagnosis and have not yet understood the consequences for their life in general.

Implications for practice

A direct causative link between the use of psychotropic drugs and mortality is difficult to prove. However, the association between the use of psychotropic medication and poor outcomes has been reported from various sources[21,42–44] and the risk needs to be taken seriously in daily clinical practice including patients with heart disease. Additionally, since physical disorders are more prevalent in people with severe mental illness, compared to the general population, at least in part due to lifestyle or preventable risk factors,[45,46] attention is required to reduce the risk of physical disorders among patients with mental illness.

For clinicians, detection of mental disorders and the use of psychotropic medication in cardiac patients are important, since it may affect overall outcomes. Early and appropriate referral to mental health providers may aid in decision-making regarding the prescription of appropriate psychotropic medication that is safe and compatible with treatment for their heart disease.

- Detection of mental disorders and the use of psychotropic medication in cardiac patients are important, since it may affect overall outcomes.
- A possible link between the use of psychotropic drugs and mortality needs to be taken seriously in daily clinical practice of patients with heart disease.
- Attention is required to reduce the risk of physical disorders, like cardiac disease, among patients with mental illness.

Conclusions

The use of psychotropic medication was found to be associated with higher mortality for the total included cohort of cardiac patients. Higher prevalence of use of psychotropic medication was found

among cardiac patients reporting symptoms of anxiety. The use of psychotropic medication might partially explain the higher mortality among cardiac patients with symptoms of anxiety. However, the higher mortality among cardiac patients with symptoms of anxiety could be attributable to an underlying psychiatric illness rather than the use of psychotropic medication.

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Data availability

The data underlying this article are available in the article and in its online supplementary material.

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