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Prevalence, 12-Month Prognosis, and Clinical Management Need of Depression in Coronary Heart Disease Patients: A Prospective Cohort Study

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Keywords
Depression · Coronary heart disease · Treatment · Prognosis · Clinical management need

Abstract
Background: Screening for depression in patients with coronary heart disease (CHD) remains controversial. There is limited data on the actual depression management need in routine care. The aim of this study was to examine the prevalence, treatment rates, prognosis, and management need of clinical and subclinical depression in CHD patients according to the American Heart Association recommendations and the National Institute for Health and Care Excellence (NICE) guideline "Depression in Adults with a Chronic Physical Health Problem". ***Methods:*** Patients were recruited at 2 German university clinics between 2012 and 2014. Depressive disorders were assessed according to the DSM-IV and depressive symptom severity at baseline and during follow-up was evaluated with the Patient Health Questionnaire (PHQ-9). Depression management need was determined by the severity and longitudinal course of depression symptoms. ***Results:*** Of 1,024 patients (19% women), 12% had clinical depression (depressive disorder) and 45% had subclinical depression (PHQ-9 score ≥5) at baseline. Among those with clinical depression, 46% were in treatment at least once dur-

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ing 12 months; 26% were continuously in treatment during follow-up. Depressive disorder and depressive symptoms were significant risk factor-adjusted predictors of the 12-months mortality (adjusted HR = 3.19; 95% CI 1.32–7.69, and adjusted HR = 1.09; 95% CI 1.02–1.16, respectively). Depressive symptoms persisted in 85% of the clinically depressed and in 47% of the subclinically depressed patients. According to current recommendations, 29% of all CHD patients would require depression management within 1 year. ***Conclusions:*** There is a need for enhanced recognition, referral, and continuous and improved clinical management of depression in CHD patients.

Introduction

The US Preventive Services Task Force (USPSTF) recommends screening for depression in all adults [1]. Patients with coronary heart disease (CHD) are at an increased risk for depressive disorders as well as subclinical elevated depressive symptoms [2]. Clinical and subclinical depression in patients with CHD and other cardiac conditions are associated with an increased risk of cardiac events and mortality [3, 4] and increased healthcare costs [5]. There is a controversial debate about screening for depression in these patients, since to date, evidence that screening improves cardiac and/or depression outcomes is lacking [6]. However, there is recent evidence that screening including patient feedback on screening results might improve depression outcomes [7]. Depression is widely acknowledged as a risk factor. Next to the prognostic and economic importance, affected patients have a decreased health-related quality of life and show significantly less adherence to secondary prevention measures [8–10]. Short screening instruments for depression exist and may be used to identify vulnerable patients [11] and to address the burden of depression regardless of cardiac consequences [12]. Ten years ago, the American Heart Association (AHA) issued a recommendation for screening, referral and treatment of depression in CHD patients [13]. The collaborative stepped care approach for the management of depression that is outlined in these recommendations is similar to the National Institute for Health and Care Excellence (NICE) guideline for "Depression in Adults with a Chronic Physical Health Problem" [14]. Both recommend routine depression screening in the context of somatic healthcare, referral to mental health care professionals in case of positive screening results, repeated screening in patients with subclinical symptoms, and continuous monitoring of patients once treatment has been initiated (online suppl. Fig. 1a, b; for all online suppl. material, see www.karger.com/doi/10.1159/000501502). Importantly, both recommendations are not based on a clinical depression diagnosis but rather on the severity and persistence of depressive symptoms, such as persistent sadness, loss of interest or pleasure in previously rewarding or enjoyable activities, and loss of energy, as well as a range of other cognitive-affective and somatic symptoms. Depression management options range from low-dose psychological and psychosocial interventions (e.g., education, lifestyle counseling, and behavioral activation) to psychotherapy, antidepressant medication, and other psychiatric treatments and depend on patient preferences, symptom severity, the psychiatric history, side effects, and the treatment response [15]. Although these recommendations are frequently cited, epidemiological data on actual treatment rates and the longitudinal course of depression in real-world clinical practice among CHD patients is scarce.

The aims of the current study were: (1) to examine the prevalence, treatment rates, and prognosis of clinical and subclinical depression in patients with CHD after a cardiac-related hospitalization; (2) to identify predictors of persistent depressive symptoms, and (3) to quantify the need for depression management in these patients according to the AHA recommendations [13] and the National Institute for Health and Care Excellence (NICE) clinical guideline "Depression in Adults with a Chronic Physical Health Problem" [14]. Clinical depression refers to the diagnosis of a depressive disorder and subclinical depression comprises self-reported depressive symptoms at an elevated level using a standard depression screening tool.

Methods

Study Design and Population

The current study was part of CDCare (Depression Care for Hospitalized Coronary Heart Disease Patients), a prospective cohort study. Patients were recruited during a hospital stay at the cardiology units of 2 German university clinics (Universitätsklinikum Münster and Charité – Universitätsmedizin Berlin). Between July 2012 and July 2014, medical charts (n = 9,170) were consecutively screened; 3,093 patients were assessed for eligibility and 1,265 were eligible and gave written consent (online suppl. Fig. 2). To be included, patients had to have a chart-documented CHD diagnosis. Exclusion criteria were cognitive impairment, unavailability for follow-up, terminal illness, or insufficient language proficiency.

Upon enrollment, patients completed a questionnaire and were administered a clinical psychiatric interview either at the clinic or via telephone within 8 weeks (the mean [±SD] time to completion was 12.9 ± 11.9 days) [16], which was completed by 1,024 patients. Follow-up questionnaires were mailed to patients after 6 and 12 months, and 837 patients completed both follow-ups.

Clinical and Subclinical Depression

The presence of a depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) was determined using a standardized diagnostic interview (Composite International Diagnostic Interview; CIDI) [17] which was conducted at baseline. Current diagnoses of dysthymia and major depressive disorder (MDD) were obtained. The presence of either or both diagnoses was categorized as "clinical depression".

The severity of depressive symptoms was assessed at 3 time points (baseline, 6-month follow-up, and 12-month follow-up) using the self-rated Patient Health Questionnaire (PHQ-9). The PHQ-9 is a brief, validated depression screening tool with scores ranging from 0 to 27. Scores of 0–4 indicate no depressive symptoms, scores of 5–9 indicate mild or subthreshold depressive symptoms, and scores ≥10 indicate moderate to severe depressive symptoms [18]. Patients with a score ≥5 and no depressive disorder diagnosis were categorized as having "subclinical depression".

Depression Treatment

Depression treatment was assessed at all time points. At each assessment, the patients indicated whether they were currently receiving depression treatment (psychotherapy and/or antidepressant medication). Antidepressant medication was additionally extracted by review of the medical charts (baseline) and from the list of medications that the patients provided (follow-up assessments).

Vital Status

Deaths reported by family members or general practice physicians were verified through the local death registries. For patients who were lost to follow-up and could not be contacted, an active search was conducted in the medical records of the study hospitals as well as through the local death registries. In 3 cases, the vital status could not be ascertained.

Predictors

Sociodemographic data (age, sex, partner status, and education) as well as smoking were assessed at baseline. A history of any depressive disorder and a history of any anxiety disorder were assessed in the clinical interview. Clinical variables were extracted from medical charts of the index hospitalization and included presence of an acute coronary syndrome (ACS), percutaneous coronary intervention, left ventricular ejection fraction (LVEF), and medical comorbidities. The Charlson Comorbidity Index (CCI) [19] was computed in a modified version (exclusion of cardiac diagnoses and dementia).

Statistical Analyses

Prevalence, Treatment Rates, and Prognosis of Depression

The prevalence of clinical and subclinical depression, treatment rates at baseline and at the 2 follow-ups, and the longitudinal course of depressive symptoms are reported descriptively.

Cox regression analyses were applied to analyze associations between the diagnosis of clinical depression (any depressive disorder) and depressive severity (PHQ-9 score) and mortality with adjustment for age, sex, LVEF, CCI, ACS at baseline, percutaneous coronary intervention at baseline, and smoking status.

Predictors of Persistent Depressive Symptoms over Time

Binary logistic regression models were used to identify predictors of depression persistence across 12 months among patients with initially elevated depressive symptoms (subclinical depression). Since only 5 patients were in remission among patients with an initial clinical diagnosis of depression, no regression analyses were conducted in this group. In addition, we employed binary logistic regression models among initially nondepressed patients to identify predictors of incident depressive symptoms which persisted at 6 and 12 months. The following predictors were preselected and entered simultaneously into the models: age, sex, ACS, antidepressant treatment, somatic comorbidity (CCI), LVEF, and baseline PHQ-9 score, as well as history of any depressive disorder or anxiety disorder. Due to low sample sizes within the subgroups, CCI (0 vs. 1 or more) and LVEF (preserved vs. mid-range or reduced) were dichotomized. Regression-based multiple imputation was conducted to deal with missing data on the PHQ, LVEF, and the CCI (SPSS module for multiple imputation).

Definition of Depression Management Need

Steps of depression care and depression management need were determined according to the AHA recommendation [13] and the NICE guideline [14] (online suppl. Fig. 1a, b). Both take into account the severity and course of depressive symptoms.

The following depression groups were defined: no depressive symptoms (no clinical diagnosis and PHQ-9 <5 at all time points), incident depressive symptoms (no clinical diagnosis and PHQ-9 of 0–4 at baseline and PHQ-9 ≥5 at both follow-ups), remitting depressive symptoms (PHQ-9 ≥5 and/or clinical depression diagnosis at baseline and PHQ-9 <5 at both follow-ups), and persistent depressive symptoms (PHQ-9 ≥5 and/or clinical depression diagnosis at baseline and PHQ-9 ≥5 at both follow-ups). Intermittent depressive symptoms were defined as a score of ≥5 at only 1 follow-up assessment.

Patients in need for depression management across the 1-year study period were defined as those with persistent depressive symptoms at both follow-up time points, comprising the groups "persistent depressive symptoms" and "incident depressive symptoms".

Analyses were performed using IBM SPSS version 24. A two-sided $p < 0.05$ was considered statistically significant.

Results

Study Sample

The characteristics of the study population are displayed in Table 1. The patients were divided into the following 3 groups at baseline based on their initial depression status: patients with clinical depression according to the DSM-IV, patients without a depressive disorder but with elevated depressive symptoms (subclinical depression), and patients without any signs of depression (online suppl. Fig. 2).

Table 1. Characteristics of the study sample

Variables	Clinical depression	Subclinical depression	No depression	p^a	Total sample
	depressive disorder (DSM-IV diagnosis)	elevated depressive symptoms (PHQ-9 ≥5, not meeting DSM-IV criteria for a depressive disorder)	no depressive symptoms		
	n = 123 (12%)	*n* = 463 (45.2%)	*n* = 438 (42.8%)		*n* = 1,024
Sociodemographic variables					
Age, years	59.8±10	62.6±10	63.5±10.3	**0.002**[i, j]	62.7±10.2
Females	36 (29.3)	91 (19.7)	70 (16)	**0.004**[i]	197 (19.2)
Education ≥12 years[b]	35 (28.5)	156 (35.1)	157 (36.5)	0.253	348 (34.9)
Living with a partner[c]	80 (65)	355 (77.9)	371 (85.1)	**<0.001**[h, i, j]	806 (79.4)
Medical variables					
Current ACS	54 (43.9)	173 (37.4)	187 (42.7)		414 (40.4)
Unstable angina pectoris	19 (15.4)	52 (11.2)	44 (10)	0.081	115 (11.2)
Non-ST elevation myocardial infarction	20 (16.3)	75 (16.2)	71 (16.2)		166 (16.2)
ST elevation myocardial infarction	15 (12.2)	46 (9.9)	72 (16.4)		133 (13)
LVEF, *n* (%)					
Preserved ejection fraction (≥50%)	78 (63.4)	278 (60)	296 (67.6)	**0.044**[h]	652 (63.7)
Mid-range ejection fraction (40–49%)	25 (20.3)	92 (19.9)	78 (17.8)		195 (19)
Reduced ejection fraction (<40%)	20 (16.3)	93 (20.1)	64 (14.6)		177 (17.3)
CCI					
Score 0	54 (43.9)	239 (51.6)	276 (63)	**<0.001**[h, i]	569 (55.6)
Score 1	38 (30.9)	130 (28.1)	95 (21.7)		263 (25.7)
Score ≥2	31 (25.2)	94 (20.3)	67 (15.3)		192 (18.8)
Depression symptom severity (PHQ-9)					
PHQ-9 score	12.5±5.2	8.5±3.4	2.2±1.4	**<0.001**[h, i, j]	6.3±4.8
One-year mortality					
Deceased[d]	7 (5.7)	15 (3.2)	6 (1.4)	**0.021**[i]	28 (2.7)
Depression and anxiety disorders (DSM-IV diagnoses)					
Lifetime history of any depressive disorder	42 (34.1)	118 (25.5)	47 (10.7)	**<0.001**[h, i]	207 (20.2)
Lifetime history of any anxiety disorder[e]	50 (49)	97 (23.4)	42 (10)	**<0.001**[h, i, j]	189 (20.2)
Depression treatment at baseline[f]					
Any depression treatment	34 (27.6)	34 (7.3)	11 (2.5)		79 (7.7)
Only psychotherapy[g]	8 (6.5)	6 (1.3)	3 (<1%)		17 (1.7)
Only antidepressant medication	20 (16.3)	19 (4.1)	8 (1.8)		47 (4.6)
Psychotherapy and antidepressant medication	6 (4.9)	9 (1.9)	0		15 (1.5)
Other psychopharmacological treatment[f]					
Use of benzodiazepines	6 (4.9)	2 (0.4)	3 (0.7)		11 (1.1)

Values are presented as means ± SD or numbers (%). ACS, acute coronary syndrome; CCI, Charlson Comorbidity Index; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; LVEF, left ventricular ejection fraction; PHQ, Patient Health Questionnaire.

[a] Values refer to overall comparisons. Significant *p* values (<0.05) are highlighted in bold. Significant post hoc comparisons are indicated by superscripts; *p* was set at <0.017 after Bonferroni correction. [b] 27 patients had missing data. [c] 13 patients had missing data. [d] In 3 patients, the vital status could not be ascertained. [e] 89 patients had missing data. [f] Because of low numbers in each category, no statistical comparison was conducted. [g] 22 patients had missing data. [h] No depressive symptoms vs. elevated depressive symptoms (all $p < 0.017$). [i] No depressive symptoms vs. clinical diagnosis (all $p < 0.017$). [j] Elevated depressive symptoms vs. clinical diagnosis (all $p < 0.017$).

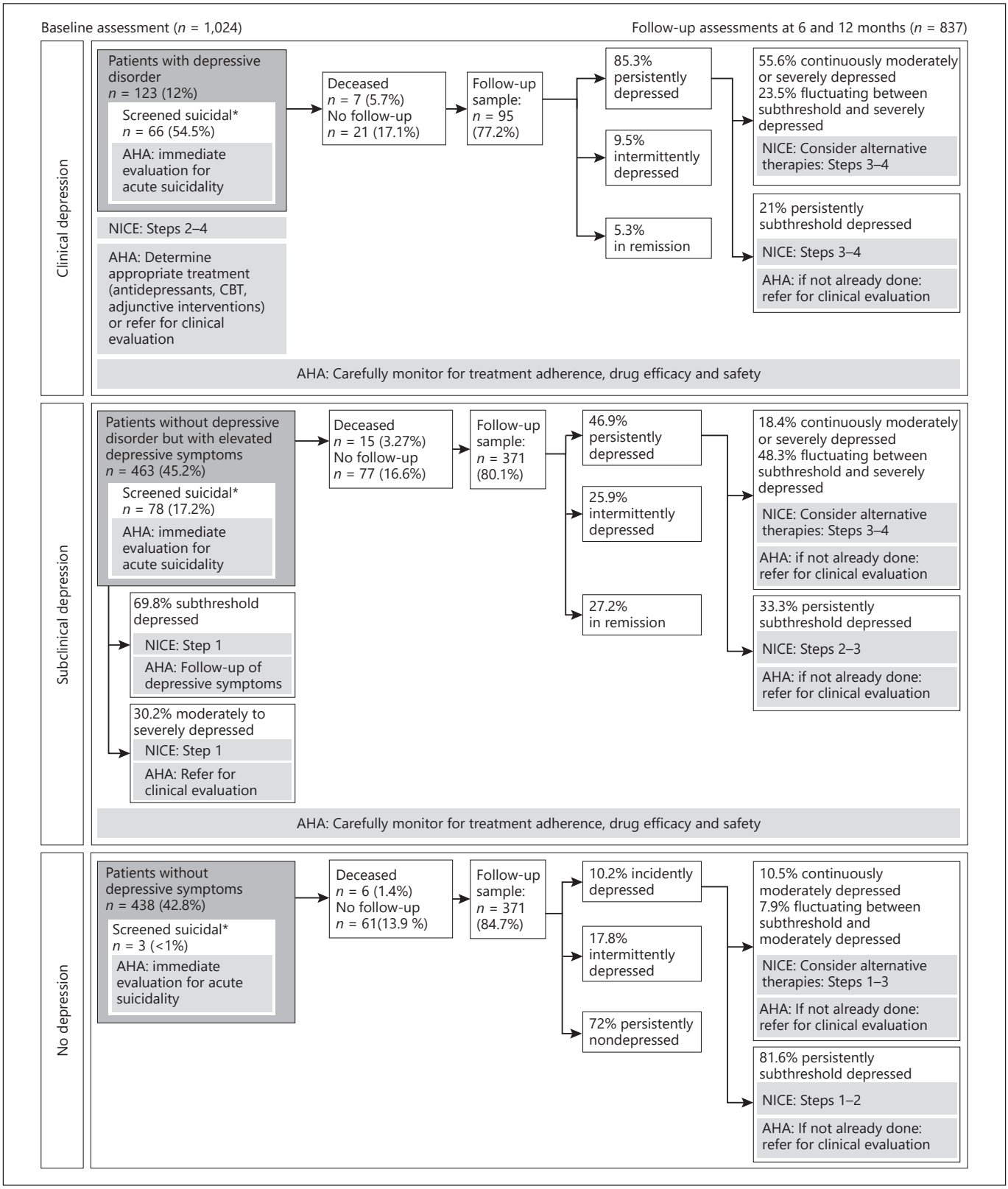

Fig. 1. Course of depression and steps of depression management according to the American Heart Association (AHA) and National Institute for Health and Care Excellence (NICE). * Patient Health Questionnaire (PHQ-9) item 9 ≤1; *n* = 12 missing data.

Prevalence of Clinical and Subclinical Depression at Baseline

According to the DSM-IV, 123 patients (overall 12%; 18.3% of the women and 10.5% of the men) met the criteria for any depressive disorder. Of those, 46 (37.4%) had an MDD, 38 (30.9%) had dysthymia, and 39 (31.7%) had both; 463 patients (45.2%; 46.2% of the women and 45% of the men) had subclinical depression (elevated depressive symptoms in the absence of a clinical depression diagnosis), and of those 69.8% were subthreshold depressed and 30.2% exhibited moderate to severe depressive symptoms. Forty-three percent had no signs of depression at baseline.

Depression Treatment at Baseline and during Follow-Up

The baseline depression treatment rates are displayed in Table 1. Of the follow-up sample (n = 837), a total of 118 (14.1%) patients received psychotherapy and/or antidepressant medication during any time point in the 12 months (online suppl. Table 1). Fifty-four (6.5%) of the patients received continuous depression treatment at all 3 time points.

Among patients with a depressive disorder (n = 123), 34 (27.6%) were in treatment at baseline. Of the follow-up sample (n = 95 with a depressive disorder at baseline), 44 (46.3%) received treatment during any time point in the 12 months; 25 (26.3%) received continuous treatment at all 3 time points.

Mortality and Availability for Follow-Up

Of all 1,024 patients, 28 (2.7%) died within 12 months (for 3 patients, the vital status could not be ascertained). After adjustment for age, sex, and risk factors, any depressive disorder and depression severity were associated with an increased risk of mortality (adjusted HR = 3.19; 95% CI 1.32–7.69 for any depressive disorder, and adjusted HR = 1.09; 95% CI 1.02–1.16 for depressive symptoms [per unit increase], respectively). Depression treatment was not included in the model because none of the patients under depression treatment died within 1 year.

One hundred fifty-nine (15.5%) patients were lost to follow-up. Compared to the study completers, these patients were significantly younger (58.9 ± 11 vs. 63.2 ± 9.8 years; $p < 0.001$), exhibited more depressive symptoms at baseline (PHQ-9 score 6.9 ± 5.2 vs. 6.1 ± 4.7; $p < 0.05$), were more likely to have an ACS at baseline (49.7 vs. 39.2%, $p < 0.05$), and had a lower LVEF (22.6 vs. 15.7% had a reduced ejection fraction <40%; Mann-Whitney U test; $p < 0.05$).

Course of Depression among Different Depression Groups

Figure 1 displays the longitudinal course of depressive symptoms among different depression groups as well as recommended steps of depression care in line with the AHA (online suppl. Fig. 1a) and NICE (online suppl. Fig. 1b) guidelines. Overall, 57% exhibited at least mild depressive symptoms at baseline. More than 85% of the patients with a depressive disorder continued to have elevated depressive symptoms at both follow-up assessments, with more than half of these reporting consistently moderate to severe symptoms.

Of patients with initially elevated symptoms, 47% (n = 174) continued to have persistent depressive symptoms over the course of 1 year and 27% (n = 101) were in remission. Among the group of patients with no signs of depression, 72% (n = 267) remained persistently nondepressed and 10% (n = 38) later developed elevated depressive symptoms. Overall, the majority of patients under depression treatment at baseline (71%) were persistently depressed at both follow-ups (i.e., 73% of the patients in the group with subclinical depression and 90% of those with clinical depression).

Predictors of Persistent Depressive Symptoms during Follow-Up

Among patients with clinical depression, 85% exhibited persistently elevated depressive symptoms during follow-up and only 5 patients were in remission. It was thus not possible to identify predictors of depression persistence among this group. Nevertheless, we analyzed the course of depression symptoms by treatment status. As shown in online supplementary Figure 3, patients with continuous depression treatment across 12 months had the highest PHQ-9 scores compared to patients with intermittent treatment and patients with no treatment. In all groups, the mean PHQ-9 score was ≥10 at all time points.

The adjusted OR for predictors of depression persistence in patients with initially subclinical depression and those with no depression symptoms are presented in Table 2.

Among patients with subclinical depression at baseline, the level of initial depressive symptoms, a history of depressive disorder, and anxiety disorder, respectively, significantly predicted depression persistence across 12 months (all $p < 0.05$). Among initially nondepressed patients, elevated depressive symptoms at the 6- and 12-month follow-up were associated with increased initial depressive symptoms, a history of depressive disor-

Table 2. Adjusted OR for persistently elevated depressive symptoms 6 and 12 months after hospitalization

Predictor	OR	95% CI	*p*
Patients with initially subclinical depression (elevated depressive symptoms) (*n* = 275); *persistent depressive symptoms (n = 174) (vs. remitted depressive symptoms at 6 and 12 months)*			
Sex (female = 0, male = 1)	0.63	(0.27–1.49)	0.292
Age	0.99	(0.96–1.03)	0.654
Education	1.02	(0.53–1.95)	0.954
Partner status	1.18	(0.51–2.71)	0.697
Antidepressant treatment (absence = 0, presence = 1)	3.46	(1.15–10.41)	**0.027**
CCI			
Score 0		Reference	
Score ≥1	1.42	(0.74–2.73)	0.292
ACS (absence = 0, presence = 1)	0.95	(0.5–1.83)	0.882
LVEF			
Preserved ejection fraction (≥50)		Reference	
Mid-range ejection fraction or reduced ejection fraction (<50)	1.27	(0.67–2.38)	0.465
Baseline PHQ-9 score	1.46	(1.27–1.69)	**<0.001**
Lifetime history of depressive disorder (absence = 0, presence = 1)	2.41	(1.06–5.47)	**0.035**
Lifetime history of anxiety disorder (absence = 0, presence = 1)	2.64	(1.11–6.29)	**0.029**
Patients with initially no depressive symptoms (*n* = 305); *incident depressive symptoms (n = 38) (vs. persistently no depressive symptoms at 6 and 12 months)*			
Sex (female = 0, male = 1)	0.77	(0.24–2.48)	0.660
Age	1.00	(0.95–1.05)	0.877
Education	0.76	(0.31–1.84)	0.542
Partner status	2.67	(0.5–14.34)	0.251
Antidepressant treatment (absence = 0, presence = 1)	1.19	(0.2–7.09)	0.847
CCI			
Score 0		Reference	
Score ≥1	2.5	(0.94–6.61)	0.065
ACS (absence = 0, presence = 1)	4.7	(1.87–11.84)	**0.001**
LVEF			
Preserved ejection (≥50)		Reference	
Mid-range EF or reduced EF (<50)	0.4	(0.17–0.92)	**0.032**
Baseline PHQ-9 score	1.76	(1.24–2.48)	**0.001**
Lifetime history of depressive disorder (absence = 0, presence = 1)	5.65	(1.78–17.88)	**0.003**
Lifetime history of anxiety disorder (absence = 0, presence = 1)	2.85	(0.76–10.73)	0.121

ACS, acute coronary syndrome; CCI, Charlson Comorbidity Index; CI, confidence interval; LVEF, left ventricular ejection fraction; OR, odds ratio; PHQ, Patient Health Questionnaire.

The binary logistic regression models simultaneously included all of the listed predictors. For continuous variables, OR correspond to 1 unit increase. Significant *p* values (<0.05) are highlighted in bold.

der, a reduced LVEF, and the occurrence of an ACS at baseline (all $p < 0.05$). Whereas the rates of unstable angina were similar in both groups, the rate of myocardial infarction was higher in patients with incident depressive symptoms than in persistently nondepressed patients (47.4 vs. 27.7%).

Depression Management Need within 1 Year

Figure 2 displays the expected depression management need according to the AHA (online suppl. Fig. 1a) and NICE (online suppl. Fig. 1b) guidelines based on the longitudinal depression course in a sample of 1,024 hospitalized CHD patients. While approximately half of all patients has no management need, around one third would require either initiation or adjustment of depression management. The exact management procedure according to NICE depends on whether treatment is already implemented. Sixteen percent of all patients were lost to follow-up, and thus the depression management need is unknown in these patients.

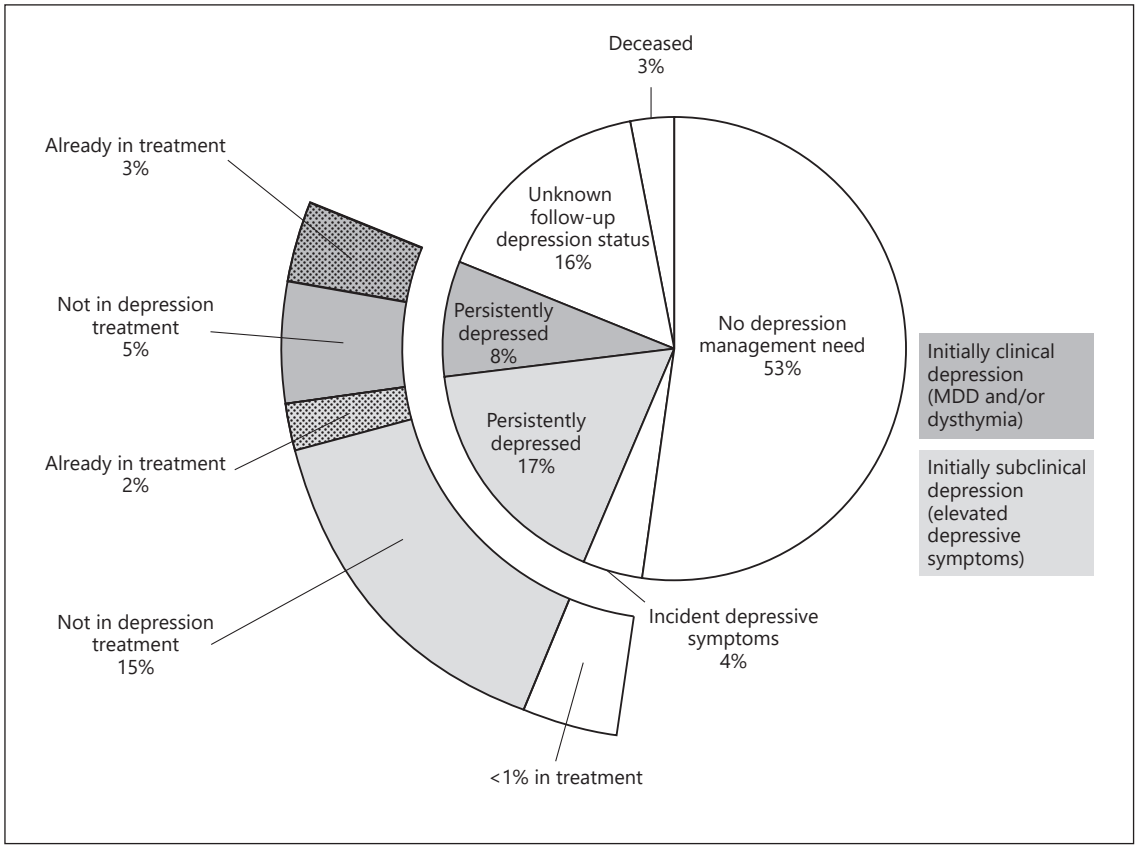

Fig. 2. Depression status and depression management need within 1 year (n = 1,024). MDD, major depressive disorder.

Discussion

In this consecutive cohort of hospital-treated CHD patients, elevated depressive symptoms at the time of hospital treatment were prevalent and they were associated with an increased 12-month mortality risk. Among survivors, the rates of depression treatment were low and persistently elevated depressive symptoms were found in 85% of patients with clinical depression, 47% of patients with subclinical depression, and 10% of patients with initially no depressive symptoms. Applying existing clinical recommendations [13, 14], one third of patients would need some form of depression management over the course of 1 year.

At hospitalization, 12% had a depressive disorder and 45% had subclinical depression. These rates are higher in comparison to the general population [20, 21] and at the lower end of prevalence rates reported in other CHD samples, which range between 7 and 45% [3, 22–24]. In contrast to most studies with CHD patients, we defined clinical depression not only as MDD but also as dysthymia, which is also common among CHD patients [25]. Dysthymia is the more chronic form of depression, which persists for at least 2 years with milder symptoms [14], is equally burdensome, and tends to progress to MDD [26].

Depressed patients were more likely to be female, be younger, be living without a partner, and have more comorbidities, which is known from other studies [3, 22]. Clinically depressed patients were more than 3 times more likely to have had a previous depressive disorder in their lifetime compared to patients without current depressive symptoms. Our data also confirms previous findings that depression is a risk factor for mortality, independently of somatic comorbidity [4, 24]. This applies to both depressive symptoms and clinical depressive disorders, which is noteworthy because few studies on depression and mortality have assessed depression using a structured interview [27].

Depression treatment rates were insufficient; less than half of the patients with clinical depression received any

depression treatment, and only 26% received continuous treatment. Similar treatment rates were found in another CHD patient cohort [28] and in the general German population [29]. Poor recognition of depression by healthcare providers has previously been reported [30, 31], yet patients may also be responsible for poor treatment rates. In a series of community surveys, only an average of 65% of patients with MDD in high-income countries reported that they had a treatment need, and, among those, 22% did not initiate treatment [32].

The rates of depression persistence were high in our study; 85% of clinically depressed and 47% of subclinically depressed patients reported elevated depressive symptoms at all time points. High levels of persistent depression have previously been shown in patients after acute myocardial infarction [23, 33, 34]. In our sample, patients with a more severe depression were more likely to receive depression treatment; however, they were also more likely to have persistent depressive symptoms. Clinically depressed patients who continuously received depression treatment had the highest symptom burden at all time points. Similar findings have previously been reported [35]. This might be an indication that antidepressant treatment is not effective enough in usual care. Nonresponse to depression treatment is a common phenomenon even in highly standardized randomized clinical trials, which typically exclude less adherent patients with comorbidities. Full remission is hard to achieve and in approximately two thirds of patients multiple treatment steps are needed [36]. Moreover, relapses are common, with the highest relapse rate among patients who need more treatment steps.

Other potential risks after antidepressant therapy are discontinuation symptoms [37], which include physical reactions (like nausea or vertigo), sleep disturbances, and mood reactions (like anxiety). These also apply to newer-generation antidepressants such as selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors [38–40]. It has been postulated that antidepressant medication could potentially contribute to depression chronicity [37, 41]. Long-term use of antidepressant medication is increasing [42] and might be associated with poorer depression outcomes [43]. However, causal inferences from observational data should be made with caution. Importantly, the design of our study did not allow us to test this hypothesis.

In several meta-analyses, the efficacy/effectiveness of antidepressant medication and psychotherapy for reducing depressive symptoms in stable and acute CHD cases have been shown to be small to moderate [6, 44–47]. Remission rates range between 26 and 69% [6, 36, 48] and response rates range between 43 and 67%, [6, 36] depending on measures and intervention. Improvements in health-related quality of life have been reported after psychological interventions with mixed results concerning mental and/or physical components of quality of life [44]. In 2 antidepressant trials with cardiac patients (1 with citalopram and 1 with escitalopram), quality of life improved significantly in the treatment group versus the placebo group [49, 50].

Several studies have investigated possible effects of antidepressant treatments on clinical outcomes and mortality in CHD patient samples. One recent meta-analysis showed a benefit of psychological interventions on cardiac mortality – albeit from studies of mixed quality [44]. Possible cardiotoxic effects of antidepressants have been discussed. Evidence from a broad range of studies suggests that selective serotonin reuptake inhibitors are relatively safe in cardiovascular patients or even beneficial with regard to mortality rates [51, 52] and cardiac events [53]. In contrast, a recent observational study showed that the longer-term risk for major adverse cardiac events might be increased for different types of antidepressants (atypical, tricyclic, and some selective serotonin reuptake inhibitors) [54]. However, due to a number of potential biases (e.g., confounding by indication), causal inferences from observational studies should be made with caution.

Importantly, RCT typically have strict inclusion/exclusion criteria (e.g., multimorbid patients are excluded and those with a poor antidepressant treatment response in the past) and thus comparisons with patients who receive depression treatment in usual care settings should be made with caution. A recent study using registry data from 4,062 patients showed that patients with treated depression had the same mortality risk as patients without depression, whereas untreated patients had a higher mortality risk [28]. In our study, we found that none of the patients in depression treatment died within 12 months. However, our sample was too small to test whether untreated depressed patients had an increased mortality risk.

What are the risk factors for persistent depression? Analyses on predictors of persistently elevated depressive symptoms showed that patients with subclinical depression who had a history of a depressive or an anxiety disorder were particularly at risk for persistent depressive symptoms, supporting recommendations to pay special attention to known depression or anxiety disorders [1, 13,

14]. In patients who were initially nondepressed, a history of depression was also a predictor of incident depressive symptoms during the 1-year follow-up. In addition, incident depression was more likely in patients with a lower LVEF and in patients who had an ACS at baseline. Our data indicates that it might primarily be acute myocardial infarction which is the driving risk factor for incident depression; however, the sample size did not allow for a differential analysis of ACS type.

Strengths and Limitations

The strengths of this study are its large sample size, the standardized diagnostic assessment of clinical depression according to DSM-IV criteria, 2 follow-up assessments, and few exclusion criteria to approximate a real-life healthcare setting for CHD patients.

Our data does not provide information on the appropriateness of the depression treatments, recognition rates, treatment refusals, or reasons for treatment discontinuations. Additionally, treatment effects are difficult to assess in usual care and the design of our study does not allow for causal conclusions. Moreover, antidepressant medication may not necessarily have been prescribed for depression but also for sleep problems or anxiety disorders. Attrition was higher in patients with more severe depressive symptoms; this could have resulted in underestimated rates of persistent depression.

Conclusions and Clinical Implications

This study confirms the high prevalence and increased mortality risk of depression in CHD patients in a real-world, usual-care setting in a country with highly specialized care. Moreover, it demonstrates a lack of sufficient depression recognition and depression management. Assessing previous depressive or anxiety disorders may help to identify patients at an increased risk for persistent depression, and heightened awareness should be exercised in relation to patients after an ACS. Overall, about one third of hospitalized CHD patients would require some form of depression management over the course of 1 year [13, 14]. The lowest level of management would be notification of the general practitioner and/or referral to a mental health specialist. Treatment response should be monitored and insufficient responses appropriately managed. Collaborative care is a promising healthcare delivery model for patients with depression with and without a somatic illness [55–57], even for subthreshold depression [58]. Whether a systematic depression screening will result in improved depression outcomes remains to be studied. Particularly in view of the limited effects of antidepressant therapy on both mental health and cardiac prognosis, other possible targets of clinical management should be considered in CHD patients. Such targets might include chronic stress, demoralization, quality of life, well-being, illness behavior, and anxiety [59, 60]. These components may have an impact on cardiovascular prognosis and interact with depression as well as its assessment and treatment. Treatment of these targets might result in cardiovascular benefits [61]. In clinical practice, a wider range of psychosocial conditions should be considered.

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Statement of Ethics

Written informed consent was obtained from all of the participants. This study was approved by the institutional review boards of both institutions.

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References

1 Siu AL, Bibbins-Domingo K, Grossman DC, Baumann LC, Davidson KW, Ebell M, et al.; US Preventive Services Task Force (USPSTF). Screening for Depression in Adults: US Preventive Services Task Force Recommendation Statement. JAMA. 2016 Jan;315(4):380–7.

2 Whooley MA, Wong JM. Depression and cardiovascular disorders. Annu Rev Clin Psychol. 2013;9(1):327–54.

3 Whooley MA, de Jonge P, Vittinghoff E, Otte C, Moos R, Carney RM, et al. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. JAMA. 2008 Nov;300(20):2379–88.

4 Freedland KE, Carney RM. Depression as a risk factor for adverse outcomes in coronary heart disease. BMC Med. 2013 May;11(1):131.

5 Palacios JE, Khondoker M, Achilla E, Tylee A, Hotopf M. A Single, One-Off Measure of Depression and Anxiety Predicts Future Symptoms, Higher Healthcare Costs, and Lower Quality of Life in Coronary Heart Disease Patients: Analysis from a Multi-Wave, Primary Care Cohort Study. PLoS One. 2016 Jul;11(7):e0158163.

6 Thombs BD, de Jonge P, Coyne JC, Whooley MA, Frasure-Smith N, Mitchell AJ, et al. Depression screening and patient outcomes in cardiovascular care: a systematic review. JAMA. 2008 Nov;300(18):2161–71.

7 Löwe B, Blankenberg S, Wegscheider K, König HH, Walter D, Murray AM, et al. Depression screening with patient-targeted feedback in cardiology: DEPSCREEN-INFO randomised clinical trial. Br J Psychiatry. 2017 Feb;210(2):132–9.

8 Ruo B, Rumsfeld JS, Hlatky MA, Liu H, Browner WS, Whooley MA. Depressive symptoms and health-related quality of life: the Heart and Soul Study. JAMA. 2003 Jul;290(2):215–21.

9 Kronish IM, Rieckmann N, Halm EA, Shimbo D, Vorchheimer D, Haas DC, et al. Persistent depression affects adherence to secondary prevention behaviors after acute coronary syndromes. J Gen Intern Med. 2006 Nov;21(11):1178–83.

10 Rieckmann N, Burg MM, Kronish IM, Chaplin WF, Schwartz JE, Davidson KW. Aspirin adherence, depression and one-year prognosis after acute coronary syndrome. Psychother Psychosom. 2011;80(5):316–8.

11 Carney RM, Freedland KE, Jaffe AS. Depression screening in patients with heart disease. JAMA. 2009 Apr;301(13):1337.

12 Whooley MA. To screen or not to screen? Depression in patients with cardiovascular disease. J Am Coll Cardiol. 2009 Sep;54(10):891–3.

13 Lichtman JH, Bigger JT Jr, Blumenthal JA, Frasure-Smith N, Kaufmann PG, Lespérance F, et al.; American Heart Association Prevention Committee of the Council on Cardiovascular Nursing; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Epidemiology and Prevention; American Heart Association Interdisciplinary Council on Quality of Care and Outcomes Research; American Psychiatric Association. Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Psychiatric Association. Circulation. 2008 Oct;118(17):1768–75.

14 National Institute for Health and Care Excellence: Depression in adults with a chronic physical health problem: NICE Clinical Guideline 91. London: NICE; 2009.

15 McCarron RM, Vanderlip ER, Rado J. Depression. Ann Intern Med. 2016 Oct;165(7):ITC49–64.

16 Tschorn M, Rieckmann N, Arolt V, Beer K, Haverkamp W, Martus P, et al. Diagnostic accuracy of German depression screenings in patients with coronary heart disease. Psychiatr Prax. 2019 Jan;46(1):41–8.

17 Wittchen HU, Pfister H. DIA-X-Interviews: Manual für Screening-Verfahren und Interview; Interviewheft Längsschnittuntersuchung (DIA-X-Lifetime); Ergänzungsheft (DIA-X-Lifetime); Interviewheft Querschnittuntersuchung (DIA-X-12 Monate); Ergänzungsheft (DIA-X-12 Monate); PC-Programm zur Durchführung des Interviews (Längs- und Querschnittuntersuchung). Frankfurt: Auswertungsprogramm. Swets & Zeitlinger; 1997.

18 Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001 Sep;16(9):606–13.

19 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.

20 Jacobi F, Höfler M, Siegert J, Mack S, Gerschler A, Scholl L, et al. Twelve-month prevalence, comorbidity and correlates of mental disorders in Germany: the Mental Health Module of the German Health Interview and Examination Survey for Adults (DEGS1-MH). Int J Methods Psychiatr Res. 2014 Sep;23(3):304–19.

21 Andreas S, Schulz H, Volkert J, Dehoust M, Sehner S, Suling A, et al. Prevalence of mental disorders in elderly people: the European MentDis_ICF65+ study. Br J Psychiatry. 2017 Feb;210(2):125–31.

22 Frasure-Smith N, Lespérance F. Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. Arch Gen Psychiatry. 2008 Jan;65(1):62–71.

23 Thombs BD, Bass EB, Ford DE, Stewart KJ, Tsilidis KK, Patel U, et al. Prevalence of depression in survivors of acute myocardial infarction. J Gen Intern Med. 2006 Jan;21(1):30–8.

24 Carney RM, Freedland KE. Depression and coronary heart disease. Nat Rev Cardiol. 2017 Mar;14(3):145–55.

25 Baune BT, Adrian I, Arolt V, Berger K. Associations between major depression, bipolar disorders, dysthymia and cardiovascular diseases in the general adult population. Psychother Psychosom. 2006;75(5):319–26.

26 Laborde-Lahoz P, El-Gabalawy R, Kinley J, Kirwin PD, Sareen J, Pietrzak RH. Subsyndromal depression among older adults in the USA: prevalence, comorbidity, and risk for new-onset psychiatric disorders in late life. Int J Geriatr Psychiatry. 2015 Jul;30(7):677–85.

27 Machado MO, Veronese N, Sanches M, Stubbs B, Koyanagi A, Thompson T, et al. The association of depression and all-cause and cause-specific mortality: an umbrella review of systematic reviews and meta-analyses. BMC Med. 2018 Jul;16(1):112.

28 Smolderen KG, Buchanan DM, Gosch K, Whooley M, Chan PS, Vaccarino V, et al. Depression Treatment and 1-Year Mortality After Acute Myocardial Infarction: Insights From the TRIUMPH Registry (Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status). Circulation. 2017 May;135(18):1681–9.

29 Mack S, Jacobi F, Gerschler A, Strehle J, Höfler M, Busch MA, et al. Self-reported utilization of mental health services in the adult German population—evidence for unmet needs? Results of the DEGS1-Mental Health Module (DEGS1-MH). Int J Methods Psychiatr Res. 2014 Sep;23(3):289–303.

30 Gerrits MM, van Marwijk HW, van Oppen P, van der Horst H, Penninx BW. The role of somatic health problems in the recognition of depressive and anxiety disorders by general practitioners. J Affect Disord. 2013 Dec;151(3):1025–32.

31 Fernández A, Pinto-Meza A, Bellón JA, Roura-Poch P, Haro JM, Autonell J, et al. Is major depression adequately diagnosed and treated by general practitioners? Results from an epidemiological study. Gen Hosp Psychiatry. 2010 Mar-Apr;32(2):201–9.

32 Thornicroft G, Chatterji S, Evans-Lacko S, Gruber M, Sampson N, Aguilar-Gaxiola S, et al. Undertreatment of people with major depressive disorder in 21 countries. Br J Psychiatry. 2017 Feb;210(2):119–24.

33 Martens EJ, Smith OR, Winter J, Denollet J, Pedersen SS. Cardiac history, prior depression and personality predict course of depressive symptoms after myocardial infarction. Psychol Med. 2008 Feb;38(2):257–64.
34 Kaptein KI, de Jonge P, van den Brink RH, Korf J. Course of depressive symptoms after myocardial infarction and cardiac prognosis: a latent class analysis. Psychosom Med. 2006 Sep-Oct;68(5):662–8.
35 Cowan MJ, Freedland KE, Burg MM, Saab PG, Youngblood ME, Cornell CE, et al.; ENRICHD Investigators. Predictors of treatment response for depression and inadequate social support—the ENRICHD randomized clinical trial. Psychother Psychosom. 2008; 77(1):27–37.
36 Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006 Nov;163(11):1905–17.
37 Fava GA, Belaise C. Discontinuing Antidepressant Drugs: Lesson from a Failed Trial and Extensive Clinical Experience. Psychother Psychosom. 2018;87(5):257–67.
38 Fava GA, Gatti A, Belaise C, Guidi J, Offidani E. Withdrawal Symptoms after Selective Serotonin Reuptake Inhibitor Discontinuation: A Systematic Review. Psychother Psychosom. 2015;84(2):72–81.
39 Carvalho AF, Sharma MS, Brunoni AR, Vieta E, Fava GA. The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature. Psychother Psychosom. 2016; 85(5):270–88.
40 Fava GA, Benasi G, Lucente M, Offidani E, Cosci F, Guidi J. Withdrawal Symptoms after Serotonin-Noradrenaline Reuptake Inhibitor Discontinuation: systematic Review. Psychother Psychosom. 2018;87(4):195–203.
41 Fava GA. Can long-term treatment with antidepressant drugs worsen the course of depression? J Clin Psychiatry. 2003 Feb;64(2): 123–33.
42 Huijbregts KM, Hoogendoorn A, Slottje P, van Balkom AJ, Batelaan NM. Long-Term and Short-Term Antidepressant Use in General Practice: Data from a Large Cohort in the Netherlands. Psychother Psychosom. 2017; 86(6):362–9.
43 Hengartner MP, Angst J, Rössler W. Antidepressant Use Prospectively Relates to a Poorer Long-Term Outcome of Depression: Results from a Prospective Community Cohort Study over 30 Years. Psychother Psychosom. 2018; 87(3):181–3.
44 Richards SH, Anderson L, Jenkinson CE, Whalley B, Rees K, Davies P, et al. Psychological interventions for coronary heart disease: cochrane systematic review and meta-analysis. Eur J Prev Cardiol. 2018 Feb;25(3): 247–59.
45 Thombs BD, Roseman M, Coyne JC, de Jonge P, Delisle VC, Arthurs E, et al. Does evidence support the American Heart Association's recommendation to screen patients for depression in cardiovascular care? An updated systematic review. PLoS One. 2013;8(1): e52654.
46 Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with coronary artery disease. Cochrane Database Syst Rev. 2011 Sep;(9):CD008012.
47 Nieuwsma JA, Williams JW Jr, Namdari N, Washam JB, Raitz G, Blumenthal JA, et al. Diagnostic Accuracy of Screening Tests and Treatment for Post-Acute Coronary Syndrome Depression: A Systematic Review. Ann Intern Med. 2017 Nov;167(10):725–35.
48 Carney RM, Freedland KE, Steinmeyer BC, Rubin EH, Rich MW. Clinical predictors of depression treatment outcomes in patients with coronary heart disease. J Psychosom Res. 2016 Sep;88:36–41.
49 Kim JM, Stewart R, Bae KY, Kang HJ, Kim SW, Shin IS, et al. Effects of depression comorbidity and treatment on quality of life in patients with acute coronary syndrome: the Korean depression in ACS (K-DEPACS) and the escitalopram for depression in ACS (EsDEPACS) study. Psychol Med. 2015 Jun; 45(8):1641–52.
50 Lespérance F, Frasure-Smith N, Koszycki D, Laliberté MA, van Zyl LT, Baker B, et al.; CREATE Investigators. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. JAMA. 2007 Jan; 297(4):367–79.
51 Maslej MM, Bolker BM, Russell MJ, Eaton K, Durisko Z, Hollon SD, et al. The Mortality and Myocardial Effects of Antidepressants Are Moderated by Preexisting Cardiovascular Disease: A Meta-Analysis. Psychother Psychosom. 2017;86(5):268–82.
52 Pizzi C, Rutjes AW, Costa GM, Fontana F, Mezzetti A, Manzoli L. Meta-analysis of selective serotonin reuptake inhibitors in patients with depression and coronary heart disease. Am J Cardiol. 2011 Apr;107(7):972–9.
53 Kim JM, Stewart R, Lee YS, Lee HJ, Kim MC, Kim JW, et al. Effect of Escitalopram vs Placebo Treatment for Depression on Long-term Cardiac Outcomes in Patients With Acute Coronary Syndrome: A Randomized Clinical Trial. JAMA. 2018 Jul;320(4):350–8.
54 Grace SL, Medina-Inojosa JR, Thomas RJ, Krause H, Vickers-Douglas KS, Palmer BA, et al. Antidepressant Use by Class: Association with Major Adverse Cardiac Events in Patients with Coronary Artery Disease. Psychother Psychosom. 2018;87(2):85–94.
55 Sighinolfi C, Nespeca C, Menchetti M, Levantesi P, Belvederi Murri M, Berardi D. Collaborative care for depression in European countries: a systematic review and meta-analysis. J Psychosom Res. 2014 Oct;77(4):247–63.
56 Härter M, Watzke B, Daubmann A, Wegscheider K, König HH, Brettschneider C, et al. Guideline-based stepped and collaborative care for patients with depression in a cluster-randomised trial. Sci Rep. 2018 Jun;8(1):9389.
57 Panagioti M, Bower P, Kontopantelis E, Lovell K, Gilbody S, Waheed W, et al. Association Between Chronic Physical Conditions and the Effectiveness of Collaborative Care for Depression: An Individual Participant Data Meta-analysis. JAMA Psychiatry. 2016 Sep;73(9):978–89.
58 Gilbody S, Lewis H, Adamson J, Atherton K, Bailey D, Birtwistle J, et al. Effect of Collaborative Care vs Usual Care on Depressive Symptoms in Older Adults With Subthreshold Depression: The CASPER Randomized Clinical Trial. JAMA. 2017 Feb;317(7):728–37.
59 Rafanelli C, Sirri L, Grandi S, Fava GA. Is depression the wrong treatment target for improving outcome in coronary artery disease? Psychother Psychosom. 2013;82(5):285–91.
60 Fava GA, Cosci F, Sonino N. Current Psychosomatic Practice. Psychother Psychosom. 2017;86(1):13–30.
61 Balon R, Rafanelli C, Sonino N. Benzodiazepines: a valuable tool in the management of cardiovascular conditions. Psychother Psychosom. 2018;87(6):327–30.