A Stepwise Psychotherapy Intervention for Reducing Risk in Coronary Artery Disease (SPIRR-CAD): Results of an Observer-Blinded, Multicenter, Randomized Trial in Depressed Patients With Coronary Artery Disease

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ABSTRACT

Background: Depression predicts adverse prognosis in patients with coronary artery disease (CAD), but previous treatment trials yielded mixed results. We tested the hypothesis that stepwise psychotherapy improves depressive symptoms more than simple information.

Methods: In a multicenter trial, we randomized 570 CAD patients scoring higher than 7 on the Hospital Anxiety and Depression Scale-depression subscale to usual care plus either one information session (UC-IS) or stepwise psychotherapy (UC-PT). UC-PT patients received three individual psychotherapy sessions. Those still depressed were offered group psychotherapy (25 sessions). The primary outcome was changed in the Hospital Anxiety and Depression Scale-depression scores from baseline to 18 months. Preplanned subgroup analyses examined whether treatment responses differed by patients' sex and personality factors (Type D).

Results: The mean (standard deviation) depression scores declined from 10.4 (2.5) to 8.7 (4.1) at 18 months in UC-PT and from 10.4 (2.5) to 8.9 (3.9) in UC-IS (both $p < .001$). There was no significant group difference in change of depressive symptoms (group-by-time effect, $p = .90$). Preplanned subgroup analyses revealed no differences in treatment effects between men versus women ($p_{\text{treatment-by-sex interaction}} = .799$) but a significant treatment-by-Type D interaction on change in depressive symptoms ($p = .026$) with a trend for stronger improvement with UC-PT than UC-IS in Type D patients ($n = 341$, $p = .057$) and no such difference in improvement in patients without Type D ($n = 227$, $p = .54$).

SDC Supplemental Content

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Conclusions: Stepwise psychotherapy failed to improve depressive symptoms in CAD patients more than UC-IS. The intervention might be beneficial for depressed CAD patients with Type D personality. However, this finding requires further study.

Trial Registration: www.clinicaltrials.gov NCT00705965; www.isrctn.com ISRCTN76240576.

Key words: coronary disease, depression, psychotherapy, type D personality, randomized controlled trial.

INTRODUCTION

Depression is a frequent comorbidity in patients with coronary artery disease (CAD), and it is associated with adverse subjective and objective outcomes (1–9). A recent scientific statement from the American Heart Association considers depression as a "risk factor for adverse medical outcomes in patients with acute coronary syndrome" (10). Even mild depressive symptoms may lead to increased cardiac event rates (11).

Several trials have attempted to treat depressive symptoms or disorders in coronary patients (12–20), but meta-analyses show no treatment effect on total mortality and mainly small, if any, effects on psychological outcomes (21,22).

One reason for the relatively poor effects of treatments for depressive symptoms in coronary patients, at least with regard to cardiac outcomes, may be that sex-specific aspects of interventions, and maladaptive personality traits have received little attention. Men and women seem to react differently to psychosocial interventions (23), requiring sex-sensitive interventions (24). The Type D personality (25), that is, a lasting tendency to experience negative emotions and to suppress expression of emotions in interpersonal interactions, may lead to both depressive symptoms and adverse cardiac outcomes (26,27). Although more recent studies (28) found smaller or null prognostic effects for Type D, it may be useful to focus not only on depressive symptoms but also on maladaptive personality traits to effectively treat depressed cardiac patients.

Secondly, it might not be ideal to include patients as soon as possible after an index cardiac event as was done in Enhancing Recovery In Coronary Heart Disease Trial (ENRICHD (17)), the largest trial in this area to date. A meta-analysis (29) found that interventions starting later after an index event yielded better results than those starting early. Finally, more individualized interventions have shown promising results (13), and the temporal course of depressive symptoms might be a useful criterion for individualizing treatment intensity.

The Stepwise Psychotherapy Intervention for Reducing Risk in Coronary Artery Disease trial (SPIRR-CAD (30)) was therefore designed to test the hypothesis that a stepwise psychotherapy intervention is more effective in alleviating depressive symptoms than one information session added to usual care. The intervention was based on principles of short-term psychodynamic psychotherapy and cognitive behavioral therapy both shown to be effective in treating depression (31) and tailored to the specific problems of depressed CAD patients, including coexisting Type D personality and the need to cope with a potentially life-threatening disease. Secondary aims were to test whether treatment effects differed by sex and the presence of Type D personality and whether the stepwise procedure offering different intensities of treatment to patients with versus without early remission of depressive symptoms seems appropriate.

ANCOVA = Analysis of covariance, **CAD** = coronary artery disease, **CREATE** = Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy Trial, **DS-14** = fourteen-item Type D scale, **ENRICHD** = Enhancing Recovery In Coronary Heart Disease Trial, **HADS** = Hospital Anxiety and Depression Scale, **HAM-D** = Hamilton Depression Rating Scale, **LOCF** = last observation carried forward, **MACE** = major adverse cardiac event(s), **MMRM** = mixed model repeated measures, **SCID** = structured clinical interview for DSM-IV, **SPIRR-CAD** = A Stepwise Psychotherapy Intervention for Reducing Risk in Coronary Artery Disease Trial

METHODS

Trial Design

As described in detail elsewhere (30), SPIRR-CAD is a randomized, controlled, two-parallel-arm, superiority trial comparing a stepwise psychotherapy intervention with one individual information session complementing usual care. The trial was conducted in accordance with Good Clinical Practice and the Helsinki Declaration. The trial protocol was approved by all local ethics committees at the participating centers. All patients gave written informed consent before inclusion.

Participants

Patients aged 18 to 75 years were eligible for the trial if they had documented CAD with recent coronary angiograms and a depression score of higher than 7 on the Hospital Anxiety and Depression Scale (HADS (32,33)). Recruitment took place between November 2008 and April 2011. Exclusion criteria were inability to speak German, severe heart failure (New York Heart Association Class IV) or scheduled cardiac surgery within the next 3 months, severe depressive episodes according to the Structured Clinical Interview for DSM-IV (SCID (34)) or other severe or life-threatening physical or mental illness.

A two-step screening procedure was applied. In step 1, consecutive patients with known CAD admitted to the participating centers were asked to participate in a psychological screening procedure and those who consented completed the HADS. Information on exclusion criteria was taken from patients' records.

In step 2, patients without obvious exclusion criteria who scored higher than 7 on the HADS were approached again and asked to participate in the main study. Those who agreed received the SCID (34) by a clinician and were included in the trial if no exclusion criteria emerged from the

interview. Because of unexpected general shortening of hospital stay in Germany, step 2 could typically not be completed before patients were discharged home. Patients returned for baseline assessment a median of 30 days after initial screening. Those returning more than 6 weeks after initial screening were rescreened for depressive symptoms, and the new HADS value was used as baseline.

Trial sites were 10 German tertiary care centers. Trial psychotherapists were physicians or psychologists with complete formalized training and board approval in psychotherapy.

Interventions

All trial participants received usual care by their primary care physicians and/or cardiologists. Patients were also allowed to receive concomitant antidepressant medication or psychotherapy outside the trial.

Patients in the usual care arm received one manualized individual information session of 30 to 45 minutes delivered by trained staff. This session provided information about healthy behaviors and psychosocial factors in CAD. Treatment options for depressive symptoms were mentioned but neither recommended nor offered.

The trial psychotherapy intervention was fully manualized and delivered in a stepwise manner. All patients in the intervention arm were offered three individual supportive-expressive psychotherapy sessions. Patients' partners were invited for the third session (35). All patients were reassessed with the HADS after the third session (4–6 weeks after inclusion, T1), and only those still depressed were offered twenty-five 90-minute sessions of group psychotherapy in closed groups of 6 to 10 participants for approximately 10 months, usually starting 3 to 6 months after randomization. For detailed descriptions of the trial psychotherapy, its rationale, and procedures for therapists' training, supervision, and quality control, see the publication by Albus et al. (30) and the full intervention manual in Supplementary Text A1, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A275.

Demographic, Clinical, and Psychological Variables

Patients' baseline demographic and medical data were taken from their medical records and standardized clinical interviews. Diagnoses of mental disorders were made by SCID interview (34) performed by trained raters. Type D personality was ascertained using the 14-item Type D scale (DS-14 (36,37)). Cronbach α for the German version of the DS-14 has been reported as .87 for the negative affectivity and .86 for the social inhibition subscale (37). Each subscale ranges from 0 to 28, and according to Denollet (36), Type D was defined as a score of 10 or higher for both negative affectivity and social inhibition. The interaction of negative affectivity and social inhibition was described as the product of z-transformed raw values on each of the two subscales.

Outcomes

Primary outcome was the change in HADS depression scores from screening (T0) to 18 months (T3), which corresponded to the end of group treatment. Additional assessments were performed 6 (T2), 12 (T2b), and 24 (T4) months after inclusion. The HADS has been extensively validated and widely used in cardiac patients, and it has shown good sensitivity to change (33). Factor analyses have confirmed the two subscales for the German version. The depression subscale shows the expected correlations with other depression scales. Its Cronbach α is reported as .81, and a score of higher than 7 has been recommended as the most widely used cutoff to detect depressive syndromes (33).

Secondary outcomes included additional measures of depressive symptoms and remission of diagnosed depression. The interviewer-administered 21-item Hamilton Depression Rating Scale (HAM-D (38,39)) and the SCID (34) were used for this purpose.

Preplanned subgroup analyses were conducted for men and women, for patients with versus without Type D personality, and for patients with versus without still elevated depression scores after the three individual sessions (T1).

Sample Size

On the basis of pilot data, we expected a within-arm SD of approximately two points on the HADS-D (see Albus et al. (30) and Supplementary Text A2, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A275). As minimal clinically relevant difference, we assumed a between-arms difference of 0.5 SDs. To detect between-arm differences on the HADS depression scale of 0.5 SDs, we needed 64 evaluable patients in each study arm under the assumption of a two-sided type 1 error of 5% and a power of 80% (t test). To achieve sufficient power for subgroup analyses of patients with or without the Type D personality crossed with men or women, altogether $2 \times 4 \times 64 = 512$ evaluable patients were needed. Accounting for an expected loss to follow-up of 10% (in terms of missing primary outcome data), 569 patients (512/0.9) needed to be randomized. There were no interim analyses of efficacy data.

Randomization

Patients were assigned to treatment arms in a 1:1 ratio using the Internet randomization service ALEA (FormsVision BV, Abcoude, NL). For details on the balancing procedure, see the publication by Albus et al. (30) and Supplementary Text A3, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A275.

Blinding/Masking

Although blinding of the interventions to patients and therapists was not possible, outcome assessments were performed by patients' self-reports and face-to-face interviews with trained raters who were masked regarding patients' treatment assignment, thus guarding against detection bias.

Quality Assurance

Monitoring and data management were organized and conducted by Clinical Trials Center Cologne. For details, see the publication by Albus et al. (30) and Supplementary Text A4, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A275.

Statistical Methods

Analysis was performed by intention-to-treat, that is, all randomized patients with valid baseline assessment were analyzed as assigned by the Internet service. The primary efficacy variable, change of depressive symptoms on the HADS-D subscale from baseline to 18 months, was subjected to analysis of covariance (ANCOVA) with the fixed effects treatment, center, treatment by center, and baseline (type 2 sums of squares). According to the intention-to-treat principle, missing values were substituted by the last observation available (possibly the baseline value; the baseline value was not substituted, $n = 2$ (40)). Moreover, a mixed model repeated-measures (MMRM) analysis was done, using nonimputed data, with the fixed effects treatment, center, time, treatment by center, treatment by time, and baseline (type 3 sums of squares, ARH1 covariance structure on time). For both approaches, that is, ANCOVA and MMRM, the focus of statistical inference was on the difference in marginal means for the change from baseline to 18 months. In a sensitivity analysis, the clustering by care providers was implemented by adding a corresponding random effect nested within center. Preplanned subgroups were analyzed (including corresponding interaction p values) by sex, Type D, sex by Type D, and persistent elevation in depression scores at the 4-week (T1) assessment. These analyses are essentially explorative and, thus, not corrected for multiple testing. Calculations were performed with the software SPSS Statistics 22 (IBM Corp, Armonk,

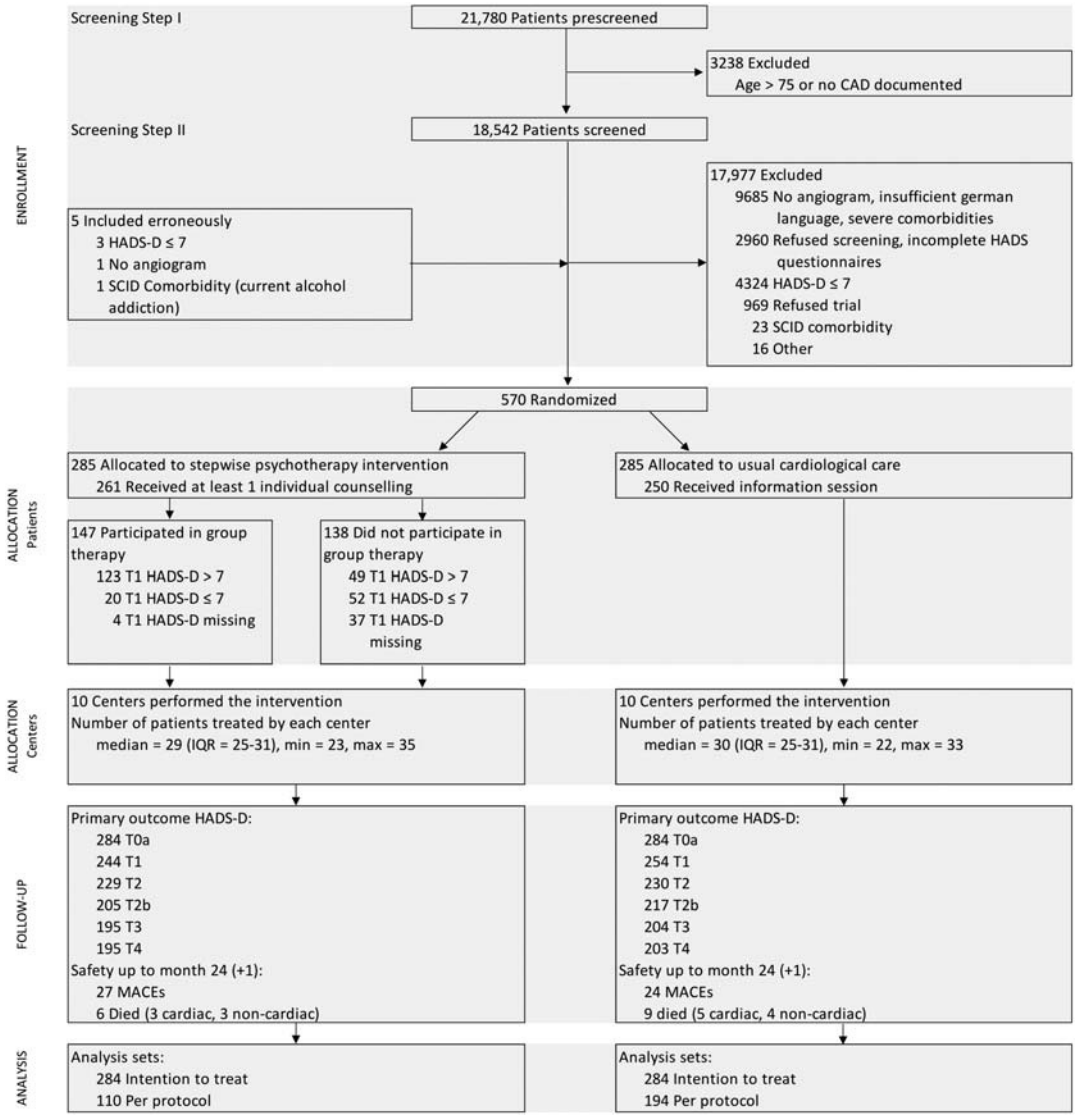

FIGURE 1. CONSORT diagram. CAD = Coronary artery disease; HADS-D = Hospital Anxiety and Depression Scale-depression subscale; SCID = Structured Clinical Interview for DSM-IV; IQR = interquartile range; MACE = major adverse cardiac events. Assessment time points: T0a = screening baseline; T1 = 4 weeks after randomization; T2 = 6 months; T2b = 12 months; T3 = 18 months; T4 = 24 months after randomization.

NY) and R 3.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Characteristics of Patient Sample

Of a total of 18,542 patients aged 18 to 75 years with documented CAD (76.9% men; 23.0% women; mean [standard deviation] [M {SD}] age, 63.6 [9.1] years; Fig. 1), 9685 showed exclusion criteria and 2960 returned no or incomplete questionnaires. Of the 5897 remaining patients who completed the HADS, 1573 (26.7%) had depression scores above the cutoff (>7). Of these, 969 refused to participate in the trial. Furthermore, 23 patients were excluded because of severe mental comorbidity found during SCID interview, and 16 were excluded for other reasons. Altogether, 565 patients fulfilled all inclusion criteria. Another five patients were erroneously randomized (Fig. 1) but kept in the trial, yielding 570 randomized patients. A comparison of the study sample and the 969 refusers without any other exclusion criteria showed that refusers were older and had lower distress as assessed by HADS anxiety scale and DS-14.

The study sample was equally distributed between trial arms. The minimization procedure led to an excellent balance in all relevant sociodemographic, clinical, and psychological data at baseline (Table 1). In both arms, approximately

TABLE 1. Baseline Characteristics by Assigned Treatment

Characteristic	Usual Care Plus Psychotherapy (n = 285)		Usual Care Plus Information Session (n = 285)	
	n/valid n*	%*	n/valid n*	%*
Demographics				
Age, M (SD), y	59.1	(9.8)	59.3	(9.3)
Female sex	61/285	(21.4)	59/285	(20.7)
Married	170/268	(63.4)	185/271	(68.3)
Socioeconomic status				
Low	117/285	(45.0)	123/261	(47.1)
Medium	84/285	(32.3)	71/261	(27.2)
High	59/285	(22.7)	67/261	(25.7)
Baseline medical data				
Hypertension	252/281	(89.7)	245/280	(87.5)
Hyperlipidemia	236/273	(86.4)	240/270	(88.9)
Diabetes mellitus	69/275	(25.1)	70/279	(25.1)
BMI, M (valid n) (SD), kg/m^2	28.5 (n = 280)	(5.0)	28.4 (n = 275)	(4.8)
Smokers	90/282	(31.9)	97/284	(34.2)
Previous myocardial infarction	139/271	(51.3)	161/273	(59.0)
Previous CABG	53/283	(18.7)	45/282	(16.0)
Recent acute myocardial infarction	93/285	(32.6)	94/285	(33.0)
Recent coronary intervention (PCI, CABG)	204/285	(71.6)	206/285	(72.3)
NYHA class I–II	240/285	(84.2)	242/285	(84.9)
NYHA class III	45/285	(15.8)	43/285	(15.1)
Charlson Comorbidity Index, median (IQR)	2	(1/3)	2	(1/3)
Medication				
ACE inhibitors	187/285	(65.6)	193/285	(67.7)
Aspirin	257/285	(90.2)	262/285	(91.9)
β-Blockers	246/285	(86.3)	257/285	(90.2)
Statins	256/285	(89.8)	265/285	(93.0)
Antidepressant medication	33/285	(11.6)	36/285	(12.6)
Baseline psychopathology				
Major depressive episode (SCID I)	101/285	(35.4)	103/285	(36.1)
Anxiety disorder (SCID I)	77/285	(27.0)	77/285	(27.0)
Dysthymia (SCID I)	53/285	(18.6)	50/285	(17.5)
Adjustment disorder (SCID I)	41/285	(14.4)	37/285	(13.0)
Any personality disorder (SCID II)	50/285	(17.5)	59/285	(20.7)
Any mental disorder	217/285	(76.1)	220/285	(77.2)
Type D (DS14)	173/285	(60.7)	169/284	(59.5)
Negative affectivity, M (valid n) (SD)	16.0 (n = 283)	(4.8)	15.5 (n = 283)	(4.8)
Social inhibition, M (valid n) (SD)	11.8 (n = 283)	(5.4)	11.8 (n = 284)	(5.5)
DS-14 NA by SI (z scores)	0.22 (n = 281)	(1.00)	0.28 (n = 283)	(0.96)
HADS-D, M (valid n) (SD)	10.4 (n = 284)	(2.5)	10.4 (n = 284)	(2.5)
Current psychotherapy (within last 12 mo)	31/285	(10.9)	32/285	(11.2)

BMI = body mass index; CABG = Coronary artery bypass graft surgery; PCI, percutaneous coronary intervention; NYHA: New York Heart Association; IQR = interquartile range; ACE = Angiotensin-converting enzyme; SCID = Structured Clinical Interview for DSM-IV; DS-14 = fourteen-item Type D scale; NA = negative affectivity; SI = social inhibition; HADS-D = Hospital Anxiety and Depression Scale-depression subscale.

*Unless indicated otherwise.

TABLE 2. Change in Depression Scores in CAD Patients Receiving Psychotherapy Versus Usual Care

		Baseline	1 mo	6 mo	12 mo	18 mo	24 mo	Difference Between Treatment Arms at 18 mo
As observed								
M (SD), *n*	Usual care	10.4 (2.5), 284	9.9 (3.8), 254	9.1 (3.9), 230	8.8 (4.0), 217	8.2 (3.8), 204	8.4 (3.9), 203	
	Psychotherapy	10.4 (2.5), 284	9.9 (4.0), 244	8.9 (3.9), 229	8.5 (4.2), 205	8.1 (4.1), 195	8.2 (4.2), 195	
LOCF ANCOVA[a]								−0.2 (−0.8 to 0.4), $p = .44$
M (SD), *n*	Usual care	10.4 (2.5), 284	10.0 (3.7), 285	9.4 (3.8), 285	9.3 (4.0), 285	8.9 (3.9), 285	9.0 (4.1), 285	
	Psychotherapy	10.4 (2.5), 284	10.0 (3.8), 284	9.3 (3.9), 284	9.1 (4.0), 284	8.7 (4.1), 284	8.8 (4.1), 284	
Change								
M (SD), *n*	Usual care	0	−0.4 (3.1), 284	−1.0 (3.4), 284	−1.1 (3.6), 284	−1.5 (3.5), 284	−1.5 (3.7), 284	
	Psychotherapy	0	−0.4 (3.4), 284	−1.2 (3.4), 284	−1.3 (3.4), 284	−1.7 (3.6), 284	−1.6 (3.8), 284	
MMRM[b]								−0.2 (−0.9 to 0.5), $p = .54$
EMM	Usual care	0	−0.4 (−0.8 to 0.0)	−1.2 (−1.6 to −0.7)	−1.3 (−1.8 to −0.8)	−1.9 (−2.4 to −1.5)	−1.8 (−2.3 to −1.3)	
(95% CI)	Psychotherapy	0	−0.5 (−0.9 to 0.0)	−1.4 (−1.9 to −0.9)	−1.7 (−2.2 to −1.2)	−2.2 (−2.6 to −1.7)	−2.0 (−2.5 to −1.5)	

LOCF = last observation carried forward; ANCOVA = analysis of covariance; MMRM = mixed model repeated measures; EMM = estimated marginal mean; CI = confidence interval.

Analyses based on primary outcome variable (HADS depression scores).

[a]Between-subjects effects: treatment $F(1,547) = 0.4$, $p = .55$; baseline $F(1,547) = 17.0$, $p < .001$; center $F(9,547) = 0.8$, $p = .62$; center by treatment $F(9,547) = 0.8$, $p = .61$.

[b]Fixed effects: time $F(4,1153) = 19.1$, $p < .001$; treatment $F(1,534) = 0.8$, $p = .37$; time by treatment $F(4,1153) = 0.3$, $p = .90$; baseline $F(1,571) = 41.3$, $p < .001$; center $F(9,564) = 1.5$, $p = .15$; center by treatment $F(9,564) = 2.8$, $p = .003$.

60% of patients were classified as Type D and the M (SD) HADS depression scores were identical at 10.4 (2.5). The M (SD) age was 59.2 (9.5) years, which was significantly lower than the age in the full screening population, whereas the percentage of men was comparable with the percentage in the screened population.

Primary Outcome

Change in HADS Depression Scores From Baseline to 18 Months

In last observation carried forward (LOCF) analysis, the M (SD) HADS depression scores decreased from 10.4 (2.5) to 8.7 (4.1) at 18 months in the psychotherapy arm and from 10.4 (2.5) to 8.9 (3.9) in the usual care arm (Table 2). Although the overall decrease was significant at a p value of less than .001, ANCOVA showed no significant difference between treatment arms at 18 months ($p = .44$). This result was confirmed by MMRM analysis.

Accordingly, remission on the HADS depression scale (score ≤ 7) at 18 months was achieved in 33.8% of patients in the psychotherapy arm ($n = 284$) and 35.8% in the usual care arm ($n = 285$), with no significant difference between treatment arms.

No treatment effects were also observed in per protocol analysis and for secondary depression outcomes (see Supplementary Text B1 and Text B2, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A275). There was no significant variability in depression outcomes across trial sites in the primary ANCOVA using the LOCF approach (see Supplementary Figure C, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A275). In contrast, a significant site-by-treatment interaction emerged in MMRM analyses (Table 2), mainly resulting from heterogeneity across sites in improvement observed in the control group.

Subgroup Analyses

Preplanned subgroup analyses using the HADS were conducted for men and women and for patients with versus without Type D personality, sex by Type D, and patients with or without persistent elevation in HADS-D scores at T1 (Fig. 2). At baseline, women had slightly higher HADS depression scores then men (10.9 [2.5] versus 10.3 [2.5], $p = .029$) and patients with Type D scored higher than those without (10.7 [2.7] versus 10.0 [2.2], $p < .001$). Adjusting for baseline HADS depression scores, we found no difference in the change of HADS depression scores between treatment arms for sex, sex by Type D, and persistent HADS-D elevation. In contrast, there was a significant treatment-by-Type D interaction on change in HADS depression scores ($p = .026$). When analyzing Type D and non–Type D patients in separate models, psychotherapy tended to be superior to usual care in the 341 Type D patients only ($p = .057$). The 227 patients without Type D improved similarly with either usual care or psychotherapy ($p = .54$).

Exploratory subgroup analysis in patients with SCID-diagnosed major depression showed that HADS depression

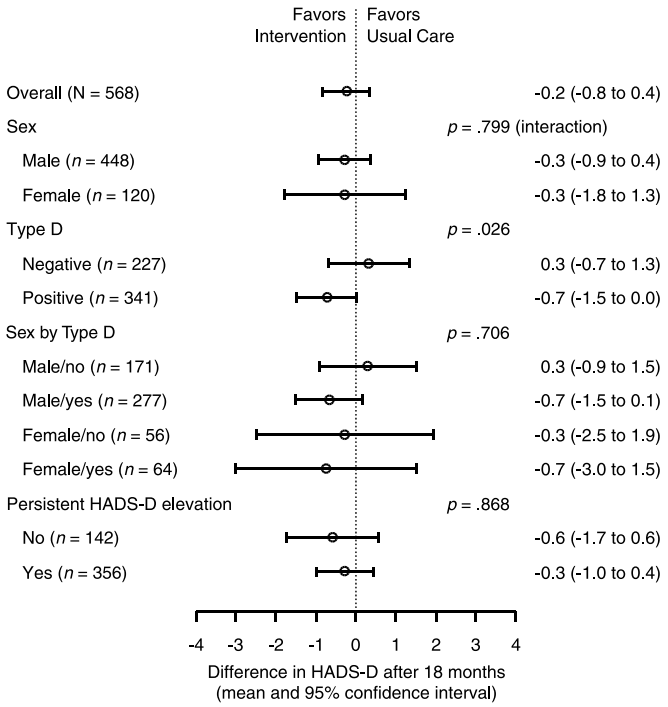

FIGURE 2. Subgroup analysis of the difference in HADS-D after 18 months by sex, Type D, and persistent HADS-D elevation at 4 weeks (ANCOVA models of LOCF data).

scores tended to decline more with stepwise psychotherapy than with the control condition (−1.6 versus −0.7, $p = .097$).

Safety Analysis

Until the end of the safety follow-up (24 [1] months, $n = 564$), we found no significant differences in time-to-event distributions between psychotherapy and usual care for death (6 versus 9 events, $p = .45$ from log-rank test), major adverse cardiac event (27 versus 24, $p = .61$), or early discontinuation (58 versus 56, $p = .83$).

Usefulness of the Stepwise Protocol and Effects of Concomitant Treatments

At T1, HADS depression scores had fallen below the cutoff in 142 patients (28.5%, $n = 498$), with no significant difference between treatment arms ($p = .63$). The reduced depression scores of those who remitted by T1 remained stable from T1 (M [SD] = 5.3 [1.7]) to the 18-month assessment (5.7 [3.3], LOCF) with no significant difference between treatment arms ($p = .32$, ANCOVA). In patients still scoring higher than 7 on the HADS at T1 ($n = 356$), depression scores decreased further until T3 ($p < .001$), but again no effect of treatment assignment or the number of group sessions attended was observed (see Supplementary Text B3, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A275).

No group differences were seen at any time point for mental health treatments or cardiac rehabilitation obtained outside the trial (see Supplementary Text B4, Supplemental Digital Content 1 http://links.lww.com/PSYMED/A275).

DISCUSSION

Interpretation

SPIRR-CAD is the largest European treatment trial for depressed CAD patients and the second largest treatment trial for this indication worldwide. It could be implemented successfully across all 10 participating centers. The stepwise procedure identified a relevant subgroup whose depressive symptoms remitted within few weeks and remained low without further treatment, thus avoiding long-term treatments for patients with early remission. Overall, depressive symptoms and the percentage of diagnosed depressive episodes significantly declined from baseline to 18 months. However, improvement with psychotherapy did not differ significantly from that observed with usual care enhanced by one information session. Psychotherapy tended to be superior to usual care in the subgroup of patients with Type D personality and in those with diagnosed major depression. These in part unexpected results need explanation.

In the initial SCID interview, many patients seemed only mildly depressed and little more than one third fulfilled diagnostic criteria for major depression. However, only 23.3% of patients had no diagnosable mental illness, whereas others suffered from dysthymia, anxiety, adjustment, or personality disorders. The psychotherapy intervention may therefore have been unnecessary for some patients and too inflexible for others. Spontaneous remission and usual care may account for the overall symptomatic improvement.

Presumably, the control condition was not inert. The information session may have provided a similar degree of reassurance as the individual psychotherapy sessions. This may indicate that only minimal (or even no) intervention is needed in a subgroup of mildly depressed patients during the first weeks after a cardiac event. Other studies (13) have addressed this problem by only including patients whose depressive symptoms had persisted for some months after the cardiac index event. In contrast, Rollman et al. (12) showed that a collaborative care intervention with an active approach to address depressive symptoms by nurse care managers starting shortly after coronary bypass surgery was superior to usual care in reducing depressive symptoms, although also in their study less than 40% were diagnosed with major depression.

A substantial proportion of patients (>35%) received external mental health treatment before and during the trial (see Supplementary Text B4, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A275). These treatments may have left little room for additional benefit from the trial intervention. However, neither external mental health treatments nor cardiac rehabilitation were related to depression outcomes in either study arm. Mean depression scores remained above the initial cutoff, and one in five patients fulfilled criteria of major depression after 18 months, pointing to a need for more effective interventions. Despite relatively easy access to mental health care in Germany, improvement in the SPIRR-CAD usual care arm was not particularly large. In ENRICHD (17), depressed control group patients improved by 0.76 SDs on the Beck Depression Inventory and by 1.31 SDs on the HAM-D between baseline and 6 months. In contrast, 6-month improvement in the SPIRR-CAD usual care arm was only 0.4 SDs on the HADS. After 18-months, SPIRR-CAD usual care patients had improved by 0.6 SDs on the HADS and even less on the Hamilton Scale, whereas cumulative prescription rates of antidepressant medication were comparable in both trials, for example, 23.2% (SPIRR-CAD, 18 months) versus 20.6% (ENRICHD, 29 months). High rates of spontaneous remission observed in many studies and relatively small effects of psychotherapy and antidepressants raise questions about the etiology of depression in cardiac patients. Some cardiac patients show transient depressive symptoms best classified as adjustment disorders with typically benign prognosis. In others, hypocortisolemic "atypical" depression with elevated inflammatory markers resembling the concept of vital exhaustion (41) might be the underlying problem.

The negative main result might also be explained by relatively low participation in group psychotherapy. In 13% of patients, eligibility for group treatment could not be assessed because of missing T1 HADS questionnaires, and in those who qualified for group psychotherapy, almost 50% attended less than half of the scheduled sessions. Reported reasons for nonattendance included medical illness and rehospitalizations, logistic problems, and dissatisfaction with group treatment. Because in previous trials (42–44), participation in group psychotherapy seemed to be associated with a reduction in adverse medical outcomes, SPIRR-CAD had laid substantial effort on motivating patients to participate in the group sessions. However, even in per protocol analyses and in the subgroup of patients who qualified for group psychotherapy, the control arm fared no worse than the intervention arm. In addition, the number of group sessions attended was unrelated to improvement in depression scores.

Because in SPIRR-CAD sex did not moderate treatment effects, the lack of a main effect cannot be explained by opposite intervention effects in men and women that have been reported from previous trials (23,45).

Finally, it is unlikely that psychometric properties of the primary outcome measure were responsible for negative overall effect. Although the HADS has been criticized for several reasons (46), this opinion has not been undisputed, and a current statement of the US Preventive Services Task Force still recommends the HADS as one of the most widely used depression screening tools (47). More importantly, the negative result obtained on the HADS was confirmed by established interview-based secondary outcome measures for depression.

We found a significant treatment by Type D interaction on change in depression scores. Whereas Type D patients tended to fare better with psychotherapy, non–Type D patients showed no benefit from the trial psychotherapy. Although this subgroup analysis was preplanned, it cannot be considered "confirmative" in a strict sense, that is, regarding conventional strong type 1 error control. However, it may guide future research. The SPIRR-CAD intervention had specifically been developed for dealing with typical problems of Type D patients, for example, their tendencies to experience negative emotions and to inhibit expression of emotion in social interactions, and it was expected a priori (30) that this treatment would particularly help patients with Type D. However, it had also been expected to ameliorate depressive symptoms in non–Type D patients, which was not the case. Hence, future research might use elements of the SPIRR-CAD intervention for treating depression in Type D patients who seem to improve little with usual care only.

The stepwise procedure identified patients whose depressive symptoms remitted during the initial 4 weeks and remained low during follow-up without further study treatment. These patients can safely be followed with watchful waiting, whereas Type D patients show little spontaneous remission and should receive more active treatment.

Generalizability

SPIRR-CAD aimed at high generalizability of results. Patients were enrolled consecutively following a well-defined screening algorithm. However, as in most trials, severely ill patients, such as those with severe major depressive episodes who might have derived special benefit from the intervention, had to be excluded because for some, it seemed unethical to leave them without specific treatment and others were too sick for regular participation in group psychotherapy. This resulted in less depressive symptoms in SPIRR-CAD than in ENRICHD (17) and CREATE (19) and limits generalization to severely depressed patients. Randomized patients were also somewhat younger than the screened population. Because patients were mainly recruited from tertiary care centers and many had recently experienced an acute cardiac event, the results may not generalize to patients with chronic stable CAD, especially those from primary care.

The easy availability of psychotherapy in the German health care system makes generalization to other health care systems difficult. Despite the generally well-documented efficacy of cognitive-behavioral therapy in treating anxiety and depression, two smaller German trials in depressed (n = 59 (48)) or anxious (n = 52 (49)) CAD patients also showed no benefit of cognitive-behavioral therapy over usual care. Adding a psychodynamic component in SPIRR-CAD obviously did not lead to better results.

Taken together, despite its reasonable size, SPIRR-CAD failed to show superiority of the stepwise psychotherapy intervention more than usual care plus one information session in reducing depressive symptoms. Equal results were observed on both self and observer ratings and for both men and women. The relatively small improvement in the usual care arm may in part be due to the moderate severity of depressive symptoms at baseline but requires further explanation.

For routine patient care, our results do not provide evidence for offering psychotherapy to mildly depressed CAD patients, at least to those without Type D personality, although these patients have been reported to be at increased risk of cardiac complications (11). A prudent approach would be to inform patients about their condition and about healthy behaviors and to reassess them 1 or 2 months later. Those with rapidly remitting depressive symptoms are likely to remain depression free for the following 18 months. Patients with persistent depressive symptoms may benefit most from collaborative care (12–16) with individualized adaptation of treatment options on the basis of shared decision making and possibly from

exercise-based rehabilitation (22). Specific antidepressant psychotherapy or medication (18,19) can currently only be recommended for patients with more severe or recurrent depression. Further research should investigate whether elements of the SPIRR-CAD intervention are beneficial for depressed CAD patients with Type D personality. Finally, only after showing that treatments addressing depression sufficiently improve depression outcomes in cardiac patients, it may be useful to test their possible effects on "hard" cardiac outcomes in larger trials. Such trials might then answer the still open question whether successful treatment for depression has the potential to improve cardiac disease outcomes.

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