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 CAD

Short title: Stepwise psychotherapy for CAD patients

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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 >7 on the Hospital Anxiety and Depression Scale (HADS) 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 change in HADS depression scores from baseline to 18 months. Preplanned subgroup analyses examined whether treatment responses differed by patients' sex and personality factors (Type D).

Results: 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*time effect, p=.90). Preplanned subgroup analyses revealed no differences in treatment effects between men versus women ($p_{\text{treatment*sex interaction}} = .799$) but a significant treatment*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=0.057) and no such difference in improvement in patients without Type D (N=227, p=0.54).

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.

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

Key words: Coronary Disease; Depression; Psychotherapy; Type D personality; Randomized Controlled Trial

Acronyms:

ANCOVA	Analysis of covariance
CAD	Coronary artery disease
CBT	Cognitive-behavioral therapy
CREATE	Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy Trial
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
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 analysis
SCID	Structured Clinical Interview for DSM-IV
SPIRR-CAD	A Stepwise Psychotherapy Intervention for Reducing Risk in Coronary Artery Disease 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 gender-sensitive interventions (24). The Type D personality (25), ie, 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 (eg, 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 in order to effectively treat depressed cardiac patients.

Second, it might not be ideal to include patients as soon as possible after an index cardiac event as was done in 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 vs. without early remission of depressive symptoms appears appropriate.

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 18-75 years were eligible for the trial if they had documented CAD with recent coronary angiograms and a depression score >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 I, 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 II, patients without obvious exclusion criteria who scored >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. Due to unexpected general shortening of hospital stay in Germany, step II 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 six weeks after

initial screening were re-screened 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 30-45 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 3rd session (4-6 weeks after inclusion; T1) and only those still depressed were offered 25 90-minute sessions of group psychotherapy in closed groups of 6-10 participants over approximately 10 months, usually starting 3-6 months after randomization. For detailed descriptions of the trial psychotherapy, its rationale, and procedures for therapists' training, supervision, and quality control see (30) and the full intervention manual in **Supplemental Digital Content text A1**.

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's alpha for the German version of the DS-14 has been reported as 0.87 for the Negative Affectivity and 0.86 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 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's alpha is reported as 0.81 and a score of >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.

Pre-planned 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 3 individual sessions (T1).

Sample Size

Based on pilot data we expected a within-arm standard deviation of about 2 points on the HADS-D (see (30) and **Supplemental Digital Content text A2**). As minimal clinically relevant difference we assumed a between-arms difference of 0.5 standard deviations. In order to detect between-arm differences on the HADS depression scale of 0.5 standard deviations we needed 64 evaluable patients in each study arm under the assumption of a two-sided type I error of 5% and a power of 80% (*t*-test). In order to achieve sufficient power for subgroup analyses of patients with / without the Type D personality crossed with men / women, altogether 2×4×64=512 evaluable patients were needed. Accounting for an expected loss to follow-up of 10% (in terms of missing primary outcome data), 512/0.9=569 patients 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 (30) and **Supplemental Digital Content text A3**.

Blinding / masking

While 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 (30) and **Supplemental Digital Content text A4**.

Statistical methods

Analysis was done by intention-to-treat, i.e. 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*center and baseline (type II 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; see (40)). Moreover, a mixed model repeated measures (MMRM) analysis was done, using non-imputed data, with the fixed effects treatment, center, time, treatment*center, treatment*time and baseline (type III sums of squares, ARH1 covariance structure on time). For both approaches, i.e. 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 (incl. corresponding interaction p-values) by sex, Type D, sex*Type D and persistent elevation in depression scores at the four week (T1) assessment. These analyses are essentially explorative and, thus, not corrected for multiple testing. Calculations were done with the software SPSS Statistics 22 (IBM Corp., Armonk, NY, USA) 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 18-75 years with documented CAD (76.9% men; 23.0% women; mean age 63.6 ± 9.1 years) (see **Figure 1**), 9,685 showed exclusion criteria and 2,960 returned no or incomplete questionnaires. Of the 5,897 remaining patients who completed the HADS, 1,573 (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 5 patients were erroneously randomized (see **Figure 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 minimisation procedure led to an excellent balance in all relevant sociodemographic, clinical and psychological data at baseline (**Table 1**). In both arms, about 60% of patients were classified as Type D and mean HADS depression scores were identical at 10.4 ± 2.5. The mean age was 59.2 ± 9.5 years, which was significantly lower than the age in the full screening population, while the percentage of men was comparable to 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, mean 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**). While the overall decrease was significant at $p<.001$, 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 **Supplemental Digital Content texts B1 and B2**). There was no significant variability in depression outcomes across trial sites in the primary ANCOVA using the LOCF approach (see **Supplemental Digital Content figure C**). In contrast, a significant site*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 * Typ D and patients with or without persistent elevation in HADS-D scores at T1 (**Figure 2**). At baseline, women had slightly higher HADS depression scores then men (10.9 ± 2.5 vs. 10.3 ±2.5; p=0.029) and patients with Type D scored higher than those without (10.7 ± 2.7 vs. 10.0 ± 2.2; p<0.001). Adjusting for baseline HADS depression scores we found no difference in the change of HADS depression scores between treatment arms for sex, sex * Type D and persistent HADS-D elevation. In contrast, there was a significant treatment*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 scores tended to decline more with stepwise psychotherapy than with the control condition (-1.6 vs. -0.7; p=0.097).

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 vs. 9 events, p=.45 from log-rank test), MACE (27 vs. 24, p=.61) or early discontinuation (58 vs. 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=0.63). The reduced depression scores of those who remitted by T1 remained stable from T1 (mean ± 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 >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 **Supplemental Digital Content text B3)**.

No group differences were seen at any time point for mental health treatments or cardiac rehabilitation obtained outside the trial (see **Supplemental Digital Content text B4**).

Discussion

Interpretation

SPIRR-CAD is the largest European treatment trial of 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 appeared only mildly depressed and little more than 1/3 fulfilled diagnostic criteria for major depression. However, only 29.8% of patients had no diagnosable mental illness, while 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 Supplemental Digital Content B4). 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 cut-off and 1 in 5 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 standard deviations on the Beck Depression Inventory and by 1.31 standard deviations on the Hamilton Depression Rating Scale between baseline and 6 months. In contrast, 6 month- improvement in the SPIRR-CAD usual care arm was only 0.4 standard deviations on the HADS. After 18 months SPIRR-CAD usual care patients had improved by 0.6 standard deviations on the HADS and even less on the Hamilton Scale, while cumulative prescription rates of antidepressant medication were comparable in both trials, e.g. 23.2% (SPIRR-CAD, 18 months) vs. 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 due to missing HADS questionnaires and in those who qualified for group psychotherapy almost 50% attended less than half of the scheduled sessions. Reported reasons for non-attendance included medical illness and re-hospitalizations, logistic problems, and dissatisfaction with group treatment. Since 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. Also the number of group sessions attended was unrelated to improvement in depression scores.

Since 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 (23,47).

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 (eg, 45) 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 (46). 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. While Type D patients tended to fare better with psychotherapy, non-Type D patients showed no benefit from the trial psychotherapy. Though this subgroup analysis was pre-planned it cannot be considered "confirmative" in a strict sense, i.e. regarding conventional strong type I 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, e.g. 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, while 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 appeared unethical to leave them without specific treatment and others were too sick for regular participation in group psychotherapy. This resulted in less depressive symptomatology 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. Since 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 (CBT) 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 CBT 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 over 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 re-assess them one or two months later. Those with rapidly remitting depressive symptoms are likely to remain depression-free over the following 18 months. Patients with persistent depressive symptoms may benefit most from collaborative care (12-16) with individualized adaptation of treatment options based on 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 if successful treatment for depression has the potential to improve cardiac disease outcomes.

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Figure Legends

Figure 1: CONSORT diagram.
Abbreviations: 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: four weeks after randomization; T2: 6 months; T2b: 12 months; T3 18 months; T4 24 months after randomization.

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

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, years (Mean (SD))		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 (kg/m²; Mean (valid n), SD)		28.5(n=280)	(5.0)	28.4 (n=275)	(4.8)
Smokers		90/282	(31.9)	97/284	(34.2)
Prior myocardial infarction		139/271	(51.3)	161/273	(59.0)
Prior 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)
	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 (Mean (valid n), (SD))		16.0 (n=283)	(4.8)	15.5 (n=283)	(4.8)
Social inhibition (Mean (valid n), (SD))		11.8 (n=283)	(5.4)	11.8 (n=284)	(5.5)
DS14 NA*SI (z-scores)		0.22 (n=281)	(1.00)	0.28 (n=283)	(0.96)
HADS-D (Mean (valid n), SD)		10.4 (n=284)	(2.5)	10.4 (n=284)	(2.5)
Current psychotherapy (within last 12 months)		31/285	(10.9)	32/285	(11.2)

Note:* Unless indicated otherwise; CABG: Coronary artery bypass graft surgery; CCS: Canadian Cardiovascular Society; NYHA: New York Heart Association; SCID: Structured Clinical Interview for DSM-IV; IQR: Interquartile range; ACE: Angiotensin-converting enzyme; NA=Negative Affectivity; SI=Social inhibition.

Table 2: Change in depression scores in CAD patients receiving psychotherapy versus usual care

		Baseline	1 month	6 months	12 months	18 months	24 months	Difference between treatment arms at 18 months
As observed								
Mean (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[1]								-0.2 (-0.8 to 0.4), p=.44
Mean (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								
Mean (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[2]								-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)	

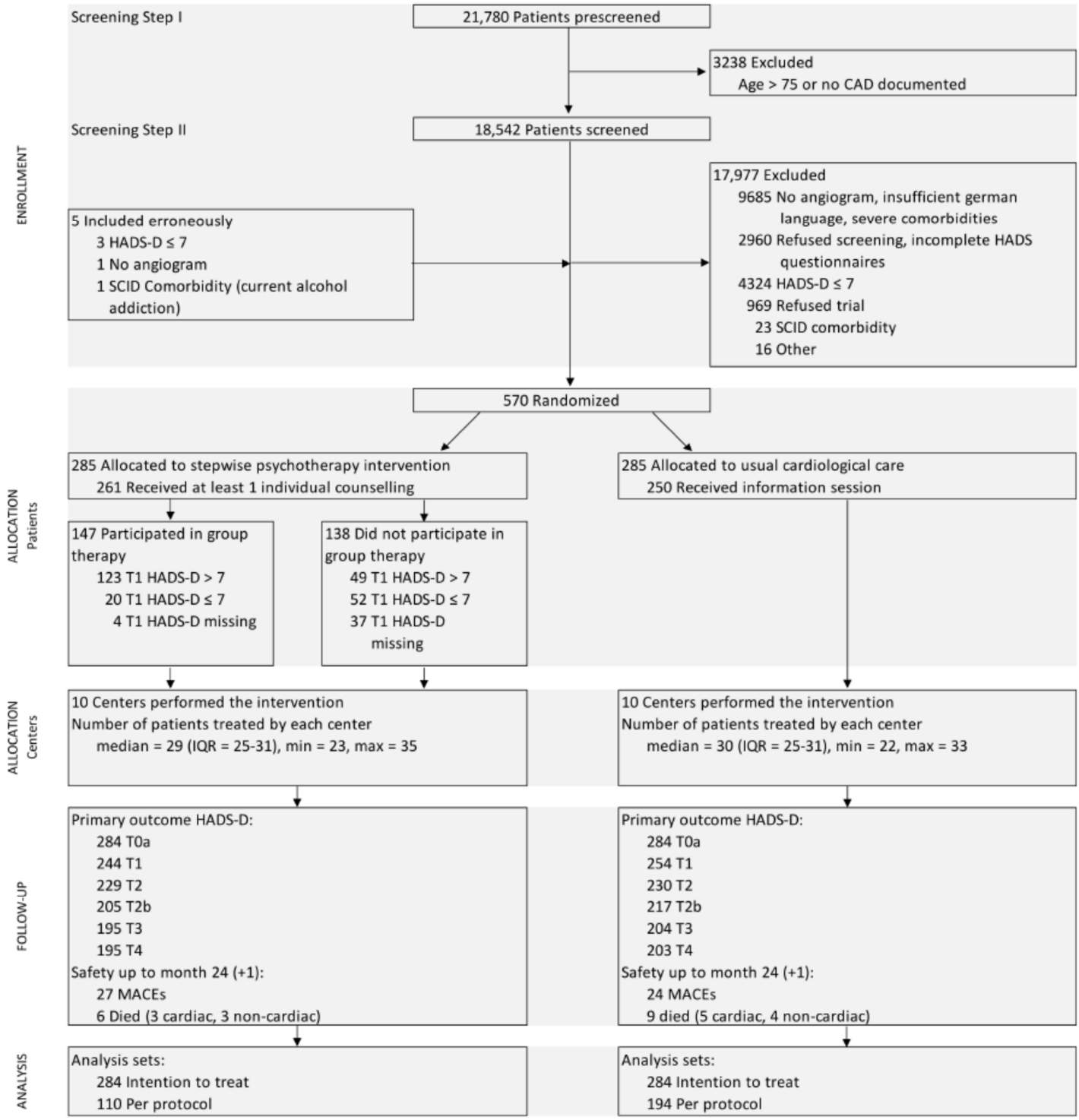
Analyses based on primary outcome variable (HADS depression scores).

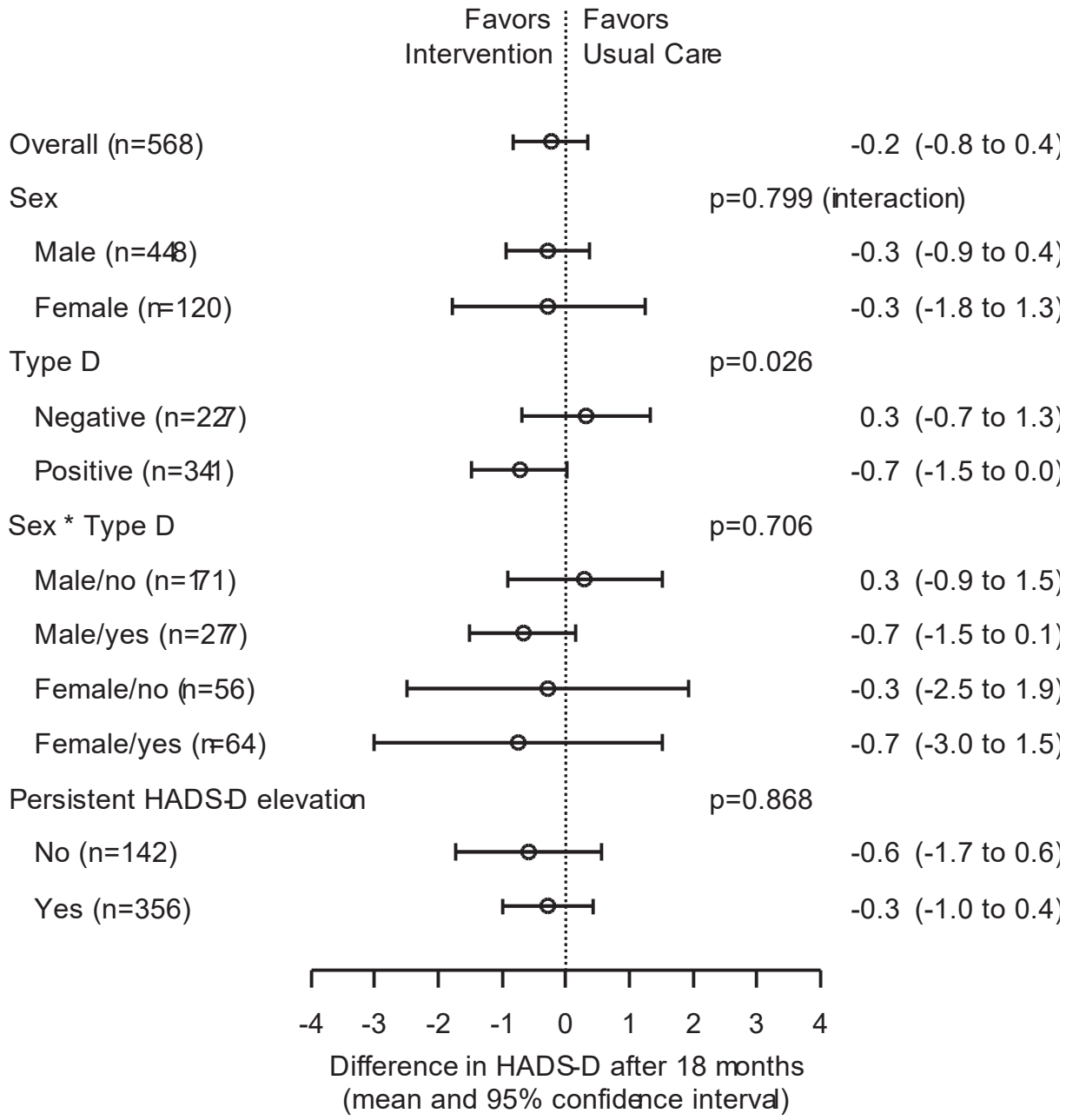
Abbr.: LOCF "last observation carried forward", ANCOVA "analysis of covariance", MMRM "mixed model repeated measures", EMM "estimated marginal mean", CI "confidence interval"

[1] 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*Treatment F(9,547)=0.8, p=.61

[2] Fixed effects: Time F(4,1153)=19.1, p<.001; Treatment F(1,534)=0.8, p=.37; Time*Treatment F(4,1153)=0.3, p=.90; Baseline F(1,571)=41.3, p<.001; Center F(9,564)=1.5, p=0.15; Center*Treatment F(9,564)=2.8, p=.003

Figure 1


ENROLLMENT
Screening Step I
21,780 Patients prescreened
3238 Excluded
Age > 75 or no CAD documented
Screening Step II
18,542 Patients screened
17,977 Excluded
9685 No angiogram, insufficient german language, severe comorbidities
2960 Refused screening, incomplete HADS questionnaires
4324 HADS-D ≤ 7
969 Refused trial
23 SCID comorbidity
16 Other
5 Included erroneously
3 HADS-D ≤ 7
1 No angiogram
1 SCID Comorbidity (current alcohol addiction)
570 Randomized
ALLOCATION Patients
285 Allocated to stepwise psychotherapy intervention
261 Received at least 1 individual counselling
285 Allocated to usual cardiological care
250 Received information session
147 Participated in group therapy
123 T1 HADS-D > 7
20 T1 HADS-D ≤ 7
4 T1 HADS-D missing
138 Did not participate in group therapy
49 T1 HADS-D > 7
52 T1 HADS-D ≤ 7
37 T1 HADS-D missing
ALLOCATION Centers
10 Centers performed the intervention
Number of patients treated by each center
median = 29 (IQR = 25-31), min = 23, max = 35
10 Centers performed the intervention
Number of patients treated by each center
median = 30 (IQR = 25-31), min = 22, max = 33
FOLLOW-UP
Primary outcome HADS-D:
284 T0a
244 T1
229 T2
205 T2b
195 T3
195 T4
Safety up to month 24 (+1):
27 MACEs
6 Died (3 cardiac, 3 non-cardiac)
Primary outcome HADS-D:
284 T0a
254 T1
230 T2
217 T2b
204 T3
203 T4
Safety up to month 24 (+1):
24 MACEs
9 died (5 cardiac, 4 non-cardiac)
ANALYSIS
Analysis sets:
284 Intention to treat
110 Per protocol
Analysis sets:
284 Intention to treat
194 Per protocol


Favors Intervention
Favors Usual Care
Overall (n=568)
-0.2 (-0.8 to 0.4)
Sex
p=0.799 (interaction)
Male (n=448)
-0.3 (-0.9 to 0.4)
Female (n=120)
-0.3 (-1.8 to 1.3)
Type D
p=0.026
Negative (n=227)
0.3 (-0.7 to 1.3)
Positive (n=341)
-0.7 (-1.5 to 0.0)
Sex * Type D
p=0.706
Male/no (n=171)
0.3 (-0.9 to 1.5)
Male/yes (n=277)
-0.7 (-1.5 to 0.1)
Female/no (n=56)
-0.3 (-2.5 to 1.9)
Female/yes (n=64)
-0.7 (-3.0 to 1.5)
Persistent HADS-D elevation
p=0.868
No (n=142)
-0.6 (-1.7 to 0.6)
Yes (n=356)
-0.3 (-1.0 to 0.4)
-4 -3 -2 -1 0 1 2 3 4
Difference in HADS-D after 18 months
(mean and 95% confidence interval)