



Published in final edited form as:

*Psychother Psychosom.* 2012 ; 81(4): 245–247. doi:10.1159/000332439.

## The Effect of Enhanced Depression Care on Anxiety Symptoms in Acute Coronary Syndrome Patients: Findings from the COPES Trial

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### Keywords

anxiety; depression; acute coronary syndrome; randomized controlled trial; problem solving therapy; antidepressant

Similar to depression, anxiety is common after acute coronary syndromes (ACS), and is an independent predictor of worse outcomes.<sup>1–3</sup> Yet, post-ACS psychological interventions have focused on treating depression. We previously reported that an enhanced depression care intervention involving patient preference for problem-solving therapy (PST), antidepressant medications, or both followed by stepped care according to treatment response was effective at reducing depressive symptoms after ACS with an effect size of 0.59 SD.<sup>4</sup> We report here the independent effect of this intervention on anxiety.

The trial design is described elsewhere.<sup>5</sup> Briefly, hospitalized ACS patients who were persistently depressed (Beck Depression Inventory (BDI)<sup>6</sup> score  $\geq 10$  within 1-week of hospitalization and again 3 months later) were recruited from 5 US hospitals between 2005 and 2008 and randomized to enhanced depression care or to usual care on a 1:1 basis. Exclusion criteria were alcohol or drug dependency; dementia; psychosis or bipolar disorder; terminal illness; unavailability for follow-up; BDI score of  $\geq 45$ ; or suicidality. The institutional review boards at all institutions approved the protocol, and all participants provided written informed consent.

Enhanced depression care consisted of patient preference for brief problem focused psychotherapy (i.e., PST) and/or pharmacotherapy and stepped-care in which symptom severity was reviewed every 8 weeks and treatment was augmented according to predetermined decision rules. Usual care was defined by the patient's treating physician(s).

Anxiety and depressive symptoms were assessed within 1-week of hospitalization, and at 3, 5, 7, and 9 months. Anxiety was measured using the 7-item anxiety subscale of the Hospital

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**Conflict of interest:** None declared.

Anxiety and Depression Scale (HADS-A).<sup>7</sup> Depressive symptoms were assessed by the BDI.<sup>6</sup> Outcome assessors were blinded to group assignment.

Given the low number and apparent randomness of missing assessments (Little's MCAR  $\chi^2 = 13.97$ ,  $p=0.12$ ), mixed effects regression was used to generate estimates of treatment effects on anxiety from month 3 to 9 and t-test to assess the differential change in anxiety between groups (group  $\times$  time interaction). Analyses were performed using SAS statistical software (version 9.2; SAS Institute Inc, Cary, NC).

The mean age of patients in the trial was 60.1 SD 10.6 years and 54% were women. Enhanced and usual care patients were similar on demographic and baseline medical variables,<sup>4</sup> on HADS-A score at baseline and 3 months (see Table), and in the percent with HADS-A in a range above normal (HADS-A $>7$ ; 61% vs 60%, respectively).

At 9 months, enhanced care patients showed a significant decrease in HADS-A compared to the 3 month pre-RCT assessment ( $-2.51$ ; 95% CI,  $-3.77$  to  $-1.26$ ;  $p<.001$ ) whereas there was no significant change in usual care patients ( $0.13$ ; 95% CI,  $-0.74$  to  $1.01$ ;  $p=0.76$ ), consistent with an effect size of enhanced care on anxiety of 0.53 (Table). Change in HADS-A was moderately correlated with change in BDI (Pearson's  $r = 0.44$ ,  $p<.001$ ). Controlling for depression, the effect of enhanced care on anxiety was decreased by about 1 point, but remained significant (mean group difference,  $-1.40$ ; 95% CI  $-2.62$  to  $-0.24$ ;  $p=0.02$ ). A subgroup analysis suggested a benefit of enhanced care on anxiety in women but not men (see Table).

These results demonstrate that enhanced depression care involving patient treatment preference of PST and/or antidepressant medications followed by stepped care has collateral benefits on anxiety in post-ACS patients. Symptoms of anxiety are common after ACS, can decrease treatment adherence,<sup>8,9</sup> lower quality of life,<sup>10</sup> and contribute to worse cardiovascular prognosis.<sup>2</sup> Yet, similar to depression, anxiety is often not assessed after ACS and patients with elevated anxiety often go untreated.<sup>11</sup> Thus the current findings demonstrate one viable approach to improving care for anxious post-ACS patients.

The use of PST may have contributed to the collateral benefit of the intervention on anxiety. PST is a patient-directed as opposed to disease-focused therapy in which patients are taught how to systematically evaluate and address individual psychosocial problems of their choosing. Interestingly, over 60% of enhanced care patients initially chose PST over antidepressant medications.<sup>4</sup>

Subgroup analysis showed an effect on anxiety for women but not men. Prior trials of enhanced depression care have been mixed with some finding gender effects in which men benefit more than women,<sup>12</sup> and others not.<sup>4,13</sup> To our knowledge, no prior trials have reported an interaction between gender and anxiety treatment in cardiovascular populations. If our finding is replicated, then future anxiety interventions may be more successful if tailored according to gender.

The secondary nature of the current analyses and sample selection (for depression vs. anxiety) limit interpretations that can be made, as does the use of HADS-A as a measure of anxiety in place of a diagnostic psychiatric interview. While an elevated HADS-A score has been associated with clinical diagnoses, anxiety disorders are heterogeneous and individual disorders may confer differing risks on post-ACS prognosis.<sup>14</sup> Nevertheless, elevated anxiety symptoms have been associated with a worse cardiac prognosis in prior studies.<sup>1</sup> Another limitation is that the comparison group was usual care rather than placebo/active control. Thus, we did not account for nonspecific effects of treatment on anxiety. Finally, 12 of the 80 patients randomized to treatment never received the intervention; this highlights

the importance of considering the availability and acceptability of psychological interventions in post-ACS patients.

In conclusion, future interventions to reduce psychological distress after ACS should assess their effectiveness on both depression and anxiety symptoms. Those interventions with pleiotropic effects on both anxiety and depression may be best suited to not only improve quality of life in ACS survivors, but potentially, to reduce the risk of psychological distress on adverse cardiovascular outcomes. Future trials should consider whether to target depressed patients, alone, or to broaden enrollment criteria to include patients with depression and/or anxiety after ACS.<sup>15</sup> Although the intervention reduced anxiety symptoms compared to usual care, 42% of intervention participants had persistently elevated anxiety symptoms (HADS-A >7) at 9 months. Accordingly, post-ACS patients with combined anxiety and depressive symptoms may benefit from a sequential approach in which anxiety symptoms are monitored alongside depressive symptoms, and are targeted by alternating treatment strategies (psychotherapy and pharmacotherapy), depending on the individual history, course, and severity of the patients' symptoms and symptom profiles.<sup>16</sup>

## Acknowledgments

**Funding:** This work was supported by grants HC-25197, HL-088117, HL-76857, and HL-84034 from the National Institutes of Health (NIH), Bethesda, MD, and by grant Number UL1 RR024156 from the National Center for Research Resources (NCRR), a component of NIH and NIH Roadmap for Medical Research. In addition, Dr. Kronish was supported in part by 1K23HL098359 from the National Heart, Lung, and Blood Institute. The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH.

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**Table**

Reduction in Anxiety Symptoms 0, 3 and 9 Months after Acute Coronary Syndrome \*

Variable			Intervention v Usual care	
	Usual Care Group (n=77)	Intervention Group (n=80)	Between-group difference	P
Anxiety score at 0 mo	7.53 (6.41 to 8.66)	7.68 (6.57 to 8.79)	-0.14 (-1.72 to 1.43)	0.86
Anxiety score at 3 mo (pre-RCT assessment)	8.29 (7.27 to 9.31)	8.87 (7.97 to 9.77)	-0.57 (-1.92 to 0.77)	0.40
Anxiety score at 9 mo	8.35 (7.19 to 9.51)	6.70 (5.75 to 7.64)	1.65 (0.17 to 3.13)	0.03
Change in anxiety score (3 – 9 months) – overall	0.13 (-0.74 to 1.01)	-2.38 (-3.29 to -1.48)	-2.51 (-3.77 to 1.26)	<.001
Change in anxiety score (3 – 9 months) – overall, adjusting for depressive symptoms	0.79 (-0.04 to 1.63)	-0.64 (-1.54 to 0.26)	-1.43 (-2.62 to -0.24)	0.02
Women only (n= 84)	1.33 (0.10 to 2.56)	-1.27 (-2.61 to 0.06)	-2.60 (-4.34 to -0.86)	0.004
Men only (n=73)	0.18 (-0.92 to 1.28)	0.11(-1.09 to 1.30)	-0.07 (-1.66 to 1.51)	0.93

\* The anxiety scores at 0, 3 and 9 months are presented as mean (95% confidence interval). The change scores (95% confidence interval) for each group are parameter estimates for the dummy coded pre-post variable from the mixed effects regression models and the between group differences (95% confidence interval) in change are the parameter estimates for the group x pre-post interaction from the mixed effects regression analysis.

Anxiety was assessed using the Hospital Anxiety and Depression Scale.<sup>7</sup>