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Pedersen, S.S.; van Domburg, R.T.; Larsen, M.L.

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The effect of low social support on short-term prognosis in patients following a first myocardial infarction

SUSANNE SCHMIDT PEDERSEN,1,2 RON THEODOOR VAN DOMBURG2 and MOGENS LYTKEN LARSEN3

1Medical Psychology, Department of Psychology and Health, Tilburg University, The Netherlands
2Department of Cardiology, Thoraxcentre, Erasmus Medical Centre Rotterdam, Rotterdam, The Netherlands
3Department of Cardiology, Aarhus University Hospital, Denmark


The objectives of the current study were (1) to assess adjustment in patients following a first myocardial infarction (MI) at 9 months compared with 4–6 weeks post-MI, (2) to examine the availability of and satisfaction with social support over time, and (3) to determine separate baseline psychosocial predictors of recurrent cardiac events. A questionnaire assessing post-traumatic stress disorder, anxiety, depression, health complaints, and social support, was distributed to consecutive patients 4–6 weeks and 9 months post-MI. Prior to assessment at follow-up, 8 (7%) of 112 patients had dropped out, and two had died due to cardiac causes. Objective clinical measures were obtained from medical records. There was an improvement in somatic and cognitive symptoms at follow-up, but no change in symptoms of arousal, depression, and anxiety.

Half of the patients were afraid of a recurrent MI. There was a significant decrease in social support between baseline and follow-up, and lower social support at baseline was associated with a 10% increased risk of recurrent cardiac events at follow-up (OR: 0.90; 95% CI: 0.84 to 0.97) adjusting for all other variables. Some patients still experienced difficulties with psychosocial adjustment 9 months post-MI despite a reduction in somatic and cognitive symptoms. Social support decreased over time, which may have serious prognostic implications; lower social support at baseline was an independent predictor of recurrent events at 9 months. An important step for future research will be to investigate how social support can be enhanced in patients at risk.

Key words: Myocardial infarction; post-traumatic stress disorder; recurrent cardiac events; social support.

Susanne Schmidt Pedersen, PhD, Medical Psychology, Department of Psychology and Health, Room P503a, Warandelaan 2, PO Box 90153, 5000 LE Tilburg, The Netherlands. Tel: +31 13 466 2503; fax: +31 13 466 2370; e-mail: s.s.pedersen@uvt.nl

INTRODUCTION

A myocardial infarction (MI) is a potentially life-threatening event that often occurs without warning. Although most patients adjust psychologically, 20–40% have residual distress even up to several years later (Ladwig, Kieser, König, Breithards & Borggreve, 1991; Lane, Carroll, Ring, Beever & Lip, 2002). Psychological distress has an adverse effect on quality of life, but it is also associated with adverse prognosis in patients with established coronary artery disease (CAD) independent of disease severity (Denollet & Brutsaert, 2001; Hemingway & Marmot, 1999). Studies have shown that depression is associated with a two- to seven-fold increased risk in mortality (Ladwig et al., 1991; Hemingway & Marmot, 1999; Barefoot et al., 2000; Frasure-Smith, Lespérance, Juneau, Talajic & Bourassa, 1999; Frasure-Smith et al., 2000). Other types of distress, including post-traumatic stress disorder (PTSD), may also influence prognosis (Dew et al., 1999; Shemesh et al., 2001). Despite some patients being at risk of developing PTSD, this disorder has to a great extent been overlooked in cardiac patients (Pedersen, 2001). Lack of social support has also been associated with adverse prognosis in cardiac patients. The magnitude of the risk on all cause mortality ranges from 1.33 to 5.62 adjusted for cardiac disease severity (Hemingway & Marmot, 1999).

Patients with lack of support also suffer from increased psychological distress (Frasure-Smith et al., 1999; Fontana, Kerns, Rosenberg & Colone, 1989; Yates, 1995; Conn, Taylor & Hayes, 1992), more cardiac symptoms (Fontana et al., 1989; Lindsay, Smith, Hanlon & Wheatley, 2001), and have more difficulty changing health-related behaviours (Conn et al., 1992).

It has been suggested that social support may not be endlessly available, and that individuals are given a limited duration in which to come to terms with a traumatic event (Paap, 1981; Buunk & Hoooren, 1992). To our knowledge, nobody has investigated the stability of social support over time in cardiac patients nor the short-term impact of low support on a composite endpoint of recurrent cardiac events defined as sudden cardiac death (SCD), reinfarction, coronary artery bypass graft surgery (CABG), and percutaneous transluminal coronary angioplasty (PTCA). Hence, the objectives of the current study were: (1) To assess the psychosocial adjustment of patients with a first MI at 9 months compared with 4–6 weeks post-MI; (2) to examine the availability of and satisfaction with social support over time; and (3) to determine which separate psychosocial baseline variables (anxiety, depression, PTSD, health symptoms, and social support) constitute independent predictors of recurrent cardiac events at 9 months post-MI.

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METHOD

Participants

Consecutive patients with a first MI, recruited from August 1999 to January 2001 from Aarhus University Hospital, and Horsens Hospital, Denmark, were assessed at 4–6 weeks and 9 months post-MI. A diagnosis of MI was based on increased levels of troponin T (> 0.10 microgram/liter) and ECG changes, according to the most recent guidelines (Joint European Society of Cardiology/American College of Cardiology Committee, 2002). Patients were excluded if they suffered from other life threatening diseases (e.g. cancer and HIV), cognitive impairments, had a history of psychiatric disorders, or were unable to understand and read Danish. Ethical approval was obtained from the ethical committees in Aarhus and Vejle Municipalities, and the study was carried out in accordance with the Helsinki Declaration.

Of the 164 patients screened for inclusion, three patients were excluded due to previous psychiatric history and other life-threatening diseases, and 12 patients were not approached due to personnel error. Of the remaining 149 patients, 37 refused to participate. Thus, 112 (75%) patients were assessed at baseline. No statistically significant differences were found between baseline patient responders and non-responders on demographic (gender and age) and clinical variables (left ventricular ejection fraction (LVEF), angina pectoris, and treatment with beta-blockers).

Prior to assessment at follow-up, 8 (7%) patients had dropped out, and two had died due to cardiac causes. Thus, analyses are based on 102 (91%) of the initial 112 patients for whom data were available at both baseline and follow-up. When investigating baseline predictors of recurrent cardiac events, the two deceased patients are included (n = 104 (93%).

Procedure

Patients were approached and informed about the project by staff in the departments of cardiology at 4–6 weeks post-MI. If they agreed to participate, they were given a questionnaire together with written information about the project and an informed consent form. The questionnaire was returned by mail. Due to logistic problems four months into data collection, we decided to adopt the policy of sending out a written reminder to patients, who had not returned their questionnaire within two weeks. At nine months, the patients received the second questionnaire by mail, which they were asked to return to the Department of Psychology. If they had not returned the questionnaire within two weeks, they were sent a written reminder.

Measures

Socio-demographic variables included gender, age, marital status, education, working status, and smoking status. Information on clinical variables (i.e. angina pectoris, LVEF, and beta-blocker therapy) was obtained from medical records. LVEF was measured by means of echocardiography.

We used the Posttraumatic Diagnostic Scale (PDS) to assess PTSD (Foa, 1995; Foa, Cashman, Jaycox & Perry, 1997). The PDS assesses all the diagnostic criteria (A-F) for PTSD according to the Diagnostic and Statistical Manual (DSM) IV (American Psychiatric Association, 1994). The scale yields three scores for each of the symptom clusters intrusion (5 items), avoidance (7 items), and arousal (5 items), a total symptom score, and a diagnosis of PTSD. The 17 symptom cluster items are measured on a four-point-Likert scale from 0 (not at all or only one time) to 3 (5 or more times a week/always almost always) (score range 0–51). The patients were asked to fill in the PDS in relation to their MI in order to ensure that their responses reflected their reaction to the MI. A similar approach has been adopted in a British study using the same scale to assess PTSD in MI patients (Bennett & Brooke, 1999). The psychometric properties of the PDS are satisfactory (Foa et al., 1997). The PDS has also been validated against the Structured Clinical Interview for DSM IV, and has satisfactory sensitivity (0.89) and specificity (0.75) (Foa et al., 1997).

Anxiety and depression were measured with the anxiety and depression subscales of the Trauma Symptom Checklist (Briere & Runtz, 1989). The two subscales contain nine items, respectively, that are answered on a four-point-Likert scale from 0 (never) to 3 (very often), yielding a score range of 0–27. The psychometric properties are adequate with Cronbach's α = 0.72 for the anxiety and depression subscales, respectively (Briere & Runtz, 1989).

The 24-item Health Complaints Scale (HCS), developed in cardiac patients, was used to assess somatic and cognitive complaints (Denollet, 1994). Each of the subscales comprises 12 items that combined into a single score reflects perceived health status. The scale has five answer categories from 0 (not at all) to 4 (extremely), yielding a score range of 0–48 for the subscales and 0–96 for the total scale. A higher score reflects more impaired perceived health. The HCS is a psychometrically sound instrument, which has also been confirmed in Danish cardiac patients (Pedersen & Denollet, 2002). The HCS measures symptoms that are distinct from symptoms of psychopathology (Pedersen & Denollet, 2002). It is also sensitive to detect change following cardiac rehabilitation (McGee, Hevey & Horgan, 1999).

We used the Crisis Support Scale (CSS) to assess social support due to the brevity of the scale and the assessment of multi-dimensional components of support (Joseph, Andrews, Williams & Yule, 1992; Joseph, Williams & Yule, 1992). The CSS consists of seven items that are rated on a seven-point Likert scale ranging from 1 (never) to 7 (always). The CSS measures two dimensions of support, i.e. total social support and satisfaction with support. The first six items are summed to yield a total score of social support. The score range for the total score is 6–42. In general, a higher score indicates a higher level of support. The last item measures overall satisfaction with support, and has a score range of 1–7. The CSS has proven to be a valid and reliable instrument (Joseph, Williams & Yule, 1992), which has also been confirmed in a recent large-scale Danish study (n = 4,213) (Elklit, Pedersen & Jind, 2001).

Outcome

The outcome was recurrent cardiac events, defined as SCD, reinfarction, CABG, and PTCA. We decided against a more restricted endpoint of SCD and MI only, since the occurrence of these events is rare in the follow-up period that was chosen for the current study. A similar endpoint has been used in a prospective study on the relation between depression after bypass and 12-months’ outcome (Connorney et al., 2001). Moreover, softer endpoints such as CABG and PTCA are clinically relevant to both patients and cardiologists.

Statistical analyses

To examine differences between responders and non-responders, we used the chi-square test (or Fisher’s exact test when appropriate) for categorical variables, and the t-test for independent samples for continuous variables. To assess psychosocial adjustment at 9 months compared with 4–6 weeks post-MI, McNemar's test was used for categorical variables, and paired t-tests were used for continuous variables. In order to evaluate whether statistically significant decreases in mood states, health complaints, and social support over time were also clinically relevant, we calculated the effect sizes by taking the difference between the mean score at entry and the mean score at final assessment.
score at follow-up and dividing it by the standard deviation of the same measure at baseline (Kazis, Anderson & Meenan, 1989). Cohen's (1988) criteria were used to determine the magnitude of the effect. To examine univariate relationships between baseline psychological variables and recurrent cardiac events at 9 months, we used the chi-square test (or Fisher's exact test when appropriate) for categorical variables, and the t-test for independent samples for continuous variables. All statistical tests were two-tailed. Odds ratios (OR) were calculated for each of the baseline psychological variables in relation to recurrent cardiac events using univariate logistic regression analyses. Multivariate logistic regression analyses were used to determine separate baseline psychosocial predictors of recurrent cardiac events adjusting for gender, age, education, LVEF, and smoking status. All statistical analyses were performed using SPSS 10.1 for Windows.

RESULTS

No statistically significant differences were found between patients who dropped out during follow-up and patients who completed the follow-up questionnaire on gender, education, marital status, psychosocial variables, health complaints, angina pectoris, and treatment with beta-blockers. However, differences were found on age ($p = 0.01$) and LVEF ($p = 0.03$) with non-responders being younger and all having a LVEF of 60%. Baseline demographic characteristics of the patients are presented in Table 1.

At 9 months' follow-up, 38% of the patients had suffered a recurrent cardiac event (SCD = 2; recurrent MI = 5; CABG = 12; PTCA = 24). Four patients had had more than one event. At follow-up, 49% of the patients denoted that they were afraid of a recurrent MI. Fourteen percent of the patients also had PTSD at baseline, whereas seven patients developed PTSD between baseline and follow-up.

The patients experienced a significant improvement in somatic and cognitive symptoms, indicating an overall improvement in perceived health at 9 months compared with baseline (Table 2). They also experienced a significant decline in symptoms of intrusion and avoidance. Social support over time were clinically relevant according to Cohen's (1988) criteria, as effect sizes ranged from small to moderate (0.19 to 0.33).

Patients with low social support (OR: 0.90; 95% CI: 0.84 to 0.97) and low satisfaction with support (OR: 0.66; 95% CI: 0.47 to 0.96) at baseline were at greater risk of a recurrent cardiac event at follow-up (Table 3). When adjusting for baseline characteristics including disease severity, low social support (OR: 0.90; 95% CI: 0.84 to 0.97) was still associated with an increased risk of recurrent cardiac events at follow-up, whereas low satisfaction with support was marginally significant (OR: 0.72; 95% CI: 0.49 to 1.06) (Table 4).

DISCUSSION

The results of the current study indicate that although there was an improvement in somatic and cognitive symptoms,

Table 1. Baseline characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>32 (31)</td>
<td>61.0 (9.5)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>8.5 (1.5)</td>
</tr>
<tr>
<td>Continuing education (years)</td>
<td></td>
<td>3.2 (3.8)</td>
</tr>
<tr>
<td>Married/partner</td>
<td>91 (88)</td>
<td></td>
</tr>
<tr>
<td>Living with others</td>
<td>91 (88)</td>
<td></td>
</tr>
<tr>
<td>Working</td>
<td>41 (40)</td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>10 (10)</td>
<td></td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>11 (11)</td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>98 (94)</td>
<td></td>
</tr>
<tr>
<td>LVEF: 0–40%</td>
<td>14 (14)</td>
<td></td>
</tr>
<tr>
<td>41–59%</td>
<td>41 (40)</td>
<td></td>
</tr>
<tr>
<td>60%+</td>
<td>48 (46)</td>
<td></td>
</tr>
<tr>
<td>missing echo</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Previous PTCA or CABG</td>
<td>5 (5)</td>
<td></td>
</tr>
</tbody>
</table>

$n = 104$.

was found on satisfaction with support between baseline and follow-up. We also found no statistically significant decrease in arousal, anxiety, and depression over time. None of the statistically significant decreases in somatopsymatology and social support over time were clinically relevant according to Cohen's (1988) criteria, as effect sizes ranged from small to moderate (0.19 to 0.33).

Patients with low social support (OR: 0.90; 95% CI: 0.84 to 0.97) and low satisfaction with support (OR: 0.66; 95% CI: 0.47 to 0.96) at baseline were at greater risk of a recurrent cardiac event at follow-up (Table 3). When adjusting for baseline characteristics including disease severity, low social support (OR: 0.90; 95% CI: 0.84 to 0.97) was still associated with an increased risk of recurrent cardiac events at follow-up, whereas low satisfaction with support was marginally significant (OR: 0.72; 95% CI: 0.49 to 1.06) (Table 4).

DISCUSSION

The results of the current study indicate that although there was an improvement in somatic and cognitive symptoms,

Table 2. Scores on psychopathology, health complaints, and social support at 9 months compared with 4–6 weeks post-MI

<table>
<thead>
<tr>
<th></th>
<th>Mean 4–6 weeks (SD)</th>
<th>Mean 9 months (SD)</th>
<th>$t$</th>
<th>df</th>
<th>mean dif.</th>
<th>$p^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrusion</td>
<td>2.31 (2.27)</td>
<td>1.57 (2.34)</td>
<td>3.091</td>
<td>101</td>
<td>0.74</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Avoidance</td>
<td>2.14 (2.17)</td>
<td>1.58 (2.22)</td>
<td>2.320</td>
<td>101</td>
<td>0.56</td>
<td>0.02</td>
</tr>
<tr>
<td>Arousal</td>
<td>2.40 (2.14)</td>
<td>2.53 (3.10)</td>
<td>−0.506</td>
<td>101</td>
<td>−0.13</td>
<td>0.61</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2.64 (2.06)</td>
<td>2.74 (2.88)</td>
<td>−0.406</td>
<td>91</td>
<td>−0.10</td>
<td>0.69</td>
</tr>
<tr>
<td>Depression</td>
<td>4.36 (3.08)</td>
<td>4.37 (3.05)</td>
<td>−0.035</td>
<td>98</td>
<td>−0.01</td>
<td>0.97</td>
</tr>
<tr>
<td>Somatic complaints</td>
<td>12.96 (9.62)</td>
<td>11.13 (8.89)</td>
<td>2.613</td>
<td>101</td>
<td>1.83</td>
<td>0.01</td>
</tr>
<tr>
<td>Cognitive complaints</td>
<td>15.26 (11.86)</td>
<td>12.29 (11.11)</td>
<td>3.036</td>
<td>101</td>
<td>2.97</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Social support (total)</td>
<td>30.27 (5.92)</td>
<td>28.56 (6.80)</td>
<td>3.084</td>
<td>100</td>
<td>1.70</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Social support (satisfaction)</td>
<td>6.10 (1.17)</td>
<td>6.05 (1.34)</td>
<td>0.407</td>
<td>100</td>
<td>0.05</td>
<td>0.69</td>
</tr>
</tbody>
</table>

$n = 102$.

*Paired $t$-test.
Trauma Symptom Checklist was not sufficiently sensitive to study may be due to cardiac denial, it is possible that the Elklit, 1998). Although the low scores found in the current study of HIV-positive that used the same scale (Pedersen &

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2 Coded as: No
1 Coded as: No event

PTSD 0.0413 1 0.94 1.04 (0.37 to 2.92)
Arousal 0.1281 1 0.22 1.14 (0.93 to 1.40)
Avoidance 0.0581 1 0.56 1.06 (0.87 to 1.29)
Intrusion 0.0620 1 0.54 1.06 (0.87 to 1.29)

Predictors Beta df p OR (95% CI)*
Intrusion 0.0620 1 0.54 1.06 (0.87 to 1.30)
Avoidance 0.0581 1 0.56 1.06 (0.87 to 1.29)
Arousal 0.1281 1 0.22 1.14 (0.93 to 1.40)
PTSD 0.0413 1 0.94 1.06 (0.57 to 2.92)
Anxiety −0.0651 1 0.60 0.94 (0.74 to 1.19)
Depression 0.0926 1 0.21 1.10 (0.95 to 1.27)
Somatic complaints 0.0252 1 0.29 1.03 (0.98 to 1.07)
Cognitive complaints 0.0073 1 0.70 1.01 (0.97 to 1.05)
Social support (total) −0.1022 1 <0.01 0.90 (0.84 to 0.97)
Social support (satisfaction) −0.3270 1 0.10 0.72 (0.49 to 1.06)

Table 4. Significant independent baseline psychosocial predictors of recurrent cardiac events at 9 months

n = 104.

1 Coded as: No event = 0; Event = 1.
2 Coded as: No = 0; Yes = 1.
*Adjusted for gender, age, education, LVEF, and smoking status.

some patients still experienced difficulties with psychosocial adjustment 9 months post-MI.

The improvement in somatic and cognitive symptoms between baseline and follow-up suggests that pharmacological and invasive treatment has been successful in these patients. It is noteworthy, however, that there was no improvement in anxiety and depression between baseline and follow-up. Although other studies (e.g. Bennett, Owen, Koutsakis & Bisson, 2002) have found similar results, baseline scores on anxiety and depression in the current study were relatively low compared with those (anxiety: mean (SD) = 11.16 (11.00); depression: mean = 17.74 (16.79)) in a study of HIV-positive that used the same scale (Pedersen & Elklit, 1998). Although the low scores found in the current study may be due to cardiac denial, it is possible that the Trauma Symptom Checklist was not sufficiently sensitive to detect these symptoms in cardiac patients (Briere & Runtz, 1989). Post-hoc analyses showed that baseline and follow-up scores in mood states were significantly correlated (p < 0.01) indicating that the non-reduction in mood states was not due to significant variability in individual outcome over time as found for anxiety in the Bennett et al. study (2002).

Although there was a decrease in the number of patients with PTSD, 14 (14%) patients had PTSD at follow-up. This is almost twice as high as the estimated life-time prevalence rate in the US (Kessler, Sonnega, Bromet, Hughes & Nelson, 1995). No comparable epidemiological data are available for the Danish population. Seven of the 14 patients also qualified for a diagnosis of PTSD at baseline, which suggests that PTSD may have become chronic in these patients. A diagnosis of PTSD may have serious implications for cardiac patients. PTSD has been associated with non-adherence to medication and poor medical outcome in survivors of MI (Shemesh et al., 2001).

At follow-up, symptoms of intrusion and avoidance had declined. Intrusion is a primary symptom emerging immediately following trauma with avoidance occurring secondarily as a means of coping with the discomfort associated with the intrusive symptoms (Creamer, Burgess & Pattison, 1992). This suggests that patients generally have adjusted to their MI or alternatively that avoidance has become a more entrenched coping strategy (Creamer et al., 1992). However, the lack of change in symptoms of arousal indicates that the patients are still on guard fearing the recurrence of a cardiac event. This is further corroborated by the fact that at follow-up 49% denoted that they were afraid of a recurrent MI. A continuous state of arousal may contribute to the progression of CAD mediated through changes in hemostatic parameters (Von Känel, Mills, Fainman & Dimsdale, 2001). PTSD has also been associated with elevations in blood pressure (Buckley & Kaloupek, 2001).
Social support decreased over time, which may be a reflection of depression, since perceptions of low social support have been noted as a feature of depressed patients. However, additional analyses showed that neither depression at baseline nor at follow-up was related to the decrease found in social support. We therefore suggest that the decrease in social support over time more likely reflects that social support may not be endlessly available. It has been suggested that there may be unspoken rules as to what constitutes a proper duration for coming to terms with a traumatic event, after which social support may be withdrawn (Paap, 1981; Buunk & Hoorens, 1992). However, the withdrawal of social support may have serious consequences for cardiac patients, since lower social support was associated with an increased risk of recurrent cardiac events at 9 months when adjusting for other factors including cardiac disease severity in the current study. Other studies have also found psychosocial factors to be associated with increased risk of morbidity and mortality despite appropriate medical and invasive intervention (Denollet, Vaes & Brutsaert, 2000; Frasure-Smith et al., 1999; Williams et al., 1992; Case, Moss, Case, McDermott & Eberly, 1992). However, these studies have usually had a longer follow-up period and restricted outcome to cardiac death and reinfarction. Lower satisfaction with support was also associated with recurrent events in the current study. However, it was no longer significant when adjusting for other variables, although the associated risk was higher than that for total social support.

The results of the current study should be interpreted with caution due to the relatively small sample size and an initial refusal rate of 25%. Although no differences were found between responders and non-responders at baseline on demographic and clinical variables, it is possible that they may have differed on psychological variables. Most of the measures used were self-report, and the scale with which we assessed depression and anxiety has not been validated against diagnostic interview. The follow-up period was relatively short, which necessitated the use of a composite endpoint of sudden cardiac death, recurrent MI, CABG, and PTCA. We may also have omitted to include pertinent clinical variables that could account for the influence of low social support on CAD outcome. Moreover, none of the statistically significant decreases in symptomatology and social support were clinically significant as evaluated by means of Cohen’s effects sizes (1988). Finally, non-responders at follow-up were also more likely to have a normal LVEF and to be younger than responders, but they only comprised eight patients. Despite these limitations, no further differences were found between responders and non-responders, and the response rate was above 90% at follow-up. To our knowledge this is also the first study to show that low social support may be an independent risk factor for a composite endpoint of recurrent cardiac events already 9 months post-MI.

In conclusion, the results of the current study indicate that some patients with a first MI still experience difficulties with psychosocial adjustment 9 months following the event despite a reduction in somatic and cognitive symptoms. Our results also suggest that social support may not be endlessly available, which may have serious prognostic implications given that lower social support at baseline was found to be an independent predictor of recurrent cardiac events already 9 months post-MI. These results, however, should be replicated in a larger sample. Although we were unable to confirm that PTSD following MI is associated with an increased risk of recurrent cardiac events, there is emerging evidence that cardiac patients with PTSD are at increased risk. Thus, it is now important for future research to include larger sample sizes to further investigate this possibility and to evaluate potential implications for clinical practice. A pivotal next step will also be to investigate how social support can be enhanced in patients at risk. In the meantime, in clinical practice there is evidence to suggest that a particularly caring and supportive relationship with healthcare providers may have considerable beneficial impact on patients’ quality of life, morbidity, and mortality (Fontana et al., 1989; Yates, 1995).

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