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Social inhibition modulates the effect of negative emotions on cardiac prognosis following percutaneous coronary intervention in the drug-eluting stent era

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Aims Negative emotions have an adverse effect on cardiac prognosis. We investigated whether social inhibition (inhibited self-expression in social interaction) modulates the effect of negative emotions on clinical outcome following percutaneous coronary intervention (PCI).

Methods and results Eight hundred and seventy-five consecutive patients from the RESEARCH registry (Erasmus Medical Centre, Rotterdam) completed depression, anxiety, negativity (negative emotions in general), and social inhibition scales 6 months following PCI. The endpoint was major adverse cardiac event (MACE—death, myocardial infarction, coronary artery bypass graft (CABG), or PCI) at 9 months following assessment. There were 100 MACE; patients who were high in both negativity and inhibition were at increased risk of MACE (38/254 \(=\) 15%) when compared with high negativity/low inhibition patients (13/136 \(=\) 10%; \(P = 0.018\)). Depression \((P = 0.23)\) or anxiety \((P = 0.63)\) did not explain away this moderating effect of inhibition. High negativity/high inhibition \((HR = 1.92, 95\%CI 1.22–3.01, P = 0.005)\) and previous CABG \((HR = 1.90, 95\%CI 1.04–3.47, P = 0.038)\) were independent predictors of MACE. Patients with high negativity but low inhibition were not at increased risk \((P = 0.76)\). High negativity/high inhibition also independently predicted death/MI \((n = 20)\) as a more specific endpoint \((HR = 5.85, P = 0.001)\).

Conclusion The interaction effect of social inhibition and negative emotions, rather than negative emotions per se, predicted poor clinical outcome following PCI. Social inhibition should not be overlooked as a modulating factor.

KEYWORDS Coronary heart disease; Prognosis; Social inhibition; Negative affectivity; Sirolimus-eluting stent; Type D personality

Introduction

The advent of drug-eluting stents has led to a reduction in repeat revascularization following percutaneous coronary intervention (PCI), but has not been shown to reduce the risk of death or myocardial infarction (MI).1–3 Negative emotions may have an adverse effect on prognosis and treatment outcome in cardiac patients.4–6 However, the effect of emotions has yet to be examined in the drug-eluting stent era; in general, little is also known about psychological factors that may modulate the impact of these emotions on cardiac prognosis.

Social isolation may potentiate the adverse effect of negative emotions. Post-MI patients with high levels of both stress and social isolation had four times the risk of death when compared with patients with low levels of stress/isolation7; a recent study of mortality in the elderly also found that isolation aggravates the adverse effect of negative emotions.8 Social isolation is a function of individual differences in behavioral inhibition9; the trait 'social inhibition' refers to the tendency to inhibit the expression of emotion and behaviour in social interaction.10 Inhibited individuals expect negative reactions from others and tend to be socially isolated.

Preliminary evidence suggests that social inhibition may also affect the clinical course of patients who have been treated with PCI. Potential pathways through which social inhibition may influence prognosis include enhanced cardiovascular reactivity to stress,11–13 reduced heart rate variability,14 and increased inflammation.15 Social inhibition may also impede communication between patient and physician and result in the under-treatment of psychological stress, which could be potentially damaging to health.16 Finally, the socially inhibited are less likely to adhere to treatment17 or to engage in health-promoting behaviour.18

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We therefore examined the role of social inhibition in the 15-month prognosis of PCI patients, who were treated with bare or sirolimus-coated stenting in the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. Initial findings from this registry indicated that Type D patients were at increased risk for death or MI. Type D personality refers to patients who are high in negative affectivity (tendency to experience negative emotions) and social inhibition. These two components of Type D were not analysed separately in this report, and the endpoint did not include revascularization procedures; hence, it is possible that the increase in risk was attributable to the main effect of either negative affectivity or social inhibition and not that inhibition modulates the effect of negative affectivity. In the present study, we therefore examined whether it is the specific interaction effect of negative affectivity. In the present study, we therefore examined whether it is the specific interaction effect of negative affectivity and social inhibition that renders Type D patients at increased risk for death, MI, or repeat revascularization following PCI treatment with stenting.

Methods

Patient population

Details of the RESEARCH registry have been published elsewhere. In brief, the purpose of the registry was to investigate the efficacy and safety of the sirolimus-eluting stent (SES) (Cypher; Johnson & Johnson-Cordis unit, Cordis Europa NV, Roden, The Netherlands) in PCI. Between October 2001 and October 2002, 1237 consecutive patients with ischaemic heart disease were included. Prior to April 2002, all patients received bare metal stents; since April 2002, all patients received the SES stent. All interventions were performed according to current standard guidelines. One-month clopidogrel treatment (75 mg/day) was recommended for patients treated with bare stents; SES-patients received clopidogrel for 3 months. If patients had had multiple SES implantations, total stented length >36 mm, chronic total occlusion, bifurcations, or treatment of in-stent restenosis, clopidogrel was maintained for at least 6 months. All patients were advised to maintain lifelong aspirin.

At 6-month post-PCI, all living patients were contacted by letter and asked to fill in questionnaires; 875 patients (71%) returned the questionnaires (Table 1). Non-responders were younger (59 vs. 62 years, P < 0.001), more likely to have had a previous MI (18 vs. 14%, P = 0.03), to suffer from diabetes (20 vs. 15%, P = 0.02), and to be treated with ACE-inhibitors (31 vs. 26%, P = 0.04), but less likely to suffer from renal impairment (23 vs. 31%, P < 0.01) and to be treated with beta-blockers (26 vs. 51%, P < 0.001) or aspirin (33 vs. 65%, P < 0.001) than responders. The study was approved by the local hospital Ethics Committee and was carried out in accordance with the Helsinki Declaration. Every patient provided written informed consent.

Social inhibition

The patient’s level of inhibition was assessed with the ‘social inhibition’ subscale of the Type D Personality Scale (DS14); this

<table>
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<tr>
<th>Table 1 Baseline characteristics at 6-month post-PCI (n = 875)</th>
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Negativity−: patients who score low on negative affectivity, irrespective of level of Inhibition; Negativity+/Inhibition−: patients who score high on negative affectivity but low on inhibition; Negativity−/Inhibition+: patients who score high on negative affectivity and inhibition. Previous MI, myocardial infarction prior to index event; previous PCI, percutaneous coronary intervention prior to index event; previous CABG, bypass surgery prior to index event.

* A post hoc Bonferroni correction was applied to all tests to adjust for multiple comparisons with P < 0.02 (0.05/3) indicating statistical significance.

**Total cholesterol levels >240 mg/dl, or on lipid lowering medication.

+Indicated by creatine clearance >61 mL/min.
subscale measures the tendency to inhibit the expression of emotion/behaviour in order to avoid negative reactions from others, such as disapproval. High scorers tend to feel inhibited, tense, and insecure when with others. Each of the seven inhibition items (e.g., 'I am a closed kind of person', 'I often feel inhibited in social interactions') is rated on a five-point Likert scale (0–4). The subscale is valid, internally consistent (Cronbach’s α = 0.86), and stable over a 3-month period (test-retest r = 0.82). According to a previously established cut-off, patients scoring ≥10 are considered high in inhibition.21

Negative emotions
Symptoms of depression22 and anxiety23 are markers of negative emotional conditions and have been linked to poor prognosis in post-MI patients. The ‘depression’ subscale of the Hospital Anxiety and Depression Scale (HADS) was used to evaluate depressive symptoms.24 This subscale consists of seven items, which are answered on a four-point Likert scale (0–3; total score range 0–21), has good reliability and validity,25 and correlates well with the clinical diagnosis of post-MI depression.26 A cut-off score of ≥8 yields an optimal balance between sensitivity and specificity25 and was used to determine elevated depression scores. The seven-item ‘anxiety’ subscale of the HADS was used to evaluate anxiety symptoms (total score range 0–21).24 A cut-off score of ≥8 was used to determine elevated anxiety scores.25 The ‘negative affectivity’ subscale of the DS14 was used to assess individual differences in patients’ tendencies to experience negative emotions in general, that is, high scorers tend to report feelings of depression, anxiety, or irritability across time and situations. This seven-item subscale is valid, consistent (Cronbach’s α = 0.88), and stable (test-retest r = 0.72).21 In this article, the term ‘negativity’ will be used to refer to individual differences in negative affectivity. According to a previously established cut-off, patients scoring ≥10 are considered high in negativity.21

Biomedical factors
Information on stent type (SES vs. bare metal stent) and clinical variables [multi-vessel disease, previous MI, previous coronary artery bypass graft (CABG) surgery, previous PCI] were obtained from the patients’ medical records. Standard cardiac risk factors included age, gender, hypercholesterolaemia, hypertension, smoking status, renal impairment, and diabetes mellitus. Medical treatment was also recorded, including prescription of beta-blockers, aspirin, clopidogrel, statins, calcium antagonists, ACE-inhibitors, and nitrates.

Endpoint
The endpoint was the occurrence of a major adverse cardiac event (MACE), defined as a composite of death, MI, CABG, or repeat PCI at 9 months following psychological assessment. Data on these endpoints were available for all patients. MI was diagnosed by a rise in the creatine kinase level to more than twice the upper normal limit with an increased creatine kinase-MB. Events occurring between the index event and administration of questionnaires were excluded as an endpoint. Non-fatal MI, CABG, or PCI that occurred prior to psychological assessment were included in the analyses as previous MI, previous CABG, or previous PCI.

Statistical analyses
Principal components analysis (varimax rotation) of items from the inhibition, depression, anxiety, and negativity scales was used to examine the structural validity of the social inhibition construct, that is, the ability of the inhibition items to reflect a psychological construct that is distinctly different from self-reported negative emotions.27 The scree-plot was used as a criterion for the number of factors to extract; Cronbach’s α was used to examine the internal consistency of the inhibition scale. On the basis of their personality test scores, patients were classified into one of three subgroups: (i) low negativity, (ii) high negativity but low inhibition, or (iii) high negativity and high inhibition. The χ² test (Fisher’s exact test when appropriate) was used to compare these three subgroups on baseline characteristics, and a post hoc Bonferroni correction was used to adjust for multiple comparisons with P < 0.02 (0.05/3), indicating statistical significance. Cox-regression analyses were performed to investigate the relative impact of depressive, anxiety, and negativity symptoms, and their interaction with social inhibition on MACE at 9-months follow-up. Non-significant interaction terms between variables and time to MACE (all P-values >0.10) showed that the hazard ratios were constant across time, indicating that the proportional hazards assumption was met. In multi-variable analyses, age, gender, stent type (SES vs. bare stent), multi-vessel disease, previous MI, previous CABG, previous PCI, hypertension, smoking, hypercholesterolaemia, renal impairment, diabetes, and psychological variables were entered at the same time. We chose to adjust for these covariates, as sex and age are included standardly in multi-variable models in biobehavioural research and have been associated with substantial variation in cardiovascular outcomes; stent type was included, as there is as yet no knowledge of the impact of drug-eluting stents on psychological functioning; multi-vessel disease and cardiac history were included to adjust for disease severity, ruling out the possibility that any relationship between psychological variables and MACE could be due to more severe cardiac disease in emotionally distressed patients; standard risk factors, renal impairment, and diabetes were included to control for somatic comorbidity. All statistical tests were two-tailed; P-value <0.05 was used to indicate statistical significance. Hazard ratios with 95% confidence intervals are reported. Analyses were performed using SPSS version 12.0.

Results
Social inhibition vs. negative emotions
Factor analysis was used to examine the structural validity of the social inhibition construct. Consistent with the theoretical model of the present study, the scree-plot yielded two dominant psychological factors that were assessed by questionnaires in the RESEARCH registry (Figure 1). Succeeding factors were much smaller (eigenvalue <1.0) and explained a minor proportion of variance in distress. All inhibition items loaded on one and the same factor, whereas all items referring to negative emotions (depression, anxiety, negativity) loaded on the other factor.
Factor analysis of the seven social inhibition items and the six items of negative emotions with the highest factor loadings (two items for depression, anxiety, and negativity, respectively) showed that the inhibition items loaded much higher on their corresponding factor than on the negative emotions factor (Table 2, factor analysis). In addition, Cronbach’s α = 0.86 and item-to-total correlations ranging from 0.49 to 0.71 indicated a high level of internal consistency for the inhibition scale (Table 2, last column). These analyses confirmed that social inhibition represents a homogeneous construct that is distinctly different from negative emotions.

**Characteristics of negativity/inhibition subgroups**

Stratifying baseline characteristics by negativity and inhibition subgroups showed that males and diabetic patients were more prevalent in the low negativity group (Table 1, subgroups). There was also a trend for previous PCI, with the high negativity/low inhibition subgroup being more likely to have undergone PCI prior to the index procedure. Finally, patients who were high in both negativity and inhibition were more likely to be current smokers.

**Negativity, inhibition, and cardiac events**

At follow-up, there were 100 MACE. None of the medical treatment variables (beta-blockers, aspirin, clopidogrel, statins, calcium antagonists, ACE-inhibitors, or nitrates) were significantly associated with clinical outcome. Previous CABG (HR = 1.78, 95%CI 1.05–3.02, P = 0.032) was associated with increased risk of MACE in univariate analyses. The interaction between inhibition and negativity was also associated with an increased risk of MACE (HR = 1.66, 95%CI 1.11–2.51, P = 0.015), whereas negativity by itself did not predict outcome. Hence, inhibition significantly modulated the effect of negativity on clinical outcome following PCI, adjusting for stent type (SES vs. bare metal stent), age, and gender (Figure 2).

The rate of MACE for patients who were high in negativity but low in inhibition (9.6%) did not differ from that for patients who were low in negativity (10.1%) and was smaller than that for patients who were high in both negativity/inhibition (15.0%; HR = 1.64, 95%CI 1.09–2.47, P = 0.018). HADS scores of depressive symptoms (P = 0.23) or anxiety symptoms (P = 0.63) did not explain away this association between high negativity/high inhibition and adverse cardiac prognosis. Hence, the increase in risk of MACE was attributable to the interaction effect of high negativity and high inhibition, but not to the main effect of negative emotions.

In order to ascertain that the increased risk of MACE in the high negative affectivity/high social inhibition group is not merely due to a high score on negative affectivity, we investigated the mean (SD) scores between the three personality subgroups, using ANOVA with a post hoc (Student–Newman–Keuls) test. The mean (SD) score for the low negativity regardless of inhibition group was 4.15 (2.95); for the high negativity/low inhibition, it was 14.90 (4.15); for the high negativity/high inhibition group, the mean was 16.44 (4.62). Differences between all groups were statistically significant at P < 0.05. It should be noted, however, that the mean difference (1.54) between Groups 2 and 3 cannot be considered clinically relevant also considering the SDs for each group. These additional results suggest that the increased risk of MACE in the high negativity/high inhibition group cannot be attributed to a high NA score alone.
Figure 2 MACE stratified by negativity and inhibition. The number of patients is presented on top of each bar. Negativity−: patients who score low on negative affectivity, irrespective of level of inhibition; negativity+/inhibition−: patients who score high on negative affectivity but low on inhibition; negativity+/inhibition+: patients who score high on negative affectivity and inhibition. *Adjusted for age, gender and stent type.

Independent predictors of cardiac events
To determine whether medical and psychological factors were independent predictors of cardiac events, we entered these factors in a multi-variable Cox-regression model (Table 3). Potential psychological risk factors included the combinations of high negative affectivity/low inhibition and high negativity/high inhibition as distinctly different subgroups. The final Cox-regression model retained high negativity/high inhibition (HR = 1.92, P = 0.005) and history of CABG (HR = 1.90, P = 0.038) as independent predictors of adverse cardiac events; there was also a trend for diabetes (P = 0.073). In contrast, PCI patients who were high in negativity but low in inhibition were not at increased risk for adverse clinical events during follow-up (P = 0.76).

These findings were replicated in secondary analyses, using a composite of death and MI as a more specific endpoint (n = 20). Rate of death/MI was 7/485 = 1.4% for patients who were low in negativity. Of note, 13 out of 254 patients who were high in both negativity and inhibition died or had an MI. In contrast, none of the 136 patients who were high in negativity but low in inhibition had one of these events (5.1 vs. 0% event rate, P = 0.004). Cox-regression analysis yielded history of CABG, male gender, and high negativity/high inhibition (HR = 5.85, P = 0.001), but not high negativity/low inhibition (P = 0.98), as independent predictors of death/MI.

Discussion
The present findings showed that social inhibition is a distinctly different psychological construct than negative emotions and that inhibition modulates the impact of these emotions on prognosis. More specifically, it was the interaction between inhibition and negativity that predicted the composite endpoint of death, MI, and repeat revascularization at 9-month follow-up, adjusting for medical confounders. This inhibition/negativity interaction effect was associated with a 92% increase in risk of cardiac events. Finally, concurrent symptoms of depression or anxiety did not explain away the modulating effect of inhibition on negativity as a predictor of poor clinical outcome. These results were also confirmed in secondary analyses using ‘hard events’ (i.e. death/MI) as an endpoint, indicating that the interaction effect of inhibition and negativity on clinical outcome following PCI was not only symptom-driven.

Patients who display this combination of high inhibition and high negativity are referred to as patients with a Type D personality.20 The present findings are consistent with those from previous studies showing that Type D independently predicts long-term cardiac events.5,20,28 However, only one study to date specifically looked at the interaction between inhibition and negativity and found that the high mortality risk among Type D patients was not attributable to the main effect of either inhibition or negativity, but rather to their interaction effect.20 In the present study, the presence of negativity also had no effect on prognosis, that is, patients with high negativity but low inhibition were not at increased risk. The findings of two recent meta-analyses indicated that depression is a risk factor for adverse prognosis.29,30 The present results indicate that social inhibition may significantly modulate this relationship.

The present findings have important implications for clinical research and practice: (i) this study is the first to confirm the initial observation20 that it is the modulating effect of social inhibition on negative emotions, which renders patients at increased risk for cardiac events and (ii) provides

Table 3 Multi-variable predictors of cardiac events post-PCI (n = 875)

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio (95%CI)</th>
<th>P</th>
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<tr>
<td>Demographics</td>
<td></td>
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<tr>
<td>Age ≥ 60</td>
<td>1.03 (0.65–1.61)</td>
<td>0.92</td>
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<tr>
<td>Female gender</td>
<td>1.33 (0.81–2.17)</td>
<td>0.26</td>
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<tr>
<td>Stent type</td>
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<tr>
<td>Sirolimus-eluting stent</td>
<td>0.79 (0.51–1.22)</td>
<td>0.28</td>
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<tr>
<td>Clinical factors</td>
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<tr>
<td>Multi-vessel disease</td>
<td>0.89 (0.57–1.37)</td>
<td>0.58</td>
</tr>
<tr>
<td>Previous MI</td>
<td>0.71 (0.46–1.12)</td>
<td>0.14</td>
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<tr>
<td>Previous CABG</td>
<td>1.90 (1.04–3.47)</td>
<td>0.038</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>1.30 (0.81–2.09)</td>
<td>0.28</td>
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<tr>
<td>Hypercholesterolaemia</td>
<td>0.69 (0.42–1.14)</td>
<td>0.15</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.87 (0.56–1.34)</td>
<td>0.52</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.69 (0.42–1.12)</td>
<td>0.13</td>
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<tr>
<td>Renal impairment</td>
<td>0.85 (0.54–1.34)</td>
<td>0.48</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.60 (0.96–2.66)</td>
<td>0.073</td>
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<td>Psychological factorsa</td>
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<td>High negativity/low inhibitionb</td>
<td>1.10 (0.59–2.08)</td>
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<tr>
<td>High negativity/high inhibitionc</td>
<td>1.92 (1.22–3.01)</td>
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*a Patients with a score ≥ 9 on the negative affectivity scale were used as comparator group.
*b Score ≥ 10 on the negative affectivity scale and ≤ 9 on the social inhibition scale coded as 1.
*c Score ≥ 10 on the negative affectivity scale and ≤ 10 on the social inhibition scale coded as 1.
more evidence for the notion that social inhibition is a psychological factor that is distinctly different from negative affect. The findings also underscore the importance of not only focusing on one psychological risk factor at a time but also to take into account the potential interaction effect of psychological factors on cardiac prognosis.  

There are several pathways through which social inhibition may modulate the effect of negative emotions on clinical outcome. Pathophysiological factors comprise one pathway. Inhibited individuals suppress the outward signs of inner feelings, which could be potentially damaging to the health of cardiac patients. Inhibited individuals appear quiet on the surface, but they may actually feel tense and insecure when with others and tend to experience substantial personal distress. In addition, inhibition may be associated with non-compliance. In women with the human immunodeficiency virus at risk of cancer, an inhibited interpersonal style was associated with non-adherence to scheduled outpatient visits. The socially inhibited may also be less likely to engage in health-promoting behaviours. Accordingly, patients from the present study who were high in both negativity and inhibition were less likely to quit smoking.

Preliminary evidence shows that it is possible to circumvent the deleterious effects of negative emotions and social inhibition on cardiac prognosis, as a reduction in these emotions through cardiac rehabilitation and the use of anti-depressants have been shown to lead to improved prognosis. With inhibited patients, it will be particularly important for cardiologists and nurses to be alert as to the communication between themselves and the patient and to be persistent in asking about symptom levels, adherence to treatment and health-promoting behaviours, such as smoking cessation. A well-established rapport with the health-care staff may in time enable the patient to feel more comfortable and free in expressing him- or herself, in turn, enhancing compliance and reducing the risk of adverse clinical outcome.

These findings should be interpreted with some caution. Psychological factors were not assessed at the time of the index event so as to present patients in a stable cardiac condition. Although this may have biased the results, as patients who died between 0 and 6 months following PCI did not have a psychological assessment, a similar approach has been adopted in other studies of PCI patients for the very same reason. In addition, there were significant differences on some baseline characteristics between responders and non-responders. Hence, we do not know whether the present results are generalizable to the total sample. We also had no information on the potential clinical confounders history of heart failure, left ventricular dysfunction, chronic obstructive pulmonary disease, cerebrovascular disease, and peripheral vascular disease or on the use of pharmacotherapy and previous history of depression. However, previous history of depression has not been shown to increase the risk of cardiac events. Finally, we did not have information on life-events as potential triggers of cardiac endpoints.

Despite these limitations, an advantage of this study is that it reflects the ‘real world’ of interventional cardiology, as no exclusion criteria were applied. Of note, 68% of the patients included in the RESEARCH registry would not have qualified for inclusion in clinical trials because of their more complex clinical profile. Moreover, the present findings are consistent with those of previous research and also expanding our knowledge of the interaction between psychological factors in relation to prognosis. Future studies are warranted to determine the nature of social inhibition and its most toxic components in terms of cardiovascular disease progression. As suggested by Habra et al., is it ‘emotional inhibition’ or ‘behavioural inhibition’ that renders patients at risk? Given that both aspects have been shown to have physiological correlates, they both seem to be likely candidates to explore the pathways through which inhibition modulates the effect of negative emotions on prognosis.

In conclusion, the findings of the present study highlight the role of social inhibition as an emerging psychological factor, which may modulate the effect of negative emotions on cardiac prognosis. These findings indicated that it was the interaction effect of social inhibition and negative emotions, rather than negative emotions per se, which had a deleterious effect on clinical outcome following PCI. Therefore, the role of social inhibition as a modulating factor should not be overlooked in clinical research and practice also not in the drug-eluting stent era, given that drug-eluting stents have not been shown to confer any benefits on survival.

Acknowledgement

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Conflict of interest: none declared.

References


