Somatic depression in the picture

Meurs, Maaike

Chapter 5

Examining the relation between post myocardial infarction depression and cardiovascular prognosis using a validated prediction model for post myocardial mortality

Maaike Meurs, Marij Zuidersma, Chris Dickens, Peter de Jonge

International Journal of Cardiology 2013; 167(6):2533-8

Abstract

Objective: The presence of depressive symptoms after myocardial infarction (MI) is associated with worsened cardiovascular (CV) prognosis. To date, it remains unclear to what extent the relationship between post-MI depression and prognosis is confounded by factors related to prognosis. We assessed the relationship between depression and prognosis while adjusting for a well validated risk score for mortality after a MI.

Methods: Data of 494 MI patients were derived from the Depression after Myocardial Infarction study (DepreMI). Scores on the Beck Depression Inventory (BDI) (cut-off ≥10) were used to relate depressive symptoms (divided in somatic/affective and cognitive/affective symptoms) to the Global Registry of Acute Coronary Events (GRACE) risk score, using Pearson correlations. Cox regression analysis was performed to investigate the predictive value of depressive symptoms for prognosis after adjusting for GRACE score.

Results: Overall, depressive symptoms were significantly correlated with GRACE score ($r=0.12$ $p=0.008$). Specifically, somatic/affective symptoms were positively correlated ($r=0.23$, $p<0.001$), whereas cognitive/affective symptoms tended to be negatively correlated ($r=-0.08$ $p=0.097$) with GRACE score. Adjusting for GRACE score did not affect the HR for recurrent CV events associated with total BDI- score (adjusted hazard ratio (HR) per point increase in BDI score 1.05 $p=0.002$ 95% CI 1.02-1.08 $n=463$). Furthermore GRACE score attenuated the HR associated with 1 SD increase in somatic/affective depressive symptoms from 1.44 (1.20-1.72) to 1.31 (1.08-1.58).

Conclusions: GRACE score was positively associated with somatic/affective depressive symptoms. GRACE score explained only partly the association between (somatic/affective) depressive symptoms and CV prognosis.

Introduction

Post-myocardial infarction (post-MI) depression is associated with a 2-2.5 times increased risk of new cardiovascular (CV) events and mortality.[1] Randomized controlled trials assessing the effect of depression treatment in post MI patients found no improvement in cardiac outcomes.[2-4] To date, it remains unclear to what extent the relationship between post-MI depression and prognosis is confounded by factors related to prognosis.[5] One important problem is that studies in this field have used different (combinations of) clinical prognostic factors as confounders, including left ventricular ejection fraction, previous MI, heart failure, arrhythmia, blood pressure and diabetes. In addition, adjustment for confounders is often incomplete. Incomplete adjustment for confounders or poorly measured confounding factors might lead to the incorrect inference that a variable predicts an outcome independent from these factors.[6]

An alternative method to evaluate the role of potential confounders in the association between depression and cardiac prognosis is the use of validated composite prognostic measures. A composite measure that may be suitable for this purpose is the Global Registry of Acute Coronary Events (GRACE) risk score. The GRACE model was specifically developed to estimate the risk of mortality of hospitalized acute coronary syndrome (ACS) patients during hospitalization[7] and within six months after admission or discharge.[8] The GRACE model even predicts prognosis within five years of discharge. The model consists of empirically derived prediction variables based on a large multinational sample of ACS patients of the entire spectrum.[8] It is widely applicable and it outperforms other ACS risk models.[9,10] The GRACE model is not a measure for disease severity per se, but its high predictive value of mortality after ACS may make it an important confounder. In addition, the use of a composite score minimizes the risk of overfitting in small studies.[11]

Surprisingly, only one study to date used the GRACE score to assess whether depression after an ACS independently predicts cardiac prognosis.[12] In that study, depression still predicted mortality after adjusting for GRACE score and left ventricular ejection fraction (LVEF), but these analyses were based on only 18 outcome events of 457 ACS patients.

In the current study, we assessed whether depressive symptom severity after MI is associated with higher GRACE scores and to what extent GRACE score explains the relationship between depression and new CV events. In a secondary analysis, we associated GRACE score with somatic/affective and cognitive/affective depressive symptoms separately, because somatic/affective depressive symptoms have been found to be more predictive of adverse outcome than cognitive/affective symptoms.[13-17]

Methods

Design and patients

We used data from the Depression after Myocardial Infarction (DepreMI) study, an observational cohort study including MI patients who were admitted for MI between September 1997 and September 2000 in one of four hospitals in the North of the Netherlands. Patients were included if they met at least two of the following three criteria for acute MI: (1) chest pain for at least 20 min, (2) creatine phosphokinase value 100% higher than normal or creatine phosphokinase MB value greater than 10%, or (3) presence of new pathological Q wave on the electrocardiogram in at least two leads. Informed consent was obtained from each patient and the study protocol was approved by the institutional review board of each hospital. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

Several studies used this database for research on the relation between post-MI depression and cardiac outcome to date. In these studies overall depressive symptoms on the Beck Depression Inventory (BDI) and specifically somatic/affective depressive symptoms and incident episodes of MDD were associated with worse prognosis, while cognitive/affective depressive symptoms and non-incident episodes of MDD were not.[13,18,19]

Assessment of depressive symptoms

The BDI was used to assess depressive symptoms during hospitalization. The BDI is the most widely used self-report questionnaire measuring depression in CV disease patients.[20] This 21-item questionnaire measures the presence and severity of depressive symptoms. In all analyses concerning CV outcomes the continuous BDI score was used. Additionally, a dichotomized BDI-score (cutoff ≥ 10) was used for describing the patient sample, and additionally to the continuous BDI-score in the analyses concerning CV outcomes to facilitate interpretation and comparison with previous studies. A score of 10 or greater on the BDI indicates at least mild symptoms of depression.[21] Additionally, we studied the contribution of GRACE score to the association between different depressive symptom dimensions and prognosis. To obtain the depressive symptom dimensions, we performed a principle component analysis with oblimin rotation on the BDI items. This yielded a somatic/affective and a cognitive/affective dimension, which were comparable to what we previously found in a principal component analysis on this dataset combined with patients from another study (MIND-IT).[13]

Assessment of prognostic clinical variables

We used the Global Registry of Acute Coronary Events (GRACE) risk model for 6 months mortality risk from hospital discharge[8] to calculate GRACE risk scores for our sample. Variables in the GRACE model include age, history of MI, past or current congestive heart failure (CHF), heart rate, systolic blood pressure, serum creatinine, elevated cardiac enzymes, ST-segment depression on ECG at admission, and no in hospital percutaneous intervention (PCI). The GRACE score ranges between 1 and 263 points.

The mean percentage of missing values for the nine variables comprising the GRACE score was 13.6%. We imputed the missing values with STATA based on non-missing values from 42 variables including clinical variables, medication use and outcome measures. When more than 3 variables comprising the GRACE were missing for the same patient, we set the total GRACE score at missing.

Cardiovascular prognosis

The average follow-up time was 2.5 (SD=0.9) years. We used fatal and non-fatal CV events as outcome measures, consistent with previous reports from this cohort. These cover hospital admissions for new MI, (un)stable angina, heart failure, arrhythmia, peripheral vascular disease or cerebral vascular accidents (CVA), which were identified in the regular post-MI control visits, or through face to face interviews at 3 and 12 month post-MI and there after telephone interviews every 6 months until end follow-up. We additionally separated CV events into 'mild' events ((un)stable angina, heart failure, arrhythmia, peripheral vascular disease) and 'severe' events (new MI, CVA and CV death).

Statistical analyses

To assess demographic and clinical characteristics for depressive symptoms we used chi-square tests and F-tests. We also used Pearson correlations to evaluate whether overall depressive symptoms and *z*-transformed cognitive/affective and somatic/affective depressive symptoms associate with GRACE score. Cox regression analysis was performed to validate the prognostic value of GRACE score and to analyze its contribution to the association between post MI depressive symptoms and CV prognosis. We performed a secondary analysis, in which we used the somatic/affective and cognitive/affective depressive symptom scores instead of total BDI scores. The proportional hazards assumption was tested by creating interaction terms of the predictors with the time-variable.

We additionally created a figure to evaluate the association of total BDI-scores, somatic/affective and cognitive/affective depressive symptom scores with mild and severe CV events separately.

Somatic/affective symptoms were associated with older age and cognitive/affective symptoms with younger age. Therefore, we did a post hoc analysis adjusting for age only to evaluate the contribution of age to the association of

somatic/affective and cognitive/affective depressive symptoms with new CV events. We did this to be able to distinguish the contribution of age from that of the other (clinical) individual GRACE variables in the association between the depressive symptom profiles and CV prognosis.

To provide more insight in the individual contributions of GRACE score and BDI in the prediction of new CV events, we generated a receiver operating characteristic (ROC) curve and compared the area under the curves (AUC) by calculating a critical ratio z.[22]

Results

Sample characteristics

The flow chart of the study population is shown in Figure 1. A total of 501 patients filled out the BDI. Of these, 7 had missing data on the GRACE and another 31 had missing data on new CV events. For the 494 patients who completed the BDI at hospitalization and had data on GRACE, the mean BDI score was 6.8 (SD 6.1). Among these patients 23% (116/494) had elevated depressive symptoms (BDI ≥10).

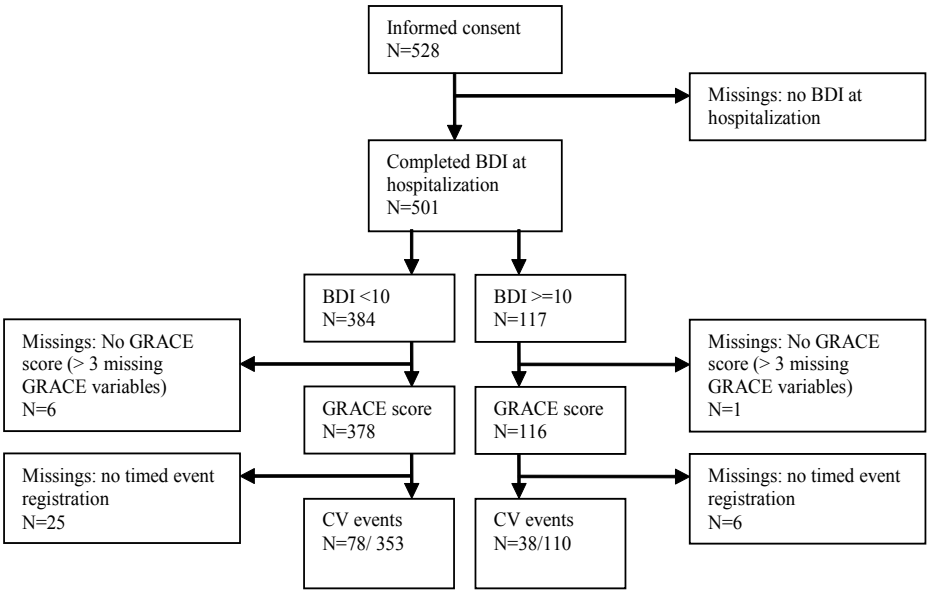

Figure 1: Flow diagram of study population

In Table 1 socio-demographic and clinical characteristics of patients according to BDI class (<10 vs. ≥10) are shown. Patients with elevated depressive symptoms were significantly more likely to be female, to live alone, to smoke, to be older, to have past or current CHF, to have higher heart rates, to have higher GRACE scores, and to experience new CV events compared to patients who did not have elevated depressive symptoms.

Table 1: Characteristics of patients according to BDI class (for patients with data on GRACE; N=494)

Characteristic	BDI<10 N=378 Mean ± SD or n (%)	BDI ≥10 N=116 Mean ± SD or n (%)	*p*
Demographic			
Female	59 (15.6)	35 (30.2)	<0.001
living alone	43 (11.4)	32 (27.6)	<0.001
Primary school only	59 (17)	29 (26.9)	0.058
Smoking	61 (17.6)	29 (27.1)	0.032
Individual GRACE variables[a]			
Age (mean)	59.9 SD 11.22	62.6 ± 12.63	0.031
History of MI	48 (12.7)	21 (18.1)	0.142
Congestive heart failure	29 (7.7)	17 (14.7)	0.024
Heart rate (mean)	73.6 ± 22.71	78.4 ± 21.63	0.045
Systolic blood pressure (mean)	138.3 ± 25.76	140.7 ± 27.42	0.394
Initial serum creatinine (mean)	1.063 ± 0.20	1.106 ± 0.25	0.059
Elevated cardiac enzymes	-	-	-
ST-segment depression on ECG	189 (50)	63 (54.3)	0.417
No in hospital PCI	275 (72.8)	91 (78.4)	0.221
GRACE total score (mean)	104.1 ± 27.66	113.7 ± 30.74	0.002
Outcome[b]			
Mild CV events[c]	56 (15.9)	24 (21.8)	0.149
Severe CV events[d]	22 (6.2)	14 (12.7)	0.026
Total CV events	78 (22.1)	38 (34.5)	0.009

SD = standard deviation; BDI = Beck Depression Inventory; GRACE = Global Registry of Acute Coronary Events; MI = myocardial infarction; ECG = electrocardiogram; PCI = percutaneous intervention; CV = cardiovascular
P-values are based on F-test and chi square. All patients (except for one) had elevated cardiac enzymes.
[a] *Missings are imputed.*
[b] *N is different than stated in the columns, because of missings in the event registration, N=353 for BDI<10; N=110 for BDI ≥10 (see flow chart).*
[c] *Mild events include (un)stable angina, heart failure, arrhythmia, peripheral vascular disease.*
[d] *Severe events include new MI, CVA and cardiovascular death.*

In Table 2 the associations between the variables making up the GRACE score and somatic/affective and cognitive/affective depressive symptoms are shown. Elevated somatic/affective depressive symptoms were significantly associated with older age, previous MI, higher heart rates, past or current CHF, higher initial serum creatinine, higher total GRACE scores and new CV events. Patients with elevated cognitive/affective symptoms were significantly younger and tended to have lower total GRACE scores.

Table 2: Characteristics of patients according to somatic/affective and cognitive/affective depressive symptoms (for patients with data on GRACE; N=494).

Characteristic	Somatic/affective symptoms 75% lowest scores N=371 Mean ± SD or n (%)	Somatic/affective symptoms 25% highest scores N=123 Mean ± SD or n (%)	*p*	Cognitive/affective symptoms 75% lowest scores N=371 Mean ± SD or n (%)	Cognitive/affective symptoms 25% highest scores N=123 Mean ± SD or n (%)	*p*
Individual GRACE variables[a]						
Age	59.4 ± 11.3	64.1 ± 11.9	<0.001	61.3 ± 11.3	58.4 ± 12.3	0.019
History of MI	43 (11.6)	26 (21.1)	0.008	53 (14.3)	16 (13.0)	0.723
Congestive heart failure	29 (7.8)	17 (13.8)	0.047	35 (9.4)	11 (8.9)	0.871
Heart rate	73.9 ± 21.8	77.3 ± 24.6	0.150	73.9 ± 22.2	77.4 ± 23.5	0.136
Systolic blood pressure	138.2 ± 25.3	141.0 ± 28.5	0.296	138.4 ± 25.6	140.2 ±27.6	0.509
Initial serum creatinine	1.061 ±SD 0.19	1.109 ± 0.27	0.031	1.073 ± 0.22	1.073 ± 0.19	0.984
Elevated cardiac enzymes	-	-	-	-	-	-
ST-segment depression on ECG	187 (50.4)	65 (52.8)	0.639	190 (51.2)	62 (50.4)	0.877
No in hospital PCI	270 (72.8)	96 (78.0)	0.247	277 (74.7)	89 (72.4)	0.613
Total GRACE score	103.2 ± 27.4	115.9 ± 30.4	<0.001	107.7 ± 27.8	102.5 ± 30.9	0.084
Outcome[b]						
Mild CV events[c]	57 (16.4)	23 (20.0)	0.373	57 (16.5)	23 (19.7)	0.431
Severe CV events[d]	22 (6.3)	14 (12.2)	0.042	31 (9.0)	5 (4.3)	0.102
CV events	79 (22.7)	37 (32.2)	0.042	88 (25.4)	28 (23.9)	0.746

SD = standard deviation; GRACE = Global Registry of Acute Coronary Events; MI = myocardial infarction; ECG = electrocardiogram; PCI = percutaneous intervention; CV = cardiovascular

P-values are based on F-test and chi square. All patients (except for one) had elevated cardiac enzymes.

[a] *Missings are imputed.*

[b] *N is different than stated in the columns, because of missings in the event registration N=348 for 75% lowest scoring somatic symptoms; N=115 for 25% highest scoring somatic symptoms; N=346 for 75% lowest scoring cognitive symptoms; N=117 for 25% highest scoring cognitive symptoms.*

[c] *Mild events include (un)stable angina, heart failure, arrhythmia, peripheral vascular disease.*

[d] *Severe events include new MI, CVA and cardiovascular death.*

Relationship between GRACE score and depressive symptoms

The GRACE score was normally distributed and ranged from 37 to 206 (mean 106, SD 28.7). Pearson correlations showed that total BDI-scores were significantly associated with higher GRACE scores (r=0.12 p=0.008). When considering somatic/affective and cognitive/affective symptoms separately, elevated somatic/affective symptoms correlated positively with higher GRACE scores (r=0.23, p<0.001), whereas cognitive/affective symptoms tended to correlate negatively with GRACE score (r=-0.08 p=0.097).

New cardiovascular events

A total of 25% (116/463) experienced a new CV event from hospital discharge until the end of follow-up, of which 69% (80/116) were classified as mild events and 31% (36/116) as severe events, and 17% (21/116) of all events were fatal. The mean time to first event was similar for mild and severe events (both mean 0.9 (SD 0.9) years). Among patients with elevated depressive symptoms (BDI ≥10) 35% (38/110) had one or more new CV events during the follow up, which was 22% (78/353) among patients with BDI score <10 (Chi-square: p=0.009, see Table 1). Mild events occurred in 15.9% of patients with BDI<10 and in 21.8% of patients with BDI≥10 (Chi-square: p=0.149). Severe events occurred in 6.2% of patients with BDI<10 and in 12.7% of patients with BDI≥10 (Chi-square: p=0.026, see table 1). Figure 2 shows the association of mild and severe CV events with total BDI-score, somatic/affective and cognitive/affective depressive

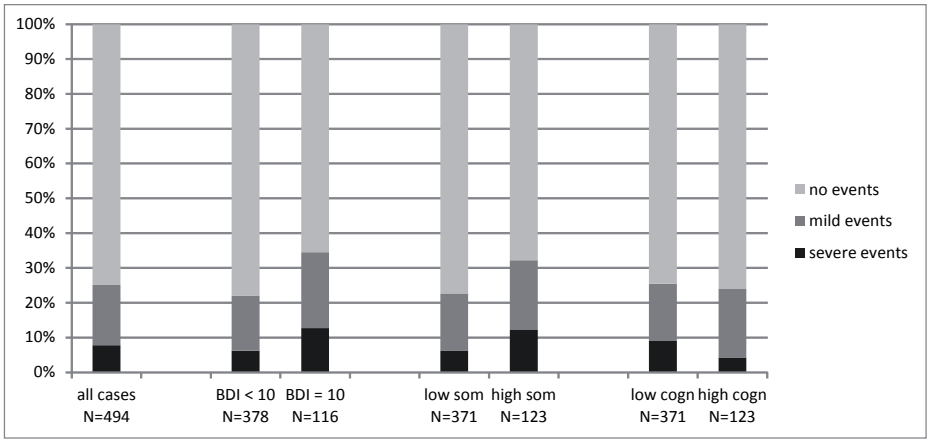

Figure 2: The distribution of first events for different classifications of the study population. Note: each classification is based on the same population. Low som = 75% lowest scores on somatic/affective depressive symptoms; high som = 75% highest scores on somatic /affective depressive symptoms; low cogn = 75% lowest scores on cognitive/affective depressive symptoms; high cogn = 75% highest scores on cognitive/affective depressive symptoms.

Table 3: Univariate and multivariate Cox regression analyses according to depression and GRACE score (for patients with data on GRACE and on events; N=463).

	Univariate hazard ratio (95% CI)	**Hazard ratio adjusted for age** (95% CI)	**Multivariate hazard ratio** (95% CI)[a]
All CV events (N=116)			
GRACE continuous score	1.01 (1.01-1.02)***		1.01 (1.00-1.02)**
GRACE dichotomized[b]	2.45 (1.70-3.54)***		2.30 (1.59-3.33)***
BDI score ≥10 vs. <10	1.74 (1.18-2.56)**	1.62 (1.10-2.41)*	1.53 (1.03-2.28)*
BDI continuous score	1.05 (1.02-1.08)***	1.05 (1.02-1.08)**	1.05 (1.02-1.08)**
Somatic/affective symptoms[c]	1.44 (1.20-1.72)***	1.35 (1.12-1.63)**	1.31 (1.08-1.58)**
Cognitive/affective symptoms[c]	1.03 (0.84-1.25)	1.08 (0.88-1.32)	1.10 (0.90-1.35)

CI = confidence interval; GRACE = Global Registry of Acute Coronary Events; BDI = Beck Depression Inventory
** = p<0.05; ** = p<0.01; *** = p<0.001*

[a] *Hazard ratios for BDI are adjusted for continuous GRACE score; hazard ratios for GRACE score are adjusted for continuous BDI; hazard ratios for somatic/affective and cognitive/affective depressive symptoms are adjusted for each other and GRACE score.*

[b] *Highest scoring 25% versus lowest scoring 75%.*

[c] *Hazard ratio is per one standard deviation difference in z-score and is for all three hazard ratios in this table adjusted for other depressive symptom cluster.*

symptoms. Somatic/affective depressive symptoms were associated with relatively more severe events, while cognitive/affective depressive symptoms were associated with relatively less severe CV events.

In table 3 the results of the Cox regression analyses are shown. The analysis confirmed that GRACE score was a predictor for new CV events in our sample (HR 1.01 per one point difference in GRACE score p<0.001 95% CI 1.01-1.02; HR 2.45 for 25% highest vs. 75% lowest GRACE scores p<0.001 95% CI 1.70-3.54). As we previously reported[18] total BDI-score at hospitalization was a significant predictor for new CV events (HR 1.05 per one point difference in BDI score p=<0.001, 95% CI 1.02-1.08). Adjustment for GRACE did not affect this HR (1.05 p=0.002, 95% CI 1.02-1.08). Somatic/affective, but not cognitive/affective symptoms, were significant predictors for new CV events before adjustment for GRACE score, as we previously reported.[13] After adjusting for GRACE score, cognitive/affective symptoms remained not associated with new CV events (unadjusted HR: 1.03 (95% CI: 0.84-1.25) per SD increase p=0.79; adjusted HR: 1.10 (95% CI: 0.90-1.35) p=0.36), and somatic/affective symptoms remained a significant predictor of new CV events, although the HR was somewhat attenuated (unadjusted HR 1.44 (95% CI: 1.20-1.72) per SD increase, p=<0.001; adjusted HR: 1.31 (95% CI: 1.08-1.58) p=0.006, see also Table 3).

Post-hoc analyses showed that adjustment for age attenuated the HR for somatic/affective depressive symptoms somewhat, but less than when adjusting for total GRACE score (age-adjusted HR: 1.35 (95% CI: 1.12-1.63) p=0.002). The HR for cognitive/affective depressive symptoms was not affected after adjustment for age (age-adjusted HR: 1.08 (95% CI: 0.88-1.32), see also Table 3).

A ROC curve was created to determine the individual contributions of GRACE score and BDI in the prediction of new CV events. The AUC was not significantly different for both predictors (for GRACE score AUC 0.60; for BDI score AUC 0.59, z=0.30, p=0.764).

Discussion

In this study, we evaluated to what extent GRACE score would explain the relation between post MI depressive symptoms assessed by the BDI and new CV events.

As expected,[8] GRACE scores significantly predicted new CV events in our sample. Also, depressive symptoms were significantly associated with GRACE score. GRACE score explained only a small part of the relation between (somatic/affective) depressive symptoms and worsened CV prognosis. Thus, we conclude that depressive symptoms predict CV prognosis beyond a well validated risk score of CV prognosis.

Only one other study used the GRACE risk score in order to explain the effect of post-MI depression on prognosis,[12] but this study had only 18 outcome events in contrast to the 116 outcome events in our study. In the study of Kronish et al[12] GRACE score could not explain the relation between depression and worsened prognosis. However, unlike our results, GRACE score did not relate significantly to depression in that study. The difference between findings from their study and ours seems to be explained by age, which is one of the variables comprising the GRACE score. In our study, patients with elevated depressive symptoms were on average 3 years older than non-depressed patients, while in the study of Kronish et al.[12] depressed patients were on average 3 years younger. Although in their study some clinical variables of the GRACE score were associated with depression, this was compensated by younger age.

From the ROC curve we could conclude that GRACE score and BDI score are similarly predictive for new CV events. This suggests that either one can be used to identify high risk patients. The AUC of 0.60 for GRACE is substantially lower than the previously reported AUC of 0.80 for GRACE in predicting mortality.[9] Therefore we additionally generated a ROC curve for fatal CV events. This curve showed an AUC for GRACE score of 0.80. The AUC of BDI score for fatal CV events was significantly smaller and remained 0.6 (z=13.1, p<0.001). Apparently GRACE score is a better predictor for fatal than for both fatal and nonfatal CV events combined, and GRACE is a better predictor for fatal events than BDI score.

Considering the two depressive symptom dimensions, we found a significant positive association between somatic/affective depressive symptoms and GRACE score, and a non-significant negative correlation between cognitive/affective depressive symptoms and GRACE score. The increased risk of CV events associated with somatic/affective depressive symptoms, which was reported previously by de Jonge et al. on this patient sample,[13] could only partly be explained by GRACE score. Cognitive/affective depressive symptoms were not associated with new CV events,[13] and GRACE score did not affect this.

To evaluate the contribution of each individual GRACE variable in the association between somatic/affective and cognitive/affective depressive symptoms and CV events, we evaluated CV prognosis associated with cognitive/affective and somatic/affective symptoms, adjusting for each of the individual GRACE variables separately, and compared these HRs to the HR after adjustment for total GRACE score (data not shown). Higher age, having had a previous MI, higher heart rates and CHF explained most of the relationship between somatic/affective depressive symptoms and GRACE score. This is in line with the previous finding in this sample that somatic/affective depressive symptoms are associated with poor somatic health status.[13] The negative, but not significant, association between cognitive/affective symptoms and total GRACE score could only be explained by age, as cognitive/affective depressive symptoms were associated with younger age, but no other clinical variable of GRACE.

Interestingly, patients scoring in the upper quartile of somatic/affective depressive symptoms were on average 4.6 years older than patients scoring in the lower three quartiles. In contrast, patients scoring in the upper quartile of the cognitive/affective depressive symptoms were on average 2.8 years *younger* than those scoring in the lower three quartiles. This reflected an age difference of as much as 5.7 years between the patients scoring in the upper quartile of somatic/affective symptoms and the patients scoring in the upper quartile of cognitive/affective symptoms (see Table 2). This age discrepancy may possibly be explained by more physical health problems in the older aged, which are reflected in elevated somatic/affective depressive symptoms. In contrast, in younger people a MI may have a higher psychological impact, resulting in higher levels of cognitive/affective depressive symptoms. These age differences among patients with different depression symptomatology demonstrate the heterogeneity of depression in MI patients.

Results from the post-hoc analyses show that age attenuated the association of (somatic/affective) depressive symptoms and CV events, but to a lesser extent than total GRACE score. Between cognitive/affective depressive symptoms and new CV events there was no association, and adjusting for age and total GRACE score had no effect on this. This suggests that only somatic/affective depressive symptoms are predictive of CV prognosis, and older age as well as some other clinical GRACE variables explain part of this association.

Interestingly, high somatic/affective symptoms were associated with relatively more severe events, while high cognitive/affective symptoms were associated with relatively less severe CV events (see Figure 2). An explanation could be that compared to somatic/affective depressive symptoms, cognitive/affective depressive symptoms are less strongly associated with heart disease severity,[13] whereas patients scoring high on cognitive/affective symptoms may have been more preoccupied by their disease and more often present themselves to the hospital with unspecified chest pain. Therefore patients scoring higher on the somatic/affective depressive symptom score may have had more severe CV events due to their more severe underlying heart disease. However, results for severe CV events must be interpreted with caution as the number of severe CV events is only 36.

Our study has some limitations. First, we only used depression measured by a depression screening instrument (BDI) instead of using clinically diagnosed major depression disorder (MDD). In fact, we did evaluate the presence of MDD with a diagnostic interview in the present study, but in contrast to findings from other studies, MDD was not associated with new CV events. Therefore, we evaluated the contribution of GRACE in the association between BDI-scores and new CV events only. Second, we used the GRACE risk score as confounder because of its high prognostic value and its validated set of predictors, which were derived from a set of 39 variables. However, as the GRACE investigators balanced the ease of use and the completeness and accuracy of their model,[7] some important clinical predictors may still be missing in the model. For example, the GRACE score does not incorporate LVEF, a clinical measure that was found to be associated with depression[23] and was found to explain a substantial part of the association between post MI depression and prognosis.[5,24] Therefore we additionally included LVEF (dichotomized to <40% or >=40%) in our survival analyses (data not shown), like Kronish et al. did.[12] However, depression was not associated with the dichotomized LVEF variable in this sample and adjustment for LVEF did not affect the HR for new CV events associated with depressive symptoms.

In summary, although we found a significant relation between GRACE and depressive symptoms, GRACE score explained only a small part of the association between post MI depression and poor CV outcome. ROC curves demonstrated that GRACE and BDI score have comparable accuracy in predicting new CV events, although GRACE score is a better predictor for fatal CV events than the BDI score. Interestingly, GRACE score was positively associated with somatic/affective depressive symptoms, but tended to be negatively associated with cognitive/affective depressive symptoms. This difference was explained by the fact that somatic/affective symptoms were associated with older age and higher scores on some other clinical variables of the GRACE score, whereas cognitive/affective symptoms were associated with *younger* age and not with other clinical

variables of the GRACE score. The GRACE score explained only a part of the worsened CV prognosis in MI patients with elevated somatic/affective depressive symptoms. In fact, as depressive symptoms and GRACE score appeared to predict CV prognosis independent from each other, incorporating them together in a single composite risk score might give an even better prediction of CV prognosis in MI patients.

References

1. Meijer A, Conradi HJ, Bos EH, Thombs BD, van Melle JP, de Jonge P. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis of 25 years of research. *Gen Hosp Psychiatry*. 2011;33(3):203-216.

2. Thombs BD, de Jonge P, Coyne JC, et al. Depression screening and patient outcomes in cardiovascular care: A systematic review. *JAMA*. 2008;300(18):2161-2171.

3. Berkman LF, Blumenthal J, Burg M, et al. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: The enhancing recovery in coronary heart disease patients (ENRICHD) randomized trial. *JAMA*. 2003;289(23):3106-3116.

4. van Melle JP, de Jonge P, Honig A, et al. Effects of antidepressant treatment following myocardial infarction. *Br J Psychiatry*. 2007;190:460-466.

5. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: A meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J.* 2006;27(23):2763-2774.

6. Christenfeld NJ, Sloan RP, Carroll D, Greenland S. Risk factors, confounding, and the illusion of statistical control. *Psychosom Med.* 2004;66(6):868-875.

7. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med.* 2003;163(19):2345-2353.

8. Eagle KA, Lim MJ, Dabbous OH, et al. A validated prediction model for all forms of acute coronary syndrome: Estimating the risk of 6-month postdischarge death in an international registry. *JAMA.* 2004;291(22):2727-2733.

9. Fox KA, Eagle KA, Gore JM, Steg PG, Anderson FA, GRACE and GRACE2 Investigators. The global registry of acute coronary events, 1999 to 2009--GRACE. *Heart.* 2010;96(14):1095-1101.

10. de Araujo Goncalves P, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: Sustained prognostic value and interaction with revascularization in NSTE-ACS. *Eur Heart J*. 2005;26(9):865-872.

11. Babyak MA. What you see may not be what you get: A brief, nontechnical introduction to overfitting in regression-type models. *Psychosom Med.* 2004;66(3):411-421.

12. Kronish IM, Rieckmann N, Schwartz JE, Schwartz DR, Davidson KW. Is depression after an acute coronary syndrome simply a marker of known prognostic factors for mortality? *Psychosom Med.* 2009;71(7):697-703.

13. de Jonge P, Ormel J, van den Brink RH, et al. Symptom dimensions of depression following myocardial infarction and their relationship with somatic health status and cardiovascular prognosis. *Am J Psychiatry.* 2006;163(1):138-144.

14. Linke SE, Rutledge T, Johnson BD, et al. Depressive symptom dimensions and cardiovascular prognosis among women with suspected myocardial ischemia: A report from the national heart, lung, and blood institute-sponsored women's ischemia syndrome evaluation. *Arch Gen Psychiatry.* 2009;66(5):499-507.

15. Martens EJ, Hoen PW, Mittelhaeuser M, de Jonge P, Denollet J. Symptom dimensions of post-myocardial infarction depression, disease severity and cardiac prognosis. *Psychol Med.* 2010;40(5):807-814.

16. Roest AM, Thombs BD, Grace SL, Stewart DE, Abbey SE, de Jonge P. Somatic/affective symptoms, but not cognitive/affective symptoms, of depression after acute coronary syndrome are associated with 12-month all-cause mortality. *J Affect Disord.* 2011;131(1-3):158-163.

17. Smolderen KG, Spertus JA, Reid KJ, et al. The association of cognitive and somatic depressive symptoms with depression recognition and outcomes after myocardial infarction. *Circ Cardiovasc Qual Outcomes.* 2009;2(4):328-337.

18. Spijkerman TA, van den Brink RH, May JF, et al. Decreased impact of post-myocardial infarction depression on cardiac prognosis? *J Psychosom Res.* 2006;61(4):493-499.

19. de Jonge P, van den Brink RH, Spijkerman TA, Ormel J. Only incident depressive episodes after myocardial infarction are associated with new cardiovascular events. *J Am Coll Cardiol.* 2006;48(11):2204-2208.

20. Davidson KW, Kupfer DJ, Bigger JT, et al. Assessment and treatment of depression in patients with cardiovascular disease: National heart, lung, and blood institute working group report. *Psychosom Med.* 2006;68(5):645-650.

21. Beck AT, Steer RA, Carbin MG. Psychometric properties of the beck depression inventory: Twenty-five years of evaluation. *Clin Psychol Rev.* 1988;8(1):77-100.

22. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology.* 1983;148(3):839-843.

23. van Melle JP, de Jonge P, Kuyper AM, et al. Prediction of depressive disorder following myocardial infarction data from the Myocardial INfarction and Depression-Intervention Trial (MIND-IT). *Int J Cardiol.* 2006;109(1):88-94.

24. van Melle JP, de Jonge P, Ormel J, et al. Relationship between left ventricular dysfunction and depression following myocardial infarction: Data from the MIND-IT. *Eur Heart J.* 2005; 26(24):2650-2656.