Only incident depressive episodes after Myocardial infarction are associated with new cardiovascular events

de Jonge, P.; van den Brink, R.H.S.; Spijkerman, T.A.; Ormel, J.

Published in:
Journal of the American College of Cardiology

Publication date:
2006

Journal of the American College of Cardiology
© 2006 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 48, No. 11, 2006
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.06.077

Only Incident Depressive Episodes After Myocardial Infarction Are Associated With New Cardiovascular Events

Peter de Jonge, PHD, Rob H. S. van den Brink, PHD, Titia A. Spijkerman, MD, Johan Ormel, PHD
Groningen, the Netherlands

OBJECTIVES The purpose of this research was to study whether incident and non-incident depression after myocardial infarction (MI) are differentially associated with prospective fatal and non-fatal cardiovascular events.

BACKGROUND Post-MI depression is defined as the presence of depression after MI. However, only about one-half of post-MI depressions represent an incident episode, whereas the other half are ongoing or recurrent depressions. We investigated whether these subtypes differ in cardiovascular prognosis.

METHODS A total of 468 MI patients were assessed for the presence of an International Classification of Diseases-10 depressive disorder during the year after index MI. A comparison was made on new cardiovascular events (mean follow up: 2.5 years) between patients with no, incident, and non-incident post-MI depression by survival analysis.

RESULTS Compared with non-depressed patients, those with an incident depression had an increased risk of cardiovascular events (hazard ratio [HR] 1.65; 95% confidence interval [CI] 1.02 to 2.65), but not those with a non-incident depression (HR 1.12; 95% CI 0.61 to 2.06), which remained after controlling for confounders (HR 1.76; 95% CI 1.06 to 2.93 and HR 1.39; 95% CI 0.74 to 2.61, respectively).

CONCLUSIONS Only patients with incident post-MI depression have an impaired cardiovascular prognosis. A more detailed subtyping of post-MI depression is needed, based on an integration of recent findings on the differential impact of depression symptom profiles and personality on cardiac outcomes. (J Am Coll Cardiol 2006;48:2204–8) © 2006 by the American College of Cardiology Foundation

The effects of depression after myocardial infarction (MI) on cardiovascular prognosis are poorly understood. Post-MI depression is associated with a 2 to 2.5 times increased risk of cardiovascular events, but in most studies that tested for the confounding effects of MI severity, the effects of depression reduced or disappeared (1). Moreover, treatment of post-MI depression does not seem to affect prognosis (2). As a result, it remains unclear whether depression should be considered a causal risk factor for cardiovascular prognosis. Meanwhile, the importance of other psychosocial factors as predictors of adverse events in patients with coronary heart disease has been increasingly acknowledged, including the type-D construct—the tendency to experience negative emotions and to inhibit self-expression in social interactions (3,4), and anxiety (5).

See page 2215

Post-MI depression is conveniently defined as the presence of depression after an MI. However, about one-half of the post-MI depressions have been preceded by or are continuations of pre-MI depressive episodes (non-incident depression) (6–8). Several reports indicate that patients with incident post-MI depressions resemble non-depressed MI patients in terms of personality but have experienced a more severe MI that may have triggered their first-ever depression (6,7). Lloyd and Cawley (7) found that these incident post-MI depressions often recovered without intervention. Recently, we confirmed that post-MI patients with incident depression had experienced more severe MIs, whereas patients with non-incident depression had higher neuroticism levels (8).

To establish whether post-MI depression is a *causal* risk factor for cardiovascular prognosis, it is crucial to compare patients with incident versus non-incident post-MI depression. Because incident post-MI depression may be confounded by the severity and consequences of the MI, the strongest non-experimental support for a causal effect of depression is found when non-incident post-MI depression predicts poor cardiovascular prognosis. However, it is important to state that this would not *prove* causality. Alternative explanations, such as a shared genetic vulnerability for depression and cardiovascular disease, recently reported by McCaffery et al. (9), may still account for this association. Of interest, recently Grace et al. (10) reported that subjects with self-reported depressive symptoms (Beck Depression Inventory) after acute coronary syndromes (ACS) but no history of depression had a 1.78 (95% confidence interval [CI] 0.96 to 3.30) increased rate of 5-year mortality, compared with depressed ACS patients with a history of

From the Department of Psychiatry, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands.

Manuscript received February 17, 2006; revised manuscript received June 5, 2006, accepted June 6, 2006.

Abbreviations and Acronyms

ACS	= acute coronary syndromes
CBT	= cognitive behavioral therapy
CI	= confidence interval
CIDI	= Composite International Diagnostic Interview
ENRICHD	= Enhancing Recovery in Coronary Heart Disease trial
HR	= hazard ratio
MI	= myocardial infarction

depression. We set out to test their findings, comparing the cardiovascular effects associated with incident and non-incident post-MI depression, but now based on a formal psychiatric diagnosis of depressive disorder.

METHODS

The DepreMI (Depression after Myocardial Infarction) study (8) is an observational cohort study of 468 patients hospitalized for an MI between 1997 and 2000 in the north of the Netherlands. Details of the study have been described elsewhere.

Assessment of depressive disorder. The presence of a lifetime depressive disorder was assessed in a face-to-face interview at 3 and 12 months post-MI with the Composite International Diagnostic Interview (CIDI) (11). The CIDI is a fully structured interview using International Classification of Diseases-10 diagnostic criteria for depression, with excellent inter-rater reliability and good test–retest reliability and validity that allows for the identification of incident and non-incident post-MI depression.

Personality traits. At 3 months post-MI, patients filled in the neuroticism and extraversion subscales of the Eysenck Personality Questionnaire (12) consisting of 12 items for each subscale. The traits neuroticism and extraversion were chosen, as they resemble the tendency to experience negative emotions and inhibit self-expression in social interactions, which are the key factors of type D personality. At 12 months post-MI, the type-D scale-16 (DS16) was administered to assess type D personality (13). The DS16 questionnaire consists of 8 statements concerning social inhibition and 8 statements concerning negative emotions. In concordance with previous work, the presence of type D personality is operationalized as having a score above the median of both subscales of the DS16.

Baseline cardiac status. Baseline cardiac status was assessed during admission by the presence of a previous MI, revascularization (percutaneous transluminal coronary angioplasty or coronary artery bypass grafting), presence of heart failure (Killip class ≥II), left ventricular ejection fraction <40%, anterior site of MI, and infarct size (log creatinine phosphokinase MB [CPK], calculated from the peak CPK level, which was based on a repeated assessment at every 6 h during the acute phase of the MI).

Disability. At 12 months post-MI, patients were asked to indicate how many days they were not able to do daily activities (i.e., work, housework, studies, leisure activities) due to physical or emotional problems during the last month, in accordance with the work by Broadhead et al. (14). The resulting variable was dichotomized as <1 week disability or at least 1 week disability.

Cardiovascular events. Cardiovascular mortality and cardiac-related readmissions after discharge from the hospital were identified using regular patient interviews, hospital records, and data from the treating specialist and primary care physician. Two cardiologists, blinded for the depression status of the patient, independently evaluated the nature (cardiovascular or not) and time of onset of end points. Mean follow-up duration was 2.5 years (SD 0.8).

Statistical analysis. Three groups of patients were defined as: 1) patients with a post-MI depressive episode who had not been depressed before the index MI (incident post-MI depression); 2) patients with a post-MI depressive episode who had also been depressed before the index MI (non-incident post-MI depression); and 3) MI patients with no post-MI depression. These 3 groups were compared on baseline demographic and cardiologic characteristics, personality traits, and disability by chi-square tests for categoric data and by analysis of variance for continuous variables using Fisher least-square differences, and on prospective (non-)fatal cardiovascular events by means of survival analysis.

To estimate the effects on event-free survival, Kaplan-Meier plots were compared for patients with no post-MI depression, incident post-MI depression, and non-incident post-MI depression using pairwise log-rank tests. Cox regression analyses were conducted, evaluating the univariate effects of incident and non-incident post-MI depression, compared with MI patients with no post-MI depression, and the multivariate effects after controlling for age, gender, and education level because they are risk factors for both depression and cardiac disease, and for left ventricular ejection fraction <40% and revascularization because they are associated with cardiac prognosis and with incident post-MI depression.

RESULTS

Of the 468 MI patients, 119 patients experienced a post-MI depression during the post-MI year, of whom 53 (44.5%) were incident and 66 (55.4%) non-incident. Of the 349 patients that did not experience a post-MI depression, 22 (6.3%) have had a pre-MI depression. In Table 1, a comparison of patients with no, incident, and non-incident post-MI depression is given. Compared with patients with non-incident depression cases, patients with incident post-MI depressions were characterized by poorer left ventricular ejection fraction ($p = 0.08$), a higher risk of revascularization ($p = 0.04$), and more disability at 12 months post-MI ($p = 0.06$). Patients with non-incident

JACC Vol. 48, No. 11, 2006
December 5, 2006:2204–8

Table 1. Characteristics of Patients With No, Incident, and Non-Incident Post-MI Depression

	No Post-MI Depression (n = 349)	Incident Post-MI Depression (n = 66)	Non-Incident Post-MI Depression (n = 53)	$p_{overall}$	$p_{incident\text{-}non\text{-}incident}$
Sociodemographic data					
Female gender (%)	16.6	28.8	28.3	**0.02**	0.95
Age (yrs), mean (SE)	61.2 (0.6)	59.6 (1.5)	57.5 (1.4)	0.07	0.34
Living alone (%)	14.0	22.7	13.2	0.18	0.18
Primary school only (%)	18.6	10.6	32.1	**0.01**	**0.004**
Cardiac status					
LVEF <40% (%)	24.1	28.8	15.1	0.21	0.08
Killip class ≥2 (%)	13.5	18.2	13.2	0.59	0.46
Previous MI (%)	13.2	16.7	15.1	0.73	0.82
Revascularization	23.3	40.0	21.3	**0.02**	**0.04**
Anterior site of MI (%)	31.8	36.4	28.3	0.63	0.35
Log max CPK, mean (SE)	1.90 (0.02)	1.83 (0.06)	1.86 (0.05)	0.36	0.71
Personality traits					
Neuroticism, mean (SD)	2.5 (2.7)	5.3 (3.5)	7.4 (2.7)	**<0.001**	**<0.001**
Negative affect, mean (SD)	5.3 (5.6)	11.0 (7.1)	13.6 (6.6)	**<0.001**	**0.03**
Extraversion, mean (SD)	6.4 (2.7)	6.3 (3.0)	5.5 (2.6)	0.16	0.16
Social inhibition, mean (SD)	12.7 (6.0)	14.4 (6.5)	15.2 (5.8)	**0.009**	0.48
Type D (%)*	19.7	38.3	57.4	<0.001	**0.05**
Disability at 12 months post-MI					
Complete disability (≥1 week during last month)*	10.3	39.0	21.7	<0.001	0.06

Bold values are statistically significant. *The corresponding patient numbers for these assessments were: no post-MI depression (n = 301), incident post-MI depression (n = 59), non-incident depression (n = 46).

CPK = creatinine phosphokinase MB; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

depression were characterized by lower education levels ($p = 0.004$), higher neuroticism scores ($p < 0.001$), and a higher prevalence of type D personality ($p = 0.05$). During follow-up, 109 patients (23.3%) had experienced a fatal (n = 10) or non-fatal (n = 99) cardiovascular event. Of the non-depressed patients, 21.5% experienced an event; these percentages were 33.3% and 22.6% for incident and non-incident post-MI depressions, respectively.

In Figure 1, the Kaplan-Meier plots for the 3 groups are shown. Significant differences were observed between non-depressed patients and patients with incident post-MI depressions (log-rank test = 4.30; $p = 0.04$), but not between non-depressed patients and patients with non-incident post-MI depressions (log-rank test = 0.13; $p = 0.72$). The hazard ratios (HR) for new cardiovascular events associated with incident and non-incident post-MI depressions, compared with non-depressed controls, were 1.65 (95% CI 1.02 to 2.65; $p = 0.04$) and 1.12 (95% CI 0.61 to 2.06; $p = 0.72$), respectively (Table 2). Controlling for age, gender, education level, left ventricular ejection fraction, and revascularization essentially did not alter the HRs (incident depression: HR 1.76 [95% CI 1.06 to 2.65]; non-incident depression: HR 1.39 [95% CI 0.74 to 2.61]).

In order to exclude the possibility that a non-fatal cardiovascular event had been the cause for the post-MI depression rather than the consequence, we performed a sensitivity analysis. Of the 109 cardiovascular events, 68 occurred during the post-MI year and 41 thereafter. When counting only those events occurring after 1 year post-MI, 9.3% of the non-depressed versus 18.5% for those with and incident and 6.8% with a non-incident post-MI depression experienced an event. The HRs for incident and non-incident post-MI depression were 2.11 (95% CI 1.02 to 4.37) and 0.76 (95% CI 0.23 to 2.51), respectively.

DISCUSSION

Our findings confirm the results that it is *incident* post-MI depression that is related to cardiovascular prognosis rather than post-MI depression per se. Patients with incident and non-incident depression differed in terms of aspects of MI severity, educational level, and neuroticism, but these factors did not alter the effects on cardiovascular prognosis. Our findings are similar to the ones reported by Grace et al. (10), despite the study difference in: 1) the assessment of depression (i.e., using self-report data vs. a standardized interview); 2) the timing of the assessment (i.e., during hospital admission vs. during 3 to 12 months post-MI); and 3) the assessment of cardiovascular prognosis (i.e., cardiac mortality vs. new fatal and non-fatal cardiovascular events).

Non-incident post-MI depression cases seemed to resemble depression seen in the general population because they shared well-known risk factors for depression, such as low educational level and high neuroticism (15,16). Results from the SADHART (Sertraline Antidepressant Heart Attack Randomized Trial) indicate that only ACS patients with non-incident depressions responded relatively well to sertraline in terms of depression (17). In combination with our current finding that this subgroup does not have an impaired cardiac prognosis, this may explain the outcomes of the ENRICHD (Enhancing Recovery in Coronary Heart Disease) trial in terms of no cardiovascular benefits of cognitive behavioral therapy (CBT) (2). In contrast, in incident post-MI depressions, the MI itself, or its direct

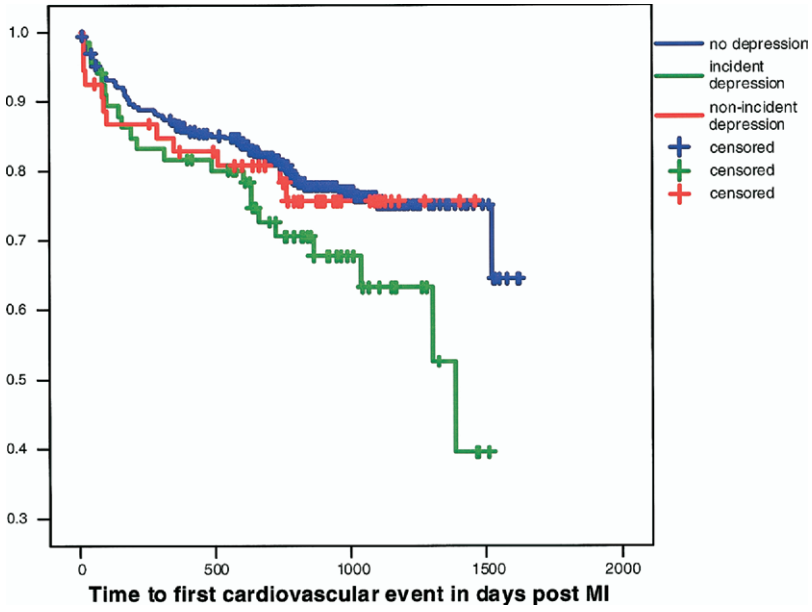

Figure 1. Event-free survival for patients with no, incident, and non-incident post-myocardial infarction (MI) depression.

physical or psychological consequences, may have been the cause for depression. Support for this hypothesis is found by relatively high levels of ejection fraction dysfunction, a higher risk of revascularization, and more disability at 12 months post-MI. Because specifically this subtype of post-MI depression had an increased risk of cardiovascular events, our findings stress the need for treatment strategies for post-MI depression, which may be closer to cardiac rehabilitation and more focused on the consequences of the MI than a purely depression-oriented approach. In fact, this finding may explain the relatively high effectiveness of psychoeducational interventions, including stress management and relaxation, to prevent cardiac events in coronary artery disease patients (18).

What are important aspects to focus on in studying the potential effects of depression on cardiovascular prognosis in the post-ENRICHD era? We have observed that depression treatment strategies based on current guidelines for depression (i.e., CBT and selective serotonin reuptake inhibitors) may not necessarily correspond to the needs of all post-MI depressed subjects. In addition, recent studies have shown that only some symptoms of post-MI depression are associated with cardiovascular prognosis (i.e., the more somatic/affective) whereas others (i.e., the more cognitive/affective) are not (19). Other lines of research indicate that other psychological risk factors, such as anxiety or type D personality, may be as important as depression in predicting cardiac outcomes and that even minimal symptoms of depression are already associated with increased risk (20). We believe that future studies on the potential cardiac effects of depression should be dedicated to: 1) a reconceptualization of depression in the context of ACS, including its diagnosis and treatment; and 2) the identification of relevant subtypes of MI depression and the development of effective treatments tailored at these specific subtypes. This could lead to new treatment strategies to prevent future cardiac events, which may be quite different than those described in current guidelines for depression in the general population.

Table 2. Unadjusted and Adjusted Cox Regression Models for Predicting New Cardiovascular Events

	Hazard Rates (95% Confidence Interval)	
	Unadjusted	**Adjusted**
Incident post-MI depression	**1.65 (1.02–2.65)**	**1.76 (1.06–2.93)**
Non-incident post-MI depression	1.12 (0.61–2.06)	1.39 (0.74–2.61)
Female gender	1.07 (0.67–1.68)	1.03 (0.64–1.68)
Age	**1.02 (1.00–1.04)**	**1.02 (1.00–1.04)**
Primary school only	1.16 (0.74–1.82)	1.10 (0.66–1.82)
LVEF <40%	**1.56 (1.05–2.33)**	**1.70 (1.12–2.60)**
Revascularization	0.74 (0.46–1.19)	0.80 (0.49–1.30)

Bold values are statistically significant.
Abbreviations as in Table 1.

Reprint requests and correspondence: Dr. Peter de Jonge, Departments of Internal Medicine and Psychiatry, University Medical Centre Groningen, P.O. Box 30.001, 9700 RB Groningen, the Netherlands. E-mail: p.de.jonge@med.umcg.nl.

REFERENCES

1. van Melle JP, de Jonge P, Spijkerman TA, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. Psychosom Med 2004;66:814–22.
2. 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;289:3106–16.
3. Denollet J, Vaes J, Brutsaert DL. Inadequate response to treatment in coronary heart disease: adverse effects of type D personality and younger age on 5-year prognosis and quality of life. Circulation 2000;102:630–5.

4. Pedersen SS, Lemos PA, van Vooren PR, et al. Type D personality predicts death or myocardial infarction after bare metal stent or sirolimus-eluting stent implantation: a Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry substudy. J Am Coll Cardiol 2004;44:997–1001.
5. Strik JJ, Denollet J, Lousberg R, Honig A. Comparing symptoms of depression and anxiety as predictors of cardiac events and increased health care consumption after myocardial infarction. J Am Coll Cardiol 2003;42:1801–7.
6. Freedland KE, Carney RM, Lustman PJ, Rich MW, Jaffe AS. Major depression in coronary artery disease patients with vs. without a prior history of depression. Psychosom Med 1992;54:416–21.
7. Lloyd GG, Cawley RH. Distress or illness? A study of psychological symptoms after myocardial infarction. Br J Psychiatry 1983;142: 120–5.
8. Spijkerman TA, de Jonge P, van den Brink RH, et al. Depression following myocardial infarction: first-ever versus ongoing and recurrent episodes. Gen Hosp Psychiatry 2005;27:411–7.
9. McCaffery JM, Frasure-Smith N, Dube M, et al. Common genetic vulnerability to depressive symptoms and coronary artery disease: a review and development of candidate genes related to inflammation and serotonin. Psychosom Med 2006;68:185–6.
10. Grace SL, Abbey SE, Kapral MK, Fang J, Nolan RP, Stewart DE. Effect of depression on five-year mortality after an acute coronary syndrome. Am J Cardiol 2005;96:1179–85.
11. Wittchen HU. Reliability and validity studies of the WHO—Composite International Diagnostic Interview (CIDI): a critical review. J Psychiatr Res 1994;28:57–84.
12. Eysenck SBG, Eysenck HJ, Barrett P. A revised version of the psychoticism scale. Pers Individ Differ 1985;6:21–9.
13. Pedersen SS, Denollet J. Validity of the type D personality construct in Danish post-MI patients and healthy controls. J Psychosom Res 2004;57:265–72.
14. Broadhead WE, Blazer DG, George LK, Tse CK. Depression, disability days, and days lost from work in a prospective epidemiologic survey. JAMA 1990;264:2524–8.
15. Cole MG, Dendukuri N. Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. Am J Psychiatry 2003;160:1147–56.
16. de Jonge P, Kempen GI, Sanderman R, et al. Depressive symptoms in elderly patients after a somatic illness event: prevalence, persistence, and risk factors. Psychosomatics 2006;47:33–42.
17. Glassman AH, O'Connor CM, Califf RM, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. JAMA 2002;288:701–9.
18. Dusseldorp E, van Elderen T, Maes S, Meulman J, Kraaij V. A meta-analysis of psychoeducational programs for coronary heart disease patients. Health Psychol 1999;18:506–19.
19. 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;163:138–44.
20. Bush DE, Ziegelstein RC, Tayback M, et al. Even minimal symptoms of depression increase mortality risk after acute myocardial infarction. Am J Cardiol 2001;88:337–41.