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Prognostic Association of Depression Following Myocardial Infarction With Mortality and Cardiovascular Events: A Meta-analysis

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Objective: To assess the association of depression following myocardial infarction (MI) and cardiovascular prognosis. **Methods:** The authors performed a meta-analysis of references derived from MEDLINE, EMBASE, and PSYCINFO (1975–2003) combined with crossreferencing without language restrictions. The authors selected prospective studies that determined the association of depression with the cardiovascular outcome of MI patients, defined as mortality and cardiovascular events within 2 years from index MI. Depression had to be assessed within 3 months after MI using established psychiatric instruments. A quality assessment was performed. **Results:** Twenty-two papers met the selection criteria. These studies described follow up (on average, 13.7 months) of 6367 MI patients (16 cohorts). Post-MI depression was significantly associated with all-cause mortality (odds ratio [OR], fixed 2.38; 95% confidence interval [CI], 1.76–3.22; $p < .00001$) and cardiac mortality (OR fixed, 2.59; 95% CI, 1.77–3.77; $p < .00001$). Depressive MI patients were also at risk for new cardiovascular events (OR random, 1.95; 95% CI, 1.33–2.85; $p = .0006$). Secondary analyses showed no significant effects of follow-up duration (0–6 months or longer) or assessment of depression (self-report questionnaire vs. interview). However, the year of data collection (before or after 1992) tended to influence the effect of depression on mortality ($p = .08$), with stronger associations found in the earlier studies (OR, 3.22; 95% CI, 2.14–4.86) compared with the later studies (OR, 2.01; 95% CI, 1.45–2.78). **Conclusions:** Post-MI depression is associated with a 2- to 2.5-fold increased risk of impaired cardiovascular outcome. The association of depression with cardiac mortality or all-cause mortality was more pronounced in the older studies (OR, 3.22 before 1992) than in the more recent studies (OR, 2.01 after 1992). **Key words:** epidemiology, depression, meta-analysis, myocardial infarction, prognosis, risk factors.

CI = confidence interval; **CA** = cardiac arrest; **CABG** = coronary artery bypass graft; **CAD** = coronary artery disease; **DIS** = modified version of the National Institute of Mental Health Diagnostic Interview Schedule; **DM** = diabetes mellitus; **DSM** = Diagnostic and Statistical Manual of Mental Disorders; **DISH** = Depression Interview and Structured Hamilton; **ENRICHD** = Enhancing Recovery in Coronary Heart Disease Patients Randomized Trial; **FU** = follow up; **HADS** = hospital anxiety and depression scale; **IHD** = ischemic heart disease; **KSb-S** = Klinische Selbstbeurteilungsskalen aus dem Münchner psychiatrische Informations-System; **LVEF** = left ventricular ejection fraction; **MADRS** = Montgomery Asberg Depression Rating Scale; **MI** = myocardial infarction; **MIND-IT** = Myocardial INfarction and Depression–Intervention Trial; **NA** = not available; **OR** = odds ratio; **PVC** = premature ventricular contraction; **SCID** = Structured Clinical Interview for DSM; **SCL-90** = 90-item Symptom Check List; **SSRI** = selective serotonin re-uptake inhibitor.

INTRODUCTION

In the year 2020, the top two contributors to the worldwide burden of disease are predicted to be ischemic heart diseases (IHD) and major depression (1). During the last decades, a large number of studies were reported discussing the relation of IHD and depressive illness. In long-term prospective studies, depression emerged as an independent risk factor for the development of IHD (2–4). On the other hand, patients with established IHD are at risk to develop depression (5). Many studies reported on the prevalence and consequences of post-myocardial infarction (MI) depression. Major depression following MI is a common disorder, affecting approximately 18% of all MI patients (5), and it is a major predictor of disability (6) and poor quality of life (7) in the year post-MI. It also causes a delayed return to work and it complicates medical therapy as a result of its association with noncompliance (8). Moreover, the question arises whether post-MI depression is a risk factor for cardiovascular morbidity and mortality (9,10). Although the number of positive studies in this field is steadily growing, the debate continues since the publication of a few negative studies (11,12). These apparently conflicting results prompted us to find an answer to the following question: What is the association of depression with the cardiovascular outcome of patients following myocardial infarction in terms of mortality and cardiovascular events?

Although a few narrative reviews have been published on this issue (13,14), to our knowledge, no meta-analysis has been carried out.

METHODS

Aim

The aim was to identify all studies that were available by January 2004 comparing cardiovascular prognosis of depressed MI patients with a control group of nondepressed MI patients. We have chosen for a systematic identification, appraisal, synthesis, and statistical aggregation according to predetermined methods (15).

Literature Search

For our search, the electronic databases MEDLINE, EMBASE, and PSYCINFO (1975–2003) were used. In our prespecified protocol, we used the following terms: "depression," "depressive disorder," "depressive symptoms," "mood disorder," "affective disorder," and "myocardial infarction" without language restrictions. We included both published and

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unpublished data (eg, doctoral dissertations). We completed the list with references derived from our personal database (eg, reference lists of review articles, books, abstracts, and personal communications).

Selection

In the resultant dataset, two independent raters from a pool of 5 investigators (J.v.M., P.d.J., T.S., R.v.d.B., M.v.d.B.) identified studies that met the eligibility criteria according to the following 3 steps:

1. Patients who were hospitalized, or had been hospitalized, for MI in whom depression as an emotional state was measured (in contrast to, for example, "ST-segment depression" on an electrocardiogram).
2. Depression had to be determined within 3 months after MI using methods originally designed to assess depression (standard self-report questionnaires, standardized psychiatric interviews) and validated elsewhere. Of note, self-report questionnaires are used to assess depressive *symptomatology*, whereas psychiatric interviews are standardized measures for the assessment of a depressive *disorder*. It is important to realize that depression is measured as a "state" and not as a "trait." Only studies presenting original data were selected (eg, reviews and editorials were excluded).
3. From the remaining set of studies, we selected in a third step, prospective studies that assessed cardiovascular prognosis in a depressed patient group compared with the cardiovascular prognosis in a control group. Only studies were used that focused on the following outcomes (or a combination of these end points): a) all-cause mortality or b) cardiac mortality; cardiovascular events (eg, myocardial infarction, unstable angina, need for revascularization, arrhythmia)

Because we were interested in the association of post-MI depression and relatively short-term prognosis, we selected studies reporting end points within 24 months after the index MI. During the whole selection procedure, in case of disagreement between two raters, the five investigators discussed the difference of opinion until consensus was reached.

Different articles using the same patient group were reviewed only if they reported on different end points or differed in follow-up period. In case of multiple analyses on the same patient group, we chose the article that represented the data best (ie, the article with the most complete representation of variables, necessary to calculate the depression associated risk of cardiovascular events post-MI). When evaluating the comprehensive work of Frasure-Smith et al. we used, when possible, the results of the Care As Usual-arm of the M-HART trial (16) and the EPPI-trial (9) as the authors did in a recent article (17). Studies on mixed patient groups (eg, MI and unstable angina) were included only when follow-up data of the patients with MI were separately presented. Data from blind placebo-controlled medication trials in which depression was measured as part of an ancillary study were included in the review process (18,19), but only data derived from patients randomized to placebo (18) were taken into analysis. If necessary, the coordinators of the eligible studies were asked for details.

The following aspects of methodologic quality were rated independently: sample size, representativeness of the study population (eg, did the researchers include specific in-/exclusion criteria such as sex or arrhythmia at baseline), percentage lost to follow up, and factors controlled for. The measure of depression was of such importance for the quality of the study that we decided to make this a separate inclusion criterion (ie, only validated measures of depression). Like Wulsin and Singal (2), we chose not to use quality scoring, which weights the contribution of each study to the meta-analysis on the basis of the quality score. The main criticism of incorporating quality scoring weights into metaanalyses is that there are no validated measures of quality and the use of subjective rating scales may lead to bias (20).

Quantitative Data Synthesis

Data from all studies reporting on identical endpoints were pooled using Review Manager (RevMan) version 4.2 for Windows of The Cochrane Collaboration. When possible, we related the end points to depressive disorder (instead of depressive symptoms), and we chose the analysis describing the longest follow-up period (up to a maximum of 24 months). To pool data across the studies, we converted the time-related data into raw data (2×2 tables). Thus, for all studies, irrespective of the presented effect measure (ie, risk ratio, odds ratio, or hazard ratio), data were converted into (unadjusted) dichotomous outcomes. We then calculated odds ratios and 95% confidence intervals. The fixed method was used to generate a summary estimate of odds ratios and the appropriateness to combine results was tested using chi-squared analysis. Depending on the outcome of the test for heterogeneity (21), we also used the random effects method and compared results of both statistical methods.

In two studies (22,23), depressive symptoms were not presented as a dichotomous variable, but as a continuous variable. In these cases, we estimated the number of patients above and below the established cutoff point of the depression scale using the mean depression score and standard deviation that were reported based on the assumption of normal distribution. We then calculated odds ratios for the depression-related cardiovascular events.

In secondary analyses, we studied the influence of year of data collection (before or after 1992), assessment of depression (psychiatric interview or questionnaire), and duration of follow up (0–6 months or longer). The year 1992 was chosen in our secondary analyses because this resulted in two, with respect to the amount of studies, comparable groups. As a result of the limited number of studies investigating the risk of cardiovascular events, we were not able to conduct secondary analyses on this end point. Differences in odds ratios between types of studies were assessed by comparing the pooled odds ratio in one group with that of the other group of studies using chi-squared analysis comparing logarithms of the odds ratios.

Funnel plots were constructed by plotting the effect measure against the inverse of its standard error (SigmaPlot 8.0 for Windows). Its asymmetry was tested by significance tests using linear regression methods.

RESULTS

A flow diagram of the literature search is shown in Figure 1. The agreement rates (Cohen's kappas) for the 3 steps in the selection procedure were 0.91 (standard error [SE] 0.01), 0.87 (SE 0.02), and 0.80 (SE 0.06), respectively, referring to a good/very good consistency of judgments by the raters (24). Our search yielded 22 prospective studies in which the association of depression following MI and prognosis was determined. These 22 studies described follow-up data of 16 different cohorts, which comprised 6367 MI patients (2056 cases and 4311 control subjects). We were forced to exclude some often-cited articles written by well-respected authors. These studies did not meet our inclusion criteria because of two reasons. First, the assessment of depression did not take place in the first 3 months post-MI (25). Second, some studies used unvalidated measurements of depression (26–28).

We were able to select 37 different analyses on the prespecified end points (Table 1). The mean age at the time of the index MI was 61 years; 75% were men; mean time to follow up was 13.7 months. The proportion of MI patients with depressive symptoms or depressive disorder at baseline ranged from 8% to 47% and from 5% to 47%, respectively.

From the 37 different analyses on the prespecified end points, 22 reported significant ($p < .05$) results and 15 reported nonsignificant results after univariate analysis (59% vs. 41%, respectively). Of the 22 studies with significant results in *univariate* analysis, 12 studies conducted *multivariate* analyses (55%). From these 12 studies (Table 2), 8 reported significant and 4 studies reported nonsignificant results after controlling for other clinical variables. The reported multivariate odds ratios were generally somewhat lower than the univariate odds ratios.

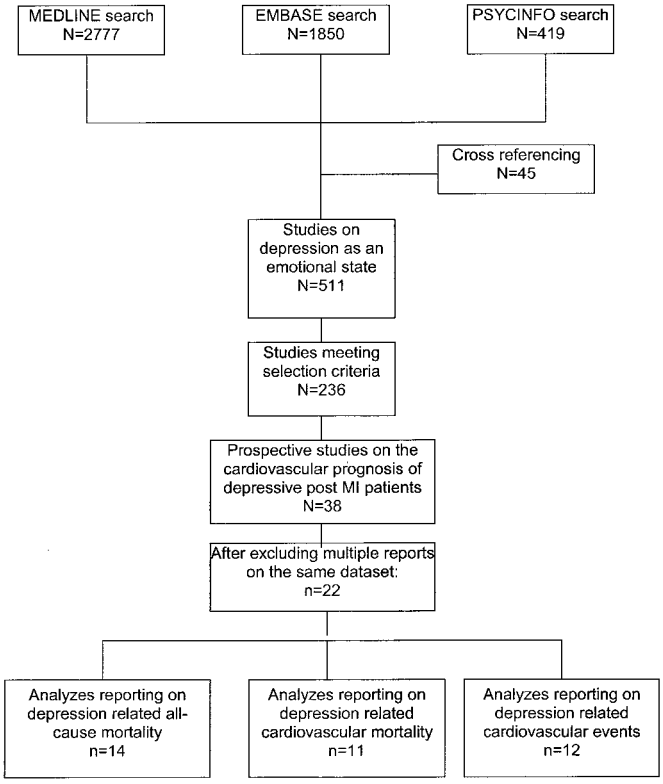

Figure 1. Flow chart representing the literature search. *N* = number of articles.

Additional Information by Personal Communication

We contacted authors of five included studies for further information on study characteristics. In the study by Mayou et al. (12), the psychiatric measure comprised the Hospital Anxiety and Depression (HAD) Scale. Based on their HAD score, MI patients were divided in distressed (depression score greater than 10 or summed depression and anxiety scores greater than 19) and nondistressed persons. The authors subsequently analyzed whether distress was significantly associated with mortality. Mayou provided us with the survival data of the depressed MI patients, Silverstone provided us with the follow-up period of his study (29), and Irvine (18) supplied the exact numbers of the depressed vs. nondepressed MI patients in the placebo arm of their study who reached an end point. Carney (30) and Strik (31) provided us with additional information concerning end points within 24 months post-MI in their studies.

Mortality and Cardiovascular Events

Nine studies (12,18,29,30,32–36) with a total of 3082 patients reported on all-cause mortality (Figure 2). The pooled odds ratio of all-cause mortality after MI in 952 depressed patients compared with 2130 nondepressed patients was 2.38 (95% confidence interval [CI], 1.76–3.22; $p < .00001$).

Nine studies (9–11,17,18,37–40), 6 cohorts with a total of 3343 patients reported on cardiac mortality (Figure 3). The pooled odds ratio of cardiac mortality after MI in 1091 depressed patients compared with 2252 nondepressed patients was 2.59 (95% CI, 1.77–3.77; $p < .00001$).

Nine studies (22,23,29,35–37,40–42) with a total of 3401 patients reported on cardiovascular events (Figure 4). Although definitions of cardiovascular events varied between studies, all studies reported on the combined end point of cardiac death, cardiac arrest, and recurrent MI. When the results were pooled, the odds ratio was 1.64 (95% CI, 1.37–1.97; $p = .0006$). Because the odds ratios among these studies were heterogeneous ($p = .005$), we pooled the results following the random method. This resulted in a comparable estimate of the overall odds ratio (odds ratio [OR], 1.95; 95% CI, 1.33–2.85; $p = .0006$).

Secondary Analyses

The significant association between post-MI depression and all-cause mortality was not influenced by the way depression was assessed (ie, questionnaire vs. psychiatric interview; $p = .60$; Table 3). The same was true for cardiac mortality ($p = .63$). The association between depression and cardiac mortality or all-cause mortality was more pronounced in the older studies (before 1992) than in the more recent studies (after 1992; old vs. new, $p = .08$). Finally, we compared studies with a short follow up (0–6 months) with studies with a longer follow up (longer than 6 months). The all-cause mortality risk in the first 6 months was not significantly different ($p = .48$) from the risk in the next 18 months. We found comparable results for cardiac mortality (short vs. long follow up: $p = .46$).

DISCUSSION

This meta-analysis shows a consistent association between post-MI depression and impaired cardiovascular prognosis. This holds true for both post-MI mortality (either cardiac mortality or all-cause mortality) and cardiovascular events. The magnitude of the increased risk was 2 to 2.5 times. The study populations were patients living in North America, Europe, and Japan. Earlier studies tended to have a more profound effect of depression on cardiovascular prognosis than later studies. It may be possible that improvements in cardiac care for hospitalized and rehabilitating MI patients are responsible for this finding, but this would need further research.

The results need to be considered in relation to the study limitations. One of the most important limitations in conducting a meta-analysis is the inevitability to combine data from studies that are not equally designed. In this meta-analysis, we assessed the potential effect of two study characteristics: the assessment of depression and the length of follow up. Because questionnaires measure only selected aspects of mental state, and a clinical interview allows for a more careful weighing of relevant information, this seems an important study characteristic. Similarly, post-MI depression may have a different association with short-term prognosis compared with long-term prognosis. However, in our study, we found no influence of the way depression was assessed on the strength of the associations with post-MI prognosis or of the follow-up duration. The first finding may have important clinical implications for

TABLE 1. Overview of Selected Studies, Grouped by Endpoints, Investigating the Influence of Depression on Prognosis in Post MI Patients

Art No	1° Author	Year of Publication	Selection of MI pts (Y/N)	Mean Age (yr)	Female (%)	Instrument	Time Post MI† (days)	Dep (%)	Lost to FU (%)	Endpoint(s)	FU (mo)	Start Data Collection	Symptoms Versus Disorder	Association Depression and Severity of Cardiac Disease (Y/N)
1	Silverstone (29)	1987	N	63	25	MADRS	1	44	NA	All-cause mortality	0.25*	NA	Symptoms	N
2	Lesperance (32)	1996	N	60	22	DIS	5–15	16	0	All-cause mortality	18	1991	Disorder	N
	Lesperance (32)	1996	N	60	22	DIS	5–15	16	0	All-cause mortality	12	1991	Disorder	N
	Lesperance (32)	1996	N	60	22	DIS	5–15	16	0	All-cause mortality	6	1991	Disorder	N
3	Irvine (18)	1999	Y§	64	18	BDI	6–45	33	5	All-cause mortality*	24	1990	Symptoms	NA
4	Kaufmann (33)	1999	N	65	34	DIS	7	27	0	All-cause mortality	6	1995	Disorder	NA
	Kaufmann (33)	1999	N	65	34	DIS	7	27	0	All-cause mortality	12	1995	Disorder	NA
5	Mayou (12)	2000	N	63	27	HADS	<3	8	0	All-cause mortality*	6	1994	Symptoms	NA
	Mayou (12)	2000	N	63	27	HADS	<3	8	0	All-cause mortality*	18	1994	Symptoms	NA
6	Bush (34)	2001	N	65	42	BDI	2–5	20	5	All-cause mortality	4	1995	Symptoms	N‡
	Bush (34)	2001	N	65	42	SCID	2–5	10	5	All-cause mortality	4	1995	Disorder	N‡
7	Lauzon (35)	2003	N	60	21	BDI	2–3	35	0	All-cause mortality	12	1996	Symptoms	N
8	Strik (36)	2003	Y††	59	24	SCID	30	31	0	All-cause mortality	6	NA	Disorder	N
9	Carney (30)	2003	N	59	40	DISH	<28	47	0	All-cause mortality*	24	1997	Disorder	N
10	Ladwig (37)	1991	Y¶	54	0	KSb-S	17–21	15	0	Cardiac mortality	6	1983	Symptoms	NA
11	Frasure-S (9)	1993	N	60	22	DIS	5–15	16	0	Cardiac mortality	6	1991	Disorder	N
12	Frasure-S (38)	1995	N	60	22	DIS	5–15	16	0	Cardiac mortality	18	1991	Disorder	N
	Frasure-S (38)	1995	N	60	22	BDI	5–15	31	0	Cardiac mortality	18	1991	Symptoms	N
	Irvine (18)	1999	Y§	64	18	BDI	6–45	33	5	Cardiac mortality*	24	1990	Symptoms	NA
13	Frasure-S (17)	1999	N	59	32	BDI	5–15	32	0	Cardiac mortality	12	1991	Symptoms	Y
14	Welin (10)	2000	Y**	NA	16	Zung	30	37	3	Cardiac mortality	12	1985	Symptoms	N
	Welin (10)	2000	Y**	NA	16	Zung	30	37	3	Cardiac mortality	24	1985	Symptoms	N
15	Lane (39)	2000	N	63	25	BDI	2–15	31	1	Cardiac mortality	4	1997	Symptoms	N
16	Lane (11)	2001	N	63	25	BDI	2–15	31	1	Cardiac mortality	12	1997	Symptoms	N
17	Shiotani (40)	2002	N	63	64	Zung	63	42	1	Cardiac mortality	12	1998	Symptoms	N
	Silverstone (29)	1987	N	63	25	MADRS	<1	44	NA	Cardiovascular events‡‡	0.25*	NA	Symptoms	N
18	Ahern (23)	1990	Y‖	NA	NA	BDI	6–60	40	1	Cardiovascular events§§	12	1983	Symptoms	NA
	Ladwig (37)	1991	Y¶	54	0	KSb-S	17–21	15	0	Cardiovascular events‖	6	1983	Symptoms	NA
19	Frasure-S (41)	1995	N	60	22	BDI	5–15	31	0	Cardiovascular events¶¶	12	1991	Symptoms	N
	Frasure-S (41)	1995	N	60	22	DIS	5–15	16	0	Cardiovascular events¶¶	12	1991	Disorder	N
20	Sydeman (22)	1998	N	62	40	SCID	2–7	5	7	Cardiovascular events***	6	1996	Disorder	N
	Sydeman (22)	1998	N	62	40	BDI	2–7	23	7	Cardiovascular events***	6	1996	Symptoms	N
21	Lane (42)	2000	N	63	25	BDI	2–15	31	6	Cardiovascular events†††	12	1997	Symptoms	N
	Shiotani (40)	2002	N	63	64	Zung	63	42	1	Cardiovascular events‡‡‡	12	1998	Symptoms	N
	Lauzon (35)	2003	N	60	21	BDI	2–3	35	0	Cardiovascular events§§§	12	1996	Symptoms	N
	Strik (36)	2003	Y††	59	24	SCID	30	31	0	Cardiovascular events‖	6	NA	Disorder	N
22	Strik (31)	2003	Y¶¶¶	58	0	SCL-90	30	47	0	Cardiovascular events****	24	1994	Symptoms	N

DIS: modified version of the National Institute of Mental Health Diagnostic Interview Schedule.
SCID: Structured Clinical Interview for DSM IIIR (nonpatient version) (34) or DSM IV (22).
KSb-S: Klinische Selbstbeurteilungsskalen aus dem Münchner psychiatrische Informations-System.
HADS: Hospital Anxiety and Depression Scale; MADRS: Montgomery Asberg Depression Rating Scale
ZUNG: Zung Selfrating Depression Scale; FU: follow up; CA: Cardiac arrest; Mo: months; LVEF: left ventricular ejection fraction; Y = Yes; N = No
NA: not available; DISH: Depression Interview and Structured Hamilton; SCL-90: 90-item Symptom Check List
* Personal communication
† Time between MI and assessment of depression
‡ Borderline significance (p = 0.07)
§ Frequent (≥ 10/hour) or repetitive ventricular depolarizations on ambulatory electrocardiograms
‖ MI patients, older than 75 years and left ventricular ejection fraction ≥20%, with a baseline 24-hour Holter monitor documenting ≥ 10 ventricular premature complexes/hour or ≥ 5 episodes of unsustained ventricular tachycardia
¶ Male MI patients < 66 years
** Patients < 65 years with first MI
†† Patients with first MI
‡‡ Cardiac death, cardiac arrest or further MI
§§ All-cause mortality, cardiac arrest
‖ Cardiac mortality, cardiac arrest
¶¶ Cardiac death, cardiac arrest, MI or unstable angina
*** Cardiac death, cardiac arrest, MI, unstable angina, ischemic leg syndrome, transient ischemic attack, stroke, atrial fibrillation, or pulmonary embolus
††† Cardiac death, MI, unstable angina, arrhythmic events, heart failure, coronary bypass surgery, angioplasty
‡‡‡ Cardiac death, MI, unstable angina, uncontrolled arrhythmia, heart failure, coronary bypass surgery, angioplasty
§§§ Death, in-hospital recurrent ischemia, recurrent MI, congestive heart failure and readmissions for angina, recurrent MI, congestive heart failure or arrythmia
‖ Death or recurrent MI
¶¶¶ Male patients with first MI
**** Cardiac death or recurrent MI

TABLE 2. Overview of Positive Studies in Which the Effects of Depression on Endpoints Were Adjusted for Other Clinical Variables

Study	Endpoint(s)	Bivariate OR (95% CI)	Multivariate OR (95% CI)	Adjusted for
Ladwig (37)	Cardiac mortality	6.31 (1.98–20.09)	*	Recurrent MI, late potentials, dyspnoea, occurrence of triplets or more complex arrhythmias in 24 h Holter ECG
Frasure-Smith (9)	Cardiac mortality	6.24 (1.88–20.67)	4.29 (3.14–5.44)	Previous MI, Killip class
Frasure-Smith (41)	Cardiovascular events	3.32 (1.69–6.53)	1.99 (0.92–4.31)	Previous MI, ACE-inhibitors at discharge, previous depression, anxiety
Frasure-Smith (38)	Cardiac mortality (disorder)	3.65 (1.32–25.27)	2.68 (0.77–9.31)	Previous MI, PVCs, Killip class
Frasure-Smith (38)	Cardiac mortality (symptoms)	7.82 (1.32–10.05)	6.64 (1.76–25.09)	Previous MI, PVCs, Killip class
Sydeman (22)	Cardiovascular events	3.50 (1.26–9.72)	†	State anger, LVEF
Frasure-Smith (17)	Cardiac mortality	3.23 (1.65–6.33)	3.66 (1.68–7.99)	Age, smoking, LVEF, Non-Q wave MI, Killip class
Bush (34)	Mortality (symptoms)	2.81 (1.03–7.64)	‡	Age, DM, known CAD, prior MI, LVEF, Killip class
Kaufmann (33)	Mortality (disorder)	2.14 (1.02–4.48)	§	Age, DM, prior MI, LVEF, stroke, heart failure, CABG, hypertension, family history of CAD
Shiotani (40)	Cardiovascular events	1.46 (1.11–1.92)	1.41 (1.04–1.92)	Age, DM, hypertension
Lauzon (35)	Cardiovascular events	1.68 (1.18–2.39)	1.40 (1.05–1.86)	Age, sex, prior MI, history of previous angina, anterior location of infarct, DM, hypertension, smoking
Carney (30)	Mortality	2.8 (1.5–5.3)	2.4 (1.2–4.7)	Age, DM, smoking, LVEF, bypass surgery after the index MI

* Ladwig et al distinguished between low, medium and highly depressed patients. For medium versus low an OR of 2.8 was found, and low versus high an OR of 4.9.

† Sydeman reported that multivariate analysis was not significant (no OR reported)

‡ Bush et al entered "any depression" (i.e. BDI ≥10 or depressive disorder as predictor). They found an RR of 3.5.

§ Kaufmann reported that multivariate analysis was not significant (no OR reported)

OR = odds ratio; CI = confidence interval; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; DM = diabetes mellitus; PVC = premature ventricular contraction; CABG = Coronary Artery Bypass Graft.

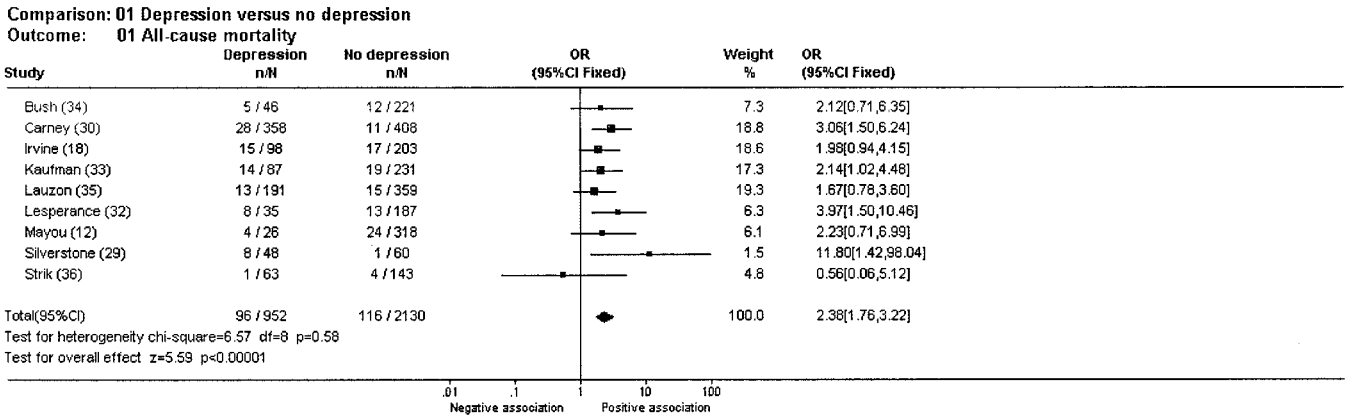

Figure 2. Association between depression and all-cause mortality.

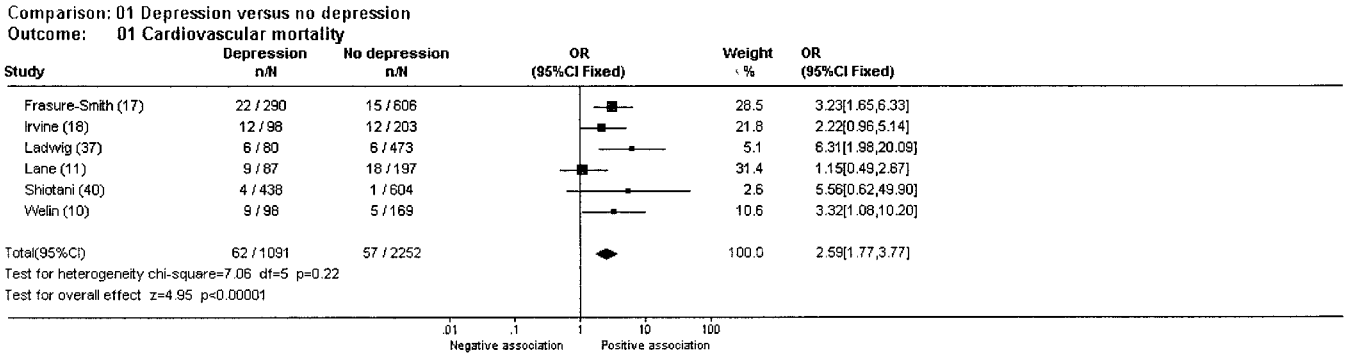

Figure 3. Association between depression and cardiac mortality.

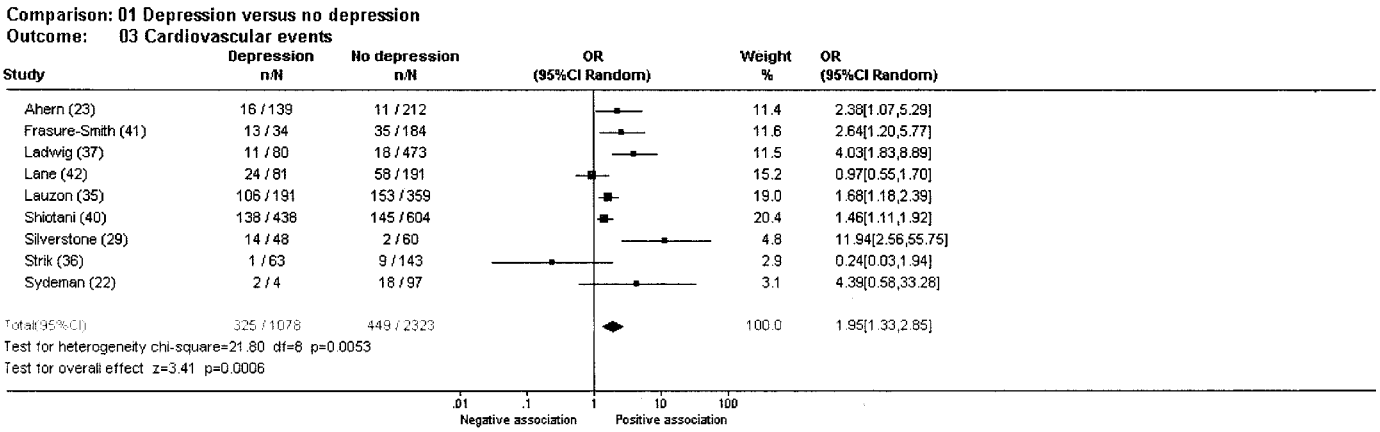

Figure 4. Association between depression and cardiovascular events.

the identification of post-MI patients with poor prognoses, because questionnaires are easier, faster, and cheaper than psychiatric interviews.

A second limitation is the fact that metaanalyses are prone to publication and other forms of selection biases. The likelihood of bias is illustrated by the funnel plots in Figure 5, ie, scatterplots of the depression's effects size in the selected studies against the sample size. Although the funnel plots of all-cause mortality and cardiovascular events resemble a symmetric inverted funnel, the plot of cardiovascular mortality is skewed and asymmetric with smaller studies showing associations that differ systematically from larger studies. Following the linear regression approach by Egger et al. (43), we tested the presence of asymmetry for the three different outcomes, resulting in nonsignificant p values of the intercept for all-cause mortality and cardiovascular events ($p = .30$ and $p = .20$, respectively) and significant p values for cardiovascular mortality ($p = .05$). Although asymmetric funnels have been associated with publication bias (43), such plots should be interpreted cautiously (44), and other sources of asymmetry as true heterogeneity must be taken into account. For example, the underlying risk may differ in MI patients, eg, MI patients with (18) or without (32) arrhythmia, study populations with different patients' characteristics with respect to age (33,37)

TABLE 3. Secondary Analyses

	Number of Studies	Number of Patients	OR (95% CI)	
Studies reporting on all-cause mortality				
Patients with depressive disorder	5	1779	2.53 (1.68–3.80)	P = 0.60
Patients with depressive symptoms	5	1470	2.17 (1.43–3.28)	
Studies with short follow-up	6	1478	2.92 (1.73–4.92)	P = 0.48
Studies with long follow-up	6	2501	2.34 (1.68–3.25)	
Studies reporting on cardiac mortality				
Patients with depressive disorder	1	222	3.65 (1.32–10.05)	P = 0.63
Patients with depressive symptoms	6	2665	2.79 (1.84–4.23)	
Studies with short follow-up	3	1060	3.52 (1.15–10.74)	P = 0.46
Studies with long follow-up	5	2116	2.23 (1.42–3.48)	
Studies reporting on either all-cause or cardiac mortality				
Old studies	5	2125	3.22 (2.14–4.86)	P = 0.08
New studies	8	3777	2.01 (1.45–2.78)	

and sex (34,37). Nonetheless, in our study, we have tried to minimize important sources of selection bias as publication bias by including both non-English and nonpublished work in our literature search.

A third limitation is the lack of information about premorbid mood disorders of the included MI patients. However, most of the selected studies were not designed to investigate precursors of post-MI depression. It is conceivable that some depressed MI patients were already depressed before the index MI.

The results of this meta-analysis are pointing to a relationship between depression and impaired cardiac prognosis. It is important to assess the extent to which this relationship is independent of other clinical variables (eg, left ventricular ejection fraction [LVEF]). It must be taken into account that sicker patients may have an increased risk to become depressed and subsequently have a worse cardiovascular prognosis. In other words, it is possible that the observed risk is in reality caused by poor cardiac function. As was pointed out in the selected studies, in most studies, depression was not related to the severity of cardiac disease. We analyzed those studies reporting significant bivariate relationships between depression and impaired prognosis. From these, several performed multivariate analyses: the described multivariate odds ratios were all, except for one, smaller than the bivariate odds ratios. This suggests that the effect of depression on post-MI prognosis may be partly dependent on other factors. In our meta-analysis, the conclusion that post-MI depression is related to impaired cardiovascular prognosis is based on bivariate analysis, not on multivariate analysis. We therefore cannot rule out the possibility of confounding factors that reduce the strength of the association between post-MI depression and cardiovascular prognosis, and we should remain careful before making causal inferences. We recommend that future studies will measure potential confounders (eg, LVEF, diabetes mellitus, hypertension, smoking, hypercholesterolemia).

The potential mechanisms linking depression and impaired cardiovascular prognosis are still poorly understood. First, unhealthy behavior of depressed MI patients (diminished compliance, smoking, unhealthy diet, inactivity) is important. Second, evidence is growing that physiological mechanisms are involved: depression in post-MI patients is associated with an increase in sympathetic nervous system activity (45,46), which could increase the risk for fatal arrhythmic events (47). Another possible explanation could be the increased platelet activation in depressed patients with IHD compared with their nondepressed counterparts, which may point to an increased tendency to form thrombi (48). Changes in the immune system (49) and the hypothalamic–pituitary–adrenocortical system (13) are also mentioned as mediators of the link between depression and impaired cardiac prognosis. Certain antidepressants, tricyclic antidepressants, are also associated with arrhythmias (50) or myocardial infarction (51). Although the information about antidepressant use in the selected studies of our meta-analysis is sparse, it is not likely that tricyclic antidepressant use is responsible for the observed association between depression and impaired cardiac prognosis, because post-MI depression is only treated in a small minority (32). Finally, in a recent report, Druss et al. (52) have shown that MI patients with comorbid mental disorders are substantially less likely to undergo coronary revascularization procedures than those without mental disorders. In addition, they pointed out that physicians also prescribed significantly less thrombolysis, aspirin, angiotensin-converting enzyme inhibitors, and β-blockers to MI patients with comorbid depression. Therefore, deficits in quality of medical care seem to explain, at least in part, the excess mortality experienced by patients with depression after MI.

The results of the present study underscore the need for intervention trials aimed at ameliorating the harmful effects of depression on cardiovascular prognosis. This is obviously a tempting speculation: treating depression and thereby improv-

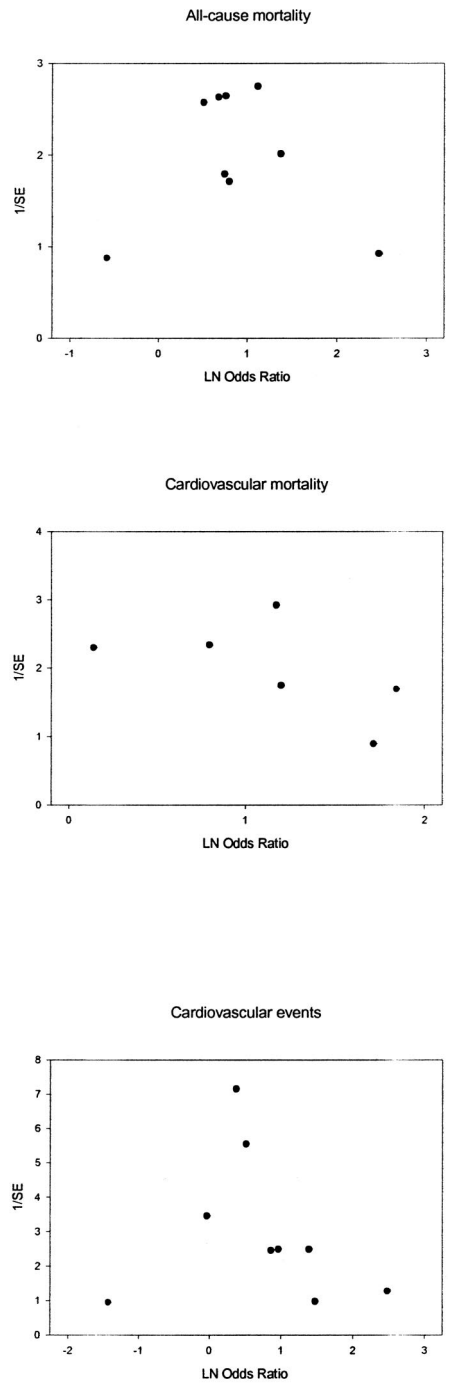

Figure 5. Funnel plots of selected studies.

ing cardiovascular outcome of depressed MI patients. Recently, the ENRICHD study (53) was the first clinical trial to test whether intervening on depression (and low perceived social support) soon after acute MI reduces mortality and reinfarction. The intervention decreased depression and improved social support more than was observed in usual care but did not affect the primary end point of death and nonfatal infarction. This important trial is probably the first in a row of intervention trials investigating the effects of antidepressant therapy for post-MI depression on cardiac prognosis. Of note, some data point to a protective role of specific serotonin reuptake inhibitors (SSRIs) in the development of cardiac events (54–56).

We are currently conducting a multicenter randomized, controlled trial, the MIND-IT study (57), in which the influence of antidepressant treatment for post-MI depression on cardiovascular prognosis and quality of life is investigated. The results of the MIND-IT study will be available in 2005.

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REFERENCES

1. Murray C, Lopez A. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. Lancet 1997;349: 1498–504.
2. Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. Psychosom Med 2003;65:201–10.
3. Anda R, Williamson D, Jones D, Macera C, Eaker E, Glassman A, Marks J. Depressed effect, hopelessness, and the risk of ischemic heart disease in a cohort of US adults. Epidemiology 1993;4:285–94.
4. Ariyo AA, Haan M, Tangen CM, Rutledge JC, Cushman M, Dobs A, Furberg CD. Depressive symptoms and risks of coronary heart disease and mortality in elderly Americans. Circulation 2000;102:1773–9.
5. Schleifer SJ, Macari-Hinson MM, Coyle DA, Slater WR, Kahn M, Gorlin R, Zucker HD. The nature and course of depression following myocardial infarction. Arch Intern Med 1989;149:1785–9.
6. Ades PA, Savage PD, Tischler MD, Poehlman ET, Dee J, Niggel J. Determinants of disability in older coronary patients. Am Heart J 2002; 143:151–6.
7. Beck CA, Joseph L, Belisle P, Pilote L, QOLAMI Investigators. Predictors of quality of life 6 months and 1 year after acute myocardial infarction. Am Heart J 2001;142:271–9.
8. Carney RM, Freedland KE, Eisen SA, Rich MW, Jaffe AS. Major depression and medication adherence in elderly patients with coronary artery disease. Health Psychol 1995;14:88–90.
9. Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction. Impact on 6-month survival. JAMA 1993;270: 1819–25.
10. Welin C, Lappas G, Wilhelmsen L. Independent importance of psychosocial factors for prognosis after myocardial infarction. J Intern Med 2000;247:629–39.
11. Lane D, Carroll D, Ring C, Beevers DG, Lip GY. Mortality and quality of life 12 months after myocardial infarction: effects of depression and anxiety. Psychosom Med 2001;63:221–30.
12. Mayou RA, Gill D, Thompson DR, Day A, Hicks N, Volmink J, Neil A. Depression and anxiety as predictors of outcome after myocardial infarction. Psychosom Med 2000;62:212–9.
13. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. Arch Gen Psychiatry 1998;55:580–92.
14. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation 1999;99:2192–217.
15. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283:2008–12.
16. Frasure-Smith N, Lesperance F, Prince RH, Verrier P, Garber RA, Juneau M, Wolfson C, Bourassa MG. Randomised trial of home-based psychosocial nursing intervention for patients recovering from myocardial infarction. Lancet 1997;350:473–9.
17. Frasure-Smith N, Lesperance F, Juneau M, Talajic M, Bourassa MG. Gender, depression, and one-year prognosis after myocardial infarction. Psychosom Med 1999;61:26–37.
18. Irvine J, Basinski A, Baker B, Jandciu S, Paquette M, Cairns J, Connolly S, Roberts R, Gent M, Dorian P. Depression and risk of sudden cardiac

death after acute myocardial infarction: testing for the confounding effects of fatigue. Psychosom Med 1999;61:729–37.
19. Thomas SA, Friedmann E, Wimbush F, Schron E. Psychological factors and survival in the cardiac arrhythmia suppression trial (CAST): a reexamination. Am J Crit Care 1997;6:116–26.
20. Petitti DB. Of babies and bathwater. Am J Epidemiol 1994;140:779–82.
21. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. BMJ 1997;315:1533–7.
22. Sydeman SJ. Impact of negative emotions on recurrent cardiovascular events following hospitalization for myocardial infarction or unstable angina. Dissertation Abstracts International: Section B: The Sciences and Engineering 1999; Abstracts.
23. Ahern DK, Gorkin L, Anderson JL, Tierney C, Hallstrom A, Ewart C, Capone RJ, Schron E, Kornfeld D, Herd JA. Biobehavioral variables and mortality or cardiac arrest in the Cardiac Arrhythmia Pilot Study (CAPS). Am J Cardiol 1990;66:59–62.
24. Brennan P, Silman A. Statistical methods for assessing observer variability in clinical measures. BMJ 1992;304:1491–4.
25. Berkman LF, Leo SL, Horwitz RI. Emotional support and survival after myocardial infarction. A prospective, population-based study of the elderly. Ann Intern Med 1992;117:1003–9.
26. Ruberman W, Weinblatt E, Goldberg JD, Chaudhary BS. Psychosocial influences on mortality after myocardial infarction. N Engl J Med 1984; 311:552–9.
27. Denollet J, Brutsaert DL. Personality, disease severity, and the risk of long-term cardiac events in patients with a decreased ejection fraction after myocardial infarction. Circulation 1998;97:128–9.
28. Jenkinson CM, Madeley RJ, Mitchell JR, Turner ID. The influence of psychosocial factors on survival after myocardial infarction. Public Health 1993;107:305–17.
29. Silverstone PH. Depression and outcome in acute myocardial infarction. BMJ 1987;294:219–20.
30. Carney RM, Blumenthal JA, Catellier D, Freedland KE, Berkman LF, Watkins LL, Czajkowski SM, Hayano J, Jaffe AS. Depression as risk factor for mortality after acute myocardial infarction. Am J Cardiol 2003;92:1277–81.
31. Strik JJMH, 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.
32. Lesperance F, Frasure-Smith N, Talajic M. Major depression before and after myocardial infarction: its nature and consequences. Psychosom Med 1996;58:99–110.
33. Kaufmann MW, Fitzgibbons JP, Sussman EJ, Reed JF 3rd, Einfalt JM, Rodgers JK, Fricchione GL. Relation between myocardial infarction, depression, hostility, and death. Am Heart J 1999;138:549–54.
34. Bush DE, Ziegelstein RC, Tayback M, Richter D, Stevens S, Zahalsky H, Fauerbach JA. Even minimal symptoms of depression increase mortality risk after acute myocardial infarction. Am J Cardiol 2001;88:337–41.
35. Lauzon C, Beck CA, Huynh T, Dion D, Racine N, Carignan S, Diodati JG, Charbonneau F, Dupuis R, Pilote L. Depression and prognosis following hospital admission because of acute myocardial infarction. CMAJ 2003;168:547–52.
36. Strik JJMH. From Thesis 'Mind the Heart' 2003. Chapter 2: One year cumulative incidence of depression following myocardial infarction and impact on cardiac outcome.
37. Ladwig KH, Kieser M, Konig J, Breithardt G, Borggrefe M. Affective disorders and survival after acute myocardial infarction. Results from the post-infarction late potential study. Eur Heart J 1991;12:959–64.
38. Frasure-Smith N, Lesperance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. Circulation 1995;91:999–1005.
39. Lane D, Carroll D, Ring C, Beevers DG, Lip GY. Effects of depression and anxiety on mortality and quality-of-life 4 months after myocardial infarction. J Psychosom Res 2000;49:229–38.
40. Shiotani I, Sato H, Kinjo K, Nakatani D, Mizuno H, Ohnishi Y, Hishida E, Kijima Y, Hori M, Sato H, Osaka Acute Coronary Insufficiency Study (OACIS) Group. Depressive symptoms predict 12-month prognosis in elderly patients with acute myocardial infarction. J Cardiovasc Risk 2002;9:153–60.
41. Frasure-Smith N, Lesperance F, Talajic M. The impact of negative emotions on prognosis following myocardial infarction: is it more than depression? Health Psychol 1995;14:388–98.
42. Lane D, Carroll D, Ring C, Beevers DG, Lip GY. Do depression and anxiety predict recurrent coronary events 12 months after myocardial infarction? QJM 2000;93:739–44.
43. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
44. Tang JL, Liu JLY. Misleading funnel plot for detection of bias in meta-analysis. J Clin Epidemiol 2000;53:477–84.
45. Carney RM, Blumenthal JA, Stein PK, Watkins L, Catellier D, Berkman LF, Czajkowski SM, O'Connor C, Stone PH, Freedland KE. Depression, heart rate variability, and acute myocardial infarction. Circulation 2001; 104:2024–8.
46. Watkins LL, Grossman P. Association of depressive symptoms with reduced baroreflex cardiac control in coronary artery disease. Am Heart J 1999;137:453–7.
47. Carney RM, Freedland KE, Rich MW, Smith LJ, Jaffe AS. Ventricular tachycardia and psychiatric depression in patients with coronary artery disease. Am J Med 1993;95:23–8.
48. Laghrissi-Thode F, Wagner WR, Pollock BG, Johnson PC, Finkel MS. Elevated platelet factor 4 and beta-thromboglobulin plasma levels in depressed patients with ischemic heart disease. Biol Psychiatry 1997;42: 290–5.
49. Irwin M. Psychoneuroimmunology of depression: clinical implications. Brain Behav Immun 2002;16:1–16.
50. Glassman AH, Roose SP, Bigger JT Jr. The safety of tricyclic antidepressants in cardiac patients. Risk-benefit reconsidered. JAMA 1993;269: 2673–5.
51. Cohen HW, Gibson G, Alderman MH. Excess risk of myocardial infarction in patients treated with antidepressant medications: association with use of tricyclic agents. Am J Med 2000;108:2–8.
52. Druss BG, Bradford DW, Rosenheck RA, Radford MJ, Krumholz HM. Mental disorders and use of cardiovascular procedures after myocardial infarction. JAMA 2000;283:506–11.
53. Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ, Czajkowski SM, DeBusk R, Hosking J, Jaffe A, Kaufmann PG, Mitchell P, Norman J, Powell LH, Raczynski JM, Schneiderman N. 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.
54. Sauer WH, Berlin JA, Kimmel SE. Selective serotonin reuptake inhibitors and myocardial infarction. Circulation 2001;104:1894–8.
55. Sauer WH, Berlin JA, Kimmel SE. Effect of antidepressants and their relative affinity for the serotonin transporter on the risk of myocardial infarction. Circulation 2003;108:32–6.
56. Glassman AH, O'Connor CM, Califf RM, Swedberg K, Schwartz P, Bigger JT Jr, Krishnan KR, van Zyl LT, Swenson JR, Finkel MS, Landau C, Shapiro PA, Pepine CJ, Mardekian J, Harrison WM, Barton D, McIvor M. Sertraline treatment of major depression in patients with acute MI or unstable angina. JAMA 2002;288:701–9.
57. Van den Brink RH, van Melle JP, Honig A, Schene AH, Crijns HJ, Lambert FP, Ormel J. Treatment of depression after myocardial infarction and the effects on cardiac prognosis and quality of life: rationale and outline of the Myocardial INfarction and Depression-Intervention Trial (MIND-IT). Am Heart J 2002;144:219–25.