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Onset and Recurrence of Depression as Predictors of Cardiovascular Prognosis in Depressed Acute Coronary Syndrome Patients: A Systematic Review

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Key Words
Depression, onset, recurrence · Cardiovascular prognosis · Acute coronary syndrome

Abstract
Background: Depression after acute coronary syndrome (ACS) is associated with worse cardiac outcomes. This systematic review evaluated whether depressed ACS patients are at differential risk depending on the recurrence and timing of onset of depressive episodes. ***Methods:*** MEDLINE, EMBASE and PsycINFO were searched from inception to 11 April 2009. Additionally, reference lists and recent tables of contents of 34 selected journals were manually searched. Eligible studies evaluated cardiovascular outcomes for subgroups of ACS patients with depression or depressive symptoms according to recurrence or onset. ***Results:*** Six studies were included that reported outcomes for subgroups of ACS patients with first-ever versus recurrent depression. Four of these reported also outcomes for post-ACS onset versus pre-ACS onset depression, and incident versus nonincident depression. Worse outcomes (odds ratio >1.4) were reported for ACS patients with first-ever depression in 3 of 6 studies (1 study $p < 0.05$), for patients with post-ACS onset depression in 3 of 4 studies (1 study $p < 0.05$, but better outcomes in one study) and for patients with incident depression in 2 of 4 studies (no studies $p < 0.05$). ***Conclusions:*** Although it is still suggested that ACS patients with first and new-onset depression are at particularly increased risk of worse prognosis, the inconsistent results from the studies included in this systematic review show that there is no consistent evidence to support such statements.

Introduction

Depression after acute coronary syndrome (ACS) is associated with an increased risk of new cardiovascular events or mortality. A meta-analysis including 22 studies found that depressed myocardial infarction (MI) patients were at 2–2.5 times higher risk of new cardiovascular events or mortality than nondepressed MI patients [1].

Recently, research is focusing on different aspects of post-ACS depression that may be especially associated with cardiovascular prognosis, such as depression severity (i.e. the distinction between minor and major depression) [2], depressive symptom profile [3, 4], persistence of

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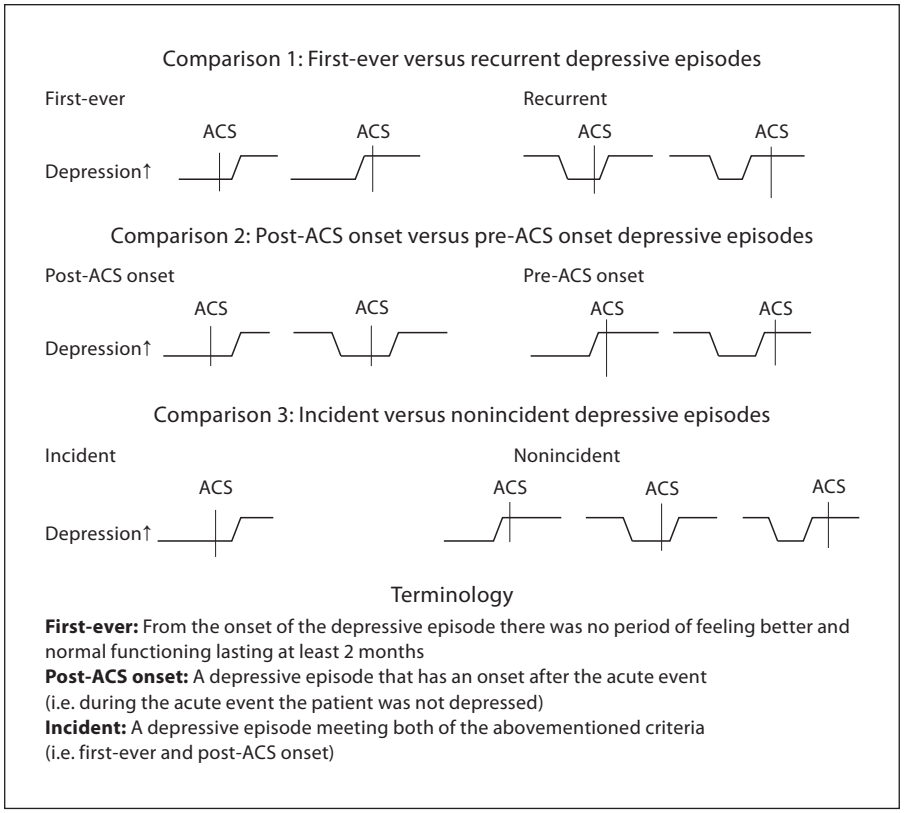

Fig. 1. Subgroups of post-ACS depressed patients, according to recurrence and onset of the depressive episode relative to the acute event.

the depressive episode after the acute event [5] and treatment resistance [6].

In addition, it has been suggested that the degree to which post-ACS depression is associated with cardiovascular prognosis may be related to the nature and timing of the depressive episode [7–11], including whether the depressive episode is first-ever or recurrent, and whether its onset is before or after the acute event. It was hypothesized that recurrent depressive episodes are associated with worse cardiovascular prognosis than first-ever depressive episodes [7, 8], which was plausible because accumulating exposure to depression may be more harmful than first-ever exposure to depression. The first study that reported data on patients with first versus recurrent depression was published by Lespérance et al. [7] in 1996. In that study, 6 of 15 MI patients with recurrent depression died by 18 months after MI (40%) compared to 2 of 20 MI patients with first episodes during their index hospitalization (10%). A study by Grace et al. [8] almost 10 years later, on the other hand, found depressed ACS patients who reported no history of depressed mood to be at higher risk of mortality 5 years after the index ACS (31 of 130, 24%) compared to those reporting a history of depressed mood (15 of 105, 14%). In addition to depression recurrence, timing of depression onset (i.e. before or after ACS) has been reported to be related to cardiovascular outcomes. Worse cardiovascular outcomes were reported for patients with post-MI onset or incident (i.e. first-ever and with an onset after the MI) depressive episodes compared to patients with pre-MI onset or nonincident episodes [9, 10]. Post-ACS onset and in particular incident depression may therefore be a distinct subtype of depression with the unique feature that it may be triggered by the acute event. As a result, this subtype may specifically be associated with worse cardiovascular prognosis.

The objective of the present systematic review was to evaluate whether subgroups of depressed ACS patients are at different risk of subsequent cardiac events or mortality, depending on whether the depressive episode is first or recurrent or whether its onset is before or after the cardiac event. To this end, 3 subgroup comparisons were examined, depending on whether the post-ACS depressive episode (1) was first-ever or recurrent, (2) had an onset before or after the cardiac event, or (3) was incident or nonincident (fig. 1).

Methods

Search Strategy

MEDLINE, EMBASE and PsycINFO were systematically searched from inception to April 11, 2009. Search strings included appropriate MeSH/EMTREE terms and free text words for cardiovascular disease, depression and possible cardiovascular outcomes (i.e. 'mortality' and 'event'). In addition, a manual search of reference lists from all articles selected for full-text review, relevant reviews and tables of contents of 34 selected journals from May 1, 2008, to April 11, 2009, was done. E-mails were sent to authors of included studies, as well as authors of 4 key trials [12–15] on antidepressant treatment in cardiac patients, to query about the possible existence of other published or unpublished eligible studies. Translators were used to evaluate non-English titles/abstracts and articles as necessary.

Study Selection

From selected abstracts, all prognostic studies or randomized controlled trials (RCTs) with data on the relationship between post-ACS depression or depressive symptoms and cardiovascular outcomes (i.e. mortality, cardiovascular mortality, recurrent cardiac events) were selected for full-text review. From these, 2 investigators independently selected papers that were eligible for inclusion. Cohen's κ was calculated to assess chance-corrected agreement. Any disagreements were resolved by consensus.

Eligible articles included studies in any language (1) that were prospective cohort studies or prospective controlled studies (including RCTs), (2) that reported data on patients with ACS (MI and/or unstable angina), (3) that assessed the presence of post-ACS depression with a validated clinical interview [for example the Composite International Diagnostic Interview (CIDI) or the Diagnostic Interview Schedule] or depressive symptoms with an established cutoff level on a validated questionnaire [such as the Beck Depression Inventory (BDI) or the 9-item Patient Health Questionnaire) within 3 months after the index event, (4) that included cardiovascular outcomes, defined as all-cause mortality, cardiovascular mortality or recurrent cardiac events, that occurred after the assessment of post-ACS depression and were assessed for a period of at least 6 months after the depression assessment, (5) that provided data on outcomes for subgroups of depressed ACS patients with (a) recurrent versus first-ever episodes, (b) pre-ACS versus post-ACS onset episodes, and/or (c) incident versus nonincident episodes, and (6) that included at least 10 patients with the cardiovascular outcome of interest.

Data Extraction and Quality Assessment

From the eligible articles, 2 authors independently extracted information about study cohorts, depression measurement and outcome measures. Any discrepancies were resolved by consensus. In some cases, data on study characteristics were retrieved from other articles reporting on the same study sample. Some studies reported outcomes for 1 or 2, but not all 3 subgroup comparisons. If from the study methods it appeared that data were available for the missing subgroup comparison(s), the authors were asked to provide additional data on the missing subgroups.

For each subgroup comparison in each study an unadjusted odds ratio (OR) with a 95% confidence interval (CI) was calculated to reflect the differential risk of the cardiovascular outcome based on subgroup definitions. Because some studies may be too small to find an increased risk for one subgroup over the other that would reach statistical significance, we did not only consider a statistically significant increased risk, but also 'potentially' increased risk as relevant. Because with binary outcomes the magnitude of an OR varies with the prevalence of the outcome, there is no agreed-upon standard for a certain OR to be considered clinically relevant [16]. We considered substantive differential risk to be potentially present between subgroups when OR >1.4 or <0.7, regardless of statistical significance. Only unadjusted results were used, because of the small numbers of patients in each subgroup with the outcome [17–19] and because each study used different control variables, which limited the ability to compare multivariable results. The following characteristics were extracted as possible confounders in order to evaluate whether they differed substantively between subgroups: age, gender, left ventricular ejection fraction, Killip class, history of MI, score on the BDI at baseline, smoking, body mass index, the presence of diabetes and use of antidepressants. When these characteristics were not described separately for subgroups in the article, the authors were asked to provide them. Whether these characteristics differed significantly between subgroups was evaluated with an independent-sample t test for continuous variables and a χ^2 test for dichotomous variables. Because of the small number of included studies, no funnel plot was made to explore possible publication bias.

To assess the quality of the included studies, 2 investigators independently rated each study on 11 criteria that were generated based on a review by Altman [20]. It should be noted that the ratings reflect the quality of each study relative to our key questions rather than the general quality of the study per se.

The search strings, the list of relevant reviews and selected journals that were used with the literature search, the variables that were extracted from the articles and the quality criteria that were used can be requested from the corresponding author.

Results

Search Strategy and Selection of Articles

The literature search yielded 1,977 unique abstracts. Of these, 104 articles were selected for full-text review. An additional 11 articles were identified for full-text review from manual searching, references of relevant reviews or references of articles identified for full-text review. Of these, 4 articles were found to be eligible for inclusion [8, 9, 21, 22], and 111 were excluded (fig. 2). Cohen's κ for interrater agreement was 0.88. In addition, our survey of study authors led to the identification of 2 more studies meeting all eligibility criteria that were therefore included as well. The first was an article by Glassman et al. [23] concerning the SADHART (Sertraline Antidepressant Heart Attack Randomized Trial) study that was in press at the time the searches were conducted. The second came from an analysis of data of the MIND-IT (Myocardial Infarction and Depression Intervention Trial) study

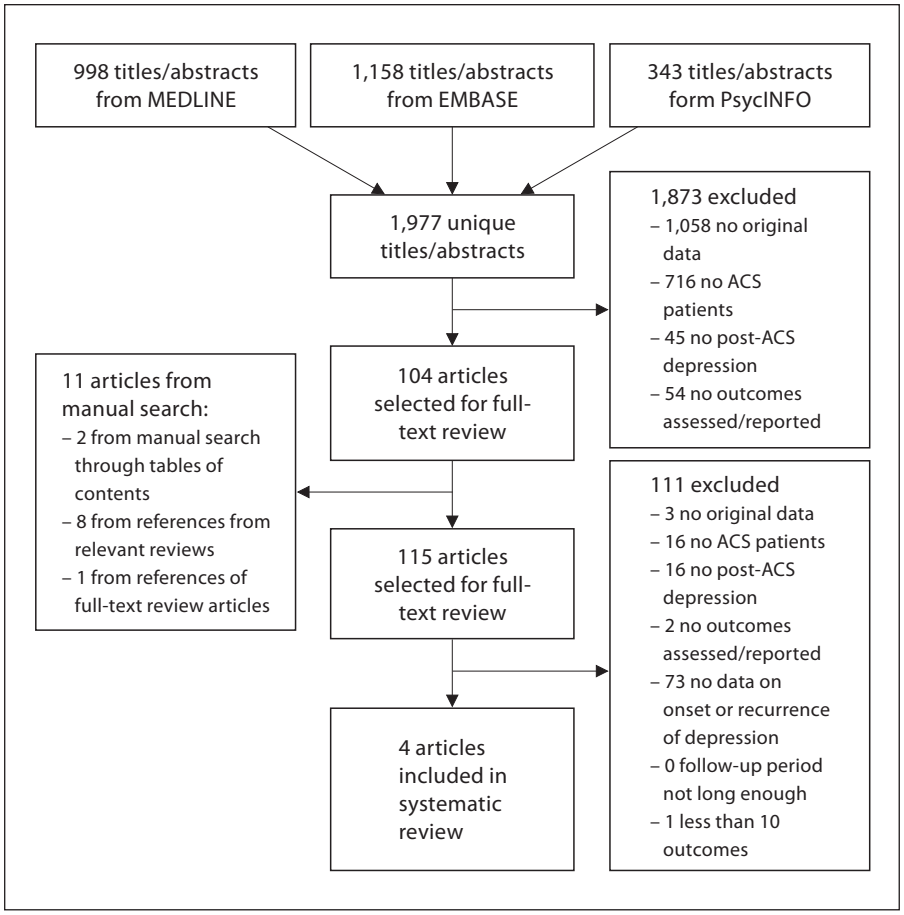

Fig. 2. Flow diagram of the search.

[14], which was presented in a letter to the editor that was in press at the time the searches were conducted [24].

Retrieval of Additional Subgroup Information on Outcomes and Baseline Characteristics

All 6 included studies reported outcomes for patients with first versus recurrent depressive episodes. Four of these reported also outcomes for patients with pre-ACS versus post-ACS onset and incident versus nonincident depression. For ENRICHD (Enhancing Recovery in Coronary Heart Disease) [22], all information for the subgroups on cardiac outcomes and baseline characteristics could be derived from the article. For the study of Grace et al. [8], the authors provided original data on subgroup characteristics. For SADHART [23] outcomes for patients in all subgroups could be derived from the article, an additional article [25], and additional data on subgroup characteristics were provided by the authors. Parker et al. [21] reported in their article only outcomes for patients with incident, nonincident and post-ACS onset depression. The authors provided original data to also determine outcomes for patients with first, recurrent and pre-ACS onset depression, as well as data on baseline characteristics for subgroups. De Jonge et al. [9, 26] reported in the original article outcomes for patients with incident versus nonincident depression at 3 or 12 months after the MI. In the present systematic review only patients diagnosed as having depression 3 months after the MI were included. Information on outcomes and baseline characteristics for subgroups of patients with first, recurrent, pre-MI onset, post-MI onset, incident and nonincident depression were retrieved from the original data. In this study, the CIDI [27] was used to assess the presence of an ICD-10 post-MI depressive episode. Information about whether the onset of the depressive episode was before or after the MI was obtained by extending the CIDI with additional questions about the presence of each of the depressive symptoms in the 4 weeks before and the period after the MI. Outcomes were counted only if they occurred after depression assessment. For MIND-

IT, a published letter presented outcomes for patients with first versus recurrent depression in a small subgroup of the MIND-IT sample that received pharmacological treatment for depression [24]. In the present systematic review all randomized MI patients from MIND-IT who were diagnosed as having depression 3 months after the MI were included. Information on outcomes and characteristics for all subgroups was retrieved from the original data. As in the de Jonge study [9], information about whether the onset of the depressive episode was before or after the MI was obtained by extending the CIDI with additional questions. Outcomes were counted only if they occurred after depression assessment.

Study Characteristics

Study characteristics and the association of different subgroups with cardiovascular outcomes for the 6 included studies are shown in table 1. In some cases, study characteristics were retrieved from additional articles about the same sample [12, 14, 25, 26, 28]. In the study of Parker et al. [21], all patients with a first episode had incident depression and all patients with nonincident depression had a recurrent episode. This resulted in the same risk estimates for those 2 subgroup comparisons, which is consistent with an overlap of 100% between subgroups. Apart from this example, for the 4 studies that presented data on multiple subgroup comparisons, the percentage of patients with a given classification that were also classified in another group (e.g. post-ACS onset and incident depression) ranged from 41 to 90%.

Association of Subgroups with Cardiovascular Outcomes and Demographical, Medical and Behavioral Characteristics

Table 2 shows the ORs with 95% CIs for cardiac outcomes for each of the subgroup comparisons. Supplementary tables 1, 2 and 3, which can be requested from the corresponding author, show for each subgroup data on age, sex, LVEF, Killip class, history of MI, BDI score at hospitalization or within 30 days after the acute event, smoking status, body mass index, the presence of diabetes mellitus and antidepressant use.

First-Ever versus Recurrent Depressive Episodes

All 6 studies reported cardiac outcomes for ACS patients with first-ever versus recurrent depressive episodes. In one of these, patients with a first-ever depressive episode were found to be at significantly increased risk of worse cardiac outcomes (i.e. $p < 0.05$). In 2 of the other studies, patients with first-ever depression were found to be at potentially increased risk (i.e. OR >1.4, but $p > 0.05$). In the other 3 studies, no association was found (table 2). Only minor differences in baseline characteristics between patients with a first-ever and a recurrent depressive episode that were consistent across studies could be identified: compared to patients with a recurrent depressive episode, patients with a first-ever depressive episode had lower BDI scores, they were somewhat older and less likely to be smokers and to have a history of MI or diabetes.

Post-ACS Onset versus Pre-ACS Onset Depressive Episodes

In 4 of the 6 studies cardiac outcomes were reported for ACS patients with post-ACS onset versus pre-ACS onset depression. In one of these studies patients with post-MI onset depression were found to be at significantly increased risk of worse cardiac outcomes than those with pre-MI onset depression. In 2 of the others, patients with post-ACS onset depression were found to be at potentially increased risk of worse cardiac outcomes compared to those with pre-ACS onset depression (OR >1.4, $p > 0.05$). In contrast, the fourth study found patients with pre-ACS onset depression to be at potentially increased risk of worse outcomes compared to those with post-ACS onset depression (OR <0.7 for patients with post-ACS onset depression, $p > 0.05$; table 2). Patients with pre-ACS onset depression tended to have higher BDI scores, and were more likely to have a history of MI and to be on antidepressants, but none of the other baseline characteristics differed consistently across studies between patients with pre-ACS and post-ACS onset depression.

Incident versus Nonincident Depressive Episodes

Four of the 6 included studies reported outcomes for patients with incident versus nonincident depression. Two of these reported a potentially increased risk of worse outcomes for patients with incident depression (OR >1.4, $p > 0.05$). The 2 other studies found no association between incident versus nonincident depression and cardiac outcomes (table 2). Patients with nonincident depression tended to have higher BDI scores and were more likely to have a history of MI, but none of the other baseline characteristics differed consistently across studies between patients with incident and nonincident depression.

Quality of Studies

An overview of the quality of the included studies can be requested from the corresponding author. Out of the 11 criteria, the number of criteria with good ratings var-

Table 1. Study characteristics and outcomes for studies reporting associations between recurrence and onset of post-ACS depression and cardiovascular prognosis

Authors and study site	Population	Definition of post-ACS depression	How and when was depression and its recurrence/onset assessed?
First versus recurrent			
Grace et al., 2005 Canada	750 ACS patients	Symptoms (BDI ≥10)	BDI during hospitalization: history of depression assessed with single question
De Jonge et al., 2006 The Netherlands	442 MI patients[1]	Current ICD-10 depressive episode	CIDI 3 months after MI + extension to assess onset of depression relative to MI
Parker et al., 2008 Australia	467 ACS patients	Depressive symptoms on DSM-IV checklist	CIDI within a mean of 3.8 days after ACS + DSM-IV symptom checklist 4 weeks after ACS
ENRICHD USA	920 depressed MI patients	Current episode MDD (DSM-IV)	DISH within 28 days after MI
SADHART USA, Canada, Europe, Australia	369 depressed ACS patients	Current episode MDD (DSM-IV)	DIS within 30 days of MI or hospitalization for unstable angina
MIND-IT The Netherlands	258 depressed MI patients	Current ICD-10 depressive episode and BDI ≥10	CIDI 3 months after MI + extension to assess onset of depression relative to MI
Post-ACS onset versus pre-ACS onset			
De Jonge et al., 2006 The Netherlands	442 MI patients[1]	Current ICD-10 depressive episode	CIDI 3 months after MI + extension to assess onset of depression relative to MI
Parker et al., 2008 Australia	467 ACS patients	Depressive symptoms on DSM-IV checklist	CIDI within a mean of 3.8 days after ACS + DSM-IV symptom checklist 4 weeks after ACS
SADHART USA, Canada, Europe, Australia	369 depressed ACS patients	Depressive symptoms on DSM-IV checklist	DIS within 30 days of MI or hospitalization for unstable angina
MIND-IT The Netherlands	258 depressed MI patients	Current ICD-10 depressive episode and BDI ≥10	CIDI 3 months after MI + extension to assess onset of depression relative to MI
Incident versus nonincident			
De Jonge et al., 2006 The Netherlands	442 MI patients[1]	Current ICD-10 depressive episode	CIDI 3 months after MI + extension to assess onset of depression relative to MI
Parker et al., 2008 Australia	467 ACS patients	Depressive symptoms on DSM-IV checklist	CIDI within a mean of 3.8 days after ACS + DSM-IV symptom checklist 4 weeks after ACS
SADHART USA, Canada, Europe, Australia	369 depressed ACS patients	Current episode MDD (DSM-IV)	DIS within 30 days of MI or hospitalization for unstable angina
MIND-IT The Netherlands	258 depressed MI patients	Current ICD-10 depressive episode and BDI ≥10	CIDI 3 months after MI + extension to assess onset of depression relative to MI

DIS = Diagnostic interview schedule; DISH = depression interview and structured Hamilton; DSM-IV = diagnostic and statistical manual of mental disorders, fourth edition; ICD-10 = international classification of diseases-10; MDD = major depressive disorder; NA = not applicable; OR = odds ratio.

[1] For de Jonge et al., 442 patients were included instead of the 468 patients mentioned in their article. The 26 patients that were excluded from the present analysis were only interviewed at 12 months after MI and not at 3 months after MI.

Table 1 (continued)

	Follow-up period (start-end)	Outcome	Reference group and number of events[2]	Subgroup and number of events	Subgroup and number of events
First versus recurrent				*First*	*Recurrent*
Grace et al., 2005 Canada	0–5 years after ACS	All-cause mortality	69/515 (13.4%)	31/130 (23.8%)	15/105 (14.3%)
De Jonge et al., 2006 The Netherlands	3–54 months after MI (mean duration 18 months)	New cardiac events	87/370 (23.5%)	12/52 (23.1%)	4/20 (20.0%)
Parker et al., 2008 Australia	1–12 months after ACS	Recurrent ACS, cardiac mortality	57/372 (15.3%)	8/25 (32.0%)	12/50 (24.0%)
ENRICHD USA	0–48 months after MI (median duration 29 months)	(1) All-cause mortality (2) Cardiovascular mortality	(1) 14/408 (3.4%) (2) 10/408 (2.5%)	(1) 68/370 (18.4%) (2) 41/370 (11.1%)	(1) 65/550 (11.8%) (2) 42/550 (7.6%)
SADHART USA, Canada, Europe, Australia	Start within 44 days after ACS: median duration 6.7 years	All-cause mortality	NA	36/176 (20.5%)	39/183 (21.3%)
MIND-IT The Netherlands	3–18 months after MI	Cardiac-related readmissions	Outcomes not assessed	58/206 (28.2%)	15/52 (28.8%)
Post-ACS onset versus pre-ACS onset				*Post-ACS*	*Pre-ACS*
De Jonge et al., 2006 The Netherlands	3–54 months after MI (mean duration 18 months)	New cardiac events	87/370 (23.5%)	14/47 (29.8%)	2/25 (8.0%)
Parker et al., 2008 Australia	1–12 months after ACS	Recurrent ACS, cardiac mortality	57/372 (15.3%)	15/46 (32.6%)	5/29 (17.2%)
SADHART USA, Canada, Europe, Australia	Start within 44 days after ACS: median duration 6.7 years	All-cause mortality	NA	30/170 (17.6%)	45/189 (23.8%)
MIND-IT The Netherlands	3–18 months after MI	Cardiac-related readmissions	Outcomes not assessed	53/170 (31.2%)	20/88 (22.7%)
Incident versus nonincident				*Incident*	*Nonincident*
De Jonge et al., 2006 The Netherlands	3–54 months after MI (mean duration 18 months)	New cardiac events	87/370 (23.5%)	10/33 (30.3%)	6/39 (15.4%)
Parker et al., 2008 Australia	1–12 months after ACS	Recurrent ACS, cardiac mortality	57/372 (15.3%)	8/25 (32.0%)	12/50 (24.0%)
SADHART USA, Canada, Europe, Australia	Start within 44 days after ACS: median duration 6.7 years	All-cause mortality	NA	16/90 (17.8%)	59/269 (21.9%)
MIND-IT The Netherlands	3–18 months after MI	Cardiac-related readmissions	Outcomes not assessed	39/130 (30.0%)	34/128 (26.6%)

[2] Reference group for Grace et al. were patients with BDI <10, for ENRICHD patients with no current MDD episode assessed with DISH + BDI <10, + no previous MDD, for de Jonge et al. no post-MI ICD-10 depressive episode on CIDI at the assessment at 3 months after the MI, for Parker et al. no depression according to DSM-IV checklist 4 weeks after ACS, for SADHART and MIND-IT there was no reference group.

Table 2. Odds ratios for cardiovascular outcomes for the different subgroup comparisons

Author (n with outcome assessed)	OR for first versus recurrent	OR for post-ACS versus pre-ACS onset	OR for incident versus nonincident
Grace et al. (n = 235)	1.88 (0.95–3.71)[3]		
De Jonge et al. (n = 72)	1.20 (0.34–4.28)	4.88 (1.01–23.55)[2]	2.39 (0.76–7.50)[3]
Parker et al. (n = 75)	1.49 (0.52–4.31)[3]	2.32 (0.74–7.29)[3]	1.49 (0.52–4.31)[3]
ENRICHD (n = 920)[1]	(1) 1.68 (1.16–2.43)[2] (2) 1.51 (0.96–2.37)[3]		
SADHART (n = 359)	0.95 (0.57–1.58)	0.69 (0.41–1.15)[3]	0.77 (0.42–1.42)
MIND-IT (n = 258)	0.97 (0.49–1.89)	1.54 (0.85–2.79)[3]	1.19 (0.69–2.04)

Figures in parentheses are 95% CI. ACS = Acute coronary syndrome; CI = confidence interval; OR = odds ratio.

[1] Outcomes evaluated for ENRICHD were (1) all-cause mortality and (2) cardiovascular mortality (for both outcomes, the number of patients with the outcome assessed was n = 920).

[2] Differential risk: significant at the $p < 0.05$ level.

[3] Potential differential risk: i.e. OR > 1.40 or OR < 0.70, but not statistically significant ($p > 0.05$).

ied between the 5 and 8 for the 6 included studies. Three of the studies were RCTs, whereas the other 3 were observational studies. In all studies, well-defined and appropriate inclusion and exclusion criteria were used. For 1 study it was clear that at least 70% of the eligible patients completed baseline data. For 2 studies this was <70%, and for the 3 RCTs this was not reported because of the different study design. In all studies, complete follow-up data were present for at least 70% of the patients with complete baseline data. Only 1 study provided information about nonparticipants. All, except 1, were multicenter studies. Two studies had <25 patients with the outcome, 1 between 25 and 50 and 3 >50. In 3 studies patients were recruited from a consecutive series of clinic admissions or appointments. In 4 studies post-ACS depression was assessed with a clinical interview (2 studies used the CIDI, 1 study the Depression Interview and Structured Hamilton and 1 study the Diagnostic Interview Schedule). In all studies the outcomes were assessed thoroughly and reliably, and in at least 5 studies the outcome assessors were blind to the subgroup status. There was no differential loss to follow-up in any of the studies (loss to follow-up occurred only in 0–4% of the patients).

Discussion

This is the first systematic review evaluating cardiac prognosis for subgroups of depressed ACS patients. Of the 14 total comparisons included in the review, only 2 reported a statistically significant ($p < 0.05$) association between recurrence or onset of depression with cardiovascular outcomes. Because of the inconsistent findings from the studies reviewed, at this time no firm conclusion can be drawn about whether or not first-ever, post-ACS onset and incident depression are related to cardiac prognosis.

There are some considerations that need to be taken into account when interpreting these results. The first consideration is that the number of identified studies is only a small proportion of the total number of studies that have evaluated the impact of post-ACS depression on cardiac prognosis. It is not clear to what degree the set of identified studies is representative of all studies that have been conducted on post-ACS depression and cardiac prognosis. The second consideration is that there were substantial differences between the reviewed studies that may have resulted in the inconsistent findings. Differences in assessment of post-ACS depression may have led to the inclusion of different patient groups. In addition, within the time frame of 3 months after the acute event studies differed in timing of depression assessment. A meta-analysis [29] found that depression assessed within 2 weeks after the cardiac event was less strongly associated with cardiac prognosis than depression assessed later than 2 weeks after the cardiac event. In the reviewed studies, however, timing of depression assessment did not seem to have affected the results. Most studies assessed recurrence and timing of onset of the depressive episode differently, and all evaluated it retrospectively, which is prone to recall bias [30]. This potentially affected the reli-

ability of subgroup classification. Three studies assessed all-cause mortality over long follow-up periods, whereas the other 3 evaluated new cardiovascular events over shorter follow-up periods. A meta-analysis [29] showed that the effect of depression on cardiac prognosis is stronger when using cardiovascular mortality as an outcome compared to all-cause mortality, but that the length of the follow-up period did not matter in this association. In the reviewed studies the risk of worse prognosis for subgroups of depressed ACS patients did not seem to be affected by the outcome measure or follow-up length. A third consideration is that 2 of the 6 studies only evaluated 1 of the three subgroup comparisons [8, 22]. The 3 subgroup comparisons are not independent of each other due to the high percentage of patients classified in multiple groups (e.g. post-ACS and incident). A fourth consideration is the quality of the included studies. Not all quality criteria were met by all studies. Three of the included studies were RCTs on antidepressant treatment and 3 were prospective cohort studies. However, in all 3 RCTs the intervention had no effect on cardiovascular prognosis, so the associations investigated in the present systematic review are not likely to be affected by the intervention. Two studies had relatively small numbers of patients with the key outcomes, increasing the chance of spurious findings. Although in the reviewed studies the follow-up rates from baseline were very high, in at least 2 studies <70% of the eligible patients had complete baseline data and in at least 2 of the 6 included studies patients were not recruited consecutively. Only 1 study provided information about nonparticipants, who were more likely to be female, less likely to be married and on average 7 years older than the participants [8]. The findings from the included studies may therefore not apply to all ACS patients. A fifth consideration is that psychological distress in patients with a somatic illness is difficult to assess. In order to diagnose and treat medically ill patients with psychological distress properly it is essential to understand many factors that go beyond DSM-IV, such as the patients' life history, temperament and health-related behaviors [31]. This inadequacy in diagnostic assessment has been suggested to be the cause of the often inconsistent results in psychosomatic studies [32] and may have contributed to the inconsistent findings of the studies included in this review.

The inconsistent findings across studies and the inability to draw firm conclusions might lead to the suggestion that there is little reason to continue to investigate the relative association of post-ACS depression subgroups with cardiac prognosis. Alternatively, we would argue that this question merits further investigation. There are important limitations in the existing literature in this area, and the question of whether subgroups of depressed ACS patients have worse cardiac outcomes compared to other subgroups is an important one. It has been argued, for instance, that assessments of depression among patients with heart disease may reflect worse underlying heart disease or comorbid conditions beyond what is effectively quantified through covariate adjustment [33, 34]. A better understanding of whether certain subtypes of post-ACS depression are qualitatively different from other subtypes would be helpful to understand the overall relationship between depression and cardiovascular outcomes.

No firm consistent pattern of demographical and clinical differences between subgroups was found. The minor differences that were found are very unlikely to underlie the (potentially) increased risk associated with first-ever, post-ACS onset and incident depression in the reviewed studies [8, 9, 21, 22]. Some of the studies adjusted for confounding variables in the originally published reports and concluded that the increased risk of worse outcome for some subgroups was independent from these characteristics. However, the number of patients in most of these studies was too small to effectively use multivariable methods. Furthermore, adjustment for confounders is often imprecise and incomplete. Associations found in studies are often confounded by unmeasured or poorly measured variables, and sometimes even key cardiac variables are, surprisingly, not found to relate to prognosis [33, 35–37]. Therefore, it cannot be ruled out that the differential risk of worse outcome between subgroups found by some of the studies is caused by subgroup imbalances in some measured or unmeasured patient characteristics, such as a severer underlying coronary artery disease [38, 39] or a deteriorating health status. This may also underlie the increased risk of worse prognosis that is found for cardiac patients with somatic rather than cognitive symptoms of depression [3, 40, 41], and ACS patients with persisting or increasing depressive symptoms and treatment-resistant depression [5, 6, 23, 42, 43]. MI patients with persisting depressive symptoms report worse physical health 12 months after the MI [44], supporting that a deteriorating health status may indeed underlie the association with worse prognosis. Some depressed ACS patients may have 'vascular depression': a type of depression caused by vascular damage in the brain due to atherosclerosis [45]. Recently, an association was found between depressive symptoms persisting up till 3 months after ACS and cerebrovascular lesions [46].

Taken together, there may be confounding between depression, somatic health and cardiovascular outcomes.

Major depression according to DSM-IV criteria is heterogeneous and associated with other psychological constructs, such as hostility and demoralization [47, 48]. Subtypes of depression are proposed to exist that differ in etiology, manifestation and are responsive to different kinds of antidepressant treatment [49]. The existence of different subtypes of depression in cardiac patients could explain why some subgroups of depressed cardiac patients have worse prognosis than others. In addition, if these subtypes are responsive to different kinds of antidepressant treatment, this could explain why RCTs on antidepressant treatment in depressed cardiac patients found in general only modest effects in improving depression and no effects in improving cardiovascular prognosis. The identification of subgroups of depressed cardiac patients with different etiology of the depression and different risk of worse prognosis could therefore help in the development of more individually targeted antidepressant treatments for depressed cardiac patients.

In summary, the findings of studies evaluating differential risk of worse cardiac outcomes for subgroups of depressed ACS patients depending on recurrence and onset of the depressive episode are inconsistent. Major methodological differences between the studies may explain the inconsistencies. It is possible that relationships between these subtypes of post-ACS depression and cardiac outcomes reported by some studies [8, 9, 21, 22] reflect ≥1 underlying risk factors, such as coronary artery disease severity at baseline, a deteriorating health status or 'vascular depression'. These underlying risk factors may also cause the increased risk for patients with persistent and treatment-resistant depression and somatic symptoms of depression found in other studies [3, 5, 6, 23, 40–42]. Identifying high-risk subgroups of depressed ACS patients and possibly underlying risk factors is important for understanding the overall relationship between depression and cardiac prognosis and may potentially lead to the development of more individually targeted interventions.

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