AHA Scientific Statement

Depression as a Risk Factor for Poor Prognosis Among Patients With Acute Coronary Syndrome: Systematic Review and Recommendations
A Scientific Statement From the American Heart Association

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Background—Although prospective studies, systematic reviews, and meta-analyses have documented an association between depression and increased morbidity and mortality in a variety of cardiac populations, depression has not yet achieved formal recognition as a risk factor for poor prognosis in patients with acute coronary syndrome by the American Heart Association and other health organizations. The purpose of this scientific statement is to review available evidence and recommend whether depression should be elevated to the status of a risk factor for patients with acute coronary syndrome.

Methods and Results—Writing group members were approved by the American Heart Association's Scientific Statement and Manuscript Oversight Committees. A systematic literature review on depression and adverse medical outcomes after acute coronary syndrome was conducted that included all-cause mortality, cardiac mortality, and composite outcomes for mortality and nonfatal events. The review assessed the strength, consistency, independence, and generalizability of the published studies. A total of 53 individual studies (32 reported on associations with all-cause mortality, 12 on cardiac mortality, and 22 on composite outcomes) and 4 meta-analyses met inclusion criteria. There was heterogeneity across studies in terms of the demographic composition of study samples, definition and measurement of depression, length of follow-up, and covariates included in the multivariable models. Despite limitations in some individual studies, our review identified generally consistent associations between depression and adverse outcomes.

Conclusions—Despite the heterogeneity of published studies included in this review, the preponderance of evidence supports the recommendation that the American Heart Association should elevate depression to the status of a risk factor for adverse medical outcomes in patients with acute coronary syndrome.

Key Words: AHA Scientific Statements ■ acute coronary syndrome ■ coronary heart disease ■ depression ■ risk factors

Depression and elevated depressive symptoms are common among the estimated 15.4 million US adults with coronary heart disease (CHD).[1] Approximately 20% of patients hospitalized for an acute coronary syndrome (ACS; myocardial infarction [MI] or unstable angina [UA]) meet the American Psychiatric Association's *Diagnostic and*

Statistical Manual of Mental Disorders (DSM) criteria for major depression, and an even larger percentage show subclinical levels of depressive symptoms.[2–4] By comparison, ≈4% of the general US adult population meets the criteria for major depression at any given time.[5] Numerous prospective studies, systematic reviews, and meta-analyses have shown a robust association between depression (major depression or elevated depressive symptoms) and increased morbidity and mortality after ACS.[3,4,6–11] However, depression has not yet achieved formal recognition as a risk factor for poor prognosis after ACS by national health organizations.

The goal of this scientific statement is to review current evidence on the role of depression as a risk factor for adverse medical outcomes among adults recovering from ACS in order to make a recommendation as to whether depression should be elevated to the status of a risk factor among patients with ACS by the American Heart Association (AHA). Guidelines for assessing a risk factor include the presence of an objective outcome measure; prospective designs; evidence of a strong, consistent association between the risk factor and outcome; evidence that the risk factor is not explained by other variables or covariates linked to both the risk factor and outcomes; and the existence of a plausible biological mechanism to account for the observed relationship.[12–14] To formulate our recommendations, we examined the strength, consistency, independence, and generalizability of the findings in a set of carefully selected studies of 3 outcomes: (1) all-cause mortality, (2) cardiac mortality, and (3) composite outcomes that included mortality and nonfatal events. In addition, this Writing Group sought to identify important areas for future research that may further our understanding of the relationship between depression and ACS.

Writing Group members were nominated by the committee co-chairs on the basis of their previous work in relevant topic areas and were approved by the AHA Scientific Statement Oversight Committee and the AHA Manuscript Oversight Committee. All members of the Writing Group had the opportunity to comment on and approve the final version of this document. The document subsequently underwent extensive AHA internal peer review, including Council Leadership review and Scientific Statement Oversight Committee review, before approval by the AHA Science Advisory and Coordinating Committee.

Literature Search Strategy

To identify relevant peer-reviewed studies, we updated previous systematic reviews[10,14–17] to include publications through July 24, 2011. We searched the MEDLINE, Current Contents, and PsycINFO databases for combinations of the following terms:

1. Coronary heart disease, coronary artery disease, ischemic heart disease, myocardial infarction, unstable angina, acute coronary syndrome, coronary bypass surgery, atherosclerosis, sudden death, ventricular fibrillation, ventricular tachycardia, or heart failure
2. Mortality, survival, or prognosis
3. Depression, depressive symptoms, dysthymia, mood, or depressive disorder

The articles were limited to English language publications. The search yielded 1559 unique citations. We restricted our review to studies of patients recovering from ACS and those meeting the following additional inclusion criteria adapted from Kuper et al[17] and Frasure-Smith and Lespérance[10,14,15]: (1) They used a prospective design, (2) included ≥100 patients, (3) used established assessment instruments to define major depression or depressive symptoms (studies that identified depression on the basis of antidepressant treatment, self-reported treatment of depression, single-item measures, study-specific measures, or nonspecific distress screening indices were excluded), and (4) reported all-cause mortality, cardiac mortality, or a combination of either of these mortality outcomes and nonfatal events. We excluded studies that did not have a nondepressed comparison sample or that focused on the comparison of particular subtypes of depression or patterns of depressive symptoms.

A minimum of 2 Writing Group members independently reviewed the titles and abstracts of each of the 1559 citations identified by the search and the 92 studies reviewed previously by Kuper et al[17] and Frasure-Smith and Lespérance[10,14,15]; a total of 1509 citations were excluded on the basis of the predefined inclusion criteria (Figure). The full-text publications of the remaining 142 potentially eligible studies were reviewed in detail, which resulted in the exclusion of 89 additional studies. Data were abstracted from the final 53 studies by use of a standardized form that included study objective, design, data source, geographic location, and time period; sample size, definition of population/cohort, and patient characteristics; depression measurement instrument and definition, timing of the interview/questionnaire, and depression prevalence; outcome definition, length of follow-up, and number of events; covariates included in risk-adjusted models; and results and conclusions. For each of the included 53 publications, 1 Writing Group member abstracted the data and a second reviewed the data for completeness and accuracy. Disagreements were resolved by consensus.

We also conducted a systematic review to identify published meta-analyses of the relationship between depression and outcomes among patients with ACS or other CHD diagnoses. We followed the same search strategy as above, adding the following set of search terms: "quantitative review" or meta-analy* (using * for truncation). This search yielded 65 unique citations, including 4 meta-analyses relevant to our review.

Findings

A total of 53 studies met the criteria for inclusion in the present review; 32 studies reported on associations with all-cause mortality, 12 on associations with cardiac mortality, and 22 on associations with a composite outcome that included mortality and nonfatal events. These outcome groupings are not mutually exclusive. Details of the 53 studies are presented by study characteristics and by outcome type. Methodological characteristics varied across studies in terms of the selection of depression measures, outcome definitions, and covariates included in models (Table 1). The majority of studies, regardless of outcome,
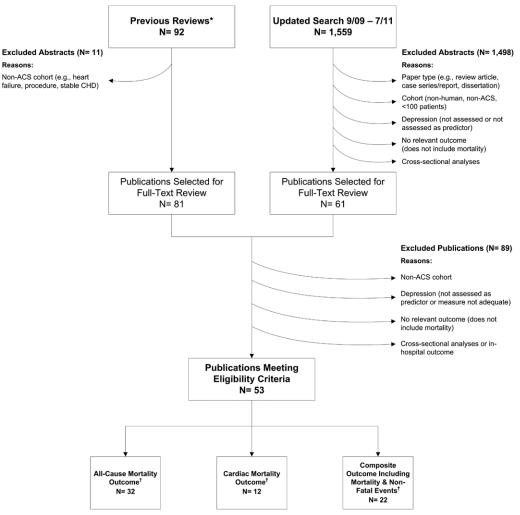
Figure. Selection of publications for abstraction. ACS indicates acute coronary syndrome; CHD, coronary heart disease. *Previous reviews included the following: Frasure-Smith and Lespérance,[10,14,15] Kuper et al,[17] and Hemingway and Marmot.[16] †Outcome categories are not mutually exclusive.

included ≥25 depressed patients in their sample, had no more than 20% of participants lost to follow-up, and adjusted for potential confounding factors. Self-report measures of depression were more common than structured or semistructured interviews, with the Beck Depression Inventory-I (BDI-I) being the most commonly used measure. Most studies assessed depression as a primary predictor of outcomes rather than merely including it as a covariate, although some of the cohorts were not specifically developed for the purpose of assessing the relationship of depression to ACS outcomes. Depression was assessed on a continuous scale in approximately half of the studies that examined all-cause and cardiac mortality outcomes; this was somewhat less common in studies that assessed a composite outcome. Few studies used troponin levels in their definition of ACS, most likely because data collection occurred before the adoption of troponin as a criterion for diagnosis. Outcome events were adjudicated independently, and adequate definitions of outcomes were provided in most analyses of all-cause mortality or cardiac mortality; the quality of the outcome definitions was more varied for composite outcomes. A more detailed discussion of selected studies and results is provided below according to the specific outcome category.

Depression and All-Cause Mortality

The 32 studies that included all-cause mortality as an outcome (Tables 1 and 2)[18–49] reported on 22 unique ACS patient cohorts. These studies included patients from 9 countries on 3 continents (North America, Europe, and Asia), with sample sizes ranging from 100[25] to 21 745[18] patients. Twenty-four studies included only patients who presented with MI,* 6 included patients with any form of ACS,[24,26,29,38,46,49] 1 included only patients presenting with UA,[34] and 1 included patients presenting with MI complicated by congestive heart failure.[47] Fifteen measures of depression were evaluated as potential predictors of all-cause mortality. Self-report questionnaires were used to assess depressive symptoms in nearly all of these studies, with the BDI-I used in 20 studies. Less than half of the studies included structured or semistructured diagnostic interviews for depression.† In most studies, the assessment of depression occurred during or within a few weeks after the index hospital admission. However, 3 studies measured depression before the ACS event,[18,19,47] and 2 included a measure of depression 1 year after the event.[33,35] The maximum

*References 18–23, 25, 27, 28, 30–33, 35–37, 39–45, 48.
†References 18, 20–23, 25, 28, 29, 33, 34, 36, 39, 49.

Table 1.   Comparison of Study Characteristics by Outcomes

	All-Cause Mortality (n=32)	Cardiac Mortality (n=12)	Composite Outcome (n=22)
Study sample			
Total sample size			
100–299	12 (38)	5 (42)	8 (36)
300–599	7 (22)	1 (8)	8 (36)
600–999	9 (28)	5 (42)	4 (18)
≥1000	4 (13)	1 (8)	2 (9)
Sample included ≥25 depressed patients	30 (94)	11 (92)	19 (86)
Inclusion/exclusion criteria clearly described	26 (81)	12 (100)	19 (86)
No more than 20% lost to follow-up	29 (91)	11 (92)	20 (91)
Definition of acute coronary syndrome			
Troponin levels	11 (34)	0 (0)	6 (27)
Enzyme levels other than troponins	24 (75)	11 (92)	9 (41)
ECG changes	25 (78)	12 (100)	12 (55)
Chest pain	22 (69)	12 (100)	10 (45)
Depression measure			
Self-report measure			
Beck Depression Inventory-I	20 (63)	9 (75)	11 (50)
Beck Depression Inventory-II	1 (3)	0 (0)	2 (9)
Center for Epidemiologic Studies Depression Scale	1 (3)	0 (0)	0 (0)
Hospital Anxiety and Depression Scale, Depression Subscale	2 (6)	0 (0)	1 (5)
Zung Self-Rating Depression Scale	2 (6)	2 (17)	2 (9)
Other	5 (16)	0 (0)	5 (23)
Structured interview			
Diagnostic Interview Schedule	3 (9)	3 (25)	3 (14)
Depression Interview and Structured Hamilton	5 (16)	0 (0)	1 (5)
Structured Clinical Interview for *DSM* Disorders	3 (9)	0 (0)	4 (18)
Composite International Diagnostic Interview	0 (0)	0 (0)	2 (9)
Other	2 (6)	0 (0)	0 (0)
Depression is a primary predictor of outcomes (vs covariate)	26 (81)	11 (92)	19 (86)
Depression measured by use of a continuous scale	14 (44)	7 (58)	8 (36)
Outcome			
Outcomes were within 1 y (early recovery)	18 (56)	5 (42)	8 (36)
Outcomes were assessed beyond 1 y	17 (53)	7 (58)	14 (64)
At least 25 end points, with ≥10 events for every model variable	10 (31)	1 (8)	10 (45)
Outcome events defined adequately	30 (94)	11 (92)	12 (54)
Outcome events adjudicated independently (vs self-report, billing codes, etc)	N/A	9 (75)	14 (64)
Covariates			
Adjusted for potential confounding factors recognized at the time the study was conducted	22 (69)	8 (67)	18 (82)
Adjusted for systolic function (eg, LVEF, Killip class)	18 (56)	7 (58)	17 (77)
Risk-adjusted results			
Statistically significant relationship observed (depression associated with poorer outcome)	21 (65)	8 (67)	17 (77)

Data are presented as n (%) and represent columnwise percentages. The number of unique cohorts represented for the 3 outcomes is as follows: 22 cohorts for all-cause mortality, 8 cohorts for cardiac mortality, and 18 cohorts for the composite outcome.

DSM indicates *Diagnostic and Statistical Manual of Mental Disorders*; LVEF, left ventricular ejection fraction; and N/A, not applicable.

Table 2. Summary of Included Studies That Examined All-Cause Mortality

Study	No. of Sites; Setting; Cohort	Enrollment Period	N	Mean Age, y	Women, %	Instrument, Prevalence	Assessment Timing	Follow-Up	No. of Events	Associations
Abrams et al, 2009[18]	144; United States; VHA Administrative Data	2003–2006	21 745	69	2	*ICD-9-CM* 296.20-36/311/ 300.4: inpatient diagnosis, 5%; outpatient diagnosis, 15%	In-hospital; prior 12 mo	1 mo; 12 mo	≈8100*	Adj inpatient: NS (1 mo; unadj, S), NS (12 mo; unadj, S); adj outpatient: S (1 mo; unadj, NS), S (12 mo; unadj, NS†)
Berkman et al, 1992[19]	2; United States; EPESE-New Haven, CT	1982–1988	194	65–74, 40%; 75–84, 44%; ≥85, 16%	48	CES-D-20 ≥16, 17%	0–3 y pre-MI	6 mo	76	Unadj: NS
Bush et al, 2001[20]	1; United States	1995–1996	271	65	42	SCID MD/ dysthymia, 17%; BDI ≥10, 20%	2–5 d	4 mo	18	Adj BDI ≥10/SCID MD/dysthymia: S; adj BDI linear trend: S
Carney et al, 2003[21]	4; United States; ENRICHD + ancillary	1997–2000	766	59*	40*	DISH MD, 21%; DISH mD/dysthymia, 25%; BDI ≥10, 47%	≤28 d	30 mo	47	Adj DISH MD/ mD: S; adj DISH MD: S; adj DISH mD: S
Carney et al, 2007[22]	4; United States; ENRICHD + ancillary	1997–2000	498	61*	39*	DISH MD/mD/ dysthymia, 47%; BDI ≥10, 47%	≤28 d‡	30 mo (median 24)	43	Adj DISH MD/ mD: NS† (1–3 y); adj DISH MD/mD: NS (1 y); adj DISH MD/mD: S (2–3 y)
Carney et al, 2008[23]	4; United States; ENRICHD + ancillary	1997–2000	766	59*	40*	DISH MD, 21%; DISH mD/dysthymia, 25%; BDI ≥10, 47%	≤28 d	Median 60 mo	106	Adj DISH MD/ mD: S; adj DISH MD: S; adj DISH mD: S
Doyle et al, 2006[24]	38; Ireland	2003	598	63*	24	HADS-D >7/ BDI-FS >3, 18%; HADS-D >7, 15%; BDI-FS >3, 22%	2–5 d	12 mo	24	Adj HADS-D >7/ BDI-FS >3: S; adj HADS-D >7: S; adj BDI-FS >3: NS
Drago et al, 2007[25]	1; Italy	1999	100	62	23	*DSM-IV* interview MD, 15%; BDI ≥10, 35%	7–14 d	Mean 60 mo	6	Adj *DSM-IV* MD: S; adj BDI ≥10: S
Grace et al, 2005[26]	12; Canada	1997–1999	750	62	35	BDI ≥10, 31%	2–5 d	5 y	115	Adj BDI ≥10: S
Irvine et al, 1999[27]	31; Canada; CAMIAT	1990–1995	671	64	17	BDI ≥10, NR	14 d after randomization	2 y	63	Adj BDI ≥10: NS
Kaufmann et al, 1999[28]	1; United States	1995	331	65	34	DIS MD, 27%	3–15 d	12 mo	33	Adj DIS MD: NS (unadj: S)
Kronish et al, 2009[29]	3; United States; COPES	2003–2005	457	61	41	BDI ≥10, 47%; DISH MD, 11%	≤7 d	12 mo	18	Adj DISH MD: S; adj BDI continuous (excluding BDI 5–9): S
Lane et al, 2001[30]	2; United Kingdom	1997–1998	288	63	25	BDI ≥10, 31%	2–15 d	12 mo	31	Unadj BDI ≥10: NS
Lane et al, 2002[31]	2; United Kingdom	1997–1998	288	63	25	BDI ≥10, 31%	2–15 d	3 y	38	Unadj BDI ≥10: NS
Lauzon et al, 2003[32]	10; Canada	1996–1998	550	60*	21	BDI ≥10, 35% (baseline)	2–3 d	12 mo	28	Adj BDI ≥10: NS
Lespérance et al, 1996[33]	1; Canada; EPPI	1991–1992	222	60	22	DIS history of MD, 27%; DIS current MD, 16%; DIS postdischarge MD, 16% (86% of these by 6 mo); DIS current/postdischarge MD, 32%	5–15 d; 6 mo; 12 mo	18 mo	21	Unadj current MD: S; unadj 6 mo MD: NS

(Continued)

Table 2.   Continued

Study	No. of Sites; Setting; Cohort	Enrollment Period	N	Mean Age, y	Women, %	Instrument, Prevalence	Assessment Timing	Follow-Up	No. of Events	Associations
Lespérance et al, 2000[34]	1; Canada	1994–1996	430	62	29	BDI ≥10, 41%	Mean 5 d	12 mo	16	Unadj BDI ≥10: S; unadj DIS MD: NS (among BDI ≥10)
Lespérance et al, 2002[35]	10; Canada; EPPI and M-HART	1991–1994	896	59	32	BDI <5, 37%; BDI 5–9, 30%; BDI 10–18, 24%; BDI ≥19, 9%	In-hospital; 12 mo	5 y	155	Unadj BDI in-hospital: 5–9 vs <5: NS‡; 10–18 vs <5: S; ≥19 vs <5: S; continuous: S; unadj BDI 12 mo: 5–9 vs <5: S; 10–18 vs <5: S; ≥19 vs <5: NS‡; continuous: S
Parakh et al, 2008[36]	1; United States	1995–1996	284	64*	43	BDI ≥10, 20%; SCID MD/dysthymia/BDI ≥10, 27%	≤5 d	12 mo; 3 y; 5 y; 8 y	136	Adj SCID MD/dysthymia/BDI ≥10: NS (12 mo, 3 y, 5 y, and 8 y); adj BDI ≥10: NS (12 mo, 3 y, 5 y, and 8 y); adj BDI continuous: NS (8 y)
Parashar et al, 2009[37]	17; United States; PREMIER	2003–2004	2411	61*	33	PHQ-9 ≥10, 22%	1–3 d	2 y	260	Adj PHQ-9 continuous, S
Roest et al, 2011[38]	12; Canada	1997–1999	874	62	35	BDI ≥10, 34%;	2–5 d	12 mo	51	Adj BDI continuous: S
Romanelli et al, 2002[39]	1; United States	NR	153	75	44	BDI ≥10/SCID MD/dysthymia, 23%	3–5 d	4 mo	17	Unadj BDI ≥10/SCID MD/dysthymia: S
Rumsfeld et al, 2005[40]	Multiple; United Kingdom, United States, Canada; EPHESUS	1999–2001	634	65*	28*	MOS-D ≥0.06, 23%	In-hospital	2 y	98	Adj MOS-D ≥0.06: S
Shiotani et al, 2002[41]	25; Japan; OACIS	1998–2000	1042	64*	20*	Zung SDS ≥40, 42%	≤3 mo	12 mo	9	Unadj Zung SDS ≥40: NS
Smolderen et al, 2009[42]	19; United States; PREMIER	2003–2004	2347	61*	32	PHQ-9 ≥10, 22%;	1–3 d	4 y	424	Adj PHQ-9 ≥10: S
Sørensen et al, 2006[43]	17; Denmark	1999–2000	761	59*	24	MDI *ICD-10* depression, 10%	Median 7 d	12 mo	25	Adj MDI depression: NS (unadj: S)
Steeds et al, 2004[44]	1; United Kingdom	1999–2000	131	NR	NR	BDI-II ≥12: in-hospital, 47%; in-hospital, 2–3 mo, and 6 mo, 7%	In-hospital (≈2–7 d); 2–3 mo; 6 mo	Median 32 mo	11	Unadj BDI-II ≥12 in-hospital: NS; unadj BDI-II ≥12 in-hospital, 2–3 mo and 6 mo: NS
Thombs et al, 2008[45]	12; Canada	1997–1999	417	61	25	BDI ≥10, 29%; BDI symptoms factor analysis, NR	2–5 d	12 mo	25	Adj BDI general depression factor: S; unadj mean BDI: S
Thombs et al, 2008[46]	12; Canada	1997–1999	800	62	33	BDI ≥10, 34%	2–5 d	12 mo	45	Adj BDI continuous: S
van Jaarsveld et al, 2006[47]	1; Netherlands; GLAS	1993–1998	198	71*	38	HADS-D ≥8, 22%	Baseline in 1993, pre-MI	1 mo; 8 y	94	Unadj HADS-D ≥8: NS (1 mo and 1 mo–8 y)
Welin et al, 2000[48]	2; Sweden	1985–1987	275	<55, 36%; 55–65, 64%	16	Zung SDS ≥40, 37%	1 mo	10 y	67	Adj Zung SDS ≥40: S

(Continued)

Table 2. Continued

Study	No. of Sites; Setting; Cohort	Enrollment Period	N	Mean Age, y	Women, %	Instrument, Prevalence	Assessment Timing	Follow-Up	No. of Events	Associations
Whang et al, 2010[49]	3; United States; COPES	2003–2005	209	61*	46	BDI ≥10, 50%; DISH MD, 14%	≤7 d	12 mo; 42 mo (mean 31)	12 mo, 9; 42 mo, 23	Adj BDI ≥10 vs 0–4: NS (12 mo; adj for only age and sex, NS†), S (42 mo); adj DISH MD: NS (12 and 42 mo)

Adj indicates adjusted analysis; BDI, Beck Depression Inventory; BDI-FS, Beck Depression Inventory–Fast Scale; CAMIAT, Canadian Amiodarone Myocardial Infarction Arrhythmia Trial; CES-D, Center for Epidemiologic Studies Depression Scale; COPES, Coronary Psychosocial Evaluation Studies; DIS, Diagnostic Interview Schedule; DISH, Depression Interview and Structured Hamilton; *DSM-IV, Diagnostic and Statistical Manual of Mental Disorders* version IV; ENRICHD, Enhancing Recovery in Coronary Heart Disease; EPESE, Established Populations for Epidemiologic Studies of the Elderly; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; EPPI, Emotions and Prognosis Post-Infarct Study; GLAS, Groningen Longitudinal Aging Study; HADS-D, Hospital Anxiety and Depression Scale-Depression; *ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10, International Classification of Diseases, Tenth Revision*; mD, minor depression; MD, major depression; MDI, Major Depression Inventory; M-HART, Montreal Heart Attack Readjustment Trial; MI, myocardial infarction; MOS-D, Medical Outcomes Study-Depression; NR, data not reported; NS, statistically nonsignificant association reported; OACIS, Osaka Acute Coronary Insufficiency Study; PHQ, Patient Health Questionnaire; PREMIER, Prospective Registry Evaluating Myocardial Infarction: Events and Recovery; S, statistically significant association reported; SCID, Structured Clinical Interview for *DSM* Disorders; Unadj, unadjusted analysis; VHA, Veterans Health Administration; and Zung SDS, Zung Self-Rating Depression Scale.

*Calculated from data provided in article.

†Result was marginally significant (ie, 0.05<*P*<0.1).

‡Data obtained from a referenced article.

follow-up period ranged from as little as 1 month[18,47] to as long as 10 years[48] after ACS. All but 10 studies‡ adjusted for potentially confounding factors, although the covariates varied widely across studies.

Of the 32 studies, 17 reported a significant risk-adjusted association and 4 reported a significant unadjusted association between at least 1 measure of depression and increased all-cause mortality.§ These significant findings were obtained from analyses of 13 different cohorts. Three additional studies reported a significant unadjusted association that became nonsignificant with risk adjustment.[27,28,43]

Four studies reported on the results of a cohort of ACS patients in south central Ontario, Canada.[26,38,45,46] The results were largely consistent in showing a significant risk-adjusted relationship between depressive symptoms measured by the BDI-I and increased all-cause mortality, despite methodological differences across the studies, including the operationalization of depression (BDI-I ≥10, continuous BDI-I score, or general depression factor from confirmatory factor analysis), analytic method (survival analysis or logistic regression), inclusion of covariates, and cardiac diagnosis (entire ACS cohort or MI patients only). Hazard ratios for BDI-I scores ≥10 versus <10 at the time of the index hospitalization ranged from a high of 1.90 at 2 years to 1.53 at 5 years.[26]

Three studies reported on a subsample of depressed patients in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) clinical trial and a group of patients who were free of depression but were otherwise eligible for ENRICHD.[21–23] These studies found that both major and minor depression, as measured by the Depression Interview and Structured Hamilton, increased the risk of all-cause mortality over 30 months[21,22] and 5 years[23] of follow-up, even after adjustment

for potential confounders and other predictors of survival. However, the significant effect of depression on mortality did not appear until nearly 12 months after the acute event.[21]

Two studies each reported on patients in the Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER),[37,42] the Coronary Psychosocial Evaluation Studies (COPES),[29,49] and either the Emotions and Prognosis Post-Infarct (EPPI) cohort[33] or pooled data from EPPI and the control group of the Montreal Heart Attack Readjustment Trial (M-HART, a psychosocial intervention trial).[35] Both continuous and dichotomized scores for depressive symptoms measured during the index hospitalization by the 9-item Patient Health Questionnaire (PHQ-9) were associated with increased risk of all-cause mortality over 2[37] to 4[42] years of follow-up, respectively, in risk-adjusted analyses among >2000 MI patients in PREMIER. Among patients with ACS in COPES, both depressive symptom severity assessed by the BDI-I and major depression assessed by the Depression Interview and Structured Hamilton within 1 week of the index event were significant predictors of all-cause mortality up to 12 months after the event in analyses that adjusted for a validated cardiac risk index and systolic function.[29] When only COPES patients with UA were considered, a BDI-I score ≥10 (versus <5) was associated with increased risk of 42-month all-cause mortality; the association with 12-month mortality bordered on significance.[49] Major depression was not significantly associated with all-cause mortality, although the few patients reporting on major depression and the reduced sample size likely limited the statistical power of the study. Unadjusted analyses from EPPI showed a significant relationship between major depression assessed in the hospital by a modified version of the National Institute of Mental Health's Diagnostic Interview Schedule (DIS) and 18-month all-cause mortality, although depression at 6 months was not related to outcome.[33] In the larger pooled EPPI and M-HART

‡*References 19, 30, 31, 33–35, 39, 41, 44, 47.*

§*References 18, 20–26, 29, 33–35, 37–40, 42, 45, 46, 48, 49.*

sample, a "dose-response" relationship was observed between BDI-I scores and mortality up to 5 years after MI; depressive symptom severity at 1 year was also associated but to a lesser extent.[35] Because all-cause mortality was a secondary outcome in these studies, covariate-adjusted analyses were not presented. Although not part of the EPPI or M-HART studies, the same research team noted a similar unadjusted association of elevated BDI-I scores with mortality at 12 months among patients with UA.[34]

Three studies were based on a sample of <300 patients with MI from 1 US site.[20,36,39] In risk-adjusted analyses, depression at the index hospitalization (BDI-I ≥10 or diagnosis of major depression, dysthymia, or bipolar disorder according to the Structured Clinical Interview for *DSM* Disorders) was associated with increased risk of all-cause mortality 4 months later among patients ≥65 years old.[20] A significant linear trend was observed for BDI-I scores, but depressive disorder diagnoses based on the Structured Clinical Interview for *DSM* Disorders were not associated with mortality. No association between depression and long-term mortality after MI was observed in this cohort, regardless of how depression was defined, length of follow-up (1, 3, 5, or 8 years), or covariate adjustment.[36]

The remaining independent studies showing a significant covariate-adjusted association between depression and all-cause mortality included data from an administrative database of the Veterans' Health Administration,[18] the Eplerenone Post-Acute MI Heart Failure Efficacy and Survival Trial (EPHESUS),[40] a multisite ACS cohort in Ireland,[24] and MI cohorts in Italy[25] and Sweden.[48] Independent studies that did not find a relationship were derived from the New Haven, CT, Established Populations for Epidemiologic Studies of the Elderly (EPESE),[19] the placebo-controlled Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT),[27] the Osaka Acute Coronary Insufficiency Study (OACIS),[41] the Groningen Longitudinal Aging Study (GLAS),[47] multisite MI cohorts in Canada[32] and Denmark,[43] and single sites in the United States[28] and the United Kingdom.[44] Among these negative studies, sample sizes were moderate and ranged from ≈100 to <800 patients. Measures of depressive symptoms differed, and only 1 study incorporated a diagnostic interview.[28] Depression was not the primary predictor in 3 studies,[19,27,47] and all-cause mortality was not a primary outcome in 2 studies.[27,47] Four studies presented analyses adjusted for potential confounders.[27,28,32,43] Depression was not associated with mortality in the multivariate models, but in 3 of the studies, there were significant univariate associations before risk adjustment.[27,28,43] In several studies, unadjusted mortality rates were markedly higher among depressed than nondepressed patients, but the differences did not reach statistical significance.[32,44] Most positive studies assessed depression during or within a few weeks of the index hospitalization; in 2 studies reporting negative results, depression was measured either before MI diagnosis[47] or up to 3 months after the event.[41] Among the negative studies, only 2 used data from the same cohort. These studies examined <300 patients with MI from the United Kingdom and reported that a BDI-I score ≥10 (versus <10) was not associated with all-cause mortality at either 12 months[30] or 3 years.[31]

In summary, the preponderance of evidence (21 of 32 published studies, including results from 17 risk-adjusted and 4 unadjusted analyses; 13 of 22 unique cohorts) suggests that depression is a risk factor for all-cause mortality after ACS. However, findings are based on a methodologically varied group of studies, and the number of mixed or negative studies highlights the complexity of the literature.

Depression and Cardiac Mortality

The 12 studies‖ that included cardiac mortality as an outcome (Tables 1 and 3) reported on 8 unique ACS patient cohorts. These studies included patients from 5 countries on 3 continents (North America, Europe, and Asia), with sample sizes ranging from 222[50,51] to 1042[41] patients. Eleven studies included patients who presented at the hospital with MI,[27,30,31,35,41,48,50–54] and 1 study included patients who presented with UA.[34] Only 3 distinct measures of depression were evaluated as potential predictors of cardiac mortality. Most studies included the BDI-I as a measure of depressive symptoms[27,30,31,34,35,51–54]; the Zung Self-Rating Depression Scale was the only other depressive symptom scale that was used.[41,48] Few studies reported on major depression as assessed by structured or semistructured interviews, and all of these studies used a version of the DIS.[34,50,51] Only 2 studies reported on depression measured by both a structured or semistructured interview and a self-report questionnaire.[34,51] Depression was most commonly measured during the index hospital admission, with only 1 study measuring depression at 1 year after ACS.[35] Follow-up ranged from 6 months[30,50] to 10 years.[48] All but 4 studies[30,31,34,41] adjusted for potentially confounding factors.

Of the 12 studies, 7 reported a significant risk-adjusted association and 1 reported a significant unadjusted association between at least 1 measure of depression and increased cardiac mortality.[27,34,35,48,50–53] These significant findings were obtained from analyses of 5 cohorts. Data from 3 of these cohorts were used to assess the impact of depression over multiple lengths of follow-up, with results consistent across reports.

Five studies were based on either the EPPI cohort[50,51] or on pooled data from EPPI and the control group of M-HART.[35,52,53] The EPPI study used a modified version of the DIS to assess depression in 222 post-MI patients. In this key study, there were ≈5 times as many cardiac deaths in the depressed as in the nondepressed group over the first 6 months after an acute MI (17% of the 35 depressed patients died versus 3% of the 187 nondepressed patients).[50] Elevated depressive symptoms, as measured by the BDI-I, were also significantly associated with 18-month cardiac mortality in risk-adjusted analyses.[51] Three subsequent studies based on 896 patients with MI in the pooled sample reported consistent risk-adjusted findings.[35,52,53] Major depression almost doubled the risk of cardiac mortality over 5 years, and there was a dose-response relationship between BDI-I scores and cardiac mortality risk. A sixth study by these investigators was based on a separate cohort and found that elevated depressive symptoms nearly tripled the risk of cardiac mortality in 430 patients with UA during the year after hospitalization in unadjusted analyses.[34] The fact that these studies were conducted by the same research team and were limited to

‖*References 27, 30, 31, 34, 35, 41, 48, 50–54.*

patients from the same geographic location in Canada potentially limits the generalizability of these findings.

Both of the remaining positive studies assessed depressive symptoms. Depression, as measured by the BDI-I, was a significant risk-adjusted predictor of sudden cardiac death in the placebo arm but not in the active drug arm of CAMIAT.[27] A Swedish MI registry of 275 patients aged <65 years who had no prior history of MI showed a significant risk-adjusted relationship between depression measured by the Zung Self-Rating Depression Scale and cardiac mortality; however, the study relied on death certificates for the determination of cause of death, without confirmation by an independent review.[48]

The 4 studies reporting negative results represent 3 distinct cohorts. In 2 studies based on a cohort of MI patients in the United Kingdom, depression did not predict cardiac mortality over any of the follow-up intervals that were studied (6 months, 12 months, or 3 years) in unadjusted analyses.[30,31] Although the studies were well designed and clearly reported, the small sample size (n=288) may have been a limitation. Despite a 4-fold difference in cardiac mortality between depressed and nondepressed patients in the OACIS cohort, the unadjusted effect of depression was not significant.[41] However, only 0.5% of the patients died of cardiac causes, and thus, there were too few events to model the effects of depression with adequate statistical power. In the final negative study, nearly two thirds of a cohort of patients with MI in Iran were classified as depressed (BDI-I ≥10).[54] This is approximately twice as high as the prevalence of depression that has been reported in most studies of patients after MI. One third of the total sample and a disproportionate number of the depressed patients were lost to follow-up. Furthermore, cardiac mortality was not well defined, and the deaths were not adjudicated.

In summary, although few studies have systematically investigated the relationship between depression and cardiac mortality, and although results have been mixed, the preponderance of evidence (8 of 12 published studies, including results from 7 risk-adjusted analyses and 1 unadjusted analysis; 5 of 8 unique cohorts) suggests that depression is a risk factor for cardiac mortality after ACS.

Depression and a Composite of Mortality and Nonfatal Events

The 22 studies[25,34,35,40,41,52,55–70] that included a composite outcome of mortality and nonfatal events (Tables 1 and 4) reported on 18 unique ACS patient cohorts. Eighteen studies examined a composite end point of cardiac mortality and rehospitalization for a cardiac diagnosis,[34,35,40,41,52,55–67] and 4 examined a composite end point of all-cause mortality and cardiac rehospitalization.[25,68–70] These studies included patients from 11 countries on 4 continents (North America, Europe, Asia, and Australia), with sample sizes ranging from 100[25] to 1803[58] patients. Thirteen studies included only patients who presented at the hospital with MI,¶ 7 included patients with any form of ACS,[56,57,63,65,66,68,70] and 1 included only patients presenting with UA.[34] Fifteen measures of depression were evaluated as potential predictors of a composite cardiac outcome after ACS. Almost half of the 22 studies used structured

or semistructured interviews to obtain a clinical diagnosis of major depression; the DIS[34,52,55] and the Structured Clinical Interview for *DSM* Disorders[25,56,57,61] were the 2 most common interview schedules. Nearly all studies used self-report depressive symptom questionnaires, of which the BDI-I was the most commonly used instrument.# Only 8 studies reported on both structured or semistructured interviews and self-report questionnaires.[25,34,52,55–57,61,68] In most studies, the assessment of depression occurred during or within a few weeks of the index hospital admission, but it occurred up to 1 year after ACS in 2 studies.[35,61] The maximum follow-up period ranged from 1 year[34,41,52,55,64,65,68,69] to 5 years.[25,35] All but 4 studies[35,52,63,64] adjusted for potentially confounding factors.

Of the 22 studies, 15 reported a significant risk-adjusted association and 2 reported a significant unadjusted association between at least 1 measure of depression and increased mortality or nonfatal cardiac events.** These findings were obtained from analyses of 14 different cohorts.

Three studies were based on either the EPPI cohort or on pooled data from EPPI and the control group of M-HART.[35,52,55] Depression was related to cardiac events in an unadjusted analysis of the 222 patients in EPPI, with an odds ratio >2, but the relationship was not statistically significant in a multivariable analysis despite an odds ratio that remained around 2.[55] However, the final model included both a depression diagnosis according to the DIS and depressive symptoms measured by the BDI-I, as well as a measure of anxiety. In 2 subsequent studies of the pooled cohorts, significant unadjusted associations were observed between depression and depressive symptom severity and a composite of cardiac death and recurrent nonfatal MI.[35,52] Because both of these publications focused on cardiac mortality, no adjusted results were reported for the composite end point.

Two studies each reported on the Epidemiological Study of Acute Coronary Syndromes and the Pathophysiology of Emotions (ESCAPE),[56,57] OACIS,[41,58] and a sample of MI patients in the Netherlands.[60,67] Studies on ESCAPE reported significant associations between major depression or depressive symptoms assessed 2 months after ACS and cardiac outcomes at 2 years.[56,57] Two studies from the OACIS cohort also reported consistent positive findings for depression in risk-adjusted analyses.[41,58] Although 2 studies on a sample of 473 MI patients from hospitals in the Netherlands reported results for depression,[60,67] only 1 of them[60] focused primarily on depression as a risk factor for poor outcomes. That study reported significant adjusted associations with cardiac death or recurrent MI for both the BDI-I and a shorter version, the BDI-10.[60] The second study focused on Type D personality but also considered depression measured with the Hamilton Rating Scale for Depression as a covariable.[67] Although depression measured with the Hamilton Rating Scale for Depression was associated with clinical outcomes in a univariate analysis, the relationship was no longer significant in multivariable models that adjusted for Type D personality in addition to cardiac risk factors. Because Type D personality

¶References 25, 35, 40, 41, 52, 55, 58–62, 64, 67, 69.

#References 25, 34, 35, 52, 55, 60, 61, 63, 64, 68, 69.
**References 25, 34, 35, 40, 41, 52, 56–60, 62, 65, 66, 68–70.

Table 3.   Summary of Included Studies That Examined Cardiac Mortality

Study	No. of Sites; Setting; Cohort	Enrollment Period	N	Mean Age, y	Women, %	Instrument, Prevalence	Assessment Timing	Follow-Up	No. of Events	Associations
Frasure-Smith et al, 1993[50]	1; Canada; EPPI	1991–1992	222	60	22	DIS MD, 16%	5–15 d	6 mo	12	Adj DIS MD: S
Frasure-Smith et al, 1995[51]	1; Canada; EPPI	1991–1992	222	60*	22	DIS MD, 16%; BDI ≥10, 31%	5–15 d	18 mo	19	Adj DIS MD: NS (unadj S); adj BDI ≥10: S; adj BDI continuous: S
Frasure-Smith et al, 1999[52]	10; Canada; EPPI and M-HART	1991–1994	896	59*	32	BDI ≥10, 32%	In-hospital	12 mo	37	Adj BDI ≥10: S
Frasure-Smith and Lespérance, 2003[53]	10; Canada; EPPI and M-HART	1991–1994	896	59	26	BDI ≥10, 32%†	In-hospital	5 y	121	Adj BDI continuous: S
Hosseini et al, 2011[54]	Multiple; Iran	2004–2006	540	58	31	BDI ≥10, 66%	≤15 d	2 y	55	Adj BDI ≥10: NS
Irvine et al, 1999[27]	31; Canada; CAMIAT	1990–1995	671	64	17	BDI ≥10, NR	14 d after randomization	2 y	50 (34 SCD)	Adj BDI ≥10: S (SCD)
Lane et al, 2001[30]	2; United Kingdom	1997–1998	288	63	25	BDI ≥10, 31%	2–15 d	6 mo; 12 mo	27	Unadj BDI ≥10: NS (6 mo and 12 mo)
Lane et al, 2002[31]	2; United Kingdom	1997–1998	288	63	25	BDI ≥10, 31%	2–15 d	3 y	33	Unadj BDI ≥10: NS
Lespérance et al, 2000[34]	1; Canada	1994–1996	430	62	29	BDI ≥10, 41%	Mean 5 d	12 mo	13	Unadj BDI ≥10: S; unadj DIS MD: NS (among BDI ≥10)
Lespérance et al, 2002[35]	10; Canada; EPPI and M-HART	1991–1994	896	59	32	BDI <5, 37%; BDI 5–9, 30%; BDI 10–18, 24%; BDI ≥19, 9%	In-hospital and 12 mo	5 y	121	Adj BDI in-hospital: 5–9 vs <5: NS‡; 10–18 vs <5: S; ≥19 vs <5: S; continuous: S; unadj BDI 12 mo: 5–9 vs <5: NS; 10–18 vs <5: S; ≥19 vs <5: S; continuous: S; unadj BDI residual change score: NS (overall; BDI 10–18: S)
Shiotani et al, 2002[41]	25; Japan; OACIS	1998–2000	1042	64*	20*	Zung SDS ≥40, 42%	≤3 mo	12 mo	5	Unadj Zung SDS ≥40: NS
Welin et al, 2000[48]	2; Sweden	1985–1987	275	<55, 36%; 55–65, 64%	16	Zung SDS ≥40, 37%	1 mo	10 y	41	Adj Zung SDS ≥40: S

Adj indicates adjusted analysis; BDI, Beck Depression Inventory; CAMIAT, Canadian Amiodarone Myocardial Infarction Arrhythmia Trial; DIS, Diagnostic Interview Schedule; EPPI, Emotions and Prognosis Post-Infarct Study; MD, major depression; M-HART, Montreal Heart Attack Readjustment Trial; OACIS, Osaka Acute Coronary Insufficiency Study; NR, data not reported; NS, statistically nonsignificant association reported; S, statistically significant association reported; SCD, sudden cardiac death; Unadj, unadjusted analysis; and Zung SDS, Zung Self-Rating Depression Scale.

*Calculated from data provided in article.

†Data obtained from a referenced article.

‡Result was marginally significant (ie, $0.05<P<0.1$).

Table 4.   Summary of Included Studies That Examined a Composite Outcome That Included All-Cause or Cardiac Mortality and Nonfatal Events

Study	No. of Sites; Setting; Cohort	Enrollment Period	N	Mean Age, y	Women, %	Instrument, Prevalence	Assessment Timing	Follow-Up	No. of Events	Associations
Ahern et al, 1990[69]	27; United States; CAPS	1983–1985	351	59* (n=502)	17* (n=502)	BDI mean score 8.4†	6–60 d	12 mo	27	Adj BDI continuous: S
Davidson et al, 2010[68]	3; United States; COPES	2003–2005	453	61	42	BDI ≥10, 47%; DISH MD, 11%; DISH depressed mood, 24%	≤7 d	12 mo (mean 10.4)	67	Adj BDI ≥10 vs <5: NS (adj only for age: S); adj DISH MD: S (adj for anhedonia: NS); adj DISH depressed mood: NS‡; adj BDI depressed mood: NS
Denollet et al, 2010[60]	4; Netherlands	2003–2006	416	60	22	BDI, mean score 6.5; BDI-10, mean score 2.7	2 mo	Mean 2.7 y	41	Adj BDI: S; adj BDI-10: S
Dias et al, 2005[63]	1; Portugal	2001–2002	240	59	15	BDI ≥19, 15%	In-hospital	Mean 16 mo	NR	Unadj BDI ≥19: NS
Doyle et al, 2010[59]	12; Ireland	2006–2007	408	61†	20†	HADS-D >7, 11%; BDI-FS >3, 24%	In-hospital	Median 67wk	59	Adj HADS-D >7: S; adj BDI-FS >3: NS
Drago et al, 2007[25]	1; Italy	1999	100	62	23	*DSM-IV* interview MD, 15%; BDI ≥10, 35%	7–14 d	Mean 60 mo	30	Adj *DSM-IV* MD: S; adj BDI ≥10: S
Frasure-Smith et al, 1995[55]	1; Canada; EPPI	1991–1992†	222	60†	22	DIS current MD, 15%†; DIS MD history, 27%†; BDI ≥10, 31%†	5–15 d	12 mo	48	Adj DIS current MD: NS (unadj: S); adj BDI ≥10: NS‡ (unadj: S); adj DIS MD history: NS (unadj: S)
Frasure-Smith et al, 1999[52]	10; Canada; EPPI and M-HART	1991–1994	896	59†	32	BDI ≥10, 32%	In-hospital	12 mo	85	Unadj BDI ≥10: S
Frasure-Smith et al, 2007[56]	2; Canada; ESCAPE	1999–2001	741	60	19	BDI-II ≥14, 27%; SCID MD, 6%	2 mo	2 y	102	Adj BDI-II ≥14, S (men only; unadj: S [overall and for men only]); adj BDI-II continuous: NS (men only; unadj: S [overall and for men only]); unadj SCID MD: S (men only)
Frasure-Smith and Lespérance, 2008[57]	2; Canada; ESCAPE	1999–2001	804	60	19	BDI-II ≥14, 27%; SCID MD, 7%	2 mo	2 y	115	Adj SCID MD: S; adj BDI-II ≥14: S; adj BDI-II continuous: NS (unadj: S); adj SCID MD vs BDI <14 and without MD: S; adj BDI-II ≥14 and without MD vs BDI <14 and without MD: NS (unadj: S)

(Continued)

Table 4.   Continued

Study	No. of Sites; Setting; Cohort	Enrollment Period	N	Mean Age, y	Women, %	Instrument, Prevalence	Assessment Timing	Follow-Up	No. of Events	Associations
Horsten et al, 2000[66]	10; Sweden; FemCorRisk Study	1991–1994	292	56	100	9-Item questionnaire from Pearlin et al[71] ≥2 symptoms, 72%	3–6 mo	Median 4.8 y	81	Adj depression symptoms ≥2: S
Lane et al, 2000[64]	2; United Kingdom	1997–1998	272	63†	26	BDI ≥10, 30%	2–15 d	12 mo	82	Unadj BDI continuous: NS; unadj BDI ≥10: NS
Leroy et al, 2010[70]	1; France	NR	291	68	21	HADS-D, mean score 5.8	1–4 d	3 y	176 (Clinical events; includes 44 severe cardiac events)	Severe cardiac events: adj HADS-D continuous: NS‡ (unadj: S); clinical events: adj HADS-D continuous: S (NS‡ when continuous vs categorical anhedonia adjustment)
Lespérance et al, 2000[34]	1; Canada	1994–1996	430	62	29	BDI ≥10, 41%	Mean 5 d	12 mo	28	Adj BDI ≥10: S; unadj DIS MD: NS (among BDI ≥10)
Lespérance et al, 2002[35]	10; Canada; EPPI and M-HART	1991–1994	896	59	32	BDI <5, 37%; BDI 5–9, 30%; BDI 10–18, 24%; BDI ≥19, 9%	In-hospital; 1 y	5 y	202	Unadj BDI in-hospital: 5–9 vs <5: NS‡; 10–18 vs <5: S; ≥19 vs <5: S; continuous: S; unadj BDI 1 y: 5–9 vs <5: NS; 10–18 vs <5: S; ≥19 vs <5: NS‡; continuous: S
Martens et al, 2010[67]	4; Netherlands	2003–2006	466	59	22	HAM-D ≥17, 5%	≤7 d	Mean 1.8 y	44	Adj HAM-D ≥17: NS (unadj: NS‡); adj HAM-D continuous: NS‡ (unadj: S)
Nakatani et al, 2005[58]	25; Japan; OACIS	1999–2003	1803	64† (n=2509)	23† (n=2509)	Zung SDS ≥40, 48%†	≤3 mo	Mean 736 d	594†	Adj Zung SDS ≥40, S
Parker et al, 2008[65]	1; Australia	2001–2003*	489	66	30	CIDI MD/ dysthymia: lifetime, 38%; pre-ACS onset, 12%; post-ACS onset, 10%	Mean 4 d; 1 mo	12 mo	86	Adj lifetime: NS; adj pre-ACS onset: NS; adj post-ACS onset: S
Rumsfeld et al, 2005[40]	Multiple; United Kingdom, United States, Canada; EPHESUS	1999–2001	634	65†	30†	MOS-D ≥0.06, 23%	In-hospital	Mean 16 mo	198	Adj MOS-D ≥0.06: S
Shiotani et al, 2002[41]	25; Japan; OACIS	1998–2000	1042	64†	20†	Zung SDS ≥40, 42%	≤3 mo	12 mo	283	Adj Zung SDS ≥40: S

(Continued)

Table 4.   Continued

Study	No. of Sites; Setting; Cohort	Enrollment Period	N	Mean Age, y	Women, %	Instrument, Prevalence	Assessment Timing	Follow-Up	No. of Events	Associations
Strik et al, 2003[62]	1; Netherlands	1994–1999	318	58	0	SCL-90 depression ≥23, 47%	1 mo	Mean 3.4 y	25	Adj SCL-90 depression ≥23: S (unadj: NS; adj for anxiety: NS)
Strik et al, 2004[61]	1; Netherlands	NR	206	59	24	SCID MD/mD, 31% (27% if only incident cases); BDI ≥10, 53%	1 mo (SCID only); 3 mo; 6 mo; 9 mo; 12 mo	3 y	16	Adj SCID MD/mD: NS; adj BDI≥10: NS

ACS indicates acute coronary syndrome; Adj, adjusted analysis; BDI, Beck Depression Inventory; BDI-FS, Beck Depression Inventory–Fast Scale; CAPS, Cardiac Arrhythmia Pilot Study; CIDI, Composite International Diagnostic Interview; COPES, Coronary Psychosocial Evaluation Studies; DIS, Diagnostic Interview Schedule; DISH, Depression Interview and Structured Hamilton; *DSM-IV, Diagnostic and Statistical Manual of Mental Disorders* version IV; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; EPPI, Emotions and Prognosis Post-Infarct Study; ESCAPE, Epidemiological Study of Acute Coronary Syndromes and Pathophysiology of Emotions; FemCorRisk study, Stockholm Female Coronary Risk Study; HADS-D, Hospital Anxiety and Depression Scale–Depression; HAM-D, Hamilton Rating Scale for Depression; mD, minor depression; MD, major depression; M-HART, Montreal Heart Attack Readjustment Trial; MOS-D, Medical Outcomes Study–Depression; NR, data not reported; NS, statistically nonsignificant association reported; OACIS, Osaka Acute Coronary Insufficiency Study; S, statistically significant association reported; SCID, Structured Clinical Interview for *DSM* Disorders; SCL-90, Symptom Checklist-90; unadj, unadjusted analysis; and Zung SDS, Zung Self-Rating Depression Scale.

*Data obtained from a referenced article.

†Calculated from data provided in article.

‡Result was marginally significant (ie, $0.05 < P < 0.1$).

is defined in part by negative affect, which is a symptom of depression, these results are difficult to interpret.

Of the remaining 13 independent studies,[25,34,40,59,61–66,68–70] all but 3 of them[61,63,64] reported an association between at least 1 measure of depression and a composite cardiac outcome. The studies that did not find an association tended to have smaller and more selective samples (<300 patients). In a single-site cohort of patients in the Netherlands with a first MI, only 16 cardiac events were reported, and no medical predictors (including left ventricular ejection fraction) were found for cardiac outcomes at 3 years.[61] These results are in conflict with a previous study by the same investigators of an independent sample drawn from the same institution,[62] which found a significant relationship between depression, measured by the depression subscale of the 90-item Symptom Check List (SCL-90), and cardiac death or recurrent MI. Depression was a significant predictor of cardiac prognosis in risk-adjusted analyses, although the association became nonsignificant when anxiety was added to the statistical model.[62] Among patients with ACS at 1 hospital in Portugal, only 158 of 240 were available for follow-up analyses, and no significant unadjusted relationship was observed.[63] The number of events was not reported, but the event rates appeared to be ≈10%, which suggests that the study may have been underpowered. There were high levels of attrition in the majority of the negative studies, either during enrollment (>30% eligible patients not enrolled[61,64]) or follow-up (>30% lost to follow-up[63]). Most of these negative studies provided few if any details on outcome definitions. Two of the negative studies did not include a multivariable analysis, possibly because no unadjusted association was found.[63,64]

Two of the 13 independent studies provided mixed results; the analysis of depression as a predictor of cardiac outcomes was a secondary aim of these studies.[65,70] In 1 of these studies, the main objective was to examine depression subgroups based on the timing of depression onset in relation to the coronary event.[65] Only depressive episodes that developed after the ACS were associated with adverse cardiac events in that study, whereas lifetime depression, included as a covariate rather than the primary predictor, was not associated with cardiac outcomes. Similarly, in a study designed to examine anhedonia,[70] depressive symptoms measured by the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D), were significant predictors of death or cardiac events in an unadjusted analysis and in multivariable analysis that included categorical but not dimensional anhedonia. Because anhedonia is itself a symptom of depression, this model may not have been appropriate for the evaluation of the effects of depression.

In summary, the preponderance of evidence (17 of 22 published studies, including results from 15 risk-adjusted and 2 unadjusted analyses; 14 of 18 unique cohorts) suggests that depression is a risk factor for combined end points composed of either cardiac mortality or all-cause mortality and nonfatal cardiac events. Among studies that examined the same cohorts, at least 1 report showed a significant association between major depression or depressive symptoms and the composite event. Studies that did not find a significant association tended to have notable methodological limitations.

Review of Meta-Analyses

We identified 4 published meta-analyses that examined depression as a predictor of mortality in patients with CHD.[6–9] Three of them assessed publications through the end of 2003,[6,8,9] and the fourth included publications through January 2011.[7] The 4 analyses included between 22 and 34 studies of 16 to 34 unique cohorts. Two of the meta-analyses were limited to patients with MI,[7,9] whereas the other 2 used broader inclusion criteria for CHD.[6,8]

The 3 early meta-analyses found overall unadjusted effects ranging from 1.8 to 2.6 for all-cause mortality and from 2.3 to 2.9 for cardiac mortality.[6,8,9] Only 1 of these meta-analyses provided an estimate for a composite outcome that included fatal and nonfatal cardiac events; the unadjusted effect was ≈2.0.[9] In the 2 meta-analyses that reported results adjusted for known cardiac risk factors, the prognostic effect remained statistically significant, although somewhat attenuated.[6,8] Two of these early meta-analytic reviews concluded that although results were limited by heterogeneity in the primary studies, depression was associated with a higher risk of mortality in patients with CHD.[6,9] The third review also noted a significant association between depression and CHD outcomes, but the authors tempered their conclusions, stating that study limitations such as the inconsistent reporting of adjusted effects raised uncertainty about the independent effect of depression on outcomes of patients with CHD.[8] This meta-analysis used the most inclusive criteria, including the use of antidepressant medication and self-reported diagnoses, as well as standardized questionnaires or clinical interviews, to assess depression.

The most recent meta-analysis, limited to patients with MI, reported unadjusted effects of 2.3 for all-cause mortality, 2.7 for cardiac mortality, and 1.6 for a composite outcome that included fatal and nonfatal events.[7] The associations were generally stable over time, with only a small decline observed for the composite outcome. The associations were not influenced by the size of the study but were more pronounced in all-cause mortality studies that used interview-based depression instruments rather than self-report questionnaires. The authors concluded that depression is associated with an increased risk of mortality in patients with MI.

Discussion

The committee conducted an extensive review and identified 53 publications that met our review criteria to assess whether depression is a risk factor for adverse medical outcomes for patients with ACS. In addition, we identified 4 meta-analyses that examined depression as a predictor of mortality in patients with CHD. Our review identified heterogeneity in the published findings from these studies in terms of the demographic composition of the samples, the definition and measurement of depression, the length of follow-up, and the covariates included in the multivariable statistical models. Despite this heterogeneity, the preponderance of evidence supports the recommendation that the AHA should elevate depression to the status of a risk factor for adverse medical outcomes in patients with ACS.

Factors Contributing to Heterogeneity

A number of factors contributed to the heterogeneity of the results identified in our review process. These are discussed below.

Inclusion Criteria

We restricted the focus of our review to studies of ACS cohorts. The majority of studies focused on patients with MI; however, definitions for MI differed by cohort and have changed over time. For example, cardiac troponins were not widely measured in the early years of this line of research. Changes over time in the detection, prevention, and treatment of CHD complicate the interpretation of this literature.[1]

Assessment of Depression

Differences related to depression assessment are particularly important. Our systematic review was limited to studies that included a standardized self-report questionnaire for depressive symptoms or a diagnostic interview, yet it included numerous measures of depression. Even among studies that used the same depression measure, methodological differences were found in the use of categorical variables versus continuous scores, the selection of cut points, and the use of multiple measures of depression over time versus a single baseline assessment. Self-report questionnaires, particularly the BDI-I, were used in more of the studies than were structured or semistructured diagnostic interviews. It is unclear how effect sizes are influenced by the method of assessment, because the most recent meta-analysis on the relationship between depression and CHD outcomes reported a more pronounced effect of depression with interview-based methods than with self-report questionnaires,[7] whereas past meta-analyses have either observed no difference[6,9] or observed the opposite.[8] The timing of the depression assessment relative to the index event also varied. Most studies measured depression within a few days or weeks after the ACS event; however, in a number of studies, it was unclear whether patients were assessed during the index hospitalization or after discharge. The committee concurs with an expert panel convened by the National Heart, Lung, and Blood Institute in recommending that future studies of the prognostic value of post-ACS depression should use well-validated questionnaires and structured interviews to assess depression and well-validated cutoff scores and diagnostic criteria to define cases of depression.[72]

Depression Subtypes

Depression is a genetically and phenotypically heterogeneous disorder. Recently, researchers have begun to identify particular symptoms and subtypes of depression that may be associated with a higher risk for cardiac morbidity and mortality after ACS.[73–75] If high-risk subtypes exist, they may have been underrepresented in some of the studies included in this review and overrepresented in others. This might help to explain some of the inconsistencies in this literature. Some studies have found that the somatic symptoms of depression[38,42,76–78] may carry a high risk. Others have reported that patients who are depressed after ACS but who have no prior history of depressive episodes are at higher risk than patients with recurrent depression, and there is also some evidence that depressive episodes that develop soon after an ACS may carry a higher risk than episodes that begin before an ACS.[26,65,76,79–81] Depressive episodes that do not respond to standard treatments[82–85] or that persist with or without treatment[86,87] have also been identified as high-risk subtypes. Some of these studies have been limited by serious methodological weaknesses, and the findings for some of the subtypes have been inconsistent.[73–75,88] Consequently, further efforts to identify high-risk subtypes of depression after ACS remain an important direction for future research.

Adequacy of Risk Adjustment

A number of demographic factors, clinical characteristics, and risk scores have well-established prognostic significance in ACS. We found that the inclusion and description of these

factors varied markedly across studies. The variability in covariate adjustment adds to the complexity of this literature and raises the possibility that the incremental prognostic value of depression, above and beyond established risk factors for post-ACS mortality, may have been overestimated in some studies. Although many of the reviewed studies adjusted for major comorbid conditions, adjustment for the presence of a comorbidity does not necessarily adjust for its severity. The selection of appropriate covariates is further complicated by our lack of understanding of how depression confers risk for CHD. For example, it has been suggested that depression plays a role in the CHD risk from metabolic syndrome by potentiating the effects of diabetes mellitus and obesity on CHD via several pathways. If so, adjustment for diabetes mellitus or body mass index may be inappropriate, because they represent mediators rather than confounders. The selection of covariates may also reflect contemporary knowledge of clinical factors available at the time the study was conducted. Finally, the selection of candidate variables may differ depending on the selected outcome. Greater consistency in risk adjustment would be desirable in future studies.

Mechanisms Linking Depression to Cardiac Events

Numerous potential mechanisms have been postulated for the relationship between depression and CHD.[89,90] A detailed review of the hypothesized mechanisms is beyond the scope of the present report, but the leading candidates include neuroendocrine dysfunction and disturbances in autonomic cardiac control,[8,22,91–94] enhanced platelet activity in depression,[95] endothelial dysfunction,[96] and inflammation.[97–100] Depression may also affect cardiac outcomes via mechanisms that involve high-risk health behaviors, such as smoking, sedentary lifestyle, delay in seeking treatment, and nonadherence to secondary prevention measures.[101–104] In patients with CHD, there is also an association between depression and the severity of functional impairment,[105] which suggests that depression may exacerbate physical inactivity and poor self-care. Finally, growing evidence suggests that depression and CHD may be, at least in part, different phenotypic expressions of the same genetic substrate.[106–110] In particular, genes related to inflammation, platelet aggregation, and the serotonin system may be predictors of both depression and CHD. It is important to recognize that candidate mechanisms are not mutually exclusive, and >1 potential mechanism may link depression with adverse outcomes.

Clinical Implications

Because depression is associated with increased risk for adverse outcomes in patients with ACS, practicing cardiologists may want guidance about depression screening and treatment. However, a detailed consideration of depression screening measures and procedures,[72,111–114] the costs and benefits of screening,[114,115] and safe and effective treatments for depression after ACS[116–119] is beyond the scope of this review. We instead refer interested readers to the sources cited above.

Only 1 trial of depression treatment after MI (ENRICHD) has been adequately powered to detect an effect on mortality and recurrent infarction, and that study found no such effect.[120] The investigators identified a number of limitations of the study that may explain the lack of an effect, including the small difference in posttreatment depression between the intervention and usual care groups. Although post hoc analyses of ENRICHD and other treatment trials have shown that patients who respond to depression treatment have better survival than those who do not,[83] this type of subgroup analysis does not justify causal inferences.[121] There is not yet any strong evidence that treating depression improves survival after ACS; however, worsening depression is associated with worse clinical outcomes, and severe or persistent depression is reason enough to consider more comprehensive evaluation and treatment or referral to a mental health specialist. More research is needed to determine the risks and benefits of routine screening for depression, to identify safe and effective treatments, and to determine whether treating depression after ACS improves clinical outcomes.

Limitations

This review has several limitations. Although we conducted a comprehensive review of the peer-reviewed research literature to formulate recommendations, we did not include studies from the "gray literature," such as agency reports, doctoral dissertations, or conference proceedings. Additionally, only English-language studies were considered. Because positive studies conducted in non–English-language countries are more likely to be published in English than null studies, a review that is limited to English-language studies may overestimate the effect.[122,123] The interpretation of study characteristics, methodology, and outcomes was limited by the availability of information provided in the publications. The literature examining the relationship between depression and ACS outcomes spanned several decades, during which there were marked changes in diagnostic criteria and treatments for ACS and for depression. We assessed the risk factor potential of depression on the basis of a strong, consistent association between the risk factor and outcome, evidence that the risk factor is not explained by other variables or covariates linked to both the risk factor and outcomes, and the existence of a plausible biological mechanism to account for the observed relationship. We did not, as others have suggested when defining a causal risk factor, require evidence that reduction of the risk factor reduces risk.[124] The evidence remains scant in this area for depression treatment, and further research is needed to determine whether treating depression will improve post-ACS outcomes. Finally, we restricted our review to ACS. Additional review is needed to assess the role of depression in the medical outcomes of other forms of heart disease, such as heart failure, and of cardiac procedures. For example, the effect of depression has been found to be greater after ACS than after elective angioplasty or coronary artery bypass graft surgery.[8]

Recommendations

On the basis of the present systematic review, the committee identified a number of ways in which the evidence linking depression with ACS, or CHD in general, could be strengthened in terms of the study design, presentation of results, and future directions for research.

Study Design

- Use of both structured diagnostic interviews and self-report questionnaires to assess depression
- Greater consistency in defining outcomes, including rigorous adjudication of events
- Consideration of individual end points (ie, assess nonfatal cardiac events, cardiac mortality, and all-cause mortality as individual outcomes rather than as a composite)
- Better differentiation between mediators and confounders in multivariable models

Presentation of Results

- Greater clarity in the description of methods, including depression measurement (timing and setting of assessment) and the rationale for the inclusion of a covariate in multivariable models
- Reporting of both unadjusted and risk-adjusted analyses

Recommendations for Future Research

- Investigate the biobehavioral mediators of the relationship between depression and cardiac outcomes
- Explore the role of depression in other potential manifestations of CHD, including heart failure and revascularization procedures, and develop a consensus statement that reviews the current evidence
- Identify the subtypes and characteristics of depression most associated with an increased risk for morbidity and mortality after ACS
- Assess the potential contributions of other comorbid psychiatric conditions (eg, anxiety disorders), which may independently or synergistically increase the risk for adverse events in patients with ACS and in other cardiac populations
- Clarify the role of depression as a potential risk factor for incident CHD
- Assess the risks and benefits of routine screening for depression, including the impact of screening in different contexts of care and the best means of implementation and coordination of care
- Identify safe and effective treatments for depression after ACS
- Conduct randomized controlled clinical trials to determine whether effective treatment of depression improves survival and other patient outcomes after ACS

Conclusions

The committee conducted an extensive review of published studies to make a recommendation as to whether depression should be elevated to the status of a risk factor for ACS by the AHA. The prognostic value of depression was considered for all-cause mortality, cardiac mortality, and composite outcomes comprising mortality or nonfatal cardiac events. We examined the strength, consistency, independence, and generalizability of published studies that met the criteria for inclusion in our review.

In summary, these studies were found to be heterogeneous with respect to the demographic characteristics of the samples, the measurement and definition of depression, the length of follow-up, and the covariates that were included in the multivariable statistical models. The positive studies varied in terms of the strength of the associations that were identified, and a minority of the studies were negative. Nevertheless, the preponderance of evidence supports the conclusion that depression after ACS is a risk factor for all-cause and cardiac mortality, as well as for composite outcomes including mortality or nonfatal cardiac events. As such, depression should be elevated to the level of a risk factor for poor prognosis after ACS by the AHA and other health organizations.

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*Modest.
†Significant.

Reviewer Disclosures

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