Depression Treatment in Patients With Coronary Artery Disease: A Systematic Review

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ABSTRACT

Objective: Depression has been linked to adverse coronary artery disease outcomes. Whether depression treatment improves or worsens coronary artery disease prognosis is unclear. This 25-year systematic review examines medical outcomes, and, secondarily, mood outcomes of depression treatment among patients with coronary artery disease.

Data Sources: We systematically reviewed the past 25 years (January 1, 1986–December 31, 2011) of prospective trials reporting on the medical outcomes of depression treatment among patients with established coronary artery disease using keywords and MESH terms from OVID MEDLINE. Search 1 combined *depression* AND *coronary artery disease* AND *antidepressants*. Search 2 combined *depression* AND *coronary artery disease* AND *psychotherapy*. Search 3 combined *depression* AND *revascularization* AND *antidepressants* OR *psychotherapy*.

Study Selection: English-language longitudinal randomized controlled trials, with at least 50 depressed coronary artery disease patients, reporting the impact of psychotherapy and/or antidepressants on cardiac and mood outcomes were included.

Data Extraction: Data extracted included author name, year published, number of participants, enrollment criteria, depression definition/measures (standardized interviews, rating scales), power analyses, description of control arms and interventions (psychotherapy and/or medications), randomization, blinding, follow-up duration, follow-up loss, depression scores, and medical outcomes

Results: The review yielded 10 trials. Antidepressant and/or psychotherapy did not significantly influence coronary artery disease outcomes in the overall population, but most studies were underpowered. There was a trend toward worse coronary artery disease outcomes after treatment with bupropion.

Conclusions: After an acute coronary syndrome, depression often spontaneously remitted without treatment. Post–acute coronary syndrome persistence of depression predicted adverse coronary artery disease outcomes. Antidepressant and/or psychotherapy, particularly as part of the Coronary Psychosocial Evaluation Studies intervention, may improve prognosis in persistent depression among post–acute coronary syndrome patients. Noradrenergic antidepressants should be prescribed cautiously in patients with coronary artery disease.

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The lifetime risk of coronary artery disease at age 40 years is ~50% among men and 33% among women.[1] One in 3 deaths in the United States is from cardiovascular disease.[2] About 17%–27% of patients with coronary artery disease have major depression, and a significantly larger percentage have subsyndromal symptoms of depression.[3] Depression has been linked to higher health care costs[4,5] and to worse outcomes in patients with coronary artery disease.

Both behaviors, such as smoking,[6] lack of exercise,[6] and/or treatment nonadherence,[7–11] and biomedical factors, particularly inflammation,[12,13] are believed to mediate the effect of depression on coronary artery disease prognosis. Other implicated biomedical factors include insulin resistance,[14,15] endothelial dysfunction,[16,17] platelet activation,[18,19] and altered autonomic nervous system activity[20,21] (eg, reduced heart rate variability).[22,23]

In a 2006 meta-analysis of 54 studies,[24] depression predicted adverse coronary artery disease outcomes (pooled adjusted relative risk [RR] = 1.53). However, in 2 systematic reviews,[25,26] only about half of the studies reported a significant association between depression and coronary artery disease prognosis.

The mixed results may be because (1) negative studies had inadequate power and (2) only some depressive subtypes predict adverse coronary artery disease outcomes[25] (eg, persistent but not transient depression correlates with poor outcomes after an acute coronary syndrome).[27,28]

DEPRESSION TREATMENT IN CORONARY ARTERY DISEASE: OTHER SYSTEMATIC REVIEWS

A 2011 systematic review[29] (16 studies) concluded that psychologic interventions and selective serotonin reuptake inhibitors (SSRIs) modestly benefited depression in patients with coronary artery disease. No evidence for improved medical outcomes from psychological interventions was found. Sparse evidence suggested that SSRIs might improve coronary artery disease prognosis.

A 2009 meta-analysis[30] (51 studies) reported that psychological interventions for patients with coronary artery disease reduced depression and mortality. Interventions included single techniques (cognitive, educational, behavioral, supportive) or combinations. Indirect evidence suggested that depression responded best to cognitive psychotherapy and to behavioral lifestyle interventions.[30] Behavioral techniques may have been best for medical outcomes.

Unlike the only other recent systematic review of this topic,[29] we included randomized clinical trials of antidepressants in patients with coronary artery disease for conditions other than depression (eg, smoking cessation) if depressed patients were enrolled. This inclusion allowed discussion about noradrenergic antidepressants.

Clinical Points

- After acute coronary syndrome, depression symptoms should be monitored. Transient mild or moderate depression does not affect prognosis, but persistence of depression is a high-risk marker for adverse coronary events.
- The Coronary Psychosocial Evaluation Studies intervention, in which patients could choose between problem-solving therapy and/or antidepressants, improved coronary artery disease outcomes in patients with persistent depression after acute coronary syndrome.
- Among patients with coronary artery disease, prescription of noradrenergic antidepressants should be done with caution in consultation with the patient's internist or cardiologist.

Antidepressant Toxicity

Are antidepressants safe in coronary artery disease? Five large longitudinal studies have conflicting results. The National Health and Nutrition Examination Survey[31] and a community-based trial by Penninx et al[32] (7,893 and 2,847 participants, respectively) reported that antidepressants did not mediate increased mortality and/or coronary artery disease incidence associated with depression. However, in the Nurses' Health Study[33] and the Women's Health Initiative[34] (63,469 and 136,293 participants, respectively), antidepressants mediated the link between depression and increased mortality. These 4 studies[31–34] enrolled participants without coronary artery disease; 1 also included coronary artery disease patients.[32]

The Women's Health Initiative[34] reported that mortality was significantly associated with both SSRIs and non-SSRIs. The Nurses' Health Study[33] reported that sudden cardiac deaths were significantly associated with SSRIs (hazard ratio [HR] = 5.07, $P \leq .05$) and trended toward significance with non-SSRIs (HR = 3.19; 95% CI, 0.92–11.00).

Mechanisms proposed to explain antidepressant toxicity include ventricular arrhythmias from prolonged QTc,[33–36] vasoconstriction from serotonin,[37] and bleeding due to platelet inhibition from SSRIs.[37]

The Heart and Soul study[38] followed 1,017 stable outpatients with coronary artery disease. Depression predicted adverse cardiovascular outcomes. The SSRIs and tricyclic antidepressants did not affect coronary artery disease prognosis.[38] "Other" antidepressants, however, partly mediated the link between depression and cardiovascular events.[38]

This systematic review focuses on how psychotherapy and antidepressants affect coronary artery disease prognosis in depressed patients. Depression outcomes from the studies were a secondary focus, allowing evaluation of the clinical benefits and risks of different treatments.

METHOD

We systematically reviewed the past 25 years of prospective trials reporting on the medical outcomes of depression treatment among patients with established coronary artery disease using OVID MEDLINE. Two searches focused on depression treatment (antidepressants or psychotherapy) of patients with coronary artery disease. Because depression also predicts adverse post–coronary artery bypass graft medical outcomes,[39–41] a third search compiled studies of depression treatment after coronary revascularization. Search criteria were as follows:

1. Antidepressant treatment of depressed coronary artery disease patients
   {exp Depression/ or depression.mp. OR exp Depressive Disorder/ or depressive.mp.} AND {coronary artery disease.mp. or exp Coronary Artery Disease/ OR myocardial ischemia.mp. or exp Myocardial Ischemia/ OR myocardial infarction.mp. or exp Myocardial Infarction/} AND {antidepressant.mp. or exp Antidepressive Agents}
2. Psychotherapy of depressed coronary artery disease patients
   {exp Depression/ or depression.mp. OR exp Depressive Disorder/ or depressive.mp.} AND {coronary artery disease.mp. or exp Coronary Artery Disease/ OR myocardial ischemia.mp. or exp Myocardial Ischemia/ OR myocardial infarction.mp. or exp Myocardial Infarction/} AND {psychotherapy.mp. or exp Psychotherapy}
3. Antidepressant treatment OR psychotherapy after coronary revascularization
   {exp Myocardial Revascularization/ OR Angioplasty/ or angioplasty.mp. OR coronary artery bypass graft.mp. OR transmyocardial laser revascularization.mp. OR coronary atherectomy.mp.} AND ({psychotherapy.mp. or exp Psychotherapy/} OR {antidepressant.mp. or exp Antidepressive Agents/}) AND {exp Depression/ or depression.mp. OR exp Depressive Disorder/ or depressive.mp}.

Inclusion and Exclusion Criteria

English–only randomized controlled trials (RCTs), published between January 1, 1986, and December 31, 2011, that included at least 50 depressed subjects (depression and/or major depression) with coronary artery disease and reported the impact of psychotherapy and/or antidepressants on coronary artery disease outcomes were included. Depression diagnosis was based on accepted cutoff scores using common, validated depression rating scales.

Included studies compared psychiatric intervention to usual care. Studies of multidisciplinary treatment with psychological care (eg, cardiac rehabilitation) were excluded. We excluded studies comparing usual care to depression intervention supplemented with cardiac treatment because outcome differences might reflect cardiac treatment rather than psychiatric care.

Antidepressant RCTs had to include placebo controls. In psychotherapy trials, control subjects received usual care plus clinical management.

Studies had to report results specific to coronary artery disease patients. Endpoints were clinical—death, acute

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Table 1. Quality of Antidepressant and Psychotherapy Trial Methodology

Study	Members of Target Population Underrepresented by the Study Population	Placebo-Controlled	Jadad Score: Randomization	Jadad Score: Double-Blinding	Jadad Score: Minimal Follow-Up Loss < 6%	Power Analysis/ Medical or Psychosocial	Blinded Review of Medical Endpoints	Methodological Accuracy of Medical Outcomes Measurement (high/good/fair/poor)	Providers Trained in Psychotherapy Technique	Typical No. of Psychotherapy Sessions	% Intervention Patients Participating in Therapy
Strik et al[43] (fluoxetine)	Already in treatment for depression	Yes	1	2	1	Yes/psychosocial	Yes	Good: repeated clinical assessment	NA	NA	NA
SADHART[45,46] (sertraline)	Already in treatment for depression Severe depression	Yes	1	2	1	Yes/medical	Yes[a]	Not reported: 6-mo follow-up High: 7-y follow-up, review of government record plus last contact	NA	NA	NA
MIND-IT (mirtazapine/ citalopram/ referral) [48–50]	Already in treatment for depression Severe depression	No	2	0	1	Yes/psychosocial and medical	Yes	High: repeated clinical assessment plus medical record review	No	Not reported	Not reported
MIND-IT nested trial (mirtazapine)[48–50]	Already in treatment for depression Severe depression	Yes	2	2	1	Yes/psychosocial	Yes	High: repeated clinical assessment plus medical record review	NA	NA	NA
CREATE (citalopram)[51]	Already in treatment for depression Severe, refractory depression Personality disorder	Yes	2	2	1	Yes/psychosocial	Yes	High: weekly patient interviews	Yes	12–20 interpersonal therapy sessions[60]	86% went to ≥ 12 sessions
Rigotti et al[44] (bupropion)	Major depression excluded, but ~ ½ of population had a BDI score > 10	Yes	2	2	0	Yes/psychosocial	Yes	Good: admission chart reviewed and patient report during 4 follow-up visits	NA	NA	NA
COPES[52,53]	Severe depression	NA	2	NA	1	Yes/psychosocial	Yes	High: patient interview plus medication record confirmation	Yes	6–8 problem-solving therapy sessions[61]	~ 69% went to ≥ 6 sessions[b]
ENRICHD[58]	Already in treatment for depression Severe depression	NA	1	NA	1	Yes/medical	Yes	High: blinded review of medication record	Yes	Traditional: 8–20[60] Brief cognitive-behavioral therapy: ~ 6[62]	71% went to ≥ 6 sessions
Women's Hearts Study[57]	Personality disorder	NA	2	NA	1	Yes/psychosocial	Not reported	Fair: 1 patient interview at end	Yes	16 cognitive-behavioral stress management sessions[63]	71% went to ≥ 16 sessions
M-HART[54–56]	None	NA	2	NA	1	Yes/medical	Yes	High: review of medical and government records plus family interviews	NA	NA	95% received nursing intervention per protocol
Bypassing the Blues[59]	Already in treatment for depression	NA	2	NA	1	Yes/psychosocial	Yes	High: multiple (3–10) phone interviews confirmed with medical records	NA	NA	By ⅓ year: 83% had ≥ 3 contacts with care manager By end: 10 median contacts (range, 0–28)

[a]Six-month outcomes were blinded; authors did not report whether reviewers of 7-year outcomes were blinded. [b]Estimated from mean and standard deviation.

Abbreviations: BDI = Beck Depression Inventory, COPES = Coronary Psychosocial Evaluation Studies, CREATE = Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy, ENRICHD = Enhancing Recovery in Coronary Heart Disease, M-HART = Montreal Heart Attack Readjustment Trial, MIND-IT = Myocardial Infarction and Depression–Intervention Trial, NA = not applicable, SADHART = Sertraline Antidepressant Heart Attack Randomized Trial.

coronary syndrome, revascularizations, or hospitalizations. We excluded subjective symptom reports to avoid bias from patient distress. Studies of the same participants, with similar measures, were excluded to avoid duplication.

Quality Assessment

Studies with Jadad scores[42] < 3 were excluded. Jadad scores for double-blinding were inapplicable to psychotherapy trials, since assignment to psychotherapy cannot be blinded.

RESULTS

We found 342 English-language articles (1986–2011) on antidepressants and coronary artery disease, 193 on psychotherapy and coronary artery disease, and 42 on depression treatment and revascularization. Application of inclusion/exclusion criteria yielded 10 RCTs (Table 1). The CREATE trial was an RCT of psychotherapy and of antidepressants; thus, there were 6 antidepressant RCTs,[43–53] 5 psychotherapy RCTs[51–58] and 1 RCT in revascularized patients.[59]

Quality Assessment of the Methodology of Depression Treatment Trials

Eight RCTs had high overall quality (Table 1). The bupropion trial was of fair quality because follow-up loss was considerable (23%).[44] The other trials had minimal follow-up loss (≤ 6%). Jadad scores ranged from 3 to 5. Medical endpoint measurement followed standard practice. Medical outcome reviews were blind to treatment status in all studies, but the Women's Hearts Study[57] did not comment on blinding.

All but 2 studies reported hard outcomes (myocardial infarction/death) separately from soft outcomes. The bupropion trial[44] and Coronary Psychosocial Evaluation Studies (COPES)[52] reported a composite of hard and soft outcomes (eg, revascularization or hospitalizations), which are more prone to bias.[64] Hospitalization or revascularization decisions may be influenced by, and confound for, patient distress. Thus, fewer soft events might reflect reduced distress from depression treatment.

Another critique relates to whether the study population represented the target population of the trial. Except for the Myocardial Infarction and Depression–Intervention Trial (MIND-IT),[48–50] all studies excluded at least 1 of these subgroups: participants already in depression treatment, those with severe depression/suicidal ideation, or those with personality disorders (Table 2). Consequently, results are less applicable to the general population of depressed patients with coronary artery disease.

Psychotherapy and Established Coronary Disease

Overview of study methodologies. Of 5 psychotherapy trials (Tables 2 and 3), 4 evaluated established psychotherapies: cognitive-behavioral therapy (CBT; Enhancing Recovery in Coronary Heart Disease [ENRICHD][58]), interpersonal therapy (Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy [CREATE][51,65]), problem-focused psychotherapy/problem-solving therapy (COPES[52,53]), and cognitive-behavioral stress management (Women's Hearts Study[57]). The Montreal Heart Attack Readjustment Trial (M-HART)[54–56] involved psychotherapeutic home visits from nurses.

Psychotherapy: outcomes in the overall study populations. In the Women's Hearts Study and M-HART, psychotherapy (cognitive-behavioral stress management and psychotherapeutic home visits by cardiology nurses, respectively) did not affect depression and coronary artery disease outcomes in the overall group (Women's Hearts Study [deaths] intervention and usual care 0%, P = not significant; M-HART [deaths] intervention 5.5% vs usual care 3.9%, $P = .18$). Less than half of the participants were depressed in both studies.

In CREATE,[51] outcomes were not significantly different after interpersonal therapy and clinical management versus clinical management alone (Hamilton Depression Rating Scale score: interpersonal therapy and clinical management vs clinical management = 12.1 vs 14.4, respectively, $P = .06$; cardiovascular events: interpersonal therapy and clinical management vs clinical management = 4 vs 2, respectively).

The ENRICHD intervention[58]—CBT, sometimes with antidepressants—modestly improved depression (6-month mean Beck Depression Inventory [BDI] score decrease, CBT vs usual care: 12.2 vs 9.1, respectively, $P < .001$), but did not affect post–acute coronary syndrome outcomes (death/myocardial infarction).

In ENRICHD[58] and the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART),[46] depression often remitted spontaneously after an acute coronary syndrome among controls. This finding suggests reserving active treatment for persistent depression. Consequently, COPES only enrolled participants with persistent depression present within a week of the acute coronary syndrome and 3 months later.[53] The COPES intervention improved depression and major post–acute coronary syndrome cardiac events over usual care.[53] Cardiac events consisted of a composite of hard (deaths, myocardial infarctions) and soft (hospitalizations for unstable angina and/or urgent revascularization) outcomes.

Psychotherapy: outcomes in patient subgroups. Like ENRICHD,[66] the M-HART treatment arm found that depression response predicted greater survival, and treatment-recalcitrant depression predicted higher mortality.[67]

The M-HART 5-year survival rates after treatment were worse among participants with repressive coping styles (repressors) (HR = 1.95, $P < .05$) and superior among highly anxious men (HR = 0.48, $P < .05$) than after usual care.[56]

Antidepressants

Overview of study methodologies. The search yielded 6 antidepressant RCTs (Table 4): SADHART,[45–47] MIND-IT,[48–50] CREATE,[51] COPES,[52] a fluoxetine trial,[43] and a bupropion trial.[44] These studies enrolled depressed participants to assess antidepressant treatment of depression, except for the bupropion trial,[44] which evaluated bupropion

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Table 2. Psychotherapy Trials: Patient Characteristics and Details of Intervention

Study	Intervention
Women's Hearts Study[57] Duration: 1 y Control: usual care Intervention: group cognitive-behavioral stress management All participants received general advice in the first wk of enrollment about diet, exercise, smoking, type A behavior, relaxation practices, qigong, and stress prevention	Group cognitive-behavioral stress management: 10 weekly meetings, then 10 more over 1 y 5–9 participants were educated about coronary artery disease and its relationship to stress; were trained in self-monitoring (behavior, thoughts, and body signals), behavior skills, and cognitive restructuring; and discussed spiritual development and life values
CREATE[51] Duration: ¼ y 4 arms: (1) clinical management and citalopram, (2) clinical management and placebo, (3) clinical management, placebo, and IPT, (4) clinical management, citalopram, and IPT All participants attended weekly individual 20-min clinical management consisting of: • Education about depression and medication use plus encouragement of adherence • Reassurance • Assessment of Montgomery-Asberg Depression Rating Scale depression scores and SSRI side effects with a checklist • Queries about serious adverse events and cardiovascular concerns • Specific psychotherapy (eg, exploration of interpersonal issues) was avoided	Arms 3 and 4: 40–60 min of IPT was provided weekly after clinical management
ENRICHD[58] Duration: ½ y of individual CBT, ½–¾ y of group CBT, 0–1 y of antidepressants; individual CBT stopped after ½ y or after 3 treatment outcome criteria were met: (1) 6 therapy sessions (2) Adequate CBT skills (3) 2 consecutive Beck Depression Inventory scores ≤ 7 Control: usual care Intervention: CBT ± antidepressants All participants received written materials about cardiac risk factors from the American Heart Association	If needed, CBT took place more than once weekly; CBT was as described by Beck; social isolation was addressed with CBT and supplemented with techniques based on social learning theory and other psychotherapeutic support trials If depression was severe or persisted past 5 wk, sertraline was prescribed; if sertraline was not tolerated or not working, alternatives (another SSRI or nortriptyline) were considered
M-HART[54–56] Duration: 1 y Control: usual care Intervention: supportive home visits by nurses if GHQ-20 score ≥ 5 or if the patient was readmitted to the hospital; visits were stopped if they no longer appeared to be needed	Each participant had ≥ 2 home visits by an assigned nurse; in the first visit, the nurse asked about physical symptoms and stressors; individualized interventions included emotional support, health education, practical advice, and health care referrals Nurses were experienced in coronary care, but not in behavioral health; groups of nurses met with a psychiatrist for weekly team case reviews to gain experience and plan care
COPES[52,53] Duration: ½ y Control: usual care; physicians informed of depression Intervention: choice of PST and/or antidepressants and then stepped care	Participants chose between PST and/or antidepressants and were then followed using a stepped-care approach: every 8 wk, patients without prespecified improvement in PHQ-9 depression scores were offered the choice to switch treatments (eg, from PST to antidepressants), add another treatment, or intensify the original treatment If psychotherapy was chosen: PST is a protocol-driven, brief, problem-focused form of CBT; weekly 30- to 45-min PST visits: (1) taught how to systematically address psychosocial problems and (2) encouraged to engage in pleasant activities; visit frequency was adjusted based on progress and patient preference If antidepressants were chosen: psychiatrist/nurse practitioner visits were every 1–2 wk for dose change, then every 3–5 wk as needed; choices included sertraline, escitalopram, venlafaxine, bupropion, and mirtazapine; for patients already taking antidepressants, decisions were coordinated with the prescribing physician
Bypassing the Blues[59] Duration: 8 mo Control: usual care; physicians informed of depression Intervention: collaborative care with participants and primary care physician Telephone-delivered care by nurse care managers was supervised by a clinical team of specialists (an internist, a psychiatrist, and a psychologist); depending on patient motivation, antidepressant acceptance, and depression severity, nurses phoned every other week for 2–6 mo, then less often; participant choice and collaboration with primary care physicians were emphasized	First phone call: nurses (1) obtained medical, cardiac, and psychiatric history; (2) discussed heart disease, depression, and its cardiac impact; and (3) promoted self-management workbooks (prioritized healthy diet, rest, exercise, pleasant activities, and avoidance of tobacco/alcohol) During next biweekly phone calls: (1) education, (2) promotion of self-management and adherence, and (3) medication adjustment based on PHQ-9 scores and side effects Treatment choices included self-management or antidepressants; if 6 wk of 1 modality alone failed, then both were recommended; watchful waiting was a choice if depression was mild and a first episode; mental health referrals were suggested for severe psychopathology, unresponsive depression, complex psychosocial problems, or patient preference Antidepressant choice based on preference, history, and insurance; suggestions were (1) replace tricyclic antidepressant/benzodiazepine with SSRI, (2) citalopram if no prior SSRI treatment or preference, and (3) SNRI, bupropion, or another SSRI after 2 failed SSRI trials; if nonadherence, nurses gave motivational interviewing and contacted primary care physicians ± clinical team

Abbreviations: CBT = cognitive-behavioral therapy, COPES = Coronary Psychosocial Evaluation Studies, CREATE = Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy, ENRICHD = Enhancing Recovery in Coronary Heart Disease, GHQ-20 = 20-item General Health Questionnaire, IPT = interpersonal therapy, M-HART = Montreal Heart Attack Readjustment Trial, MIND-IT = Myocardial Infarction and Depression–Intervention Trial, PHQ-9 = 9-item Patient Health Questionnaire, PST = problem-solving therapy, SADHART = Sertraline Antidepressant Heart Attack Randomized Trial, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

Table 3. Psychotherapy Trial Outcomes in the Overall Population and Subgroups

	Change in Depression Score From Intervention Over Controls		Change in Prognosis From Intervention Over Controls	
Study	Overall Population	Subgroups With Worse/Better Depression	Overall Population	Subgroups With Worse/Better Medical Outcomes
Women's Hearts Study[57] (N = 198) Control: usual care Intervention: 1-y group-based cognitive-behavioral stress management	Myocardial infarction/revascularization/angina > 4 mo ago; ~50% depressed CPRS-S-A score after 1 y: NS	NA	NS	NA
M-HART[54–56] (N = 1,376) Control: usual care Intervention: 3 mo; psychotherapeutic home visits by nurses	Myocardial infarction within 1 wk; ~33% depressed GHQ-20 after 3 mo and BDI after 1 y: NS	Worse distress: women or repressors?[a] Better mood: highly anxious men?[a]	1-y survival: NS	Worse 5-y survival: Treatment-resistant distress[c] Repressors (HR = 1.95, $P < .05$) Better 5-y survival: Treatment-responsive depression[c] Men with high anxiety (HR = 0.48, $P < .05$)
ENRICHD[58] (N = 2,481) Control: usual care; physicians informed of depression and social isolation Intervention: CBT ± antidepressants Duration: Individual CBT: ≤ 6 mo Group CBT: ≤ 9 mo Antidepressants: ≤ 1 y	Myocardial infarction within 28 d; 73% depressed 6-mo BDI score CBT: modestly better; 12.2 mean decrease ($P < .001$) Usual care: 9.1 mean decrease 30-mo BDI score: NS	NA	~2.5-y death/myocardial infarction: NS	Worse late mortality (½ y to 1 y post–acute coronary syndrome): treatment-resistant depression[d] Better outcomes (nonfatal myocardial infarction, death): treatment-responsive depression (HR = 0.37, $P < .03$); white men (HR = 0.63, $P = .006$)
CREATE[51] (N = 284) 4 arms (all had clinical management): (1) Clinical management and placebo (2) Clinical management and citalopram (3) IPT, clinical management, and placebo (4) IPT, clinical management, and citalopram	Stable coronary artery disease; 100% depressed Arm 1 vs 3 HDRS score: NS Arm 2 vs 4 HDRS score: NS (ie, no benefit from adding IPT)	Worse mood: low social support	NS	NA
COPES[52,53] (N = 237) Control: usual care, physicians informed of depression Intervention: choice of PST and/or antidepressants, then a stepped approach	Depression persisting 3 mo after myocardial infarction/ unstable angina BDI score: Intervention: 5.7 mean decrease ($P = .05$) Usual care: 1.9 mean decrease	NA	Major cardiac events[b]: Usual care: 13% Intervention: 4% ($P = .047$)	NA
Bypassing the Blues[59] (N = 302) Control: usual care; physicians informed of depression Intervention: telephone-delivered care by nurse managers supervised by specialists; treatment options included self-management and antidepressants	About to be discharged from hospital after coronary artery bypass surgery 100% depressed HAM-D decrease after 8 mo from baseline: Intervention better ($P = .001$) Usual care: 4.5 mean decrease Intervention: 7.6 mean decrease	NA	Rehospitalization: NS	NA

[a]See discussion about M-HART subgroups.
[b]Major adverse cardiac events include deaths, myocardial infarctions, and hospitalizations for unstable angina and/or urgent revascularization.
[c]Hazard ratio not reported but $P < .000163$; repressors are study participants with repressive coping styles.
[d]Association of BDI change with survival: $P < .007$; HR mortality = 1.6; BDI change ≤ 10 vs BDI change = 0.
Abbreviations: BDI = Beck Depression Inventory, CBT = cognitive behavioral therapy, COPES = Coronary Psychosocial Evaluation Studies, CPRS-S-A = Comprehensive Psychopathological Rating Scale-Self-Affective, CREATE = Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy, ENRICHD = Enhancing Recovery in Coronary Heart Disease, GHQ-20 = 20-item General Health Questionnaire, HDRS = Hamilton Depression Rating Scale, HR = hazard ratio, IPT = interpersonal therapy, M-HART = Montreal Heart Attack Readjustment Trial, NA = not applicable, NS = no significant difference, PST = problem-solving therapy.

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Table 4. Findings of Randomized Placebo-Controlled Antidepressant Trials

Drug (Study)	Population	Follow-Up, y	Overall Group Depression Improvement	Subgroups With Lower Likelihood of Depression Improvement	Overall Group: Effect on Medical Outcome of Antidepressant Versus Placebo	Subgroups With Worse Medical Outcomes
Sertraline 50–200 mg/d × 24 wk (SADHART[45,46])	369 participants 1 mo after an acute coronary syndrome	1 y: myocardial infarction/death 7 y: death only	CGI-I responders Sertraline: 72% Placebo: 51% (P = .049) Mean HDRS score change: NS	Mild/moderate depression (not severe) First depression episode Post–acute coronary syndrome onset (except severe depression) All 3 of above	No significant difference Vitals, electrocardiograph, including QTc left ventricle ejection fraction 1-y mortality or myocardial infarction Sertraline: 5 myocardial infarction, 2 deaths Placebo: 7 myocardial infarction, 5 deaths 7-y mortality Sertraline: 20.8% Placebo: 21.0%	Worse 7-y mortality in both placebo and sertraline arms Treatment-resistant depression 28% (HR = 2.3 vs transient depression, P < .006) Severe baseline depression: 26% (HR = 2.7 vs mild/moderate depression, P < .001)
Citalopram 20–40 mg/d × 20 wk (CREATE[51])	284 participants with established coronary artery disease	0.25 y	HDRS responders Citalopram: 53% Placebo: 40% (P = .03)	First depression episode Post–acute coronary syndrome onset (within 6 mo) Angiotensin-converting enzyme inhibitor use	No significant difference Vitals, electrocardiograph, including QTc Myocardial infarction IPT ± citalopram: 0 myocardial infarctions IPT ± placebo: 2 myocardial infarctions	NA
Sustained-release bupropion 300 mg/d × 12 wk (Rigotti et al[44])	248 smokers with coronary artery disease admitted for cardiovascular disease	1 y	BDI change: bupropion vs placebo P = NS, RR not reported	NA	1-y cardiovascular events Overall: no significant difference After 12-wk medication trial: First 30 d: RR = 1.02, P = NS 30 d to 1 y after trial: RR = 3.93, P < .005 No significant difference Blood pressure Serious noncardiac events	NA
Fluoxetine 20–60 mg/d × 25 wk (Strik et al[43])	54 participants 3–12 mo after a first myocardial infarction	0.5 y	Responders as measured by HDRS Fluoxetine: 48% Placebo: 26% (P = .05)	Moderate/severe depression (HDRS score > 21)	No significant difference Vitals, electrocardiograph, including QTc Death/myocardial infarction (0 for each arm) Cardiac hospitalizations (mirtazapine = 8 vs placebo = 10, P = .34)	NA
Mirtazapine 15–45 mg × 8–24 wk OR citalopram[b] × 16–24 wk OR nonspecific antidepressant × 6 mo (MIND-IT[48–50])	331 participants 3–12 mo after a myocardial infarction	1.5 y	Mean BDI score Intervention: 11.0 Usual care: 10.2	NA	No significant difference Cardiac event rate[a] Intervention (14%) vs usual care (12%) (P = NS) Any antidepressants = 13% vs no antidepressants = 15% (P = NS)	Treatment-resistant depression: Nonresponder to antidepressants vs usual care cardiac events at 1y (death and hospitalization): HR = 2.6 (P = .02) Nonresponders: 25.6% Usual care: 11.2%
Mirtazapine 15–45 mg/d × 8–24 wk[b] (MIND-IT nested trial[48–50])	94 participants 3–12 mo after a myocardial infarction	0.5 y	Mean DSCL improvement: After 8 wk: mirtazapine = 4.6, placebo = 1.72 (P = .02) After 24 wk: mirtazapine =6.91, placebo = 1.82 (P = .02) Remission measured by HDRS: NS	NA	Significant difference Mean weight gain: 1.7 kg (P < .0001) No significant difference Vitals, electrocardiograph, including QTc Deaths/myocardial infarction (each arm = 0) Cardiac hospitalizations (mirtazapine = 8 vs placebo = 10, P = .34)	NA

[a]Cardiac events = cardiac death/myocardial infarction/ventricular arrhythmia/revascularization/congestive heart failure/myocardial ischemia.
[b]Nonresponders to mirtazapine/placebo after 8 weeks were withdrawn from nested trial and returned to larger treatment trial to receive citalopram × 16 weeks.
Abbreviations: BDI = Beck Depression Inventory, CGI-I = Clinical Global Impressions–Improvement, CREATE = Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy, DSCL = Depression Symptom Checklist, HDRS = Hamilton Depression Rating Scale, HR = hazard ratio, IPT = interpersonal therapy, MIND-IT = Myocardial Infarction and Depression–Intervention Trial, NA = not applicable, NS = not significant, RR = risk ratio, SADHART = Sertraline Antidepressant Heart Attack Randomized Trial.

for smoking cessation. Although the bupropion trial did not enroll anyone diagnosed with MDD, about half of the participants were depressed (BDI score > 10).

In MIND-IT,[50] 2 RCTs (one nested in the other) included 331 depressed post–myocardial infarction participants who were randomized to usual care or a depression treatment intervention. Depression treatment options included citalopram, referral to tailored psychiatric treatment, or enrollment in the nested RCT. The nested RCT[48] further randomized 94 participants to placebo or mirtazapine for 8 weeks. Responders continued treatment for 16 weeks. Nonresponders were withdrawn from the nested mirtazapine/placebo trial and prescribed citalopram.[48]

All but 2 antidepressant RCTs enrolled patients after a recent acute coronary syndrome; most bupropion trial participants had a recent acute coronary syndrome.[44] Some participants had other acute cardiovascular conditions, such as peripheral vascular disease. The CREATE participants had stable coronary artery disease, and only some of the participants also had a recent acute coronary syndrome.[51]

Antidepressant trials: outcomes in overall study populations. Sertraline,[45] citalopram,[51] fluoxetine,[43] and mirtazapine[48,50] improved depression in the overall study population (Table 4). These 4 antidepressants had no significant effect on vital signs, electrocardiogram parameters, or medical prognosis (Table 4). Mirtazapine was associated with weight gain (mean of 1.7 kg).[48]

Bupropion for 3 months did not benefit depression.[44] However, the study power was low; only about half of the study population had depression (BDI score ≥ 10). Bupropion had no significant effect on 1-year cardiovascular events over placebo (RR = 1.56; 95% CI, 0.91–2.69).[44] Cardiovascular events were a composite of both soft (hospitalizations, revascularizations) and hard (death, myocardial infarction) outcomes. Although a nonsignificant trend suggested that bupropion increased cardiovascular events, a post hoc analysis found that cardiovascular outcomes during the first 30 days after stopping medications were unaffected by bupropion (RR = 1.02; 95% CI, 0.51–2.01). However, more cardiovascular events occurred after the first month of completing bupropion treatment than placebo (covariate-adjusted RR = 3.12, $P = .05$).

Antidepressant trials: outcomes in patient subgroups. Table 4 lists subgroups with no significant mood benefit from antidepressants. Participants with first-time depressive episodes had no benefit from citalopram[65] or sertraline.[46] Among participants with a recent acute coronary syndrome, depression improved with sertraline,[45] fluoxetine,[43] and mirtazapine[48] but not with citalopram.[65]

Sertraline had no antidepressant benefit over placebo in 3 subgroups: first-time episode, mild-moderate depression, and onset after the acute coronary syndrome.[46] Recurrent, severe depressive episodes preceding the acute coronary syndrome were 70% more likely to improve with sertraline than with placebo.[46]

Depression severity is inconsistent in predicting the mood benefit of antidepressants. Mood response to citalopram[51] was unaffected by depression severity. Fluoxetine improved mild depression but not moderate/severe depression.[43] Conversely, sertraline was more likely to improve severe depression.[46]

The SADHART study[47] reported that severe depression predicted higher 7-year mortality rates (HR = 2.30, $P < .006$) compared to mild-moderate depression. Like ENRICHD[66] and M-HART,[55,56,67] MIND-IT[68] and SADHART[47] (Tables 3 and 4) found that improved depression after an acute coronary syndrome predicted survival. In MIND-IT,[68] post–acute coronary syndrome mood improvement predicted survival for participants in treatment but not for those in usual care. In contrast, SADHART participants with persistent depression had higher rates of mortality whether taking sertraline or placebo.[47]

Depression in Patients After Coronary Revascularization

Our third search yielded 1 RCT, the Bypassing the Blues trial, that enrolled 302 depressed patients.[59] Weeks after a coronary artery bypass graft, patients in the intervention arm underwent an 8-month telephone-delivered depression treatment by nurse care managers with as-needed mental health referrals (Table 2). Patient choice and collaboration between specialists and primary care physicians were emphasized. The intervention improved depression over usual care. Rehospitalization rates were unaffected. "Hard" cardiac outcomes were also unaffected, but power was low.[59]

DISCUSSION

Psychotherapy Studies: Outcomes in Overall Study Populations

Of the psychotherapy studies, only CREATE and the Women's Hearts Study interventions involved psychotherapy without medication (Table 2). The M-HART, ENRICHD, and COPES interventions specifically prescribed antidepressants among some patients; thus, all psychotherapy studies emphasized psychotherapy, but 3 also included antidepressant treatment.

Of the psychotherapy studies, only the COPES and ENRICHD interventions significantly improved depression. Only the COPES intervention significantly improved coronary artery disease prognosis. Negative findings do not necessarily indicate that all other study interventions were ineffective, as discussed below.

The M-HART and Women's Hearts Study interventions did not affect outcomes. However, the intervention may have been more useful for depressed participants than nondepressed patients. Outcomes specific to depressed patients were not separately reported. Thus, the impact of cognitive-behavioral stress management or nurses' home visits among depressed patients with coronary artery disease is still unknown.

The CREATE intervention, which added interpersonal therapy to clinical management, had no mood benefit over clinical management alone. This finding does not imply that interpersonal therapy has no benefit for depression over usual care. Unlike usual care, clinical management involved close

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follow-up, education, and support. Interpersonal therapy did not affect medical prognosis, but CREATE was not adequately powered for coronary artery disease outcomes.

The ENRICHD intervention, CBT with and without antidepressants, modestly improved depression but not coronary artery disease outcomes.[58] Depression often spontaneously improves after an acute coronary syndrome.[46,58] Furthermore, transient depression after a myocardial infarction has a benign prognosis.[27,28] Thus, high rates of spontaneous remissions may have diluted the mood and medical benefits of depression treatment.

Only the COPES intervention, focused on persistent depression after an acute coronary syndrome, improved mood and coronary artery disease outcomes.[53] Excluding transient post–acute coronary syndrome depression likely highlighted the treatment benefit. Also, COPES emphasized patient choice between treatment options (problem-solving psychotherapy and/or antidepressants). Support for patient autonomy may have enhanced mood response[69] and medical outcomes.

Unlike other studies, COPES only reported a composite cardiac endpoint of hard and soft cardiac events, which were not reported separately. Fewer soft cardiac events might reflect reduced distress from depression treatment. The COPES findings need confirmation with studies measuring hard endpoints.

The Prognostic Impact of Responsiveness to Depression Treatment

A link between persistence of depression beyond 6 months after an acute coronary syndrome with increased mortality was consistently reported across multiple studies (ENRICHD,[66] MIND-IT,[68] SADHART[47]; Tables 3 and 4) whether treatment involved psychotherapy or antidepressants. Two longitudinal trials also reported that after an acute coronary syndrome, persistent depression was linked to poor cardiac outcomes, while transient depression was benign.[27,28] Cardiac outcomes after transient depression were similar to those of nondepressed patients. Treatment-recalcitrant depression carried a higher mortality rate.[47,66–68]

Carney and Freedland's[67] review suggested that persistence of depression predicts adverse post–acute coronary syndrome outcomes when persistence reflects treatment recalcitrance. They reported a personal communication from the M-HART authors (R.M. Carney, K.E. Freedland; personal communication; 2004) noting higher mortality associated with depression persistence only in the treatment group, but not among usual care patients.[67]

Similarly, among ENRICHD participants without treatment, persistence or transience of depression did not impact coronary artery disease prognosis.[66] However, responders to the ENRICHD intervention predicted lower mortality (HR = 0.37) than nonresponders.[66] Increased BDI scores predicted higher mortality (HR ≥ 1.6) than did unchanged mood.[66]

The SADHART participants with persistent depression had higher mortality whether taking sertraline or placebo.[47] Thus, perhaps persistent depression carries a poor prognosis regardless of treatment. However, placebo-arm patients underwent clinical management, which may have felt therapeutic. Thus, Carney and Freedland[67] suggested that persistent depression in both the sertraline and placebo arms reflects treatment resistance.

If transient depression predicts better survival in intervention patients, but not in usual care patients, then improved depression alone does not explain lower mortality. As noted by Carney and Freedland,[67] depression response to treatment identifies patients with better survival (treatment responsiveness) and those with higher mortality (treatment recalcitrance).

On the other hand, 2 longitudinal observational studies reported that, after an acute coronary syndrome, persistent depression was linked to poor cardiac outcomes, while transient depression was benign.[27,28] Cardiac outcomes after transient depression were similar to those of nondepressed patients. One study[28] reported that 3.2% of participants were taking antidepressants, and 4.4% saw a mental health specialist. Thus, although most participants appeared to receive no treatment for depression, persistent depression predicted poor cardiac outcomes. Future research needs to clarify if an adverse coronary artery disease prognosis is specific to treatment-recalcitrant depression or to the persistence of depression irrespective of whether treatment was attempted.

In COPES,[70] researchers investigated whether the adverse prognosis of persistent depression resulted from a distinct pathophysiology (eg, greater inflammation or vascular depression). Three months after an acute coronary syndrome, 14 patients with persistent depression had more cerebrovascular white matter lesions than the 8 nondepressed patients. The difference became insignificant after adjustments for cardiovascular risk factors, but the pilot study had low power.[70] If persistent depression reflects cerebral and coronary atherosclerosis, its adverse prognosis may relate to extensive atherosclerosis.

Psychotherapy: Outcomes in Patient Subgroups

Identifying patient subgroups with particularly positive or adverse coronary artery disease outcomes after treatment can guide clinical decision-making. In M-HART,[56] repressors had worse 5-year survival rates after treatment with usual care. The M-HART researchers cited evidence that repressive coping predicts adverse post–myocardial infarction cardiac outcomes,[71] which may worsen further after repressors are confronted with psychological aspects of their illness.[72] Indirect measures of distress—benzodiazepine prescriptions and emergency department visits—were higher among repressors and mediated their lower survival rates. The authors suggested that nurse visits reduced survival by interfering with repressive defenses against awareness of their illness or mood.[55] However, if distress explained the

worse outcomes, why did adjusted BDI scores fail to mediate survival rates? The hypothesis that treatment lowers survival rates among repressors because of iatrogenic distress is interesting but remains speculative.

Highly anxious men had superior 5-year survival rates after treatment compared to usual care. Better survival was not linked to lower total depression or anxiety scores but was mediated by greater improvement of somatic BDI subscores. Why somatic depressive symptoms improved is unknown. Perhaps, highly anxious men were more receptive to nurses' advice and became healthier, thereby improving somatic symptoms and survival.

Psychotherapy: Gender as a Patient Subgroup

Some researchers cite the M-HART and ENRICHD results to suggest that women with coronary artery disease have adverse outcomes from psychotherapy.[73] In both trials, women had worse unadjusted medical event rates after psychotherapy than usual care.[54,58] However, this adverse effect became insignificant after post hoc adjustment for age and comorbidity.

The other psychotherapy trials either enrolled only women[57] or were presumably too underpowered[51,52] to detect gender differences in coronary artery disease outcomes. To summarize, evidence for adverse medical outcomes from psychotherapy in women with coronary artery disease is weak.

Among the M-HART[71] and ENRICHD[74] male subgroups, medical outcomes improved with psychotherapy. However, the 2 studies do not truly reinforce each other. The M-HART subgroup[71] of men with high anxiety is not equivalent to white men from ENRICHD.[74] Psychotherapies in the 2 trials were quite different (nurse visits versus CBT).

Antidepressants

The antidepressant trials reported no change in coronary artery disease prognosis from antidepressants. However, detection of a 20% risk reduction in medical events has been estimated to need 4,000 subjects.[45,51] The antidepressant trials were underpowered to detect such changes. Additionally, most studies did not address long-term safety, except for sertraline, which was evaluated over 7 years.[47] Extended follow-up is important because antidepressants could theoretically disrupt post–myocardial infarction cardiac remodeling, thereby impairing left ventricular function, a central determinant of long-term prognosis.[75]

Selective Serotonin Reuptake Inhibitors

No antidepressant RCTs had enough power to evaluate the effect of antidepressants on coronary artery disease prognosis. A secondary analysis of ENRICHD was intriguing,[76] as some participants received antidepressants.[76] Regardless of the treatment arm, SSRIs were associated with a lower risk of death/recurrent myocardial infarction. Non-SSRI antidepressants did not influence outcomes. The nonrandom assignment of antidepressants among controls, however, makes this result less certain.

As discussed in the introduction, evidence for antidepressant toxicity is mixed. The ENRICHD study[76] suggested that SSRIs might protect against post–acute coronary syndrome mortality/myocardial infarction, but non-SSRIs had no effect. The Heart and Soul study[38] reported that SSRIs did not affect adverse cardiac outcomes, but "other" antidepressants mediated the adverse effect of antidepressants on outcomes.

The Heart and Soul Study suggests that SSRIs are at least benign, whereas "other" antidepressants (non-SSRIs) might risk antidepressant toxicity in patients with coronary artery disease. A definitive conclusion is impossible, since the antidepressant RCTs were not sufficiently powered. It remains concerning that 2 large-scale studies of subjects without coronary artery disease reported adverse medical outcomes associated with antidepressants, including SSRIs, independently of depression.[33,34]

Obviously, it is difficult to derive clinical recommendations from evidence that antidepressants have no effect,[31,32] a benefit,[76] and an adverse effect[33,34,38] on outcomes. Experts have recommended adequately powered prospective studies to assess antidepressant safety.[35,36,77]

Given current evidence, when antidepressants are indicated, SSRIs should be first-line antidepressants among patients with coronary artery disease. The safety of citalopram and sertraline is not defined for conditions excluded from the studies, such as nonatherosclerotic coronary disease, severe angina, uncontrolled hypertension, and severe bradycardia.[45–47,51] Although the RCTs reported no change in heart rate from SSRIs, exclusionary criteria and underpowering could have prevented detection of uncommon side effects. The SSRIs have been associated with infrequent cardiac side effects, such as bradycardia/heart block from fluoxetine (86 reported cases of the first 2.5 million patients taking fluoxetine[78]). This result suggests a benefit from serial electrocardiograms and cardiac/internal medicine consultation when adding SSRIs to patients with preexisting arrhythmias, particularly bradycardia/atrioventricular block.

A recent US Food and Drug Association warning (http://www.fda.gov/drugs/drugsafety/ucm297391.htm) advised that citalopram not exceed 40 mg daily to prevent torsades de pointes from a prolonged QTc. A maximum of 20 mg daily of citalopram was recommended if there was a risk of increased serum concentration (hepatic impairment, age > 60 years, P450 2C19 inhibitors).

Serotonin reuptake inhibition may increase perioperative bleeding in orthopedic surgery,[79] bringing up the question of its safety in patients requiring a coronary artery bypass graft. The only study that met our inclusion criteria, the Bypassing the Blues trial,[59] was too underpowered to address this question. Fortunately, another study of 3,454 patients reported that SSRIs/serotonin-norepinephrine reuptake inhibitors (SNRIs) did not predict increased post–coronary artery bypass graft bleeding events.[80]

Specific patient subgroups. The medical risks of antidepressants in specific subgroups cannot be discussed

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outside the context of their mood benefits. If a patient subgroup tends to respond poorly to the mood benefit of antidepressants, then the antidepressant benefit/risk ratio is low.

According to SADHART[46] and CREATE,[51] incident or new-onset (ie, no prior episodes) depression was less likely to respond to SSRIs over placebo. Thus, first-time depression in patients with coronary artery disease may be less likely to benefit from SSRIs. Depression responsiveness to other antidepressant classes, such as SNRIs, is unknown.

In SADHART,[46] sertraline was a superior antidepressant when depression preceded a myocardial infarction, but not in post–myocardial infarction depression. Some experts suggest that post–myocardial infarction depression reflects transient grief[81] that spontaneously resolves.[45,58] Alternatively, new post–myocardial infarction depression might be due to brain dysfunction from atherosclerosis[65] or inflammation.[81] Three studies reported "depressive" behavior among rats after a surgically induced myocardial infarction, which was prevented by antidepressants (desipramine,[82] sertraline,[83] escitalopram[84]). Escitalopram prevented increased inflammatory cytokines after the myocardial infarction.[84] The "depression" correlated with apoptosis of limbic regions, possibly derived from inflammation triggered by the myocardial infarction.

Human studies have implicated inflammation's role in depression after an acute coronary syndrome. Anti-inflammatory effects of statins are posited to explain their association with lower depression prevalence (by 69%, $P = .045$) after an acute coronary syndrome.[85] In a study among post–myocardial infarction MIND-IT patients, depression response to mirtazapine correlated with altered receptors for inflammatory cytokines (increased serum TNF-R1).[86] The MIND-IT authors proposed that mirtazapine reduced inflammation in depression responders, but not among nonresponders. Further research is needed to investigate whether inflammation underlies the association of poor post–acute coronary syndrome outcomes with treatment-recalcitrant depression.[86]

Noradrenergic Antidepressants

In the Heart and Soul study,[38] "other" antidepressants included medications with noradrenergic activity—venlafaxine, mirtazapine, and bupropion.[87] Hypertension, a common side effect of venlafaxine,[88] is less frequent with bupropion[89] or duloxetine.[87] Mirtazapine can cause obesity and hyperlipidemia.[90]

Of concern is whether noradrenergic antidepressants cause sympathetic hyperactivity. High sympathetic activity is probably cardiotoxic, given its suspected role in atherogenesis,[91] post–myocardial infarction cardiac remodeling,[92] and arrhythmias.[93]

Psychostimulants, such as methylphenidate, increase noradrenergic activity.[94] Two retrospective cohort studies examining their cardiovascular safety[95,96] ran subgroup analyses of adults with preexisting cardiovascular disease/risk. One study[95] showed a significant increase in arrhythmia/sudden death (HR = 1.96; 95% CI, 1.36–2.81) in this subgroup. The other[96] showed no increase (RR = 0.87; 95% CI, 0.73–1.03). Due to this small signal for cardiac risk/sudden death in patients with preexisting cardiac conditions, current guidelines suggest consultation with a cardiologist prior to psychostimulant treatment of patients with preexisting cardiac conditions.[97]

The β-adrenergic blockers, though cardioprotective,[98] may not prevent adverse consequences from noradrenergic antidepressants. In patients with congestive heart failure taking β-blockers, mortality correlated with "adrenergic escape" (ie, elevated norepinephrine levels despite β-blockers).[99]

It is unclear whether noradrenergic antidepressants increase sympathetic activity and thereby adversely influence prognosis. Rather than uniformly increasing activity, norepinephrine reuptake inhibition changes peripheral sympathetic[97] output in complex ways.[100] Correlates of sympathetic activity, such as norepinephrine levels or heart rate variability, did not mediate the prognostic effect of depression in the Heart and Soul study.[38]

Our literature review yielded trials of 2 noradrenergic antidepressants, mirtazapine[48,50] and bupropion.[44] The mirtazapine trial (MIND-IT) was too underpowered for cardiac outcomes[48,50]; the bupropion trial results raised safety concerns.

Bupropion had no overall effect on coronary artery disease prognosis. A post hoc analysis dividing cardiovascular events into the first follow-up month and the rest of the follow-up year were concerning. After the 12-week bupropion versus placebo trial, cardiovascular outcomes during the first month were unaffected by bupropion. However, for the rest of the year (months 2–12, inclusive), the bupropion arm had significantly more cardiovascular events (covariate-adjusted RR = 3.12, $P = .05$). Did bupropion increase revascularizations and hospitalizations 1 month after being stopped by affecting participants' psychological states? It appears implausible for psychological states to change more after bupropion is stopped than while bupropion is administered.

Rigotti et al[44] could not "[explain] how bupropion could trigger cardiovascular events after it was stopped, but not while . . . taken."(p1,086) Perhaps the results are invalid, with the analysis being post hoc and with a 23% follow-up loss. Alternatively, the results may reflect an adverse effect of norepinephrine reuptake inhibitors. We hypothesize that increased sympathetic output from bupropion's norepinephrine reuptake inhibition negatively affected cardiac remodeling. The consequent left ventricular dysfunction robustly predicts adverse long-term cardiac outcomes.[101]

Although definitive conclusions require further research, noradrenergic drugs should be given cautiously to patients with coronary artery disease, particularly if there are arrhythmias or left ventricular dysfunction. Left ventricular dysfunction, a key prognostic factor, can be exacerbated by pathological cardiac remodeling.[75]

Table 5. Summary of Clinical Recommendations for Different Subgroups of Depressed Patients With Coronary Artery Disease

Patient Subgroup	Recommended Treatment	Strength of Recommendation (Benefit/Risk Ratio)	Grade of Evidence[a]
Depressive episode that begins after an acute coronary syndrome	Promote exercise	Strong	Strong
	Refer to cardiac rehabilitation	Moderate	Moderate
	Watchful waiting for 4–6 wk if mild-moderate depression	Strong	Moderate
	No antidepressants or psychotherapy	Weak	Moderate
	Sertraline for severe baseline depression	Moderate	Moderate
	Avoid tricyclic antidepressants	Strong	Moderate
	If citalopram is chosen, review US Food and Drug Administration warning regarding dose limits	Strong	NR
	Monitor mood closely to identify patients with treatment-recalcitrant depression	Strong	Strong
Treatment-recalcitrant depression 6 wk after acute coronary syndrome	Offer psychotherapy and/or antidepressants	Strong	Moderate
	Monitor mood closely	Strong	Strong
	If no mood improvement, change treatment strategy (intensify treatment, augment treatment, or change modality)	Strong	Moderate
Consider these clinical recommendations for depression that persists without treatment (moderate strength and evidence)	If antidepressant treatment is chosen, SSRIs (not SNRIs) are first-line	Strong	Moderate
	COPES intervention	Moderate	Moderate
Presence of any of these CREATE and SADHART exclusionary criteria: • Severe angina • Uncontrolled hypertension • Severe bradycardia • Nonatherosclerotic coronary disease	Antidepressant safety is unknown in coronary artery disease patients with these conditions because such patients were generally excluded from RCTs; if these conditions are present, a cardiologist or internist should be consulted	Strong	Weak
Repressive coping	Avoid confronting patients with threatening information	Weak	Weak
Arrhythmias: left ventricular dysfunction	Avoid noradrenergic drugs if possible	Strong	Moderate
	If noradrenergic drugs are necessary, obtain a consult from an internist or cardiologist	Strong	Moderate
	Monitor blood pressure, particularly in patients prescribed venlafaxine	Strong	NR
	Monitor lipids and weight in patients prescribed mirtazapine	Strong	NR
Acute coronary syndrome 6 mo ago	Sertraline may be a more effective antidepressant than citalopram	Moderate	Moderate

[a]Evidence grade: strong = consistent evidence from excellent RCTs, unlikely to change with further research; moderate = evidence is from RCTs with flaws/inconsistent RCTs/excellent non-RCTs, but duplication needed; weak = evidence is limited, needs further study.
Abbreviations: COPES = Coronary Psychosocial Evaluation Studies, CREATE = Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy, NR = not reviewed (outside scope of this article), RCT = randomized controlled trial, SADHART = Sertraline Antidepressant Heart Attack Randomized Trial, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

Summary and Clinical Recommendations

The literature does not indicate clear superiority of any particular psychotherapy. The COPES intervention, CBT, and antidepressants effectively improve depression in patients with coronary artery disease. We found no RCTs addressing whether interpersonal therapy specifically improves depression among patients with coronary artery disease. However, interpersonal therapy does improve depression in the general population,[102] and would be a reasonable, though less empirically supported, psychotherapy for depressed patients with coronary artery disease.

Psychotherapy may not improve medical outcomes in the overall population. Antidepressants and/or psychotherapy, particularly the COPES intervention, improve mood and, perhaps, cardiac prognosis in persistent depression among post–acute coronary syndrome patients. However, in the overall population, antidepressants should be prescribed primarily for mood rather than for improving prognosis. When mediators (inflammation,[38] inactivity,[38] or nonadherence[10,38]) of the adverse prognosis of depression are prominent, psychotherapy or antidepressants might improve coronary artery disease outcomes.

The treatment response and medical prognosis of different patient subgroups appear heterogeneous. For example, among post–acute coronary syndrome patients, depression, particularly if mild, may be monitored for remission without treatment. Conversely, persistent depression, particularly if treatment recalcitrant, should be treated, given the link to adverse post–acute coronary syndrome outcomes.

It is important to identify and treat high-risk subgroups, such as post–acute coronary syndrome patients with treatment-resistant depression. Clinical recommendations for different subgroups are summarized in Table 5.

The 2010 American Heart Association science advisory recommends screening with the 2-item Patient Health Questionnaire (PHQ-2), which contains 2 affective items: anhedonia and depression.[103] If the PHQ-2 is positive, the patient is given the PHQ-9, which contains somatic, affective, and cognitive items. If the PHQ-9 score is ≥ 10, major depression is likely, and a mental health referral is recommended.

Comorbid medical illness can make the diagnosis of depression more challenging. Depression scales often include somatic symptoms, such as fatigue or excessive sleep.

In a coronary artery disease patient with congestive heart failure, does fatigue support a diagnosis of depression or is fatigue merely from congestive heart failure? Dismissing somatic symptoms to avoid falsely elevating depression scores is, unfortunately, too facile. Both affective and somatic dimensions of depression independently predict poor coronary artery disease outcomes.[104–109]

Large-scale studies are needed to define the risks and benefits of psychotherapy and antidepressants, particularly norepinephrine reuptake inhibitors. More RCTs on the effect of treating recalcitrant post–acute coronary syndrome depression, with enough power to assess hard medical endpoints, are a priority. Research should also investigate prognosis of subgroups based on depression severity and/or onset, gender, coping styles, and comorbid conditions (eg, anxiety, left ventricular dysfunction, inflammation).

Drug names: bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), desipramine (Norpramin and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), methylphenidate (Focalin, Daytrana, and others), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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