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# Depression and Cardiovascular Disease: Selected Findings, Controversies, and Clinical Implications From 2009

**Karina W. Davidson, PhD** and **Maya Rom Korin, PhD**
Department of Medicine, Columbia University College of Physicians and Surgeons, New York, NY

## Abstract

We systematically searched published empirical research on depression and cardiovascular disease (CVD) and found 494 unique articles published in 2009. Herein, we present selected provocative findings or interesting controversies, and, where appropriate, we discuss the clinical implications of these findings.

In 2009, there were many scientific advances in understanding the relationship between depression and CVD. As the study of this phenomenon encompasses the fields of cardiology, psychiatry, behavioral medicine, as well as many others, it is difficult to keep abreast of new developments. Relevant papers may be found in a variety of journals. Therefore, we used a systematic search strategy to retrieve the most relevant articles about depression and coronary heart disease (CHD) from the MEDLINE and PsycINFO (Ovid interface) databases. The most relevant subject headings and free text terms were identified and combined with "or." The 2 sets were then combined with "and." Terms included "depression," "depressive disorder," "depress$," "coronary artery disease" (CAD) "coronary disease," "acute coronary syndrome" (ACS), "cardiovascular disease" (CVD), "coronary heart disease," and "heart diseas$." The final set was limited to the English-language literature and identified almost 500 articles published during 2009. Closer inspection of titles and abstracts revealed well over 100 articles that were directly relevant to the science and management of patients with CVD and depression or pronounced depressive symptoms. Therefore, a thorough review of all new findings, editorials, and reviews is not feasible. Herein, we present a few of the many exciting or potentially influential articles published in 2009 that could affect the views of the relationship between depression and CVD, and how we screen or treat depression in patients with CVD. As with any review that is not evidenced based, our choice of articles is subjective and is incomplete, but we hope it will serve as a stimulus for discussion and further exploration.

Previous evidence demonstrated that depressive symptoms as well as a diagnosis of a depressive disorder predict poor prognosis and reduced survival rates after any CAD diagnosis, including myocardial infarction (MI) and unstable angina, as well as after coronary artery bypass graft (CABG) surgery.[1] Investigations in 2009 focused on better understanding outcomes, the type of depression implicated in this association, and the risks and benefits of antidepressant use, psychotherapy, and omega-3 fatty acid supplementation. We start by reviewing the recent observational literature on antidepressant use and clinical outcomes.

**Correspondence**: Karina W. Davidson, PhD, Department of Medicine, Columbia University College of Physicians and Surgeons, Room 948, PH9 Center, 622 W 168th St, New York, NY 10032 (kd2124@columbia.edu)..

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## Observational Evidence on Antidepressant Use and CVD Outcomes

An analysis of the Nurses' Health Study conducted by Whang et al[2] examined depressive symptoms and antidepressant use in 63 469 women without CVD using the Mental Health Index, a 5-item subscale of the Short Form-36 Health Survey, and their relationship to sudden cardiac death and adverse cardiac events. Most women who reported antidepressant use (61%) were taking a selective serotonin reuptake inhibitor (SSRI; sertraline, fluoxetine, paroxetine, or citalopram), while 39% reported other antidepressant use. Women taking antidepressants were more likely to have sudden cardiac death. The fully adjusted hazard ratio (HR) for sudden cardiac death in women taking antidepressants was 3.34 (95% confidence interval [CI], 2.03–5.50).

A study by Krantz et al[3] examined psychotropic medication use and risk of adverse cardiovascular events in 519 women from the Women's Ischemia Syndrome Evaluation (WISE) study. Enrolled women underwent coronary angiography, were separated into 4 groups according to their psychotropic medication use (no medication, anxiolytics only, antidepressants only, and a combination of anxiolytics and antidepressants), and were observed for a median of 5.9 years. Results revealed that women who received both medications had a higher risk for adverse cardiovascular events as well as all-cause mortality compared with those using neither medication, even when controlling for anxious and depressive symptoms. In addition, while the use of antidepressant medication was associated with a doubling of risk for subsequent CVD events (hazard ratio, 2.16; 95% CI, 1.21–3.93) and all-cause mortality (hazard ratio, 2.15; 95% CI, 1.16–3.98), use of anxiolytic medication alone was not.[3] There was no investigation in this study of cause of death, although in this cohort selected for likelihood of coronary artery disease, cardiac death is likely to have comprised a large proportion of total mortality.

Although CVD and death have long been outcomes of interest for those studying depression's effect, some other end points have recently been investigated. Smoller et al[4] found that new antidepressant use was significantly associated with increased incidence of stroke and all-cause mortality, but it was not associated with incidence of CHD in a prospective cohort study of 136293 community-dwelling postmenopausal women in the Women's Health Initiative (WHI) study. For subjects with no antidepressant use and SSRI use, the reported annualized rates per 1000 person-years were 2.99 and 4.16, respectively, for stroke and 7.79 and 12.77, respectively, for all-cause mortality. The annualized death rate for subjects taking new tricyclic antidepressant medication was 14.14 per 1000 person-years. To address potential confounding by indication, Smoller et al obtained a propensity score from a logistic regression model to predict any new antidepressant use from demographic, lifestyle, risk factor, and comorbidity variables measured at baseline. New SSRI use was associated with a doubling of the risk of incident hemorrhagic stroke as well as fatal stroke. There were no significant interactions between use of SSRIs and use of statins or aspirin for the risk of hemorrhagic stroke.

In an interesting observational study of 7709 patients with confirmed CAD[5] but without a diagnosis of heart failure, or of depression, or current use of antidepressants, a subsequent diagnosis of depression was associated with a significant 50% increased risk of heart failure. However, there was no difference between depressed patients who were using antidepressants and those who were not.

Increased risk of bleeding with SSRI use, particularly in patients with CAD, has also been a concern. Kim et al[6] evaluated 1380 adults who received any antidepressant before CABG for in-hospital mortality or any bleeding events. After controlling for the percentage of patients taking SSRIs (78%) there were no significant differences between those taking

SSRIs and those who were not in any bleeding events (6.5% vs 7.2%; odds ratio, 0.93; 95% CI, 0.50–1.76) or in-hospital mortality (3.1% vs 2.3%; odds ratio, 0.88; 95% CI, 0.47–1.65). There was no increased risk of bleeding associated with SSRI use when the analysis was restricted to patients who received antiplatelet and anticoagulant therapy. Thus, compared with patients who were not taking SSRIs, the preoperative use of SSRIs did not increase the risk for bleeding or in-hospital mortality after CABG; however, this study did not evaluate the effect of no antidepressant use.

Another study hypothesized that use of any drug with the potential to prolong cardiac repolarization would be associated with an increased risk of sudden death.[7] Among 1010 cases (sudden unexplained death) and 3030 living primary care controls all from the community, risks for individual drugs were tested.[7] SSRI use was associated with a doubling of sudden death risk (odds ratio 2.21; %95 CI 1.61, 3.05) and a non-significant trend was noted among users of tricyclic antidepressants (odds ratio= 1.44; %95 CI 0.96, 2.13). When the analysis was re-analyzed to stratify on prior CVD, most of this SSRI sudden death risk was in those with existing CVD, and not in those without CVD. Other drugs found to raise sudden death risk included the typical and atypical antipsychotics.

## Summary and Clinical Implications for Antidepressant Use in Patients With CVD

The analysis by Whang and colleagues[2] of the Nurses' Health Study suggested a tripling of the risk of sudden cardiac death for healthy women who take antidepressant medication, and the authors suggested that the association between fatal ventricular arrhythmias and antidepressant use should be examined further. The analysis by Smoller et al[4] of the WHI study found that use of SSRIs and tricyclic antidepressants doubled the risk of fatal stroke in healthy women. The analysis by Krantz et al[3] of the WISE study found a doubling of the risk of CVD and death in women taking antidepressants who had been referred for coronary angiography. May et al[5] did not find that antidepressant use increased the risk for heart failure conversion in patients with CAD, and Kim et al[6] did not find an increased risk of bleeding in patients with CAD undergoing CABG when SSRI use was compared with non-SSRI antidepressant use. Finally, in a population- and community-based case-control study, SSRI use was associated with an increased risk of sudden death, particularly in patients with CHD.[7] So what are we to make of these findings?[8]

With all observational studies (including those reviewed above), unmeasured confounders pose a threat to the validity of any causal conclusions. A study recently tested some of the proposed confounders that might have existed in the above studies. Waldman et al[9] examined racial differences in depressive symptoms and antidepressant treatment in a cohort of 864 consecutive patients with CHD undergoing diagnostic coronary angiography (727 white and 137 African American patients). While both whites and African Americans had similar levels of depression, African Americans with CHD were less likely than their white counterparts to receive antidepressant medications. In fact, those undergoing CABG and African Americans were the only two groups who were significantly less likely to receive a prescription for antidepressants. Patients with a only some high school, men, and patients with more severe depressive symptoms were significantly more likely to receive a prescription for antidepressants.[9] Clearly, many of these variables are related to poor prognosis for CHD, and the simple interpretation that antidepressant use is causing poorer outcomes is problematic.[8]

Two additional interpretations of the observational findings should be considered. First, confounding by indication (depressive symptom severity) might exist in these studies.[10] That is, patients who are prescribed antidepressant medication may be those with the most

severe depressive illness, and it could be this severity, rather than the antidepressant use, that is causally implicated in the risk of CVD incidence.[11] However, all of the studies reviewed above either directly controlled for depressive symptom severity (at least as obtained at baseline) or used propensity scores or stratified subjects based on depression severity. The results showed an increased risk for those who were taking antidepressants. However, none of the studies examined depressive symptom severity during or at the end of the study or depression diagnosis and severity before antidepressant use; these data are needed to more clearly understand if the results were confounded by indication.

Second, these findings are also consistent with a treatment-resistant depression phenotype.[12] Krantz and others[3] caution that it is not clear from their observational study if medication use itself or depression refractory to treatment is implicated in the increased risk of CVD events and mortality. Depression that is refractory to treatment may be the type of depression that places patients at risk for sudden death, stroke, or CHD recurrence, and thus it may not be the antidepressant use per se that is associated with this risk. This phenomenon had been documented in a secondary analysis[13] of the largest-to-date randomized controlled trial of patients with MI undergoing treatment for depression (ENRICHD).[14] The results showed that those whose depression symptoms did not respond to treatment had a higher risk of late mortality (ie, death occurring ≥6 months after acute MI). This finding was replicated in 2009 in an important follow-up[15] of the SADHART trial;[16] patients with MI and major depression, treatment-resistant depression (ie, depression that failed to improve substantially during treatment with either sertraline or placebo) was strongly and independently associated with long-term mortality (hazard ratio, 2.39; 95% CI, 1.39–2.44; $P < .001$).

What is needed next? To test the alternative hypothesis that an unmeasured confounder may exist is difficult. It requires conducting new observational studies and measuring the putative third common causes or previously unmeasured confounder. Other putative confounders will then be hypothesized and will need to be included in additional observational studies. To properly test the putative confounding by depressive symptom severity, future observational studies should examine initial depressive symptom severity prior to antidepressant use and then collect depressive symptom severity and antidepressant use as time-varying covariates to CVD outcomes. To test if treatment-resistant depression is the phenotype driving the spurious observational association between antidepressant use and increased risk of CVD, the phenotype and its underlying causal mechanisms need to be better understood. Of course, adequately powered, rigorous, randomized controlled trials of antidepressant use in patients with CVD would be a more straightforward way to test the observational association between antidepressant use and increased risk of CVD. We turn now to the recently published randomized controlled trials in this field.

## New Evidence From Randomized Controlled Trials in Patients With CVD and Depression

Concerns have been voiced for some time about the ability to effectively treat depression and whether an effective depression treatment will affect the risk of CVD recurrence and mortality.[8] Adding to these concerns is that we know little about the causal pathways and behavioral and biological mechanisms implicated in this risk association.[1] For these reasons, results from new randomized controlled trials, such as the 4 summarized below, are important. Rollman and others[17] tested the effectiveness of telephone-delivered collaborative care (treatment group) vs usual physician care (control group) for improving mental health quality of life and reducing depressive symptoms in patients with depression after CABG. Patients with depression after CABG (N=302) were randomized to either the treatment or control group and observed for 8 months; mental health quality of life and

depressive symptoms were significantly improved in the treatment vs control group. Significantly more patients in the treatment group had a 50% or greater reduction in depression symptoms compared with usual care patients (P <.001; 50.0% vs 29.6%; number needed to treat, 4.9 [95% CI, 3.2–10.4]). Men particularly benefited from the treatment. This trial suggests that collaborative care can be effectively (and potentially cost-efficiently) delivered over the phone.

Freedland and others[18] also tested depression treatment in 123 patients with major or minor depression who underwent CABG. The primary purpose of the trial was to determine the efficacy of 2 behavioral treatments (cognitive behavioral therapy or supportive stress management) compared with usual care. Significantly more patients in the depression treatment group (71%) and the stress treatment group (57%) had a low score on the clinician-based Hamilton rating scale compared with the usual care group (33%). These results were maintained 6 months after the end of the trial. Secondary measures of depressive symptoms, anxiety, and quality of life were also significantly improved in the depression treatment group compared with the usual care group. This trial is important for the following reasons: (1) The use of a second control group, the stress management group, is a strict, high-quality design that controls for professional attention, generic or placebo therapy effect, and time or effort on the part of the patient. (2) The second control group also provides treatment options for the patient because both cognitive behavioral therapy and stress management were beneficial. (3) Second outcome assessors were blinded to treatment assignment, an important design feature in behavioral trials.

In a rigorously conducted randomized double-blind placebo-controlled trial, Carney and others[19] tested if omega-3 acid ethyl esters (2 g; combined EPA and DHA) improved depressive symptoms in 122 patients with major depression and CHD. Patients in both the omega-3 and placebo groups received sertraline (50 mg) during the 10-week trial. A deficiency of omega-3 has been implicated in both depression and CHD and was a possible causal link between the 2 diseases. Also, there is some evidence that the efficacy of antidepressants is increased when an omega-3 fatty acid supplement is added. Unfortunately, there were no differences in self-reported or clinician-based depressive symptoms or in predefined depression remission at trial end The trial added a 2-week adherence run-in period, ensuring that medication adherence in the trial was excellent (97%) and concluded that, at least at these dosage levels, omega-3 does not improve depression outcomes.

Davidson et al[20] conducted the Coronary Psychosocial Evaluation Studies (COPES) randomized controlled trial including 157 patients with ACS and persistently elevated depressive symptoms in which a patient-preference, stepped depression (enhanced care) algorithm was compared with usual care for 6 months. The purpose of the trial was to determine acceptability and efficacy of depression treatment among patients with ACS, who often neither agree with the diagnosis of depression nor sought treatment for depression. At the beginning of treatment, patients received either problem-solving therapy or antidepressant medication, depending on their choice, with the option of later augmentation with the other treatment. Significantly more patients were satisfied with their depression care in the treatment arm, and depressive symptoms and major adverse cardiac events (nonfatal MI, hospitalization for unstable angina, or all-cause mortality) were significantly reduced compared with the usual care arm. The absolute numbers were very small; at the end of the trial, 3 patients in the intervention group and 10 patients in the usual care group had major adverse cardiac events (4% and 13%, respectively; log-rank test, $\chi^2_1=3.93$; $P=.047$). The results suggested that involving patients in the type of depression care (medication and/or psychotherapy) they receive and stepping treatments aggressively may be methods to improve the treatment of depression in patients with CVD. In addition, persistently

depressed patients may be an interesting patient group to select for future trials; usual care has resulted in large reductions in depressive symptoms in some previous trials.

## Summary and Clinical Implications for Recent Randomized Controlled Trials in Patients With CVD and Depression

Each of these 4 efficacy trials adds critical information to the evidence base. Depressed patients who have undergone CABG can be effectively treated in primary care settings with integrative care, and cognitive behavioral therapy for these patients is also extremely effective. Additional studies of omega-3 supplements should not be pursued at this time, but using a run-in period to better identify patients who are prepared to engage in treatment is a prudent idea and should be used in future trials in this area. Patients with CHD and persistent depressive symptoms are a promising group to target for depression treatment. Asking patients to choose the type of depression treatment may improve the response to treatment for both depression and CVD.

## Depression Screening, Referral, and Treatment in Patients With CVD

We finish with the least evidence-based and most controversial issue in the area of depression and CVD. This controversy started in 2008 when the American Heart Association recommended (and the American Psychiatric Association endorsed)[21] that "screening tests for depressive symptoms should be applied to identify patients who may require further assessment and treatment" if appropriate referral for further depression assessment and treatment is available. Partly in response to this advisory, Thombs et al[22] conducted a systematic review of the evidence that screening or treatment improves outcomes of depression or CVD in patients with CVD. They found no trial that tested if depression screening was beneficial in patients with CVD, and the randomized controlled trials of depression treatment provided evidence of only mild improvement of depression symptoms and no improvement in CVD outcome. Therefore, they questioned whether routine depression screening was appropriate.

In at least 7 editorials and reviews published in 2009, authors continued to debate this issue.[23–30] Below, we provide a simplified list of reasons presented for and against screening and subsequent treatment raised in these articles.

## Arguments for Depression Screening, Referral, and Treatment in Patients With CVD

The proponents for screening stated that depression is highly prevalent in CVD patient populations and is clearly a risk marker for increased adverse events as well as decreased quality of life and adherence to treatment.[24] As there are plausible biological and behavioral mechanisms for this association, and SSRI use improves depression symptoms in other patient populations and is safe in CVD patient populations, health care providers should not hesitate to screen and refer patients for appropriate depression treatment. Pozuelo et al[24] cautioned that SSRIs interact with anticoagulants and bleeding should be monitored closely in patients with CVD who are taking SSRIs.

Whooley[28] argued that although there are controversial findings in this area, depression screening provided in conjunction with collaborative care depression management[17,31] is cost-effective and has a documented positive impact on depression, if not on CVD outcomes. Whooley noted that there are some costs to screening (eg, false-positive findings, resulting in stigma for patients incorrectly diagnosed; diversion of health care resources from other health care needs). However, Whooley suggested that primary care providers,

rather than cardiologists, should conduct depression screening, and patients should undergo screening only when an established collaborative care treatment protocol exists.

Carney and others[23] argued that depression, like age, clearly marks CVD risk, and health care providers should treat aggressively the readily modifiable CVD risk factors. In addition, because of the strong association between depression and medication nonadherence,[32] health care providers should carefully monitor patient adherence to life-saving therapies.

Taking another tack, Shemesh and others[25] thought it would be important to document the prevalence of suicidal ideation and intent if the recommendation to screen depression in CVD patient populations were implemented. In a sample of over 1000 patients with CVD, they determined the prevalence of suicidal ideation (12.0%) and the number of patients who required hospitalization for risk of suicide (0.5%) when routine depression screening occurred in a large cardiology clinic. They concluded that discovery and stabilization of imminently suicidal patients would be a benefit of universal screening and that there is a high societal cost to neglecting suicidal ideation, intent, and risk in patients with CVD. However, more patients would need immediate thorough psychiatric evaluations for safety, which would affect resource allocation and cost in cardiology clinics.

## Arguments Against Depression Screening, Referral, and Treatment in Patients With CVD

The main argument against screening for and treating depression in patients with CVD was this: there are neither randomized controlled trials nor systematic evidence-based reviews showing that screening for depression or screening for depression and referring for additional treatment sufficiently improves outcomes for depression or CVD, and the existing evidence does not support the recommendation to screen all patients with CVD.[22,30] Furthermore, antidepressant use is associated with only mild improvement in depression symptoms, even in other patient populations,[33] and there have been publication bias (also known as the file-drawer problem) preventing the publication of antidepressant trials with null results.[34] In addition, considerable health care resources would be required to mount such a large screening effort, and this resource allocation would be at the expense of other efforts. Finally, the adverse effects of medications and false-positive results to less-than-perfect screening must be weighed against any benefit that might occur with universal screening.[35]

In addition to the arguments listed above, Ziegelstein and others,[29] in commenting on the American Heart Association advisory[21] made the wry observation that there is far greater observational evidence that depressed patients seen in mental health settings are at risk for CVD incidence and recurrence and that there should be universal screening and referral for CVD in patients with depression. They again contended that the evidence is insufficient to recommend that patients with CVD undergo universal depression screening and referral.

## Summary and Clinical Implications for Depression Screening, Referral, and Treatment in Patients With CVD

Although we were initially hesitant to raise this tense and frequently emotional issue, we are in favor of routine, algorithm-based depression screening by all cardiologists, with the following critical proviso: a nationwide and/or Centers for Medicare & Medicaid Studies–based or randomized controlled trial should be designed and in place. All patients with pronounced depressive symptoms should be referred to the trial, and 2 depression treatments should be tested, such as usual referral vs telephone-based collaborative[17] or enhanced depression care.[20] In doing so, we can ensure that data are collected on the cost,[36] the

benefit, and even the possible harms associated with recommending depression screening for patients with CVD, and we can ascertain if there is an acceptable, beneficial treatment for depression that can be delivered and definitively tested.

### Key Findings and Controversies

1. In surprising findings, antidepressant use was associated with increased risk of incident stroke, CVD, and sudden cardiac death in multiple large observational cohort studies. It is not known if unmeasured confounders or depressive symptom severity causes the association, although in some studies controlling for symptom severity did not decrease this elevated risk. Another interesting possibility is that the treatment-resistant depressed patient is at particularly high risk of CVD and mortality.
2. Four exciting randomized controlled trials on depression intervention reported important efficacy results and suggested future directions for larger, definitive trials of depression treatment for patients with CVD.
3. A current hotly debated topic is whether patients with CVD should be routinely screened and subsequently treated for depression. Less controversial, and so less discussed, is the important insight that psychiatric patients with depression should be routinely screened for cardiac disease and risk factors, as they are clearly at risk of CVD; we await clinical trials in this area to ensure that screening leads to improved CVD outcomes.
4. In the absence of large, randomized controlled trials, the debate continues on whether depression screening or any type of depression treatment is beneficial, harmless, or harmful to patients. This debate does not serve patients' or the public's health and well-being. Researchers, clinicians, and policy makers must and should resolve to initiate these desperately needed trials.

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