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Depression and cardiovascular disease: Selected findings, controversies, and clinical implications from 2009

ABSTRACT

We systematically searched published empirical research on depression and cardiovascular disease (CVD) and found 494 unique articles published in 2009. Several particularly notable and provocative findings and controversies emerged from this survey of the 2009 literature. First, multiple large observational studies found that antidepressant use was associated with increased risk of incident stroke, CVD, or sudden cardiac death. Second, four randomized controlled trials on depression interventions in CVD patients reported important efficacy results that should guide future trials. Finally, the vigorous debate on whether patients with CVD should be routinely screened (and subsequently treated) for depression continued in 2009 even as some observed that routine screening for CVD in depressed patients is more evidence-based and appropriate. This article reviews these selected provocative findings and controversies from our search and explores their clinical implications.

Many advances in the understanding of the relationship between depression and cardiovascular disease (CVD) were reported in 2009. As the study of this relationship encompasses cardiology, psychiatry, behavioral medicine, and many other fields, it is difficult to keep abreast of new developments. Relevant papers are found in a variety of journals. Therefore, we systematically searched the empirical research on depression and CVD published in English in 2009. Our search yielded nearly 500 articles. We review here a few of the most provocative and potentially influential findings. We begin with an overview of the methodology of our systematic review and then summarize the key findings and controversies we identified from the 2009 literature before exploring each key finding in detail.

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METHODOLOGY OF OUR SYSTEMATIC SEARCH AND RATIONALE FOR FINDINGS REVIEWED

Previous evidence demonstrated that the presence of depressive symptoms or a diagnosis of a depressive disorder predicts poor prognosis and reduced survival rates after any coronary artery disease diagnosis, including myocardial infarction (MI) and unstable angina, as well as after coronary artery bypass graft surgery (CABG).[1]

We aimed to see how this evidence base was expanded in 2009 by using 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 two 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 494 unique articles published during 2009.

Closer inspection of titles and abstracts revealed well more than 100 articles directly relevant to the science and management of patients with CVD and depression or pronounced depressive symptoms. In light of this quantity, a thorough review of all new findings, editorials, and reviews is not feasible. Thus, we review here a few exciting articles in several distinct topical areas that could influence views of the relationship between depression and CVD as well as how we screen for and treat depression in patients with CVD. As with any review that is not strictly evidence-based, our choice of articles is subjective and incomplete, but we hope it will stimulate discussion and further exploration.

SUMMARY OF KEY FINDINGS AND CONTROVERSIES

The following numbered topics emerged as common themes or controversies from our survey of the 2009 literature. The remainder of this article will review find-

ings in each of these areas in detail and discuss important clinical implications as appropriate.

1. Antidepressant use and adverse cardiac events. 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 the association is caused by unmeasured confounders or depressive symptom severity, although controlling for symptom severity did not reduce this elevated risk in some studies. Another interesting possibility is that the treatment-resistant depressed patient is at particularly high risk of CVD and death.

2. Effects of depression intervention in CVD patients. Four exciting randomized controlled trials on depression intervention in patients with CVD reported important efficacy results and suggested future directions for larger, definitive trials of depression treatment for these patients.

3. Depression screening and treatment in CVD patients. 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 with CVD. Continuation of this debate does not serve the health and well-being of patients or the public. Less controversial—and thus 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.

OBSERVATIONAL EVIDENCE ON ANTIDEPRESSANT USE AND CVD OUTCOMES

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

Krantz et al examined psychotropic medication use and risk of adverse cardiovascular events in 519 women from the Women's Ischemia Syndrome Evaluation.[3] Enrolled women underwent coronary angiography, were separated into four groups according to their psychotropic medication use (none, anxiolytics only, antidepressants only, or both 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 and higher all-cause mortality compared with those using neither medication, even after controlling for anxious and depressive symptoms. In addition, whereas the use of antidepressant medication was associated with a doubling of risk for subsequent CVD events (HR = 2.16; 95% CI, 1.21–3.93) and all-cause mortality (HR = 2.15; 95% CI, 1.16–3.98), use of anxiolytic medication alone was not. While this study did not examine cause of death, cardiac death is likely to have constituted a large proportion of total mortality in this cohort selected for likelihood of CAD.

Although CVD and death have long been outcomes of interest for those studying the effects of depression, additional end points have recently been investigated as well. In a prospective cohort study of 136,293 community-dwelling postmenopausal women in the Women's Health Initiative, Smoller et al found that new antidepressant use was significantly associated with increased incidence of stroke and all-cause mortality but not with incidence of CHD.[4] The rate of stroke per 1,000 person-years was 2.99 for subjects with no antidepressant use versus 4.16 for patients with new SSRI use; the rate of all-cause death was 7.79 versus 12.77, respectively. The rate of all-cause death for subjects with new tricyclic antidepressant use was 14.14 per 1,000 person-years. To address potential confounding by indication, the researchers 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 in terms of risk of hemorrhagic stroke.

In an interesting observational study of 7,709 patients with confirmed CAD but without a diagnosis of heart failure or depression (and without current antidepressant use), May et al found that a subsequent diagnosis of depression was associated with a significant 50% increase in the risk of heart failure.[5] There was no difference, however, 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 evaluated 1,380 adults who received any antidepressant before CABG for in-hospital mortality or any bleeding events.[6] After controlling for the percentage of patients taking SSRIs (78%), there were no significant differences between those taking SSRIs and those taking non-SSRIs in the rate of any bleeding events (6.5% vs 7.2%; odds ratio [OR] = 0.93; 95% CI, 0.50–1.76) or in-hospital mortality (3.1% vs 2.3%; OR = 0.88; 95% CI, 0.47–1.65). There was no increased risk of bleeding asso-

ciated with SSRI use when the analysis was restricted to patients who received antiplatelet and anticoagulant therapy. Thus, compared with patients who received non-SSRI antidepressants, patients who received SSRIs preoperatively had no increased risk of bleeding or in-hospital mortality after CABG; however, this study did not evaluate the effect of no antidepressant use.

Another study hypothesized that the use of any drug with the potential to prolong cardiac repolarization would be associated with an increased risk of sudden death.[7] Use of individual drugs was analyzed among 1,010 cases of sudden unexplained death and 3,030 living primary care controls, all from the community. SSRI use was associated with a doubling of risk of sudden death (OR = 2.21; 95% CI, 1.61–3.05), and tricyclic antidepressant use was associated with a nonsignificant trend toward increased risk (OR = 1.44; 95% CI, 0.96–2.13). Further analysis that stratified patients according to prior CVD showed that most of the association of SSRIs with sudden death 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

The Nurses' Health Study analysis by Whang et al suggested that antidepressant use triples the risk of sudden cardiac death in healthy women, and the authors suggested that the association between fatal ventricular arrhythmias and antidepressant use be examined further.[2] The analysis of the Women's Health Initiative by Smoller et al found that use of SSRIs and tricyclic antidepressants doubled the risk of fatal stroke in healthy women.[4] The analysis of the Women's Ischemia Syndrome Evaluation by Krantz et al revealed a doubling of the risk of CVD and death in women taking antidepressants who had been referred for coronary angiography.[3] At the same time, May et al found no increase in the risk of heart failure conversion with antidepressant use in patients with CAD,[5] and Kim et al found no increase in the risk of bleeding with use of SSRIs compared with non-SSRI antidepressants in patients with CAD undergoing CABG.[6] 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 CVD.[7] So what are we to make of these findings?[8]

In 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 examined racial differences in depressive symptoms and antidepressant treatment among a cohort of 864 consecutive patients with CHD undergoing diagnostic coronary angiography (727 white and 137 African American).[9] While levels of depression were similar between the white and African American patients, the African Americans were less likely than their white counterparts to receive antidepressant medications. Patients with only some high school, men, and patients with more severe depressive symptoms were significantly more likely to receive a prescription for antidepressants. Clearly, low education, male sex, and elevated depressive symptoms 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] In other words, 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 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 among 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 for a clearer understanding of whether the results were confounded by indication.

Second, these findings are also consistent with a treatment-resistant depression phenotype.[12] Krantz et al caution that it is not clear from their observational study[3] whether 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, so it may not be the antidepressant use per se that is associated with this risk. This phenomenon was documented in a secondary analysis[13] of the largest-to-date randomized controlled trial of patients with MI undergoing treatment for depression (ENRICHD).[14] It showed that those whose depressive symptoms did not respond to treatment had a higher risk of late mortality (ie, death ≥ 6 months after acute MI). This finding was replicated in 2009 in an important follow-up[15] of the SADHART trial[16]; among 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 (HR = 2.39; 95% CI, 1.39–2.44; $P < .001$).[15]

What is needed next? Testing the alternative hypothesis—ie, that an unmeasured confounder may exist—is difficult, requiring new observational studies and mea-

surement of the putative third common causes or previously unmeasured confounder. Other putative confounders would then be hypothesized and would 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 data on depressive symptom severity and antidepressant use as time-varying covariates to CVD outcomes. To test whether 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, rigorous and adequately powered 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 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 our limited knowledge of the causal pathways and behavioral and biologic mechanisms implicated in this risk association.[1] For these reasons, results from new randomized controlled trials, such as the four summarized below, are important.

Rollman et al compared the effectiveness of telephone-delivered collaborative care (treatment group) and usual physician care (control group) for improving mental health quality of life and reducing depressive symptoms in 302 patients with depression after CABG.[17] Patients were observed for 8 months following randomization. Mental health quality of life and depressive symptoms were both significantly improved in the treatment group relative to the control group. Significantly more patients in the treatment group had a 50% or greater reduction in depressive symptoms (50.0% vs 29.6% in control group, $P < .001$; 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 delivered effectively (and potentially cost-efficiently) over the phone.

Freedland et al also evaluated depression treatment in 123 patients with major or minor depression who underwent CABG.[18] Their primary objective was to determine the efficacy of two behavioral treatments (cognitive behavioral therapy [CBT] or supportive stress management) compared with usual care. Significantly more patients in both the CBT group (71%) and the stress management group (57%) had a low score (indicating less severe depressive symptoms) on the clinician-based Hamilton Rating Scale for Depression 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 groups compared with the usual care group. This trial is important for the following reasons:

- The use of a second control group, the stress management group, represents 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.
- The second control group also provides treatment options for the patient, as both CBT and stress management were beneficial.
- 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 et al tested whether 2 g/day of omega-3 acid ethyl esters (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) improved depressive symptoms in 122 patients with major depression and CHD.[19] Patients in both the omega-3 and placebo groups received sertraline (50 mg/day) during the 10-week trial. A deficiency of omega-3 fatty acids has been implicated in both depression and CHD and is a possible causal link between the two diseases. Also, there is some evidence that the efficacy of antidepressants is increased by the addition of omega-3 supplementation. Unfortunately, there were no differences in self-reported or clinician-assessed depressive symptoms or in predefined depression remission at the study's end. The trial included a 2-week adherence run-in period, ensuring that medication adherence in the trial was excellent (97%), and concluded that omega-3 supplementation, at least at these dosage levels, does not improve depression outcomes.

In the Coronary Psychosocial Evaluation Studies (COPES) randomized controlled trial, Davidson et al compared 6 months of an enhanced care intervention with usual depression care among 157 patients with ACS and persistently elevated depressive symptoms.[20] Under the enhanced care intervention, patients received either problem-solving therapy or antidepressant medication, depending on their preference, and then had the option of later augmentation with the other treatment, intensification of the initial treatment, or switching of treatments, if indicated by depressive symptom severity (stepped care). The purpose of the trial was to determine the acceptability and efficacy of depression treatment among patients with ACS, who often neither agree with the diagnosis of depression nor had been seeking treatment for depression. Significantly

more patients were satisfied with their depression care in the intervention arm, and depressive symptoms and major adverse cardiac events (nonfatal MI, hospitalization for unstable angina, or all-cause mortality) were significantly reduced in the intervention arm 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 they receive (medication and/or psychotherapy) and stepping treatments aggressively may be methods to improve the treatment of depression in patients with CHD. In addition, persistently depressed patients may be an interesting patient group to select for future trials, as usual care has resulted in large reductions in depressive symptoms in some previous trials but not in this study of patients with persistent depression.

Summary and clinical implications

Each of these four 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,[17] and CBT is also extremely effective for these patients.[18] Additional studies of omega-3 supplementation 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.[19] Patients with CHD and persistent depressive symptoms are a promising group to target for depression therapy, and asking patients to choose their type of depression treatment may improve response to therapy for both depression and CHD.[20]

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 in an advisory (endorsed by the American Psychiatric Association) 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.[21] Partly in response to this advisory, Thombs et al conducted a systematic review of the evidence on whether screening or treatment improves outcomes of depression or CVD in patients with CVD.[22] They found no trial that tested whether depression screening was beneficial in patients with CVD, and the randomized controlled trials of depression treatment provided evidence of only mild improvement of depressive symptoms and no improvement in CVD outcome. Therefore, they questioned whether routine depression screening was appropriate.[22]

In at least eight editorials, letters, and reviews published on this subject in 2009, investigators 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 and treatment

The proponents of screening contend that depression is highly prevalent in patients with CVD and is clearly a risk marker for increased adverse events, reduced quality of life, and poorer adherence to treatment.[24] They argue that since there are plausible biologic and behavioral mechanisms for this association, and since SSRI use improves depressive symptoms in other patient populations and is safe in patients with CVD, health care providers should not hesitate to screen and refer patients for appropriate depression treatment. At the same time, they have cautioned that SSRIs interact with anticoagulants and that bleeding should be monitored closely in patients with CVD who are taking SSRIs.[24]

Whooley[28] noted that although there are controversial findings in this area, depression screening provided in conjunction with collaborative care depression management is cost-effective and has a documented positive impact on depression, if not on CVD outcomes.[17,31] She observed that there are some costs to screening, such as false-positive findings (resulting in stigma for patients incorrectly diagnosed) and diversion of resources from other health care needs. However, Whooley suggested that primary care providers, rather than cardiologists, should conduct depression screening and that patients should undergo screening only when an established collaborative care treatment protocol exists.[28]

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

Taking another tack, Shemesh and colleagues advocated the importance of documenting the prevalence of suicidal ideation and intent if recommendations to screen for depression in CVD patient populations were implemented.[25] Using a sample of more than 1,000 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 identification 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 and treatment

The main argument against screening for and treating depression in patients with CVD is that there are neither randomized controlled trials nor systematic evidence-based reviews showing that screening for depression and/or referring for additional treatment sufficiently improves outcomes for depression or CVD, and that 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 depressive symptoms, even in other patient populations,[33] and publication bias ("the file-drawer problem") has prevented the publication of antidepressant trials with null results, thereby skewing the evidence base.[34] In addition, considerable health care resources would be needed to mount such a large screening effort, and these resources would come at the expense of other efforts. Finally, the adverse effects of medications and the inevitability of some false-positive screening results must be weighed against any benefit that might occur with universal screening.[35]

In addition to the arguments above, Ziegelstein et al,[29] in commenting on the American Heart Association advisory,[21] wryly observed that there is far greater observational evidence that depressed patients seen in mental health settings are at risk for incident and recurrent CVD and that there should be universal screening and referral *for CVD* in patients with depression. They contended as well that the evidence is insufficient to recommend that patients with CVD undergo universal depression screening and referral.

Summary and clinical implications

Although we were hesitant to raise this tense and often emotional issue, we are in favor of routine, algorithm-based depression screening by all cardiologists, with the critical proviso that a nationwide and/or Centers for Medicare and Medicaid Services–coordinated randomized controlled trial be conducted to evaluate this practice. All patients with pronounced depressive symptoms should be referred to the trial, and two depression treatments should be evaluated, such as usual referral versus telephone-based collaborative care[17] or enhanced depression care.[20] Such a trial would allow us to ensure that data are collected on the cost,[36] the benefit, and even the possible harms associated with routine depression screening for patients with CVD, and we could ascertain if there is an acceptable, beneficial treatment for depression that can be delivered and definitively tested.

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