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Depression in patients with heart disease: the case for more trials

Stanley S Liu¹ and Roy C Ziegelstein^{†,1}

¹Johns Hopkins Bayview Medical Center, Department of Medicine, B-1-North, 4940 Eastern Avenue, Baltimore, MD 21224-2780, USA

Abstract

Depression is common among patients with heart disease. It is an important comorbidity, both because of its well-known effect on the quality of life and also because it has a significant impact on the ability of patients with heart disease to engage in healthy behaviors and to avoid unhealthy ones. In addition, depression is associated with increased morbidity and mortality in those with established cardiovascular disease. However, no study has demonstrated that treatment of depression improves cardiac outcomes in patients with heart disease. Some have argued that additional trials are not necessary, and that the importance of depression argues for increased recognition and treatment even if it cannot be demonstrated that this improves morbidity and mortality. This article makes the case for more trials in this area, highlighting the importance of using the results of prior trials to generate hypotheses and provide directions for future studies in this area and noting the effect that demonstrating improved survival might have on clinical practice.

Keywords

antidepressant treatment; cardiovascular disease; depression; mortality; randomized controlled trial

Depression is prevalent among patients with cardiovascular disease (CVD). Approximately 20% of patients who sustain a myocardial infarction meet the criteria for a major depressive episode at the time of their cardiac event [1], and at least as great a proportion of those with heart failure are depressed [2]. Many studies have demonstrated a strong link between depression and adverse CVD outcome, with approximately a twofold increase in mortality observed in depressed patients with heart disease, depending on the cardiac diagnosis, length of follow-up, measure of depression used and comorbidities controlled for [3]. A variety of biological, behavioral and psychological mechanisms may contribute to this increase in mortality. Depression is associated with low heart rate variability, a manifestation of autonomic nervous system dysfunction, which may predispose individuals with heart disease to ventricular arrhythmias, and sudden cardiac death [4]. There is also evidence that

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[†]Author for correspondence: Tel.: +1 410 550 0523 ■ Fax: +1 410 550 1094 ■ rziegel2@jhmi.edu.

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depression is associated with abnormalities in platelet function, that may predispose individuals to ischemic cardiac events [5,6]. Patients with depression are more likely to engage in behaviors (e.g., cigarette smoking) that increase their risk for cardiac events [7-9]. Conversely, depressed individuals are less likely to engage in behaviors that would be expected to reduce their cardiac risk (e.g., following a healthy diet and regularly exercising) [10]. Depressed individuals are also more likely to be nonadherent to prescription medications [11,12]. This is significant, as reduced adherence to medications that have been shown to reduce cardiovascular mortality would probably increase the risk for cardiac events. Moreover, good adherence has been shown to be associated with improved prognosis even in the placebo arms of randomized controlled trials (RCTs) in CVD [13-16].

Some RCTs have compared the treatment of depression with usual care or placebo in an attempt to determine the safety and efficacy of depression treatment in those with a recent acute coronary syndrome [17,18]. Other trials have compared depression treatment with usual care or placebo in order to examine whether depression treatment improves CVD outcomes in these patients [19,20]. Studies suggest that sertraline [17], mirtazapine [18] and citalopram [19] are safe among patients with acute ischemic heart disease. However, no study has demonstrated that treatment of depression improves cardiac outcomes in patients with CVD. The Enhancing Recovery in Coronary Heart Disease Patients (ENRICH) trial was the largest randomized trial to date, examining the treatment of depression in patients with acute cardiac disease. In ENRICH, treatment of depression with a cognitive behavior therapy-based psychosocial intervention, with use of selective serotonin reuptake inhibitors (SSRIs) when indicated, did not improve event-free survival among patients surviving a myocardial infarction [19]. The Myocardial Infarction and Depression – Intervention Trial (MIND-IT) [20] and the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) [17], both of which examined the effects of antidepressant medications in depressed patients with acute cardiac disease, also failed to show that depression treatment reduces cardiac events, although it must be noted that MIND-IT was underpowered to detect differences in cardiac outcomes [20] and SADHART [17] was designed primarily to evaluate the cardiovascular safety and efficacy of sertraline in patients with major depression after an acute coronary syndrome rather than to evaluate its effect on cardiovascular mortality or morbidity. Even though data on potential harms of antidepressant therapy are quite limited and despite the lack of evidence that treatment of depression improves cardiovascular outcomes in patients with acute cardiac disease, it has still been recommended that patients with heart disease should be routinely screened [21,22] and treated [23,24] for depression. This may leave some wondering whether additional trials are needed in this area.

What if there are no more trials?

It has been argued that the relatively high prevalence of depression in CVD patients and the association of depression with increased morbidity and mortality are reasons enough for CVD patients to be screened for depression and treated if this condition is present. Indeed, the American Heart Association recently recommended routine screening for depression in patients with cardiac disease, with evaluation of those who screen positive by a professional qualified in the diagnosis and management of depression [21]. It remains to be seen whether routine depression screening will become part of cardiovascular care as recommended, since attention to depression would have to compete with attention to the acute and often imminently life-threatening cardiac issues in the inpatient setting and time constraints in a busy outpatient cardiology practice. Cardiologists also typically lack the expertise to diagnose and treat depression, and they do not often have ready access to systems that provide ongoing depression diagnosis and care. Without these systems in place, the benefits of screening for depression are not clear. Indeed, the US Preventive Services Task Force

(USPSTF) recently recommended against routinely screening of adults for depression in primary care settings when staff are not available to provide depression care support or coordination, case management or mental health treatment [25]. The notion that patients with heart disease should be routinely screened for depression because it is prevalent, negatively impacts on quality of life and is associated with an increased risk of CVD morbidity and mortality can actually be applied to other health conditions such as glaucoma [26,27] and age-related macular degeneration [28], which are certainly not routinely screened for in patients with heart disease. Additional trials demonstrating that treating depression improves cardiovascular outcomes would therefore distinguish depression from these other conditions and certainly make a more compelling case for screening and treatment.

For these reasons and others, a more compelling case is almost certainly needed before the recognition and treatment of depression becomes part of the routine clinical care of patients with heart disease. Cardiologists are more accustomed than almost any other group to basing therapy on the results of RCTs demonstrating a mortality benefit of treatment. As Rumsfeld and Ho concluded, "Depression, however, remains largely off the radar screen of cardiac care, in a large part because of confusion regarding the nature of the association between depression and CVD and the role of cardiovascular clinicians with regard to depressed patients" [29]. It is likely that a more compelling case will also have to be made to primary care physicians who provide care to patients with heart disease, particularly given the recently updated USPSTF guidelines for depression screening in primary care [25] and the significant time limitation facing primary care providers today. Indeed, it has been estimated that it would take 7.4 h each working day just for primary care physicians to provide those preventive services already recommended by the USPSTF for primary care physicians [30].

The case for more trials

There are many areas that need to be addressed by additional trials in patients with heart disease and depression. Many of the trials to date can be looked at as hypothesis-generating, and their findings may be used to guide the design of additional trials. An important lesson from previous trials is that future trials should be designed to examine the effects of depression treatment on mortality in patients whose depression is likely to benefit from depression treatment compared with placebo or usual care. It is unrealistic to expect depression treatment to have a favorable impact on mortality if it does not have one on depression. Finally, additional trials are warranted to more thoroughly evaluate the possibility that antidepressant drug treatment or cognitive-behavioral therapy does not cause harm in CVD patients. Each of these issues will be considered below.

Studying selected patient populations or depression subtypes

Post hoc analyses from ENRICHD that were conducted to examine the consistency of the effect of the intervention across different patient subgroups provided interesting findings [31]. It must be noted, however, that these observations were retrospective and must therefore be interpreted with caution. An analysis of the ENRICHD data demonstrates that white men (973 of 2481 participants in the trial) may have benefited from the intervention. There was a trend towards reduced total mortality or recurrent nonfatal myocardial infarction for white men randomized to the ENRICHD intervention (hazard ratio [HR]: 0.80, 95% CI: 0.61–1.05; $p = 0.10$) and a significant reduction in cardiac death or recurrent nonfatal myocardial infarction (HR: 0.63; 95% CI: 0.46–0.87; $p = 0.004$) [31]. The effect on cardiac death or recurrent nonfatal myocardial infarction for white men in the trial remained significant after adjustment for age, education, use of antidepressants, living alone, comorbidities, left ventricular ejection fraction, history of hypertension and whether a

cardiac catheterization was performed at the time of the myocardial infarction. Additional trials are needed to better understand this gender difference and to perhaps define subgroups of patients whose survival may be improved by depression treatment.

Recent evidence suggests that patients with a first-ever episode of depression (so-called 'incident depression') may be at the highest risk of mortality after a myocardial infarction. Given that this observation has now been made by several groups of investigators [32-34], it may be reasonable to focus future trials of depression treatment on patients with incident depression after myocardial infarction in order to determine whether their outcomes may be improved by antidepressant therapy.

Studying different methods of delivering depression treatment

In ENRICH, most of the patients randomized to the cognitive-behavioral therapy intervention received individual therapy; only 31% also received group training. In a recently published secondary analysis of the ENRICH data [35], group plus individual therapy was associated with a 33% reduction in all-cause mortality or nonfatal myocardial infarction (HR: 0.67; 95% CI: 0.49-0.92; $p = 0.01$) compared with usual care. This suggests that the method of delivery of depression treatment, either its format or dose, may have differential effects on mortality. This concept merits evaluation in an RCT specifically designed to address this question.

Recently, Rollman *et al.* reported the results of the Bypassing the Blues study, in which telephone-delivered collaborative care of depression after coronary artery bypass graft surgery was found to improve health-related quality of life, physical functioning and mood symptoms compared with usual care [36]. Delivering treatment for depression in the context of collaborative care involves the facilitation of depression treatment by a nonphysician care manager who recommends antidepressant drug types and doses guided by evidence-based antidepressant treatment protocols that also take into consideration the prior treatment experiences and preferences of the individual patient. The care manager works with both the patient (by providing support and education) and the patient's physician (by monitoring the patient's response to treatment, by providing information and advice to the physician and by either facilitating depression comanagement or by the transfer of non-responders or particularly complicated patients to specialists when indicated). Examining this form of delivery of depression care to patients in other CVD settings appears warranted.

Studying patients whose depression is likely to benefit from treatment

A recent meta-analysis of antidepressant drug effects by Fournier *et al.* demonstrated that differences between medication and placebo varied substantially based on the pretreatment depression severity [37], a finding that was also reported in an earlier meta-analysis of depression treatment [38]. Fournier *et al.* concluded that the benefit of antidepressant therapy is minimal or nonexistent in patients with mild or moderate symptoms of depression [37]. Notably, scores on depression severity rating scales in the three major trials examining the effects of depression treatment on mortality in CVD outcomes in heart disease patients are all in the mild-to-moderate range. In MIND-IT, baseline scores on the Hamilton Depression Rating Scale (HAM-D) in the mirtazapine and placebo groups were 18.6 and 16.8, respectively [20]. In SADHART, the mean HAM-D score was 19.6 [17]. In ENRICH, which recruited patients with depression, low perceived social support or both, the mean HAM-D scores among depressed patients were 17.8 in the usual care arm and 17.7 in the intervention arm [19]. In the report by Fournier *et al.*, among patients with a HAM-D score below 23, Cohen d effect sizes for the difference between medication and placebo were estimated to be less than 0.20, consistent with a small effect [37].

Differences between medication and placebo may be minimal or nonexistent in patients with mild or moderate symptoms of depression for several reasons. These patients may have significant spontaneous remission rates or placebo responses. There is also little evidence that currently available antidepressants produce specific pharmacological benefits for most patients with less severe forms of depression [37]. The current situation with antidepressant therapy is reminiscent of the situation that prevailed with lipid-lowering therapy several decades ago. In fact, it is useful to reflect on the lipid-lowering therapy ‘story’ in order to put the current situation with depression treatment in context.

Many younger physicians may be unaware that before statins, RCTs examining the effect of lipid-lowering treatments on mortality yielded rather disappointing results. In 1990, Holme reviewed all RCTs of cholesterol-lowering treatment (both diet and drug) published until that time [39]. Holme analyzed the relationship between the net difference in cholesterol change between the study group and the control group in 19 trials and reported findings that provide lessons of possible importance to the depression treatment paradigm. First, there was a clear relationship between the degree to which cholesterol was lowered and the effect on mortality. Second, the effect was dependent on the baseline cholesterol level before treatment. Third, and perhaps most importantly, there seemed to be a threshold effect of cholesterol reduction such that when cholesterol was lowered minimally compared with placebo, there was no effect on mortality owing to diet or drug treatment [39]. Indeed, Holme noted that cholesterol reduction had to be at least 8–9% for an effect on mortality to be observed. The Holme article provides a history lesson of relevance to the discussion regarding whether additional trials are needed in the area of depression treatment in patients with heart disease. It must be noted that by 1990, cholesterol reduction could not be shown to significantly reduce total mortality, and there was even some concern about harm. Indeed, Holme notes, “... the treatments used in these trials may have a small adverse effect on mortality when cholesterol levels are not reduced and that cholesterol lowering appears to offset this effect” [39].

The situation began to change slightly over the next few years. In a meta-analysis of 35 trials published in 1995, Gould *et al.* noted that while almost all trials demonstrated a favorable trend of cholesterol treatment on coronary heart disease mortality, only two reported a significant reduction, and three trials actually demonstrated a nonsignificant trend toward increases in mortality that was not due to heart disease. The authors noted that based on all RCTs published until that time, “...most treatments had no discernible effect on total mortality, exceptions being significant increases in 2 trials and a significant increase in 1” [40]. The situation changed dramatically once more effective lipid-lowering treatment (i.e., with statins) was studied in RCTs. Indeed, the same authors used the same analytic approach just 3 years later and found that when they included statin trials in their analysis, for every 10% of cholesterol lower ing, there was a significant 11% reduction in total mortality [41]. The ‘statin story’ suggests that we may have to wait for the development and availability of more effective antidepressants (i.e., the ‘statins’ of depression) before a mortality benefit can be demonstrated.

Evaluating the potential for harm

Epidemiologic data suggest that tricyclic antidepressants (TCAs) may increase cardiovascular risk [42]. This is not surprising, since TCAs are class IA antiarrhythmic drugs (e.g., quinidine), and may therefore increase the risk of serious ventricular arrhythmias in patients with ischemic heart disease [43]. In one trial of patients with ischemic heart disease, treatment with the TCA nortriptyline led to a sustained 11% increase in heart rate and a reduction in heart rate variability [44]. Adverse cardiac events occurred in only one of

41 patients with ischemic heart disease treated with the SSRI paroxetine and in 18% of the patients treated with nortriptyline.

The SSRIs appear to be safe even in patients with acute cardiac disease [17,18], although it must be noted that this conclusion is based primarily on studies that examined the effect of SSRIs on left ventricular ejection fraction or on changes on a routine ECG or 24-h Holter ECG recording in relatively small numbers of patients, and not on mortality or cardiac events. Data on potential harms such as adverse effects are quite limited [45]. In addition, it has been argued that many RCTs do not report harms or report them incompletely, and that trials of interventions such as psychotherapy almost never report harms [46].

Three recent observational studies, all published in 2009, suggest the possibility of harm related to antidepressant treatment in women [47-49]. Although caution must be used in interpreting the results of observational studies, and in particular in assuming causality, at the very least these reports call for additional RCTs that carefully examine the effects of antidepressant treatment on cardiovascular events and mortality. In a cohort of women without baseline CVD enrolled in the Nurses' Health Study (NHS), use of antidepressants was associated with a more than a three-fold increased risk of sudden cardiac death [47]. In the Womens' Ischemia Syndrome Evaluation (WISE) study, antidepressant use by women with symptoms of myocardial ischemia who were undergoing coronary angiography was associated with an increased risk of cardiovascular events and death [48]. In the Women's Health Initiative (WHI) study, antidepressant use by postmenopausal women was associated with an increased risk of mortality [49]. Use of SSRIs was associated with an increased risk of stroke, particularly hemorrhagic stroke, in this study [49].

In addition to concerns regarding the risks of antidepressant drug treatment, there are concerns regarding harms from psychotherapy, again particularly in women, from the Montreal Heart Attack Readjustment Trial (M-HART) [50] and from ENRICHD [19]. In M-HART, the impact of a home-based psychosocial nursing intervention program on 1-year cardiac and all-cause mortality was assessed in a RCT in patients recovering from a myocardial infarction [50]. Although the program had no overall impact on survival, increases in cardiac and all-cause mortality were demonstrated among the women in the trial, who comprised more than a third of the total sample. This suggested the possibility that there may be gender-specific differences in treatment responses for patients who sustain a heart attack, and it also raised a cautionary note concerning the possibility that treatment may do harm. ENRICHD demonstrated a treatment group by sex interaction on the risk of death or nonfatal myocardial infarction. Viewed in the context of the M-HART results, the ENRICHD authors concluded that additional research was needed to better understand the potential for differential effects of psychosocial treatments by sex [19]. Notably, no interaction between gender and interpersonal psychotherapy was observed in the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial [51], which examined the effects of citalopram and interpersonal psychotherapy in reducing depressive symptoms in patients with coronary artery disease and major depression.

Evaluating other treatments for depression

Most trials to date have evaluated the effect of antidepressant drugs (e.g., SADHART [17] and MIND-IT [20]) or psychotherapy (e.g., ENRICHD [19]) or both (e.g., CREATE [51]) on depression in patients with coronary disease. Other treatments for depression have been evaluated to a lesser extent in RCTs in this patient population. Among the most promising nondrug treatments of depression in patients with heart disease is exercise, which has the potential advantage of not only improving depressive symptoms but also addressing

important pathways that may link depression and increased cardiovascular risk. The effect of exercise appears to be comparable with that of antidepressant medication in patients with major depression [52]. One RCT in patients with stable ischemic heart disease demonstrated that aerobic exercise and stress management training each improved measures of depressive symptoms and stress compared with usual care. Although the trial was too small to detect differences in cardiovascular morbidity or mortality, the intervention groups did exhibit improved markers of cardiovascular risk compared with usual care alone [53]. Larger-scale RCTs comparing the effects of aerobic exercise with usual care on cardiovascular morbidity and mortality in patients recovering from an acute coronary event appear warranted.

Summary

At the opening ceremony of the Summit of the Americas in April 2009, President Barack Obama stated, “I didn’t come here to debate the past – I came here to deal with the future. I believe ... that we must learn from history, but we can’t be trapped by it” [101]. It appears reasonable to follow this lesson when considering the case for more trials in patients with depression and heart disease. Instead of debating the findings of previous trials in this area, we must deal with the future. We should learn from these trials and view their findings as having the potential to guide the design of additional trials, but we must not be trapped by the notion that *post hoc* analyses of subgroups of patients are anything more than hypothesis-generating. There are many reasons as to why more trials in this area are warranted, but there are also some potential drawbacks that must be dealt with in their design and implementation (TABLE 1). One hypothesis that has been generated by prior trials is that RCTs of antidepressant treatment should be designed to focus on specific subgroups of patients who may be more likely than others to have a favorable response to antidepressant treatment. Another hypothesis that comes from prior studies is that RCTs that focus on patients with heart disease who have more severe symptoms of depression may be particularly fruitful. Previous studies that failed to demonstrate that the treatment of depression improves survival of patients with heart disease also failed to show important differences in depression itself between those who received usual care and those who received protocol-driven depression treatment, perhaps because so many of the patients with mild depression who were included in these trials improved without specific treatment. Patients with more severe depression would be more likely to demonstrate an improvement in their depression with antidepressant treatment compared with those treated with placebo, and possibly an improvement in mortality as well. However, it must be noted that the proportion of patients with heart disease who have severe depression is small. This fact, coupled with the other exclusions that must be considered, including suicidal ideation, comorbid psychiatric disorders and cognitive impairment, would pose virtually insurmountable problems for recruitment, since most depressed patients with heart disease would be ineligible. In the end, a trial of this type may be unfeasible, since it would not only be large and expensive, but it would also pose ethical issues related to placebo or usual care comparison groups for patients with severe depressive illness.

Additional research that examines the basis for the apparent gender-specific effect of depression treatment on mortality may lead to new treatment strategies that can be examined in RCTs in women with comorbid depression and heart disease. RCTs are also warranted to examine newer depression treatment strategies in patients with heart disease, including the collaborative care model recently examined by Rollman *et al.* [36]. New RCTs should be designed with extended periods of follow-up that enable more complete ascertainment of side effects and harm. Finally, there is the matter of patients with treatment-resistant or persistent depression, who seem to have the highest mortality risk [54-56]. New RCTs that examine the effects of strategies that specifically target cardiovascular risk factors, which enhance adherence to medical treatment, exercise programs and diet or that simultaneously

treat depression and more aggressively treat potential biological mediators of increased risk (e.g., platelet activation or inflammation) appear appropriate [55]. It must also be noted that depression is a serious disease that has significant negative effects on quality of life, physical function and adherence to medical treatment regimens. In addition to addressing mortality as an outcome, future trials should address the effect of depression treatment on these outcomes and on healthcare utilization.

By making the case for more trials in patients with heart disease and depression, we do not mean to dismiss or minimize the very real challenges to designing and implementing additional RCTs of depression treatment in patients with heart disease. Recruiting patients for trials of this nature is challenging. Many of the obstacles and issues rather unique to this area of research are outlined elegantly by Jiang *et al.* [57] and will not be described in detail here. We recognize that these trials are expensive, take a long time and even under the best circumstances may need to exclude patients at the highest risk as a result of their depression or heart disease. In addition, the previously negative trials on the effect of antidepressant therapy on mortality in CVD patients may make it more difficult to secure funding for additional RCTs. History teaches us that we should not lose our patience; the cholesterol drug treatment story teaches us that more effective treatment may take time before it is available, and effects on mortality may not be possible to demonstrate until that time.

Future perspective

Heart disease and depression are both associated with significant negative effects on health and quality of life. The two conditions are common, and they commonly occur together. Over the past two decades, a large body of evidence has emerged showing that individuals with an acute coronary syndrome who have comorbid depression have a higher morbidity and mortality than those who do not. As this became evident, trials examining the safety and efficacy of antidepressant drugs and/or psychotherapy in depressed patients recovering from an acute coronary syndrome were conducted, and in some cases, these trials also examined the effect of depression treatment on cardiovascular morbidity and mortality. Although the better part of a decade has passed since the first of these trials was published, no trial has demonstrated that treatment of depression in those recovering from an acute coronary syndrome reduces cardiovascular morbidity or mortality to date. Indeed, there are still some questions regarding the safety of depression treatment in this setting, especially in certain patient groups. Moreover, the benefit of antidepressant therapy on depression itself appears to be minimal in patients with mild or moderate depression, and most randomized trials in this field to date have enrolled patients with relatively mild depressive symptoms.

In the next decade, the field is likely to evolve in one of two ways, or down one of two paths. The first path will be traveled if it is accepted that the importance of depression in patients with acute coronary syndromes, along with our current knowledge of the benefits and harms of depression treatment, are sufficient at present to make the diagnosis and treatment of depression in patients with acute coronary syndromes part of standard care. In this path, research will probably be focused on how depression treatment is delivered or perhaps on further clarifying the mechanisms that link depression and increased cardiovascular morbidity and mortality, but not on the effect of depression treatment on cardiovascular morbidity and mortality or on more completely addressing the possibility of harm. The second path involves a continued push to identify more efficacious treatments for depression in patients with acute coronary syndromes, focusing on their effects on depression and also on cardiovascular morbidity and mortality. The push will include more efforts to completely address the possibility of harm from antidepressant drug treatment and/or psychotherapy. It will also involve an examination of different models of antidepressant therapy delivery, probably including teams of healthcare providers collaborating to provide

optimal treatments for both depression and heart disease, and addressing adherence to medical therapy and to heart-healthy behaviors. The second path is paved with more trials, and this article makes the case that this is the path that will lead to the greatest benefits for our patients.

Executive summary

- Patients recovering from an acute coronary syndrome who have comorbid depression are at a greater risk of cardiovascular morbidity and mortality than those who are not depressed.
- There is no evidence that treating depression in this setting improves cardiovascular morbidity or mortality.
- The care of many of the conditions treated by cardiologists is based on evidence from randomized controlled trials.
- Although no trial has demonstrated that depression treatment improves cardiovascular outcomes, there is evidence that suggests directions for future trials.
- Some studies suggest that certain subgroups of patients with comorbid depression and heart disease may be at a particularly high risk for cardiovascular morbidity or mortality or may benefit more than others from depression treatment. Future trials may be targeted to these patient subgroups.
- There is also some evidence that depression treatment may be harmful to certain subgroups of patients and ascertainment of adverse effects and duration of follow-up in previous trials may have been insufficient to fully address the potential for harm.
- Additional trials are needed to properly characterize the correct care of patients with comorbid depression and heart disease.

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- of interest
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Table 1
Advantages and disadvantages of future trials investigating patients with depression and heart disease

Potential new trials	Why trials are needed	Advantages	Disadvantages	Ref.
Larger RCTs	Previous studies (e.g., SADHART and MIND-IT) were too underpowered to detect differences in cardiac outcomes	Larger RCTs could have the power to detect differences in morbidity and mortality	Recruitment and retention of large numbers of patients would be extremely challenging and costly and may be impractical	[17,20]
RCTs examining patient subgroups	<i>Post hoc</i> analysis suggests mortality benefit of ENRICHD intervention in white men	RCTs focused on patient subgroups may provide important information regarding differential treatment effects and can more specifically test hypotheses generated by prior trials	Findings of <i>post hoc</i> analyses must be interpreted with caution. Excluding subjects based on gender or race may be difficult to justify	[31]
RCTs examining patients with severe depression	Many previous RCTs in patients with heart disease enrolled patients with mild depression for whom the benefit of antidepressant therapy (compared with placebo) is minimal or nonexistent	Patients with more severe depression would probably benefit from antidepressant therapy compared with those given placebo	Relatively few patients with heart disease have severe depression. Recruitment and retention of such patients would be difficult, and placebo-controlled trials may be impractical and possibly unethical	[37]
RCTs examining potential for harm	Previous RCTs were often too small, and follow-up too short, to adequately assess harm	RCTs with longer follow-up and more thorough ascertainment of adverse effects would better clarify the risk associated with depression treatment	Recruiting sufficient numbers of patients, and retaining them for a sufficiently long follow-up, may be challenging and expensive	[47-49]
Trials examining specific depression treatment delivery models	A recent trial of telephone-delivered collaborative care for the treatment of post-CABG depression demonstrated that this improved health-related quality of life, physical functioning and mood, but this has not been examined in patients with acute coronary syndromes	Depression treatment may be more effective if systems are in place to ensure effective treatment and follow-up, especially in collaboration with experts in the management of depression	Large numbers of trained personnel are needed to carry out interventions	[35,36]
RCTs of exercise as treatment for depression	Large RCTs of exercise that are sufficiently powered to detect differences in cardiovascular morbidity and mortality in depressed patients have not been performed	The effect of exercise appears to be comparable with that of antidepressant medication in patients with major depression	It may be difficult to motivate sufficient numbers of cardiac patients with depression to engage in regular aerobic exercise programs, especially those with more severe depressive symptoms	[52,53]
RCTs examining specific depression phenotypes	Some studies have demonstrated that patients with a first-ever episode of depression after an acute coronary syndrome may have the highest mortality	RCTs of depression treatment in patients with specific depression phenotypes may better clarify whether these groups are at greater risk and whether they have differential treatment responses	A standard definition of 'incident depression' is needed	[32-34]
RCTs examining effects of antidepressants	SSRIs may inhibit platelet activation	RCTs of antidepressants that more thoroughly examine biological pathways may clarify their effects in	Positive effects in secondary outcomes may not correlate with differences in cardiovascular	[5,6]

Potential new trials	Why trials are needed	Advantages	Disadvantages	Ref.
on specific biological pathways		patients treated with conventional cardiovascular drugs (e.g., aspirin, clopidogrel, β -blockers and statins)	morbidity and mortality	
RCTs examining the effects of antidepressant treatment and adherence-enhancing interventions	Depressed patients are less likely to adhere to medication regimens. Good adherers have lower mortality in prior cardiovascular disease RCTs	Adherence-enhancing interventions may allow depressed patients to benefit maximally from antidepressant treatments and to potentially show improved cardiovascular morbidity and mortality	Multiple 'real world' factors besides depression would probably need to be addressed in order to affect treatment adherence (e.g., financial challenges, complexity of medical regimens and poor patient understanding)	[13-16]

CABG: Coronary artery bypass graft; ENRICHD: Enhancing Recovery in Coronary Heart Disease Patients; MIND-IT: Myocardial Infarction and Depression – Intervention Trial; RCT: Randomized controlled trial; SADHART: Sertraline Antidepressant Heart Attack Randomized Trial; SSRI: Selective serotonin reuptake inhibitor.