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Guidelines

Screening, referral and treatment for depression in patients with coronary heart disease

A consensus statement from the National Heart Foundation of Australia

In 2003, an Expert Working Group of the National Heart Foundation of Australia (NHFA) issued a position statement on the relationship between “stress” and heart disease. They concluded that depression was an important independent risk factor for first and recurrent coronary heart disease (CHD) events.¹ Here, we provide an update on evidence obtained since 2003 regarding depression in patients with CHD, and include guidance for health professionals on screening and treatment for depression in these patients. Our statement refers to depression in general (mild, moderate and severe), as all grades of depression have an impact on CHD prognosis. The process for developing this consensus statement is described in Box 1. Treatment decisions should take into account the individual clinical circumstances of each patient.

Epidemiology

The prevalence of depression is high in patients with CHD. Rates of major depressive disorder of around 15% have been reported in patients after myocardial infarction (MI) or coronary artery bypass grafts.^{3,4} If milder forms of depression are included, a prevalence of greater than 40% has been documented.^{3,4} Recently, the EUROASPIRE III study investigated 8580 patients after hospitalisation for CHD.⁵ The proportion of patients with depression, measured by the Hospital Anxiety and Depression Scale, varied from 8.2% to 35.7% in men and 10.3% to 62.5% in women. This is consistent with Australian and New Zealand data from a 6-year study, Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID).^{6,7} At the end of this trial, 27% of men and 35% of women were identified as depressed, using the Beck Depression Inventory II (BDI-II) questionnaire.

A large systematic review in 2006 suggested that individuals with depression, but no current CHD, have a moderately elevated risk of 1.6 for a later index CHD event.⁸ This elevated risk was confirmed in the Whitehall II study of 5936 healthy individuals over a 6-year period, in which depression was associated with a hazard ratio of 1.93 for cardiovascular events.⁹ In the Nurses Health Study, 78 282 healthy women were assessed for depression. In the 6-year follow-up period, 4654 deaths were reported, including 979 deaths from cardiovascular disease.¹⁰ Depression was associated with increased all-cause

Summary

- In 2003, the National Heart Foundation of Australia position statement on “stress” and heart disease found that depression was an important risk factor for coronary heart disease (CHD). This 2013 statement updates the evidence on depression (mild, moderate and severe) in patients with CHD, and provides guidance for health professionals on screening and treatment for depression in patients with CHD.
- The prevalence of depression is high in patients with CHD and it has a significant impact on the patient’s quality of life and adherence to therapy, and an independent effect on prognosis. Rates of major depressive disorder of around 15% have been reported in patients after myocardial infarction or coronary artery bypass grafting.
- To provide the best possible care, it is important to recognise depression in patients with CHD. Routine screening for depression in all patients with CHD is indicated at first presentation, and again at the next follow-up appointment. A follow-up screen should occur 2–3 months after a CHD event. Screening should then be considered on a yearly basis, as for any other major risk factor for CHD.
- A simple tool for initial screening, such as the Patient Health Questionnaire-2 (PHQ-2) or the short-form Cardiac Depression Scale (CDS), can be incorporated into usual clinical practice with minimum interference, and may increase uptake of screening.
- Patients with positive screening results may need further evaluation. Appropriate treatment should be commenced, and the patient monitored. If screening is followed by comprehensive care, depression outcomes are likely to be improved.
- Patients with CHD and depression respond to cognitive behaviour therapy, collaborative care, exercise and some drug therapies in a similar way to the general population. However, tricyclic antidepressant drugs may worsen CHD outcomes and should be avoided.
- Coordination of care between health care providers is essential for optimal outcomes for patients. The benefits of treating depression include improved quality of life, improved adherence to other therapies and, potentially, improved CHD outcomes.

mortality, with an age-adjusted relative risk of 1.76 (95% CI, 1.64–1.89).¹⁰ The effect of depression on CHD incidence is thought to be strongest around the time of the depressive episode, with longer-term effects mediated via

1 Process used to develop this National Heart Foundation of Australia consensus statement

The Expert Working Group members performed relevant literature searches using key search phrases including, but not limited to, "stress", "depression", "anxiety", "treatment of depression", "acute coronary syndromes", "adherence and depression" and "screening for depression". This was complemented by reference lists compiled from reviews and personal collections of the Expert Writing Group members. Searches were limited to evidence available for human subjects with coronary heart disease published in English up to December 2012. The recommendations made in this consensus statement have been graded according to the National Health and Medical Research Council guidelines (see Appendix).² The Cardiac Society of Australia and New Zealand, *beyondblue*: the national depression initiative and the Royal Australian and New Zealand College of Psychiatrists were consulted during the development of this document and have endorsed its content. ◆

recurrence of depression.¹¹ In young people the association between depression and CHD may be stronger.¹²

The case-control INTERHEART Study included 11 119 patients with MI from 52 countries.¹³ Perceived stress and depression were shown to be important risk factors, which together accounted for 32.5% of the population attributable risk (PAR) for CHD, suggesting that together they were as important as smoking and more important than diabetes (PAR, 9.9%) and hypertension (PAR, 17.9%) as risk factors for CHD.¹³

For people with CHD and comorbid depression, the relative risk (RR) of death is increased (RR, 1.80 [95% CI, 1.50–2.15]), independent of standard risk factors for secondary prevention.⁸ Comorbid depression also leads to a higher risk of other adverse outcomes in patients with CHD, such as a lower likelihood of return to work, poorer exercise tolerance, less adherence to therapy, greater disability, poorer quality of life, cognitive decline and earlier dependency.^{14–20} Individuals with CHD and comorbid depression often have less access to interventions for CHD, despite being in a higher-risk group.^{21–23}

Definition of depression and types of depression

The diagnosis of depression can be difficult in people with cardiovascular disease, as depressive symptoms such as fatigue and low energy are common to both CHD and heart failure, and may also be a side effect of some drugs used to treat cardiovascular disease, such as β -blockers.²⁴ The diagnosis may be further complicated in such patients by their responses to their disease (and the associated stigma), which may include denial, avoidance, withdrawal and anxiety.

According to the *Diagnostic and statistical manual of mental disorders*, fourth edition (DSM-IV),²⁵ major depression is diagnosed when there is a minimum of 2 weeks of depressed mood and/or lack of pleasure (anhedonia), accompanied by four or more other (listed) symptoms such as sleep disturbance, appetite disturbance, poor energy, psychomotor impairment or agitation, poor concentration or poor decision making, and suicidal ideas or thoughts of death. The association with CHD appears to increase with greater severity of depressive symptoms across the spectrum, with no discrete cut-off point at "major depression".

Some studies have suggested links between particular subtypes of depression, such as somatic or anhedonic depression, but these are not consistent findings.^{26–28}

Screening for depression in patients with coronary heart disease

Screening of a population group for a risk factor or disease is worthwhile when the risk factor or disease has a reasonably high prevalence, there is a robust screening test, and effective and cost-effective treatments are readily available.^{29,30} Depression is both a risk factor and a disease in its own right, and fulfils these criteria for population screening. Screening for depression in patients with CHD would be expected to produce a higher yield than screening for depression in the general population, owing to a much higher prevalence of depression in patients with CHD. It is important to recognise depression in patients with CHD in order to provide the best possible care. Asymptomatic patients with significant cardiovascular risk factors (eg, those with diabetes) may also be considered for screening, as they have a high risk of depression.³¹

Many self-reported screening tools exist with the aim of detecting possible depression. These include the Patient Health Questionnaire (PHQ-2, PHQ-9), the Cardiac Depression Scale (CDS), the BDI-I and -II, and the Hospital Anxiety and Depression Scale.^{32,33} The BDI appears to be the most commonly used tool in studies involving cardiac patients. The CDS was developed by a member of the Expert Working Group (DLH) specifically for patients with cardiac disease.³³ The short version (short form) has only five items. There is limited but expanding information on the use of the PHQ-9 in patients with cardiac disease.^{34,35} It is used widely in primary care. Simple tools such as the Kessler Psychological Distress Scale (K10),³⁶ a measure of general distress, will often overdiagnose depression. This tool is currently used in mental health plans in Australia; however, there is no evidence of its use specifically for patients with CHD.

Recognising the need for a simple screening tool for depression in cardiovascular patients, the 2008 American Heart Association (AHA) Science Advisory suggested the use of the PHQ-2.³⁷ The PHQ-2 is an abbreviated form of the PHQ-9, with only the first two of the nine questions in the PHQ-9 (Box 2).³⁸ There are also other versions of the PHQ-2, which may use shorter time frames. The AHA recommended the use of the PHQ-9 if depression was noted using the PHQ-2.³⁷ The Royal Australian College of General Practitioners' *Guidelines for preventive activities in general practice* (the red book) also uses a categorical (Yes/No) version of the PHQ-2.³⁹

The PHQ-2 and the PHQ-9 screening tools are associated with reasonable sensitivity and specificity.³⁴ Importantly, depression diagnosed with the PHQ-2 and the

2 Patient Health Questionnaire (PHQ-2) Yes/No version³⁵

- During the past month, have you often been bothered by feeling down, depressed or hopeless?
- During the past month, have you often been bothered by little interest or pleasure in doing things? ◆

PHQ-9 has been shown to predict worse CHD outcomes. In the Heart and Soul Study, positive responses to either question in the PHQ-2 (Yes/No version) predicted a 55% greater risk of cardiovascular events.³⁵ Furthermore, the validity of the PHQ-2 and the PHQ-9 has been assessed in a variety of patients with varying clinical problems, ages and ethnicities, including in Australian Aboriginal people from urban and rural areas and people from the Torres Strait Islands.⁴⁰⁻⁴² Adapted versions exist for use with Indigenous people.

Access to each of the tools varies. No copyright is breached by use of the PHQ-2 and the PHQ-9, and the PHQs and the CDS are free.⁴³ However, some questionnaires such as the BDI-I and -II are subject to copyright and a royalty must be paid each time they are used.⁴⁴

Implicit in the AHA Science Advisory³⁷ is that screening and identification of patients with depression leads to appropriate treatment, or referral for treatment, by the responsible attending medical practitioner. Unfortunately, research has shown that screening may have little or no impact on the treatment of depression or on outcomes.^{45,46} Screening by nurses, researchers, receptionists or social workers is not sufficient without appropriate referral or treatment.

It is recommended that a simple tool, such as the PHQ-2 or the short-form CDS, is incorporated into routine screening of patients with CHD. Routine screening for depression is indicated at first presentation, and again at the next follow-up appointment. A follow-up screen should occur 2–3 months after a CHD event. Screening should then be considered on a yearly basis, as for any other major risk factor for CHD. Consideration should also be given to screening the partner or spouse of these patients for depression, as studies show that they are at an increased risk of developing depression.⁴⁷ If screening is followed by comprehensive care, depression outcomes are likely to be improved.

Treatment of depression in patients with CHD

Collaborative care

Although individual treatment approaches and strategies have been studied, in practice a collaborative-care or stepped-care approach is probably optimal for managing patients with CHD and comorbid depression. The concept of collaborative care involves a group of health professionals working together in a coordinated manner, and this approach has consistently been shown to be associated with greater improvement in depression for patients with CHD compared with standard care, and to be cost-effective.⁴⁸⁻⁵² For example, collaborative care after coronary artery bypass grafting improved depression scores, but not physical function or re-hospitalisation rates.⁴⁸ In patients with depression comorbid with poorly controlled diabetes and/or CHD, the collaborative approach resulted in improvement in depression scores, glycated haemoglobin levels, low-density lipoprotein cholesterol levels, and systolic blood pressure.⁵⁰

The Coronary Psychosocial Evaluation Studies (COPES) trial^{52,53} used a stepped-care treatment approach in

patients with acute coronary syndromes (ACS) and persistent depression. Depressive symptoms decreased substantially in the intervention (stepped-care) group. Only three (4%) of the intervention patients experienced major adverse cardiac events compared with 10 (13%) of the patients given usual care, suggesting improved cardiovascular outcomes. Moreover, this stepped-care approach was associated with a 43% lower total health cost over the 6-month trial period.⁵⁴

Pharmacological therapy

The efficacies of fluoxetine,⁵⁵ sertraline (Sertraline Antidepressant Heart Attack Randomized Trial [SADHART]),⁵⁶ Enhancing Recovery in Coronary Heart Disease Patients [ENRICHD] trial),⁵⁷ citalopram (Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy trial [CREATE])⁵⁸ and mirtazapine (Myocardial Infarction and Depression Intervention Trial [MIND-IT])⁵⁹ have been evaluated in clinical trials involving patients with CHD.

SADHART studied depression after ACS over 6 months. Depression scores in patients taking sertraline improved significantly more than in those receiving placebo. Most patients were also prescribed aspirin, statins and β -blockers. Life-threatening cardiovascular events occurred less frequently in the sertraline group; however, this result was not statistically significant.⁵⁶

ENRICHD was a large trial that evaluated the effect of cognitive behaviour therapy (CBT) on depression or low social support in patients with a recent MI. Depression was diagnosed in 74% of participants. CBT improved depression but failed to reduce the number of CHD events. Patients whose depression did not respond to CBT were referred for treatment with antidepressant drugs. Selective serotonin reuptake inhibitors (SSRIs) (mainly sertraline) significantly improved depression in those patients. In the SSRI-treated group, there was a 43% ($P < 0.005$) reduction in deaths or recurrent MIs.⁵⁷ However, this was a subset analysis, and therefore is hypothesis generating only.

In the Canadian CREATE trial⁵⁸ and the MIND-IT trial,⁵⁹ there were too few CHD events reported to enable analysis of cardiovascular outcomes.

Tricyclic antidepressants may worsen CHD outcomes and should be avoided in patients with CHD. Importantly, tricyclic antidepressants have been associated with increased mortality in patients with CHD.⁶⁰⁻⁶² In contrast, a recent meta-analysis of trials involving SSRIs in patients with CHD concluded that this class of drugs was well tolerated, with the risk of adverse events being similar to that for placebo.⁶³

Psychological therapy

Of the various psychological therapies, CBT and integrative therapies (eg, interpersonal psychotherapy) have the best documented efficacy for treatment of major depressive disorder.^{64,65} CBT was used in the ENRICHD trial,⁵⁷ interpersonal psychotherapy in the CREATE trial,⁵⁸ and problem-solving therapy in the COPES trial.^{52,53} These therapies were all beneficial for depression but did not affect CHD outcomes. The efficacy of psychological therapy as a treatment for major or minor depression was evaluated in patients who underwent coronary artery

bypass surgery.⁶⁶ Significantly more patients in the CBT group (71%) and the stress management group (57%) had low depressive symptom levels, compared with those having usual care (33%), and these results were maintained at 6 months.⁶⁶

A Cochrane review of psychological interventions for patients with CHD found evidence of small-to-moderate improvements in depression and anxiety symptoms with such interventions, but no strong evidence that the interventions reduced total deaths, risk of revascularisation, or non-fatal infarction.⁶⁷ The interventions that were less effective were those that aimed to educate patients about cardiac risk factors; those that included client-led discussion and emotional support; or those that included family members in the treatment process.⁶⁷ Uncertainty remains regarding the subgroups of patients who would benefit most from psychological treatments and the characteristics of successful interventions.

Exercise

Many patients with mild depression respond well to regular exercise and cardiac rehabilitation (exercise-based). A recent Cochrane review of exercise as a treatment for depression concluded that exercise improves depression with a similar efficacy to CBT.⁶⁸ The benefit of exercise appears to have a dose-response relationship, needing at least 30 minutes of moderate aerobic activity on 5 days per week.^{69,70} This is consistent with usual public health recommendations.

The benefit of exercise in patients with CHD and depression has been demonstrated in the recent UPBEAT (Understanding the Prognostic Benefits of Exercise and Antidepressant Therapy) trial.⁷¹ Patients with CHD with at least a mildly elevated score for depressive symptoms (BDI score >7) were allocated at random to treatment with SSRIs, exercise or neither. Exercise was equivalent to SSRI treatment in improving depression scores, with patients in both groups showing greater improvement than the control group.⁷¹ In a large randomised controlled trial (RCT) of 2322 patients with heart failure (of whom 28% were depressed), exercise, in addition to reducing mortality and hospitalisation ($P=0.03$), significantly reduced depression ($P=0.002$).⁷²

Complementary and alternative therapies

Up to 50% of patients with depression have been shown to use complementary and alternative medicines without disclosing this to their treating clinician.⁷³ Therapies that may be effective in depression are supplemental marine n-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]), S-adenosylmethionine (SAME) and St John's wort.⁷⁴ Specific trials in patients with CHD and depression have not been performed with the latter two therapies.

Marine n-3 fatty acids (at a dose of 1 g per day of combined EPA-DHA) are recommended by the NHFA and the AHA for all patients with CHD.⁷⁵ This dose also may improve mild depression. However, the addition of 2 g/day of combined EPA and DHA to sertraline 50 mg daily for depressive symptoms appears to provide no added benefit over sertraline alone.⁷⁶ Some trials compar-

ing St John's wort and SAME to antidepressant medications suggest a similar effectiveness in improving depression to antidepressant medications.⁷⁷⁻⁷⁹ However, most commercial brands of St John's wort have not undergone randomised trials.^{78,79}

Adherence

Depression is a major predictor of poor adherence in patients with CHD, be it to drug therapy or lifestyle measures.^{80,81} Patients with depression are three times more likely to be non-compliant with medical treatment than patients without depression.⁸² Greater severity and chronicity of depression have been associated with poorer adherence to aspirin therapy after MI.⁸³ Adherence to aspirin therapy after ACS has been shown to be significantly lower in persistently depressed patients (76.1%) than in those whose depression improved (87.4%), or who were not depressed (89.5%).⁸³ Patients who are persistently depressed are also less likely to undertake behaviours that reduce risk; for example, quitting smoking, taking medications, exercising and attending cardiac rehabilitation.⁸¹ The SADHART trial showed adherence to medication increased after remission of depression in 68.4% of participants taking the trial medication.⁸⁴

A recent RCT of a collaborative-care depression treatment program in 134 patients with depression after ACS demonstrated improved adherence to medications and secondary prevention behaviours and was independently associated with improvement in depression.⁸⁵ However, in another RCT of 157 patients undergoing treatment for depression after ACS, there were no improvements in adherence to risk-reducing behaviours in spite of a significant reduction in depression.⁸⁶

Referral

Once depression is identified through screening, treatment may be initiated immediately, or referral to psychological or psychiatric services may also be considered appropriate. Most patients with depression in Australia are managed by general practitioners.⁸⁷

Members of the Cardiac Society of Australia and New Zealand, the majority of whom are clinical cardiologists, were surveyed regarding assessment of depression. Most respondents screened for depression occasionally, with only 3% using a formal tool. Lack of confidence in identifying depression was the strongest predictor of a low screening frequency. Cardiologists rarely initiated treatment for depression, and 43% did not feel they were responsible for treating depression.⁸⁸

There can be a reluctance to treat depression in patients with CHD because of a belief that depression is normal after an acute cardiovascular event. Mild depression may resolve spontaneously; however, for most individuals with CHD, depression remains long term.⁸⁹

Conclusion

A summary of the key evidence-based points is provided in Box 3 and Box 4, and the Appendix gives the National

3 National Heart Foundation of Australia grades of recommendation and levels of evidence for screening, referral and treatment for depression in patients with coronary heart disease (CHD)²

Recommendation	Grade ²	Level ²
1 For patients with CHD, it is reasonable to screen for depression	A	I
2 Treatment of depression in patients with CHD is effective in decreasing depression	A	I
3 Treatment of depression in patients with CHD improves CHD outcomes	D	II
4 Treatment of depression in patients with CHD changes behavioural risk factors/adherence	B	III-2
5 Exercise is an effective treatment of depression in patients with CHD	A	I
6 Exercise improves CHD outcomes in patients with CHD	B	II
7 Psychological interventions improve depression in patients with CHD	B	II
8 Psychological interventions improve CHD outcomes in patients with CHD and depression	D	II
9 SSRIs improve depression in patients with CHD	A	I
10 SSRIs improve CHD outcomes in patients with CHD and depression	D	III-1
11 Collaborative-care approach improves depression in patients with CHD	B	II
12 Collaborative-care approach improves CHD outcomes in patients with CHD and depression	D	II

SSRIs = selective serotonin reuptake inhibitors. ◆

4 Treatment of depression in patients with coronary heart disease (CHD) — summary of treatment subgroup effects showing grade of recommendation and level of evidence

Treatment	Depression		CHD outcome	
	Grade ²	Level ²	Grade ²	Level ²
Non-drug				
Exercise	A	I	B	II
Psychological, including CBT	B	II	D	II
St John's wort*	D	—*	D	—*
n-3 fatty acids	D	II	D [†]	II
SAMe*	D	—*	D	—*
Collaborative	B	II	D	II
Drug				
SSRIs	A	I	D	III-1

CBT = cognitive behaviour therapy. SAMe = S-adenosylmethionine. SSRIs = selective serotonin reuptake inhibitors. * Insufficient evidence to rate or no trials have been performed. † Data not available in patients with CHD. ◆

Health and Medical Research Council grades of recommendations and evidence hierarchy.

High-quality care for treatment of depression is achievable and affordable. The benefits of treating depression in people with CHD include improved quality of life, improved adherence to other therapies and potentially improved CHD outcomes.⁹⁰ Effective treatment of depression may decrease CHD events but this is not proven, as no adequately powered trials have been completed, nor are there any ongoing.

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Biotronic, BMS, Boehringer Ingelheim, CSL-Biotherapies, Hoffmann-LaRoche, Hospira, Lundbeck (Denmark), Medtronic, Menarini, Merck KA (Germany), Merck (US), MSD, Pfizer, Roche, Sanofi-Aventis, Servier and Wyeth. Ian Hickie was supported by an NHMRC Australia Fellowship (No. 464914). He was a director of *headspace*: the national youth mental health foundation until January 2012. He is the executive director of the Brain and Mind Research Institute, which operates two early intervention youth services under contract to *headspace*. He is a member of the new Australian National Mental Health Commission and was previously the CEO of *beyondblue*. He has led a range of community-based and pharmaceutical industry-supported depression awareness and education and training programs, and depression and other mental health research projects supported by a variety of pharmaceutical partners. His current investigator-initiated studies are supported by Servier and Pfizer. He has received honoraria for his contributions to professional educational seminars supported by the pharmaceutical industry (including Servier, Pfizer, AstraZeneca, Janssen and Eli Lilly). Nick Glozier has been funded under a strategic research grant program by *beyondblue* and the NHFA. He has received other depression-related research funds from the NHMRC, *beyondblue*, the Australian Research Council and Servier Laboratories. He has received travel and consultancy fees from Servier Laboratories. There are no relevant disclosures for the other authors.

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Appendix: Definition of National Health and Medical Research Council (NHMRC) grades of recommendations and evidence hierarchy*

Definition of NHMRC grades of recommendations

Grade	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

NHMRC evidence hierarchy: designation of levels of evidence

Level	Intervention
I	A systematic review of level II studies
II	A randomised controlled trial
III-1	A pseudorandomised controlled trial (ie, alternate allocation or some other method)
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> ● Non-randomised, experimental trial ● Cohort study ● Case-control study ● Interrupted time series with a control group
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> ● Historical control study ● Two or more single arm study ● Interrupted time series without a parallel control group
IV	Case series with either post-test or pre-test/post-test outcomes

* From NHMRC additional levels of evidence and grades for recommendations for developers of guidelines.² ◆