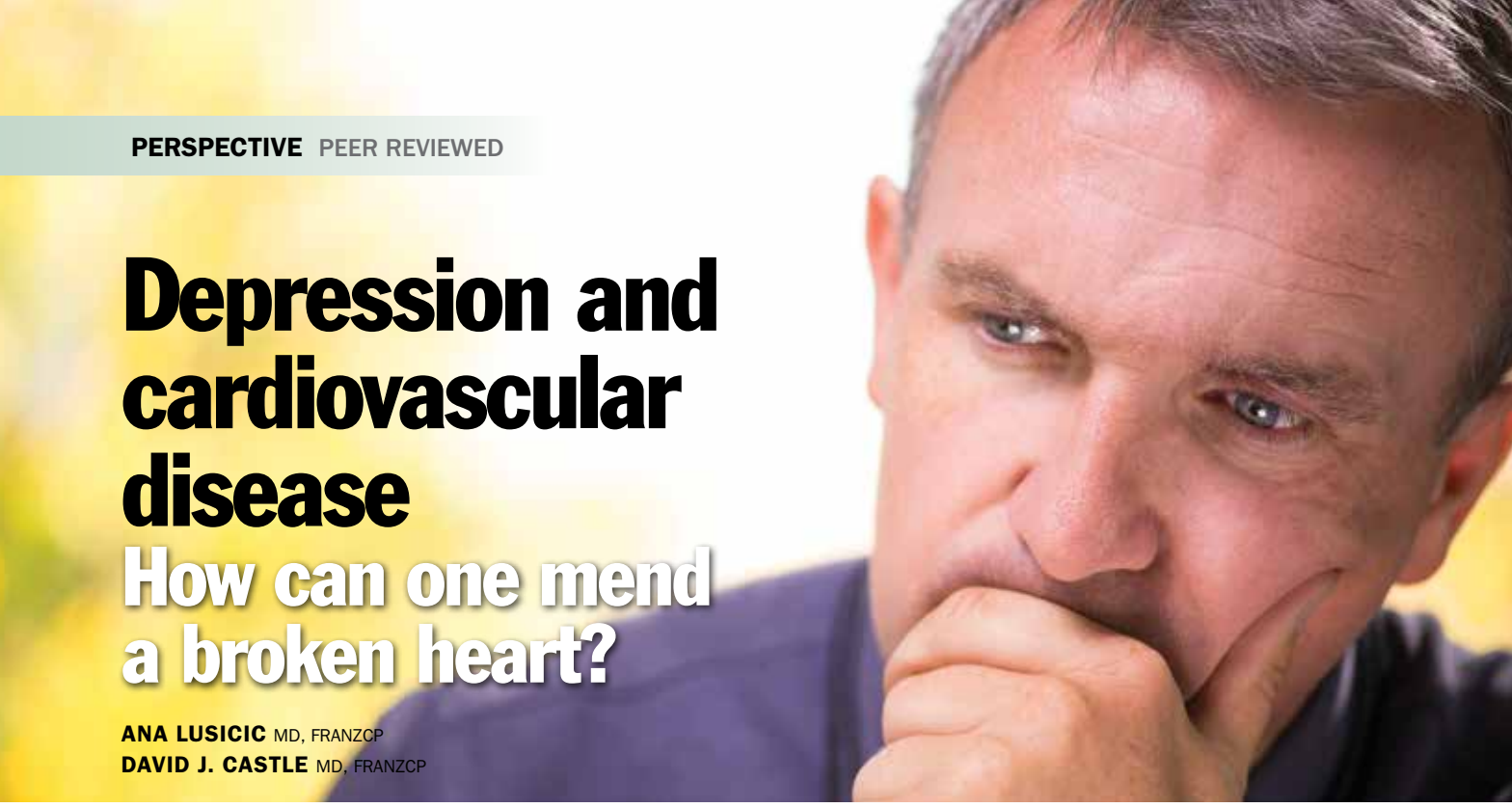

Depression and cardiovascular disease

How can one mend a broken heart?

ANA LUSICIC MD, FRANZCP
DAVID J. CASTLE MD, FRANZCP

A strong association has been found between depression and cardiovascular disease. The GP plays an important role in screening cardiac patients for depression and monitoring cardiac and depressive outcomes.

Key points

- **Epidemiological and clinical studies indicate a bidirectional association between depression and cardiovascular disease.**
- **Interplay between depression and cardiovascular disease contributes to risk and outcomes of both conditions.**
- **Screening for depression in patients with cardiovascular disease is recommended in routine clinical practice.**
- **Treatment should encompass lifestyle modification (e.g. diet, exercise), and specific psychological interventions should be offered where appropriate.**
- **Pharmacotherapy requires careful balancing of efficacy versus risk, specifically cardiac risk issues.**

© STURTI/ISTOCKPHOTO. MODEL USED FOR ILLUSTRATIVE PURPOSES ONLY.

CARDIOLOGY TODAY 2016; 6(2): 31-35

Dr Lusicic is Consultant Psychiatrist in the Youth Mood Clinic (YMC), Orygen Youth Health, Melbourne.
Professor Castle is Chair of Psychiatry at St Vincent's Hospital, Melbourne; and Professor at The University of Melbourne, Melbourne, Vic.

Depression is often encountered in patients with cardiovascular conditions and carries a negative impact on their longitudinal outcomes.[1] Also, people with depression are known to have a higher risk of developing an atherosclerotic heart condition.[2] Competence in the diagnosis and treatment of depression in people with cardiovascular disease (CVD) and the monitoring of cardiovascular risk factors in patients with depression, as well as understanding the link between the two conditions, are therefore important in everyday clinical practice. This article outlines the epidemiology, putative causal mechanisms and treatment of people with depression and CVD.

Epidemiology

The relation between heart disease and depression has been of interest to clinicians since early in the 20th century. In 1937, Malzberg and colleagues noted that the leading cause of increased mortality in patients with melancholia was a 'disease of heart'.[3]

More recent reviews have noted that depressive symptoms are found in 31 to 45% of patients with atherosclerotic heart disease, whereas a defined depressive disorder is diagnosed in 15 to 20% of such patients.[4,5] In individuals with coronary heart disease (CHD), development of depression is increased threefold within a year of an acute coronary event, and this temporal pattern appears especially prominent for men.[6] Similarly, patients with congestive heart failure and arrhythmia (atrial fibrillation) have been reported to be at increased risk of developing de novo depression.[7]

Furthermore, depression is considered to be a risk factor for CVD.[1,8] Kendler and colleagues found that the risk of CHD was increased 2.5-fold in the year after a diagnosis of a depressive disorder.[6] The strength of the association appeared to be related to the severity of the depressive episode.[6]

INTERHEART, a worldwide case-control study of risk factors associated with acute myocardial infarction (MI), emphasised the

Downloaded for personal use only. No other uses permitted without permission. © **Medicine**Today 2016.

Table 1. Selected screening and diagnostic scales for depression

Scale	Clinical use	Scoring	Comment
PHQ-2	Two-item depression screening tool; abbreviated version of PHQ-9	Total score 6 Score >3 or a yes answer on yes/no version = depression	Ultra-brief depression screening tool
PHQ-9	0 to 3 scores on each of nine items covering *DSM*-IV diagnostic criteria for depressive disorder	0 to 27 severity score	Short; easy to administer; validated in cardiac patients; free access via www.phqscreeners.com
Cardiac Depression Scale[23]	26-item scale for cardiac patients; Likert scale 0 to 7 on each item	Cut-off 90 = mild depression; 100 = more severe depression	Disease specific; self-rating scale
Beck Depression Inventory II[24]	21-item scale reviewing past seven days; 0 to 3 scores on each item	Cut-off score of 10 identifies depression with sensitivity and specificity close to 80%	Commonly used; threshold for detecting depression varies with type of patients[25]
Hospital Anxiety and Depression Scale[26]	Symptoms of anxiety and depression in patients with somatic illness 0 to 3 score on 14 items over the past seven days	Total score 21 Score >11 = probable presence of mood disorder	Simple but reliable tool for medical practice; 2 to 5 minutes to complete
Kessler psychological distress scale K-10[27]	10 items reviewing psychological distress over past four weeks; 1 to 5 score on each item	Total score 50 Low to very high level of psychological distress	Measures general distress without identifying cause; high score = need for further assessment for depression or anxiety

Abbreviations: *DSM = Diagnostic and Statistical Manual of Mental Disorders*; PHQ = Patient Health Questionnaire.

importance of psychosocial risk factors, namely general stress and depression, in the development of acute MI.[9] According to INTERHEART, alteration of habits such as eating fruit and vegetables, exercising and cessation of smoking could lower the risk of developing AMI by up to 80%.[10] The recent epidemiological study, European Action on Secondary and Primary Prevention through Intervention to Reduce Events (EUROASPIRE III), found that having a mild or severe form of depression interfered with both secondary prevention of CHD and modification of established risk factors such as smoking, hypertension and high cholesterol.[11]

Meta-analyses have also shown a potential negative impact of a depressive disorder on outcomes and mortality in patients with CHD.[12,13] The morbidity and mortality risk appears greatest in patients with new-onset depression after cardiac events.[14]

Overall, these findings suggest that depression has a bidirectional association with cardiac disease in the development and progression of these conditions as well as the clinical outcomes of affected patients.

Causal explanations

Mechanisms that underlie the link between depression and CVD are becoming increasingly better understood.[15] It is assumed that the interplay of different neurobiological pathways and health behaviours contributes to the co-occurrence of both conditions.[16] In-depth analysis of this relation has been systematically covered in several recent reviews[16,17] and only a summary is presented here.

Atherosclerosis is well known as a leading cause of CVD. Pathophysiological mechanisms in the development of atherosclerotic disease involve endothelial dysfunction that occurs as a response to the presence of conventional risk factors such as hypercholesterolaemia, hypertension and oxidative stress on the background of genetic vulnerability. This in turn is thought to activate complex proinflammatory signalling pathways, leading to activation of an inflammation cascade involved in the genesis of atherosclerotic plaques.[18]

Depression is associated with altered inflammatory markers, which could possibly contribute to or worsen the atherosclerotic process.[19-21] Also, dysregulation of the hypothalamic–pituitary–adrenal axis and altered sympathetic nervous system tone in patients with depression can further contribute to the inflammatory response, promote platelet aggregation and vasoconstriction, and reduce heart rate variability.[17] All of the above can adversely affect the course of atherosclerosis and clinical expression of cardiac disease.

Furthermore, poor health behaviours associated with depressive illness, as mentioned in the EUROASPIRE study, are shown to affect outcomes in patients with established heart disease and increase their secondary risk.[11]

It is clear that there is an interplay between depression and CVD that contributes to both risk and poor outcomes for both conditions. Therefore, it is important that GPs screen for and effectively manage depression in patients at risk of or suffering from CVD.

Downloaded for personal use only. No other uses permitted without permission. © MedicineToday 2016.

Screening in general practice

Screening for depression in cardiac patients is recommended in routine clinical practice.[22] Challenges in recognising depression in this patient group lie in the overlap between symptoms of depression and common complaints associated with acute and chronic physical illnesses (e.g. lack of energy, tiredness and loss of appetite and weight). Furthermore, illness behaviours or individual responses to illness, such as transient low mood, irritability and lack of interest in usual activities, could potentially trigger prescription of antidepressant medication instead of cautious longitudinal observation for depressive symptoms.

Careful questioning about the core features of depression, including pervasive low mood and loss of interest and enjoyment in daily activities, is crucial. Certain screening tools and rating scales can help to identify and monitor depression (Table 1).[22-27]

Treatment

The treatment of patients with depression in the face of CVD follows many of the basic tenets of depression management but with certain modifications, notably in the area of pharmacotherapy. This is because some antidepressant medications (such as tricyclic antidepressants [TCAs]) carry cardiac risk that leads to caution about their use in people with cardiac disease, notably those with recent MI, dysrhythmias, prolonged QTc interval and/or postural hypotension. Also, many people with cardiac disease are taking medications for their physical health and caution needs to be exercised regarding potential exacerbation of side effects and drug–drug interactions.

In terms of pharmacological management, given the extent of the association between depression and CVD, it is surprising how few rigorous randomised controlled trials (RCTs) have been published examining the efficacy and safety of antidepressants in this context. Published studies have been reviewed,[28] and Table 2 provides an outline of some of the main pertinent RCTs that included a placebo arm.[29-36] In essence, the data support (in most but not all trials) the efficacy and safety of several selective serotonin reuptake inhibitors (SSRIs; i.e. sertraline, fluoxetine, citalopram, paroxetine and escitalopram) in people with cardiovascular problems (most studies have been of those with recent MI). Dose ranges employed have been compatible with those used in usual clinical practice and cardiac safety has largely been satisfactory.

Several other studies that are not RCTs have also been used to inform clinical practice. Some studies have specifically examined the cardiac safety of TCAs. This is important because cardiac toxicity caused by higher doses and overdose of TCAs is well recognised.[28] It has been noted that the pharmacology of TCAs is similar to that of class 1 antiarrhythmic agents such as quinidine and use of TCAs can cause prolongation of the QTc interval.[28] In fact, a fear of cardiac toxicity is one of the main reasons why TCAs are not often used now.

Some clinicians believe TCAs are potentially more efficacious than SSRIs, but this has not been confirmed in patients with depression and CVD. Several trials have established that the TCAs imipramine, doxepin and nortriptyline (in usual clinical doses) are largely safe and effective in patients with cardiac disease.[28] However, QTc prolongation was observed in some patients and caution is advised in patients with a long baseline QTc and/or bundle branch block.[37]

Downloaded for personal use only. No other uses permitted without permission. © MedicineToday 2016.

Table 2. Summary of placebo-controlled trials of antidepressant use in depressed people with cardiac disease[28-36]

Study details	Medications	Number of patients	Duration (weeks)	Depression outcomes	Comments
Veith et al[29]	Imipramine; doxepin	24	4	Both active drugs associated with improvement on depression scores	Both treatment groups showed increased heart rate; mean number of premature ventricular contractions decreased in imipramine group; no significant ECG changes
Glassman et al[30] (SADHART)	Sertraline	369 (74% had acute MI)	24	No differences in HAM-D score at 16 weeks but sertraline superior on the CGI scale at 24 weeks and on both measures in patients with recurrent depression	No significant difference in ejection fraction or cardiac adverse events
Strik et al[31]	Fluoxetine	54	25	Increased response rates after 52 weeks on fluoxetine (measured by HAM-D)	No significant differences on cardiac measures
Habra et al[32] (CREATE)	Citalopram (2 x 2 factorial design with IPT)	284	12	Citalopram superior to placebo at week 6 on HAM-D and BDI scales; IPT no better than routine care	No significant difference on cardiac measures
O'Connor et al[33] (SADHART-CHF)	Sertraline	469	12	Both sertraline and placebo associated with significant decrease in HAM-D score; no significant difference between them	No significant difference in mortality but 11.5% of patients taking sertraline withdrew due to side effects compared with 6% of those taking placebo
Hanash et al[34] (DECARD)	Escitalopram	240	52	Significantly fewer patients taking escitalopram developed depression compared with placebo	No significant difference in cardiac events
Gottlieb et al[35]	Paroxetine	28	12	Paroxetine significantly better than placebo on BDI scale and quality of life	No major cardiac event signal
Honig et al[36] (MIND-IT)	Mirtazapine	91	24	No significant difference between mirtazapine and placebo on HAM-D score; mirtazapine and placebo showed trend towards decrease in mean BDI scores over 24-week treatment period; during first eight weeks, decrease in BDI score was significant for mirtazapine compared with placebo	Depression nonresponders had higher rates of cardiac events than responders

Abbreviations: BDI = Beck Depression Inventory; CGI = Clinical Global Impression Scale; CREATE = Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy; DECARD = DEpression in patients with Coronary Artery Disease; HAM-D = Hamilton Depression Rating Scale; IPT = interpersonal therapy; MI = myocardial infarction; MIND-IT = Myocardial Infarction and Depression-Intervention Trial; SADHART = Sertraline Antidepressant Heart Attack Randomised Trial; SADHART-CHF = Sertraline Against Depression and Heart Disease in Chronic Heart Failure.

Downloaded for personal use only. No other uses permitted without permission. © MedicineToday 2016.

1. Summary of treatments for depression in patients with cardiovascular disease

- Comprehensive assessment of mental and physical health status
- Treat physical health problems that might contribute to depressive symptoms (e.g. anaemia)
- Avoid potentially 'depressogenic' physical health medications (e.g. beta blockers)
- Liaison between GP and mental health and cardiovascular/endocrine specialists
- Risk assessment and management plan (notably suicidality)
- Encourage general measures such as healthy diet, regular exercise and smoking cessation
- Use specific psychological therapies (e.g. cognitive behavioural therapy) where indicated and available
- Prescribe medications as indicated (see Box 2)

2. Guidelines for the use of antidepressant medications in patients with cardiovascular disease

- Start low dose and build dose slowly dependent on tolerability and efficacy
- Adjust dose if hepatic or renal insufficiency
- Be aware of drug–drug interactions
- Selective serotonin reuptake inhibitors generally have a safe profile (note concerns regarding citalopram at higher doses)
- Serotonin and noradrenaline reuptake inhibitors are not well tested in patients with cardiovascular disease and may cause hypertension
- Only prescribe tricyclic antidepressants if absolutely necessary – requires monitoring of plasma levels, ECG and postural blood pressure

Also, orthostatic hypotension was found to be a particular problem in the use of TCAs: for example, almost half of the patients in one study taking imipramine experienced postural hypotension severe enough to warrant discontinuation of the agent.[37] Overall, nortriptyline seems to have the most favourable cardiac profile of the TCAs that have been tested in cardiac populations.

A further important set of studies have used antidepressants in an indicated manner rather than as part of an RCT. The largest of these is the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study, which included 2481 patients with depression (broadly defined) and acute MI and randomised them to receive cognitive behavioural therapy (CBT) or treatment as usual.[38] Those with a score of more than 23 on the Hamilton Depression Rating Scale (HAM-D) received an SSRI as well. At six months, there was a lower rate of recurrent MI or death among patients on an SSRI; CBT showed some benefit for depression but not for cardiac events.

The efficacy and safety of antidepressants other that SSRIs and TCAs have been only scantily addressed in the literature. Mirtazapine did not show benefit over placebo in a recent trial (Table 2) and as this agent is associated with weight gain it might contribute to metabolic risk.[36] Boxes 1 and 2 provide a summary of medication approaches for treating depression in people with CVD.

One of the fascinating findings of these studies has been that, although overall depression seems largely treatable in people with cardiac disease, antidepressant response does not usually translate into superior cardiac outcomes (with the exception of the ENRICHD study). This is despite the fact that depression has been shown to be a risk factor for poor cardiac outcomes in epidemiological studies.

As indicated above, the treatment of patients with depression requires a multifaceted approach. For the GP, liaison with the treating psychiatrist and cardiologist is important and would be considered good clinical practice. It has, however, been difficult to establish a particular model of collaborative care that has unequivocal advantages in terms of patient outcomes.

Furthermore, specific psychological techniques with established efficacy for depression (e.g. CBT and interpersonal therapy) have been examined in cardiac patients in only a few rigorous studies. One instructive study of 123 depressed patients who had undergone a coronary artery bypass graft showed clear benefits in terms of remission from depression at three and nine months for both CBT and a supportive stress management intervention, compared with usual care.[39] In general, it would seem sensible to offer depressed patients with cardiac disease psychological assistance as one would with other depressed patients, and incorporate elements of psychological work that help address specific cardiac-related issues as they arise.

Conclusions

It is clear from epidemiological and clinical studies that there is a strong association between depression and CVD. The explanations for this finding are complex and encompass psychosocial and biological domains. It also seems increasingly clear that depression worsens the physical health outcomes for patients with cardiac problems, and that depression is a contributory causal factor for cardiac disease. The GP plays a key role in screening for depression in patients with cardiac problems and co-ordinating (with appropriate liaison with other specialists including psychiatrists and cardiologists) comprehensive ongoing management and monitoring of cardiac and depressive outcomes. Antidepressant medication choice needs to be focused on achieving efficacy with as few side effects as possible, and with a particular emphasis on cardiac safety: therefore, several SSRIs appear to be the best first-choice options. **CT**

References

A list of references is included in the website version of this article (www.cardiologytoday.com.au).

COMPETING INTERESTS: Dr. Castle has received personal fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Hospira, Janssen-Cilag, Lundbeck, Organon, Pfizer, Sanofi-Aventis, Servier and Wyeth. He has also received grants from Allergen, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Hospira, Janssen-Cilag, Lundbeck, Pfizer and Roche. Dr Lusicic: None.

Downloaded for personal use only. No other uses permitted without permission. © **Medicine**Today 2016.

Depression and cardiovascular disease

How can one mend a broken heart?

ANA LUSICIC MD, FRANZCP; **DAVID J. CASTLE** MD, FRANZCP

References

1. Frasure-Smith N, Lespérance F. Reflections on depression as a cardiac risk factor. Psychosom Med 2005; 67 Suppl 1: S19-S25.
2. Glassman AH. Depression and cardiovascular comorbidity. Dialogues Clin Neurosci 2007; 9: 9-17.
3. Malzberg B. Mortality among patients with involution melancholia. Am J Psychiatry 1937; 93: 1231-1238.
4. Celano CM, Huffman JC. Depression and cardiac disease: a review. Cardiol Rev 2011; 19: 130-142.
5. Huffman JC, Celano CM, Beach SR, Motiwala SR, Januzzi JL. Depression and cardiac disease: epidemiology, mechanisms, and diagnosis. Cardiovasc Psychiatry Neurol 2013; 2013: 695925.
6. Kendler KS, Gardner CO, Fiske A, Gatz M. Major depression and coronary artery disease in the Swedish twin registry: phenotypic, genetic, and environmental sources of comorbidity. Arch Gen Psychiatry 2009; 66: 857-863.
7. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure: a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J Am Coll Cardiol 2006; 48: 1527-1537.
8. Frasure-Smith N, Lespérance F. Depression and cardiac risk: present status and future directions. Heart 2010; 96: 173-176.
9. Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, Yusuf S. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. Lancet 2004; 364: 953-962.
10. Yusuf PS, Hawken S, Ôunpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004; 364: 937-952.
11. Cooney MT, Kotseva K, Dudina A, De Backer G, Wood D, Graham I. Determinants of risk factor control in subjects with coronary heart disease: a report from the EUROASPIRE III investigators. Eur J Prev Cardiol 2013; 20: 686-691.
12. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. Psychosom Med 2004; 66: 802-813.
13. Lichtman JH, Froelicher ES, Blumenthal JA, et al. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association. Circulation 2014; 129: 1350-1369.
14. Leung YW, Flora DB, Gravely S, Irvine J, Carney RM, Grace SL. The impact of premorbid and postmorbid depression onset on mortality and cardiac morbidity among patients with coronary heart disease: meta-analysis. Psychosom Med 2012; 74: 786-801.
15. Joynt KE, Whellan DJ, O'Connor CM. Depression and cardiovascular disease: mechanisms of interaction. Biol Psychiatry 2003; 54: 248-261.
16. Nemeroff CB, Goldschmidt-Clermont PJ. Heartache and heartbreak the link between depression and cardiovascular disease. Nat Rev Cardiol 2012; 9: 526-539.
17. Baune BT, Stuart M, Gilmour A, et al. The relationship between subtypes of depression and cardiovascular disease: a systematic review of biological models. Transl Psychiatry 2012; 2: e92.
18. Falk E. Pathogenesis of atherosclerosis. J Am Coll Cardiol 2006; 47 (8 Suppl): c7-12.
19. Rosenblat JD, Cha DS, Mansur RB, McIntyre RS. Inflamed moods: a review of the interactions between inflammation and mood disorders. Prog Neuropsychopharmacol Biol Psychiatry 2014; 53: 23-34.
20. Pizzi C, Costa GM, Santarella L, et al. Depression symptoms and the progression of carotid intima-media thickness: a 5-year follow-up study. Atherosclerosis 2014; 233: 530-536.
21. Pizzi C, Manzoli L, Mancini S, Bedetti G, Fontana F, Costa GM. Autonomic nervous system, inflammation and preclinical carotid atherosclerosis in depressed subjects with coronary risk factors. Atherosclerosis 2010; 212: 292-298.
22. Colquhoun DM, Bunker SJ, Clarke DM, et al. Screening, referral and treatment for depression in patients with coronary heart disease. Med J Aust 2013; 198: 483-484.
23. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. Eur Heart J 2014; 35: 1365-1372.
24. Beck AT, Steer RA, Brown G. BDI-II, Beck depression inventory: manual, 2nd ed. San Antonio, TX: Psychological Corp; Boston: Harcourt Brace; 1996.
25. Wang YP, Gorenstein C. Assessment of depression in medical patient: a systematic review of the utility of the Beck Depression Inventory-II Clinics 2013; 68: 1274-1287.
26. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67: 361-370.
27. Andrews G, Slade T. Interpreting scores on the Kessler Psychological Distress Scale (K10). Aust N Z J Publ Heal 2001; 25: 494-497.
28. Mavrides N, Nemeroff C. Treatment of depression in cardiovascular disease. Depress Anxiety 2013; 30: 328-341.
29. Veith RC, Raskind MA, Caldwell JH, Barnes RF, Gumbrecht G, Ritchie JL. Cardiovascular effects of tricyclic antidepressants in depressed patients with chronic heart disease. N Engl J Med 1982; 306: 954-959.
30. Glassman AH, O'Connor CM, Califf RM, et al; Sertraline Antidepressant Heart Attack Randomised Trial (SADHART) Group. Sertraline treatment of major depression in patients with acute MI or unstable angina. JAMA 2002; 288: 701-709.
31. Strik JJ, Honig A, Lousberg R. Efficacy and safety of fluoxetine in the treatment of patients with major depression after first myocardial infarction: findings from a

Downloaded for personal use only. No other uses permitted without permission. © **Medicine**Today 2016.

double-blind placebo-controlled trial. Psychosom Med 2000; 62: 783-789.
32. Habra ME, Baker B, Frasure-Smith N, et al. First episode of major depressive disorder and vascular factors in coronary artery disease. Baseline characteristics and response to antidepressant treatment in the CREATE trial. J Psychosom Res 2010; 69: 133-141.
33. O'Connor CM, Jiang W, Kuchibhatla M, et al. Safety and efficacy of sertraline for depression in patients with heart failure. Results of the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) Trial. J Am Coll Cardiol 2010; 56: 692-699.
34. Hanash JA, Hansen BH, Hansen JF, Nielsen OW, Rasmussen A, Birket-Smith M. Cardiovascular safety of one-year escitalopram therapy in clinically nondepressed patients with acute coronary syndrome: results from the DEpression in patients with Coronary ARtery Disease (DECARD) trial. J Cardiovasc Pharmacol 2012; 60: 397-405.
35. Gottlieb SS, Kop WJ, Thomas SA, et al. A double-blind placebo-controlled pilot study of controlled-release paroxetine on depression and quality of life in chronic heart failure. Am Heart J 2007; 153: 868-873.
36. Honig A, Kuyper AMG, Schene AH, et al. Treatment of post-myocardial infarction depressive disorder: a randomised, placebo-controlled trial with mirtazapine. Psychosom Med 2007; 69: 606-613.
37. Roose SP, Glassman AH. Antidepressant choice in the patient with cardiac disease: lessons from the cardiac arrhythmias suppression trials (CAST) studies. J Clin Psychiatry 1994; 55 (suppl A): 83-87.
38. Bekke-Hansern S, Trockel M, Burg MM, Taylor CB. Depressive symptom dimensions and cardiac prognosis following myocardial infarction: results from the ENRICHD clinical trial. Psychol Med 2012; 42: 51-60.
39. Freedland KE, Skala JA, Carney RM, et al. Treatment of depression after coronary artery bypass surgery. Arch Gen Psychiatry 2009; 66: 387-396.

Downloaded for personal use only. No other uses permitted without permission. © **Medicine**Today 2016.