

Depression and coronary heart disease: 2018 position paper of the ESC working group on coronary pathophysiology and microcirculation

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Introduction

Major depression is a highly prevalent condition, affecting approximately 10% of the population.¹ It is also a growing global problem,² and has been consistently associated with increased risk of coronary heart disease (CHD).³ It is therefore not surprising that depression is highly comorbid with CHD, being two to three times more common among patients with CHD than in the general population. The prevalence of depression is 15–30% in patients with CHD,⁴ and is approximately twice as high in women than men, especially affecting young women in the aftermath of acute myocardial infarction (MI).⁵

Depression as a risk factor for CHD has been characterized from mild depressive symptoms to a clinical diagnosis of major depression.

As defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), clinical depression, or major depression, is characterized by depressed mood or anhedonia (loss of interest or pleasure) for at least 2 weeks accompanied by significant functional impairment and additional somatic or cognitive symptoms.⁶ Most epidemiological studies of depression and incidence of CHD have used depressive symptom scales, and have frequently demonstrated a dose–response pattern, with higher levels of depressive symptoms being associated with higher risk.³

The exact mechanisms linking depression to increased CHD risk are complex and multifactorial, and still incompletely understood.⁷ Although adverse lifestyle behaviours and traditional CHD risk factors, such as smoking and sedentary lifestyle, largely contribute to the risk, they do not explain it entirely. In CHD patients, depression is

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also associated with severity of functional impairment, lower adherence to therapy and lower participation in cardiac rehabilitation. Whether and to what extent these factors explain the relationship between depression and CHD deserves future study. The present paper summarizes key aspects in our current knowledge linking depression and CHD within the intersecting fields of neuroscience, cardiovascular physiology, and behavioural medicine, with the objective of bringing attention to this area and stimulating interdisciplinary research, clinical awareness, and improved care.

Epidemiological aspects

Depression and coronary heart disease

Many studies have shown a relationship between major depression, or depressive symptoms, and CHD.^{3,8,9} This literature has been summarized by a number of meta-analyses,^{8–10} all providing evidence for an association between clinical depression (or depressive symptoms) and CHD. This link is seen in individuals initially free of CHD and in a variety of CHD patient populations, including patients with acute coronary syndromes (ACS), heart failure, stable CHD, and post-coronary bypass surgery. However, individual studies have produced heterogeneous risk estimates and have varied in their ability to adjust for other factors such as smoking, physical inactivity, other risk factors, and severity of CHD. Indeed, depression is associated with several CHD risk factors and health behaviours as described above. In statistical models that adjust for these risk factors, depression usually remains an independent risk factor for CHD, suggesting a biological relationship between these two disease states that remains in part unexplained by an increase in traditional risk factors or lifestyle behaviours.

In one of the relatively recent meta-analyses, which included 30 prospective cohort studies of individuals initially free of CHD, depression was associated with a 30% increased risk of future coronary events.⁹ The association remained significant in the group of studies that adjusted for socio-demographic factors and lifestyle behaviours.⁸ In community samples and in general practice clinics, the rate of depression is about 10%¹¹ but it goes up to about 15–30% in patients with CHD.^{11,12}

Studies have also suggested that specific subtypes of depression may be more strongly associated with CHD risk than others. For instance, patients with a new-onset of depression after ACS, with treatment resistant depression, or with somatic depressive symptoms as opposed to cognitive symptoms, are all at increased risk of developing adverse CHD outcomes. However, there is no clear consensus on whether these different phenotypes carry variations in risk.¹³

Gender differences

Among women, depression is approximately twice as prevalent as in men and has shown some of the most robust associations with CHD.¹⁴ Depression in women is also on average more severe than in men and has an earlier age of onset. Women with CHD similarly have twice the rates of depression as men with CHD.^{15–17} The condition is especially common in young women who have survived a MI^{15,16,18}; about half of women younger than 60 years with a previous MI have a history of major depression.^{16–18} Of note, young women are more likely to die MI than men.¹⁹ Depression is linked to early life adversities and psychological trauma, which tend to be more common in girls than boys and may result in chronic dysregulation of

neurohormonal stress systems. This may begin at an early age, setting the stage for an increase in cardiovascular risk in women many years before CHD becomes manifest.⁵

Among women, depression increases their risk for CHD between 30% and two-fold depending on depression measures and CHD endpoints.^{20,21} Two follow-up studies of young community samples (<40 years old) found that the impact of depression on CHD risk was higher among women than men.^{22,23} In the Third National Health and Nutrition Examination Survey (NHANES III), a history of major depression or suicide attempt was associated with almost 15-fold increased risk of ischaemic heart disease among women, and 3.5 in men.²² In the prospective Community Mental Health Epidemiology Study of Washington County, MD, women younger than 40 years with depression had a six-fold increased risk of CHD compared with women of the same age without depression, while depression was not associated with CHD in men or older individuals.²³ Even among patients referred for coronary angiography, depression is more predictive of adverse cardiovascular outcomes in young women than in other groups.²⁴ After an acute MI, however, depression seems to affect prognosis to a similar extent in women and men.²⁵ Overall, the evidence suggests that depression is more closely associated with CHD for women than for men, with the strongest effects for younger women.

Clinical and prognostic considerations

Depression as a prognostic factor in acute coronary syndromes

Despite some heterogeneity of findings, the bulk of the evidence supports the notion that depression after ACS is a risk factor for all-cause and cardiac mortality, as well as for composite outcomes including mortality or non-fatal cardiac events.⁴ Among patients hospitalized for ACS, the increased risk occurs regardless of whether depression pre-dated the ACS event or developed subsequently,^{4,26,27} although some evidence suggests that depressive episodes that develop soon after an ACS may carry a higher risk than episodes that begin before the event.^{28–30} Depression is also a major determinant of unplanned rehospitalizations within 30 days after a hospital discharge for MI.³¹

Some studies have found that the somatic symptoms of depression may carry a high risk than cognitive symptoms.^{32–34} Depressive episodes that do not respond to standard treatments have also been identified as high-risk subtypes.³⁵ However, evidence suggests that recognition and treatment of depression improves prognosis. In a previous study, patients with depression that was recognized or treated during an MI hospitalization or at discharge had similar 1-year mortality than those without depression, while a higher mortality was confined to patients with untreated depression.³⁶ These data are important since depression in ACS patients is frequently under-recognized and untreated.^{33,37,38}

Patients with comorbid depression and CHD have lower adherence to treatments and lifestyle changes; for example, they are significantly less likely to adhere to medication regimens^{39,40} and to follow lifestyle recommendations (e.g. smoking cessation, exercise) and practice self-management (e.g. weight monitoring in heart failure).⁴¹ They

are also less likely to participate in cardiac rehabilitation programmes, and more likely to drop out of these programmes.^{39,42,43} Improvement in depression is associated with better self-reported adherence to medications and secondary prevention lifestyle.^{44,45}

During the first year post-MI the presence of depression is associated with about 40% higher healthcare costs, including outpatient care and hospital readmissions.⁴⁶ In addition, the presence of major depression in the past 12 months can affect societal costs indirectly through work absence.⁴⁷ For all the above reasons, major depression has been proposed as a risk factor for adverse medical outcomes in patients with ACS.⁴ The application of collaborative care interventions for depression in CHD populations has emerged as a promising healthcare model to reduce the societal impact of this common comorbidity.^{48,49}

Depression and quality of life

In the setting of CHD, depression is the strongest predictor of quality of life (QoL).⁵⁰ Depression has a greater impact on QoL than symptoms related to the severity of cardiac disease, such as functional impairment or dyspnoea in patients with heart failure, and angina or exercise capacity in patients with stable CHD.^{26,44,51,52} After a MI, depressive symptoms are associated with more physical limitations and worse QoL.^{26,53} In patients with systolic dysfunction, depression is a major determinant of QoL, whereas cardiac indicators of severity of the disease (i.e. NT-proBNP and left ventricular ejection fraction) are not related to QoL.⁵¹ A change in depressive symptoms is the strongest predictor of 1-year health-related QoL in this population, even after accounting for functional status and clinical variables.⁵⁴

Depression and chest pain

Epidemiological evidence suggests a close relationship between depression and angina, with these two clinical entities frequently co-existing. Presence of depression is associated with increased reporting of shortness of breath and/or chest pain symptoms in patients with established CHD.⁵⁵ Not only is depression associated with everyday life angina independently of CHD severity, but it is a stronger predictor of angina than severity of coronary artery disease or other traditional risk indicators.⁵⁶ Depression post-MI predicts new angina during follow-up,²⁶ and improvement in depression leads to improvement in angina symptoms. A cause and effect relationship between depression and angina, however, is difficult to prove. Over-reporting of chest pain in depressed patients could be related to alterations in pain perception. Furthermore, patients with chronic pain, including angina, may develop depressive symptoms as a consequence of their symptom burden or disability.⁵⁷ Evidence also suggests that chest pain and depression share common neurohormonal pathways⁵⁷ and a common genetic background,⁵⁸ which could explain their co-existence. The links between depression and chest pain are summarized in Figure 1.

Depression, atrial fibrillation, and ventricular arrhythmias

Atrial fibrillation (AF) can profoundly affect patients' QoL and long-term outcome, and depression, which has been associated with AF, may worsen the symptoms and clinical course of this condition.^{59–63} Depression is associated with increased inflammatory and adrenergic activity and reduced heart rate variability (HRV), which is the normal

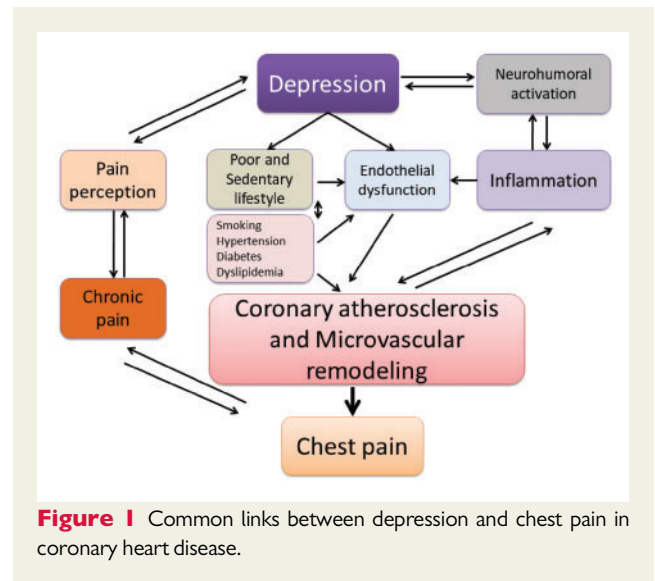


Figure 1 Common links between depression and chest pain in coronary heart disease.

beat-to-beat variability of heart rate. These factors can shorten atrial refractory periods, trigger AF, and foster a substrate that perpetuates AF, suggesting a mechanism for the observed association of depression with AF.^{59,63,64}

Depression has been associated with an almost three-fold increase in the odds of the reoccurrence of AF after successful electric cardioversion,⁶⁵ and negative emotions have been shown to trigger AF episodes in persons with paroxysmal AF.⁶⁶ Furthermore, negative life events like the death of a partner have been associated with transiently increased risk of AF.⁶⁷ The opposite pathway may also be true, however, as AF can have substantial impact on the risk or worsening of depression.^{62,68} Thus, AF can cause depression and anxiety in patients, and depression and anxiety, in turn, may create an environment that is conducive for the initiation and perpetuation of AF.⁶⁸

Individuals with depression, as well as those exposed to various forms of chronic and acute psychological distress, have also an increased risk of developing ventricular arrhythmias and sudden cardiac arrest, a finding reported both in initially CHD-free populations and in patients with CHD.^{69–72} Yet, whether treating depression would affect cardiac arrhythmias still remains an open question.

Mechanisms linking depression to coronary heart disease

Neurobiological aspects of relevance to coronary heart disease

The well-documented association between depression and CHD has prompted a search for underlying mechanisms. One possibility is that changes in neurobiology in depressed patients alter cardiovascular function and structure.^{73–75} Additionally, because of the known link between stressful exposures and depression,⁷⁶ dysregulation of stress-response pathways may contribute to CHD in vulnerable individuals. Thus, neurobiological mechanisms associated with stress and depression may be relevant for CHD risk. These mechanisms include changes in sympathetic nervous system and neurohormonal function as well as alterations in central brain function.^{77,78}

Neuroendocrine pathways

Acute and chronic stress exposure can lead to altered neurochemical function, such as disruptions in the synthesis or activity of norepinephrine, dopamine, or serotonin,⁷⁹ which, in turn, may influence mood and cardiovascular risk.^{80,81} Endocrine changes associated with depression include alterations in corticotropin-releasing factor (CRF),⁸² dysregulated adrenocorticotropic hormone (ACTH) responses to CRF,⁸³ enhanced adrenal responses to ACTH,⁸³ and elevated circulating cortisol levels.⁸⁴ Several of these changes may affect the immune system leading to excessive secretion of cytokines such as interleukin (IL)-1, IL-6, and tumour necrosis factor (TNF)- α . Enhanced inflammation is common in mood disorders and cardiovascular disease and thus might play a role in the association of these conditions.

Brain systems and cardiovascular physiology

Brain areas that likely play a role in cardiovascular regulation based on imaging studies include those involved in stress and memory that have also been shown to be altered in patients with major depression. These include the amygdala, hippocampus, medial prefrontal cortex, and anterior cingulate (part of the prefrontal cortex).^{85–87} Structural and functional magnetic resonance imaging (MRI) studies have shown changes in hippocampal structure and function in depression.^{88–108} Moreover, MRI data have demonstrated that acute psychological stressors may reduce baroreflex sensitivity by increasing the functional connectivity of a discrete area of the anterior insula with both the cingulate cortex and the amygdala.¹⁰⁹ Asymmetric sympathetic inputs from these brain areas to the heart may increase the risk of ventricular arrhythmias.¹¹⁰ Studies have shown that asymmetric brain responses to stress result in pro-arrhythmic sympathetic inputs to the heart.¹¹¹ In a recent study,¹¹² amygdalar activity measured by 18F-fluorodeoxyglucose positron emission tomography independently predicted cardiovascular disease events, providing further evidence of brain mechanisms through which emotional stress can lead to cardiovascular disease.

Subjects who exhibit a larger cardiovascular reactivity and acute mental stress are at risk for hypertension and other cardiovascular risk indicators.¹¹³ There is an association between increased blood pressure and heart rate during mental stress and activation in the right insula, cerebellum, and anterior cingulate.¹¹⁴ Furthermore, myocardial ischaemia provoked by acute psychological stress in CHD patients has been associated with increased activation of the anterior cingulate.¹¹⁵ Studies have also implicated the insula and the somatosensory cortex in peripheral autonomic function.¹¹⁶ These studies, as a whole, suggest that brain regulatory systems are implicated in CHD pathophysiology, and imply that disruption of these systems may contribute to the observed associations of stress and depression with CHD risk.

Depression and mental stress

Brain areas involved in stress may modulate peripheral vascular and autonomic function,^{115,117} which may mediate the effects of stress acting through the brain to cause myocardial ischaemia in patients with CHD. Mental stress, which can be studied in the laboratory, can induce myocardial ischaemia in susceptible patients with

CHD.^{73,118,119} and this phenomenon has been linked to depression.^{120,121} Such observations suggest that some individuals with CHD, especially those with depression, may experience stress-induced myocardial ischaemia on a daily basis, even in the absence of symptoms,^{74,122–124} possibly through a mechanism of increased coronary or peripheral vasoconstriction due to sympathetic nervous system stimulation during emotional stress.^{125,126} This phenomenon may be especially pronounced among women.^{5,127,128}

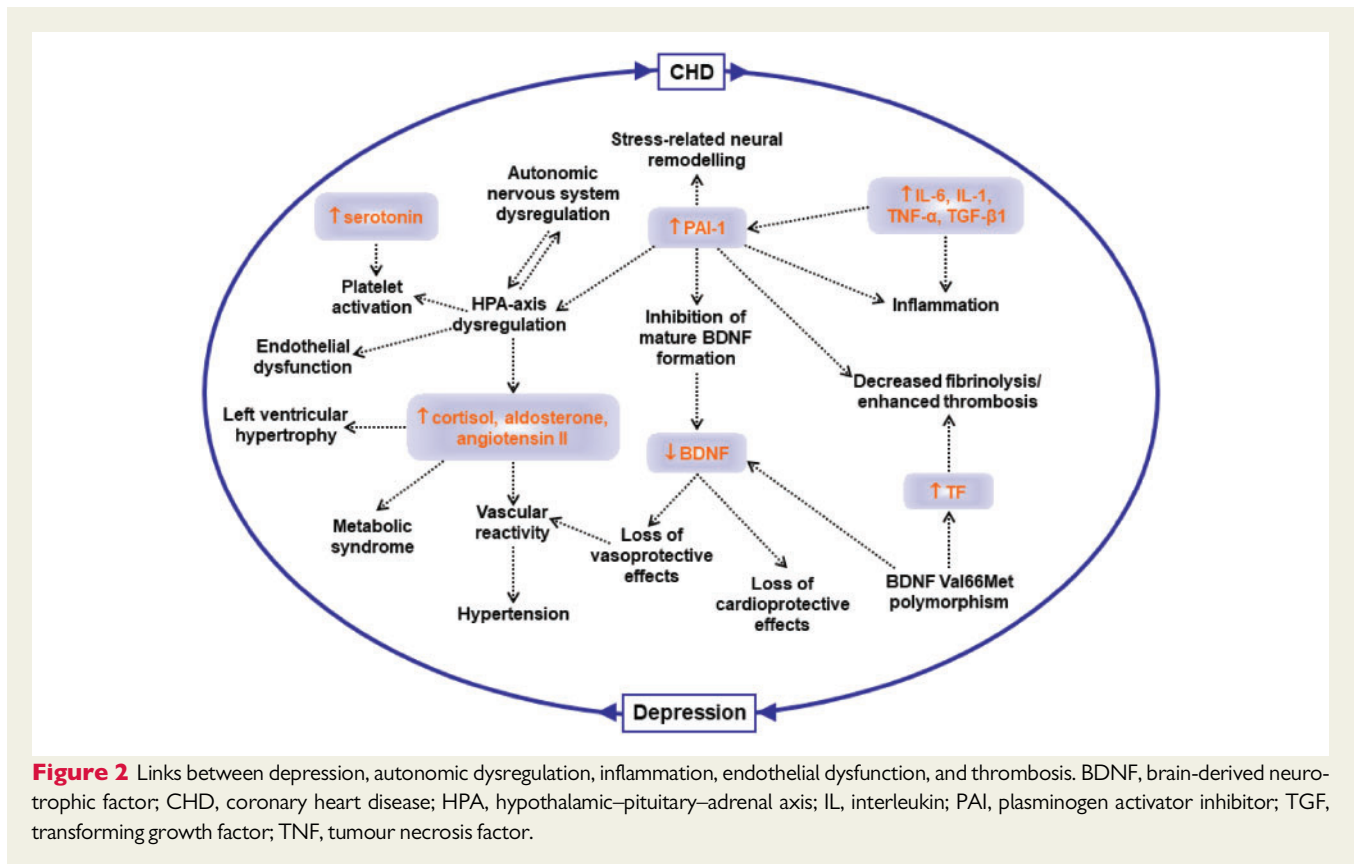
Depression and autonomic dysfunction

In part as a consequence of neurobiological alterations described above, chronic dysregulation of autonomic function (*Figure 2*), characterized by an imbalance between the sympathetic and parasympathetic systems, is thought to be a key mechanism linking depression to CHD risk and adverse cardiovascular outcomes.⁷ Sympathetic hyperactivity and parasympathetic withdrawal may lower the threshold for myocardial ischaemia and ventricular arrhythmias, and potentially pre-dispose to sudden cardiac death. Data from animal models suggest that depression is associated with cardiovascular and autonomic imbalance, characterized by elevated heart rate, reduced HRV,¹²⁹ and elevated cardiac sympathetic tone.^{130,131}

Most studies of patients with CHD have found lower HRV and higher heart rate in patients with depression compared with those without depression, together with other indicators of cardiac autonomic dysregulation including decreased baroreceptor sensitivity, increased QT interval variability (reflecting abnormal ventricular repolarization) and increased heart rate turbulence.^{3,7} Heart rate variability is probably the most widely used method to assess cardiac autonomic function in humans. Lower HRV, reflecting cardiac autonomic imbalance, predicts mortality after MI,^{132,133} and morbidity and mortality in the general population and among patients with stable CHD.^{134,135} However, the association between depression and reduced HRV (or other measures of autonomic dysregulation) is not entirely consistent across all studies.^{136–138} Part of the effect may be driven by antidepressant medications.^{136,137,139,140} Furthermore, the link between depression and HRV is likely bidirectional,¹⁴⁰ and depression and HRV may also share a genetic substrate, suggesting shared neurobiological alterations pre-disposing to both depression and autonomic dysfunction.¹⁴¹

Depression and inflammation

Another hypothesized mechanism for the increased risk of CHD associated with depression is chronic inflammation (*Figure 2*), which is a known risk factor for development of atherosclerosis and CHD.¹⁴² Depression has been associated with a sustained state of inflammation and increased concentrations of inflammatory molecules, including C-reactive protein and various cytokines, such as TNF- α , IL-1 β , and IL-6^{143,144} with known adverse effects on the heart and circulation.^{145,146} Depression has been also associated with elevated markers of oxidative stress,^{147,148} which is involved in the initiation, progression, and complications of atherosclerosis. Nevertheless, the direction of the association between depression and inflammation and/or oxidative stress remains unclear. Some studies suggested that depression drives the inflammatory state rather than the reverse,^{149,150} while others supported the opposite pathway of inflammation predicting depression.^{151–153} In fact, inflammation has been considered a potential aetiological factor and treatment target for clinically depressed patients.¹⁴⁴ It also remains unclear to what



degree inflammation is the result of depression-related co-morbidities and risk factors, such as smoking, obesity, diabetes, and physical inactivity.^{142,143,150,154–157} Finally, as for autonomic function, depression and inflammation could share a pathophysiological pathway, such as common genetic precursors or shared behavioural or environmental risk factors.^{158,159}

Depression and endothelial dysfunction

Various studies support an inverse correlation between depressed mood and endothelial function, as measured by flow-mediated dilation (FMD).^{160–162} The relationship between depression and endothelial dysfunction (Figure 2) is likely due to reduced endothelium-derived nitric oxide (NO),¹⁶³ as shown by lower FMD of brachial arteries and reduced NO bioavailability in subcutaneous micro-vessels in patients with depressed mood.^{161,164,165} Animal models of human depression are useful to gain deeper understanding of underlying mechanisms. One such model is the so-called ‘unpredictable chronic mild stress (UCMS)’ rat model.¹⁶⁶ Due to activation of neuroendocrine and immune systems the level of TNF- α is elevated in the UCMS rats. The endothelium dependent vasomotor response to carbachol is substantially reduced, whereas the direct NO donor, sodium nitroprusside, or the non-NO dependent agonist, papaverine, elicit similar dilation in vessels of UCMS and control rats.¹⁶⁶ The reduced NO-dependent response is likely due to lower expression of endothelial NO synthase (eNOS). Higher levels of cortisol and increased inflammation in depression can down-regulate eNOS

expression and NO production.^{167,168} In addition to the NO system, other endothelial mechanisms may play a role, for example, the arachidonic acid pathway with production of constrictor prostanoids.¹⁶⁹ There is also evidence from experimental models that reduction in endothelium-dependent hyperpolarization is an important mechanism underlying the reduced endothelial function in the microcirculation. Endothelin is a powerful vasoconstrictor, and its levels are higher in patients with depression.^{170,171} The metabolic syndrome is associated with depression¹⁷² and can contribute to the development of vascular endothelial dysfunction.¹⁵⁶ It is also likely that the effects of depression on the endothelium are due to upstream alterations of autonomic system circuits related to stress. Psychological stress evokes autonomic, hemodynamic, and metabolic changes that may contribute to endothelial dysfunction. Indeed, acute mental stress in the laboratory induces transient endothelial dysfunction, as measured by FMD, which lasts up to 4 h.¹⁷³ This effect may be mediated through sympathetic activation,¹⁷⁴ and may have implications for patients with increased sympathetic outflow including those with depression.

Platelet activation and thrombosis

Increased platelet activation and thrombosis represent another pathological mechanism for the association between depression and CHD. Several studies have shown increased platelet activity in major depression.^{175–179} Of note, plasminogen activator inhibitor (PAI)-1, an anti-fibrinolytic factor, may also play a pivotal role,¹⁵⁵ as increased

PAI-1 levels have been reported in major depression.^{180,181} PAI-1 may also affect hypothalamic–pituitary–adrenal (HPA) axis function and cardiovascular risk factors such as metabolic syndrome and hypertension (Figure 2). Furthermore, PAI-1 inhibits the formation of mature brain-derived neurotrophic factor (BDNF), and decreased BDNF levels have been described as a potential link between thrombosis and depression.¹⁸² These data extend a growing body of evidence linking increased PAI-1 concentration with major depression. Furthermore, they provide support for the vascular hypothesis of depression which has been implicated in the two-way association between CHD and depression.^{183,184} This hypothesis postulates that deficits in perfusion caused by small-vessel disease (which could be a result of hypercoagulability) induce structural and functional changes in the white matter, which, in turn, may affect brain function and mood.¹⁸⁵

Health behaviours and cardiometabolic risk factors

Although positive behaviour changes for CHD primary and secondary prevention is recommended,¹⁸⁶ a sizeable proportion of patients do not make any changes.¹⁸⁷ One factor that may shape individuals' responses to a health behaviour change is their emotional state, such as the presence of depression. Prior studies have extensively documented the association of depression with adverse health behaviours, including smoking,¹⁸⁸ excessive drinking,¹⁸⁹ physical inactivity, and overeating.^{190–192} For example, depression is associated with an increased risk of becoming a smoker, with an increased rate of daily smoking, and with a lower probability of quitting smoking.^{193–196} Depression is also associated with overweight and obesity, and with approximately 40% higher risk of developing Type 2 diabetes.^{197–204} Some of these associations appear bidirectional.^{205,206} Obesity and other cardiometabolic risk factors have been linked to increased oxidative stress, inflammation, and microvascular dysfunction,^{156,207,208} which lend further support for a central role of inflammation and microvascular disease as possible links between cardiometabolic disturbances, depression and CHD (Figure 2).^{209–212}

Depression, CHD, and genetic vulnerability

Genetic studies can be instructive in clarifying the association between depression and CHD. The heritability of depression, or the proportion of the variance due to genetic factors, is estimated to be 37%,²¹³ and individuals with a first-degree relative with depression have an almost three-fold higher risk for depression themselves, compared to others from the general population.²¹³ This has led to genome-wide association studies aimed at the identification of common genetic variants that contribute to the risk of depression. Despite comprehensive efforts, no consistent genetic variation has yet been identified.²¹⁴ These surprising results may be due to the heterogeneity of the depression phenotype, and the co-existence of depression and CHD may contribute to this heterogeneity.²¹⁵

It is also possible that there is a core biological pathway that leads to both depression and CHD, as suggested by twin studies showing a common genetic vulnerability between these two phenotypes.^{212,216} Additional work has suggested shared, genetically influenced biological pathways underlying the association between depression and CHD that involve autonomic function,²¹⁷ inflammation,^{218,219} and

the serotonergic system.¹⁵⁸ Patients with depression also show distinct patterns of DNA methylation that are also associated with an increase in inflammatory markers, suggesting epigenetics as another pathway by which core biological changes may lead to both disorders.²²⁰

All these observations point to common genetic pathways involving neuroendocrine, immune and inflammatory systems that, when disrupted, may simultaneously increase the risk for both depression and CHD. Thus, genetically predisposed individuals could be at risk for both depression and CHD.

Telomere length and depression

Telomeres, the caps at the end of DNA strands, shorten with each cell division and have been proposed to reflect biological age. Studies have shown a relationship between shortened telomere length and risk for CHD.^{221–223} Results from studies examining the association between telomere length and depression have been conflicting. Some studies have reported an association,^{224,225} whereas other studies have shown no association.^{226,227} A study²²⁷ on a sample of more than 67 000 individuals from the Danish general population found that those who attended the hospital for depression treatment had shorter telomere length compared with those who did not attend hospital for depression or use antidepressant medication. However, a large part of this association was explained by confounders such as age, gender, lifestyle factors, and chronic disease. Furthermore, shorter telomere length was not prospectively associated with increased risk of depression and a Mendelian randomization approach showed no causal relationship with depression. This suggests that shortening of telomere length *per se* does not increase risk of depression.

Evaluation of depression in coronary heart disease patients

Recognition and screening

Recognition of depression is an important part of the management of patients with CHD. Depressive symptoms are highly prevalent in this population and can affect patients' well-being and QoL. They can also influence treatment adherence, including fidelity to taking medications as prescribed, cooperating with follow-up care, and making risk factor and lifestyle changes needed to enhance recovery. In spite of this, depression is often unrecognized and untreated in CHD patients. Barriers to recognition of depression include lack of mental health expertise and training in cardiology practices, and the perception that this is not part of the treatment mission. Additionally, many symptoms of psychological distress are easily confused with physical disease, for example, fatigue, weight loss, poor appetite, or trouble sleeping.

There is no consensus on whether screening for and treatment of emotional problems, such as depression, should become a routine part of the cardiology practice. This is related to the fact that there is little evidence one way or another whether screening for and treating these problems will translate into better QoL or improved prognosis.⁴ The few studies of interventions for psychiatric disorders in patients with CHD that have been performed have shown only modest improvements in psychological status and no clear evidence of an improvement in cardiac outcomes.^{3,228} Nevertheless, psychological

interventions such as stress management, individual, or group counselling, and support for self-care and pharmacotherapy, are recommended for patients with CHD and comorbid depression. This is because these interventions can help promote modifications in standard risk factors, encourage lifestyle changes, and mitigate distress when added to standard cardiac rehabilitation or as part of a coordinated care management approach.⁴⁸

Current clinical guidelines in the USA only mention depression as a psychosocial factor that is reasonable for the non-mental health clinician to recognize if patients have access to adequate care support systems (class of recommendation IIa, level of evidence B). These guidelines further state that treatment of depression may be reasonable for its clinical benefits other than improving CHD outcomes (class IIb, level of evidence C).²²⁹ In contrast, the European guidelines, while noting limitations for depression screening, recognize the importance of a comprehensive approach for the detection of psychosocial risk factors, using at least a preliminary assessment with a short series of yes/no questions and recommend a multimodal behavioural intervention approach integrating health education, physical activity, and psychological therapy (class Ia, level of evidence A).¹⁸⁶ In the case of clinically significant symptoms of depression or other psychosocial factors, the European guidelines recommend consideration of interventions such as psychotherapy, medication, or collaborative care (class IIa, level of evidence A). These treatments are reviewed in more detail in the following sections of this paper.

Assessment of depression

Several reliable and valid instruments have been developed for the assessment of depression. The standard for research in the field at least in the USA is the Structured Clinical Interview for the DSM-5 (SCID) interview.²³⁰ This interview requires training and must be administered by someone with clinical experience or with close supervision by a mental health professional. It permits diagnosis based on DSM-5 criteria of major depression and related disorders, including dysthymia and bipolar disorder. Assessment of severity of depressive symptoms can be performed with the Hamilton Depression Scale, a reliable and valid measure of depressive symptoms based on a clinician interview.²³¹ A score of greater than 9 is indicative of moderate to severe depression.²³² Both of these instruments, however, rely on a mental health clinician to administer, which is not usually practical in busy cardiology clinics. An alternative that can be self-administered by patients with CHD is the Beck Depression Inventory. This is a reliable and valid assessment that can be used to screen for the presence of depression, although it does not provide a diagnosis.²³³ If suicidal ideation is a concern, the Sheehan Suicidality Tracking Index is another self-report instrument that can be employed. A score greater than 0 indicates the need for further timely follow-up by a mental health clinician.²³⁴

Management of depression in patients with coronary heart disease

A number of interventions can be useful for CHD patients with depression. Psychotherapy helps people with depression understand

the behaviours, emotions, and ideas that contribute to depression, regain a sense of control and pleasure in life, and learn coping skills.²³⁵

Psychodynamic therapy is based on the assumption that a person is depressed because of unresolved, generally unconscious conflicts, often stemming from childhood. Interpersonal therapy focuses on patient's behaviours and interactions with family and friends. The primary goal of this therapy is to improve communication skills and increase self-esteem during a short period of time. Cognitive behavioural therapy (CBT) involves examining thought patterns that can be negative and self-defeating, and going over the basis of such thoughts and how they contribute to negative emotions. Other therapies useful for depression include stress management and stress reduction techniques such as deep breathing, progressive muscle relaxation, yoga, meditation, and mindfulness-based stress reduction. These interventions can be provided in group format or individually by trained personnel. Psychotherapy has been shown to be equally effective for depression as medications, and some people, especially with early life stress issues, may not respond to medication without psychotherapy.

The Enhanced Recovery in Coronary Heart Disease Patients (ENRICH) trial could not demonstrate a benefit for CBT, with medication intervention for severe depression, for the improvement of cardiac outcomes in depressed or socially isolated patients with CHD.²³⁶ The effects of the intervention on depression, however, were modest, and patients who responded to treatment did have a better outcome than those who did not respond.¹³ Unanswered questions, therefore, remain on whether treatment of depression may improve CHD outcomes.

Antidepressant medications

Antidepressant medications (*Table 1*) are a useful tool for the treatment of depression in patients with CHD, especially those with moderate-to-severe depression.^{237,238} Antidepressants act on the serotonin, dopamine, and norepinephrine systems and other neurotransmitter circuits in the brain.

Tricyclic antidepressants

Tricyclics represent the first class of medications found to work for the treatment of depression. Tricyclics increase norepinephrine and serotonin levels in the synapse. These medications have been associated with a lengthening of the PR interval, QRS duration, and QT interval, and a flattening of the T wave on the electrocardiogram (*Table 1*). Likely because of these effects, tricyclics have been linked to malignant ventricular arrhythmias and sudden cardiac death. For patients who suffer a cardiac event while being treated with a tricyclic or who develop a lengthening of the QT interval, abrupt withdrawal from the tricyclic medication can be associated with an increased risk of arrhythmias. Therefore, these medications should be tapered slowly over a period of time. For all of these reasons, tricyclics should be avoided in patients with CHD, especially those with pre-existing cardiac conduction defects, congestive heart failure, or recent MI, and elderly patients.

Selective serotonin reuptake inhibitors

The selective serotonin reuptake inhibitors (SSRIs) block the transporter that brings the serotonin back from the synapse into the

Table 1 Pharmacological management of depression in patients with coronary heart disease

Drug classification/ generic name	Indication	Cardiovascular adverse effects	Other adverse effects
Selective serotonin reuptake inhibitors			
Fluoxetine	• Agents of choice in CHD	• Fewer to no anticholinergic and cardiac effects	Nausea, diarrhoea, headache, insomnia, agitation, loss of libido,
Sertraline	• Sertraline: agent of choice in post-MI patients	• Concomitant use with aspirin and other antiplatelet/anticoagulation treatment may increase risk bleeding especially in the elderly	delayed ejaculation, and erectile dysfunction
Paroxetine	• Citalopram: should be used with caution in patients at high risk of QTc prolongation or Torsades de Pointes such as those with congestive heart failure, recent MI, bradyarrhythmias hypokalaemia or hypomagnesaemia, congenital long QT syndrome.	• Citalopram is associated with dose-related QTc interval prolongation	
Fluvoxamine			
Citalopram			
Escitalopram			
Tricyclic antidepressants			
Imipramine	• Avoid in CHD, conduction defects, congestive heart failure, and elderly	• Increase heart rate	Anticholinergic effects: dry mouth, constipation, memory problems, confusion, blurred vision, sexual dysfunction, and decreased urination, and memory impairment especially in the elderly
Doxepine	• Contraindicated in post-MI patients	• Prolongation of the PR interval, QRS duration and QTc interval, and a flattening of the T wave on the electrocardiogram	
Amoxapine		• Orthostatic hypotension	
Nortriptyline		• Abrupt withdraw may associated with increased risk of arrhythmias	
Amitriptyline			
Serotonin-norepinephrine reuptake inhibitors			
Desvenlafaxine	• Venlafaxine: avoid in patients at high risk of malignant ventricular arrhythmias or with uncontrolled hypertension	• Fewer to no cardiac effects	Dizziness, constipation, dry mouth, headache, changes in sleep, or more rarely a serotonin syndrome, with restlessness, shivering, and sweating
Duloxetine		• Have been associated with a dose dependent increase in blood pressure and heart rate	
Levomilnacipran		• Regular blood pressure monitoring	
Milnacipran		• Venlafaxine: Minor degree of QTc prolongation	
Venlafaxine			
Antidepressants with novel mechanisms of action			
Bupropion	• Smoking cessation in CHD patients	• Possible increases in blood pressure	Weight loss, restlessness, high doses can rarely cause seizures
		• Minor degree of QTc prolongation	
Mirtazapine	• Use with caution in CHD and post-MI patients	• Mild orthostatic hypotension	Sweating and shivering, tiredness, strange dreams, dyslipidemia, weight gain, anxiety, and agitation
		• Minor degree of QTc prolongation	weight gain, anxiety, and agitation
Trazodone	• Use with caution in CHD, patients with atrioventricular conduction blocks or other conduction disorders and post-MI patients	• Orthostatic hypotension	Rarely, it can cause priapism
		• Minor to low degree of QTc prolongation	

CHD, coronary heart disease; MI, myocardial infarction; QTc: corrected QT interval.

neuron (Table 1). Because of their different mechanism of action, they have fewer to no anticholinergic and cardiac effects. Therefore, they are first line of treatment for CHD patients.

The SSRIs have only modest efficacy over placebo,^{239,240} and about 80% of the improvement is due to placebo response. They show their greatest effect on patients with severe depression.²³⁸

Antidepressants without sexual dysfunction side effects can be given instead of an SSRI in case this is an issue, for example, bupropion. The SSRIs stopped suddenly can result in a potent withdrawal syndrome, including agitation, nervousness, and sometimes suicidal thoughts. Patients on aspirin or other antiplatelet/anticoagulation treatment can have an increase in bleeding risk with SSRIs.

Studies of SSRIs have found them to be safe and effective for patients with CHD, although their effects on improving cardiac outcomes are unclear. Some data suggest that patients whose depression improves with SSRIs, typically those with severe depression, may have better cardiac outcomes.¹³ However, some data suggest that SSRIs, like tricyclics, when used long-term may increase the risk of cardiac events and death.^{21,241} These events are rare, however, and a proper risk-benefit evaluation should be performed case by case.

Serotonin and norepinephrine dual reuptake inhibitors

The latest group of antidepressants has dual reuptake inhibition for serotonin and norepinephrine (Table 1). These drugs are moderately more effective than the SSRIs for the treatment of depression, although they can have more side effects. Venlafaxine has been associated with a dose-dependent increase in blood pressure, which is of particular concern for CHD patients, especially those with pre-existing hypertension. In addition, venlafaxine seems to carry the greatest risk of suicidality amongst all of the antidepressants, with a three-fold increased risk of attempted or completed suicides.

Antidepressants with novel mechanisms of action

Some drugs act on various neurotransmitter systems or have poorly understood mechanisms of action (Table 1). Bupropion primarily acts on dopamine systems and is used for both depression and smoking cessation. Mirtazapine is a tetracyclic antidepressant that has actions on a number of different receptor systems. It blocks presynaptic noradrenergic alpha-2 receptors with associated enhancement of norepinephrine release. Mirtazapine also increases serotonin release. It can be associated with mild orthostatic hypotension and anticholinergic side effects. Trazodone is a safe and effective antidepressant that can also be an effective non-addicting sleep aid.

Electroconvulsive therapy

Electroconvulsive therapy (ECT) is used as a last resort for the treatment of depression in patients who have had multiple failed trials of psychotherapy and medication. Electroconvulsive therapy has an 80% overall response rate, and contrary to popular belief, is a safe procedure. Although ECT causes profound hemodynamic changes, including bradycardia (up to frank asystole which may last for a few seconds), tachycardia and hypertension, these effects are transient and typically resolve within 20 min. Possible complications include persistent hypertension, arrhythmias, asystole lasting more than 5 s, ischaemia, and heart failure. Older age and pre-existing cardiovascular diseases, including hypertension, CHD, congestive heart failure, aortic stenosis, implanted cardiac devices, and AF, have been associated with increased complication rates. However, most complications remain minor and transient, and the vast majority of patients can safely complete treatment. The procedure should be delayed in patients who are haemodynamically unstable or have new-onset or uncontrolled hypertension. In patients with stable CHD and controlled hypertension, medications can be continued through the morning of the procedure. Electroconvulsive therapy appears safe in patients with an implantable cardioverter defibrillator with detection mode turned off during ECT and continuous electrocardiographic monitoring and life resuscitation equipment on hand. Pacemakers

should be tested before and after ECT and the magnet should be placed at the patient bedside.

Exercise

Exercise has been consistently found to be efficacious for the treatment of depression, at least equivalent to the effects of SSRIs or psychotherapy.^{242,243} Aerobic exercise seems to work best; therefore, aerobic exercise at a dose consistent with public health recommendations for CHD prevention is an effective treatment for mild-to-moderate depression. Exercise may also complement the effects of antidepressant medications in depressed patients who do not have a complete response to medications. Finally, in patients with CHD, cardiac rehabilitation is highly effective in improving mental health, including depression, as well as physical health outcomes including subsequent CHD events and mortality.²⁴⁴ Cardiac rehab enhanced by stress management training has been shown to be effective in reducing stress and improving medical outcomes compared with standard cardiac rehabilitation.²⁴⁵

Summary of management considerations

There are several treatment options for the CHD patient with depression, from medications to various forms of psychotherapy, to exercise and stress management approaches. Although treatment of depression has not been shown to improve cardiovascular outcomes in CHD patients, depression should still be addressed if severe enough, in order to promote patient wellness and QoL. Tricyclics should be avoided in this patient population.

Concluding remarks

Converging evidence from both experimental and epidemiological studies indicates that there is a bidirectional association between depression and CHD. Depression is very common in patients with CHD and is an independent risk factor for poorer CHD outcomes. The underlying mechanisms linking depression and worse CHD outcomes are complex and potentially multifactorial. Further research is necessary to elucidate them. Nonetheless, there is growing consensus for considering depression as a modifiable prognostic factor for CHD, and for the need of improved efforts towards better recognition and management of this problem in the clinical practice of cardiology.^{3,4} Whether effective and safe treatment of depression may improve CHD outcomes, and whether specific patient subgroups may benefit more from such treatments, require further evaluation.

Recommendations

- Clinicians should be aware of the high prevalence of depression in CHD patients. Screening for depression is recommended if patients have access to adequate care support systems
- Patients with positive screening results should be referred to a qualified health care provider in the management of depression
- Non-pharmacologic interventions such as exercise and psychotherapy should be considered as additional treatment options for CHD patients

- Harmonization of care between healthcare providers is essential in patients with combined CHD and depression

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