REVIEW ARTICLE

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Cardiovascular Abnormalities in Patients with Major Depressive Disorder

Autonomic Mechanisms and Implications for Treatment

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Abstract

This article provides a detailed review of the association of major depression with coronary heart disease (CHD), examines the biological variables underpinning the linkage and discusses the clinical implications for treatment. When considering the co-morbidity between major depressive disorder (MDD) and CHD it is important to differentiate between (i) the prevalence and impact of MDD in those with existing CHD and (ii) MDD as a risk factor for the development of CHD. Whether the same biological mechanisms are at play in these two instances remains unknown. Depression is common in patients with CHD. Importantly, depression in these patients increases mortality. There is also consistent evidence that MDD is a risk factor for the development of CHD. The relative risk of developing CHD is proportional to the severity of depression and is independent of smoking, obesity, hypercholesterolaemia, diabetes mellitus and hypertension.

There is a clear need to identify the underlying neurochemical mechanisms responsible for MDD and their linkage to the heart and vascular system. Of particular interest are activation of stress pathways, including both the sympathetic nervous system and hypothalamic-pituitary-adrenal axis, and inflammatory-mediated atherogenesis. Elevated sympathetic activity, reduced heart rate variability and increased plasma cortisol levels have been

documented in patients with MDD. In addition to direct effects on the heart and vasculature, activation of stress pathways may also be associated with increased release of inflammatory cytokines such as interleukin-6 and tumour necrosis factor-α. Elevated levels of C-reactive protein are commonly observed in patients with MDD.

The majority of investigations examining treatment of depression following myocardial infarction have focused on safety and efficacy; there is little evidence to indicate that treating depression in these patients improves survival. Given that strategies for preventive therapy remain incompletely formulated, future research should focus on generating a better understanding of the neurobiology of MDD and heart disease as a basis for rational and effective therapy.

Over recent years substantial advances have been made in delineating the causes of coronary heart disease (CHD). At the population level, the importance of abnormal blood lipids, tobacco smoking and high blood pressure as contributing factors is well established. Recent large-scale epidemiological studies[1] have further increased our understanding of the mechanisms generating cardiac risk and have provided evidence indicating that psychosocial factors, particularly depressive illness, are involved in 'triggering' clinical cardiovascular events, and may also contribute to disease development and poorer outcomes in terms of both mortality[2] and quality of life.[3,4]

While the links between the brain and the heart are enshrined in history and literature, and have long been accepted by the lay community, scientific investigations examining the biological interactions between the heart and mind are difficult and remain a relatively recent development. In this article we begin by reviewing evidence that major depressive disorder (MDD) is associated with increased risk of clinical cardiovascular events and then discuss several mechanisms that may underpin this increased risk and the implications for the treatment of patients with MDD.

1. Prevalence of Depression in Patients with Cardiovascular Disease

When considering the co-morbidity between MDD and CHD it is important to differentiate between (i) the prevalence and impact of MDD in those with existing CHD and (ii) MDD as a risk factor for the development of CHD. Whether the same biological mechanisms are at play in these two distinct cohorts remains unknown and merits further investigation.

Evidence in support of the relationship between depression and cardiovascular disease derives from a growing array of cross-sectional surveys demonstrating the disproportionately elevated rates of depression among people with documented CHD compared with matched community-based samples. Carney and colleagues[5] found that 26% of patients undergoing angiography for assessment of CHD met the criteria for MDD, and Barefoot at al.[6] observed that about a quarter of patients with angiographically demonstrated coronary atherosclerosis recorded mild depressive symptoms and a further 11% had moderate to severe depression. Elevated depressive symptomatology is present in approximately 10% of patients in primary care settings,[7] as compared with approximately 20–30% of outpatients with CHD,[5-8] 30–40% of outpatients with heart failure[9,10] and up to 50% of people recently hospitalized for coronary artery bypass graft surgery or acute coronary syndrome.[11] van Melle and colleagues[12] recently identified younger age and severe left ventricular dysfunction as the clinical factors that correctly predicted post-discharge depression status in approximately 80% of cases.

Importantly, the presence of depression in patients with CHD has been convincingly

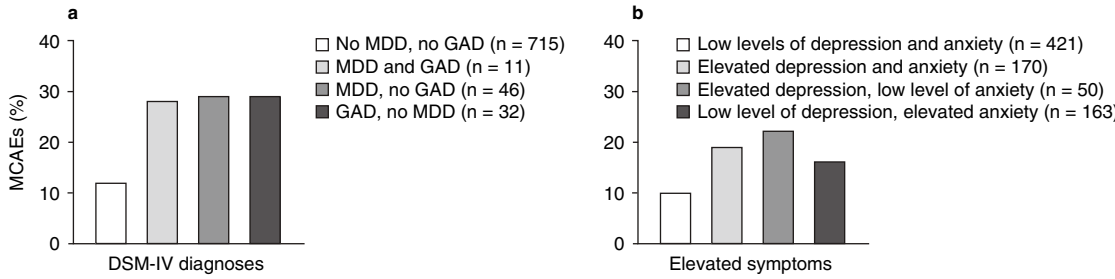

Fig. 1. Percentage of patients experiencing major cardiac adverse events (MCAEs) across 2 years associated with (**a**) DSM-IV diagnoses of major depressive disorder (MDD) and generalized anxiety disorder (GAD) and their co-morbidity, and (**b**) elevated levels of depression and anxiety symptoms and their co-morbidity in 804 patients assessed 2 months after an acute coronary syndrome (reproduced from Frasure-Smith and Lesperance,[14] with permission. Copyright © 2008 American Medical Association).

demonstrated to materially increase mortality.[2,6,13] Frasure-Smith and Lesperance[14] recently extended this observation, documenting that depression and generalized anxiety disorder predict greater risk of major adverse cardiac events in the 2 years following myocardial infarction (MI) [figure 1]. On balance, systematic reviews and meta-analyses exploring the contribution of depression and depressive symptoms to adverse events seem to confirm these findings.[15-17] Given the variability in factors such as the (psychometric) diagnostic tool used, severity of depression, cardiovascular diagnosis and duration of follow-up, it is not surprising that there is some heterogeneity in results. Furthermore, there are of course views to the contrary.[18,19] However, in these latter studies, while depression did not predict subsequent mortality, it was associated with impaired quality of life, increased reports of chest pain and use of primary care resources, and non-compliance with lifestyle changes,[18,19] including attendance at cardiac rehabilitation.[20]

2. Depression and the Development of Coronary Heart Disease

The association between mental and cardiovascular health was noted early in the 20th century when Malzberg[21] reported high mortality rates in hospital inpatients with melancholia. It was not until 50 years later that evidence from prospective trials indicated that affective disorders participated in the development of cardiovascular disease. Indeed, on balance, the majority of studies have demonstrated a positive association between symptoms of depression, a history of MDD and the development of CHD. This elevated risk is independent of classical risk factors such as smoking, obesity, hypercholesterolaemia, diabetes mellitus and hypertension.

Using meta-analytic techniques, Wulsin and Singal[15] and Rugulies[16] examined studies of community-based samples of people without clinically apparent coronary disease at baseline that were followed prospectively over significant periods of time, and included control for a number of potentially confounding risk factors. Despite a degree of heterogeneity in studies (table I), the majority of investigations documented significant positive associations between depression and the development of CHD. Overall, depression increased the risk of incident CHD (hospitalizations, fatal or nonfatal events or physician diagnosis of CHD) by 64% compared with those without depression. In the most recently released meta-analysis on the significance of depression in contributing to CHD development, Van der Kooy and colleagues[17] found that depression at baseline was associated with the increased risk of development of a wide range of cardiovascular outcomes including MI, fatal and nonfatal CHD and stroke. These findings were consistent among community-dwelling or primary care samples of patients, among those initially free of disease (relative risk [RR] 1.57) or those with established CHD at baseline (RR 1.35). This is also in agreement with results of the INTERHEART study (where the association

between psychosocial stress, including depression, and coronary artery disease was found to be present in men and women, across different age groups and in individuals living in different countries)[1] and the recently published EPIC-Norfolk United Kingdom prospective cohort study.[37] Importantly, as demonstrated in many other studies, the relative risk of developing CHD is proportional to the severity of the depression.

3. Depression and the Heart: Physiological Mechanisms of Cardiac Risk

Given the complexities in the pathology of both depressive illness and cardiac disease it is truly a Panglossian view that would link CHD to depression in a simple manner. Indeed, the aetiology of MDD has been linked, variously, to brain

Table I. Depression and the risk of developing heart disease (for more information see Wulsin and Singal[15] and Rugulies[16])

Reference	Diagnostic tool	Relative risk	95% CI
Anda et al.[22]	General well-being scale	Fatal CAD: 1.50	1.0, 2.3
		Nonfatal CAD: 1.6	1.1, 2.4
Aromaa et al.[23]	Present State Exam, General Health Questionnaire	MI	
		males (40–64 y): 3.45	1.76, 6.76
		females (40–64 y): 2.59	1.12, 5.99
Vogt et al.[24]	Author's 'depression index'	CAD: 1.06	0.78, 1.42
Pratt et al.[25]	Diagnostic Interview Schedule	MI	
		dysphoria: 2.07	1.65, 2.37
		major depression: 4.54	1.65, 12.45
Barefoot and Schroll[6]	MMPI	MI: 1.70	1.23, 2.34
Sesso et al.[26]	MMPI-2 SCL-90	Incident CHD	
		SCL-90: 1.73	0.97, 3.10
		MMPI-2 D: 1.46	0.83, 2.57
		MMPI-2 Dep: 2.07	1.13, 3.81
Ford et al.[27]	Self-report	CAD: 2.12	1.24, 3.63
Penninx et al.[28]	CES-D	CAD	
		chronic depression: 1.17	0.83, 1.64
		new depression: 1.47	1.10, 1.98
Ariyo et al.[29]	CES-D	CAD: 1.45	1.34, 1.57
Ferketich et al.[30]	CES-D	CAD incidence	
		males: 1.71	1.14, 2.56
		females: 1.73	1.11, 2.68
Mendes de Leon et al.[31]	CES-D	Nonfatal MI and CHD death	
		women: 1.67	0.96, 2.90
		men: 0.70	0.34, 1.42
Schwartz et al.[32]	CES-D	Fatal and nonfatal MI: 2.23	1.34, 3.71
Wassertheil-Smoller et al.[33]	CES-D	Fatal and nonfatal MI	
		women: 1.2	0.97, 1.48
		men: 1.07	0.83, 1.38
Whooley and Browner[34]	Geriatric Depression Scale	CHD death: 1.7	1.0, 3.0

CAD = coronary artery disease; **CES-D** = Center for Epidemiological Studies Depression Scale;[35] **CHD** = coronary heart disease; **MI** = myocardial infarction; **MMPI** = Minnesota Multiphasic Personality Inventory; **MMPI-2** = revised Minnesota Multiphasic Personality Inventory; **MMPI-2 D** = revised Minnesota Multiphasic Personality Inventory (basic depression);[36] **MMPI-2 Dep** = revised Minnesota Multiphasic Personality Inventory (content depression);[36] **SCL-90** = 90-item symptom checklist.

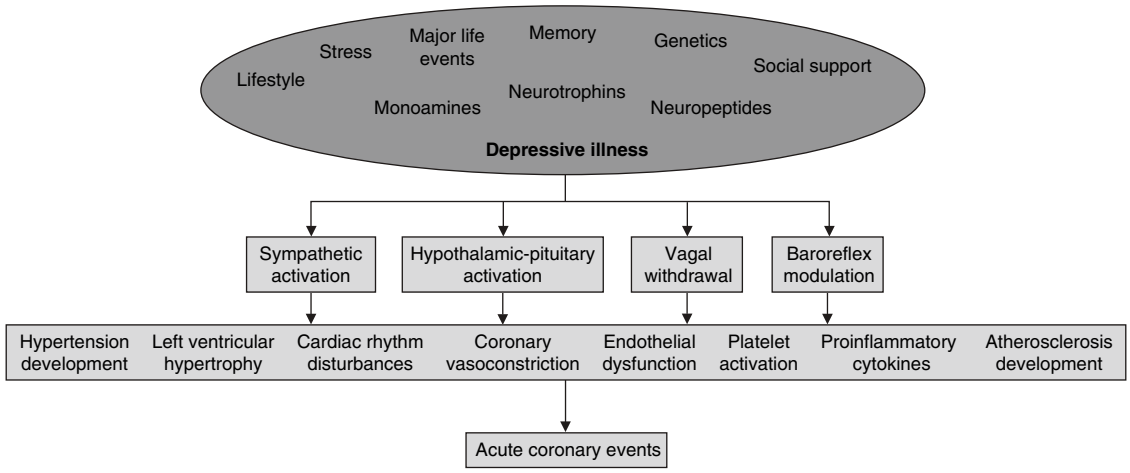

Fig. 2. Depression and the heart; possible mechanisms increasing cardiac risk. Recent epidemiological studies have provided evidence indicating that psychosocial factors, including stress, recent major life events and the presence of depressive illness, are linked with the development of clinical cardiovascular events and possibly also contribute to hypertension and atherosclerosis development. While the underlying mechanisms in play are most likely multifactorial in origin, involving the autonomic nervous system, platelet activation, thrombogenesis and endothelial dysfunction, in this review we focus principally on the autonomic and hypothalamic-pituitary-adrenal axis mechanisms implicated in generating increased cardiac risk.

monoaminergic neuronal dysfunction,[38-40] alterations in monoamine receptor sensitivity[41] and stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis[42] with concomitant reduction in brain neurotrophins.[43] Intuitively, through their interaction with the autonomic nervous system, these biological pathways provide a convenient point of departure in examining the mechanisms involved in generating elevated cardiac risk in patients with depression (figure 2).

3.1 Disturbances in Autonomic Regulation

3.1.1 Sympathetic Nervous System

In previous reports we have documented the importance of subcortical noradrenaline (norepinephrine) in the regulation of sympathetic activity in patients with heart failure[44] and hypertension[45] and, more recently, elevated brain serotonin turnover in unmedicated patients with MDD.[46] Interestingly, in this latter investigation, brain serotonin turnover was elevated further in patients carrying the short allele of the serotonin transporter. Consistent with this report, Otte and colleagues[47] documented an association between carriage of the short allele of the serotonin transporter and elevated urinary noradrenaline levels and, by inference, sympathetic nervous activation.

In a range of clinical contexts, stimulation of the cardiac sympathetic outflow has been demonstrated to contribute to ventricular arrhythmias[48] and sudden death.[49] In healthy individuals, laboratory mental stress is associated with a specific activation of the cardiac sympathetic nervous outflow[50] (figure 3a). Consistent with this observation, Wittstein and colleagues examined the neurohumoral features of Takotsubo[52] cardiomyopathy due to sudden emotional stress and concluded that exaggerated sympathetic stimulation was probably central to the cause of this syndrome. The importance of the link between stress and acute coronary syndromes is further reinforced by the increased cardiac events associated with such events as natural disasters[53] and terrorist attacks.[54] Moreover, a recent report indicates that viewing a stressful soccer match more than doubles the risk of an acute cardiovascular event (figure 3b).[51] Through elevation in blood pressure and generation of increased vascular shear

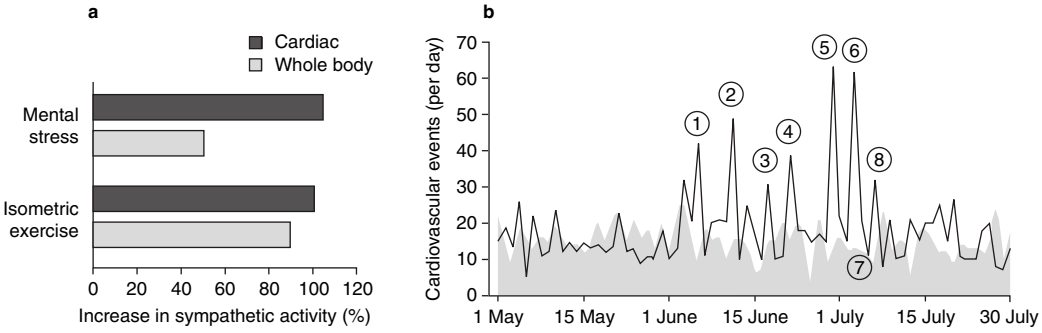

Fig. 3. The sympathetic nervous system, stress and heart disease. (**a**) The cardiac sympathetic nerves are preferentially activated during laboratory mental stress, whereas during isometric exercise cardiac and whole body sympathetic activity are elevated proportionally. (**b**) Daily cardiovascular events from 1 May to 31 July in 2003, 2005 and 2006 in the Munich (Germany) region. The shaded area depicts the mean of these 3 years and the line indicates the events in 2006. The FIFA World Cup 2006 in Germany started on 9 June 2006 and ended on 9 July 2006. The 2006 World Cup matches with German participation are indicated by numbers 1 through 7: match 1, Germany vs Costa Rica; match 2, Germany vs Poland; match 3, Germany vs Ecuador; match 4, Germany vs Sweden; match 5, Germany vs Argentina; match 6, Germany vs Italy; and match 7, Germany vs Portugal. Match 8 was the final match, Italy vs France. It is of particular interest that match 3 was of little consequence as the German team had already qualified to advance through the tournament, matches 5 and 6 were close and victory would ensure progression towards the final and match 7, for third-place standing, was associated with minimal cardiovascular events. These data suggest a 'dose-relation' between perceived stress and cardiac disease (reproduced from Wilbert-Lampen et al.,[51] with permission. Copyright © 2008 Massachusetts Medical Society. All rights reserved).

stress, it is likely that the rupturing of vulnerable plaques contributes to this increased rate of cardiac events. In addition to possible blood pressure elevation, sympathetically mediated neural vasoconstriction may also exert metabolic effects in skeletal muscle, impairing glucose delivery to muscle,[55] causing insulin resistance and hyperinsulinaemia and retarding postprandial clearing of lipids in the liver,[56] contributing to hyperlipidaemia. Sympathetic nervous activation accompanying stress may also affect platelet reactivity,[57,58] arrhythmic potential[48,59] and cardiac ischaemia[60] and accelerate the development of carotid atherosclerosis (for a review see Rozanski et al.[61]).

Examination of indices of sympathetic nervous function in patients with depression has yielded conflicting results. Some studies indicate a tendency for the urinary excretion of noradrenaline and its metabolites to be diminished,[38,40] whereas other reports documented elevated plasma levels of noradrenaline[62] and increased rates of noradrenaline spillover to plasma[63,64] in patients with MDD. Our recent observations paint a more intriguing picture, with whole body sympathetic activity showing a bimodal distribution, some values being extraordinarily high and others being very low (figure 4).[65] Interestingly, cardiac sympathetic activity in the 'high' group was quantitatively similar to that observed in patients with hypertension in whom we have previously demonstrated a trophic effect of sympathetic nervous activation on cardiovascular growth, contributing to the development of left ventricular hypertrophy.[66] Left ventricular hypertrophy is an independent risk factor for cardiovascular morbidity and mortality[67] and predicts cardiovascular complications in patients with hypertension.[68] While depression commonly coexists with hypertension,[69] there is little evidence documenting an association between left ventricular hypertrophy and MDD.

3.1.2 Parasympathetic Nervous System

In contrast with the sympathetic nervous system, cardiac vagal neural outflow is protective, with high vagal activity in the heart protecting against MI and the development of ventricular tachyarrhythmias. In the absence of neurochemical methodology to investigate cardiac vagal activity, since the transmitter, acetylcholine, is so rapidly inactivated by acetylcholinesterase, much attention has focused on measures of baroreflex sensitivity and heart rate variability as markers of

vagal function and indicators of future cardiac events.[70] The potential importance of baroreflex sensitivity as a measure of cardiac risk emerged following experiments in dogs,[71] where reduced baroreflex sensitivity was associated with a greater susceptibility to ventricular fibrillation during subsequent ischaemic episodes. Subsequently, a large prospective study provided evidence that low values of baroreflex sensitivity and heart rate variability following MI were associated with an increased risk of developing ventricular arrhythmia.[72] Reduced baroreflex sensitivity has also been associated with elevated death rates due to other conditions, such as hypertension,[73] obesity[74] and diabetes.[75]

In patients with MDD with no underlying heart disease there is evidence that reduced baroreflex sensitivity is associated with the number of previous depressive episodes.[76] Using cross-spectral analysis, although no comparison was made with non-depressed individuals, Watkins and Grossman[77] have previously demonstrated that anxiety, rather than depression severity, is associated with reduced baroreflex sensitivity. Reduced heart rate variability has been proposed as one of the mechanisms by which depressive illness is associated with increased mortality in patients following MI. Diminished heart rate variability, which is also attributable to reduced modulation of heart rate by the cardiac vagus, has been described in patients with MDD.[78] Moreover, the presence of co-morbid depression in patients presenting with coronary artery disease has been demonstrated to be associated with a reduction in heart rate variability.[79-81] In the large multicentre trial, ENRICHD (Enhancing Recovery In Coronary Heart Disease), reduced heart rate variability was significantly associated with depressive illness in patients following MI.[82] Similarly, Frasure-Smith et al.[83] followed the progress of patients after MI over a 6-month period and reported that patients with depressive illness had a 5-fold increase in mortality rate when compared with non-depressed patients. While Carney and colleagues[84] recently documented that low heart rate variability partially mediates the effect of depression on survival in patients following acute MI, Gehi et al.[85] found no evidence of an association between depression and diminished heart rate variability.

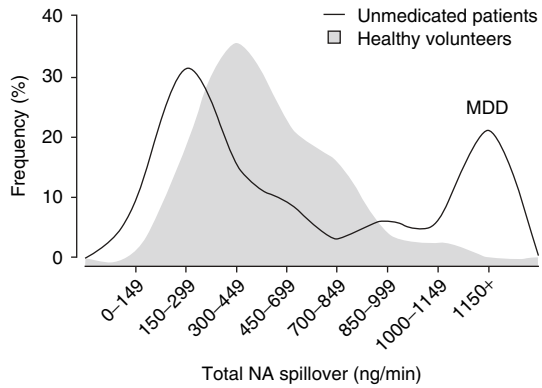

Fig. 4. Distribution of sympathetic nervous activity in patients with major depressive disorder (MDD). Kernel density estimate of the spillover rate of noradrenaline (norepinephrine) [NA] to plasma in unmedicated patients with MDD and in healthy volunteers. The distribution of data was estimated using a Gaussian kernel and bandwidth of 94.8. Data indicate that in patients with MDD sympathetic activity follows a bimodal distribution (reproduced from Barton et al.,[65] with permission. Copyright © Lippincott, Williams & Wilkins, 2007).

In their study involving over 2300 subjects, Licht et al.[86] documented a reduction in heart rate variability in patients with MDD. The association between diminished heart rate variability and MDD was driven largely by the use of antidepressants, with the diminution in heart rate variability in MDD being related to dose in all three antidepressant classes. This observation is in agreement with our[76] and Volkers et al.[87] previous observations of a marked reduction in heart rate variability in patients with MDD following treatment with a selective serotonin reuptake inhibitor (SSRI).

Given the consensus that measures of heart rate variability largely reflect vagal activity and, importantly, that diminished heart rate variability has consistently been shown to be a strong independent predictor of post-MI mortality,[70] these observations may be of considerable clinical relevance and raise the spectre that the increased cardiac morbidity and mortality that accompanies MDD may be at least partially due to the effect of antidepressants on heart rate variability.

Examination of the association between antidepressant use and MI development has yielded inconsistent results.[25,88-91] While issues relating

to the power of the studies, the therapeutic agents examined and psychiatric co-morbidity may account for these different outcomes, on balance the majority of studies demonstrate no adverse effect of antidepressants on MI; this is particularly so for SSRIs. Interestingly, in one of the largest case-control analyses of this type, Tata et al.[91] evaluated the impact of prior antidepressant administration in over 60 000 cases of first-time MI and found patients to be at significantly increased risk of MI only within the initial stage (28 days) of antidepressant use. Their observation that prolonged antidepressant exposure was not associated with increased risk of MI suggests that it is depression *per se* rather than the therapeutic agents that confer increased cardiovascular risk. However, one cannot discount that the acute and long-term physiological response to antidepressant agents differs.

The impact of aberrations in the autonomic nervous system in MDD is not confined to direct cardiac disturbances such as the generation of arrhythmias. Recent reports provide evidence of a link between vagal activity and inflammation,[92] which may in turn encourage the development of inflammatory-mediated atherogenesis.[93] Inflammatory cytokines produced in damaged tissues activate afferent signals that input to the nucleus tractus solitarius, resulting in activation of vagus efferent activity, which may inhibit cytokine synthesis through the cholinergic anti-inflammatory pathway. A dampening of this pathway may lead to the production of inflammatory cytokines. Information can also be relayed to the hypothalamus and the dorsal vagal complex to stimulate the release of adrenocorticotropic hormone (ACTH), thereby activating the humoral anti-inflammatory pathway. The role of the sympathetic nervous system in immune function is complicated and may exert both pro- and anti-inflammatory effects (for a review see Straub et al.[94]).

3.2 Stress-Induced Activation of the Hypothalamic-Pituitary-Adrenal Axis

In addition to activation of the sympathetic nervous system, psychological stress is associated with activation of the HPA axis. There is a large body of evidence illustrating cortisol hypersecretion in untreated patients with depressive illness[95-97] and, despite not being ubiquitous (for a review see Gold and Chrousos[95]), it remains the most consistent biochemical marker of MDD (to date). This may be due to chronic hypersecretion of corticotropin-releasing factor[98] and ACTH,[99] although elevated[99,100] and normal to low[101,102] ACTH levels in MDD patients have both been described.

The physiological consequences of increased circulating cortisol are diverse and include importantly, in the context of cardiac risk, the onset of metabolic changes, such as insulin resistance, hyperinsulinaemia, glucose intolerance and hyperlipidaemia, and increased visceral fat mass.[103] Obesity, including being moderately overweight, is associated with a significant increase in the odds of mood and anxiety disorders.[104-106] Indeed, a growing body of evidence links 'stress' to the development of the metabolic syndrome. In a nested case-control study of the metabolic syndrome, the authors of the Whitehall II Study concluded that stress pathways, including both the HPA axis and the sympathetic nervous system, are activated in individuals with the metabolic syndrome.[107] They were further able to demonstrate that psychosocial factors were associated with the increased normetanephrine levels observed in individuals with the metabolic syndrome. In a more recent publication of the Whitehall II Study, work-related stress over 14 years of follow-up was related to the metabolic syndrome in a dose-response fashion.[108] These observations are consistent with our own data, where we have demonstrated that insulin-resistant individuals with the metabolic syndrome exhibit a pronounced sympathetic activation[109] and elevated plasma cortisol levels. Koponen et al.[110] recently found that individuals with the metabolic syndrome at baseline were twice as likely to have depressive symptoms at 7-year follow-up compared with those without the metabolic syndrome at baseline.[111] Importantly, individuals with the metabolic syndrome are at an increased risk of incident diabetes[112] and cardiovascular disease.[113] While Vaccarino and

colleagues,[114] in their examination of data derived from the Women's Ischemia Syndrome Evaluation study,[115] concluded that the metabolic syndrome was independently associated with depression, it accounted for only a small fraction of the association between depression and incident cardiovascular disease over a 7-year follow-up. Whether the same is seen in men or whether a longer follow-up would influence the association remains to be established but merits further attention.

3.3 Inflammation and the Development of Cardiac Risk in Depression

The importance of inflammatory-mediated atherogenesis in the development of cardiac disease is widely acknowledged.[116,117] The observation of elevated plasma levels of interleukin (IL)-6, tumour necrosis factor (TNF)-α and high sensitivity C-reactive protein (CRP) in patients with MDD[76,118-121] raises the possibility that enhanced inflammatory-mediated atherogenesis may also be important in generating cardiac risk in MDD (for a review see Raison et al.[122]). CRP, IL-6, and TNFα have demonstrated the most consistent findings in terms of predictive consequence of future cardiac events in prospective epidemiological research.[123] Adding credence to the linkage between depression, inflammation and cardiac risk, administration or induction of proinflammatory cytokines has been shown to produce depression-like symptoms in non-depressed human individuals[124] and in animals.[124-126]

Studies in healthy volunteers examining the link between plasma CRP level and symptoms of depression have yielded both positive[127,128] and negative[129] findings. Interestingly, Leo and colleagues[121] documented an association between Hamilton Depression Rating Scale (HAM-D) scores[130] and inflammatory cytokine levels in patients with MDD but not in healthy volunteers. Elevated circulating levels of inflammatory cytokines are commonly observed in individuals with the metabolic syndrome[109] and adiposity possibly accounts for some of the relationship between depression and increased expression of inflammatory markers.[119] CRP is an acute-phase inflammatory marker and is an independent predictor of death from MI.[131] Lower, moderate and higher risk of coronary heart disease are expressed by CRP levels in the order of <1, 1–3 and >3 mg/L, respectively.[131] In MDD, CRP levels in the moderate to higher risk category have been described.[76,119,121] Recent studies have documented that the lowering of CRP levels following statin therapy in patients with acute coronary syndromes results in better clinical outcomes and a reduction in the progression of atherosclerosis, independent of lipid lowering.[132,133] Whether SSRIs also reduce mediators of inflammation is uncertain.[76,121]

4. Treatment

Despite improved diagnosis and the refining and development of treatment paradigms,[134] depression remains a significant public health challenge. Indeed, depression is currently the fourth highest cause of disability globally and, if epidemiological projections are correct, by 2020 it will reach second place behind ischaemic heart disease.[135] Consequently, these two conditions will frequently coexist and pose significant challenges for treatment. This is further complicated by the fact that when physical illness and depression occur together the overall outcome for both diseases is worse. Treatment modalities for MDD in those with no existing heart disease are varied (table II) and may involve pharmacotherapy, psychotherapy, the combination of medications plus psychotherapy or electroconvulsive therapy (ECT).[134] Selection of treatment may be influenced by clinical (e.g. severity and/or duration of symptoms) and other factors (e.g. patient's previous experience/preference). Importantly, with regard to treatment considerations and the pathways to recovery, depression is a condition that may involve phases of debilitation, recovery and relapse (figure 5). In patients with CHD, depression is associated with medication nonadherence.[136] Inadequate treatment and episodic worsening of depressive symptoms have been demonstrated to increase the likelihood of developing chronicity and only

Table II. Representative list[a] of antidepressant medications; for more information see American Psychiatric Association Practice Guidelines[134]

Generic name
Selective serotonin reuptake inhibitors
Citalopram
Fluoxetine
Paroxetine
Sertraline
Serotonin-noradrenaline reuptake inhibitors
Venlafaxine
Tricyclic antidepressants
Amitriptyline
Clomipramine
Desipramine
Imipramine
Nortriptyline
Tetracyclic antidepressants
Amoxapine
Dopamine-noradrenaline reuptake inhibitors
Bupropion
Selective noradrenaline reuptake inhibitors
Reboxetine
Serotonin modulators
Trazodone
Noradrenaline-serotonin modulators
Mirtazapine
Monoamine oxidase inhibitors
Moclobemide
Phenelzine

a This is not a comprehensive list of all medications. Choice of agent and dose needs to be determined in association with other clinical factors, e.g. lower starting doses may be indicated in the elderly or those with kidney or liver disease, and some drugs may be contraindicated for those with co-morbidities such as cardiac, renal or liver disease.

partial recovery (for a review see Kupfer and Frank[137]), thereby making the choice of, and adherence to, therapy important considerations. The establishment and maintenance of a therapeutic alliance between patient and physician is essential in this regard.

The majority of investigations examining treatment of depression following MI have focused on safety and efficacy; there is little evidence to indicate that treating depression in these patients improves survival. While van Melle and colleagues[138] found no evidence of improved outcome following MI, Santangelo et al.[139] demonstrated a reduction in cardiac events in an elderly population. In a recent meta-analysis, Swensson and colleagues[140] were equivocal as to whether SSRIs are associated with a greater or lesser risk of cardiovascular adverse events. Monster et al.[141] found that antidepressant use was associated with a decreased risk of hospitalization for MI only among persons with a history of cardiovascular disease.

Rasmussen et al.[142] randomized patients after an ischaemic stroke to either sertraline or placebo and observed that those receiving sertraline also had significantly less severe cardiovascular and non-cardiovascular adverse events. While the SADHART (Sertraline AntiDepressant Heart Attack Randomized Trial) indicated the rate of serious adverse events for patients receiving sertraline to be 20% less than for those receiving placebo,[143] the study was not powered sufficiently to conclude unequivocally that treating depression resulted in a reduction in future cardiac events. The ENRICHD (Enhancing Recovery In Coronary Heart Disease patients) trial demonstrated that therapy improved depression symptoms but this was not associated with an increase in event-free survival.[144] Taylor and colleagues,[145] in a *post hoc* subgroup analysis of antidepressant drug use in the ENRICHD trial, demonstrated that the risk of death or recurrent MI was significantly lower in patients taking SSRIs compared with patients not taking SSRIs. It is important to note that, given the importance of sympathetic activation in generating cardiac events, in their analysis, patients using SSRIs were less likely to be using antiarrhythmic drugs and β-blockers; i.e. clinical considerations necessitated the administration of sympatholytic medication in the 'non-SSRI' group.[145] This suggests that the grouping of SSRI versus non-SSRI was non-homogeneous and that, perhaps, the non-SSRI group had elevated sympathetic outflow and was therefore more likely to experience a cardiac event.

It may never be known whether treating depression after a cardiac event decreases mortality, as the definitive mortality study may never be done owing to the cost and complexity involved.

Depressed patients do have significant impairment[18,146,147] and, even if treatment does not improve longevity, it is certainly worth improving their depressive symptoms and quality of life.

Indicative of an increased risk of thrombotic complications, the co-morbid presence of ischaemic heart disease and depression is associated with elevated platelet reactivity.[148] Both paroxetine[149,150] and sertraline[151] have been demonstrated to improve platelet reactivity whereas the tricyclic antidepressant nortriptyline was without effect.[150] Consequently, treatment with an SSRI as add-on therapy may confer additional beneficial effects even in the presence of other thrombolytic agents; however, it is unclear whether this is the only mechanism of action for any putative benefit. Indeed, in patients with MDD (with no existing cardiac disease) SSRIs have been demonstrated to significantly reduce sympathetic nervous activity in a manner likely to reduce cardiac risk.[65]

While a number of trials have demonstrated SSRIs to be safe in the 'cardiac disease' setting, there are properties of SSRIs that should be addressed prior to dispensing. Of particular note are the potential of SSRIs to induce weight gain and the effect of SSRIs on cytochrome P450 (CYP) liver enzymes. There exist reports indicating that SSRI use may be associated with increased bodyweight and development of metabolic abnormalities.[152,153] It is difficult to establish whether possible weight gain following therapy is due to the return of normal appetite in those whose appetites have been decreased as part of their depression or is due to a direct effect of the drug acting on orexigenic centres in the brain. Interestingly, the propensity for SSRIs to induce weight gain seems to be dependent on the drug used. For instance, paroxetine has been associated with weight gain,[152-155] whereas citalopram,[153] fluoxetine and sertraline seem not to cause significant increases in weight.[152,153,156] The SSRIs also vary widely in their interaction with CYP isoenzymes in the liver,[157,158] and hence the possibility of adverse drug-drug interactions should be carefully monitored. For instance, paroxetine and fluoxetine, but not citalopram and sertraline, are strong inhibitors of

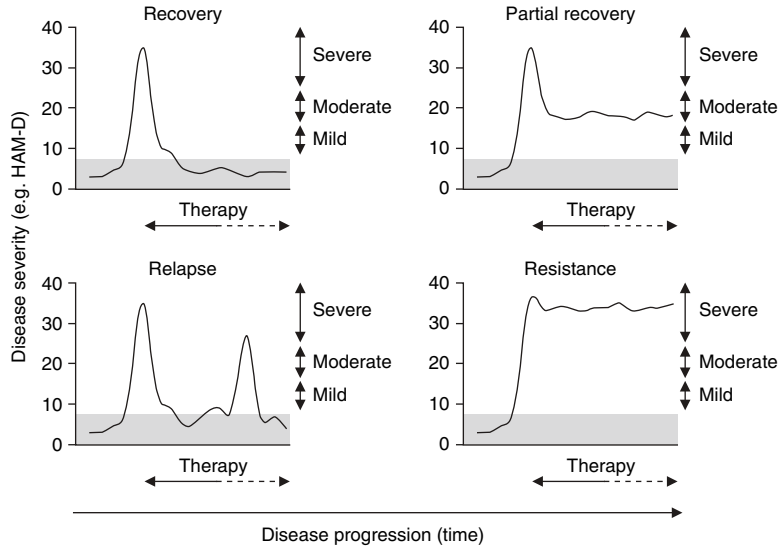

Fig. 5. Major depressive disorder (MDD); pathways to recovery. Graphs depicting the possible disease path in patients with MDD using the Hamilton Depression Rating Scale (HAM-D) as an indicator of disease severity. A HAM-D score < 8 generally signifies the absence of depression (grey shaded area), 8–17 mildly depressed, 18–24 moderately depressed and >25 severely depressed. Significant clinical improvement is typically defined as a decrease of >50% in HAM-D scores and remission is defined as a HAM-D < 8. For information on the development of the HAM-D see Endicott et al.[130]

CYP2D6 and may therefore cause serious interactions with drugs metabolized by this isoenzyme. In other words, although drugs of this class share a common target, they are not all the same and have differing effects that need to be considered when selecting the appropriate drug for the individual patient. This also suggests that better identification and delineation of patient subgroups at elevated risk of adverse events, and the pathways by which they occur, may better target appropriate therapy of depression, CHD and their co-occurrence.

There is a reasonably sound theoretical basis indicating that certain antidepressant drugs should be avoided in patients with existing cardiac disease. The CAST (Cardiac Arrhythmia Suppression Trial) demonstrated an increase in mortality among patients given antiarrhythmic agents.[159] Therefore, tricyclic antidepressants should be avoided in patients after a MI because of their 1A antiarrhythmic action. The ability of this class of drug to block the neuronal reuptake of noradrenaline provides further grounds for avoidance in these patients. Reuptake of noradrenaline into sympathetic nerves after its release terminates the neural signal. A fault in transmitter inactivation augments the effects of sympathetic nerve traffic. In the heart, approximately 95% of released noradrenaline is recaptured into sympathetic nerves,[160] so the heart is more sensitive than all other organs to impairments in transmitter reuptake.[161,162] An abnormality in neuronal noradrenaline reuptake could sensitize the heart to sympathetic activation and mediate further cardiac risk. The use of monoamine oxidase inhibitors is probably also not advisable in this cohort, given that use of these drugs requires avoidance of tyramine-containing foods, and dietary noncompliance can trigger a hypertensive crisis. Similarly, serotonin-noradrenaline reuptake inhibitors, such as venlafaxine[163] and sibutramine,[156] may not be suitable for those with vascular disease because of their propensity to raise blood pressure.

Given that HPA axis activation is commonly observed in patients with MDD, it is perhaps surprising that there are limited therapeutic agents that specifically target the HPA axis. The HPA axis is regulated by the neuropeptides corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which are synthesized in parvocellular neurons in the paraventricular nucleus of the hypothalamus. Both CRH and AVP are secreted into the hypophysial portal blood system and are transported to the anterior pituitary gland, where they stimulate the release of ACTH which, in turn, stimulates the adrenal gland to secrete cortisol. Cortisol exerts negative feedback control on the secretion of CRH, AVP and ACTH. The synthesis and secretion of CRH and AVP are influenced by various stimulatory and inhibitory neural inputs from within the CNS (for a review see Tilbrook[164]). Indeed, activation of the HPA axis, as is frequently documented in patients with MDD, could occur as a result of alteration in regulation at a number of levels. There may be reduced synthesis of CRH and AVP; decreases in CNS stimulatory inputs, such as noradrenaline; increases in CNS inhibitory inputs, such as from oxytocin; and reduced responsiveness of the pituitary to the actions of CRH and AVP or of the adrenal gland to ACTH.

Given this complexity of HPA axis regulation it is difficult to ascertain which pathways should be preferentially targeted in order to normalize HPA axis function in MDD. The inability of CP-316311, a selective antagonist of CRH type 1 receptors, to demonstrate efficacy in the treatment of MDD[165] indicates that CRH is not the prime mover in HPA axis regulation in MDD. In theory, the increase in cortisol commonly observed in patients with MDD could also be targeted by treatments utilizing oxytocin, a hormone that has anxiolytic effects and has been shown to suppress the activity of the HPA axis and reduce levels of cortisol.[166] Given that oxytocin can easily and safely be administered to humans intranasally[166] and that a negative association between oxytocin and severity of illness in patients with depression has been demonstrated,[167] the merit of oxytocin therapy in limiting HPA axis activation in MDD should be considered.

The effective completion of cardiac rehabilitation programmes in patients following MI improves exercise tolerance, quality of life and

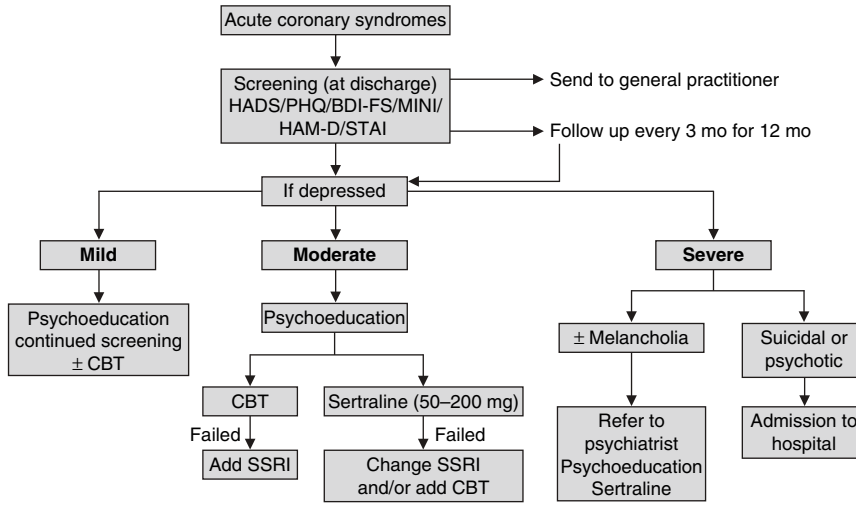

Fig. 6. Possible evidence-based treatment algorithm for cardiac patients with major depressive disorder. Screening tools include, but are not limited to, the Beck Depression Inventory Fast Screen (BDI-FS),[174] Hamilton Depression Rating Scale (HAM-D),[179] Patient Health Questionnaire (PHQ),[180] Hospital Anxiety Depression Scale (HADS),[181] Spielberger's State and Trait Anxiety Inventories (STAI)[182,183] and the Mini International Neuropsychiatric Interview (MINI).[178] Note: while at present the best evidence is for sertraline,[143] other selective serotonin reuptake inhibitors (SSRIs) may also be utilized. **CBT** = cognitive-behavioural treatment.

cardiac risk factors such as cholesterol and triglycerides.[168] Importantly, attendance at cardiac rehabilitation is not an arbitrary matter, with data indicating diminished compliance in those with more severe illness or with symptoms of depression and anxiety, those not in paid employment, those from deprived areas and those who exercise infrequently.[20,169] This strongly supports the development and implementation of strategies that will facilitate participation in cardiac rehabilitation programmes. Milani and Lavie[168] demonstrated the effectiveness of a structured cardiac rehabilitation programme in reducing depressive symptoms in elderly patients following MI. Importantly, significant improvements in depressive symptoms were evident in both moderately and severely depressed individuals. Which aspects of the cardiac rehabilitation confer the beneficial effect on depression symptoms is not known. In patients following a recent MI, Stern et al.[170] compared exercise therapy and group counselling versus usual care; both exercise and counselling were demonstrated to significantly reduce symptoms of depression. Regular exercise has been found to be therapeutic, especially in patients with mild depression,[171] and the magnitude of improvement in symptoms was similar to that observed with sertraline but, in this study, not significantly different from placebo.[172] Given that responses were no different from placebo for both interventions, it is possible that this represents a general nonspecific effect in a mildly unwell group. In an analysis of the ENRICHD cohort, Blumenthal and colleagues[173] documented that patients who reported regular exercise had fewer than half the subsequent cardiac events 6 months after MI compared with those who did not regularly exercise. Although patients who exercised more had lower baseline Beck Depression Inventory (BDI)[174] scores and a more pronounced improvement in BDI at 6 months than patients who did not exercise, the survival benefit of exercise was not mediated by changes in depression symptoms.[173]

ECT is not absolutely contraindicated in the post-MI period. It is an effective and safe treatment and may have to be given to a patient with underlying cardiac disease when a severe psychiatric illness threatens the patient's life. It is critical in this situation that all relevant specialties and individuals are consulted and the decision to

treat is a collaborative one. Treatment should be left as long as possible after the acute cardiac event. There is now good evidence that patients with significant cardiac illness can be treated safely and effectively by ECT as long as their medical condition is optimized prior to commencing treatment.[175,176]

5. Conclusion

In summary, the presence of depression in patients with CHD has been demonstrated to increase mortality, with the effect being most prominent in the first 6 months following the cardiac event.[2] While there is currently no definitive evidence that treatment of depression improves longevity in these patients, it is certainly worth improving their depressive symptoms and quality of life. While psychotherapy alone may be the treatment of choice for those with mild to moderate depression, or where pharmacological treatment is either refused or contraindicated or where pharmacotherapy alone has failed, there are few studies documenting the effectiveness of psychotherapy as a treatment for depression in CHD patients. Lesperance and colleagues[177] recently examined the efficacy of citalopram and interpersonal psychotherapy in reducing depressive symptoms in patients with CHD and major depression. While citalopram was superior to placebo in reducing 12-week HAM-D scores, there was no evidence of a benefit of interpersonal psychotherapy over clinical management.

Recognition of patients with depression may be improved if routine screening using validated instruments was instituted for all those leaving hospital after a cardiac event. For patients who screen positive for depression, clinical algorithms could then be developed to assist the general practitioner in implementing evidence-based, safe treatment (see figure 6).

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