

Clinical update

# Depression and cardiovascular disease: a clinical review

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Cardiovascular disease (CVD) and depression are common. Patients with CVD have more depression than the general population. Persons with depression are more likely to eventually develop CVD and also have a higher mortality rate than the general population. Patients with CVD, who are also depressed, have a worse outcome than those patients who are not depressed. There is a graded relationship: the more severe the depression, the higher the subsequent risk of mortality and other cardiovascular events.

It is possible that depression is only a marker for more severe CVD which so far cannot be detected using our currently available investigations. However, given the increased prevalence of depression in patients with CVD, a causal relationship with either CVD causing more depression or depression causing more CVD and a worse prognosis for CVD is probable. There are many possible pathogenetic mechanisms that have been described, which are plausible and that might well be important.

However, whether or not there is a causal relationship, depression is the main driver of quality of life and requires prevention, detection, and management in its own right. Depression after an acute cardiac event is commonly an adjustment disorder than can improve spontaneously with comprehensive cardiac management. Additional management strategies for depressed cardiac patients include cardiac rehabilitation and exercise programmes, general support, cognitive behavioural therapy, antidepressant medication, combined approaches, and probably disease management programmes.

## Keywords

Cardiovascular disease • Depression • Quality of life • Prognosis • Screening • Management

## Introduction

Cardiovascular disease (CVD) and depression are currently the two most common causes of disability in high-income countries and expected to become so for countries of all income levels by 2030.<sup>1</sup> The key health system and economic indicators relating to CVD and depression reveal rising medical costs,<sup>2</sup> increased health service utilization,<sup>3</sup> and lost productivity.<sup>4,5</sup> Additionally, CVD and depression profoundly impact the overall quality of life,<sup>6,7</sup> even more so for heart failure patients.<sup>8</sup> One could argue that depression is probably the most important driver of overall quality of life.

The prevalence of unrecognized depression in cardiac patients has been noted for more than 40 years. In a seminal paper from Australia by Wynn in 1967, of patients with perceived disability after myocardial infarction, 40% were depressed and in many of them this had not been previously recognized.<sup>9</sup> In 1972, Cay *et al.* found symptoms of depression and anxiety in two-thirds of consecutive patients after admission for cardiac events.<sup>10</sup>

The patient burden of co-morbid CVD and depression would seem to warrant targeted intervention. In this review, we clarify the prevalence, aetiology, and prognosis of depression in CVD patients. We also explore the relationship between depression and other psychosocial factors, such as anxiety and social isolation. Drawing on the most recent research evidence, we examine psychosocial and pharmacological intervention strategies to manage depression in the context of CVD, noting the need for ongoing randomized controlled trials. Finally, we review the potential benefits of using an integrated, multi-disciplinary approach to CVD patient care and management.

## Diagnostic issues: characterizing depression in cardiovascular disease

The word 'depression' has many meanings ranging from a transient feeling of flat mood, through to serious clinical syndromes that can

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be severe, disabling, and recurrent. In addition, some persons seem to have a more distressed, enduring personality including some features of depression.<sup>11</sup> Depression generally involves symptoms such as a feeling of depressed mood, a loss of interest or pleasure in activities, sleep disturbance, fatigue, or impaired concentration.

Mostly the severity of what is experienced as depression occurs as a continuous variable. However, sometimes we use specific criteria for dichotomizing data. This allows us to organize information into useful 'diagnostic' groups. There are a number of ways in which this is done. One of the most commonly used is the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) of the American Psychiatric Association that has evolved over a number of decades.<sup>12</sup> Certain criteria are used to classify an individual as having dysthymia (a disorder of mood), grief (a reaction to loss), adjustment disorder with depressed mood (a time limited reaction to an event) or major depressive disorder (MDD—with a greater number and severity of symptoms associated with depression). All of these syndromal clusters can occur in cardiac patients.

There are a number of psychological reactions that can potentially occur after acute medical events.<sup>13</sup> Depressed mood is commonly experienced as a reaction to an acute coronary event, or for that matter to any illness or operation perceived to threaten one's life and well-being. If patients are comprehensively managed, this depression can be of a temporary nature and therefore, classified as an adjustment disorder. Thus, the most common form of depression experienced after acute coronary events is an 'adjustment disorder with depressed mood'.<sup>14,15</sup> This is seen in the non-treatment control groups of randomized trials treating depression in cardiac patients, in whom there is a marked reduction in depression over time.<sup>16–18</sup>

While preventing and managing any depression is important for all cardiac patients, patients who fulfil criteria for MDD are at high risk for further events and have particularly poor quality of life. Thus, these patients especially require sensitive detection, accurate diagnosis, and careful management.<sup>19–22</sup>

## Epidemiology, aetiological relationship, and prognostic implications of depression in cardiovascular disease

### Epidemiology

The reported prevalence of depression in patients with cardiac disease is quite variable.<sup>23,24</sup> It has long been recognized that mild forms of depression are found in up to two-thirds of patients in hospital after acute myocardial infarction (AMI),<sup>10</sup> with major depression generally being found in ~15% of CVD patients.<sup>23</sup> This prevalence is over two to three times that found in the general population, although perhaps not much greater than the predicted life-time prevalence for the general population.<sup>25</sup> It is even more prevalent in chronic heart failure (CHF) patients, generally over 20%, with the prevalence being related to the severity of the functional class, ranging from 10% in asymptomatic patients to 40% in those with severe functional impairment.<sup>26</sup> Depression in CHF patients is also an independent predictor of mortality and rehospitalization.<sup>27</sup>

Two years after receiving an implantable cardioverter defibrillator, over one quarter of patients are depressed, those patients experiencing more shocks being significantly more likely to be depressed.<sup>28</sup> On average, it would appear that 15–20% of patients have major depression after coronary artery bypass surgery and probably another 15% experience minor depression or significantly depressed mood.<sup>29</sup>

### Aetiology

Given that depression is more common in cardiac patients, it would seem that either depression leads to CVD, CVD leads to depression, or maybe both.<sup>30</sup> There is no argument that depression is a risk marker for an increased incidence of new CVD (aetiology) and a worse outcome in existing CVD (prognosis).<sup>23,31</sup> For depression to be causally related to CVD incidence and prognosis, one would need to demonstrate that depression was a 'risk factor' rather than just a 'risk marker'. This predicates longitudinal assessment of patients, including: objective and prospective measurement of CVD; a consistent, strong, and graded relationship; the association not being explicable by known covariates; potential biologically plausible mechanisms; and eventually trial evidence, demonstrating that altering the risk factor changes the prognosis. All except for the last have been demonstrated for depression and CVD, putting it in a similar category to high-density lipoprotein cholesterol or C-reactive protein.

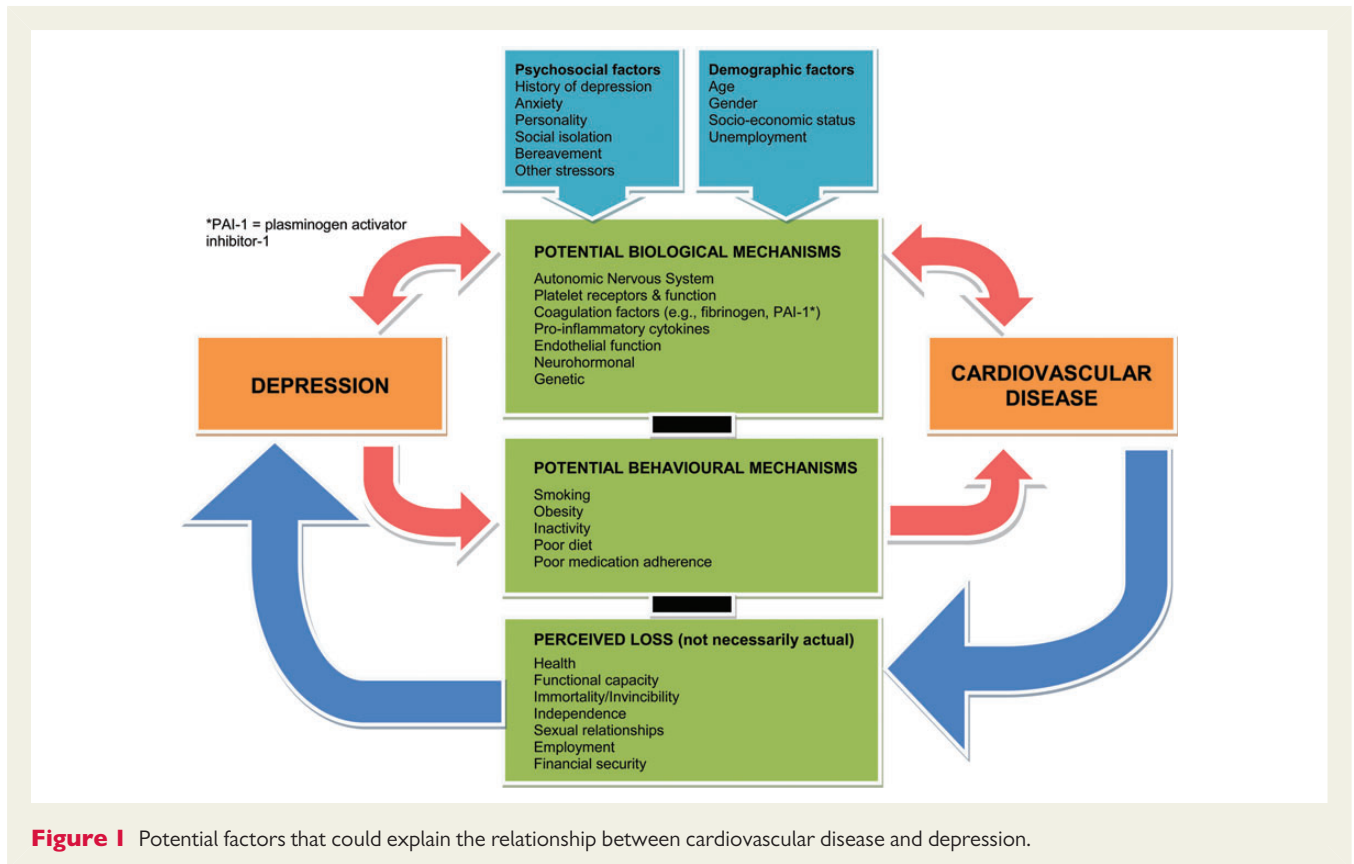
On average, aetiological studies suggest that the presence of depression doubles the risk of developing new CVD.<sup>31</sup> An important longitudinal study of Danes born in 1914 demonstrated that depression, assessed in 1964 and 1974, predicted a highly significant 70% increase in myocardial infarction, and a 60% increase in all-cause mortality, at follow-up 17 years later in 1991.<sup>32</sup>

Another approach has been to use case-control studies. In the large INTERHEART study, the four most important factors contributing to presentation with acute coronary syndromes were a comprehensive lipid profile using Apolipoprotein B/Apolipoprotein A ratio, smoking, psychosocial factors (predominantly depression, stress, life events and locus of control) and then diabetes.<sup>33</sup> In the control group, the prevalence of major depression was about the same as in most non-cardiac populations (7%), but ~50% higher in the AMI group. However, this only contributed about 9% of the attributable risk, less than some of the other psychosocial factors.<sup>34</sup>

There are a number of putative mechanisms that are biologically plausible. These include alterations in the autonomic nervous system,<sup>35</sup> platelet receptors and function,<sup>36</sup> coagulopathic factors such as plasminogen activator inhibitor-1 and fibrinogen, pro-inflammatory cytokines,<sup>37</sup> endothelial function, neurohormonal factors, and genetic linkages such as with the serotonin transporter mechanism.<sup>38,39</sup> In addition, depression is associated with poor adherence to medical treatment.<sup>40</sup> However, it is not likely that a single simplistic aetiological model will be found (Figure 1).<sup>41</sup>

### Prognosis

Depression is a powerful predictor of survival after AMI<sup>31,42,43</sup> and also in CHF patients.<sup>27,44,45</sup> Patients with depression after AMI have a three-fold increase in mortality, even when adjusted for age, sex, smoking, clinical severity using the Killip class and left ventricular ejection fraction. There is also a gradient of relationship with the degree of depression predicting the 5-year survival rate.<sup>46</sup> This



increased mortality in depressed patients is also true for patients admitted with unstable angina.<sup>47</sup>

#### Depression in CVD

- (a) *Adjustment disorder with depressed mood*
  - (i) Response to stressful life events
  - (ii) Observed in as many as half of CVD patients
  - (iii) Often resolves with reassurance, social support, and education
  - (iv) Sometimes continues as a major depressive disorder
- (b) *Major depressive disorder*
  - (i) Maladaptive response to stressful life events
  - (ii) Often an underlying 'biological' substrate
  - (iii) Prevalence compared with the general population: double for ischaemic heart disease and triple for CHF patients
  - (iv) Indicates a higher risk of mortality and morbidity
  - (v) Requires specific intervention

## Depression and other psychosocial issues

### Anxiety

Anxiety is common in CVD<sup>48</sup> and a high proportion of depressed CVD patients suffer a co-morbid anxiety disorder.<sup>49</sup> Anxiety is

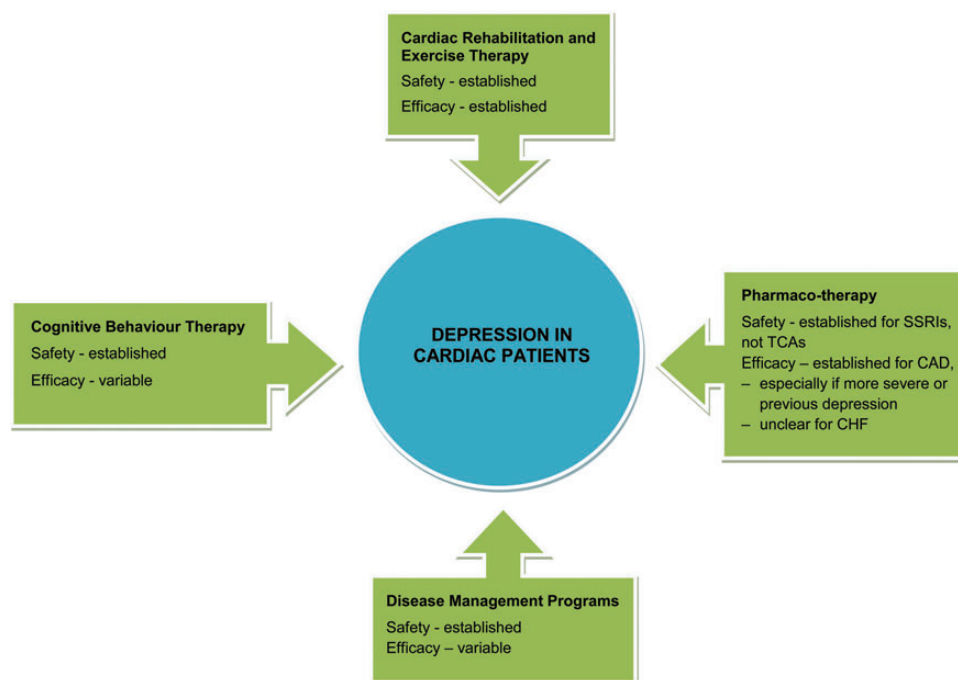
independently associated with increased mortality in coronary heart disease patients, particularly in the presence of comorbid depression.<sup>50</sup> Anxiety and depression share some similar pathophysiological features. The changing trajectory of anxiety and depression after AMI was first described many years ago.<sup>51</sup> The presence of anxiety early after an acute cardiac event predicts the later development of depression.<sup>52</sup> Clearly, the presence of anxiety together with depression requires further consideration when planning appropriate management strategies.

### Quality of life

Improvement or restoration of quality of life is an important aspect in the management of CVD patients. Cross-sectional studies of CVD patients confirm a strong association between depression and quality of life.<sup>53</sup> One could argue that depression is actually the most important driver of overall quality of life.<sup>54</sup> In CHF patients, it seems that depression more strongly predicts the quality of life than sociodemographic variables, lifestyle issues such as alcohol and smoking, heart failure severity (using NYHA functional class, left ventricular ejection fraction, N-terminal pro-brain natriuretic peptide), or co-morbidities.<sup>55</sup> Conversely, social factors and health status, with poor quality of life on the Kansas City Cardiomyopathy Questionnaire, also can predict the later development of depression in CHF patients.<sup>56</sup>

### Social isolation

There are many psychosocial issues that are important to managing CVD patients<sup>54</sup> that cannot be discussed in detail here but a few



**Figure 2** The effects of interventional therapies on depression in cardiac patients.

will be alluded to. The association between social isolation and subsequent mortality has been recognized for many years.<sup>57</sup> In addition, there is a close relationship between depression and social isolation, with both having a major impact on the quality of life as well as mortality. It has been suggested that the diminished quality of life associated with social isolation in CHF patients might be mediated by depression.<sup>58</sup> It is important to prevent worsening social isolation by minimizing additional contributing factors such as loss of employment.<sup>59,60</sup> The provision of social support by caregivers, such as family members, is very important. However, they in turn need support.<sup>61</sup> Using path analytic modelling in CHF patients, it has been demonstrated that depression in a partner has a much greater detrimental effect on patient depression than either poor left ventricular ejection fraction or functional class.<sup>62</sup> In addition, caregiver 'burnout' has been demonstrated to place the patient at additional risk of depression.<sup>63</sup>

## Adherence and self-care

Non-adherence has a significant clinical and economic burden.<sup>64</sup> There is a close association between depression and medication adherence.<sup>40,65–67</sup> The rate of medication non-adherence in depressed CVD patients is probably double that of non-depressed patients.<sup>65</sup> Similarly, depressed patients are less likely to adhere to beneficial lifestyle behaviours, such as engaging in regular physical activity and smoking cessation. It has been shown that improvement in depression is independently associated with superior self-reported adherence to medications and secondary prevention behaviours, whereas improvement in anxiety is not.<sup>68</sup> So, it is possible that preventing and treating depression might improve patient adherence. In a recent randomized trial, improving depression did not seem to

have a big impact on patient adherence.<sup>69</sup> However, this needs to be further tested in larger randomized trials, maybe with further interventions specifically designed to improve adherence. A number of interventional proposals have been suggested to improve outcomes,<sup>70</sup> but there is a need for much more research in this area *Figure 2*.

## Management

### Cardiac rehabilitation programmes

Cardiac rehabilitation is an essential component of the comprehensive management of cardiac patients, largely to reduce the detrimental emotional, psychosocial, and physical sequelae of cardiac events, while setting the pattern for long-term secondary prevention.<sup>59</sup> The key components of programmes include reassurance, education, and exercise.

While there is an ongoing debate as to whether or not, in the current era of patient management, cardiac rehabilitation programmes still significantly reduce cardiovascular events,<sup>71,72</sup> there are plenty of data showing improvement in depression and other aspects of quality of life.

Cardiac rehabilitation, based on exercise training in a group setting, results in less depression.<sup>73</sup> It is unclear as to whether the benefit is primarily from the exercise itself or the accompanying group dynamics that can foster camaraderie as a source of psychological support.<sup>59</sup> There are randomized trial data suggesting that when comparing high with low intensity exercise in a group setting, there is no significant difference in the level of depression either early at 3 months or later at 12 months after AMI.<sup>74</sup>

A comprehensive, structured home-based cardiac rehabilitation programme has been demonstrated to reduce both depression and anxiety<sup>75</sup> and might be as effective as a hospital-based programme.<sup>76</sup> However, a recent meta-analysis of selected cardiac rehabilitation programmes in both coronary artery disease and CHF settings, while generally showing significant reduction in depression, shows some variability in outcomes.<sup>77</sup> The exact components of cardiac rehabilitation programmes that result in the benefits are still not completely clear.

## Exercise programmes

In coronary heart disease patients, aerobic exercise in a group setting appears to have a similar impact on reducing depression to anti-depressant medication, those randomized to exercise also having a higher VO<sub>2</sub> peak.<sup>78</sup>

It also appears that exercise training reduces depression in heart failure patients. In the HF-ACTION trial, the pre-specified combined end-point of death or hospitalization, adjusted for baseline variables, was approximately 10% lower for the exercise group. The exercise group had significantly less depression at both 3 and 12 months.<sup>79</sup>

## Talking therapies

### General support

It is likely that general information, advice, and reassurance from a perceived medical authority figure is beneficial. However, this is difficult to test in clinical trials: an adequate control group would really be unethical. If facilitated by appropriately experienced personnel, general support from a group provides reassurance, camaraderie, positive modelling (on other patients), and appropriate planning for involvement in usual occupational and leisure activities.<sup>59</sup>

### Cognitive behaviour therapy and problem solving

Cognitive behaviour therapy (CBT) was originally developed 50 years ago for the management of depression. Cognitive behaviour therapy aims to counteract psychological disorders or problems that arise from dysfunctional thoughts, feelings, and behaviours that develop early in life and can become activated in response to stress.<sup>80</sup> In the context of depression, negative perceptions of the 'self, experience and future' (p.400) are maintained through selective information processing that focuses attention on, and thus recall of, information that reinforces it.<sup>80</sup> Patients are taught to modify thoughts (that are not consistent with evidence), change maladaptive behaviours, and develop skills for coping with negative feelings.

The outcomes of studies using CBT in depressed cardiac patients have been variable. A recent meta-analytic review by Dickens *et al.*<sup>81</sup> proposed that CBT and problem solving may benefit CVD patients, but that the small treatment effects suggest the need for ongoing development to optimize treatment efficacy. A number of studies demonstrating the efficacy of CBT in reducing depression in cardiac patients have used CBT in combination with other treatment strategies, such as anti-depressant medication<sup>16</sup> or exercise.<sup>82</sup>

Cognitive behaviour therapy is as overall effective for improving depression as changing anti-depressant medication in those having an initially unsatisfactory response. However, increasing the dose of anti-depressant medication seems to produce more rapid remission than adding CBT.<sup>83</sup> There is even some evidence raising the

possibility that CBT might even reduce subsequent cardiovascular events.<sup>84</sup>

### Interpersonal psychotherapy

The CREATE study involved a three-way randomization to explore the effects of interpersonal psychotherapy as well as selective serotonin receptor reuptake inhibitor (SSRI) therapy. Those randomized to interpersonal psychotherapy had no improvement in depression, when compared with the control group. This indicates that, if this kind of therapy is to be recommended, much more thought will need to be given as to what is provided and by whom it is provided.<sup>18</sup>

## Pharmacological treatment: anti-depressant medications

Anti-depressant medications, most commonly used are those in the SSRI class, have been demonstrated to improve depression in cardiac patients, particularly those with recurrent or severe depression.<sup>16–18</sup> Patients with more severe or recurrent depression generally need referral for formal psychiatric consultation (Table 1).

The intervention in the ENRICH study was actually a combination of CBT and SSRI, with sub-group analysis suggesting that perhaps there was more effect on reducing cardiovascular events in those who actually received the SSRI.<sup>16</sup>

These randomized trials showed that the greatest benefits were for those who had a previous history of major depression or had more severe depression at trial entry. While to a lesser degree than the intervention group, the control groups also had an overall significant reduction in depression, in keeping with the concept that much depression in cardiac patients is actually an adjustment disorder with depressed mood rather than a major depression disorder.<sup>14</sup> There was no reduction in cardiovascular events from treating the depression in the ENRICH and SADHART studies.<sup>16,17</sup> The CREATE study did not have clinical events as a primary end-point.<sup>18</sup> Some trials have not shown benefit from anti-depressant medication in cardiac patients, possibly because of methodological issues.<sup>85</sup>

Up until now, anti-depressant medication has not been demonstrated to significantly reduce the burden of depression in CHF patients.<sup>86</sup> This could be because either the good care of the control group overshadowed the additional benefits of the SSRI, the majority of patients remained on fairly low doses of SSRI, the treatment duration of only 3 months was too short, the nature of the heart failure drove the depression to a level that was not reversible with an SSRI anyway, or all of the above.

With pharmacological treatment of depression, there is always a balance between efficacy and acceptability. For example, there is some evidence that mirtazapine (a tetracyclic), venlafaxine (SSRI at low dose, noradrenergic at moderate dose, and dopaminergic at high dose), escitalopram, and sertraline (both SSRI medications) have the best efficacy, while the best balance between efficacy and acceptability is perhaps best for escitalopram and sertraline.<sup>87</sup>

With pharmacological treatment of depression in cardiac patients, there is also always the issue of efficacy vs. potential risks. One of the principal potential risks of anti-depressant medications is their effect on lengthening cardiac myocyte action potentials. This is particularly true for tricyclic anti-depressants, somewhat less for tetracyclics and significantly less so for the SSRI class.



**Table 1** Major randomized controlled trials to evaluate the effects of anti-depressant pharmacotherapy on depression in cardiovascular disease settings

Trial	Study Population	Entry Criteria	RCT Groups	Treatment Period	Outcome		
ENRICH <sup>16</sup>	2481 patients >28 days post-AMI	Depression (major, minor, dysthymia) +/or low perceived social support	Usual care vs. CBT with stepped SSRI after 5 weeks if indicated	CBT 6M SSRI 6-12M	Depression (BDI): Recurrent MI + All-cause mortality:	6 months 4 years	Benefit No benefit
SADHART <sup>17</sup>	369 patients <30 days post-ACS	MDD	Placebo or Sertraline	6 months	Depression (HAM-D): Previous MDD or severe depression LVEF:	6 months	No benefit Benefit
SADHART-CHF <sup>86</sup>	469 patients CHF	MDD	Placebo or Sertraline	3 months	Depression (HAM-D): Composite CV Score:	3 months 3 months	No benefit No benefit
CREATE <sup>18</sup>	284 patients Previously documented CAD	MDD	Usual care or IPT and Citalopram or Placebo	3 months	Depression (HAM-D, BDI-II)	3 months 3 months	Benefit— citalopram No benefit— IPT
UPBEAT <sup>78</sup>	101 patients Documented CAD	BDI $\geq 7 \pm$ MDD	Placebo or Exercise (x3/week) or Sertraline	4 months	Depression (HAM-D):	4 months Exercise = Sertraline	Benefit

ACS, acute coronary syndrome; BDI, Beck depression inventory; CAD, coronary artery disease; CBT, cognitive behaviour therapy; CHF, chronic heart failure; CV, cardiovascular; HAM-D, Hamilton Depression; IPT, interpersonal psychotherapy; LVEF, left ventricular ejection fraction; MDD, major depressive disorder; MI, myocardial infarct; RCT, randomized clinical trial; SSRI, selective serotonin reuptake inhibitor.

In isolated cardiac myocytes, anti-depressants have differing potency on the inhibition of the rapidly activating, delayed rectifier cardiac outward potassium current (IKr) that predisposes to serious cardiac arrhythmias, and in particular torsade de pointes ventricular tachycardia. This is more pronounced for tricyclic anti-depressants than SSRIs. This channel is also blocked by sotalol and amiodarone, although amiodarone contributes somewhat less overall torsade de pointes risk. In addition, this risk could be accentuated by the concomitant use of medications that share or actually inhibit metabolic pathways with the anti-depressants, such as cytochrome-2D6 metabolism that is inhibited by amiodarone and partly used by both metoprolol and carvedilol.

Overall, SSRI medications have good efficacy in treating depression and for reasons of safety, they are generally the anti-depressants of choice for cardiac patients. Of the SSRIs currently on the market, escitalopram has the highest affinity for the human serotonin transporter. It is the dextro (S) - enantiomer of racemic citalopram with about twice the efficacy of citalopram. One would need a good reason for exceeding either 20 mg of escitalopram or 40 mg of citalopram in cardiac patients because of safety concerns, especially in patients who are over 65 years of age, have low serum potassium or magnesium levels, have CHF, or are on other medications that could potentially inhibit cytochrome-2C19 metabolism, such as omeprazole. In general, tricyclic anti-depressants are not used as first-line therapy in cardiac patients because of the potential increased risk of ventricular arrhythmias.

There can be some benefit from switching to another anti-depressant if the first is either not tolerated or fails to produce remission of depressive symptoms. In non-cardiac patients, after initially trying the SSRI citalopram, switching to another anti-depressant can result in additional benefits.<sup>88</sup> Because it more resembles a tricyclic antidepressant when used in higher doses, venlafaxine should be avoided in high doses in cardiac patients unless the slow-release form is used with regular ECG monitoring. Mirtazapine seems to have less cardiac side-effects than tricyclic anti-depressants, although its peripheral alpha-receptor blockade occasionally leads to orthostatic hypotension.

It cannot be assumed that all anti-depressants have equivalent safety in cardiac patients, especially in CHF patients who can have prolonged myocyte action potentials in the middle M-band of the myocardium, even in the presence of a normal QTc interval on the surface electrocardiogram. Thus, particular care should be taken when using anti-depressant medication in CHF patients. When the QTc interval is borderline, such as 450 ms for a male or 470 ms for a female, the improved quality of life for the patient has to be balanced against any potential arrhythmic risk. The cardiologist needs to take responsibility to ensure that any anti-depressant treatment is being undertaken safely.

### Genetics

The target of SSRIs is the serotonin transporter (SERT), a trans-membrane monoamine transporter protein that transports the

serotonin or 5-hydroxy-tryptamine neurotransmitter from synaptic spaces back into the presynaptic neurons. Of interest is that SERT is also present in platelets where serotonin acts as a vasoconstrictor. This provides a potential pathogenetic link between the depression and increased cardiovascular events.

However, the relationship between SERT and depression remains unclear. The gene that encodes SERT is found on chromosome 17 and is called solute carrier family 6, member 4 (SLC6A4). The promotor region of this gene contains a polymorphism called the serotonin-transporter-gene-linked polymorphic region or 5-HTT-linked polymorphic region (5-HTTLPR). The promotor gene was initially shown to be related to the development of depression, although a subsequent meta-analysis has failed to confirm this.<sup>89</sup>

Another non-coding polymorphism is a variable number tandem repeat in intron 2. This has also been associated with affective disorders, major depressive disorder and bipolar disorder. However, further investigation is needed.<sup>90</sup>

There have also been studies associating brain imaging with genetics. For example, there are changes in the perigenual anterior cingulate cortex and amygdala in subjects that carry the short rather than long allele of the 5-HTTLPR polymorphism.<sup>91</sup> These findings remain intriguing.

## Combined approaches

The use of combination therapies has been shown to reduce depression after acute coronary syndrome (ACS). The ENRICHED randomised trial of 2481 patients with depression or low perceived social support after myocardial infarction, started with CBT and, if there was still significant depression after 5 weeks, the patients were referred for the initiation of sertraline.<sup>16</sup> There was a significant reduction in depression at 6 months, this difference being lost by 30 months of follow-up. Whilst there was no overall effect of the combined intervention on the primary end-point of death or non-fatal myocardial infarction, sub-group analysis produced the tantalising finding that the introduction of the anti-depressant medication was associated with a significant 33% reduction in the primary end-point and a 39% reduction in all-cause mortality. Whilst not all data are concordant, there is some evidence that platelet activation, in depressed patients with ischaemic heart disease, seems to be inhibited by SSRI anti-depressants.<sup>92</sup>

In a recent multicentre randomised controlled trial of patients with at least some depression (Beck Depression Inventory score  $\geq 10$ ) 2–6 months after an ACS, a combined therapeutic approach of 'stepped' care resulted in significantly less depression after 6 months compared with usual care.<sup>93</sup> Whilst most participants chose to start with a problem-solving intervention, half were also receiving anti-depressant medication by the end of the study because of persisting depression.

## Disease management programs

Disease management programs (DMPs) are now used in a range of chronic disorders, both cardiac and non-cardiac,<sup>94</sup> with the goal of reducing hospital admissions and improving patient health outcomes.<sup>95</sup> These aim to optimise medication regimens and to improve both patient adherence and self care through education and skills-based training. DMPs are commonly put in place for CVD patients, although their clinical efficacy still remains uncertain.<sup>96</sup> The six month

structured telephone management of the Coaching patients On Achieving Cardiovascular Health (COACH) programme significantly improved lipids, diet, weight, exercise and mood, the improvement being maintained two years later.<sup>97</sup> Depression was a significant predictor of overall poor adherence. The Coordinating study evaluating Outcomes of Advising and Counseling in Heart Failure (COACH), a completely separate study using the same 'COACH' acronym, found no significant difference in mortality or hospital admission rates in HF patients randomly assigned to an 18 month program of moderate or intensive DMP compared to usual care<sup>98</sup> and in a secondary subgroup analysis they even found worse outcomes for depressed patients.

The need for patients to assume an active role in their DMP may mean that those most likely to benefit from such programs (such as depressed CVD patients) are also least likely to be sufficiently motivated to engage in self-management.<sup>99</sup>

A 12 week multi-component collaborative care programme has been demonstrated to significantly reduce depression.<sup>100</sup> Similarly, another randomised trial has demonstrated significant improvements in depression with the use of nurses as case managers.<sup>101</sup> Future research is needed to test the differing elements of DMPs.

## Detection of depression

### Screening Tools

Most studies have predominantly screened for MDD or a cut-off score on a self-report scale that purports to 'diagnose' MDD. These self-report questionnaires have variable sensitivity and specificity and the higher the area under the receiver operating characteristic curves (AUC), the better. Some are used as a first-step screening that requires a subsequent 'clinical diagnosis' of MDD. Others have satisfactory psychometric properties for 'diagnosing' MDD as a single step.

Self-report questionnaires include the Patient Health Questionnaire (PHQ), Beck Depression Inventory (BDI),<sup>102</sup> Hospital Anxiety Depression Scale (HADS),<sup>103</sup> Cardiac Depression Scale (CDS),<sup>14,21</sup> and the Center for Epidemiologic Studies Depression Scale-10 (CES-D).<sup>104</sup> The majority of these scales are available, and have been validated in many different languages. Some such as the BDI are under copyright but most are in the public domain. Some of the outcomes related to screening have been summarized by Thombs *et al.*<sup>22</sup>

An American Heart Association Science Advisory suggested that the PHQ might be the most useful.<sup>20</sup> The PHQ2 comprises two items that inquire about the patients' mood and experience of anhedonia in the last 2 weeks. The PHQ9 expands upon the PHQ2 to include seven additional DSM-IV depression symptoms. Whilst well validated in many non-cardiac populations, in coronary artery disease patients, McManus<sup>105</sup> found that while having good specificity, the PHQ2 had only 39% (AUC 0.84) and the PHQ9 54% sensitivity (AUC 0.87) at the recommended cut scores. A simple yes/no answer on the PHQ2 performed better. Stafford *et al.*<sup>106</sup> found a similar 54% sensitivity for the PHQ9 diagnosing MDD (AUC 0.88) at the generally accepted cut score of 10 with sensitivity coming up to 82% when the cut-off score was dropped to  $\geq 6$  but with a drop in specificity to 79%.

Using the standard score of  $\geq 8$  on the HADS for diagnosing depression in cardiac patients, Stafford *et al.*<sup>106</sup> found that the sensitivity

was only 46%, with AUC 0.87. Dropping the cut-off score to  $\geq 5$  improved the sensitivity to 86%, while dropping the specificity down to 75%. Nevertheless, the HADS has been used successfully as a diagnostic and monitoring tool in cardiac populations.

The BDI has the advantage of possibly being the most common tool used in studies with cardiac patients. Its disadvantage is that it forms a very skewed distribution of scores in cardiac patients<sup>14</sup> because it was originally designed to measure the severity of depression in psychiatric patients. In the majority of studies, a score of  $\geq 10$  is used to diagnose clinical depression.

The CDS was originally developed in cardiac patients for measuring the full range of depressive symptoms in this population<sup>14</sup> and to have responsiveness to change over time and sensitivity to detect differences between interventions. However, it also has excellent properties for the diagnosis of MDD, a score of  $\geq 95$  having a 97% sensitivity at 85% specificity (AUC 0.96).<sup>21</sup>

McManus et al.<sup>105</sup> found that the shorter 10-item CES-D, using the standard cut-point of  $\geq 10$  for diagnosing depression, had 76% sensitivity at 79% specificity (AUC 0.87).

The European Guidelines on cardiovascular disease prevention suggest two core questions that cover elements of the two mandatory criteria for the diagnosis of MDD: 'Do you feel down, depressed, or hopeless?' and 'Have you lost interest and pleasure in life?'<sup>107</sup> For Type D Personality, a personality characterized by enduring features of depression, they recommend asking: 'In general, do you often feel anxious, irritable, or depressed' and 'Do you avoid sharing your thoughts and feelings with other people?'

## Target population and timing of screening

Given that patients after ACS have two to three times the prevalence of MDD compared with the general population, all post-ACS patients should be screened for depression. Reported depression is often repressed or suppressed in hospital because of initial denial of affect.<sup>51</sup> Therefore, patients should be rescreened for depression 2 months after the acute event. With adequate rehabilitation strategies, development or persistence of depression can be attenuated. Otherwise, it can continue unchanged for at least 12 months.<sup>10,75</sup> Chronic heart failure patients have three to five times the frequency of depression, compared to the normal population. Therefore all of these patients should be screened at least annually.

## Responsibility for screening

The European Guidelines on CVD prevention in clinical practice suggest that depression should be detected, and that patients with clinically significant depression should be offered treatment.<sup>107</sup> Similarly the European Society of Cardiology guidelines for the diagnosis and treatment of heart failure suggest that routine screening for depression with a validated questionnaire is good practice.<sup>108</sup> However, the majority of cardiologists do not believe that they have a role in the detection of depression in their patients. Most believe that it is the responsibility of someone else such as a nurse, rehabilitation programme, or the family physician.<sup>109</sup> In Australia, only 3% of cardiologists routinely screen for depression in their patients.<sup>109</sup> Given that depression is the main driver of quality of life in cardiac patients, cardiologists should not abrogate their responsibility in ensuring that depression is detected. Screening needs to be repeated at regular intervals.<sup>8</sup> Cardiologists can ensure that patients complete a

brief screening tool for depression while they are in the waiting room. Alternatively the cardiologist can ask two simple questions that have some validity for detecting depression: 'Do you feel down or depressed' and 'Have you lost interest and pleasure in life?' There is likely to be an increasing role for other health care professionals including nurse practitioners for detection, discussion and subsequent implementation strategies.

## Summary

Cardiovascular disease is the leading cause of death, disability, and disease burden in the developed world. Depression is common in CVD patients and is linked to higher mortality and morbidity rates. There is sufficient evidence to support the introduction of exercise, talking therapies, and anti-depressant medications to reduce depression in CVD patients. Although research is yet to clearly and consistently identify cardiovascular benefits in this regard, depression is a fundamental determinant of quality of life. In addition, it is a major determinant of patient adherence to appropriate medical and life-style strategies. Many questions remain, and further research is clearly required to unravel potential pathophysiological mechanisms and to determine both the best management strategies and the effects on clinical outcomes.

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