Vascular Health and Risk Management

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REVIEW

# Depression in vascular pathologies: the neurologist's point of view



This article was published in the following Dove Press journal:
Vascular Health and Risk Management
8 July 2011
Number of times this article has been viewed

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**Abstract:** The coexistence of depression and cardiovascular disease (CVD) is regularly discussed, and much debated. There is strong evidence that there are pathophysiological mechanisms, particularly endothelial dysfunction, altered platelet aggregation, and hyperactivation of the thrombosis cascade, which coexist with hypothalamic-pituitary-adrenocortical axis dysfunction, and link depression to CVD. Therefore, depression should not be automatically considered to be a consequence of life impairment due to myocardial infarction or major stroke. Probably, it should be considered as one of the many other stressful events, or "genetic reactions to life", which are risk factors for CVD development. This review will examine the significance of depression in clinical daily practice, its pathophysiology as a determinant in vascular events, and its real importance in, before, and after many CVD events.

**Keywords:** depression, cardiovascular disease, stressful events, cardiovascular risks

## Introduction

Depression is a major condition in the 21st century. Clinicians should consider quality of life, pain, anxiety, loss of sense of humor, depression, and apathy as clinical conditions which have an impact on every specialist field. When dealing with older persons, especially those with chronic disease conditions and comorbidities, depression is an everyday problem for the neurologist and the internal medicine specialist. Behavioral disturbances may have a contribution to the overall morbidity of every disease, especially in elderly patients, and depression may lead to institutionalization,[1,2] mainly due to consequent inadequate nutrition, altered sleep, and problems in adhering to prescription medicine regimes.

There is a well-known relationship between cardiovascular disease (CVD) and depressive disorders.[3–6] The connection is unclear: studies have focused on etiopathogenesis, consequences of inadequate or non-target therapies, and the socio-economic impact of under-diagnosis. However, the effects of antidepressive therapy on CVD overall mortality seem to be limited[7,8] and the analysis of a causal link with cardiovascular drugs has generated conflicting results. The debate is whether altered behavior is generated by CVD, or conversely, whether it precedes CVD.[9] Compared with euthymics, depressed patients are significantly less likely to adhere to prescribed medications, follow lifestyle recommendations, practice self-management, and even attend follow-up cardiac testing. Hence, depression itself may not necessarily be a direct cause of adverse outcome but may serve as a barrier to the delivery of optimal care.

A further possibility is that depression is a secondary event in cardiac patients. In this view, the adverse outcome is the result of the greater disease burden, not of

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depression per se. Several factors go against this explanation. Many studies[6,10,11] have used risk adjustment for cardiac and non-cardiac disease burden in their analyses, and adjustment for these variables does not appear to rule out the relationship, supporting the conclusion that depression is an independent predictor of CV outcome. Moreover, depression precedes cardiovascular disease in community studies, being predictive of first myocardial infarction (MI) and cardiac death in healthy individuals.[9,10]

Antidepressants may well increase the survival of the cardiovascular patient, as shown in a preliminary study on post-stroke depression,[8] although some data reported the persistence of endothelial dysfunction even in treated depression,[12] giving a scientifically plausible explanation of the limited result of the Enhancing Recovery in Coronary Heart Disease Patients Randomized (ENRICHD) trial.[7] Mood may be influenced by health and the pharmacological consequences of a cardiovascular event, so that individuals with more severe disease are more likely to suffer from depressive symptoms.

## Epidemiology

Recently, many studies[4,10,14] have demonstrated that depressive symptoms are a strong predictor of CVD mortality, as are previous MI, diabetes, and cardiac ejection fraction. These studies, however, do not clarify the nature of the relationship between depression and cardiac disease. Depression not only has known neuroendocrine effects that could influence stroke risk, but also may negatively impact on other stroke risk factors.

Several studies have analyzed and supported this association.[14–16] The best epidemiological evidence for a significant positive relationship between depressive symptoms and stroke mortality has been provided by Everson et al.[16] In a 29-year follow-up, they evaluated the association between depressive symptoms and stroke mortality in a community sample of 6676 stroke-free men. After adjustment for established stroke risk factors, individuals reporting 5 or more symptoms of depression at baseline experienced more than a 50% excess risk of mortality due to stroke during the subsequent 29 years, providing compelling evidence that depressive symptoms are significant factors in subsequent stroke mortality.

Another fundamental step in the comprehension of the stroke-depression link comes from the results of Multiple Risk Factor Intervention Trial (MRFIT).[17] Stroke turns out to be the specific CVD cause with which depressive symptoms are associated. Its clinical significance lies in the fact that the risk of stroke in severely depressed patients was twice as high as in nondepressed subjects. However, this study has some limitations. Firstly, the findings are restricted to men at a high risk of CVD and the strength of the depression-stroke association may be typical of populations with a high prevalence of hypertension. Secondly, the assessment of depressive state occurred towards the end of MRFIT and by this time 22% of participants were no longer free of CVD.

It is important to bear in mind that there are also studies that did not confirm the previous association.[18,19]

O'Donnell et al[20] have studied the contribution of known and emerging risk factors to stroke and its primary subtypes, assessed the contribution of these risk factors to the burden of stroke, and explored the differences between risk factors for stroke and myocardial infarction. They undertook a standardized case–control study in 22 countries worldwide between March 1, 2007, and April 23, 2010. Cases were patients with acute first stroke (within 5 days of onset of symptoms and 72 hours of hospital admission). Controls had no history of stroke, and were matched with cases for age and sex. The authors calculated odds ratios (ORs) and population-attributable risks (PARs) for the association of all strokes, ischemic stroke, and intracerebral hemorrhagic stroke with selected risk factors. In the first 3000 cases (n = 2337, 78%, with ischemic stroke; n = 663, 22%, with intracerebral hemorrhagic stroke) and 3000 controls, significant risk factors for all strokes were: history of hypertension; current smoking; waist-to-hip ratio; diet risk score; regular physical activity; diabetes mellitus; alcohol intake, which is normally regarded in general clinical practice as being related to anxiety and mood alteration (OR: 1.51, 95% CI: 1.18–1.92 for more than 30 drinks per month or binge drinking; OR: 3.8%, 95% CI: 0.9–14.4); psychosocial stress (OR: 1.30, 95% CI: 1.06–1.60; OR: 4.6%, 95% CI: 2.1–9.6) and depression (OR: 1.35, 95% CI: 1.10–1.66; OR: 5.2%, 95% CI: 2.7–9.8); cardiac causes; and ratio of apolipoproteins B to A1. Collectively, these risk factors accounted for 88.1% (99% CI: 82.3–92.2) of the PAR for all strokes. These risk factors were all significant for ischemic stroke, whereas hypertension, smoking, waist-to-hip ratio, diet, and alcohol intake were significant risk factors for intracerebral hemorrhagic stroke. The fact that these ten risk factors are associated with 90% of the risk of stroke provided evidence that altered mood, depression, anxiety, binge drinking and psychosocial stress are linked to CVD.

Paranthaman et al[21] tried to explain vascular function in depression. Their study assessed endothelial function, arterial stiffness, and atherosclerosis in a variety of vessel beds in 25 elderly subjects with depressive disorder, compared with 21 nondepressed control subjects. Subjects underwent pulse

wave velocity, pulse wave analysis, carotid intima/media thickness analysis, and magnetic resonance imaging. A subset (16 patients and 15 control subjects) had assessment of biopsied small artery dilatation to acetylcholine to further assess endothelial function. The mean sample age was 72.4 years with an average age at onset of depression of 60 years. Mean carotid intima media thickness was significantly higher in depressed subjects ($P < 0.01$). Pulse wave velocity was 1.6 m/s higher in depressed subjects (borderline significance). There was a significant reduction in the dilatation response to acetylcholine in preconstricted small arteries ($P = 0.01$). On magnetic resonance imaging, depressed subjects had significantly more dilated Virchow-Robin spaces in the basal ganglia ($P = 0.01$). Depressed subjects had a greater volume of white matter lesions in all regions, but this did not reach statistical significance. There were no baseline differences in vascular risk. Paranthaman et al[21] concluded that depression in the elderly is associated with poorer endothelial function and more atherosclerosis. This is associated with a greater white matter lesion load and basal ganglia microangiopathy.

Few studies have examined the relationship between cerebrovascular changes, depression, and long-term prognosis. Yamashita et al[22] examined the effects of cerebrovascular changes on the course of geriatric depressive symptoms, dementia rates, and mortality over a follow-up period of approximately 10 years. Eighty-four patients with major depression (age of onset over 50 years) were enrolled in this study; patients suffering from strokes, neurological disorders, and other psychiatric disorders were excluded. Magnetic resonance imaging findings were used to classify all patients into silent cerebral infarction (SCI)-positive (n = 37) or SCI-negative groups (n = 47). Prognoses were ascertained using a review of clinical charts and mailed questionnaires. Yamashita et al[22] pointed out that only 5% of patients with SCI maintained remission whereas 36% of patients without SCI did so. Total duration of depressive episodes was significantly longer in the SCI-positive group than in the SCI-negative group. SCI was also associated with a higher risk of dementia. The results of this long-term follow-up study demonstrate that the presence of SCI is associated with a relatively poor prognosis in geriatric depression.[22]

These data have been confirmed by other recently published studies. Wouts et al[23] examined the interaction between vascular disease and neuroticism as determinants of clinically relevant depressive symptoms in late-life: the study involved a multivariate logistic regression on data from a survey of 1396 people aged ≥70 years. Clinically relevant depressive symptoms (CRDS) were defined as high scores in the appropriate scale, in particular by the 20-item Epidemiological Studies Depression Scale (CESD) and defined as a score of ≥16. Vascular disease was categorized into four levels: none, ≥2 vascular risk factors, cardiac disease or stroke. Neuroticism was strongly associated with CRDS in women (OR: 1.6, 95% CI: 1.4–1.8). In men, vascular disease interacted negatively but significantly with neuroticism (cardiac disease by neuroticism: OR: 0.8, 95% CI: 0.6–0.9; stroke by neuroticism: OR: 0.8, 95% CI: 0.6–0.96) when predicting CRDS. These authors suggested that in men, vascular disease attenuates the predictive value of neuroticism in CRDS, which might be mediated by apathy caused by cerebrovascular disease.

Apathy, one major determinant of geriatric depression, has been considered a major determinant of poorer outcomes in various clinical conditions;[24,25] very recently, Jorge et al[26] reviewed the available evidence on the frequency, clinical correlates, mechanism, and treatment of apathy following stroke. The frequency of apathy following stroke has been consistently estimated at between 20% and 25%. Jorge et al[26] found that apathy appears to be associated with the presence of cognitive impairment, a chronic course characterized by progressive functional decline, and with disruption of neural networks connecting the anterior cingulate gyrus, the dorsomedial frontal cortex, and the frontal pole with the ventral aspects of the caudate nucleus, the anterior and ventral globus pallidus, and the dorsomedian and intralaminar thalamic nuclei. Apathy is a frequent neuropsychiatric complication of stroke that, although often associated with depression and cognitive impairment, may occur independently of both. Its presence has been consistently associated with greater functional decline. However, there is no conclusive evidence about what is the best treatment for this condition.

There is a newly emerged concept of "vascular depression".[27–29] The depression-executive dysfunction syndrome has been conceptualized as an entity with pronounced frontostriatal-limbic dysfunction. Clinically, it is characterized by reduced interest in activities, psychomotor retardation, impaired function in daily living, suspiciousness, impaired insight, and limited vegetative signs.[30] This syndrome has also been shown to have a poor, slow and unstable response to antidepressant medications[27–30] and may respond better to problem-solving therapy.[31]

These observations formed the basis of the vascular depression hypothesis, according to which cerebrovascular disease may predispose, precipitate, or perpetuate some geriatric depressive syndromes.[32,33] Elderly patients with vascular depression have more apathy, retardation,

and lack of insight and less agitation and guilt than those with nonvascular depression.[32,34] Verbal fluency and naming are the most impaired cognitive functions in vascular depression. Finally, patients with this form of depression have greater disability compared to those who are depressed but have no vascular impairment.[34] The vascular depression hypothesis has led to hypotheses with clinical ramifications. Ameliorating cerebrovascular risk factors (eg, hypertension or hypercholesterolemia) or employing agents promoting vascular integrity (eg, antiplatelet agents, calcium channel blockers, or antioxidants) might reduce the risk of vascular depression. A study using the calcium channel blocker nimodipine as an augmenting agent led to improved antidepressant treatment outcomes compared to antidepressant monotherapy among patients with vascular depression.[35] Furthermore, the choice of antidepressant treatment may be guided by the presumptive knowledge of the underlying vascular etiology. Catecholaminergic enhancing agents promote better functional recovery from ischemic brain lesions in comparison with serotoninergic agents or antidepressants with alpha blocking action.[33]

## Depression and predisposing factors for CVD

Depression is associated with several physiological derangements that could contribute to adverse cardiac outcomes, such as high sympathetic tone, hypercortisolemia, elevated catecholamine levels, abnormal platelet activation and endothelial dysfunction. However, these physiological abnormalities, constantly present in depressed patients, do not always produce CVD.[3,12,36]

In particular, depressive disorder might be characterized by the presence of an abnormal feedback loop involving the prefrontal cortex, the amygdala, hypothalamic-pituitary axis[37] and noradrenergic brainstem nuclei.[2,24] The medical consequence of these alterations is widespread, including coagulation alterations, endothelial injury[38] and hypertension.[39]

Depression is evoked as a major determinant in the alteration of various basic systems involved in homeostasis. First of all, mental stress and depression seem to be involved in endothelial alteration. Healthy endothelium maintains vascular tone via nitric oxide (NO) metabolites, inhibits smooth-muscle cell proliferation, and inhibits the adhesion of leukocytes and platelet adhesion/aggregation. In humans, several risk factors for CVD (including smoking, diabetes, and hypertension) have been shown to induce endothelial dysfunction from an early stage, with alterations in the NO system. Rajagopalan et al[38] and Broadely et al[12] have shown that flow-mediated dilatation (FMD) is impaired both in untreated and treated depression, suggesting a possible contribution to the increased CVD risk seen in depression. On the other hand, a more recent study, using a selective serotonin reuptake inhibitor (SSRI) as antidepressant therapy, showed endothelium-protective properties associated with the use of sertraline.[40] More recently, Chrapko et al[41] have shown that platelet NOS activity and plasma levels of NO metabolites were dramatically lower in patients with major depression, compared to healthy controls.[41] The decreased NO production is particularly relevant in depressive patients with cardiovascular risk and might contribute to the observed increased platelet reactivity found in these patents.[42]

Along with endothelium integrity, platelets are the coprotagonists of the scenario called "atherothrombosis", which remains the leading cause of cardiovascular deaths. Under physiological conditions, platelets' relationship with damaged vessels determines the arrest of platelets, followed by spreading aggregation. This is mainly caused by the activation of Gp IIb-IIIa.[43] This interaction triggers platelet's procoagulant activities,[44] via the 5-hydroxytryptamine (5-HT) pathway. 5-HT receptors are widely involved in several recognized functions, including attention, perception, pain sensation, mood, and anxiety. Therefore, many authors have linked the alteration of central serotoninergic pathways (typical of depression and dysthymia) and atherosclerotic process of CVD.[7] Laghrissi-Thode et al[46] showed that depressed patients with ischemic heart disease showed elevated β-thromboglobulin levels, increased plasma levels of platelet factor 4, and increased surface receptor expression of Gp IIb-IIIa and P-selectin, when compared with nondepressed ones.

Musselman et al[42] evaluated the response of platelets (in vivo activation, secretion and dose response aggregation) to antidepressant treatment. In vivo platelet activation, secretion, and dose-response aggregation in the controls and patients was measured after overnight bedrest under basal conditions, and after a mild exercise challenge. After 6 weeks of open-label treatment with the SSRI paroxetine (20 mg/day), the patients with depression were readmitted and tests were repeated. Compared with matched controls (12 subjects without CVD risk factors), the depressed group exhibited, at baseline, a 125% increase in binding of the monoclonal antibody anti ligand-induced binding site (mAb anti-LIBS anti-GPIIIa), a 50% increase of mAb anti-GA6 binding (anti-P-selectin), and a 150% plasma concentration increase in the platelet-specific secretion protein PF4. After paroxetine treatment, the patients with depression

exhibited significant reductions in all three parameters. After 6 weeks of paroxetine treatment, 12 (80%) out of 15 patients were good responders, and exhibited a 48% decrease in m-Ab anti-LIBS binding, a 17% decrease in mAb GA6 binding and a 54% decrease in PF4 plasma level; measures not significantly different from the baseline values of the controls. Normalization of platelet activation is associated with paroxetine treatment of patients with depression. Because this study design did not allow for the determination of whether this effect of paroxetine on platelet function is a direct effect of the drug or a placebo effect, or, alternatively, because of recovery from depression, studies containing a placebo and/or psychotherapy treatment arm may be needed to resolve this issue. Interestingly, the increased anti-LIBS platelet binding of depressed patients was observed not only in subjects with conventional CVD risk factors, but also in ones without, suggesting that increased anti-LIBS platelet binding is not a surrogate marker for conventionally accepted CVD risk factors.[42]

These findings, together with results from the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) substudy,[40] confirm the central role of platelets in the genesis of both depressive and cardiovascular disorders and suggest that SSRIs not only may diminish CVD risk among depressed subjects, but also could be a safe and a useful tool for secondary CVD prevention in cardiopathic depressed patients.

Finally, there is an increased activation of the hypothalamic-pituitary-adrenal (HPA) axis in major depression, resulting in a high cortisol level and sympathetic tone. Considering that depression has been associated with increased cortisol in ischemic heart disease (IHD) patients[36] and that hypercortisolism is well known to redistribute body fat, promote the development of atherosclerosis, and accelerate injury to endothelial cells, cortisol may act as a mediator between depression and cardiovascular events. Cortisol induces a downregulation of endothelial nitric oxide synthetase (eNOS), as well as a decrease in plasma NO levels.[39] Cortisol therefore may increase cardiovascular risk in depressed patients inducing endothelial dysfunction. More recently, Wilbert-Lampen et al[37] have suggested that corticotropin-releasing hormone (CRH) induces a significant increase of cell adhesion as well as monocytic MAC-1 expression and increases monocytic ET-1 release, diminishing NO release. All these effects have been abolished by the CRH-antagonist "astressin". These data support the hypothesis that, in depression, cortisol increases cardiovascular risk via endothelial dysfunction, providing also a novel concept of how specific CRH-antagonists may prevent CRH (stress)-related endothelial dysfunction leading to cardiovascular complications. Stress has been shown to be one of the most powerful inducers of depression,[46] via the HPA axis. Once stress has been resolved, normally all the underlying biochemical and hormonal alterations should return to their base states. However, genetic predisposition, such as specific 5-HT transporter gene polymorphisms, coupled with gene–environment interaction, may explain why some subjects recover from life stress factors while others develop depression, anxiety, somatic pain and so on.[47] Genetic association studies in geriatric depression have implicated the serotonin pathway, especially in men. In elderly twin studies, both the serotonin 2A receptor gene promoter A/A genotype and a specific haplotype in VMAT2, the gene encoding the vesicular monoamine transporter, were associated with depression symptoms in men, but not in women.[48,49] The serotonin transporter gene has been implicated in the emergence of depression following medical stress or psychosocial adversity. In young adults, the presence of a specific allele (s allele) predicted increased rates of major depressive disorder, depressive symptoms, and suicidal ideation after various life stressors (eg, medical insults, psychosocial, or financial hardships).[47] This is consistent with the finding of increased rates of major depressive disorder and depressive symptoms among elderly patients who suffered a hip fracture and carried at least one s allele of the serotonin transporter gene-linked polymorphic region (5-HTTLPR), compared to elderly patients who also suffered a hip fracture but carried no s alleles.[47] The s allele, as opposed to the l allele of 5-HTTLPR, was also found to be associated with slower speed of response and more pronounced side effects in pharmacogenetic studies of elderly depressives.[50,51]

The BDNF-gene Val66Met polymorphism is more frequent among elderly depressed patients than among controls[52] and seems, along with the s allele of 5-HTTLPR, to increase the risk of depression following various environmental stressors.[53]

Patients with late-onset major depression carried the C677T mutation of the enzyme methylene tetrahydrofolate reductase (MTHFR) more frequently than controls.[54] Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, a condition characterized by recurrent subcortical strokes and frequently presenting with depression, is caused by mutations in the notch3 gene.[55] The ε4 allele of apolipoprotein-E increases the risk for two conditions associated with geriatric depression, Alzheimer's disease[56] and cerebrovascular disease,[57] but in a community sample it was not associated with late-life depression.[58]

The stress-induced hypothesis suggests that depression could be a direct risk factor for both the development of cardiovascular disease and increased CVD morbidity and mortality for patients with preexisting disease; conversely, a genetic pathway which renders a patient a "good stress responder", should protect the subject from CVD complication after prolonged stress factors.

## Cardiovascular side-effects of antidepressant drugs

Given that depression might potentiate CVD, coexist with it, or eventually predispose to its development, clinicians should treat it, while taking into account that many antidepressant drugs have cardiovascular side effects. In recent years, with the introduction of new antidepressants, the number of treatment options, as well as the safety of these treatments, has increased.[59]

It is known that tricyclic antidepressants (TCAs) currently available are associated with anticholinergic and cardiotoxic side effects. In addition, research into the possible role of oxidative stress in TCA-induced cardiotoxicity has found that free radical generation and oxidative stress play a role in clomipramine-induced cardiotoxicity.[60] TCAs may induce sinus tachycardia in many patients and orthostatic hypotension occurs in up to 20% of patients receiving TCAs. Postural hypotension is responsible for a number of injuries in the elderly. For this reason, it is necessary to suspend treatment in 25%–50% of patients with pre-existing cardiovascular disorders.[61] The TCA compound with minimal orthostatic hypotensive properties is nortriptyline. Therefore, when other antidepressant treatments have been ineffective, nortriptyline is considered to be the TCA of choice for treatment of depression in patients suffering from cardiovascular disorders, and the elderly.[59]

TCAs concentrate in the myocardium leading to significant changes in conduction and myocardial contractility. Indeed, TCAs may cause first and second-degree atrioventricular block, asystole and sudden cardiac death.[62] Additional studies have suggested that for low doses of TCAs (less than 100 mg/day amitriptyline or its equivalent), there is no evidence of increased risk of sudden cardiac death.[63,64] However, since higher doses of TCAs are found to increase relative risk, such doses should be used cautiously, particularly in patients with preexisting cardiovascular disease.[63] During TCA treatment, asymptomatic ECG modifications (ie, lengthening of the QT, PR and QRS intervals) have been observed. These alterations are generally clinically insignificant in healthy subjects, but in patients with pre-existing conduction disorders (in particular bundle branch block) they may cause serious conduction disorders in approximately 20% of cases. There is evidence that these effects are due to the anti-arrhythmic properties of these drugs which resemble those of class I anti-arrhythmics (including quinidine, procainamide, disopyramide, encainide, flecainide, propafenone and moricizine). This quinidine-like action is highly potent for imipramine.[64] The effects of TCAs have been investigated in patients who experience frequent premature ventricular contractions (PVCs). In this connection, TCAs have been reported to be effective in decreasing the frequency of PVCs in non-depressed patients with cardiac disorder.[64,65] However, although patients who suffer from frequent PVCs after a myocardial infarction show a higher mortality rate than those with fewer PVCs, it would appear that TCAs lower the frequency of PVCs at the cost of further decreasing long-term survival.[66] In conclusion, TCAs must be considered unsafe in patients with cardiovascular disorders.

Today, given the dietary and drug restrictions, non-selective and irreversible monoamine oxidase inhibitors (MAOIs) have been virtually abandoned by clinicians for the treatment of depression. Moclobemide, which appears to be the only MAOI actually employed, does not appear to alter cardiac conduction or QT interval. Isolated cases of marginal decrease in the heart rate have been reported.[67] Therefore, caution is recommended in the treatment of patients with cardiovascular disease.

Selective serotonin reuptake inhibitors (SSRIs) are generally considered safer than TCAs in patients with cardiac disorder. In fact, SSRIs are devoid of antimuscarinic properties, and do not induce postural hypotension, tachycardia, or alterations in the PR or QRS intervals. Unlike TCAs, SSRIs do not have anti-arrhythmic effects.[59]

A number of specific studies aimed at assessing the safety of SSRIs in patients with depression and cardiovascular disorder were conducted. In particular, an open 7-week study was conducted on patients with DSM-III-R criteria for major depression, Hamilton Rating Scale for Depression (HAM-D) score $\geq$ 16, with a variety of cardiac states. The cardiovascular effects of fluoxetine at a dose of up 60 mg/kg day (n = 27) were compared with those (n = 60) of nortriptyline (1 mg/kg of body weight and titrated to a therapeutic plasma level of 50–150 ng/mL). Fluoxetine did not exhibit the cardiovascular side-effects seen with nortriptyline (such as orthostatic hypotension, cardiac conduction abnormalities or tachycardia).[68]

A double-blind randomized placebo-controlled trial was conducted to gather information on efficacy and

cardiovascular responses to treatment with sertraline in 369 depressed patients with either acute MI or unstable angina. At the end of 24 weeks of treatment, sertraline (mean dose 68.8 ± 40.1 mg/day) was found to be safe and effective in these patients.[69]

A case control study of 5236 patients demonstrated a significant reduction in risk of MI associated with current use of high affinity SSRIs (sertraline and paroxetine) compared with both non-use of antidepressants and use of other antidepressants. In addition, the extent of 5-HT inhibition among SSRIs correlated with the degree of reduced odds of MI. These results suggest that the relative reduction in platelet 5-HT uptake caused by SSRIs is the reason for the risk reduction.[70]

Probably the most important side-effect of SSRIs in patients with cardiovascular comorbidity is their potential to interact with drugs these patients are taking for cardiac arrhythmias, congestive heart failure or hypertension.

The SSRIs paroxetine and fluoxetine are potent CYP2D6 inhibitors, whereas citalopram, fluvoxamine and sertraline are weak inhibitors. Also, escitalopram, the active S-enantiomer of citalopram is a weak inhibitor of CYP2D6.[43] With respect to CYP3A4, all SSRIs are weak inhibitors (fluvoxamine moderate). Therefore, SSRIs can increase plasma concentrations of cardiovascular drugs metabolized by CYP2D6, such as propranolol, metoprolol, flecainide, and encainide, or metabolized by CYP3A4, such as simvastatin, lovastatin, amlodipine, nicardipine, nifedipine, diltiazem and amiodarone.[71]

Attention should also be paid to the interaction between SSRIs and other serotoninergic drugs (ie, clomipramine, lithium, MAOIs, moclobemide, selegiline, SSRIs, tramadol, L-tryptophan, meperidine, dextromethorphan) in view of the occurrence of the 5-HT syndrome.[72]

There is also emerging insight into the importance of the interaction between SSRIs and thiazide diuretics. The careful monitoring of patients prescribed both an SSRI and a thiazide diuretic is suggested, since severe hyponatremia may occur through inappropriate ADH release.[73]

In conclusion, SSRIs are considered first choice drugs for treatment of patients with cardiovascular disorders. Patients who have experienced a myocardial infarction may be treated either with fluoxetine or sertraline. Sertraline, however, may be preferable, due to its better side-effect profile. Patients with ischemic heart disease who have not had a myocardial infarction may be treated either with paroxetine or sertraline. Patients with heart failure may be treated with fluoxetine or sertraline. Again, sertraline may be preferred in these patients given its lack of effect on left ventricular ejection function.[74]

Cardiovascular tolerability of any serotonin noradrenaline reuptake inhibitors (SNRIs) varies within the class, venlafaxine seeming to be the least well-tolerated, principally due to dose-dependent hypertension.

A meta-analysis of original data on blood pressure of 3774 patients indicated that venlafaxine treatment caused dose-dependent increase in supine diastolic blood pressure, but clinically significant hypertension is only induced at doses $>$ 200 mg/day.[75]

Blood pressure increases with milnacipran are minimal. A review of over 4000 patients treated with milnacipran reported that the mean increase in blood pressure was 1 mmHg while the mean increase in heart rate was 3.6 bpm. However, milnacipran can, at high doses, cause tachycardia and hypertension in certain patients.[76]

With respect to duloxetine, a recent meta-analysis of cardiovascular safety indicated small but significant increases in heart rate and systolic blood pressure, compared with placebo, but these were similar to the effects seen with fluoxetine and paroxetine. Mean changes in ECG were neither clinically nor statistically significant.[77] In conclusion, milnacipran and duloxetine appear better tolerated than venlafaxine, and are essentially devoid of cardiovascular toxicity.[78]

Evidence has accumulated for the role of noradrenaline serotonin specific antidepressants (NASSAs), such as mirtazapine in the treatment of patients with depression and cardiac disease.

In a double-blind study, 50 healthy subjects were randomized to receive either mirtazapine (up to blind 30 mg/day) or placebo for a 4-week period. Mirtazapine subjects showed significantly increased total cholesterol (TC) at week 4, but no significant changes in HDL, LDL levels and TC/HDL ratios.[79] Isolated cases of hypertensive episodes and tachycardia have been reported during treatment with mirtazapine.[80] In conclusion, mirtazapine would seem relatively safe in patients with cardiac disorders.

Noradrenaline selective reuptake inhibitors (NARIs) such as reboxetine are thought to be problematic in patients with heart disease. However, a single-blind study compared the acute and long-term effects of reboxetine (2 mg twice a day) administered to twelve depressed patients with those of placebo; long-term treatment with reboxetine did not cause any significant change in cardiac autonomic function.[81] A double-blind placebo controlled study evaluated the efficacy and tolerability of reboxetine (4 mg twice daily for 16 weeks) in

**Table 1** A synopsis of cardiovascular disease (CVD) side effects of antidepressants

| Class of agents | Specific effects | General effects | Not CVD patients | CVD patients |
|---|---|---|---|---|
| Tricyclic antidepressants (TCA) | Free radical generation; oxidative stress (clomipramine)<br>The quinidine-like action is highly potent for imipramine | Sinus tachycardia<br>Orthostatic hypotension (20%)<br>Significant changes in conduction and myocardial contractility (first and second degree atrioventricular block)<br>Quinidine-like action<br>Premature ventricular contractions<br>Asystole<br>Lengthening QT, PR and QRS intervals<br>Sudden death | Caution in hypotensive patients | Caution in patients with pre-existing cardiovascular disease; caution in patients with pre-existing conduction disorders (bundle branch block); caution in CVD |
| Monoamine oxidase inhibitors (MAO-Is) | Interactions with tyramine;<br>Interactions with methyl-dopa; reserpine and guanethidine, employed (even if rarely as anti-hypertensive drugs) | Isolated cases of marginal decrease in heart rate | No recommendation | Virtually abandoned; caution in CVD |
| Selective serotonin reuptake inhibitors (SSRI) | SSRIs can increase plasma concentrations of cardiovascular drugs metabolized by CYP2D6, such as propranolol, metoprolol, flecainide and encainide or metabolized by CYP3A4, such as simvastatin, lovastatin, amlodipine, nicardipine, nifedipine, diltiazem and amiodarone | Hyponatremia (and therefore major attention to thiazide and SSRI interactions) | No specific recommendation | Caution in patients with acute left ventricular altered functions<br>First choice drugs for the treatment of patients with CVD |
| Serotonin noradrenaline reuptake inhibitors (SNRI) | | Dose-dependent hypertension<br>Dose dependent increase in supine diastolic blood pressure<br>Small but significant increase in heart rate | No recommendation | No recommendation |
| Noradrenaline serotonin specific antidepressants (NASSA) | Single cases of reported hypertension<br>Tachycardia | Significant increase levels of total cholesterol | No recommendation | No recommendation |
| Noradrenaline-selective reuptake Inhibitors (NARI) | | Hypertension | No serious event in patients without CVD | No recommendation in patients with CVD |
| Serotonin-antagonists/ reuptake inhibitors (SARI) | | Arrhythmias<br>Minor effects on systolic time intervals;<br>Asymptomatic bradycardia hypotension | No serious event in patients without CVD | Warning in CVD patients |
| Dopamine/noradrenaline reuptake inhibitors | | Significant rise in supine systolic and diastolic blood pressure | No serious event in patients without CVD | Not extensively studied in CVD patients; warning in pre-existing hypertension |

a subset of post-stroke depressed patients (PSD) (classified as affected by "retarded depression"). Results showed the safety and good tolerability of this antidepressant that may be a useful option in PSD patients not responsive to SSRIs.[82]

In the category of serotonin-antagonists/reuptake inhibitors (SARIs), trazodone appears to have no anticholinergic or quinidine-like properties in comparison with amitriptyline in depressed patients with cardiac abnormalities, although it can induce minor effects on systolic time intervals.[83] Case reports of arrhythmias have been described.[84] Because of its cardiac side effects, trazodone is less desirable for use in cardiac patients. Trazodone prolonged-release may be a therapeutic option in the treatment of patients with major depression with major sleep disturbances,[85] but its cardiac properties should be taken into account.

Nefazodone, related chemically to trazodone, has also noradrenaline reuptake-inhibiting properties.[86] Cardiovascular safety evaluations conducted on the ECGs of 1,153 patients receiving nefazodone in placebo-controlled trials showed no significant differences between the treatments. An asymptomatic sinus bradycardia occurred in 1.3% of placebo patients ($P \leq 0.05$). There was no evidence that nefazodone can alter cardiac conduction or rhythm.[87] Nefazodone may be considered relatively safe in patients with depression and heart disease. Caution is required in patients with recent MI.

Dopamine/noradrenaline reuptake inhibitors such as bupropion seem not to be as cardiotoxic as TCAs but have not been studied extensively in patients with cardiac disease. A prospective observational trial conducted for 3 weeks evaluated 36 patients suffering from major depression (DSM criteria) and a variety of cardiac diseases. Patients were given bupropion 150 mg/day (starting dose) up to 450 mg/day (by day 7). Results showed no significant changes in left ventricular function or PR and QRS intervals. Bupropion did, however, cause a significant rise in supine systolic ($P < 0.01$) and diastolic blood pressure ($P < 0.005$) as compared with baseline (145/79 + 20/9 mmHg vs 140/76 ± 16/7 mmHg).[88]

The available data suggest that care must be taken in patients with pre-existing hypertension treated with butropion, due to its potential to increase blood pressure.[88]

A summary of the side effects of antidepressant drugs used in CVD is given in Table 1.

## Conclusion

Twenty years ago there was a general tendency to consider depression a natural part of old age, especially when elderly patients had CVD, either cerebral or cardiac. An elderly patient, or one with a major stroke or myocardial infarction became, de facto, depressed and anxious. After 20 years, we need a different approach.

Depression and anxiety may be predisposing factors for major CVD. They are also a direct consequence, and their occurrence is a major predictor for a poorer recovery from CVD events. Correct antidepressive treatment should be considered a specific primary or secondary prevention strategy, while bearing in mind that many studies suggest that antidepressants may modify platelet aggregation and alter the endothelium in CVD patients. Clinicians should take into account that many antidepressant drugs have cardiotoxic side effects which limit their use, and should evaluate the best ones to use for tailored therapy in frail elderly patients with CVD, multiple drug therapies, and depression.

## Disclosure

No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest that are directly relevant to the content of this review.

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