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GLOBAL CARDIOLOGY
Global Cardiology 2023; **1**: 13-21
Published online 27 November 2023 | **DOI**: 10.4081/cardio.2023.5

REVIEW

Intervention options: depression and cardiovascular disease during COVID-19

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Abstract

An attempt to review links of cardiovascular disease (CVD) and depression and present appropriate treatment methods for handling depression in the COVID-19 pandemic is made. Although depression constitutes one of the major mental health challenges that humankind must encounter in the 21st century it remains undiagnosed and untreated in CVD patients. Its great influence on the progress of CVD led to its classification as a risk factor along with dyslipidemia, arterial hypertension, diabetes, obesity, substance use, sedentary lifestyle (poor diet, stress) making imperative the need for treatment methods. As during COVID-19 pandemic we witnessed the elevation of mental distress as involving both lifestyle choices and dealing with unprecedented life situations while inducing psychological distress or exacerbating pre-existing physical and mental health problems – depression could act both as a contributor to and as the result of CVD. A 4-step intervention program is suggested.

Key words depression, cardiovascular disease, COVID-19 and cardiovascular disease, depression and COVID-19.

Received: 6 November 2023; Accepted: 8 November 2023.
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Introduction

According to the World Health Organization, more than 264 million people of all age-groups worldwide are estimated to suffer from depression. Within a 10-year period (2005 *vs* 2015), the ratio of people suffering from depression has increased by more than 18%. Women regardless of nation, culture and ethnicity face a greater chance of experiencing depression.[1] Several studies have established the positive relationship between depression and cardiovascular disease [*e.g.* coronary artery disease (CAD), peripheral artery disease (PAD), myocardial infarction (MI)]. According to Correll *et al.*,[2] depression is associated with increased CVD morbidity, and its prevalence ratio highly depends on CVD type. Based on Thombs *et al.* study,[3] patients with MI present a 3-time higher risk to develop depression in comparison to the general population. In another study conducted by Tully & Baker (2012), almost 1 out of 3 patients who had undergone a coronary artery bypass graft surgery developed depression.[4]

There seems to be a bidirectional relationship between depression and CVD: depression also constitutes a high-risk factor for individuals to develop CVD in the future. Depression may either lead to cardiovascular issues (etiology) or may be responsible for poor prognosis considering CVD treatment.[5] Yet it remains undiagnosed and untreated. Although, there seems to be a worldwide consensus on the relationship of depression and CVD,[6] there are scarce results for the actual rates of screening for depression.

Clinicians worldwide still do not screen for depression in the initial assessment of CVD. One reason could be that there is no consensuses which of the available screening tools should be used while the issue of the optimal screening tools cut-off is still open.[7] Another reason reported is that there is no evidence that routine screening actually improves the patient outcome.[5,8] It seems that screening to be beneficial has to be followed by a management protocol or system of care (*e.g.*, a care management program) for the treatment of depression. Patient outcome (reduced cardiac symptoms, reduced cardiac events along with improved adherence, and

improved blood pressure and lipids) has improved only when an intervention protocol has been followed.[9-11]

An association between COVID-19 and cardiovascular disease is reported.[12] Pre-existing cardiovascular disease seems to be linked with worse outcomes and increased risk of death in patients with COVID-19, whereas COVID-19 itself can also induce myocardial injury, arrhythmia, acute coronary syndrome and venous thromboembolism. Potential drug-disease interactions affecting patients with COVID-19 and comorbid cardiovascular diseases are also becoming a serious concern. An important factor in the co-existence of COVID-19 and CVD is that they both threaten mostly the same age group: although 40-65 years of age is the group reposted to be infected by WHO more often, mortality rates are escalating with age, 60-87 remaining the group with highest mortality risk. CVD risk for heart disease also increases with age (the prevalence of CVD, increases from about 40% in men and women 40-59 years of age), to 70-75% in persons 60-79 years of age, and to 79-86% among those aged 80 years or older for those who are over 65. Mortality rates from CVD (including coronary heart disease, heart failure, and stroke are nearly 2-fold higher in the 75-84-year age group compared to the 65-74-year age group.[13,14] In patients aged >65 years, depression remains the most common psychiatric disorder.[15] The presentation of depression differs in older adults compared to younger ones. Older adults with CVD and depression are less likely to endorse affective symptoms and are more likely to display cognitive changes, somatic symptoms, loss of interest along with dysfunctional defense mechanisms regarding health problems (*e.g*. refusal to accept actual state of health) and failure to conform to doctor's instructions than are younger adults.[16] The main concern with COVID-19 lies in this area: it is currently unknown whether older people are more (or less) likely than younger ones to initiate changes in their way of living so to be proactive.[17] Intervening and motivating older people in hygiene adherence and self-care could relate to preventing self-neglect. The impact of self-neglect on health outcomes include mortality, hospitalizations, emergency room visits, functional decline, and becoming victims of other forms of elder abuse such as financial exploitation, caregiver neglect, and physical abuse.[18,19] For the time being, this might mean motivating older people to indulge in the only effective response to COVID-19, social distancing. Social distancing that leads to social isolation in seniors has been linked to increased depression and suicidality as well as to increased proinflammatory and decreased anti-viral immune responses.[20] Quarantine measures, in the general population, have raised a number of issues for mental health. In a study in Australia, the COVID-19 impact and quarantine measures include an array of mental health concerns that may aggravate or trigger existing distress.[21] Rates of elevated psychological distress were higher than expected, with 62%, 50%, and 64% of respondents reporting elevated depression, anxiety and stress levels respectively, and one in four reporting elevated health anxiety. Participants with self-reported history of a mental health diagnosis had significantly higher distress, health anxiety, and COVID-19 fears than those without a prior mental health diagnosis. Higher engagement in hygiene behaviors was associated with higher stress and anxiety levels.

As the COVID-19 crisis developed, the psychological impact of COVID-19 related quarantine has been reported to include post-traumatic stress disorder, confusion and frustration.[22] Mental distress, grief and bereavement, deliberate or unintentional harm to family, loss/separation from family, self-injury, shame, guilt, helplessness, addiction or substance use, medical mistrust and inclination towards conspiracies, panic attacks, stress, anxiety, depression, loneliness, suicidal ideation, mood problems, sleep problems, worry, denial, boredom, ambivalence, uncertainty, frustration, anger, fear, stigmatization, marginalization, xenophobia, mass hysteria, socio-economic status, and other mental health concerns have also been indicated worldwide.[23-28]

Data collection

We searched PsychInfo, Google Scholar and PUBMED (after 2000 and before August 2020) in the English language using keywords: depression and cardiovascular disease, COVID-19, counselling, intervention, mortality, survival or prognosis, old age, older patients, elderly, depressive symptoms, dysthymia, or mood. This article summarizes contemporary studies relevant to depression and CVD and situates the COVID-19 pandemic as an essential concept for the community of researchers, investigators, and practitioners. This article is not a systematic review, given the expansive nature of the topics of depression and CVD, nor is it a guideline for clinical practice. Rather, this article is a summary of the contemporary science of CVD and depression with the purpose of enhancing the knowledge and awareness of healthcare professionals.

Mechanisms explaining depression link to cardiovascular disease

Throughout the years, various theories based on behavioral and lifestyle or biological patterns, have been developed aiming to shed light on the connection between depression and cardiovascular issues. A short description of the major mechanisms identified follows.

Lifestyle and other behavioral elements

Various studies have shown that specific lifestyle and behavioral characteristics of depressed individuals increase the likelihood of CVD. Smoking,[29] alcohol consumption,[30] absence of any physical and exercise activity,[31] unhealthy eating habits, which in many cases lead to obesity and social isolation,[32] and loss (*e.g.* death of a significant other) are factors also responsible for CVD.

Biological factors

Autonomic dysregulation. Depression and CVD are associated with problems in autonomic functioning (increased activation of the sympathetic nervous system, which may also lead to increased metabolic abnormalities, and relative less activation of the parasympathetic one), which result in tachycardia, reduced heart rate, and hypertension.[33]

The function of the immune system,[34] *and the function hypothalamic-pituitary axis and the secretion of cytokines, interleukin IL-1 and IL-6*.[35] Depression can lead to changes in the central nervous system (CNS) that cause the secretion of neurohormones and activation of the hypothalamic-pituitary axis, resulting in destabilization of the sympathovagal balance. Suppression of the immune system with the increase in secretion of proinflammatory cytokines can lead to the gradual development of CAD, plaque activation, and an acute episode. Hyperactivation of HPA axis and subsequently increased levels of cortisol is well proven in depression.[35] High cortisol levels may be linked to CVD and other chronic conditions, since cortisol is responsible for hypertension, atherosclerosis, prothrombotic incidents and diabetes mellitus.[36]

The presence of the S allele of the serotonin transporter (5-HTTLPR).[37] Cardiac dysfunction is caused by a change in the blood concentration of serotonin. The absence of peripheral serotonin synthesis (*i.e*. absence of serotonin mainly in platelets) is associated with heart failure. Elevated serotonin levels are associated with arrhythmias, possible heart block, and valvular fibrosis.[38]

Metabolic syndrome. This term entails various factors of high risk to cause CVD and diabetes like abdominal obesity, increased blood glucose (hyperglycemia), higher level of blood pressure, increased triglycerides, and decreased high-density lipoprotein cholesterol (HDL).[39] Other studies have presented an association of metabolic dysregulation and depression and its increased contribution to chronic depression.[40]

Insulin resistance syndrome. According to Reaven (2003), individuals suffering from insulin-resistant/hyperinsulinemic are more likely to be i) intolerant to glucose, ii) hypertensive, and have a high plasma triglyceride and low high-density lipoprotein cholesterol concentration. These changes are related to increased risk of cardiovascular disease.[41] On the other hand, depressive symptoms, according to a study conducted in China were also found to be positively related to insulin resistance.[42]

Inflammation. According to Khandaker *et al*., (2019), the following three conventional cardiovascular inflammation-related risk factors: i) triglycerides (TG), ii) C-reactive protein (CRP) and iii) IL-6 are likely to be causally linked to depression.[43] These results support the theory that inflammation related to the immune system may be a common mechanism between depression and heart disease.

Arterial wall function. *Platelet aggregation and endothelial dysfunction*. Increased level of serotonin has been proven to act as a predictor of coronary artery disease and other cardiac incidents. Since it has a special binding receptor site on the surface of the platelets, serotonin influences greatly the biology of the platelet and its aggregation and therefore is also linked to depressive symptoms, alongside its cardio effects. Increased platelet aggregation in patients with depression is also related to endothelial dysfunction, which has also proven to cause CVD.[44-47] It should be noted that only platelet function and heart rate variability improve under antidepressant therapy (selective serotonin reuptake inhibitors).[48] In addition, taking drugs can cause depression: *e.g.* beta-blockers, methyldopa, calcium channel blockers, corticosteroids (prednisolone. It is important to note that 40% of those aged >65 years take an average of 5 drugs per week, while 12% take 10 drugs per week, a fact that requires careful prescribing.

Sociodemographic elements like age, gender, financial status, and health conditions seem to play a crucial role in the development of depression, as well as in the presence of cardiovascular disease. Various studies, by examining individuals of similar sociodemographic elements (sex, age, education level, finance) have shown that depressed individuals exhibited higher risk to present CVD compared to the non-depressed individuals; although the given risk linked to depression was reduced by 20%, still remained at high level. Prognosis improves when depression improves.[6] Potential biological and behavioral mechanisms for this risk have been identified, but no single factor has been shown to account for more than a fraction of the total risk. Further research on the biobehavioral mechanisms linking depression with CVD is needed.

Other mechanisms

Other factors and events in the life of an individual may also lead to depression and cardiovascular deterioration. History of childhood maltreatment, referring to emotional, physical, or sexual abuse, neglect, and household dysfunction, has proven to be highly related to the onset at a later stage of depression.[49] Maltreatment in childhood has also been proven to act as a highly risk factor for cardiovascular problems.[50] Although, childhood maltreatment may trigger both conditions, this does not prove causality between depression and CVD. Additionally, personality traits such as neuroticism, negative emotionality, and type-D personality have been related to cardiovascular issues as well as depression.[47,51-53]

The prevalence of mental health problems with heart disease is threefold higher than the general population and there is about 80% increase in the risk of developing new or exacerbation of pre-existing CVD (complications or hospital-

ization) during a perceived or actual threatening or stressful situation such as the advent of COVID-19.[23-28,53] The prevalence of depression and anxiety is seen more common among individuals with angina, at risk of developing myocardial infarction, stroke, and atrial fibrillation. The increase in anxiety and depression (general anxiety, psychological distress, anger, negative emotions, fear, worry, grief, severe emotional stress,[20] can increase the risk of developing CVD and CVD can increase the risk of developing mental health problems.[12-17]

Treatment methods of depression to individuals suffering also from cardiovascular disease

A wide range of treatment methods concerning depression in patients with CVD is available. Medication, referring mainly to antidepressants, can be combined with other forms of non-pharmacological treatment aiming to increase treatment's efficacy. However, depression in many cases of patients with CVD remains unrecognized, mainly due to the common symptomatology that a patient can present once being hospitalized like sleep disturbance, loss of appetite, and fatigue.[47] The existence of a multi-disciplinary team (cardiologist, neurologist/psychiatrist, nurse, counselor) is important for appropriate treatment to be designed and followed.

Antidepressants: mainly selective serotonin reuptake inhibitors

Medication refers mainly to antidepressants like selective serotonin reuptake inhibitors (SSRIs), or serotonin-norepinephrine reuptake inhibitors (SNRIs). Several studies have been conducted, aiming to prove the efficacy of SRRIs antidepressants such as escitalopram, fluoxetine, paroxetine and sertraline. The efficacy of sertraline and escitalopram *versus* placebo, have been tested in a large number of patients suffering from depression and after having experienced an Acute Coronary Syndrome (ACS). Based on the Sertraline Antidepressant Heart-Attack Randomized Trial testing sertraline,[54] and on another trial conducted by Kim *et al*., testing escitalopram, both SRRIs have proven to be effective in reducing symptoms of depression in patients with CVD.[55]

Sertraline had a positive effect in the reduction of depression without increasing the risk of negative cardio effects, while escitalopram led to the reduction of major adverse cardiac events within 6 months after the ACS.[56] Other studies testing the efficacy of paroxetine and fluoxetine *versus* placebo and *versus* nortriptyline, which belongs to the drug-class of tricyclic antidepressant shared similar results.[57] Paroxetine and fluoxetine led to the reduction of depressive symptoms, without having the negative effects on cardiac side like in the case of nortriptyline, where ventricular arrhythmias have been presented.[47] Tricyclic antidepressants and monoamine-oxidase inhibitors are usually not used for treatment, since these are proven to be unsafe in cases of cardiovascular problems; for instance monoamine-oxidase inhibitors may interact negatively with other drugs used in specific cardiovascular therapies, increasing the risk of hypertension.[58]

Cognitive behavior therapy, problem solving therapy and interpersonal therapy

According to Wang *et al.,* the American Psychological Association has classified cognitive behavior, problem solving and interpersonal therapies in the list of modalities having *strong research support* proving their efficacy towards depression, which is defined as at least two well-designed clinical trials implemented by independent organizations/investigators.[59] Based on a study conducted by Freedland *et al.,* patients with cardiac problems and depression after being exposed to cognitive behavior therapy (CBT), while taking antidepressant at baseline live, managed to reduce depressive symptoms as reported by the Beck Depression Inventory after a period of 6 months. Another study also implemented by Freedland *et al*., proved the efficacy of CBT in reducing depression severity in patients, who had undertaken a coronary artery bypass surgery, regardless of whether they were or not on antidepressants medication. Problem solving therapy (PST) seems to have also prominent results. This form of therapy helps CVD patients to acknowledge everyday problems that lead to depression and to develop the appropriate skills to cope against those. Based on the Coronary Psychosocial Evaluation Study, patients diagnosed with depression in the last 3 months, after their hospitalization for ACS, were randomly assigned to PST and/or pharmacologic treatment groups. Patients assigned in the PST group, after a period of 6 months, presented increased satisfaction ratings, reduced depressive symptoms and equally important lower rates of risky cardiac outcomes.[60] Interpersonal therapy (IPT) focuses on revealing the connections between individuals' interactions and mental health and acknowledging how current relationships and social framework lead to and maintain depressive symptoms. Despite its efficacy in treating depression, given result has not been proven in the cases of depressed patients with CVD. The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy trial, during which the efficacy of IPT, citalopram, the combination of the two, and usual care have been tested, has shown that IPT had no added value over usual clinical care, while the citalopram presented better results in reducing depression.[56]

Mindfulness based cognitive therapy

Mindfulness based cognitive therapy (MBCT) is a group-based therapy focusing to prevent relapses of currently depressed patients, or on patients who are in remission. This therapy entails elements of CBT and it is enriched with mindfulness-based stress reduction techniques. MBCT evolves dur-

ing an 8-session program and its aim is to enable patients to adapt to a new way of everyday living routines.[61] According to a study conducted by O'Doherty *et al.,* depressed patients suffering from coronary heart disease, after the completion of the 8-week MBCT program reported significant improvement on depressive symptoms.[62] At the 6-month follow up, 71% of the MBCT group reported recovery whereas only 50% of the control group had a similar outcome. According to the members assigned to the MBCT, program's key advantages related to meditation, group support and to the development of optimism. Additionally, according to the evidence-based map conducted by Farah *et al.*, MBCT presented increased benefits to traditional CBT.[63]

Relaxation practices

Lifestyle changes aiming to reduce stress through relaxation practices (*e.g.* yoga, meditation), are of great significance and may even help to reduce levels of IL-6 in blood tests.[64] Moreover, according to a study conducted by Parswani *et al*., on 30 male patients with CHD, practicing mindfulness-based stress reduction techniques, depression and anxiety levels, alongside overall and perceived stress were significantly reduced after the completion of the program, while given results were evident even after a follow up period of 3 months.[65]

Exercise

Literature provides a growing number of evidence that exercise is an effective treatment towards depression on patients with CVD. Based on a meta-analysis of 23 randomized clinical trials49 exercise was linked to positive clinical effects. Additional studies have deciphered the effectiveness of exercise,[66] since their positive results have been associated with reduction of depressive symptoms, lower death ratio of patients with chronic heart failure, and even improved cardiovascular biomarkers affecting positively not only the clinical outcomes, but also the quality of life of respective patients.[67-69]

Cardiac rehabilitation

Cardiac rehabilitation programs are medically supervised and aim to improve patients' quality of life and future living. They may consist of three important elements: i) exercise counseling and training, ii) education for healthy living patterns related to heart issues and iii) counseling sessions aiming to reduce stress. Respective studies have shown that patients suffering from depression and ACS, after the completion of this type of program have presented a lower mortality rate (summing up to 73%), and reduced depression (summing up to 63%), compared to patients who had not taken part in cardiac rehabilitation programs.[56] Another study by Anderson *et al.,* showed that exercise performed within the framework of a cardiac rehabilitation program had better results compared to no exercise, in the areas of concerning cardiovascular mortality and hospitalization, while improving the quality of daily living amongst patients with CVD.[63]

Combined or stepped care approach

The adaptation of therapeutic modalities to the needs of every patient has also proven to be effective. Davidson *et al.* showed that patients who had developed depression after an acute coronary syndrome, and had selected a combined treatment methodology, had significant beneficial results compared to usual care group, related to reduced depressive symptomatology. The target group of the study comprised of 150 depressed patients with ACS, who have been assigned randomly to centralized depression care for a period of 6 months. Each participant had expressed their preferred treatment approach, problem – solving treatment, pharmacotherapy, both, or none – by telephone or via the internet contact.[64,70]

Conclusions and model of practice

Depressive symptoms are highly linked to the recovery period following cardiovascular diseases, affecting morbidity and mortality rates as well as the patients' quality of life. They are also considered a high-risk factor for CVD deployment. Emphasis should be placed on the early acknowledgment of depression in the cases of patients with CVD, therefore the alertness and contribution of medical doctors (*e.g*. cardiologists) and staff (*e.g*. nurses) is of great importance. Considering the wide range of treatment methods, the appropriate ones should be selected considering the adverse effects of each modality. Research that might link COVID-19 infection and adaptive intervention strategies on the mental health of CVD patients is essential. Some factors that may be expected to affect treatment response are: fear and attitudes towards the disease (both CVD and COVID-19), outcome expectancies, the intellectual functioning of the patient, relationship with the doctor and treatment history, substance use history, social and family issues. Both CVD and depression are treated as long-term health issues while COVID-19 remains still on a crisis intervention modality. To adhere to this crisis modality but also to its long-term quality we suggest the following model.

1st stage: assessment

Proper assessment is an integral step in the development of an individualized treatment plan. History of CVD and depression and history of dealing with crisis and behavior patterns when in a crisis might lead to better adherence to designed prevention and intervention plans for patients. Old maladaptive choices and failures in treatments must be clarified so to gather information and match patients to appropriate treatments but also to monitor the progress and effectiveness of treatment. This can be done through screening, so to determine in a time- and cost- efficient manner if a potential prob-

lem exists and requires further evaluation. Use of DSM-V,[21] interviews or self-administered questionnaires can give a first indication of the level and reason of psychological distress.[71] Some proponents of screening suggest that systematic screening should be performed only when there is an available and consistent resource for treatment available for patients who screen positive,[9] such as collaborative care programs. Such a policy would ensure that positive-screen patients would receive a more thorough depression evaluation and, if depression were diagnosed, would be able to obtain longitudinal treatment. Recommendations for screening and treatment for depression should be population specific since results from one patient group may not generalize to others. Screening tools and cutoff scores that optimize diagnostic accuracy in primary care, for instance, may not be appropriate for patients with CVD since some heart disease symptoms may overlap or be confused with symptoms of depression.[72] An evaluation of self-neglect especially for the elderly could give an indication of proactive measures for COVID-19 and promote good practice. For example, the Elder Self-Neglect Assessment might give an indication of the ability of the person for self-care.[73]

2nd stage: triage

Triage, so to decide the appropriate setting and intensity of treatment (*e.g*. counselling while inpatient, or pharmacological treatment at home). For example, the prevalence of depression and anxiety is more common among individuals with angina at risk of developing myocardial infarction, stroke, and atrial fibrillation.[74] Cardiac rehabilitation with relaxation exercises could be of benefit.

3rd stage: planning

Treatment planning, to establish individualized treatment goals and interventions directed to identified problem areas. This is the phase to attain to the person's difficulty to self-care or to address his/her difficulties relating to behavioral patterns or living arrangements related to COVID-19 especially for the elderly. A combined- stepped care approach would be of benefit in cases of self-neglect. We recommend establishing a self-care plan for every patient. Self-care in CVD and stroke prevention and management are captured in the American Heart Association *Life's Simple 7* (*i.e,* smoking cessation, maintenance of body mass index, physical activity, healthy diet, maintaining low cholesterol, maintaining normal blood pressure, and maintaining normal fasting plasma glucose).[74] These behaviors have been shown to reduce incident stroke,[75] heart failure,[76] venous thromboembolism and chronic kidney disease.[77,78]

4th stage: contingency management

Contingency management: outcome monitoring, which addresses response to treatment and whether the patient requires further or different treatment. Even the exploration of possible plans for the future may enhance a future oriented mentality. The worried-well patient (afraid of COVID-19 infection) might benefit at this stage from exercise protocols so to ascertain his physical strength. Sustaining a cardiac rehabilitation program or expanding time wise its offer to patients might be of benefit. As Riegel *et al.* (2017) point out knowledge, skills, confidence, and motivation are required to effectively perform self-care.[79] What might impede self-care includes depression, poor self-efficacy,

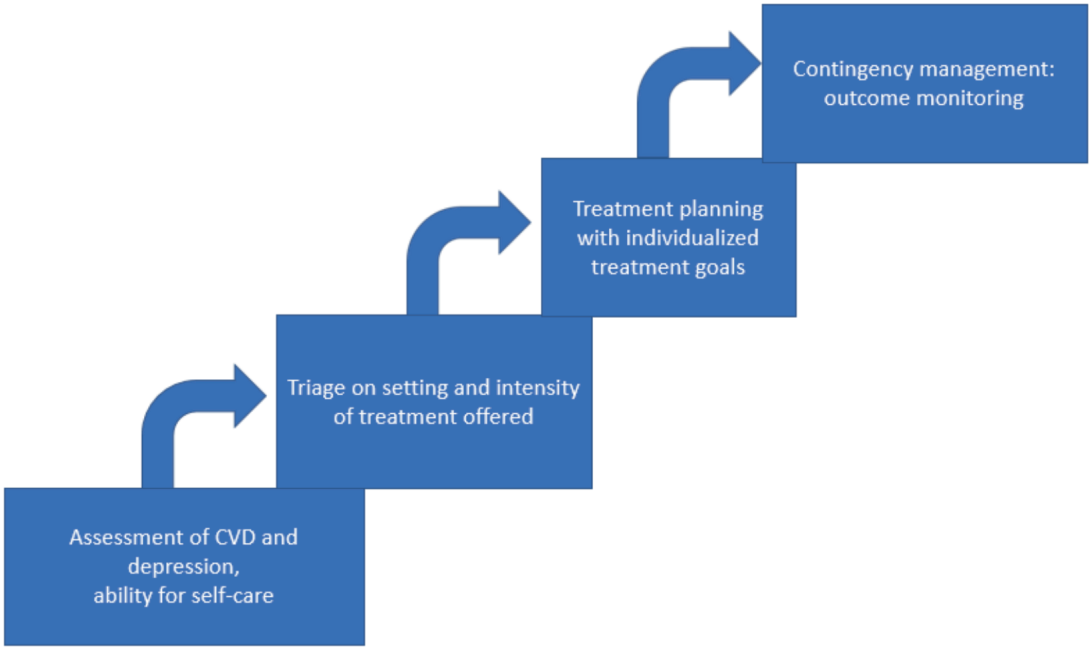

Figure 1. A model of staged care for people suffering from cardiovascular disease (CVD) and depression during COVID-19.

cognitive decline, and multimorbidity. Lack of social support is the most important family-level factor influencing self-care while lack of social capital at the community-level limits access and affordability of care (Figure 1).

We attempted a presentation of the existing research on the topic of depression and CVD and tried to share a model that might foster intervention in the time of the COVID-19 pandemic. We stated that suffering from depression when a CVD patient in the COVID-19 era may impose unpredicted hardship to the individual. Gaining control and having choices in treatment might help deal with uncertainty and foster resilience.

Contributions

All the authors made a substantive intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

The authors declare no potential conflict of interest.

Ethics approval and consent to participate

Informed consent is not necessary, since it is a review.

References

1. Bucciarelli V, Caterino AL, Bianco F, et al. Depression and cardiovascular disease: the deep blue sea of women's heart. Trends Cardiovasc Med 2020;30:170-6.
2. Correll CU, Solmi M, Veronese N, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry 2017;16:163-80.
3. Thombs BD, Bass EB, Ford DE, et al. Prevalence of depression in survivors of acute myocardial infarction. J Gen Intern Med 2006;21:30–8.
4. Phillip JT, Robert AB. Depression, anxiety, and cardiac morbidity outcomes after coronary artery bypass surgery: a contemporary and practical review. J Geriatr Cardiol 2012;9:197–208.
5. Colquhoun DM, Bunker SJ, Clarke DM, et al. Screening, referral and treatment for depression in patients with coronary heart disease. Med J Austral 2013;198:483–4.
6. Carney RM, Freedland KE. Depression and coronary heart disease. Nat Rev Cardiol 2016;14:145–55.
7. Liu M. Performance of screening tools in detecting major depressive disorder among patients with coronary heart disease: a systematic review. Med Sci Monitor 2015;21:646–53.
8. Ziegelstein RC, Thombs BD, Coyne JC, de Jonge P. Routine screening for depression in patients with coronary heart disease. J Am Coll Cardiol 2009;54:886–90.
9. Huffman JC, Mastromauro CA, Sowden G, Fricchione GL, Healy BC, Januzzi JL. Impact of a depression care management program for hospitalized cardiac patients. Circ Cardiovasc Qual Outcomes 2011;4:198-205.
10. Davidson KW, Rieckmann N, Clemow L, et al. Enhanced depression care for patients with acute coronary syndrome and persistent depressive symptoms. Arch Intern Med 2010. doi:10.1001/archinternmed.2010.29.
11. Katon WJ, Lin EHB, Von Korff M, et al. collaborative care for patients with depression and chronic illnesses. New Engl J Med 2010;363:2611-20.
12. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nat Rev Cardiol 2020;17:543–58.
13. North BJ, Sinclair DA. The intersection between aging and cardiovascular disease. Circ Res 2012;110:1097-108.
14. World Health Organisation (WHO). Cardiovascular disease. Available from: https://www.who.int/health-topics/cardiovascular-diseases/#tab=tab_1 (retrieved 25/8/2020)
15. Walker ER, McGee RE, Druss BG. Mortality in Mental Disorders and Global Disease Burden Implications. JAMA Psychiatry 2015;72:334.
16. Sakamoto. Association between depression and development of coronary artery disease: pathophysiologic and diagnostic implications. Vasc Health Risk Manag 2011:159.
17. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in Heart Failure. J Am Coll Cardiol 2006;48:1527-37.
18. Hansen MC, Flores DV, Coverdale J, Burnett J. Correlates of depression in self-neglecting older adults: A cross-sectional study examining the role of alcohol abuse and pain in increasing vulnerability. J Elder Abuse Neglect 2015;28:41-56.
19. Papaioannou E-SC, Räihä I, Kivelä S-L. Self-neglect of the elderly. An overview. Eur J Gen Practice 2012;18:187-90.i
20. Riba M Wulsin L Rubenfire M. Ravindranath D Hoboken, Psychiatry and Heart Disease: The Mind, Brain, and Heart Wiley-Blackwell; NJ: 2011.
21. Guze SB. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV). Am J Psychiatry 1995;152:1228-28.
22. Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S. Greenberg N. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. The Lancet 2020;395:10227.
23. Mukhtar S. Pakistanis' mental health during the COVID-19. Asian J Psychiatr 2020;51:102127.
24. Mukhtar S. Mental wellbeing of nursing staff during the COVID-19 outbreak: a cultural perspective. J Emerg Nurs 2020;46:426-7.
25. Mukhtar S. Preparedness and proactive infection control measures of Pakistan during COVID-19 pandemic outbreak. Res Social Adm Pharm 2021;17:2052.
26. Mukhtar S. Mental Health and psychosocial aspects of coronavirus outbreak in Pakistan: psychological intervention for public mental health crisis. Asian J Psychiatr 2020:51;102069.
27. Mukhtar S, Mukhtar S. Mental health and psychological distress in people with diabetes during COVID-19. Metabolism 2020;108:154248.
28. Mukhtar S. Mental health and emotional impact of COVID-19: applying Health Belief Model for medical staff to general public of Pakistan. Brain Behav Immun 2020:87:28-9.

29. Erhardt L. Cigarette smoking: an undertreated risk factor for cardiovascular disease. Atherosclerosis 2009;205:23-32.
30. Freiberg MS, Kraemer KL. Focus on the heart: alcohol consumption, HIV infection, and cardiovascular disease. Alcohol Res Health 2010;33:237-46.
31. Booth FW, Roberts CK, Matthew J, Laye MJ. Lack of exercise is a major cause of chronic diseases. Compr Physiol 2012;2:1143-11.
32. Sanhueza C, Ryan L, Foxcroft DR. Diet and the risk of unipolar depression in adults: systematic review of cohort studies. J Human Nutr Diet 2013;26:56-70.
33. Licht CMM, de Geus EJC, Penninx BWJH. Dysregulation of the autonomic nervous system predicts the development of the metabolic syndrome. J Clin Endocrinol Metabol 2013;98:2484-93.
34. Kop WJ, Gottdiener JS. The role of immune system parameters in the relationship between depression and coronary artery disease. Psychosom Med 2005;67:S37-41.
35. Theoharides TC, Weinkauf C, Conti P. Brain cytokines and neuropsychiatric disorders. J Clin Psychopharmacol 2004;24:577-81.
36. Stetler C, Miller GE. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. Psychosom Med 2011;73:114-26.
37. Serretti A, Kato M, De Ronchi D, Kinoshita T. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients. Mol Psychiatry 2007;12:247-57.
38. Dietricha EA, Kircha GA, Maroteaux L, Monassier L. Cardiovascular remodeling and the peripheral serotonergic system. Arch Cardiovasc Dis 2017;110:51-9.
39. Mottillo S, Filion KB, Genest J, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol 2010;56:1113-32.
40. Vogelzangs N, Beekman ATF, Boelhouwer IG, et al. Metabolic depression: a chronic depressive subtype? Findings from the InCHIANTI study of older persons. J Clin Psychiatry 2011;72:598-604.
41. Reaven GM. The insulin resistance syndrome. Curr Atherosclerosis Rep 2003;5:364-71.
42. Pan A, Ye X, Franco OH, et al. Insulin resistance and depressive symptoms in middle-aged and elderly Chinese: findings from the Nutrition and Health of Aging Population in China Study. J Affect Disord 2008;109:75-82.
43. Khandaker GM, Zuber V, Rees JMB, et al. Shared mechanisms between coronary heart disease and depression: findings from a large UK general population-based cohort. Mol Psychiatry 2020; 25:1477-86.
44. Le Mellédo JM, Mahil N, Baker GB. Nitric oxide: a key player in the relation between cardiovascular disease and major depressive disorder? J Psychiatry Neurosci 2004;29:414-16.
45. Lerman A. Endothelial function: cardiac events. Circulation 2005;111:363-8.
46. Oluwabunmi O, Himmelfarb D, Commodore-Mensah Y. Improving medication adherence in cardiovascular disease prevention: what's new? J Cardiovasc Nurs 2020;35:6-10.
47. Mavrides N, Nemeroff C. Treatment of depression in cardiovascular disease. Depression Anxiety 2013;30:328-41.
48. Cote F, Fligny C, Fromes Y, Mallet J, Vodjdani G. Recent advances in understanding serotonin regulation of cardiovascular function. Trends Mol Med 2004;10:232-8.
49. Li M, D'Arcy C, Meng X. Maltreatment in childhood substantially increases the risk of adult depression and anxiety in prospective cohort studies: systematic review, meta-analysis, and proportional attributable fractions. Psychol Med 2015;46:717-30.
50. Su S, Jimenez MP, Roberts CTF, Loucks EB. The role of adverse childhood experiences in cardiovascular disease risk: a review with emphasis on plausible mechanisms. Curr Cardiol Rep 2015;17.
51. Jokela M, Pulkki-Raback L, Elovainio M, Kivimäki M. Personality traits as risk factors for stroke and coronary heart disease mortality: pooled analysis of three cohort studies. J Behav Med 2013;37:881-9.
52. Klein DN, Kotov R, Bufferd SJ. Personality and depression: explanatory models and review of the evidence. Ann Rev Clin Psychol 2011;7:269-5.
53. Penninx BWJH. Depression and cardiovascular disease: Epidemiological evidence on their linking mechanisms. Neurosci Biobehav Rev 2016;74:277-86.
54. Glassman AH, O'Connor CM, Califf RM, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. JAMA 2002;288:701-09.
55. Kim JM, Stewart R, Lee YS, et al. Effect of escitalopram vs placebo treatment for depression on long-term cardiac outcomes in patients with acute coronary syndrome. JAMA 2018;320:350-7.
56. Freedland KE, Skala JA, Carney RM, et al. Treatment of depression after coronary artery bypass surgery: a randomized controlled trial. Arch Gen Psychiatry 2009;66:387-96.
57. Cipriani A, Brambilla P, Furukawa T, et al. Fluoxetine versus other types of pharmacotherapy for depression. Cochrane Database Syst Rev 2005;4:CD004185.
58. Pina IL, Di Palo KE, Ventura HO. Psychopharmacology and cardiovascular disease. J Am Coll Cardiol 2018;71:2346-59.
59. Wang JT, Hoffman B, Blumenthal JA. Management of depression in patients with coronary heart disease: association, mechanisms, and treatment implications for depressed cardiac patients. Exp Opin Pharmacother 2010;12:85-98.
60. Elderon L, Whooley MA. Depression and cardiovascular disease. Progr Cardiovasc Dis 2013;55:511-23.
61. Sipe WEB, Eisendrath SJ. Mindfulness-based cognitive therapy: theory and practice. Canad J Psychiatry 2012;57:63-9.
62. O'Doherty V, Carr A, McGrann A, et al. A controlled evaluation of mindfulness-based cognitive therapy for patients with coronary heart disease and depression. Mindfulness 2015;6:405-16.
63. Anderson L, Oldridge N, Thompson DR, et al. Exercise-based cardiac rehabilitation for coronary heart disease. J Am Coll Cardiol 2016;67:1-12.
64. Davidson KW, Bigger JT, Burg MM, et al. Centralized, stepped, patient preference-based treatment for patients with post-acute coronary syndrome depression. J Am Med Assoc Internal Med 2013;173:997.
65. Parswani MJ, Sharma MP, Iyengar SS. Mindfulness-based stress reduction program in coronary heart disease: a randomized control trial. Int J Yoga 2013;6:111-7.
66. Nystoriak MA, Bhatnagar A. Cardiovascular effects and benefits of exercise. Front Cardiovasc Med 2018;5:135.
67. Lespérance F, Frasure-Smith N, Koszycki D, et al. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease. Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) Trial. J Am Med Assoc 2007;297:367-79.

68. Blumenthal JA, Sherwood A, Babyak MA, et al. Exercise and pharmacological treatment of depressive symptoms in patients with coronary heart disease. J Am Coll Cardiol 2012;60: 1053-63.
69. Freedland KE, Carney RM, Rich MW, Steinmeyer BC, Rubin EH. Cognitive behavior therapy for depression and self-care in heart failure patients. JAMA Intern Med 2015;175:1773.
70. Farah WH, Alsawas M, Mainou M, et al. Non-pharmacological treatment of depression: a systematic review and evidence map. Evid Based Med 2016;21:214-21.
71. Palmer SC. Hospital anxiety depression scale. In: Gellman MD, Turner JR, eds. Encyclopedia of behavioral medicine. Springer, New York, NY: 2013.
72. Borowsky SJ, Rubenstein LV, Meredith LS, Camp P, Jackson-Triche M, Wells KB. Who is at risk of nondetection of mental health problems in primary care? J Gen Intern Med 2000;15:381-8.
73. Iris M, Ridings J, Conrad K. The development of a conceptual model for understanding elder self-neglect. Gerontologist 2010;50:303-15.
74. Player MS, Peterson LE. Anxiety disorders, hypertension, and cardiovascular risk: a review. Int J Psychiatry Med 2011;41:365-77.
75. Kulshreshtha A, Vaccarino V, Judd SE, et al. Life's Simple 7 and risk of incident stroke: the reasons for geographic and racial differences in stroke study. Stroke 2013;44:1909-14.
76. Folsom AR, Shah AM, Lutsey PL, et al. American Heart Association's Life's Simple 7: avoiding heart failure and preserving cardiac structure and function. Am J Med 2015;128:e972.
77. Olson NC, Cushman M, Judd SE, et al. American Heart Association's Life's Simple 7 and risk of venous thromboembolism: the reasons for geographic and racial differences in stroke (REGARDS) study. J Am Heart Assoc 2015;4:e001494.
78. Rebholz CM, Anderson CA, Grams ME, et al. Relationship of the American Heart Association's Impact Goals (Life's Simple 7) with risk of chronic kidney disease: results from the atherosclerosis risk in communities (ARIC) cohort study. J Am Heart Assoc 2016;5: e003192.
79. Riegel B, Moser DK, Buck HG, et al. Self-care for the prevention and management of cardiovascular disease and stroke: a scientific statement for healthcare professionals from the American Heart Association. J Am Heart Assoc 2017;6:e006997.

This manuscript was originally published in the *International Cardiovascular Forum Journal*, which has now ceased publication.
It has been given permission to be published in *Global Cardiology* in a revised form.