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Depression and cardiovascular disease: The deep blue sea of women's heart ☆,☆☆

Valentina Bucciarelli[a,1], Anna Laura Caterino[b,1], Francesco Bianco[b,*], Cristiano Giovanni Caputi[b], Sara Salerni[b], Susanna Sciomer[c], Silvia Maffei[d], Sabina Gallina[b]

[a] Department of Pharmacy, "G. d'Annunzio", University of Chieti, Italy
[b] Department of Neuroscience, Imaging and Clinical Sciences, "G. d'Annunzio", University of Chieti, Italy
[c] Department of Cardiovascular, Respiratory, Nephrological, Anesthesiological and Geriatric Sciences, University of Rome "Sapienza", Italy
[d] Fondazione G. Monasterio – CNR - Regione Toscana, Pisa, Italy

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ABSTRACT

Cardiovascular disease (CVD) constitutes a leading worldwide health problem, with increasing evidence of differences between women and men both in epidemiology, pathophysiology, clinical management, and outcomes. Data from the literature suggest that women experience a doubled incidence of CVD related deaths, while angina, heart failure and stroke are increasingly prevalent in females. About 20–25% of women go through depression during their life, and depressive symptoms have been considered a relevant emergent, non-traditional risk factor for CVD in this part of the general population. Underlying mechanisms explaining the link between depression and CVD may range from behavioral to biological risk factors, including sympathetic nervous system hyperactivity and impairment in hypothalamic-pituitary-adrenal function. However, the neuroendocrine-driven background could only partially explain the differences mentioned above for chronic systemic inflammation, altered hemostasis and modulation of cardiac autonomic control. In addition, some evidence also suggests the existence of gender-specific differences in biological responses to mental stress. Given these premises, we here summarize the current knowledge about depression and CVD relationship in women, highlighting the sex differences in physiopathology, clinical presentation and treatments.

Contents

Abbreviations: ADT, Antidepressant therapy; AMI, Acute myocardial infarction; CAD, Coronary artery disease; CBT, Cognitive behavioral therapy; CRP, C-reactive protein; CVD, Cardiovascular disease; CV, Cardiovascular; DD, Depressive disorders; HF, Heart Failure; MAOIs, Monoamine oxidase inhibitors; MI, Myocardial infarction; SSRIs, Selective serotonin reuptake inhibitors; TCAs, Tricyclic antidepressants.

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* Correspondence to: Department of Neuroscience, Imaging and Clinical Sciences, Institute of Cardiology, "G. d'Annunzio" University, Chieti, Italy.
E-mail address: francesco.bianco@unich.it (F. Bianco).

[1] These two authors contributed equally to this manuscript.

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Introduction

Depression is a psychiatric condition characterized by alterations in regulators of mood, behavior and affection [1]. According to the latest data from the World Health Organization, cardiovascular disease (CVD) and depressive disorders (DD) currently represent the most common causes of disability in high-income countries [2]. In addition, there is increasing evidence that patients with CVD suffer from DD more than the general population and people with DD are more prone to develop acute myocardial infarction (AMI), heart failure (HF) or stroke [3,4].

Peculiar differences between women and men in CVD epidemiology, pathophysiology, clinical features and prognosis have been increasingly investigated and demonstrated. In this sense, coronary artery disease (CAD) represents a unique example of how sex and gender can affect every step of a disease, from pathophysiology to outcome [5]. Conversely, the relationship between DD and CVD has been for years a matter of debate [4], assuming that DD may be influenced both by sex and gender, and may act as an early precipitating cardiovascular (CV) risk factor [3,6].

The American Heart Association (AHA) and the European Society of Cardiology (ESC) recently adopted and considered depression as a modifiable risk factor in CAD patients [4,7,8]. Unfortunately, despite all the efforts to promote and support the mental health among CVD patients, to date, DD are still under-recognized and under-treated, particularly in women [9]. Therefore, we aimed at pointing out the current evidence about gender differences in the interplay between CVD and depression, principally focusing on CAD. We also highlight the potential gender-related physiopathology, and their clinical spectrum of presentation; finally, we discuss the relevant evidence-based treatments and results from clinical trials.

Depression: clinical presentation and epidemiology

DD are usually characterized by anhedonia, the inability to experience pleasure, even in circumstances and usually enjoyable activities such as sleeping, feeding, sexual experiences and social contact [1]. DD may also be accompanied by somatic symptoms (psychological disturbance, fatigue and weight fluctuations) and cognitive symptoms (poor concentration and negative cognitions). DD are sub-categorized into major depressive disorder (MDD) and dysthymia, the latter with similar symptoms but longer duration and less intensity than MDD [1,3].

Symptoms are unspecific and may overlap with individual behavioral attitudes. Moreover, an emotional impairment during hospitalization is ordinarily recognized as a normal reaction to organic illness or disease. Thus, DD in CAD patients, and CVD in general, is somehow difficult to diagnose and study [8]. To avoid any misdiagnosis, the current European Guidelines on CVD prevention suggest two simple questions that assemble the principal criteria for both MDD and DD diagnosis: “Do you feel down, depressed or hopeless?” and “Have you lost interest and pleasure in life?”[8].

To date, 4% of the general United States adult population meets the criteria for MDD [4]. The prevalence of CVD among adults with MDD is nearly 3-fold greater than among adults without mood disorders, and adults with CVD and MDD currently are ≈ 7.5 years younger than adults with CVD who did not have mood disorders [3]. In addition, almost 2/3 of patients hospitalized for AMI develop mild forms of depression, while DD also seems to be prevalent in heart failure (HF) and stroke, with 30% of patients developing depression during the early stages, or later, of the disease [1,2] (Table 1).

Sex and gender differences

Sex chromosomes are responsible for sex differences, as they influence gene expression, leading to specific sexual hormones secretion, which in turn act explicitly on biological factors, including neurotransmitter [5]. Also, specific environmental exposure and social processes specifically affect gender differences, involving everyday aspects of life as nutrition, cultural behaviors, stress response and disease prevention [5,10].

DD are more prevalent in women than men, with a doubled chance of suffering from depression across a variety of nations, cultures and ethnicities [2]. While during childhood and early-puberty there are no differences about DD epidemiology between male and female population, DD became more frequent in women only during the mid-puberty and later life [3,4]. Indeed, it seems that all the phases of women’s life, characterized by greatest hormonal changes and inherent modulations of estrogen and progesterone levels, are affected and influenced by both biological and psychosocial factors [11].

Cardiovascular diseases

CAD has been considered for years a predominantly male disease since recent epidemiological studies registered a trend-reversal. In fact, 55% of women currently die in Europe due to CAD or stroke [10]. Despite women and men sharing similar “traditional” CV risk factors (i.e., arterial hypertension, diabetes mellitus, smoking, dyslipidemia and obesity), their relative weight and impact on CVD seems to be modulated by gender, as shown in the INTERHEART study, while traditional algorithms for CV risk (i.e., the Framingham risk score) underestimate the female risk of CAD [12].

Coronary artery disease

In the last few years, many studies, both prospective and epidemiological, tried to clarify the relationship existing between DD and CAD [13,14]. Compared to sporadically manifest depression, DD are associated with a higher incidence of myocardial infarction (MI), especially in long-lasting anxious-depressive syndromes. A diagnosis of DD at any time after angiographically confirmed diagnosis of CAD is associated with a two-fold risk of death [13]. Moreover, a high percentage of people with MI frequently develop a DD during the first months after the acute event, while the most significant rate is observed among younger women as compared to men [14].

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Table 1
Relevant clinical trials that explored the association between CVD and depression.

References	Total pts (*n*), % women (*n*)	Population	Aim	Results
Anand et al. [12]	27,098, 24% (3002 cases)	Pts with AMI (cases) compared with pts without AMI (controls), 52 countries	Gender differences in CV risk factors distribution	All risk factors significantly associated with AMI in both sexes, with some variations in OR; stronger association between hypertension, DM, alcohol intake, PhA and MI in women compared to men; no gender differences in the association of current smoking, high-risk diet, obesity, and psychosocial factors with MI
Shah et al. [11]	3237, 34% (129)	Pts undergoing CABG, screened for DD with PHQ – 9	Sex and age interactions in the association of DD with both CAD severity and AE	DD predicted CAD presence and increased risk of death in women aged ≤55 years but not in women >55 years and men
Smolderen et al. [14]	3572, 67.1% (2397)	Pts 18 to 55 years old with AMI recruited into the VIRGO study	Prevalence, clinical profile and sex differences of DD in young pts with AMI	Greater lifetime history of DD in women than men, with greater prevalence of PHQ-9 scores >10 and greater need for ADT at discharge
Wassertheil-Smoller et al. [16]	93,676, 100% (93,676)	Multiethnic postmenopausal healthy women, aged 50–79 years, screened for DD and followed up for CVD events for 4 years	Prevalence and relationship of DD with subsequent CV events among healthy postmenopausal women	Increased risk for hypertension, DM, angina, AF, stroke, congestive HF, CVD death and all-cause mortality in depressed women; DD as an independent predictor of CVD and all-cause mortality in women without CVD history and as further odds for stroke in women with known CVD history
Guimaraes et al. [17]	15,828, 19% (2967)	Post hoc analysis of the STABILITY trial, pts with history of CAD on statin	Gender differences in baseline characteristics, psychosocial factors and treatment for CAD	Independent association between female sex and better long-term clinical outcomes, although these are modified by frequency of DD
Meyer et al. [19]	2033, 33% (669)	Pts hospitalized with acute decompensated HF, enrolled in the PROTECT trial	Gender differences in clinical presentation and outcomes in AHF	Women were slightly older, with more hypertension, DM and DD than men; no gender differences in terms of treatment success, hospitalization rates, multivariable risk-adjusted mortality
Samad et al. [27]	310, 18% (56)	Pts with stable CAD previously enrolled in REMIT study	Gender differences in psychological and CV response to mental stress	Higher levels of DD and anxiety, raised PLT reactivity to serotonin and epinephrine at baseline and heightened MSIMI, enhanced negative feelings and higher PLT aggregation after stressors in women

List of abbreviations: CVD, cardiovascular disease; Pts, patients; OR, odds ratio; AE, adverse events; DM, diabetes mellitus; PhA, physical activity; AMI, acute myocardial infarction; PHQ-9, Patient Health Questionnaire-9; CAG, coronary angiography; AF, atrial fibrillation; MSIMI, mental stress-induced myocardial ischemia; PLT, platelet.

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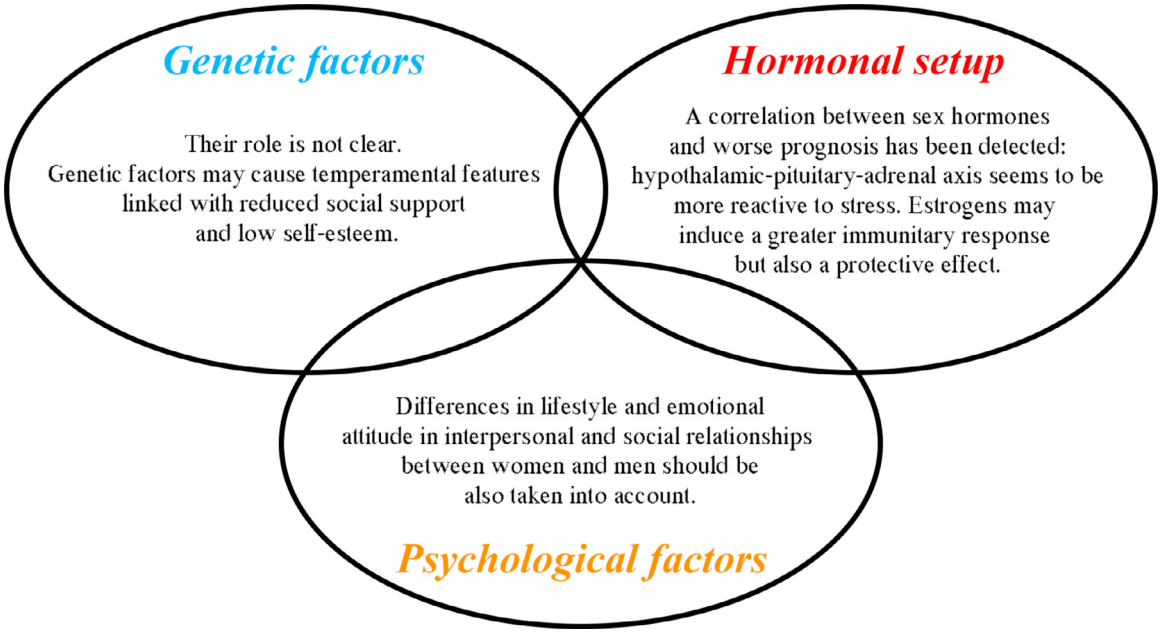

Fig. 1. Pathophysiological factors related to Depression and CVD onset. The Venn's diagram shows the overlap between genetic, hormonal and physiological factors.

Looking at women-focused studies, a Russian observational study including 560 women, 25–64 years old, showed that the prevalence of DD was higher than 50%, strongly associated with economic and political conditions. After 16 years of follow-up, depressed women showed a superior risk to develop MI (HR = 2.53) or stroke (HR = 4.63) [15]. The "Women's Health Initiative", an observational study involving 93,676 post-menopausal women during 4-years of follow-up, reported 15.8% of DD participants. In addition, the onset of DD was more frequent among patients with CVD (i.e., patients with a previous MI, OR = 1.45), being significantly linked to an increased incidence of CVD, even after correction for other traditional risk factors [16].

Finally, the STABILITY trial evaluated the role of the emotional state in a population of 15,828 patients affected by stable CAD, showing that female sex was independently associated with better clinical outcomes at a 24 months follow-up; however, the recurrence of depressive symptoms modified this relationship [17].

Heart failure

Among HF patients, there are significant differences in comorbidities and precipitating factors between male and female populations [18]. In particular, data derived from the PROTECT study showed that women with acute HF present a different clinical profile as compared to men. Preserved left ventricle ejection fraction, arterial hypertension, diabetes and depression are the most frequent features [19]. In addition, it seems that women are treated differently during hospitalization; in particular, they are commonly less intensively diuresed than men [19]. Nevertheless, both the ALARM-HF and the PROTECT showed that in-hospital mortality due to HF was similar between men and women [18,19].

Stroke

Depression adversely affects the risk of stroke through a variety of mechanisms and it is associated with higher mortality after an acute event. In the INTERSTROKE study, self-reported depressive symptoms were associated with 35% increased odds of stroke [20].

Furthermore, late-life depression may be the first clinical presentation of subclinical vascular disease and DD are common neuropsychiatric sequelae of stroke. When compared with men, women also presented a doubled propensity to develop MDD after stroke, while the early administration of antidepressant therapy (ADT) seems to prevent the disease, and enhances both physical and cognitive recovery from stroke [21].

Pathophysiological mechanisms

Depressed patients commonly adopt habits that overlap with CV risk factors, such as sleep deprivation, physical inactivity, smoking and alcohol abuse, little hygiene and poor adherence to pharmacological treatments [3,4]. Nevertheless, many other pathophysiological factors must be taken into account (Fig. 1). Psychosocial factors can affect all the biological steps leading to atherothrombosis, as shown by measuring circulating biomarkers of endothelial dysfunction in patients with DD [22].

Endothelial dysfunction plays a paramount role in the physiopathology of CAD. Actually, nonobstructive coronary acute events such as MI with nonobstructive coronary arteries (MINOCA) and Takotsubo cardiomyopathy are more prevalent in women than men, highlighting the importance of these processes [3,4] Furthermore, both immune and hemostasis systems could be negatively affected by stress-related chronic adaptations in the hypothalamic-pituitary-adrenal axis activity and autonomic nervous system, leading to enhanced inflammation, coagulation and platelet activation [23].

Circulating estrogens stimulate the T- and B-lymphocytes, with a greater immune and inflammatory response than men [3,4]. However, hormonal status alone is not sufficient to explain the different prevalence of DD between women and men. The higher frequency among families underlines the potential role, and interaction, between genetical predisposition and psychological adaptation, especially in daily activities, where women are more vulnerable to depression (Fig. 2) [24].

Behavioral mechanisms

Behavioral mechanisms are also involved in the relationship between DD and CVD. Reduced adherence to medications and

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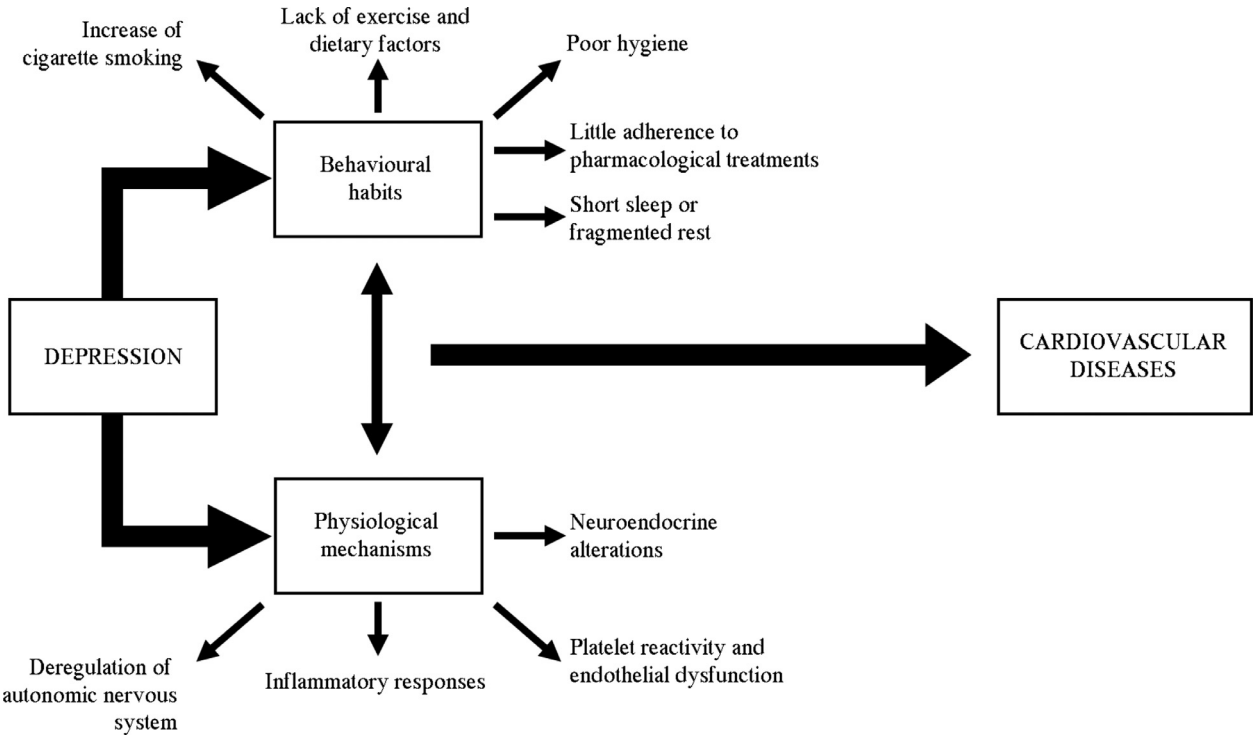

Fig. 2. The relationship between Depression and Cardiovascular diseases. The figure describes the complex mechanisms that link behavioral habits to DD and CVD. As shown, physiological mechanisms are tightly correlated with behavioral habits.

desertion of cardiac rehabilitation programs following MI, sleep disorders and inability to modify lifestyle factors are all putative factors [3,4]. In addition, inadequate care for personal hygiene, resulting in periodontal pathologies, may also play a role [3,4]. A strong association between psychobiological distress and the use of tobacco has been recently demonstrated in women [25]. Given a similar tobacco use, women suffer a 25% higher risk of CAD than men. Thus, the reported sex imbalance for CAD in smokers could be a consequence of the higher prevalence of depression consistently noted in women [25].

Autonomic nervous system

It is demonstrated that men have a higher sympathetic cardiac autonomic activity and women a higher parasympathetic one [26]. During an overnight, deep and restoring sleep, there is a parasympathetic vagal activation and a sympathetic inhibition. This modulation is responsible for a physiological tonic reduction of blood pressure and heart rate. Short sleep and fragmented rest, often detected in depressed women, prevent the modulation of the autonomic nervous system and is associated with cortisol hypersecretion, thus increasing heart rate and blood pressure [26].

Other factors that potentially modulate autonomic cardiac activity and influence gender differences comprise age, obesity, inflammation, and psychological disorder. Some studies suggested that DD are associated with greater sympathetic nervous system activation and reduced parasympathetic modulation of heart rate and blood pressure [3,4]. This phenomenon could be of greatest relevance in women, where it is demonstrated a worse imbalance in autonomic function than men [26].

Platelet aggregation and endothelial dysfunction

Elevated plasma levels of serotonin have been demonstrated to predict CAD, and future cardiac events [3,4]. In fact, serotonin has a specific binding receptor site on the surface of the platelets, playing a pivotal role in platelet's biology and aggregation [27]. In the Responses of Myocardial Ischemia to Escitalopram Treatment (REMIT) trial, when compared with men, women had heightened platelet aggregation responses to serotonin and epinephrine circulating levels ($P = 0.007$ and $P = 0.004$, respectively), at the baseline. Following mental stress, women showed more mental stress-induced myocardial ischemia (57% vs. 41%, $P < 0.04$), expressed more negative ($P = 0.02$) and less positive emotion ($P < 0.001$), and demonstrated higher collagen-stimulated platelet aggregation responses ($P = 0.04$) [27].

Along with platelet aggregation, the endothelial dysfunction, as mentioned above, can also be related to DD, both in animal models and human studies [22], even if subclinical, depression has been reported to be associated with a higher impairment of the endothelium in adolescent women [28].

Inflammatory conditions

Inflammatory processes may influence the development of CAD in DD women. Accordingly, incremented levels of acute phase proteins levels (i.e., CRP, α-1 acid glycoprotein, alfa-1 antichymotrypsin and haptoglobin), cellular adhesion molecules and circulating cytokines are commonly found in DD patients, especially if women [29]. Regardless of the history of CVD, the mediators of inflammation are predictive of CV mortality [30], while the pro-inflammatory metabolic status, if DD-associated, has a different impact in women, in which highest cytokines levels can be assayed [31].

Neuroendocrine alterations

In DD patients, it is possible to observe hyperstimulation of the sympathetic nervous system and reduction of parasympathetic tone. About 25% of women with hyperactivity of the hypothalamic-pituitary-adrenocortical axis experience a significant release of thyroid stimulating hormone (TSH) in response to hypothalamic

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thyrotrophic releasing hormone (TRH) secretion, responsible for self-immune thyroiditis and other thyroid pathologies, further predisposing to DD [32].

Antidepressive treatment and cardiovascular diseases

Despite the initial mistrust, the current European and American Guidelines recommend and encourage the DD screening as part of the routine practice [4,8]. After a DD diagnosis has been made, a fully comprehensive management of CVD and depression, including a pharmacological and non-pharmacological approach, is of crucial importance. The non-pharmacological approach is divided into cardiac rehabilitation programs, exercise activity, cognitive behavior therapy (CBT) and general support. The effectiveness of cognitive behavioral therapy (CBT) on CVD prognosis is still a matter of debate. A recent metanalysis showed that although CBT played a relevant role decreasing depression and anxiety levels in patients with CVD, it did not have any influence on long-term events [33].

On the other hand, antidepressive pharmacological treatment (ADT) has been largely demonstrated as an effective tool from both the psychological and CV points of view.

In fact, relevant to greater depressive symptoms, lower depressive symptoms, associated with high cardiorespiratory fitness, are independently associated with a lower risk of all-cause mortality in a long-term follow-up, as demonstrated in The Nord-Trondelag Health Study [34]. In addition, Bangalore and colleagues demonstrated that depression care inadequacy was associated with a significantly higher risk of the composite CVD endpoint [hazard ratio (HR) 1.20, 95% confidence interval (CI) 1.04–1.39], stroke (HR 1.20, 95% CI 1.02–1.42), and angina (HR 1.95, 95% CI 1.21–3.16); although, no significant interaction was found between (MI vs. stroke) or the definition of inadequate depression (dose vs. duration inadequacy) (P-interaction $>$ 0.05) [35]. Furthermore, two additional studies confirmed these data, reporting that ADT can be effective on CV outcomes both in chronic and acute patients [36,37].

The pharmacological approach includes several classes of drugs that induce an increment of neurotransmitters synaptic levels: serotonin, noradrenaline and dopamine. The first-generation of antidepressants includes the inhibitors of monoamine oxidase (MAOIs) and tricyclic/tetracyclic antidepressants (TCAs); the second-generation includes the selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), and atypical antidepressants [3]. All of these drugs potentially affect the CV system through hypotension and tachycardia, especially in the elderly patient, QTc prolongation and potentially life-threating arrhythmias, such as ventricular tachycardia and torsade de points although, SSRIs presented the safest profile. CV adverse effects rarely occur at therapeutic levels, even if minor side effects have been described under their use [38].

The most relevant study about the effect of a combination of CBT and ADT was the ENRICHD study. It analyzed patients suffering from DD and hospitalized for MI with a 29-months of follow-up, treated with a combination of CBT and SSRIs. The most significant benefit was observed in patients with the previous diagnosis of MDD, with no significant reduction of the overall CV events [39].

Regarding sex differences on the ADT metabolism, female hormones, particularly the estrogens, may enhance the effects of these drugs, especially in the post-menopausal women cohort. Unfortunately, to date there are no studies available that specifically assessed the gender differences in DD patients on CV outcomes according to ADT [40].

Future prospective

The impact of depression on healthcare and costs is crucial, as depression acts as one of the primary determinants of quality of life for cardiac patients. An emotional impairment can be considered a normal reaction to organic illness; on the contrary, DD are a severe disease, with a relevant impact on hospitalizations and costs. In fact, DD and MDD are tightly correlated to disability (especially after stroke) and work productivity (reduced or lost) [3,4,8].

Cardiologists, physicians and healthcare providers are thus encouraged to inquire for depression among CVD patients, avoiding misdiagnosis, and considering all the DD aspects, especially in women. In this view, screening programs and specific tools should be adopted and promoted. Also, it remains unknown whether routine screening for psychosocial risk factors contributes in reducing future cardiac events, while focused clinical trials could probably overcome the current gap in evidence [8].

Conclusions

CVD and DD currently represent the most common causes of disability in high-income countries. Although an emotional impairment may be considered usual as a reaction to organic illness, cardiac patients develop DD with higher frequency than the general population. Women seem to be more prone to DD development, with a doubled incidence than men. The reasons are different and mainly linked to a peculiar neuroendocrine setup. The occurrence of depression can worsen CV morbidity and mortality, particularly in CAD, HF and stroke, while DD treatments also seem to be effective on CVD outcomes. Even though international guidelines currently recommend the screening for DD, whether routine screening for psychosocial risk factors contributes toward reducing future cardiac events is still debated. Awareness should be promoted among practitioner and cardiologists, and gender-specific issues must be taken into account to provide specific answers to male and female CVD patients. Further studies are necessary to characterize the pathophysiological mechanisms better underlining gender differences in depression and CVD, especially focusing on ADT metabolism in women and men and its specific interactions of CV outcomes.

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References

[1] American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5). 5th ed; 2013. Washington, D.C.
[2] World Health Organization. Depression and other common mental disorders: global health estimates. 2018. Available from: https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf?sequence=1.
[3] Goldstein BI, Carnethon MR, Matthews KA, McIntyre RS, Miller GE, Raghuveer G, et al. Major depressive disorder and bipolar disorder predispose youth to accelerated atherosclerosis and early cardiovascular disease: a scientific statement from the American Heart Association. Circulation 2015;132(10):965–86.
[4] Lichtman JH, Froelicher ES, Blumenthal JA, Carney RM, Doering LV, Frasure–Smith N, et al. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association. Circulation 2014;129(12):1350–69.
[5] Garcia M, Mulvagh SL, Bairey Merz CN, Buring JE, Manson JE. Cardiovascular disease in women. Circ Res 2016;118(8):1273–93.
[6] Divanji P, Divanji D, Arnaout R, Albert M, Epel E, Nah G, et al. Postpartum depression: a novel predictor of cardiovascular disease risk in women. Circulation 2018;138(Suppl_1).
[7] Vaccarino V, Badimon L, Bremner JD, Cenko E, Cubedo J, Dorobantu M, et al. Depression and coronary heart disease: 2018 ESC position paper of the working group of coronary pathophysiology and microcirculation developed under the auspices of the ESC Committee for Practice Guidelines. Eur Heart J 2019.

[8] Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and other societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016;37(29):2315–81.
[9] Huffman JC, Smith FA, Blais MA, Beiser ME, Januzzi JL, Fricchione GL. Recognition and treatment of depression and anxiety in patients with acute myocardial infarction. Am J Cardiol 2006;98(3):319–24.
[10] Stramba-Badiale M, Fox KM, Priori SG, Collins P, Daly C, Graham I, et al. Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology. Eur Heart J 2006;27(8):994–1005.
[11] Shah AJ, Ghasemzadeh N, Zaragoza-Macias E, Patel R, Eapen DJ, Neeland IJ, et al. Sex and age differences in the association of depression with obstructive coronary artery disease and adverse cardiovascular events. J Am Heart Assoc 2014;3(3):e000741.
[12] Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusufali AH, et al. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. Eur Heart J 2008;29(7):932–40.
[13] May HT, Horne BD, Knight S, Knowlton KU, Bair TL, Lappé DL, et al. The association of depression at any time to the risk of death following coronary artery disease diagnosis. Eur Heart J 2017;3(4):296–302.
[14] Smolderen KG, Strait KM, Dreyer RP, D'Onofrio G, Zhou S, Lichtman JH, et al. Depressive symptoms in younger women and men with acute myocardial infarction: insights from the VIRGO study. J Am Heart Assoc 2015;4(4).
[15] Gafarov VV, Panov DO, Gromova EA, Gagulin IV, Gafarova AV. The influence of depression on risk development of acute cardiovascular diseases in the female population aged 25-64 in Russia. Int J Circumpolar Health 2013;72.
[16] Wassertheil-Smoller S, Shumaker S, Ockene J, Talavera GA, Greenland P, Cochrane B, et al. Depression and cardiovascular sequelae in postmenopausal women. The Women's Health Initiative (WHI). Arch Intern Med 2004;164(3):289–98.
[17] Guimaraes PO, Granger CB, Stebbins A, Chiswell K, Held C, Hochman JS, et al. Sex differences in clinical characteristics, psychosocial factors, and outcomes among patients with stable coronary heart disease: insights from the STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) trial. J Am Heart Assoc 2017;6(9).
[18] Parissis JT, Mantziari L, Kaldoglou N, Ikonomidis I, Nikolaou M, Mebazaa A, et al. Gender-related differences in patients with acute heart failure: management and predictors of in-hospital mortality. Int J Cardiol 2013;168(1):185–9.
[19] Meyer S, van der Meer P, Massie BM, O'Connor CM, Metra M, Ponikowski P, et al. Sex-specific acute heart failure phenotypes and outcomes from PROTECT. Eur J Heart Fail 2013;15(12):1374–81.
[20] O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P. Risk factors for ischemic and intracerebral hemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet 2010;376:112–23.
[21] Zerriaa O, Moula O, Ben Saadi S, Jelalia I, Ghachem R. Benefits of antidepressant treatment after a stroke. Eur Psychiatry 2017;41:S315.
[22] Greaney JL, Saunders EF, Santhanam L, Alexander LM. Oxidative stress contributes to microvascular endothelial dysfunction in men and women with major depressive disorder. Circ Res 2018;124(4):564–74.
[23] Gehi A, Musselman D, Otte C, Royster EB, Ali S, Whooley MA. Depression and platelet activation in outpatients with stable coronary heart disease: findings from the heart and soul study. Psychiatry Res 2010;175(3):200–4.
[24] Karkowski LM, Prescott CA. Casual relationship between stressful life events and the onset of major depression. Am J Psychiatry 1999;156(6):837–41.
[25] Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. Lancet 2011;378:1297–305.
[26] Voss A, Boettger MK, Schulz S, Gross K, Bar KJ. Gender-dependent impact of major depression on autonomic cardiovascular modulation. Prog Neuropsychopharmacol Biol Psychiatry 2011;35(4):1131–8.
[27] Samad Z, Boyle S, Ersboll M, Vora AN, Zhang Y, Becker RC, et al. Sex differences in platelet reactivity and cardiovascular and psychological response to mental stress in patients with stable ischemic heart disease: insights from the REMIT study. J Am Coll Cardiol 2014;64(16):1669–78.
[28] Tomfohr LM, Martin TM, Miller GE. Symptoms of depression and impaired endothelial function in healthy adolescent women. J Behav Med 2007;31(2):137–43.
[29] Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med 2009;71(2):171–86.
[30] Kell R, Haunstetter A, Dengler TJ, Zugck C, Kubler W, Haass M. Do cytokines enable risk stratification to be improved in NYHA functional class III patients? Comparison with other potential predictors of prognosis. Eur Heart J 2002;23(1):70–8.
[31] Buchowski M, Webb MB, Davies M, Ashra N, Bodicoat D, Brady E, et al. The association between depressive symptoms and insulin resistance, inflammation and adiposity in men and women. PLoS One 2017;12(11).
[32] Hage MP, Azar ST. The link between thyroid function and depression. J Thyroid Res 2012;2012:590648.
[33] Reavell J, Hopkinson M, Clarkesmith D, Lane DA. Effectiveness of cognitive behavioral therapy for depression and anxiety in patients with cardiovascular disease: a systematic review and meta-analysis. Psychosom Med 2018;80(8):742–53.
[34] Carlsen T, Salvesen O, Sui X, Lavie CJ, Blair SN, Wisloff U, et al. Long-term changes in depressive symptoms and estimated cardiorespiratory fitness and risk of all-cause mortality: the Nord-Trondelag Health Study. Mayo Clin Proc 2018;93(8):1054–64.
[35] Bangalore S, Shah R, Pappadopulos E, Deshpande CG, Shelbaya A, Prieto R, et al. Cardiovascular hazards of insufficient treatment of depression among patients with known cardiovascular disease: a propensity score adjusted analysis. Eur Heart J 2018;4(4):258–66.
[36] Lavoie KL, Paine NJ, Pelletier R, Arsenault A, Diodati JG, Campbell TS, et al. Relationship between antidepressant therapy and risk for cardiovascular events in patients with and without cardiovascular disease. Health Psychol 2018;37(11):989–99.
[37] Kim JM, Stewart R, Lee YS, Lee HJ, Kim MC, Kim JW, et al. Effect of escitalopram vs placebo treatment for depression on long-term cardiac outcomes in patients with acute coronary syndrome: a randomized clinical trial. JAMA 2018;320(4):350–8.
[38] Amare AT, Schubert KO, Tekola-Ayele F, Hsu Y-H, Sangkuhl K, Jenkins G, et al. The association of obesity and coronary artery disease genes with response to SSRIs treatment in major depression. J Neural Transm 2019.
[39] Carney RM, Blumenthal JA, Freedland KE, Youngblood M, Veith RC, Burg MM, et al. Depression and late mortality after myocardial infarction in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study. Psychosom Med 2004;66(4):466–74.
[40] Sramek JJ, Cutler NR. The impact of gender on antidepressants. Curr Top Behav Neurosci 2011;8:231–49.

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