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Psychosomatic Interrelations in Cardiovascular Diseases and Their Consequences on Patient's Quality of Life

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Abstract

At present, the cardiovascular diseases (CVD) are among the major concerns of World Health Organization (WHO), assurance health systems and researchers in the specific field, because they are the number one cause of deaths globally, and according to several perspective studies, they will become the pathology that generates the greatest economic burden worldwide, through morbidity, disability, poor quality of life, and cause of death. Nowadays, the psychic field and the vulnerability of individual mental level to stress are an important link in the development of mental illness, CVD (included in the group of psychosomatic disorders), and also of interrelationship between them. The combined effects of these factors are reflected in the behavioral and cardiovascular (CV) system's pathophysiological changes, which determine the impairment of health-related quality of life for the CV patients, on both short-term and long-term. This chapter aims to address both the interrelationship of psychosocial factors with CVD in terms of its multifactorial etiology and the mark of this bidirectional link on the quality of life of the patients. In several sections, the following issues will be described: general aspects regarding the relationship between homeostasis-stress-pathology; the role of stress as a psychosocial factor in the multifactorial etiology of CVD; the implications of mental disorders in the pathogenesis of CVD; behavioral aspects of CV patient during his illness, and strategies for improving therapeutic adherence and the quality of life of these patients.

Keywords: stress, anxiety, depression, cardiovascular diseases, quality of life

1. Introduction

In 1978, World Health Organization (WHO) defines health not only as a mere absence of disease or infirmity but as a state of complete well-being, physically, mentally, and socially. Also, in 2013, in its report regarding the global health, the same organization specifies that the

cardiovascular diseases (CVD) are the leading cause of premature adult death in the world, and one of the major causes of disability worldwide. In Europe, statistics of the European Commission (EUROSTAT) on causes of death identified CVD as occupying the first position in the 2013 ranking [1]. All these determine a cost increase in the health insurance system and a decrease in the individuals' quality of life (QOL). According to the 2016 recommendations of the European Society of Cardiology [2], prevention of CVD is a major public health objective. Due to an increased prevalence of CVD in the general population and a negative effect on both social and economic status today, they are considered "civilization diseases" [3]. Numerous clinical studies have revealed a very close correlation between the occurrence of cardiovascular (CV) pathology, genetic, and life style factors and modifiable physiological and biochemical factors during the individuals' lifetime. Also, it was demonstrated that a better management of the traditional modifiable CV risk factors (through measures of therapeutic education of the patient) may help reduce mortality and morbidity from CVD in the general population, especially in patients who have an increased risk of developing complications [4]. In recent decades, researchers' attention was directed toward other CV risk factors, including nontraditional psychosocial variables. These risk factors, insufficiently approached before, but potentially modifiable, have become object of the INTERHEART study, including one called "psychosocial stress" (and reunited under the name of psychosocial factors) [5]. An association between emotions and CVD was observed since ancient times. Hence, clinical observations of Hippocrates and Galien led to the establishment of the four fundamental human temperaments: sanguine, choleric, melancholic, and phlegmatic. The effect of negative emotions (e.g., anger, anxiety, and depression) on the health of the individual is already a well known, fact sustained by several clinical trials. Nowadays, the anxiety and mood disorders are widely recognized as two psychosocial factors, the presence of which has been observed in a large number of patients with CVD.

2. General aspects regarding the relationship between homeostasis—stress—pathology

2.1. The concepts of homeostasis and stress

The "homeostasis" term was first introduced in medicine by Hippocrates and its dysregulation consequences were called pathologies. "Any dyscrasia or rupture of the normal equilibrium is the cause of diseases" [6]. Walter Bradford Cannon, a Harvard physiologist, connects the concept of homeostasis and the concept of stress in 1915, and 20 years later, in 1935 he recognizes that the connectedness is a secretion of adrenaline produced by the adrenal medulla, consequence of an adaptive hyperfunction of the sympathetic nervous system (SNS), required to maintain normal limits of homeostasis [7]. The structures by which the body controls and regulates its own homeostasis are the interventions of the central nervous system (CNS), autonomic, endocrinal, and immune systems. The main control mechanism at the base homeostasis is a negative "feedback." The concept of "mental stress" was first introduced in 1956 and perfected over many decades of research by Hans Selye, pioneering endocrinologist, recognized as the "father of stress," who defined it as "the nonspecific response of the body to a series of

external stressor agents of physical, chemical, biological, and psychological origin" and which can trigger future pleasant or unpleasant events. He depicted the existence of two stress-response syndromes, one local and one general [8]. Local adaptation syndrome is a localized response, limited to the aggression area of the stress agent, immediate and short-termed, and manifested by an acute inflammatory response, while the general adaptation syndrome is defined by a general reaction of the body, it is a long-term reaction and involves the activation of the CNS by neuroendocrine axis, hypothalamic-pituitary-adrenal axis (HPA axis), and the autonomic nervous system (ANS) through the SNS [8]. Nevertheless, this biological theory of Hans Selye is just a description of adaptive physiological reactions to the presence of stress factors and discusses only the behavior of different organ systems and omits one's subjective perception of stressful situation emerging in one's life, the relational, cognitive, behavioral, and affective aspects that can develop after such a situation being ignored. In the context of the new approach, in 1984, R. Lazarus defines stress in a broader sense and comes up together with Folkman with the model "Theory of Cognitive Appraisal," which explained the mental process that influences the stressors [9].

2.2. Biological stress effects on the body

The systemic response to stress is a general nonspecific reaction and has at its base the intervention of numerous biological systems, two of which are major components: local and CNS through neuroendocrine axis and immune axis, but particular roles in modulating it play the basal nuclei, hippocampus, and amygdala [10].

2.2.1. The role of the amygdala and hippocampus in the stress response

The subjective perception of the stimuli is possible due to the intervention of two limbic structures: the amygdala and the hippocampus. The amygdala is a meeting point for neuronal sensory afferents for most perceptions that receive information from the entire cortex it generates efferent to the hypothalamus and thus modulates the ANS and the hypothalamo-hypophyseal axis [8]. The amygdala affects the emotional valence of sensory stimuli playing a very important role in the behavioral response and facial expressions associated with feelings of fear and anxiety. Both of them being involved, the thalamus and the amygdala activate an almost immediate response for fear [11, 12]. The hippocampus is, on the other hand, a structure designed to generate an appropriate behavioral response to a stimulus. Through functional integration of the two structures, it is possible to adapt the individual's vigilance and attention to stress [11, 12].

2.2.2. Neuroendocrine axis response to stress

This type of response is triggered and modulated by the hypothalamus that integrates received afferents and is highly interconnected with other parts of the CNS, limbic system, and ascending reticular activating system (ascending RAS) and is also connected with areas of the ANS through the locus coeruleus-norepinephrine system which is the principal site for brain synthesis of nor-adrenaline, and the HPA axis by the release of the corticotropin-releasing hormone (CRH) [13]. The role of the cerebral cortex is to increase alertness and attention through incoming afferents

by thalamus and ascending RAS, under stress conditions; the role of the limbic system is to imprint the emotional component to the stress response (manifested by states of fear, anger, joy, or elation), while the ascending RAS is the one that induces the cortical alertness state (manifested by vigilance and excitement), increasing the activity of SNS and reactive of the muscle tone [13]. In the periphery, the neuroendocrine axis response to stress is mediated through the effects of increased plasma levels of catecholamines (adrenaline and noradrenaline) and cortisol, hormonal messengers responsible for CV stimulatory effects in the context of organism's adaptive responses to stress [13]. These effects are treated as a whole for preparing the body for *fight and flight* [14]. Besides these two major systems, in the neuroendocrine response of organism to stress, a number of other hormones are involved such as: thyroid's hormones, antidiuretic hormone (ADH), aldosterone hormone, etc.

2.2.3. *The immune response to stress*

There is a bidirectional relationship, of mutual modulation, between the neuroendocrine and immune response to stress. It has been found that stress, both the cognitive (e.g., an emotional shock), recognized by the CNS, and the noncognitive (e.g., secondary to an infection, inflammation) have the capacity to trigger a cascade of biological reactions that will directly or indirectly involve the immune system. Thus, activation of the immune system is considered to be a noncognitive stressor using neural and neuroendocrine circuits identical to those that occur in cognitive stress. The immune response, both local and systemic, to stress may be one of the inhibitions (with anti-inflammatory action) in the context of eustress and one of the stimulations (with pro-inflammatory action) in the context of distress. Two mechanisms underlie the immune response to stress: hormonal and nervous. In the hormonal mechanism, lymphocytes secrete pro-inflammatory cytokines type IL-1 β , IL-6, TNF- α that activate both the HPA axis with consecutive hypersecretion of cortisol [15] and contribute to expression of receptors for cortisol and adrenaline with direct consequences in mediating innate and, respectively, acquired immune response; increased circulating levels of above mentioned cytokines IL-1 β , IL-6, and IFN γ (interferon gamma) have been emphasized in depression [16]. Cytokine function in modulating the process of organisms adapting to stress and their direct relation with a series of neurotransmitters puts them nowadays in the spotlight, playing a key role in the body's immune response to stress [17]. In the context of the nervous mechanism, the main role is played by the sympatho-adrenergic mechanism and stress neuropeptides with implications both in the periphery on lymph nodes, of the spleen, and thymus, but also centrally through CRH intervention that activates ANS, a situation that leads to summing the action of adrenaline with cortisol and have as final effects the functional inhibition of the immune system.

3. The role of stress as a psychosocial factor in the plurifactorial etiology of CVD

Numerous studies have proven the role of psychosocial factors in increasing incidence of CVD and short- and long-term prognosis of patients with manifest CVD [18]. The impact of

psychosocial factors for both QOL and prognosis is becoming increasingly well defined in patients with heart failure (HF) [19], postcoronary bypass surgery [18], and implantation of a cardioverter defibrillator [20]. A distinction between psychosocial stress and psychosocial factors must be made. Defining the scientific concept of psychosocial stress implies the creation of a model for CVD (**Figure 1**) and its integration at various levels of all potential psychosocial factors involved in the development of these pathologies [21].

According to this model, it can be recognized by all experts that not only negative life events (financial loss, loss of partner, workplace, etc.), but also the negative emotions (depression, anxiety, fear, etc.) can become CV risk factors [18]. There is no official definition of psychosocial stress. Thus, we can consider that the psychosocial stress model on the CV system is the released expression by the CV system itself to the action of psychosocial factors on it.

3.1. Mechanisms involving psychosocial stress in the pathogenesis of CVD and psychosomatic disorders induced by it on the heart level

Stress is an important part of our lives, essential in the short term, but it can become dangerous as a long-term presence. Mechanisms through which psychosocial factors can increase the risk of developing or worsening CVD are various and complex.

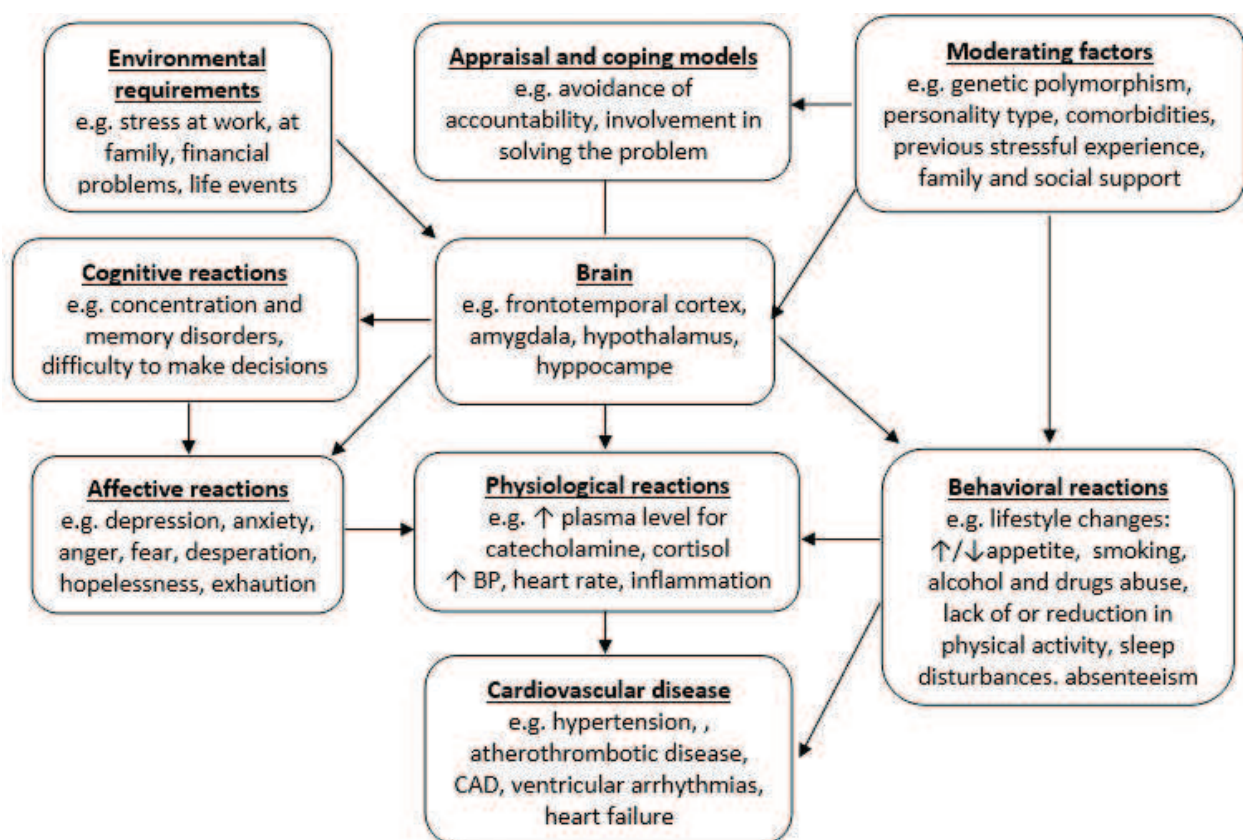


Figure 1. A stress model integrating psychosocial risk factors of CVD (after Ref. [21]).

3.1.1. *An unhealthy lifestyle*

One first impact of long term of psychosocial stress is the individual's recourse to an unhealthy lifestyle. Therefore, these patients smoke and drink more, often adopt an unhealthy diet, reduce their physical activity, etc., in comparison to the patients with no psychosocial factors [18]. Financial barriers of a high-quality healthcare are also contributing to an unfavorable prognosis, as after an acute myocardial infarction (MI), for example.

3.1.2. *Pathophysiological changes*

In CVD, participation of the psychosocial factor in both constitution and modulation of their evolution, together with other etiopathogenic factors is uneven, but it is proven by a series of experimental and epidemiological studies [22]. The leading role is the one of SNS hyperactivities (by disrupting the physiological balance between sympathetic and parasympathetic), being the body's first defense mechanism that not only occurs both in acute conditions (requiring its rapid adaptation), but also in conditions of chronic persistence of stressor factors [23]. CV changes induced by the SNS hyperactivity during acute stress are represented by: short-term increase of blood pressure (BP) values, mediated through the activation of alpha-adrenergic receptors and heart rate (HR) by stimulating beta-adrenergic receptors, transient endothelial dysfunction, lowering the threshold for triggering the cardiac arrhythmias and increasing the risk of MI, left ventricular dysfunction, and even the sudden death [18, 24]. Under normal conditions, the simultaneous growth of both the HR and the BP involves modulation of baroreflex function. Particularly, under stress conditions, the sensitivity of baroreflex mechanisms is reduced, with loss of the major cardioprotective mechanism autonomic reflex [25], and finally, the persistence of this disorder favors the appearance of high BP. The risk of MI induced by psychological stress appears due to the simultaneous increase of both the systemic vascular resistance and the myocardial oxygen requirements, effects of the SNS stimulation, and concurrent discharge of catecholamines. Adaptive response of the CV system under stress conditions occurs as a physiological response, but the generation alterations of autonomic impulses can trigger ventricular arrhythmias especially in the presence of a pre-existing CVD [21, 25].

A series of recent studies indicate that the asymmetrical brain activity plays an important role, too, in the heart vulnerability to ventricular arrhythmias, an aspect proven by the fact that the lateralization of brain activity during emotional stress may stimulate asymmetric heart, and by inhomogeneous repolarization which creates conditions of electrical instability that underlie the generation of ventricular arrhythmias [26]. It has been found that patients with CAD have this exaggerated asymmetric brain activity in several cortical areas during periods of psychosocial stress, such as the left parietal cortex, the left anterior cingulate, the right visual association cortex, the left fusiform gyrus, and the cerebellum [27].

The presence of the long-term stress creates favorable conditions for the persistence of arterial hypertension (HT), initiation, and progression of the atherosclerotic vascular process [17] through both persistence at high levels of sympathetic tonus and as a result of its association with inflammatory process [17, 28] initiated by the elevated plasma levels of cortisol following the entry into action of the HPA axis [14, 28] and the development of resistance of the glucocorticoid receptor [29], also due to activation of the sympathetic renin-angiotensin-aldosterone

system (RAA system). A number of behavioral disorders (increased appetite, sedentariness, and excess consumption of energy drinks) can be added, that the individual can acquire even some pathologies developed over a long period of stress, such as metabolic syndrome. The persistence of elevated BP beyond the moment of acute stress and its transformation into chronic stress conditions in a chronic pathology—arterial HT—are both due to the role the CNS plays in part through autonomic regulation of BP, hydro electrolytic balance, and ADH release [22], and entry into action of RAA system and the occurrence of inflammatory process at a vascular level, particularly the adaptive immune response that plays an important role in the pathogenesis of this disease [30]. It was initially revealed that experimental damage to certain regions of the brain like the anteroventral third ventricle, the subfornical organ, prevents many forms of experimental HT [31], but recent studies have shown that these forebrain region plays an important role to peripheral activation of T cells and vascular inflammation during angiotensin II-dependent HT [32]. One of the principal pathways activating the RAA system is the SNS. Both, acute and chronic stress can increase renal renin levels and plasma levels of angiotensin II (ANG II) that acts to maintain the constant extracellular volume and BP by different mechanisms. High levels of renin and AGT II are attenuated by β -adrenergic blockade [33], thereby demonstrating the relationship between the two systems. The local renin-angiotensin systems (RASs) exist at the level of solid tissues (e.g., heart, kidney), but it is also present in the circulating RAS in a variety of circulating cells [34], and the ANG II type 1 receptors (AGTR1) are the most numerous expressed, and they mediate most of the known functions of ANG II [35]. Stimulation of these receptors, by increased plasma levels of AGT II, is responsible for the persistence of HT, pro-inflammatory, and pro-oxidative actions [35]. AGTR1 expression in all immune cells that were observed has contributed to involvement of the RAS in vascular inflammation and the atherosclerotic process [35, 36]. According to the latest discoveries, both CNS and increased levels of ANG II and salt from the body are responsible for T-lymphocytes activation, which once activated, reached the peripheral blood vessels, and kidneys start the release of pro-inflammatory cytokines responsible for vasoconstriction and retention of sodium thereby contributing to the long-term maintenance of high BP values, respectively, arterial HT [31, 32, 36]. Reduction of the inflammatory process at the vascular level both through direct blocking of the production of ANG II by means of pharmacological agents like angiotensin converting enzyme inhibitors (ACE inhibitors) or indirectly by other pharmacological agents such as statins, is associated with the decrease of plasma levels of various pro-inflammatory and pro-coagulant markers from the old, high sensitive C-reactive protein, soluble cellular adhesion molecules of immunoglobulin family, the selectins group, up to long pentraxin 3, a new multimeric inflammatory biomarker, from the family of pentraxins that is nowadays one of the mechanisms of intervention in reducing BP values in hypertensive patients and reduction of the progression of the atherosclerotic process, issue proven by numerous clinical studies [37–39].

3.2. The psychosocial consequences of cardiovascular diseases

Psychosomatic disorders in CV patients are manifested through the appearance of psychological disorders echoing the suffering of the somatic, at the CV system level. Development of atheroma plaque both peripherally and at the cerebral level and also the decrease of cardiac output that has repercussions over the cerebral flow in patients with cardiac insufficiency can

induce the process of chronic cerebral hypoxia and is the cause of developing symptoms such as asthenia, fatigue, headache, and sleep disorders, in which over time can lead to diminished cognitive performance (attention, memory, and learning) and even ideational flow. A series of studies have pointed out that the cerebral vascular disease is associated with cognitive function and shows a key role in the decline of memory [40]. It has been found that 25–75% of the stroke patients can develop vascular cognitive impairment [40]. The development of carotid artery stenosis was associated with the decrease in neuropsychological performance due to the chronic drop of cerebral blood flow [40] and by affecting the neurovascular unit increases the likelihood for dementia [41]. It seems that both symptomatic and asymptomatic carotid stenoses are associated with cognitive impairment [42]. Withal, hypertensive individuals are more susceptible to developing cognitive impairments than those whose BP values are within normal limits [43]. Other cardiac conditions such as atrial fibrillation or HF, both reducing cardiac output and increasing the risk for thromboembolism, have been associated by some, but not all, researches with cognitive decline [44, 45]. Frequently, the people with CAD develop illness-related symptoms in the recovery period, such as breathlessness and chest pain, both of which are associated with post-MI fatigue [46]. Majority of patients with heart disease from a hospital reported a poor quality of sleep and that subjective quality of sleep associated with fatigue post-MI and daytime dysfunction were predictors of depressive symptoms [47]. Among 15–20% of CV patients are depressed and as many of those who have suffered a heart attack later developed a major depressive relapse [48]. Approximately, 25% of patients with HF can develop a major depressive disorder and the share of depression symptoms among them can reach 30–50% [48]. CV patients acquire a special social status, starting from their removal from a number of stressful physical activities (household routine) to reduction or suspension of practicing sports activities, hiking or even limiting sexual activity and ending with granting priority to emergency medical services. All these behavioral changes to which a cardiac patient must suddenly undergo summed up with a number of other lifestyle restrictions concerning quitting smoking, alcohol, coffee intake, or the potential risk of relapse of acute MI are actually new sources of mental stress for him and culminate with the prospect of sudden death or possible long-term disabilities (physical, cognitive, emotional, and social) after stroke. Thus, the CV patient develops a state of fear and restlessness, of constant anxiety, as an expression of the presence of a continuous mental stress in one's life with varying degrees of intensity, playing an important and negative role in the development of one's heart disease itself.

4. The implications of mental disorders in the pathogenesis of CVD

In recent decades, scientists began to increasingly focus their attention toward a group of nontraditional risk factors for CVD, also, including many psychosocial variables in their studies. The most studied issues are represented by the impact that negative emotions (e.g., anger, anxiety, and depression) have on the general health of the individual and further in initiating, precipitating, or worsening of pre-existing pathologies [18]. Although various negative emotions have been studied, the results of several researchers have led to similar conclusions regarding the impact of anxiety disorders and mood disorders which appear as two psychiatric factors with a higher incidence among people with CVD [19, 48, 49].

4.1. Depression and cardiovascular disease

Both experimental and epidemiological studies revealed a bidirectional association between depression and CVD. The changes in homeostatic and neuroendocrine function during the CVD create favorable conditions for the development of mood disorders, such as depression [47, 48], and depression, through behavioral and pathophysiological changes produced by it, is a recognized risk factor for CVD-related morbidity and mortality [48–51]. The major depression is the most common mood disorder frequently encountered among patients with CVD [52] and is the one that portends adverse CV outcomes and increased healthcare costs. The prevalence of depression is at least three times greater in patients with CAD or HF than in the general population, and one in five CV patients is depressed [48, 53]. If a series of depressive symptoms are added to the major depression diagnosis itself (present but not enough to meet the diagnostic criteria), which frequently develop in a patient who recently suffered a heart attack, the share among these patients may increase at 40–65% [48]. The depressive symptoms developed by the CHD and HF patients are susceptible to contribute toward too limiting physical activity and impaired their QOL [53, 54]. Also the occurrence of depressive symptoms on the background of CVD is, as well, involved in both relapsed acute cardiac events (stroke, MI) and increased mortality [50]. Since the CV consequences of depressive symptoms continue to generate events with poor prognosis after acute coronary syndrome, the American Heart Association (AHA) issued a 2014 Scientific Statement recommending that depression be elevated to the status of a risk factor in acute coronary syndrome [55]. As regards to the relationship of depression with other CVD, such as arterial HT study, results are controversial [56].

Despite growing evidence of the close link between depression and CVD, the pathophysiological mechanisms underlying these interconnections are still unclear. A series of the neurobiological processes and mediators that are common to both mood and CVD are considered to underlie this interconnection, consequence of their activation by psychosocial stress. These include the following behavioral and pathophysiological mechanisms: (a) neuroendocrine and neurohumoral changes involving dysfunction of the HPA axis and consecutive activation of the RAA system; (b) immune system alterations including activation of pro-inflammatory cytokines; (c) autonomic and CV dysregulation, which include increasing the sympathetic activity, decreasing the parasympathetic tone, HR and rhythm disturbances, and altered baroreceptor reflex function; (d) central neurotransmitter system dysfunction including dopamine, noradrenaline, and serotonin; and (e) behavioral changes including fatigue and physical inactivity [57].

More and more studies have emphasized the connection between depression and ANS and CNS dysfunction. The response of the HPA axis and consecutive activation of the RAA system are similar to the body's physiological responses to stress factors and has been linked directly or indirectly to CV regulation and endocrine changes associated with depression [57, 58]. Dysfunction of the HPA axis was described for the first time by Carroll [59, 60] and the functional consequences at its different levels translate into alterations in the release of CRF, dysregulated adrenocorticotrophic hormone (ACTH) (response to CRF's alterations), and elevated circulating cortisol or cortisone levels [61], which have been observed at the depressive patient in the cerebrospinal fluid, hypothalamus, and locus coeruleus [62]. Damage of

the hippocampus caused by stress seems to be the key of the dysregulation of the CNS and is responsible for the depressive symptoms, through its consequences generated on HPA axis' activity [63]. Endocrine and immune systems interact with each other and some of their functional disorders are common to mood disorders and CV disease, playing a role in the combination of the two pathologies. In 1991, Smith was the first to propose the macrophage theory, the pathophysiological mechanism of dysfunction of the immune system associated with depression, as a result of an excessive secretion of monokines such as interleukin (IL)-1, tumor necrosis factor (TNF)- α , and interferon [64, 65]. Similar pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6 are released into the systemic circulation of post-MI patients, demonstrating an activation of the immune system that is directly linked to specific CVD [16, 65, 66]. Once synthesized, they have negative consequences in both the CV and CNS [66], thus being responsible for occurrences of not only depression symptoms but also neuroendocrine and autonomic systems disorders. Also, peripheral cytokines play an important role in the release and metabolism of several CNS neurotransmitters, including monoamine neurotransmitter (dopamine, noradrenaline, and serotonin) [67], alter the glucocorticoid axis and increasing the plasma levels of cortisol [68], aspects directly related to the onset of clinical depression [69]. A different mechanism underlying the link between depression and CVD is that of the combination of hypercortisolemia and platelet function disorders, including enhanced platelet reactivity and release of different platelet products [61, 70], one can say that it creates the theoretical foundations that explain the pro-atherosclerosis effects of depression. An interesting aspect is represented by the increased levels and reactivity of platelets that has been associated with the presence of depression among both healthy individuals and patients with CVD [70]. Possibly this quantitative and qualitative exaggerated response of the platelets could be responsible for the connection between depression and CVD [71]. An influence of depression in reducing HR variability and baroreflex cardiac control in CAD patients [72], and impaired coronary flow reserve that increases risk of acute coronary syndromes have also been observed. All these mechanisms suggest that patients with depression have an increased risk of developing heart rhythm disorders. Recent studies results have revealed that behind these complex interactions between depression and CVD is a genetic predisposition, further research focused on identifying specific genes that link depression/negative affect and CVD. It was thus determined that the serotonin transporter (SERT) gene polymorphism plays an important role in both pathologies [73]. Under the behavioral aspect, depression is associated with decreased adherence to recommended risk-reducing behaviors for different chronic diseases, including CVD [74], diabetes mellitus, etc. For instance, the development of depressive symptoms in patients with CAD has been associated with decreased adherence to taking CV medications, attending cardiac rehabilitation, quit smoking, physical activity, and modified diet [75]. Many studies suggest that the poor adherence to these recommended behaviors is the link between depression and increased mortality in patients, after MI and poor prognosis in general for the CV patient [74, 76].

4.2. The association between anxiety disorders and cardiovascular diseases

A series of study results suggest that anxiety, too, plays an important role in prognosis of coronary heart disease (CHD) patients independent of depression [18, 19, 49, 52, 77], but there

are still many unclear aspects regarding its role as an etiologic factor in the pathogenesis of CVD. The main issue derives from the fact that it is difficult to establish a certain diagnosis of anxiety disease with a CV patient, because many symptoms characteristic of a panic attack (one form of manifestation of anxiety disease) overlap with the clinical symptoms of CHD, and in these circumstances, it becomes difficult to make a differential diagnosis [77]. A meta-analysis was carried out by Roest et al., assessing the association of anxiety disorder with risk of CHD [78]. Their results showed that anxiety seemed to be an independent risk factor for incident CHD and cardiac mortality, independent of sociodemographic variables, biological risk factors, and health behaviors. Anxiety takes different forms in relation to the types of CVD. For example, a patient with atrial fibrillation does not particularly associate symptoms of anxiety, but worry and phobic anxiety have the highest rate of association with CHD [79] and posttraumatic stress disorders are frequently linked with risk of stroke and CHD [80]. Most studies have revealed a close link between anxiety disease and CHD. The mechanisms proposed to underlie this link are represented by the fact that anxiety was associated with a higher risk of developing the ventricular arrhythmias, as a consequence of HR variability after MI [81], and a progression of atherosclerosis [82]. Also, anxiety is associated with an unhealthy lifestyle in patients at risk of CHD [75], such as excess of cigarette smoking or alcohol consumption, lower physical activity, and poor adherence to CV medications [74], which increase the risk of CVD. Pathophysiological mechanisms' model proposed for anxiety's intervention in the pathogenesis of CVD is the one for accumulation of anxiety as a chronic stressor factor along with other negative emotions and its intervention at the level of the two systems: ANS and CNS with the activation of the HPA axis and increased release of plasma catecholamines, and endothelial damage, underlying the initiation and progression of atherosclerosis and development the CAD (also known as CHD), and acute coronary events. If this model is viable, it may be expected that anxiety would be frequently associated with increased BP. However, in medical practice study, results are controversial. There is a link between anxiety and HT, but anxiety as a risk factor for incident HT is unclear [83]. Another model which could explain the conflicting results of various epidemiological studies is represented by the emotional triggering model in which the individual's timing of anxiety measurement is essential [84]. Acute anxiety is often associated with hyperreactivity of the CV system to stress [18]. The close connection between anxiety, CVD, and sudden death, suggests that ventricular arrhythmias may be the principal mechanism for cardiac death. The pathophysiological mechanism that underlies this hypothesis is the reduced HR variability by increased SNS stimulation or impaired vagal control [85]. It was also revealed that anxiety alone is associated with higher platelet levels [71], and co-occurring with depression, when the two comorbidities have the highest platelet levels [86], increases the risk of acute events in CAD patients. The direct effects of the SNS together with the activation of HPA axis increase the risk of developing a CVD and lowering the threshold for myocardial ischemia, arrhythmias, and sudden cardiac death in patients with symptoms associated with anxiety [79, 81].

4.3. The importance of personality type

An important role in increasing the risk of CVD is apparently played by the individual's personality type. Thus, two kinds of personality Type A and Type D have been related to

increased risk of CVD. Initial studies have revealed that personality Type A, characterized by hostility, ambition, competitiveness, etc., is more prone to CVD [87]. However, subsequent studies have reported that the association between Type A behavior and the risk of developing the CVD is insignificant or reduced to a limited number of cases [87]. In recent years, attention was also directed on the Type D personality, which is characterized by a combination of negative affectivity and social inhibition. This individual accumulates high levels of chronic distress that are not recognized by him and, therefore, are not to be expressed. The patients with CAD and Type D personality profile have associated a risk almost 2–2.5 times higher for developing adverse cardiac events [88] and in this association, Type D personality appears to be an independent risk factor for CVD.

4.4. Pharmacological implications during depression, anxiety, and CVD treatment

Regarding depression, its prevalence among patients with CVD is high (20–25%), both the immediate and the long-term prognosis of a CV patient worsens 2.2 times if one develops depression, but there is also a controversy about the use of antidepressants, selective serotonin reuptake inhibitors (SSRIs), in particular, whether or not it increases the risk [89]. As follows, antidepressant medication is among the most frequently prescribed medication in the world, and its consumption has skyrocketed in the last decade [90]. However, information concerning antidepressants' relationship with CAD is rather less known. Numerous studies have highlighted an increased risk of CHD during use of antidepressants, especially in tricyclic antidepressants [91]; reports have also emerged in this regard for patients who are users of SSRIs [92]. From a theoretical perspective, antidepressants such as SSRIs (which have potent antiplatelet activities) should have good effects in terms of coagulation. Tri- and tetracyclic antidepressants should not be used for the pharmacotherapy of patients with CVD associated with depression too [91], because by increasing the concentration of monoamines in the synaptic space can have multiple CV side effects by increased catecholamine activity on adrenergic and serotonergic receptors. Therapy with monoamine oxidase inhibitors (MAOI) is contraindicated in CV patients, as antidepressants are, because they irreversibly or reversibly inactivate the enzyme monoamine oxidase and increase concentrations of the noradrenaline in the synaptic space, leading once more to CV stimulation [91]. The US Food and Drug Administration (FDA) issued in 2011 a drug safety communication regarding citalopram (SSRIs) administration not to exceed the dose of 40 mg/day, based on study findings of QT interval prolongation, with different doses of citalopram [93]. A similar warning was also issued by the European Medicines Agency in 2011. QT interval prolongation is a favoring condition for development of arrhythmias including potentially fatal torsades de pointes [94], issue that has also been recognized with other antidepressants such as escitalopram and amitriptyline [94]. Old age along with other factors such as female gender, family/personal history or concomitant use of drugs with a potential for QT interval prolongation, increase the risk of cardiac toxicity of SSRIs antidepressants particularly in conditions of overcoming the therapeutic plasma concentrations [95]. Sertraline, a SSRIs molecule with a favorable cardiac-safety profile, is still considered a safe and effective treatment for recurrent depression in patients with recent myocardial infarction or unstable angina [96]. Because stress and anxiety disorders are prevalent in patients with CVD, in coronary care units, the use of the benzodiazepines

as anxiolytics drugs is reasonable [78]. The benzodiazepines are considered as one of the safest groups of drugs in patients with CVD, because they are free of adverse cardiac effects and can be safely used by them even in the coming period after MI. A number of CV medications can, in their turn, exert neuropsychiatric influences with the consequences on the affect and physical status of an individual. The link between the use of β -adrenergic blocker agents and neuropsychiatric consequences, especially fatigue and depression, has long been described [97]. Many case reports and several small reviews support the link between propranolol and depression and, also, the increase in the number of antidepressant prescriptions in patients under treatment with propranolol supports this point [98]. A recent study has highlighted that all antihypertensive agents in monotherapy used in arterial HT treatment were associated with symptoms of depression, anxiety, or both [99]. Only the intensity of effects on mood is differentiated from one class of antihypertensive agents to another: β -blockers and calcium antagonists may be associated with increased risk, whereas ACE inhibitors and sartans may be associated with a decreased risk of mood disorders [100]. Fatigue alone or in combination with sedation occurs with greater frequency than placebo during therapy with calcium channel blockers, without requiring dose reduction. Diuretics may produce neuropsychiatric symptoms mainly indirectly, through electrolyte disorders or vitamin deficiencies (the loop diuretics-associated with thiamine deficiency), but are not frequently associated with fatigue, sedation, or cognitive impairment [101]. During the treatment with methyldopa, Paykel et al. found that sedation occurs in approximately 30–35% of the patients associated with marked fatigue and other studies reported a cognitive impairment [101], both through direct action of methyldopa or following sedation and translated by impaired concentration and decreased cognitive performance. Digoxin, used in the treatment of congestive HF (secondary after MI or other CVD) and as a rate control drug for atrial fibrillation and atrial flutter, can also have considerable central actions and has been shown to induce a variety of neuropsychiatric side effects, both at therapeutic levels and in toxicity, as: fatigue, depression, “mental disturbance” in 5% of patients taking this tonicardiac drug [102], psychosis, and delirium.

5. Behavioral aspects of the cardiovascular patient during his illness

In case of psychosomatic diseases, category that includes CVD, in which the psychological factors play an important role in their triggering or worsening, numerous studies have highlighted that cognitive representation of illness is a significant predictor of patient's recovery and social reintegration and indirectly through its consequences is reflected on the quality of one's life. Also, studies have shown that individuals can directly influence the results of different interventions on their health, both positive and negative, depending on the mental representation of the illness. The cognitive model of the illness (valid for all psychosomatic illnesses) was created by Leventhal et al. [103] and structures the beliefs of the individual about illness in five dimensions, represented by: identity (name and all signs and symptoms of the disease); cause (perception of possible triggers of the disease); time-line (perception about how long the illness might last and how will it evolve); consequences (perception of effects of the illness in the physical, social, emotional, and economic levels); and curability and controllability (perception of the degree to which the disease is curable and manageable).

This model that best explains the relationship between the illness perceptions and emotional and behavioral responses is called the self-regulatory model, and this process is performed through three stages of interpretation, coping, and appraisal. The patients' cognitive representations and perceptions model of their illness, proposed by Leventhal et al. [103], are known to influence patients' motivation to engage in preventive behavior, or curative healthy behavior with healthy outcomes, all expressed in health-related quality of life (HRQOL). This model explains that based on the individual cognitive and emotional perceptions about the illness, the individual reacts to various internal and external stimuli and generates illness-related cognitive and emotional representations that will be the basis of one's decisions on adaptation strategies in the new context of the disease.

5.1. Patients' quality of life

CVD in general and CAD in particular are nowadays the major cause of premature death in Europe [1] and also an important cause of morbidity, contributing substantially to increasing healthcare costs. It is a known fact that health services around the world are more oriented toward improving the quality of patient care than toward prevention measures, and acute care programs are more common than chronic care programs. For these reasons, WHO in The European Health Report from 2015 sets as its main objective the reduction of premature mortality from CVD, cancer, diabetes mellitus, and chronic respiratory diseases by 1.5% annually, until 2020 [104]. By adopting a Health 2020 Monitoring Framework Program in 2012 as the new European health policy framework, member states mandated the WHO Regional Office for Europe to measure and report on the well-being of the European population as a tool to measure health improvement of the European population. The Murray & Lopez study regarding plausible projections of future mortality and disability between 1990 and 2020 [105] highlighted that the leading causes of disability-adjusted life years predicted by the baseline model were (in descending order): ischemic heart disease, unipolar disorder/major depression, and cerebrovascular disease—three pathologies out of total top four of their results. Both, acute and chronic cardiac illnesses are widely recognized to have a negative impact on patient's QOL. Patrick and Erickson define HRQOL as “the value assigned to duration of life, as the patient's subjective perception about the impact of disease, injury, treatment or policy on their everyday life through the impact on physical, functional, and emotional status” [106].

Essential HT is one of the main risk factors of CVD, and at the same time, one of the main causes of death from noncommunicable diseases, still remaining a public health problem despite early diagnosis and the therapeutic advances in recent years. Undiagnosed and untreated or poorly monitored and treated diseases cause a number of CV complications: from CAD to HF, ischemic stroke, etc., with the impact on family, social, and professional life of patients and implicitly on their HRQOL. Many aspects of the relationship between HT and QOL are still unclear and unsolved. The impact of psychological disorders such as depression and anxiety on CV health is well known and studied by the scientific community, but the relationship of these two comorbidities with arterial HT is still controversial and not well understood [56, 83]. Results of a 2010 study emphasized that both comorbidities significantly associate with essential HT, depression more than anxiety, indeed, and that this

association had a significant effect on hypertensive patients' worsened QOL [107]. Awareness of their hypertensive status was highlighted as another factor that can exert influence on the hypertensive patients' QOL. According to the results of some studies, awareness of HT was negatively correlated to HRQOL in hypertensive patients [108] and the methods of modifying the attitudes of the hypertensive patient facing illness (from a passive to an active and positive one) have shown that a positive active attitude is an important element of self-efficacy, which is the most important component of social cognitive theory [109]. Self-efficacy requires motivating the patient to perform their duties and obligations deriving from their new condition, especially the chronically ill, in this case, the CV chronic conditions in order to produce the desired results that will lead to improvements in health-related behaviors and medication compliance. We can say, starting from Leventhal's self-regulatory model, that the change (in a negative or positive sense) of cognitive perception of the disease on the mental level of the patient with chronic cardiac condition will help address the patient's reaction to this disease, respectively, increasing self-efficacy expressed by improving HRQOL and cost reduction in health insurance systems. The poor QOL of treated hypertensive patients seems to be attributed to a more intensive drug treatment for controlling BP and changes in lifestyle, also, issues that may negatively impact on HRQOL [110], but this association was not attributed to adverse effects of BP-lowering drugs or any particular class. Analyzing the impact of association of various comorbidities with the appropriate drug therapy and high BP, it has been observed that the number of comorbidities does not significantly affect the hypertensive patient's QOL; however, the number of drugs exerts significant influences on different aspects in their QOL [111]. This issue could be explained by negative perceptions of patients about a large number of co-prescribed drugs as a result of poly pathologies, perception that entails a low adherence to antihypertensive treatment. All this suggests that awareness of being sick and not the disease itself, the need to respect a medical treatment for life, changes in lifestyle that impose restrictions on smoking, alcohol consumption, physical activity limitation, etc., are reasons for lower QOL of the hypertensive patient.

CAD is one of these chronic CVDs characterized by impaired functional capacity and quality of life. QOL of patients with CAD is influenced by a number of risk factors among which the most important are represented by depression, anxiety, and other associated comorbidities. Study results from the last decade revealed a prevalence of depression among 10–40% of the patients with CAD [50, 52, 53]. Since depression is both a primary and secondary risk factor in the development of morbidity and mortality in patients with CAD, independent of traditional risk factors such as smoking, HT, atherosclerosis, the new guidelines recommend a psychological profile screening of these patients for early detection of the tendency to develop depression [55, 112]. Among these patients, the results of various studies have highlighted that depression is strongly related to the presence of angina [49], and angina severity is directly related to their QOL. An interesting aspect is the fact that self-reporting on the perception of cardiac health status is independently predictive of long-term mortality in those with CAD [78]. Depressed patients with CAD vs. nondepressive reported a wider cognitive perception of the illness' burden [53]. Anxiety is another psychological state whose relationship with CAD was analyzed in a smaller number of studies, and it has been observed that its share in those patients was approximately 36% [78, 79]. The impact of CAD on the HRQOL differs according

to gender too; thus in women an unfavorable impact is reported in contrast to men [113]. But other factors may influence the QOL of CAD patients such as age, physical limitation due to angina, and angina frequency has an impact on prognosis as well as on HRQOL. Potential unfavorable prognosis of patients with CAD (at risk of developing MI, unstable angina, cardiac arrhythmias, etc.,) has a strong negative impact on the emotional component of the QOL assessment questionnaire, issue supported by the results of clinical studies highlighting the frequent association of depression and anxiety disorder with CAD. The patient's physical function component is also impaired in patients with CAD, but its intervention is in the background of QOL. The fact is that by summing up the consequences of both components, emotional and physical activity, CAD has a significant negative impact on the HRQOL of these patients. According to new discoveries, the healthcare professionals have an obligation to recognize, identify, and treat these variables that interfere with maximizing the benefits of cardiac surgery and pharmacological interventions aiming to improve a patient's physical QOL. The public health interventions, such as cardiac rehabilitation programs promoting physical activity, changes in diet, and quitting smoking are nowadays the main methods to improve CAD outcomes and their benefits are recognized today. These programs should improve perceived health status in the CAD population, especially in women. It is generally agreed today that benefits and risks of different therapeutic strategies of the underlying disease must be viewed from the individual perspective of the patient, an aspect known as personalized therapy. These principles underlie the concept of the "person-centered care," a concept with dynamic development in the CVD management sector in particular [114].

A large number of studies have tracked the impact of HF on HRQOL, given the fact that it is a disorder with consequences for all assessment dimensions of QOL, and this quality alteration of life reflects back on HF further contributing to increasing its severity. HF is a condition with a large share in the general population, particularly in the aged population, with a prevalence of up to 12%, with high financial costs, high mortality that reaches 50% in the 5 years following diagnosis, and frequent hospital admission [115]. HF has become today a major public health problem worldwide because of its incidence, prevalence, and evolutionary prognosis. The impact of HF on the functional component of QOL appears to be the most important and with the most severe consequences, aspect highlighted by the EPICAL study specifying that a QOL score reduction by 10 points is associated with a 25–35% increase of death rate and hospitalization for HF [116]. Limiting physical activity will hinder the patient's participation in a number of social activities that will restrict its network of social support, the patient becoming increasingly dependent on his family, leading to the development of a sense of burden for them. In this phase, the emotional component is added to deterioration in the QOL; patients face an increasing risk of developing anxiety and/or depression symptoms due to anxiety generated by fear of occurrence of decompensation moments and even sudden death, which further limits the autonomy and their activities [51, 53]. Anxiety symptoms are frequently reported by patients with HF, and these patients have a much higher anxiety level than healthy older adults. It has been found that patients with chronic HF and depressive symptoms (which account for 30–50% among them) have a significantly increased risk of death, repeated hospitalizations, and worsened HRQOL [53, 54]. The association of anxiety

and depression symptoms was observed in approximately 30–35% of patients with HF, an association that increases the risk for both reductions in QOL concerning health [117] and shortening of the survival rate. Taking into consideration that patients with HF show a high prevalence of physical symptoms, including dyspnea and fatigue, and more than 30% of these patients also have depressive symptoms [48], both with consequences for the subsequent evolution of the disease and also on the HRQOL of these patients. Heo et al. [118] investigated if a relationship between the two variables exists and found that physical and depressive symptoms have a dose-response relationship with HRQOL. Perception of loss of control exercised by these patients over variables such as physical and depressive symptoms and functional status seem to play an important role, hindering their improvement, an aspect that leads to considerable deterioration of their QOL [119]. Family support offered to patients with chronic illness seems to play an important role, too, in general and in particular in this case in relation to chronic HF patients' QOL. Family support must provide encouragement, empathy, and increase feelings of trust of the patient's own resources to regain their autonomy previous to the disease. Depending on the success of changing these perceptions about their disease, the HF patient may recourse to modification of behavioral self-regulatory model of Leventhal, and so these patients can engage in their care regime, choose whether to adhere or not to their prescribed regimen, thus becoming an active part of patient-centered care programs in order to improve health-related quality of their life, reduce hospitalization rate, and costs in the healthcare system and not least the reduced death rate. All these observations of previous studies support the view that better relationships between patient's perspective on family functioning, greater autonomy support, lower family criticism, and greater knowledge of family members and HF patients are associated with lower levels of depressive symptoms and better HRQOL, aspects proven by results obtained from the analysis of the impact of these factors by Stamp et al. [120]. Complex drug therapy that requires daily administration, also, presents increased risks of adverse effects and interactions that implicitly call for careful biological monitoring, respectively, increased cost, and is an added stress factor for this patient. All this calls for greater economic and social resources from the chronic HF patient, and their absence, especially in the elderly, may be related to HRQOL, rehospitalization, and high mortality. The new behavioral changes (dietary salt restriction, weight control, regular physical activity, self-monitoring of symptoms, etc.,) are part of nonpharmacological treatment of these patients and also have an impact on their QOL and entourage.

Of all the previously presented psychosocial factors, being in a stronger or a weaker relationship associated with deterioration of the QOL of the patient with CVD, depression has received the most attention from researchers in the last decade. The results of these studies have brought a clear evidence of depression association with CVD which is why recent clinical recommendations include mandatory screening for depression and its treatment, as a standard of efficient care of these patients [112].

It is already well known that the type D personality, which is a combination of two characteristics, namely negative affectivity and social inhibition, is associated with an increased incidence and risk of mortality due to CVD [88], and only few studies indicate that type D personality is associated with QOL both in health and in disease [121]. Type D personality

is considered an independent predictor of CV morbidity and mortality, the worsening QOL in patients with CAD and HF [122]. Type D personality becomes a pre-morbid condition for affective disorders especially among CV patients and hence the consequences in their HRQOL.

5.2. Therapeutic adherence in cardiovascular disease

Analyzing worldwide data on the global burden of disease, it can be observed that HT ranks first, before smoking and obesity: 26.4% of world adult population had HT in 2000, and its incidence is expected to reach 29.2% in 2025 [123]. Furthermore, today one of the major causes of mortality in the world is the CVD, which is expected to be the world's leading cause of death in 2020, the CHD being the first among them [124]. The high BP level is the most important modifiable risk factor of CVD, but despite the large number of potent antihypertensive drugs they succeed in achieving an optimal control of BP values only in 50–66% of patients [125, 126]. One possible reason for this low rate of BP control is that the antihypertensive medication is not taken as prescribed or not taken at all by the vast majority of patients [127]. In other words, the simple nonadherence to existing CV medication becomes a new risk factor for CVD. In the current context, the main objective of WHO in the 2015 European Health Report is to reduce premature mortality by CVD, cancer, diabetes mellitus, and chronic respiratory diseases by 2020 [104] due to the fact that chronic diseases generate high costs in the health insurance system and affect HRQOL, and they require providing services for their better management. Among the many factors that can increase the effectiveness and efficiency of these services, patients' treatment adherence and compliance to medication play an increasingly important role today, counseling patients is the main objective of the new policy in health for 2025 [128].

5.2.1. Adherence to medication and illness perceptions

Nowadays, in a broader sense, the concept of therapeutic adherence stands for the extent to which a person's behavior regarding the use of prescribed medication, respecting a diet, and/or a lifestyle change (reducing salt intake, stopping smoking, weight loss, etc.) correspond to the therapist's recommendations [129]. This newly introduced term in medical practice tends to replace the previous term of therapeutic compliance that has its origin in physics, given that the latter transmits an authoritative message from medical and pharmaceutical staff, which implies a passive attitude, of subjecting the patient to therapist decisions and failure of noncompliance can be seen from this perspective being only the fault of the patient. The adhesion term also includes the patient in making decisions about the treatment of his own disease, by establishing a partnership between the patient and the specialist, where the patient is a direct, active, and responsible partner on the results of his own treatment, thus becoming a major player in one's disease management [129]. Compliance can be defined as "taking medications as prescribed" [130] and involves an understanding of the correct use of medication and a positive attitude of the patient facing treatment due to a perceived personal benefit from its application. Therefore, patient compliance to treatment is mirrored in the individual's health and QOL.

Regarding arterial HT, clinical practice reveals that around 16–55% of hypertensive patients give up treatment during the first year of diagnosis and initiation of appropriate therapy of

the disease. Because many patients are reluctant to voluntarily provide information on their adherence to antihypertensive treatment, the true rate of nonadherence to medication may be even higher. Nonadherence to antihypertensive therapy is responsible for poor treatment outcomes or treatment failure, finally determining an increase in the rate of hospitalization and thus impairment of their medication-therapy-related QOL [131]. A number of studies have shown that various factors, such as demographic, clinical, treatment related, or behavioral, are responsible for adherence/nonadherence of antihypertensive medication, but in older adults, a major role seems to be played by psychosocial factors [132]. A study conducted in the USA highlighted that including a decline in physical and mental quality of the individual, as components for assessing QOL among hypertensive elderly people, is associated with lack of adherence to medication [133]. The results of numerous studies certify that an increased BP controlled by antihypertensive medication can at the same time improve HRQOL for these patients, reduce the risk of complications, and repeated hospitalizations of the hypertensive patients. A systematic 2016 review analyzing the relationship between QOL and treatment adherence in hypertensive patients certainly emphasizes: "nonpharmacological treatment improves the overall QOL and physical domain of people with arterial HT and adherence to pharmacological treatment has a positive impact on the mental and physical domains of patients, as it did on the overall QOL score" [134]. As predictors of nonadherence to antihypertensive medication, the following factors have been identified: poor knowledge of complications of HT, unavailability of antihypertensive drugs in the healthcare facilities, lack of education of hypertensive patients in the healthcare facilities, prior experience of medication side effects, uncontrolled BP, and taking nonprescribed medications (as self-medication) [135]. Another aspect of adhesion is the persistence of the treatment of patients. In case of HT, it has been observed that tolerance and self-perception that the adverse effects of antihypertensive medications play an important role in the patient's motivation to follow this treatment for the rest of his lives [136]. Thus, hypertensive patient's adherence and persistence to pharmacological and nonpharmacological treatment is a key component of HT management.

Despite advances in the field of CV pharmacology and interventional cardiology that contributed to increasing the rate of survival after heart attack, CAD remains worldwide an important cause of morbidity and mortality [137]. In this context, attention and efforts of specialists, in this pathology, must be directed toward secondary prevention, prevention that involves better management of both lifestyle factors and physiologic parameters, most often with medications. Although the number of prescriptions for CV medications among these patients increased significantly in the last 20 years [138], a large percentage fail to meet therapeutic goals aspect highlighted by the results of the European Action on Secondary and Primary Prevention by Intervention to Reduce Events III (EUROASPIRE III) survey [139]. Therefore, the main issue that was raised in this study was if the patient with CAD is compliant with medical therapy or not [140], an aspect appears to be closely related with a paternal clinician-patient relationship and not of the partnership.

The CV medications, according to clinical evidence, are now responsible for more than 40% reduction in mortality in CAD, and premature discontinuation, willingly by the patient, of some classes as beta blockers, antiplatelet agents, or lipid-lowering drugs [141] have shown unfavorable outcomes on morbidity, mortality, and HRQOL of these patients. A supply of

more information specific to pharmacological treatment (e.g., the consequences of nonobservance or sudden withdrawal of treatment) when initiating therapy improving the transition between secondary and primary care and a better explanation of the risk of relapse and the development of other possible complications of the disease, may contribute to attitude and behavior changes toward better patient treatment adherence. Under conditions in which HF is characterized by a high rate of hospitalization and has a negative impact on physical activity and on HRQOL, with high mortality, taking CV medications is essential to control HF symptoms and prevent exacerbations. The low adherence to HF pharmacological and non-pharmacological treatment (physical activity, diet modification, and weight control) increases mortality, morbidity, hospitalization rates, and healthcare costs. The negative affectivity and social inhibition, type D personality characteristic features, which are associated with poor health, a greater number of cardiac symptoms, impaired physical and mental health are known predictor factors of nonadherence to prescribed medication regimens, and if encountered among patients with HF, it translates into a poorer adherence to medication, which may lead to adverse health outcomes implicitly and QOL [142]. It seems that an important role in mediating the relationship between type D personality and adherence to medication is played by medication self-efficacy. Self-efficacy or personal efficacy, which is defined as confidence of the individual in their own ability to complete tasks and achieve objectives [143], seems to be associated with medication adherence, thus being an intermediate measure for health outcomes among HF patients. Low levels of self-efficacy have been associated with poor self-care adherence in patients with HF, and a better medication adherence was observed after improving self-efficacy to medication for type D patients with HF [144]. Therefore, the chronic HF becomes the most frequent diagnosis of hospital discharge, of all chronic conditions, generating a medical and psychological burden that impacts on HRQOL of those patients and economic burden on national healthcare systems. Improvement of their outpatient management by good-quality primary healthcare services becomes a necessity and can only be achieved when the two partners, specialist and patient, establish a partnership and understand that a treatment has more benefits than risks or costs, in other words, a strong degree of therapeutic adherence is essential by developing and applying interventions to enhance medication self-efficacy.

Another general problem of nonadherence is the so-called profligate patients, that is, those patients to whom medication was prescribed but is never followed in the long term. It has been found that more than 20% of prescriptions are never picked up from the pharmacy (given the high cost of medication, patient acceptance of the new status, etc.), others 20% are honored although used incorrectly (errors in dosage, rhythm by omitting doses, etc.) or are not consumed in 50% of cases by patient-initiated drug holidays [145]. Nonadherence to treatment appears to be the result of patients' decision, more or less thought-out, and translated by a change in the behavior toward their health, following a partial compliance or an infringement of the healthcare practitioners' guidance on therapeutic recommendations. Nonadherence is a complex phenomenon that is characterized mainly by two concepts tightly connected to each other: adherence (denoting the level of patient taking his medication and respecting the indications of healthcare practitioners regarding self-monitoring treatment and periodical controls) and persistence (denoting the time in complying with medication consumption)

[129, 131]. Medication adherence is thus a crucial self-care behavior for all the patients with chronic disease and especially for the CV patients. For these reasons, all needed efforts are made to develop predictive models for screening to better identify prospective patients at risk of nonadherence to treatment [146].

Leventhal's self-regulatory model is the basic explanatory model of patient adherence to treatment [147]. According to this model, when people try to understand the unfortunate event that suddenly appeared in their lives, sometimes with permanent consequences on personal and family life, they develop their own model at the mental level of its individual perception which brings together the five key components: what is the disease; what are its underlying factors; what are its consequences in everyday life; the time duration of disease and not least if they can cure or control it [147]. The uniqueness of illness representation derives from the fact that it is originated in the person's own intrinsic beliefs, they do not necessarily comply with scientific arguments and is in a permanent dynamics, suffering a series of changes, depending on the age and sex of the patient, the disease and one's experiences throughout it [147]. On the basis of their illness representations, patients subsequently develop their own response and coping strategies in order to adjust or minimize the impact of disease on the health of their own organism. Patients' decision to become adherent to medication is one of the health-related coping strategies. An individual's choice to adhere or not to the treatment regimen depends on one's beliefs about the disease and their perception of the importance of taking medication. Patient behavior for continued treatment, the persistence to treatment, once initiated, is dependent on personal assessments of the obtained results.

5.2.2. Strategies for improving therapeutic adherence

Detection of nonadherence share among CV patients and medication noncompliant individual profile is very important but not enough to overcome this problem, if not followed by management plans and existing/emerging technologies. As the phenomenon of nonadherence to therapy has grown in recent years, a number of interventions have been proposed to improve medication compliance of patients, which are centered in three directions: the health system, the therapist, and the patient, the three main players on which the therapeutic adherence behavior of an individual depends. The health system should be so organized as to put more emphasis on the quality of care in both primary and secondary prevention, to take initiatives with regard to organizing health education and therapeutic programs for patients, to use counseling strategies in primary care as the patient's motivational interventions for adoption of healthier CV lifestyles and reduction of their CVD risk, to monitor more closely the non-compliance to treatment, and to find solutions to correct the potential problems in a timely manner; all these actions will lead to improvements in outcomes and cost savings. A number of interventions (improvement of physician-patient communication, counting pills, the use of reminder packaging or electronic event monitoring systems, etc.,) have been approached targeting individuals with medication adherence problems. The benefits were modest as specified by the trial results but had significant effects on medication-taking behavior [148, 149]. The use of packaging interventions (like using pill boxes and blister packs, especially recommended for aging adults with multiple chronic diseases) effectively increase medication

adherence, aspect highlighted by a series of studies in this direction [150]. A review of different patient-centered interventions to increase adherence to treatment, which analyzed a total of 141 studies, revealed that a major problem is the lack of patient knowledge about the disease and its proper medication, misunderstanding of their active and direct role responsible for the results of therapy, its relationship to their health and implicitly to HRQOL and their physical activity [151]. Since the HRQOL is a multidimensional evaluative concept that is based on the patients' illness perception, the specialists' attention should be centered less on the intrinsic disease outcomes (e.g., CV morbidity or mortality) and more on the changing perception outcomes in patients with CAD. In order to improve patient-centered care, counseling programs and therapeutic education of patients are, thus, necessary to be introduced. The lack or low levels of knowledge (both patients and their family members) is an important and foundational element regarding their HF care regimen aspect supported by one's education and counseling programs that have improved outcomes such as better adherence to a hygienic-dietary regime, medication adherence, and a reduction in the rate of inpatient. All previous study results show that the presence of different CV risk factors in the general population and the emergence of the CVD, also, are related to a decreased QOL in these patients and support the idea that the events on healthcare education by health-related public programs should promote the importance of preventive measures associated with regular physical activity, with a special focus on women [114].

The conclusion derived from here regards the need to implement interventions on patient-centered care and education. Increased awareness, knowledge, and education of CV patients especially on the benefits/risks of adherence/nonadherence to treatment is an essential component in the increased ability of patients to manage their medication but not sufficient to ensure medication adherence and persistence. Alongside these educational programs, others are required to improve the skills of self-control and auto-management of therapy and disease, aspects derived from the fact that in the long term, these patients need to rely on daily personal effort unattended closely by a therapist. When behavioral strategies are associated with continuous therapeutic education programs, chances for adherence and persistence to medication increase greatly for the CV patient and therapeutic results will not wait to happen. Furthermore, implementing individual educational sessions and not the group one may be better suited to the specific needs of each individual, contributing to a better therapy personalization.

6. Conclusion and suggestions for future developments

As a result of current developments in society, stress is a component increasingly present in everyday life of the individual and even a necessary one to a certain point. Due to the close interrelationship with the CV system (which responds first to its presence), excessive stress generates a range of behavioral disorders (e.g., unhealthy lifestyle) and pathophysiological changes which create conditions favoring development of CVD. Through the high mortality rate, they induce in the general population and from the perspective of evolutionary trend analysis studies, in 2020, CVD will become the pathology that generates the greatest economic burden in the world, as morbidity, disability, reduced QOL, and cause of death.

Once triggered by induced pathophysiology changes, CVD also creates the prerequisites for the development of anxiety and mood disorders, and changes in patient behavior in this phase translate into a high rate of nonadherence to treatment. In these new conditions, it is required to implement ever more acutely in primary care practice of the CV patient strategies for the prevention of CVD and increasing/improving therapeutic adherence. An earlier identification of CV patient's psychosocial profile in view of new discoveries and a patient-centered health education can help in reducing CV mortality and morbidity and thus improving their QOL.

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