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PANIC DISORDER, ANXIETY, AND CARDIOVASCULAR DISEASES

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Abstract

Different data indicate that psychological and/or emotional disorders may play an important role in the natural history of heart diseases. Although the major evidence is that related to depression, epidemiological data would indicate that anxiety and panic disorders are highly represented in cardiac patient, thus influencing mortality and morbidity.

The diagnosis of panic disorder in patients with chest pain is crucial to a correct therapeutic approach, as well as to reduce the risks and costs of inappropriate treatments.

Anxiety and panic may accelerate different direct and indirect processes involved in the pathogenesis of cardiovascular diseases: lifestyle risk factors, arterial hypertension, myocardial perfusion, autonomic nervous system or hypothalamus-pituitary-adrenal axis, platelet activation, and inflammation processes. Panic disorder seems to correlate particularly with sudden death: this suggests that it may be considered one of the main inducers of life-threatening arrhythmias, rather than to be linked to the development and progression of coronary atherosclerosis.

Beyond hard outcomes, panic disorders produce negative effects on both global adjustment and life quality that may impair the course of the cardiac diseases. Interestingly, specific antipanic and anxiolytic agents seem to be particularly effective upon life quality. In any case, adequate controlled clinical trials are necessary in order to confirm the possibility of cardiovascular risk reduction by means of anxiety and panic disorder treatment.

Key words: panic disorder, anxiety, cardiovascular diseases, epidemiology, pathophysiology, treatment

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Introduction

Anxiety disorders represent the most prevalent psychiatric disorders, with a considerable burden associated with them, not only for individual sufferers, but also for the health care system. A milestone in this field was represented by the Donald Klein's recogniton of panic disorder (Klein 1981), its inclusion in the standard diagnostic systems (ICD or DSM-5), and subdivision into distinct entities until the latest nosological standardization (DSM-5).

Generally, anxiety disorders show an early onset and, as such, impair school and work performances, and later psychosocial functioning (Martin 2003). Although the traditional opinion was that that most anxiety disorders do not last too long, prospective studies suggest they are amongst the most chronic conditions (Martin 2003).

Anxiety disorders are very frequent in community settings, as well as in primary and secondary medical care, with a lifetime prevalence of about 25% (Katzman 2007). In the USA, anxiety disorders affect 20 million people yearly, and in other countries the prevalence is almost the same (Schulman 2005).

Panic disorder is one of the most frequent anxiety disorders (American Psychiatric Association 2013), with higher rates in women than men. The National Comorbidity Survey reported an annual prevalence of 2.2%, and a lifetime prevalence of 22.7% (Kessler et al 2006) Recently, there has been a dramatic increase in rates of panic attacks from 5.3% to 12.7% (Chen et al. 2009). Panic disorder is a condition characterized by recurring severe panic attacks. These attacks typically last about 10-15 minutes, but can be as short-lived as 1–5 minutes and last as long as 30 minutes or until medical intervention. However, attacks can wax and wane for a period of hours (panic attacks rolling into one another), and the intensity and specific symptoms of panic may vary over the duration. Common symptoms of an attack include rapid heartbeat, perspiration, dizziness, dyspnea, trembling, uncontrollable fear and hyperventilation. Other symptoms are sweating, shortness of breath, sensation of choking, chest pain, nausea, numbness or tingling, chills or hot flashes, and some sense of

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altered reality. In addition the person usually has some thoughts of impending doom. Individuals suffering from an episode have often a strong wish of escaping from the situation that provoked the attack. It may also include significant behavioral change lasting at least a month and ongoing worries about the implications or concerns about developing other attacks.

Panic disorder has been long associated with an increased risk for other psychiatric disorders, and also of heart diseases (Schulman et al. 2005).

This review aims to deal with the complex relationship between anxiety, with a specific focus on panic disorder, and cardiovascular diseases, in particular cardiac arrhythmias and coronary heart disease.

Anxiety and panic disorder

Intense anxiety with sudden onset and brief duration characterizes a panic attack (American Psychiatric Association 2013). In particular, a panic attack is a paroxysmal episode of anxiety occurring abruptly, reaching its maximal intensity in a few minutes and with a duration of about ten minutes. Subjectively, the patient experiences anxiety not psychologically derivable, during which concomitant sensations of impotence, imminent catastrophe and extreme discomfort are present, often resulting in fear of dying, becoming mad, or losing control of one's actions. (American Psychiatric Association 2013).

According to the DSM-5, to diagnose a panic attack requires the presence or four (or more) of the somatic and cognitive symptoms listed in table IIa, occurring abruptly and having their peak within about 10 minutes. In the latest DSM-5, panic attacks are no longer related to agoraphobia but function as a marker and prognostic factor for severity of diagnosis, course, and comorbidity across an array of disorders, including (but not limited to) anxiety disorders; hence, the panic attack became a specifier for all DSM-5 disorders (American Psychiatric Association 2013).

Expected panic attacks are those that occur due to a specific fear, such as when a person with a fear of flying is on an airplane. Unexpected panic attacks occur suddenly or unexpectedly, without any external cue that the attack is about to occur.

When individuals suffer from recurrent panic attacks, they may be diagnosed as patients with a panic disorder, the main symptom being the experience of persistent and typically unanticipated panic attacks. The diagnostic criteria also specifies that these panic attacks are marked by continual fear of having future attacks, shifts in one's behavior to avoid these attacks, or both of these issues for at least one month (American Psychiatric Association 2013). Finally, anxiety sensitivity is the fear of bodily sensations associated with anxiety (Taylor 1995). People with higher anxiety sensitivity tend to overinterpret and catastrophize in response to sensations such as sweaty palms, shallow breathing, rapid pulse, and other symptoms accompanying stress, which can be perceived as warnings of impending doom. Anxiety sensitivity is a relatively constant personality factor, distinct from anxiety itself, which fluctuates with events (Olatunji and Wolitzky-Taylor 2009). Most research on anxiety sensitivity has focused on panic disorder (Taylor 2006). Patients with panic disorder have higher scores than normal individuals on anxiety sensitivity measures, and conversely people with higher anxiety sensitivity are more likely to have panic attacks (McNally 2002).

Coronary heart disease

Coronary heart disease is the most frequent cardiac disease and, together with stroke, represents the first cause of death and disability in the world. Angina pectoris and myocardial infarction are its main forms (Bonow et al. 2012).

Angina is characterized by a thoracic, retrosternal pain, often irradiated to the neck or to the arms, perceived as oppressive or constrictive, and sometimes accompanied by breathlessness, algid sweating, tachycardia, paleness, anxiety, nausea, vomit and the sensation of imminent death. Blood pressure values may be high, and a marked bradycardia may also be present. The duration of these symptoms may vary from one to 20 minutes.

Angina may manifest itself in different forms: stable, unstable, Prinzmetal, and X syndrome (Bonow et al. 2012). Stable angina occurs after physical or emotional stress, and is due to the presence of a fixed coronary stenosis allowing, at rest, a normal coronary flow that becomes insufficient, causing myocardial ischemia, when oxygen requests augment. With rest ischemia ends, thus no cardiac damage is present. The electrocardiogram may be normal, whereas during an ergometer stress test or a dynamic electrocardiographic recording, alterations of the ST-T segment may occur, normalizing themselves with rest. Also, defects in Thallium or Technetium radionuclides captation shown up by the myocardial scintigraphy, or abnormalities of the cardiac cynesis by the echocardiogram during exercise or pharmacologic stress may manifest themselves, disappearing at rest.

Unstable angina may occur also at rest, and is generally the expression of an unstable coronary plaque; this form is more severe, as it may evolve towards a myocardial infarction. Also variant, or Prinzmetal angina occurs at rest, with a typical, transitory ST segment elevation at the electrocardiogram; this form is consequent to a spasm in an otherwise normal coronary artery, thus it is more benign than the unstable one. Also in X syndrome no significant coronary stenosis is observed, notwithstanding the presence of both angina and electrocardiogram changes (without ST segment elevation) at rest or during stress. Finally, a transitory myocardial ischemia with electrocardiogram changes, due to coronary atherosclerosis, may also be observed in absence of chest pain (silent ischemia), particularly in diabetic patients, whose pain threshold is reduced.

Acute myocardial infarction is a clinical syndrome consequent to a total or subtotal occlusion of a coronary vessel, often due to a thrombus superimposed on an unstable coronary plaque, causing a severe, prolonged (more than 20 minutes) reduction of the coronary flow (Bonow et al. 2012). The consequent acute ischemia determines myocardial cell necrosis (releasing cardiac enzymes and troponins into the blood flow); the damage to myocardial tissue is thus irreversible, without restitutio ad integrum. This may even lead to arrhythmic sudden death or left ventricular pump dysfunction, with consequent congestive heart failure. The symptoms of acute myocardial infarction are analogous, although more prolonged and severe than those of angina. The electrocardiogram may exhibit an ST segment elevation in the case of total occlusion, and an ST segment depression or other alterations (including a normal aspect) in the case of subtotal occlusion. Elevation of cardiac enzymes and troponins is thus often necessary in order to confirm the diagnosis.

Arrhythmias

The term cardiac arrhythmia covers a wide range of different conditions due to heart rhythm disorders, in which the cardiac electrical activity is irregular, or faster (over 100 beats per minute) or slower (less than 60 beats per minute) than normal (Bonow et al. 2012). The most common symptom of arrhythmia is an abnormal awareness of heartbeat, called palpitations. Also, when the heartbeat is too fast, too slow or too weak to supply the body's needs, it manifests itself as a lower blood pressure and may cause lightheadedness, dizziness, or syncope. Direct assessment of the abnormality using an electrocardiogram is the main way to diagnose any cardiac rhythm disorder. Arrhythmias can occur in the upper (atria) or in the lower chambers of the heart (ventricles). Atrial fibrillation is the most common arrhythmia (Bonow et al. 2012). In this form, the normal regular electrical impulses generated by the sino-atrial node are overwhelmed by disorganized electrical impulses, usually originating in the roots of the pulmonary veins, leading to the irregular conduction of ventricular impulses that generate the heartbeat. Atrial fibrillation may occur in episodes lasting from minutes to days ("paroxysmal") or may be permanent. It may cause no symptoms, but it is often associated with symptoms related to a rapid, uncoordinated heart rate (the heart being unable to provide adequate blood flow and oxygen delivery to the rest of the body) that may be perceived as palpitations, fainting, or exercise intolerance and occasionally may produce chest discomfort or even angina (if the faster rate puts the heart under strain) as well as congestive symptoms of shortness of breath or even acute pulmonary oedema. It may be identified clinically when taking a pulse; a heart examination will reveal an irregular, rapid rhythm and its presence must be confirmed with an electrocardiogram showing the absence of p waves with disorganized electrical activity in their place, and an irregular ventricular rate due to the irregular conduction of impulses to the ventricles. Atrial fibrillation may be treated with medications aimed at either slowing the heart rate to a normal range ("rate control") or reverting the heart rhythm to normal ("rhythm control").

Supraventricular ectopic beats also originate in the atria and when repeated present themselves as a supraventricular paroxysmal tachycardia (Bonow et al. 2012), that may generate symptoms like those of atrial fibrillation. Supraventricular arrhythmias are, however, normally harmless (although disturbing for patients).

In contrast, some ventricular arrhythmias can be more dramatic. Ventricular tachycardia or fibrillation are always a life-threatening medical emergency (Bonow et al. 2012). When the heart goes into ventricular fibrillation, effective pumping of the blood stops (cardiac arrest). If left untreated, ventricular fibrillation can lead to death within minutes.

Differential diagnosis

To distinguish between a panic attack and an acute coronary syndrome is particularly complex, due to the overlapping of the clinical-symptomatic pattern, as shown in table IIa-b. Panic disorders, previously described as "*cardiac neurosis, irritable cardiac syndrome or soldier's heart*", are commonly associated with symptoms such as chest pain, tachycardia, and dyspnoea. In particular, chest pain is so frequent among patients with panic disorder that it is considered as one of its 14 diagnostic, albeit non pathognonomic criteria (Katerndahl 2004) (**table IIa**), as 3 other symptoms are needed to confirm the diagnosis. The prevalence of panic disorders is high (about 57%) in patients with non-cardiac chest pain, i.e. atypical, without electrocardiogram changes and associated to normal coronary arteries (Soh and Lee 2010). Many patients admitted to an emergency care unit for a suspected acute coronary syndrome could suffer from a panic attack. Even among patients with a previous history of cardiovascular disease who are referred to medical attention for non-ischemic (parietal or oesophageal) chest pain, the prevalence of panic disorder is 34% (Fleet et al. 2005).

Patients with panic attacks and chest pain fear illness and death so much (Katerndahl 2004) that they easily request medical assistance. Indeed, patients with higher anxiety sensitivity pay more attention to their heartbeats and heart rate (Stewart et al. 2001) and to the electrocardiogram, relating their symptoms to an ischemic heart disease (Katerndahl 2004). Chest pain during a panic attack is thus related with hospitalization (Fleet et al. 2005) and to the fruition of the assistance of family doctors, psychiatrists and cardiologists. Physicians and non-psychiatric specialists very often underestimate this psychiatric condition in patients with a history of recurrent chest pain and without a coronary atherosclerotic disease (Katerndahl 2004), and this may lead to inappropriate treatments and avoidable costs. A high number of patients with no atherosclerotic disease of the coronary arteries, but rather affected by a panic disorder, underwent coronary angiography (Katerndahl 2004).

Commonly patients with non-cardiac chest pain who are diagnosed with panic disorders are reassured and referred back to primary care, leaving them undiagnosed and untreated. However, the presence of chest pain during a panic attack seems to be also related to the severity of the psychiatric disease (with possible suicidal thoughts) (Fleet et al. 2005) and to a lower quality of life (Katerndahl 2004). Thus, patients presenting noncardiac chest pain should be screened for psychopathology. Identifying these patients might be useful to establish ad hoc interventions, i.e. brief cognitive behavioral therapy sessions, or pharmacological treatment, while improving patients' morbidity with superior incremental cost-effectiveness ratios (Marchand et al. 2012, Poirier-Bisson et al. 2013, Buccelletti et al. 2013, Van Beek et al. 2013).

The diagnosis of panic disorders in patients with chest pain is crucial not only to a correct treatment, but also to reduce the risks and costs of inappropriate and unnecessary treatments, although there are no exact data of the costs of health care related to panic disorders and mistakenly attributed to heart disease.

A correct aetiological diagnosis of chest pain during a panic attack is often difficult in the emergency care unit (Fleet et al. 2005), although it is easier for the general practitioners, who know their patients and their psychological habits (Aikens et al. 1998). Some "atypical" characteristics of the chest pain may suggest a panic disorder **(table IIa-b)**. An atypical pain without evidence of atherosclerotic coronary disease has high probability of deriving from a panic disorder. In general, we should suspect panic disorder in patients with chest pain in the presence of young age, female gender, atypical pain, absence of organic diseases, or mitral valve prolapse. The relief of pain after the administration of sublingual nitrates does not, per se, rule out panic disorders, that are often associated with oesophageal abnormalities (i.e. oesophageal spasm) (Soh and Lee 2010). Anxiolytic and placebo drugs may

reduce the recurrence of pain in patients with normal coronary arteries. When the pain has a prolonged duration, negativity of cardiac enzymes and troponins may exclude acute coronary syndromes. Viceversa, when symptoms are of short duration, a stress ergometer electrocardiogram or imaging test must be performed to exclude forms of angina pectoris. Many psycho-diagnostic tests (Panic Disorder Module of the Structured Clinical Interview, Quick PsychoDiagnostic Panel, etc.) allow emergency care unit physicians to make diagnosis of panic disorders (Halgren et al. 2007; Foldes-Busque et al. 2011). Agoraphobia and hypocalcaemia (or its indirect signs, like those of Chvostek and Trosseau), which is subsequent to hyperventilation, may be useful to orientate diagnosis. However, the presence of panic disorder does not exclude a concomitant coronary disease, thus it has the important role of inducing these patients to look for medical assistance.

As regards cardiac arrhythmias, anxiety and panic symptoms such as a racing or pounding heartbeat, dizziness, light-headedness, nausea, difficulty in breathing, tingling or numbness in the hands, flushes or chills, may be similar to those of atrial fibrillation or supraventricular and ventricular ectopic beats or tachycardia, i.e. paroxysmal supraventricular tachycardia (Bonow et al. 2012). Cardiac arrhythmias are difficult to document on the electrocardiogram, since they have often ceased before the patient comes to medical attention. Besides, a sinusal tachycardia may still be present and even be documented, but interpreted as a phenomenon secondary to the panic attack. When palpitations are present without evidence of documented arrhythmias on the electrocardiogram, a cardiac involvement may be excluded. In the absence of symptoms and electrocardiographic evidence of arrhythmias at the moment of medical observation, a 24-hour dynamic electrocardiogram recording may be a useful tool for the differential diagnosis. However, the evidence that in some patients paroxysmal supraventricular tachycardia is the cause, but not the consequence, of a panic attack is based on observations that catheter ablation was able to cure symptoms in patients presenting panic disorders (Frommeyer et al. 2012). It was thus hypothesized that a certain proportion of panic disorders may mutate into an underlying arrhythmia rather than a primary psychiatric disorder (Frommeyer et al. 2012).

Incidence and prevalence of panic disorder in heart diseases

The onset of anxiety disorders soon after a cardiovascular event is very common (Moser and Dracup 1996, Roy-Byrne et al. 1999, Konstam et al. 2005, Bjerkeset et al. 2005, Grace et al. 2004). In a recent prospective study on more than 20,000 patients, the incidence of anxiety symptoms was higher after a myocardial infarction than in the general population (Bjerkeset et al. 2005). As far as prevalence is concerned, a precise estimation of the problem is difficult, due both to the ample variability of clinical and instrumental definitions and to the different (in terms of comorbidity, age, gender, or socioeconomic condition) populations examined. In particular, the strict and immediate correlation between acute coronary syndromes and anxiety and panic disorders has been revealed in many studies that reported a prevalence of up to 65% for anxiety disorders (Moser and Dracup 1996, Grace et al. 2004) and up to 50% for panic disorders (Roy-Byrne et al. 1999) (whereas the prevalence of panic attacks in the general population is about 2%) (Frommeyer et al. 2012). Last, but not least, it is known that significant anxiety disorders can persist even after an acute phase of coronary syndromes (Grace et al. 2004). It has been estimated that almost 55% of the candidate patients for aortic-coronary bypass have high levels of anxiety in the preoperative period, which remain high in 32% of cases in the three following months (Pignay-Demaria et al. 2003).

Anxiety and panic are observed also in cardiovascular diseases other than coronary heart disease. In a recent survey on a German general population, in which 12-month prevalence of psychiatric disorders was assessed through the Composite International Diagnostic Interview, panic disorder was associated with cerebrovascular disease (adjusted OR 2.28; 95 % CI 1.09-4.77) and peripheral vascular diseases (adjusted OR 2.97; 95 % CI 1.55-5.69) (Tully and Baune 2013). Few data are currently available regarding prevalence of anxiety disorders in heart failure (MacMahon and Lip 2002). In the SOLVD study, women with heart failure had levels of anxiety higher than neoplastic controls (Riedinger et al. 2002). Panic disorders have also been associated with aortic aneurisms (Benjamin et al. 2000), pulmonary hypertension (Sietsema et al. 1987), and, in particolar, with mitral valve prolapse, although this is not clearly proven (Katerndahl 1993). The important overlapping of symptoms between panic disorder and this latter condition may be related to an autonomic dysfunction. Probably the reduction in left ventricular volume, that is consequent to tachycardia (common in panic disorder), may cause a functional and reversible mitral valve prolapse (Katerndahl 1993). Finally, in spite of improved survival of patients with implantable cardiac defibrillators, their electric discharges may induce unexpected discomfort and are associated with a high rate of anxiety symptoms (Burg et al 2004).

In general, thus, there is a large consensus that cardiac patients show a high prevalence of psychiatric comorbidities with anxiety disorders, in particular panic (27%) and generalized anxiety disorders (GAD, 5-30%) (Bankier et al. 2004, Konstam et al. 2005; (Schulman et al. 2005). Lower values of absolute prevalence of panic disorder (although frequently coexistent with GAD) in patients with cardiovascular diseases have been detected, in contrast, by using brief screening tools, such as the GAD-2 scale (Celano et al. 2013). Commonly, in fact, patients with chronic heart diseases have at least two associated psychiatric disorders (Bankier et al. 2004).

Panic disorder as a trigger of acute cardiac events

Acute psychosocial stressors (events that require individual adaptive reaction within minutes, hours or days), like excitement, catastrophes, terroristic attacks, wars, earthquakes, and bereavements, can trigger a sudden cardiac event (Tennant and McLean 2001, Strike and Steptoe 2005, Davidson 2008). Data regarding trigger events can be obtained from retrospective studies or from prospective electronic daily records correlated with outpatient electrocardiogram recording or implantable cardiac defibrillators. A meta-analysis has suggested that an emotional stress precedes a myocardial infarction in 7% of cases, especially in women (Culic et al. 2005).

Some years ago a new cardiomyopathy was defined whose clinical presentation is very similar to an acute coronary syndrome, with electrocardiographic changes

and troponin release in the absence of significant atherosclerotic lesions of coronary arteries (Novo et al. 2008). It is often preceded by intense emotional stress and is characterized by typical wall motion abnormalities detectable with echocardiography. These abnormalities confer to the left ventricle the aspect of "Takotsubo", a Japanese octopus trap. The pathophysiological mechanism underlying the association between stress and Takotsubo cardiomyopathy, however, remain yet to be established. Association with worse outcomes after heart surgery exists, being more evident in patients with preoperative acute anxiety than in patients with anxiety tracts (Pignay-Demaria et al. 2003, Nemati and Astaneh 2011). Indeed, preoperative stress is associated with haemostasis, lipids and cellular antioxidant system alteration with evidence of ischemia or arrhythmia at preoperative Holter recording (Pignay-Demaria et al. 2003).

Panic disorder as a cardiovascular risk factor

Still more uncertain is the association between global cardiovascular risk and stressors (even of minor intensity but prolonged) as those observed in the work or relationship area. Anxiety in general, and specific disorders, such as generalized anxiety disorder or panic disorder, have been independently associated with increased risk of fatal myocardial infarction and sudden cardiac death in epidemiological retrospective population studies and prospective trials, both in healthy subjects (Kawachi et al. 1994a, b; Kubzansky and Kawachi 2000; Bunker et al. 2003; Albert et al. 2005; Barger and Sydeman 2005; Chen et al. 2009; Scherrer et al. 2010; Cheng et al. 2013; Scott et al. 2013) and, particularly, in patients with a previous history of cardiovascular diseases (Frasure-Smith et al. 1995, Moser and Dracup 1996, Thomas et al. 1997, Kuper et al. 2002, Strik et al. 2003, Grace et al. 2004, Pfiffner and Hoffmann 2004, Carpeggiani et al. 2005, Huffman et al. 2008, Frasure-Smith and Lespérance 2008, Huffman et al. 2010, Martens et al. 2010).

In the general population, a dose-dependent relation has been demonstrated: minimal signs of anxiety, and in particular panic disorders, are sufficient, according to some studies, to increase cardiovascular risk up to 5-fold (Kawachi et al. 1994a, b, Kubzansky and Kawachi 2000; Albert et al. 2005; Barger and Sydeman 2005; Chen et al. 2009; Scherrer et al. 2010). Finally, a recent study in the general population in Taiwan showed that panic disorders are associated with higher incidence of atrial fibrillation (Cheng et al. 2013).

In a large recent survey conducted in 19 countries, panic disorder and specific phobia were associated, after comorbidity adjustment, with heart disease onset (ORs 1.3-1.6) (Scott et al. 2013). In contrast, some systematic reviews on this matter (Kuper et al. 2002, Bunker et al. 2003) failed to report any casual and independent association between anxiety (or panic disorders) and coronary risk. By contrast, different epidemiological studies demonstrated a significant relation between anxiety disorders and sudden cardiac death. The Health Professional Study reported a 6-fold increase of sudden death in healthy men with phobic anxiety, as defined by using Crown-Crisp Anxiety Index (Kawachi et al. 1994a). In the Normative Aging Study (Kawachi et al. 1994b), anxiety was associated with a 1.9-fold increase of fatal cardiovascular events and with a significantly greater 4.7-fold increase of sudden death in a 32-year follow up. Even in the Nurses' Health Study, that analyzed about 700,000 women without previous history of cardiovascular events, high levels of phobic anxiety were associated with the greater risk of sudden cardiac death, but not of non-fatal cardiovascular events (Albert et al. 2005). These observations suggest, as a principal mechanism, the induction of life-threatening arrhythmias rather than the development and progression of coronary atherosclerosis.

Patients with previous heart disease behave in a different way from the general population. In atrial fibrillation patients, anxiety sensitivity has been explored only as a cross-sectional correlate of lower quality of life and greater symptom severity and worry (Ong et al. 2006). More noticeably, anxiety presence in a pre-existent acute coronary event predicts both sudden death and future non fatal outcomes (Frasure-Smith et al. 1995, Moser and Dracup 1996, Thomas et al. 1997, Kubzansky and Kawachi 2000, Strik et al. 2003, Pfiffner and Hoffmann 2004, Carpeggiani et al. 2005, Frasure-Smith and Lespérance 2008).

Pathophysiological correlations

Pathophysiology of panic disorders is still poorly understood. A number of hypotheses involve different cerebral areas (locus coeruleus or neuroanatomical model) or neurotransmitter pathways (serotonergic, adrenergic, lactates, carbon dioxide, and GABAergic models) (Freire et al. 2011). Panic disorder seems due, at biochemical level, to metabolic acidosis as a compensatory response to chronic hyperventilation. The described mechanism may be a triggering factor in the initiation of panic attacks, but many other explanations have been put forward (e.g. failure to control restraining inputs). It is supposed that anxiety and panic accelerate different direct and indirect processes involved in the pathogenesis of cardiovascular diseases: lifestyle, autonomic nervous system or hypothalamus-pituitary-adrenal (HPA) axis dysregulation, reduced myocardial perfusion, platelet activation, and inflammation (Tennant and MacLean 2001).

Lifestyle risk factors, arterial hypertension, and subclinical atherosclerosis

Additional effects of behavioral risk factor (nicotine, caffeine, inadequate diet, poor adherence to treatment, sedentariety) must not be underestimated in anxious patients (Mathew et al. 2011). Not surprisingly, diabetic or hyperlipidemic patients show high scores on the Hamilton rating scales for panic or agoraphobia (Vural et al. 2008).

Panic disorder prevalence seems to be increased three-fold in essential hypertension (Esler et al. 2008). Multiple cross sectional studies revealed a positive, bidirectional association between anxiety and hypertension; those with hypertension being more likely to suffer from anxiety, and viceversa. However, a few other studies showed no association. Longitudinal studies point to an increased risk of development of hypertension in patients who suffer from anxiety (Player and Peterson 2010). A negative emotional profile with anxiety was independently associated with arterial hypertension incidence in NHANES 1 (Jonas and Lando 2000). Further, there is also evidence emerging from the Norwegian HUNT study (Krokstad et al. 2013) that this association is valid in large population samples. In particular, patients with panic show a significantly higher incidence of non-dipper blood pressure pattern (the lack of physiological decrease of blood pressure during nocturnal hours, which is a negative prognostic

index) than control subjects (Alici et al 2013).

The negative effects on all of these risk factors may explain the observed association between anxiety and panic and subclinical markers of atherosclerosis (Seldenrijk et al. 2010 and 2012). In the Netherlands Study of Depression and Anxiety, a large cohort of patients with anxiety disorders (social phobia, GAD, panic disorder, agoraphobia) was compared to non-anxious control subjects. Higher scores of anxiety sensitivity, measured by the Anxiety Sensitivity Index, were associated with both increased likelihood of carotid plaques using B-mode ultrasonography (OR per SD increase=1.34, 95%CI=1.06-1.68) and increased central arterial hardening (augmentation index) using calibrated radial applanation tonometry (p=.01). These observations suggest that vulnerability to anxiety, rather than to depression, represents a correlate of subclinical atherosclerosis (Seldenrik et al 2012). Also, patients with current (i.e., past year) anxiety or comorbid depressive and anxiety disorders showed two- to three-fold increased odds of low (<or=0.90) ankle-brachial Index (Seldenrik et al 2012). Moreover, carotid-femoral pulse wave velocity, the gold standard measurement of arterial hardening, is increased in patients with panic disorder (Cicek et al. 2012).

Myocardial perfusion

Some anxiety effects on the heart are considered consequences of an excessive sensibility to external stresses. Hyperventilation, that is common in panic disorders, provokes an increase of cardiac output and contractility and it is a well known precipitant factor for coronary spasm that can lead, in turn, to ventricular arrhythmias and myocardial infarction, and also to the rupture of atherosclerotic plaque, both in known coronary patients and in apparently healthy people (Tennant and McLean 2001).

Another possible ischemic mechanism in panic disorders is micro-vascular angina, often observed in women with healthy coronary arteries. Vasomotor abnormalities of epicardial arteries and coronary microcirculation were observed in coronary patients during mental stress (Samuels 2007). Levels of nitric oxide, a gas considered to play an important role in mediating anxiety and stress responses, with a marked vasodilator effect, were significantly lower in patients with panic depression than in control subjects (Yapislar et al. 2012). In turn, in patients with both panic disorder and heart disease, myocardial ischemia can favour panic attacks due to increased cerebral levels of cathecholamine or carbon dioxide consequent to lactate accumulation. In coronary heart disease patients with comorbid panic disorder, myocardial scintigraphy showed higher perfusion defects, indicative of myocardial ischemia, than in controls (Fleet et al. 2005).

The same phenomenon follows induction of panic attack with carbon dioxide inhalation in coronary artery disease patients with previous positive nuclear exercise stress tests (Fleet et al. 2005). In contrast, in coronary artery disease patients with panic disorder but with normal exercise stress tests, a potent mental stressor, such as a panic challenge, induces ischemia only in a few patients, while suggesting that panic attacks among panic disorder patients with lower-risk coronary artery disease may not confer a risk of myocardial ischemia (Fleet et al. 2014).

Other studies in patients with panic disorder show, by 24-hour electrocardiogram monitoring, diffuse abnormalities of repolarization associated to panic attacks with chest pain. Postmenopausal women with a recent history of panic attacks, by contrast, do not appear to have more daily life ischemia, as measured by occurrence of ST depression during 24-hour monitoring, but do show more chest pain and possibly lower heart rate variability, suggesting that even sporadic panic attacks may be related to cardiovascular risk (Smoller et al. 2006).

Mediated effects of the autonomic nervous system dysregulation

Increased activity of the sympathetic nervous system and reduced parasympathetic activity are invoked as important mechanisms bridging stress and ischemic heart disease (Samuels 2007). Clinical research in this area uses evaluations of plasmatic catecholamines and heart rate variability (HRV).

Patients with anxiety or panic disorder and heart disease show an excessive systemic response to stress, characterized by persistent stress-related changes in sympathetic nerve biology with augmented catecholamine production (Samuels 2007), which in turn lead to elevation in the heart rate, systolic and diastolic blood pressure, and vascular resistance, with a consequent increase in myocardial oxygen request (Fleet et al. 2005). In particular, patients with panic disorder and those with hypertension show similar patterns (Esler et al. 2008, Jonas and Lando 2000): in both, epinephrine cotransmission is present in sympathetic nerves. Single-fibre sympathetic nerve firing spikes (spikes of multiple firings within a cardiac cycle) occur; tissue nerve growth factor (a stress index) is increased; there is induction of phenylethanolamine N-methyltransferase (that synthesizes in situ epinephrine) in sympathetic nerves; finally, there is activation of noradrenergic brain stem neurons projecting to the hypothalamus and amygdala. These pathophysiological findings strongly support the view that panic disorders and chronic mental stress with autonomic nervous system dysfunction are important in the pathogenesis of essential hypertension (Jonas and Lando 2000).

A hypothesis now under testing is whether in both disorders, under prevailing conditions of ongoing stress, phenylethanolamine N-methyltransferase acts as a DNA methylase, causing the silencing norepinephrine transporter gene that is present in both conditions (Esler et al. 2008). Panic symptoms of autonomic origin such as sweating and flushes, indeed, are more common in attacks experienced by hypertensive than by normotensive patients (Davies et al. 2008). After hyperventilation, patients with panic disorder and GAD demonstrated also a greater heart rate than that of control subjects (Pittig et al. 2012). In addition, adrenergic effects on platelet aggregation, vascular reactivity and permeability may reduce coronary perfusion (Jonas and Lando 2000). Particularly in patients with atrial fibrillation and chronic heart failure who have high anxiety sensibility, heightened awareness of anxiety symptoms including palpitations and heart rate changes may increase fear, augmenting physiological sensations and thoughts of catastrophe, increasing sympathetic arousal, catecholamine levels, and heart rate in a vicious cycle, and potentially increasing arrhythmic risk (Frasure-Smith et al. 2012).

HRV (described as standard deviation of RR intervals at electrocardiographic recording), that is controlled, centrally, from the hypothalamus and the limbic system and, peripherally, from vagus nerve, can be utilized as an index of the ability to maintain

cardiovascular homeostasis. DeMeersman et al. (1996), studying effects of stress factors in real life (speakers that did a presentation alone in front of a critic audience), showed significant HRV changes. Spectral power analysis of HRV gives a valid measure of cardiac autonomic function, high frequency being a measure of the parasympathetic system and the low frequency of sympathetic-parasympathetic equilibrium. Reduced high frequency HRV, related to hypoactivity in the prefrontal cortex, which negatively affects executive functioning, is observed in patients who suffer from panic disorders, GAD and social anxiety (Tennant and McLean 2001, Hovland et al. 2012, Pittig et al. 2013), which is consistent with the notion of autonomic inflexibility in anxiety disorders. Panic disorder patients also show more low frequency components in basal conditions and increased ratio between high and low frequency, both in basal condition and during tilt test (Martinez et al. 2010) or in the presence of threatening stimuli (Wang et al. 2013). Elevated HRV responses to hyperventilation, finally, are specific to panic and GAD (Pittig et al. 2013). A lower parasympathetic activity has been demonstrated in s/s carriers for the serotonin transporter polymorphic region (Agorastos et al. 2014). The s/s genotype represents a genetic vulnerability factor, associated with inadequate hyporeactivity to stress and suggests a role of the central serotonergic activity on the sympathoadrenal pathway. In addition, anxious patients develop a compromised baroreceptorial response, another marker of vagal control dysfunction (Hemingway et al. 2001).

Subjects with reduced HRV have higher risk of arrhythmias and sudden death, as autonomic cardiac function can lower the arrhythmic threshold, and this is specular to the observed increase of sudden death in anxious or panic disorder patients (Hemingway et al. 2001). In patients with implanted cardiac defibrillators, predisposed to anxiety or rage, arrhythmias can be induced by these emotions (Burg et al. 2004). Animal studies give important evidence of a sudden death model where nervous system and ventricular arrhythmias are related to environmental stress factors, psychosocial ones in particular: in the presence of acute ischemia or vulnerable myocardium, stress induces ventricular tachycardia. This effect can be prevented by the use of beta-blockers (Hemingway et al. 2001).

Acute emotive stress is the precipitant factor common to syncope or arrhythmia in patients with the rare genetic long QT syndrome (Hemingway et al. 2001). Longer QT intervals, which can also predispose to ventricular arrhythmias, were demonstrated in anxious patients. Toivonen et al. (1997) found lengthening of the QT interval in 30 healthy physicians that were subjected to the acute stress of an emergency call during sleep. Even objective QT dispersion, defined as the maximal inter-lead difference in QT intervals on 12 leads of the surface electrocardiogram, reflecting the regional heterogeneity of ventricular repolarization, has been suggested as an important marker for risk of arrhythmia and sudden death. Q(max) and Q(min) values, as well as the mean corrected QT dispersion, were significantly higher in panic disorder patients than in healthy controls (Atmaca et al. 2012).

HPA axis activation

Stress events (every situation that can lead to anxiety or loss of self-control) favour cortisol secretion (Meewisse et al. 2007). During stress, the hypothalamus, under the influence of amygdala-released serotonin, produces corticotropin-releasing factor (CRF), stimulating the anterior pituitary to release adrenocorticotropic hormone (ACTH) which, in turn, modulates cortisol production in the adrenal gland (Meewisse et al. 2007). Correlations with cortisol activity were documented in different studies that used structured stress factors, like speaking in public or mental calculation. Chronic stimulation of the hypothalamus-hypophysis axis can determine an increased cortisolemia by a negative feedback mechanism. High cortisolemia has been related to the development of atherosclerotic lesions and can determine increase of appetite as well as of visceral adipose tissue, weight and insulin resistance (Meewisse et al. 2007). These metabolic alterations worsen the cardiovascular risk profile (increasing incidence of diabetes, hypertension, dyslipidemia and inducing endothelial damage). Cortisol inhibits the growth hormone too, whose deficit (powerful stimulant of visceral fat) is associated to premature cardiovascular diseases. In addition, the hyperactivity of ACTH-secreting hypothalamic neurons can indirectly stimulate, in turn, different autonomic nervous centres (Meewisse et al. 2007).

Altered platelet function

Platelet functions are likey to be involved (Tennant and McLean 2007), in particular through adrenergic hypersecretion, or the influence of cytokines and/or dysregulation on the metabolism of platelet 5-HT. In contrast to depressed patients, those with panic disorder do not show 5-HT-2 platelet receptor alterations, but a higher plasmatic concentration of platelet factor-4 and beta-thromboglobulin and of augmented platelet aggregability (Yapislar et al. 2012). However, both depressed and panic disorder patients show a decreased number of 5-HT transporter proteins (Marazziti et al, 1999). In addition, platelet released 5-HT favours platelet aggregation and coronary vasoconstriction through its effect on reuptake on sites, contributing to endothelial damage and potentially inducing thrombotic events (Pignay-Demaria et al 2007). Finally, alterations of the fibrinolytic system (with elevated plasminogen activator inhibitor-1 levels) are observed in chronic stress.

Inflammation

Subjects with anxiety disorders show increased levels of inflammation markers such as leukocyte count, C reactive protein, interleukins, tumor necrosis factor, fibrinogen, and homocysteine (Brydon et al. 2005, Yapislar et al. 2012).

Treatment

The evident negative impacts of anxiety disorders make it mandatory to prevent or limit personal suffering, economic costs, and connected social disadvantage. Even when panic disorder coexists with ischemic heart disease, patient perceived discomfort is typically more related to the first condition. Psychological benefits of anxiety treatment in coronary patients are obvious, but cardiovascular ones are uncertain.

Non-pharmacological treatment

Non pharmacological interventions, that can be as

effective as the pharmacological ones, range from pet therapy to cognitive behavioral educational programs (Januzzi et al. 2000, Sardinha et al. 2011). These, in particular, are a psychotherapy form based on learning theory, that rely on modifications of emotions and dysfunctional behaviour using diaries (for example on diet or physical exercise), and problem solving techniques, in order to modify the lifestyle of patients with chronic pathologies like obesity or diabetes, and in particular heart diseases, emphasizing a collaborative relation between therapist and patient (Januzzi et al 2000). Stress management is the essential component of cardiac rehabilitation programs, which reduce mortality by about 25% (Sommaruga et al. 2008) and provide interesting means to identify anxiety in patients after an acute coronary syndrome, permitting eventual interventions too. This "comprehensive cardiovascular rehabilitation" improves psycho-affective conditions, self-image, coping capacity, exercise tolerance and thus quality of life (Januzzi et al. 2000). It reduces some biological risk factors like smoking (Linden et al. 1996), and improves significantly HRV (reducing also ventricular premature beats) (Tennant and McLean 2001).

However, can non-pharmacological treatment of associated psychiatric conditions ameliorate prognosis in heart disease patients? The results of controlled clinical trials, which verified in post-acute ischemic heart disease patients the impact of stress reduction programs, are less congruent. In the Montreal Heart Attack Readjustment Trial (M-HART), a program of home nursing assistance aimed at stress reduction on post-infarction patients, the intervention (probably minimal) had a low impact on anxiety symptoms, but produced a significant benefit on male mortality (showing instead an increased mortality trend on women) suggesting, in responders, a beneficial effect on outcome, too (Frasure-Smith et al. 1997). Some meta-analysis (Linden et al. 1996, Dusseldorp et al. 1999) on psycho-social intervention effects in heart disease patients showed reduction of systolic blood pressure, heart rate, cholesterolemia, and even mortality and morbidity. However, there were also negative results in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial (Sheps et al. 2003), whose primary aim was to determine whether non-pharmacological treatment of depression and low perceived social support increases reinfarction-free survival after acute myocardial infarction. In a psychological intervention group, a Cochrane review showed a significant reduction of myocardial infarction incidence (HR 0,78;CI 95% 0,67-0,90), together with decreased anxiety symptoms; on the other hand no effects were observed for general and cardiovascular mortality (Rees et al. 2004). These results, however, are unreliable because of trial heterogeneity, different bias presence and short follow-up (probably due to difficulties in non-pharmacological fundraising). In any case, psycho-social interventions should be considered an integral part of cardiologic clinical practice. Italian cardiologic rehabilitation guidelines (Sommaruga et al. 2008) are a valid attempt to formalize needed interventions in an optimal program that should include educational and psychological interventions (single or in group) in order to help patients (and their relatives) to recognize and express their emotions regarding the disease, apply strategies for lifestyle modification, implement correct self-management of treatments and recover a satisfying quality of life, encouraging familiar and social everyday reintegration.

Pharmacological treatment

Panic disorder patients show significant psychosocial impairment and a high risk of psychiatric comorbidities and suicide. This condition should be treated effectively as soon as the symptoms emerge because the longer these patients remain without treatment, the worse the prognosis will be. A safe treatment in heart disease patients with psychoactive drugs must consider the cardioactive effect, pharmacological interactions and co-morbidity (Schulman et al. 2005, Vaccarino 2011). In a recent systematic review of the literature regarding the pharmacological treatment of panic disorder, selecting only open studies, placebo-controlled studies or comparative clinical trials, the experts considered as compounds with reported effectiveness in the treatment of panic disorders, tricyclic antidepressants, benzodiazepines, selective 5-HT reuptake inhibitors (SSRIs), and 5-HT and noradrenaline reuptake inhibitors (SNRIs). The last two are now the first-line compounds in the treatment of panic disorders, as these drugs were better tolerated than tricyclics and benzodiazepines having a low risk of dependence and overdosing complications (Freire et al. 2011, Batelaan et al. 2011, Marazziti et al. 2012). However, in the real world the Harvard/Brown Anxiety Research Project (HARP), a naturalistic, longitudinal, multisite study with nine years of follow-up in middle-aged and older adults with diagnoses of panic disorder with or without agoraphobia, social phobia, or GAD, has shown that rates of benzodiazepines use persist high among both the older (53% at baseline) and the younger (57.4%) age groups. Although there was a statistically significant increase in SSRI/SNRI use over time, only 35% of participants were utilizing these medications at the end of the follow up, while more than one-half were continuing to use benzodiazepines (Benitez et al. 2008).

SSRIs

Selective SSRIs (like citalopram, dapoxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) are a class of compounds typically used in the treatment of anxiety disorders. SSRIs are believed to increase the extracellular level of 5-HT by inhibiting its reuptake into the presynaptic cell, thus increasing the level of the neurotransmitter in the synaptic cleft. They show varying degrees of selectivity for the other monoamine transporters, such as noradrenaline and dopamine transporter. SSRIs are recommended by the National Institute for Health and Clinical Excellence (www.nice.org.uk) for the treatment of GAD that has failed to respond to conservative measures such as education and self-help activities. The available evidence suggests that SSRIs are superior to the placebo in treating these forms (Kapczinski et al. 2003). There appears to be no significant difference in effectiveness between these drugs and tricyclics or benzodiazepines. However, SSRIs are quite tolerable in terms of side effects and relatively safe in suicidal overdosing. Further, they have fewer and milder side effects (Nardi et al. 2012).

Cardiovascular side effects are rare with SSRIs use. Due to the inhibition of different cytochrome P450 isoenzymes, some SSRIs can alter the metabolism of lipophilic beta-blockers, calcium channel blockers, class IC anti-arrhythmic agents, and warfarin (Batelaan et al. 2011). SSRIs inhibit also cardiac and vascular sodium, calcium and potassium channels and prolong QT intervals, but a number of wide studies of patients

without known pre-existing heart disease have reported no electrocardiographic changes related to their use. In contrast, an increased parasympathetic activity, with reduction of panic disorder and consequently a drastic slowing of sino-atrial node and positive effects on HRV, is observed (Batelaan et al. 2011). SSRIs can also decrease thrombotic risk, because they reduce platelet storage capacity of 5-HT, with potential advantages in patients with increased platelet activation like smokers (Batelaan et al. 2011). Angina, hypercholesterolemia and hypertension are rare side effects of SSRI treatment (Katerndahl et al. 2004), although this is controversial and not widely accepted. SSRIs, in fact, have actually been reported to reduce blood pressure in a large scale study when hypertension was comorbid with panic disorder (Polyak 2001). Large scale trials of drug treatment after an acute myocardial infarction (although focused on depression) such as the Sertraline Antidepressant Heart Attack Trial (SADHART) did not show effects on mortality. However, the results suggest that sertraline is a safe treatment in patients with a recent myocardial infarction or unstable angina, even raising the possibility that it might help to prevent recurrent cardiac events (Sheps et al. 2003). More recently, however, concerns about cardiac problems have led to a reduction in the recommended maximum dose of citalopram and escitalopram. In overdose, fluoxetine has been reported to cause sinus tachycardia, myocardial infarction, junctional rhythms and trigeminy and escitalopram QT prolongation and bradycardia (van Gorp et al. 2009). Clinicians should be more alert with regard to these potential adverse reactions and electrocardiogram monitoring may be suggested during therapy, especially in patients with pre-existing cardiovascular disorders (Pacher and Kecskemeti 2004).

SNRIs

SNRIs (such as duloxetine and venlafaxine) are a class of drugs used in the treatment of major depression and anxiety disorders. They are potent inhibitors of serotonin (5-Hydroxytryptamine) and norepinephrine reuptake acting on serotonin transporter and norepinephrine transporter, and on membrane proteins that are responsible for the reuptake of serotonin and norepinephrine. Balanced dual inhibition of monoamine reuptake can possibly offer advantages over other antidepressant drugs by treating a wider range of symptoms (Cashman and Ghirmai 2009). Venlafaxine, a well established treatment for panic disorder (Baldwin 2014), is generally well tolerated, with side effects that usually decrease with long-term treatment (Katzman and Jacobs 2007, Spina et al. 2008). However, it shows very strong evidence of increasing blood pressure at higher doses, thus blood pressure monitoring, particularly in people at risk of hypertension and heart disease, is mandatory above doses of 150 mg/day. Duloxetine, which has greater initial noradrenergic effects and is currently approved in many countries for the treatment of GAD, appears to be well tolerated, showing limited rates of mild intensity side effects (Simon et al. 2009, Dell'Osso et al. 2012).

Other antidepressant drugs

Although these drugs (e.g. amitriptyline, clomipramine, desipramine, and imipramine) may be effective in panic disorders, their cardiac toxicity, in particular secondary to increases in blood pressure or heart rate, precludes their use in heart patients (Batelaan et al- 2011). They have antimuscarinic properties and can behave like class 1A antiarrhythmics, inhibiting cardiovascular Na+, Ca2+ and K+channels, often leading to life-threatening arrhythmia (Pacher and Kecskemeti 2004). They can also, theoretically, decrease cardiac contractility and increase myocardial irritability.

The traditional irreversible monoamine oxidase inhibitor phenelzine has proven efficacy in panic disorder, but side effects and the need to follow dietary restrictions limit its use (Baldwin 2014).

Anxiolytics

Benzodiazepines are frequently used drugs in anxiety disorders (in the United Kingdom in 2010 there were 6 million diazepam and lorazepam prescriptions). Their principal mode of action involves the interaction with a specific site on one of the gamma amino-butyric acid receptors that increases the affinity to that inhibitory transmitter (Batelaan et al. 2011). Benzodiazepines attenuate the response to stress adrenergic activation, improving HRV and reducing blood pressure, heart rate and myocardial contractility and, probably by direct vasodilatation, increasing coronary flow, with possible reduction of myocardial oxygen consumption (Batelaan et al. 2011). Their fast efficacy and relatively safe side effect profile (they can be administered soon after myocardial infarction) make them particularly useful to treat short-term, transient GAD and panic attacks, rather than persistent anxiety disorders. It is only relevant side effect is a possible depressive action on respiratory centres. In addition, they should not be used in elderly patients and in patients with a history of drug-addiction or personality disorders, because chronic treatment can be complicated by abuse (Batelaan et al. 2011). There is documented evidence of adverse effects of the chronic use of benzodiazepines and the risk of developing addiction in older populations (Benitez et al. 2008). However, up to date there are no studies which permit a definitive conclusion regarding the relation between their administration and cardiovascular events, although beneficial effects of these drugs were demonstrated on replaced outcomes such as cortisolemia (Meewisse et al. 2007), blood pressure and other cardiovascular risk factors (cholesterol and glycaemia), perhaps attributable to a greater adherence to medical prescription and to their positive effect on catecholamine and insulin regulation hormone levels.

Combined interventions

A significant decline in the frequency of panic attacks was observed during cognitive behavioral therapy, SSRI treatment, or both combined (Van Apeldoorn et al. 2013).

The MOSAIC (Management of Sadness and Anxiety in Cardiology) trial is an ongoing prospective randomized trial of a low-intensity intervention collaborative care programs, which use care managers to assess patients, coordinate care, and perform therapeutic interventions for patients hospitalized for acute coronary syndrome, heart failure, or arrhythmia, and diagnosed with depression, GAD, or panic disorder. Compared to enhanced usual care, this will provide data regarding whether an intervention that concurrently manages these common psychiatric disorders results in meaningful improvements in quality of life, psychiatric symptoms, and medical outcomes in cardiac patients at

Table I. *Classification of Anxiety Disorders according to DSM-5*

Disorder	Description
Separation Anxiety Disorder	It is a psychological condition in which an individual experiences excessive anxiety regarding separation from home or from people to whom the individual has a strong emotional attachment (e.g. a parent, grandparents, or siblings).
Selective Mutism	Consistent failure to speak in specific social situations in which there is an expectation for speaking (e.g., at school) despite speaking in other situations
Specific Phobia	people with specific phobias, or strong irrational fear reactions, work hard to avoid common places, situations, or objects even though they know there's no threat or danger. The fear may not make any sense, but they feel powerless to stop it. People who experience these seemingly excessive and unreasonable fears in the presence of or in anticipation of a specific object, place, or situation have a specific phobia.
Social Anxiety Disorder (Social Phobia)	It's the extreme fear of being scrutinized and judged by others in social or performance situations: Social anxiety disorder can wreak havoc on the lives of those who suffer from it.
Panic Disorder	It is diagnosed in people who experience spontaneous seemingly out-of-the-blue panic attacks and are preoccupied with the fear of a recurring attack.
Panic Attack (Specifier)	The DSM-5 simplified panic attacks as fitting into two simplified types: expected or unexpected.
Agoraphobia	Some people stop going into situations or places in which they have previously had a panic attack in anticipation of it happening again. They typically avoid public places where they feel immediate escape might be difficult, such as shopping malls, public transportation, or large sports arenas.
Generalized Anxiety Disorder (GAD)	It is characterized by persistent, excessive, and unrealistic worry about everyday things. People experience exaggerated worry and tension, often expecting the worst, even when there is no apparent reason for concern. They anticipate disaster and are overly concerned about money, health, family, work, or other issues. GAD is diagnosed when a person worries excessively about a variety of everyday problems for at least 6 months
Substance/Medication-Induced Anxiety Disorder	When there is evidence that persistent relevant anxiety symptoms have physiologically arisen out of use of or withdrawal from either prescribed or "recreational" drug use or toxic factors exposition.
Anxiety Disorder Due to Another Medical Condition	When there is evidence that persistent, relevant anxiety symptoms have physiologically arisen out of a general medical condition.
Other Specified Anxiety Disorder	The clinician communicates the specific reason criteria are not met for any anxiety disorder within the diagnosis.
Unspecified Anxiety Disorder	Unspecified anxiety disorder can be used when the clinician chooses not to specify why criteria are not met for an anxiety disorder, for instance, when sufficient information is not available to make a diagnosis.

high risk for adverse outcomes (Huffman et al. 2013).

In patients candidate for aortic-coronary bypass, preoperative individuation of anxiety symptoms by means of structured interview or self-administered questionnaire can guide psycho-therapeutic or pharmacological interventions, which are efficacious in improving anxiety symptoms and significantly reducing analgesia, hospital stay and postoperative events (Pignay-DeMaria et al. 2003; Vaccarino 2011). In presence of evident post-surgical stress, an early intervention with drugs is opportune, but particular attention must be paid to postoperative early administration of benzodiazepine, which increases delirium risk (Pignay-DeMaria et al. 2003).

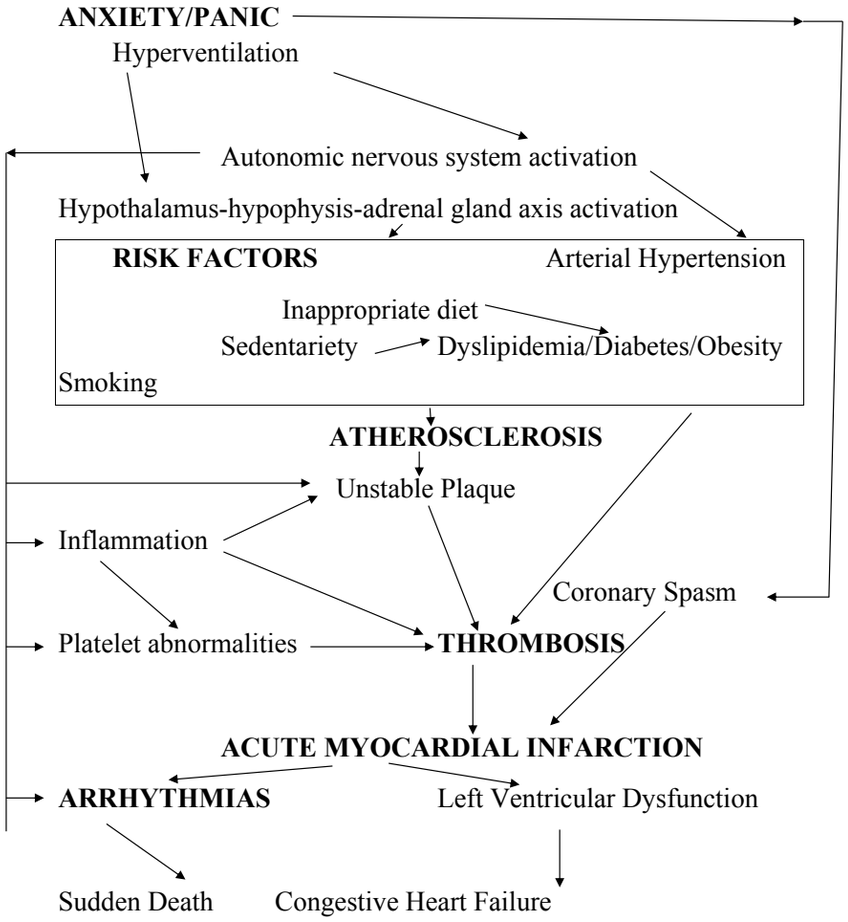
Cardiovascular drugs

It has also been suggested that patients with increased anxiety sensitivity might benefit from beta-blocker treatment (Domschke et al. 2010), as these drugs can decrease performance anxiety and at least some of its

Table II. *Symptoms in panic disorders and acute coronary syndromes/myocardial ischemia*

a) **Panic disorders**	b) **Acute coronary syndrome/myocardial ischemia**
1. Palpitations, pounding heart, or accelerated heart rate	1. palpitation
2. Sweating	2. sweating
3. Trembling or shaking	3. pain (usually it is described like sensation of oppression, laceration, burning at precordium that can be radiated to neck, shoulders, jowl, arms or epigastrium)
4. Sensations of shortness of breath or smothering	
5. Feeling of choking	
6. Chest pain or discomfort	4. effort dyspnoea
7. Nausea or abdominal distress	5. nausea
8. Feeling dizzy, unsteady, lightheaded, or faint	6. thoracic pain or discomfort
9. Chills or heat sensations	7. atypical presentation in diabetic and old patients:
10. Paresthesias (numbness or tingling sensations)	- fatigue
11. Derealization (feelings of unreality) or depersonalization (being detached from oneself)	- syncope
	- asthenia
12. Fear of losing control or going crazy	- mental confusion
13. Fear of dying	- no symptoms

Figure 1. *Physiopathologic mechanisms*



physiological effects; also, in such patients, the benefits of preventing ventricular arrhythmias and lowering heart rate may be particularly important. However, the literature about the impact of beta-blockers on anxiety/anxiety disorders is inconsistent (Bachmann et al. 2011, Frasure-Smith et al. 2012). In atrial fibrillation, finally, the tendency to fear and catastrophize in response to bodily symptoms of anxiety derived a prognostic benefit more from rhythm-control than from rate-control (Frasure-Smith et al. 2012).

Conclusions

Epidemiological data indicate that anxiety and panic disorder show a high prevalence in cardiac patients and can influence mortality and morbidity. The association between psychopathology and onset of heart disease has substantial clinical and public health implications. Beyond hard outcomes, psychological and emotional disorders produce negative effects on the global adjustment. Several pathophysiological alterations, due to anxiety disorders seem to be effectively treated with proved and safe pharmacological agents in heart patients and to decresae risk factors. In any case, improvement in quality of life and the comfort of heart patients with anxiety comorbidities is an essential clinical objective.

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