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THE IMPACT OF CARDIAC REHABILITATION ON LIFESTYLES, PSYCHOLOGICAL CORRELATES AND THE CLINICAL COURSE OF CARDIAC DISEASE

L'impatto della riabilitazione cardiologica su stili di vita, correlati psicologici e decorso clinico della malattia cardiaca

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Abstract

Objectives: The aim of this research was to evaluate the impact of Cardiac Rehabilitation (CR) on risky lifestyles, quality of life, psychopathology, psychological distress and well-being, considering the potential moderating role of depression, anxiety and psychosomatic syndromes on lifestyles modification. The influence of CR on cardiac morbidity and mortality was also evaluated.

Methods: The experimental group (N=108), undergoing CR, was compared to a control group (N=85) of patients affected by cardiovascular diseases, not undergoing CR, at baseline and at 1-month, 6- and 12-months follow-ups. The assessment included: the Structured Clinical Interview for DSM-IV, the structured interview based on Diagnostic Criteria for Psychosomatic Research (DCPR), GOSPEL questionnaire on lifestyles, Pittsburgh Sleep Quality Index, Morisky Medication Adherence Scale, MOS 36-Item Short Form Health Survey, Symptom Questionnaire, Psychological Well-Being Scale and 14-items Type D Scale.

Results: Compared to the control group, CR was associated to: maintenance of the level of physical activity, improvement of correct dietary behaviors and stress management, enhancement of quality of life and sleep; reduction of the most frequently observed psychiatric diagnoses and psychosomatic syndromes at baseline. On the contrary, CR was not found to be associated with: healthy dietary habits, weight loss and improvement on medications adherence. In addition, there were no relevant effects on sub-clinical psychological distress and well-being, except for personal growth and purpose in life (PWB). Also, CR did not seem to play a protective role against cardiac recurrences. The presence of psychosomatic syndromes and depressive disorders was a mediating factor on the modification of specific lifestyles.

Conclusions: The findings highlight the need of a psychosomatic assessment and an evaluation of psychological sub-clinical symptomatology in cardiac rehabilitation, in order to identify and address specific factors potentially associated with the clinical course of the heart disease.

Chapter 1

CARDIOVASCULAR RISK FACTORS

The 2008 overall rate of death attributable to cardiovascular disease (CVD) was 244.8 per 100000. From 1998 to 2008, the rate of death attributable to CVD declined 30.6%. Mortality data for 2008 show that CVD accounted for 32.8% of all 2471984 deaths in 2008, or 1 of every 3 deaths in the United States (1). Despite therapies improvement, the leading cause of death in the Western world, including Italy, remains cardiovascular diseases (2). Indeed, cardiovascular diseases (including ischemic heart disease, stroke and other cerebro-vascular disease, and hypertensive heart disease) accounts for 28.7% of the total causes of death in middle-income countries and 26.6% in high-income countries (3).

Increased awareness of both the prognostic role of cardiovascular risk factors, and the effectiveness of prevention strategies. The knowledge of the main risk factors is essential to improve measures for cardiovascular diseases prevention. The cardiovascular risk factors are specific factors that are statistically associated with coronary heart disease (CHD) and therefore are believed to play a role in its pathogenesis, interacting with each other and intervening on it in a factorial and not simply additive way (4, 5). Risk factors should not be considered as a direct cause, but indicators of the probability of cardiovascular diseases occurrence. However, since the risk of death from myocardial infarction (MI) increases significantly in the presence of 2 or more risk factors, it is essential to consider all the characteristics that may influence both the onset and a poor prognosis of these disorders (6).

In the recent years, the concept of "global CHD risk" has been introduced. It represents the absolute risk of a CHD-related event over a specific period, usually 10 years. The event can be "hard", such

as myocardial infarction (MI) or sudden cardiac death, or “soft”, such as chest pain. The risk value is based on major risk factors and is calculated using an empiric equation. The most commonly used parameters are the Framingham Heart Study risk score, FRS (7), the Systematic Coronary Risk Evaluation, SCORE (8), and, in Italy, the CUORE project risk score (9).

The INTERHEART study (10), a multi-centre large controlled study, highlighted that more than 90% of the risk to develop an acute myocardial infarction is explained by nine traditional risk factors: hypertension, diabetes, dyslipidemia, smoking, obesity, low consumption of fruit and vegetables, alcohol consumption, poor exercise, and psychosocial factors.

Risk factors can be included into three categories: medical, behavioral and psychological risk factors, the latter being officially recognized by the European guidelines for cardiovascular diseases prevention (11).

1.1 MEDICAL RISK FACTORS

Medical risk factors can be divided into non-modifiable and modifiable. The first category includes risk factors that cannot be changed (age, sex and family history of cardiovascular disease); people in these high-risk categories should receive regular check-ups. The second includes hypertension, hypercholesterolemia and diabetes.

1.1.1 Age

As for the majority of medical illnesses, older age is associated with an increased risk. Since as a person gets older the heart undergoes subtle physiologic changes, even in the absence of disease, cardiovascular diseases become increasingly common with advancing age. The heart muscle of the aged heart may relax less completely between beats, and as a result, the pumping chambers become stiffer and may work less efficiently. When a cardiovascular disease affects the heart, these age-

related changes may compound the problem or its treatment (12). World Health Organization defined advanced age as the most powerful independent risk factor for cardiovascular diseases, with a 2-folds higher risk of stroke every decade after age 55 (2).

1.1.2 Sex

Cardiovascular diseases have a higher incidence among men rather than women. Specifically, higher rates of coronary heart disease among men compared with pre-menopausal women have been observed; however, once past the menopause, a woman's risk is similar to that of a man (2). Despite this evidence, American Heart Association (13) found that only 13% of women perceive heart disease as a major health problem to be treated and only one third think that cardiovascular diseases represent the leading cause of death.

1.1.3 Family history of cardiovascular diseases

World Health Organization observed an increased risk of developing a cardiovascular disease if a first-degree blood relative had had coronary heart disease or stroke before the age of 55 years (for a male relative) or 65 years (for a female relative) (2).

There is consistent evidence from multiple large-scale prospective epidemiology studies for a strong and significant association of a reported family history of premature parental CHD with incident MI or CHD in offspring. The INTERHEART study (14) found that familiarity had a strong predictive value on cardiovascular diseases, independently from other common risk factors. Moreover, the study found that this association is strong worldwide. The Framingham Heart Study highlighted that the occurrence of a premature atherosclerotic CVD event in either a parent (15) or a sibling (16) was associated with around a 2-folds elevated risk for cardiovascular events, independently from other traditional risk factors. Moreover, parental history of coronary heart disease is associated with

increased burden of atherosclerosis in the coronary arteries and the abdominal aorta (17, 18). A family history of early-onset sudden cardiac death in a first-degree relative is associated with more than 2-folds greater risk for the same cardiac event in the offspring (19). Although in most people with a family history of a CVD event they are not identified, an accurate and complete family history assessment should be taken in order to identify rare mendelian conditions (i.e., hypertrophic cardiomyopathy, long-QT syndrome, or familial hypercholesterolemia) (20).

1.1.4 High blood pressure

High blood pressure (hypertension) is the leading cause cardiovascular diseases (21) and one of the most important preventable causes of premature death worldwide. Even a blood pressure at the top end of the normal range increases risk. It is defined as a repeatedly elevated systolic blood pressure (SBP) of 140 mmHg or higher, or a diastolic blood pressure (DBP) of 90 mmHg or higher. It has been found to be a major risk for heart attack and the most important risk factor for stroke (2). In most countries, up to 30% of adults suffer from hypertension and a further 50% to 60% would be in better health if they reduced their blood pressure, by increasing physical activity, maintaining an ideal body weight and eating more fruits and vegetables. In people aged up to 50 years, both DBP and SBP are associated with cardiovascular risk; above this age, SBP is a far more important predictor (2). Blood pressure usually rises with age; however, in most cases, hypertension is due to modifiable un-healthy lifestyles, such as a salty diet, smoke and physical inactivity. Moreover, people with hypertension are more likely to develop complications of diabetes (22).

1.1.5 Hypercholesterolemia

High levels of LDL-cholesterol, and other abnormal lipids (fats), are risk factors for cardiovascular disease. Cholesterol is a waxy substance found among the lipids in the bloodstream and in all the

body's cells, that is needed to form cell membranes and hormones, and for other bodily functions. Food, especially animal products such as meats, poultry, fish, eggs, and dairy products, can produce cholesterol. Fruit, vegetables and cereals do not contain cholesterol at all. Certain saturated vegetable fats and oils (such as coconut fat and palm oil) are cholesterol-free but cause an increase in blood cholesterol. Some foods that do not contain animal products may contain trans-fats, which also cause the body to make more cholesterol. Low-density lipoprotein (LDL) and high density lipoprotein (HDL) transport cholesterol around the body: a high level of LDL can lead to clogging of the arteries, increasing the risk of heart attack and ischemic stroke, while HDL reduces the risk of coronary heart disease and stroke. Estrogen (the female sex hormone) has the tendency to raise HDL cholesterol levels, thus explaining why premenopausal women are relatively protected from developing coronary heart disease.

In 2008, the prevalence of raised total cholesterol among adults – defined as total cholesterol of 6.2 mmol/l (240 mg/dl) or higher – was 9.7%, 8.5% males and 10.7% females (21). The Seven Countries Study (23), observed for 25 years over 12 thousand men aged between 40 and 59 years belonging to seven different countries; hypertension and hypercholesterolemia were the two main risk factors detected.

1.1.6 Diabetes

Other than one the traditional cardiovascular risk factors, diabetes is the most common cause of amputation that is not the result of an accident. Insulin is a hormone produced by the pancreas and used by the body to regulate glucose (sugar). Diabetes occurs when the body does not produce enough insulin, or cannot use it properly, leading to too much sugar in the blood. It is defined as having a fasting plasma glucose value of 7.0 mmol/l (126 mg/dl) or higher. Symptoms include thirst, excessive urination, tiredness, and unexplained weight loss. There are two main types of diabetes. Type 1 diabetes, in which the pancreas stops making insulin, accounts for 10% to 15% of

cases (2). However, type 2 diabetes is the most common type of diabetes: in this case, insulin is produced in smaller amounts than needed, or it is not properly effective. This form is preventable, because it is related to physical inactivity, unhealthy diet (excessive sugars intake) and obesity. Diabetes is more prevalent in developed countries, but modernization and lifestyle changes are likely to result in a future epidemic of diabetes in developing countries (2).

The INTERHEART study (10) estimated that 15% of heart attacks in Western Europe are due to diabetes. People with diabetes seem to be more prone to heart attack complications, such as re-infarction, chronic congestive heart failure, and cardiogenic shock. Also, since silent ischemia is very common among diabetics, there may be a dangerous delay in obtaining a diagnosis. In 2008, the global prevalence of diabetes was estimated to be 10% and, in general, CVD accounts for about 60% of all mortality in people with diabetes (21). The risk of cardiovascular events has been found to be 2/3 folds higher in people with type 1 or type 2 diabetes and the risk is disproportionately higher in women (21).

1.2 BEHAVIORAL RISK FACTORS

1.2.1 Physical inactivity

Industrialization, urbanization and modern transportation have reduced physical activity, even in developing countries. Although it has been showed that physical exercise is linked to longevity, independently from genetic factors, currently more than 60% of the global population are not sufficiently active (2). Insufficient physical activity can be defined as less than 30 minutes of moderate activity five times *per* week, or less than 20 minutes of vigorous activity three times *per* week, or equivalent. Among middle-aged and older persons, those with coronary heart disease have higher rates of self-reported diminished ability to perform activities of daily life, than do persons without CHD (24). Moreover, older age, female sex, and clinical manifestations of angina pectoris

or chronic heart failure are associated with the highest rates of disability (24); other factors include a low level of aerobic fitness, a high levels of depression, and diminished muscular strength (25). However, a patient's perceived inability to perform an activity is not necessarily correlated with actual physical incapacity (26). Poor physical activity has been found to be the fourth leading risk factor for mortality (21). People who are insufficiently physically active have a 20% to 30% increased risk of all-cause mortality compared to those who engage in at least 30 minutes of moderate intensity exercise most days of the week (21). Sedentary individuals are almost twice as likely to die from heart disease when compared with those who have a high physical activity; moreover, 16% of deaths due to coronary heart disease appears to be associated with physical inactivity (27). On the contrary, physical activity - even among elderly - seems to have a cardio-protective function (28-30) and can significantly reduce the risk of coronary heart disease, diabetes, high blood pressure, and obesity; moreover, it helps to reduce stress, anxiety and depression, and improve lipid profile (2).

1.2.2 Unhealthy diet

Low fruit and vegetable intake is estimated to cause about 31% of coronary heart disease and 11% of stroke worldwide (2), and approximately 2.8% of deaths (21). High saturated fat intake increases the risk of heart disease and stroke through its effect on blood lipids and thrombosis. As already mentioned, the amount of dietary salt consumed is an important determinant of blood pressure levels and overall cardiovascular risk. To prevent CVD, World Health Organization recommends a population salt intake of less than 5 grams *per* day (*per* person), *versus* the current global levels of 9/12 grams *per* day. Compared to low-energy foods, frequent consumption of high-energy foods (i.e., processed foods that are high in fats and sugars) promotes obesity, while a high consumption of saturated fats and trans-fatty acids is linked to heart disease (21). On the contrary, the elimination of trans-fat and the replacement of saturated with polyunsaturated vegetable oils decreases coronary

heart disease risk. An adequate consumption of fruit and vegetables reduces the risk of CVD, contributing to a healthy body weight, a desirable lipid profile and a desirable blood pressure (21). Indeed, studies highlighted that a diet rich in fibers is associated with a decrease of coronary risk, independently from sex, age, physical activity, smoking and alcohol abuse (31). Eating more than 10 grams of fiber *per* day results in a 19% decrease of cardiovascular risk (32).

1.2.3 Overweight and obesity

To achieve optimal health, the median Body Mass Index (BMI) for adult populations should be in the range of 21–23 kg/m^2, while the goal for individuals should be to maintain a BMI in the range 18.5–24.9 kg/m^2. Belt size, abdominal girth and waist-to-hip ratio are useful indicators of obesity. BMI, a measure of weight in relation to height, is commonly used for classifying overweight and obesity (a person with a BMI of over 25 kg/m^2 is considered overweight, while someone with a BMI of over 30 kg/m^2 is obese). In 2008, 9.8% of men and 13.8% of women were obese, compared to 4.8% for men and 7.9% for women in 1980 (21). The raised prevalence of BMI increases with income level of countries, up to upper-middle-income levels. The risks of cardiovascular disease and type 2 diabetes are directly associated with increasing BMI (2), while that of myocardial infarction increases for each level of BMI above the norm and, conversely, weight loss is associated with a significant reduction in the risk of cardiovascular (33, 34). Obesity has been found to be strongly related to other major cardiovascular risk factors such as raised blood pressure, glucose intolerance, and dyslipidemia (21). Among women, a BMI as low as 21 may be have a protective effect against coronary heart disease death (2). World Health Organization underlines how low fruit and vegetable intake accounts for about 20% of CVD worldwide. Obese smokers live 14 fewer years than nonsmokers of normal weight. Dietary habits are influenced by a number of environmental factors including family practices, food distribution marketing trade policies, agricultural policies. Currently, many cultural factors encourage poor dietary habits, increasing the

risk of obesity. For example, many meals are not consumed at home and often they consist of quick snacks with high calories, and many jobs are quite sedentary.

1.2.4 Smoking

In 1940, a link was identified between cigarette use and coronary heart disease, and there is now a huge body of scientific literature linking tobacco with CVD. Currently, smokers in the world are about 1 billion and smoking is estimated to cause nearly 10% of all CVD (21). The risk of developing CVD is higher in female smokers, young men, and heavy smokers (2, 35). Women who smoke only three to five cigarettes a day double their risk of heart attack, while men who smoke six to nine cigarettes a day double their risk (2). Within two years of stopping, the risk of coronary heart disease is substantially reduced, and within 15 years the risk of CVD returns to that of a non-smoker (36). Other than smoking, tobacco use and passive smoking are also implicated as CVD risks (2). Smoking may trigger cardiovascular diseases through several mechanisms, such as damages to the endothelium lining of the blood vessels, increases of cholesterol plaques, clotting, and LDL-cholesterol, decrement of HDL, and inaction of coronary artery spasm. Moreover, nicotine accelerates the heart rate and raises blood pressure. A gene has been discovered that increases smokers' risk of developing coronary heart disease by up to four times. Around a quarter of the population seems to carry one or more copies of this gene (2).

1.2.5 Alcohol abuse

The influence of alcohol on cardiovascular disease is somewhat different from that of other risk factors. It has been highlighted that one to two drinks per day may lead to a 30% reduction in heart disease, but heavy drinking damages the heart muscle (2). Indeed, a moderate consumption of alcohol stimulates the production of HDL cholesterol, which is a cardio-protective factor. On the

contrary, an excessive consumption of alcohol constitutes a risk factor because of its cardio-toxic action and the increase in blood pressure produced (37).

1.3 PSYCHOLOGICAL RISK FACTORS

1.3.1 Depression

Several studies analyzed the impact of depression on the prognosis of patients with cardiovascular conditions, showing almost unanimously that depressive disorders increase the risk of new acute cardiovascular events, re-hospitalizations (38-41), cardiovascular and non-cardiovascular death (42-46). Indeed, major depressive disorder but also minor depression represent risk factors for patients with cardiovascular diseases (47-50).

After being among the first to demonstrate the negative effect of depression on cardiac outcomes following myocardial infarction, independently from cardiovascular history, severity of the disease or residual function of the left ventricle (51-53), Frasure-Smith and Lesperance (54) showed that depressive symptoms, but not anxiety, predict 5-years mortality even after adjustment for disease clinical severity parameters, in patients with recent myocardial infarction. On the same vein, Barefoot and Schroll (43), found depressive symptoms being independently associated with an increased risk of death in more than one thousand patients enrolled after recent myocardial infarction and evaluated again with long-term follow-up (19.4 years). Another prospective study (55) with a 3-years follow-up, showed that among patients with MI depressive and/or anxious symptomatology was associated to more than 2-folds risk of new cardiac events. Similar findings have been found in patients undergoing coronary artery bypass grafting (56).

INTERHEART study (10) highlighted that the association between depression and cardiovascular diseases is common to both sexes and all ages, showing minimum geographical differences, the associated risk being around 2.5 times higher than that of not depressed patients. A systematic

review (57) showed that among depressed patients the risk of developing a cardiovascular disease at four years follow-up is about 1.64, being higher than the risk resulting from cigarette smoking (1.25). Longitudinal studies with a large sample size (43, 58-60) suggest that depression may precede the development of a cardiovascular disorder. The risk has been found to be directly related to the severity of depressive symptomatology; in particular, from one to two times greater for the minor depression and from three to five times greater for major depression (61, 62). However, the role of depression on the development of cardiovascular diseases in subjects initially healthy is not entirely clear, also due to different criteria and methods used to diagnose depression (63). According to some authors (64), dysthymia is more frequently associated to cardiovascular diseases than acute depression. Quite recently, Rafanelli and colleagues (65) showed a prevalence of dysthymia of 13.4% in patients with acute coronary syndrome; the diagnosis represented a risk factor for cardiac morbidity at a mean follow-up of 2.5 years.

Not surprisingly, the close association between depression and increased incidence of cardiovascular diseases has been attributed to indirect effects, such as the high frequency of traditional cardiovascular risk factors among depressed patients (66). However, the link between depression and cardiovascular diseases is complex and involves biological, psychological, and behavioral factors, such as illness behavior and adherence to treatment modification. The fact that depression may facilitate the onset of cardiovascular diseases and adversely affect the course of the illness may be the result of unhealthy lifestyles frequently adopted by depressed patients, such as physical inactivity and smoking habit (67), psychotropic substances abuse, carelessness about their own health. The latter, in particular, can lead to an unhealthy diet habits (i.e., skipping meals or eating unhealthy food), an irregular sleep-wake rhythm, a lack of medications compliance (68).

1.3.2 Anxiety

About the relationship between anxiety and cardiovascular diseases' prognosis, less evidence is depicted in literature. Most of the studies focused on initially healthy individuals, showed that a variety of anxiety disorders (i.e., panic attacks, anxious symptoms and phobic anxiety) predicted acute myocardial infarction and mortality due to coronary heart disease. This association was independent from the impact of other major cardiovascular risk factors (69). Although other studies suggest that anxious symptoms positively correlate with an increased risk of coronary events in the general population (69-73), an unanimous consensus about the role of anxiety disorders in the pathogenesis of cardiovascular disease is not reached (74, 75).

A meta-analysis on the association between anxiety and the incidence of coronary artery diseases, with a median follow-up of 11.2 years (76), detected a 26% greater risk of developing coronary heart disease and a 48% higher risk of cardiac death among people with anxiety disorders, even after multivariate adjustments. On the same vein, a Swedish longitudinal study conducted on a large healthy population (77), with a long-term follow-up (around 37 years), found a 2.17-folds higher incidence of coronary artery disease and a 2.51-folds higher incidence of myocardial infarction among patients with anxiety disorders. Anxiety was more likely than depression to predispose to coronary heart disease or to acute myocardial infarction.

Several studies on the association between anxiety and risk of subsequent cardiac events among patients with a history of cardiovascular diseases (78, 79), underlined that high levels of anxiety predict subsequent cardiovascular episodes (i.e., re-infarction, unstable angina, cardiac mortality). More recently, Martens and colleagues (80) pointed out that patients with stable coronary artery disease and generalized anxiety disorder had a significantly higher risk (74%) to be subjected to other cardiovascular events (such as stroke, myocardial infarction and cardiac death), than those affected only by the coronary artery disease.

As depression, anxiety disorders appear to be associated with certain behavioral risk factors for cardiovascular diseases. Compared to non-anxious individuals, those with a high level of anxiety are more likely to follow a less healthy diet, have a poor physical activity, abuse alcohol and drugs, smoke, have a poor compliance to treatment and bad sleep (51, 52, 81).

1.3.3 Type A behavior

Flanders Dunbar first described coronary disease patients as aggressive compulsive personalities with a tendency to work long hours and to size authority ("coronary personality"). Based on these assumptions, in 1959, the American researchers Friedman and Rosenman (82), described a specific behavioral style which they called "Type A Behavior" (Type A coronary-prone behavior, TAPB), associated with high cholesterol, increased curdling time and high risk of developing coronary artery disease. This pattern was characterized by hard driving and competitive behavior, ambition, drive for success, potential for hostility, subjective sense of time urgency, devotion to work, restlessness, pronounced impatience, and vigorous speech stylistic and abruptness of gesture (83, 84). Type A behavior is exhibited by people who are constantly engaged in a struggle to achieve, to outdo others, and to meet deadlines. It does not represent a response to life stress; rather, it constitutes a habitual behavioral state whose precursors have been observed in children (83). It seems that type A behavior represents specific manifest features of an interaction between a set of psychological characteristics and specific stimulus situations that provoke them and promote their full expression (the social environment that offers opportunities and rewards for competitive striving and a related value system, the easy access to a diet rich in saturated fats and calories, tobacco and transportation) (83). According to Friedman and Rosenman, type A does not correspond to a particular personality structure but it should be regarded as a tendency to show a typical set of behaviors in stressful situations.

Longitudinal studies highlighted type A behavior as a predictor of cardiovascular diseases onset and outcomes. The Western Collaborative Group Study (85) evaluated more than 3 thousand healthy subjects over eight years. The results revealed that those who showed type A behavior, independently of other cardiovascular risk factors (i.e., diabetes, hypertension or smoking), had a 2-folds greater risk of developing coronary artery disease than individuals who had opposite characteristics to type A, defined type B (82).

Since the association between type A behavior and development of cardiovascular disease has been proved by several studies in the 70s (86), the National Heart, Lung and Blood Institute officially recognized type A behavior as an independent risk factor against coronary heart disease (87). However, starting from mid-80s, research in this area showed contrasting findings. For example, a retrospective study (88) did not find any significant relationship between ischemic heart disease and type A behavior in a population under 45 years of age. The un-conclusive findings could be attributed to the different diagnostic measures used. A substantial problem of psychosomatic research in this field has been the fact of using dimensional instruments and postulating the presence of type A behavior pattern in every cardiac patient (89). Moreover, recently it has been suggested that - among all the components of type A behavior – the most associated with the development of cardiovascular disease are hostility and time urgency (90). Thus, the concept of type A behavior as a risk factor for cardiovascular diseases has been restricted to these specific aspects.

Diagnostic criteria for type A behavior were also included in the Diagnostic Criteria for Psychosomatic Research (DCPR) (91, 92), currently one the most used tool to detect this kind of behavior. Rafanelli and colleagues (49, 89) conducted one study on patients referred to cardiac rehabilitation and another on patients undergone bypass surgery; the Authors recorded that 40% (in the first study) and the 48.9% (in the second study) of the entire sample met criteria for at least one DCPR psychosomatic syndrome, type A behavior being the most frequently detected syndrome. Although it has been found also among patients with dermatological (10% of the cases) (93) and

gastroenterological (8% of the cases) (94) conditions, among patients with cardiovascular diseases type A behavior shows the greatest prevalence. A recent study (95) aimed to assess type A behavior prevalence in cardiology or in other medical fields by means of reliable instruments, found a significantly higher prevalence of type A behavior pattern among patients suffering from cardiovascular disorders (36.1%) rather than from other medical conditions (10.8%).

1.3.4 Demoralization

Schmale and Engel (96) have provided a detailed account for demoralization, which they defined as the 'giving up-given up complex' syndrome. Since such a sub-syndromal state cannot be identified with traditional psychiatric categories (97), DCPR (91) included demoralization among the other psychosomatic syndromes, and described it as a syndrome characterized by the patient's consciousness of having failed to meet his/her own expectations or those of others, or being unable to cope with some pressing problems. The demoralized patient experiences feelings of helplessness, or hopelessness or giving up. Prospective epidemiological studies have underlined a relationship between symptoms of hopelessness and the development of carotid atherosclerosis (98, 99). Rafanelli et al. (63) used DCPR nosographic system to detect demoralization: 20% of patients were identified as suffering from demoralization one year before the first episode of MI or angina. Among the subjects, 12% showed an overlap between major depression and demoralization. Demoralization could not be considered a cardiac risk factor *per se*, but the addition of this sub-clinical state to major depression could individuate a subgroup of patients at a greater risk of a cardiovascular morbidity (63). Ottolini et al. (100) observed at least one DCPR diagnosis in all the sample constituted by patients with myocardial infarction: 51% of patients reported demoralization, and 14.8% was the overlap rate between DCPR demoralization and DSM-IV mood disorders. It can be argued that there is a phenomenological ground whereby demoralization can be differentiated from major depression (101). Indeed, in the samples of the cited studies (63, 100), the subjects who

had a mood disorder did not necessarily satisfied criteria for demoralization and *vice versa*. The diagnostic criteria for demoralization attempt to capture the state of feeling that Schmale and Engel (96) outlined as a facilitating factor for the onset of disease to which the individual may be predisposed.

1.3.5 Irritable Mood

Everyday stresses, such as noise, traffic, a long wait, a rude answer, may elicit irritable mood (102). The experience of irritability is part of the normal human behavior. A basic problem of research on irritability lies in the various conceptualizations used to define it (103). Slater and Roth (104) regarded to irritability as a mode of response to specific psychological *stimuli*, such as those in which the individual is threatened or frustrated. A considerable body of evidence has suggested a pathogenetic role for anger, hostility and irritable mood in physical illness, both of organic and functional nature (104). The DCPR concept of irritable mood (91), is largely based on the work of Snaith and Taylor (105). Irritable mood was then defined as a feeling state which requires an increased effort of control over temper by the individual or results in irascible verbal or behavioral outbursts. It may be experienced as brief and isolated episodes, in particular circumstances, or it may be prolonged and generalized. Irritability can be associated with depressed mood but differs from it. It may be part of the type A personality associated with hostile cynicism. Ottolini et al. (100) observed that irritable mood was the most frequent DCPR diagnosis (56% of the patients) among 92 patients with a first episode of myocardial infarction.

1.3.6 Health Anxiety

A major problem with the DSM-IV classification of hypochondrial fears and attitudes is that it define only the most severe extremity of the spectrum (i.e., hypochondriasis, characterized by

resistance to medical reassurance and multiple fears). There is evidence (106, 107) that other worries are worthy of clinical attention, such as health anxiety, indicating preoccupations about health in the absence of a pathology or excessive concern in case pathology is present. The key feature of health anxiety seems to be dysfunctional beliefs about health and illnesses which could derive from past experiences of illness in oneself or others (108, 109). These worries are part of a vicious circle characterized by selective perception and misinterpretation of bodily symptoms which could – in turn – increase health anxiety. DCPR (91) define health anxiety as a generic worry about illness, concern about pain and bodily preoccupations (tendency to amplify somatic sensations). Worries and fears are characterized by a readily response to appropriate medical reassurance, even though new worries may arise after some time. As irritable mood, health anxiety was one of the most frequent diagnoses (41% of the total sample) found among patients with myocardial infarction (100).

1.3.7 Illness Denial

One of the most common immediate responses to myocardial infarction is the minimization of it and its consequences. Illness denial is a abnormal illness behavior, defined as the persistence of a maladaptive mode of perceiving, evaluating and responding to one's health status, despite the fact that a doctor has provided a lucid and accurate appraisal of the situation and management to be followed (110). Since denial interferes with the decision process to seek immediate help, it could be a primary reason for patient's delay, even if a prompt medical treatment is crucial to the survival from MI. However, the direct association between denial and patient's delay has yet to be ascertained (111). Although denial may be an functional behavior towards the first 3 days of recovery from MI (112), there is strong evidence that prolonged denial of the illness negatively affects MI recovery outcomes after discharge from hospital (112), having a long-term negative effect on cardiovascular health (113). The DCPR illness denial category (91) provides room for

various psychosomatic situations occurring in medical settings. Two explanations have been offered for the denial: (1) denial as a defense against death anxiety and a tendency to rationalize the symptoms as not related to the heart; (2) denial as minimization of the symptoms' significance to avoid the acceptance of the helplessness of being sick. Education of high-risk patients, such as those with a history of previous infarction, could reduce the tendency to delay seeking help. Adaptive or maladaptive responses and coping strategies are influenced by personality, family and medical factors. Persons who habitually deny or minimize the threatening significance of events tend to do so after an MI (83).

1.3.8 Anger and hostility

Other than being type A behavior key components, anger and hostility are considered two independent factors associated to coronary heart disease (114-117) and atherosclerosis progression (118). Typically, anger represents the emotional component of hostility that is, instead, a longer lasting individual disposition.

Barefoot and collaborators (119) found that high levels of hostility were predictive of both cardiovascular disease incidence and overall mortality. Hostility is also associated to unhealthy lifestyles, including smoking, obesity, poor dietary habits, alcoholism (120). Moreover, subjects displaying high levels of hostility have been found to be more likely to manifest comorbid psychosocial factors associated with heart disease, such as social isolation (73). A research conducted among healthy male subjects (121), showed that symptoms of anger were directly associated to the risk of heart disease at 7-years follow-up

Several studies investigated the role of hostility and anger traits on the development and progression of hypertension. A meta-analysis (122) sustained the anger-hypertension hypothesis, by showing that the inhibition of anger was positively correlated to systolic and diastolic blood pressure (BP) levels at rest, while its expression was negatively associated to the levels of systolic BP at rest.

Several studies have examined the influence of suppressed hostility or anger ("anger-in") on BP and found that anger-in was positively related to resting BP and/or prevalent hypertension (123), particularly under conditions of stress (124). However, data from the Framingham study and others do not support this association (125) and some research has found that expressed anger and high levels of trait anger are related to higher BP levels (126). Moreover, individuals with high levels of expressive hostility or potential for hostility (behavioral measures of hostility associated with both physical and verbal expressions of anger) have shown exaggerated BP responses under conditions of stress or harassment (127, 128) and anger expression has been associated with increased risk of fatal and nonfatal CHD, including MI and angina pectoris (70, 120).

1.3.9 Type D personality

A group of researchers from Netherlands and Belgium first described a constellation of psychological traits related to cardiovascular disease which they called "Type D Distressed Personality" (129). This personality is characterized by two specific traits which are: the tendency to experience negative emotions and the tendency to inhibit these emotions in social interactions. While type A constitutes a behavioral style that manifests itself in certain circumstances, type D is a personality construct characterized by relatively stable psychological traits. However, a recent study focused on type D personality and its relationship with anxiety, depression and quality of life (130), evaluated the stability of the construct before and after surgery in patients with cardiovascular conditions. The results showed that only 11% of the sample had a type D personality both before and after surgery; however, this group was formed by patients with the highest level of symptoms and the more compromised quality of life.

Considering the key features of people with type D personality, this construct can be regarded as a chronic psychological risk factor. It is conceivable that is exactly the joint effect of the tendency to experience negative emotions and to inhibit their expression, rather than negative emotions *per se*,

to produce a negative effect on health (131, 132). The first study which regarded to type D personality as a potential risk factor for heart disease (129), highlighted that in a sample of 105 patients who had myocardial infarction, 73% of the deaths involved patients with type D. Moreover, this personality has been associated to a six-folds higher risk of mortality than that of people without type D personality, increasing the predictive power of mortality of traditional biomedical risk factors (i.e., poor exercise tolerance, history of myocardial infarction, smoke, old age). These findings were confirmed by subsequent studies with larger sample size and longer follow-ups (131, 133). A Hungarian study (134) identified type D as a risk factor associated to myocardial infarction and cardiovascular mortality in patients without any other risk factors. More recently, de Jonge and colleagues (135), pointed out the difficulties to diagnose depression following myocardial infarction among people with comorbid type D personality, because of the somatic symptoms overlap; type D personality seemed to be relatively independent from physical health but, at the same time, it is an important predictor of long-term consequences of health impairment.

The pathophysiological mechanism underlining the relation between type D personality and predisposition to cardiovascular disease is not yet cleared. Some studies suggested that an impaired response to stress with increased blood pressure, and levels of cortisol and pro-inflammatory cytokines, could be involved (136). Indeed, both type D dimensions were found to be associated with greater levels of cortisol (134, 137).

Literature showed also that specific dysfunctional behaviors (such as the reluctance of looking for appropriate medical care, or avoidance of medical routine checks) are indicators of type D personality in healthy people (138-140). This construct is also associated with risky behaviors, such as poor dietary habits and physical inactivity (138).

Chapter 2

CARDIAC REHABILITATION

2.1 DEFINITION

Cardiac rehabilitation belong to secondary prevention programs and it is a structured set of services that enables people with coronary heart disease (CHD) to have the best possible help (physical, psychological and social) to preserve or resume their optimal functioning in society.

In 1993, the World Health Organization has defined cardiac rehabilitation as "the sum of activities required to influence favorably the underlying cause of the disease, as well as the best possible, physical, mental and social conditions, so that they (people) may, by their own efforts preserve or resume when lost, as normal a place as possible in the community. Rehabilitation cannot be regarded as an isolated form or stage of therapy but must be integrated within secondary prevention services of which it forms only one facet" (141).

As the benefits of ambulation during prolonged hospitalization for coronary events had been recognized (142), the hospital stay for acute coronary syndromes had been shortened and de-conditioning had became minimal (143), cardiac rehabilitation programs began to develop (144, 145). Initially, the process of physical re-conditioning was continued at home after discharge from the hospital; however, there was concern about the safety of unsupervised exercise after discharge (26). This led to the development of highly structured rehabilitation programs, including electrocardiographic monitoring and exercise training, that were supervised by physician. Agency for Health Care Policy and Research and National Institutes of Health Clinical practice guidelines, have widened the scope of cardiac-rehabilitation programs to include the assessment and

modification of risk factors and to enhance secondary prevention (146). The benefits of secondary prevention seem to be wide and compelling: the first controlled trials of exercise after MI displayed reductions in overall mortality and in mortality from cardiovascular causes (147, 148); trials of exercise combined with nutritional counseling demonstrated a slowing of the atherosclerotic process (149, 150) and a decrease of subsequent relapses rates (149).

2.1.1 Goals

As highlighted by World Health Organization (141), the main objective of cardiac rehabilitation is to enhance patient's function and quality of life, and to relieve symptoms. Secondary prevention aims to slow progression of the underlying disease and thus reduce rates of cardiovascular relapses (re-infarction, graft closure and cardiac death). Specific goals of cardiac rehabilitation are:

1. *Medical goals*: prevention of cardiac mortality; decrement of cardiac morbidity, re-infarction, graft closure; relief of cardiovascular symptoms, angina, shortness of breath.
2. *Psychological goals*: restoration of self-confidence; decrement of anxious and depressive symptomatology; improvement of adaptation to stress; restoration of enjoyable sexual activity.
3. *Socio-economic goals*: resume work, if appropriate; autonomy in daily activities; reduction of direct medical costs (i.e., early discharge, early rehabilitation, fewer medications, fewer re-admissions).

Long-term compliance is difficult to achieve as only half of the patients exercise regularly a year later. Compliance could be improved by means of motivation enhancement by the team members, or including family, spouse and social backgrounds in the rehabilitation process, or insisting that patients assume responsibility for their own risky behaviors modification.

2.1.2 Indications and contra-indications

Originally, cardiac rehabilitation was developed only for patients who suffered from myocardial infarction. As soon as it became clear that a poor outcome after other cardiac events was the result joint effect of physical, psychological, social and economic factors, the indications for CR program became wider. Currently, also patients who undergone to CABGs, valvular heart disease surgery or heart transplant, with stable angina, poor left ventricular ejection fraction (LVEF) or with a low ischemic threshold, have been included in comprehensive cardiac rehabilitation programs. CR is also considered in patients with ischemic heart disease or who are free of symptoms after angioplasty, with silent ischemia. The goals of cardiac rehabilitation and secondary prevention are to prevent disability resulting from coronary disease, particularly in elderly and those with occupations that involve physical exertion, and to prevent subsequent coronary events, subsequent hospitalization, and death from cardiac causes through a program of prescribed exercise and interventions designed to modify coronary risk factors, including drug therapy.

Contra-indications are strictly related to the physical training component of cardiac rehabilitation. Patients not indicated for this kind of program are those with severe ventricular arrhythmias at rest or increasing with exercise, not stabilized cardiac insufficiency and unstable angina.

2.1.3 Implementation phases

The cardiac rehabilitation process could be divided into three subsequent phases (151):

- *Step 1*: this first phase takes place during the acute stage of the cardiovascular illness (i.e., acute coronary syndrome, valvulopathy, congestive heart failure). During this phase, the key elements are clinical evaluation, physician's reassurance of patient and his/her family (which should be involved in the rehabilitative program), health education, misconceptions

about the disease and its consequences correction, evaluation of risk factors, early mobilization, adequate discharge planning.

- *Step 2*: typically this stage consists of a structured program aimed to evaluate patients' global risk, to intervene on physical activity in health care facilities and to supply educational and psychological support in order to change patients' specific risk factors.
- *Step 3*: this last phase includes long-term maintenance of physical activity and change in lifestyles. In order to maintain benefits over time, available evidence suggests that both should be pursued (152, 153). Attendance to a local group of heart support or a self-help group which involve physical activity in a gym or in a recreational centre could help to maintain physical activity and a healthy lifestyle over time.

From an organizational point of view the rehabilitation program can be run in outpatient facilities, as day-hospital in cardiology acute care facilities, in inpatient facilities during hospitalization.

Treatment choice is made on the basis of the degree of patient's clinical stabilization at discharge from the ward, considering logistical and social situation as well.

2.1.4 Members of the multidisciplinary team

Staff engaged in CR should be clinically competent in their own discipline and be able to motivate patients' change to healthier lifestyles. The multidisciplinary team include the cardiologist (as medical director), nurses, physiotherapist, dietician and clinical psychologist. Depending on the size of the rehabilitation unit, other physicians (cardiologist, nutritionist, exercise physiologist), occupational therapists and social workers may be involved.

2.1.5 Risk stratification

Severity of the ischemic heart disease varies from “normalized” heart after percutaneous angioplasty for single vessel disease to sever heart failure. The goals of cardiac rehabilitation vary depending on the severity of heart disease. The stratification of patients depending on their level of coronary risk allows an informed choice of the most suitable type of rehabilitation program for each patient.

2.1.6 Expected outcomes

The multi-factorial outcomes of cardiac rehabilitation can be summarized as follows:

1. *Physical*: 20% increment of the maximal work capacity and decrease of the pain due to angina
2. *Psychological*: increment of energy, enthusiasm, well-being; decrement of depressive and anxious symptomatology; improvement of self-image, ability to deal with stress, relaxation, quality of sleep, and sexual activity; fewer tranquillizers and hypnotics.
3. *Socio-economic*: less invalidism and absenteeism; reduced expenses.

Patients satisfaction and needs should be taken into account; moreover, since the outcome of CR depends also on patients’ expectation of recovery and it is improved when his/her spouse and family are involved, these features should be constantly monitored.

Historically, only “hard” endpoints (cardiac mortality and re-infarction) have been used as indicators of CR outcomes. Currently, however, there is a general consensus regarding the multi-factoriality of the outcomes; not only the physical conditions is taken into account, but also the functional capacity, psychological state, personal functioning in daily activities, symptoms and risks as a result of the illness. Moreover, physician’s feasibility perception should always match with that of the patients. Outcomes depend on the stage of illness and the clinical state of the patient and

should be calibrated case-by-case; indeed, treatment's goals are not the same for patients during hospital admission (immediately after myocardial infarction), for those who have no symptoms or only minimal angina, for those undergoing bypass graft surgery or with congestive heart failure.

Even if a precise definition remains elusive, the concept of quality of life is a crucial issue and it changed radically the evaluation of cardiac rehabilitation outcomes. Usually a good quality of life involves the ability to perform the daily tasks with the least physical and psychological restrictions and the least threat to life or health. Currently, the definition of quality of life changed from a mere relief of symptoms, return to work and absence of emotional distress, to a concept regarding the ischemic heart disease as a starting point for positive changes of risky lifestyles (141).

2.2 CARDIAC REHABILITATION COMPONENTS

Even though a general agreement on the components of CR has been reached, the method of implementing the program can vary considerably from place to place. Moreover, since most of the attention in exercise-based cardiac rehabilitation programs is often addressed to the exercise component only, it should be emphasized that these kind of programs also includes educational sessions regarding intensive dietary therapy and risk factor modification, that allow patients and their relatives to learn more about CHD and to exert more control over their disease. Thus, endurance training, educational counseling, risk factors behavioral modification, vocational guidance, relaxation, stress management and, when appropriate, pharmacological therapy should be included in a comprehensive CR program.

Exercise training is prescribed after a symptom limited exercise test. The aim is to maintain a training heart rate for 30 to 45 minutes at 50% to 75% of the peak of maximal oxygen consumption (VO_2) or 70%-85% of the peak heart rate on testing. Training sessions may vary from 3-5 times per week with a maximum of 20 sessions in total. The benefits of exercise training include:

- improvements of maximal functional capacity of post MI patients (from 11% to 56%) and of post surgical patients (from 14% to 66%);
- improvements of cardiovascular efficiency for sub-maximal efforts: patient can do more and is less tired by his/her daily activities because heart rate and blood pressure at a given level of physical exercise decreased;
- decrease of risk factors: CR component of physical training improves HDL cholesterol level and glucose tolerance, promotes weight lost, and reduces high blood pressure.

Prevention of risk factors and educational counseling, education on a suitable diet, physical and stress management training, social support and/or pharmacological treatment, can control most of the modifiable cardiovascular risk factors (hypercholesterolemia, hypertension, smoking habit, diabetes, bad stress management).

Vocational guidance, by means of the assessment of patients' clinical state, results of exercise testing, and motivation to go back to work, should be carried out at the beginning of the program in order to evaluate patients' potential to return to work.

These three components are integrated as much as possible in an individualized treatment plan trying to achieve the following objectives:

- pursuit of clinical stability;
- decrease of the physiological and psychological consequences of cardiovascular disease;
- improvement of the overall functional capacity, thus favorably affecting the degree of autonomy, independence, and quality of life;
- decrease of the risk of subsequent cardiovascular events;
- delay of the atherosclerotic process progression, of the underlying heart disease and clinical deterioration;
- decrease of morbidity and mortality.

2.2.1 Exercise training

The central goals of cardiac rehabilitation include the elimination of the negative effects of physical de-conditioning, the resumption of activities enhancing quality of life of the subject and the prevention of premature disability. Thus, exercise is a key component of cardiac rehabilitation. Aerobics and prudently administered, programmed physical activity is recommended when the acute phase of artery disease (or in general the clinical instability) is passed, and it should continue possibly for life. Among patients with documented coronary artery disease, the primary goals of physical training are to improve patients' psycho-social asymptomatic functionality and to reduce morbidity and mortality. The main symptoms of coronary heart disease, angina and dyspnea, reflect vascular function and cardiac hemo-dynamics abnormalities, compounded by physical de-conditioning and psychological factors. Angina pectoris and ischemic left ventricular dysfunction result from an imbalance between the supply of and the demand for myocardial oxygen. In the presence of coronary atherosclerosis, blood flow exercise-induced increases are limited both by atheroma and by an abnormal vascular endothelial response that results in vasoconstriction on physical effort (154, 155). Abnormalities of left ventricular diastolic inflow, common among elderly with coronary heart disease, also lead to dyspnea due to exertion which may limit exercise capacity (156). Moreover, patients with coronary heart disease frequently limit their physical activities because of the fear of adverse consequences, giving rise to a vicious cycle of inactivity and de-conditioning (157). Many patients may benefit from formal exercise training programs (*Table 1*).

Although, occasionally, some of the details of these programs should be strictly individualized (in terms of method, frequency and intensity) to meet special needs of certain patients (158), generally, they begin as soon as possible after major CHD events; they generally last for 12 weeks and consist of 3 exercise and education classes weekly, for a total of 36 education and exercise sessions. *Table 2* displays all potential benefits of exercise training (159).

Table 1: exercise prescription according to the characteristics of the patient

CHARACTERISTIC	*TRAINING REGIMEN*	*INTENSITY*	*TYPE OF EXERCISE*	*FREQUENCY OF SESSIONS (n/wk)*	*DURATION OF EACH SESSION (min)*
Age < 65 yr, not overweight	High-intensity aerobic	75%-85% of maximal heart rate	Walking, jogging, cycling, rowing	3 or 4	30-45 (continuous or interval)
Age ≥ 65 yr	Low-intensity aerobic and resistance	65%-75% of maximal heart rate	Walking, cycling, rowing	3 or 4	30 (may be intermittent)
Overweight	Aerobic – high caloric expenditure	65%-80% of maximal heart rate	Walking	5 or 6	45-60
Age > 65 yr and disabled, engaged in physical work, or overweight	Resistance	50%-75% of single-repetition maximal lift	Weight machine and dumbbells, with the focus on upper legs, shoulders, and arms	2 or 3	10-20 (10 repetitions of each of 5 to 7 exercises)

Source: Ades, P.A. (2001). Cardiac Rehabilitation and Secondary Prevention of Coronary Heart Disease. *New England Journal of Medicine* 345(12): 892-902.

Although one of the main potential benefits of exercise is the promotion of weight reduction, the "obesity paradox" has created controversy regarding the role of weight loss among patients with established CVDs. Indeed, several studies suggested that obese patients with CHD, heart failure, and hypertension show a better prognosis than those normal weighted with CV disease (160-163). Many studies focused on physical training of patients with different risk profile have demonstrated the effectiveness of appropriate programs on short-term goals (increment of exercise tolerance and symptom control). However, due to some methodological limitations (such as small sample sizes and high rate of drop-outs), it has been more difficult to demonstrate the benefits on long-term goals (morbidity and mortality). Several observational studies as well as randomized trials have assessed the benefits of exercise training in cohorts with established CHD (164-166). However, as Bentley and colleagues (167) pointed out that, while they found that three quarters of study participants reported a physical activity level meeting the current Canadian PA guidelines (168) at an average of 3.5 years after CR completion, a considerable variability among studies is evident. Few studies have reported such high percentages of physical activity post-CR. For example, both Zullo et al. (169) and Moore et al. (170) reported a low activity adherence of 41% and 48%, respectively, whereas Bock and colleagues (171) observed a high activity compliance of 84%.

Table 2: potential benefits of exercise training

Related to coronary heart disease risk factors
Increases serum high-density lipoprotein cholesterol levels
Reduces serum triglyceride and possibly low-density lipoprotein cholesterol levels
Reduces indices of obesity
Reduces arterial blood pressure
Improves insulin sensitivity and glucose levels
Improves endothelial function
Helps with smoking cessation efforts
Reduces psychological stress
Hematologic
Decreases hematocrit and blood viscosity
Expands blood plasma volume
Increases red blood cell deformability and tissue level perfusion
Increases circulatory fibrinolytic activity
Other
Increases coronary flow reserve
Increases coronary collateral circulation
Increases tolerance of ischemia
Increases myocardial capillary density
Increases ventricular fibrillation thresholds
Reduces atherosclerosis
Possibly increases epicardial coronary artery size
Reduces major morbidity and mortality

Source: Lavie, C.J., et al. (2009). Exercise Training and Cardiac Rehabilitation in Primary and Secondary Prevention of Coronary Heart Disease. *Mayo Clinic Proceedings* 84(4): 373-383.

2.2.1.1 Exercise compliance

The rate of compliance with an exercise regimen for cardiac rehabilitation has been found to be approximately 50% at one year follow-up (172, 173) *versus* a compliance rates of 64% for antihypertensive medication (174) and of 82% for lipid-lowering agents (175). Several interventions have been shown to optimize compliance with an exercise regimen. In one study, a rehabilitation program that included a gradual transition from supervised, out-patients exercise sessions to self-monitored sessions performed at home with resulted in a compliance rate of 92% at 6-months follow-up, *versus* a rate of 76% for a program that did not include this kind of transition (176). Moreover, other specific features, such as the use of low-intensity exercise (177), nurse case

managers (149, 178), and the patient's written, signed agreement to follow the prescribed regimen (179), have also been found to be associated with increased long-term compliance.

2.2.2 Comprehensive risk reduction: secondary prevention of the other cardiovascular risk factors

Secondary prevention focuses on risk reduction in patients with established coronary heart disease who are at high risk for recurrent cardiac events and death from cardiac causes. Other than exercise training, nutritional counseling, behavioral interventions, and pharmacological treatment have equally important roles. The cardiac-rehabilitation or preventive-cardiology nurse immediately initiates efforts to help the patient abstain from smoking. Nutritional counseling and behavioral interventions are also initiated in the hospital to maintain abstinence from smoking, lower blood lipid levels, control weight and blood pressure, and manage psychological symptoms. However, due to the shortening of the length of hospital admission for coronary events, much of the behavioral intervention has been shifted to the outpatient setting.

2.2.2.1 Smoking cessation

Cessation of smoking in patients with coronary heart disease is associated with a marked reduction in the rate of coronary events (180). The best results have been obtained with a strong recommendation by the physician to stop smoking combined with interventions managed by a nurse during the hospitalization (181). The goal is to prevent a relapse after discharge, since patients cannot smoke in the hospital. The interventions include teaching the patient behavioral skills for coping with high-risk situations, providing relaxation training, selectively prescribing bupropion or providing nicotine supplements (or both), and maintaining periodic, long-term follow-up telephone contact with the patient (26). In one study (181), the rate of smoking cessation one year after

myocardial infarction was 61% among patients assigned to these interventions but only 32% among controls.

2.2.2.2 Weight control

The combination of dietary intervention and exercise results in a 4% to 9% reduction of BMI (149, 182, 183). Indeed, exercise alone, without individualized nutritional counseling, has been less successful in achieving a substantial reduction in weight (184). When weight loss is accomplished, it is associated with improvements in lipid levels, insulin resistance, blood pressure, and clotting abnormalities (185, 186); indeed, the goal is not only to reach the ideal body weight but rather to achieve improvements in obesity-related risk factors. Since weight loss as part of cardiac rehabilitation is not a passive process, an associated program of behavioral modification is used as appropriate to address this key issue (187). The intervention includes behavioral concepts of stimulus control, self-monitoring, problem solving, social support, and a daily calorie count (26). In many cases, a sustained loss of 5% to 10%t of body weight substantially improves risk factors such as dyslipidemia and insulin resistance (188).

2.2.2.3 Hypertension and diabetes management

Although the beneficial effects of exercise training, weight reduction, and dietary modification on blood-pressure control and type 2 diabetes are well known (189-191), studies in the cardiac-rehabilitation setting are complicated by ongoing pharmacological treatment for patients with these conditions and by the need for frequent dose adjustments (26). Indeed, since exercise increases sensitivity to insulin, doses of oral hypoglycemic agents or insulin are usually reduced during exercise training to prevent hypoglycemia (191). Even if patients are also taught techniques of self-monitoring, a key role of the cardiac-rehabilitation staff is to assist primary care physicians with the

monitoring of blood pressure and diabetes. Such surveillance may result in adjustments of medications. In a study of cardiac rehabilitation that involved 666 patients, surveillance led to an alteration in the care received by 11% of the sample, most of whom had uncontrolled blood pressure, chest pain, or arrhythmia (192).

2.2.2.4 Psychosocial intervention

From the patient's point of view, the most prominent effects of cardiac rehabilitation fall within the psychological realm. Literature showed that levels of anxiety, emotional stress, depression, social isolation, self-confidence, and patient-reported quality of life improve after cardiac rehabilitation (193-196). Depression and social isolation after a coronary event have been found to be associated with increased mortality rates (42, 197). Most cardiac-rehabilitation programs include specific psychosocial interventions such as educational interventions, individual and group counseling, stress management, individual psychotherapy and self-help group (195, 198, 199). Patients enrolled in rehabilitation programs that include psychosocial interventions show greater improvements than do those enrolled in programs without a psychosocial component, such as a decrease of anxious and depressive symptomatology, lower blood pressure, and lower rates of mortality and recurrent cardiac events at 2-years follow-up (195).

Chapter 3

EXPERIMENTAL STUDY

3.1 OBJECTIVES

In the light of the considerations and findings detected in literature, the objectives of the present study were:

1. to evaluate, by means of reliable measures:
    a. lifestyles (smoking habits, body mass index, physical activity, dietary habits, stress management, quality of sleep, and medication adherence),
    b. health-related quality of life,
    c. the presence of depressive disorders (including the diagnosis of minor depression) and anxiety disorders according to DSM-IV criteria,
    d. the presence of psychosomatic syndromes according to DCPR,
    e. the frequency of type D personality, as defined by Denollet, and
    f. the extent of the psychological well-being, according to Ryff's model,

    of patients who underwent percutaneous coronary intervention, valve replacement/plastic, or bypass surgery, referred to a program of cardiac rehabilitation (CR);
2. the effectiveness of the CR program in the modification of risky lifestyles, by comparing the outcomes of the experimental group to those of a control group not subjected to CR;
3. the steadiness of the lifestyles changes over a period of 6 and 12 months after the end of the rehabilitation program;

4. the modification of clinical and subclinical psychological distress at the same time points (from baseline to 1-month, 6-months and 1-year follow-ups);
5. whether the presence of psychiatric or psychosomatic distress constitute moderators of lifestyles modification over time;
6. the effectiveness of CR to reduce the number of adverse cardiovascular events (defined as the number of hospitalizations for deteriorated cardiac conditions, cardiovascular relapses and cardiac death), at 6 and 12 months;
7. whether the presence of psychological distress and/or impairments in specific dimensions of psychological well-being constitute predictors of adverse cardiovascular events.

3.2 RESEARCH DESIGN

The present research involves the enrolment of two clinical groups of patients suffering from cardiovascular diseases. The experimental group is made up of patients referred to a cardiac rehabilitation program, and the control group consists of patients who did not undergo cardiac rehabilitation selected according to the main demographic and medical variables of those belonging to the experimental group. Patients belonging to the experimental group have been approached during the first day of the CR program, which typically lasts four weeks, and informed about the aims of the research. It has been explained to patients that the study would have entailed 4 subsequent evaluations, at the beginning of the CR (baseline, T1), at the end of the program (T2), and after 6 (T3) and 12 (T4) months from the end of the CR. The control group has been enrolled in two hospitals that do not provide cardiac rehabilitation programs. Control subjects have been approached during their admission to the Cardiology Divisions. Even in this case, the patients were informed about aims and duration of the study. The four-times assessment has been performed during the admission (T1), after one month (T2), 6 (T3) and 12 (T4) months from discharge.

3.3 SAMPLE

3.3.1 Experimental group

Participants of the experimental group have been recruited at the Cardiac Rehabilitation Unit of Bellaria Hospital Cardiology Division (Bologna), over a one-year period, from January 2011 to December 2011. Patients have been approached at the CR program facilities on a face-to-face basis. A study information sheet was made available to all patients attending medical assessment prior to their participation to the CR exercise program, advising patients who were interested in the study to speak to the investigator prior to or following their first CR class. Also, new patients attending CR classes have then been reminded about the study by CR nurses and technicians. The experimental group consisted then in a consecutive series of 108 patients referred to cardiac rehabilitation. These subjects were scheduled to join the CR program at Bellaria Hospital (Bologna), after having been discharged from different hospitals in the Bologna area. After the patients agreed to participate, signed informed consent was obtained.

The inclusion criteria used to select patients for this study have been intended to be as inclusive as possible. As such, all patients who attended the CR program during the recruitment period (year 2011) have been considered to be eligible to participate, provided that written consent was given. The only exclusion criteria have been lack of comprehension of the Italian language and missing signed consent forms.

3.3.2 Control group

Participants of the control group were recruited at the Cardiology Divisions of Bufalini Hospital (Cesena) and Infermi Hospital (Rimini), over an eight-month period, from August 2011 to March 2012. Patients have been approached during their admission in the above-mentioned wards and, if

necessary, some of them were then reminded about the study by the nurses and advised to speak to the investigator if they wished to discuss the study further. A study information sheet has been given to all patients approached. Following a discussion of study purposes, signed consent from participants was obtained. The control group then consisted of a consecutive series of 85 patients who were not being referred for cardiac rehabilitation.

As for the experimental group, the inclusion criteria have been intended to be as inclusive as possible. As such, all patients who did not attend the CR program during recruitment were considered to be eligible to participate, provided that written consent was given. The only exclusion criteria have been lack of comprehension of the Italian language and missing signed consent forms.

3.4 CARDIAC REHABILITATION PROTOCOL AT BELLARIA HOSPITAL (BOLOGNA)

Cardiac rehabilitation program at Bellaria Hospital (Bologna, Italy) follows an operational procedure specifically designed for patients who had undergone cardiac surgery or with heart failure. The purpose of this protocol is to provide recommendations and instructions and to define a standardized procedure to implement the secondary prevention program. The protocol is based on applicable standards and national guidelines for cardiac rehabilitation (151, 200). The operative procedure clearly defines the roles and specific responsibilities of the multidisciplinary team. The team consists of the leading cardiologist - responsible for the structure - who ensures a constant presence during the program; other cardiologists who manage the medical examinations and see patients when necessary; some technicians on cardiovascular physiopathology and cardiovascular perfusion; a physiotherapist; a few nurses who take care of patients during blood sampling, medications and co-morbidities (complications and emergencies) management; a dietician and a psychologist present on specific days/a week for individual meetings and voluntary classes on dietary education (dietician) and on stress management (psychologist).

Upon admission to the program, the steps to be followed include:

1. enrolment by the cardiologist;
2. personalized rehabilitative cycle programming;
3. prognostic stratification, i.e. risk stratification that allows the identification of subgroups of patients with different prognostic evolution (course of the disease in terms of recovery or deteriorating);
4. individualized programming, aimed to resume sports, work, social and family activities, including a supervised physical training by means of vital signs monitoring, floor exercises, and use of the ergo-meter (158);
5. psychological counselling based on behavioral indications;
6. management of co-morbidities;
7. structured secondary prevention program based on:
    a. nutritional education
    b. promotion of weight loss (particularly focused on obese patients) and diabetes management
    c. anxiety, depression, and stress management
    d. anti-smoke program
    e. physical activity prescriptions
    f. health education
8. final evaluation and follow-up scheduling.

Based on guidelines, the training program is planned by the leading cardiologist and managed by the cardiovascular physiopathology technicians and by a physiotherapist, alternating aerobic training sessions (by means of the cycle ergo-meter) to floor exercises or muscular strengthening. Patients follow a customized physical training for about a hour and they are continuously monitored through ECG. They are also supported constantly with health and therapeutic education, and expert advice scheduling. Patients with co-morbid medical conditions are carefully supervised and

evaluated by means of motor-functional evaluations. Standardized multidisciplinary interventions are generally provided once a week, including a meeting with the psychologist (individual interviews; analysis of the routinely administered questionnaires – Hospital Anxiety-Depression scale (201) and MOS 36-item Short-Form Health Survey (202, 203); weekly voluntary group meetings focused on stress management; unstructured meetings for smokers), a meeting with the dietitian (individual interviews; analysis of questionnaires on food knowledge; weekly voluntary group meetings focused on dietary habits), and a meeting with the diabetologist (weekly counselling and individual interviews with patients with – or at high risk of – diabetes).

A multidisciplinary structured and customized (as there are different types of interventions targeted according to the individual degree of risk) program of secondary prevention with long term follow-ups is then scheduled to each patient.

3.5 ASSESSMENT

The assessment included a wide range of instruments, both self- and observer-rated measures, in order to take into account all the clinical and psychological variables that could affect the prognosis of cardiovascular diseases.

3.5.1 Medical variables

The assessment of the medical conditions of patients has been performed by means of a schedule created *ad-hoc* to note data collected from chart reviews and patients self-reports. This schedule allowed to collect data concerning socio-demographic variables, date of admission and length of the CR program, dates of the interviews, voluntary group classes (stress management and dietary habits) attendance.

With regards to the collection of strictly medical-related information, the following variables have been collected:

- *main cardiovascular disease* (such as myocardial infarction, congestive heart failure, valvulopathy);
- *medical procedure* (such as percutaneous angioplasty, bypass surgery, valve plastic/replacement);
- *cardiovascular comorbidities* (other cardiovascular diseases, such as heart failure, atrial fibrillation, history of myocardial infarction, history of bypass surgery and/or valve replacement/plastic surgery, history of angioplasty);
- *medical comorbidities* (other medical conditions, such as diabetes, thyroid diseases, cancer);
- *cardiac risk factors*: smoke, Left Ventricular Ejection Fraction (LVEF) ≤40, hypertension, hypercholesterolemia, dyslipidemia, family history of cardiovascular problems, low level of physical activity as defined by the physician, diabetes, overweight/obesity (BMI≥25), alcohol/caffeine abuse;
- height, weight and *Body Mass Index* (BMI);
- *pharmacotherapy*;
- *blood parameters*: LVEF, hemoglobin (Hb), total cholesterol, LDL cholesterol, triglycerides, glycemia;
- *electrocardiographic* (ECG) *report*.

3.5.2 Lifestyles

3.5.2.1 GOSPEL Study questionnaire: physical activity, diet and stress management

The questionnaire designed for GOSPEL Study (204, 205) has been selected to assess patients' lifestyles. Since GOSPEL Study was designed as a large-scale, pragmatic trial with patients

enrolled and followed by their own cardiologists in the real-world setting, it was deemed unlikely that full-scale questionnaires on food frequency and leisure time physical activity could be effectively administered in a busy clinical setting at multiple follow-ups. Thus, a brief questionnaire was designed with food items selected to maximize detection of dietary variation among Italian adults (206, 207). Questions focused on the frequency of usual consumption of cooked and raw vegetables, fruit, fish, olive and seeds oil, butter, wine and coffee. Each item has scored on an ordinal scale from 1 to 4 based on frequency of consumption (from "*never*" to "*frequently*", the latter defined with different time intervals depending on the item); scores have been summed to obtain a Mediterranean diet score (ranging from 0 "*worst*" to 30 "*best*"). Additional items focus on dietary behavior and aim to describe behaviors during the meals (i.e., habit to divide the diet into 3 main meals, to eat slowly, to avoid stress during meals); each item has been scored on a 4-items Likert scale and the dietary behavior scale may range from 0 ("*bad dietary behavior*") to 9 ("*healthy dietary behavior*"). Also, the questionnaire includes one item to assess current and past smoking habits, 8 items to evaluate leisure time physical activity (which might score from 0 - "*poor/absent physical activity*", to 20 - "*very high physical activity*"), and 7 items to investigate self stress management (with a total score range from 0 - "*inadequate stress management*", to 21 - "*optimal stress management*"). Almost all items have a Likert-scale type of answers and they have been worded referring to the past 6 months at baseline and to follow-up periods at further evaluations.

3.5.2.2 Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) (208) is a 19-items self-rated questionnaire which assesses sleep quality and disturbances during the past month, and it is specifically designed to measure sleep quality in clinical populations. Nineteen individual items generate seven component scores: 1) subjective sleep quality, 2) sleep latency, 3) sleep duration, 4) habitual sleep efficiency,

5) sleep disturbances, 6) use of sleeping medication, and 7) daytime dysfunction. The sum of scores for these seven components yields one global score. A cut-off score (≥5) was set to indicate poor sleep quality; it yielded a diagnostic sensitivity of 89.6% and specificity of 86.5% (k=0.75, p<0.001) in distinguishing good and bad sleepers (208). Moreover, the validation study assessed clinical and clinimetric properties of the PSQI over an 18-month period with 52 good sleepers, 54 depressed patients and 62 poor sleepers, obtaining acceptable measures of internal homogeneity, consistency (test-retest reliability), and validity (208). The clinimetric and clinical properties of the PSQI suggest its utility both in psychiatric clinical practice and research activities.

We used the Italian adaptation of the instrument, recently validated by Curcio and colleagues (209). The Italian version of PSQI showed an overall reliability coefficient (Cronbach's α) of 0.835, indicating a high degree of internal consistency. Also, results from Curcio et al.'s study (209) confirmed that the best cut-off score (to differentiate "good" from "bad" sleepers) is 5. The Italian version of the questionnaire provides a good and reliable differentiation between normal and pathological groups, with higher scores reported by people characterized by impaired objectively evaluated sleep quality.

3.5.2.3 8-items Morisky Medication Adherence Scale

The 8-items Morisky Medication Adherence Scale (8-MMAS) (210) is a self-reported measure of medication compliance, developed from a previously validated four-item scale (211) and supplemented with additional items addressing the circumstances surrounding adherence behavior. The theory underlying this measure is that failure to adhere to a medication regimen could occur due to several factors such as problems remembering to take the medication or carelessness, and problems managing the complexity of the treatment plan. Since patients tend to give their physicians or other health care providers positive compliant answers, items are phrased by reversing the wording to avoid bias, especially questions about the way patients might experience failure in

following their medications regimen. Each item evaluates a specific medication-taking behavior and not a determinant of adherence behavior. Possible answers are dichotomous (yes/no) for each item with and on a 5-points Likert response for the last item. The total score may range from 0 to 8 and three different categories could be identified: "low" medication adherence (<6), "medium" medication adherence (range from ≤6 to <8), and "high" medication adherence (=8). The instrument has been found to be reliable (Cronbach's α=0.83) and significantly associated with blood pressure control (p<0.05). Using a cut-off of <6, the sensitivity of the measure to identify patients with poor blood pressure control has been estimated to be 93%, and the specificity 53% (210). An Italian adaptation of the original version of Morisky et al.'s (210) has been used in this research.

3.5.3 Quality of life

3.5.3.1 MOS 36-items Short Form Survey

The MOS 36-items Short-Form Health Survey (SF-36) (202, 203) was designed for use in clinical practice and research, health policy evaluations, and general population surveys. The SF-36 yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index; the scales are: 1) limitations of physical activities due to health problems; 2) limitations of social activities due to physical or emotional problems; 3) limitations of usual role activities due to physical health problems; 4) body pain; 5) general mental health (psychological distress and well-being); 6) limitations of usual role activities due to emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. The SF-36 is suitable for self-administration, computerized administration, or administration by a trained interviewer (in person or by telephone), to people aged 14 and older.

Table 3: Summary of information about SF-36® Scales and Physical and Mental Component Summary Measures

	Correlation		***Number of***						***Definition (% observed)***	
Scales	***PCS***	***MCS***	***Items***	***Levels***	***Mean***	***SD***	***Reliability***	***CI[a]***	***Lowest Possible Score (Floor)[c]***	***Highest Possible Score (Ceiling)[c]***
PHYSICAL FUNCTIONING	0.85	0.12	10	21	84.2	23.3	0.93	12.3	Very limited in performing all physical activities, including bathing or dressing (0.8%)	Performs all types of physical activities including the most vigorous without limitations due to health (38.8%)
ROLE-PHYSICAL (RP)	0.81	0.27	4	5	80.9	34.0	0.89	22.6	Problems with work or other daily activities as a result of physical health (10.3%)	No problems with work or other daily activities (70.9%)
BODILY PAIN	0.76	0.28	2	11	75.2	23.7	0.90	15.0	Very severe and extremely limiting pain (0.6%)	No pain or limitations due to pain (31.9%)
GENERAL HEALTH (GH)	0.69	0.37	5	21	71.9	20.3	0.81	17.6	Evaluates personal health as poor and believes it is likely to get worse (0.0%)	Evaluates personal health as excellent (7.4%)
VITALITY	0.47	0.65	4	21	60.9	20.9	0.86	15.6	Feels tired and worn out all of the time (0.5%)	Feels full of pep and energy all of the time (1.5%)
SOCIAL FUNCTIONING	0.42	0.67	2	9	83.3	22.7	0.68	25.7	Extreme and frequent interference with normal social activities due to physical and emotional problems (0.6%)	Performs normal social activities without interference due to physical or emotional problems (52.3%)
ROLE-EMOTIONAL (RE)	0.16	0.78	3	4	81.3	33.0	0.82	28.0	Problems with work or other daily activities as a result of emotional problems (9.6%)	No problems with work or other daily activities (71.0%)
MENTAL HEALTH (MH)	0.17	0.87	5	26	74.7	18.1	0.84	14.0	Feelings of nervousness and depression all of the time (0.0%)	Feels peaceful, happy, and calm all of the time (0.2%)
PHYSICAL COMPONENT SUMMARY			35	567[b]	50.0	10.0	0.92	5.7	Limitations in self-care, physical, social, and role activities, severe body pain, frequent tiredness, health rated "poor" (0.0%)	No physical limitations, disabilities, or decrements in well-being, high energy level, health rated "excellent" (0.0%)
MENTAL COMPONENT SUMMARY			35	493[b]	50.0	10.0	0.88	6.3	Frequent psychological distress, social and role disability due to emotional problems, health rated "poor" (0.0%)	Frequent positive affect, absence of psychological distress and limitations in usual social/role activities due to emotional problems, health rated "excellent" (0.0%)

Source: Ware, J.E., Kosinski, M., Keller, S.K. (1994). *SF-36® Physical and Mental Health Summary Scales: A User's Manual*. Boston, MA: The Health Institute.

[a] CI=95% confidence interval
[b] Number of levels observed at baseline; scores rounded to the first decimal place (*n*=2,474).
[c] Percentage observed comes from general U.S. population sample.
[d] Scores for eight scales are the percentage of the total possible score achieved for each of these scales. Scores of Physical Component Summary (PCS) and Mental Component Summary (MCS) are *T-scores.*

It has been administered in general population surveys in the United States and other countries (212), as well as to young and old adult patients with specific diseases (202, 213). It can be administered in 5-10 minutes with a high degree of acceptability and data quality (202). *Table 3* shows psychometric properties of the instruments.

The SF-36 was constructed to satisfy minimum psychometric standards necessary for group comparisons. The 8 health concepts were selected from 40 included in the Medical Outcomes Study (MOS) (214), to represent the most frequently measured concepts in widely-used health surveys and those most affected by disease and treatment (202, 212, 215). Most SF-36 items have their roots in instruments that have been in use since the 1970's and 1980's (214). The interpretation of results has been made much easier with the standardization of mean scores and standard deviations for all SF-36 scales. In the present study, the Italian validated version of the measure (216) has been used.

3.5.4 Psychological correlates

The psychological evaluation has been carried out through interviews that involved both observer- and self-rated measures.

3.5.4.1 Observer-rated measures

Structured Clinical Interview for DSM-IV

The Structured Clinical Interview for DSM-IV-TR (SCID) Axis I Disorders, Research Version (217) is a structured interview for the diagnostic formulation according to DSM-IV-TR criteria (218). The SCID is made up of six independent modules which allow to investigate the presence of different psychiatric disorders. The modules are:

A. *Mood episodes* (major depressive episode, manic episode, hypo-manic episode, dysthymic disorder, mood disorder due to a general medical condition, and substances-induced mood disorder);

B. *Psychotic and associated symptoms* (delusions, hallucinations, disorganized speech and behavior, catatonic behavior, negative symptoms);

C. *Psychotic disorders* (paranoid, catatonic, disorganized, indifferentiated, residual schizophrenia; schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, psychotic disorder due to a general medical condition, and substances-induced psychotic disorder, NOS psychotic disorder);

D. *Mood disorders* (bipolar disorder, major depressive disorder, minor depressive disorder, NOS mood disorder);

E. *Substance use disorders* (alcohol, amphetamine, cannabis, cocaine, hallucinogens, opioids, sedatives, anxiolytics, hypnotics dependence and abuse);

F. *Anxiety and other disorders* (panic disorder with agoraphobia, agoraphobia without panic disorder, obsessive-compulsive disorders, post-traumatic stress disorder, anxiety due to general medical conditions, substances-induced anxiety, adjustment disorders, eating disorders, somatoform disorders).

Since we investigated only anxiety and depression areas, we adopted the Italian version of SCID (219), modules A and F only.

Interview for the Diagnostic Criteria for Psychosomatic Research

The interview based on the Diagnostic Criteria for Psychosomatic Research - DCPR (89) is a semi-structured interview constituted by dichotomous (yes/no) kind of answers and skip questions concerning the past six or twelve months; it allows the detection of 12 psychosomatic syndromes (91). This interview aimed to identify and develop common criteria to several diseases through the study of patients with different medical conditions and, once defined the psychosomatic syndrome,

try to modify it with specific tools (91). The DCPR may be used in a multi-axial approach and could provide supplementary diagnoses to the first and second axis of the DSM-IV (220). The criteria proposed by DCPR took place from the need to think in terms of psychosomatic syndromes and to highlight the variety of somatic and mental responses of individuals to different life circumstances. This perspective goes beyond pathogenetic implications and allows, particularly in the field of medical disorders without an organic cause, to standardize many conditions that do not seem related to each other.

Among DCPR three different clusters are detected. The first cluster is related to *abnormal illness behavior*.

- *Disease phobia*: it has been defined as a persistent and unfounded fear of suffering from a specific disease, despite doctors' assurances and negative results of diagnostic tests; compared to hypochondriasis, the two diseases show different phobic quality of fears (acute in disease phobia, constant in hypochondriasis) and nature of the phobic object (stable over time in disease phobia, changeable in hypochondriasis) (92). The differential diagnosis between hypochondriasis and disease phobia is relevant for treatment planning. The phobic quality of symptoms typically leads to avoidance and thus may be treated with in vivo exposure strategies, while hypochondriacal patients do not respond to exposure because they tend to engage in "doctor-shopping behavior" rather than avoidance (92). Anxiety manifests itself as panic attacks and symptoms focused on a specific disease or part of the body.

- *Tanatophobia*: it is defined by a sense of impending death or by the conviction of dying quickly in the absence of objective medical causes. According to Kellner (221), these beliefs are often accompanied by the avoidance of every circumstance that remind of death (i.e., funerals and obituaries).

- *Health anxiety*: characterized by the amplification of bodily sensations related to a general concern about the outbreak of a disease, pain and somatic concerns. It is issued from Kellner's Illness Attitude Scale (IAS) (222) and may be viewed as a less severe form of hypochondriasis. Unlike disease phobia and hypochondriasis, health anxiety worries and fears readily respond to appropriate doctor's reassurance and has a shorter duration (less than 6 months'). A psychological treatment focused on explaining to the patient the mechanisms that link emotional distress to selective

perceptions of somatic symptoms in a self-perpetuating vicious circle has also been validated for health anxiety (223).

- *Illness denial*: it represents the negation of having an illness or needing extra care and it is placed at the opposite pole relative to hypochondriasis. This attitude manifests itself through delays in seeking medical advice, medications' non-compliance and unhealthy lifestyles. Denying the burden of physical disease may be an adaptive coping mechanism in some circumstances (i.e., in the early stage after diagnosis or in the terminal phase of a life-threatening disease) because it may alleviate psychological distress. However, denying, distorting, or minimizing clinical relevance, personal responsibility, long-term prognosis, and the need for treatment may have serious health-related consequences (92). Despite its clinical relevance and possible health-related consequences, illness denial has been neglected by the ICD-10 and DSM-IV.

The second cluster includes psychosomatic diagnoses related to the process of *somatization*. Specifically, these syndromes have been developed as a replacement or additional diagnoses to the categories of DSM somatoform disorders. Studies in literature have shown a higher prevalence of these syndromes rather than DSM-IV psychiatric diagnoses among patients with medical conditions (103, 224).

- *Functional symptoms secondary to a psychiatric disorder (FSS)*: they include autonomic arousal or functional medical disorder causing distress or repeated medical care or resulting in impaired quality of life. In order to diagnose FSS, an appropriate medical evaluation should uncover no organic pathology to account for the physical complaints and it should be assessed in the presence of a history of at least one psychiatric disorder preceding the onset of functional somatic symptoms which should include among its manifestations somatic features (i.e., cardiac symptoms in panic disorder).

- *Persistent somatization*: it has been issued from the concept of symptom clustering that highlights the fact that people with a psychosomatic condition (i.e., irritable bowel syndrome) are more likely to subsequently get another functional gastrointestinal (i.e., non-ulcer dyspepsia) or extra-gastrointestinal (eg, chronic fatigue) syndrome over time (221), it is characterized by the presence of a functional somatic disorder which has produced subjective discomfort, worsening of the quality of life and repeated medical treatments seeking. A difference between DCPR persistent somatization and DSM-IV somatization disorder concerns the duration: the latter's multiple physical complaints persist over years, while those of the former at least six months. Important aspects of persistent

somatization are: reduced pain threshold, additional symptoms of autonomic arousal (also involving other organ systems) and the side effects of exaggerated medications. The prevalence of the DCPR category of persistent somatization, together with the parent category of "functional somatic symptoms secondary to a psychiatric disorder" (FSS) is low in community individuals (2%–3%) (225) but high in several medical settings (226).

- *Conversion symptoms*: characterized by one or more motor or functional symptoms, not adequate with respect to the anatomy and physiology of the human organism, the clinical and laboratory reports emerged negative. If there are symptoms of autonomic arousal of a functional medical disorder, this should be considered secondary to conversion. With respect to DSM-IV, the innovative element is constituted by criterion B which requires the presence of at least two of the following aspects: ambivalence of the subject about the symptoms, histrionic personality traits, symptomatology triggered by a specific stressful event that the patient is unable to link to the symptoms, a history of the same physical symptoms or observation of the same symptoms in someone else.

- *Anniversaries reaction*: it is a particular form of somatization or conversion whose symptoms (neuro-vegetative arousal, symptoms of a somatic disease or functional conversion) occur at a precise date. The onset of the psychological distress generally coincides with an anniversary of death or of a serious illness of a parent or a close relative of the patient.

The third cluster concerns syndromes identifiable as *psychological factors affecting medical conditions*.

- *Type A behavior (TAB)*: this behavior has been defined as "specific emotion–action complex" of individuals aggressively committed to struggle to achieve more and more in less and less time (227). Over the last thirty years, numerous studies have found TAB pathogenic role over cardiac illnesses. However, after the National Heart, Lung, and Blood Institute recognized TAB as an independent risk factor for coronary heart disease in 1981, subsequent studies found contradictory results, and the two main components of cynicism and time urgency have been suggested as the most predictive TAB aspects for coronary heart disease (228).

- *Irritable mood*: DCPR criteria of irritable mood are issued from the description by Snaith and Taylor (105) and define it as a feeling state characterized by an irritable mood that may be experienced as brief episodes in particular circumstances, or it may be prolonged and generalized. The individual is aware of his or her negative feeling state, even though he or she cannot gain full control over it (ego-

dystonic condition); it requires an increased effort of control over temper by the individual or results in irascible verbal or behavioral outbursts. The experience of irritability is always unpleasant for the individual, and overt manifestation lacks the cathartic effect of justified outbursts of anger. The behavior elicits stress-related physiologic responses that precipitate or exacerbate symptoms of a medical condition and predispose unhealthy behaviors (92, 228).

- *Demoralization*: it is defined as a psychological state characterized by patient's awareness of having failed to meet his/her own expectations (or those of others) or being unable to cope with some pressing problem (229); the patient experiences feelings of helplessness, hopelessness, and/or giving up. The feeling state should be prolonged (at least 1 month) and generalized. Subjective incompetence is considered the clinical hallmark of demoralization and of related feelings of hopelessness and helplessness (230). The DCPR criteria of demoralization include all these clinical aspects. The clinical relevance of demoralization in physical syndromes is highlighted by the high prevalence in all medical settings and the low frequency in the community sample (3%) (225).

- *Alexithymia*: it is now recognized to include two high-order factors: lack of affect awareness and operative thinking. Other features that define alexithymia are: inability to use appropriate words to describe emotions; tendency to describe details instead of feelings; lack of a rich fantasy life as a result of inhibition of the symbolic function; thought content associated more with external events than fantasy or emotions; unawareness of the common somatic reactions that accompany the experience of a variety of feelings; occasional but violent and often inappropriate outbursts of affective behavior; increased social conformity and poor social relationships; lack of self-awareness and inability to reflect on themselves. Alexithymia is considered one of the vulnerability factors for the development of medical and psychiatric disorders of affect regulation (231). Although alexithymia is heterogeneous, the observer-rated criteria of the DCPR and the self-report assessment with the Toronto Alexithymia Scales were found to be consistent as they were for construct validity (232, 233).

Data from different studies have shown that DCPR interview has good levels of inter-rater reliability: used by trained investigators, the interview showed substantial inter-rater agreement for all 12 syndromes (K>0.61) and nearly perfect agreement for 9 syndromes (K>0.81) (234). Moreover, the joint administration of DCPR and DSM-IV allows a better assessment of the psychological profile of patients with a variety of medical diseases (234).

Although the instrument allows the evaluation of each syndrome independently, in this study we evaluated all 12 psychosomatic syndromes by means of the Italian version of the interview (235).

3.5.4.2 Self-rated measures

Symptom Questionnaire

Kellner's Symptom Questionnaire (SQ) (236) is a self-report questionnaire which originates from Symptom Rating Test (237), but is simpler and shorter than the previous version (i.e., it contains mainly single word items instead of questions). The total number of items (92 items) has been increased in order to improve the scale's sensitivity (238). Instead of a Likert measurement of the frequency and severity of symptoms , answers to each item are dichotomous (YES/NO or TRUE/FALSE). The final SQ version yields 4 main scales: "anxiety", "depression", "somatization" and "hostility-irritability", which can each be divided into 8 subscales : 4 symptoms subscales ("anxiety", "depression", "somatization" and "hostility") and 4 corresponding well-being subscales ("relaxation", "contentment", "physical well-being" and "friendliness"). Since each symptoms scale score may range from 0 to 17 and each well-being scale score from 0 to 6, each of the 4 total dimensions may range from 0 to 23; the higher the total score, the higher the psychological distress. The SQ has been applied in many clinical investigations, as well as in the psychosomatic setting, and it was found to be able to discriminate between patients with different medical disorders, such as endocrinological (239, 240), gynecological (241, 242), cancer (243), or psychiatric problems (244-246). In cardiology, the SQ questionnaire was used to assess the role of psychological distress and sub-clinical depressive symptoms in the short term prognosis of heart failure (50). It was also administered to patients with coronary artery diseases, highlighting 2.5 higher hostility symptoms and a greater association of cardiovascular risk profiles in younger patients compared to older ones (247). Symptom Questionnaire was also used for testing the effect of cardiac rehabilitation in decreasing psychological distress in patients with cardiac disorders (248). In another study (249),

the SQ was administered to examine the predictive effect of anxiety in the medium term (mean follow-up of 3.4 years) on the occurrence of adverse cardiac events (i.e., mortality and non-fatal myocardial infarction).

Studies in literature showed that SQ depression scale correlates positively with Hamilton Rating Scale for Depression (+0.66 for depressed patients and +0.65 for control subjects from the general patients) (250); anxiety dimension with Hamilton Anxiety Rating Test (+0.69). SQ also showed good correlations with Hopkins Symptom Checklist (251) for corresponding scales (+0.39 for hostility, +0.63 for anxiety, +0.86 for depression; *p* values ranging from <0.002 to <0.001) (236). It can be used in psychiatric and psychosomatic investigations, where the measurement of a particular change in the patient's psychological condition is required, with a test-retest assessment procedure. The instrument has also been validated in Italy (252).

Psychological Well-being scale

Psychological Well-Being Scale (PWB) (253) has been used to evaluate psychological well-being. PWB is a 84-items questionnaire with a multidimensional structure that allows patients' self-evaluation of the six main psychological well-being dimensions as conceptualized by Ryff (autonomy, environmental mastery, personal growth, positive relationships, purpose in life, self-acceptance). Each item is defined in terms of high or low agreement on a 6-points Likert scale (from 1 - "*strongly disagree*" - to 6 - "*strongly agree*"); each scale score may range from 14 to 84 and higher scores correspond to higher psychological well-being. The items contain definitions of both optimal and impaired functioning in a certain dimension. *Table 4* shows the description of the different psychological well-being profiles, based on the score to each dimension. During the first draft of the instrument, the correlation of each item with their scale was calculated and all items that correlated more strongly with other scales than their own, or that have low correlations with their scale, were removed.

Table 4: psychological well-being profiles on the basis of the score

PWB dimensions	***DEFINITIONS***	
	HIGH scores profile	***LOW scores profile***
AUTONOMY	Confident and independent people; they are able to withstand the social pressures that would make them think and act like most of the people. They are able to regulate their own behavior in light of an internal point of view, using personal standards.	People whose behavior is deeply influenced by other people's judgment and expectations. To make any kind of decision, they ask advice from others and base their choices on those. Their way to think and act is influenced by social pressures.
ENVIRONMENTAL MASTERY	These individuals have a good sense of mastery and competence in controlling the surrounding environment. They are able to handle a wide range of activities and to take every opportunity offered by the environment. They are also able to make the environment more suitable to their needs.	These individuals have great difficulties to manage their everyday lives. They are unable to grasp the available opportunities and do not seem to be able to control the surroundings.
PERSONAL GROWTH	These individuals have the feeling of continuous growth and interpret them as a person who continues to expand. They are open to new experiences and try to develop their potential. If they look to the future, they see themselves improved, and they have a great predisposition to change.	These individuals feel to live in a stalemate and to have lost the urge to grow and to improve. They feel unable to behave in a different way, also feeling bored and uninterested in their lives.
POSITIVE RELATIONSHIPS	Relationships with others are based on trust and warmth. These people are able to experience strong feelings of empathy and to create intimate relationships. They are able to give and to get the most out from these relationships.	Relationships with others are few and unreliable. For these people it is hard to be warm, open and interested in the affairs of others. They are isolated and frustrated by interpersonal relationships. They are not willing to reach a compromise in maintaining important links with others.
PURPOSE IN LIFE	These people have goals, and a sense of direction in their lives. They confer great significance to their past and present life. They developed beliefs that give meaning to their lives.	These people do not attribute any particular meaning to their lives, they have few goals and objectives. They consider their past life meaningless and do not have any kind of perspective for their present life.
SELF-ACCEPTANCE	It implies to have positive attitudes towards themselves. These individuals show awareness of their own positive and negative qualities. In general, the recollection of their life arouses positive feelings.	These individuals show a feeling of dissatisfaction towards themselves and how they held things in their lives. These people would like to be different from what they really are, because some aspects of their personalities are conflicting.

The internal consistency for each scale was as follows: self-acceptance=0.93, positive relations with others=0.91, autonomy=0.86, environmental mastery=0.90, purpose in life=0.90, personal growth=0.87 (254). The test-retest reliability coefficients after a period of six weeks were as follows: self-acceptance=0.85, positive relations with others=0.83, autonomy=0.88, environmental mastery=0.81, purpose in life=0.82, personal growth=0.81 (254). The Italian validation of the instrument has been published in 2003 (255).

Type-D Scale

The 14-items Type-D scale (DS-14) (256) was used to assess Type D personality. DS-14 was specifically developed to assess Negative Affectivity (NA), Social Inhibition (SI), and Type D

personality in a reliable and standardized way that poses little burden to respondents. NA refers to the tendency to experience feelings of dysphoria, anxiety, and irritability, while SI refers to discomfort in social interactions, lack of social poise, and the tendency to avoid confrontation in social interaction leading to non-expression. Items of the DS-14 were derived from its predecessor, the DS-16 (257), but also included new items that were developed to enhance the assessment of NA and SI (258). The DS16 was initially revised to include the most prominent low-order traits from the NA and SI domains. Four new NA items were added to better reflect feelings of anxiety and irritability (i.e., "*I often make a fuss about unimportant things*" and "*I am often irritated*") and 4 new SI items to enhance the assessment of social inhibition and lack of social poise (i.e., "*I often feel inhibited in social interactions*"). The 3 DS-16 dominance items were deleted and replaced by 3 new SI items to adequately reflect the tendency to avoid potential dangers involved in social interaction (i.e., "*I am a closed kind of person*", "*I would rather keep other people at a distance*" and "*I am a reserved kind of person*"). As described previously, this strategy resulted in a pool of 24 items that were selected to cover the NA and SI personality domains by 12 items each (258). To devise a brief measure with little burden to patients, 7 items were selected to cover the domains of NA and SI, respectively. Inclusion of items in the DS-14 was based on conceptual and psychometric grounds. Conceptually, the NA items had to cover the tendency to experience feelings of dysphoria, anxious apprehension, and irritability, and the SI items social discomfort, reticence, and lack of social poise (258). Psychometrically, items with the highest item-total correlations were selected. Answers are on a 5-points Likert scale ranging from 0 (false) to 4 (true). The NA and SI scales can be scored as continuous variables (score's range: from 0 to 28; higher the scores, worse the psychological distress) to assess these personality traits in their own right. A cut-off of 10 and higher on both scales is used to classify subjects as Type D.

Factor analysis of the DS14 yielded 2 dominant traits; all of the NA and SI items loaded between 0.62 to 0.82 on their corresponding factor. The NA and SI scales were internally consistent (respectively 0.88 and 0.86), stable over a 3-month period (test–retest r respectively 0.72 and 0.82)

and not dependent on mood and health status (256). The instrument has also been translated and validated in Italian (259).

3.6 STATISTICAL ANALYSES

Data analysis was performed using the IBM Statistical Package for Social Science (SPSS), version 19.0. The statistical analyses were performed with a confidence interval of 95% and significance level was set to 0.05, two-tailed.

3.6.1 Baseline – Description of the sample

Discrete variables at baseline, such as socio-demographic and medical variables, risk factors, psychiatric (DSM-IV-TR) and psychosomatic (DCPR) diagnoses, have been analyzed and compared between experimental and control groups by means of Pearson χ^2 test applied to contingency tables; continuity correction was applied for the 2^x2 tables.

Continuous variable, such as age, Body Mass Index (BMI), lifestyles (psychical activity, diet, stress management, medication adherence, quality of sleep), quality of life and psychological questionnaires (psychological distress and well-being, type D personality traits) mean scores, have been analyzed and compared between experimental and control group by means of independent samples Student t-test after controlling for Levene's Test for Equality of Variances.

3.6.2 Follow-ups – Lifestyles, quality of life and psychological factors modification

Data relating to lifestyles, quality of life and psychological questionnaires have been examined by means of a Repeated Measures Analysis of Variance (ANOVA), mixed model (2^x4). The dichotomous variables "*group*" (experimental group *versus* control group) and "*medical procedure*"

(non-invasive *versus* invasive medical procedure) have been considered as between-subjects factors to evaluate their potential role as mediating factors on lifestyles, quality of life and psychological factors' mean scores modification over *time* (from T1 to T2, T3 and T4). Specifically, since the medical variable "*medical procedure*" (invasive *versus* non-invasive surgery) appeared to be a discriminating factor between the two clinical groups from the beginning, it has been chosen to assess its overall influence in the model. Mauchly's sphericity test used to test the assumption of sphericity in Repeated Measures ANOVA; if sphericity condition was not met (i.e., Mauchly's Sphericity test was significant), Greenhouse-Geisser parameter was chosen to evaluate the significance of univariate tests.

To evaluate the modification of the psychological diagnoses (i.e., type D personality, DSM psychiatric diagnoses, and DCPR psychosomatic syndromes) over time, McNemar's approximation has been applied. Specifically, in order to verify the modification of the frequencies of the above-mentioned variables at different time points, the two groups (experimental and control) were analyzed by means of pair-wise comparisons separately (experimental group T1-T2, T2-T3, T3-T4; control group T1-T2, T2-T3, T3-T4).

Discrete variables, such as smoke habit and psychological diagnoses, have been compared between experimental and control groups at different times by means of Pearson χ^2 test applied to contingency tables; continuity correction was applied for the 2^x2 tables

3.6.3 Follow-ups – Psychological factors mediating lifestyles modification

Repeated Measures ANOVA mixed model has been performed to test the potential effect of the presence of DSM psychiatric diagnoses ("*Depressive disorder*"= presence of at least one depressive disorder; "*Anxiety disorder*"= presence of at least one anxiety disorder) or DCPR psychosomatic syndromes (presence of at least one syndrome belonging to the DCPR cluster "*Abnormal Illness behavior*", "*Somatization*" or "*Psychological Factors Affecting Medical Conditions*") as mediator

on lifestyles modification, other than cardiac rehabilitation. These variables have been treated as between-subjects factors, by adding them to those above-mentioned ("*Groups*" and "*Medical Procedure*").

3.6.4 Follow-ups – Survival analyses

First of all, Kaplan-Meier survival analysis has been performed in order to compare the survival curves of experimental and control groups. Log Rank test has been chosen to compare the survival distributions of the two samples. Survival analysis has been used for coronary events (re-hospitalization due to deterioration of the cardiac conditions, cardiovascular relapse, cardiac death) and time of survival has been expressed in months.

Subsequently, the same statistical analysis has been performed considering as between-subjects factors DSM diagnoses and DCPR syndromes, testing their effect on survival overall the whole sample and among different subgroups: experimental group, control group, invasive surgery group, and non-invasive surgery group.

Cox regression, performed by means of ENTER method, has been applied in order to test all psychological questionnaires' mean scores at baseline as potential predictors of outcome (cardiovascular events). As previously mentioned , also in this case, their effect has been tested on survival overall the whole sample and among different subgroups: experimental group, control group, invasive surgery group, and non-invasive surgery group. Each factor resulted significant has then been dichotomized for measurement-type factor with a selected cut-off point around the median. Subsequently, for each factor, we performed the following procedure: the new dichotomous variable was applied to the sample, dividing it into two groups: again, the Kaplan-Meier method (by means of Log Rank test) for estimating survival curves for them has been used.

3.7 RESULTS

3.7.1 Baseline – Description of the sample

3.7.1.1 Socio-demographic variables

Table 5 shows the socio-demographic profile of the study population. The mean age of the entire sample is 68.90 (SD=9.91), ranging from 40 to 88 years old. The sample consists mainly of males (72.0%) and married people (76.2%).

Table 5: Socio-demographic profile of the sample

	TOTAL SAMPLE (N=195)	**Experimental Group** (N=108)	**Control Group** (N=85)		
	mean±SD	*mean±SD*	*mean±SD*	*t*	*p*
Age	68.90±9.91	69.41±9.77	68.26±10.12	0.80	*ns*
	N (%)	*N (%)*	*N (%)*	χ^2	*p*
Sex					
Male	139 (72)	73 (67.6)	66 (77.6)	1.91	*ns*
Female	54 (28)	35 (32.4)	19 (22.4)		
Marital status					
Single	17 (8.8)	13 (12.0)	4 (4.7)	4.71	*ns*
Married	147 (76.2)	81 (75.0)	66 (77.6)		
Separated	5 (2.6)	2 (1.9)	3 (3.5)		
Divorced	6 (3.1)	2 (1.9)	4 (4.7)		
Widower/Widow	18 (9.3)	10 (9.3)	8 (9.4)		
Level of education					
Elementary or less	81 (42.0)	37 (34.3)	44 (51.8)	11.75	*ns*
Junior High School	44 (22.8)	23 (21.3)	21 (24.7)		
Senior High School (NC)	6 (3.1)	5 (4.6)	1 (1.2)		
Senior High School	44 (22.8)	30 (27.8)	14 (16.5)		
College (NC)	1 (0.5)	1 (0.9)	0 (0.0)		
College	14 (7.3)	9 (8.3)	5 (5.9)		
Post-graduated Course	1 (0.5)	1 (0.9)	0 (0.0)		
PhD/Specialization	2 (1.0)	2 (1.9)	0 (0.0)		
Occupation					
Employed	51 (26.4)	25 (23.1)	26 (30.6)	4.12	*ns*
Unemployed	4 (2.1)	1 (0.9)	3 (3.5)		
Retired	133 (68.9)	78 (72.2)	55 (64.7)		
Homemaker	5 (2.6)	4 (3.7)	1 (1.2)		

NC= not completed
ns= not significant

With regards to the level of education, most of them attended elementary school or less (42.0%), followed by junior and senior high school (22.8%, both cases). Most of the subjects are already retired from work (68.9%). If compared, the two clinical groups (patients who attended the CR program – experimental group, and those who did not – control group) do not show any statistical difference among the above-mentioned variables.

3.7.1.2 Medical variables

As highlighted in *Table 6*, the most frequent cardiovascular pathologies were myocardial infarction (37.8%) and valvulopathy (31.1%); consequently, the commonest medical procedures the patients underwent were percutaneous angioplasty (49.2%) and valvuloplasty or valve replacement (25.4%). Looking at the two clinical groups, it can be observed that most of the CR participants suffered from valvulopathy (43.5%), while the controls from myocardial infarction (48.2%), statistically differing one from another ($\chi^2_{(6)}$=34.98, p<0.001). On the same vein, the most frequent medical procedure for the experimental group was valvuloplasty or valve replacement (37.0%), while for the controls it was percutaneous angioplasty (84.7%), the difference being statistically significant ($\chi^2_{(4)}$=77.74, p<0.001). Simplifying the medical procedures into two categories (invasive *versus* non-invasive surgery), the result was that most of the patients of the CR group underwent an invasive surgery (73.1%), while patients of the control groups did not undergo an open-heart surgery (84.7%). This difference was statistically significant ($\chi^2_{(1)}$=61.52, p<0.001).

With regards to cardiovascular risk factors (*Table 6*), the most frequent among the entire sample were hypertension (70.5%) and poor physical activity (68.2%). If compared, the two clinical groups did not differ between each other, except for hypercholesterolemia ($\chi^2_{(1)}$=7.58, p<0.001) and family history of cardiovascular diseases ($\chi^2_{(1)}$=11.73, p<0.001); in both cases the above-mentioned risk factors were more frequent among the individuals of the control group.

Table 6: Medical profile of the sample

	TOTAL SAMPLE (N=195)	**Experimental Group** (N=108)	**Control Group** (N=85)		
	N (%)	*N (%)*	*N (%)*	χ^2	*p*
Cardiovascular Pathology					
MI	73 (37.8)	32 (29.6)	41 (48.2)		
Instable angina	34 (17.6)	9 (8.3)	25 (29.4)		
MI + instable angina	10 (5.2)	8 (7.4)	2 (2.4)		
Valvulopathy	60 (31.1)	47 (43.5)	13 (15.3)	34.98	*0.001*
Valvulopathy + MI	7 (3.6)	6 (5.6)	1 (1.2)		
Valvulopathy + instable angina	2 (1.0)	2 (1.9)	0 (0.0)		
Congestive heart failure	7 (3.6)	4 (3.7)	3 (3.5)		
Medical Procedure					
Percutaneous angioplasty	95 (49.2)	23 (21.3)	72 (84.7)		
Bypass graft surgery	32 (16.6)	29 (26.9)	3 (3.5)		
Valvuloplasty or valve replacement	49 (25.4)	40 (37.0)	9 (10.6)	77.74	*0.001*
Valvuloplasty/replacement + bypass	11 (5.7)	10 (9.3)	1 (1.2)		
no procedure	6 (3.1)	6 (5.6)	0 (0.0)		
Cardiovascular Risk Factors					
LVEF ≤ 40	28 (14.7)	18 (17.0)	10 (11.8)	0.65	*ns*
Hypertension	136 (70.5)	74 (68.5)	62 (72.9)	0.26	*ns*
Hypercholesterolemia	82 (42.5)	36 (33.3)	46 (54.1)	7.58	*0.006*
Dyslipidemia	72 (37.5)	34 (31.8)	38 (44.7)	2.85	*ns*
Type 2 diabetes mellitus	44 (22.8)	23 (21.3)	21 (24.7)	0.15	*ns*
Family history of CD	58 (30.2)	21 (19.6)	37 (43.5)	11.73	*0.001*
Smoke habit (current or past)	114 (59.1)	57 (52.8)	57 (67.1)	3.44	*ns*
Boby mass index ≥25	124 (64.9)	72 (67.9)	52 (61.2)	0.67	*ns*
Poor physical activity	131 (68.2)	79 (73.8)	52 (61.2)	2.94	*ns*
Caffeine abuse	7 (3.6)	2 (1.9)	5 (6.0)	1.25	*ns*
Alcohol abuse	7 (3.6)	4 (3.7)	3 (3.5)	0.00	*ns*

MI= Myocardial Infarction; CD= cardiovascular diseases LVEF= Left Ventricular Ejection Fraction; *ns*= not significant

3.7.1.3 Lifestyles and health-related quality of life

Table 7 shows lifestyles and health-related quality of life mean scores of the sample. Even if the two clinical groups obtained similar scores in more than a half of the scales, they showed a few statistical differences. The first difference in lifestyles' mean scores is related to stress management (GOSPEL questionnaire): the control group obtained higher scores than those of the CR group ($t_{(189)}$=2.10, p<0.05), showing better baseline abilities of stress management

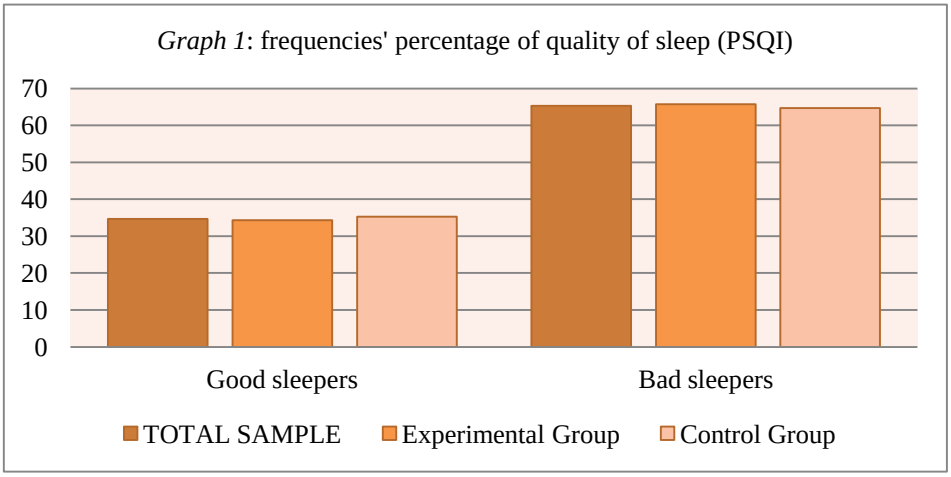
Table 7: Baseline life styles and quality of life of the sample

		TOTAL SAMPLE (N=195)	**Experimental Group** (N=108)	**Control Group** (N=85)		
	*score range**	*mean±SD*	*mean±SD*	*mean±SD*	*t*	*p*
GOSPEL questionnaire						
Physical activity	**0**-20	4.87±3.60	4.54±3.31	5.28±3.92	1.42	*ns*
Mediterranean diet	**0**-30	17.50±2.95	17.62±2.69	17.35±3.25	0.62	*ns*
Dietary behavior	**0**-9	6.31±2.04	6.43±1.82	6.16±2.29	0.88	*ns*
Diet (*total score*)	**0**-39	23.82±3.93	24.06±3.68	23.52±4.21	0.94	*ns*
Stress management	**0**-21	12.52±3.54	12.05±3.58	13.12±3.41	2.10	*0.037*
Pittsburgh Sleep Quality Index	0-**21**	6.34±3.27	6.15±3.23	6.58±3.31	0.90	*ns*
Morisky Medications Adherence Scale	**0**-8	7.24±1.06	7.25±1.10	7.24±1.02	0.05	*ns*
MOS36-items Short Form Survey						
Physical health-related QoL	**0**-100	49.12±19.68	44.04±16.82	55.39±21.19	4.02	*0.001*
Mental health-related QoL	**0**-100	55.66±19.31	51.78±18.60	60.46±19.20	3.15	*0.002*
Health-related QoL (*total score*)	**0**-100	52.49±19.95	47.15±17.65	59.09±20.73	4.29	*0.001*

* *Note*: bolded numbers represent the worst or poorest scores
QoL= quality of life; *ns*= not significant

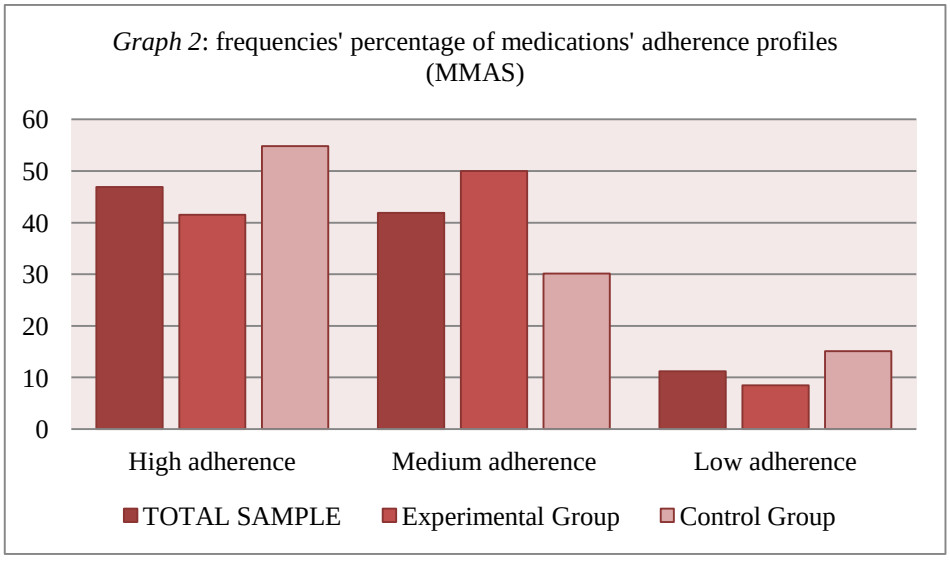
In the same vein, the results of SF-36 showed that people who were not referred to cardiac rehabilitation obtained higher scores of both health-related quality of life sub-scales and main scale. The controls self-reported better baseline scores of physical health-related ($t_{(188)}$=4.02, p<0.001), mental health-related ($t_{(188)}$=3.15, p<0.01) and total health-related ($t_{(188)}$=4.29, p<0.001) quality of life.

Assuming quality of sleep as a categorical variable on the basis of PSQI cut-off score, it has been observed that among the participants of both groups there was a great frequency of poor sleepers (*Graph 1*). The frequencies were also similar, showing no statistical difference.



Graph 1: frequencies' percentage of quality of sleep (PSQI)

Contrary to quality of sleep, the transformation of MMAS scores into categorical variables highlighted different medications' compliance profiles. As showed in *Graph 2*, control group subjects were more frequently adherent to medications and less represented in the "medium adherence" profile but, at the same time, more in the "low adherence" section than CR patients. The distribution of the two groups among the three categories was statistically different ($\chi^2_{(2)}=7.37$, $p=0.025$).



Graph 2: frequencies' percentage of medications' adherence profiles (MMAS)

3.7.1.4 Psychological distress and well-being

With regards to psychological distress and well-being, experimental and control groups did not show any statistical difference in all the SQ and DS-14 dimensions (*Table 8*).

Table 8: Baseline psychological profile of the sample

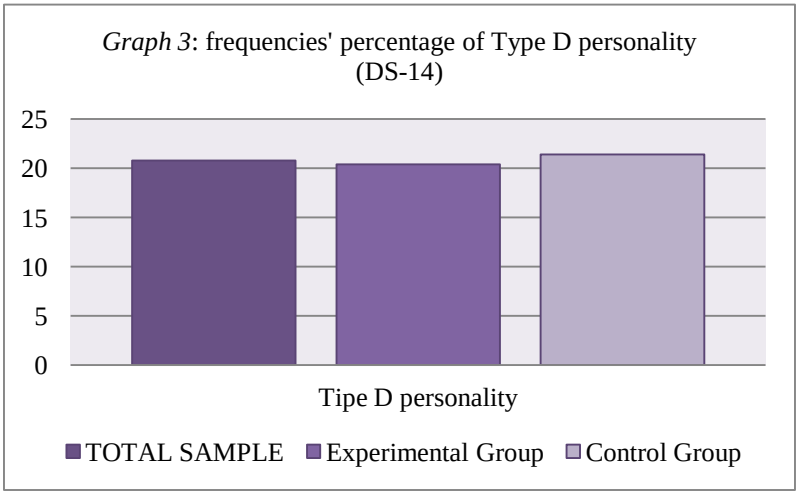
		TOTAL SAMPLE (N=195)	**Experimental Group** (N=108)	**Control Group** (N=85)		
	*score range**	*mean±SD*	*mean±SD*	*mean±SD*	t	*p*
Symptom Questionnaire						
Anxiety	0-**23**	5.95±4.79	5.47±4.43	6.57±5.18	1.59	*ns*
Depression	0-**23**	5.96±4.24	5.56±3.88	6.48±4.64	1.48	*ns*
Somatization	0-**23**	8.78±5.33	8.56±5.24	9.07±5.47	0.66	*ns*
Hostility	0-**23**	3.92±4.05	4.06±3.41	3.74±4.77	0.52	*ns*
Psychological Well-Being Scale						
Autonomy	**14**-84	66.75±11.24	66.90±8.97	66.57±13.62	0.19	*ns*
Enviromental mastery	**14**-84	63.86±12.28	66.30±11.60	60.82±12.50	3.11	*0.002*
Personal growth	**14**-84	56.56±12.31	59.73±12.03	52.58±11.54	4.13	*0.001*
Positive relationships	**14**-84	66.65±11.89	67.62±9.53	65.44±14.27	1.20	*ns*
Purpose in life	**14**-84	57.35±13.16	59.99±12.68	54.05±13.09	3.16	*0.002*
Self-acceptance	**14**-84	66.11±12.06	67.04±11.08	64.95±13.16	1.16	*ns*
14-items Type D Scale						
Negative affectivity	0-**28**	8.98±6.72	8.14±6.14	10.06±7.30	1.94	*ns*
Social inhibition	0-**28**	8.19±6.54	8.77±6.36	7.45±6.72	1.39	*ns*

* *Note*: bolded numbers represent the worst or poorest scores
ns= not significant

The only differences detected were on PWB "environmental mastery" ($t_{(187)}$=3.11, p<0.01), "personal growth" ($t_{(187)}$=4.13, p<0.001) and "purpose in life" ($t_{(187)}$=3.16, p<0.01) sub-scales. In all the cases, the CR group self-reported higher levels of psychological well-being than those of the controls.

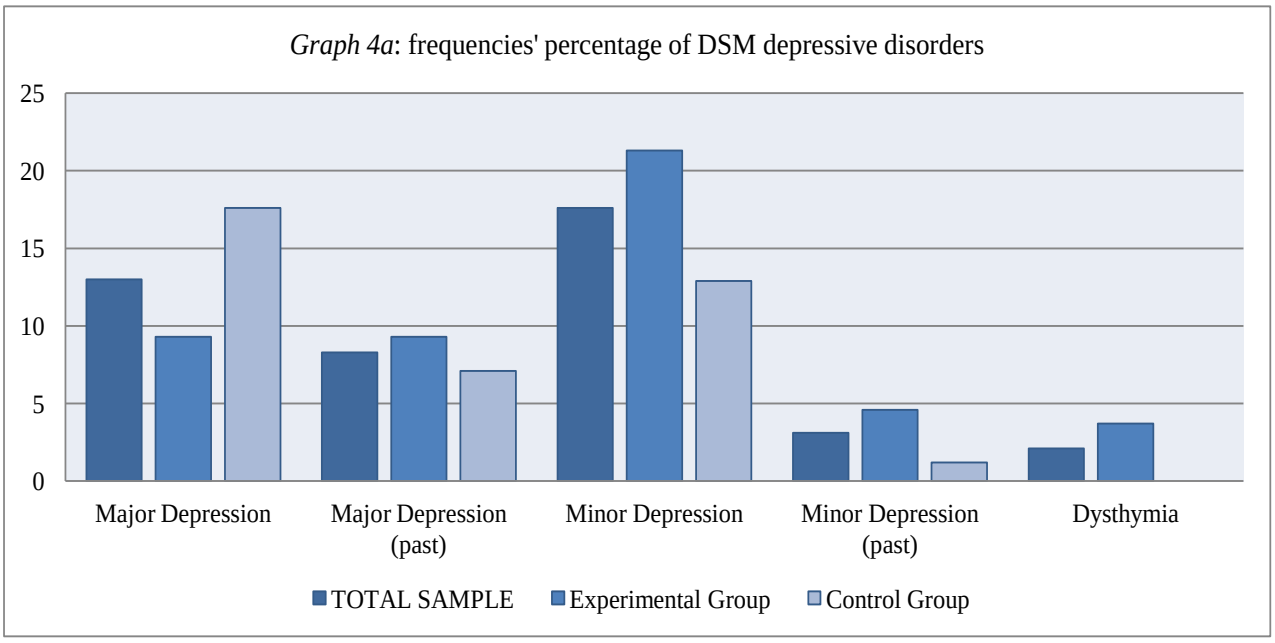
3.7.1.5 Type D personality, psychiatric diagnoses and psychosomatic syndromes

Graph 3 represents Type D personality frequency among the participants. About one fifth of the sample (20.8%) satisfied the diagnostic criteria of this personality disorder, showing no differences between the two clinical groups.

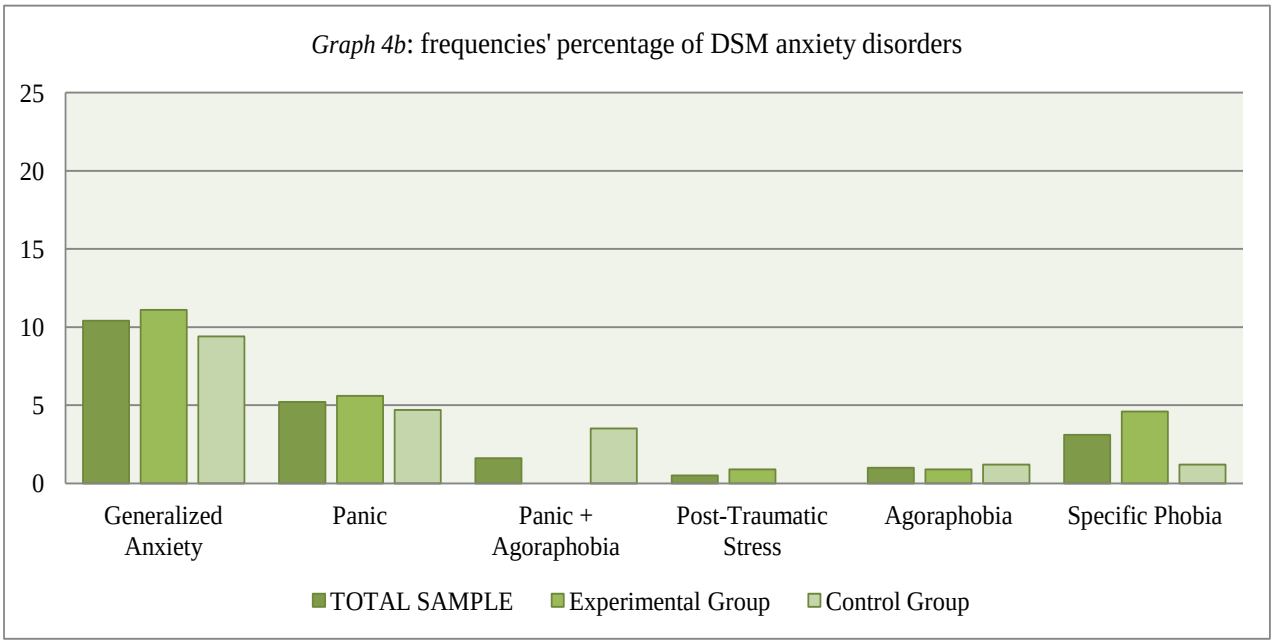


40.4% of the sample showed a diagnosis belonging to the DSM modules of depressive or anxiety disorder. No differences were detected between the two groups.

Specifically, 32.1% of the sample satisfied criteria for a depressive disorder. The most frequent depressive diagnosis in the CR group was minor depression (21.3%), while in the control group it was major depression (17.6%). No case of dysthymia was found in the latter group (*Graph 4a*). Also in these cases, no statistical difference between the two groups has been found.

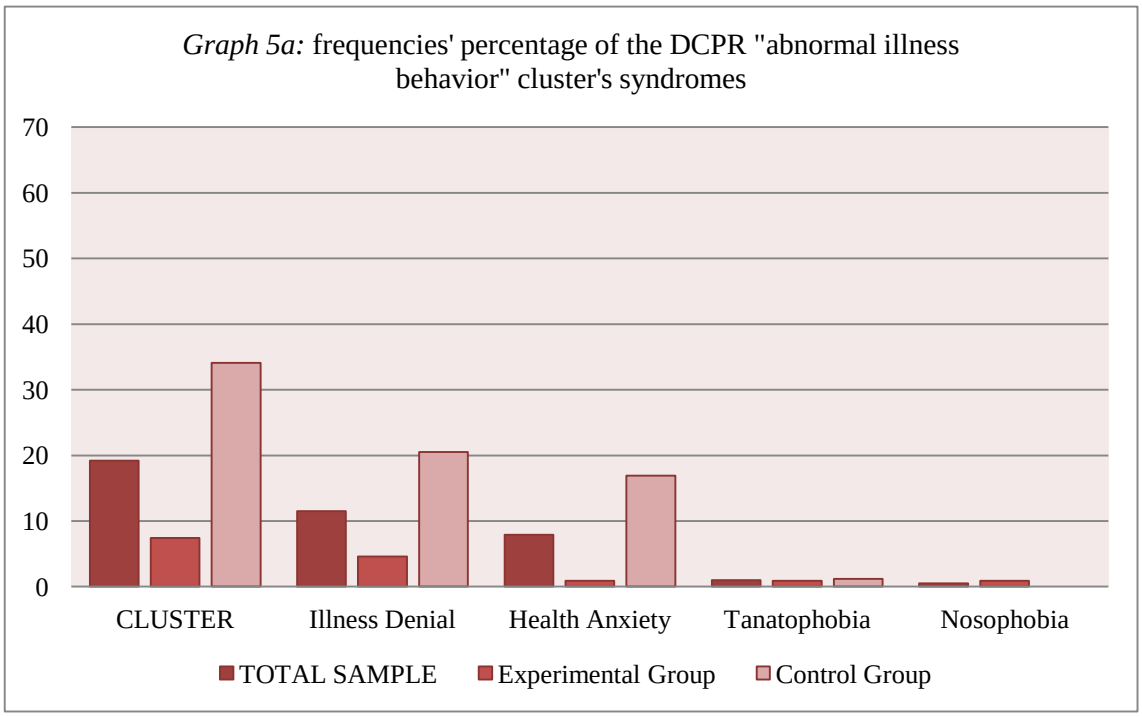


Anxiety disorders were detected in a lower percentage (19.2% of the total sample). The most represented diagnosis was generalized anxiety disorder, among the participants of both the experimental (11.1%) and control (9.4) group (*Graph 4b*). Also in the case of anxiety disorders, no statistical difference between the two clinical groups has been observed.



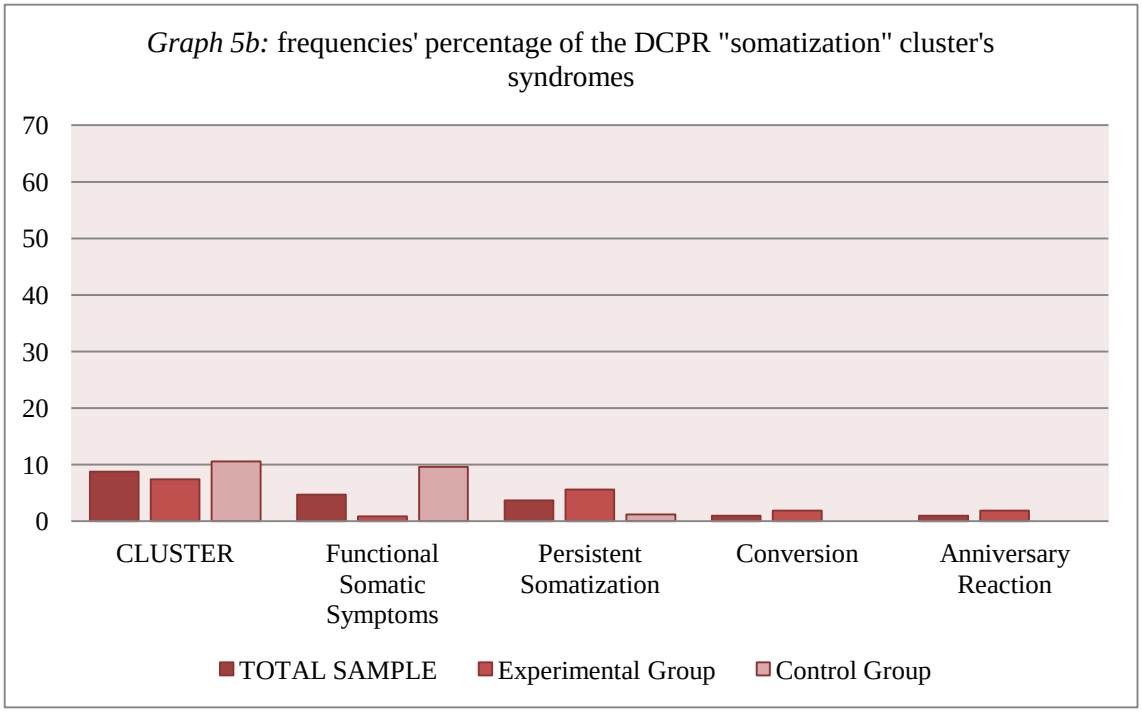
A great percentage of the sample satisfied criteria for at least one DCPR psychosomatic syndrome (62.1%), particularly the group that did not undergo cardiac rehabilitation (experimental group: 49.1%, control group: 79.3%; $\chi^2_{(1)}=16.80$, $p<0.001$).

The "abnormal illness denial" cluster showed some statistical differences, the control group being more frequently affected by these psychosomatic syndromes (*Graph 5a*). If compared to the experimental group, patients who were not referred to cardiac rehabilitation, showed a higher frequency of illness denial (experimental group: 4.6%, control group: 20.5%; $\chi^2_{(1)}=10.07$, $p=0.002$) and health anxiety (experimental group: 0.9%, control group: 16.9%; $\chi^2_{(1)}=14.35$, $p<0.001$). Also the main cluster was more frequently represented by the controls (experimental group: 7.4%, control group: 34.1%; $\chi^2_{(1)}=20.21$, $p<0.001$).



Graph 5a: frequencies' percentage of the DCPR "abnormal illness behavior" cluster's syndromes

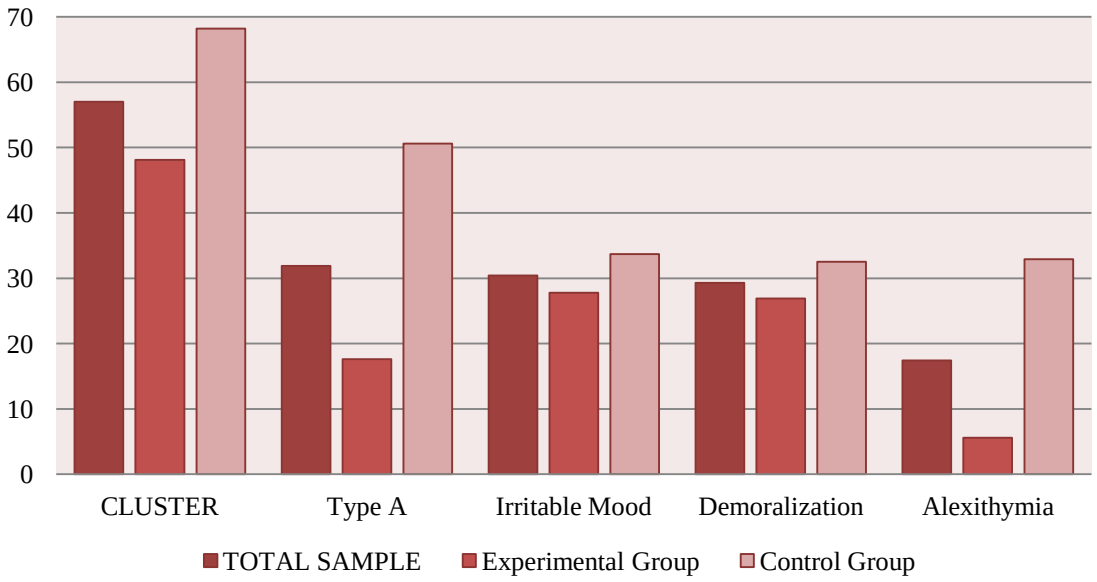
With regards to "somatization" cluster, only one statistical difference was found. Control patients were statistically more frequently diagnosed to have functional somatic symptoms secondary to a psychiatric illness (experimental group: 0.9%, control group: 9.6%; $\chi^2_{(1)}=6.11$, $p=0.013$). However, this was the less represented DCPR cluster among the overall sample (*Graph 5b*).



Graph 5b: frequencies' percentage of the DCPR "somatization" cluster's syndromes

Finally, the DCPR cluster including "psychological factors affecting medical conditions" was the most represented among the participants (*Graph 5c*).

Graph 5c: frequencies' percentage of the DCPR "psychological factors affecting medical conditions" cluster's syndromes



The most frequent psychosomatic syndromes among patients referred to CR were irritable mood (27.8%) and demoralization (26.9%), while among control subjects it was type A behavior (50.6%), which was detected in a significantly higher frequency ($\chi^2_{(1)}$=22.03, p<0.001). Alexithymia was more frequently detected among patients who did not also undergo CR (experimental group: 5,6%, control group: 32.9%; $\chi^2_{(1)}$=22.46, p<0.001). Moreover, also in this case, the main cluster was more frequently represented among controls (experimental group: 48.1%, control group: 68.2%; $\chi^2_{(1)}$=7.03, p=0.008).

3.7.2 Follow-ups – Lifestyles, quality of life and psychological factors modification

3.7.2.1 Lifestyles and health-related quality of life

Smoking

With regards to smoking habits, pair-wise comparisons showed an overall stability over time. As displayed in *Table 9a*, among CR patients who stopped smoking, only a few of them re-started to smoke at the end of the program (1%) and at 6-months (5.2%) follow-up. A small part of the subjects referred to rehabilitation did not stop smoking after the cardiac event (6.2%), but some of them did it at the end of the program (2.1%). At 6-months follow-up, some patients stopped (6.5%) while others re-started to smoke (5.2%). After 1 year from the end of CR, 4 patients (5.1%) were currently smoking.

Table 9a: Smoke habit frequencies over time among patients who attended cardiac rehabilitation

		*Smoke **T1***			
		never smoked	stopped smoking	continued to smoke	*TOTAL*
*Smoke **T2***	never smoked	44 (45.4)	0 (0)	0 (0)	44 (45.4)
	Stopped smoking / continued abstinence	0 (0)	46 (47.4)	2 (2.1)	48 (49.5)
	continued / started to smoke	0 (0)	1 (1)	4 (4.1)	5 (5.2)
	TOTAL	44 (45.4)	47 (48.5)	6 (6.2)	97 (100)
		*Smoke **T2***			
		never smoked	stopped smoking / continued abstinence	continued / started to smoke	*TOTAL*
*Smoke **T3***	never smoked	37 (48.1)	0 (0)	0 (0)	37 (48.1)
	stopped smoking / continued abstinence	0 (0)	31 (40.3)	5 (6.5)	36 (46.8)
	continued/started to smoke	0 (0)	4 (5.2)	0 (0)	4 (5.2)
	TOTAL	37 (48.1)	35 (45.5)	5 (6.5)	77 (100)
		*Smoke **T3***			
		never smoked	stopped smoking / continued abstinence	continued / started to smoke	*TOTAL*
*Smoke **T4***	never smoked	36 (46.2)	0 (0)	0 (0)	36 (46.2)
	stopped smoking / continued abstinence	0 (0)	38 (48.7)	0 (0)	38 (48.7)
	continued / started to smoke	0 (0)	0 (0)	4 (5.1)	4 (5.1)
	TOTAL	36 (46.2)	38 (48.7)	4 (5.1)	78 (100)

Note: all frequencies are expressed as N (%)

Among control patients, instead, a greater percentage than CR subjects did not stop smoking after the cardiac event (22.2%), but half of them did it after one month (11.1%) (*Graph 9b*). At 6-months follow-up, some patients stopped (12.5%) while others re-started to smoke (8.9%). After 1 year, 4 patients (7.3%) were currently smoking.

Table 9b: Smoking habit frequencies over time among patients belonging to control group

		*Smoke **T1***			
		never smoked	stopped smoking	continued to smoke	*TOTAL*
*Smoke **T2***	never smoked	23 (31.9)	0 (0)	0 (0)	23 (31.9)
	stopped smoking / continued abstinence	0 (0)	33 (45.8)	8 (11.1)	41 (56.9)
	continued / started to smoke	0 (0)	0 (0)	8 (11.1)	8 (11.1)
	TOTAL	23 (31.9)	33 (45.8)	16 (22.2)	72 (100)

		*Smoke **T2***			
		never smoked	stopped smoking / continued abstinence	continued / started to smoke	*TOTAL*
*Smoke **T3***	never smoked	16 (28.6)	0 (0)	0 (0)	16 (28.6)
	stopped smoking / continued abstinence	0 (0)	27 (48.2)	7 (12.5)	34 (60.7)
	continued / started to smoke	1 (1.8)	5 (8.9)	0 (0)	6 (10.7)
	TOTAL	17 (30.4)	32 (57.1)	7 (12.5)	56 (100)

		*Smoke **T3***			
		never smoked	stopped smoking / continued abstinence	continued / started to smoke	*TOTAL*
*Smoke **T4***	never smoked	15 (27.3)	0 (0)	0 (0)	15 (27.3)
	stopped smoking / continued abstinence	0 (0)	35 (63.6)	0 (0)	35 (63.6)
	continued / started to smoke	1 (1.8)	0 (0)	4 (7.3)	5 (9.1)
	TOTAL	16 (29.1)	35 (63.6)	4 (7.3)	55 (100)

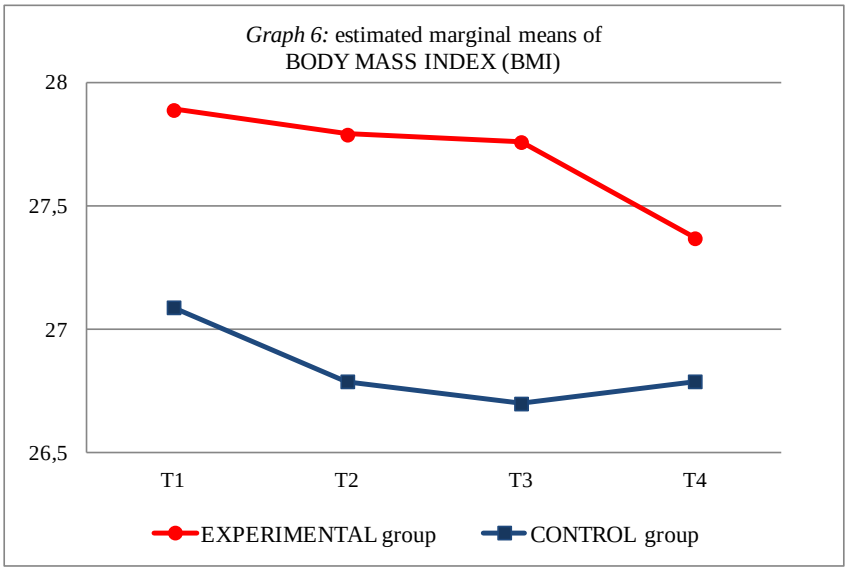
Note: all frequencies are expressed as N (%)

Comparing current smoking habits between experimental and control group patients, we found a statistical difference only at baseline: after the cardiac event 5.6% of CR subjects *versus* 20% of

controls were currently smoking ($\chi^2_{(1)}$=8.13, *p*=0.004). Since no differences have been found at the following evaluations, it means that the initial difference between the two clinical groups evened out: indeed, as displayed in the table above, half of the current smokers of the control group stopped after 1 month from the discharge from the admission to the hospital

Body Mass Index (BMI)

The main effect of "*time*", as well as the main effect of the variable "*group*" and the interaction "*time*" X "*group*" effect, were not statistically significant. Therefore, it can be assumed that there is not a direct effect of the passage of time as well as that of cardiac rehabilitation and of their interaction, on the reduction of the Body Mass Index (*Graph 6*).

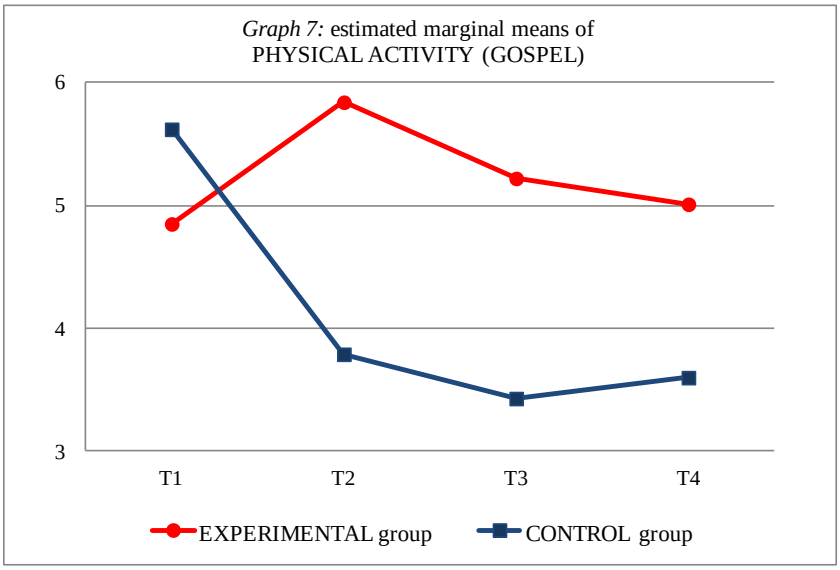


Physical activity

The main effect of "*time*" was significant ($F_{(2.737)}$=4.50, *p*=0.005), as well as the main effect of the variable "*group*" ($F_{(1)}$=5.33, *p*=0.023) and the interaction "*time*" X "*group*" effect ($F_{(2.737)}$=9.46, *p*<0.001). Therefore, it can be assumed that there is a direct effect of the passage of time as well as that of cardiac rehabilitation and their interaction, on the levels of physical activity.

Post-hoc comparisons showed that the main effect of "*time*" was due to a significant decrease of the mean scores of the whole sample from baseline to the 6 months follow-up. The main effect of "*group*" was due to the fact that the experimental group showed significantly higher physical activity levels than those of the control group.

With regards to the interaction between "*time*" and "*groups*", *Graph 7* shows the trends of the two clinical groups. It can be observed that there are no statistical differences on physical activity mean scores at baseline between experimental and control groups, while it occurred at T2 (p<0.001), T3 (p=0.005) and T4 (p=0.018). Moreover, the CR group mean scores were quite stable over time, showing no statistical differences, while those of the control group significantly decreased between the first and the second evaluation (p=0.001), then remaining stable at 6- and 12-months follow-ups.



Controlling the variable "*medical procedure*" (invasive *versus* non-invasive surgery), the effect of the interaction "*time*" X "*group*" was maintained ($F_{(2.733)}$=6.82, p<0.001).

<u>Diet: dietary habits, behavior and total score</u>

The main effect of "*time*" was significant only for the Mediterranean diet ($F_{(2.680)}$=15.74, p<0.001) and total diet score ($F_{(2.660)}$=8.17, p<0.001), while the main effect of the variable "*group*" was significant only for dietary behavior ($F_{(1)}$=14.41, p<0.001). The interaction "*time*" X "*group*" effect

was significant for both the dietary subscales and the total scores (Mediterranean diet: $F_{(2.680)}$=2.80, p=0.046; dietary behavior: $F_{(2.644)}$=4.49, p=0.006; total score: $F_{(2.660)}$=2.93, p=0.040).

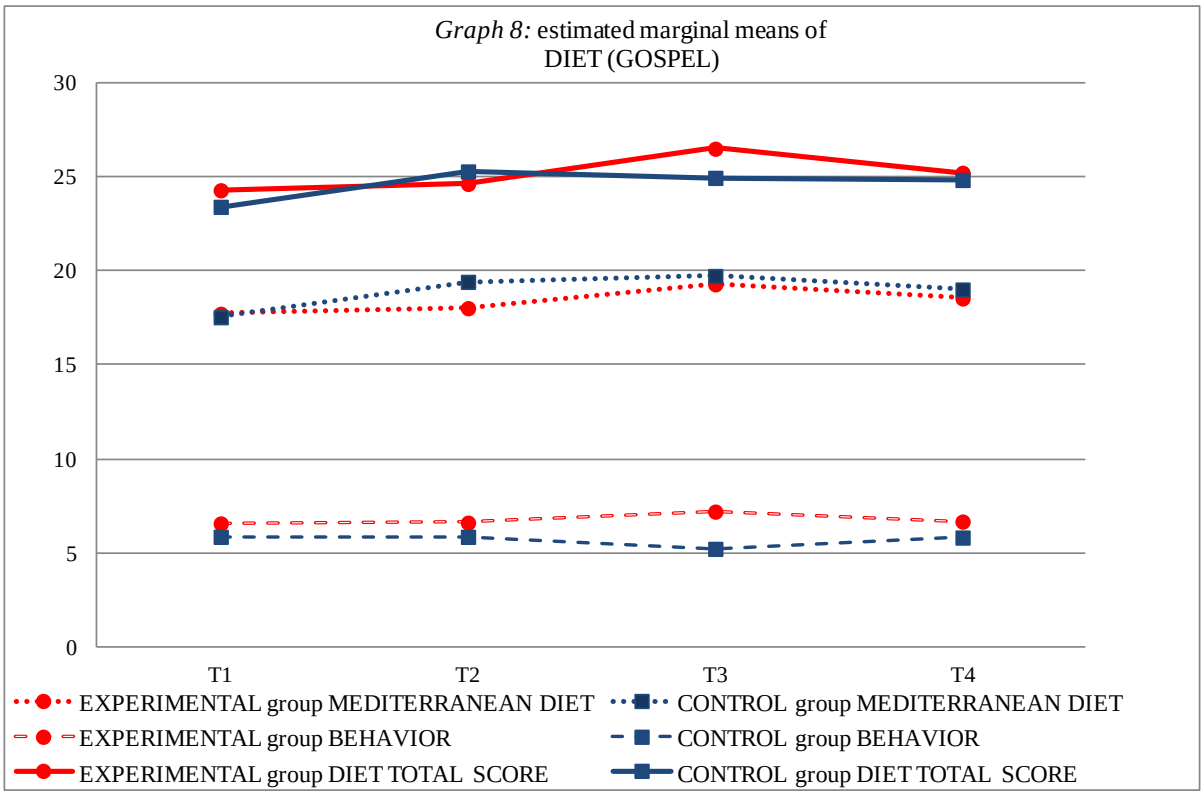
Post-hoc comparisons showed that the main effect of "*time*" on Mediterranean diet was due to a significant progressive increase of the mean scores from baseline to 6-months follow-up (T1-T2: p<0.001; T2-T3: p=0.035), and then a decrease of them from 6-months to 12-months follow-up (p=0.013). The main effect of the variable "*group*" was due to the fact that the experimental group showed significantly higher scores of dietary behavior than the control group.

Graph 8 shows the trends of the interaction between "*time*" and "*group*" of the two clinical groups. It can be observed that no statistical differences on the Mediterranean diet mean score has been found between experimental and control groups, except at the first follow-up (T2: p=0.009), the former having a lower score. Moreover, the CR group mean scores improved only after 6 months from the end of the rehabilitation (p=0.001), then remaining stable at the one-year follow-up. The control group showed higher scores at the second evaluation (p=0.001), remaining stable at 6 and 12 months.

The case of dietary behavior is somewhat different. No modifications over time of each group have been detected, but only significantly different mean scores between the two groups at T3 (p<0.001) and at T4 (p=0.027), experimental groups' ones being higher than those of the controls.

Finally, no statistical differences on total diet score have been found between experimental and control groups, except at the second follow-up (T3: p=0.040), the former having a higher score. As for the dietary habits subscale, also in this case the CR group mean scores improved only after 6 months from the end of the rehabilitation (p<0.001), but unlike the subscale, then the mean scores significantly decreases at the 12-months follow-up (T3-T4: p=0.009). The control group showed an improvement of the mean score from the baseline to the second evaluation (p=0.006) and then it remained stable at 6 and 12 months.

Controlling the variable "*medical procedure*" (invasive *versus* non-invasive surgery), the effect of the interaction "*time*" X "*group*" was maintained only on dietary behavior ($F_{(2.607)}$=6.18, p=0.001). With regards to the Mediterranean diet, it was found to be significant the interaction "*time*" X "*group*" X "*medical procedure*" ($F_{(2.688)}$=4.16, p=0.009). Post-hoc comparisons showed that CR patients who underwent an invasive surgery had lower mean scores of the Mediterranean diet than the counterpart in the control group at 6 months follow-up (18.78±0.47 versus 21.33±1.11; p=0.036). Moreover, in the CR group only subjects who underwent a non-invasive surgery had a slight improvement from baseline to 6-months follow-up (p<0.001) and then a deterioration from T3 to T4 (p=0.003). On the contrary, in the control group patients who underwent a non-invasive surgery showed an increment of the scores from baseline to 1-month follow-up (p<0.001), then remaining stable over time, while those who underwent open-heart surgery reported higher scores from baseline to 6-months follow-up (p=0.004).



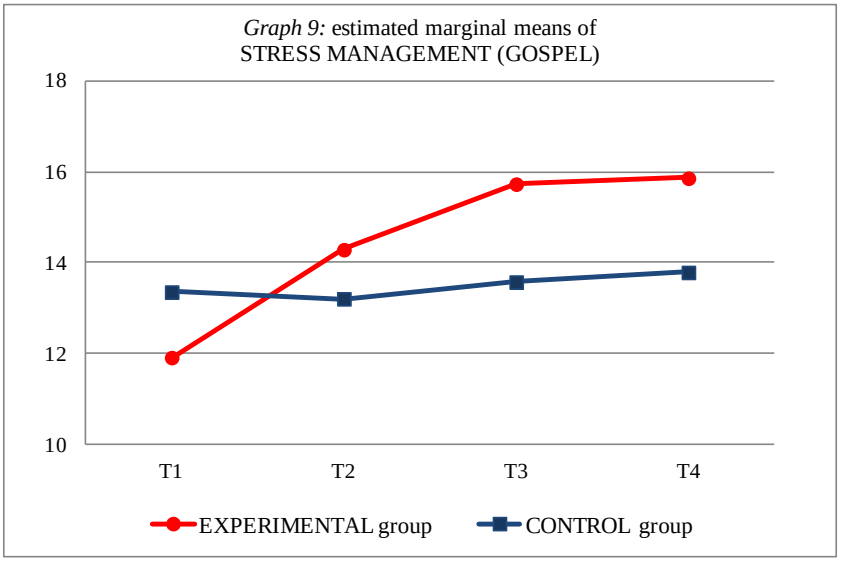
Total diet score was subjected only to the effect of "*time*" X "*medical procedure*" ($F_{(2.632)}$=2.75, p=0.050): patients who underwent open-heart surgery showed an improvement in total diet mean

score only after one year from baseline (p=0.017), while patients who received only a non-invasive intervention improved after one month (p=0.007) remaining stable until a statistical deterioration from T3 to T4 (p=0.008).

Stress management

The main effect of "*time*" was significant ($F_{(2.766)}$=16.40, p<0.001), as well as the interaction "*time*" ^{X} "*group*" effect ($F_{(2.766)}$=11.38, p<0.001); the main effect of the variable "*group*" showed only a trend to significance ($F_{(1)}$=3.80, p=0.054). Therefore, it can be assumed that there is a direct effect of the passage of time as well as that of the interaction between the latter and cardiac rehabilitation attendance, on the degree of stress management.

Post-hoc comparisons showed that the main effect of "*time*" was due to a progressive increase in the mean scores of the whole sample from baseline to 6-months follow-up (T1-T2: p=0.016; T2-T3: p=0.034), while the scores of stress management remain stable from the 6-months to the 12-months follow-up.



Graph 9: estimated marginal means of STRESS MANAGEMENT (GOSPEL)

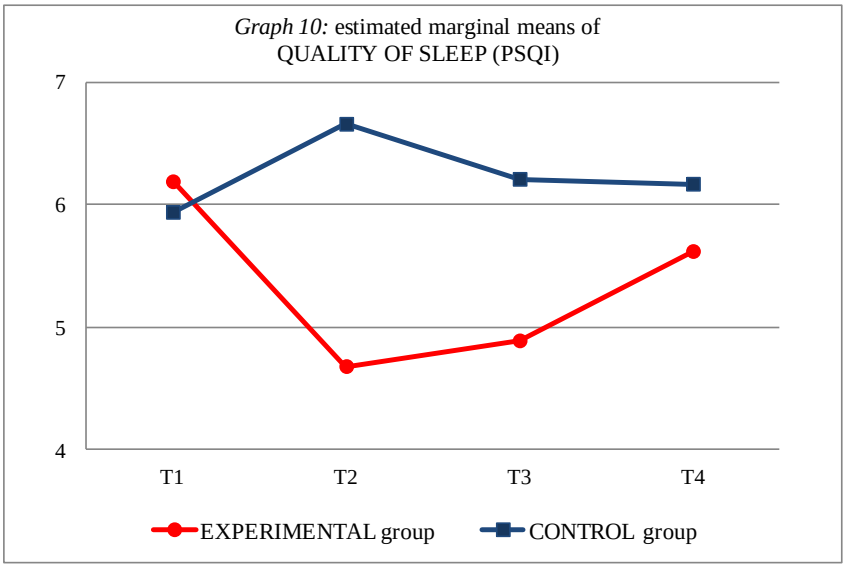
With regards to the interaction between "*time*" and "*groups*", the experimental group self-reported significantly lower scores (p=0.033) than controls at baseline, while at T3 (p=0.001) and T4 (p=0.001) they became higher (*Graph 9*). Patients undergone to CR, indeed, significantly improved

their "stress management" mean scores from baseline to 6-months follow-up (T1-T2: $p<0.001$; T2-T3: $p=0.005$). On the contrary, those of the control group remained stable over time.

Controlling for the between-subjects factor "*medical procedure*", the effect of the interaction "*time*" X "*group*" was maintained ($F_{(2.771)}=10.25$, $p<0.001$).

Quality of sleep

The main effect of "*time*" was insignificant, while the main effect of the variable "*group*" ($F_{(1)}=4.12$, $p=0.044$) and the "*time*" X "*group*" interaction effect ($F_{(2.766)}=11.38$, $p<0.001$) resulted to be statistically significant. Therefore, it can be assumed that there is a direct effect of belonging to the experimental or the control group as well as that of its interaction with time, on quality of sleep. Generally speaking, patients in the control group showed higher PSQI scores than the participants of the CR group ($p=0.044$).



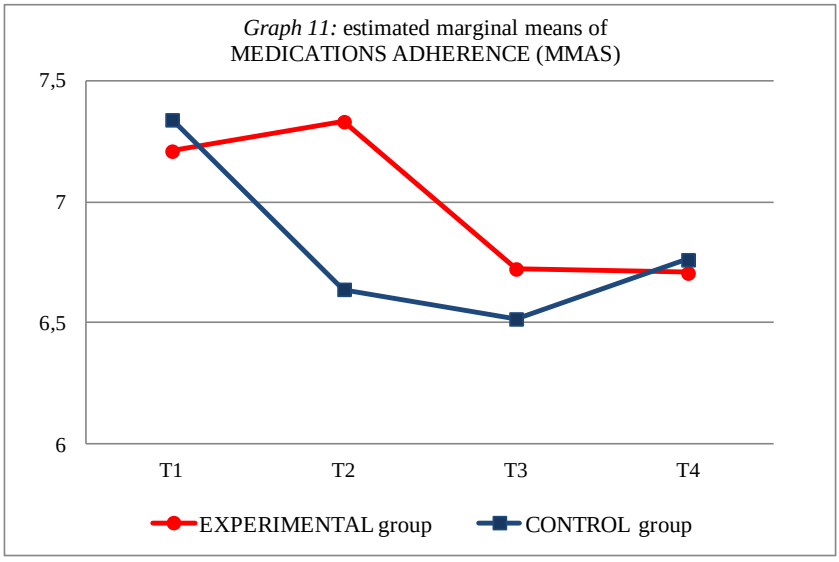
Post-hoc comparisons illustrate that – even if they self-reported similar PSQI scores at baseline – CR group patients showed lower scores than the control group at the end of the rehabilitation program ($p<0.001$) and at 6-months follow-up ($p=0.024$) (*Graph 10*). They also showed an

improvement of quality of sleep between the baseline and the end of the program (T1-T2: $p<0.001$), remaining then quite stable over time. The controls instead did not report any change in their sleep.

Controlling for the variable "*medical procedure*", the effect of the interaction "*time*" X "*group*" was maintained ($F_{(2.574)}=3.97$, $p=0.012$).

Medication adherence

The main effect of "*group*" was insignificant, while the main effect of the variable "*time*" ($F_{(2.807)}=9.88$, $p<0.001$) and the "*time*" X "*group*" interaction effect ($F_{(2.807)}=4.03$, $p=0.009$) resulted to be statistically significant. Therefore, it can be hypothesized that there is a direct effect of time as well as that of its interaction with attendance to cardiac rehabilitation, on medications compliance. Overall MMAS mean scores statistically decreased from baseline to 6-months follow-up ($p<0.001$). Moreover, even although both groups self-reported a similar compliance at baseline, CR patients showed higher MMAS scores than those of the control group at the end of the rehabilitation program ($p<0.001$) (*Graph 11*). They showed a scores decrement from baseline to 6-months follow-up ($p=0.015$), remaining stable at 12-months follow-up, while the controls showed statistically deteriorated scores from baseline to T2 ($p=0.003$), remaining then stable over time (*Graph 11*).



Graph 11: estimated marginal means of MEDICATIONS ADHERENCE (MMAS)

Controlling for the variable "*medical procedure*", the effect of the interaction "*time*" X "*group*" was not maintained anymore. Only the main effect of "time" continued to be significant on medication compliance ($F_{(2.800)}$=3.83, p=0.012).

Health-related quality of life

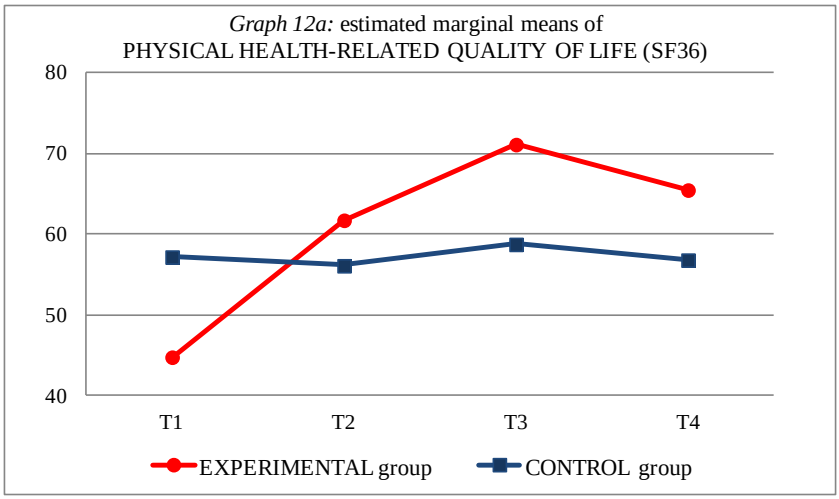
The main effect of "*time*" was significant for both SF-36 subscales (physical health-related quality of life: $F_{(2.797)}$=21.01, p<0.001; mental health-related quality of life: $F_{(2.663)}$=12.12, p<0.001) and total score ($F_{(2.605)}$=26.77, p<0.001), while the main effect of the variable "*group*" was significant only for mental health-related quality of life ($F_{(1)}$=4.28, p=0.041). The interaction "*time*" X "*group*" effect was significant for both SF-36 subscales (physical health-related quality of life: $F_{(2.797)}$=18.31, p<0.001; mental health-related quality of life: $F_{(2.663)}$=23.49, p<0.001) and total score ($F_{(2.605)}$=24.75, p<0.001).

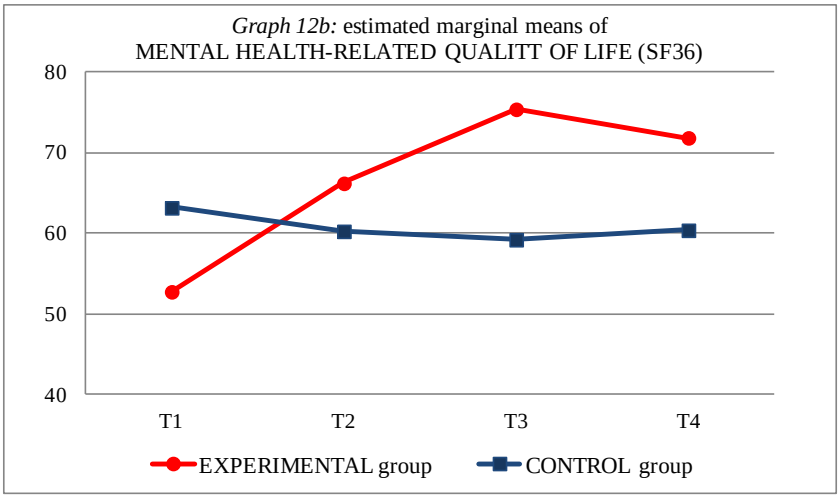
Post-hoc comparisons showed that the main effect of "*time*" was due to a significant progressive increase of the mean scores from baseline to 6-months follow-up of both SF-36 subscales (physical health-related quality of life: T1-T2: p< 0.001, T2-T3: p= 0.006; mental health-related quality of life: T1-T2: p= 0.012, T2-T3: p= 0.037) and total score (total health-related quality of life: T1-T2: p< 0.001; T2-T3: p< 0.001); only the total score significantly decreased from 6- to 12-months follow-up (p= 0.024). The main effect of "*group*" was due to the fact that the CR group self-reported a significantly higher level of mental health-related quality of life than controls.

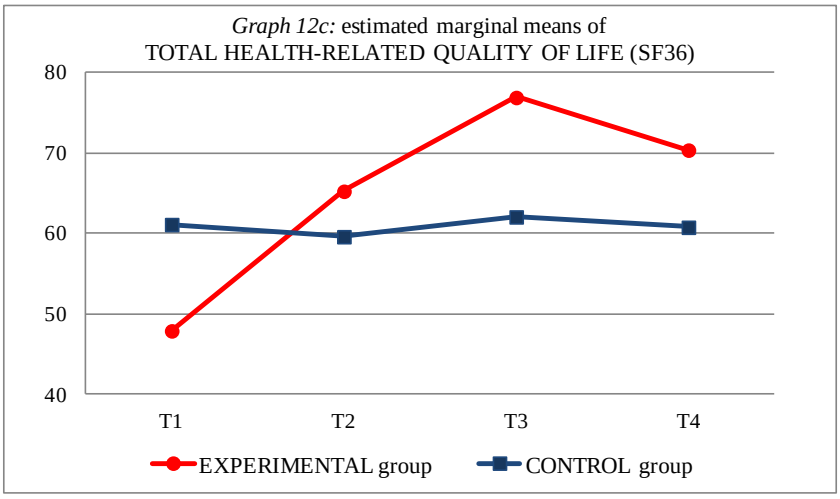
With regards to the interaction between "*time*" and "*group*", we found a similar trend in all three cases. If compared to patients of the control group, those referred to cardiac rehabilitation had significantly lower levels of self-reported quality of life at baseline (physical health-related QoL: p<0.001; mental health-related QoL: p=0.002; total health-related QoL: p<0.001), and then higher levels at 6- (physical health-related QoL: p=0.001; mental health-related QoL: p<0.001; total health-related QoL: p<0.001) and 12-months (physical health-related QoL: p=0.034; mental health-

related QoL: p=0.005; total health-related QoL: p=0.015) follow-ups (*Graph 12a*, *Graph 12b* and *Graph 12c*).

While control patients' mean scores did not differ between the four evaluations in both SF-36 subscales and total score, CR patients' scores significantly improved from baseline to 6-months follow-up (physical health-related QoL: T1-T2 p<0.001, T2-T3 p=0.001; total health-related QoL: T1-T2 p<0.001, T2-T3 p<0.001) and then deteriorated from T3 to T4 (physical health-related QoL: p=0.036; total health-related QoL: p=0.001) (*Graph 12a* and *Graph 12c*). Also, with regards to mental health-related quality of life , CR participants' mean scores significantly increased until 6-months follow-up (T1-T2 p<0.001, T2-T3 p<0.001), but then remaining stable at T4 (*Graph 12b*).





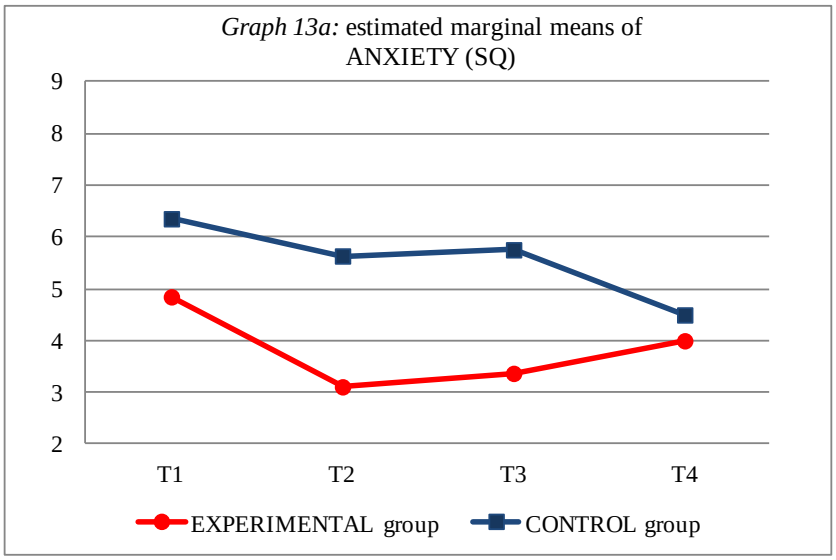


The effect of the interaction "*time*" X "*group*" continued to be statistically significant even after controlling for "*medical procedure*", over all the three SF-36 scales (physical health-related QoL: $F_{(2.794)}$=10.71, p<0.001; mental health-related QoL: $F_{(2.655)}$=15.14, p<0.001; total health-related QoL: $F_{(2.605)}$=14.94, p<0.001).

3.7.2.2 Psychological factors

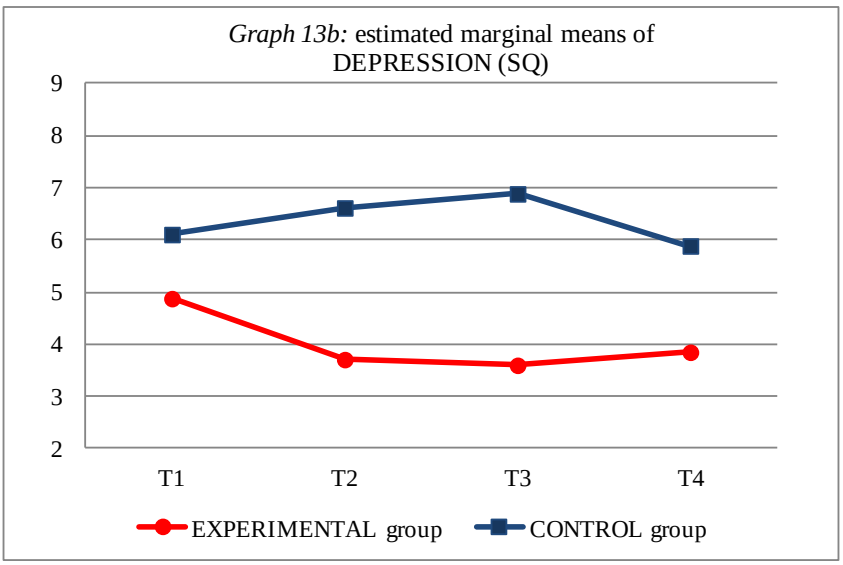
Symptom Questionnaire: anxiety, depression, somatization and hostility

The main effect of "*time*" ($F_{(2.669)}$= 4.24, p=0.008) as well as that of "*group*" ($F_{(1)}$= 6.31, p= 0.013), but not their interaction, were significant on the anxiety scale (*Graph 13a*).



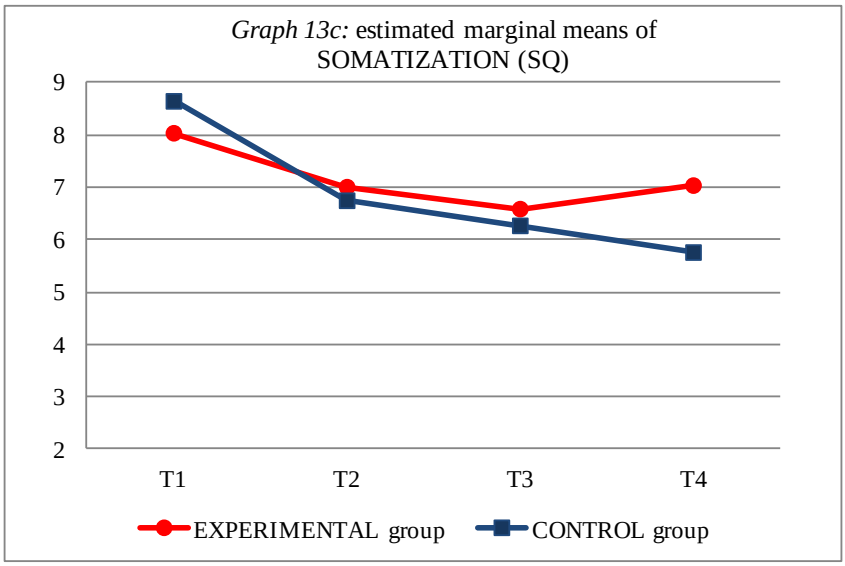
Specifically, the whole sample self-reported lower scores of anxiety from baseline to 1-year follow-up (p=0.035), the CR group showing general higher scores than the control group.

With regards to the depression scale, the main effect of "*time*" was insignificant, while that of "*group*" ($F_{(1)}$= 12.38, p= 0.001) and their interaction ($F_{(2.570)}$= 3.31, p= 0.026) were. Specifically, the CR group showed an overall lower score than controls, especially at the end of the rehabilitation program (p<0.001), and at 6- (p<0.001) and 12-months (p=0.015) follow-ups (*Graph 13b*). No variation of scores over time has been detected among CR group patients, while controls got a significant decrement of depression mean scores from T3 to T4 (p=0.044).



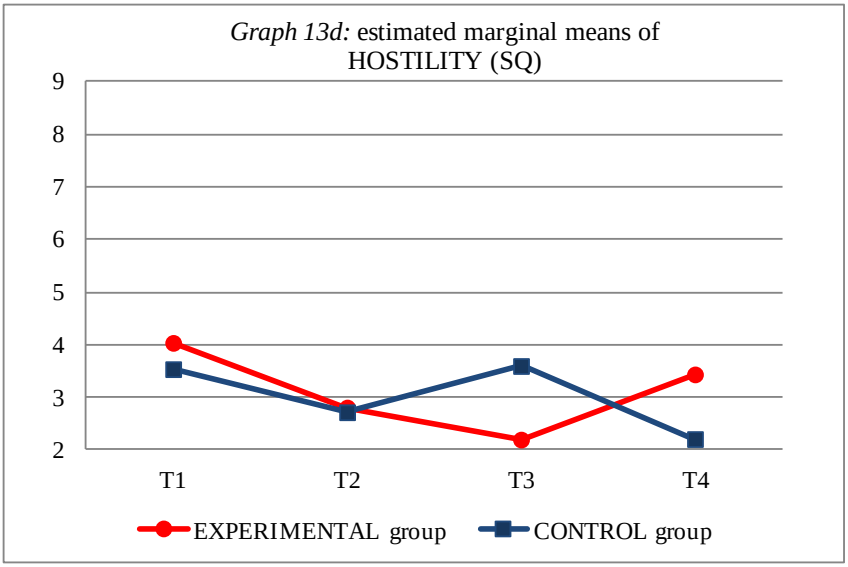
Controlling for the variable "*medical procedure*", the significant effect of the interaction "*time*" [X] "*group*" on the SQ depression scale was not maintained anymore.

On the scale of somatization, only the main effect of "*time*" ($F_{(2.712)}$= 8.83, p<0.001) was statistically significant (*Graph 13c*): the two groups had similar trends over time, the whole sample showing overall lower levels of somatization from baseline to T2 (p=0.007).



With regards to hostility, the main effect of "*time*" was significant ($F_{(3)}$= 3.92, *p*=0.009), but not that of the variable "*group*". Their interaction was also found to be statistically significant ($F_{(3)}$= 5.18, *p*=0.002).

Post-hoc comparisons show that the sample had an overall decrement of hostility mean scores by the second evaluation (*p*=0.027). Compared to patients who attended CR, controls had higher scores at 6-months follow-up (*p*=0.043). The former showed a slightly decrement of hostility mean scores starting from baseline to 1-month follow-up (*p*=0.053), then an increment from T3 to T4 (*p*=0.026); the controls remained stable except for a decrement between T3 and T4 (*p*=0.036) (*Graph 13d*).

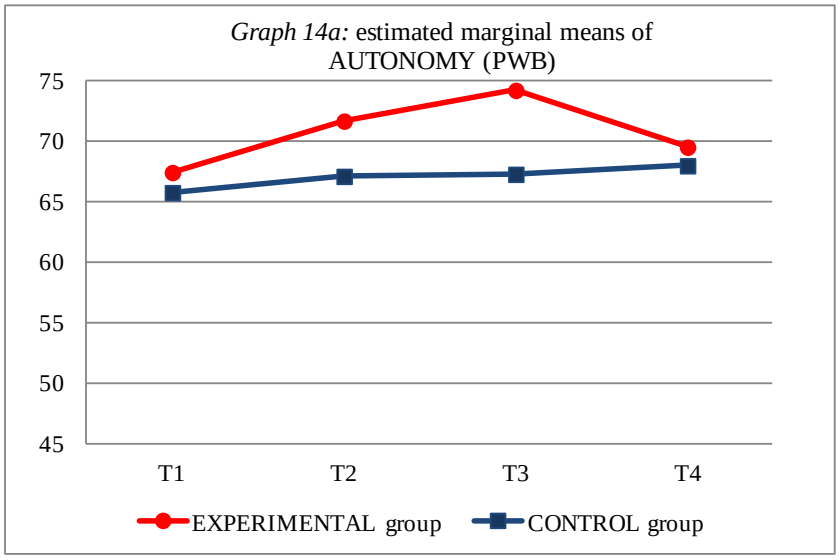


Controlling for the variable "*medical procedure*", the interaction "*time*" X "*group*" effect continued to be statistically significant ($F_{(3)}$=3.69, *p*=0.012).

Psychological Well-Being scale: autonomy, environmental mastery, personal growth, positive relationships, purpose in life and self-acceptance

Autonomy scores were subjected to the interaction "*time*" X "*group*" effect ($F_{(2.723)}$= 3.24, *p*=0.026) and to the main effect of "*time*" ($F_{(2.723)}$= 5.83, *p*=0.001) but not to that of the variable "*group*".

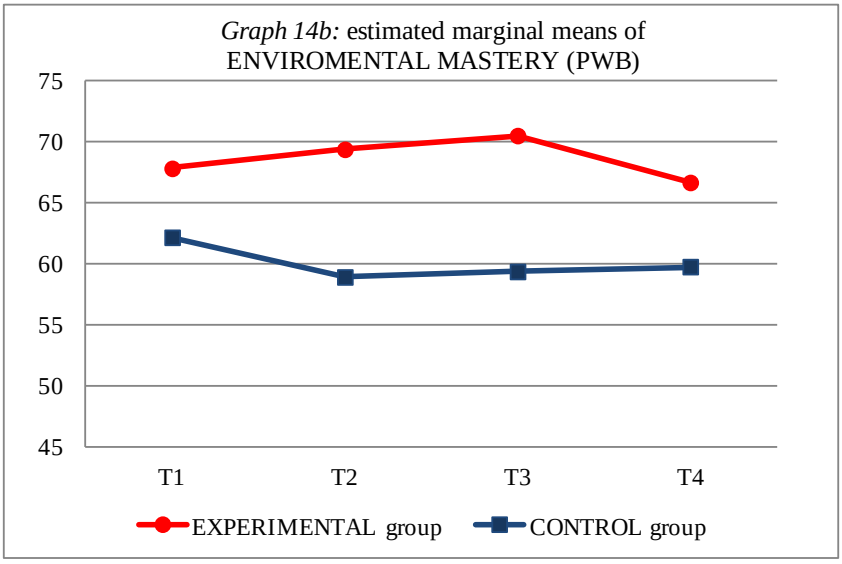
Post-hoc comparisons show that the entire sample got their scores increased from the first to the second evaluation (*p*=0.010). Experimental and control group differed from each other at T2 (*p*=0.018) and T3 (*p*=0.001), the former having significantly higher scores. Moreover, the CR group obtained an increment of the autonomy scale scores from baseline to the end of the rehabilitation (*p*=0.002) and then a decrement from 6-months to 1-year follow-up (*p*=0.002) (*Graph 14a*). Controls' scores remained stable over time.



Controlling for the variable "*medical procedure*", the effect of the interaction "*time*" X "*group*" on PWB autonomy dimension was not maintained anymore.

Environmental mastery scores were subjected to the interaction "*time*" X "*group*" effect ($F_{(2.585)}$= 3.91, p=0.013) and to the main effect of the variable "*group*" ($F_{(1)}$= 19.92, p<0.001) but not to that of the variable "*time*".

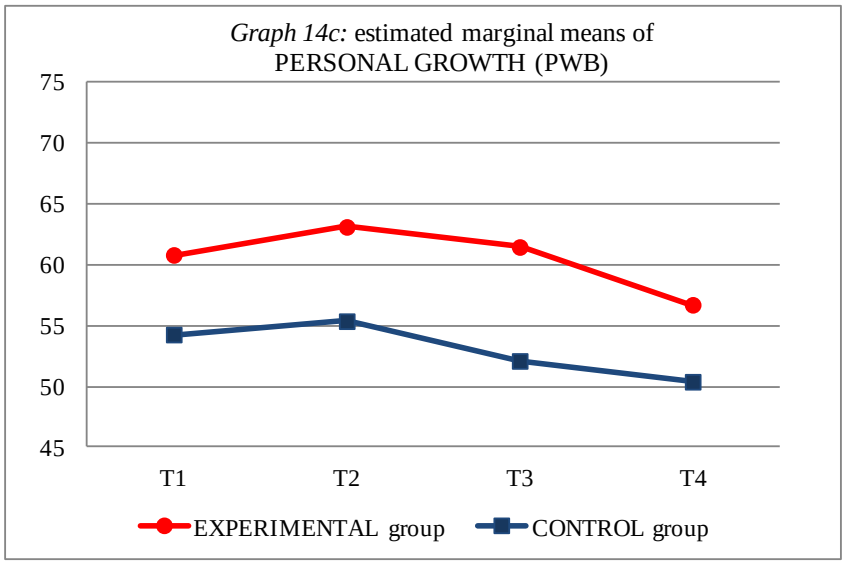
Post-hoc comparisons showed that, compared to patients who did not undergo cardiac rehabilitation, subjects belonging to the experimental group had both an overall and a time by time (T1: p=0.008; T2: p<0.001; T3: p<0.001; T4: p=0.006) higher mean score of environmental mastery (*Graph 14b*). While the controls maintained stable scores over time, CR subjects showed a significant decrement of their mean scores from 6-months to 12-months follow-up (p=0.007).



Controlling for the variable "*medical procedure*", the effect of the interaction "*time*" X "*group*" on PWB environmental mastery dimension was not maintained anymore.

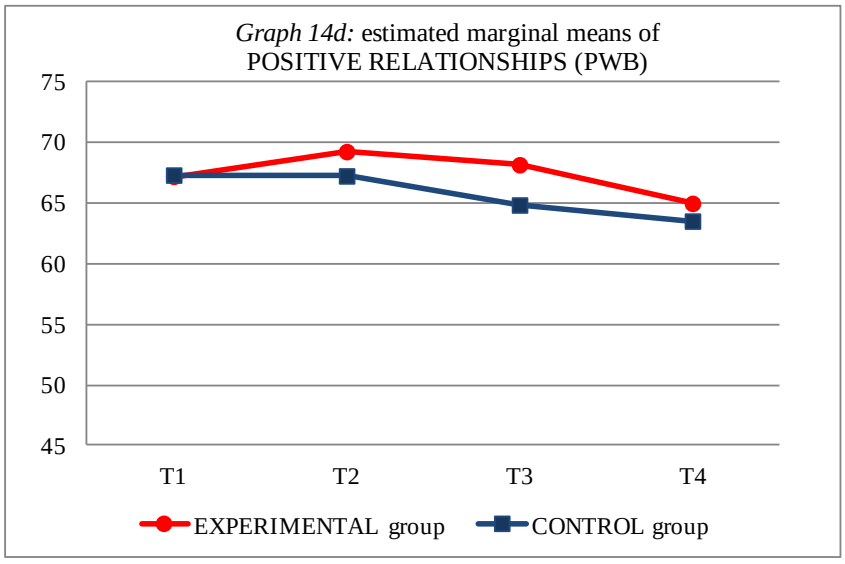
The main effects of "*time*" ($F_{(3)}$=11.113, p<0.001) and of the variable "*group*" ($F_{(1)}$=15.96, p<0.001), but not the effect of their interaction, were significant on personal growth.

The mean score of the whole sample significantly diminished from the third to the fourth evaluation (p=0.002), the control group having both an overall and a time by time (T1: p=0.003; T2: p=0.001; T3: p<0.001; T4: p=0.008) lower mean score (*Graph 14c*).



Controlling for the variable "*medical procedure*", the interaction "*time*" X "*group*" X "*type of intervention*" resulted to be significant ($F_{(2.727)}$=2.72, p=0.045). In the CR group, only patients who underwent an invasive surgery showed a deterioration of personal growth's mean scores from 6-months to 1-year follow-up (p=0.002). In the control group, instead, only patients who underwent a non-invasive procedure reported worse scores from the second to the fourth evaluation (p=0.008).

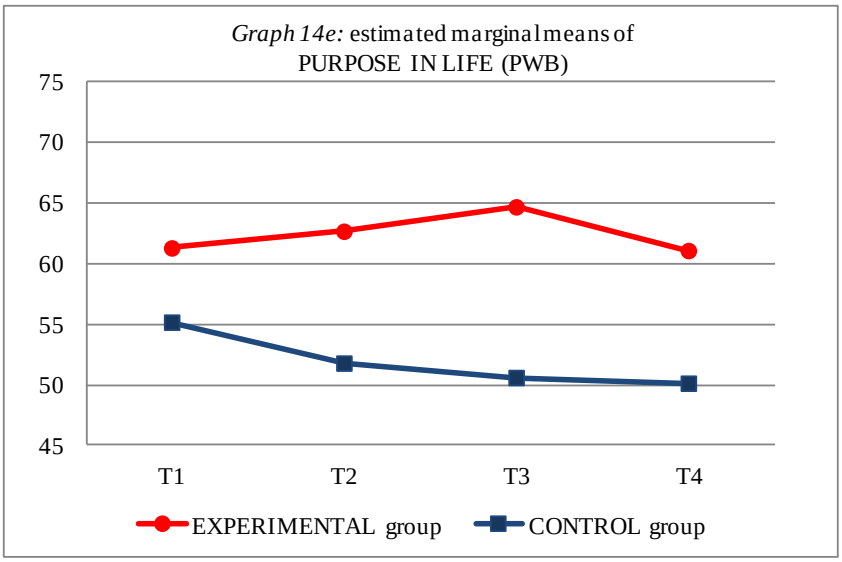
With regards to positive relationships scale, only the main effect of "*time*" was significant ($F_{(2.727)}$=4.87, p=0.003): the entire sample showed a decrement of their mean scores from T2 to T4 (p=0.003). The trends of the two clinical groups was then quite similar (*Graph 14d*).



Similarly to previous dimension, we also found a significant interaction effect of "*time*" X "*group*" X "*medical procedure*" ($F_{(2.755)}$=3.19, p=0.028) for positive relationships . Among CR group patients, only those who underwent open-heart surgery showed a deterioration of the mean scores from the second to the fourth evaluation (p=0.004). In the control group, instead, only patients who underwent a non-invasive medical procedure reported worse scores from baseline to 1-year follow-up (p=0.037).

The main effects of "*time*" ($F_{(2.769)}$=3.05, p=0.032) and of the variable "*group*" ($F_{(1)}$=24.70, p<0.001), as well as that of their interaction ($F_{(2.769)}$=6.48, p<0.001) were statistically significant on PWB purpose in life scale.

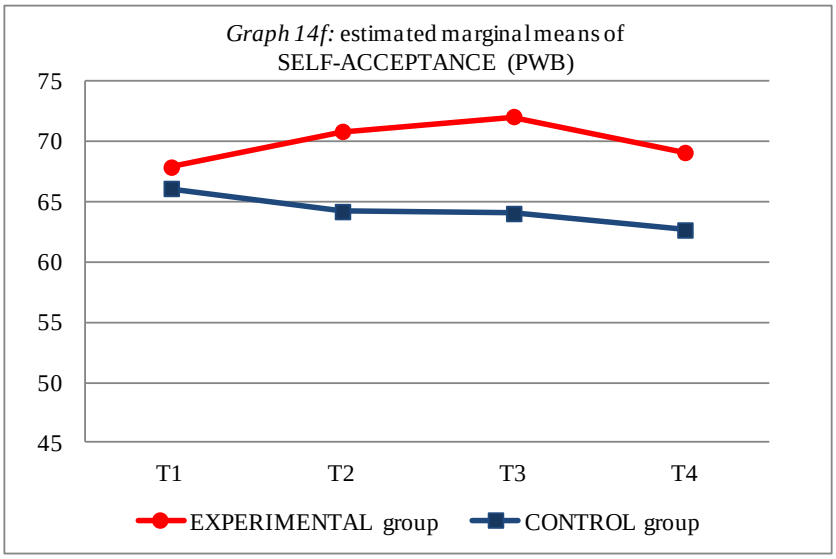
Patients who attended cardiac rehabilitation showed overall evaluation-by-evaluation higher scores (T1: p=0.008; T2: p<0.001; T3: p<0.001; T4: p<0.001) than controls (*Graph 14e*). Moreover, the former displayed a scores' improvement from baseline to 6-months follow-up (p=0.044) and then a decrement from T3 to T4 (p=0.005). Controls, instead, showed a significant deterioration of the scores from baseline to 6-months follow-up (p=0.012), then remaining stable until 1-year evaluation.



Controlling for the variable "*medical procedure*", the effect of the interaction "*time*" X "*group*" on PWB purpose in life dimension lost part of its significance but it was still a trend toward significance ($F_{(2.759)}$=2.67, *p*=0.052).

Finally, self-acceptance has been subjected to the main effect of the variable "*group*" ($F_{(1)}$=8.94, *p*=0.003) and of its interaction with "*time*" ($F_{(2.596)}$=3.73, *p*=0.016).

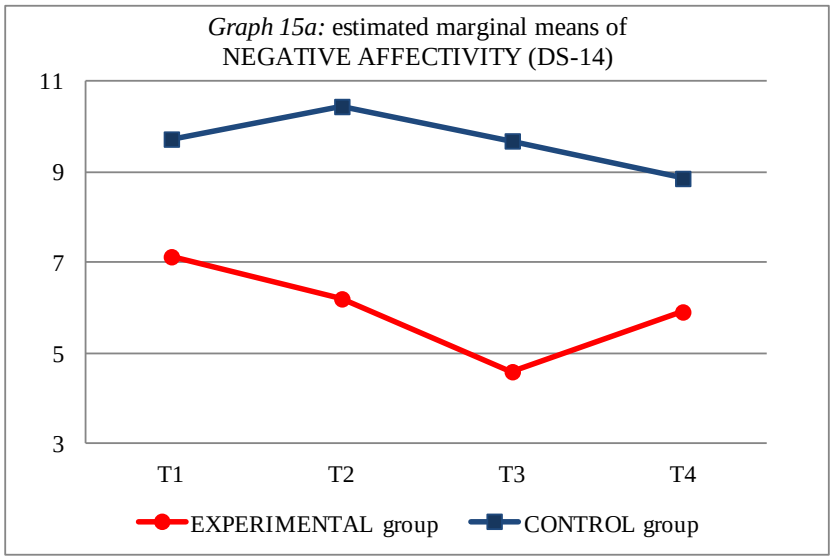
Compared to controls, the experimental group showed overall higher scores of self-acceptance, as well at T2 (*p*=0.003), T3 (*p*=0.001) and T4 (*p*=0.010), as highlighted in *Graph 14f*. Subjects of the CR group displayed a slightly significant improvement of self-acceptance scores from baseline to 6-months follow-up (*p*=0.023), while the controls' mean scores remained stable over time.



Controlling for the variable "*medical procedure*", the effect of the interaction "*time*" X "*group*" on PWB self-acceptance dimension was not maintained anymore.

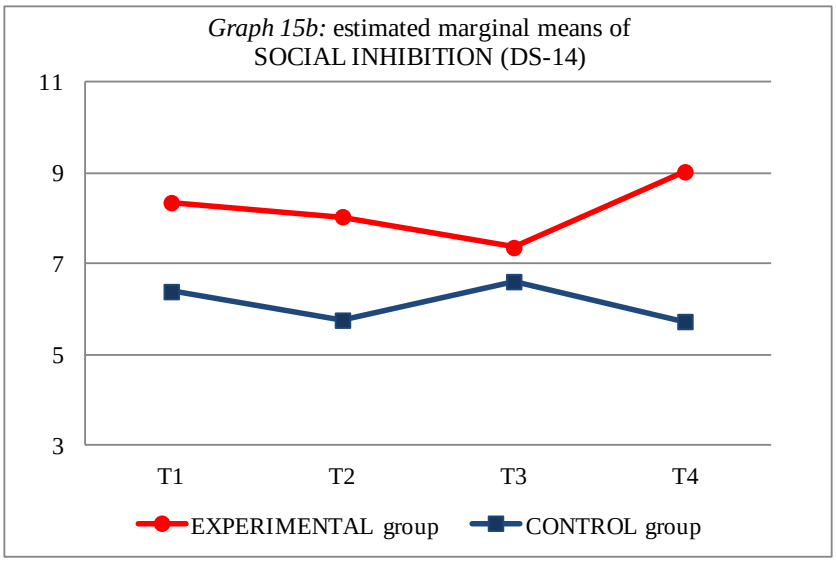
<u>14-items Type D Scale: negative affectivity and social inhibition</u>

Negative affectivity has been subjected to the main effect of "*time*" ($F_{(2.710)}$=3.02, *p*=0.035) as well as of the variable "*group*" ($F_{(1)}$=10.92, *p*=0.001), but not to the effect of their interaction.



Patients of the CR group showed overall and time-by-time (T1: p=0.036; T2: p=0.001; T3: p<0.001; T4: p=0.033) significantly lower scores than those of the control group (*Graph 15a*).

With regards to social inhibition, the only significant effect was that of the variable "*group*" ($F_{(1)}$=4.38, p=0.038), the CR patients having overall higher mean scores than controls. No effect of "*time*" or of the interaction "*time*" ^{X} "*groups*" has been found (*Graph 15b*).



Diagnoses: type D personality, DSM depression and anxiety, and DCPR psychosomatic syndromes

With regards to Type D personality, *Table 12* shows the modification over time of its frequencies among subjects of the sample. The experimental group displayed a significant decrease of cases of Type D personality from the end of the rehabilitation program to 6-months follow-up (p<0.05): among the 16 subjects who had these personality traits at T2, only 5 still showed them at T3. Two new cases have also been recorded. Among controls, instead, no significant changes of the diagnosis' frequencies have been observed. In general, where no modifications of the number of diagnoses have been found, new cases compensated a decrement of previous cases.

Moreover, if compared at each time point, the two clinical groups did not differ on the frequencies of Type D personality.

Table 12: Type D personality frequencies over time among experimental and control group patients

EXPERIMENTAL group

		T1	
		yes	no
T2	yes	11 (11.3)	10 (10.3)
	no	10 (10.3)	66 (68.1)

significance (p)= ns

		T2	
		yes	no
T3	yes	5 (6.4)	2 (2.6)
	no	11 (14.1)	60 (76.9)

significance (p)= 0.022

		T3	
		yes	no
T4	yes	6 (8)	6 (8)
	no	1 (1.3)	62 (82.7)

significance (p)= ns

CONTROL group

		T1	
		yes	no
T2	yes	6 (9.1)	5 (7.6)
	no	8 (12.1)	47 (71.2)

significance (p)= ns

		T2	
		yes	no
T3	yes	7 (11.3)	4 (6.5)
	no	3 (4.8)	48 (77.4)

significance (p)= ns

		T3	
		yes	no
T4	yes	4 (7.4)	5 (9.3)
	no	6 (10.9)	40 (74.1)

significance (p)= ns

Note: all frequencies are expressed as N (%)
ns= not significant

With regards to DSM diagnoses, we found an overall stability over time of depressive and anxiety disorders in both groups, except for a significant decrement of Major Depression (p<0.05), Minor Depression (p<0.01) and Generalized Anxiety Disorder (p<0.05), from baseline to the end of the

rehabilitation program, among experimental group patients (*Tables 13-15*). Also, the two clinical groups differed on the frequencies of Major Depression at T2 (2.1% *versus* 14.7%; $\chi^2_{(1)}$=7.70, *p*=0.006) and at T3 (1.3% *versus* 9.7%; $\chi^2_{(1)}$=3.85, *p*=0.050), and of Generalized Anxiety Disorder at T3 (1.3% *versus* 9.7%; $\chi^2_{(1)}$=3.85, *p*=0.050) and at T4 (1.2% *versus* 10.5%; $\chi^2_{(1)}$=4.60, *p*=0.032), the control group showing the greater number of cases.

Table 13: Major Depression frequencies over time among experimental and control group patients

EXPERIMENTAL group

		T1	
		yes	no
T2	yes	2 (2.1)	0 (0)
	no	6 (6.2)	89 (91.7)

significance (p)=0.031

		T2	
		yes	no
T3	yes	1 (1.3)	0 (0)
	no	1 (1.3)	76 (97.4)

significance (p)= ns

		T3	
		yes	no
T4	yes	1 (1.3)	1 (1.3)
	no	0 (0)	75 (97.4)

significance (p)= ns

CONTROL group

		T1	
		yes	no
T2	yes	7 (10.3)	3 (4.4)
	no	3 (4.4)	55 (80.9)

significance (p)= ns

		T2	
		yes	no
T3	yes	4 (6.5)	2 (3.2)
	no	4 (6.5)	52 (83.9)

significance (p)= ns

		T3	
		yes	no
T4	yes	3 (5.5)	1 (1.8)
	no	1 (1.8)	50 (90.9)

significance (p)= ns

Note: all frequencies are expressed as N (%)
ns= not significant

Table 14: Minor Depression frequencies over time among experimental and control group patients

EXPERIMENTAL group

		T1	
		yes	no
T2	yes	11 (11.3)	1 (1)
	no	11 (11.3)	74 (76.3)

significance (p)=0.006

		T2	
		yes	no
T3	yes	2 (2.6)	11 (14.1)
	no	5 (6.4)	60 (76.9)

significance (p)= ns

CONTROL group

		T1	
		yes	no
T2	yes	6 (8.8)	8 (11.8)
	no	3 (4.4)	51 (75)

significance (p)= ns

		T2	
		yes	no
T3	yes	8 (12.9)	4 (6.5)
	no	5 (8)	45 (72.6)

significance (p)= ns

		T3	
		yes	no
T4	yes	6 (7.8)	2 (2.6)
	no	7 (9.1)	62 (80.5)

significance (p)= ns

		T3	
		yes	no
T4	yes	4 (7.3)	1 (1.8)
	no	6 (10.9)	44 (80)

significance (p)= ns

Note: all frequencies are expressed as N (%)
ns= not significant

Table 15: Generalized Anxiety disorder frequencies over time among experimental and control group patients

EXPERIMENTAL group

		T1	
		yes	no
T2	yes	3 (3.1)	1 (1)
	no	9 (9.3)	84 (86.6)

significance (p)=0.021

		T2	
		yes	no
T3	yes	0 (0)	1 (1.3)
	no	4 (5.1)	73 (93.6)

significance (p)= ns

		T3	
		yes	no
T4	yes	1 (1.3)	0 (0)
	no	0 (0)	76 (98.7)

significance (p)= ns

CONTROL group

		T1	
		yes	no
T2	yes	6 (8.8)	1 (1.5)
	no	0 (0)	61 (89.7)

significance (p)= ns

		T2	
		yes	no
T3	yes	6 (9.7)	0 (0)
	no	1 (1.6)	55 (88.7)

significance (p)= ns

		T3	
		yes	no
T4	yes	4 (7.3)	2 (3.6)
	no	1 (1.8)	48 (87.3)

significance (p)= ns

Note: all frequencies are expressed as N (%)
ns= not significant

With regards to DCPR syndromes, the outline is more complex. We found an overall stability over time of the psychosomatic syndromes among control patients, except for a decrement of health anxiety cases ($p<0.05$) from third to fourth evaluation, and an increment of the frequency of demoralization from baseline to second follow-up ($p<0.05$) (*Tables 16-21*). Patients who attended cardiac rehabilitation, instead, displayed a significant reduction of illness denial ($p<0.05$), demoralization ($p<0.01$) and irritable mood ($p<0.05$) from baseline to the end of the rehabilitation program. Irritable mood cases diminished further from T2 to T3 ($p<0.01$), as well as Type A behavior ($p<0.01$), while the frequency of Alexythimia increased ($p<0.01$).

Table 16: Health Anxiety frequencies over time among experimental and control group patients

EXPERIMENTAL group

		T1	
		yes	no
T2	yes	0 (0)	3 (3.1)
	no	1 (1)	93 (95.9)

significance (p)= ns

		T2	
		yes	no
T3	yes	0 (0)	2 (2.6)
	no	3 (3.8)	73 (93.6)

significance (p)= ns

		T3	
		yes	no
T4	yes	1 (1.3)	0 (0)
	no	1 (1.3)	75 (97.4)

significance (p)= ns

CONTROL group

		T1	
		yes	no
T2	yes	11 (16.7)	2 (3)
	no	2 (3)	51 (77.3)

significance (p)= ns

		T2	
		yes	no
T3	yes	6 (9.8)	6 (9.8)
	no	7 (11.5)	42 (68.9)

significance (p)= ns

		T3	
		yes	no
T4	yes	2 (3.6)	1 (1.8)
	no	9 (16.4)	43 (78.2)

significance (p)= 0.021

Note: all frequencies are expressed as N (%)
ns= not significant

Table 17: Illness Denial frequencies over time among experimental and control group patients

EXPERIMENTAL group

		T1	
		yes	no
T2	yes	0 (0)	0 (0)
	no	6 (6.2)	91 (93.8)

significance (p)=0.031

		T2	
		yes	no
T3	yes	0 (0)	0 (0)
	no	0 (0)	78 (100)

significance (p)= ns

		T3	
		yes	no
T4	yes	0 (0)	2 (2.6)
	no	0 (0)	75 (97.4)

significance (p)= ns

CONTROL group

		T1	
		yes	no
T2	yes	10 (15.2)	0 (0)
	no	2 (3)	54 (81.8)

significance (p)= ns

		T2	
		yes	no
T3	yes	3 (4.9)	0 (0)
	no	5 (8.2)	53 (86.9)

significance (p)= ns

		T3	
		yes	no
T4	yes	1 (1.8)	0 (0)
	no	2 (3.6)	52 (94.6)

significance (p)= ns

Note: all frequencies are expressed as N (%)
ns= not significant

Table 18: Type A behavior frequencies over time among experimental and control group patients

EXPERIMENTAL group

		T1	
		yes	no
T2	yes	10 (10.3)	1 (1)
	no	7 (7.2)	79 (81.4)

significance (p)= ns

		T2	
		yes	no
T3	yes	0 (0)	0 (0)
	no	8 (10.3)	70 (89.7)

significance (p)= 0.008

		T3	
		yes	no
T4	yes	0 (0)	3 (3.9)
	no	0 (0)	74 (96.1)

significance (p)= ns

CONTROL group

		T1	
		yes	no
T2	yes	30 (45.4)	4 (6.1)
	no	4 (6.1)	28 (42.4)

significance (p)= ns

		T2	
		yes	no
T3	yes	18 (29.5)	5 (8.2)
	no	14 (23)	24 (39.3)

significance (p)= ns

		T3	
		yes	no
T4	yes	15 (27.3)	4 (7.3)
	no	5 (9.1)	31 (56.3)

significance (p)= ns

Note: all frequencies are expressed as N (%)
ns= not significant

Table 19: Irritable Mood frequencies over time among experimental and control group patients

EXPERIMENTAL group

		T1	
		yes	no
T2	yes	15 (15.5)	4 (4.1)
	no	14 (14.4)	64 (66)

significance (p)=0.031

		T2	
		yes	no
T3	yes	1 (1.3)	0 (0)
	no	13 (16.7)	64 (82)

significance (p)<0.001

		T3	
		yes	no
T4	yes	1 (1.3)	3 (3.9)
	no	0 (0)	73 (94.8)

significance (p)= ns

CONTROL group

		T1	
		yes	no
T2	yes	20 (30.3)	3 (4.5)
	no	3 (4.5)	40 (60.6)

significance (p)= ns

		T2	
		yes	no
T3	yes	14 (22.9)	7 (11.5)
	no	7 (11.5)	33 (54.1)

significance (p)= ns

		T3	
		yes	no
T4	yes	14 (25.5)	3 (5.5)
	no	3 (5.5)	35 (63.6)

significance (p)= ns

Note: all frequencies are expressed as N (%)
ns= not significant

Table 20: Demoralization frequencies over time among experimental and control group patients

EXPERIMENTAL group

		T1	
		yes	no
T2	yes	12 (12.4)	2 (2)
	no	16 (16.5)	67 (69.1)

significance (p)=0.001

		T2	
		yes	no
T3	yes	0 (0)	6 (7.7)
	no	10 (12.8)	62 (79.5)

significance (p)= ns

		T3	
		yes	no
T4	yes	2 (2.6)	6 (7.8)
	no	3 (3.9)	66 (85.7)

significance (p)= ns

CONTROL group

		T1	
		yes	no
T2	yes	15 (22.7)	13 (19.7)
	no	4 (6.1)	34 (51.5)

significance (p)= 0.049

		T2	
		yes	no
T3	yes	17 (27.9)	7 (11.5)
	no	10 (16.4)	27 (44.2)

significance (p)= ns

		T3	
		yes	no
T4	yes	14 (25.5)	2 (3.6)
	no	6 (10.9)	33 (60)

significance (p)= ns

Note: all frequencies are expressed as N (%)
ns= not significant

Table 21: Alexythimia frequencies over time among experimental and control group patients

EXPERIMENTAL group

		T1	
		yes	no
T2	yes	5 (5.2)	0 (0)
	no	1 (1)	91 (93.8)

significance (p)= ns

		T2	
		yes	no
T3	yes	1 (1.3)	16 (20.5)
	no	2 (2.6)	59 (75.6)

significance (p)=0.001

		T3	
		yes	no
T4	yes	7 (9.1)	5 (6.5)
	no	10 (13)	55 (71.4)

significance (p)= ns

CONTROL group

		T1	
		yes	no
T2	yes	22 (34.4)	2 (3.1)
	no	2 (3.1)	38 (59.4)

significance (p)= ns

		T2	
		yes	no
T3	yes	16 (26.7)	3 (5)
	no	8 (13.3)	33 (55)

significance (p)= ns

		T3	
		yes	no
T4	yes	14 (25.5)	4 (7.3)
	no	1 (1.8)	36 (65.4)

significance (p)= ns

Note: all frequencies are expressed as N (%)
ns= not significant

Also, the two clinical groups differed on the frequencies of several psychosomatic syndrome, at different time points, the control group showing the greater number of cases. Specifically, the differences refer to:

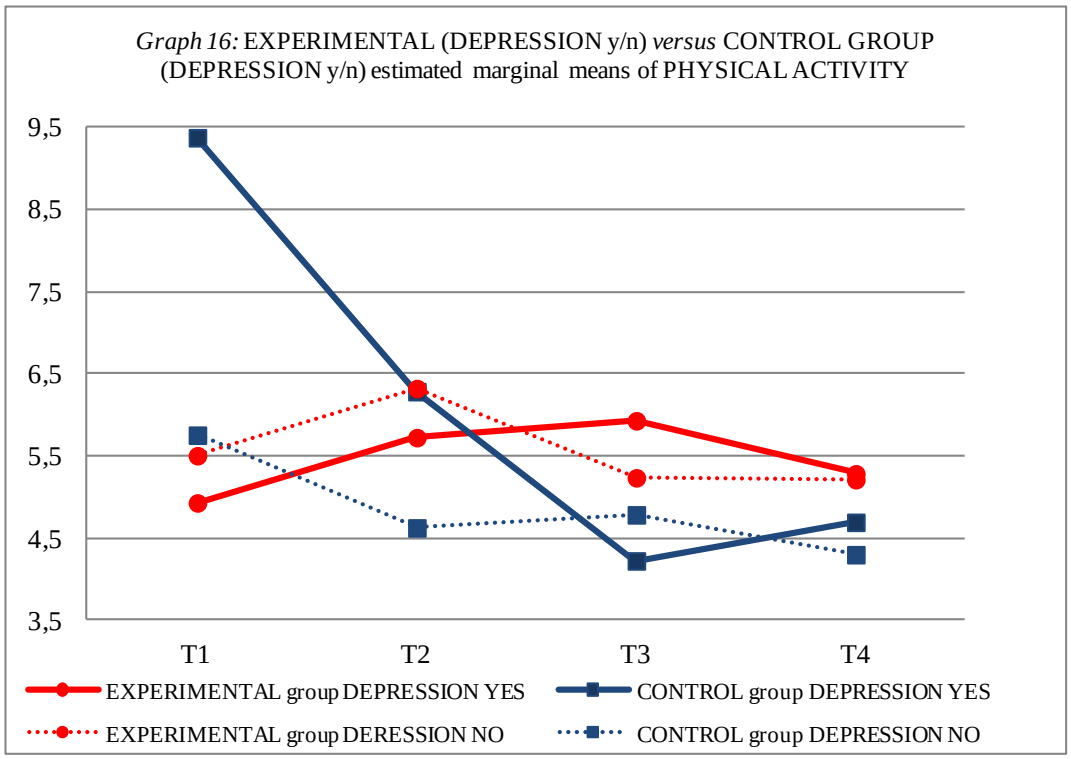
- Health Anxiety at T2 (3.1% *versus* 19.7%; $\chi^2_{(1)}$=10.19, *p*=0.001) and at T3 (2.6% *versus* 19.6%; $\chi^2_{(1)}$=9.82, *p*=0.002);
- Illness Denial at T2 (0% *versus* 15.2%; $\chi^2_{(1)}$=12.92, *p*<0.001);
- Functional Somatic Symptoms at T2 (0% *versus* 7.5%; $\chi^2_{(1)}$=5.16, *p*=0.023) and at T4 (0% *versus* 7.0%; $\chi^2_{(1)}$=3.90, *p*=0.048);
- Type A behavior at T2 (11.3% *versus* 51.5%; $\chi^2_{(1)}$=28.96, *p*<0.001), at T3 (0% *versus* 37.7%; $\chi^2_{(1)}$=33.87, *p*<0.001) and at T4 (3.9% *versus* 35.1%; $\chi^2_{(1)}$=23.07, *p*<0.001);
- Irritable Mood (19.6% *versus* 34.8%; $\chi^2_{(1)}$=3.78, *p*=0.052), at T3 (1.3% *versus* 34.4%; $\chi^2_{(1)}$=26.94, *p*<0.001) and at T4 (5.2% *versus* 31.6%; $\chi^2_{(1)}$=17.08, *p*<0.001);
- Demoralization at T2 (14.4% *versus* 42.4%; $\chi^2_{(1)}$=14.17, *p*<0.001), at T3 (7.7% *versus* 39.4%; $\chi^2_{(1)}$=19.56, *p*<0.001) and at T4 (10.5% *versus* 29.1%; $\chi^2_{(1)}$=6.20, *p*=0.013);
- Alexythimia at T2 (5.2% *versus* 37.5%; $\chi^2_{(1)}$=24.61, *p*<0.001) and at T4 (15.1% *versus* 32.8%; $\chi^2_{(1)}$=4.55, *p*=0.033).

3.7.3 Follow-ups – Psychological factors mediating lifestyles modification

3.7.3.1 DSM cluster of depressive disorders

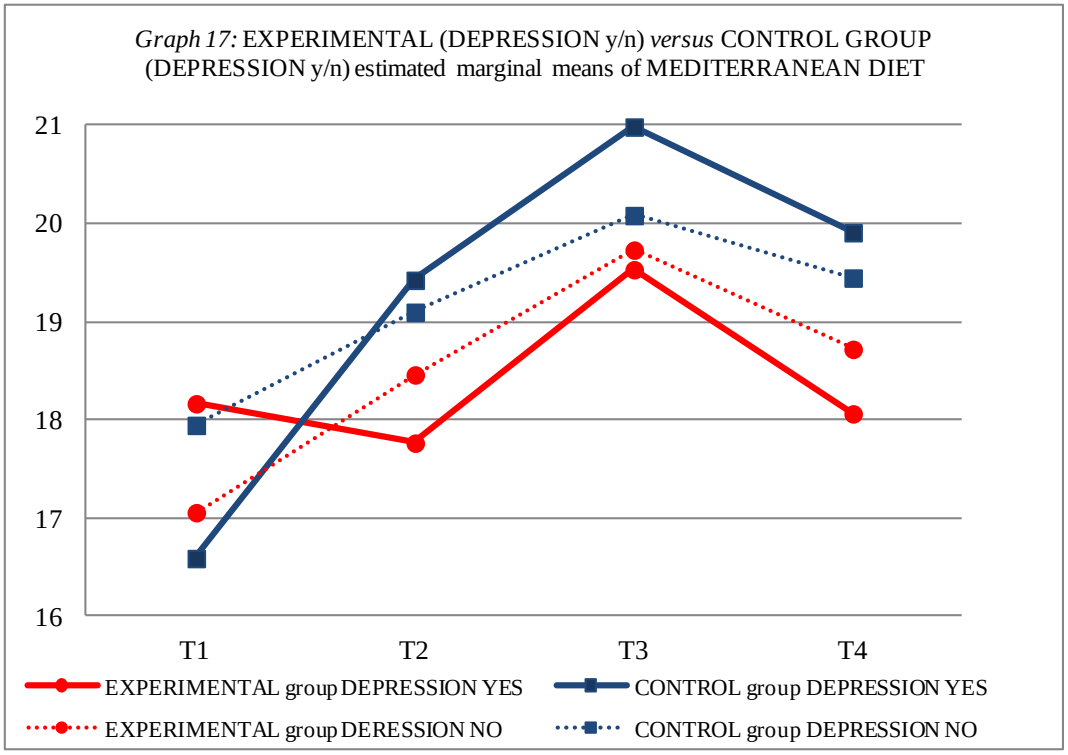
Having a DSM depressive diagnosis (major/minor depression or dysthymia) has been found to be a mediator on the effect of cardiac rehabilitation on physical activity and the Mediterranean diet modification. Indeed, the effect of the interaction "*time*" ^{X} "*group*" ^{X} "*depressive disorders*" on psychical activity ($F_{(2.783)}$=4.65, *p*=0.004) and on the Mediterranean diet ($F_{(2.689)}$=3.09, *p*=0.032) was significant.

With regards to physical activity, *Graph 16* shows that, even if they showed a higher baseline mean score than their counterparts in CR group (p<0.001), only people in the control group with a diagnosis of depression self-reported a significant decrement of physical activity scores from baseline to second evaluation (p=0.028), while all the other sub-groups remained stable over time. As depicted in the graph below, this sub-group also showed higher baseline scores than that of controls without the depressive diagnosis (p=0.005). Also, patients without diagnoses significantly differed between the 2 clinical groups at T2 (p=0.038), those of the experimental group being higher.



Graph 17 shows that patients of the CR group who did not satisfy criteria for a depressive diagnosis displayed an improvement of Mediterranean diet habits from baseline to the end of the rehabilitation program (p=0.034), while those who did meet the criteria significantly improved from the end of it to 6-months follow-up (p=0.030) and then showed a deterioration from T3 to 1-year evaluation (p=0.028). Depressed control subjects, instead, significantly improved from baseline to

1-month follow-up (p=0.014), then remaining stable, while their counterparts without depression improved after 6-months (p=0.033).



Graph 17: EXPERIMENTAL (DEPRESSION y/n) *versus* CONTROL GROUP (DEPRESSION y/n) estimated marginal means of MEDITERRANEAN DIET

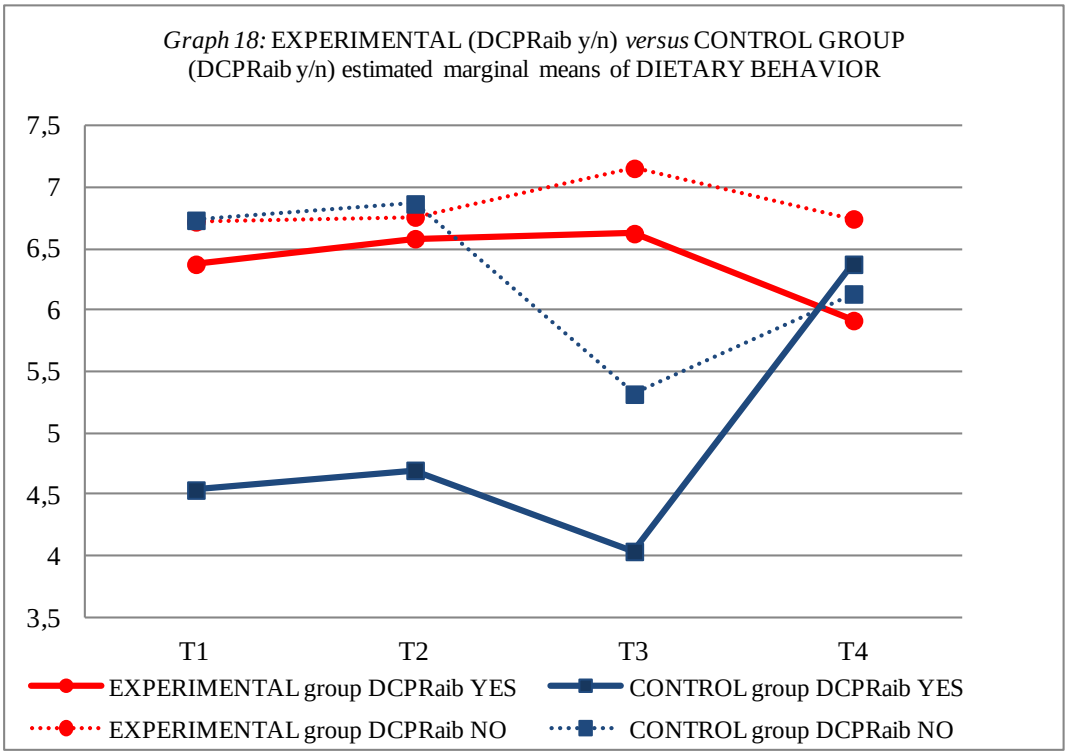
3.7.3.2 DSM cluster of anxiety disorders

Having a DSM diagnosis of anxiety has not been found to be a mediator of the effect of cardiac rehabilitation on any of the lifestyles considered.

3.7.3.3 DCPR cluster of "abnormal illness behavior"

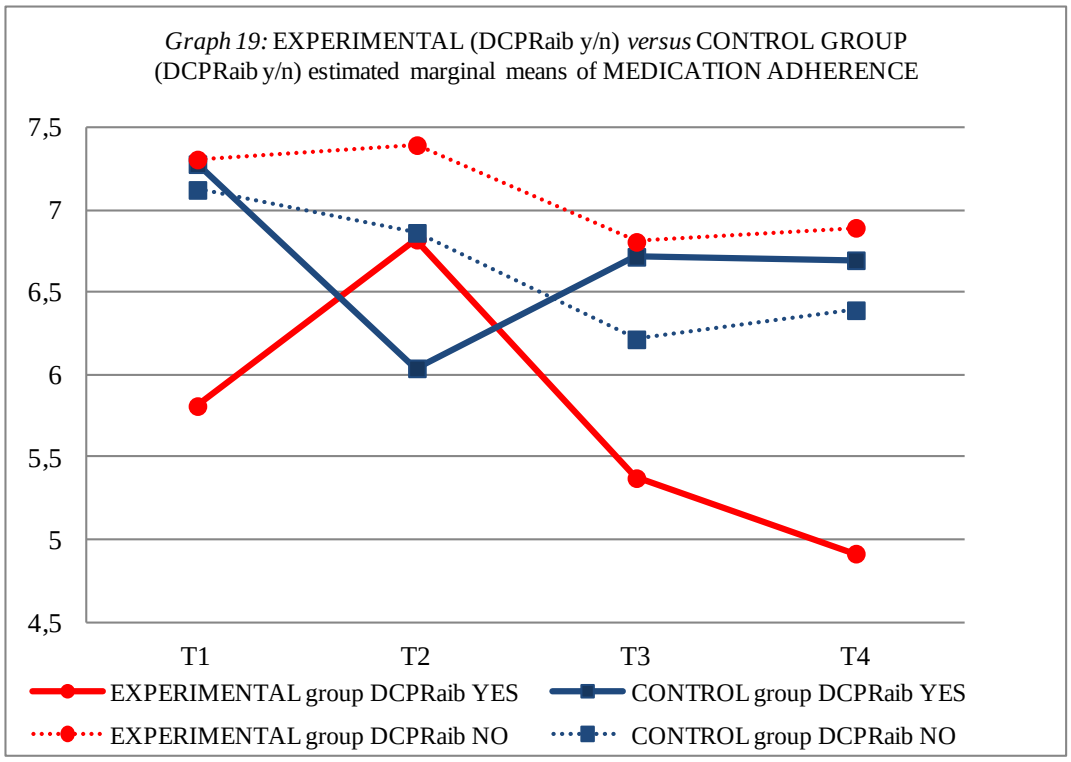
DCPR cluster of abnormal illness behavior has been found to be a mediator of the effect of cardiac rehabilitation on dietary behavior and on medication adherence. The interaction "*time*" ^{X} "*group*" ^{X} "*AIB cluster*" on dietary behavior ($F_{(2.622)}$=2.74, p=0.051) and on medication compliance ($F_{(2.732)}$=3.23, p=0.027) was significant.

Specifically, we found that only in the control group patients without a syndrome belonging to DCPR cluster of "abnormal illness behavior" showed a significant decrement of dietary behavior scores (p=0.049) from T2 to T3, then remaining stable (*Graph 18*). On the contrary, patients with at least one of those syndromes remained stable over time and then, from 6- to 12-months follow-up, displayed a significant increase in the mean scores (p<0.001). At T3, we found significant differences on the mean scores of dietary behavior between CR and control group patients, depending on the presence (p=0.006) or absence (p=0.001) of one of the DCPR AIB cluster, the experimental group having higher scores in both cases. Also, between patients with or without at least one AIB syndrome, we found statistically different scores at baseline (p=0.004) and T2 (p=0.008), only in the control group (*Graph 18*).



With regards to medication adherence, we did not find any modification of MMAS mean scores of control patients with or without a syndrome of DCPR abnormal illness behavior cluster, except for a worsening from the first to the second evaluation (p=0.042) of those with AIB (*Graph 19*). In the CR group, instead, both types of patients (with or without an AIB psychosomatic syndrome)

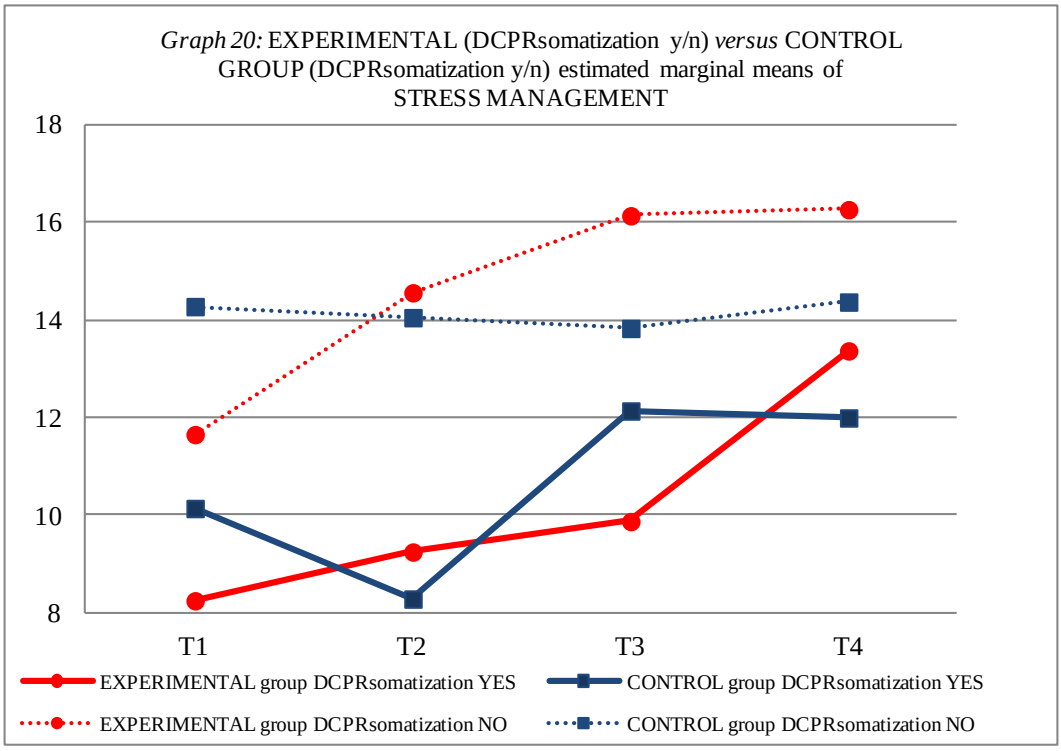
showed a significant deterioration starting from the end of the rehabilitation program to the 6-months follow-up (with DCPR AIB syndrome: p=0.027; without DCPR AIB syndrome: p=0.005). As showed in *Graph 19*, control patients with at least one AIB psychosomatic syndrome self-reported significant better MMAS scores than those of their counterparts in the CR group at baseline (p=0.005), at 6-months (p=0.034) and 1-year follow-ups (p=0.012). Among patients in the experimental group, moreover, we found statistical differences of MMAS mean scores between subjects with or without syndromes, at baseline (p<0.001), 6-months (p=0.003) and 1-year follow-up (p<0.001), the former having lower scores.



3.7.3.4 DCPR cluster of "somatization"

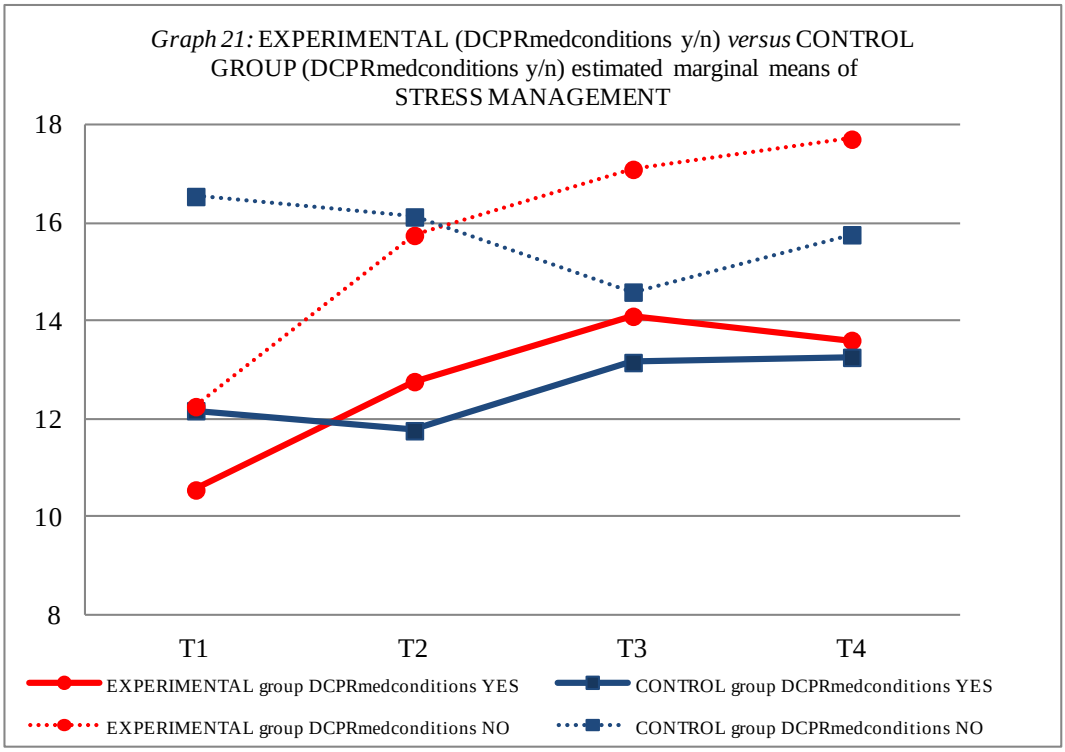
DCPR cluster of somatization has been found to be a mediator of the effect of cardiac rehabilitation on stress management. Indeed, the interactions "*time*" X "*group*" X "*somatization cluster*" on stress management was found to be highly significant ($F_{(2.767)}$=5.76, p=0.001).

Patients of the CR group without any somatization syndrome progressively improved their level of stress management from baseline to 6-months follow-up (T1-T2: $p<0.001$; T2-T3: $p=0.006$), then remaining stable at 1-year follow-up. On the contrary, those who satisfied criteria for at least one DCPR somatization syndrome did not significantly improve over time. Control subjects without diagnoses did not show significant variations over time, while those with a DCPR somatization disorder improved from T2 to T3 ($p=0.025$). As shown in *Graph 20*, CR patients without somatization syndromes self-reported worse stress management scores than those of their counterparts in the control group at baseline ($p=0.002$), and then better scores at 6-months ($p=0.002$) and 1-year follow-ups ($p=0.016$). Also, among patients with or without at least one of the syndromes in each clinical group, we found statistically different scores at T2 ($p=0.013$) and T3 ($p=0.001$) among CR subjects, and at baseline ($p=0.007$) and T2 ($p<0.001$) among controls.



3.7.3.5 DCPR cluster of "psychological factors frequently affecting medical conditions"

DCPR cluster of psychological factors frequently affecting medical conditions has been found to be a mediator of the effect of cardiac rehabilitation on stress management. The interaction "*time*" X "*group*" X "*psychological factors frequently affecting medical conditions cluster*" on stress management was found to be significant ($F_{(2.795)}$=2.70, p=0.050).



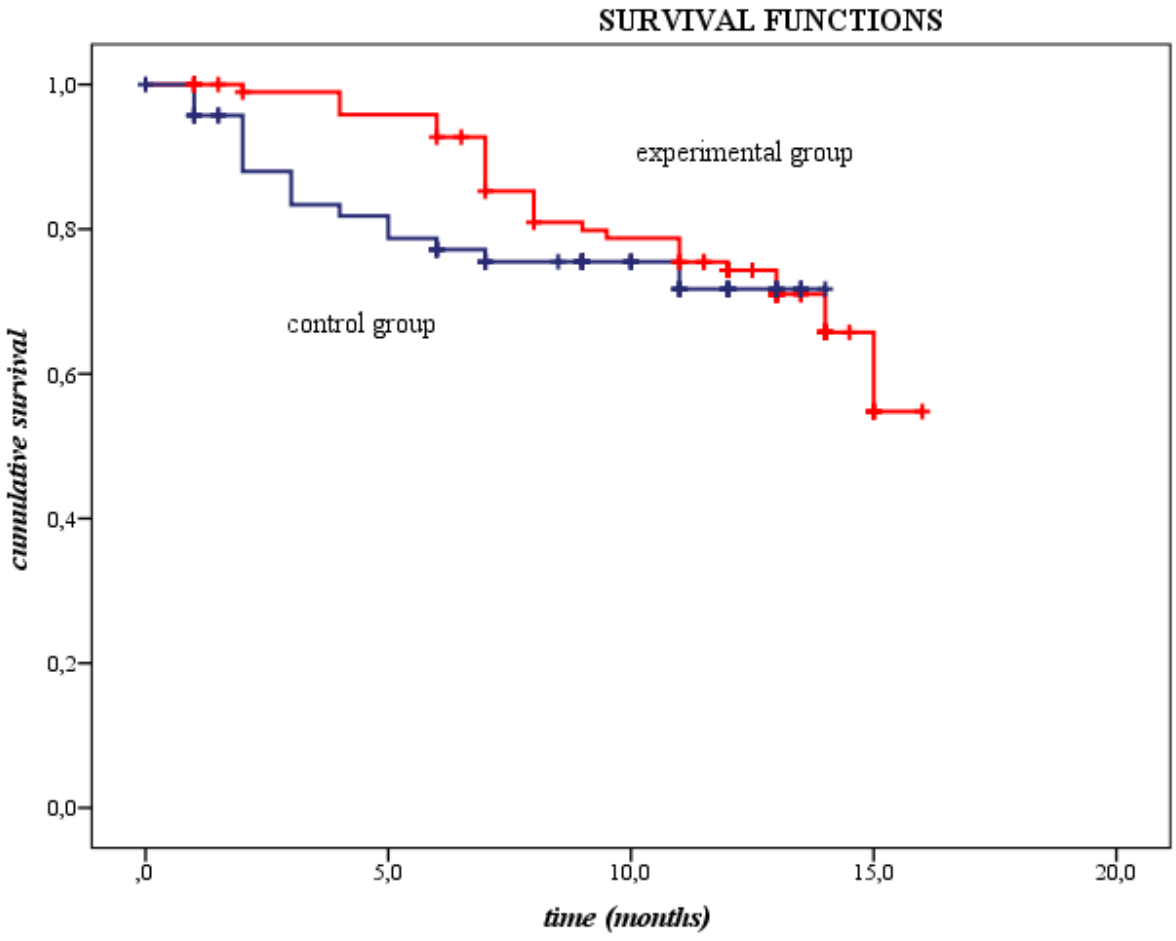
CR patients both with and without at least one of the above-mentioned syndromes improved their level of stress management from baseline to the end of the rehabilitation (respectively p=0.014 and p<0.001), then remaining stable at 6-months and 1-year follow-ups (*Graph 21*). On the contrary, control subjects with or without diagnoses did not display significant variations over time. As shown in *Graph 21*, CR patients without psychosomatic syndromes belonging to the cluster self-reported worse stress management scores than those of their counterparts in the control group at baseline (p<0.001), and then better scores at 6-months follow-up (p=0.019). Also, among patients with or without at least one of the syndromes in each clinical group, we found statistically different

scores at all stages, except for controls at T3 (experimental group – DCPR y/n: T1 p=0.046, T2 p=0.001, T3 p<0.001, T4 p<0.001; control group – DCPR y/n: T1 p=0.001, T2 p=0.003, T4 p=0.051); in each case, those without any syndrome displayed higher levels of stress management.

3.7.4 Follow-ups – Survival analyses

Kaplan-Meier analysis was performed on 103 patients of the CR group and on 71 patients of the control group: the number of cardiac events assessed has been 29 in the first case and 17 in the second. The survival analysis did not show any significant difference between the two survival curves (Log Rank $\chi^2_{(1)}$=0.674, p=0.412): CR and control group did not statistically differ on the basis of the number of cardiovascular events associated with recurrences.

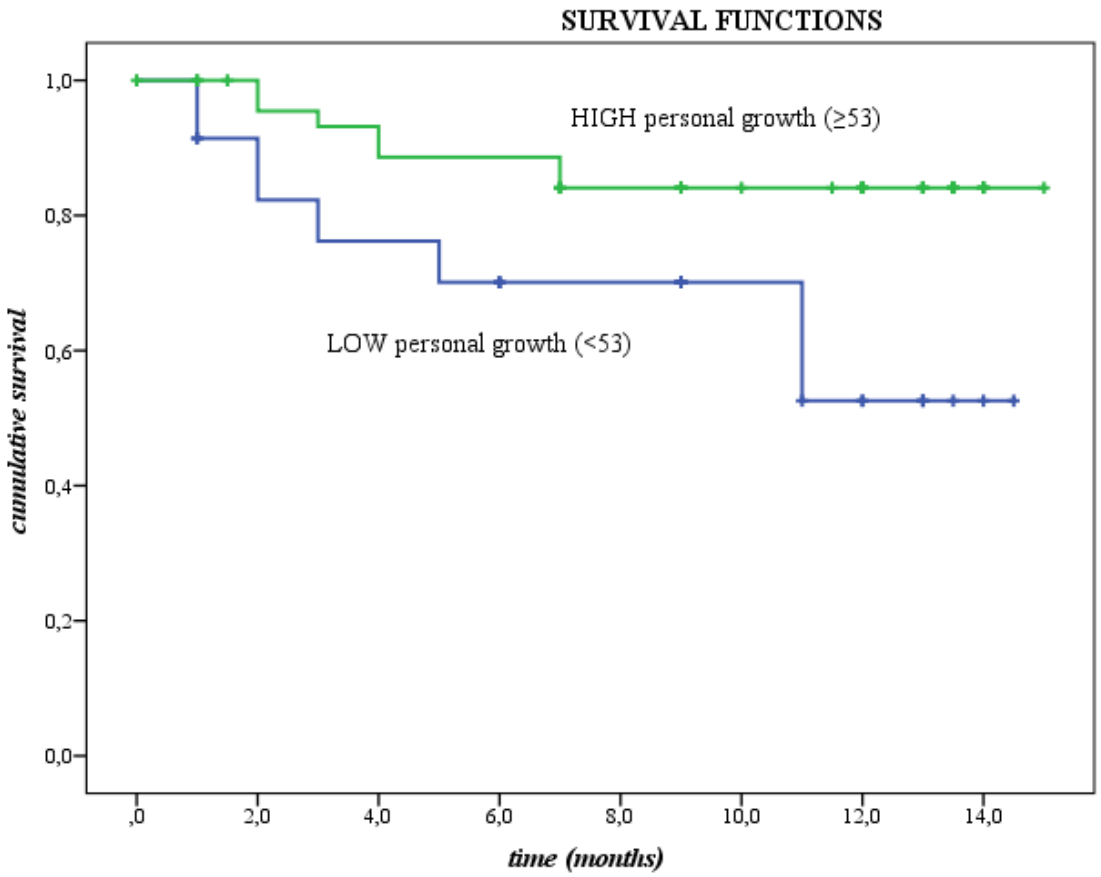
Graph 22: 12-months follow-up survival curves of experimental and control group



Graph 22 shows the trend of the two survival functions; the axis of abscissas shows the survival time expressed in months while the axis of ordinates shows the presence (1) and the absence of the event (0). As highlighted in *Graph 22*, the two groups have similar trends over time.

Although there were no differences between the two clinical groups, it has been examined whether any psychological characteristic might have predicted recurrence, analyzing different sub-groups. Cox regression showed that PWB dimension of "personal growth" significantly predicted cardiac recurrence only among patients who underwent non-invasive medical procedures, regardless of the group (Exp(B)=0.966, 95%CI= 0.934-0.999; Wald=4.074, *p*=0.044).

Graph 23: 12-months follow-up survival curves of patients who underwent non-invasive medical procedures with high or low level of personal growth



Since the parameter B is negative (B=-0.035), this means that to a decrease of 1 unit of PWB personal growth scores corresponds to an increase of the risk of recurrence equal to 3.4% [100% - (100% x 0.966)]. On the basis of the median value (median=53), personal growth scores were then dichotomized (low level of personal growth <53; high level of personal growth ≥53) and used as a between-subjects factor in the Kaplan-Meier survival analysis. As shown in *Graph 23*, the survival curve of those who have higher personal growth is significantly different from that of patients who self-reported lower scores on that scale. Subjects with a score of personal growth <53 (N=35) showed a greater number of relapses (N=13 *versus* N=7; Log Rank $\chi^2_{(1)}$=6.252, *p*=0.012) than patients with higher personal growth score (N=48).

3.8 DISCUSSION

One of the main objectives of this research was to evaluate lifestyles and quality of life modification over time, differences between the two clinical groups and the role played by Cardiac Rehabilitation in this process.

The first lifestyle examined was smoking habits. Many epidemiological studies have shown that cigarette smoking is associated with an increased risk of myocardial infarction and death from coronary artery disease, including sudden death (35). Despite this, the research has shown that smoking cessation after a first coronary event significantly reduces the risk of mortality, hospitalization rates and reoccurrence (260-262). Smoking abstinence is thus very relevant to patients with established coronary heart disease and it is one of the fundamental objectives (both short and long term) of any rehabilitation program. In our sample, before the cardiac event control patients were more frequently smokers (67.1%) than the experimental group (52.80%), but they did not differ statistically. At baseline, a greater percentage of control patients did not stop smoking (22.2% *versus* 6.2%). While the sub-group of patients who did not stop even after attending cardiac rehabilitation remained quite stable over time (5.1%), the smokers among controls already

decreased in percentage after one month, being 9.1% at 1-year follow-up. Although the smoking rate was overall rather low in the experimental group – some studies showed that over half of those patients who were smokers prior to hospitalization for coronary heart disease continue smoking after discharge (263, 264), it could be arguable that CR did not have a proactive effect in reducing the number of patients who continued to smoke, but only a protective effect against those who had already stopped smoking. However, in the light of the results shown by control group (in terms of stability of non-smokers percentage), it could be hypothesized that the effect of the Cardiac Rehabilitation appear rather modest. This finding is supported by previous research (265-267) that highlighted that rehabilitation did not influence smoking habits. Also, it has been shown that smoking habits at the time of MI are the key aspect to determine the continuation of cigarette smoking (266). Cardiac patients who continue smoking after hospitalization can be defined as highly dependent smokers with no or low future intentions to stop (268). Earlier research showed that providing brief cessation support is not effective enough to help cardiac patients to stop smoking permanently (269, 270). Hence, more intensive smoking cessation interventions for this patient group are needed.

It has been shown that the risk of cardiovascular disease and myocardial infarction incidence increases for each level of body mass index (BMI) greater than the threshold value (BMI=25); conversely, weight lost is associated with a significant reduction of cardiovascular mortality risk (33, 34). In this research, neither differences between the two clinical groups, nor an overall modification of BMI over time, have been found. Therefore it could be argued that BMI was not indirectly modified by attendance to CR. Given that more than a half of the subjects had and maintained a BMI greater than 25, we identified this as a potential limit of the rehabilitation program. These findings are in contrast with outcomes of previous studies that showed the combination of dietary intervention and exercise being successful to reduce (from 4% to 9%) body-mass index (149, 182, 183).

Physical activity is a key component of Cardiac Rehabilitation programs and of any program of secondary prevention. Research demonstrated the effectiveness of physical training to improve physical activity (271), by enhancing both the training of good heart functioning, the physical form and the lipid profile of the individuals (272). Moreover, physical activity appears to improve indirectly negative emotions such as anxiety (273) and depression (274). As reported in previous studies (28), it is very common that patients in post-acute phase refer high levels of physical inactivity. Despite a similar situation it has also been depicted in our sample, the physical training attended by experimental patients seems to have been effective, at least in maintaining such values stable over time. Indeed, the effect of CR seems to be more protective against a deterioration, than proactive towards an improvement. It has been seen that rehabilitation programs focused only on physical exercise can improve physical performance, muscle strength and to restrain symptoms of dyspnoea and angina. However, programs that combine psychological and educational components to mere physical exercise (such as the one held at the rehabilitation centre at Bellaria Hospital in Bologna), foster psychological well-being, social recovery, return to work and contribute to the reduction of risk factors (275). Many studies (6) confirmed that a regular moderate physical activity has a protective effect, and increase well-being and quality of life, while findings concerning the effect on the decrement of risk factors are weaker and contrasting (276). In the post-acute phase both groups were mostly sedentary as defined by their physician at baseline, but after completion of CR, the experimental group remained at least stable over time, while the control group was likely to get worse. A review (277) highlighted that exercise-referral schemes appear to increase physical activity levels only in specific populations, people who are not sedentary but already slightly active, older adults and those who are overweight (but not obese). Moreover, it has been found that increases in the level of physical activity may not be sustained over time (277). It can therefore be hypothesized that the CR exerts a protective effect on physical activity deterioration, and it also allows a stability at 1-year follow-up, as already highlighted by Giannuzzi et al. (204). Non-attendance to Cardiac Rehabilitation programs might lead to a progressive deterioration of the

levels of physical activity. Our results also showed that physical activity is somehow related to mood disorders. Depressed patients who did not undergo CR self-reported significantly worse levels of physical activity after a month from discharge, while those who have not received such diagnosis remain constant over time. Mood disorders have been shown to worsen adherence to healthy lifestyles such as physical activity (278) and this deterioration may occur after 30 days of post-acute phase (279). Depressive disorders involve both psychological (such as sadness and loss of interest) and autonomic (such as tiredness and fatigue) symptoms which contrast with the implementation of regular exercise. Moreover, depression leads to misrepresented perception of the ability to complete a task (280, 281) due to the greater emphasis on obstacles rather than positive aspects (280). CR programs promoting physical activity should trigger a bidirectional link between the two factors (mood and physical activity) to allow an improvement of both aspects (274).

Another lifestyle examined in this research is dietary habits. On November 16th, 2010, UNESCO recognized the Mediterranean diet pattern as an Intangible Cultural Heritage of Italy, Greece, Spain and Morocco, because of its positive effect on cellular aging, cardiovascular diseases and obesity. This diet - characterized by a high consumption of fruit, vegetables, whole grains, olive oil, fish and (moderate) wine – has been shown to be adequate for the prevention of cardiovascular diseases. The beneficial effects of the Mediterranean diet in reducing risk factors such as total cholesterol, LDL cholesterol, blood pressure and then the incidence of myocardial infarction, are well known (282). However, in the present study, CR does not seem to improve the Mediterranean diet, especially in the case of patients who underwent invasive surgery did not change over time. On the contrary, patients who received a non-invasive medical procedure showed a slight improvement in their levels of Mediterranean diet at 6-months follow-up but did not maintain these results after one year.

The Mediterranean diet also seems to be associated with mood disorders, as only in the absence of such diagnosis, among experimental subjects an increment of Mediterranean diet consumption has been detected at 6-months follow-up. With regards to dietary behavior, the CR has been found to be effective in changing them. While at baseline and after one month the two groups did not differ, at

6-months follow-up, experimental subjects displayed more appropriate behaviors than those of the control group. Even if an improvement in diet is one of the first aims taken into account by CR programs by means of patients' education about diet composition and suggestions concerning how to change the poor dietary habits, the data does not seem to be indicators of an overall positive effect of the CR on diet. Given the high frequency of risk factors closely related to nutrition at baseline, such as overweight and obesity (experimental group=67.9%, control group=61.2%), hypercholesteroloemia (experimental group=33.3%, control group=54.1%) and diabetes (experimental group=21.3%, control group=24.7%), as detected in other studies (283), it is very important that the Cardiac Rehabilitation would improve eating habits. The present data seems to be inconsistent with the findings of Giannuzzi et al. research (2008). The study showed the comparison of two different rehabilitation treatments (intensive *versus* conventional) and in both cases there was a significant improvement in food issues after six months. The lack of physical activity and diet improvement also reflect findings concerning the analysis of BMI which did not show any change over time. Despite Cardiac Rehabilitation appearing to have a protective role against worsening of sedentary habits, the poor effect on diet modification did not allow a weight loss among high risk subjects. In the literature, there is evidence that nutritional intervention is effective in producing positive changes in patients attending Cardiac Rehabilitation, contributing to secondary prevention of cardiovascular diseases (284, 285). Randomized controlled trials have shown dietary therapy benefits related to a significant reduction in fatal and non-fatal events and total mortality (286). However, other studies have shown that a strictly prescriptive approach is ineffective to achieve long term therapeutic goals (such as weight loss and control of the concentration of blood glucose), especially among diabetic and overweight patients (287, 288). On the contrary, new educational programs and treatment strategies, based on motivational approach and active involvement of the patient, have proven their effectiveness, especially in chronic disease (289, 290). It is therefore conceivable that, in addition to other characteristics of the sample considered, a lack of motivation could have played a key role in the non-change of body weight through healthy eating habits and

physical activity. Motivational interview (291) is of particular utility when people are undecided or not yet fully motivated to change. It represents an approach to help individuals building a commitment and to reach a decision to change. It could allow to enhance patients' intrinsic motivation and let the change become a result of a personal choice, rather than an external imposition. The motivational interview has been successfully used with cardiac patients in a randomized trial on behavioral change before a coronary revascularization (292).

Within the rehabilitation programs there were also voluntary group meetings of "Stress Management", attended by most of the CR patients, that seem to have had a positive effect. The effect of Cardiac Rehabilitation on the ability to manage stress in daily life resulted to be significant, as highlighted by other previous research (56, 204, 275, 293). Despite a baseline lower capacity to cope with stress, the experimental group strengthened better coping skills over time becoming more functional than the control group, and remaining stable even after one year. This aspect does not seem to be influenced by the type of medical procedures the patients underwent. Although the experimental group subjects have been subjected to invasive surgery more frequently and – presumably – to a more stressful situation, thanks to the influence of Cardiac Rehabilitation they have been able to handle the arisen stress positively, and to implement and maintain this ability over time (204). Further analyses showed that the ability to cope with stress management seems to be influenced by the DCPR somatization syndromes. Indeed, the effect of the rehabilitation program seems to be limited only to the sub-group of subjects who did not receive any of these psychosomatic diagnosis. The experimental group improved and differed from the control group only in the case of the sub-groups of patients who did not present any of the psychosomatic syndromes related to somatization. These results confirm the findings from Porcelli and colleagues (294) showing that in a population with medical conditions, the presence of somatization was predictive of a lack of improvement concerning the perception of symptoms after having received a treatment. Persistent somatization is associated with certain psychological characteristics theoretically consistent with a lower probability to respond to a treatment, such as long-term

somatic symptoms, somatic amplification, conviction of disease, that could reduce the ability to perceive a reduction in symptoms after treatment (295).

Another lifestyle taken into account was quality of sleep. In literature there are not many studies that examine the quality of sleep prior to and subsequent to cardiac pathology. Quality of sleep is a very important aspect in clinical practice, both for the widespread problems among the general population related to the beginning of sleep and sleep maintenance (296, 297), and relevance of sleep disorders as secondary symptoms of psychological and medical diseases. As described by Hemenway (298), we also found a relationship between sleep and cardiovascular diseases: the entire sample self-reported borderline baseline scores of quality of sleep. It is well-known that the chronic symptoms of cardiovascular diseases involve a disturbed sleep characterized by a marked reduction in the amount of hours of effective rest and an increase in the time spent awake on the bed (299). The CR has shown a mediator effect on the improvement of this lifestyle. At the end of the rehabilitation program the experimental group shows a significantly better quality of sleep than the control group. However, these results do not seem to persist over time and one year follow-up of the two groups did not differ, contrary to the finding reported by Schiza et al. (300). The Authors showed that after acute coronary syndrome patient had altered sleep parameters, leading to poor sleep quality; however, these alterations tend to fade away after 6 months confirming the link with the underlying disease. Therefore, it is possible to conclude that CR programs have temporarily facilitated an improvement in the quality of sleep, but this improvement does not persist over time, so that after a year, the control group and the experimental group have similar qualities of sleep.

With regards to medications adherence through the self-assessment questionnaire MMAS, contrary to what was expected and what is known in the literature regarding the positive effects of CR on drug compliance (301), the sample does not seem to maintain a good medications adherence over time. We found no significant differences between the experimental and control group on compliance, the control group showing a worsening of drug adherence after only one month from discharge, the experimental group after 6 months from the end of the rehabilitation program. This

may have severe adverse effects on the improvement of other risk factors, such as hypertension, hypercholesteroloemia, and diabetes, which require medications (283). Some research has shown that adherence to medical prescriptions, also including the pharmacological regimen, may be mediated by social support (302). A meta-analysis (303) highlighted that those who have low levels of social support show a risk up to 1.35 times higher to not adhere to medical prescription than those who are socially supported. The interesting thing is that the lack of social support also appears to mediate smoking cessation and adoption of healthy behaviors (304). The social and emotional support can act as a mediator of unpleasant emotion, providing encouragement to adherence of the instructions, but also providing material support, for example by accompanying the patient to the rehabilitation meetings (302). In addition, support may allow for the maintenance of good self-esteem, especially needed when significant changes in lifestyles are required, such as those experienced by cardiac patients (302). Pharmacological adherence seems to be subjected to the effect of the DCPR cluster "Abnormal Illness behavior". This specific result is quite controversial; our findings highlight a negative effect of CR attendance, as it seems that when one of these syndromes are present it is even preferable not to participate to any rehabilitation program. CR patients with AIB benefited from rehabilitation at one-month follow-up, not differing from the control group however, but after six months show significantly worse levels of drugs compliance than the control group. Pilowsky (305) defines abnormal illness behavior as a way of perceiving one's own health in an inappropriate manner. This misperception persists even when a physician offers a reasonable explanation of the nature of the disease and appropriate therapy. An incorrect self-evaluation of one's own health status is then associated, even when attending a structured rehabilitation program, to a poor pharmacological compliance, as highlighted in previous studies (306). The intention whether to adhere or not to drug prescriptions derive from the knowledge and beliefs about a specific disease and its treatment (307). Thus the presence of abnormal illness behavior may have an adverse effect on the intentions of these populations. We can hypothesize that specific syndromes, such as Illness Denial (the most represented syndrome of AIB cluster among

experimental subjects), could have had a main role against the adoption of healthy behaviors, undermining adherence to treatment and lifestyles modification (308).

Another objective was to evaluate the health-related quality of life. Some studies showed that the CR significantly improve the quality of life and such improvements can persist for more than a year (309). Despite baseline scores worse than those of controls, probably due to a greater severity of the cardiovascular illness that could have caused physical, psychological, social and occupational restrictions, adversely affecting quality of life (310), CR patients' health-related quality of life mean scores were similar to those of controls at the end of the rehabilitation program, and then higher after six months, being stable after one year. SF-36 Italian validation study (216) has defined normative values for the general population ("physical health-related quality of life": mean=72.69, SD=25.93; "mental health-related quality of life": mean=69.46, SD=24.87; "health-related quality of life": mean=72.95, SD=26.39). Comparing normative means with those of our sample, we can observe that experimental group baseline mean score of physical health-related QoL is more than a standard deviation lower than that of the general population, while from 6-months after admission it self-reported scores similar to those of the general population. The control group, instead, maintains acceptable levels quality of life stable over time. This finding contrasts with results of Chan et al. study (310) who found an overall improvement of patients' quality of life at 6-months follow-up, whether or not they attended the cardiac rehabilitation program. It could be hypothesized that improvement of quality of life may be mediated by enhancement of physical activity, quality of sleep and stress management elapsed during the same time period (276). Moreover, a systematic review focused on a rehabilitation program based only on the component of exercise (311), found no differences between the experimental and the control group in quality of life improvement. Thus, it could be hypothesized that one of the most important contributions to quality of life improvement could be psycho-social components of rehabilitation programs.

From the psychological and psychosomatic points of view, both the experimental and the control group satisfied criteria for DSM depressive and, to a lesser extent, anxious diagnoses, and for DCPR psychosomatic syndromes.

A study of Balestroni and Giannuzzi (312) highlighted the relevant frequency of patients referred to cardiac rehabilitation who present emotional reactions above the clinical cut-off: 27.8% anxiety, 22.1% health-related fears and 10% depression. In line with this data, the baseline evaluation of this sample revealed a high incidence of psychological factors were frequently associated to cardiovascular disorders in the literature. As in Rafanelli et al. research (49), the diagnosis of minor depression has also been taken into account , occurring to a greater extent than major depression. in the same study, the authors have identified minor depression as a potential cardiovascular risk factor in patients who had undergone coronary artery bypass surgery, and therefore they underlined the importance to include the diagnosis of minor depression in the evaluation of these types of patients, in addition to that of major depression. Also in another study by the same authors (50), minor depression has been proved to be a variable that can affect patients with congestive heart failure survival, in terms of increased numbers of re-hospitalizations and cardiac death. At baseline, only a small percentage of patients satisfied criteria for dysthymia in contrast to the findings of Baune et al. (64) who claimed that dysthymia is more frequently associated with acute coronary syndrome than with major depression. Rafanelli and colleagues (65) found a 13.4% prevalence of dysthymia among patients with acute coronary syndrome and showed that it is a risk factor for cardiac morbidity at 2.5 years follow-up.

Anxiety disorders appeared to be associated with certain behavioral risk factors linked to cardiovascular disease susceptibility: compared to non-anxious individuals, those with high levels of anxiety tend to adhere to a healthy diet less frequently, to abuse alcohol and drugs, to smoke, to have a poor medical therapy compliance, to sleep badly and to have poor physical activity (52, 81). Among anxiety disorders, only generalized anxiety disorder has been detected to a greater extent in our sample. GAD has been associated with a 5-folds higher cardiovascular risk in the general

population (313) and a study of Martens and colleagues (80) found that patients with stable coronary artery disease and generalized anxiety disorder had a 74% risk of other cardiovascular events (such as stroke, myocardial infarction and cardiac death), flatly higher than those with only coronary artery disease.

Cardiac rehabilitation attendance has been associated with a significant reduction in the cases of major and minor depression, and generalized anxiety disorder, maintained at 12-months follow-up. In the light of these findings, a positive impact of cardiac rehabilitation is conceivable on such psychiatric disorders, in line with what has been shown in the literature (275, 314, 315). Yohannes and colleagues (314) found that a 6-week rehabilitation program improved not only quality of life and physical activity, but also the levels of depression and anxiety (assessed by means of Hospital Anxiety and Depression Scale), maintaining these benefits at 12-months follow-up. In the study by Milani and Lavie (315), cardiac rehabilitation was associated with the reduction of both depressive symptoms and mortality. In the above-mentioned study, patients were considered depressed if they reported a score greater than 6 on the depression scale of SQ. It can be assumed that the decrement of the diagnoses of major and minor depression found in the experimental group could have been promoted by physical exercise, as shown in a previous study (316).

With regards to psychosomatic syndromes, in line with previous research focused on DCPR among a variety of clinical populations (63, 89, 100, 103, 224, 225), we found a high prevalence of Irritable Mood, Demoralization, Type A behavior, and Alexythimia ("psychological factors affecting medical conditions" cluster), and, to a lesser extent, psychosomatic syndromes within the "abnormal illness behavior" (Health Anxiety and Illness Denial) and "somatization" (Functional Somatic Symptoms and Persistent Somatization) clusters. Also in this case, the rehabilitation program has been found to be associated to a reduction of the frequencies of irritable mood, demoralization, Type A behavior and illness denial, while, an overall stability of DCPR syndromes among control subjects, except for an increment of demoralization cases has been observed. The finding of an association between cardiac rehabilitation and reduction of some of the psychosomatic

syndromes, and its maintenance even a year after the end of the rehabilitation program, constitutes an innovative result of considerable interest, especially in the light of findings in literature showing the negative association between specific psychosomatic syndromes, such as type A behavior and demoralization, and cardiovascular diseases. Recurrent Coronary Prevention Project Study (317) showed that group therapy aimed to behavior modification reduced the number of subjects with type A behavior, negative emotions intensity and also cardiovascular mortality and nonfatal myocardial infarction rates. Moreover, a recent meta-analysis (318), focused on the effectiveness of psychological treatments for patients with cardiovascular disease, has highlighted that a treatment aimed to reduce type A traits as a primary goal, makes the treatment itself more effective than other types of treatment with different objectives. The most relevant clinical features of DCPR type A behavior pattern, such as excessive degree of involvement in work and pervasive sense of time urgency, may elicit stress-related physiologic responses that precipitate or exacerbate symptoms of the medical condition. In one study (100), 40% of the patients presented type A behavior; however not all cardiac patients present with type A behavior. In those who do, the onset of irritable mood may interact with type A personality characteristics to increase psychosomatic vulnerability. In those who do not present type A features, the clinical development of symptoms may be different.

Other relevant psychosomatic feature related to medical conditions are illness denial and demoralization. For some patients, denying the burden of physical disease may be an adaptive coping mechanism in some circumstances and at certain degrees. However, denying, distorting, or minimizing clinical relevance, personal responsibility and the need for treatment may have serious health-related consequences. Other patients could react to the same adverse event with demoralization, characterized by prolonged and generalized feelings of helplessness, hopelessness, or giving up, and the awareness of being unable to cope with a pressing problem or of having failed to meet one's own or others' expectations (91). The clinical relevance of demoralization in medical diseases is highlighted by its high prevalence in all medical settings and its low frequency among

healthy people (92, 224): demoralization may be then strictly related to the onset of medical disturbances and do not simply identify a generic psychological distress.

Type D personality has been diagnosed to one fifth of the sample. Already in 1995, Denollet (129) highlighted that this type of personality increases up to six times the risk of cardiac mortality, independently from other risk factors. By administering DS-14 in coronary patients, it was possible to demonstrate the association between type D personality, the alteration laboratory examination parameters, such as the level of cortisol, heart rate, and a higher rate of cardiac mortality (319). We found a significant reduction in the cases of type D personality among subjects referred to CR, while the controls did not show any changes. However, considering the two specific sub-scales of DS-14, we did not observe any significant effect of CR on "negative affectivity" and "social inhibition" traits. Thus, it cannot be assumed that the variations of type D personality frequency are attributable solely to cardiac rehabilitation. Denollet (258) defined social inhibition as the tendency to inhibit negative emotions and behaviors in social interactions and assumed that it is not the experience of negative emotions *per se*, but rather the chronic psychological distress arisen from this inhibition, to influence physical health in a negative way. Given the lack of changes of social inhibition degree over time, it can be assumed that in order to change this relatively stable personality trait in an enduring way, a targeted intervention is needed (320). Type D personality seems to be associated with not only greater emotional distress, cardiovascular events, and poorer quality of life, but also to be able to modify negatively the course of invasive and pharmacological interventions (320). Pedersen and Denollet (320) emphasized the importance of identifying type D patients through effective screening and of intervening on the modification of this risk factor. The Authors pointed out that, even if type D personality should be considered as a relatively stable aspect, the associated psychological distress can be reduced and these kind of patients can benefit from interventions aimed to reduce their distress and to manage depression, type A behavior, anger and hostility. Thus, even if treatments specifically designed to modify type D personality traits and its deleterious effects on health are not yet available, indirect results suggest that it is possible to

intervene at least on part of this personality. This hypothesis also seems to be confirmed by the findings of this study .

It is known that cardiac rehabilitation programs including physical exercise may improve neuropsychological conditions among elderly patients, in particular reducing depressive symptoms, and those of anxiety, hostility, and somatization (200, 321). Even among younger cardiac patients, cardiac rehabilitation has been shown to reduce the symptoms of depression, anxiety, hostility, and somatization (322). Results of our study are in line in part with those detected in literature. With regard to Symptom Questionnaire (SQ), the two clinical groups did not show any difference. Compared to the means of the general population (anxiety: M=3.84, SD=3.87; depression: M=2.56, SD=2.87, somatic symptoms: M=4.49, SD=4.14; anger-hostility: M=3.90 SD=3.79) (236, 323), at baseline, our sample showed similar levels of anxiety and hostility, while mean scores of depression and somatization exceeded more than a standard deviation normative data, indicating moderate distress (323). Symptom Questionnaire scores, as other self-assessment questionnaires, provide important data for the quantification of a patient's levels of distress and well-being. Two patients may both meet the diagnostic criteria for major depression, but they may present very different scores on a self-assessment questionnaire. Their different scores may reflect different symptom severity, perception, and illness attitudes, and these variables may affect the clinical course of the disorder in these two patients. Frequently, in fact, patients with affective disorders, even although treated effectively with psychotherapy or pharmacological interventions, can continue to present high subclinical symptomatology and impaired levels of psychological well-being compared to healthy control subjects (324, 325). We found an association between attendance to cardiac rehabilitation and a decrement of hostility traits and a slightly protective effect of the program towards depression symptoms increment; however, we did not find any clear association between CR and the modification of anxiety and somatic symptoms. Even if depression scores did not change over time in both groups (except for a decrement among controls between 6- and 12-months follow-up), starting from the second evaluation, CR patients showed significantly lower scores of

depression than control groups. With regards to hostility, among experimental patients its levels decreased by the end of the rehabilitation, but then after 6 months they increased again, while those of controls decreased. However, hostility remained within the normative scores range. From this we may deduce that in order to promote a more permanent change in the symptoms anger and hostility would need to be monitored and any more specific treatment that can affect more durable. It was interesting to note that patients undergoing non-invasive, contained significantly higher levels of hostility than patients undergoing open-heart surgery. Cardiac rehabilitation has then been found to produce a secondary effect on depression and hostility but not on anxiety and somatization symptoms. The lack of effect on these psychological distress symptoms, especially somatization, highlight the need of more specific intervention strategies to also address these sub-clinical symptoms .

With regards to psychological well-being, we found that patients referred to Cardiac Rehabilitation self-reported higher baseline levels of "environmental mastery", "personal growth" and "purpose in life" than controls. As reported in the paper of Psychological Well-being Scales Italian validation (255), the scores obtained by the general population over 60 years old were: 63.38 (SD=8.72) for "autonomy", 57.95 (SD=9.88) for "environmental mastery", 56.00 (SD=7.43) for "personal growth", 58.71 (SD=8.58) for "positive relationships", 58.90 (SD=8.33) for "purpose in life", and 57.57 (SD=10.08) for the scale "self-acceptance". The comparison between these normative values with those of our sample shows that the experimental group's levels of well-being are similar to (or even better than) those of the general population, while the control group displayed lower scores of "personal growth" and "purpose in life". However, at least at baseline, the difference between these scores and the general population's means was not greater than one standard deviation. Cardiac rehabilitation does not seem to be related to psychological well-being modification over time, except for the dimension "purpose in life". Indeed, experimental patients self-reported an improvement first and later a deterioration, then remaining quite stable after 12 months. On the contrary, controls deteriorated after 6-months, showing mean scores of purpose in life a standard

deviation lower than those of the general population. Therefore, this may suggest an association between cardiac rehabilitation and this specific psychological well-being aspect. As Ryff and Singer (326) argued, deep feelings of "purpose in life" together with other aspects of psychological well-being (i.e., positive relations with others) seem to be an important psychological resource that can modulate immune factors and neuro-endocrine response. Moreover, having a purpose in life and a sense of personal growth helps to preserve the physical health over time through different physiological mechanisms, which include optimal allostasis, immune competence, and asymmetric brain activation (326). A study which assessed the association between psychological well-being and distress with some biological correlates (327), underlined that some dimensions of psychological well-being are correlated with indicators of cardiovascular risk: "positive relationships" negatively correlates with weight, waist/hip ratio and glycosylated hemoglobin; "personal growth" positively with the level of HDL cholesterol and negatively with total cholesterol; "purpose in life" positively with the level of HDL cholesterol and negatively with waist/hip ratio. These findings underline relevant clinical implications that should be taken into account when treating patients with cardiovascular conditions. However, in this specific case it can be hypothesized that the lack of impact of cardiac rehabilitation on almost all dimensions of psychological well-being is due to an overall good baseline level of it, attention should be paid to patients who were not referred to any rehabilitation program after discharge from the hospital.

As pointed out by Balestroni and Giannuzzi (312), in the field of cardiac rehabilitation the frequency of patients who have emotional reactions above clinical cut-offs cannot be ignored or regarded as a mere statistical curiosity, but it is a confirmation of the fact that the psychological components also play a fundamental role within a rehabilitation program. To allow an active involvement of the patient in the rehabilitation process it is thus necessary to intervene with specific psychological and educational approaches (312). Furthermore, although the ENRICHD study (328) did not demonstrate a significant reduction of mortality and morbidity with an intervention aimed to reduce depression and isolation after an acute cardiovascular event, the emotional state of the

patients cannot be ignored but rather represent a boost for future research and improvement of psychosocial interventions in cardiac rehabilitation programs.

Another aim of this study has been to evaluate the protective role of the cardiac rehabilitation against the recurrence of cardiovascular relapses. No differences between the two groups in terms of events recurrence have been found. Despite patients who had undergone CR were expected to incur relapses less frequently than controls (329), the number of adverse events was similar in the two groups. The percentage of patients who, despite the CR attendance, relapsed within 12 months is rather high, as already observed Willich and colleagues in a previous study (330). It is arguable that this outcome could be influenced by the poor effect of CR on smoking cessation, BMI reduction, diet and medication adherence improvement (33, 330, 331).

The final objective was to evaluate whether any of the psychological characteristics of the sample were related relapses' recurrence. Contrary to literature showing that depression, anxiety and hostility may predict cardiac recurrences (51, 52, 332, 333), our findings do not seem to confirm any particular effect of sub-clinical psychological symptomatology on adverse events. We found only an evidence concerning well-being psychological dimension of personal growth, among patients who had undergone non-invasive medical procedures. This dimension corresponds to the ability to choose or build a favorable environment for one's own self (253). From a psychological point of view, after a cardiac event, patients with cardiovascular diseases have to face a period of transition that activates elaboration processes of changes in health status and the consequences that this may entail (334). People with a high level of personal growth are defined as individuals who have the feeling of continuous growth and interpret them as people who continue to expand and develop their potential, being open to new experiences; also, they are characterized by a great predisposition to change (255). This predisposition to change allows them to achieve a higher understanding of themselves. On the contrary, low levels of personal growth correspond to subjects who have the perception of being stuck and having lost the urge to improve over time, feeling unable to develop new behaviors and becoming bored and disinterested in their lives. Personal

growth and purpose in life have been found to be two fundamental psychological well-being dimensions because of the implications they have on physical health (326, 335). Individuals with high personal growth seem to mediate its positive effects through three mechanisms: a different brain activation (left prefrontal area) able to elicit positive affect in response to stressful events, proper functioning of the immune system, and good allostasis. The allostasis allows people to adjust their internal system in the case of stress. When this mechanism is not efficient, an "allostatic" load leads to an increased physiological reactivity when negative stimuli occur (336); this physiological arousal may trigger, in turn, symptoms such as high diastolic and systolic pressure, increased accumulation of adipose tissue, cholesterol and glycated hemoglobin levels, and cortisol. The consequences could affect the incidence of cardiovascular disease in people without a history of cardiac problems and increase the number of hospitalizations. In addition, good levels of personal growth positively influences the implementation of healthy behaviors such as exercise, diet and quality of sleep (335), supporting our findings regarding the association between low levels of personal growth and the increased risk of recurrence on relapses.

3.9 LIMITATIONS OF THE STUDY

The present study presents some limitations that should be discussed. The most important limits regard the sample size and specific medical characteristics of the two clinical groups.

With regards to the former, the small sample size and the expected and natural loss of subjects over time is certainly a limitation of this study. A small sample size may not be representative of the entire population with cardiovascular diseases, and may have narrowed the power to detect significant differences where they were not found; at the same time, however, the significant differences found between the two groups gain strength.

With regards to the second limitation, differences on medical complaints, we found that the population of this study is characterized by an imbalance regarding the frequencies of

cardiovascular diseases and related medical procedures. Patients who had undergone cardiac rehabilitation, indeed, were mainly subjected to invasive surgical procedures (bypass grafting surgery and valve replacement or plasty), as they were affected by valvular heart disease and stenosis more frequently than control patients. On the contrary, most of the patients who did not undergo the rehabilitative program, were subjects to non invasive interventions, such as percutaneous angioplasty, since the most frequent cardiovascular disease they were affected by was myocardial infarction and unstable angina As already mentioned, such framework is in line with inclusion criteria for access to rehabilitation programs and research suggesting that patients who have been subjected to open-heart surgery should be referred to rehabilitation programs with priority (337). Moreover, since Bufalini (Cesena) and Infermi (Rimini) Hospitals do not have a cardiovascular surgery department, patients needing to undergo bypass or valve surgery have to be transferred to other facilities; the only cases of patients who had undergone open-heart surgery were those transferred to the above-mentioned hospitals in case of post-surgery complications or need of hospitalizations longer than usual. In order to obviate potential biases deriving from this relevant difference in medical conditions between the two groups compared, we controlled for this variable by including it in the statistical model.

3.10 CONCLUSIONS AND CLINICAL IMPLICATIONS

The present study allowed to evaluate the impact of a program of cardiac rehabilitation on lifestyles modification, quality of life, psychiatric and psychosomatic pathology, psychological distress and well-being. Also, it consented to estimate the influence of CR on cardiac morbidity and mortality.

A protective effect of CR on physical activity, and improvements towards healthier eating behaviors, more functional stress management abilities, better quality of sleep and quality of life, have been found. It could be hypothesized that these results are, at least in part, connected. Some studies highlighted an association between improved physical exercise and a decrease in

psychological impairment, such as improvement of quality of life and stress coping strategies (276). On the contrary, cardiac rehabilitation did not show any particular effect on risky lifestyles such as smoking, dietary habits, over-weight/obesity and medication adherence. This framework is consistent with what emerged from survival analysis about a lack of the expected protective effect of CR against cardiac recurrences evaluated 6 and 12 months after the end of the program. The persistence of relevant cardiovascular risk factors (smoking, overweight/obesity, unhealthy diet and poor medications compliance) may have contributed to the rate of cardiovascular events which was not statistically different from that of the control group.

Despite the limitations imposed by the small sample size it is possible to formulate hypotheses concerning potential clinical implications of these findings. Current rehabilitation programs are no more focused on physical training only, but also on behavioral modification of all modifiable risk factors. However, it is likely that the psycho-educational approach focused on unhealthy risk factors modification is too much prescriptive. Prescriptive approaches, indeed, in some research have been proven to be ineffective in facilitating the change. On the contrary, new treatment strategies based on a motivational approach and an active role of the patient, proved their effectiveness among patients with chronic diseases, such as cardiovascular illnesses (289, 290). It should be kept in mind that commonly patients referred to cardiac rehabilitation are in the third age; thus, specific lifestyles such as smoking, diet and medications adherence, being stable for a long time could be very embedded in cognitive style and personal history of the patient. Psycho-educational interventions are crucial for lifestyles modification, as the intention to adhere to medical prescriptions reflects patient's knowledge and beliefs on disease and its treatment (307). These kind of interventions may be accompanied by more specific individualized interventions, such as motivational interviews, which may allow to explore patient's intrinsic motivation to change in order to make his/her improvement the result of a personal choice rather than an external imposition. Also, the use of cognitive-behavioral techniques, such as cognitive restructuring, could encourage the modification of dysfunctional beliefs, while self-monitoring diary, problem-solving skills and coping strategies

improvement, could be helpful techniques in everyday life. The integration of these components could allow to become aware of the risks of maintaining risky lifestyles and to enhance positive aspects of change by learning specific skills.

Another crucial issue is medications adherence. In some circumstances, rather than a voluntary denial to take medications, pharmacological compliance in the elderly may be impaired due to cognitive deficits, which may lead to forgetfulness. When these patients do not have either an adequate social support or external help, it would be useful to schedule interventions that could develop and teach behavioral strategies to plan medications intake. In general, social support has been found to be crucial for the adherence to medical prescriptions and treatments (302). Thus, it might be helpful to pay more attention to the involvement of patient's family or spouse in the rehabilitation process, for example by planning psycho-educational meetings addressed to the families, to help the patient to be followed even at home properly.

Findings from this study also suggest the importance of specific psychological and psychosomatic aspects to be considered. Indeed, the following associations have been found: mood disorder and negative effects on physical activity; both somatization and "psychological factors affecting medical conditions" with poorer stress management; abnormal illness behavior and worse medication adherence. Also, personal growth impairment (PWB) is associated with a higher risk of cardiac events among patients who had undergone non-invasive medical procedure. Given the influence of both clinical and sub-clinical psychological aspects on the modification of cardiovascular risk factors, it would therefore be desirable that rehabilitation programs provide a multi-dimensional assessment including the evaluation of sub-threshold psychological symptoms, psychosomatic syndromes, and psychological well-being. Moreover, it is necessary to schedule an individualized treatment plan on the basis of what emerged during the initial assessment.

In line with the literature, patients with post-acute cardiovascular diseases show clinically significant psychological distress and psychosomatic vulnerability. Moreover, since no variations among control group subjects on diagnoses frequencies have been found, our findings suggest that

the attendance to cardiac rehabilitation program is associated to a secondary positive effect on depressive and anxious DSM disorders, in line with previous research. Given the negative impact that depression and anxiety may have on the course of heart disease, the potential role of CR in improving the prognosis in these kind of patients should be emphasized. Also, CR is associated with a decrease (maintained over time) of the frequencies of DCPR illness denial, irritable mood, demoralization and type A behavior. On the contrary, no effect on type D personality has been found. The persistence of such personality traits, as predictable, should thus be taken into account and monitored because of their potential effect on prognosis.

The maintenance of the decrease of anger/hostility at 6-months follow-up and of sub-clinical depressive symptomatology at 12-months follow-up, in the experimental group only, represents a major achievement. The persistence of residual sub-clinical depressive symptoms is associated with the occurrence of depressive disorder in the long term. Anger and hostility, on the other hand, were associated with the incidence of cardiovascular disease (119, 121), unhealthy lifestyles (120), metabolic syndrome (338) and progression of atherosclerosis (118).

In addition, although it was not maintained at 12-months follow-up, cardiac rehabilitation has been found to be related to an improvement of psychological well-being dimension of purpose in life, not detected among controls. On the contrary, a progressive worsening in the control group has been found. According to Ryff and Singer (253), the increase of psychological well-being may have a protective effect towards the individual vulnerability to acute and chronic stress. Specifically, positive interpersonal relationships, autonomy and purpose in life can provide valuable protection against the adversities of life. Although cardiac rehabilitation focuses mainly on exercise and lifestyles modification, the improvement of some psychological sub-clinical factors in the experimental group, but not among controls, suggests a possible secondary effect exerted by rehabilitation. All specialists working in the cardiac rehabilitation facilities should be aware of the possible benefits of CR and encourage patients with cardiovascular disease to attend such programs. At the same time, cardiac rehabilitation failed on type D traits modification, anxious and somatic

symptomatology relief, and improvement of certain psychological well-being dimensions (i.e., personal growth, and purpose in life). Given the ascertained high psychological distress in patients with cardiovascular conditions and its well-known negative effect on cardiac prognosis, the development of cost-effective interventions aimed at the modification of these psychological aspects is desirable.

National guidelines of cardiac rehabilitation (151) emphasize its multi-factorial nature. Research suggests both the need of the integration of psycho-educational interventions addressed to patient and his/her family, targeted cognitive-behavioral strategies and promotion of psychological well-being. Taken together, these techniques could respond to the need of both a modification of unhealthy lifestyles, and attention to underlinying psychological mechanisms that can influence cardiac rehabilitation outcomes.

With respect to the stability over time of lifestyles modification, it could be inferred that almost all positive results remain stable within one year after the end of the program. However, future research should verify whether these findings are maintained at long-term follow-ups. To be effective, indeed, a rehabilitation program should produce long lasting lifestyles modifications, especially in the case of chronic cardiac diseases (151). At the end of the rehabilitation program people with heart disease should be recommended to join local groups of cardiac support or self-help groups, and to continue with physical exercises in a gym or a recreational centre, in order to maintain physical activity and healthy lifestyles.

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