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PhD THESIS

**THE IMPORTANCE OF PSYCHOLOGICAL STRESS IN
EVOLUTION OF CORONARY ARTERY DISEASE AND TYPE
2 DIABETES**

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SUMMARY

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Keywords: coronary artery disease; anxiety; depression; psychological stress parameters; comprehensive rehabilitation Type 2 diabetes mellitus, risk factors.

1. General part

Coronary artery disease (CAD) with about a third of all globally deaths has become the most common cause of death (1). Each year CAD causes over 4 million deaths in Europe. Mortality reports from CAD over the past 20 years classify Romania as a country with high cardiovascular mortality (2).

In addition to traditional risk factors: hypertension, diabetes, smoking obesity, dyslipidemia, psychological stress receives increased recognition as a clinically important contributor to cardiovascular morbidity and mortality. Psychological symptoms are prevalent for people with CAD and reduce the adherence to a healthy lifestyle and drug treatment. Identification and therapeutic modulation of all its risk factors is necessary to ensure a lower burden on the patient and on society (3).

Beliefs and emotions could affect on functional status, quality of life, and mortality amongst patients who are suffering coronary heart disease. Since antiquity, people have been intuitively aware of the connection between the heart and emotional stress. Quality of life is influenced by a number of factors: ability to work, health and disabilities, support from relatives and friends, accommodation appropriate to expectations (4).

The physiological response to acute and chronic stress exposure has long been recognized as a potent modulator of endocrine, metabolic and immune pathway. More and more attention is given to the bidirectional interaction between psychological and physical health in relation to cardiovascular disease (5).

Stress is clearly an important and potentially modifiable risk factor for acute and chronic adverse cardiovascular disorders and effective medications are already in use (such as β -adrenergic antagonists) that restrict some of the downstream effects of stress-axis activation. Ample evidence exists for a strong and consistent association of acute and chronic psychological stress with cardiovascular risk factors, such as hypertension and insulin resistance, and with outcomes such as ischaemia, arrhythmia, and pump failure (6-8).

Anxiety is a modifiable experience that is highly prevalent among the general population (9). Anxiety increases the risk of all secondary outcomes (myocardial infarction, CAD, stroke); there is therefore no reason to assume that different mechanisms are causing CAD in specific locations only (10).

Anxiety is not considered pathologic if it is not defined as dread or apprehension, but seen across the life span can be adaptive. Anxiety has both a cognitive-behavioral component, expressed in worrying and wariness, and a physiological part, mediated by the autonomic nervous system (ANS). Anxiety disorders are characterized by **pathologic anxiety**, in which anxiety becomes disabling, interfering with social interactions, development, and achievement of goals or quality of life, and can lead to low self-esteem and social withdrawal. Anxiety may have physical manifestations such as weight loss, tachycardia, tremors, pallor, muscle cramps, paresthesias (11, 12).

Furthermore, anxiety disorders are common and are associated with poor prognosis in CAD patients, but self-assessment scales can be reliably identified (13).

Depressive symptoms are also common in patients with coronary artery disease and are associated with an unfavorable outcome. Depression is associated with an increased risk of mortality and new cardiovascular events in these patients. Thus, establishing prognostic profiles of these patients can facilitate greater effectiveness of targeted interventions before the start of mental health care (14). Because depression and cardiovascular disease are both multifactorial and heterogeneous disorders, there is no specific factor that explains a substantial part of the association between depression and cardiovascular disease as all factors exposed interact and accumulate (15).

If finding the common mechanisms of CVD and depression becomes more difficult, preventing the development of both conditions can be made easier.

During the past decade studies have shown that Type D personality is associated with increased risk of cardiac events, poor quality of life mortality and mortality (16).

In this context, we considered the opportunity to evaluate the importance of psychological stress in evolution of coronary artery disease and type 2 diabetes.

In this research we compared parameters of psychological stress in CAD patients with and without myocardial revascularization procedures and to analyze all lifestyle contributors that might influence this type of stress, including socio-economic status and quantify anxiety, depression and presence of type D personality and to correlate the scores obtained with cardiovascular risk factors and disease severity in diabetic patients.

At present, research provide a framework for monitoring anxiety, depression and type D personality in coronary patients before inclusion in comprehensive rehabilitation programs. Behavioral and psychological stress responses in patients with CAD significantly correlate with risk factors, and could influence the evolution of the disease. Other factors like gender, income and marital status also seem to play a decisive role. The anxiety/depression questionnaires used: The Hospital Anxiety and Depression Scale (HADS) HADS, Duke Anxiety-Depression Scale (DUKE), DUKE și scala Type D personality scale (DS-14), have proven useful to identify coronary patients in need of special psychological care and should be introduced as additional means of evaluation for a better individualization of rehabilitation programs.

Evaluation of psychological stress parameters contributes to a better individualization at the start of these programs, because it allows adjusting of all potential factors that may influence positive outcomes.

Moreover, behavioral and psychological responses to stress in diabetic patients have a very important role in prognosis and disease progression. Monitoring of emotional state and depression should be included in the therapeutic plan of these patients.

2. Special part

Although numerous retrospective studies have shown that the relationship between depression / coronary heart disease and depression / diabetes is bidirectional (17-19), prospective analyzes are needed to understand this relationship during the natural course of the disease .

Clinical trials are needed in this new field of research that associates cardiovascular diseases, metabolic and mental disorders, thus creating an integrative orientation focused on neuroendocrine-psycho-metabolic dysfunction, which characterizes these morbid associations.

This research intended to answer following questions:

- ✓ Could evaluation of psychological stress have a relevant role in individualization for cardiac rehabilitation of coronary patients, related to progression of the disease?

- ✓ How do behavioral and psychological responses to stress influence the prognosis and progression of disease in diabetic patients?

Types of study: retrospective, interdisciplinary.

Populations studied:

- coronary patients confirmed angiographically; with / without myocardial revascularization procedures (aorto-coronary bypass = CABG, percutaneous transluminal coronary angioplasty (PTCA));

- type 2 diabetes mellitus (T2DM) patients previously diagnosed according to the consensus report of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) in 2018 (20)

Working background: These studies started from following assumptions:

- a) Recently, numerous epidemiological studies have proven that psychosocial factors, especially anxiety and depression, are associated with an increased risk of developing coronary artery disease (21, 22)

- b) T2DM is a chronic disease with a constantly increasing global prevalence, which very often associates a psychological profile characterized by depression and / or anxiety (23).

Overall Objectives:

1. To detect the best screening tools in patients who associate comorbidities represented by coronary heart disease / diabetes / anxiety-depression. This association is a particularly serious public health problem and its implications in morbidity / mortality represent an additional risk for an increasing number of patients
2. To maximize prognostic information by incorporating available data from biological samples (metabolic parameters), and HAD and DS14 scores to as an integral part of a multi-disciplinary strategy in cardiovascular prevention

Specific objectives include:

- To analyze all lifestyle contributors that might influence stress, including socio-economic status and to compare parameters of psychological stress in CAD patients with and without myocardial revascularization procedures
- To quantify anxiety, depression and presence of type D personality and to correlate the scores obtained with cardiovascular risk factors and disease severity in diabetic patients.

Studied parameters:

A. **Clinical data:** personal data including age, gender, marital status, income, medical history of premature CVD in first-degree relatives (age < 55 years for M subjects, age < 65 years for F subjects) and smoking status; clinical evaluation including: measurement of systolic (SBP), diastolic blood pressures (DBP) and body mass index (BMI)

B. Biochemical evaluation:

- Metabolic parameters: glycemia, fasting blood glucose, HbA1c, total cholesterol (TC), triglycerides (TG), LDL-C, HDL-C
- Renal parameters: serum creatinine, uric acid, eGFR

C. **Cardiac echographic evaluation:** was performed in all patients included in the study. Two-dimensional ultrasound provided morphological and functional information about: dimensions, cavities, heart walls, presence of valvular lesions, ejection fraction and systolic performance.

D. Assessment of Psychological Stress:

- Duke Anxiety-Depression Scale (DUKE),
- Hospital Anxiety and Depression Scale (HADS), with anxiety subscale HAD-A and depression HAD-D;
- Type D Personality (DS-14) with social inhibition subscale DS-14 SI and negative affectivity DS NA.

The first part of research: Personal contribution “**Evaluation of Psychological Stress Parameters in Coronary Patients by Three Different Questionnaires as Pre-Requisite for Comprehensive Rehabilitation**” analyzed all lifestyle contributors that might influence this type of stress, including socio-economic status and compared parameters of psychological stress in CAD patients with and without myocardial revascularization procedures.

To the best of our knowledge, to investigate the incidence of anxiety, depression and type D personality by three different questionnaires, with the intention to better individualize coronary patients for cardiac rehabilitation, represents a novel approach in cardiac prevention.

The results obtained in this study emphasize that behavioral and psychological stress responses in patients with CAD do not only correlate with risk factors, but that other factors like gender, income and marital status also seem to play a decisive role, as shown by our multinomial and multivariate linear regression analyses.

Each patient’s biological and health parameters including personality traits and socio-economic aspects may contribute to the course of cardiovascular disease. The three anxiety/depression questionnaires used, HADS, DUKE and the DS-14 scale, have proven useful to identify coronary patients in need of special psychological care and should be introduced as additional means of evaluation for a better individualization of rehabilitation programs.

Furthermore, these results provide a framework for monitoring anxiety, depression and type D personality because comprehensive cardiac rehabilitation, with its global approach, offers the perfect setting to diagnose and help patients to cope with their emotional disorders. Psychological stress could have a relevant role

in the outcomes of cardiac rehabilitation, which is related to progression of the disease.

Spending time in rehabilitation groups gives patients the opportunity to understand the influence of psychological and biological risk factors, and to share responsibility in building strategies to manage daily stress. The questionnaires should also be applied at the end of the rehabilitation programs, for comparison, as proof of beneficial effects of these programs on all aspects of health.

The second part of research: Personal contribution: **“Study of The Importance of DS-14 and HADS Questionnaires in Quantifying Psychological Stress in Type 2 Diabetes Mellitus”** showed that: behavioral and psychological responses to stress in diabetic patients with or without macrovascular complications have a very important role in prognosis and disease progression.

The use of self-administered questionnaires and anxiety/ depression scales is required for the screening of diabetic and coronary patients, whether in hospital or outpatient settings. The HADS and DS-14 scales are short and easy to apply, the fill-in duration is only 2-5 minutes, and their accessibility allows individual completion.

The DS-14 scale is useful for detecting type D personality, for which therapeutic measures should include psychotherapeutic interventions in addition to drug treatment.

For both studies, eligible patients were selected from the databases of the Institute of Cardiovascular Diseases Timisoara, Cardiovascular Prevention and Rehabilitation Clinic.

Retrospective investigation was made by selection of consecutive cases based on inclusion / exclusion criteria established according to scientific objectives.

The selection of patients for the two studies is shown in Figure 1.

The studies were made in conformation to the Declaration of Helsinki and were approved by the Ethics Committee of the Institute of Cardiovascular Diseases Timisoara. All patients provided written informed consent.

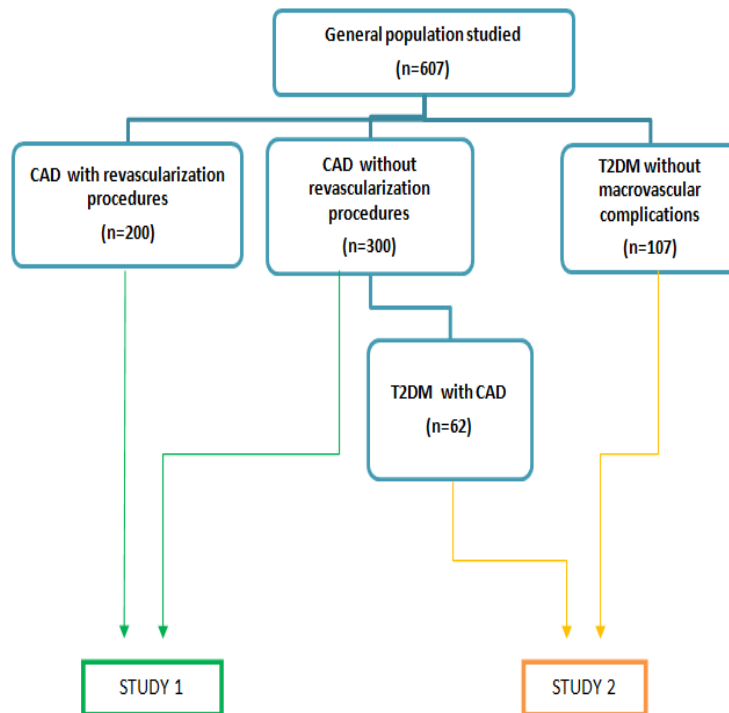


Figure 1. Structure of study populations

Results

Study 1

There were significant differences in Group 1 (the revascularized group) regarding male gender (78.2% in CABG subgroup vs. 61.7% in PTCA subgroup, $p=0.012$) and HAD-A score (7.1 ± 3.77 in CABG subgroup vs. 8.8 ± 4.2 in PTCA subgroup, $p=0.010$).

The HAD-A scores were significantly higher in patients who underwent PTCA vs. CABG ($p = 0.01$).

DUKE scores were also significantly higher in patients who underwent PTCA vs. CABG ($p = 0.04$).

In Group 1, severe anxiety was present in proportion of 13.6% ($n=12$) and was significantly higher in patients with PTCA vs. CABG (Chi2 test, $p = 0.027$)

Results after applying HADS showed that CAD patients without myocardial revascularization (Group 2, $n = 300$) presented anxiety in a proportion of 72.3% ($n = 217$) out of which 10.7% ($n = 32$) had severe anxiety.

By applying the Mann-Whitney U Test and Chi2 Test to patients with severe anxiety from both groups we observed that those without myocardial revascularization and without income ($n = 6$), had HAD-A score significantly higher compared to those with income ($n = 26$).

Moreover, we observed that in coronary patients with myocardial revascularization and without a partner ($n = 5$), HAD-A ($p = 0.041$) and DUKE ($p = 0.037$) scores were significantly different than in those with a partner ($n = 7$).

Significant differences were also observed in coronary patients without myocardial revascularization with a partner ($n = 18$) and without a partner ($n = 14$) in terms of HAD-A ($p = 0.049$) and DUKE ($p = 0.042$).

By applying the Kruskal–Wallis nonparametric test it was observed that in Group 2 ($n=300$) HAD-D values were significantly increased according to severity of **New York Heart Association (NYHA)** functional class ($p=0.029$). DUKE score values decreased significantly with the increase of NYHA class ($p<0.001$).

In CAD patients without myocardial revascularization (Group 2, $n=300$), 180 patients had depression (a proportion of 60%) out of which 1.3% ($n=4$) presented severe depression.

Risk analysis for the whole of the coronary patients in the study ($n = 500$), revealed that patients without a partner or with low income were at risk for developing severe depression (Chi2 test, $p=0.002$, OR=12.35, 95%CI=(2.36, 64.74)) and (Chi2 test, $p=0.008$, OR=4.10, 95%CI=(1.53, 10.93)), respectively.

In revascularized patients with type 2 diabetes mellitus ($n = 62$), significantly increased HAD-A scores compared with scores of patients without diabetes mellitus were observed (Mann-Whitney test, $p = 0.002$). We also observed significantly increased DS-14 NA scores in revascularized patients with T2DM (Mann-Whitney test, $p = 0.024$).

The correlation between the presence of T2DM and type D personality in revascularized patients ($n=200$) was significant (Chi2 test, $p = 0.010$). However, by applying multivariate linear regression according to the Enter method, using the DUKE scores as dependent variable, and age, gender, marital status and income as independent variables, age and marital status proved significant predictors for psychological stress.

Study2

Anxiety was present in 105 patients (62.2%), and depression in 96 patients (56.8%).

Anxiety was observed in 55.1% ($n = 59$) of patients in group 1 compared to 74.2% ($n = 46$) in group 2 ($p = 0.014$), while the results of the HAD-D questionnaire did not show significant differences between the two groups.

Social inhibition was present in 56 patients (33%) and negative affectivity in 105 patients (62%). Type D personality, resulting from scores above 10 in both DS-14 parameter categories, was present in 51 patients of the study group (30%).

Groups 1 and 2 were compared based on the scores of HAD-A, HAD-D, DS-14 individual scores and type D personality also by applying the non-parametric Mann-Whitney test. The comparison revealed significantly higher HAD-A scores in group 2 ($p=0.011$) compared to group 1. The DS-14 IS score was significantly higher in group 2 compared to group 1 ($p=0.036$)

Discussions

Our findings suggest that these symptoms are more prevalent in coronary patients who have undergone a revascularization procedure compared to no revascularization.

Increased prevalence of both anxiety and depression symptoms in patients with CAD was found by Gu et al., before and after PTCA in a study conducted on 170 patients, aged 33–80 years old, who also sustained that the symptoms of anxiety and depression change over time in CAD patients, being more severe after PTCA (24). In Group 1, there was a higher prevalence of male gender (78.2% in the CABG subgroup vs. 61.7% in the PTCA subgroup, $p=0.012$). These results are in line with similar published findings (25, 26).

In Group 1 with revascularization procedures, we observed significantly higher HAD-A scores in patients with PTCA vs. CABG (Chi2, $p=0.027$). Numerous recent studies have demonstrated a relationship between CAD and anxiety (24, 27), or both anxiety and depression, in patients who underwent myocardial revascularization interventions (CABG and PTCA), regardless of whether the questionnaires were applied before (27), after (28) or both before and after procedures (24).

We also observed that severe anxiety was significantly increased in patients with PTCA (Chi2 test, $p = 0.027$). Dahale et al. studied the association between CAD

and anxiety and, based on the evidence, found that presence of anxiety is correlated with development and progression of coronary heart disease. The authors suggest that cardiologists should be trained to identify these patients for more effective management (29).

Until now, no studies that used the DUKE scale for screening anxiety and depression in cardiovascular patients were reported in coronary artery disease, supporting the uniqueness of the current study.

After applying the DS-14 scale, we observed that only DS-14 NA scores were significantly increased in revascularized coronary patients with T2DM ($n=62$) (Mann–Whitney test, $p = 0.024$). The association between the presence of T2DM and type D personality was significant (Chi2 test, $p = 0.010$). Kupper and Dennolet, in a review that synthesizes recent research findings, observed that in patients with CAD, type D personality is an established independent risk marker for worsening clinical and patient-reported outcomes (30).

Understanding anxiety and depression makes it possible to prevent cardiovascular disease. The high prevalence of depression and anxiety in CAD patients and the relationship with lifestyle change requires the integration of methods to identify and minimize adverse effects of depression and anxiety in cardiac rehabilitation and prevention programs (31, 32)

In the present study, the application of the DS-14 questionnaire demonstrated significant association of the DS-14 IS score with macrovascular complications of DZ2 (Mann-Whitney nonparametric test, $p = 0.036$).

Emotional instability moods such as anger, anxiety, and depression, that is emotional stress itself, cause dysregulation of hypothalamic and thalamic centers resulting in exhaustion of the secretion balance of insulin, glucagon, thyroid hormones, cortisol, and catecholamines. Therefore, for the effective treatment of diabetes, control of emotional stress is mandatory along with diet and medical treatment (33)

The purpose of identifying diabetic individuals with high risk of depression is to implement preventive measures and cognitive-behavioral treatments and change their lifestyle. These preventive measures can contribute to a significant decrease in DZ2 / depression comorbidity and, implicitly, the cost of treating them, which burdens the health system.

3. General conclusions

1. The influence of behavior and psychological responses to stress in coronary and diabetic patients has been documented by numerous evidences. However, evidence that treatment of clinically significant depression and anxiety will improve cardiac endpoints is still missing. This fact is due to the lack of recommendations for reliable screening of subjects at risk.
2. The contribution and novelty of the present studies resides in the comparison of three different validated tools to identify psychological stress in an effort to fill in the screening gap.
3. The three questionnaires used, HADS, DUKE and the DS-14 scale, have proven useful to identify coronary and diabetic patients in need of special psychological care and should be introduced as additional means of evaluation.
4. Behavioral and psychological stress responses in coronary and diabetic patients significantly correlate with risk factors, and other socio-economic factors like gender, income and marital status also play a decisive role, as shown by the multinomial and multivariate linear regression analyses made for coronary patients.
5. The use of the self-administered questionnaires HADS, DUKE and DS-14 is recommended for the screening of diabetic and coronary patients, whether in hospital or outpatient settings. They are easy to apply, the fill-in duration is short, and they bring valuable information for therapeutic and psychotherapeutic interventions in addition to drug treatment in subjects at high risk.
6. The high prevalence of depression and anxiety in coronary and diabetic patients correlated with unhealthy lifestyle requires integrated methods to identify subjects at risk and to individualize the programs of prevention and/or cardiac rehabilitation. The presence of a psychologist is mandatory in the team.

7. Future perspectives in the field of psycho-cardiology and psycho-diabetology refer to clinical studies needed to understand the development of these bidirectional relationships in order to better influence the course of diseases.

BIBLIOGRAPHY

1. Richards SH, Anderson L, Jenkinson CE, Whalley B, Rees K, Davies P, et al. Psychological interventions for coronary heart disease. *Cochrane Database Syst Rev.* 2017;4(4):Cd002902.
2. Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. *European Heart Journal.* 2014;35(42):2950-9.
3. Albus C. Psychological and social factors in coronary heart disease. *Annals of Medicine.* 2010;42(7):487-94.
4. Allahverdipour H, Asgharijafarabadi M, Heshmati R, Hashemiparast M. Functional status, anxiety, cardiac self-efficacy, and health beliefs of patients with coronary heart disease. *Health Promot Perspect.* 2013;3(2):217-29.
5. Lagraauw HM, Kuiper J, Bot I. Acute and chronic psychological stress as risk factors for cardiovascular disease: Insights gained from epidemiological, clinical and experimental studies. *Brain Behav Immun.* 2015;50:18-30.
6. Stephens MAC, Wand G. Stress and the HPA axis: role of glucocorticoids in alcohol dependence. *Alcohol Res.* 2012;34(4):468-83.
7. Rejack G, Brown A, Nicholls S, Keage H. Associations Between Cardiovascular Burden, Gender and Depression in Indigenous Australians. *Heart, Lung and Circulation.* 2019;28:S62.
8. Jones KT, Shelton RC, Wan J, Li L. Impact of acute psychological stress on cardiovascular risk factors in face of insulin resistance. *Stress.* 2016;19(6):585-92.
9. Lambiase MJ, Kubzansky LD, Thurston RC. Prospective study of anxiety and incident stroke. *Stroke.* 2014;45(2):438-43.
10. Ouakinin SRS. Anxiety as a Risk Factor for Cardiovascular Diseases. *Front Psychiatry.* 2016;7:25-.
11. Bystritsky A, Khalsa SS, Cameron ME, Schiffman J. Current diagnosis and treatment of anxiety disorders. *P T.* 2013;38(1):30-57.
12. Thibaut F. Anxiety disorders: a review of current literature. *Dialogues Clin Neurosci.* 2017;19(2):87-8.
13. Bunevicius A, Staniute M, Brozaitiene J, Pop VJ, Neverauskas J, Bunevicius R. Screening for anxiety disorders in patients with coronary artery disease. *Health Qual Life Outcomes.* 2013;11:37.
14. Vitinius F, Escherich S, Deter H-C, Hellmich M, Jünger J, Petrowski K, et al. Somatic and sociodemographic predictors of depression outcome among depressed patients with coronary artery disease - a secondary analysis of the SPIRR-CAD study. *BMC Psychiatry.* 2019;19(1):57.
15. de Jonge P, Roest AM. Depression and cardiovascular disease: the end of simple models. *Br J Psychiatry.* 2012;201(5):337-8.
16. Kupper N, Denollet J. Type D Personality as a Risk Factor in Coronary Heart Disease: a Review of Current Evidence. *Curr Cardiol Rep.* 2018;20(11):104-.
17. Herbst S, Pietrzak RH, Wagner J, White WB, Petry NM. Lifetime major depression is associated with coronary heart disease in older adults: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychosom Med.* 2007;69(8):729-34.
18. Salinero-Fort MA, Gómez-Campelo P, San Andrés-Rebollo FJ, Cárdenas-Valladolid J, Abánades-Herranz JC, Carrillo de Santa Pau E, et al. Prevalence of depression in patients with type 2 diabetes mellitus in Spain (the DIADEMA Study) : results from the MADIABETES cohort. *BMJ Open.* 2018;8(9):e020768.
19. Gemeay EM, Moawed SA, Mansour EA, Ebrahiem NE, Moussa IM, Nadrah WO. The association between diabetes and depression. *Saudi Med J.* 2015;36(10):1210-5.
20. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia.* 2018;61(12):2461-98.

21. Cohen BE, Edmondson D, Kronish IM. State of the Art Review: Depression, Stress, Anxiety, and Cardiovascular Disease. *American journal of hypertension*. 2015;28(11):1295-302.
22. Kyrou I, Kollia N, Panagiotakos D, Georgousopoulou E, Chrysoshoou C, Tsigos C, et al. Association of depression and anxiety status with 10-year cardiovascular disease incidence among apparently healthy Greek adults: The ATTICA Study. *Eur J Prev Cardiol*. 2017;24(2):145-52.
23. Bădescu SV, Tătaru C, Kobylinska L, Georgescu EL, Zahiu DM, Zăgrean AM, et al. The association between Diabetes mellitus and Depression. *J Med Life*. 2016;9(2):120-5.
24. Gu GZ, Y.; Zhang, Y.; Cui, W. Increased prevalence of anxiety and depression symptoms in patients with coronary artery disease before and after percutaneous coronary intervention treatment. *BMC Psychiatry* 2016, 16, 259–259.
25. Finegold JAA, P.; Francis, D.P. Mortality from ischaemic heart disease by country, region, and age: Statistics from World Health Organisation and United Nations. *Int. J. Cardiol*. 2013, 168, 934–945.
26. Wakabayashi IGdicrfipwcatatwtdJTD, 9, E503–E506.
27. Pawlak AK, M.; Janas-Kozik, M.; Krupka-Matuszczyk, I.; Rajewska, J.; Bochenek, A. Evaluation of anxiety and depression in the perioperative period in patients subjected to myocardial revascularization. *Psychiatriapolska* 2012, 46, 63–74.
28. Park JHT, S.J.; Bae, S.H. Depression and anxiety as predictors of recurrent cardiac events 12 months after percutaneous coronary interventions. *J. Cardiovasc. Nurs*. 2015, 30, 351–359.
29. Dahale ABM, J.C.; Jaisoorya, T.S. A Narrative Review of the Relationship Between Coronary Heart Disease and Anxiety. *Iran. J. Psychiatry Behav. Sci*. 2017, 11, e7722.
30. Kupper ND, J. Type D Personality as a Risk Factor in Coronary Heart Disease: A Review of Current Evidence. *Curr. Cardiol. Rep*. 2018, 20, 104–104.
31. Pogosova NK, K.; De Bacquer, D.; von Kanel, R.; De Smedt, D.; Bruthans, J.; Dolzhenko, M. Psychosocial risk factors in relation to other cardiovascular risk factors in coronary heart disease: Results from the EUROASPIRE IV survey. A registry from the European Society of Cardiology. *Eur. J. Prev. Cardiol*. 2017, 24, 1371–1380.
32. Crisan SP, L.; Lazar, M.A.; Vacarescu, C.; Nicola, A.R.; Cozma, D.; Mornos, C., Luca C.T. Reduced ejection fraction heart failure—New data from multicenter studies and national registries regarding general and elderly populations: Hopes and disappointments. *Clin. Interv. Aging* 2018, 13, 651–656.
33. Bradley RT, McCraty R, Atkinson M, Tomasino D, Daugherty A, Arguelles L. Emotion self-regulation, psychophysiological coherence, and test anxiety: results from an experiment using electrophysiological measures. *Applied psychophysiology and biofeedback*. 2010;35(4):261-83.