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Stress, Anxiety and Depressive Symptoms are Predictors of Worse Outcomes in Outpatients With Arterial Hypertension and Coronary Heart Disease: Results of 1.5 Years Follow-up From the COMETA Multicenter Study

Aim — To study associations between the risk of severe adverse cardiovascular outcomes (SACVO) and all-cause death with psychosocial risk factors (PS RFs), such as stress, anxiety and depressive symptoms, low level of education, low income, social isolation, and type D personality, in patients with arterial hypertension (AH) and ischemic heart disease (IHD) managed in primary health care institutions in a multi-year prospective study.

Material and methods — PS RFs were assessed in patients with AH or IHD, who participated in a multi-year prospective COMETA study, using the Hospital Anxiety and Depression Scale (HADS), DS-14 questionnaire, and a visual analogue scale (VAS) for assessment of stress level. Associations of PS FRs with SACVO and all-cause death after a 1.5-year follow-up were analyzed using multivariate Cox regression models.

Results — At 1.5 years after patients were included in the study, it was possible to obtain data for 2,538 patients (age at baseline, 66.6 ± 7.8 years, 28.1% men), 106 of whom died during that period. The incidence of SACVO was 40.0 per 1000 person-years. According to the results of multivariate regression analysis, a very high level of anxiety symptoms (HADS-A≥14) was significantly associated with SACVO (odds ratio (OR), 1.81; 95% confidence interval (CI), 1.04–3.15; p=0. 02). The composite endpoint that included all-cause death and/or SACVO was significantly associated with a high (VAS score ≥8) stress level (OR, 1.53; 95% CI, 1.00–2.33; p=0.04) and a very high (HADS-D≥14) level of depressive symptoms (OR, 2.11; 95% CI, 1.22–3.62; p=0.02). A low level of education adjusted for gender and age increased the likelihood of SACVO by 1.7 (95% CI, 1.19–2.43) times. No significant associations were found between the analyzed outcomes and type D personality or with social isolation.

Conclusion — In patients with AH or IHD, the presence of high-grade stress and severe depressive symptoms increased the likelihoods of all-cause death and SACVO while a low level of education and severe anxiety symptoms were associated with SACVO. The study results showed that PS RFs for cardiovascular diseases keep the PS RF prognostic significance in the conditions of modern treatment of AH and IHD. Due to the negative impact on the prognosis, PS RFs should be taken into account when taking measures for secondary prevention of AH and IHD.

Keywords — Psychosocial risk factors; anxiety symptoms; depressive symptoms; stress; arterial hypertension; ischemic heart disease; severe adverse cardiovascular outcomes

For citations — Pogosova N.V., Ausheva A.K., Saner H., Boytsov S.A. Stress, Anxiety and Depressive Symptoms are Predictors of Worse Outcomes in Outpatients With Arterial Hypertension and Coronary Heart Disease: Results of 1.5 Years Follow-up From the COMETA Multicenter Study. Kardiologiia. 2023;63(12):3–10. [Russian: Погосова Н.В., Аушева А.К., Санер Х., Бойцов С.А. Тревожная, депрессивная симптоматика и стресс как факторы, повышающие риск неблагоприятных исходов у амбулаторных пациентов с артериальной гипертонией и ишемической болезнью сердца: результаты 1,5-годичного наблюдения в многоцентровом исследовании КОМЕТА. Кардиология. 2023;63(12):3–10].

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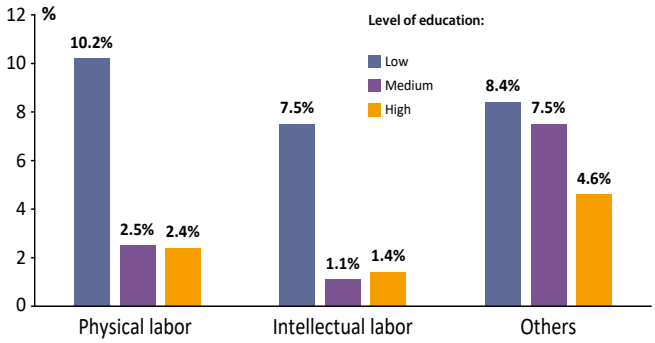
Introduction

There is a large body of evidence showing that psychosocial risk factors (RFs) contribute significantly to the development and prognosis of cardiovascular disease (CVD) [1–5]. The greatest evidence base is available regarding such psychosocial RFs as depression, anxiety, acute and chronic stress, type D personality, social isolation, low level of education and income. The relationship between psychosocial RFs and CVDs seems to be bidirectional: these factors, especially anxiety and

Central illustration. Stress, Anxiety and Depressive Symptoms are Predictors of Worse Outcomes in Outpatients With Arterial Hypertension and Coronary Heart Disease: Results of 1.5 Years Follow-up From the COMETA Multicenter Study

The study included 2,775 patients with AH and/or CHD from 30 Russian cities. Reliable long-term follow-up results were obtained in 1.5 years for 91.5 % (2,538) of patients (69 patients changed their places of residence, 37 individuals refused to be interviewed again, and 131 patients were lost to follow-up for various reasons). The mean age was 66.6 ± 7.8 years, 28.1 % ofpatients were male and 71.9 % were female. Of the 2,538 patients, 44 males and 62 females died, with the majority of deaths resulting from cardiovascular disease. Moreover, 27 patients had myocardial infarction, 25 patients had stroke, and 33 patients were subjected to coronary heart bypass grafting or percutaneous coronary intervention.

Frequency of MACE in patients with AH and CHD depending on levels of education and types of labor



Incidence of MACE was 40.0 per 1000 person-years. Only very high levels of anxiety and depression (HADS-A and HADS-D ≥14) were significantly associated with MACE rather than generally accepted thresholds (≥8 or ≥10): odds ratio (OR) was 1.77 (95 % confidence interval (CI); 1.03–3.05) for patients with very high HADS-A scores and 2.24 (95 % CI; 1.25–4.04) for patients with very high HADS-D scores. At the same time, a very high level of depression (HADS-D ≥ 14) increased the likelihood of all-cause death almost 3-fold: OR 2.92 (1.55–5.49), p = 0.0024, adjusted for age and gender only.

Associations between levels of stress, anxiety and depressive symptoms and MACE in patients with AH and CHD

Parameter	Odds ratio (95 % CI), P value	
	Adjusted for age, gender, history of CHD and diabetes mellitus	Adjusted for age, gender, history of CHD and diabetes, smoking status, and body mass index
Level of stress, VAS score		
< 5	1	1
5-7	1.12 (0.74-1.67), P=0,55	1.06 (0.71-1.60), P=0.40
≥ 8	1.54 (0.97-2.45), P=0.06	1.52 (0.96-2.43), P=0.05
HADS-A score		
< 8	1	1
8-10	0.92 (0.58-1.46), P=0.27	0.95 (0.60-1.52), P=0.35
11-13	0.96 (0.58-1.58), P=0.42	0.93 (0.56-1.55), P=0.32
≥ 14	1.76 (1.01-3.05), P=0.03	1.81 (1.04-3.15), P=0.02
HADS-D score		
< 8	1	1
8-10	1.20 (0.80-1.80), P=0.64	1.25 (0.83-1.88), P=0.84
11-13	1.20 (0.69-2.09), P=0.72	1.14 (0.64-2.01), P=0.55
≥ 14	1.94 (1.07-3.53), P=0.07	1.95 (1.07-3.55), P=0.06

The intellectual labor category also includes business owners, and the «Others» category includes pensioners and the unemployed.

depression, are associated with an increased likelihood of developing arterial hypertension (AH) [6, 7] and coronary heart disease (CHD) [8, 9], on the one hand, and patients with CVDs have a 2- to 3-fold risk of new mental health disorders compared to healthy people, on the other hand [10, 11]. Even individual symptoms of anxiety and depression affect the prognosis of CVDs [12–14]. Depression and CVDs appear to have some common origin including biological, behavioral, psychological, and genetic mechanisms responsible for the deterioration of the prognosis in the combination of the two conditions [14]. Psychosocial RFs can act as barriers to patient adherence to the treatment and cardiac rehabilitation [15]. Low levels of income and education also have a negative impact on the incidence of CVDs and the prognosis for patients [16, 17]. They are significantly associated with stress [18], depression [19], and anxiety [20], which can lead to synergistic effects regarding stroke and CHD mortality [21].

However, some papers contain contradictory data on the role of psychosocial RFs in the prognosis of CVDs [22–25]. This heterogeneity is clearly due to methodological differences between studies and differences between the studied populations, including ethnic differences. The role of psychosocial RFs in the onset and development of CVDs does require further study. A Russian prospective multicenter study COMET was initiated for this purpose [26] to examine the prevalence of psychosocial RFs in patients with AH and CHD in primary health care and their influence on the prognosis. This article presents the 1.5-year results of long-term follow-up of the COMET cohort.

Objective

Estimate the significance of a number of psychosocial RFs for CVDs (stress, anxiety and depressive symptoms, low level of education, low income, social isolation, and type D personality) for the prognosis in patients with AH and CHD according to the long-term prospective study.

Material and Methods

The COMET study (Clinical-epidemiOlogical prograM of studying psychosocial risk factors in cardiological practice in patiEnts with arterial hyperTension and ischemic heArt disease) is a multicenter study consisting of clinical epidemiological and prospective parts (with patient status followed up for 1.5 and 3 years after inclusion in the study) and covering 30 large Russian cities located in a large geographical area (from Kaliningrad to Khabarovsk). The study design and baseline characteristics of the subjects have been previously described in detail [26]. In each city, 2–5 territorial polyclinics were randomly selected, in each of which 2–5 primary care physicians or general practitioners were invited to participate in the study. Each physician included 8–10 consecutive patients with AH and/or CHD at scheduled visits within 1–2 workdays. The age of ≥55 years, confirmed diagnosis of AH and/or CHD, and signed informed consent were the inclusion

ISSN 0022-9040. Kardiologiia. 2023;63(12). DOI: 10.18087/cardio.2023.12.n2564

criteria. AH was verified at BP ≥ 140 and/or ≥90 mm Hg or in case of the administration of antihypertensive drugs at the time of the visit. The diagnosis of CHD was verified by the presence of a documented history of myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), or typical angina pectoris in combination with positive findings of non-invasive examinations (load tests or coronary computed tomography angiography) or hemodynamically significant coronary artery stenosis (≥ 50%) according to invasive coronary angiography. Exclusion criteria included severe acute health conditions or exacerbations of chronic diseases, any diagnosis of mental disorders and drug or alcohol abuse based on the medical records during the previous 5 years. This inclusion strategy produced a cohort of 2,775 patients included by 325 general practitioners. All patients signed informed consent to be included in the trial.

Demographic and anthropometric data, traditional and psychosocial RFs of CVDs were registered at the baseline examination. Patients completed a questionnaire including age, gender, data on lifestyle RFs (smoking, eating habits, alcohol consumption, physical activity level), marital and occupational status (intellectual labor, physical labor, self-employed, retired, unemployed persons), social support, income level, and stress. The level of social support was self-reported as low or high, and the level of income was assessed as low, medium, or high (according to personal perception). The level of physical activity was also self-reported and defined as low, moderate and high (less than 30 minutes per day; 30–60 minutes per day; > 60 minutes per day). Self-reported eating habits included consumption of fruits and vegetables (more or less than 500 g per day), fish (more or less once a week), adding salt to cooked food, restricting saturated fat, and drinking alcohol (yes or no; if yes, the number of standard drinks per day and per month in case of a positive response). The stress level was assessed using a 10 point visual analog scale (VAS) as low (VAS <4), moderate (VAS 5–7), and high (VAS >8). Anxiety and depressive symptoms were assessed using by the Hospital Anxiety and Depression Scale (HADS) [27]: a score of 8–10 points on HADS-A and HADS-D subscales was considered as subclinical anxiety and depressive symptoms, and a score of ≥11 as indicating to clinically significant symptoms. The DS14 questionnaire [28] was utilized to detect type D personality. It consists of 14 Likert-type questions that form two subscales – negative affectivity and social inhibition. A combination of ≥10 scores for both subscales corresponds to type D personality. Patients were instructed on how to complete all questionnaires, after which they completed the questionnaires independently in the recreational areas of the out-patient clinics and handed them in to the medical staff.

A physician filled out a separate questionnaire for each included patient with data on a history of revascularization procedures (coronary or carotid arteries), mean frequency of angina attacks (if any), concomitant diseases, drugs administered for AH and CHD, psychotropic drugs, hospital admission within the previous year. Physical examination data (height, body weight, waist circumference, blood pressure) and the latest available levels of fasting serum cholesterol and glucose for the previous year were also entered based on medical records. Information on total cholesterol was missing in 234 (9.2%) patients.

One and a half years after inclusion, patients were contacted by phone for information on their vital status and MACE, including cardiovascular death and non-fatal complications – MI, CABG, and PCI, stroke/transient ischemic attack (TIA). Information on other clinically significant changes in the patients' state of health, prescribed drugs and adherence to drug treatment, and hospital admissions was collected. If a patient was deceased, the date and cause of death were found out from his/her relatives or the primary care physician who included him/her in the study.

Statistical analysis

Distribution of patient characteristics were summarized using the means and standard deviations for continuous variables and the absolute numbers and percentages for categorical variables. Logistic regression analysis was used to investigate factors associated with symptoms of anxiety and depression independently of age, gender, and level of education. Associations were expressed as adjusted odds ratios (OR) and 95% confidence intervals (CI). The p-values were based on Wald statistics (chi-squared test). Homogeneity of OR depending on gender and the presence of CHD was assessed by including interaction effects in the models. Model assumptions were verified by graphical analysis of residuals. Statistical significance was indicated by a type I error level $\alpha = 0.05$ (two-tailed test). Data analysis was performed in SAS version 9.4 in the Department of Public Health and Primary Care, Ghent University, Belgium.

Results

Reliable long-term follow-up results were obtained in 1.5 years for 2,538 of 2,775 patients with AH and/or CHD who had undergone the baseline examination. However, 69 subjects changed their places of residence, another 37 patients refused follow-up interview, and 131 were lost for follow-up for different reasons. Thus, the response was 91.5%.

At the time of the baseline examination, the mean age of subjects with 1.5 year follow-up data available was 66.6 ± 7.8 years; 28.1% of them were males, 97.4% patients had AH, 38.8% had CHD, 13.2% had a history of MI, and 10.4% had a history of coronary artery revascularization. Other comorbidities were atrial fibrillation (9.1%), diabetes mellitus (22.6%), chronic kidney disease (8.0%), history of cerebral stroke (6.2%). Up to 40.7% of the cohort were obese, of whom 56.5% patients had abdominal obesity. As for behavioral RFs, 8.3% of subjects continued to smoke, 37.8% stated insufficient fruit and vegetable intake, 59.3% ate fish less than once a week, 29.4% did not restrict intake of saturated fats, and 19.5% reported exercising less than 30 minutes per day. In general, more than 60% of patients with AH and CHD received acetylsalicylic acid (ASA) and statins, angiotensin-converting enzyme (ACE) inhibitors were administered by more than 80% patients, beta-blockers – 58%, calcium channel blockers – 26%, diuretics – 50%, anticoagulants – 7%, and antidiabetic drugs – 4% [26].

Table 1 (see Appendix to article n2564 Supplementary Materials in the journal's website) presents the baseline prevalence of psychosocial RFs in 2,538 patients included in the COMET study. Only 23.9% of subjects had a low level of education (secondary education or lower); most patients were no longer working (at the time of the baseline examination, the retirement age was 55 years for females and 60 years for males). 44% of subjects considered their income to be low. Although 25.0% of subjects lived alone, only 6.1% of them reported social isolation. 13.4% of patients, mainly females, had a history of psychiatric disorders. About ⅔ of patients experienced increased stress and 21.5% had a high level of stress (VAS > 8). The criteria for type D personality were met by 37.6% of patients.

Using antidepressants was very rare (1.6%) within a year before inclusion. However, 42.4% of patients with AH and CHD had depression symptoms of varying severity at the baseline examination; 5.5% of patients had HADS-D > 14, that is, they were very likely to have major depression. At baseline, anxiety symptoms (HADS-A ≥ 8) were present in 47.4% of patients, 8.6% had very high levels of anxiety symptoms (HADS-A >14) (2 times more often in female patients than in male patients).

In 1.5 years of follow-up, 44 male and 62 female patients died. The majority of deaths were caused by CVDs (n = 69), 17 patients died of malignancies, and another 20 deaths had other causes. Moreover, 27 patients had non-fatal MI, 33 patients were hospitalized for CABG or PCI, and 25 patients had stroke. A total of 148 patients experienced MACE, which were defined as a combination of cardiovascular death, non-fatal MI, non-fatal stroke/TIA, or coronary revascularization (CABG or PCI). The estimated incidence of MACE was 40.0 per 1000 person-years of follow-up in the entire study cohort: 67.9 per 1000 person-years in males and 29.5 per 1000 patient-years in females. It is not surprising that the rate of MACE was higher in patients with CHD than in patients with AH without a history of CHD (66.9 and 23.6 per 1,000 person-years, respectively).

The associations between the initial psychosocial RFs and the subsequent development of MACE adjusted for age and gender are presented in Table 2 (see Appendix to article n2564 Supplementary Materials in the journal's website). Low level of education and unemployment at the time of inclusion in the study significantly increased the likelihood of MACE by 70% and 72%, respectively, over the follow-up period. Labor status demonstrated correlated significantly with gender and a history of CHD.

The percentage of patients with MACE was significantly higher among those with lower level of education, both those engaged in physical labor and those engaged in intellectual labor (Central figure). After adjusting for age and gender, low income, living alone, and low social support did not demonstrate independent associations with MACE. History of mental health disorders, using antidepressants and anxiolytics also did not affect the likelihood of the onset of MACE. In contrast, antipsychotic use was associated at baseline with a 4 fold risk of MACE.

The association between MACE and high levels of stress (VAS ≥ 8) had borderline significance (p = 0.06). Only very high levels of anxiety and depression (HADS-A and HADS-D ≥ 14) were significantly associated with MACE, rather than generally accepted threshold values (≥ 8 or ≥ 10): OR for patients with very high HADS-A scores 1.77 (95% CI 1.03–3.05) and patients with very high HADS-D scores 2.24 (95% CI 1.25–4.04). Type D personality and its individual components, such as negative affectivity and social inhibition, did not have significant associations with MACE in 1.5 years of follow-up.

Since psychosocial RFs contribute to adverse outcomes largely through suboptimal control of traditional RFs for CVDs, an analysis of associations between levels of stress and MACE was conducted with adjustments for traditional RFs. Unfortunately, it was not possible to make adjustments for blood lipid levels due to the lack of those data in a significant number of patients. It is shown in Table 3 (see Appendix to article n2564 Supplementary Materials in the journal's website) that very high levels of stress increased the likelihood of MACE by about 50% in both models, but these associations had borderline statistical significance. Very high HADS-A scores (> 14) were significantly associated with the risk of MACE after adjusting for (1) age, gender, the presence of CHD and diabetes mellitus, and (2) the same set of covariates and smoking and body mass index. Very high HADS-D scores (≥14) were associated with an almost two-fold increase in the risk of developing MACE, but statistical significance was borderline in both models.

ISSN 0022-9040. Kardiologiia. 2023;63(12). DOI: 10.18087/cardio.2023.12.n2564

Given that psychosocial RFs can affect prognosis through some non-cardiovascular health determinants, a separate analysis of associations between stress levels, anxiety and depressive symptoms, and all-cause mortality was conducted.

As with MACE, these associations were evaluated in the models adjusted for age and gender only; for age, gender, history of CHD or diabetes mellitus; for age, gender, history of CHD or diabetes mellitus, smoking status, and body mass index. Neither increased levels of stress (VAS 5–7) nor high stress (VAS ≥ 8) had statistically significant associations with all-cause mortality in any of these models, the same applies for any cut-off points for anxiety symptoms.

At the same time, a very high level of depression (HADS-D ≥ 14) increased the likelihood of all-cause death almost 3-fold: OR 2.92 (95% CI 1.55–5.49; p = 0.0024) adjusted for age and gender only, with very similar results for the other two models: OR 2.85 (95% CI 1,51–5,38; p = 0,0031) and OR 2.88 (95% CI 1.51–5.49; p = 0.0028), respectively.

High level of stress (VAS ≥ 8) increased the likelihood of composite endpoint including all-cause death and/or MACE by more than 50% (after adjusting for age, gender, smoking status and body mass index, history of CHD and diabetes mellitus), this association for anxiety symptoms slightly did not reach statistical significance in all three models (Table 4) (see Appendix to article n2564 Supplementary Materials in the journal's website). Severe depression symptoms (HADS-D ≥ 14) increased the likelihood of all-cause death and/or MACE more than 2-fold, and this trend remained statistically significant after adjusting for all the above indicators.

Discussion

This was the first Russian large-scale long-term prospective study to assess the significance of a large number of psychosocial RFs for the prognosis of AH and CHD adjusted for traditional cardiovascular RFs. The COMET findings confirm that psychosocial RFs, such as low level of education, low income, stress, anxiety, and depressive symptoms, are significant determinants of unfavorable prognosis for patients with AH and/or CHD.

The most recent ESC Guidelines on CVD prevention in clinical practice suggest assessing psychosocial stress in patients with CVD and taking it into account as a risk modifier [5]. Moreover, anxiety and depressive symptoms were included in the new EUROASPIRE prognostic calculator for patients with chronic CHD based on a multivariate model using long-term follow-up data from the EUROASPIRE IV and EUROASPIRE V studies [29].

In addition to obtaining further confirmation of the significance of anxiety and depressive symptoms for prognosis, the association between high levels of stress and the composite endpoint, including all-cause death and MACE, was shown this analysis. There is plenty of evidence of the prognostic significance of stress in the development of CVDs, for example, with regard to new cases of CHD [30, 31] or strokes [32]. In these meta-analyses, the hazard ratio for CHD was approximately 1.3, and as for stroke, it differed depending on the type of stroke (1.40 for ischemic stroke and 1.73 for hemorrhagic stroke). However, the relationship of stress with subsequent outcomes is less studied in patients with CVDs. A significant increase in mortality was shown in a relatively large cohort of 4,204 patients with MI in the United States over 2 years of follow-up of patients with moderate to high stress (hazard ratio 1.42, 95% CI 1.15–1.76) [33]. In the multicenter PORTRAIT study [34], the elevated levels of stress during the first year after diagnosing peripheral arterial disease was independently associated with an increased risk of all-cause death in the subsequent 4 years of follow-up (hazard ratio 2.12; 95% CI 1.14–3.94). A recent Chinese study [35] shown an activation of blood clotting in patients with CHD and high levels of stress, and this may be a possible mechanism underlying the observed associations. Anyway, the COMET study is the first Russian study to provide prospective data on the role of a variety of psychosocial RFs for CVDs, including low levels of education, low income, social isolation, stress, anxiety and depressive symptoms, and type D personality, for 1.5 year prognosis of AH and CHD. There are very few such studies in the global perspective. Particular attention should be paid to the data obtained on the role of high levels of stress.

Notably, all associations between psychosocial RFs and MACE and/or all-cause mortality were statistically significant in this analysis only for high or very high levels of stress, anxiety, and depression, rather than generally accepted thresholds of the HADS subscales (8–10 or ≥ 11). A strong association between the prior use of antipsychotics and MACE (OR 4.0; 95% CI 1.55–10.36) cannot be ignored. This can be explained, on the one hand, by the adverse cardiovascular and metabolic effects of antipsychotic drugs, on the other hand, since the presence of documented mental disorders within the previous 5 years was the exclusion criterion in this study, the need for this class drugs can serve as a surrogate marker of severe stress.

The fact that the associations of interest achieved statistical significance only at very high levels of psychosocial RFs may be explained by the relatively low number of outcomes against decreasing cardiovascular mortality across the country and improving the social and economic situation. In addition to the mentioned work by Lazzarino et al. [21], who demonstrated the synergistic effects of low socioeconomic status and stress with regard to stroke or CHD mortality, a more recent Korean cohort study provided similar data on depression [36]. This synergy most definitely appears to be true, given that low socioeconomic status affects access to medical care, and is associated with stressful events occurring

more frequently and fewer resources available to deal with them. There are also several recent papers demonstrating an association between low socioeconomic status and abnormal physiological responses to stress involving the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system [37, 38]. From this point of view, it seems important that patients with low levels of education, regardless of their further labor status, had the highest frequency of MACE in our study.

In the COMET study, there were no statistically significant associations of MACE and/or all-cause mortality with low income, social isolation, and type D personality. One possible explanation is the insufficient number of clinical outcomes and, thus, a lack of statistical power of the study to analyze the effects of these psychosocial RFs, which have only a moderate effect on risk according to the literature. For example, Valtorta et al. [39] showed in their meta-analysis that low social support increased the risk of CHD or stroke by only about 30%. Moreover, there is recent evidence [40] of the existence of cultural differences between evaluations of the effects on the outcomes of loneliness and social isolation. It should also be emphasized that the COMET study was conducted in territorial polyclinics, which may have reduced the possibility that study subjects included very wealthy people. As for type D personality, this concept has recently been criticized [41, 42] with regard to the validity of this psychological construct and its direct association with CVDs.

The COMET study is one of the largest scientific projects in Europe, which focuses specifically on the role of psychosocial RFs in the prognosis of AH and CHD. The advantages of this study include very high (91.5%) response at the prospective stage and a wide range of psychosocial RFs of interest including low levels of education, low income, social isolation, stress, anxiety and depressive symptoms, and type D personality. The COMET study findings emphasize the significance of low levels of education, unemployment, high stress, very severe symptoms of anxiety and depression as determinants of an unfavorable prognosis for patients with AH and/or CHD. It should be noted that these data were collected during modern cardioprotective drug therapy: ASA and statins were administered by more than 60% of the subjects, ACE inhibitors – more than 80%, beta-blockers – 58%, calcium channel blockers – 26%, diuretics – 50%, anticoagulants – 7%, and antidiabetic drugs – 4% [25]. With the exception of statins, most of the drug classes that are commonly used for AH and CHD were not associated with the prevalence of anxiety or depressive symptoms. 27.4% of patients receiving statins and 22.7% of statin-naïve patients had HADS-A ≥ 11 ($p < 0.01$).

However, the COMET study has several limitations. In addition to the previously noted lack of data on blood cholesterol levels in some subjects, it is worth noting that a number of psychosocial RFs, such as stress and income levels, and social isolation, were registered. The presence of anxiety and depressive symptoms was assessed only using the HADS questionnaire, the subjects were not examined by a psychiatrist. Finally, the results obtained may not be applicable to other groups of patients with CVDs, such as those residing in rural areas or those receiving care under privately purchased medical insurance.

Conclusion

Very high levels of stress and severe depressive symptoms are independently associated with a higher all-cause mortality and incidence of MACE, and low levels of education and severe anxiety symptoms are associated with a higher incidence of MACE in patients with arterial hypertension and/or coronary heart disease in primary health care settings. Our findings show that stress, anxiety, and depressive symptoms remain to be significant predictors of adverse outcomes in patients with arterial hypertension and coronary heart disease in the modern era of clinical practice. The most significant psychosocial risk factors should be considered in the context of their influence on the prognosis when developing secondary prevention strategies for arterial hypertension and coronary heart disease.

Acknowledgements

The COMETA study group thanks the administrative staff, doctors, nurses, and other staff of the medical institutions where the study was conducted, as well as all the participating patients.

Funding

Funding was provided by the National Medical Society of Preventive Cardiology Association.

No conflict of interest is reported.

The article was received on 28/07/2023

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