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"CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST

DOCTORAL SCHOOL

MEDICINE FIELD

THE MANAGEMENT OF PATIENTS WITH CORONARY ATHEROSCLEROTIC DISEASE USING MODERN IMAGING TECHNIQUES

PHD THESIS SUMMARY

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1. **Capisizu AS,** Cuzino D, Stanciu SM. The role of coronary CT angiography in the management of patients with coronary atherosclerotic disease. *Romanian Journal of Military Medicine*. 2023 May; CXXVI(2):160-165. https://doi.org/10.55453/rjmm.2023.126.2.6.
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   (Chapter 1. Current nosology of atherosclerotic coronary artery disease, subchapter 1.2. Management guidelines in coronary atherosclerotic disease, pages 10-12; Chapter 2. Diagnosis of atherosclerotic coronary artery disease, subchapter 2.2. Diagnostic imaging methods and means, 2.2.3. Computed Cardiac Tomography, pages 19-21.)

2. **Capisizu AS,** Cuzino D, Stanciu SM. A Pilot Study on the Role of Computed Tomography in the Management of Patients with Coronary Artery Anomalies in Romania. *Journal of Cardiovascular Development and Disease*. 2023 Apr 15; 10(4):170. https://doi.org/10.3390/jcdd10040170.
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3. **Capisizu AS**, Stanciu S, Cuzino D. Reliability of cardiac computed tomography examination in cardiac pathology – a case series and literature review. *Journal of Medicine and Life*. 2023 Jul; 16(7):1140-1146. https:// doi.org/10.25122/jml-2023-0268
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4. **Capisizu AS,** Stanciu S, Cuzino D. A Pilot Study on the Association between Cardiovascular Risk Factors and Coronary Artery Calcification in a Group of Patients Investigated via Cardiac Computed Tomography in a European Country with High Cardiovascular Risk. *Biomedicines*. 2023; 11(11):2926. https:// doi.org/10.3390/biomedicines11112926
   - Journal indexing: PubMed, PMC, SCIE (Web of Science), Scopus, Embase, CAPlus/ SciFinder, ProQuest, EBSCO. Impact factor: **4.7.**
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Introduction

The leading cause of death in Europe is cardiovascular disease (CVD), which is a more common cause of death than cancer [1-3]. Lifestyle risk factors (smoking, diet, weight, level of physical activity, etc.) and biological risk factors (hypercholesterolemia, hyperglycemia, hypertension) contribute to the presence of cardiovascular disease [3, 4].

According to European statistics published in the 2021 European Society of Cardiology Report, there is a 30% incidence of cardiovascular disease in low- and middle-income European countries [5]. Romania, however, is a country with a very high risk and is part of the European countries with 50-60% mortality through CVD [6-9].

Modern and current diagnostic management of cardiovascular diseases is complex and includes numerous diagnostic methods. Due to technological progress in the last decade and the improvement of the method, cardiac computer tomography (CT) examination, more precisely coronary tomography angiography (CCTA), has become the method of choice for investigating coronary atherosclerotic disease [3, 9-11].

In the Romanian population, however, there are a limited number of studies on coronary atherosclerotic pathology evaluated by cardiac CT. Taking into account these considerations, the main objectives of the research were to assess the presence of cardiovascular disease risk factors in a Romanian population investigated by cardiac CT and to establish the correlation between the presence of cardiovascular risk factors and the degree of coronary lesions identified.

For a complex evaluation, the thesis included two substudies, in the first we investigated clinical and morphofunctional correlations in patients with coronary atherosclerotic disease and in the second substudy we investigated the correlations between modern imaging techniques and atherosclerotic degrees of damage, mainly by cardiac CT.

I. General part

1. Current nosology of atherosclerotic coronary artery disease

1.1. Definition, classification, epidemiology, pathophysiogenesis and risk factors

1.1.1. Definitions

Cardiovascular disease (CVD) includes a broad picture of diseases of the heart and blood vessels. Atherosclerotic diseases of the coronary artery is the most common, both in the chronic form and in acute coronary syndromes [12, 13]. Coronary artery disease (CAD), also called ischemic heart disease, is a heart condition in which atheroma is deposited in the coronary arteries [13-15].

1.1.2. Classification

The clinical classification of coronary artery disease according to the European Society of Cardiology (ESC) Guidelines is made into : stable ischemic heart disease and acute coronary syndromes [14].

1.1.3. Epidemiology

According to European statistics, Romania is a country with a very high risk of CVD, with mortality of 50% to 60% due to circulatory diseases [6-8].

1.1.4. Pathophysiogenesis of atherosclerosis

The initiation of atherosclerosis occurs through the adhesion and aggregation of small circulating lipoprotein particles of proteoglycans, from the vascular intimal extracellular matrix, over time the progression of lesions occurs, resulting in stenosis of the vascular lumen [12-14, 16].

1.1.5. Cardiovascular risk factors

Among the risk factors for CAD we mention age over 65 years, male sex, heredity, obesity, smoking, alcohol, hypertension, dyslipidemia, diabetes, sedentary lifestyle.

1.2. Management guidelines in atherosclerotic coronary artery disease

The **European Society of Cardiology (ESC) Guidelines** indicates the management in *six steps* of patients with angina pectoris [3, 5, 10, 11].

The **CAD-RADS reporting system)** it is done according to the degrees of stenosis, in five stages [3, 17].

2. Diagnosis of coronary atherosclerotic disease

2.1. Clinical, electrocardiographic and laboratory diagnosis

2.1.1. Examination of the patient

The diagnosis of cardiovascular disease is complex and requires careful examination (anamnestic and clinical) plus targeted investigations and biological analyzes [12, 13].

2.1.2. Resting electrocardiogram (ECG)

The resting electrocardiogram (ECG), typically with 12 standard leads, is the most commonly used method to assess the electrical activity of the heart [10, 12, 14, 18, 19].

2.1.3. Serum biomarkers – indicators of cardiovascular disease

Depending on their place in the pathophysiology of heart disease, biomarkers may be specific to myocyte lesions such as cardiac troponins I and T, creatine kinase [12, 14].

2.2. Diagnostic imaging methods and means

2.2.1. Echocardiography

Echocardiography is the most used imaging method of cardiac investigation due to its many advantages, including accessibility, with low technical requirements [12].

2.2.2. Stress test, Stress echocardiography

Stress electrocardiogram consists of artificially exposing the heart to stress with recording the ECG route before, during and after stress. Echocardiography can also be integrated into the stress test [14].

2.2.3. Computed cardiac tomography

The main indication of cardiac CT examination is the visualization of the coronary arteries. The CT exams are made with ECG-gating. The calcium score is evaluated initially, then the acquisition with contrast is obtained by coronary CT angiography (CCTA) [11, 20].

2.2.4. Nuclear imaging

Myocardial perfusion scintigraphy is a method of noninvasive nuclear imaging investigation consisting in intravenous administration of radiotracers, positron emission tomography (PET) uses the same principle of radiotracer administration [12, 21].

2.2.5. Cardiac magnetic resonance imaging (MRI)

Magnetic resonance imaging investigation is based on the application of radiofrequency pulses to hydrogen atoms to structures located in the magnet [12].

2.2.6. Coronary angiography

It is an invasive, irradiating method that allows visualization of the coronary arteries [12, 14].

II. Personal contributions

3. The contribution of imaging in the diagnostic management of the patient with coronary atherosclerotic disease

3.1. Research hypotheses and general objectives

General research hypotheses

Hypothesis 1 The presence of chronic heart disease risk factors in a community may indicate an increase in cardiovascular disease morbidity in a group of patients who have addressed a medical center specialized in cardiology and imaging investigations.

Hypothesis 2 We started from the premise that cardiovascular disease risk factors and clinical symptoms are the determining precursors that help diagnose ischemic heart disease through imaging investigations.

Hypothesis 3 The complementarity between risk factors, clinical symptoms and modern imaging investigations can lead to an accurate and early diagnosis of ischemic heart disease.

The purpose and main objectives of the research

The purpose of the research thesis is to determine the most effective medical management of atherosclerotic cardiovascular disease diagnosis, evaluating risk factors, present symptomatology and especially the effectiveness of imaging evaluations.

3.2. General research methodology

A cross-sectional descriptive research was carried out in which patients who presented to the Center for Radiology and Medical Imaging of the Central University Emergency Military Hospital "Carol Davila", Bucharest, between February 2021 and April 2023. Patients were investigated clinically and paraclinically by the attending physician, were investigated by cardiac CT to establish coronary atherosclerotic involvement.

The study was carried out in accordance with the Helsinki Declaration and approved by the Ethics Commission of the Central University Emergency Military Hospital "Dr. Carol Davila", Bucharest, Romania, decision No. 433/ 12.01.2021 [9].

For statistical analysis we used IBM SPSS Statistics version 21. For numerical quantitative variables, mean and standard deviation were used, and percentages were used for nominal variables. Category/nominal variables analyzed by the Chi square test of association or independence were used.

4. Substudy A. Evaluation of socio-demographic profile, clinical and morphofunctional correlations in patients with coronary atherosclerotic disease

4.1. Research hypotheses and specific research objectives

Research hypotheses

1. The presence of cardiovascular disease risk factors may indicate an increase in morbidity through chronic coronary artery disease in a group of patients who have addressed a medical center specialized in cardiology and imaging investigations.

2. We started from the hypothesis that cardiovascular disease risk factors and clinical symptoms are the determining precursors that help diagnose ischemic heart disease through imaging investigations.

Specific objectives

1. Determination of the presence of risk factors of cardiovascular disease in the group of patients.

2. Establishing the presence of cardiac symptoms according to the assessment by the attending clinician and the association with cardiovascular disease risk factors.

3. Evaluation of patient management and establishing correlations between the investigations -resting electrocardiogram (ECG), and the presence of cardiovascular disease risk factors.

4.2. Research methods

4.2.1. Study design and participants

A cross-sectional descriptive research was carried out in which **222 patients** were included who presented themselves in the Central Military Emergency University Hospital "Carol Davila", Bucharest, between February 2021 and April 2023, in order to perform cardiac tomography. We evaluated cardiovascular risk factors, the presence of cardiac symptoms and ECG [9].

The *inclusion criteria* were: adults over 18 years, patients with suspected atherosclerotic coronary artery disease according to the clinician's assessment, patients with known coronary atherosclerotic disease to monitor the evolution of the disease.

The *exclusion criteria* were: patients suspected of acute coronary syndrome, unstable angina, patients who had myocardial infarction in the last 40 days, insufficient data in

patients' medical records, conditions that determine poor quality CT imaging information, patients with contraindications to contrast agents, pregnancy.

4.2.2. Methodology

The variables analyzed in the patients were as follows:

I. Anthropomorphic data: age and sex;

II. Clinical data:

-presence of cardiac symptoms;

-presence of cardiovascular disease risk factors: hypertension, increased weight, smoking;

III. Paraclinical data

a. *Biological variables*:

- dyslipidemia: triglycerides, total cholesterol, LDL cholesterol, HDL-C cholesterol;

- diabetes: serum glucose.

b. *Cardiac examination data*: resting ECG in 12 leads.

4.2.3. Definition of cardiovascular disease risk factors

Blood pressure (BP)- hypertension was defined as the presence of systolic BP values equal to and above 140 mmHg and diastolic BP values of 90 mmHg and above.

Body Mass Index (BMI) > 30 kg/sqm signifies *obesity*.

Dyslipidemia was defined as the presence of one or more lipid parameters with elevated values, plus the existence of treatment to lower cholesterol or history of dyslipidemia.

Diabetes was defined as the presence of glucose-lowering therapy, serum glucose levels >120 mg/dL.

Smoking-patients who smoked and those with a history of smoking were considered smokers [9].

4.3. Results

4.3.1. Determination of the presence of cardiovascular risk factors in the group of patients

4.3.1.1. Characterisation of the patient group

The study included 222 subjects, including 107 (48.2%) men and 115 (51.8%) women, aged 21-84 years..

4.3.1.2. Establishing the presence of hypertension in the group of patients and association with the rest of the cardiovascular risk factors

Considering hypertension values of 140 mmHg and above for systolic blood pressure or values of 90 mmHg and above for diastolic blood pressure, hypertension was present in 66.7% of patients.

Out of the entire sample of patients, 74 (33.3%) had normal blood pressure, 36 (16.2%) had grade I hypertension, 69 (31.1%) had grade II hypertension, and 43 (19.4%) had grade III hypertension.

Statistically significant associations have been established between the presence of hypertension and the presence of age over 50 years, the presence of obesity (Chi-square=14.63, p=0.001), dyslipidemia (Chi-squared=14.78, p=0.001) and diabetes mellitus (Chi-squared=13.85, p=0.001).

4.3.1.3. BMI determination and the association with cardiovascular disease risk factors

Out of the group of patients, 92 (41.4%) were overweight with BMI between 25.0 - 29.9 kg /m^2 and 67 patients (30.2%) were obese with BMI $\geq$ 30 kg /m^2. Among obese patients, 60 (89.66%) were over 50 years of age. The majority of obese patients were women 38 (56.7%). There is a statistically significant association between obese people and the presence of diabetes (Chi-squared = 4.96, *p=0.02*).

4.3.1.4. Determination of dyslipidaemia and correlation with cardiovascular disease risk factors

In the study, 141 (63.5%) patients with dyslipidaemia were present. There was a statistically significant difference between the presence of dyslipidemia and the age of patients under 50 years and over 50 years (Chi-squared = 12.61, *p = 0.001*). There was a statistically significant association between the presence of dyslipidemia and the presence of diabetes mellitus (Chi-square=7.35, *p=0.007*).

4.3.1.5. Determination of the presence of diabetes mellitus and the association with cardiovascular disease risk factors

Diabetes mellitus was present in 43 (19.4%) of patients. Of the patients with diabetes, the majority were women 25 (58.1%). There is a statistically significant difference between people with diabetes and the age of patients under 50 and over 50 years (Chi-squared = 6.74, *p = 0.009*).

4.3.1.6. Establishing the presence of smoking and association with other cardiovascular disease risk factors

Regarding the presence of smoking, 56 (25.2%) patients were smokers. Among smokers, the majority were men 30 (53.6%). There is a statistically significant difference between people who smoke and the age <50 years and over 50 years (Chi-squared = 11.14, *p = 0.001*).

4.3.2. Determination of the association between the presence of cardiac symptoms and cardiovascular disease risk factors

Cardiac symptoms were present in 164 (73.9%) of patients, the majority of patiens 96 (58.5%) were women. There is a statistically significant difference between people with angina and their sex (Chi-squared = 11.40, *p = 0.001*).

4.3.3. The management of ECG diagnosis in patients with atherosclerotic coronary artery disease

All subjects included in the study were evaluated by ECG and 107 patiens (48.2%) had ischemia changes on the ECG. The age of patients with ischemia changes on ECG ranged from 22 to 84 years, mean age was 58.01 (+/- 12.26) and most of the patients with ischemia 86 (80.4%) were over 50 years of age, most of them were men 55 (51.4%). There is a statistically significant difference between people with ischemic changes on the ECG and the presence of diabetes mellitus (Chi-square=12.19, *p=0.001*).

4.4. Discussion

According to European statistics, Romania is a country with a very high risk of CVD and is part of the European countries with 50-60% mortality due to circulatory diseases [6-9].

In national studies, the prevalence of cardiovascular risk factors varies: hypertension 45.1%, dyslipidemia 61.3%-73.3%, diabetes mellitus 11.6%-12.4%, obesity 30%-31.90% and smoking 28% [22-26].

According to the National Institute of Public Health in Romania, the most important risk factors for death by cardiovascular disease are: hypertension responsible for 31.8% of deaths, smoking 16.3%, hypercholesterolemia 14.4%, obesity 13.9%, alcohol consumption 12.4%, sedentary lifestyle 6.6% [22].

According to European data presented in the ESC 2021 report, the prevalence of age-standardized hypertension is 30%. The prevalence of obesity in Romania among adults is 22.4%. The prevalence of type 1 and type 2 diabetes, standardized by age, among adults

aged 20-79 years, is 6.9% in Romania. The prevalence of smokers in the population aged over 15 years is 26.7% in Romania [2].

High blood pressure is the leading modifiable risk factor, responsible for mortality worldwide, which contributed to 10.8 million deaths from cardiovascular disease in 2021 [27].

In this study, 74 patients (33.3%) had normal blood pressure, 36 patients (16.2%) had grade I hypertension, 69 patients (31.1%) had grade II hypertension, and 43 patients (19.4%) had grade III hypertension [9].

The strongest associations of hypertension were as follows: with dyslipidemia, obesity and diabetes. Thus, the prevalence of hypertension of 66.7% is closer to the values established by Popa et al [8] of 74.5% and higher than other values from national studies 45.1% [24] and 46% [28].

Regarding BMI values, out of the entire sample, 92 (41.4%) patients were overweight with BMI between 25.0 -29.9 and 67 (30.2%) were obese [9].

Therefore, the prevalence of obesity of 30.2% established in the current study is similar to the prevalence established in other national studies with values above 30% [8]. Popa et al [26] conducted an epidemiological study on 2681 subjects, which established the prevalence of obesity and overweight patients in the Romanian adult population. The study established the prevalence of obesity at 31.9%, as well as a prevalence of overweight patients at 34.7%, lower than that in the current study, 41.4%. Also, the prevalence of obesity is higher than the values presented in European studies referring to the presence of obesity in Romania, approximately 22% [2].

Regarding the prevalence of dyslipidemia in the entire sample, 63.5% patients had dyslipidemia [9]. The age of dyslipidemia patients ranged from 39 to 83 years, mean age was 60.49 (+/- 10.02) years. Levels of LDL cholesterol and low-weight lipoproteins are associated with increased risk of cardiovascular disease, which increases exponentially through exposure to young and middle ages. In family involvement with heterozygous involvement, affecting about 1:500 people, hypercholesterolemia and increased incidence of premature myocardial infarction are associated [2, 12]. In the current study, of the patients with dyslipidemia, the majority, 121 (85.8%) were over 50 years old and there is a statistically significant difference between the presence of dyslipidemia and the age of patients under 50 years and over 50 years (Chi-squared = 12.61, p = 0.001). No statistically significant difference has been established between the presence of dyslipidemia and the sex of individuals (Chi-square=0.001, p=0.99).

Similar to studies in the literature, the prevalence of dyslipidemia in Romania is high, with values over 60%, as established by other studies conducted in the country of 69.7% - 77.3% [8, 9, 24].

Type 2 diabetes is an independent risk factor for cardiovascular disease affecting 422 million people globally, including 60 million in the European region. Regarding the age-standardized prevalence of diabetes mellitus for Romania, European statistics estimate a prevalence of 6.9% [2]. Regarding the prevalence of diabetes, in the current study 43 (19.4%) of patients had diabetes mellitus [9]. The established prevalence had similar value to the one in the study conducted by Popa et al [8] which showed a prevalence of diabetes mellitus of 19.3%.

The first national study evaluating the prevalence of diabetes mellitus, the study conducted by Mota et al [25] included 2728 participants and established the overall age- and sex-adjusted prevalence of diabetes mellitus at 11.6% (95% CI 9.6% - 13.6%), with higher prevalence in women and advancing age. It also established the association between altered glucose metabolism and obesity and dyslipidemia. Similarly, the present study established that there is a statistically significant difference between people with diabetes and the age of patients under 50 and over 50 years old (Chi-squared = 6.74, p = 0.009).

Type 2 diabetes mellitus is associated with unbalanced diet, overweight and obesity. The presence of diabetes doubles the risk of death, more than half of these deaths are by cardiovascular disease, largely by ischemic heart disease and strokes [2, 12, 15, 16]. This study established a statistically significant association between obese people and the presence of diabetes (Chi-squared=4.96, p=0.02) and between the presence of dyslipidemia and the presence of diabetes (Chi-squared=7.35, p=0.007).

Regarding the prevalence of smoking, out of the entire sample of patients 56 (25.2%) were smokers [9]. The age of smoking patients ranged from 21 to 79 years, mean age was 54.91 (+/- 11.88) years. Among smoking patients, the majority were men (53.6%). There is a statistically significant difference between people who smoke and the age of patients under 50 years and over 50 years (Chi-squared = 11.14, p = 0.001). In the literature, the prevalence of smoking in Romania was similar, 26.7% [2].

Regarding cardiac symptoms, 73.9% of patients had cardiac symptoms [9]. Among patients with cardiac symptoms, the majority were women 96 (58.5%), a statistically significant difference was established between persons with symptoms and their sex (Chi-square=11.40, p=0.001). The prevalence of cardiac symptoms was similar to the study

conducted by Popa et al [8] which established a prevalence of typical and atypical cardiac symptoms in the Romanian population investigated by CCTA of 72.6%.

All included subjects performed ECG, of which 107 (48.2%) had ischemia changes on ECG, and 86 (80.4%) were patients over 50 years of age, and most were men (51.4%).

4.5. Partial conclusions

- Study A was a cross-sectional study of 222 subjects with a mean age of 58.16 (+/-12.56) years, of whom 78.4% were patients over 50 years of age. In the research group, 48.2% were men and 51.8% women.
- The prevalence of risk factors was in descending order, as follows- 66.7% of patients had hypertension, dyslipidemia was present in 63.5% of patients, prevalence of obesity was 30.2%, smoking 25.2% and diabetes mellitus 19.5% [9].
- Correlations between risk factors show statistically significant associations between the presence of hypertension and obesity, dyslipidemia and diabetes. There are also statistically significant associations between dyslipidemia and the presence of diabetes, between obesity and the presence of diabetes.
- A percentage of 73.9% of the entire group of patients had cardiac symptoms (angina pectoris, retrosternal pain, etc.).
- There was a statistically significant association between people with angina and their gender, with the majority being female (58.5%).
- A percentage of 48.2% of the entire sample of patients showed ischemic changes on resting ECG.

5. Substudy B. The role of modern imaging techniques in the diagnostic management of atherosclerotic coronary artery disease

5.1. Research hypotheses and specific objectives

- **Research hypothesis 1** - whether there is a correlation between the presence of cardiovascular risk factors and coronary changes identified by cardiac CT, according to Agatston calcium score and CAD-RADS score.

- **Research hypothesis 2** - whether there is a correlation between the presence of cardiac symptoms as assessed by the attending physician and the presence of coronary lesions identified by cardiac CT.

- **Research hypothesis 3** - the type of imaging investigations chosen depending on symptoms and risk factors can lead to a complete and rapid diagnosis.

The purpose of this substudy was to determine the prevalence of coronary atherosclerosis in a group of patients who were recommended *Cardiac CT* investigation to evaluate the atherosclerotic coronary artery disease, and to determine the correlation between the presence of risk factors and the presence of atherosclerotic coronary artery disease.

The **specific objectives** of the study were:

1. Evaluating the patients by cardiac CT and determining the degree of coronary atherosclerotic involvement using coronary heart disease reporting systems (AGATSTON CALCIUM SCORE, CAD-RADS).

2. Establishing the association between atherosclerotic vascular disease risk factors and the presence of coronary atherosclerosis assessed by cardiac CT.

3. Determining the association between the presence of cardiac symptoms and the presence of coronary atherosclerosis evaluated by cardiac CT.

4. Coronary evaluation from an anatomical point of view, establishing anatomical variants and the presence of post-therapeutic aspects such as stent or graft.

5. Evaluation of patient management through exercise tests, cardiac ultrasound, coronary angiography, myocardial perfusion scintigraphy and cardiac MRI.

5.2. Research methods

5.2.1. Study design and participants

We conducted a cross-sectional descriptive study that included **222 patients** who presented themselves to the Central Military Emergency University Hospital "Carol Davila", Bucharest, Romania, between February 2021 and April 2023 and performed cardiac CT

according to the recommendation of the attending physician, in order to establish the presence of coronary atherosclerotic disease. The criteria for inclusion and exclusion of patients were the same as in substudy A.

5.2.2. Methodology

The working methodology included the following steps:

I. Identification of patients based on inclusion and exclusion criteria.

II. Evaluation of the patient's medical history.

III. Evaluation of clinical and laboratory data.

IV. Evaluation of coronary CT angiography imaging investigations to establish coronary atherosclerotic involvement.

V. Evaluation of complementary tests: cardiac ultrasound, stress test, myocardial perfusion scintigraphy, cardiac MRI, coronary angiography.

VI. Analysis and statistical interpretation of the resulting data.

5.2.3. Medical investigations

Computer tomography examination for coronary evaluation

Cardiac protocol CT acquisitions were performed for coronary evaluation on a 128 detectors CT system GE Healthcare Revolution. A cardiac protocol with ECG monitoring and synchronization and retrospective acquisitions was performed [9, 10].

In the first stage, the "smart score" scan for calcium score was performed, and afterwards the contrast examination with 60ml of contrast substance at a speed of 5.5mL/s [9-11].

5.3. Results

5.3.1. Establishing the degree of coronary atherosclerotic involvement by cardiac CT evaluation

The study included 222 cardiac CT subjects, with an average age of 58.16 (+/-12.56) years. As assessed by cardiac CT Agatston calcium score, coronary artery calcifications were present in 111 (50%) of patients. Thus, regarding coronary calcifications, 13 patients (5.9%) had calcium score between 1-10 UA, 34 patients (15.3%) had calcium score between 11-100 UA, 36 patients (16.2%) had calcium score between 101-400 UA, 14 patients (6.3%) had calcium score between >400-1000 UA and 14 patients (6.3%) had calcium score above 1000 UA [9]. Of the 222 cardiac CT scans, 222 performed native acquisition to assess calcium score and 211 of the patients had CAD-RADS score evaluation, these were patients with contrast examination and coronary stenosis. According to CAD-RADS reporting, 92 (43.6%) patients were patients without coronary stenosis who had a CAD-RDS score of 0,

33 (15.6%) had a CAD-RADS score of 1-24%, 58 (27.5%) had CAD-RADS score 2 with mild coronary stenosis significance 25-49%, 17 (8.0%) had CAD-RADS score 3 corresponding to moderate coronary stenosis 50-70%, 11 (5.2%) had CAD-RADS score 4 and above with severe coronary stenosis significance.

5.3.2. Establishing the association between the degree of coronary atherosclerotic involvement and cardiovascular disease risk factors

5.3.2.1. Gender and age characterisation of patients with coronary atherosclerotic involvement

Half of the group of patients, 111 patients, did not have coronary calcifications, most of them were women 56.8% and were over 50 years old 64.9% [9]. Of the patients with zero CAD-RADS score, 57 (62%) were patients over 50 years of age, 53 (57.6%) were women.

5.3.2.2. The association between coronary artery disease and hypertension

Of the entire sample of patients, 74 (33.3%) had normal blood pressure, 36 (16.2%) had grade I hypertension, 69 (31.1%) had grade II hypertension, and 43 (19.4%) had grade III hypertension. There are statistically significant associations between hypertensive patients and CAD-RADS levels (Chi-squared=16.56, *p=0.002*).

5.3.2.3. The association between BMI and atherosclerotic coronary artery disease

According to BMI, of the patients included in the study, 30.2%, 67 patients, were obese. No associations with degrees of coronary atherosclerotic involvement have been established [9].

5.3.2.4.The association between coronary artery disease and dyslipidaemia

Dyslipidemia was present in 63.5% of patients. There is a statistically significant difference between patients having dyslipidemia and different levels of CAD-RADS (Chi-squared=18.35, *p=0.001*).

5.3.2.5. The association between coronary artery disease and diabetes

There is a statistically significant difference between patients having diabetes and different levels of CADS-RAD (Chi-square=12.60, *p=0.01*). Thus, patients with diabetes do not have stenosis (7 vs 85).

5.3.2.6. The correlation between coronary artery disease and smoking

A percentage of 25.2% of patients were smokers [9].

5.3.2.7. Establishing the association between degrees of coronary atherosclerotic involvement and cardiovascular risk factors

The presence of statistically significant associations between degrees of coronary calcification has been established**,** as well as between degrees of CAD-RADS stenosis, with

the presence of individual cardiovascular risk factors and the presence of several cardiovascular risk factors [9].

5.3.3. Determination of the association between cardiac symptoms and the presence of coronary atherosclerosis

Cardiac symptoms were present in 73.9% of patients.

5.3.4. CT characterisation of coronary anatomy, coronary anomalies and post-therapeutic aspects

5.3.4.1. Anatomical particularitys, CT characterisation of coronary arteries from anatomical perspective, coronary anatomical variations and abnormalities

A percentage of 9.95%, 21 of the patients, had coronary artery abnormalities. Of these, according to Angelini's classification, 8 (34.8%) had abnormalities of origin and trajectory and 13 (56.5%) had intramuscular bridges.

5.3.4.2. Cardiac CT evaluation of coronary posttherapeutic aspects

Regarding the evaluation of posttherapeutic aspects of coronary arteries, the presence of coronary stents and grafts was evaluated in 211 patients with contrast examination, of which 2.3% had coronary stents and 0.9% had coronary grafts.

5.3.5. Management of patients by stress tests, echocardiography, coronary angiography, myocardial perfusion scintigraphy and cardiac MRI

Of all 222 subjects included in the study, 107 (48.2%) performed *stress test,* Of these, 21 (19.6%) tested positive, 35 (32.7%) had equivocal studies, and 51 (47.7%) tested negative. Of the subjects included in the study, 71.2% performed cardiac ultrasound, 9% performed coronary angiography, 2.3% performed myocardial perfusion scintigraphy, 4.1% performed cardiac MRI.

5.5. Discussion

The prevalence of coronary calcifications according to the Agatston calcium score is similar to other studies in the literature that established values of 40% [29] and 55.4% [30].

According to CAD-RADS reporting, of the patients investigated coronary angiography CT, 92 (44.5%) patients were patients without coronary stenosis measured angiography coronary CT. Popa et al [8] conducted a study on the prevalence of coronary atherosclerotic disease evaluated by CCTA and expressed by CAD-RADS classification in a Romanian population. The results of the study are similar to those in the current study, the largest differences are for the categories CAD-RADS 2 and CAD-RADS 1.

There are statistically significant associations between hypertensive patients and CAD-RADS levels (Chi-squared=16.56, p=0.002). Regarding the existence of an

association between the presence of hypertension and coronary calcifications, there have been several studies that have shown the association of hypertension with the presence of coronary calcifications evaluated CCTA [29-31].

The values obtained for obesity prevalence are similar to other studies for the Romanian population [8] and international [29]. Similarly, the study conducted by Popa et al [8] on a Romanian population, found no statistically significant differences between the presence of obesity and different CAD-RADS levels (p=0.3.6).

There is a statistically significant difference between patients having dyslipidemia and different levels of CAD-RADS (Chi-squared=18.35, p=0.001). In the study conducted by Popa et al [8] on subjects in Romania, the prevalence of dyslipidemia was similar (69.7%) and there were statistically significant associations between the presence of dyslipidemia and the presence of CAD-RADS score 3 and above. There have been several international studies that have shown the existence of an association between the presence of dyslipidemia and the presence of coronary calcifications evaluated by CCTA [31, 32].

There is a statistically significant difference between the fact that patients have diabetes and different levels of CADS-RAD (Chi-squared = 12.60, p = 0.01), patients with diabetes do not have stenoses (7 vs 85). In the study conducted by Popa et al [8] on subjects from Romania, the prevalence of diabetes mellitus was similar 19.3% and there were significant associations between the presence of diabetes mellitus and the presence of CAD-RADS score 3 and above.

Of the patients, 25.2% were smokers [9]. There is no statistically significant difference between patients smoking and CAD-RADS levels. In another study conducted on subjects in Romania, smoking prevalence was higher than 46.3% and there were statistically significant associations between the presence of smoking and the presence of CAD-RADS score 3 and above [8]. Regarding the existence of a statistically significant association between the presence of smoking and coronary atherosclerotic involvement, Wada et al [33] and multiple other studies, including Yazdi et al [29], Min et al [31], Mamudu et al [30], have shown the association of smoking with the presence of CCTA-evaluated coronary calcifications.

In recent years, CCTA has gained more popularity and is now considered the gold standard for diagnosing and characterizing CAA [10, 34, 35].

Thus, two cases of abnormal origin of the left coronary artery with origin in the right coronary sinus were found. This is a rare anomaly, the prevalence of anomalies of the coronary arteries originating from the opposite coronary sinus is 0.1%. In addition, this

coronary abnormality is considered a high-risk anomaly of sudden death 0.17% - 0.35% [10, 36, 37]. An abnormality of origin of the right coronary artery in the left coronary sinus was identified, which also associates malignant trajectory between the pulmonary artery and the aorta. A case of congenital heart malformation was found with transposition of large arteries, with incomplete rotation of the root of the aorta with the association of variation in the origin and course of the coronary arteries.

There are contraindications to CCTA, some related to radiological aspects such as pregnancy, others to contraindications to the administration of contrast agent such as chronic renal failure and iodine allergy. Other contraindications are related to obtaining qualitative images, such as cardiac arrhythmias. Other limitations are related to situations in which qualitative images cannot be obtained: extensive calcifications, impossibility to perform respiratory commands [3, 10, 11].

Regarding the advantages of use compared to other cardiac investigation methods, CCTA is a non-invasive, accessible and low-cost method unlike coronary angiography [10, 11, 34, 38]. The main advantages of CCTA compared to magnetic resonance angiography (MRA) are accessibility, shorter examination time, and higher coronary spatial resolution [10, 39].

5.6. Partial conclusions

- The purpose of study B was to determine the prevalence of coronary atherosclerosis in a Romanian population investigated by *cardiac CT* and the correlations between cardiovascular risk factors and coronary atherosclerotic disease.
- 50% of patients had calcifications in the coronary arteries according to the Agatston calcium score to varying degrees.
- Of the patients, 44.5% had no coronary stenosis according to CAD-RADS reporting, the rest had varying degrees as follows in ascending order—5.2% had CAD-RADS score 4 and above, 8% had CAD-RADS score 3, 15.6% had CAD-RADS score 1, and 27.5% had CAD-RADS score 2.
- CAD-RADS 2 stenoses were statistically significantly associated with patients' age older than 50 years, the presence of dyslipidaemia and the presence of HTA. CAD-RADS 2 and 3 stenoses were statistically significantly associated with the presence of dyslipidemia.

6. Conclusions and personal contributions

Conclusions

1. The management of patients with coronary atherosclerotic disease is complex and involves numerous means of investigation from the usual ones (resting electrocardiogram, echocardiography, effort tests) to the most modern ones such as cardiac CT.

2. Coronary CT angiography is currently the first-line diagnostic method for noninvasive analysis of coronary atherosclerotic pathology.

3. From the analysis of risk factors of cardiovascular disease corroborated with the use of modern imaging techniques, an early and complete diagnosis of ischemic heart disease can be established.

4. The prevalence of risk factors was in descending order, as follows- 66.7% of patients had hypertension, dyslipidemia was present in 63.5% of patients, obesity prevalence was 30.2%, smoking 25.2% and diabetes mellitus 19.5% [9].

5. Correlations between risk factors show statistically significant associations between the presence of hypertension with obesity, dyslipidemia and diabetes. There are also statistically significant associations between dyslipidemia and the presence of diabetes, between obesity and the presence of diabetes.

6. A proportion of 73.9% of the entire group of patients had cardiac symptoms (angina pectoris, retrosternal pain, etc.). There was a statistically significant association between people with angina and their gender, with the majority being female (58.5%).

7. A percentage of 48.2% of the entire sample of patients showed changes in ischemia on resting ECG.

8. Following correlations between risk factors and results obtained in cardiac CT acquisitions - Agatston calcium score (for coronary calcifications) and CAD-RADS score (for coronary stenosis) resulted that 50% of patients had calcifications in the coronary arteries according to Agatston calcium score in varying degrees [9].

9. The following associations are statistically significant: between mild calcifications and age older than 50 years, between moderate calcifications and the presence of dyslipidemia, hypertension and age older than 50 years, between severe calcifications and hypertension, between very severe calcifications and the presence of smoking, diabetes and hypertension [9].

10. A percentage of 44.5% of patients did not have coronary stenosis according to CAD-RADS reporting, the rest had in varying degrees as follows in ascending order- 5.2% had CAD-RADS score 4 and above, 8% had CAD-RADS score 3, 15.6% had CAD-RADS score 1 and 27.5% had CAD-RADS score 2. The strongest predictor for CAD-RADS 2 was the age of patients over 50 years, the second predictor for CAD-RADS 2 was dyslipidemia.

11. The prevalence of coronary anomalies found at CCTA was 9.95%, demonstrating the usefulness of CCTA in anatomy analysis and detection of coronary anomalies.

12. Of the exercise tests performed, 19.6% were positive, and of the patients with positive exercise tests, the majority were men (52.4%).

The main advantages of the study from a technical and economic point of view were: access to modern CT machines, equipped with the latest cardiac acquisition protocols and to workstations with dedicated post-processing software. Thus, the study achieved its objective of establishing the degree of coronary damage by the presence of calcifications and/or coronary stenosis, using a modern imaging method, by Cardiac CT, whose specific assessments – Agatston calcium score and CAD-RADS score – allowed the detection and evaluation of patients with atherosclerotic coronary artery disease.

Personal contributions

- The research study was part of the analysis direction of international studies that followed and analyzed the results obtained by modern cardiac *tomography investigations* in order to diagnose coronary atherosclerotic disease.

- In addition, the present study contributed to establishing results in a Romanian population evaluated by cardiac CT, being *among the first studies in the country to evaluate these aspects.*

- Thus, the study established the prevalence of cardiovascular disease risk factors investigated by cardiac CT in a Romanian population – *chapter 4, pages 35-44.*

- The study established the prevalence of coronary calcifications according to the Agatston calcium score and the correlation with cardiovascular risk factors – *chapter 5 pages 67-75.*

- The study established statistically significant associations between coronary stenosis grades, according to the CAD-RADS score, and cardiovascular risk factors – *chapter 5 pages 68-73.*

- In addition to studies in the literature, the study provided information about the association between the presence *of several cardiovascular risk factors with different levels of* coronary calcification, respectively with different levels of CAD-RADS stenosis. Regarding the predictive value between the presence of several cardiovascular risk factors and the degrees of coronary calcification according to the Agatston calcium score, for very severe calcifications, people who have diabetes and are smokers have a 13.46 times risk of presenting very severe calcifications. People who have the three cardiovascular risk factors: smoking, diabetes and hypertension are 9.18 times more likely to have very severe calcifications – *chapter 5, pages 76-83.*
- A significant finding is that half of the patients investigated by cardiac CT had zero calcium score. Currently, among the tools for predicting the risk of vascular heart disease, the zero calcium score has a superior predictive value than conventional cardiovascular risk factors and serum biomarkers – *chapter 5 page 68.*
- Coronary characterization was performed from an anatomical point of view, the study discovered several coronary anomalies, being the first in a southeastern region of the country to analyze the prevalence of coronary anomalies using CCTA in the population and to analyze the degree of coronary atheromatous damage by CCTA in patients with coronary anomalies. – *Chapter 5 pages 84-92.*

The limits of research

The main limitations of the study were *the exclusion criteria* which limited the use of cardiac CT, having radiological limits referring to claustrophobic patients who cannot withstand investigation in the CT machine, pregnancy, patients who cannot tolerate the administration of iodized contrast substance with known adverse reactions or with chronic renal failure.

Future research directions

Future research directions include increasing the number of CCTA investigations, increasing the addressability of doctors and patients to this investigation and spreading it's use in as many centers in the country as possible.

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