MEDICAL UNIVERSITY OF PLOVDIV
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MANAGEMENT OF CARDIO-VASCULAR RISK IN GENERAL PRACTICE BY THE SCORE SYSTEM

SUMMARY

Of a Dissertation for
obtaining a scientific degree "Doctor"

Professional Field: 7.1. Medicine
Scientific Speciality: General Practice

Scientific supervisor**: Rositsa Tsvetanova Dimova**
Scientific Consultant: **Rumyana Gencheva Stoyanova**

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The dissertation contains 181 standard pages. It is illustrated with 48 tables, 24 figures and 6 appendices. The reference section includes 150 sources.

* The numbering of the figures and tables in the present Summary of a Dissertation do not correspond to the one in the Dissertation.

CONTENTS

SYMBOLS AND ABBREVIATIONS USED

ABP	Arterial Blood Pressure
AH	Arterial Hypertension
CRAS	Civil Registration and Administrative Services
DAP	Diastolic Arterial Pressure
EU	European Union
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
IHD	Ischaemic Heart Disease
IPPMC	Individual Practice for Primary Medical Care
BMI	Body Mass Index
MH	Ministry of Healthcare
CeVD	Cerebro-vascular Disease
NHIF	National Health Insurance Fund
NFA	National Framework Agreement
AMI	Acute Myocardial Infarction
GP	General Practitioner
NPV	Negative Predictive Value
POMC	Primary Outpatient Medical Care
PPV	Positive Predictive Value
RF	Risk Factor
SAP	Systolic Arterial Pressure
WHO	World Health Organisation
CVD	Cardio-vascular Diseases
CVS	Cardio-vascular System
COPD	Chronic Obstructive Pulmonary Disease
ACC	American College of Cardiology,
ADMA	Asymmetric Dimethylarginine
AHA	American Heart Association
ESC	European Society of Cardiology
FRS	Framingham Risk Score
GFR	Glomerular filtration rate
HDL	High-Density Lipoprotein
HDL-C	High-Density Lipoprotein-Cholesterol
IMT	Intima-media thickness
LDL	Low-Density Lipoprotein
Nt-proBNP	N-Terminal Fragment of the Prohormone Brain-Type Natriuretic Peptide
PA	Physical Activity
PAD	Peripheral Artery Disease
PlGF	Placental Growth Factor
RR	Relative risk
SCORE	Systematic Coronary Risk Evaluation
UKPDS	United Kingdom Prospective Diabetes Study

INTRODUCTION

Cardio-vascular diseases together with a number of oncological, metabolic (Diabetes Mellitus and thyroid diseases), pulmonary ones (COPD and bronchial asthma) etc. exert a huge negative influence not only on public and individual health but also on the economies of the countries throughout the world. In the past the most common causes of death were infectious diseases. Undoubtedly, during the last decades cardio-vascular diseases (CVD) have been socially significant, they predominate in the contemporary world and are a leading cause of death. However, with the advances in medical science and technology, an improvement in the quality of life and extension of the average duration are observed, in the developed countries it reaches 80 and more years. The global medical society and international healthcare institutions pay specific attention to non-infectious diseases which are the causes for the morbidity and mortality of a considerable part of the population. CVD are a priority in most national health strategies with a focus on promotion, prevention, and dispensary treatment. In this respect, huge efforts are paid by scientists, physicians and public health specialists worldwide for elucidating the causes of CVD on the basis of atherosclerosis and, of course, for their early diagnosis and treatment. Although the achievements in some countries are hopeful, there are still great expectations in the field of early prevention and morbidity of CVD, and premature mortality. However, this fact does not stop the strife of physicians, devoted to science, to search for new and numerous solutions.

After its beginning in 1948, the Framingham Heart Study turned out to be extremely important for forming and improving our understanding of the history and initial causes of coronary artery disease.

Risk assessment for development of major or fatal cardio-vascular disease in Europe dates to 1994 when the European Society of Cardiology, European Society of Hypertension and European Atherosclerosis Society combined their efforts and published their first guideline on IHD prevention.

International studies and results in this field are performed and published constantly.

The present paper aims at clarifying the manners of implementing the Assessment of risk for occurrence of a major or a fatal CVD performed by GPs in the Republic of Bulgaria and regulated by the NFA. In this respect, it is important to establish the benefits and restrictions for patients from the application of Coronary risk assessment SCORE, especially in target groups with average and high risk. The dissertation compares the results from the regulated by NFA SCORE cardio-vascular risk during regular physical examinations with the ones of the European Society of

Cardiology from 2016 for prevention of cardio-vascular diseases in clinical practice and with the ones of the European Society of Cardiology from 2019 in the Guidelines for management of dyslipidemias. In the Results and Discussion chapter of the dissertation, the presented original results are compared to similar ones from different studies. The comparative analysis from monitoring patients from different risk groups will serve for drawing valuable original conclusions, as well as for recommendations for possible future improvements.

AIM AND TASKS AND WORKING HYPOTHESES

1. AIM

The aim of the dissertation is to measure and evaluate the atherosclerotic cardio-vascular risk of people with health insurance in General Practice with the following methods: SCORE ESC (2016), SCORE NFA, and SCORE ESC (2019) and to propose an improved model for managing risk of CVD.

2. Tasks of the dissertation

1. To assess and compare the absolute cardio-vascular risk by the three methods of the SCORE system: SCORE ESC (2016), SCORE NFA, and SCORE ESC (2019).
2. Based on the absolute individual risk, to calculate the population's relative risk (RR) for the occurrence of severe or fatal CV event in the group of *exposed* (high and very high risk) compared to the *non-exposed* (low and average risk), attributive risk (AR) and the prognostic validity of each of the three methods.
3. To compare and analyse clinical and laboratory health indicators and results (outcome) from the occurred atherosclerotic CVD and/or cardio-vascular death according to the three methods of the SCORE system.
4. To study the incidence and impact of some main risk factors by the SCORE estimation for occurrence of cardio-vascular event.
5. To study the additional, modifying risk factors which influence patient classification in risk categories and to determine whether their reclassification is possible.
6. To develop and propose a comprehensive model for cardio-vascular risk management among the Bulgarian population consistent with the European guidelines.

3. Working hypotheses

First hypothesis: The regulated criteria for SCORE for the three methods: ESC (2016), NFA, and ESC (2019) lead to differences in patient classification in risk groups.

Second hypothesis: The prognostic validity of the SCORE algorithm for the three methods SCORE ESC (2016), SCORE NFA and SCORE ESC (2019) differs significantly.

Third hypothesis: The system for evaluation of cardio-vascular risk SCORE NFA for the occurrence of severe or fatal CVD does not include sufficient criteria in number and precision which would be the basis for the correct identification, classification, and monitoring of the people in categories with higher risk.

Fourth hypothesis: The inclusion of additional modifying risk factors in the SCORE NFA evaluation will improve risk management for CVD occurrence.

MATERIALS AND METHODS OF THE RESEARCH

Design of the study

The study is closed, prospective, cohort (longitudinal) with retrospective data search for risk assessment of CVD occurrence in health-insured individuals from POMC in the town of Pavlikeni with a duration of two years and a monitoring interval from 01.01.2019 to 32.12.2020.

During the first year, prophylactic examinations were conducted and categorization of the patients, simultaneously by all three methods- SCORE ESC (2016), SCORE NFA and SCORE ESC (2019), was performed and during the second year their health status and the changes occurring (incl. data from CRAS register) were followed-up.

MATERIAL

1. Objects of the study

Objects of the study are health insured individuals included in the patient list of the practice who have come for their annual physical examination during the first year of the study.

2. Subject of the study

Evaluation of the atherosclerotic cardio-vascular risk from the occurrence of a severe or fatal CV event due to atherosclerosis measured by the SCORE system and classification of patients in groups according to their risk category.

3. Logical units of observation

Units of observation are all health insured individuals of full age who came for their annual physical examination during the first year of the study and filled a prophylactic health card and measured SCORE cardio-vascular risk. The same patients were followed-up during the second year of the study.

4. Signs of the units of observation

Inclusion criteria

All patients who fall within the age range according to the SCORE NFA, ESC 2016 and ESC 2019 system.

Exclusion criteria

All patients who do not fall within the age range according to SCORE NFA, ESC 2016 and ESC 2019 methods and those with dementia or other severe mental disorders.

Factorial characteristics of the units of observation:

- Biological sex.
- Age.
- Cigarette smoking, regular smoking of 10 and more cigarettes daily.
- Fasting total cholesterol [mmol/l].
- Systolic blood pressure [mmHg].

Documented data for the presence of diseases, which alone place the individual in a high-risk group, were also gathered and included. These diseases are:

- Type 1 or Type 2 Diabetes with complications such as: ocular complications, renal complications, neurological complications, peripheral vascular complications, multiple complications.
- Chronic renal insufficiency in a terminal stage. The criterion is GFR<30 ml/min/1,73 м^2.
- Cardio-vascular diseases such as: arterial hypertension with complications incl. CVD without the cases with essential hypertension; all cases of IHD, myocardial infarction, cardiac insufficiency and/or rhythm and conduction disturbances, as well as valvular lesions due to IHD; cerebro-vascular disease based on atherosclerosis. Aortic aneurism.

Diseases and conditions which placed patients only in the high-risk group were documented as well:

- Chronic renal insufficiency in initial stage. GFR 30-59 ml/min/1,73 m^2 is the criterion.
- Diabetes Mellitus.

On the third place for all unites of observation, the presence or values of the indicators which are modifying factors in SCORE risk assessment, were registered and followed -up.

Additional or modifying risk factors which were followed-up:

- Low physical activity [YES/NO]. A criterion for sedentary lifestyle is physical activity less than 30 minutes daily.
- Regular food intake consisting of fruit and vegetables [YES/NO]. The inclusion criterion is the minimum intake of 100 gr. Fruit and/or vegetables daily.
- Abdominal obesity- waist circumference at the level of the navel.
- Body mass index [kg/m^2]
- Fasting LDL-cholesterol [mmol/l].
- Fasting triglycerides [mmol/l].
- Fasting blood glucose [years]. Regardless of the presence or lack of Diabetes Mellitus.

- Early CVD in the family [YES/NO]. For men- father or brother suffering from IHD or CVD under 50 years of age; for women- mother or sister suffering from IHD or CVD under 65 years of age.
- Diastolic blood pressure [mmHg]
- Regular medicine intake in the presence of arterial hypertension [YES/NO], the criterion is the regular intake of antihypertensive medications at present or in the past.
- Diabetes.
- Presence of Hyperuricaemia and Gout [YES/NO]. Documented diagnosis Hyperuricaemia or Gout with/without complications, treated with/without reaching the target values or untreated.

Resultative features of the units of observation

- Registering a newly occurred severe atherosclerotic CVD.
- Mortality by an atherosclerotic CVD.

5. Technical units of observation

The study took place at "Mediana" IPPMC in the town of Pavlikeni.

6. Ethical norms of the research

The longitudinal epidemiological study meets the standards and criterion for scientificity and ethics and is consistent with the requirements of: Declaration of Helsinki - Ethical Principles for Medical Research, principles of good clinical practice, Bulgarian laws and regulations for conducting clinical and scientific research with the participation of people from the Republic of Bulgaria. The study was approved by the Committee for Research Ethics at Medical University of Plovdiv with Decision №8 from 15.12.2021.

All respondents gave their informed consent for participation in the study in advance. According to the European requirements for personal data protection, each patient received a unique personal identification number for the data entry and result analysis from the conducted research. The full information for each participant was available only to the head researcher.

7. **Number and characteristic of the studied population**

The average age of all 4551 adult health-insured citizens form "Mediana" IPPMC in the town of Pavlikeni is 51.59 years (SD±17.67), with a minimum and maximum age of 18 and 99, respectively, women -2619,men -1932.

The majority is of men aged 70 – 60 patients, followed by the ones at 71 years-58 patients and the smallest number is of the individuals aged 92, 95 and 97 (one patient for each age category). The largest number is of women aged 71 (77 patients) followed by the 70-year olds (76 patients) and the smallest number is for the ones aged 95 and 99 (one patient for each age category).

Of all adult patients three Cohorts were formed depending on the inclusion criteria of the units of observation:

- **Cohort 1** includes 1908 people in total who meet the SCORE (ECS 2016) inclusion criteria with average age - 53.97 years (SD±7.39), minimum and maximum 40 and 65, respectively. The distribution of the contingent of the study according to gender is: women- 1014 (53.1%) and men – 894 (46.9%).

- In **Cohort 2** a total of 1598 units for observation are included, they meet the evaluation criteria of CV risk in accordance with NFA among them women- 704 (44.1%) and men – 894 (55.9%), at an average age – 55.77 (SD±6.60), minimum age -40 years for men and 55 years for women and maximum age – 65 years for men and women.

- **Cohort 3** includes individuals who meet the criterion for CV risk assessment in accordance with SCORE (ECS 2019)- total number 2458. The average age of the cohort was 57.12 years (SD±8.80), the minimum and maximum age (the same for men and women), respectively, 40 and 70 years. The women in Cohort 3 account for 54.6% (1342), and men – 45.4% (1116).

METHODS OF THE STUDY

8. **A short description of the SCORE system for cardio-vascular risk assessment.**

The SCORE method is applied in the assessment and categorisation of risk in four categories for each of the modifications (2016, NFA and 2019). For each of the patients we followed up the morbidity and mortality by atherosclerotic CVD during the second year. Special attention was paid to the follow-up of patients with confirmed high risk in order to check to what extent, at the time of the examination, no measures were taken except routine examinations with annual testing.

Comparing the data from the first year of the assessed risk and the SCORE risk group and the second year from the morbidity and mortality of CVD, we found a difference between the assessment from the first year and the second year in the confirmed cases of severe or fatal CVD, the type of category of assessed risk by the three methods.

The following main factors are included in the SCORE system for assessment:

- Sex
- Age
- Tobacco smoking
- Total cholesterol
- Systolic blood pressure

Apart from the SCORE system for cardio-vascular risk assessment, all individuals, units of observation, are categorised according to risk for cardio-vascular disease prevention in clinical practice corresponding to the same European guidelines from 2016 and 2019, and for this purpose during the prophylactic examination was gathered and documented data on:

Factors and conditions directly pointing to risk categories:

1. For the Very high-risk category:

- Presence of Diabetes Mellitus with complications
- Presence of chronic renal insufficiency in terminal stage
- Presence of cardio-vascular disease

2. For the High-risk category:

- Presence of Diabetes Mellitus
- Presence of chronic renal insufficiency in initial stage
- High total cholesterol > 8 mmol/l
- High arterial blood pressure ≥ 180/110 mmHg
- High LDL-cholesterol > 4,9 mmol/l

Factors, markers, and conditions followed-up in the study with the aim of establishing whether there is additional, modifying predictive value:

- Low physical activity – Regular physical activity at least 30 minutes daily (on the workplace and/or free time).
- Regular food intake of fruits and vegetables- 200 gr. fruit and 200 gr. vegetables for 24 h.
- Abdominal obesity- waist circumference at the level of the navel- waist circumference ≥94 cm for men and ≥80 cm for women
- Body mass index – BMI > 25 kg/m2
- Early CVDs in the family- before 40 years of age
- Low HDL-cholesterol levels ≤ 0,9 mmol/L
- Fasting triglycerides > 1.7 mmol/L
- LDL-cholesterol > 2,6 mmol/L
- Past dyslipidemia
- Diastolic blood pressure > 90 mmHg

- Regular intake of medications in the presence of arterial hypertension in the past or present.
- Fasting blood glucose level > 5,5 mmol/L
- Presence of Hyperuricemia and Gout

During the first year of the study, prophylactic examinations of 4551 adult citizens, registered in the IPPMC were organised and performed. We took a history and health status, performed laboratory tests and filled in a questionnaire in an application software for each of the patients. After obtaining the test results, a questionnaire was filled with the new results and the SCORE cardio-vascular risk was estimated. The results were stored in a data base of application software NISET used under contract.

We estimated the SCORE cardio-vascular risk of all patients who participated in the first year of the study and categorised the patients in accordance with their risk category. Depending on the kind, number and values of the risk factors for each individual patient, we calculated the individual cardio-vascular risk. According to these signs, the patients were distributed to one of the following groups:

- Individuals with very high SCORE risk **(≥ 10%)**
- Individuals with high SCORE risk **(≥ 5% < 10%)**
- Individuals with average SCORE risk **(≥1% < 5%)**
- Individuals with low SCORE risk **(< 1%)**

The distribution is strict: according to the European guidelines from 2016 for cardio-vascular diseases prevention in clinical practice, to the methods described in the first part of the study and to the Guidelines on managing dyslipidemia: modification of lipids for decreasing cardio-vascular risk of the European Cardiology Society from 2019, namely:

- The **very high-risk group** is comprised of patients with **SCORE above 10%.** These are the individuals with a confirmed diagnosis of Type 1 Diabetes Mellitus or Type 2 Diabetes Mellitus, presence of chronic renal insufficiency in terminal stage, presence of CVD documented, clinically manifested, or confirmed by an imaging study such as: arterial hypertension with complications incl. CeVD without the cases of essential hypertension; all cases of IHD, myocardial infarction, cardiac insufficiency and/or rhythm and conduction disorders as well as valve lesions due to IHD, cerebrovascular disease based on atherosclerosis. Aortic aneurism.

- The **high-risk group** is comprised of patients with **SCORE between 5% – 9%** or only the presence of one of the following risk factors: essential hypertension with SAP and DAP values, above 180 and 110 mmHg, respectively; diagnosed Type 2 Diabetes Mellitus above 50 years of age, total cholesterol values above 8 mmol/l or initial renal insufficiency.

- The **average-risk group** is comprised of patients with **SCORE between 1% – 4%** in the presence of one risk factor such as Type 2 Diabetes Mellitus without complications up to 50 years of age, essential hypertension with achieved target values with the help of treatment.

- The **low-risk group** is comprised of patients with **SCORE CV risk below 1%.**

All patients with a certain risk in the first year were followed-up during the last year of the study for the occurrence of new fatal or severe life-threatening atherosclerotic cardio-vascular diseases. This concerns morbidity from cerebral infarction, myocardial infarction (with or without stent) and mortality due to cardio-vascular disease. We retrieved data on CVD morbidity from the medical record of patients, namely: newly occurred diseases (during the second year of the study) such as myocardial infarction with or without stent insertion as well as cerebral stroke as a result of complicated atherosclerosis (mainly Cerebral infarction). We obtained data on mortality cases by CVD from the medical records, death notices from the practice and death notices requested by Pavlikeni Municipality, GRAS Unit. Due to the special additional instructions in the practice for coding the causes of death and the impossibility to ask for this information colleagues, doctors and PAs, from other healthcare institutions (affiliates of the Emergency medical care centers), the death notices received by GRAS are subject to further analysis and comparison with the records due to the possibility for incorrect coding of the causes.

Patients from the very high-risk group are usually known to suffer from adisease and they are patients who are monitored according to a special dispensary programme and a Ministry of Health Regulation. The highest new morbidity and mortality may be expected in this group.

The high-risk group is of particular interest. The cause for this is the fact that it includes non-dispensary patients (with exception of patients with essential hypertension) and it is to the patients from the high-risk group that attention has to be paid regarding the compliance with preventive measures on special regime and monitoring with a view to prevention from developing a CVD. We made an analysis of the significance of the additional, modifying factors and of the epidemiological risk.

For the individuals with average risk, we performed a thorough analysis of the modifying risk factor or conditions which can impact their risk recategorization, i.e. reclassification of the individuals with average risk to the high risk category.

The gathered and processed data was analysed and the corresponding conclusions from the obtained results of the study were drawn.

In conclusion, it can be claimed that the focus of the dissertation is the categorisation of patients according to SCORE CV risk by the three methods and the outcome or development of severe or fatal CVD during the second year in each of the risk categories. The individual cardio-vascular risk is measured in percent depending on the category in which every individual falls and the used SCORE method. We performed an analysis to what extent the SCORE percent is proportional to the percent of patients who developed a severe or fatal CVD. Such an analysis was performed for each of the three modifications according to age and sex, the most appropriate for application being the one in which the expected results in percent are closest to the percent of the observed results.

9. Information gathering methods and techniques

9.1.Inquiry method. Medical interview and history.

One of the methods for gathering information in the present study is a personal, face-to-face structured medical interview.

By the method medical interview, we gathered data from the history and the condition of the patient which we used for calculating the cardio-vascular SCORE risk and the modifying factors. Such RF are:

- Sex
- Age
- Height
- Waist circumference
- Body mass index
- Tobacco smoking
- Systolic blood pressure
- Diastolic blood pressure
- Low physical activity
- Regular food intake of vegetables and fruit
- Early occurred CVD in the family (family history)
- Family history of Diabetes Mellitus
- Dyslipidemia treated in the past
- Regular drug intake in the presence of Arterial Hypertension.

9.2.Document method

With the help of the document method, we gathered data for the identifying already registered diseases and/or performed clinical and laboratory investigations with the aim of risk categorisation or determining risk modifying data in accordance with the European guidelines from 2016 for cardio-vascular risk prevention in clinical practice.

These medical documents are the ones for the presence of identified diseases:

- Diabetes Mellitus without complications
- Diabetes Mellitus with complications
- Chronic renal insufficiency in initial stage
- Chronic renal insufficiency in terminal stage
- Cardio-vascular disease
- Hyperuricemia and/or Gout.

We used online and paper documents for data on laboratory tests and their results for:

- Fasting blood glucose level
- Total cholesterol
- LDL-cholesterol
- HDL-cholesterol
- Triglycerides

9.3.Direct inclusive observation

In parallel with the medical interview medical and prophylactic examinations, diagnostic and treatment procedures were performed by the author of the dissertation.

9.4.Expert evaluation

The expert evaluation is performed on the basis of analysis and evaluation of the obtained empirical results from the clinical and laboratory investigations, medical examinations by a qualified specialist.

9.5. Epidemiological method

From the studied population, presented by all health-insured individuals, registered at IPPMC in the town of Pavlikeni, we formed a cohort meeting the inclusion criteria and followed-up for a period of two years. The following coefficients were measured with the help of the epidemiological method:

- ***Incidence in the group of individuals exposed to high-risk, (Incidence***, ***Ie***),

- ***Incidence in the group of individuals non-exposed to high-risk, (Incidence, Inon***),

- ***Relative risk, Risk Ratio (RR)*** for the occurrence of a severe or fatal CV event. The relative risk compares the absolute disease risk among people with particular risk factor to the risk among people without this risk factor. The relative risk is a measure of the association between the end health result, in this case newly occurred atherosclerotic CVD or death and exposure (the degree or category atherosclerotic cardio-vascular risk, calculated by the SCORE system). It is estimated as a correlation of the incidence in the exposed group (***Ie)*** to the incidence of the individuals in the non-exposed group (***Inon).***

- ***Attributable risk (AR)*** is the degree of incidence of CVD of death which can be related to the specific RF or exposure.

- ***Rate Ratio (Rate Ratio)*** – is the ratio of the number of individuals with atherosclerotic CVD from the exposed group to the number of individuals with atherosclerotic CVD from the non-exposed group.

9.6. STATISTICAL METHODS

The systemisation, processing, and analysis of the primary data in the form of quantitative and qualitative variables is conducted by a statistical software pack for social sciences IBM SPSS Statistics v. 22 and the software product MedCalc Software. The level of significance of the null hypothesis is $P<0.05$. The following statistical analyses are used:

- Variational analysis – for the calculation of average values and dispersion indices of quantitative signs. With the help of the Kolmogorov-Smirnov test, the variational lines are verified for normal distribution (Laplace–Gauss distribution);
- Non-parametric analysis- for the assessment of hypotheses (Pearson's agreement criterion (χ^2), Fisher's exact test) for differences of two related populations (The paired samples Wilcoxon test), for difference of non-related populations (Mann Whitney *U* test, Kruskal-Wallis test);
- Alternative analysis – with qualitative characteristics;
- Correlational analysis – Pearson's coefficient, Spearman's Rank correlation coefficient;
- Epidemiological risk assessment- relative risk (RR), incidence of the exposed group (Ie) and incidence in the non-exposed groups of individuals (I non), attributive risk (AR), Rate Ratio (RR).
- ROC curve – for the assessment of the predicative ability of the studied methods.
- Logistic regression and decision tree

9.7.Assessment of the validity of the three SCORE methods

To assess the validity of the three methodologies SCORE ESC (2016), SCORE NFA and SCORE ESC (2019) we used the following criteria:

- Sensitivity
- Specificity
- Positive predictive value (PPV)
- Negative predictive value (NPV)

The graphic method was used for visual representation of the results.

10. Time and place of the study

The study was conducted by the personal participation and control of the researcher, under the guidance of the scientific supervisor and the scientific consultant.

The duration of the research is two calendar years. In the first year, during the prophylactic examinations, the values of the factorial and resultative signs of observation were measured and documented, the individual CVD risk according to SCORE was calculated. During the second year the same patients were monitored for the occurrence of complications or fatal CV accident. The research is conducted at POMC in the town of Pavlikeni which provides medical service to nine settlements.

11. Stages of administration of the study

11.1. Staff preparation and instruction

During the first year we gathered data through medical interviews in which doctors hired in the practice and working together with the owner participated. They were instructed how to conduct the interview in advance. The interview itself does not imply interpretations before the filling and the questions are clear, however, there needs to be unity in the interpretations of the answers and in the filling of the results in the Questionnaire (prophylactic health card)

11.2. Data preparation and gathering. Interview and questionnaire for prevention. Filling the main table with data.

The data gathering during the first year was performed during the annual prophylactic examination with the general practitioner of each of the patients. During this examination numerous history data was gathered, data for the present status and test results in the so-called ***Prophylactic card***. The questionnaire is part of it. Apart from the data in the Prophylactic card, which is supplied by the NHIF, the Questionnaire also includes the presence of gout/hyperuricemia as an aggravating/modifying factor for the development of CVD.

11.3. Entering the preliminary data in the main table

All requirements for privacy, confidentiality, and personal data protection are observed in correspondence with Regulation (EU) 2018/1725 of the European Parliament and Commission and the Law for Protection of the Personal Data.

All patient data are entered in advance in the statistical table. The patient's identificatory is the number of his/her record. Date of birth and sex are available.

11.4. Data gathering and entering from the interview and investigations in the main table

The data from the interview was recorded in each questionnaire. After scheduling investigations, the questionnaire was opened again, the results were recorded, and the

risk was calculated. Thus, for each patient the data from the first year is gathered and entered in the statistical table each month for the period before two months in order to for patients to perform their investigations and bring the results. Laboratory test results were sought so that there are no unfilled questionnaires.

11.5.*CVD morbidity and mortality analysis during the second year for each unit of observation and its comparison to the categories of risk groups.*

During the second year of the study, medical examinations and follow-up examinations for the health status were also performed. At the end of the observation period, based on the data in the patients' e-records, the issued death notices with their causes, data supplied by GRAS and NHIF, we made a list of patients with newly found, severe or fatal CVD. It is of extreme importance to be careful especially with the fatal cases and their cause of death. The difference between the assessment methods ESC 2016, NFA and ESC 2019 , on the one hand, and the present study, on the other, is that the results include and are analysed not only the lethal cases, but also the cases with a new severe disease- acute myocardial infarction and cerebral stroke. The reason for this is the much better treatment of acute infarction cases (e.g. coronary angioplasty, stenting, aorto-coronary bypass), on the one hand, which improve the prognosis for fatal outcome and may influence the results. On the other hand, the cause of death in the death notices is not always clear, quite often colleagues from the Emergency help, not knowing the patient and in lack of evidence for violence, list the main reason a cardio-vascular disease which alters the statistics.

Schematic presentation of the overall organisation of the research conduction is presented in the following figures 1, 2, 3 and 4.

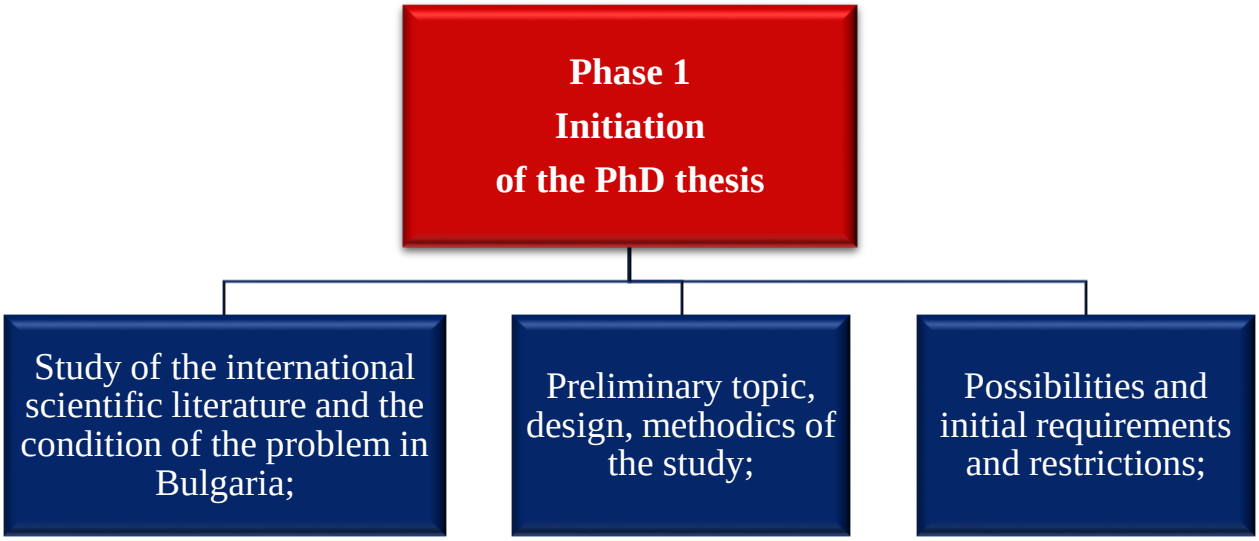

Figure 1. First stage of the administration of the research

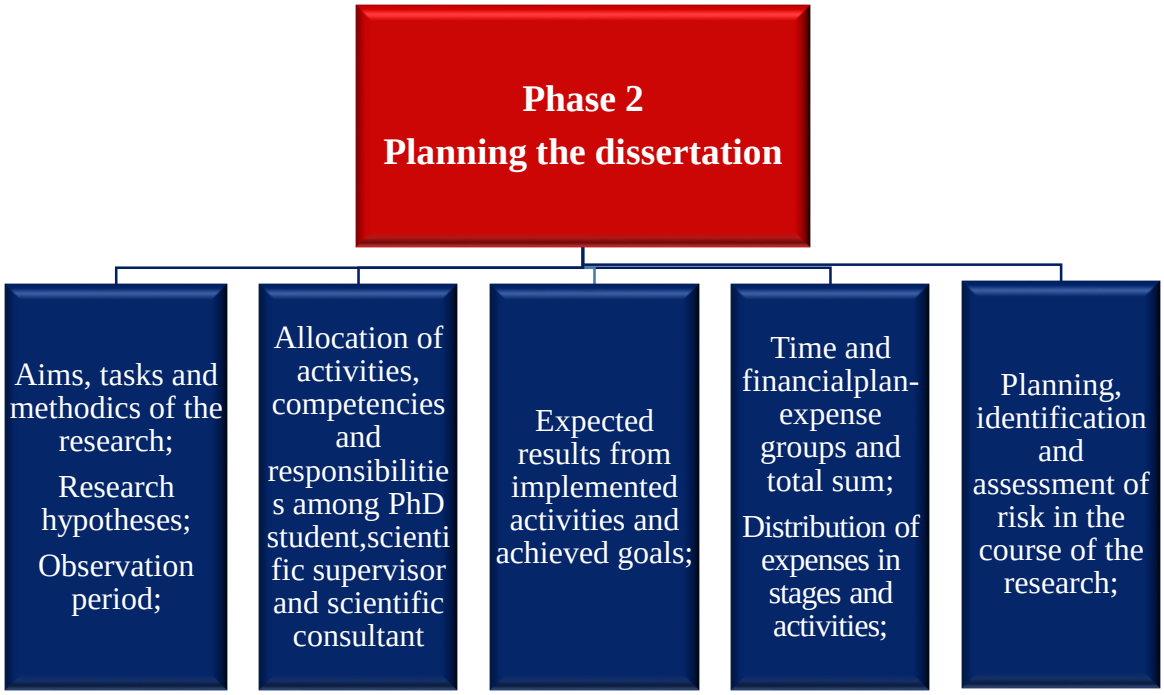

Figure 2. Second stage of the research administration

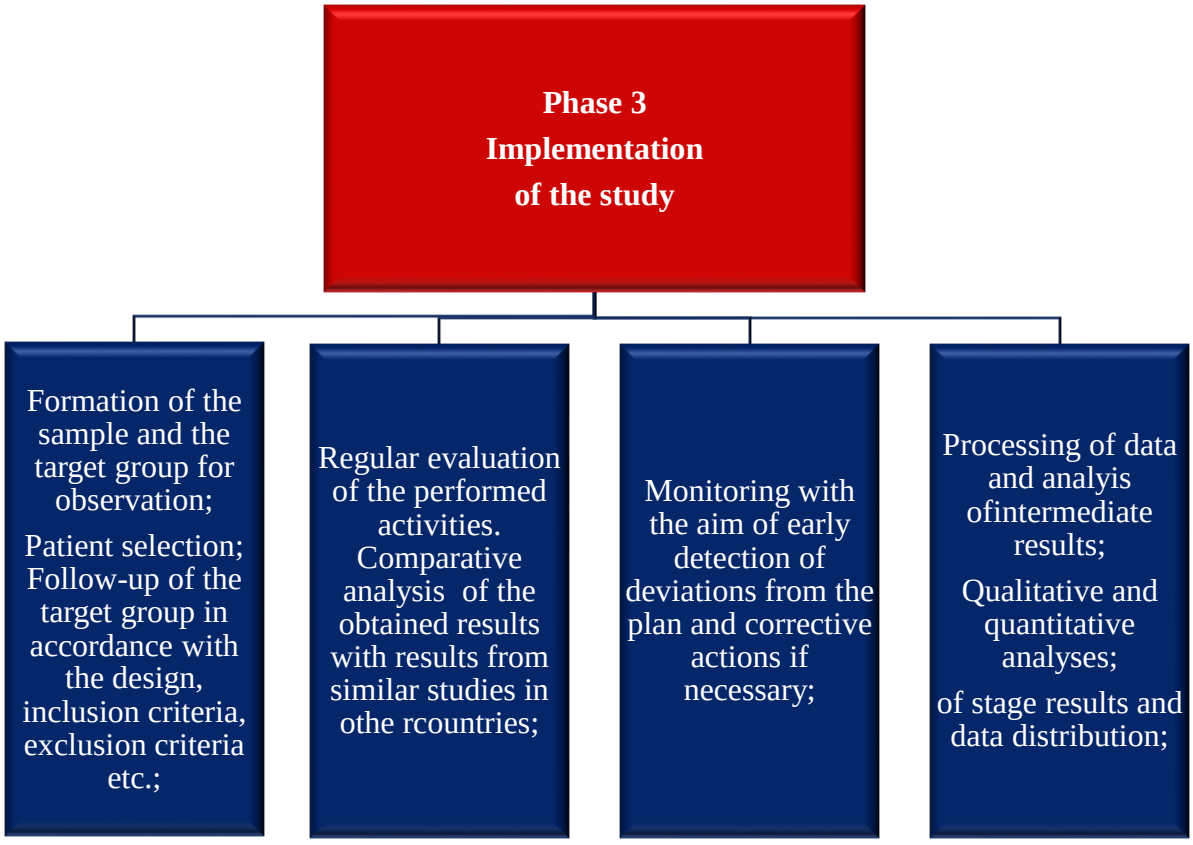

Figure 3. Third stage of the research administration

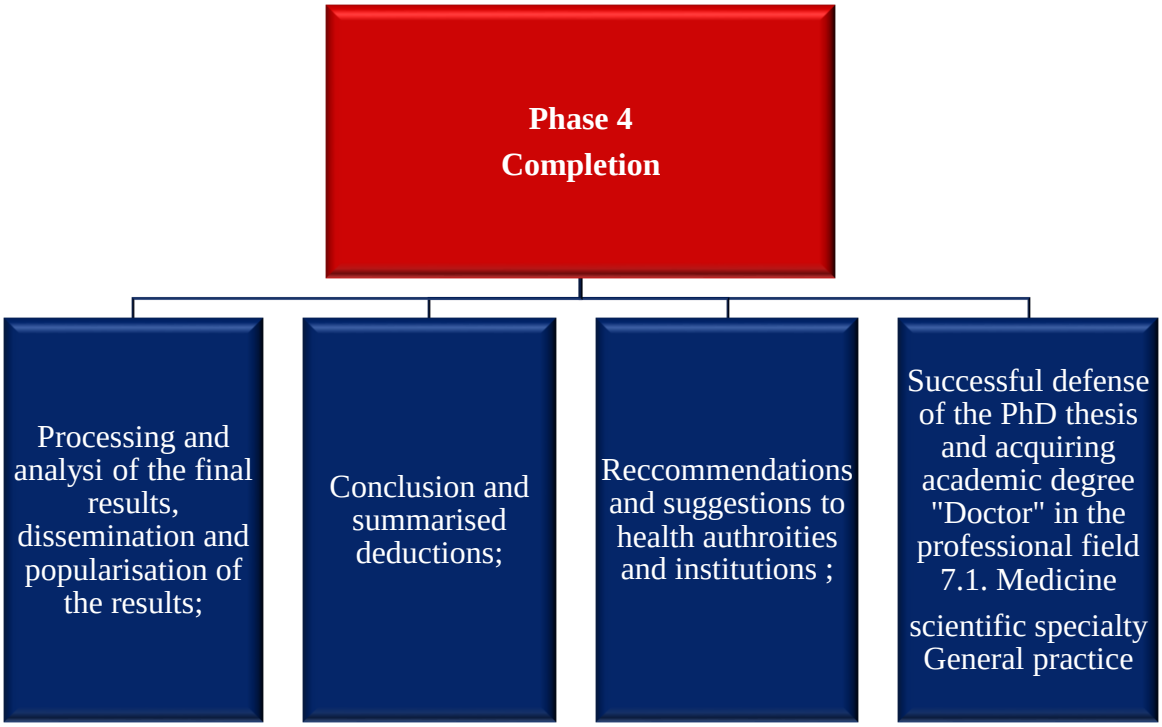

Figure 4. Fourth stage of the research administration

RESULTS AND DISCUSSION

1. Demographic characteristics of the studied population

1.1. Age distribution

During the first year of the research, prophylactic examinations of a total of 4551 people above 18 years of age were performed. The average age of the overall sample is 58,59±17,674. A considerable part of the individuals falls in the 40-70-year group, the most numerous being those above 70 years who fall in the target group only by the SCORE 2019 ESC method.

1.2. Sex distribution

According to the obtained data we found that there is a statistically significant difference in the sex distribution of the patients t=215.052, P=0.000, women predominating 2620 (58%), men being 1931 (42%).

Според получените резултати установихме, че съществува статистически значима разлика в разпределението на лицата по пол t=215.052, P=0.000, като в генералната съвкупност преобладават жените – 2620 (58%), а мъжете са 1931 (42%).

1.3. Other important characteristics of the studied population.

The results show that a considerable part of the individuals from the patient list are not diagnosed with Type 1 Diabetes Mellitus- 4548 and Type 2 Diabetes Mellitus- 3969 patients.

Only 45 (1.0%) of the monitored patients had family history of CVD.

A minor part of the patients are non-smokers - 448 (11%).

Body mass index is within the generally accepted norms 20–25 kg/m2 in 1724 people (37%). 2827 patients (63%) are overweight with body mass index above 25 kg/m2. Results show that almost 2/3 of the monitored group are overweight which presents an increased cardio-vascular risk.

2. Comparative analysis of patients' grouping in risk categories in applying the SCORE method with ESC 2016, NFA and ESC 2019.

According to the 2016 European guidelines in determining the atherosclerotic CV risk, related to CVD prevention in clinical practice, all individuals aged 40-65 are included, in this case these are 1908 people. They form **Cohort 1** in our research**.** The age distribution of **Cohort 1** in the analysed practice is shown in Figure 5.

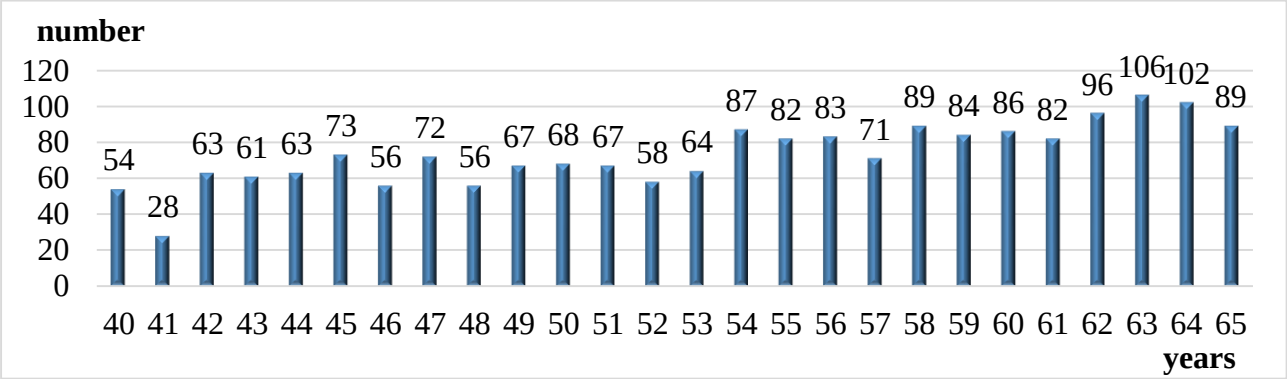

Figure 5. Age distribution of the monitored individuals with SCORE (ESC 2016)

Patients who meet the CV risk criteria in accordance with SCORE (NFA) from the global cohort are 1598 people aged 40-65 for men and 55-65 years for women. All of them form **Cohort 2.** Figure 6 shows their age distribution.

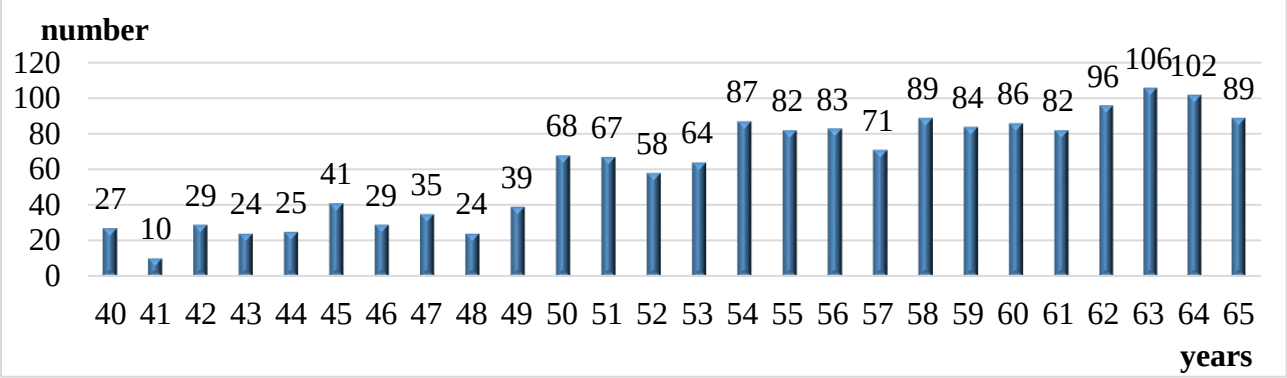

Figure 6. Age distribution of the monitored individuals with SCORE(NFA)

Patients who meet the criteria for CV risk in accordance with SCORE (ESC 2019) are individuals aged 40-70 years. The total number of the monitored units is 2458 and they form **Cohort 3**. Figure 7 shows their age distribution.

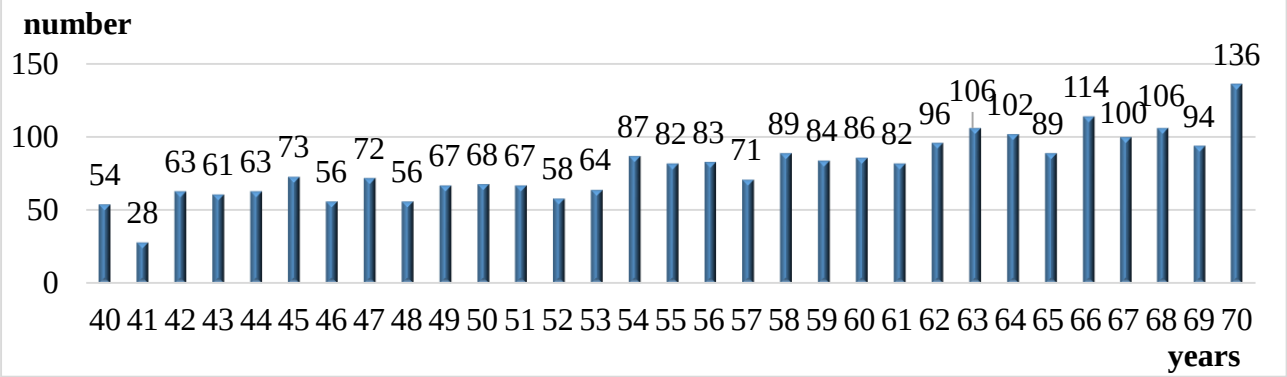

Figure 7. Age distribution of the monitored individuals with SCORE(ESC 2019)

We used the non-parametric Mann-Whitney analysis for establishing differences in grouping the individuals in risk categories based on the SCORE method and for comparing data in the two independent samples.

Following result analysis, we found that there is no statistically significant difference in patients' grouping in risk categories according to the SCORE (NFA) in comparison to SCORE (2016) (P>0.05), while in patients' grouping in risk categories according to SCORE (NFA) in comparison to SCORE (ASC 2019) a statistically significant difference was found (P=0.000).

Patient classification according to the cardio-vascular risk assessment according to the SCORE system for all three methods

Tables 1-3 show patient distribution in risk groups according to the occurrence of the sclerotic CVD and CV death for all three methods.

Table 1. Distribution of individuals in risk categories according to newly registered CVD and death cases by SCORE ESC (2016)

Risk category	ICHI* in risk n (%)	CVD during the second year n (%)	Deceased due to CVD n (%)
Very high risk	288 (15.09)	5 (35.71)	4 (80.00)
High risk	349 (18.29)	3 (21.43)	0 (0.00)
Average risk	848 (44.44)	5 (35.71)	1 (20.00)
Low risk	423 (22.17)	1 (7.14)	0 (0.00)
Total	**1908 (100.0)**	**14 (100.0)**	**5 (100.0)**

* ICHI (Individual with compulsory health insurance)

Table 2. Patient distribution in risk categories according to newly registered CVD and death cases by SCORE (NFA).

Risk category	ICHI* in risk n (%)	CVD during the second year n (%)	Deceased due to CVD n (%)
Very high risk	279 (17.46)	5 (35.71)	4 (80.00)
High risk	345 (21.59)	3 (21.43)	0 (0.00)
Average risk	819 (51.25)	5 (35.71)	1 (20.00)
Low risk	155 (9.70)	1 (7.14)	0 (0.00)
Total	**1598 (100.0)**	**14 (100.0)**	**5 (100.0)**

Table 3. Patient distribution in risk categories according to newly registered CVD and death cases by SCORE (ESC 2019).

Risk category	ICHI* in risk n (%)	CVD during the second year n (%)	Deceased due to CVD n (%)
Very high risk	587 (23.88)	11 (52.38)	9 (69.23)
High risk	530 (21.56)	4 (19.05)	3 (23.08)
Average risk	899 (36.57)	5 (23.81)	1 (7.69)
Low risk	442 (17.98)	1 (4.76)	0 (0.00)
Total	**2458 (100.0)**	**21 (100.0)**	**13 (100.0)**

From the obtained results we found that there is no statistically significant difference with reference to morbidity between the low-risk and average-risk groups in comparison to the high-risk and very-high risk groups both for SCORE (NFA) (P=0.062), and for SCORE (ESC 2019) (P=0.097). However, the non-parametric analysis found that in the SCORE (ESC 2019) there is a statistically significant difference in the intergroup result distribution regarding CVD mortality between the low-risk and average-risk groups in comparison to the high-risk and very-high risk groups (P=0.036), while with the NFA method, no such difference was found again (P=0.067).

3. Atherosclerotic CVD morbidity among patients who underwent SCORE risk assessment by the three methods.

Atherosclerotic CVD morbidity by the three methods is presented in Tables 4-6.

Table 4. Morbidity by atherosclerotic CVS diseases by SCORE ESC (2016)

Risk category	Number of ICHI in risk n (%)	From them patients with CVD n (%)
Very high risk SCORE (≥ 10%)	288 (15.09)	266 (25.90)
High risk SCORE (≥ 5% < 10%)	349 (18.29)	248 (24.15)
Average risk SCORE (≥1% < 5%)	848 (44.44)	407 (39.63)
Low risk SCORE (< 1%)	423(22.17)	106 (10.32)
Total	**1908 (100.0)**	**1027 (100.0)**

Table 5. Morbidity by atherosclerotic CVS diseases by SCORE (NFA)

Risk category	Number of ICHI in risk n (%)	From them patients with CVD n (%)
Very high risk SCORE (≥ 10%)	279 (17.46)	257 (27.28)
High risk SCORE (≥ 5% < 10%)	345 (21.59)	244 (25.90)
Average risk SCORE (≥1% < 5%)	819 (51.25)	393 (41.72)
Low risk SCORE (< 1%)	155 (9.70)	48 (5.10)
Total	**1598 (100.0)**	**942 (100.0)**

Table 6. Morbidity by atherosclerotic CVS diseases by SCORE ESC (2019)

Risk category	Number of ICHI in risk n (%)	From them patients with CVD n (%)
Very high risk SCORE (≥ 10%)	587 (23.88)	518 (35.34)
High risk SCORE (≥ 5% < 10%)	530 (21.56)	384 (26.19)
Average risk SCORE (≥1% < 5%)	899 (36.57)	452 (30.83)
Low risk SCORE (< 1%)	442 (17.98)	112 (7.64)
Total	**2458 (100.0)**	**1466 (100.0)**

There is no way to ignore the not insignificant number of patients who have a diagnosed disease carrying cardio-vascular risk but who have fallen in the low-risk and average-risk groups. Naturally and expectedly, their frequency increases with the increase in SCORE. The cause for this is that by the three methods the mild arterial hypertension cases with no impact on the heart and other organs, as well as the mild Diabetes Mellitus cases without complications do not allow for risk recatecorisation, although severe CVD cases are sometimes found among them. Many additional risk factors are also significant and their identification, as well as their "contribution", are part of the tasks of the present research.

4. Epidemiological risk assessment. Epidemiological indicators calculated by the SCORE system by the three methods ESC (2016), NFA and ESC (2019)

Calculation of the relative risk for developing severe or fatal CV event-comparative analysis by the three SCORE modifications.

We calculated several important epidemiological indications by the three modifications SCORE ESC (2016), SCORE (NFA) and SCORE ESC (2019).

- **Incidence in the exposed group** (**Incidence$_e$, Ie)** (individuals in the groups with high or very high risk), Ie = a/a+b

- **Incidence in the non-exposed group** (**Incidence $_{non,}$ Inon**) (individuals in the groups with low or average risk), Inon = b/a+b
- **Relative risk (Risk ratio, RR**) – RR = Ie/Inon – shows how many times the probability for CVD development is higher or lower in the group of the exposed patients in comparison to the non-exposed patients. This is a measure for association between the ***final health outcome*** (in this case CVD or mortality) and ***exposure*** (the calculated degree of atherosclerotic cardio-vascular risk) by the SCORE system or the so-called absolute risk).
- **Attributable risk** (**AR**) – measures the quantity of absolute risk which can be attributed to the exposure to the risk factor, (i.e. patients with high and very high SCORE risk) and shows the incidence of severe or fatal event in the monitored sample.

We divided the individuals from each cohort according to the SCORE modification for assessment of atherosclerotic cardio-vascular risk. The ***individuals with high and very high risk*** were included in the ***exposed*** group and the ***non-exposed*** group included the individuals with ***low and average risk***.

- **Rate Ratio** – is the ratio of the number of individuals with atherosclerotic CVD from the exposed group to the number of individuals with atherosclerotic CVD from the non-exposed group.

The following epidemiological indications were calculated by the SCORE (ESC 2016) modification (Table 7):

Table 7. Calculation of the relative risk (RR) 2x2 by the SCORE ESC (2016)*

	Exposed (high and very high risk)	**Non-exposed (low and average risk)**	**Total**
Presence of CV accident	12 A	7 B	19 a+b
Lack of CV accident	625 C	1264 D	1889 c+d
All	637	1271	1908

*P=0.012

- **Morbidity in the exposed group**– **Ie= 12/19=0.63**
- **Morbidity in the non-exposed group** – **Inon=625/1889=0.33**

The morbidity of individuals from atherosclerotic CVD occurrence in the exposed group classified according to the SCORE (ESC 2016) criteria is 630 per 100 000 of the population and the individuals from the non-exposed group 330 per 100 000 of the population.

- **Relative Risk** – **RR= Ie/Inon = 0.63/0.33=1.90,** the risk from occurrence of severe or fatal CV accident in the exposed group is 1.9 times higher than that in the non-exposed group.
- **Attributive Risk** – **AR=Ie-Inon=0.30**, it shows that 30 patients out of 1927 can have severe or fatal CV accidents.
- **Rate Ratio (RR) – Ie/Inon=12/7=1.71,** the individuals from the high-risk group have 1.7 times higher CVD incidence in comparison to the group with low CV risk.

The distribution of the exposed and non-exposed individuals according to the SCORE NFA in relation to CVD occurrence is presented in Table 8.

Table 8. Calculation of the relative risk 2x2 in SCORE calculated by NFA*

	Exposed (high and very high risk)	**Non-exposed (low and average risk)**	**Total**
Presence of CV accident	12 A	7 B	19 a+b
Lack of CV accident	612 C	967 D	1579 c+d
All	624	974	1598

*P=0.035

The following results were obtained according to the NFA modification:

- **Morbidity in the exposed group** – **Ie= 12/19=0.63**
- **Morbidity in the non-exposed group** – **Inon=612/1579=0.39**

Morbidity from atherosclerotic CVD among individuals in the exposed group, classified according to the SCORE (NFA) criteria was calculated to be 630 per 100 000 of the population and the individuals from the non-exposed group 390 per 100 000 of the population.

- **Relative Risk** – **RR=Ie/Inon =1.62**, therefore, the risk for occurrence of svere or fatal CV accident in the exposed group is 1.62 times higher than that of the non-exposed group.
- **Attributive Risk** – **AR=Ie-Inon=0.63-0.39=0.24**, it shows that 24 fatal or severe CV accidents may happen to 1598 people.
- **Rate Ratio (RR) – Ie/Inon=12/7=1.71,** the individuals from the high-risk group have 1.71 times higher CVD incidence in comparison to the group with low CV risk.

The following epidemiological indicators were calculated by the SCORE ESC (2019) modification (Table 9).

Table 9. Calculation of the relative risk 2x2 in SCORE calculated by ESC (2019) *

	Exposed (high and very high risk)	Non-exposed (low and average risk)	Total
Presence of CV accident	27 A	7 B	34 a+b
Lack of CV accident	1090 C	1334 D	2424 c+d
All	1117	1341	2458

P=0.000

The following results, which show the strength of the association between the risk category of the monitored individuals and the CV accident occurrence, were obtained by the ESC (2019) modification:

- **Morbidity in the exposed group**, **Ie= 27/34=0.79**
- **Morbidity in the non-exposed group**, **Inon=1090/2424=0.45**

Therefore, the morbidity from atherosclerotic CVD among the individuals in the exposed group, classified according to the SCORE (ESC 2019) criteria, is 790 per 100 000 of the population and in the non-exposed group- 450/100 000.

- **Risk Ratio – RR=Ie/Inon=1.75**, therefore, the risk for occurrence of a CV accident or a fatality in the exposed is 1.75 times higher in comparison to the non-exposed group.
- **Attributable risk – AR=Ie-Inon=0.79-0.45=0.34,** this means that 34 fatal or severe CV events may happen among 2458 people, i.e. if the exposure is eliminated, 34 sever of fatal cases will be removed or eliminated.
- **Rate Ratio (RR) – Ie/Ine=27/7=3.86,** the individuals from the high-risk group have 3.86 times higher CVD incidence in comparison to the group with low CV risk.

The obtained results confirm that in all three modifications of the SCORE system the probability to develop severe or fatal CV events depends on the degree or category of the atherosclerotic cardio-vascular risk (P<0.005). The minimum differences in the calculated coefficients do not underestimate the predictive validity of neither of the three modifications. As is apparent, the calculated relative risk in the exposed group (with high or very high risk) is higher with the SCORE ESC (2016) and SCORE ESC (2019) method than with the SCORE (NFA) method. Furthermore, the epidemiological indications Morbidity, Attributable Risk and Rate Ratio have the highest values with the SCORE ESC (2019) method in comparison to the other two methods.

In conclusion, we can state that the calculated epidemiological indicators: Morbidity, Attributable Risk, Rate Ratio and Relative Risk have the highest values with the SCORE ESC (2019) method in comparison to the other two methods.

The analysis of the obtained data shows that the units of observation from the same cohort can fall in different groups or categories CV risk in the used SCORE ESC 2016,

SCORE NFA and SCORE ESC 2019 methods. Determinant causes for this fact are the factors- age range of the units of observation, and cholesterol values which are components of the risk assessment in each method, described in detail in Chapter Materials and Methods. As a consequence, the number of individuals in each cohort is different.

5. Sensitivity, specificity, positive predictive validity, and negative predictive validity of the three methods.

A statistical evaluation of the diagnostic possibilities of the three methods- SCORE ESC (2016), SCORE NFA and SCORE ESC (2019) by the indicators sensitivity, specificity, positive and negative predictive value was performed.

To fulfill the aims and tasks of the dissertation, we measured the diagnostic accuracy, sensitivity and specificity of the SCORE system for CV risk assessment by the three methods.

Sensitivity – the possibility (in percent) a given result to be positive when a disease is present.

$$\textbf{Sensitivity} = TP/\ TP + FN \times 100\ (\%)$$

Specificity – the possibility (in percent) that a given result is negative among individuals not suffering from the disease. вероятността (в процент) даден резултат да е отрицателен сред индивидите без заболяването.

$$\textbf{Specificity} = TN/\ TN + FP \times 100\ (\%)$$

Positive Predictive Value, PPV – is the possibility (in percent) that a certain patient has a positive result, i.e. he/she suffers from a particular disease.

$$\textbf{Positive PV} = TP\ /TP + FP \times 100\ (\%)$$

Negative Predictive Value, NPV – is the possibility (in percent) that a certain patient has a negative result, i.e. he/she does not suffer from a particular disease.

$$\textbf{Negative PV} = TN/\ TN + FN \times 100\ (\%)$$

PPV calculated for SCORE ESC (2016) is 63.16% which shows the possibility for the individuals in the high-risk or very high-risk group to develop a severe or fatal CVD (Table 10).

Table 10. Values of the prognostic indicators for SCORE ESC (2016)

	High and very high risk	Low and average risk	Total
Presence of CVD	12	7	19
Lack of CVD	625	1264	1889
Total	637	1271	1908

Statistic	*Value*	*95% CI*
Sensitivity	1.88%	0.98% to 3.27%
Specificity	99.45%	98.87% to 99.78%
Positive Likelihood Ratio	3.42	1.35 to 8.65
Negative Likelihood Ratio	0.99	0.98 to 1.00
Disease prevalence (*)	33.39%	31.27% to 35.55%
Positive Predictive Value (*)	63.16%	40.41% to 81.25%
Negative Predictive Value (*)	66.91%	66.66% to 67.17%
Accuracy (*)	66.88%	64.71% to 68.99%

(*) These values dependend on disease prevalence.

The calculated plot under the SCORE 2016 curve is 0.621, 95% CI= 0.254÷ 0.989, P=0.468, and is presented on Figure 8.

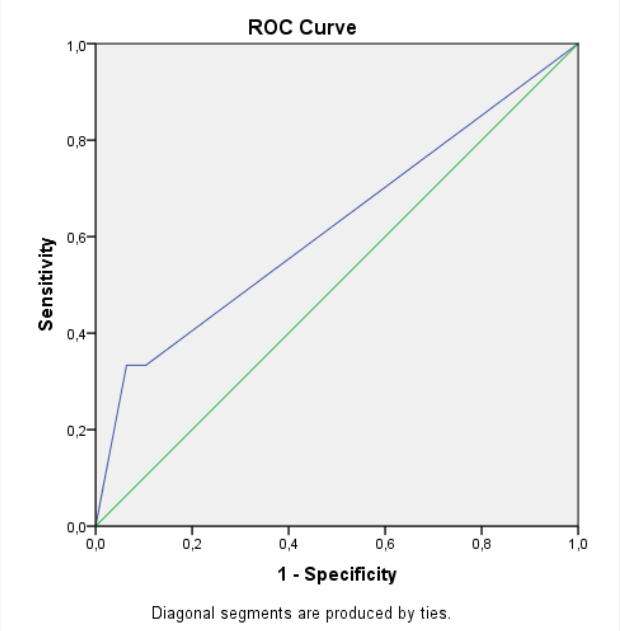

Figure 6. ROC curve for measurement of CV risk by the SCORE ESC (2016) method

PPV is also 63.16% by the SCORE NFA method which reveals full correspondence with the SCORE ESC (2016) method (Table 11).

Table 11. Values of the prognostic indicators for SCORE NFA

	High and very high risk	Low and average risk	Total
Presence of CVD	12	7	19
Lack of CVD	612	967	1579
Total	624	974	1598
Statistic	*Value*		*95% CI*
Sensitivity	1.92%		1.00% to 3.34%
Specificity	99.28%		98.52% to 99.71%
Positive Likelihood Ratio	2.68		1.06 to 6.76
Negative Likelihood Ratio	0.99		0.98 to 1.00
Disease prevalence (*)	39.05%		36.65% to 41.49%
Positive Predictive Value (*)	63.16%		40.43% to 81.24%
Negative Predictive Value (*)	61.24%		60.95% to 61.53%
Accuracy (*)	61.26%		58.83% to 63.66%

(*) These values depend on disease prevalence.

The calculated plot for the SCORE NFA curve is 0.662, 95% CI= 0.527÷ 0.796, при P=0.015., and is presented in Figure 9.

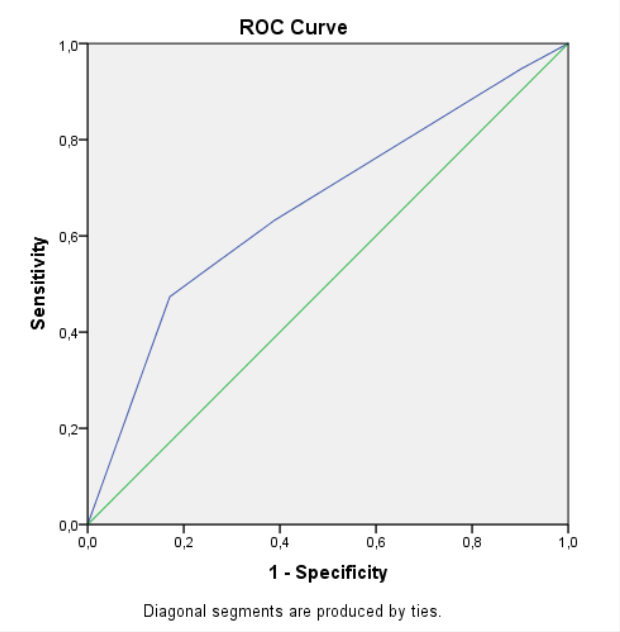

Figure 7. ROC curve for measurement of CV risk by the SCORE NFA method

PPV is highest and shows that 79.41% of individuals in the group with high or very high risk can develop severe or fatal CVD (Table 12).

Table 12. Values of the prognostic indicators for SCORE ESC (2019)

	High and very high risk	Low and average risk	Total
Presence of CVD	27	7	34
Lack of CVD	1090	1334	2424
Total	1117	1341	2458
Statistic	*Value*		*95% CI*
Sensitivity	2.42%		1.60% to 3.50%
Specificity	99.48%		98.93% to 99.79%
Positive Likelihood Ratio	4.63		2.02 to 10.59
Negative Likelihood Ratio	0.98		0.97 to 0.99
Disease prevalence (*)	45.44%		43.46% to 47.44%
Positive Predictive Value (*)	79.41%		62.77% to 89.82%
Negative Predictive Value (*)	55.03%		54.79% to 55.28%
Accuracy (*)	55.37%		53.38% to 57.35%

(*) These values are dependent on disease prevalence.

The calculated plot for the SCORE ESC (2019) curve is 0.722, 95% CI= 0.642÷ 0.802, in P=0.000 (Figure 10).

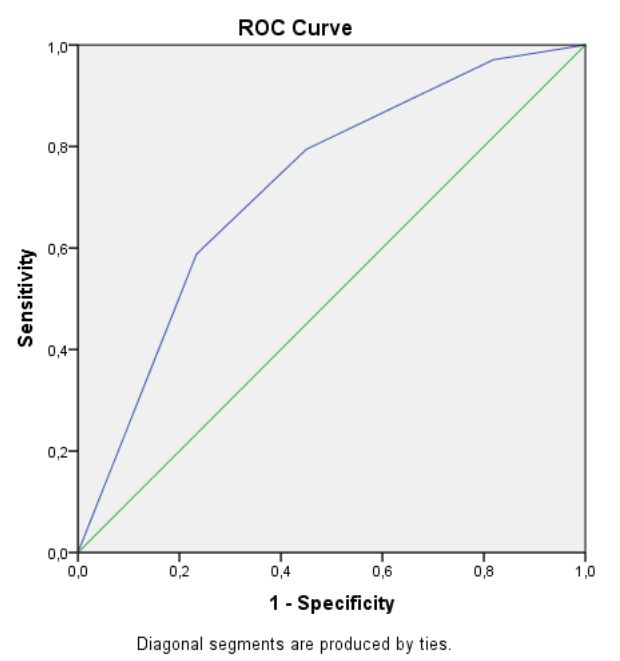

Figure 10. ROC curve for measurement of CV risk by the SCORE ESC (2019) method

The measured values for PPV and sensitivity by the three methods show that thy are highest in SCORE ESC (2019) in comparison to the methods SCORE ESC (2016)

and SCORE NFA. This fact confirms the better predictive strength of the SCORE ESC (2019) method.

6. Calculating the golden standard and index ratio morbidity/ mortality by atherosclerotic CVD in the three cohorts.

To identify the golden standard in relation to occurrence of severe or fatal atherosclerotic CV event, we compared all newly occurred atherosclerotic CV diseases to all death cases caused by atherosclerotic diseases in the monitored population (Table 13).

The resulting index was accepted as the golden standard which we later compared to the indices of each of the analyzed cohorts. In this respect we analogically calculated the following indices for **Cohort 1, Cohort 2,** and **Cohort 3** (Table 13).

Table 13. Calculation of the golden standard regarding the risk for CV event occurrence in the monitored population.

Description of the event	Number of cases from the studied population (N=4551)	Number of cases by SCORE (ESC 2019) – Cohort 3 (N=2458)	Number of cases by SCORE (ESC 2016) – Cohort 1 (N=1908)	Number of cases by SCORE (NFA) – Cohort 2 (N=1598)
Newly occurred CV disease (Incidence)	50	15	8	8
Deceased from atherosclerotic CV disease (Mortality)	75	12	4	4
Index= Incidence/ Mortality	**0.67* (gold standard)**	**1.25**	**2**	**2**

*gold standard

When comparing the resulting indices, the results show that the smallest ratio which is close to the calculated gold standard (0.67) is achieved by the **SCORE (ESC 2019)** method.

The resulting indices by the **SCORE (ESC 2016) and SCORE (NFA)** methods are equal as is evident from Table 13, which once again confirms the similarity in the prognostic ability of the two methods.

7. Predictive validity of the three SCORE methods.

Measurement of the ratio expected to observed morbidity and or/ mortality by atherosclerotic CVD for the *high-risk* and *very-high risk* categories by the three methods

Of all 1908 monitored individuals from **Cohort 1**, 637 fall in the *high-risk* and *very high-risk* category. Expected **(expectation, E)** incidence for the occurrence of severe or fatal atherosclerotic CV event in the individuals from the high-risk and very high-risk groups is calculated by **SCORE ≥ 5%** or 32 cases, and the **observed (O)** incidence – 12 cases**.**

The ratio index between the expected **(E)** and the observed **(O)** incidence calculated by the SCORE (ESC 2016) method is:

$$\mathbf{I_{COHORT1}=E/O=32/12=2.67}$$

Of all monitored individuals from **Cohort 2**, 624 fall in the *high-risk* and *very high-risk* category. The calculated **expectation** for the occurrence of severe or fatal atherosclerotic CV event in the high-risk and very high-risk category is SCORE ≥ 5% or 32 cases, and the **observed** or real incidence is 12 cases.

The calculated ratio index between the expected and the observed incidence of CV events by the SCORE (NFA) method is:

$$\mathbf{I_{COHORT2}=E/O=\ 32/12=2.67}$$

Of all monitored individuals from **Cohort 3**, 1117 fall in the *high-risk and very high-risk* category. The expectation SCORE ≥ 5% and the observed incidence for the occurrence of severe or fatal atherosclerotic CV event are 56 and 27 cases, respectively.

The ratio index between the expected and the observed incidence of CV event by the SCORE (ESC 2019) method is:

$$\mathbf{I_{COHORT3}=E/O=56/27=2.07}$$

According to the obtained results and comparing the predictive value for the occurrence of a CV event among the three methods, it is evident that the highest predictive value from the three methods is again with the SCORE (ESC 2019) since it has the lowest value. According to Saidj M, Jørgensen T et. Al. the threshold should be below 20 and the closer it is to one, the better the predictive validity.

8. Relative risk for occurrence of cardio-vascular event by sex in individuals from the high-risk and very-high risk category

In order to establish the chance of men and women to develop severe or fatal CV events, we calculated the relative risk by sex for CV event occurrence in the high-risk and very-high risk groups for each of the three cohorts.

Table14. Relative risk of the individuals from the *high-risk and very-high* risk groups by sex by SCORE (2016)

	Presence of CV event	Absence of CV event	Total
Men	10	433	443
Women	2	192	194
Total	12	625	637

P=0.3626
RR=2.190, 95% CI (0.4841÷9.903)
Odds ratio=2.217

Table 15. Relative risk of the individuals from the *high-risk* and *very-high* risk groups by sex by SCORE (NFA)

	Presence of CV event	Absence of CV event	Total
Men	10	433	443
Women	2	179	181
Total	12	612	624

P=0.5238
RR=2.043, 95% CI (0.4519÷9.235)
Odds ratio=2.067

Table 16. Relative risk of the individuals from the *high-risk* and *very-high* risk groups by sex by SCORE (ESC 2019)

	Presence of CV event	Absence of CV event	Total
Men	18	645	663
Women	9	445	454
Total	27	1090	1117

P=0.5529
RR=1.370, 95% CI (0.6207÷3.022)
Odds ratio=1.380

Despite no statistically significant differences by the three methods are not found, what cannot be ignored is that the relative risk for the occurrence of atherosclerotic severe or fatal CV event in men is higher than in women (Table 14-16).

Population relative risk for occurrence of severe or fatal CV event in women depending on the risk category

For each cohort we studied the intragroup distribution of the chance for occurrence of a severe or fatal CV event in the categories high-risk and very high-risk and the categories low and average risk, separately for women and men (Table 17, 18).

Table 17. Intragroup distribution of the relative risk in women from Cohort 1 by SCORE (ESC 2016)

	High and very high risk	Low and average risk	Total
Presence of CV event	2	4	6
Absence of CV event	192	816	1008
Total	194	820	1014

P=0.0323
RR=1.750, 95% CI (0.5602÷5.466)
Odds ratio=2.125

The probability for women from the high-risk and very high-risk categories to develop a CV event by SCORE (ESC 2016) is 1.75 times higher than that for women from the low and average risk categories

Table 18. Intragroup distribution of the relative risk in women from Cohort 2 by SCORE (NFA)

	High and very high risk	Low and average risk	Total
Presence of CV event	2	4	6
Absence of CV event	179	518	697
Total	181	522	703

P=0.0650
RR=1.298
95% CI (0.4156÷4.054)
Odds ratio=1.447

The probability for women from the high-risk and very high-risk categories to develop a CV event is 1.29 times higher than that for women from the low and average risk categories by SCORE (NFA).

Table 19. Intragroup distribution of the relative risk in women from Cohort 3 by SCORE (ESC 2019)

	High and very high risk	Low and average risk	Total
Presence of CV event	9	4	13
Absence of CV event	445	884	1329
Total	454	888	1342

P=0.0140
RR=2.068, 95% CI (1.428÷2.994)
Odds ratio=4.470

Once again, by the SCORE (ESC 2019) method, statistically significant difference between the two groups and the relative risk for CVD occurrence is the highest (RR=2,068) in comparison to the other two methods (SCORE (ESC 2016) – RR=1,750 and SCORE (NFA) – RR=1,298) (Table 19).

Relative risk for occurrence of severe or fatal CV event in men depending on the risk category and the SCORE method

Table 20. Intragroup distribution of the relative risk in men from Cohort 1 by SCORE (ESC 2016)

	High and very high risk	Low and average risk	Total
Presence	10	3	13
Absence	433	448	881
Total	443	451	894

P=0.0537
RR=1.565
95% CI (1.153÷2.124)
Odds ratio=3.449

No statistically significant difference was found in men for the CV event occurrence by the risk categories (Table 20)

Table 21. Intragroup distribution of the relative risk in men from Cohort 2 by SCORE (NFA**)**

	High and very high risk	Low and average risk	Total
Presence	10	3	13
Absence	433	448	881
Total	443	451	894

P=0.0537
RR=1.565
95% CI (1.153÷2.124)
Odds ratio=3.449

Table 22. Intragroup distribution of the relative risk in men from Cohort 3 by SCORE (ESC 2019)

	High and very high risk	Low and average risk	Total
Presence	18	3	21
Absence	645	450	1095
Total	663	453	1116

P=0.0130
RR=1.455, 95% CI (1.214÷1.745)
Odds ratio=4.186

The result analysis shows that a statistically significant difference in the probability for CV event occurrence in men is found only with the SCORE (ESC 2019) method in the high and very high risk and low and average risk groups. The probability that a CV event occurs in men in the group with high and very high risk is 1.455 times higher than that for the individuals with low and average risk (Table 21,22).

9. Risk factors for CVD and absolute cardio-vascular risk in the three cohorts

In accordance with the guidelines and classification of the European Atherosclerosis Society, in the present research we studied the *metabolic* (related to metabolic processes), *endogenous* (originating from the body) and *exogenous* (external) risk factors.

The distribution of all cardio-vascular RF and the measured absolute SCORE risk by the three methods is presented in Tables 23-25.

Table 23 presents the average values of the most important risk factors and the average values of the global absolute cardio-vascular risk measured by the SCORE ESC (2016) criteria of the units of observation from **Cohort 1**. For the whole Cohort 1 the measured global absolute risk is SCORE= 2.312.

Table 23. Distribution of the measured cardio-vascular RF and the calculated global absolute risk with SCORE ESC (2016).

	ESC 2016 method				
	N	Median	Mode	Mean	SD
Age	1908	55	63	53.965	7.391
Smoker with cigarettes daily	1908	0	0	2.665	6.498
Systolic AP	1908	130	130	125.497	10.928
Total Cholesterol	1908	0	0	2.149	2.768
Weight	1908	78	80	77.369	16.524
Waist	1908	90	90	94.126	15.204
Diastolic AP	1908	80	80	81.372	6.368
BMI	1908	26	25	26.735	6.324
HDL Cholesterol	1908	0	0	0.448	0.676
Triglycerides	1908	0	0	0.599	1.203
Non-HDL Cholesterol	1908	0	0	1.246	2.012
LDL Cholesterol	1908	0	0	1.038	1.722
Fasting blood glucose	1908	0	0	2.695	3.099
Calculated SCORE	1908	2	0	2.312	2.451

Table 24. Distribution of the measured cardio-vascular RF and the calculated global absolute risk witn SCORE NFA.

	NFA method				
	N	Median	Mode	Mean	SD
Age	1598	57	63	55.775	6.604
Smoker with cigarettes daily	1598	0	0	2.620	6.524
Systolic AP	1598	130	130	127.120	10.308
Total Cholesterol	1598	0	0	2.434	2.821
Weight	1598	80	80	79.424	16.104
Waist	1598	90	90	95.573	14.740
Diastolic AP	1598	80	80	82.195	6.063
BMI	1598	26	25	27.202	6.433
HDL Cholesterol	1598	0	0	0.510	0.700
Triglycerides	1598	0	0	0.673	1.178
Non-HDL Cholesterol	1598	0	0	1.415	2.082
LDL Cholesterol	1598	0	0	1.177	1.793
Fasting blood glucose	1598	3.9	0	2.911	3.125
Calculated SCORE	1598	2	1	2.740	2.455

The measured global absolute risk for the whole Cohort 2 is SCORE=2.740. It should be noted that the global absolute cardio-vascular risk measured by the **SCORE** NFA method is higher than the one by the **SCORE** 2016 method.

Table 25. Distribution of the measured cardio-vascular RF and the calculated global absolute risk with SCORE ESC (2019).

	ESC 2019				
	N	**Median**	**Mode**	**Mean**	**SD**
Age	2458	58	70	57.121	8.800
Smoker with cigarettes daily	2458	0	0	2.391	6.238
Systolic AP	2458	130	130	126.639	10.854
Total Cholesterol	2458	0	0	2.205	2.774
Weight	2458	168	160	167.860	9.102
Waist	2458	77	80	77.111	16.015
Diastolic AP	2458	90	90	94.620	15.027
BMI	2458	80	80	81.727	6.296
HDL Cholesterol	2458	26	25	26.841	6.029
Triglycerides	2458	0	0	0.492	0.697
Non-HDL Cholesterol	2458	0	0	0.633	1.164
LDL Cholesterol	2458	0	0	1.336	2.047
Fasting blood glucose	2458	0	0	1.159	1.780
Calculated SCORE	2458	0	0	2.814	3.132
Age	2458	3	0	4.304	4.758

The calculated global absolute risk for the whole Cohort 3 is 4.304 which is significantly higher than the obtained results for the previous two methods. This means that a much greater number of the monitored individuals are categorised in the high or very high-risk groups by the SCORE (ESC 2019) method.

The average absolute risk by sex is presented in Table 26.

Table 26. Average values and standard deviation of the global absolute SCORE CV risk by the three methods by sex.

METHOD		**Total**	**Women**	**Men**
SCORE 2016	N	1908	1014	894
	Mean	2.31	1.31	3.45
	SD	2.451	1.369	2.873
	U=219480.00; P=0.000			
SCORE NFA	N	1598	704	894
	Mean	2.74	1.84	3.45
	SD	2.455	1.319	2.873
	U=199555.00; P=0.000			
SCORE 2019	N	2458	1342	1116
	Mean	4.30	2.69	6.24
	SD	4.758	2.809	5.788
	U=450549.00; P=0.000			

Following the application of the non-parametric analysis we found statistically significant differences in the absolute SCORE CV risk by the three methods and sex in which the values for men are higher than those of women (Table 26). It is visible from the table that the CV risk has the highest value in both sexes by the SCORE 2019 method.

The result analysis shows that there is a statistically significant difference between the average values of the absolute risk by sex by all three methods, the CV risk in Cohort 3 being the highest (4.30) in comparison to the one in the other two cohorts, 2.31 for Cohort 1 and 2.74 for Cohort 2, respectively.

In each of the three cohorts (Cohort 1, Cohort 2, and Cohort 3) the interrelationship between the *main* or *unchanging* RF (sex, age, family history) and the *changing* or *modifying* RF (tobacco smoking, SAP, lipid profile, chronic concomitant disease) which increase the risk from atherosclerotic CVD or death.

The results from the performed non-parametric analysis reveal a statistically significant difference in the distribution of tobacco smoking with respect to the factors sex and age. Tobacco smoking as a CV risk factor is present more commonly among men ($P<0.05$) and among the individuals from the younger age group ($P=0.000$), i.e. with the increase in age, the number of smoker decreases (Table 27). On the other hand, it was found that those who have a chronic disease smoke more rarely ($P=0.000$).

Sex, age and the presence of a concomitant disease among the individuals from Cohort 1 exert influence on SAP ($P<0.05$). Higher SAP were found in men, elderly subjects ($P<0.05$) and the ones with chronic diseases ($P = 0.000$).

The elevated risk factor values of total and LDL-cholesterol and TG, as well as the decreased HDL-cholesterol levels are also influenced by age and the presence of a chronic disease ($P=0.000$).

In Cohort 2 smokers predominate among men and the individuals at younger age ($P=0.001$) (Table 28).

The results show that there is no statistically significant difference in the distribution of elevated SAP values for the factors sex and age ($P>0.05$), however, there is one with the individuals who have at least one diagnosed concomitant disease ($P=0.001$).

There are sex differences in the distribution of total and LDL-cholesterol. Higher total and LDL-cholesterol levels as well as lower LDL-cholesterol levels are found more commonly among women ($P<0.05$), among the elderly ($P<0.05$) and individuals with a chronic disease ($P=0.000$).

The result analysis reveals that the distribution of the high triglyceride values is not influenced by the sex of the participants. The higher serum triglyceride levels are more common among the elderly and the ones who have at least one concomitant disease ($P<0.05$).

The result analysis shows that with minimum exception between the **SCORE (ESC 2016) и SCORE (NFA)** methods, no statistically significant differences are found in the distribution of the studied RF (Tables 27-29).

The distribution of the measured RF- tobacco smoking, elevated SAP levels, total and LDL-cholesterol as well as decreased levels of HDL-cholesterol (lower than 1.29 mmol/l) in the individuals from **Cohort 3** reveals a dependence on the factors sex, age, presence of chronic disease and family history of CVD (Table 29).

The comparative analysis of the distribution of the observed CV risk factors by the three SCORE methods showed insignificant differences (Table 27-29).

The results revealed small minimum intragroup differences regarding the incidence and distribution of the studied risk factors.

The analysis of the tobacco smoking distribution by the three methods showed that it is more common in men, in people at younger age and the ones without a chronic disease ($P<0.000$) but have a family history of CVD ($P<0.05$).

We also found that there is a interrelationship between the high SAP levels and the sex and age from the two cohorts (Cohort 1 and Cohort 3) while in the individuals from Cohort 2 there is an interrelationship between SAP and the presence of chronic diseases. Higher values of SAP and total cholesterol are measured in the individuals from Cohort 1 and Cohort 3 above 55 years of age and the ones with a concomitant chronic disease ($P<0.000$), while in the monitored from Cohort 2, there is no statistically significant difference between the high SAP values and the factors sex and age. In all three cohorts the low HDL-cholesterol levels < 1.29 mmol/l are more common with the individuals at a younger age as well as with those without a concomitant chronic disease.

Table 27. Association between risk factors (tobacco smoking, TG, cholesterol, HDL- and LDL-cholesterol) and demographic factors (sex, age, presence of chronic disease, family history of CVD) in individuals from Cohort 2 by SCORE ESC (2016).

		Total by ESC 2016 n (%)	Smoker		p	Systolic pressure		p	Triglycerides		p
			no n (%)	yes n (%)		below 140 n (%)	above 141 n (%)		below 1,69 n (%)	Above 1,70 n (%)	
Sex	**Women**	1014 (100)	869 (85,7)	145 (14,3)		985 (97,1)	29 (2,9)		916 (90,3)	98 (9,7)	
	Men	894 (100)	723 (80,9)	171(19,1)	0,005	852 (95,3)	42 (4,7)	0,039	757 (84,7)	137 (15,3)	0,000
	Total	1908 (100)	1592 (83,4)	316 (16,6)		1837 (96,3)	71 (3,7)		1673 (87,7)	235 (12,3)	
Age	**40-55**	1020 (100)	809 (79,3)	211 (20,7)		991 (97,2)	29 (2,8)		925 (90,7)	95 (9,3)	
	56-70	888 (100)	783 (88,2)	105 (11,8)	0,000	846 (95,3)	42 (4,7)	0,039	748 (84,2)	140 (15,8)	0,000
	Total	1908 (100)	1592 (83,4)	316 (16,6)		1837 (96,3)	71 (3,7)		1673 (87,7)	235 (12,3)	
Chronic disease	**no**	881 (100)	706 (80,1)	175 (19,9)		869 (98,6)	12 (1,4)		847 (96,1)	34 (3,9)	
	yes	1027 (100)	886 (86,3)	141 (13,7)	0,000	968 (94,3)	59 (5,7)	0,000	826 (80,4)	201 (19,6)	0,000
	Total	1908 (100)	1592 (83,4)	316 (16,6)		1837 (96,3)	71 (3,7)		1673 (87,7)	235 (12,3)	
Family history of CVD	**no**	1880 (100)	1573 (83,7)	307 (16,3)		1809 (96,2)	71 (3,8)		1647 (87,6)	233 (12,4)	
	yes	28 (100)	19 (67,9)	9 (32,1)	0,037	28 (100)	0 (0,0)	0,623	26 (92,9)	2 (7,1)	0,567
	Total	1908 (100)	1592 (83,4)	316 (16,6)		1837 (96,3)	71 (3,7)		1673 (87,7)	235 (12,3)	

Table 27. (continuation)

		Total by ESC 2016 n (%)	Total cholesterol		P	HDL cholesterol		P	LDL cholesterol		P
			below 5,2 n (%)	above 5,3 n (%)		below 1,29 n (%)	above 1,3 n (%)		below 2,6 n (%)	above 2,61 n (%)	
Sex	**Women**	1014 (100)	786 (77,5)	228 (22,5)		838 (92,6)	176 (17,4)		781 (77,0)	233 (23,0)	
	Men	894 (100)	695 (77,7)	199 (22,3)	0,912	767 (85,8)	127 (14,2)	0,069	671 (75,1)	223 (24,9)	0,333
	Total	1908 (100)	1481 (77,6)	427 (22,4)		1605 (84,1)	303 (15,9)		1452 (76,1)	456 (23,9)	
Age	**40-55**	1020 (100)	840 (82,4)	180 (17,6)		907 (88,9)	113 (11,1)		854 (83,7)	166 (16,3)	
	56-70	888 (100)	641 (72,2)	247 (27,8)	0,000	698 (78,6)	190 (21,4)	0,000	598 (67,3)	290 (32,7)	
	Total	1908 (100)	1481 (77,6)	427 (22,4)		1605 (84,1)	303 (15,9)		1452 (76,1)	456 (23,9)	
Chronic disease	**no**	881 (100)	746 (84,7)	135 (15,3)		818 (92,8)	63 (7,2)		840 (95,3)	41 (4,7)	
	yes	1027 (100)	735 (71,6)	292 (28,4)	0,000	787 (76,6)	240 (23,4)	0,000	612 (59,6)	415 (40,4)	0,000
	Total	1908 (100)	735 (77,6)	292 (22,4)		1605 (84,1)	303 (15,9)		1452 (76,1)	456 (23,9)	
Family history of CVD	**no**	1880 (100)	1461 (77,7)	419 (22,3)		1585 (84,3)	295 (15,7)		1433 (76,2)	447 (23,8)	
	yes	28 (100)	20 (71,4)	8 (28,6)	0,492	20 (71,4)	8 (28,6)	0,071	19 (67,9)	9 (32,1)	0,370
	Total	1908 (100)	1481 (77,6)	427 (22,4)		1605 (84,1)	303 (15,9)		1452 (76,1)	456 (23,9)	

Table 28. Association between risk factors (tobacco smoking, TG, cholesterol, HDL- and LDL-cholesterol) and demographic factors (sex, age, presence of chronic disease, family history of CVD) in individuals from Cohort 2 by SCORE NFA.

		Total by NFA n (%)	Smoker		P	Systolic pressure		P	Triglycerides		P
			no n (%)	yes n (%)		below 140 n (%)	above 141 n (%)		below 1,69 n (%)	above 1,70 n (%)	
Sex	**Women**	704 (100)	623 (88,5)	81 (11,5)		675 (95,9)	29 (4,1)		615 (87,4)	89 (12,6)	
	Men	894 (100)	723 (80,9)	171 (19,1)	0,000	852 (95,3)	42 (4,7)	0,626	757 (84,7)	137 (15,3)	0,130
	Total	1598 (100)	1346 (84,2)	252 (15,8)		1527 (95,6)	71 (4,4)		1372 (85,9)	226 (14,1)	
Age	**40-55**	710 (100)	563 (79,3)	147 (20,7)		681 (95,9)	29 (4,1)		624 (87,9)	86 (12,1)	
	56-70	888 (100)	783 (88,2)	105 (11,8)	0,000	846 (95,3)	42 (4,7)	0,545	748 (84,2)	140 (15,8)	0,043
	Total	1598 (100)	1346 (84,2)	252 (15,8)		1527 (95,6)	71 (4,4)		1372 (85,9)	226 (14,1)	
Chronic disease	**no**	656 (100)	529 (80,6)	127 (19,4)		644 (98,2)	12 (1,8)		622 (94,8)	34 (5,2)	
	yes	942 (100)	817 (86,7)	125 (13,3)	0,001	883 (93,7)	59 (6,3)	0,000	750 (79,6)	192 (20,4)	0,000
	Total	1598 (100)	1346 (84,2)	252 (15,8)		1527 (95,6)	71 (4,4)		1372 (85,9)	226 (14,1)	
Family history of CVD	**no**	1577 (100)	1333 (84,5)	244 (15,5)		1506 (95,5)	71 (4,5)		1353 (85,8)	224 (14,2)	
	yes	21 (100)	13 (61,9)	8 (38,1)	0,011	21 (100)	0 (0,0)	1,000	19 (90,5)	2 (9,5)	0,757
	Total	1598 (100)	1346 (84,2)	252 (15,8)		1527 (95,6)	71 (4,4)		1372 (85,9)	226 (14,1)	

Table 28. (continuation)

		Total by NFA n (%)	Total cholesterol		P	HDL cholesterol		P	LDL cholesterol		P
			below 5,2 n (%)	above 5,3 n (%)		below 1,29 n (%)	above 1,3 n (%)		below 2,6 n (%)	above 2,61 n (%)	
Sex	**Women**	704 (100)	501 (71,2)	203 (28,8)		542 (77,0)	162 (23,0)		496 (70,5)	208 (29,5)	
	Men	894 (100)	695 (77,7)	199 (22,3)	0,003	767 (85,8)	127 (14,2)	0,000	671 (75,1)	223 (24,9)	0,041
	Total	1598 (100)	1196 (74,8)	402 (25,2)		1309 (81,9)	289 (18,1)		1167 (73,0)	431 (27,0)	
Age	**40-55**	710 (100)	555 (78,2)	155 (21,8)		611 (86,1)	99 (13,9)		569 (80,1)	141 (19,9)	
	56-70	888 (100)	641 (72,2)	247 (27,8)	0,006	698 (78,6)	190 (21,4)	0,000	598 (67,3)	290 (32,7)	0,000
	Total	1598 (100)	1196 (74,8)	402 (25,2)		1309 (81,9)	289 (18,1)		1167 (73,0)	431 (27,0)	
Chronic disease	**no**	656 (100)	527 (80,3)	129 (19,7)		595 (90,7)	61 (9,3)		619 (94,4)	37 (5,6)	
	yes	942 (100)	669 (71,0)	273 (29,0)	0,000	714 (75,8)	228 (24,2)	0,000	548 (58,2)	394 (41,8)	0,000
	Total	1598 (100)	1196 (74,8)	402 (25,2)		1309 (81,9)	289 (18,1)		1167 (73,0)	431 (27,0)	
Family history of CVD	**no**	1577 (100)	1181 (74,9)	396 (25,1)		1294 (82,1)	283 (17,9)		1154 (73,2)	423 (26,8)	
	yes	21 (100)	15 (71,4)	8 (28,6)	0,800	15 (71,4)	6 (28,6)	0,248	13 (61,9)	8 (38,1)	0,320
	Total	1598 (100)	1196 (74,8)	402 (25,2)		1309 (81,9)	289 (18,1)		1167 (73,0)	431 (27,0)	

Table 29. Association between risk factors (tobacco smoking, TG, cholesterol, HDL- and LDL-cholesterol) and demographic factors (sex, age, presence of chronic disease, family history of CVD) in individuals from Cohort 3 by SCORE (ESC 2019) criteria.

		Total by ESC 2019 n (%)	Smoker		P	Systolic pressure		P	Triglycerides		P
			no n (%)	yes n (%)		below 140 n (%)	above 141 n (%)		below 1,69 n (%)	above 1,70 n (%)	
Sex	**Women**	1342 (100)	1187 (88,5)	155 (11,5)		1291 (96,2)	51 (3,8)		1187 (88,5)	155 (11,5)	
	Men	1116 (100)	910 (81,5)	206 (18,5)	0,000	1065 (95,4)	51 (4,6)	0,361	946 (84,8)	170 (15,2)	0,008
	Total	2458 (100)	2097 (85,3)	361 (14,7)		2356 (95,9)	102 (4,1)		2133 (86,8)	325 (13,2)	
Age	**40-55**	1020 (100)	809 (79,3)	211 (20,7)		991 (97,2)	29 (2,8)		925 (90,7)	95 (9,3)	
	56-70	1438 (100)	1288 (89,6)	150 (10,4)	0,000	1365 (94,9)	73 (5,1)	0,007	1208 (84,0)	230 (16,0)	0,000
	Total	2458 (100)	2097 (85,3)	361 (14,7)		2356 (95,9)	102 (4,1)		2133 (86,8)	325 (13,2)	
Chronic disease	**no**	992 (100)	792 (79,8)	200 (20,2)		974 (98,2)	18 (1,8)		954 (96,2)	38 (3,8)	
	yes	1466 (100)	1305 (89,0)	161 (11,0)	0,000	1382 (94,3)	84 (5,7)	0,000	1179 (80,4)	287 (19,6)	0,000
	Total	2458 (100)	2097 (85,3)	361 (14,7)		2356 (95,9)	102 (4,1)		2133 (86,8)	325 (13,2)	
Family history of CVD	**no**	2427 (100)	2075 (85,5)	352 (24,5)		2325 (95,8)	102 (4,2)		2105 (86,7)	322 (13,3)	
	yes	31 (100)	22 (71,0)	9 (29,0)	0,036	31 (100)	0 (0,0)	0,638	28 (90,3)	3 (9,7)	0,790
	Total	2458 (100)	2097 (85,3)	361 (14,7)		2356 (95,9)	102 (4,1)		2133 (86,8)	325 (13,2)	

Table 29. (continuation)

		Total by ESC 2019 n (%)	Total cholesterol		P	HDL cholesterol		P	LDL cholesterol		P
			below 5,2 n (%)	above 5,3 n (%)		below 1,29 n (%)	above 1,3 n (%)		below 2,6 n (%)	above 2,61 n (%)	
Sex	**Women**	1342 (100)	1024 (76,3)	318 (23,7)		1076 (80,2)	266 (19,8)		981 (73,1)	361 (26,9)	
	Men	1116 (100)	880 (78,9)	236 (21,1)	0,133	948 (84,9)	168 (15,1)	0,002	828 (74,2)	288 (25,8)	0,550
	Total	2458 (100)	1904 (77,5)	554 (22,5)		2024 (82,3)	434 (17,7)		1809 (73,6)	649 (26,4)	
Age	**40-55**	1020 (100)	840 (82,4)	180 (17,6)		907 (88,9)	113 (11,1)		854 (83,7)	166 (16,3)	
	56-70	1438 (100)	1064 (74,0)	374 (26,0)	0,000	1117 (77,7)	321 (22,3)	0,000	955 (66,4)	483 (33,6)	0,000
	Total	2458 (100)	1904 (77,5)	554 (22,5)		2024 (82,3)	434 (17,7)		1809 (73,6)	649 (26,4)	
Chronic disease	**no**	992 (100)	843 (85,0)	149 (15,0)		916 (92,3)	76 (7,7)		946 (95,4)	46 (4,6)	
	yes	1466 (100)	1061 (72,4)	405 (27,6)	0,000	1108 (75,6)	358 (24,4)	0,000	863 (58,9)	603 (41,1)	0,000
	Total	2458 (100)	1904 (77,5)	554 (22,5)		2024 (82,3)	434 (17,7)		1809 (73,6)	649 (26,4)	
Family history of CVD	**no**	2427 (100)	1882 (77,5)	545 (22,5)		2002 (82,5)	425 (17,5)		1789 (73,7)	638 (26,3)	
	yes	31 (100)	22 (71,0)	9 (29,0)	0,388	22 (71,0)	9 (29,0)	0,099	20 (64,5)	11 (35,5)	0,304
	Total	2458 (100)	1904 (77,5)	554 (22,5)		2024 (82,3)	434 (17,7)		1809 (73,6)	649 (26,4)	

10. Comparison of low and average risk groups as well as those with high and very high risk by the SCORE (NFA) and SCORE ESC (2019) methods and their connection with different groups of risk factors such as lifestyle, laboratory and other health indicators

As already mentioned, there is a difference in the grouping of individuals in risk categories by SCORE (NFA) and SCORE ESC (2019). By SCORE NFA, 1598 individuals participate in the analysis, average age 55,77±6,604 years while by SCORE ESC (2019)- 2458 individuals aged 57,12±8,800 years. The results confirmed that there is a statistically significant difference in the age between the groups with low and average risk and the ones with high and very high risk by the two methods- SCORE (NFA) and SCORE ESC (2019).

The distribution of the individuals by sex by SCORE NFA is – women - 704 (44%) and men 894 (56%), and the distribution of the individuals by sex by SCORE ESC (2019) – women 1342 (55%) and men 1116 (45%).

With the help of Mann-Whitney non-parametric analysis we found that there is a statistically significant difference in the sex distribution between the two methods (P=0,000). What is noteworthy is that women participating in the SCORE ESC (2019) are substantially more, on the one hand, due to the high age of the sample and on the other, due to the fact that only women from 55 to 65 years of age are included in SCORE NFA.

Table 30 presents the dependence of the risk factors by the two methods (SCORE NFA and SCORE ESC 2019) in the low and average risk categories.

Table 31 presents the dependence of the risk factors in the high and very high risk categories by the two methods (SCORE NFA and SCORE ESC 2019).

Table 30. Dependence of the risk factors by the two methods in the low and average risk categories.

	Low and average risk group by NFA (N=974) – average rank	Low and average risk group by ESC 2019 (N=1341) – average rank	Mann-Whitney U	Wilcoxon W	Z	Asymp. Sig. (2-tailed)
Smoker with cigarettes daily	1150.27	1163.61	645541.000	1120366.000	-0.794	0.427
Systolic AP	1216.41	1115.57	596174.000	1495985.000	-3.818	0.000
Total cholesterol	1202.04	1126.01	610173.000	1509984.000	-3.130	0.002
Low physical activity	1157.63	1158.27	652706.500	1127531.500	-0.049	0.961
T1DM	1158.00	1158.00	653067.000	1552878.000	0.000	1.000
T2DM	1158.00	1158.00	653067.000	1552878.000	0.000	1.000
Dyslipidemia in the past	1173.60	1146.67	637873.500	1537684.500	-1.190	0.234
Intake of fruit and vegetables	1153.66	1161.15	648843.000	1123668.000	-0.308	0.758
Intake of AH drugs in the past or present	1166.70	1151.68	644591.500	1544402.500	-0.859	0.390
High fasting glucose in the past	1157.82	1158.13	652890.500	1127715.500	-0.075	0.940
DM in distant relatives	1158.51	1157.63	652566.000	1552377.000	-0.145	0.884
DM in close relatives	1155.24	1160.01	650377.500	1125202.500	-0.409	0.683
Family history of CVD	1157.14	1158.63	652227.000	1127052.000	-0.250	0.802
Weight	1232.89	1103.60	580121.000	1479932.000	-4.602	0.000
Waist	1209.99	1120.24	602428.000	1502239.000	-3.217	0.001
Diastolic AP	1208.89	1121.04	603497.500	1503308.500	-3.675	0.000
BMI	1208.46	1121.35	603918.000	1503729.000	-3.104	0.002
HDL cholesterol	1189.23	1135.32	622652.500	1522463.500	-2.447	0.014
Triglycerides	1191.51	1133.66	620431.500	1520242.500	-2.602	0.009
Non-HDL cholesterol	1186.83	1137.06	624982.000	1524793.000	-2.329	0.020
LDL cholesterol	1176.50	1144.56	635044.000	1534855.000	-1.613	0.107
Fasting glucose	1187.07	1136.89	624753.000	1524564.000	-1.973	0.048
Hyperuricemia or gout	1159.95	1156.58	651168.500	1550979.500	-0.643	0.520

Table 31. Dependence of the risk factors by the two methods in the high and very hig risk categories

	High and very high-risk group by NFA (N=624) – average rank	High and very high-risk group by ESC 2019 (N=1117) – Average rank	Mann-Whitney U	Wilcoxon W	Z	Asymp. Sig. (2-tailed)
Smoker with cigarettes daily	898.37	855.71	331424.000	955827.000	-2.597	0.009
Systolic AP	865.13	874.28	344844.000	539844.000	-0.396	0.692
Total cholesterol	890.54	860.09	336313.000	960716.000	-1.300	0.193
Low physical activity	850.34	882.54	335614.000	530614.000	-1.964	0.049
T1DM	870.40	871.34	348126.500	543126.500	-0.453	0.651
T2DM	886.53	862.32	338812.500	963215.500	-1.220	0.222
Dyslipidemia in the past	888.34	861.31	337681.500	962084.500	-1.260	0.208
Intake of fruit and vegetables	868.70	872.28	347069.000	542069.000	-0.165	0.869
Intake of AH drugs in the past or present	873.04	869.86	347229.500	971632.500	-0.151	0.880
High fasting glucose in the past	869.24	871.98	347406.000	542406.000	-0.437	0.662
DM in distant relatives	872.37	870.23	347649.000	972052.000	-0.549	0.583
DM in close relatives	879.44	866.29	343239.500	967642.500	-1.145	0.252
Family history of CVD	872.27	870.29	347714.500	972117.500	-0.461	0.645
Weight	923.06	841.92	316021.000	940424.000	-3.235	0.001
Waist	887.05	862.03	338488.500	962891.500	-1.003	0.316
Diastolic AP	878.98	866.54	343527.000	967930.000	-0.550	0.582
BMI	885.61	862.84	339385.000	963788.000	-0.909	0.363
HDL cholesterol	869.11	872.06	347322.000	542322.000	-0.125	0.900
Triglycerides	884.86	863.26	339854.500	964257.500	-0.912	0.362
Non-HDL cholesterol	882.29	864.69	341460.000	965863.000	-0.773	0.440
LDL cholesterol	881.73	865.00	341807.000	966210.000	-0.715	0.475
Fasting glucose	886.86	862.14	338608.000	963011.000	-1.021	0.307
Hyperuricemia or gout	869.43	871.88	347521.500	542521.500	-0.355	0.722

As shown by Table 30, there are statistically significant differences in a considerable number of the factors regarding some factors related to lifestyle as well as those related to laboratory and other health indicators in the low and average risk groups by SCORE NFA in comparison to the group with low and average risk by SCORE ESC 2019.

Table 31 shows that the statistically significant differences regarding some factors related to lifestyle as well as those related to laboratory and other health indicators in the high and very high-risk groups by SCORE NFA in comparison to the with high and very high-risk groups by SCORE ESC 2019 are present again.

The results show that in the low and average risk groups there are much more risk factors with statistically significant differences while in the high- and very high-risk categories, the number of risk factors is reduced. This leads to the conclusion that in classifying the individuals in the low and average risk, there is a statistically significant difference in the studied individuals (by number and demographic characteristics) as well as in the risk factors that these individuals have.

The results from the distribution and manifestation of all risk factors (main and additional) are different if we compare the two groups: on the one hand, smaller differences in the frequency of risk factors in the patient groups with high and very high risk are observed. Bearing in mind the fact that these patients have already been under dispensary care or are part of the high-risk group, they are going to be followed-up, examined and monitored frequently. The patients part of the low and average risk group are of particular interest, only for them no particular additional measures are provided. The distribution of the risk factors and their manifestation, respectively, are much more diverse and presents intense interest when compared to the morbidity and mortality precisely in these groups.

11. Influence of the additional risk factors on patient classification in the high risk and very high-risk groups by the SCORE NFA and SCORE ESC (2019) methods

In the research we studied the probability of the patients from the average risk group to be categorised in the high-risk group.

In this respect, we had to establish the influence of the additional (modifying) factors on the cardio-vascular risk assessment.

Based on the gathered data for each separate patient, the author of the dissertation performed an assessment, a comparison, an analysis and a summary of the additional risk factors by determining their frequency and intensity. In our longitudinal prospective study, we monitored the influence of the RF on the development of atherosclerotic CV accident- cardio-vascular morbidity and mortality or the CV risk.

The obtained results revealed which risk factors in the studied population have pronounced significance on the morbidity and mortality by an atherosclerotic CVD.

Study of the additional risk factors by the SCORE NFA method by applying logistic regression

In the present study, with the help of non-parametric analysis, we proved that there is no statistically significant difference regarding the occurrence of an event between the average and high-risk groups in the CV risk assessment by the SCORE NFA method (P=0.729).

This gave us the grounds to study the additional, modifying RF and to determine which of them exert influence on the recategorization of the individuals from the average risk group.

We performed a binary logistic impression with the aim of predicting the probability for belonging to the variables average or high risk as well as to determine the impact of RF (factorial signs) on the classification of patients by the studied risk categories by the SCORE NFA method.

The analysis found that the regression method Omnibus Tests of Model Coefficients $\chi 2$=311,485, df=7, P=0.000, Hosmer and Lemeshow Test is statistically significant P>0.05.

The factors included in the logistic model account for 23.6% (Nagelkerke R Square) of the studied variable, i.e. 23.6% of the individuals have the chance to fall in the average risk category (Table 32). The factors which exert influence on patient categorisation in the average risk group are presented.

Table 32. Factors exerting influence on patient classification in the average risk group by SCORE NFA.

		B	S.E.	Wald	df	Sig.	Exp(B)= OR	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Sex	-1,497	,124	145,953	1	,000	,224	,176	,285
	Age	-,046	,009	25,244	1	,000	,955	,938	,972
	Systolic AP	-,045	,006	52,571	1	,000	,956	,944	,967
	Low physical activity	-,379	,191	3,931	1	,047	,685	,471	,996
	Intake of fruit and vegetables	,382	,124	9,513	1	,002	1,465	1,149	1,867
	Intake of medicines for AH in the past or present	-,647	,152	18,124	1	,000	,523	,388	,705
	LDL Cholesterol	-,105	,033	10,053	1	,002	,900	,844	,961
	Constant	9,344	,905	106,649	1	,000	11430,846		

In order to study the factors which exert influence on patient classification in the high risk group, we tested another model with the same factors as in the previous one (Table 33).

In the high risk group the regression model is also statistically significant Omnibus Tests of Model Coefficients χ2=388,784, df=7, P=0.000. Hosmer and Lemeshow Test, P>0.05 (Table 33).

The factors included in the model account for 33.3% of the studied variable, namely that there is a probability that 33% of individuals may fall in the high risk category by SCORE NFA (Table 33).

Table 33. Factors exerting influence on patient classification in the high risk group by SCORE NFA.

		B	S.E.	Wald	df	Sig.	Exp(B)= OR	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Sex	1,517	,155	95,752	1	,000	4,558	3,364	6,176
	Age	,164	,014	136,472	1	,000	1,179	1,147	1,212
	Smoker	,044	,010	17,768	1	,000	1,045	1,024	1,066
	Systolic AP	,037	,007	27,961	1	,000	1,037	1,023	1,052
	T2DM	1,232	,184	44,921	1	,000	3,429	2,391	4,916
	Intake of medicines for AH in the past or present	-,377	,167	5,102	1	,024	,686	,495	,951
	LDL Cholesterol	,165	,038	18,600	1	,000	1,180	1,094	1,272
	Constant	-16,814	1,240	183,954	1	,000	,000		

All listed factors from table 33 are responsible for the increased risk of patient s to fall in the high-risk group except for the intake of medicines for AH.

The common factors for both regression models by SCORE NFA are sex, age, SAP, intake of medicines for AH, LDL cholesterol. The factors sex, age,SAP and tobacco smoking form the risk assessment by the SCORE system and were excluded from their further analysis.

However, the other two factors- intake of medicines for AH, LDL-cholesterol which are not included as base ones in the SCORE method, may play a key role as modifying ones and the individuals who have them may be classified in a higher risk group.

In the classification of individuals in the high-risk group, the factors T2DM and high values of LDL-cholesterol exerted influence. Individuals with T2DM (OR=3.429, 95% CI 2.391÷4.916) and high levels of LDL-cholesterol are more probable to fall in the high-risk group (Table 33).

Study of the additional risk factors by the SCORE ESC 2019 method by application of logistic regression

The previous analyses were repeated for the SCORE ESC (2019) analysis.

First, with the help of the non-parametric analysis we proved once more that there is no statistically significant difference in the registered new events between the average risk and high-risk groups by SCORE ESC(2019), (P=0.252), i.e. in the groups with average and high risk approximately identical relative shares of new atherosclerotic CV events were registered.

This fact gave us the grounds to study the additional, modifying RF and determine which of them exert influence on the classification of individuals in the average risk group.

The additional RF which are not included in the factors forming the assessment for SCORE ESC 2019 and exerting influence on patient classification in the average risk group are presented in Table 34. These factors are to be monitored and controlled by a GP with a view of prevention of patients' falling in the higher risk group, namely the high-risk group instead of remaining in the average risk group.

Table 34. Factors exerting influence on patient classification in the average risk group by the SCORE 2019 method.

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Sex	-,466	,090	27,003	1	,000	,628	,526	,748
	Systolic AP	-,026	,006	21,583	1	,000	,975	,964	,985
	Total cholesterol	,267	,034	62,781	1	,000	1,306	1,223	1,395
	Low physical activity	-,518	,144	12,884	1	,000	,596	,449	,790
	DM in distant relatives	1,122	,400	7,879	1	,005	3,072	1,403	6,725
	Diastolic AP	,022	,009	5,929	1	,015	1,023	1,004	1,041
	Non-HDL cholesterol	-,104	,048	4,691	1	,030	,902	,821	,990
	LDL cholesterol	-,201	,044	20,459	1	,000	,818	,750	,893
	Fasting blood glucose	-,100	,023	19,498	1	,000	,904	,865	,946
	Constant	1,143	,622	3,377	1	,066	3,135		

Of all factors included in the regression model only 25.8% of them explain the probability of individuals to fall in the average risk category. Patients having distant family relation to individuals suffering from T2DM (OR=3.075, 95% CI 1.403÷6.725) and high DAP level (OR=1.023, 95% CI 1.004÷1.041) are more probable to fall in the average risk category.

Table 35 shows that the additional modifying RF factors which exert influence on grouping patients with high risk are T2DM, past dyslipidemia and LDL-cholesterol.

Table 35. Factors exerting influence on patient classification in the high-risk group**.**

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Sex	,466	,107	18,815	1	,000	1,593	1,291	1,966
	Age	,093	,008	147,218	1	,000	1,097	1,081	1,114
	Systolic AP	,024	,005	20,297	1	,000	1,024	1,014	1,035
	T2DM	,590	,136	18,722	1	,000	1,803	1,381	2,356
	Past dyslipidemia	,357	,120	8,875	1	,003	1,429	1,130	1,808
	LDL cholesterol	,075	,031	5,672	1	,017	1,077	1,013	1,146
	Constant	-10,462	,777	181,163	1	,000	,000		

The factors (sex, age SAP and cholesterol) which participate in the SCORE ESC (2019) score were excluded from the analysis. It is obvious from Table 34 and 35 that the common factors for the two regression models are sex, SAP, LDL-cholesterol. Individuals with T2DM (OR=1.803, 95% CI 1.381÷2.356), diagnosed dyslipidemia (OR=1.429, 95% CI 1.130÷1.808) and high values of LDL-cholesterol (OR=1.077, 95% CI 1.013÷1.146) are more probable to fall in the high-risk category.

In both methods for CV risk assessment SCORE ESC (2019) and SCORE (NFA), different number of additional, modifying RF were found- 6 with the SCORE ESC (2019) and 4 with the SCORE NFA which exert influence on the classification of individuals in the average risk and high-risk categories.

In order to determine more precisely the influence of the different modifying factors on patient classification in risk categories, another statistical method, known as the Decision Tree was applied. This method, similarly to the logistic regression, is a classification method, however the difference between the two is that the trees are non-parametric methods, i.e. there is no requirement for a linear connection between the independent and factor variables, as well as the absence of multicollinearity. The other advantage of the Decision Tree is that it not only reveals the factors (variables) facilitating the prediction of the dependent variable value but with quantitative factors the value leading to different levels or different probabilities for a level of the dependent variable are determined.

CRT (Classification and Regression Trees) algorithm which constructs a binary tree, was used for the purposes of the research. This algorithm was chosen due to the presence of low risk in the deviation between the real and prognostic values. With both methods the results were very good- 0.262 by SCORE NFA and 0.304 by SCORE ESC (2019). Furthermore, the predictive power of the models with both methods was satisfactory. The total percent of the correctly classified cases of the predictive variable with SCORE NFA is 73.8%, 96.8% for average risk and 19.1% for high risk. The results for the SCORE ESC (2019) are 69.6% for the whole sample, 91.7% for average risk and 32.1% for high risk.

The factors which exert influence on the degree of risk- high or average as well as on the probability for occurrence of both risks are presented separately for each method- SCORE NFA and SCORE ESC (2019).

Study of the additional risk factors by the SCORE NFA method by application of the statistical method "Decision Tree"

Figure 11 shows a Decision Tree by the **SCORE NFA method.**

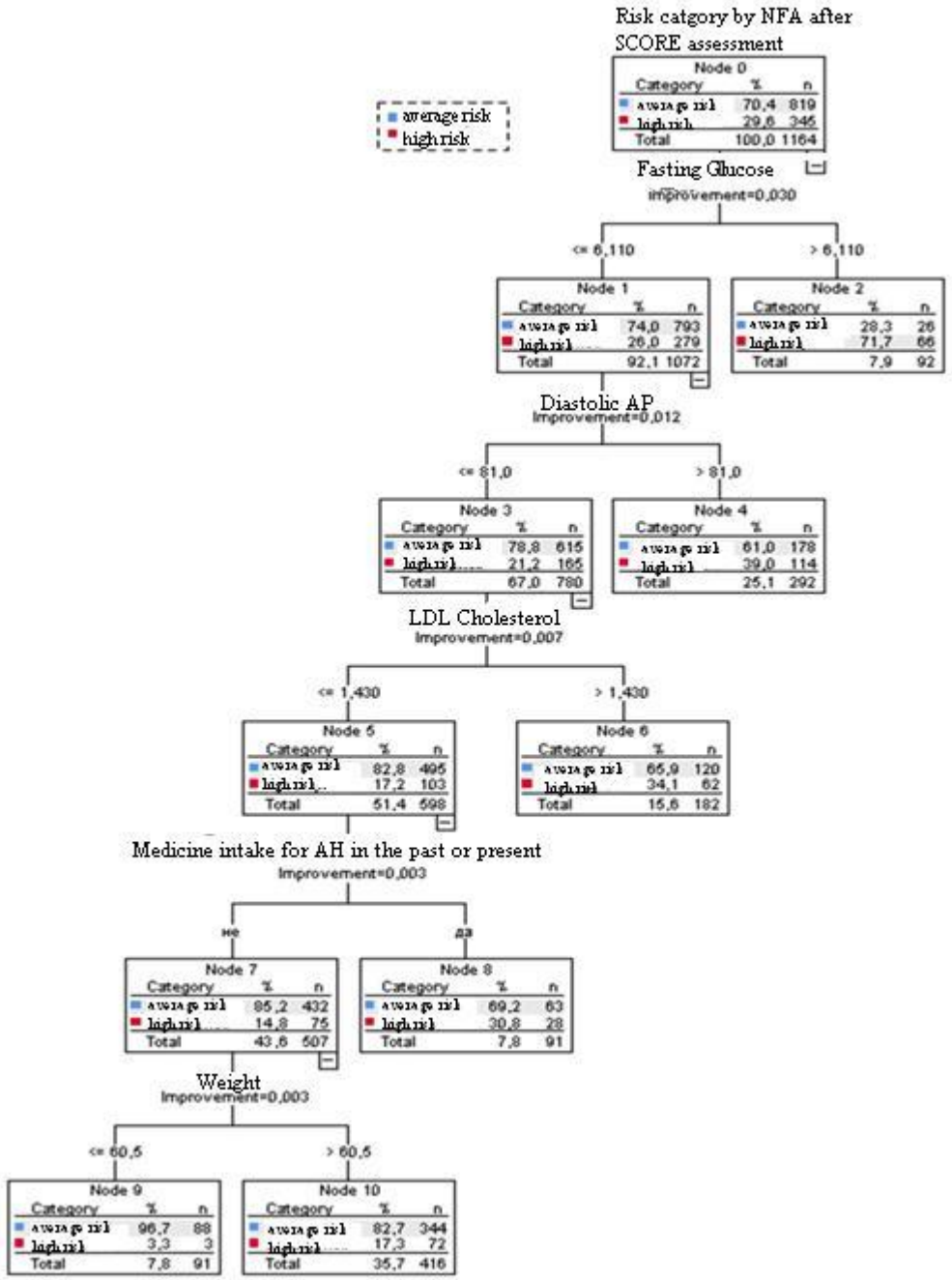

Figure 8. Decision tree with the SCORE NFA method

In order to establish the factors which exert influence on the studied variable, namely whether the patient falls in the average risk category or the high risk category,

the end nodes of the base are analysed. Only those with prognostic probability (Response) higher than 50% and Index higher than 100% are taken into account. For the average risk category these are nodes 9 and 10 from the Decision Tree and for the high-risk category- only node 2 (Table 36,37)

Table 36. End nodes with the *average* risk category for SCORE NFA.

Gains for Nodes

	Node		Gain			
Node	N	Percent	N	Percent	Response	Index
9	91	7.8%	88	10.7%	96.7%	137.4%
10	416	35.7%	344	42.0%	82.7%	117.5%
8	91	7.8%	63	7.7%	69.2%	98.4%
6	182	15.6%	120	14.7%	65.9%	93.7%
4	292	25.1%	178	21.7%	61.0%	86.6%
2	92	7.9%	26	3.2%	28.3%	40.2%

Growing Method: CRT Dependent Variable: Risk category by NFA after SCORE assessment.

Table 37. End nodes with the *high* risk category for SCORE NFA.

Gains for Nodes

	Node		Gain			
Node	N	Percent	N	Percent	Response	Index
2	92	7.9%	66	19.1%	71.7%	242.0%
4	292	25.1%	114	33.0%	39.0%	131.7%
6	182	15.6%	62	18.0%	34.1%	114.9%
8	91	7.8%	28	8.1%	30.8%	103.8%
10	416	35.7%	72	20.9%	17.3%	58.4%
9	91	7.8%	3	0.9%	3.3%	11.1%

Growing Method: CRT Dependent Variable: Risk category by NFA after SCORE assessment

Based on these results, the factors which exert influence on the probability that a certain individual falls into the corresponding risk category are derived. The risk can be classified as "average" by the SCORE NFA method with the following groups of patients:

- With fasting glucose ≤ 6.110, with DAP ≤ 81.0, with LDL cholesterol ≤ 1.43, without intake of medicines for AH in the past and present and weight ≤ 60.5 kg. (96.7%) (node 9);
- With fasting glucose ≤ 6.110, with Diastolic AP ≤ 81.0, with LDL cholesterol ≤ 1.43, without intake of medicines for AH in the past and present and weight > 60.5 kg. (82.7%) (node 10).

The risk can be classified as "high" by the SCORE NFA method in patients with fasting glucose > 6.110 (71.7%) (node 2).

Study of the additional risk factors by the SCORE ESC (2019) method by application of the statistical method "Decision Tree"

Figure 12 presents a Decision Tree with the SCORE ESC (2019) method.

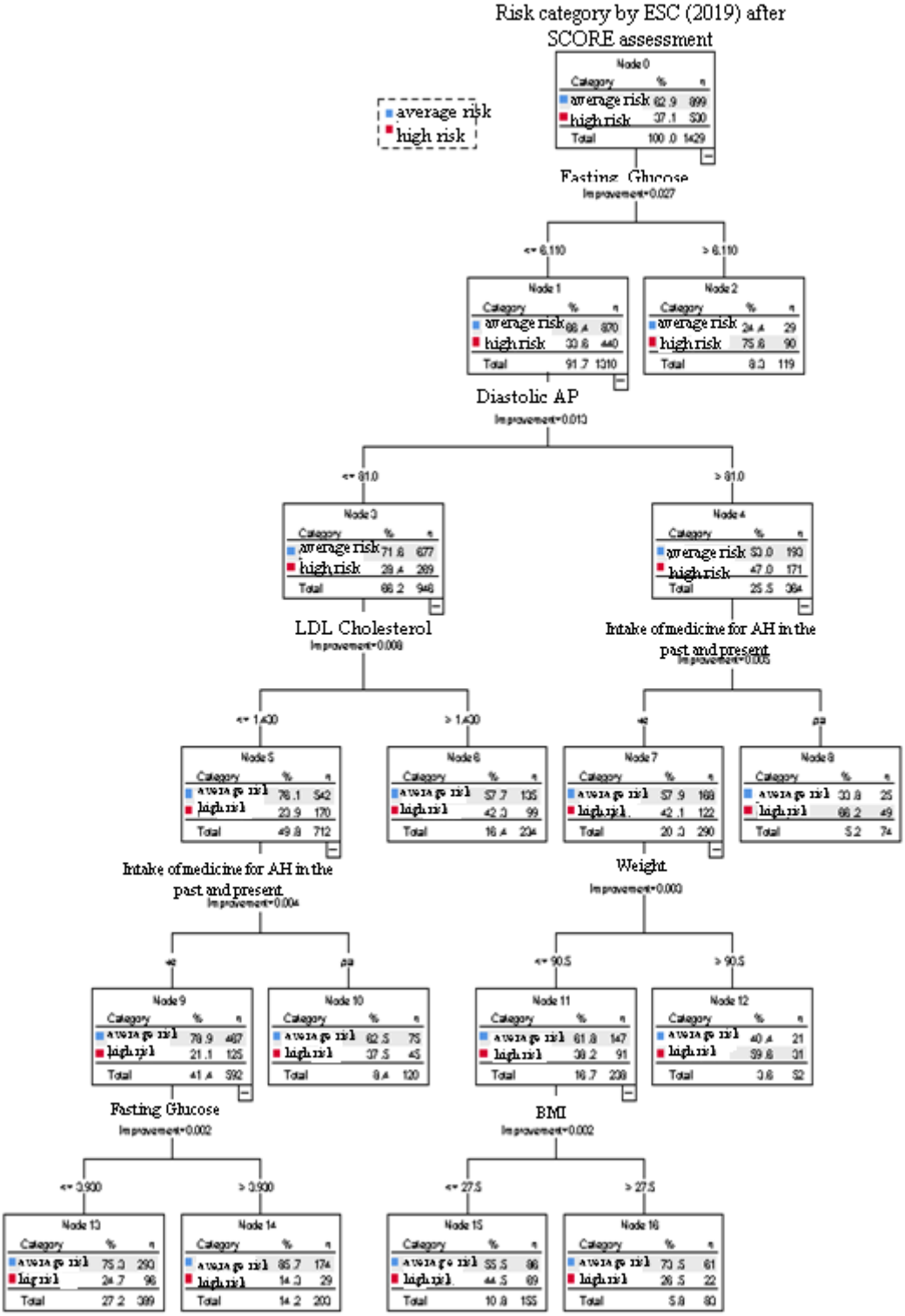

Figure 9. Decision tree with the SCORE ESC 2019 method

The factors exerting influence on the individuals in order to fall in the *average* risk category are determined on the basis of end nodes 14,13 and 16 from the decision tree and for the *high-risk* category- these are nodes 2, and 12 (Table 38, 39).

Table 38. End nodes with the *average* risk category for SCORE ESC 2019.

Gains for Nodes

	Node		Gain			
Node	N	Percent	N	Percent	Response	Index
14	203	14.2%	174	19.4%	85.7%	136.2%
13	389	27.2%	293	32.6%	75.3%	119.7%
16	83	5.8%	61	6.8%	73.5%	116.8%
10	120	8.4%	75	8.3%	62.5%	99.3%
6	234	16.4%	135	15.0%	57.7%	91.7%
15	155	10.8%	86	9.6%	55.5%	88.2%
12	52	3.6%	21	2.3%	40.4%	64.2%
8	74	5.2%	25	2.8%	33.8%	53.7%
2	119	8.3%	29	3.2%	24.4%	38.7%

Growing Method: CRT
Dependent Variable: Risk category by ESC 2019 after SCORE assessment

Table 39. End nodes with the *high* risk category for SCORE ESC 2019.

Gains for Nodes

	Node		Gain			
Node	N	Percent	N	Percent	Response	Index
2	119	8.3%	90	17.0%	75.6%	203.9%
8	74	5.2%	49	9.2%	66.2%	178.5%
12	52	3.6%	31	5.8%	59.6%	160.7%
15	155	10.8%	69	13.0%	44.5%	120.0%
6	234	16.4%	99	18.7%	42.3%	114.1%
10	120	8.4%	45	8.5%	37.5%	101.1%
16	83	5.8%	22	4.2%	26.5%	71.5%
13	389	27.2%	96	18.1%	24.7%	66.5%
14	203	14.2%	29	5.5%	14.3%	38.5%

Growing Method: CRT
Dependent Variable: Risk category by ESC 2019 after SCORE assessment

Based on the obtained results, we can conclude that the change for average risk is higher in patients with:

- Fasting glucose in the interval from 3.930 to 6.110, DAP ≤ 81.0, LDL cholesterol ≤ 1.43 and without intake of medicines for AH in the past and present (85.7%) (node 14);

- Fasting glucose ≤ 3,930, DAP ≤ 81.0, LDL cholesterol ≤ 1.43 without intake of medicines for AH in the past and present (75.3%) (node 13);
- Fasting glucose ≤ 6.110, DAP > 81.0, without intake of medicines for AH in the past and present, weight ≤ 90.5 kg. and BMI > 27.5 (73.5%) (node 16).

Therefore, risk can be classified as "high" in the following three patient groups:

- With fasting glucose > 6.110 (75.6%) (node 2);
- With fasting glucose ≤ 6.110 and DAP > 81.0, intake of medicines for AH in the past or present (66.2%) (node 8);
- With fasting glucose ≤ 6.110 and with DAP > 81.0, without intake of medicines for AH in the past or present but with weight > 90.5 kg. (59.6%) (node 12).

12. Improved model for cardio-vascular risk management in General Practice

One of the important results, if not the most important one, from the performed thorough research presented in this paper, as well as a step forward in the prevention of cardio-vascular diseases on the national level is a new improved model for risk assessment on the national level, including in primary help without eliminating the obligations of the MH for comprehensive policy for health promotion and CVD prevention.

The basis for the improved model is the results and conclusions made by the present research which are compared to the models for assessment of additional, attributive risk proposed in the European guidelines themselves for cardio-vascular disease prevention in clinical practice by the European Society of Cardiology from 2016 and 2019 as well as the methods implemented in the NFA.

The attributive risk, or the severity of each additional risk factor, forms the basis of the new improved model.

✓ In the first place and as a first step in the development of the new model, new additional factors to the calculated SCORE were added as they are suggested by the European guidelines for cardio-vascular disease prevention in clinical practice from 2016 and in the appendices of the NFA.

In the European guidelines 2016 for the prevention of cardio-vascular disease in clinical practice, a number of different described and suggested risk factors are present, however, they do not mention the attributive risk as a number and as specified almost everywhere in the Guidelines, further studies are necessary on the national level and numerous race differences are possible. The methodology for risk assessment from 2019 is used as a basis for the new model since it has the best predictive results.

Tot the model proposal for cardio-vascular risk management and SCORE results which NFA suggests are added additional risk factors with severity coefficient (in points as described in NFA) as follows:

- ***Regular physical activity at least 30 minutes daily*** (on the working place and/or in the free time) – yes (0 p.), no (2 p.)

- ***Daily consumption of fruit and vegetables*** – yes (0 p.), no (1 p.)
- ***Regula intake of antihypertensive medicines at present or in the past*** – yes (2 p.), no (0 p.)
- ***Increased blood glucose level in the past*** (during a regular physical examination, during another disease, during pregnancy) above 6,1mmol/l – yes (5 p.), no (0 p.)
- ***Waist circumference in men*** – below 94 cm. (0 p.), 94-102 cm. (3 p.), above 102 cm. (4 p.); women – below 80 cm. (0 p.), 80-88 cm. (3 p.), above 88 cm. (4 p.)
- ***Body Mass Index*** – below 25 kg./m^2 (0 p.), 25-30 kg./m^2 (1 p.), above 30 kg./m^2 (2 p.).

Before the recategorization, the following results were available:

- 2458 are all patients with calculated risk according to the 2019 methodology, 34 of them suffered severe or fatal CVD during the second year of the research. Out of them:
- 1117 (45%) are the patients with high and very high risk which are separated and are followed-up (patients in dispensary care and risk patients), 27 of them suffered a CV accident during the second year.
- 1341 (55%) of patients are with low or average risk, 7 of them suffered a severe or fatal CVD during the second year of the research and need to be recategorised.

After adding the above-mentioned points, in accordance with the presence of each additional risk factor and its manifestation, the risk was assessed again and the following results were obtained:

- 1944 (79%) patients are with high and very high risk, 33 of them suffer a CV accident.
- 512 patients are with low and average risk, 1 patient suffered a CV accident during the second year of the research.

Based on the obtained results, we can conclude that the SCORE 2019 method has a better predictive value but also one big disadvantage- too many patients from the cohort will need to be allocated to a risk group and together with the patients under dispensary care (patients with very high risk) they are 79% in total which is not very acceptable from a financial and organisational point of view. This high relative share shows the current condition but at the same time requires actions related to health promotion and CVD prevention consisting of follow-up and performing additional activities for healthy people (despite being in risk) several times a year which is not always appropriate and effective.

✓ The second step in the development of the new model is solely based on the statistical results from the present research. Just as described in chapter *Results*, patients who are subject to recategorization are in initial low or average risk and are characterised by the following risk factors:

- Fasting glucose > 6.11

- DAP > 81.0, but this is the factor which is least important in comparison with the other three
- Taking AH medicines in the past or present
- Patients with weight > 90.5 kg.

Thus, with 1341 patients with low and average risk, 326 new patients were selected which are to be relocated in the group with high risk and to be monitored. Results:

- 1443 (1117+326 new patients with high risk, 59%) are the patients with high and very high risk, 30 of them suffered a CV accident.
- 1015 (41%) are the patients with low and average risk, 4 of them suffered a CV accident during the second year of the research.

A new model for calculating CV risk, which is to be applied to the whole population, requires a much bigger cohort for observation and requires a longer observation.

The proposed improved risk assessment model in general medical practice includes the algorithm, presented in figure 13:

1. Use of the SCORE ESC (2019) method together with the tables for risk assessment for occurrence of a fatal event with main risk factors: age, SAP, total cholesterol, tobacco smoking and sex.

2. Following stratification by SCORE ESC (2019) by categories, patients with low and average risk with at least one of the additional factors:

- Fasting glucose > 6.11mmol/l
- Intake of AH medicines in the past or present
- Patients with BMI > 30

Are to be recategorised to high-risk patients.

3. All patients from the high-risk group are separated into a risk group for CVD occurrence for monitoring and activities similar to the ones for the patients under dispensary care for CVD.

4. All described additional risk factors continue to be examined and monitored and new ones are to be introduced and monitored.

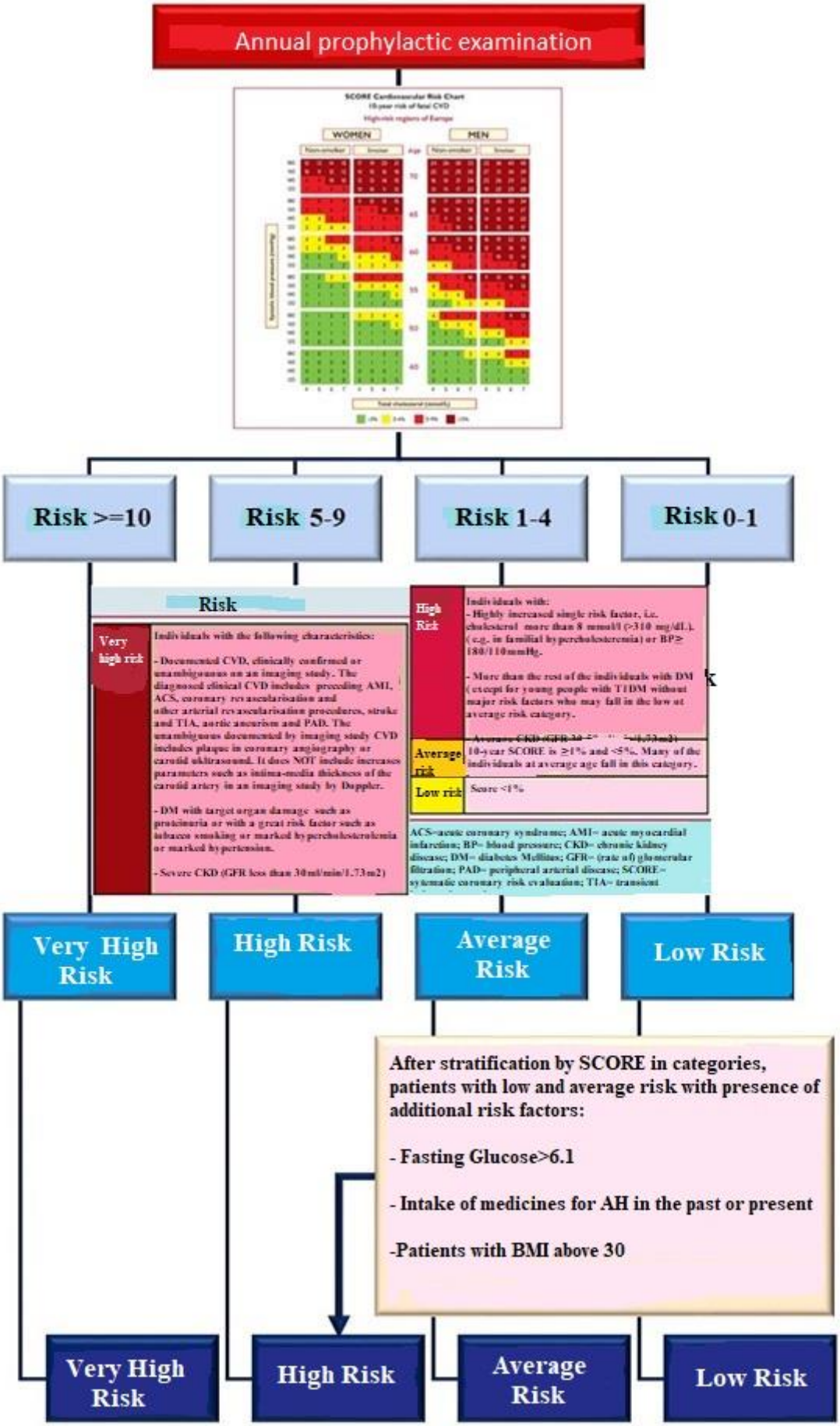

Figure 10. Improved model for CV risk assessment

CONCLUSION

The present dissertation follows in historical aspect the CV risk assessment SCORE for occurrence of CVD.

4551 patients are followed-up in the research within two consecutive calendar years, grouped in three cohorts, during the first year a prophylactic examination, test and a questionnaire for all risk factors were performed, the risk being assessed according to all three methods. During the second year, data for the patients from each cohort for newly occurred severe or fatal CVD from the medical records in the information system, discharge summaries, GRAS and death notices were gathered.

The results show that there is no statistically significant difference in determining risk categories between the methods - SCORE ESC-2016 and SCORE NFA. However, when comparing the data of all three methods, we found that the ESC Guidelines for behaviour in dyslipidemia from 2019 method shows results which have statistically significant difference compared to the other two methods. Herby the determining of the "High risk" category, which is the primary goal of all methods, is much more precise having in mind the CVD morbidity during the second year. The results from ESC Guidelines for behaviour in dyslipidemia from 2019 method could successfully be used in the application of individual measures for cardio-vascular risk control.

Our own results confirm the advantage of the 2019 method and the validity of the SCORE system of the European Cardiology Society as a whole.

The longitudinal study in the three Cohorts examines numerous additional risk factors which have greater contribution in determining the risk. Due to the obtained results, a new, modified model for risk assessment was developed which requires recategorization of the risk with consideration of three additional risk factors. They are to be borne in mind in the next patient categorisation from low and average risk group to the high-risk group. The additional risk factors are as follows:

- Body Mass Index above 30
- Fasting blood glucose more than 6,1mmol/l (only as a statement this could be all patients with identified Diabetes Mellitus without complications, however, high blood glucose values may even be the cause for diagnosing Diabetes Mellitus with complications)
- The fact that a patient takes medicines for treatment of Arterial Hypertension in the present or past (i.e. underlying hypertension, not recognised as a serious disease, not under dispensary care, silent hypertension)leads to determining high-risk cases which are not too much to deplete financial and organisation resource but are crucial for CVD prevention.

MAIN CONCLUSIONS

1. The study proved that there is a statistically significant difference in patient classification in risk groups between the SCORE ESC (2019) method in comparison to SCORE ESC (2016) and SCORE NFA, while in SCORE ESC (2016) and SCORE NFA no statistical differences were found. The greatest relative share of the individuals from the *very high* risk category is with SCORE ESC (2019).

2. The calculated absolute cardio-vascular risk is highest with the SCORE ESC (2019) method, in comparison to the SCORE ESC (2016) and SCORE NFA methods.

3. The SCORE ESC (2019) method has the highest predictive value as measured by the population relative risk (RR), attributive risk (AR) and logistic regression analysis. The predictive validity for occurrence of a severe or fatal atherosclerotic CV event in the group of the exposed (individuals in high and very high risk) compared to the non-exposed (individuals in *low* and *average* risk) is highest with the SCORE ESC (2019) method when compared to SCORE ESC (2016) and SCORE NFA methods.

4. Despite not establishing a statistically significant difference in the prognostic validity for CV event occurrence in the high and very high-risk groups by the three methods by sex, the relative risk for the occurrence of an atherosclerotic severe or fatal CV event in men is higher than in women. Significant differences are found between the average values of the absolute risk by sex in all three methods, CV risk being highest for Cohort 3.

5. There are minimum intergroup differences regarding the distribution of the risk factors- tobacco smoking, SAP, TG, cholesterol, HDL- and LDL-cholesterol in the monitored individuals from the three cohorts.

6. The comparative analysis of the health, clinical and laboratory indicators confirms the differences in the cardio-vascular risk assessment and patient classification by with the two methods SCORE NFA and SCORE ESC (2019). In the SCORE NFA method individuals with higher RF values fall in the categories low and average risk.

7. The comparative analysis between the two methods SCORE NFA and SCORE ESC (2019) found that the number of RF in the groups with low and average risk, in which statistically significant differences were established, is considerably higher than in the groups with high and very high risk. Therefore, when classifying individuals in the categories with low and average risk, there are differences in the observed individuals (number and demographic characteristics) as well as in the risk factors of these individuals . This presumes their reclassification from the categories with low and average risk to the high-risk category.

8. With both methods for CV risk assessment SCORE ESC (2019) and SCORE NFA, different number of additional, modifying RF were found and they exert influence on the classification of the individuals in the categories with average or high risk. The modifying risk factors: BMI above 30, Fasting Blood Glucose above 6,1mmol/l and medicine intake for arterial hypertension treatment in the past or present, which are different from the ones suggested by the SCORE NFA method, influence the final CV risk assessment.

9. A new, improved model for CV risk SCORE management model consistent with the European guidelines and adapted for the Bulgarian population is proposed.

SCIENTIFIC CONTRIBUTIONS OF ORIGINAL NATURE

- This is the first research in Bulgaria which compares the absolute, comparative and attributive risk and the predictive value in determining the SCORE risk assessment by three methods- two of the European Cardiology Society from 2016 and 2019 and the manner in which it is implemented in the NFA.
- This is the first research in Bulgaria which identifies and estimates the attributive contribution of the additional risk factors for the SCORE for CVD development.
- The dissertation proved that the predictive value of the methodology of the European Cardiology Society, as described in the Guideline for treatment of dyslipidemia from 2019, is greater than the SCORE ESC from 2016 and SCORE NFA methods.
- The dissertation proposes a new, improved model for risk assessment with reclassification of the individuals from the low and average risk category into the high-risk category in the presence of at least one of the additional, modifying factors – BMI above 30, Serum Fasting Blood Glucose above 6,1 mmol/l or Intake of medicines for the treatment of Arterial Hypertension without recalculating the SCORE points.

SCIENTIFIC CONTRIBUTIONS OF CONFIRMATORY NATURE

- The present dissertation confirmed the main RF for development of atherosclerotic CVD and their influence on patient categorisation by the three SCORE methods.
- The prognostic value of the three SCORE methods for relatively correct classification of patients in risk groups was also confirmed.
- The presence of additional modifying RF which exert influence on the final results was confirmed.

RECOMMENDATIONS

- GPs should continue to have a leading role in the identification and management of the risk for developing CVD among patients from the Republic of Bulgaria due to their daily contact, knowledge of the population and presence of sufficient information and organisation resource.

- MH should continue performing a leading role in health promotion and policy of CVD prevention.

- In the courses of postgraduate education (PGE), seminars and lectures should be organised for medical staff regarding the correct identification and registering of causes of death.

- Financial resources should be provided and the follow-up of all health-insured individuals, including one for new risk factors with the aim of their study, should be contracted in the NFA.

- The development of the risk assessment methodology in preventive cardiology should be followed and the latest developments should be included in the NFA annually with the aim of better risk stratification.

- The ESC Guideline for behaviour in dyslipidemias (2019) method with the distribution in risk categories should be implemented.

- Activities should be undertaken for the individuals from the “high” risk group, and they should be implemented in the NFA. Annual testing of laboratory indications and ECG and annual cardiology consultations, similar to those in the dispensary care for CVD, should be performed which would lead to better risk control in the group with the aim of reducing CVD morbidity and mortality in the Republic of Bulgaria. All these activities should be financially secure by the NHF in the same way.

- It is necessary that studies for the influence of the main and additional risk factors on the risk assessment for developing CVD continue. The follow-up of the additional, modifying risk factors is of crucial importance with a view to the contemporary CV risk assessment and their attributive risk. Performing large-scale cohort studies based on the scientific achievements would contribute to the identification and addition of new risk factors to the systems for CV risk assessment which have higher cost-effectiveness and cost- benefit value.

- Much more through studies for the follow-up of the proposed model for classification of individuals into risk categories are necessary as well as ensuring the necessary resource for its implementation in the NFA and general medical practice.

SCIENTIFIC PUBLICATIONS RELATED TO THE DISSERTATION

Topic	Place of publication
Does Implementation of the Cardiovascular Risk Score in Primary Care Meet Our Expectations and Patients' Needs? Plamen N. Latev	JOURNAL OF BIOMEDICAL AND CLINICAL RESEARCH (Vol.12 Number 1,Supplement 2, 2019) Abstracts from Jubilee Scientific Conference "45 years Medical University – Pleven", 31 October - 2 November, 2019, Pleven, ISSN 1313-6917
DISTRIBUTION OF RISK FACTORS ACCORDING TO THE SCORE (ESC 2016) AND SCORE (ESC 2019) SYSTEMS– PRELIMINARY RESULTS Plamen Latev, Rositsa Dimova, Rumyana Stoyanova	Scientific Works of the Union of Scientists in Bulgaria- Plovdiv, series G. Medicine, Pharmacy and Dental medicine, Vol. XXVII. ISSN 1311-9427 (Print), ISSN 2534-9392 (On-line). 2022. (A report and publication of a full-text article)
RISK FACTORS AND ASSESSMENT OF ABSOLUTE CARDIOVASCULAR RISK IN THE BULGARIAN POPULATION"	7th International Zeugma Conference on scientific research which was held on 21-23 January, Gaziantep, Turkey, (A report and publication of an abstract in an abstract book, ISBN- 978-625-8423-98-3)
RISK FACTORS AND CARDIO-VASCULAR RISK ASSESSMENT – COHORT STUDY AMONG THE BULGARIAN POPULATION	General Medicine Journal, issue 3, 2022 (to be printed)
PREDICTIVE VALIDITY, SENSITIVITY AND SPECIFICITY OF THE SCORE SYSTEM BY THE ESC (2016), NFA AND ESC (2019) MEHTODS	International Scientific Conference "Education, Science, Economics and Technologies", June 23-24 2022, "Prof. Asen Zlatarov"University, Burgas