Universitatea „Ovidius” din Constanța
Școala Doctorală de Medicină
Domeniul de doctorat Medicină

REZUMATUL TEZEI DE DOCTORAT

CARDIOVASCULAR RISK IMPACT OVER THE HYPERTENSIVE PATIENT MONITORIZED IN THE FAMILY MEDICINE CABINET

Conducător de doctorat:
Prof. Univ. Dr. Craiu Elvira

Student-doctorand:
Marian (Condur) Laura Maria

Constanța, 2018

Content

Keywords: Cardiovascular risk, high blood pressure

The doctoral thesis has:

General part consisting of four chapters summing 68 pages

Personal part consisting of five chapters summing 104 pages

259 bibliographic references

83 de figures

78 de tables

Notă: Tables and figures inserted in the summary of the doctoral thesis retain the original numbering from the thesis. The table of contents from the summary retains the structure and page number from the thesis.

Introduction

ARTERIAL HYPERTENSION (HBP) is the most common cardiovascular disease (CVD) and has become a real public health problem at this time.

Statistics show that we are witnessing an alarming increase in the incidence of high blood pressure in the late stages of the disease worldwide, in general, and in Romania in particular.

The presence of target organ complications or cases that at the time of diagnosis, although treated, are not sufficiently covered by treatment appear to be more common in practice.

The World Health Organization (WHO) believes that CVDs are the first cause of mortality in the world. Statistics show a rising incidence, so that there were 17.3 million deaths in 2012, 7.3 million of which were due to coronary artery disease, 6.2 million had a stroke and 9.4 million had a cause direct, high blood pressure. Also, an analysis by the WHO and the International Society of Hypertension conducted in 2014 highlighted that HBP is the most important "risk factor for death and disability worldwide". In the same report, attention is drawn to the fact that HTA "has reached endemic dimensions". Thus, if in 1980 there were approximately 600 million adults with HTA in the world in 2008, the number reached 1 billion, with estimates predicting a figure of up to 1.56 billion in 2025.

The phenomenon is extremely worrying and can be explained both by the increase in the population on the globe and by the aging process that shows a tendency to increase life expectancy at all stages of age (65 years is estimated to increase by 17 years to 75 11 years old, 85 years old by 6 years, 90 years old by 4 years and 100 years by 2 years).

At the same time, it is emphasized that HTA is considered to be "the most common cardiovascular risk factor in the world" until the age of 50 - 1 out of 5 people have HTA, between 50-65 years - 1 out of 3 and over 65 years - 2 out of 3 people have HTA.

As far as the situation in Romania is concerned, HTA has a very high, worrying prevalence, about 7 million people, representing about 40% of the country's population.

Also, the occurrence of HTA at a younger age, even before the age of 40, is also a sign of alarm.

At the same time, Romania has a high CV mortality rate in Europe, clearly higher than other EU countries: 61% in Romania vs. 37% in the EU and 53% in countries that have recently joined the EU. Practically, "of 100 people die, 62 are heartbroken, and HTA has the most important role in processing mortality."

In Romania, high blood pressure is "the second pathology as a frequency" and occupies the 5th place in the "top" of diseases with the highest number of hospitalization days, while there are still a small number of "known, treated and therapeutically controlled hypertensive patients".

It is very important to note that there is a clear "interdependence" between HTA and cardiovascular risk, sometimes even "independent" of other risk factors.

Studies show, on the one hand, that elevated TA levels can lead to CV complications (eg stroke: 54%, BCI: 47%, other CV conditions: 25%) and, on the other hand, have shown that detection at time and correct treatment of HTA reduces the risk of CV and the incidence of cardiovascular events.

So the role of the Family Doctor is extremely important, HTA being probably the most common form of chronic illness monitored in his cabinet.

Therefore, prevention is a priority, Family Medicine is the only specialty that also makes prevention, so its role is essential.

Timely detection of elevated TA and other CV risk factors, correct treatment, prevention of target organ damage, and complications are the main goals the family physician must have in addressing the HTA patient and the risk of cardiovascular disease. Because this pathology still has many unknowns, with the emergence of new risk factors presented by the literature, factors involved in the occurrence of HTA and the pathology of CV, I intend in this paper to deepen this subject.

For this purpose, we analyzed a selected group of patients from their own list who had elevated TA values and were subsequently diagnosed with HTA, CV risk factors most commonly found in the clinic, including a number of "new" risk factors.

Finally, I tried to create a profile of the patient with cardiovascular risk in the family medicine cabinet, which could be personalized for each case.

This profile would then allow a preventive, targeted, patient-specific intervention, applying the principles of "4P Medicine": PREVENTION; PREDICTION; predictability; PARTICIPATIVITATE.

The result would be to increase life and quality of life. Also, by identifying targeted prevention measures, then applied to each patient, you could get a decrease in the incidence of HTA, CV risk, and complications, because it's always easier to prevent than to treat.

General Part

The general part is structured in four chapters. We have synthesized existing data on cardiovascular risk and risk factors currently known.

Chapter I - HTA and cardiovascular risk factors - the chapter is structured in subchapters analyzing the role that "classical" risk factors have increased cardiovascular risk.

The role of epigenetics, a concept that has emerged in recent years that might explain some aspects of disease emergence and could modify existing theories of chronic diseases, has been further evaluated. The third subchapter is the analysis of the "new" risk factors identified.

Chapter II - Current state of research. Epidemiological studies - performs a synthesis of the main epidemiological studies conducted globally, these being analyzed regionally (Asia, USA, Europe and Romania).

Chapter III - HTA and the evaluation of the hypertensive patient in the family medicine cabinet reviews the way in which the evaluation of the patient with hypertension is currently recommended. Methods for determining tension values, anamnesis, paraclinical analyzes, and complementary examinations are performed to establish the cardiovascular risk of each patient and the use of specially performed scores for the assessment of cardiovascular risk. Also, within this chapter are described specific methods of evaluation of target organs affected by the presence of hypertension.

Chapter IV - Global cardiovascular risk presents how cardiovascular risk is defined, ie the risk of producing an acute cardiovascular or cerebral event in the hypertensive population. The chapter reviews the various scores used in medical practice, pointing to the elements that define global cardiovascular risk.

Personal part

Chapter V – "New" cardiovascular risk factors and the hypertensive patient monitored by the family doctor present "new" cardiovascular risk factors that are in continuous research and would play an important role in the development of cardiovascular disease. There are "modifiable" factors that can act independently and also associate, thus increasing cardiovascular risk. Early detection and correct treatment of these risk factors are important elements in preventing cardiovascular disease. The family doctor is best placed to highlight their presence in patients in time. That is why I chose to deepen some of these "new" cardiovascular risk factors, much discussed in the specialized literature and still subject to current research in many specialist studies.

"New" cardiovascular risk factors analyzed are:

- Psychological factors
- Non-HDL-cholesterol
- Inflammation
- Blood pressure variability
- Vitamin D

Chapter VI – Material and methods

The study is a prospective one. The period of the study was 2011-2017, on a group of 692 patients evaluated in the family medicine medical office. They were evaluated successively over a three-month period in order to establish the diagnosis of hypertension. They were monitored annually, following the evolution over time, TA values, association with "new" risk factors, target organ damage and/or complications.

The paper used subgroups of patients to evaluate the various aspects of the inclusion, and the inclusion and exclusion criteria are detailed when presenting the results of each of them. The major criteria for inclusion of patients in joint studies are:

- age between 35 and 65 years,

- the presence of high blood pressure (TA greater than 140 mmHg / 90 mmHg at repeated measurements, constantly elevated values for one month),

- patients newly diagnosed with HTA.

Exclusion criteria were

- secondary arterial hypertension,

- lack of agreement to participate in the study.

Evaluated parameters were:

- Lipid metabolism
  - Total cholesterol
  - HDL-Cholesterol
  - LDL-Cholesterol
  - Non-HDL-Cholesterol
  - triglyceride
- Carbohydrate metabolism
  - Blood glucose
- Renal function
  - Urea
  - creatinine
  - Glomerular filtration rate
  - Uric acid
- Factors of inflammation
  - ESR
  - Fibrinogen
  - Reactive Protein C
  - High sensitivity reactive protein C - as a specific inflammation factor for cardiovascular risk
- Ag. Helicobacter Pylori
- The dosage of vitamin D (25 (OH) D)
- Blood ionogram
- Anthropometric parameters
  - height
  - Weight
  - Body Mass Index
  - Abdominal circumference
- Blood pressure
- Cardiac frequency

Also, electrocardiogram, eye exam, ankle-arm index, and osteodensimetry were also performed.

In order to perform the statistical analysis, we used the Microsoft Office Excel 2016 and IBM SPSS Statistics 24 applications respectively. To determine the statistical significance of the observed differences between the different groups analyzed, we applied specific statistical tests, depending on the type and number of variables analyzed. The threshold for statistical significance was set at a value of $p \leq 0.05$.

Chapter VII – Results

High blood pressure prevalence

Concerning the overall prevalence of HBP, it was 456.65 cases / 1000 subjects tested (Table XIV) within the analyzed group of patients. The highest prevalence was observed for the age group 61-65 years, and the lowest, as expected for people aged 35-40 years.

Tabel XIV High Blood Pressure prevalence by age group

Age group	*Prevalence (1000 tested people)*
35-40 years	250.00
41-50 years	336.73
51-60 years	486.59
61-65 years	586.39
Total	456.65

Statistical analysis of the group of patients with cardiovascular risk

Distribution according to gender

The studied group comprised 316 hypertensive patients identified with cardiovascular risk. Of these, 147 representing 46.5% are male, and 169 representing 53.5% are female.

Distribution according to age

The average age of the patients was 56.09 years, with a median of 58 years and standard deviation of 7.31 years.

Heredo-collateral history

Of the 316 patients with hypertension, about one third had no heredo-collateral history (32.28%). Only 108 maternal-line heredo-collaterals were identified in 108 patients (31.18%), while only paternal-like history was identified in 77 patients (24.37%). In 29 of the patients (9.18%), the heredo-collateral history was identified in both parents. For patients who had at least one affected parent, about 35% identified and at least one affected brother.

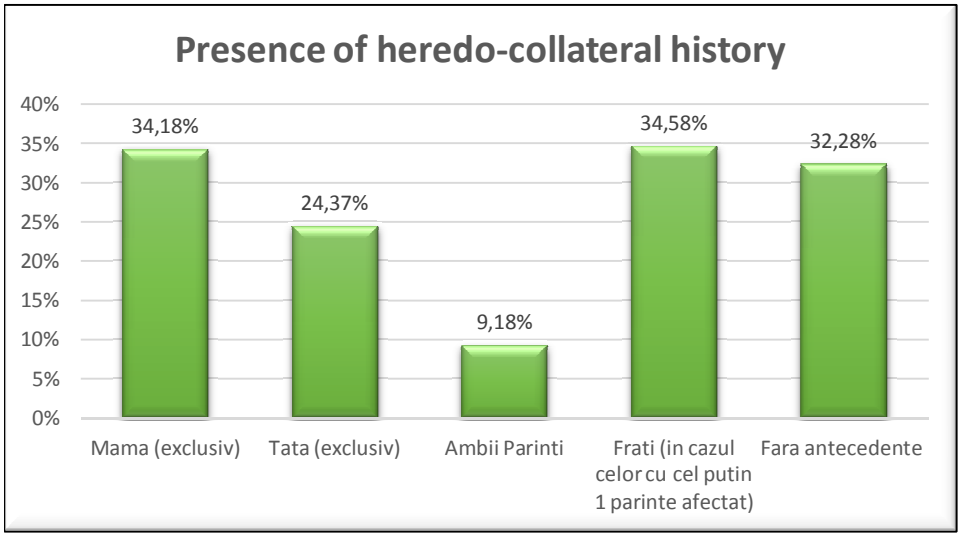

Figure 14 Presence of heredo-collateral history

Modifiable risk factors

Smoking

From the point of view of smoking, more than half of the patients with hypertension are smokers (52%). The remaining 48% of patients are either former smokers (34%) or non-smokers (14%) (Figure 25).

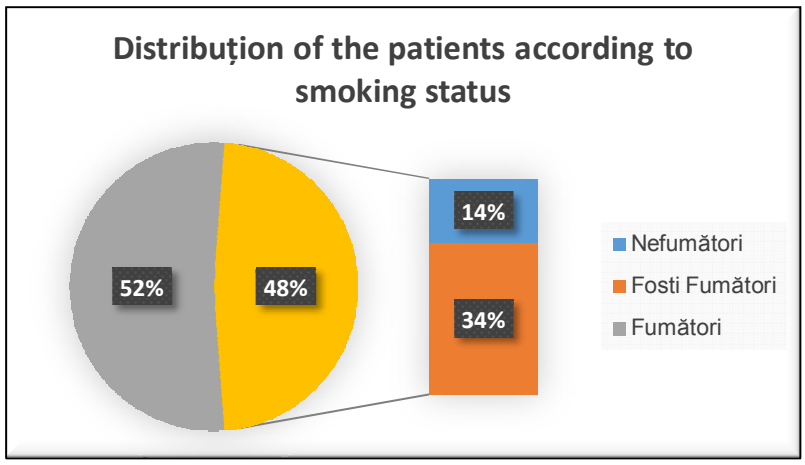

Figure 25 Distribution of the patients according to smoking status

Estimation of the cardiovascular risk: SCORE chart

Estimating the cardiovascular risk achieved using the SCORE chart was performed for all patients over the age of 40 years. It was also not calculated, according to the ESC criteria, for patients with high cardiovascular risk. These accounted for 43% of patients aged at least 40 years. In terms of risk-based distribution based on the SCORE chart, most patients, respectively 34.8%, present a risk of 0-5%, followed by those with a risk of between 5 and 10% with a percentage 26.14% (Figure 33).

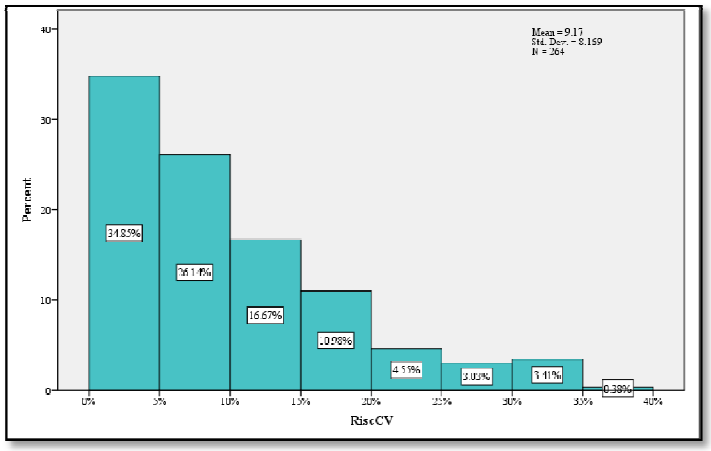

Figure 33 Distribution of the patients according to outcome obtained from cardiovascular risk assessment through SCORE chart

Cardiovascular risk estimation: Reynolds score

The mean value of cardiovascular risk estimated by Reynolds score is 11.04, with a standard deviation of 7.93. In terms of distribution, the majority of patients have a risk of between 5 and 10% (29.96%), followed by patients with a risk of less than 5% (21.94%) and those at risk of 10 and 15% (Figure 34).

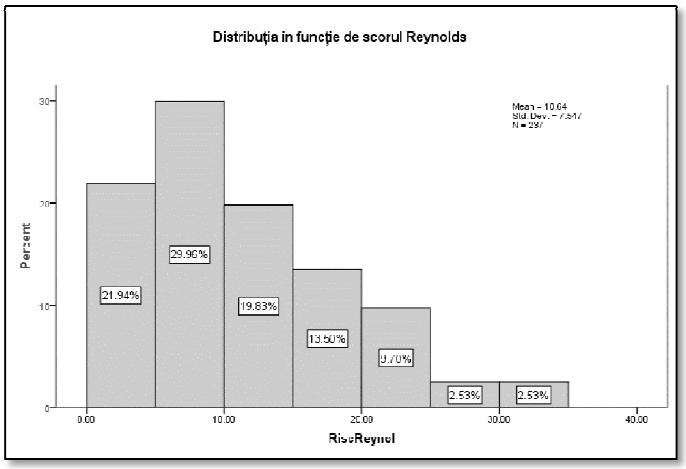

Figure 34 Distribution of the patients according to Reynolds score

Chapter VIII – Studies of new cardiovascular risk factors

Study 1: Stress and cardiovascular risk

We evaluated the stress by applying a specialized questionnaire to estimate the stress level (Appendix 3 Stress Questionnaire). The result indicates that more than half of the patients have a high level of stress (51%), followed by one-third of the average stressed (33%) and those with an exaggerated stress (16%) (Figure 35)

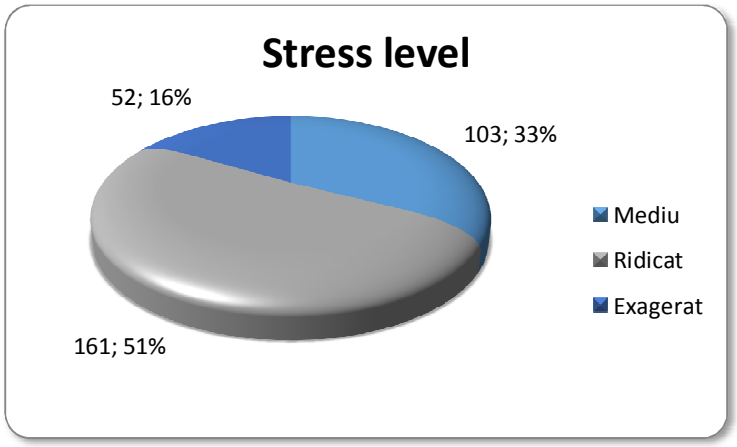

Figure 35 Distribution according to the stress level

Study 2: Non-HDL-cholesterol and cardiovascular risk

Non-HDL-Cholesterol

The mean non-HDL-cholesterol was 187.87 mg / dL, with the standard deviation of 44.49 mg / dL. Thus, there is an important variability of the measured values of non-HDL cholesterol. Graphically, most patients in this study showed non-HDL-cholesterol values between 180-200 (22.47%) and 200-220 (21.2%) respectively. (Figure 49). These values are elevated values, which induce an increased cardiovascular risk, even if triglycerides have values less than 200mg / dl.

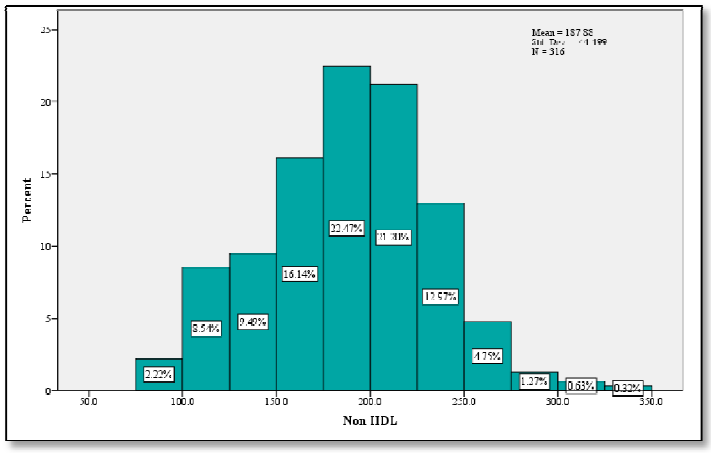

Figure 49 Distribution according to Non-HDL-Cholesterol level

Non-HDL-Cholesterol and age

We further evaluated the influence of age on non-HDL cholesterol values. The first step is to create a dot cloud chart (Figure 51). It can be noticed that there is no distinction between a certain way of distributing non-HDL cholesterol values by age.

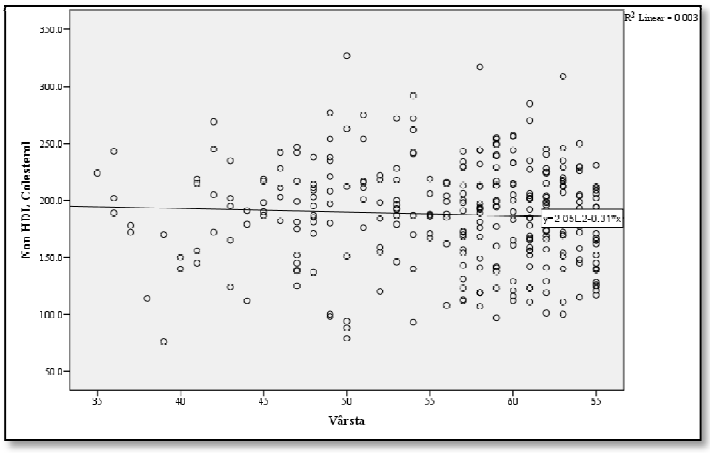

Figure 51 Scatter plot of Non-HDL-Cholesterol and age

Confirmation of the above conclusions is also achieved through the Pearson correlation test. It indicates the existence of a very weak, negative correlation (-0,051), the test is considered statistically insignificant (p = 0,370).

Study 3: Inflammation and cardiovascular risk

In this part of the thesis, we analyzed how inflammation tests are modified in patients with hypertension.

High sensitivity C-reactive protein – hs-PCR

It is also an acute phase reactant. However, it appears that high sensitivity C reactive protein is a good indicator used in cardiovascular risk assessment, being an indirect risk factor. The mean value for patients with hypertension is 0.226 mg / L, with a standard deviation of 0.2 mg / dL.

From the point of view of the distribution of the patients, we observed that, in the case of the studied group of patients, 28.5% have values corresponding to a low cardiovascular risk (Figure 57).

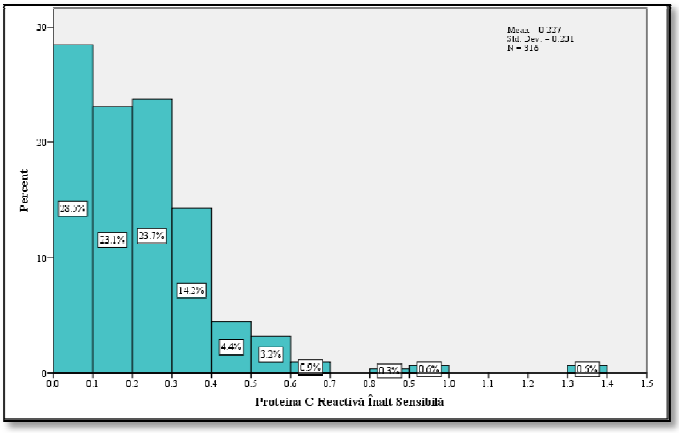

Figure 57 Distribution according to hs-CRP values

We found that in the study group, almost half of patients show moderate cardiovascular risk based on hs-PRC values (Figure 58).

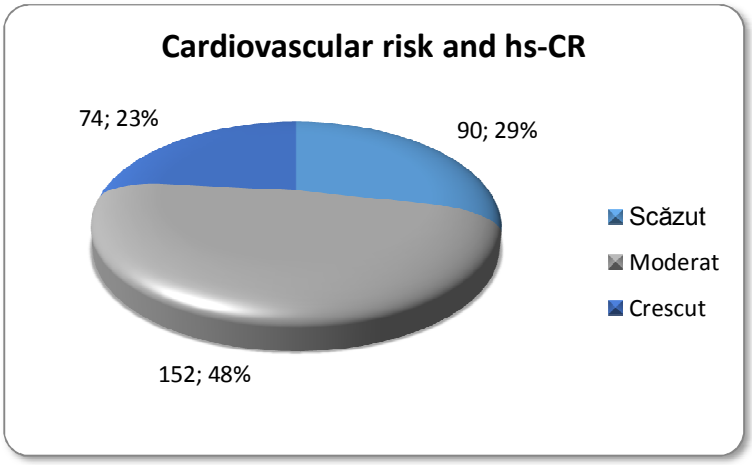

Figure 58 Cardiovascular risk and hs-CRP

Study 4: Blood pressure variability and cardiovascular risk

Blood pressure variability

To determine the variability of blood pressure, we used daily measurements at home. Thus, we considered variations between 20 - 45 mmHg as significant variations, the small variation being considered when the differences are less than 20 mmHg.

In terms of blood pressure variability, 45% of patients experienced significant blood pressure variations. (Figure 71)

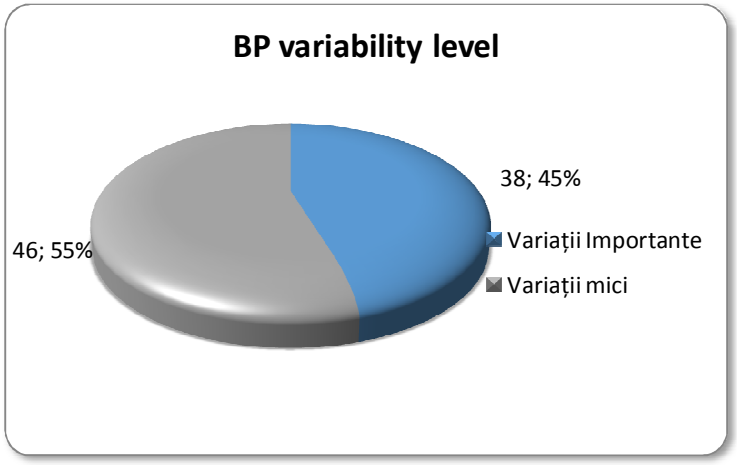

Figure 71 Distribuțion according to blood pressure variability level

BP variability in patients with cardiovascular events

For patients with a history of cardiovascular events, the percentage of those with high blood pressure variability is 77% (Figure 72).

It can be noticed that in patients with a significantly higher cardiovascular risk, manifested by cardiovascular events, significant blood pressure variations are present in a

significantly higher percentage compared to that observed in the whole group of patients in this study.

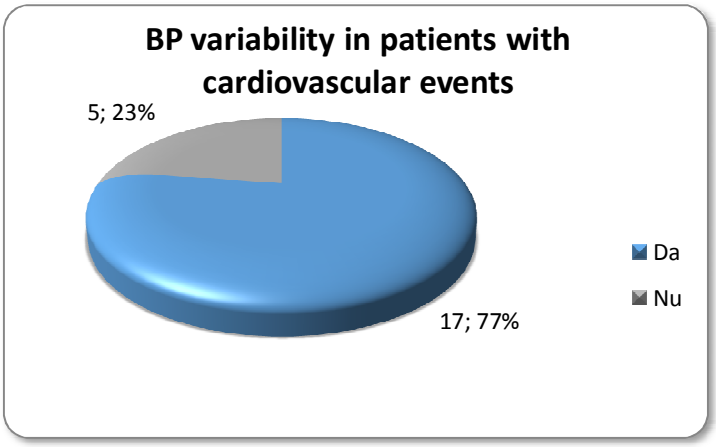

Figure 72 Distribution of the patients with cardiovascular events according to the presence of blood pressure variability

Study 5: Vitamin D and cardiovascular risk

Vitamin D

The mean vitamin D value was 23.27 ng/ml, with the standard deviation of 9.6 ng/ml. It can be noticed that most people have insufficient vitamin D levels

Analyzing the distribution of the values (Figure 73), it is noticed that the majority (78.08%) of the migrants present values within their range of values corresponding to the "insufficient level" category. Only 18.5% of patients have an optimal level of vitamin D, and about 3.5% have severe vitamin D deficiency.

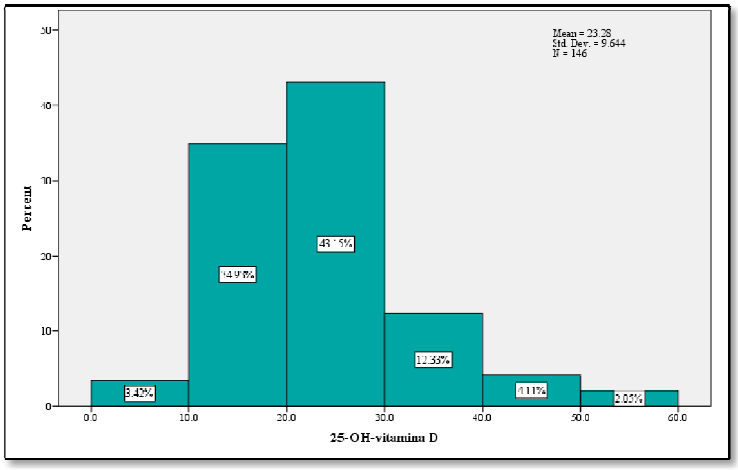

Figure 73 Distribution according to vitamin D values

Vitamin D and body mass index

Depending on the category of patients, defined according to body mass index values, it is noted that the highest mean vitamin D values are recorded in patients with a BMI falling within the "Normal" category, the concentration decreasing inversely proportional to the increase in

BMI. A significant decrease, with mean values below 20 ng/ml (moderate deficit), is seen in patients classified as Grade 2 and Grade 3 Obesity.

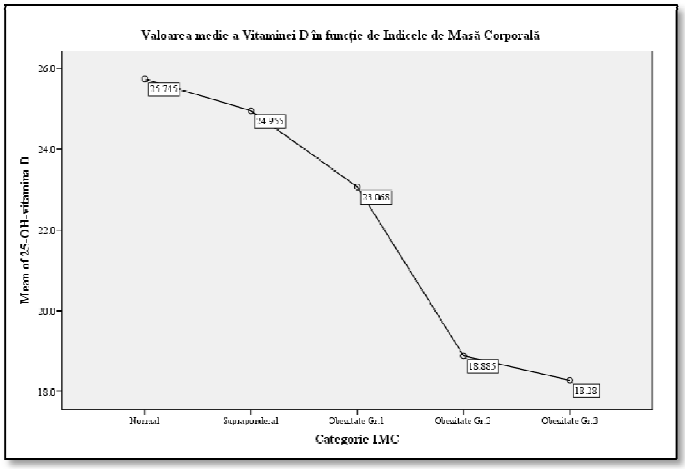

Figure 75 Average values of vitamin D by body mass index

The observed differences are statistically significant, the result of the ANOVA test were statistically significant, with p = 0.041)

The presence of myalgia and the relationship with Vitamin D level

Of the total patients who participated in the study, 198 received long-term statin therapy; of these, 9% had myalgia (Figure 78).

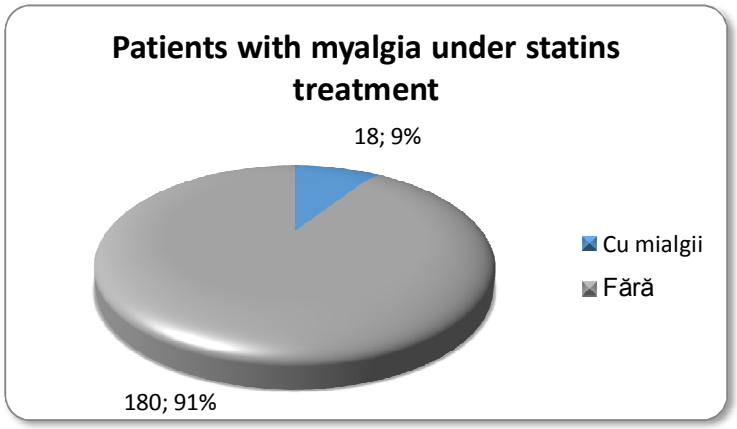

Figure 78 Percentage of patients with myalgia in patients with long-term treatment with statins

For these patients, we dose 25 (OH) Vitamin D. Two-thirds (Figure 79) of these patients showed 25 (OH) Vitamin D values lower than 15 ng/ml.

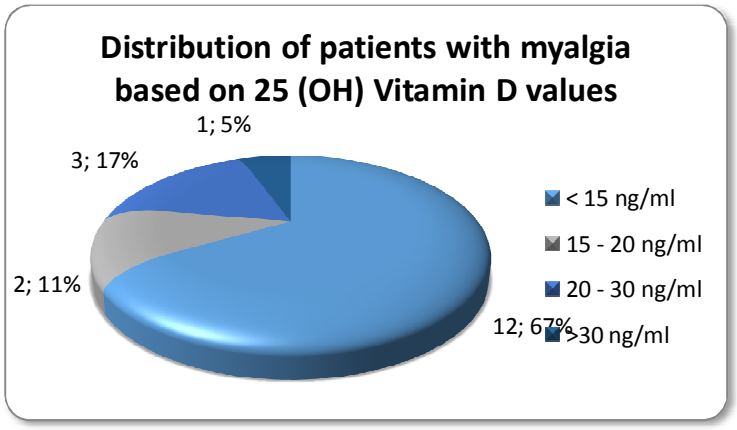

Figure 79 Distribution of patients with myalgia based on 25 (OH) Vitamin D values

The proposed intervention in patients with severe and moderate vitamin D deficiency was the correction of Vitamin D by treatment with 7000 IU / day of Vitamin D for 8 weeks according to the Prevention and Treatment Guidelines of osteoporosis [259]. At the end of this period, 25 (OH) Vitamin D was dosed again, with all those involved being normalized. Thereafter, the maintenance dose was 2000 IU / day, with the concomitant resumption of statin therapy.

These patients were further monitored in terms of how they tolerated statin therapy following the correction of Vitamin D deficiency. During the study, most of them tolerated well, out of a total of 11 patients who completed the study (3 refused, 1 abandoned the study), 9 tolerated well and 2 did not tolerate it (Figure 80).

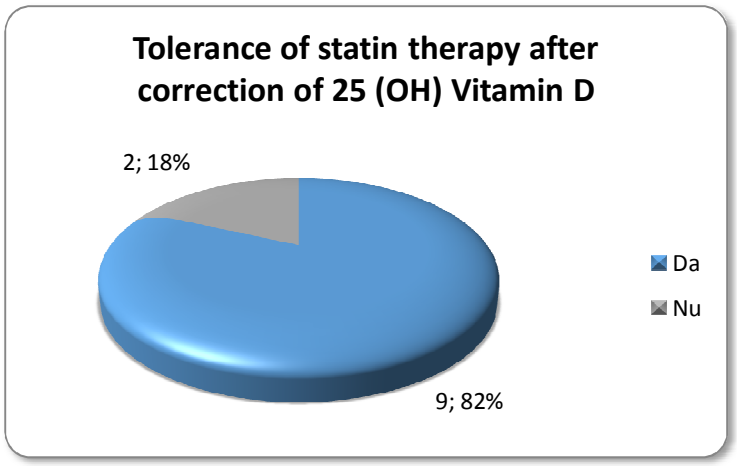

Figure 80 Tolerance of statin therapy after correction of 25 (OH) Vitamin D

The Influence of Vitamin D Treatment on Blood Pressure

To determine the role that vitamin D supplementation has on blood pressure, we have monitored how changes in blood pressure, osteoarticular pain, myalgias, and subjective symptoms have occurred following the correction of vitamin D deficiency.

Thus, patients with vitamin D deficiency were treated according to the following scheme:

- 8 weeks 7000 IU / day; continued maintenance dose 2000 IU / day for 4 months

The patients evaluation was performed at the start of the study through a complete clinical examination and the application of visual analog pain scale to assess osteoarticular pain. Patient monitoring and evaluation were performed weekly for the evaluation of blood pressure. At the end of the study period, TA was measured, the values obtained were compared with the initial values.

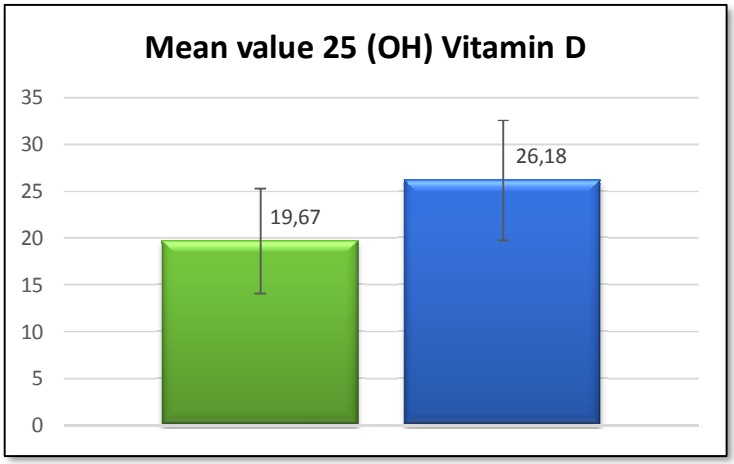

Figure 82 Mean value 25 (OH) Vitamin D

The initial mean value of 25 (OH) Vitamin D was 19.67ng / ml (± 5.6 ng / ml). In the final evaluation, the mean 25 (OG) Vitamin D was 26.18 ng / ml (± 6.4 ng / ml). The mean difference of 6.51 ng / ml is statistically significant (p <0.001), with IC95% 4.97-8.05 ng / ml (Figure 82).

Effects on blood pressure

Following vitamin D supplementation in the case of deficient patients, a significant decrease in blood pressure was observed with 10-15 mmHg in the majority of patients. The mean reduction in blood pressure in patients with vitamin D deficiency was 11.4 mmHg (IC 95% 6.23 - 16.57, p <0.001) (Figure 83).

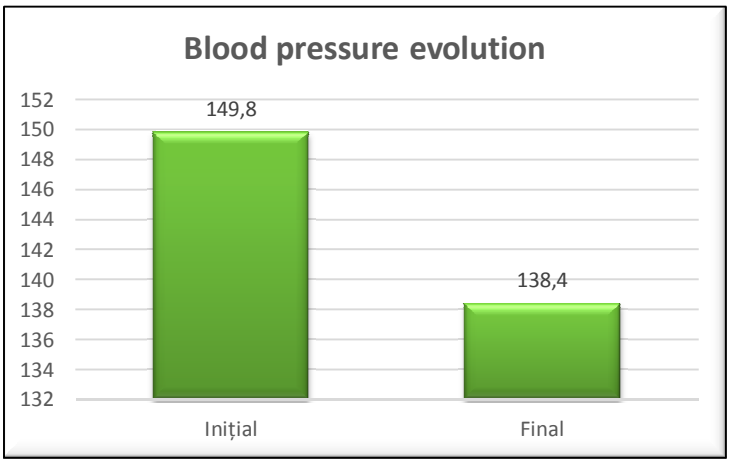

Figure 83 Blood pressure evolution

Another observation was related to the fact that the variability in blood pressure decreased, with a higher constancy of these values.

Chapter IX - Conclusions

By synthesizing all of the studies above and presented above, I could highlight several aspects and conclusions.

High blood pressure prevalence

1. AGE: HTA has a growing prevalence, and occurs at an ever-increasing age.

HTA and cardiovascular risk are present at a younger age, which is an alarm signal. (61.01% HTA share in the age group 41-60 years).

2. GENDER: Prevalence is higher in the female sex, relative to the entire batch, and by age groups, we have noticed that HTA prevalence is higher for male gender in the 35-40 and 41-50 age groups; and female sex for the 50-60 age group and 61-65 years old. The findings of the research come close to the data from the specialized literature except for the 50-60 age group; in literature, studies show gender equality; in their own research, the female / male ratio is in favor of female gender in this age group.

3. Environment: shows a higher prevalence in the urban environment than in rural areas, but this conclusion can also be influenced by the structure of the patient group, is the list of their own capita.

4. Occupation: There was a higher prevalence over the average for the employed and the retired, while the under-prevalence was observed in the case of unemployed or without occupation.

5. Educational level - people with higher education have a higher prevalence of HTA.

Cardiovascular risk in the studied group

1. AGE - Cardiovascular risk increases with age, indicating that there may be an increased risk in the 40-50 age group (18.99%) versus 12.97% in the 51-55 age group.

2. SEX - women have a higher risk.

3. CARDIOVASCULAR SEX-RISK

Although distribution by age and sex is somewhat similar, we noted a difference from the existing studies, a notable difference in the 55-59 age group (F-27,22%, B-21,09%); the literature presents equality.

MONITORED PARAMETERS

HEREDO-COLATERAL ANTECEDENTS

HTA is present in a family history (relatives of grade I) in 67.72% and absent in 32.28% of cases.

Analyzing the data from the study group we could conclude on several aspects:

· The genetic factor should be considered as a risk factor to be taken into account in the cardiovascular risk assessment

· The maternal lineage is more responsible for the occurrence of HTA in children (future adults)

· Not all children in a family with one of the parents with HTA develop throughout HTA.

The explanation in these situations can be given by EPIGENETICS, which attempts to demonstrate the role of "environmental factors on the genome, genetic DNA".

EPIGENETICS is the "interface between the environment and the genome", which regulates the genome and adapts it to the environment. This is a relatively new approach to medicine in recent years, a concept that could explain why two people who have the same genetic (family) predisposition, one makes the disease (HTA), another does not, depending on the genetic factors.

This emphasizes the importance of early identification of altered cardiovascular risk factors and, last but not least, of "new" factors that could play an important role in the development of cardiovascular risk.

MODIFIABLE RISK FACTORS

- PREMATURE MENOPAUSE
- CONSUMPTION OF ANTICONCEPTION,

These are risk factors that need to be evaluated in women with HTA in the 35-45 age group.

- ALCOHOL CONSUMPTION, EXCESS SALT
- SMOKING
- MOVEMENT LIP (SEDENTARISM),

It influences cardiovascular risk in the patients in the studied group.

- dyslipidemia
- METABOLIC SYNDROME
- OBESITY (BMI, CA)
- hyperuricemia

They are present in the patient's HTA profile and cardiovascular risk in the examined group and should be evaluated constantly.

- Concerning cardiovascular risk according to abdominal circumference, the study showed a significant association between female sex and increased cardiovascular risk.

- BMI is also an important element, most patients being overweight (37%), obesity of varying degrees (50%) and only 13% of normal weight. These results are an alarming situation that could, however, be prevented and treated.

- Metabolic syndrome has an important presence in the studied group, which strengthens existing studies that show that metabolic syndrome is a cardiovascular risk factor that a family physician should consider in addressing patients.

- Assessment of target organs obliges the family doctor to recommend renal function assessment (urea, creatinine, uric acid, GFR).

In the case of the studied group, we found that RFG is a much more accurate diagnostic element for the evaluation of renal function.

According to KDIGO Guides 2012, RFG with a value between 60-89 ml/min shows a slight decrease and constitutes an ALARM SIGNAL.

CARDIOVASCULAR RISK FACTORS

Concluding the personal studies presented in the thesis, which aimed to identify "new" cardiovascular risk factors in the studied group, we found the following**:**

1. PSYCHOLOGICAL FACTORS, especially STRESS, are a very important contributing factor, more and more present in the lives of our patients.

According to the study results:

· Most patients have a high-stress level (51%);

· Although there is no significant difference in sex, we found that the proportion of women with an exaggerated stress level is 2 times higher than that of men (20.1% versus 12.2%);

· The environment of origin is very important for the level of stress (rural environment - medium stress, over high and excessive stress that prevails in the urban environment).

So we can talk about an important association between the environment of origin -study- stress levels of patients with cardiovascular risk.

In STUDY LOT, we found the following:

· Active age (40-50 years and 51-60 years) have a high-risk level compared to other age groups;

· The level of training is directly proportional to the level of stress (people with higher education have a high level of stress (57%) than those with secondary education (44.4%) and 31.3% in those with gymnasium studies).

Therefore, we could say that a 40- to 60-year-old urban person with a high level of professional, high-level workout and high-stress level could achieve the profile of a high-risk cardiovascular patient who will be evaluated correctly, as early as possible and periodically**.**

2. NON-HDL-CHOLESTEROL-CARDIOVASCULAR HAZARD

In the studied group I presented:

· Total cholesterol ranged between 240-260 mg/dl (1/5 of the total patients), with an average of 238.2 mg/dl not related to gender and/or age;

· LDL-cholesterol with an average of 152.66mg / dl, gender showing a difference, with higher values in women; evolution of values is independent of age;

· HDL-cholesterol with an average of 40-45 mg/dl, significantly lower in male; age does not influence HDL cholesterol;

· Non-HDL-cholesterol, a new marker with mean values of 187.87 mg/dl (increased), with small differences between genders (women show higher values, however, 200-220mg / dl, compared to 180 -200 mg/dl in men); age does not influence the values, but its presence with high values shows a high cardiovascular risk.

· Triglycerides with an average of 157.55 mg/dl (52.85%), slightly above the limit, with an F> B ratio, with no differences in age.

The conclusion we note is that non-HDL-cholesterol is important to consider in all patients, not only those with triglycerides> 400 mg/dl but also those with triglycerides <200 mg/dl.

Non-HDL-cholesterol may be a risk factor along with LDL-cholesterol in assessing cardiovascular risk and the 2nd target of treatment according to Guides.

3. CRONIC INFLAMMATION (hs-CRP) and CARDIOVASCULAR RISK

Chronic inflammation, quantified in the studied group by hs-CRP determination, showed an average of 0.226 mg/dl, which according to the laboratory reference values indicates moderate cardiovascular risk. This finding suggests that hs-CRP could be a risk factor to be taken into account in the evaluation of hypertensive patients and cardiovascular risk. (as is the case with the Reynolds score)**.**

4. ESTIMATION OF CARDIOVASCULAR RISK

We ranked different risk grids of the patients in the study group, taking into account the risk factors we monitored. Thus, in the SCORE chart, we evaluated age, sex, smoker status or not, total cholesterol, TAS, and HDL-cholesterol and we obtained a 5% risk score of 34.8%, 5-10% in 26.14% and 10-15% 16.62%. (ie more than 1/3 of patients have a low cardiovascular risk). Applying the REYNOLDS grid to monitor age, sex, smoker or non-smoker status, TAS, total cholesterol, HDL-cholesterol and hs-CRP, we achieved a <5% risk score of 21.94% 10% of 29.94% and 10-15% of 19.83% (higher risk for 5-10%, so a moderate cardiovascular risk), suggesting that the Reynolds grid is more specific and should be taken into account in the cardiovascular risk assessment of patients, at the same time of course with SCORE grid**.**

5. VARIABILITY AND CARDIOVASCULAR RISK.

· There is a clear correlation between blood pressure variability and cardiovascular risk, especially in patients aged 41-60 years.

· There is a relationship between TA variability and target organ damage.

· Patients with increased variability of TA values more frequently exhibited associated cardiovascular risk factors and target organ damage than those who did not show any variation.

· There is a definite relationship between TA variability and ATS, on the one hand, and increased arterial stiffness, on the other hand (assessed by IGB).

· Variability of TA may influence the prognosis of HTA evolution, but may be due to both patient compliance, but also, in some cases, limits to existing therapeutic solutions.

· Significant variations in TA are associated with a significantly increased cardiovascular risk.

6. Helicobacter pylori infection and cardiovascular risk.

The increased presence of Helicobacter pylori infection is evident in the studied group of patients. Although I have not been able to establish a clear relationship between this infection and cardiovascular risk, I believe it is important to investigate the presence of this bacterium in HTA patients and cardiovascular risk and to treat it where it exists to prevent the risk of gastric bleeding when treated with Aspirin administered according to these patients' guidelines for the primary and secondary prevention of cardiovascular accidents.

7. VITAMIN D AND CARDIOVASCULAR RISK

Research in the personal study has shown several aspects:

Low values (<10 and 10-20 ng/ml), respectively severe and moderate vitamin D deficiency are more common in women than in men

· The age group 41-50 years and 51-60 years old are the most exposed, especially in women

• Obesity (assessed by BMI, abdominal circumference) in relation to vitamin D - there is an inverse relationship (BMI and CA increased - low vitamin D), BMI is higher in women than in men, age groups 41-50 and 51-60 years old being more exposed.

· The relationship between hs-CRP and vitamin D: Moderate and increased cardiovascular risk (according to data and laboratory values) is present in more than 50% of the patients in the study group. An inversely proportional relationship between the vitamin D value and the value of hs-CRP (vitamin D decreases, cardiovascular risk increases).

· Correction of vitamin D deficiency by vitamin D administration according to the guidelines of the European Endocrinology Society revealed the normalization of 25 (OH)

vitamin D values after 8 weeks of treatment in most treated patients, followed by maintenance doses for another 4 months.

· Patients with TAB variability found a stabilization of values, a decrease in systolic TA with 10-15 mm Hg in 82% of study patients and diastolic TA by 5-10 mmHg to 35%

· Osteo-articular pains decreased by 40-100% (assessed using the analog pain scale).

· Asthenia, chronic fatigue, memory impairment have been greatly reduced.

· We also found a possible association between moderate and severe vitamin D deficiency and the occurrence of menses in statin treatment.

Therefore, I would conclude on several dates:

· Vitamin D has an important role in the body, vitamin D deficiency is very common in the population and can be considered a "new" cardiovascular risk factor

· The 40-50 age group is the most exposed and has the lowest vitamin D values

· Deficiency of vitamin D may be associated with:

- increased abdominal circumference,
- increased body mass index,
- abdominal obesity,
- dyslipidemia,
- hypertension,
- metabolic syndrome,
- Chronic inflammation, etc.

Representing basically a CARDIOVASCULAR RISK RISK.

· The 40-50 age group has the most variables and is the one that can best be addressed for PREVENTION

· Vitamin D treatment in people with vitamin D and HTA deficiency has shown that, at the same time, it can evolve with normalization of vitamin D values and a slight decrease in TA, respectively, the reduction of TA variability, which would improve cardiovascular prognosis.

Vitamin D deficiency could explain the appearance of menses in statin treatment (as a secondary reaction), correcting vitamin D deficiency as a possible solution in this case.

• There are also a number of limits that future studies should overcome (evidence is still needed to explain the relationship between vitamin D deficiency and cardiovascular disease, the role of vitamin D supplements in cardiovascular protection, etc.)

The age of HTA is decreasing, which is an alarm signal, and prevention is required to be done as early as possible. The 50-60 year age group is the most exposed and presents the most risk factors. Treating them on time could reduce the risk of cardiovascular disease and the incidence of cardiovascular disease.

In conclusion, we can assert with certainty that there are "new" cardiovascular risk factors to be considered in cardiovascular risk assessment in a patient with or without HTA. The family doctor will also consider these factors in assessing his patients to achieve effective prevention, proper cardiovascular risk management, appropriate treatment and, last but not least, active monitoring.

Selective References

Andone, G.O. & Avram, R. (2013). Ankle brachial index as vascular risk factor. *Journal of experimental medical & surgical research*. *XX*(2).

Apetrei, E. (2015). *Cardiologie Clinică*. Bucureşti: Ed. Medicala Callisto.

Apetrei, E., Kulcsar, I., Cioranu, R.S., Matei, C., Cochino, E. & Ginghină, C. (2008). Studiul Urziceni-Studiu populaţional prospectiv de depistare a factorilor de risc pentru bolile cardiovasculare şi intervenţie în populaţie, depistarea precoce a bolilor cardiovasculare. Partea I. *Revista Romana de Cardiologie*. *23*(2), 136-145.

Apetrei, E., Kulcsar, I., Matei, C., Rugină, M. & Cochino, C. (2008). „Urziceni "–Studiu populaţional prospectiv de depistare a factorilor de risc pentru bolile cardiovasculare. Partea a II-a.

Arora, P., Song, Y., Dusek, J., Plotnikoff, G., Sabatine, M.S., Cheng, S., Valcour, A., Swales, H., Taylor, B., Carney, E., Guanaga, D., Young, J.R., Karol, C., Torre, M., Azzahir, A., Strachan, S.M., O'Neill, D.C., Wolf, M., Harrell, F., Newton-Cheh, C. & Wang, T.J. (2015). Vitamin D therapy in individuals with prehypertension or hypertension: the DAYLIGHT trial. *Circulation*. *131*(3), 254-262. doi: 10.1161/CIRCULATIONAHA.114.011732

Bejan, G.C., Ghilencea, L.N., Iancu, M.A., Baltă, M.D. & Matei, D. (2015). Impactul factorilor de risc cardiovascular moderni asociaţi sindromului metabolic asupra prognosticului pe termen lung. *Practica Medicală*. *10*(4).

Benjamin, E.J., Blaha, M.J., Chiuve, S.E., Cushman, M., Das, S.R., Deo, R., de Ferranti, S.D., Floyd, J., Fornage, M., Gillespie, C., Isasi, C.R., Jimenez, M.C., Jordan, L.C., Judd, S.E., Lackland, D., Lichtman, J.H., Lisabeth, L., Liu, S., Longenecker, C.T., Mackey, R.H., Matsushita, K., Mozaffarian, D., Mussolino, M.E., Nasir, K., Neumar, R.W., Palaniappan, L., Pandey, D.K., Thiagarajan, R.R., Reeves, M.J., Ritchey, M., Rodriguez, C.J., Roth, G.A., Rosamond, W.D., Sasson, C., Towfighi, A., Tsao, C.W., Turner, M.B., Virani, S.S., Voeks, J.H., Willey, J.Z., Wilkins, J.T., Wu, J.H., Alger, H.M., Wong, S.S., Muntner, P., American Heart Association Statistics, C. & Stroke Statistics, S. (2017). Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation*. *135*(10), e146-e603. doi: 10.1161/CIR.0000000000000485

Bikle, D.D. (2014). Vitamin D metabolism, mechanism of action, and clinical applications. *Chem Biol*. *21*(3), 319-329. doi: 10.1016/j.chembiol.2013.12.016

Bischoff-Ferrari, K. *DO-HEALTH / Vitamin D3 - Omega3 - Home Exercise - Healthy Ageing and Longevity Trial (DO-HEALTH)*. from https://clinicaltrials.gov/ct2/show/NCT01745263

Boekholdt, S.M., Hovingh, G.K., Mora, S., Arsenault, B.J., Amarenco, P., Pedersen, T.R., LaRosa, J.C., Waters, D.D., DeMicco, D.A., Simes, R.J., Keech, A.C., Colquhoun, D., Hitman, G.A., Betteridge, D.J., Clearfield, M.B., Downs, J.R., Colhoun, H.M., Gotto, A.M., Jr., Ridker, P.M., Grundy, S.M. & Kastelein, J.J. (2014). Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. *J Am Coll Cardiol*. *64*(5), 485-494. doi: 10.1016/j.jacc.2014.02.615

Bombelli, M., Toso, E., Peronio, M., Fodri, D., Volpe, M., Brambilla, G., Facchetti, R., Sega, R., Grassi, G. & Mancia, G. (2013). The Pamela study: main findings and perspectives. *Curr Hypertens Rep*. *15*(3), 238-243. doi: 10.1007/s11906-013-0348-1

Brînza, I. & Chiţanu, L. (2016). *Cartea Noastră de Ghiduri Comentate*: Editura Media Med Publicis.

Buzinschi, S. (2017). *Epigenetica în practica medicală. Ghid pentru clinician*: Amaltea.

Carrara, D., Bernini, M., Bacca, A., Rugani, I., Duranti, E., Virdis, A., Ghiadoni, L., Taddei, S. & Bernini, G. (2014). Cholecalciferol administration blunts the systemic renin-angiotensin system in essential hypertensives with hypovitaminosis D. *J Renin Angiotensin Aldosterone Syst*. *15*(1), 82-87. doi: 10.1177/1470320312471149

Catapano, A.L., Graham, I., De Backer, G., Wiklund, O., Chapman, M.J., Drexel, H., Hoes, A.W., Jennings, C.S., Landmesser, U., Pedersen, T.R., Reiner, Ž., Riccardi, G., Taskinen, M.-R., Tokgozoglu, L., Verschuren, W.M.M., Vlachopoulos, C., Wood, D.A. & Zamorano, J.L. (2016). 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *European heart journal*. *37*(39), 2999-3058. doi: 10.1093/eurheartj/ehw272

Chen, S., Sun, Y. & Agrawal, D.K. (2015). Vitamin D deficiency and essential hypertension. *J Am Soc Hypertens*. *9*(11), 885-901. doi: 10.1016/j.jash.2015.08.009

Chen, W.R., Liu, Z.Y., Shi, Y., Yin, D.W., Wang, H., Sha, Y. & Chen, Y.D. (2014). Vitamin D and nifedipine in the treatment of Chinese patients with grades I-II essential hypertension: a randomized placebo-controlled trial. *Atherosclerosis*. *235*(1), 102-109. doi: 10.1016/j.atherosclerosis.2014.04.011

Cheung, A. (july 2013). *the MIRACL trial: atorvastatin reduces recurrent ischemia post-ACS [classics series]. 2 minute medicine - concise curated evidence.* Retrieved 2017, from https://www.2minutemedicine.com/the-miracl-trial-atorvastatin-reduces-recurrent-ischemia-post-acs-classics-series/

Cinteza, M. & Vinereanu, D. (2003). Tratamentul hipertensiunii arteriale in sindromul metabolic. *BMJ*(5).

Cinteza, M., Pana, B., Cochino, E., Florescu, M., Margulescu, A., Florian, A. & Vinereanu, D. (2007). Prevalence and control of cardiovascular factors in Romania cardio-zone national study. *Medica - a journal for Clinical Medicine*. *2*(4), 277-288.

Colectiv CNSMF, Colectiv INSP & Colectiv ALIAT. (2016). *Ghid de Prevenție. Stilul de viață sănătos și alte intervenții preventive prioritare pentru boli netransmisibile, în asistența medicală primară. Abordare integrată a riscului pentru bolile netransmisibile asociate stilului de viață. Riscul cardiometabolic. Cancerul* (Vol. 5). Bucuresti.

Cosman, F., de Beur, S.J., LeBoff, M.S., Lewiecki, E.M., Tanner, B., Randall, S. & Lindsay, R. (2014). Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporosis International*. *25*(10), 2359-2381. doi: 10.1007/s00198-014-2794-2

Danik, J.S. & Manson, J.E. (2012). Vitamin D and Cardiovascular Disease. *Current treatment options in cardiovascular medicine*. *14*(4), 414-424. doi: 10.1007/s11936-012-0183-8

Daraba, R. (2009). Evaluarea riscului cardiovascular in cazul persoanelor asimptomatice. *The Britisjh Medical Journal Editia in Limba Romana*. *Aprilie*(3).

Darabont, R., Tautu, O.F., Pop, D., Fruntelata, A., Deaconu, A., Onciul, S., Salaru, D., Micoara, A. & Dorobantu, M. (2015). Visit-to-Visit Blood Pressure Variability and Arterial Stiffness Independently Predict Cardiovascular Risk Category in a General Population: Results from the SEPHAR II Study. *Hellenic J Cardiol*. *56*(3), 208-216.

de Oliveira Alvim, R., Mourao, C.A., Magalhães, G.L., de Oliveira, C.M., Krieger, J.E., Mill, J.G. & Pereira, A.C. (2017). Non-HDL cholesterol is a good predictor of the risk of increased arterial stiffness in postmenopausal women in an urban Brazilian population. *Clinics*. *72*(2), 106-110. doi: 10.6061/clinics/2017(02)07

Dorjgochoo, T., Ou Shu, X., Xiang, Y.B., Yang, G., Cai, Q., Li, H., Ji, B.T., Cai, H., Gao, Y.T. & Zheng, W. (2012). Circulating 25-hydroxyvitamin D levels in relation to blood pressure parameters and hypertension in the Shanghai Women's and Men's Health Studies. *Br J Nutr*. *108*(3), 449-458. doi: 10.1017/s0007114511005745

Dorobantu, M. (2015). Why do we need a new national survey? SEPHAR III–The next step. *J Hypertens Res*. *1*, 9-15.

Dorobantu, M., Badila, E., Ghiorghe, S., Darabont, R.O., Olteanu, M. & Flondor, P. (2008). Total cardiovascular risk estimation in Romania. Data from the SEPHAR study. *Rom J Intern Med*. *46*(1), 29-37.

Dorobantu, M., Tautu, O. & Deaconu, A. (2013). *Resurse noi dintr-un concept vechi: variabilitatea pe termen lung a tensiunii arteriale. Factor de risc cardiovascular. Punct si contrapunct in hipertensiunea arteriala. Program educational a societatii romana de hipertensiune 2012-2013*.

Dorobanțu, M. & Tautu, O. (2015). Hipertensiunea arteriala esentiala. In E. Apetrei (Ed.), *Cardiologie Clinică* (pp. 627-628). Bucuresti: Ed. Medicala Callisto.

Dorobanțu, M. (2010). *Compendiu de boli cardiovasculare* (Vol. II). Bucuresti: Ed. Universitara "Carol Davila".

Dorobanțu, M., Badila, E. & Dorobont, R. (2006). Studiul SEPHAR –Studiu de Prevalenta a Hipertensiunii Arteriale si de evaluare a riscului cardio-vascular in Romania.Partea aIIa. Rezultate. *Revista Romana de Cardiologie*. *XXI*(3), 4-19.

Dorobanțu, M., Bartoş, D., Apetrei, E., Arsenescu-Georgescu, C., Pop, D., Ghiorghe, S., Tănăsescu, R., Craiu, E., Manițiu, I. & Tăutu, O. (2012). Hypertension in Romania: where are we and what can we do? Results from SEPHAR II study. *Romanian Journal of Cardiology| Vol*. *22*(4).

Fanari, Z., Hammami, S., Hammami, M.B., Hammami, S. & Abdellatif, A. (2015). Vitamin D deficiency plays an important role in cardiac disease and affects patient outcome: Still a myth or a fact that needs exploration? *Journal of the Saudi Heart Association*. *27*(4), 264-271. doi: 10.1016/j.jsha.2015.02.003

Forman, J.P., Scott, J.B., Ng, K., Drake, B.F., Suarez, E.G., Hayden, D.L., Bennett, G.G., Chandler, P.D., Hollis, B.W., Emmons, K.M., Giovannucci, E.L., Fuchs, C.S. & Chan, A.T. (2013). Effect of vitamin D supplementation on blood pressure in blacks. *Hypertension*. *61*(4), 779-785. doi: 10.1161/HYPERTENSIONAHA.111.00659

Franklin, S.S. & Wong, N.D. (2013). Hypertension and cardiovascular disease: contributions of the Framingham Heart Study. *Global heart*. *8*(1), 49-57. doi: doi.org/10.1016/j.gheart.2012.12.004

Gherasim, L. & Dorobanțu, M. (2004). *Tratamentul Hipertensiunii Arteriale. Principii și practică*. București: Ed. InfoMedica.

Gică, A. & Dumitrașcu, D.L. (2014). Tipul D de personalitate la pacienții cu boală coronariană. *Viața Medicală*. *44*(1294).

Ginghină, C. (2010). *Mic tratat de cardiologie* (2 ed. Vol. II). Bucuresti: Editura Academiei Române.

Glozier, N., Tofler, G.H., Colquhoun, D.M., Bunker, S.J., Clarke, D.M., Hare, D.L., Hickie, I.B., Tatoulis, J., Thompson, D.R., Wilson, A. & Branagan, M.G. (2013). Psychosocial risk factors for coronary heart disease. *Med J Aust*. *199*(3), 179-180.

Grupul de lucru de diabet, p.-d.s.b.c.a.S.E.d.C.E., în colaborare cu Asociația Europeană pentru Studiul Diabetului (EASD),. (2013). Ghidul ESC de Diabet, Pre-diabet și Boli cardiovasculare elaborat în colaborare cu EASD. *Romanian Journal of Cardiology*. *23*(Supplement D), 84.

Grupul de lucru pentru managementul dislipidemiilor al Societății Europene de Cardiologie (ESC) și Societății Europene de Ateroscleroză (EAS). (2017). Ghid de management al dislipidemiei 016 (elaborat de Societatea Europeană de Cardiologie și Societatea Europeană de Ateroscleroză). *Romanian Journal of Cardiology*. *27*(1), 51-132.

Grupul de lucru pentru managementul hipertensiunii arteriale al societatii europene de hipertensiune (ESH) si al societatii europene de cardiologie (ESC). (2013). Ghidul ESH/ESC Managementul hipertensiunii arteriale 2013. *Romanian Journal of Cardiology*. *23*(Supplement C), 91.

Guberna, S., Avram, N., Andrei, C.L. & Sinescu, C. (2016). Parametrii variabilitatii tensiunii arteriale si afectarea vasculara in hipertensiunea arteriala. *Revista Medicală Română*. *LXIII*(4), 325 - 330.

Hajar, R. (2016). Framingham Contribution to Cardiovascular Disease. *Heart Views : The Official Journal of the Gulf Heart Association*. *17*(2), 78-81. doi: 10.4103/1995-705X.185130

Halade, G.V., Jin, Y.-F. & Lindsey, M.L. (2013). Matrix metalloproteinase (MMP)-9: A proximal biomarker for cardiac remodeling and a distal biomarker for inflammation. *Pharmacology & Therapeutics*. *139*(1), 32-40. doi: https://doi.org/10.1016/j.pharmthera.2013.03.009

Hoțoleanu, C. & Dumitrașcu, D.L. (2016). ASPECTE PSIHOSOMATICE ÎN BOLILE CARDIOVASCULARE. *Internal Medicine/Medicina Interna*. *13*(1).

Huang, Y., Wang, S., Cai, X., Mai, W., Hu, Y., Tang, H. & Xu, D. (2013). Prehypertension and incidence of cardiovascular disease: a meta-analysis. *BMC Medicine*. *11*(1), 177. doi: 10.1186/1741-7015-11-177

Institutul National de Sănătate Publică. (2013). *Ghid de prevenție*.

Ke, L., Graubard, B.I., Albanes, D., Fraser, D.R., Weinstein, S.J., Virtamo, J. & Brock, K.E. (2013). Hypertension, pulse, and other cardiovascular risk factors and vitamin D status in Finnish men. *Am J Hypertens*. *26*(8), 951-956. doi: 10.1093/ajh/hpt051

Kivimaki, M. & Kawachi, I. (2015). Work Stress as a Risk Factor for Cardiovascular Disease. *Curr Cardiol Rep*. *17*(9), 630. doi: 10.1007/s11886-015-0630-8

Kotseva, K., Wood, D., De Bacquer, D., De Backer, G., Ryden, L., Jennings, C., Gyberg, V., Amouyel, P., Bruthans, J., Castro Conde, A., Cifkova, R., Deckers, J.W., De Sutter, J., Dilic, M., Dolzhenko, M., Erglis, A., Fras, Z., Gaita, D., Gotcheva, N., Goudevenos, J., Heuschmann, P., Laucevicius, A., Lehto, S., Lovic, D., Milicic, D., Moore, D., Nicolaides, E., Oganov, R., Pajak, A., Pogosova, N., Reiner, Z., Stagmo, M., Stork, S., Tokgozoglu, L., Vulic, D. & Investigators, E. (2016). EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *Eur J Prev Cardiol*. *23*(6), 636-648. doi: 10.1177/2047487315569401

Kunutsor, S.K., Apekey, T.A. & Steur, M. (2013). Vitamin D and risk of future hypertension: meta-analysis of 283,537 participants. *Eur J Epidemiol*. *28*(3), 205-221. doi: 10.1007/s10654-013-9790-2

Kunutsor, S.K., Burgess, S., Munroe, P.B. & Khan, H. (2014). Vitamin D and high blood pressure: causal association or epiphenomenon? *Eur J Epidemiol*. *29*(1), 1-14. doi: 10.1007/s10654-013-9874-z

Loscalzo, J. (2013). *Harrison-Medicină Cardiovasculară*: Editura All.

Mahmood, S.S., Levy, D., Vasan, R.S. & Wang, T.J. (2014). The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. *Lancet*. *383*(9921), 999-1008. doi: 10.1016/s0140-6736(13)61752-3

Margolis, K.L., Martin, L.W., Ray, R.M., Kerby, T.J., Allison, M.A., Curb, J.D., Kotchen, T.A., Liu, S., Wassertheil-Smoller, S., Manson, J.E. & Women's Health Initiative, I. (2012). A prospective study of serum 25-hydroxyvitamin D levels, blood pressure, and incident hypertension in postmenopausal women. *Am J Epidemiol*. *175*(1), 22-32. doi: 10.1093/aje/kwr274

Matei, C., Pop, I., Jurcut, R., Suceveanu, M., Predescu, D., Nechita, E., Ionescu, P., Ciovica, D. & Ginghina, C. (2008). Romanian multicentric study of the prevalence of metabolic syndrome-ROMES. *Hellenic J Cardiol*. *49*(5), 303-309.

May, R.W., Sanchez-Gonzalez, M.A., Brown, P.C., Koutnik, A.P. & Fincham, F.D. (2014). School burnout and cardiovascular functioning in young adult males: a hemodynamic perspective. *Stress*. *17*(1), 79-87. doi: 10.3109/10253890.2013.872618

Mehta, V. & Agarwal, S. (2017). Does Vitamin D Deficiency Lead to Hypertension? *Cureus*. *9*(2), e1038. doi: 10.7759/cureus.1038

Mergenhagen, K., Ott, M., Heckman, K., Rubin, L.M. & Kellick, K. (2014). Low vitamin D as a risk factor for the development of myalgia in patients taking high-dose simvastatin: a retrospective review. *Clin Ther*. *36*(5), 770-777. doi: 10.1016/j.clinthera.2014.02.023

Moriyama, K. & Takahashi, E. (2016). Non-HDL Cholesterol is a More Superior Predictor of Small-Dense LDL Cholesterol than LDL Cholesterol in Japanese Subjects with TG Levels 400 mg/dL. *J Atheroscler Thromb*. *23*(9), 1126-1137. doi: 10.5551/jat.33985

Mozaffari-Khosravi, H., Loloei, S., Mirjalili, M.R. & Barzegar, K. (2015). The effect of vitamin D supplementation on blood pressure in patients with elevated blood pressure and vitamin D deficiency: a randomized, double-blind, placebo-controlled trial. *Blood Press Monit*. *20*(2), 83-91. doi: 10.1097/MBP.0000000000000091

Mozos, I. & Marginean, O. (2015). Links between Vitamin D Deficiency and Cardiovascular Diseases. *Biomed Res Int*. *2015*, 109275. doi: 10.1155/2015/109275

Nichols, M., Townsend, N., Scarborough, P. & Rayner, M. (2013). Cardiovascular disease in Europe: epidemiological update. *European heart journal*. *34*(39), 3028-3034. doi: 10.1093/eurheartj/eht356

Noble, D. (2015). Conrad Waddington and the origin of epigenetics. *The Journal of Experimental Biology*. *218*(6), 816-818. doi: 10.1242/jeb.120071

Novartis Phase III CANTOS study demonstrates that targeting inflammation with ACZ885 reduces cardiovascular risk. (2017). [Press release]. Retrieved from https://novartis.gcs-web.com/novartis-cantos-study-demonstrates-ACZ885-reduces-cardiovascular-risk

Nyberg, S.T., Fransson, E.I., Heikkila, K., Alfredsson, L., Casini, A., Clays, E., De Bacquer, D., Dragano, N., Erbel, R., Ferrie, J.E., Hamer, M., Jockel, K.H., Kittel, F., Knutsson, A., Ladwig, K.H., Lunau, T., Marmot, M.G., Nordin, M., Rugulies, R., Siegrist, J., Steptoe, A., Westerholm, P.J., Westerlund, H., Theorell, T., Brunner, E.J., Singh-Manoux, A., Batty, G.D., Kivimaki, M. & Consortium, I.P.-W. (2013). Job strain and cardiovascular disease risk factors: meta-analysis of individual-participant data from 47,000 men and women. *PLoS One*. *8*(6), e67323. doi: 10.1371/journal.pone.0067323

Piepoli, M.F., Hoes, A.W., Agewall, S., Albus, C., Brotons, C., Catapano, A.L., Cooney, M.-T., Corrà, U., Cosyns, B. & Deaton, C. (2016). 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *European heart journal*. *37*(29), 2315-2381.

Pradhan, A.D. & Manson, J.E. (2016). Update on the Vitamin D and OmegA-3 trial (VITAL). *J Steroid Biochem Mol Biol*. *155*(Pt B), 252-256. doi: 10.1016/j.jsbmb.2015.04.006

Preda, M., Gheorghe, S.-A. & Popa, M.I. (2016). Infecțiile în hipertensiunea arterială: o posibilă contribuție etiologică. *Medic.ro*. *XIII*(2).

Rasheed, K., Sethi, P. & Bixby, E. (2013). Severe vitamin d deficiency induced myopathy associated with rhabydomyolysis. *N Am J Med Sci*. *5*(5), 334-336. doi: 10.4103/1947-2714.112491

Rendina, D., Ippolito, R., D'Elia, L., Giacchetti, G., Lonati, C., Gianfrancesco, F., Fallo, F., Rebellato, A., Ruggiero, C., Rubattu, S., Volpe, M., Gennari, L., Merlotti, D., Isaia, G.C., D'Amelio, P., Spertino, E., Fabris, B., Sechi, L.A., Catena, C., Maresca, A.M., Gessi, V., Dalbeni, A. & Strazzullo, P. (2015). Hypovitaminosis D and organ damage in patients with arterial hypertension: a multicenter double blind randomised controlled trial of cholecalciferol supplementation (HYPODD) : study design, clinical procedures and treatment protocol. *High Blood Press Cardiovasc Prev*. *22*(2), 135-142. doi: 10.1007/s40292-015-0080-9

Riche, K.D., Arnall, J., Rieser, K., East, H.E. & Riche, D.M. (2016). Impact of vitamin D status on statin-induced myopathy. *Journal of Clinical & Translational Endocrinology*. *6*, 56-59. doi: https://doi.org/10.1016/j.jcte.2016.11.002

Ridker, P.M. (2013). Closing the loop on inflammation and atherothrombosis: why perform the CIRT and CANTOS trials? *Trans Am Clin Climatol Assoc*. *124*, 174-190.

Ridker, P.M., Everett, B.M., Thuren, T., MacFadyen, J.G., Chang, W.H., Ballantyne, C., Fonseca, F., Nicolau, J., Koenig, W., Anker, S.D., Kastelein, J.J.P., Cornel, J.H., Pais, P., Pella, D., Genest, J., Cifkova, R., Lorenzatti, A., Forster, T., Kobalava, Z., Vida-Simiti, L., Flather, M., Shimokawa, H., Ogawa, H., Dellborg, M., Rossi, P.R.F., Troquay, R.P.T., Libby, P. & Glynn, R.J. (2017). Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *New England Journal of Medicine*. *377*(12), 1119-1131. doi: 10.1056/NEJMoa1707914

Sabanayagam, C., Shankar, A. & Somasundaram, S. (2012). Serum vitamin D level and prehypertension among subjects free of hypertension. *Kidney Blood Press Res*. *35*(2), 106-113. doi: 10.1159/000330716

Salazar, J., Martínez, M.S., Chávez, M., Toledo, A., Añez, R., Torres, Y., Apruzzese, V., Silva, C., Rojas, J. & Bermúdez, V. (2014). C-Reactive Protein: Clinical and Epidemiological Perspectives. *Cardiology Research and Practice*. *2014*, 605810. doi: 10.1155/2014/605810

Santos, K.O.B., Araujo, T.M., Carvalho, F.M. & Karasek, R. (2017). The job content questionnaire in various occupational contexts: applying a latent class model. *BMJ Open*. *7*(5), e013596. doi: 10.1136/bmjopen-2016-013596

Sascău, R.A., Anghel, L., Enea, D., Stătescu, C. & Arsenescu-Georgescu, C. (2011). Sindromul metabolic și afectarea subclinică de organ țintă la pacienții hipertensivi. In Societatea Română de Cardiologie (Ed.), *Progrese în cardiologie 2011* (pp. 470-479): Media Med Publicis.

Scragg, R., Slow, S., Stewart, A.W., Jennings, L.C., Chambers, S.T., Priest, P.C., Florkowski, C.M., Camargo, C.A., Jr. & Murdoch, D.R. (2014). Long-term high-dose vitamin D3 supplementation and blood pressure in healthy adults: a randomized controlled trial. *Hypertension*. *64*(4), 725-730. doi: 10.1161/HYPERTENSIONAHA.114.03466

Scragg, R., Waayer, D., Stewart, A.W., Lawes, C.M.M., Toop, L., Murphy, J., Khaw, K.T. & Camargo, C.A., Jr. (2016). The Vitamin D Assessment (ViDA) Study: design of a randomized controlled trial of vitamin D supplementation for the prevention of cardiovascular disease, acute respiratory infection, falls and non-vertebral fractures. *J Steroid Biochem Mol Biol*. *164*, 318-325. doi: 10.1016/j.jsbmb.2015.09.010

Shi, A., Tao, Z., Wei, P. & Zhao, J. (2016). Epidemiological aspects of heart diseases. *Experimental and Therapeutic Medicine*. *12*(3), 1645-1650. doi: 10.3892/etm.2016.3541

Skaaby, T., Husemoen, L.L., Pisinger, C., Jorgensen, T., Thuesen, B.H., Fenger, M. & Linneberg, A. (2012). Vitamin D status and changes in cardiovascular risk factors: a prospective study of a general population. *Cardiology*. *123*(1), 62-70. doi: 10.1159/000341277

Sparks, J.A., Barbhaiya, M., Karlson, E.W., Ritter, S.Y., Raychaudhuri, S., Corrigan, C.C., Lu, F., Selhub, J., Chasman, D.I., Paynter, N.P., Ridker, P.M. & Solomon, D.H. (2017). Investigating methotrexate toxicity within a randomized double-blinded, placebo-controlled trial: Rationale and design of the Cardiovascular Inflammation Reduction Trial-Adverse Events (CIRT-AE) Study. *Semin Arthritis Rheum*. *47*(1), 133-142. doi: 10.1016/j.semarthrit.2017.02.003

Spring, B., Moller, A.C., Colangelo, L.A., Siddique, J., Roehrig, M., Daviglus, M.L., Polak, J.F., Reis, J.P., Sidney, S. & Liu, K. (2014). Healthy Lifestyle Change and Subclinical Atherosclerosis in Young Adults: Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Circulation*. doi: 10.1161/circulationaha.113.005445

Steptoe, A., Breeze, E., Banks, J. & Nazroo, J. (2013). Cohort profile: the English longitudinal study of ageing. *Int J Epidemiol*. *42*(6), 1640-1648. doi: 10.1093/ije/dys168

Stevens, S.L., Wood, S., Koshiaris, C., Law, K., Glasziou, P., Stevens, R.J. & McManus, R.J. (2016). Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. *The BMJ*. *354*, i4098. doi: 10.1136/bmj.i4098

Stokić, E., Hakkak, R., Romani, A., Kupusinac, A. & Isenović, E. (2017). Influence of Vitamin D Deficiency on Cardiometabolic Risk in Obesity. *J Obes Chronic Dis*. *1*(2), 21-30.

Sulistiowati, E. & Sihombing, M. (2016). NCEP-ATP III and IDF criteria for metabolic syndrome predict type 2 diabetes mellitus. *Universa Medicina*. *35*(1), 46-55. doi: 10.18051/Univ.Med.2016.v35.46-55

Tamez, H., Kalim, S. & Thadhani, R.I. (2013). Does vitamin D modulate blood pressure? *Curr Opin Nephrol Hypertens*. *22*(2), 204-209. doi: 10.1097/MNH.0b013e32835d919b

Toumanien, T.-P. *Finnish Vitamin D Trial (FIND) (FIND)*. from https://clinicaltrials.gov/ct2/show/NCT01463813

Townsend, N., Wilson, L., Bhatnagar, P., Wickramasinghe, K., Rayner, M. & Nichols, M. (2016). Cardiovascular disease in Europe: epidemiological update 2016. *European heart journal*. *37*(42), 3232-3245. doi: 10.1093/eurheartj/ehw334

Tudose, C., Tudose, F., Oană, C., Dobranici, L. & Crasan, A. (2013). *Psihiatria Medicului de Familie*. Bucureşti: Editura Medicală.

US Department of Health and Human Services and US Departments of Agriculture. (2015). Dietary Guidelines for Americans. 8th Edition.

van Ballegooijen, A.J., Cepelis, A., Visser, M., Brouwer, I.A., van Schoor, N.M. & Beulens, J.W. (2017). Joint Association of Low Vitamin D and Vitamin K Status With Blood Pressure and Hypertension. *Hypertension*. *69*(6), 1165-1172. doi: 10.1161/hypertensionaha.116.08869

Wang, L., Ma, J., Manson, J.E., Buring, J.E., Gaziano, J.M. & Sesso, H.D. (2013). A prospective study of plasma vitamin D metabolites, vitamin D receptor gene polymorphisms, and risk of hypertension in men. *Eur J Nutr*. *52*(7), 1771-1779. doi: 10.1007/s00394-012-0480-8

Whelton, P.K., Carey, R.M., Aronow, W.S., Casey, D.E., Collins, K.J., Dennison Himmelfarb, C., DePalma, S.M., Gidding, S., Jamerson, K.A., Jones, D.W., MacLaughlin, E.J., Muntner, P., Ovbiagele, B., Smith, S.C., Spencer, C.C., Stafford, R.S., Taler, S.J., Thomas, R.J., Williams, K.A., Williamson, J.D. & Wright, J.T. (2017). 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. *A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines*. doi: 10.1016/j.jacc.2017.11.006

Wilkins, E., Wilson, L., Wickramasinghe, K., Bhatnagar, P., Rayner, M. & Townsend, N. (2017) European Cardiovascular Disease Statistics 2017 Edition. Brussels: European Heart Network.

Wongcharoen, W., Sutthiwutthichai, S., Gunaparn, S. & Phrommintikul, A. (2017). Is non-HDL-cholesterol a better predictor of long-term outcome in patients after acute myocardial infarction compared to LDL-cholesterol? : a retrospective study. *BMC Cardiovasc Disord*. *17*(1), 10. doi: 10.1186/s12872-016-0450-9

Xia, Y., Liu, X., Wu, D., Xiong, H., Ren, L., Xu, L., Wu, W. & Zhang, H. (2017). Influence of beat-to-beat blood pressure variability on vascular elasticity in hypertensive population. *Scientific Reports*. *7*(1), 8394. doi: 10.1038/s41598-017-08640-4

Xue, Y.T., Tan, Q.W., Li, P., Mou, S.F., Liu, S.J., Bao, Y., Jiao, H.C. & Su, W.G. (2015). Investigating the role of acute mental stress on endothelial dysfunction: a systematic review and meta-analysis. *Clin Res Cardiol*. *104*(4), 310-319. doi: 10.1007/s00392-014-0782-3

Zaidi, S. (2015). *Puterea vitaminei D: cele mai folositoare si practice sfaturi stiintifice despre Vitamina D sau Hormonul D*: Editura Benefica.